



NTRK
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HIGHLIGHTS BY

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DISCLOSURES

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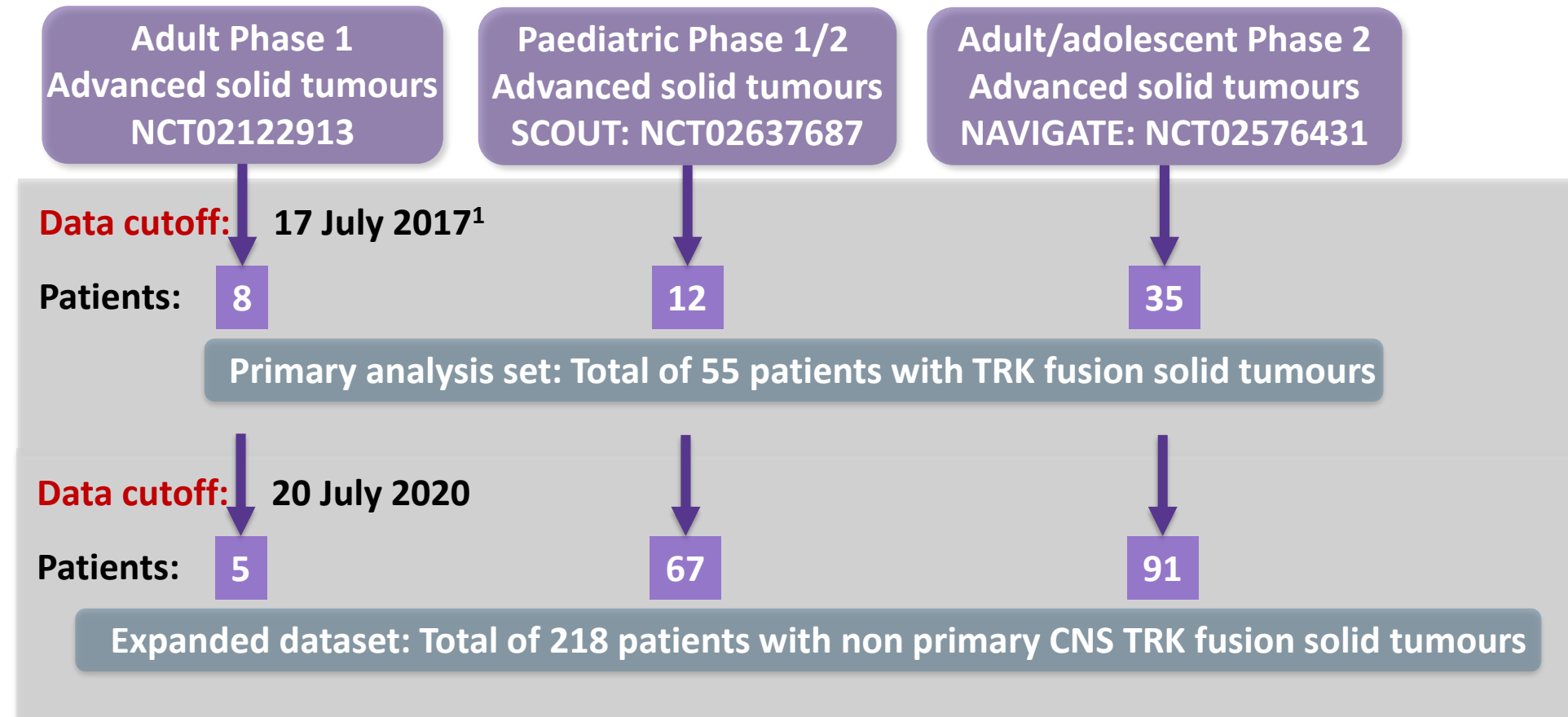
Disclosures: **Prof. Andrea Sartore-Bianchi** has received honoraria from the following:

- Amgen, Bayer, Sanofi and Servier

LONG-TERM EFFICACY AND SAFETY OF LAROTRECTINIB IN AN INTEGRATED DATASET OF PATIENTS WITH TRK FUSION CANCER

Hong D.S, et al. ASCO 2021, #3108

LONG-TERM EFFICACY AND SAFETY FOLLOW-UP FOR LAROTRECTINIB



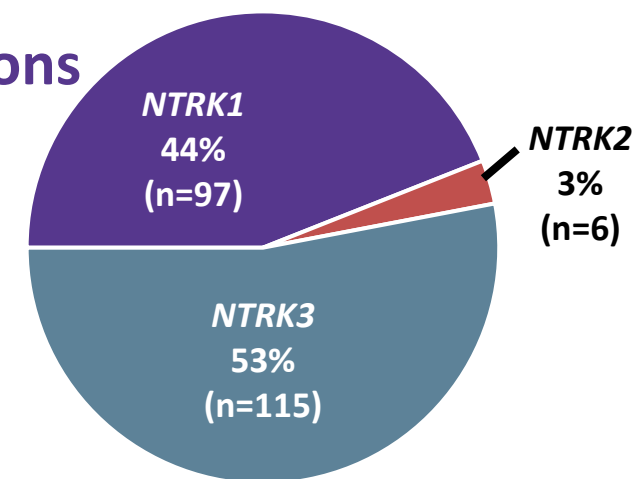
This analysis reports updated safety and efficacy data with longer follow-up in an expanded dataset of adult and paediatric patients with TRK fusion cancer treated with larotrectinib (N=218)

BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS IN TRK-POSITIVE NON PRIMARY CNS TUMOURS

Characteristics	N=218
Age, median (range), years	38 (0.1-84)
Pediatic (<18), n (%)	78 (36)
Adult (≥18), n (%)	140 (64)
Female, n (%)	106 (49)
Male, n (%)	112 (51)
ECOG or equivalent Lansky performance status, n (%)	
0	114 (52)
1	78 (36)
2	23 (11)
3	3 (1)
Known CNS metastases at enrolment, n (%)	19 (9)
Prior cancer treatments, median (range)	1 (1-10)
Number of prior systemic therapies, n (%)	
0	59 (27)
1	60 (28)
2	42 (19)
3 or more	57 (26)

Main Primary tumour type (>2%)	N=218
Soft tissue sarcoma	26%
Infantile fibrosarcoma	20%
Thyroid	13%
Salivary gland	11%
Lung	9%
Colon	4%
Melanoma	3%
Breast	3%
GIST	2%

