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REVIEW ARTICLE

Transforming approaches to treating TRK fusion cancer: historical comparison of larotrectinib and histology-specific therapies

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ABSTRACT

Objective: The results from basket trials utilized to gain regulatory approval of tumor-agnostic therapies can be difficult to interpret without the context of a comparator arm. We describe the role and efficacy of histology-based treatments to provide a historical comparison with larotrectinib.

Methods: A systematic literature review (SLR) was conducted on the clinical outcomes of current histology-based standard of care treatments used in non-small cell lung cancer, colorectal cancer, thyroid cancer, gliomas, soft tissue sarcoma, salivary gland cancer, and infantile fibrosarcoma (7 of the 21 tumor histologies in the larotrectinib trials). The review focused on advanced stage/metastatic disease to make a historical comparison with larotrectinib.

Results: Larotrectinib provides positive outcomes in both adult and pediatric patients with advanced or metastatic solid tumors known to harbor *NTRK* gene fusions across a wide range of tumor types. Although the numbers of patients per tumor type are limited, the results of this historical comparison demonstrated that larotrectinib is an efficacious treatment option when naïvely indirectly compared with historical treatments across all 7 reviewed tumor types, especially in comparison to later lines of therapy.

Conclusions: Utilizing larotrectinib as a case example across these types of historical comparisons shows that larotrectinib provides positive efficacy outcomes in TRK fusion cancer across tumor histologies known to harbor *NTRK* gene fusions that may be preferable to historical treatments.

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Introduction

The tropomyosin receptor kinase (TRK) inhibitor, larotrectinib, marks the first European Medicines Agency (EMA) approval of a tumor-agnostic therapy[1]. Larotrectinib is a potent and specific inhibitor of all three TRK proteins: TRKA, TRKB, and TRKC[2]. In addition to the EMA, the Food and Drug Administration (FDA), Agência Nacional de Vigilância Sanitária (ANVISA), Health Canada (HC), Taiwan Food and Drug Administration (TFDA), Saudi Food and Drug Administration (SFDA), and the Swiss Agency for Therapeutic Products (Swissmedic) have approved larotrectinib for use in adult or pediatric patients with solid tumors that display a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion who have disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options[3]. Larotrectinib is the first drug to be approved with a tumor-agnostic indication as the first and only indication. Since the approval of larotrectinib, entrectinib has also received approval in the US and Japan for the treatment of adult and pediatric patients (≥12 years of age) with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy[4].

Although the frequency of *NTRK* gene fusions varies by tumor localization, *NTRK* gene fusions occur in only a few thousand patients in the European Union (EU) annually, meeting the criteria of an ultra-rare disease[5]. Rare primary genomic alterations, such as *NTRK* gene fusions, pose unique problems to clinical research programs. The randomized controlled trial (RCT) design is considered methodologically the gold standard; however, in cases of a rare oncogenic driver where the prevalence in any single tumor histology is extremely low, this study design would face significant enrollment challenges[6,7]. Besides the low number of patients available for recruitment, the choice of comparator arm challenges the feasibility of designing an RCT, particularly when the targetable alteration is spread across a wide range of tumor types, all of which differ in natural history and treatment options[7]. For these reasons, there is a need to use

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novel, adaptive study designs to advance the drug development process[6,8,9]. One such design is the single-arm basket trial; in this trial design, patients who have the same molecular feature, regardless of their cancer histology, are enrolled. If efficacy and safety are identified across tumor histologies in early trials, the basket trial design becomes the registrational trial design. The EMA has recognized the need for and validity of clinical trials with adaptive characteristics in the clinical development of novel therapies[10].

However, clinical interpretation of the results from basket trials can be challenging due to the histological heterogeneity of the patient population[11]. Further, because of the single arm design, there cannot be a defined standard of care treatment compared across various tumor histologies; therefore, making time-to-event endpoints, such as survival, difficult to interpret and extrapolate to the clinical setting[12]. Despite these challenges, basket trials are being used in the drug regulatory review and approval process, and there needs to be a way to incorporate such tissue agnostic therapies into clinical practice[11]. As such, the question becomes, how does an oncology clinician take the data from an adaptive trial and apply them within a single histology to make them applicable to the patient populations they are treating? Herein, we use the example of the agnostic (histology-independent) development of larotrectinib, the first targeted therapy for *NTRK* gene fusions, to describe for the oncology practitioner one method of evaluating outcomes from the larotrectinib basket trial relative to historical, histology-based treatments. Such historical comparisons against the novel treatment approach help to put the relative clinical outcomes of larotrectinib in context for the provider. This review seeks to summarize the efficacy of treatments for select TRK fusion tumor histologies in order to conduct a historical comparison with larotrectinib.

