Assessing Companion Diagnostics (CDx) for Reimbursement Within Alberta: Pilot Study Using Health Technology Assessment of Programmed Death Ligand 1 (PD-L1) Testing in Non-Small Cell Lung Cancer (NSCLC)

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

HEALTH TECHNOLOGY ASSESSMENT

Departmemt of Public Health Sciences

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Abstract

Introduction: The number of investigational and licensed indications for companion diagnostic (CDx)-drug pairs is increasing. National assessments of the linked drug to support provincial funding decisions do not specifically address the CDx. The project objectives were to: (1) review a proposed process for Alberta to undertake health technology assessments (HTAs) of CDx and the rationale for a pilot, (2) provide background on the pilot HTA topic and identify the information elements for assessing CDx, (3) conduct the pilot HTA, (4) assess the proposed process for feasibility (timeliness, resources, and efficiencies), and compare the HTA findings with assessments in other jurisdictions/countries.

Methods: Documents were reviewed describing a previous jurisdictional scan, literature review, workshop with Australian, British and American representatives, and process for CDx assessments as proposed to a provincial cross-sectoral, multidisciplinary CDx working group. A pilot of the proposed process using programmed-death ligand-1 (PD-L1) testing for advanced non-small cell lung cancer (NSCLC) was initiated. Using available guidance and literature, information elements related to CDx—specific to clinical utility, clinical validity and analytical validity—were identified. Research questions for the pilot HTA were developed using input from a topic working group, on clinical use of, and the laboratory capacity for PD-L1 testing in Alberta. For research questions about the prognostic role, clinical utility, analytical validity, cost-effectiveness, and patient perspectives of PD-L1 testing for advanced NSLC, a systematic review using standard methodology was conducted. Other research questions (i.e., budget impact, social and ethical considerations) were answered based on literature from the systematic review and input/data from the topic working group. The HTA focused on use of the 22C3 PharmDx assay for PD-L1 testing to determine eligibility for pembrolizumab treatment in NSCLC. A process

evaluation was conducted, based on: (i) data collection on timing, skill requirements and resources for all HTA steps, (ii) assessment (in retrospect) on how and when the information provided in reports by the national body providing recommendations on the linked drug(s) may be incorporated and/or impact the results, (iii) comparison of the findings with those of other countries.

Results: The proposed process was designed to coincide with the pan-Canadian review of the drug and focus on information elements specific to the CDx. Findings from the pilot revealed that very low quality evidence exists for clinical utility of PD-L1 testing at the thresholds currently used for eligibility in advanced NSCLC for treatment with pembolizumab. PD-L1 expression may not greatly impact cost-effectiveness of the drug, because the benefits and costs change in the same direction as PD-L1 expression changes. The analytical validity of the PharmDx assay is sub-optimal; important considerations are that quality assurance is essential for local laboratories to undertake, and that a single biopsy in patients with multifocal lung cancer, as well as tissue samples from early stage disease, may not accurately capture PD-L1 expression status as used for treatment decisions. The budget impact to Alberta in 2017 was estimated at $535,296 annually when using actual cases submitted for testing (approx. 1,600); this cost may not be required if only cases of newly diagnosed advanced NSCLC (approx.. 450-500 per year) are tested in the future. The pilot was completed using 5.4 full-time equivalent months of effort (across personnel having expertise in systematic reviews, information science, and statistics), and could be conducted over a 5- to 6-month period to align with the current national assessments of the linked drug. Information on the cost-effectiveness and patient experiences with the CDx from the initial and/or final reports from the national assessments will likely prove very valuable. Assessment for reimbursement of the CDx alone, without concurrent

and similar considerations applied for decisions about funding the drug, may lead to differences in access to the drug and CDx. This could limit the available options for funding the CDx and may lend towards lack of credibility to both processes.

Conclusions: The proposed CDx review process appears feasible and generates the type and level of information required to support decision-making in Alberta. Rationale for decisions should be made transparent to assist with comparisons between provinces and other countries.

Acknowledgments

This thesis would not have been possible without the ongoing support, guidance, and patience of my supervisor Dr. Tania Stafinski. Dr. Devidas Menon also deserves special mention for his mentorship and encouragement during the planning of this work and his advice and support when presenting the research plan to stakeholders and findings at a conference. I feel very privileged to have learned from these exceptional individuals and also greatly enjoyed several events they hosted over the years in appreciation of their team, at which I felt welcome. Thank you to Dr. Carolyn O'Hara and Ms. Tammy Hofer for their input related to the pathology and management perspectives related to companion diagnostics (CDx). Together these four formed my supervisory committee for which I am greatly indebted. Thanks to the members of the Provincial CDx Working Group for their review of the pilot project proposal and agreeing to undertake this pilot. Dr. Gilbert Bigras, Robin Stocks, Lori Berry, and Dr. Randeep Sangha also deserve many special thanks for spending time to answer questions during the pilot project, on the clinical, pathology, and laboratory context for PD-L1 testing in Alberta. The calculations for the budget impact of PD-L1 testing in Alberta were undertaken by Lori Berry and colleagues, and I am grateful that they shared this data. I would also like to acknowledge Ms. Robin Featherstone and Tara MacGregor at the Alberta Research Centre for Health Evidence for their assistance during the systematic review, when developing and implementing the database and grey literature searches (RF) and when screening citations and verifying a sample of the data extraction (TM); their work was supported financially through the Alberta Strategies for Patient-Orientated Research (SPOR) Knowledge Translation platform.

Although not held during the conduct of this research, I am grateful for a generous studentship I held during 2013-2015 from Pfizer Canada that supported my course work and other professional development activities related to personalized medicine.

It needs to be acknowledged that the background planning for this project, as described in the section of Review of Proposed Approach to Health Technology Assessment for CDx in Alberta was undertaken by the Health Technology and Policy Unit in the School of Public Health at the University of Alberta, directed by Drs Stafinski and Menon. Without this work and their long-standing working relationships within Alberta, this project would not have been possible.

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List of Abbreviations

AH	Alberta Health
AHS	Alberta Health Services
AHTDP	Alberta Health Technologies Decision Process
ALK	Anaplastic lymphoma kinase
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CDx	Companion diagnostic
CI	Confidence interval
CTA	Clinical trial assay
ECDET	Expert Committee on Drug Evaluation and Therapeutics
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGP	Economic Guidance Panel
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQual 5D
FDA	U.S. Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FNA	Fine-needle aspiration
HTA	Health Technology Assessment
HTPU	Health Technology Policy Unit
HR	Hazard ratio
IC	Immune cell
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
LDT	Laboratory-developed test
NCSLC	Non-small cell lung cancer
NICE	National Institute for Health and Care Excellence
NPA	Negative percent agreement
NPV	Negative predictive value
NR	Not reported
OPA	Overall percent agreement

ORR	Objective response rate
pCODR	pan-Canadian Oncology Review
PD-1	Programmed-death 1 receptor
PD-L1	Programmed-death ligand 1
PFS	Progression-free survival
PPA	Positive percent agreement
PPV	Positive predictive value
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
RT	Radiation therapy
RR	Relative risk
TC	Tumor cell
TKI	Tyrosine kinase inhibitor
TMA	Tissue microarray
TPS	Tumor proportion score
TRAE	Treatment-related adverse effect

Glossary of Terms

Alberta Health Technologies Decision Process (AHTDP) — Process for reviewing non-drug technologies in Alberta by independent HTA groups and funded by the government (Alberta Health).	
Alberta Health	Government of Alberta's ministry of health.
Alberta Health Services	Single provincial health services provider in Alberta.
Analytical validity	Ability of a test to correctly and reliably measure what it is supposed to measure. Table 1 on page 20 defines several components of analytical validity*: analytical sensitivity* (i.e., the proportion of samples with positive test result correctly classified as positive); *analytical specificity* (i.e., the proportion of samples that have a negative test result correctly classified as negative); *precision/ reproducibility/repeatability* (i.e., inter and intra-reader, within-run/intra-day, between-run/inter-day, inter-antibody lot, between-laboratory, across-section agreements; positive and negative with respect to PD-L1 cut-off); *robustness* (i.e., precision with small deliberate changes to conditions such as prolonged delays, tissue thickness, tissue fixatives, temperature or ischemia); *variations/limitations in performance related to experience of personnel, sample types* (fresh vs. different archival timings, large/surgical specimens vs. small biopsies, tissue section thickness), *methods of antibody retrieval, and within-tumor expression heterogeneity* (in different cores), including different tumor locations and location of expression in tumor cells (cell membrane vs. cytoplasm)
CDx Working Group	Multidisciplinary, multi-stakeholder working group convened to propose a process for reviewing CDx to inform funding decisions in the province.
Clinical utility	Ability to predict a response to the particular drug in those deemed positive (or meeting a certain threshold) for the test value. To meet this criterion there should be (i) no impact on the response to other therapies or on disease outcomes in the absence of therapy, as one would define a prognostic marker, and (ii) a large differential between response in those positive compared with those negative for the biomarker. Moreover, clinical utility encompasses how a CDx predicts a response based on patient-important clinical outcomes as compared with an appropriate standard of care and guides decisions by patients and clinicians.
Clinical validity	Ability of the test result to sensitively measure and determine likelihood of response to the drug in patients.

	Different measurements include: *clinical sensitivity* (i.e., proportion of individuals who respond and are PD-L1 positive at different cut-offs); *clinical specificity* (i.e., proportion of individuals who do not respond and who have negative or below-threshold PD-L1 levels); *positive predictive value* (i.e., proportion of PD-L1^{+} patients who respond); *negative predictive value* (i.e., proportion of PD-L1^{-} patients who do not respond); *positive and negative likelihood ratios for response* (i.e., likelihood that a given test result would be expected in a patient who responds compared to the likelihood that the response would be expected in a patient without the target disorder).
Companion diagnostic test	I*n vitro* diagnostic tests that measure levels of particular biomarkers, on the basis of which patients can be stratified into sub-groups that are likely to respond differently to a drug.
Economic evaluation	An evaluation comparing the relative costs and outcomes of an intervention.
Health Technology and Policy Unit (HTPU)	— One of the three groups performing health technology assessments for non-drug technologies in the province's AHTDP. Working with Alberta Health and Alberta Health Services to develop a process for evaluating CDx.
Indirect evidence	Comparing results between studies rather than within a single study. May also relate to using a different, but similar, drug or patient population from that under direct investigation.
Laboratory-developed test (LDT)	Type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory. Validation of LDTs in the presence of a (analytically and clinically) valid assay for comparison requires assessment of their concordance/agreement with the comparative method, as well as their precision (e.g., inter-run and inter-operator). When using monoclonal antibodies (e.g. 22C3 as reviewed in this HTA), if the antibody clone is different than that used in the comparator assay, a full analytical and clinical validation should be undertaken.
Linked-evidence	Using more than one study to capture evidence when adequate study designs have not been conducted. For example, findings from marker-enriched trials are compared with those from single-arm trials including patients without the marker, to provide an estimate of clinical utility.

Marker-based Strategy Design, with Randomization	— Study design that randomizes patients to a test or no test scenario, to simulate the real-world choice for choosing whether or not to implement a testing strategy. The design captures the effects of the new intervention (proposed to require the CDx) and the standard of care in marker negative and positive patients. Design enables demonstration of clinical utility.
Marker-by-Treatment Interaction	Study design comparing the marker-based intervention with standard of care in both marker positive and negative patients. There is no comparison with an unselected ("all-comers") population. These trials may use stratification by marker status during randomization in a standard parallel-arm design, or be undertaken in two separate but identical trials. Design enables demonstration of clinical utility.
Marker-Enriched Design	Trial comparing marker-based intervention to standard of care only in patients who express the marker. Fails to capture the relative effect between the interventions for marker negative patients, and therefore does not allow demonstration by itself of clinical utility.
Pan-Canadian Oncology Review	Program within the national independent organization, Canadian Agency for Drugs and Technologies in Health (CADTH), that reviews new oncology drugs and provides recommendations to the provinces and territories (with the exception of Quebec) to inform their reimbursement decisions.
Programmed–death ligand 1 (PD-L1)	— Ligand that binds to the programmed-death 1 (PD-1) receptor found on tumor-specific cytotoxic T lymphocytes to suppress antitumor immunity in the PD-1 pathway (representing one of the so-called "immune checkpoints"). The therapeutic antibodies pembrolizumab and nivolumab block the PD-1 receptor such that the PD-L1 cannot bind to inhibit the body's immune attack on the tumor cells. In contrast, atezolizumab, durvalumab, and avelumab all target the ligand (PD-L1).
Risk of bias	Based on study design and conduct, the degree of potential risk to the study's ability to accurately measure the effects of an intervention (internal validity). Main conceptual domains contributing to this risk include sequence generation (truly random process should be used to ensure prognostic balance for known and unknown confounders between groups at baseline), allocation concealment (to maintain randomization when assigning patients), blinding (of participants, personnel and outcome assessors, to avoid performance bias and ascertainment biases), incomplete

	outcome data (failure to undertake intent-to-treat analysis or attrition that is unbalanced between groups especially if possibly related to the intervention effects), and selective outcome reporting (e.g., reporting only significant findings, changing analysis to reflect better findings).
Single-arm Trial	Experimental study whereby investigators apply the intervention using defined a priori protocol in a defined sample, without a comparator**.**
Subgroup effects	Referring to a comparison of effects between different population or intervention subgroups (e.g., 1-49% vs. ≥50% PD-L1 expression). Credibility of a difference in effects may be provided when there is a statistically significant difference when comparing the effects between groups (interaction effect), but may also be dependant on the magnitude of effect for each group as well as other factors such as biological plausibility. Lack of a meaningful effect for one group with a meaningful effect for the other would support credibility.

Chapter 1: Introduction

Targeted therapies have been widely recognized as holding promise for patients and healthcare systems.[1] The appropriate selection of patients to treat or not to treat with a specific therapy promises to optimize the magnitude of any clinical effect and minimize unnecessary exposure to harm, both of which can lead to improved efficiencies in a healthcare system. Over the past 5 years, the majority of new oncology drugs have been targeted therapies, and approximately half of those in the 'pipeline' fall into this category.[2]

Companion diagnostics (CDx) are *in vitro* diagnostic tests that measure levels of particular biomarkers, on the basis of which patients can be stratified into sub-groups that are likely to respond differently to a drug. Stratification may be through qualitative (binary) means such as when the biomarker is measured as being detected or not, or may be considered semi-quantitative when the detection method measures the biomarker on a continuous scale and one or more thresholds are used. Less often, biomarkers are measured quantitatively with the drug response correlated to the amount of biomarker and no threshold used. Although some countries may consider a test a CDx if it is recommended prior to prescribing a specific drug therapy, many limit this term to those that are required through regulatory labelling (i.e., testing of biomarkers prior to prescribing the companion drug). Other terms such as "complimentary diagnostic" are now helping to define those tests that have shown to inform improvement of the benefit-to-harm ratio without restricting drug access.[3] In some cases, the requirement and label of CDx may be based on the fact that the clinical trials did not examine effects in patients who were negative for the biomarker, rather than clear evidence of clinical utility from the biomarker.

Guidance for evaluating CDx consistently[4-8] define a CDx as a test demonstrating **clinical utility** to *predict* a response to the particular drug in those deemed positive (or meeting a certain threshold) for the test value. To meet this criterion there should be (i) no impact on the response to other therapies or on disease outcomes in the absence of therapy, as one would define a prognostic marker,[6,9] and (ii) a large differential between response in those positive compared with those negative for the biomarker. Moreover, clinical utility encompasses how a CDx predicts a response based on patient-important clinical outcomes as compared with an appropriate standard of care and guides decisions by patients and clinicians. Without demonstration of clinical utility there are equity and efficiency issues, such as whether patients shown to lack a particular biomarker (or enough of one) may also benefit from the drug,

especially if few alternatives exist,[8] and whether or not clinicians rely on the particular CDx during treatment decisions. Health economic considerations are warranted and will be particularly important when the diagnostic test is expensive or where only a small proportion of those tested are identified as eligible for the treatment.[4]

The global market for CDx is growing, with worldwide sales expected to grow ten-fold by 2024. This growth will likely have significant implications for the Canadian healthcare system.[10] Mechanisms for assessing CDx-drug pairs to inform reimbursement decisions have emerged quite recently.[11] Challenges exist when considering the differences in how drugs and diagnostic tests are currently evaluated for both regulatory and reimbursement review. In Canada, as in most developed countries, the federal government (through Health Canada) is responsible for the regulatory approval of new drugs and devices (including diagnostic tests). For regulatory review, evidence demonstrating the safety, efficacy, and quality of a certain product is typically needed, but the kind and amount of evidence required vary between drugs and diagnostic tests. While market approval of drugs and devices is centralized, decisions on reimbursement/coverage are decentralized, with individual jurisdictions, as payers, determining whether such technologies should be offered within the publicly funded healthcare system. For drugs, these decisions are informed by centralized reviews/health technology assessments (HTAs) conducted by the **pan-Canadian Oncology Drug Review (pCODR)** or Common Drug Review (CDR) (https://www.cadth.ca/about-cadth/what-we-do/products-services). However, for non-drugs (including CDx) no centralized review mechanisms exist, leaving the responsibility for assessing the scientific evidence to individual jurisdictions.

In Alberta, some non-drug technologies are reviewed through the **Alberta Health Technologies Decision Process (AHTDP)**.[12] For the review of CDx, one option proposed is the AHTDP, which has an established framework for its HTAs that could be modified for CDx. A Provincial CDx Working Group has been formed to propose methods and processes for these assessments.

Evidence available to payers is largely driven by the expectations of regulatory bodies, since sponsors/manufacturers seek coverage of their technologies soon after they receive market approval. The decision problem is further complicated for CDx because of the additional evidence requirements related to their predictive nature in terms of health outcomes when paired with one or more drugs. The agency that coordinates the pan-Canadian centralized review

process for drugs, the Canadian Agency for Drugs and Technologies in Health (CADTH) recently developed a process for the assessment of drugs with CDx that came into effect in October 2017. Within this process, there is no evaluation of the CDx's test performance (i.e., **analytical validity**) and no criteria about the extent or quality of evidence on its clinical utility. Rather, the focus is to "investigate factors relevant to testing that would inform the implementation of associated drugs under review by CADTH pCODR or CDR."[13] Information from sponsor-provided and, in some cases, CADTH generated references of literature about the clinical utility will be provided. The costs of the CDx will also be incorporated into the economic model and budget impact analysis. In addition, their patient input template now has specific questions about experiences with testing or treatment decisions based on the CDx test results.

Unique needs of each jurisdiction require consideration of: (1) whether and how the CDx will fit into local clinical pathways, (2) whether clinicians envision using the CDx as indicated by the current evidence and recommendations from pCODR, (3) whether the same test assay, as used in the clinical evidence review for CADTH, is the focus or if alternative tests (e.g., **laboratory-developed tests** [LDTs]) are options due to costs or local infrastructure and resource needs, (4) whether local laboratories can readily implement the testing, (5) what the specific criteria are for each of the relevant outcomes within each domain of analytical and clinical validity (e.g., reliability and clinical sensitivity, respectively), clinical utility (e.g., patient-important outcomes) and cost-effectiveness (e.g., whether offering the particular CDx test will yield sufficient benefits at a system-wide level to justify its costs).

The aim of this project was to determine the feasibility, efficiency, and acceptability of conducting an HTA to inform CDx test reimbursement decisions in Alberta.

To accomplish this, the following objectives were established:

1. Review the proposed process for Alberta to undertake HTAs of CDx and the rationale for the pilot project.
2. Provide background on the pilot project topic, and describe the information elements for assessing the ability of the relevant test to serve as a CDx for this topic.
3. Conduct a pilot HTA based on the proposed process of a relevant and timely biomarker test proposed for reimbursement as a CDx in Alberta.

4. Conduct a process evaluation to assess the HTA process in terms of timeliness, resource requirements, and efficiencies, and to compare the HTA findings with assessments in other jurisdictions/countries.

Chapter 2: Review of Proposed Approach to Health Technology Assessment (HTA) of Companion Diagnostics (CDx) in Alberta

2.1. Proposed Approach to HTA for CDx

In May 2014, the **Health Technology and Policy Unit (HTPU)** in the School of Public Health at the University of Alberta held a workshop with **Alberta Health** (AH) and **Alberta Health Services** (AHS) to explore the need for an approach to the assessment of CDx tests for reimbursement in Alberta (unpublished work: Companion Diagnostic Tests: Backgrounder Paper, prepared by the HTPU). The workshop followed concerns at the time related to the time taken to make funding recommendations on CDx for drugs that had received a positive reimbursement decision (e.g., crizotinib as second-line therapy for patients with ALK-positive advanced non-small-cell lung cancer in 2013). The workshop included a review of processes established in the United Kingdom, Australia, and the United States, as well as CDx case studies. Following the workshop, an environmental scan of processes used by other organizations around the world to make funding decisions on CDx was completed.

Building on findings from the workshop and an environmental scan, the HTPU was asked to propose 'next steps' for Alberta. They included both a review of current and proposed standards, guidelines, or criteria for the evaluation of CDx throughout their lifecycle and the establishment of a multidisciplinary, multi-stakeholder working group (**CDx Working Group**). The role of the working group was to propose options for the assessment of CDx in Alberta.

During the February 2016 meeting of the CDx Working Group, next steps were identified. They included the development of possible options of review processes for CDx. It was agreed that of priority were options that ensure coordination of CDx reviews with those of linked drugs underway by pCODR or the CDR at CADTH. Further, the scope of the CDx review was to be limited to an assessment of testing strategies (i.e., the cost-effectiveness of the linked drug would not be considered).

In October 2016, the HTPU made several recommendations for possible outcomes from the process, an approach to HTA content and review, and decision-making considerations

(unpublished work: Draft Options for a Provincial Process to Review Companion Diagnostic Tests in Alberta, prepared by HTPU).

1. For consistency with other provincial health technology review processes (e.g., AHTDP), the recommended range of outcomes of the proposed process were:
    a. Provide to all patients with a particular disease
    b. Provide to a subgroup of patients with a particular disease who meet certain eligibility criteria
    c. Provide for an interim period while additional evidence is collected
    d. Do not provide

    These outcomes could take the form of a recommendation or a decision, depending on the authority delegated to the process. For each of the first three outcomes, there could be two possibilities: 1) Specify a particular test or testing strategy (an approach to or method for conducting a test) or 2) Do not specify a particular test or testing strategy (leaving that decision to laboratory services).
2. Recommendations should be made by an advisory group to ensure that the multiple factors, issues and stakeholder perspectives involved are captured during group deliberations.
3. Taking into account existing structures, the advisory group should be a multi-stakeholder, multi-disciplinary advisory committee, whose membership includes, at a minimum, specialists with relevant clinical and diagnostic expertise, senior level administrators of lab services from AHS, relevant senior level policy-makers in AH, and academic researchers with appropriate methodological expertise.
4. The addition of a drug requiring a CDx to the CADTH queue should initiate a review of that CDx through the proposed process.
5. A standard protocol for CDx assessments should be developed by the advisory group. The current approach used by the AHTDP may serve as a useful starting point.
6. The HTA expertise needed to conduct assessments and surveys of local practice already exists within academic groups in the province. Therefore, it is recommended that these groups be involved in the CDx assessments for the proposed process and develop mechanisms for engaging laboratory services within the province.

7. To ensure that assessments reflect current international practice and local practice, those conducted for the proposed process should address analytical validity, clinical utility, local clinical and laboratory practice and system implications, and economic implications.
8. Assessments should include a survey of local laboratories that perform CDx, as well as analyses of secondary information sources.
9. Given the need to ensure that any CDx review is completed within the timeframes established and adhered to by the CDR/pCODR, it is recommended that the proposed process obtain stakeholder input through the advisory committee recommended above, whose membership includes representatives from key stakeholder communities.
10. In Alberta, the Alberta Advisory Committee on Health Technologies (AACHT), which governs the AHTDP, has adopted the following decision-making considerations: 1) Clinical need, 2) Health impact, 3) Affordability, 4) Implementation feasibility, and 5) Relevant social/ethical/legal considerations. While these examples offer possible options, it may be important to elicit the views of the Expert Committee on Drug Evaluation and Therapeutics, the provincial committee involved in making recommendations on the linked drug, to ensure consistency across processes.
11. A draft 3-6-month timeline was proposed, to align approximately with the limited time period between the submission of the drug to pCODR/CDR and its recommendation. The amount of time allotted for the assessment is significantly less than what is used by some other diagnostic assessment programs (e.g., NICE) and other HTAs. Because it is recommended that none of the components proposed be excluded in order to accommodate the shorter timeframes, the depth of analyses expected within each component may need to be adjusted.
12. A facilitated discussion with executives from AHS and AH to identify feasible funding options should be organized.

The proposed approach follows the model currently used for HTAs conducted for the AHTDP and includes a checklist for policy makers and others to ensure that the broad spectrum of issues with an impact on the policy-making process have been taken into account.[12] The model identifies areas of information and evidence that can inform a specific decision, with the use of a STEP framework which comprises the following topics: Social and System

Demographics (S), Technological Effects and Effectiveness (T), Economic Evaluation (E), Public Policy Analysis (P). Certain requirements for evaluating CDx would be incorporated, expanding the information and evidence included. For example, the system demographics topic would include information on how CDx testing will fit within the current clinical algorithms, and technological effects and effectiveness topic would cover analytical validity, clinical validity, and clinical utility (see section 3.2 on Elements and Evidentiary Requirements). When defining components specific to the analytical and clinical validity, approaches for validating diagnostic tests (primarily molecular pathology and immunohistochemistry [IHC] tests),[7,14,15] as well as CDx specifically[4-7] would be considered in order to ensure important elements are captured. Moreover, stakeholder input would need to be broadened beyond clinical and policy arenas, to include expertise in laboratory services administration and test validation as well as pathology. To facilitate this, the CDx Working Group would convene topic-specific working groups for each HTA, to which they would invite participation by local specialists in the clinical area as well as laboratory services and pathology.

To further evaluate the proposed approach, it was determined that a pilot should be conducted on a timely and relevant topic with a comparison with assessments in other jurisdictions/countries, and an assessment of the feasibility, timeliness, resource requirements, and efficiencies of the process. A major consideration was whether or not conduct of the HTAs can be performed simultaneous to pCODR assessments or if there would be a need to wait for sufficient availability of evidence after their completion.

2.2. Rationale for Pilot HTA

CADTH regularly publishes Cancer Drug Pipeline Tracking Updates (https://cadth.ca/sites/default/files/pcodr/Communications/cancer-drug-pipeline-tracking-info-2017.pdf) based on drug manufacturer surveys to identify and monitor novel oncology drugs and new indications for pre-existing oncology drugs in order to assist provincial drug programs, cancer agencies and pCODR proactively plan for health system changes, resource allocation, and possibly prioritization for implementation. In 2017, 50 of 277 drug-indication pairs (including new drugs and new indications for existing drugs) for were for lung cancer. Twenty-seven percent were being tested with a companion test, and PD-L1 testing led the way (12 of 54) in those tests that were considered developed (20 of 74 under development). These findings highlighted PD-L1 testing as a potential major player in future assessments. Further, pCODR's

positive recommendation (pending improvements in cost-effectiveness) in November 2016, for pembrolizumab for second-line or beyond treatment in non-small cell lung cancer (NSCLC) in patients expressing PD-L1 made this case of particular interest, given the impending need for provincial decision making about reimbursement of the drug and PD-L1 testing.

Focusing on NSCLC was viewed as appropriate for the pilot since no other cancer site has a drug recommendation including PD-L1 testing at this time. Moreover, PD-L1 is in extensive use investigationally and for licensed indications, is sufficiently complicated because multiple testing strategies are available, and requires a funding decision.

Chapter 3: Background on Pilot HTA Topic and Proposed Elements for the Assessment

3.1 Background on Pilot HTA Topic: Programmed Death Ligand-1 (PD-L1) Testing for Non-Small Cell Lung Cancer (NSCLC)

Tumor **programmed–death ligand 1** (PD-L1) binds to the PD-1 receptor found on tumor-specific cytotoxic T lymphocytes to suppress antitumor immunity via these lymphocytes in the PD-1 pathway (representing one of the so-called "immune checkpoints"). The therapeutic antibody pembrolizumab blocks the programmed death (PD-1) receptor such that the PD-L1 cannot bind to inhibit the body's immune attack on the tumor cells. Pembrolizumab was approved by Health Canada in 2015. In November 2016, it received a positive reimbursement recommendation by pCODR for patients 1) with metastatic (stage IIIb or IV) non-small cell lung cancer (NSCLC), 2) whose tumors express (as determined by a validated IHC assay) PD-L1 on at least 1% of their cell membrane surface area, 3) who have had disease progression on or after cytotoxic chemotherapy, or targeted therapies for epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements (i.e., requiring second line or beyond therapy), and 4) have good performance status.[16] In August 2017, pCODR expanded their recommendations for pembrolizumab from second-line to include untreated (first-line) patients with locally advanced or metastatic NSCLC whose tumor cells express PD-L1 (≥50%) and do not harbor a sensitizing EGFR mutation or ALK rearrangement.[17] Both pCODR recommendations were conditional to the cost-effectiveness being substantially improved. Moreover, although they reflect a codependency of the drug and PD-L1 test (i.e., a companion diagnostic [CDx]), in neither case was the clinical utility/predictive ability of PD-L1 testing an

explicit criterion for the positive recommendation. One additional PD-1 inhibitor, nivolumab, has been recommended for funding for second-line treatment in NSCLC, with all provinces except Newfoundland and Prince Edward Island choosing to fund the drug for this indication as of April/May 2017.[18] Importantly, there is no requirement for PD-L1 testing for nivolumab. As such, for second-line treatment, nivolumab is a key comparator to pembrolizumab when considering reimbursement for a PD-L1 IHC as a CDx to predict response to therapy. Further, three other drugs targeting the PD-1/PD-L1 pathway (e.g., atezolizumab, durvalumab, and avelumab all targeting PD-L1) are pending review[19] in Canada or are in the late stages of development for NSCLC, and several other cancers have or will likely have approved indications for anti-PD-1/PD-L1 drugs. Pembrolizumab for NSCLC is the only one with a labeling requirement for PD-L1 testing, which may reflect this cancer's prevalence (and hence need for a cost-effective approach) rather than the strength of evidence for the test's predictive ability.[20] Pembrolizumab has also been approved for melanoma and for head and neck squamous cell carcinoma (HNSCC), although treatment in both cases does not require PD-L1 testing.

3.2 Proposed Information Elements Specific to Assessment of the CDx

Evidence requirements can be complex for demonstrating a CDx's clinical utility and cost-effectiveness (i.e., how the test positively benefits health care delivery at a justifiable cost, within patient trajectories, clinical pathways, societal and patients' expectations and other perspectives). Two important factors are that optimal study designs are infrequently used in trials of CDx and that several alternative CDx tests may be available. The need to evaluate the analytical validity (does the test correctly and reliably measure what it is supposed to measure?)[15] of the CDx should also be a prime consideration especially when demonstrating whether or not the CDx test will perform in local practice as it did in clinical trials. Clinical validity[15,21] (ability of the test result to sensitively measure and determine likelihood of response to the drug in patients [no comparison with standard of care incorporated]), should not be essential to evaluate if sufficient utility is evident but may be helpful to support utility data of low quality. Evidence considerations are described below for clinical utility and analytical and clinical validity. Specific criteria for analytical validity were developed based on knowledge of the pilot study to be conducted on PD-L1 testing with IHC to predict responses to immunotherapy drugs targeting PD-L1 or its receptor PD-1. Consideration of possible comparisons between different assays, including antibody clones and detection systems, or drugs, where effects have been measured

based on PD-L1 status, was incorporated. Assessments of other CDx may require slightly different criteria depending on the biomarker and testing methodology.

3.2.1. Clinical utility

Available guidance for evaluating CDx consistently defines a CDx as a test demonstrating clinical utility to predict a response for patient-important clinical outcomes as compared with an appropriate standard of care and to guide decisions by patients and clinicians.[4-6,8] It is important to rule out, or at least account for, that the test/marker is only serving as a *prognostic* marker, where its presence may signal better (or worse) response to all treatments, or even outcomes in the absence of treatment.[9] In this case, its use with any particular therapy would not be informative in clinical practice. There must also be the prediction of a highly differential response between those positive and negative for the marker, based on one or more thresholds of positivity. If all patients, regardless of biomarker status, will respond better to the investigated drug than to the standard of care, the test may actually not provide clinical utility.[9]

Study designs

Optimal study designs for demonstrating clinical utility, in a hierarchal order from most to least valid, are described below.[9] Generally, these designs are distinguishing between the test's ability to serve as a predictive versus prognostic marker (in this case defined as predicting response regardless of the treatment), with the former being necessary for a claim as a CDx.

Marker-based Strategy Design, with Randomization simulates the real-world choice for choosing whether or not to implement a testing strategy.[9] The design captures the effects of the new intervention (treatment B) and the standard of care (treatment A) in marker negative and positive patients. Because of a small effect size expected for the new treatment in unselected, "all-comer", patients (i.e., non-marker based strategy) these studies need to be very large to have sufficient power. Few trials are designed this way, but it has been recognized that they may not be necessary in most cases. Some trial designs may appear to have this design, but only provide standard of care (treatment A) to the non-marker-based strategy group. This fails to account for the effect of the new treatment in the marker negative patients (they are never receiving this) which is a strong determinant of a predictive over a prognostic nature.

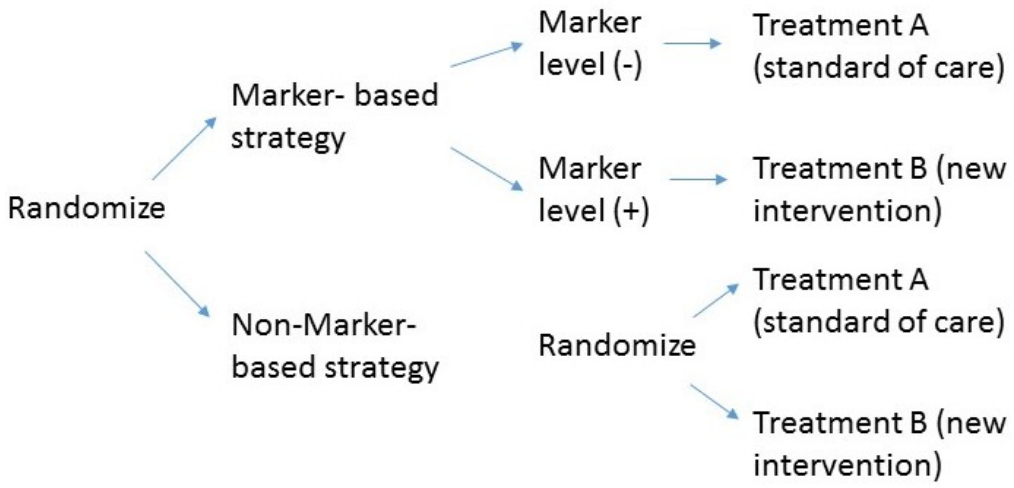

Figure 1. Marker-based strategy study design, with randomization (adapted from Sargent[9])

Marker-by-Treatment Interaction trials compare the marker-based (new) intervention with standard of care in both marker positive and negative patients.[9] There is no comparison with an unselected ("all-comers") population. These trials may use stratification by marker status during randomization in a standard parallel-arm design, or be undertaken in two separate but identical trials. They should be powered using the hypothesized difference in treatment outcomes in each of two marker groups, or analyzed in a way to detect an interaction effect between the marker value and the treatment efficacy. Retrospective subgroup analysis, based on marker status, of standard findings from randomized controlled trials (RCTs) is another possible approach but it may limit the study's power, if all patients are not able to provide results on marker status at the trial's completion (e.g., tumor sample not if sufficient quality). It also risks having baseline imbalances between groups based on marker status, and possibly other clinicopathologic factors particularly if they are correlated with marker status. Retrospective analysis of trials that prospectively collected samples from all patients (and had this as inclusion criteria) may help ensure adequate power. However, the issues of imbalances between samples must be carefully examined.

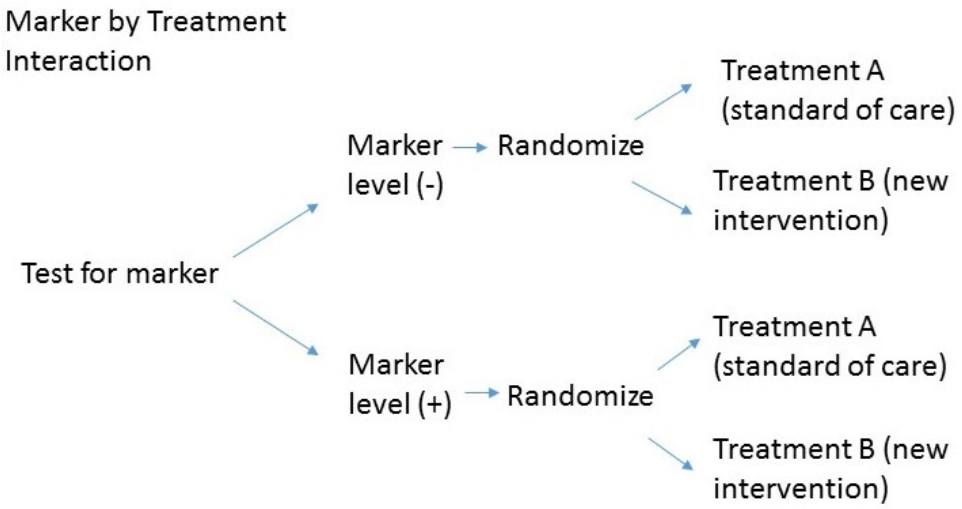

Figure 2. Marker-by-treatment interaction study design (adapted from Sargent[9])

Marker-Enriched Designs only enroll marker positive patients and randomize them to the two treatment groups (lower half of above marker-by-treatment interaction design).[9] This approach fails to directly assess the new treatment's effects in marker negative patients or the prognostic significance of the marker status. For example, the effects seen may be due to a negative prognostic role with the standard of care and/or the benefit from the new treatment. As available, additional evidence on the (negative/reduced) effects from the new treatment in marker-negative patients and on the (limited/lack of) prognostic role of the marker status for the comparator may lend support to the findings.

Single-arm Trial data with analysis by marker status may provide information on differences based on marker status, but there will be uncertainty about whether the same effects would occur with the comparator, which could indicate the marker is prognostic rather than predictive. These designs are used with the most caution, but nevertheless may be useful with strong supporting evidence particularly on the possible prognostic effect of the marker in standard of care. Data for marker negative patients may also support to some extent findings from marker-enriched trials.

Linked and indirect evidence

Ideally, marker-based strategy or marker-by-treatment interaction studies will be available to rigorously examine clinical utility of the CDx-drug pair. Often, a flexible, **linked-evidence** approach will be necessary to provide an estimate of the degree of clinical utility for the CDx—using, for example, marker-enriched trials supplemented with retrospective subgroup analyses of

trial data where tumor tissue is available to correlate biomarker level to response.[4,9] **Indirect evidence** from similar studies of other treatments where effects by biomarker status have been evaluated, even if the treatment has not been approved with the requirement of a CDx, may also be useful. Data on both benefits and harms of the treatment alternatives should be considered when determining clinical utility.

3.2.2. Analytical and clinical validity

Even if a CDx test provides evidence of predictive power, it is important to consider analytical performance in local contexts. The clinical trials may not capture the effects of all variation that may occur at different laboratories or during specimen collection. A set of key parameters useful for evaluating analytical validity was created based on several sources on validating diagnostic tests (primarily molecular pathology and IHC tests),[7,14,15] as well as CDx specifically.[4-6] Table 1 outlines the parameters that were evaluated with some specifics on requirements of sufficiency for validation. Some of the variables were chosen to be necessary (e.g., inter-case heterogeneity,[22] section stability and timing of sample[23]) based on literature about their potentially high relevance for the pilot study on PD-L1 IHC.

Table 1. CDx test validation parameters and requirements: using IHC

Parameter	Requirements of sufficiency
Analytic sensitivity (positive agreement to comparable method)	In the absence of a gold standard test, IHC validation studies often incorporate orthogonal strategies (Western blot, flow cytometry, mRNA testing) using previously characterized tissue validation sets (or genetically altered cell lines), as well as normal and neoplastic tissues with literature supporting their typical expression levels (e.g., lymphocytes and epithelial tissues express the biomarker whereas some placental tissues do not). Multiple approaches using relevant patient samples are beneficial. Negative controls should have <0.5 grade staining intensity.
Analytic specificity (negative agreement to comparable method)	
Precision/repeatability: intra-day	**Degree of concordance**: At least 85% but ideally 90% overall concordance/agreement (OA). If less than 90% the results should be investigated for positive (PA) and negative (NA) percent agreement to help characterize the cause of low concordance. Other statistical tests may also be reported (e.g., Kendall concordance, Cohen's or Light's kappa, Fliess k statistic), each having their own interpretations. Validation tissues should, if possible, use tissues that have undergone the same processing
Precision/repeatability: inter-day	
Precision/repeatability: intra-run	
Precision/repeatability: inter-lot	
Precision/repeatability: inter-instrument	
Precision/repeatability: intra-operator	
Precision/reproducibility: inter-operator	
Precision/reproducibility: inter-site	

Parameter	Requirements of sufficiency
	(fixative, other processing methods) that have been tested clinically. Whole tissue sections should be used over tissue microarrays (TMAs) when differences in fixation and processing are apparent; in cases of substantial inter-tumoral heterogeneity in expression are reported, whole tissue is most valid. **Number of cases**: Initial validation: 20 positive and 20 negative cases; cases should include high and low expressors for positive cases and should span the expected range of clinical results. Comparison with validated assay (change in fixative type, antigen detection system, antigen retrieval method): there is no guidance on the number of cases that are required, but this may be similar to validation of non-predictive assays (10 positive and 10 negative cases). **If a new antibody clone is used an entire initial validation process should be undertaken**.
Robustness: tissue thickness	As per the discretion of laboratory director and clinicians collecting samples, to be within their testing, collection, and storing conditions.
Robustness: antigen retrieval solution (pH, timing, temp)	
Robustness: pre-analytic delays (fixation times, fixative type)	
Robustness: type of fixation (biopsy, resection, cytology, as used)	
Robustness: specimen collection variables	
Robustness: ischemia	
Robustness: environmental conditions	
Stability: storage time and conditions for blocks, sections, and assay	
Intra-block heterogeneity	As per the discretion of clinical oncologists, acknowledging that this may increase the false negative rate.
Sample timing: new vs archival (effects of treatment on biomarker expression)	Accounting for all possible treatment effects that may influence these results.
Sample type: biopsy vs resection vs cytology	At laboratory director's discretion.
Sample location: primary tumor vs metastases	Noted differences that may influence clinical utility.
Interfering substances/clinical or biological variation in biomarker expression	Noted differences that may influence clinical utility.
Effect on training/experience	Noted differences that may influence test performance and capacity within laboratories.

When evaluating analytical validity, assessment should be focused on key variables (i.e., populations, diagnostic test thresholds, IHC assays) that have been examined in the clinical evidence. Although a very useful diagnostic technique, IHC interpretation is complicated for

monoclonal antibodies because different clones raised against the same protein will be specific for different protein epitopes; this, together with variation in detection systems, can lead to true biologic variability in IHC outcomes for what might be considered the "same test".[24] *Evidence of one clone's ability to predict differential response to a therapy may not transfer to another clone even if raised against the same protein. Even if major differences in staining or other technical factors are not apparent, the predictive equivalence in terms of patient outcomes would require clinical validation of any clone proposed for use in place of the trial-proven one.*[24] This matter is of critical importance when considering the emerging PD-1/PDL-1 inhibitors which have all been developed using different clones (Table 2).

Table 2. Comparison of assays used for different PD1/PD-L1 inhibitors

Drug	Pembrolizumab	Nivolumab	Atezolizumab	Durvalumab	Avelumab
Diagnostic assay (clone and detection system)	Dako 22C3 antibody w/ EnVision FLEX visualization system on Automated Link 48 staining platform with DakoLink software	Dako 28-8 antibody w/ Dako EnVision FLEX visualization system on Dako Automated Link 48 staining platform with DakoLink software	Ventana SP142 w/ Benchmark Ultra with OptiView Universal DAB Detection Kit and OptiView Amplification Kit	Ventana SP263 antibody w/ Benchmark Ultra with OptiView Universal DAB Detection Kit	Proprietary assay with 73-10 antibody (Dako)
Scoring method	% tumor cells with membrane staining at any intensity	% tumor cells with membrane staining at any intensity	% tumor cell *or* % area with tumor-infiltrating immune cells	% tumor cells with membrane staining	% tumor cells with membrane stained at any (1 & 5%) and moderate-to-high intensity (25%)
Thresholds in trials	<1%, ≥1%-49%, ≥50%	<1%, ≥1%, ≥5%, ≥10%	≥1-<5%, ≥5-49%, ≥10% (IC only), ≥50% (TC)	≥25%	≥1%, ≥5%, ≥25% (moderate-to-high intensity)

Development or assessment of other LDTs may be an option to consider if substantial costs or efficiencies can be realized. For this method to be valid, it must be confirmed that the

reference/comparative test has been adequately validated for the particular use at hand. Validation of LDTs in the presence of a (analytically and clinically) valid assay for comparison requires assessment of their concordance/agreement with the comparative method, as well as their precision (e.g., inter-run and inter-operator). As mentioned above, if the antibody clone is different than the comparator assay, a full analytical and clinical validation should be undertaken.

Clinical validity is defined as the specificity and sensitivity for a reference, or "evidentiary" standard which in the case of CDx is often clinical response to the treatment. This evidence would often come from single-arm trials of the drug of interest. If there is sufficient evidence supporting or refuting the clinical utility of the CDx-drug pair compared with standard of care, this will often supersede the need for clinical validity data. However, in some cases, the clinical utility data may be insufficient, supporting the use of data on clinical validity. An example would be when a marker-enriched trial does not provide sufficient information on the potential effects on biomarker negative patients. A high specificity or negative predictive value for CDx testing from a study providing this data may be used to help determine the validity of the assay as well as (indirectly) its clinical utility.

Chapter 4: Pilot Study of HTA of Programmed Death Ligand-1 Testing for Non-Small Cell Lung Cancer

4.1 Summary

The CDx Working Group convened a PD-L1 Working Group for this topic. Members with expertise in thoracic oncology, pathology, and oncology laboratory services provided input on the current and short-term future clinical treatment needs for advanced NSCLC and on the laboratory capacity (e.g., equipment, personnel, procedural issues) for PD-L1 testing in Alberta. This information helped ensure that the broad spectrum of issues with an impact on the policy-making process would be taken into account. For research questions about the prognostic role, clinical utility, analytical validity, cost-effectiveness, and patient perspectives of PD-L1 testing for advanced NSLC, a systematic review was conducted. Other research questions were answered based on this information and input from the PD-L1 Working Group.

In the systematic review, evidence sources providing the most relevant/direct and valid data for a particular question (e.g., marker-based strategy or marker-by-treatment interaction study

designs for clinical utility offered by PD-L1 testing for pembrolizumab) were prioritized. If such data were not available or sufficient, linked evidence (e.g., marker-enriched with single–arm trials in negative patients) and/or indirect evidence (e.g., PD-L1 utility in other drugs where it is not labelled as a CDx) was incorporated. Decisions on study selection were based on available guidance for both assessing a test's clinical utility (to serve as a CDx) and its analytical validity. Further, they were made in an unbiased manner with respect to the findings of the studies (i.e., decisions relied only on design and methods, not magnitude of effect). Anticipation about future needs were considered but not prioritized, partly because of considerable uncertainty about these directions within a highly evolving field. The following sections describe the policy and research questions and their development, the methods, and the results.

4.2. Research and Policy Questions

4.2.1. Research questions

The research questions were developed iteratively based on the needs within Alberta. Initially, the questions below, related to system demographics, were posed to the oncology, pathology and laboratory members of the PD-L1 Working Group to determine current and anticipated practices. These led to the identification of further questions to answer through available evidence.

1. Is PD-L1 testing anticipated to be used within clinical practice for NSCLC to inform treatment decisions? Where does PL-L1 testing currently fit within the treatment algorithms for NSCLC?
2. What is the experience and capacity for PD-L1 testing in Alberta, including use of tests included in clinical trials and other available commercial or LDTs? Would the capacity change in the future depending on the patient populations indicated for PD-L1 testing?

Based on responses to the above questions (see results section for details), it was decided to focus the review on PD-L1 testing using the 22C3 antibody clone for pembrolizumab treatment. The exception for assessing other antibodies/clones (e.g., Dako 28-8) would only arise if evidence was found for their use in clinical practice with pembolizumab where their predictive equivalency could be demonstrated. With interests in cost savings from a LDT, evidence on concordance (i.e., agreement) and precision (e.g., inter/intra-rater agreements) of LDTs using 22C3 compared with the 22C3 assay used in the pembrolizumab trials was of interest. Since the

main trials of pembrolizumab relied on marker-enriched designs (i.e., PD-L1 positive patients only) and therefore would not provide direct, high-quality evidence on clinical utility, there would be the need to examine the prognostic role of PD-L1 expression to determine whether any differential benefit based on PD-L1 status in these trials was specific to pembrolizumab rather than being independent of treatment or also applicable to the standard of care. Linked evidence from marker-enriched and single-arm trials of pembrolizumab would need to be examined, as may indirect evidence from comparators including nivolumab and other drugs targeting PD-L1 or PD1, particularly those with evidence from marker-by-treatment interaction studies with findings for both PD-L1 positive and negative patients.

The remainder of the research questions were:

3. Is PD-L1 a prognostic marker, whereby outcomes based on PD-L1 status are differential but not dependent on treatment? Is PD-L1 predictive of outcomes in patients receiving the standard of care chemotherapy, or other therapies apart from PD-L1 inhibitors?
4. Does PD-L1 testing using the Dako 22C3 PharmDx assay provide clinical utility, in terms of patient-important benefits and harms, for medical decision making with respect to using pembrolizumab? What biological or clinical factors (i.e., histology, treatment history/lines of treatment, tumor stage, mutational [EGFR] status, gender, age) influence the validity?
5. Is the currently available Dako 22C3 PharmDx PD-L1 assay analytically valid? What factors (e.g., tissue heterogeneity, type and timing of tissue tested) influence the analytical validity? Are there LDTs using the 22C3 clone that have shown to be highly concordant with the Dako 22C3 PharmDx assay?
6. Is the currently available Dako 22C3 PharmDx PD-L1 assay clinically valid, as compared with response and overall survival outcomes? Does this information support the evidence on clinical utility?
7. What are the experiences of patients with PD-L1 testing and what is their treatment experience with pembrolizumab?
8. Is testing with PD-L1 for treatment with pembrolizumab cost-effective?
9. What is the expected impact on the budget for Alberta's laboratory services? What are the unit and total costs of providing PD-L1 testing to the population for which it is

currently indicated? Would the cost be expected to change in the future, and if so, by how much?

10. What social, ethical, legal, and policy considerations are relevant to answering the policy question? Might there be considerable inequity or legal implications if PD-L1 testing is not reimbursed, or for NSCLC patients testing negative for PD-L1 or not meeting current eligibility requirements and thus not eligible for treatment with pembrolizumab?
11. What considerations are there with respect to the (potential or existing) inappropriate use of PD-L1 testing?
12. How will resources (e.g., infrastructure, people, training, programs, existing services, etc.) be impacted by a policy decision?

Research questions 3 to 8 were considered in the systematic review with methods elaborated on below in section 4.3. Questions 9 to 12 were not directly based on systematic review methodology and instead relied mostly on input from the PD-L1 Working Group. For question 9 on budget impact of the CDx, because there was only the need to assess the impact of the diagnostic test (i.e., specific to laboratory services) the full methodology of a Budget Impact Analysis was not undertaken.[25] A micro-costing approach was used (data kindly provided by Alberta Health Services) with explanation of inputs as well as some sensitivity analysis based on possible future needs.

4.2.2. Policy questions

1. Should PD-L1 testing be provided through the publicly funded healthcare system in Alberta?
2. What is the appropriate use of PD-L1 testing in Alberta's publicly funded healthcare system?

4.3. Systematic Review Methods

4.3.1. Eligibility criteria

Patients

1. Analytical validity: human NSCLC tumors, or
2. Prognosis, clinical validity, clinical utility, cost-effectiveness, patient experiences: patients with advanced-stage NSCLC

Sub-groups: gender, age, smoking status, histological subtype, tumor stage, mutational [EGFR] status, history/lines of treatment, different expression levels for PD-L1 (e.g., <1%/below limit of detection, ≥1% [as approved in second-line], ≥50% [as approved in first-line], others as reported)

Interventions (i.e., CDx)

1. Analytical validity: Dako 22C3 PharmDx assay, LDTs using 22C3 antibody clone, assays using other clones if clinically validated for use with pembrolizumab, or
2. Prognosis: Dako 22C3 PharmDx assay, LDTs using 22C3 antibody clone, assays using other clones if clinically validated for use with pembrolizumab or other drugs; treatment with acceptable standard of care based on tumor stage and previous treatment (e.g., second-line single agent treatment with a drug that has not been previously used, e.g., docetaxel, erlotinib or pemetrexed; tyrosine kinase inhibitors [TKIs] for targetable mutations [EGFR, ALK]; radiotherapy [RT]), or
3. Clinical validity: Dako 22C3 PharmDx assay, LDTs using 22C3 antibody clone, assays using other clones if clinically validated for use with pembrolizumab, or
4. Clinical utility and cost-effectiveness: PD-L1 testing with 22C3 or other clones for pembrolizumab treatment; indirect evidence from PD-L1 testing in treatment comparators nivolumab, atezolizumab, avelumab, durvalumab

Comparators

1. Analytical validity: test reference standard (positive [e.g. engineered cell lines, human placental tissue] and negative control), low-positive, high-positive, or
2. Prognosis: different standard of care treatments (see interventions), or
3. Clinical validity: response (objective response rate [ORR] and median overall survival) to pembrolizumab, or
4. Clinical utility and cost-effectiveness: No PD-L1 testing (ideally) and acceptable standard of care based on tumor stage and previous treatment (e.g., second-line single agent treatment with a drug that has not been previously used, e.g., docetaxel, erlotinib or pemetrexed).[15] Linked evidence (e.g., marker-enriched and **single-arm trials** of pembrolizumab) was expected to be required in order to "model" the effects of no PD-L1 testing, or at least evaluate the effects in patients negative for PD-L1 expression. Indirect

evidence (e.g., PD-L1 testing used for nivolumab) was also considered to potentially help provide supporting evidence.

Outcomes

1. Analytical validity/performance (*in vitro* technical variation and performance using PD-L1 cut-offs): analytical sensitivity (i.e., proportion of samples with positive test result that are correctly classified as positive); analytical specificity (i.e., proportion of samples that have a negative test result that are correctly classified as negative); precision/ reproducibility/repeatability (i.e., inter and intra-reader, within-run/intra-day, between-run/inter-day, inter-antibody lot, between-laboratory, across-section agreements; positive and negative with respect to PD-L1 cut-off); robustness (i.e., precision with small deliberate changes to conditions such as prolonged delays, tissue thickness, tissue fixatives, temperature or ischemia); variations/limitations in performance related to experience of personnel, sample types (fresh vs. different archival timings, large/surgical specimens vs. small biopsies, tissue section thickness), methods of antibody retrieval, and within-tumor expression heterogeneity (in different cores), including different tumor locations and location of expression in tumor cells (cell membrane vs. cytoplasm), or
2. Prognosis: response rate (full and partial); time to progression/duration of response; progression-free survival (PFS); mean overall survival, or
3. Clinical validity: clinical sensitivity (i.e., proportion of individuals who respond and are PD-L1 positive at different cut-offs); clinical specificity (i.e., proportion of individuals who do not respond and who have negative or below-threshold PD-L1 levels); positive predictive value (i.e., proportion of PD-L1^{+} patients who respond); negative predictive value (i.e., proportion of PD-L1^{-} patients who do not respond); positive and negative likelihood ratios for response; variations related to method used to determine scoring criteria (e.g., median values, based on clinical response, other factors) and sample types (e.g., fresh vs. archival, large specimens vs. small biopsies), or
4. Clinical utility (by PD-L1 expression level): response rate (full and partial); time to progression/duration of response; PFS; mean overall survival; proportion surviving at longest follow-up; overall/general and disease-specific quality of life; treatment-related adverse events (TRAEs) (most common, ≥ stage 3, deaths); immune-related events (all and ≥ stage 3), or

5. Cost-effectiveness: cost per quality-adjusted life year (QALY) or other patient-important outcome (defined a priori), or
6. Patient experiences: any relevant outcome; may include acceptance of PD-L1 testing, experiences/perceptions about being ineligible for treatment

Study designs

As outlined in section 3.2.1., a design hierarchy was used for clinical utility. RCTs using marker-based strategy and marker-by-treatment interaction designs were considered to offer direct evidence on clinical utility. In the absence of this evidence, a linked approach—using marker-enriched RCTs supplemented by studies of marker-negative patients—as well as indirect evidence from trials of other PD1/PD-L1 inhibitors (using the same hierarchy as for pembrolizumab trials) was considered.

Single-arm trials (or one arm of an RCT), retrospective and prospective cohort studies, and case series were eligible for questions about prognosis, clinical utility (if required to support poor evidence from available trials) and clinical validity. Systematic reviews were reviewed and included if they directly and fully answered one or more research question. Case reports were excluded, as were papers not reporting primary research (e.g., editorials, commentaries, opinion pieces). Abstracts were included if no full paper or report of the study was available, or if they reported on outcomes not reported in the papers.

4.3.2. Literature search and selection

A comprehensive literature search was developed in consultation with an experienced research librarian and designed to capture all studies answering the relevant research questions (3 to 8). The main search was designed for and implemented in June 2017 in three electronic databases: Ovid Medline (1946-), Ovid Embase (1996-), and CENTRAL via Wiley Cochrane Library (inception-). The database search strategies consisted of combined subject headings and text words for concepts relating to two main concepts of (PD-L1 OR the relevant drugs) AND (NSCLC), without study design filters and with adaptation for each database. Search results were limited to English-language publications from 2002 to the present, aligning with the emergence of in vivo evidence in this field.[26] Other search sources included trial registries (ClinicalTrials.gov and the WHO's International Clinical Trial Registry Platform), regulatory agencies' websites (Health Canada, US Food and Drug Administration, and the European Medicines Agency), and the websites of Health Technology Assessment (HTA) Agencies and

Health Economics institutions identified in CADTH's checklist document for finding grey literature (https://www.cadth.ca/resources/finding-evidence/grey-matters). Finally, meeting abstracts from 2015-2017 were hand-searched (American Society of Clinical Oncology, European Society for Medical Oncology, World Conference of Lung Cancer - International Association for the Study of Lung Cancer). **Appendix A** includes the search strategies and results for all of these searches which were conducted by the librarian in consultation with the lead reviewer (JP).

