Critical Reviews in Oncology / Hematology 169 (2022) 103564

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Belgian expert consensus for tumor-agnostic treatment of NTRK gene fusion-driven solid tumors with larotrectinib

Ahmad Awada [a,*], Thierry Berghmans [b], Paul M. Clement [c], Kristof Cuppens [d], Bram De Wilde [e], Jean-Pascal Machiels [f], Patrick Pauwels [g], Marc Peeters [h], Sylvie Rottey [i], Eric Van Cutsem [j]

[a] Oncology Medicine Department, Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium
[b] Thoracic Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[c] Leuven Cancer Institute, Department of Oncology, Katholieke Universiteit Leuven, Leuven, Belgium
[d] Department of Pulmonology and Thoracic Oncology, Jessa Hospital, Hasselt, Belgium
[e] Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, Belgium
[f] Institut Roi Albert II, Department of Medical Oncology, Cliniques universitaires Saint-Luc and Institut de Recherche Clinique et Expérimentale (POLE MIRO), Université catholique de Louvain, Brussels, Belgium
[g] Department of Pathology, University Hospital Antwerp, Edegem, Belgium
[h] Multidisciplinary Oncology Center Antwerp UZA, Antwerp Belgium, MIPRO UA, B-2650, Edegem, Belgium
[i] Department of Medical Oncology, University Hospital of Ghent, Ghent, Belgium
[j] Department of Digestive Oncology, University Hospital Gasthuisberg-University of Leuven, Leuven, Belgium

ARTICLE INFO

Keywords:
Larotrectinib
NTRK gene fusion
Trk inhibitor
Tumor-agnostic
Expert opinion
Oncogene proteins
Protein kinase inhibitors

ABSTRACT

Fusions of NTRK (neurotrophic tyrosine receptor kinase) genes with 5′ partner genes can result in the expression of chimeric proteins that drive oncogenesis through ligand-independent kinase activation. Despite variable frequencies of *NTRK* fusions in different tumor types, the fact that they are common to a wide range of cancers raises the possibility of developing tumor-agnostic treatments specifically targeting *NTRK* fusion products, irrespective of tumor type.

The first-generation Trk (tropomyosin receptor kinase) inhibitor, larotrectinib, was the first tumor-agnostic treatment of *NTRK* fusion-positive cancers in adults and children, to be approved in the European Union.

This consensus, developed by a Belgian multidisciplinary expert panel, aims to highlight the unmet medical need associated to *NTRK* fusion-driven cancer treatment and, based on current knowledge of *NTRK* fusions and larotrectinib treatment outcome and safety, provide comprehensive guidance to oncologists regarding *NTRK* fusion-driven cancer diagnostics and the best use of larotrectinib in real-world clinical settings.

1. NTRK (neurotrophic tyrosine receptor) genes: function and oncogenic fusions

The NTRK genes (*NTRK1*, *NTRK2*, and *NTRK3*) encode the tropomyosin receptor kinase (Trk) family of proteins (respectively TrkA, TrkB, and TrkC), which play a critical role in the modulation of various biological processes and cellular functions (Amatu et al., 2019). Due to intra- or inter-chromosomal rearrangements, fusions of NTRK genes with a wide range of 5′ partner genes can occur, leading to the expression of chimeric proteins that drive oncogenesis through constitutive (i.e., ligand-independent) kinase activation (Cocco et al., 2018; Kojadinovic et al., 2021). As a result, NTRK gene fusions act as primary oncogenic drivers for a broad range of adult and pediatric cancers, including rare tumors frequently associated with NTRK gene fusions and more common tumors where NTRK gene fusions are rarer (Cocco et al., 2018; Kojadinovic et al., 2021; Bourgeois et al., 2000; El Demellawy et al., 2016; Skalova et al., 2010; Tognon et al., 2002; Stransky et al., 2014) and represent an important clinically actionable target (Fig. 1). Moreover, these fusions generally do not co-occur with other known oncogenic driver mutations (Rosen et al., 2020). Detection of NTRK gene fusions can be done by prescreening with immunohistochemistry (IHC) and, in the case of positive IHC results, subsequent confirmation by fluorescence in-situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR), or DNA/RNA next-generation

* Corresponding author at: Oncology Medecine Departement, Institut Jules Bordet,Université Libre de Bruxelles, Rue Héger-Bordetstraat 1, B - 1000 Bruxelles, Brussels, Belgium.
E-mail address: ahmad.awada@bordet.be (A. Awada).

https://doi.org/10.1016/j.critrevonc.2021.103564
Received 9 July 2021; Received in revised form 26 November 2021; Accepted 29 November 2021
Available online 30 November 2021

sequencing (NGS) (Solomon et al., 2019).

2. The case for larotrectinib: a pan-Trk inhibitor

Larotrectinib is a highly-selective, pan-Trk inhibitor that potently blocks the adenosine triphosphate binding site of TrkA, TrkB, and TrkC, with half maximal inhibitory concentration (IC_{50}) values in the low nanomolar range (5–11 nM) (European Medicines Agency, 2021a; Federman and McDermott, 2019).

To date, larotrectinib has been evaluated in three clinical trials: an adult phase I trial (NCT02122913) (Drilon et al., 2018), a pediatric phase I/II trial (SCOUT; NCT02637687) (Laetsch et al., 2018), and an adult/adolescent phase II basket trial (NAVIGATE; NCT02576431) (Drilon et al., 2018; Drilon et al., 2016). In a pooled analysis of 175 NTRK gene fusion-positive patients from these three studies, larotrectinib was shown to induce an early and durable response. Time to response ranged from 0.9 to 6.6 months, with a median time to response of 1.8 months; 12-month and 24-month durations of response (DOR) were 81 % and 66 %, respectively with an objective response rate (ORR) of 78 %, independent of tumor histology, age, and/or NTRK gene fusion status (McDermott et al., 2020). Larotrectinib has also been shown to cross the blood/brain barrier (Drilon et al., 2019; Ziegler et al., 2018). Analysis of a subset of 24 NTRK gene fusion-positive patients with primary central nervous system tumors showed that larotrectinib was

