Title

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Elective Discontinuation of Larotrectinib in Pediatric Patients With TRK Fusion Sarcomas and Related Mesenchymal Tumors

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ABSTRACT

Larotrectinib is a highly selective tropomyosin receptor kinase (TRK) inhibitor with efficacy in children with TRK fusion tumors. We evaluated patient outcomes after elective discontinuation of larotrectinib in the absence of disease progression in a protocol-defined wait-and-see subset analysis of eligible patients where treatment resumption with larotrectinib was allowed if disease progressed. We also assessed the safety and efficacy of larotrectinib in all pediatric patients with sarcoma. This cohort included 91 patients (younger than 18 years) from two clinical trials: infantile fibrosarcoma (49), other soft tissue sarcomas or related mesenchymal tumors (41), and bone sarcoma (1). Treatment-related adverse events were of maximum grade 1 or 2 in 25% and 25% of patients, respectively. The overall response rate was 87% (95% CI, 78 to 93). In the wait-and-see analysis, 47 patients discontinued larotrectinib. Median time from discontinuation to disease progression was not reached. Sixteen patients had tumor progression during the wait-and-see period. All 16 patients resumed larotrectinib, and 15 (94%) achieved disease control, with 11 objective responses. Larotrectinib continues to demonstrate durable responses with favorable safety in children with TRK fusion sarcomas. Treatment discontinuation is feasible in select patients with objective response and clinical benefit noted in those who have disease progression after elective treatment discontinuation.

ACCOMPANYING CONTENT

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INTRODUCTION

NTRK gene fusions are oncogenic drivers in infantile fibrosarcoma (IFS) and other sarcomas in pediatric patients.[1-5] Larotrectinib is a first-in-class, highly selective, tumor-agnostic tropomyosin receptor kinase (TRK) inhibitor used to treat patients with TRK fusion cancer.[2,6-8]

The optimal treatment duration and long-term adverse effects of larotrectinib in children are unknown. We evaluated the safety and efficacy of larotrectinib in the cohort of pediatric patients with TRK fusion sarcomas and related mesenchymal tumors from two larotrectinib clinical trials: SCOUT and NAVIGATE. SCOUT allowed the treating investigator to electively discontinue larotrectinib in the absence of on-treatment progressive disease (PD) and permitted the resumption of larotrectinib in patients who experienced disease progression after elective discontinuation in a wait-and-see cohort. To the best of our knowledge, this is the first report of patient outcomes from this wait-and-see analysis.

METHODS

Larotrectinib-treated pediatric patients with sarcoma in the SCOUT (ClinicalTrials.gov identifier: NCT02637687) phase I/II study and NAVIGATE (ClinicalTrials.gov identifier: NCT02576431) phase II basket trial formed the analytic cohort; the trial designs were previously published.[2,9,10] Protocols were approved by the independent review board/ethics committee at each site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. Patients and/or their parents signed an informed consent form before inclusion in the trials. Additional details are provided in the Data Supplement (online only).

In SCOUT, patients could stop larotrectinib in the event of on-study surgical resection or ongoing nonsurgical complete response (CR), partial response (PR) ≥1 year, or stable disease (SD) ≥2 years (wait-and-see). Patients who stopped

