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MEETING SUMMARY
ESMO 2020, VIRTUAL MEETING

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HIGHLIGHTS FROM NTRK CONNECT
SEPTEMBER 2020

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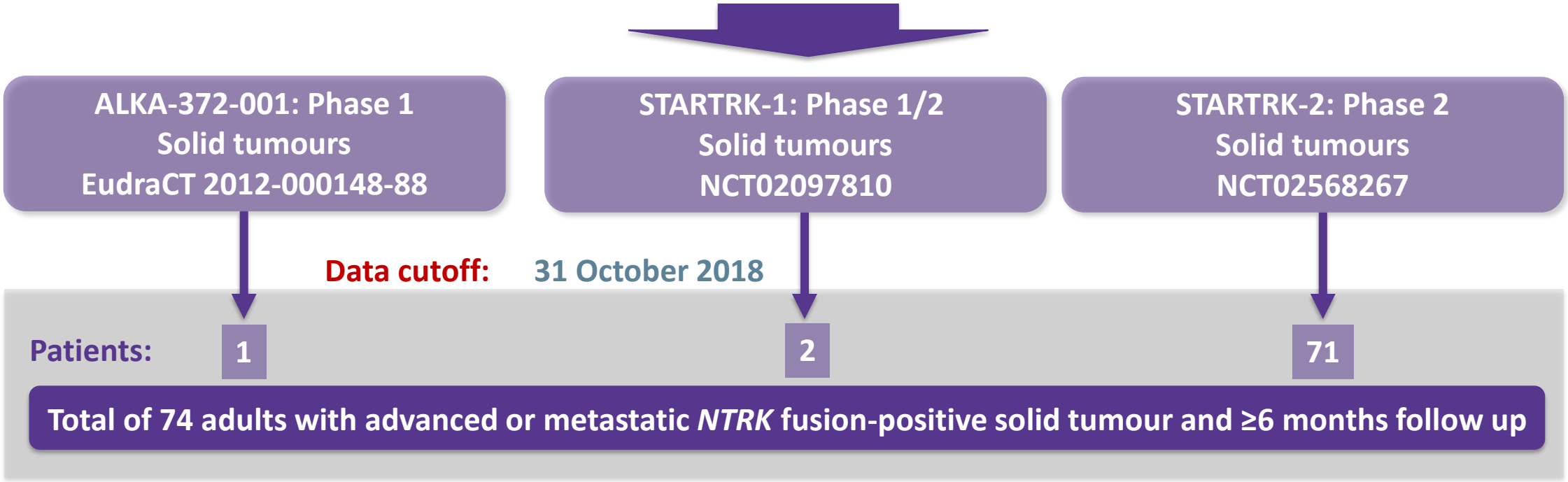
Disclosures: Dr Viktor Grünwald has received honoraria from the following:

- Bayer, Roche

ENTRECTINIB RELATED DATA

BACKGROUND

Entrectinib = potent inhibitor of TRK, ROS1 and ALK tyrosine kinase



- **Abstract #364O: Assessment of the patients with *NTRK* fusion-positive tumours and with CNS disease.** Assessment of one of the secondary endpoints = intracranial (IC) objective response rate (ORR) and IC duration of response (DoR)
- **Abstract #540P: Results about the impact of the number of prior lines of systemic therapy on the response to entrectinib in patients with *NTRK* fusion-positive tumours** (Note: *ROS1*-positive non-small-cell lung carcinoma [NSCLC] is not covered here)

ALK, anaplastic lymphoma kinase; CNS, central nervous system; NTRK, neurotrophic receptor tyrosine kinase; ROS1, ROS proto-oncogene 1; TRK, tropomyosin receptor kinase

INTRACRANIAL EFFICACY OF ENTRECTINIB IN PATIENTS WITH *NTRK* FUSION-POSITIVE SOLID TUMOURS AND BASELINE CNS METASTASES

John T, et al.
ESMO 2020. Abstract #364O. Oral presentation

CNS, central nervous system; NTRK, neurotrophic tyrosine receptor kinase

RESULTS: BASELINE CHARACTERISTICS

Baseline characteristics	Patients with *NTRK* fusion-positive tumours (n=74)
ECOG PS, %	
0	40.5
1	45.9
2	13.5
Prior lines of systemic therapy, %	
0	27.0
1	28.4
2	27.0
≥3	17.6
CNS metastases at baseline, %	
Yes	25.7
no	74.3