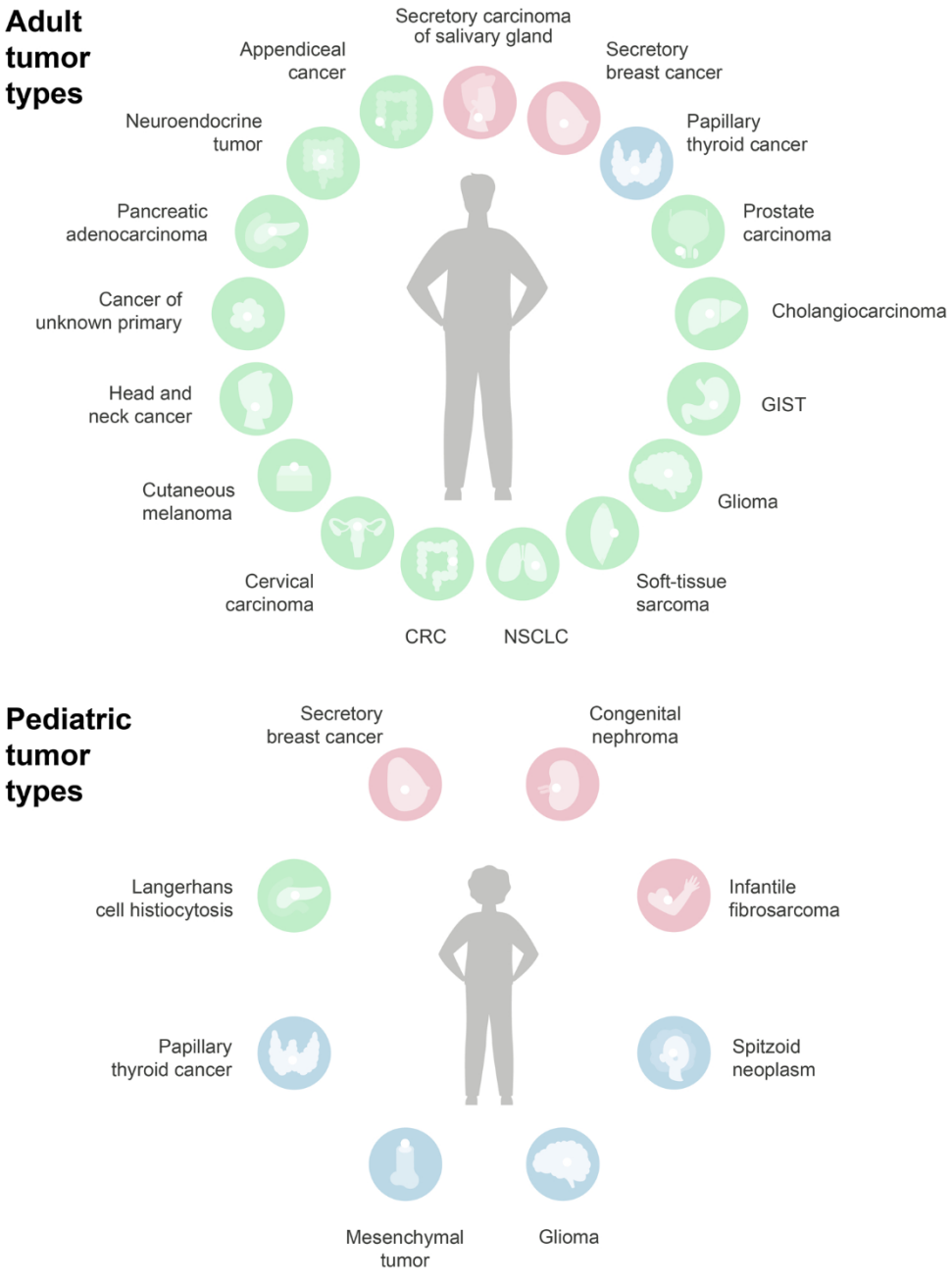

Fig. 1. Prevalence of NTRK gene fusions according to tumor type.
For ranges of NTRK gene fusion prevalence associated to each cancer type and corresponding references, please refer to table T1 of supplementary materials. CRC, colorectal cancer; GIST, gastrointestinal stromal tumors; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase. This list of tumor types is non-exhaustive.

active in the central nervous system, with a disease control rate at ≥24 weeks of 63 % (Perreault et al., 2020). For larotrectinib efficacy data by tumor type, please refer to Table T2.

Response rates in treatment-naive patients appeared to be higher than in patients with prior lines of treatment (ORR = 91 % for naive patients vs. ORR ≥ 70 % for non-naive patients). However, in light of the high response rates observed for patients with prior lines of treatment and since no cross-resistance between larotrectinib and other treatments was evidenced, it is clear that larotrectinib is also beneficial to previously treated patients (Drilon et al., 2020). In addition, a rapid, sustained, and clinically meaningful improvement of quality of life (QoL) was reported for both adult and pediatric patients with NTRK gene fusion-driven cancers treated with larotrectinib, with improvements in QoL scoring observed for 91 % of adults and 67 % of children who initially reported suboptimal QoL (Kummar et al., 2020).

Overall, larotrectinib is well tolerated. In a pooled safety analysis of 279 patients from the three studies mentioned above (McDermott et al., 2020), the majority (>90 %) of adverse events were grade 1 and 2; the most common grade 3/4 treatment-related adverse events were increased levels of alanine aminotransferase (4 %), decreased neutrophil count (2 %), and anemia (3 %). Dose reductions due to treatment-related adverse events were reported in 11 % of NTRK gene fusion-positive patients and discontinuations in only 2 % of all patients. No treatment-related deaths were reported (McDermott et al., 2020).

In addition to these studies, a global, prospective, multi-cohort, non-interventional phase IV study (NCT04142437, ON-TRK) is currently recruiting patients with the aim of collecting real-world efficacy and safety data for larotrectinib (ClinicalTrials.gov, 2021).

While randomized controlled trials (RCTs) are in general the gold standard to evaluate the efficacy and safety of a given treatment versus the current standard of care (SoC), such study designs are difficult to apply to tumors driven by biomarkers that rarely occur in cancers. Basket trial designs are a valid alternative and are typically preferred to RCTs for the assessment of cancer treatments, such as larotrectinib, that target specific oncogenic genomic alterations rather than specific tumor histologies.

In addition, the growth modulation index (GMI), a metric which uses the patients as their own control, has also been proposed to assess investigational drugs targeting disease for which RCT data are unavailable (Italiano et al., 2020a). GMI is defined as the ratio of progression-free survival (PFS) on the current line of therapy over time to progression on the last prior line of therapy. A drug is deemed to display meaningful clinical activity if the calculated GMI is ≥1.33 (Von Hoff, 1998). In an analysis of 122 eligible patients with NTRK gene fusion-positive cancers, 63 % of adult patients and 82 % of pediatric patients had a GMI ≥ 1.33, suggesting that PFS was improved following treatment with larotrectinib compared to the previous line of treatment (Italiano et al., 2020a; Italiano et al., 2020b). The GMI presents several limitations such as potential differences in how PFS and time to disease progression are assessed for different treatment lines or the fact that it cannot be used to assess front-line treatments. However, in addition to the high ORR observed for larotrectinib, the results obtained using the GMI support the benefits of larotrectinib for the treatment of patients with NTRK gene fusion-positive cancers.

Based on the results of the three aforementioned clinical trials, the use of larotrectinib as tumor-agnostic treatment for both adults and children with NTRK gene fusion-positive solid tumors was approved by the Food and Drug Administration (FDA) in 2018 (Food and Drug Administration, 2018) and by the European Medicines Agency (EMA) in 2019 (European Medicines Agency, 2019). It was the second drug to be approved with tumor agnostic indications by the FDA, and the first by the EMA. According to the EMA, larotrectinib monotherapy is indicated for the treatment of adult and pediatric patients with solid tumors that display a NTRK gene fusion (i) who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and (ii) who have no satisfactory treatment options (European Medicines Agency, 2021a). Larotrectinib is available in oral liquid (20 mg/mL) and capsule (25 and 100 mg) formulations; the recommended dosage is two 100 mg doses a day for adults and two doses of 100 mg/m^2 of body surface a day for children (with a maximum dose of 100 mg) (European Medicines Agency, 2021a). Besides larotrectinib, another Trk inhibitor, entrectinib, has been approved by the FDA and EMA for use as a monotherapy for the treatment of adult and pediatric patients of at least 12 years of age with NTRK gene fusion-positive solid tumors, and for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors (Food and Drug Administration, 2021; European Medicines Agency, 2021b).Further discussion relative to entrectinib or other Trk-inhibitors is beyond the scope of the present consensus.

