The Potential of Real-World Evidence to Complement Basket Trials for Tissue-Agnostic Drugs Targeting Neurotrophic Tropomyosin-Related Kinase Gene Fusions

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INTRODUCTION

- Conventionally, tumors have been diagnosed, categorized, and treated based on their site of origin and further subdivided histologically.[1]
- The introduction of next-generation sequencing (NGS) technologies has led to a shift in treatment strategy. Tumor-agnostic therapy is one increasingly popular strategy, where treatment is tailored to target specific biomarkers regardless of tumor location.[2]
- The neurotrophic tyrosine receptor kinase (NTRK) gene is responsible for the formation of tropomyosin-related kinase (TRK) proteins, and gene fusions involving TRKs are one set of biomarkers targeted using tissue agnostic therapy.[3]
- Because NTRK gene fusions in single tumor types are rare, accounting for 0.3% across all tumor types, the evaluation of tissue agnostic drugs has relied on non-randomized controlled trials such as basket trials.[4]
- A basket trial is a study design in which study drug is tested simultaneously on patients with the same genetic mutation or biomarkers, regardless of the specificity of the cancer type. The goal is to identify whether the intervention drug is effective in treating the targeted genetic mutation or biomarker, rather than a specific type of cancer.[5]
- The approval of TRK inhibitor drugs larotrectinib and entrectinib has demonstrated the feasibility of basket trials; however, there is limited evidence of the drugs' benefits in a heterogenous, real-world patient population with NTRK gene fusion cancers present in routine clinical practice.[6]

OBJECTIVE

- This study aims to identify how alternative studies (including pooled analyses, real world studies, etc.) have been used to address the limitations of basket trials for rare patient populations treated with tissue-agnostic drugs.

METHODS

- A targeted literature review (TLR) was conducted using PubMed, Google Scholar, and Clinicaltrials.gov databases/websites for the period 2017-2022 to investigate the use of real-world data used to enhance the reliability of clinical outcomes reported in basket trials.
- The terms "tissue-agnostic drugs," "multi-cancer drugs," "basket trials," "NTRK fusion", "precision medicine"," next-generation sequencing", "precision oncology", "Gene-targeted agents", "real-world evidence", "entrectinib", " larotrectinib", " TRK fusion cancer", " Genomic profiling", "targeted therapies", " circulating tumor DNA", "NTRK tissue agnostic drugs", "real-world data and NTRK gene fusions" were used as keywords to identify the studies.
- Publications were selected based on the exclusion criteria, wherein studies were excluded if they were duplicates, irrelevant drugs, or mutations, and failed to meet the study objective **(Figure 1)**.
- Three researchers conducted the TLR along with screening the studies at the title/abstract phase. Selected publications were then independently reviewed at the full-text phase by two researchers.
- Furthermore, data extraction was carried out independently by two researchers. One researcher primarily focused on collating the population size details of the clinical studies whereas the other one summarized the findings of the real-world evidence (RWE) studies.

RESULTS

- Out of a total of 53 identified publications, 15 met the inclusion criteria, including 9 clinical studies, 1 opinion article, 2 reviews, and 3 RWE studies **(Figure 1)**.
- The clinical trials generally included patients with many different types of cancers, with as many as 19 distinct cancers included.
- Despite this, sample sizes remained small, ranging from 20-164, explaining the need to conduct single-arm trials without a comparator group **(Figure 2)**.
- These trials assessed a range of outcomes, including OS, PFS and median treatment duration (Table 2).
- In a clinical study conducted by Bokemeyer et al, 2021, data pooled from three clinical trials were analyzed to determine whether the number of prior lines of therapy or duration of advanced/metastatic (adv/met) disease affected treatment initiation with larotrectinib (NCT02122913, NCT02637687, and NCT02576431)- a total of 164 patients were included with 19 different tumor types.
- Overall, the study found that the efficacy of larotrectinib was independent of prior lines of therapy or disease course before larotrectinib initiation. The overall response rate (ORR) of patients on larotrectinib was high and sustained.
- The single-arm clinical trial of entrectinib by Krebs et al, 2021 enrolled a total of 71 patients and found that the objective response rate and the progression-free survival was longer on entrectinib versus time to discontinuation on prior therapy (60.5% and 11.2 months vs 15.8% and 2.9 months respectively).
- Three RWE studies were identified, with one study utilizing sizable data from 110 NTRK+ patients .
- Results from one study showed that using NTRK inhibitors as a first line of therapy resulted in longer median treatment durations compared to using standard lines of therapy as first-line (16.8 months vs 5.6 months respectively). Two additional RWE studies reported on overall survival (OS) estimates for the standard of care versus treatment with NTRK inhibitors for NTRK+ patients using sizable real-world data. The key findings for the RWE studies are summarized in Table 1.
- Result summary reports that all the RWE studies contained a comparator arm and considered either OS or median treatment duration as outcomes which were lagging in majority of clinical study designs **(Table 2)**.

