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

CHERE is committed to the principles of the PBAC and the National Medicines Policy as they relate to providing timely access to cost-effective medicines for Australians. By world standards, the systematic assessment of evidence of the efficacy, safety and cost-effectiveness of medicines has served to provide the Australian public with timely access to subsidised medicines.

The proposal for subsidy of checkpoint inhibitors on a multi-tumour basis must be considered against this background. CHERE notes that there is no one set proposal; of the two submitted to date one did not call for a change in PBAC processes, the other suggested that checkpoint inhibitors be listed for multi-tumours at an average price, with new indications added once registered. Both of these proposals thus suggest that a multi-tumour listing could only apply to a registered indication. However, it has also been suggested that other reimbursement pathways need to be considered for rare cancers where there is insufficient evidence to satisfy the current reimbursement processes. The latter thus implies subsidy for multi-tumours in the absence of a registered indication, which would sit outside of the current legislative arrangements governing the PBAC and PBS.

In general, CHERE is of the view that any new subsidies for medicines should abide by that legislation in being assessed for efficacy, safety and cost-effectiveness. Medicines to be subsidised for indications for which they are not registered, and for which evidence of efficacy and safety does not exist, could be better addressed through Australia's world class clinical trial network. Discussion of how the current PBAC processes (might) accommodate multi-tumour listings, and further discussion of the role of clinical trials is provided in our responses to the questions posed by the PBAC.

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 potential advantage of the PBAC considering multi-tumour listing for checkpoint inhibitors (PD-1 and PD-L1) is that it may present opportunities for efficiency gains in terms of the assessment and evaluation of data (clinical, safety and cost-effectiveness) for those checkpoint inhibitors.

That is, it is likely that within an application for a multi-tumour listing of checkpoint inhibitors, issues affecting the assessment of evidence for clinical efficacy/safety and cost-effectiveness would apply across tumour types. This may include the following:

- questions on the appropriateness of the comparator;
- the applicability of observational data, or evidence from small, non-randomised studies (particularly in the case of tumours that may be considered rare);
- the use of early stage clinical data (surrogate outcomes) to demonstrate longer term outcomes;
- the implications of cross-over treatment effects within clinical trials;
- uncertainty on the ability to determine clinical benefit (and in particular the absence of progression);
- uncertainty on the appropriate duration of treatment;
- the methods used to extrapolate observed evidence for use in the economic evaluation;
- the methods used to derive assessments of the impact of treatment on patients' quality of life; and
- the methods used to estimate the proposed cost to Government (including estimating the potential patient population and their use of the proposed checkpoint inhibitor).

Where these issues arise within the one submission (submitted by the same sponsor) there is the potential for efficiency gains (in terms of time) in understanding the approaches taken and in addressing any questions that might arise. Whether such synergies would result in earlier positive recommendations to list from the PBAC depends on the quality of the data submitted, as well as the ability of those data to support a recommendation of effective, safe and cost-effective treatment. Theoretically, if such a recommendation were to proceed to listing, it would offer clinicians the opportunity to prescribe the subsidised checkpoint inhibitor for any patient for whom it may be considered beneficial. This will depend on the nature of the underlying registered indication (e.g. whether it is tumour specific) and may not always represent an acceptable advance in the use of subsidised treatments (see Question 2).

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?

The potential disadvantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings are:

1. The potential for unknown benefits foregone (harm). There is an implicit assumption in such an approach that because a tumour is PD-1/PD-L1 positive that it will respond in the same manner to a checkpoint inhibitor as have other tumours, both in terms of safety and efficacy. This may not always be the case, with varied efficacy and safety outcomes observed with the existing checkpoint inhibitors currently in use.(1-3) There is also evidence from the use of other anti-cancer therapies that the underlying tumour type cannot be ignored, and that different tumour types will behave differently even in the presence of the same treatment target. For example, colorectal cancer expresses epidermal growth factor receptor (EGFR) and is therefore a candidate for EGFR inhibitors; agents such as cetuximab and panitumumab which target KRAS. Early use of these agents in all CRC patients (without differentiation of KRAS type) found that in those with a

