PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types

General/overall comments

Please note, comments that are beyond the scope of PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types will not be considered

Bristol Myers Squibb Australia (BMSA) is pleased to provide the following submission to the August 2018 Pharmaceutical Benefits Advisory Committee (PBAC) Special Meeting where options for listing programmed death-ligand [PD-(L)1] cancer immunotherapies for the treatment of multiple tumours (pan-tumour indications) on the Pharmaceutical Benefits Scheme (PBS) will be considered.

Over the past four years, the PBAC have reviewed the clinical data, economic models and proposed cost-effectiveness of nivolumab on more than 15 occasions across 5 distinct tumour types, leading to 4 current PBS listings. BMSA believes that this shared level of knowledge and experience, together with the promise of future data, and the sponsor's willingness to work with the PBAC and Australian Government, provides the greatest potential for a solution to the Minister for Health's call for a multiple tumour approach to the reimbursement of PD-(L)1 cancer immunotherapies.

In addition to responding to each of the PBACs 16 questions outlined in the submission template, BMSA also outlines its key recommendation for PBAC consideration, specifically:

RECOMMENDATION

- ***That a pilot be established whereby PD-(L)1 cancer immunotherapies used in the monotherapy setting are PBS listed 3 months post TGA registration:***
  - ***with initial value to be determined by the application of an algorithm derived from PBAC precedence [redacted], and***
  - ***confirmation or adjustment of this value to occur via a Managed Entry Scheme (MES) type mechanism for PDL1 cancer immunotherapies [redacted]***

[redacted]

About BMS

BMS is a global BioPharma company firmly focused on its mission to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. Our vision for the future of cancer care is focused on researching and developing transformational medicines, including Immuno-Oncology (I-O) therapeutic approaches, for hard-to-treat cancers that could potentially improve outcomes for these patients.

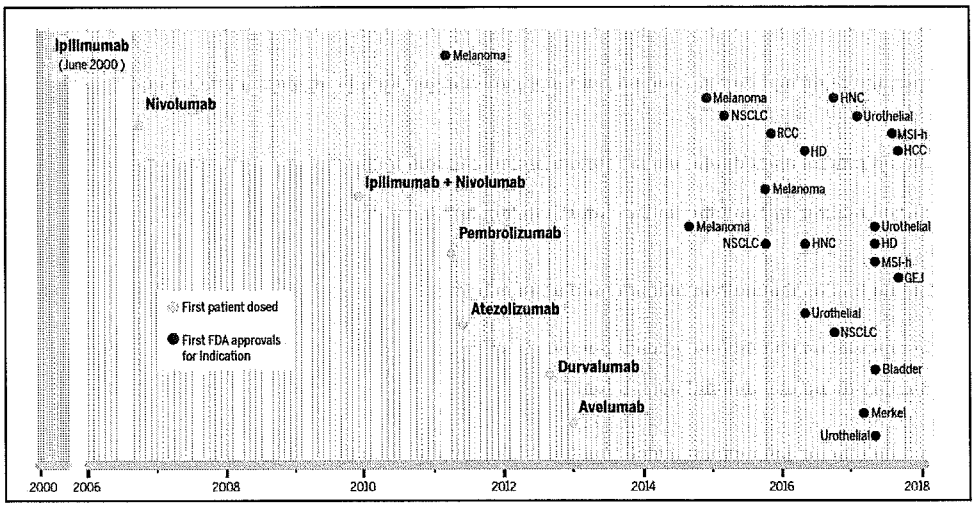
We are leading the integrated scientific understanding of both tumour cell and immune system pathways, through our extensive portfolio of investigational compounds and approved agents. Our differentiated clinical development program is studying broad patient populations across more than 50 types of cancers with 24 clinical-stage molecules designed to target different immune system pathways.

We understand making the promise of transformational medicines like I-O therapies a reality for the many patients who may benefit from these therapies requires not only innovation on our part but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy and biotech companies support our collective goal of providing new treatment options to advance the standards of clinical practice.

About Immuno-Oncology (I-O)

While cancer immunotherapy—the science of mobilizing the immune system to kill cancer—has been pursued for more than a century, it is only recently that this powerful strategy has been successfully implemented in mainstream oncology. *Science* selected 'cancer immunotherapy' as Breakthrough of the Year in 2013.[1], with unprecedented clinical responses, rapid drug development, and first-in-kind approvals from Regulatory Agencies around the world following in the subsequent 5 years (Figure 1).

Figure 1: Timing of clinical development of anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies.[2]



There are currently several types of I-O therapy in development (Table 1) which have different modes of action to tackle cancers.

Table 1: Types of Immuno-Oncology therapies

Immuno-Oncology Therapy	Mode of Action	Medicine
Checkpoint inhibitors	• Release "brakes" on the immune system allowing stronger immune response. • CTLA4 and PD-1/PD-L1 inhibitors	• Nivolumab • Pembrolizumab • Ipilimumab • LAG-3 inhibitor
Immune targets	• Blocks or stimulates modulators of the immune system	• Anti-GITR
Cancer vaccines	• Trigger immune system to recognise and attack certain markers, or antigens, present in or on cancer cells	• Sipuleucel-T
Adoptive T cell transfer	• Enhances natural cancer fighting ability of the body's T cells by removing immune cells, growing them outside the body and re-infusing them back into the patient	• Axicabtagene ciloleucel • Tisagenleuleucel
Oncolytic virus immunotherapy	• Directly kills cancer cells and can also activate the immune system to target cancer	• Talimogene laherparepvec
Cytokines	• Do not target cancer cells specifically but stimulate the immune system in a more general way	• Interleukin-2 • Interleukin-alpha • NKTR-214

However, for the purposes of this submission, the focus will be kept to PD-1 and PD-L1 checkpoint immunotherapies as:

- it these checkpoint inhibitors that are predicted to revolutionise cancer therapy across the widest range of tumour types and malignancies over the next 5 years, and
- the purpose of the August 2018 PBAC Special Meeting is to allow the Committee to consider potential future options for the evaluation and consideration of PD-1 and PD-L1 checkpoint inhibitors for multiple cancer types.[3].

[1] *http://science.sciencemag.org/content/sci/342/6165/1417.full.pdf*

[2] Figure derived from: *http://science.sciencemag.org/content/sci/359/6382/1350.full.pdf*

[3] *http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/august-2018-pbac-special-meeting-background-paper.pdf*

About PD-L1

The programmed cell death 1 (PD-1) receptor has emerged as a dominant negative regulator of antitumour T cell effector function when engaged by its ligand programmed cell death ligand 1 (PD-L1), expressed on the surface of cells within a tumour. However, monoclonal antibodies, which target PD-1 and PD-L1 block the binding of these proteins and remove an inhibitor of an immune response against the cancer cells.

PD-1 pathway blockade has a more specific effect on antitumour T cells than CTLA-4 blockade, perhaps because of their chronically stimulated state, resulting in increased therapeutic activity and reduced toxicity.

