# 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

AstraZeneca welcomes the opportunity to engage with the Australian Government and the Pharmaceutical Benefits Advisory Committee (PBAC) on how oncology drugs may be made available on the Pharmaceutical Benefits Scheme (PBS) on a multi-tumour basis.

AstraZeneca supports initiatives and reforms which improve access to new medicines – and this discussion holds the potential to revolutionise how Australian patients with rare and less common cancers access treatment. The aim of this contribution is to constructively and responsibly progress this initiative, and to ensure applicability to other medicines.

In opening, we would like to highlight two important contextual points from which the options presented below emerge:

1. There is a distinction between indications currently being researched (i.e. for which a future PBAC submission is planned) and rare indications for which sufficient data to support a PBAC submission may never be available. AstraZeneca has elected to focus on the latter, which encompass rare cancers; rare and less common cancers are responsible for half of cancer deaths in Australia[1]
2. Although discussion of PD1/PD-L1 immuno-oncology (IO) drugs is the focus of this Special PBAC meeting, AstraZeneca considers that a precision medicine, multi-tumour approach would readily apply to targeted therapies such as PARP inhibitors for BRCA mutations. Accordingly, the options proposed below were developed mindful of the possibility that they could be applied to cancer drugs beyond IO.

AstraZeneca notes and supports the submission made by Medicines Australia to this consultation and commends the points and recommendations advanced in that document, including in regard to rare and less common cancers, to the PBAC's attention.

[1] Rare Cancers Australia (2017). Rare Solutions – a Time to Act

## 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?

The readily apparent advantages of a multi-tumour listing include speed of access for Australian patients and efficiency in the PBAC process. The most important benefit, however, is the opportunity to provide subsidised treatment for patients whose rare diseases cannot be studied as effectively as more common conditions – this must not be overlooked in the discussion of how larger populations can be handled.

**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?

Applying a multi-indication approach to only one medicine, one group of medicines or one therapeutic area - to the exclusion of others - is inequitable and problematic. Thus, one disadvantage to the PBAC is that the approach and processes which emerge from the present consideration will need to be broadly applicable, and transparent so that stakeholders can understand the Committee's reasoning.

Additionally, the importance of developing reliable data on the cancers being treated cannot be understated – the recent release of the Framework for Secondary Use of the My Health Record database highlights the opportunities to enhance how Australian patients receive treatment using data-driven insights. Accordingly, the means by which a multi-tumour listing is implemented should not compromise those opportunities.

**Question 3**

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

Unmet clinical need could be established by examining extended indications for currently-available drugs for which supporting data exist but for which PBS listing has not been sought. While there may be a variety of reasons why a sponsor would not seek PBS listing for a drug, the fact remains that they remain unavailable to Australian patients.

Below are some examples of indications that are FDA-approved but not PBS-listed:

- Erlotinib for pancreatic cancer;
- Bevacizumab for glioblastoma;
- Alemtuzumab for B-cell CLL;
- Sorefenib for differentiated thyroid carcinoma.

In addition, there are numerous examples of drugs which have been on the market overseas for some time but are not available on the PBS:

- Faslodex for breast cancer;
- Daunorubicin for AML and CLL;
- Dacarbazine for Hodgkin Lymphoma.

These examples are the result of only a cursory comparison of PBS listings with FDA registrations – a comprehensive analysis would undoubtedly produce more instances of patient groups for whom treatments have not been pursued outside the US.

Although an FDA approval for a drug or indication does not in and of itself establish comparative cost effectiveness in the Australian setting, it is concerning that no company has been able to establish the feasibility of pursuing these indications. This is a matter of concern to Australian patients, doctors, the pharmaceutical industry and the Australian Government.

**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?

AstraZeneca does not have a preconceived position on a level of evidence of effectiveness of a drug for any certain condition prior to PBAC consideration, but flexibility in this regard is essential. Where there is reasonable basis to conclude that a clinical benefit is likely and significant harms are unlikely, the evidence must be considered in the context of the rarity of the disease and the intent of treatment.

For illustrative purposes, the factors taken into account by AstraZeneca in handling requests for compassionate access are:

- The serious or life-threatening nature of the disease;
- Whether all other comparable or satisfactory alternative therapeutic options have been exhausted;
- Whether the patient is otherwise eligible to enrol in a clinical study.
- Whether there are sufficient clinical data available with respect to both the drug (monotherapy or combination therapy) and the disease to anticipate that any potential benefits from treatment are likely to outweigh any associated risks to the patient.

