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# Entrectinib approval by EMA reinforces options for ROS1 and tumour agnostic *NTRK* targeted cancer therapies

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On 28 May 2020, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended the granting of a conditional marketing authorisation for entrectinib (Rozlytrek), for the treatment of patients whose solid tumours have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion or for patients with *ROS1* fusion-positive advanced non-small cell lung cancer (NSCLC).[1] Based on the full indication, entrectinib represents a new therapeutic option for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours *NTRK* fusion-positive, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior *NTRK* inhibitor, who have no satisfactory treatment options. In addition, entrectinib is indicated as monotherapy for the treatment of adult patients with *ROS1* fusion-positive, advanced NSCLC not previously treated with ROS1 inhibitors.

The present CHMP recommendation is based on the analysis of combined results of four clinical studies, the pivotal phase II STARTRK-2, the ALKA-372–001 and the STARTRK-1 phase I trials, and the phase I/II STARTRK-NG paediatric study.[2] Overall in these studies, the efficacy of entrectinib was observed in patients with *NTRK* fusion-positive locally advanced or metastatic tumours, with an objective response rate (ORR) of 63.5% and a median duration of response (DoR) of 12.9 months.[2] The clinical benefit reported across several different *NTRK* fusion-positive tumour types is in our opinion a very compelling evidence and supports the tissue-agnostic indication approval for entrectinib. This approval would represent the second case, after larotrectinib, of an EMA granted approval based on a common driver molecular alteration across different tumour types rather than on tumour histology. In *ROS1* fusion-positive advanced NSCLC patients enrolled in the trials, entrectinib achieved ORR in 73.4% of cases with a median DoR of 16.5 months (14.6–28.6 months).[2] Importantly, ORR of 67.1% was observed in the subset of patients with central nervous system (CNS) metastases at baseline, consistent with the efficient brain penetration of entrectinib clearly demonstrated during its preclinical characterisation[3] and then confirmed in the clinical settings.[2] The most common adverse reactions were fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, nervous system disorders (dysesthesia), shortness of breath (dyspnoea), anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough and fever.[1] In light of these clinical results and in the context of affirmation of precision oncology, entrectinib approval by EMA reinforces options for ROS1 and tumour-agnostic *NTRK* targeted cancer therapies.

## THE PAST OF ENTRECTINIB

The recommendation of the CHMP for conditional marketing authorisation is the most recent achievement in the all recent history of this compound that in 2017 had been granted Priority Medicines designation by the EMA and Breakthrough Therapy Designation by Food and Drug Administration (FDA) for the treatment of *NTRK* fusion-positive, locally advanced or metastatic solid tumours. Entrectinib is already marketed in the USA where on 15 August 2019 FDA has issued an accelerated, tissue-agnostic approval to the drug to target solid tumour types bearing *NTRK* fusions and for the treatment of metastatic *ROS1* fusion-positive NSCLC and in Japan where it was approved in June 2019 for the treatment of patients with *NTRK* fusion-positive tumours and in February 2020 for the treatment of patients with *ROS1* fusion-positive NSCLC.[4–7]

