Record of the Cancer Treatments Advisory Committee Meeting held on Friday, 14 October 2022

This meeting was held virtually via Zoom

Cancer Treatments Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Cancer Treatments Advisory Committee meeting; only the relevant portions of the meeting record relating to Cancer Treatments Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Cancer Treatments Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present	Apologies
Marius Rademaker (Chair)	Allanah Kilfoyle
Anne O'Donnell	Lochie Teague
Christopher Frampton	Oliver Brake
Matthew Strother (parts of)	Peter Ganly
Michelle Wilson	Stephen Munn
Richard Isaacs	Vidya Mathavan
Scott Babington (parts of)	

2. The role of Specialist Advisory Committees and records of meetings

2.1. This meeting record of the Cancer Treatments Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

2.2. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

2.3. The Cancer Treatments Advisory Committee is a Specialist Advisory Committee of Pharmac. The Cancer Treatments Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Cancer Treatments Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for cancer that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for cancer that differ from the Cancer Treatments Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

2.4. Pharmac considers the recommendations provided by both the Cancer Treatments Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for cancer.

3. Pembrolizumab and atezolizumab monotherapy for the first line treatment of NSCLC

Discussion

3.1. The Advisory Committee noted that Pharmac was seeking advice regarding the use of immune checkpoint inhibitors as monotherapy in the first line treatment of non-small cell lung cancer in relation to a recent Request for Proposals (RFP).

3.2. The Committee noted that Pharmac was seeking advice particularly on testing considerations and the selectivity of various testing platforms in relation to the RFP.

3.3. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

3.4. The Committee considered that either atezolizumab or pembrolizumab should be funded as monotherapy for the first line treatment of advanced non-small cell lung cancer (NSCLC) subject to the following Special Authority criteria:

> **Initial application - (non-small cell lung cancer first-line monotherapy)** only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist.
> Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced or metastatic, unresectable, non-small cell lung cancer; and
> 2. The patient has not had chemotherapy for their disease in the palliative setting; and
> 3. Patient has not received prior funded treatment with an immune checkpoint inhibitor for NSCLC; and
> 4. There is documentation confirming that the disease does not express activating mutations of EGFR or ALK tyrosine kinase unless not possible to ascertain; and
> 5. Both
>   - 5.1. XXXXX to be used as monotherapy; and
>   - 5.2. There is documentation confirming the disease expresses PD-L1 at a level ≥50% as determined by a validated test unless not possible to ascertain; and
> 6. Patient has an ECOG 0-2; and
> 7. XXXXX to be used at a maximum dose of XXXX every XXX weeks (or equivalent) for a maximum of 12 weeks; and
> 8. Baseline measurement of overall tumour burden is documented clinically and radiologically.
>
> **Renewal – (non-small cell lung cancer first line monotherapy)** only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist.
> Approvals valid for 3 months for applications meeting the following criteria:
> All of the following
> 1. Any of the following:
>   - 1.1. Patient's disease has had a complete response to treatment; or
>   - 1.2. Patient's disease has had a partial response to treatment; or
>   - 1.3. Patient has stable disease; and
> 2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
> 3. No evidence of disease progression; and
> 4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
> 5. XXXXX to be used at a maximum dose of XXXX every XXXX weeks (or equivalent); and
> 6. XXXXX to be discontinued at signs of disease progression; and
> 7. Treatment with XXXXX to cease after a total duration of 24 months from commencement (or equivalent).

Discussion

Background

3.5. The Committee noted that atezolizumab and pembrolizumab have been previously considered as first line monotherapy treatment for NSCLC, and that both have previously received high funding recommendations from the Cancer Treatments Advisory Committee (CTAC).

3.6. The Committee noted that in April 2022, CTAC provided advice to Pharmac regarding commercial options for stage IV lung cancer treatments. The Committee noted at the April 2022 meeting, the available evidence and that it remained appropriate to consider that atezolizumab and pembrolizumab provide the same, or similar, health benefit for first line NSCLC monotherapy, such that funding of either agent in this line of therapy would be clinically appropriate. The Committee also considered at the April 2022 meeting that it was appropriate to assess previously assessed ICI agents as having a class effect for the purpose of enabling listing.

Pembrolizumab and atezolizumab monotherapy

3.7. The Committee noted additional follow-up data for pembrolizumab first-line monotherapy (Reck et al. J Clin Oncol. 2021;39:2339-49; de Castro et al. J Immunother Cancer. 2021; 0.1136/jitc-2021-SITC2021.363), and atezolizumab first line monotherapy (Jassem et al. J Thorac Oncol. 2021;16:1872-82). The data reviewed for both included three-year follow-up data for atezolizumab and five-year follow-up data for pembrolizumab.

3.8. The Committee noted that Phase III randomised controlled trials often assume a baseline hazard ratio (HR), and that the proportional change in hazard stays the same over time, so that theoretically the hazard ratios are the same at all time points which does not account for a time-treatment interaction. The Committee noted that deviations from proportional hazards are common for immunotherapy trials (57% of 263 trials studied), with hazard ratios dropping over time (Rahman et al. Clin Cancer Res. 2019;25:6339-45). The Committee noted that the changes in HR over time with immunotherapies is further confounded by cross-over within the trial and subsequent therapies.

3.9. The Committee considered that the longer-term data from KEYNOTE-024 shows a smaller percentage benefit than the proportional hazard ratio would imply, but that there may be a small, yet undefined subpopulation with a longer-term benefit. The Committee also noted that earlier exposure to immunotherapy shows a greater benefit than those who received chemotherapy and then crossed over to pembrolizumab (ie the hazard ratio advantage for immunotherapy increases with time).

3.10. The Committee noted that the longer-term follow-up data for atezolizumab in Impower110 reported around 20% of patients experienced long term survival and considered this similar to the long-term results reported for pembrolizumab.

Selectivity and specificity of PD-L1 antibodies

3.11. The Committee noted that immunohistochemical analysis testing for PD-L1 requires many components, including antigens, antibodies, testing platforms and their associated software. The Committee noted that immunohistochemical tests can either be commercially marketed biomarkers (externally validated package and linked to an FDA approval as a companion diagnostic or complementary diagnostic) or lab developed (with potentially uncertain validation standards). The Committee noted that immunohistochemistry requires subjective assessment of staining and can be assessed with inter-reader reliability to determine stability of the subjective quantitative assessment by pathologists. The Committee noted that the tests are usually developed prior to trial outcomes data being available and are optimised to laboratory-based criteria and subsequently applied to clinical studies.

3.12. The Committee noted that atezolizumab has two FDA approved diagnostic tests; one using the SP263 antibody, and one using the SP142 antibody. The Committee noted that the use of SP263 for lung cancer was based on IMpower010, and that this trial was underpowered to infer the utility of PD-L1 stain percentage as a predictor of disease-free survival using this assay. The Committee noted however that there was high test-retest reliability, in that, if there was a negative test, resampling would not result in a positive result.

3.13. The Committee noted that evidence for the use of the SP142 assay is based on the IMpower110 trial where it was reported that PD-L1 expression in ≥ 50% of tumour

cells or ≥10 tumour infiltrating immune cells determined by the SP142 assay may be associated with enhanced overall survival with atezolizumab in NSCLC patients.

3.14. The Committee considered that the difference between the SP142 assay and the SP263 assay may be due to the difference in evidential threshold requirements for companion versus complimentary tests, and that these tests may select for different populations.

3.15. The Committee noted that the approved antibody for pembrolizumab is the 22C3 assay. The Committee considered that based on the BLUEPRINT study (Hirsch et al. J Thorac Oncol. 2017;12:208-22), the SP263 and 22C3 assays are largely interchangeable. However, the Committee noted that none of the immunohistochemistry assays have been validated with other scoring systems and that they are sensitive to the assay package which may have commercial implications for replication.

3.16. The Committee noted that different assays define different population sizes, with the least sensitive assay (SP142) defining the smallest population eligible for monotherapy treatment based on PD-L1 expression. The Committee noted that there was high concordance between the SP263 and 22C3 antibodies from BLUEPRINT2 (Taso et al. J Thorac Oncol. 2018;13:1302-11), which select for larger populations and that these would likely be the antibodies used if PD-L1 testing were required for access to monotherapy.