NTRK gene fusions

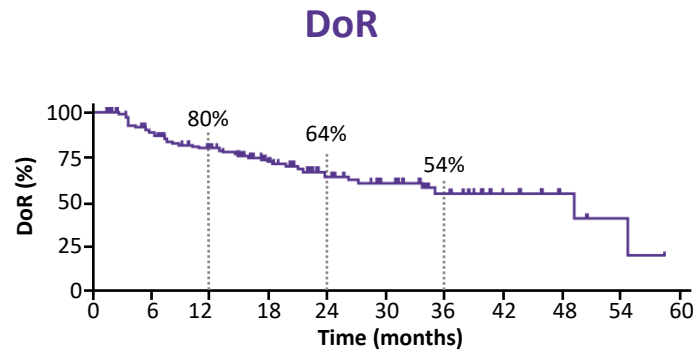


EFFICACY OF LAROTRECTINIB IN TRK FUSION CANCER

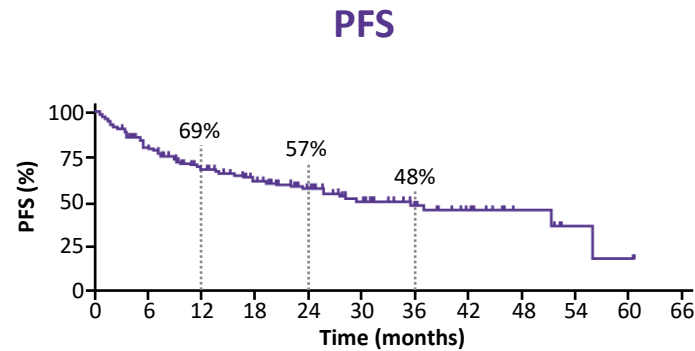
	All patients (N=218)	CNS metastases at baseline (N=19)
Evaluable patients, n	206	15
ORR, % (95% CI)	75 (68-81)	73 (45-92)
Best overall response, n (%)		
Complete response	45 (22)	0
Partial response	109 (53)	11 (73)
Stable disease	33 (16)	2 (13)
Progressive disease	13 (6)	2 (13)
Not determined	6 (3)	0

- Treatment duration ranged from 0.03+ to 60.4+ months
- At the data-cut off date, 108 patients (50%) still on treatment and 48 patients (22%) continued treatment post-progression
- Median time to response: 1.84 months (range 0.89-9.07)

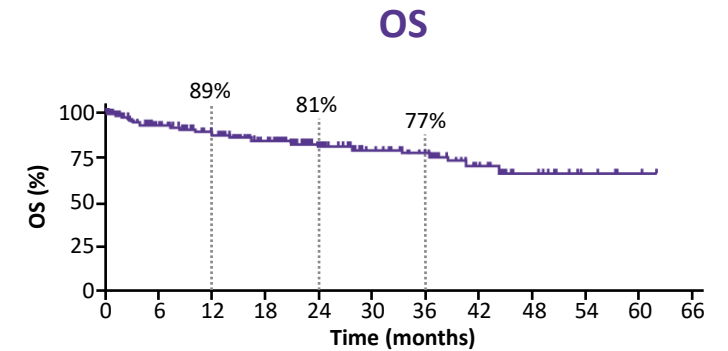
DOR, PFS AND OS IN PATIENTS WITH TRK-POSITIVE TUMOURS TREATED WITH LAROTRECTINIB



No. at risk 143 110 93 63 39 27 17 9 4 2 0



No. at risk 218 138 103 79 50 34 19 11 5 2 1 0



No. at risk 218 172 141 116 77 57 42 23 12 5 2 0

Integrated dataset (N=143)

Median DoR , (95% CI), months	49.3 (27.3-NE)
Median follow-up, months	22.3

Integrated dataset (N=218)

Median PFS , (95% CI), months	35.4 (23.4-55.7)
Median follow-up, months	20.3

Integrated dataset (N=218)

Median OS , (95% CI), months	Not reached
Median follow-up, months	22.3

CNS metastases at baseline (N=19)

Median DoR , (95% CI), months	17.4 (3.7-NE)
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CNS metastases at baseline (N=19)

Median PFS , (95% CI), months	9.9 (1.9-NE)
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CNS metastases at baseline (N=19)

Median OS , (95% CI), months	27.8 (8.5-NE)
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SAFETY PROFILE OF LAROTRECTINIB IN TRK-POSITIVE TUMOURS

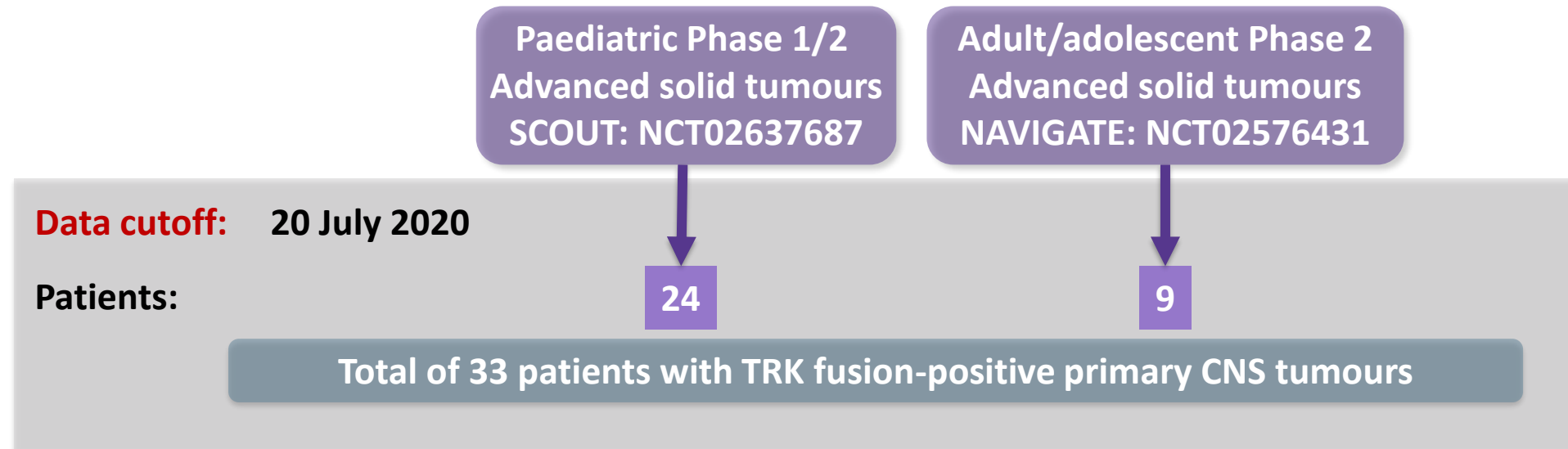
- TRAEs: predominantly Grade 1 or 2
- 2% of patients discontinued treatment due to TRAEs
- Grade 3 and 4 TRAEs were reported in 18% of patients