It is also worth highlighting that methods of data generation are emerging which are likely to be important and deserving of PBAC consideration for the checkpoint inhibitors and other medicines:

- Real World Evidence (non-randomised controlled data), and the value of ongoing data collection using registries, prospective data capture or a mechanism such as the My Health Record;
- New trial designs such as the Cancer Molecular Screening and Therapeutics (MoST) Program have emerged from a belief that changes and improvements in clinical trials are needed to rapidly translate discovery into improved health outcomes – AstraZeneca supports these types of trials globally, including the MoST study;
- Bolt-on to phase 3 trials of a rare cohort as proposed in the Treat Rare, Collect and Share (TRICEPS) approach.

**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?

AstraZeneca believes that it is possible for PBAC to do this and to make appropriate recommendations.

Extrapolating or applying evidence of effectiveness of a drug in one setting to another is not an unfamiliar situation for the PBAC – on several occasions it has found it necessary to do this, including:

- Crizotinib and ceritinib for ALK-positive non-small cell lung cancer – according to the ceritinib Public Summary Document, *"[t]he PBAC noted that, while the submission's proposed PBS restriction positioned ceritinib after crizotinib, the evidence presented in the submission was in a different setting. The PBAC recalled it had previously recommended crizotinib as a first-line therapy for this condition, also largely on the basis of data from its use in a different setting (crizotinib Public Summary Document, November 2014 PBAC meeting). The PBAC therefore considered that allowing ceritinib treatment in any line of therapy was appropriate."*
- Ipilimumab for metastatic melanoma – *"The PBAC noted the proposed treatment algorithm placed ipilimumab as a second line therapy after… failure of… systemic chemotherapy. The PBAC noted that systemic chemotherapy… has minimal efficacy and significant toxicity. Further, the PBAC noted that the sponsor's expert advisory panel considered a requirement to use DTIC or fotemustine to be contrary to clinical judgment and would therefore be unlikely to be observed in practice… [t]herefore, the PBAC concluded that a requirement for patients to first try then fail ineffective and toxic first-line chemotherapy would not be clinically appropriate and requested that the PBS restriction be developed so as to permit first-line use of*

*ipilimumab."*

It may therefore be reasonable to expect a similar approach by the PBAC for multi-tumour listings, if appropriate and indicated by circumstances.

In regard to extrapolation between molecules, it should be noted that all therapies may not be equal and that effectiveness may be strongly dependent on the immunogenicity of the tumour and presence of some biomarkers (PD-L1, Tumour Mutational Burden, Gamma Interferon); this explains AstraZeneca's position that in the absence of evidence, it is generally not appropriate for the PBAC to extrapolate evidence from one molecule to other molecules in the same class(es).

**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?

AstraZeneca believes that it is indeed possible for PBAC to satisfy itself as above and this has been done previously.

"Bundling" of multiple indications in a single PBAC submission

The precedent of Novartis' imatinib being considered for five rare conditions in a single PBAC submission in July 2007 and March 2008 could be a useful approach in presenting multiple rare indications to support a PBS listing. From publicly available information, the following key points are noted:

- The clinical data were of limited quality – a non-randomised trial and an assortment of case series were presented in the March 2008 resubmission;
- A cost effectiveness analysis (incremental cost per extra responder) was presented and, despite having significant uncertainty, was accepted by the PBAC;
- The list price of imatinib does not appear to have been reduced in the PBS Schedule (noting that imatinib did and does not have a published vs effective price), meaning that in the context of a group of small populations the PBAC appears to have been able to conclude that imatinib was at least as effective in these rare indications as in CLL and other larger populations.

It is not clear why no other sponsors have pursued a similar submission strategy by bundling multiple rare indications into a single PBAC submission, although the technical complexity both in constructing the submission and in fully evaluating it were likely to have been considerable. AstraZeneca suggests that, to the extent made possible by confidentiality concerns, a discussion of the context in which this submission was approved may help to clarify when a sponsor could pursue a similar approach to present multiple rare indications to the PBAC.

**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?

As noted below in answer to Question 10, the PBAC routinely takes the rarity of the disease into account when assessing the available evidence.

**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?

As described below, AstraZeneca's position is that in the absence of evidence, it is generally not be appropriate for

the PBAC to extrapolate evidence from one molecule to other molecules in the same class(es).