KRAS mutation, the use of either agent was detrimental to the patient compared with standard chemotherapy – there was harm in the form of shorter survival.(4, 5) It was only in further characterising the CRC tumour, and targeting treatment to patients with KRAS-wild type mutations, that a benefit in CRC was identified for both agents.(4, 5) Having applied a "pan-tumour" approach in this case would have resulted in harm to some patients. Another examples is the use of imatinib, a tyrosine kinase inhibitor which has activity in a broad range of tumour types, but has not demonstrated activity in other tumours which also express the platelet derived growth factor receptor (PDGFR) and c-kit proteins (such as breast cancer).(6-8) Thus in some cases it will be unclear if (a) there is a positive treatment effect, and (b) whether the magnitude of that effect would be considered meaningful (both statistically and clinically). In the absence of information on positive outcomes, the use of checkpoint inhibitors in place of current therapies (where available) may thus represent potential harm. Our existing knowledge of the role of PD-1/PD-L1 across different tumours, as well as the potential impact of immunotherapies on other aspects of the tumour microenvironment(2, 9), mean that such an effect cannot be ruled out in applying a "pan-tumour" approach to immunotherapies.

2. The potential for adverse safety outcomes (harm). One of the pitfalls of adopting a multi-tumour approach to reimbursement, potentially without corroborating assessments of evidence for efficacy and safety, is the unknown safety outcomes of checkpoint inhibitors within different tumour types and in the longer term.(1, 3, 10) While the incidence of immune related adverse events within existing studies for these checkpoint inhibitors is well documented, there is evidence of a difference across tumours in the nature of events that have occurred.(1) Thus, expanding the use of checkpoint inhibitors into untested indications (as defined by tumour type) presents an immediate risk in terms of as yet unobserved safety events.

3. Increasing the burden on the preparation, evaluation and assessment of cost-effectiveness. The application of a multi-tumour approach within the current legislative system of comparative cost and effectiveness would require aggregation across tumour groups to produce an assessment of the overall cost-effectiveness (see also the responses to Question 5 and 6 below). This would require robust data on the relative proportion of patients in each tumour group, and the proportion that each contributes to total checkpoint inhibitor use (particularly if the duration of therapy varies across tumour types), as well as an estimate of the cost-effectiveness within each indication. Combined, or weighted estimates of cost-effectiveness are not new within the Australian reimbursement process but represent another source of uncertainty and computational burden.

4. A potential source of inequity. Adopting such an approach would appear to be at odds with the goal of equity of access for the PBS. Proponents of multi-tumour (or pan-tumour) approaches claim that the process for considering applications for reimbursement is inequitable(11) since many of the rarer conditions are unfairly penalised by an inability to provide the level of evidence that is perceived to be a requirement of the PBAC. While it is challenging to accumulate evidence for rarer conditions, the PBAC does not have a required minimum level of evidence and has in the past made positive recommendations for small patient groups, with rare conditions, on the basis of the data available (including data from single arm studies). From a system equity perspective, allowing multi-tumour funding for immunotherapies begs the question, why not multi-tumour funding for inhibitors of other molecular/protein targets in cancer patients (such as MEK, EGFR, FLT-3), or indeed in non-cancer indications (inhibitors of TNF-a or MTOR). The potential inequities induced by adopting such an approach should not be underestimated.

Question 3

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

A definition of urgent unmet clinical need can be applied from the following criteria within the existing PBAC Guidelines used to establish whether the 'rule-of-rescue' may apply to a given medication:

- No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological

or pharmacological interventions for these patients.

- The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the PBAC's consideration.
- The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the PBAC's consideration. However, the PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.
- The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the PBAC's consideration. (PBAC Guidelines, p123)

For the purposes of establishing unmet clinical need as it may apply to considerations of funding for multi-tumour use of checkpoint inhibitors, the key criteria are the absence of an effective alternative, that the condition is severe (but not necessarily resulting in imminent death), and that there is evidence of a worthwhile clinical improvement from the proposed medicine. While the first and second of these criteria may be demonstrated more readily, the third will be more challenging particularly where an application is seeking funding for multi-tumours on the basis of an argument of biological plausibility or early phase data, rather than observed evidence of clinical efficacy and safety.

