Suboptimal Clinician Awareness of Appropriate *NTRK* Fusion Testing and TRK Inhibitor Use in Solid Tumors

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Background

Since late 2018, 2 TRK inhibitors—larotrectinib and entrectinib—have been approved by the EMA and FDA for treating patients with advanced solid tumors harboring an *NTRK* fusion and progressive disease or no therapeutic alternatives. Although *NTRK* fusions occur with relatively low frequency in many tumor types, it is recommended that testing for *NTRK* fusions occur as early as possible after a diagnosis of advanced disease in all patients with solid tumors to inform potential use of TRK inhibitors, which have been associated with high response rates (~60%-80%) in basket clinical trials in patients with multiple solid tumor types.

This study evaluated baseline data from a series of educational activities to determine knowledge and competence gaps in oncology healthcare professional (HCP) awareness of expert recommendations on *NTRK* fusion testing and the selection of TRK inhibitor therapy for appropriate patients.

Methods

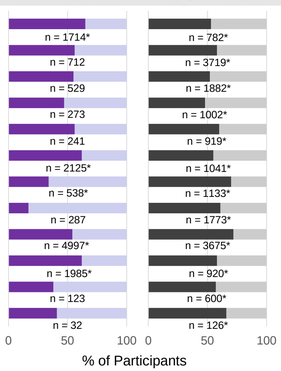
Between April 2018 and August 2021, we conducted multiple expert-led live and online educational activities for HCPs focused on *NTRK* fusion testing and/or TRK inhibitor treatment for varied solid tumors (see Educational Activities below). Each activity included baseline polling questions designed to assess HCP knowledge and practice patterns prior to the education. In this analysis, we assessed HCP responses to these questions to evaluate awareness of expert recommendations on *NTRK* fusion testing and appropriate patients for TRK inhibitor therapy.

Results

Educational Activities and Participant Demographics

Most participants in the educational activities were US-based MDs.

	Activity No. and Timing	Focus of Education
1	4.2018-4.2019	*NTRK* testing/TRKi use in solid Ca
2	6.2018-7.2019	Actionable biomarkers in solid Ca
3	5.2019-7.2020	Actionable biomarkers in solid Ca
4	6.2019-7.2020	*NTRK* testing/TRKi use in solid Ca
5	11.2019-1.2021	Novel treatments for GBM
6	1.2020-1.2021	Actionable biomarkers in GI Ca
7	2.2020-3.2021	Treating advanced lung Ca
8	5.2020-8.2021	Actionable biomarkers in solid Ca
9	7.2020-12.2020	*NTRK* testing/TRKi use in solid Ca
10	7.2020-3.2021	Treating advanced head/neck Ca
11	12.2020-4.2021	*NTRK* testing/TRKi use in lung Ca
12	6.2021	*NTRK* testing/TRKi use in solid Ca



*Indicates demographic data only available from entire educational program, including participants who may not have answered a polling question. Nonasterisk n values indicate data available for participants who answered the demographic polling question for that specific activity.

Knowledge of *NTRK* Fusions/TRK Inhibitors

Question	Optimal Response	Correctly Answered (%)	n	Activity†/ Dates
Which of the following is a first-generation TRKi indicated for *NTRK* fusion head and neck cancers?	Larotrectinib	55	20	10/7.2020-3.2021
Which of the following types of CRC is enriched with *NTRK* fusions?	dMMR/MSI-high	57	240	6 + 9/1.2020-1.2021
Which of the following is a selective second-generation TRKi for which clinical trials are currently enrolling patients who have progressed on a first-generation TRKi?	Selitrectinib	19	113	9/7.2020-12.2020

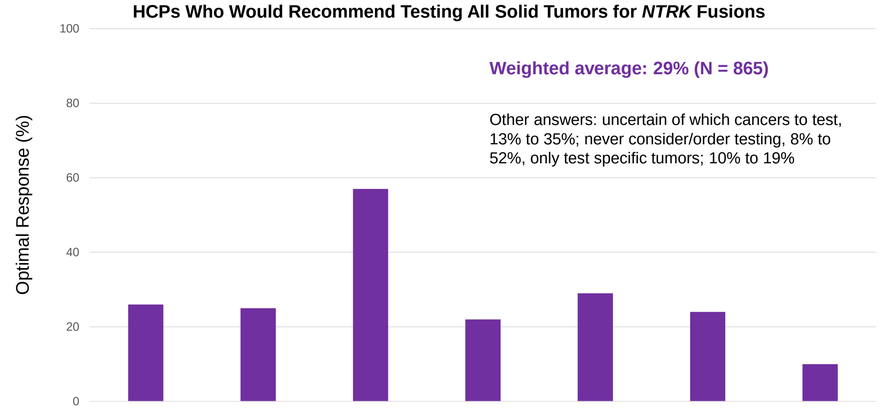
Results

Testing for *NTRK* Fusions

Across educational activities, only 29% of HCPs test all solid tumors for *NTRK* fusions. The percentage of HCPs who test has not improved substantially over time.

