NTRK in NSCLC

Subjects: Oncology

Contributor: Massimiliano Grassi

In the scenario of systemic treatment for advanced non-small cell lung cancer (NSCLC) patients, one of the most relevant breakthroughs is represented by targeted therapies. NTRK genes rearrangement is certainly one of the latest and attracting not only in NSCLC but also across different neoplasms. Even though this alteration is a rare finding and diagnostic methodologies are not standardized, recent studies higlighted a significant benefit on this population treated with NTRK inhibitors.

non-small cell lung cancer NTRK

1. Epidemiology

Alterations of the neurotrophic tyrosine kinase (NTRK) genes (i.e., NTRK1, NTRK2, and NTRK3) are rare in NSCLC, representing less than 1% (about 0.1–0.6%) of the NSCLC population [1][2][3]. Although the proportion is very small, the global incidence of NSCLC patients is high, making these relatively few cases a relevant number of patients in absolute terms. Given the rarity and the relatively recent discovery of this target, any solid data on morphological and clinical characteristics of NSCLC with NTRK involvement are still lacking.The largest study on NSCLC retrospectively included 4872 cases and identified only 11 cases with NTRK1-3 fusions. Of these cases, nine were adenocarcinoma, including two mucinous and one with neuroendocrine features, while one was a squamous cell carcinoma (SCC), and one a large-cell neuroendocrine carcinoma [3].High expression of the protein encoded by NTRK2 (TrkB) and of its ligand, namely brain-derived neurotrophic factor (BDNF), are the only proteins found to be correlated with a higher prevalence of vascular invasion, lymph nodes metastases, and advanced stage in NSCLC patients. These factors resulted in a poorer prognosis for this population [4][5].The other relevant clinical characteristic that has emerged is that the majority of NTRK-driven NSCLC patients were never-smoker (about 80%), as it is usually observed for other kinase fusion-positive NSCLCs [6].Interestingly, different studies highlighted that NTRK fusions seem to be almost mutually exclusive with alterations in other known genes, such as ALK, ROS-1, MET, and RET [7][8].

2. Molecular Pathway

The NTRK genes encode the TrkA, TrkB, and TrkC transmembrane glycoproteins, respectively, that together with their natural ligands, which are the nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and NT-4, are involved in the physiological development and function of the central and peripheral nervous systems [3][4][5]. Fusions of NTRK genes lead to overexpression of Trk proteins and, therefore, to the constitutive activation of downstream signaling pathways such as RAS/MAPK, PI3K/AKT, and PLC-γ, responsible for cancer cells

transformation, proliferation, and survival [1][5]. The most commonly detected fusions are ETS Variant Transcription Factor 6 (ETV6)-NTRK3 and Echinoderm Microtubule Associated Protein Like 4 (EML4)-NTRK3, although more than 50 other fusion partners are currently known [9].Interestingly, another role for one of these transmembrane proteins has been recently found. Indeed, preclinical studies have shown that the increased expression of TrkB promotes the suppression of E-cadherin expression and enhances the activity of the matrix metalloproteinase-2 (MMP-2) in lung SCC cells, promoting cancer aggressiveness [4][5].

3. Diagnostic Methodology

The NTRK fusions can be studied with different methods, among which IHC is one of the most widespread used and characterized by high sensitivity (95 to 100%) and specificity (93% to 100%); although these data derive from very small studies, this technique can be considered a good screening tool as of today, given the rarity of NTRK gene alterations [2][6].Another relevant diagnostic tool is represented by FISH, which may be helpful when the histologic tumor type is known to frequently harbor an NTRK fusion, although this may not be the best option in NSCLC due to its aforementioned low prevalence [3][6]. Nowadays, the employment of newly approved targeted therapies may be either approved for patients with an NTRK gene fusion diagnosed by NGS techniques or within clinical trials. IHC testing can be accepted but needs to be validated with another diagnostic method, thus resulting in a more time-consuming procedure for each patient. Thus, the NGS approach may be proposed either as front-line or after positivity at the IHC screening as it is recommended in the latest ESMO guidelines [10].

