Submission to the Pharmaceutical Benefits Advisory Committee (PBAC) August 2018 special meeting

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

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Abbreviations

ADCC	antibody-dependent T-cellular cytotoxicity
AKT	v-akt murine thymoma viral oncogene homologue
BDGF	brain-derived growth factor
BRAF	serine/threonine-protein kinase B-Raf
CNS	Central nervous system
CIT	Cancer immunotherapy
CSR	Clinical study report
DAG	diacyl-glycerol
ERK	extracellular signal-regulated kinase
ES-SCLC	extensive stage small cell lung cancer
GABl	GRB2-associated-binding protein 1
GRB2	growth factor receptor-bound protein 2
HTA	Health technology assessment
IC	Inhibitory concentration
IP3	inositol trisphosphate
MEK	mitogen-activated protein kinase
mNSCLC	metastatic non-small cell lung cancer
mTNBC	metastatic triple negative breast cancer
NB	Neuroblastoma
NTRK	neurotropic tropomyosin receptor kinase
NGF	nerve growth factor
NTF-3	neurotrophin 3
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PD-L1	Programmed death-ligand 1
PD-1	Programmed cell death protein 1
PI3K	phosphatidylinositol 4,5-bisphosphate 3-kinase
PIP2	phosphatidylinositol 4,5-bisphosphate
PKC	protein kinase C
PLC	phospholipase C
RCT	Randomised controlled trial
QUM	Quality use of medicines
RSA	Risk share arrangement
RAF	rapidly accelerated fibrosarcoma kinase
RAS	rat sarcoma kinase
RCC	renal cell carcinoma
ROS1	receptor tyrosine kinase 1
SHC	Src homology 2 domain containing
TRK	tropomyosin receptor kinase

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

This submission provides suggestions on two methods via which PD-1 and PD-L1s could be most appropriately PBS subsidised:

1. In situations where data are available or expected to become available, to inform a standard health technology assessment (HTA), the current approaches to HTA are applied. That is, explicit changes to the existing regulatory and reimbursement framework for medicines are not required and a refined *status quo* process is maintained. Nonetheless, in order to expedite patient access to PD-1 and PD-L1s and other innovative treatments with rapidly evolving clinical development pathways and addressing high unmet clinical needs, Roche is proposing pragmatic application of guidelines such as the Therapeutic Goods Administration (TGA)/PBAC parallel process guidelines as well as streamlining of the Managed Access Program (MAP) (see 'Quick wins' described in **Question 16** and examples provided below). Roche also suggests that in light of the speed and rapid evolution of the clinical development pathways for PD-1 and PD-L1s that a pragmatic approach to the inherent uncertainty will also be required.
2. Where there are no data currently available nor are there ongoing data collection projects underway to inform relative effectiveness via a standard HTA BUT a biological rationale exists for efficacy (e.g., clinical plausibility, existence of a biomarker, an alternate PD-1 and/or PD-L1 checkpoint inhibitor immunotherapy has shown benefit in a particular tumour/patient type etc) then Roche is proposing that timely shared funded access to PD-1 and PD-L1 checkpoint inhibitors is made available until evidence is generated to confirm effectiveness.

Answers to **Question 12** below provide further details on these distinct suggestions. It is relevant to highlight that the suggestions made in this submission for refinement of the existing regulatory and reimbursement framework for medicines do not seek multi-tumour listings, which Roche have defined (see **Question 1**) as one single PBS listing with broad clinical criteria sufficient to cover reimbursement of multiple tumour types.

Overall, Roche believes that the science ultimately should guide treatment in order to ensure the best possible outcomes for all stakeholders. The Australian regulatory and reimbursement framework for medicines has been founded on the principles of evidence-based and quality use of medicines. Therefore, it is Roche's position that biological plausibility of efficacy and safety of a PD-1 and/or PD-L1 checkpoint inhibitor immunotherapy is required before their consideration for subsidy.

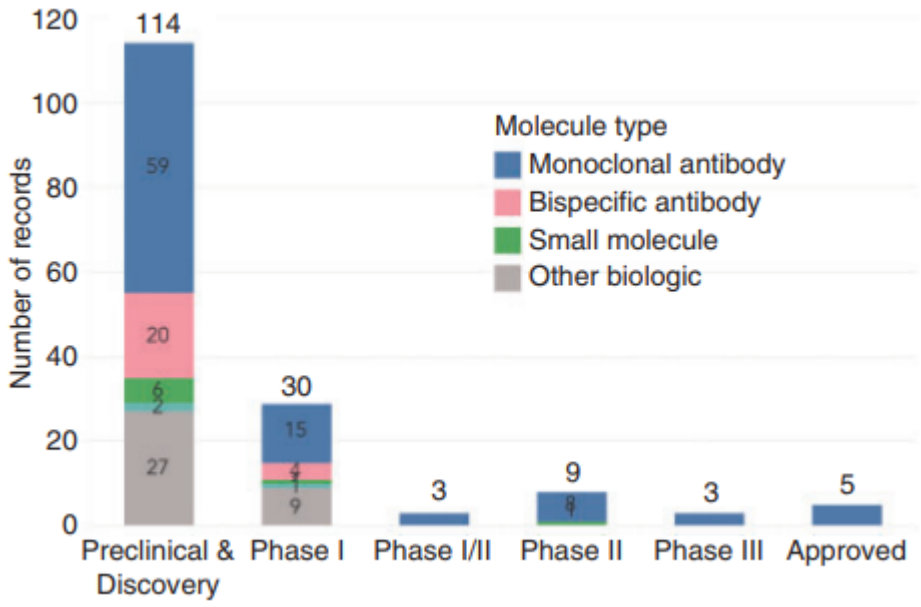
It is conceivable that evidence to inform the biological plausibility of efficacy and safety of PD-1 and PD-L1s could be gleaned via extrapolation from one molecule to the next. No evidence exists to date to suggest that available PD-1 and PD-L1 checkpoint inhibitor immunotherapies are materially different from one another in terms of their efficacy or safety profiles and this is generally supported by the

intended prescribers of these medicines.

With no head-to-head trials having been conducted, or likely to be so in the future, it would seem that the current evidence base is supportive of extrapolating data from one to another. However, we must also remain mindful of the voluminous, rapidly evolving extraordinarily complex clinical development programs for PD-1 and PD-L1s which will soon provide exponentially greater volumes of evidence to inform treatment and subsidy considerations.

Roche commends to PBAC a recent article by the Cancer Research Institute which 'presents an unbiased, neutral, scientifically curated, and timely updated analysis of all the current immuno-oncology agents in clinical development and the clinical trials testing these agents' (Tang 2018). The Cancer Research Institute have developed two databases; one which tracks 2004 immuno-oncology agents (940 in clinical stage and 1064 in preclinical stage) against 303 targets, from 864 companies; the other tracks 3042 active clinical trials of these agents with a target enrolment of 577 076 patients. The anti-PD-1/L1s are a subset of these and represent 1502 different studies, where 1105 are combination trials that combine anti-PD-1/L1 agents with other immuno-oncology therapies, targeted therapies, chemotherapies, radiotherapies, or chemoradiotherapies (Tang 2018). Figure 1 below provides an overview of the 164 anti-PD-1/L1 agents which are in development.

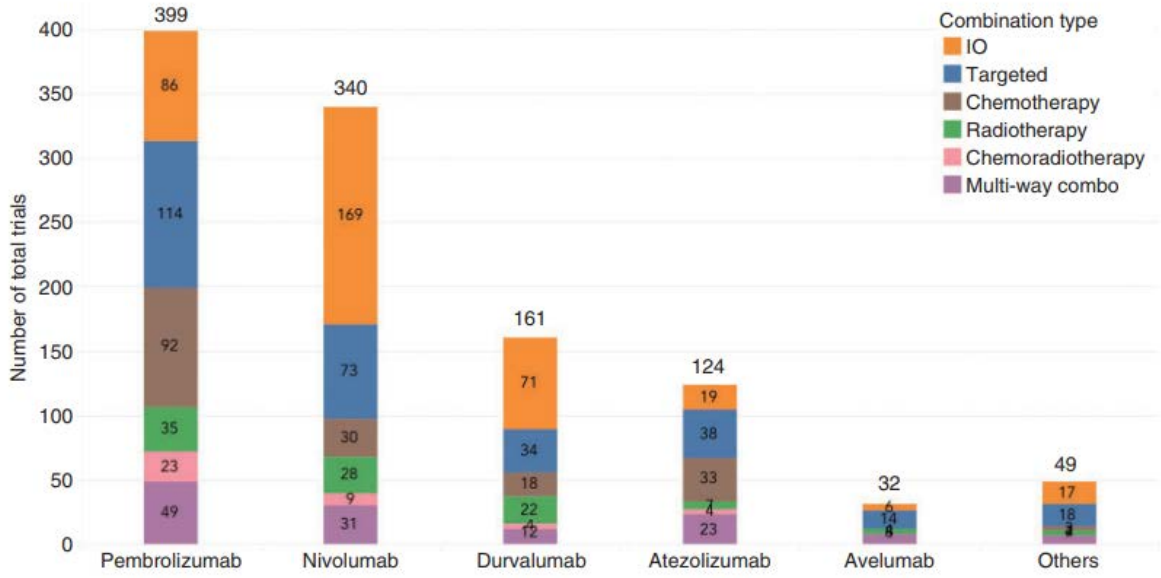
Figure 1: 164 anti-PD-1/L1 agents in development



Source: Tang 2018

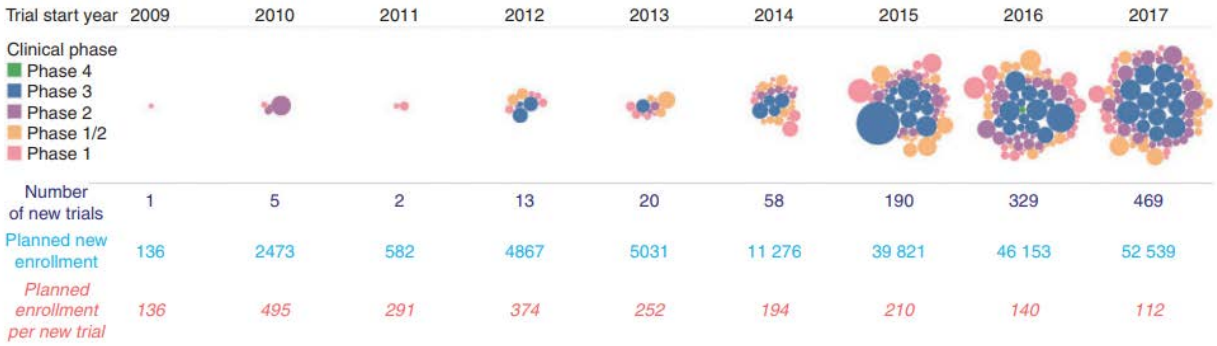
The authors note that despite being already approved as monotherapies or in combination with standard systemic chemotherapies, the majority of the ongoing anti-PD-1/L1 trials are examining the use of these agents in combination with other innovative agents such as other immuno-oncology agents and/or targeted therapies (see Figure 2 and Figure 3).