In addition to the fact that NTRK gene fusions act as primary oncogenic drivers, recently also trends suggest the existence of an association between NTRK gene fusions and poor prognosis (Bazhenova et al., 2020), further underlining the importance of early detection and treatment of NTRK gene fusion-driven cancers.

3. Tailoring NTRK gene fusion-driven cancer diagnostics and treatment

The present consensus was developed by a Belgian multidisciplinary expert panel composed of 10 Health Care Professionals specialized in adult and pediatric oncology, and/or pathology. All members of the panel participated in the preparation, review, and finalization of the document, and declare having worked according to their best medical judgement. In addition, though Bayer was involved in the coordination of the manuscript's development, the members also declare having worked freely and without undue influence from external entities. In this document, we, the authors, aim to provide guidance to physicians regarding NTRK gene fusion-driven cancer diagnostics and the use of larotrectinib in clinical settings.

The conclusions of this consensus with regards to NTRK gene fusion-driven cancer diagnostics and treatment, as well as a non-exhaustive list of cancer types to which these may apply, are summarized in Fig. 2. The different categories **[AH$_{SoC}$, AH$_{not}$, AL$_{SoC\text{-}T+}$, AL$_{SoC\text{-}T}$, AL$_{not}$, LocA, and Loc]** are also referred to in the text below, whenever relevant.

Of note, this consensus was built on the basis of currently available data and knowledge regarding NTRK gene fusion-driven cancers and Trk inhibitors as well as the available standard of care for tumor types. As precision oncology is a rapidly evolving field, the recommendations put forth here may have to be updated in the future should new information come to light.

3.1. *Diagnostic approach for NTRK gene fusion-driven cancers*

We agree that, **ideally, all locally advanced and metastatic solid tumors [AH$_{SoC}$, AH$_{not}$, AL$_{SoC\text{-}T+}$, AL$_{SoC\text{-}T}$, AL$_{not}$, LocA]** should be systematically tested for NTRK gene fusions (eventually via pre-screening with IHC followed or directly by confirmatory testing by RNA-NGS, RT-PCR, or FISH) in parallel to other actionable oncogenic drivers. Molecular testing should be conducted **at the time of diagnosis**, as recommended by the Belgian Personalized Medicine Commission (ComPerMed, 2021).

However, for tumor types that already undergo **broad genomic testing via DNA and RNA-NGS** at the time of diagnosis **[AL$_{SoC\text{-}T+}$]** (e.g., advanced lung adenocarcinoma and squamous cell), we suggest the inclusion of NTRK gene fusion testing in the RNA-NGS testing panel. In particular for small biopsies (e.g., small bronchial biopsies in lung cancer patient), DNA-NGS and/or RNA-NGS testing should be prioritized over IHC as NGS analyses deliver optimum results with minimum sample requirements, and the inclusion of NTRK gene fusion testing in the testing panel would entail little to no additional cost or burden of work.

While testing **all locally advanced and metastatic** solid tumors in

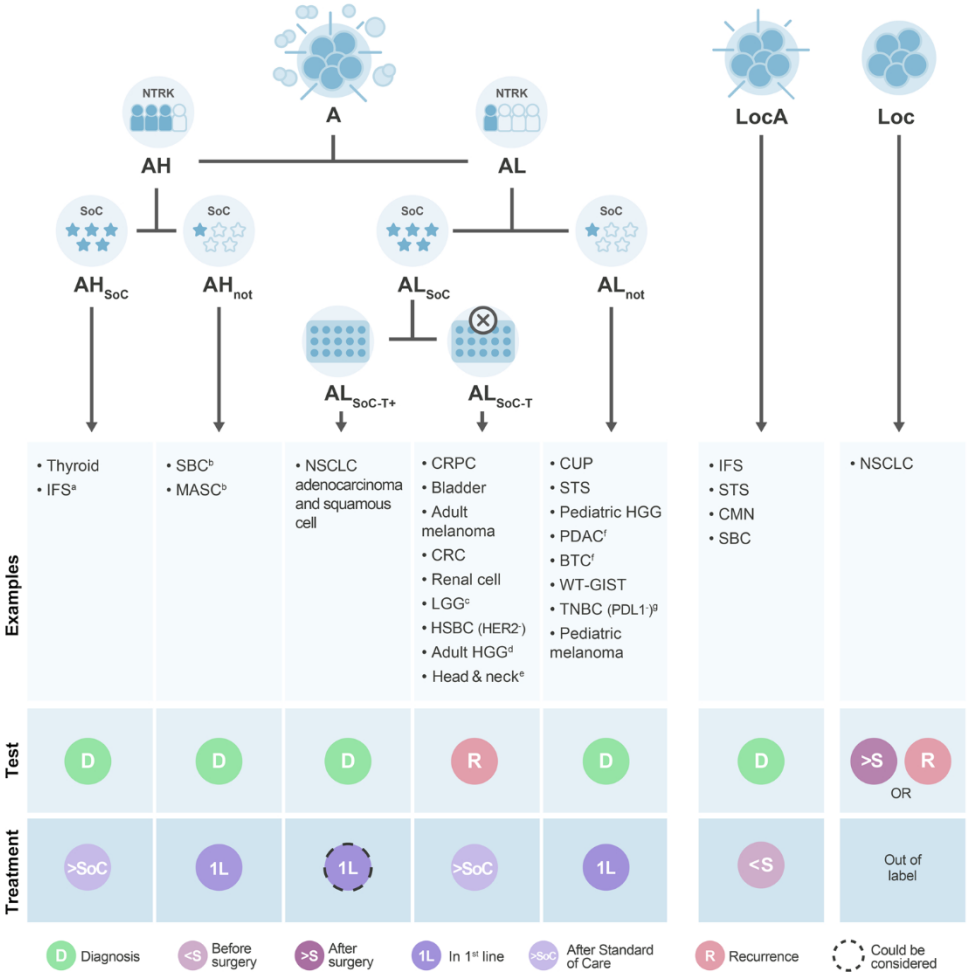

Fig. 2. Algorithm for the timing of NTRK gene fusion testing and larotrectinib treatment for given cancer types according to disease advancement, NTRK gene fusion prevalence, and availability of a satisfactory standard of care.

A, advanced (unresectable/metastatic) solid tumors; **LocA**, locally advanced solid tumors; **Loc**, localized solid tumors (in which clinically actionable information can be useful in later disease stage); **AH**, A tumors with high prevalence of NTRK gene fusions; **AL**, A tumors with low prevalence of NTRK gene fusions; **AH_{SoC}**, AH tumors with satisfactory SoC available; **AH_{not}**, AH tumors with non-satisfactory SoC; **AL_{SoC}**, AL tumors with satisfactory SoC available; **AL_{not}**, AL tumors with non-satisfactory SoC; **AL_{SoC-T+}**, AL_{soc} tumors on which broad molecular testing is carried out in routine; **AL_{SoC-T}**, AL_{soc} tumors on which broad molecular testing is not carried out in routine.

