Uncertainties around tumour-agnostic therapies in Europe: barriers and facilitators of patient access to novel medicines

Christine van Hattem
5866669
Master student Drug Innovation

Examiner: dr. Lourens T. Bloem
Daily supervisor: Milou Hogervorst / dr. Rick Vreman
Second examiner: dr. ir. Wim G. Goettsch

Division of Pharmacoepidemiology and Clinical Pharmacology,
Utrecht Institute for Pharmaceutical Sciences

Abstract

With the approval of two tumour-agnostic therapies by the European Medicines Agency for the treatment of NTRK gene fusion-positive solid tumours, a new era of personalised cancer medicine has begun in Europe. Larotrectinib and entrectinib represent the recent advance in pharmacological tumour treatments, by targeting substrates (NTRK gene fusions) throughout the body. However, their stories have not been without difficulties.

Clinical trials were complicated by the overall rarity of NTRK gene fusion tumours and specific tumour types. The single-arm, uncontrolled basket trials were reason for concern. Still, both therapies were granted CMA by the EMA, after withdrawal of their initial orphan designations, on the condition of gathering more data to increase sample size, and on the role of NTRK fusions as oncogenic drivers. The complete EMA procedure took 6 months longer for entrectinib, despite PRIME.

HTA organisations struggled to assess the added benefit of these tumour-agnostic therapies. To a more or lesser extent, the sufficiency of decision framework, generalisability of the trial populations with the clinical practice population, the use of basket trials, and the absence of data comparing with a comparator therapy formed causes for concern. Still, all HTA organisations (ZIN, NICE, HAS, GBA) recommended both therapies for inclusion in national reimbursement lists based on the tumour-agnostic indication. However, in Germany, the extent of reimbursement is unclear, and in France, only larotrectinib was reimbursed for certain sarcomas. Meanwhile, the European Society for Medical Oncology recognised NTRK-gene fusion tumours as a separate tumour type, possibly enabling the recommendation of these therapies in a tumour-agnostic guideline in addition to the few tumour-specific guidelines. Still, limited reimbursement and recommendations for use may vitiate achievements made by developing these innovative therapies.

More tumour-agnostic therapies may be introduced to the European market. So, the lifecycle experiences of larotrectinib an entrectinib can provide pivotal insights in advancing the drug lifecycle for these types of therapies, regarding development, market approval, reimbursement, and ultimate patient access. Here, we review all these aspects for larotrectinib and entrectinib.

Introduction

A recent advance in the pharmacological treatment of cancers is the development of tumour-agnostic therapies. These medicines exert their effect by targeting substrates that are present in a variety of tumour types throughout the whole body. So far, most of the tumour-agnostic therapies that have reached clinical practice target neurotrophic tropomyosin receptor kinase (NTRK) gene fusions. Larotrectinib (Vitrakvi; Bayer) and entrectinib (Rozlytrek; Roche/Chugai) are the first EMA-approved tumour-agnostic therapies (1,2).

Their pharmacological effect results from inhibition of NTRKs genes, in which many genomic alterations occur. NTRK fusions, resulting in a constitutively active dimerised NTRK, are currently considered the sole clinically targetable and relevant genomic rearrangement (3). Its most important members are TRKA, TRKB, and TRKC, which are encoded by *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively. Normally, NTRK activation occurs upon binding by neurotrophin (NT) family ligands, leading to dimerization of receptors, and subsequent phosphorylation of kinase domains. However, upon NTRK fusions, these receptors are constitutively in their dimerised active state. Consequently, there is a constitutive activation of the subsequent cascade of intracellular signal transduction pathways that are responsible for promoting cell survival, proliferation, and differentiation, resulting in unregulated cell growth (3,4).

Such oncogenic NTRK fusions are present in ~0.3% of all solid tumours, and they have been acknowledged as central oncogenic drivers in a variety of rare tumour types (5). For instance, *NTRK* fusions have been observed in 92% of secretory breast carcinomas, 100% of mammary analogue secretory carcinomas of the salivary gland, and in 92% of congenital fibrosarcomas (3). In addition to these rare tumours,, these oncogenic fusions are found in more common tumours such as in 0.1–3.3% of non-small-cell lung carcinoma (NSCLC), 0.5–2.0% of colorectal cancer (CRC), 12% of papillary thyroid carcinomas (PTCs), in 3% of adult and 40% of paediatric brain tumours, in 1% of sarcomas (3). Considering all localisations of NTRK fusion positive tumours, the annual incidence of NTRK fusion-driven tumours comprises a mere few thousand cases in the European Union, posing challenges for conducting clinical trials (EU) (2).

NTRK fusion-positive tumours are the first type of tumours for which a tumour-agnostic therapy has been developed and approved. These include the only two currently EMA-approved tumour-agnostic therapies larotrectinib and entrectinib that we discuss here.

Pre-clinical development

Larotrectinib is a small molecule, highly selective for the ATP-binding site of TRK family members, specifically TRKA, TRKB, and TRKC. Its IC_{50} was established in a low nanomolecular range (3,6). Doebele *et al.* (2015) have demonstrated its inhibitory potency towards TRK fusions in pre-clinical *in vitro* and *in vivo* studies (6). Larotrectinib was able to inhibit growth of tumours in a murine model by targeting constitutively active TRK fusions (6).

In comparison, entrectinib is a highly-potent, orally-available, ATP-competitive TRK inhibitor, with low- to sub-nanomolar efficacy range, with additional action against ROS1 and ALK. Entrectinib was specifically designed to cross the blood-brain barriers to address both primary and metastatic brain tumours in patients with *NTRK1,-2,-3, ROS1*, and *ALK*-rearranged tumours (7).

The tumour-agnostic nature of these therapies may require a novel approach in further clinical development and authorisation procedures. Given the novelty of these medicines, this may provide difficulties in decision making by the different stakeholders involved throughout the drug lifecycle, which may ultimately lead to limited patient access. The development has not been without its difficulties, for despite their EMA approval, reimbursement was denied in several European countries. The consequent lack of patient access to these therapies due to lack of reimbursement

negates the innovative achievements.

As more tumour agnostic therapies may be introduced to the European market in the near future, the life cycle experiences of larotrectinib and entrectinib are valuable. This may provide us with clinical insights in how to advance the drug lifecycle for these tumour -agnostic therapies in the context of (clinical) development, approval, reimbursement, implementation in clinical guidelines, and ultimately patient access. Here, all these aspects will be reviewed for larotrectinib and entrectinib [Figure 1].

Review process

Here, we review the drug lifecycle of larotrectinib and entrectinib in European context. We reviewed published literature to gather information about the ongoing and previously performed clinical trials, regulatory and HTA processes, as well as the implementation in clinical guidelines and the extent of patient access. For clinical trials, study aspects and forthcoming evidence was compared. Regulatory actions by the EMA were reviewed using EPARs, summary of characteristics, orphan designation (withdrawals), EC decisions. Reimbursement recommendations were reviewed for the Netherlands (ZIN/WAR), England and Wales (NICE/ERG), France (HAS/CT), and Germany (GBA/IQWiG) by their HTA organisations and committees, respectively. We reviewed the trials used, evidence, uncertainties, and decision-making outcomes, and inclusion on national reimbursement lists, using HTA decision-making documents retrieved from corresponding websites. Finally, European Society for Medical Oncology (ESMO) guidelines for the most prevalent tumour types with NTRK gene fusions were consulted for this purpose.

Clinical development

The rarity and low incidence of NTRK-fusion tumours poses challenges for developing clinical trials. Specifically, the low incidence within each indication area in combination with the final heterogeneity of the compatible population, restrains the performance of randomized controlled trials (RCTs). RCTs, in which the novel treatment is compared to placebo or an active comparator, are considered the golden standard. However, placebo would be unethical as other treatments are available and comparator treatments may depend on the tumour types involved. For these reasons, single armed 'basket trials, i.e., without a comparator arm, are usually used for NTRK fusion positive tumours.

In Table 1, an overview of the initiated clinical trials for larotrectinib and entrectinib that are used during the different stages of the drug lifecycle is provided, along with several study characteristics, data cut-off dates and populations accounted for. Indeed, all studies are designed as open label, multicentre trials that are uncontrolled, single armed.

A striking observation is the difference in duration of studies, for where larotrectinib clinical trials are estimated at 129 months, the longest estimated study duration is 160 months. However, the exact length cannot be calculated, as NAVIGATE and SCOUT, and STARTRK-2 and STARTRK-NG, are still ongoing, for larotrectinib and entrectinib, respectively, as requested by the EMA on the basis for CMA. However, the first phase I trial for entrectinib (ALKA-372-001) started already in October 2012 and was finished, 2 years before the phase I trial for larotrectinib (LOXO-TRK-14001).

The phase II population (NAVIGATE) accounted for regarding larotrectinib comprises of younger patients than the initial phase I trial (LOXO-TRK-14001), next to the specific paediatric population (SCOUT). For entrectinib, both phase I and II trials involve adult (≥18 years) patients (ALKA-372-001, STARTRK-1, STARTRK-2), next to the specific paediatric population (STARTRK-NG).

However, while SCOUT is taken into consideration in the EMA and HTA procedures, its equivalent for entrectinib STARTRK-NG is not in those procedures, because it does not include patients in the present therapeutic indication that match the age, the EPAR and IQWiG state for instance. Besides, LOXO-TRK-14001 and SCOUT did not all harbour NTRK gene fusions, while NAVIGATE specifically required this.

Regarding the intervention, dose escalation in phase I, for both therapies, the recommended phase II dose (RP2D) was established, and consequently used in next trials. However, for entrectinib, a pooled analysis (ALKA, STARTRK-1, STARTRK-2) that was provided by the company also involved patients who received more than the recommended dose of 600 mg daily, which was not compliant with the market authorisation, was stated by IQWiG. And endpoint category side effect was lacking.

Another striking finding is the difference in outcome measures used across the trials. Drug-limiting toxicity (DLT) and maximum tolerated dose (MTD) were assessed, and not reached, and RP2D established for both therapies during phase I trials as primary safety endpoints. However, during the phase I trials, larotrectinib also assessed best overall response, duration of response (DoR), overall survival (OS)/ For entrectinib, patient reported outcomes (PROs) were assessed as secondary outcomes in STARTRK-2, however, these seem not of distinct importance in EMA and HTA procedures. Regarding efficacy endpoints, ORR was only used as primary endpoint for the phase II trials of larotrectinib and entrectinib (NAVIGATE and SCOUT phase II, and STARTRK-2), and as secondary for the remainder. However, ORR by investigator assessment (by RECIST v.1.1) or DOR was used across all trials as a secondary endpoint, and BOR only for larotrectinib trials, except for SCOUT Phase I. CBR, PFS, OS were used as secondary for NAVIGATE, and for STARTRK-1 and STARTRK-2. Remarkably, both paediatric trials (SCOUT and STARTRK-NG) did not utilise PFS. QoL was assessed as exploratory endpoint across phase II trials for both. Safety along with adverse events (AEs) were assessed across all trials, as primary or secondary for phase I and II, respectively.

All these trials were utilised during regulatory and reimbursement procedures, to different extents and with different cut-off dates. The main studies were NAVIGATE for larotrectinib, and STARTRK-2 for entrectinib, as reported throughout. For larotrectinib, the cut-off date of 30 July 2018 was reported by the EMA, NICE, and IQWiG, all regarding the same population. Of all three trials for larotrectinib, patients harbouring NTRK gene fusion positive tumours contribute to the integrated efficacy study population (second extended primary analysis set (ePAS2)) and CNS primary tumour study population (supplemental analysis set 3 (SAS3)). HAS however, commissioned an additional analysis, resulting in two cut-off dates and corresponding populations, which are eventually larger than those involved in the EMA, NICE, and IQWiG analyses.

In addition to these major trials and corresponding analyses, Drilon *et al*. (2017) assessed the potency of a next-generation NTRK inhibitor (LOXO-195) to overcome acquired resistance to prior larotrectinib-mediated NTRK inhibition in two patients with NTRK fusion positive tumours (8). And although these are briefly mentioned, not much attention is paid to this study.