Figure 2: Analysis of PD-1/L1 combination trial types



Notes: The majority of combination trials focus on the five approved agents. Combination with other immuno-oncology agents, targeted therapies, and chemotherapies are the top common strategies.
Source: Tang 2018

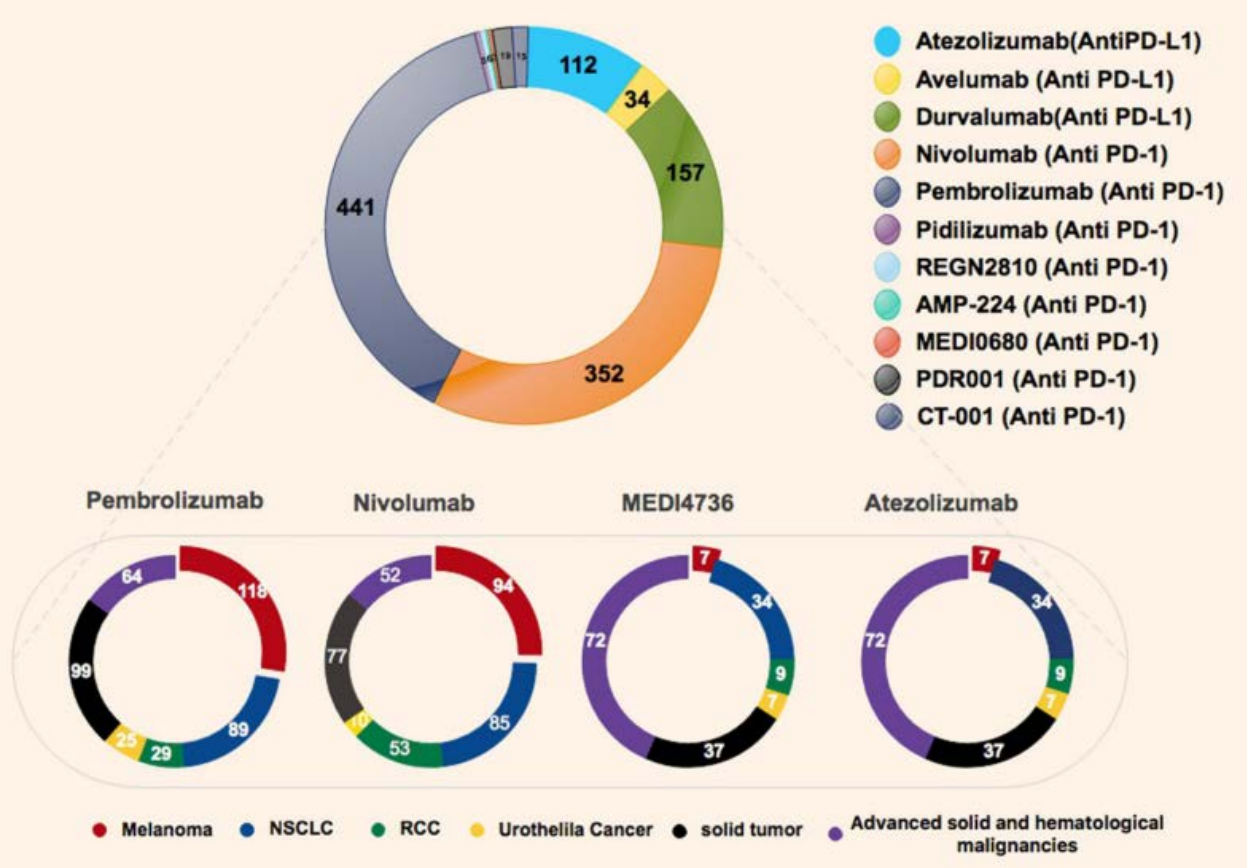
Figure 3: The rapid increase of new anti-PD-1/L1combination trials in the past 5 years



Note: The size of the bubble correlates to the target enrolment of patients. Multiple bubbles of the same colour represent multiple cancer types that are being tested in these trials
Source: Tang 2018

Alsaab et al, also published a review in August 2017 (based on the available data) specifically focusing on the current landscape for PD-1 and PD-L1 therapies and include the following useful figure (Figure 4).

Figure 4: Number of clinical trials for PD-1 and PD-L1 inhibitors



Notes: All data were obtained from FDA website, Clinicaltrials.gov, and National Cancer Institute.
Source: Alsaab 2017

Alsaab et al, conclude by saying that 'PD-1/PDL1 therapies have made a remarkable journey from the bench to the bedside over the past few years' and note that multiple ongoing studies are estimated to further establish the value of PD-1/PD-L1 pathway inhibitors. They recommend expediting biomarker development to focus therapy on patients who will be most likely to benefit and propose that a better understanding of the tumour immune microenvironment will eventually result in impactful advances in cancer therapy and management. Furthermore, Alsaab et al, observe that some patients fail to respond and the current strategy to address this is via the combination use of these agents.

A range of techniques are available for biomarker detection in cancer immunotherapy and Roche is a leader in the enormous and fast paced development occurring in this space. In particular Roche has established Roche Foundation Medicine and the offering of a next-generation sequencing (NGS) test, Foundation One®, which is a comprehensive genomic profiling test. Foundation One detects the full range of genomic alterations: insertion/deletion events; base pair substitutions; copy number alterations (aka copy number variations); and gene rearrangements. Using a NGS test is more accurate and comprehensive than the more common single-gene or multi-gene 'hotspot' panels, thereby generating significantly greater volumes of data to inform whether there is an optimal biomarker to determine eligibility to treatment with PD-1 and PD-L1s.

Further to the issue of extrapolation between PD-1 and/or PD-L1 checkpoint inhibitors in the same

class(es) as a basis for subsidy, Roche has highlighted several points of clarification for all stakeholders regarding the mechanics of such an arrangement (see **Question 9**). For example, 'Would products in the 'class' which do not have evidence in a particular indication be given PBS listing for that indication via extrapolation of data from another agent in the 'class'?' Roche also wishes to draw PBAC's attention to alternate methods such as therapeutic relativities established via cost-minimisation analyses, which have been successfully used to negotiate competitive subsidy prices where competition exists.

While Roche is committed to an evidence-based regulatory and reimbursement framework for medicines and acknowledges that PBAC processes have been evolving over the years, we believe that the framework must be continually improved to accommodate the new and evolving evidence packages available to support subsidy of new medicines. The PBAC's August special meeting, activities surrounding it and subsequent discussions provide an excellent opportunity to consider refinement of the current regulatory and reimbursement framework to assist with the;

- volume and speed of clinical development for PD-1 and PD-L1s (and other treatments in the future)
- to capitalise on the broadly similar safety profile of PD-1 and PD-L1s across indications
- profile of responses showing durable benefit and OS improvement across tumour types
- improve efficiencies through PBAC, clinician, patient, sponsor and other stakeholder 'familiarity' with the class
- tension created between patients' expectations of faster access, especially for subsequent indications
- alignment between the new TGA streamlined pathways and reimbursement pathways
- requirement for long-term follow-up data in order to reduce uncertainty and enable funding in a health care system where clinicians, patients and industry are continually demanding faster access; and
- address the inequity of access for rare cancer patients.

With a view to expediting access to PD-1 and PD-L1 checkpoint inhibitor immunotherapies and addressing the unmet need, Roche has identified steps in the regulatory and reimbursement framework which are not legislated, rather are described in policies and guidelines only (see **Question 12**). Roche suggests that a more relaxed application of these policies and guidelines may afford all stakeholders the opportunity for some 'quick wins'. That is, sponsors are given greater autonomy regarding the timing of lodging submissions to PBAC where submissions can be lodged at any time and the PBAC can assess a product prior to the availability of a Delegate's Overview. PBAC may also like to consider a review of the existing MAP approach. Importantly, PBS listing would not occur prior to TGA approval but improved alignment of the parallel process, especially in light of the new TGA priority review process, could expedite patient access to PD-1 and/or PD-L1 checkpoint inhibitor immunotherapies.

[redacted]

[redacted]

[redacted]

1.1 Atezolizumab (TECENTRIQ)

Roche's PD-L1 inhibitor immunotherapy is atezolizumab (TECENTRIQ).