There are currently five anti–PD-1 or anti–PDL1 antibodies approved by the FDA in 11 cancer indications[4] (Table 2). The first FDA approvals of PD-1–blocking antibodies were through accelerated and breakthrough filing pathways, with nivolumab and pembrolizumab approved for the treatment of patients with refractory melanoma in 2014 and for patients with advanced NSCLC in 2015. The broad range of approvals that have occurred over the intervening three years are based upon a series of characteristics of the clinical activity of PD-1 pathway–blocking antibodies and should provide the PBAC with adequate scientific reasoning as to why these medicines are active across tumour types.

Antitumour activity of PD-1–pathway blockade has been observed across a broad range of cancers, particularly in carcinogen-induced cancers or cancers driven by viral infections (Table 2). The highest antitumour activities (i.e. response rates of 50% - 90%) of single-agent PD-1–blockade therapy are in:

- Hodgkin's lymphoma - in which there is constitutive expression of PD-L1 through a common amplification of the PD-L1–encoding locus together with PD-L2 and Janus kinase 2 (JAK2)
- Merkel cell carcinoma of the skin
- Microsatellite-instability cancers with high mutational load from mismatch-repair deficiency - leading to a high frequency of insertions and/or deletions (indels); and
- Desmoplastic melanoma - a rare subtype of melanoma that has a very high mutational load arising from chronic ultraviolet light–induced point mutations.

A second group of cancers with intermediate response rates (15% to 40%) are:

- Carcinogen-induced cancers - such as the more common variants of melanoma (response rates of 35% - 40%); and
- A series of cancers associated with the carcinogenic effects of cigarette smoking - such as NSCLC, head and neck, gastroesophageal, and bladder & urothelial cancers (response rates of 15% - 25%).

The other two approvals of single agent anti–PD-1 therapies are in hepatocellular carcinoma, with its known relationship to hepatitis virus infection, and renal cell carcinoma, which has a low single-nucleotide mutational load but a higher frequency of indels than other common cancers, resulting in increased immunogenicity.

Table 2: Major indications approved for the use of anti-PD-1 and anti-PD-L1 therapies and the attributed mechanism of action of the anti-tumour response[5].

Group	Indication	ORR	Medicines Approved	Main Driver of Response
High response rate	Hodgkin's disease	87%	nivolumab pembrolizumab	PDJ amplicon
	Desmoplastic melanoma	70%	nivolumab pembrolizumab	Mutations from chronic sun exposure
	Merkel cell	56%	avelumab pembrolizumab	Merkel cell virus
	MSI-h cancers	53%	nivolumab pembrolizumab	Mutations from mismatch-repair deficiency
Intermediate response rate	Skin melanoma	35 – 40%	nivolumab pembrolizumab	Mutations from intermittent sun exposure
	NSCLC	20%	atezolizumab nivolumab pembrolizumab	Mutations from cigarette smoking

[4] *http://science.sciencemag.org/content/sci/359/6382/1350.full.pdf*

[5] Table derived from *http://science.sciencemag.org/content/sci/359/6382/1350.full.pdf*

	Head & neck	15%	nivolumab pembrolizumab	Mutations from cigarette smoking
	Gastroesophageal	15%	pembrolizumab	Mutations from cigarette smoking
	Bladder & urinary tract	15%	atezolizumab avelumab durvalumab nivolumab pembrolizumab	Mutations from cigarette smoking
	Renal cell carcinoma	25%	nivolumab pembrolizumab	Insertions and deletions (indels)
	Hepatocellular carcinoma	20%	nivolumab	Hepatitis virus

The underlying biology and durable response rates in patients with multiple types of cancer indicate that therapeutic blockade of the PD-1 pathway is arguably one of the most important advances in the history of cancer treatment. Some patients keep responding even after the antibody has been discontinued, suggesting that their immune system has been fundamentally changed.[6]. For physicians and patients alike, this "deep and rapid tumour regression" bring a hope they couldn't have fathomed a few years ago.

About Nivolumab

Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody that works as a programmed death-1 (PD-1) immune checkpoint inhibitor designed to uniquely harness the body's own immune system, thereby helping to restore anti-tumour immune response.[7].

In July 2014, nivolumab was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. Nivolumab is currently approved in more than 60 countries, including the United States, the European Union, Japan and Australia. To date, the nivolumab clinical development program has enrolled more than 25,000 patients. The level of experience that Australian patients and Australian physicians have with nivolumab across clinical trials, access programs and via the PBS is extensive, with estimates that around 10,000 Australian patients have been treated with nivolumab for their specific cancer – via clinical trials, access programs or the PBA.

Nivolumab is the leading immuno-oncology agent in Australia when measured by the number of Therapeutic Goods Administration (TGA) indications and the number of PBS listings. Nivolumab has nine indications across six distinct tumour types registered by the TGA with four indications across four distinct tumour types listed on the PBS (Table 3).

Table 3: Outline of TGA indications and PBS listings for nivolumab

TGA Indication.[8]	PBS Listing.[9]
Melanoma • Nivolumab, as monotherapy is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. • Nivolumab, as monotherapy is indicated for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma. • Nivolumab, in combination with ipilimumab, is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).	**Melanoma** • Nivolumab, as monotherapy is indicated for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma
Non Small Cell Lung Cancer • Nivolumab, as monotherapy is indicated for the treatment of locally advanced or metastatic squamous non-small cell	**Non Small Cell Lung Cancer** • Nivolumab, as monotherapy is indicated for the treatment of locally advanced or metastatic non-small

[6] *http://science.sciencemag.org/content/sci/342/6165/1432.full.pdf*
[7] *Pardoll, DM 2012. "The blockade of immune checkpoints in cancer immunotherapy". Nature Revs. Cancer. 12 (4): 252–64*
[8] *https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01052-1&d=20180621161146224 83*
[9] *https://www.pbs.gov.au/pbs/search?term=nivolumab*

lung cancer (NSCLC) with progression on or after prior chemotherapy. • Nivolumab, as monotherapy is indicated for the treatment of locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, OPDIVO should be used after progression on or after targeted therapy.	cell lung cancer (NSCLC) following progression on or after prior platinum based chemotherapy.
Renal Cell Carcinoma • Nivolumab as monotherapy is indicated for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults.	**Renal Cell Carcinoma** • Nivolumab, as monotherapy is indicated for the treatment of patients with Stage IV clear cell variant renal cell carcinoma following progression on or after first-line treatment with a tyrosine kinase inhibitor; or development of intolerance to a tyrosine kinase inhibitor of a severity necessitating patient treatment withdrawal.
Classical Hodgkin Lymphoma • Nivolumab, as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin. The approval of this indication is based on objective response rate in a single arm study.	**Classical Hodgkin Lymphoma**
Squamous Cell Carcinoma of the Head & Neck • Nivolumab, as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum based therapy.	**Squamous Cell Carcinoma of the Head & Neck*** • Nivolumab, as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx. The condition must have progressed within 6 months of receiving prior platinum based chemotherapy. • PBS Listed Aug 1, 2018
Urothelial Carcinoma • Nivolumab, as monotherapy is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response in a single arm study.	**Urothelial Carcinoma**