The searches were supplemented by a review of studies cited in included papers and relevant systematic reviews. If publications were identified during the review process from routine searches (e.g., google, PubMed) conducted after other searches were finished, they were also considered for inclusion with documentation of this source.

For the database searches, two reviewers independently screened the titles and abstracts (when available) using broad inclusion/exclusion criteria. Citations were classified as "include/unsure," "exclude," or "reference" (i.e., protocols, and systematic reviews). The lead reviewer further reviewed the "reference" group. The full text of all studies classified as "include/unsure" or identified in additional searches were retrieved for full review, and two reviewers independently assessed eligibility using a standard form that outlined the inclusion and exclusion criteria. An iterative approach to final study inclusion was employed based on the hierarchy of study designs for demonstrating clinical utility, taking into account the need to fill gaps where the primary evidence base was deficient.

The title/abstract screening and full-text selection processes were conducted and documented in DistillerSR. The flow of literature and reasons for full text exclusions were recorded in a PRISMA Flow Chart.

4.3.3. Data extraction

Data extraction forms were developed in Microsoft Word (study characteristics and outcome data separately) with key data for analysis also extracted and entered into Review Manager (RevMan) for generating forest plots. One reviewer independently extracted data from studies; a second reviewer verified a 10% sample of data and only found inconsequential errors (e.g., unrelated to data analysis or interpretation). For economic evaluations, data were extracted according to the consolidated health economic reporting standards (CHEERS) statement.[27]

When there were multiple publications associated with a study, the earliest report of the main (primary) outcome data was considered to be the primary data source. Associated publications were reviewed to obtain additional findings, especially for longer follow-up, and are cited where applicable.

Study characteristics tables were created for each study to include information on studies by design, country of origin, sample sizes, population(s) (including subgroups), intervention(s) (including data on screening criteria and for subgroup questions), comparator(s), setting, and outcome measures, as reported by studies.

4.3.4. Quality of studies and certainty of evidence for clinical utility

For studies on clinical utility, the lead reviewer independently assessed the **risk of bias** of each included trial using the Cochrane Risk of Bias tool.[28] The assessments were then compared with those reported in pCODR and FDA reports to identify areas for further consideration and discussion with another reviewer. The risk of bias for each study was assessed on an outcome basis where needed, particularly when different outcomes were assumed to have different susceptibilities to bias; for example, subjective outcomes (i.e., quality of life, investigator-assessed response) and expected harms are more prone to bias from non-blinding than objective outcomes and unexpected/rare harms.

This tool consists of six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias) and a categorization of the overall risk of bias. For each domain a rating of low, unclear, or high risk of bias is determined. The overall assessment was based on the responses to individual domains. If one or more individual domains were assessed as having a high risk, the overall score was rated as high risk of bias. The overall risk was low only if all components were rated as having a low risk, and was unclear for all other studies.

For assessing the quality of the body of evidence for the clinical utility of PD-L1 testing, the certainty of evidence for the main outcomes reported for each PD-L1 subgroup used in clinical practice (≥ 1% for second-line or beyond; ≥50% for first-line treatment) was evaluated using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[29-34] As a starting point the quality was assigned as high for evidence from RCTs using marker-based strategies or marker-interaction study designs; less rigorous study designs (e.g., marker-enriched supported by single-arm) were assigned a moderate level of evidence. Thereafter, the evidence

was potentially downgraded for quality based on the five core domains: study limitations/risk of bias, inconsistency, indirectness, imprecision, and reporting bias. The additional domains of dose-response association, plausible confounding, and strength of association (i.e., large magnitude of effect [i.e., large ≤ 0.5 or ≥ 2.0 or very large RR ≤ 0.2 or ≥ 5.0]) were also considered, to potentially upgrade the quality when no other serious concerns existed. In addition to assessing the quality for each subgroup, commonly used criteria was used for interpreting the credibility of the **subgroup effects**.[31,35]

4.3.5. Reporting quality of economic evaluations

For **economic evaluations**, the CHEERS checklist was used to assess reporting quality. This checklist was developed to optimize reporting of health economic evaluations. It is "neutral about the conduct of economic evaluation, allowing analysts the freedom to choose different methods" and intended to "facilitate interpretation and provide a means of comparing studies."[27] Criteria were assessed by whether they were fully met, partially met (e.g., described but no rationale provided), not met, or not applicable (e.g., no abstract).

4.4 Results

4.4.1. System demographics

Current and proposed use of test in clinical practice

Pembrolizumab and nivolumab are anticipated to remain in use across Alberta with the treatment algorithms aligned with current pCODR recommendations (Personal communication: Dr. Randeep Sangha, Chair of Provincial Lung Cancer Team, June, 2017). Nivolumab is funded through the provincial formulary and pembrolizumab is currently funded through a special access program.

For first-line treatment in patients with advanced stage NSCLC (i.e., not eligible for treatment with curative intent), pembrolizumab is being prescribed for patients who have good performance status, no major immunologic contra-indications (e.g., severe hypothyroidism, autoimmune disease), no EGFR mutations or ALK translocations, and ≥50% expression of PD-L1. Patients not meeting these criteria are typically receiving either platinum-based chemotherapy or a tyrosine-kinase inhibitor (TKI), if they have a targetable mutation. Where a patient is not eligible for first-line treatment with pembrolizumab, they may become eligible for pembrolizumab or nivolumab in the second–line setting after progression of their disease on

chemotherapy or a TKI. PD-L1 positivity using a threshold of ≥1% is being used for second-line treatment decisions with pembrolizumab, but not for nivolumab. The main factor contributing to the decision between these drugs for second-line treatment in PD-L1 positive patients (all patients are tested at diagnosis) is the dosing schedule; pembrolizumab is infused every 3 weeks while nivolumab is infused every 2 weeks. The lower frequency is considered preferable in terms of patient convenience and burden (e.g., possibly fewer infusion reactions), as well as health system resources.

No apparent differences in effectiveness or harms between the two anti-PD-1 inhibitors have been noted. Currently, pembrolizumab is the only choice for first-line treatment because of the failure of nivolumab to demonstrate benefit over chemotherapy in a recently completed trial.[36] At this time, pembrolizumab in combination with chemotherapy for first-line treatment (as approved by the FDA based on the phase 1 trial KEYNOTE 021 cohort G[37]) is not being offered, although pending results from phase 3 trials, the treatment algorithm may be revised (Personal communication: Dr. Randeep Sangha). Based on local experience, there have been superior treatment outcomes, with less burdensome adverse effects, compared with chemotherapy for several patients after receiving anti-PD1 inhibitors (Personal communication: Dr. Randeep Sangha). Pembrolizumab as first-line treatment is viewed as positive, in part due to the significant deterioration that can occur between treatment lines and the need to provide the best possible care in first-line settings. The province currently sees approximately 400-500 advanced stage NSCLC patients per year (Personal communication: Lori Berry, Alberta Health Services, November, 2017).

Current testing process and capacity in Alberta

In Alberta, PD-L1 testing is performed using the Dako 22C3 PD-L1 assay, for which the Medical Lead of the Edmonton IHC Lab has received extensive training, become experienced in its interpretation, and trained other pathologists (Personal communication with Dr. Gilbert Bigras, Medical Lead of Edmonton IHC Lab, August 2017).

All advanced NSCLC patients with suitable tissue samples (not cytology) are currently undergoing testing for PD-L1 upon diagnosis. Reflex testing of diagnostic samples is also being performed when a diagnosis changes to advanced stage from indeterminate or otherwise. Over the past several months, approximately 135 cases have been tested monthly although a few of these cases represent the same patient if the initial sample was insufficient for the test (Personal

communication Ms. Robin Stocks, Manager of Edmonton IHC lab). There is no evidence that decisions about testing take into account whether or not patients are otherwise ineligible for treatment with the PD1/PD-L1 inhibitors (e.g., active brain metastases, poor performance score, active autoimmune disease).

The Edmonton IHC Lab is the largest of such laboratories in Canada and has the capacity to maintain PD-L1 testing for patients in Alberta (Personal communication: Dr. Gilbert Bigras). The Calgary IHC laboratory has stated an interest in performing PD-L1 testing, but because of differing tissue fixatives compared to Edmonton there would be a requirement to modify the assay (Personal communication: Dr. Gilbert Bigras). There are considerable time, resource, and procedural requirements (e.g., running extra control samples, batch requirements of the commercial kit due to retrieval solution stability, etc.) for these assays; thus, providing testing using more than one assay was not considered a feasible option. Because pembrolizumab is the only drug being prescribed based on PD-L1 testing, there are currently no difficulties related to selection of assays. However, this may change if PD-L1 testing becomes used for other anti-PD-1/PD-L1 drugs which use different antibody clones and detection systems (see Table 2). Should multiple sites perform PD-L1 testing in the province, there would be a need for routine verification including inter-site comparisons for quality assurance purposes. If significant inter-site variation existed between results, there could be the risk of higher resource utilization, since patients may seek testing at the alternative location should their first result be negative.

An LDT using the 22C3 clone is being studied by a pan-Canadian research alliance, and if it proves to have sufficient technical equivalence to the validated Dako 22C3 assay it may become a reasonable alternative (Personal communication: Dr. Gilbert Bigras). Considering that the LDT will only be using the 22C3 clone, its main benefit would be cost savings, rather than an ability to test for other PD-1/PD-L1 inhibitors.

4.4.2. Summary of studies used for systematic review of PD-L1 testing for pembrolizumab in NSCLC

Since PD-L1 testing is exclusively being used to support decisions around treatment for pembrolizumab, this anti-PD1 inhibitor and the currently available Dako 22C3 assay were the primary interventions examined in the systematic review. Additional evidence on other interventions/comparators and assays was examined in some situations, such as when

information on the prognostic significance of PD-L1 for one or more parameters used in analytical validation were missing from the primary studies.

Fifty-nine primary studies or reports[16-18,23,36-90] and 10 associated publications/abstracts[91-100] were used for one or more aspects of the reviews on prognosis, clinical utility, and analytical and clinical validity. One study, [101] one systematic review,[102] and two CADTH reports[16,17] provided information on patient experiences on pembrolizumab, and five reports[16,17] or publications[103-105] reported economic analyses incorporating PD-L1 testing. Figure 3 shows the flow of literature, and Table 3 summarizes the types and number of studies reviewed. Appendix E lists the excluded studies, with reasons provided.

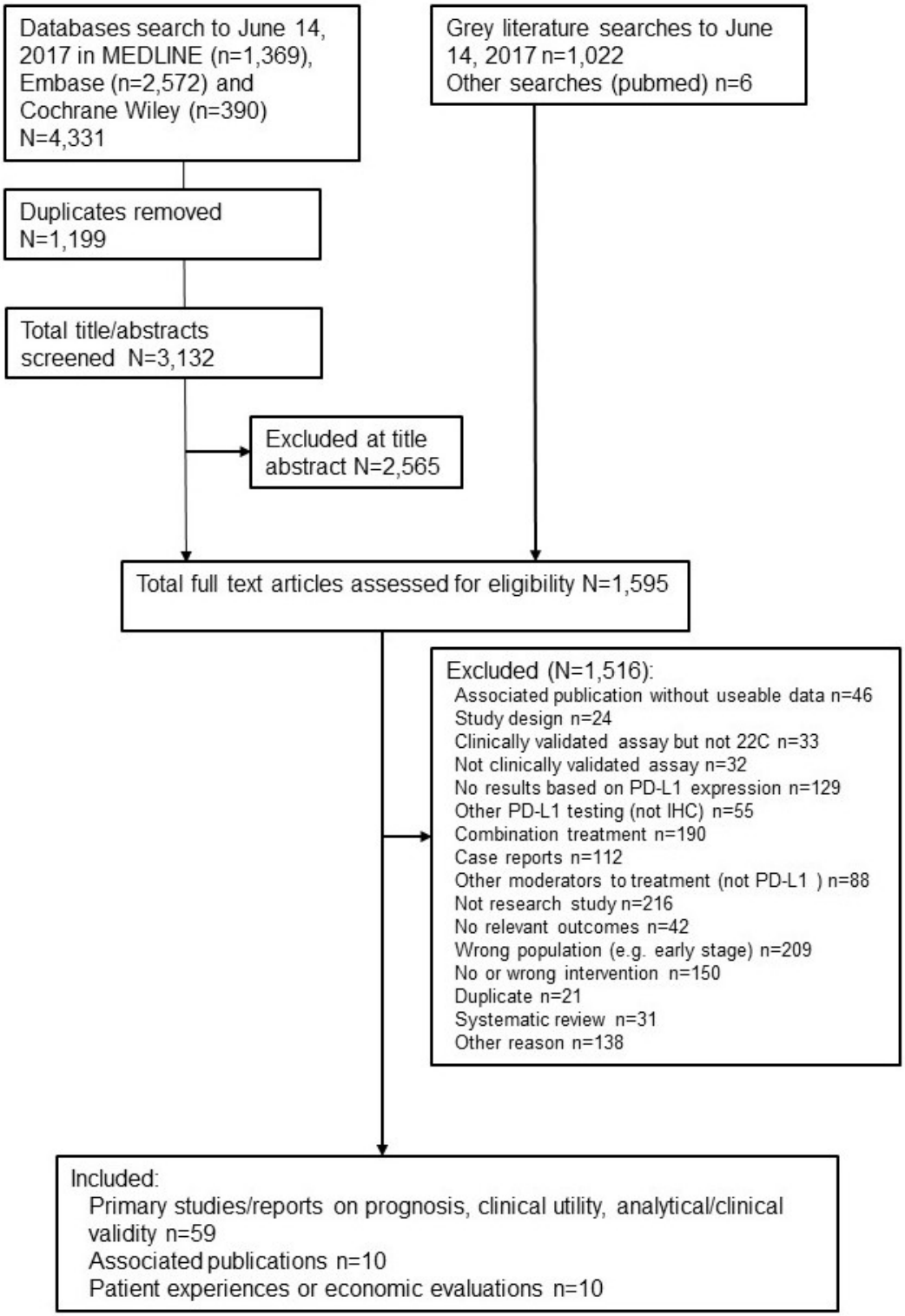

Figure 3. Literature flow diagram

Table 3. Summary of number of primary studies used in the technical review

Question	Primary studies/reports directly addressing question	Additional (linked and indirect) evidence to support assessment
Prognostic role of PD-L1 in standard of care	N=12 on prognosis in advanced NSCLC with chemotherapy	N=8 on prognosis in advanced NSCLC with targeted therapy (TKIs) or chemoradiotherapy
Clinical utility	N=0	First line: N=1 RCT of pembrolizumab vs chemotherapy; N=1 RCT of pembrolizumab added to chemotherapy; N=2 single-arm trials of pembrolizumab alone or with chemotherapy; N=1 RCT nivolumab vs chemotherapy; N=4 single-arm trials of nivolumab, atezolizumab and avelumab Second line: N=1 RCT of pembrolizumab vs docetaxel; N=1 single-arm trial of pembrolizumab; N=4 RCTs of nivolumab and atezolizumab; N=4 single-arm trials of avelumab, durvalumab
Analytical and clinical validity	N=26 including FDA document	N=4 studies on 22C3 laboratory developed tests
Patient experiences	N=0	N=4 (1 study, 1 systematic review, and 2 CADTH reviews)
Cost-effectiveness	N=0 assessed cost-effectiveness in test vs no test scenario	First line: N=1 pCODR Second line: N=5 (1 pCODR and 2 publications for pembrolizumab; 2 publications for nivolumab)

CADTH= Canadian Agency for Drugs and Technologies in Health; N=number of studies; RCT=randomized controlled trial

4.4.3. Prognostic role of PD-L1 in standard of care for advanced NSCLC

The definition of clinical utility encompasses criteria that the predictive marker will have no impact (i.e., prognostic role) on 1) response to other therapies or 2) disease outcome in the absence of therapy.[9] This is particularly relevant when there is a predominance of trials in marker-enriched populations (i.e., only PD-L1+ patients receive both PD-L1 inhibitor and standard of care), making it difficult to determine whether outcomes from the comparator group receiving standard of care would be the same for an unselected population.

With reports in the literature of an "adaptive immune resistance" hypothesis, in which the expression of immune-checkpoint ligands by tumors can be induced by an antitumor immune response as an adaptive immune-protective mechanism,[106] there has been active research on and evolving controversy over the existence of a prognostic role of PD-L1 for clinical outcomes. This issue of PD-L1 inducibility complicates interpretation of the clinical evidence on anti-PD-1/PD-L1 inhibitors especially when it relates to claims of clinical utility for a CDx performed on

a tissue specimen that may not represent the current status of the tumor (i.e., if induced by intervening treatment) or may be prognostic without treatment but based on other immunologic mechanisms.

Examination of available systematic reviews

Several systematic reviews have examined studies reporting data on associations between PD-L1 expression and clinical outcomes in patients with NSCLC.[107-114] These reviews were closely examined to determine their eligibility for this review. Several factors, as outlined below, made them ineligible; however, it is useful to document these reasons because other organizations have cited one or more of these reviews and referred to their findings when evaluating PD-L1 testing for PD1/PD-L1 inhibitors in advanced stage disease.

Table B1 in the appendix contains the main findings from these reviews. While findings from some meta-analyses[107,109,114] have demonstrated that positive PD-L1 expression is prognostic for shorter survival, others have found no correlation (on average) of PD-L1 with prognosis.[108,110-113] Subgroup analyses within the meta-analyses (not analyzing individual patient data) have also found inconsistent results around further characterization of prognosis by stage of disease and other variables. Further, the fast-paced research in this area has generated several studies that have not yet been reviewed. For example, Table B1 indicates how the search used for this technical review identified (but did not examine further because of their focus on early stage NSCLC) 31 studies on the prognostic impact of PD-L1 expression in early-stage NSCLC. Other reviews have included between five[107,113] and 15[112] studies across all tumor stages. None focused only on advanced stage NSCLC. Further, there are some discrepancies in their methods and analyses.

The previous systematic reviews differed in their inclusion/exclusion criteria and in their interpretation of two large patient groups by Velcheti and colleagues,[115] where PD-L1 was measured by quantitative immunofluorescence rather than IHC, as was common in the other studies. The three reviews[107,109,114] that reported PD-L1 as having a negative prognostic role for survival misinterpreted the data from the two patient groups (see Table B1; all using hazard ratios [HR] >1.0 rather than <1), as per the conclusions of Velcheti et al.: "Patients with PD-L1 (both protein and mRNA) expression above the detection threshold showed statistically significant better outcome in both series [log-rank P=0.036 and P=0.027]").[115] Two of the most recent reviews,[111,112] which included more studies and correctly analyzed these two large series,

found a lack of evidence of a prognostic role. The validity of these findings are still complicated by the large degree of between-study heterogeneity (I^2 values of 78% and 88% from the meta-analyses, indicating substantial statistical heterogeneity).

Factors contributing to this heterogeneity include variations in IHC technique (and assay validity), tissue sample (resections vs. biopsy), PD-L1 scoring algorithm, failure to account for treatment history, and possible differences in patient populations (if PD-L1 status is correlated with demographic, social, or physical [e.g., sex] characteristics). In these reviews, most of the studies examined patients with primary, not metastatic, tumors. Three reported that patients with advanced stage (III/IV) disease were found to have higher levels of PD-L1 expression than those with earlier stages (I-II).[111,112,114]

Based on this analysis, it was only possible to conclude that there is high variability in the prognostic role of PD-L1 between studies, especially in early stage NSCLC and when treatments have not been taken into account. A negative prognostic role cannot be confirmed based on this evidence, especially for advanced stage NSCLC. Although these systematic reviews (together with the reviewed studies) were not considered included studies for this question on prognosis in advanced stage NSCLC, the findings about changes in PD-L1 expression throughout disease advancement were considered during assessment of the test's analytical validity (see section 4.5.5. on sample type – timing).

Included studies

Regarding the possible prognostic role of PD-L1 expression for treatment outcomes in advanced NSCLC (excluding anti-PD-1/PD-L1 inhibitors), 20 studies provided data on how PD-L1 expression levels may be associated with outcomes from first- or second-line chemotherapy (n=12),[36,37,42,43,47,55,57,69,71,74,77,79] TKIs (n=5),[45,49,62,78,82] or chemoradiation (n=3)[38,83,86] in advanced stages. The most direct evidence examined first-and second-line chemotherapy because this is the main comparator used in the trials of pembrolizumab. Table C1 contains study and sample characteristics for these studies with an overview of key differentiating aspects below.

First-line treatment with chemotherapy

Data relating to first-line treatment with chemotherapy came from reports on the platinum-containing chemotherapy arms of three RCTs investigating pembrolizumab (KEYNOTE 021[37]

and 024[69]) and nivolumab (CheckMate 026),[36] and three additional case series (2 prospective[55,77] and 1 retrospective[79]).

Patient characteristics: Sample sizes ranged from 34[77] to 270[36] (median 115). The three trial arms were similar in terms of age, smoking history (86-87%), performance scores (0 or 1, on range from 0 [fully active] to 5 [dead] using standard criteria for measuring how the disease impacts a patient's daily living abilities), and proportion of patients with stage IV NSCLC (90.4 [026] -100% [024]). The ethnicity of participants in these RCTs was largely Caucasian (~90%). Patients in the two KEYNOTE trials were all wild-type for EGFR and ALK mutations, while some of those in CheckMate 026 deemed insensitive to targeted therapies were eligible (number enrolled was not reported). Two of the trials enrolled a lower than expected number of men (only 41% [KEYNOTE 21] and 55% [CheckMate 026]). In addition, more than 30 Gy of radiation therapy (RT) over the previous 6 months was an exclusion criterion for the KEYNOTE RCTs, whereas 40% of the CheckMate population had previous RT (timing not reported).

The observational study reported by Sorenson[79] appears to have a similar population to the trials in terms of demographics. The two remaining studies examined patients with squamous cell NSCLC in Chinese populations, with fewer patients at stage IV than the other studies. Sixty percent and 40% in Guo et al.[55] were at stage III and IV, respectively, and patients in Song et al.[77] were enrolled at stage IIIb although had progressed on neoadjuvant chemotherapy (another portion of this study) during follow up before receiving platinum-based chemotherapy.

Treatment protocols: The control arms in the three trials all received platinum-doublet chemotherapy (4-6 cycles) with pemetrexed for maintenance for those with non-squamous cell tumors. They all permitted patients to cross-over to the anti-PD-1/PD-L1 therapy, if meeting criteria, although were still analyzed based on initial allocation to chemotherapy. Similar numbers in each trial received such therapy during the follow-up period (CheckMate 026 60%, KEYNOTE 024 53%, and KEYNOTE 021 51%). With respect to the observational studies, patients in the case series by Sorenson et al. were all starting first-line platinum-based doublet chemotherapy, and 32% were also receiving concomitant RT. Patients studied by Song et al. had all progressed on neoadjuvant chemotherapy without exposure to RT. In Guo et al. it was only specified that all patients had received platinum-containing chemotherapy (gemcitabine). To avoid confounding of treatment effects from the cross-over to anti-PD-1/PD-L1 therapy in the trials, data on response rates, rather than overall survival (i.e., no report of results for those only

receiving chemotherapy), were considered the most appropriate outcome measure for prognosis on chemotherapy.

Second-line or beyond treatment with chemotherapy

For second-line therapy in advanced disease, data were used from the control arm (receiving the same doses of docetaxel) of five available RCTs on anti-PD-1/PD-L1 inhibitors pembrolizumab (KEYNOTE 010[57] with data on response for 1-49% from Garon 2016[98]), nivolumab (CheckMate 017[43] and 057[42]), and atezolizumab (OAK[71] and POPLAR[47]), in addition to a retrospective study of heavily-treated patients receiving standard chemotherapy, reported by Scabath et al.[74]

Patient characteristics: Sample sizes ranged from 136[74] to 425[71] (median 217). Patient populations were similar in terms of performance status (0-1; not reported by Scabath et al.), age, sex, and smoking history (>80%). However, ethnicity varied, with three trials having larger non-Caucasian subgroups (OAK 30%, POPLAR 19%, KEYNOTE 010 27%) than the other two (CheckMate 017 5% and CheckMate 057 8%). Also, in four trials and the observational study the majority of patients had adenocarcinoma whereas in one trial (CheckMate 017) only patients having squamous cell NSCLC were included. Three trials and the observational study included a considerable proportion (25-33%) of patients on third-line treatment or beyond, while two trials had no (CheckMate 017) or few (CheckMate 057 11%) patients at this treatment stage.

Treatment protocols: All studies provided docetaxel as the treatment with no per protocol cross-over to the PD1/PD-L1 inhibitor.

Use of PD-L1 Assay

In all studies, a PD-L1 assay with documented validity for detecting PD-L1 was used (Dako 22C3, Dako 28-8, Ventana 263, Ventana SP142) and testing was conducted in a central laboratory. Nevertheless, the sensitivity and specificity for PD-L1 expression will have varied between assays as do the scoring systems.

Analysis and findings for chemotherapy

Table 4 contains the findings, where reported, from these studies for PFS, overall survival, and response rates. A random-effects meta-analysis (controlling for between-study variances) was conducted for the outcome of response rates (Figure 4) by using data reported for PD-L1 positive versus PD-L1 negative patients. When studies did not state a threshold of positivity (or had more than one), but reported response rates for multiple PD-L1 expression levels, data from

two groups representing the largest differential in PD-L1 expression was used. For instance, when response at < and ≥ each of 1%, 5% and 10% PD-L1 expressions were reported, the <1% versus ≥10% data were used (Table 4 response rate column highlights the groups used in the meta-analysis). This approach was considered most likely to indicate a prognostic effect should there be one. Further, to assess PD-L1 negative/low patients relative to those with ≥50% PD-L1 expression (all patients) in KEYNOTE 024, an indirect comparison approach was used, which incorporated data from the PD-L1 negative (<1%) group in KEYNOTE 021.

Findings from the meta-analysis demonstrated no statistically significant difference between PD-L1 positive/high and negative/low groups for response rates (all studies: RR, 1.08, 95% CI 0.88-1.33; subgroups by line of therapy did not find any differences [subgroup p value 0.27]): first-line RR, 1.21, 95% CI 0.83-1.77, I^2=33%, and second-line: RR 0.89, 95% CI 0.60-1.32, I^2=0%;). In KEYNOTE 021, the group of PD-L1 negative/low patients was small, which likely contributed to greater heterogeneity and imprecision in the results for the first-line KEYNOTE comparisons. Of note, the patients with 1-49% PD-L1 expression in KEYNOTE 021 had a similar response rate from chemotherapy to those with PD-L1 ≥50% (9 of 23 [39%] vs. 6 of 17 [35%], respectively).

Hazard ratios (HRs) are considered the most appropriate effect measure for meta-analysis of time-to-event data.[116] However, available data were insufficient to estimate HRs. As a result, quantitative analyses for overall survival or PFS were not conducted. Based on observations of the median duration of survival between patient groups differing by PD-L1 expression, there does not appear to be a prognostic role for PD-L1 expression in first- or second-line chemotherapy treatment. The main results in the study by Song et al.[77] included some patients in stage II disease, and the statistical significance of the findings of poor prognosis were removed when limiting the analysis to stage III or beyond.

Table 4. Findings on prognostic effect of PD-L1 expression in chemotherapy for advanced stage NSCLC

Study, Sample size	Clone	Progression-free survival (mos with 95% CI, if reported)	Median Overall Survival (mos with 95% CI, if reported) (Bolded values indicate findings of poor prognosis for PD-L1 positive/higher PD-L1 expression)	Response rates (Bolded values represent data used in meta-analysis)
First line				
Carbone, 2017 Checkmate 026 N=270 with PD-L1 ≥1%	28-8	PD-L1 ≥1%: 5.8 (5.4 to 6.9) PD-L1 ≥5%: 5.9 (5.4 to 6.9) PD-L1 ≥50%: 5.8 (NR)	PD-L1 ≥1%: 13.8 (11.0 to 17.9) PD-L1 ≥5%: 13.2 (10.7 to 17.1) PD-L1 ≥50%: 13.9 (NR)	PD-L1 ≥1%: NR PD-L1 **≥5%**: 33.5% (27 to 40%) PD-L1 **≥50%**: 39 (30-48) (exploratory)
Langer, 2016 KEYNOTE 021 (Cohort G) N=63	22C3	NR	NR	PD-L1 **<1%**: 13% (3-34) PD-L1 1-49%: 39% (20-61) PD-L1 **≥50%**: 35% (14-62)
Reck, 2016 KEYNOTE 024 N=151 with PD-L1 ≥50%	22C3	PD-L1 ≥50%: 6 (4.2 to 6.2)	NR	**≥50%**: 27.8% (20.8 to 35.7) (Indirect comparison with PD-L1 <1% in KEYNOTE 021; PD-L1 <1%: 13% (3-34)
Sorenson, 2016* Denmark N=204	Prototype 22C3 assay (Merck)	NR	PD-L1+ strong (9.0 [6.4-11.1]) vs. PD-L1- (7.5 [6.4-12.4]): adjusted HR 1.36 95% CI 0.90 to 2.06 PD-L1+ weak (9.8 [8.2-12.3]) vs. PD-L1-: adjusted HR 1.09 95% CI 0.76 to 1.58 Adjusted for age, sex, histology, smoking, PS (crude HR NS also)	NR
Guo, 2017* China N=77	ab58810	NR	NR	PD-L1+ 36.2% vs PD-L1- 43.3%
Song, 2016* China N=63 (56 receiving 1L)	NR	NR	All patients (some having stage II disease): PD-L1+ 27.0 vs. PD-L1- 36.5 mos, HR 0.50, 95% CI 0.27–0.94, p = 0.003 **Subgroup in stage III+ only: 25.5 vs. 35.0 mos, p = 0.063** (At baseline before progression and	NR

Study, Sample size	Clone	Progression-free survival (mos with 95% CI, if reported)	Median Overall Survival (mos with 95% CI, if reported) (Bolded values indicate findings of poor prognosis for PD-L1 positive/higher PD-L1 expression)	Response rates (Bolded values represent data used in meta-analysis)
			subsequent treatment, 46% of patients were stage I/II)	
Second line or beyond				
Borghaei, 2015 Checkmate 057 N=290	28-8	PD-L1 <1%: 3.6 (NR) PD-L1 ≥1%: 4.5 (NR) PD-L1 <5%: 4.2 (NR) PD-L1 ≥5%: 3.8 (NR) PD-L1 <10%: 4.2 (NR) PD-L1 ≥10%: 3.7 (NR)	PD-L1 <1%: 10.09 (7.36 to 11.93) PD-L1 ≥1%: 9.0 (7.10 to 10.55) PD-L1 <5%: 10.1 (NR) PD-L1 ≥5%: 8.1 (NR) PD-L1 <10%: 10.3 (NR) PD-L1 ≥10%: 8 (NR)	PD-L1 **<1%:** 14.9% (8.6 to 23.3) PD-L1 **≥1%:** 12.2% (7.0 to 19.3)
Brahmer, 2015 Checkmate 017 N=137	28-8	PD-L1 <1%: 3.0 (NR) PD-L1 ≥1%: 2.8 (NR) PD-L1 <5%: 2.9 (NR) PD-L1 ≥5%: 3.1 (NR) PD-L1 <10%: 2.8 (NR) PD-L1 ≥10%: 3.1 (NR)	PD-L1 <1%: 5.9 (NR) PD-L1 ≥1%: 7.2 (NR) PD-L1 <5%: 6.1 (NR) PD-L1 ≥5%: 6.4 (NR) PD-L1 <10%: 6.1 (NR) PD-L1 ≥10%: 7.1 (NR)	PD-L1: **<1%** (10%), ≥1% (11%), <5% (12%) ≥5 (8%),<10% (11%) **≥10%** (9%)
Herbst, 2016 KEYNOTE 010 N=343 with PD-L1 ≥1%	22C3	PD-L1 ≥1%: 4.0 (3.1 to 4.2) PD-L1 ≥50%: 4.1 (3.6 to 4.3) PD-L1 1-24%: 4.0 PD-L1 25-49%: 3.8 PD-L1 50-74%: 4.3 PD-L1 >75%: 4.0	PD-L1 ≥1%: 8.5 (7.5 to 9.8) PD-L1 ≥50%: 8.2 (6.4 to 10.7) PD-L1 1-24%: 8.5 PD-L1 25-49%: 9.9 PD-L1 50-74%: 8.2 PD-L1 >75%: 8.2	All patients ≥1%: 9.3% PD-L1 **1-49%:** 10.5% PD-L1 **≥50%:** 7.9%
Rittmeyer, 2017 OAK trial[†] N=425	SP142	TC0 and IC0:4.0 (3.1 to 4.2) TC1/2/3/ or IC ½/3: 4.1 (2.9 to 4.3) TC2/3 or IC2/3: 4.1 (2.8 to 5.3) TC3 or IC3: 4.2 (2.9 to 7.0)	TC0 and IC0: 8.9 (7.7 to 11.5) TC0 and IC 1/2/3: 9.8 (7.3 to 13.7) TC1/2/3 and IC0: 12.0 (3.7 to 14.7) TC1/2/3/ or IC 1/2/3: 10.3 (8.8 to 12.0)	**TC0 or IC0**: 10.6% (NR) TC1/2/3/ or IC ½/3: 16.2% (11.6 to 21.7) **TC3 or IC3:** 10.8% (NR) TC2/3 or IC 2/3: 10.8 (NR)

Study, Sample size	Clone	Progression-free survival (mos with 95% CI, if reported)	Median Overall Survival (mos with 95% CI, if reported) (Bolded values indicate findings of poor prognosis for PD-L1 positive/higher PD-L1 expression)	Response rates (Bolded values represent data used in meta-analysis)
			TC3 or IC3: 8.9 (5.6 to 11.6) TC0/1/2 or IC0/1/2: 9.8	
Fehrenbacher, 2016 POPLAR trial† N=143	SP142	All patients: 3.0 (2.8 to 4.1) TC0 and IC0: 4.1 (NR) TC1/2/3 or IC1/2/3: 3.0 (NR) TC2/3 or IC2/3: 2.8 (NR) TC3 or IC3: 3.9 (NR)	All patients: 9.7 (8.6 to 12.0) TC0 and IC0: 9.7 (8.6 to 12.0) TC1/2/3 or IC1/2/3: 9.2 (7.3 to 12.8) TC2/3 or IC2/3: 7.4 (6.0 to 12.5) TC3 or IC3: 11.1 (6.7 to 14.4)	All patients: 14.7% (9.33 to 21.6) **TCO or ICO**: 9.8%, TC1/2/3/ or IC ½/3: 16.7%, TC2/3 or IC2/3: 14.5%; **TC3 or IC3**: 13%
Schabath, 2017* Country NR N=136	SP263	NS difference	NS difference	NR

CI: confidence interval; IC: immune cells; mos: months; NS: not significant; NR: not reported; TC: tumor cells

*PD-L1 positivity thresholds: Scabath: ≥25% tumor cells; Guo: Immunoreactive score (0-12): % tumor cells graded 0-4 (<5%, 5-25%, 26-50%, 51-75%, >75% multiplied by and intensity graded 1-3; PD-L1+ IRS ≥3 (61.7%); Song PD-L1+ at ≥5% membrane staining at any intensity; Sorenson used the 22C3 prototype assay which has higher staining intensity than does the assay used in the clinical trials but has been shown to be traceable to clinical trial PS in study with 242 patients (89% concordance) such that ≥95% tumor cell staining with this assay approximates ≥50% ("strong positive") using staining with Dako 22C3, and ≤95% approximates 1-49% ("weak positive") (<1% similar for both).

†The OAK and POPLAR trials combined the expression of PD-L1 on tumor cells OR immune cells for their assessments. In both studies the authors reported that there was minimal overlap between tumor and immune-cell expression.

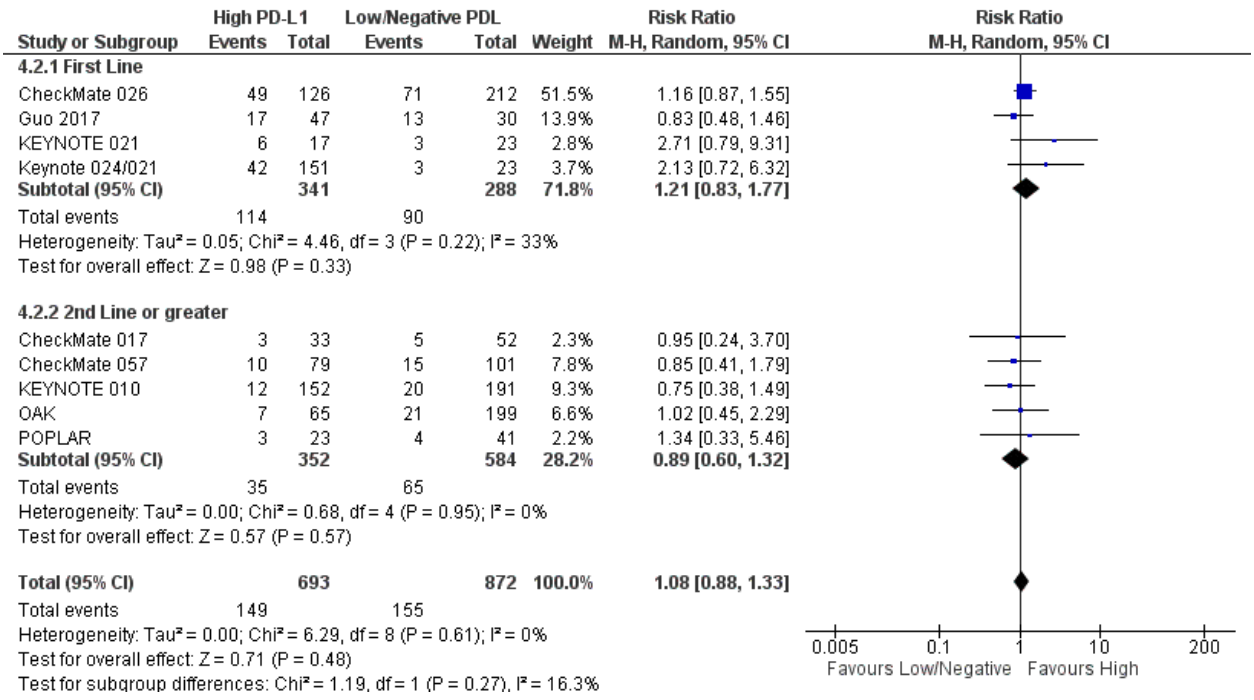

Figure 4. Prognostic effect of positive/high versus negative/low PD-L1 expression on response rates from first- and second-line therapy

Findings from studies of TKIs or chemoradiotherapy

Five observational studies (n=56 to 170)[45,49,62,78,82] examined the prognostic effect of PD-L1 in patients with advanced NSCLC and EGFR mutations or ALK rearrangements taking TKIs. Findings varied. Two studies[45,62] demonstrated a trend towards improved outcomes in PD-L1 patients, while the remaining three found poorer outcomes[49,78,82] (Table 5). Examination of patient characteristics did not reveal any obvious reason for the discrepancy, although the use of assays that have not been validated clinically may be a factor. Three other studies (n=44 to 74)[38,83,86] included patients with inoperable NSCLC who received chemoradiotherapy. Two found PD-L1 positivity to be associated with poorer outcomes[38,86] and the third[83] found numerically (but not statistically significantly) poorer outcomes (Table 5). In general, these studies had small sample sizes and used varying IHC assays (often without documentation of validity) and thresholds. The results were not pooled.

Table 5. Findings on prognosis of PD-L1 for response and clinical outcomes after TKIs or chemoradiotherapy in advanced stage/inoperable NSCLC

Study, Sample size	Clone, scoring method, % positive	Progression-free survival	Overall survival	Response rate
TKI therapy				
Tang, 2015 N=170 China EGFR/ALK/KRAS (%): 58/NR/NR 49% first line/51% second-line	EIL3N >5% tumor cells (66%)	HR 1.315 95% CI 0.831 to 2.080; Log rank p=0.990 Multivariate cox regression	HR 1.901 95% CI 0.953 to 3.79; Log rank p=0.233 Multivariate cox regression	NR
Gainor, 2015 N=98 Country NR EGRF/ALK/KRAS: 69/31/NR First-line	EIL3N ≥5% tumor cells (EGFR 15%, ALK 52%)	EGFR TKIs: 6.7 vs. 13.2 mos; p=0.08 ALK TKIs: 5.6 vs. 11.1 mos; p=0.28	EGRF TKIs: 31.8 vs. 35.63 mos; p=0.307 **Shorter survival: ALK TKIs: 26.5 vs. 51.6 mos; p=0.045**	NR
Soo, 2017 N=90 Korea EGRF/ALK/KRAS: 100/NR/NR First-line	SP142 Continual H score via digital assessment (highly correlated to manual scoring; R^2=98%) (using continual values)	**Shorter PFS (HR 1.008, 95% CI 1.001-1.005**) (univariate Cox proportion). Using smallest p value in Kaplan Meier's analysis of deciles best cut-off H score ≥109.23, p<0.001 for shorter PFS	HR, 1.001, 0.991-1.012; remained NS in multivariate analyses	No association between H score and response to TKIs (p=0.529)
Lin, 2015 **N=56** China EGRF/ALK/KRAS (%): 100/NR/NR Second-line	ab58810 Mean H score (53.6%)	**Longer PFS 16.5 vs. 8.6 mos; p=0.001** H score 0: 13.5 mos vs H score 3: 25.1mos. With multivariate Cox regression, independent prognostic factor: HR 0.46; p=0.014	**Longer survival 35.3 vs.19.8 mos**; p=0.004 H score 0: 22.0 mos; 3: 33.6 mos. With multivariate Cox regression, independent prognostic factor: HR 0.26; p=0.002	NR
D'Incecco, 2015 N=95 Italy EGRF/ALK/KRAS (%): 45/8/23 72% second-line	ab58810 Moderate/high staining on >5% tumor cells (51.6%)	NR	21.9 vs 12.5 mos log rank p=0.09	**RR 61.2% vs 34.8% (p=0.01)**

Study, Sample size	Clone, scoring method, % positive	Progression-free survival	Overall survival	Response rate
Chemoradiotherapy in inoperable NSCLC				
Vrankar, 2016 **N=44** **Slovenia**	SP142 Tumor expression ≥5% (16%)	**Shorter PFS 10.1 vs 19.9 mos, p=0.008**	**Shorter OS 12.0 vs 28.0 mos, p=0.010** No PD-L1+ & 10 PD-L1- alive at 92.3 mo PD-L1+ received lower doses of radiation and chemotherapy	NR
Tokito, 2016 **N=74** **Japan**	EPR1161 Tumor expression ≥5% (74%)	10.8 vs 17.3 mos, p=0.73	24.9 vs. 36.9 mos, p=0.85 Multivariate	NR
Adam, 2015 **N=50** **France**	E1L3N Tumor cell and cytoplasmic staining; threshold NR (44%)	**Shorter PFS 0.7 yr (95% CI 0.6 to 0.8) vs. 1.0 yr (95% CI 0.8 to1.5), p=0.04** **HR 2.1 (95% CI1.1- 4.0), p=0.03**	**Shorter OS 1.1 yr (95% CI 0.6 to 1.5) vs. 2.0 yr (95% CI 1.5 to 3.8), p=0.01** **HR 2.3, 95% CI 1.2 to 4.5, p=0.01** Multivariate	NR

HR: hazard ratio; mos: months; OS: overall survival; RR: relative risk; PFS: progression-free survival

4.4.4. Clinical utility: benefits and harms of PD-L1 testing in first-line and second or beyond line settings

This section divides the evidence into categories based on line of therapy and by the source of evidence for demonstrating clinical utility of PD-L1 testing for treatment with pembrolizumab. Within each line of treatment, there are sections on three levels of evidence, categorized by the use of different study designs and comparators: 1) Direct evidence, from studies using a marker-based strategy (i.e., PD-L1 testing vs. no testing) with randomization to different treatments, or marker-treatment interaction effects (i.e., patients of any, but known, PD-L1 expression level randomized to different treatments with analysis by PD-L1 subgroups) comparing pembrolizumab with standard of care, 2) Linked evidence from multiple sources (e.g., using data from marker-enriched trials and single-arm trials with PD-L1 negative patients) examining pembrolizumab, and 3) Indirect evidence from studies of comparators to pembrolizumab assessing effects based on PD-L1 status. Detailed descriptions of the

pembrolizumab studies have been included, while information of the other studies is provided as applicable. Full study characteristics for all studies are tabulated in the appendix Table C2, and the risk of bias assessments for the RCTs are in Table C3.

First-Line Therapy

Direct evidence

No marker-based strategy or marker-by-treatment interaction studies were identified to directly examine the clinical utility of PD-L1 testing for treatment pembrolizumab compared with standard of care in first-line treatment. One RCT (KEYNOTE 021) enrolling patients regardless of PD-L1 expression level studied adjuvant pembrolizumab (added to chemotherapy received by both arms) so was not considered direct evidence and is discussed below.

Linked evidence from marker-enriched RCTs of pembrolizumab

Study characteristics: There are two RCTs of pembrolizumab for first-line treatment in advanced NCSLC: KEYNOTE 024[69] and KEYNOTE 021[37] (Cohort G of this multi-cohort study). KEYNOTE 024 randomized 305 patients to receive pembrolizumab 200 mg (fixed dose every 3 weeks, up to 35 cycles with opportunity for re-treatment) or investigator's choice of platinum-based chemotherapy (4-6 cycles), whereas KEYNOTE 021 (n=123) added the same pembrolizumab regime onto 4 cycles of chemotherapy (carboplatin [AUC 5 mg/ml/min] and pemetrexed [500 mg/m^2]) which was also administered to patients in the control arm. Maintenance with pemetrexed was permitted for patients with non-squamous histology in either arm of both trials. Both trials allowed for cross-over to pembrolizumab treatment after progression on the standard of care regime, but used intention-to-treat analysis with patients analyzed in the groups to which they were randomized. Including this per protocol cross-over and subsequent post-study use, approximately 62% (KEYNOTE 024) and 52% (KEYNOTE 021) of patients in the control arms received pembrolizumab at some point during follow-up.

For enrollment, patients in both trials were required to provide a tumor sample evaluable for PD-L1 testing using the 22C3 PharmDx assay; both trials required that the sample had not been irradiated (i.e., patients could not have received RT to the lung in the past 6 months) and in KEYNOTE 024, samples collected before the administration of adjuvant or neoadjuvant therapy were not permitted. KEYNOTE 024 was a marker-enriched trial that only enrolled patients with ≥50% PD-L1 tumor expression, whereas KEYNOTE 021 enrolled all patients and stratified by PD-L1 (<1% vs. ≥1%) during randomization. Patients in both trials were not allowed to have

sensitizing EGFR mutations or ALK translocations, and all patients in KEYNOTE 021 had non-squamous histology.

Study quality of RCTs: Risk of bias for both RTCs was assessed as low for the objective outcomes of objective response rates (ORR; blinded evaluation), PFS, and major harms. Sequence generation and allocation concealment were adequate. Although trials were open-label, patients and providers were masked to the patient's PD-L1 level. Evaluation of response was conducted by masked and independent central review. Further, there was little (<10%) incomplete outcome data. Risk of bias was considered unclear for overall survival because of the large amount of cross-over which, although hypothesized to favor the control arm, limits the certainty in the effect size between groups. A couple of statistically nonsignificant baseline imbalances existed within the trials (e.g., about 9% more [KEYNOTE 24] and less [KEYNOTE 021] smokers in pembrolizumab vs. control groups), and in KEYNOTE 021 the proportion of male patients (41%) was substantially less than in KEYNOTE 024 (61%).

Findings: Figures 5-9 present findings from these two RCTs, as well as another trial comparing nivolumab with platinum-based chemotherapy (CheckMate 026[36]) which is discussed below when considering indirect evidence from other anti-PD1/PD-L1 drugs. Data on ORR, PFS, overall survival (at 14.5 mos), and 12-month survival for all patients in KEYNOTE 021, and for overall (at 19 mos) and 12-month survival for KEYNOTE 024 patients (≥50% PDL) were taken from conference abstracts.[91,93]

Patients with tumor PD-L1 expression ≥50% appear to respond well to pembrolizumab treatment. However, the results of KEYNOTE 021, in which over half of PD-L1 negative patients also experienced a response, limit conclusions about the predictive ability for PD-L1 for response. Findings for PFS, overall survival, and 12-month survival with pembrolizumab do not provide any insight into the effects on patients without PD-L1 expression. Results from KEYNOTE 021 by PD-L1 status are only available for response rates.

The findings from KEYNOTE 024 for overall (HR 0.63, 95% CI 0.46-0.87) and 12-month survival (RR 1.28, 95% CI 1.07-1.52) at a median follow-up of 19.2 months for patients with ≥50% PD-L1 expression may be considered within the context of the large amount of cross-over in the chemotherapy arm. Cross-over adjusted results have been reported for overall survival (HR 0.50; 95% CI 0.34 to 0.76) and were accepted as data for the appraisal of this drug in the first-line setting by NICE, but not by pCODR. In KEYNOTE 021, no beneficial effect for

survival from combination treatment with pembrolizumab and chemotherapy, compared with using chemotherapy alone, was observed (HR 0.69, 95% CI 0.36-1.32). The investigators also noted that the combination treatment could heighten the risks for adverse effects and, therefore, reduce the benefit-to-harm balance. Nevertheless, the cross-over nature of these trials limits conclusions about harms.

Fewer smokers and more women in the KEYNOTE 021 pembrolizumab arm may explain its apparent lower relative benefit over chemotherapy in this trial. Subgroup analysis for the outcome of PFS in KEYNOTE 024 found reduced effects in women (n=118; HR 0.75 [0.46-1.21]) and in patients who had never smoked (n=24; HR 0.90 [0.11-7.59] vs. former smoker, n=216; HR 0.47 [0.33-0.67] or current smokers, n=65; HR 0.68 [0.36-1.31], although samples are small for some subgroups.

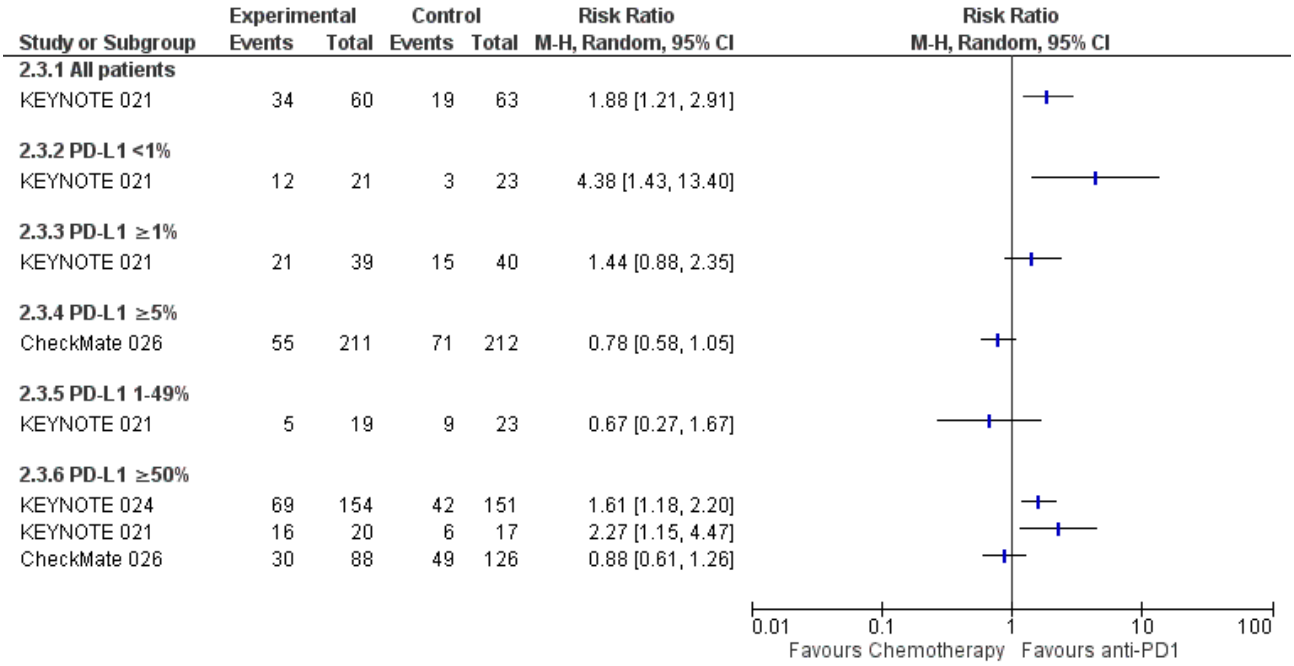

Figure 5. Objective response rate in first-line treatment for anti-PD-1 inhibitors compared with standard of care (KEYNOTE 024 and Checkmate 026) or added to standard of care (KEYNOTE 021)

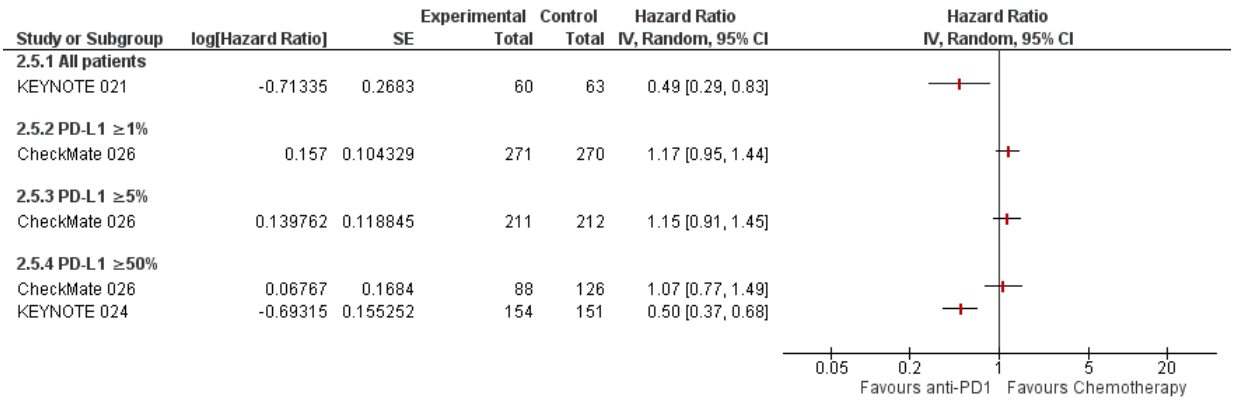

Figure 6. Progression-free survival in first-line treatment for anti-PD-1 inhibitors compared with standard of care (KEYNOTE 024 and Checkmate 026) or added to standard of care (KEYNOTE 021)

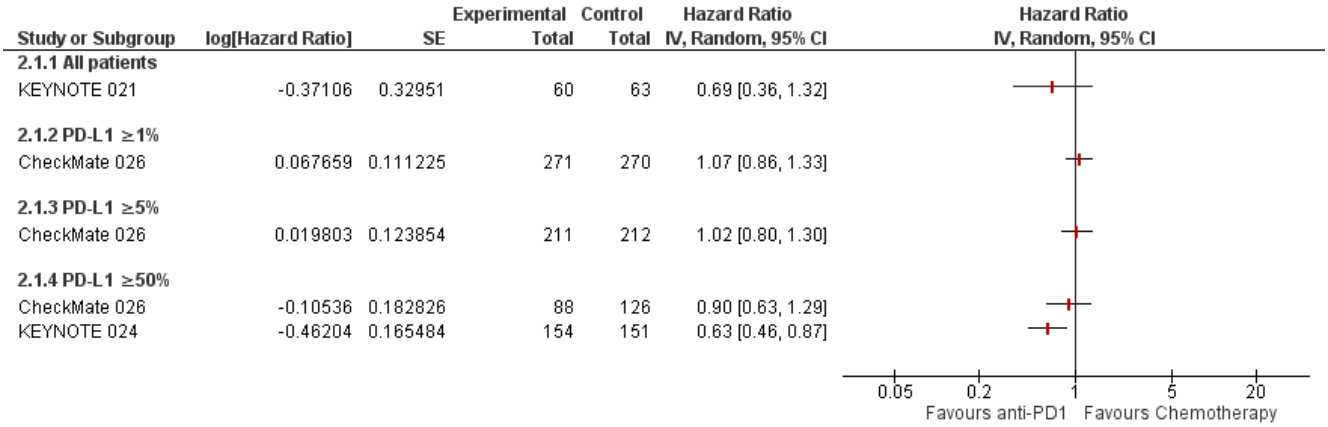

Figure 7. Overall survival in first-line treatment for anti-PD-1 inhibitors compared with standard of care (KEYNOTE 024 and Checkmate 026) or added to standard of care (KEYNOTE 021)

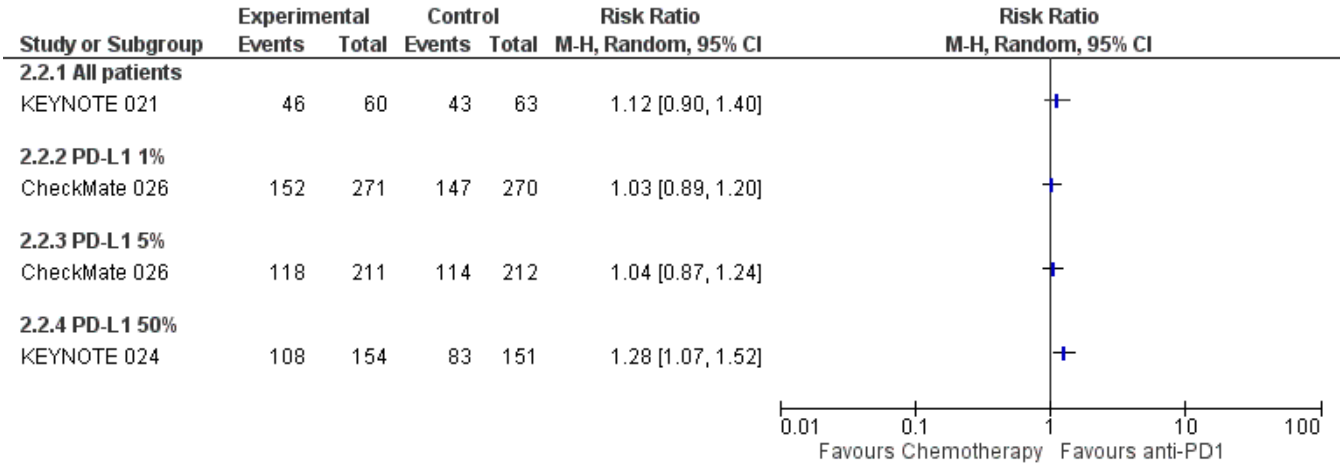

Figure 8. 12-month survival in first-line treatment for anti-PD-1 inhibitors compared with standard of care (KEYNOTE 024 and Checkmate 026) or added to standard of care (KEYNOTE 021)

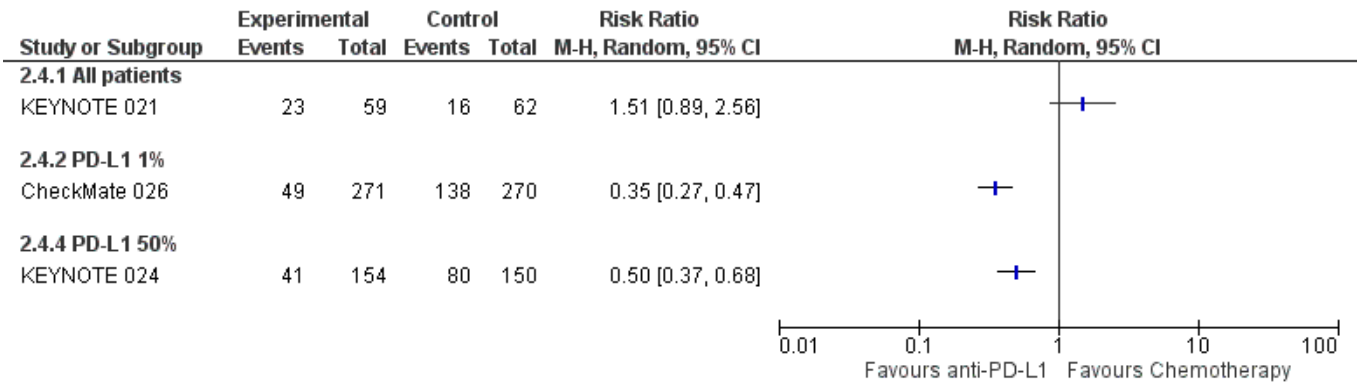

Figure 9. Treatment-related adverse effects of Grade 3 or higher in first-line treatment for anti-PD-1 inhibitors compared with standard of care (KEYNOTE 024 and Checkmate 026) or added to standard of care (KEYNOTE 021)

Linked evidence from single-arm trials of pembrolizumab in PD-L1 negative patients

Only one of the RCTs described above, KEYNOTE 021 (Cohort G), included patients negative (<1%) for PD-L1 tumor expression and the only outcome data within this subgroup related to ORR. This trial's focus on combination treatment with chemotherapy also limits its relevance to current clinical practice, which does not provide this treatment approach. However, single-arm trials of anti-PD-1/PD-L1 inhibitors have been undertaken, and comparing findings for PD-L1 negative patients from these studies with those for PD-L1 positive patients in the maker-enriched KEYNOTE 024 may provide insights into PD-L1's clinical utility.