19 patients with investigator assessed CNS metastases at baseline

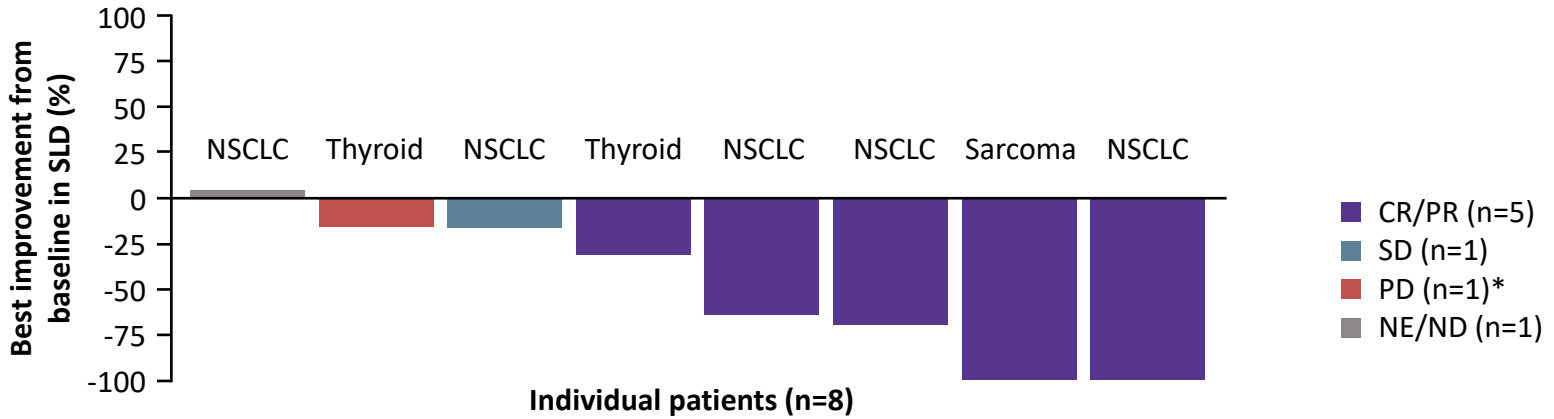
16 patients confirmed to have baseline CNS metastases per blinded independent central review (BICR)

- NSCLC (n=8)
- Thyroid (n=4)
- Sarcoma (n=2)
- Salivary (n=1)
- Breast (n=1)

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase

RESULTS: INTRACRANIAL ORR AND DOR

Intracranial response	Patients with *NTRK* fusion-positive tumours and baseline CNS metastases per BICR	
	Measurable (n=8)	Measurable/non measurable (n=16)
Intracranial ORR, % (95% CI)	62.5 (24.5-91.5)	50.0 (24.7-75.4)
Median intracranial DoR in responders (95% CI), months	NE (5.0-NE)	8.0 (6.7-NE)
Median intracranial PFS (95% CI), months	10.1 (2.8-NE)	8.9 (5.9-14.3)



* Radiographic CNS metastases progression was defined as an occurrence of a new CNS lesion or progression in pre-existing CNS lesions per RECIST v1.1

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; ND, not determined; NE, not estimable; NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; PD, disease progression; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; SLD, sum of longest diameter

RESULTS: NEUROLOGICAL SAFETY SUMMARY

Neurological AE, n (%)	Overall safety population*	
	CNS metastases at baseline (n=176)**	No CNS metastases at baseline (n=328)
Treatment-related AE	116 (65.9)	256 (78.0)
Treatment-related AE grade ≥3	12 (6.8)	18 (5.5)
Treatment-related serious AE	8 (4.5)	11 (3.4)
Neurological AE leading to discontinuation	2 (1.1)	4 (1.2)
Neurological AE leading to dose reduction	21 (11.9)	32 (9.8)
Neurological AE leading to dose interruption	15 (8.5)	41 (12.5)

* Safety population includes all patients receiving ≥1 dose of entrectinib regardless of tumour type and gene rearrangement (*NTRK1, ROS1, ALK*)
** CNS metastases determined by investigator

AE, adverse event; ALK, anaplastic lymphoma kinase; CNS, central nervous system; NTRK, neurotrophic receptor tyrosine kinase; ROS1, ROS proto-oncogene 1

ENTRECTINIB IN PATIENTS WITH *ROS1* FUSION-POSITIVE NSCLC OR *NTRK* FUSION-POSITIVE SOLID TUMOURS: ANALYSIS OF RESPONSE BY LINE OF THERAPY

Liu SV, et al.

ESMO 2020. Abstract #540P. Poster presentation

NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; ROS1, ROS proto-oncogene 1