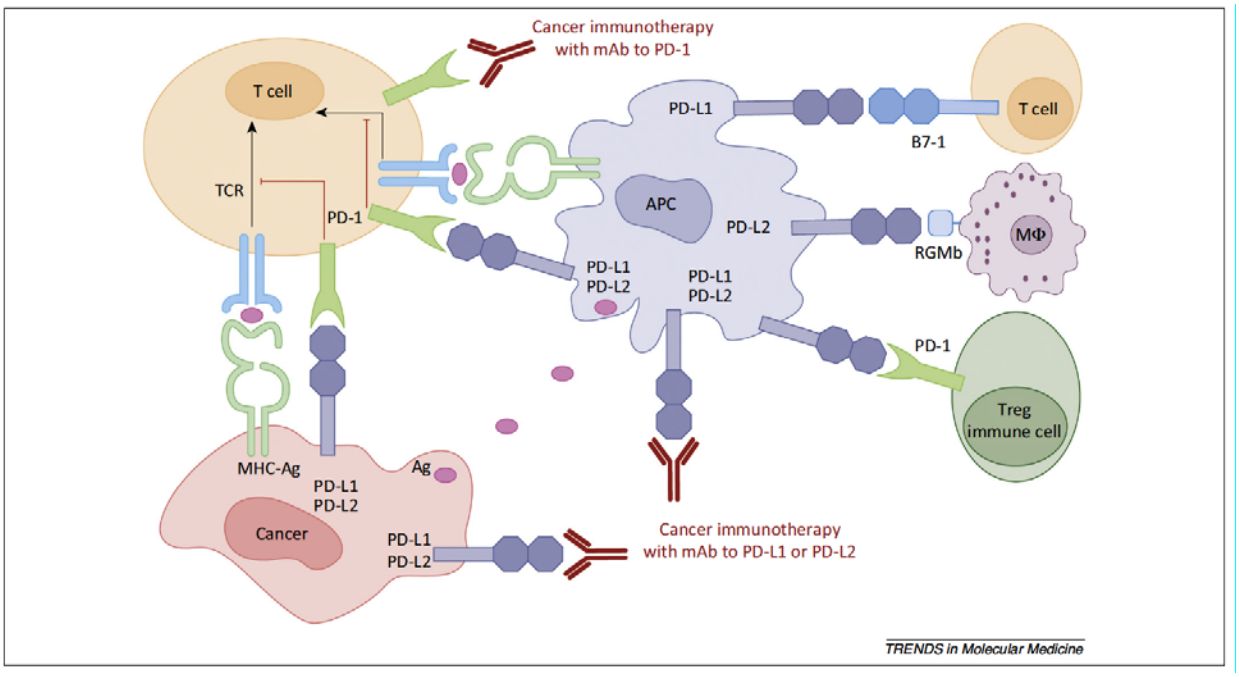
PD-L1 is an immune-checkpoint protein expressed on tumour cells and tumour infiltrating immune cells that when activated, down regulates anti-tumour T-cell function by binding to PD-1 and B7.1 receptors (Figure 5).

Atezolizumab is a humanised immunoglobulin monoclonal antibody that facilitates anticancer immune response through the binding to PD-L1 and the blockage of the interaction with the PD-1 and B7.1 receptors. The consequent inhibition of immune suppressive signalling reactivates dormant T-cells to enhance cytotoxic cancer immunity.

Atezolizumab binds directly and selectively to PD-L1 on the surface of tumour cells and tumour infiltrating immune cells in the tumour microenvironment preventing its binding with PD-1 (Taube 2012, Zou 2005). Inhibiting interactions of PD-L1 with its receptors PD-1 and B7.1, prevents the down regulation of T-cell activity while allowing for the priming of new T-cells (Herbst 2014). Blocking PD-L1 from binding to PD-1 can result in the restoration of anti-cancer T-cell activity, reinvigorating suppressed T-cells to attack and kill cancer cells in the tumour microenvironment (Chen 2012, Herbst 2014).

Blocking the PD-L1/B7.1 interaction by atezolizumab, left intact by anti-PD-1 antibodies (such as nivolumab), allows B7.1 to bind to CD28. This binding to CD28 provides a co-stimulatory signal to T-cells for priming and activation. Atezolizumab may enhance T-cell priming and activation in the lymph node, potentially leading to increased duration of response and durable survival (Chen 2012, Park 2010, Paterson 2011, Yang 2011).

Figure 5: Cancer immunotherapy with anti-PD-1 and anti-PD-L1 antibodies



Source: (Ohaegbulam 2015)

Unlike anti-PD-1 antibodies nivolumab and pembrolizumab, atezolizumab leaves the PD L2/PD-1 interaction intact which may help to preserve peripheral immune homeostasis. Leaving the PD-L2/PD-1 interaction intact prevents the triggering of antibody-dependent T-cellular cytotoxicity (ADCC) which is a process whereby antibody-coated cells are targeted for destruction by cytotoxic immune cells, principally natural killer cells. If ADCC occurs, it could potentially result in the depletion of primed tumour-specific T-cells and suppression of the immune response. Furthermore, unlike nivolumab and pembrolizumab, atezolizumab is engineered to avoid ADCC via a modified hinge Fc region.

Table 1: Differences in agents targeting PD-L1/PD-1 axis

Agents targeting PD-L1/PD-1 axis	**PD-L1:PD-1**	**PD-L1:B7.1**	**PD-L2:PD-1**
	Reinvigorate suppressed T-cells	**Enhance T-cell priming and function**	**Autoimmune reactions in normal tissue**
Anti-PD1 agents (e.g. nivolumab, pembrolizumab)	Yes	No	Yes
Anti-PD-L1 agents (e.g. atezolizumab)	Yes	Yes	No

Source: (Brown 2003, Chen 2012, Herbst 2014, Latchman 2001, Park 2010, Paterson 2011, Schmid 2016, Yang 2011)

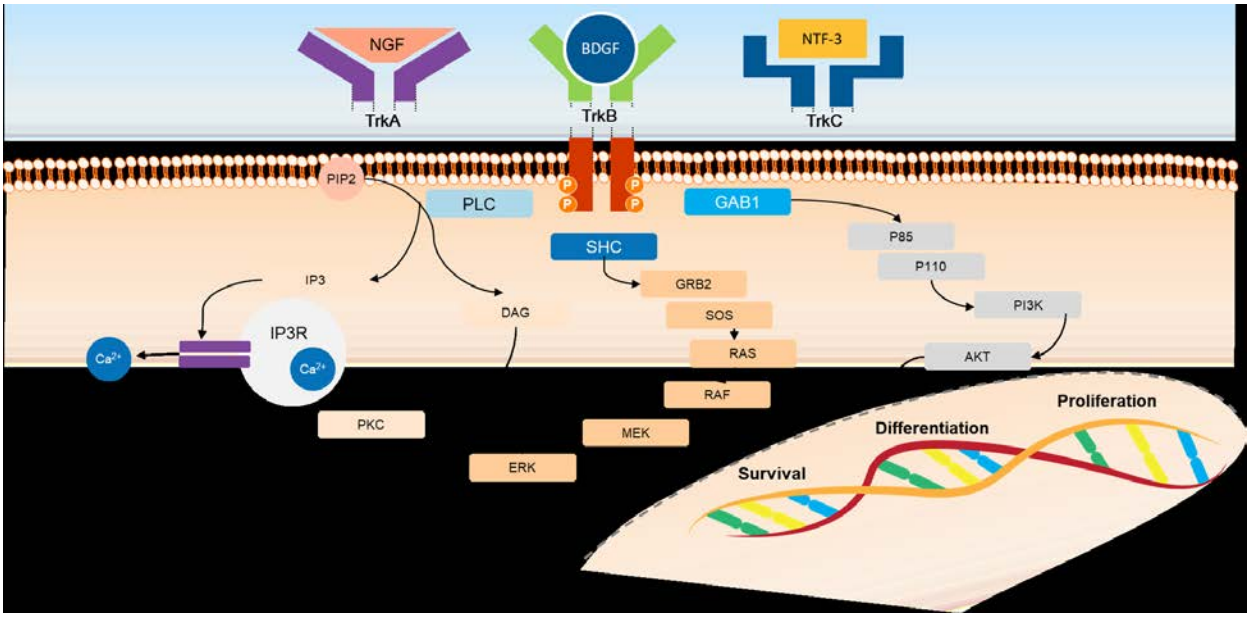
Atezolizumab was granted a positive recommendation by PBAC for second-line non-small cell lung cancer (November 2017 PBAC meeting) and was subsequently PBS listed for this indication on 1 April 2018.

1.2 Entrectinib (RXDX-101)

While not a PD-1 or PD-L1 inhibitor, Roche would like to provide the PBAC with a line of sight to a pipeline molecule that has pan-tumour evidence of effectiveness. Entrectinib (RXDX-101), is an example of a near future, pan tumour non checkpoint inhibitor targeted therapy, which [redacted]

Entrectinib inhibits tropomyosin receptor kinase A/B/C (TRKA/B/C), receptor tyrosine kinase 1 (ROS1), and anaplastic lymphoma kinase (ALK) tyrosine kinases with inhibitory concentration (IC) < 2 nM. In vivo, entrectinib is active in several fusion-driven solid tumour and TRKB-expressing neuroblastoma (NB) models. The TRK pathway is shown in Figure 6 below.

Figure 6: TRK receptor signalling leads to cell proliferation, differentiation and survival



Notes: AKT=v-akt murine thymoma viral oncogene homologue; BDGF=brain-derived growth factor; DAG=diacyl-glycerol; ERK=extracellular signal-regulated kinase; GABl=GRB2-associated-binding protein 1; GRB2=growth factor receptor-bound protein 2; IP3=inositol trisphosphate; MEK=mitogen-activated protein kinase; NGF=nerve growth factor; NTF-3=neurotrophin 3; PI3K=phosphatidylinositol 4,5-bisphosphate 3-kinase; PIP2=phosphatidylinositol 4,5-bisphosphate; PKC=protein kinase C; PLC=phospholipase C; RAF=rapidly accelerated fibrosarcoma kinase; RAS=rat sarcoma kinase; SHC=Src homology 2 domain containing

Adapted from Amatu A, et al. ESMO Open. 2016. Research Focus: Targeting Tropomyosin Receptor Kinases in Cancer, Todd M. Bauer, MD.

Entrectinib has clinical activity in adults with malignancies harbouring neurotropic tropomyosin receptor kinase (NTRK), ROS1, or ALK gene fusions. Preliminary anti-tumour activity has been seen in gene fusion-positive patients. Central nervous system (CNS) penetration enables targeting of CNS metastases and primary tumours. Entrectinib continues to be investigated in expansion cohorts of patients with primary CNS tumours, extracranial solid tumours harbouring NTRK, ROS1, or ALK fusions, and patients with NB.

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TRK fusions have been identified across a wide variety of solid and haematologic malignancies as shown in Table 2 below.

