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HIGHLIGHTS BY

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DISCLOSURES

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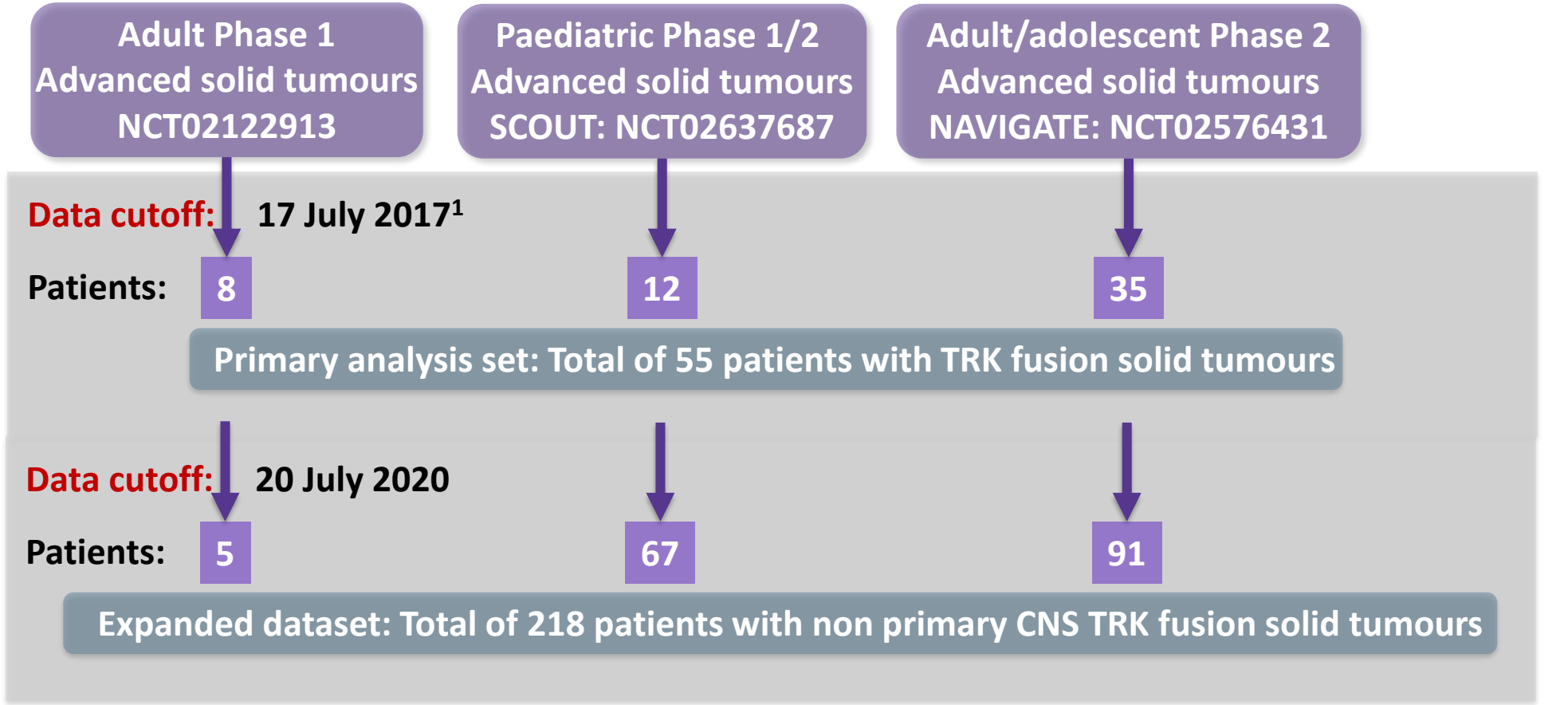
LONG-TERM EFFICACY AND SAFETY OF LAROTRECTINIB IN AN INTEGRATED DATASET OF PATIENTS WITH TRK FUSION CANCER

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

TRK, tropomyosin receptor kinase

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)

CNS, central nervous system; TRK, tropomyosin receptor kinase

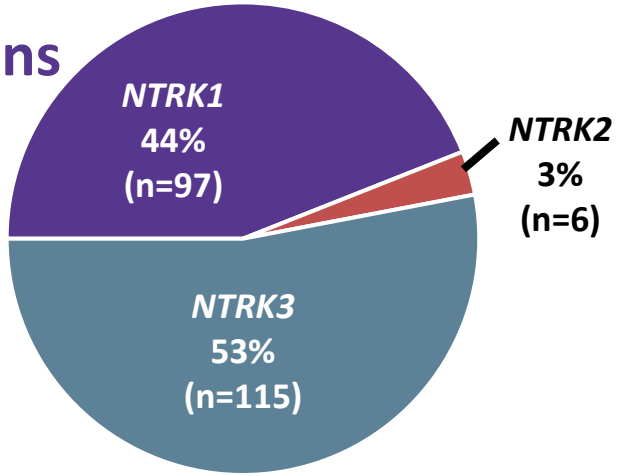
1. Drilon A, et al. N Engl J Med. 2018;378:731-9

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

Characteristics	N=218
Age, median (range), years	38 (0.1-84)
Peadiatric (<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



CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumour; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

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)

CI, confidence interval; CNS, central nervous system; ORR; objective response rate; TRK, tropomyosin receptor kinase