Methods

Literature review of historical treatments for TRK fusion cancer

Historically, *NTRK* gene fusions in patients with solid tumor cancer were not routinely screened for or identified. In the minority of patients with a known *NTRK* gene fusion at diagnosis, treatment was initiated per guideline recommendations for the specific tumor histology and disease stage, where available, rather than with a therapy targeted to the oncogenic driver because of the lack of targeted treatment options available for these patients prior to the availability of larotrectinib or entrectinib. TRK fusion cancer was historically treated with a selection of chemotherapy or, potentially, biologic therapy or immunotherapy, based largely upon tumor histology[13–15].

In order to provide a thorough assessment of the historical treatments for TRK fusion cancer, a systematic literature review (SLR) evaluating patient populations within each of the relevant tumor histologies and stage of disease appropriate for larotrectinib treatment was conducted. The goal of the SLR was to provide historical data on which a generalized naïve indirect comparison of larotrectinib against current treatment approaches or standard of care could be based. The SLR excluded any historical molecularly targeted therapies due to the mutual exclusivity of oncogenic drivers[16]. The SLR was conducted for 21 histologies and in accordance with the United Kingdom (UK) National Institute for Health and Care and Excellence (NICE) guidance and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance. Bibliographic databases including MEDLINE (*via* PubMed), Embase (*via* Embase.com), and the Cochrane Library were searched for relevant studies published from database inception to February/March 2019. The database searches used medical subheading (MeSH) and Emtree index terms as well as free text terms appropriate for each database and included relevant terms to identify each patient population of interest based on tumor histology. Additional terms for specific comparators of interest, clinical outcomes, or study designs were included for some tumor histologies with a larger body of available published evidence to focus the SLR on the most pertinent data. The full search strategies for each tumor type are provided in the Supplementary Appendix. Grey literature sources, including conference abstracts and clinical trial registries, also were hand-searched for relevant information. Study selection criteria describing the population, interventions/comparators, outcomes, and study designs of interest for each SLR were defined in an SLR protocol developed *a priori*. The complete SLR protocols are available upon request from the authors. Dual screening of the literature and quality assessment of all included studies were performed by two researchers, and all data extraction was independently validated.

Tumor type and stage selection

The tumor histologies reported here represent a subset of the 21 histologies included in the larotrectinib clinical development program and include non-small cell lung cancer (NSCLC), colorectal cancer (CRC), thyroid cancer, gliomas, soft tissue sarcoma (STS) (excluding gastrointestinal stromal tumor [GIST]), salivary gland cancer, and infantile fibrosarcoma (IFS). These seven tumor types were chosen as representing both the more frequently occurring tumor types with a low reported frequency of *NTRK* gene fusions (i.e. NSCLC, CRC) as well as those more rare tumors which have a higher reported frequency of *NTRK* gene fusions (i.e. thyroid cancer, salivary gland cancer, and IFS) (Table 1). Additionally, non-GIST STS and gliomas were included as representative of a high unmet needs patient population, as these tumor types largely lack therapies that target specific oncogenic drivers. The historical data drawn from the SLR are used here to highlight the importance of this type of data in approved therapies utilizing adaptive clinical trial designs. The focus is on an "all-comer" (defined as all patients within a specific histology) patient population because *NTRK* gene fusions were not routinely screened for or identified historically prior to the approval of larotrectinib. The review also focused on advanced or metastatic disease, as this stage of disease is more representative of the TRK fusion cancer population included in the larotrectinib clinical development program.

Table 1. Global incidence and *NTRK* gene fusion frequency amongst the 7 tumor types included in this analysis.

