Phase 1/1B trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors

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Disclosure information

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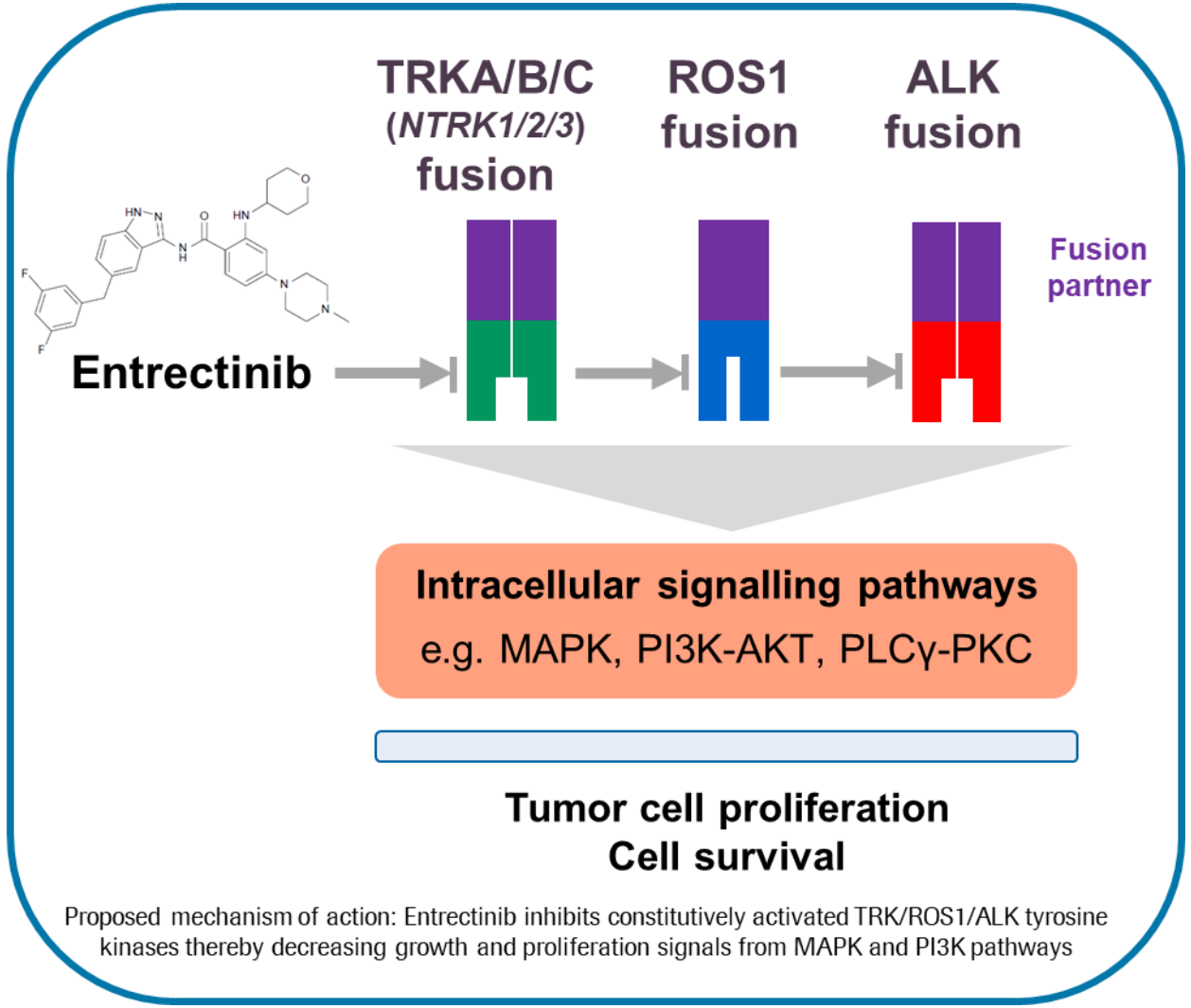
Background