Table 2: Detection of NTRK gene fusions in various types of cancer

Tumor type	NTRK1	NTRK2	NTRK3	Tumor type	NTRK1	NTRK2	NTRK3
NSCLC		<1%-3%[6-8]		Glioblastoma (adult)	1%[19,20]	1%[21]	<1%[21]
Papillary thyroid	<12%[9]		2%-21%[10-12]	Non-brainstem high-grade glioblastoma (pediatric)		40%[22]	
Secretory carcinoma of salivary gland (MASC)			91%-100%[13-14]	Low-grade gliomas		<1%[7]	
Head and neck cancer		<1%[7]	<1%[7]	Pilocytic astrocytoma		3%[23]	
Sarcoma	<1%[7,15]			Mesoblastic nephroma			75%[3]
CRC		<1%[7,16]		Congenital fibrosarcoma			91%-100%[3,4]
Melanoma (spitzoid)	21%[17]			Infantile myofibroblastic tumor			3%[24]
Breast (secretory)			92%[18]	Cholangiocarcinoma	4%[25]		
Neuroendocrine tumor			<1%[27]	AML			<1%[26]

Notes : AML=acute myeloid leukemia, CRC=colorectal cancer, MASC=mammary analogue secretory carcinoma

1. Passiglia F. et al. Expert Opin Investig Drugs. 2016; 2. Bishop JA, et al. Hum Pathol. 2013; 3. Rubin BP, et al. Am J Pathol. 1998; 4. Knezevich SR. et al. Nat Genet 1998; 5. Tognon C, et al. Cancer Cell. 2002; 6. Vaishnavi A. et al. Nat Med. 2013; 7. Stransky N, et al. Nat Commun. 2014; 8. Suh JH, et al. Oncologist. 2016; 9. Greco A, et al. Mol Cell Endocrinol. 2010; 10. Leeman-Neill RJ, et al. Cancer. 2014; 11. Ricarte-Filho JC, et al. J Clin Invest.2013; 12. Prasad ML, et al. Cancer 2016; 13. Balanza R, et al. Lnt J Surg Case Rep. 2015; 14. Bishop JA, et al. Cancer Cytopathol. 2013; 15. Morosini D. et al. J Clin Oncol. 2015; 16. Ardini E. et al. Mol Oncol. 2014; 17.Wiesner T et al. Nat Commun. 2014; 18. Tognon C, et al. Cancer Cell. 2002; 19. Frattini V,et al. Nat Genet. 2013; 20. Kim J, et al. PLoS One. 2014; 21. Subramaniam DS, et al. ASCO 2017. 22; Wu G, et al. Nat Genet. 2014; 23. Jones DT, et al. Nat Genet. 2013; 24. Yamamoto H. et al. Histopathlology 2016; 25. Ross JS, et al. Oncologist. 2014; 26. Kralik JM, et al. Diagn Pathol. 2011; 27. Sigal D. et al. J Natl Compr Canc Netw. 2017.

A summary of the ongoing entrectinib studies is shown in Table 3 below.

Table 3: Summary of entrectinib clinical studies

Entrectinib Clinical Study	Study Design	Estimated Data Readout	Publications	Countries and Status
RXDX-101-02 (STARTRK-2)	Registration-enabling phase 2, global, multicenter, open-label, basket study	July 2018: DBL NTRK and ROS1 Nov 2018: CSR NTRK and ROS1	Case reports: NET-TRK: Sigal D, et al. *J Natl Compr Canc Netw.* 2017. Pancreatic Cancer-TRK/ROS1: Pishvaian M, et al. *ASCO-GI.* 2018. Sarcoma-TRK, ALK: Sant Chawla, et al. CTOS 2017. Thyroid cancer-ROS1: Liu SV, et al. *JCO Precision Oncology.* 2017. Interim: NSCLC-ROS1: Ahn MJ, et al. WCLC 2017.	US, UK, EU, Australia, and Asia: Ongoing
ALKA-372-001	First-in-human phase 1, multicenter, open-label, ascending-dose study with dose escalation	Published primary analysis; additional data cut TBC	Primary publication: Drilon A, et al. *Cancer Discov.* 2017. Case reports: CRC-TRK: Russo M, et al. *Cancer Discov.* 2016. CRC-TRK: Sartore-Bianchi A, et al. *J Nat Can Ins.* 2016. CRC-ALK: Amatu A, et al. *Br J Cancer.* 2015.	Italy: Ongoing
RXDX-101-01 (STARTRK-1)	Phase 1, multicenter, open-label, ascending-dose study with dose escalation	Published primary analysis; additional data cut TBC	Primary publication: Drilon A, et al. *Cancer Discov.* 2017. Case reports: Glioneuronal tumor: Alvarez-Breckenridge C, et al. *NPJ Precision Oncology.* 2017. ALM-ROS1: Couts KL, et al. *JCO Precision Oncology.* 2017. NSCLC-TRK: Farago AF, et al. *J Thorac Oncol.* 2015. MASC-TRK: Drilon A, et al. *Ann Onc.* 2016.	US and South Korea: Ongoing
RXDX-101-03 (STARTRK-NG)	Phase 1/1b, pediatric, open-label, dose escalation and expansion study	2019	Case reports: IMT-ROS1, ALK: Publication submitted Interim: ASCO 2018 abstract accepted	US: Ongoing

Notes: ALM = acral lentiginous melanoma, CSR = clinical study report, DBL = database lock, IMT = inflammatory myofibroblastic tumour, MASC = mammary analogue secretory carcinoma, NET = neuroendocrine tumour, TBC = to be confirmed

Of note, is that the pivotal registration enabling study RXDX-101-02 (STARTRK-2) is a single arm open-label basket study across multiple cancer tumours. Following the demonstration of activity with entrectinib in patients with NTRK, ROS1, or ALK fusions, in earlier phase I and Ib studies, it could be considered unethical to randomly expose these patients with any other treatment other than entrectinib. Such a trial design would also bias the results in favour of entrectinib and render the trial invalid, further precluding the use of such a trial design. Lastly, due to the rarity of NTRK 0.7% of solid tumours, ROS1 1.4% of NSCLC, or ALK fusions 3% of non SQ, advanced metastatic NSCLC (MSAC application 1250, pg 5), small numbers of patients would further hamper the ability to conduct a controlled clinical trial in these patients.

Therefore, the entrectinib clinical data package will be an interesting proposition for PBAC considering the Committee's preference for direct head-to-head randomised controlled trials (RCTs). Entrectinib further emphasises the need to consider how PBAC processes may be evolved to accommodate the evaluation of such data packages for subsidy considerations.

Of note, Roche has contributed to and is supportive of the submission made by Medicines Australia to the August special meeting of PBAC. In the interests of brevity and to avoid duplication of material submitted to the August PBAC meeting, we have not replicated material in the submission by Medicines Australia, rather have cross referred to it wherever appropriate.

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?

To clarify, when responding to Questions 1 and 2, Roche has interpreted 'multi-tumour listings' as one single PBS listing with broad clinical criteria sufficient to cover reimbursement of multiple tumour types.

- Reduced workload and efficiencies for Roche and other sponsors, evaluation groups, PBAC, PBAC Secretariat, Office of HTA, Department of Health, Department of Finance, Health Minister, Finance Minister and others in the preparation, evaluation, processing, assessment etc of individual submissions for individual indications for PD-1 and PD-L1 inhibitors. Therefore, it is possible that via multi-tumour listing(s), PD-1 and PD-L1 inhibitors will be made available to Australians in a more-timely manner than otherwise, and avoid the situation where the volume of work required for separate submissions for individual indications for PD-1 and PD-L1 inhibitors monopolises the capacity of the Australian reimbursement system.
- For patients with rare cancers, 'the current models for drug discovery, development and reimbursement are not designed in a way that delivers outcomes for these patients' (Rare Cancers 2017). Multi-tumour listings for PD-1 and PD-L1s would allow people with rare cancers (which can plausibly be treated with checkpoint inhibitors, where there is insufficient clinical trial information) to access reimbursed medicines in a way that is consistent with the National Medicines Policy, i.e., in a timely manner. While PBAC processes have been evolving over the years to include changes such as the MAP and 'pay for performance' pricing arrangements, some of these mechanisms could be further refined to assist with the potential volume of immunotherapy treatments and to address the inequity of access for rare cancer patients.
- Provide Australian prescribers broad access to PD-1 and PD-L1 inhibitors, thereby affording flexibility to apply clinical judgement on an individual patient basis, regarding choice and use of a PD-1 and/or PD-L1 inhibitor.
- Leverage uniqueness of the PD-1 and PD-L1 checkpoint inhibitors' mechanisms of action, which already have a demonstrated safety and efficacy profile across a number of tumour types, thereby affording a more efficient means of assessing cost-effectiveness.
- Earlier access to treatment through avoidance of the need to wait for mature evidence for indications where there is demonstrated clinical benefit (or plausibility of in rare cancers). Assumes rapid reimbursement is facilitated through an agreement to confirm cost-effectiveness thereafter (or for agreed outcomes to be met for rare cancers).
- Greater budget certainty for government and sponsors should methodology like Recommendation 1 from the Medicines Australia submission be adopted (i.e., follow-on indications over 3-years, with demonstrated clinical benefit are reimbursed for agreed numbers of patients via a cost-sharing agreement).

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?

- One disadvantage for the current consideration of multi-tumour listings for PD-1 and PD-L1 inhibitors is the uncertainty associated with such a proposal. Given the state of play of the available evidence for PD-1 and PD-L1s, there would be considerable uncertainty in the consideration of multi-tumour listings, especially regarding the identification of the types of patients likely to gain the greatest benefit from treatment.
- Misalignment between regulatory and reimbursement processes and timelines. The expedited access solutions proposed in this paper may present challenges such as; reimbursed access being provided prior to marketing authorisation which could undermine the regulatory process, enabling access to a medicine for an indication which it has not yet been deemed safe and effective by the regulatory body and creating compliance issues relating to promotional activities. Specifically, clinician/patient education and choice would be hampered by the fact that a sponsor could not discuss unapproved indications.
- Limitations of the current regulatory framework as outlined in Section s101 (3A) of the National Health Act are a further disadvantage, i.e.:
  '(3A) For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of drugs and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations'. Therefore, there is presently a paucity of evidence from which to 'compare the effectiveness and cost' of PD-1 and PD-1s for the specific purpose of multi-tumour listings.
- Likewise, section s101 (3B) of the National Health Act states:
  '(3B) Without limiting the generality of subsection (3A), where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee: (a) shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies; and (b) if the Committee does recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part, the Committee shall include in its recommendation a statement that the Committee is satisfied as mentioned in paragraph (a).' Further highlighting that should PD-1 and PD-L1 inhibitors be 'substantially more-costly than an alternative therapy or alternative therapies' that robust evidence is required to support a claim of 'significant improvement' across all possible tumour types which may be included in a multi-tumour indication.
- In summary, it would seem that change to the current regulatory and reimbursement framework will be required to enable consideration of multi-tumour listings for PD-1 and PD-L1 inhibitors and that such a change would require considerable time, thereby delaying access to treatment.