RESULTS: BASELINE CHARACTERISTICS

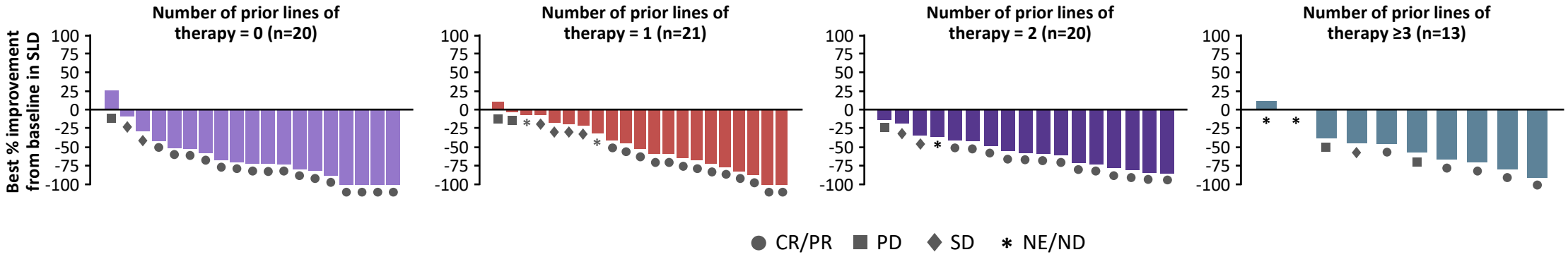
Baseline characteristics	Patients with *NTRK* fusion-positive tumours (n=74)				
	Prior LOT: 0 (n=20, 27%)	Prior LOT: 1 (n=21, 28%)	Prior LOT: 2 (n=20, 27%)	Prior LOT: ≥3 (n=13, 18%)	Total (n=74)
ECOG PS, %					
0	55.0	52.4	35.0	7.7	40.5
1	45.0	28.6	55.0	61.5	45.9
2	0	19.0	10.0	30.8	13.5
Tumour type, n (%)					
Breast	3 (15.0)	1 (4.8)	0	2 (15.4)	6 (8.1)
Cholangiocarcinoma	0	0	1 (5.0)	0	1 (1.4)
Colon	1 (5.0)	2 (9.5)	2 (10.0)	2 (15.4)	7 (9.5)
Non-CRC GI, NOS	1 (5.0)	0	0	0	1 (1.4)
Gynaecological	0	0	2 (10.0)	0	2 (2.7)
Neuroblastoma	0	0	0	1 (7.7)	1 (1.4)
Neuroendocrine	0	3 (14.3)	0	1 (7.7)	4 (5.4)
NSCLC	3 (15.0)	4 (19.0)	3 (15.0)	3 (23.1)	13 (17.6)
Pancreatic	1 (5.0)	1 (4.8)	1 (5.0)	0	3 (4.1)
Salivary (MASC)	6 (30.0)	2 (9.5)	3 (15.0)	2 (15.4)	13 (17.6)
Sarcoma	3 (15.0)	7 (33.3)	4 (20.0)	2 (15.4)	16 (21.6)
Thyroid	2 (10.0)	1 (4.8)	4 (20.0)	0	7 (9.5)

CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; LOT, lines of therapy; MASC, mammary analogue secretory carcinoma; NOS, not otherwise specified; NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase

RESULTS: ORR AND DOR BY PRIOR LINES OF SYSTEMIC THERAPY

	Patients with *NTRK* fusion-positive tumours (n=74)			
	Prior LOT: 0 (N=20, 27%)	Prior LOT: 1 (N=21, 28%)	Prior LOT: 2 (N=20, 27%)	Prior LOT: ≥3 (N=13, 18%)
ORR, % (n) 95% CI	80.0 (16) 56.3-94.3	61.9 (13) 38.4-81.9	65.0 (13) 40.8-84.6	38.5 (5) 13.9-68.4
Median DoR, responders (n) 95% CI, months	NE (16) 5.6-NE	15.1 (13) 10.4-15.1	11.1 (13) 7.9-15.0	9.4 (5) 2.8-NE

- **ORR = 57.4% in patients who had received prior systemic therapy** in the metastatic setting
- **ORR = 80% in patients who had no prior systemic therapy** in metastatic setting



CI, confidence interval; CR, complete response; DoR, duration of response; LOT, lines of therapy; ND, not determined; NE, not estimable; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease; SLD, sum of longest diameter

RESULTS: SAFETY SUMMARY BY PRIOR LINES OF SYSTEMIC THERAPY

TRAEs by LOT, n/N (%)	Patients with *NTRK* fusion-positive tumours (safety evaluable population=113)			
	Prior LOT: 0	Prior LOT: 1	Prior LOT: 2	Prior LOT: ≥3
Any grade	28/34 (82.4)	28/31 (90.3)	24/27 (88.9)	16/21 (76.2)
Discontinuation due to TRAE	0	5/31 (16.1)	0	2/21 (9.5)
Dose reduction due to TRAE	14/34 (41.2)	6/31 (19.4)	7/27 (25.9)	3/21 (14.3)

LOT, lines of therapy; NTRK, neurotrophic tyrosine receptor kinase; TRAE, treatment-related adverse event

CONCLUSIONS AND DISCUSSIONS

KEY FINDINGS

- Patients with *NTRK* fusion-positive tumours and baseline CNS metastases treated with entrectinib (n=16) **showed promising intracranial responses** and **similar safety profile** in patients with and without baseline CNS metastases
- Patients with *NTRK* fusion-positive tumours showed **numerically better responses with no prior treatment** in the metastatic setting

