

**6.01 DABRAFENIB,
Capsule 50 mg (as mesilate),
Capsule 75 mg (as mesilate),
Tafinlar®
TRAMETINIB
Tablet 500 micrograms
Tablet 2 mg,
Mekinist®
NOVARTIS PHARMACEUTICALS AUSTRALIA PTY. LTD.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing for dabrafenib in combination with trametinib (hereafter D+T) for the treatment of adult patients with BRAF V600E mutation positive advanced or metastatic (Stage IV) non-small cell lung cancer (NSCLC).
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus pembrolizumab in combination with platinum-based chemotherapy (hereafter pembrolizumab+PBC). The key components of the clinical issue addressed by the submission are addressed below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adult patients with advanced (metastatic) non-small cell lung cancer (NSCLC) with a BRAF V600E mutation and ECOG PS 0-2
Intervention	Dabrafenib 150 mg (two 75 mg capsules) taken twice daily (i.e., total daily dose of 300 mg) and trametinib 2 mg (one 2 mg tablet) once daily
Comparator	ECOG PS 0-1: Pembrolizumab + platinum-based chemotherapy ECOG PS 2: Platinum-based chemotherapy
Outcomes	ORR, PFS, and OS
Clinical claim	For ECOG PS 0-1: D+T has non-inferior efficacy versus pembrolizumab + platinum-based chemotherapy based on ORR, PFS and OS D+T has different but non-inferior safety to pembrolizumab + platinum-based chemotherapy For ECOG PS 2: D+T has superior efficacy and safety to platinum-based chemotherapy

Source: Table 1.1, p3 of the submission.

D+T = dabrafenib and trametinib; ECOG PS= Eastern Cooperative Oncology Group Performance Status; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

2 Background

Registration status

- 2.1 D+T was TGA registered on 13 May 2019 for the treatment of patients with advanced NSCLC with a BRAF V600 mutation.

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DABRAFENIB					
Dabrafenib 75 mg capsule, 120	\$3,369.08 ^a	1	120	5	Tafinlar
Dabrafenib 50 mg capsule, 120	\$2,300.25 ^a	2 -1	240 -120	5	Tafinlar
TRAMETINIB					
Trametinib 2 mg tablet, 30	\$3,537.84 ^a	1	30	5	Mekinist
Trametinib 500 mcg tablet, 30	\$2,694.03 ^a	4-3	120 -90	5	Mekinist
Category / Program: General Schedule					
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>					
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)					
Condition: Non-small cell lung cancer (NSCLC)					
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)					
Treatment Phase: Initial					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					
AND					
Clinical criteria:					
Patient must have a ECOG performance status of 2 or less Patient must have/have had a WHO performance status of no greater than 2 at treatment initiation with this drug for this condition.					
AND					
Clinical criteria:					
Patient must have evidence of BRAF V600E mutation The condition must be positive for a BRAF V600E mutation					
AND					
Clinical criteria:					
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition					
Treatment Criteria:					
Must be used in combination with trametinib Patient must be receiving trametinib and dabrafenib concomitantly for this condition					
Treatment criteria:					
Patient must be undergoing initial treatment with this drug; or					
Patient must be undergoing continuing treatment with this drug, with an absence of further disease progression while being treated with this drug; or					
Patient must be undergoing non-PBS subsidised treatment with this drug for this PBS indication, with an absence of further disease progression since commencing non-PBS subsidised supply.					

Administrative Advice:

No increase in the maximum quantity or number of units may be authorised.

Administrative Advice:

No increase in the maximum number of repeats may be authorised.

^a Dispensed price for maximum quantity (DPMQ) based on indicative approved ex-manufacturer price (AEMPs) presented in the cost-minimisation approach. A special pricing arrangement (SPA) exists for the comparator pembrolizumab and thus the D+T DPMQ is unknown and could not be determined at this stage. Corrected during evaluation to account for correct proportion of patients with non-squamous and squamous NSCLC in cells 'G63 and H63' of 'Results' worksheet in the Mekinist (trametinib) Tafinlar (dabrafenib) – CMA'.xlsx workbook as reported by Mitchell et al. (2013). DMPQ for Dabrafenib 50 mg (240 capsules of 50 mg for two packs) was calculated using the proposed price per mg based on DPMQ of Dabrafenib 75 mg (120 capsules of 75 mg per pack), i.e., \$0.37

- 3.2 The submission requested a special pricing arrangement for D+T. The submission proposed that the effective price of D+T will be based on the effective price of pembrolizumab+PBC, on a cost-minimisation basis.
- 3.3 The proposed wording of the requested restriction was consistent with the inclusion criteria of the key clinical evidence (E2201 study) for D+T. However, the TGA PI for D+T does not specify the variant for BRAF V600 mutation, whereas both the requested restriction and the key clinical study specifically require the presence for BRAF V600E variant for treatment with D+T eligibility. The ESC considered it would be reasonable for the minority of patients with other BRAF V600 variants to access D+T.
- 3.4 The requested restriction for D+T is agnostic to line of treatment. This aligns with the key clinical evidence from the E2201 study, which included patients who were either untreated patients (first-line) and those who had received up to three lines of prior systemic therapy (second-line and beyond).
- 3.5 Currently, the PBS restriction for pembrolizumab requires that patients must not have been previously treated for their NSCLC in the metastatic setting, or that they have progressed after treatment with either tepotinib or selpercatinib. The submission proposed flow on changes to the listing of pembrolizumab to also permit its use in patients who have progressed after initial treatment with D+T. The ESC considered this was reasonable.
- 3.6 The Secretariat advised a maximum quantity of 120 tablets for dabrafenib 100 mg and 90 tablets for trametinib 500 mcg would be more appropriate as these strengths would be used for dose titration and consistent with other listings.
- 3.7 The submission included a grandfather restriction to facilitate the transition from non-PBS to PBS-subsidised supply. The submission stated that only one patient is currently enrolled in a compassionate access scheme.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Lung cancer is the fifth most diagnosed cancer and the leading cause of cancer death in Australia.¹ The median age at diagnosis of Australian patients is approximately 72 years, with historically higher rates in males but rising cases in females. NSCLC accounts for 85-90% of lung cancer cases², and are broadly categorised into two histologic subtypes: non-squamous (NSQ; 75-85%), squamous (SQ; 15-25%). Approximately 30-40% of NSCLC patients present with Stage IV disease at the time of diagnosis³. The prognosis of lung cancer is poor with a five-year relative survival rate of 24% in 2015-2019, with worse outcomes for patients with Stage IV disease.¹
- 4.2 BRAF mutations are genetic alterations identified in a subset of patients with NSCLC, occurring in approximately 3-5% of cases, with the BRAF V600E variant found in approximately half of these cases. These mutations are significantly associated with adenocarcinomas, occurring more frequently in women and individuals who have never smoked.^{4,5} The role and impact of BRAF as a prognostic marker in NSCLC remains unclear (refer to paragraph 6.13 and 6.14 for more details). To aid in the diagnosis and classification of NSCLC, two MBS-listed multi-gene panel tests (items 73437 and 73438) currently include BRAF mutation testing.
- 4.3 The targeted population is metastatic (Stage IV) BRAF V600E mutation positive NSCLC patients, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. This was consistent with the inclusion criteria of the E2201 study.
- 4.4 Although a line-agnostic listing was requested for D+T, the submission proposed that D+T would be predominantly used as a first-line treatment, with immunotherapy agents reserved for subsequent treatments following disease progression. This aligned with international guidelines, which recommend D+T as the preferred first-line therapy for patients with BRAF V600E mutation-positive Stage IV NSCLC and as a subsequent therapy option for patients who have not previously received a BRAF inhibitor in first-line setting.^{7,6}

¹ Cancer Australia, (2022), Lung cancer in Australia statistics. Available at: <https://www.canceraustralia.gov.au/cancer-types/lung-cancer/statistics>.

² Cancer Australia, (2022), Types of lung cancer. Available at: <https://www.canceraustralia.gov.au/cancer-types/lung-cancer/types>.

³ Li, J. et al., (2019), 'Prognostic value of site-specific metastases in lung cancer: A population-based study'. *Journal of Cancer*, 10, 3079-3086.

⁴ Marchetti, A. et al., (2011), 'Clinical features and outcome of patients with non-small-cell lung cancer harbouring BRAF mutations', *J Clin Oncol*, 29 (26):3574-9, <https://ascopubs.org/doi/10.1200/JCO.2011.35.9638>

⁵ Luk, P. et al., (2015) 'BRAF mutations in non-small cell lung cancer', *Translational Lung Cancer Res*, 4(2):142-8, <https://doi.org/10.3978/j.issn.2218-6751.2014.08.08>

⁶ NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer, Version 1.2025, Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

- 4.5 Standard systemic therapies are recommended by the guidelines as subsequent treatment options for patients whose disease progresses after first-line treatment with D+T. The choice of treatment in subsequent lines varied across guidelines (generally aligns with the non-driver mutation recommendations), and depends upon various factors such as histology, ECOG PS, programmed death ligand-1 (PD-L1) expression, or smoking status.
- 4.6 Dabrafenib is a selective inhibitor of BRAF kinase activity. Trametinib is a selective, allosteric inhibitor of mitogen-activated protein kinase 1 and 2 (MEK1 and MEK2) and inhibits both MEK activation and kinase activity. Together, they act on the mitogen-activated protein kinase (MAPK) pathway by inhibiting cell proliferation at two points, leading to inhibition of the signalling cascade and prevents aberrant cell signalling.

5 Comparator

- 5.1 The submission nominated two comparators for two different groups of patients, depending on the ECOG PS status. For patients with ECOG PS of 0-1, the submission nominated pembrolizumab+PBC as the main comparator. The main argument provided in support of this nomination was that, according to ESMO and NCCN guidelines, pembrolizumab+PBC is the preferred and widely used standard of care for patients with Stage IV BRAF V600E NSCLC with an ECOG PS of 0-1. The ESC considered the nominated comparator was reasonable. The ESC noted that, to a lesser extent, D+T may also substitute for pembrolizumab monotherapy or PBC.
- 5.2 For patients with ECOG PS of 2, the submission nominated PBC as the main comparator, as poor functional status limits the efficacy and safety of more intensive treatments, such as combination of immunotherapy and chemotherapy. The ESC considered the nominated comparator was reasonable but considered the comparison in this population was of little clinical relevance given the subjective nature of PS assessment.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3), a health care professional and organisations (3) via the Consumer Comments facility on the PBS website. The comments from the health care professional noted the good overall response rate observed with D+T. Comments from individuals noted the high burden of NSCLC on patients and their families and the high cost of D+T.
- 6.3 The PBAC noted the Lung Foundation Australia and Rare Cancers Australia commented on the importance of having access to targeted therapies for NSCLC. The

Lung Foundation Australia summarised input it had received from 83 members, including some who had BRAF V600E mutations. The comments noted the high burden of NSCLC and provided strong support for the availability of targeted therapies. Additionally, Rare Caners Australia noted the benefit of the availability of an oral treatment.

- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the D+T submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the E2201 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for D+T, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on single arm data⁷.

Clinical studies

- 6.5 The submission presented an unanchored and unadjusted indirect treatment comparison (ITC), comparing the following studies:
- E2201: A Phase II, multi-centre, single-arm study of D+T in adult patients with BRAF V600E mutant NSCLC.
 - KN-189: A Phase III, multi-centre, randomised, double-blind, placebo-controlled trial of pembrolizumab+PBC in untreated adult patients with Stage IV NSCLC with NSQ histology without EGFR and ALK genomic mutations.
 - KN-407: A Phase III, multi-centre, randomised, double-blind, placebo-controlled trial of pembrolizumab+PBC in untreated adult patients with Stage IV NSCLC with SQ histology without EGFR and ALK genomic mutations.
- 6.6 The E2201 study enrolled both untreated and pretreated patients with BRAF V600E mutation positive Stage IV NSCLC with the following cohorts:
- Cohort A (N=78): Patients with documented tumour progression after receiving at least one prior PBC regimen for metastatic NSCLC were treated with single-agent dabrafenib. This cohort was reasonably excluded as the submission specifically focused on treatment involving the combination of D+T.
 - Cohort B (N=57; hereafter second and subsequent line D+T): Patients with documented tumour progression after receiving at least one prior PBC regimen, and no more than three previous systemic treatments for metastatic NSCLC were treated with the combination of D+T.
 - Cohort C (N=36; hereafter first-line D+T): Patients who had not received any prior systemic therapy for metastatic NSCLC were treated with the combination of D+T.

⁷ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Two untreated patients were initially enrolled in Cohort B and were later included in this cohort.

6.7 For patients with an ECOG PS of 2, the submission did not present any comparative evidence between D+T and PBC alone. The ESC noted only six patients in the E2201 study had an ECOG PS of 2; one in first-line and five in the second-line cohort.