For the present consensus, a satisfactory SoC is defined as a SoC significantly improving patient outcome as determined by efficacy (ORR, OS), duration of response (DOR, PFS), time to response, safety, and QoL. The lists of cancer types used as examples for each category are non-exhaustive; tumor types should be assessed on a case-by-case basis to determine if they belong to a given category. [a] For IFS patients, it is reasonable to consider larotrectinib as 1 L treatment in case of severe illness and/or toxicity of SoC. [b] Testing for NTRK gene fusions is needed for proper diagnosis of this specific tumor type. [c] With the exception of IDH-WT astrocytoma which is considered as a HGG. [d] For adult glioblastoma, testing should be done at diagnosis and larotrectinib treatment could be considered after the 1 L SoC, i.e., chemo-radiotherapy. [e] With the exception of salivary gland tumors, for which NTRK fusion testing should be done at diagnosis and larotrectinib treatment considered as 1 L. [f] For aggressive forms of PDAC and BTC, larotrectinib could be considered after 1 L SoC. [g] PDL1-positive subtypes should be tested at recurrence after 1 L SoC and larotrectinib treatment could be considered in 2 L. 1 L, first line treatment; 2 L, second line treatment; BTC, Biliary tract carcinoma; CMN, congenital mesoblastic nephroma; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CUP, cancers of unknown primary site; DOR, duration of response; HGG, high grade glioma; HER2, human epidermal growth factor receptor 2; HSBC (HER2$^-$), hormone-sensitive HER2-negative breast cancer; IDH-WT, isocitrate dehydrogenase-wild type; IFS, infantile fibrosarcoma; LGG, low grade glioma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PDL1, programmed death-ligand 1; PFS, progression-free survival; SBC, secretory breast cancer; SCC, squamous cell carcinoma; SoC, standard of care; STS, soft tissue sarcoma; TNBC (PDL1$^-$), PDL1-negative triple-negative breast cancer; WT-GIST, wild type gastrointestinal stromal tumors; QoL, quality of life.

parallel would without doubt enable early detection of clinically actionable oncogenic drivers and generally improve first line treatment choices, several obstacles associated to the reality of clinical settings, such as limitations in testing capacities and in the number of tests that can be carried out on some tumor tissue samples, can impede the testing process. Therefore, we suggest an alternative testing strategy, namely that **systematic NTRK gene fusion testing** should be done at diagnosis, at the very least in rare tumor types or tumor types with unsatisfactory treatment options, such as undifferentiated and anaplastic thyroid cancer, high grade glioma (HGG), pancreatic cancer, cholangiocarcinoma, microsatellite instability-high (MSI-H) colorectal cancer (CRC), salivary gland carcinoma, soft tissue sarcoma (STS) and pediatric cancers, etc. **For other tumor types**, we propose carrying out **NTRK gene fusion testing serially**, after testing for other more common clinically actionable oncogenic drivers. However, such an approach would come at the price of failing to detect NTRK gene fusions early enough for first line treatment of a number of patients.

[Loc] with high risk of recurrence in which clinically actionable information can be useful in later disease stage (e.g., HGG, surgical or locoregional stage lung adenocarcinoma, etc.), testing for NTRK gene fusions could be done immediately after surgery or, alternatively, at first disease recurrence or tumor progression.

Finally, for tumor types with a very high prevalence of NTRK gene fusions (>80 %), such as secretory breast cancer (SBC), infantile fibrosarcoma (IFS), mammary analogue of the salivary gland carcinoma (MASC), and congenital mesoblastic nephroma (CMN), NTRK gene fusion testing is required for complete, reliable diagnosis. For such cancer types, testing should be carried out at diagnosis using confirmatory testing methods (RNA-NGS, RT-PCR, or FISH) directly rather than an initial IHC prescreening followed by subsequent confirmatory testing.

Additionally, we would also like to highlight the continuous research being performed to facilitate NTRK gene fusion testing further, e.g. by adding plasma next-generation sequencing of circulating tumour DNA (ctDNA) to tissue-based testing the detection rate of oncogenic drivers is

increased. Rolfo et al. demonstrated that ctDNA NGS is a rapid, non-invasive screening method for this rare genomic target that may improve identification of patients who can benefit from TRK-targeted therapy (Rolfo et al., 2021).

3.2. Larotrectinib treatment in NTRK gene fusion positive cancers

To define the place of larotrectinib in the treatment sequence for patients with NTRK gene fusion-driven tumors, we propose a categorization based on the degree of **disease advancement** (unresectable/metastatic vs. locally advanced), the **prevalence of NTRK gene fusions**, and, most importantly, the non-satisfactory outcome for **the SoC** of given cancer types.

For the present consensus, tumor types with unmet medical need are defined as cancers lacking a SoC that significantly improves patient outcome, assessed with regards to treatment efficacy (ORR, PFS, overall survival [OS]), DOR, time to response, safety profile, and patient QoL.

The criterion referring to the prevalence of NTRK gene fusions was specifically included in the categorization to highlight the importance of the testing and treatment not only for tumor types with high frequencies of NTRK gene fusions, but also for tumors with lower prevalence of these genetic alterations.

3.2.1. Advanced solid tumors with non-satisfactory SoC

For patients with **advanced** (unresectable, metastatic) solid tumors with **unmet medical need [AH_{not}, AL_{not}]**, larotrectinib should be considered as a **first line** treatment regardless of the prevalence of NTRK gene fusions. Examples of tumor types that fit into this category include salivary gland carcinoma, cancers of unknown primary site, most STS (especially rare sub-types), pediatric HGG, pancreatic ductal adenocarcinoma, cholangiocarcinoma, wild-type gastrointestinal stromal tumors (GIST), triple negative breast cancer (with the exception of programmed death-ligand 1 [PDL1] positive subtypes), and pediatric melanoma. Please note that the previous list is non-exhaustive; The treating physician should evaluate on case by case basis if certain tumor types provide his patient adequately satisfactory SoC or not.

Salivary gland carcinoma, such as MASC (known for its very high prevalence of NTRK gene fusions) are considered not to have a satisfactory SoC because response to chemotherapy is limited and presents high toxicity. In these tumor types, NTRK gene fusion testing should be performed at diagnosis and, for NTRK gene fusion-positive cases, larotrectinib should be considered as first line treatment, particularly in absence of other targets such as AR (androgen receptor). This contrasts to other head and neck cancers (mainly squamous cell and lymphoma subtypes), for which a satisfactory SoC is available (see Section 3.2.2 'Advanced solid tumors with satisfactory SoC' below for further information).

Similarly, chemotherapeutic SoC for **cancers of unknown primary site** are currently non satisfactory and these cancer types should be tested for NTRK gene fusions prior to the first line of treatment to keep larotrectinib as an early treatment option.

While a SoC currently exists for **STS,** response rates suggest it does not significantly improve patient outcome. In addition, most sarcoma subtypes are not very sensitive to chemotherapy. NTRK gene fusion testing should therefore be carried out at early stages (in particular for rare sub-types of STS) in order for larotrectinib to be potentially used as a first line treatment.

