INTRAPATIENT COMPARISONS IN SINGLE ARM TRIALS FOR TUMOR AGNOSTIC INDICATIONS WITH APPLICATION TO ENTRECTINIB

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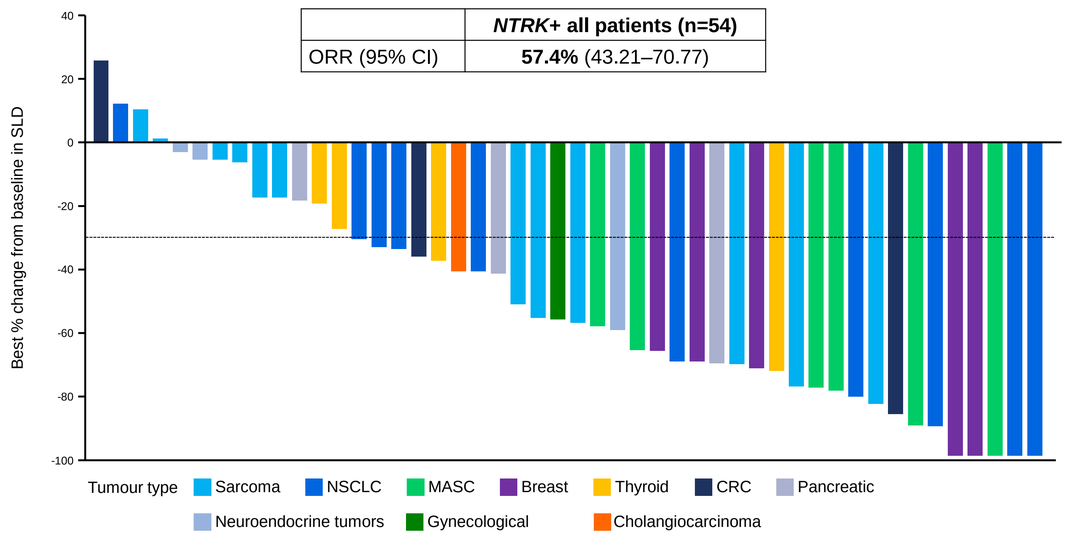
INTRODUCTION

- Comparative efficacy is a key criterion of HTA. Comparative clinical trials are challenging in rare cancers especially for tumor agnostic drugs with varying therapeutic choices.
- Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions can act as oncogenic drivers in a variety of cancer types[1]. *NTRK* gene fusions occur in ~0.3% of solid tumors[2].
- Entrectinib is a novel, systemic and central nervous system (CNS)-active, potent inhibitor of TRKA/B/C, ROS1 and ALK, specifically designed to have systemic activity as well as to cross the blood-brain barrier[3-6].
- In August 2019 the FDA granted accelerated approval to entrectinib for the treatment of adult patients with solid tumors that have an *NTRK* gene fusion[7].
- This approval was based on results from an integrated analysis of entrectinib clinical trials[8] (ALKA-372-001, STARTRK-1, STARTRK-2), which included patients with *NTRK* fusion-positive (*NTRK+*) solid tumors, including patients with CNS disease summarized in **Figure 1**.
- The objective of the presentation here is to explore intrapatient analysis as a potential approach to derive comparative evidence.

Figure 1. Summary of Integrated Summary of Effectiveness (ISE) results[8]

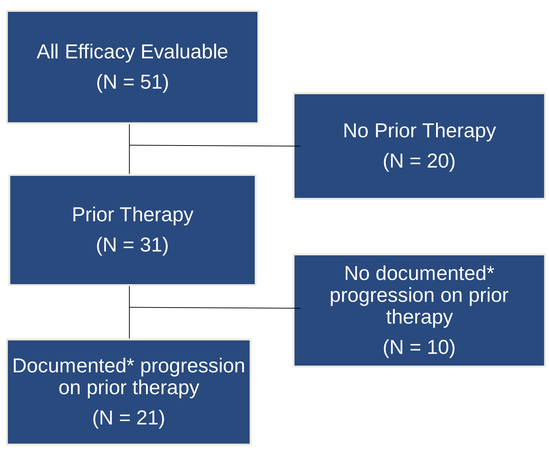
	***NTRK*+ all patients (n=54)**
ORR (95% CI)	**57.4%** (43.21–70.77)