- Lastly, while government budgets are constrained and it is possible that investing in multi-tumour listings for PD-1 and PD-L1s may preclude investment in other medicines; the converse may also be true in that the competitive nature of this class of drugs may avail government of a highly attractive price for multi-tumour listings for PD-1 and PD-L1 than they would have secured otherwise. Similarly, there may be learnings from funding PD-1 and PD-L1s which can be applied to other multi-indication classes of drugs.

Question 3

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

- These questions are best informed by clinicians, patients and patient organisations who have a first-hand lived experience of urgent unmet need. It is Roche's understanding that the perspectives of these important stakeholders has been sought and will be provided to inform PBAC's consideration at their August meeting. We have also posed this question to numerous eminent Australian oncologists and they have made the following comments:
    - 'An area where chemotherapy/actionable mutations are lacking,
    - 'Triple negative breast cancer (TNBC), upper gastrointestinal cancers, first-line non-small cell lung cancer (NSCLC) combination therapy',
    - 'PD-L1+ diseases, genitourinary (GU), TNBC, penile, microsatellite instability (MSI) high, head and neck',
    - 'Tumour streams where there is clear checkpoint inhibitor activity but no available (approved) therapy – glioblastoma multiforme (GBM), central nervous system (CNS), bladder, upper gastrointestinal (GI), pancreas, TNBC',
    - 'Rare diseases where limited data or lack of Pharma/PBS enthusiasm',
    - 'Rare cancers, cervix, diseases where there is no current standard of care (SOC)',
    - 'patients that are underserved by current SOC treatment – e.g. rare cancers, pancreatic, TNBC',
    - 'Any disease where there is good Phase III evidence (Phase II for rare diseases) that cancer immunotherapy is showing benefit',
    - 'GU, head and neck, upper GI',
    - 'Rare cancers, GI, mesothelioma, pancreatic, MSI-high patients',
    - 'All of the current FDA approved agents',
    - 'KRAS mutant group is an unmet need and other GI carcinoembryonic antigen (CEA) expressing cancers' and
    - 'WRT GI cancers: MSI group and later line CRC'.
- As per the Medicines Australia submission, Roche proposes that the established criteria such as the ESMO Magnitude of Clinical Benefit Scale (Cherny 2018) is used and that alignment with the TGA's criteria for expedited pathways is sought wherever possible (TGA 2016).

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?

As discussed above, and in **Question 12** below, Roche offers suggestions on two methods via which PD-1 and PD-L1s could be most appropriately PBS subsidised, i.e., a refined *status quo* HTA process where data are available, and a shared funded access mechanism where data are collected prospectively to confirm the biological rationale and confirm effectiveness.

- The minimum level of evidence of effectiveness in situations where data are available should remain as per a refined *status quo* process*;* consistent with PBAC's decision making and the current wording of the National Health Act which states the requirement for '(3A)…..comparing the effectiveness and cost of that therapy with that of alternative therapies…'. The minimum level of evidence is not currently prescribed to a specific type or design of a clinical trial etc. And Roche proposes that this flexibility should remain as it may be that in certain situations and diseases, different types of evidence will allow PBAC to make their comparative assessment with an acceptable level of certainty, for example a Phase II RCT against an appropriate comparator may fulfil PBAC's needs. Furthermore, specifying a minimum level of evidence for PD-1 and PD-L1s under the current PBAC process would be inconsistent with how other medicines are assessed.
- Under the shared funded access model, there are two critical questions to answer regarding the minimum level of evidence; one, the evidence required to demonstrate the initial biological rationale for use of a PD-1 and/or PD-L1, and two, the evidence to confirm the effectiveness after commencement of funded access. As discussed in **Question 12** below, Roche is aware that the evolution of the current PBAC processes will be the subject of ongoing discussions and as such we have provided suggestions for consideration and reiterate that we are very keen to be involved in the co-creation of solutions to this challenge.

Roche have sought to understand the perspectives of Australian clinicians regarding this question and have posed this question to numerous eminent Australian oncologists during recent interactions. The clinicians surveyed have not provided a definitive minimum level of evidence required for consideration of subsidy of PD-1 and PD-L1s, rather their preferred level of evidence varies according to the tumour type, rapidity of progression and rarity of disease. Consistent with the objectives of the National Health Act (comparing the effectiveness and cost of that therapy with that of alternative therapies), several oncologists have noted the importance of evidence being generated relative to the SOC. Thus, the opinions of the surveyed clinicians are consistent with Roche's position articulated above and the current regulatory and reimbursement framework when it comes to the level of evidence required for subsidy. Specific statements made by those surveyed are provided below:

- 'PFS at the minimum. A favourable QoL to current SOC',
- 'OS, greater than 3 month PFS benefit',
- 'OS is what we'd prefer however substantial PFS benefit (depending on the tumour type) should be the default',
- 'PFS although depends upon the tumour stream- some will need ORR vs PFS for example',
- 'Need good quality Phase II or III level evidence of effect. For rarer cancers, high response rate may be sufficient',

- 'OS is preferred but a good PFS in rapidly progressing disease is also significant',
- 'Indication of definitive activity (i.e. Phase III study). Currently all checkpoint inhibitors appear to be equi-effective but there are no head-to head studies that demonstrate they are the same',
- 'Positive Phase III trials with favourable OS. For rarer diseases, Phase II with meaningful PFS benefits',
- 'Generally speaking it should be efficacy/QoL benefits vs SoC',
- 'Phase III Level A evidence. Published in leading journal',
- 'OS ideal - landmark benefits (12 and 24 months). Time to next treatment is also becoming very important' and
- 'The current evidence at least for MSI group in GI cancer (and others) is compelling based on the long survivors. If we are looking at HR's then I think the current target is closer to 0.6 in most peoples' minds, but the 'tail' is also important as above'.

Question 5

Do you/your organisation think it is possible for the PBAC to be able 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?

As above Roche have sought the perspectives of Australian clinicians regarding this question; the conclusion from the vast majority is that it is <u>not generally appropriate</u> to make such extrapolations across lines of therapy or to cancers without any pivotal data at the present time. It may be appropriate to extrapolate in the following instances:

1. Clear pivotal data is available for a PD-1 and/or PD-L1 in a specific population and other PD-1 and/or PD-L1s have some data (e.g. phase II) indicating a similar profile (this assumes that all PD-1 and PD-L1s are the same despite the absence of head to head data).
2. One PD-1 and/or PD-L1 is already PBS listed and another has pivotal data but not TGA indicated yet in that indication

Specific comments made were:

- 'No, limited data',
- 'No, evidence too immature',
- 'No',
- 'Not across the board - would consider this for an identified driver mutation (example given - BRAF mutation for squamous head and neck cancer, patient privately funded CIT)',
- 'Not really. Different diseases behave differently to immunotherapies, melanoma vs lung is a good example of this',
- 'more comfortable extrapolating across cancers / lines of cancer with a targeted therapy and an identified driver mutation (i.e. same biology) e.g. BRAF, HER2+, NTRK, ALK, etc. The biology for the use of checkpoint inhibitors is not conserved across different cancer types – some cancers are unresponsive ('cold')',
- 'No',
- 'Definitely not at this stage. Toxicity concerns are particularly relevant when considering early disease vs late disease',

- 'Obviously not at this stage'
- 'No, particularly difficult to extrapolate from late to early disease' and
- 'Also questions a pan indication for all GI CEA expressing cancers (pancreatic, gastric, CRC or other CEA expressing tumours like lung)- a large basket trial for CEA expressing cancers, first and later line, atezolizumab + T-cell bispecific antibody (TCB), atezolizumab + TCB + chemotherapy?' and
- 'Yes for the identified subgroups in cancer, again MSI example. By stage I think is different outside these defined groups.'

- Importantly, the oncologists we spoke to emphasised that it would be highly inappropriate to extrapolate evidence on PD-1 and/or PD-L1s from tumour types which are known to be immunogenic (i.e., 'hot tumours') to tumours where there is no evidence of PD-1 and/or PD-L1s working (i.e., 'cold tumours'). This is not considered to have clinical plausibility.
- Whilst most clinicians were not currently in favour of extrapolating evidence, it is relevant to recall that the current evidence base on PD-1 and PD-L1s is immature, rapidly evolving and will soon increase exponentially based on the findings of the horizon scan described earlier in this submission. This was noted by the oncologists we spoke to.
- Therefore, it is Roche's position that great care should be taken when considering extrapolating or applying 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. One needs to ensure clinical plausibility of effectiveness exists for the tumour type(s) of interest and that the data to support such extrapolation is sufficiently robust, which at present may not be the case; however, this may not always be the case given the voluminous and rapidly evolving nature of clinical development in this therapeutic area. It demonstrates that this may provide an idea situation for a MAP.

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?

Sections101 (3A and 3B) of the National Health Act state:

'(3A) .. the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies…

(3B) …substantially more costly than an alternative therapy or alternative therapies…shall not recommend … unless …. provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies…'

Nowhere in the Act does it state that an economic model is required to demonstrate cost-effectiveness, neither is a model specific to a particular type of cancer required by the legislation. One of the strengths

of the Australian reimbursement system, which many stakeholders are particularly proud of, is the fact that it is a pragmatic system with no fixed cost-effectiveness threshold or approach to determining cost-effectiveness. Thus, it must be plausible that PBAC are able to satisfy themselves that a PD-1 and/or PD-L1 is cost-effective without an economic model specific to the kind of cancer under consideration.

As noted elsewhere in this submission the clinical development of PD-1, PD-L1s, other cancer immunotherapies and other products with multiple cancer indications is rapidly evolving via the use of innovative approaches such as adaptive trial design and platforms. Therefore, reimbursement systems are also going to need to adapt as clinical trial datasets of head to head, RCTs from which traditional economic models are built could soon be a thing of the past.

