Australian Government

Medical Services Advisory Committee

MSAC Position Statement on programmed death-ligand 1 (PD-L1) immunohistochemistry testing to determine eligibility for treatment with PD-(L)1 checkpoint inhibitors

The Medical Services Advisory Committee (MSAC) has considered many applications requesting funding for immunohistochemistry (IHC) testing of programmed death-ligand 1 (PD-L1) for the purpose of helping to determine the eligibility of patients with various cancer types for treatment with PD-L1 and PD-1 checkpoint inhibitors (Attachment 1) and is aware of other cancer types, where eligibility of patients or treatment with PD-L1 and PD-1 checkpoint inhibitors does not require PD-L1 IHC testing (Attachment 2).

MSAC has undertaken a short review (as summarised in the attachments) and has concluded that it will not, in future, support the use of PD-L1 IHC testing as being essential for the purpose of helping to make decisions affecting the eligibility of patients for treatment involving PD-L1 or PD-1 checkpoint inhibitors. This document sets out the basis for MSAC's conclusion.

Comparative analytical performance

MSAC's primary concern stems from the evidence of the poor real-world analytical performance of PD-L1 IHC testing that limits its confidence in relying on the results of this PD-L1 assessment. This poor analytical performance of PD-L1 IHC can be attributed to several factors including the use of different test protocols and platforms, intra-tumour heterogeneity, inter-observer variability and intra-observer variability. Additionally, PD-L1 expression is inducible and may vary during the course of disease.

MSAC considers that there is potential for confusion in the reporting and interpretation of PD-L1 IHC testing due to the multiple metrics and thresholds for PD-L1 positivity.

Clinical utility

The biological rationale for the codependency between response to PD-(L)1 checkpoint inhibitors and PD-L1 expression is not strong. There are multiple metrics used to assess PD-L1 expression. These assess PD-L1 expression in different cell types found in a tumour sample including tumour cells (tumour positive score, TPS), tumour-infiltrating immune cells, and combinations of both (combined positive score, CPS). The threshold for positivity can vary across tumour types and within tumour types for the same PD-(L)1 checkpoint inhibitor. For example, pembrolizumab is approved by the Therapeutic Goods Administration (TGA) and other international drug regulators for the treatment of several different tumour types with varying requirements and measurements of PD-L1 positivity, with some indications requiring other biomarkers and some indications not

requiring any evidence of any biomarker at all (**Attachment 3**) and in the requests for consideration by the Pharmaceutical Benefits Advisory Committee (**Attachment 4**).

PD-L1 is part of a normal cell pathway and hence is unlikely to have a clear threshold indicating markedly different effect sizes of treatments targeting this pathway. This appears to differ from tests for clinically significant variants in oncogenes (such as *EGFR*) where there are more consistent and larger consequences for the size of the effect of the targeted treatment across a range of medicines. MSAC remains concerned that, in contrast, relatively small and inconsistent consequences for the size of the effect of the targeted treatment appears evident for medicines targeting the PD-1 pathway. For example, in NSCLC, there was weak evidence of a weak dose-response relationship in overall response rate to pembrolizumab with increasing PD-L1 expression (measured by TPS). However, across a range of different tumour types and treatment settings, the various PD-L1 expression metrics and thresholds nominated do not consistently suggest an underlying point at which treatment effects become apparent. A biological rationale explaining this inconsistency has not been clearly elucidated.

Given this, MSAC has reservations about the ability of the nominated PD-L1 IHC testing metrics and thresholds in regular clinical practice to generate the claimed improvements in patient outcomes beyond either an "all comers" population (which is not selected according to PD-L1 IHC test results) or beyond other possible PD-L1 metrics and thresholds. Many of these PD-L1 metrics and thresholds were retrospectively selected from across multiple exploratory sub-group analyses. Not all of these subgroup analyses were prespecified or from appropriately stratified populations, and sometimes only a subset of the overall trial population received any PD-L1 testing. Further, not all of the nominated metrics and thresholds have subsequently been validated using another sample of patients.

Therefore, overall, MSAC considers PD-L1 to be a poor biomarker, there is a likelihood that patients who might benefit from PD-(L)1 checkpoint inhibitor treatment would be excluded by the test result and a likelihood that claimed sizes of improvements in cancer outcomes would not be realised.

As already noted, the inconsistent clinical utility of PD-L1 IHC testing is reflected in the variation in PD-L1 testing requirements in the indications for PD-(L)1 checkpoint inhibitors approved by international regulators and the TGA (**Attachment 3**). The Food and Drug Administration (FDA) in the United States of America has introduced the concept of a "complementary diagnostic" in some approved indications for some PD-(L)1 checkpoint inhibitors. Complementary diagnostics are distinct from companion diagnostics in that they provide additional information to help guide the use of a medicine but are not essential for the safe and effective use of that medicine. Companion diagnostics are essential for the safe and effective use of the corresponding medicine.[1]

New evidence

MSAC remains open to reconsidering this conclusion in the light of any compelling new evidence to suggest that the evidence available to date should be superseded.