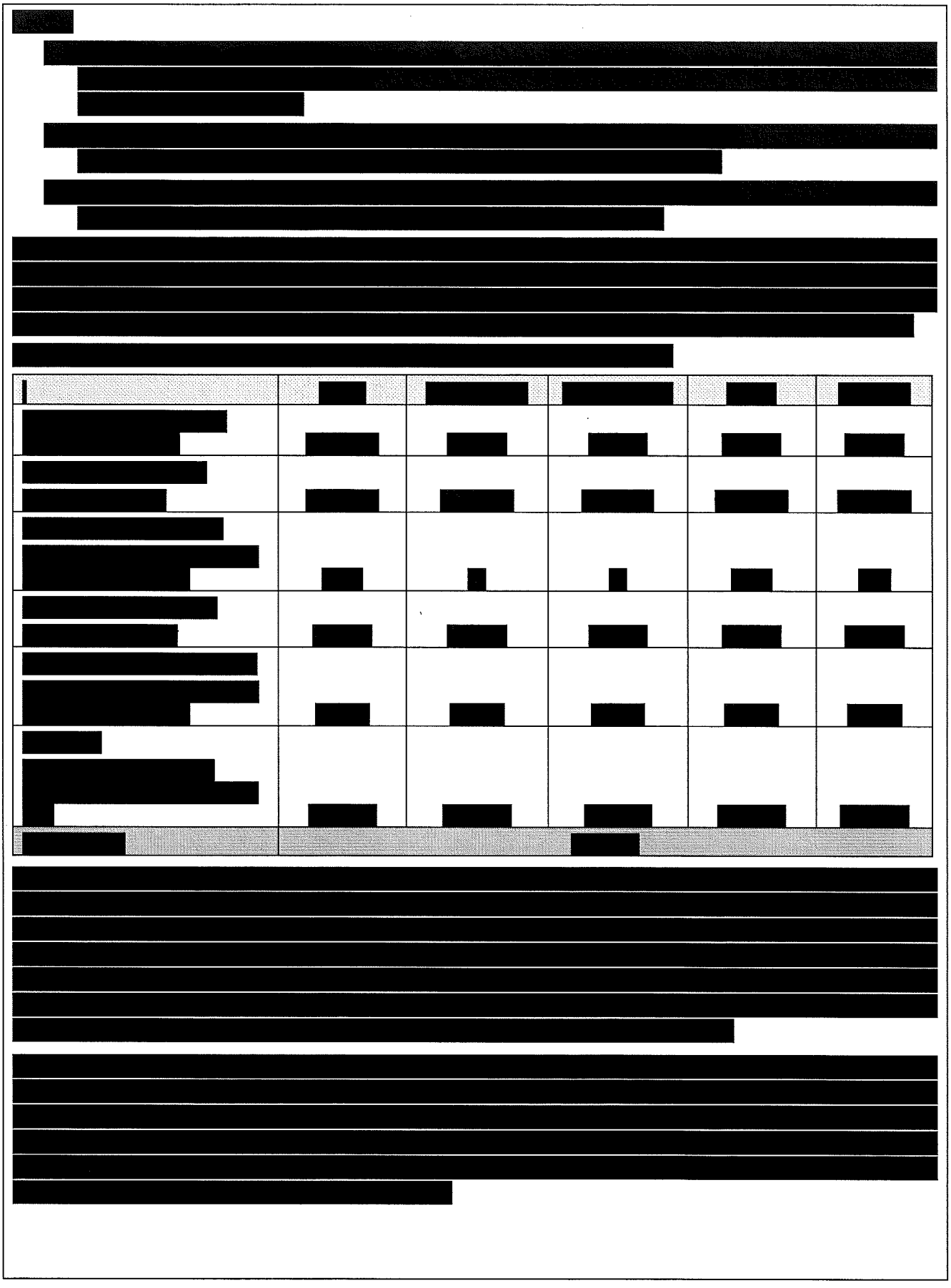
** To be PBS listed August 1, 2018*

Over the past four years, the PBAC have reviewed the clinical data, economic models and proposed cost-effectiveness of nivolumab on more than 15 occasions across five distinct tumour types, leading to 4 PBS listings. BMSA believes that this shared level of knowledge and experience, together with the promise of future data, and the sponsor's willingness to work with the PBAC and Australian Government, provides the greatest potential for a solution to the Minister for Health's call to arms. Details specific to BMSA's multiple tumour proposal are outlined in full below with relevant areas of the proposal also worked into BMSA's responses to the 16 specific questions within the submission template.

BMSA's Multiple Tumour Proposal

As detailed in Table 2 above, antitumour activity of PD-1 pathway blockade has been observed across a broad range of cancers. [redacted]

[redacted]



[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

BMSA proposes that the PBAC consider the validity and utility of using data from the above analysis to assist in a streamlined pathway process for PBS listing anti-PD-1/PD-L1 medicines that are proven effective in future cancer indications. BMSA proposes that rather than the traditional HTA cost-effectiveness submission for every future cancer indication involving a PD-1/PD-L1 checkpoint inhibitor immunotherapy, [redacted] to derive a surrogate "value" for the PD-1/PD-L1 checkpoint inhibitor immunotherapy.

BMSA is proposing that a pilot be initially conducted across 2018-2020, and that depending upon the success or otherwise, options may be to extend, broaden or cease the pilot. It is important to note that the proposed pilot is specific to anti-PD-1/ PD-L1 monotherapy use only. It does not cover combination therapies, co-dependent therapies, nor rare cancers where registrational trial data is not available.

BMSA appreciates that the level of change and work upfront is likely to be great, however in doing so, has attempted to map out a potential process framework for PBAC consideration (refer to text box overleaf; also Attachment 2 for diagrammatical representation of the proposed pilot). Being closer and more experienced in each of the process components outlined below, it is likely that the PBAC/ Department will have their own ideas around the practicality of the proposed process framework and level of efficiency that it may / may not deliver. [redacted]

[redacted]

PD(L)1 Cancer Immunotherapy – Streamlined PBS Listing Pilot

Eligibility to Participate in the Pilot:

- *PD-1/PD-L1 immunotherapy.*
- *TGA registration for monotherapy use occurring within the 2018-2020 timeframe.*

Confirmation of Efficacy/ Safety/ Tolerability:

- *Assumed at TGA registration.*

[redacted]

Post PBS:

- *Review of any RSA requirements at assigned time post PBS listing (sponsor, Dept, DUSC, PBAC).*

Cost Recovery:

- *Sponsors to be charged cost recovery fees commensurate with all work pre and post PBAC meeting - noting current cost recovery fees are not aligned with proposed pilot work activities and would require work up front to agree/ legislate.*

[redacted]

Conclusion

BMSA is presenting this proposal as our company's contribution to meeting Minister Hunt's challenge of 9 August 2017 to introduce a multiple tumour approach to the reimbursement of medicines for a broad number of cancers.

It is BMSA's intention that any multi-indication approach be kept as simple as possible. To that end, our proposal is restricted to a pilot program using anti-PD-1/ PD-L1 medicines that gain TGA registration over the period 2018-2020. BMSA is not proposing any treatments which require the identification of a biomarker, nor the use of PDL1 in combination with any other medicines or lines of treatment.

Both the government and BMSA are committed to ensuring patients have speedy access to the right medicine at the right time. Minister Hunt's call for a multiple tumour approach to reimbursing new medicines is an important circuit breaker in improving speed of access for an important group of patients with limited options. BMSA looks forward to the outcome from the August Special PBAC meeting and subsequently working with all stakeholders to deliver on the Minister's request.