The PBAC's special meeting in August 2018 examining subsidy of PD-1 and PD-L1 checkpoint inhibitor immunotherapies for multiple cancer types provides an excellent opportunity to capitalise on the rapid evolution in clinical trial design and clinical practice in oncology. This meeting is a platform for change to alter the Australian reimbursement system such that it is prepared to evaluate the tidal wave of forthcoming innovative treatments, their combinations with new and existing agents and pairing with new and existing diagnostic tests and biomarkers.

A specific example of an innovative clinical trial design from which signals and confirmation of clinical plausibility of PD-1, PD-L1 and other cancer immunotherapies can be derived is a 'basket study'. An example of a 'basket study' is provided in the **General overall comments – entrectinib** section above and further detail on innovative clinical trial designs is provided in response to **Question 13** below. Such trials often include many tumour types and while efficacy from such a trial may not have historically been approximated via a single economic model, there is no reason why this cannot be done. Cost-effectiveness analyses are typically assessed as the average incremental benefit and cost across a cohort of patients; therefore, it seems reasonable that cost-effectiveness could also be established via a weighted average of incremental benefit and cost across a 'basket' of tumour types.

It is also pertinent that of the Australian oncologists with whom we discussed subsidy of PD-1 and PD-L1s for multiple cancer types, the following unprompted comments were made:

- 'Grouping different cancer types together based on particular characteristics would be very tricky',
- 'In the future it may be possible to group different cancer types together based on particular mutational profile. As personalised medicine advances with more attainable technology (e.g. comprehensive genomic profiling with tests such as Foundation One etc), tumour types may prove to be more similar than different' and
- 'Tumours could be grouped based on genomic profile or immunogenic markers'.

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?

The two methods which Roche proposes for PD-1 and PD-L1s to be PBS subsidised are intended to apply to all cancer types, irrespective of the magnitude of benefit conferred by PD-1 and/or PD-L1s. That is, a refined *status quo* HTA process where data are available, and a shared funded access mechanism where data are collected prospectively to confirm the biological rationale and confirm effectiveness are both aligned with the current legislation where a cost-effective price is agreed between government and the

sponsor. Thus, the effectiveness and cost of therapy is intended to be compared to alternative therapies (3A) and any incremental cost is consistent with the incremental benefit (3B) (as summarised from the National Health Act).

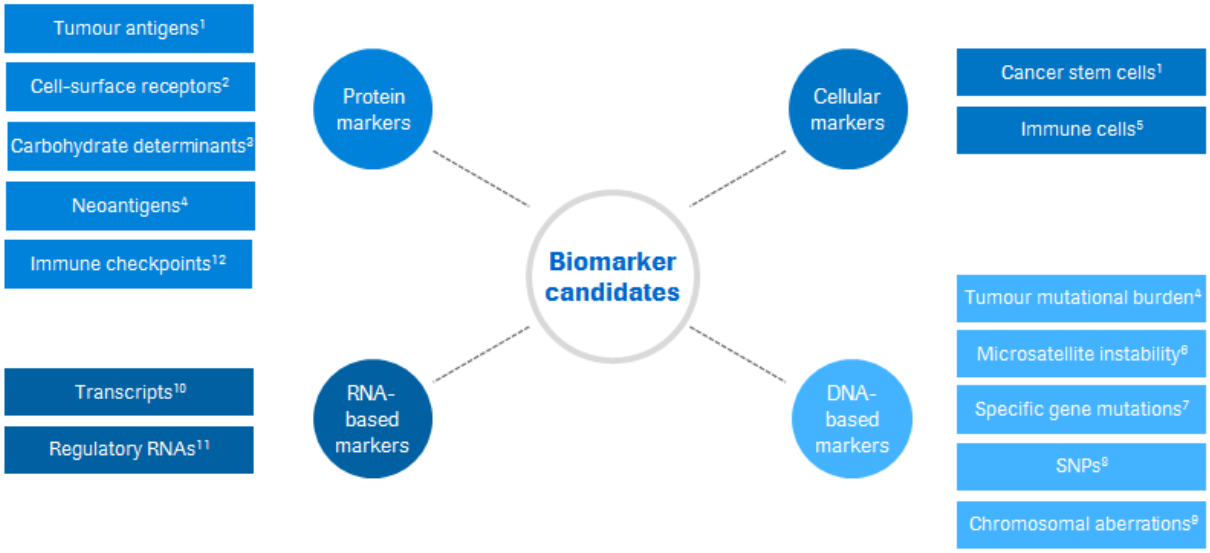
[redacted]

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?

Roche agrees with the general consensus that a single ideal biomarker to confirm clinical utility of PD-1 and PD-L1s is yet to be identified. This is discussed in the letter from the PBAC chair, which states *'..results for different immunotherapies have been inconsistent as to whether it is necessary to classify patients by PDL1 tumour marker expression'* (PBAC letter February 2018). There are clear limitations with the current PD-L1 test including the absence of a discrete cut-off and different proprietary test offerings. However, whilst acknowledging that the ideal biomarker is yet to be identified, there is consensus that biomarkers are indicators that can be used to predict outcomes for individual patients and as indicators of response to a specific individual treatment. There is great expectation surrounding this issue as reflected in the numerous 'potential' biomarker candidates that already exist and the innumerable number under investigation with a view to fulfilling these goals (Figure 7).

Figure 7: Potential biomarker candidates



Source: 1 = Bhatt AN, et al. Indian J Med Res 2010; 2 = Elliott S, et al. Ann Hematol 2014; 3 = Cazet A, et al. Breast Cancer Res 2010; 4 = Snyder A, et al. N Engl J Med 2014; 5 = Morse MA, et al. Am Soc Clin Oncol Educ Book 2013; 6 = Sideris M and Papagrigoriadis S. Anticancer Res 2014; 7 = de Mello RA, et al. Pharmacogenomics 2013; 8 = Yang IA, et al. J Thorac Dis 2013; 9 = NCCN Guidelines – Chronic myelogenous leukemia v1 2016; 10 = Yi Q and Tang L. Curr Drug Metab 2011; 11 = Liloglou T, et al. Cancer Lett 2014; 12 = Chen DS, et al. Clin Cancer Res 2012

As highlighted via entrectinib (**General/overall comments**), conserved biology, through identification of a driver mutation such as NTRK, BRAF, etc. with demonstrated (high) activity in matched biomarker inhibition across multi-tumours (e.g. basket study) would indicate the potential for a tumour agnostic listing in the presence of an identified driver mutation.

A range of techniques are available for biomarker detection in cancer immunotherapy and the development of these is quite enormous and fast paced:

- **Immunohistochemistry (IHC):** Detects the quantity and distribution of specific proteins within the sample.
- **Quantitative polymerase chain reaction (qPCR):** Measures expression of genes (RNA) or specific mutations by amplifying cellular DNA; by detecting with fluorescent dyes.
- **Next-generation sequencing (NGS):** Modern parallel sequencing technique that allows comprehensive characterisation of all relevant mutation types and affords high sensitivity for somatic mutations. Roche Foundation Medicine's suite of comprehensive genomic profiling tests are examples of this (e.g. Foundation One).

Roche has established Roche Foundation Medicine with a commitment to advancing the science of cancer immunotherapy, via a deep understanding of tumour biology and immune biomarkers. Roche Foundation Medicine's comprehensive genomic profiling test, Foundation One, uses a hybrid capture based NGS technology to sequence the entire coding regions and select intronic regions of cancer-related genes. The use of NGS technology allows Foundation Medicine's assays to detect the full range of genomic alterations: insertion/deletion events; base pair substitutions; copy number alterations (aka copy number variations); and gene rearrangements.

The use of genomic testing to inform cancer care is increasing in clinical practice, single-gene or

multi-gene 'hotspot' panels are the most common approach to genomic testing today, however these approaches have limitations such as:

- They are not as accurate (sensitive and specific) as hybrid capture-based NGS tests, meaning some patients will test negative for biomarkers that are actually present in the tumour
- Limiting the number of genes analysed and / or limiting analysis to certain coding areas of specific genes means that alterations outside of these focus areas are missed, meaning that patients may miss out on potentially effective therapies; and
- Limiting analysis to a small number of genes means that potentially clinically relevant information like Tumour Mutational Burden (TMB) is not assessed or requires a separate test.

As per previous questions, Roche have sought to understand the perspectives of Australian clinicians regarding this question. Among these clinicians there is some interest in DNA based markers influencing the overall mutation load such as TMB and MicroSatelite Instability (MSI), which have been demonstrated to influence the response to cancer immunotherapy across a variety of tumour indications. However, those surveyed also noted that the current biomarkers are suboptimal, stating:

- 'No current biomarkers provide conclusive efficacy benefit for all patients across tumour types',
- 'Not for all patients but a good starting point would be PD-L1 high patients, MSI high patients, high TMB patients,
- 'Maybe, if you could prove that the biomarker is accurate. Right now the evidence suggest that it is too early to definitively choose an optimal biomarker',
- 'Biomarker evidence to date has been very varied across tumour types. Could be a role for Foundation Medicine (or similar comprehensive testing)',
- 'Not yet, MSI-high is looking promising though',
- 'No good biomarker currently exists – TMB may have some utility. Neither TMB nor PD-L1 identifies a patient population that either responds or does not (there are responders with low TMB and low PD-L1 expression) but they can both enrich the population of responders. MSI could be a pan-cancer biomarker for cancer immunotherapy, but it is for a very small number of patients',
- 'Not at this point. The best reference might be MSI-high patients',
- 'Likely to be TMB-high patients',
- 'TMB high and MSI high are the most promising biomarkers at this point',
- 'Not PD-L1. Patients could potentially be grouped based on TMB and MSI. The microbiome is also emerging as an important consideration'
- 'As a starting point PD-L1 high pts do receive more benefit',
- 'MSI for GI cancers, CEA, TMB possible for PDL-1' and
- 'MSI (for GI cancers)'.

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.