TABLE 1. Demographic and Clinical Characteristics

Characteristic	All Patients (N = 91)	Patients Who Entered the Wait-and-See Analysis (n = 47)
Age, years, median (range)	2.3 (0-18)	0.9 (0-13)
Sex, No. (%)		
Male	53 (58)	25 (53)
Female	38 (42)	22 (47)
ECOG performance status or equivalent Karnofsky/Lansky, No. (%)		
0	71 (78)	39 (83)
1	13 (14)	6 (13)
2	7 (8)	2 (4)
Disease status at enrollment, No. (%)		
Locally advanced	62 (68)	39 (83)
Metastatic	29 (32)	8 (17)
Years since diagnosis, median (range)	0.4 (0-18)	0.3 (0-6)
Histologic subtype, No. (%)		
IFS	49 (54)	30 (64)
Other STS and related mesenchymal tumors	41 (45)	17 (36)
Spindle cell	19 (21)	9 (19)
NOS	7 (8)	1 (2)
Malignant peripheral nerve sheath tumor	5 (6)	—
Inflammatory myofibroblastic tumor	4 (4)	3 (7)
Lipofibromatosis	1 (1)	1 (2)
Lipofibroma	1 (1)	1 (2)
Malignant mesenchymal tumor	1 (1)	—
Myofibromatosis	1 (1)	1 (2)
Myopericytoma	1 (1)	1 (2)
Small round cell	1 (1)	—
Bone sarcoma	1 (1)	—
Previous therapy, No. (%)[a]		
Surgery	38 (42)	13 (28)
Radiotherapy	6 (7)	1 (2)
Systemic therapy	57 (63)	26 (55)
No. of previous systemic therapies, No. (%)[b]		
Treatment-naïve	34 (37)	21 (45)
1	29 (32)	16 (34)
2	17 (19)	8 (17)
≥3	11 (12)	2 (4)
Best response to most recent previous therapy, No. (%)[c]		
CR	2 (2)	1 (2)
PR	9 (10)	4 (9)
SD	29 (32)	13 (28)
PD	11 (12)	4 (9)
Other[d]	9 (10)	4 (9)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; IFS, infantile fibrosarcoma; NOS, not otherwise specified; PD, progressive disease; PR, partial response; SD, stable disease; STS, soft tissue sarcoma.

[a]Patients may be counted in more than one row.

[b]Number of previous systemic regimens (excluding previous radioactive iodine) in the metastatic and/or unresectable setting.

[c]Percentages on the basis of the number of patients who received previous systemic therapy.

[d]Other includes unknown and not evaluable.