4. Therapeutic Implications

The discovery of actionable NTRK gene fusions represented a revolution in oncology. The first-generation TRK inhibitors entrectinib and larotrectinib received, in fact, an agnostic approval by the FDA for patients with NTRK fusion-positive solid tumors because of their impressive results in Phase I/II trials [1][3].

Entrectinib is a TRKA, TRKB, TRKC, ROS1, and ALK multi-inhibitor, and data from three Phase I/II trials (ALKA-372-001, STARTRK-1, and STARTRK-2) reported an ORR for NSCLC patients of 70–75% with 10% of complete responses (CR), an mDOR of 12.9 months, and an mOS of 23.9 months (Table 1) [11][12][13]. Larotrectinib, by contrast, is a pan-TRK inhibitor and a recently published pooled analysis of three Phase I/II trials showed, among NSCLC patients, an ORR of 75%, an mPFS of 28.3 months, and an mOS of 44.4 months [14].

Table 1. Principal single-arm Phase I–II trials on NTRK inhibitors in NTRK-fused advanced NSCLC patients.

Drug	Trial	Phase	Therapy Line *	*N* pts	Main Results	Status ***
Entrectinib	ALKA-372-001 (EudraCT2012–000148–88)	I	Any	10 **	ORR = 70% mDOR = 12.9 mo mPFS = 14.9 mo mOS = 23.9 mo	Closed
	STARTRK-1 (NCT02097810)	I	Any			Closed

Drug	Trial	Phase	Therapy Line *	*N* pts	Main Results	Status ***
Larotrectinib	STARTRK-2 (NCT02568267)	II	Any	12 **	ORR = 75% mDOR = NE mPFS = 28.3 mo mOS = 44.4 mo	Ongoing
	LOXO-TRK-14001 (NCT02122913)	I	Any			Closed
	LOXO-TRK-15003 (NCT02637687)	I/II	Any			Ongoing
	NAVIGATE (NCT02576431)	II	Any			Ongoing

N—number; pts patients; ORR—overall response rate; mo—month; mDOR—median duration of response; mPFS—median progression-free survival; mOS—median overall survival; NE—not estimable. An asterisk (*) indicates the line or lines of treatment for advanced NSCLC in which the investigational agent or regimen was employed in each reported trial. Two asterisks (**) indicate that the studies were pooled analyses. Three asterisks (***) indicate that Entrectinib and Larotrectinib FDA approved for NTRK-fused solid tumors.

These two drugs are both very effective and very well tolerated with few side effects. The main difference is the central nervous system (CNS) penetration as entrectinib can cross more effectively the blood–brain barrier. As a matter of fact, entrectinib has proved its efficacy in patients with brain metastases, although it has also shown some CNS side-effects, such as dizziness [11][12][13].

Across time, as in many other targeted therapies, the tumor can develop acquired resistance, but new generations of TRK inhibitors, such as taletrectinib (TPX-0005), selirectinib (LOXO-195), and repotrectinib, are currently under evaluation in ongoing Phase I/II clinical trials [1][3].

References

1. Russo, A.; Lopes, A.R.; McCusker, M.G.; Garrigues, S.G.; Ricciardi, G.R.; Arensmeyer, K.E.; Scilla, K.A.; Mehra, R.; Rolfo, C. New Targets in Lung Cancer (Excluding EGFR, ALK, ROS1). Curr. Oncol. Rep. 2020, 22, 48.
2. Elfving, H.; Broström, E.; Moens, L.N.J.; Almlöf, J.; Cerjan, D.; Lauter, G.; Nord, H.; Mattsson, J.S.M.; Ullenhag, G.J.; Strell, C.; et al. Evaluation of NTRK Immunohistochemistry as a Screening Method for NTRK Gene Fusion Detection in Non-Small Cell Lung Cancer. Lung Cancer Amst. Neth. 2021, 151, 53–59.
3. Farago, A.F.; Taylor, M.S.; Doebele, R.C.; Zhu, V.W.; Kummar, S.; Spira, A.I.; Boyle, T.A.; Haura, E.B.; Arcila, M.E.; Benayed, R.; et al. Clinicopathologic Features of Non-Small-Cell Lung Cancer Harboring an NTRK Gene Fusion. JCO Precis. Oncol. 2018, 2018.