AstraZeneca suggests a flexible approach to nominating a plausible biomarker (e.g. Tumour Mutational Burden, Gamma Interferon) would allow for future evidence development while avoiding disadvantaging individual patients based on rigid thresholds of PD-1/PD-L1 status. The inconsistency of IO treatment outcomes across PDL-1/PD-L1 expression levels is one reason why AstraZeneca considers that a multi-tumour listing in other classes (e.g. PARP inhibitors in BRCAm positive tumours) may be a more appropriate pilot for this approach.

**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 a general rule, in the absence of evidence, AstraZeneca does not think it is appropriate for the PBAC to extrapolate evidence from one molecule to other molecule(s). AstraZeneca cautions against class effect complacency until these molecules are studied further. Differences have been observed in lung cancer, and in the case of Malignant Pleural Mesothelioma, the recently presented DREAM study (Nowak et al[2]) showed a 61% objective response rate – this is inconsistent with other IO based Ph II studies which showed up to ~41% response rates. The use of IO within combinations of chemotherapy or radiotherapy also potentially accentuates the differences between the IO molecules.

However, it should be acknowledged that in the context of rare cancers for which it is challenging to generate any high-quality evidence, the risk/benefit ratio for a patient with a rare cancer may be quite different compared with that of a patient suffering a disease for which there are already proven treatments. Therefore, AstraZeneca thinks it is appropriate for the PBAC to utilise a degree of pragmatism in weighing up the body of evidence as a whole when making a recommendation.

**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?

AstraZeneca supports initiatives and reforms which improve access to new medicines. We also agree that different evidentiary requirements are appropriate for rare and less common cancers, which are a unique public health issue and for which there is a paucity of data. This concurs with the views expressed on multiple occasions by the PBAC that disease rarity provides important context to the quality of available evidence. Some instances include:

- Brentuximab vedotin/BV for sALCL (March 2014 PSD) – "*The PBAC considered that the non-randomised, single-arm comparison of Study 0004 and the BC lymphoid cancer registry, presented in the submission, represented the best-case scenario for treatment with brentuximab vedotin. The PBAC recognised that it was unlikely that better data would be available given the rare nature of sALCL. The PBAC accepted that BV represented an advance in therapy for a disease where a high clinical need exists.*
- Anakinra for cryopyrin-associated periodic syndromes (CAPS) (November 2014 PSD) – "*The clinical evidence presented in the submission from four quasi-experimental studies made it difficult to reliably estimate the magnitude of the clinical benefit of anakinra in CAPS due to the open-label administration, subjective nature of the outcomes, differences in some patient characteristic between treatment and control groups, absence of control groups, very small sample numbers and very limited long term data. The PBAC acknowledged the difficulties associated with obtaining clinical data in rare conditions such as CAPS but recognised that it was unlikely that better data would become available. Noting the limitations with the clinical evidence presented, the PBAC accepted the submission's clinical claim that anakinra ± best supportive care is superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care alone.*"

AstraZeneca would support the PBAC continuing to make such assessments in future where merited by the circumstances of the disease. There are theoretical adjustments which could be made to current HTA process (such

[2] http://abstracts.asco.org/214/AbstView_214_212261.html

as a multiplication factor to adjust the ICER to reflect disease rarity) to both preserve established modelling principles and improve transparency into how standard processes are applied to rare indications.

AstraZeneca also concurs with the Medicines Australia submission which sets out approaches to provide equitable access to new medicines for people with rare and less common cancers, concurrent with data generation. Studies such as the MoST, or other data collection vehicles, can collect safety and efficacy information concurrently to reimbursed access. Thus, AstraZeneca supports PBS access for rare and less common cancers with different evidentiary requirement.

**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.)

AstraZeneca does not support this.

The PBAC has always balanced its attention across all therapeutic areas in an equitable manner. AZ considers that excluding all non-IO submissions for a complete PBAC cycle would be problematic in that it would delay consideration of other worthwhile medicines. Multi-tumour submissions, whether for IO or other medicines, should therefore follow the usual procedural timeframes.

**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?

AstraZeneca notes and supports the submission made by Medicines Australia to this consultation and commends the points and recommendations advanced in that document, including those comments which relate to rare and less common cancers, to the PBAC's attention.

[redacted]

[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?