PERSPECTIVES

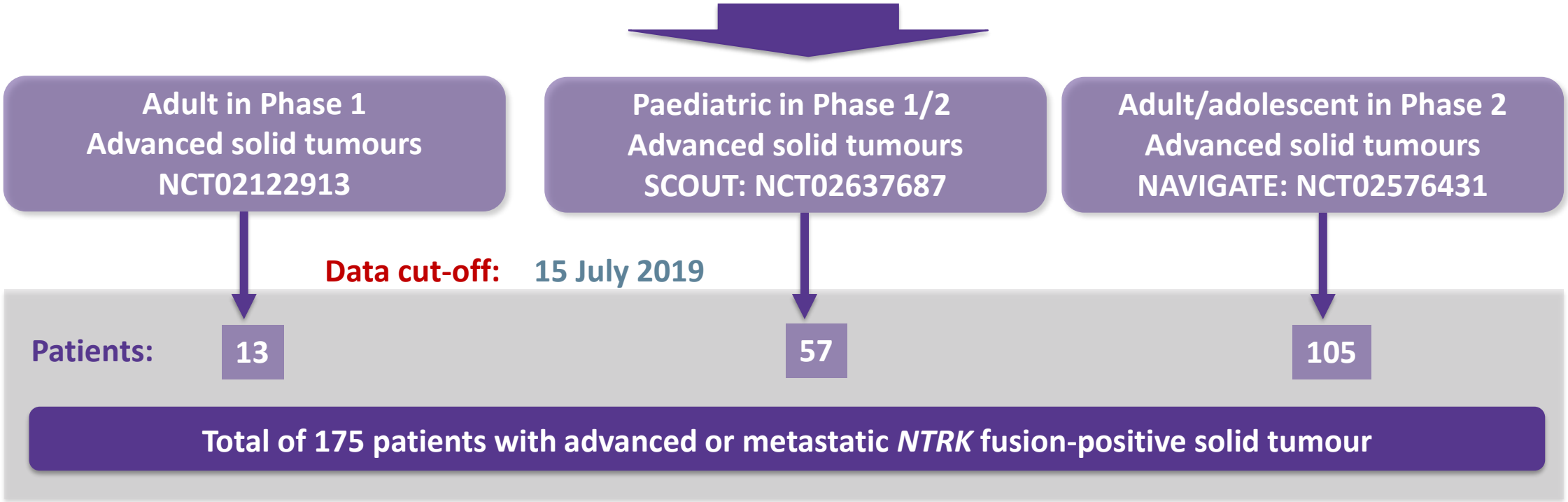
- Because of the small numbers of patients (n=8 with measurable disease), **further investigations** are required in order **to assess the role of TRK inhibitors in patients with CNS metastases**
- Given that patient characteristics were consistent across all prior LOT groups, it would interesting to **further explore** the **difference in ORR and DoR between no prior treatment vs with prior LOT**
- Further investigations are required to **establish** if there is a **link between response and tumour type**
- **Additional information on the safety profile** in both abstracts would have been welcomed

CNS, central nervous system; DoR, duration of response; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; TRK, tropomyosin receptor kinase

LAROTRECTINIB RELATED DATA

BACKGROUND

larotrectinib = potent TRK specific inhibitor



- **Abstract #1289P: Assessment of larotrectinib efficacy and safety in a subset of patients with *NTRK* fusion-positive lung cancer (n=14)**
- **Abstract #1916P: Assessment of larotrectinib efficacy and safety in a subset of patients with *NTRK* fusion-positive thyroid cancer (n=28)**

NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

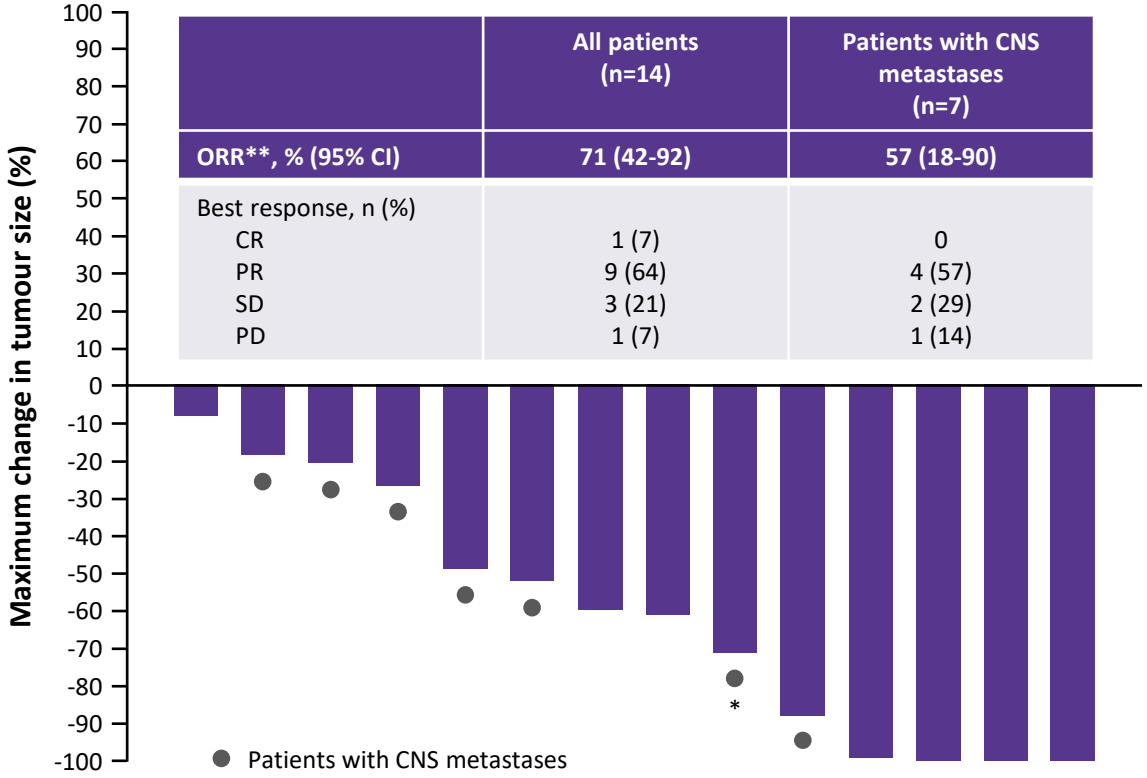
EFFICACY AND SAFETY OF LAROTRECTINIB IN PATIENTS WITH TRK FUSION LUNG CANCER

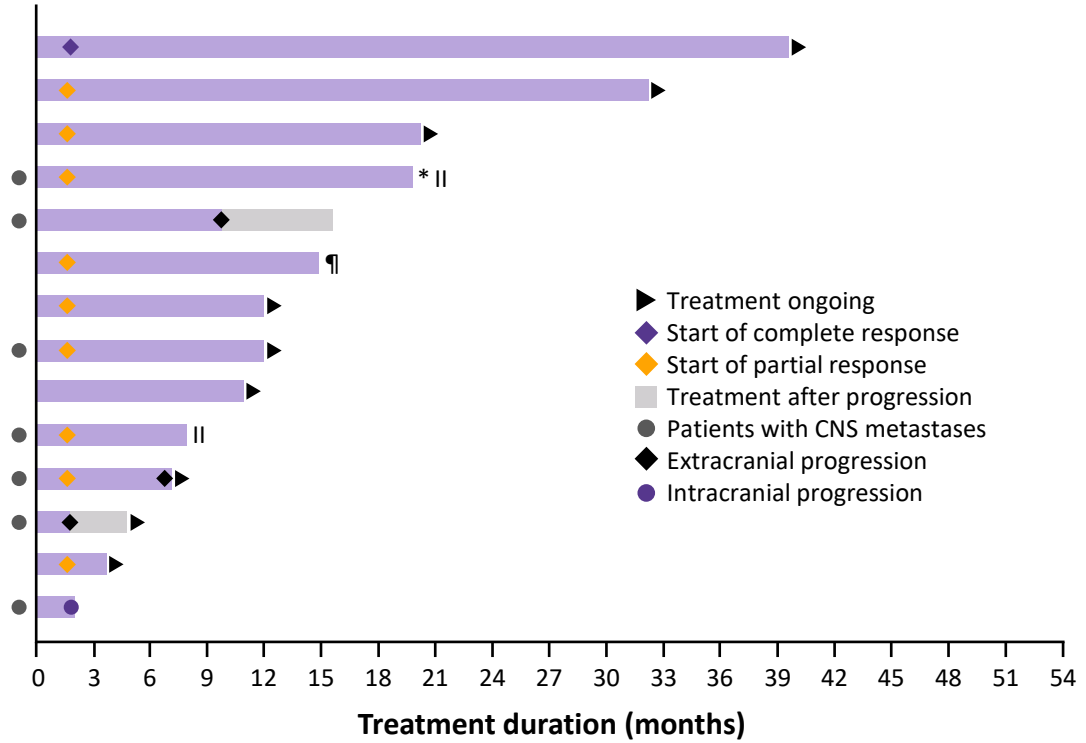
Drilon A, et al.
ESMO 2020. Abstract #1289P. Poster presentation

TRK, tropomyosin receptor kinase

RESULTS: EFFICACY

	All patients (n=14)	Patients with CNS metastases (n=7)
ORR**, % (95% CI)	71 (42-92)	57 (18-90)
Best response, n (%)		
CR	1 (7)	0
PR	9 (64)	4 (57)
SD	3 (21)	2 (29)
PD	1 (7)	1 (14)