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

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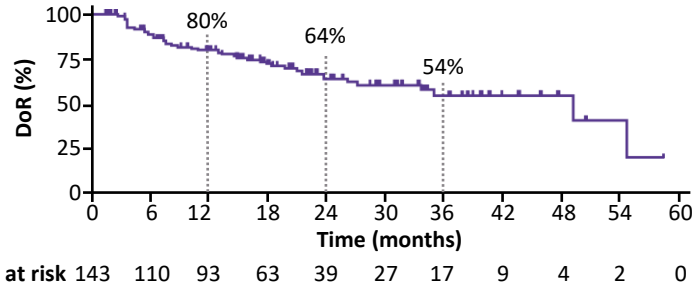
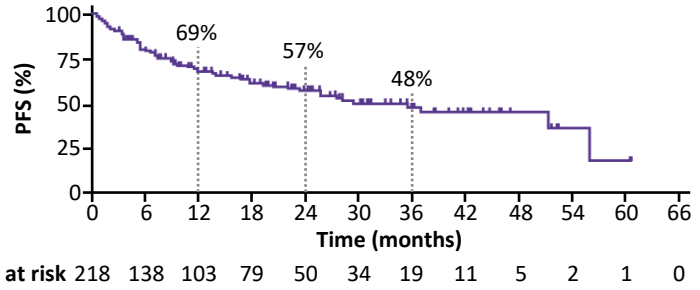
DoR



Integrated dataset (N=143)	
Median **DoR**, (95% CI), months	49.3 (27.3-NE)
Median follow-up, months	22.3

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

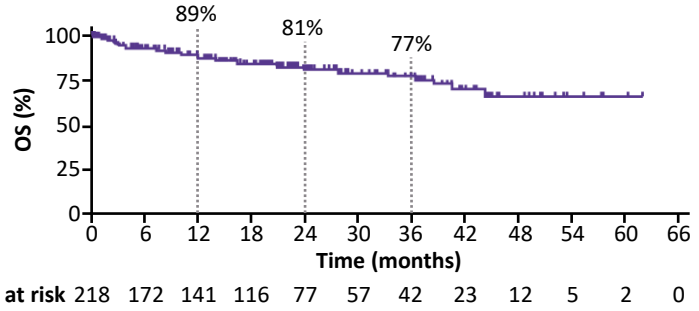
PFS



Integrated dataset (N=218)	
Median **PFS**, (95% CI), months	35.4 (23.4-55.7)
Median follow-up, months	20.3

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

OS



Integrated dataset (N=218)	
Median **OS**, (95% CI), months	Not reached
Median follow-up, months	22.3

CNS metastases at baseline (N=19)	
Median **OS**, (95% CI), months	27.8 (8.5-NE)

CI, confidence interval; CNS, central nervous system; DoR, duration of response; NE; not estimable; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

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

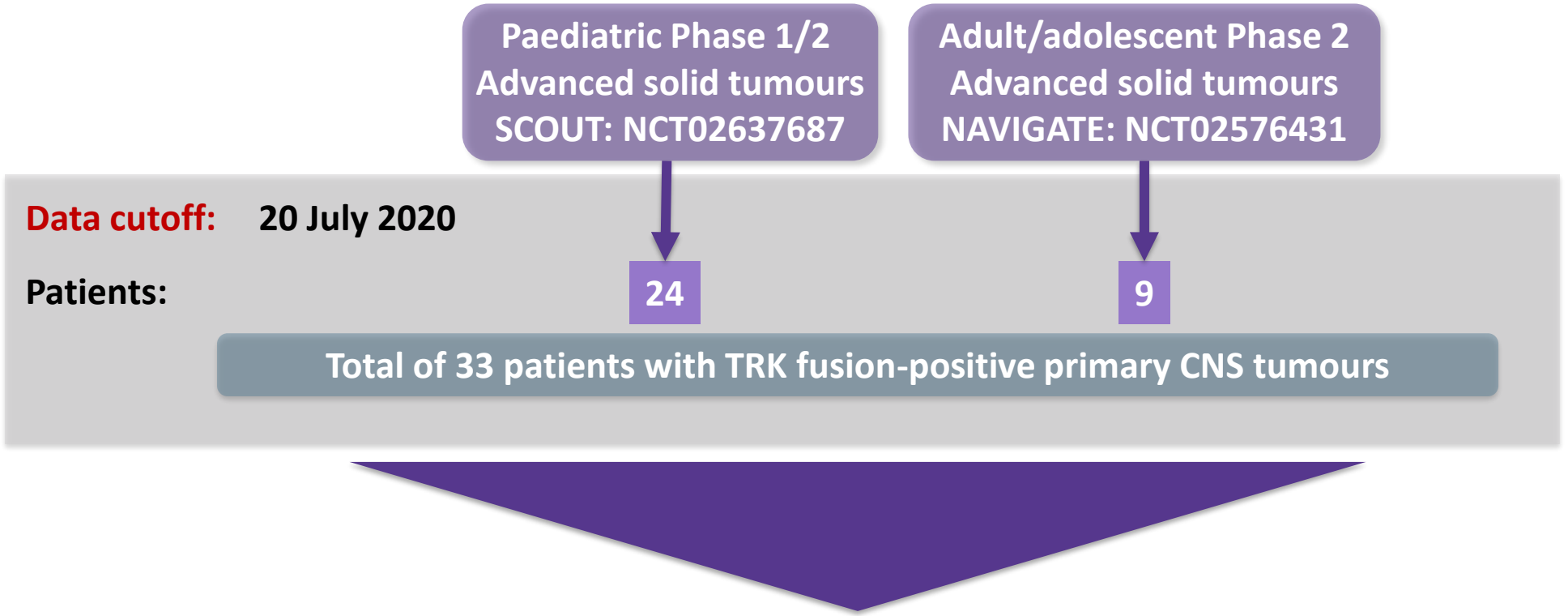
TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase

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

CNS, central nervous system; TRK, tropomyosin receptor kinase

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)

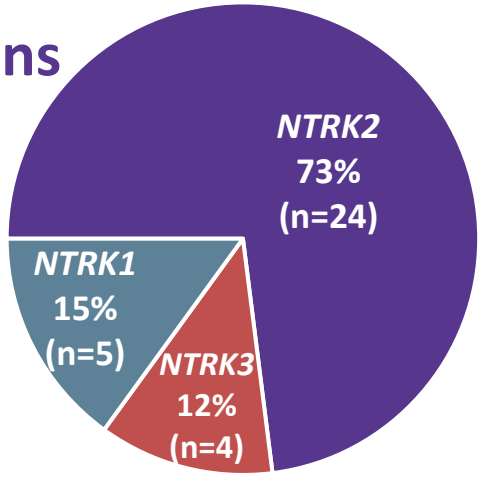
CNS, central nervous system; TRK, tropomyosin receptor kinase

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

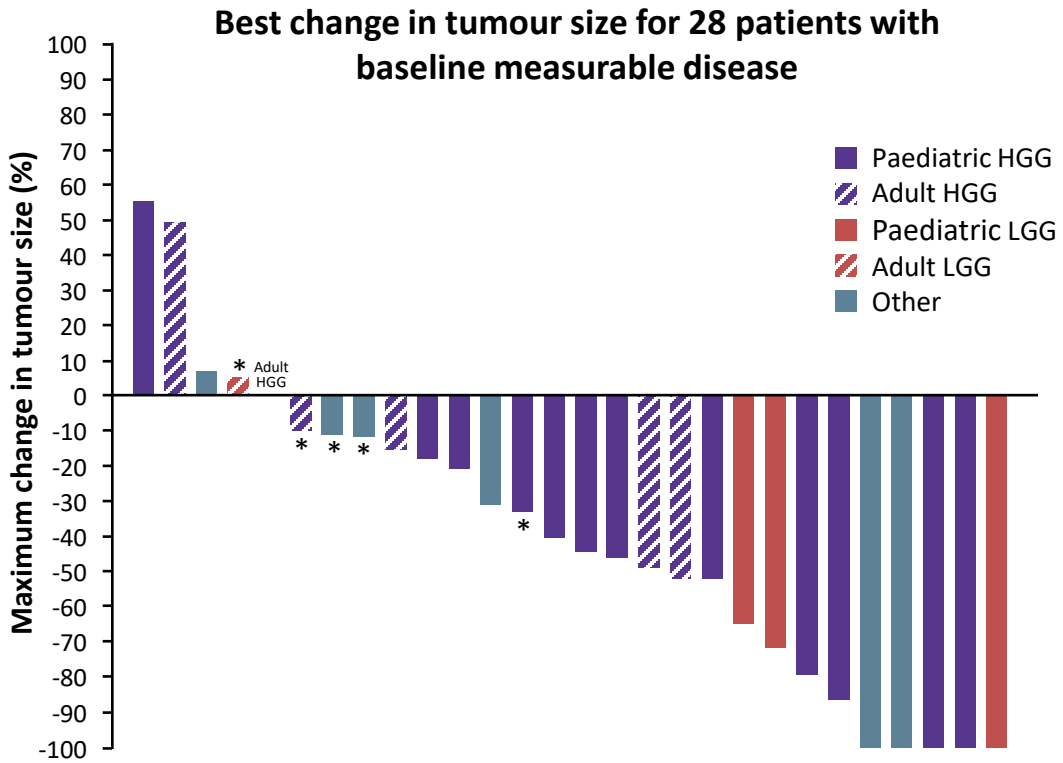


[a] ECOG PS not reported in one patient; [b] Patients may be counted in more than one category; [c] One patient who reported "yes" to prior systemic therapies had the number of prior systemic therapies reported as zero

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NTRK, neurotrophic tyrosine receptor kinase; PS, performance status; TRK, tropomyosin receptor kinase

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

CI, confidence interval; CNS, central nervous system; HGG, high grade glioma; LGG, low grade glioma; NE, not estimable; ORR; objective response rate; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

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)
  - Hypernatremia (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)