Tumor type	Global incidence, 2018[a,17]	*NTRK* gene fusion frequency (%)
NSCLC	2,093,876	0.2[18]
CRC	1,800,977	0.5[19]
Thyroid	567,233	2–26[b,20–24]
Gliomas	296,851	0.6–25[c,19,25]
Salivary gland cancer	NR	50[d,26]
Non-GIST STS	NR	0.97[19]
IFS	NR	91[e,27–30]

[a]As reported in by IARC, Globocan 2018.
[b]*NTRK* gene fusion frequency varies in thyroid cancer as patients with iodizing radiation exposure and pediatric patients appear to have a higher frequency of *NTRK* gene fusions.
[c]*NTRK* gene fusion frequency varies in patients with gliomas as certain pediatric gliomas have been associated with a higher frequency of *NTRK* gene fusions (ranging from 5% to 25%); whereas the frequency of *NTRK* gene fusions in adult gliomas has been reported at <1% to-date.
[d]In an analysis of 30 tumor samples from patients with mammary analog secretory carcinoma of the salivary gland, 15 patients had *ETV6-NTRK3* gene fusions, whereas 10 harbored *ETV6-RET* fusions and four cases had no result of rearrangements/fusions (1 result was unanalyzable).
[d]IFS is characterized by the *ETV6-NTRK* gene fusion; however, recent data has shown that other genes may be involved, including other *NTRK* gene fusions.
Abbreviations. CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; IARC, International Agency for Research on Cancer; IFS, infantile fibrosarcoma; NSCLC, non-small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; STS, soft tissue sarcoma.

Additionally, the historical treatments included for comparison were based on tumor type and also aligned to the line of therapy in which larotrectinib would be used based on its labeled indication, which states that larotrectinib is indicated for use in pediatric and adult patients with solid tumors that harbor an *NTRK* gene fusion and are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory or alternative treatments, or that have progressed following treatment[3]; in practice, this generally means later lines of therapy for those tumor types with established standard of care treatment options.

Results

Clinical outcomes of historical treatment for specific tumor histologies that harbor NTRK *gene fusions*

In prevalent solid tumor cancer histologies harboring *NTRK* gene fusions, such as NSCLC and CRC, the histology-based treatment paradigm in the metastatic setting is continually evolving, but it is generally well-established and guideline-based. The efficacy of historical treatments for NSCLC and CRC is shown in Table 2. Despite improved outcomes with first-line treatment of NSCLC, the overall response rate (ORR) for patients with second-line or subsequent therapy utilizing histology-based treatment in metastatic NSCLC is <30%. Further, the median progression-free survival (PFS) in this same population is <6 months. Although outcomes are similar for metastatic CRC, with a median PFS ranging from 1.4 months to 13.2 months for second-line or subsequent therapy, ORR worsens through each line of therapy. In patients receiving third-line or subsequent therapy, the ORR reported ranges from 1% to 13% compared with 11% to 47.7% in the second-line setting (Table 2).

Solid tumor cancer histologies that harbor *NTRK* gene fusions and occur with a lower prevalence, including radioiodine (RAI)-refractory thyroid, glioma, STS (non-GIST), and salivary gland, are generally treated with biological therapy (non-molecularly targeted therapies such as vascular endothelial growth factor [VEGF] inhibitors), molecularly targeted therapy, or chemotherapy. The efficacy of historical treatments for thyroid and salivary gland cancer are shown in Table 2. In metastatic RAI-refractory thyroid cancer, the histology-based therapies include chemotherapy and VEGF inhibition. Although VEGF inhibitors are frequently used in this setting, the ORR in the first-line or subsequent setting is poor, ranging from 0% to 64.8% (Table 2). This same treatment pattern is commonly employed for gliomas, with VEGF inhibitors being used as single agent or in combination with chemotherapy. Although these glioma therapies can produce higher ORR (range: 63–95.2%), the median PFS in this population is poor, with the majority of studies reporting <6 months in the second or subsequent line of therapy. In patients without targetable oncogenic drivers with STS (non-GIST), the therapies for metastatic disease primarily consist of chemotherapy. Even in the first-line setting, the ORR for chemotherapy ranges from 17.2% to 44.4%, with the ORR decreasing to 13.2% as additional lines of therapy are included. Salivary gland cancer is not well studied, as the majority of data come from small, prospective studies. However, in these studies, the ORR in metastatic salivary gland cancer for chemotherapy is 31% in the first-line setting and decreases to 5% in the second-line setting. Further, the median PFS for the first-line setting is only 6 months (Table 2).