With regards to **pediatric HGG**, due to the absence of standard treatment guidelines and the fact that the most common therapeutic approaches (surgery, radiotherapy, and chemotherapy) are rarely curative, early testing for NTRK gene fusion and first line treatment with larotrectinib appears of particular interest, in particular for younger children with non-brainstem disease, for which NTRK gene fusion prevalence is notoriously high (Wu et al., 2014). Such an approach was recently the object of a case report, wherein regression of ETV6-NTRK3 [illegible] 8-month old child after first line treatment with larotrectinib (Alharbi et al., 2020). This contrasts with **adult HGG**, for which radiotherapy, generally in combination with temozolomide or other chemotherapy is considered to be a satisfactory first line SoC (please refer to Section 3.2.2 'Advanced solid tumors with satisfactory SoC' below for further information).

NTRK gene fusion testing should be performed at diagnosis for **pancreatic ductal adenocarcinoma** (ideally after excluding the presence of KRAS mutations) and **cholangiocarcinoma**, and, in NTRK gene fusion-positive cases, larotrectinib could be considered as a first line treatment, in particular in young and fit patients. However, as these tumor types are notoriously aggressive, should the treating physician anticipate delays in obtaining results, chemotherapeutic treatment may be initiated while testing is still being carried out. In such cases, larotrectinib may be considered as a second line treatment following this initial round of chemotherapy treatment or, if there is a lack of response or excessive toxicity of chemotherapy, first line treatment may be shifted towards larotrectinib. In addition, if there are indications that disease is progressing despite larotrectinib treatment administration, we advise not waiting three months before re-assessing treatment options.

As **wild-type subtypes of GIST** show relatively poor response to chemotherapy and other treatments, NTRK gene fusion testing should ideally be carried out at diagnosis, and, if the presence of NTRK gene fusions is highlighted, larotrectinib treatment should be considered as a first line treatment.

For **PDL1-negative triple negative breast cancer and breast cancer of the secretory type** (known for its very high prevalence of NTRK gene fusions), we advise NTRK gene fusions to be tested at diagnosis. Larotrectinib can be considered as first line treatment in NTRK gene fusion-positive cases. For PDL1-positive triple negative breast cancer subtypes, NTRK gene fusion testing should be done at disease recurrence or after failure of first line immune-oncology treatment and larotrectinib could be considered as a subsequent line of treatment in positive cases.

Finally, due to its rarity and the subsequent lack of research and satisfactory treatment options, **pediatric melanoma** should also be tested at diagnosis to keep larotrectinib as a potential first line treatment. This contrasts with adult melanoma, for which immune-oncology treatment and BRAF/MEK-inhibitors are considered as a satisfactory first line SoC (see Section 3.2.2 'Advanced solid tumors with satisfactory SoC' below for further information).

3.2.2. Advanced solid tumors with satisfactory SoC

For patients with **advanced** (unresectable, metastatic) solid tumors for which there is a satisfactory **SoC [AH_{SoC}, AL_{SoC}]**, larotrectinib treatment should be considered **in a second or later line** (after failure of SoC). Such a strategy may, for example, be applied to metastatic castration-resistant prostate cancer, bladder cancer, renal cell carcinoma, thyroid cancer, SCC and lymphoma subtypes of the head & neck, IFS, adult melanoma, adult HGG, CRC, advanced NSCLC adenocarcinoma and squamous cell subtypes, low grade glioma (with the exception of isocitrate dehydrogenase [IDH] wild type astrocytoma), and hormone-sensitive human epidermal growth factor receptor 2 (HER2) negative breast cancer. Please note that the previous list is non-exhaustive; tumor types should be assessed on a case-by-case basis to determine if they belong to this category.

For **prostate cancer**, specifically **metastatic castration-resistant** disease, NTRK gene fusion testing should be carried out immediately after the first line treatment due to the fact that a high proportion (~40 %) of patients have rapidly progressive disease despite treatment with the SoC. This early assessment of the NTRK gene fusion status would enable the use of larotrectinib as a second line treatment for NTRK gene fusion-positive cases. The same approach could be applied to **bladder cancer** and **renal cell cancer**, in particular if the patient does not respond to treatment with checkpoint inhibitors.

As the NTRK gene fusion-driven variants of **thyroid cancer** appear to be particularly aggressive and also display good responses to Trk

inhibition (Chu et al., 2020), larotrectinib should be administered after failure of radioactive iodine treatment in order to limit the burden and long-term adverse effects of repeated exposure to radioactive treatment, which implies that testing should ideally occur at diagnosis in order to have an immediate next line option in case of relapse.

Head and neck cancers of squamous cell and lymphoma subtype should ideally already be tested at time of diagnosis of metastatic disease, however larotrectinib treatment could be considered after first line SoC. As discussed above, these recommendations do not apply to salivary gland carcinoma (please refer to Section 3.2.1 'Advanced solid tumors with non-satisfactory SoC' above for more information).

Chemotherapy is currently the recommended first line treatment for **IFS**. However, as argued in a 2020 international consensus, an exception to this guideline should be made for IFS patients with metastatic disease or who require quick treatment response (Orbach et al., 2020). In these specific cases and cases where conventional treatment might result in severe adverse events, it is reasonable to consider larotrectinib as a first line treatment, which implies that testing should ideally occur at diagnosis. In light of the high prevalence of NTRK gene fusions driving IFS (>95 %), testing for NTRK fusions is even required to properly diagnose this specific tumor type (Cocco et al., 2018).

For **adult melanoma** (regardless of PDL1 status), NTRK gene fusion testing should be done in all unresectable or metastatic patients for whom other actionable drivers, in particular *BRAF* and *NRAS* mutations, have not been detected, and larotrectinib may be considered after first line immune-oncology treatment. As discussed above, these recommendations do not apply to pediatric melanoma (please refer to Section 3.2.1 'Advanced solid tumors with non-satisfactory SoC' above for more information).

Adult HGG patients should ideally already be tested for NTRK gene fusions at diagnosis, due to the high chances of recurrence. This would enable the use of larotrectinib as a second line treatment for NTRK gene fusion-positive cases, after first line radiotherapy – chemotherapy treatment. As discussed above, these recommendations do not apply to pediatric HGG (please refer to Section 3.2.1 'Advanced solid tumors with non-satisfactory SoC' above for more information).

For **CRC**, NTRK gene fusion testing should ideally be done at diagnosis, however, due to the fact that there is little concordance between the MSI-H/mismatch repair-deficient (MMRd) status and NTRK gene fusion status, testing is likely to be carried out after the first line of treatment. In patients with MSI-H/MMRd tumors undergoing first line pembrolizumab treatment, testing for NTRK gene fusions should be done after this first line so that larotrectinib can be considered for the second line of treatment. In patients with microsatellite stable (MSS)/ mismatch repair (MMR) proficient tumors, NTRK gene fusion testing should be done in wild type patients (*RAS* & *BRAF*-negative) following failure of first line chemotherapy combinations, and larotrectinib could be considered as a subsequent line of treatment. As described in the previous section, if NTRK gene fusion testing is included as part of a broad genomic testing panel (duo DNA & RNA NGS) carried out at the time of diagnosis of metastatic CRC or advanced NSCLC adenocarcinoma and squamous cell subtypes, larotrectinib can only be considered a first line treatment option if the treating physician considers the available treatment option not adequately satisfactory. The treating physician should evaluate on case by case basis if certain tumor types provide his/her patient adequately satisfactory SoC or not (Planchard et al., 2018).

