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TREATMENT DISCONTINUATION OUTCOMES IN PAEDIATRIC PATIENTS WITH TRK FUSION SARCOMAS TREATED WITH LAROTRECTINIB

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

DECLARATION OF INTERESTS

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Nothing to report.

LAROTRECTINIB IS HIGHLY ACTIVE AGAINST TRK FUSION CANCER

- *NTRK* gene fusions are oncogenic drivers in multiple tumour types, including infantile fibrosarcoma and other sarcomas in paediatric patients[1]
  - There is a high prevalence of *NTRK* gene fusions in infantile fibrosarcoma (~70%)[1]
- Larotrectinib is a first-in-class, highly selective TRK inhibitor approved for tumour-agnostic use in patients with TRK fusion cancer[2,3]

We report outcomes in paediatric patients with TRK fusion sarcomas who could electively discontinue larotrectinib (drug holiday) while in response

1. O'Haire S et al. *Sci Rep*. 2023;13(1):4116. 2. Bayer. VITRAKVI US PI. 2023. Accessed 5 February 2025. 3. Bayer. VITRAKVI SmPC. 2023. Accessed 5 February 2025.

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STUDY DESIGN

'Wait-and-see' analysis

SCOUT: paediatric phase 1/2 (NCT02637687)

- Age ≤21 years
- Advanced solid tumours

Data cutoff: 20 July 2023

- Of the 99 paediatric patients enrolled in SCOUT, 47 patients with TRK fusion sarcoma were permitted to discontinue larotrectinib in the absence of on-treatment disease progression ('wait-and-see')
- Patients were actively followed for progression according to protocol
  - If re-treated with larotrectinib due to progression, response was re-assessed by investigators per RECIST v1.1

Endpoints

Primary
- Time to discontinuation
- Time from discontinuation to progression
- Time from progression to resumption of treatment

Secondary
- Safety

Dose: 100 mg/m^2 BID (max 100 mg BID)†

†Patients in the phase 1 dose-escalation cohort received 9.6–120 mg/m^2 BID based on target dosing calculation tables per protocol.
BID, twice daily; RECIST, Response Evaluation Criteria in Solid Tumors.

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BASELINE CHARACTERISTICS

Characteristics	N=47
Age, median (range), years	0.9 (0–13)
Sex, n (%)	
Male	25 (53)
Female	22 (47)
ECOG performance status, n (%)	
0	39 (83)
1	6 (13)
2	2 (4)
Tumour histology, n (%)	
Infantile fibrosarcoma	30 (64)
Other soft tissue sarcoma†	17 (36)
***NTRK* gene fusion,** n (%)‡	
NTRK1	17 (36)
NTRK2	0
NTRK3	30 (64)

Characteristics	N=47
Prior therapies, n (%)§	
Surgery	13 (28)
Radiotherapy	1 (2)
Systemic therapy	26 (55)
Prior systemic therapies, median (range)‖	1 (0–3)
Number of prior systemic therapies, n (%)‖	
0	21 (45)
1	16 (34)
2	8 (17)
≥3	2 (4)
Best response to prior systemic therapy, n (%)	
CR	1 (2)
PR	4 (9)
SD	13 (28)
PD	4 (9)
Other¶	4 (9)
No prior systemic therapy	21 (45)

†Includes spindle cell sarcoma (n=9), inflammatory myofibroblastic tumour (n=3) and one each of myopericytoma, lipofibromatosis, lipofibroma, myofibromatosis and not otherwise specified. ‡*NTRK* gene fusions were identified by next-generation sequencing (n=26), fluorescence in situ hybridisation (n=11), polymerase chain reaction (n=8), NanoString (n=1) and chromosome microarray (n=1). § Patients may be counted in more than 1 row. ‖Number of previous systemic regimens (excluding previous radioactive iodine) in the metastatic and/or unresectable setting. ¶Other includes unknown and not evaluable.
CR, complete response; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; SD, stable disease.