4. Ozono, K.; Ohishi, Y.; Onishi, H.; Nakamura, K.; Motoshita, J.; Kato, M.; Nakanishi, R.; Nakamura, M.; Oda, Y. Brain-Derived Neurotrophic Factor/Tropomyosin-Related Kinase B Signaling Pathway Contributes to the Aggressive Behavior of Lung Squamous Cell Carcinoma. Lab. Investig. J. Tech. Methods Pathol. 2017, 97, 1332–1342.
5. Okamura, K.; Harada, T.; Wang, S.; Ijichi, K.; Furuyama, K.; Koga, T.; Okamoto, T.; Takayama, K.; Yano, T.; Nakanishi, Y. Expression of TrkB and BDNF Is Associated with Poor Prognosis in Non-Small Cell Lung Cancer. Lung Cancer Amst. Neth. 2012, 78, 100–106.
6. Gatalica, Z.; Xiu, J.; Swensen, J.; Vranic, S. Molecular Characterization of Cancers with NTRK Gene Fusions. Mod. Pathol. Off. J. US Can. Acad. Pathol. Inc. 2019, 32, 147–153.
7. Haratake, N.; Seto, T. NTRK Fusion-Positive Non-Small-Cell Lung Cancer: The Diagnosis and Targeted Therapy. Clin. Lung Cancer 2021, 22, 1–5.
8. Liu, D.; Offin, M.; Harnicar, S.; Li, B.T.; Drilon, A. Entrectinib: An Orally Available, Selective Tyrosine Kinase Inhibitor for the Treatment of NTRK, ROS1, and ALK Fusion-Positive Solid Tumors. Ther. Clin. Risk Manag. 2018, 14, 1247–1252.
9. Kummar, S.; Lassen, U.N. TRK Inhibition: A New Tumor-Agnostic Treatment Strategy. Target. Oncol. 2018, 13, 545–556.
10. Marchiò, C.; Scaltriti, M.; Ladanyi, M.; Iafrate, A.J.; Bibeau, F.; Dietel, M.; Hechtman, J.F.; Troiani, T.; López-Rios, F.; Douillard, J.-Y.; et al. ESMO Recommendations on the Standard Methods to Detect NTRK Fusions in Daily Practice and Clinical Research. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2019, 30, 1417–1427.
11. Lee, J.; Park, S.; Jung, H.A.; Sun, J.-M.; Lee, S.-H.; Ahn, J.S.; Park, K.; Ahn, M.-J. Evaluating Entrectinib as a Treatment Option for Non-Small Cell Lung Cancer. Expert Opin. Pharmacother. 2020, 21, 1935–1942.
12. Sartore-Bianchi, A.; Pizzutilo, E.G.; Marrapese, G.; Tosi, F.; Cerea, G.; Siena, S. Entrectinib for the Treatment of Metastatic NSCLC: Safety and Efficacy. Expert Rev. Anticancer Ther. 2020, 20, 333–341.
13. Doebele, R.C.; Drilon, A.; Paz-Ares, L.; Siena, S.; Shaw, A.T.; Farago, A.F.; Blakely, C.M.; Seto, T.; Cho, B.C.; Tosi, D.; et al. Entrectinib in Patients with Advanced or Metastatic NTRK Fusion-Positive Solid Tumours: Integrated Analysis of Three Phase 1-2 Trials. Lancet Oncol. 2020, 21, 271–282.
14. Hong, D.S.; DuBois, S.G.; Kummar, S.; Farago, A.F.; Albert, C.M.; Rohrberg, K.S.; van Tilburg, C.M.; Nagasubramanian, R.; Berlin, J.D.; Federman, N.; et al. Larotrectinib in Patients with TRK Fusion-Positive Solid Tumours: A Pooled Analysis of Three Phase 1/2 Clinical Trials. Lancet Oncol. 2020, 21, 531–540.