3.17. The Committee considered that the evidence for the efficacy and population size of atezolizumab for people with high expression of PD-L1 identified by the various antibodies would come from the evidence for the SP263 assay (Herbst et al. N Engl J Med. 2020;383;1328-39 and Jassem et al. J Thorac Oncol. 2021;16:1872-82). The Committee considered that the evidence for efficacy and population size of pembrolizumab would be derived from the KEYNOTE-024 trial (Reck et al. J Clin Oncol. 2021;39:2339-49).

3.18. The Committee was not aware of any evidence that any given antibody works differently across different ethnicities and populations, or the prevalence of PD-L1 expression by ethnicity. The Committee considered that either atezolizumab or pembrolizumab would likely provide a similar benefit in first line monotherapy, but that this efficacy is derived from the population size inferred from the relevant companion diagnostic.

PD-L1 testing and implications

3.19. The Committee noted that the evidence for testing in these cases is tied to specific devices and instrumentation with explicit external criteria for scoring, which a lab developed test may not necessarily achieve. The Committee noted that funding an ICI treatment tied to a specific test would require testing centres to be locked into infrastructure development for that particular test. The Committee noted that although some assays may be interchangeable, the performance of validated antibodies with other scoring systems is unknown. The Committee noted that if centres do not commit to the currently validated tests, and instead developed their own or used other laboratory developed tests, then the extent to which the process has been validated would be up to the individual laboratory, which may lead to variation between centres.

3.20. The Committee also noted a systematic review and meta-analysis comparing biomarker modalities for predicting response to PD-L1 checkpoint inhibitors for ten

different solid tumour types (Lu et al. JAMA Oncol. 2019;5:1195-1204). The Committee noted that when each modality was evaluated with summary receiver operating characteristic (sROC) curves, PD-L1 immunohistochemistry, regardless of antibody used, had an area under the curve score of 0.65 ($p < .001$). The Committee considered that this indicated that immunohistochemical testing as a predictor of response to an ICI may be limited.

3.21. The Committee noted a meta-analysis of individual-level data from 14 randomised clinical trials to investigate the clinical significance of PD-L1 expression scores on overall survival (Arfe et al. JCO Precis Oncol. 2020;4:1196-1206). The Committee considered that higher staining may not necessarily be predictive of response, but rather a slightly longer overall survival than those with low or no staining.

3.22. The Committee considered that current evidence supports that some antibodies used in immunohistochemistry are more sensitive than others (meaning that populations eligible for treatment would differ between tests), and that the scoring systems include different elements and have often not been cross-compared with different antibodies. The Committee also considered that the evidence supporting the scoring systems as being predictive of an individual's response is weak but noted that by FDA and EMA regulatory standards these define treatment-eligible populations.

3.23. The Committee considered that, generally, evidence for predictive benefit of immunohistochemical assays for ICI agents is limited, and that evidence for differing sensitivity and specificity of each antibody is of moderate to good quality. The Committee noted that less sensitive assays define smaller populations. The Committee considered that the evidence supporting the value of PD-L1 testing for clinical decision making is limited, but that this inference would benefit from the reporting of outcomes for people with high expression of PD-L1 compared to those with no expression of PD-L1 in the relevant trials. The Committee considered that the primary benefit of PD-L1 testing would occur when used in conjunction with an individual's performance status to inform treatment decision making (ie whether or not they should receive ICI monotherapy or chemotherapy).

3.24. The Committee noted that in April 2022, CTAC noted the sub-group analysis of the patient population with PD-L1 1-49% in KEYNOTE 042 indicated minimal benefit from pembrolizumab therapy and the benefit seen in the PD-L1 >1% cohort was skewed by the significant benefit seen from the PD-L1 >50% cohort.

3.25. The Committee noted that in New Zealand, MedSafe does not require a specific test to be used with ICIs, simply a "validated test", but that the language specific to each scoring system is used for each agent, which theoretically ties the ICI to its companion or complimentary diagnostic. The Committee noted that it is unclear whether or not the same holds for the identified scoring system associated with each validated test. The Committee considered that the definition of a validated test in the New Zealand context is unclear. The Committee considered that requiring infrastructure and skill development around specific testing has short term implications in terms of which ICI agents are used, but also in the long term if other ICIs are funded in future which may require a different diagnostic test.

3.26. The Committee considered that, if either pembrolizumab or atezolizumab were funded in this setting, there would be benefit in the supplier offering access to testing in the short term but noted that this may mean that testing centres are locked into using specific testing platforms in the long term. The Committee considered it important that the validation of an in-house lab test would be derived from its ability

to identify the same population as the relevant complimentary/companion diagnostics.

3.27. The Committee considered that there may be variable access to diagnostic biopsy procedures in New Zealand currently, primarily those with less access to tertiary hospitals, but that Pharmac's ability to impact this inequity was limited. The Committee considered that, in addition to access to PD-L1 testing, access to diagnostic biopsy procedures (and the obtaining of sufficient tissue amounts) to enable the testing may present a barrier to accessing monotherapy. The Committee considered that, in the absence of having available tissue from biopsy, it may be appropriate to offer individuals first-line ICI monotherapy for NSCLC if they are not fit to receive combination with chemotherapy. The Committee considered that overall, approximately 10% would not be able to undergo the biopsy, and that this group would need to be accounted for in population number estimates.

3.28. The Committee noted that the use of immunotherapy in individuals with EGFR or ALK activating mutations would not be evidence based. The Committee however considered that confirmation of EGFR and ALK activating mutations would be sought if possible. The Committee considered that it was uncertain of the sequence of testing if there was a small volume of tissue obtained from biopsy, however this could be confirmed with pathologists and would likely vary across the country in the absence of national alignment.

3.29. The Committee considered that given the limited infusion capacity across the country, treatment schedules and therefore dosing frequency are important and that this should be considered beyond the immediate cost attributable to this variation during evaluation. The Committee considered that the relative shelf life and stability of the agent was an important consideration and that the value of extended shelf life and stability was of particular importance for smaller centres.

4. First-line combination therapy for the treatment of advanced non-small cell lung cancer (NSCLC)

Application

4.1. The Advisory Committee reviewed the following funding applications for the first-line combination therapy of advanced non-small cell lung cancer (NSCLC):

- Pembrolizumab (submitted by Merck Sharp and Dohme [MSD] in August 2018)
- Atezolizumab +/- bevacizumab (submitted by Roche in November 2018)
- Nivolumab + ipilimumab (submitted Bristol-Myers Squibb NZ Limited in August 2022)
- Tislelizumab (submitted by BeiGene in July 2022)

4.2. The Committee noted that Pharmac staff sought advice in the context of this RFP for ICIs for advanced NSCLC, noting that Pharmac has received previous advice regarding atezolizumab, nivolumab and pembrolizumab in this setting.

4.3. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

4.4. The Advisory Committee **recommended** that an agent in the immune checkpoint inhibitor class be recommended with a **high** priority for the first-line combination treatment of advanced non-small cell lung cancer within the context of treatments of malignancy, subject to the following Special Authority criteria:

> **Initial application – (non-small cell lung cancer first-line combination)** only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist.
> Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced or metastatic, unresectable, non-small cell lung cancer; and
> 2. The patient has not had chemotherapy for their disease in the palliative setting; and
> 3. Patient has not received prior funded treatment with an immune checkpoint inhibitor for NSCLC; and
> 4. There is documentation confirming that the disease does not express activating mutations of EGFR or ALK tyrosine kinase unless not possible to ascertain; and
> 5. XXXXX to be used in combination with platinum-based chemotherapy; or
> 6. Patient has an ECOG 0-2; and
> 7. XXXXX to be used at a maximum dose of XXX every XXX weeks (or equivalent) for a maximum of 12 weeks; and
> 8. Baseline measurement of overall tumour burden is documented clinically and radiologically.
>
> **Renewal – (non-small cell lung cancer first line combination therapy)** only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist.
> Approvals valid for 3 months for applications meeting the following criteria:
> All of the following
> 1. Any of the following:
> 1.1. Patient's disease has had a complete response to treatment; or
> 1.2. Patient's disease has had a partial response to treatment; or
> 1.3. Patient has stable disease; and
> 2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
> 3. No evidence of disease progression; and
> 4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
> 5. XXXX to be used at a maximum dose of XXXX every XXXX weeks (or equivalent); and
> 6. XXXX to be discontinued at signs of disease progression; and
> 7. Treatment with XXXXX to cease after a total duration of 24 months from commencement (or equivalent).