[1] Therapeutic Goods Administration. IVD companion diagnostics - Guidance on regulatory requirements. Available from https://www.tga.gov.au/publication/ivd-companion-diagnostics#fn2 (Accessed 19 May 2022)

Advice for applicants

Applicants wishing to seek Medicare Benefits Schedule (MBS) listing of PD-L1 IHC testing to determine eligibility for treatment with PD-(L)1 checkpoint inhibitors should lodge a MSAC Application Form that addresses the rationale for PD-L1 IHC testing and address the clinical utility and analytical performance considerations in this Position Statement.

Attachment 1

Table 1: Applications for PD-L1 IHC testing considered by MSAC with MSAC advice up to July 2022

App and date	Testing population	PD-L1 metric and threshold	Therapy decision	MSAC advice
1414	NSCLC (locally advanced or metastatic)	TPS ≥50%	Pembrolizumab monotherapy eligibility (second line)	***Not supported.*** PD-L1 IHC as a companion diagnostic test has insufficient evidence of analytical validity (and documented poor reproducibility), weak evidence of clinical validity (lacks ability to predict response to therapy) and weak evidence of clinical utility (insufficient information to guide treatment). stability of PD-L1 as a biomarker varied before and after treatment and across different stages of disease making the identification of patients likely to benefit from PD-L1 agents challenging. MSAC also noted that PD-L1 expression is inducible and may vary during the course of disease. The selection of a TPS threshold of 50% for effectiveness may be arbitrary and that a proportion of patients with a lower TPS score may still benefit from pembrolizumab treatment.
1440	NSCLC (locally advanced or metastatic, *EGFR* and *ALK* negative)	TPS ≥50%	Pembrolizumab monotherapy eligibility (first line)	***Not supported.*** PD-L1 IHC is a poor companion diagnostic test with insufficient evidence of analytical and clinical validity, and clinical utility. MSAC advised that, as PD-L1 is an imperfect biomarker, there is a likelihood that patients who might benefit from pembrolizumab treatment would be excluded by the test result. A number of the criteria important for reproducibility were not defined in these studies, such as the extent of staining in each cell contributing to the TPS count, and the biological definition of the per-tumour threshold. The concordance data presented in the submission remained insufficient to establish whether the different PD-L1 IHC assays could be used interchangeably. The potential clinical significance of misclassification from the estimated 10% discordance had not been explored. MSAC also noted that the applicant had advised that a number of international regulatory and reimbursement agencies have approved PD-L1 IHC testing in the context of pembrolizumab. MSAC was concerned however, that issues regarding test performance remained, and agreed with advice provided at the joint ESCs that the variation in reporting between laboratories may lead to samples being sent for repeat testing in different laboratories in order to gain access to pembrolizumab. PD-L1 expression level threshold was determined using the Receiver Operating Characteristic (ROC) curves from the Biomarker Training Set in the 'training subpopulation'. The TPS threshold of 50% for PD-L1 positivity was selected as the closest point to the optimum of all true positives and no false positives on the ROC curves (i.e. 'by maximising Youden's index'). MSAC noted that the TPS threshold was then validated with 'validation subpopulation'. MSAC recalled that it had considered this to be a simplistic approach as it did not consider the trade-off between false positives and true positives, which should reflect the differing downstream consequences in terms of under- versus over- treatment (see 1414). False negatives and true negatives would also result in differing downstream consequences. MSAC considered the nominated PD-L1 test to have poor performance (for overall tumour response) at the nominated threshold of 50% TPS.