Study characteristics: Two phase Ib trials on pembrolizumab examined its effects in PD-L1 negative patients. The large KEYNOTE 001[23] (n=550 NSCLC patients) included 101 advanced NSCLC patients without EGFR mutations who had completed adjuvant therapy >1 year before recurrent/metastatic disease and received pembrolizumab as first-line treatment (89% at the 10 mg/kg dose). Although enrollment was based on a new tumor sample (i.e., not having been subjected to treatment) showing PD-L1 positivity (≥1%) as per the prototype 22C3 assay (known to produce a high staining intensity), data were analyzed using results from the clinical trial assay (CTA). The CTA is very similar to the currently available PharmDx 22C3 assay, and when using this assay 12 (11.9%) patients were PD-L1 <1%. The KEYNOTE 001 authors report that patient characteristics were similar between PD-L1 subgroups, although only 1 patient in the ≥50% group had squamous histology. Cohort G of KEYNOTE 021, the RCT adding pembrolizumab to chemotherapy, was examined above but the dose-finding single-arm Cohorts A to C (pembrolizumab added to different chemotherapy protocols) provided data for patients with and without PD-L1 expression.[48]

Findings: At median follow-up of 22.2 months in KEYNOTE 001, in all patients receiving at least one dose of pembrolizumab (n=91), ORR (independent central review) was 26.7% (95% CI 18.4–36.5), median PFS was 6.2 months (95% CI 4.1–8.6), and overall survival was 22.1 months (95% CI 17.1–27.2) (reported in associated paper).[99] Among patients with ≥50% PD-L1 (n=27), the ORR was 52%, median PFS was 12.5 months (6.2 to not reached), and overall survival was not reached (22.1 months – not reached). Among patients with 1-49% (n=52) and <1% PD-L1 (n=12), ORR was 17% and 8%, PFS was 4.2 (3.1-6.4) and 3.5 (2.1-19) months, and overall survival was 19.5 (10.7-22.2) and 14.7 (3.4-not reached) months. A sub-study, including most but not all of these patients, that was used to validate the 50% cut-point found disparate results with ORRs of 50%, 19.2%, and 16.7% for subgroups of ≥50% (n=16), 1-49% (n=26), and <1% PD-L1 (n=6).[23] In comparison, patients with ≥ 50% PD-L1 expression receiving *chemotherapy* in KEYNOTE 024 had an ORR of 28%, PFS of 6.0 (4.2-6.2) months, overall survival of 14.5 months (9.8-19.6). Comparing KEYNOTE 001 (pembrolizumab) and KEYNOTE 024 (chemotherapy) findings for survival in patients with PD-L1 <1%, and possibly 1-49%, there does not appear to be a benefit from pembrolizumab for these patients; any conclusions are limited due to the indirect/between-study comparison and the small sample sizes from KEYNOTE 001.

In Cohorts A to C of KEYNOTE 021, there was no apparent relationship between PD-L1 expression and ORR. Sixty percent (15 of 25) of patients with ≥50% PD-L1 expression and 55% (12 of 22) without PD-L1 expression experienced a response. Overall survival was numerically longer in the PD-L1 ≥50% vs <1% group (17 mos [95% CI 15 mos – not reached] vs. 11 mos [7 mos – not reached]; p values not reported). In PD-L1 negative patients, there does not appear to be any difference in survival when compared with the chemotherapy arms of the RCTs.

Indirect evidence from nivolumab studies

Findings from studies of pembrolizumab have not provided strong evidence of clinical utility for PD-L1 testing. Outcome data for PD-L1 subgroups in other anti-PD1/PD-L1 drugs may lend further support to or against this claim. Nivolumab is the main comparison because of its current use in routine practice.

Study characteristics: One marker-enriched RCT and one single-arm trial of nivolumab have reported data by PD-L1 status in advanced-stage NSCLC. CheckMate 026 compared nivolumab (3 mg/kg every 2 weeks) with investigator's choice of chemotherapy in 541 patients with stage

IV or with recurrent NSCLC, without EGRF or ALK aberrations and with ≥1% PD-L1 expression measured using the 28-8 PharmDx assay.[36] Randomization was stratified by PD-L1 expression (1-4% vs ≥5%) and histology. Cross-over to nivolumab was permitted after progression on chemotherapy. Fifty-eight percent of patients crossed over during the study period and another 2% received nivolumab after chemotherapy during follow-up.

A single-arm trial of nivolumab in the first-line setting, CheckMate 012, enrolled 52 patients, of which 46 had PD-L1 measurement.[52]

Study quality: Risk of bias for CheckMate 026 was assessed as low for ORR and PFS, unclear for major harms, and high for overall survival. Similar to KEYNOTE 021 and 024, the cross-over is expected to bias findings for survival, but CheckMate 026 was also imbalanced between groups for PD-L1 status (15% more PD-L1 ≥50% in chemotherapy arm). This may increase the potential bias when considering the main objective of PD-L1's predictive ability.

Findings: In CheckMate 026, nivolumab was not shown to be superior to chemotherapy for any outcome in any PD-L1 subgroup. This included patients with ≥50% PD-L1 expression (n=214), although the data for this subgroup was not based on pre-determined power determinations and may have been influenced by the imbalance between groups for this variable. Both nivolumab and pembrolizumab are antibodies to the PD-1 receptor (vs. targeting the PD-L1 ligand as other drugs in this class do) and therefore the large difference in effects particularly at the high PD-L1 expression levels between KEYNOTE 24 and CheckMate 026 are noteworthy and without any clear explanation. Subgroup analysis in CheckMate 026 found that PFS may favor *chemotherapy* more than nivolumab for patients with good performance status (ECOG 0, n=178; HR 1.69 [1.18-2.42]), who have never smoked (n=59; HR 2.51 [1.31-4.83]) and are female (n=209; HR 1.36 [0.98-1.90]).

CheckMate 012 reported ORRs (investigator assessed) of 50%, 28%, and 14% for PD-L1 ≥50% (n=26), ≥1% (n=32), and <1% (n=14), respectively.[52] Duration of PFS was 8.3 (95% CI 2.2-28+), 3.5 (95% CI <0.1-28+), and 6.6 (95% CI 0.1-12.4) months, and 18-month survival rates were 83%, 53%, and 64%. Patients with PD-L1 ≥50% benefitted more than other groups, although there did not appear to be lack of benefit for other subgroups. Without direct comparison to chemotherapy it is difficult to know the relative benefits for nivolumab, but looking at results in chemotherapy arms where approximately 30% response rates (Figure 5) and

50-60% 12-month survival rates (Figure 8) were observed suggests no benefit from nivolumab over chemotherapy for PD-L1 negative patients.

Indirect evidence from studies of PD-L1 inhibitors

Three other single-arm trials have examined efficacy by PD-L1 status when using PD-L1 inhibitors for first-line treatment. Atezolizumab was examined in two phase 2 trials enrolling patients with advanced NSCLC of any histology and positive for PD-L1 expression on tumor cells (TC) or immune cells (IC) using the SP142 antibody clone. The FIR trial (n=31 first-line) reported investigator-assessed response rates of 25.8% and 29% for patients classified as TC2/3 or IC2/3 (≥5% PD-L1 expression on either cell type; n=31) or TC3 or IC3 (≥50% on TCs or ≥10% on ICs; n=7), respectively.[80] The BIRCH trial (n=139 first-line) reported investigator-assessed response rates of 22% and 31%, PFS of 5.4 (95% CI 3.0-6.9) and 5.6 (95% CI 2.7-8.3) months, and overall survival at median 22.5-month follow-up of 23.5 (95% CI 18.0-not estimable) and 26.9 (95% CI 12.9-not estimable) months for patients classified as TC2/3 or IC2/3 (n=139) or TC3 or IC3 (n=65).[66] The Javelin Solid Tumor phase Ib trial studying avelumab in first-line treatment for advanced NSCLC reported no responders in 10 PD-L1 <1% patients and 20% response for 35 patients with ≥1% PD-L1.[85] A study of durvalumab was not included because of no reported results for patients based on different PD-L1 levels.[117]

Ongoing studies

More data may help better ascertain the predictive effect of PD-L1 for pembrolizumab in first-line treatment. Ongoing phase 3 trials, such as KEYNOTE-042 (ClinicalTrials.gov number, NCT02220894), are assessing pembrolizumab over chemotherapy in patients with ≥1% tumor PD-L1. Two international, randomized, double-blind, phase 3 trials are also ongoing: KEYNOTE-189 studying platinum and pemetrexed with or without pembrolizumab in patients with non-squamous NSCLC (NCT02578680) and KEYNOTE-407 of carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab in patients with squamous NSCLC (NCT02775435). These latter studies are not enrolling based on PD-L1 status, although they require a sample of tumor (not previously irradiated).

Second-Line or Beyond

Direct evidence

No marker-based strategy or marker-by-treatment interaction studies were identified to directly examine the clinical utility of PD-L1 testing for treatment pembrolizumab compared with standard of care in second- or beyond-line treatment.

Linked evidence from marker-enriched RCTs of pembrolizumab

Study characteristics: The marker-enriched KEYNOTE 010 randomized 1034 patients using a 1:1:1 ratio to 2 mg/kg (n=345) or 10 mg/kg (n=346) of pembrolizumab, or docetaxel 75 mg/m^2 (n=343), all administered intravenously every 3 weeks.[57] Randomization was stratified by performance status (ECOG 0 or 1), East Asian vs not East Asian countries, and PD-L1 tumor proportion score (TPS) after the first 441 patients were enrolled and the IHC 50% cut-point was established. Patients were PD-L1 positive (≥1%) using the 22C3 CTA on a fresh (no intervening treatment) (56%) or archival (44%) tumor sample and had progressed on or after platinum-based chemotherapy. Approximately 29% of patients were beyond second-line treatment, although all had good performance status (ECOG 0 or 1). Over 25% patients were reported to be non-Caucasian, the proportion of males was 62%, and average age was 63.

Study quality: Risk of bias was unclear for ORR, PFS, survival, and harms, because of concerns about incomplete and imbalanced outcome data (1.3% in pembrolizumab groups and 10% in docetaxel group not receiving drug; 2% vs 13% withdrew consent). Unclear risk, rather than high, was given because of uncertainty about the influence of attrition on effects by PD-L1 status. Risk of bias was considered high for patient-reported outcomes because of high attrition at longer-term time points, differential attrition between the pembrolizumab and docetaxel groups, and possible selective outcome reporting, or analysis, due to limited predetermined outcome definitions. The duration of treatment was longer in the pembrolizumab groups (median 3.5 vs 2 months) which may reflect the better harms profile for this drug. More patients in the docetaxel group (8.7%) than in the pembrolizumab groups (1%) received another PD-L1 inhibitor (nivolumab) after progression. There were no meaningful differences between groups or patients with TPS 1-49% versus ≥50% at baseline.

Findings: Figures 10-15 present the results by PD-L1 status for KEYNOTE 010 and other RCTs of different anti-PD1/PD-L1 drugs, as discussed in the following sections. Survival data were based on reporting in abstracts (Herbst 2016 for 1% and 50% cut-offs;[100] Bass 2016[96] and Garon

2016[98] for other subgroups) with a data cut-off of March 31, 2016. Median follow up of patients was 19.2 months.

For ORR, while patients as a whole (≥1% PD-L1) responded better taking pembrolizumab, the effects appear to be largely driven by patients having ≥50% PD-L1 because of findings of no significant difference between treatment groups for the 1-24%, 24-49% and 1-49% PD-L1 subgroups (latter results reported in abstracts).[98,100]

At 13.2-month follow-up, pembrolizumab was favorable over docetaxel for PFS in patients with ≥50% PD-L1 but not in those with ≥1% expression.[57] At 19-months of follow-up, reported in an abstract, 60% of pembrolizumab and 15% of docetaxel responders, including 65% and 15% with TPS ≥50%, were alive, progression free, and without new anticancer therapy.[100]

For overall and 18-month survival, patients in all subgroups (except for one small group at 25-49% PD-L1 having imprecise results[96]) benefitted in relative terms to the docetaxel group.[96,100] Comparing overall survival HRs between exclusive subgroups with 1-49% PD-L1 (n=591; HR, 0.77; 95% CI 0.68-0.88) and ≥50% PD-L1 (n=442; HR 0.51; 95% CI 0.41-0.64), found a statistically significant difference (Chi^2 p=0.001) (Figure 15). Moreover, the *absolute* benefit over docetaxel in median survival in the 1-49% (0.8 mos for 2 mg and 2.2 mos for 10 mg groups; no 95% CIs)[98] compared with the ≥50% (7.6 mos for 2 mg and 10.6 mos for 10 mg),[100] group appears to differ to a meaningful degree.

Pembrolizumab treatment was associated with many fewer grade 3+ TRAEs than was docetaxel (13% and 16% pembrolizumab vs. 35% docetaxel). There were three deaths in each pembrolizumab group and five in the docetaxel group. No adverse effects were reported based on PD-L1 expression levels.

All quality of life data came from the pCODR report, as submitted by the sponsor and without peer-review.[16] The only findings published (in abstract form[118]) were specific to the ≥50% PD-L1 group receiving 2 mg pembrolizumab (because of statistical significance), reported higher compliance than that reported in the pCODR report, and did not provide additional data. For the Global Health Status Score of the EORTC Quality of Life Questionnaire C30 at 12 weeks, all patients (≥ 1% PD-L1) in both 2 mg and 10 mg dose groups reported less deterioration than patients receiving docetaxel, although the only statistically significant results were for the ≥50% PD-L1 group receiving 2 mg pembrolizumab. No results reached the minimum difference of >10% change. Pembrolizumab patients also reported improvements in lung cancer symptoms,

as compared to worsening symptoms in the docetaxel group, on the EORTC-QLQ-LC13. In the ≥50% PD-L1 group, results for some symptoms reached statistical significance. Findings on the EQ-5D questionnaire were quite similar between groups. More patients in the pembrolizumab groups completed the questionnaires (e.g., for EORTC-QLQ-C30 >70% vs. 55% in pembrolizumab and docetaxel groups, respectively) and pCODR commented on possible selective reporting of the patient-reported outcome data. Nevertheless, results suggest there may be more benefit for patients in the ≥50% compared with ≥1% PD-L1 groups. The measurements focused on symptoms and did not capture other aspects such as anxiety or worry that may differ between groups.

Subgroup effects: Findings from this analysis, comparing overall survival for the 1-49% and ≥50% subgroups, are described above and presented in Figure 15. The Keynote 10 authors stratified the results of overall survival for several demographic and clinicopathologic variables, and found that EGFR status and histology may influence effectiveness with pembrolizumab (EGFRmut, n=86, HR 0.88, 95% CI 0.45-1.70; squamous cell histology, n=222, HR 0.74, 95% CI 0.50-1.09 vs adenocarcinoma, n=708, HR 0.63, 95% CI 0.50-0.79).[57] Further, multivariable regression analysis using a cox proportional regression model, with individual patient data, found seven factors that independently moderated survival at follow-up 12 months beyond the original publication, including PD-L1 (adjusted HRs):[97]

- Race (Asian vs non-Asian): aHR 0.70 (0.54-0.91); p=0.0067
- Tumor size (≥80mm vs <80 mm): aHR 0.71 (0.59-0.87); p=0.0007
- ECOG 0 vs 1: aHR 0.79 (0.65-0.97); p=0.0265
- nonSC vs SC: aHR 0.55 (0.43-0.70) p<0.0001
- PD-L1 ≥50% vs 1-49%: aHR 0.64 (0.52-0.77); p<0.0001
- EGFR wild-type vs mutant: aHR 0.65 (0.46-0.91); p=0.0122

Linked evidence from single-arm trials of pembrolizumab in PD-L1 negative patients

KEYNOTE 010 did not enroll patients without at least 1% PD-L1 tumor expression. Results have been reported for patients with <1% PD-L1 who received second-line treatment in the KEYNOTE 001 phase Ib study. In the set of patients used for validation of the ≥50% threshold with the CTA version of the PharmDx 22C3 assay (n=156), ORR was 9.1% (2 of 22 patients) for patients with <1% expression.[23] These results were very similar to those of the docetaxel arm in KEYNOTE 010. A report of 3-year survival in the KEYNOTE 001 second-line population found lower rates for patients with <1% PD-L1 (8 of 90; 8.9%) compared with ≥1% (65 of 306; 21.2%)

or ≥50% (41 of 138; 29.7%) as per the CTA assay.[95] Data on <1% PD-L1 patients for mean overall survival or PFS were not found.

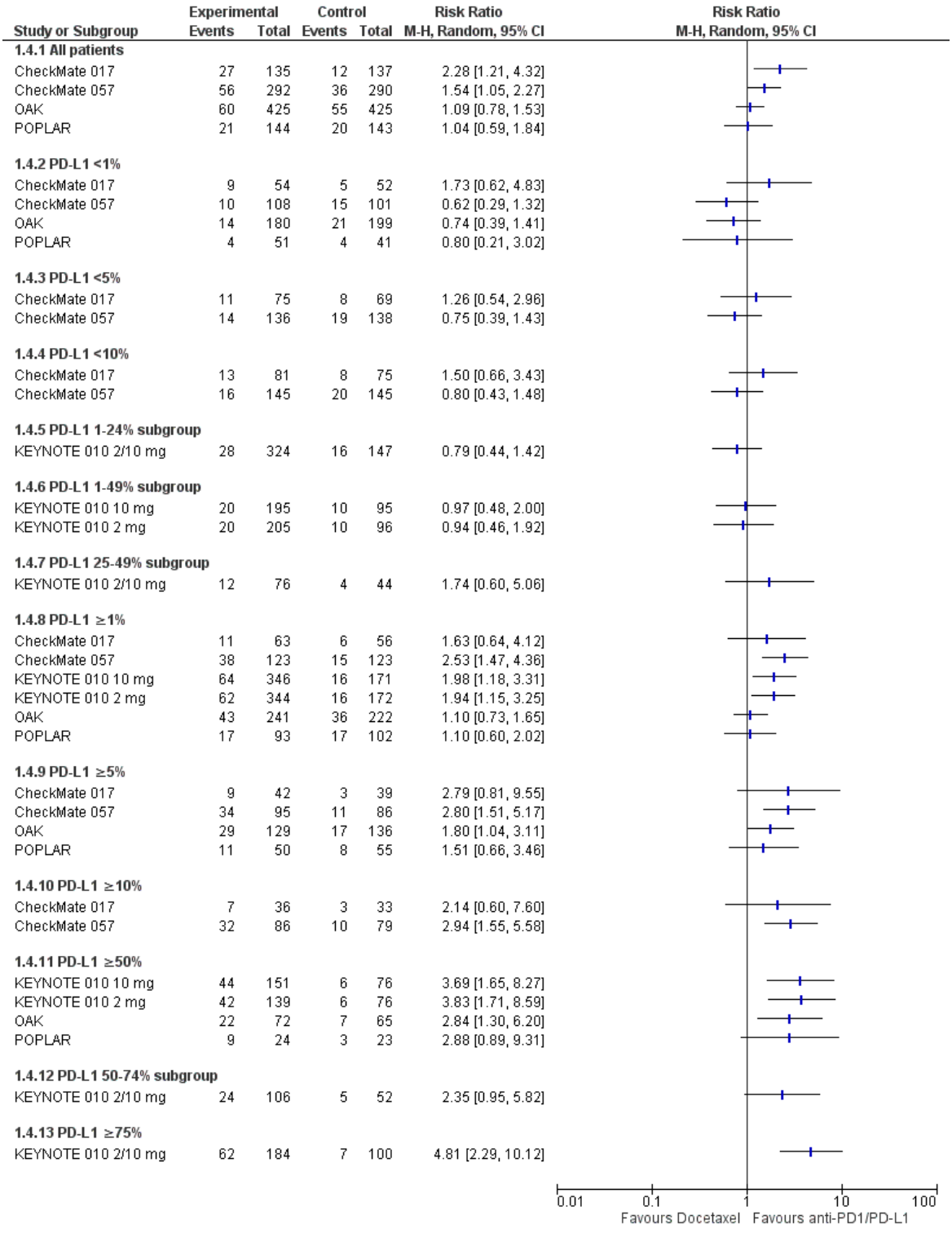

Figure 10. Objective response rate in second-line or beyond treatment with PD-1/PD-L1 inhibitors compared with docetaxel in patients with advanced NSCLC

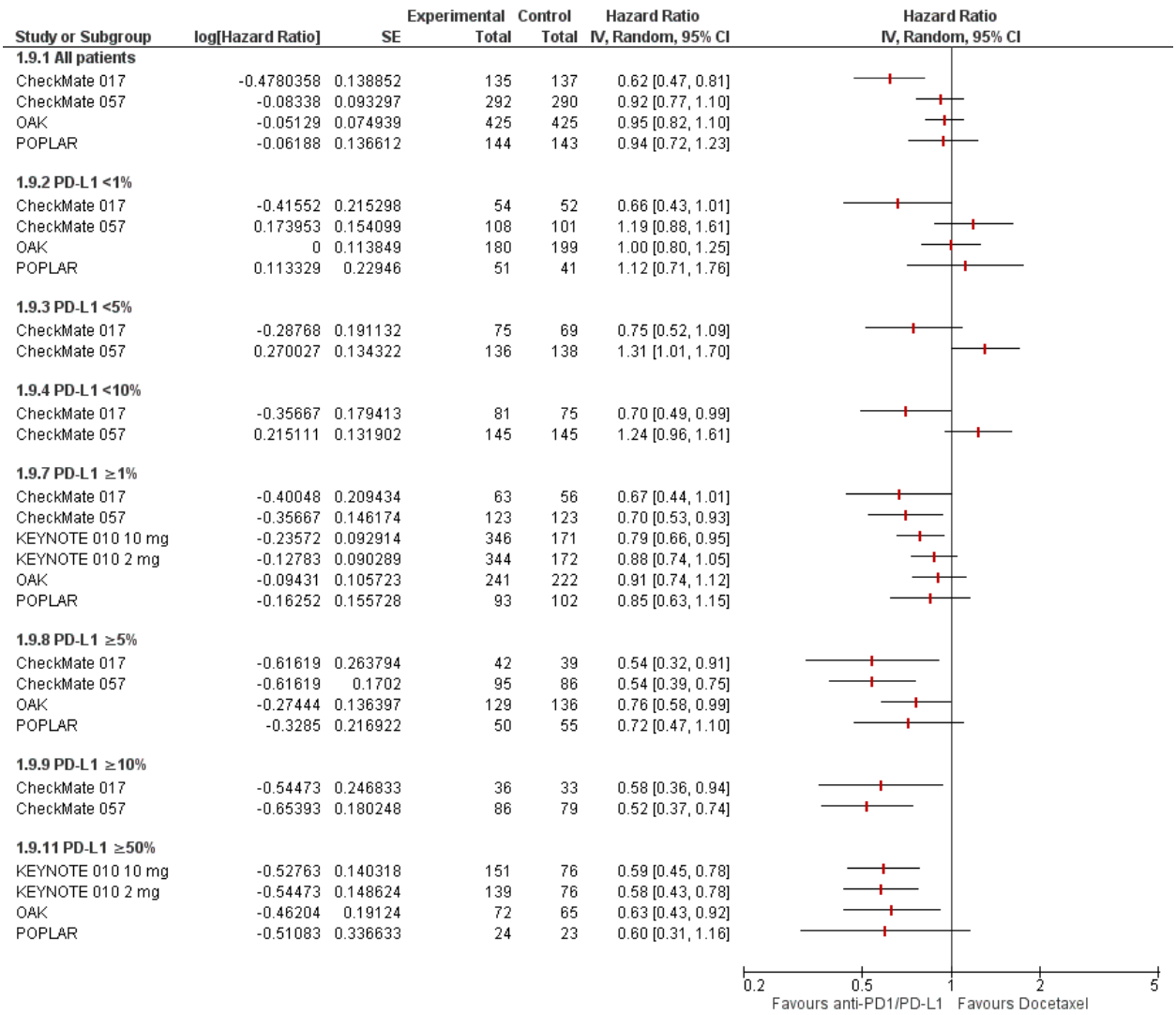

Figure 11. Progression-free survival in second-line or beyond treatment with PD-1/PD-L1 inhibitors compared with docetaxel in patients with advanced NSCLC

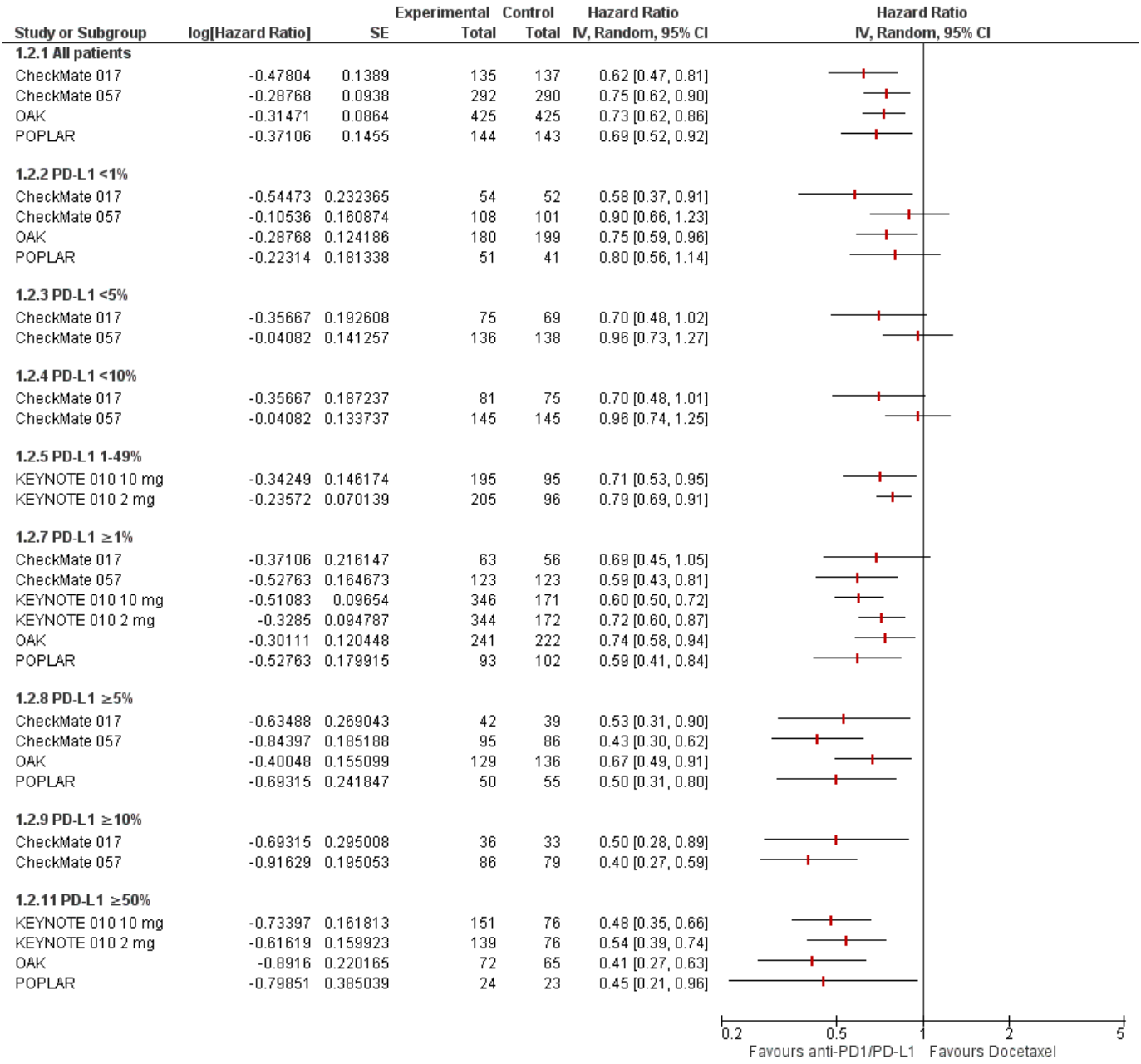

Figure 12. Overall survival in second-line or beyond treatment with PD-1/PD-L1 inhibitors compared with docetaxel in patients with advanced NSCLC

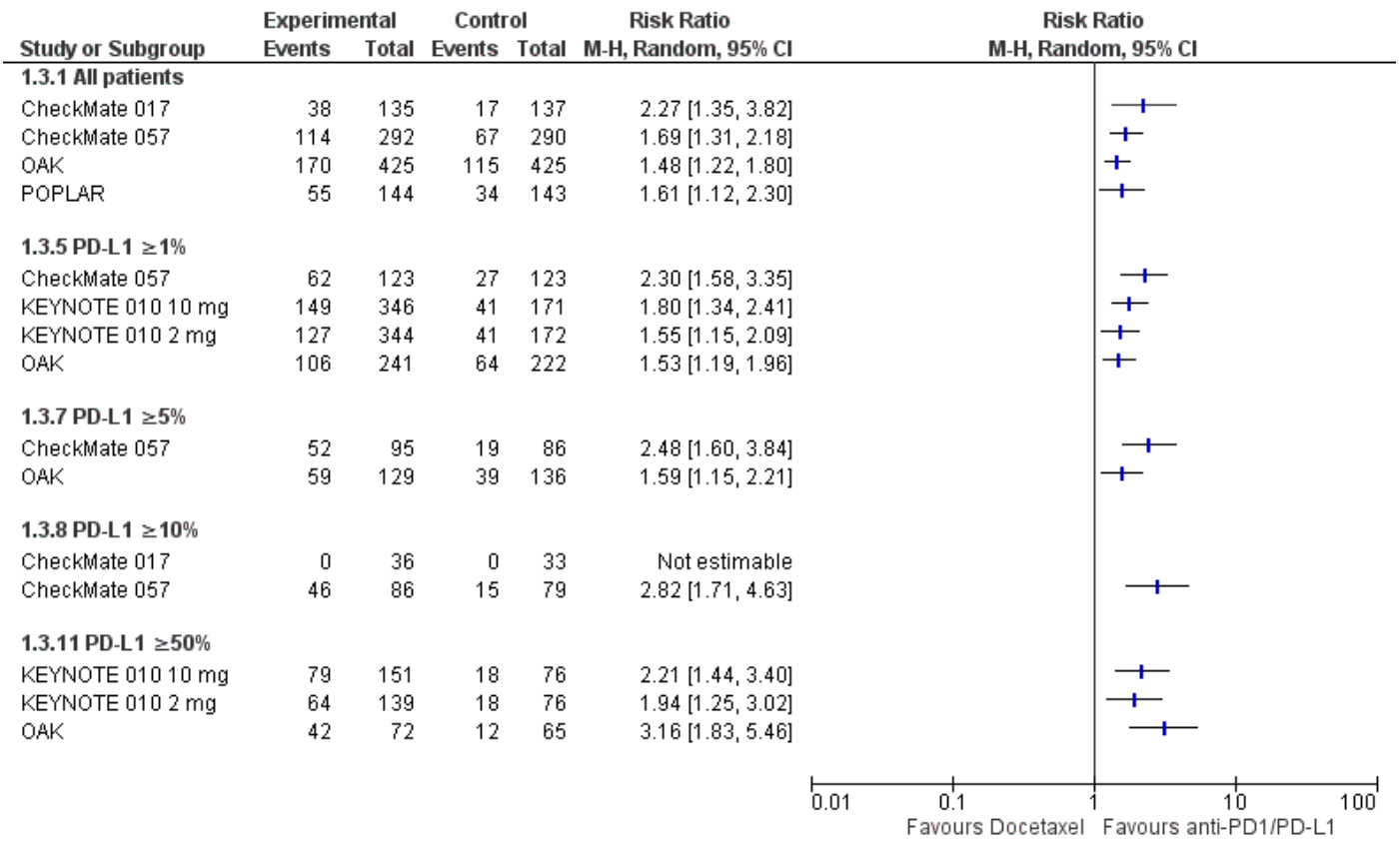

Figure 13. 18-month survival in second-line or beyond treatment with PD-1/PD-L1 inhibitors compared with docetaxel in patients with advanced NSCLC

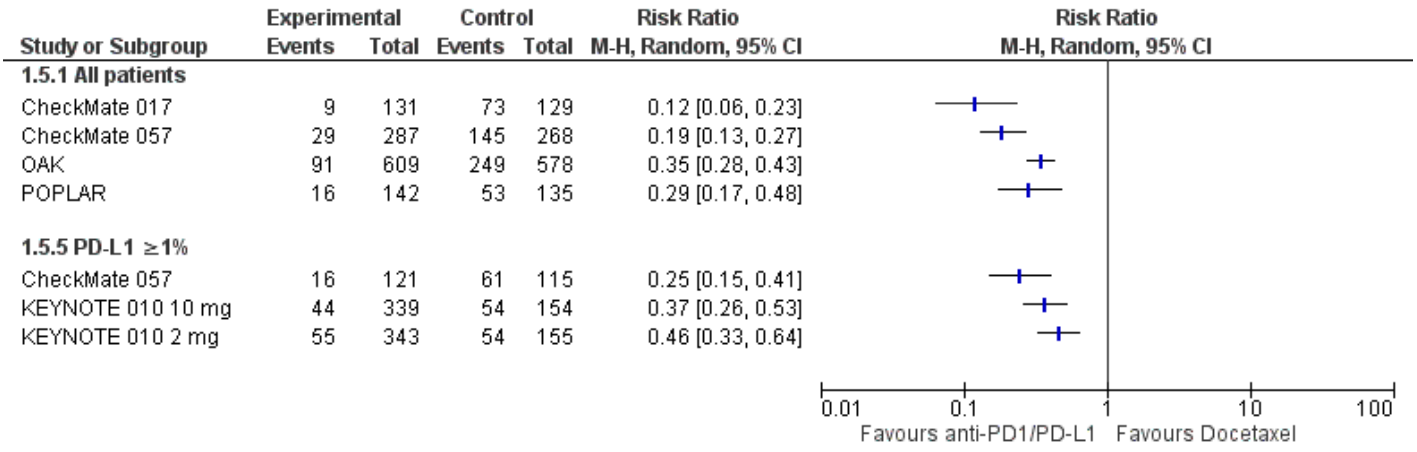

Figure 14. Treatment-related adverse effects (grade 3 or higher) in second-line or beyond treatment with PD-1/PD-L1 inhibitors compared with docetaxel in patients with advanced NSCLC

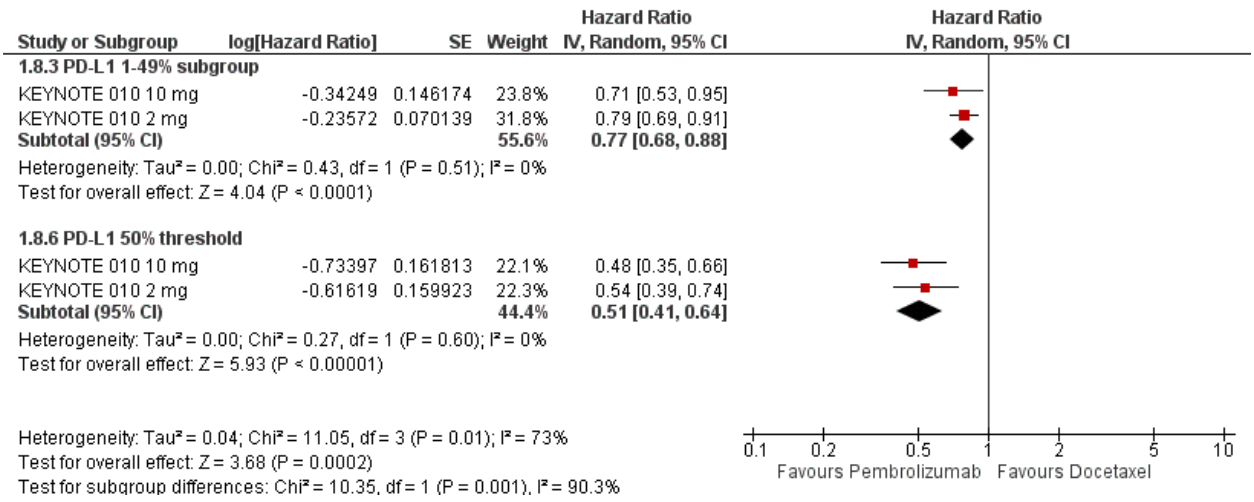

Figure 15. Subgroup analysis comparing overall survival between pembrolizumab and docetaxel in patients with advanced NSCLC having 1-49% versus ≥50% PD-L1 expression

Indirect evidence from nivolumab studies

Study characteristics: Two marker-by-treatment interaction RCTs have compared nivolumab with docetaxel. CheckMate 017 enrolled 272 patients with stage IIIB or IV squamous-cell NSCLC and disease recurrence after (only) one prior platinum-containing regimen and randomized them to nivolumab 3 mg/kg every 2 weeks (median 8 [1-48] doses) or docetaxel 75 mg/m^2 IV every 3 weeks (median 3 [1-29] doses).[43] CheckMate 057 enrolled 582 patients with non-squamous NSCLC who had progressed on platinum-containing doublet therapy and also received nivolumab (median 6 [1-52] doses) or docetaxel (median 4 [1-23] doses).[42] Some patients (11%) in CheckMate 057 had received two lines of previous chemotherapy, and TKI therapy was allowed. Continuation or switch to maintenance therapy with pemetrexed, bevacizumab, or erlotinib was also allowed. In both trials, patients were required to submit fresh or archival tumor samples for PD-L1 measurement with the 28-8 clone, but a particular expression level was not required for enrollment. Approximately 8% of patients were classified as non-Caucasian. There were fewer males in CheckMate 057 (54%) than in CheckMate 017 (76%). Patients were permitted to continue to receive nivolumab beyond radiological progression, if per protocol criteria were met; this occurred for 24% and 21% of patients in CheckMate 057 and 017, respectively.

Study quality: Risk of bias was considered high for the outcomes of ORR, PFS, and patient-reported outcomes due to lack of blinding and use of investigator assessment for response. For the outcome of survival, CheckMate 017 was at low risk of bias and CheckMate 057 was at

unclear risk of bias because of concerns over incomplete outcome data (i.e., imbalance between groups in number not receiving treatment [5% more in docetaxel] and number of withdrawals [5% more in docetaxel]).

Findings: In both RCTs, nivolumab provided no benefit over docetaxel in terms of response rates for patient subgroups having <1%, <5% or <10% PD-L1 expression. In CheckMate 057, there was benefit from nivolumab for subgroups with ≥1%, ≥5%, and ≥10% expression and this appeared to have a small dose-effect response based on PD-L1 level. The authors undertook Cox proportion tests for interaction between treatment and PD-L1 status (using $p<0.2$ to signal prediction) with results of $p=0.002$ for each of the three subgroups. CheckMate 017 found no statistically significant benefit for the ≥1%, ≥5%, and ≥10% subgroups, although this may be related to the small sample sizes. Results were similar for PFS and overall survival, where in CheckMate 057 the subgroups having ≥1%, ≥5%, and ≥10% PD-L1 attained more benefit than the <1%, <5%, and <10% groups, where no benefit over docetaxel was seen. Interaction p values for PFS were 0.02, <0.001, <0.001 and or overall survival were 0.06, <0.001, and <0.001, respectively. In CheckMate 017 where all subgroups benefitted similarly, interaction p values were 0.70, 0.16, and 0.35, respectively, for PFS, and 0.56, 0.47, and 0.41, respectively, for overall survival. Results for 18-month survival in CheckMate 057 appear similar, although no interaction test results were reported. For overall survival at 2 years (from abstract[94]) and 18-month survival, all patients, regardless of PD-L1 expression, benefitted from nivolumab in both trials.

Information on patient-reported outcomes was taken from the pCODR submission,[18] based on data submitted by the sponsor as well as conference abstracts.[119-122] The Lung Cancer Symptom Scale and EQ-5D were used for both trials although the latter were not reported for CheckMate 057. Response rates between groups were similar. For CheckMate 057, several analyses demonstrated comparable results between treatment groups (e.g., clinically meaningful improvement in global symptoms at week 12) with some findings of a greater time to deterioration with nivolumab. Results for CheckMate 017 were similar to CheckMate 057, but demonstrated better EQ-5D scores from nivolumab (comparison between groups not provided). No results were provided by PD-L1 status.

Indirect evidence from trials in PD-L1 inhibitors

RCTs

Study characteristics: Two other RCTs have been completed, both comparing PD-L1 inhibitor atezolizumab (1200 mg IV every 3 weeks) with docetaxel. POPLAR (n=287)[47] and OAK (n=850 in efficacy population)[71] were phase II and III RCTs similar in design and patient populations. The average age of participants was 63 years, and the majority were male (POPLAR had more 12% more females in the atezolizumab group). In OAK, about 25% of patients were non-Caucasian. POPLAR did not report ethnicity but patients were recruited in Korea, Turkey and Thailand. At least 25% of patients were beyond second-line treatment in both trials. Patients in both trials received atezolizumab for a longer duration (median 3.4 months) than docetaxel (median 2.1 months), and about 40% of patients receiving atezolizumab continued on the drug after radiological progression. Tumor samples were prospectively collected with measurement of PD-L1 on tumor cells (TCs) and immune cells (ICs) using the SP142 clone. Randomization was stratified by IC (not TC) PD-L1 expression. The study investigators categorized subgroups using TC or IC staining at various levels of PD-L1 (i.e., TC0 or IC0 patients would have no expression of either, but TC3 or IC3 patients had ≥50% TC PD-L1 or ≥10% IC staining and it was noted there was little overlap between TC and IC staining). Baseline characteristics between atezolizumab and docetaxel arms within PD-L1 subgroups were balanced, with the exception of the TC1/2/3 or IC1/2/3 (≥1% TC or IC) population, where there was a difference of 5% or more between groups in age, sex, and race.

Study quality: Both OAK and POPLAR trials were assessed to have unclear risk of bias for overall survival and TRAEs. Allocation concealment was not concealed, although patients, investigators and study site staff were blinded to PD-L1 results at enrollment and numerous variables were balanced at baseline between groups. Intent-to-treat analysis was performed but there were differences between intervention and control groups for the number of patients not treated (1% vs 5-6%) and withdrawing from the study (4-5 vs 10%). Risk was high for subjective outcomes of PFS and response (both investigator-assessed), and for patient-reported outcomes, but to the above reasons in addition to lack of blinding of outcome assessors.

Findings: There was no statistically significant difference in response rates or PFS between atezolizumab and docetaxel treatment arms, across all patients or in subgroups having <1% TC and IC (TC0 and IC0 group) or ≥1% TC or IC (TC1/2/3 or IC1/2/3 group) PD-L1 expression.

The larger OAK trial found a statistically significant benefit in response rates and PFS for patients with ≥5% TC or IC (TC2/3 or IC 2/3 group) and with ≥50% TC and ≥10% IC (TC3 or IC3 group) expression. The smaller POPLAR trial failed to generate significant findings which may relate to the small samples particularly in the TC3 or IC3 group (n=47 total). For overall (min 20 mos) and 18-month survival, atezolizumab was favored over docetaxel for all subgroups having some PD-L1 expression in both trials. OAK also found a statistically significant benefit for overall and 18-month survival in the PD-L1 negative group (12.6 vs 8.9 months [HR 0.75, 95% CI 0.59-0.96] and 36% vs 25% [RR 1.44, 95% CI 1.06-1.98]). Atezolizumab is under review for use in Canada and would be anticipated to seek a recommendation for use in patients regardless of PD-L1 status.

Single-arm trials

Single-arm trials studying avelumab (Javelin Solid Tumor[54]) and durvalumab (Atlantic,[50,51] SWOG S1400A,[65] NCT01693562[41]) do not appear to support use of PD-L1 testing for predicting overall survival. For avelumab, PD-L1 negative patients (n=20) had a numerically but not statistically significantly lower survival than PD-L1 positive (≥1%; n=122) patients (4.6 vs 8.9 months, HR 0.64 95% CI 0.34-1.20), but the small sample sizes lead to high imprecision and uncertainty in the findings. No relative survival benefit over PD-L1 negative patients was found for ≥5% or ≥25% PD-L1 expressors. Durvalumab trials used a 25% PD-L1 threshold and one of three (NCT01693562) found a difference for overall survival based on PD-L1 status (≥25% PD-L1 15.4 months, 95% CI 9.7-22.4 vs <25% PD-L1 7.6 months, 95% CI 5.6-10.0). Neither of these drugs has received regulatory approval in Canada.

4.4.5. Clinical and analytical validity of the Dako PD-L1 IHC 22C3 pharmDx assay and laboratory-developed tests (LDTs) with 22C3 antibody

With pembrolizumab being the only drug guided by PD-L1 testing at this time, the evidence for assessment of clinical and analytical validity of PD-L1 testing as a CDx focused on studies of the Dako PD-L1 IHC 22C3 PharmDx assay for NSCLC. No papers were identified showing clinical validity from a different antibody clone for pembrolizumab treatment. Twenty-six papers (n=13) and abstracts (n=13) reported on one or more aspects/parameters of analytical and clinical validity of this assay. Study characteristics and findings are presented in detail in Table E3,

except for the study by Sorenson et al.[79], which is described in Table E1 because it was also used for the question on prognosis with treatment. Three publications[23,46,72] and one FDA document[84] reported a group of studies that served as the basis for obtaining regulatory approval for the assay as a CDx in the United States. Findings from these studies relate to most of the necessary parameters (see Table 1, section 3.2.2.). However, it should be noted that the studies on analytical validity by the manufacturer and the subsequent FDA approval of the test as a CDx are specific to the 50% PD-L1 threshold, yet the 1% threshold is used in clinical practice for second-line treatment in Alberta. Five additional studies used data from patients enrolled or screened for one or more KEYNOTE trials.[40,56,92,95,99] Otherwise, 17 studies unrelated to the KEYNOTE study sponsors or assay manufacturers were identified; eight[39,68,70,75,76,87,88,90] of which studied the Dako 22C3 assay as part of a comparison of different validated assays or LDTs. The findings for the 1% and 50% PD-L1 threshold are reported below by the main parameters of interest for demonstrating clinical and analytical validity. In each section, comments specific to requirements of sufficiency (Table 1) are highlighted up front.

Three reports of analytical validity for LDTs using the 22C3 antibody are also described. Study characteristics are included in Table C4.

Clinical validity of Dako 22C3 PharmDx

As mentioned in Section 3.2.2., evidence on clinical validity of the CDx should not be essential to evaluate if high-quality evidence exists (e.g., marker-by-treatment interaction RCTs) on the clinical application of the CDx-drug pair compared with standard of care. Positive results from the comparative trial, if including a large sample of patients who are either not tested or marker-negative, will naturally confirm clinical validity and also account for the possible prognostic role of the CDx for those receiving the comparator. Low quality evidence on clinical utility may be supported by measures of clinical validity, should high quality evidence exist.

Data on several samples of patients in KEYNOTE 001 have been reported and can be used to calculate different values for clinical sensitivity and specificity for ORR and survival using the approved thresholds of ≥50% and ≥1% for patients receiving first- or second-line treatment with pembrolizumab, respectively. Also relevant is the approach used to determine the ≥50% (membranous staining at any intensity) threshold.

Garon et al.[23] and Dolled-Fillart et al.[46] reported on a training set of 182 (94% second-line) patients from which 146 were eligible (slides cut within 6 months of staining with CTA) for

determining the selection of a cut-point for further use in a validation set and subsequent RCTs. Four possible scoring systems were tested by a single pathologist from Dako: 1. Proportion score (PS) = partial or complete membrane (not cytoplasmic) staining at any intensity, 2. PS2 = membrane staining at moderate (2+) or strong (3+) staining, 3. PS3 = membrane staining with strong intensity, and 4. H-score (HS) = PS + PS2 + PS3 (value for % staining at each intensity). Selection of the cut-point at 50% PS was based on ease of use (e.g., versus H-score which performed similarly), receiver operating characteristic (ROC) analysis (maximizing Youden's index with closest point to the optimum of all true positives and no false positives), PPV, NPV, and prevalence with best overall response. There was no major difference between ROC area under the curves for four different possible cut-points (i.e., PS2 at 1 or 11%, HS at 63%, or PS at 50%), and area under curve values are all moderate (e.g., PS 50% 0.743). The values for other possible cut-offs with each scoring method (e.g., PS at 1%) were not provided. Based on data in the study reports, calculations were made as shown in Table 6 (rounding from % values led to 147 total samples rather than 146). Values do not indicate a very good test, although the NPV (proportion with negative results that do not respond) is high, which agrees with earlier findings that although patients with ≥1% expression responded, most responders have tumors at the higher expression levels. Nevertheless, the PPV (number of positive patients who will respond) was found to be low, suggesting the test better determines who will not versus who will respond. Based on guidance for interpreting positive (>10 very useful; 5-10 useful) and negative (<0.1 very useful; 0.1-0.2 useful) likelihood ratios, the test would not be considered useful for changing likelihood to an important degree.[123,124]

Table 6. Clinical accuracy statistics for objective response (ORR) using 50% threshold for cut-point selection cohort (94% second line)

Test result	ORR	No ORR	Totals
Positive (≥50%)	19	26	45
Negative (<50%)	9	94	102
Totals	28	120	147
Sensitivity: 0.679 Specificity: 0.783 PPV: 0.42 NPV: 0.922 Likelihood ratio positive test: 3.12 Likelihood negative test: 0.41			

NPV=negative predictive value; ORR=objective response rate; PPV=positive predictive value

Two different validation sets were reported by Garon et al.[23] (CTA) and Roach et al.[72] (22C3 PharmDx), and two other studies reported values (using CTA) for the 1) entire KEYNOTE 001 group (training and validation sets, plus others) of second-line patients,[95] and 2) the sample comprising first-line patients.[99] The first validation set used results from 204 (156 second-line) patients having new samples and slides sectioned within 6 months of assessment.[23] Roach et al.[72] used data from the entire second-line KEYNOTE 001 validation set (n=223; including second-line in validation set #1 and others) which included 61 patients with ≥50% PD-L1, 58 with unknown status (because of staining >6 months [44], unevaluable due to insufficient number of cells [9], bone tissue present [2], or not tested [3]), and 104 patients with PD-L1 expression <50%. Validation sets 1 (Table 7) and 2 (Table 8) and findings for all first-line patients (Table 9) are based on ORR, while data for the entire second-line KEYNOTE 001 (Table 10) are based on rates of 3-year survival.

The values at each threshold and within each patient group (first vs second line) do not appear to vary much based on the slight differences in inclusion criteria used for each data set. In second-line treatment, PPV and NPV for response may range between 0.41-0.44 and 0.85-0.88 for ≥50% and were 0.28 and 0.91 for the ≥1% threshold. Values for first-line PPV and NPV were 0.50-0.52 and 0.81-0.84 (50%) and 0.29-0.31 and 0.83-0.92 (1%). PD-L1 testing predicts much better who will not likely versus who will likely respond (i.e., NPV is much higher than PPV), and PPV for the 50% is not that much higher than it is for the 1% PD-L1 threshold.

Table 7. Clinical accuracy statistics for objective response (ORR) based on 50% and 1% thresholds in first validation cohort using clinical trial assay with new samples sliced 6 months or less before staining (Garon et al.[23])

Second-Line							
Test result	ORR	No ORR	Totals	Test result	ORR	No ORR	Totals
Positive (≥50%)	25	32	57	Positive (≥1%)	37	97	134
Negative (<50%)	14	84	99	Negative (<1%)	2	20	22
Totals	39	116	156	Totals	39	117	156
Sensitivity: 0.641 Specificity: 0.724 PPV: 0.438 NPV: 0.848 Likelihood ratio positive test: 2.32 Likelihood negative test: 0.496				Sensitivity: 0.949 Specificity: 0.171 PPV: 0.276 NPV: 0.910 Likelihood ratio positive test: 1.14 Likelihood negative test: 0.298			

First-Line							
Test result	ORR	No ORR	Totals	Test result	ORR	No ORR	Totals
Positive (≥50%)	8	8	16	Positive (≥1%)	13	29	42
Negative (<50%)	6	26	32	Negative (<1%)	1	5	6
Totals	14	34	48	Totals	14	34	48
Sensitivity: 0.571 Specificity: 0.764 PPV: 0.5 NPV: 0.813 Likelihood ratio positive test: 2.42 Likelihood negative test: 0.562				Sensitivity: 0.923 Specificity: 0.147 PPV: 0.310 NPV: 0.833 Likelihood ratio positive test: 1.08 Likelihood negative test: 0.524			

NPV=negative predictive value; ORR=objective response rate; PPV=positive predictive value

Table 8. Clinical accuracy statistics for objective response (ORR) based on 50% threshold using Dako 22C3 PharmDx in all second-line patients in KEYNOTE 001 validation cohort (Roach et al.[72])

Test result	ORR	No ORR	Totals
Positive (≥50%)	25	36	61
Negative (<50%)	13	91	104
Totals	38	127	165
Sensitivity: 0.658 Specificity: 0.717 PPV: 0.410 NPV: 0.875 Likelihood ratio positive test: 2.33 Likelihood negative test: 0.477			

NPV=negative predictive value; ORR=objective response rate; PPV=positive predictive value

Table 9. Clinical accuracy statistics for objective response based on 50% and 1% thresholds using the clinical trial assay in first-line cohort who received at least once dose of pembrolizumab (Hui et al.[99])

Test result	ORR	No ORR	Totals	Test result	ORR	No ORR	Totals
Positive (≥50%)	14	13	27	Positive (≥1%)	23	56	79
Negative (<50%)	10	54	64	Negative (<1%)	1	11	12
Totals	24	67	91	Totals	24	67	91
Sensitivity: 0.583 Specificity: 0.806 PPV: 0.519 NPV: 0.844 Likelihood ratio positive test: 3.01 Likelihood negative test: 0.517				Sensitivity: 0.958 Specificity: 0.164 PPV: 0.291 NPV: 0.916 Likelihood ratio positive test: 1.146 Likelihood negative test: 0.256			

NPV=negative predictive value; ORR=objective response rate; PPV=positive predictive value

Table 10. Clinical accuracy statistics for 3-year survival based on 50% and 1% thresholds using clinical trial assay in entire second-line KEYNOTE 001 cohort (Leighl et al.[95])

Test result	3-yr survival	No 3-yr survival	Totals	Test result	3-yr survival	No 3-yr survival	Totals
Positive (≥50%)	41	97	138	Positive (≥1%)	65	241	306
Negative (<50%)	20	160	180	Negative (<1%)	8	82	90
Totals	61	257	318	Totals	73	323	396
Sensitivity: 0.672 Specificity: 0.623 PPV: 0.297 NPV: 0.889 Likelihood ratio positive test: 1.78 Likelihood negative test: 0.526				Sensitivity: 0.890 Specificity: 0.254 PPV: 0.212 NPV: 0.911 Likelihood ratio positive test: 1.19 Likelihood negative test: 0.433			

NPV=negative predictive value; ORR=objective response rate; PPV=positive predictive value

Roach et al.[72] also compared ORR between those having PD-L1 ≥50% (n=61; 41%, 95% CI 28.6-54.3) versus the whole second-line cohort (n=223), including those without PD-L1 results (20.6%, 95% CI 15.5-26.5).