Hormone-sensitive HER2 negative breast cancer patients should be tested for NTRK gene fusions after other treatment options (hormone-based therapy, biological agents, and first line chemotherapy) have been exhausted, and larotrectinib could thereafter be considered for treatment of NTRK gene fusion-positive cases.

Patients with **low grade glioma (with exception of IDH-wild type astrocytoma)** generally have a good prognosis, and current SoC (resection, concurrent chemotherapy and radiotherapy) provides dura- control of the disease while being relatively well tolerated. There- on testing should be carried out after disease relapse or if the disease progresses to a HGG subtype (please refer to Section 3.2.1 'Advanced solid tumors with non-satisfactory SoC' above for testing and treatment recommendations for HGG), and, for NTRK gene fusion-positive disease, larotrectinib can be considered as second line treatment. For **IDH-wild type astrocytoma**, which is generally considered and treated as a HGG (please refer to Section 3.2.1 'Advanced solid tumors with non-satisfactory SoC' above), early testing and use of larotrectinib as a second line treatment for NTRK gene fusion-positive disease is preferable.

For cancers where the treating physician considers the available SoC not as adequately satisfactory, the use of larotrectinib as a first line treatment could be considered in order to alleviate the risk of treatment attrition associated with sequential lines of therapy. Examples of this adapted strategy could include **advanced NSCLC adenocarcinoma** or **metastatic CRC patients** with of a positive result following the NTRK gene fusion testing carried out at the time of diagnosis.

3.2.3. *Locally advanced solid tumours*

For patients with **locally advanced** tumors **[LocA]** where surgery can result in severe morbidity, larotrectinib could be considered as **neoadjuvant** therapy.

Such a recommendation was previously made by the 2020 international consensus for locally advanced cases of **IFS** in order to avoid potentially debilitating surgery (Orbach et al., 2020). The successful use of larotrectinib as neoadjuvant therapy in an **STS** patient was previously reported in Belgium, with the patient achieving a partial response enabling curative limb-sparing surgery (Percy et al., 2021). Similarly, neoadjuvant larotrectinib treatment may also be considered for **congenital mesoblastic nephroma** (**CMN**; which the present consensus posits may in fact be a renal form of IFS) if the tumor cannot be surgically removed (DuBois et al., 2018), though such cases are rare. **Secretory breast cancer** (both adult and pediatric forms) is another tumor type that is included in this category, with the aim of improving chances of successful resectability during later surgical procedures.

4. Conclusions and perspectives

The benefits of larotrectinib as a tumor-agnostic treatment for adult and pediatric patients with NTRK gene fusion-driven cancers are currently supported by the recent efficacy data, rapid and durable clinical responses, improvements in QoL, and favorable safety profile of the drug. Despite the overall rarity of NTRK gene fusions, the availability of a targeted treatment, added to the fact that gene fusions-positive cancer patients have a relatively poor prognosis, highlights the importance of early testing for this clinically actionable target and subsequent treatment of NTRK gene fusion-positive patients.

While screening of all metastatic and locally advanced patients for NTRK gene fusions should be considered with the aim of providing adequate treatment to target patients as early as indicated, the reality of clinical settings requires some degree of compromise. In this consensus, considering the limitations and obstacles of real-world clinical settings, we propose a categorization of cancer types based on disease advancement, NTRK gene fusion prevalence, and unmet medical need with regards to SoC and, for each category, provide concrete guidance regarding the timing of NTRK gene fusion testing and place of larotrectinib in the treatment algorithm.

Author contributions

Authors contributed equally to the development of the present consensus.

Role of the funding source

Bayer SA-NV Belgium set up two expert meetings to discuss the NTRK fusion-driven cancer diagnostics and the best use of larotrectinib

in real-world clinical settings. All authors, with the exception of Thierry Berghmans, received a consultancy honorarium from Bayer. Bayer also provided funding to Modis for writing the meeting minutes, drafting the manuscript and manuscript submission.

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.

Acknowledgements

We wish to thank the Modis platform for editorial assistance and manuscript coordination, on behalf of Bayer. Marc Pirson provided medical writing support and Pauline De Berdt coordinated manuscript development.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2021.103564.

References

Alharbi, M., Mobark, N.A., Balbaid, A.A.O., Alanazi, F.A., Aljabarat, W.A.R., Bakhsh, E. A., et al., 2020. Regression of ETV6-NTRK3 infantile glioblastoma after first-line treatment with larotrectinib. JCO Precis. Oncol. 4 https://doi.org/10.1200/PO.20.00017. PO.20.00017.

Amatu, A., Sartore-Bianchi, A., Bencardino, K., Pizzutilo, E.G., Tosi, F., Siena, S., 2019. Tropomyosin receptor kinase (TRK) biology and the role of NTRK gene fusions in cancer. Ann. Oncol. 30, viii5–15. https://doi.org/10.1093/annonc/mdz383.

Bazhenova, L., Jiao, X., Lokker, A., Snider, J., Castellanos, E., Nanda, S., et al., 2020. Abstract 09: cancers with NTRK gene fusions: molecular characteristics and prognosis. Clin. Cancer Res. 26, 09. https://doi.org/10.1158/1557-3265.ADVPRECMED20-09.

Bourgeois, J.M., Knezevich, S.R., Mathers, J.A., Sorensen, P.H., 2000. Molecular detection of the ETV6-NTRK3 gene fusion differentiates congenital fibrosarcoma from other childhood spindle cell tumors. Am. J. Surg. Pathol. 24, 937–946. https://doi.org/10.1097/00000478-200007000-00005.

Chu, Y.-H., Dias-Santagata, D., Farahani, A.A., Boyraz, B., Faquin, W.C., Nosé, V., et al., 2020. Clinicopathologic and molecular characterization of NTRK-rearranged thyroid carcinoma (NRTC). Mod. Pathol. 33, 2186–2197. https://doi.org/10.1038/s41379-020-0574-4.

ClinicalTrials.gov. Study to Learn More about the Safety and Effectiveness of the Drug Vitrakvi During Routine Use in Patients With Trk Fusion Cancer Which Is Locally Advanced or Spread From the Place Where It Started to Other Places in the Body (ON-TRK) [NCT04142437] [last accessed 23/03/2021]. https://clinicaltrials.gov/ct2/show/NCT04142437?cond=NTRK&cntry=BE&draw=2&rank=4.

Cocco, E., Scaltriti, M., Drilon, A., 2018. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat. Rev. Clin. Oncol. 15, 731–747. https://doi.org/10.1038/s41571-018-0113-0.

ComPerMed. Workflows [last accessed 22/03/2021]. https://www.compermed.be/en/workflows.

Drilon, A.E., Hong, D.S., Cruickshank, S., Deegan, M., Ku, N., Hyman, D.M., 2016. A phase II basket study of the oral TRK inhibitor LOXO-101 in adult subjects with NTRK fusion-positive tumors. Clin. Oncol. 34, TPS2599. https://doi.org/10.1200/JCO.2016.34.15_suppl.TPS2599.

Drilon, A., Laetsch, T.W., Kummar, S., DuBois, S.G., Lassen, U.N., Demetri, G.D., et al., 2018. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N. Engl. J. Med. 378, 731–739. https://doi.org/10.1056/NEJMoa1714448.