4.5. The Committee considered that the agents within this class are likely to provide similar health benefits. The Committee considered that the evidence strength and quality is highly variable between these agents in the given population, however, that there appears to be a class effect across the ICIs discussed. The Committee considered that funding an agent within this class in combination with chemotherapy in the first line setting would have a significant impact on addressing the unmet need for those with advanced NSCLC. The Committee considered that the infusion burden and health sector costs of each agent should be considered, beyond just cost in determining the agent progressed for funding. The Committee considered that selecting a treatment which is practical, improves accessibility, and addresses equity issues is pertinent.

Discussion

Māori Impact

4.6. The Committee considered that the disproportionate impact of advanced NSCLC for Māori had been described well in its previous considerations for agents for funding in this context (non small cell lung cancer).The Committee considered that the impact of funding an agent for this indication on Māori health outcomes would be

substantial given the disproportionate rates of diagnosis, the late stage of disease at diagnosis, and the inequitable outcomes for Māori.

Pembrolizumab

4.7. The Committee noted that the funding application for pembrolizumab was submitted by MSD in August 2018.

4.8. The Committee noted the previous clinical advice received for this funding application, which included a medium recommendation by PTAC in both the November 2018 and February 2019 meetings, and a review of evidence with no formal recommendation by the Cancer Treatments Subcommittee of PTAC in July 2020. The Committee noted that this application was also reviewed by the Cancer Treatments Advisory Committee in April 2022 in preparation for the release of the RFP.

4.9. The Committee noted that pembrolizumab is Medsafe approved in combination with pemetrexed and platinum chemotherapy for the first-line treatment of individuals with metastatic NSCLC, with no EGFR or ALK genomic tumour aberrations, and in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of those with metastatic squamous NSCLC.

4.10. The Committee noted that pembrolizumab in combination with pemetrexed and platinum chemotherapy is currently recommended for use in the first line treatment of non-squamous NSCLC by PBAC (Australia), CADTH (Canada), SMC (NHS Scotland) and NICE (NHS England/Wales). It was also noted that pembrolizumab in combination with carboplatin and paclitaxel chemotherapy is currently recommended for the requested indication in NSCLC by CADTH, SMC, and NICE; CADTH and SMC also recommended the combined use of nab-paclitaxel. The Committee noted that no information was available regarding the assessment of pembrolizumab for squamous NSCLC by PBAC.

4.11. The Committee noted that the recommended dose of pembrolizumab for advanced squamous NSCLC is 200 mg intravenously (IV) (flat dosing) over 30 minutes every 3 weeks (continued until disease progression or toxicity) in combination with carboplatin 6 AUC (area under the curve) IV over 60 minutes and paclitaxel 200 mg/m^2 IV over 3 hours every 3 weeks (continued for a maximum of 4 cycles). The Committee noted that the recommended dose of pembrolizumab for advanced non-squamous NSCLC is 200 mg IV (flat dosing) over 30 minutes every 3 weeks, in combination with pemetrexed 500 mg/m^2 IV over 10 minutes every 21 days (continued until disease progression or toxicity) and either carboplatin 5 AUC IV over 60 minutes or cisplatin 75 mg/m^2 IV over 60 minutes (continued for a maximum of 4 cycles) (New Zealand Formulary [NZF]. July 2022. Lung NSCLC metastatic – carboplatin, paclitaxel and pembrolizumab; NZF. July 2022. Lung NSCLC metastatic –carboplatin, pemetrexed and pembrolizumab; eviQ. May 2022. NSCLC metastatic cisplatin, pemetrexed and pembrolizumab).

4.12. The Committee noted that the key evidence for pembrolizumab comes from three clinical trials, KEYNOTE 189 (non-squamous), KEYNOTE 407 (squamous), and KEYNOTE 021G (non-squamous). The Committee also noted the follow up analyses of these trials which were provided by the supplier (MSD).

- The Committee noted the results from the KEYNOTE-189 updated analysis and 5-year survival update. It was noted that after a median follow up of approximately 46.3 months, first-line pembrolizumab in combination with

chemotherapy reduced risk of death by 40% in patients with metastatic non-squamous NSCLC, vs chemotherapy alone, regardless of PD-L1 status (hazard ratio [HR], 0.60; 95% confidence interval [CI] 0.50 to 0.72), doubled the median overall survival (OS) outcomes for patients (22.0 vs 10.6 months), and significantly increased the proportion of patients alive at 3 years (31.3% vs 17.4%). It was noted that after a median follow up of 64.6 months (range 60.1 to 72.4 months), the 5-year survival rate was 19.4% for patients treated with pembrolizumab + pemetrexed + platinum-based chemotherapy, compared to 11.3% for placebo + pemetrexed + platinum-based chemotherapy.

- The Committee noted the results from the updated analysis and 5-year survival update. It was noted that after a median follow up of 40.1 months, first-line pembrolizumab in combination with chemotherapy reduced risk of death by 29% in patients with metastatic squamous NSCLC vs chemotherapy alone, regardless of PD-L1 status (HR, 0.71; 95% CI, 0.59 to 0.86); increased median OS (17.2 vs 11.6 months); and increased the proportion of patients alive at 3 years (29.7% vs 18.2%). It was noted that after a median follow up of 59.9 months (range 49.9 to 66.2), pembrolizumab doubled five-year survival (18.4% vs 9.7%) (Novello, S. et al. Annals of Oncology. 2022; 33, S993 - S994).

- The Committee noted the results from the KEYNOTE-021G report of long-term outcomes. The Committee noted that median PFS was improved with pembrolizumab + PC vs PC alone (HR: 0.54; 95% CI 0.35 to 0.83), and that the 3-year PFS rates were 37% and 16%. The Committee noted that the median duration of response (DOR) was 36.3 months with pembrolizumab + PC and 22.8 months with PC alone, with estimated DOR rates of 71% and 47% at 2 years and 51% and 47% at 3 years. The Committee noted that the OS HR was 0.71 (95% CI 0.45 to 1.12), and 3-year OS rates were 50% and 37% (Awad et al. J Thorac Oncol. 2021;16:162-8).

4.13. The Committee also noted an additional study identified by Pharmac staff comparing pembrolizumab + chemotherapy vs atezolizumab + chemotherapy +/- bevacizumab in patients with previously untreated non-squamous NSCLC patients without EGFR/ALK aberrations (Halmos et al. Lung cancer. 2021;155:175-82).

4.14. The Committee considered the strength and quality of evidence for pembrolizumab combination therapy for advanced NSCLC to be strong. The Committee considered that the studies discussed are of good design, good power, and demonstrate OS benefit despite crossover with consistent secondary endpoints. It was also considered that self-reported outcomes of those treated support the evidence and that the chemotherapy backbones included in these trials are relevant to the New Zealand setting.

Atezolizumab +/- bevacizumab

4.15. The Committee noted that the funding application for atezolizumab +/- bevacizumab was submitted by Roche in November 2018.

4.16. The Committee noted the previous clinical advice received for this funding application, which included a decline recommendation by CaTSoP in April 2019, July 2020, and October 2020. The Committee noted that this application was also reviewed by CTAC in April 2022 in preparation for the release of the RFP.

4.17. The Committee noted that atezolizumab +/- bevacizumab is Medsafe approved in combination with paclitaxel and carboplatin for the first-line treatment of people with non-squamous metastatic NSCLC. The Committee noted that atezolizumab + bevacizumab + chemotherapy is currently recommended for use in the first line treatment of non-squamous NSCLC by PBAC and NICE. NICE has recommended atezolizumab with bevacizumab in combination with carboplatin + paclitaxel chemotherapy, but not yet with carboplatin + nab-paclitaxel. It was noted that CADTH has not yet assessed atezolizumab + bevacizumab for this indication and was not recommended for use by the SMC.

4.18. The Committee noted that atezolizumab + bevacizumab + carboplatin + paclitaxel (ACBP) has been approved by PBAC and by NICE, rather than atezolizumab + carboplatin + paclitaxel (ACP). The Committee noted that NICE and PBAC conducted indirect comparison modelling which suggests that atezolizumab + bevacizumab provides a significant improvement over the backbone of chemotherapy alone. Members considered that indirect comparisons are not ideal, however there were no specific concerns about this data above and beyond the usual caveats associated indirect comparisons (NICE: Atezolizumab in combination for treating metastatic squamous NSCLC. June 2019; PBAC: Atezolizumab + bevacizumab for NSCLC. March 2019).