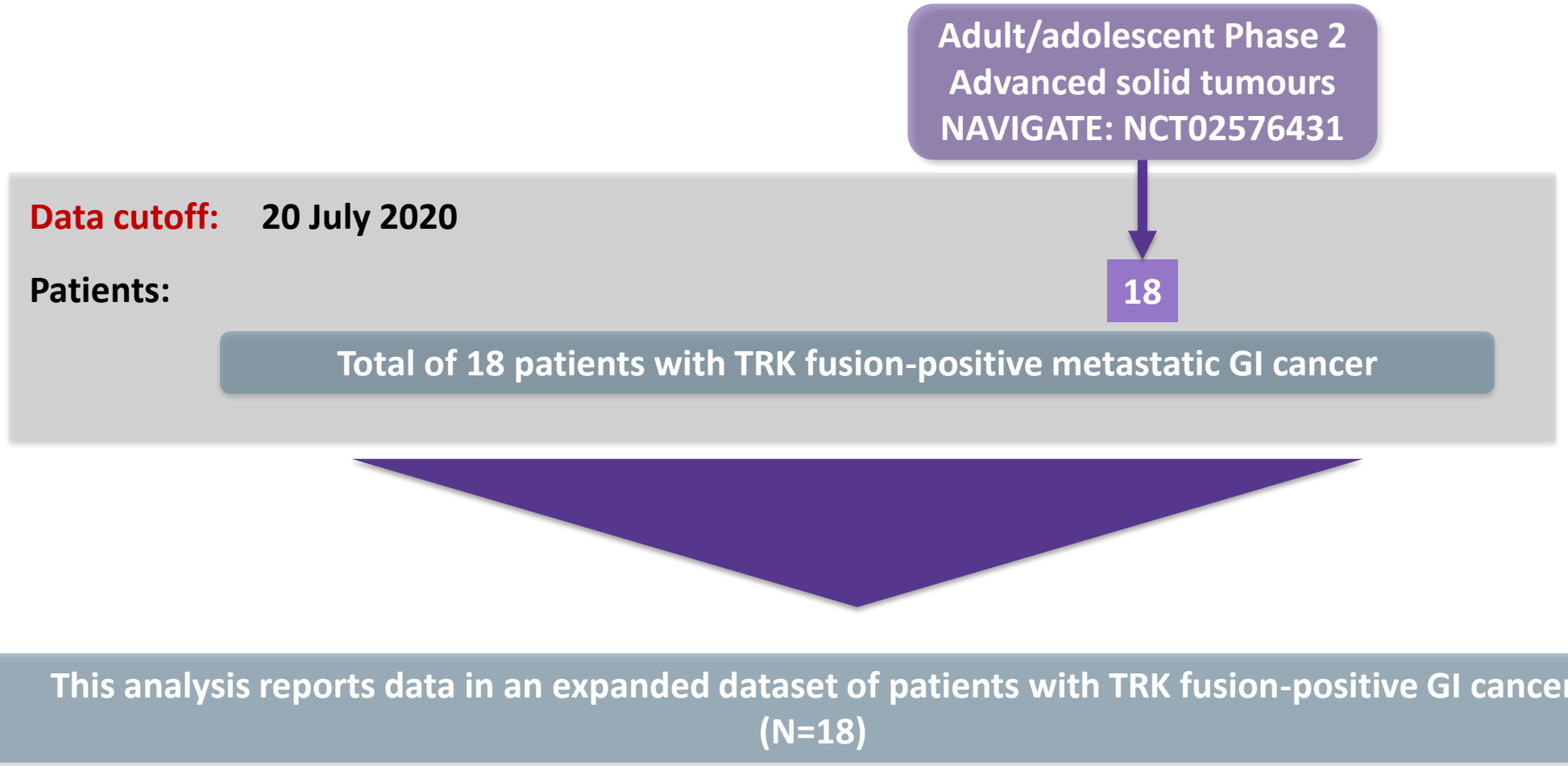
AE, adverse event; CNS, central nervous system; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase

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

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

GI, gastrointestinal; TRK, tropomyosin receptor kinase

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



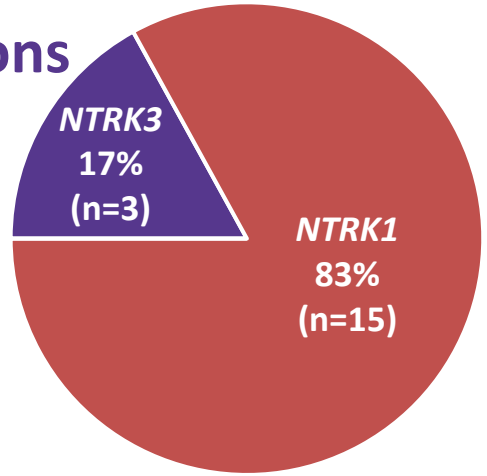
GI, gastrointestinal; TRK, tropomyosin receptor kinase