6.8 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study E2201 (NCT01336634)	A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer Planchard, D. et al. Phase 2 Study of Dabrafenib Plus Trametinib in Patients With BRAF V600E-Mutant Metastatic NSCLC: Updated 5-Year Survival Rates and Genomic Analysis. Planchard, D. et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Planchard, D. et al. Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial.	June 2021 <i>Journal of Thoracic Oncology</i> 2022; 17(1):103-115 <i>The Lancet Oncology</i> 2017; 18:1307-1316 <i>The Lancet Oncology</i> 2016; 17:984-993
KN-189 (NCT02578680) (NCT03950674)	Garassino, M. et al. Pembrolizumab plus pemetrexed and platinum in non-squamous non-small cell lung cancer: 5-year outcomes from the Phase 3 KEYNOTE-189 study. Gadgeel, S. et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic non squamous non-small cell lung cancer. Gandhi, L. et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer.	<i>Journal of Clinical Oncology</i> 2023; 41(11):1992-1998. <i>Journal of Clinical Oncology</i> 2020; 38(14):1505-1517. <i>New England Journal of Medicine</i> 2018; 378(22):2078-2092.
KN-407 (NCT02775435)	Novello, S. et al. Pembrolizumab plus chemotherapy in squamous non-small cell lung cancer: 5-year update of the Phase III Paz-Ares, L. et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol specified final analysis of KEYNOTE 407. Paz-Ares, L. et al Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer.	<i>Journal of Clinical Oncology</i> 2023; 41(11):1999-2006. <i>Journal of Thoracic Oncology</i> 2020; 15(10):1657-1669. <i>New England Journal of Medicine</i> 2018; 379(21):2040-2051.

Source: Table 2.7, pp40-41 of the submission.

6.9 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ median duration of follow-up	Risk of bias for ITC	Patient population	Outcomes	
Dabrafenib with trametinib						
E2201	Total: 93 ^a ; 1st Line D+T: 36 2nd Line D+T: 57	Single arm, OL, MC, Phase II 16.3 months in untreated and 16.6 in pretreated patients	High	Patients with BRAF V600E-mutant Stage IV (metastatic) NSCLC	ORR, PFS, OS, DoR, AEs	
Pembrolizumab+PBC vs. PBC						
KN-189	616	R, DB, MC, Phase III 64.6 months ^b		Non-squamous NSCLC patients with Stage IV (metastatic) disease.	ORR, PFS, OS, DoR, AEs	
KN-407	559	R, DB, MC, Phase II 56.9 months ^c	Squamous NSCLC patients with Stage IV (metastatic) disease.	ORR, PFS, OS, DoR, AEs		

Source: Table 2.8, pp44-45; Table 2.13, pp56-57 of the submission; Garassino, M. et al (2023) and Novello, S. et al. (2023). AEs = adverse events; DB = double blind; D+T = dabrafenib and trametinib; DoR = duration of response; ITC = indirect treatment comparison; MC = multi-centre; N = total participants in group; NSCLC = non-small cell lung cancer; OL = open label; ORR = objective response rate; OS = overall survival; PBC = platinum-based chemotherapy; PFS = progression-free survival; R = randomised.

^a The patient number reflects Cohort B (second and subsequent line D+T) and Cohort C (first-line D+T)

^b The median time from random assignment to data cutoff of March 2022

^c The median time from random assignment to data cutoff of February 2022

6.10 The clinical claim of non-inferior efficacy and safety was based on an ITC (unanchored and unadjusted) of the first-line D+T treatment arm from E2201 study versus the pooled pembrolizumab+PBC treatment arms from KN-189 and KN-407 trials for objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). Safety outcomes for D+T treatment were assessed using data from all patients treated with D+T in E2201 study, irrespective of the line of therapy. No patient-reported outcomes were collected in the E2201 study.

6.11 The key differences in the baseline characteristics, treatments, and outcomes across the D+T study (Study E2201) and the two pembrolizumab trials (KN-189 and KN-407) that may affect the transitivity assumptions are summarised below:

- While the E2201 study specifically enrolled patients with BRAF V600E mutation, the KN-189 and KN-407 trials both included patients irrespective of their mutation status. As a result, the proportion of patients with BRAF V600E mutation is unknown. The clinical impact of this difference is uncertain, given the unclear prognostic significance of the BRAF V600E mutation in NSCLC (refer to paragraph 6.13 and 6.14 for further details).
- The E2201 enrolled patients with Stage IV NSCLC, regardless of histology, whereas KN-189 included only NSQ NSCLC patients and KN-407 included only SQ NSCLC patients. A smaller proportion of patients had SQ NSCLC in the first-line D+T arm compared to the pooled pembrolizumab+PBC arm (6% vs. 40%). While SQ NSCLC, in general, has poorer prognosis than NSQ NSCLC, both histology types show good response to immunotherapy; and therefore, the impact of this difference is uncertain.

- A higher proportion of patients in the first-line D+T arm were females compared to pooled pembrolizumab+PBC arm (61% vs. 31%). This may bias against D+T.
- A smaller proportion of patients had brain metastasis in the first-line D+T arm compared to the pooled pembrolizumab+PBC arm (6% vs. 14%). This may favour D+T.
- A smaller proportion of patients in the first-line D+T arm compared to the pooled pembrolizumab+PBC arm were former or current smokers (72% vs. 90%). This may favour D+T.
- More patients treated with first-line D+T in the E2201 study compared to the pooled pembrolizumab+PBC arms received subsequent anti-cancer therapies (56% vs. 49%). These differences are expected to affect the OS outcomes, though the direction of bias remains unclear due to variations in subsequent treatments and lines of treatment.
- The E2201 study assessed tumour response and disease progression by an unblinded investigator and independent review committee (IRC) as supportive analyses, whereas KN-189 and KN-407 assessed disease progression and tumour response using a blinded independent committee review (BICR). The non-randomised, open-label design of the E2201 study may bias the results in favour of D+T.
- The median duration of follow-up at the most recent data cut-off for the E2201 study (January 2021) was 16.30 months (range: 0.41, 80) for those treated with first-line D+T and 16.60 months (range: 0.5, 78.5) for those treated with second and subsequent line D+T. The median duration of follow-up was not reported at the most recent data cut-off for both KN-189 (March 2022) and KN-407 (February 2022). However, the median time from random assignment to data cut-off was 64.6 months (range: 60.1, 72.4) for KN-189 and 56.9 months (range: 49.9, 66.2) for KN-407.

6.12 Overall, the results from the unadjusted and unanchored ITC are associated with a high risk of bias due to transitivity concerns across the E2201 study and the KN-189 and KN-407 trials in terms of disease histology, gender, brain metastases, smoking status, subsequent treatment, and the follow-up duration.

Comparative effectiveness

Prognostic value of BRAF V600E

6.13 To justify the comparison between the E2201 study, which included patients with the BRAF V600E mutation, and the KN-189 and KN-407 trials, which enrolled patients regardless of mutation status, the submission conducted a systematic literature review to determine the prognostic value of the BRAF V600E mutation. The submission referenced two retrospective observational studies assessing the efficacy of immunotherapy, with or without PBC, in patients with advanced NSCLC harbouring

the BRAF V600E mutation versus those with wildtype (WT). Brambilla et al. (2023) found no statistically significant differences in either OS (p=0.12) or PFS (p=0.35). Similarly, Li et al. (2022) reported no statistically significant difference in OS (p=0.15) and PFS (p=0.53). Notably, these studies were not specifically designed to evaluate the prognostic effect of the presence of a BRAF V600E mutation in NSCLC and included a small number of patients (five and 43, respectively).

- 6.14 A literature search conducted during the evaluation on the prognostic value of BRAF V600E mutation in NSCLC showed inconsistent findings. While some studies reported no significant differences in survival or response^{8,9}, others indicated improved survival outcomes for patients with BRAF V600E mutations.^{10,11} Conversely, a few studies showed that patients with BRAF V600E mutations may have poorer prognosis compared to those with BRAF WT or non-V600E mutation.^{12,13} Overall, *the* evaluation considered it was difficult to draw any robust conclusions regarding the prognostic value of BRAF mutations in NSCLC. The Pre-Sub-Committee Response (PSCR) stated these additional studies were not appropriate for assessing whether BRAF V600E is a treatment effect modifier in metastatic NSCLC treated with immunotherapy as they were not conducted this patient population (i.e., metastatic disease, treated with immunotherapy). The PSCR maintained that the evidence presented in the submission is the most reliable evidence that BRAF V600E is not a treatment effect modifier in the population of interest.
- 6.15 The PBAC considered BRAF mutations were not strongly prognostic in NSCLC and treatment with immunotherapy was not a treatment effect modifier¹⁴.

⁸ Perrone, F. et al., (2022), 'Multicenter Observational Study on Metastatic Non-Small Cell Lung Cancer Harboring BRAF Mutations: Focus on Clinical Characteristics and Treatment Outcome of V600E and Non-V600E Subgroups', *Cancers*, 14(8):2019, <https://doi.org/10.3390/cancers14082019>.

⁹ Tan, I. et al., (2019), 'Therapeutic outcomes in non-small cell lung cancer with BRAF mutations: a single institution, retrospective cohort study', *Transl Lung Cancer Res*, 8(3): 258-267, <https://doi.org/10.21037/tlcr.2019.04.03>

¹⁰ Litvak, A. et al., (2014), 'Clinical Characteristics and Course of 63 Patients with BRAF Mutant Lung Cancers', *J Thorac Oncol*, 9: 1669-1674, [https://www.jto.org/article/S1556-0864\(15\)30735-8/pdf](https://www.jto.org/article/S1556-0864(15)30735-8/pdf)

¹¹ EMA Assessment report (2017), Dabrafenib and Trametinib. Available at: https://www.ema.europa.eu/en/documents/assessment-report/tafinlar-epar-public-assessment-report_en.pdf

¹² Marchetti, A., et al. (2011), 'Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations', *J Clin Oncol*, 29(26):3574-9. <https://doi.org/10.1200/jco.2011.35.9638>

¹³ Cardella, S. et al., (2013), 'Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer', *Clin Cancer Res*, 19:4532-4540, <https://pubmed.ncbi.nlm.nih.gov/23833300/>

¹⁴ Liu, R., Rizzo, S., Wang, L. et al. Characterizing mutation-treatment effects using clinico-genomics data of 78,287 patients with 20 types of cancers. *Nat Commun* 15, 10884 (2024). <https://doi.org/10.1038/s41467-024-55251-5>.

Objective response rate

6.16 Table 4 summarises the results of ORR from the intention-to-treat (ITT) population at the most recent data cut-off from E2201 study, and KN-189 and KN-407 trials.

Table 4: Summary of ORR across the studies

	E2201 ^a		KN-189 ^b		KN-407 ^c	
	1 st Line D+T (untreated) N=36	2 nd Line+ D+T (pretreated) N=57	PEMBRO+ PBC N=410	PBC N=206	PEMBRO+ PBC N=278	PBC N=281
Best response, n (%)						
CR	2 (6%)	3 (5%)	10 (2.4%)	1 (0.5%)	10 (3.6%)	11 (3.9%)
PR	21 (58%)	36 (63%)	188 (45.9%)	40 (19.4%)	163 (58.6%)	98 (34.9%)
SD	4 (11%)	7 (12%)	149 (36.3%)	104 (50.5%)	66 (23.7%)	102 (36.3%)
PD	5 (14%)	7 (12%)	37 (9.0%)	36 (17.5%)	17 (6.1%)	40 (14.2%)
Not evaluable	4 (11%)	4 (7%)	12 (2.9%)	8 (3.9%)	6 (2.2%)	7 (2.5%)
No assessment	-	-	14 (3.4%)	17 (8.3%)	16 (5.8%)	23 (8.2%)
Objective Response Rate, n (%)						
CR+PR	23 (63.9%)	39 (68.4%)	198 (48.3%)	41 (19.9%)	173 (62.2%)	109 (38.8%)
[95% CI]	[46.2%, 79.2%]	[54.8%, 80.1%]	[43.4, 53.2]	[14.7, 26.0]	[56.2, 68.0]	[33.1, 44.8]

Source: Table 2.20, p70; Table 2.29, p79 and Table 2.33, p83 of the submission.

CI = confidence interval; CR = complete response; DCO = date cut-off; D+T = dabrafenib and trametinib; n = number of participants with event; N = total participants in group; ORR = objective response rate; PEMBRO = pembrolizumab; PBC = platinum-based chemotherapy; PR = partial response; PD = progressive disease; SD = stable disease.

^a Assessed by the investigator per Response Evaluation Criteria In Solid Tumours (RECIST) v 1.1 at the January 2021 DCO

^b By blinded Independent Central Review per RECIST v 1.1 at the March 2022 DCO

^c By blinded Independent Central Review per RECIST v 1.1 at the February 2022 DCO

6.17 In E2201 study, ORR in first-line D+T patients was 64% (95% CI: 46, 79) and second and subsequent line patients was 68% (95% CI: 55, 80) based on investigator assessment. ORR based on IRC assessment compared to ORR based on investigator assessment was consistent for patients treated with first-line D+T (64% vs. 64%) but lower for those treated with second and subsequent line D+T (63% vs. 68%).

6.18 For the pembrolizumab+PBC arm, the ORR assessed by BICR was 48% (95% CI: 43, 53) in the KN-189 and 62% (95% CI: 56, 68) in the KN-407.