- There were no new or unexpected safety signals, with a longer follow-up to the previous report and with 53 patients (24%) on larotrectinib treatment for ≥ 24 months

EFFICACY AND SAFETY OF LAROTRECTINIB IN ADULT AND PEDIATRIC PATIENTS WITH TRK FUSION-POSITIVE PRIMARY CNS TUMORS

Perreault S, et al. ASCO 2021, Abstract #2002

STUDY DESIGN ON THE INVESTIGATION OF TRK FUSION PRIMARY CNS TUMOURS TREATED WITH LAROTRECTINIB



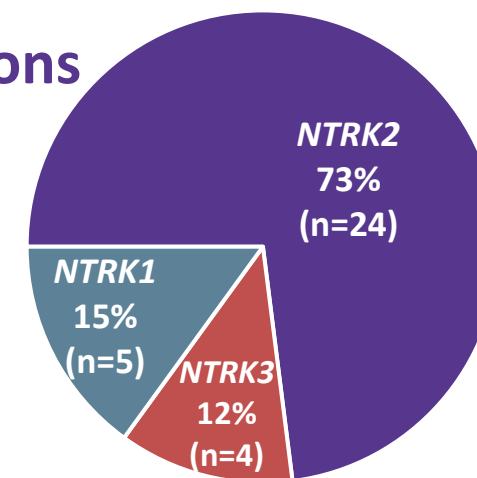
This analysis reports data in an expanded set of TRK fusion primary CNS tumors treated with larotrectinib (N=33)

BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS IN TRK-POSITIVE PRIMARY CNS TUMOURS

Characteristics	N=33
Age, median (range), years	8.9 (1.3-79.0)
Female, n (%)	16 (48)
Male, n (%)	17 (52)
ECOG or equivalent Lansky performance status ^a , n (%)	
0	18 (55)
1	10 (30)
2	4 (12)
Prior therapies ^b , n (%)	
Radiotherapy	18 (55)
Surgery	22 (67)
Systemic therapy	28 (85) ^c
Number of prior systemic therapies, n (%)	
0	6 (18) ^c
1	12 (36)
2	8 (24)
3 or more	7 (21)

Primary tumour type, n (%)	N=33
Glioma	27 (82)
High grade	19 (58)
Low grade	8 (24)
Other	6 (18)
Glioneuronal tumour	2 (6)
Neuroepithelial tumour	2 (6)
CNS neuroblastoma	1 (3)
Small round blue cell brain tumour	1(3)

NTRK gene fusions

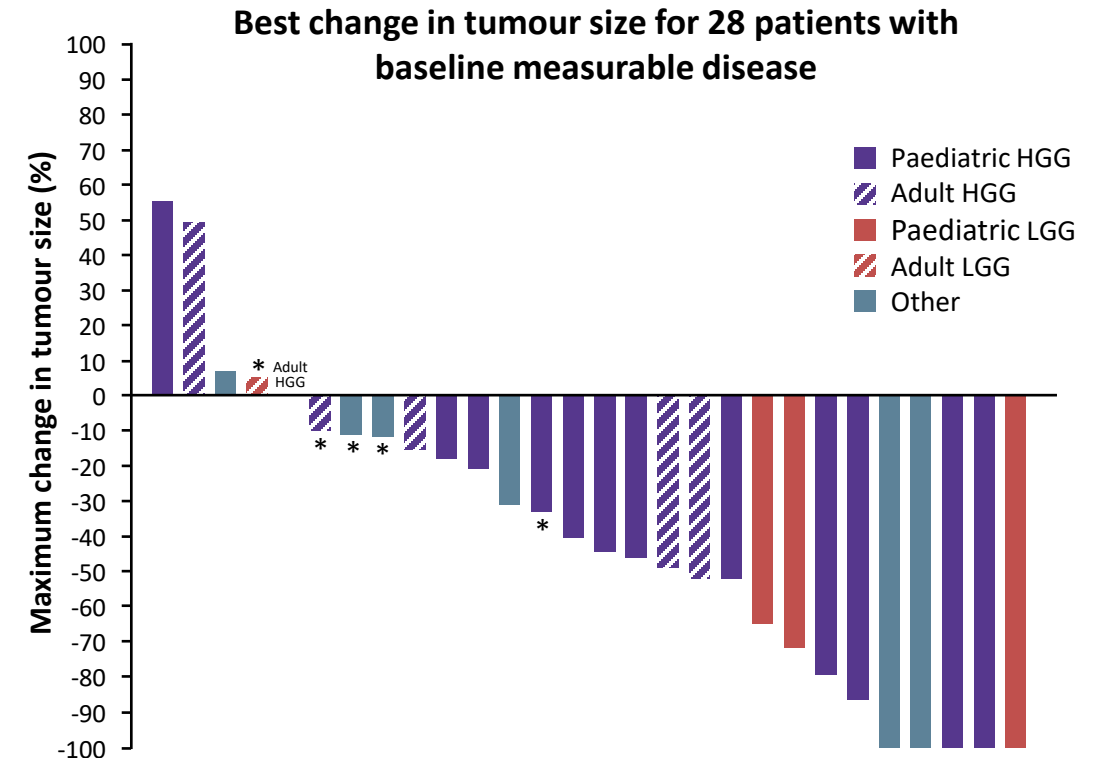


^a ECOG PS not reported in one patient; ^b Patients may be counted in more than one category; ^c One patient who reported “yes” to prior systemic therapies had the number of prior systemic therapies reported as zero

EFFICACY OF LAROTRECTINIB IN TRK-POSITIVE PRIMARY CNS TUMOURS

	Evaluable patients (N=33)
ORR, % (95% CI)	
Total	30 (16-49)
High grade glioma	26 (9-51)
Low grade glioma	38 (9-76)
Median PFS, (95% CI), months	18.3 (6.7-NE)
12-month PFS rate, % (95% CI)	56 (38-74)
Median OS, (95% CI), months	Not reached (16.9-NE)
12-months OS rate, % (95% CI)	85 (71-99)

- Treatment duration ranged from 1.2 to 31.3+ months
- At the data-cut off date, 18 patients still receiving treatment
- Median time to best response: 1.87 months (range 0.99-3.75)