4.19. The Committee noted that the recommended dose of atezolizumab is 1200 mg IV over 60 minutes, every 3 weeks in combination with bevacizumab 15 mg/kg IV over 90 minutes, every 3 weeks (continued until disease progression or toxicity), carboplatin 6 AUC IV over 60 minutes, and paclitaxel 200 mg/m^2 IV over 3 hours every 3 weeks (continued for a maximum of 6 cycles) (NZF. July 2022. Lung NSCLC metastatic – Carboplatin, paclitaxel, atezolizumab and bevacizumab).

4.20. The Committee noted that the key evidence for atezolizumab +/- bevacizumab comes from the IMpower 150 trial (advanced non-squamous NSCLC). The Committee also noted an indirect treatment comparison provided by Roche comparing the survival outcome of the IMPower150 ACBP treatment arm against the New Zealand standard of care (platinum/pemetrexed chemotherapy) as well as against another ICI, pembrolizumab.

4.21. The Committee noted the updated published evidence provided by the supplier (Roche) from the IMPower 150 final analysis. The Committee noted that this was a global, open label, randomised, phase III study in patients with chemo-therapy-naïve, Stage IV, recurrent, metastatic, non-squamous NSCLC. The Committee noted that after a minimum duration of follow up of 32.4 months the median PFS in the intention to treat (ITT) wild type (WT) was 6.3 months in the ACP arm and 8.4 months in the ABCP arm vs 6.8 months in the BCP arm (ACP vs BCP, HR 0.82, 95% CI 0.70 to 0.97; ABCP vs BCP, HR 0.57, 95% CI 0.48 to 0.67). The Committee noted that the median OS in the ITT-WT population was 19.0 months, 19.5 months, and 14.7 months in the ACP, ABCP and BCP arms respectively (ACP vs BCP HR 0.84, 95% CI 0.71 to 1.00, *P*=0.05; ABCP vs BCP HR 0.80, 95% CI 0.67 to 0.95) (Socinski et al. J Thorac Oncol. 2021;16:1909-24). The Committee noted that the median OS in the ITT population was 19.0 months, 19.8 months, and 15.0 months in the ACP, ABCP and BCP arms respectively (ACP vs BCP HR=0.86, 95% CI 0.73 to 1.01, *P*=0.07; ABCP vs BCP (HR=0.80, 95% CI 0.68 to 0.95). The Committee also noted an additional publication reporting the patient-reported outcomes from the IMpower 150 trial (Reck et al. J Clin Oncol. 2020;38:2530-42).

4.22. The Committee also noted the following studies:

- IMPOWER 130: A randomised, multicentre, open-label, phase III study designed to evaluate the safety and efficacy of atezolizumab + carboplatin + nab-paclitaxel vs carboplatin + nab-paclitaxel in chemotherapy-naive participants with non-squamous NSCLC. The Committee noted that the results showed a PFS and OS benefit (ClinicalTrials.gov IMPOWER 130).

- IMPOWER 131: A randomised, open-label, multicentre, phase III study evaluating the efficacy and safety of atezolizumab + carboplatin + paclitaxel or atezolizumab + carboplatin + nab-paclitaxel vs carboplatin + nab-paclitaxel in chemotherapy-naive patients with squamous NSCLC. The Committee noted that the results showed a PFS benefit but no OS benefit (ClinicalTrials.gov IMPOWER 131).

- IMPOWER 132: A randomised, multicentre, open-label, phase III study evaluating the efficacy and safety of atezolizumab + cisplatin/carboplatin + pemetrexed vs cisplatin/carboplatin + pemetrexed in participants who are chemotherapy-naive and have Stage IV non-squamous NSCLC. The Committee noted that the results showed a PFS benefit but no OS benefit (ClinicalTrials.gov IMPOWER 132).

- IMPOWER 110: A randomised, open-label study evaluating the efficacy and safety of atezolizumab compared with chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion) combined with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in PD-L1-selected, chemotherapy-naive participants with non-squamous or squamous NSCLC. The Committee considered the outcomes of this trial were not particularly impressive (ClinicalTrials.gov IMPOWER 110).

4.23. The Committee considered the strength and quality of evidence for atezolizumab +/- bevacizumab combination therapy for advanced NSCLC to be poor. The Committee considered that, due to hierarchical testing, the third arm of IMPOWER 131 is unable to be reported. The Committee considered that the evidence for ACP vs CP relies on data provided by IMPOWER 130, however the chemotherapy arm is nab-paclitaxel, not paclitaxel. The Committee considered that the relevance of the evidence supporting the benefit of atezolizumab +/- bevacizumab combination therapy to the New Zealand setting to be poor.

4.24. The Committee considered that the data for atezolizumab +/- bevacizumab combination therapy for advanced squamous NSCLC is very limited, and that the advanced squamous NSCLC data available is largely extrapolated and the OS benefit is not proven. The Committee however considered that IMPOWER 110 may provide additional support for the use of atezolizumab in squamous NSCLC. The Committee considered that, given the paucity of evidence of health benefit in the advanced squamous NSCLC population, atezolizumab would pragmatically provide a similar health benefit to that seen in the advanced non-squamous NSCLC population, however the evidence is poor, and this is uncertain.

4.25. The Committee considered that the role of bevacizumab when used in combination with atezolizumab and chemotherapy in advanced NSCLC is unclear, and that the benefit of ABCP over CP is not yet proven. The Committee also considered that, if ABCP were to be funded, bevacizumab would not be given to those with advanced squamous NSCLC due to the risk of haemoptysis. The Committee also considered that the addition of bevacizumab would add significant chair time, as well as increased toxicity and monitoring requirements.

4.26. The Committee considered that the reason for the differences in outcomes between the atezolizumab and pembrolizumab trials, despite using the same chemotherapy regimens, is unknown. It was considered that the cause for these inconsistencies may be a result of nuances around the heterogeneity of the populations (eg IMPOWER 132 was not stratified for PD1 status), selection of the chemotherapies, or ethnicity demographics leading to differences in outcome (eg KEYNOTE 402 2% Asian, IMPOWER 132 25% Asian).

4.27. The Committee considered that the additional survival data provided by Roche does not resolve the Committee's previous concerns regarding the quality and strength of the evidence for atezolizumab +/- bevacizumab in combination with chemotherapy in the first-line treatment of advanced NSCLC.

Nivolumab + ipilimumab

4.28. The Committee noted that the funding application for nivolumab + ipilimumab was submitted by Bristol-Myers Squibb (NZ) Limited in August 2022 in response to the advanced NSCLC RFP. The Committee noted that Pharmac has not previously received a funding application for nivolumab and ipilimumab for the first line combination treatment of advanced NSCLC.

4.29. The Committee noted that nivolumab + ipilimumab are ICIs that target the programmed death-1 (PD-1) receptor and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor, respectively (New Zealand Formulary. Immune checkpoint inhibitors).

4.30. The Committee noted that nivolumab + ipilimumab is Medsafe approved in combination with two cycles of platinum-doublet chemotherapy for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations. The Committee noted that nivolumab + ipilimumab in combination with platinum-based chemotherapy is currently recommended for use in the first line treatment of NSCLC by PBAC, CADTH, and SMC. It was noted that PBAC specifically recommended nivolumab with ipilimumab for squamous NSCLC, and that NICE did not recommend nivolumab with ipilimumab for this indication.

4.31. The Committee noted that the recommended dose is nivolumab 360 mg IV over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab IV over 30 minutes every 6 weeks, until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression (Medsafe Datasheet. DOR Jan 2022) in combination with platinum chemotherapy administered every 3 weeks for two cycles; after completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab IV every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks.

4.32. The Committee noted that the key evidence for nivolumab plus ipilimumab comes from the CheckMate 9LA trial:

- The Committee noted that CheckMate 9LA is an international, randomised (1:1), open label, phase III study investigating the effectiveness of nivolumab + ipilimumab with chemotherapy in adult patients with treatment naïve, histologically confirmed stage IV/recurrent squamous and non-squamous advanced NSCLC. The Committee noted that patients were randomised to receive nivolumab (360 mg IV every 3 weeks) + ipilimumab (1 mg/kg IV every 6 weeks) combined with platinum doublet chemotherapy (IV every 3 weeks for two cycles), or chemotherapy alone (every 3 weeks for four cycles).