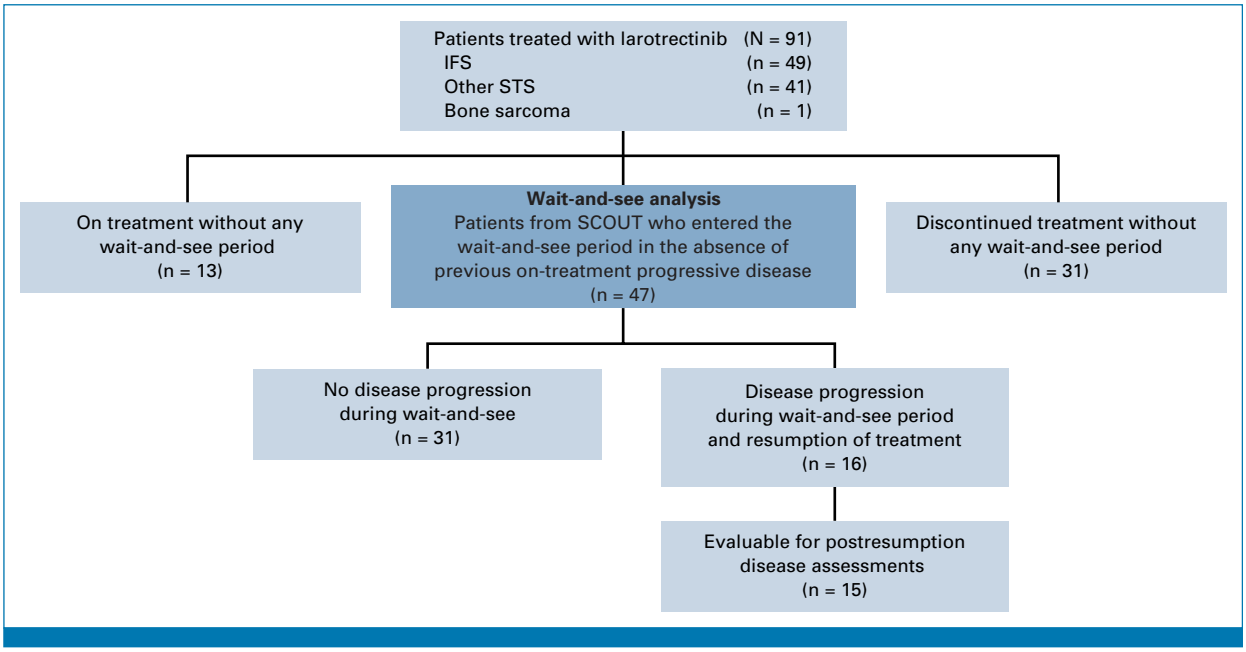

FIG 1. Flow diagram showing patient disposition at data cutoff. IFS, infantile fibrosarcoma; STS, soft tissue sarcoma.

larotrectinib were actively followed for disease progression and were allowed to resume larotrectinib if their tumor progressed (data cutoff: July 20, 2023).

RESULTS

Patient and Tumor Characteristics

The analytic cohort included 91 patients (SCOUT [90] and NAVIGATE [1]). Forty-nine (54%) patients had IFS, 41 (45%) had various other soft tissue sarcomas/related mesenchymal tumors (STS), and 1 (1%) had bone sarcoma (Table 1). Details on *NTRK* gene fusions, fusion partners, and testing methods used to identify *NTRK* gene fusions are provided in the Data Supplement (Tables A1 and A2).

Safety and Tolerability

The treatment duration in the 91 patients ranged from 1 to 87+ months (Data Supplement, Fig S1). Treatment-related adverse events were of maximum grade 1 or 2 in 23 (25%) and 23 (25%) patients, respectively (Data Supplement, Table A3).

Efficacy Outcomes

Ninety-one patients were assessed by the independent review committee for response. The overall response rate was 87% (95% CI, 78 to 93): 47 (52%) CR (including 13 pathologic complete response [pCR]), 32 (35%) PR, seven (8%) SD, three (3%) PD, and two (2%) not evaluable (Data Supplement, Fig S2). Additional efficacy outcomes are reported in the Data Supplement and Figures S3-S6.

Wait-and-See Analysis

Forty-seven patients entered a wait-and-see period; 30 (64%) had IFS and 17 (36%) had other STS (Fig 1). There were eight (17%) and 39 (83%) patients with metastatic and locally advanced disease, respectively. The median time from the start of initial larotrectinib treatment to discontinuation was 14.7 months in all patients (range, 3.0-64.6), 17.2 months in patients with IFS (range, 3.7-58.9), and 9.0 months in patients with other STS (range, 3.0-64.6). Twenty-one (45%) patients discontinued larotrectinib after an on-study tumor resection: 11 R0 resection (negative surgical margins including 10 pCR), 8 R1 resection (microscopic residual tumor), one R2 resection (macroscopic residual tumor), and one unknown surgery outcome. The median time from initial treatment start to discontinuation for these 21 surgical patients was 6.9 months (range, 3.0-25.7). The median time to discontinuation in the 26 (55%) patients without tumor resection after achieving CR (n = 15), PR (n = 10), or SD (n = 1) was 19.8 months (range, 11.1-64.6).

Of the 47 patients in the wait-and-see period, 16 (34%) had documented disease progression after elective discontinuation of larotrectinib (Fig 2). The time from larotrectinib discontinuation to disease progression in these 16 patients was <3 months (nine patients), 3 to <6 months (three patients), 6 to <12 months (two patients), 12 to <18 months (one patient), and ≥24 months (one patient). After a median follow-up of 41.3 months (95% CI, 31.0 to 50.0), the median time to progression in the 47 patients was not reached (range, 0+ to 77.6+). Median time from discontinuation to subsequent progression for the 21 surgical patients and for