*Based on RECIST v1.1 sum of longest diameters

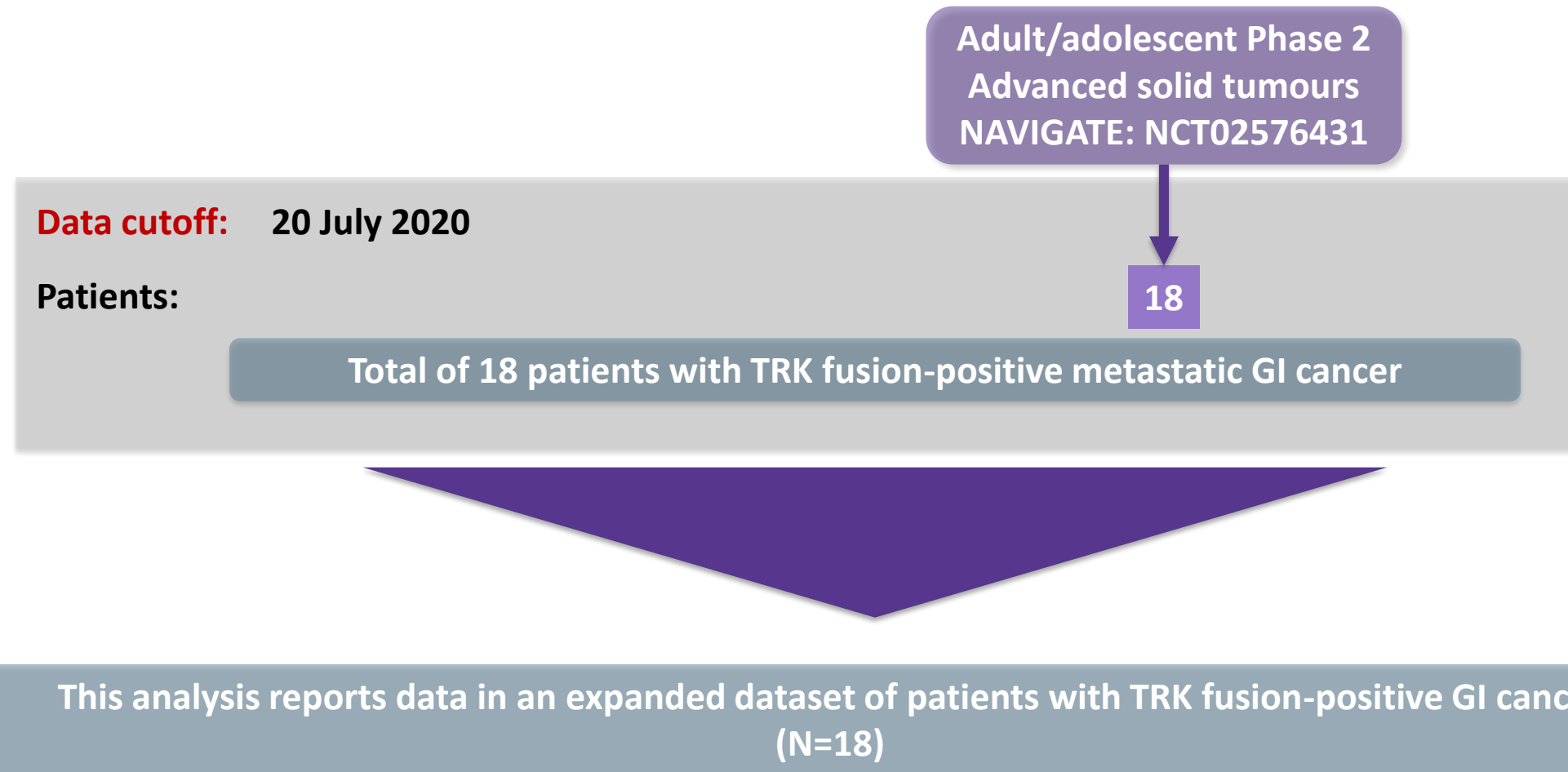
SAFETY PROFILE OF LAROTRECTINIB IN TRK-POSITIVE PRIMARY CNS TUMOURS

- TEAEs were mainly grade 1 and 2
- 39% (13/33) of patients had Grade 3 or 4 TEAE
- 9% (3/33) of patients had Grade 3 or 4 AEs related to Larotrectinib:
 - Decrease neutrophil count (Grade 3)
 - Increased gamma-glutamyltransferase (Grade 3)
 - Hyperglycemia (Grade 3)
 - Hyponatremia (Grade 3)
 - Hyponatremia (Grade 4)
- 6% (2/33) required dose reductions due to a TEAE
- 33% (11/33) had doses skipped, missed or delayed due to a TEAE
- No discontinuation due to TRAEs
- Neurological AEs:
 - Most common neurological TEAE = Headache at Grade 1 or 2 (6 patients) and Grade 3 (1 patient)
 - 6 patients had neurological AEs related to Larotrectinib (all Grade 1 or 2)

EFFICACY AND SAFETY OF LAROTRECTINIB IN PATIENTS WITH TRK FUSION-POSITIVE GI CANCER: AN EXPANDED DATASET

Boni V, et al. WCGIC 2021, #SO-29

STUDY DESIGN ON THE INVESTIGATION OF TRK FUSION METASTATIC GI TUMOURS TREATED WITH LAROTRECTINIB

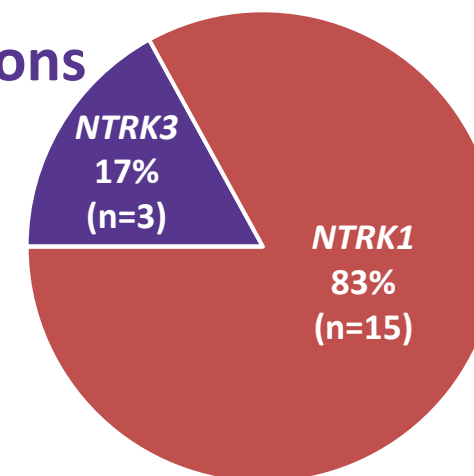


BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS IN TRK-POSITIVE METASTATIC GI TUMOURS

Characteristics	N=18
Age, median (range), years	67.0 (32.0-84.0)
Female, n (%)	11 (61)
Male, n (%)	7 (39)
ECOG performance status, n (%)	
0	3 (17)
1	11 (61)
2	3 (17)
3	1 (6)
Prior therapies, n (%)	
Surgery	14 (78)
Systemic therapy ^a	17 (94)
Radiotherapy	2 (11)
Number of prior systemic therapies, n (%)	
0	1 (6)
1	4 (22)
2	9 (50)
3 or more	4 (22)