- The Committee noted that after a median follow up of 13.2 months (inter-quartile range [IQR] 6.4 to 17.0), pre-planned interim analysis and long-term follow up analysis reported that median OS was 15.6 months (95% CI 13.9 to 20.0) in the experimental group vs 10.9 months (9.5 to 12.6) in the control group (HR 0.66 [95% CI 0.55 to 0.80]) (Paz-Area et al. Lancet Oncol. 2021;22:198-211).

- The Committee noted that the most common grade 3-4 treatment-related adverse events (TRAEs) (experimental vs control) were neutropenia (7% vs 9%), anaemia (6% vs 14%), diarrhoea (4% vs 1%), increased lipase (6% vs 1%), and asthenia (1% vs 2%). The Committee noted that the proportion of serious TRAEs of any grade was 30% vs 18%, with seven vs six deaths. The Committee considered that the deaths linked to acute renal failure, diarrhoea, and liver would likely be related to immune-related toxicity however were not reported as such. The Committee considered that deaths linked to sepsis and thrombocytopenia are likely to be related to the chemotherapy component (Paz-Area et al. Lancet Oncol. 2021;22:198-211).

- The Committee noted that after a median follow up of 30.7 months, the 2-year update reported that nivolumab + ipilimumab + chemotherapy continued to prolong OS vs chemotherapy, with a median OS of 15.8 vs 11.0 months (HR 0.72; 95% CI 0.61 to 0.86) and two-year OS rate of 38% vs 26%. The Committee noted the two-year PFS rate was 20% vs 8%, and that the median PFS after next line of treatment was 13.9 vs 8.7 months. It was also noted that the ORR was 38% vs 25%, respectively; 34% vs 12% of all responses were ongoing at 2 years. (Reck et al. ESMO Open. 2021;6:100273).

4.33. The Committee considered the strength and quality of evidence for ipilimumab + nivolumab + chemotherapy for advanced NSCLC to be moderate. The Committee considered that CheckMate 9LA was a well-powered, randomised phase III study which demonstrates an OS benefit. However, the Committee considered that the control arm does not measure benefit of ipilimumab + nivolumab + chemotherapy against nivolumab + chemotherapy, and that the additional benefit of ipilimumab is therefore unclear. The Committee considered that it remains unclear whether the effects of nivolumab + ipilimumab are synergistic, additive, or due to interpatient variability.

4.34. The Committee considered that nivolumab + ipilimumab would provide the same or similar health benefit to the previously considered pembrolizumab, yet with greater toxicity. The Committee considered the toxicity of nivolumab + ipilimumab may be higher compared to the other treatments discussed for advanced NSCLC, even with the attenuated schedule. The Committee considered that grade III/IV toxicity will like increase health sector expenditure through increased outpatient visits, day ward attendance, and supportive care meds.

4.35. The Committee considered that those with poorer performance status and those with autoimmune disease (namely interstitial lung disease) may not receive first line nivolumab + ipilimumab combination therapy if it were to be funded. The Committee considered that, due to the toxicity of ipilimumab + nivolumab, it would be expected that less people would receive this treatment if it were to be funded, which could increase inequities.

Tislelizumab

4.36. The Committee noted that the funding application for tislelizumab was submitted by BeiGene in July 2022 in response to the advanced NSCLC RFP for treatment in combination with pemetrexed + platinum containing chemotherapy for the first-line treatment of those with locally advanced or metastatic non-squamous NSCLC, and for treatment in combination with carboplatin + paclitaxel for the first-line treatment of those with locally advanced or metastatic squamous NSCLC.

4.37. The Committee noted that tislelizumab is not currently Medsafe approved, however an application has been submitted for the proposed indications. The Committee considered that Medsafe approval is required to ensure product quality. The Committee also considered that many New Zealand centres have experience with tislelizumab due to clinical trial participation, and the side effect profile seems to reflect that of other agents in this class. The Committee noted that applications for the registration of tislelizumab remain under evaluation in the United States, European Union, and Australia at the time of writing. The Committee noted that the indications proposed for submission to Medsafe for approval are identical to those proposed for approval in the European Union and Australia, and that in the United States approval for use in advanced NSCLC has not been sought at this time.

4.38. The Committee noted that the recommended dosage of tislelizumab is 200mg (flat dosing) IV every 3 weeks until progression in combination with carboplatin + paclitaxel/nab-paclitaxel for advanced squamous NSCLC, and pemetrexed + platinum containing chemotherapy for advanced non-squamous NSCLC. The Committee noted that the RATIONALE-304 and RATIONALE-307 administered tislelizumab over 1 hour for the first two doses, and over 30 minutes for remaining doses, and considered this to be appropriate.

4.39. The Committee noted that the key evidence for tislelizumab comes from two clinical trials, RATIONALE-304 (non-squamous NSCLC) and RATIONALE-307 (squamous NSCLC):

- RATIONALE-304 is an open label, randomised, multicentre, phase III trial investigating the effectiveness of platinum-based chemotherapy with (Arm A; n=222) and without (Arm B; n=110) 200 mg tislelizumab in 332 adult patients (18 to 75 years) with treatment naïve, histologically confirmed locally advanced (stage IIIB) or metastatic (stage IV) advanced non-squamous NSCLC. The Committee noted that after a median follow-up of 9.8 months, a significantly longer PFS was observed in arm A compared with arm B (HR 0.645, 95% CI 0.462 to 0.902, *P*=0.0044), and the median PFS was 9.7 months (95% CI: 7.7 to 11.5) and 7.6 months (95% CI: 5.6 to 8.0) in arms A and B, respectively. The Committee also noted that a higher ORR was observed in Arm A (57.4%; 95% CI 50.6 to 64.0) compared with Arm B (36.9%; 95% CI 28.0 to 46.6), and that median OS was not reached in either arm (Lu et al. J Thorac Oncol. 2021;16:1512-22).

- RATIONALE-307 is an open label, randomised, multicentre, phase III clinical trial investigating the effectiveness of tislelizumab in adult patients (18 to 75 years) with treatment naïve, histologically confirmed locally advanced (stage IIIB) or metastatic (stage IV) squamous NSCLC. The Committee noted that patients were randomised to receive tislelizumab (200 mg, day 1) + paclitaxel (175 mg/m^2, day 1) + carboplatin (AUC of 5, day 1) (arm A, n=120); tislelizumab (200 mg day 1) + nab-paclitaxel (100 mg/m^2, days 1, 8, and 15) + carboplatin (AUC of 5, day 1) (arm B, n=119); and paclitaxel (175 mg/m^2, day 1) + carboplatin (AUC of 5, day 1) (arm C, n=121). The Committee noted that after a median follow-up of 8.6 months (95% CI, 8.1 to 9.0 months),

tislelizumab plus chemotherapy (arms A and B) vs chemotherapy (arm C) significantly prolonged PFS. The Committee noted that the median PFS for arms A, B, and C was 7.6 months (95% CI 6.0 to 9.8), 7.6 months (95% CI 5.8 to 11.0), and 5.5 months (95% CI 4.2 to 5.7), respectively. The Committee noted that higher response rates were observed in arms A (73%; 95% CI 63.6% to 80.3%) and B (75%; 95% CI 66.0% to 82.3%) vs C (50%; 95% CI to 40.4% to 58.8%) (Wang et al. JAMA Oncol. 2021;7:709-17).

4.40. The Committee noted the following additional sub-analysis studies:

- RATIONALE-304 Study (1L Non-Squamous NSCLC) Sub-analysis: Smokers vs Non-Smokers
- RATIONALE -307 Study (1L Squamous NSCLC) Sub-analysis: Stage IIIB vs Stage IV Patients
- RATIONALE -307 Study (1L Squamous NSCLC) Sub-analysis: Patients Aged ≥65 years
- RATIONALE -307 Study (1L Squamous NSCLC) Sub-analysis: Smokers vs Non-Smokers

4.41. The Committee considered the strength and quality of evidence for tislelizumab combination therapy for advanced NSCLC to be limited but not poor. The Committee considered that two studies are well designed however reported with short follow-up and have a PFS endpoint with no patient reported outcomes. The Committee however considered that the chemotherapy backbones are applicable to New Zealand, and that the population demographics (other than ethnicity) appear similar.