Specific responses

Please insert your comments against the consultation questions below.

Question 1

What do you/your organisation see as the potential advantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings?

BMSA believes that there are a number of potential advantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings. The most significant and important is the potential for Australian patients to gain earlier PBS access to these medicines, however other potential advantages are also detailed below.

Australian patients gain earlier PBS access to revolutionary medicines

Increasing patient and clinician demand for early access to medicines that promise significant clinical advances, together with an evolving clinical trial model, has led to the establishment of fast-track regulatory pathways for breakthrough therapies in areas of high clinical need.[13]. In Australia, reform to the regulatory process to allow earlier registration for innovative new medicines has recently been introduced (Priority Review and Provisional Approval pathways).[14]. It has been argued that in order for changes to the Australian regulatory system to truly translate to earlier access to innovative medicines for Australian patients, a reimbursement pathway capable of dealing with increased levels of uncertainty is also required.[15].

Immunotherapies are a revolutionary development in the oncology treatment landscape and currently include checkpoint inhibitors, immune targets, cancer vaccines, adaptive T cell transfer agents, oncolytic virus immunotherapy and cytokines. Over the next 5 years, anti-PD-1 and anti-PD-L1 agents are predicted to have the greatest impact on cancer therapy across the largest number of malignancies.[16]. There is an ability to leverage the uniqueness of the PD-1/PD-L1 checkpoint inhibitor's mechanism of action, which already have demonstrated safety, efficacy and cost-effectiveness profiles across a number of tumour types, to develop a more efficient means of assessing value in follow-on indications, thereby delivering earlier PBS access for Australian patients. BMSA believes that the pilot proposed within this submission can help achieve this while still maintaining the principles of the National Medicine's Policy (i.e. equitable and affordable access) and remaining within the current legislative framework of the National Health Act.

Horizon scanning in real time delivers greater certainty for all stakeholders

Under the PD-1/PD-L1 multi-tumour pilot proposed by BMSA in this submission, it would be possible for sponsors, the PBAC, Department and Government to establish greater certainty around the timing of potential PD-1/PD-L1 checkpoint inhibitor PBS listings and budgetary impact across the 2018-2020 timeframe. This increased level of certainty would benefit all stakeholders.

Generation of local RWD de-risks early PBS access and helps to drive the science

The proposed pilot allows for verification of outcomes after longer durations of follow-up (either through longer-term clinical trial data or generation of local real world data) to confirm original value assessments and/or answer uncertainties the PBAC may have at the time of PBS listing. Not only will this de-risk the back end of the process from a PBAC perspective, but the generation of further data specific to the PD-1/PD-L1 checkpoint inhibitor medicines can only help evolve scientific thinking and clinical practice.

Efficiencies in process will be derived

As noted in response to Q13 below, there are currently over 3000 clinical trials being conducted that are investigating immunotherapies in cancer, with approximately half of these involving PD-1/PD-L1 checkpoint inhibitor medicines. Significant challenges lie ahead for sponsors, the Department and the PBAC in regard to the number of upcoming submissions and evaluations. This could lead to inequities in timely access for patients whose tumours are included in smaller, follow-on indications, despite there being evidence of an effective treatment option that works across a patient's entire immune system. BMSAs proposed pilot, covering PD-1/PD-L1 checkpoint inhibitors used in the monotherapy setting across the 2018-2020 timeframe will lead to a reduction in the overall number of submissions to the PBAC. Should

[13] https://link.springer.com/content/pdf/10.1186%2Fs40545-018-0131-4.pdf

[14] https://www.tga.gov.au/mmdr

[15] https://link.springer.com/content/pdf/10.1186%2Fs40545-018-0131-4.pdf

[16] http://science.sciencemag.org/content/sci/359/6382/1350.full.pdf

the pilot be successful and deemed worthy of expanding to other innovative I-O or non I-O medicines, greater efficiencies across the process may be possible.

Question 2

What do you/your organisation see as the potential disadvantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings?

In requesting that the PBAC consider options for the PBS listing of programmed death-ligand 1 cancer immunotherapies in a pan-tumour setting, the Minister has signalled the prioritisation of these treatments within current funding mechanisms. For PD-1 checkpoint inhibitor immunotherapies to be emphasised for further consideration within the finite resources of the pharmaceutical benefits scheme (PBS), demonstrates an inequity of outcomes for cancer patients within current access timeframes and misalignment of the current framework with the expectations of the Minister and thereby, the Australian community.

Overall, the current disconnect between the priorities signalled by the Minister and reimbursement outcomes should not be framed within an assumption of disadvantage, but an opportunity to enhance the current process to meet the expectations of the community.

Question 3

What is urgent unmet clinical need? How should it be established? For which patient groups?

What is urgent unmet clinical need? How should it be established?

The views of patients and physicians are clearly needed to appropriately address these questions.

However, BMSA believes that the consideration of clinical need should involve an assessment of the disease severity, disease prognosis, availability of alternative treatments, and the effectiveness of the new therapy. There are a number of frameworks established and under consideration that provide implicit guidance as to which disease areas are of urgent unmet clinical need and which medicines potentially help address this urgent unmet clinical need – e.g. ESMO MCBS.[17]; TGA's criteria for priority and provisional reviews.[18]; Access to Medicines Working Groups (AMWGs) work on streamlined pathways.[19].

For which patient groups?

Any patient or patient group can have an urgent and unmet clinical need when the above are assessed. For people with a rare cancer, consideration of the above factors will almost always lead to this conclusion. The definition of what is a rare and less common cancer is therefore a relevant aspect when identifying relevant patient groups. The Rare Solutions Report[20] defines rare, less common, and super rare cancers as follows:

- ***'Less common'*** are defined as those cancers with an incidence of b/w 6 and 12 (inclusive) per 100,000 Australians per annum;
- ***'Rare cancers'*** are defined as those with an incidence of less than 6 per 100,000 Australians per annum;
- ***'Super rare cancers'*** are defined as those with an incidence of equal to, or less than, 2 per 100,000 Australians per annum.

Question 4

What is the minimum level of evidence of effectiveness that you/your organisation think should be required before a PD-1 and PD-L1 checkpoint inhibitors is considered for subsidy for a particular kind of cancer? Why?

Under the PD-1/PD-L1 checkpoint inhibitor multiple tumour pilot proposal detailed in the introduction to this submission, BMSA recommends that a PD-1/ PD-L1 checkpoint inhibitor be considered for subsidy for a cancer indication under the pilot if the TGA approve and register the medicine for use in that specific indication.

The TGA are charged with assessing the efficacy, safety and tolerability of a medicine in a specific indication. Should a medicine be deemed to be effective by the TGA, it will be registered on the ARTG and made available for potential use by Australian patients. BMSA believes that TGA approval and registration provides an appropriate level of safety and effectiveness for a PD-1/ PD-L1 checkpoint inhibitor medicine to be considered for subsidy under the proposed pilot.