As per Question 5 above, Roche have sought to understand the perspectives of Australian clinicians regarding this question; their collective assessment is that the products generally appear to be similar but the data to inform this are immature and/or incapable of guaranteeing this presently. Some of their comments were:

- 'Yes',
- 'Not yet, although seems they are broadly similar',
- 'No, I believe that there are differences between products and as more trials readout this will become evident. Many factors, including trial design and patient populations are driving factors in determining efficacy',
- 'Still in the dark based on the current evidence. Too many variables including cross-trial comparisons, patient populations',
- 'No indication currently that checkpoint inhibitors are different, but no definitive evidence (i.e. a head-to-head) to suggest that they are the same',
- 'Again, too early to suggest all class agents behave the same. Evidence from NSCLC suggest this is not the case',
- 'Too early based on current evidence',
- 'Not at this point',
- 'No. Even nivolumab and pembrolizumab are emerging as different. Avelumab is proving to be different to other PD-L1 inhibitors as well. AE differences are also emerging - PD-1 vs PD-L1 pneumonitis rates',
- 'all PD-L1 and PD-1s are the same and would use them interchangeably across all tumour types and stages of disease and thinks his colleagues would do the same' and
- 'the activity in lung in PDL1-ve tumours is interesting, hypothesis generating. Melanoma I am not sure, just started the trial, so will see'.

There is also the patient perspective to consider here. One clinician we spoke to commented that his:

- 'first preference to use products which he has trial experience with, secondly products where the evidence exists BUT he would do whatever he needed to in order to get the cheapest access to an immunotherapy for a patient who needed one'.

This same oncologist noted:

- 'patients want access to these products faster than any others before, principally driven by the growing understanding that they work across a range of tumour types' and that 'the risks of serious adverse events (i.e., doing harm) with immunotherapies is so low that it is very difficult to justify NOT using them, even in the absence of evidence and especially when patients have no alternatives and are asking for them'.

[redacted]

[redacted]

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?

As discussed above, Roche have suggested a shared funded access mechanism be applied in situations such as rare cancers where a biological rationale exists for efficacy of PD-1 and/or PD-L1s. This would enable timely access to treatment for the very small numbers of patients with rare cancers where traditional comparative effectiveness data is not available to inform a standard HTA. After commencement of such an access mechanism, fit-for-purpose data would then be collected prospectively to confirm the biological rationale and effectiveness of the particular PD-1 and/or PD-L1 in the specific rare cancer of interest. Roche have presented a range of ideas for the operationalisation of such an early access mechanism in response to **Question 12** below.

To clarify, it is particularly important that a realistic and pragmatic approach is taken to considering the available clinical evidence for rare diseases, as it will frequently not be possible to develop 'gold standard' evidence in small populations. Evaluation tools that allow transparent consideration of clinical, economic, societal and ethical factors in funding decisions; and a pragmatic approach to evidence could all assist in resolving access delays. Roche suggests that via the agreed, prospective collection of evidence described under the shared funded access mechanism it will be possible to confirm the effectiveness of PD-1 and PD-L1s in a given rare cancer. Thereby adhering to the intent of the current legislation which requires an assessment of the 'effectiveness and cost of therapy' and 'comparing the effectiveness and cost of that therapy with that of alternative therapies' (3A).

Whilst it is not clear if there is a single solution for addressing the nexus between unmet clinical need and sufficient available evidence for rare cancers; there is a case for a pragmatic view by the PBAC in examining very early evidence for medicines that could be used by patients with rarer conditions.

One option which PBAC might like to explore further is the 'right to try' model as used in the United States. This model allows terminal patients to access medicines based on Phase I data as the medicine is being submitted to the FDA. A modified version of this model could be adapted to the Australian system to allow early access for patients with a terminal diagnosis to Phase I or Phase II medicines that have not yet completed trials, and have not yet been approved for use.

As there is likely to be a smaller patient pool with limited comparator options, the issue of cost-effectiveness could be addressed through a tiered model based on the clinical trial results, and aligned with the proposed MAP for confirming effectiveness.

Roche have also sought comment from Australian oncologists on this question and they have identified the issue of small patient numbers precluding the conduct of large clinical trials in rare cancers. They note that the smaller numbers of patients should lessen the concern regarding the cost of treating these patients. Their specific comments included:

- 'Difficult to answer with low patient numbers. Broader access to these patients would be ideal',
- 'Very difficult given low patient numbers for large clinical trials to determine efficacy benefits',
- 'Absolutely, rare cancers do need broader access to cancer immunotherapies. It is difficult to establish cost-effectiveness given lower patient numbers but we should be less cautious in

weighing up cost/benefit in this population',

- 'Very difficult with low patient numbers. There should be a lower stringency and broader access. Newer trials and better design - including surrogate endpoints outside of OS could be used for cost-effectiveness',
- 'Yes, because you are not going to be able to run a large, randomised Phase III trials in a rare cancer population. Basket studies based on genomic profiling were considered to be a reasonable evidentiary target. This is more for targeted therapies than checkpoint inhibitors',
- 'Always going to be difficult based on an incremental cost effectiveness ratio (ICER). Phase II data at the minimum, and where possible a favourable toxicity profile vs the current SOC',
- 'Yes lower patient numbers should mean lower level of evidence',
- 'A lower evidentiary requirement should be required. An expanded access program with the collection of RWD might be a measure'
- 'It is a very important aspect. Political reasons and lobbying from rare cancer groups are proving extremely important. A government funded expanded access program would be ideal. The MRFF (Medical Research Future Fund) is a pool of money that could be utilised', and
- 'The International Rare Cancers Initiative (part of COSA) will prove to be very important in demonstrating cost-effectiveness at a global level. Suggests more trials in rare cancers with valid endpoints to really validate this point'.

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.)

No. Roche is supportive of an equitable reimbursement process in Australia and has made two suggestions for PD-1 and PD-L1 subsidy in this submission which are consistent with an equitable reimbursement process. These are; one, a refined *status quo* HTA process and, two, enabling a new shared funded access mechanism which can operate within the current regulatory and reimbursement framework and objectives of the existing legislation, that is, via confirmation of effectiveness at a later date.

The means by which PBAC operationalise their assessment of PD-1 and PD-L1 submissions via either method suggested by Roche is an issue for PBAC. However, given the fast paced nature of clinical development and rapidly changing clinical practice in this therapeutic area, one would expect that PBAC will need to consider submissions for PD-1 and PD-L1s more frequently than just once per year. As noted in the Medicines Australia submission, it may be necessary for PBAC to hold one special meeting per year to review evidence collected as part of the MAPs.

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?

In summary, this paper provides suggestions on two methods via which PD-1 and PD-L1s could be most appropriately PBS subsidised. These suggestions are:

1. In situations where data are available or expected to become available, to inform a standard HTA, the current approaches to HTA are applied. That is, explicit changes to the existing regulatory and reimbursement framework for medicines are not required, rather a refined *status quo* process is developed. Nonetheless, in order to expedite patient access to PD-1 and PD-L1s and other innovative treatments with rapidly evolving clinical development pathways and addressing high unmet clinical needs, Roche is proposing pragmatic application of guidelines such as the TGA/PBAC parallel process guidelines (see 'Quick wins' described in **Question 16** and examples provided below). Roche also suggests that in light of the speed and rapid evolution of the clinical development pathways for PD-1 and PD-L1s that a pragmatic approach to the inherent uncertainty will also be required.

2. Where there are no data currently available nor are there ongoing data collection projects underway to inform relative effectiveness via a standard HTA BUT a biological rationale exists for efficacy (e.g., clinical plausibility, existence of a biomarker, an alternate PD-1 and/or PD-L1 checkpoint inhibitor immunotherapy has shown benefit in a particular tumour/patient type etc) then Roche is proposing that timely shared funded access to PD-1 and PD-L1 checkpoint inhibitors is made available until evidence is generated to confirm effectiveness.

Roche is mindful of the current regulatory framework as set out in Sections101 (3A and 3B) of the National Health Act:

'(3A) For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of drugs and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations.

(3B) Without limiting the generality of subsection (3A), where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee: (a) shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies; and (b) if the Committee does recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part, the Committee shall include in its recommendation a statement that the Committee is satisfied as mentioned in paragraph (a).'

And as noted in the PBAC Background to invitations for submissions:

'4.4 Any options put to the Minister will also need to meet the core objectives of the Australian Government HTA framework and take into account the role of the Therapeutic Goods Administration in approving medicines for marketing in Australia, whilst allowing the PBAC to meet its statutory

obligations. Those obligations are set out in Section 101 of the National Health Act 1953….

4.5 …. Any process designed to fast track / accelerate access will need to be integrated within the existing regulatory and reimbursement framework for medicines and will necessarily require additional resources, timeline flexibilities and new criteria for engagement with all stakeholders'.

Therefore, in situations where data are available or expected to become available to inform a standard HTA Roche sees that it is possible for PD-1 and PD-L1s to be subsidised while; meeting the core objectives of the Australian Government HTA framework, taking into account the role of the TGA in approving medicines for marketing in Australia, and allowing the PBAC to meet its statutory obligations. That is, explicit changes to the existing regulatory and reimbursement framework for medicines are not required and a refined *status quo* process is established. Nonetheless, in order to expedite patient access to PD-1 and PD-L1s and other innovative treatments (such as entrectinib, see **General/overall comments** above) with rapidly evolving clinical development pathways and addressing high unmet clinical needs, Roche is proposing pragmatic application of guidelines such as the TGA/PBAC parallel process guidelines and streamlining of the MAP process (see 'Quick wins' described in **Question 16** and individual product examples provided below).

In order for PBAC to make PD-1 and PD-L1s available in a manner which is congruent with their speed of clinical development, it will be necessary for PBAC to demonstrate pragmatism in their approach to dealing with uncertainty. Such pragmatism may extend to subsidy prices (see **Question 7**) and acceptance of innovative outcome measures such as time to next treatment (TNT). This new surrogate marker is an example of a therapeutic medical decision and is increasingly gaining acceptance among the clinical community as a valid measure to be used in lieu of OS data (Marshall 2016).

Whereas, where there are no data currently available nor are there ongoing data collection projects underway to inform relative effectiveness BUT a biological rationale exists for efficacy (e.g., clinical plausibility, existence of a biomarker, an alternate PD-1 and/or PD-L1 checkpoint inhibitor immunotherapy has shown benefit in a particular tumour/patient type etc) then Roche is proposing that timely shared funded access to PD-1 and PD-L1 checkpoint inhibitors is made available until evidence is generated to confirm effectiveness.