Primary tumour type, n (%)	N=18
Colorectal cancer:	10 (56)
MSI-H	7 (70)
MSS	2 (20)
Unknown	1 (10)
Cholangiocarcinoma	3 (17)
Pancreas	2 (11)
Appendix	1 (6)
Oesophageal	1 (6)
Hepatic	1 (6)

NTRK gene fusions

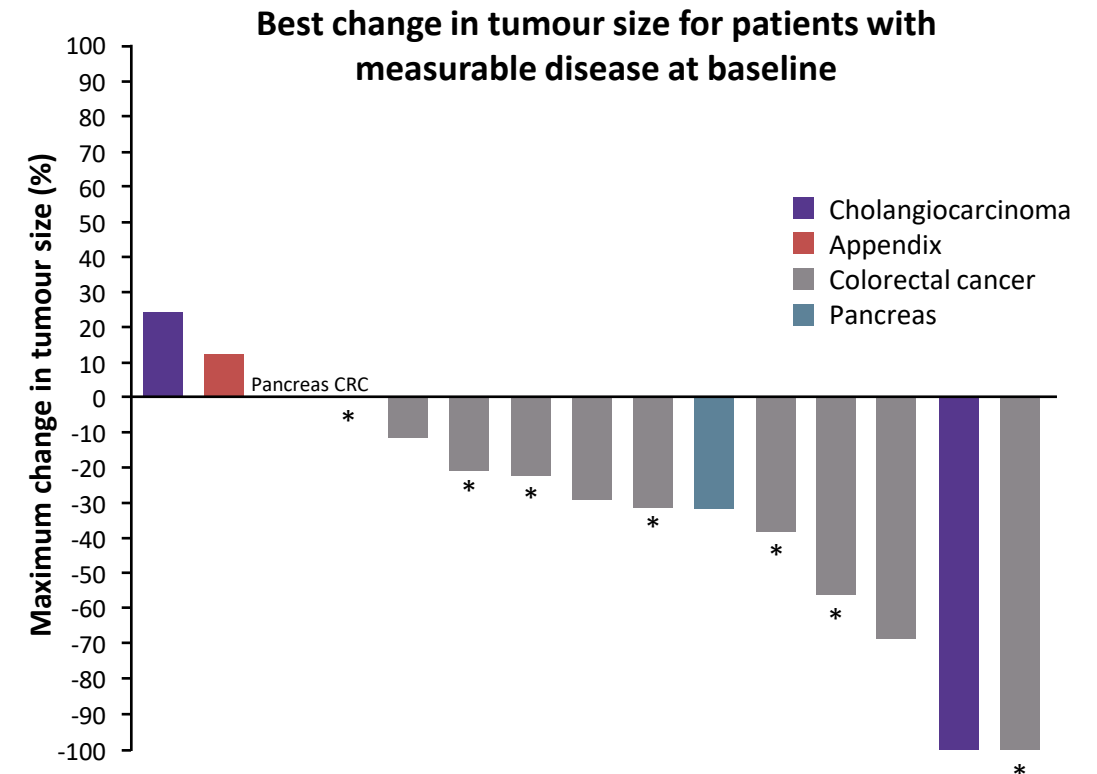


^a 3 patients had received prior immunotherapy: one with colorectal cancer had progressive disease as best response after 2.8 months IO therapy, one with hepatic cancer had progressive disease and one with oesophageal cancer had unknown response.

EFFICACY OF LAROTRECTINIB IN TRK-POSITIVE METASTATIC GI TUMOURS

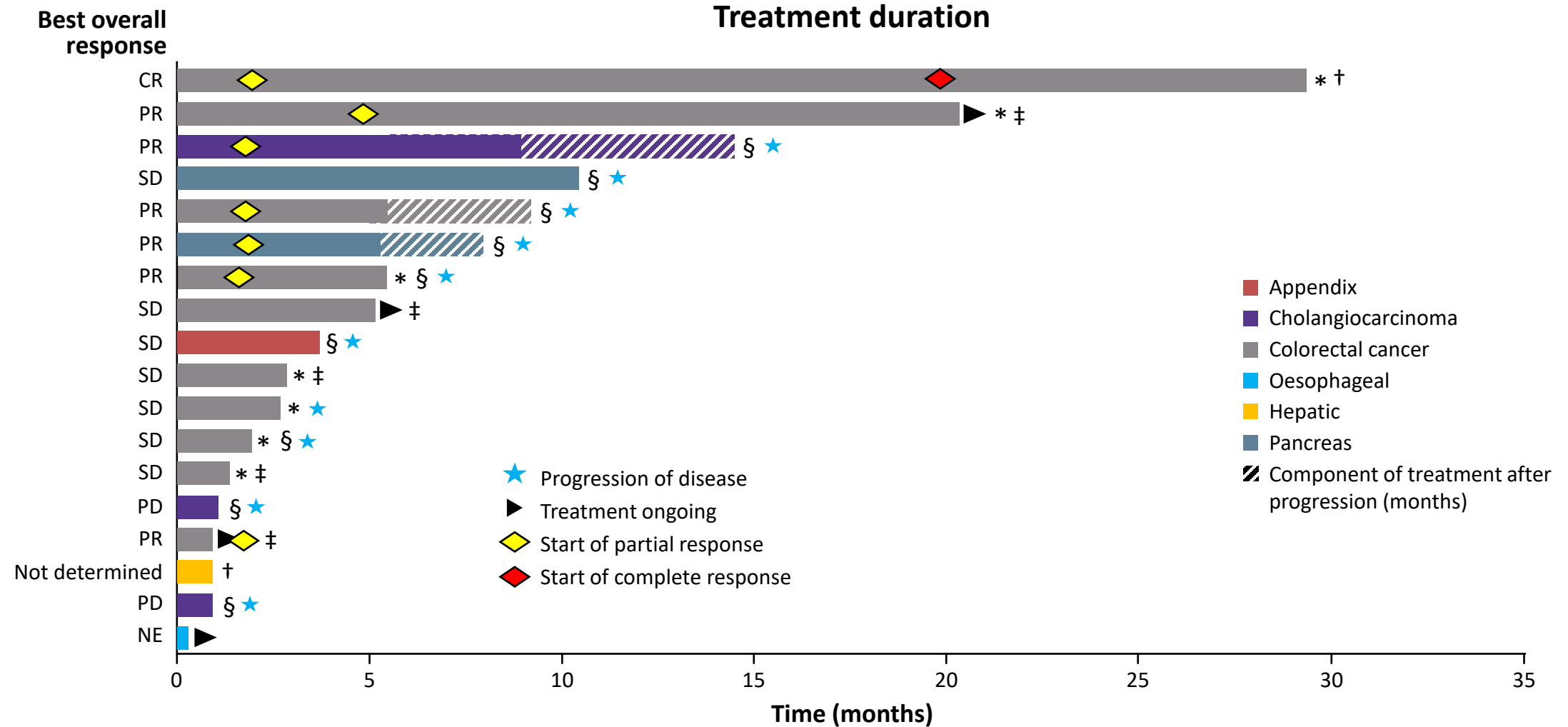
	All patients (N=18)	CRC patients (N=10)
Evaluable patients	17	10
ORR, % (95% CI)	41 (18-67)	50 (19-81)
Best overall response, n (%)		
Complete response	1 (6)	1 (10)
Partial response	6 (35)	4 (40)
Stable disease	7 (41)	5 (50)
Progressive disease	2 (12)	0
Not determined	1 (6)	0