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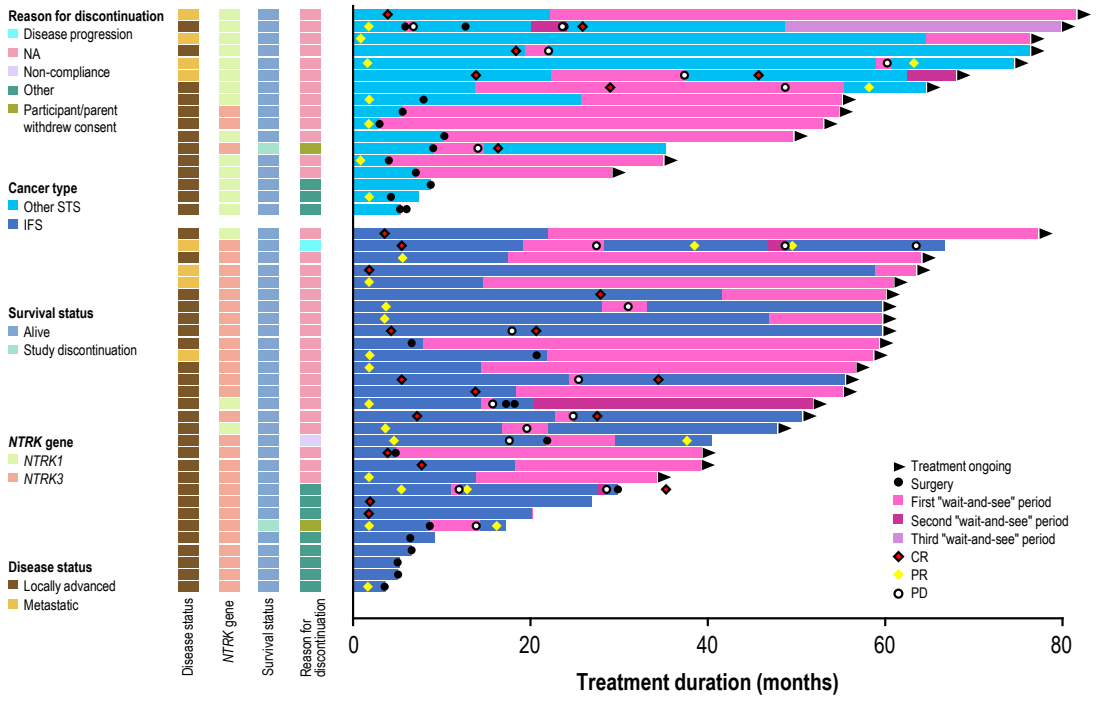
PAEDIATRIC PATIENTS WITH TRK FUSION SARCOMAS WHO ENTERED THE WAIT-AND-SEE ANALYSIS (N=47)

- By the data cut-off, a total of 30 (64%) patients with IFS and 17 (36%) with other STS discontinued larotrectinib and entered a wait-and-see period in the absence of on-treatment progression
- Twenty-five (53%) patients discontinued after achieving CR (including 10 surgical patients with pCR), 18 (38%) with PR and 4 (9%) with SD
- Twenty-one (45%) patients electively discontinued larotrectinib after surgery† and 26 (55%) did not have surgery



†Surgery took place before or ≤1 week after discontinuation.

CR, complete response; IFS, infantile fibrosarcoma; NA, not applicable; pCR, pathologic complete response; PD, progressive disease; PR, partial response; SD, stable disease; STS, soft tissue sarcoma.

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TIME TO DISCONTINUATION AND PROGRESSION (N=47)

- Median time to discontinuing larotrectinib was 15 months (range 3–65)
- Sixteen (34%) patients who discontinued larotrectinib had subsequent progression

Best response before or at the time of stopping larotrectinib, n	**Surgical (n=21)†**					**Non-surgical (n=26)**	**Total (N=47)**
	pCR‡ (n=10)	**Unknown (n=1)**	**R0 (n=1)**	**R1 (n=8)**	**R2 (n=1)**		
Median time to stopping larotrectinib, months (range)	7 (5–22)	3 (3–3)	22 (22–22)	8 (4–26)	6 (6–6)	20 (11–65)	15 (3–65)
Progressed, n	2	0	0	1	1	12	16
Median time from stopping larotrectinib to progression, months (range)§	NR (0–76)	NA	NA	NR (1–78)	1 (1–1)	NR (1–59)	NR (0–78)
Median duration of follow-up, months‖	49	50	36	39	NR	41	41

†Surgery took place before or ≤1 week after discontinuation. ‡pCR was defined as no pathologic evidence of tumour, negative surgical margins and no other evidence of disease. § Kaplan–Meier estimate.
‖Inverse Kaplan–Meier estimate.
NA, not applicable; NR, not reached; pCR, pathologic complete response; R0, no residual tumour; R1, microscopic residual tumour; R2, macroscopic residual tumour.