* Patient had 100% reduction in CNS lesions; **: investigator-assessed; II: patient discontinued at the physician's decision; ¶: patient discontinued due to protocol deviation

- **Median time to response (TTP) = 1.8 months (range: 1.6-1.9)**
- **Median progression-free survival (PFS), DoR and OS not reached at the median follow-up:**
  - **PFS rate at 12 months = 69%**
  - **OS rate at 12 months = 91%**

CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; ORR, objective response rate; OS, overall survival; PD, disease progression; PR, partial response; SD, stable disease

RESULTS: SAFETY

- Adverse events (AEs): mostly Grade 1 or 2 and no unexpected safety signals
- Six patients (43%) experienced a Grade 3 AE
  - Two patients (14%) experienced a Grade 3 AE considered to be related to larotrectinib (hypersensitivity and myalgia)
- No Grade 4 or 5 AEs
- Dose reduction in two patients (14%) due to AEs:
  - One patient: increased alanine aminotransferase and increased aspartate aminotransferase
  - One patient: decreased neutrophil count
- No AE leading to permanent treatment discontinuation

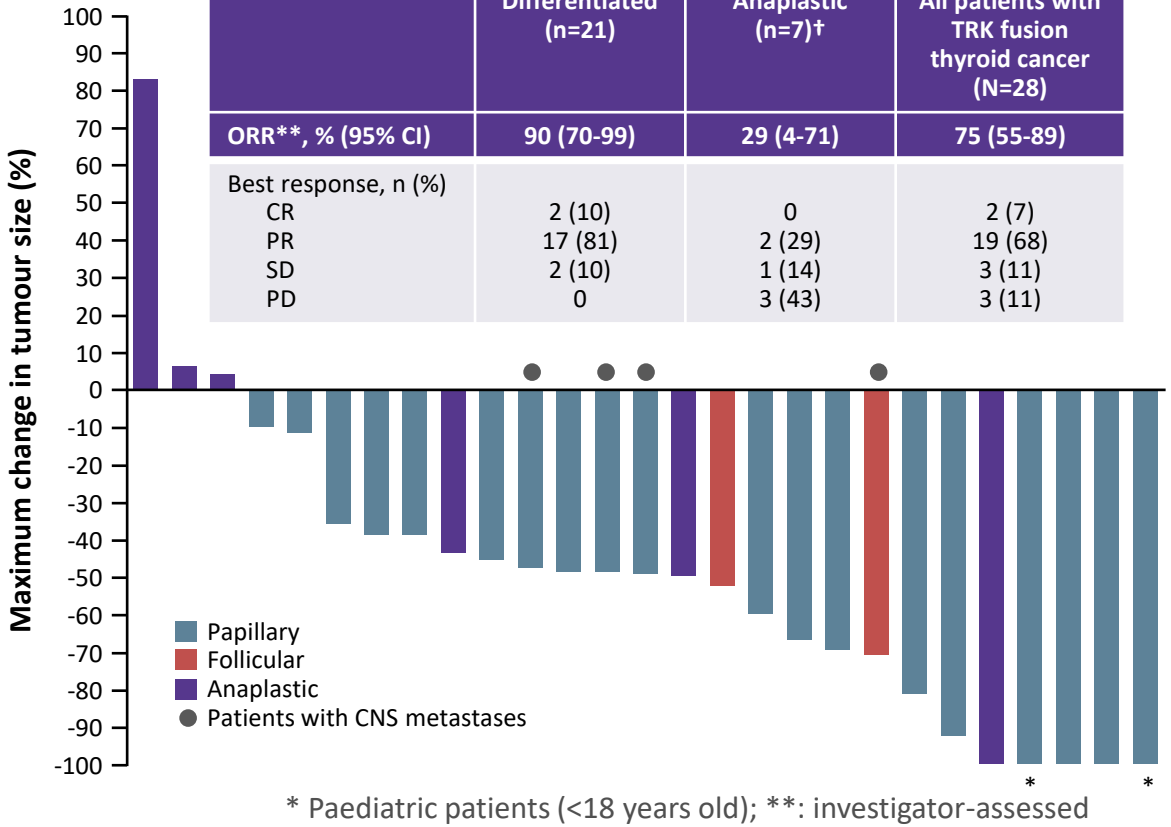
LAROTRECTINIB TREATMENT OF ADVANCED TRK FUSION THYROID CANCER

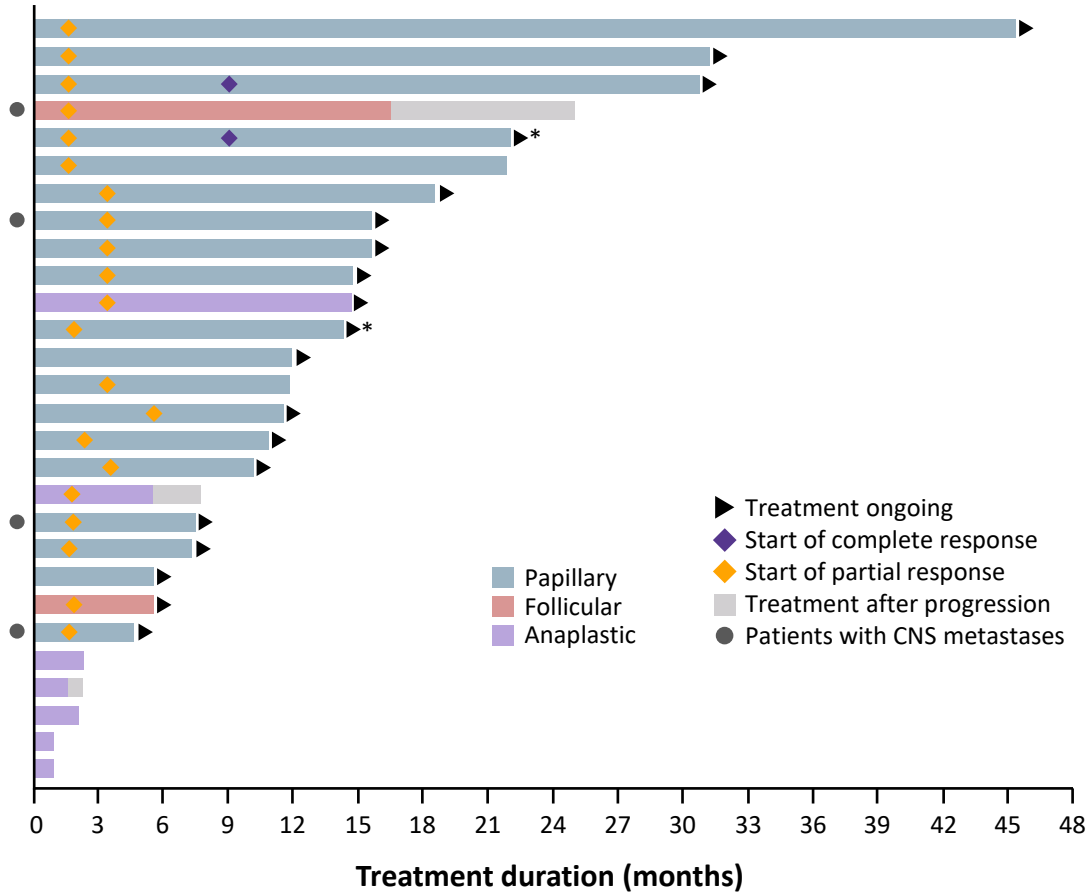
Cabanillas ME, et al.
ESMO 2020. Abstract #1916P. Poster presentation

TRK, tropomyosin receptor kinase

RESULTS: EFFICACY

	Differentiated (n=21)	Anaplastic (n=7)†	All patients with TRK fusion thyroid cancer (N=28)
ORR**, % (95% CI)	90 (70-99)	29 (4-71)	75 (55-89)
Best response, n (%)			
CR	2 (10)	0	2 (7)
PR	17 (81)	2 (29)	19 (68)