- Treatment duration ranged from 0.26+ to 29.3 months
- At the data cut-off, 10 patients had progressed, with 3 continuing treatment post-progression (range 2.7-5.5 months)
- Median time to response: 1.86 months (range 1.68-4.96)



*MSI-high

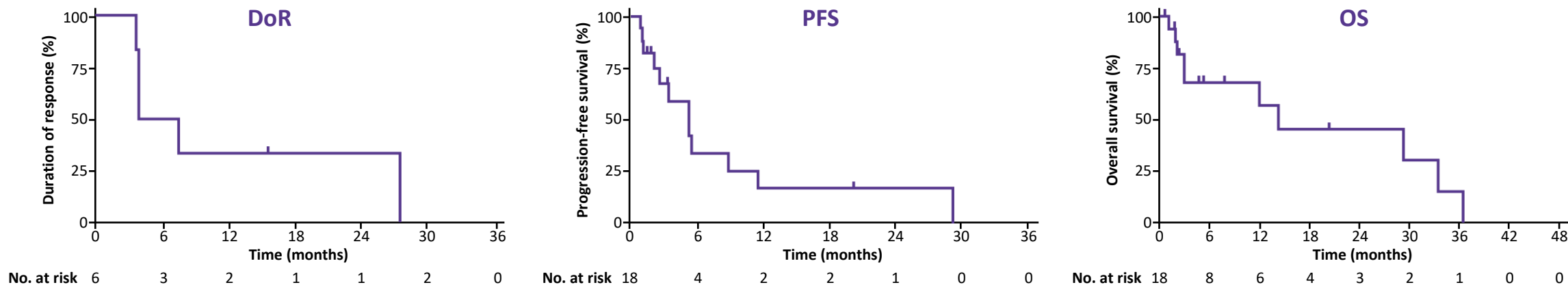
TREATMENT DURATION WITH LAROTRECTINIB IN TRK-POSITIVE METASTATIC GI TUMOURS



*MSI-high; †Died without disease progression beforehand; ‡Alive without disease progression; §Stopped treatment due to progression

CR, complete response; GI, gastrointestinal; MSI, microsatellite instability; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TRK, tropomyosin receptor kinase

DOR, PFS AND OS IN PATIENTS WITH TRK-POSITIVE METASTATIC GI TUMOURS TREATED WITH LAROTRECTINIB



All patients (N=18)		All patients (N=18)		All patients (N=18)	
Median DoR , (95% CI), months	5.5 (3.5-27.3)	Median PFS , (95% CI), months	5.4 (2.2-11.6)	Median OS , (95% CI), months	14.1 (2.8-33.4)
Median follow-up, months	Not reached	Median follow-up, months	20.3	Median follow-up, months	7.8
Patients with CRC (n=10)		Patients with CRC (n=10)		Patients with CRC (n=10)	
Median DoR , (95% CI), months	15.5 (3.7-27.3)	Median PFS , (95% CI), months	5.5 (2.2-29.4)	Median OS , (95% CI), months	29.4 (2.8-36.5)
Median follow-up, months	Not reached	Median follow-up, months	20.3	Median follow-up, months	7.8

SAFETY PROFILE OF LAROTRECTINIB IN TRK-POSITIVE METASTATIC GI TUMOURS

- TEAEs were mainly Grade 1–2
- 56% (10/18) of patients had Grade 3 or 4 TEAEs
- 11% (2/18) of patients had Grade 3 or 4 AEs related to Larotrectinib:
 - Nausea (Grade 3)
 - Increased ALT and AST (Grade 4)
- 6% (1/18) required dose reductions due to a TEAE
- No discontinuation due to TRAEs

INTRA-PATIENT COMPARISON FROM LAROTRECTINIB CLINICAL TRIALS IN TRK FUSION CANCER: AN EXPANDED DATASET

Italiano A, et al. ASCO 2021, #3114

GMI ANALYSIS IN A LONG-TERM FOLLOW-UP WITH LAROTRECTINIB

Adult Phase 1
Advanced solid tumours
NCT02122913

Paediatric Phase 1/2
Advanced solid tumours
SCOUT: NCT02637687

Adult/adolescent Phase 2
Advanced solid tumours
NAVIGATE: NCT02576431

Data cutoff: July 2019¹

GMI analysis reported in a cohort of 122 patients with TRK fusion cancer¹

$$\text{GMI} = \frac{\text{PFS}_{\text{larotectinib}}^{\text{a}}}{\text{TTP}_{\text{prior line}}^{\text{b}}}$$

Data cutoff: July 2020

This analysis reports the GMI analysis in a long-term follow-up in an expanded cohort (N=140)

^a Defined as the time from the start of Larotrectinib treatment to radiological progression as determined by an independent review committee per RECIST v1.1, clinical progression or death by any cause

^b Defined as the time from the start of the last prior treatment to investigator-assessed radiological progression (RECIST v1.1), clinical progression or treatment end date