App and date	Testing population	PD-L1 metric and threshold	Therapy decision	MSAC advice
				The KN-001 trial showed a dose-response relationship in overall response rate to pembrolizumab with increasing PD-L1 TPS. TPS threshold may not reflect the underlying point at which biological differences become apparent. MSAC noted that patients with a lower TPS may still benefit from pembrolizumab treatment over chemotherapy even though the response may be reduced when compared to patients with a higher TPS. In the KN-024 trial, pembrolizumab was associated with a significant benefit in patients with TPS ≥50% PD-L1 expression compared to platinum-based chemotherapy in the first-line setting. In contrast to EGFR and HER2, the expression of PD-L1 is not driven by mutation or amplification and hence is unlikely to have a clear threshold indicating markedly different effects of associated treatments. The KN-024 trial only included patients who had a PD-L1 positive tumour (TPS ≥50%) and hence, the treatment effect of pembrolizumab in patients with a TPS <50% could not be established. MSAC reflected on the circumstances of this codependent application compared to other recent applications which have provided comparative clinical trial data from an "all comers" population in addition to those who test positive for a particular biomarker, which has enabled a comparison the comparative effectiveness of treatment for those who test negative for the biomarker. MSAC considered that comparative clinical trial data from such an "all comers" population would be particularly preferred for test and medicine codependencies which involve: • expression-based biomarkers rather than mutation-based biomarkers, because of the greater uncertainty in determining a threshold of "positivity" to help determine eligibility of the medicine using expression-based biomarkers; or • a quantitative variation rather than a qualitative variation in the treatment effect of the medicine, because predicting reduced effect is harder to detect than predicting no effect.
1440.1	NSCLC (locally advanced or metastatic)	TPS ≥50%	Pembrolizumab monotherapy eligibility (first line)	***Supported.*** MSAC considered that the development of a Royal College of Pathologists of Australasia (RCPA) quality assurance program which is currently in the pilot stage had addressed one of its concerns. However, the most influential development since the previous consideration was the PBS listing of an alternative PD-L1 inhibitor, nivolumab, for second-line treatment of patients with locally advanced or metastatic NSCLC whose disease had progressed following treatment with platinum-based chemotherapy without there being a requirement for PD-L1 testing. This changed the clinical utility consequences of poor PD-L1 IHC test performance, because most patients with metastatic NSCLC who test negative (correctly or not) for treatment with pembrolizumab would now have access to nivolumab in due course.
1570	Breast cancer (locally advanced or metastatic,	IC ≥1%	Atezolizumab + chemotherapy	***Deferred (inclined to support).*** MSAC noted the applicant's claim of benefit for overall survival in PD-L1 positive patients, but considered that the study design had statistical complications that introduced uncertainty in this claim. In breast cancer, more cases show PD-L1 expression on tumour-infiltrating immune cells (ICs) than on tumour cells (TCs), with most TC-positive cases also being IC-positive (unlike other solid tumours). For this application, PD-L1 positivity was defined as PD-L1 expression on ICs covering ≥1% of the tumour area. MSAC noted the potential for

App and date	Testing population	PD-L1 metric and threshold	Therapy decision	MSAC advice
	triple negative)			confusion in the reporting and interpretation of PD-L1 testing across different cell types assessed using different assays and threshold of positivity across different cancers for different immunotherapy medicines. MSAC therefore emphasised the need for appropriate training and a satisfactory quality assurance program to be in place. US Food and Drug Administration (FDA) criteria for concordant assays specify that overall per cent agreement (OPA) should be at least 90%. Trends towards greatest progression-free survival and overall survival benefits were suggested in patients who were identified as positive using SP142. Regarding potential variation between archival and recent biopsies of tissue samples, MSAC considered that genuine triple-negative breast cancers would not change in PD-L1 status over time to the same extent as in lung cancer, and the cut-off of 1% of the tumour area for PD-L1–expressing ICs was a low threshold. MSAC also considered that, if the laboratory does not have access to a TGA-listed assay (that is, SP142), it should not undertake testing, so a limitation to the SP142 assay may not be needed in the item descriptor, and a note indicating that testing should be performed by a TGA-listed assay might suffice.
1522	Head and neck SCC (metastatic or recurrent unresectable)	CPS ≥1	Pembrolizumab eligibility (monotherapy or with chemotherapy)	***Not supported.*** MSAC considered that the biological rationale for the proposed codependence was weak. Reflecting this lack of a cohesive rationale, pembrolizumab is approved by the Therapeutic Goods Administration (TGA) for the treatment of several different tumour types with varying requirements of PD-L1 positivity, with some indications requiring other biomarkers and some indications not requiring any evidence of any biomarker at all. Notably, the submission to PBAC for second-line pembrolizumab monotherapy for recurrent or metastatic HNSCC (after failure of platinum-based chemotherapy) was not limited to patients whose tumours express PD-L1 (Pembrolizumab July 2018 PBAC Public Summary Document [PSD]). This was based on the 20 March 2017 TGA approval of this second-line indication. Alongside its approval of the first-line HNSCC indication based on the KN-048 trial, the TGA subsequently amended the second-line HNSCC indication (based on the KN-040 trial) to also require second-line HNSCC patients to have a PD-L1 CPS ≥1. MSAC noted the high sensitivity and low specificity reported for the test at the threshold of CPS ≥1, and agreed with the ESCs and the Commentary that the apparently high sensitivity might be due to the test classifying over 80% of patients as being CPS ≥1 rather than the test accurately identifying patients who will respond to pembrolizumab. MSAC agreed with the Commentary that this indicated there was a poor correlation between the proposed PD-L1 CPS positivity threshold and extent of response to pembrolizumab. MSAC noted that the main clinical evidence for supporting PD-L1 testing to help determine pembrolizumab eligibility was from the KN-048 trial. KN-048 recruited patients irrespective of PD-L1 status, and stratification by PD-L1 status was initially based on a tumour positive score (TPS) ≥50%, not CPS ≥1. MSAC agreed with the Commentary and the TGA clinical evaluator that the randomised stratification by TPS status in KN-048 no longer holds and so the comparisons on the basis of CPS (whether ≥1 or the alternative threshold explored of ≥20) were effectively non-randomised, and therefore had a higher risk of bias.