[17] http://www.esmo.org/Policy/Magnitude-of-Clinical-Benefit-Scale

[18] https://www.tga.gov.au/sites/default/files/consultation-expedited-pathways-prescription-medicines.pdf

[19] https://www.pbs.gov.au/info/general/working-groups/amwg/amwg-october-2017

[20] https://engonetrca2.blob.core.windows.net/assets/uploads/files/2017%20Rare%20Solutions%20Report_%20FINAL%20DIGITAL%20VERSION.pdf

It is important to note that the multiple tumour proposal is specific to indications in which PD-1/ PD-L1 checkpoint inhibitor registrational studies are currently being conducted and that BMSA's views on funding of PD-1/ PD-L1 checkpoint inhibitor medicines for rare cancers - where evidence can be extremely limited - is detailed in response to question 10 below.

Question 5

Do you/your organisation think it is possible for the PBAC to be able to extrapolate, or apply, the evidence of effectiveness of a checkpoint inhibitor in one kind of cancer to another kind of cancer, or from late stage cancer to early stage cancer? Why? How?

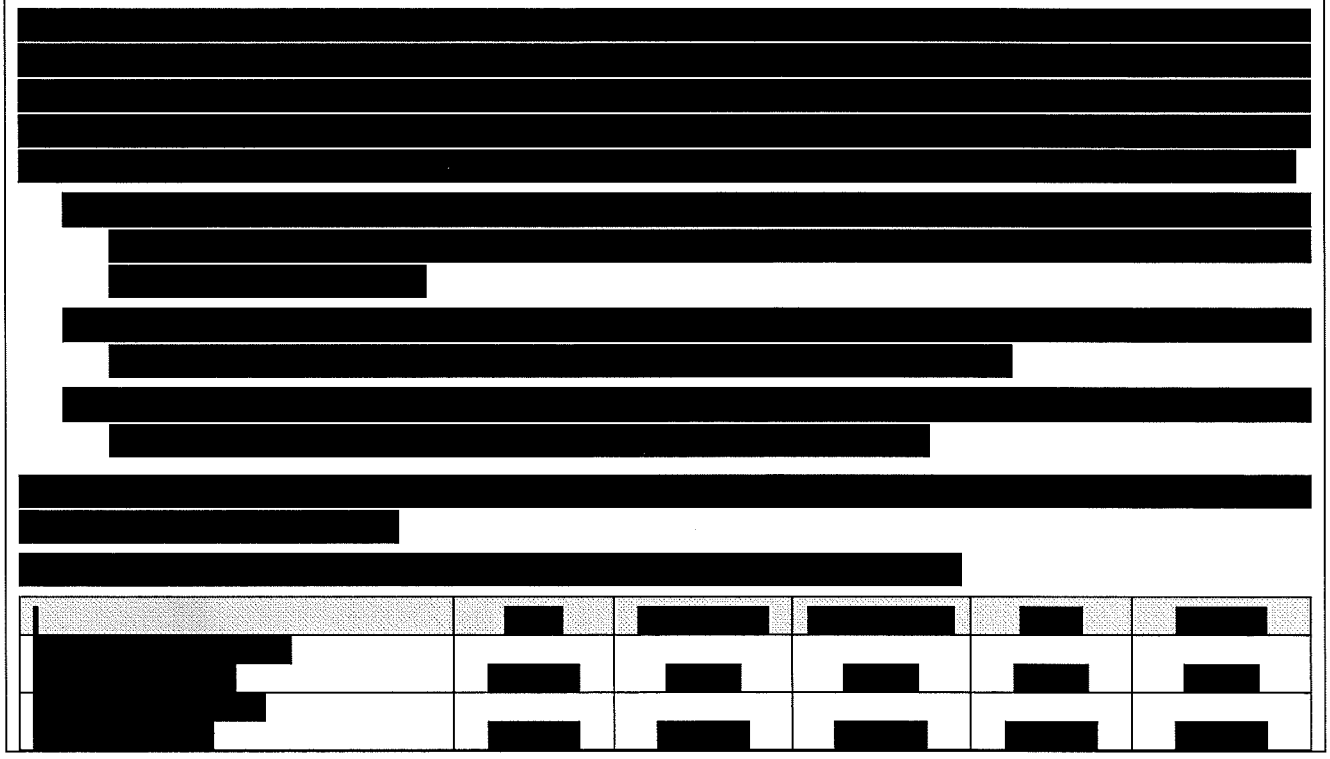
Question 6

Do you/your organisation think it is possible for PBAC to satisfy itself that treatment with a PD-1 or PD-L1 checkpoint inhibitor is cost-effective without an economic model that is specific to that kind of cancer? How?

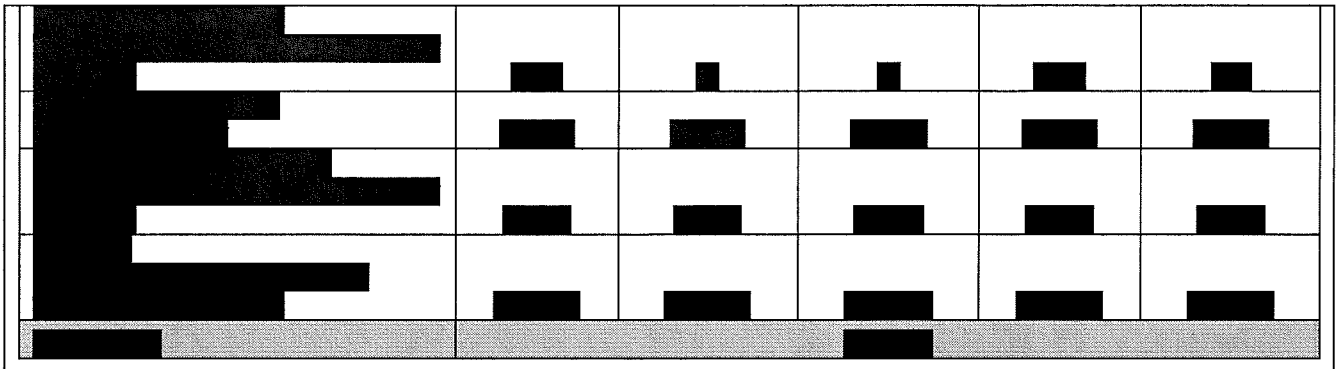
- Is it possible to group different cancer types together based on particular characteristics that are similar, and construct a single model for the group?
- Are other approaches to establishing cost-effectiveness across cancer types possible? What are those approaches and how would they operate?

Over the past four years, the PBAC have reviewed the clinical data, economic models and cost-effectiveness of nivolumab on more than 15 occasions across five distinct tumour types, leading to 4 PBS listings. BMSA believes that this shared level of knowledge and experience, together with the results of a recent surrogate endpoint analysis conducted by BMSA (see below) will allow the PBAC to i) apply evidence of effectiveness of a checkpoint inhibitor in one kind of cancer to another kind of cancer and ii) satisfy itself that treatment with a PD-1 or PD-L1 checkpoint inhibitor can be ascribed an initial value without an economic model specific to that kind of cancer. An overview of why and potentially how is provided below.

The underlying biology and durable response rates in patients with multiple types of cancer indicate that therapeutic blockade of the PD-1 pathway is arguably one of the most important advances in the history of cancer treatment. Some patients keep responding even after the antibody has been discontinued, suggesting that their immune system has been fundamentally changed.[21].