	Larotrectinib				***Entrectinib***			
	Pooled analyses of NCT02122913, NCT02576431, and NCT02637687	LOXO-TRK-14001 (NCT02122913)	NAVIGATE LOXO-TRK-15002 (NCT02576431)	SCOUT LOXO-TRK-15003 (NCT02637687)	ALKA-372-001	STARTRK-1 (NCT02097810)	STARTRK-2 (NCT02568267)	STARTRK-NG
Publications	Lassen (2018) Hong (2020) (9) Drilon (2018) (10)	Doebele (2015) (6) Hong (2019) (11) Data cut-off: FEB 2018	See pooled analyses – not separately	Laetsch (2018) (12) DuBois (2018) (13)	Drilon (2017) – combined results from ALKA and STARTRK-1	Drilon (2017) – combined results from ALKA and STARTRK-1	Paz-Are (2021) (14)	
Duration of study	MAR 2015 - 30 JUL 2018 (42 months)	4 MAY 2014 – 9 APR 2021 (83 months)	15 OCT 2015 – ongoing (est. 15 AUG 2023/30 SEP 2025) (94-120 months)	16 DEC 2015 – 22 SEP 2026 (129 months)	26 OCT 2012 – 20 MAR 2018 (64 months)	28 JUL 2014 – 2 JUN 2020 (70 months)	16 NOV 2015 – ongoing (est. EC 2022/2024) (85-109 months)	3 MAY 2016 – ongoing (est. 30 AUG 2029) (160 months)
Design	Integrated safety and efficacy analysis of adult and paediatric patients with prospectively identified NTRK fusion cancers involved in NCT02122913, SCOUT, or NAVIGATE	Multicentre, single-arm, open label 3+3 dose escalation with expansion phase in patients with NTRK gene fusions only Phase I	Multicentre, single-arm, open label Basket study Phase II	Multicentre, single-arm, open label, dose-escalation and expansion Phase I/II	Multicentre, open label, ascending dose study (3*3 escalation scheme Phase I (first-in-human)	ALKA & STARTRK-1: single arm open label studies in patients with solid tumour with NTRK, ROS1 or ALK molecular alterations Phase I	Global single arm, multicentre, open label, basket study of at the RP2D in patients with solid tumour with NTRK, ROS1 or ALK gene fusions. Phase II	Multicentre, 5-part, open-label, dose-escalation and expansion study Phase I/II
Population		Adult (≥18 years) patients with locally advanced or metastatic solid tumour with documented NTRK gene fusion that could be assessed according to RECIST, version 1.1	Patients (≥12 years) with locally advanced or metastatic solid tumour (NTRK gene fusion tumours in expansion phase of study)	Paediatric (age 1 month-21 years) patients with advanced or metastatic solid or primary CNS tumours, assessed according to RECIST v1.1 CCOD: 17 JUL 2017 (12) CCOD: 19 FEB 2018 [DuBois]: n=5 (IFS n=3, other soft-tissue sarcoma: n=2)	Adult patients (≥18 years) with advanced/ metastatic solid tumours, including patients with NTRK1/2/3, ROS1, or ALK molecular alterations NTRK efficacy evaluable analysis n=1 Safety-evaluable: n=57 N=54 for DLT and efficacy	Patients (≥18 years) with solid tumours with NTRK1/2/3, ROS1, or ALK molecular alterations. NTRK efficacy evaluable analysis set n=2 Patients evaluable for safety n=76	Patients (≥18 years) with advanced or metastatic solid tumours with NTRK1/2/3, ROS1, or ALK gene fusion, excluding ALK positive NSCLC. NTRK efficacy evaluable analysis n=51 Non-measurable disease n=1 Safety-evaluable n=206	Children and adolescents (2 to 22 years) with recurrent or refractory solid tumours and primary brain tumours, including tumours carrying NTRK1/2/3, ROS1, and ALK gene fusions. Paediatric patient n=1 Safety-evaluable n=16
Intervention	100-150mg orally BID	Dose escalation: 50 mg QD - 200 mg BID Expansion phase: 100 mg BID oral capsules/oral solution	100 mg BID Continuous 28-day cycles	100 or 150 mg BID, oral capsules/oral solution Continuous 28-day cycles, until MTD	100-800 mg/m2/day QD continuous 4-day cycles, until PD, withdrawal patient	100-800 mg QD continuous 28-day cycles	600 mg QD, oral capsules repeated 28-day cycles	250-750 mg/m2 F2B or F1 formulation, continuous 28-day cycles

		continuous 28-day cycles until MTD reached			consent, or unacceptable toxicity			
Comparator	uncontrolled	uncontrolled	uncontrolled	uncontrolled	uncontrolled	uncontrolled	uncontrolled	uncontrolled
Outcomes (primary & secondary)	Primary: ORR by IRC assessment (CR or PR) Secondary: ORR by investigator assessment (RECIST v1.1), TTR, TTBR, DOR, TTR, disease control rate, PFS, OS	Primary: MTD, RP2D, Secondary: ORR, DOR, BOR, PK, antitumour efficacy, AEs	Primary: ORR (CR+PR) according to RECIST v1.1 Secondary: BOR, DOR, PFS, OS, CBR Exploratory: quality of life, safety, tolerability	Phase I: Primary: DLTs Secondary: PK, MTD, RP2D, antitumour activity, HRQoL Phase II: Primary: ORR Secondary: DOR, BOR, safety, tolerability.	Primary: first cycle DLTs and MTD Secondary: overall safety profile, PK, ORR by investigator assessment Exploratory: DOR, SD duration, PFS, OS	Primary: first cycle DLTs, MTD, and RP2D Secondary: safety, PK, efficacy (ORR by RECIST v1.1, PFS, OS, CBR, DOR), PD profile, tumour assessment	Primary: ORR Secondary: DOR, TTR, CBR (CR, PR, or SD at 6 months after first dose), PFS, OS. And for CNS disease patients: intracranial tumour response (BICR), CNS-PFS. AEs, popPK, ventricular repolarisation, QoL, health status PROs Exploratory: potential resistance mechanisms, analysis of potential difference among NTRK1/2/3 gene fusion tumour types	Primary: DLT
EMA (CCOD (nr of patients (incl. NTRK fusion tumours))	ePAS (extended PAS) n=73 (enrolled patients with sufficient duration of follow-up) – trial supports MAA	30 JUL 2018 72(10) For ePAS2: 8 30 JUL 2018 ePAS2 and SAS3: 70(8) for NTRK fusion: ORR: 88%) DOR not estimable: 17.2-38.7 months) BOR: CR (25%) PR (63%)	30 JUL 2018 ePAS2 and SAS3: n=62 CR 11%, PR 56% ORR 68% mDOR 19.8 months PFS n.a. OS n.a.	30 JUL 2018 ePAS2 and SAS3: n=41(32) ORR 81% BOR 22% PR 56% DOR not estimable (1.6-26.7 months)	For MAA : primary analysis (n=54), updated analysis n=74 (D180) **CCOD 31 OCT 2018** ORR : 63.5% DoR : 44.7% patients with event : mDOR : 12.9 months PFS : 55.4% patients with events : mPFS : 11.2 months OS : 32.4%, median OS : 23.9 months Trials support MAA as integrated efficacy analysis (n=54) and pooled safety population (n=355)			Only dose escalation phase included in submission. CCOD 31 MAY 2018. Paediatric efficacy and primary brain tumour with NTRK gene fusion data presented separately, excluded from main analysis Trial support MAA only as part of pooled safety population (n=355)
					Safety : Pooled patients from ALKA, STARTRK 1, STARTRK 2 and STARTRK-NG (paediatric).			

					CCOD: 31 MAY 2018, n=355 At time of D120 and D180: Safety: Pooled patients from ALKA, STARTRK 1, STARTRK 2 and STARTRK NG. Full updated safety information included in new D180 safety supplementary report in Module 5.		
ZIN			Only mentioned in follow-up advice to Minister of Health				Only mentioned in follow-up advice to Minister of Health
NICE (CCOD (nr of patients (incl. NTRK fusion tumours))	Primary dataset: 55(55) Supplementary: n=67(67) Integrated dataset: n=122(122)	30 JUL 2018 72(10)	… 70(8) 30 JUL 2018 N=83	30 JUL 2018 54(46)	Trial used in economic model, as integrated efficacy analysis (n=54) and pooled safety population (n=355) Trial used in economic model: more evaluable patients, data (as at JUL 2018) for 102 patients is used		Trials used in economic model only as part of pooled safety population (n=355)
	Trial used in economic model: more evaluable patients (JUL 2018, n=102)						
HAS (CCOD : nr of patients (incl. NTRK fusion tumours), evaluable for response (incl. NTRK fusion tumours)	Last extraction date: 15 JUL 2019 164(164), 109 adults, 55 children MA dosage received: n=153: ORR 79% Incl. subgroup analyses, and separate analysis for CNS tumours	Duration until 19 DEC 2018 2 CCODs: 17 JUL 2017: 66(8), 65(8) 15 JUL 2019: 75 (13), 66(12)	17 JUL 2017 47(47) 40 evaluable for response 15 JUL 2019 116 patients, 112 evaluable for response	2 CCODs: 17 JUL 2017: 31(8) 15 JUL 2019: 88(9)	Because of their purpose, they will not be detailed in this document, But they are used in extrapolating adult data from ALKA, STARTRK-1, and STARTRK-2 and paediatric from STARTRK-NG trial to assess efficacy in paediatric patients ≥12 years (n=5, all <12 years, solid tumours n=3, and primary brain tumours n=2)	Interim analysis: 31 MAY 2018 Additional safety analysis: 31 OCT 2018 Supplemental efficacy analysis: 1 MAY 2019 71(71)	Not considered by the application for inclusion
IQWiG (CCOD : nr of patients (incl NTRK fusion tumours)	30 JUL 2018: ePAS2: n=93 15 JUL 2019 ePAS4: n=164 (ePAS2 + n=71) primary CNS tumours: n=24 30 JUL 2018:	30 JUL 2018 72(10)	30 JUL 2018 82(82)	30 JUL 2018 54(45)	Both not used for assessment, because of exclusion criterium <6 months of follow-up	31 AUG 2018: 108(108) ECOD: 30 APR 2018: NTRK EE: 71, for mortality, morbidity, HRQoL 31 OCT 2018 NTRK SE: n=108 for side effects	In accordance with EPAR: 31 OCT 2018 29(7) → does not include patients in present therapeutic indication until 31 OCT 2018, company did not provide information on nr of patients ≥12

	SAS3: n=9 (with NTRK gene fusion and primary CNS tumours 19 FEB 2019: ESMO 2019 evaluation population: n=159 (not per tumour type)				Company provided pooled analysis of NTRK EE of STARTRK-2 (n=71) and n=3 from STARTRK-1 and ALSKA-372-001 (NTRK gene fusion, ≥600 mg), data cut-of 31 OCT 2018. However, no results available in the dossier for the endpoint category side effects as well as no results separated by tumour entity. And patients included who received >600 mg, not compliant with MA	years and NTRK gene fusion in this study.
ESMO	Drilon (2018) and Hong (2020) used. mDOR and PFS were only reached in Hong (2020) with median follow-up of 12.9 months, and not in Drilon (2018) with median follow-up of 8.3 and 9.9 months, respectively. So only Hong (2020) used, and although Drilon (2018) ORR at 75% according to independent review and 80% according to investigator assessment, ORR of 79% was reported as grounds for ESMO score (Hong 2020) (9,10) mPFS: 28.3 months ORR: 79% DoR: 35.2 months				Doebele (2020) used as sole reference for recommendation score, STARTRK-NG not considered (15) mPFS: 11.2 months ORR: 57% DoR: 10.4 months	

Table 1. Overview of clinical trials for larotrectinib and entrectinib used by EMA, HTA organisations (ZIN, NICE, HAS, IQWiG) and ESMO as evidence for the respective market authorisation, reimbursement decisions and implementation in clinical guidelines. Adverse events (AEs), best overall response (BOR), Blinded Independent Central Review (BICR), clinical benefit rate (CBR), complete response (CR), central nervous system (CNS), dose-limiting toxicity (DLT), median (m) duration of response (DOR), extended primary analysis set (ePAS2), health-related quality of life (HRQoL), market authorisation (application) (MA(A)), maximum tolerated dose (MTD), pharmacodynamics (PD), partial response (PR), patient-reported outcomes (PROs), pharmacokinetics (PK), progression-free survival (PFS), objective response rate (ORR), overall survival (OS), stable disease (SD), supplemental analysis set 3 (SAS3), time to response (TTR), time to best response (TTBR).

Regulatory actions

Novel therapeutic indication

Larotrectinib was the first of the two to request market authorisation through the centralised procedure of the European Medicines Agency (EMA) on 15 June 2018, 6 months before entrectinib. The tumour-agnostic indication that was requested at this time, was not the first indication, as larotrectinib was granted orphan designations for four tumour types (soft tissue sarcoma, salivary gland cancer, glioma, and papillary thyroid cancer) before (16). Still, before a COMP adoption of a List of Issues, all orphan designations were withdrawn by the sponsor (Bayer AG) (11 July 2019), as the COMP would not fall within the scope of the cluster of designated orphan conditions, arguing that "a tissue independent therapeutic indication cannot be considered to be within the scope of a limited number of orphan designations covering separate tumour types" (17). This was only 2 weeks before the CHMP decision on MAA for the tumour-agnostic indication (25 July 2019) (16). Interestingly, the initial orphan designation for entrectinib (for neuroblastoma) was also withdrawn from the EC community register (17 December 2018) by the sponsor (Pharma Gateway AB, Sweden). However, this was already before submitting MAA (7 January 2019) (18–20).