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?

Currently, there is no minimum level of evidence for the consideration of products for subsidy; neither in terms of the type of evidence (from randomised controlled trials, single arm studies or observational) or the duration of follow-up. The critical questions are how that evidence might reflect the likely clinical and cost-effective use of the proposed drug in Australian clinical practice and quantifying the uncertainty around the evidence to facilitate decision-making by the PBAC.

Establishing a minimum level of evidence in the case of multi-tumour funding for checkpoint inhibitors depends on the nature of the reimbursement application: (a) seeking funding for a registered indication (noting the possibility of parallel processing of registration and reimbursement applications); or (b) seeking a reimbursed indication that is not-tumour specific but would allow use in tumour types other than that for which the product is registered. In the case of the former, it would be expected that at least the same evidence of safety and efficacy presented to the Therapeutic Goods Administration would also be presented to the PBAC – with the need for additional evidence to support cost-effectiveness. In the case of the latter, a minimum requirement would be evidence of biological plausibility for efficacy and safety within the proposed multi-tumour indication (see Question 5).

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?

Prima-facie, it is not possible for the PBAC to extrapolate or apply the evidence of effectiveness of a checkpoint inhibitor in one tumour type (or stage) to another directly. Underpinning the presentation of evidence for the use of checkpoint inhibitors on a multi-tumour basis is the notion that the mechanism of action of observed by a PD-1 inhibitor in one setting (say pembrolizumab in non-small cell lung cancer) will mirror that observed in another (metastatic urothelial cell carcinoma), resulting in clinical outcomes that can be measured in a consistent manner (e.g. progression free survival (PFS) and overall survival). The same questions apply in extrapolating evidence across tumour stages; is there evidence that the proposed treatment effect is the same? This is of particular relevance where tumour activity (including the emergence and activation of new mutations) may alter through the course of

disease. The rationale for the efficacy of immunotherapy is that it relies on the activation of the body's immune system to target tumour cells. Theoretically then, a tumour that was responsive to immunotherapy at an early stage might well be at later stages. However, there is currently insufficient evidence on the longer-term activity of these agents, including how tumour responses may alter with the immergence of "resistance" throughout the course of disease.(2)

The presentation and consideration of evidence in submissions for multi-tumours may well be guided by the recommendations within the PBAC Guidelines for the presentation of evidence to justify the transformation of evidence from a surrogate endpoint (such as tumour response or PFS) to a final outcome (overall survival). Two of those recommendations are key in the context of multi-tumour funding:

1. Establish the biological plausibility of the proposed surrogate relationship i.e. that checkpoint inhibition (through targeting of PD-1 or PD-L1) in all of the tumours in a 'multi-tumour' application would be expected to have an anti-tumour effect akin to that observed previously.
2. Provide evidence that the surrogate relationship applies to the proposed medication. On the assumption that multi-tumour applications will seek subsidy before the availability of "final-outcomes" data, the corollary in this setting is to establish that achieving a given surrogate clinical outcome (e.g. PFS) is of clinical value in each tumour type, and to establish its implications for the final outcome in each tumour type. By its nature, a progression event will differ between tumour types (notwithstanding the controversy in the radiological assessment of progression in the presence of immunotherapies), and therefore the clinical implications of those events may also differ. It would therefore be important for submissions to articulate the proposed clinical implications of the chosen surrogate for each tumour, and that the proposed relationship applies for the proposed drug.

Taking this into account, adopting a 'multi-tumour' approach may result in more complex submissions, adding further pressure to the reimbursement system at all levels (including the development, evaluation and utilisation of evidence from submissions for decision-making). No – but expand and potentially refer to the STFOWG criteria.

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?

Attempting to reach a conclusion on cost-effectiveness (as required by the National Health Act 1953) without the construction of economic models for each tumour type would be challenging at best; different tumours would have different comparators, different treatment pathways, different prognostic associations for survival and different impacts on patients' quality of life.