While PBAC processes have been evolving over the years to include changes such as the MAP and 'pay for performance' pricing arrangements, some of these mechanisms could be further refined to assist with the;

- volume and speed of clinical development for PD-1 and PD-L1s (and other treatments in the future)
- to capitalise on the broadly similar safety profile of PD-1 and PD-L1s across indications
- profile of responses showing durable benefit and OS improvement across tumour types
- improve efficiencies through PBAC, clinician, patient, sponsor and other stakeholder 'familiarity' with the class
- tension created between patients' expectations of faster access, especially for subsequent indications
- alignment between the new TGA streamlined pathways and reimbursement pathways
- requirement for long-term follow-up data in order to reduce uncertainty and enable funding in a

health care system where clinicians and patients are continually demanding faster access
- address the inequity of access for rare cancer patients.

Roche is mindful that there are many ways by which the current PBAC processes could be evolved to best achieve the objectives of the National Medicines Policy as it relates to PD-1 and PD-L1s and that it is likely that this will be the subject of ongoing discussions. Roche is very keen to be involved in the co-creation of solutions to this challenge and to this end offers several ideas below for consideration by PBAC at their August special meeting.

In the interests of brevity and to avoid duplication of material submitted to the August PBAC meeting, we have not replicated the two recommendations outlined in the submission by Medicines Australia, which Roche has contributed to and is supportive of. In brief, these can be summarised as follows:

Recommendation 1: Follow-on indications which are the subject of RCT-based checkpoint inhibitor development

A streamlined process for reviewing subsequent indications:

1. Initial full Health Technology Assessment (HTA) performed on lead indication.
2. Follow-on indications over subsequent 3-years, with demonstrated clinical benefit are reimbursed for agreed numbers of patients via a cost-sharing agreement.
3. Deed specifies requirements for subsequent determination of cost-effectiveness.
4. Post-listing cost-effectiveness verification occurs across multiple indications at the end of the agreement period (i.e. Year 4).

Recommendation 2: Rare cancers which can plausibly be treated with checkpoint inhibitors, but have insufficient data

An access model for patients with rare cancers:

1. Plausibility of activity must exist.
2. Establish a modified pay-for-performance structure where; treatment criteria, outcome measure, minimally important improvement, outcome for continued reimbursed access, outcome assessors, method of data collection and cost sharing, are all agreed prior to enabling access.

Roche's own ideas for consideration by PBAC at their August special meeting are as follows:

- Access would be restricted to a limited patient population for a finite period of time
    - Could include rare cancers
    - Not limited to certain diseases; therefore, equitable
- Ongoing evidence could be collected via a registry (i.e., broader in scope than current MAP) which cites a firm preference for RCT evidence (http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-

managed-entry-scheme-for-PBAC-submissions)

- MES states: *'there is a randomised clinical trial (or comparable 'fit-for-purpose' evidence), due to report within a reasonable timeframe, which the PBAC is satisfied will resolve the identified area of uncertainty'*. Whereas, this proposal would operate in an environment of greater uncertainty where it may not be possible for all stakeholders to be 'satisfied' that the forthcoming evidence will resolve the area(s) of uncertainty.
- Registry could be a national registry established through a multi-stakeholder collaboration with the involvement of; government, clinical and academic groups and pharmaceutical companies, each of whom can contribute to its funding and share the outputs
  - Registry could be accessed by pharmaceutical companies on a subscription type basis, e.g., user pay or financial contribution linked to revenue
  - Registry fees to be reviewed as appropriate
  - Similar to the cancer registry in Italy
  - Could be run as a pilot
  - Would be a significant database and place Australia on the world stage in terms of evidence generation
  - Would need all sponsors to take consistent approach
- Pharmaceutical companies could contribute to a project to facilitate co-ordination of existing registries; thereby harnessing existing data sources which may not currently be optimally accessed; thus, contributing to the greater public good of society. Such an example already exists in the OPAL registry (http://www.clinexprheumatol.org/article.asp?a=8532)
- Would need to consider data transparency and ownership issues

- Ongoing evidence could be collected via a clinical trial.
  - Including:
    - An ongoing clinical development trial by the respective pharmaceutical company(ies) and/or
    - Funded via a Medical Research Futures Fund (MRFF) or National Health and Medical Research Council (NHMRC) grant – linking research funding (MRFF/NHMRC) in the short-term while additional data are being collected to support long-term sustainable funding (PBS) upon the availability of further evidence.
  - Patients who are shown to respond move from trial funded access to PBS funded access. This could be done on an individual patient basis for rare cancers eg MOST study (https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/clinical-genomics/sydney-genomics-collaborative/gcmp). Learnings regarding individual patient use could be gained from the Department of Veterans Affairs program for access to medicines for veterans and the National Blood Authority program for blood products.
- Would need agreement on endpoints to assess efficacy and the timing of their collection
  - Could use duration of treatment as a proxy for efficacy
  - Could assess data prospectively and retrospectively
- Access to shared funded treatment would most likely be provided before TGA approval (especially if access was via a clinical trial) (i.e., earlier than current MAP pathway)
- Ongoing evidence may be evaluated in the form of a post-market review, i.e., every 12 months

at an annual PD-1 and PD-L1 meeting of PBAC

- Funding of early access to treatment could be shared by; Pharmaceutical company, Government, Hospital and/or patient.
    - Develop a deed of agreement to cover this shared arrangement
    - Could be linked to e-health records
    - Prescribers/patients would only be allowed access to treatment if they agreed to the data collection project
    - Patient cost capped
- Once data is available to demonstrate effectiveness companies may choose to seek a price increase for a particular indication if justified by the evidence OR to build upon newly created evidence to extrapolate use into another unregistered indication
- Should data not support a price increase or maintenance, then price would be decreased
- Biomarkers to be employed wherever possible in evidence generation projects
    - Use of biomarkers will inform types of patients likely to benefit the most
    - Comprehensive genomic profiling (for example Foundation One®) to be used to ensure accuracy and reproducibility of the test results
- Consider a system where not only PBAC are the evaluators of data collected via such an evolving system, rather bodies such as NHMRC, Clinician groups and academic institutions may be involved.

Answers to the specific questions posed are generally covered above but to assist readability, brief answers are provided here:

- Should sponsors be required to collect more evidence?

When limited evidence is available at the time of subsidy, Roche agrees that more evidence should be collected by the sponsor in order to confirm effectiveness. Several ideas are proposed to fulfil the requirements of the current regulatory framework which mandates that the PBAC 'compare the effectiveness and cost of that therapy with that of alternative therapies'.

- What should happen if the new evidence shows the medicine is less effective or has greater safety risks than expected?

Agreements should be made at the outset between all stakeholders to cover all possible eventualities from a shared funded access mechanism. Such agreements should not be limited to sponsors and government only but include prescribers and patients and cover all eventualities, including where clinical equipoise exists and ethical decision making would dictate that treatment cessation is required. Likewise, the implications of new evidence on pricing should be agreed in advance and it is Roche's position that sponsors and Government should be willing to adjust price up and down accordingly.

- 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?

Roche has consistently stated throughout this submission that all medicines funded on the PBS should be subsidised at a price commensurate with their benefit.

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?

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Question 14

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

Please refer to Question 15

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?

The Medicines Australia submission presents findings from an extensive review of international methods for multi-tumour subsidy and as such Roche has not re-presented these here.

As stated in the Medicines Australia submission, Roche agrees that while many of these agreements would not fit within the Australian legislative requirements, there are elements (e.g. initial horizon scanning of upcoming indications) that could be useful locally. Furthermore, there is great interest within the Australian clinical community to discuss with a view to operationalising a driver mutation, multi-tumour PBS listing. PBAC may wish to engage these stakeholders to further explore this.

Question 16

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

Quick wins

Roche is mindful of the current regulatory framework as set out in Sections 101 (3A and 3B) of the National Health Act (described above) and Sections 4.4 and 4.5 noted in the PBAC Background to invitations for submissions (see above in full):

- '4.4 Any options put to the Minister will also need to meet the core objectives of the Australian Government HTA framework and take into account the role of the Therapeutic Goods Administration …. whilst allowing the PBAC to meet its statutory obligations…..
- 4.5…. any process designed to fast track / accelerate access will need to be integrated within the existing regulatory and reimbursement framework…'

However, with a view to expediting access to PD-1 and PD-L1 checkpoint inhibitor immunotherapies and addressing the unmet need, Roche has identified processes in the regulatory and reimbursement framework which are not legislated, rather are described in policies and guidelines only. Roche suggests that a more relaxed application of these policies and guidelines may afford all stakeholders the opportunity for some 'quick wins'. Application of greater flexibility to these policies and guidelines by the Department of Health and the PBAC, should enable patient's earlier access to treatment.

It is Roche's position that Sponsors should be given greater autonomy regarding the timing of lodging submissions to PBAC, rather than reimbursement process timelines being dictated by guidelines. It is sponsors, after-all who have the greatest insight into their product, its evidence package, most likely indication statement to be approved by TGA and will incur the consequences of their choices for the timing of lodging submissions with the regulator and funding body.

Therefore, Roche proposes that submissions to PBAC can be lodged at any time (no need to wait until after TGA dossier submitted) AND that the PBAC can assess a product prior to the availability of a Delegate's Overview. There is an international precedent for such a process in the UK with NICE recently updating their guidance for oncology appraisals stating that 'most will be performed 7 months in advance of marketing authorisation (MA) and a final guidance published at MA' (NICE 2018).

PBAC may also like to consider a review of the existing MAP approach, potentially under the Streamlined Pathways framework.

While we are not proposing that PBS listing would occur prior to TGA approval, these simple changes could expedite patient access to PD-1 and PD-L1 checkpoint inhibitor immunotherapies.

Furthermore, such a proposal could also be extended to allow sponsors to submit to PBAC before TGA submission. This would avoid any potential misalignment in TGA and PBAC evaluations arising from the new TGA priority review process and avoid unnecessary delays in patients accessing PD-1 and PD-L1 checkpoint inhibitor immunotherapies.

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