METHODS

- Patients with *NTRK* fusion-positive cancers from STARTRK-2 who have received at least one prior systemic therapy for metastatic disease were included. Only data from the STARTRK-2 Phase II multicenter basket trial were used for analysis due to differences in eCRF design for other studies included in the ISE (leading 3 patients to be excluded).
- As a conservative approach the reasons for prior therapy discontinuation were investigated and classified as valid if there was clear documentation in the eCRF that discontinuation was due to disease progression.
- For prior therapies time to next treatment (TTNT) is defined as time from start of therapy to start of the next line of therapy/start of entrectinib. If the start date day was missing it is imputed as 1st of the month. For entrectinib TTNT is defined as time from start of entrectinib until end of entrectinib therapy. Patients ongoing therapy are censored.
- For entrectinib responses and progression-free survival (PFS) were assessed by a blinded independent central review using RECIST[8]. For prior therapies this was recorded on eCRF per standard practice.
- Time-to-event analysis used Kaplan-Meier methods as implemented using R statistical software.

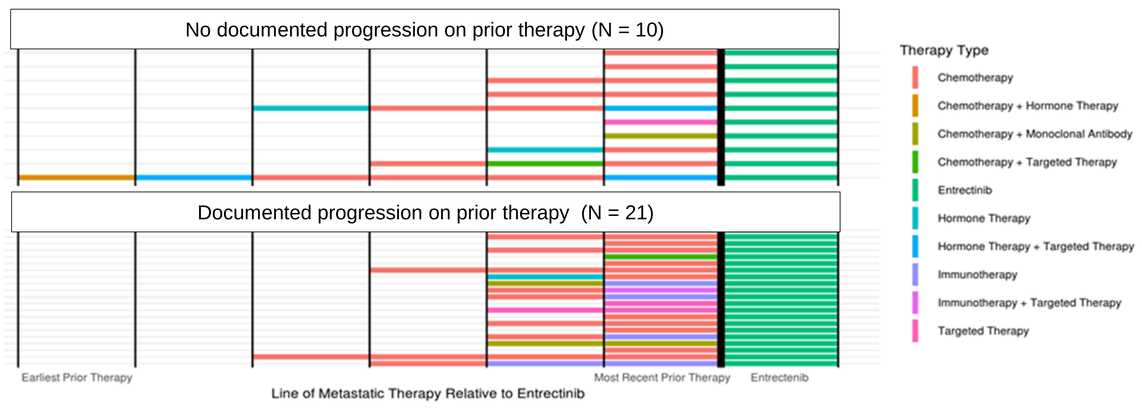
Figure 2. Disposition of patients



*Documented progression included recorded reason for discontinuation of Primary resistance (no response to therapy) (N=9), Progressive Disease (response followed by relapse) (N=7) or Other reason combined with non missing date for progression (N=5)

Tumor Type	All Efficacy Evaluable (N = 51)	Prior Therapy (N = 31)	Documented* progression on prior therapy (N = 21)
Sarcoma	25.5 %	29.0 %	23.8 %
NSCLC	17.6 %	19.4 %	19 %
MASC	11.8 %	6.5 %	4.8 %
Breast	11.8 %	9.7 %	4.8 %
Thyroid	9.8 %	9.7 %	14.3 %
CRC	5.9 %	3.2 %	4.8 %
Pancreatic	5.9 %	6.5 %	4.8 %
Neuroendocrine tumors	5.9 %	6.5 %	9.5 %
Gynaecological	3.9 %	6.5 %	9.5 %
Cholangiocarcinoma	2.0 %	3.2 %	4.8 %