Theoretically, it would be possible to construct a model (albeit a complex one) that addressed multiple-tumours. Such a model could include separate compartments (or modules) that would effectively conduct within tumour economic evaluations, producing an overarching summary (of cost-effectiveness) that combined the tumour specific incremental cost-effectiveness ratios (ICERs) based on the relative prevalence and utilisation of the proposed drug in each tumour type.

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?

This is a challenging question. First, it requires a consistent definition of what might be considered a modest benefit, which is relative: a gain in survival of 2 months in the life of a patient with newly diagnosed non-Hodgkins lymphoma may be considered modest, but the same gain for a patient with stage III ovarian cancer would be

considered of benefit. Second, it is difficult to establish a price based on benefit without taking into account the nature of that benefit (including the impact on adverse events, quality of life and other patient experience factors) and the implications for health care resource use (costs). This is the premise of conducting an economic evaluation. It is thus not possible, a-priori, to establish a reasonable subsidy price for PD-1 and PD-L1 medicines without considering the evidence on safety, efficacy and health care resource use (costs).

It is possible to establish a principle for the pricing of checkpoint inhibitors whereby those for which data on efficacy and safety are yet immature could be priced at their comparator price, with the potential for a price increase to what could be acceptable as cost-effective once additional data are provided. While this sort of Coverage with Evidence Development (CED) approach has been discussed within the Australian system, to date it has not yet been adopted (with pay-for-performance or other managed entry programmes predominating).

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?

Currently within Australia there are no checkpoint inhibitors registered for use on the basis of a biomarker, across tumour types. In the USA pembrolizumab is registered for use in tumours expressing the mismatched repair gene, without restriction on the origin of the tumour. Implementing a subsidy on the basis of the presence of such a biomarker, or on the basis of PD-1/PD-L1, would be challenging given the complexity in the assessment and interpretation of biomarkers for use with immunotherapies.(2, 9) In particular, there are questions regarding:

(1) what level of expression of such biomarkers predicts for drug activity?;

(2) what level of expression of such biomarkers predicts for a positive prognostic value (beyond the predictive value associated with the proposed drug)?; and

(3) how is drug activity affected by the presence of gene mutations (other than those which may be associated with the biomarker) within the tumour?

In order to preserve equity of access, making subsidised access to drugs conditional on the presence of a biomarker would necessitate that there are accessible (publicly funded), reliable methods for the detection and quantification of that biomarker available in clinical practice in Australia. Where such methods are not yet subsidised, there is an established method for the consideration of co-dependent technologies (test and drug combinations) for subsidy; to date, only one checkpoint inhibitor has sought subsidy via the co-dependent technology pathway - pembrolizumab for the testing of PD-1 expression in NSCLC. This suggests that the importance of PD-1 expression differs across tumour types (since no similar requirements exist for other immunotherapies in other tumour types) and may indicate a potential difficulty in establishing a multi-tumour approach to funding (particularly where there is an absence of evidence of the importance of PD-1/PD-L1 expression across those tumour types) without a corresponding consideration of the need for and access to appropriate testing.

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.

The PBAC has previously applied class effects when considering drugs within an indication, particularly with respect to pricing arrangements. However, such class effects are based on a commonality of effect (efficacy and safety) across drugs within a class.(2) The current evidence would suggest that there are differences across checkpoint inhibitors (beyond whether they inhibit PD-1 or PD-L1) that would argue against the application of a class effect.

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?

There are no set evidentiary requirements for applications seeking PBS listing of a drug, other than that the available

data be presented systematically, in an unbiased manner and present evidence of comparative efficacy, safety and cost-effectiveness. Within this system, the PBAC considers evidence from many different sources, and gives appropriate weight to those alternative sources in the context of the medical condition for which listing is sought.

Establishing cost-effectiveness is formulaic: the incremental costs of the proposed drug divided by the incremental benefits. Typically, cost-effectiveness is considered as the cost per quality adjusted life year (QALY) gained. While the same process for determining cost-effectiveness should apply to rare cancers it may be that outcomes other than an incremental cost per QALY could be considered, such as the cost per responder. This may be required if the data presented for the rare cancers are immature (e.g. for survival) or there are no data on the QoL effects of the cancer or its treatment to allow the estimation of QALYs. However, it is difficult to compare the value of a drug when expressed as an ICERs based on 'natural outcomes', e.g. the prognostic value of a response differs between tumour types, making it difficult to judge their cost-effectiveness. The lack of such comparability and the absence of an acknowledged standard for what might be considered cost-effective, may hamper decision-making.