Best Response Before or at the Time of Stopping Larotrectinib, No.	Surgical (n = 21)[a] pCR[b] (n = 10)	Unknown (n = 1)	R0 (n = 1)	R1 (n = 8)	R2 (n = 1)	Nonsurgical (n = 26)	Total (N = 47)
Time to stopping larotrectinib, months, median (range)	7 (5-22)	3 (3-3)	22 (22-22)	8 (4-26)	6 (6-6)	20 (11-65)	15 (3-65)
Progressed, No.	2	0	0	1	1	12	16
Time from stopping larotrectinib to progression, months, median (range)[c]	NR (0-76)	NR (50-50)	NR (36-36)	NR (1-78)	1 (1-1)	NR (1-59)	NR (0-78)
Duration of follow-up, months, median[d]	49	50	36	39	NR	41	41

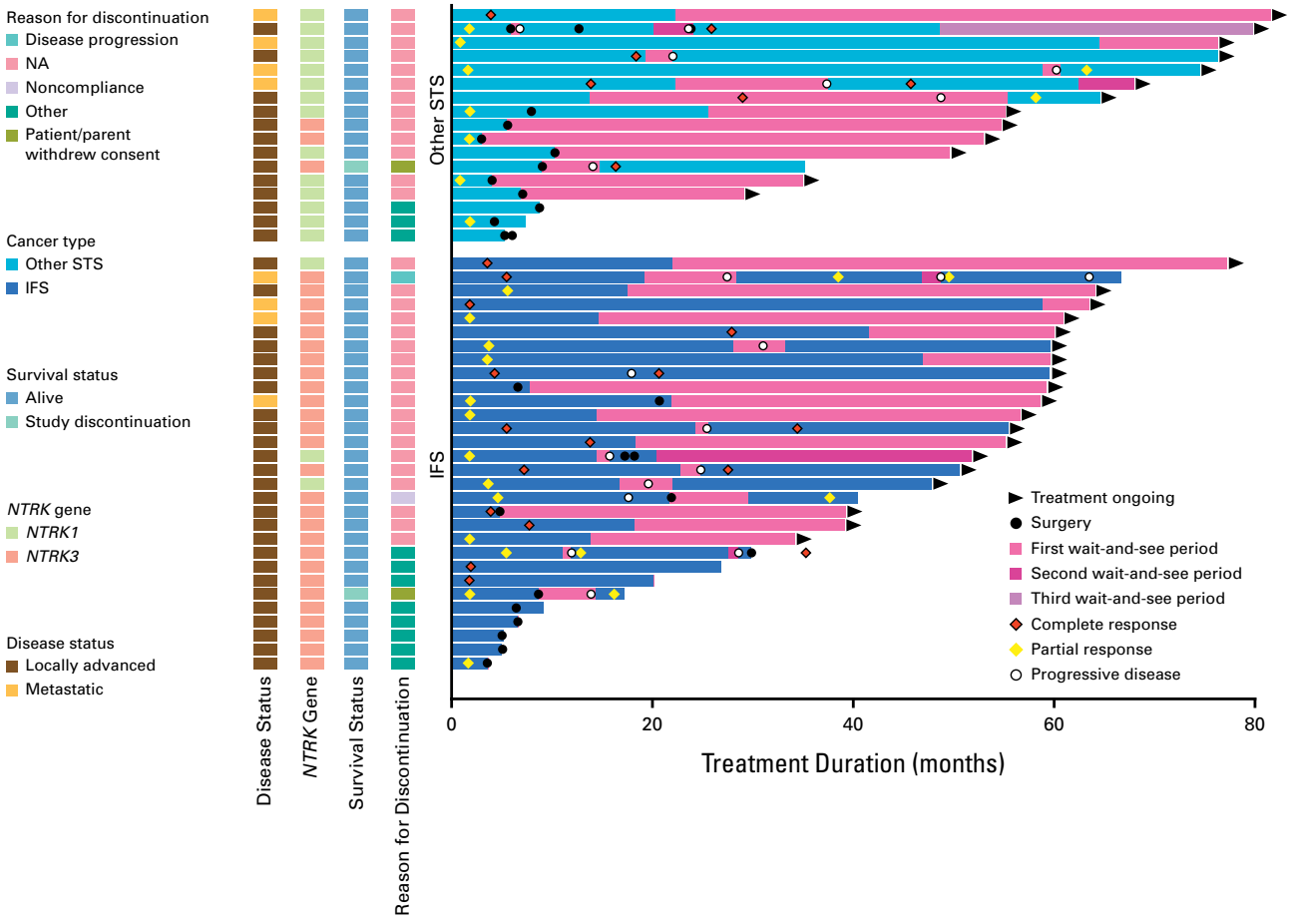

FIG 2. Pediatric patients with TRK fusion sarcoma who entered the wait-and-see analysis. [a]Surgery took place before or ≤1 week after discontinuation. [b]pCR is defined as no pathologic evidence of tumor, negative surgical margins, and no other evidence of disease. [c]Kaplan-Meier estimate. [d]Inverse Kaplan-Meier estimate. IFS, infantile fibrosarcoma; NA, not applicable; NR, not reached; pCR, pathologic complete response; STS, soft tissue sarcoma; TRK, tropomyosin receptor kinase.

the 26 nonsurgical patients was not reached (range, 0+ to 77.6+ and range, 0.9 to 59.2+, respectively) and was similar for patients with IFS or other STS (Figs 3A and 3B).

The 16 patients who progressed/relapsed during wait-and-see period resumed treatment with single-agent larotrectinib. The median time from drug hold to resumption of larotrectinib was 3.9 months (range, 0.9-41.6). Of the 16 patients who resumed larotrectinib, 11 patients (69%) had an objective response to treatment (five CR and six PR [two pending confirmation]) and four had SD. One patient restarted treatment and then had surgery, so the best overall response was undefined. The patient later had a second surgery which led to pCR, entered a second wait-and-see period, and was still in wait-and-see period at the time of the data cutoff. All 47 patients in the wait-and-see cohort were alive at the data cutoff time.

DISCUSSION

In this global multicenter clinical trial data set of, to our knowledge, the largest pediatric TRK fusion sarcoma population treated with a TRK inhibitor to date, larotrectinib