Figure 3. Types of therapy received in prior lines



Tumor	Therapy Type	Preferred Term
Sarcoma	Chemotherapy	DOXORUBICIN (n = 4), GEMCITABINE - DOCETAXEL (n = 3), DOXORUBICIN -, IFOSFAMIDE - MESNA (n = 1), DOXORUBICIN HYDROCHLORIDE – IFOSFAMIDE (n = 1), GEMCITABINE (n = 1), GEMCITABINE - DOCETAXEL - DOXORUBICIN (n = 1), IFOSFAMIDE (n = 1), IFOSFAMIDE - DOXORUBICIN (n = 1), TEMOZOLOMIDE (n = 1)
Sarcoma	Chemotherapy + Monoclonal Antibody	DOXORUBICIN - OLARATUMAB (n = 1)
Sarcoma	Chemotherapy + Targeted Therapy	GEMCITABINE HYDROCHLORIDE - DOCETAXEL - PAZOPANIB (n = 1)
Sarcoma	Hormone Therapy	ANASTROZOLE (n = 1)
Sarcoma	Targeted Therapy	PAZOPANIB (n = 1)
NSCLC	Chemotherapy	CARBOPLATIN - PEMETREXED (n = 2), CARBOPLATIN - PEMETREXED DISODIUM (n = 2), CARBOPLATIN - PACLITAXEL (n = 1)
NSCLC	Chemotherapy + Monoclonal Antibody	PEMETREXED DISODIUM HEPTAHYDRATE - CARBOPLATIN - PEMETREXED DISODIUM HEPTAHYDRATE - BEVACIZUMAB - BEVACIZUMAB (n = 1)
NSCLC	Immunotherapy	PEMBROLIZUMAB (n = 3), NIVOLUMAB (n = 1)
MASC	Chemotherapy	CARBOPLATIN - CAPECITABINE (n = 1), DOXORUBICIN (n = 1), GEMCITABINE (n = 1), VINORELBINE - CISPLATIN (n = 1)
MASC	Hormone Therapy	GOSERELIN - BICALUTAMIDE (n = 1)
Breast	Chemotherapy	CAPECITABINE (n = 2), DOXORUBICIN (n = 1), GEMCITABINE HYDROCHLORIDE - PACLITAXEL (n = 1), PACLITAXEL (n = 1)
Breast	Chemotherapy + Hormone Therapy	CARBOPLATIN - PACLITAXEL - ANASTROZOLE (n = 1)
Breast	Chemotherapy + Targeted Therapy	CISPLATIN - VELIPARIB (n = 1)
Breast	Hormone Therapy	TAMOXIFEN (n = 1)
Breast	Hormone Therapy + Targeted Therapy	FULVESTRANT - PALBOCICLIB (n = 2), EXEMESTANE - EVEROLIMUS (n = 1)
Thyroid	Chemotherapy	CISPLATIN (n = 1)
Thyroid	Immunotherapy + Targeted Therapy	LAMBROLIZUMAB - LENVATINIB (n = 1)
Thyroid	Targeted Therapy	LENVATINIB (n = 2), PAZOPANIB (n = 1)
CRC	Chemotherapy + Monoclonal Antibody	IRINOTECAN - FLUOROURACIL - CETUXIMAB (n = 1), OXALIPLATIN - FLUOROURACIL - PANITUMUMAB (n = 1)
Pancreatic	Chemotherapy	CALCIUM FOLINATE W/FLUOROURACIL/IRI/08193001/ (n = 1), CISPLATIN - GEMCITABINE (n = 1), FLUOROURACIL - IRINOTECAN - OXALIPLATIN (n = 1)
Neuroendocrine tumors	Chemotherapy	CAPECITABINE - TEMOZOLOMIDE (n = 1), IRINOTECAN (n = 1)
Gynaecological	Chemotherapy	PACLITAXEL - CARBOPLATIN (n = 2), CARBOPLATIN - PEGYLATED LIPOSOMAL DOXORUBICIN HYDROCHLORIDE (n = 1)
Gynaecological	Immunotherapy	OTHER ANTINEOPLASTIC AGENTS (n = 1)
Cholangiocarcinoma	Chemotherapy	CAPECITABINE (n = 1), CISPLATIN - GEMCITABINE (n = 1)