App and date	Testing population	PD-L1 metric and threshold	Therapy decision	MSAC advice
				From the KN-048 trial, and in the intention-to-treat population irrespective of PD-L1 status, MSAC accepted that pembrolizumab in combination with chemotherapy was more effective than the comparator arm, but concluded that greater effectiveness was not convincingly demonstrated for pembrolizumab as monotherapy. MSAC noted that pembrolizumab monotherapy appeared worse in terms of overall survival for patients with CPS <1, but considered the result was not convincing because of the trial design and conduct problems, which also resulted in the subgroup of patients with CPS <1 being too small to conclude that pembrolizumab had no effect in this subgroup. MSAC queried whether the postulated codependency between PD-L1 status and the clinical benefit from pembrolizumab differed when it was used as monotherapy compared with its use in combination with chemotherapy. MSAC concluded several issues in the trial contributed to a complicated trial that was difficult to understand and interpret, and did not fully inform whether PD-L1 CPS testing identified patients most likely to benefit from pembrolizumab treatment. These difficulties are illustrated by the different conclusions drawn by the TGA and the European Medicines Agency compared with the United States' Food and Drug Administration. MSAC noted there was poor concordance between 22C3 antibody used to test PD-L1 positivity in the KN-048 trial and other PD-L1 IHC antibodies (SP263, SP142 and 28-8). MSAC considered Meulenaere 2018 assessed inter observer variability in a research setting and reported a correlation coefficient of agreement of r=0.621 with only 65% of samples classified consistently. MSAC considered variability would be expected to be greater in clinical practice whether based on CPS or not. MSAC recalled a similar application (1440.1) but considered any precedent to not be completely relevant. Although apparently similar in that the PBS listing of nivolumab as second-line treatment of NSCLC irrespective of PD-L1 status changed the clinical utility consequences of poor PD-L1 test performance, the NSCLC application was based on a stronger trial with a stronger evidence base, the cut-off point between positive and negative PD-L1 results was more persuasively developed.
1522.1	Head and neck SCC (metastatic or recurrent unresectable)	CPS ≥1 and CPS ≥20	Pembrolizumab eligibility (monotherapy or with chemotherapy)	***Supported.*** MSAC considered the impact of different testing protocols on PD-L1 scoring. MSAC considered that the SP263 antibody was mostly commonly used in Australia whereas the 22C3 antibody was used in the KN-048 trial. MSAC highlighted that Crosta (2021) demonstrated that there may be false negatives at the CPS ≥20 threshold using Protocol 4 (most informative for Australian clinical practice) compared with the clinical utility standard. MSAC considered that this suggested that using CPS ≥20 would lead to more false negatives and very few false positives, which may be an appropriately conservative threshold. MSAC noted issues relating to discordance in CPS scoring results among pathologists. MSAC noted that all pathologists demonstrated at least 85% concordance, however all pathologists were discordant from the consensus score in at least one case. MSAC noted that there was high variation in scoring of some tissue samples. MSAC noted that there were high CPS samples with highly variable scoring as well as samples with low CPS scores (0-2) that were difficult to score.

App and date	Testing population	PD-L1 metric and threshold	Therapy decision	MSAC advice
				MSAC noted a range of factors that may affect scoring. PD-L1 assessment requires careful assessment of cells within a sample that could contribute to inter-observer variability of CPS scoring. This includes assessment of individual cells as some do not contribute to the assessment of CPS score, differentiation of granular membrane staining and granular cytoplasmic staining which can be difficult, exclusion of tissue with edge and crush artifacts. MSAC also noted that PD-L1 expression could be affected by inflammation and radiation, and whether samples had undergone appropriate fixation. MSAC noted that there is also a lack of detail in the PD-L1 IHC 22C3 pharmDx kit Interpretation Manual3 on how to score borderline cases. The interpretation manual also does not advise on reporting a score between 0 and 1 (i.e. 1 positive cell per 200 tumour cells), meaning that pathologists may be more likely to round up to 1 rather than down to 0. If this is the case, then the proportion of patients given a score of 1 or more would likely be greater than 85%. MSAC also noted the possibility that pathologists may be inclined overestimate CPS scores close to the threshold for treatment eligibility so that patients can access more treatment options. MSAC considered this may also be true for samples with a CPS close to 20 if a CPS score of 20 is defined in a PBS restriction to allow patients to avoid chemotherapy. MSAC considered that quality assurance measures and peer-to-peer training would not sufficiently reduce inter observer variability given the many issues that may lead to variability in CPS scoring. MSAC advised against relying on a CPS threshold of ≥1 because all HNSCC tumours are expected to have some sections that would meet this threshold. MSAC considered that the PD-L1 CPS result may usefully add to the variables that clinicians may use to determine the best treatment for their patient.
1642	NSCLC (locally advanced or metastatic)	TPS ≥ 50%	Cemiplimab or Pembrolizumab	***Supported.*** MSAC supported public funding for PD-L1 testing in patients with non-small cell lung cancer in alignment with PBAC's decision to recommend cemiplimab in this codependent submission. MSAC noted that the relevant cemiplimab clinical trial used the same PD-L1 test as pembrolizumab trials, the Dako PD-L1 IHC 22C3 pharmDx test (Dako 22C3 assay). The Dako 22C3 assay was used eligibility for enrolment in the KEYNOTE 024 trial. MSAC recalled that this test was evaluated in previous applications. Regarding safety and quality assurance, MSAC noted that the listing of another similar drug on the PBS would not make any difference to the laboratories apart from a different TPS threshold for eligibility.