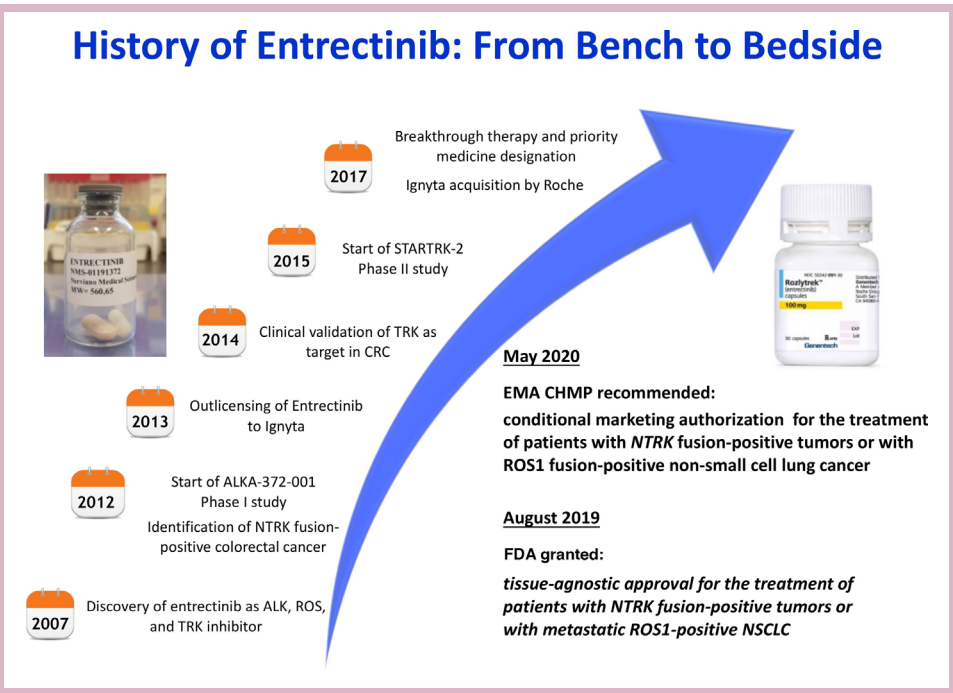


**Figure 1** Main steps and years of entrectinib history from discovery to clinical application. CHMP; Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; NSCLC, non-small cell lung cancer.

The registration of entrectinib for *NTRK* fusion-positive tumours represents the pharmaceutical conclusion of a scientific history lasting for more than three decades (figure 1). In 1983 Mariano Barbacid, working in the lab of Stuart Aaronson, identified in a colorectal cancer specimen an inversion within chromosome 1 resulting in a fusion oncogene that was named *TRK* (tropomyosin receptor kinase). This fusion oncogene was not found in subsequent analyses and it was considered an oddity.[8] The full length neurotrophin receptor *TRK* was identified a few years later, and the chromosome 1 inversion was not further investigated.[9] Probably at that time, nobody could have imagined that the clinical relevance of that finding would have been fully exploited many years later when thank to the availability of new sequencing technology but also to a certain dose of serendipity we stepped into during our work of preclinical and clinical investigators.

More than two decades later, at the Italian pharmaceutical company Nerviano Medical Sciences, as part of a standard drug discovery process, the preclinical characterisation of a novel drug was going to be completed. The molecule, now known as entrectinib (former NMS-E628), discovered and optimised to be a potent, brain penetrant ROS1- and ALK-inhibitor was indeed found to be also active on TRK kinases, encoded by the *NTRK* genes.[3 10] This activity was considered since the very beginning an interesting opportunity for the development of the drug but it is fair to say that at that time the reports of *NTRK* fusions were still mostly anecdotal. The full exploitation of this opportunity became clear when the extensive cellular profiling of entrectinib revealed an exquisitely high antiproliferative activity of the drug in a colorectal cancer cell line that did not express either ALK or ROS1. The subsequent genetic characterisation demonstrated that this peculiar sensitivity was due to the presence of an inversion within chromosome 1 resulting in the generation of a *NTRK* fusion oncogene that was the driver for proliferation and survival of those cells. The very same chromosomal alteration found by Barbacid many years before in a surgically removed colorectal cancer specimen was indeed present in this cell line.[11]

The valuable and productive collaboration between Nerviano Medical Science and Niguarda Cancer Center resulted in the setup in a record time of a validated screening method based on the use of immunohistochemistry (IHC), reverse transcriptase-polymerase chain reaction (RT-PCR) and in-situ hybridisation (ISH) that allowed to screen a number of colorectal cancer patients and to demonstrate that, even if with low incidence, *NTRK* rearrangements could be identified in a discrete subset of patients with colorectal cancer. This evidence represented the rationale for the inclusion of patients with *NTRK* fusion-positive tumours in the upcoming ALKA-372–001 phase I clinical trial of entrectinib.[11] The clinical benefit observed with a partial response achieved after 1 month of treatment in the first patient with *NTRK* fusion-positive colorectal cancer enrolled represented the first clinical proof of concept validation of *NTRK* fusions as targets for therapy in patients with colorectal cancer and spurred the search of such rearrangements in many additional tumour types.[12–14] Both Ignyta, a US biotech company that in 2013 acquired the rights for the development of entrectinib, and Roche that after the acquisition of Ignyta in 2017 developed the molecule up to the registration, have continued with wilfulness and determination the clinical exploration of entrectinib activity

across many different *NTRK* fusion-positive tumour types. These joint efforts resulted, as already mentioned, in the tumour-agnostic approval of entrectinib and most importantly to high and durable therapeutic benefits for most of the treated patients.[5]