Progression-free survival

6.19 Table 5 summarises the PFS results from the ITT population at the most recent data cut-off from the E2201 study, and KN-189 and KN-407 trials.

Table 5: Summary of PFS across studies

	E2201		KN-189		KN-407	
	1 st Line D+T (untreated) N=36	2 nd Line+ D+T (pretreated) N=57	PEMBRO+ PBC N=410	PBC N=206	PEMBRO+ PBC N=278	PBC N=281
Progression-free survival						
Events, n (%)	28 (78%)	48 (84%)	369 (90.0%)	201 (97.6%)	241 (86.7%)	265 (94.3%)
Median PFS, months (95% CI)	10.8 (7.0, 14.5)	10.2 (6.9, 16.7)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)	8.0 (6.3, 8.5)	5.1 (4.3, 6.0)
HR (95% CI)	NA	NA	0.50 (0.42, 0.60)		0.62 (0.52, 0.74)	

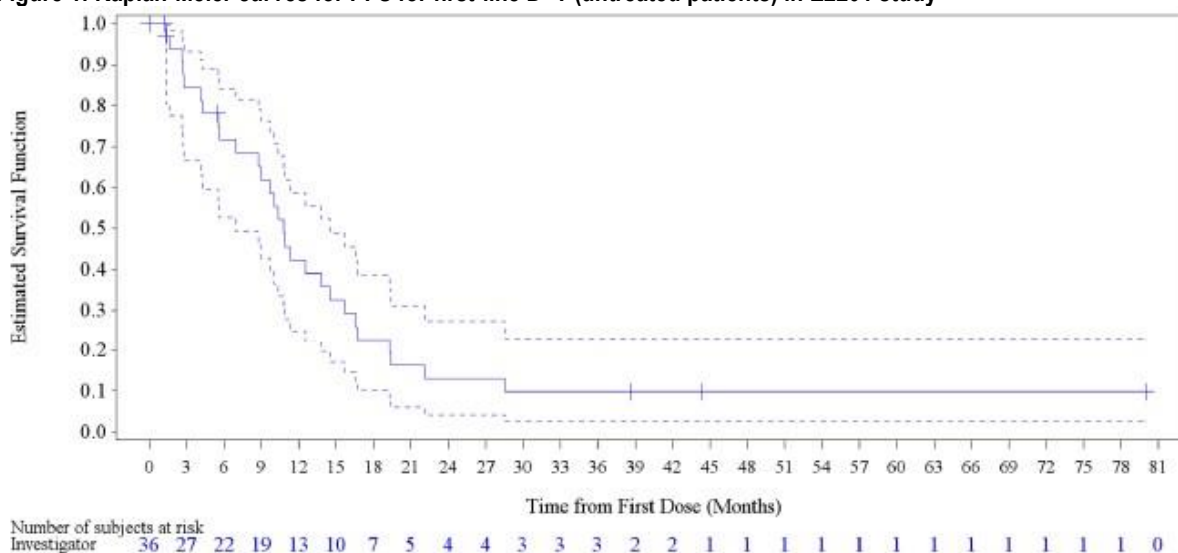
Source: Table 2.22, p71; Table 2.27, p77 and Table 2.31, p81 of the submission.

CI = confidence interval; CR = complete response; D+T = dabrafenib and trametinib; HR = hazard ratio; n = number of participants with event; N = total participants in group; NA = not applicable; ORR = objective response rate; PEMBRO = pembrolizumab; PBC = platinum-based chemotherapy; PFS = progression-free survival.

6.20 In E2201 study, based on investigator assessment, approximately 78% patients treated with first-line D+T and 84% patients treated with second and subsequent line D+T had disease progression or died, with a median PFS of 10.8 months (95% CI: 7.0, 14.5) and 10.2 months (95% CI: 6.9, 16.7), respectively. Median PFS based on IRC assessment was 14.6 months for patients treated with first-line D+T and 8.6 months for those treated with second and subsequent line D+T.

6.21 Figure 1 and Figure 2 present the Kaplan-Meier plots for PFS in the D+T treatment arms from the E2201 study. In the E2201 study, the PFS rates for patients treated with first-line D+T were 42% at 12 months and 13% at 24 months. For those receiving treatment with second and subsequent line D+T, the PFS rates were 43% at 12 months and 25% at 24 months.

Figure 1: Kaplan-Meier curves for PFS for first-line D+T (untreated patients) in E2201 study

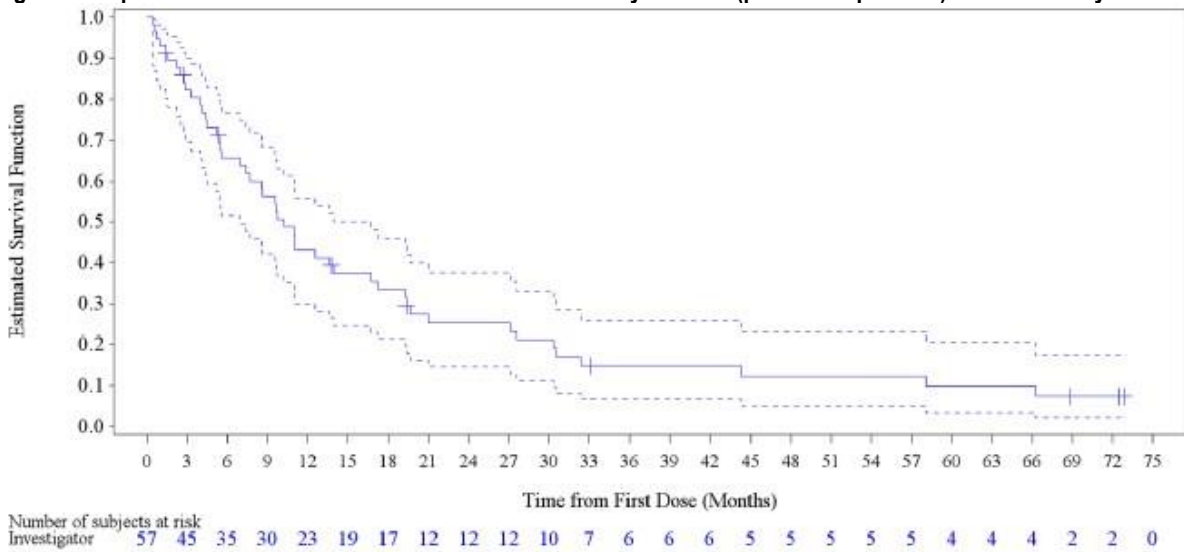


Source: Figure 2.3, p72 of the submission.

D+T = Dabrafenib and trametinib; PFS = progression-free survival.

Note: Lines represent Kaplan-Meier estimate with 95% confidence interval

Figure 2: Kaplan-Meier curves for PFS for second-line and beyond D+T (pretreated patients) in E2201 study



Source: Figure 2.3, p72 of the submission.

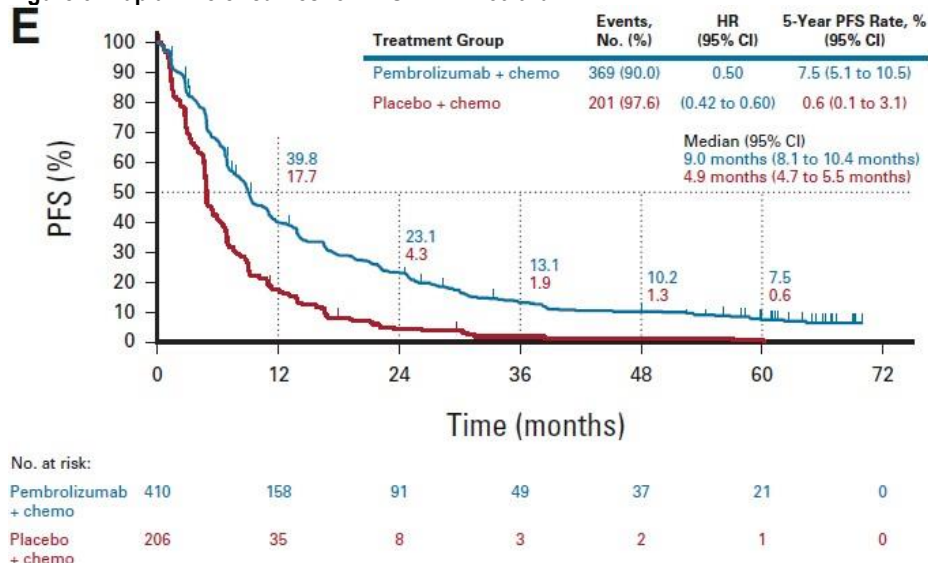
D+T = dabrafenib and trametinib; PFS = progression-free survival.

Note: Lines represent Kaplan-Meier estimate with 95% confidence interval.

6.22 In the KN-189 and KN-407 trials, approximately 90% and 87% of patients treated with pembrolizumab+PBC had progressed at the five-year follow-up, respectively. The median PFS, as per BICR, for pembrolizumab+PBC was 9.0 months (95% CI: 8.1, 10.4) in KN-189 and 8.0 months (95% CI: 6.3, 8.5) in KN-407.

6.23 Figure 3 and Figure 4 present the Kaplan-Meier plots for PFS in the KN-189 and KN-407 trials. In KN-189, the PFS rates with pembrolizumab+PBC were 40% at 12 months and 23% at 24 months. In KN-407, the PFS rates with pembrolizumab+PBC were 36% at 12 months and 21% at 24 months. At 60 months, the PFS rates were 8% in KN-189 and 11% in KN-407 with pembrolizumab+PBC.

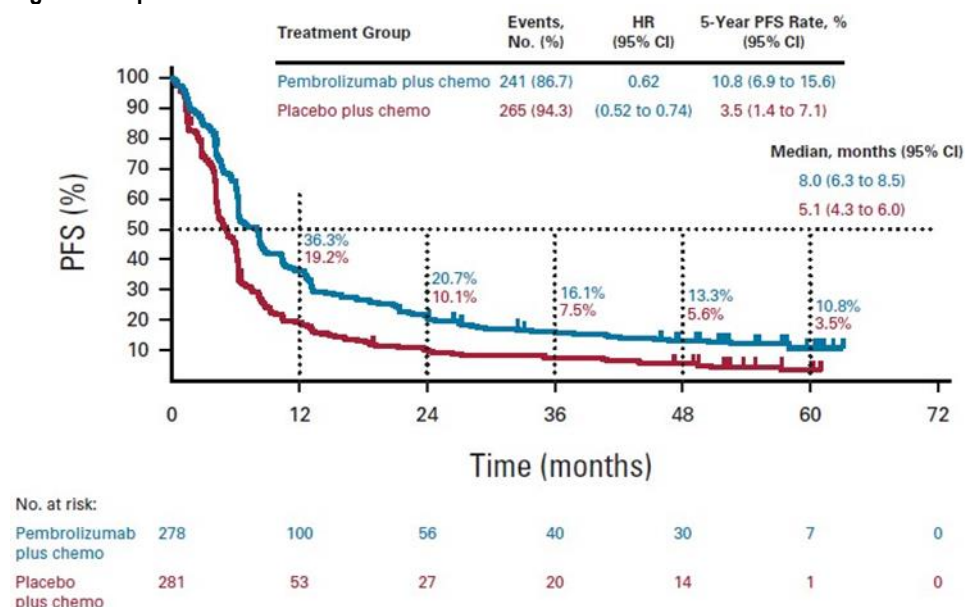
Figure 3: Kaplan-Meier curves for PFS in KN-189 trial



Source: Figure 2.6, p78 of the submission.

CI = Confidence interval; chemo = chemotherapy; HR = Hazard ratio; PFS = progression-free survival.

Figure 4: Kaplan-Meier curves for PFS in KN-407 trial



Source: Figure 2.9, p81 of the submission.

CI = Confidence interval; chemo = chemotherapy; HR = Hazard ratio; PFS = progression-free survival

Overall survival

6.24 Table 6 summarises the OS results from the ITT population at the most recent data cut-off from the E2201 study, and KN-189 and KN-407 trials.