The authorised indications for both larotrectinib and entrectinib were different from the initially requested indications [Table 2] (16,21). The requested tumour agnostic indication for solid tumours independent of tumour type or histology was intended as an overarching later stage palliative indication. Still, the indication leaves room for earlier treatment lines for those tumours without available or failing standard therapy. However, the ultimately authorised indication enables treatment with larotrectinib based on benefit/risk evaluation, possibly bypassing poorly effective therapies that are nevertheless recommended in therapy guidelines, in the absence of more effective treatments, enabling larotrectinib to be an earlier stage treatment option rather than later stage only. Additionally, larotrectinib is now covered as treatment option for CNS tumours as well, as the CHMP considered that there is no scientific rational for excluding this previously treatment patient population without satisfactory treatment option, in spite of their exclusion in the pooled primary analysis populations.

As for entrectinib, two separate therapeutic indications were applied for, of which only the first, the tumour-agnostic, NTRK gene fusion positive solid tumour indication will be discussed here (21). Similarly, entrectinib is covered as treatment option in the absence of satisfactory treatment options. The authorised indication specifically regards entrectinib as palliative treatment for patients that have a life-threatening malignancy who are currently surgically curable, but at the expense of severe mutilating surgery. Entrectinib could represent a non-invasive approach for these patients. Strikingly, for larotrectinib, the indication did not specify any prior administration of an NTRK inhibitor, although >28-day TRK inhibitor (entrectinib, crizotinib, or lestaurtinib) treatment was regarded as an exclusion criterium for SCOUT. This is possibly because of its recent discovery, irrelevant therapy for the tumour-agnostic indication, or lack of evidence for the role of prior TRK inhibitor in developing acquired resistance over time, whereas this latter matter was discussed more thoroughly for entrectinib.

	Requested indication	**Authorised indication**
Larotrectinib	*"Treatment of adult and paediatric patients with locally advanced or metastatic solid tumours (excluding primary central nervous system (CNS) tumours) with a NTRK gene fusion after prior standard therapy or as initial therapy when there is no adequate treatment option".*	*"Monotherapy for treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion, a) who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and b) who have no satisfactory treatment options."*

Entrectinib	*"Adult and paediatric patients with NTRK fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies" and "patients with ROS1-positive, advanced NSCLC."*	*"Entrectinib as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours that have a NTRK gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and - who have not received a prior NTRK inhibitor, - who have no satisfactory treatment options."*

Table 2. Requested and eventual authorised indications for larotrectinib and entrectinib by the EMA.

Scientific & protocol advice: PRIME scheme

Furthermore, in contrast to its tumour-agnostic predecessor, entrectinib was granted eligibility to the PRIME scheme (13 October 2017, kick-off 5 February 2018), only for the requested NTRK indication (21,22). Consequently, the applicant received Scientific Advice from the CHMP on the development on four occasions, concerning quality aspects, adequacy of the non-clinical program to support an MAA, and a proposal for clinical pharmacology characterisations. Advice was also provided for clinical trial design, in which the use of a basket trial design (STARTRK-2) was advised to register multiple tumour types based on gene rearrangements, as well as using a two-step assay (immunohistochemistry followed by Next-Generation Sequencing) to identify patients eligible for enrolment. Also, ORR was recommended as a primary endpoint, and primary and secondary efficacy analyses were discussed, as well as required sample sizes for the three NTRK genotypes, and the suitable type of MA for this non-conventional clinical programme. Finally, the pooled analysis of ALKA-372-001, STARTRK-1, STARTRK-2, and STARTRK-NG was discussed, also with regard to the pooled safety data and the size of the safety database. While at the time of PRIME kick-off, STARTRK-1 was already initiated (patients enrolled between October 2012 and March 2016), STARTRK-2 was initiated at 30 April 2018, possibly allowing any improvements of the study (7,21).

Moreover, it is reported that the applicant (Bayer) did not seek protocol assistance at the CHMP for larotrectinib, but only the aforementioned SAG and BSWP advice was provided in a later stage of the procedure. To our knowledge, PRIME support was not offered, neither for the tumour-agnostic nor for the initial orphan designations. However, it is unknown whether the sponsor applied for PRIME, or considered this at the time Bayer submitted the request for orphan designation, which was only a few months before the PRIME launch (March 2016), and if it requested eligibility to the PRIME scheme for the tumour-agnostic indication (16).

Accelerated assessment

Interestingly, the advice provided by PRIME appeared no guarantee for accelerated assessment, as the request was not granted on the basis that entrectinib was not recognised as a major public health interest. This decision was based on the uncertainty regarding the ROS1-positive NSCLC indication, despite the promising data in patients with NTRK-fusion positive tumours, without a notion on treatment options with larotrectinib.

For larotrectinib, requested accelerated assessment was granted forthwith (26 July 2018). However, after Rapporteur and Co-Rapporteur first Assessment Reports and after the List of Question was sent to the applicant (Bayer), the CHMP no longer deemed it appropriate to pursue accelerated assessment, as "the uncertainties raised during the assessment required a thorough review of the quality, clinical pharmacology and clinical efficacy aspects". Consequently, the procedure was changed to normal timetable (on 17 December 2018), prior to day 120 (16,21).

Uncertainties EMA

For larotrectinib, the List of Questions (25 January 2019) addressed to the Scientific Advisory

Group (SAG) concerned particularly the role of NTRK gene fusions as oncogenic drivers. The SAG emphasised the lack of studies for identification of NTRK gene fusion as a possible strategy for reducing tumour progression. Concerns were raised whether the impact of larotrectinib on the prognosis may depend on gene fusion partner, for which data were very limited for all tumours but the rare tumour types. For entrectinib as well, there is uncertainty to what extent and which specific mutation is related to treatment efficacy. The CHMP demanded confirmation of the presence of an NTRK gene fusion by a validated test prior to initiation of treatment for both (16,21).

Lack of both clinical evidence and predictive ability of clinical decision algorithms warranted the need for further investigation for a true evidence-based decision, the SAG claimed. To further confirm the assumption of tissue-independent activity of larotrectinib, retrospective analyses, and comprehensive Next-Generation Sequencing to assess tumour characteristics at the time of larotrectinib treatment studies were proposed. No List of Questions was found for entrectinib (16,21).

Regarding concerns about the exact magnitude of effect, due to the study conduct, and incomplete understanding of the extent that tissue of origin is an effect modifier, still, the observed overall ORRs of 72% for larotrectinib and 63.5% for entrectinib were considered outstanding (16,21). This was especially considered as such because of the context of advanced cancer that has exhausted or lacks established therapeutic options, an outstanding ORR along with clinically meaningful DOR is considered to establish clinical benefit (16). However, only for larotrectinib the ORR was specified for NTRK fusion type in subgroup analyses, in addition to the varying ORRs across tumour types. For both therapies, the rarity of NTRK gene fusions was acknowledged, but increasing sample sizes are accounted for in the post-marketing studies. Time to response (TTR) were not considered in the end for entrectinib, while consistently short for larotrectinib (1.8 months) and considered of high clinical value for its present indication. In contrast, entrectinib showed mDOR >12 months, and a similar value was expected but not yet reported, as it was not reached due to immature data, for larotrectinib. Still, while DOR estimates per tumour type were considered uncertain due to small sample sizes for entrectinib, activity in NTRK gene fusion tumours is such that clinically relevant effects may be anticipated (16,21).

Furthermore, the safety profile for both were considered tolerable with manageable toxicity. However, the safety databases for the claimed indication were considered limited, but acceptable in the context of a rare conditions. Still, both safety populations were deemed heterogenic (n=113, n=208, respectively), and especially for entrectinib it was emphasised that comprehensive data was lacking for paediatric patients.

Interestingly, potential risks for severe on-target neurologic reactions due to NTRK signalling, as well as the long-term safety in the paediatric population are specifically and rather detailed included as important potential risks in the Risk Management Plan (RMP) for larotrectinib, whereas this safety concern was addressed to a much lesser extent for entrectinib (16,21).

Finally, many concerns were raised for the paediatric population of entrectinib, due to the low number of 12–18-year-old patients with NTRK gene fusion. In light of the tumour-agnostic indication, the non-clinical pharmacological data is considered insufficient for extrapolating activity to for instance paediatric tumours (21).

Authorisation decision

For both larotrectinib and entrectinib, during the assessment, the CHMP presumably proposed the request for conditional market authorisation (CMA) (23). This was subsequently done on the following grounds: the therapy exhibits a positive benefit-risk balance; comprehensive data can be provided to further study the clinical benefit; unmet medical needs will be addressed for patients with tumour types for which satisfactory treatment are not available or are already

exhausted without success. Intriguingly, for larotrectinib, the risks inherent to lacking additional data are considered acceptable in light of the life-threatening nature of these tumours given the magnitude of the observed ORR, whereas this is not specifically based on the ORR for entrectinib. However, both medicines are expected to address the unmet medical need to a similar extent, according to the EPAR of entrectinib (21). Interestingly, the Rapporteur for larotrectinib was also appointed Co-Rapporteur for entrectinib.

Whereas the positive CHMP recommendation was unanimous for larotrectinib, three CHMP members beheld a divergent opinion for entrectinib's positive recommendation (16,21). Although the overall B/R of entrectinib was considered positive, they were concerned that the overall dataset was too limited to conclude that the data would represent clinical benefit. Thus, claiming that with the current ORR, the B/R was not obvious or indisputable positive. And additionally, the available results would not address the unmet medical need to an at least similar extent to what is understood for the already conditionally authorised product (larotrectinib), mainly regarding safety (21).

Post-approval measures ('specific obligations')

Being conditional, additional post-approval measures (so-called "specific obligations" (SOBs)) were imposed by the EMA for both therapies. In line with the SAG advice for larotrectinib, these were primarily aimed to further confirm the tissue-independent efficacy, studying primary and secondary resistance mechanisms. The NAVIGATE study sample size will be increased for an additional pooled analysis. Also, the SCOUT study will be expanded, including 5-year follow-up data, to study the long-term toxicity and developmental effects in paediatric patients. Additionally, an updated population pharmacokinetic model in paediatric patients (1 month-6 years) to further confirm the appropriate dose in this population was agreed upon (due 30 September 2021) (16,21).

SOB-1 for entrectinib is being carried out to further confirm entrectinib's histology-independent efficacy in adult and paediatric patients. This will be done by increasing the sample size of the NTRK fusion-positive patients from the ongoing pivotal STARTRK-2 and STARTRK-NG studies, and submitting a pooled analysis. The market authorisation holder (MAH) should also submit interim safety and efficacy analysis results for both populations, including adolescents, by the end of 2023. Moreover, SOB-2 is aimed to further examine the impact of the presence or absence of other molecular alterations on entrectinib's efficacy. Therefore, tumour genomic profiling will be performed at baseline and progression will be characterised, together with clinical outcome associations per tumour histology.

Importantly, the available data appear to support the conclusion that both larotrectinib and entrectinib "address the unmet medical need to a similar extent", despite limitations of cross-study comparison, heterogeneity in dataset composition, and small populations for each tumour type (21). It is emphasised in the EPAR that uncertainties remain on the precise efficacy estimates and on the activity across tumour types, underlining post-approval measures for market authorisation for both tumour-agnostic treatments.