Rare solid tumor cancer histologies that harbor *NTRK* gene fusions, including IFS, differ from the above-mentioned histologies as metastatic spread of disease is uncommon, and most patients are considered curative with surgical resection alone, although 3 of 50 infants have considerable morbidity associated with surgery, including amputation[139]. Due to this risk for significant morbidity associated with surgery, many IFS patients require neoadjuvant treatment[139]. The ORR associated with neoadjuvant chemotherapy + surgery ranges from 71% to 88.9%, leaving room for improvement in this pediatric population (Table 2).

Tumor histology-based clinical outcomes comparison of historical treatment vs larotrectinib

Clinical trials for larotrectinib enrolled pediatric and adult patients with TRK fusion cancer across solid tumor histologies. The rarity of TRK fusion cancer, in addition to the lack of equipoise in tumor histologies without available standard therapies or where recommended therapies exist but fail to provide a documented and relevantly sized clinical benefit, and the expectations for patient cross-over (if an RCT were conducted) made it not feasible or appropriate to conduct a randomized trial to demonstrate improvement in overall survival (OS). Therefore, the results from the larotrectinib trials

were pooled to provide evidence of efficacy and safety per regulatory request. The data presented here are drawn from two separate data cutoffs of the pooled analysis data for larotrectinib. The first dataset, including 93 patients with solid tumor and nine patients with primary central nervous system (CNS) tumors, is independent review committee-assessed data with a data cutoff date of 30 July 2018 that were used for the EMA submission and approval; the ORR for the total population ($N = 102$, including patients with solid tumors and primary CNS tumors) was 67%[3]. The second dataset, which included the 93 patients with solid tumors from the 30 July 2018 data cutoff plus an additional 66 patients with TRK fusion solid tumors, is investigator-assessed data published by Hong et al in 2020 with a data cutoff date of 19 February 2019[31]. The ORR for the total population ($N = 159$, including only patients with solid tumors [no primary CNS tumors included in this analysis]) was 79%[31]. Each of these datasets has response rate data available by primary tumor type as outlined in Table 2.

When comparing within specific tumor histologies, larotrectinib remains an efficacious treatment option compared with historical treatments. Within NSCLC, the ORR observed for the 12 patients with NSCLC who received larotrectinib was 75%; this is higher than what has been reported to date within the historical treatment setting, as ORR in the second-line or beyond treatment setting has been reported up to 29% (Table 2). This same trend was reported in both salivary gland tumors ($n = 20$) and non-GIST STS ($n = 36$), where the ORR was 90% and 81%, respectively. Historically, the ORR for salivary gland tumors has only been reported up to 31%, and this was in the first-line setting, with second-line therapy reporting an ORR of only 5% (Table 2). In non-GIST STS, the historical ORR across lines of therapy has ranged from 13.2% to 44.4% in the first-line setting or beyond (Table 2). In CRC, there are more well-established treatment options across multiple lines of therapy; however, the response rates in the third-line setting or beyond range from 0% to 13%, falling short of the 50% response rate reported for CRC patients with *NTRK* gene fusions treated with larotrectinib ($n = 8$) (Table 2).

Discussion

Clinical trials for larotrectinib enrolled pediatric and adult patients with TRK fusion cancer across solid tumor histologies[2,30,140]. The rarity of TRK fusion cancer, in addition to the lack of equipoise in tumor histologies without available standard therapies or where recommended therapies exist but fail to provide a documented and relevantly sized clinical benefit, and the expectations for patient cross-over (if an RCT were conducted), made it not feasible or appropriate to conduct an RCT to demonstrate improvement in OS[141]. Furthermore, given the large number of primary tumor types that have different natural histories, it was not scientifically appropriate to "lump" these tumor types together into a single randomized trial[141]. Therefore, the results from the larotrectinib trials were pooled to provide evidence of efficacy and safety per regulatory request[141].