CPS = combined positive score; EGFR = Epidermal Growth Factor Receptor; ESCs = Evaluation Sub-Committee and Economics Sub-Committee; IC = immune cells; IHC = immunohistochemistry; MSAC = Medical Services Advisory Committee; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PSD = Public Summary Document. HNSCC = head and neck squamous cell carcinoma; TC = tumour cells; TGA = Therapeutic Goods Administration; TPS = tumour proportion score

Table 2 Applications for PD-L1 IHC testing to MSAC up to July 2022

App	Testing population	PD-L1 metric and threshold	Therapy decision	MSAC outcome	PBAC outcome
Considered by MSAC					
1414	NSCLC (locally advanced or metastatic)	TPS ≥50%	Pembrolizumab monotherapy (2L)	**Not supported**	Rejected November 2016
1440	NSCLC (locally advanced or metastatic, *EGFR* and *ALK* negative)	TPS ≥50%	Pembrolizumab monotherapy (1L)	**Not supported**	Recommended July 2018
1440.1	NSCLC (locally advanced or metastatic)	TPS ≥50%	Pembrolizumab monotherapy eligibility (1L)	**Supported**	
1522	Head and neck SCC (metastatic or recurrent unresectable)	CPS ≥1	Pembrolizumab ± chemotherapy (1L)	Not supported	Recommended March 2022
1522.1		CPS ≥1 and CPS ≥20	Pembrolizumab monotherapy (CPS ≥20) Pembrolizumab +chemotherapy (CPS ≥1)	**Supported**	
1570	Breast cancer (locally advanced or metastatic, triple negative)	PD-L1 expression on ICs covering ≥1% of the tumour area	Atezolizumab + taxane (1L)	Deferred (inclined to support)	Rejected March 2021
1642	NSCLC	TPS ≥50%	Cemiplimab monotherapy (1L)	**Supported**	Recommended November 2021
Not considered by MSAC					
1445	Urothelial cancer (recurrent or progressive metastatic or locally advanced/unresectable)	CPS ≥1%	Pembrolizumab monotherapy eligibility (1L)	Not considered	Not considered
1453	Mesothelioma (unresectable)	TPS ≥1%	Pembrolizumab monotherapy (1L+)	Not considered	Not considered
1457	Urothelial cancer (locally advanced or metastatic)	CPS ≥10 [a]	Pembrolizumab monotherapy eligibility (2L)	Not considered	Recommended July 2018
1486	NSCLC (locally advanced or metastatic)	PD-L1 ≥25% (metric not specified)	1L durvalumab monotherapy (if positive) 1L durvalumab + tremelimumab (if negative)	Not considered	Not considered
1505	Head and neck SCC (metastatic or recurrent unresectable)	TPS PD-L1 ≥25%	1L or 2L durvalumab monotherapy (if positive) 1L or 2L durvalumab ± tremelimumab	Not considered	Not considered
1506	Urothelial cancer (1L, unresectable Stage IV)	≥25% tumour cell membrane staining OR ≥25% immune cell (if >1% immune cells) OR 100% immune cell (if immune cells 1%) [b]	1L durvalumab monotherapy (if positive) 1L durvalumab + tremelimumab (if negative)	Not considered	Not considered (2L durvalumab rejected July 2019)

App	Testing population	PD-L1 metric and threshold	Therapy decision	MSAC outcome	PBAC outcome
1520	Stomach or GOJ adenocarcinoma (recurrent or metastatic, unresectable)	CPS ≥1	Pembrolizumab monotherapy (2L+)	Not considered	Not considered (1L recommended May 2022)
1549	Breast cancer (recurrent inoperable or metastatic triple-negative)	CPS ≥10	Pembrolizumab + chemotherapy (1L+)	-	-
1718	Cervical cancer (persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma)	CPS ≥1	Pembrolizumab + chemotherapy ± bevacizumab (1L+)	-	-

1L = first line; 2L = second line; CPS = combined positive score; GOJ = gastro-oesophageal junction; IC = immune cells; MSAC = Medical Services Advisory Committee; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PSD = Public Summary Document. SCC = squamous cell carcinoma; TNBC = triple negative breast cancer; TPS = tumour proportion score

[a] Based on the KN-052 trial.

