5.08 LAROTRECTINIB

 **Capsule 25 mg, Capsule 100 mg**

**Oral solution 20 mg per mL, 100 mL**

**Vitrakvi®,**

 **Bayer Australia Ltd**

1. Purpose of submission
	* + - 1. An application was received requesting MBS listing of neurotrophic tropomyosin receptor kinase (*NTRK)* fusion testing using FISH or NGS and a PBS listing of larotrectinib for the targeted treatment of *NTRK* fusion solid tumours that are either unresectable locally advanced, metastatic, or locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection. This was the first submission requesting the listing of larotrectinib on the PBS for the above indication.
				2. Larotrectinib is an orally bioavailable, adenosine triphosphate (ATP)-competitive and highly selective tropomyosin receptor kinase (TRK) inhibitor, rationally designed to avoid activity with off-target kinase.
				3. The recommended dosage regimen as per the TGA approved product information (PI) is as follows. For adults: 100 mg larotrectinib, twice daily, until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Dosing in paediatric patients is based on body surface area (BSA): 100 mg/m2 larotrectinib, twice daily, with a maximum of 100 mg per dose. These are consistent with the larotrectinib single arm studies.
				4. The requested basis for listing is cost-effectiveness to standard of care (SoC).

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

| Component | Description |
| --- | --- |
| Population | **Test:** Locally advanced or metastatic solid tumour patient subpopulations:1. Paediatric patients newly diagnosed with locally advanced or metastatic solid tumours with high-frequency *NTRK* gene fusions;2. Adult patients newly diagnosed with locally advanced or metastatic solid tumours with high-frequency *NTRK* gene fusions;3. Paediatric patients newly diagnosed with locally advanced or metastatic solid tumours with low-frequency *NTRK* gene fusions;4. Adult patients with locally advanced or metastatic solid tumours with low-frequency *NTRK* gene fusions who have progressed following one or more standard of care therapies.**Treatment:** patients with locally advanced or metastatic solid tumours with confirmed *NTRK* gene fusions who would become eligible for Trk inhibitor treatment (first-line for Populations 1, 2 and 3 and second- or later-line for Population 4) |
| Intervention | **Test:** IHC, FISH or NGS**Treatment:** larotrectinib 100 mg BID for adults or 100 mg/m2 BID with a maximum of 100 mg BID administered for paediatric patients |
| Comparator | No test + SoC |
| Outcomes | **Test:** sensitivity, specificity, PPV, NPV, NNT**Treatment:** overall response rate, duration of response, overall survival, progression free survival, safety  |
| Clinical claim | In patients with a locally advanced or metastatic solid tumour with confirmed *NTRK* fusion, larotrectinib + *NTRK* gene fusion testing (FISH or NGS +/- IHC) is superior in terms of efficacy and safety when compared to no *NTRK* gene fusion testing + SoC |

Source: Table 1.1 and section 1.1.2.5 of the submission

BID = “bis in die” or twice a day; FISH = Fluorescence is situ hybridisation; IHC = immunohistochemistry; NGS = next generation sequencing; NNT = number needed to treat; NPV = negative predictive value; NTRK = neurotrophic tropomyosin receptor kinase; PPV = positive predictive value; SoC = standard of care

* + - * 1. Proposed place in the clinical management algorithm: for adult and paediatric with high fusion frequency and paediatric patients with low fusion frequency cancers, first-line treatment was proposed; and for adults with low frequency fusion solid tumour cancers, patients need to have progressed on or after one or more systemic therapies.
				2. Larotrectinib is expected to directly replace the SoC therapies available for the proposed treatment lines (as described above). Clinicians may potentially use larotrectinib either as earlier or later line therapy beyond those proposed by the submission. The proposed first-line use is broader than the provisionally approved TGA indication which is for patients who have either progressed following treatment or who do not have any satisfactory alternative therapy.
1. Requested listing

| **Name, restriction, manner of administration, form** | **Maximum amount (units)** | **No. of repeats** | **Dispensed price for maximum amount**  | **Proprietary name and manufacturer** |
| --- | --- | --- | --- | --- |
| Larotrectinib, 100 mg, oral capsules | 56 | 5 | PublicPublished $ '''''''''''''''''''''''Effective $ '''''''''''''''''''''''PrivatePublished *$ '''''''''''''''''''''''''*Effective *$ ''''''''''''''''''''''''* | VITRAKVI®,Bayer Australia Ltd |
| Larotrectinib, 25 mg, oral capsules | 56 | 5 | PublicPublished $ ''''''''''''''''''''''Effective $ ''''''''''''''''''''''PrivatePublished *$ '''''''''''''''''''''*Effective *$ '''''''''''''''''''* |
| Larotrectinib, 20 mg/ml, 1 × 100 ml bottle solution, oral administration | 100 | 5 | PublicPublished $ '''''''''''''''''''''''Effective $ ''''''''''''''''''''''PrivatePublished *$ ''''''''''''''''''''*Effective *$ '''''''''''''''''''''* |

Source: Table 1.13 of the submission.

Note: Estimates in italics have been revised during the evaluation to reflect the updated PBS fees from July 1, 2020

**Proposed PBS listing for adults and paediatric patients with high frequency NTRK fusion tumour and paediatric patients with low frequency NTRK fusion tumour – initial treatment**

| Category / Program | Section 100 – HSD |
| --- | --- |
| Prescriber type | [ ]  Dental [x]  Medical Practitioners [ ]  Nurse practitioners [ ]  Optometrists [ ]  Midwives |
| Condition | Locally advanced or metastatic solid tumours harbouring *NTRK* gene fusion |
| Treatment phase | Initial treatment |
| Restriction | [ ]  Restricted benefit[x]  Authority Required – In Writing[ ]  Authority Required – Telephone[ ]  Authority Required – Emergency[ ]  Authority Required – Electronic[ ]  Streamlined |
| Treatment criteria |  |
| Clinical criteria | The condition must be positive for a neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusion confirmed by next-generation sequencing or fluorescence in-situ hybridisationANDFor patients aged under 18 years, must be diagnosed with a solid tumour OR for patients aged 18 years or over, must be diagnosed with a solid tumour that harbours *NTRK* gene fusions at high frequency (≥75%)ANDDisease must be metastatic OR unresectable locally advanced OR locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resectionANDPatient must not have received prior treatment with a *NTRK* inhibitor |

**Proposed PBS listing for adults and paediatric patients with high frequency NTRK fusion tumour and paediatric patients with low frequency NTRK fusion tumour – continuing treatment**

| Category / Program | Section 100 – HSD |
| --- | --- |
| Prescriber type | [ ]  Dental [x]  Medical Practitioners [ ]  Nurse practitioners [ ]  Optometrists [ ]  Midwives |
| Condition | Locally advanced or metastatic solid tumours harbouring *NTRK* gene fusion |
| Treatment phase | Continuing treatment |
| Restriction | [ ]  Restricted benefit[x]  Authority Required – In Writing[ ]  Authority Required – Telephone[ ]  Authority Required – Emergency[ ]  Authority Required – Electronic[ ]  Streamlined |
| Treatment criteria |  |
| Clinical criteria | The treatment must be the sole PBS-subsidised treatment with this drug for this conditionANDPatient must have previously received PBS-subsidised treatment with this drug for this conditionANDPBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs |

Proposed PBS listing for adult patients with low frequency NTRK fusion tumour – initial treatment

| Category / Program | Section 100 – HSD |
| --- | --- |
| Prescriber type | [ ]  Dental [x]  Medical Practitioners [ ]  Nurse practitioners [ ]  Optometrists [ ]  Midwives |
| Condition | Locally advanced or metastatic solid tumours harbouring *NTRK* gene fusion |
| Treatment phase | Initial treatment |
| Restriction | [ ]  Restricted benefit[x]  Authority Required – In Writing[ ]  Authority Required – Telephone[ ]  Authority Required – Emergency[ ]  Authority Required – Electronic[ ]  Streamlined |
| Treatment criteria |  |
| Clinical criteria | The condition must be positive for a neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusion confirmed by next-generation sequencing or fluorescence in-situ hybridisationANDThe condition must be a solid tumour that harbours *NTRK* gene fusions at low frequency (<75%)ANDDisease must be metastatic OR unresectable locally advanced OR locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resectionANDPatients must have progressed on or after one or more systemic therapies appropriate for their tumour type in the locally advanced or metastatic setting, or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapyANDPatients must have an ECOG score of 3 or lessANDPatient must not have received prior treatment with a *NTRK* inhibitor |

**Proposed PBS listing for adult patients with low frequency NTRK fusion tumour – continuing treatment**

| Category / Program | Section 100 – HSD |
| --- | --- |
| Prescriber type | [ ]  Dental [x]  Medical Practitioners [ ]  Nurse practitioners [ ]  Optometrists [ ]  Midwives |
| Condition | Locally advanced or metastatic solid tumours harbouring *NTRK* gene fusion |
| Treatment phase | Continuing treatment |
| Restriction | [ ]  Restricted benefit[x]  Authority Required – In Writing[ ]  Authority Required – Telephone[ ]  Authority Required – Emergency[ ]  Authority Required – Electronic[ ]  Streamlined |
| Treatment criteria |  |
| Clinical criteria | The treatment must be the sole PBS-subsidised treatment with this drug for this conditionANDPatient must have previously received PBS-subsidised treatment with this drug for this conditionANDPBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs |

**Requested PBS Restriction – Grandfather treatment**

| Category / Program | Section 100 – HSD |
| --- | --- |
| Prescriber type | [ ]  Dental [x]  Medical Practitioners [ ]  Nurse practitioners [ ]  Optometrists [ ]  Midwives |
| Condition | Locally advanced or metastatic solid tumours harbouring *NTRK* gene fusion |
| Treatment phase | Grandfather treatment |
| Restriction | [ ]  Restricted benefit[x]  Authority Required – In Writing[ ]  Authority Required – Telephone[ ]  Authority Required – Emergency[ ]  Authority Required – Electronic[ ]  Streamlined |
| Treatment criteria |  |
| Clinical criteria | The condition must be positive for a neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusionANDDisease must be metastatic OR unresectable locally advanced OR locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection.ANDThe patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (to be determined)ANDThe treatment must be the sole PBS-subsidised therapy for this condition |

Source: Tables 1.14-1.18 of the submission

* + - * 1. The ESCs considered it may be helpful to specify the names of the high and low frequency tumours in each subgroup in the restriction to minimise use beyond the intended populations. The pre-PBAC Response requested that the PBS restrictions should allow enough flexibility so that high-frequency tumour types could be added when new *NTRK* fusions are uncovered. However, the PBAC agreed with the ESC – see section 7.
				2. The submission proposed a special pricing arrangement (SPA) to achieve a price deemed cost-effective given the challenges of estimating the magnitude of benefit from single-arm studies. In addition, the submission proposed a risk sharing arrangement (RSA) to enable access to larotrectinib, while addressing these uncertainties.
				3. The submission proposed that an individual utilisation based program (UBP) approach, specifying a duration based cap, and subsequent additional rebate would be the most suitable RSA for larotrectinib.
				4. For the UBP, the submission proposed that the treatment duration for individual patients be tracked through the PBS database, and after '''''' months on continuous treatment, ''''''''% rebate will be paid to the government for ongoing treatment. After ''''' months, patients who continue to have clinical benefit, would be allowed to stay on therapy until disease progression or no further clinical benefit. The ESCs considered the proposed RSA was not an appropriate way to achieve cost-effectiveness, particularly given the use of single-arm studies to inform the listing decision — and then, effectively, single-arm assessment to determine patients’ continued benefit — the magnitude of benefit (if any) obtained from larotrectinib over the benefit obtained from existing SoC will remain uncertain.
				5. The ESCs also considered the proposal was administratively burdensome for the Department and affected clinicians for several reasons:
* The RSA could only start to be administered after ''''''' or more years of listing, and duration of tracking seems open-ended.
* Tracking and analysis of patient level data would be required for ~< 500 patients and increasing per year, and then continuous tracking of individuals taking treatment beyond ''''' months.
* The definition of “continuous treatment” and how “treatment breaks” would be assessed were both uncertain.
* There are data privacy issues with sharing this granular level of individual patient data with the sponsor for validation of rebates.
	+ - * 1. The submission noted that the proposed continuation criteria require patients to still be benefiting from treatment with larotrectinib (i.e. not have disease progression or unacceptable toxicity). The sponsor was willing to remove the continuation criteria should a simplified listing be deemed appropriate. An unknown proportion of patients in the larotrectinib studies continued larotrectinib post-progression, likely because they were considered to be deriving clinical benefit according to the investigator. It is uncertain whether in Australian clinical practice, clinicians will treat a patient with larotrectinib beyond RECIST-based disease progression. There is also uncertainty regarding whether there were any post-progression gains in survival for patients receiving larotrectinib, which may have been driven, at least in part, by continued use beyond progression in the studies. This uncertainty is likely to be addressed at the earliest with evidence on the extent to which treated cancers become resistant to larotrectinib. The PBAC considered that the continuation criterion ‘PBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs’ should be amended to specify that patients must only be treated until disease progression as there may be various interpretations of ‘clinical benefit’ in practice.
				2. The surgical criterion “would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection” appears reasonable, particularly for the paediatric population. This may represent a scenario where larotrectinib may be used in an earlier treatment line for locally advanced resectable paediatric cancer.
				3. There was limited evidence for patients with an Eastern Cooperative Oncology Group (ECOG) score of greater than 3 in the larotrectinib studies.

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

1. Background
	* 1. Registration status
			+ 1. The proposed TGA indication in Australia was for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours harbouring a NTRK gene fusion.
				2. **TGA status at time of PBAC consideration**: The TGA Delegate’s overview was received during the evaluation process. Larotrectinib was provisionally registered on 7 September 2020 in Australia: for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours that:
* have a NTRK gene fusion without a known acquired resistance mutation,
* are metastatic or where surgical resection is likely to result in severe morbidity, and
* have either progressed following treatment or have no satisfactory alternative therapy.
	+ - * 1. The decision to approve the provisional indication was made on the basis of objective response rate (ORR) and duration of response from the single-arm clinical studies. The sponsor is expected to be required to submit further clinical data to confirm the clinical benefit of the medicine.
				2. The above indication aligns with the FDA approved indication and partially with the approved Australian indication for entrectinib (age eligibility is specified for entrectinib): for the treatment of adult and paediatric patients 12 years of age and older with solid tumours that:
* have a NTRK gene fusion without a known acquired resistance mutation,
* are metastatic or where surgical resection is likely to result in severe morbidity, and
* have either progressed following treatment or have no satisfactory alternative therapy*.*
	+ - * 1. The wording “satisfactory” in the above indications for larotrectinib and entrectinib is open to interpretation and may result in the use of these Trk inhibitors in earlier treatment lines than intended.
				2. Regarding the positioning of larotrectinib in the clinical management algorithm of patients with NTRK fusions, a recently published international expert consensus[[1]](#footnote-1) recommend TRK inhibitors for patients with NTRK fusions during the course of therapy when no other satisfactory treatment options exist depending on the clinical context.

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

1. Population and disease
	* + - 1. NTRK gene fusions occur in <5% of most solid tumour types, both common (such as lung cancer, breast cancer, melanoma, prostate cancer and colorectal cancer [CRC]) and less common (thyroid cancer, pancreatic cancer, bone carcinomas and hepatic cancer). In Australia, CRC is the second most common cancer tumour. CNS (mainly brain tumours) account for the largest number of cancer deaths for children in Australia with the frequency of NTRK fusions in CNS/glioma tumours being estimated at 2.2%. However, in some rare solid tumour types, such as a type of salivary gland mammary analogue secretory carcinoma (MASC), secretory breast carcinoma (SBC), infantile fibrosarcoma (IFS) and congenital mesoblastic nephroma (CMN), NTRK gene fusions are found at frequencies above 75%[[2]](#footnote-2).
				2. Consistent with PICO Advisory Sub-Committee (PASC) recommendations, four subpopulations based on age (adult and paediatric patients) and *NTRK* fusion frequency were proposed in the submission.
				3. **Paediatric high-frequency *NTRK* fusions:** In the larotrectinib studies, most paediatric patients were categorised as having either IFS (n=32) or paediatric soft tissue sarcoma (STS; n=19). The submission nominated IFS as the main representative tumour type for paediatric high-frequency NTRK fusion tumours. However, as no prospective SoC studies could be identified, paediatric STS was the nominated alternative representative tumour type. However, paediatric STS did not align with the NTRK fusion frequency classification scheme preferred by PASC. The justification for nominating paediatric STS, as a high fusion frequency, could not be verified from the sources provided in the submission. The study used by the submission to classify STS as a high frequency *NTRK* fusion cancer did not report the source of their information[[3]](#footnote-3). However, the authors specified that the paediatric STS cases included IFS (proportion was not reported) and that other types of STS had lower *NTRK* fusion frequencies. *The* ESCs noted that studies reporting on the most common oncogenic driver mutations for various paediatric STS histological subtypes indicate that the prevalence of the *NTRK* fusion oncogenic driver mutations is likely to be low (<5%) in most of them. As such, the ESCs considered that the inclusion of paediatric STS in the paediatric high-frequency *NTRK* fusion population was not appropriate. The ESCs considered the assumption presented in the Pre-Sub Committee Response (PSCR) that paediatric STS was a high frequency *NTRK* fusion cancer based on local clinician advice, was not strong enough to counter the known scientific evidence from the literature.
				4. **Adult** **high-frequency** ***NTRK*** **fusions:** The representative tumour type for this subpopulation is MASC, a distinct type of salivary gland carcinoma. MASC was the most represented high frequency NTRK fusion cancer occurring in adults who participated in the larotrectinib trials.
				5. **Paediatric low frequency *NTRK* fusions:** The representative tumour type for this subpopulation is primary central nervous system (CNS)/glioma. In the larotrectinib studies, 24 patients had a primary CNS tumour of which 20 where aged < 18 years. Of these, the most commonly diagnosed tumour subtype was glioblastoma multiforme (GBM), which is a grade IV tumour.
				6. **Adult low-frequency *NTRK* fusions:** The submission considered two representative tumour types for this patient population: adult STS and CRC. Adult STS is a rare cancer with a NTRK fusion frequency of approximately 1.4% in adults. In the larotrectinib trials, there were 17 adults with STS, which was the second most common low frequency NTRK fusion cancer type for adults. Eight patients in the larotrectinib studies had CRC. The submission noted that NTRK fusions have been extensively characterised in CRC and it is likely that NTRK fusion testing may be more prevalent in this cancer type.
				7. In the intended management algorithm, first-line treatment was proposed for adult and paediatric patients with high fusion frequency and paediatric patients with low fusion frequency tumours, and a refractory line for adult patients with low fusion frequency tumours. First-line treatment with larotrectinib is broader (or earlier) than the provisionally approved TGA indication (see paragraph 1.6). The PSCR contended that the requested restrictions are consistent with the TGA indication. The PSCR stated that current SoC for NTRK-fusion positive paediatric cancers generally consist of chemotherapy or radiotherapy which clinicians consider to be ‘unsatisfactory treatments’ given cytotoxic chemotherapy in children can lead to lifelong detriment such as reduced fertility and cognitive impairment in addition to short-term adverse events. The PSCR stated that for adult patients with high NTRK-fusion frequency tumours, satisfactory treatments are often considered to be targeted therapies noting that for high NTRK fusion frequency cancers such as salivary gland cancer, there are no effective targeted therapies for advanced disease. The ESCs considered that in clinical practice, whether larotrectinib is used as earlier or later line would be dependent on the intent of treatment (for e.g. larotrectinib may be used first-line with the intent to reduce tumour bulk to allow the opportunity for curative resection).