Analytic sensitivity (positive agreement to comparable method) and specificity (negative agreement to a comparable method)

In the absence of a gold standard test, sensitivity and specificity for IHC validation studies are usually measured using orthogonal strategies (Western blot, flow cytometry, mRNA testing) on previously characterized tissue validation sets (or genetically altered cell lines), as well as normal and neoplastic tissues with literature supporting their typical expression levels (e.g., lymphocytes and epithelial tissues express PD-L1 whereas some placental tissues do not).[14] There is no specific requirement for the number of samples. Multiple approaches using relevant patient samples are beneficial. Negative controls should have <0.5 grade staining intensity.[14]

For sensitivity, Roach et al.[72] used a random selection of 127 formalin-fixed paraffin-embedded (FFPE) specimens including stage III and IV NSCLC (proportion not reported) with a wide range of PD-L1 expression, and reported that PD-L1 was visualized over a dynamic staining intensity range; 57.5% of specimens did not express and 18.4% expressed at ≥50%. Using 60 FFPE tissue micro-arrays (TMAs) from surgical resections (early stage), Copper et al.[44] compared scoring by 10 pathologists (having a variety of experience and practice types) with a reference standard of consensus by two trained (Dako 2-day course) pathologists. At the 1% threshold level, the sensitivity, specificity, and positive and negative predictive values (PPV and

NPV) were 84.3%, 91.3%, 90.7% and 85.4%, respectively. For the 50% threshold the values were 56.3%, 94%, 90.4%, and 68.3%, respectively, indicating a high false negative rate. The authors stated that variability in scoring was high for 30-80% PD-L1 expression levels, and that the tendency to underestimate PD-L1 levels was greatest if there was weak staining or concomitant cytoplasmic staining (which needs to be excluded in the scoring algorithm).

For specificity, Roach et al.[72] used i) western blot on control cell lysates using 22C3 assay, ii) immunoreactivity in human tissues (3 cases from 30 normal tissues) and neoplastic tissues (1-7 cases from 82 neoplasms), iii) orthogonal methods (mRNA and flow cytometry) with 6 FFPE tumor cell lines with known and broad-spectrum PD-L1 expression) and Hamster ovary (transfected and parental) cell lines. The assay detected purified PD-L1 protein and had low cross-reactivity to other proteins; background staining in all human tissues was <0.5 grade and expression patterns were consistent with reported literature (e.g., immune cells and cells of epithelial origin mostly). There was equivalent expression when assay results were compared with those from mRNA and flow cytometry analysis.

Precision/repeatability & reproducibility

For precision studies, at least 85% but ideally 90% overall concordance/agreement (OPA) should be achieved.[14] If less than 90% OPA, the results should be investigated for positive (PPA) and negative (NPA) percent agreement to help characterize the cause of low concordance.[14] Validation tissues should, to the extent possible, use tissues that have undergone the same processing (fixative, other processing methods) tested clinically. Whole tissue sections should be used over TMAs when differences in fixation and processing are apparent. In cases of substantial inter-tumoral heterogeneity in expression, whole tissue is most valid.[14] For initial IHC assay validation, 20 positive and 20 negative cases should be used; cases should include high and low expressors for positive cases and should span the expected range of clinical results.

For studies of precision for the 50% threshold at a Dako laboratory, Roach et al.[72] used 16 NSCLC specimens (histology and stage not reported), 10 negative and 6 positive for PD-L1. Twenty-five percent of samples had PD-L1 expressions between 40% and 60%. For inter-instrument (n=6), inter-observer (n=6), inter-day (n=6), inter-lot (n=3), intra-day, and intra-run (n=6) tests, there was 100% OPA, NPA, and PPA. All lower boundaries of the 95% CIs were >85%, except for intra-day repeatability where the lower boundary for PPA was 82.4%. The authors also reported results for inter- and intra-observer (62 specimens interpreted by 3

pathologists over 9 days) and inter- and intra-site (36 specimens over 5 days) agreements from three external Clinical Laboratory Improvement Amendments laboratories, where specimens (in random order) having a full range of expression were scored. Six other research groups have reported on either, or both of, inter-observer[44,68,70,76,88] or intra-observer[44,90] agreement, and an additional two have reported inter-site agreements.[39,75] Table 11 includes results for both thresholds. Concordance and agreement statistics were high across all parameters for both thresholds. Intra-observer agreement appears to be higher than inter-observer agreement, especially as the number of observers rises. Of five studies collecting data for both ≥1% and ≥50% thresholds, two[44,76] found similar results between the thresholds whereas three[68,70,125] found that inter-observer agreement was higher for the 50% threshold.

Table 11. Inter- and intra-observer and inter-site agreements for the Dako 22C3 pharmDx assay

Study & Samples/Personnel	Overall percent agreement (OPA)	Positive percent agreement (PPA)	Negative percent agreement (NPA)	Other statistics
Inter-observer: 50% Threshold				
Roach, 2016; FDA SSED, 2015 Internally at Dako 6 pathologists	100% (95.4-100)	100% (88.6-100)	100% (92.7-100)	
Roach, 2016; FDA SSED, 2015 At 3 external sites; 1674 comparisons	92.7% (88.1-96.8)	92.8% (88.1-96.8)	92.6% (87.8-96.7)	
Cooper, 2017 60 samples (TMAs), 2700 pair-wise w/ 10 pathologists	81.9% (80.4-83.3)	84.6% (81.7-87.0)	80.9% (79.2-82.6)	aKappa* 0.64 (0.61-0.67) (substantial)
Scheel, 2016 15 cases; 9 pathologists				Light's kappa unweighted 0.66 (0.42-0.89)
Rimm, 2017 90 samples; 13 pathologists at 3 sites				Fliess k statistic 0.773 (substantial); Kendall concordance 0.794 (strong)
Ratcliff, 2017 200 samples; 2 pathologists	94.5% (91.1-NR)			
Brunnstrom, 2017 55 samples (resections), 7 pathologists				Compared with reference standard of consensus, 7 pathologists all scored correctly for all negative cases (n=45), and 4 pathologists scored 1 of the positive cases (n=10) as negative.

Study & Samples/Personnel	Overall percent agreement (OPA)	Positive percent agreement (PPA)	Negative percent agreement (NPA)	Other statistics
Inter-observer: 1% threshold				
Cooper, 2017 60 samples (TMAs), 2700 pair-wise w/ 10 pathologists	84.2% (82.8-85.5)	83.2% (81.1-85.2)	85.0% (83.1-86.8)	Cohen's kappa 0.68 (0.65-0.71) (substantial)
Scheel, 2016 15 cases; 9 pathologists				Light's kappa unweighted 0.74 (0.44-0.94)
Rimm, 2017 90 samples; 13 pathologists at 3 sites				Fliess k statistic (agreement) 0.535 (moderate); Kendall concordance 0.608 (moderate)
Ratcliff, 2017 200 samples; 2 pathologists	76.5% (71.0-NR)			
Brunnstrom, 2017 55 samples (resections), 7 pathologists				Compared with reference standard of consensus, 0-10 (median 1) cases were classified incorrectly as positive when negative by any one pathologist, and 0-2 (median 1) cases were scored as negative when positive. ≥1% worse than all other cut-offs, (p<0.001)
Intra-observer; 50% threshold				
Roach, 2016; FDA SSED, 2015 At 3 external sites; 558 comparisons	96.4% (94.3-98.6)	96.5% (94.3%-98.6%)	96.4% (94.0%-98.5%)	
Cooper, 2017 300 pair-wise (60 cases [TMAs] by 5 pathologists)	91.3% (87.6-94.0)	85.4%	93.8%	
Skov, 2017 86 samples; 1 pathologist				R^2 0.95 (scoring <1, ≥1, ≥5, ≥10, and 10% increments)
Intra-observer: 1% threshold				
Cooper, 2017 300 pair-wise (60 cases [TMAs] by 5 pathologists)	89.7% (85.7-92.6)	86.7%	92.4%	
Skov, 2017 86 samples; 1 pathologist				R^2 0.95 (scoring <1, ≥1, ≥5, ≥10, and 10% increments)
Inter-site: 50% threshold				
Roach 2016 36 specimens in 5 sets at 3 sites	88.3% (81.4-94.3)	85.2% (75.6-92.9)	90.3% (84.4-95.2)	

Study & Samples/Personnel	Overall percent agreement (OPA)	Positive percent agreement (PPA)	Negative percent agreement (NPA)	Other statistics
Adam, 2017 41 cases at 3 sites				Weighted kappa concordance at 1% and 50% cut-offs: 0.82-0.91 (highly concordant)
Scheel, 2017 21 cases (TMAs) at 10 sites				Kappas; ≥1% & ≥50%: 0.73-0.89 (all 4 assays examined; no sig diffs)
Inter-site: 1% threshold				
Adam, 2017 41 cases at 3 sites				Weighted kappa concordance at 1% and 50% cut-offs: 0.82-0.91 (highly concordant)
Scheel, 2017 21 cases (TMAs) at 10 sites				Kappas: ≥1% & ≥50%: 0.73-0.89 (all 4 assays examined; no sig diffs)

* Prevalence-adjusted bias-adjusted kappa (PABAK)

Robustness & stability

Roach et al.[72] performed several studies using the 22C3 pharmDx assay on NSCLC specimens to examine robustness and stability, with brief methods and findings listed below within Table 12, which also outlines the required parameters to study. Half of the required parameters were adequately studied and results will be reflected on assay instructions available to laboratories. Data on variability from type of fixation, specimen collection variables, and environmental conditions were not generated. Further, ischemia was tested in human placenta blocks but the potential differences between this tissue and tumor tissue were not described. Because these studies focused on the 50% PD-L1 threshold, results for a 1% threshold may not be equivalent.

Table 12. Robustness and stability studies on 22C3 PharmDx conducted by Dako

Required parameters to study	Dako 22C3 PharmDx brief method and results
Robustness: tissue thickness	Tested 2-6µm slides • 2µm slides not equivalent staining
Robustness: antigen retrieval solution (pH, timing, temp)	Tested solution time (18-22 mins), temp (95-99^{0}C), pH (5.8-6.4), 3 re-uses, 3 lots • pH <5.9 gave erroneous results and no other differences
Robustness: pre-analytic delays (fixation times)	Fixation times: n=11 blocks fixation times 3-168 hrs • No systematic differences but ≤ 3 hrs may be incompatible with robustness and reproducibility
Robustness: type of fixation (for each of biopsy, resection, cytology, as used)	Not reported

Required parameters to study	Dako 22C3 PharmDx brief method and results
Robustness: specimen collection variables	Not reported
Robustness: ischemia	Ischemia time: 216 human placenta blocks • 0-24 hrs similar
Robustness: environmental conditions	Not reported
Stability: storage time and conditions for blocks, sections, and assay	Blocks (44 blocks with 37 PD-L1- and 7 PD-L1+), sections, and assays (3 lots with 6 blocks [3 PD-L1+ and 3 PD-L1-]); • Sections should be stained within 6 months of sectioning • Blocks can be stored up to 5 yrs • Assay: total and finished good shelf-life 9 mos at 2-8^{0}C; in-use/on-board stability 18 cycles at room temp.; DAB Substrate-Chromogen solution 5 days at 2-8^{0}C; target retrieval system 5 days at room temp with up to 3 uses

Other parameters

Intra-block and intra-case heterogeneity

Using the first and fiftieth slides in 20 NSCLC blocks (5 PD-L1 positive), there was 100% diagnostic (< vs. ≥50% PD-L1) concordance in scoring.[72] The same results were achieved by these authors when comparing scoring in 2-5 blocks for 20 patients (2 PD-L1 positive). Results of Skov et al.[90] were different, with 25% of 87 histology sections being categorized as heterogeneous (intra-block), as defined by having one or more obvious areas with a majority of negative cells and a separate area with a majority of positive cells. It is not clear to what degree this definition of heterogeneity would impact diagnostic concordance, although other literature (not using 22C3 clone) has cited heterogeneity as an issue with PD-L1 IHC.[126,127]

Results of other studies may help explain the discrepancy. Roach et al.[72] compared staining in 23 pairs of primary and metastatic tumors and found that 20 of 23 were diagnostically concordant (at 50% threshold). Mansfield et al.[63] compared IHC results (clone E1L3N using Leica Bond RX stainer) between pairs of multifocal tumor samples in 32 patients. Tumors underwent mate pair next-generation sequencing to determine whether they were independent primary tumors or related/intrapulmonary metastases. The authors found that PD-L1 expression (5% threshold) on tumor cells had poor concordance (k=0.31) in the independent tumors (n=23 pairs), but high concordance (k=0.73) in the related tumors (n=9 pairs). In these studies, the sample sizes were small, and the intra-observer concordance for Mansfield's assay was not examined. However, the findings suggest that heterogeneity is complex and may be most

relevant when patients have multiple primary tumors. A single biopsy in patients with multifocal lung cancer may not accurately capture PD-L1 expression status.

When results from the 22C3 CTA were compared based on tumor sample type (1727 primary vs. 1281 metastatic) of patients screened for enrollment in KEYNOTE 001, 010, and 024, similar numbers of each sample type were positive at three categories <1% (35% vs 35%), 1-49% (40% vs 36%), and ≥50% (25% vs 29%).[40] However, these findings may not be reliable for representing heterogeneity within any given patient having multiple tumors.

Sample type—resection vs. biopsy vs cytology

The current clinical data for PD-L1 testing has relied on tissue samples acquired via resection or biopsy. This has important implications because of refinement to minimally invasive procedures that allow for diagnosis (in one-third to one-half of patients)[128] to be made based on cytological material. In Alberta, approximately 15-20% of advanced NSCLC patients do not have a tissue sample for PD-L1 testing (Personal communication from Dr. Randeep Sangha, August 2017).

Two full publications[67,90] and four abstracts[53,58,60,61] (all published in 2017) reporting on four studies were included; all used the IHC 22C3 pharmDx assay. In Skov et al.[90], one experienced pathologist scored 86 pairs of histology (31% biopsies) and cytology (57% computed tomography fine-needle aspiration [CT FNA], 22% FNA, 17.4% EBUS or endoscopic ultrasound-guided fine-needle aspiration, 3.5% pleura effusion) samples taken from the same lesion within 6 weeks of each other. At the ≥1% and ≥50% thresholds, samples were positive in 47% (95% CI 36-57) and 13% (95% CI 7-21) of cases for histology compared with 43% (95% CI 33-54) and 19% (95% CI 12-28) of cases for cytology. Considering the width of the CIs and the fact that data are correlated there was no relevant difference. OA, PPA, NPA between sample types at the 1% PD-L1 cut-point were 85% (95% CI 76-91), 80% (95% CI 70-87), and 89% (81-94) and at the 50% cut-point were 94% (95% CI 87-98), 100% (95% CI 96-100), and 93% (95% CI 86-97). The authors noted that the correlations did not change by exclusion of the cytology cell blocks containing <100 cells, and that there was no bias towards lower prevalence of positivity with cytology than with histology. Rangachari et al.[67] studied samples from 71 patients (resections n=21, small biopsies n=25, FNA cell block n=16, and pleural effusion cell block n=9) and found no statistically significant difference (p=0.778) between the surgical specimens versus the other samples in the proportion of reaching the ≥50% cut-point.

Grange et al.[53] retrospectively compared PD-L1 expression in core needle biopsy then subsequent resection specimens in 28 patients. At the 50% PD-L1 cut-off, 5 of 28 core biopsy samples were positive and 4 of 28 tissue samples were positive; there was concordance in 96.4% cases and the kappa coefficient was 0.87 (95% CI 0.61-1.00).

Three abstracts[58,60,61] reported on a retrospective feasibility study comparing 200 samples based on cytology (n=37 all cell blocks of ≥100 viable cells), small biopsy (n=80), and resection (n=83) from 183 patients with NSCLC at lung (n=129), regional lymph nodes (n=17), pleura/pericardium (n=15), distant metastases (n=28), and other sites (n=11). Prevalence of PD-L1 at 1% in cytology was 38%, in resection 22%, and in small biopsies 25%.[58] In the pleural (n=10) or pericardial (n=2) effusions, prevalence of 1% PD-L1 was 67%,[60] and in endobronchial ultrasound-guided fine-needle aspiration or transbronchial needle aspiration (EBUS-TBNA) samples there was 46% prevalence.[61] Samples had insufficient cellularity in 8 (4%) cases (1 resection, 2 cytology, 5 other small biopsies). Because of the descriptive nature of this study, without any within-patient sample comparisons, no conclusions can be drawn except that testing in these samples seems feasible.

Sample type—timing (e.g. archival vs. fresh with no intervening treatment)

This parameter looks at whether the PD-L1 expression level used to make treatment decisions actually reflects the current state of the tumor. When sufficient time has elapsed since the sample was obtained, a change in the patient's disease stage or the treatments they receive may affect their PD-L1 status and possibly their benefit with the PD-L1 inhibitor. The parameter is important when considering all samples currently tested for treatment decisions in Alberta are original diagnostic samples (Personal communication: Robin Stocks and Gilbert Bigras, Edmonton IHC Lab, August 2017).

Six studies reporting on prevalence or other outcomes in relation to samples differing by treatment history, stage of disease, or elapsed time were examined. Four studies used the Dako 22C3 pharmDx assay,[40,62,67,92] and two[59,81] used an earlier version of the assay, but employed scoring that has been found to have high concordance (0.89) with the 1-49% and ≥50% thresholds of the pharmDx assay. In advanced stage NSCLC patients enrolled in KEYNOTE 010 based on archival (n=456) or new (n=578) tumor samples, prevalence of PD-L1 ≥50% was not significantly different between sample types (40% vs. 45%, respectively).[92] Similarly, the prevalence of samples at ≥50%, 1-49%, and ≥1% in patients screened for enrollment in

KEYNOTE 001, 010, and 024 were similar in archival (n=2351; 31%, 42%, 27%) and fresh samples (35%, 48%, 17%).[40] In these studies, the intervening treatment in the archival samples was often platinum-based chemotherapy. Differences in prevalence based on previous treatment for advanced stage disease in these same patients was also examined, with 35%, 38%, 27% (treatment naïve) and 31%, 40%, and 30% (previously treated) of samples at ≥50%, 1-49%, and ≥1% PD-L1 expression, respectively.[40] Although major differences do not appear to exist, a trend towards higher PD-L1 expression in fresh samples after patients receive chemotherapy for advanced disease was noted. Findings were different when looking at PD-L1 prevalence in resections of 185 early stage NSCLC tumors based on whether or not patients had received neoadjuvant chemotherapy. Lin et al.[62] found a large difference of 88.9% versus 33.0% in PD-L1 positivity (p=0.009 using multivariate analysis).

Three studies reported on associations between PD-L1 status and either stage of disease or elapsing time. Kim et al.[59] studied PD-L1 expression in 90 paired samples (83% stage I-IIIA at baseline) with a median interval between samples of 20.9 months (91% >3 mos). At the second time point, scores were identical, higher or lower in 39%, 32%, and 29% of paired samples, respectively. Using a ≥1% cut-off, 12% of PD-L1 negative cases became positive and 20% of PD-L1 positive cases became negative. The overall concordance was 56% (95% CI 46-67) when PD-L1 expression was categorized as strong (≥50%) or weak positive (1-49%) or negative (<1%). In 1070 surgically resected NSCLC tumors of various stages (6.1% stages IIIB/IV), there was a progressive increase in PD-L1 expression with higher stage (at ≥1% and ≥50% PD-L1 cut-offs: stage I 33.8% and 3.7%, II 49.6% and 6.7%, IIIA 55.2% and 10.5%, IIIB/IV 76.9% and 13.9%).[81] After controlling for age, sex, smoking status, and histologic type through multivariate logistic regressions, advanced stage remained significant for PD-L1 positivity (IIIb/IV vs I-IIIa: adjusted OR 5.49, 95% CI 2.99-10.05). In contrast, in another study expression of PD-L1 at the 50% cut-off was not different in 71 samples based on disease stage (38.4% in I-III vs. 43.2% in IV/recurrent); however, this analysis did not account for multiple confounding factors.[67] Higher PD-L1 positivity with late versus early stages (perhaps more so than smaller increments of for example stage IIIb vs IV) agrees with the three systematic reviews cited earlier looking at prognosis of PD-L1 across stages of NSCLC.[111,112,114]

Analytical validity for laboratory developed tests (LDTs) using the 22C3 antibody

Four harmonization studies (i.e., calibrating alternative staining and detection protocols, using combinations of antibody clones and detection systems, to those previously validated) evaluated LDTs using the 22C3 antibody. Three were funded by one or more pharmaceutical companies. Adam et al.[39] developed LDTs for the 22C3 antibody on Ventana Benchmark Ultra and Leica Bond platforms (2 protocols for each) based on tonsil tissue staining and reference pictures from assays staining. For each protocol, each of 41 cases was scored by one of seven pathologists from different centres who were blinded to antibody and platform. Concordance of the LDTs with Dako 22C3 (not reported whether FDA-validated PharmDx version) was variable and better with the Ventana platform (2 LDTs with 0.81 and 0.77 weighted kappa coefficients) than with the Leica (0.50 and 0.62) (coefficients of ≥0.75 were defined as sufficient). The authors noted that results need to be validated on a larger sample and by external quality assessment programs in France.

Neuman et al.[64] calibrated 22C3 staining on the Ventana Benchmark XT platform using two detection systems (Ultraview and Optiview) and stained samples from 41 randomly selected NSCLC cases. Scoring was conducted independently by two pathologists. Scores were compared with the Dako 22C3 PharmDx using two sets of (identical) scoring by a Dako study pathologist as the standard. Dako and Ventana reagents were not modified but calibration was undertaken using normal tonsil tissue; slides from the calibration were used as on-slide controls for each case. The harmonization protocols are available as supplementary files. In total, 66 different protocols were reviewed. Classifying results as strongly positive (≥50%), weakly positive (1-49%), and negative (<1%) for PD-L1, the Ultraview protocol was similar in 87.8% of cases and the Optiview was similar in 85.3%. All strongly positive cases were similar.

Roge et al.[73] developed automated staining protocols for 22C3 staining on Dako Omnis, Ventana Ultra Benchmark, and Leica Bond III on tissue microarrays consisting of NSCLC (n=19) and different normal tissues (n=25; to avoid non-specific staining). Optimized protocols selected by a panel of pathologists and formalin-fixed tissue from 77 NSCLC cases were used for validation based on consensus by three pathologists. Cases were grouped according to 1% and 50% thresholds. Compared with the Dako PharmDx, 37% had lower scores with Leica, 29% had lower scores with Dako Omnis, and 8% had lower and 8% had higher scores with Ventana

Ultra protocols. Average % PD-L1 scores were close (within 2-4%) although varied the most for the Leica LDT. Categorization into thresholds was almost identical between LDTs and the Dako (19% at ≥50% and 32% 1-49%). The authors noted a darker chromogen on the Dako assay and that more macrophages and lymphocytes were stained using the Ventana protocol. Because of the consensus procedure, with all four cores viewed simultaneously, evaluation of inter-observer variation is still necessary.

Finally, Ilie et al.[89] evaluated several technical conditions for LDTs in tonsil specimens and a training set of three NSCLC samples. Optimized protocols were then validated in 120 NSCLC specimens with independent and blind scoring at one site by three pathologists trained using the Dako PharmDx 22C3 kit and Autostainer 49 platform. When using the Leica Bond autostainer, high concentrations of the 22C3 antibody were required and the LDT was not assessed further due to financial feasibility. To complement the manual scoring, automated densitometry measurements of immunoprecipitates in scanned whole slides were made that allowed for tissue recognition in order to analyze only the epithelial component (membranous/cytoplasmic). This method was used for some but not all of the 120 validation samples. Concordance between the 2 LDTs (22C3 antibody on Dako Autostainer 48 and Ventana Benchmark Ultra) and the Dako PharmDx kit on the Dako Autostainer 48 were 100% at both 1% and 50% thresholds. Raw scores were similar except for one case using the Ventana protocol. Inter-pathologist agreement was perfect (kappa = 1) for both LDTs at 1% PD-L1, and excellent (k=1 for Ventana and 0.99 for Dako) for 50% thresholds.

In summary, LDTs using the 22C3 antibody on either the Dako Autostainer 48 or the Ventana Benchmark or Ultra platforms appear to be promising for attaining high agreement with the Dako 22C3 PharmDx test, particularly when scoring is dichotomized into thresholds currently used to guide treatment. The best results occurred with highly trained pathologists at one centre, when using automated measurements for many of the readings.[89] Inter-site agreement is largely unknown.

4.4.6. Patient experiences of PD-L1 testing

No study or data were found on patient reports of experience with PD-L1 testing.

However, one study was considered relevant to the context of PD-L1 negative patients, for which there may be low probability of effect, yet some chance of a durable response. Shafrin et al.[101] conducted a survey to compare preferences between patients with advanced stage

melanoma (n=81) or lung cancer (n=84) and oncologists (n=98), for treatments with a positive probability of durable but variable survival gains ("tail-of-the-curve" gains for some and shorter survival for others) relative to those with fixed survival gains. For lung cancer, 65.5% of patients preferred the therapy with a variable survival profile, compared with 40.8% of physicians (P<0.001). The variable survival profile was preferred by patients unless the treatment with fixed survival had 11.6 months longer mean survival for all patients (fixed). The fixed survival benefit only needed to be 1 extra month based on the oncologists' replies. (RCTs of chemotherapy plus supportive care versus best supportive care alone for metastatic NSCLC found a median of 1.5 month survival gain [6 vs 4.5 months]).[129] The authors concluded that value frameworks should incorporate this high value placed by patients on a chance for durable survival gains.

A systematic review on patient preferences for chemotherapy in NSCLC also provided some insight into patient preferences when considering between different medication regimes based on their toxicity profile. Blinman et al.[102] reported on results from three preference-based (trade-off) studies measuring the added duration of life expectancy that would be sufficient for undergoing chemotherapy with either "mild" ("well-tolerated") or "severe" ("possibly leading to hospitalization and rarely death") toxicity in metastatic NSCLC. The median benefit required for chemotherapy with mild toxicity was 6 months, while that for chemotherapy with severe toxicity was 12 months. These findings support the idea that harms from treatment are very important considerations when patients choose treatments in NSCLC. The review authors also concluded that treatments with small benefits in the context of short life expectancy may be more attractive to patients than their doctors expect. Considering that many fewer patients (about half) experienced grade 3 or higher TRAEs when taking pembrolizumab than the comparators in first- and second-line treatment, a small or even equivalent gain in survival may be meaningful for these patients.

Input from 17 patients and 10 caregivers with experience with pembrolizumab was described in the submission for second-line treatment to CADTH from Lung Cancer Canada.[16] Data collection was either through phone interviews (n=5) or a scan of online forums or blogs. Patients reported improved symptom burden, better quality-of-life, ability to return to normal activities, and fewer side effects with pembrolizumab. The Committee agreed that pembrolizumab was better tolerated, had fewer side effects, and required shorter infusion times compared with docetaxel. Pembrolizumab appeared to align well with patient expectations. For

the submission for first-line treatment with pembrolizumab, the above input was supplemented with data from interviews (n=3) or online forums (n=3) from patients with first-line experience.[17] Similar findings were noted, with emphasis on durable responses, and no to mild side effects that were easily managed and allowed many to leave the hospital right after infusions by themselves. None of the input from patients was specific to testing for PD-L1 status, particularly on the views of patients who are either negative or who do not have evaluable tumors. The advocacy group Lung Cancer Canada commented on prolonged wait times for PD-L1 testing in some cases and emphasized the need to not keep patients waiting. CADTH has since updated its template for patient advocacy group input, to ask about experiences with and perspectives on companion diagnostic tests.

4.4.7. Economic evaluations on PD-L1 testing for pembrolizumab

Economic evaluations of pembolizumab or other PD-L1/1 inhibitors where patients were selected by PD-L1 status were included. Tables C5 and C6 contain the characteristics of the economic evaluations and an assessment of their reporting quality based on the CHEERS checklist[27], respectively. One evaluation examined first-line, and four examined second- or beyond-line treatment. The two performed for submissions to pCODR for first- and second/beyond-line treatment of pembrolizumab were from the Canadian heath care perspective. One on pembrolizumab for second/beyond-line, and another for pembrolizumab, nivolumab, and atezolizumab for second/beyond-line, were from the perspective of US third-party payer perspective. Another on nivolumab based on PD-L1 expression levels for non-squamous NSCLC was from the Swiss health care system perspective. Only two provided cost-utility results based on different PD-L1 expression levels,[16,103] although results of one in second/beyond-line therapy that only considered patients with PD-L1 ≥50%[104] can be indirectly compared with those reporting on the ≥1% PD-L1 expression level. All of the economic analyses for pembrolizumab used the same utilities for both treatment arms.

Reporting quality varied between the pCODR reports—both with 11, 8, and 3 of 24 criteria fully, partially, or not met, respectively, and 2 not applicable—because the reports made publically available are summaries. The published evaluations were well reported, with between 19 and 23 criteria fully met and all but 1 of the remainder partially met.

First-Line

Merck submitted an economic analysis to pCODR comparing pembrolizumab with platinum-based doublets for patients with previously untreated metastatic NSCLC whose tumors express PD-L1 at 50% or greater.[17] The technical details of the model and all assumptions are not available, except that a three health state (progression free, progressive disease, death) partitioned-survival model was employed with a 10-year time horizon. Survival data from 11.2 months follow up in the trial was supplemented with SEER (Surveillance, Epidemiology and End Results Program of U.S. National Cancer Institute) data from 5.5 years onward. Utility values from Keynote 024 data were used. This data was pooled for both treatment arms, which was considered conservative because of the lower rates of TRAEs in the pembrolizumab arm. Little information is available on costs apart from drug costs and mention of accounting for adverse effects. Submitted estimates for life years gained, quality-adjusted life years (QALYs), and costs were 1.23, 0.99, and $98,298, respectively. The incremental cost-effectiveness ratio (ICER) was $99,392/QALY. Reanalysis by the Economic Guidance Panel (EGP) resulted in lower and upper bound ICERs of $111,769 and $154,273, neither of which were considered cost-effective. Major considerations in the reanalysis were (i) changing the number of patients without progression at 5 years to close to none, (ii) modification to long-term survival based on the assumption that SEER data may overestimate survival especially because EGFR+ and ALK+ patients (who tend to live longer) are included in the SEER database, and (iii) applying a gradually reducing treatment effect to reach a hazard ratio of 1 at 260 weeks as a best estimate (reducing QALYs to 0.76). No details about PD-L1 testing costs or otherwise were noted. Additional considerations that may influence the findings are the recommendations by pCODR that clinical judgement be used for deciding to treat patients with worse performance scores or stage IIIb rather than IV who were not eligible for the trial but may derive benefit. Moreover, the fixed-dose of 200 mg was applied in all cases even though some patients (especially if lighter in weight) may benefit from the 2 mg/kg dose a used for second-line treatment.

Second-Line or Beyond

The analysis submitted to pCODR for second-line treatment with pembrolizumab versus docetaxel in patients expressing PD-L1 (≥1%) used a similar model to that for first-line treatment (partitioned-survival, 10-year time horizon, government perspective). However, there is mention that PD-L1 testing was assumed for all patients in the pembrolizumab arm, the treatment effect

for docetaxel in PD-L1 negative and PD-L1 undetermined patients was assumed to be similar, and that a small portion of the patients would need to be re-biopsied.[16] Submitted estimates for life years gained, QALYs, and costs were 0.75, 0.53, and $76,742, respectively, and the ICER was $143,730/QALY. Reanalysis by the EGP resulted in lower and upper bound ICERs of $149,342 and $254,945, neither of which were considered cost-effective. A major revision was the use of a 5-year versus the submitted 10-year time horizon for this patient population; a 100-week treatment effect cap was also used. A one-way sensitivity analysis was conducted using the treatment effects of patients with PD-L1 ≥50%, and the difference was minimal ($185/QALY lower) because of increased treatment costs (longer duration) as well as benefits. It was noted that the costs did not include drug wastage due to having one vial size available (50 mg), because vial sharing could be possible.

Aguiar et al.[103] conducted a cost-effectiveness analysis for pembrolizumab, nivolumab and atezolizumab based on whether or not PD-L1 data were used (nivolumab and atezolizumab only) and using differing PD-L1 cut-offs (all three drugs). A three-health state decision-analytical model was developed. Data from area under curves for PFS and overall survival in the trials and follow-up reports were used to provide estimates for their 5-year time horizon. Duration of treatment values were taken from the median number of cycles in the trial reports. The same utility data, based on studies of docetaxel using EQ-5D data, were used for both immunotherapy and docetaxel arms; disutilities were applied for TRAEs. For pembrolizumab, base case scenario figures for QALYs, costs, and ICERs for ≥ 1% PD-L1 were 0.346, $34,019, $98,421/QALY and for ≥ 50% PD-L1 were 0.409, not reported, $83,176/QALY. It appears that the authors used the same treatment duration (and hence costs) of 9 cycles for both PD-L1 populations, rather than adjusting treatment duration downwards for PD-L1 1%, as was used for the pCODR sensitivity analysis which found a much smaller difference in ICER between groups. Overall survival duration and body weight (for calculating dose) had the largest impact on the ICERs. The ICERs from this group were considerably lower than those calculated by Merck and the pCODR EGP. This appears to be largely due to the lower number of life years gained although data on unit costs and valuation in the pCODR reports are largely unavailable for comparison.

A third economic evaluation of pembrolizumab (for ≥50% PD-L1) used a partitioned survival model, valuing outcomes using a five-category time-to-death approach and based on a 20-year time horizon (base case projecting 0.7% alive at 20 years).[104] Price of PD-L1 testing was

included at $US209, although this was assumed to be for patients in the intervention group rather than all people that would receive testing to determine eligibility. Treatment duration was assumed to last for up to 2 years and the authors used time-on-treatment data from the Keynote 10 trial. Utilities and disutilities were based on trial data (for benefits) and literature sources (for TRAEs), respectively. The authors calculated an ICER of $168,619, although only 80% of the costs were included because of the Unites States payer perspective. The largest contributors to uncertainty were related to extrapolation of overall survival duration and time-on-treatment inputs.

Two evaluations studied the cost-effectiveness of nivolumab based on PD-L1 expression.[103,105] One included the cost of PD-L1 testing at CHF 136 (178CAN). Not testing for nivolumab treatment for non-squamous NSCLC resulted in a large decrease in cost-effectiveness ($50-70,000/ICER higher) than when using PD-L1 at a 1%, 5% or 10% threshold for treatment decisions. The large range may have been in part due to a more similar treatment duration/costs between groups treated with nivolumab (patients could be treated beyond progression) and a substantially lower benefit (due to fast disease progression) in the PD-L1 <1% groups. Further details for both of these analyses are included in Table C5.

Two additional economic evaluations for nivolumab were not included because they only examined patients unselected by PD-L1 status.[130,131] The economic analysis submitted to pCODR for nivolumab did not examine PD-L1 expression levels either.[18]

4.4.8. Budget impact of PD-L1 testing in Alberta

Over several months during 2017, an average of 136 NSCLC cases were tested for PD-L1 expression each month in Alberta (Personal communication: Robin Stocks, Manager of Edmonton IHC Lab). Micro-costing by Alberta Health Services Laboratory Services when using the Dako PharmDx 22C3 assay resulted in a calculated average cost per case of $328, of which $74 is for the kit cost (on each of 2 slides [1 test and 1 negative] per patient and one control per batch) and the remainder is for laboratory personnel time, pathologist interpretation (10 min per slide), and overhead (25%) (**Appendix D**). Based on these numbers, the total cost per month for Alberta is expected to be $44,608, resulting in an annual cost of $535,296. Estimates provided by the Provincial Lung Cancer Team were that testing would be required for about 450-500 patients per year (advanced NSCLC patients), and although some patients may require more than one test, the majority will not. A lower estimate may be closer to $147,600 per year if the 450

number is more accurate than 136 per month (1,632 per year). Moreover, the 450-500 patient estimate does not account for the possibility of eliminating sample testing for those patients otherwise ineligible for pembrolizumab treatment based on targetable mutations (e.g., EGFR mutations for first-line) or contraindications (e.g., active brain metastases, poor performance status, some autoimmune conditions). These estimates do not include the possibility of re-testing with a fresh sample, if for example, PD-L1 expression may be thought to increase after one line of immunotherapy (e.g., nivolumab) fails and treatment with pembrolizumab is re-considered. No data on changes to PD-L1 expression after anti-PD1/PD-L therapy were found.

An LDT using the 22C3 antibody clone on the Ventana platform is being studied by a pan-Canadian research alliance, and if this proves to have technical equivalence to the validated Dako assay, it may offer a feasible, less costly alternative. Considering that the LDT will only be using the 22C3 antibody clone, its main benefit would be cost savings, rather than an ability to test for other PD-1/PD-L1 inhibitors, which use other clones. The savings are estimated to be $65 per case (total cost per case $260 instead of $325). Results from these studies have yet to be released, although other studies as described in the section on Analytical Validity show some promise for at least good within-site performance for LDTs. Further, the costs used for research and innovation when developing the LDT have not been accounted for when estimating savings.

4.4.9. Social, ethical, legal, and policy considerations

There exist several value frameworks for cancer treatment, although it is well recognized by many stakeholder groups that an era has been reached where cancer immunotherapies need a distinct value proposition.[132] Proponents for modifying value frameworks suggest more emphasis be placed on, for example, the highly durable responses (sustained off-treatment) seen in select patients; the manageable toxicities that together may greatly enhance a patients' quality of life, as well as that of their family and community; and the value of hope in the potential for a cure. These factors align well with the evidence reviewed on patient perspectives on lung cancer treatments, whereby chances for "tail of the curve" responses[101] and reduced toxicities[102] were reported to offer substantial value. Biomarkers to select patients expected to receive the most benefit may greatly advance the clinical and societal benefit, although the hope for durable benefit and the reduced harm for patients without evaluable tumors or with negative results cannot be ignored, particularly when no treatment alternatives are available. However, the studies reviewed that described patient treatment decisions appear to indicate perceptions of

higher absolute benefits from treatment (e.g., mild chemotherapy should prolong life approximately 6 months)[102] than can be achieved for many patients. A suggested meaningful overall survival benefit of 2.5-4 months for NSCLC[133] may not meet many patient's expectations.

The impacts from these considerations will be larger for first-line versus second-line care because of larger expectations of benefit in first-line settings and lack of treatment alternatives, such as targeted TKI therapies, for many. The availability of nivolumab as an option for second-line treatment, regardless of PD-L1 expression level, greatly reduces uncertainty that patients can receive care that may offer value. Without direct evidence on comparative efficacy between the drugs, the main benefit for choosing pembrolizumab over nivolumab treatment appears to be the convenience of use and potential healthcare cost savings related to the lower infusion times and frequency of pembrolizumab administration (e.g., 1-hour treatment every 2 weeks with nivolumab instead of 3-6 hours every 3 weeks with pembrolizumab). Although cost of administration would be incorporated into any economic model, the value of convenience was not chosen by the pCODR Economic Guidance Panel for use in the cost-effectiveness evaluation. The pCODR report also noted that the potential for drug wastage (due to single vial size for pembrolizumab) and impact on pharmacy resources (shorter stability of the product with single use vials requiring reconstitution and weight-based doing) were constraints for pembrolizumab.[16] Further, the cost-effectiveness was greater for nivolumab (ICER lower and upper bound range $183,000-236,000/QALY vs. $149000-255,000/QALY for pembrolizumab).[18]

Apart from gains to society from the few patients who gain long survival durations, additional societal and ethical considerations exist when determining who should receive treatment with immunotherapies. Novel drug discoveries are soaring and the economic sustainability of this trend needs close attention. The prevalence of certain cancers may have considerable influence on sustainability, while also influencing equitable access to treatment across all types of cancer. Analyzing the population-level costs incurred based on type of cancer and World Health Organization projections for new cases in 2012, worldwide 1-year costs for pembrolizumab in NSCLC (in PD-L1 positive patients) were $83.9 billion compared with $3.8 billion for melanoma.[134] Further, WHO projections for 2030 show larger increases for NSCLC (57%) than for melanoma (39%) in Canada (http://globocan.iarc.fr/Pages/burden_sel.aspx).

A key policy consideration is that regulatory approval of drugs relies on efficacy and safety of the drug for the patient population reflected in the data submitted by the sponsor. There is currently no requirement for demonstrating lack of benefit in certain patient populations that may theoretically benefit, and the label of requirement for a CDx can therefore rely on lack of, rather than supporting, evidence between subgroups of patients. In the case of pembrolizumab, approval has not been granted for patients whose tumors express <1% PD-L1 in the second-line, or <50% in the first-line settings. Regardless of the (very low) strength of evidence about clinical utility from the PD-L1 test for these thresholds, these restrictions are currently in place. Moreover, reimbursement decisions for the drug across Canada are not currently using the criteria of the CDx's predictive ability as a criterion. Decisions to fund the CDx will be restrained by these considerations because lack of reimbursement will place the onus on the patient to pay for a test (if even feasible) to determine eligibility for what is an approved treatment.

4.4.10. Considerations about inappropriate use of PD-L1 testing

Currently, PD-L1 testing is being performed for all advanced-stage NSCLC patients. Because EGFR status, as well as some other criteria such as severe immune disorders, limit eligibility for first-line treatment with pembrolizumab, there may need to be consideration for restricting or delaying testing for some patients. Findings from this review related to the influence of treatment on PD-L1 status (i.e., fresh vs archival samples) were mostly applicable to chemotherapy rather than TKI therapy, such that it is uncertain if there will be changes to PD-L1 status of a patient after treatment in the first-line setting by TKIs. If diagnosed at an earlier stage of disease, evidence indicates that the PD-L1 expression level in the sample may differ from that existing in the tumor at a later stage, especially if neoadjuvant chemotherapy was received. Moreover, there was no evidence reviewed on whether or not PD-L1 expression changes after immunotherapy treatment. Therefore, the usefulness of re-testing a patient (should a new tissue sample be possible) for PD-L1 after TKI treatment in the first-line setting, or after nivolumab treatment (in case they may be now eligible for pembrolizumab as a third-line), is not known. Should multiple sites perform PD-L1 testing in the province, there would be a concern that patients may seek testing at the alternative location should their first result be negative.

PD-L1 testing for other cancers is not expected to occur at the present time or in the immediate future. Should other drugs be approved with this CDx, or should multiple treatment

alternatives become available whereby PD-L1 testing may help determine preference among alternatives, the situation would change. Future evidence of success for survival from first-line pembrolizumab regardless of PD-L1 status, as being investigated, may greatly reduce the impact.

4.4.11. Impact of policy decision on resources

A policy decision to fund PD-L1 testing could greatly impact the ability of AHS laboratory services to provide diagnostic testing for other patients. Although the laboratory has the capacity in terms of personnel and the equipment necessary to undertake the testing volume, its current budget does not include the high costs for this test.

4.4.12. Policy questions

Potential policy options proposed during the initial planning for this project included:

i. Provide to all patients with a particular disease
ii. Provide to a subgroup of patients with a particular disease who meet certain eligibility criteria
iii. Provide for an interim period while additional evidence is collected
iv. Do not provide

Reviewing and making funding decisions for the CDx, based on emerging standards for clinical utility of CDx-drug pairs, without similar criteria used in the regulatory or drug funding arenas has limitations. The option to not provide the CDx positions the patient with the only alternative to pay for their own test, which may not be a realistic option (e.g., no access to private testing). One province's decision may set a benchmark against which other provinces decisions are compared, particularly by patients, which could lead to perceived inequities and legal implications. The options (i) and (ii) which fund the test unconditionally are not supported by high confidence in the evidence on clinical utility and analytical validity, or differences between cost-effectiveness for differing PD-L1 threshold levels. Setting a precedent by accepting low evidence standards may be difficult to overcome particularly once choosing between CDx alternatives becomes necessary. The other option (iii) of funding with research/evidence development (on survival, TRAEs and costs for PD-L1<1% expressors in especially first-line treatment) appears most suitable.

The appropriate use of PD-L1 testing in Alberta, while developing a better evidence base on which to base decisions, appears to be for patients with advanced stage NSCLC who are otherwise eligible for first-line pembrolizumab (e.g., no EGFR mutation, poor performance

score, not seriously immunocompromised). Evidence is quite strong that PD-L1 expression varies by stage of disease, and may change after radiation or neoadjuvant chemotherapy, therefore results from testing diagnostic or surgical tumor samples from an earlier stage of disease are not likely to accurately reflect the PD-L1 status of the tumor at later stages. Therefore, exclusive testing of tissue samples in advanced stage disease should likely be implemented. Because chemotherapy for advanced stage does not appear to change PD-L1 status, PD-L1 expression results (<50%) in patients with advanced stage disease who were not eligible for first-line pembrolizumab can probably be used for determining second-line eligibility. Since a trend towards higher PD-L1 expression in fresh samples after patients receive chemotherapy for advanced disease was noted, patients with previous negative samples may benefit from re-testing should a fresh sample be feasible and acceptable for the patient. Ongoing surveillance of the (promising) evidence for using cytology samples should be undertaken.

4.5. Discussion

4.5.1. Summary of systematic review findings

The clinical utility of the currently available Dako PharmDx 22C3 assay for use with pembrolizumab was the primary focus of this assessment. In order to evaluate the clinical utility of PD-L1 testing for NSCLC in the absence of ideal trial designs, the systematic review assessed the effects of PD-L1 status when patients receive standard of care (to determine whether or not PD-L1 is prognostic for response regardless of pembrolizumab treatment) and also used an approach incorporating linked (marker-enriched and single-arm trials with PD-L1 negative patients) as well as indirect (PD-L1 status in treatment with comparators to pembrolizumab) effects. Results on the clinical validity were also used to provide supporting information about clinical utility. Further, the degree of analytical validity was assessed to determine if the performance of the test as used in controlled trials will likely transfer well to routine clinical practice where pre-analytical (e.g., sampling criteria and protocols) and laboratory conditions (e.g., environment, number and training of pathologists) will likely differ. Results from the findings on analytical validity (based on timing and treatment history) also contributed to suggestions for appropriate testing for PPD-L1.

Prognosis from PD-L1 status: No definitive conclusions can be made about the prognostic role of PD-L1 in patients with advanced stage NSCLC receiving standard treatment. PD-L1

expression may have some prognostic role for response to some treatments other than anti-PD-1/PD-L1 inhibitors, but it appears to make little to no difference for response to chemotherapy. There was some confidence from findings of a negative prognostic role for PD-L1 (i.e., poorer response in higher PD-L1 expression levels) in chemoradiotherapy. The findings for chemotherapy suggest that results from standard-of-care arms in RCTs of immunotherapy (regardless of PD-L1 expression level of participants) may be used to gain insight into clinical utility by way of indirect comparisons with results from single-arm or marker-enriched trials by PD-L1 status.

Clinical utility in first-line treatment: No studies were identified that directly examined the clinical utility of PD-L1 testing for treatment with pembrolizumab compared with standard of care in first-line treatment. ***Response rates***: Patients with tumor PD-L1 expression ≥50% appear to respond well (> 50% response) to pembrolizumab treatment. An RCT of adjuvant pembrolizumab indicated benefit in patients unselected for PD-L1 as well as those with <1% expression; nevertheless, findings of no significant benefit in response for categories of 1-49% and ≥1% PD-L1 limit any conclusions about the <50% groups. The single-arm trials reported conflicting results, with significantly higher response rates for the ≥50% versus <50% PD-L1 groups with pembrolizumab alone, compared with no difference in response in the trial of adjuvant pembrolizumab. Using a linked evidence approach comparing results from the single-arm trial of pembrolizumab alone and the chemotherapy arms in other trials, response in the <50% PD-L1 group was lower with pembrolizumab. Indirect evidence came from an RCT of nivolumab that found no differences in response between PD-L1 subgroups ≥5% and ≥50% PD-L1 (neither benefitting over chemotherapy). ***Progression-free and overall survival***: Patients with tumor PD-L1 expression ≥50% benefited in PFS and overall survival from pembrolizumab in the primary RCT (versus chemotherapy) and a single-arm trial. For patients with <1% PD-L1, there may be no difference in PFS or overall survival when indirectly compared with chemotherapy. For the 1-49% PD-L1 group, although PFS was not prolonged there may be some benefit in overall survival. Lack of support was found when looking at indirect evidence; no benefit was found for any PD-L1 subgroup in the RCT comparing nivolumab with chemotherapy. ***Harms***: There have been large risk reductions in grade 3+ TRAEs from pembrolizumab when compared with chemotherapy, although no direct comparisons between PD-L1 groups have been reported. ***Conclusions*:** Very low quality evidence exists for there being clinical utility for using PD-L1

50% as a threshold for treatment benefits between pembrolizumab and chemotherapy. This is due to serious concerns about indirectness (reliance on between-study comparisons), inconsistency (lack of support from studies of adjuvant pembrolizumab and other anti-PD1 comparators), and imprecision (very small sample sizes for <50% PD-L1 patient groups) when comparing <50% and ≥50% PD-L1 patient groups. Without direct evidence of lack of meaningful benefit from pembrolizumab versus chemotherapy in patients with <50% PD-L1, the fewer harms from this treatment over chemotherapy suggest a positive benefit-to-harm balance for patients regardless of PD-L1 status. Results are specific to patients without EGFR or ALK aberrations, and to fresh (after neoadjuvant or adjuvant therapy) sampling of tumors without recent irradiation.

Clinical utility in second- or beyond-line treatment: No direct evidence for PD-L1 positive (≥1%) versus negative (<1%) patients taking pembrolizumab compared with standard-of-care was found. The marker-enriched (≥1% PD-L1) RCT of pembrolizumab versus docetaxel, together with the single-arm trial of pembrolizumab, provided linked evidence on clinical utility. RCTs and single-arm trials of other PD-L or PD-L1 inhibitors were examined as indirect evidence. ***Response rates*****:** While patients as a whole (≥1% PD-L1) responded better with pembrolizumab in the RCT, the effects appear to be largely driven by patients having ≥50% PD-L1. In the few patients having <1% PD-L1 in the single-arm trial, ORR was very similar to that in all PD-L1 subgroups in the docetaxel arm of the RCT. Indirect evidence from marker-by-treatment interaction RCTs (in non-squamous and squamous NSCLC) of nivolumab versus docetaxel found significant interaction effects for response rates in comparisons at <1 vs ≥1% PD-L1 levels for patients with non-squamous NSCLC, and no benefit over docetaxel was found for the <1% PD-L1 sub-groups in either trial. Two RCTs of atezolizumab had similar findings, with no benefit in response for <1% or ≥1% PD-L1 groups and benefit in the larger trial for the ≥5% and ≥50% subgroups. ***Progression-free and overall survival***: In the marker-enriched RCT, pembrolizumab was favorable over docetaxel for PFS in patients with ≥50% PD-L1 but not in those with ≥1% expression. For overall and 18-month survival, patients in all PD-L1 positive subgroups (except for one small group at 25-49% PD-L1 having imprecise results) benefitted compared with the docetaxel groups, but post-hoc subgroup findings were significant for a difference between ≥50% and 1-49% PD-L1 groups. Findings appear credible in support of larger effects on survival for the ≥50% patient group, with absolute effects (approximately 1-2

months survival benefit) being minimal for the 1-49% group. Data on <1% PD-L1 patients for mean overall survival or PFS with pembrolizumab were not found, although 3–year survival in the single-arm trial indicated poorer benefit may exist for <1% versus ≥1% groups. Indirect evidence from trials of other PD-L and PD-L1 inhibitors suggest that patients with <1% PD-L1 levels may benefit for overall and 18-month survival. ***Harms:*** There have been large risk reductions for grade 3+ TRAEs from pembrolizumab when compared with docetaxel, although no direct comparisons between PD-L1 groups have been reported. ***Patient-reported outcomes***: Patients taking pembrolizumab may have less deterioration in their quality of life, and improvements in lung cancer symptoms, at least over the short-term. Some findings suggested more positive effects for those with ≥50% versus ≥1% PD-L1 expression. Risk of bias was high for these outcomes and they should be interpreted with caution. ***Conclusions:*** For clinical utility in terms of benefits from pembrolizumab using the current 1% PD-L1 threshold, there is very low quality evidence supporting a meaningful difference in effect between patients with <1% versus ≥1% PD-L1 expression. Findings for pembrolizumab treatment relied on data from a small sample of <1% patients in a single-arm trial, and use of indirect comparison with standard-of-care. No significant or meaningful differences for any outcome between subgroups have been demonstrated. There was lack of strong support from other treatment comparators, which showed inconsistent findings. Without direct evidence of lack of meaningful benefits from pembrolizumab versus chemotherapy in patients with <1% PD-L1, the fewer harms from this treatment over chemotherapy suggest a positive benefit-to-harm balance for patients regardless of PD-L1 status. Apart from PD-L1 status, other clinicopathologic features may influence the effectiveness of pembrolizumab treatment (i.e., greater effects seen for patients with wild-type EGRF status, non-squamous histology, larger tumors, and Asian race). Nevertheless, the degree to which these factors are correlated with PD-L1 status is not clear, and the lack of effect in such groups (particularly for squamous NSCLC for which nivolumab was beneficial) to demonstrate clinical utility has not been clearly demonstrated.

Clinical validity: In addition to the relative effects from pembrolizumab versus standard of care, clinical validity data from a single-arm trial of pembrolizumab provided further information about the possible clinical utility of PD-L1 testing for pembrolizumab. In first- and second-line treatment, PPVs were much lower than NPVs for both 50% and 1% thresholds. PD-L1 testing predicts much better who will not likely versus who will likely respond, and the PPV for the 50%

is not that much higher than it is for the 1% PD-L1 threshold. Based on guidance for interpreting positive and negative likelihood ratios, the test would not be considered clinically useful. **Analytical validity of Dako PharmDx 22C3:** ***Analytical sensitivity and specificity***: PD-L1 was visualized over a dynamic staining intensity range. In comparisons of scoring between multiple pathologists and a Dako pathologist, variability in scoring was high for 30-80% PD-L1 expression levels. There was a tendency to underestimate PD-L1 levels especially in situations of weak staining or concomitant cytoplasmic staining (which needs to be excluded in the scoring algorithm). In Dako laboratory studies, the assay detected purified PD-L1 protein and had low cross-reactivity to other proteins; background staining in all human tissues was <0.5 grade and expression patterns were consistent with reported literature (e.g., immune cells and cells of epithelial origin mostly). There was equivalent expression when assay results were compared with those from mRNA and flow cytometry analysis. ***Precision/repeatability & reproducibility***: High overall agreements were reported for within- and between-site precision and reproducibility tests undertaken at Dako, using the 50% threshold; slightly lower agreement was reported for intra-day precision. Intra-observer agreement appears to be higher than inter-observer agreement, especially as the number of observers rises; inter-observer agreement may be higher for the 50% threshold. ***Robustness and stability***: Half of the required parameters were adequately studied by the manufacturer, and results will be reflected on assay instructions available to laboratories. Data on variability from type of fixation, specimen collection variables, and environmental conditions were not reported. Further, ischemia was tested in human placenta blocks and the potential differences between this tissue and NSCLC tumor tissue were not described. Because these studies focused on the 50% PD-L1 threshold, results for a 1% threshold may not be equivalent. ***Intra-block and intra-case heterogeneity:*** Heterogeneity may not influence diagnostic concordance (at a 50% PD-L1 threshold) within the same tumor. Findings from a few studies suggest that heterogeneity is complex and may be most relevant when comparing multiple primary tumors. A single biopsy in patients with multifocal lung cancer may not accurately capture PD-L1 expression status. ***Sample type—resection vs. biopsy vs cytology***: In Alberta, approximately 15-20% of advanced NSCLC patients do not have a tissue sample for PD-L1 testing (resection or biopsy with adequate cellularity). Three studies have assessed agreement between histology (surgical specimens) and cytology specimens and found high agreements when using a 50% PD-L1 threshold. One study evaluated the 1% threshold and

found slightly lower agreement which was influenced by lower PPA. One group of authors noted that the correlations did not change by exclusion of the cytology cell blocks containing <100 cells (as currently required for tissue specimens), and that there was no bias towards lower prevalence of positivity with cytology than with histology. ***Sample type—timing (e.g. archival vs. fresh with no intervening treatment)***: All samples currently tested for treatment decisions in Alberta are original diagnostic samples. Six studies reporting on prevalence or other outcomes in relation to samples differing by treatment history, stage of disease, or elapsed time were examined. Although major differences do not appear to exist based on whether tissue is archival or new, or sampled before or after chemotherapy in advanced NSCLC, a trend towards higher PD-L1 expression in fresh samples after patients receive chemotherapy for advanced disease was noted. One study found a large difference in PD-L1 positivity between early stage resection specimens that had and had not received neoadjuvant chemotherapy. Progressively higher PD-L1 positivity was seen in late versus early stages of disease, which agreed with three systematic reviews examining prognosis of PD-L1 across stages of NSCLC. Using results from PD-L1 testing in early stage disease, especially if neoadjuvant chemotherapy was provided, may not reflect the status of the tumor in advanced NSCLC.

Without clinical validity or utility data from any other antibody clone, apart from 22C3, for pembrolizumab treatment, there would be great uncertainty in the effects on patients from using other clones, even if they are shown to have comparable analytical precision.

Laboratory-developed tests with 22C3 antibody: LDTs using the 22C3 antibody on either the Dako Autostainer 48 or the Ventana Benchmark or Ultra platforms appear to be promising for attaining high agreement with the Dako 22C3 PharmDx test, particularly when scoring is dichotomized into thresholds currently used to guide treatment. The best results occurred by highly trained pathologists at one centre, when using automated measurements for many of the readings. Inter-site agreement is largely unknown.