Drilon, A.E., DuBois, S.G., Farago, A.F., Geoerger, B., Grilley-Olson, J.E., Hong, D.S., et al., 2019. Activity of larotrectinib in TRK fusion cancer patients with brain metastases or primary central nervous system tumors. J. Clin. Oncol. 37, 2006-. https://doi.org/10.1200/JCO.2019.37.15_suppl.2006.

Drilon, A., van Tilburg, C.M., Farago, A.F., Kummar, S., Berlin, J., Albert, C.M., et al., 2020. Abstract CT199: Larotrectinib in TRK fusion cancer patients: Outcomes by prior therapy and performance status. Cancer Res. 80, CT199. https://doi.org/10.1158/1538-7445.AM2020-CT199.

DuBois, S.G., Laetsch, T.W., Federman, N., Turpin, B.K., Albert, C.M., Nagasubramanian, R., et al., 2018. The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. Cancer 124, 4241–4247. https://doi.org/10.1002/cncr.31701.

El Demellawy, D., Cundiff, C.A., Nasr, A., Ozolek, J.A., Elawabdeh, N., Caltharp, S.A., et al., 2016. Congenital mesoblastic nephroma: a study of 19 cases using [illegible]gene rearrangement. J. Pathol. 48, [illegible]007.

European Medicines Agency, 2019. First 'Histology-Independent' Treatment for Solid Tumours with a Specific Gene Mutation.

European Medicines Agency. Vitrakvi: Annex 1 - Summary of Product Characteristics [last accessed 05/11/2929]. https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf.

European Medicines Agency. Rozlytrek, INN Entrectinib: Annex 1 - Summary of Product Characteristics [last accessed 23/03/2021]. https://www.ema.europa.eu/en/documents/product-information/rozlytrek-epar-product-information_en.pdf.

Federman, N., McDermott, R., 2019. Larotrectinib, a highly selective tropomyosin receptor kinase (TRK) inhibitor for the treatment of TRK fusion cancer. Expert Rev. Clin. Pharmacol. 12, 931–939. https://doi.org/10.1080/17512433.2019.1661775.

Food and Drug Administration, 2018. FDA Approves Larotrectinib for Solid Tumors with NTRK Gene Fusions.

Food and Drug Administration. Highlights of Prescribing Information: Rozlytrek (entrectinib). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212725s000lbl.pdf.

Italiano, A., Nanda, S., Briggs, A., Garcia-Foncillas, J., Lassen, U., Vassal, G., et al., 2020a. Larotrectinib versus prior therapies in tropomyosin receptor kinase fusion cancer: an intra-patient comparative analysis. Cancers (Basel) 12, 3246. https://doi.org/10.3390/cancers12113246.

Italiano, A., Hong, D., Briggs, A., Garcia-Foncillas, J., Lassen, U.N., Vassal, G., et al., 2020b. 542P Growth modulation index (GMI) of larotrectinib versus prior systemic treatments for TRK fusion cancer patients. Ann. Oncol. 31, S473. https://doi.org/10.1016/j.annonc.2020.08.656.

Kojadinovic, A., Laderian, B., Mundi, P.S., 2021. Targeting TRK: a fast-tracked application of precision oncology and future directions. Crit. Rev. Oncol. Hematol. 165, 103451. https://doi.org/10.1016/j.critrevonc.2021.103451.

Kummar, S., Van Tilburg, C.M., Albert, C.M., Berlin, J., Farago, A.F., McDermott, R.S., et al., 2020. Quality of life of adults and children with TRK fusion cancer treated with larotrectinib compared to the general population. Clin. Oncol. 38, 3614. https://doi.org/10.1200/JCO.2020.38.15_suppl.3614.

Laetsch, T.W., DuBois, S.G., Mascarenhas, L., Turpin, B., Federman, N., Albert, C.M., et al., 2018. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol. 19, 705–714. https://doi.org/10.1016/s1470-2045(18)30119-0.

McDermott, R., van Tilburg, C.M., Farago, A.F., Kummar, S., Tan, D.S.W., Albert, C.M., et al., 2020. 1955P Survival benefits of larotrectinib in an integrated dataset of patients with TRK fusion cancer. Ann. Oncol. 31, S1101. https://doi.org/10.1016/j.annonc.2020.08.1347.

Orbach, D., Sparber-Sauer, M., Laetsch, T.W., Minard-Colin, V., Bielack, S.S., Casanova, M., et al., 2020. Spotlight on the treatment of infantile fibrosarcoma in the era of neurotrophic tropomyosin receptor kinase inhibitors: International consensus and remaining controversies. Eur. J. Cancer 137, 183–192. https://doi.org/10.1016/j.ejca.2020.06.028.

Percy, C., Schubert, T., Galant, C., Kirchgesner, T., Mazzeo, F., 2021. Larotrectinib in a NTRK-rearranged soft tissue sarcoma in the neoadjuvant setting: a case report. Clin. Case Rep. 9, 1694–1698. https://doi.org/10.1002/ccr3.3878.

Perreault, S., Doz, F., Drilon, A., Geoerger, B., Boni, V., Chisholm, J., et al., 2020. CTNI-67. Efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (Trk) fusion primary central nervous system (CNS) tumors: an expanded dataset. Neuro-Oncol. 22, ii58. https://doi.org/10.1093/neuonc/noaa215.233.

Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E.F., Faivre-Finn, C., et al., 2018. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 29, iv192–iv237. https://doi.org/10.1093/annonc/mdy275.

Rolfo, C., Drilon, A., Hong, D., McCoach, C., Dowlati, A., Lin, J.J., et al., 2021. NTRK1 Fusions identified by non-invasive plasma next-generation sequencing (NGS) across 9 cancer types. Br. J. Cancer. https://doi.org/10.1038/s41416-021-01536-1.

Rosen, E.Y., Goldman, D.A., Hechtman, J.F., Benayed, R., Schram, A.M., Cocco, E., et al., 2020. TRK fusions are enriched in cancers with uncommon histologies and the absence of canonical driver mutations. Clin. Cancer Res. 26, 1624–1632. https://doi.org/10.1158/1078-0432.Ccr-19-3165.

Skalova, A., Vanecek, T., Sima, R., Laco, J., Weinreb, I., Perez-Ordonez, B., et al., 2010. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am. J. Surg. Pathol. 34, 599–608. https://doi.org/10.1097/PAS.0b013e3181d9efcc.

Solomon, J.P., Benayed, R., Hechtman, J.F., Ladanyi, M., 2019. Identifying patients with NTRK fusion cancer. Ann. Oncol. 30, viii16–22. https://doi.org/10.1093/annonc/mdz384.

Stransky, N., Cerami, E., Schalm, S., Kim, J.L., Lengauer, C., 2014. The landscape of kinase fusions in cancer. Nat. Commun. 5, 4846. https://doi.org/10.1038/ncomms5846.

Tognon, C., Knezevich, S.R., Huntsman, D., Roskelley, C.D., Melnyk, N., Mathers, J.A., et al., 2002. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell 2, 367–376. https://doi.org/10.1016/s1535-6108(02)00180-0.

Von Hoff, D.D., 1998. There are no bad anticancer agents, only bad clinical trial designs–twenty-first Richard and Hinda Rosenthal Foundation Award Lecture. Clin. Cancer Res. 4, 1079–1086 https://doi.org/N/A.