Table 6: Summary of OS across studies

	E2201		KN-189		KN-407	
	1 st Line D+T (untreated) N=36	2 nd Line+ D+T (pretreated) N=57	PEMBRO+ PBC N=410	PBC N=206	PEMBRO+ PBC N=278	PBC N=281
Overall survival						
Deaths, n (%)	27 (75%)	49 (86%)	329 (80.2%)	183 (88.8%)	225 (80.9%)	248 (88.3%)
Median months OS (95% CI)	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)	22.0 (19.5 to 24.5)	10.6 (8.7 to 13.6)	17.2 (14.4, 19.7)	11.6 (10.1, 13.7)
HR (95% CI)	NA	NA	0.60 (0.50, 0.72)		0.71 (0.59 to 0.85)	

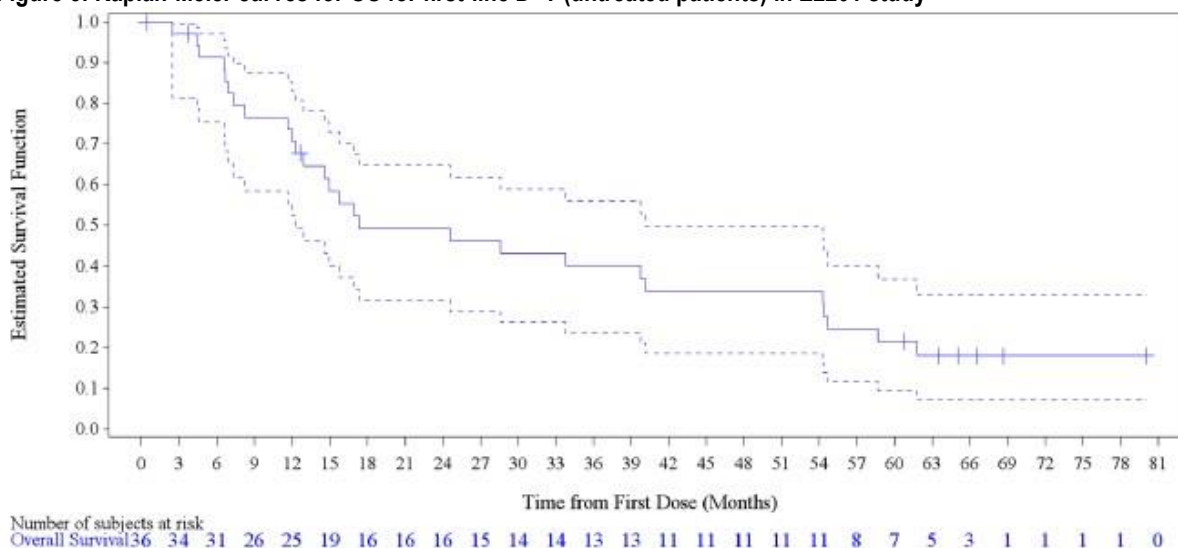
Source: Source: Table 2.24, p73; Table 2.28, p78 and Table 2.32, p82 of the submission.

CI = confidence interval; CR = complete response; D+T = dabrafenib and trametinib; HR = hazard ratio; n = number of participants with event; N = total participants in group; NA = not applicable; ORR = objective response rate; PEMBRO = pembrolizumab; PBC = platinum-based chemotherapy; OS = overall survival.

6.25 In E2201 study, at the most recent data cut-off, approximately 75% patients treated with first-line D+T and 86% patients treated with second and subsequent line D+T had died, with median OS of 17.3 months (95% CI: 12.3, 40.2) and 18.2 months (95% CI: 14.3, 28.6), respectively.

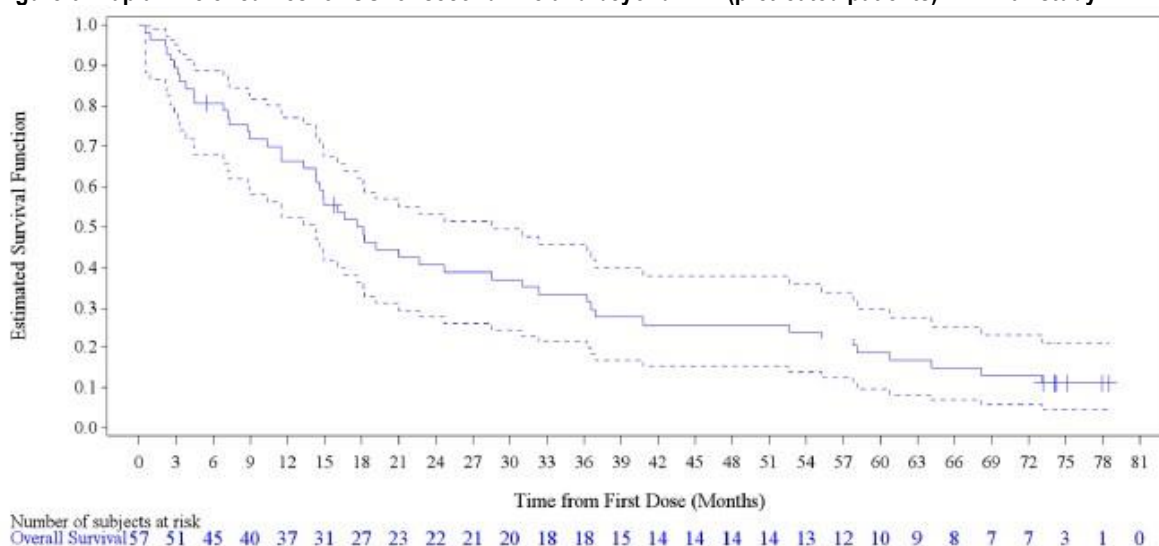
6.26 Figure 5 and Figure 6 present the Kaplan-Meier plots for OS in the D+T treatment arms from the E2201 study. In the E2201 study, the OS rates for patients treated with first-line D+T were 74% at 12 months and 49% at 24 months. For those receiving treatment with second and subsequent line D+T treatment, the OS rates were 66% at 12 months and 41% at 24 months.

Figure 5: Kaplan-Meier curves for OS for first-line D+T (untreated patients) in E2201 study



Source: Figure 2.4, p74 of the submission.
 D+T = dabrafenib and trametinib; OS = overall survival.
 Note: Lines represent Kaplan-Meier estimate with 95% confidence interval

Figure 6: Kaplan-Meier curves for OS for second-line and beyond D+T (pretreated patients) in E2201 study



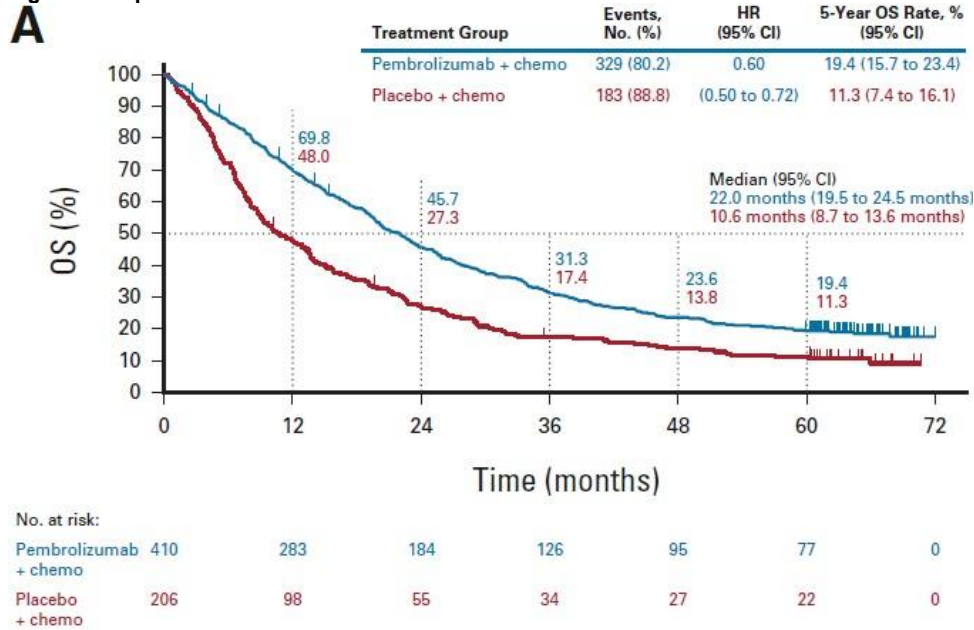
Source: Figure 2.4, p74 of the submission.
 D+T = dabrafenib and trametinib; OS = overall survival.
 Note: Lines represent Kaplan-Meier estimate with 95% confidence interval.

6.27 In the KN-189 and KN-407 trials, approximately 80% and 81% of patients treated with pembrolizumab+PBC had died at the five-year follow-up, respectively. The median OS

for pembrolizumab+PBC was 22.0 months (95% CI: 19.5, 24.5) in KN-189 and 17.2 months (95% CI: 14.4, 19.7) in KN-407.

6.28 Figure 7 and Figure 8 present the Kaplan-Meier plots for OS in the KN-189 and KN-407 trials. In KN-189, the OS rates with pembrolizumab+PBC were 70% at 12 months and 46% at 24 months. In KN-407, the OS rates with pembrolizumab+PBC were 65% at 12 months and 36% at 24 months. At 60 months, the OS rates were 19% in KN-189 and 18% in KN-407 with pembrolizumab+PBC.

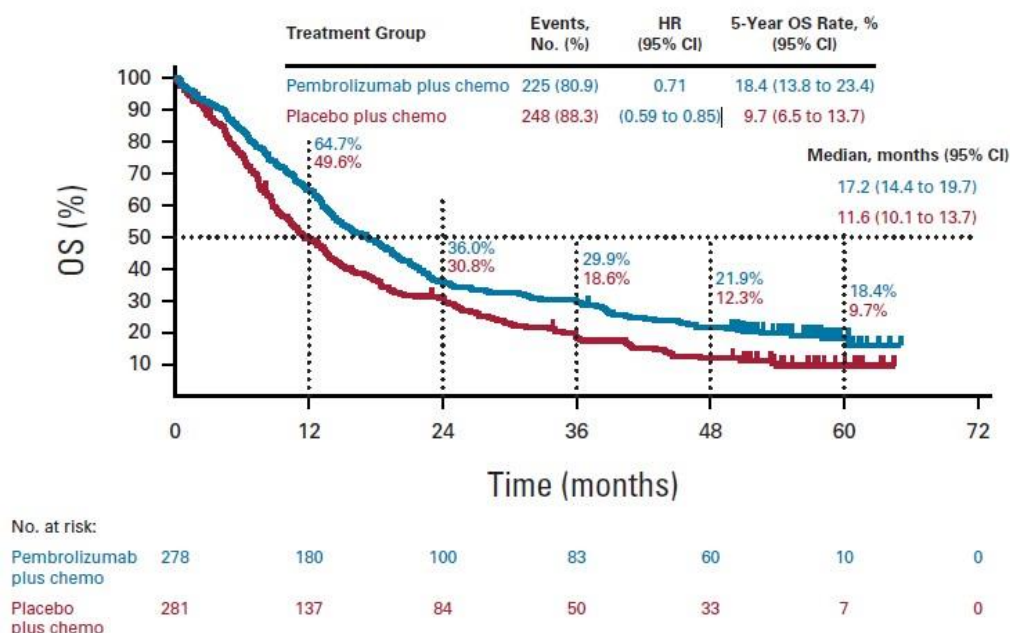
Figure 7: Kaplan-Meier curves for OS in KN-189 trial



Source: Figure 2.7, p79 of the submission.

CI = Confidence interval; chemo = chemotherapy; HR = Hazard ratio; OS = overall survival.

Figure 8: Kaplan-Meier curves for OS in KN-407 trial



Source: Figure 2.10, p82 of the submission.

CI = Confidence interval; chemo = chemotherapy; HR = Hazard ratio; OS = overall survival.

Duration of response

6.29 In E2201 study, the median duration of response (DoR), assessed by the investigator, was 10.2 months (95% CI: 8.3, 15.2) for first-line D+T arm and 9.8 months (95% CI: 5.4, 23.5) for second and subsequent line D+T. The median DoR evaluated by IRC assessments, was 15.2 months for the first-line D+T arm) and 12.6 months for second and subsequent line D+T arm.

6.30 The DoR, assessed by blinded IRC, was longer for patients treated with pembrolizumab+PBC arm compared to placebo+PBC arm in both KN-189 (12.7 months vs. 7.1 months) and KN-407 (9.0 months vs. 4.9 months) trials.

Indirect Comparisons

6.31 The submission presented an unadjusted and unanchored ITC of first-line D+T arm from the E2201 study and pooled pembrolizumab+PBC arms from the KN-189 and KN-407 trials. The ESC noted the median OS for patients with SQ NSCLC in KN-407 (17.2 months) was less than for patients with NSQ NSCLC in KN-189 (22 months) and considered this may favour D+T. The pre-PBAC response presented results of the comparison between D+T and the individual pembrolizumab studies for the outcomes of PFS and OS. The pre-PBAC response noted that, consistent with the results based on the pooled data for pembrolizumab, there was no statistically significant difference in the risk of disease progression or death between D+T and pembrolizumab using the individual studies.

Objective response rate

6.32 Table 7 summarises the ITC results of ORR between first-line D+T and pooled pembrolizumab+PBC arms.

Table 7: Unanchored and unadjusted indirect comparison of ORR between D+T and PEMBRO+PBC

Comparison	1 st Line D+T (untreated)	Pooled PEMB + PBC	RD (95% CI)	RR (95% CI)	OR (95% CI)
1st line D+T vs pooled PEMBRO+PBC	23/36 (63.9%)	371/688 (53.9%)	0.10 (-0.06, 0.26)	1.18 (0.92, 1.53)	1.51 (0.75, 3.03)

Source: Table 2.46, p92 of the submission.

CI = confidence interval; D+T = dabrafenib and trametinib; OR = odds ratio; ORR = objective response rate; PEMBRO = pembrolizumab; PBC = platinum-based chemotherapy; RD= risk difference; RR = relative risk.