Patient experiences with PD-L1 testing: No study or data were found on patient reports of experience with PD-L1 testing, particularly on views of those who are either negative or who do not have evaluable tumors. Indirect evidence was found indicating that a majority of patients prefer a treatment with some probability of a durable but variable survival gain ("tail-of-the-curve" gains for some and shorter survival for others) to treatments with fixed (but not durable) survival gains for all. Moreover, in studies asking patients to trade-off added life expectancy

gains from chemotherapy having mild versus severe toxicity profiles, there was a large (6 months) difference in acceptable survival gains which suggests that patients' treatment choices are sensitive to the magnitude of harms. In submissions to pCODR from patient groups that conducted interviews or reviewed blogs, patients reported improved symptom burden, better quality-of-life, ability to return to normal activities, and fewer side effects with pembrolizumab. The input specific for the first-line treatment submission mentioned that favorability for the possibility of durable responses.

Cost-effectiveness of PD-L1 testing: Despite using similar short-term effectiveness data, results across cost-effectiveness evaluations differed in how the cost-utility varied based on PD-L1 status. A major factor contributing to the differences appears to be whether or not treatment duration inputs were shorter for those having lower (≥1%) versus higher (≥50%) PD-L1 expression. If in clinical practice patients are treated only until disease progression, it does not appear to be likely that there will be large differences between the cost-effectiveness between PD-L1 1% and 50% groups for second-line treatment, due to costs and benefits both changing in the same direction. This may also be true if patients with <1% PD-L1 were treated, if one assumed that many would not receive many cycles of treatment, that some would have a durable response, and several would have lower costs than from receiving chemotherapy related to serious TRAEs. All ICERs for pembrolizumab may have been overestimated, considering that similar utility values were used for both trial comparators. Considering the large differences between arms in TRAEs and patients' comments about meaningful differences in quality of life factors (e.g., side effects, fewer infusions), the utilities for pembrolizumab, especially during the progression-free period, may be higher than for the standard of care. Uncertainty exists in the expected duration of treatment benefit after discontinuation of the immunotherapies. No study incorporated a societal perspective incorporating effects such as productivity gains in patients or impacts on caregiver costs or quality of life.

4.5.2. Summary of other considerations

Budget impact of PD-L1 testing in Alberta: Based on an average of 136 cases tested per month during 2017 and micro-costing for the Dako PharmDx 22C3 assay, the total cost per month for Alberta is expected to be $44,608, resulting in an annual cost of $535,296. If realized, lower estimates of 450-500 advanced NSCLC patients per year may bring the value closer to $147,600 per year. These estimates do not include the possibility of re-testing with a fresh

sample, if for example, PD-L1 expression may be thought to increase after one line of immunotherapy (e.g., nivolumab) fails and treatment with pembrolizumab is re-considered. No data on changes to PD-L1 expression after anti-PD1/PD-L therapy were found. These estimates may change considerably if PD-L1 testing becomes indicated for treatment in other cancers, or if the indication changes based on findings from future studies of pembrolizumab in NSCLC.

Social, ethical, legal and policy considerations:

Proponents for modifying value frameworks for immunotherapies suggest more emphasis be placed on, for example, the highly durable responses (sustained off-treatment) seen in select patients; the manageable toxicities that together may greatly enhance a patients' quality of life, as well as that of their family and community; and the value of hope in the potential for a cure. A suggested meaningful overall survival benefit of 2.5-4 months for NSCLC, though, may not meet many patient's expectations.

The impacts from these considerations will be larger for first-line versus second-line care because of larger expectations of benefit in first-line settings and lack of treatment alternatives for many. The availability of nivolumab as an option for second-line treatment, regardless of PD-L1 expression level, greatly reduces uncertainty that patients can receive care that may offer value.

Due to its high prevalence, the large budget impact from treatment with expensive therapies for all patients with NSCLC may greatly influence equitable access to treatment across all types of cancer. For example, the population-level, worldwide 1-year costs incurred in 2012 for pembrolizumab in NSCLC (in PD-L1 positive patients) were $83.9 billion compared with $3.8 billion for melanoma.

Currently, the labelling requirement for a CDx in Canada essentially relies on lack of evidence, rather than evidence of lack of benefit, for patients who do not undergo testing or are negative for the biomarker. In the case of pembrolizumab, approval has not been granted for patients whose tumors express <1% PD-L1 in the second-line, or <50% in the first-line settings. Regardless of the (very low) strength of evidence about clinical utility from the PD-L1 test, these restrictions are currently in place. Moreover, reimbursement decisions for the drug across Canada are not currently using the criteria of the CDx's predictive ability as a criterion. Decisions to fund the CDx will be restrained by these considerations because lack of

reimbursement will place the onus on the patient to (if feasible) pay for a test to determine eligibility for treatment.

4.5.3. Limitations of the systematic review

This review followed rigorous methodological standards, which were detailed a priori in a protocol. Nevertheless, several limitations are inherent within systematic reviews.

There is a possibility of selective reporting bias (e.g., researchers only reporting positive outcomes) and small study bias (including publication bias), whereby small trials are only published when unexpectedly strong results are found. There was extensive searching in conference proceedings and gray literature sources to help overcome publication bias. Because the main trials for immunotherapy are being undertaken by industry, and hence require registration, there is good confidence of at least the primary outcomes being reported. Results in the papers were supplemented by careful evaluation of reports submitted to the FDA and pCODR, such that missing outcomes (e.g., patient-reported) in publications were identified. Selective outcome reporting for patient-reported outcomes was considered during the risk of bias ratings for studies and integrated into final assessments. Only studies published in English were included, and trials published in other languages may have differing results; effect sizes in language restricted reviews have shown to not differ significantly (overestimating effect sizes by 2%) from those not having restrictions.[135] Many of the results for effects based on PD-L1 status in pembrolizumab treatment were based on indirect comparisons, and should be considered with caution. Systematic reviews may become outdated, at least in part, if new studies are published that change some or all of their conclusions. Immunotherapy is a very active area of research and new studies should be sought regularly to determine if the evidence will change conclusions.

4.5.4. Future considerations

Unavailability of a tissue sample for some patients (estimated 15-20% based on Alberta experience) currently leaves them without the opportunity to test for eligibility. The results here for studies examining cytological samples seem promising, such that if practice changed more patients may become eligible for PD-L1 testing and, therefore, possibly treatment. Re-evaluation of this evidence base soon would be prudent.

Apart from tumor sample type, research is ongoing to determine whether or not other forms of PD-L1 testing, such as expression on circulating tumor cells (using liquid biopsies) or genetic expression or polymorphisms, may offer promise with the ability to greatly reduce costs and

expand access (Appendix E). Although PD-L1 testing using liquid biopsies is being marketed (https://biocept.com/), no studies validating this approach clinically were identified in our search or via company websites. Other biomarkers, such as tumor mutational burden or the tumor lymphocyte-neutrophil ratio, are being actively investigated (Appendix E).

Future studies may help better ascertain the predictive effect of PD-L1 for pembrolizumab in first-line treatment. Ongoing phase 3 first-line trials are assessing efficacy for pembrolizumab over chemotherapy in patients with ≥1% tumor PD-L1 expression (NCT02220894 KEYNOTE 042). Two international, randomized, double-blind, phase 3 studies investigating adjunctive pembrolizumab are also ongoing, neither of which are enrolling based on PD-L1 status although require a sample of tumor without intervening irradiation. This latter note suggests that investigators predict that irradiation modifies PD-L1 expression.

Because there are several drugs approved (e.g., nivolumab for second-line treatment in melanoma, NSCLC, renal cell carcinoma) or in development targeting the PD-1 pathway ("checkpoint inhibitors") and patients with different stages and treatment histories (e.g., no second line therapy), as well as other promising biomarkers under investigation (e.g., molecular smoking signatures and neoantigens in peripheral blood lymphocytes),[13] it is unknown what the future impact of PD-L1 IHC as a CDx will be, although this needs to considered in any decision to use existing and/or develop LDTs.

Chapter 5: Process Evaluation of HTA and Conclusions

5.1 Introduction

The forth objective of this work was to assess the HTA process in terms of its feasibility (e.g., timeliness, resource requirements, efficiencies), and how the findings compare with assessments in other jurisdictions/countries. Considering the CDx Working Group's priority to conduct the evaluation simultaneously with assessments of pCODR—for drugs first submitted for evaluation with a new CDx—a key consideration was the impacts this may have on the timeliness and information needs of the HTA. Conclusions about this process assessment and other aspects of this work are then presented.

5.2 Methods

5.2.1. Feasibility

Timeliness and resource requirements

Data were collected for all steps in the development of the topic proposal and conduct and reporting of the review. Work effort in terms of full-time equivalents (FTEs), as well as duration, were accounted for separately, particularly since some activities (e.g., review of the proposal by the CDx and PD-L1 Working Groups) required time but not HTA staff effort. After consideration of the possible efficiencies (or inefficiencies) from conducting the review simultaneously with pCODR assessments (see below), potential revisions in the workload and resources were considered.

Efficiencies with respect to pCODR assessments

Because this pilot was undertaken after the assessments of pembrolizumab by pCODR, and therefore incorporated their findings in the review, this assessment examined, in retrospect, how the information provided by the pCODR reports may impact the results. The assessment focused on the scenario related to the first submission for pembrolizumab in second-line treatment, with consideration of how the following assessment for first-line treatment may have impacted the feasibility. The assessment assumes that a) the HTA would have been initiated in early April 2016 (aligning with 1-month advance public notice of the submission[136] on April 21), and b) that 5 and 7 months were required for access to the initial and final, respectively, clinical and economic guidance reports and pCODR recommendations. Data available in the literature and through the pCODR reports were considered.

5.2.2. Comparisons with results of assessments in other countries

The grey literature search undertaken for the systematic review was in part targeted towards identifying reports from other countries on assessments of pembrolizumab. After conducting the HTA, these reports were reviewed in-depth to appraise them in terms of their methods, evidence requirements, information sources, interpretations of the evidence, and conclusions.

5.3 Results

5.3.1. Timeliness and resource requirements

Table 13 contains the data and calculations used for estimating the total workload and duration that would be feasible for this HTA. Primarily, the HTA was conducted by a project lead, an information specialist, and a second reviewer, all having at least 5-year experience in systematic reviews. A biostatistician was available and used for brief consult to confirm accuracy of calculations and data interpretations (e.g., relying on HRs for prognostic review). Although this HTA was conducted on a part-time basis (conducted over 1 year), the calculations of

workload and durations reflect what would be accurate should 1 full-time and 2 part-time (librarian and second reviewer) staff be available at all times during the timeframe of the project.

The calculations for FTE did not account for some unproductive work time, such that additional (approx.10-15%) FTEs would be required to assume for determining total budget. Having multiple people undertake some of the activities (e.g., two reviewers extracting data) would likely be required to maintain this timeframe, although would not impact total resources. The 1-month duration of the last stage in which the report is reviewed by the PD-L1 Working Group, with revisions thereafter, was estimated. Overall, the timeline would be most influenced by the duration of review of the protocol and draft report by the working group, as well the number of citations identified for screening and full text selection. With multiple possible diagnostic assays that may have had clinical validity data with pembrolizumab, and the multiple immunotherapies for which indirect data was sought, there were a considerable number of citations reviewed at full text for this topic.

One full-time equivalent for 5.4 months would be required. Because this effort is spread over the various personnel (project lead, research assistant/second reviewer, librarian, statistician), a total duration of 5 months is likely sufficient to undertake an HTA of most CDx.

Table 13. Pilot project activity and workload

Tasks	Personnel	Workload	Duration
Background reading on topic including review of relevant submissions in other countries and evidence requirements for type of CDx	Project lead	60 hrs	1 month
Invite topic/clinical experts to join PD-L1 working group	Project lead	2 hrs	
Draft protocol with background, research questions (RQ), criteria (population, intervention, comparators, outcomes), and methods	Project lead	40 hrs	
Consult with PD-L1 working group, especially clinicians, laboratory staff and pathologists, about contextual needs	Project lead	6 hrs	
Send protocol for review 1 week prior to presenting plan to working group; revise protocol	Project lead	16 hrs	

Tasks	Personnel	Workload	Duration
Create search strategy	Librarian	16 hrs **Total 140 hours (0.80 FTE*)**	
Implement searches (published and unpublished literature) Prepare screening and selection forms; pilot forms with 40-50 citations Duplicate screening (approx. 3,000-4,000 citations) Duplicate full text selection (approx. 20% -25% screened citations)	Librarian Project lead and research assistant/second reviewer	40 hrs 16 hrs x 2 staff 48 hrs x 2 staff 80 hrs x 2 staff **Total 328 hrs (1.9 FTE)**	1 month
Prepare data extraction forms per each RQ; pilot forms for 2 studies for each main RQ (prognosis, clinical utility, clinical validity, analytical validity, economic evaluations) Data extraction with quality assessment (average 2.5 hrs per study x 63 studies) Data verification (7 studies)	Project lead and research assistant/second reviewer Project lead Research assistant/second reviewer	24 hrs x 2 staff 158 hrs 18 hrs **Total 224 hrs (1.3 FTE)**	1 month
Data analysis (including data conversions, calculations) and interpretation Preparation of figures (including literature flow), tables, reference lists including excluded studies Preparation of draft technical report	Project lead/statistical consult Project lead Project lead	40 hrs 40 hrs 80 hrs **Total 160 hrs (0.92 FTE)**	1 month
Review of draft report (2 weeks) Revision of report Creation of evidence summary	PD-L1 Working Group Project lead Project lead	 40 hrs 40 hrs **Total 80 hrs (0.46 FTE)**	1 month

Tasks	Personnel	Workload	Duration
Total work effort: 932 hrs (5.4 FTE months); Total duration: 5 months			

FTE: full-time equivalent; hrs: hours

*When calculating FTE equivalents, an 8-hour day was assumed with 173 hours per month worked.

5.3.2. Feasibility and efficiencies: alignment with national assessment and provincial drug reimbursement

This evaluation considers a possible HTA start date in early April 2016 based on a 1-month notice before the actual submission of the application to pCODR occurred for pembrolizumab in second-line treatment. A 5-month HTA duration would enable completion to align approximately with the 5-month timeframe before the initial clinical, economic and recommendation reports were released in early September 2016. Considering the information needs and availability, this timeframe would result in deficiencies, some of which could be avoided with a short delay. Related to the information provided by pCODR, the initial reports contained the economic evaluation; in the future they will contain data from patient input on the experiences and perspectives about biomarker testing; and data on patient-reported outcomes (not reported in the primary trial publication in April 2016) was undisclosed until the final report was released 7 months after submission (November 2016).

With respect to data used for the HTA, much of the evidence relied upon for prognosis with standard-of-care (4 of 5 RCTs with PD-L1 data for docetaxel), clinical utility (<1% vs ≥1% PD-L1 indirect comparison but not for secondary 1-49% vs ≥50% comparison released in 2017) and clinical validity would have been available by the summer of 2016 in published papers or reports. The data on analytical validity were variably available, depending on outcome. For example, of all of the studies evaluating the 1% threshold for precision/repeatability and the assessment of LDTs were published in late 2016 or 2017. Many papers were published mid-2016 such that regular search updates would be prudent to capture ongoing paper and abstract reports. Although the missing information would result in deficiencies to the findings (i.e., acceptable inter-observer and uncertain intra-observer reliability for the 1% threshold would have been unknown), this is expected when undertaking HTAs in highly and rapidly evolving fields. The identification in the search of many emerging studies investigating additional biomarkers would not have been as apparent in an earlier search, although the impact of this knowledge on decision making about PD-L1 reimbursement is unknown. The notice of submission for pembrolizumab

in first-line treatment (as well as study characteristics but no peer-reviewed results of the RCT) would have been available immediately following the final second-line reports, such that any decisions could factor in this uncertainty. In summary, a 5-month HTA timeframe may miss any information unreleased in the initial recommendation, as well as many ongoing studies, and judgements about this uncertainty will need to be taken into consideration. Consideration of some form of conditional recommendation for reimbursement may be a highly valuable option considering the highly evolving research in CDx. This timeframe would also be ideal should drug reimbursement also consider the findings of the CDx HTA such that decisions for the drug and CDx reimbursement could align.

In terms of workload, the resources used for this pilot HTA may be higher than would be expected should it have been undertaken during April-September 2016. Fewer than half the reports would have been available, including but not limited to studies in first-line treatment. Although reliance on fewer resources may be possible in some future HTAs, shortening the timeframe to under 5-months does not seem to be required based on alignment with pCODR recommendations.

5.3.3. Comparison with findings within Canada and other Countries

Canada

Reviews[16,17] by CADTH for pembrolizumab in patients with advanced stage NSCLC who are treatment naïve or have progressed on or after first-line platinum-based chemotherapy did not focus on PD-L1 testing. Criteria for PD-L1 testing to be considered a CDx were not incorporated, nor were issues related to the assay's analytical validity. Considering issues with implementation of a pembrolizumab recommendation, the Provincial Advisory Group (providing comments on the pCODR recommendations) noted that additional costs would be incurred on testing for PD-L1. The review for second-line treatment concluded that the 1% and 50% cut-offs both offered clinically meaningful improvements in overall survival compared with docetaxel. It also noted that a scenario analysis, in the cost-effectiveness analysis, comparing the incremental cost-effectiveness ratio (ICER) between 1% and 50% PD-L1 expression was minimal (185$/quality-adjusted life year [QALY]); the greater benefits in the 50% cut-off group are also associated with increased costs due to treatment until progression. A lack of comparative evidence to support the efficacy or harm of pembrolizumab compared with docetaxel or nivolumab in patients with PD-L1 <1% was noted.

The review for first-line treatment also noted that some patients are not able to tolerate chemotherapy, due to toxicities, and thus do not receive treatment. Having a better toxicity profile than chemotherapy, more patients may be eligible for treatment with pembrolizumab than was estimated in the budget impact based on current first-line patients. This comment brings forth the argument that patients with PD-L1 <50% may have few/no alternatives and miss out on a treatment with pembrolizumab that may be not be superior in benefit to chemotherapy but offer less toxicity and thus an overall net benefit.

For drugs approved with a CDx, the agency conducting HTAs, Canadian Agency for Drugs and Technologies in Health (CADTH) for pCODR has recently released a draft proposal for consultation in which they explicate requirements for drug manufacturers to submit additional evidence for review, on the analytical and clinical validity and clinical utility of the CDx. The evidentiary requirements for the assessment are not described.

Australia

PD-L1 testing for second/third-line (November 2016)[20] and first-line (April 2017)[137] pembrolizumab treatment was considered through the Australian government's integrated approach for co-dependent services, whereby the drug and test are assessed concurrently but considered separately by the Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC), respectively. In this case, the sponsor (Merck) submitted applications in 2015 (second/third-line) and 2017 (first-line), based on protocols outlining the evidentiary requirements of this co-dependent program which outlines requires for analytical validity and clinical utility of the test-drug combination. Both applications for public funding were declined with rationale that the test is a poor CDx with insufficient evidence of analytical validity, weak evidence of clinical validity, and weak evidence of clinical utility. It was acknowledged that higher levels of PD-L1 expression are associated with increased likelihood of response to pembrolizumab, yet exclusion of PD-L1 negative patients who might respond was not acceptable.

In terms of analytical validity, issues about sub-optimal reproducibility and agreement with other PD-L1 tests were contributing factors. The available Public Summary Document outlines several concerns:

- A per-cell threshold (i.e. weak compared with strong staining) was not defined, and a per tumor threshold was not defined biologically;

- Four studies (Dako Reproducibility Study 1 and 2, the DREAM study, and initial Australian data) found modest reliability for the PD-L1 IHC 22C3 pharmDx based on Cohen's kappa coefficients for inter-observer agreement ranging between 0.58 and 0.68;
- Non-constant scatter presenting the correlation of percentages of tumor cell membrane was seen in a study (Ratcliff et al. 2017[68]) comparing the Dako 22C3 assay to two other commercially available assays. Other concordance data presented in the submission were insufficient to establish whether the different PD-L1 IHC assays could be used interchangeably, although MSAC acknowledged that additional studies supported equivalence between the assays.
- Wide variation was evident in the results submitted by the applicant using testing of the 22C3 antibody on the Ventana platform;
- Variations in reporting between laboratories may lead to samples being sent for repeat testing in different laboratories in order to gain access to pembrolizumab;
- The best timing for the test has not been determined based on some evidence (not cited) suggesting PD-L1 status may differ in metastases compared with primary tumors and may change after treatment. Heterogeneity was also noted without clear reference.
- Lack of an existing quality assurance program throughout the country to address interpretation of PD-L1 using all assays/antibodies likely to be available. Difficulties in establishing an inter-laboratory quality assurance program were thought to be likely because of lack of endorsement of PD-L1 testing by the Royal College of Pathologists of Australia. Movement was noted in efforts to develop a quality assurance program in collaboration with the United Kingdom National External Quality Assessment program.

This application differs from the current assessment in that it closely examined agreement between Dako 22C3 and other assays (which are not used in Alberta at present) and needed to consider the requirements of multiple testing facilities throughout the country (not required in Alberta with one or very few centres). A systematic review to capture all relevant studies was not conducted (sponsor supplied studies) and evidence for some findings (i.e., inter-tumoral heterogeneity) may have relied upon literature reporting on other antibody clones which would limit their reliability.

The MSAC also noted issues regarding the evidence for clinical validity and utility of the Dako 22C3 PD-L1 test. Concerns about an insufficient justification for the 50% threshold were

noted and largely related to the overly simplistic manner in which the ROC analysis was conducted. Trade-offs between false positives (prioritized) and false negatives based on different downstream consequences of each were not considered. Failure to report all results across scoring methods and thresholds was noted. Sensitivity and specificity values were considered poor. Findings from KEYNOTE 001 as used for threshold validation for use in first-line patients were also considered to be of questionable applicability, possibly due to the small sample in this patient group. The application for second/third-line testing noted evidence of variation in PD-L1 expression before and after treatment and across different stages of disease (unknown references). Part of the reason the claim of co-dependency failed appears to have relied upon conclusions that PD-L1 has a (poor) prognostic role in NSCLC, although as the current review indicates, the two systematic reviews cited[107,114] for this finding had errors in their interpretation. However, much of the failure rested on an inability to confidently rule out any benefit for PD-L1 negative patients and for the lack of a defined clinical algorithm in place within Australia.

United Kingdom

A full report on the assessment by NICE is not available, but committee discussion papers were reviewed.[138,139] Pembrolizumab will be available to the NHS in line with the conditions of the managed access agreement with NHS England. As part of this, NHS England and Merck, Sharp & Dohme have a commercial access agreement that makes pembrolizumab available to the NHS at a reduced cost. The financial terms of the agreement are in confidence.

The National Institute for Health and Care Excellence (NICE) has not conducted a comprehensive evaluation of PD-L1 testing. During the assessment of pembrolizumab by NICE's Technology Assessment programme, the committee noted that the costs of testing for PD-L1 expression were included in the company's economic analysis. Based on input from the clinical expert, the committee concluded that PD-L1 testing could be standardised quickly and, with training, implemented as standard clinical practice in the NHS. However, the clinical expert noted that PD-L1 tests are complex to interpret. It heard from NHS England that all lung cancers will be tested for PD-L1 status from April 2017.

United States

Limited information was found for funding of PD-L1 testing in the United States, although the Molecular Diagnostic Program (MolDx) which many Medicare jurisdictions have implemented for determining coding, coverage and pricing for molecule test appear to approve

tests approved by the FDA as a companion diagnostic which includes the Dako PharmDx 22C3 assay.[140]

5.4 Discussion and Conclusions

This pilot HTA project demonstrated that it is feasible to undertake an HTA on a CDx alongside pCODR's assessment on the drug. However, there is uncertainty around whether or the timing of the process should be strictly aligned with the notice of a drug-CDx submission and availability of the initial pCODR reports since the final recommendations from pCODR, which are typically released 1-2 months later, may contain additional data or interpretations. The extremely fast pace of research in this area makes it inevitable that new data may change the findings substantially, and this should be taken into account when making decisions about the reimbursement of CDx.

Findings from the pilot revealed the importance of working closely with laboratory and clinical experts throughout the review process to ensure the review reflected the local environment. From this example, a single IHC laboratory in Alberta, one of the largest in Canada, has the capacity and experience to perform all PD-L1 testing for the province; therefore, it is feasible and preferable to evaluate one PD-L1 assay rather than requiring allowance for the possibility of multiple laboratories each using different testing platforms. As a result, the review approach described in this work and the findings differ from the national Australian assessment, where there was a need to evaluate the equivalence between multiple testing strategies being used across the country. Further, because oncologists in Alberta are only using PD-L1 for treatment decisions with pembrolizumab (not for nivolumab or atezolizumab as others may), this review focused on pembrolizumab while looking to PD-L1's use for other drugs as indirect and comparative evidence. This contextual approach should be made transparent in any evaluation in order to compare rationale and evidence needs for differing decisions between provinces. Otherwise, one province's decision may set a benchmark for other provinces, which could, in turn, foster perceptions of inequities in care.

National drug reimbursement evaluations in Canada do not fully incorporate the value of clinical utility or analytical validity. There is no explicit requirement for determination of lack of a meaningful effect in patients negative for the biomarker, or below the threshold used for the submission. Assessment for reimbursement of the CDx alone, without concurrent and similar

considerations applied for decisions about funding the drug, may lead to differences in access to the drug and CDx and therefore limit the available options for funding the CDx and may lend towards lack of credibility to both processes. The option to not fund the CDx positions the patient with the only alternative to pay for their own test, which may not be a realistic option (e.g. no access to private testing). The option to fund is not supported by high confidence in the evidence on clinical utility or differences between cost-effectiveness for the thresholds approved and within clinical use. An alternative option of funding with research/evidence development appears most suitable, but has yet to be deliberated upon.

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Appendices

- **A. Search Strategies**
- **B. Prognosis Across Tumor Stages and Without Treatment**
- **C. Characteristics of Included Studies, Risk of Bias of Randiomized Trials, and Reporting of Economic Evaluations**
- **D. Micro-costing Values and Calculations**
- **E. Excluded Studies**

A.Search Strategies

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Strategy:

1	Adenocarcinoma, Bronchiolo-Alveolar/ (2644)
2	Carcinoma, Non-Small-Cell Lung/ (43113)
3	*Lung Neoplasms/dt, th (29732)
4	(non small cell adj3 (bronch* or lung* or pulmon*)).tw,kf. (48975)
5	NSCLC.tw,kf. (32720)
6	or/1-5 (76877)
7	Adenocarcinoma/ (144473)
8	Carcinoma/ (84910)
9	Carcinoma, Adenosquamous/ (1830)
10	Carcinoma, Large Cell/ (2262)
11	Carcinoma, Squamous Cell/ (120415)
12	(adenocarcinoma* or carcinoma*).tw,kf. (670538)
13	(adeno-squamous* or adenosquamous* or non-squamous* or nonsquamous*).tw,kf. (4295)
14	(antitumo* or cancer* or malignan* or neoplas* or tumo*).tw,kf. (2753234)
15	or/7-14 (2948872)
16	(bronch* or lung* or pulmon* or thora*).mp. (1454830)
17	15 and 16 (344803)
18	or/6,17 [Combined search concepts for NSCLC] (348396)
19	Antigens, CD274/ (2010)
20	Programmed Cell Death 1 Receptor/ag, ai, de, tu [Agonists, Antagonists & Inhibitors, Drug Effects, Therapeutic Use] (710)
21	(anti PD-1* or anti PD1* or ((PD-1* or PD1* or PD-CD1* or PDCD1*) and inhibitor*)).tw,kf. (5382)
22	atezolizumab*.af. (182)
23	avelumab*.af. (48)
24	bavencio*.af. (2)
25	(B7-H1* or B7H1*).tw,kf. (671)
26	(BMS-936559* or BMS936559*).tw,kf. (16)
27	(CD-274* or CD274*).tw,kf. (273)
28	((check point or checkpoint) adj1 inhibitor*).tw,kf. (2270)
29	DPT0O3T46P.rn. (283)
30	durvalumab*.af. (54)
31	keytruda*.tw,kf. (28)
32	lambrolizumab*.af. (24)
33	((ligand* or receptor*) and (programmed adj2 death*)).tw,kf. (5914)
34	MED14736*.tw,kf. (1)
35	(Merck-3475* or Merck3475* or MK-3475* or MK3475*).tw,kf. (40)
36	nivolumab*.af. (1362)

37 opdivo*.tw,kf. (36)
38 (PD-L1* or PDL1*).tw,kf. (4038)
39 PDR001*.tw,kf. (0)
40 pembrolizumab*.af. (934)
41 pidilizumab*.af. (36)
42 tecentriq*.af. (7)
43 or/19-42 [Combined searches for PD-L1 antigens and therapies] (14158)
44 and/18,43 [Combined concepts for NSCLC and PD-L1] (1604)
45 limit 44 to english (1510)
46 limit 45 to yr="2002-Current" (1488)
47 remove duplicates from 46 (1369)

Database: Ovid Embase 1996 to 2017 Week 24

Strategy:

1 lung alveolus cell carcinoma/ (2677)
2 *lung cancer/dt, th (5248)
3 exp non small cell lung cancer/ (48062)
4 (non small cell adj3 (bronch* or lung* or pulmon*)).tw,kw. (66751)
5 NSCLC.tw,kw. (52362)
6 or/1-5 (103577)
7 adenocarcinoma/ (58155)
8 adenosquamous carcinoma/ (5414)
9 carcinoma/ (33761)
10 large cell carcinoma/ (3491)
11 squamous cell carcinoma/ (81587)
12 (adenocarcinoma* or carcinoma*).tw,kw. (648593)
13 (adeno-squamous* or adenosquamous* or non-squamous* or nonsquamous*).tw,kw. (6051)
14 (antitumo* or cancer* or malignan* or neoplas* or tumo*).tw,kw. (2718781)
15 or/7-14 (2847675)
16 (bronch* or lung* or pulmon* or thora*).mp. (1457683)
17 15 and 16 (413316)
18 or/6,17 [Combined search concepts for NSCLC] (418090)
19 "programmed death 1 ligand 1"/ (6194)
20 programmed death 1 receptor/ (5870)
21 (anti PD-1* or anti PD1* or ((PD-1* or PD1* or PD-CD1* or PDCD1*) and inhibitor*)).tw,kw. (10196)
22 atezolizumab*.af. (771)
23 avelumab*.af. (305)
24 bavencio*.af. (2)
25 (B7-H1* or B7H1*).tw,kw. (1086)
26 (BMS-936559* or BMS936559*).tw,kw. (241)
27 (CD-274* or CD274*).tw,kw. (482)
28 ((check point or checkpoint) adj1 inhibitor*).tw,kw. (3479)
29 durvalumab*.af. (646)
30 keytruda*.tw,kw. (287)
31 lambrolizumab*.af. (97)
32 ((ligand* or receptor*) and (programmed adj2 death*)).tw,kw. (7661)
33 MED14736*.tw,kw. (2)
34 (Merck-3475* or Merck3475* or MK-3475* or MK3475*).tw,kw. (512)
35 nivolumab*.af. (4240)
36 opdivo*.tw,kw. (293)
37 (PD-L1* or PDL1*).tw,kw. (8001)
38 PDR001*.tw,kw. (1)
39 pembrolizumab*.af. (3376)

40	pidilizumab*.af. (350)
41	tecentriq*.af. (48)
42	or/19-41 [Combined searches for PD-L1] (26926)
43	and/18,42 [Combined concepts for NSCLC and PD-L1] (4555)
44	limit 43 to english (4429)
45	limit 44 to yr="2002-Current" (4398)
46	remove duplicates from 45 (4179)
47	46 not conference*.pt. (2572)

Database: Cochrane Library via Wiley

Strategy:

#1	[mh ^"Adenocarcinoma, Bronchiolo-Alveolar"] 32
#2	[mh ^"Carcinoma, Non-Small-Cell Lung"] 2959
#3	[mh ^"Lung Neoplasms" [mj]/DT,TH] 13
#4	("non small cell" near/3 (bronch* or lung* or pulmon*)):ti,ab,kw 6827
#5	NSCLC:ti,ab,kw 4366
#6	{or #1-#5} 7224
#7	[mh ^Adenocarcinoma] 2785
#8	[mh ^Carcinoma] 1115
#9	[mh ^"Carcinoma, Adenosquamous"] 44
#10	[mh ^"Carcinoma, Large Cell"] 88
#11	[mh ^"Carcinoma, Squamous Cell"] 2413
#12	(adenocarcinoma* or carcinoma*):ti,ab,kw 30069
#13	("adeno-squamous*" or adenosquamous* or "non-squamous*" or nonsquamous*):ti,ab,kw 625
#14	(antitumo* or cancer* or malignan* or neoplas* or tumo*):ti,ab,kw 128486
#15	{or #7-#14} 133569
#16	(bronch* or lung* or pulmon* or thora*):ti,ab,kw 84102
#17	#15 and #16 18456
#18	#6 or #17 18689
#19	[mh ^"Antigens, CD274"] 16
#20	[mh ^"Programmed Cell Death 1 Receptor"] 28
#21	("anti PD-1*" or "anti PD1*" or (("PD-1*" or PD1* or "PD-CD1*" or PDCD1*) and inhibitor*)):ti,ab,kw 2711
#22	atezolizumab*:ti,ab,kw 59
#23	avelumab*:ti,ab,kw 28
#24	("B7-H1*" or B7H1*):ti,ab,kw 5
#25	bavencio*:ti,ab,kw 0
#26	("BMS-936559*" or BMS936559*):ti,ab,kw 2
#27	("CD-274*" or CD274*):ti,ab,kw 25
#28	(("check point" or checkpoint) near/1 inhibitor*):ti,ab,kw 261
#29	durvalumab*:ti,ab,kw 51
#30	keytruda*:ti,ab,kw 10
#31	lambrolizumab*:ti,ab,kw 2
#32	((ligand* or receptor*) and (programmed near/2 death*)):ti,ab,kw 490
#33	MED14736*:ti,ab,kw 0
#34	("Merck-3475*" or Merck3475* or "MK-3475*" or MK3475*):ti,ab,kw 25
#35	nivolumab*:ti,ab,kw 324
#36	opdivo*:ti,ab,kw 15
#37	("PD-L1*" or PDL1*):ti,ab,kw 376
#38	PDR001*:ti,ab,kw 1
#39	pembrolizumab*:ti,ab,kw 247
#40	pidilizumab*:ti,ab,kw 5
#41	tecentriq*:ti,ab,kw 1

#42 {or #19-#41} 3215
#43 #18 and #42 Publication Year from 2002 to 2017 390

Results by Database:
CDSR: 1
CENTRAL: 380
HTA DB: 9

Other Source: Proceedings of the American Society of Clinical Oncology (ASCO)

URL: http://abstracts.asco.org/199/CatView_199_B.html;

http://ascopubs.org/jco/meeting?expanded=2016&expanded=34

Strategy:

>2017
Hand searched online conference proceeding records from the ASCO 2017 meeting listed under the categories 'Lung cancer' >> (a) 'Metastatic Non-Small Cell Lung Cancer', (b) 'Adjuvant Therapy' & (c) 'Local-Regional Non-Small Cell Lung Cancer'. The Late Breaking Abstracts (d) from the 2017 meeting were also hand searched.

(a) http://abstracts.asco.org/199/CatAbstView_199_462_AT.html
(b) http://abstracts.asco.org/199/CatAbstView_199_457_AT.html
(c) http://abstracts.asco.org/199/CatAbstView_199_456_AT.html
(d) http://meetinglibrary.asco.org/collections/asco-collections/0

keywords: programmed death, ligand, PD-L1, atezolizumab, avelumab, bavencio, durvalumab, keytruda, lambrolizumab, nivolumab, opdivo, pidilizumab, pembrolizumab, tecentriq (93)

>2016
Hand searched online conference proceeding records from the ASCO 2016 meeting listed under the "Topic" heading of 'Lung cancer' >> 'Non-small cell lung cancer'.
http://meetinglibrary.asco.org/results/Meeting%3A%222016%20ASCO%20Annual%20Meeting%22;page=1

keywords: programmed death, ligand, PD-L1, atezolizumab, avelumab, bavencio, durvalumab, keytruda, lambrolizumab, nivolumab, opdivo, pidilizumab, pembrolizumab, tecentriq (78)

Other Source: Proceedings of the European Society for Medical Oncology (ESMO)

URL: http://oncologypro.esmo.org/Meeting-Resources/Past-Meeting-Abstracts

Strategy:

> 2016
Hand searched the abstract book of the 41st ESMO Congress (ESMO 2016), published in the Annals of Oncology, 1 October – Vol 27, Supplement 6
keywords: lung, nsclc, programmed death, ligand, PD-L1, atezolizumab, avelumab, keytruda, lambrolizumab, nivolumab, opdivo, pembrolizumab (183)

> 2015
Hand searched the abstract book of the ESMO Asia Congress (Dec 2015), published in the Annals of Oncology, 1 December – Vol 26, Supplement 9
keywords: lung, nsclc, programmed death, ligand, PD-L1, atezolizumab, avelumab, bavencio, durvalumab, keytruda, lambrolizumab, nivolumab, opdivo, pembrolizumab, pidilizumab, tecentriq (11)

Other Source: European Lung Cancer Congress

URL: http://oncologypro.esmo.org/Meeting-Resources/Past-Meeting-Abstracts

Strategy:

> 2017
Hand searched the program book of the ELCC (Geneva). No abstracts available yet
keywords: programmed death, ligand, PD-L1, atezolizumab, avelumab, bavencio, durvalumab, keytruda, lambrolizumab, nivolumab, opdivo, pembrolizumab, pidilizumab, tecentriq (23)

> 2016
Searched within the issue (searched Article Title, Abstract, Keywords): abstracts of the European Lung Cancer Conference (ELSS), published in Journal of Thoracic Oncology, April 2016, Vol 11, issue 4, Supplement, S57-S166
keywords: programmed death, ligand, PD-L1, atezolizumab, avelumab, bavencio, durvalumab, keytruda, lambrolizumab, nivolumab, opdivo, pembrolizumab, pidilizumab, tecentriq (22)

> 2015
Hand searched the abstract book of the ELCC (Geneva), published in the Annals of Oncology, April 2015 – Vol 26, Supplement 1
keywords: programmed death, ligand, PD-L1, atezolizumab, avelumab, keytruda, lambrolizumab, nivolumab, opdivo, pembrolizumab (4)

Other Source: International Association for the Study of Lung Cancer

URL: https://www.iaslc.org/

Strategy:

> 2016
Searched the abstract book of the 2016 World Conference on Lung Cancer:
http://wclc2016.iaslc.org/wp-content/uploads/2016/12/WCLC2016-Abstract-Book_vF-WEB_revDec12.pdf

keywords: programmed death, ligand, PD-L1, atezolizumab, avelumab, bavencio, durvalumab, keytruda, lambrolizumab, nivolumab, opdivo, pidilizumab, pembrolizumab, tecentriq

> 2015
Searched the abstract book of the 2015 World Conference on Lung Cancer:
http://wclc2015.iaslc.org/wp-content/uploads/2015/11/WCLC-2015-Abstract-Book_vF_FOR-JTO-Website_low-res_REV-NOV-2015.pdf

keywords: programmed death, ligand, PD-L1, atezolizumab, avelumab, bavencio, durvalumab, keytruda, lambrolizumab, nivolumab, opdivo, pidilizumab, pembrolizumab, tecentriq

Other Source: Conference Proceedings Citation Index – Science (CPCI-S) – 1990-present

URL:

http://apps.webofknowledge.com.login.ezproxy.library.ualberta.ca/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch&SID=2DwadrBh4kZd5g4xBhV&preferencesSaved=&editions=IST

P#44;ISSHP

Strategy:

TOPIC: (("lung cancer" OR nsclc)) AND TOPIC: (("programmed death" OR ligand* OR "PD L1*" OR PDL1* OR atezolizumab OR avelumab OR bavencio OR durvalumab OR keytruda OR lambrolizumab OR nivolumab OR opdivo OR pidilizumab OR pembrolizumab OR tecentriq))
Indexes=CPCI-S Timespan=2015-2017 (144)

Other Source: ClinicalTrials.gov*

URL: https://clinicaltrials.gov/beta/

Strategy:

Search 1 (12 June 2017) >
Condition / Disease: Lung Cancer, Nonsmall Cell
AND
Other Terms: atezolizumab OR avelumab OR keytruda OR lambrolizumab OR nivolumab OR opdivo OR pembrolizumab
Studies received from 01/01/2015 to 12/31/2017 (183)

Search 2 (20 June 2017) >
Condition / Disease: Lung Cancer, Nonsmall Cell
AND
Other Terms: bavencio OR durvalumab OR pidilizumab OR tecentriq (56)**

Other Source: WHO International Clinical Trials Registry Platform

URL: http://apps.who.int/trialsearch/

Strategy:

Search 1 >
Title: (atezolizumab OR avelumab OR keytruda OR lambrolizumab OR nivolumab OR opdivo OR pembrolizumab)
AND
non-small cell lung cancer OR nonsmall cell lung cancer OR NSCLC
Date of registration is between 01/01/2015 to 06/12/2017 (138)

Search 2 >
Title: (bavencio OR durvalumab OR pidilizumab OR tecentriq)
AND
non-small cell lung cancer OR nonsmall cell lung cancer OR NSCLC
Date of registration is between 01/01/2015 to 12/31/2017 (13)

Total – both searches (151)

Other Source: Health Canada – The Drug and Health Product Register

URL: https://hpr-rps.hres.ca/reg-content/summary-basis-decision.php

Strategy:

Searched keyword: atezolizumab (0)
Searched keyword: avelumab (0)
Searched keyword: bavencio (0)

Searched keyword: durvalumab (0)
Searched keyword: keytruda (1)
Searched keyword: lambrolizumab (0)
Searched keyword: nivolumab (1)
Searched keyword: opdivo (1) – same SBD as Nivolumab
Searched keyword: pidilizumab (0)
Searched keyword: pembrolizumab (1) – same SBD as Keytruda
Searched keyword: tecentriq (1)

Total: all searches (3)

Other Source: US Food and Drug Administration – Drugs@FDA: Approved Drug Products*

URL: https://www.accessdata.fda.gov/scripts/cder/daf/

Strategy:

Searched keyword: atezolizumab (3)
Searched keyword: avelumab (0) – approval for Merkel cell carcinoma and urothelial carcinoma only
Searched keyword: bavencio (0) – also results for avelumab
Searched keyword: durvalumab (0) – approval for urothelial carcinoma only
Searched keyword: keytruda (0) – original approval for metastatic melanoma (has since been approved for nsclc, but there are no updated reviews)
Searched keyword: lambrolizumab (0)
Searched keyword: nivolumab (1)
Searched keyword: opdivo (1) – also results for nivolumab
Searched keyword: pidilizumab (0)
Searched keyword: pembrolizumab (0) – also results for pembrolizumab
Searched keyword: tecentriq (3) – also results for atezolizumab

Total: all searches (4)

*Only retained records when approval letter includes nsclc indication

Other Source: US Food and Drug Administration – Premarket Approval (PMA) Database

URL: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Strategy:

Searched keyword in "device" field: PD-L1 (22)
See: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Kept 4 PDFs (most of the 22 were duplicate search results)

Other Source: European Medicines Agency – European Public Assessment Reports (EPAR)

URL: http://www.ema.europa.eu/ema/

Strategy:

Searched keyword: atezolizumab (0)
Searched keyword: avelumab (0)
Searched keyword: bavencio (0)
Searched keyword: durvalumab (0)
Searched keyword: keytruda (1)
Searched keyword: lambrolizumab (0)
Searched keyword: nivolumab (1)

Searched keyword: opdivo (1)
Searched keyword: pidilizumab (0)
Searched keyword: pembrolizumab (1) – same EPAR as Keytruda
Searched keyword: tecentriq (0)

Total: all searches (3)

Other Source: Alberta Health & Wellness

URL: http://www.health.alberta.ca/initiatives/AHTDP-reviews.html

Strategy:

CTRL-F search on website: lung, cancer, nsclc, PDL1, pembro, nivolumab, keytruda
No results found

Other Source: CADTH

URL: https://www.cadth.ca/search?keywords

Strategy:

Searched keyword: PDL1 (1)
Searched keyword: PD-L1 (7)
Searched keyword: programmed death (29)
Searched keyword: atezolizumab (2) – same results as for PD-L1
Searched keyword: avelumab (2) – same results as for PD-L1
Searched keyword: bavencio (0)
Searched keyword: durvalumab (2) – same results as for PD-L1
Searched keyword: keytruda (10)
Searched keyword: lambrolizumab (1)
Searched keyword: nivolumab (20)
Searched keyword: opdivo (10)
Searched keyword: pidilizumab (0)
Searched keyword: pembrolizumab (16)
Searched keyword: tecentriq (1)

Total: all searches (8)

Other Source: Health Quality Council of Alberta

URL: http://hqca.ca/studies-and-reviews/completed-reviews/

Strategy:

Browsed reviews & CTRL-F searched page – nothing relevant (0)

Other Source: Health Quality Ontario

URL: http://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment

Strategy:

Searched site with keywords – nothing relevant (0)

Other Source: Manitoba Centre for Health Policy

URL: http://mchp-appserv.cpe.umanitoba.ca/deliverablesList.html

Strategy:

Browsed reports – nothing relevant (0)

Other Source: Technology Assessment Unit of the MUHC

URL: http://www.mcgill.ca/tau/publications/

Strategy:

Browsed reports – nothing relevant (0)

Other Source: Newfoundland & Labrador Centre for Applied Health Research

URL: http://www.nlcahr.mun.ca/CHRSP/CompletedCHRSP.php

Strategy:

Browsed reports – nothing relevant (0)

Other Source: University of York Centre for Reviews and Dissemination – CRD Database

URL: https://www.crd.york.ac.uk/CRDWeb/Homepage.asp

Strategy:

Any field: ("lung cancer" OR nsclc) AND Any field: ("programmed death" OR ligand* OR "PD L1*" OR PDL1* OR atezolizumab OR avelumab OR bavencio OR durvalumab OR keytruda OR lambrolizumab OR nivolumab OR opdivo OR pidilizumab OR pembrolizumab OR tecentriq) Publication year=2015-2017 in HTA Database (14) RF Note: Removed 6 non-English language HTAs (8)

Other Source: UBC Centre for Health Services and Policy Research

URL: http://chspr.ubc.ca/publications/

Strategy:

CTRL-F search on website: lung, cancer, nsclc, PDL1, pembro, nivolumab, keytruda No results found (0)

Other Source: INAHTA

URL: http://www.inahta.org/publications/

Strategy:

Search 1 >
Keywords: ("lung cancer" OR nsclc) AND ("programmed death" OR ligand* OR "PD L1" OR PDL1* OR atezolizumab OR avelumab OR bavencio OR durvalumab OR keytruda OR lambrolizumab OR nivolumab OR opdivo OR pidilizumab OR pembrolizumab OR tecentriq) (0)

Search 2 >
("lung cancer" OR nsclc) (33)

B. Prognosis Across Tumor Stages and Without Treatment

Table B1. A. Comparison of studies in available systematic reviews and the search for this assessment (Pillay 2017) on the prognostic impact of PD-L1, across all tumor stages and without reference to treatment

	Zhou, 2015[1]	Zhong, 2015[2]	Zhang, 2015[3]	Wu, 2015[4]	Wang, 2015[5]	Pan, 2015[6]	Hu, 2016[7]	Xia, 2017[8]	Pillay, 2017
Alvarex, 2017									X
Ascucion, 2015									X
Azuma, 2014		X	X		X	X	X	X	X
Cardona, 2015									X
Cha, 2016									X
Chen, 2012	X	X	X	X	X	X	X	X	X
Chen, 2013						X	X		X
Chen, 2016								X	X
Cho, 2017									X
Cooper, 2015							X	X	X
Cronin-Fenton, 2016									X
Cronin-Fenton, 2017									X
De Petri, 2016									X
Hung, 2016								X	X (study withdrawn since)
Igarashi, 2016									X

Igawa, 2017									X
Ji, 2016									X
Jia, 2016									X
Kim, 2015							X	X	X
Koh, 2015							X		X
Konishi, 2004				X		X	X		X
Ma, 2011	X	X				X	X		
Mao, 2015		X					X	X	X
Mu, 2011	X	X	X	X	X	X	X	X	X
Ohue, 2016									X
Scheel, 2016									X
Schmidt, 2015							X	X	X
Sharma, 2014							X (Master's dissertation. Tianjin Medical University, 2014)		
Takada, 2016									X
Takada, 2017									X
Velcheti, 2013 (Greek cohort)[9]	X	X	X	X	X	X	X		X
Wang, 2017									X
Yang, 2014		X	X	X	X	X	X	X	X
Zhang, 2014	X	X	X		X	X	X	X	X
Zhou, 2017									X
Findings (HR >1.0 with statistical	**HR 1.43 (1.24-1.63);** I^2=13.4%; in Asian	HR 1.21 (0.85-1.71; I^2=82%); poor OS	HR 1.35 (0.81-2.23)	3-year OS OR 1.57 (0.38-6.48)	**HR, 1.75 (1.4-2.2)**, I^2=0%; no difference between	**HR 1.47 (1.19-1.83)** No association of	HR 1.60 (0.88-2.89; I^2=88%); poor OS prognosis	HR, 1.18 (0.90-1.56); I^2=78%; poor OS prognosis	NA

significance indicating a poor prognosis for survival with PD-L1 over-expression)	studies (HR 1.35 [1.08-1.63]) and non-Asian studies (HR 1.51 [1.24-1.79])	prognosis for Chinese studies (HR 1.55 [1.04-2.29])			European (I^2=0%) and Asian studies (I^2=78%). PD-L1+ associated with late stage (OR 1.21 [0.46, 3.20])	PD-L1+ with stage (OR 0.86 [0.51-1.45]).	for Asian studies (HR 2.0 [1.55-2.57]). PD-L1+ associated with late stage (OR 1.21 [1.02-1.43)	found for Asian studies (HR 1.84 [1.14-2.28]). PD-L1+ associated with stages IIIb/IV vs stage I-IIIa (HR 1.27 [1.06-1.48])	
Values used by reviews for 2 Velcheti cohorts. As per Velcheti:[9] Greek cohort n=340 (HR=0.61 CI (0.39–0.95), p=0.031) **Yale cohort n=204 (HR=0.63 CI (0.40–0.98), p=0.043)** **Used HR > 1 for poorer survival for PD-L1 positive**	**Greek: HR 1.32 (1.09-1.75)** **Yale: HR 1.43 (1.12-1.79)**	As per Velcheti	As per Velcheti	Used 3-yr survival (but same direction as Velcheti)	**Greek: HR 1.56 (0.9-2.70)** **Yale: HR 1.50 (0.71-3.71)**	**Greek: HR 1.30 (0.83-2.62)** **Yale: HR 0.79 (0.42-1.49)**	As per Velcheti	Excluded because not IHC	NA
Studies in advanced stage not included here	0	3	0	0	0	0	0	4	20

Appendix B References

1. Hu XY, Zhang W, Hu Y et al. A Meta-Analysis Reveals Prognostic Role of Programmed Death Ligand-1 in Asian Patients with Non-Small Cell Lung Cancer. Journal of Huazhong University of Science and Technology. Medical Sciences 36, no. 3 (Jun 2016): 313-20.
2. Pan ZK, Ye F, Wu X. et al. Clinicopathological and Prognostic Significance of Programmed Cell Death Ligand1 (Pd-L1) Expression in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis. Journal of Thoracic Disease 7, no. 3 (Mar 2015): 462-70.
3. Wang AHY, Wang Y, Liu MC, et al. The Prognostic Value of Pd-L1 Expression for Non-Small Cell Lung Cancer Patients: A Meta-Analysis. European Journal of Surgical Oncology 41, no. 4 (Apr 2015): 450-6.
4. Wu PD, Wu L, Li Y et al. PD-L1 and Survival in Solid Tumors: A Meta-Analysis. PLoS ONE 10 (6) (no pagination), no. e0131403 (26 Jun 2015).
5. Xia HJ, Shen F, Hu S, et al. PD-L1 over-Expression Is Associated with a Poor Prognosis in Asian Non-Small Cell Lung Cancer Patients. Clinica Chimica Acta 469 (Feb 07 2017): 191-94.
6. Zhang Y, Kang S, Shen J, et al. Prognostic Significance of Programmed Cell Death 1 (Pd-1) or Pd-1 Ligand 1 (Pd-L1) Expression in Epithelial-Originated Cancer: A Meta-Analysis. Medicine (United States) 94, no. 6 (02 Feb 2015): e515.
7. Zhong AY, Xing X, Pan M, et al. Prognostic Value of Programmed Cell Death-Ligand 1 Expression in Patients with Non-Small-Cell Lung Cancer: Evidence from an Updated Meta-Analysis. OncoTargets and therapy 8 (2015): 3595-601.
8. Zhou ZJP, Zhan, Song Y. PD-L1 over-Expression and Survival in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis. Translational Lung Cancer Research 4, no. 2 (Apr 2015): 203-8.
9. Velcheti V, Schalper KA, Carvajal DE, et al. Programmed Death Ligand-1 Expression in Non-Small Cell Lung Cancer. Laboratory Investigation 94, no. 1 (Jan 2014): 107-16.