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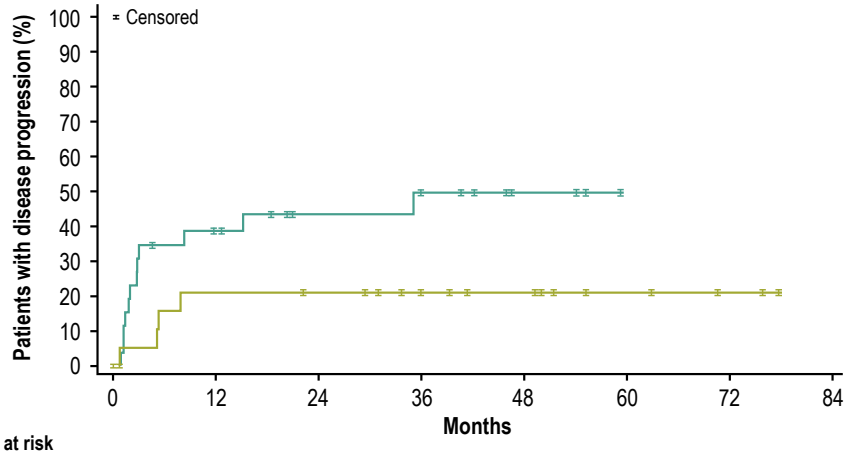
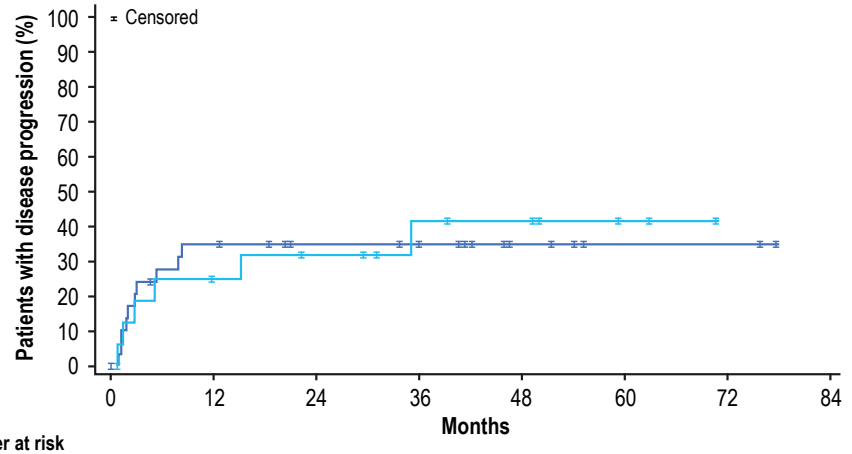
TIME FROM DISCONTINUATION TO PROGRESSION BY SURGERY STATUS AND HISTOLOGY

- Four patients with surgery† and 12 without surgery experienced disease progression
  - The median time from discontinuation to progression was not reached in both the surgical and non-surgical groups



Number at risk								
Non-surgical	26	14	9	7	3	0	0	0
Surgical†	21	15	14	10	8	4	2	0

- Ten patients with IFS and 6 with other STS had disease progression
  - The median time from discontinuation to progression was not reached in both the IFS and other STS groups



Number at risk								
IFS	30	18	14	11	6	2	2	0
Other STS	17	11	9	6	5	2	0	0

†Surgery took place before or ≤1 week after discontinuation. IFS, infantile fibrosarcoma; STS, soft tissue sarcoma.

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BEST RESPONSE AFTER PROGRESSION AND RESUMPTION OF TREATMENT

Best response before or at the time of stopping larotrectinib, n	Surgical (n=21)†					Non-surgical (n=26)	Total (N=47)
	pCR‡ (n=10)	Unknown (n=1)	R0 (n=1)	R1 (n=8)	R2 (n=1)		
Progressed and resumed treatment, n	2	0	0	1	1	12	16
Best response after resumption	1 CR, 1 PR	-	-	1 PR	1 SD	4 CR, 4 PR, 3 SD, 1 undefined	5 CR, 6 PR,§ 4 SD, 1 undefined

- In the 16 (34%) patients who discontinued larotrectinib and had subsequent progression, the median time from discontinuing larotrectinib to progression was 3 months (range 1–35)
- All 16 patients resumed larotrectinib after documented progression: 11 had response to re-treatment, § 4 had SD, and 1 restarted treatment and then had surgery, so response was undefined
- All 47 patients were alive at data cut-off

Best response before or at the time of stopping larotrectinib	Best response after resumption			
	CR	PR	SD	Undefined
CR	4	2	1	0
pCR	1	0	0	0
PR	0	4	3	1

†Surgery took place before or ≤1 week after discontinuation. ‡pCR is defined as no pathologic evidence of tumour, negative surgical margins and no other evidence of disease. § Two patients with PR pending confirmation.
CR, complete response; pCR, pathologic complete response; PR, partial response; SD, stable disease.