	Uncertainties / Concerns					
	Population	**I**ntervention	**C**omparator	**O**utcome	**T**rial design	**O**ther reasons
EMA	Small sample size	Predicted exposure in smallest children: insufficient data to propose dose	n/a	Precise magnitude of effect – unbiased estimate of efficacy	Single arm, uncontrolled, non-randomised nature of studies	Incomplete understanding of tissue of origin as effect modifier, or concomitant genetic alterations → SOB
	Low number of adolescents (12-18 years) with NTRK fusion tumours			Immature efficacy data (mDOR not reached)		Role of NTRK gene fusions as oncogenic drivers
		Efficacy and safety of adolescent dose based on extrapolated adult data		Non-comprehensive data	Lack of prospective cohorts	Potential on-target central effect (neurological reactions) due to neurotrophin signalling
				Limited safety database, but acceptable for rare condition for adults – problematic for paediatric patients	Explorative and adaptive nature of study program	Primary and secondary resistance mechanisms → post-approval measure
				High heterogeneity of data		
ZIN	Number of patients eligible for treatment in clinical practice: diagnostic pathway not yet organised			Immature data: median PFS could increase	Worldwide uncertainty about applicable research methodologies	Current framework not suitable for these tumour-agnostic therapies: complies with 'established medical science and medical practice'
				Unknown if substitution will occur		
				Uncertain interchangeability with entrectinib, not different market division considered		
NICE	Over-representation of high NTRK-prevalent and rare tumour types, unrepresented common tumours		Not compared to other treatments	Implausible modelled post-progression survival outputs – requiring extrapolation of survival outcomes	Inappropriately assumed equal response for all tumour types and fusion types → adjust for subgroups	No defined clinical pathway for NTRK fusion patients
	Key clinical evidence is not generalisable to NHS clinical practice		Unadjusted bias in naïve indirect comparison with pooled comparator arm	Immature data (to what extent response translated in clinical meaningful survival benefits): OS, PFS incomplete	None of statistical protocols of trials included in pooled analysis designed to test heterogeneity in response by any factor	Role of NTRK gene fusions other than ETV6-NTRK in driving cancer growth improperly studied: role in prognosis, associated with other prognosis-affecting factors
	Prevalence estimates and number of eligible patients → collected in CDF		Both confirmatory analyses with substantial bias, structural uncertainty	Little to no evidence of efficacy for some tumour types	Poor characterisation of NTRK gene fusions	Tissue-specific mechanisms for bypassing response
	Trial inclusion criteria different from MA indication ('satisfactory' is ambiguous)		Unfeasible to establish universal comparator standard of care across tumour type	TRK inhibitor resistance not well characterised	Uncertainty in most appropriate economic model structure for decision making	Place in therapeutic strategy unclear
	Unknown effect of patient characteristics		Inappropriate, highly unreliable company compactor arm: median OS and PFS averaged, pooled, and	ORR may not be generalisable to the broader range of tumour types in clinical practice	Inappropriate alternative approaches (use of landmark analysis for trial-based non-	Important but yet uncertain diagnostic pathway

			weighed for available NICE-recommended comparators for tumour types included trial population: median, weighed overall PFS and OS.		responders as comparator population): overly optimistic estimate of incremental effectiveness, introduced unnecessary uncertainty	
	Primary CNS tumours not included in response analysis		Comparator population not consistent with population for CNS metastases and other prognostic factors, not consistent with clinical practice → 2 further approaches for decision making	CEA: unknown how long people would live after disease worsens – survival extrapolation (key driver of model) – could meet end-of life criteria → further data	Revised base case does not include committee's preferred assumptions	Challenges in appraising histology-independent treatment within NICE's single technology appraisal process
	Highly heterogenous (trial) population		Sample size of non-responders too small for meaningful comparator sample	Uncertainties in understanding baseline clinical outcomes		
				ICER range		
HAS	Heterogeneous adults and paediatric populations (clinical situations, previous treatment, tumour sites)		Absent comparative data vs. standard care (direct comparison)	Preliminary data (short follow-up) & pending new (paediatric) efficacy and safety data	Basket studies, in principle, do not preclude integrations of control groups adapted to tumour site	Demonstration in multi-organ indication with a biomarker does not justify downgraded methodology, in particular without comparison and rarity of fusion/tumour should not prevail over level of evidence of the data
	Not restrictive inclusion criteria for NAVIGATE (progression under previous treatment not required here)		Very limited (and non-comparative) data for paediatric patients	Questionable transposability of results (limited numbers for or absence of tumour types; broad inclusion and heterogeneity of clinical situations, diagnostic methods need validation and standardisation)	Pivotal phase II study does not meet minimum requirements of the Committee to provide formal proof of clinical benefit regardless of tumour having NTRK fusion	Prognostic value of NTRK fusions in solid tumours not known, and not well characterised natural history of NTRK fusion tumours
	Unclear to which line of treatment response rates have reliable reliability to clinical practice		Larotrectinib considered alternative for NTRK gene fusion in IFS and in other soft tissue sarcomas	Absence of response estimates in tumour-site specific subgroups	Single arm studies intrinsically unsuitable for demonstrating benefit of new treatment	Medical need and place in therapeutic strategy differs per tumour type
	Multiple situations covered in wording of MA indication led to varying clinically relevant comparators according to situation and line of treatment			Low level of evidence of data	Post-hoc nature of post-hoc pooled analysis for CNS tumours	
				Absence of data on criteria other than response rate (OS, QoL)	Insufficient data to consider homogeneity of benefit regardless of solid tumour	
				Poorly established efficacy/adverse effects ratio	Short follow-up	

				Safety profile with serious adverse events	Significant toxicity noted with short follow-up in time for patient follow-up	
IQWiG	Uncertain number of patients in Germany: based on non-German data (larotrectinib) and (entrectinib) uncertain estimate numbers of advanced/ metastatic stage		Absence of comparative data: comparison with appropriate comparator therapy best supportive care not possible	Unknown to which extent mean values for pooled data (from ePAS2, and NTRK EE and SE) can be representative → GBA considers separate analysis useful and necessary	Deviating from company: results separately for tumour types and not regardless of tumour histology	Lack of scientific consensus on universal oncogenic driver status of NTRK fusions
	Comparability of larotrectinib-treated patients across studies separated by tumour entity with patients from comparator-treated populations		Absence of effect estimates compared with appropriate comparator therapy	No subgroup analyses separated by tumour type presented, or patient-relevant outcomes: incomplete data	Only separate for primary CNS tumours	Unclear prognostic relevance, except for tumour types where fusion is pathognomonic (i.e., sufficient criterion for the diagnosis)
	Without clinical characteristic information unknown if patients included in present larotrectinib studies concurred with patient population described in SPC.		Comparative data only available separately for tumour histology	Lack of information on median observation time and OS separated by tumour type		Unclear if NTRK gene fusion patients that are currently treated are fundamentally differently from patients without or with unknown NTRK gene fusion.
	Company redundantly restricted SHI target population to patient with proven NTRK gene fusion, while may not yet be proven in clinical practice population		Company presents historical BSC-treated patient population data for 2 tumour types, but description of procedure for search and study selection is missing	Heterogeneity of prognoses is expected based on very distinct natural histories of tumour types included		
	Lacking description of patients treated in individual tumour entities			Only comparative data for OS submitted, but not separately for tumour types		
				Results missing for endpoint category side effects		
				Indirect comparison effect favourable for entrectinib (vs. patient-individual therapy) statistically significant, but still possible result of systematic bias in comparison of individual arms from different studies		
				Paediatric data not suitable for assessment of additional benefit in present indication		

Table 3. Uncertainties raised by regulatory (EMA) and HTA organisations (ZIN, NICE, HAS, GBA) during market authorisation and reimbursement decisions, respectively.
Uncertainties are categorised by PICOT and other reasons, and concern larotrectinib (light grey), entrectinib (white), or both (dark grey).

Reimbursement

After being granted CMA, both larotrectinib and entrectinib were proposed by their respective companies as candidates to be reimbursed in several countries. Here, the Health Technology Assessment (HTA) procedures are discussed regarding the Netherlands, England and Wales (NICE), France, and Germany.

HTA outcome

For both larotrectinib and entrectinib, before CMA was formally granted by the European Commission, the company evidence was submitted to the National Institute for Health and Care Excellence (NICE), which was after the EMA issued a positive opinion for larotrectinib, but a year before recommendation for entrectinib. Both procedures in Germany started a months after their formal CMA granting, while it was not until 2021 that they were submitted to the Dutch National Health Care Institute (ZIN). For entrectinib, this was quickly followed by the procedures at Haute Autorité de Santé (HAS), while the opinion of the HAS committee (Commission de la Transparance) was adopted before [Table 4].

At ZIN, the assessment was performed in parallel for both therapies, was shortest, potentially because no complete 'Pakketadvies' was reported. Here, after initial discussion with the Scientific Advisory Board (WAR), ZIN concluded that it was impossible to determine to what extent the therapies complied with 'established medical science and medical practice' (stand van de wetenschap en praktijk) (24–28). ZIN considered the current assessment framework not sufficient for these highly innovative tumour-agnostic therapies, and even claimed that a fitting framework for these type of therapies would be developed. However, NICE had reviewed and modelled its framework prior to the start of the assessment (29). Although the other countries mentioned the innovative nature and novel indication strategy of both therapies, the adequacy of the assessment framework was not debated.

In NL, both therapies were granted 'conditional inclusion for orphan drugs, conditionals and exceptionals' for the national insurance for a period of 3.5 years, ending January 1st, 2025 unless stopped or elongated by that time. The first step of this step-by-step approach is aimed to determine compliance with 'established medical science and medical practice'. The criteria for starting the first phase were recommended to the Minister of Health, and include 1) additional data collection, 2) exit-criteria and exit-strategy, 3) start- and stopcriteria, 4) patient education, 5) monitoring progress of additional data collection. Together with this novel framework, this should allow an adequate cost- and relative effectiveness assessment (CEA, REA) for inclusion in the national health insurance, was the final opinion of ZIN (25,27).

Similarly, in France, larotrectinib was granted a cohort Temporary Authorization for Use (cATU) granted by the ANSM, the French equivalent of the European Commission, allowing reimbursement for a group of patients while applying for MA at the EMA (12 April – 12 November, 2019, 15 patients treated) (30–32). Besides, HAS provided the only report in which opinions of other European and North American HTA bodies were mentioned. Neither larotrectinib nor entrectinib was recommended by NICE for routine use in the national health service (NHS), but they are now included in the Cancer Drugs Fund (CDF) list that allows reimbursement for clinically promising drugs, on the condition that managed entry agreement (MEA) requirements are fulfilled (33,34). In Germany, IQWiG concluded that no added benefit was proven, both therapies were included in Annex XII, comprising medicines with new active ingredients that have received benefit assessment under AMNOG legislation, are included for reimbursement [Table 4] (35–38).

So, in all four countries, the tumour-agnostic therapies are, although conditionally, included in reimbursement lists. However, in the Dutch law, there is a difference in their inclusion, as larotrectinib is not included in the national health insurance, and not to be reimbursed, except for

until January 1st, 2025, while entrectinib is reimbursed, but only until January 1st, 2025, unless prior stop or elongation. Despite this apparent difference in legal approach and nature, both therapies are reimbursed for this specific period of time (25,27,39) .

HTA	**Larotrectinib**	**Entrectinib**
ZIN	Conditional inclusion (VT) in national health insurance for adult and paediatric patients with solid tumours harbouring NTRK gene fusion (splitted into two phases, in the expanded VT specifically for tumour-agnostic medicinal products)	Conditional inclusion (VT) in national health insurance for adult and paediatric patients with solid tumours harbouring NTRK gene fusion (splitted into two phases, in the expanded VT specifically for tumour-agnostic medicinal products
NICE	Not recommended for routine use, met criteria to be included in CDF as an option for treating adults and children who have solid tumours (including primary cerebral tumours) that have a NTRK gene fusion AND disease which is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options if the conditions in the managed entry agreement are followed	Not recommended for routine use in the NHS, but considered for use only within the CDF as an option for the treatment of **patients aged 12 and over** who have solid tumours (including primary cerebral tumours) that have a NTRK gene fusion AND disease which is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options. It is recommended only if the conditions in the managed entry agreement are followed.
HAS	The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use only in infantile fibrosarcoma and in other pediatric soft tissue sarcomas, with fusion of the NTRK gene, locally advanced or metastatic, and refractory or in relapse and at the Marketing Authorization dosage. The maintenance of this favorable opinion is conditional on the submission of data comparing VITRAKVI with the usual management of these patients, within a maximum period of 12 months, as well as the setting up of a register exhaustive list of all the children treated by VITRAKVI in France (see description of the request below). In other pediatric situations and in adults for the MA indication, the Committee gives an unfavorable opinion on inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by communities.	Adverse opinion for reimbursement in adult patients and pediatric patients aged 12 years and over, with solid tumors expressing a fusion of the NTRK gene with locally advanced or metastatic disease or for which surgical resection would risk causing severe morbidity and, not previously treated with NTRK inhibitors, when there is no satisfactory therapeutic option).
GBA/ IQWIG	Additional clinical benefit not proved, but larotrectinib is included in Annex XII	Additional clinical benefit not proved, but entrectinib is included in Annex XII

Table 4. Overview of reimbursement recommendations for larotrectinib and entrectinib of the different HTA organisations. (ZIN, NICE/ERG, HAS/CT, GBA/IQWiG)

Uncertainties in REAs

The conditional inclusions in national health insurances resulted from various aspects that created uncertainty in the evidence [Table 3]. While some concerns are shared, there are specific differences between the two therapies, and HTA organisations.

Population

Overall, generalisability of the trial population in evidence provided by the companies to the clinical practice population is a major concern, but on different grounds. According to ZIN, due to a yet unestablished diagnostic pathway, the number of patients eligible for treatment in clinical practice is unclear, while IQWiG remarked that estimates are based on insufficient and non-German data on the number of eligible patients for larotrectinib treatment (24,26,40,41). In England, the ERG concluded that the trial population was not generalisable to the clinical practice population for both therapies, as the distribution of tumour types was not representative nor explored by the company. IQWiG mentioned this reason as well. Namely, that the company restricted the population unnecessarily to patients whose NTRK gene fusion was verified, while actually, the clinical practice population also includes patients with a yet unproven NTRK gene fusion status. And in France, the heterogeneity and broad inclusion criteria of the trial populations raised uncertainties for both.