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

1. Comparator
	* + - 1. There are no currently PBS-listed comparators for patients with advanced stage cancer harbouring *NTRK* fusions, and current SoC will differ depending on the specific tumour type by site or histology. Table 2 summarises the SoC comparators nominated in the submission, by subpopulation, representative tumour type, and proposed treatment line for larotrectinib. SoC therapies, by treatment line, were identified during the evaluation from the European Medicines Agency (EMA) assessment report for larotrectinib[[4]](#footnote-4), and have been included for comparison.

Table 2: Summary of proposed subpopulations, corresponding representative tumours, and SoC comparators in the submission and from EMA

| **Submission patient subpopulation** | **Representative tumour(s) in submission** | **N = 188a (larotrectinib studies)** | **Comparators nominated in submission (*with or without NTRK fusions*)**  | **Rationale in submission** | **EMA assessment report:****SoC by tumour type (not age specified)** |
| --- | --- | --- | --- | --- | --- |
| **Proposed line of treatment: first line** |
| Paediatric patients with locally advanced or metastatic solid tumours with high-frequency NTRK fusions | IFS | 32 | First line: vincristine, actinomycin-D, cyclophosphamide (VAC)Later line: not identified. | Most common tumour type in trial | Soft tissue sarcoma (STS)Refer to adult STS (age not specified)  |
| Other STS | 19 | First line: ifosfamide + doxorubicinLater line: irinotecan with vincristine | Most common tumour type in trial |
| Paediatric patients with locally advanced or metastatic solid tumours with low-frequency NTRK fusions | CNS/glioma | 24 | First line: temozolomide above 3 years of ageProgressed: lomustine | Most common tumour type in trial | Not presented |
| Adult patients with locally advanced or metastatic solid tumours with high-frequency NTRK fusions | Salivary gland(MASC) | 21 | First line: cisplatin + vinorelbineProgressed: not identified | Most common tumour type in trial | Salivary gland carcinomabFirst line: platinum/doxorubicin, paclitaxel, vinorelbine, mitoxantrone, cetuximab+cisplatin, gefitinib+lapatinib, clinical trialsSecond or further therapy: none |
| **Proposed line of treatment: relapsed/refractory** |
| Adult patients with locally advanced or metastatic solid tumours with low-frequency NTRK fusions | STS | 17 | Dacarbazine | Rare low frequency example | STSFirst line: doxorubicin +/- olaratumab or ifosfamide or docetaxel, paclitaxel, gemcitabineSecond line: trabectedin, pazopanib, eribulin, paclitaxel |
| Colorectal Carcinoma | 8 | BSC (trifluridine/ tipiracil) | Common low frequency example. Best characterised genetically | Colorectal cancerFirst line: FOLFOX, FOLFIRI, CAPOX, FOLFOXFIRI, or fluoropyrimidine bevacizumab, cetuximab, panitumumabSecond line: FOLFOX, XELOX, FOLFIRI, cetuximab, panitumumab, aflibercept, ramucirumab.Further line: cetuximab, panitumumab, irinotecan, regorafenib, trifluridine/ tipiracil |

Source: Table 1.5of the submission. Source for EMA comparators: larotrectinib assessment report (EMA/CHMP/469135/2019, p16)

aRefers to ePAS4 (excludes primary CNS tumours) + SAS3 (restricted to primary CNS tumours) analysis sets.

bIt is unclear whether salivary gland carcinoma in the EMA table specifically referred to mammary analogue secretory gland which is specifically characterised by ETV6-NTRK3 fusion

IFS, infantile fibrosarcoma; STS. Soft tissue sarcoma; MASC, mammary analogue secretory carcinoma; PSD, Public Summary Document; BSC, best supportive care; CNS, central nervous system; BSC, best supportive care; NTRK, neurotrophic tropomyosin receptor kinase; SoC, standard of care; TMZ, temozolomide; VAC, vincristine, actinomycin-D, cyclophosphamide

* + - * 1. There were no comparator data, by fusion status, provided for the evidence base. The submission noted that the subpopulations, representative tumour types, and corresponding proposed lines of therapy determined the SoC therapies that were included. Some additional SoC therapies used in the later-line setting were selected for some tumour types to match the refractory population in the larotrectinib studies (further details below).
				2. There were important concerns with the SoC comparators nominated for the four subpopulations, as well as the respective efficacy data used for the naïve indirect comparisons. The concerns (as summarised further below) mainly relate to the appropriateness and applicability of the SoC data, the transitivity of the populations and whether these factors favoured larotrectinib in the naïve indirect comparisons.
				3. **For paediatric high fusion frequency**, there were no SoC data included in the submission for IFS, the main representative tumour type. The justification for other paediatric STS, as a high frequency tumour, remains unclear and inclusion of this tumour type as a high frequency tumour is inconsistent with data from the literature. Notwithstanding this uncertainty, the first-line SoC data were obtained from a study more than two decades old[[5]](#footnote-5) which was unlikely to represent current SoC treatment outcomes. The choice of a second-line study[[6]](#footnote-6) to match the larotrectinib pre-treated population was a decade old and did not appear to represent a conservative approach. The ESC noted that with the exclusion of paediatric STS, there are no available SoC data for paediatric high fusion frequency tumours.
				4. **For paediatric low frequency** (representative tumour CNS/glioma), one SoC comparator study was provided in adults with progressive glioblastoma[[7]](#footnote-7). Its inclusion was as a proxy for SoC for paediatric CNS in a later-line setting, as other studies were not identified. This may not be conservative and the comparator study has limited applicability.
				5. **For adult high frequency** (representative tumour salivary gland, MASC), the SoC was sourced from Airoldi 2001. This SoC study was conducted more than two decades ago (April 1993 to February 1997) and its use in an indirect comparison is likely to favour larotrectinib given that SoC has evolved since study conduct. Furthermore, MASC was not recognised as a distinct form of salivary gland carcinoma until 2010 (Skalova(2010). The ESCs noted that prior to 2010, MASC cases were also identified as acinic cell carcinoma and adenocarcinoma or not otherwise specified. The ESCs therefore considered that Airoldi 2001 may not be adequately representative of MASC. Given that MASC is approximately only 4.5 % of salivary gland tumours,[[8]](#footnote-8)[[9]](#footnote-9) the ESCs considered the Airoldi study had limited applicability to the adult high frequency population.
				6. **For adult low frequency** (representative tumours STS and CRC), the SoC comparators nominated in the submission for STS and CRC were dacarbazine and best supportive care (BSC, represented by TAS or trifluridine/tipiracil). The choice of these comparators was not reasonable as they are likely to favour larotrectinib (further details below).

For STS, SoC data were sourced from the dacarbazine treatment arm in a direct randomised controlled trial comparing eribulin[[10]](#footnote-10) with dacarbazine in patients with advanced STS (Study 309, N = 452)[[11]](#footnote-11) (see also table of included studies further below). However, Study 309 demonstrated that eribulin was superior to dacarbazine in terms of OS benefit. This formed the clinical basis for listing eribulin on the PBS for liposarcoma, a common STS subtype[[12]](#footnote-12). Therefore, at least for liposarcoma, eribulin may be a more reasonable comparator.

For CRC, the submission nominated last-line or best supportive care (BSC) as the SoC (represented by TAS or trifluridine/tipiracil). The requested restriction for this subpopulation requires patients to be refractory to a prior therapy however permits use of larotrectinib in earlier treatment lines such as second-line. There are multiple targeted therapies available on the PBS, depending on specific eligibility criteria (such as panitumumab for RAS wild-type metastatic colorectal cancer refractory to first-line chemotherapy). Other effective targeted therapies are also available other adult low fusion frequency cancers. The submission did not fully address the co-occurrence of other predictive biomarkers (such as microsatellite instability (MSI-H), tumour burden (TMB) and programmed cell death ligand (PD-L1) expression) in NTRK fusion positive tumours, and the possible implications for targeted treatment options.

* + - * 1. The ESCs noted that aside from the above concerns around the age of the studies and misalignment between the populations in the SoC studies and populations for which treatment with larotrectinib is proposed, there is high heterogeneity in efficacy outcomes across the broad range of different SoC therapies in clinical practice. This heterogeneity was apparent within specific tumour types, between tumour types, treatment lines, and types of SoC therapy. This wide range of variability is reflective of clinical heterogeneity by site/histology tumour type. The ESCs considered that selection of a most appropriate SoC comparator for each population is complex given this depended on treatment line and given the uncertainty around how larotrectinib would be used in clinical practice. Overall, the ESC considered the SoC data presented are unlikely to reflect current SoC in these cancers and therefore could not be used to reliably inform any incremental benefit of larotrectinib.The pre-PBAC Response noted that, irrespective of the comparators selected, incremental benefit would still need to be informed by naïve indirect comparisons which would not mitigate concerns around heterogeneity.

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

1. Consideration of the evidence
	* 1. Sponsor hearing
			+ 1. There was no hearing for this item.
		2. Consumer comments
			+ 1. The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. Rare Cancers Australia supported listing larotrectinib on the PBS for the treatment of patients with *NTRK* fusion solid tumours. Lung Foundation Australia supported the larotrectinib submission in relation to patients with locally advanced or metastatic lung cancer tumours that have *NTRK* fusions. Lung Foundation Australia stated that the prognosis of lung cancer is relatively poor compared to other commonly diagnosed cancers and noted evidence in the literature indicates a treatment effect in patients with *NTRK* fusion positive non-small cell lung cancer (NSCLC). Lung Foundation Australia considered that larotrectinib would provide an important treatment option, particularly for patients with *NTRK* fusion positive NSCLC with no alternative satisfactory treatments, which would allow patients to continue to participate in the community.
				2. The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the larotrectinib submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis pooled data from the LOXO-001, NAVIGATE and SCOUT trials. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for larotrectinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[[13]](#footnote-13), based on a comparison with various chemotherapies.
		3. Overview of the evidence base
			+ 1. The approach taken in the submission was to present evidence that *NTRK* fusion testing (FISH or NGS ± IHC) plus larotrectinib is superior to no *NTRK*-testing plus SoC in terms of efficacy and safety, in the proposed testing and treatment population.

Table 3: Summary of the linked evidence approach

|  | **Type of evidence supplied** | **Extent of evidence supplied** |
| --- | --- | --- |
| Accuracy and performance of the test (analytical validity) | DNA- vs RNA-NGS: 3 comparative studiesFISH vs RNA-NGS:1 comparative studyIHC vs RNA-NGS: 1 comparative study 2 case-control studiesIHC vs DNA-NGS: 1 case-control study | ☒ k=3; n=34,450☒ k=1; n=44☒ k=3; n=4,603☒ k=1; n=78 |
| Prognostic evidence | 2 prospective and 1 retrospective cohort studies | [x]  k=3 n=696 |
| Change in patient management | No evidence provided | [ ]  k=0 n=0 |
| Treatment effectiveness |  |  |
| Predictive effect(treatment effect variation) | [Comparison of outcomes in patients with and without the biomarker who receive the medicine or comparator] | [ ]  k=0 n=0 |
| Treatment effect (enriched) | [Single randomised controlled trial of medicine vs usual care in patients that are test positive in both arms] | [ ]  k=0 n=0 |
| Naïve indirect comparisons | [NTRK fusion positive patients from 3 single-arm larotrectinib studies and SoC patients, regardless of NTRK status, from single arms of 7 historical studies] | [x]  k=3 n=164[x]  k=7 n=919 |

k=number of studies, n=number of patients.

Source: Constructed during evaluation

* + - * 1. The submission presented evidence as outlined in Table 4.
				2. The evidence to support the comparative clinical benefit of larotrectinib was based on naïve indirect comparisons between pooled data from single-arm larotrectinib studies and single-arm SoC data from historical studies.

Table 4: Data availability to inform comparisons

|  |  |
| --- | --- |
| Proposed test vs no test | No evidence presented |
| Proposed test vs alternative test | DNA- vs RNA-NGS: 3 comparative studiesFISH vs RNA-NGS:1 comparative studyIHC vs RNA-NGS: 1 comparative study; 2 case-control studiesIHC vs DNA-NGS: 1 case-control study |
|  | **Proposed medicine** | **Comparator medicine** |
| Biomarker test positive | LOXO-001, NAVIGATE, SCOUT single-arm studies | No evidence presented |
| Biomarker test negative | LOXO-001 and SCOUT single-arm studies | No evidence presented |
| Biomarker untested | No evidence presented | Sandler 2001, Mascarenhas 2010, Airoldi 2001, Grill 2018, Wick 2017, Schöffski 2016, Mayer 2015 |

Source: Sections 2B and 2D of the submission

* + - * 1. The populations, tests and treatment regimens were not always transferrable across the evidence linkages, as they varied considerably.
				2. The three larotrectinib studies had different design/objectives, patient/disease characteristics, and there was an indication of heterogeneity of treatment effects by tumour type. This is likely to result in an inflated Type 1 error (false positives).[[14]](#footnote-14) Additionally, clinical and statistical heterogeneity between the studies (and within studies where there are multiple cohorts) could not be ruled out, making the pooled results difficult to interpret. Based on these uncertainties, the ESC considered that the pooled results should be interpreted with caution.
				3. Limitations of the efficacy data for SoC mainly involve the heterogeneity of response to SoC therapies by tumour type, treatment line, and agents used, and the use of historical data that are unlikely to represent current SoC data.
				4. The two bodies of evidence, therefore, do not appear to be transitive. All these comparator issues contribute to the uncertainty of the incremental benefit of larotrectinib.

Comparative effectiveness (Naïve indirect comparisons)

* + - * 1. Details of the included studies in the submission are provided in the table below.

Table 5: Listing of all included studies for the naive indirect comparisons

|  |  |  |
| --- | --- | --- |
| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| **Single-arm larotrectinib studies** |
| LOXO-TRK-14001(LOXO-001) | LOXO-TRK-14001 CSR: A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumours Interim CSR. | 18 February 2020. |
| Hong D, Bauer T, Lee J, Dowlati A, Brose M, Farago A et al. Larotrectinib in adult patients with solid tumours: A multi-centre, open-label, phase I dose-escalation study. | Annals of Oncology. 2019;30(2):325-331. |
| LOXO-TRK-14002(LOXO-002 or NAVIGATE) | LOXO-TRK-15002 (NAVIGATE) CSR: A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with NTRK Fusion-Positive Tumours Interim CSR. | 19 February 2020. |
| LOXO-TRK-14003(LOXO-003 or SCOUT) | Laetsch T, DuBois S, Mascarenhas L, Turpin B, Federman N, Albert C et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. | The Lancet Oncology. 2018;19(5):705-714. |
| DuBois S, Laetsch T, Federman N, Turpin B, Albert C, Nagasubramanian R et al. The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. | Cancer. 2018;124(21):4241-4247. |
| Pooled/combined larotrectinib studies: LOXO-001, NAVIGATE, SCOUT | Drilon A, Laetsch T, Kummar S, DuBois S, Lassen U, Demetri G et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. | New England Journal of Medicine. 2018;378(8):731-739. |
| Hong D, DuBois S, Kummar S, Farago A, Albert C, Rohrberg K et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. | The Lancet Oncology. 2020; 21(4): 531-540 |
| Italiano A, Nanda S, Keating K, Childs B, Fellous M, Drillon A et al. Retrospective Analysis to evaluate the growth modulation index (GMI) as a measure of clinical activity of larotrectinib in adult and paediatric TRK fusion cancers. | Annals of Oncology (2019) 30 (suppl\_5): v159-v193. |
| Drilon A et al. Activity and Safety of Larotrectinib in Adult Patients With TRK Fusion Cancer: An Expanded Data Set. | American Society of Clinical Oncology (ASCO) Virtual Scientific Program, May 29–31, 2020. |
| **Single-arm standard of care (SOC)β studies by the four subgroups proposed in the submission** |
| *Subgroup 1: paediatric tumour type with high NTRK fusion frequency* |
| *Representative tumour type - soft tissue sarcoma* |
| Sandler (2001) | Sandler E, Lyden E, Ruymann F, Maurer H, Wharam M, Parham D, Link M, Crist W. Efficacy of ifosfamide and doxorubicin given as a phase II “window” in children with newly diagnosed metastatic rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. | Medical and Paediatric Oncology. 2001 Nov;37(5):442-8. |
| Mascarenhas (2010) | Mascarenhas L, Lyden ER, Breitfeld PP, Walterhouse DO, Donaldson SS, Paidas CN, Parham DM, Anderson JR, Meyer WH, Hawkins DS. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. | Journal of clinical oncology. 2010 Oct 20;28(30):4658. |
| *Representative tumour type - infantile fibrosarcoma* |
| None identified∞ | - | - |
| Subgroup 2 – adult tumour type with high NTRK fusion frequency |
| Representative tumour type - salivary gland (MASC) |
| Airoldi (2001) | Airoldi M, Pedani F, Succo G, Gabriele AM, Ragona R, Marchionatti S, Bumma C. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. | Cancer. 2001 Feb 1; 91(3):541-7. |
| *Subgroup 3: “paediatric” tumour type with low NTRK fusion frequency* |
| *Representative tumour type - CNS/glioma* |
| Grill (2018): Age > 3 years | Grill J, Massimino M, Bouffet E, Azizi AA, McCowage G, Cañete A, Saran F, Le Deley MC, Varlet P, Morgan PS, Jaspan T. Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in paediatric patients with newly diagnosed high-grade glioma. | Journal of Clinical Oncology. 2018 Apr 1; 36(10):951-8. |
| Wick (2017): *Adults*π | \*Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, Brandes AA, Taal W, Domont J, Idbaih A, Campone M. Lomustine and bevacizumab in progressive glioblastoma. | New England Journal of Medicine. 2017 Nov 16; 377(20):1954-63. |
| *Subgroup 4 – adult tumour type with low NTRK fusion frequency* |
| *Representative tumour type – soft tissue sarcoma* |
| Schöffski 2016 | Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, Grignani G, Camargo V, Bauer S, Rha SY, Blay JY. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. | The Lancet. 2016 Apr 16;387(10028):1629-37. |
| Representative tumour type – colorectal carcinoma |
| Mayer 2015 | Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. | New England Journal of Medicine. 2015 May 14;372(20):1909-19. |

Source: Table 2.27 of the main body of the submission.