6.33 The ORR for first-line D+T was not statistically significantly different to that for the pooled estimate for pembrolizumab+PBC (RR: 1.18, 95% CI: 0.92, 1.53).

Progression-free survival and overall survival

6.34 The ITC results of OS and PFS between first-line D+T and pooled pembrolizumab+PBC arms are summarised in Table 8. The corresponding Kaplan-Meier curves are presented in Figure 9 and Figure 10.

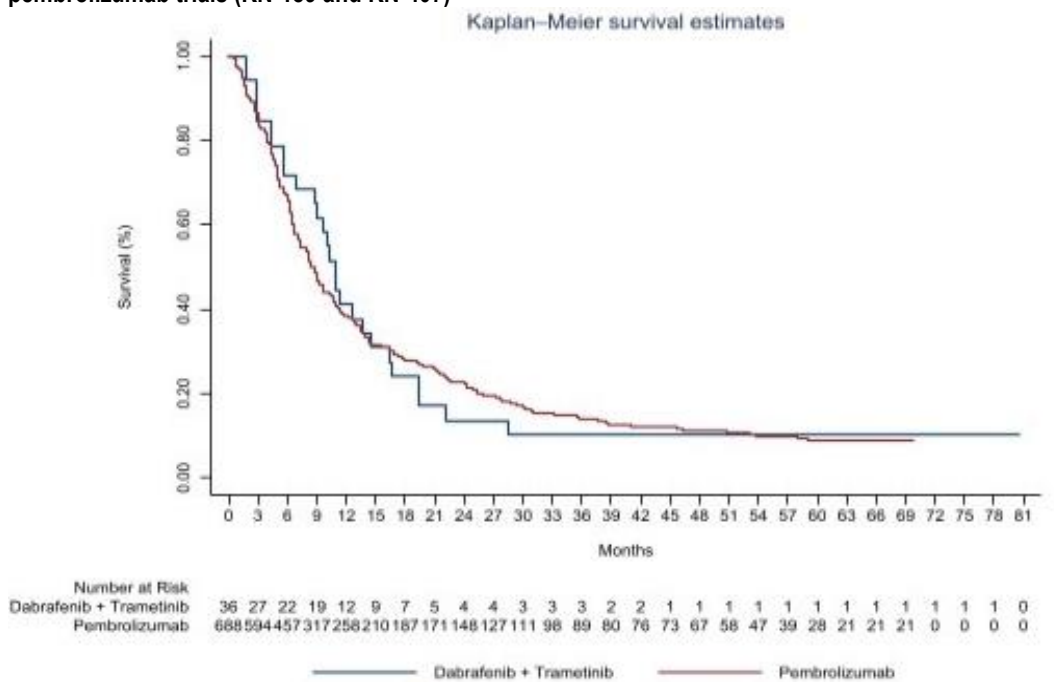
Table 8: Unanchored and unadjusted indirect comparison of PFS and OS between D+T and PEMBRO+PBC

	1 st Line D+T (untreated) N=36	Pooled PEMBRO+PBC N=688
PFS		
Median PFS (IQR), months	10.85 (5.60, 16.65)	8.48 (4.73, 21.43)
D+T vs PEMBRO+PBC, HR (95% CI)	1.02 (0.70, 1.51)	
OS		
Median OS (IQR), months	17.30 (11.70, 58.70)	19.85 (9.50, 44.63)
D+T vs PEMBRO+PBC, HR (95% CI)	1.10 (0.74, 1.64)	

Source: Table 2.47, p93 and Table 2.48, p94 of the submission.

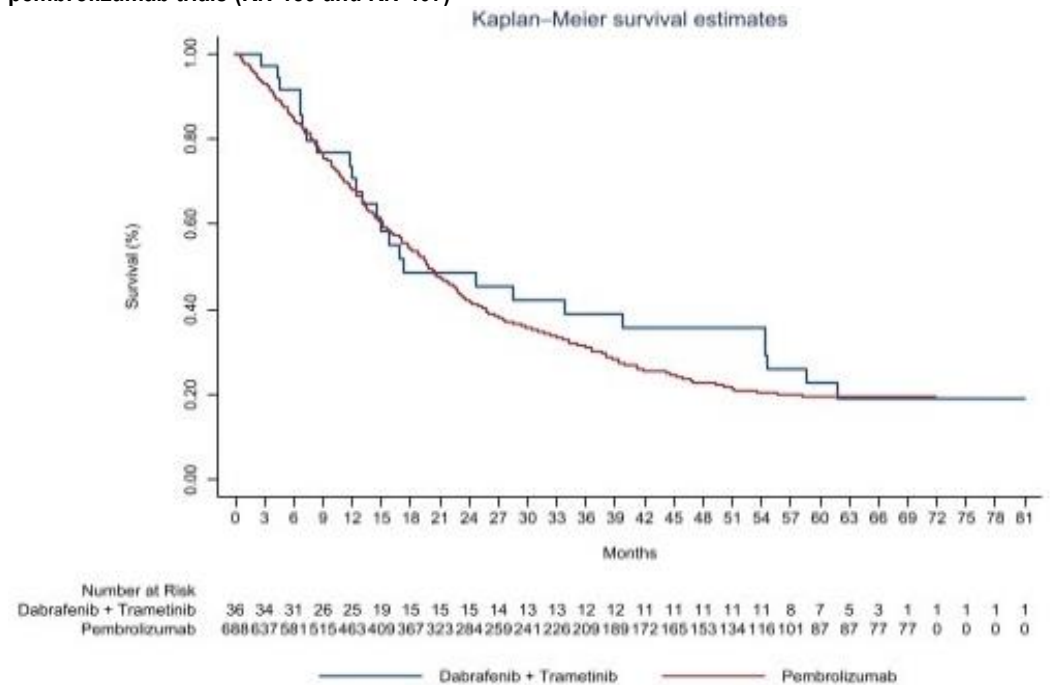
CI = confidence interval; D+T = dabrafenib and trametinib; HR = hazard ratio; IQR = interquartile range; N = total participants in group; OS = overall survival; PEMBRO = pembrolizumab; PBC = platinum-based chemotherapy; PFS = progression-free survival.

Figure 9: Overlay of Kaplan-Meier PFS curves for first-line D+T (untreated patients) from E2201 study and pooled pembrolizumab trials (KN-189 and KN-407)



Source: Figure 2.14, p93 of the submission.
D+T = dabrafenib and trametinib; PFS = progression-free survival.

Figure 10: Overlay of Kaplan-Meier OS curves for first-line D+T (untreated patients) from E2201 study and pooled pembrolizumab trials (KN-189 and KN-407)



Source: Figure 2.15, p94 of the submission.
D+T = dabrafenib and trametinib; OS = overall survival.

- 6.35 The indirect comparison of efficacy showed no significant difference in PFS (HR: 1.02; 95% CI: 0.70, 1.51) and OS (HR: 1.10; 95% CI: 0.74, 1.64) between first-line D+T arm and pooled pembrolizumab+PBC arm.
- 6.36 Although the median PFS was numerically higher in first-line D+T arm compared to pooled pembrolizumab+PBC arm (10.9 months vs. 8.5 months), the HR for PFS was approximately 1.
- 6.37 The median OS was numerically lower in the first-line D+T arm compared to pooled pembrolizumab+PBC arm (17.3 months vs. 19.9 months), with a hazard ratio for OS of 1.10.
- 6.38 The results from the unadjusted and unanchored ITC should be interpreted with caution because:
- The relative treatment effect for D+T and pembrolizumab+PBC did not appear to be constant over time.
 - D+T, a targeted therapy, and pembrolizumab+PBC, combination of immunotherapy and chemotherapy, have distinct mechanisms of action, resulting in different response patterns.
 - The number of patients at risk for informing the PFS and OS curves was relatively small for the D+T group compared to pembrolizumab+PBC group.
 - As stated in paragraph 6.11 and 6.12, there were differences across the studies, in terms of disease histology, gender, brain metastases, smoking status, subsequent treatment, and the trial follow-up duration.

Comparative harms

- 6.39 In the E2201 study, all patients except one experienced an adverse event (AE), with 89% experiencing a treatment-related AEs. A high proportion of patients experienced a serious AE (SAE; 67%), with 43% experiencing a treatment-related SAE. A total of 25% permanently discontinued treatment due to an AE. Death occurred in 9% of patients due to AE.
- 6.40 In the KN-189 trial, all but one patient in the pembrolizumab+PBC arm experienced an AE, with 93% experiencing a treatment-related AEs. In the KN-407 trial, approximately 99% of patients experienced an AE, with 96% experiencing a treatment-related AEs. Treatment discontinuation due to AEs occurred in 36% of patients in KN-189 and 29% in KN-407 trials. Death due to AEs occurred in 7% of patients in KN-189 and 4% in KN-407 trials.
- 6.41 D+T and pembrolizumab+PBC have distinct safety profiles. In the D+T treatment arm, the most common Grade ≥ 3 AEs were hypertension and hyponatraemia (10% each), followed by dyspnoea (8%), neutropenia (8%), pyrexia (6%), increased alanine aminotransferase (6%), and anaemia (5%). In the pembrolizumab+PBC arm, the most common Grade ≥ 3 AEs arm were neutropenia (17%), thrombocytopenia (9%), fatigue

(8%), asthenia (7%), and diarrhoea (5%) in the KN-189 trial, and neutropenia (23%), anaemia (16%), and thrombocytopenia (8%) in KN-407 trial.

- 6.42 The submission presented an unanchored and unadjusted ITC of safety data for D+T, including both first-line D+T and second and subsequent line D+T, from the E2201 study and the pooled pembrolizumab+PBC arms from KN-189 and KN-407 trials. The results of ITC for safety outcomes are presented in Table 9.

Table 9: Unadjusted and unanchored indirect comparison for safety outcomes

n with event (%)	D+T N=93	Pooled PEMBRO +PBC N=683	RD (95% CI)	RR (95% CI)	OR (95% CI)
Any AE	92 (98.9%)	678 (99.3%)	-0.00 (-0.03, 0.02)	1.00 (0.97, 1.02)	0.68 (0.08, 5.87)
Any TRAE	83 (89.2%)	643 (94.1%)	-0.05 (-0.11, 0.02)	0.95 (0.88, 1.02)	0.52 (0.25, 1.07)
Grade ≥ 3 AE	69 (74.2%)	503 (73.6%)	0.01 (-0.09, 0.10)	1.01 (0.89, 1.14)	1.03 (0.63, 1.69)
Neutropenia	7 (7.5%)	132 (19.3%)	-0.12 (-0.18, -0.06)	0.39 (0.19, 0.81)	0.34 (0.15, 0.75)
Anaemia	5 (5.4%)	121 (17.7%)	-0.12 (-0.18, -0.07)	0.30 (0.13, 0.72)	0.26 (0.10, 0.66)
Diarrhoea	2 (2.2%)	33 (4.8%)	-0.03 (-0.06, 0.01)	0.45 (0.11, 1.82)	0.43 (0.10, 1.83)
Fatigue	3 (3.2%)	44 (6.4%)	-0.03 (-0.07, 0.01)	0.50 (0.16, 1.58)	0.48 (0.15, 1.59)
Asthenia	4 (4.3%)	33 (4.8%)	-0.01 (-0.05, 0.04)	0.89 (0.32, 2.46)	0.89 (0.31, 2.56)
Thrombocytopenia	1 (1.1%)	58 (8.5%)	-0.07 (-0.10, -0.04)	0.13 (0.02, 0.90)	0.12 (0.02, 0.86)
Dyspnoea	7 (7.5%)	21 (3.1%)	0.04 (-0.01, 0.10)	2.45 (1.07, 5.60)	2.57 (1.06, 6.21)
Pyrexia	6 (6.5%)	3 (0.4%)	0.06 (0.01, 0.11)	14.69 (3.74, 57.74)	15.63 (3.84, 63.63)
Discontinuation due to AEs	23 (24.7%)	225 (32.9%)	-0.08 (-0.18, 0.01)	0.75 (0.52, 1.09)	0.67 (0.41, 1.10)
AEs leading to death	8 (8.6%)	61 (8.9%)	-0.00 (-0.06, 0.06)	0.96 (0.48, 1.95)	0.96 (0.44, 2.07)

Source: Table 2.49, p95 and Table 2.50, p96 of the submission.

AEs = adverse events; CI = confidence interval; D+T = dabrafenib with trametinib; n = number of participants reporting data; N = total participants in group; OR= odds ratio; PEMBRO = pembrolizumab; PBC = platinum-based chemotherapy; RD = risk difference; RR = relative risk; TRAE = treatment-related adverse events.

Bold indicates statistical significance.

- 6.43 Overall, it was difficult to assess the comparative safety, given the unanchored and unadjusted ITC, and considerable differences in the safety profiles between D+T and pembrolizumab+PBC. Additionally, the safety outcomes for D+T treatment included all patients treated with D+T in E2201 study, irrespective of the line of therapy, whereas the safety outcomes for the pooled pembrolizumab+PBC arm were based on patients treated in the first-line setting.