Moreover, the trial inclusion criteria differ from the CMA approved indication, mainly due to the ambiguous wording 'satisfactory', as both NICE and HAS, but not GBA, claim. In their opinion, it is thus unclear to which line of treatment and corresponding clinically relevant comparators the reported outcomes refer to in clinical practice.

Intervention

For both therapies, no uncertainties or concerns were raised relating to the intervention for any of therapies by the HTA organisations. Only the EMA was concerned about the dose of larotrectinib for children and entrectinib for adolescents, due to insufficiency of extrapolation of the available data for adult patients (16,21).

Comparator

Establishing an appropriate comparator formed the primary reason for uncertainty, and different approaches were carried out by the HTA bodies. Larotrectinib being the first assessed tumour-agnostic therapy, had no compatible comparator therapy with a similar tumour-agnostic indication. Still, IQWiG/GBA explicitly considered larotrectinib not an appropriate comparator for entrectinib. For, as larotrectinib lacked an ACT itself, its clinical value could not be assessed, and consequently not adequately be compared to another therapy (42,43). NICE considered larotrectinib's indirect comparison substantially biased (44). In contrast, for entrectinib, the company had established rather a unique comparator arm, but ERG (NICE) considered this approach highly unreliable (44) [Table 4]. The trial population reflected the clinical practice population poorly, so alternatively ERG proposed a previous line of treatment approach (intra-patient analysis, assessing time to next treatment) and an exploratory response-based approach (non-responders as comparator arm) (44). Interestingly, IQWiG emphasised the absence of comparative data with an appropriate comparator therapy for both treatments, while agreeing that comparison with (historical) best supportive care was not possible. Consequently, an additional benefit could not be proven (35,36,40,41).

Outcomes

Furthermore, all HTA bodies except IQWiG/GBA, regarded incompleteness and immaturity of the provided data as a limitation. For, according to NICE, short follow-up biased survival extrapolation and impeded an accurate estimation of actual clinical meaningful survival benefits (45,46). However, even HAS, while its second cut-off date was 12 months later, was concerned about an accurate estimation of actual clinical meaningful survival benefits (15 July, 2019) [Table 1, Table 3] (30,33,44,47). Despite that, reported efficacy outcomes are almost similar for NICE and HAS (30,33,44,47). Additionally, in the pooled analyses, it was universally doubted if the reported overall efficacy outcomes account for the heterogeneity of tumour response, as tumour-site specific estimates lacked. Illustratively, IQWiG separated the provided results per tumour type to assess

instead of regardless of tumour type, but as the comparative data were lacking, this was considered impossible. And eventually, GBA considered results per tumour type useful and necessary (36). Strikingly, only HAS was evidently concerned about entrectinib's safety profile (47).

Trial design

Furthermore, the single arm, uncontrolled basket trials were cause for concern for all HTA bodies. ZIN recalled the worldwide uncertainty about applicable research methodologies for tumour-agnostic therapies, with HAS proving its point. There, both pivotal phase II studies (NAVIGATE, STARTRK-2) could not meet minimal requirements to formally prove clinical benefit regardless of tumour NTRK fusion status (30,47). HAS even regarded this as 'downgraded methodology' for both efficacy and safety analyses (30,47). In contrast, NICE and IQWiG approved of the single arm basket-trial designs in this context. Illustratively, ERG considered entrectinib's pooled safety-evaluable population (n=355, entrectinib-treated, with and without NTRK fusion) sufficient for safety analysis. Only, for larotrectinib, the company unjustifiably assumed equal response for all tumour and fusion types, in ERG's view. G-BA/IQWiG found that for the pooled analysis of the clinical studies STARTRK-2, STARTRK-1, and ALKA372-001, no results are available in the dossier regarding side effects, nor for tumour-type specific efficacy.

Compared to EMA

The EMA and HTA organisations used the same data cut-off dates for the used trials and corresponding populations, expect for HAS, which used two cut-off dates. Besides, paediatric data from STARTRK-NG was considered by EMA and NICE as part of the poled safety population (n=355), but not by HAS and IQWiG [Table 1].

Notably, while the EMA considered the wording 'satisfactory' in the MA indication an improvement to treatment strategies, NICE and HAS instead considered it ambiguous. In which line of treatment larotrectinib should be used was considered unclear. Additionally, including infantile fibrosarcoma from diagnosis without consideration of reference chemotherapy in STARTRK-2, is not compliant with the MA indication, according to HAS.

For both therapies, no uncertainties or concerns were raised relating to the interventions for any of therapies by the HTA organisations. Only the EMA was concerned about the dose of larotrectinib for children and entrectinib for adolescents, due to insufficiency of extrapolation of the available data for adult patients (16,21).

Uncertainties in CEAs

As expected, cost-effectiveness was not assessed by HAS and GBA, to minor extent by ZIN, while NICE did this rather elaborately (48).

ZIN only mentions the uncertainty whether substitution will occur and whether larotrectinib is interchangeable with entrectinib. So different market divisions are not (yet) considered. The estimated costs for duration of treatment are €148,801 or €148,731 for adult and €110,031 or €99,154-€148,731 for paediatric patients for larotrectinib and entrectinib, respectively (24,26).

Due to lack of generalisability with clinical practice population, ERG considers larotrectinib's CEA very uncertain, especially due to unreliable survival estimates after disease progression (49). Still, ERG considers the company's deterministic incremental cost-effectiveness ratio (ICER) of £16,155 per quality-adjusted life year (QALY) compared to current clinical management as promising. Although higher, entrectinib shows plausible potential for cost-effectiveness as meets the end-of-life criteria, compared to current standard of care for tumour histologies represented in its integrated efficacy analysis. Including a discount agreed upon in the commercial agreement, the base case deterministic ICER range is £49,358 per QALY compared to current therapies. Still, the ICER range was associated with considerable uncertainty, for similar reasons as larotrectinib. So, ERG recommends

neither for routine use in the NHS, as the actual ICER range may be above the threshold of what is considered 'cost-effective use of NHS resources' (33,44). Besides, according to the companies, the screening costs for identifying eligible patients should be excluded from its assessment, while NICE is yet uncertain in that regard.

Altogether, despite a plethora of uncertainties raised, and forthcoming REAs and CEAs, conditional reimbursement decisions by ZIN, NICE and HAS for (a part of) the indications applied for, show faith in the additional benefit of these novel tumour-agnostic therapies. Only IQWiG could not prove the additional benefit.

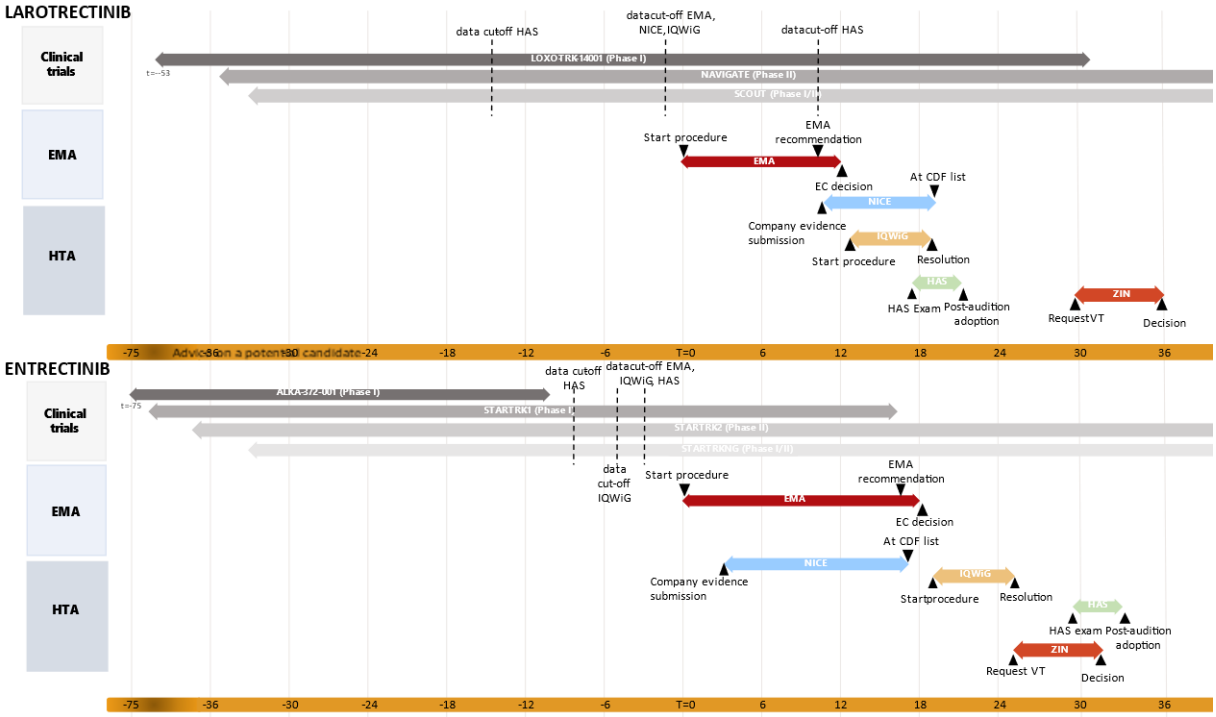

Figure 1: Overview of the complete drug life cycles of the first two EMA-approved tumour-agnostic therapies: larotrectinib and entrectinib. T=0 is set at the moment the EMA procedure was started.

Clinical guidelines and patient access

When new therapies become accessible for patients through authorization and reimbursement, their use should be incorporated in clinical guidelines. ESMO guidelines for the most prevalent tumour types with NTRK gene fusions were consulted for this purpose. Solid tumours with the most prevalent NTRK gene fusions, as well as those represented in the trial patient populations, include the following: rare cancer types include secretory breast carcinomas, mammary analogue secretory carcinomas of the salivary gland, and congenital fibrosarcomas, and more common cancer types, including gastrointestinal stromal tumours (GIST), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), salivary, thyroid, brain, and sarcomas (3,16,21,50).

Tumour-agnostic guidelines

Interestingly, as an exception to the rule of tumour-specific indications, ESMO considers the histology-independent 'refractory NTRK fusion-positive cancers' as a separate tumour type, for which larotrectinib and entrectinib are the only recommended therapies. Both have an ESMO-Magnitude of Clinical Benefit Scale (EMSO-MCBS) non-curative score of 3, the highest grade possible according to evaluation form 3 (51,52). This form accounts for single-arm studies of orphan diseases with PFS or ORR as primary outcomes (53). However, there are no signs that a corresponding ESMO guideline will

soon be published. Still, on September 2, 2020, an expert recommendation from the World Sarcoma Network was published, regarding the diagnosis and management of this specific tumour-agnostic indication, recommending larotrectinib and entrectinib (54). While regulatory and HTA organisations appear rather reluctant in regarding NTRK gene fusions as true oncogenic drivers, this expert panel emphasised their 'pan-tumour' nature instead (54).

Tumour-specific guidelines

Possible clinical benefit for specific tumour types of larotrectinib and entrectinib was for the first time recognised for the treatment of metastatic NSCLC (55). As they were not recommended for routine care at that time, enrolment in clinical trials was encouraged (55). Later, both therapies were recommended as standard treatment for patients with advanced or metastatic NTRK-rearranged sarcoma (56). Additionally, they were recommended as later-line management of advanced/metastatic GIST, with an ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score of I-C (level of evidence III, grade of recommendation A) (57). This agrees with the regulatory and reimbursement decisions, supporting the observed clinical benefit of both drugs in the presence of NTRK gene fusions during clinical trials (57).

In the ESMO thyroid cancer guideline, larotrectinib was regarded as treatment option for (poorly) differentiated but not anaplastic thyroid cancers, probably because the latter were not specifically studied in clinical trials, despite targetable NTRK rearrangements (58). Presumably, entrectinib was not considered, as it was not yet authorised.

Recently, although not explicitly recommended for the treatment of rare secretory breast carcinomas, both therapies are considered as relevant therapies in the context of 'tissue- and site agnostic' personalised medicine in the metastatic breast cancer (MBC) guideline (59,60). Even, once subtype-specific standard therapies have been exhausted, screening for NTRK gene fusions is recommended (prevalence <0.1% in MBC) (60).

Finally, for salivary gland related guidelines, ESMO does not include larotrectinib and entrectinib, but its American equivalent, the American Society of Clinical Oncology (ASCO), recommends both drugs for salivary gland malignancies (type: evidence based; evidence quality: low; strength of recommendation: moderate) (61–63). Patients harbouring NTRK gene-fusion positive salivary gland secretory carcinomas, without a known acquired resistance, are even recommended first-line or subsequent-line NTRK inhibitor treatments rather than chemotherapy, based on the high ORR and favourable toxicity profile of the clinical trial patient population (61).