Note: Exemplars were nominated for each subgroup and these nominated tumour types are assumed to inform the comparative effectiveness and safety for the subgroup of tumours they represent.

βRegardless of the inclusion of randomised trials, SOC data were sourced from single arms from the studies

∞No studies examining vincristine, actinomycin D, and cyclophosphamide (VAC) in advanced unresectable population were identified in the submission

πStudy conducted in adult patients – used as a proxy in the submission as paediatric studies were not identified

* + - * 1. The key evidence for larotrectinib was based on pooled efficacy results across the three single-arm Phase 1/2 studies (LOXO-001, NAVIGATE, SCOUT) with individual study results included only for completeness. The justification provided for this approach was because of “the small patient numbers in each individual trial and to increase statistical validity of the results”.
				2. The pooled efficacy analysis sets (19 July 2019 data cut) included only patients with documented *NTRK* fusion: an extended primary analysis set ePAS4 (N=164; paediatric and adult tumour types other than primary CNS with documented *NTRK* fusion) and a supplementary analysis set SAS3 (N=24; paediatric and adult primary CNS patients with documented *NTRK* fusion tumours).
				3. The presentation of separate pooled analyses of efficacy by CNS status (ePAS4 included all tumour types except for primary CNS and SAS3 which only included primary CNS tumours) appears inconsistent with the site agnostic listing proposal for larotrectinib in the submission.
				4. The larotrectinib studies indicate inconsistency in the larotrectinib treatment effect between different tumour types. Recognising the limitation of small patient numbers, the efficacy data from the NAVIGATE study indicated response to larotrectinib treatment varied by tumour type (see further below). Data by tumour type were not presented separately for LOXO-001 and SCOUT.
				5. The larotrectinib studies were conducted in patients with different tumour types in the later-line treatment setting. The studies varied in terms of their primary objectives, eligibility criteria, baseline characteristics and treatment durations.
				6. The ESC noted that the clinical trial data were limited in varying degrees across all four proposed populations. The ESC acknowledged that due to the rarity of *NTRK* fusion cancers comparative randomised trial data was unlikely to be forthcoming.
				7. Naïve indirect comparisons were presented between pooled larotrectinib data and single-arm SoC data from seven studies in “representative tumour types” (IFS, paediatric STS, CNS/glioma, salivary gland (MASC), adult STS and colorectal cancer) for the four subpopulations categorised by age and *NTRK* fusion frequency.
				8. Table 6 summarises the SoC and larotrectinib data used for the naïve indirect comparisons. The risk of bias was generally high. The uncertainties of the SoC data have been discussed above.
				9. For the larotrectinib evidence, the following concerns were noted:
* The data for larotrectinib are unreliable due to small patient numbers by tumour type. The studies varied by design, patient characteristics, and efficacy. Pooling was conducted in the submission to address the limited reliability – however, interpreting the pooled results from the three different studies is problematic.
* NAVIGATE and SCOUT are open label ongoing studies. An applicability issue would arise if there is selective enrolment of patients with highly responding tumour types over time, which may not be representative of the distribution of tumour types in clinical practice.
* Subsequent therapies that were received by patients post progression in the larotrectinib studies — to treat resistance mutations to larotrectinib — may have contributed to gains in overall survival (OS). There were 41% (15/36) of patients in NAVIGATE administered either selitrectinib or entrectinib post progression. This proportion in SCOUT was 9%. Second generation Trk inhibitors are not currently PBS-subsidised and thus any observed OS benefit in the studies may not be realised in Australian clinical practice.

Table 6: SoC and larotrectinib data included for the naive indirect comparisons (OS and PFS) in the submission

| **Population subgroup** | **Representative tumour type** | **Single-arm SoC** | **SoC study** | **Single-arm larotrectinib data****Pooled across LOXO-001, NAVIGATE, and SCOUT depending on tumour type** | **Risk of bias /other limitations** |
| --- | --- | --- | --- | --- | --- |
| Paediatric high *NTRK* fusion frequency | IFS | VAC | No studies were identified in the submission | - | No data for key representative tumour type for subgroup with high clinical need |
| STS | Ifosfamide + doxorubicinN=152 | Sandler 2001First-line metastatic (Stage 4) rhabdomyosarcoma patients (aged <21 years) | Larotrectinib N=51 | Uncertainty on *NTRK* fusion frequency categorisationOld study may underestimate survival in current SoCNo transitivity assessedHigh risk of bias |
| Irinotecan + VincristineaN=47 | Mascarenhas 2010Later-line progressed rhabdomyosarcoma | No transitivity assessedSoC later line may not be conservative (not reflective of best outcomes with the comparator)High risk of bias |
| Adults high *NTRK* fusion frequency | Salivary gland (MASC) | Cisplatin + vinorelbine N=20 | Airoldi 2001First-line treatmentConducted between April 1993 and February 1997. (aged >20 yrs)b | Larotrectinib N=21 | Old study may underestimate survival in current SoCMASC was not recognised as a distinct salivary gland tumour before 2010.[[15]](#footnote-15)No transitivity assessedHigh risk of bias |
| Paediatric low *NTRK* fusion frequency | CNS/glioma | TMZcN=59 | Grill 2018First linePatients aged between 3 and 18 with localised, centrally neuropathology-confirmed, non-brainstem high grade glioma (HGG)c | Larotrectinib N=21 | No transitivity assessedHigh risk of bias |
| Lomustine | d Wick 2017Later lineBetween November 2011 through to December 2014, adultd patients aged >21 yrs with progressed glioblastoma received lomustine alone or lomustine + bevacizumab over a period of 37 months | Important applicability issue with adults in the studyNo transitivity assessedHigh risk of bias |
| Adults low *NTRK* fusion frequency | STS | DacarbazineN=224 | Schöffski 2016 Later linePatients aged ≥18 yrs with locally recurrent, advanced, or metastatic liposarcoma or leiomyosarcoma. Inclusion required not amenable to curative surgery or radiotherapy | Larotrectinib N=17 | More effective comparators available such as eribulin for liposarcomaNo transitivity assessedHigh risk of bias |
| CRC | BSC (TAS)N=266 | Mayer 2015Last linePatients >27 yrs with refractory metastatic colorectal cancer or who had had clinically significant adverse events that precluded the re-administration of prior therapies | Larotrectinib N=8 | Comparator not representative of potential use in earlier lineNo transitivity assessedHigh risk of bias |

Sources: Individual CSRs for the larotrectinib studies, publications for SoC comparator studies and Section 2D.4 of the submission.

a Two treatment schedules of I+V: regimen 1A included irinotecan 20 mg/m2/day IV for 5 days at weeks 1, 2, 4, and 5 with vincristine 1.5 mg/m2 administered IV on day 1 of weeks 1, 2, 4, and 5; regimen. 1B included irinotecan 50 mg/m2/day intravenously for 5 days at weeks 1 and 4 with vincristine as in regimen 1A. Disease response was assessed at week 6. Those with responsive disease continued to receive 44 weeks of multi-agent chemotherapy that incorporated the assigned I+V regimen. Only Regimen 1B was considered in the indirect comparison.

b Recurrent malignancy of major (parotid, submandibular, sublingual) or minor (hard palate, buccal mucosa, base of tongue, floor of mouth, paranasal sinus, nasopharynx, retromolar trigone, or other) salivary gland origin and one of the following histologies: adenoid cystic carcinoma, malignant mixed carcinoma, adenocarcinoma, or poorly differentiated mucoepidermoid carcinoma.

c Study aimed to evaluate the efficacy and safety of adding bevacizumab to postoperative radiotherapy + temozolomide (RT+TMZ+BEV) in in these patients.

d Study conducted in adult patients – used as a proxy as paediatric studies were not identified.

BSC, best supportive care (TAC = trifluridine with tipiracil); CNS, central nervous system; *NTRK*, tropomyosin receptor kinase; PSD, public summary document; TMZ, temozolomide; VAC, vincristine, actinomycin D, and cyclophosphamide; I+V, irinotecan + vincristine; IFS infantile fibrosarcoma; STS, soft tissue sarcoma; CRC, colorectal cancer; OS, overall survival; PFS, progression-free survival

* + - * 1. OS and PFS outcomes by tumour type, were presented only for NAVIGATE. For LOXO-001, the numbers of participants by tumour type were too small to be informative (lung: 1; STS: 2; salivary: 3; thyroid: 4; GIST: 2; cancer of unknown origin: 1). OS results for NAVIGATE and SCOUT are summarised in Table 8 and Table 9. LOXO-001 did not provide OS results. However, as PFS results are available by *NTRK* fusion status, they are summarised in Table 7.

Table 7: LOXO-001 Progression-free survival by NTRK fusion status

| **Status** | ***NTRK* fusion****N = 13** | **Non-*NTRK* fusion****N = 62** |
| --- | --- | --- |
| Progressed a,b | 4 (31%) | 54 (87%) |
| Duration of PFS (months) c,d |
| Median (95% CI) | NE (9.9, NE) | 1.8 (1.4, 1.9) |
| Range: minimum, maximum | 0.03+, 51.6+ | 0.03+, 25.2+ |
| Duration of follow-up (months) c,d |
| Median (months) | 38.9 | 25.2 |
| Rate (%) of PFS 12 months, c,d  | 80% | 5% |
| 95% CI | 55%, 100% | 0, 12% |

Source: Modified from Table 2.65 of the submission

Note: Based on Investigator assessment of response and on the subgroup of the Full Analysis Set

with *NTRK* fusions. + denotes censored observation.

a Based on investigator assessments using RECIST v1.1.

b Status as of cut-off visit.

c Estimate based on Kaplan-Meier method.

d 95% CI was calculated using Greenwood’s formula

CI = confidence interval; NE = Not estimable; *NTRK* = neurotrophic tropomyosin receptor kinase

Table 8: NAVIGATE - Overall survival by tumour type cohort (July 2019 data cut)

|  | **NSCLC** | **Thyroid** | **Sarcoma** | **CRC** | **Salivary gland** | **Biliary** | **CNS/****glioma** | **Other** | **Uncon-firmed** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| OS (months)a |
| N/cohort | 13 | 23 | 20 | 8 | 19 | 2 | 7 | 21 | 3 |
| Median | NE | 27.8 | NE | 36.5 | NE | 17.6 | NE | NE | NE |
| 95% CI | 7.56, NE | 16.72, NE | NE | 2.8, 36.5 | NE | 1.8, 33.4 | NE | 8.4, NE | NE |
| Rate of OS for at least |
| 12 mnths | 90.0 | 90.5 | 89.7 | 71.4 | 94.4 | 50.0 | NE | 79.2 | NE |
| 95% CI | 47.3, 98.5 | 67.0, 97.5 | 64.8, 97.3 | 25.8, 92.0 | 66.6, 99.2 | 0.6, 91.0 | NE | 45.8, 93.2 | NE |
| 18 mnths | 90.0 | 71.6 | 89.7 | 71.4 | 87.7 | 50.0 | NE | 66.0 | NE |
| 95% CI | 47.3, 98.5 | 36.6, 89.5 | 64.8, 97.3 | 25.8, 92.0 | 58.8, 96.8 | 0.6, 91.0 | NE | 28.8, 87.0 | NE |
| Follow-up time for OS (months)b |
| Median | 12.7 | 15.2 | 23.85 | 8.31 | 19.9 | NE | 8.08 | 8.31 | 7.85 |
| 95% CI | 7.4, 20.3 | 10.2, 22.1 | 9.2, 26.4 | 2.17, NE | 15.8, 29.3 | NE | 3.15, 11.04 | 5.6, 19.4 | 4.7, 12.9 |
| Rangemin, max | 3.8, 39.6 | 1.2, 31.3 | 1.2+, 42.8 | 2.2, 36.5+ | 2.7, 45.1 | 11.8+, 33.4+ | 3.2, 15.4 | 1.0, 37.5 | 4.7, 12.8 |

Source: Table 2.68 of the main body of the submission (rounded to 1 decimal place)

Interim data cut: July 2019.

a Median, Q1, and Q3 are Kaplan-Meier estimate. CI (2-sided) for median was computed using Greenwood’s formula. Minimum and maximum included the censored observations where using “+” after value indicates censoring.

b Median, Q1, and Q3 are Kaplan-Meier estimate of potential follow-up using the method by Schemper and Smith (9). CI (2-sided) for median was computed using the Greenwood’s formula. Minimum and maximum included the censored observations where using “+” after value indicates censoring.

CI = confidence interval; CNS = central nervous system; NE = not estimable; NSCLC = non-small cell lung cancer; OS = overall survival. Notes: Percentage was calculated using the number of patients in the column heading as the denominator. The table is based on the Full Analysis Set, N = 116

Table 9: SCOUT - Overall survival by NTRK fusion status (July 2019 data cut)

|  | ***NTRK* fusion****N = 79** | **Non-*NTRK* fusion****N = 9** |
| --- | --- | --- |
| Patients who died, n (%) | 3 (4) | 7 (78) |
| OS (months), Kaplan-Meier estimate a |
| Median | NE | 4.3 |
| 95% CI | NE | 0.4, 12.5 |
| Minimum, maximum | 1.8+, 38.6+ | 0.4, 30.7+ |
| Rate (%) of being alive for at least a |
| 12 months | 94 | 26 |
| 95% CI | 87, 100 | 0, 57 |
| Follow-up time for OS (months), Kaplan-Meier estimate b |
| Median | 12.9 | 30.7 |

Source: Table 2.72 of the submission

Interim data cut: July 2019.

a Medians are Kaplan-Meier estimate. CI (2-sided) for median was computed using Greenwood’s formula. Minimum and maximum included the censored observations where using “+” after value indicates censoring.

b Median, Q1, and Q3 are Kaplan-Meier estimate of potential follow-up using the method by Schemper and Smith.

CI = confidence interval; NE = not estimable; *NTRK* = neurotrophic tropomyosin receptor kinase; OS = overall survival

* + - * 1. LOXO-OO1: For *NTRK* fusion patients, median PFS was not reached whereas for non *NTRK* fusion patients (only 9 patients), it was 1.8 months. PFS rates at ≥ 12 months were substantially different between *NTRK* fusion and non *NTRK* fusion patients (80% versus 5%). These results were unreliable as the data were based on a small number of patients. Furthermore, there was inadequate evidence provided in the submission on the prognostic value of having an *NTRK* fusion. Given the single-arm nature of the study, the treatment effect variation, by NTRK fusion status, could not be isolated from the prognostic effects of *NTRK* fusion status.
				2. NAVIGATE: At the July 2019 data cut-off, the OS results were immature*.* Twenty of 116 (17.2%) patients had died and median OS had not been reached at the time of the analysis for all cohorts combined or for each tumour-specific disease cohort. The median follow-up time for OS was 15.01 months (95% CI: 11.96, 17.91) for all cohorts. The OS rate at 18 months varied from 90% in NSCLC patients to 50% in patients with biliary tumours (50%). Point estimates for median PFS duration varied among the different tumour type cohorts (25.76 months in salivary gland (MASC) tumours to 3.68 months in primary CNS tumours, and 5.44 months in biliary tumours). The PFS rate at 18 months was highest in NSCLC (75.2%; 95% CI: 40.7, 91.4) and salivary gland (75.3%; 95% CI: 46.0, 90.1) patients, and lowest in CRC patients (33.3%; 95% CI: 4.6, 67.6) and patients with other tumour types (26.1%; 95% CI: 5.5, 53.7).
				3. SCOUT: The median follow-up time in the *NTRK* fusion subgroup was 12.9 months. The median OS duration was not reached. The Kaplan-Meier estimate of OS of at least 12 months was 94% (95% CI: 87, 100). The estimated median OS in the non *NTRK* fusion subgroup was 4.3 months (95% CI: 0.4, 12.5) with a Kaplan-Meier estimate of OS rate of 26% (95% CI, 0, 57), for at least 12 months. At the time of the interim July 2019 data cut, the median duration of follow-up was 10.9 months. The median duration of PFS was not reached for the fusion subgroup (minimum of 22.1 months) compared to only 1.3 months in the non-fusion subgroup.
				4. Pooled larotrectinib OS results: With a median follow-up period of 15.8 months for patients in the EPAS4 dataset, median OS was not estimable (95% CI: 44.4, not estimable). At 24 months, 82% (95% CI: 75%, 90%) of non-CNS tumour larotrectinib patients were alive. With a median follow-up period of 6.0 months for SAS3 patients, median OS was not estimable (95% CI: 9.4, not estimable). At 12 months, the probability of being alive was 88% (95% CI: 65%, 100%) for SAS3 patients treated with larotrectinib. The rate of OS at 24 months was not estimable. The OS Kaplan-Meier plots for the EPAS4 and SAS3 data sets are presented below.