Benefits/harms

- 6.44 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.45 The submission described D+T as non-inferior in terms of effectiveness compared to pembrolizumab+PBC. The ESC considered this claim was uncertain:

- The evidence was based on an unadjusted and unanchored ITC for D+T from the E2201 study, a Phase II, open-label, single arm study with a small sample size

(N=36), and pooled pembrolizumab+PBC data from the KN-189 and KN-407, two Phase III randomised, double-blind, placebo-controlled trials.

- Evidence of D+T (E2201 study) in terms of efficacy and safety was limited to patients with BRAF V600E mutation positive Stage IV NSCLC, whereas the BRAF V600E mutation status was not assessed in the pembrolizumab+PBC trials (KN-189 and KN-407). Additionally, the prognostic value of BRAF V600E mutation is uncertain.
 - The results of the ITC may not be reliable due to potential transitivity issues between the D+T study and pembrolizumab+PBC trials, including differences in terms of disease histology, gender, brain metastases, smoking status, subsequent treatment, and the follow-up duration.
 - The relative treatment effect for D+T and pembrolizumab+PBC was not constant over time. D+T, a targeted therapy, and pembrolizumab+PBC, combination of immunotherapy and chemotherapy, have different mechanisms of action and therefore different patterns of response.
- 6.46 The submission described D+T as non-inferior in terms of safety compared to pembrolizumab+PBC. It was difficult to assess the comparative safety, given the unanchored and unadjusted ITC, and differences in the safety profiles between D+T and pembrolizumab+PBC.
- 6.47 The submission did not present any comparative evidence between D+T and PBC alone for patients with ECOG PS of 2. The ESC considered this was reasonable as the evidence base for D+T in this subpopulation was limited, with only six patients in the E2201 study having an ECOG PS of 2.
- 6.48 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.49 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.50 The submission presented a cost-minimisation approach (CMA) comparing D+T with pembrolizumab+PBC based on the claim of non-inferiority in terms of effectiveness and safety.
- 6.51 The submission presented two separate CMAs for NSQ and SQ NSCLC, given the differences in the components of PBC and treatment duration of pembrolizumab+PBC based on histology. The comparator therapies considered in the CMA were pembrolizumab with cisplatin/carboplatin and pemetrexed for NSQ NSCLC and pembrolizumab with carboplatin and paclitaxel for SQ NSCLC.
- 6.52 The equi-effective doses were estimated for D+T from the E2201 study and pembrolizumab+PBC from the KN-189 and KN-407 trials as follows:

- NSQ: Dabrafenib 249 mg/day for 18.91 months + trametinib 1.8 mg/day for 17.72 months = Pembrolizumab 200 mg Q3W for 14.13 cycles in combination with cisplatin 137 mg Q3W or carboplatin 530 mg Q3W for 3.60 cycles and pemetrexed 911 mg Q3W for 13.58 cycles.
 - SQ: Dabrafenib 249 mg/day for 18.91 months + trametinib 1.8 mg/day for 17.72 months = Pembrolizumab 200 mg Q3W for 14.02 cycles in combination with carboplatin 636 mg Q3W for 3.62 cycles and paclitaxel 364 mg Q3W for 3.60 cycles.
- 6.53 The submission used the time to treatment discontinuation (TTD) Kaplan-Meier curves from the E2201 study to determine the mean treatment duration of dabrafenib (18.91 months) and trametinib (17.72 months), with all patients completing treatment with D+T. The mean dose and treatment duration of D+T was calculated based on all treated patients, regardless of the treatment line and histology (NSQ or SQ).
- 6.54 TTD Kaplan-Meier curves or mean treatment duration were not available for pembrolizumab+PBC from the most recent data-cut off of KN-189 (March 2022) and KN-407 (February 2022). For KN-189, the submission relied on data from Gadgeel et al. (2020), which reported a truncated mean duration of treatment of 9.8 months for pembrolizumab+PBC based on the September 2018 data cut-off of the KN-189. Similarly, for KN-407, the submission used data from Paz-Ares et al. (2018), which reported a truncated mean duration of treatment of 6.3 months with pembrolizumab+PBC based on the April 2018 data cut-off of the KN-407 trial, with 43.5% of patients remained on treatment.
- 6.55 The submission modelled a TTD curve for pembrolizumab+PBC, for both SQ and NSQ, assuming that treatment discontinuation follows an exponential distribution, citing a previous pembrolizumab submission which used an exponential distribution to extrapolate TTD data from the KN-189 trial (paragraph 6.44, pembrolizumab, Public Summary Document (PSD), July 2019 PBAC Meeting).
- 6.56 Based on the dosing frequency, exponential extrapolation and maximum number of cycles for pembrolizumab (35 cycles), the submission estimated the mean administrations for pembrolizumab+PBC as presented in Table 10. To estimate compliance, the submission compared the estimated mean administration to the reported administration in the respective trials.

Table 10: Mean administrations and compliance for pembrolizumab+PBC for NSQ and SQ NSCLC

NSQ NSCLC	Pembrolizumab	Cisplatin/Carboplatin	Pemetrexed
Mean administrations (truncated mean treatment duration: 9.8 months; patient on treatment: 14.1%)			
Gadgeel et al., 2020	13.76	3.60	11.69
Estimated administrations	14.43	3.66	14.43
Estimated compliance (%)	95% (13.76/14.43)	98% (3.60/3.66)	81% (11.69/14.43)
Total mean administrations (extrapolated)			
Estimated administrations	14.82	3.66	16.76
Compliance adjusted administrations	14.13 (14.82 x 95%)	3.60 (3.66 x 98%)	13.58 (16.76 x 81%)
SQ NSCLC	Pembrolizumab	Carboplatin	Paclitaxel
Mean administrations (truncated mean treatment duration: 6.3 months; patient on treatment: 43.5%)			
Paz-Ares et al., 2018	9.29	3.62	3.60
Estimated administrations	9.55	3.64	3.64
Estimated compliance (%)	97% (9.29/9.55)	99% (3.62/3.64)	99% (3.60/3.60)
Total mean administrations (extrapolated)			
Estimated administrations	14.41	3.64	3.64
Compliance adjusted administrations	14.02 (14.41 x 97%)	3.62 (3.64 x 99%)	3.60 (3.64 x 99%)

Source: Table 3.2, p118 and Table 3.3, p120 of the submission.

PBC = platinum-based chemotherapy; NSCLC = non-small cell lung cancer; NSQ = non-squamous; SQ = squamous.

6.57 The TTD model traces, presented in Figure 11, over the time horizon of 80 months, was prepared during evaluation using the model provided by the submission. The mean duration of treatment was longer with dabrafenib (18.91 months) and trametinib (17.72 months) compared to pembrolizumab (10.26 months for NSQ and 9.98 months for SQ) and PBC (2.53 months for cisplatin/carboplatin/paclitaxel and 11.75 months for pemetrexed). The PSCR considered the approach was conservative and noted the number of administrations for pembrolizumab estimated in the submission (14.13 for NSQ and 14.02 for SQ) was lower than that used in the tepotinib submission (15.6).

Figure 11: Model traces for TTD



Source: Prepared during evaluation using the 'Mekinist (trametinib) Tafinlar (dabrafenib) – CMA' .xlsx workbook.

NSQ = non-squamous; PBC = platinum-based chemotherapy; SQ = squamous; TTD = time to treatment discontinuation.

Note: The red dotted line corresponds to the maximum duration of pembrolizumab (35 cycles or approximately 2 years). Maintenance treatment with pemetrexed continued beyond 2 years.

- 6.58 Due to differences in administration methods, the submission included a cost offset for the IV administration of pembrolizumab+PBC, based on MBS item 13950 (Fee: \$123.50).
- 6.59 The submission also included monitoring cost associated with D+T, pembrolizumab, and PBC components (cisplatin, carboplatin, pemetrexed and paclitaxel) based on requirements specified in their respective TGA PIs. The costs were estimated by multiplying MBS item fee with monitoring requirement for each medicine, adjusted for proportion of patients on treatment.
- 6.60 The CMA presented did not include additional costs for managing AEs, based on the absence of a statistically significant difference in the proportion of patients who experienced any AE any treatment-related AE, any Grade ≥ 3 or the discontinuation rate due to an AE. The submission further stated that while a smaller proportion of patients treated with D+T experienced Grade ≥ 3 neutropenia, anaemia and thrombocytopenia, a greater proportion experienced hypertension, dyspnoea and pyrexia, compared with pembrolizumab+PBC. While the comparative safety between D+T was uncertain, excluding the cost of AEs in the CMA was considered to be conservative, given the potentially higher costs of managing treatment-related AEs such as neutropenia and anaemia in the pembrolizumab+PBC arm, compared to hypertension, dyspnoea, and pyrexia in the D+T arm.
- 6.61 The submission did not include the cost of subsequent therapy in the CMA. The evaluation considered this was inappropriate, as the type of subsequent therapy

differs between the two treatments. The ESC noted there were differences in the proportion of subsequent therapies received by patients following disease progression with D+T in the E2201 study and pembrolizumab+PBC in the KN-189 and KN-407 trials (see paragraph 6.11). However, the ESC considered that, in clinical practice, it was likely patients would receive D+T followed by pembrolizumab or pembrolizumab followed by D+T and therefore overall it is unlikely that there will be a substantive difference in the cost of the subsequent therapies received.

6.62 The results of CMA for NSQ and SQ NSCLC are summarised below in Table 11 and Table 12, respectively.

Table 11: Cost minimisation analysis - Non-squamous Stage IV BRAF V600E NSCLC

	Dabrafenib + Trametinib		Pembrolizumab + Cisplatin + Pemetrexed		Pembrolizumab + Carboplatin + Pemetrexed	
Population	100%		27.6%		72.4%	
Medicines costs	Dabrafenib	\$51,247.34	Pembrolizumab	\$108,082.96	Pembrolizumab	\$108,082.96
	Trametinib	\$54,820.46	Cisplatin	\$106.88	Carboplatin	\$191.38
			Pemetrexed	\$721.21	Pemetrexed	\$721.21
Total medicines costs	\$106,067.80		\$108,911.06		\$108,995.55	
Administration costs	\$0.00		\$2,062.65		\$2,062.65	
Monitoring costs	\$6,416.41		\$1,271.29		\$1,517.02	
Total cost	\$112,484.22		\$112,245.01		\$112,575.23	
Weighted average total cost	\$112,484.22		\$112,484.22			
Incremental cost	\$0.00					

Source: Table 3.9, p129 of the submission.

NSCLC = non-small cell lung cancer.

Table 12: Cost minimisation analysis - Squamous Stage IV BRAF V600E NSCLC

	Dabrafenib + Trametinib		Pembrolizumab + Carboplatin + Paclitaxel	
Medicines costs	Dabrafenib	\$50,454.38	Pembrolizumab	\$107,217.81
	Trametinib	\$53,972.21	Carboplatin	\$192.52
			Paclitaxel	\$264.82
Total medicines costs	\$104,426.59		\$107,675.15	
Administration costs	\$0.00		\$1,773.24	
Monitoring costs	\$6,416.41		\$1,394.61	
Total cost	\$110,843.00		\$110,843.00	
Incremental cost	\$0.00			

Source: Table 3.10, p130 of the submission.

NSCLC = non-small cell lung cancer.

6.63 The weighted average AEMP per pack for dabrafenib and trametinib, based on the CMAs, is presented in Table 13.

Table 13: Weighted average AEMP for D+T – using published prices for pembrolizumab

	Non-squamous (AEMP/unit)	Squamous (AEMP/unit)	Weighted average (AEMP/unit)	Units per pack	Weighted AEMP per pack
Population ^a	76.79%	23.21%	100.00%	-	-
Dabrafenib 75 mg	\$26.82	\$26.40	\$26.72	120	\$3,206.48
Trametinib 2 mg	\$112.91	\$111.17	\$112.51	30	\$3,375.24

Source: Table 3.11, p130 of the submission.

AEMP = approved ex-manufacturer price; D+T = dabrafenib and trametinib.

^a The distribution of NSQ and SQ NSCLC was derived from Mitchell et al. (2013), a retrospective survey of lung cancer cases reported to the Victorian Cancer registry between January 1 and June 30, 2003, with a follow-up period of five years. Corrected during evaluation to account for correct proportion of patients with non-squamous and squamous NSCLC in cells 'G63 and H63' of 'Results' worksheet in the Mekinist (trametinib) Tafinlar (dabrafenib) – CMA'.xlsx workbook as reported by Mitchell et al. (2013).