[b] Three step assessment: ≥5% of tumour cells exhibit membrane staining; OR in specimens where the immune cells present is greater than 1%: 25% of immune cells (or greater) exhibit positive staining, OR; in specimens where the immune cells present is only 1%: all immune cells present show positive staining (considered exceptional cases).

[c] Based on the KN-61 trial.

Attachment 2

Table 3: Summary of indications for PD-[L]1 checkpoint inhibitors approved by drug regulators up to July 2022

Drug	Indication	Australian TGA	EMA	United States FDA
Atezolizumab	NSCLC (1L mono)	-	TC ≥50% or ≥10% IC	TC ≥50% or IC ≥10%
	NSCLC (adjuvant post resection and chemo)	TC ≥50%	TC ≥50%	TC ≥1%
	NSCLC (1L with chemo)	Agnostic	Agnostic	Agnostic
	NSCLC (2L mono)	Agnostic	Agnostic	Agnostic
	SCLC	Agnostic	Agnostic	Agnostic
	Urothelial (cisplatin ineligible)	IC ≥5%	IC ≥5%	IC ≥5%
	Urothelial (platinum ineligible)	Agnostic	-	Agnostic
	Urothelial (post platinum)	-	Agnostic	-
	TNBC	IC ≥1%	IC ≥1%	-
	Melanoma	-	-	Agnostic
	HCC	Agnostic	Agnostic	Agnostic
Avelumab	mMCC	Agnostic	Agnostic	Agnostic
	Urothelial	Agnostic	Agnostic	Agnostic
	RCC	Agnostic	Agnostic	Agnostic
Cemiplimab	CSCC	Agnostic	Agnostic	Agnostic
	BCC	Agnostic	Agnostic	Agnostic
	NSCLC	TPS ≥50%	TC ≥50%	TPS ≥50%
Durvalumab	NSCLC	Agnostic	TC ≥1%	Agnostic
	SCLC	Agnostic	Agnostic	Agnostic
Nivolumab	Melanoma	Agnostic	Agnostic	Agnostic
	NSCLC (resectable with chemo)	-	-	Agnostic
	NSCLC (with IPI)	-	-	TC ≥1%
	NSCLC (with IPI +chemo)	Agnostic	Agnostic	Agnostic

Drug	Indication	Australian TGA	EMA	United States FDA
	NSCLC (post chemo or targeted therapy)	Agnostic	Agnostic	Agnostic
	Mesothelioma	Agnostic	Agnostic	Agnostic
	RCC	Agnostic	Agnostic	Agnostic
	Hodgkin lymphoma	Agnostic	Agnostic	Agnostic
	Head and neck SCC (2L)	Agnostic	Agnostic	Agnostic
	Urothelial (post platinum)	Agnostic	Agnostic	Agnostic
	Urothelial (adjuvant)	Agnostic	TC ≥1%	Agnostic
	HCC	Agnostic	-	Agnostic
	Oesophageal (1L + IPI)	-	TC ≥1%	Agnostic
	Oesophageal (1L + chemo)	-	TC ≥1%	Agnostic
	Oesophageal (post chemo)	Agnostic	Agnostic	Agnostic
	Oesophageal or GOJ (adjuvant, post chemo, mono)	Agnostic	Agnostic	Agnostic
	Oesophageal, gastric, GOJ (adenocarcinoma)	Agnostic	CPS ≥5	Agnostic
Pembrolizumab	Melanoma	Agnostic	Agnostic	Agnostic
	NSCLC (1L with chemo)	Agnostic	Agnostic	Agnostic
	NSCLC (1L mono)	TPS ≥1%	TPS ≥50%	TPS ≥1%
	NSCLC (post chemo or targeted therapy)	TPS ≥1%	TPS ≥1%	TPS ≥1%
	Head and neck SCC (1L + with chemo)	CPS ≥1	CPS ≥1	Agnostic
	Head and neck SCC (1L mono)	CPS ≥1	CPS ≥1	CPS ≥1
	Head and neck SCC (2L)	CPS ≥1	TPS ≥50%	Agnostic
	Hodgkin lymphoma	Agnostic	Agnostic	Agnostic
	PMBCL	Agnostic	-	Agnostic
	Urothelial (BCG unresponsive)	Agnostic	-	Agnostic
	Urothelial (post chemo)	Agnostic	Agnostic	Agnostic
	Urothelial (chemo ineligible)	Agnostic	CPS ≥10	Agnostic
	RCC	Agnostic	Agnostic	Agnostic
	CSCC	Agnostic	-	Agnostic