C. Characteristics of Included Studies, Risk of Bias of Randiomized Trials, and Reporting of Economic Evaluations

Table C1. Studies on prognostic role of PD-L1 for treatment outcomes in advanced stage NSCLC

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
Chemotherapy in advanced stage										
Borghaei, 2015 Checkmate 057 docetaxel arm of 2L in AC NSCLC	290	Age: 64 (21-85) Males: 58 Non-Caucasian: 8 Smokers: 78 PS: 0 (33), 1 (67), 2 (0) Stage: IIIB (8), IV (92) Histology: SC (0), AC (94), LC (2), other (3) EGRF/ALK/KRAS: 13/3/12 Prior RT: 48	Docetaxel, minimum follow-up 13.2 mos (average 29)	Pretreatment, archival or new tumor-biopsy specimens	Dako 28-8	PS <1% (45%), ≥1% (53%),<5% (62%) ≥5 (38%),<10% (65%) ≥10% (35%)	All patients: 4.21 (3.45 to 4.86) mos PD-L1 <1%: 3.6 (NR) mo PD-L1 ≥1%: 4.5 (NR) mos PD-L1 <5%: 4.2 (NR) mos PD-L1 ≥5%: 3.8 (NR) mos PD-L1 <10%: 4.2 (NR) mos PD-L1 ≥10%: 3.7 (NR) mos	17.2 mos fu All patients: 9.36 (8.05 to 10.68) mos PD-L1 <1%: 10.09 (7.36 to 11.93) mos PD-L1 ≥1%: 9.0 (7.10 to 10.55) mos PD-L1 <5%: 10.1 (NR) PD-L1 ≥5%: 8.1 (NR) PD-L1 <10%: 10.3 (NR) PD-L1 ≥10%: 8 (NR)	<u>ORR</u> All patients: 12.4% (8.8 to 16.8) PD-L1 <1%: 14.9% (8.6-23.3) PD-L1 ≥1%: 12.2% (7.0 to 19.3)	
Brahmer, 2015 Checkmate 017 docetaxel arm in 2L in SC NSCLC	137	Age: 64 (42-84) Males: 71 Non-Caucasian: 5 Smokers: 94 PS: 0 (27), 1 (73) Stage: IIIB (18), IV (82)	Docetaxel, minimum follow-up 11 mos	Pretreatment archival (mostly) or new tumor-biopsy specimens	Dako 28-8 pharmDx	PS <1% (38%), ≥1% (41%), <5% (50%) ≥5 (29%),<10% (55%) ≥10% (24%)	All patients: 2.8 (2.1 to 3.5) mos PD-L1 <1%: 3.0 (NR) mos	All patients: 6.0 (5.1 to 7.3) mos PD-L1 <1%: 5.9 (NR) mos PD-L1 ≥1%: 7.2 (NR) mos	<u>ORR</u> All patients: 9% (5-15) PD-L1: <1% (10%), ≥1% (11%), <5% (12%) ≥5	

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
		Histology: SC (100) EGRF/ALK/KRAS: (prior TKI 2) Prior RT: 53					PD-L1 ≥1%: 2.8 (NR) mos PD-L1 <5%: 2.9 (NR) mos PD-L1 ≥5%: 3.1 (NR) mos PD-L1 <10%: 2.8 (NR) mos PD-L1 ≥10%: 3.1 (NR) mos	PD-L1 <5%: 6.1 (NR) mos PD-L1 ≥5%: 6.4 (NR) mos PD-L1 <10%: 6.1 (NR) mos PD-L1 ≥10%: 7.1 (NR) mos	(8%),<10% (11%) ≥10% (9%)	
Carbone, 2017 Checkmate 026 chemotherapy arm in 1L in stage IV or recurrent NSCLC with PD-L1 ≥1%	270	Age: 65 (29-87) Males: 55 Non-Caucasian: 10 Smokers: 87 PS: 0 (34), 1 (64) Stage: IV (90.4), recurrent (9.3) Histology: SC (24), nonSC (76) EGRF/ALK/KRAS: NR/NR/NR (eligible if not sensitive to targeted therapy) Prior RT: 40	Platinum-doublet chemotherapy (4-6 cycles) and maintenance with pemetrexed in nonSC with stable disease or response; patients could cross-over to receive nivolumab after disease progression (60%), 2014-2016, median 13.5 mos Previous palliative RT (>2wks prior to randomization (40% patients)	Fresh or archival within 6 mos before enrollment	Dako 28-8 pharmDx	PD-L1 ≥1% (100), PD-L1 ≥1% to <5% (22), PD-L1 ≥5% (78), PD-L1 ≥50% (47)	PD-L1 ≥1%: 5.8 mos (5.4 to 6.9) PD-L1 ≥5%: 5.9 mos (5.4 to 6.9) PD-L1 ≥50%: 5.8 mos (NR)	PD-L1 ≥1%: 13.8 mos (11.0 to 17.9) PD-L1 ≥5%: 13.2 mos (10.7 to 17.1) PD-L1 ≥50%: 13.9 mos (NR)	<u>ORR</u> PD-L1 ≥1%: NR PD-L1 ≥5%: 33 (27 to 40)% PD-L1 ≥50%: 39 (30- to 48)% (exploratory)	PD-L1 ≥50% results are exploratory OS results may be influenced by cross-over by 60% to receive nivolumab after progression (but may be similar proportions within each PD-L1 group)

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
			and previous adjuvant or neoadjuvant chemotherapy >6mos before enrollment were permitted.							
Herbst, 2016 Keynote 010 docetaxel arm of 2L trial in NSCLC with PD-L1 ≥1% (Bass et al ASCO 2016 report on 1-24%, 25-49%, 50-74%, >75%)	343	Age: 62 (56-69) Males: 61 Non-Caucasian: 27 (21% Asian, mostly east) Smokers: 78 PS: 0 (34), 1 (65), 2+ (1) Stage: Histology: SC (19), AC (70), other/unknown (11) EGRF/ALK/KRAS: 8/1/NR Previous RT: NR	Docetaxel, minimum follow-up 13.1 mos	Pretreatment archival or new tumor-biopsy specimens	Dako 22C3 pharmDx	PS 1-49% (56%), ≥50% (44%) (Bass et al report on 1-24%, 25-49%, 50-74%, >75%)	All patients ≥1%: 4.0 (3.1 to 4.2) mos PD-L1 ≥50%: 4.1 (3.6 to 4.3) mos PD-L1 1-24%: 4.0 PD-L1 25-49%: 3.8 PD-L1 50-74%: 4.3 PD-L1 >75%: 4.0 Bass et al 2016 report no significant differences	All patients ≥1%: 8.5 (7.5 to 9.8) mos 1yr survival rate 34.6% PD-L1 ≥50%: 8.2 (6.4 to 10.7) mos PD-L1 1-24%: 8.5 PD-L1 25-49%: 9.9 PD-L1 50-74%: 8.2 PD-L1 >75%: 8.2 Bass et al 2016 report no significant differences	<u>ORR</u> All patients ≥1%: 9% PD-L1 ≥50%: 8% <u>Duration of response</u>: All patients ≥1%: 27 wks (6 to N/A) PD-L1 ≥50%: 35 wks (9 to 38)	
Langer, 2016 Keynote 021 Cohort G chemotherapy arm in	63	Age: 63.2 (58-70) Males: 41 Non-Caucasian: 8 Smokers: 86 PS: 0 (46), 1 (54)	Carboplatin + pemetrexed, 2014-2016, median 10.6 mos (longer follow-up reports not by PD-L1 status)	Pretreatment tumor biopsy sample	Dako 22C3 pharmDx	PS <1% (37), 1-49% (37), ≥50% (27)	All patients 8.9 mos (quite long for 1L, possibly due to	NR	<u>ORR</u> All patients: 29% (18-41) Duration of response not reached	

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
1L trial in NSCLC		Stage: IIIA (2), IIIB (3) IV (95) Histology: SC EGRF/ALK/KRAS: 0/0/NR Prior RT: no more than 30 Gy in past 6 mos					more women)		(IQR 3.5 to 10.4) PD-L1 <1%: 13% (3-34) PD-L1 1-49%: 39% (20-61) PD-L1 ≥50%: 35% (14-62)	
Reck, 2016 Keynote 024 1L chemotherapy in advanced NSCLC in PD-L1 ≥50%	151	Age: 66 (38-85) Males: 62.9 Non-Caucasian: NR (12.6% East Asian) Smokers: 87.4 PS: 0 (35), 1 (65) Stage: IV (100) Histology: SC (18), nonSC (82) EGRF/ALK/KRAS: 0/0/NR Prior RT: NR	Investigator's choice of platinum-based chemotherapy (44% carboplatin + pemetrexed), 2014-2016, median follow-up 11.2 mos	Pretreatment tumor biopsy sample	Dako 22C3 pharmDx	PS ≥50% (100)	All patients ≥50%: 6 mos (4.2 to 6.2)		<u>ORR</u> All patients (≥50%): 27.8% (20.8 to 35.7) (Indirect comparison with PD-L1 <1% in Keynote 021; PD-L1 <1%: 13% (3-34) Duration of response 6.3 mos (2.1+ to 12.6+; response ongoing at cut-off)	
Rittmeyer, 2017 OAK trial docetaxel arm in 2L chemother	425	Age: 64 (34-85) Males: 61 Non-Caucasian: 30 (22 Asian) Smokers: 83	Docetaxel, 2014-2016, median follow-up 21 mos	Pretreatment archival or fresh biopsy sample	Ventana SP142	TC0 and IC0 = PD-L1 <1% (47) TC 1/2/3 or IC 1/2/3 = ≥1% on TC or IC (52)	All patients: 4.0 mos (3.3 to 4.2)	All patients: 9.6 mos (8.6 to 11.2)	<u>ORR</u> All patients: 13.4% (10 to 17%)	

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
apy in stage IIIB or IV NSCLC		PS: 0 (38), 1 (62) Stage: NR all IIIB or IV Histology: SC (26), nonSC (74) EGRF/ALK/KRAS: 10/0/8% (many unknown) Prior RT: NR				TC 2/3 or IC 2/3 = ≥5% on TC or ICs (32) TC 3 or IC 3 = ≥50% on TCs and ≥10% on ICs (15)	TC0 and IC0:4.0 (3.1 to 4.2) TC1/2/3/or IC 1/2/3: 4.1 mos (2.9 to 4.3) TC2/3 or IC2/3: 4.1 (2.8 to 5.3) TC3 or IC3: 4.2 (2.9 to 7.0)	TC0 and IC0: 8.9 mos (7.7 to 11.5) TC0 and IC 1/2/3: 9.8 mos (7.3 to 13.7) **TC1/2/3 and IC0: 12.0 mos (3.7 to 14.7)** TC1/2/3/or IC 1/2/3: 10.3 mos (8.8 to 12.0) TC3 or IC3: 8.9 mos (5.6 to 11.6) TC0/1/2 or IC0/1/2: 9.8	TC0 or IC0: 11% (NR) TC1/2/3/or IC 1/2/3: 16.2% (11.6 to 21.7) TC3 or IC3: 11% (NR) TC2/3 or IC 2/3: 10.8 (NR) <u>Duration of response:</u> All patients: 6.2 mos (4.9 to 7.6) TC0 or IC0: 6.2 (NR) TC1/2/3/or IC 1/2/3: 6.2 mos (4.9 to 9.2) TC3 or IC3: 6.3 (NR) TC2/3 or IC2/3: 9.2 (NR)	
Fehrenbacher, 2016 POPLAR trial docetaxel arm in 2L chemotherapy in advanced NSCLC	143	Age: 62 (36-84) Males: 53 Non-Caucasian: 19 Smokers: 80 PS: 0 (32), 1 (68) Stage: NR Histology: SC (34), nonSC (66) EGRF/ALK/KRAS: 10/5/43	Docetaxel, 2013-2015, median follow-up 15.7 mos	Pretreatment sample	Ventana SP142	TC0 or IC0 = PD-L1 <1% (32) TC 1/2/3 or IC 1/2/3 = ≥1% on TC or IC (68) TC 2/3 or IC 2/3 = ≥5% on TC or ICs (37) TC3 or IC 3 = ≥50% on TCs	All patients: 3.0 mos (2.8 to 4.1) TC0 and IC0: 4.1 mos (NR) TC1/2/3 or IC 1/2/3: 3.0 mos (NR)	All patients: 9.7 mos (8.6 to 12.0) TC0 and IC0: 9.7 mos (8.6 to 12.0) TC1/2/3 or IC1/2/3: 9.2 mos (7.3 to 12.8)	<u>ORR</u> All patients: 14.7% (9.33 to 21.6) TC3 or IC3: 13% Duration of response:	

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
Also used CDER medical review		Prior RT: NR				and ≥10% on ICs (16) TC3 and IC3 showed minimal overlap	TC2/3 or IC2/3: 2.8 mos (NR0 TC3 or IC3: 3.9 (NR)	TC2/3 or IC2/3: 7.4 mos (6.0 to 12.5) TC3 or IC3: 11.1 mos (6.7 to 14.4)	All patients: 7.2 mos (5.6 to 12.5)	
Sorenson, 2016 **Denmark** **Prognosis in advanced NSCLC with chemotherapy**	204	Age: 65 (33-86) Males: 45 Non-Caucasian: NR Smokers: 68 (current) PS: 0 (45), 1 or 2 (52), unknown (3 Stage: IV (88) Histology: SC 21.5, nonSC 78.5 EGRF/ALK/KRAS: NR	Starting 1L platinum-based doublet chemotherapy (83% up to 4 cycles of carboplatin/vinorelbine; followed by bevacizumabin 15%), 2007-2012, median follow-up duration 10.6 mos **Concomitant radiotherapy in 32%**	Tumor biopsies, FFPE	Prototype 22C3 assay (Merck), darker stain due to longer incubation and/or double antigen retrieval; traceable to clinical trial PS in study with 242 patients (89% concordance)	Tumor membrane strong ≥96% and weak 1-95% (corresponding to Dako 22C3 50% and 1-49%), PD-L1+ strong 25%, weak 50%, 1 board-certified pathologist	NR	Overall: log rank p=0.33 PD-L1+ strong (median 9.0 mos [6.4-11.1]) vs. PD-L1- (7.5 mos [6.4-12.4]): aHR 1.36 95% CI 0.90 to 2.06 PD-L1+ weak (9.8 mos [8.2-12.3]) vs. PD-L1-: aHR 1.09 95% CI 0.76 to 1.58 Adjusted for age, sex, histology, smoking, and PS (crude HR NS also)	Similar associations when OS from starting 2L No association for OS seen when dividing PD-L1 expression into median or tertiles, or as continuous variable NS association of PD-L1 with age, sex, histology, smoking, PS	No major
Guo, 2017 **China** **Prognosis in stage**	128 (78 received chemotherapy)	Age: 60 (36-78) Males: 93 Non-Caucasian: 100 Smokers: 80 PS: NR	Gemcitabine plus platinum 2009-2014	Tumor tissues; FFPE	ab58810 (Abcam) antibody	Immunoreactive score (0-12): % tumor cells graded 0-4 (<5%, 5-25%, 26-50%, 51-	NR	All: median 32 mos (8.1 to 67.5) **(Not specific to treatment)**	No correlation of PD-L1+ with age , stage, lymph node	Validity of IHC methods unknown

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
III/IV SCC and platinum-based chemotherapy		Stage: III (60), IV (40) Histology: SC 100 EGRF/ALK/KRAS: NR Prior RT: NR				75%, >75% multiplied by and intensity graded 1-3; PD-L1+ IRS ≥3; 61.7%; different investigators and a pathologist independently evaluated		19.3 (95% CI 14.1-24.5) vs. 41.5 (95% CI 35.3 to 54.5) mos, p=0.001 Independent factor (OR 2.38, 95% CI 1.35- to 4.17) Diagnosis to last follow-up or date of death; log rank test & multivariate Cox regression with smoking, stage, lymph node metastases, degree of differentiation	metastases; higher in smokers (66% vs 44%, p=0.042) In 77 patients receiving gemcitabine plus cisplatin: ORR 36.2% vs 43.3%	
Schabath, 2017 **Country NR** **PD-L1 expression and prognostic role in stage IIIb and IV NSCLC receiving 2L+ chemotherapy**	136	Age: NR Males: 51.5 Non-Caucasian: 9.5 Smokers: 83 PS: NR Stage: IIIB (61), V (39) Histology: SC NR, AC (71.3) EGRF/ALK/KRAS: NR/NR/NR Prior RT: NR	2+L standard chemotherapy (4+L 28.7%),1997-2015	Archival tumor tissue (resection 85%; biopsy 15%); mean 7.2yrs sample age	Ventana SP263 validated assay	PS ≥25%, 24.2%	NS difference	NS difference	NS for PD-L1+ and patient characteristics including EGRF, ALK, KRAS; mutational load (# non-synonymous mutations correlated)	

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
Song, 2016 **China** **Expression of PD-L1 in patients with SC NSCLC taking neoadjuvant chemotherapy (data not used) & 1L after progression**	76 with matched tumor samples (63 progressing after surgery with 56 receiving first line chemotherpay)	Age: 60 (39–72) Males: 67 Non-Caucasian: 100 Smokers: 61 PS: NR Stage: I/II 46, III 54 Histology: SC 100 EGRF/ALK/KRAS: 4 of 42 tested/NR/NR	2-4 cycles of neoadjuvant chemotherapy (gemcitabine/ platinum (n =42),docetaxel/platinum (n = 23) and paclitaxel/platinum (n = 11); **no prior radiotherapy or other concurrent therapies but 74% received 1L chemotherapy after progression;** 2010-2014; median 37.5 (6.0–54) mos	Biopsies; FFPE	4µm slices stained with PD-L1 (Proteintech Group Inc, Chicago, IL, USA); UltraVision Quanto Detection System HRP DAB (Thermo Fisher Scientific Inc, Fremont, CA, USA)	H score (0-300), cut-off ≥5% at any staining and average H scores; PD-L1+ 61.8% (after neoadjuvant chemotherapy); 2 pathologists independently assessed	NR From the therapy to documented progression or death from any cause; ; uni and multi-variate analyses with a Cox proportional hazard model	All: median 32.1 mos (95% CI: 27.8–36.4) Neoadjuvant tx PD-L1: 27.0 vs. 34.2 mos; HR 0.57 95% CI 0.33-1.01) p = 0.052 1L chemotherapy ; 27.0 vs. 36.5 mos, HR 0.50 95% CI 0.27-0.94; p = 0.003 Subgroup stage III: 25.5 vs. 35.0 mos, p = 0.063 Start of confirmed pathology to death or the last follow-up; uni and multi-variate analyses with a Cox proportional hazard model	No correlations between gender, age, stage or status of PD-L1 expression; smokers had higher PD-L1 prior to neoadjuvant chemotherapy (63.0% vs. 36.7%,p = 0.02) Other clinical factors, such as gender, age and smoking history, had no correlation with survival Pre-post neoadjuvant treatment PD-L1+: 52.6% vs. 61.8%); 9 switched from – to + and 2 from + to -	Small sample for paired sample analysis Validity of IHC methods unknown Pre tx PD-L1 results may have limited relevance to stage IV advanced stage

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
TKIs										
Tang, 2015 **China** **Prognosis in EGRF mutant and wild-type patients using EGRF TKIs**	170	Age: 57yr (range 32-80) Males: 54.7 Non-Caucasian: 100 Smokers: 33.5 PS: NR Stage: IIIb (5), IV (95) Histology: AC 85.3, nonAC14.7 EGRF/ALK/KRAS: 58.2/NR/NR	All on EGRF-TKIs (49% 1L, 51% 2L), 2008-2014	Archival tumor tissue from surgery or biopsy; FFPE tumor blocks	5µm sections stained with E1L3N antibody and manual LDT	H score (% cells by intensity; max 300) ≥5 membrane H score (65.9% PD-L1+) 2 blinded pathologists, independently (method for assessing final value NR)	All: Log rank p=0.990; HR 1.315 95% CI 0.831 to 2.080 EGFR mut: p=0.990 EGRF wt: p=0.0400 From tx date with TKIs to recurrence or last follow-up; p values using log rank; multivariate cox regression	Mean OS: 39.9 mos All: Log rank p=0.233; HR 1.901 95% CI 0.953 to 3.79 EGFR mut: p=0.932 **EGRF wt: p=0.029 (shorter OS)** Exploratory multivariate in subgroups: EGRF mut: HR 0.888 95% CI 0.356 to 2.015 EGRF wt: HR 3.74 95% CI 1.32 to 10.42 From diagnosis to end of follow-up; p values using log rank; multivariate cox regression	Prevalence NS for age, sex, histopathological type, tumor stage, EGRF status; **line of TKIs (p=0.041)** AC pts: EGRF mut vs wt (72% vs 57%p=0.067) PFS: EGRFmut vs wt: HR 0.499, 95% CI 0.264 to 0.942, p=0.032) OS: EGRFmut vs WT: HR 0.419, 95% CI 0.252 to 0.672, p<0.001	Validity of IHC methods unknown PD-L1 results in each subgroup are exploratory
Gainor, 2015 ASCO 2015	98	Age: NR Males: NR	EGRF TKIs or ALK TKIs, NR, >52 mos	Biopsy and resection	E1L3N antibody	PS >5%, EGRF 15%, ALK 52%	EGFR TKIs: 6.7 vs. 13.2	EGRF TKIs: 31.8 vs. 35.63 mos; p=0.307	Pre-post PD-L1+:	Small samples

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
NR **Expression and prognosis in EGFR mutant and ALK rearranged in metastatic NSCLC; pre and post PD-L1**		Non-Caucasian: NR Smokers: NR PS: NR Stage: metastatic Histology: NR EGRF/ALK/KRAS: 69/31/NR		specimens, FFPE			mos; p=0.08 ALK TKIs: 5.6 vs. 11.1 mos; p=0.28	ALK TKIs: 26.5 vs. 51.6 mos; p=0.045	EGRF (n=58): PD-L1+ changed for 22% ALK (n=8): PD-L1+ changed for 25%	Validity of IHC methods unknown
Soo, 2017 **Korea** **Prognostic significance of PD-L1 in advanced NSCLC with EGFR-TKI**	90 (20 excluded because of inadequate tumor or immune cells)	Age: 61 Males: 29 Non-Caucasian: 100 Smokers: 23 PS: NR Stage: advanced Histology: AC 100 EGRF/ALK/KRAS: 100/NR/NR	1L EGFR-TKIs (gefitinib 76%, erlotinib 23%), 2011-2014, median 13 mo (1-44 mo)	Tumor samples: NR if pre-treatment	4µm sections using SP142 antibody with Bondmax autostainer (Leica); manual and digital scoring with Vectra slide imaging system and InForm software; positive and negative	Tumor cells <1%, ≥1-<5%, ≥5-<50%, ≥50% and average H score; 2 blinded pathologists	High H score associated with shorter PFS (HR 1.008, 95% CI 1.001-1.005) (univariate Cox proportion) Using smallest p value in Kaplan Meier's analysis of deciles best cut-off ≥109.23, p<0.001	Not significant in uni- (HR, 1.001, 0.991-1.012) or multivariate analyses Treatment initiation to death from any cause; censoring on last date of assessment	Manual and digital assessment of PD-L1 highly correlated (R^2 98%, p<0.0001) No association between H score and response to TKIs (p=0.529)	Sample timing and type unclear Validity of IHC methods unknown

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
					controls each time		for shorter PFS); retained in multivariate model Treatment initiation to progression or death; censoring on last date of assessment			
Lin, 2015 **China** **Prognostic role of PD-L1 in advanced NSCLC with EGFR-TKI**	56	Age: 59 (34-85) Males: 37.5 Non-Caucasian: 100 Smokers: 32 PS: 0/1 70 Stage: advanced Histology: AC 100 EGRF/ALK/KRAS: 100/NR/NR Previous chemotherapy: 52	EGFR-TKI therapy (gefitinib or erlotinib); tx after recurrence with radiotherapy for metastatic lesions in the bone and brain, chemotherapy, and regional therapy; median follow-up 20.6 mo (3.0-54.0).	Biopsy and surgical resection specimens; FFPE	ab58810 (Abcam) antibody	Visual grading of TC expression; H score; intensity graded 0 to 3 & positive cells graded using a 0 to 3 scale (0, 0%; 1, 1%-10%; 2, 11%-50%; 3, 51%-100%); mean H score used as cut-off; PD-L1+ 53.6%; 2 blinded pathologists	Via cut-off: 16.5 vs. 8.6 mos; p=0.001 H score 0: 13.5 mos; 3: 25.1mos With multivariate Cox regression, independent prognostic factor: HR 0.46; p=0.014) From start of EGRF-TKI tx to	Via cut-off: 35.3 vs.19.8 mos; p=0.004 H score 0: 22.0 mos; 3: 33.6 mos With multivariate Cox regression, independent prognostic factor: HR 0.26; p=0.002 From the date of diagnosis to the date of death	PD-L1 not associated with age at diagnosis, gender, smoking, PS, previous chemotherapy (p=0.85), tumor grade, and brain metastases (all p>0.05)	Sample timing and type unclear Validity of IHC methods unknown

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
							progression			
D'Incecco, 2015 **Italy** **Prognostic role of PD1 and PD-L1 with EGFR-TKIs**	N=95 (evaluable for response)	In total population 125: Age: 62 (41-84) Males: 53.6 Non-Caucasian: NR Smokers: 60 PS: NR Stage: NR; >60 with metastases Histology: AC 66.4, SC 18.4, other 15.2 EGRF/ALK/KRAS: 45/8/23	EGFR-TKI therapy (gefitinib or erlotinib); 29.3% 1L & 70.7% 2L; dates & follow-up NR	Pre-treatment tumor samples (78.4% primary tumors); sectioned	ab58810	PD-L1+ = ≥2+ staining on >5% TC; PD-L1+ 51.6%; 2 experienced pathologists	NR	21.9 vs 12.5 mos log rank p=0.09 From date of therapy start to death or last follow-up date.	Response (methods NR): 61.2% vs 34.8%, p=0.01	
Chemoradiotherapy										
Vrankar, 2016 ELCC 2016 Meeting Abstract **Slovenia** **Prognosis in locally advanced NSCLC patients using concurrent CRT**	44	Age: NR Males: 82 Non-Caucasian: NR Smokers: NR PS: NR Stage: inoperable locally advanced Histology: NR EGRF/ALK/KRAS: NR	Concurrent chemoradiotherapy, 2005-2010, median 92.3 mo	Tumor samples	Antibody SP142	PS ≥5% 16% PD-L1+ Personnel NR	Median PFS 10.1 vs 19.9 mos, p=0.008	Median OS 12.0 vs 28.0 mos, p=0.010 No PD-L1+ & 10 PD-L1- alive at 92.3 mo	Prevalence NS for age, smoking, sex PD-L1+ received lower doses of radiation and chemotherapy	Small sample Validity of IHC methods unknown Differences in treatment doses
Tokito, 2016 **Japan**	74	Age: 67 (43-81) Males: 86 Non-Caucasian: 100 Smokers: 92	CCRT with combined platinum-containing chemotherapy as 1L, median	Transbronchial biopsy in most, FFPE	EPR1161 (Abcam) antibody on 4µm sections,	≥5% tumor staining, PD-L1+ 74%, 2 experienced pathologists blinded to	10.8 vs 17.3 mos, p=0.73 From date of 1L tx to	24.9 vs. 36.9 mos, p=0.85 ("tended to be associated with poor prognosis")	NS correlation between PD-L1 and age, sex, smoking	Small sample Unclear definition of overall survival Discussion mentions

Authors, Date, Country, Funding	Sample size	Patient Characteristics (%):	Treatment Type, Dates, Follow-up	Specimen Type and Preparation for IHC	IHC Assay	PD-L1 Scoring Method, Cutoff(s) & Prevalence, Personnel	Progression Free Survival (PD-L1+ vs -)	Overall Survival (PD-L1+ vs -) (HR < 1.0 = longer survival)	Other Outcomes & Biological/ clinical Associations with PD-L1	Limitations:
Prognosis in locally advanced stage III receiving concurrent CRT		PS: 0 (72), 1 or 2 (28) Stage: stage IIIa (54), IIIb (46) Histology: SC (54), AC (46) EGRF/ALK/KRAS: NR	duration 53 mos		using BenchMark ULTRA automation and UltraView DAB detection kit	condition using consensus,	disease progression or death; log rank test and multivariable Cox proportional hazard model	Start of treatment or diagnosis to death or last follow-up; log rank test and multivariable Cox proportional hazard model	status, ECOG, histology or stage.	several antibodies used, cut-point not well-defined, and reproducibility not determined
Adam, 2015 **NR** **Prognostic value of PDL1 expression in stage III NSCLC treated by CRT**	50	Age: Males: 72 Non-Caucasian: Smokers: 52 PS: Stage: IIIa 46, IIIb 54 Histology: AC 34% EGRF/ALK/KRAS:	Chemoradiotherapy, 2002-2013, median 7.6 yrs		Ventana Benchmark Ultra platform using the E1L3N clone	Tumor cells including membrane and cytoplasmic; IHC scores 0-3: 1%, ≥1-<5%, ≥5-<10%, ≥10%of cells per area; NR PD-L1+; 44%, centrally reviewed	Median 0.7 yr (95% CI 0.6 to 0.8) vs. 1.0 yr (95% CI 0.8 to1.5), p=0.04 HR 2.1 (95% CI1.1-4.0), p=0.03	Median 1.1yr (95% CI 0.6 to 1.5) vs. 2.0 yr (95% CI 1.5 to 3.8), p=0.01 HR 2.3, 95% CI 1.2 to 4.5, p=0.01 Kaplan-Meier methods, log-rank test, and Cox proportional hazards models were used for survival analysis, adjusting for performance status (0, ≥ 1), stage (IIIA, IIIB) and thoracic surgery (yes, no)	No difference in terms of acute toxicity according to PD-L1 status (positive or negative): 25 had oesophagitis (grade≥ 2) and 16 had pneumonitis (p=0.57 and p=0.23 respectively)	PD-L1+ threshold NR refer to Herbst 2014 but unclear

Table C2. Trials of anti-PD-1/PD-L1 inhibitors in first and second-line therapy

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
First Line				
Reck, 2016 **Trial phase and identifier:** Phase 3; KEYNOTE-024; NCT02142738 **Setting:** 142 sites, 16 countries **Patient population**: treatment naïve stage IV NSCLC lacking EGFRmut or ALK rearrangements with PD-L1 ≥50% **Funding:** Merck Sharp & Dohme Corp.	**Recruitment dates:** Sept 19, 2014 – Oct 29, 2015 **Study design:** RCT, 1:1, stratified by ECOG performance status, histology, and geographical region. **Recruitment:** 1934 entered screening; 1729 with samples for PD-L1 assessment; 1653 with PD-L1 assay results (500 ≥50%, 1153 <50%); 305 randomly allocated **Median follow-up:** 11.2 mos (6.3-19.7); updated Jan 5, 2017 for OS also with reports of PFS on 2L **Analysis date**: May 9, 2016 (2nd interim analysis) **Key inclusion criteria:** ≥18, histologically or cytologically confirmed stage IV NSCLC with no	**Pembrolizumab** **n=**154,154,154,80 **Age=**64.5 (33-90) **Male=**59.7% **Non-Caucasian=**NR (40 pts in total from Japan) **Former/current smoker=**96.8% **ECOG 0/1=**35.1%; 64.3% **Nonsquamous=**81.2% **Stage IV=** 100% **TPS ≥50%=**100% **Stable brain metastases=**11.7% **EGRF mutant=**0 **ALK translocation=**0 **Previous systemic chemotherapy:** 1.9% **Previous RT=** **Other types of therapy=**3.9% (adjuvant therapy) **Chemotherapy** **n=**151,151,150,106 **Age=**66.0(38-85) **Male=**62.9% **Non-Caucasian=**NR (40 pts in total from Japan) **Former/current smoker=**87.4 **ECOG 0/1=**35.1%; 64.9% **Nonsquamous=**82.1% **TPS ≥50%=**100% **EGRF mutant=**0 **ALK translocation=**0 **Previous systemic chemotherapy:** 0.7%	**Drug, dose and administration:** Pembrolizumab IV 200mg q 3 wks; up to 35 cycles; re-treatment if not progressed during 35; for nonSC maintenance with pemetrexed Post-Pembro therapy: 31.2% Investigator's choice of carboplatin plus pemetrexed, cisplatin plus pemetrexed (only for nonsquamous tumors), carboplatin plus gemcitabine, cisplatin plus gemcitabine or carboplatin plus paclitaxel; up to 4 to 6 cycles; for nonSC maintenance with pemetrexed Post-chemo therapy: 62.4% (including 53% cross-over during study) **Other details:** Treatment was continued for the specified number of cycles or until the pt had radiologic disease progression, treatment related AEs of unacceptable severity or withdrew consent or investigator decided to withdraw the pt. Both groups could continue therapy after disease progression based on	**Primary:** • Progression Free Survival at 6 mos (time from randomization to documented disease progression per RECIST 1.1, or death due to any cause), as per blinded IRC; progressive Disease (≥20% increase in the sum of diameters of target lesions and an absolute increase of ≥5 mm or appearance of 1 or more new lesions), response assessed q 9 wks **Secondary:** • Overall survival rate at 6 mos (time from randomization to death due to any cause) • ORR (complete or partial response, as per blinded IRC q 9 wks) • Safety **Analysis**: Efficacy (ITT) Safety (all pts who received at least one dose)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	sensitizing EGFR mutations or ALK translocations, at least 1 measureable lesion , life expectancy of at least 3 mos and PD-L1 ≥50%, completion of chemotherapy or RT for adjuvant or neoadjuvant if >6 mos prior to diagnosis of metastatic disease **Key exclusion criteria:** Receiving systemic glucocorticoids or other immunosuppressive treatment, untreated brain metastases, active autoimmune disease, active interstitial lung disease or a history of pneumonitis; HIV, Hep B or C **Assay:** Formalin-fixed tumor samples, 22C3 (Dako North America); newly obtained at/after metastatic disease diagnosed and not if site previously irradiated	**Previous RT**: **Other types of therapy=**2.0% (systemic adjuvant therapy)	clinical judgement. Pts in chemotherapy group who had disease progression could cross over to pembrolizumab group (44%).	

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
Langer, 2016 **Trial phase and identifier:** Phase 2; KEYNOTE-021 Cohort G; NCT02039674 **Setting:** 26 medical centres in the USA and Taiwan (3) **Funding:** Merck & Co. **Patient population:** treatment naïve (1L) metastatic or recurrent stage IIIb or IV NSCLC	**Recruitment dates:** Nov 25, 2014 – Jan 25, 2016 **Study design:** RCT (1:1); blocks of 4 stratified by PD-L1 tumour proportion score (<1% vs ≥1%) **Recruitment:** 219 entered screening; 123 (56%) met all eligibility and randomly assigned (67 ineligible, 29 withdrew consent) **Median follow-up:** 10.6 mos (IQR 8.2 – 13.3); OS update at median 14.5 **Analysis date:** cut-off Aug 8, 2016 (6 mos after last pt enrolled); OS update Dec 31, 2016 **Key inclusion criteria:** ≥18 yrs, stage IIIb/IV NSCLC; progression >1yr after adjuvant therapy for stage I-IIIa and no systemic therapy for the recurrent disease; ECOG 0-1; without targetable EGFR or ALK genetic	**Pembrolizumab plus chemotherapy** **n=**60 **Age=**62.5(54-70) **Male=**37% **Non-Caucasian=**18% **Former/current smoker=**75% **ECOG 0/1=**40%; 58% **Adenocarcinoma=** 97% **Stage IV=**98% **TPS <1%, 1-49%, ≥50%=**35%,32%,33% **Stable brain metastases=**15% **EGRF mutant=**0 **ALK translocation=**0 **Previous lines (1, 2, ≥3)=**none **Previous systemic (neo)adjuvant therapy=**7% **Previous RT=**NR (not within 6 mos) **Other types of therapy=** **Chemotherapy** **n=**63 **Age=**63.2(58-70) **Male=**41% **Non-Caucasian=**8% **Former/current smoker=**86% **ECOG 0/1=**46%; 54% **Adenocarcinoma=**87% **Stage IV=95%** **TPS <1%, 1-49%, ≥50%=**37%, 37%, 27% **EGRF mutant=**0 **ALK translocation=**0 **Previous lines (1, 2, ≥3)=**none **Previous systemic neoadjuvant therapy:**8% **Previous RT=** NR (not within 6 mos) **Other types of therapy=**	**Drug, dose and administration:** P+C: Pembro 200 mg plus carboplatin AUC 5 mg/ml/min and pemetrexed 500 mg/m^2 (q 3 wks for 4 cycles); followed by 24 mos Pembro and indefinite pemetrexed (85%) Post-P+C cancer treatment: 22%; 0 PD1/PD-L1 therapy C: Carboplatin AUC 5 mg/ml/min plus pemetrexed 500 mg/m2 (q 3 wks for 4 cycles) and indefinite pemetrexed (69%) Post-P+C cancer treatment: 27% (including in-study cross-over, 32 of 43 pts who discontinued received anti-PD1/PD-L1 therapy **Other details:** Premedication with folic acid, vitamin B12 and corticosteroids administered by local guidelines. Pembro given at least 30 mins before chemotherapy. **Pts in Chemo only group who experienced radiological disease progression could cross over to pembrolizumab monotherapy after 21 day washout (32%).** Treatment continued for maximum cycles allowed or until disease progression, intolerable	**Primary:** • ORR (radiologically confirmed complete or partial response according to RECIST version 1.1) assessed q 6 wks for 18 wks then 9 wks to 12 mos and 12 wks thereafter, by masked, independent central review **Secondary:** • Progression-free survival (time from randomization to documented RECIST disease progression or death from any cause) • Duration of response (time from first documentation of complete or partial response to radiological disease progression) • Overall survival (time from randomisation to death from any cause, assessed q 8 wks) • Safety q 3 wks with exceptions eg TSH • Correlation between PD-L1 expression levels and antitumor activity **Analysis**: • Efficacy ITT (Response and PRS) • Safety as-treated, # received ≥1 dose (does not account for dose reductions in Chemo)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	aberrations; at least 1 radiographically measurable lesion **Key exclusion criteria:** currently participating in a study investigational agent within 4 wks prior; received prior systemic cytotoxic chemo, antineoplastic biological therapy or major surgery within 3 wks; no lung RT within 6 mos or TKI or palliative RT within 7 days; severe hypersensitivity reaction to treatment with another monoclonal antibody; clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction or abdominal carcinomatosis; HIV, hep B or C; active CNS metastases and/or carcinomatous meningitis **Assay:** 22C3 pharmDx (Dako North America, Carpinteria, CA, USA) from FFPE		toxicity, physician decision or pt withdrawal consent (whichever first); continuation after radiological progression could continue until progression confirmed 4 wks later. Dose reductions of Pembro not allowed; withheld for toxicities as per protocol.	

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	from core needle or excisional biopsies or resected tissue at diagnosis, not previously irradiated			
Carbone, 2017 **Trial phase and identifier:** phase 3, Checkmate 026, NCT02041533 **Setting:** 26 countries **Funding:** BMS **Patient population:** treatment naïve stage IV or recurrent NSCLC with PD-L1 ≥5%	**Recruitment dates:** Mar 2014-April 2015 **Study design:** RCT 1:1 stratified by PD-L1 1-4% vs ≥5% and histology **Recruitment:** 1325 assessed; 541 randomized (most not meeting criteria) **Follow-up:** median 13.5 (min for survival 13.7 mos) **Analysis date:** final analysis Aug 2, 2016 **Key inclusion criteria:** PD-L1 ≥1%, stage IV or recurrent NSCLC, ECOG 0 or 1, no previous systemic anticancer therapy for advanced disease **Key exclusion criteria:** EGFRmut & ALK+; untreated CNS mets; previous chemotherapy if >6 mos or palliative RT if <2 wks; active,	**Nivolizumab (≥1% TPS):** **n=**271,271,267,224 **Age=**63(32-89) **Male=68**% **Non-Caucasian=**16% **Former/current smoker=**89% **ECOG 0, 1=**31.4%,67.5% **Non-squamous=**75.6% **Stage IV=**94% **TPS ≥1%, ≥5%=**100%, 76.8% (**32.5% ≥50%**) **EGRF mutant=**0% **ALK translocation=**0% **Previous systemic chemotherapy=**adjuvant (8%), neoadjuvant (2%) **Previous RT=**palliative (>2 wks prior) 37.6% **Investigator's choice chemotherapy:** **n=**270,270,263,251 **Age=**65(29-87) **Male=54.8**% **Non-Caucasian=**10.4% **Former/current smoker=**89% **ECOG 0, 1=**34.4%, 64.4% **Non-squamous=**76.3% **Stage IV=**90.4% **TPS ≥1, ≥5%=**100%, 77.8% (**46.7% ≥50%)** **EGRF mutant=**0% **ALK translocation=**0% **Previous systemic chemotherapy=**adjuvant (9.3%), neoadjuvant (1.5%)	**Drug, dose and administration:** Nivolumab 3 mg/kg IV q 2 wks; median duration of treatment 3.7 (0-26.9+) mos Post-Nivo cancer treatment: 44% Investigator's choice chemotherapy IV q 3 weeks; median duration of treatment 3.4 (0.0-20.9+) mos Pemetrexed/carboplatin (44%), pemetrexed/cisplatin (33%), gemcitabine/carboplatin (12.5%), gemcitabine/cisplatin (5%), paclitaxel/carboplatin 6%); maintenance pemetrexed 38% Post-chemo cancer treatment: 64% (60% Nivo) **Other details:** Nivo patients could receive post-progression as per protocol (29%); chemo patients could cross-over to Nivo group after progression (58%); chemo ≤2 dose reductions and dose delays allowed; Nivo no dose reductions but delays allowed; concomitant systemic	**Primary (≥5% PD-L1):** • Progression-free survival in ≥ 5% PD-L1 (time from randomization to documented & confirmed RECIST disease progression or death from any cause), by blinded ICR **Secondary:** • Progression-free survival in ≥ 1% PD-L1 (time from randomization to documented & confirmed RECIST disease progression or death from any cause), by blinded ICR • Overall survival in PD-L1 ≥5% and ≥1% (time from randomization to death from any cause; q2 mos after progression) • ORR in PD-L1 ≥5% (RECIST complete or partial response by blinded ICR; q 6 wks until wk 48, then q 12 wks) • Duration of response (time from first evidence of complete or partial response until progression or death) • Disease-related Symptom Improvement Rate by Week 12

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	known or suspected autoimmune disease; previous malignancy **PD-L1 Sample & Assay:** fresh or archival within 6 mos of enrollment, 28-8 assay	**Previous RT=**palliative (>2 wks prior, 40%)	glucocorticoids (<3 wks) for non-automimmune conditions allowed	**Analysis:** • Efficacy ITT (central review) • Safety # received ≥1 dose **Subgroup analysis:** **PFS: age, sex, ECOG, histology, smoking, ≥50 PD-L1**
Spigel, 2015 **ESMO 2015** **&** **ClincialTrials.gov** **Trial phase and identifier:** phase 2, FIR NCT01846416 **(1L Cohort)** **Setting:** 31 countries **Funding:** Genentech Inc. **Patient population:** PD-L1+ stage IIIb, IV, or recurrent NSCLC who have not received systemic chemotherapy	**Recruitment dates:** May 2013-Jun 2014 **Study design:** phase 2 open label **Recruitment:** NR **Follow-up:** ≥3 mos for preliminary findings; approximately 20 mos in ClinicalTrials.gov but NR by PD-L1 **Analysis date:** ORR results for TC3 or IC3 Oct 23 2014; all patientsTC2/3 or IC2/3 at Jan 7, 2015 via ClinicalTrials.gov **Key inclusion criteria:** ≥18 yrs; stage IIIb (not eligible for definitive chemoradiotherapy), IV, or recurrent NSCLC; ECOG 0 or 1; measureable	**Atezolizumab (anti-PD-L1):** **n=**31 **Age=**68 (SD 10.8) **Male=**45.2% **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**NR **Non-squamous=**NR **TC3 or IC3=**23% **EGRF mutant=**NR **ALK translocation=**NR **Previous lines (1, 2, ≥3)=**0 **Previous systemic chemotherapy=**none **Previous RT:**NR **Other types of therapy=**NR	**Drug, dose and administration:** Atezolizumab 1L: 1200 mg IV q 3 weeks; median duration of treatment mos Post-Atezo cancer treatment: NR **Other details:** treatment until progression	**Results for PD-L1 TC3 or IC3 (ORR RECIST, duration of response, & 24-wk PFS) are from Oct 2014** **Primary:** • ORR (Modified RECIST complete or partial by investigator; q 6 wk for 12 mos, then q 9wk until progression) **Secondary:** • ORR (RECIST complete or partial response by investigator; q 6 wk for 12 mos, then q 9 wk until progression [up to 20 mos]) • Duration of response via RECIST (time from first evidence of complete or partial response until progression or death) • % with duration 6-mos • Progression-free survival via RECIST (time from randomization to documented & confirmed RECIST disease progression or death from any cause within 30 days of last treatment)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	disease; adequate hematologic and end organ function; TC2/3 or IC2/3 **Key exclusion criteria:** anti-cancer therapy within 3 wks (TKIs within 7 days); CNS disease including metastases; previous chemotherapy for advanced disease **PD-L1 Sample & Assay:** central review using SP142; archival or fresh and could have been undergoing chemotherapy or chemoradiation			• Progression-free survival via Modified RECIST • % with PFS at 6 and 12 mos (RECIST and modified RECIST) • OS (first dose until death from any cause) • Safety (incidence of AEs) **Analysis:** efficacy in all, safety in all who received treatment **Subgroup analysis:** none specified in NCT and NR
Peters, 2017 **Trial phase and identifier:** phase 2, BIRCH NCT 02031458 (1L Cohort findings) **Setting:** global, multicenter (19 diverse countries) **Funding:** Genentech Inc. of Hoffmann-La Roche	**Recruitment dates: Jan** 2014-Dec 2014 **Study design:** phase 2 open label **Recruitment:** 3914 screened (36% TC2/3 or IC2/3) with 667 enrolled in 3 cohorts **Follow-up:** ORR, PFS, DOR min 12 mos; OS min 20 mos/median 22.5 mos	**Atezolizumab (anti-PD-L1): n=**139 **Age=**67 (35-88) **Male=**51% **Non-Caucasian=**12% **Former/current smoker=**84% **ECOG 0, 1=**43%, 57**%** **Non-squamous=**77% **TC3 or IC3=**47% **EGRF mutant=**11% **ALK translocation=**4% **KRAS=**33% **Previous lines (1, 2, ≥3)=**0 **Previous systemic chemotherapy=**none **Previous RT:**NR **Other types of therapy=**NR	**Drug, dose and administration:** Atezolizumab 1L: 1200 mg IV q 3 weeks; median duration of treatment 4.2 mos (all 3 cohorts) Post-Atezo cancer treatment: 1.1% received immunotherapy after study **Other details:** treatment until progression; no dose reductions	**Primary:** • ORR (RECIST complete or partial response by independent-review facility (IRF); q 6 wk for 12 mos, then q 9 wk until progression [up to 16 mos]) **Secondary:** • Progression-free survival via IRF RECIST (time from first dose to documented & confirmed RECIST disease progression or death from any cause within 30 days of last treatment) • Duration of response via IRF RECIST (date of first

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
Patient population: stage IIIb, IV, or recurrent NSCLC with TC2/3 or IC2/3 who have not received systemic chemotherapy	**Analysis date:** ORR, PFS, DOR Dec 1, 2015; OS Aug 1, 2016 **Key inclusion criteria:** ≥18 yrs; stage IIIb (not eligible for definitive chemoradiotherapy), IV, or recurrent NSCLC; ECOG 0 or 1; measureable disease; adequate hematologic and end organ function; PD-L1 TC2/3 or IC2/3; pts with EGRF or ALK must have progressed on targeted therapy **Key exclusion criteria:** anti-cancer therapy within 3 wks (TKIs within 7 days); CNS disease including metastases; other malignancies within 5 yrs; history of autoimmune disease, history of idiopathic pulmonary fibrosis, drug-induced pneumonitis, hepatitis B or C, HIV, prior treatment with PD-L1/PD-1 or CTLA4 or CD137 drugs; previous			occurrence of a CR or PR that is subsequently confirmed (whichever status is recorded first) and the first date that PD or death is documented) • Investigator reviewed response, PFS and duration using RECIST and modified RECIST • Overall survival (first dose until death from any cause; q 6 wks 12 mos and 9 wk thereafter) • Progression-free survival at 6 and 12-mos • Time in response • Safety (incidence of AEs) • **Analysis:** efficacy in all, safety in all who received treatment • **Exploratory**: by PD-L1 status • **Subgroup analysis:** none specified in NCT and NR • **Used historical (2013) controls for ORR 20%**

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	chemotherapy for advanced disease **PD-L1 Sample & Assay:** central review using SP142; archival or fresh TC2 ≥5% to <50%, TC3 ≥50%; IC2 ≥5% to <10%, IC3 ≥10%			
Antonia, 2017 **2017 ASCO Annual** **Trial phase and identifier:** phase 1/2, NCT01693562 **Setting**: USA, Canada, Korea, United Kingdom **Funding:** Medimmune **Patient population:** stage III/IV NSCLC either naïve (1L) or with previous treatment for advanced disease (≥2L)	**Recruitment dates:** Aug 2012-NR **Study design:** single-arm trial **Recruitment:** NR **Follow-up:** **1L**: median 17.3 mos (1.0-36.8) **≥2L**: median 29.2 mos (0.3-40.5) **Analysis date:** Oct 24, 2016 (Primary completion date July 2017) **Key inclusion criteria:** ECOG 0 or 1, tumor sample, adequate organ and marrow function, **Key exclusion criteria:** prior Grade ≥ 3 irAE while receiving immunotherapy, previous PD-1/PD-L1	**Durvalumab** **1L** **n=**59 **Age=**NR **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**37%, 63% **Non-squamous=**51% **TPS ≥25%=**83% **EGRF mutant=**NR **ALK translocation=**NR **Previous lines (1, 2, ≥3)=**0% **Previous systemic chemotherapy=**none **Previous RT:** NR **Other types of therapy=**NR **≥2L** **n=**245 **Age=**NR **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**NR **Non-squamous=**47% **TPS ≥25%=**50% **EGRF mutant=**NR **ALK translocation=**NR	**Drug, dose and administration:** Durvalumab 10mg/kg q 2 wk, median duration of treatment NR Post-Durvalumab cancer treatment: NR **Other details:** until unacceptable toxicity or disease progression, up to 12 mos with retreatment permitted for those progressing after 12 mos	**Primary:** • Safety (AEs, SAEs) **Secondary:** • ORR, investigator assessed confirmed complete or partial • DOR (first documentation of objective response to the first documented disease progression or death due to any cause) • PFS (start of treatment until the documentation of confirmed **immune-related disease progression** or death due to any cause) • Overall survival (first dose of study drug until death or up to 2 years)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	treatment, autoimmune disease, immunodeficiency, untreated central nervous system (CNS) metastases requiring concurrent treatment, other invasive malignancy within 2 years, hepatitis B, C. HIV **PD-L1 Sample & Assay:** fresh or archival sample, Ventana SP263 (high ≥25% PS; low/neg <25%)	**Previous lines (1, 2, ≥3)=**0%,33%, 67% (from 2016 ESMO abstract with n=211) **Previous systemic chemotherapy=**NR **Previous RT:**NR **Other types of therapy=**NR		
Verschraegen, 2016 ESMO **Trial phase and identifier:** phase 1b, Javelin Solid Tumor, NCT01772004 **Setting:** 58 centers in USA **Funding:** Merck KGaA and Pfizer **Patient population:** treatment naïve (1L) and previously treated metastatic or recurrent stage IIIb or IV NSCLC	**Recruitment dates:** Sept 2013-June 2014 **Study design:** open-label phase 1b dose-expansion **Recruitment:** **1L:** NR **2L+**: 288 assessed; 184 enrolled and analyzed **Follow-up:** **1L:** ORR data reported for 75 with ≥3 mos; PFS for all patients median 13 wks (0-31) **2L+**: median 8.8 mos (7.2-11.9); min 6 mos **Analysis date:**	**Avelumab** **1L** **n=**145 (PD-L1 evaluable in 45 of 75 assessed) **Age=**70 (41-90) **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**31%, 69% **Non-squamous=**73% **TPS ≥1%=**77.8% (of 45 pts) **EGRF mutant=**0 **ALK translocation=**0 **Previous lines (1, 2, ≥3)=**0 **Previous systemic chemotherapy=**0 **Previous RT=**NR **Other types of therapy=**NR **≥2L** **n=**184, 184, 184, 143 **Age=**65 (58-69.5) **Male=**54%	**Drug, dose and administration:** Avelumab 10 mg/kg IV q 2 wks; median 6 doses (IQR 3-15); duration of treatment 10 wks (1L) and 12.2 wks (IQR 6.1-30) (2L+) Post-Avelumab cancer treatment: 21% (drugs 18%, RT 9%) drugs included cytotoxic chemotherapy 15% and targeted therapy in 7% **Other details:** treated until progression or toxicity; premedication with paracetamol and diphenhydramine; dose modifications (5%) and delays permitted for grade 2 AEs	**Primary:** • None (dose limiting toxicity during dose-escalation portion) **Secondary:** • Best OR (6 weeks for first 12 months, then 12-weekly until end of treatment and post treatment every 3 months [up to 52 months]); investigator assessed • ORR confirmed complete or partial (RECIST)(2L+) • Unconfirmed response at week 13 (1L) • Duration of response (first complete or partial until progression or death) • Overall survival (time from first administration to death from any cause)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	1L: Oct 23, 2016 **2L+:** cut-off Jan 2015 **Key inclusion criteria:** stage IIIb or IV NSCLC either treatment naïve for advanced NSCLC (1L) or progressed after platinum-based chemotherapy for metastatic disease (≥2L); ECOG 0-1, no active or history of brain metastases; adequate hematological, hepatic, and renal function, measureable disease **Key exclusion criteria:** EGRFmut or ALK+ (for 1L); other cancer diagnosis within 5 years, rapidly progressing disease, autoimmune disease **PD-L1 Sample & Assay:** fresh biopsy or archival sample**;** clone 73-10 on proprietary assay (Dako), prospectively determined scoring on TC (membranous) as ≥1% and ≥5% with any staining intensity and ≥25%	**Non-Caucasian=**13% **Former/current smoker=**86% **ECOG 0, 1=**30%, 70% **Non-squamous=**71% **TPS ≥1, ≥5%, ≥25%=**86%, 59%, 37% (n=142 evaluable) **EGRF mutant=**5% (40% unknown) **ALK translocation=**1% (44% unknown) **KRAS mutant=**11% (68% unknown) **Previous lines (1, 2, ≥3)=**66%, 24%, 9% **Previous systemic chemotherapy=** carboplatin 85%, pemetrexed 54%, cisplatin 25%, gemcitabine 17%, erlotinib 11% **Previous RT=**51% **Other types of therapy=**surgery 53%		• Progression-free survival (time from first administration to documented disease progression or death from any cause) • Safety (each biweekly visit • Activity according to PD-L1 **Exploratory subgroups post hoc:** age, sex, histology, previous lines, smoking history, EGFR/ALK (for 2L+) **Analysis:** safety and activity for those with 1+ doses

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	with moderate-to-high staining intensity (2+ to 3+), and IC as ≥10% staining of any intensity within hotspots (dense aggregates of tumor-associated immune cells adjacent to tumor cells)			
Study, Country, Funding	**Study Characteristics**	**Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)**	**Treatment Characteristics**	**Outcomes & Analysis**
Second-line				
Herbst, 2016 **Trial phase and identifier:** Phase 2/3; KEYNOTE-010; NCT01905657 **Setting:** 202 centres in 24 countries **Funding:** Merck & Co. **Patient population:** PD-L1 positive advanced NSCLC with disease progression on platinum-doublet chemotherapy	**Recruitment dates:** Aug 28, 2013 – Feb 27, 2015 **Study design:** RCT (1:1:1); blocks of 6 per stratum (ECOG 0 or 1, east Asia vs not east Asia, TPS after 441 patients when IHC cut-point established) **Recruitment:** 2699 screened – (477 no PD-L1 assay + 747 <1% TPS + 441 ineligible) = 1034 randomized **Follow-up:** median 13.1 mos (IQR 8.6 - 17.7)	**Pembrolizumab (anti-PD-1; ≥1% TPS):** **n=**345, 344, 339, 271 **Age=**63 (56-69) **Male=**62% **Non-Caucasian=**28% **Former/current smoker=**81% **ECOG 0, 1=**33%, 67% **Non-squamous=**70% **TPS ≥50%=**40% **EGRF mutant=**8% **ALK translocation=**1% **Previous lines (1, 2, ≥3)=**71%, 19%, 8% **Previous systemic chemotherapy=** 97% **Other types of therapy=** immunotherapy 1%, EGFR TKI 12%, ALK inhibitor 1% **Pembrolizumab 10 mg/kg (≥1% TPS):** **n=**346, 346, 343, 271 **Age=**63 (56-69) **Male=**62%	**Drug, dose and administration:** Pembrolizumab 2 mg/kg IV q 3 weeks; median duration of treatment 3.5 (1.4-7.2) mos Post-Pembro cancer treatment: 40% (35% chemotherapy;1% immunotherapy; 8% erlotinib) Pembrolizumab 10 mg/kg IV q 3 weeks; median duration of treatment 3.5 (1.4-7) mos Post-Pembro cancer treatment: 38% (29% chemotherapy; 2% immunotherapy [1% nivolumab]; 8% erlotinib) Docetaxel 75 mg/m^2 IV q 3 weeks; median duration of treatment 2 (0.8-3.6) mos	**Primary (≥1% and ≥50% TPS):** • Overall survival (time from randomization to death from any cause; q2 mos after progression) • Progression-free survival (time from randomization to documented & confirmed RECIST disease progression or death from any cause) • Safety & tolerability (NCI grade 3-5 TRAEs, immune-related TRAEs, WTRAEs, deaths due to treatment) **Secondary (≥1% and ≥50% TPS):** • ORR (RECIST complete or partial response by blinded radiologist; q 9 weeks; did not account for immune-related criteria)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	Analysis date: Sept 30, 2015 (2nd interim analysis); also Herbst 2016 ESMO abstract med 19.2 mos **Key inclusion criteria:** age ≥18 yr, progression after ≥2 cycles platinum-doublet chemotherapy as well as tyrosine-kinase inhibitor (if applicable), measurable disease, ECOG 0 or 1, tumor sample, PD-L1 TPS ≥1% **Key exclusion criteria:** previous PD-L1/1 inhibitor, active brain metatastasis, active autoimmune disease, interstitial lung disease or hx of pneumonitis **PD-L1 Sample & Assay:** archived 44% vs fresh 56% (no radiation & intervening treatment); Dako IHC assay with Merck murine 22C3 anti-human PD-L1 antibody; 66% of pts with samples had	**Non-Caucasian=**27% **Former/current smoker=**82% **ECOG 0, 1=** 35%, 65% **Non-squamous=**71% **TPS ≥50%=**44% **EGRF mutant=**9% **ALK translocation=**1% **Previous lines (1, 2, ≥3)=**68%, 20%, 10% **Previous systemic chemotherapy:** 97% **Other types of therapy=**immunotherapy <1%, EGFR TKI 16%, ALK inhibitor 1% **Docetaxel (≥1% TPS):** **n=**343, 343, 309, 317 (10% more than other arms withdrew consent) **Age=**62 (56-69) **Male=**61% **Non-Caucasian=**27% **Former/current smoker=**78% **ECOG 0, 1=** 34%, 65%, **Non-squamous=**70% **TPS ≥50%=**44% **EGRF mutant=**8% **ALK translocation=**1% **Previous lines (1, 2, ≥3)=**69%, 22%, 8% **Previous systemic chemotherapy:** 99% **Other types of therapy=**immunotherapy <1%, EGFR TKI 14%, ALK inhibitor 1%	Post-docetaxel cancer treatment: 44% (27% chemotherapy; 13% immunotherapy [8.7% nivolumab]; 11% erlotinib) **Other details:** treatment continued for 24 months unless progression, intolerable toxic effects, physician decision, patient withdrawal, or others; can be treated again up to 12 mos if progression after response; progressing on immune-related response criteria could remain on Pembro treatment until confirmatory scan 4-6 weeks later Crossover upon progression from docetaxel to Pembro allowed after Dec 2105	• Duration of response (time from first evidence of complete or partial response until progression or death) **Exploratory outcomes:** • ORR & PFS by immune-related response criteria • QoL: EuroQoL EQ-5D. • Disease-specific QoL: EORTC QLQ C-30 and EORTC QLQ LC-13 *QoL up to treatment discontinuation **Analysis:** • Efficacy ITT (central review) • Safety # received ≥1 dose • HRs using Cox proportional hazard; p values using logrank **Subgroup analysis:** age, sex, EOCG, EGFR mutation status, age of tumor sample (planned); histology (post-hoc)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	≥1% + 28% had ≥50%			
Brahmer, 2015 **Trial phase and identifier:** Phase 3; CheckMate017; NCT01642004 **Setting:** The Netherlands, Germany, Italy, Moscow, Poland, USA, Spain, Chile, Czech Republic **Funding:** Bristol-Myers Squibb **Patient population:** advanced squamous-cell NSCLC with disease progression during or after (one regime) first-line therapy	**Recruitment dates:** Oct 2012 – Dec 2013 **Study design:** RCT; stratified by prior use of paclitaxel, geographic region (US or Canada vs Europe, vs rest of world) **Recruitment:** 352 enrolled; 272 randomized **Follow-up:** minimum 11 mos (OS updated July 2015) **Analysis date**: database lock Dec 2014; Jan 10, 2015 early termination due to OS superiority of nivolumab with 100% planned enrollment; ≥2 yr data for all patients (Barlesi 2016, 2016) **Key inclusion criteria:** stage IIIB or IV squamous-cell NSCLC, disease recurrence after one prior platinum-containing regimen, ≥18yrs, ECOG 0 or 1, submitted a	**Nivolumab (anti-PD-1)** **n=**135,135,131,110 **Age=**median 62 (39-85); <65yr 59% **Male=**82% **Non-Caucasian=**10% **Former/current smoker=**90% **ECOG 0, 1=**20%, 79% **Non-squamous=**0% **EGRF mutant=**NR but no prior treatment **ALK translocation=**NR **Previous lines of systemic therapy (1, 2, ≥3**)=99%, 1% **Previous systemic chemotherapy:** 100% **Other types of therapy=0% EGFR TKI** **PD-L1 expression**=<1% 40%, ≥1% 47%, ≥5% 31%, ≥10% 27%, unquantifiable 13% **Docetaxel** **n=**137,137,129,127 **Age=**median 62 (42-84); <65yr 53% **Male=**71% **Non-Caucasian=**5% **Former/current smoker=**94% **ECOG 0, 1=**27%, 73% **Non-squamous=**0% **EGRF mutant=**NR but 2% previous treatment **ALK translocation=**NR **Previous lines prior systemic therapy (1, 2, ≥3)=**100%, 0%, 0% **Previous systemic chemotherapy:** 99% **Other types of therapy=**EGFR TKI 2%	**Drug, dose and administration:** Nivolumab 3mg/kg IV q 2 weeks; median 8 (1-48) doses Post-nivolumab cancer treatment: 36% chemotherapy (24% docetaxel), 27% radiotherapy, 4% EGFR TKI, 1% immunotherapy Docetaxel 75 mg/m^2 IV q 3 weeks (limited by regional algorithms); median 3 (1-29) doses; 27% had dose reductions Post-docetaxel cancer treatment: 30% systemic therapy (24% chemotherapy mainly antimetabolites), 18% radiotherapy, 2% immunotherapy, 6% EGFR TKI **Other details:** treatment with nivolumab was permitted as per protocol after initial RECIST progression (n=28 including 9 meeting nonconventional benefit/pseudoprogression criteria); reductions in docetaxel dose for toxic effects based on product label but no reduction in nivolumab dose	**Primary:** • Overall survival (time from randomization to death from any cause; followed q 3 mos after study drug discontinued) **Others:** • ORR (investigator assessed and confirmed; best response between randomization and progression or subsequent anti-cancer therapy; RECIST complete or partial response; at 9wks and then q6 wks; did not account for immune-related criteria) • Survival at 6, 12 and 18 mos (up to 3 yrs per protocol) • Duration and time to response • Progression-free survival (time from randomization to documented RECIST disease progression or death from any cause) • Lung Cancer Symptom Scale (% with 10 point change at wk 12) • Safety (NCI grades, immune-related TRAEs; WTRAE, death due to treatment) **Analysis:** • Efficacy ITT (central review)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	pretreatment tumor-tissue specimen (83% quantifiable later), stable brain metastasis were eligible **Key exclusion criteria:** autoimmune disease, interstitial lung disease, systemic immunosuppression, prior therapy with T-cell costimulation or checkpoint-targeted agents, prior docetaxel therapy; more than one prior systemic therapy for metastatic disease, but prior maintenance therapy allowed **PD-L1 Sample & Assay:** pretreatment, archival or recent tumor-biopsy specimens; validated automated Dako IHC assay with clone 28-8 antibody (Epitomics); positive with staining of tumor cell membrane (any intensity) at 1%, 5%, or 10% of cells in a section ≥100 tumor cells	**PD-L1 expression**=<1% 38%, ≥1% 41%, ≥5% 29%, ≥10% 24%, unquantifiable 21%		• Safety # received ≥1 dose • HRs using Cox proportional hazard; p values using logrank **Subgroup/exploratory analysis:** • PD-L1 levels • EuroQol 5D (exploratory) • Serum and tumor biomarkers