Health Need

4.42. The Committee considered the health need for this population to be high, in line with its considerations at previous meetings. The Committee considered that those receiving combination chemotherapy alongside immunotherapy would need to be of good performance status.

Suitability

4.43. The Committee considered that a key issue for New Zealand Blood and Cancer Centres is the pressure on infusion services, including infrastructure and staffing, compounding space and staffing, and medical staff. The Committee considered that if one of these treatments were to be funded for advanced NSCLC, this would result in a significant increment in numbers of people both at implementation and with conditional survival improvements, leading to increased pressure on infusion services. The Committee also considered that infusion times with increasing numbers of agents included in regimens would exacerbate the burden on infusion services.

4.44. The Committee considered the shelf life of the treatments to be crucial in terms of equity of access. The Committee considered that a minimum of 24 hours (ideally 7 days) stability is required for pressured compounding and day unit infusion services. Members however considered that stability data may vary between compounding facilities depending on the availability of stability data. The Committee noted the lack of stability data for tislelizumab and considered this may result in implementation issues.

4.45. The Committee considered it would be preferable for the treatment to have the widest dosing interval as possible, ideally with the option for widening treatment intervals to beyond 3 weeks. The Committee also considered that toxicity of treatments is likely to add to pressures on the health sector by creating a need for outpatient medical review and inpatient care.

Cost and Savings

4.46. The Committee considered that funding an ICI for first-line combination therapy for advanced NSCLC will increase health sector expenditure due to the increased impact on infusion services and management of toxicities related to treatment.

4.47. The Committee considered that approximately 25-30% of individuals who have disease progression on chemotherapy would receive docetaxel as a subsequent treatment. The Committee agreed that this estimate replaced their previous estimate of 50%.

Funding Criteria

4.48. The Committee considered that Special Authority criteria for an ICI for first-line combination therapy for advanced NSCLC should:

- Target individuals with ECOG performance status of zero to two instead of zero to one.

- No requirement for documentation that the disease does not express activating mutations of EGFR or ALK as this might create a barrier to access due to reliance on biopsy for tissue testing, and that such a criterion should be pragmatic and equitable.

- Omit the requirement for the use of RECIST for assessment, as this assessment is onerous to the current health system constraints. Members considered that RECIST is not an ideal measure for lung tumour burden, that radiologist availability and cost are factors which can create barriers, and that it is challenging to have consistent assessment. However, the Committee noted the need to document disease burden at baseline to enable subsequent assessment.

- Require confirmation that there is no evidence of disease progression at renewal, and that it would be important that the same modality was used to establish response to treatment.

Summary for Assessment

4.49. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICOs (population, intervention, comparator, outcomes) information for pembrolizumab, atezolizumab +/- bevacizumab, nivolumab + ipilimumab and tislelizumab in combination with chemotherapy, if each were to be funded in New Zealand for first-line treatment of advanced NSCLC. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with EGFR-wildtype, unresectable, locally advanced or metastatic non-small cell lung cancer who have not yet received any treatment for their advanced disease			
Intervention	Tislelizumab 200mg intravenous 30 (subsequent cycles) to 60-minute (initial 1-2 cycles) infusion every 3 weeks until disease progression, for a maximum of two years. Tislelizumab is administered in combination with chemotherapy: • In the squamous population, the chemotherapy regimen is carboplatin 6 AUC and paclitaxel 200 mg/m^2 every 3 weeks for 4-6 cycles • In the non-squamous population, the regimen is either carboplatin (5 AUC) or cisplatin (75 mg/m^2) in combination with pemetrexed (500 mg/m^2). The two agents are taken together for 4 cycles after which only the pemetrexed component is continued on a 3-weekly basis. The proportion of patients taking each regimen was weighted by the percentage of people on either regimen in KEYNOTE189 (72% carboplatin and 28% cisplatin). 25% to 30% of patients are assumed to receive docetaxel as second-line treatment upon disease progression	Atezolizumab 1200 mg intravenous 60-minute infusion and bevacizumab 15 mg/kg 90-minute infusion every 3 weeks until disease progression, for a maximum of two years. Atezolizumab is administered in combination with chemotherapy: • In the squamous population, the chemotherapy regimen is carboplatin 6 AUC and paclitaxel 200 mg/m^2 every 3 weeks for 4-6 cycles • In the non-squamous population, the regimen is either carboplatin (5 AUC) or cisplatin (75 mg/m^2) in combination with pemetrexed (500 mg/m^2). The two agents are taken together for 6 cycles after which only the pemetrexed component is continued on a 3-weekly basis. The proportion of patients taking each regimen was weighted by the percentage of people on either regimen in KEYNOTE189 (72% carboplatin and 28% cisplatin). 25% to 30% of patients are assumed to receive docetaxel as second-line treatment upon disease progression	Nivolumab 360 mg intravenous 30-minute infusion every 3 weeks in combination with 1 mg/kg ipilimumab 30-minute infusion every 6 weeks until disease progression, for a maximum of two years. Nivolumab with ipilimumab is administered in combination with chemotherapy: • In the squamous population, the chemotherapy regimen is carboplatin 6 AUC and paclitaxel 200 mg/m^2 5 AUC every 3 weeks for 2 cycles • In the non-squamous population, the regimen is either carboplatin (5 AUC) or cisplatin (75 mg/m^2) in combination with pemetrexed (500 mg/m^2). The two agents are taken together for 2 cycles after which only the pemetrexed component is continued on a 3-weekly basis. The proportion of patients taking each regimen was weighted by the percentage of people on either regimen in KEYNOTE189 (72% carboplatin and 28% cisplatin). 25 to 30% of patients are assumed to receive docetaxel as second-line treatment upon disease progression	Pembrolizumab 200 mg intravenous 30-minute infusion every 3 weeks or 400 mg infusion every 6 weeks until disease progression, for a maximum of two years. Pembrolizumab is administered in combination with chemotherapy: • In the squamous population, the chemotherapy regimen is carboplatin 6 AUC and paclitaxel 200 mg/m^2 5 AUC every 3 weeks for 4-6 cycles • In the non-squamous population, the regimen is either carboplatin (5 AUC) or cisplatin (75 mg/m^2) in combination with pemetrexed (500 mg/m^2). The two agents are taken together for 6 cycles after which only the pemetrexed component is continued on a 3-weekly basis. The proportion of patients taking each regimen was weighted by the percentage of people on either regimen in KEYNOTE189 (72% carboplatin and 28% cisplatin). 25% to 30% of patients are assumed to receive docetaxel as second-line treatment upon disease progression
Comparator(s) (NZ context)	Platinum-based chemotherapy as outlined above. 25-30% of individuals are assumed to receive docetaxel as second-line treatment upon disease progression.			
Outcome(s)	Improvement in the time to disease progression (improvement in progression free survival (PFS) and time to death (improvement in overall survival (OS))			

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

5. Tislelizumab for advanced NSCLC 2L monotherapy irrespective of PD-L1 status

Application

5.1. The Committee reviewed the application from BeiGene NZ Unlimited for the use of tislelizumab (Tevimbra) for the second-line treatment of non-small cell lung cancer (NSCLC) which was received in response to Pharmac's 2022 Request For Proposals (RFP) for immune checkpoint inhibitors (ICIs).

5.2. The Committee noted that Pharmac staff sought advice in the context of this RFP for ICIs for advanced NSCLC, noting that Pharmac has received previous advice regarding atezolizumab, nivolumab and pembrolizumab in this setting.

5.3. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

5.4. The Committee considered that tislelizumab would be expected to provide the same health benefits for the second-line treatment of advanced non-small cell lung cancer (NSCLC) as other immune checkpoint inhibitors (ICIs) in this class for the second-line treatment of non-small cell lung cancer (NSCLC), and that that an agent in this class should be funded for the second line treatment of advanced non-small cell lung cancer.

- In making this consideration, the Committee noted that the second-line clinical trial evidence for tislelizumab (including its statistical analyses) was not yet published or peer reviewed and considered its appraisal of the data was somewhat limited by this.