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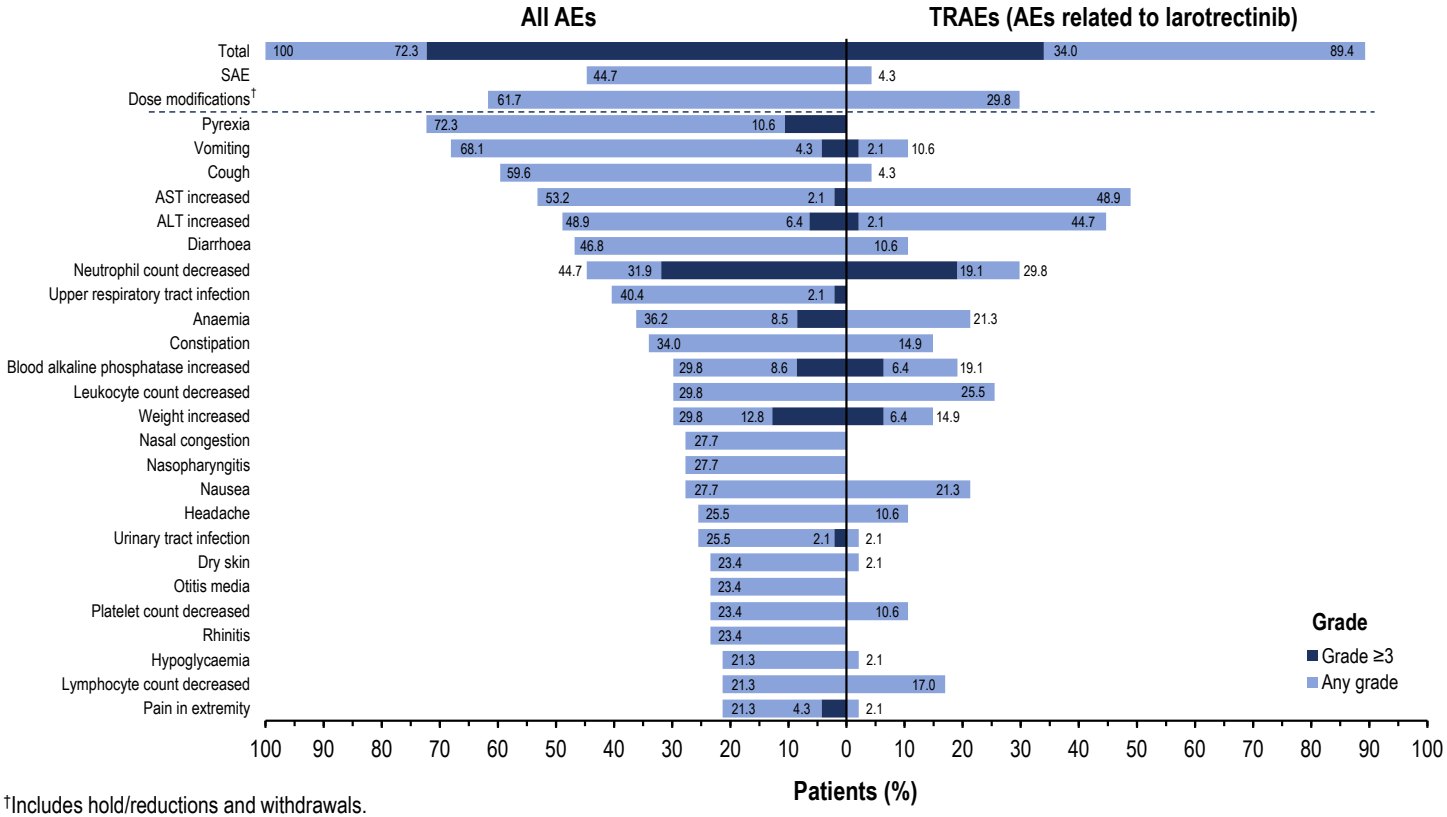
ADVERSE EVENTS IN >20% OF PATIENTS (N=47)



- TRAEs were mostly Grade 1/2
- Grade 3/4 TRAEs occurred in 16 (34%) patients
  - The most common Grade 3/4 TRAE was neutrophil count decreased
- No patients discontinued due to a TRAE

†Includes hold/reductions and withdrawals.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TRAE, treatment-related adverse event.

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CONCLUSIONS

- Larotrectinib demonstrated robust, durable responses and favourable safety in paediatric patients with TRK fusion sarcomas who had a drug holiday
  - Approximately one-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
- These data suggest that patients with completely resected localized tumors can discontinue larotrectinib
  - After response to larotrectinib, surgical local control should be strongly considered as soon as feasible without significant morbidity
  - Elective discontinuation with close monitoring after prolonged disease response, even without surgical local control, could potentially be considered in some patients
- A recent publication of this study in the *Journal of Clinical Oncology* (Mascarenhas L, et al. 2025. PMID: 39869835) includes additional data on paediatric patients with TRK fusion sarcomas

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