Figure 1: Kaplan-Meier Plot of Overall Survival (Extended Primary Analysis Set 4, data Cut 15-JUL-2019)



Source: Pooled efficacy, Attachment A2.4 to the submission.

Figure 2: Kaplan-Meier Plot of Overall Survival (Supplementary Analysis Set 3, data cut 15-JUL-2019)



Source: Pooled efficacy, Attachment A2.4 to the submission

* + - * 1. The pre-PBAC Response presented results of an update to the July 2019 ePAS4 dataset which included the same data cut with 16 additional patients. At 24 months, 83% (95% CI: 75%, 90%) of non-CNS tumour larotrectinib patients were alive and 68% (95% CI: 51%, 70%) of non-CNS tumour larotrectinib patients had not progressed based on the updated ePAS4 dataset. The pre-PBAC Response noted there were marginal improvements in PFS and OS from this more mature dataset, but the results were mostly comparable to that of the ePAS4 dataset originally presented in the submission. The pre-PBAC Response noted that, given the rarity of *NTRK* fusion cancers, the number of patients in the trials is unlikely to increase substantially.
				2. Median PFS was estimated to be 33.1 months for the overall larotrectinib population. Median PFS ranged from 7.1 to 10.8 months in the subgroups where median PFS had been reached. Median PFS had not been reached for salivary gland and paediatric STS.
				3. Pooled subgroup analyses by tumour type in ePAS4: ORR was high for STS (81%), IFS (97%), and salivary gland (86%). Thyroid, colon, melanoma, and breast had response rates from 38% to 60%. The remaining tumour types were too sparsely represented. The ORR for the ePAS4 dataset was 73% (95% CI: 65%, 79%). The ORR by tumour type and subpopulations are presented below.

Table 9A: Pooled overall response rate (ePAS4 and SAS3) by independent review committee

| Tumour type | N | CR + PR | ORR% (95% CI) |
| --- | --- | --- | --- |
| **Populations 1 and 2 (high frequency *NTRK* fusion cancers** |
| IFS (paediatric) | 32 | 31 | 97 (84, 100) |
| SBC (unclear) | 2 | 1 | 50 (1, 99) |
| MASC (adult) | 21 | 18 | 86 (64, 97) |
| **Tumour types with misclassification issues** |
| STSa (mixed) | 36 | 29 | 81 (64, 92) |
| CMNb (paediatric) | 1 | 1 | 100 (3, 100) |
| **Population 3 and 4 (low frequency NTRK fusion cancers** |
| Primary CNS (mixed) | 26 | 5 | 21 (7, 42). |
| Thyroid (mixed) | 27 | 15 | 56 (35, 75) |
| NSCLC (adult) | 13 | 10 | 77 (46, 95) |
| Colon (adult) | 8 | 3 | 38 (9, 76) |
| Melanoma (mixed) | 7 | 3 | 43 (10, 82) |
| Non-SBC | 3 | 2 | 67 (9, 99) |
| GIST | 4 | 4 | 100 (40, 100) |
| Bone sarcoma | 2 | 1 | 50 (1, 99) |
| Cholangiocarcinoma | 2 | 0 | 0 (NC) |
| Pancreas  | 2 | 0 | 0 (NC) |
| Appendix  | 1 | 0 | 0 (NC) |
| Cancer of unknown origin (adult) | 1 | 1 | 100 (3, 100) |
| Hepatic (adult) | 1 | 0 | 0 (NC) |
| Prostate (adult) | 1 | 0 | 0 (NC) |
| **ORRs for tumour types that can be classified by the subpopulations proposed for listing** |
| **Paediatric high frequency** |
| IFS | 32 | 31 | 97 (84, 100) |
| **Adult high frequency** |
| MASC | 21 | 18 | 86 (64, 97) |
| **Adult low frequency** |
| Primary CNS (NAVIGATE) | 7 | 1 | 14.3 (0.4, -)c |
| NSCLC | 13 | 10 | 77 (46, 95) |
| Colon | 8 | 3 | 38 (9, 76) |
| Hepatic | 1 | 0 | 0 (NC) |
| Prostate | 1 | 0 | 0 (NC) |
| Thyroid (NAVIGATE)  | 23 | 17 | 73.9 (51.6, -)c |
| Cancer of unknown origin | 1 | 1 | 100 (3, 100) |

Source: Modified from Table 3-22 of the Summary of Clinical Efficacy report provided during the evaluation

Investigator based ORRs from NAVIGATE specified where applicable.

a The STS population consists of 19 paediatric patients misclassified as belonging to Population 1 and 17 adult patients belonging to Population 4

b The histological subtype of CMN was not specified and therefore has an intermediate NTRK fusion frequency. Thus, this patient should have been included in Population 3 instead of Population 1.

c Source: investigator-based ORR from NAVIGATE Interim CSR July 2019 Table 9¬–3.

CI = confidence interval; CMN =congenital mesoblastic nephroma; CR = complete response; ePAS = extended primary analysis set; GIST = gastrointestinal stromal tumour; IFS = infantile sarcoma; IRC = Independent Review Committee; MASC = mammary analogue secretory carcinoma; NC = not calculable; NTRK = neurotrophic tropomyosin receptor kinase; NSCLC = non-small cell lung cancer; ORR = overall response rate; PR = partial response; SBC = secretory breast cancer; STS = soft tissue sarcoma.

* + - * 1. The ESCs noted that the clinical data indicated a potential treatment effect with larotrectinib for some cancers, particularly those classified as high frequency NTRK fusion cancers. However the ESCs considered that no firm conclusions could be drawn from the clinical evidence due to the issues outlined in paragraph 6.20.
				2. Naïve indirect comparisons between larotrectinib and SoC for the adult high and low frequency subpopulations are presented in Table 10 and Table 11, respectively and for the paediatric high and low frequency subpopulations in Table 12 and Table 13, respectively. 95% CIs were not presented. Data from all studies of larotrectinib were based on a July 2019 data cut. There is high uncertainty with the naïve indirect comparisons given the problems with the SoC data and transitivity issues.

Table 10: PFS and OS - Larotrectinib and SoC in adult high frequency *NTRK* tumours (salivary gland tumours)

|  | **Larotrectinib (salivary gland)****N=21****MASC** | **Cisplatin + VNB (Airoldi 2001)****N=20***Not specific for MASCa* |
| --- | --- | --- |
| Median PFS (months) | Not reached | 6.9 |
| PFS at 12 months | 85% | 31% |
| PFS at 24 months | 79% | 10% |
| Median OS (months) | Not reached | 10.8 |
| OS at 12 months | 95% | 33% |
| OS at 24 months | 90% | 19% |

Source: Table 2.100 of the submission

MASC = mammary analogue secretory carcinoma; PFS, progression-free survival; OS, overall survival; VNB, vinorelbine

aMASC was not recognised as a distinct form of salivary gland carcinoma when the Airoldi study was conducted. It was described in 2010 (Skalova, 2010)*[[16]](#footnote-16)*

Table 11: PFS and OS - Larotrectinib and SoC in adult low frequency *NTRK* tumours (colorectal tumours and STS)

|  | **Larotrectinib (CRC)****N=8** | **BSC (Meyer 2015)****N=266** | **Larotrectinib (STS)****N=17** | **Dacarbazine (Schoffski 2016)****N=224** |
| --- | --- | --- | --- | --- |
| Median PFS (months) | 7.1 | 1.8 | 9.4 | 2.3 |
| PFS at 12 months | 33% | 3% | 48% | 5% |
| PFS at 24 months | 33% | 2% | 48% | 0% |
| Median OS (months) | 36.3 | 7.1 | Not reached | 11.3 |
| OS at 12 months | 71% | 27% | 87% | 47% |
| OS at 24 months | 71% | 12% | 87% | 20% |

Source: Table 2.101 of the submission

PFS, progression-free survival; OS, overall survival CRC, colorectal; BSC, best supportive care; PFS, progression-free survival; OS, overall survival; STS, soft tissue sarcoma

Table 12: PFS and OS - Larotrectinib and SoC in paediatric high frequency *NTRK* tumours (STS)

|  | **Larotrectinib (STS)****N=51** | **I+D (Sandler 2001) – 1L****N=152** | **I+V (Mascarenhas 2010) – 2L****N=47** |
| --- | --- | --- | --- |
| Median PFS (months) | Not reached | 15.6 | 8.0 |
| PFS at 12 months | 74% | 61% | 38% |
| PFS at 24 months | 66% | 35% | 15% |
| Median OS (months) | Not reached | 22.1 | 15.9 |
| OS at 12 months | 95% | 76% | 62% |
| OS at 24 months | 95% | 49% | 30% |

Source: Table 2.102 of the submission

1L, first-line; 2L, second-line; I+D, ifosfamide and doxorubicin; I+V, irinotecan and vincristine; IFS, infantile fibrosarcoma; STS, soft tissue sarcoma, PFS, progression-free survival; OS, overall survival

Table 13: PFS and OS - Larotrectinib and SoC in paediatric low frequency NTRK tumours (CNS/glioma)

|  | **Larotrectinib****N=21** | **RT+TMZ (Grill 2019) – 1L****N=59** | **Lomustine (Wick 2017) – 2L****N=149** |
| --- | --- | --- | --- |
| Median PFS (months) | 10.8 | 12.2 | 1.6 |
| PFS at 12 months | 31% | 51% | 3% |
| PFS at 24 months | 31% | 34% | 1% |
| Median OS (months) | Not reached | 17.7 | 8.0 |
| OS at 12 months | 90% | 69% | 30% |
| OS at 24 months | 83% | 50% | 9% |

Source: Table 2.103 of the submission

RT+TMZ, radiotherapy plus temozolomide; PFS, progression-free survival; OS, overall survival

* + - * 1. Adult high frequency (salivary gland, MASC): The median duration of OS was not reached for larotrectinib compared with 10.8 months in the SoC arm (all salivary gland tumours; not necessarily restricted to MASC). The OS rate at 24 months was 90% in patients treated with larotrectinib compared to 19% in the SoC arm.
				2. Adult low frequency (STS and CRC): For CRC, the median durations of OS for larotrectinib and SoC were 36.3 months, and 7.1 months, respectively. The OS rate at 24 months for larotrectinib and SoC were 71% and 12%, respectively. For STS, the median duration of OS for larotrectinib was not reached compared to 11.3 months for SoC. The OS rate at 24 months for larotrectinib and SoC were 87% and 20%, respectively.
				3. Paediatric high frequency: For STS, the median duration of OS for larotrectinib was not reached compared to 22.1 months for first-line SoC and 15.9 months for second-line SoC. The OS rate at 24 months was 95% compared to 49% in first-line SoC and 30% in second-line SoC.
				4. Paediatric low frequency: For CNS/glioma, the median duration of OS for larotrectinib was not reached compared to 17.7 months in first-line SoC. The second-line SoC data were from adults (used as a proxy in the submission for the paediatric population). The median duration of OS in second-line SoC for adult progressive glioblastoma was 8.0 months. The OS rate at 24 months was 83% for larotrectinib and 50% for first-line SoC. in paediatric patients.
				5. The indirect comparisons should be interpreted with caution given their naïve nature and other limitations with 1) the limited reliability and potential heterogeneity associated with the larotrectinib data, and 2) the appropriateness of the representative tumour types for the subpopulations and the age of the corresponding SoC data.
		1. Comparative harms (Naïve indirect comparison)
			- 1. The summary of overall AEs, pooled from the larotrectinib studies (regardless of NTRK fusion status), is presented in the table below.

Table 14: Summary of adverse events (Overall Safety Analysis Set regardless of fusion status)

| **TEAE** | **Overall safety set****n = 279** |
| --- | --- |
| Patients with TEAE | 275 (99%) |
| Patients with TEAE related to larotrectinib | 216 (77%) |
| Patients with TEAE Grade 3 or 4 | 148 (53%) |
| Patients with TEAE Grade 3 or 4 and related to larotrectinib | 43 (15%) |
| Patients with TEAE and action taken of larotrectinib permanently discontinued  | 26 (9%) |
| Patients with TEAE and action taken of larotrectinib permanently discontinued and related to larotrectinib | 6 (2%) |
| Patients with serious TEAE | 96 (34%) |
| Patients with serious TEAE and related to larotrectinib | 15 (5%) |
| Patients with fatal TEAEa | 16 (6%) |

Source: Table 2.93 of the submission

Larotrectinib July 2019 data-cut

 aRefers to TEAEs both related and unrelated to larotrectinib treatment

TEAEs are defined as adverse events that start on or after the first administration of Larotrectinib. Related events are those judged by the Investigator as related to Larotrectinib. Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), Grade 4 (life-threatening). Percentages are calculated based on the number of patients in the column heading as the denominator.

TEAE, treatment emergent adverse event; CTCAE, Common Terminology Criteria for Adverse Events

* + - * 1. Approximately half of the patients (53%) had at least one TEAE that was of Grade 3 or Grade 4 severity. The proportion of patients with Grade 3 or Grade 4 TEAEs, potentially related to larotrectinib, was 15%. There were 26 patients (9%) who had TEAEs that led to permanent treatment discontinuation. TEAEs were not independently assessed and outcome assessors were not blinded to the treatment received. Given this, these results should be interpreted cautiously.
				2. The TGA Delegate’s Overview for larotrectinib presented pooled safety data for three paediatric subgroups (infants/toddlers (28 days to 23 months of age), children (2 to 3 years of age), and adolescents (12 to <18 years of age)).
				3. For the majority of TEAEs, the incidence was higher in the infants/toddler subgroup compared to children. AEs in paediatric patients were assessed to be serious by the investigator for 12 (36%) infants/toddlers, 10 (26%) children and 7 (33%) adolescents.
				4. The risk of “neurodevelopment impairment in paediatric patients” was evaluated in the context of an important potential risk of “severe neurologic reactions”. Paediatric patients experienced dizziness at 8%, insomnia at 4%, paraesthesia at 2%, dysgeusia at 2%, gait disturbance at 4%, delirium at 1%, and somnolence at 5%, and there were no paediatric patients with memory impairment.
				5. A meaningful interpretation of the naïve indirect comparison of safety is problematic as SoC data were not reported for many of these events. Furthermore, some of the Grade ≥3 AEs observed across the SoC studies of different tumour types may have been disease related rather than drug related.
				6. AEs were considered in the economic evaluation. However, the SoC AEs for the paediatric population were sourced exclusively from Sandler (2001). This did not appear to be a reasonable approach. Management of chemotherapy-related AEs in current SoC has improved over time with more frequent monitoring and earlier recognition of these events, with more effective prophylaxis and treatment compared to that employed in a study conducted more than 20 years ago. The toxicity profile also differs between larotrectinib (neurological) and chemotherapy (haematological). Neurological AEs reflective of larotrectinib mechanism of action are relevant in the assessment of benefit risk, particularly in the paediatric population.
		1. Benefits and harms
			- 1. The optimal testing strategy would minimise the numbers of falsely diagnosed patients (i.e. false positives and false negatives), limiting any lack of improved benefits and potential harms from incorrect treatment.
				2. The basis of the evidence in the submission was naïve indirect comparisons. Therefore, the magnitude of the incremental benefit of larotrectinib could not be quantified. Accordingly, a benefits/harms table was not presented.
		2. Interpretation of clinical evidence
			- 1. The therapeutic conclusion in the submission was that *NTRK* fusion testing plus larotrectinib was superior to no NTRK-testing plus SoC, in terms of efficacy and safety, in the proposed testing and treatment population.
				2. There were several uncertainties associated with the evidence presented in Section 2 of the submission. Collectively, the single-arm design of the larotrectinib studies, the small number of patients by tumour type enrolled, apparent heterogeneity in the larotrectinib efficacy results by tumour type, suitability of the representative tumour types, applicability of the SoC data presented to current Australian SoC, and the naïve indirect nature of the comparison, all resulted in a high level of uncertainty regarding the magnitude of incremental benefit of larotrectinib. Furthermore, there was also uncertainty as to whether the incremental benefit of larotrectinib, observed for a representative tumour type for a subpopulation, is also likely to vary among member tumour types within the same category. For adult low frequency tumours for example, there was inadequate information presented to help determine whether the treatment effect of larotrectinib is consistent across NSCLC, CRC, and melanoma. Given the different SoC for these tumours with likely varying clinical benefit, the incremental benefit of larotrectinib is also likely to vary. Thus the incremental benefit and benefit-risk balance of larotrectinib are likely to vary by subpopulation and within a subpopulation.
				3. Absolute response rates appeared to be greater in high fusion frequency tumour types although the relative benefit was uncertain. Acknowledging the several limitations associated with the evidence, and aside of the response rates, treatment with larotrectinib may provide the paediatric high frequency subpopulation the additional advantage of avoiding both the short and long-term complications of chemotherapy.
				4. The ESCs acknowledged the PSCR showed tumour shrinkage across all included tumour types in both adult and paediatric population; however it was considered highly uncertain what the magnitude of clinical benefit was in any of the subpopulations presented over current SoC. The most representative tumour types and SoC data have not been presented in this submission, but will be needed to inform decision-making.
				5. For safety, pooled larotrectinib safety data indicated a manageable safety profile, although comparative safety is uncertain and likely to be variable. Longer-term data from a larger patient population are required to assess any rare neurological/other TEAEs.
				6. The efficacy data provided in the submission and discussed above were based on the July 2019 data cut. The NAVIGATE and SCOUT studies are ongoing, and thus data for an additional 12 months may be currently available to the sponsor.
				7. The PBAC considered that the claim of superior effectiveness compared to SoC was likely acceptable for the high frequency adult and paediatric populations, but the magnitude of the benefit was uncertain given the data presented for SoC are unlikely to represent current standard of care and the uncertainties around the naïve indirect comparisons. The PBAC considered the claim of superior effectiveness compared to SoC for the low frequency adult and paediatric populations was not sufficiently supported.
		3. Claim of co-dependency
			- 1. The therapeutic conclusion presented in the submission was that *NTRK* fusion testing (FISH or NGS ± IHC) plus larotrectinib was superior to no *NTRK*-testing plus SoC in terms of efficacy and safety, in the proposed testing and treatment population. There were several uncertainties associated with the evidence, which did not allow a definitive conclusion regarding this claim.
		4. Economic analysis
			- 1. The submission presented a stepped economic evaluation based on naïve indirect comparisons of single-arm studies (comparing larotrectinib and SoC). The types of economic evaluation presented were a cost-effectiveness analysis and a cost-utility analysis, measuring outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. The key components of the economic evaluation are summarised below.