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.)

We do not believe that the PBAC should not set aside one of its three meeting to consider only PD-1 or PD-L1 inhibitors for cancer. On the assumption that if the PBAC set aside a meeting for checkpoint inhibitors those drugs could only ever be considered at that one meeting, it would add undue pressure on the outcomes from such a meeting. This could result in delays to listing for some drugs (if they cannot be considered at subsequent meetings). Moreover, it is inequitable for drugs for other cancer indications (for which PD-1/PD-L1 are not treatment options) and non-cancer indications given that they would be restricted to be considered by the PBAC at only two meetings per year.

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?

If limited evidence is available at the time of subsidy of a PD-1 or PD-L1 inhibitor for a cancer, it is possible to establish a principle for pricing whereby:

- If the data on efficacy and safety for the checkpoint inhibitor are limited, resulting in an uncertain ICER, the drug could be priced initially at the price of its comparator price;
- The listing could proceed on the basis of Coverage with Evidence Development (CED); the sponsor would be required to provide either further (more mature) data from the submitted studies, or collect and provide evidence on the ongoing safety and efficacy of the drug as observed in clinical practice;
- Those data submitted through CED could then be used to review the price of the checkpoint inhibitor – potentially to justify a (higher) price as requested initially. In the event that data show that the drug is less effective than its comparator, consideration could be given to preventing any new patients from accessing that drug on a subsidised basis (essentially a staged withdrawal).

While this sort of CED approach has been discussed within the Australian system, to date it has not yet been adopted (with pay-for-performance or other managed entry programmes predominating).

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?

CHERE is not responsible for the conduct of clinical trials, and does not prepare applications for the registration or subsidy of pharmaceutical products. However, CHERE is involved in an NHMRC funded clinical trial which is investigating the use of intermittent or continuous immunotherapies (PD-1 or PD-L1 inhibitors) for the treatment of patients with metastatic melanoma (NHMRC APP1146174); the STOP-GAP trial. Funding for this five year trial commenced in 2018.

Question 14

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

CHERE is not aware of any international models of public funding for multi-tumour subsidy. However, it notes that private funders in the USA (such as the BlueCross BlueShield of North Carolina) list unresectable or metastatic solid tumours with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers as an area of clinical need, and one for which pembrolizumab will be covered.(12) Note, pembrolizumab is registered by the FDA for use in the multi-tumour indication.

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?

CHERE is not aware of any international agreements for multi-tumour subsidy.

Question 16

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

The calls for funding of multi-tumours seem to rest on the premise of making immunotherapies (PD-1/PD-L1) available to patients earlier, possibly before registration in each indication, and that a “cover-all” subsidy arrangement would exist.

Establishing a “cover-all” reimbursed indication would be challenging since it would either be: “Treatment of cancer” with the onus then placed on the physician to observe the relevant registered indications, or “Treatment of cancers expressing PD-1/PD-L1” which would then establish a need to test all cancers for PD-1/PD-L1 even though the prognostic/predictive value of such testing has not been proven.

Moreover, establishing a “cover-all” listing presents challenges in terms of ongoing pricing arrangements. In effect, the price established at the time of first listing would apply to all subsequent use. Theoretically, the need to ensure that such use remains cost-effective could be addressed through a Deed of Agreement by applying an ongoing price-volume cap (potentially with underlying pay-for-performance arrangements). This would establish a high administrative burden on both companies and the Department of Health.