Drug	Indication	Australian TGA	EMA	United States FDA
	Oesophageal (mono)	-	-	CPS ≥10
	Oesophageal (with chemo)	Agnostic	CPS ≥10	Agnostic
	TNBC (early)	-	Agnostic	Agnostic
	TNBC (recurrent or advanced)	-	CPS ≥10	CPS ≥10
	Cervical	-	CPS ≥1	CPS ≥1

Source: Australian Approved Product Information; European Summary of Product Characteristics; United States Food and Drug Administration Product Label.
Note: Excludes indications based on other biomarkers such as mismatch repair deficiency.
1L = first line; 2L = second line; BCG = Bacillus Calmette-Guerin; CPS = combined positive score; CSCC = cutaneous squamous cell carcinoma; EMA = European Medicines Agency; FDA = Food and Drug Administration; GOJ = gastro-oesophageal junction; HCC = hepatocellular carcinoma; IC = immune cells; IPI = ipilimumab; mMCC = metastatic Merkel cell carcinoma; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PMBCL = primary mediastinal B-cell lymphoma; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SCLC = small cell lung cancer; TGA = Therapeutic Goods Administration; TNBC = triple negative breast cancer; TPS = tumour proportion score; TC = tumour cell; TS = tumour score

Attachment 3

Table 4: Summary of PBAC considerations of PD-[L]1 checkpoint inhibitors up to July 2022

Drug and treatment population	Therapy decision	PD-L1-based (metric)	PBAC outcome and date
Atezolizumab			
NSCLC (adjuvant post resection and chemo)	-	Yes	For consideration at July 2022 PBAC meeting
TNBC (1L, metastatic)	Atezolizumab + nab-paclitaxel (if PD-L1 positive) or nab-paclitaxel	IC ≥5%	Rejected. March 2021
HCC (1L, unresectable locally advanced or metastatic)	Atezolizumab + bevacizumab or TKIs (such as sorafenib)	No	Recommended. July 2020
SCLC (1L, extensive stage)	Atezolizumab + chemo then monotherapy or chemo	No	Recommended. November 2019
NSCLC (1L, metastatic, non-squamous)	Atezolizumab + bevacizumab + chemo then Atezolizumab + bevacizumab maintenance or chemo	No	Recommended. March 2019
NSCLC (2L+, locally advanced or metastatic)	Atezolizumab or nivolumab	No	Recommended. November 2017
Avelumab			
RCC (1L, Stage IV, clear cell variant)	Avelumab + axitinib or nivolumab + ipilimumab	No	Recommended. March 2021
Urothelial (Stage III or IV, 1L maintenance)	Avelumab or monitoring (watch and wait)	No	Recommended. March 2021
MCC (2L, metastatic)	Avelumab or chemotherapy	No	Recommended (line agnostic). July 2018
Cemiplimab			
CSCC (locally advanced or metastatic, not candidates for curative surgery or curative radiation)	Cemiplimab or best supportive care (may include chemo)	No	Recommended. March 2022
NSCLC (1L, metastatic, *EGFR*-wt, *ALK*-neg, *ROS*-neg)	Cemiplimab or pembrolizumab	TPS ≥50%	Recommended. November 2021
Durvalumab			
SCLC (1L, extensive stage)	Durvalumab + chemo then monotherapy or atezolizumab + chemo	No	Recommended. November 2020
NSCLC (adjuvant post chemoradiation, unresectable Stage III)	Durvalumab or 'watch and wait' monitoring	No	Recommended. November 2019
Urothelial (post chemo, locally advanced or metastatic)	Durvalumab or pembrolizumab	No (discussed by PBAC)	Rejected. July 2019