Table 15: Summary of model structure, key inputs and rationale

| **Component** | **Description** |
| --- | --- |
| Cohorts modelled | Patients with *NTRK* fusion positive solid tumours:* Larotrectinib: overall cohort of patients from the pooled larotrectinib analysis (i.e. mix of adult and paediatric patients and a mix of high and low frequency *NTRK* fusion tumour types)
* Comparator: five cohorts, chosen to represent the tumour types in the larotrectinib studies:
	+ Paediatric STS (1L) (paediatric high frequency *NTRK* fusion tumour types), weight: 27.7%
	+ Paediatric glioma (1L) (paediatric low frequency *NTRK* fusion tumour types), weight: 10.6%
	+ Salivary gland (1L) (adult high frequency *NTRK* fusion tumour types), weight: 13.8%
	+ Colorectal cancer (adult low frequency *NTRK* fusion, common, tumour types), weight: 31.4%
	+ Adult STS (adult low frequency *NTRK* fusion, rare, tumour types), weight: 16.5%

Tumour type subgroup analyses of the pooled larotrectinib studies were also presented to allow within-tumour comparisonsThe naïve indirect comparisons compared larotrectinib to SoC therapies across a select number of representative tumour types. As within tumour type analyses have also been presented, a weighted analysis based on these tumour type analyses may be a more appropriate approach. Furthermore, the modelled incremental benefits, both within the tumour type specific analyses and the base case analysis, need to be interpreted with caution given the inherent caveats of the naïve indirect comparisons presented. |
| Type of analysis | Cost-utility analysis.  |
| Outcomes | Quality-adjusted life years gained, life-years gained. This is reasonable. |
| Time horizon | Base case: 20 years (compared to a median follow-up of 16 months).Sensitivity analysis: 5 and 10 years.The selection of the time horizon has not been justified. At the end of 20 years, 13% of patients treated with larotrectinib remained alive (10% progression-free). |
| Methods used to generate results | Partitioned survival analysis. This is reasonable. |
| Health states | Progression-free, Progressed, Dead. This is reasonable. |
| Cycle length | Weekly. This is reasonable. |
| Test parameters | NGS or FISH: assumed to perform as per the evidentiary standard (i.e. 100% sensitivity and 100% specificity). The assumption that NGS and FISH in practice would reflect the performance of the test in the larotrectinib studies may not be reasonable, as the performance of NGS in detecting NTRK fusions varies depending on the NGS methodology – if the item is restricted to RNA-NGS this may be reasonable. The performance of FISH is uncertain due to a lack of data.Where IHC is proposed as a triage test, the accuracy of pan-Trk IHC relative to RNA-NGS was used as reported in Solomon[[17]](#footnote-17). |
| False positives/negatives | The cost of *NTRK* fusion testing required to identify one *NTRK* fusion positive patient was back-calculated and weighted across the nominated tumour types. The cost implications of IHC test performance can be considered in the model. While the back-calculations presented consider the cost implications of IHC false positive results, they do not take into account the implications of IHC false negatives.The submission assumed that NGS and FISH testing would perform as the evidentiary standard, and so the model structure does not allow for the implications of false positive results to be examined. |
| Transition probabilities | Health state allocation over time was determined by progression free and overall survival curves from the larotrectinib pooled analysis and comparator trials. Health state allocation based on the OS and PFS curves is a reasonable approach, however as noted above, the use of the PFS and OS data from the overall larotrectinib analysis may not be an appropriate choice. |
| Utilities | Baseline health state utility weights were mapped from HRQoL assessments from the NAVIGATE and SCOUT studies. The baseline health state utility applied in the progression-free health state was adjusted for response to therapy and for AEs. As the relationship between HRQoL and adverse events is clear, adjustment for adverse events is appropriate. However, the relationship between HRQoL and response is less clear and may not be reasonable. |

Source: Table 3.1 of the submission.

CNS = central nervous system; FISH = fluorescence *in situ* hybridisation; HRQoL = health-related quality-of-life; IFS = infantile fibrosarcoma; IHC = immunohistochemistry; KM = Kaplan-Meier; NTRK = neurotrophic tropomyosin receptor kinase; NGS = next generation sequencing; OS = overall survival; PFS = progression-free survival; STS = soft tissue sarcoma; SoC = standard of care; ToT = time-on-treatment.

* + - * 1. Entry into the model is at the point of treatment. In the larotrectinib arm, the number and cost of *NTRK* fusion tests was back-calculated using estimates of prevalence and test performance for each of the representative tumour types. As stated in the PBAC and MSAC Guidelines for co-dependent technologies this approach is less-preferred than where entry into the model is at the point of testing.
				2. Different testing strategies are proposed based on patient age and the frequency of *NTRK* fusions within that tumour type. Tumour types that are associated with high *NTRK* fusion frequencies and paediatric patients with tumours that have a low frequency of *NTRK* fusions are proposed to receive either NGS or FISH testing. NGS and FISH were considered to be the evidentiary standard, and so the impact of inaccurate testing by the evidentiary standard is considered to be incorporated in the larotrectinib study results. Little detail was provided regarding the test methodology used in the larotrectinib studies. The performance of NGS in detecting *NTRK* fusions varies depending on the NGS methodology (i.e. DNA or RNA) and the performance of FISH is uncertain due to a lack of data. Therefore, the assumption that NGS and FISH in practice would reflect the performance of the test in the larotrectinib studies may not be reasonable. Adults with low frequency *NTRK* fusion tumours are proposed to receive IHC testing first, with confirmatory NGS or FISH testing only in those who are found to be IHC-positive.
				3. While the estimates of prevalence used in the economic evaluation were not derived from the diagnostic accuracy studies, these were generally consistent for all tumour types, except paediatric STS. The source of this prevalence estimate could not be verified during the evaluation. Paediatric STS may not be representative of paediatric high *NTRK* frequency tumours (and so the comparison modelled may have limited applicability to paediatric patients with high *NTRK* frequency tumour types).
				4. Modelled costs and outcomes from larotrectinib or comparator treatment were generated through a partitioned survival analysis. In the larotrectinib arm of the model, PFS and OS curves were derived from the pooled analysis of the larotrectinib studies (combined ePAS4 + SAS3 data sets, July 2019). These data are immature and as such, extrapolation is associated with a high degree of uncertainty. The comparator arm of the model was constructed based on five weighted sub-models, with modelled costs and outcomes for each sub-model generated using PFS and OS curves identified from the published literature for the chosen representative tumour type. Therefore, the model is based on naïve indirect comparisons of studies, comparing larotrectinib use in a number of tumour types, to SoC therapies across five representative tumour types. While it may be reasonable to nominate tumour types in which the relative treatment effect of larotrectinib could be considered representative across the proposed subgroups, it is not reasonable to assume that absolute survival on SoC in the representative tumour type would apply across all tumour types within the subgroup. However, there was also uncertainty as to whether the incremental benefit of larotrectinib, observed for a representative tumour type for a subpopulation, is also likely to vary among member tumour types within the same category.
				5. Subgroup analyses of larotrectinib were additionally presented for each of the chosen representative tumour types. While a weighted analysis based on these may have been a more appropriate approach, given the small patient numbers (and small number of events experienced) within each of the tumour-specific subgroups, there is substantial uncertainty in the estimates modelled.
				6. Furthermore, the modelled incremental benefits, both within the tumour type specific analyses and the base case analysis, need to be interpreted with caution, given the inherent caveats of the naïve indirect comparisons which are the basis of the ensuing modelled incremental benefit.

Figure 3: Kaplan-Meier and modelled curves for PFS and OS used in the base case analysis



Source: Constructed during the evaluation from the ‘A3.1\_Larotrectinib\_PBACMSAC\_CEA\_June2020.xlsm’ workbook included in the submission.

KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; ToT = time-on-treatment.

* + - * 1. Despite differences noted between the overall proportion of NTRK fusion-positive tumour types in the larotrectinib studies and the Australian population, the submission used the distribution of *NTRK* fusion-positive tumour types as observed in the larotrectinib pooled analyses. This was not justified. Sensitivity analyses were presented using the expected distribution, based on the estimated utilisation in practice, and the ICER was observed to improve (16% reduction). However, these analyses relied on small subsets of the larotrectinib pooled analysis, from which estimates of extrapolated survival are highly uncertain.
				2. The submission has not considered the applicability of second generation Trk-inhibitors after disease progression in the SCOUT and NAVIGATE studies. As these agents are not available in practice, adjustment of the OS benefit of larotrectinib to account for the effect of such post-progression therapies may have been a reasonable approach, as there is some evidence that patients do benefit. As observed in Table 18, post-progression survival is a main driver of the survival benefit in a number of the tumour type subgroups.
				3. The ESCs considered an ICER that depends on downstream outcomes far beyond the follow-up duration of the clinical studies is inherently subject to substantial uncertainty and may be unreliable for decision-making.
				4. The key drivers of the model are summarised below.

Table 16: Key drivers of the model

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Larotrectinib use and cost | The effects of the proposed RSA to cap costs to '''' years of treatment were assumed in the base case analysis.Actual (rather than planned) dosing was used in the base case analysis. | High, favours larotrectinib. When the effects of the proposed RSA are excluded, or when planned dosing is modelled, a substantial increase in the ICER is observed.As noted above in paragraphs 2.4 and 2.5, the proposed RSA would not be acceptable and should not be included in the base case. |
| Time horizon | 20 years | High, favours larotrectinib. Reductions in the time horizon lead to substantial increases in the ICER. |
| Larotrectinib clinical data | As per the overall pooled larotrectinib analysis | Moderate, favours SoC. When the weighted larotrectinib data are used, a moderate decrease in the ICER is observed. |
| Extrapolation | Parametric models for extrapolation were selected based on Akaike's Information Criterion and Bayesian Information Criterion, in addition to an assessment of face-validity and plausibility. | Moderate. The use of the next best fit for OS was associated with a substantial reduction in the ICER. However, a moderate increase was observed when the most conservative PFS and OS functions were applied. Given the high level of uncertainty in the evidence and the extrapolations, this may be a reasonable approach. |

Source: Compiled during the evaluation.

ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; RSA = risk sharing arrangement; SoC = standard or care.

* + - * 1. The results of the stepped economic evaluation are summarised below.

Table 17: Results of the stepped economic evaluation

|  |  |  |  |
| --- | --- | --- | --- |
| **Step and component** | **Overall larotrectinib** | **Weighted SoC** | **Increment** |
| **Step 1: Modelled economic evaluation comparing *NTRK* fusion testing and larotrectinib treatment with no *NTRK* fusion testing and SOC (19-month time horizon)** |
| Cost | $''''''''''''''''''' | $'''''''''''''''' | $'''''''''''''''''' |
| *Revised* | *$''''''''''''''''''''* | *$'''''''''''''''''* | *$''''''''''''''''''* |
| LY gained | 1.4125 | 0.9905 | 0.4220 |
| **Incremental cost/extra LY gained** |  |  | **$''''''''''''''1** |
| ***Revised*** |  |  | ***$'''''''''*''''''''1** |
| **Step 2: Extrapolation of the modelled economic evaluation to 20 years** |
| Cost | $'''''''''''''''''''' | $'''''''''''''''' | $''''''''''''''''' |
| *Revised* | *$'''''''''''''''''* | *$'''''''''''''''''* | *$''''''''''''''''''''* |
| LY gained | 6.2670 | 2.2593 | 4.0077 |
| **Incremental cost/extra LY gained** |  |  | **$'''''''''''''2** |
| ***Revised*** |  |  | ***$'''''''''''''*2** |
| **Step 3: Transformation of outcomes into QALYs** |  |  |  |
| Cost | $'''''''''''''''''''' | $'''''''''''''''''' | $'''''''''''''''''' |
| *Revised* | *$'''''''''''''''''* | *$'''''''''''''''* | *$'''''''''''''''''''''* |
| QALY gained | 4.9698 | 1.6790 | 3.2907 |
| **Incremental cost/extra QALY gained** |  |  | **$''''''''''''''3** |
| ***Revised*** |  |  | ***$'''''''*''''''''3** |

Source: Table 3.33 of the submission.

LY = life year; NTRK = neurotrophic tropomyosin receptor kinase; QALY = quality adjusted life year; SoC = standard of care; STS = soft tissue sarcoma.

Note: Analyses in italics have been revised during the evaluation to account for IHC false negative test results; use the efficient price for the average dispensed dose of infusible chemotherapies, apply per pack costing of temozolomide (rather than cost on a per mg basis) and update PBS fees as of July 1, 2020.

*The redacted values correspond to the following ranges*

*1$255,000 to < $355,000*

*2$45,000 to < $55,000*

*3$55,000 to < $75,000*

* + - * 1. The differences in Step 1 between larotrectinib and SoC were based on non-comparative data, making the results highly uncertain. Therefore, the results at each subsequent modelled step retain this fundamental uncertainty, no matter how robust or reasonable the modelling methodology.
				2. The extrapolation of outcomes to the 20-year time horizon contributed most to the final ICER. Given the immaturity of the larotrectinib data presented, there is substantial uncertainty in the extrapolated estimates.
				3. The ESCs provided the following breakdown of the costs and outcomes for the base case ICER for the total population:

Costs

* Mean duration of therapy is 3.5 years
* Cost per/patient/course is $'''''''''''''''' for an average of 1.3 years treatment per patient (based on the proposed RSA that caps treatment cost at '' years)
* Cost of testing to identify one *NTRK* fusion positive patient is $14,423
* Disease management is $63.22 per week, with a total incremental cost to larotrectinib of $13,174 (Goldsbury 2018)
* Terminal care costs applied on entering death state, $51,335, with an incremental saving to larotrectinib of $10,713 (Goldsbury 2018)
* Total incremental cost in the range of $155,000 to < $255,000

Outcomes

* Survival and progression outcomes based on naïve ITC, results in Tables 7-8
* LYs gained of 2.3 years without larotrectinib based on observed Kaplan-Meier data from each of the comparator studies until median follow-up, or if not reported, until median OS. Beyond this time point, OS data extrapolated using parametric functions over the modelled time horizon
* LYs gained with larotrectinib increase to 6.3 years based on 2.4 years gained in the progressed state
* Progression-free life years gained are 3.8 for larotrectinib, 1.4 without larotrectinib, resulting in incremental gain of 2.4 years
* Utility is 0.8 for progression-free health state; 0.73 for progressed health state (NAVIGATE and SCOUT trials EQ-5D-3L mapped from EQ-5D-5L or PedsQL)
* Total 4.00 incremental LYs gained and 3.29 incremental QALYs gained
	+ - * 1. The results for each of the tumour type analyses are presented in Table 18. The results for each tumour type excluding the proposed RSA rebate are presented in Table 18A. These results are subject to substantial uncertainty for similar reasons to that for the overall result as well as the small number of patients enrolled by some tumour types.

Table 18: Results of the economic evaluation, tumour type analyses

|  | Larotrectinib | SoC | Increment |
| --- | --- | --- | --- |
| **Paediatric high *NTRK* frequency fusion tumour types (represented by paediatric IFS and STS)** |
| Total cost | $''''''''''''''''''''' | $''''''''''''''''' | $''''''''''''''''''''' |
| *Revised* | *$'''''''''''''''''''* | *$'''''''''''''''* | *$''''''''''''''''''* |
| Progression-free QALYs | 2.788 | 2.549 | 0.239 |
| Progressed QALYs | 4.976 | 0.619 | 4.357 |
| Total QALYs | 7.764 | 3.168 | 4.596 |
| **Incremental cost/extra QALY gained** |  |  | **$''''''''''''''1** |
| ***Revised*** |  |  | ***$''''''''''''*1** |
| **Adult high *NTRK* frequency fusion tumour types (represented by MASC)** |
| Total cost | $''''''''''''''''''' | $''''''''''''''' | $''''''''''''''''''''' |
| *Revised* | *$''''''''''''''''''* | *$'''''''''''''''* | *$''''''''''''''''''''* |
| Progression-free QALYs | 6.932 | 0.658 | 6.274 |
| Progressed QALYs | 0.205 | 0.240 | –0.035 |
| Total QALYs | 7.137 | 0.898 | 6.239 |
| **Incremental cost/extra QALY gained** |  |  | **$'''''''''''''2** |
| ***Revised*** |  |  | ***$'''''''''''''''*2** |
| **Paediatric low *NTRK* frequency fusion tumour types (represented by paediatric CNS/glioma)** |
| Total cost | $''''''''''''''''' | $''''''''''''''''' | $'''''''''''''''''' |
| *Revised* | *$'''''''''''''''''''''* | *$'''''''''''''''''* | *$'''''''''''''''''* |
| Progression-free QALYs | 0.999 | 1.577 | –0.578 |
| Progressed QALYs | 4.389 | 1.413 | 2.976 |
| Total QALYs | 5.388 | 2.990 | 2.398 |
| **Incremental cost/extra QALY gained** |  |  | **$'''''''''''''3** |
| ***Revised*** |  |  | ***$'''''''''''''*3** |
| **Adult low *NTRK* frequency fusion common tumour types (represented by colorectal cancer)** |
| Total cost | $'''''''''''''''''' | $'''''''''''''''''' | $''''''''''''''''''' |
| *Revised* | *$''''''''''''''''''* | *$''''''''''''''''''* | *$''''''''''''''''''''* |
| Progression-free QALYs | 0.819 | 0.229 | 0.590 |
| Progressed QALYs | 1.053 | 0.400 | 0.652 |
| Total QALYs | 1.871 | 0.629 | 1.242 |
| **Incremental cost/extra QALY gained** |  |  | **$''''''''''''''3** |
| ***Revised*** |  |  | ***$'''''''''''''*3** |
| **Adult low *NTRK* frequency fusion rare tumour types (represented by adult STS)** |
| Total cost | $''''''''''''''''''''' | $''''''''''''''''' | $'''''''''''''''''' |
| *Revised* | *$'''''''''''''''''* | *$'''''''''''''''''* | *$'''''''''''''''''''* |
| Progression-free QALYs | 2.661 | 0.197 | 2.463 |
| Progressed QALYs | 2.858 | 0.791 | 2.067 |
| Total QALYs | 5.519 | 0.988 | 4.530 |
| **Incremental cost/extra QALY gained** |  |  | **$'''''''''''''4** |
| ***Revised*** |  |  | ***$''''''''''''''*4** |

Source: Table 3.37 of the submission.