Utilizing larotrectinib as the case example across these types of historical comparisons shows that larotrectinib provides positive efficacy outcomes in TRK fusion cancer across tumor histologies known to harbor *NTRK* gene fusions that may be preferable to historical treatments. As the case example, larotrectinib has shown consistent efficacy and safety in TRK fusion cancer across multiple tumor types in both pediatric and adult patients[2,30,140]. Historical therapies for tumor histologies that harbor *NTRK* gene fusions, although lacking data specifically in TRK fusion cancer, have highly variable efficacy (Table 2). Utilizing historical data provides for a non-statistical side-by-side comparison of data that is histology-specific; comparing the data in this manner shows that larotrectinib appears to be more efficacious within these tumor types compared with historical treatments.

Safety was not a part of this review, but is an important consideration when making therapeutic decisions. Many patients with TRK fusion cancer were historically treated with chemotherapy per guideline recommendations, the adverse event (AE) profiles of which can be detrimental to patient's quality of life, leading to both short-term and long-term toxicities[142,143]. A patient's ability or willingness to tolerate such AEs, rather than uncontrolled disease or lack of potential active anticancer therapy, may rapidly become the limiting factor for treatment success[143]. TRK inhibitors offer patients an efficacious targeted therapy option with a favorable tolerability profile[3,144,145].

As precision medicine in oncology continues to progress, an increasing number of studies with adaptive designs, such as basket trials, will be conducted[9]. There are multiple tumor-agnostic therapies in development, including merestinib, TPX-0005, and selitrectinib (LOXO-195), that are being studied in an adaptive design clinical development program. Larotrectinib is one of the first agents to be studied in a tumor-agnostic manner and receive approval in the United States (US)—and the first to receive approval in the EU; as such, it provides clinicians the first opportunity to understand the clinical development program and basis for comparison for these agents[3,143]. Since the approval of larotrectinib, entrectinib has also received approval based on data from a basket trial in the US[4]. Although both larotrectinib and entrectinib are approved in a tumor-agnostic manner for TRK fusion cancer, larotrectinib is a highly selective TRK inhibitor, whereas entrectinib is a multi-kinase inhibitor with lower specificity for TRK and also specificity for ROS1 and ALK[3,4,144].

There are some drawbacks associated with this type of historical comparison. First, only ORR data is available for larotrectinib by tumor type. Due to both the small number of patients in each tumor type, and the study design for larotrectinib (single-arm, basket trial), time-to-event endpoints such as PFS and OS are not adequately characterized by tumor type. Secondly, this is just a general comparison of the outcomes of therapies in unselected, tumor histology-based patient populations vs the outcomes reported for larotrectinib across tumor histologies. These outcomes were not matched based on any demographic or clinical parameters.

Table 2. Efficacy of historical tumor histology-specific treatments.