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

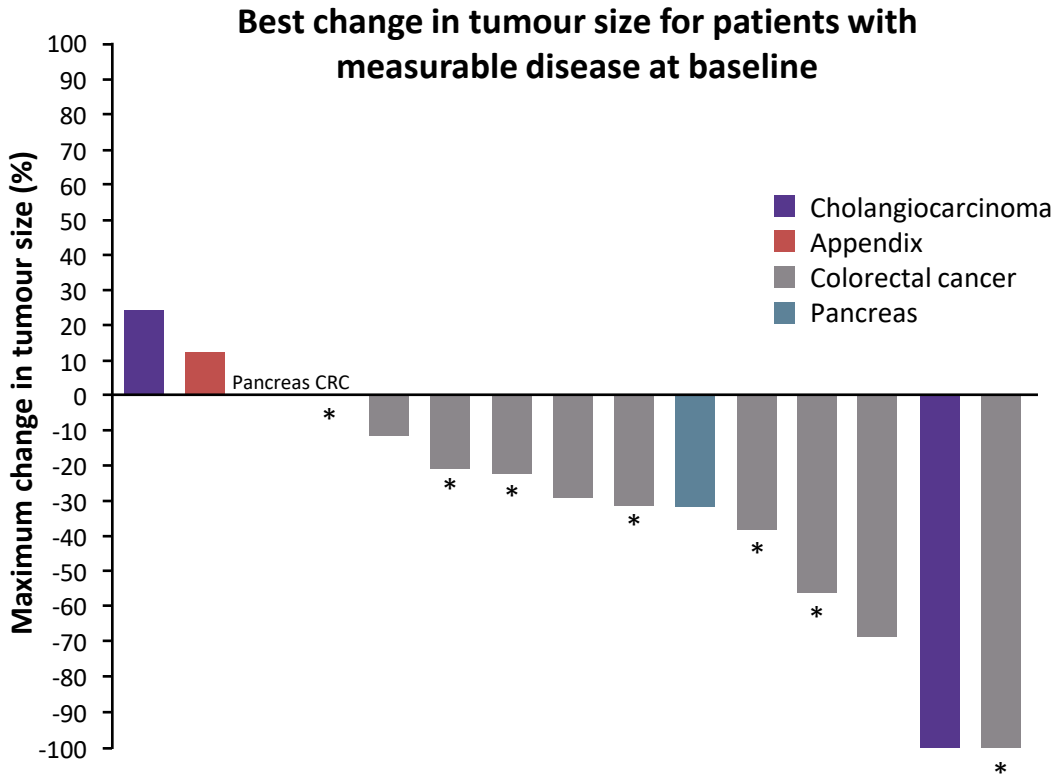


[a] 3 patients had received prior immunotherapy: one with colorectal cancer had progressive disease as best response after 2.8 months IO therapy, one with hepatic cancer had progressive disease and one with oesophageal cancer had unknown response.

ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; IO, immuno-oncology; MSI-H, microsatellite instability high, MSS, microsatellite stable; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

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

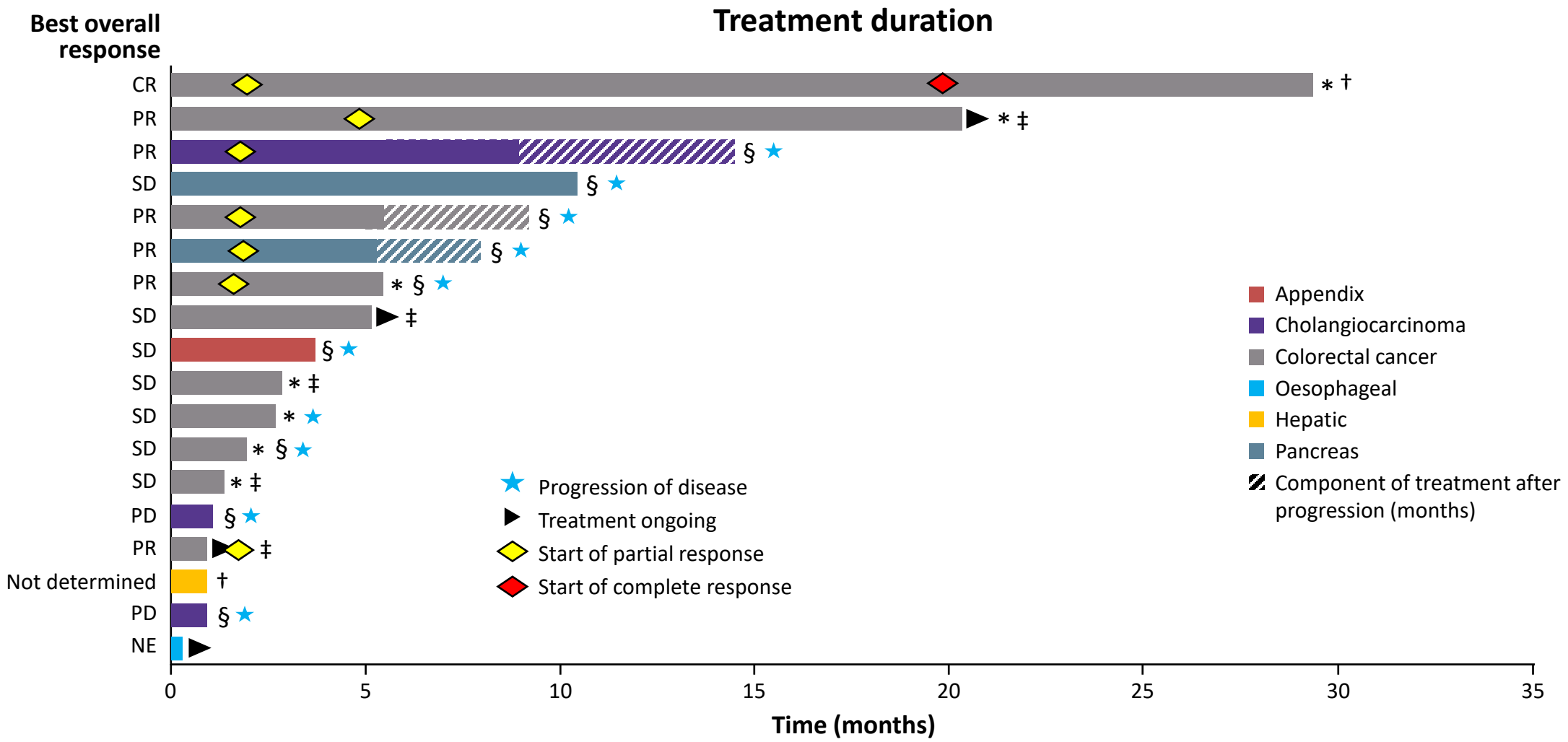


- Treatment duration ranged from 0.26+ to 29.3 months
- At the data cut-off, 10 patients had progressed, with 3 continuing treatment post-progression (range 2.7-5.5 months)
- Median time to response: 1.86 months (range 1.68-4.96)