Compared to the development of the drug in *NTRK* fusion-positive tumours, the exploration of entrectinib efficacy in *ROS1* fusion-positive NSCLC patients was quite straightforward. In the preclinical models entrectinib was shown to be an extremely potent *ROS1* inhibitor and the direct comparison of activity in cells demonstrated its superiority with respect to crizotinib.[3] In addition, as already mentioned, the molecule had been specifically optimised to penetrate the CNS and all the subsequent preclinical investigations demonstrated that entrectinib was indeed able to efficiently cross the blood brain barrier and to achieve efficacious exposure in the brain in all preclinical models tested.[3 10] This evidence supported the inclusion of patients with CNS involvement at baseline since the initial phase I study of the clinical development. The substantial intracranial activity of entrectinib confirmed in the clinical settings is particularly relevant for the treatment of patients with ROS1-positive NSCLC because of the high frequency of brain metastases at the diagnosis in this population and the suboptimal ability of crizotinib to penetrate the brain.[6]

## THE FUTURE OF ENTRECTINIB

The granting of marketing authorisation of entrectinib by EMA will represent for many European patients the availability of a new valuable therapeutic option. For the 1%–2% of patients with NSCLC bearing *ROS1* fusions and especially for those with CNS involvement at diagnosis, this drug will represent a remarkable opportunity for achieving durable clinical benefit as foreseen in the plethora of *NTRK* fusion-positive tumours across different histologies. The application of the most appropriate approaches to optimise the selection of patients who can benefits from entrectinib treatment is crucial.

The testing of *ROS1* gene fusions in metastatic non-squamous NSCLC is considered mandatory in most European countries and based on European Society for Medical Oncology (ESMO) recommendation should be performed with ISH while IHC may be used to identify candidate tumours for confirmatory ISH testing.[15 16]

The testing of *NTRK* fusions remains definitely more challenging mostly because of the broad patient population to be tested. Based on the recently issued ESMO recommendations, a conservative approach should be applied in order to identify any potential patients who can harbour these targetable genetic alterations and might benefit from a treatment with a *NTRK* inhibitor. Still, this approach will imply that different screening strategies should be applied to different patient populations.[17] For *NTRK* testing in histological tumour types where *NTRK* genes are frequently rearranged any chemiluminescence immunoassay (CLIA) validated method is applicable with ISH and nested RT-PCR being probably the most cost-effective ones.

On the other hand, for the identification of *NTRK* fusions in an unselected population (histology-agnostic screening) the combination of next generation sequencing (NGS) and IHC is recommended. Depending on the health institution availability of the NGS targeted panel (DNA or RNA-based) the approach for testing could be different. NGS as initial screening with IHC used for confirmation of protein expression in positive cases would be ideal but, in case on unavailability of a targeted sequencing assay, IHC for initial screening followed by external sequencing for confirmation of any detected positivity is acceptable.[17] The EMA conditional approval of entrectinib further highlights the need to routinely test for *NTRK* fusions to broaden the therapeutic options available for patients. At this point, as part of a fruitful marketing strategy, we expect Roche, leveraging on its well-recognised expertise in diagnostics and in conjunction with its allied company Foundation Medicine, to make available a companion diagnostic that will help identify individuals with malignancies who may benefit from treatment with entrectinib.

In an ideal world, all patients with cancer should have rapid access to all newly available anticancer drugs when approved. However, this is far from the reality and with the variations in economic standard across the EU, access to new cancer medicines differs significantly, especially in Eastern and South-Eastern European countries.[18] Access delays can be caused directly or indirectly by national or regional decision-making processes on reimbursement.[18] The two key aspects for those involved in reimbursement decisions are first the level of evidence required to decide and second pricing, which can be challenging for some innovative oncology compounds such as entrectinib. The ESMO has declared achieving equal access to cancer care as one of its major goals[19] and we wish that choral collaboration and dialogue between regulators, payers, governments, patient stakeholders and industry will help to ensure that in all countries in EU, high quality cost-effective medical oncology care will include compounds such as the newcomer entrectinib.

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