Assessment: HCPs were asked 1 of the following:
- In your current practice, for patients with which of the following solid tumors would you consider using broad-based molecular profiling to test for *NTRK* fusions?
- In your current practice, for which cancers do you typically order molecular profiling to test for *NTRK* fusions?

Optimal response: **All solid tumors**



Activity No.†	1	2	3	4	9	11	12
Timing	4.2018-4.2019	6.2018-7.2019	5.2019-7.2020	6.2019-7.2020	7.2020-12.2020	12.2020-3.2021	6.2021
n	182	207	116	148	104	89	21
Focus	NTRK/ solid Ca	Solid Ca biomarkers	Solid Ca biomarkers	NTRK/ solid Ca	NTRK/ solid Ca	NTRK/ lung Ca	NTRK/ solid Ca

†Refers to the Activity Number list in the Educational Activities section.

Conclusions

The rate of broad testing for *NTRK* fusions across patients with solid tumors remains low, and many HCPs lack awareness of when to consider a TRK inhibitor.

Educational activities designed to address these deficiencies would be of clear benefit to HCPs treating patients with advanced solid tumors.

Acknowledgments
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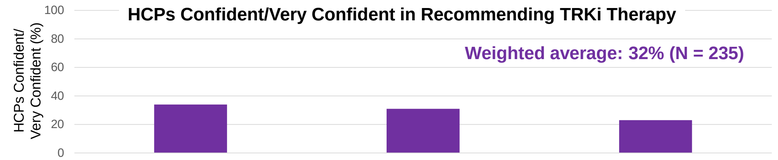
Abbreviations: Ca, cancer; CRC, colorectal cancer; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; GBM, glioblastoma; GI, gastrointestinal; i, inhibitor; IHC, immunohistochemistry; MSI, microsatellite instability; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PD, progressive disease; PS, performance status; RoW, rest of the world; TMB, tumor mutational burden; TMZ, temozolomide.

Results

Optimal Use of TRK Inhibitors

Many HCPs lack awareness of which patients may benefit from TRK inhibitors.

Assessment: HCPs were asked, "In your current practice, how confident are you in recommending TRK inhibitor therapy for appropriate patients?"

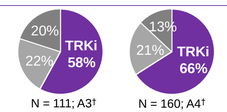


Activity no.†	9	11	12
n	130	83	22

Assessment: HCPs were asked their optimal treatment choice for case patients for whom experts would select a TRK inhibitor (larotrectinib and/or entrectinib).

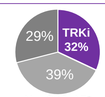
Case — **HCP Treatment Choice** (TRK inhibitor / Other treatment / Uncertain)

- 57-year-old man with swelling under jaw diagnosed with **salivary gland myoepithelial carcinoma**; underwent maximal debulking and adjuvant radiation, but recurrent disease noted 6 months later
- Completed first-line therapy with carboplatin + vinorelbine; at progression, NGS testing revealed an *ETV6-NTRK3* fusion



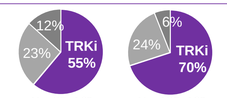
N = 111; A3† 5.2019-7.2020 — N = 160; A4† 6.2019-7.2020

- 35-year-old woman with recurrent *IDH*-mutated **GBM**
- Initial extensive subtotal resection + radiotherapy + TMZ followed by TMZ and tumor-treating fields; asymptomatic radiographic PD during 2 years after initial diagnosis
- NGS (original tissue): *EML4-NTRK3* fusion (intratumoral heterogeneity by IHC)



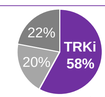
N = 207; A5† 11.2019-1.2021

- 43-year-old woman diagnosed with pT4aN0 **colon cancer**; deferred chemotherapy; right lower quadrant mass later recurred, with carcinomatosis and ascites
- Cancer is dMMR/MSI-high, TMB-high, and *NTRK* fusion positive; pembrolizumab started but PD after 2 months; nivolumab/ipilimumab started but PD again after 2 months



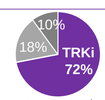
N = 85; A6† 1.2020-1.2021 — N = 135; A9† 7.2020-12.2020

- 50-year-old nonsmoker with metastatic **lung adenocarcinoma**
- *EGFR/ALK/ROS1/BRAF* all negative, PD-L1 <1%; patient received carboplatin, pemetrexed, and pembrolizumab but PD
- NGS panel of original biopsy showed *NTRK* fusion



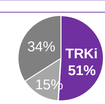
N = 591; A7† 2.2020-3.2021

- 42-year-old woman with metastatic, radioiodine-refractory **papillary thyroid cancer** with multiple lung nodules; rapid disease progression noted on imaging
- Sequencing identified *NTRK3* gene fusion



N = 71; A10† 7.2020-3.2021

- 68-year-old man presents with *EPS15-NTRK1* **NSCLC** with metastases to liver; past medical history: fatigue, cough, hyperlipidemia; ECOG PS 1
- No previous surgery, radiation, or chemotherapy



N = 86; A11† 12.2020-4.2021