*MSI-high

CI, confidence interval; CRC, colorectal cancer; GI, gastrointestinal; MSI; microsatellite instability; ORR, objective response rate; TRK, tropomyosin receptor kinase

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

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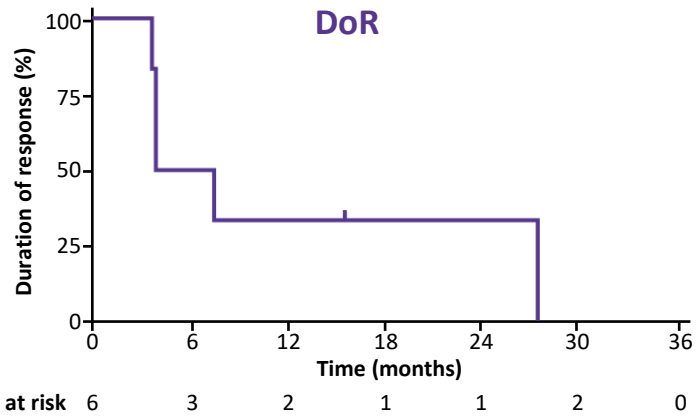
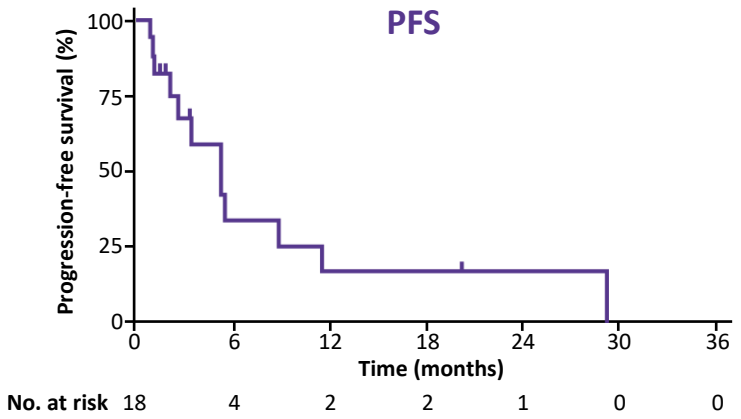
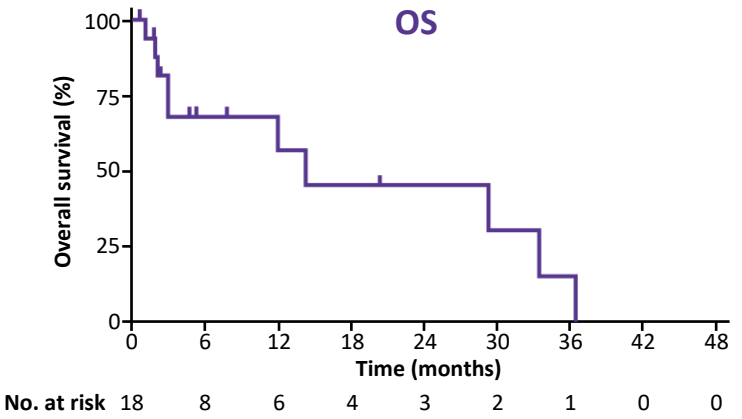






All patients (N=18)	
Median **DoR**, (95% CI), months	5.5 (3.5-27.3)
Median follow-up, months	Not reached
Patients with CRC (n=10)	
Median **DoR**, (95% CI), months	15.5 (3.7-27.3)
Median follow-up, months	Not reached

All patients (N=18)	
Median **PFS**, (95% CI), months	5.4 (2.2-11.6)
Median follow-up, months	20.3
Patients with CRC (n=10)	
Median **PFS**, (95% CI), months	5.5 (2.2-29.4)
Median follow-up, months	20.3

All patients (N=18)	
Median **OS**, (95% CI), months	14.1 (2.8-33.4)
Median follow-up, months	7.8
Patients with CRC (n=10)	
Median **OS**, (95% CI), months	29.4 (2.8-36.5)
Median follow-up, months	7.8

CI, confidence interval; CRC, colorectal cancer; DoR, duration of response; GI, gastrointestinal; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

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

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase

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

Italiano A, et al. ASCO 2021, #3114

TRK, tropomyosin receptor kinase

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

NTRK connect® POWERED BY COR2ED

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 2019**[1]

GMI analysis reported in a cohort of 122 patients with TRK fusion cancer[1]

$$GMI = \frac{PFS_{larotectinib}{}^{a}}{TTP_{prior\ line}{}^{b}}$$

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, growth modulation index; PFS; progression-free survival; TRK, tropomyosin receptor kinase; TTP, time to progression or treatment failure