5.5. The Committee considered that CTAC should review new evidence when it eventuates regarding ICI retreatment for NSCLC (ie where progression did not occur while on ICI treatment) or regarding ICI treatment beyond progression in NSCLC.

5.6. The Committee considered that that an ICI such as tislelizumab for second-line treatment of NSCLC should be funded according to the following criteria:

> **Initial application- (non-small cell lung cancer second line monotherapy)** only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced or metastatic non-small cell lung cancer; and
> 2. Patient has not received prior funded treatment with an immune checkpoint inhibitor for NSCLC; and
> 3. There is documentation confirming that the disease does not express activating mutations of EGFR or ALK tyrosine kinase unless not possible to ascertain; and
> 4. Patient has an ECOG 0-2; and
> 5. Patient has documented disease progression following treatment with at least two cycles of platinum-based chemotherapy; and
> 6. XXXX is to be used as monotherapy at a dose of XXXXX every XXX weeks (or equivalent) for a maximum of 12 weeks; and
> 7. Baseline measurement of overall tumour burden is documented clinically and radiologically.
>
> **Renewal – (non-small cell lung cancer second line monotherapy** only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following
1. Any of the following:
    1.1. Patient's disease has had a complete response to treatment; or
    1.2. Patient's disease has had a partial response to treatment; or
    1.3. Patient has stable disease; and
2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
3. No evidence of disease progression; and
4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
5. XXXX to be used at a maximum dose of XXX every XXX weeks (or equivalent); and
6. XXXX to be discontinued at signs of disease progression; and
7. Treatment with XXXX to cease after a total duration of 24 months from commencement (or equivalent).

Discussion

Māori Impact

5.7. The Committee considered that the disproportionate impact of advanced NSCLC for Māori had been described well in its previous considerations for agents for funding in this context. The Committee noted that Māori with any lung cancer have a very high health need and considered this was a particularly important gap to address.

Background

5.8. The Committee noted the clinical advice and recommendations previously provided for the following ICIs for second-line treatment of NSCLC:

- Atezolizumab (Tecentriq) for locally advanced or metastatic NSCLC after prior chemotherapy (CaTSoP - Low August 2017; PTAC – Low August 2017)
- Nivolumab (Opdivo) for locally advanced or metastatic squamous and non-squamous NSCLC (CaTSoP - Low/Medium April 2016; PTAC – Low May 2016)
- Pembrolizumab (Keytruda) for locally advanced, or metastatic, unresectable NSCLC whose tumours express PD-L1 at a level of ≥ 1% (PTAC – Low November 2016; CaTSoP – Low March 2017).

5.9. The Committee noted that the clinical trial evidence for each of these previously considered ICIs used docetaxel chemotherapy as a control and that this is the current standard of care in New Zealand for the second-line treatment of NSCLC.

Health Need

5.10. The Committee noted that the health need of this population and current treatment paradigm has been extensively discussed previously by PTAC and CTAC. Members considered that health need of this population remained very high and noted that international access to new treatments is increasing for all lines of NSCLC treatment.

5.11. The Committee noted that Māori with any lung cancer have a very high health need, experiencing higher lung cancer registration and mortality rates than non-Māori, and considered this was a particularly important gap to address.

Health Benefits and Suitability

5.12. The Committee noted that tislelizumab 100 mg/10mL concentrate for injection is currently being evaluated by Medsafe for oesophageal cancer and three NSCLC indications, including use as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy. The Committee noted that at the time of submission, the application was considered to meet Pharmac's criteria for consideration under the parallel assessment pathway, which provides for consideration of cancer medicines at the same time as they are assessed by Medsafe.

5.13. The Committee noted that the key evidence for tislelizumab for the second-line treatment of NSCLC comes from one key clinical trial, RATIONALE-303: a randomised (2:1), open-label, multi-centre, phase 3 study of 805 adults with histologically confirmed, locally advanced or metastatic NSCLC who had disease progression during or after a platinum-containing regimen. Participants received either tislelizumab 200 mg IV Q3W or docetaxel 75 mg/m2 IV Q3W until unacceptable toxicity or disease progression, and those in the tislelizumab arm had the option of subsequent tislelizumab 200 mg IV Q3W post-disease progression at the investigator's discretion. The Committee noted that the following data from RATIONALE-303 was submitted for review:

- Huang et al. J Clin Oncol. 2018; 36(15_Supplement)
- Zhou et al. Cancer Res. 2021; 81(13_Supplement):CT039
- RATIONALE-303 Clinical Study Report (CSR) 2022
- Zhou et al. J Clin Oncol. 2021;39(15_Supplement):9069
- Fan et al. J Thorac Oncol. 2021;16:S1021

5.14. The Committee noted that 80% of RATIONALE-303 participants were from China and that 14 (<2%) of patients were enrolled in New Zealand. The Committee considered that patient characteristics were similar across treatment groups and although there were differences between the trial patient populations, it was not unreasonable to compare with the results of the second-line trials for atezolizumab, nivolumab and pembrolizumab. The Committee noted that about half of the RATIONALE-303 participants had non-squamous NSCLC and that large proportions of patients had unknown EGFR mutation (>30%) or ALK rearrangement (>50%) status. The Committee noted that for 15% of patients the trial treatment was a third-line therapy (ie had received two prior lines) and that disease progression was the most common reason for trial treatment discontinuation.

5.15. The Committee noted that the primary endpoint of RATIONALE-303 was overall survival (OS) in the intention-to-treat (ITT) and PD-L1 positive (≥25%) populations, which was reported after median 31.1 months and 27.9 months follow-up for the tislelizumab and docetaxel arms, respectively.

- The Committee noted that the median OS in the ITT group was 16.9 months (95% CI: 15.24 to 19.09 months) with tislelizumab compared with 11.9 months (95% CI: 9.6 to 13.54 months) with docetaxel; hazard ratio (HR) for death: 0.66 (95% CI: 0.56 to 0.79; P<0.0001). The Committee noted that the OS benefit with docetaxel appeared slightly better than that seen in the control arm of the studies previously considered for other ICIs for this indication, however, considered that this difference might be due to improvements in patient care and management of adverse events occurring in the years since the trials were initiated.

- The Committee noted that 29.5% of patients in the tislelizumab arm continued tislelizumab after radiographic progression, and that 20.4% of patients in the docetaxel arm subsequently received immunotherapy. The Committee considered that, although occurring in large proportions, this crossover and treatment beyond progression was unlikely to have a material impact on survival outcomes given the benefit seen despite the crossover. Members noted that the duration of treatment beyond progression was unknown but considered that in this disease, patients generally become symptomatic in a short time and then discontinue such treatment.

- The Committee noted that median OS in the PD-L1 positive group was 19.3 months with tislelizumab compared with 11.5 months with docetaxel; HR 0.53 (95% CI: 0.404 to 0.696; P<0.0001). The Committee noted that the study assessed different PD-L1 thresholds and that the results indicated that all participants received a benefit regardless of PD-L1 expression.

5.16. The Committee noted that the duration of response (DOR) in the RATIONALE-303 ITT population, a secondary outcome, was a median of 13.5 months (95% CI: 8.54 to 19.58 months) with tislelizumab compared with 6.0 months (95% CI: 2.10 to 7.16 months) with docetaxel (HR 0.31; 95% CI: 0.176 to 0.536; P<0.0001). The Committee considered this to be an important outcome for patients because a durable benefit leads to long-term benefits.

5.17. The Committee noted that the median progression-free survival (PFS) in RATIONALE-303 was 4.2 months (95% CI: 3.88 to 22.6 months) with tislelizumab compared with 2.6 months (95% CI: 2.2 to 3.8 months) with docetaxel; HR: 0.63 (95% CI: 0.53 to 0.75).

5.18. The Committee noted that treatment-emergent adverse events led to discontinuation in about 12% of RATIONALE-303 participants in each arm. The Committee considered that there was a relatively high rate of grade three or higher immune-related adverse events (irAEs) in the tislelizumab arm, however, members considered this was similar to what would be expected based on the evidence and experience with other ICIs. The Committee noted that there were no new irAE signals with tislelizumab.

5.19. The Committee noted that the second-line clinical trial evidence for tislelizumab from RATIONALE-303 (including its statistical analyses) was not yet published or peer reviewed and considered its appraisal of the data was somewhat limited by this, however, the Committee considered this status was not surprising given that trial completion is expected in December 2022.