Drug cost/patient/course

Table 14: Drug cost per patient per course for the proposed drug and comparator drugs

	Dabrafenib and trametinib			Comparator drugs		
	Trial	Model (Based on AEMP)	Financial estimates (Based on weighted cost-minimised DPMQ)	Trial	Model (Based on AEMP)	Financial estimates (Based on weighted public/private DPMA)
NSQ NSCLC						
Mean number of doses (adjusted for RDI)	Dabrafenib=249 mg/day Trametinib=1.8 mg/day	Dabrafenib=249 mg/day Trametinib=1.8 mg/day	Dabrafenib=249 mg/day Trametinib=1.8 mg/day	NR	Pembro=14.13 Platinum=3.60 Pem=13.58	Combination therapy Pembro=14.13 Platinum=3.60 Pem=13.58
						Monotherapy Pembro =14.13
						PBC Platinum=3.42 Pem=9.61
Mean duration of treatment (months)	Dabrafenib=18.57 Trametinib=17.60	Dabrafenib=18.91 Trametinib=17.72	Dabrafenib=18.91 Trametinib=17.72	NR	Pembro=10.26 Platinum=2.53 Pem=11.60	Combination therapy Pembro=10.26 Platinum=2.53 Pem=11.60
						Monotherapy Pembro =10.26
						PBC Platinum=2.37 Pem=6.65
Cost/dose	-	Dabrafenib=\$107.27 Trametinib=\$112.91	Dabrafenib=\$112.30 Trametinib=\$117.93	-	Pembro=\$7,647.50 Cis=\$29.69 Carb=\$53.16 Pem=\$53.09	Pembro=\$7,833.64 Cis=\$146.90 Carb=\$173.15 Pem=\$171.37
SQ NSCLC						
Mean number of doses (adjusted for RDI)	Dabrafenib=249 mg/day Trametinib=1.8 mg/day	Dabrafenib=249 mg/day Trametinib=1.8 mg/day	Dabrafenib=249 mg/day Trametinib=1.8 mg/day	NR	Pembro=14.02 Platinum=3.62 Paclitaxel=3.60	Pembro+PBC Pembro=14.02 Platinum=3.64 Paclitaxel=3.64
						Monotherapy Pembro =14.02
						PBC Platinum=3.55 Paclitaxel=3.55
Mean duration of treatment (months)	Dabrafenib=18.57 Trametinib=17.60	Dabrafenib=18.91 Trametinib=17.72	Dabrafenib=18.91 Trametinib=17.72	NR	Pembro=9.98 Platinum=2.52 Paclitaxel=2.52	Pembro=9.98 Platinum=2.52 Paclitaxel=2.52
						Monotherapy Pembro =9.98
						PBC Platinum=2.45 Paclitaxel=2.45

	Dabrafenib and trametinib			Comparator drugs			
	Trial	Model (Based on AEMP)	Financial estimates (Based on weighted cost-minimised DPMQ)	Trial	Model (Based on AEMP)	Financial estimates (Based on weighted public/private DPMA)	
Cost/dose	-	Dabrafenib= \$105.61 Trametinib= \$111.17	Dabrafenib=\$112.30 Trametinib=\$117.93	-	Pembro=\$7,647.50 Platinum=\$192.52 Paclitaxel=\$73.56	Pembro=\$7,833.64 Platinum=\$173.15 Paclitaxel=\$194.72	
Cost/patient/ course ^a	-	NSQ: Dabrafenib= \$51,247.34 Trametinib= \$54,820.46 Total= \$106,067.80	NSQ and SQ= \$110,907.80 ^b	-	NSQ: Pembro= \$108,082.96 Platinum= \$168.06 Pem= \$721.21 Total= \$108,972.27	Pembro+PBC NSQ= \$113,613.88 SQ= \$111,140.43	
		SQ: Dabrafenib= \$50,454.38 Trametinib= \$53,972.21 Total= \$104,426.59			SQ: Pembro= \$107,217.81 Platinum= \$192.52 Paclitaxel= \$264.82 Total= \$107,675.15		Monotherapy NSQ= \$110,689.40 SQ= \$109,827.70
							PBC NSQ= \$2,214.28 SQ=\$1,280.28

Source: Table 3.0060, p213 and Table 3.0061, p215 of the E2201 study CSR, 'Mekinist (trametinib) Tafinlar (dabrafenib) – NSCLC-UCM.xlsx' workbook, and 'Mekinist (trametinib) Tafinlar (dabrafenib) – CMA' .xlsx workbook.

AEMP = approved ex-manufacturer price; Carb = carboplatin, cis = cisplatin, DPMQ/DPMA = dispensed price for maximum quantity/amount, PBC = platinum-based chemotherapy; Pem = pemetrexed, Pembro = pembrolizumab, pts = patients; RDI = relative dose intensity, NR = not reported, NSQ = non-squamous, SQ = squamous.

^a Cost/patient/course for financials was calculated using the duration of treatment reported for each medicine multiplied by cost per dose and includes patient co-payment.

^b The cost was not differentiated by NSQ or SQ histology, as the submission proposed a weighted AEMP (76.79% for NSQ and 23.21% for SQ) calculated using the economic model.

Italics calculated during evaluation.

Estimated PBS usage & financial implications

6.64 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact of listing D+T for the treatment of patients with BRAF V600E mutation positive Stage IV NSCLC.

6.65 To aid in the diagnosis and classification of NSCLC, two MBS-listed multi-gene panel tests (items 73437 and 73438) currently include BRAF mutation testing. Patients with NSCLC would undergo the multi-gene panel test regardless of the availability of D+T, with no re-testing required for BRAF V600E mutation.

6.66 Table 15 summarises the key inputs and data sources to estimate the utilisation of D+T.

Table 15: Key inputs for financial estimates

Parameter	Value applied	Source	Comment
Eligible population			

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Parameter	Value applied	Source	Comment	
Incidence population	█ ¹ in Yr 1 increasing to █ ¹ in Yr 6	Based on extrapolating lung cancer incidence data from AIHW reports for the year 2001-2020.		
% NSCLC	86.6%	Based on Mitchell et al. (2013)		
% Stage IV NSCLC	51.5%			
% ECOG 0-1 and 2	80.1%			
% NSQ and SQ	76.8% and 23.2%			
% BRAF mutation	1.13%	Based on the average prevalence rate reported in a literature review of 32 studies.	This approach was reasonable	
Incident patients	█ ² in Yr 1 increasing to █ ² in Yr 6	Calculated		
Patients progressing from Stage I-II	█ ² patients each year	Described in detail in paragraph 6.69	This was uncertain due to the various sources and estimates used.	
Patients progressing from Stage III	█ ² in Yr 1 increasing to █ ² in Yr 6			
Treatment utilisation				
Pembrolizumab monotherapy	22.4%	Based on Dietel et al. (2019)		
Duration of treatment (months)		NSQ SQ	E2201 study Kaplan-Meier TTD While this was consistent with the economic estimates, the absence of Kaplan-Meier TTD data from the pembrolizumab trials introduces uncertainty regarding the mean duration of treatment and the resulting mean administration.	
	Dabrafenib	18.91 18.91		
	Trametinib	17.72 17.72		
	<u>ECOG PS 0-1</u>			
	Pembrolizumab	10.26 9.98		
	Platinum	2.53 2.52		
	Pemetrexed/Paclitaxel	11.60 2.52		
	<u>ECOG PS 2</u>			
Platinum	2.37 2.45			
Pemetrexed	6.65 2.45			
Compliance rate		NSQ SQ	E2201 Kaplan-Meier TTD Estimated using the methods described in the cost minimisation approach	
	Dabrafenib	83.0% 83.0%		
	Trametinib	90.0% 90.0%		
	<u>ECOG PS 0-1</u>			
	Pembrolizumab	95.3% 97.3%		
	Platinum	98.5% 99.4%		
	Pemetrexed/Paclitaxel	81.0% 98.8%		
	<u>ECOG PS 2</u>			
Platinum	99.5% 98.7%			
Pemetrexed	87.2% 95.9%			
Uptake rate of D+T	█ ² %	Based on Sponsor's assumption		
Cost of medicines (AEMP)	Dabrafenib (75 mg)	\$6,995.23	DPMQ/DPMA was calculated based on the AEMP reported in the Schedule of Pharmaceutical Benefits, October 2024	For D+T, the submission did not use the cost-minimised price derived in the economic analysis section. The financial implications presented below were recalculated during the evaluation using the cost-minimised DPMQ for both dabrafenib (DPMQ per pack of \$3,369.08) and trametinib (AEMP per pack of \$3,537.84).
	Trametinib (2 mg)	\$7,363.40		
	Pembrolizumab (100 mg)	\$3,823.75		
	Cisplatin (50 mg)	\$10.41		
	Cisplatin (100 mg)	\$19.28		
	Carboplatin (450 mg)	\$26.58		
	Pemetrexed (1,000 mg)	\$53.09		

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Parameter	Value applied	Source	Comment
	Paclitaxel (50 mg) \$36.78		

Source: Table 4.1, pp 129-132 of the submission.

AEMP = Approved Ex-Manufacturer Price; AIHW = Australian Institute of Health and Welfare; BRAF = B-Raf serine-threonine kinase, CT = Computed Tomography, D+T = Dabrafenib + Trametinib, ECOG PS = Eastern Cooperative Oncology Group Performance Status; HbA1c = Haemoglobin A1c (glycated haemoglobin test); IV = intravenous; MBS = Medicare Benefits Schedule; MUGA = Multigated Acquisition Scan; NSCLC = Non-Small Cell Lung Cancer; NSQ = Non-squamous; PBS = Pharmaceutical Benefits Scheme; PBC = platinum-based chemotherapy; RPBS = Repatriation Pharmaceutical Benefits Scheme; SQ = Squamous; TSH = thyroid stimulating hormone; TTD = time to treatment discontinuation; Yr = year.

The redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² < 500

- 6.67 Incident patients were estimated using a linear trend analysis of lung cancer incidence data reported by the Australian Institute of Health and Family Welfare (AIHW) for the year 2001-2020. Based on Mitchell et al. (2013), a retrospective survey of lung cancer in Victoria, the submission estimated that 86.6% of incident cases would have NSCLC, 51.5% would have advanced or metastatic disease (Stage IV), with 63.3% having an ECOG PS of 0-1, and 16.8% an ECOG PS of 2. Additionally, 76.8% were estimated to have NSQ histology, while the remaining 23.2% were assumed to have SQ histology. The estimates of proportion of NSCLC and advanced or metastatic disease were consistent with those previously presented to the PBAC (paragraph 6.91, selpercatinib, PSD, July 2023 PBAC meeting).
- 6.68 The eligible population was further limited to those with BRAF V600E mutations, estimated at 1.13%. This was based on a weighted average prevalence calculated using data from 32 studies identified in a systematic literature review conducted by the submission. While the approach was reasonable, only two studies were conducted in Australia, reporting prevalence rates between 1.5% and 2.9%, while the remaining studies were conducted internationally.
- 6.69 The submission also assumed that some patients with earlier-stage disease (i.e., Stage I-III) would become eligible for treatment with D+T upon progression to Stage IV:
- For patients with ECOG PS 0-1 and 2, 30% of the newly diagnosed patients with Stage I-II NSCLC were estimated to progress to Stage IIIb-IV within a year, with 51.5% of these patients having Stage IV NSCLC. This was based on the DUSC 24-month predicted versus actual analysis for erlotinib and gefitinib for patients with Stage I-IIIa progressed to Stage IIIb-IV.¹⁵
 - For ECOG PS 0-1, newly diagnosed patients with Stage III NSCLC may progress to Stage IV, but the rate of progression differs if they receive treatment with durvalumab. To be eligible for treatment with durvalumab, patient must have

¹⁵ Drug utilisation sub-committee (DUSC), 'Erlotinib and Gefitinib: 24 month predicted versus actual analysis', Available at: <https://m.pbs.gov.au/industry/listing/participants/public-release-docs/2017-02/tkis-nsclc-24-month-review-dusc-prd-2017-02.docx>

unresectable disease and have not experienced disease progression with platinum-based chemotherapy radiation (CRT).

- For patients who received treatment with durvalumab, the proportion of patients with unresectable Stage III NSCLC (86%) was estimated from Vinod et al. (2017), a retrospective cohort study. The proportion of patients with unresectable disease who did not receive CRT was estimated at 83.9% based on a literature review. The submission assumed an uptake rate of 90% for durvalumab, with 75% of patients experiencing progression at 72 months, as outlined in the durvalumab submission to the PBAC (paragraphs 4.16 and 4.22, durvalumab, PSD, November 2019 PBAC meeting).
- For patients who did not receive treatment with durvalumab, the submission assumed that 60% and 100% of patients with Stage IIIA and Stage IIIB disease will progress to Stage IV in the year of diagnosis, respectively. The submission referenced a previous PBAC submission for pembrolizumab, stating its appropriateness given that durvalumab was not listed on the PBS and patients did not receive treatment with durvalumab at that time (Table 17, p25, pembrolizumab, PSD, November 2018 PBAC meeting).
- For patients with ECOG PS of 2, all newly diagnosed patients with Stage IIIB NSCLC were assumed to progress to Stage IV in the year of diagnosis. The submission stated that was in line with the approach previously presented to the PBAC (Table 17, p25, pembrolizumab, PSD, November 2018 PBAC meeting).
- Based on the above stated estimates, the submission projected a total of <500 patients per year would progress from Stage I-II to Stage IV, while the number of patients progressing from Stage III to Stage IV was projected to be <500 patients in Year 1, increasing to <500 patients by Year 6. The number of patients with early-stage disease was uncertain due to the use of various sources and estimates.