[21] *http://science.sciencemag.org/content/sci/359/6382/1350.full.pdf*



[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

PD-1/PD-L1 Checkpoint Inhibitor Immunotherapy – Streamlined PBS Listing Pilot

Eligibility to Participate in the Pilot:

- *PD-1/ PD-L1 immunotherapy.*
- *TGA registration for monotherapy use occurring within the 2018-2020 timeframe.*

Confirmation of Efficacy/ Safety/ Tolerability:

- *Assumed at TGA registration.*

[redacted]

Post PBS:

- *Review of any RSA requirements at assigned time post PBS listing (sponsor, Dept, DUSC, PBAC).*

Cost Recovery:

- *Sponsors to be charged cost recovery fees commensurate with all work pre and post PBAC meeting - noting current cost recovery fees are not aligned with proposed pilot work activities and would require work up front to agree/ legislate.*

In order to provide the PBAC with a guide as to the potential impact of such a pilot, BMSA has mapped out the potential PBS indications, patient numbers and budgetary impact using the nivolumab monotherapy clinical trial program as a surrogate for PD-1/PD-L1 checkpoint inhibitor medicines (refer to Table 6 in the Introduction to this submission). [redacted]

[redacted]

While alternate approaches to establishing cost-effectiveness/ value across different cancer types are possible - *such as constructing a single PD-1/PD-L1 checkpoint inhibitor economic model or grouping PD-1/ PD-L1 checkpoint inhibitor medicines according to their suspected mechanism of action of antitumour response (e.g. PDJ amplicon, mutations from chronic sun exposure, mutations from cigarette smoking, indels)* – BMSA believes that the proposed multiple tumour pilot outlined above provides the PBAC with a robust, yet efficient method to value PD-1/ PD-L1 checkpoint inhibitor medicines that are demonstrated to be effective in future cancer indications.

Question 7

What do you/your organisation think is a reasonable subsidy price for Government to pay for a PD-1 or PD-L1 medicines for cancer types where the benefit is potentially very modest?

[redacted]

Question 8

Do you/your organisation think PD-1 and PD-L1 medicines should be made available to all patients whose cancers display a particular biomarker? Why? Which biomarker?

PD-L1 expression levels are associated with an increased responsiveness to immunotherapies working on the PD-1/PD-L1 axis.[25]. However, there are patients that are classified as PD-L1 negative (based on various cut offs) that still respond to PD-(L)1 inhibitors. This makes clinical decision-making based solely on PD-L1 expression by IHC difficult. In addition to this, there are factors associated with PD-L1 testing that need to be considered, such as analytic performance of PD-L1 assays, concordance between PD-L1 antibodies and demonstration of clinical utility of specific cut offs for PD-L1 expression .[26,27,28]

ANALYTIC PERFORMANCE

Several studies have assessed the analytic performance of PD-L1 IHC assays as determined by membrane staining of tumor cells only or in combination with immune cells.[29]. One such study is Blueprint 2, an international study to assess the feasibility of harmonising five PD-L1 assays (22C3, 28-8, SP142, SP263 and 73-10) using real world clinical lung cancer samples (N=81). This study provides evidence of the interchangeability among three different assays (22C3, 28-8 and

[25] *Cyriac and Gandhi. Emerging Biomarkers for Immune Checkpoint Inhibition in Lung Cancer. Semin Cancer Biol. 2018 May 19. pii: S1044-579X(17)30250-X.(Epub ahead of print)*

[26] *Santini and Hellmann. PD-1/PD-L1 Axis in Lung Cancer. The Cancer Journal 2018. Vol 24(1):15-19*

[27] *Ahmadzada et al. An Update on Predictive Biomarkers for Treatment Selection in Non-Small Cell Lung Cancer. J. Clin. Med. 2018, 7:6-article 153*

[28] *Buttner et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. J Clin Oncol. 2017 Dec 1;35(34):3867-3876.*

[29] *Buttner et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. J Clin Oncol. 2017 Dec 1;35(34):3867-3876.*

SP263) for use in tumour cell PD-L1 expression scoring, but not immune cell scoring. Interobserver and intraobserver concordance is high across all assays (>82%) and highest when scoring only tumor cells.[30],[31],[32].

Despite good overall percent agreement (OPA) between 22C3, 28-8 and SP263 PD-L1 assays, there is variation in the literature with respect to heterogeneity of PD-L1 expression (intra- and inter-tumoural) and that these inherent biological uncertainties may be compounded by poor quality IHC or interpretation by pathologists. In a position statement by the RCPA, they stated concerns that patients that may potentially benefit from PD-(L)1 therapy may be excluded on the basis of an imperfect PD-L1 biomarker.[33].

CLINICAL UTILITY

Based on the multiple PBAC and MSAC reviews of PD-1 / PD-L1 biomarker utility, reimbursement was not supported at this point.[34],[35],[36],[37]:

- "PD-L1 immunohistochemistry (IHC) as a companion diagnostic test has weak evidence of clinical validity (lacks ability to predict response to therapy) and clinical utility (insufficient information to guide treatment).
- Unlike many other companion tests, PD-L1 has a wide range of expression and hence the results reported are not dichotomous and are challenging to quantify.
- The issue of the optimum threshold for PD-L1 positivity remains unresolved.
- If other programmed death 1 (PD-1)/PD-L1 inhibitors become listed in the PBS for NSCLC in the future that also require PD-L1 testing, the required tumour proportion score (TPS) threshold for eligibility may vary."

Ribas and Walchok (2018).[38] have suggested that the current understanding of response and resistance to PD-1–blockade therapy suggests that there cannot be a single biomarker to select patients. Therefore, selection of patients who are highly likely to respond to single-agent anti–PD-1 therapy (as opposed to being exposed to the greater toxicity and expense of combined therapy) would require a combination of studies in baseline tumor biopsies with sufficient tissue to include: (i) DNA analyses for tumor mutational load and absence of deleterious mutations in key immune signaling pathways, (ii) RNA analyses to detect the presence or absence of IFN-g signaling and a favorable tumor phenotype, and (iii) morphological analyses documenting the colocalization of CD8+ T cells expressing PD-1 and interacting with reactively expressed PD-L1 in the tumor microenvironment. However, such extensive testing is currently not done routinely and in a timely enough manner to inform therapeutic decisions in patients with advanced cancer.

In a move toward this suggested selection pathway for patients most likely to respond to single agent PD-1 blockade, the FDA has recently approved a PD-1 inhibitor for solid tumours based on the presence of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumour originated.[39].