Tumor type	Historical treatments[a]					Larotrectinib[3,31,32,33]			
	Treatment line	*N*	ORR (%)	Median PFS (months)	Median OS (months)	Data cutoff date: 30 July 2018[b]		Data cutoff date: 19 February 2019[c]	
						N	ORR (%)	*N*	ORR (%)
NSCLC	Second[d]					7	71	12	75
	Chemotherapy[34–57]	19–625	2.7–24	2.5–4.2	4.7–12.2				
	Chemotherapy + VEGF inhibitor[41,42,53,54]	76–628	23–28.9	4.5–5.8	10.5–15.2				
	Immunotherapy[34–40]	135	20	3.5	9.2				
	Second or further[e]								
	Chemotherapy[37–39,58–72]	33–612	4.3–25.5	2.5–4.3	5.9–16				
	Immunotherapy[37–39,58,61–63,66–69,73]	76–613	13.7–19	2.3–not reached	12.2–not reached				
CRC	First or further[f]					6	33	8	50
	Chemotherapy[74]	205	NR	NR	16.2–16.4				
	Second[g]								
	Chemotherapy[75–82]	17–614	11–28.5	3–10.5	4–15.5				
	Chemotherapy + VEGF inhibitor[75,76,78–81,83]	16–612	13.4–47.7	5.7–8.5	6.7–17				
	Second or further[h]								
	Chemotherapy[84–89]	24–291	0–28	1.4–6.2	9.2–14.3				
	Chemotherapy + VEGF inhibitor[84]	286	22.7	7.3	12.9				
	VEGF inhibitor[90,91]	134–505	1–3.3	1.9–3.2	6.4–10.2				
	Third[i]								
	Chemotherapy[92]	91–124	8–9	12.9–13.2	NR				
	Third or further[j]								
	Chemotherapy[92–98]	104–534	1–13	2–4.8	7.1–11.4				
	VEGF inhibitor[99]	136	4	3.2	8.8				
Thyroid cancer	First[k]					10	70	24	79
	VEGF inhibitor[100,101]	24–207	12.2	8–11	30–not reached				
	Chemotherapy[102–104]	9–56	21.4–53	1.6	5.5–6.7				
	Surgery + chemotherapy + XRT[105]	12–18	55.6–61.1	4	7				
	First or further[l]								
	VEGF inhibitor[106–110]	10–17	0–64.8	2.8–18.3	3.7–not reached				
	Chemotherapy[111,112]	11–55	NR	1.6–3.3	4–5.2				
	Chemotherapy + XRT[113]	19	NR	NR	12				
	Second or further[m]								
	VEGF inhibitor[114]	20	NR	1.9	3.9				
	Chemotherapy[115]	23–34	0	NR	4.7–12.3				
Gliomas	First or further[n]					9	11	14	36[r]
	VEGF inhibitor[116]	119	NR	NR	5.2				
	VEGF inhibitor + chemotherapy[116]	55	NR	NR	11.3				
	Second[o]								
	VEGF inhibitor[117]	32	63	23 weeks	NR				
	VEGF inhibitor ± chemotherapy[118]	40	NR	3.8	6.9				
	Second or further[p]								
	VEGF inhibitor + chemotherapy[119]	22	95.2	3	4.6				
	Chemotherapy[120–125]	15–40	NR	4.6–28	7–19.6				
	VEGF inhibitor + XRT[126]	14	NR	NR	8.4				
	Third or further[q]								
	VEGF inhibitor[127,128]	20–31	NR	2.9–8.5	12				
	Chemotherapy[129]	9	NR	12.4	NR				
Salivary gland cancer	First[s]					17	88	20	90
	Chemotherapy[130]	42	31	6	10				
	Second[t]								
	Chemotherapy[130]	18	5	3.5	4				
Non-GIST STS	First[u]					21	81	36	81

(*continued*)

Table 2. Continued.

Tumor type	Historical treatments[a]					Larotrectinib[3,31,32,33]			
	Treatment line	*N*	ORR (%)	Median PFS (months)	Median OS (months)	Data cutoff date: 30 July 2018[b]		Data cutoff date: 19 February 2019[c]	
						N	ORR (%)	*N*	ORR (%)
	Chemotherapy[131,132]	12–34	17.2–44.4	NR	NR				
	First or further[v]								
	Chemotherapy[133]	175	13.2	9.4 weeks–26.9 weeks	48 weeks				
	mTOR inhibitor[134]	29	NR	15.4	NR				
	Surgery + chemotherapy + XRT[135]	6–8	NR	2.4–3.9	12.7–46.9				
	Second or further[w]								
	VEGF inhibitor[136]	5	NR	6.5	8.9				
IFS	First[x]					13	92	28	96
	Surgery + chemotherapy[137,138]	6–20	71–88.9	NR	NR				