1. Italiano A. et al. Presented at the ESMO virtual Congress 2020, #542P

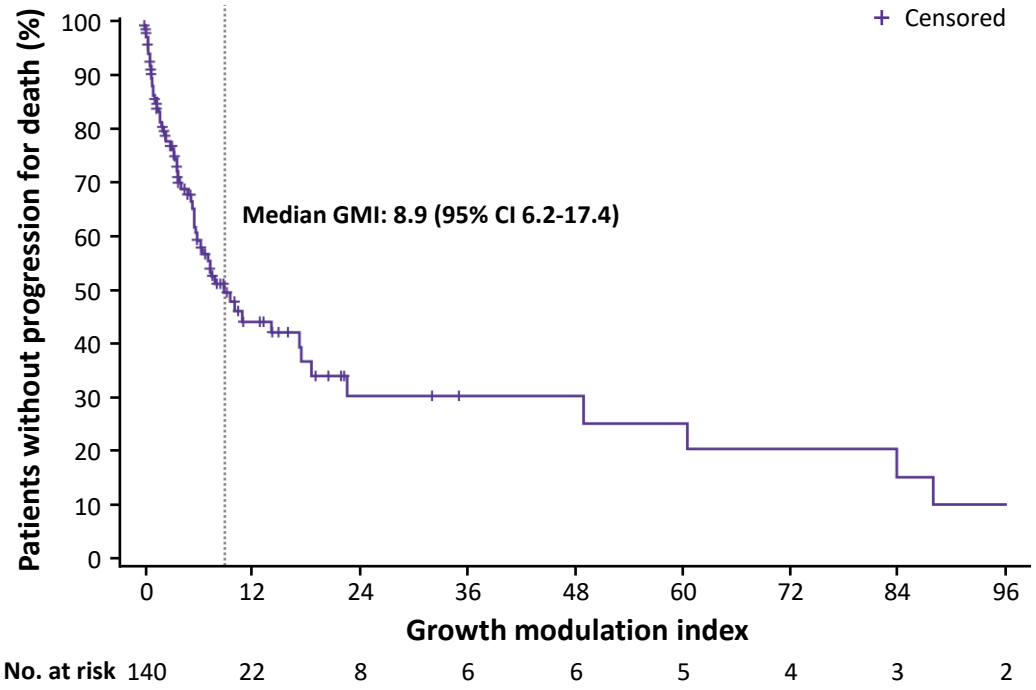
GMI ANALYSIS OF 140 PATIENTS TREATED WITH LAROTRECTINIB

	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

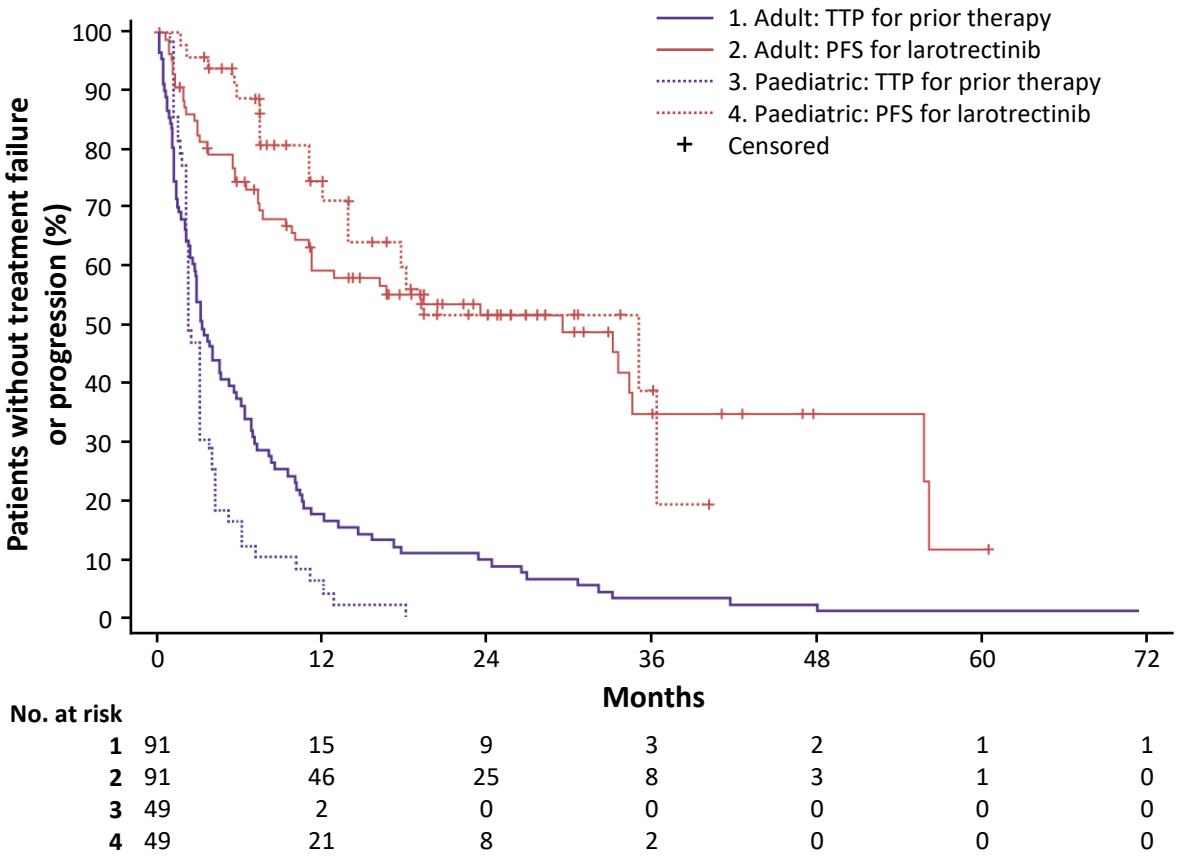
[b] Only tumours reported in ≥7 patients are listed