An alternative to implementing a “cover-all” listing would be to provide patients with access to immunotherapies outside of the PBS, while collecting the evidence that would be required to lodge an application to the PBAC. Such an arrangement could be established under the Medical Research Futures Fund, with an ongoing “basket” clinical trial established to provide access to immunotherapies to cancer patients for which it is as yet unregistered/not reimbursed while collecting evidence of efficacy, safety and resource use. Such a trial could be coordinated by the Cancer Australia Genomic Cancer Clinical Trials Initiative, a group established by Cancer Australia with the express purpose of investigating opportunities for cross-tumour studies which involve common genetic or protein targets for treatment.

References

1. El Osta B, Hu F, Sadek R, Chintalapally R, Tang SC. Not all immune-checkpoint inhibitors are created equal: Meta-analysis and systematic review of immune-related adverse events in cancer trials. Crit Rev Oncol Hematol. 2017;119:1-12. Epub 2017/10/27. doi: 10.1016/j.critrevonc.2017.09.002. PubMed PMID: 29065979.

2. Thallinger C, Fureder T, Preusser M, Heller G, Mullauer L, Holler C, et al. Review of cancer treatment with immune checkpoint inhibitors : Current concepts, expectations, limitations and pitfalls. Wien Klin Wochenschr. 2018;130(3-4):85-91. Epub 2017/11/04. doi: 10.1007/s00508-017-1285-9. PubMed PMID: 29098404; PubMed Central PMCID: PMCPMC5816095.

3. The Lancet O. Calling time on the immunotherapy gold rush. Lancet Oncol. 2017;18(8):981. Epub 2017/08/02. doi: 10.1016/S1470-2045(17)30521-1. PubMed PMID: 28759366.

4. Bokemeyer C, Kohne CH, Ciardiello F, Lenz HJ, Heinemann V, Klinkhardt U, et al. FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. Eur J Cancer. 2015;51(10):1243-52. Epub 2015/05/06. doi: 10.1016/j.ejca.2015.04.007. PubMed PMID: 25937522.

5. Gong J, Cho M, Fakih M. RAS and BRAF in metastatic colorectal cancer management. J Gastrointest Oncol. 2016;7(5):687-704. Epub 2016/10/18. doi: 10.21037/jgo.2016.06.12. PubMed PMID: 27747083; PubMed Central PMCID: PMCPMC5056249.

6. Cristofanilli M, Morandi P, Krishnamurthy S, Reuben JM, Lee BN, Francis D, et al. Imatinib mesylate (Gleevec) in advanced breast cancer-expressing C-Kit or PDGFR-beta: clinical activity and biological correlations. Ann Oncol. 2008;19(10):1713-9. Epub 2008/06/03. doi: 10.1093/annonc/mdn352. PubMed PMID: 18515258; PubMed Central PMCID: PMCPMC2735063.

7. Modi S, Seidman AD, Dickler M, Moasser M, D'Andrea G, Moynahan ME, et al. A phase II trial of imatinib mesylate monotherapy in patients with metastatic breast cancer. Breast Cancer Res Treat. 2005;90(2):157-63. Epub 2005/04/02. doi: 10.1007/s10549-004-3974-0. PubMed PMID: 15803362.

8. Raica M, Cimpean AM. Platelet-Derived Growth Factor (PDGF)/PDGF Receptors (PDGFR) Axis as Target for Antitumor and Antiangiogenic Therapy. Pharmaceuticals (Basel). 2010;3(3):572-99. Epub 2010/03/11. doi: 10.3390/ph3030572. PubMed PMID: 27713269; PubMed Central PMCID: PMCPMC4033970.

9. Cesano A, Warren S. Bringing the next Generation of Immuno-Oncology Biomarkers to the Clinic. Biomedicines. 2018;6(1). Epub 2018/02/03. doi: 10.3390/biomedicines6010014. PubMed PMID: 29393888; PubMed Central PMCID: PMCPMC5874671.

10. Fernandes M, Brabek J. Cancer, checkpoint inhibitors, and confusion. Lancet Oncol. 2017;18(11):e632. Epub 2017/12/07. doi: 10.1016/S1470-2045(17)30810-0. PubMed PMID: 29208386.

11. Deloitte Access Economics. The New Wave of Immunotherapy Cancer Medicines –The Untapped Potential for Australians. 2017.

12. BlueCross BlueShield. PD-1 Inhibitors. 2018.