AstraZeneca's development pipeline is available at https://www.astrazeneca.com/our-science/pipeline.html

**Question 14**

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

Although AstraZeneca is aware of several subsidy models which have been debated internationally, the effectiveness of these approaches has not been established.

**Question 15**

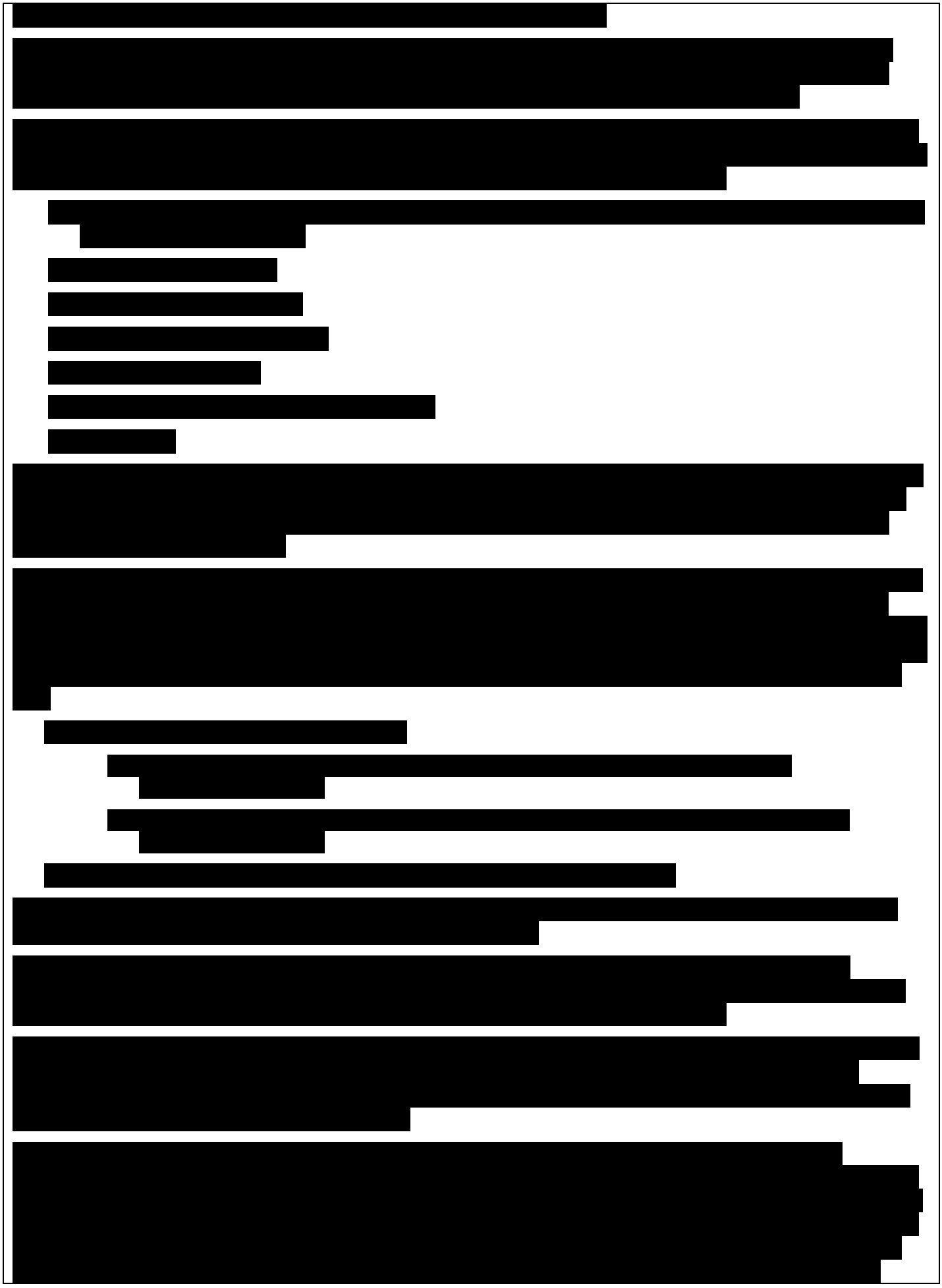
**(For Industry)** What information can you provide regarding established international agreements for multi-tumour subsidy and how could these apply in the Australian regulatory context?

Please see answer to question 14 above.

**Question 16**

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

[redacted]



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