[a]Therapies targeted to a specific molecular alteration were excluded from this analysis on the basis that oncogenic drivers appear to be mutually exclusive.
[b]Tumor histology-specific response rate data from 30 July 2018 data cutoff date are drawn directly from the Vitrakvi (larotrectinib) summary of product characteristics and are independent review committee assessed.
[c]Tumor histology-specific response data from 19 February 2019 data cutoff date are drawn from Hong et al., 2020 for NSCLC, CRC, thyroid cancer, salivary gland cancer, STS, and IFS and from Drilon et al. 2019 and Doz et al. 2019 for gliomas; these data are investigator assessed.
[d]Nivolumab; docetaxel; docetaxel + ramucirumab; docetaxel + placebo; pemetrexed; gemcitabine.
[e]Nivolumab; docetaxel; pemetrexed; atezolizumab; pembrolizumab; BSC.
[f]Leucovorin + fluorouracil; FOLFOX; FOLFIRI; investigator's choice.
[g]Aflibercept + FOLFIRI; FOLFIRI + placebo; irinotecan; FOLFIRI; FOLFIRI + bevacizumab; ramucirumab + FOLFIRI; FOLFOX; FOLFOX + bevacizumab, bevacizumab; BSC + chemotherapy; chemotherapy + bevacizumab; leucovorin + fluorouracil; investigator's choice chemotherapy.
[h]Regorafenib + BSC; FOLFOX + bevacizumab; FOLFOX; bevacizumab; irinotecan + BSC; irinotecan; FOLFIRI; leucovorin + fluorouracil; oxaliplatin; irinotecan + oxaliplatin.
[i]Leucovorin + fluorouracil; FOLFOX; FOLFIRI; investigator's choice chemotherapy.
[j]TAS-102 + BSC; regorafenib + BSC, TAS-102, leucovorin + fluorouracil, FOLFOX.
[k]Sorafenib; paclitaxel; surgery + radiotherapy + docetaxel.
[l]Sorafenib; lenvatinib; paclitaxel + valproic acid; paclitaxel; fosbretabulin + paclitaxel/carboplatin; paclitaxel/carboplatin; pazopanib; doxorubicin + radiotherapy.
[m]Sorafenib; fosbretabulin.
[n]Bevacizumab monotherapy; bevacizumab + irinotecan.
[o]Bevacizumab monotherapy; bevacizumab + carboplatin; bevacizumab + dasatinib; bevacizumab + irinotecan; bevacizumab + lomustine; bevacizumab + temozolomide.
[p]Re-irradiation with external beam radiation therapy; bevacizumab + re-irradiation with external beam radiation therapy; temozolomide; carmustine; procarbazine, lomustine, + vincristine; bevacizumab; temozolomide + VT-122.
[q]Bevacizumab.
[r]The 24-week disease control rate (defined as complete response + partial response + stable disease) for this population with primary CNS tumors was 71%.
[s]Cisplatin + vinorelbine.
[t]Cisplatin + vinorelbine.
[u]Ifosfamide + doxorubicin; ifosfamide + etoposide; mesna + filgrastim + dexrazoxane; ifosfamide, vincristine, + dactinomycin; vincristine, dactinomycin, + cyclophosphamide; vincristine, dactinomycin, ifosfamide, + doxorubicin; cyclophosphamide monotherapy; methotrexate + vinblastine with or without dexamethasone; other systemic anti-inflammatory drugs.
[v]Multiple interventions including surgery, radiotherapy, and chemotherapy.
[w]Pazopanib.
[x]Surgery + chemotherapy; chemotherapy.
Abbreviations. BSC, best supportive care; CRC, colorectal cancer; FOLFIRI, fluorouracil, leucovorin, irinotecan; FOLFOX, fluorouracil, leucovorin, oxaliplatin; FUOX, high-dose fluorouracil plus oxaliplatin; IFS, infantile fibrosarcoma; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; STS, soft tissue sarcoma; VEGF, vascular endothelial growth factor.

Third, the numbers of patients within each tumor histology included in the larotrectinib clinical trials are low, making meaningful comparisons to historical outcomes more difficult. Also, within the comparison of response rate data, it should be noted that in the first published pooled analysis of larotrectinib including 55 patients with TRK fusion cancer, acquired drug resistance was noted in 10 patients; acquired drug resistance was defined as disease progression during treatment after a documented objective response or stable disease[2]. However, the impact of acquired drug resistance on treatment outcomes remains unknown. Finally, as stated previously, we do not know if any of the patients enrolled in the standard of care treatments had *NTRK* gene fusion-positive tumors; this is important as information pertaining to the prognosis of this patient population in relation to other genotypes or wild-type tumors is currently not available. There is limited evidence to suggest that *NTRK* gene fusions are predictive of poorer outcomes[146–149]; however, there are currently no long-term studies specifically following TRK fusion-positive cancer patients. A recent retrospective review identified 76 cases of TRK fusion-positive cancer across 17 distinct tumor types; the ORR across all first-line therapies (exclusive of TRK inhibitor therapy) in this population was 46.7% ($n = 7/15$)[150]. Further, the ORR was 62.5% ($n = 15/24$) for those patients who received chemotherapy across all lines of therapy for advanced disease and 11.1% ($n = 1/12$) for those who received immunotherapy across all lines of therapy for advanced disease[150]. It is difficult to garner outcomes from this review as the population sizes are small for efficacy data; however, patients with TRK fusion-positive cancers may respond to alternative standards of care, although efficacy of immunotherapy in the absence of other predictive biomarkers (i.e. microsatellite instability-high) appears limited[150].