Altogether, out of all the relevant tumour-specific guidelines for the tumour types that frequently harbour NTRK gene fusions or were studied in pivotal clinical trials, larotrectinib was only explicitly recommended in 3 out of 13, and entrectinib in 2 out of 13 [Table 5]. The number of recommendations will likely increase in time, as most guidelines were published around the authorisation of larotrectinib and entrectinib (between 2018 and 2020), two in 2014 and 2016. Besides, updated recommendations for the management during the current COVID-19 pandemic focused on securing sufficient health care for these cancer patients, without reporting any new therapies.

Patient access

So far, evidence of any revenues from both companies is lacking. So, an estimation of the number of patients, outside of the clinical trials, that have received the therapies until now, is yet unclear. In other respects, Bayer's financial reports for 2021 were not published yet, but are expected soon. The financial report of Roche stated that the intangible asset in use, referring to its intellectual property, Rozlytrek (acquired from Ignyta) has a net book value of 1.281 million of CHF, with a remaining amortisation period of 10 years (64). In Bayer's 2020 Annual Report, the patent expiration date was 2029 in Germany, France, and the U.K., it was applied for extension (65).

	Larotrectinib and/or entrectinib mentioned / recommended	*Author*	*Ref.*
ESMO guideline			
High-grade glioma	-	Stupp *et al*., 2014	(66)
Metastatic colorectal cancer	-	Van Cutsem *et al.*, 2016	(67)
Metastatic non-small cell lung cancer	Both, promising	Planchard *et al*., 2018	(55)
Thyroid cancer	Larotrectinib, recommended	Filetti *et al*., 2019	(58)
Cutaneous melanoma	-	Michielin *et al*., 2019	(68)
Advanced breast cancer	Both, 'TRK inhibitors' mentioned	Cardoso *et al*., 2020	(60)
Neurological and vascular complications of primary and secondary brain tumours	-	Roth *et al*., 2020	(69)
Metastatic breast cancer	Both, mentioned	Gennari *et al*., 2021	(59)
Soft tissue and visceral sarcomas	Both, recommended	Gronchi *et al.,* 2021	(56)
Brain metastasis from solid tumours	-	Le Rhun *et al*., 2021	(70)
Gastrointestinal stromal tumours	Both, recommended	Casali *et al*., 2022	(57)
ESMO consensus conference recommendations			
Locoregional melanoma	-	Michielin *et al*., 2020	(71)
Metastatic melanoma	-	Keilholz *et al*., 2020	(72)
Expert recommendations			
TRK fusion sarcomas: expert recommendations from the World Sarcoma Network	Both, recommended	Demetri *et al*., 2020	(54)
ASCO guideline			
Management of Salivary Gland Malignancy	Both, recommended	Geiger *et al*., 2020	(61)

Table 5. Overview of relevant clinical guidelines for tumour-agnostic and tumour-specific guidelines and recommendations. Regarding Europe (ESMO) and USA (ASCO), and relevant expert recommendations.

Discussion

Here, for the first time, we present an overview of the complete drug lifecycle of the first two EMA-approved tumour-agnostic therapies, larotrectinib and entrectinib. Their life cycle experiences are valuable lessons for future tumour-agnostic therapies [Figure 1, A1].

Summary of findings

Clinical development of entrectinib started in 2012, and larotrectinib not until 2014, but still, their EMA procedures were not started until September 2018 and January 2019, respectively. The rarity of NTRK gene fusion tumours, and specific tumour types, complicated clinical development. Consequently, basket trials were conducted.

Both larotrectinib and entrectinib were granted orphan designation first, but those were withdrawn before CMA was granted or even the EMA procedure was initiated, respectively. Withdrawal before authorising a tumour-agnostic indication was considered crucial for granting (C)MA, according to the EPAR for larotrectinib. The complete EMA procedure took 6 months longer for entrectinib, despite PRIME and a second phase I study, possibly because more concerns were raised. Safety uncertainties were raised primarily.

Although shared uncertainties about the available evidence and consequent safety and efficacy profiles more specific uncertainties per therapy and HTA organisation were raised as well. ZIN was concerned about the sufficiency of the assessment framework, so no full assessment was performed. Rather conditional inclusion in the national health insurance was recommended, along with additional data gathering and developing an appropriate assessment framework in this novel context. NICE was particularly concerned about the generalisability of the trial populations with the clinical practice population. HAS showed strong disapproval of the downgraded methodology of using uncontrolled, single arm basket trials. IQWiG was most uncertain about the absence of comparative data, due to an infeasible comparison with the appropriate comparator therapy. Still, all HTA organisations recommended both therapies for inclusion in national reimbursement lists based on the tumour-agnostic indication. However, in Germany, the extent of reimbursement is unclear. And in France, larotrectinib is only reimbursed for infantile fibrosarcoma and other soft tissue sarcomas, while entrectinib was not reimbursed at all.

Until now, both therapies have been mentioned and recommended as treatment options in only a few tumour type-specific guidelines. However, this number may increase, and possibly an actual NTRK-tumour specific guideline may be published, as an addition to the published expert recommendation. Finally, evidence of any revenues from both companies is lacking, impeding an estimation of the number of patients. However, in March 2022, Bayer's annual report is anticipated, possibly enabling more insight.

In context

The exact reasons why EMA considered withdrawal of orphan designations vital for larotrectinib, are unclear and little is reported about the reasons for withdrawal in general (73). Interestingly, the four rare tumour types for which larotrectinib was initially granted orphan designation, actually represent the most prevalent tumour types with NTRK gene fusions (16,21).

As reported before by this group, the EMA proposed applying for CMA, as a rescue option when it appeared that regular MAA would not be successful (23). Indeed, this option has now allowed market authorisation.

Notably, a considerable observation is that entrectinib was involved in the PRIME scheme, while to our knowledge, larotrectinib was not. And conversely, larotrectinib was granted accelerated assessment, although it was later withdrawn, while entrectinib was not granted this in the first place. Perhaps, by this time, the EMA may have considered this procedure unsuitable for a similar tumour-

agnostic indication, as well as its not being a major health interest.

A conditional reimbursement option is absent in Germany, so as for most new medicines, reimbursement starts upon (C)MA. Subsequent assessment of the clinical benefit by GBA/IQWiG provides grounds for negotiating its reimbursable price. As for most therapies, despite an unproven additional benefit, larotrectinib and entrectinib are both included in Annex XII (74,75). Notably, in their review, Brogaard *et al.* (2021) stated that "both therapies were categorised as having no added benefit, while in Denmark an added benefit could not be determined" (75). However, we argue that this is actually the case for Germany as well, for an adequate benefit assessment could merely not be performed, according to the GBA justification.

Regarding the decision-framework, the Dutch conditional inclusion (VT) framework was temporarily expanded, specifically for tumour-agnostic therapies (76). In contrast, Murphy *et al.* (2022) reported recently, that NICE had thoroughly reviewed its decision framework, in anticipation of the assessment of these novel therapies, and modelled it to allow adequate assessment (29). Strikingly enough, the assessment procedure at NICE was the longest of all countries considered here. To what extent this is different from other NICE assessment durations, or if it due to an adapted framework, or other unforeseeable factors, is yet to be studied.

While GBA did not consider larotrectinib an appropriate comparator therapy for entrectinib, recently, Carlson *et al.* (2022) compared their effectiveness (50). Upon matching-adjusted indirect comparison and simulation, survival outcomes suggest a greater benefit with larotrectinib than entrectinib for a variety of NTRK gene fusion positive tumour types (50). More specifically, Roth *et al.* (2020) assessed the long-term effectiveness in metastatic NSCLC, using a partitioned survival model and lifetime survival curves (77). This comparison was also favourable for larotrectinib over entrectinib (77).

Limitations

As the current search methodology may not consider all available, or openly accessible, data valuable information may be missing, even stated within the abundance of data reviewed. Of course, confidential documents regarding prices or study outcomes will remain inaccessible.

Comparing HTA organisations and their procedures, while still acknowledging their incomparable differences, is complicated, and may be subjected to misguided similarities. However, to improve accurate understanding of the facilitators and barriers for patient access, interviewing the different stakeholders would be most valuable.

Although no other tumour-agnostic therapies are expected to apply for market approval in the near future, still individual complicated aspects observed in this specific group of medicinal products are relevant for other new therapies (78,79). Consequently, the insights obtained from these novel therapies are translational, and may benefit patient access to therapies beyond a tumour-agnostic approach.

Future research perspectives

If the post-approval imposed measures, including the SOBs, will account and remove uncertainties raised by the EMA, and possibly HTA organisations, is of substantial importance and to what extent this is in agreement with previous studies (80). If indeed, this may improve clinical trial designs and requirements for other (tumour-agnostic) therapies. For instance, the post-approval non-interventional ON-TRK study for larotrectinib, for which no results are published yet, may improve decision making outcomes (81).

Finally, interviewing stakeholders involved would provide better insight in the actual strengths and limitations for decision-making, in addition to the published literature.

References

1. Chu P, Batson S, Hodgson M, Mitchell CR, Steenrod A. Systematic review of neurotrophic tropomyosin-related kinase inhibition as a tumor-agnostic management strategy. Futur Oncol [Internet]. 2020 Jan 16 [cited 2022 Jan 19];16(4):61–74. Available from: https://www.futuremedicine.com/doi/abs/10.2217/fon-2019-0534
2. Pollack M, Keating K, Wissinger E, Jackson L, Sarnes E, Cuffel B. Transforming approaches to treating TRK fusion cancer: historical comparison of larotrectinib and histology-specific therapies. Curr Med Res Opin [Internet]. 2021 [cited 2022 Jan 21];37(1):59–70. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=icmo20
3. Carmagnani Pestana R, Sen S, Hobbs BP, Hong DS. Histology-agnostic drug development — considering issues beyond the tissue. [cited 2022 Jan 18]; Available from: www.nature.com/nrclinonc
4. Looney A-M, Nawaz K, Webster RM. Tumour-agnostic therapies. 2020 Jun [cited 2022 Jan 18];19:383–284. Available from: https://doi.org/10.1038/d41573-020-00015-1
5. Krebs MG, Blay JY, Le Tourneau C, Hong D, Veronese L, Antoniou M, et al. Intrapatient comparisons of efficacy in a single-arm trial of entrectinib in tumour-agnostic indications. ESMO Open [Internet]. 2021 Apr 1 [cited 2022 Jan 21];6(2):100072. Available from: /pmc/articles/PMC8103537/
6. Doebele RC, Davis LE, Vaishnavi A, Le AT, Estrada-Bernal A, Keysar S, et al. An oncogenic NTRK fusion in a soft tissue sarcoma patient with response to the tropomyosin-related kinase (TRK) inhibitor LOXO-101. Cancer Discov [Internet]. 2015 Oct 1 [cited 2022 Jan 19];5(10):1049. Available from: /pmc/articles/PMC4635026/
7. Drilon A, Siena S, Ou SHI, Patel M, Ahn MJ, Lee J, et al. Safety and Antitumor Activity of the Multi-Targeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib (RXDX-101): Combined Results from Two Phase 1 Trials (ALKA-372-001 and STARTRK-1). Cancer Discov [Internet]. 2017 Apr 1 [cited 2022 Jan 21];7(4):400. Available from: /pmc/articles/PMC5380583/
8. Drilon A, Nagasubramanian R, Blake JF, Ku N, Tuch BB, Ebata K, et al. A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion-Positive Solid Tumors. Cancer Discov [Internet]. 2017 Sep 1 [cited 2022 Jan 19];7(9):963. Available from: /pmc/articles/PMC5581710/
9. Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol [Internet]. 2020 Apr 1 [cited 2022 Feb 27];21(4):531. Available from: /pmc/articles/PMC7497841/
10. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med [Internet]. 2018 Feb 22 [cited 2022 Feb 27];378(8):731–9. Available from: https://pubmed.ncbi.nlm.nih.gov/29466156/
11. Hong DS, Bauer TM, Lee JJ, Dowlati A, Brose MS, Farago AF, et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol Off J Eur Soc Med Oncol [Internet]. 2019 Feb 1 [cited 2022 Feb 27];30(2):325–31. Available from: https://pubmed.ncbi.nlm.nih.gov/30624546/
12. Laetsch TW, DuBois SG, Mascarenhas L, Turpin B, Federman N, Albert CM, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol [Internet]. 2018 May 1 [cited 2022 Feb 27];19(5):705–14. Available from: https://pubmed.ncbi.nlm.nih.gov/29606586/
13. DuBois SG, Laetsch TW, Federman N, Turpin BK, Albert CM, Nagasubramanian R, et al. The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. Cancer [Internet]. 2018 Nov 1 [cited 2022 Feb 27];124(21):4241–7. Available from: https://pubmed.ncbi.nlm.nih.gov/30204247/
14. Paz-Ares L, Barlesi F, Siena S, Ahn MJ, Drilon A, Conley A, et al. Patient-reported outcomes from STARTRK-2: a global phase II basket study of entrectinib for ROS1 fusion-positive non-small-cell lung cancer and NTRK fusion-positive solid tumours. ESMO Open [Internet]. 2021 Jun 1 [cited 2022 Jan 21];6(3):100113. Available from: /pmc/articles/PMC8100628/
15. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol [Internet]. 2020 Feb 1 [cited 2022 Feb 27];21(2):271–82. Available from: http://www.thelancet.com/article/S1470204519306916/fulltext
16. CHMP. Committee for Medicinal Products for Human Use (CHMP) Assessment report for Vitrakvi (larotrectinib) [Internet]. 2019 Jul [cited 2022 Jan 28]. Available from:

https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi
17. Frederique D. Committee for Orphan Medicinal Products Orphan designation withdrawal assessment report for Vitrakvi (larotrectinib) [Internet]. 2019 Jul [cited 2022 Jan 28]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi#product-information-section
18. Medicines Agency E. Public summary of opinion on orphan designation N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide for treatment of neuroblastoma. 2016 [cited 2022 Feb 27]; Available from: www.ema.europa.eu/contact
19. EU/3/15/1580 | European Medicines Agency [Internet]. [cited 2022 Feb 27]. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151580
20. Commsion Implementing Decision relating to the designation of "N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide" as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council [Internet]. Bruxelles; 2015 Nov [cited 2022 Feb 27]. Available from: https://ec.europa.eu/health/documents/community-register/html/o1580.htm#mod_download
21. CHMP. Committee for Medicinal Products for Human Use (CHMP) CHMP assessment report for Rozlytrek (entrectinib) [Internet]. 2020 May [cited 2022 Jan 28]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/rozlytrek
22. PRIME: priority medicines | European Medicines Agency [Internet]. [cited 2022 Feb 27]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
23. Hoekman J, Boon WPC, Bouvy JC, Ebbers HC, De Jong JP, De Bruin ML. Use of the conditional marketing authorization pathway for oncology medicines in Europe. Clin Pharmacol Ther [Internet]. 2015 Nov 1 [cited 2022 Jan 28];98(5):534–41. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/cpt.174
24. Advies over kandidaat voorwaardelijke toelating larotrectinib (Vitrakvi®) | Advies | Zorginstituut Nederland [Internet]. [cited 2022 Feb 27]. Available from: https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/03/10/advies-over-kandidaat-voorwaardelijke-toelating-larotrectinib-vitrakvi
25. Vervolgadvies over voorwaardelijke toelating larotrectinib (Vitrakvi®) | Advies | Zorginstituut Nederland [Internet]. [cited 2022 Feb 27]. Available from: https://www.zorginstituutnederland.nl/werkagenda/publicaties/adviezen/2021/08/16/vervolgadvies-over-voorwaardelijke-toelating-larotrectinib-vitrakvi
26. Advies over kandidaat voorwaardelijke toelating entrectinib (Rozlytrek®) | Advies | Zorginstituut Nederland [Internet]. [cited 2022 Feb 27]. Available from: https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/03/10/advies-over-kandidaat-voorwaardelijke-toelating-entrectinib-rozlytrek
27. Vervolgadvies over voorwaardelijke toelating entrectinib (Rozlytrek®) | Advies | Zorginstituut Nederland [Internet]. [cited 2022 Feb 27]. Available from: https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/08/16/vervolgadvies-over-voorwaardelijke-toelating-entrectinib-rozlytrek
28. Advice on a potential candidate for conditional inclusion of larotrectinib (Vitrakvi®) for solid tumours with NTRK gene fusion | Letter | National Health Care Institute [Internet]. [cited 2022 Feb 27]. Available from: https://english.zorginstituutnederland.nl/publications/reports/2021/03/10/advice-on-a-potential-candidate-for-conditional-inclusion-of-larotrectinib-vitrakvi
29. Murphy P, Glynn D, Dias S, Hodgson R, Claxton L, Beresford L, et al. Modelling approaches for histology-independent cancer drugs to inform NICE appraisals: a systematic review and decision-framework. Health Technol Assess (Rockv) [Internet]. 2022 Jan 5 [cited 2022 Jan 17];25(76):1–228. Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta25760
30. COMMISSION DE LA TRANSPARENCE AVIS DÉFINITIF Première évaluation larotrectinib (VITRAKVI). 2020 Jul.
31. Christen C, Belgodère L, Guillot B, Jumeau C, Lorence A, Kerouani-Lafaye G, et al. Access to innovation through the national early access program and clinical trials for patients with malignant melanoma. Cancer [Internet]. 2021 Jul 1 [cited 2022 Feb 23];127(13):2262–70. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.33492
32. Cosset D, Legros C, Haugen J, Meddeb L. ATU in France: The Case for Early Consideration in Local and European P&MA Strategy [Internet]. 2020 [cited 2022 Feb 23]. Available from: https://www.simon-kucher.com/nl/blog/atu-france-case-early-consideration-local-and-european-pma-strategy
33. Larotrectinib for treating NTRK fusion-positive solid tumours Technology appraisal guidance [Internet].

2020 May [cited 2022 Feb 27]. Available from: www.nice.org.uk/guidance/ta630
34. Entrectinib for treating NTRK fusion-positive solid tumours. Technology appraisal guidance. 2020 Aug 12 [cited 2022 Feb 27]; Available from: www.nice.org.uk/guidance/ta644
35. Justification to the Resolution of the Federal Joint Committe (G-BA) on an AMendment of apharmaceuticals Directive (AM-RL): Annex XII - Befefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Larotrectinib (Soli. 2020.
36. Justification to the Resolution of the Federal Joint Committe (G-BA) on an AMendment of apharmaceuticals Directive (AM-RL): Annex XII - Befefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Entrectinib (Solid. 2021.
37. Resolution of the Federal Joint Committe (G-BA) on an AMendment of apharmaceuticals Directive (AM-RL): Annex XII - Befefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Entrectinib (Solid Tumours, Histology In. 2021.
38. Bundesausschusses G, Xii A. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Larotrectinib (solide Tumore, Histologie-unabhängig). 2020.
39. wetten.nl - Regeling - Regeling zorgverzekering - BWBR0018715 [Internet]. [cited 2022 Feb 27]. Available from: https://wetten.overheid.nl/BWBR0018715/2022-01-01/#Hoofdstuk2_Paragraaf1_Sub-paragraaf1.1_Artikel2.1
40. für Qualität I, im Gesundheitswesen W. Larotrectinib (solide Tumore mit einer neurotrophen Tyrosin-Rezeptor-Kinase [NTRK]-Genfusion)-Nutzenbewertung gemäß § 35a SGB V. [cited 2022 Feb 27]; Available from: www.iqwig.de
41. für Qualität I, im Gesundheitswesen W. Entrectinib (solide Tumore mit einer neurotrophen Tyrosin-Rezeptor-Kinase [NTRK]-Genfusion)-Nutzenbewertung gemäß § 35a SGB V. 2020 [cited 2022 Feb 27]; Available from: www.iqwig.de
42. GBA. Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie und Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V Vorgang 2019-B-147 Larotrectinib [Internet]. 2019. Available from: https://www.g-ba.de/downloads/92-975-3350/2019-10-01_Informationen-zVT_D-490.pdf
43. GBA. Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie und Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V Vorgang : 2020-B-148-z Entrectinib [Internet]. 2019. Available from: https://www.g-ba.de/downloads/92-975-3350/2019-10-01_Informationen-zVT_D-490.pdf
44. Entrectinib for treating NTRK fusion-positive solid tumours : Technology Appraisal guidance [Internet]. 2020 Aug [cited 2022 Feb 7]. Available from: https://www.nice.org.uk/guidance/ta644/resources/entrectinib-for-treating-ntrk-fusionpositive-solid-tumours-pdf-82609138188997
45. Final Appraisal Document : Entrectinib for treating NTRK fusion-positive solid tumours [Internet]. 2020 Jun [cited 2022 Feb 7]. Available from: https://www.nice.org.uk/guidance/ta644/documents/final-appraisal-determination-document
46. Single Technology Appraisal Larotrectinib for treating NTRK fusion-positive advanced solid tumours [ID1299] Committee Papers.
47. COMMISSION DE LA TRANSPARENCE AVIS entrectinib (ROZLYTREK). 2021 Jul.
48. Vreman RA, Mantel-Teeuwisse AK, Hövels AM, Leufkens HGM, Goettsch WG. Differences in Health Technology Assessment Recommendations Among European Jurisdictions: The Role of Practice Variations. Value Heal [Internet]. 2020 Jan 1 [cited 2022 Feb 27];23(1):10–6. Available from: http://www.valueinhealthjournal.com/article/S1098301519323411/fulltext
49. Single Technology Appraisal Entrectinib for treating NTRK fusion-positive solid tumours [ID1512] Committee Papers SINGLE TECHNOLOGY APPRAISAL Entrectinib for treating NTRK fusion-positive solid tumours [ID1512] Contents [Internet]. 2020 Jun [cited 2022 Feb 7]. Available from: https://www.nice.org.uk/guidance/ta644/documents/committee-papers
50. Carlson J, Italiano A, Brose M, Federman N, Lassen U, Kummar S, et al. Comparative Effectiveness of Larotrectinib and Entrectinib for TRK Fusion Cancer. Suppl Featur Publ [Internet]. 2022;28(2). Available from: https://cdn.sanity.io/files/0vv8moc6/ajmc/13b29811dbaf84e23b862d5ae3c224639f6be7ed.pdf
51. Larotrectinib Scorecard ESMO-MCBS v1.1 [Internet]. [cited 2022 Feb 16]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-143-1
52. Entrectinib Scorecard ESMO-MCBS v1.1 [Internet]. [cited 2022 Feb 16]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-209-1

53. European Society for Medical Oncology (ESMO). ESMO-Magnitude of Clinical Benefit scale : Evidence-based standards for patient care A tool to assist in the prioritisation of medicines in cancer care.
54. Demetri GD, Antonescu CR, Bjerkehagen B, Bovée JVMG, Boye K, Chacón M, et al. Diagnosis and management of tropomyosin receptor kinase (TRK) fusion sarcomas: expert recommendations from the World Sarcoma Network. Ann Oncol [Internet]. 2020 Nov 1 [cited 2022 Feb 16];31(11):1506–17. Available from: http://www.annalsofoncology.org/article/S0923753420422975/fulltext
55. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol [Internet]. 2018 Oct 1 [cited 2022 Feb 16];29:iv192–237. Available from: http://www.annalsofoncology.org/article/S0923753419317107/fulltext
56. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Ann Oncol [Internet]. 2021 Nov 1 [cited 2022 Feb 26];32(11):1348–65. Available from: http://www.annalsofoncology.org/article/S0923753421021840/fulltext
57. Casali PG, Blay JY, Abecassis N, Bajpai J, Bauer S, Biagini R, et al. Gastrointestinal stromal tumours: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022 Jan 1;33(1):20–33.
58. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019 Dec 1;30(12):1856–83.
59. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021 Dec 1;32(12):1475–95.
60. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol [Internet]. 2020 Dec 1 [cited 2022 Feb 16];31(12):1623–49. Available from: http://www.annalsofoncology.org/article/S0923753420424603/fulltext
61. Geiger JL, Ismaila N, Beadle B, Caudell JJ, Chau N, Deschler D, et al. Management of salivary gland malignancy: ASCO guideline. J Clin Oncol. 2021 Jun 10;39(17).
62. Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol [Internet]. 2020 Nov 1 [cited 2022 Feb 16];31(11):1462–75. Available from: http://www.annalsofoncology.org/article/S092375342039949X/fulltext
63. Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, et al. Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2021 Apr 1 [cited 2022 Feb 16];32(4):452–65. Available from: http://www.annalsofoncology.org/article/S0923753420432107/fulltext
64. Roche Finance Report 2021.
65. Bayer-Geschäftsbericht. Bayer RESTRICTED Annual Report 2020. 2021;
66. Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis G. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. Ann Oncol [Internet]. 2014 Sep 1 [cited 2022 Feb 16];25:iii93–101. Available from: http://www.annalsofoncology.org/article/S0923753419340773/fulltext
67. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016 Aug 1;27(8):1386–422.
68. Michielin O, Van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. Ann Oncol [Internet]. 2019 Dec 1 [cited 2022 Feb 16];30(12):1884–901. Available from: http://www.annalsofoncology.org/article/S0923753420325631/fulltext
69. Roth P, Pace A, Le Rhun E, Weller M, Ay C, Cohen-Jonathan Moyal E, et al. Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up †. Ann Oncol [Internet]. 2021 Feb 1 [cited 2022 Feb 26];32(2):171–82. Available from: http://www.annalsofoncology.org/article/S0923753420431461/fulltext
70. Le Rhun E, Guckenberger M, Smits M, Dummer R, Bachelot T, Sahm F, et al. EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid

tumours. Ann Oncol [Internet]. 2021 Nov 1 [cited 2022 Feb 26];32(11):1332–47. Available from: http://www.annalsofoncology.org/article/S0923753421022146/fulltext
71. Michielin O, van Akkooi A, Lorigan P, Ascierto PA, Dummer R, Robert C, et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol [Internet]. 2020 Nov 1 [cited 2022 Feb 26];31(11):1449–61. Available from: http://www.annalsofoncology.org/article/S0923753420399403/fulltext
72. Keilholz U, Ascierto PA, Dummer R, Robert C, Lorigan P, van Akkooi A, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol [Internet]. 2020 Nov 1 [cited 2022 Feb 26];31(11):1435–48. Available from: http://www.annalsofoncology.org/article/S0923753420399397/fulltext
73. Montanaro N, Bonaldo G, Motola D. Removal of the EMA orphan designation upon request of the sponsor: cui prodest? Eur J Clin Pharmacol [Internet]. 2021 Jul 1 [cited 2022 Feb 27];77(7):1057–63. Available from: https://link-springer-com.proxy.library.uu.nl/article/10.1007/s00228-021-03096-y
74. Wenzl M, Paris V. 2 | PHARMACEUTICAL REIMBURSEMENT AND PRICING IN GERMANY © OECD 2018. 2018;
75. Brogaard NJ, Steuten L, Bréant A. Learnings from the Assessments of Entrectinib and Larotrectinib: Health Technology Assessment Challenges Associated with Tumour-Agnostic Therapies | OHE. 2021; Available from: https://www.ohe.org/publications/learnings-assessments-entrectinib-and-larotrectinib-health-technology-assessment#
76. Kamerbrief over beleidskader voorwaardelijke toelating geneesmiddelen | Kamerstuk | Rijksoverheid.nl [Internet]. 2019 [cited 2022 Feb 27]. Available from: https://www.rijksoverheid.nl/documenten/kamerstukken/2019/10/22/kamerbrief-over-beleidskader-voorwaardelijke-toelating-geneesmiddelen
77. Roth JA, Carlson JJ, Xia F, Williamson T, Sullivan SD. The potential long-term comparative effectiveness of larotrectinib and entrectinib for second-line treatment of TRK fusion-positive metastatic lung cancer. J Manag Care Spec Pharm [Internet]. 2020 Aug 1 [cited 2022 Jan 21];26(8):981–6. Available from: https://www.jmcp.org/doi/abs/10.18553/jmcp.2020.20045
78. The Drug Rediscovery Protocol (DRUP Trial) [Internet]. [cited 2022 Feb 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT02925234?term=NCT02925234&rank=1
79. Horizonscan geneesmiddelen [Internet]. [cited 2022 Feb 27]. Available from: https://www.horizonscangeneesmiddelen.nl/
80. Vreman RA, Id ¶, Bloem LT, Van Oirschot S, Hoekman J, Van Der Elst ME, et al. The Role of Regulator-Imposed Post-Approval Studies in Health Technology Assessments for Conditionally Approved Drugs. Int J Heal Policy Manag [Internet]. 2020 [cited 2022 Jan 17];2020:1–9. Available from: http://ijhpm.com
81. Leyvraz S, Yang J.-H, Casali PG, Castro G, Kim ES, Lassen UN, et al. 604TiP ON-TRK: A non-interventional study of larotrectinib in patients with TRK fusion cancer. Ann Oncol [Internet]. 2020 Sep 1 [cited 2022 Feb 27];31:S503. Available from: http://www.annalsofoncology.org/article/S0923753420407148/fulltext

Appendix 1 – Overview of actions during drug lifecycles of larotrectinib and entrectinib

Actions during drug-lifecycle of larotrectinib	**Date**	**t**(months)	**Actions during drug-lifecycle of entrectinib**	**Date**	**t**(months)
			Start first-in-human study, phase I (ALKA-372-001)	26 October 2012	t=-75 m
Start phase-1 dose-escalation study (LOXO-TRK-14001)	25 April 2014	T=-52,6 m	Start phase-1 dose-escalation study (STARTRK-1)	28 July 2014	t=-54 m
			CHMP positive opinion for orphan designation for treatment of neuroblastoma	8 October 2015	
			The applicant received Scientific Advice from the CHMP on the development for the indication from the CHMP (EMEA/H/SA/3140/1/2015/SME/III)	22 October 2015	T=--39 m
			EC granted orphan designation (EU/3/15/1580) to Pharma Gateway AB, Sweden for N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2- (tetrahydro-2H-pyran-4-ylamino)benzamide (entrectinib) for treatment of neuroblastoma	11 November 2015	
Start Phase II study (NAVIGATE)	25 October 2015	T=-34,6 m	Start Phase II study (STARTRK-2)	19 November 2015	t=-38 m
			Public summary of opinion on orphan designation for treatment of neuroblastoma	5 January 2016	
			Stop enrolment STARTRK-1?	March 2016	
Start phase I/II paediatric (SCOUT)	21 December 2015	T=-33 m	Start phase I/II paediatric study (STARTRK-NG)	3 May 2016	t=-33 m
Orphan designation for the treatment of soft tissue sarcoma	11 January 2016				
Cut-off date (1 of 2) for all larotrectinib studies for HAS	17 July 2017	T=-14	The applicant received Scientific Advice from the CHMP on the development for the indication from the CHMP (EMEA/H/SA/3140/2/2017/SME/II)	20 July 2017	
Eligibility for centralised procedure agreed upon by EMA/CHMP	14 September 2017		Eligibility for centralised procedure agreed upon by EMA/CHMP	12 October 2017	t=-15,6 m
			Rozlytrek is granted eligibility to PRIME in the indication related to NTRK fusion positive solid tumours	13 October 2017	t=-15,6 m
Orphan designation for the treatment of salivary gland cancer	21 March 2018		The applicant received Scientific Advice from the CHMP on the development for the indication from the CHMP (EMEA/H/SA/3140/3/2017/SME/II, EMEA/H/SA/3140/2/FU/1/2017/SME/II and EMEA/H/SA/3140/4/2017/SME/I)	9 November 2017	
The application was received by the EMA	15 June 2018		Kick-off meeting PRIME support	5 February 2018	t=-11,8 m
Accelerated Assessment procedure was granted by CHMP	26 July 2018		ALKA-372-001 completed	20 March 2018	t=-10 m
Cut-off date for EMA, NICE, and IQWiG	30 July 2018	T=-1,5 m	HAS interim analysis cut-off date	31 May 2018	t=-8 m

Bayer AG submitted application for MAA	24 August 2018		The applicant received Scientific Advice from the CHMP on the development for the indication from the CHMP (EMEA/H/SA/3140/FU/1/2018/PR/I)	26 July 2018	
The procedure started on	**13 September 2018**	**T=0**	IQWiG cut-off date	31 August 2018	t=-5 m
Orphan designation for the treatment of glioma	19 November 2018		Data cut-off date for EMA, IQWiG, and additional HAS analysis	31 October 2018	t=-3 m
Orphan designation for the treatment of papillary thyroid cancer	19 November 2018		Orphan designation for treatment of neuroblastoma withdrawn from Community Register of designated Orphan Medicinal Products on request of Sponsor (Pharma Gateway AB, Sweden)	17 December 2018	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 December 2018		The application was received by the EMA	7 January 2019	
The Procedure changed from Accelerated to normal Timetable after a clarification meeting	17 December 2018		**The procedure started on**	**30 January 2019**	**t=0**
Applicant's submitted responses to the CHMP consolidated List of Questions	25 January 2019				
Scientific Advisory Group (SAG) on Oncology was convened to address questions raised by the CHMP	27 February 2019		Company evidence submission for reimbursement to NICE	20 May 2019	t=3,6 m
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members	5 March 2019		The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	29 May 2019	
ANSM grants a cohort Temporary Authorization for Use (cATU) for "LAROTRECTINIB is indicated as monotherapy in the treatment of adult and pediatric patients from a months, suffering from locally advanced or metastatic solid tumors presenting an NTRK (Neurotrophic Tyrosine Receptor Kinase) fusion, refractory to standard treatments or in the absence of an appropriate therapeutic alternative"	13 March 2019				
Cohort ATU actually started (after order of 8 April 2019)	12 April 2019		Applicant's submitted responses to the CHMP consolidated List of Questions	13 August 2019	
Company evidence submission for reimbursement to NICE [not final]	June 2019		ACT approved by G-BA/IGWiG	27 August 2019	t=6,9 m
All orphan designations granted for larotrectinib withdrawn	11 July 2019		The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members	23 September 2019	
Cut-off date (2 of 2) for HAS	15 July 2019	T=10 m			
Data cut-off for IQWiG (as commissioned by GBA)	15 July 2019				
The CHMP adopted a report on similarity of Vitrakvi with authorised orphan medicinal product(s) on (Appendix 1)	25 July 2019				

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to VITRAKVI on	25 July 2019	T=10,4 m			
Company evidence submission for reimbursement to NICE [update]	August 2019	T≈10,8 m	The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to VITRAKVI on	28 May 2020	T=16 m
ACT approved by G-BA/IGWiG	27 August 2019	T=11,4 m			
European Commission granting conditional marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "VITRAKVI - larotrectinib", a medicinal product for human use"	19 September 2019	T=12,2 m	STARTRK-1 completed	2 June 2020	T=16,6 m
Start IQWiG procedure	15 October 2019	T=13 m	CDF MAA & at CDF list & available to new patients	25 June 2020	T=16,8 m
End of cohort ATU	12 November 2019		ACT redefined	7 July 2020	T=17,2
In ESMO Guideline for thyroid cancer regarded as treatment option for (poorly) differentiated thyroid cancers	December 2019		European Commission granting a conditional marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "Rozlytrek - entrectinib", a medicinal product for human use	31 July 2020	T=18 months
Dossier assessment IQWiG is sent to G-BA	13 January 2020		Dossier submission	5 August 2020	t=18,2 m
Publication benefit assessment by IQWiG	15 January 2020		Final NICE appraisal guidance:	12 August 2020	t=18,4
Larotrectinib is classified on list I of poisonous substances	30 January 2020				
Oral hearing	24 February 2020		IGWiG commissioned (start procedure)	1 September 2020	t=19 m
Supplementary assessment commissioned	25 February 2020		Expert recommendation of World Sarcoma Network	2 September 2020	
Addendum	13 March 2020				
HAS Exam date	4 March 2020	T=17,7 m			
Subcommittee meeting	24 March 2020				
G-BA amend drug directive in written procedure	2 April 2020	T=18,6 m			
HAS adoption date	15 april 2020	T=19 m			
At CDF list & available to new patients	21 April 2020	T=19,3 m			
CDF MEA & NICE appraisal guidance published	27 May 2020	T=20,4 m			
Audition date	24 June 2020	T=21,4 m			
Oral hearing	24 June 2020				
Post-audition adoption:	9 July 2020	T=21,9 m	Resolution & Decision into force	18 February 2021	t=24,6 m
Expert recommendation of World Sarcoma Network	2 September 2020		Request VT weesgeneesmiddelen, conditionals en exceptionals'	25 February 2021	t=24,9 m

Reimbursement for only paediatric IFS and soft tissue sarcomas terminated	1 February 2021		Follow-up advice for conditional inclusion	16 August 2021	t=30,5 m
Request VT weesgeneesmiddelen, conditionals en exceptionals':	17 February 2021	T=29,2 m			
Actual study completion date of LOXO-TRK-14001	9 April 2021	T=31 m	Administrative validation	1 April 2021	t=26 m
Larotrectinib deregistered from list of medicines benefitting from cATU	10 May 2021		HAS Exam date	30 June 2021	t=29 m
Follow-up advice for conditional inclusion	16 August 2021	T=35,1 m	CT opinion & Adoption date	21 July 2021	t=29,7m
Reimbursement decision	September 2021	T=36 m	Interim safety and efficacy analysis will be submitted.	End 2023	
In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).	30 September 2021		In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol. The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-evaluable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan.	31 March 2027	
In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE).	30 June 2024		In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis.	31 March 2027	
In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data.	31 March 2027				

Table A1. Overview of actions during drug life cycle of larotrectinib and entrectinib. Coloured actions refer to ZIN (red), NICE/ERG (blue), HAS/CT (green), IQWiG/GBA (yellow), rest (grey). Calculated t=0 refers to the date the EMA procedure started.