IFS = infantile fibrosarcoma; MASC = mammary analogue secretory carcinoma; NTRK = neurotrophic tropomyosin receptor kinase; QALY = quality adjusted life year; SoC = standard of care; STS = soft tissue sarcoma.

Note: Analyses have been revised during the evaluation to use the efficient price for the average dispensed dose of infusible chemotherapies, apply per pack costing of temozolomide (rather than cost on a per mg basis) and update PBS fees as of July 1, 2020.

*The redacted values correspond to the following ranges*

*1 $25,000 to < $35,000*

*2 $35,000 to < $45,000*

*3 $75,000 to < $95,000*

*4 $45,000 to < $55,000*

Table 18A: Results of the economic evaluation, tumour type analyses (excluding proposed RSA rebate)

|  | Larotrectinib | SoC | Increment |
| --- | --- | --- | --- |
| **Paediatric high *NTRK* frequency fusion tumour types (represented by paediatric IFS and STS)** |
| Total cost | $''''''''''''''''''''' | $'''''''''''''''''' | $'''''''''''''''''' |
| *Revised* | *$''''''''''''''''''* | *$'''''''''''''''* | *$'''''''''''''''''''* |
| Total QALYs | 7.764 | 3.168 | 4.596 |
| **Incremental cost/extra QALY gained** |  |  | **$'''''''''''''''''1** |
| ***Revised*** |  |  | ***$'''''''''''''''''*1** |
| **Adult high *NTRK* frequency fusion tumour types (represented by MASC)** |
| Total cost | $''''''''''''''''''''' | $'''''''''''''''' | $'''''''''''''''''' |
| *Revised* | *$''''''''''''''''''* | *$'''''''''''''''''* | *$''''''''''''''''''* |
| Total QALYs | 7.137 | 0.898 | 6.239 |
| **Incremental cost/extra QALY gained** |  |  | **$'''''''''''''''''2** |
| ***Revised*** |  |  | ***$'''''''''''''''''*2** |
| **Paediatric low *NTRK* frequency fusion tumour types (represented by paediatric glioma)** |
| Total cost | $''''''''''''''''' | $'''''''''''''''' | $''''''''''''''''''''' |
| *Revised* | *$'''''''''''''''''''* | *$''''''''''''''''* | *$''''''''''''''''''* |
| Total QALYs | 5.388 | 2.990 | 2.398 |
| **Incremental cost/extra QALY gained** |  |  | **$'''''''''''''''3** |
| ***Revised*** |  |  | ***$'''''''''''''''''*3** |
| **Adult low *NTRK* frequency fusion common tumour types (represented by colorectal cancer)** |
| Total cost | $''''''''''''''''''''' | $'''''''''''''''' | $''''''''''''''''''''' |
| *Revised* | *$'''''''''''''''''* | *$'''''''''''''''* | *$''''''''''''''''''''* |
| Total QALYs | 1.871 | 0.629 | 1.242 |
| **Incremental cost/extra QALY gained** |  |  | **$''''''''''''''''3** |
| ***Revised*** |  |  | ***$''''''''''''''''*3** |
| **Adult low *NTRK* frequency fusion rare tumour types (represented by adult STS)** |
| Total cost | $'''''''''''''''''' | $'''''''''''''''' | $'''''''''''''''''' |
| *Revised* | *$''''''''''''''''''''* | *$'''''''''''''''* | *$'''''''''''''''''''''* |
| Total QALYs | 5.519 | 0.988 | 4.530 |
| **Incremental cost/extra QALY gained** |  |  | **$'''''''''''''''3** |
| ***Revised*** |  |  | ***$''''''''''''''*3** |

Source: Table 3.37 of the submission.

IFS = infantile fibrosarcoma; MASC = mammary analogue secretory carcinoma; *NTRK* = neurotrophic tropomyosin receptor kinase; QALY = quality adjusted life year; SoC = standard of care; STS = soft tissue sarcoma.

Note: Analyses in italics have been revised during the evaluation to account for IHC false negative test results; use of the efficient price for the average dispensed dose of infusible chemotherapies, apply per pack costing of temozolomide (rather than cost on a per mg basis) and updated PBS fees as of July 1, 2020 .

*The redacted values correspond to the following ranges*

*1 $135,000 to < $155,000*

*2 $115,000 to < $135,000*

*3 $95,000 to < $115,000*

* + - * 1. An analysis to identify the cumulative ICER that would be associated with a stepped introduction of larotrectinib to each subgroup (from the most to least cost-effective) was performed during the evaluation, and is depicted on the cost-effectiveness plane in Figure 4, below. This is based on weighting of the tumour types according to the Australian population which is likely most applicable. This approach reaches the cumulative overall ICER based on the Australian weighting of matched tumour types (as per the sensitivity analysis presented in Table 19); it was not possible to disaggregate readily the submission’s base case ICER that collated all populations and did not match tumour types.

Figure 4: Depiction of the cumulative effect on the ICER associated with stepped addition of use in the different classifications of tumour type, from most to least cost-effective



Source: Constructed during the evaluation from the ‘A3.1\_Larotrectinib\_PBACMSAC\_CEA\_June2020.xlsm’ workbook included in the submission.

CE = cost-effectiveness; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

* + - * 1. This same analysis excluding the proposed RSA rebate is presented in Figure 4A. It should be noted that the order of the subpopulations in the updated figure (by increasing estimates of the ICER) changes – excluding the rebate in the low NTRK frequency subgroups has a smaller effect on the updated ICERs than in the high frequency subgroups, and so the low frequency subgroups now have lower ICERs than the high frequency groups. This is because the average duration on treatment in the low frequency groups is shorter and so fewer patients in these subgroups remain on treatment beyond two years.
				2. The results of the economic evaluation excluding the proposed RSA rebate for the high NTRK frequency fusion tumour types (the subpopulations most likely to have a potential treatment effect with larotrectinib – see paragraph 6.28), is presented in Table 18B below. It should be noted that for these results excluding STS from the analysis of the high frequency paediatric population was not possible as the Kaplan-Meier data included in the submission combined both paediatric STS with the IFS patients, and so the individual patient level data would be required to generate the new Kaplan-Meier curves (which would then require extrapolation). While this would remove paediatric STS patients from this subgroup in the larotrectinib arm of the model, the SoC arm would still be based only on patients with paediatric STS (as no SoC data were identified for patients with IFS).

Figure 4A: Depiction of the cumulative effect on the ICER associated with stepped addition of use in the different classifications of tumour type, from most to least cost-effective (excluding proposed RSA rebate)



Table 18B: Results of the economic evaluation, high NTRK fusion frequency tumour types over the 20-year time horizon (excluding proposed RSA rebate)

|  | Larotrectinib | SoC | Increment |
| --- | --- | --- | --- |
| **High *NTRK* fusion frequency tumour types (77.7% paediatric, 22.3% adult)a** |
| Total cost | $''''''''''''''''''' | $'''''''''''''''' | $''''''''''''''''''' |
| *Revised* | *$'''''''''''''''''''* | *$''''''''''''''''* | *$'''''''''''''''''''''* |
| Total QALYs | 7.624 | 2.661 | 4.963 |
| **Incremental cost/extra QALY gained** |  |  | **$''''''''''''''** |
| ***Revised*** |  |  | ***$'''''''''''''''''*** |

*NTRK* = neurotrophic tropomyosin receptor kinase; QALY = quality adjusted life year; SoC = standard of care.

Note: Analyses in italics have been revised during the evaluation to account for IHC false negative test results; use of the efficient price for the average dispensed dose of infusible chemotherapies, apply per pack costing of temozolomide (rather than cost on a per mg basis) and updated PBS fees as of July 1, 2020.

a Weighted based on the expected relative distribution of the subgroups in Australian clinical practice (22.6% paediatric high NTRK frequency fusion tumour types, and 6.5% adult high NTRK frequency fusion tumour types)

*The redacted value correspondences with the range of $135,000 to < $155,000*

* + - * 1. The PBAC considered that the RSA rebate should be excluded from any analysis of cost-effectiveness as the RSA proposed was not practical to implement. Further, the PBAC considered that given the uncertainties associated with the larotrectinib data, use of conservative assumptions around the treatment benefit in addition to exclusion of the RSA rebate in the analysis would likely produce ICERs more reflective of the actual cost-effectiveness of larotrectinib. The PBAC also considered it was appropriate to exclude paediatric STS patients from the paediatric high frequency *NTRK* fusion subpopulation in the analysis, however, it was noted that the structure of the model did not allow for these patients to be completely removed. As such, the PBAC considered that the estimated median *NTRK* fusion frequency estimated for this tumour type from the literature of 0.68% could instead be used.
				2. The PBAC noted that the resulting ICER for the combined high *NTRK* fusion frequency population was $155,000 to < $255,000 /QALY when i) the most conservative OS and PFS extrapolations; ii) an *NTRK* fusion frequency of 0.68% for paediatric STS and; iii) exclusion of the RSA rebate was applied in the economic analysis. The PBAC noted that the resulting ICER was $155,000 to < $255,000 /QALY for the high *NTRK* fusion frequency and low *NTRK* fusion frequency paediatric populations combined when the abovementioned adjustments to the economic analysis were applied. The PBAC further noted that the ICER of $155,000 to < $255,000 /QALY increased to $155,000 to < $255,000 /QALY when a 10-year time horizon was used instead of the 20-year time horizon in the submission’s base case analysis.
				3. An analysis of the disaggregated costs and outcomes in the tumour type subgroups observed that while the drivers of the incremental cost were generally consistent to that in the overall analysis, QALYs gained in the progressed health state were observed to be a main driver of the incremental QALY gain in all sub-models except adult high *NTRK* fusion frequency. This may be due to the high degree of uncertainty in the extrapolated estimates, immature data on subgroups of small patient numbers, or may reflect use of second generation Trk-inhibitors after disease progression.
				4. Results of the univariate sensitivity analyses presented by the submission and additional analyses conducted during the evaluation are summarised in Table 19.

Table 19: Results of univariate sensitivity analyses

|  | **Inc. cost** | **Inc. QALYs** | **ICER** | **%** |
| --- | --- | --- | --- | --- |
| **Base case** | ***$'''''''''''''''*** | **3.291** | ***$'''''''''''''****1* |  |
| Discount rate (base case: 5%) |  |  |  |  |
| 0% | *$'''''''''''''''''''* | 4.543 | *$''''''''''''''''''2* | –19% |
| Time horizon (base case: 20 years) |  |  |  |  |
| *5 years* | *$'''''''''''''''''''* | *1.664* | *$'''''''''''''''''''''3* | *78%* |
| 10 years | *$''''''''''''''''''* | 2.662 | *$'''''''''''''''1* | 18% |
| *Prevalence in paediatric STS, 0.68% (base case: 80%)* | *$'''''''''''''''''* | *3.291* | *$''''''''''''''''''1* | *11%* |
| Use comparators in paediatric patients with progressed disease | *$''''''''''''''''''* | 3.828 | *$''''''''''''''''''2* | –12% |
| *IHC triage in paediatric patients with low* NTRK *fusion frequency tumour types* |
| *IHC accuracy in CNS, 100% sensitivity, 20.8% specificity* | *$'''''''''''''''''''''* | *3.291* | *$'''''''''''''''1* | *–1%* |
| *Median IHC accuracy, 87.9% sensitivity, 95.6% specificity* | *$'''''''''''''''''''''* | *3.291* | *$'''''''''''''''1* | *–3%* |
| Weighting of the representative tumour types (base case: larotrectinib overall versus comparator weighted using the pooled larotrectinib analysis |
| *Weight comparator and larotrectinib arms using the pooled larotrectinib analysis* | *$'''''''''''''''''* | *3.526* | *$''''''''''''''''2* | *–21%* |
| Weight comparator and larotrectinib arms using Australian epidemiology estimates | *$'''''''''''''''''''''* | 2.894 | *$'''''''''''''''2* | –16% |
| Extrapolation a |  |  |  |  |
| Use OS curves next best fit | *$''''''''''''''''''* | 4.422 | *$'''''''''''''''4* | –26% |
| *Most conservative PFS and OS* | *$'''''''''''''''''''* | *2.915* | *$'''''''''''''''1* | *13%* |
| Larotrectinib costs |  |  |  |  |
| Remove proposed larotrectinib rebate | *$'''''''''''''''''''* | 3.291 | *$''''''''''''''''''5* | 163% |
| *Larotrectinib treatment cost, based on an average of ''''''''' years* | *$'''''''''''''''''''''* | *3.291* | *$'''''''''''''''''6* | *41%* |
| Use planned dose of larotrectinib | *$'''''''''''''''''''''* | *3.291* | *$'''''''''''''''''1* | 16% |

Source: Table 3.39 of the submission.

ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year.

Note: Analyses in italics have been revised during the evaluation to account for IHC false negative test results; use of the efficient price for the average dispensed dose of infusible chemotherapies, apply per pack costing of temozolomide (rather than cost on a per mg basis) and updated PBS fees as of July 1, 2020.

a The exponential parametric model was used in the base case analysis to extrapolate larotrectinib OS. To extrapolate SoC, the parametric models used in the base case were generalised gamma for paediatric STS and paediatric CNS; log-logistic for salivary and CRC; and log-normal for adult STS.

b The average daily dose used in the base case was 188.6 mg in adults, and 128.7 mg in paediatrics. The planned doses were 200 mg in adults and 184.2 mg in paediatrics.

*The redacted values correspond to the following ranges*

*1$55,000 to < $75,000*

*2$45,000 to < $55,000*

*3$95,000 to < $115,000*

*4$35,000 to < $45,000*

*5$155,000 to < $255,000*

*6$75,000 to < $95,000*

* + - * 1. The analyses were most sensitive to changes in the utilisation and cost of larotrectinib, with moderate effects on the ICER due to reducing the time horizon, altering the weighting of the tumour types used in the analysis and survival curve extrapolation. The high degree of uncertainty due to unmeasured confounding or bias that invariably is present in the naïve indirect comparisons cannot be captured by any sensitivity analysis.
				2. The analysis presented where tumour types were weighted according to the expected distribution of NTRK fusion positive patients in clinical practice may be a more reasonable basis for the economic analysis. This was associated with a 16% reduction in the ICER relative to the base case analysis. However this decrease was not driven by the change in the distribution of tumour types, rather the change in model approach from overall larotrectinib data to weighted larotrectinib data. When the same distribution of tumour types is applied (i.e. assuming the distribution in the pooled larotrectinib studies), a 21% decrease in the ICER is observed. The weighted subgroup analysis is associated with lower costs and more QALYs relative to SoC, which is driven by a reduction in larotrectinib treatment costs and an increase in time spent in the progressive disease health state.
				3. Given the nature of the naïve indirect comparisons presented, and that the larotrectinib data are immature, with subgroup analyses by tumour type based on small patient numbers, there is a high degree of uncertainty in the underlying data, which extends to the extrapolated estimates and the modelled incremental benefit of larotrectinib.
		1. Drug cost/patient/course
			- 1. The costs per patient for larotrectinib and SoC are presented in the table below. The larotrectinib cost per patient in the submission’s base case economic analysis was $''''''''''''''''. This was calculated by assuming an average time on treatment of 1.3 years (67 weeks), derived from the extrapolated time on treatment (ToT) curve to '''''''' years, at an average modelled cost per week of $'''''''''''. While this approach does reflect the intended individual-based RSA, if the RSA is implemented on a cohort-volume basis, whereby expenditure is capped at an average of ''''''' years, the average costs applied in the model would not be realised. The weighted modelled cost of SoC treatment was $3,099 (revised: $2,701). Patients continued on SoC treatment until disease progression or until a maximum number of treatment cycles had been reached.

Table 20: Drug cost per patient for larotrectinib and SoC treatment

|  | Use in the clinical evidence | Modelled a | Financial estimates b |
| --- | --- | --- | --- |
| ToT | Modelled cost | Duration | Cost |
| **Larotrectinib** |
| Larotrectinib overall | ePAS4: 14.7 mths cSAS3: 6.9 mths c | '''''''' years d | $'''''''''''''''''' d | ''' years | Paeds: $''''''''''''''''''''1Adults: $'''''''''''''''''''2 |
| Tumour-type subgroup analyses |
| Paediatric IFS and STS | NR | ''''''''''' years e | $''''''''''''''''''''' | ''' years | $''''''''''''''''''1 |
| Paediatric CNS/glioma | NR | '''''''''' years f | $'''''''''''''''''' | ''' years | $''''''''''''''''''''1 |
| MASC | NR | ''''''''''' years g | $''''''''''''''''''' | ''' years | $''''''''''''''''''''2 |
| Colorectal | NR | '''''''''' years h | $'''''''''''''''' | ''' years | $''''''''''''''''''2 |
| Adult STS | NR | '''''''''' years i | $''''''''''''''''''' | '''' years | $''''''''''''''''''''2 |
| **SoC** |  |  |  |  |  |
| Paediatric IFS and STS*Revised* | 4 cycles (12 weeks) | 15 weeks | IFS: $'''''''''''''' (63%)STS: $'''''''''''''''' (37%)*IFS: $'''''''''''' (63%)**STS: $'''''''''''''' (37%)* | IFS: 18 weeksSTS: 12 weeks | IFS: $''''''''''''''3 (7%)STS: $'''''''''''''3 (93%) *IFS: $''''''''''''4 (7%)**STS: $''''''''''''''3 (93%)* |
| Paediatric CNS/glioma*Revised* | Up to 54 weeks | 37 weeks | $'''''''''''''*$''''''''''''* | 10 weeks | $''''''''''4 |
| Salivary*Revised* | Median 5 cycles (18 weeks) | 12 weeks | $''''''''''''''*$''''''''''''''* | 18 weeks | $'''''''''''''4*$''''''''''''''*4 |
| Colorectal | - | - | - | - | - |
| Adult STS | Until disease progression (11.3 weeks) | 15 weeks | $'''''''''' | 16 weeks | $'''''''''4 *Revised: $'''*4 |

Source: Constructed during the evaluation.