6.70 The submission stated that the current standard of care for patients with Stage IV BRAF V600E NSCLC and an ECOG performance status of 0-1 is pembrolizumab+PBC or pembrolizumab monotherapy (22.4%). However, patients with unresectable Stage III NSCLC treated with durvalumab are ineligible for further treatment with pembrolizumab or another PD-(L)1 therapy in Stage IV. For these patients, as well as those with an ECOG performance status of 2, PBC remains the only available treatment option, with its components determined by histology.

6.71 Consistent with the methodology used in the CMA, the submission estimated the duration of treatment, dose per administration, and compliance for D+T and pembrolizumab+PBC. It further assumed that the duration of treatment with pembrolizumab monotherapy would be similar to pembrolizumab+PBC, with no expected differences between patients with an ECOG PS of 0-1 and those with an ECOG PS of 2.

6.72 The submission also incorporated monitoring costs for D+T, pembrolizumab, and PBC components (cisplatin, carboplatin, pemetrexed, and paclitaxel) in accordance with the requirements outlined in their respective TGA PIs. These costs were consistent with those used in the CMA.

6.73 The estimated financial implications of listing D+T are presented in Table 16.

Table 16: Estimated use and financial implications – published price

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated ^a	1	1	1	1	1	1
Number of scripts dispensed	2	2	2	2	2	2
Estimated financial implications of D+T						
Cost to PBS/RPBS less copayments ^c	3	3	3	3	3	3
Estimated financial implications for substituted medicines						
Total cost-offset to PBS/RPBS less copayments	4	4	4	4	4	4
Net financial implications						
Net cost to PBS/RPBS	4	3	3	3	3	3
Net cost to MBS	3	3	3	3	3	3
Net cost to PBS/RPBS/MBS	4	3	3	3	3	3

Source: Prepared during evaluation using the 'Mekinist (trametinib) Tafinlar (dabrafenib) – NSCLC- UCM.xlsx' workbook.

D+T = Dabrafenib + Trametinib, ECOG PS = Eastern Cooperative Oncology Group Performance Status; MBS = Medicare Benefits Schedule; NSQ = Non-squamous; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SQ = Squamous.

^a Includes untreated patients for Stage IV NSCLC from both newly diagnosed patients and those progressing from earlier stage disease.

^b Assuming 10.11 scripts for dabrafenib and 10.96 for trametinib per year as estimated by the submission.

^c Recalculated during the evaluation using the cost-minimised DPMQ for both dabrafenib (AEMP per pack of \$3,206.48) and trametinib (AEMP per pack of \$3,375.24) instead of the DPMQ for dabrafenib (AEMP per pack of \$6,995.23) and trametinib (AEMP per pack of \$7,363.40) used by the submission based on price listed for melanoma on the Schedule of Pharmaceutical Benefits, October 2024.

^d Calculated during evaluation given the cost of pemetrexed in the financial worksheet was zero due to error in selecting DTG in the 'S108' cell in the '4a. Scripts-affected' worksheet in the 'Mekinist (trametinib) Tafinlar (dabrafenib) – NSCLC- UCM.xlsx' workbook.

Italics corrected during evaluation to account for correct AEMP for D+T and patient numbers for pemetrexed.

The redacted values correspond to the following ranges

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ net cost saving

6.74 The total net cost to the PBS/RPBS/MBS of listing D+T was estimated to be \$0 to < \$10 million in Year 6, and a total of \$10 million to < \$20 million in the first 6 years of listing. This was based on the cost-minimised price of D+T calculated using the published price of the comparator.

6.75 Although D+T was cost-minimised to pembrolizumab+PBC, it resulted in a net cost to the PBS/RPBS due to the replacement of pembrolizumab monotherapy and PBC alone along with pembrolizumab+PBC. While the inclusion of pembrolizumab monotherapy does not significantly impact the net cost to the PBS/RPBS, a total of <500 patients in Year 1 increasing to <500 patients were assumed to receive treatment with PBC alone. Furthermore, the financial estimates were based on DPMQ/DPMA (the CMA was based on AEMP) and accounted for patient co-payments (the CMA did not include any co-payments).

- 6.76 The absence of Kaplan-Meier TTD data from the pembrolizumab trials introduces uncertainty regarding the mean duration of treatment with pembrolizumab with or without PBC. The ESC noted that, unlike pembrolizumab, D+T is not limited to a maximum of 24 months of therapy.
- 6.77 Given the submission requested a line-agnostic listing for D+T, some patients treated with pembrolizumab+PBC in the first-line setting may receive treatment with D+T in latter setting. This was not considered in the financial estimates and may underestimate the impact the financial impact of listing D+T.
- 6.78 Although the submission included a grandfathered restriction and identified that one patient is currently enrolled in a compassionate access scheme, this was not reflected in the financial estimates.
- 6.79 The evaluation noted that if D+T is listed on the PBS, standard systemic therapies, such as pembrolizumab+PBC or PBC alone, are likely to be displaced to later lines rather than replaced. The PSCR stated this assumption may be reasonable if PD-(L1) therapies are allowed post-progression with D+T.

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority Required (STREAMLINED) listing of dabrafenib in combination with trametinib (D+T) for the treatment of adult patients with BRAF V600E mutation positive metastatic (Stage IV) non-small cell lung cancer (NSCLC). The PBAC considered that, despite the uncertainties associated with the indirect comparisons presented in the submission, on balance, it was likely D+T provided similar health outcomes to pembrolizumab in combination with chemotherapy in the proposed population. The PBAC considered that D+T would be acceptably cost effective if it were cost-minimised against pembrolizumab in combination with chemotherapy.
- 7.2 The PBAC noted the small population of patients with BRAF V600E mutations and the moderate clinical need for additional therapies for NSCLC, which was supported by the consumer comments received.
- 7.3 The PBAC advised a single, line agnostic restriction criteria for initial, continuing and grandfather treatment that allows patients to transition from non-PBS subsidised treatment would be appropriate as proposed by the Secretariat in Section 3. The PBAC considered it was appropriate for D+T to be listed only for patients with BRAF V600E mutations, consistent with clinical guidelines including NCCN¹⁶.
- 7.4 The PBAC noted the submission nominated pembrolizumab in combination with chemotherapy as the main comparator and considered this was reasonable. The PBAC

¹⁶ NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer, Version 1.2025, Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

noted that, to a lesser extent, D+T may also substitute for pembrolizumab monotherapy or chemotherapy alone. The PBAC noted that while D+T would replace pembrolizumab in combination with chemotherapy in the first line setting, it is likely immunotherapy would be displaced to second line treatment. However, the PBAC noted the current PBS restrictions for immunotherapies would preclude their use second line to D+T; therefore, flow on changes will be required (see paragraph 7.10).

- 7.5 The PBAC noted the clinical evidence for D+T was from one single arm study in patients with BRAF V600E positive metastatic NSCLC receiving either first line treatment (N=36) or second and subsequent line treatment (N=57). The PBAC noted the objective response rate (ORR) was 63.9%, median progression free survival (PFS) was 10.8 months and median overall survival (OS) was 17.3 months in the first line treatment setting. The ORR was 68.4%, median PFS was 10.2 months and median OS was 18.2 months in the second and subsequent line treatment setting.
- 7.6 The PBAC noted the submission claimed D+T was non-inferior to pembrolizumab in combination with chemotherapy in terms of comparative effectiveness. The PBAC noted the submission presented an unanchored and unadjusted indirect treatment comparison (ITC) of the D+T study (E2201, first line patients only) and the pooled results of two pembrolizumab studies (KN-189 and KN-407) to support the clinical claim. The PBAC noted the ORR, median PFS and median OS were broadly similar for D+T and pembrolizumab + PBC and there was no statistically significant differences for any outcome. The PBAC agreed with the ESC that there were uncertainties associated with the ITC (as outlined in paragraph 6.45) but considered that, on balance, the claim that D+T is non-inferior in terms of comparative effectiveness was reasonable.
- 7.7 The PBAC considered it was difficult to assess the comparative safety, given the unanchored and unadjusted ITC, and considerable differences in the safety profiles between D+T and pembrolizumab in combination with chemotherapy. However, the PBAC considered the claim that D+T had a different but non-inferior safety profile compared to pembrolizumab in combination with chemotherapy was reasonable.
- 7.8 The PBAC considered the cost minimisation approach presented in the submission was reasonable and should use the effective price of pembrolizumab. The PBAC advised the following equi-effective doses were appropriate:
- For non-squamous NSCLC: Dabrafenib 249 mg/day for 18.91 months + trametinib 1.8 mg/day for 17.72 months = Pembrolizumab 200 mg Q3W for 14.13 cycles in combination with cisplatin 137 mg Q3W or carboplatin 530 mg Q3W for 3.60 cycles and pemetrexed 911 mg Q3W for 13.58 cycles.
 - For squamous NSCLC: Dabrafenib 249 mg/day for 18.91 months + trametinib 1.8 mg/day for 17.72 months = Pembrolizumab 200 mg Q3W for 14.02 cycles in combination with carboplatin 636 mg Q3W for 3.62 cycles and paclitaxel 364 mg Q3W for 3.60 cycles.

- 7.9 The PBAC considered the estimated utilisation of D+T provided in the submission was reasonable; however, the PBAC considered the offsets from reduced utilisation of pembrolizumab and chemotherapy were unlikely to be realised as use of these agents will be displaced rather than replaced.
- 7.10 The PBAC noted that flow-on changes to the immunotherapy listings including pembrolizumab would be required to ensure patients treated with D+T can access second line immunotherapy treatment (as discussed in paragraph 7.3) and advised the following changes to the relevant items:
- Amend the following criterion in the first line immunotherapy listings for stage IV (metastatic) non-small cell lung cancer (NSCLC): to “Patient must not have previously been treated for this condition in the metastatic setting OR The condition must have progressed after treatment with *only one of (i) tepotinib, (ii) selpercatinib, (iii) dabrafenib in combination with trametinib*”.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because D+T is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over pembrolizumab in combination with chemotherapy, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new items:

Dabrafenib

MEDICINAL PRODUCT Medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
DABRAFENIB					
Dabrafenib 75 mg capsule, 120	NEW	1	120	5	Tafinlar
Dabrafenib 50 mg capsule, 120	NEW	1	120	5	Tafinlar
Restriction Summary [new1] / Treatment of Concept: [new1A]					
Concept ID (for internal Dept. use)	Category / Program: GENERAL - General Schedule (Code GE)				
	Prescriber type: Medical Practitioners				
	Restriction type: Authority Required (Streamlined) [new code]				
ᱠᱟᱨᱢᱟ	Administrative Advice:				

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	No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
	Clinical criteria:
	Patient must have/have had a WHO performance status of no greater than 2 at treatment initiation with this drug for this condition.
	AND
	Clinical criteria:
	The condition must be positive for a BRAF V600E mutation
	AND
	Clinical criteria:
	Patient must be receiving trametinib and dabrafenib concomitantly for this condition
	AND
	Treatment criteria:
	Patient must be undergoing initial treatment with this drug; or
	Patient must be undergoing continuing treatment with this drug, with an absence of further disease progression while being treated with this drug; or
	Patient must be undergoing non-PBS subsidised treatment with this drug for this PBS indication, with an absence of further disease progression since commencing non-PBS subsidised supply.

Trametinib

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TRAMETINIB					
trametinib 2 mg tablet, 30	NEW	1	30	5	Mekinist
trametinib 500 mcg tablet, 30	NEW	3	90	5	Mekinist
Restriction Summary [new2] / Treatment of Concept: [new2A]					
Concept ID (for internal Dept. use)	Category / Program: GENERAL - General Schedule (Code GE)				
	Prescriber type: Medical Practitioners				
	Restriction type: Authority Required (Streamlined) [new code]				
Prescribing rule level	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)					
Clinical criteria:					
Patient must have/have had a WHO performance status of no greater than 2 at treatment initiation with this drug for this condition.					
AND					
Clinical criteria:					
The condition must be positive for a BRAF V600E mutation					
AND					
Clinical criteria:					
Patient must be receiving trametinib and dabrafenib concomitantly for this condition					
Treatment criteria:					

	Patient must be undergoing initial treatment with this drug; or
	Patient must be undergoing continuing treatment with this drug, with an absence of further disease progression while being treated with this drug; or
	Patient must be undergoing non-PBS subsidised treatment with this drug for this PBS indication, with an absence of further disease progression since commencing non-PBS subsidised supply.

8.2 Flow-on to the immunotherapy PBS listings for Stage IV (metastatic) non-small cell lung cancer:

- Amend the clinical criterion that currently exists in atezolizumab (11792P,11807K, 14266W,14298M), cemiplimab (13160P, 13169D), nivolumab in combination with ipilimumab (12315E, 12323N) and pembrolizumab (11492W,11494Y,12121Y,12119W) listings to allow them to be used after D+T.

Amend CC	<p>Patient must not have previously been treated for this condition in the metastatic setting, OR</p> <p><i>The condition must have progressed after treatment with only one of: (i) tepotinib, (ii) selpercatinib, (iii) dabrafenib in combination with trametinib.</i></p>
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These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.