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
Borghaei 2015 **Trial phase and identifier:** Phase3, CheckMate 057; NCT01673867 **Setting:** USA, Spain, Germany, France, Mexico, Italy, Russia **Funding:** Bristol-Myers Squibb **Patient population:** advanced nonsquamous-cell NSCLC with disease progression during or after platinum-based doublet chemotherapy	**Recruitment dates:** Nov 2012 – Dec 2013 **Study design:** RCT; stratified by prior maintenance therapy, line of therapy and used permuted blocks **Recruitment:** 582 **Follow-up:** minimum 13.2 mos; 17.2 for OS **Analysis date:** database lock March 16, 2015; Apr 16, 2015 superiority achieved but study continuation (followup at July 2 2015 for OS) **Key inclusion criteria:** stage IIIB or IV or recurrent nonsquamous-cell NSCLC after radiation or surgical resection and disease progression during or after one prior platinum-containing chemotherapy regimen, ≥18yrs, ECOG 0 or 1, stable brain metastasis	**Nivolumab (anit-PD-1)** **n=**292,292,287,244 **Age=**median 61 (37-84); ≥65 yr 37% **Male=**52% **Non-Caucasian=**8% **Former/current smoker=**79% **ECOG 0, 1=**29%, 71% **Non-squamous=**100% **EGRF mutant=**15% **ALK translocation=**4% **Previous lines of systemic therapy (1, 2, ≥3)=**88%, 12% **Other types of therapy=**EGFR TKI 10%, other experimental 8% **PD-L1 expression**=<1% 47%, ≥1% 53%, ≥5% 41%, ≥10% 37%, unquantifiable 21% **Docetaxel** **n=**290,290,268,268 **Age=median** 64 (21-85); ≥65 yr 47% **Male=**58% **Non-Caucasian=**8% **Former/current smoker=**78% **ECOG 0, 1=**33%, 67% **Non-squamous=**100% **EGRF mutant=**13% **ALK translocation=**3% **Previous lines of systemic therapy (1, 2, ≥3)=**89%, 11% **Other types of therapy=** EGFR TKI 8%, other experimental 6% **PD-L1 expression**=<1% 45%, ≥1% 55%, ≥5% 38%, ≥10% 35%, unquantifiable 23%	**Drug, dose and administration:** Nivolumab 3mg/kg IV q 2 wks; median 6 (1-52) doses Post-nivolumab cancer treatment: radiotherapy 26%, systemic therapy 42%; ALK/EGFR inhibitors 12%; immunotherapy n=1 Docetaxel 75 mg/m^2 IV q 3 wks; median 4 (1-23) doses; 26% had dose reductions Post-docetaxel cancer treatment: radiotherapy 30%, systemic therapy 50%; ALK/EGFR inhibitors 23%; immunotherapy n=6 **Other details:** treatment with nivolumab was permitted as per protocol after initial RECIST progression (n= 71 including 16 meeting nonconventional benefit/psuodoprogression criteria); reductions in docetaxel dose for toxic effects based on product label but no reduction in nivolumab dose	**Primary:** • Overall survival (time from randomization to death from any cause; followed q 3 mos after study drug discontinued) **Others:** • ORR (investigator assessed; confirmed RECIST complete or partial response; at 9wks and then q 6 wks; did not account for immune-related criteria) • Progression-free survival (time from randomization to documented RECIST disease progression or death from any cause) • Lung Cancer Symptom Scale questionnaire (% with 10-point decrease at 12 wks) • Efficacy & safety by tumor PD-L1 expression • Safety **Analysis:** • Efficacy ITT (central review) • Safety # received ≥1 dose • HRs using Cox proportional hazard; p values using logrank

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	eligible, prior TKI therapy allowed as was continuation or switch to maintenance therapy with pemetrexed, bevacizumab, or erlotinib **Key exclusion criteria:** autoimmune disease, interstitial lung disease, systemic immunosuppression, prior therapy with T-cell costimulation or checkpoint-targeted agents, prior docetaxel therapy; more than one prior systemic therapy for metastatic disease, but prior maintenance therapy allowed **PD-L1 Sample & Assay:** pretreatment, archival or recent tumor-biopsy specimens; validated automated Dako IHC assay with clone 28-8 antibody (Epitomics); positive with staining of tumor cell membrane (any intensity) at 1%, 5%, or 10% of cells in a			

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	section ≥100 tumor cells			
Fehrenbacher 2016 **Trial phase and identifier:** phase 2, POPLAR; NCT01903993 **Setting:** Belgium, Canada, France, Germany, Italy, Korea, Poland, Spain, Sweden, Thailand, Turkey, UK, USA **Funding:** F Hoffmann-La Roche/Genentech	**Recruitment dates:** Aug 2013-Mar 2014 **Study design:** RCT stratified by immune cell (IC) PD-L1, histology, previous lines of therapy and in permuted 1:1 with block size 4 **Recruitment:** 527 assessed-47 no tissue, 287 enrolled **Median follow-up:** 14.8 mos (0.2-18.8 mos) in atezolizumab; 15.7 mos in docetaxel **Analysis date:** May 8, 2015 (minimum 13 mos follow-up) **Key inclusion criteria:** ≥ 18 yrs, ECOG 0 or 1, measurable disease by RECIST, adequate haematological and end-organ function, provided tissue specimens **Key exclusion criteria:** active or untreated brain	**Atezolizumab (anti-PL-D1)** **n=**144,144,142,118 **Age=**median 62 (42-82) **Male=**65% **Non-Caucasian=**NR **Former/current smoker=**81% **ECOG 0, 1=**32%, 68% **Non-squamous=**66% **EGRF mutant=**13% (in 83 pts with known status) **ALK translocation=**0% **Previous lines of systemic therapy (1, 2, ≥3)=**65%,35% **Other types of therapy=** **TPS/IC =**TC3 10%, TC2 **10%**, TC1 13%, TC0 **67%**/ IC3 7%, IC2 13%, IC1 37%, IC 43% **Docetaxel** **n=**143,143,135,134 **Age=**median 62 (36-84) **Male=**53% **Non-Caucasian=**NR **Former/current smoker=**80% **ECOG 0, 1=**32%, 68% **Non-squamous=**66% **EGRF mutant=**10% (in 83 pts with known status) **ALK translocation=**5% **Previous lines systemic therapy (1, 2, ≥3)=**67%, 33% **Other types of therapy=** **TPS/IC** = TC3 11%, TC2 **18%**, TC1 15%, TC0 **57%**/ IC3 6%, IC2 13%, IC1 38%, IC44% *TC3 and IC3 tumors showed minimal overlap	**Drug, dose and administration:** Atezolizumab 1200 mg IV q 3 wks; median duration 3.7 mos (0-19) Post-atezolizumab cancer treatment: total 40.3%; chemotherapy 37.5% (docetaxel 27.1%); immunotherapy 0%; targeted therapy 11.8% (erlotinib 5.6%) Docetaxel 75mg/m^2 IV q 3 wks; median duration 2.1 mos (0-17) Post-docetaxel cancer treatment: total 41.3%; chemotherapy 32.2% (gencitabine 16.8%); immunotherapy 4.9% (atezolizumab, nivolumab 3.5%); targeted therapy 14.7% (erlotinib 9.1%); median lines 1.8 **Other details:** Atezolizumab continued as long as patients received clinical benefit according to investigator assessment (toxicity, progression after radiological, biopsy and clinical status) (42%); docetaxel given until radiological progression or unacceptable toxicity	**Primary (Overall and PD-L1 subgroups):** • Overall survival (time from randomization to death from any cause; centrally assessed q 3 mos after treatment discontinuation) • Final analysis at 173 deaths 80% power if HR 0.35 for TC3, 0.5 for TC2/3, 0.6 for TC1/2/3 **Others:** • Progression-free survival (investigator assessed; time from randomization to documented RECIST disease progression or death from any cause) • ORR (investigator assessed; RECIST complete or partial response; imaging q 6 wks for 36 wks then q 9 wks until treatment discontinuation) • Duration of response (investigator assessed; time from first occurrence of OR to time of RECIST progression [confirmed], or death from any cause) • Efficacy according to immune-modified RECIST criteria • Time to deterioration EORTC QLQLC-13

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	metastases, history of pneumonitis, autoimmune or chronic viral diseases, or previous treatment with docetaxel, CD137 agonists, antiCTLA4, anti-PD-L1, or anti-PD-1 therapeutic antibodies, or PD-L1–PD-1 pathway-targeting agents **PD-L1 Sample and Assay:** formalin-fixed paraffin-embedded specimen; expression on tumor cells and immune cells using Ventana SP142 IHC assay. Scored tumor cells as % of tumor cells (TC) (TC3≥50%, TC2≥5%-<50%, TC1≥1%-<5%, TC0<1%) and tumor infiltrating immune cells (IC) (IC3≥10%, IC2≥5%-<10%, IC1≥1%-<5%, IC<1%) **Other biomarkers:** immune gene expression (T-effector and interferon-ɣ gene signatures, PD-L1, PD-1, PD-L2, B7.1 gene expression		More concomitant systemic steroids used by atezolizumab group (would tend to bias away from atezolizumab as per FDA report)	• EORTC QLQ C30 (single items at each time point) • Safety **Analysis:** • Efficacy ITT (central review) • Safety # received ≥1 dose • HRs using Cox proportional hazard; p values using logrank

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	(high levels as at or above median level			
Rittmeyer 2017 **Trial phase and identifier:** phase 3, OAK; NCT02008227 **Setting:** 194 centres in 31 countries **Funding:** F Hoffmann-La Roche/Genentech	**Recruitment dates:** Mar 2014-April 2015 (Nov 2014 for primary efficacy) **Study design:** RCT 1:1 permuted block size 8 stratified by immune cell (IC) PD-L1 expression, lines chemotherapy **Recruitment: 2050** assessed-612 not meeting criteria; 1225 enrolled **Median follow-up:** 21 mos **Analysis date:** data cut-off July 7 2016 **Key inclusion criteria:** ≥ 18 yrs, ECOG 0 or 1, measurable disease by RECIST, 1 or 2 previous lines of chemotherapy for stage IIIB or IV (1+ platinum-based), patients with EGRF or ALK required to have TKI therapy; adequate haematological and end-organ function,	**Atezolizumab** **n=**613,425 (primary efficacy),613 (secondary efficacy),609,555 **Age=**median 63 (33-82); 45%≥65 **Male=**61% **Non-Caucasian=**24% (5% unknown) **Former/current smoker=**80% **ECOG 0, 1=**36, 64% **Non-squamous=**74% **EGRF mutant=**10% (15% unknown) **ALK translocation=**<1% **Previous lines of systemic therapy (1, 2, ≥3)=**75%,25% **Other types of therapy=** **TPS/IC =**TC3 or IC3 17%, TC2/3 or IC2/3 30%, TC1/2/3 or IC1/2/3 57%, TC0 and IC0 42% **Docetaxel** **n=612**,425 (primary efficacy), 612 (secondary efficacy), 578, 609 **Age=**median 64 (34-85); 49% ≥65 **Male=**61% **Non-Caucasian=**27% (3% unknown) **Former/current smoker=**83% **ECOG 0, 1=**38%, 62% **Non-squamous=**74% **EGRF mutant=**10% (17 unknown) **ALK translocation=**0% **Previous lines systemic therapy (1, 2, ≥3)=**75%, 25% **Other types of therapy=** **TPS/IC** = TC3 or IC3 15%, TC2/3 or IC 2/3 32%, TC1/2/3 or IC 1/2/3 52%, TC0 or IC0 47% **TC/IC very similar even though not stratified by TC**	**Drug, dose and administration:** Atezolizumab 1200 mg IVq 3 wks; median duration 3.4 mos (0-26) (21% longer than 12 mos) Post-atezolizumab cancer treatment: total 48.5%; chemotherapy 41.5% (docetaxel 25.9%); immunotherapy 4.5% nivolumab 3.8%); targeted therapy 14.8% (erlotinib 7.5%) Docetaxel 75mg/m^2 IV q 3 wks; median duration 2.1 mos (0-23) (2% longer than 12 mos) Post-docetaxel cancer treatment: total 45.2%; chemotherapy 30.8%; immunotherapy 17.2% (nivolumab 13.6); targeted therapy 15.5% (erlotinib 11.1%) **Other details:** Atezolizumab continued as long as patients received clinical benefit according to investigator assessment (toxicity, progression after radiological, biopsy and clinical status)(40% beyond progression; median 3 cycles (1-34); docetaxel given	**Primary (All pts and TC1/2/3 or IC1/2/3):** • Overall survival (time from randomization to death from any cause; centrally assessed; q 3 mos after treatment discontinuation) • Final analysis powered for 850 patients for all patients (ITT; 95.3% power); 1300 patients for high PD-L1 expression (98.6% power) **Others (all pts and TC1/2/3 or IC1/2/3):** • Progression-free survival (investigator assessed; time from randomization to documented RECIST disease progression or death from any cause) • ORR (investigator assessed; RECIST complete or partial response; imaging q 6 wks for 36 wks then q 9 wks until treatment discontinuation) • Duration of response (investigator assessed; time from first occurrence of OR to time of RECIST progression [confirmed], or death from any cause) • Safety • Time to deterioration EORTC QLQLC-13

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	provided tissue specimens **Key exclusion criteria:** active or untreated brain metastases, history of pneumonitis, autoimmune or chronic viral diseases, or previous treatment with docetaxel, CD137 agonists, antiCTLA4, anti-PD-L1, or anti-PD-1 therapeutic antibodies, or PD-L1–PD-1 pathway-targeting agents **PD-L1 Sample and Assay:** archival or fresh; formalin-fixed paraffin-embedded specimen; expression on tumor cells and immune cells using Ventana SP142 IHC assay. Scored tumor cells as % of tumor cells (TC) (TC3≥50%, TC2≥5%-<50%, TC1≥1%-<5%, TC0<1%) and tumor infiltrating immune cells (IC) (IC3≥10%, IC2≥5%-<10%, IC1≥1%-<5%, IC0<1%)	**In TC1/2/3 or IC1/2/3 population, 5% or more differences between groups in age, sex, race**	until progression or unacceptable toxicity	• EORTC QLQ C30 (single items at each time point) **Analysis:** • Efficacy ITT (central review) • Safety # received ≥1 dose • HRs using Cox proportional hazard; p values using logrank

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	Other biomarkers: PD-L1 gene expression (high levels as at or above median level)			
Balmanoukian, 2017 2017 ASCO Annual **Trial phase and identifier:** phase 1/2, NCT 01693562 **Setting**: USA, Canada, Korea, United Kingdom **Funding:** Medimmune **Patient population:** stage III/IV NSCLC either naïve (1L) or with previous treatment for advanced disease (≥2L) **Risk of Bias:** no blinding pts, personnel, OA (except OS), no control, loss of follow-up NR	**Recruitment dates:** Aug 2012-NR **Study design:** single-arm trial **Recruitment:** NR **Follow-up:** **1L**: median 17.3 mos (1.0-36.8) **≥2L**: median 29.2 mos (0.3-40.5) **Analysis date:** Oct 24, 2016 (Primary completion date July 2017) **Key inclusion criteria:** ECOG 0 or 1, tumor sample, adequate organ and marrow function, **Key exclusion criteria:** prior Grade ≥ 3 irAE while receiving immunotherapy, previous PD-1/PD-L1 treatment, autoimmune disease, immunodeficiency, untreated central nervous system	**1L** **n=**59 **Age=**NR **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**37%, 63% **Non-squamous=**51% **TPS ≥25%=**83% **EGRF mutant=**NR **ALK translocation=**NR **Previous lines (1, 2, ≥3)=**0% **Previous systemic chemotherapy=**none **Previous RT:** NR **Other types of therapy=**NR **≥2L** **n=**245 **Age=**NR **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**NR **Non-squamous=**47% **TPS ≥25%=**50% **EGRF mutant=**NR **ALK translocation=**NR **Previous lines (1, 2, ≥3)=**0%,33%, 67% (from 2016 ESMO abstract with n=211) **Previous systemic chemotherapy=**NR **Previous RT:**NR **Other types of therapy=**NR	**Drug, dose and administration:** Durvalumab 10mg/kg q 2 wk, median duration of treatment NR Post-Durvalumab cancer treatment: NR **Other details:** until unacceptable toxicity or disease progression, up to 12 mos with retreatment permitted for those progressing after 12 mos	**Primary:** • Safety (AEs, SAEs) **Secondary:** • ORR, investigator assessed confirmed complete or partial • DOR (first documentation of objective response to the first documented disease progression or death due to any cause) • PFS (start of treatment until the documentation of confirmed **immune-related disease progression** or death due to any cause) • Overall survival (first dose of study drug until death or up to 2 years)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	(CNS) metastases requiring concurrent treatment, other invasive malignancy within 2 years, hepatitis B, C. HIV **PD-L1 Sample & Assay:** fresh or archival sample, Ventana SP263 (high ≥25% PS; low/neg <25%)			
Garassino, 2017 ELCC 2017 & ESMO 2017 **Trial phase and identifier:** phase 2, ATLANTIC, NCT02087423 **Setting:** 18 countries **Funding:** AstraZeneca PLC **Patient population:** stage III/IV NSCLC after ≥2 previous lines (no max) of treatment for advanced disease; 3 cohorts (C1 EGRFmut/ALK+ pts, C2 EGFRwt/ALK-, C3 EGFRwt/ALK- and PD-L1 ≥90%)	**Recruitment dates:** start date Feb 2015 **Study design:** single-arm phase 2 **Recruitment:** NR **Follow-up:** **C1:** **C2:** 9.3 mos **C3:** 7.0 mos **Analysis date:** June 3, 2016 (cut-off for primary) **Key inclusion criteria:** WHO PS 0 or 1, ≥2 previous lines (including 1 platinum-based and 1 TKI if ALK+/EGRFmut), brain mets permitted if asymptomatic, treated and stable; cohort 3 PD-L1	**C1 (EGRFmut/ALK+)** **n=**111 (results for 102) **Age=**61 **Male=**37 **Non-Caucasian=**NR **Former/current smoker=**41% **ECOG 0, 1=**41%, 59% **Non-squamous=**99% **TPS ≥25%=**73% **EGRF mutant=**NR **ALK translocation=**NR **Previous lines (1, 2, ≥3)=**mean 3.8 **Previous systemic chemotherapy=**NR **Previous RT=**NR **Other types of therapy=**TKI **C2 (EGRFwt/ALK- or unknown status):** **n=**265 (results for 239) **Age=**62 **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**67%, 31% **Non-squamous=**79% **TPS ≥25%=**61% **EGRF mutant=**NR	**Drug, dose and administration:** Durvalumab 10mg/kg IV q 2 wk for ≤12 mos; median duration of treatment NR Post-Durvalumab cancer treatment: NR **Other details:**	**Primary:** • ORR (RECIST) confirmed via ICR **Secondary:** • Overall survival • Progression-free survival • Safety • Duration of response (time from first evidence of complete or partial response until progression or death)

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
Risk of Bias: no blinding of pts, personnel, ICR for OA, incomplete outcome (ITT but loss-to-followup NR)	≥90%; cohorts 1 and 2 initially all-comers then restricted to PD-L1 ≥25% **Key exclusion criteria:** prior Grade ≥3 immune-related adverse event, active or prior inflammatory bowel disease, active or prior autoimmune disease or history of immunodeficiency, severe or uncontrolled systemic diseases including hepatitis B, C and HIV, any unresolved toxicity CTCAE >Grade 2 from previous anti-cancer therapy **PD-L1 Sample & Assay: Ventana SP263 PS**	**ALK translocation=**NR **Previous lines (1, 2, ≥3)=**mean 3.2 **Previous systemic chemotherapy=**NR **Previous RT=**NR **Other types of therapy=**NR **C3 (EGRFwt/ALK- or unknown status & ≥90% PD-L1):** **n=**68 **Age=**61 **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**72%, 28% **Non-squamous=**71% **TPS ≥90%=**100% **EGFR mutant=**NR **ALK translocation=**NR **Previous lines (1, 2, ≥3)=**mean 2.6 **Previous systemic chemotherapy=**NR **Previous RT=**NR **Other types of therapy=**NR		
Papadimitrakopoulou, 2017 **Trial phase and identifier:** phase 2, part of Lung Master Protocol S1400, NCT02766335 **Setting:** USA **Funding:** Industry and non-industry	**Recruitment dates:** start date June 2014-Dec 2015 **Study design:** single-arm phase 2 **Recruitment:** NR **Follow-up:**NR (at least 11 mos) **Analysis date:** NR	**Durvalumab:** **n=**68 **Age=**66 (35-92) **Male=** **Non-Caucasian=** **Former/current smoker=** **ECOG 0, 1, 2=**26%, 62%, 12% **Non-squamous=0%** **TPS ≥25%=**21% **EGRF mutant=**0% **ALK translocation=**0% **Previous lines (1, 2, ≥3)=**NR **Previous systemic chemotherapy=**NR	**Drug, dose and administration:** Durvalumab 10mg/kg q 2 weeks; median duration of treatment NR Post-Durvalumab cancer treatment: NR **Other details:** treatment for 12 months in the absence of disease progression or	**Primary:** • ORR (RECIST) **Secondary:** • Overall survival • Progression-free survival (investigator assessed; RECIST and irRECIST) • Duration of response • Disease control rate • ORR among PD-L1+ pts • Safety

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
Patient population: previously treated stage IV SC NSCLC **Risk of Bias:** no blinding, no control/randomization, loss to followup NR	**Key inclusion criteria:** stage IV SC NSCLC**, EGFR/ALK wt,** ECOG 0-2, ≥1 previous systemic treatment including 1 platinum-based **Key exclusion criteria:** prior exposure to immunotherapy, any active or prior documented autoimmune or inflammatory disease within 3 yrs, history of primary immunodeficiency, prior grade ≥ 3 immune-related adverse event (irAE) or any unresolved irAE > grade 1, history of tuberculosis, hepatitis B, C or HIV **PD-L1 Sample & Assay:** Ventana SP263, PD-L1+ ≥25%	**Previous RT=** NR **Other types of therapy=**NR	unacceptable toxicity; can repeat for 12 mos if progression after receiving 12 mos treatment	
Gulley, 2017 **Trial phase and identifier:** phase 1b, Javelin Solid Tumor, NCT01772004 **Setting:** 58 centers in USA	**Recruitment dates:** Sept 2013-June 2014 **Study design:** open-label phase 1b dose-expansion **Recruitment:** **1L:** NR	**1L** **n=**145 (PD-L1 evaluable in 45 of 75 assessed) **Age=**70 (41-90) **Male=**NR **Non-Caucasian=**NR **Former/current smoker=**NR **ECOG 0, 1=**31%, 69% **Non-squamous=**73%	**Drug, dose and administration:** Avelumab 10 mg/kg IV q 2 wks; median 6 doses (IQR 3-15); duration of treatment 10 wks (1L) and 12.2 wks (IQR 6.1-30) (2L+)	**Primary:** • None (dose limiting toxicity during doe-escalation portion) **Secondary:** • Best OR (6 weeks for first 12 months, then 12-weekly until end of treatment and

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
Funding: Merck KGaA and Pfizer **Patient population:** treatment naïve (1L) and previously treated metastatic or recurrent stage IIIb or IV NSCLC **Risk of Bias:**	**2L+**: 288 assessed; 184 enrolled and analyzed **Follow-up:** **1L:** median 13 wks (0-31) **2L+**: median 8.8 mos (7.2-11.9); min 6 mos **Analysis date:** **1L:** Oct 23, 2016 **2L+:** cut-off Jan 2015 **Key inclusion criteria:** stage IIIb or IV NSCLC either treatment naïve for advanced NSCLC (1L) or progressed after platinum-based chemotherapy for metastatic disease (≥2L); ECOG 0-1, no active or history of brain metastases; adequate hematological, hepatic, and renal function, measureable disease **Key exclusion criteria:** EGRFmut or ALK+ (for 1L); other cancer diagnosis within 5 years, rapidly progressing disease, autoimmune disease	**TPS ≥1%=**77.8% (of 45 pts) **EGRF mutant=**0 **ALK translocation=**0 **Previous lines (1, 2, ≥3)=**0 **Previous systemic chemotherapy=**0 **Previous RT=**NR **Other types of therapy=**NR **≥2L** **n=**184, 184, 184, 143 **Age=**65 (58-69.5) **Male=**54% **Non-Caucasian=**13% **Former/current smoker=**86% **ECOG 0, 1=**30%, 70% **Non-squamous=**71% **TPS ≥1, ≥5%, ≥25%=**86%, 59%, 37% (n=142 evaluable) **EGRF mutant=**5% (40% unknown) **ALK translocation=**1% (44% unknown) **KRAS mutant=**11% (68% unknown) **Previous lines (1, 2, ≥3)=**66%, 24%, 9% **Previous systemic chemotherapy=** carboplatin 85%, pemetrexed 54%, cisplatin 25%, gemcitabine 17%, erlotinib 11% **Previous RT=**51% **Other types of therapy=**surgery 53%	Post-Avelumab cancer treatment: 21% (drugs 18%, RT 9%) drugs included cytotoxic chemotherapy 15% and targeted therapy in 7% **Other details:** treated until progression or toxicity; premedication with paracetamol and diphenhydramine; dose modifications (5%) and delays permitted for grade 2 AEs	post treatment every 3 months [up to 52 months]); investigator assessed • ORR confirmed complete or partial (RECIST)(2L+) • Unconfirmed response at week 13 (1L) • Duration of response (first complete or partial until progression or death) • Overall survival (time from first administration to death from any cause) • Progression-free survival (time from first administration to documented disease progression or death from any cause) • Safety (each biweekly visit • Activity according to PD-L1 **Exploratory subgroups post hoc:** age, sex, histology, previous lines, smoking history, EGFR/ALK (for 2L+) **Analysis:** safety and activity for those with 1+ doses

Study, Country, Funding	Study Characteristics	Patient Characteristics: Sample size (randomized, efficacy population, safety population, discontinued treatment)	Treatment Characteristics	Outcomes & Analysis
	PD-L1 Sample & Assay: fresh biopsy or archival sample**;** clone 73-10 on proprietary assay (Dako), prospectively determined scoring on TC (membranous) as ≥1% and ≥5% with any staining intensity and ≥25% with moderate-to-high staining intensity (2+ to 3+), and IC as ≥10% staining of any intensity within hotspots (dense aggregates of tumor-associated immune cells adjacent to tumor cells)			

Table C3. Risk of bias of randomized controlled trials

Study	Sequence generation	Allocation concealment	Blinding Patients and Providers	Blinding Outcome Assessors	Incomplete Outcome Data	Selective Reporting	Other Sources (baseline imbalance, size of blocks in randomization; cross-over)	Overall Risk
Second+ Line								
Keynote-010	Low	Low	Low (OS, PFS, ORR, TRAEs)*	Low (OS, PFS, ORR; radiologists assessing response were blinded)	Unclear ITT with censoring; 1.3% in Pembrolizumab groups and 10% in Docetaxel not receiving drug; 2% vs 13% withdrew consent†	Low Unclear (PROs; few outcome measurements defined as per protocol)	Low No meaningful difference between groups or patients with TPS 1-49% vs. ≥50% at baseline; blocks of 6 in each stratum (ECOG, region, PD-L1 [after	Unclear (OS, PFS, ORR, response, TRAEs) High (PROs)

Study	Sequence generation	Allocation concealment	Blinding Patients and Providers	Blinding Outcome Assessors	Incomplete Outcome Data	Selective Reporting	Other Sources (baseline imbalance, size of blocks in randomization; cross-over)	Overall Risk
				Unclear: TRAEs High (PROs)	High: long-term PROs		first 441 patients]); no cross-over permitted; 13% of docetaxel group receiving immunotherapy after discontinuing but would favor control group	
Checkmate 017	Low	Low	Low (OS, PFS, ORR, TRAEs)*	Low (OS) Unclear: TRAEs High (PFS, ORR; investigator-assessed response; PROs)	Low ITT with censoring; 3% vs 6% not receiving drug; 4% vs. 7% discontinued/withdrew consent High: long-term PROs	Low Unclear (PROs; few outcome measurements defined as per protocol)	Low No meaningful difference between treatment groups at baseline, and no differences in PD-L1 expression levels in subgroup based on retrospective analysis of PD-L1; 86.7% vs 78.8% had evaluable samples	Low (OS) Unclear (TRAEs) High (PFS, ORR, PROs)
Checkmate 057	Low	Low	Low (OS, PFS, ORR, TRAEs)*	Low (OS) Unclear: TRAEs High (PFS, ORR; investigator-assessed response, PROs)	Unclear ITT with censoring; 1.7% vs 7.6% not receiving treatment; 3% vs 8% discontinued/withdrew consent High: long-term PROs	Low Unclear (PROs; few outcome measurements defined as per protocol)	Low No meaningful difference between treatment groups at baseline, and no differences in PD-L1 expression levels in subgroup based on retrospective analysis of PD-L1; 71.2% vs 77.2% had PD-L1 expression for analysis	Unclear (OS, TRAEs) High (PFS, ORR, PROs
OAK	Low	Unclear (allocation unmasked; patients, investigators and study site staff were blinded to PD-L1 at enrollment and numerous variables	Low (OS, PFS, ORR, TRAEs)*	Low (OS) Unclear: TRAEs High (PFS, ORR; investigator-assessed response; PROs)	Unclear ITT with censoring; 0.8% vs. 5.3% not treated; 5.5% vs 10.3% withdrawal High: long-term PROs	Low Unclear (PROs; few outcome measurements defined as per protocol)	Low No meaningful difference between treatment groups at baseline; stratification was for immune-cell not tumor cell PD-L1 but there appears to be fairly good balance between groups by tumor PD-L1, except TC1/2/3 5% more	Unclear (OS, TRAEs) High (PFS, ORR, PROs

Study	Sequence generation	Allocation concealment	Blinding Patients and Providers	Blinding Outcome Assessors	Incomplete Outcome Data	Selective Reporting	Other Sources (baseline imbalance, size of blocks in randomization; cross-over)	Overall Risk
		balanced at baseline)					common in docetaxel arm, which would tend to favor docetaxel arm; block size of 8	
POPLAR	Low	Unclear (allocation unmasked; patients, investigators and study site staff were blinded to PD-L1 at enrollment and numerous variables balanced at baseline)	Low (OS, PFS, ORR, TRAEs)*	Low (OS) Unclear: TRAEs High (PFS, ORR; investigator-assessed response; PROs)	Unclear ITT with censoring; 1% vs. 6% not receiving treatment; 4.1% vs. 10% loss-to-follow up/ withdrawal by patient High: long-term PROs	Low Unclear (PROs; few outcome measurements defined as per protocol)	Low No meaningful difference between treatment groups at baseline; stratification was for immune-cell not tumor cell PD-L1 but there appears to be fairly good balance between groups by tumor PD-L1, except TC2 8% more common in docetaxel arm TC0 group 9% more common in atezolizumab arm, which would tend to favor docetaxel arm; 5% in docetaxel arm received post-discontinuation immunotherapy, although this would favor this arm; block size of 4	Unclear (OS, TRAEs) High (PFS, ORR, PROs
First Line								
Keynote 024	Low	Low (via protocol)	Low (OS, PFS, ORR, TRAEs)* Patients and providers masked to PD-L1 level	Low (OS, PFS, ORR; blinded independent central review assessing response) Unclear: TRAEs	Low ITT with censoring; 0% vs 1 pt not receiving treatment; 2.6% vs 3.3% withdrawal	Low	Unclear (OS)/Low More never smokers in chemotherapy group (9%) and more brain metastases in pembrolizumab group (not significant); cross-over after progression by 43.7% (plus others receiving later) in chemotherapy group would tend to favor	Unclear (OS; cross-over, TRAEs) Low (PFS, ORR)

Study	Sequence generation	Allocation concealment	Blinding Patients and Providers	Blinding Outcome Assessors	Incomplete Outcome Data	Selective Reporting	Other Sources (baseline imbalance, size of blocks in randomization; cross-over)	Overall Risk
							chemotherapy and only affect OS	
Keynote 021 (Cohort G)	Low	Low	Low (OS, PFS, ORR, TRAEs)* Patients and providers masked to PD-L1 level	Low (OS, PFS, ORR; blinded independent central review assessing response) Unclear: TRAEs	Low ITT with censoring; 1.6% vs 1.6% pt not receiving treatment ; 6.6% vs 4.7% withdrawal	Low	Unclear (OS)/Low Some small baseline imbalances (more non-white [10%], never smoked [11%] and AC [10%] in pembrolizumab group); blocks of 4; cross-over from chemo to pembrolizumab monotherapy (32%, plus others receiving later) would tend to favor chemotherapy and only affect OS	Unclear (OS; cross-over, TRAEs) Low (PFS, ORR)
Checkmate 026	Low	Low	Low (OS, PFS, ORR, TRAEs)*	Low (OS, PFS, ORR; blinded independent central review for response) Unclear: TRAEs	Low ITT with censoring; 1.8% vs 1.2% received treatment; 2.6% vs 3.7% withdrew	Low	High Baseline imbalances: 13% more females & 15% more PD-L1 ≥50% in chemotherapy; cross-over to nivolumab by 58%	High (OS) Unclear (TRAEs) Low (ORR, PFS)

*Decisions to continue treatment based on investigator assessment of response or clinical condition and may have been different between groups, which was thought to have greater potential to favor patients in control arm who may have then changed to a more effective treatment (e.g. Keynote 010 13% received immunotherapy). The unmasked protocol was likely a contributor to longer treatment duration with the immunotherapy drugs, although their better toxicity profile, and the protocol allowing treatment beyond progression for nivolumab and atezolizumab trials will have also contributed; it is unclear whether or not treatment beyond progression may have provided more harm or benefit.[1]

†Unclear which direction more withdrawals in control group would have (baseline characteristics unknown); censoring unlikely to be biased substantially.

Abbreviations: PRO: patient-reported outcomes (e.g., EuroQol and other heath state assessments); TRAEs: treatment-related adverse effects

1. Kazandjian D, Keegan P, Suzman DL, et al. Characterization of outcomes in patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors past RECIST version 1.1-defined disease progression in clinical trials. Seminars in Oncology. 2017 Feb;44(1):3-7. doi: 10.1053/j.seminoncol.2017.01.001. PMID: 28395760.

Table C4. Studies on the analytical and clinical validity of the Dako pharmDx 22C3 assay

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
Dako 22C3									
Garon, 2015 Dolled-Filhart, 2016 Roach, 2016 PMA P150013 FDA SSED, 2015, Leighl, 2017 (ASCO 2017), Hui 2017, Hellmann 2015 (WCLC 2015) Dako IHC 22C3	Training set N= 182 (171 2L) Cut-point selection (146 of training set; most 2L) Validation Set #1 for CTA (Garon, 2015) n= 204; 76% 2L Set #2 for final assay (Roach, 2016) N=223 2L (61	Cut-point set: archival (25) or new (104) samples Validation set #1: new samples (after previous tx using tru cut core or surgical biopsy) and slides sectioned within 6 mos of assessment Validation set #2: 61 2L with ≥50% PS vs 223 2L irrespective	Validation set #1: SC 44 AC 170 ASC 4 Unknown 2 Validation set #2 ≥50% group 75% nSC; <50% group NR	Locally advanced or metastatic NSCLC Type NR	FFPE tissue specimens with ≥100 viable cells Note: chosen based "appropriateness" compared with previously approved tests and minimum thresholds for tumor content (Dolled-Filhart 2016)	Validation set: Dako EnVision FLEX+HRP-Polymer kit on Dako Automated Link 48 staining platform with DakoLink software and pathologist using light microscope Antibody: 22C3 mouse	Cut-point selection study 1. PS = partial or complete membrane (not cytoplasmic) staining at any intensity 2. PS2 = membrane staining at moderate (2+) or strong (3+) staining 3. PS3 = membrane staining with	Cut-point selection: single pathologist from Dako Validation set: 1 of 3 pathologists at LabCorp with certification program including microscope session with the Dako pathologist and a proficiency challenge (heavily weighted at TPS 50%) that tested accuracy (i.e., agreement with the Dako pathologist) and intrapathologist reproducibility	**With 10 mg Q2W or Q3W Pembro until progression or unacceptable toxicity (not after confirmed progression after 4-6 wks)** **Cut-point selection using CTA (Dolled-Filhart, 2016):** FP rate (PS at 50% TC, PS2 at 11% TC, PS3 at 1% TC, HS at 63% TC): 0.210, 0.168, 0.185, 0.202 TP rate (PS, PS2, PS3, HS as above): 0.704, 0.630, 0.630, 0.704) RR (**confirmed [129 of 146] and unconfirmed via investigator assessed irRC**) ≥50% 19/45 (34.5%) <50% 8/102 (7.8%) OR 8.93 (95% CI NR) (Methods performed similarly but PS chosen over HS [best 2] due to simplicity) Area under ROC curve for PS 0.743 50% cut-off Test result | Response | No respon | Totals

<table>
<tr><th>Paper(s)</th><th>Sample size</th><th>Age, treatment history, and type of tissue specimens</th><th>Histology (%)</th><th>Stage of Disease/Type of tumor (primary vs metastasized)</th><th>Tissue Preparation</th><th>IHC Method</th><th>PD-L1 Cutoffs Evaluated</th><th>Personnel & details for studies</th><th>Outcomes:</th></tr>
<tr>
<td>pharmDx clinical validation

Cut-point selection, 2 forms of validation and single-arm for first line in KEYNOTE 001 patients from 10 countries

Funding: Merck and Dako</td>
<td>≥50%, 104
<50%, 58 unkwown)

Other outcomes for all patients via CTA sections within 6 mos n=294 2L and 62 1L</td>
<td>of PDL and 104 with <50%; new samples

Patients were excluded if they had more than 30 Gy thoracic radiation in the prior 26 weeks</td>
<td></td>
<td></td>
<td></td>
<td>monoclonal</td>
<td>strong intensity
4. HS = PS + PS2 + PS3; value for % staining at each intensity

Validation set (TPS ≥50% at any intensity)</td>
<td>Cut-point selection: ease of use (e.g. versus H score), and ROC analysis (maximizing Youden's index with closest point to the optimum of all true positives and no false positives) & PPV, NPV, prevalence with best overall response</td>
<td>
<table>
<tr><td>Positive (≥50%)</td><td>19</td><td>26</td><td>45</td></tr>
<tr><td>Negative (<50%)</td><td>9</td><td>94</td><td>102</td></tr>
<tr><td>Totals</td><td>28</td><td>120</td><td>147</td></tr>
</table>
Sensitivity: .679
Specificity: .783
PPV: .42
NPV: .922
Likelihood ratio positive test: 3.12
Likelihood negative test: 0.41

Validation of PS ≥50% cut-point (Set #1; Garon, 2015)
2L:
ORR (RECIST central review Q9W)
≥50% 43.9% [30.7-57.6] (n=57)
1-49% 15.6% [8.3-25.6] (n=77)
<1% 9.1% [1.1-29.2] (n=22)
P<0.001

50% cut-off
<table>
<tr><td>Test result</td><td>ORR</td><td>No ORR</td><td>Totals</td></tr>
<tr><td>Positive (≥50%)</td><td>25</td><td>32</td><td>57</td></tr>
<tr><td>Negative (<50%)</td><td>14</td><td>84</td><td>99</td></tr>
<tr><td>Totals</td><td>39</td><td>116</td><td>156</td></tr>
</table>
Sensitivity: .641
Specificity: .724
PPV: .438
NPV: .848
Likelihood ratio positive test: 2.32
Likelihood negative test: .496

1% cut-off:
<table>
<tr><td>Test result</td><td>ORR</td><td>No ORR</td><td>Totals</td></tr>
<tr><td>Positive (≥1%)</td><td>37</td><td>97</td><td>134</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Paper(s)</th><th>Sample size</th><th>Age, treatment history, and type of tissue specimens</th><th>Histology (%)</th><th>Stage of Disease/Type of tumor (primary vs metastasized)</th><th>Tissue Preparation</th><th>IHC Method</th><th>PD-L1 Cutoffs Evaluated</th><th>Personnel & details for studies</th><th>Outcomes:</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Negative (<1%)</td><td>2</td><td>20</td><td>22</td></tr>
<tr><td>Totals</td><td>39</td><td>117</td><td>156</td></tr>
<tr><td colspan="4">Sensitivity: .949
Specificity: .171
PPV: .276
NPV: .910
Likelihood ratio positive test: 1.14
Likelihood negative test: .298</td></tr>
</table>

1L:
ORR (RECIST central review):
≥50% 50.0% [24.7-75.3] (n=16)
1-49% 19.2% [6.6-39.4] (n=26)
≤1% 16.7% [0.4-64.7] (n=6)
P=0.01
50% cut-off
<table>
<tr><td>Test result</td><td>ORR</td><td>No ORR</td><td>Totals</td></tr>
<tr><td>Positive (≥50%)</td><td>8</td><td>8</td><td>16</td></tr>
<tr><td>Negative (<50%)</td><td>6</td><td>26</td><td>32</td></tr>
<tr><td>Totals</td><td>14</td><td>34</td><td>48</td></tr>
<tr><td colspan="4">Sensitivity: .571
Specificity: .764
PPV: 0.5
NPV: .813
Likelihood ratio positive test: 2.42
Likelihood negative test: 0.562</td></tr>
</table>

1% cut-off
<table>
<tr><td>Test result</td><td>ORR</td><td>No ORR</td><td>Totals</td></tr>
<tr><td>Positive (≥1%)</td><td>13</td><td>29</td><td>42</td></tr>
<tr><td>Negative (<1%)</td><td>1</td><td>5</td><td>6</td></tr>
<tr><td>Totals</td><td>14</td><td>34</td><td>48</td></tr>
<tr><td colspan="4">Sensitivity: .923
Specificity: .147
PPV: .310
NPV: .833
Likelihood ratio positive test: 1.08
Likelihood negative test: .524</td></tr>
</table>

No difference in PD-L1 for EGFR; numerically higher in KRAS (PD-L1</td></tr>
</table>

<table>
<tr><th>Paper(s)</th><th>Sample size</th><th>Age, treatment history, and type of tissue specimens</th><th>Histology (%)</th><th>Stage of Disease/Type of tumor (primary vs metastasized)</th><th>Tissue Preparation</th><th>IHC Method</th><th>PD-L1 Cutoffs Evaluated</th><th>Personnel & details for studies</th><th>Outcomes:</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>50% 44.2% KRAS+ vs 26.8% KRAS -).

Validation in PS ≥50% Set #2 (Roach, 2016 & PMA P150013): Roach, 2016: ≥50% n=61 2+L (44% 3+L; 75% nonSC) vs. entire 2L in KEYNOTE 001 validation set (n=223; includes 61 with ≥50% and 58 with unknown status because staining >6 mo [44] unevaluable due to insufficient # cells [9] or bone tissue present [2], not tested [3]; 104 negative)

PMA P150013: ≥50%(n=61) vs <50% (n=104)

<u>ORR</u> (all confirmed; all partial responses):
≥50% vs whole cohort: 41% (28.6-54.3) vs. 20.6% (15.5-26.5)
≥50% vs <50%: 41% (28.6-54.3) vs. 13% (8-22)
≥50% vs <50%:<table><tr><td>Test result</td><td>ORR</td><td>No ORR</td><td>Totals</td></tr><tr><td>Positive (≥50%)</td><td>25</td><td>36</td><td>61</td></tr><tr><td>Negative (<50%)</td><td>13</td><td>91</td><td>104</td></tr><tr><td>Totals</td><td>38</td><td>127</td><td>165</td></tr><tr><td colspan="4">Sensitivity: .658
Specificity: .717
PPV: .410
NPV: .875
Likelihood ratio positive test: 2.33
Likelihood negative test: .477</td></tr></table>
Sensitivity analysis for those with missing PD-L1 data using data from different enrolment assay (≥50% vs <50%: 37.4%, 34.5 to 40.5 vs 11.3%, 10.2 to 12.7)</td></tr>
</table>

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
									Duration of response for ≥50%: not reached (2.1+-9.2+ mos) [all 25 onoing]; >6mos for 11 **Other outcomes (Garon, 2015)**: ORR in entire KEYNOTE 001 population (n=495) 19.4% (16.0-23.2) ORR via RECIST using central review for all patients assessed by CTA (n=372) <1%: 8.1% (3.3 to15.9) 1-24%: 12.9% (8.0-19.4) 25-49%: 19.4% (7.5-37.5) 50-74%: 29.6% (16.8-45.2) 75-100%: 45.4% (34.6-56.5) Median PFS (all pts via CTA sectioned within 6 mos) 2L ≥50% 6.1 (2.1 to 12.5) mo 1-49% NR ≤1% NR 1L ≥50% 12.5 (2.4 to 12.5) mo 1-49% NR ≤1% NR Median OS (all pts via CTA sectioned within 6 mos) 2L ≥50% not reached (9.3 –not reached) 1-49% NR ≤1% NR 1L ≥50% not reached (not reached to not reached) 1-49% NR ≤1% NR Median duration of response

<table>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>NR by line of treatment (but no differences)

<u>Prevalence of PDL in all screened patients:</u>
2L (n=643)
≥50% 22.7%
1-49% 35.9%
≤1% 41.4%
1L (n=181)
≥50% 24.9%
1-49% 43.6%
≤1% 31.5%

ORR in 1L (Hui 2017)

<table>
<tr><td>Test result</td><td>Response</td><td>No response</td><td>Totals</td></tr>
<tr><td>Positive (≥50%)</td><td>14</td><td>13</td><td>27</td></tr>
<tr><td>Negative (<50%)</td><td>10</td><td>54</td><td>64</td></tr>
<tr><td>Totals</td><td>24</td><td>67</td><td>91</td></tr>
<tr><td colspan="4">Sensitivity: 0.583
Specificity: 0.806
PPV: 0.519
NPV: 0.844
Likelihood ratio positive test: 3.01
Likelihood negative test: 0.517</td></tr>
</table>

<table>
<tr><td>Test result</td><td>Response</td><td>No response</td><td>Totals</td></tr>
<tr><td>Positive (≥1%)</td><td>23</td><td>56</td><td>79</td></tr>
<tr><td>Negative (<1%)</td><td>1</td><td>11</td><td>12</td></tr>
</table>
</td></tr>
</table>

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:

									Totals | 24 | 67 | 91 Sensitivity: 0.958 Specificity: 0.164 PPV: 0.291 NPV: 0.916 Likelihood ratio positive test: 1.146 Likelihood negative test: 0.256 **3-year OS rates (Leighl, 2017): 2L patients (validation and training sets using CTA)** Test result | 3-yr OS | No 3-yr OS | Totals Positive (≥1%) | 65 | 241 | 306 Negative (<1%) | 8 | 82 | 90 Totals | 73 | 323 | 396 Sensitivity: .890 Specificity: .254 PPV: .212 NPV: .911 Likelihood ratio positive test: 1.19 Likelihood negative test: .433 Test result | 3-yr OS | 3-yr OS | Totals Positive (≥50%) | 41 | 97 | 138 Negative (<50%) | 20 | 160 | 180 Totals | 61 | 257 | 318 Sensitivity: .672 Specificity: .623 PPV: .297 NPV: .889 Likelihood ratio positive test: 1.78 Likelihood negative test: .526

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
									Subgroups (Hellmann 2015): Hellmann: various subgroups - **>50%** cut-off ORR ever smokers (n=115) 39.1% (30.2-48.7) vs never smokers (n=29) 27.6% (12.7-47.2) and **<1%** cut-off ever smokers (n=60) 13.3% (5.9-24.6) vs never smokers (n=20) 0% (0.0-16.8%); **all PDL1** smokers (n=415) 21.9% (18-26.3) vs never smokers (n=135) 9.6% (5.2-15.9) **>50%** EGFRmut (n=20) 20% (5.7-43.7) vs wt (n=113) 38.1% (29.1-47.7) and **<1%** EGFRmut (n=15) 0% (0-21.8) vs wt 12.9% (5.7-23.9), **all PDL1** EGFRmut (n=78) 7.7% (2.9-16) vs EGFR wt (n=449) 20.0% (16.4-24.1); Less difference for ECOG, age >65, histology, KRAS
Roach, 2016 PMA P150013 FDA SSED, 2015 Dako IHC 22C3 pharmDx analytical validation United States	Assay sensitivity n=127 Assay repeatability/preicison (n=16) Intersite & intrasite reproducibility (n=36)	NR	NR	Assay sensitivity: primary and metastasized, stage III and IV	FFPE, sections with ≥100 viable cells, cut at 4-5 µm; mounted on charged slides and stored in dark at 2-8^{0}C and stained within 6 mos	EnVision FLEX visualization system on Autostainer Link 48 platform with automated staining protocol and DakoLink	PS ≥50% vs. <50% Partial or complete membrane staining at any intensity; counting all viable celles and not counting immune cells of cytoplasmic staining	Assay sensitivity: random selection of 127 FFPE with wide range of PS Assay specificity: i) western blot on control cell lysates using 22C3 assay, ii) immunoreactivity in human tissues (3 cases from 30 normal tissues) and neoplastic tissues (1-7	<u>Assay sensitivity</u>: PD-L1 visualized over dynamic staining intensity range; 57.5% specimens did not express, 23.6% 1-19%, and 18.4% ≥50% <u>Assay specificity</u>: detected purified PD-L1 protein and low cross-reactivity to other proteins; background staining in human tissues <0.5 grade in all and expression patterns consistent with reported literature; equivalent expression when compared to mRNA and flow cytometry analysis <u>Repeatability/precision</u>: 100% for NPA, PPA, and OA for inter-instrument, inter-operator, inter-day,

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
and Europe Funding: Dako & Merck	Inter- and intraobserver (n=62) Robustness n=16 Primary and metastatic tumors n =23 pairs					software requiring all reagents used together Interpretation by pathologist with light microscope (compared with CTA, final assay optimized for sensitivity with minimum nonspecific staining by adjusting antibody concentration and reagent incubation times)		cases from 82 neoplasms), iii) orthogonal methods (mRNA and flow cytometry) with 6 FFPE tumor cell lines with known and broad-spectrum PD-L1 expression) and Hamster ovary (transfected and parental) Assay repeatability: at Dako with 6 instruments, 6 operators, 6 nonconsecutive days (interday), 3 lots of reagents, 6 replicates (intrarun & intraday): 16 NSCLC specimens used (histology and stage NR) 25% samples close to 50% Intersite (2700 pair-wise) & intrasite (1080 pair-wise) reproducibility: at 3 external CLIA with 5	inter-lot, intra-day, intra-run; all lower boundaries of 95% Cis >85 except for intra-day PPA @ 82.4% Reproducibility: Inter-site, intra-site, inter-observer, intra-observer: all ANA, APA, OA > 85% (lower bounds >81 except for inter-site APA 75.6%) Robustness: • 2µm slides not equivalent staining • pH <5.9 erroneous results • no other differences Stability: • Sections should be stained within 6 mo of sectioning • Blocks can be stored up to 5 yrs • Assay: total and finished good shelf-life 9 mos at 2-8^{0}C; in-use/on-board stability 18 cycles at room temp.; DAB Substrate-Chromogen solution 5 days at 2-8^{0}C; target retrieval system 5 days at room temp with up to 3 uses Primary vs metastatic tumors: 20/23 diagnostically concordant Fixation times: no systematic differences but ≤ 3 hrs may be incompatible with robustness and reproducibility Ischemia time: 0-24 hrs similar Intra-case heterogeneity: 100% diagnostically concordant Intra-block heterogeneity: 100% diagnostically concordant

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
								nonconsecutive days (n=36 specimens in 5 sets) by 1 technician Inter (1674 pair-wise) & intraobserver (558 pair-wise) reproducibility: 1 pathologist at each of 3 sites doing 3 interpretations over 9 days of 62 specimens (in random order) slides having full range of expression Robustness (1 lot): • Tissue thinkness 2-6µm • Microscope Slide type • Target retrieval solution time (18-22 mins), temp (95-99^{0}C), pH (5.8-6.4), 3 re-uses, 3 lots Stability: • Cut section (in positive cases and cases near	

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
								threshold; each time fresh slice used as reference) • Blocks (44 blocks with 37 neg and 7 pos) • Assay (3 lots with 6 blocks [3+ and 3-)) Primary vs metastatic tumor: 23 pairs Impact on ischemia/fixation: n=11 blocks fixation times 3-168 hrs; 216 human placenta blocks for ischemia Intra-case heterogeneity: 2-5 blocks for 20 patients (only 2 PD-L1+) Intra-block heterogeneity: 1st and 50th in 20 blocks (5 PD-L1+)	
Cooper, 2017 Australia	60 samples in each of 2 sets (for 1%	Less than 15 yrs old; surgically resected	NR	Early	FFPE **TMAs** with 1mm cores and >100 cells per sample	EnVision FLEX visualization system	PS ≥1% and ≥50%; any staining intensity that was distinct	10 pathologists randomly assigned to 2 groups	Intra-observer (300 pair-wise): 1% cut-point OPA 89.7% (85.7-92.6) NPA (calculated) PPA

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Dako IHC 22C3 pharmDx: inter- and intra-observer reproducibility and impact of training at 1% and 50% Funded by Merck	and 50% cut-points with equal distribution of - and + samples) 10 pathologists across all states with varying experience (median 15 yrs; all some IHC training; 8 public, 1 private, 1 mixed)					on Autostainer Link 48 platform with automated staining protocol and DakoLink software	to cytoplasmic	Group 1: all samples on 2 consecutive days (in different order) with written instruction Group 2: same assessments except received a 1-hour training before 2nd Gold standard PS: subjective = consensus by 2 lead investigators trained in 2 day Dako course assessed all samples For each set: after gold standard assessments on 781 samples (**75.7% <1%, 14% 1-49%, 10.3% ≥50%**) independent statistician assigned using stratified randomization with 1/3 around cut-point 300 pair-wise comparisons required for	50% cut-point OPA 91.3% NPA PPA Lower bound of OPAs ≥85% <u>Inter-observer</u> (2700 pair-wise): 1% cut-point OPA 84.2% NPA 85.0% PPA 83.2% Kappa 0.68 (95% CI 0.65-0.71)(substantial) 50% cut-point OPA 81.9% (only 4.3% of 489 non-concordant were in PD-L1 range 40-60% although fewer samples here) NPA 80.9% PPA 84.6% Kappa 0.58 (moderate) but prevalence bias (aKappa 0.64)(95% CI 0.61-0.67) No lower bounds ≥85% Impact on training: no effect at 1% cut-off (OPAs 82% and 82.3% each round), **slight improvement at 50% cut-off especially 40-60%** (OPA 81.7% vs 78.3%) Comparison to gold standard: Sensitivity/TP 1% cut point 84.3% 50% cut-off 56.3% Specificity/TN 1% cut point 91.3% 50% cut-off 94.0% PPV 1% cut point 90.7%

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
								power for OPA at ≥85%	50% cut-off 90.4& NPV 1% cut point 85.4% 50% cut-off 68.3% (difficulty assessing positive specimens) Variability high for 30-80**%, tendency to underestimate especially if weak staining or concomitant cytoplasmic staining**
Herbst, 2016 IASLC 7th Latin American Conference on Lung Cancer KEYNOTE 010 patients Dako IHC 22C3 pharmDx Archival vs. new tumor samples Funded by Merck	Archival n=456 New (no intervening treatment) N=578	Archival: median 250d (3-2510), at least 1L platinum-doublet chemotherapy, NR types New: median 11d (1-371), no tx after, tru cut or surgical biopsy	Archival: SC 23% AC 68% Other 9%	Advanced stage	FFPE tissue specimens with ≥100 viable cells	Validation set: Dako EnVision FLEX+HRP-Polymer kit on Dako Automated Link 48 staining platform with DakoLink software and pathologist using light microscope Antibody: 22C3 mouse monoclonal	PS ≥1% and ≥50%	OS and PFS Response using RECIST via blinded independent review	**Pembro 2 and 20 mg/kg vs. Docetaxel Q3W pooled** <u>Prevalence:</u> ≥50% for 40% archival and 45% new (no difference) <u>OS (≥1%; Pembro/docetaxel))</u> Archival: 10.5/8.3 mo; HR 0.70 (0.54-0.89) New: 12.6/8.6 mo; HR 0.64 (0.50-0.83) <u>OS (≥50%)</u> Archival: 11.5/7.5 mo; HR 0.60 (0.40-0.90) New: NR/8.3 mo; HR 0.44 (0.29-0.66) <u>PFS (≥1%)</u> Archival: 2.9/ 3.8 mo; HR 0.81 (0.65-1.01) New: 4.1/4.2 mo; HR 0.86 (0.70-1.07) <u>PFS (≥50%)</u> Archival: 3.9/4.0 mo; HR 0.64 (0.45-0.90) New: 6.3/4.3 mo; HR 0.54 (0.39-0.75)