CNS = central nervous system; IFS = infantile fibrosarcoma; STS = soft tissue sarcoma; ToT = time-on-treatment

a The modelled cost of SoC therapies was revised during the evaluation to use the efficient price for the average dispensed dose of infusible chemotherapies, apply per pack costing of temozolomide (rather than cost on a per mg basis) and updated PBS fees as of July 1, 2020.

b The financial SoC estimates were revised during the evaluation to use the efficient price for the average dose, to incorporate the increase in the PBS fees, as at July 1 2020, and to exclude cost-offsets related to the use of non-PBS medicines. The number of cisplatin infusions was revised to reflect one administration per treatment cycle (where two had been assumed in the submission).

c Truncated mean treatment duration

d Cost applied to an average '''''''' years over the first ''''''''' years, as per the proposed risk sharing arrangement

e Cost applied to an average ''''''' years over the first '''''''' years, as per the proposed risk sharing arrangement

f Cost applied to an average '''''''' years over the first ''''''''' years, as per the proposed risk sharing arrangement

g Cost applied to an average ''''''''' years over the first '''''''' years, as per the proposed risk sharing arrangement

h Cost applied to an average '''''''' years over the first ''''''''' years, as per the proposed risk sharing arrangement

i Cost applied to an average ''''''' years over the first '''''''' years, as per the proposed risk sharing arrangement

*The redacted values correspond to the following ranges*

*1 $155,000 to < $255,000*

*2 $255,000 to < $355,000*

*3 $5,000 to < $15,000*

*4 $0 to < $5,000*

* + 1. Estimated PBS & financial implications
			- 1. The submission was considered by DUSC.
				2. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the requested PBS listing of larotrectinib for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours harbouring the *NTRK* gene fusion.
				3. The estimated extent of use and financial implications, as estimated in the submission are provided in Table 21 below.

**Table 21: Estimated use and financial implications**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated number of larotrectinib eligible patients, by subpopulation** |
| Adult high frequency NTRK tumour | '''1 | ''''1 | '''1 | '''1 | '''1 | '''1 |
| Adult low frequency NTRK tumour | ''''''1 | ''''''1 | '''''''1 | ''''''1 | ''''''1 | ''''''1 |
| Paediatric high frequency NTRK tumour | '''''''1 | ''''''1 | '''''''1 | ''''''1 | ''''''1 | ''''''1 |
| Paediatric low frequency NTRK tumour | '''1 | '''1 | '''1 | ''''1 | ''''1 | '''1 |
| Total initiating population | ''''''1 | ''''''1 | ''''''''''1 | '''''''''1 | ''''''''1 | '''''''''1 |
| **Estimated extent of use of *NTRK* fusion testing** |
| No. IHC tests with additional cost | '''''''1 | '''''''''1 | ''''''''1 | ''''''''''1 | ''''''''''1 | ''''''''1 |
| *Revised a* | *''''''''''''''*2 | *'''''''''''''*2 | *'''''''''''''*8 | *'''''''''''''*8 | *''''''''''''''*8 | *'''''''''''''*8 |
| Number of NGS/FISH tests | ''''''''''1 | ''''''''''1 | '''''''''2 | ''''''''2 | ''''''''''2 | '''''''''2 |
| Number of patients likely to receive a positive test result | ''''''1 | ''''''1 | ''''''''1 | ''''''''''1 | ''''''''1 | ''''''''''1 |
| **Estimated extent of use of larotrectinib** |
| Number of patients likely to be treated with proposed medicine | ''''''1 | ''''''1 | '''''''''1 | ''''''''1 | ''''''''''1 | '''''''''1 |
| Number of scripts dispensed b | ''''''''''''''2 | '''''''''''''2 | '''''''''''''2 | ''''''''''''''2 | '''''''''''''2 | '''''''''''''''2 |
| *Revised* c | *'''''''''*2 | *''''''''''''''*2 | *'''''''''''''*2 | *'''''''''''''*2 | *''''''''''''*2 | *'''''''''''''*2 |
| **Net financial implications to the MBS** |
| Cost of *NTRK* fusion testing to the MBS | $'''''''''''''''''''''2 | $''''''''''''''''''2 | $'''''''''''''''''''''2 | $''''''''''''''''''''2 | $''''''''''''''''''2 | $'''''''''''''''''''''''2 |
| *Revised d* | *$'''''''''''''''''''''*2 | *$''''''''''''''''''*2 | *$''''''''''''''''''*2 | *$'''''''''''''''''''*2 | *$'''''''''''''''''''''''2* | *$'''''''''''''''''''''''''*2 |
| Cost offsets to the MBS | $''''''''''''''''''''2 | $'''''''''''''''''''''2 | $''''''''''''''''''2 | $'''''''''''''''''''2 | $''''''''''''''''''2 | $'''''''''''''''''2 |
| *Revised e* | *$''''''''''''''''*2 | *$''''''''''''''''*2 | *$''''''''''''''''''*2 | *$''''''''''''''''*2 | *$'''''''''''''''*2 | *$''''''''''''''''*2 |
| **Net cost to the MBS** | **$'''''''''''''''**2 | **$''''''''''''''**2 | **$'''''''''''''''''**2 | **$''''''''''''''**2 | **$'''''''''''''''''**2 | **$''''''''''''''''**2 |
| ***Revised*** | ***$'''''''''''''''***2 | ***$''''''''''''''''***2 | ***$'''''''''''''''***2 | ***$''''''''''''''***2 | ***$''''''''''''''''''''***2 | ***$''''''''''''''''''***2 |
| **Net financial implications of to the PBS/RPBS** |
| Cost of larotrectinib to the PBS | $''''''''''''''''''''''''5 | $''''''''''''''''''''''''''''5 | $''''''''''''''''''''''''6 | $''''''''''''''''''''''''''''6 | $''''''''''''''''''''''''6 | $''''''''''''''''''''''''''''7 |
| *Revised f* | *$'''''''''''''''''''''''''''*4 | *$'''''''''''''''''''''''''''''*5 | *$'''''''''''''''''''''''''''*5 | *$''''''''''''''''''''''''''*6 | *$''''''''''''''''''''''''*6 | *$''''''''''''''''''''''''''''*7 |
| Cost offsets to the PBS | $''''''''''''''''''2 | $''''''''''''''''''2 | $'''''''''''''''''2 | $''''''''''''''''''''2 | $''''''''''''''''''2 | $'''''''''''''''''''''2 |
| *Revised g* | *$''''''''''''''''''''*2 | *$''''''''''''''''''*2 | *$'''''''''''''''''*2 | *$''''''''''''''''''''*2 | *$'''''''''''''''''''*2 | *$''''''''''''''''''*2 |
| **Net cost to the PBS** | **$'''''''''''''''''''''''**4 | **$''''''''''''''''''''''**5 | **$''''''''''''''''''''**6 | **$''''''''''''''''''''''''**6 | **$''''''''''''''''''''''**6 | **$'''''''''''''''''''''**7 |
| ***Revised*** | ***$'''''''''''''''''***3 | ***$'''''''''''''''''''''''***5 | ***$''''''''''''''''''''''***5 | ***$'''''''''''''''''''''***6 | ***$''''''''''''''''''''''***6 | ***$''''''''''''''''''''''''***7 |
| **Net financial implications**  |
| Net cost to Government | $''''''''''''''''''''''''''5 | $''''''''''''''''''''''''5 | $'''''''''''''''''''''''''''6 | $'''''''''''''''''''''''''6 | $''''''''''''''''''''''''6 | $''''''''''''''''''''''''''7 |
| *Revised* | *$'''''''''''''''''''''''''''''*4 | *$'''''''''''''''''''''''''*5 | *$''''''''''''''''''''''''*5 | *$''''''''''''''''''''''''*6 | *$'''''''''''''''''''''''''''''*6 | *$''''''''''''''''''''''''''*7 |

Source: Constructed during the evaluation from the ‘A4.2 Larotrectinib\_PBACMSAC\_Section4\_June2.xlsx’ workbook.

*a The number of IHC tests required to identify one NTRK fusion positive patient was revised from < 500 to < 500 during the evaluation. In both the submission’s estimates and the revised estimates, 33% of IHC tests were assumed to be associated with an additional cost.*

b Assuming < 500 scripts in adult patients and an average < 500 scripts in paediatric patients per year as estimated by the submission. These total number of scripts represent the total number of scripts for two years.

*c The number of larotrectinib scripts were revised during the evaluation to split the total scripts per treatment course across two years.*

*d In addition to the revised number of IHC tests, the cost to the MBS for NGS testing was revised to take into account the implications of the Greatest Permissible Gap.*

*e The cost offsets to the MBS were revised to reflect offsets related to the reduction in the number of infusions or radiotherapy sessions.*

*f In addition to the revised number of larotrectinib scripts, the costs to the PBS were also revised during the evaluation to increase in the PBS fees, as at July 1 2020.*

*g The cost offsets to the PBS were revised to use the efficient price for the average dose, to incorporate the increase in the PBS fees, as at July 1 2020, and to exclude cost-offsets related to the use of non-PBS medicines. The number of cisplatin infusions was revised to reflect one administration per treatment cycle (where two had been assumed in the submission). Patient co-payments were revised to assume only one co-payment per original script of infusible PBS items (as per the Efficient Funding of Chemotherapy arrangements). No PBS co-payments were applied for non-PBS scripts*

*The redacted values correspond to the following ranges:*

*1 <500*

*2 500 to <5,000*

*3 $0 to < $10 million*

*4 $10 million to < $20 million*

*5 $20 million to < $30 million*

*6 $30 million to < $40 million*

*7 $40 million to < $50 million*

*8 5,000 to < 10,000*

* + - * 1. DUSC considered the estimates presented in the submission to be slightly underestimated overall. The main issues identified were:
* There is a paucity of large population *NTRK* frequency data across many tumour types. Thus it was difficult to accurately predict *NTRK* fusion frequency across all advanced cancer patients in Australia and this was the main area of uncertainty in the estimates. DUSC estimated that number of patients would be approximately twice that estimated in the submission if the *NTRK* fusion frequency was 0.5% averaged across all patients with 100% uptake of IHC testing. This was based on the calculation that there are 51,000 cancer deaths per year in Australia and 75% of these are treatable. If the *NTRK* fusion rate is 0.5%, this gives 192 eligible patients. The submission estimated <500 eligible patients which reduced to <500 due to testing rates.
* The non-inclusion of some tumour types not represented in the trials presented in the submission. However due to rarity of the *NTRK* fusion, the impact of including additional cancers was likely to be low.
* Not having regard to a prevalent pool of patients in Year 1.
* A likely underestimation of the *NTRK* fusion testing rate, particularly for low frequency *NTRK* tumours in adults in Years 1 to 4. Provided IHC testing is logistically straightforward, DUSC expected approximately 90% testing uptake for all metastatic cancer by year 2. This testing may reveal higher *NTRK* fusion rates than expected.
	+ - * 1. Incidence estimates from the Australian Institute of Health and Welfare (AIHW) or from the published literature were applied to population estimates projected by the Australian Bureau of Statistics (ABS). DUSC noted a number of the cited AIHW estimates used could not be verified during the evaluation because web links appeared to have changed; these may have been updated since being cited in the submission.
				2. Estimates of *NTRK* fusion frequency, proportion with advanced disease at diagnosis and, where relevant, the proportion of patients eligible for later-line treatment were applied to the estimated incident population for each tumour type to estimate the population eligible for larotrectinib treatment. The *NTRK* fusion frequency estimates applied were reasonable except for paediatric soft tissue sarcoma (STS) (see paragraph 4.3). DUSC noted the evaluation estimate of *NTRK* fusion frequency for non-IFS paediatric STS was 0.68%. DUSC noted that prevalent patients had been excluded from the estimates and that this was likely to result in an underestimate of patient numbers in the earlier years.
				3. Uptakes of *NTRK* fusion testing and larotrectinib treatment were assumed to vary between the tumour type subgroups. All paediatric patients were assumed to take up testing and treatment, whereas uptake in adults with high *NTRK* fusion frequency types was assumed to increase from 70% in Year 1 to 100% by Year 4, and uptake in adults with low *NTRK* fusion frequency tumours was assumed to increase from 40% in Year 1 to 100% by Year 6. Uptake rates in adults with high *NTRK* fusion frequency tumour types may be an underestimate in Years 1-3 given the proposed claimed benefits of larotrectinib over SoC in this patient group. Uptake rates in adults with low *NTRK* fusion frequency tumours may be underestimated in years 1-5 since pan-tumour histopathological protocols are likely to rapidly include reflex *NTRK* fusion IHC testing due to the low cost and ease of testing. The pre-PBAC Response presented additional sensitivity analyses that increased the testing rates but these changed the estimates only marginally.
				4. The proposed RSA (see paragraph 6.97) capped the cost of larotrectinib to '''''''' years of treatment; all patients were assumed to receive larotrectinib for ''''''' years. This was not consistent with costed use in the economic evaluation, which assumed that average costed time-on-treatment was ''''''''' years (undiscounted). Further, the submission assumed that there is no wastage and that all scripts would be dispensed per patient in the year of treatment initiation. DUSC considered that, overall, the assumption of ''''''' years of PBS subsidised therapy (equating to < 500 scripts) was reasonable for the purposes of the financial estimates with a reimbursement beyond ''''' months of treatment in place. However, DUSC noted that for the purposes of utilisation analysis (predicted versus actuals), the utilisation would be overestimated in the earlier years and underestimated in later years since the median pooled PFS presented in the submission was 33 months.
				5. The submission expected that listing of larotrectinib would result in a reduction in costs related to SoC treatment. The submission did not consider that where an active therapy is proposed to be substituted by larotrectinib, SoC would be displaced rather than replaced in a proportion of patients. Furthermore, errors were noted regarding the estimated utilisation and cost offsets, including double the cisplatin infusions per cycle, the application of the DPMA rather than dispensed efficient price for the average dose and offsetting costs to the PBS for non-PBS medicines. DUSC considered that the cost-offsets were likely to be overestimated. DUSC further noted that the cost-offsets included mostly low cost, off patent treatments.
				6. To estimate the number of patients eligible for *NTRK* fusion testing, the submission applied the number of tests required to identify one patient with *NTRK* fusions to the number of patients estimated to receive larotrectinib. This approach implicitly assumed that the rate of uptake between testing and treatment was the same and that testing occurs at the time at which treatment decisions regarding larotrectinib are being taken. In adult patients with low *NTRK* fusion tumour types, this may not be a reasonable approach given that *NTRK* fusion testing can occur on diagnosis of advanced disease before initiation of first-line treatment.
				7. The submission assumed that, for each adult patient with a low *NTRK* fusion frequency tumour type that exhibited *NTRK* fusions and received larotrectinib treatment, 8.04 IHC tests were required to identify that one patient. This was based on the weighted number of NGS/ FISH tests required in this patient group to identify one patient with *NTRK* fusions after IHC testing. Based on the submission’s assumptions of *NTRK* fusion prevalence and (IHC) performance, approximately < 500 IHC tests are required in this subgroup to identify one patient with an *NTRK* fusion. The number of IHC tests assumed in the financial implications was therefore substantially underestimated. The number of IHC tests may be even higher in practice as it was implicitly assumed that testing would occur after failure of earlier lines of treatment whereas testing could occur at diagnosis of advanced disease.
				8. The cost applied per IHC test may also be an underestimate as the submission assumed that Trk-IHC testing would occur within the same patient episode as part of an IHC panel to identify a number of other oncogenic biomarkers. Therefore, with the introduction of *NTRK* fusion testing, the incremental cost for an increase in IHC panel size from 7−10 to 11 or more was applied in one-third of patients. This was been justified. No information was provided to support a minimum number of relevant oncogenic biomarkers broadly across tumour types (and whether these would be tested at the same time as testing for *NTRK* fusions). The incremental cost of IHC testing may be higher if no IHC testing is assumed in the comparator or if the panel size increases from 1−3 to 4−6 antibodies with *NTRK* fusion testing. DUSC noted that false positive results could substantially increase testing costs. DUSC further noted that the overall coverage of testing would be highly dependent on the logistics and replicability of rolling out the IHC tests.
				9. The submission assumed that 50% of patients would, on average, either receive two FISH tests (at a proposed MBS fee of $400 each) or receive one NGS test (at a proposed fee of $'''''''''''). The cost per NGS test was not reasonable as analysis of the sequence variants of only three genes is required. The PICO ratified by PASC suggested that the fee could be $'''''''. Further, the split of test use has not been justified. The submission acknowledged that use of NGS is likely to increase over time. The weighted MBS fee was assumed to be $'''''''''''. With the 80% level of MBS rebate applied, the cost to the MBS of *NTRK* fusion testing is $'''''''''''. This approach did not take into account the implications of the Greatest Permissible Gap, which increases the MBS rebate payable above 85% in the outpatient setting for items costing $565.00 or more.
				10. The net effect to the PBS of the uncertainties identified regarding the estimates of the population eligible for larotrectinib use was unclear. Uncertainties leading to an underestimate in the net cost to the PBS included that tumour types broader than those included may also be eligible for larotrectinib treatment, that the uptake rate in adults with high *NTRK* fusion frequency tumour types may be underestimated, and that SoC costs were likely to be overestimated. However, factors contributing to an overestimation of costs may include the assumption that all patients would receive ''''''' years of larotrectinib treatment, that all patients with advanced disease have unresectable disease, and that all patients that fail to respond to first-line treatment would be suitable for larotrectinib treatment.
				11. Given that the estimated use and cost of IHC were underestimated, the cost of NGS to the MBS were underestimated and the cost-offsets related to a reduction in infusion and radiotherapy MBS items were overestimated, the net costs to the MBS were likely to be underestimated.
		1. Quality use of medicines
			- 1. A QUM issue will arise should larotrectinib be prescribed or be made available for a treatment line where it may substitute for more effective available therapies.
				2. DUSC considered that risk of use outside the restriction was low, especially if a pathology report is required as part of the written authority application.
		2. Financial management – risk sharing arrangements
			- 1. In addition to the proposed SPA, the submission proposed an RSA to enable access to larotrectinib, while addressing uncertainties to be implemented though an individual utilisation based program approach, specifying a duration-based cap, and subsequent additional rebate. The submission proposed administration of the RSA as follows:
* the duration of treatment of individual patients would be tracked through the PBS database and, after ''''' months on continuous treatment, a '''''''% rebate would be paid to the government for ongoing treatment;
* after ''''' months, if patients continue to have clinical benefit, they are allowed to stay on therapy until disease progression or no further clinical benefit.
	+ - * 1. The submission suggested that estimates for annualised rebates could be validated by third-party providers who have access to the PBS dataset, and that the RSA could be implemented through existing mechanisms available within establishing a Deed of Agreement as there is industry precedence in which individual, instead of cohort volume based agreements have been previously implemented. The proposal to collect and analyse individual patient data from the PBS would be administratively burdensome (see paragraph 2.6 above).
				2. The pre-PBAC Response acknowledged there may be practical issues with regards to an individual utilisation based program RSA. The pre-PBAC Response indicated the sponsor was willing to consider shorter-term RSAs with evolving terms as more data becomes available, and to work with the Department to implement an appropriate RSA to mitigate underlying uncertainties should larotrectinib be recommended for listing.