Figure 4. Best response to therapy by line of prior systemic therapy relative to entrectinib

No documented progression on prior therapy (N = 10)

Site	Earliest Prior Therapy					Most Recent Prior Therapy	Entrectinib
T2						PR	PR
T2						PR	PR
T6					PR	SD	PR
T3					Unknown	SD	PR
T9			PD	SD	SD	Unknown	PR
T3						SD	SD
T3						SD	PD
T8					PD	Unknown	NON CR/PD
T3				SD	SD	SD	NE
T9	SD	PR	Unknown	Unknown	Unknown	Unknown	NE

Documented progression on prior therapy (N = 21)

Site	Earliest Prior Therapy			Most Recent Prior Therapy	Entrectinib
T10			SD	PR	PR
T5			PD	PR	PR
T3				SD	PR
T3			NE	SD	PR
T9				PD	PR
T4				PD	PR
T8		SD	PD	PD	PR
T3			NE	PD	PR
T2			Unknown	PD	PR
T7			Unknown	PD	PR
T2			NON CR/PD	Unknown	PR
T7				SD	SD
T7			SD	SD	SD
T6				PD	SD
T3			Unknown	Unknown	SD
T4				PD	PD
T10			SD	SD	NON CR/PD
T1			SD	SD	NE
T2				PD	NE
T3	PD	PD	SD	PD	NE
T2		Unknown	Unknown	Unknown	NE

Tumor Type
T1 = CRC
T2 = NSCLC
T3 = Sarcoma
T4 = Neuroendocrine tumors
T5 = Cholangiocarcinoma
T6 = Pancreatic
T7 = Thyroid
T8 = MASC
T9 = Breast
T10 = Gynaecological