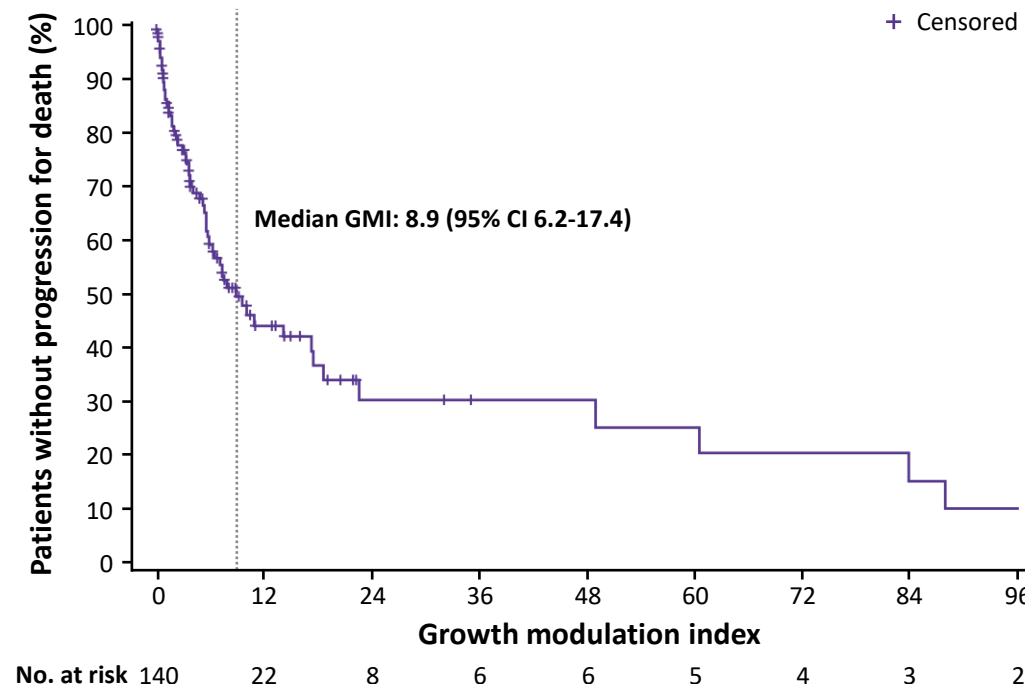
GMI ANALYSIS OF 140 PATIENTS TREATED WITH LAROTRECTINIB

	GMI <1	GMI: 1 to <1.33	GMI ≥1.33
Overall patients, n (%)^a	30 (21)	7 (5)	103 (74)
Lines of prior therapy, n (%)			
1 (N=53)	10 (19)	4 (8)	39 (74)
2 (N=37)	10 (27)	3 (8)	24 (65)
≥3 (N=50)	10 (20)	0	40 (80)
Tumour type, n (%)^b			
Soft tissue sarcoma (n=35)	8 (23)	1 (3)	26 (74)
Infantile fibrosarcoma (n=27)	1 (4)	2 (7)	24 (89)
Thyroid (n=21)	5 (24)	2 (10)	14 (67)
Lung (n=14)	2 (14)	0	12 (86)
Salivary gland (n=10)	2 (20)	0	8 (80)
Colon (n=7)	2 (29)	2 (29)	3 (43)
Melanoma (n=7)	4 (57)	0	3 (43)

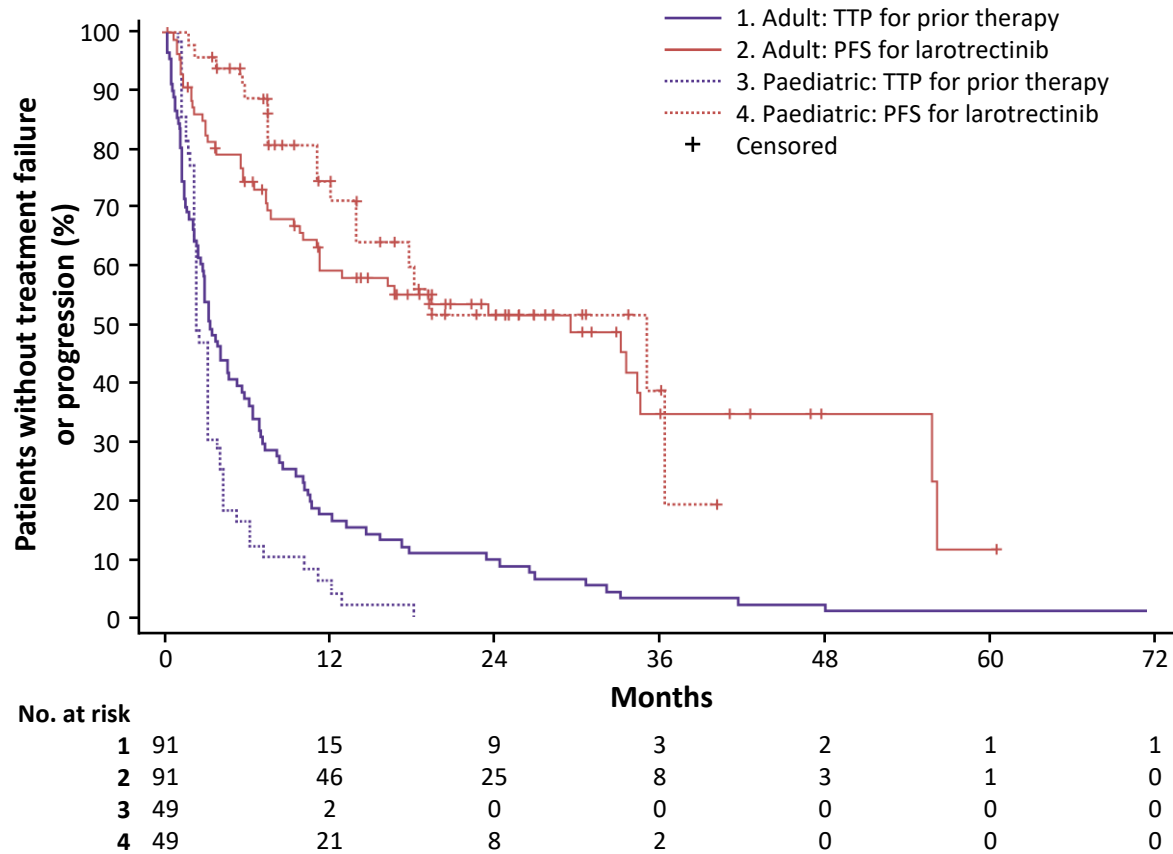
^a A total of 78 patients (56%) had not progressed and were censored for progression-free survival as of data cut-off. Six of the 37 patients with a GMI <1.33 were censored and still receiving treatment

^b Only tumours reported in ≥7 patients are listed

Kaplan-Meier estimate of GMI in the July 2020 dataset (N=140)



PFS AND TTP IN PATIENTS WITH TRK-POSITIVE TUMOURS TREATED WITH LAROTRECTINIB BY AGE GROUP



	Overall (N=140)	Adult (n=91)	Paediatric (n=49)
Median PFS on Larotrectinib, (95% CI), months	33.0 (16.6-34.9)	29.4	34.9
Median TTP on prior therapy^a, (95% CI), months	3.0 (2.1-3.5)	3.1	2.0
Hazard ratio, (95% CI)	0.22 (0.16-0.30)	0.29 (0.20-0.41)	0.10 (0.05-0.18)