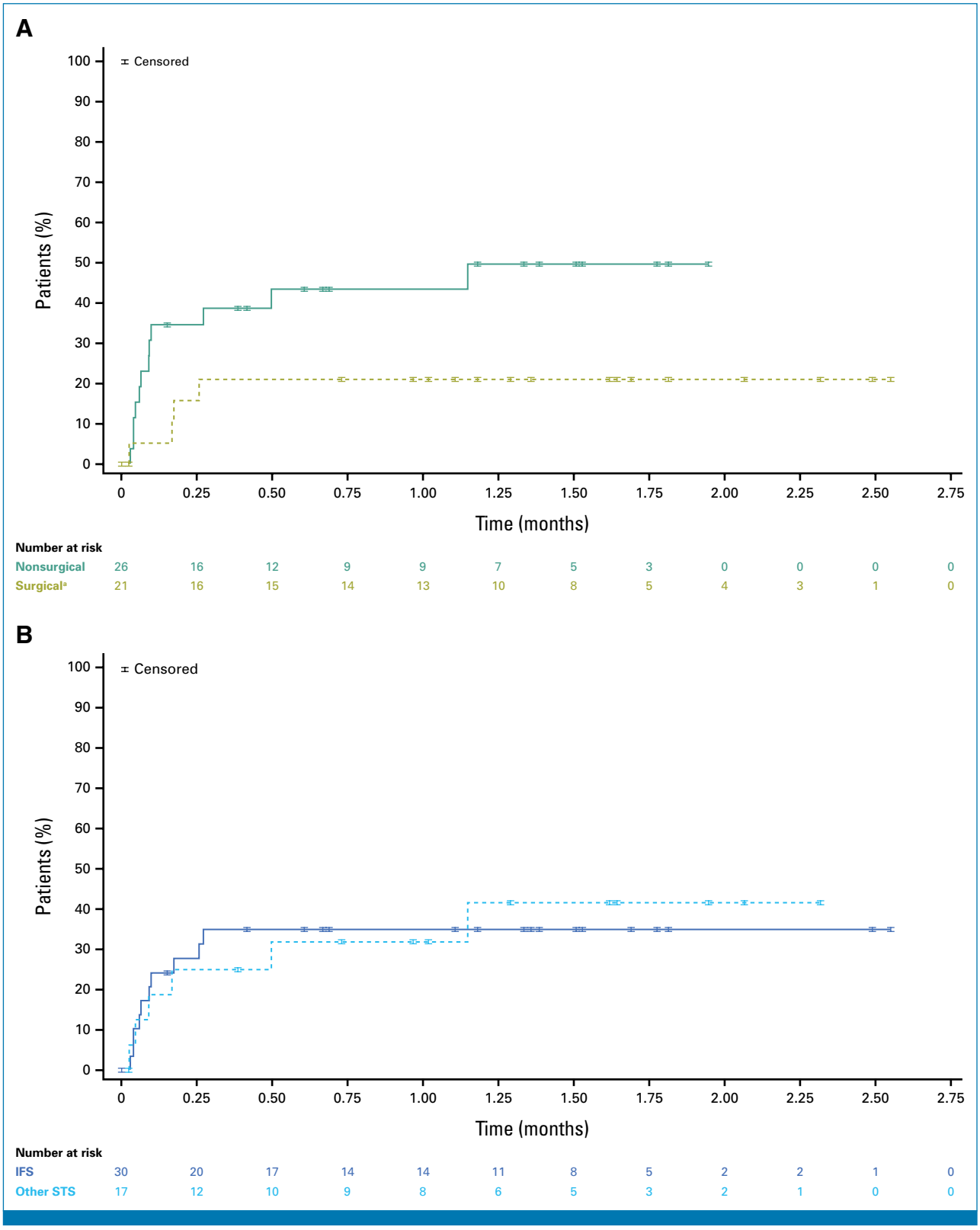

FIG 3. Time from discontinuation to progression by (A) surgery status and (B) histology for the patients in the wait-and-see analysis. [a]Surgery took place before or ≤1 week after discontinuation. IFS, infantile fibrosarcoma; STS, soft tissue sarcoma.

demonstrated long-lasting activity that affected the survival of pediatric patients with IFS or other STS and related mesenchymal tumors. No new safety signals were observed, and adverse events were consistent with the known safety profile of larotrectinib.[2,9] Liver enzyme elevation, mostly grade 1/2, was the most common toxicity.

Approximately a third of the patients who electively discontinued larotrectinib had disease progression. Fifteen of the 16 (94%) patients who progressed or relapsed achieved disease control when larotrectinib was resumed, with 69% (11 of 16) having an objective response. All patients in the wait-and-see cohort were alive at the cutoff. This suggests that patients with localized completely resected tumors can discontinue larotrectinib and surgical local control should be strongly considered as soon as feasible without significant morbidity after response to larotrectinib. Moreover, elective discontinuation with close monitoring after prolonged disease response, even without surgical local control, could potentially be considered in some patients. However, longer follow-up is necessary to determine the optimal length of therapy to allow for larotrectinib discontinuation in this group.

Larotrectinib leads to rapid clinical improvement in patients, allowing for less morbid surgical procedures in responding patients.[11] This rapid response can be especially important when there are life-threatening complications including compression of vital structures or tumoral hemorrhage.[12]

A limitation was that decisions to discontinue treatment in the absence of disease progression and treatment duration before discontinuation varied according to investigator discretion. The Children's Oncology Group conducted a prospective study, ADVL1823 (ClinicalTrials.gov identifier: NCT03834961), which assessed the optimal duration of larotrectinib; follow-up is ongoing to evaluate durability of response after patients stop treatment.[13]

A strength of this analysis is the large sample size for a rare disease and a clinical trial design that permitted the wait-and-see analysis. The EPI-VITRAKVI study (ClinicalTrials.gov identifier: NCT05236257) compared results from the larotrectinib SCOUT trial with external historical controls treated with chemotherapy.[14,15] The findings indicate that in patients with IFS, larotrectinib reduced morbidity and the need for aggressive local therapies compared with chemotherapy and should be considered as first-line therapy.[15]

The larotrectinib wait-and-see analysis results suggest that there is a subset of patients who maintain durable remissions off treatment. For those who had tumor progression after treatment was withheld, the clinical benefit noted on resumption of larotrectinib is encouraging.