5.20. The Committee noted a cost-effectiveness analysis of tislelizumab relative to each nivolumab and docetaxel, as second- and third-line for advanced or metastatic non-small cell lung cancer in China (Zhou et al. Front Pharmacol. 2022;13:880280), and was made aware of another cost-effectiveness analysis of tislelizumab vs docetaxel for previously treated NSCLC in China (Gong et al. Front Pharmacol. 2022;13:830380).

5.21. The Committee noted there is longer-term evidence now published from the clinical trials previously considered for second-line use of atezolizumab, nivolumab, and pembrolizumab. The Committee noted that the pembrolizumab KEYNOTE-010 trial included a more limited population (PD-L1 positive ≥1%) than that of the other trials which did not restrict eligibility to PD-L1 positive participants. The Committee noted that across these trials there were small proportions of patients with EGFR

mutations or ALK rearrangement, that about a third had ECOG performance status of zero, and that 75-80% were receiving trial treatment as a second-line therapy. The Committee considered that the longer-term evidence from these trials showed similar PFS, OS and durable benefits and reinforced the impression of the class effect consideration with these ICIs in the first-line treatment of NSCLC:

- Mazieres et al. J Thorac Oncol. 2021;16:140-50 - After 47.7 months follow-up in the Oak trial, the median OS was 13.3 months with atezolizumab vs 9.8 months with docetaxel; HR 0.78 (0.68 to 0.89; P<0.0001).

- Borghaei et al. J Clin Oncol. 2021;39:723-33 – After 64.2 and 64.5 months follow-up in the Checkmate 057 and 017 trials, respectively, the median pooled OS for squamous and non-squamous 9.2 months (95% CI: 7.3 to 12.6) with nivolumab vs 6.0 months (95% CI: 5.1 to 7.3) with docetaxel; HR 0.62 (95% CI: 0.48 to 0.79).

- Herbst et al. J Thorac Oncol. 2021;16:1718-32 – After 67.4 months follow-up in KEYNOTE-010, the median OS was 11.8 months (95% CI: 10.4 to 13.1) with pembrolizumab vs 8.4 months (95% CI: 7.6 to 9.5) with docetaxel; HR for death 0.70 (95% CI: 0.61–0.80). 21 patients received second-course pembrolizumab and there was 22.2% crossover in the docetaxel arm.

5.22. The Committee noted that there were no direct comparisons of ICIs for second-line treatment of NSCLC but considered that the evidence reported relatively consistent OS improvement across trials with these ICIs despite some differences in the patient populations within the trials. The Committee further considered that there was no evidence to suggest any ICI might be better tolerated or more efficacious than any other, and therefore a class effect was likely to exist for these ICIs including tislelizumab based on the evidence available in this setting. The Committee considered that tislelizumab would have similar ability to address the unmet need in New Zealand for the second-line use of an ICI and that the evidence for tislelizumab's safety profile also suggested a class effect.

5.23. The Committee considered that tislelizumab would not be expected to provide any additional health benefits or create any additional risks compared with other ICIs (ie atezolizumab, nivolumab and pembrolizumab) considered for second-line treatment of advanced NSCLC. The Committee noted that a similar duration of treatment, similar side effects and considered that a similar frequency of treatment would be expected.

5.24. The Committee noted the three-weekly frequency of tislelizumab treatment and considered that this may differ from that of other ICIs for second-line treatment of advanced NSCLC which may also have options for longer dosing intervals (eg four- or six-weekly). The Committee was made aware of evidence for longer dosing intervals of pembrolizumab from pharmacology modelling and international guidelines in response to the COVID-19 pandemic (Higashiyama et al. J Thorac Oncol. 2022;17:1227-32; Mountzios et al. J Thorac Oncol. 2022;17:1155-7). Members noted the number of patients who experienced new irAEs was slightly higher than expected although considered it unclear whether this was caused by the dosing interval change as this as it was not a controlled trial, and on balance, considered the dosing intervals likely to be safe. The Committee considered that the impact on the health system would be determined by the chosen ICI and the level of comfort with using different dosing schedules.

5.25. The Committee noted the stability of the ICI solutions for infusion (once diluted, if applicable) at 2-8°C ranged from 24 hours for tislelizumab and atezolizumab to four or seven days for pembrolizumab and nivolumab, respectively. The Committee considered that the ease of treatment delivery differed between these ICIs and that these could be important factors for New Zealanders in regard to inequities and access to treatment, particularly those living in rural areas.

5.26. The Committee considered it reasonable to have a maximum funded treatment duration of 24 months with an option to have ICI retreatment where no progression occurred while on ICI treatment, noting that most clinical trials with a two-year ICI treatment duration include an option for retreatment. Members considered that it would be difficult to delineate whether people with NSCLC receiving retreatment would be considered to have first- or second-line treatment as clinically this might be approached as first-line with late progression, indicating a good response to first-line treatment.

5.27. The Committee considered that CTAC should review new evidence when it eventuates regarding ICI retreatment for NSCLC (ie where progression did not occur while on ICI treatment) or regarding ICI treatment beyond progression in NSCLC. The Committee acknowledged its previous view regarding this may be amenable to newer information becoming available to support retreatment or treatment beyond progression. The Committee noted that at this time, the evidence supporting retreatment came from small numbers of patients who initially received 24 months of pembrolizumab and were then retreated post-progression in the KEYNOTE-010 trial (Herbst et al. J Clin Oncol. 2020;38:1580-90) or patients who received 12 months of durvalumab and then treatment with durvalumab at progression in the PACIFIC trial (Spigel et al. J Clin Oncol. 2022;40:1301-11).

Costs and Savings

5.28. The Committee considered that if an ICI were funded for both first- and second-line treatment of NSCLC (but as a single line of treatment), that initially a large number of individuals would receive this as second-line ICI treatment, although this would reduce over time as first-line ICI therapy became common. The Committee considered that changes in health-sector expenditure with tislelizumab would be comparable to those with other ICIs for second-line treatment of advanced NSCLC but that there could be wastage associated with the reduced stability of tislelizumab as currently stated.

5.29. The Committee considered that a two-year maximum treatment duration was appropriate to include in the PICO for assessment, noting its previous comments regarding the option for retreatment in only a small number of patients.

Special Authority Criteria

5.30. The Committee considered that Special Authority criteria for an ICI (such as tislelizumab) for second-line treatment of NSCLC should:

- Target individuals with ECOG performance status of zero to two instead of zero to one, as most have ECOG of two after progression and would be considered able to tolerate this treatment.
- Not require documentation confirming that the disease does not express activating mutations of EGFR or ALK as this might create a barrier to access

due to reliance on biopsy for tissue testing, and that such a criterion should be pragmatic and equitable.

- Omit the requirement for the use of RECIST for assessment, as this onerous assessment is difficult to do in the current health system constraints. Members considered that RECIST is not an ideal measure for lung tumour burden, that radiologist availability and cost are factors which can create barriers, and that it is challenging to have consistent assessment. However, the Committee noted the need to document disease burden at baseline to enable subsequent assessment.

- Require confirmation that there is no evidence of disease progression at renewal, and that it would be important that the same modality was used to establish response to treatment.

Summary for Assessment

5.31. The Committee considered that the evidence for tislelizumab as second-line treatment of NSCLC was limited but not poor and that, for the purposes of economic modelling, it would be appropriate to assume that tislelizumab provided the same or similar health benefit to other agents currently under consideration.

5.32. The Committee considered that the proportion of people who receive docetaxel in the second- and third-line setting was likely to be closer to 30%, rather than the current estimate of 50%.

5.33. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for tislelizumab if it were to be funded in New Zealand for second-line treatment of NSCLC. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with EGFR-wildtype, unresectable, locally advanced or metastatic non-small cell lung cancer who experience disease progression following platinum-based chemotherapy.
Intervention	Tislelizumab 200mg intravenous 30 (subsequent cycles) or 60-minute (first cycle) infusion Q3W until unacceptable toxicity or disease progression, for a maximum of two years.
Comparator(s)	Docetaxel 75 mg/m^2 IV Q3W until unacceptable toxicity or disease progression.
Outcome(s)	Improvement in overall survival (OS) and progression-free survival (PFS).
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	