SD	2 (10)	1 (14)	3 (11)
PD	0	3 (43)	3 (11)





* Paediatric patients (<18 years old); **: investigator-assessed

- Median TTP= 1.9 months (range: 1.6-5.6)
- Median OS= 27.8 months (95% CI; 16.7-NE) for all patients; 14.1 months (95% CI 2.6-NE) for patients with ATC and not reached for DTC
- Median PFS and DoR not estimable:
  - Estimated DoR at 12 months = 95% (95% CI, 85-100)
  - Estimated PFS rate at 18 months = 70% (95%CI 45-94) for all patients and 86% (95% CI 460-100) for patients with DTC

ATC, anaplastic thyroid cancer; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; DTC, differentiated thyroid cancer; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease; TRK, tropomyosin receptor kinase; TTP, time to response

RESULTS: SAFETY

- AEs: mostly Grade 1 or 2 and no unexpected safety signals
- Nine patients (32%) experienced a Grade 3 AE
  - Two patients (7%) experienced a Grade 3 AE considered to be related to larotrectinib (anaemia and decreased lymphocyte count)
- Two patients (7%) experienced Grade 4 and 5 AEs
- Dose reduction in two patients (7%) due to AEs:
  - One patient: increased alanine aminotransferase
  - One patient: decreased neutrophil count
- No AE leading to permanent treatment discontinuation

AE, adverse event

CONCLUSIONS AND DISCUSSIONS

KEY FINDINGS

- Larotrectinib showed a **high survival benefit (PFS and OS)** and **high response rate with long durability in patients with *NTRK* fusion-positive lung and thyroid tumours** with **no unexpected safety findings**
- Larotrectinib showed an explicit activity in **anaplastic thyroid cancer**