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DISCLAIMER

The sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors. The views expressed are those of the authors and not necessarily those of the

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EQUAL CONTRIBUTION

L.M., S.G.D., C.M.v.T., and T.W.L. contributed equally to this work.

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DATA SHARING STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing." This pertains to scope, time point, and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014.

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Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: Amgen (Inst)

Daniel A. Morgenstern
Honoraria: Ology Medical Education, HMP, Takeda Israel Ltd
Consulting or Advisory Role: Clarity Pharmaceuticals, Y-mAbs Therapeutics, Inc, US World Meds, RayzeBio, Regeneron, AbbVie
Speakers' Bureau: Y-mAbs Therapeutics, Inc, Takeda Israel Ltd
Research Funding: Bristol Myers Squibb (Inst), AbbVie (Inst), Lilly (Inst), Bayer (Inst), Cellectar (Inst), Roche (Inst), Blueprint Medicines (Inst)
Travel, Accommodations, Expenses: AbbVie
Uncompensated Relationships: Oncoheroes Biosciences

Cormac Owens
Consulting or Advisory Role: Y-mAbs Therapeutics, Inc, Norgine, BMSi
Patents, Royalties, Other Intellectual Property: Board member of SIOPEN which gets royalty payments from EUSA for sales of Qarziba (Inst)

Alberto S. Pappo
Honoraria: Bayer, Roche, Lilly, Pfizer
Consulting or Advisory Role: Merck, Loxo/Bayer, EUSA Pharma, Debbio, Lilly, Pfizer

Sébastien Perreault
Leadership: Bayer
Stock and Other Ownership Interests: novocure, Day One Therapeutics
Honoraria: Bayer
Consulting or Advisory Role: Bayer
Speakers' Bureau: Bayer
Expert Testimony: Bayer

Neerav Shukla
Consulting or Advisory Role: Illumina

Christian Michel Zwaan
Consulting or Advisory Role: Takeda (Inst), Pfizer (Inst), AbbVie (Inst), Jazz Pharmaceuticals (Inst), Incyte (Inst), Novartis (Inst), Kura Oncology (Inst), Gilead Sciences (Inst), Sutro Biopharma (Inst), BeiGene (Inst)
Research Funding: Takeda (Inst), AbbVie/Genentech (Inst), Pfizer (Inst), Jazz Pharmaceuticals (Inst), Kura Oncology (Inst), Daiichi Sankyo (Inst)
Travel, Accommodations, Expenses: Syndax, AbbVie

Natascha Neu
Other Relationship: Bayer

Vadim Bernard-Gauthier
Employment: Bayer

Esther De La Cuesta
Employment: Bayer
Stock and Other Ownership Interests: Bayer
Travel, Accommodations, Expenses: Bayer

Cornelis M. van Tilburg
Consulting or Advisory Role: Novartis, Bayer, Alexion Pharmaceuticals, Roche
Travel, Accommodations, Expenses: Lilly

Theodore W. Laetsch
Stock and Other Ownership Interests: Advanced Microbubbles
Consulting or Advisory Role: Bayer, Massive Bio, AI Therapeutics, Jazz Pharmaceuticals, GentiBio, ITM Oncologics, GlaxoSmithKline
Research Funding: Pfizer (Inst), Bayer (Inst), Turning Point Therapeutics (Inst), Lilly (Inst), Roche/Genentech (Inst), Taiho Oncology (Inst), Advanced Accelerator Applications/Novartis (Inst), BioAtla (Inst), Roche (Inst), Jazz Pharmaceuticals (Inst), Exelixis (Inst), Adaptimmune (Inst), Adaptimmune (Inst)

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