In the search for other biomarkers of response to immune acting therapies, there is accumulating evidence that next generation sequencing-based tumor mutational burden measures can predict outcome for PD-(L)1 and/or CTLA-4 - based therapies.[40],[41]. In addition, TMB appears to be independent of PD-L1 expression levels.[42]. Recent data in 1st line metastatic NSCLC setting has shown that PFS among patients with high TMB (>10mut/Mb) was significantly longer with

---

[30] *Buttner et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. J Clin Oncol. 2017 Dec 1;35(34):3867-3876.*

[31] *Tsao et al. PD-L1 Immunohistochemistry comparability study in real life clinical samples: results of Blueprint phase 2 project. J Thorac Oncol. 2018 May 22. pii: S1556-0864(18)30626-9.*

[32] *Cooper et al. Intra- and Interobserver Reproducibility Assessment of PD-L1 Biomarker in Non-Small Cell Lung Cancer. Clin. Cancer Res. 2017 Aug 15;23(16):4569-4577.*

[33] *Debra Graves CEO RCPA, Letter titled: PD-L1 Immunohistochemistry testing. 27th March 2017.*

[34] *Nov 2016 Application No. 1414 – PD-L1 testing for access to pembrolizumab for the treatment of locally advanced or metastatic NSCLC. http://www.msac.gov.au/internet/msac/publishing.nsf/content/154DEF7A9C4C4D2BCA25801000123C11/$File/1414%20-%20Public%20Summary%20Document.pdf*

[35] *April 2017 Application No. 1440 – PDL1 testing for access to pembrolizumab in treatment naïve patients with locally advanced or metastatic nonsmall cell lung cancer. NSCLC http://www.msac.gov.au/internet/msac/publishing.nsf/content/8D0D2D7EEEFF52A2CA25801000123C23/$File/1440-FinalPSD-accessible.pdf*

[36] *Nov 2016 PBAC PSD. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-11/files/pembrolizumab-nsclc-psd-november-2016.pdf*

[37] *Nov 2017 PBAC PSD. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-11/files/pembrolizumab-nsclc-psd-november-2017.pdf*

[38] *Ribas and Wolchok. Cancer Immunotherapy using Checkpoint Blockade. 2018 Science 359, 1350-1355.*

[39] *https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm.*

[40] *Cyriac and Gandhi. Emerging Biomarkers for Immune Checkpoint Inhibition in Lung Cancer. Semin Cancer Biol. 2018 May 19. pii: S1044-579X(17)30250-X.(Epub ahead of print).*

[41] *Hellmann et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutation Burden. N Engl J Med 2018; 378:2093-2104.*

[42] *Rizvi et al. Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients with Non-Small-Cell Lung Cancer Profiled with Targeted Next-Generation Sequencing. JCO Vol 36(7):633-641.*

nivolumab plus ipilimumab than chemotherapy.[43]. The value of high TMB as a predictor for response to IO therapies will continue to be assessed prospectively in clinical trials.

In the era of precision medicine there is a need to identify biomarkers for response to therapy to aid clinician treatment decisions which optimise patient responses and avoid therapies unlikely to provide benefit. Prof. Ian Olver has recently published a report with recommendations for cancer biomarkers in Australia which summarises some of the issues facing the field of precision medicine.[44]:

1. Allow approvals and reimbursement of targeted drugs to be based on the genomic similarities of cancers expressing the target, rather than approving drugs only on histopathology
2. Align the approval and funding of a targeted drug with that of its co-dependent biomarker preferably by the same agency where end user benefit can be a part of decision making.
3. Allow provisional drug approval based on surrogate biomarker endpoints.
4. Develop standards for evaluation of biomarkers as predictive tools
5. Develop bioinformatics capabilities to analyse large genomic datasets.
6. Develop electronic health records and laboratory systems to allow for capturing and linking biomarker tests and data
7. Develop guidelines for the use of biomarkers
8. Ensure that patent law does not restrict biomarker development.

Clearly biomarkers in the IO space will be important in the future, yet much research is still required. For the purposes of the proposed pilot, medicines requiring biomarker identification have not been included.

Question 9

Do you/your organisation think it is appropriate for the PBAC to extrapolate the evidence from one PD-1 or PD-L1 checkpoint inhibitor to other medicines in the same class(es)? This could provide patients with more choice and give Government the opportunity to negotiate better subsidy prices by utilising the competition between sponsors of medicines.

BMSA considers that, where data is available, multiple treatment options in the same class is a clear benefit for patients and clinicians. Variation with regards to dosing, tolerability, and even response, translates to the need for options within the same class to be made available on the PBS.

[redacted]

43 *Hellmann et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutation Burden. N Engl J Med 2018; 378:2093-2104.*

44 *Olver et al. Cancer Biomarkers in Australia. Report from Sansom Institute for Health Research at the University of South Australia. 2017. http://www.unisa.edu.au/Global/Health/Research/Cancer%20Biomarkers%20in%20Australia%20Report.pdf.*

Question 10

Do you/your organisation think that different evidentiary requirements are appropriate for rare cancers? How do you think cost-effectiveness should be established in this case?

Clinically advanced rare cancers pose a significant clinical challenge because evidence based treatments are seldom available for patients suffering from these malignancies. Despite little evidence demonstrating clinical benefit, these patients are often treated with chemotherapeutic agents that are used in patients with more common malignancies that arise from the same anatomical site. The cancer specific survival of patients diagnosed with a rare malignancy is significantly lower than with common cancers highlighting the need to improve management and treatment of these patients.

The definition of what is a rare and less common cancer is therefore a relevant aspect when identifying relevant patient groups. For the purposes of this submission, we align on definitions with the The Rare Solutions Report[45], which defines rare, less common, and super rare cancers as follows:

- 'Less common' are defined as those cancers with an incidence of b/w 6 and 12 (inclusive) per 100,000 Australians per annum;
- 'Rare cancers' are defined as those with an incidence of less than 6 per 100,000 Australians per annum;
- 'Super rare cancers' are defined as those with an incidence of equal to, or less than, 2 per 100,000 Australians per annum

Evidence generation in rare cancers is often challenging because of small numbers, they are often excluded from clinical trials with newer agents. Frequently, non-comparative trials are all that may be available in some rare cancers. This complicates PBAC considerations in a necessarily comparative framework. BMSA believes that a national database of cancer outcomes (including but not limited to rare cancers) should be established to describe the natural history of disease which can be utilised in submissions to the PBAC where only non-comparative data exists

Programs and initiatives such as the MRFF and various 'Missions' need to balance inquiry into basic science, with evidence generation that may be 'fit for purpose' in the context of regulatory and reimbursed approval.

- New approaches are being pioneered globally and in Australia to use molecular pathology, rather than a single biomarker or primary cancer location to understand patient responses to treatment. For example, the MoST program from the Garvan Institute tests a novel paradigm for evaluation of biomarker-driven treatment of patients with advanced cancer. The key elements of the design are a molecular screening platform to identify 'actionable' variants and an overarching protocol for multiple, parallel, signal-seeking clinical substudies. In this study, patients with advanced solid cancer of any histologic type, having failed all standard therapies will undergo tumor molecular profiling on archival tissue with a 393-gene panel and other molecular assays. The primary objective is to identify signals of clinical activity, as measured by objective tumor response or the ratio of time-to-progression on study treatment over the preceding period. Novel approaches such as this have the potential to have true 'pan-tumour' impact. How these approaches would traverse the MSAC and PBAC pathway to reimbursement is unclear.

