



Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

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TRK inhibition in cholangiocarcinoma: Trying to teach an old dog new tricks

Advanced CCA is largely resistant to systemic chemotherapy and lack effective therapies [1]. Unfortunately, most patients are diagnosed with metastatic disease when treatment options are limited to palliative approaches, and overall survival is less than 12 months [2]. Thus, there is an urgent need to improve outcomes and to provide novel, more effective treatment strategies in patients diagnosed with advanced CCA [3]. The last decade has seen the identification of several promising treatment targets that are paving the way towards a new era in CCA management, including fibroblast growth factor receptor (FGFR) fusions and isocitrate dehydrogenase (IDH)-1 and IDH-2 mutations [4]. Additionally, other targets are under evaluation in this setting, including Neurotrophic Tropomyosin Receptor Kinase (NTRK), HER2, and BRAF [5].

NTRK1, NTRK2, and NTRK3 gene fusions act as oncogenic drivers in a range of solid tumors, including gastrointestinal malignancies such as CCA [6]. These aberrations usually occur following the fusion of the C-terminal tyrosine kinase of the NTRK gene with an N-terminal fusion partner; the fusion hesitates in a ligand-independent phosphorylation and subsequent activation of pathways leading to increased proliferation and cellular growth [7]. These fusions, occurring in approximately 1% of pediatric and adult solid tumors, have recently emerged as promising therapeutic targets for cancer therapy [8]. Firstly, on November 26, 2018, the Food and Drug Administration (FDA) granted accelerated approval to larotrectinib for adult and pediatric patients with solid tumors NTRK gene fusions; more recently, on August 15, 2019, the FDA granted accelerated approval also to entrectinib for adults and pediatric patients 12 years of age and older with metastatic solid tumors that have a NTRK gene fusion.

A recent report presented at ESMO World Congress on Gastrointestinal Cancer 2020 has tried to assess NTRK gene fusions incidence in biliopancreatic malignancies, including pancreatic adenocarcinomas and CCAs, by using different techniques [9]. In particular, Demols and colleagues used a two-step diagnostic method which provided for immunohistochemistry and RNA-based next-generation sequencing (NGS); of note, the prevalence of NTRK gene fusions in CCAs was 0.67% (1/149), with only one patient reporting gene fusion [9]. This percentage has been even lower in another recent study by Solomon and colleagues, where the authors identified the 0.25% of NTRK gene fusions in 787 CCA patients [10].

Among the targeted agents currently under evaluation in NTRK fusion-positive cancers, entrectinib (RXDX-101) and larotrectinib (LOXO-101) are potent TRK inhibitors; in addition, entrectinib and larotrectinib have shown antitumor activity against ALK and ROS1 fusions, observed in approximately the 3% of CCAs. Thus, these two agents present a broad range of action [11]. Previous studies have reported that entrectinib could have durable and clinically meaningful responses in

cancer patients harboring NTRK gene fusions, with impressive response rates observed in studies evaluating tumor-agnostic therapeutic approaches [12]. More specifically, according to results of recent basket trials, remarkable overall response rates (ORRs) between 55% and 75% have been detected in pretreated patients, with entrectinib who is a candidate to become an important treatment option in NTRK fusion-positive malignancies [13]. In addition, TRK inhibition-related more common toxicities include weight gain, dizziness, and withdrawal pain, showing a unique safety profile compared to other anti-cancer therapies [11-13]. However, these on-target toxicities have been suggested to be manageable with pharmacologic intervention and dose modification.

As regards CCAs, an updated integrated analysis of three clinical trials (ALKA-372-001, STARTRK-1, STARTRK-2) evaluating entrectinib in NTRK fusion-positive gastrointestinal tumors has been recently presented [14]. In this analysis, entrectinib showed meaningful responses in 12 patients with a range of NTRK fusion-positive gastrointestinal carcinomas, with ORR of 50%, median duration of response of 12.9 months and median PFS of 7.1 months [14]. In addition, entrectinib was well tolerated, with most adverse events that were managed with dose reduction or interruption, and an overall low discontinuation rate. Interestingly, the analysis included one CCA patient, that achieved partial response (PR), with a PFS of 12.0 months, while OS was not yet reached at the data cut-off [14]. Additionally, the TRK inhibitor larotrectinib is actually under investigation as single-agent in a phase II NAVIGATE basket trial on NTRK fusion-positive solid cancers, including advanced CCAs (NCT02576431). Moreover, secondary mutations following treatment with TRK inhibitors may cause resistance to larotrectinib or entrectinib, and several second-generation TRK inhibitors (such as selitrectinib and repotrectinib) have proven antitumor activity in animal models and are being investigated in ongoing clinical trials.

Despite the paucity of data and the overall low prevalence observed, recent findings from large basket trials in previously treated advanced solid tumors should encourage a wider NTRK gene fusions screening of patients with CCA, as they may benefit from TRK inhibitors [15]. In fact, given the limited therapeutic options for CCA, we recommend deep molecular sequencing as a standard, with these patients that should be seen and treated by CCA experts. Of note, the classical, "historical" approach to the identification and development of targeted treatments in oncology research has been oriented by histology, with this strategy leading to the approval of a wide range of monoclonal antibodies and small-molecule inhibitors. However, a different model is in development, following the level of efficacy and antitumor activity shown by TRK inhibitors across NTRK fusion-positive solid cancers. In fact, entrectinib and larotrectinib have provided two important examples of

<https://doi.org/10.1016/j.ctarc.2021.100351>

Available online 13 March 2021

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histology-independent efficacy of targeted treatments in a molecularly defined subcohort of malignancies [16]. Further studies are needed to comprehend which role TRK inhibitors could play in NTRK fusion-positive cancers, and how these agents can integrate in the evolving landscape of targeted treatments in advanced CCA [17].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Alessandro Rizzo^{a,b,*}, Giovanni Brandi^{a,b}

^a Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi University Hospital, Bologna, Italy

^b Oncologia Medica, Azienda Ospedaliero-Universitaria di Bologna, via Albertoni 15, 40128 Bologna, Italy

* Corresponding author at: Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi University Hospital, Bologna, Italy.

E-mail address: rizzo.alessandro179@gmail.com (A. Rizzo).