^a Calculated as time from start of most recent prior therapy (regardless of metastatic setting) until progression. For the 85 patients with no data of progression, the end date of the last prior therapy was considered the date of progression. One paediatric patient progressed at 151 months

**TUMOR-AGNOSTIC PRECISION IMMUNO-
ONCOLOGY AND SOMATIC TARGETING
RATIONALE FOR YOU (TAPISTRY):
A NOVEL PLATFORM UMBRELLA TRIAL**

Drilon A.E. et al. ASCO 2021, #TPS3154

TAPISTRY STUDY DESIGN

TAPISTRY: Phase 2, open-label, multi-cohort study to evaluate the efficacy and safety of targeted therapy or immunotherapy as single agents or in combination in patients with unresectable, locally advanced or metastatic solid tumours

Main eligibility criteria:

PD on prior treatment
Advanced and unresectable or metastatic solid tumours
Adequate PS

- ≥18 years: ECOG PS 0-2
- 16-<18 years: Karnofsky score ≥50%
- <16 years: Lansky score ≥50%

Positive status per NGS for a cohort specified biomarker

10 cohorts

Cohort B: entrectinib *NTRK1/2/3* fusion
Target enrollment: 200 adult patients

Dose in 28-day treatment cycles:

BSA ≥1.51 m²: 600mg QD
BSA <1.51 m²: 100-400mg QD

Primary efficacy endpoint:

- Confirmed ORR ≥28 days after initial response determined by IRC per RECIST v1.1

Key secondary endpoints for cohort B:

- ORR DoR, CBR, PFS, Time to CNS PD per RECIST v1.1
- OS
- ORR, DoR, CBR, PFS per INRC
- CNS-ORR, DoR, CBR, PFS per RANO
- Intracranial ORR; DoR, CBR, PFF per RECIST v1.1^a
- Safety
- PROs
- PK

As of 19 April 2021, 21 patients have been recruited

^a In patients with CNS metastases at baseline

IN SUMMARY

- **Larotectinib** continues to demonstrate a **robust** and **durable** response rate and is **well tolerated** in patients with TRK fusion cancer:
 - **Confirmed** in patients with **TRK fusion primary CNS tumours**
 - **Confirmed** in patients with **TRK fusion GI tumours (including CRC)**
- Three-quarters of patients with TRK fusion cancer treated with larotrectinib had **a better than 33% increase in PFS compared to most recent prior therapy**
 - Suggest **improved disease response over prior therapy**
- These data highlight the importance of **identifying *NTRK* gene fusions** in patients with cancer → **Testing is critical**
- **TAPISTRY Phase 2 trial** has been initiated and worth following up

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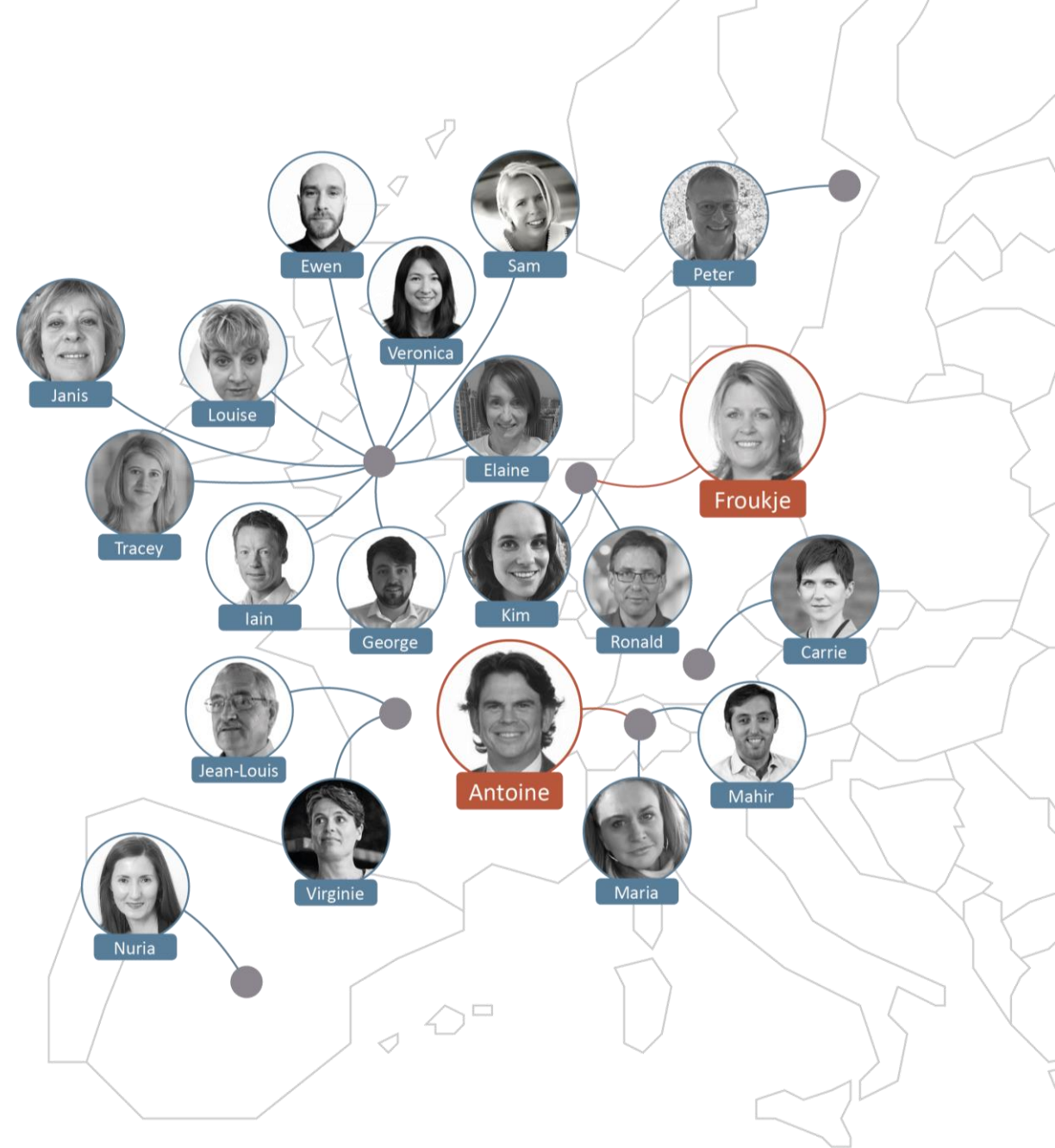
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