PERSPECTIVES

- **Testing** to find those patients harbouring *NTRK* fusion-positive tumours is the **most challenging step** but necessary step in order **to identify those patients that can benefit from therapy**
- Evidence supports the **efficacy of larotrectinib against multiple tumour types** and specially in **differentiated thyroid carcinoma** and in **anaplastic thyroid carcinoma**
- McDermott R. et al.* showed that in the overall population (n=175), ORR was 78% consistent with prior communication and ORR in brain metastases patients (n=14) was 71% with a mDOR of 14.8 months, demonstrating **a durable response of larotrectinib in patients with brain metastases**

*McDermott R et al, Abstracts #1955P ESMO 2020

mDOR, median duration of response; NTRK, neurotrophic receptor tyrosine kinase, OS, overall survival; ORR, objective response rate; PFS, progression-free survival

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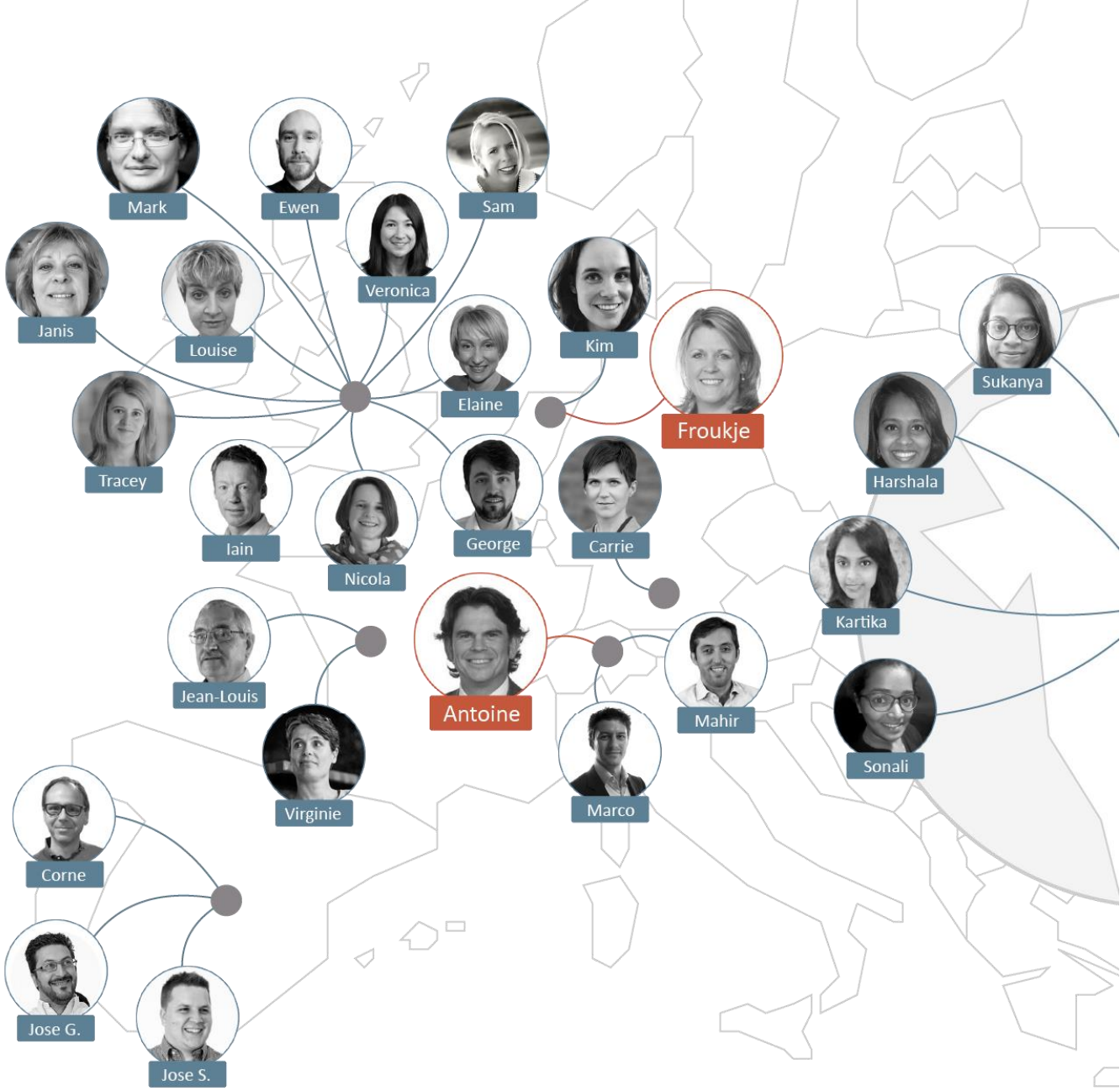

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