Figure 1: PRISMA Diagram

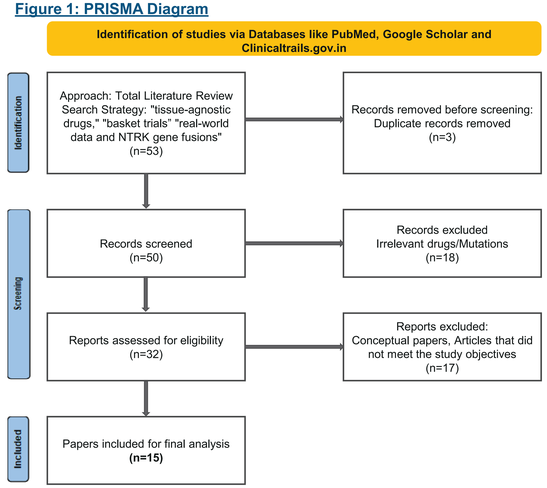

Figure 2: Sample Sizes for Basket and Pooled Trials By Tumor Type

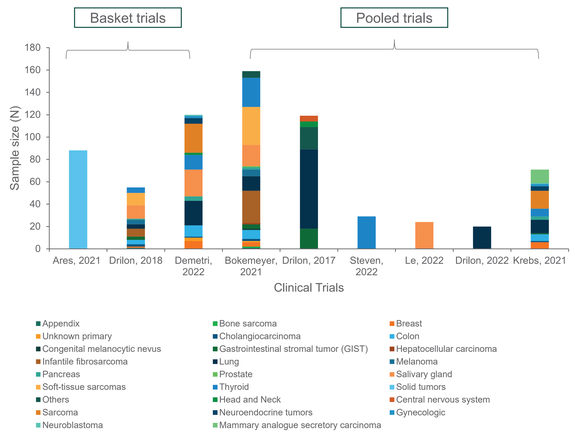

Table 1. Real-world Evidence Studies for NTRK Gene Fusion Cancers

	Author	Data source	Outcome reported	Result summary	Limitation addressed
1	Klink, et al., 2022	Multi-site patient chart abstraction by oncology practices in the USA from June to September 2020	Kaplan-Meier estimates, duration of therapy (DOT) for patients receiving a TRKi therapy versus patients receiving a non-TRKi therapy	DOT for TRKi = 16.83 months, DOT for non-TRKi = 5.56 months	Lack of active comparator
2	Hibar, et al., 2022	United States electronic health record-derived clinicogenomic data-base (Flatiron Health-Foundation Medicine)	Analysis of clinical characteristics and survival outcomes of patients with NTRK+ tumors treated in clinical practice	Median Overall survival for SoC: 10.2 months, Median Overall survival with entrectinib (integrated from three phase 1/2 trials): 33.8 months	Indirect comparisons between data from clinical trials of TRK inhibitors and the real-world assessment presented here support the hypothesis that OS in patients with NTRK+ solid tumors may be considerably improved with treatment of TRK inhibitors versus the current SoC.
3	Carsten, et al., 2023	Real-world data from patients with locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron Health/ Foundation Medicine database	Matching population characteristics and OS estimates	Median Overall survival for SoC: 10.2 months, Median Overall survival with larotrectinib: 39.7 months	Lack of head-to-head trials and limited evidence on efficacy outcomes

DOT: Duration of Treatment; TRK: Tropomyosin receptor kinase; OS: Overall Survival; SoC: Standard of Care; NTRK: Neurotrophic tyrosine receptor kinase

Table 2. Study Design and End Outcomes Reported for Real-world and Clinical Studies

Author	Study design	OS	PFS	ORR	Comparator	Sample size (>75)	Median treatment duration
Ares, 2021	Basket					■	■
Drilon, 2018	Basket		■	■			■
Demetri, 2022	Basket	■	■	■		■	■
Drilon, 2017	Pooled analysis	■	■	■		■	■
Bokemeyer, 2021	Pooled analysis		■	■		■	
Steven, 2022	Pooled analysis	■	■	■			
Le, 2022	Pooled analysis		■	■			
Drilon, 2022	Pooled analysis	■	■	■			
Krebs, 2021	Retrospective		■	■			
Klink, 2022	RWE				■	■	■
Hibar, 2022	RWE	■			■		
Carsten, 2023	RWE	■			■	■	

OS: Overall Survival; PFS: Progression Free Survival; ORR: Objective Response Rate; ■ = Reported

CONCLUSIONS

- Clinical studies were characterized by small sample sizes, multiple molecular aberrations, short follow-up periods, and the absence of a control arm, making it difficult to draw valid conclusions and to generalize their findings to routine clinical practice .
- These clinical studies can be supplemented with RWE to increase sample size, provide a comparator arm and information on outcomes not easily assessed in a clinical trial, helping to:
  - Determine the optimal timing of NTRK inhibitor initiation during therapy
  - Determine the optimal use of NTRK inhibitors in combination with other treatments
  - Generate more data on the long-term effects of NTRK inhibitors
  - Generating cost-effectiveness analyses of NTRK inhibitor therapy versus current standard of care therapies

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