The PBAC should endorse a horizon scanning exercise to assess the suitability of current HTA frameworks (via MSAC and the PBAC) to consider the reimbursement pathway for medicine approvals defined by molecular pathology rather than discrete biomarkers

The PBAC should consider TGA approved rare cancers with a lower level of evidence, and apply a subsidy price linked to patient benefit within a rare indication which had been established for previously approved indications [redacted]

Question 11

Do you/your organisation think PBAC should set aside one of its meetings each year to consider only PD-1 or PD-L1 inhibitors for cancer? (This would mean no other submissions for other medicines, including other cancer medicines, or other diseases would be considered at that meeting).

BMSA believes that it will be unnecessary to set aside one of its meetings each year to consider only PD-1 or PD-L1 checkpoint inhibitors for cancer. In fact, should the PBAC agree with the proposed pilot outlined within this submission,

45 https://engonetrca2.blob.core.windows.net/assets/uploads/files/2017%20Rare%20Solutions%20Report_%20FINAL%20DIGITAL%20VERSION.pdf

BMSA believes that the PBAC will need to consider fewer PBAC submissions at their meetings over the 2018 to 2020 time period.

Importantly, should the proposal be adopted, Australian patients will have earlier PBS access to PBS PD-1/PD-L1 checkpoint inhibitors for future cancer indications.

Question 12

If limited evidence is available at the time of subsidy of a PD-1 or PD-L1 inhibitor for a type of cancer, what do you/your organisation think should happen afterwards?

- Should sponsors be required to collect more evidence?
- What should happen if the new evidence shows the medicine is less effective or has greater safety risks than expected?
- Should the medicine continue to be subsidised but at a price commensurate with its benefit? Should the sponsor be compelled to continue to make the medicine available even if it thinks the price is too low?

BMSA believes that the algorithm key to the proposed pilot will provides a robust estimate of value [redacted] This concept is a key component of the Belgium multi-tumour pilot program. However, to reduce any remaining risk in the minds of the PBAC, BMSA proposes that a Managed Entry Scheme (MES) approach could be adopted [redacted] Under the proposed pilot, there are provisions for the sponsor, Department and PBAC to discuss and agree whether or not further evidence is required to confirm the original valuation or address any outstanding clinical or economic uncertainties. Further evidence may constitute future planned read-outs from clinical trials or real-world evidence - captured either internationally or locally via studies or registries.

While limited in number, BMSA believes that the Department, PBAC and the Australian pharmaceutical industry have sufficient experience with MES-type cases to be able to establish a robust yet simple and fair way to address uncertainty and share risk post PBS listing for medicines/ indications that fit this category. [redacted]

Question 13

(For industry/clinical groups) Clinical study information: (Please use the template provided for this information.)

- In what indications has your organisation completed clinical trials with a PD-1 and PDL1 inhibitor? Please include both positive and negative studies.
- In what indications is your organisation currently conducting or planning to conduct clinical trials with PD-1 or PD-L1 inhibitors? If usual PBAC processes were to be followed, when would you expect to make an application for subsidy for these indications?
- How does your organisation decide which indications to study and which to prioritise for registration or subsidy?

Research and development in the area of immunotherapy is vast, with recent estimates revealing that there are currently 3,042 active clinical trials testing immunotherapy treatments.[46]. Studies testing medicines that target PD-1 or PD-L1 make

[46] http://science.sciencemag.org/content/359/6382/1346/tab-pdf

up the majority of these active clinical trials, with greater than 1,000 studies alone investigating PD-1 or PD-L1 checkpoint inhibitor medicines in combination with other cancer fighting modalities.[47].

A review of PD-1 and PD-L1 checkpoint inhibitor immunotherapy studies being conducted by BMS reveals 694 studies currently registered with ClinicalTrials.Gov. Information specific to each of these 694 clinical trials is provided in the excel spreadsheet attachment to this submission. As the information in the Excel attachment to this submission matches that requested in the template provided (albeit not in exact column order), BMSA has decided (for efficiency reasons) not to transpose the information across from the excel spreadsheet to the template. This was flagged and agreed at a meeting with the Department to discuss the August 2018 PBAC Special meeting (June 20th 2018).

In relation to the query, *"How does your organisation decide which indications to study and which to prioritise for registration or subsidy?"*, BMS selects areas to study on the basis of degree of unmet need – i.e. What is the current survival benefit seen with standard of care? Where is the greatest patient need? Indications to study will then be based on early signs of efficacy and tolerability, with high response rates and manageable adverse event rates in early phase studies warranting development through to Phase III.

Question 14

Are there effective international models for multi-tumour subsidy that could be applied in Australia within the current regulatory framework?

Question 15

(For Industry) What information can you provide regarding established international agreements for multi-tumour subsidy and how could these apply in the Australian regulatory context?

Medicines Australia (MA) was able to pull together information specific to overseas jurisdictions where multi-tumour subsidy programmes for PD-1/PD-L1 checkpoint inhibitor medicines currently exist or are being considered. The MA summary table is provided below.

BMSA notes that in a number of these overseas examples (Netherlands, Belgium, Denmark), BMS has led the way and demonstrated great flexibility in working with the Governments on finding a mutually agreeable solution. BMSA believes that the pilot proposed within this submission demonstrates the same willingness to find a solution that benefits not only patients, but all stakeholders.

	Belgium	Denmark	Netherlands	Germany	Italy
New indication delay to Market Access	Up to 30 days	Up to 60 days	Immediate	Immediate	Immediate (if deemed innovative)
Form of value assessment for each new indication at launch	None, available in one month	Mini HTA	Abbreviated HTA	None, available in one month	Risk-sharing, payment by results, Fee for efficacy
Form of agreement	2-tiered discount	PVA	PVA	None	MEA
Duration of agreement	2+1 years	2+1 years	3 years	NA	2 years
Budget allocation	✓ For IO products – €200 M (2018)	No	✓ Product specific	✓ Product specific	€ 1 billion fund for innovative therapies

[47] http://science.sciencemag.org/content/359/6382/1346/tab-pdf

Price	Price based on volume tiers	Price based on volume tiers	Price based on volume tiers	Volume-weighted average price per indication	Net price for each indication with payback depending on performance
Budget cap + payback	✓	No	✓ Product specific	✓ Product specific	✓ Product specific
Any re-assessment of new indication after launch	✓ On-going. CE study required to show impact on all indications	Possible, for any uncertainties in assessment	Possible, for any uncertainties in assessment	✓ Comparator based value assessment within 1 year.	Possible, if MEA is re-negotiated

Question 16

Is there anything else you/your organisation would like to add?

PD-1/PD-L1 checkpoint inhibitor medicines such as nivolumab have changed the way cancer is being treated, and along with it the potential health outcomes of many Australians.

To date 15 nivolumab PBAC submissions have led to 4 separate PBS listings. [redacted]

[redacted]

BMSA believe a great amount has been achieved and that learnings can be applied to future indications. Where the TGA has deemed nivolumab both safe and effective in a given indication, the faster we can work to define an agreeable subsidy level has the potential to positively impact the health outcomes many more Australians.

At BMS locally and globally we pride ourselves on being able to work collaboratively to find mutually agreeable solutions to important health problems. We thank the PBAC for taking the time to consider this issue, and would welcome the opportunity to further discuss the proposed pilot with the PBAC, Department and Ministers Office.

Attachment 1: Clinical Overview of Potential Indications within the Proposed Pilot

[redacted]

[redacted]