CR = Complete Response

PR = Partial Response

SD = Stable Disease

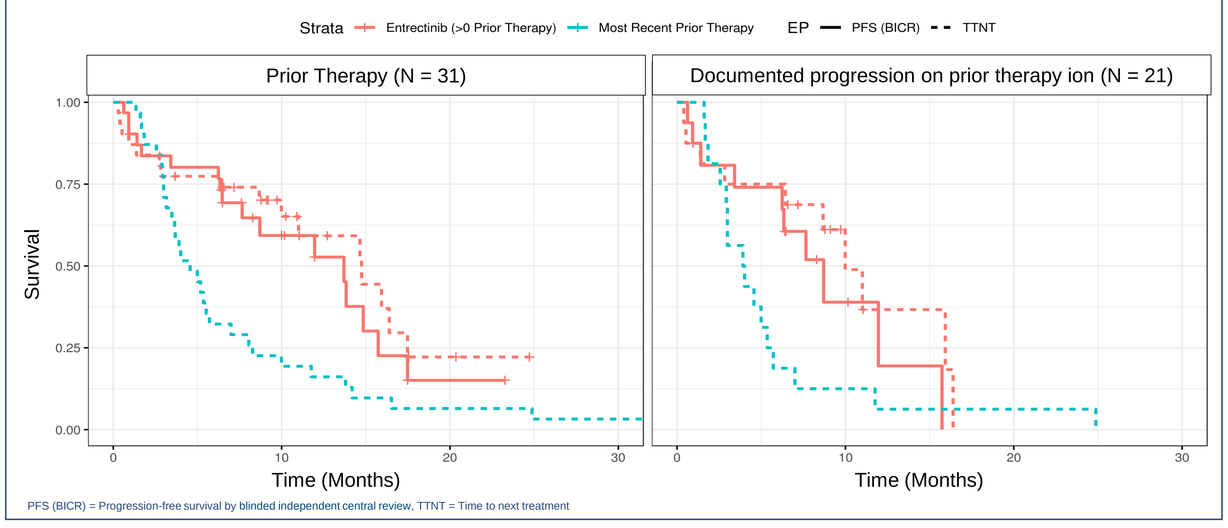
PD = Progressive Disease

NE = Not evaluable

For Entrectiib best response is as assessed by BICR. For prior therapies response is as captured on eCRF.

For Patients with no prior therapy (N=20) there were 4 CR, 9 PR, 4 SD, 1 PD, 1 NON CR/PD and 1 NE best response to Entrectinib

Figure 5. Time to next treatment entrectinib vs most recent prior therapy



PFS (BICR) = Progression-free survival by blinded independent central review, TTNT = Time to next treatment

RESULTS

- 31 patients in STARTRK-2 received prior systemic therapy of whom 21 had documented progression on the most recent prior therapy as shown in **Figure 2.**
- Of these 31 patients a variety of therapies were received including chemotherapy, immunotherapy and targeted therapies with full details provided in **Figure 3.**
- Of the 31 patients with prior therapy there were 16 responses (PR or CR) to entrectinib compared to 4 responses on most recent prior therapy. For the 21 with documented progression on prior therapy there were 11 responses on entrectinib compared to 2 responses on most recent prior therapy. A full breakdown of response by line is shown in **Figure 4**.
- Median TTNT and median PFS were similar for entrectinib and longer than estimated median TTNT in most recent prior therapy as shown in **Figure 5** and **Table 1.** The estimated median TTNT for prior therapy is similar to that seen in a weighted SoC arm derived from a review of the literature.

Table 1. Time to next treatment entrectinib vs most recent prior therapy

Subgroup	Treatment	Median (95% CI) TTNT	Median (95% CI) PFS (BICR)
Patients with Prior Therapy (N = 31)	Most recent prior therapy	4.6 (3.5, 8.0)	NA
Patients with Prior Therapy (N = 31)	Entrectinib	14.8 (10.0, NA)	13.7 (7.7, NA)
Documented progression on prior therapy (N = 21)	Most recent prior therapy	4.0 (2.9, 7.0)	NA
Documented progression on prior therapy (N = 21)	Entrectinib	10.0 (6.4, NA)	8.7 (6.2, NA)

N/A, not applicable; NR, not reported, BICR blinded independent central review, TTNT = Time to next Treatment

CAVEATS

- Given for prior therapies TTNT is used, while for entrectinib duration of therapy is used, this can be expected to be a conservative analysis. Unclear relationship between TTNT and PFS.
- Potential that patients selected into a clinical trial are not representative of overall *NTRK+* patient population.
- Given the global population recruited into STARTRK-2, there is a heterogeneous mix of prior therapies that may not be considered standard of care in all territories.
- Missing data from screening eCRF
  - for most recent prior therapy 6/31 response assessments are unknown. Overall 12/62 response assessments are unknown.
  - for most recent prior therapy 2/31 start days have the date of month imputed.

CONCLUSIONS

- The wide variety of regimens that *NTRK+* patients have received illustrates how multiple SoC/regimens would make very difficult any randomized trial with entrectinib or for other tumor agnostic therapies.
- The intrapatient response analysis indicates the trial population is not a heavily selected population predetermined to be good responders to any therapy.
- The intrapatient TTNT analysis suggests
  - despite receiving entrectinib in a later line patients tend to remain longer on therapy with entrectinib than with their most recent prior therapy
  - despite duration of entrectinib therapy being heavily censored as trial ongoing the observed median is longer than seen on most recent prior therapy
- Median duration of prior therapy is consistent with estimated literature-based weighted analysis of PFS[9].

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