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Aggarwal, 2016 Screened for KEYNOTE 001, 010, 024 enrollment Dako IHC 22C3 pharmDx Prevalence based on patient characteristics (previous tx), specimen type (archival vs new), specimen source (primary vs metastatic), specimen histology (SC vs nonSC) Funded by Merck	4784 (PD-L1 evaluable from 5879 screened)	Various across patients	SC 19% nonSC 81% (n=2720)	Locally advanced or metastatic	FFPE	Dako IHC 22C3 pharmDx (KEYNOTE 001 screened with prototype assay though, n=1242)	<1%, 1-49%, ≥50%	Central laboratory	<u>Prevalence</u>: All patients (n=4784): <1%: 33% 1-49%: 38% ≥50%: 28% Treatment naïve (n=1834) vs previously treated (n=2950) : >1%: 35% vs 31% 1-49%: 38% vs 40% ≥50%: 27% vs 30% Archival (n=2351) vs new (n=1199): >1%: 27% vs 17% 1-49%: 42% vs 48% ≥50%: 31% vs 35% Primary (n=1727) vs metastasis (n=1281): >1%: 35% vs 35% 1-49%: 40% vs 36% ≥50%: 25% vs 29% Nonsquamous (n=2193) vs squamous (n=527): >1%: 26% vs 19% 1-49%: 37% vs 41% ≥50%: 37% vs 40%

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Rangachari, 2017 USA Dako IHC 22C3 pharmDx Sample type and correlation with driver mutations Funding: non-industry	71 tumor-patient pairs	Type: surgical resection (21), small biopsy (25), FNA cell block (16), Pleural effusion cell block (9) Sample origin: lung (25), lymph node (17), pleura (10), bone/sof tissue (9), liver (2), brain (5) other (3)	AC	I-III n=18 IV/recurrent n=52	FFPE tissue specimens with ≥100 viable cells	Validation set: Dako EnVision FLEX+HRP-Polymer kit on Dako Automated Link 48 staining platform with DakoLink software and pathologist using light microscope Antibody: 22C3 mouse monoclonal	PS ≥50%	IHC interpreted by pathologist	Prevalence of ≥50%: 29.6% (0%; 42%, 1-24%: 24%) PS ≥50% vs <50% positively associated with smoking p=0.0111; not associated with sex, ethnicity, tumor stage (p=1.0), biopsy site, or biopsy type/preparation (p=0.7768) 18/19 EGRF, ALK, or ROS1 mutations were <50% PD-L1
Kim, 2015	90 paired samples (73 from	Mean 20.9 mos between	SC 37%	I-IIIa 83%	FFPE tissue specimens with NR	Prototype 22C3 but PS	Tumor membrane strong ≥96%	Concordance between samples using	PD-L1 prevalence between samples: First sample: ≥50% 7%, 1-49%49%, <1% 43%

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Annual meeting AACR 2015 Korea and Denmark Prototype 22C3 but PS traceable to Dako 22C3 Expression over time in paired tumor samples	Korea, 17 Denmark)	samples (91% >3 mos); 89% first and 63% second samples surgical Tx NR Sample origin: 97% first sample and 53% second samples from lung			number viable cells	traceable to Dako 22C3 Staining reagents identical but longer incubation and 2 retreival steps making staining have higher intensity	and weak 1-95% (corresponding to Dako 22C3 50% and 1-49%)	continuous and categorical PD-L1	Second sample: ≥50% 11%, 1-49% 37%, <1% 51% Correlation between samples 0.62, p<0.001 At second time point, 39% identical, higher in 32%, lower in 29% 12% of negative cases became positive and 20% of positive became negative (assume cut-point >1%) Concordance rate 56% (95%CI 46 to 67%) when PD-L1 categorized as strong, weak or negative
Lin, 2017 Hong Kong Prevalence of PD-L1 (22C3) with and without previous neoadjuvant therapy	185	Age NR but follow-up for OS analysis >64 mos; resected	SC 43%, AC 57%	Most I/II	FFPE	Dako 22C3 pharmDx kit	PS ≥50%, 1-19%, <1%	Retrospective analysis of samples from patients, including time frame for OS, IHC personnel NR	Prevalence: PS ≥50% 11.4%, 1-49% 24.3% Prevalence with and without neoadjuvant chemotherapy: 88.9% vs 33.0%, p=0.009 using multivariate analysis Notes on heterogeneous expression; also influenced by tumor size and smoking status

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
Grange, 2017 United States & Canadian Academy of Pathology 106th Annual Meeting Abstracts USA Concordance between core needle biopsies and resection specimens with Dako 22C3 Finding: NR	28 cases	NR, resection specimens	SC 46% AC 54%	Resected	FFPE	Dako 22C3 clone; assay NR	PS 0%, 1-49%, ≥50% (positive)	Retrospectively compared PD-L1 expression in core needle then subsequent resection specimens	Concordance: Core biopsy 5/28 vs tissue 4/28: concordant in 96.4% cases, kappa 0.87, 95% CI 0.61-1.00 1 discordant result on AC with 50% biopsy and 5% tissue
Heyman n, 2017 United States & Canadian Academy of Patholog	200 from 183 patients	NR, NR Cytology 37 (20 endobronchial ultrasound aspirates, 12 effusions);	SC 17% AC 72% Other 11%	Stage NR but 83 resections Lung (129), regional lymph nodes (17),	Cell blocks for cytology FFPE for others Both ≥100 viable cells	Dako 22C3 pharmDx	Complete or partial membrane staining ≥1+ (quanitified not necessarily positive; also intensity or		Prevalence: cytology 38%, resection 22%, small biopsies 25% (comparable); no concordance or correlation stats Sample had insufficient cellularity in 8 (4%) cases (1 resection, 2 cytology, 5 other small biopsies)

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y 106th Annual Meeting Abstracts USA Feasibility of cytology and comparison between cytology, biopsy, and histology Funding: NR		resections 83; small biopsies 80		pleura/pericardium (15), distant metastases (28), other sites (11)			just any staining NR)		
Kim, 2017 ATS 2017 Annual Conference USA Feasibility in pleural and pericardial effusions using 22C3 pharmDx	12	Up to 9 mos, NR but imply diagnostic samples, cytology from pleural (n=10) or pericardial effusions (n=2)	NR	NR but all effusions	Cell blocks with ≥100 viable tumor cells	Dako 22C3 pharmDx	Complete or partial membrane staining ≥1+		<u>Prevalence</u>: PD-L1 positive in 8 (67%) and negative in 4 (33%)

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Funding: none									
Lee, 2017 ATS 2017 Annual Conference USA Feasibility in EBUS-TBNA using 22C3 pharmDx Funding: none	26	Up to 9 mos, NR but imply diagnostic samples; lymph nodes (73%), lung masses (23%)	SC 19% AC 65% Other 15%	NR but all aspirations	Cell blocks with ≥100 viable tumor cells	Dako 22C3 pharmDx	Complete or partial membrane staining ≥1+		Prevalence: PD-L1% in 46% and negative in 50% Insufficient cellularity 1 (4%) 4 patients also had excisional or effusion cytology; all concordant with EBUS-TBNA samples
Brunnstrom, 2017 Sweden Compare the staining properties of tumor cells between the antibody clones 28-8 (2	55	2006-2010; resections	SC 42 AC 53 Other 5	All resections	Consecutive slices from TMA made from FFPEs of 2 1-mm cores	28-8 & 22C3 Dako pharmDx SP142 and SP263 on a Ventana Benchmark Ultra with OptiView Universal DAB Detection Kit	<1% TCs (score 0), 1–4% (score 1), 5–9% (score 2), 10–24% (score 3), 25–49% (score 4), and ≥50% (score 5) Membranous staining Average of each case's 2 cores	7 pathologists (3 board certified, 3 senior residents, 1 junior resident); 4 formally trained on 22C3; all blinded to others and their previous assessments Reference scores: majority (≥4 raters)(95%) or median (5%)	Prevalence: • ≥1% TC: 28-8 38%, 22C3 29%, SP142 16%, SP263 42%, 28-8A 37% • ≥50% TC: 28-8 20%, 22C3 18%, SP142 5%, SP263 24%, 28-8A 20% • All slightly higher in AC • Many macrophages had membranous staining Inter-assay: • Pairwise analysis of antibody clones showed weighted kappa values in the range of 0.45–0.91 with the highest values for comparisons with 22C3 and 28-8 and the lowest involving SP142.

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assays), 22C3, SP142, and SP263 and investigate inter-rater variation between pathologists						Also clone 28-8 ("28-8A") on the Ventana Benchmark Ultra with OptiView Universal DAB Detection Kit	All >100 viable cells		• Excluding SP142 resulted in kappa 0.75–0.91. • ≥1% cut-off: 3–8 of the 55 cases (5–15%; median 4.5 cases) were differently classified as positive or negative when comparing any two assays excluding SP142 (11 cases with SP142). • ≥50% cutoff: only 1–3 of 55 cases (2–5%; median 2 cases) differently annotated (8 cases with SP142) • P<0.01 between ≥1% and ≥50% <u>Inter-observer:</u> • weighted kappa 0.71–0.96 (SP142 (0.81–0.96), followed by 22C3 (0.71–0.95), 28-8A (0.80–0.95), 28-8 (0.80–0.93), and SP263 (0.75–0.91) • Five or more pathologists were in agreement for 237 (86% of 274) of the cases. • Up to 20% (median 3) of the cases were differently classified as positive or negative by any pathologist compared with consensus score using ≥1% positive tumor cells as cutoff. A significantly better agreement between pathologists was seen using ≥ 50% as cutoff (0–5% of cases; median 1); also ≥25% • ≥1% worse than all other cut-offs, (p<0.001) • No obvious association between experience (specialist vs resident and formal PD-L1 training vs no training) and either high kappa value for interobserver variation or number

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
									of cases in agreement with consensus score.
Scheel, 2016 Germany Comparisons between 2 laboratory and 4 validated assays (22C3, 28-8, SP142, SP263) for proportion scores using dichotomous and new 6-step scoring system Finding by BMS, Roche, MSD and AstraZeneca	30 split between training set (15) for laboratory developed assays and validation set (15) for validated assays	Resection specimens	Validation set SC 4 AC 11		FFPE with consecutive sections for 2 LDTs and 4 validated assays Cut, stored at 2-4^{0}Cand stained within 1 month	2 LDTs using E1L3N and SP142 antibodies on an automated staining system with polymer-based detection system and DAB-chromogen (Leica Bond Polymer Refine) Dako 28-8 pharmDx, Dako 22C3 pharmDx, Ventana SP142 an SP263 as per manufacturer's instructions	TC PS (no cytoplasmic staining) using PS Proportion of area IC if any staining "Integrated proportion score": 6-step with categories 0-5 covering all currently used cut-offs: >1%, 1-<5%, 5-<10%, 10-<25%, 25-<50%, 50-<75%	9 pathologists blinded to assays Comparison of dichotomous PS (e.g. <1% vs ≥1%) vs classifying into 6 scores Raw proportions: pair-wise comparisons for each validated assay (each with 135 data points) plotted No reference standard	<u>Interobserver condordance</u> (kappa's) for TC: LDTs: • E1L3N: 0.50 (0.37-0.64) on 6-step vs 0.73-0.79 for dichotomous scoring • SP142 on LDT: 0.49 (0.34-0.66) on 6-step vs 0.61 – 0.80 on dichotomous Validation set (Light's kappa unweighted): • 0.47-0.49 on 6-step (22C3 0.47 [0.34-0.63]); 0.59-0.80 (mean 0.72) on dichotomous • 22C3 ≥1% 0.74 [0.44-0.94]; ≥5% 0.78 [0.58-0.94]l ≥10% 0.75 [0.52-0.89]; ≥50% 0.66 [0.42-0.89] • No significant differences between 4 assays • In 540 pairwise comparsions (using 6-step) between any 2 pathologists plotted for each assay, similar frequencies of discordant and concordant pairs were differing by 1 (25-32%) or ≥2 (10-15%) categories in 6-step for each assay (22C3 discordant pairs 0.57 (309/540); by 1 category 32% and 2 categories 11% <u>Interobserver concordance</u> for IC: • Mostly kappa <0.2 <u>Raw proportion scores (pairwise using data from 9 pathologists [135 data points each]</u>: • 28-8 vs 22C3: 72% concordant (13% higher for 28-8 and 16% higher for 22C3); 24 and 26% were

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
									negative and 24 and 27% strongly positive. • SP263 vs others: **higher proportions for SP263** in 46% (28-8), 44% (22C3), and 59% (SP142) pairs; 16% negative and 41% strongly positive • SP142 vs others: **lower proportions for SP142** than 36% (28-8), 39% (22C3), and 59% (SP263); 40% negative and 22 strongy positive Raw proportion scores (pairwise using median scores across 9 pathologists): • 28-8 and 22C3 scored similar proportions in 12 of 15 cases; SP142 stained fewer than other 3 assasy in 4 of 15 cases and SP263 scored more in 9 cases ≥1% cut-off: 22C3 and 28-8 same (11 of 15 positive cases), SP142 (9 of 15), SP263 (13 of 15) ≥50% cut-off: 22C3, 28-8, and SP142 similar (4 of 15 positive), but SP263 more (6 of 15)
Rimm, 2017 (Including author contact for results for all scoring methods) USA To compare	4 serial sections from 90 cases	Samples up to 8 yrs old, untreated surgically resected	SC 50% AC 50%	Stages I-III, primary	FFPE 5µm sections cut and sent to 3 institutions for staining	22C3 and 28-8 as per FDA approved assays; SP142 as per FDA approved with slightly different incubation times	Unified categorical scoring method for PS TC and ICs that fits into all clinical algorithms: TC categories A-G 0%, 1-4%, 5-9%, 10-24%, 25-49, ≥50%	13 pathologists Slides scanned by Leica Aperio scanner and placed into database for viewing on the internet Scoring instructions provided to pathologists Assay comparisons	SP142 lower mean scores in expression than others Interassay variability (using mean of 13 categorical scores as continuous numbers); 28-8 and E1L3N not significantly different (but different from others); SP142 greatest magnitude of difference from others; 22C3 slightly lower labelling (significantly from 28-8 and E1L3N); high concordance across antibodies for TC (0.813, 0.815-0.839) but low for IC (0.277, 0.222-0.334); TC ICC

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
2 FDA approved (22C3, 28-8) with 1 investigational (SP142) and 1 LDT (E1L3N) assays for assay concordance and pathologist concordance Sponsored by NCCN and funded by BMS						at 3 steps; E1L3N on Lieca Bond platform	IC categories A-C: 0%, 1-9%, ≥10% Scoring including membrane and cytoplasmic staining of any intensity	mean scores from 13 plotted for each antibody by case Concordance between pathologists for each antibody in 6-category, 3-category <1%, 1-49% and ≥50% (ICC values), and dichotomous >1% and >50% (Fleiss K coefficient for agreement and Kendall concordance coefficient) Using mean of 13 scores as "true", calculated analog sensitivity (correctly positive) and specificity (correctly negative) for >1% >5%, and 50%1-49% and 50% cut-offs	increased to 0.971 when removing SP142 NR ICC at each category <u>Reproducibility between pathologists for each assay</u>: 22C3: 6-category scoring: ICC 0.882 (0.873-0.891) for TCs 3-category scoring: ICC 0.743 50% dichotomous: Fleiss agreement 0.773; Kendall concordance 0.794 1% dichotomous: : Fleiss agreement 0.535; Kendall concordance 0.608 <u>Concordance for mean of all 4 assays at 50% cut-off</u> 0.749, and at 1% 0.537 Analog specificity scores for >1% cut-off <80%
Skov, 2017 Denmark Paired comparison on cytologic	86 paired samples	No treatment given Histologic : lobectomy (55%), wedge resection	SC 32.2% AC 52.9 % Neuroendocrine 4.7%	NR but 69% resection and no tx	FFPE 3-4µm, stained within 1 month <100 cells in 17 of 86 cell blocks; all histologic	22C3 pharmDx and 28-8 pharmDx, as per manufacturer's	PS ≥1%, ≥5%, ≥10%, and thereafter in 10% increments (11 categories) (report >1	1 pathologist with 20 yrs experience in diagnosing histology and cytology specimens; blinded to	<u>Intra-assay agreement on same material:</u> On regression plots Pearson R^2 0.95 whether applied to histology or cytology specimens Cytology: OAs 93-98%, APA 80-97% (80% at >50%), ANA 95-98% Histology: OAs 93-99%, APA 80-98% (80% at >50%), ANA 95-98%

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
and histologic specimens with 22C3 pharmDx and 28-8 pharmDx, and impact of tumor heterogeneity Funding MSD and BMS		(14%), core needle (18%), mucosa biopsy (13%) Cytologic samples: CT FNA (57%), FNA (22%), EBUS/EUS 17.4%, pleura effusion (3.5%) Both from same lesion within 6 wks	Mesothelioma 1.2% Metastases from non-lung malignancy 8.2%		samples had >100 cells	No IHC was performed on smeared material Evaluation using Olympus BX60 microscope	and 50% for Dako and >1, 5, 10% for 28-8	previous assessments Scoring of like materials for assay comparisons Scoring of different materials with like assays for agreement between cytology and histology (histology serving as nonreference standard) Assessment of heterogeneity in histology samples (within single slides, based on uniformity of distribution across whole slide) Reproducibility: pathologist repeated scoing on 22C3 stained histology samples after 2 mo	<u>Agreement for each assay between 2 rounds on same material</u> also high R^2 0.95 <u>Agreement between cytology and histology</u> (all cut-offs): • OA (85-95%), PPA (79-100%), and NPA (89-98%); R^2 0.87 to 0.89 • Numerically higher for 22C3 with 50% (OA 94%; PPA 100%, NPA 93%) vs 1% (OA 85%, PPA 80%, NPA 89%) • No change when removing <100 cell blocks or restricting to NSCLC <u>OAs</u> between 85% and 95% No bias towards lower prevalence of positivity with cytology than with histology Between 2 rounds with 22C3 R^2 0.95 Heterogeneity in 25% tumors; disagreement related to heterogeneity within histologic material (especially at 5% and 10% cut-offs)

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Ratcliffe, 2017 USA and UK Comparison between Dako 22C3, Dako 28-8, and Ventana SP263 assays Funding: AstraZeneca	493 from commercial sources	1 to 4 years,	SC 42.6% AC 54.8% AS 2.6%	I-IV (0.4%)	FFPE from consecutive sections freshly cut	As per each assay's manufacturer's instructions	PS (%) SP263: <1, 1–4, 5–9, ≥10, and 10% increments to 100 22C3: 0 to 5 in increments of 1%, 10, 20, 25, 30 and 10% increments 28-8: 0 to 10 in increments of 1%, 20, 25, 30	1 pathologist trained in each assay, in CLIA laboratory; another pathologist scored 200 Samples read in assay-to assay batches, wash-out periods if sample from same patient Assays compared at raw %, multiple cut-offs and in comparison with each assays reference standard per clinical trials (22C3 1, 50%; SP263 25%, 28-8 1, 10%)	<u>Prevalence</u>: 41% samples PD-L1 0% <u>Plotted agreements</u> (pair-wise) across range of cut-offs: spearman correlation coefficients all >90% <u>OA</u>: >90% at multiple expression levels (e.g., 1, 5, 10, 25, 50) <u>Agreements at clinically validated cut-offs</u>: NPA and PPA >85% for all • Only one with lower boundary <85% (80.8) was PPA for 22C3 at ≥25% • PPA varied more (86-97.5%) than NPA (93.5-98.8%) <u>Intraobserver analysis</u> (200 samples): **OPAs >75%; lowest at cut-offs <10%**; over 85% at 10, 25, and 50% (OPAs for 22C3 at 1 and 50% cut-offs: 76.5% (lower limit 71%) and 94.5% (lower 91.1)
Adam, 2016 IASLS 17th World Conference on Lung Cancer (from abstract and presentation)	41	NR, NR, resections	NR	NR but resected	FFPE, as per standards	BenchMark Ultra (2 centres), Dako Autostainer Link 48 (3 centres), Leica Bond III (2 centres) either using	TC PS: 1, 5, 25, 50% ICs PS (NR if % cells or area): 1, 5, 10%	7 thoracic pathologists trained in expert course; each analysed 6 cases and compared staining of 5 clones on all platforms; blinded from centre, clone and platform	<u>Concordance of assays:</u> • 22C3, 28-8, SP263 assays across all 5 Dako and Benchmark platforms: R^2 0.886 to 0.953 for TC and 0.65 to 0.71 for ICs • Weighted concordance at 1% and 50% cut-offs: 22C3 0.82-0.91; 28-8 0.79-0.94; SP263 0.81 (>75% defined as min) • **OA for all assays at 50% cut-off: 95.1%** <u>Concordance of LDTs vs. 3 assays</u>:

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
France (7 centres) Harmonization study: Comparison of clones (22C3, SP263, 28-8, SP142, E1L3N) on different platforms (BenchMark Ultra, Dako Autostainer Link 48, Leica Bond III, with reference sample as applicable Funding/ support: BMS, Merck, AstraZeneca, Roche						validated assay method (if matched clone) or a developed LDT if clone not matched with their platform		41 tested by 5 clones (35 stainings for each case); 1435 slides	• For 27 LDTs 52% had similar concordance compared with reference assays • With 28-8 assay: only 1 LDT good (Ventana LDT kappa 0.80) • With 22C3 assay: only 2 LDTs good (2 Ventanas LDTs kappas 0.77 & 0.81) • With SP263 assay: all 5 LDTs on Dako and Leica good kappas 0.83-0.86 • Clone SP263 most concordance across LDT platforms for TCs (kappa 0.81) and ICs; for TCs clone 28-8 0.73, SP142 0.64, 22C3 0.73, E1L3N 0.78 • Some select LDTs with clones 28-8, 22C3 and E1L3N (but not SP142) showed good correlation with 3 assays for TCs • Poor concordance for ICs <u>Selection of LDTs</u>: Dako: E1L3N, SP263 Ventana: 28-8, 22C3, E1L3N Leica: E1L3N, SP142, SP263

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
Scheel, 2017 2017 ASCO Annual Meeting Germany Inter-laboratory concordance between 2 laboratory and 4 validated assays (22C3, 28-8, SP142, SP263) Funding NR	21	NR	NR	NR	TMA centrally prepared	22C3, 28-8, SP142, SP263 assays as per manuals 2 LDTs NR	"Integrated proportion score": 6-step with categories 0-5 covering all currently used cut-offs: >1%, 1-<5%, 5-<10%, 10-<25%, 25-<50%, 50-<75% (as per Scheel 2016) PS ≥1% & ≥50%	Stained at 10 sites Assay performance assessed with a 2nd TMA with 11 cell lines with defined PD-L1 expressions Slides evaluated by central quality control and image analysis	<u>Reproducibility at all sites:</u> 4 assays comparable while LDTs mixed; 6 protocols appropriate IHC quality with staining patterns similar to 22C3 and 28-8, but 5 protocols less DAB-deposits and reduced staining intensity <u>Inter-laboratory concordance:</u> Using 6-step system kappas 0.43-0.69 Cut-off ≥1% & ≥50%: 0.73-0.89 for assays and 0.50 for LDTs No significant differences between assays LDTs with staining patterns similar to assays are possible but need to be carefully calibrated to match the staining intensity-range
Yeh, 2016 ESMO 2016 Taiwan	219	NR, resections	AC 100%	Resections	TMA	• Dako 22C3 pharm Dx • SP142 on Leica autostainer • SP263 on Ventana autostainer	PS ≥1%	NR	<u>Prevalence</u>: 22C3 16.9%, SP142 15.5%, SP263 40.6% <u>Inter-assay concordance</u>: With all assays: 158/219 (72.1% concordance) of whom 129 (58.9%) were negative and 29 (13.2%) were positive 22C3 and SP142: 94% SP263 with 22C3: 76.3% SP263 with SP142: 74% <u>Others</u>:

Paper(s)	Sample size	Age, treatment history, and type of tissue specimens	Histology (%)	Stage of Disease/Type of tumor (primary vs metastasized)	Tissue Preparation	IHC Method	PD-L1 Cutoffs Evaluated	Personnel & details for studies	Outcomes:
						(platform NR)			Solid histology associated with higher expression in all assays (p<0.001) EGFR mutation negatively correlated with expression in all assays (P<0.05) Positive prognostic for poor survival (P<0.001) (but no account for treatment)

Table C5. Characteristics of economic evaluations

Cheers checklist item*	pCODR (First line)	pCODR (Second line)	Huang et al, 2017	Aguiar, 2017	Matter-Walstra, 2016
Type of analysis	CUA & CEA	CUA & CEA	CEA (life saved) and CUA	CEA and CUA and BIA	CUA
Target population and subgroups	Advanced NSCLC with **PD-L1 ≥50%** and naïve to treatment in advanced stage and without sensitizing mutations Subgroups: none	Advanced stage NSCLC with **PD-L1 ≥1%** on or after progression on platinum-based chemotherapy Subgroups: one-way analysis for pD-L1 ≥50%	Advanced NSCLC with **PD-L1 TPS ≥50**% and progressing on or after platinum-based chemotherapy or TKI if appropriate Subgroups: none (no rationale)	Advanced NSCLC 2L treatment Subgroups: with and without selection based on PD-L1 at different levels	Advanced **non-squamous** NSCLC, pretreated
Setting and location	Canada	Canada	USA, oncology centres	USA	Sweden
Study perspective	Canadian heath care system	Canadian heath care system	US third party payer (**80% drug and disease management costs**)	US Medicare system	Swiss healthcare system
Comparators	Pembrolizumab vs platinum-based doublet chemotherapy (cisplatin + pemetrexed; carboplatin +	Pembrolizumab vs docetaxel	Pembrolizumab vs 2L chemotherapy with docetaxel	Pembro, Nivolumab and Atezolizumab vs 2L docetaxel	Nivolumab vs 2L docetaxel

	pemetrexed; cisplatin + gemcitabine				
Time horizon	10 years	10 years (5 years with Economic Guidance Panel re-analysis)	Base case 20 yrs	5 yrs	Life-long
Discount rate	NR	NR	3%	None evident from tables	Not discounted assuming short life-expectancy
Choice of health outcomes	Rationale provided in clinical submission	Rationale provided in clinical submission	Rationale provided	Rationale provided	Rationale provided
Measurement of effectiveness	OS, PFS and TRAEs from phase 3 RCT Keynote 024 at median follow up of 11.2 months not later cut-off at 19.1 months Use of SEER data for OS from 5.5 years Cross-over from chemotherapy to pembrolizumab (44% patients) was not accounted for in base case	OS, PFS and TRAEs from phase 3 RCT Keynote 010 at median follow up of 13.1 months with KM data to 12 months then extrapolation Effectiveness of docetaxel for patients not tested for PD-L1 so unclear if adjusted results from trial where patients were PD-L1 positive	Time-on-treatment (ToT; because many received Pembro beyond progression base case max 2 yrs), PFS, and OS from KEYNOTE 010 primary publication All-cause Grade 3+ AEs in ≥5% patients in KEYNOTE 010 Subsequent treatments: 40% pembro and 44% docetaxel; impact assumed to be included in KM KEYNOTE 010 data. One line modelled; top 7 therapies included Best supportive care: all patients beyond progression	Three phase III trials (Checkmate 017, 057) Keynote 010, OAK with **3 strategies: 1) no PD-L1 testing and all patients tx with docetaxel, 2) no testing and all patients treated with immunotherapy, 3) immunotherapy for PD-L1 positive and docetaxel for negative** Used trial reports on AUC data for PFS and OS from longest follow-up; lifetime model used with a horizon of 5 yrs Duration of treatment values using cycles in trials **(Nivo 14SC/15nonSC; Doc 5/7), (Pembro 9; Doc 7), (Atezo 8; Doc 7)** Which AEs used NR	OS, PFS, and TRAEs Grade 3+ from Checkmate 057 **3 main strategies: 1) all pts treated with docetaxel, 2) all patients treated with Nivo, 3) PD-L1 ≥1% and ≥10% treated with NIvo and all others treated with docetaxel** Accounted for dose reductions in Docetaxel arm as per trial (i.e. 25.9% receiving 60mg/m^2)
Measurement and valuation of preference-based outcomes	Utilites from KN 024 trial pooled between treatment arms; considered conservative Nothing about disutilties for harms	NR (may assume similar to first line by pooling HRQL ultilities from KN10 between arms; nothing about harms)	• KEYNOTE 010 EQ-5D data (during tx, at discontinuation and 30-d follow-up) & converted to population-based for US, UK and EU/other patients: time-to-death (5 categories) base case but also progression-based health states (mean for	Utilities for PF and PD health states derived from literature (Doyle et al, Lung Cancer 2008,62(3):374; Nafees Health Quality Life Outcomes 2008;6:84); same for each arm PF: 0.65 PD: 0.43	Utilities derived from literature (Borget Eur Respir J 2012;39:172-179; Lewis J Int Med Res 2010;38:9-21) using EQ5D for Doc; **values for PFS with Nivo made assumptions of 0.05 to 0.15 higher due to fewer AEs** Docetaxel: PFS 0.652 (0.431-0.833), PD 0.470 (0.184-0.733) Nivolumab: PFS 0.756 (0.437-0.974), PD 0.470 (0.184-0.733)

			each of PF and PD states) approaches; same utilities for both comparators Time-to-death (base case): 5-point scale from <30d (0.396) to ≥360 d (0.807) Progression-based approach: PF: 0.761, PF without AEs 0.770, PD: 0.687 (**carries over utility at 30-d post progression visit without decline**) Death: 0 • AEs: disutilities from literature on NSCLC (mainly Nafees Health Quality Life Outcomes 2008;6:84) & mean duration 21.6d from KEYNOTE 010: febrile neutropenia -0.09, pneumonia or lung infection -0.09, fatigue or asthenia (-0.07), neutropenia or decreased neutrophils (-0.09)	AEs: disutilities from literature on NSCLC (mainly Nafees Health Quality Life Outcomes 2008;6:84)	Utilities for Docetaxel and Nivolumab in PFS assumed to include AEs
Estimating resources and costs	Costs (Merck drug costs; IMS Brogan for other drugs): 1. Pembro: $44/mg for 200 mg every 3 weeks ($8,800); $11,733.33 per 28-day cycle 2. Chemetherapy range $1,401-$2,125 per 28-day cycle **3. Other costs NR including use of PD-L1 test costs** 4. Mention of fewer harms with pembrolizumab and will have been reflected in costs	Costs (Merck drug costs; IMS Brogan for other drugs): 1. Pembro: $44/mg for 2mg/kg using average weight in Keynote 010 every 3 weeks and no wastage ($8,800); $8,237 per 28-day cycle 2. Docetaxel $11,42/mg; $1,942 per 28-day cycle **3. PD-L1 cost NR but used for all patients in Pembro arm**	Cited sources (CMS, Keynote 010, literature) 1. Pembro ($4,380 per 100 mg for 73.3kg base case $8,805 per dose; 80% assumed paid by third party healthcare payers); docetaxel $1281 2. Administration costs: $280; 80% paid 3. Concomitant medication 4. Disease management: weekly (PF for Pembro-$1282, Docet $1623; PD $1938)	Cited literature and Keynote 010 sources for 1. Costs of Dako 22C3 pharmDx 2. Drug acquisition Nivo USD 24.69/mg, Pembro USD 43.80/mg, Atezo USD 10.42/mg; used 70kg body weight, BSA 1.8m^2 3. Drug administration 4. Monitoring/disease management (based on # cycles ($5,856-8,238 for	Checkmate 057 data, BMS public prices for Nivo, local Swiss data for subsequent therapies, AE in-patient and out-patient costs 1. Study drugs (Nivo CHF 18.05/mg in 100-mg vial, Docetaxel CHF 5.79/mg) 2. Drug administration 3. CT scan Q6W **4. PD-L1 test CHF 136 (73 technical work, 63 for interpretation)** 5. AEs (febrile neutropenia [CHF 8,150, anemia [3,358], alopecia [1,500]) 6. Best supportive care in progressive phase (per cycle: 2,860 (95% CI 1,375-4,503)

		4. **Other costs: NR;** mention that side effects adequately accounted or in analysis	5. Post-progression therapy: Pembro $3328, Docet $5903 (more immunotherapy); average 88 days & one-time monitoring cost at first post-progression 6. Terminal care: $31114 7. AEs (e.g., febrile neutropenia $7970, pneumonia $5964, fatigue $2226): base case $346 pembro vs $889 docetaxel **8. PD-L1 test $209**	immune vs $3,290-4,606 for docetaxel) 5. AEs: base case $202 to1,388 for immune vs $3,513 to 7,002 for docetaxel 6. Drugs prescribed after progression (each drug in each trial; duration NR) ($5,947-$9,599 for immune vs $5,925-12,457 docetaxel) 7. End-of-life NR what % assumed paid by payer	7. Post-progressive therapies: used average monthly treatment costs with wide distribution from region (Trial did not report durations, scheme, doses etc)
Currency, price date and conversion	2016 CAN	2015 CAN	Updated to 2016 USD based on Medical care component of Consumer Price Index	Costs of AEs correct by inflation	NR but all recent data
Choice of model	3-health state partitioned-survival: PFS, progressed disease, death	3-health state partitioned-survival: PFS, progressed disease, death	• 3 health state cohort simulation model (progression-free, progressed disease, and death); model cycle length of 1 week • Partitioned survival approach: OS partitioned into PFS and post-progression and no transition probabilities but directly using survival curves	3 health state decision-analytic model (progression-free, post progression disease, and death) PD-L1+ arms; 1%, 5%, and 10% thresholds for Nivo; 1% and 50% for Pembro; TC or IC score 1 or 3 for Atezolizumab	Markov decision tree: 3 states PF, PD and death Transition probabilities from Checkmate 057
Assumptions	10-year time horizon thought appropriate for first-line treatment Use of SEER data from year 5.5 onwards may overestimate OS because data includes EGFR+ and ALK+ patients who tend to live longer & median survival of US patients not reflective of Canada	Patients unselected for PD-L1+ receive same benefits from docetaxel as those selected Patients only received one line of subsequent treatment (only 10% in trial received 2+) Patients continue to receive incremental benefit post-progression	Treatment up to 2 years, used ToT data	NR	Only febrile neutropenia and alopecia considered to impact costs and quality of life even though 10% vs 54% TRAEs in Nivo vs Docetaxel Treatment duration assumptions NR

Analytic methods & study parameters	Scenario analysis for cross-over Economic Guidance Panel re-analysis: • PFS modelling changed from Weibull to Generalized Gamma distribution which projected almost no patients progression free at 5 years (validated by clinicians) • No use of SEER data beyond 5.5 years • Treatment effect: rather than by projections, OS was made to gradually decline reaching hazard ratio of 1 at 260 weeks	Economic Guidance Panel re-analysis: • Time horizon 5 years • Utilities by time to death approach instead of progression status, because sometimes patients do not have a response in progression-free state and if they do have response it may be for long duration • OS benefit capped at trial end date (100 weeks) • PD-L1 50% one-way sensitivity analysis	Parametric extrapolation: Base case projected that 0.7% patients would still be alive at 20 yrs Parametric models fit to KM ToT, PFS and OS; NICE Decision Support Guidelines <u>ToT</u>: only needed for Pembrolizumab; fit to KM data using AIC, BIC, and visual inspection to select Gompertz distribution for base case <u>PFS</u>: KM data used directly for first 9 wks (response first assessed at this time and large drop in PFS at this time hard to fit curve), proportional hazards assumptions failed so separate models for each comparator. Pembro: fit to KM data using AIC, BIC, and visual inspection to select Weibull function for base case; docetaxel exponential parametric function <u>OS:</u> • 0-5 yrs; All tested parametric curves appeared to underestimate OS at 21-39 wks and overestimate at 39-65 wks; a 2-phase piecewise model (unadjusted KM data in 1st and exponential model in 2nd phase; turning point at 52 wks, 2nd phase to 5 yrs); used for both comparators • 5-20 yrs: cumulative hazard plot from SEER stage IIIb and IV data	<u>For uncertainty</u>: One-way deterministic for input parameters, using 95% CIs or plausible ranges Discount rates for drug acquisition (10 and 20%) Body weight, BSA Costs of admin, monitoring Utilities of PF and PD HR for PFS and OS Tornado diagrams presented CEACs: Probability of reaching WTP threshold of 100,000 per QALY gained	Cycle length of 1 month; dosing at Q2W (Nivo) or Q3W (Doce) adapted to fit model PFS and OS HRs assumed to be constant over time; calculated mean time in state <u>For uncertainty</u>: One-way deterministic for input parameters, using 95% CIs or plausible ranges 3 scenarios: dose reduction of Nivo 1mg/kg (Topalian 2012), max treatment duration of 3 mos/6 applications, Nivo price reductions (all with similar efficacy) 2nd order Monte Carlo probabilistic for parameters subject to uncertainty (distributions provided) Tornado diagrams, scatterplots presented CEACs: Probability of reaching WTP threshold of CHF 100,000 per QALY gained Validation: Trackers for PFS and OS included as a basis for analysing correct data fit. Model calibrated to match PF and OS data in publication. All outputs reviewed for plausibility. Extreme variation was used in sensitivity analysis for key parameters

			derived a constant HR (assume long-term survival trend similar between comparators) For uncertainty: Methodological: one-way deterministic using 95% CI or variations, treatment durations, utility measure (±20%; explored QLQ-C30 instrument), costs ±25%, AE management ±50%, 5-20 time horizon, 0 and 3% discounting; probabilistic using log-normal distribution with SE set at 20% of base case; two-way and scenario-based also performed Parameter: one-way (95% CI of parameter estimates) and 2nd order Monte Carlo simulations (1000 iterations) with random numbers generated from multivariate normal distribution for utility approaches (state-based vs time-to-death) and choice of extrapolation distributional family, Tornado diagram for one-way Scatter plots and CEACs for probabilistic Validation by independent clinical experts		
Incremental costs and outcomes	**Submitted incremental costs and outcomes:** Life-years: 1.23 QALYs: 0.99 Costs: $98, 298 $/QALY: $99,392	**Submitted incremental costs and outcomes:** Life-years: 0.75 QALYs: 0.53 Costs: $76, 742 $/QALY: $143,730	Incremental costs and outcomes: Costs: $160,522 (drug: $90,969, disease management $72,867) Outcomes: Life years: 1.18 (PF 7.86, PD 6.35)	Nivolumab for squamous: • QALY gained 0.417; cost per QALY $155,605 • Life years gained: 0.71; cost per LYG $91,034	Base case: No testing: Incremental cost vs Doc for all CHF $28,589, effect 0.17; ICER $177,478 PD-L1 ≥1%: Incremental cost vs Doc for all CHF $35,530, effect 0.27; ICER $133,267

	EGP re-analysis (lower and upper bounds): Life years: 1.2 and 0.84 QALYs: 0.96 and 0.67 Costs: $107,632 and $103,406 ICUR ($/QALY): $111,769 and $154,273	**EGP re-analysis (lower and upper bounds):** Life years: 0.58 and 0.34 QALYs: 0.48 and 0.27 Costs: $71,649 and $68,441 ICUR ($/QALY): $149,342 and $254, 945	QALYs: 0.95 **Cost per life-year gained:** $135,552 **Cost per QALY**: $168,619	• With PD-L1 QALYs worse for 1% (0.322) better for 5% (15% better 0.481) and 10% (18% better 0.495) **Cost per QALY: 1% $301,246, 5% $135,080; 10% $131,159** Nivolumab for non-squamous: • QALY gained 0.287; cost per QALY $187,685 • Life years gained: 0.53; cost per LYG $102,896 • With PD-L1 QALYs better for 1% (67% 0.480), 5% (157% better 0.740) and 10% (137% better 0.683) **Cost per QALY: 1% $112,311, 5% $135,080; 10% $131,159** Pembrolizumab • QALY gained ≥1% 0.346; **cost per QALY ≥1% $98,421** • Life years gained ≥1% 0.69; cost per LYG $49,007 • With PD-L1 ≥50%: QALY better by 18% (0.409) **Cost per QALY ≥50%: $80,735** Atezolizumab • QALY gained: 0.354; cost per QALY $215,802 • Life years gained: 0.74 cost per LYG $103,095 • With TC or IC ≥1 QALY better by	PD-L1 ≥10%: Incremental cost vs Doc for all CHF $32,274, effect 0.26; ICER $124,891 (Costs rise with PD-L1 due to longer PFS)

				18% (0.405), TC or IC ≥3 better by 183% (0.999) **Cost per QALY ≥1 $ $188,632, ≥3 $76,459**	
Characterizing uncertainty	Re-analysis changes to ICUR: • PFS modelling changed from Weibull to Generalized Gamma distribution: $9,603 • No use of SEER data beyond 5.5 years: $2,613 • Treatment effect: $26,038	Re-analysis changes to ICUR: • Time horizon 5 years: $28,905 • Utilities by time to death: -$18,380 • OS benefit capped at trial end date (100 weeks): $135,265 • PD-L1 50% one-way sensitivity analysis: $185	Scenario: Time horizon 5 yrs vs 20c: cost per QALY: $194,884 Treatment until progression vs max 2 yrs: cost per QALY $214,735 State-based (0.86 QALYs gained) vs 5-time-to-death: cost per QALY $186,213 QLQ-C30 utilities: $154,450 One-way: Tornado diagram: extrapolation of OS (up to $420,000) and ToT, and utilities for >360 to death Probabilistic: Cost per QALY $167,476 (95% Crl 114,055 to 424,787) 75% probability that ICER below $200,000/QALY	One-way: Overall survival OS 95% CIs largest impact on outcomes (QALY lowest 0.047 to highest 1.202); body weight ($68,171 for lowest to $250,953 for highest) Also impacted by discounts on drugs: 21.9%probability of immunotherapy being cost-effective (WTP of 100,000) increased to 23.1% with 10% discount and 24.3% with 20% discount	One-way: Utility scores for PFS and PD strongest impact (95% CI ~105,000 to >350,000) but neither brought base case ICER below CHF100,000 WTP; costs for best supportive care and body weight also big influence Scenario analyses: • Vs providing Nivo to all: PD-L1 ≥1%: Incremental cost vs Nivo for all CHF 6,941, effect 0.11; ICER 65,774 PD-L1 ≥10%: Incremental cost vs Nivo for all CHF 3,685, effect 0.10; ICER 37,860 • Reducing Nivo dose to 1mg/kg: no testing ICER 60,787 (74.4% being cost-effective) • Restricting treatment to 3 mos: no testing ICER 110,349 (46.6% probability of cost-effective) • Both 2 above in PD-L1 testing scenarios became cost-effective • Price reduction analyses: price reduction by at least 45% required for WT 100,000 in base case, 27-33% if PD-L1 testing Probabilistic: 14-22% probability of cost-effective in all 3 base case
Characterizing heterogeneity	NR	See results for PD-L1 testing	None		See results for PD-L1 testing
Discussion/limitations	Short term follow up on OS Difficulty knowing about long-term survival projections and treatment duration	Short term follow up on OS vs 10 year time horizon submitted Magnitude of benefit in post-progression period unknown	Due to patient inclusion/exclusion in trial, study sites large urban Consequences of follow-up therapies uncertain without data	BIA: Using SEER and other literature; PD-L1+ at 1% and 50% taken from trials, assumed 100% market penetration Results: n=37,638 eligible for 2L (SC 8,656 & nonSC	How patients will be treated after Nivo vs Doc largely unknown Did not know time in progressive disease so estimated from OS data; e.g. median PFS was 2.3 vs 4.2 but rates of PFS differed at 1 yr which the authors could not account for and this would increase costs for Nivo

				28,982); tx with nivilumab incremental cost 1.6 billion annually; tx with Atezolizumab 2.4 billion If ≥1% PD-L1 (46%), tx with nivolumab 849 million, pembrolizumab 971 million If ≥50% (28%), tx with pembro 411 million Limitations: utilities from literature and not using drugs in trials	
Source of funding	Merck & pCODR	Merck & pCODR	Merck	None	Non-industry
Conflicts of interest			Authors BMS employment, shares and stocks Peer reviewers no COIs	None to declare	Only funding source reported

* Husereau, D., M. Drummond, S. Petrou, C. Carswell, D. Moher, D. Greenberg, F. Augustovski*, et al.* "Consolidated Health Economic Evaluation Reporting Standards (Cheers) Statement." [In eng]. *BMJ* 346 (Mar 25 2013): f1049.

Table C6. Reporting quality of economic evaluations

Using CHEERS Checklist (*BMJ* 346 [Mar 25 2013]: f1049) for reporting of economic evaluations.

Y=yes; P=partial (e.g., no rationale provided); N=No; NA=not applicable (e.g., not reported in published manuscript)

Section/Item	Item no.	Recommendation	pCODR (First-line)	pCODR (Second-line; ≥1% PD-L1)	Huang 2017 (Second-line; ≥50% PD-L1)	Aguiar 2017	Matters-Walstra 2016
Title and abstract							
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	NA	NA	Y	Y	Y
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	NA	NA	Y	P (Not perspective or uncertainty apart from PD-l1)	Y
Introduction							
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Y (Implied via pCODR submission)	Y (Implied via pCODR submission)	Y	Y	Y
Methods							
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Y (Via Clinical submission of KN24)	Y (Via Clinical submission of KN10; PD-L1 ≥50% subgroup analyzed but not used for pCODR	Y (Indicated for ≥50% PD-L1 in USA)	Y	Y

				because of application)			
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Y (Implied with pCODR submission)	Y (Implied with pCODR submission)	Y	Y	Y
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Y	Y	Y	Y	Y
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Y (Rationale provided)	Y (Rationale provided)	Y	Y	Y
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Y	Y (Submitter and EGP Reanalysis)	Y	Y	Y
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N	N	Y	P (No rationale)	Y
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Y (Clinical submission)	Y (Clinical submission)	Y	Y	Y
Measurement of effectiveness	11a 11b	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. *Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	P (for KN10 but not for data used for extrapolation)	P (for KN10 but not for data used for extrapolation)	Y	P (Limited design features)	Y
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	P	N	Y (Benefits and harms)	P (Benefits and harms but no details of methods from	P (Benefits only)

						literature source)	
Estimating resources and costs	13a 13b	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. *Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	P (Drug costs only)	P (Drug costs only)	Y	Y	Y
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Y	Y	Y	Y	P (Uncertain for heath care and post-progression treatment dates)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Y	Y	Y	Y	Y

Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	P/Unclear if some missing	P/Unclear if some missing	Y	P	Y
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P (Limited for cost and extrapolation data)	P (Limited for cost and extrapolation data)	Y	Y	Y
Results							
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	P (Not for extrapolation values, most costs)	P (Not for extrapolation values, most costs)	Y	Y	Y
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	P (Not specific to comparators)	P (Not specific to comparators)	Y	Y	Y
Characterising uncertainty	20	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions	P (Only for EGP's re-analysis)	P (Only for EGP's re-analysis)	Y	Y	Y

		(such as discount rate, study perspective). *Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.					
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N	P (≥ 50% PD-L1 univariate analysis reported)	N	Y (≥ 1% & 50% PD-L1)	Y (≥1 and ≥10% PD-L1)
Discussion							
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	N	N	Y	Y	Y
Other							
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Y	Y	Y	Y	P (But not industry)
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Y	Y	Y	Y	N

Total			11 Y; 8 P; 3 N; 2 NA	11 Y; 8 P; 3 N; 2 NA	23 Y; 1 N	19 Y; 5 P	21 Y; 3 P

Appendix D. Micro-costing values and calculations

Table D1. Dako costs (Reagents and supplies)

Step	Reagent / Product	Volume (mL) / Amount Per Unit	Cost Per Unit	Amount Used Per Test Per Run (mL)	Avg # Tests Per Container	Cost Per Slide
Primary	PD-L1 kit		$3,677.00		50	$73.54
Stain/Rinse	Wash Buffer (working)	20000	$0.00			$0.00
Detection (included in kit)	Peroxidase-Blocking Reagent	1	$0.00	0.3	50	$0.00
	HRP	1	$0.00	0.3	50	$0.00
	DAB+ Chromogen	15	$0.00	0.3	50	$0.00
	Mouse Linker	1	$0.00	0.3	50	$0.00
Retrieval	TRS Low pH (working)	6	$0.00	500		$0.00
Counterstain	Hematoxlin (Link)	45	$0.00	0.3	150	$0.00
Label	Vantage Label	1700	$238.00	1	1700	$0.14
Overlay	Overlays	3750	$525.00	1	3750	$0.14
					Total	**$73.82**

Table D1. Personnel cost data

Step	Time (min)
Data Entry (per case)	7.15
Dako run	29.00
Unloading & Coverslipping (per slide)	0.25
Slide Sorting (per slide)	0.25
Case Assembly (per case)	0.50

Position	Cost/min
Laboratory Assistant II	$0.56
Medical Laboratory Technologist I	$0.81
Pathologist	$4.05

Table D3. Total costing and calcualtions for per case cost

Description	Unit	Cost/Unit	Minimum Cost/Case	Control Cost	Block test
Specimen Handling and Documentation	per case	$22.51	$22.51	$22.51	$0.00
Tissue Sectioning/Mounting on Slides	per slide	$6.75	$13.50	$0.00	$0.00
Running of Dako instrument		$23.49	$23.49	$23.49	$23.49
Cost of Reagents and Supplies	per slide	$73.82	$147.64	$73.82	$73.82
Instrument unloading, coverslipping	per slide	$0.18	$0.73	$0.73	$0.73
Slide Sorting	per slide	$0.18	$0.73	$0.73	$0.73
Case Assembly	per case	$0.41	$0.41	$0.41	$0.00
Pathologist Interpretation Fee	per case	$224.42	$40.50	$0.00	$0.00
Subtotal			$249.50	$121.69	$98.77
Overhead cost		25%	$62.37	$30.42	$24.69
Total			**$311.87**	**$152.11**	**$123.46**

PD-L1 requires 1 batch controls (vendor or in-house) and 2 patient slides (1 test & 1 negative)

Calculations for per case costs

Formula: Average cost per case = ($311.87 x ave number of cases per month) + $2253.00 (controls and block cost for month) divided by ave # of cases per month

Calculation: Average cost per case= (311x136) + 2253= 44500/136= $327.56

Appendix E. Excluded studies

1516 studies were excluded and are grouped below in the following categories:

Associated publications without useable data (n=46)
Study design (n=24)
Clinically validated assay but not 22C3 and not for pembrolizumab (n=33)
Not clinically validated assay (n=32)
No results based on PD-L1 expression (n=129)
Other PD-L1 testing (not immunohistochemistry) (n=55)
Combination treatment (n=190)
Case reports (n=112)
Other moderators to treatment (not PD-L1) (n=88)
Not research study (n=216)
No relevant outcomes (n=42)
Wrong population (n=209)
No or wrong intervention (n=150)
Duplicates (n=21)
Systematic reviews (n=31)
Other reasons (n=138)

Associated publications without useable data

1. Antonia SJ, Brahmer JR, Balmanoukian AS, et al. Safety and clinical activity of first-line durvalumab in advanced NSCLC: Updated results from a Phase 1/2 study.2017.

2. Antonia SJ, Kim S-W, Spira AI, et al. Safety and clinical activity of durvalumab (MEDI4736), an anti-PD-L1 antibody, in treatment-naïve patients with advanced non–small-cell lung cancer. Paper presented at: 2016 American Society for Clinical Oncology (ASCO) Annual Meeting; 3-7 June, 2017, 2016; Chicago, USA.

3. Barlesi F, Garon E, Kim D-W, et al. Assessment of health-related quality of life (HRQoL) in KEYNOTE-010: a phase 2/3 study of pembrolizumab vs docetaxel in patients with previously treated advanced NSCLC. *Annals of oncology. Conference: 41st European society for medical oncology congress, ESMO 2016. Denmark. Conference start: 20161007. Conference end: 20161011.* 2016;27(no pagination). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/766/CN-01295766/frame.html.

4. Barlesi F, Park K, Ciardiello F, et al. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC. *Ann Oncol.* 2016;27(suppl_6):LBA44_PR-LBA44_PR.

5. Barlesi F, Steins M, Horn L, et al. Long-term outcomes with nivolumab vesrsus docetaxel in patients with advanced NSCLC: checkmate 017 and checkmate 057 2-year update. *Asia-pacific journal of clinical oncology. Conference: 43rd annual scientific meeting of the clinical oncological society of Australia, COSA 2016. Australia. Conference start: 20161115. Conference end: 20161117.* 2016;12:115-116. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/575/CN-01249575/frame.html.

6. Cooper W, Russel P, Huot-Marchand P, et al. P2.01-047 Intra- and Inter-Observer Reproducibility Study of PD-L1 Biomarker in Non-Small Cell Lung Cancer (NSCLC) - The Dream Study. *2016 World Conference on Lung Cancer*. Vienna, Austria2016.

7. Gadgeel S, Ciardiello F, Rittmeyer A, et al. PL04A.02 Oak, a Randomized Ph III Study of Atezolizumab Vs Docetaxel in Patients with Advanced NSCLC: Results from Subgroup Analyses. *2016 World Conference on Lung Cancer*. Vienna, Austria2016.

8. Gandara DR, Von Pawel J, Sullivan RN, et al. Impact of atezolizumab (atezo) treatment beyond disease progression (TBP) in advanced NSCLC: Results from the randomized phase III OAK study.2017.
9. Garon EB, Rizvi N, Hui RN, et al. Efficacy of pembrolizumab (MK-3475) and relationship with PD-L1 expression in patients with non-small cell lung cancer: Findings from KEYNOTE-001). *Cancer Res.* Aug 2015;75.
10. Gettinger SN, Hellmann MD, Shepherd FA, et al. First-line monotherapy with nivolumab (NIVO; anti-programmed death-1 [PD-1]) in advanced non-small cell lung cancer (NSCLC): Safety, efficacy and correlation of outcomes with PD-1 ligand (PD-L1) expression. *J Clin Oncol.* May 2015;33(15).
11. Gralla R, Coon C, Taylor F, et al. Evaluation of disease-related symptoms in patients (pts) with advanced squamous (SQ) non-small cell lung cancer (NSCLC) treated with nivolumab (NIVO) or docetaxel (DOC). *Oncology Research and Treatment. (var.pagings).* 2015;38:14-16. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/178/CN-01136178/frame.html http://www.karger.com/Article/Pdf/439070.
12. Gralla R, Coon C, Taylor F, et al. ORAL31.03 Evaluation of Disease-Related Symptoms in Patients with Advanced Squamous Non-Small Cell Lung Cancer Treated with Nivolumab or Docetaxel. *2015 World Conference on Lung Cancer*. Denver, USA2015.
13. Gralla RJ, Spigel D, Bennett B, et al. P2.46 (also presented as PD1.01): LCSS as a Marker of Treatment Benefit With Nivolumab vs Docetaxel in Pts With Advanced Non-Squamous NSCLC From Checkmate 057: Track: Immunotherapy. *J Thorac Oncol.* Oct 2016;11(10S):S247.
14. Gulley JL, Rajan A, Spigel DR, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with metastatic or recurrent non-small-cell lung cancer progressing after platinum-based chemotherapy: A phase Ib trial. *Eur J Cancer.* Sep 2015;51:S629-S629.
15. Gulley JL, Spigel D, Kelly K, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in advanced NSCLC patients: A phase 1b, open-label expansion trial in patients progressing after platinum-based chemotherapy. *J Clin Oncol.* May 2015;33(15).
16. Herbst R, Baas P, Kim D-W, et al. Pembrolizumab (pembro) vs docetaxel (Doce) for previously treated, PD-L1-expressing NSCLC: updated outcomes of KEYNOTE-010. *Annals of oncology. Conference: 41st european society for medical oncology congress, ESMO 2016. Denmark. Conference start: 20161007. Conference end: 20161011.* 2016;27(no pagination). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/021/CN-01296021/frame.html.
17. Herbst RS, Baas P, Perez-Gracia JL, et al. Archival vs new tumor samples for assessing PD-L1 expression in the KEYNOTE-010 study of pembrolizumab (pembro) vs docetaxel (doce) for previously treated advanced NSCLC. Paper presented at: 2016 American Society for Clinical Oncology (ASCO) Annual Meeting; 3-7 June, 2017, 2016; Chicago, USA.
18. Herbst RS, Kim DW, Felip E, et al. KEYNOTE-010: Phase 2/3 study of pembrolizumab (MK-3475) vs docetaxel for PD-L1-positive NSCLC after platinum-based therapy. *Ann Oncol.* Dec 2015;26:162-162.
19. Herbst RS, Kim DW, Felip E, et al. LBA3_PRKEYNOTE-010: Phase 2/3 study of pembrolizumab (MK-3475) vs docetaxel for PD-L1–positive NSCLC after platinum-based therapy. *Ann Oncol.* 2015;26(suppl_9):ix162-ix162.
20. Horn L, Brahmer J, Reck M, et al. Phase 3, randomized trial (CheckMate 057) of nivolumab (NIVO) vs docetaxel (DOC) in advanced non-squamous (non-SQ) non-small cell lung cancer (NSCLC): Subgroup analyses and patient reported outcomes (PROs). *European Journal of Cancer. (var.pagings).* 2015;51:S599. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/268/CN-01136268/frame.html.
21. Horn L, Brahmer J, Reck M, et al. Phase 3, randomized trial (CheckMate 057) of nivolumab (NIVO) vs. Docetaxel (DOC) in advanced non-squamous (non- SQ) non-small cell lung cancer (NSCLC)-subgroup analyses and patient reported outcomes (PROs). *Oncology Research and Treatment. Conference: 32. Deutscher Krebskongress, DKK 2016 Berlin Germany. Conference*

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No relevant outcomes

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Wrong population (mostly early stage)

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