Drug and treatment population	Therapy decision	PD-L1-based (metric)	PBAC outcome and date
Nivolumab			
GOJ or oesophageal (adjuvant, post chemoradiation and surgery)	Nivolumab	-	For consideration at July 2022 PBAC meeting
Urothelial (adjuvant, muscle invasive, post resection, high recurrence risk)	Nivolumab	-	For consideration at July 2022 PBAC meeting
Melanoma (Stage III or IV)	Nivolumab + relatlimab	-	For consideration at July 2022 PBAC meeting
Gastric, GOJ, or oesophageal adenocarcinoma (locally advanced or metastatic, non-HER2-positive)	Nivolumab + chemo or chemo	No	Recommended. March 2022
Oesophageal SCC (2L, advanced or metastatic)	Nivolumab	No	Recommended. July 2021 Reconsidered (recommended) March 2022
Mesothelioma (unresectable, pleural)	Nivolumab + ipilimumab or chemotherapy	No	Recommended. March 2021
NSCLC (1L, Stage IV, EGFR and ALK negative)	Nivolumab + ipilimumab + chemo (2 cycles) or pembrolizumab + chemo or other PD-(L)1 ± chemo regimens	No	Recommended. November 2020
Melanoma (adjuvant, completely resected Stage IIB-IV)	Nivolumab (± ipilimumab) or dabrafenib + trametinib (*BRAF*-pos) or 'watch and wait' monitoring (*BRAF*-neg)	No	Recommended. November 2019
Melanoma (1L *BRAF*-pos, unresectable or metastatic)	Nivolumab (± ipilimumab) or BRAF inhibitor ± MEK inhibitor	No	Recommended. November 2019
Melanoma (unresectable Stage III or Stage IV, 1L if *BRAF*-neg, 2L if *BRAF*-pos)	Nivolumab + ipilimumab or nivolumab mono then ipilimumab post-progression	No	Recommended. July 2018
RCC (1L, Stage IV, clear cell variant, poor to intermediate risk)	Nivolumab + ipilimumab or sunitinib	No	Recommended. November 2018
Head and neck SCC (2L, recurrent or metastatic)	Nivolumab or chemo	No	Recommended. March 2018
NSCLC (2L, locally advanced or metastatic)	Nivolumab or chemo	No (discussed by PBAC)	Recommended. March 2017
RCC (2L post TKI, clear cell variant)	Nivolumab or everolimus	No	Recommended. March 2017
Melanoma (unresectable Stage III or Stage IV)	Nivolumab mono or pembrolizumab or ipilimumab	No	Recommended. November 2015
Pembrolizumab			
Head and neck SCC (1L, recurrent or metastatic)	Pembrolizumab (± chemo) or chemo	CPS ≥1 or ≥20	Recommended. March 2022 Pembrolizumab monotherapy (CPS ≥20) Pembrolizumab + chemo (PD-L1 agnostic)

Drug and treatment population	Therapy decision	PD-L1-based (metric)	PBAC outcome and date
RCC (1L, advanced clear cell variant)	Pembrolizumab + lenvatinib or nivolumab + ipilimumab	No	Recommended. March 2022
Oesophageal or GOJ (1L, locally advanced or metastatic, *HER2*-negative if adenocarcinoma of GOJ)	Pembrolizumab + chemo or chemo	No	Recommended. May 2022
Melanoma (adjuvant, stage IIIB/C/D, completely resected)	Pembrolizumab mono or nivolumab	No	Recommended. March 2020
Melanoma (1L, *BRAF*-pos unresectable Stage III or Stage IV)	Pembrolizumab mono or nivolumab	No	Recommended. March 2020
PMBCL (relapsed or refractory)	Pembrolizumab mono or chemo (± rituximab)	No	Recommended. March 2020
NSCLC (1L, Stage IV, non-squamous, *EGFR*-wt, *ALK*-neg, *ROS1*-neg)	Pembrolizumab + chemo or pembrolizumab mono (TPS ≥50%); chemo (TPS <50%)	No	Recommended. July 2019
Head and neck SCC (2L, Stage III or Stage IV)	Pembrolizumab mono or nivolumab	No	Rejected. July 2018
Urothelial (2L, locally advanced or metastatic)	Pembrolizumab mono or chemo	No	Recommended. July 2018
NSCLC (1L, *EGFR*-wt, *ALK*-neg, metastatic)	Pembrolizumab mono or chemo	TPS ≥50%	Recommended. July 2018
Hodgkin lymphoma (relapsed or refractory, post ASCT or ineligible for ASCT)	Pembrolizumab mono vs brentuximab vedotin	No	Recommended. August 2017
NSCLC (2L+, Stage IIIb or Stage IV)	Pembrolizumab or chemo	TPS ≥50%	Rejected. November 2016
Melanoma (unresectable Stage III or Stage IV, 1L if *BRAF*-neg, 2L+ if *BRAF*-pos)	Pembrolizumab mono	No	Recommended March 2015

Source: PBAC Public Summary Documents and published outcomes.

Note: The table presents the most recent PBAC consideration for each treatment population. The table excludes PBAC considerations related to dosing changes, Managed Entry Schemes and submissions for PD-(L)1 checkpoint inhibitors based on other biomarkers such as mismatch repair deficiency.

1L = first line; 2L = second line; 2L+ = second line or later; ASCT = autologous stem cell transplant; BCG = Bacillus Calmette-Guerin; CPS = combined positive score; chemo = chemotherapy; CSCC = cutaneous squamous cell carcinoma; GOJ = gastro-oesophageal junction; HCC = hepatocellular carcinoma; IC = immune cells; IPI = ipilimumab; mono = monotherapy; MCC = Merkel cell carcinoma; neg = negative; NSCLC = non-small cell lung cancer; PBAC = Pharmaceutical Benefits Advisory Committee; PD-L1 = programmed death-ligand 1; PMBCL = primary mediastinal B-cell lymphoma; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SCLC = small cell lung cancer; TKI = tyrosine kinase inhibitors; TNBC = triple negative breast cancer; TPS = tumour proportion score; TS = tumour score; wt = wild-type