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



CI, confidence interval; GMI, growth modulation index

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 pediatric patient progressed at 151 months

CI, confidence interval; PFS, progression-free survival; TRK, tropomyosin receptor kinase; TTP, time to progression or treatment failure

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 evalute 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 m^2: 600mg QD
BSA <1.51 m^2: 100-400mg QD

Primary efficacy endpoint:
- Confirmed ORR ≥28 days after intitial 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

BSA, body surface area; CBR, clinical benefit rate; CNS, central nervous system; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; INRC, International Neuroblastoma Response Criteria; IRC, independent review committee; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PROs, patient-reported outcomes; PS, performance status; QD, once daily; RANO, response assessment in neuro-oncology; RECISTv1.1, response evaluation criteria in solid tumours version 1.1

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

CNS, central nervous system; CRC, colorectal cancer; NTRK, neurotrophic tyrosine receptor kinase; PFS; progression-free survival; TRK, tropomyosin receptor kinase

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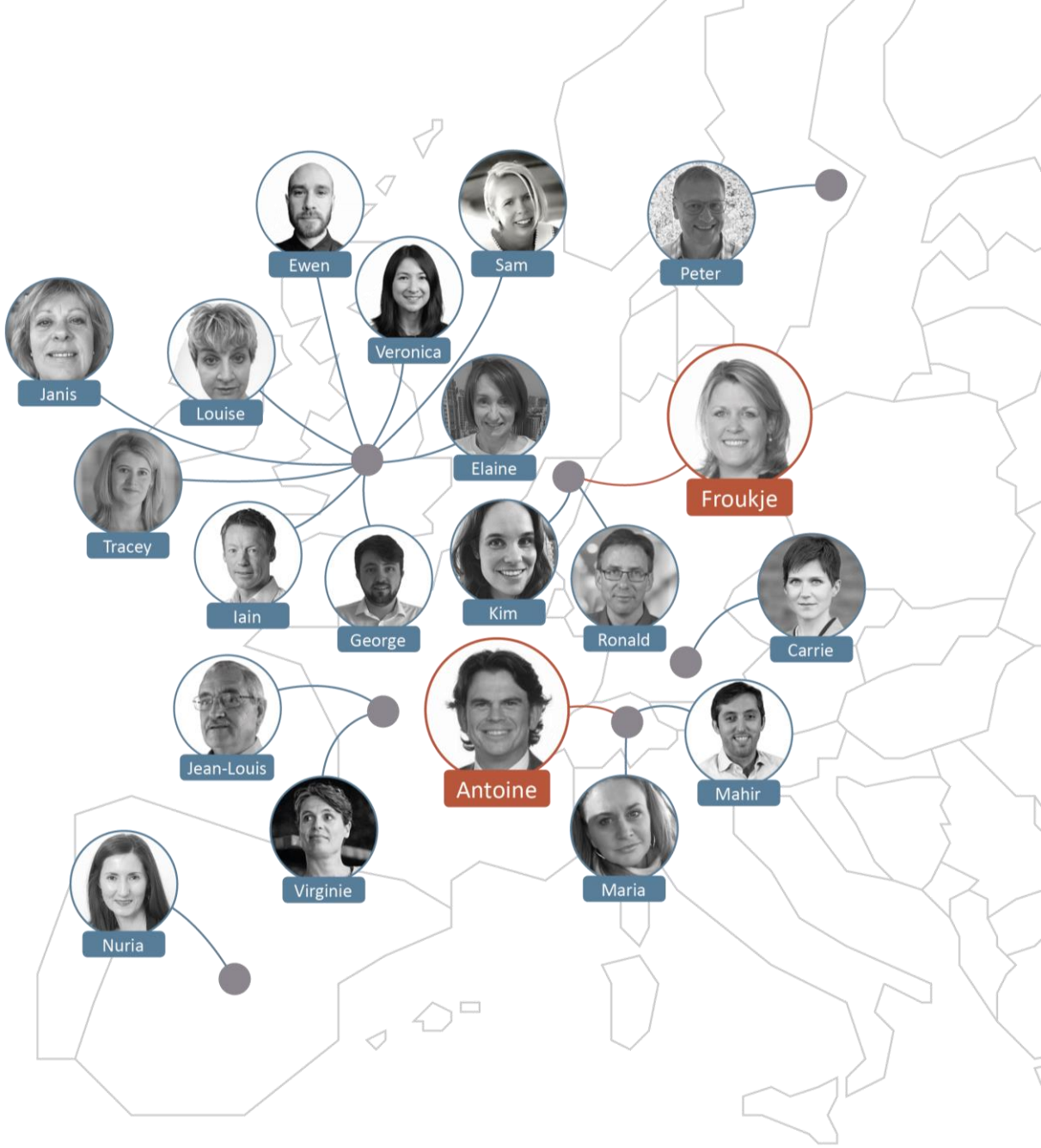

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