When translating basket trial data into clinical practice, historical treatment comparisons are just one way in which to understand the efficacy of a tumor-agnostic therapy across tumor histology types. Other options exist, including intrapatient comparison and tools/scales developed to assess the benefit of therapies. A retrospective exploratory intrapatient comparison analysis using successive time to progression (TTP) as a way to detect whether a new agent is having a modulating effect on tumor growth effectively uses a patient as their own control. If a new agent has an antitumor effect, it will change the natural history of the disease; so, if TTP_n is greater than TTP_{n-1}, then it is likely that the new agent is having an effect on the natural history of that patient's tumor. Growth modulation index (GMI) is the ratio of the TTP_n and TTP_{n-1}, and GMI $\geq$ 1.33 was defined as a sign of clinical activity by Von Hoff[151]. Further, the European Society for Medical Oncology (ESMO) developed a validated and reproducible tool to assess the magnitude of the clinical benefit for cancer therapies[152]. Per the Magnitude of Clinical Benefit Scale (MCBS), single-arm trials in orphan disease states or those with a high unmet need that show an ORR $>$ 60%, or a median PFS $>$ 6 months, or an ORR $\geq$ 20% to $<$60% and a duration of response $\geq$9 months are considered to have the highest magnitude of clinical benefit based on a preliminary score[153]. This preliminary score is further adjusted based on toxicity (downgrade 1 level if there are $\geq$30% grade 3–4 toxicities affecting daily well-being), quality of life (QoL) (upgrade 1 level if improved QoL), or confirmatory phase 4 experience (upgrade 1 level for confirmatory, adequately sized, phase 4 experience)[153]. Use of an intrapatient analysis or validated tools allows both clinicians and decision makers to gain a greater understanding of the place in therapy of a drug for which there is no comparator arm in clinical trials.

Conclusions

In a tumor-agnostic scenario, many individual and rare tumor histologies are brought together with a common oncogenic driver. As more novel therapeutics are being studied in a tumor-agnostic manner, there will be an increasing need for level-setting the data produced from these studies with data that have been reported for historically available therapies across tumor histologies. There is no perfect method for understanding the clinical impact of these therapies in specific tumor histologies, and it is likely many different methodologies for comparison will emerge as we move further into the era of precision medicine. A few methodologies likely to play key roles in the interpretation of these data across tumor histologies include historical comparisons and intra-patient comparison of TTP/PFS on successive lines of therapy[151,152,154]. Although historical comparisons are general comparisons that do not provide statistical comparative efficacy, these types of comparisons do provide clinicians with side-by-side data for understanding the place in therapy of a novel tumor-agnostic therapy within a specific tumor histology. However, it should be noted that the status of genomic alteration is usually not known in historical studies.

In this review, we highlighted the historical treatment data for specific tumor histologies and compared them to the data from the larotrectinib basket trial. Although the numbers of patients are small, the ORR of larotrectinib is higher than what has been historically reported across most specific tumor histologies in the line of therapy where larotrectinib is most likely to be used based on the approved label; the approval for larotrectinib is in patients with TRK fusion cancer with locally advanced or metastatic disease or where surgical resection is likely to result in severe morbidity and who have no satisfactory treatment options[3]. These data provide clinicians with an understanding of where larotrectinib may best fit into treatment paradigms in specific tumor histologies. Based on its efficacy from the basket trial, larotrectinib is now included as a recommended therapy across a range of solid tumor histologies, as denoted by inclusion in 19 National Comprehensive Cancer Network (NCCN) guidelines. Considering the growing complexities of precision medicine along with increasing variation in clinical trial design, both clinicians and healthcare decision makers will need to assess therapies to determine their clinical benefit vs currently used therapies. It becomes imperative that we strive to create a reasonable basis for comparisons for these therapies so that patients not only gain access to them but

also that clinicians and healthcare decision makers have an understanding of where these therapies would provide the greatest benefit in the treatment course.

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Authors' contributions/authorship

MP helped design the SLR and subsequent targeted review and helped write the manuscript. KK helped design the SLR and helped write the manuscript. EW designed the SLR and helped write the manuscript. ES helped design the SLR and helped write the manuscript. BC helped design the SLR and helped write the manuscript.

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