Wu, G., Diaz, A.K., Paugh, B.S., Rankin, S.L., Ju, B., Li, Y., et al., 2014. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat. Genet. 46, 444–450. https://doi.org/10.1038/ng.2938.

Ziegler, D.S., Wong, M., Mayoh, C., Kumar, A., Tsoli, M., Mould, E., et al., 2018. Brief Report: Potent clinical and radiological response to larotrectinib in TRK fusion-driven high-grade glioma. Br. J. Cancer 119, 693–696. https://doi.org/10.1038/s41416-018-0251-2.

Ahmad Awada is since 2005 Head of the Medical Oncology Clinic at Jules Bordet Cancer Institute Brussels, Belgium. In 2011, Dr Awada was held Associate Head of the Medicine Department. Then, in 2017, he became Head of the Oncology Medicine Department. He has an important clinical activity in the treatment of solid tumors and particularly breast cancer. Dr. Awada took an active part in the development of new drugs (cytotoxics, molecular-targeted therapies, immunotherapy). He is member of several international scientific societies (ASCO, EORTC, ESMO) and Professor of Clinical Medicine at the Université Libre de Bruxelles. He published 32 book chapters and 316 articles in international journals.

Thierry Berghmans is Doctor in Medicine since 1990 at the Université Libre de Bruxelles (ULB). He obtained his recognition in Internal Medicine in 1995, was further recognized in Medical Oncology and obtained his PhD in medical science in 2008. Currently he is Head of the Thoracic Oncology Clinic at the Institute Jules Bordet, Brussels, Belgium. He is Professor of Evidence-based Medicine at the ULB. He is (co-)author of more than 180 original articles in peer-reviewed journals and 15 book chapters. He is president of the European Lung Cancer Working Party and treasurer of the EORTC Lung Cancer Group. He is coordinator of cooperative academic trials as well as systematic reviews, meta-analyses and guidelines in thoracic oncology, and worked as expert at consensus conferences on mesothelioma. He is reviewer of scientific journals and is Editor-in-Chief of a French language journal as well as associate editor of two "lung" journals.

Paul Clement received his medical doctor degree in 1995 at the University of Leuven, Belgium. He obtained his recognition in Internal Medicine with special title in Medical Oncology in 2003, and obtained a Ph.D. in Biomedical Sciences in 2005. He is a board-certified medical oncologist and head of the Department of General Medical Oncology, at UZ Leuven. He is Associate Professor at the Faculty of Medicine, Department of Oncology, KU Leuven. He holds leadership roles in several national and international professional organizations. Prof. Clement is author of 120 peer reviewed papers, more than 150 abstracts, 5 book chapters and 3 worldwide patents.

Kristof Cuppens (MD MSc) received his medical degree in 2007 at the University of Leuven, Belgium. Dr. Cuppens further specialized in pulmonary medicine, thoracic oncology and endoscopy. He is currently staff member at the Jessa Hospital in Hasselt, Belgium where he is head of the thoracic oncology trial unit.

Bram De Wilde received his medical degree and his master in Biotechnology in 2005 and obtained his PhD in Health Sciences in 2015 of the University of Ghent, Belgium. He is currently a paediatric haemato-oncologist at Ghent University Hospital and a professor at the Ghent University. He is invested in basic and translational research in the field of paediatric oncology and takes up a PI role in multiple early phase clinical trials. He published more than 25 articles in international journals.

Jean-Pascal Machiels received his medical doctor degree in 1993 and obtained his PhD in medical sciences in 2003 at the Université catholique de Louvain (UCLouvain), Brussels, Belgium. He is head of the department of medical oncology and director of the oncology center Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels Belgium. His main interests are Head and Neck cancer, translational research, and early clinical trials (phase 1). Prof. Machiels published more than two hundreds papers reporting on clinical trials and translational research and is editor for 'Section Editor (Head and neck cancer' and 'European Journal of cancer'.

Patrick Pauwels obtained his MD certificate at the Catholic University of Leuven in 1985. After a two years fellowship in Internal Medicine, he started a residency in Pathology at the University of Leuven and worked then as a staff pathologist in Eindhoven till 2002. He went to the Maastricht University Medical Center till 2005. From 2005 till 2009 he was pathologist at the Ghent University Hospital. Since 2009 he works at the Antwerp University Medical Center. He obtained his PhD at the University of Leiden in 2004 in the field of molecular pathology. He is head of the laboratory of molecular pathology and co director of the Center of Oncology Research (CORE) of the Antwerp University. He became professor in Molecular Oncopathology at the Antwerp University in 2012 and is scientific advisor of the Luxemburg National Health Service since 2013. His principal interest is biomarker research in oncology, with a particular focus on liquid biopsy in cancer.

Marc Peeters is Professor of oncology at the Antwerp University, Belgium. He is head of the oncology department at the Antwerp University Hospital, coordinator of the Multidisciplinary Oncology Center Antwerp and also chairman of the College of Oncology. Previously, he was Coordinator of the Digestive Oncology Unit at the University Hospital in Ghent, Belgium. He completed his medical studies at the Catholic University in Leuven, Belgium and underwent additional training in Oncology and Digestive Oncology at several renowned international institutes. Dr. Peeters is board member of the Flemish Society of Gastroenterology, chair of the Belgian Group of Digestive Oncology and member of national and international Societies of Medical Oncology and the gastrointestinal group of the European Organisation for Research and Treatment of Cancer. Within EORTC, he is co-chair of the metastatic colorectal task force. He has been involved in many clinical studies on therapeutic agents for gastrointestinal tumors, published numerous articles in peer reviewed journals and was author of several chapters in oncology books.

Sylvie Rottey is trained as medical oncologist and clinical pharmacologist. In the clinical field she is involved in the treatment of urological cancers, head and neck cancers and thyroid cancers. She is heading the department of Medical Oncology and the Drug Research Unit Ghent at the Ghent University Hospital. She is involved in phase I-III clinical trials as a PI since more than 15 years. She is president of BSMO and BMUC, member of ASCO, ESMO, VWHHT, NVKFB, board member of Haelixia. She is publishing $>$ 10 articles on a yearly basis in national and international journals.

Eric Van Cutsem, MD, PhD, is full professor and Division Head of Digestive Oncology at University of Leuven (KUL) and University Hospitals Gasthuisberg, Leuven, Belgium. He became in 2018 doctor honoris causa of the Medical University of Warsaw, Poland. He is Member of the Belgian Royal Academy of Medicine and president of the Belgian Foundation against Cancer. His research focuses on the development of new treatment strategies for GI cancers, incl. drug development and identification of molecular markers and diagnostic tools. He published $>$ 616 articles in Pubmed and more than 1333 according Thomson Web of Science. He co-founded ESMO GI/World Congress on Gastrointestinal Cancer, and is Chair of the meeting in Barcelona, Spain. He serves/served on the board or key committee of ESMO, ASCO, EORTC, ENET, ECCO, ESDO, UEG, ESO and of the patient advocacy groups, Europacolon (medical director) and Digestive Cancers Europe. He was chairman of the governmental colon cancer prevention task force in Flanders, Belgium and was president of Belgian Group Digestive Oncology (BGDO) from 2010 to 2016 and is now treasurer. He was president of FAPA (Familial Adenomatous Polyposis Association) until 2016 and is now vice-president of FAPA.