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

1. PBAC Outcome
	* + - 1. The PBAC deferred its decision about whether to recommend the listing of larotrectinib for the treatment of patients with tropomyosin receptor kinase (*NTRK*) fusion tumours that are either unresectable locally advanced, metastatic, or locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection. The PBAC acknowledged there is a high clinical need for effective treatments for patients with *NTRK* fusion tumours noting that *NTRK* fusions are found in a number of rare cancer types. The PBAC noted that the limited clinical data suggested the potential comparative treatment benefit of larotrectinib would mostly be in paediatric patient populations and adult patients with tumours harbouring *NTRK* fusions at high frequency. The PBAC was of a mind to not recommend the listing of larotrectinib on the basis that the cost-effectiveness ratio was unacceptably high and uncertain at the price proposed. The PBAC requested the Department approach the sponsor to seek a suitable price reduction for larotrectinib. The PBAC also advised it would await the Medical Services Advisory Committee (MSAC) advice on the funding of the co-dependent *NTRK* testing before making a final decision on PBS funding.
				2. In acknowledging the clinical need for effective therapies for patients with *NTRK* fusion positive cancers, the PBAC considered this need was highest for rare cancer types for which there are few effective standard of care treatments. The PBAC noted that, in the larotrectinib trials, the majority of *NTRK* fusion positive tumours in adult patients with high frequency *NTRK* fusion positive tumours and in paediatric patients, were rare cancers.
				3. The PBAC noted the TGA-approved registration was for patients who have either progressed following treatment or have no satisfactory alternative therapy. The PBAC advised that a criterion restricting treatment to patients with prior treatment or patients who are not suitable for other treatments should be included in the PBS restriction.
				4. The PBAC further advised that specifying the names of the tumour types in the high and low frequency subgroups may reduce the risk of use beyond the intended populations. This may be particularly important for the adult populations if adult patients with low frequency *NTRK* fusion tumours remain ineligible for PBS subsidy.
				5. The PBAC advised that the proposed continuing treatment restriction should be amended to specify that patients must only be treated until disease progression as there may be various interpretations of ‘clinical benefit’ in practice. The PBAC noted that an unknown proportion of patients in the larotrectinib trials received larotrectinib following disease progression, likely due to perceived continued benefit according to the trial investigator. However, the PBAC noted there was insufficient data to determine whether there was a treatment benefit for patients receiving larotrectinib following disease progression and considered that larotrectinib is unlikely to be cost-effective beyond disease progression.
				6. The PBAC considered the clinical studies may not reflect the efficacy and safety of larotrectinib in patients with an Eastern Cooperative Oncology Group (ECOG) performance of 3 or more as there were only 3 patients with an ECOG performance status of 3 in the pooled larotrectinib dataset. The PBAC considered the inclusion of a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less would be appropriate.
				7. The PBAC noted that the submission nominated comparators based on SoC treatments for the representative tumour types and proposed line of treatment for each proposed subpopulation. The PBAC noted that the proposed first-line use in adult patients with high frequency *NTRK* fusion tumours and in paediatric patients is broader than the provisionally approved TGA indication for larotrectinib (see paragraph 1.6). The PBAC noted there was currently no clinical consensus regarding the use of larotrectinib in practice and agreed with the ESCs that use of larotrectinib as earlier- or later-line treatment would depend on the intent of the treatment. In this regard, the PBAC considered the clinical place of larotrectinib and the most appropriate comparators for each subpopulation were uncertain.
				8. The PBAC noted that the comparative clinical benefit of larotrectinib was based on naïve indirect comparisons between pooled efficacy data (19 July 2019 data cut) across three open label single-arm studies (LOXO-001, NAVIGATE, SCOUT) in patients with documented *NTRK* fusion tumours and single-arm SoC data from historical studies. The PBAC noted that, since NAVIGATE and SCOUT are ongoing studies, the results of the pooled analysis would be subject to change as more data become available. However, the PBAC noted the pre-PBAC Response indicated that the number of patients in the trials may not increase substantially given *NTRK* fusion positive cancers are generally rare.
				9. The PBAC noted the overall response rate for the ePAS dataset was 73% (95% CI: 65%, 79%) and the median progression free survival was estimated to be 33.1 months (95% CI: not calculated) for the overall larotrectinib population. The PBAC noted that median overall survival had not been reached (95% CI: 44.4, not estimable) for the overall larotrectinib population or any of the tumour type subgroups with the exception of colorectal cancer (median overall survival of 36.3 months). The PBAC noted that second generation Trk-inhibitors administered in some patients in the larotrectinib trials following disease progression could have contributed to overall survival gains. The PBAC considered that, while the results were indicative of a treatment effect of larotrectinib, there were limitations around the interpretation of the results due to the data being immature and heterogeneity between individual studies (see paragraph 6.8).
				10. The PBAC noted that, despite pooling of data across larotrectinib trials, response rates for the tumour type subgroups were generally associated with large confidence intervals as a result of small patient numbers. On this basis, the PBAC was uncertain whether there was a consistent treatment effect across different tumour types. However, notwithstanding the limitations around the data, the PBAC considered the evidence was indicative of a larger treatment effect in patients with high frequency *NTRK* fusion tumours compared to patients with low frequency *NTRK* fusion tumours.
				11. The PBAC agreed with the ESCs that paediatric STS was misclassified in the submission as a representative tumour type in the paediatric high frequency *NTRK* fusionsubpopulation noting that studies in the literature reported a prevalence of *NTRK* fusions of <5% for various paediatric STS subtypes. The PBAC noted that it was not possible to exclude the paediatric STS data from the analysis of the paediatric high frequency *NTRK* fusion subpopulation based on the data provided in the submission (see paragraph 6.71).
				12. The PBAC considered the claim of superior effectiveness compared to SoC was likely acceptable for the high frequency adult and paediatric populations, but the magnitude of the benefit was uncertain due to issues around the larotrectinib trial data noted above and applicability of the data presented for standard of care to current standard of care, and the uncertainties around the naïve indirect comparisons. The PBAC noted the treatment effect of standard of care therapies varied between tumour types, line of treatment and types of standard of care therapy and noted this variability was consistent with heterogeneity in treatment effect by tumour type/site. The PBAC considered that the efficacy results from the standard of care data was unlikely to reflect that of current clinical practice given the inclusion of historic studies and studies which did not include the most effective therapy for the treatment setting. The PBAC also considered that the uncertainty around the most appropriate comparators (see paragraph 7.7) contributed to the overall uncertainty of the comparative benefit of larotrectinib. The PBAC considered the claim of superior effectiveness compared to SoC for the low frequency adult and paediatric populations was not sufficiently supported.
				13. The PBAC noted the pre-PBAC Response indicated that additional single-arm data in adult patients with low frequency *NTRK* fusion tumours from the ongoing NAVIGATE and MoST trials is expected in the future. The PBAC considered that this additional data would be useful for assessing the overall efficacy of larotrectinib in the adult low frequency *NTRK* fusion subpopulation, for which the claim of superior effectiveness compared to SoC was not sufficiently supported.
				14. The PBAC noted that the impact of any prognostic effect of *NTRK* fusion status on the treatment effect of larotrectinib could not be assessed due to the limited evidence base.
				15. The PBAC acknowledged that direct comparative clinical data for larotrectinib was unlikely to be forthcoming in the future given the rarity of *NTRK* fusions.
				16. The PBAC considered that a large proportion of adverse events in patients treated with larotrectinib appear to be related to the inhibition of TRK. The PBAC accepted that an informative comparison of safety between larotrectinib and standard of care was not feasible given the limited data. The PBAC noted advice from the TGA Delegate that treatment-related adverse events may generally be higher in younger paediatric patients (i.e. infants/toddlers) and of the risk of neurodevelopment impairment in paediatric patients. The PBAC considered that the risk of neurodevelopment impairment for paediatric patients may increase the longer patients remain on treatment. The PBAC considered that overall, the available data indicated a manageable safety profile for larotrectinib, although there were insufficient data to assess the long-term safety of larotrectinib.
				17. The PBAC noted the submission presented a cost-utility analysis comparing *NTRK* gene fusion testing and larotrectinib with standard of care. The PBAC considered the cost-effectiveness of larotrectinib was difficult to ascertain and ICERs likely to be underestimated, particularly due to the following:
* The model is based on the naïve indirect comparisons which compared the pooled larotrectinib studies to standard of care studies for five different tumour types selected to be representative of the proposed subpopulations. As such, the uncertainties around the larotrectinib and standard of care data and naïve indirect comparisons were retained in the model.
* The 20-year time horizon used in the economic analysis is substantially longer than the median duration of follow-up (16 months) in the pooled larotrectinib analysis. Most of the treatment benefit of larotrectinib in the base case analysis was from the extrapolated portion of the model. Given the immature data and the small number of patients which inform each tumour-specific subgroup, the extrapolated treatment benefit of larotrectinib were unlikely to be reliable.
* The proposed RSA where ''''''''% of larotrectinib treatment costs for each individual patient will be rebated after '''''' months of continuous treatment, was included in the base case analysis. The PBAC considered that the individual patient based RSA proposed was not a feasible method of achieving cost-effectiveness, noting that it may not be possible to share confidential patient level data with the sponsor to validate RSA rebates (see paragraph 2.6) and that the cost-effective price would not be realised until larotrectinib had been listed for at least two years. The PBAC noted that the base case ICER increased substantially to $155,000 to < $255,000 /QALY when the proposed RSA rebate was removed from the analysis.
	+ - * 1. The model did not take into consideration the possibility of false test results, which contributed to the ICERs being underestimated, albeit to an unknown extent.
				2. Overall, the PBAC considered that larotrectinib was not sufficiently cost-effective at the price proposed. The PBAC noted that the proposed cost of larotrectinib in the submission was disproportionately high in the context of other targeted therapies for rare cancers previously recommended by the Committee.
				3. The PBAC considered that, at a reduced price, larotrectinib may be sufficiently cost-effective in the high *NTRK* fusion frequency population for which the available data indicates a potential large treatment benefit. The PBAC noted that the true ICER for this population could potentially be over $180,000/QALY (see paragraph 6.73). The PBAC noted that, while the treatment benefit of larotrectinib in paediatric patients with low frequency *NTRK* fusion tumours was uncertain, the addition of this patient population to high *NTRK* fusion frequency population did not have a material impact on the ICER. In this regard and taking into consideration the high clinical need in paediatric patients, the PBAC advised that a price reduction offer for adult patients with high frequency *NTRK* fusion tumours and all paediatric patients would also be acceptable. The PBAC advised that the price reduction for larotrectinib should be of a magnitude sufficient to achieve an ICER within the range of $70,000/QALY to $80,000/QALY, which the PBAC considered was consistent with the ICERs accepted for other targeted therapies for rare cancers. The PBAC advised that the adjustments to the economic analysis, as specified in paragraph 6.73 to account for the uncertainties of the larotrectinib data, should be used to determine the magnitude of price reduction required. The PBAC considered that the price reduction could be achieved through either a special pricing arrangement or an alternative means such as an RSA which does not impose an unnecessary administrative burden or privacy issues.
				4. The PBAC noted that DUSC considered the financial estimates to be slightly underestimated. DUSC noted that prevalent patients and some tumour types not represented in the trials presented in the submission were not included in the estimates. DUSC noted that uptake rates in adults with high *NTRK* fusion frequency tumour types could be an underestimate given the claimed benefits of larotrectinib over standard of care. The PBAC considered these factors were unlikely to have a substantial impact on the estimates.
				5. The PBAC noted that the financial estimates may need to be revised depending on further negotiations with the sponsor and whether a price reduction for all or some subpopulations within all paediatric patients and adult patients with high *NTRK* fusion frequency tumours is proposed.
				6. The PBAC advised that any further consideration of listing larotrectinib for adult patients with low *NTRK* fusion frequency tumours would need to be through a future major resubmission which includes the forthcoming data from NAVIGATE and MoST trials to address the uncertainty of the treatment effect of larotrectinib in this patient population with modified cost-effectiveness analyses incorporating more conservative assumptions and a price reduction. In order to minimise the potential for any confusion, the PBAC foreshadowed that, in the event that patients with high *NTRK* fusion frequency tumours were listed earlier, the specific tumour types would be identified in the PBS restriction.

**Outcome:**

Deferred

1. 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.

1. Sponsor’s Comment

Bayer are committed to working with the PBAC to achieve sustainable PBS listing conditions and timely patient access to Vitrakvi® (larotrectinib) for patients with NTRK fusion cancers.

**Addendum to the November 2020 PBAC Minutes:**

**4.01 LAROTRECTINIB**

 **Capsule 25 mg, Capsule 100 mg**

**Oral solution 20 mg per mL, 100 mL**

**Vitrakvi®,**

 **Bayer Australia Ltd**

1. **Background**

8.1 In November 2020, the PBAC deferred its decision about whether to recommend the listing of larotrectinib for the treatment of patients with tropomyosin receptor kinase (NTRK) fusion tumours that are either unresectable locally advanced, metastatic, or locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection.

8.2 At the November 2020 meeting, the PBAC was of a mind to not recommend the listing of larotrectinib on the basis that the cost-effectiveness ratio was unacceptably high and uncertain at the price proposed. The PBAC reached different conclusions across different subgroups of the requested eligible population, and had asked the Department to approach the applicant to seek a suitable price reduction for larotrectinib to enable an early reconsideration for some of these subgroups.

8.3 The applicant was asked to consider an alternative price proposal for larotrectinib to achieve an ICER/QALY within the range of $70,000 to $80,000 based on PBAC’s re-specifications of the submitted modelled economic evaluation to enable an early resolution and potential PBS listing for the subgroups suggested by the PBAC in November 2020:

* + Adult high frequency *NTRK* fusion cancer subgroup
	+ Paediatric high frequency *NTRK* fusion cancer subgroup
	+ Paediatric low frequency *NTRK* fusion cancer subgroup

8.4 The PBAC noted that the applicant responded on 4 December 2020 and was unable to make a new price proposal at this stage

1. **PBAC Outcome**

9.1 The PBAC did not recommend the listing of larotrectinib for the treatment of patients with tropomyosin receptor kinase (*NTRK*) fusion tumours that are either unresectable locally advanced, metastatic, or locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection. This decision was made on the basis that the incremental cost-effectiveness ratio was unacceptably high and uncertain at the price proposed.

9.2 The PBAC reiterated its advice from November 2020 that a sufficient price reduction offer for adult patients with high frequency *NTRK* fusion tumours and all paediatric patients would be acceptable as a basis to recommend listing for these subgroups. However, any further consideration for adult patients with low *NTRK* fusion frequency tumours would need to be through a future major resubmission which includes the forthcoming data from NAVIGATE and MoST trials to address the uncertainty of the treatment effect of larotrectinib in this patient population with modified cost-effectiveness analyses incorporating more conservative assumptions and a price reduction.

 **Outcome:**

Rejected

1. **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.

1. **Sponsor’s Comment**

The sponsor had no comment.

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4. Larotrectinib assessment report (EMA/CHMP/469135/2019) –P16 [↑](#footnote-ref-4)
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8. Luk PP, Selinger CI, Eviston TJ, Lum T, Yu B, O'Toole SA, et al. Mammary analogue secretory carcinoma: an evaluation of its clinicopathological and genetic characteristics. Pathology. 2015;47(7):659-66. [↑](#footnote-ref-8)
9. Majewska H, Skalova A, Stodulski D, Klimkova A, Steiner P, Stankiewicz C, et al. Mammary analogue secretory carcinoma of salivary glands: a new entity associated with ETV6 gene rearrangement. Virchows Arch. 2015;466(3):245-54. [↑](#footnote-ref-9)
10. Halichondrin B-based, microtubule dynamics inhibitor [↑](#footnote-ref-10)
11. Schöffski P *et al*. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. The Lancet. 2016;387(10028):1629-37 [↑](#footnote-ref-11)
12. Soft tissue sarcomas are rare malignancies. There are more than 50 histological subtypes of sarcoma, with US data from the Surveillance, Epidemiology, and End Results (SEER) Program indicating the most common sarcomas were liposarcomas (17.1%), leiomyosarcomas (13.6%), and malignant fibrous histiocytoma (8.2%). Source: Paragraph 4.1, Eribulin Public Summary Document –November 2016 PBAC Meeting. [↑](#footnote-ref-12)
13. Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017 [↑](#footnote-ref-13)
14. Chu Y, Yuan Y. A Bayesian basket trial design using a calibrated Bayesian hierarchical model. Clinical Trials. 2018;15(2):149-58. [↑](#footnote-ref-14)
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