- Fusions and alterations in the ***NTRK1/2/3***, ***ROS1*** and ***ALK*** genes act as drivers of certain cancers[1–3]
- Entrectinib is an oral, potent inhibitor of **TRKA/B/C, ROS1**, and **ALK** proteins that also **penetrates into the CNS** to reach tumors in the brain and spine[4,5]
- Clinical activity was seen in adult solid tumor patients with target gene rearrangements[6,7] even with **brain metastases** or when the tumor was **primarily located in the brain**[8]
- A variety of pediatric cancers harbor mutations and fusions in *NTRK1/2/3, ROS1* and *ALK*:[9]
  - **infantile fibrosarcomas** (*NTRK*), **pediatric high grade gliomas** (*NTRK, ROS1, ALK*), **neuroblastoma** (*ALK*), **inflammatory myofibroblastic tumor** (*ALK, ROS1*)
  - while rare, this list is growing as mutations and fusions are detectable with next-generation sequencing
- Here, we report on the activity of **entrectinib in children** with recurrent or refractory solid tumors including primary CNS tumors



Proposed mechanism of action: Entrectinib inhibits constitutively activated TRK/ROS1/ALK tyrosine kinases thereby decreasing growth and proliferation signals from MAPK and PI3K pathways

ALK, anaplastic lymphoma kinase; CNS, central nervous system; *NTRK*, neurotrophic tropomyosin receptor kinase; TRKA, tropomyosin receptor kinase A

1. Vaishnavi, et al. Cancer Discov 2014; 2. Lin, et al. J Thorac Oncol 2017; 3. Hofman. Cancers 2017; 4. Menichincheri, et al. J Med Chem 2016
5. Ardini, et al. Mol Cancer Ther 2016; 6. Doebele, et al. J Thorac Oncl 2018; 7. Demetri, et al. Ann Oncol 2018;
8. Drilon, et al. Cancer Discov 2017; 9. Okaruma, et al. JCO Precis Oncol. 2018

STARTRK-NG (RXDX-101-03) study design

Pediatric and adolescent patients
Total enrolled (n=29); data cut-off October 31, 2018

Eligibility criteria
- Birth–21 years
- Relapsed or refractory solid tumors (including primary CNS tumors)
- Karnofsky or Lansky score ≥60%, minimum life expectancy ≥4 weeks
- Measurable or evaluable disease (dose escalation), measurable disease (dose expansion)
- With or without target molecular aberrations in *NTRK1/2/3*, *ROS1* or *ALK*

Treatment
- Oral administration
- QD, 28-day cycles

Primary endpoints*
- MTD, RP2D

Key secondary endpoints
- Safety and tolerability
- Plasma PK: C_{max}, CSS, $T_{1/2}$, AUC
- Anti-tumor activity: ORR, PFS

Dose-finding phase 1 (N=16) in patients with relapsed or refractory solid tumors
Dose level 250–750mg/m²

Sequential assignment to escalating doses of entrectinib (3+3 design), initially dosed by BSA

- **250mg/m²** (n=3)
- **400mg/m²** (n=3)
- **550mg/m²** (n=7)
- **750mg/m²** (n=3)

Basket trial phase 1b (N=13)
Dose level 550mg/m² (n=7) OR 400mg/m² in patients unable to swallow intact capsules (n=6)

- **Primary CNS tumors** (n=6)
- **Neuroblastoma** (n=3)
- **Extracranial solid tumors** (n=4)

*Investigator assessed. AUC, area under curve; BSA, body surface area; CSS, concentration at steady state; MTD, maximum tolerated dose; NG, next generation; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase II dose; STARTRK-NG, **S**tudies of **T**umour **A**lterations **R**esponsive to **T**argeting **R**eceptor **K**inases – **N**ext **G**eneration

STARTRK-NG baseline patient characteristics

Characteristic		Phase 1 dose-escalation (n=16)				Phase 1b (n=13)	All patients (n=29)
		250 mg/m² (n=3)	400 mg/m² (n=3)	550 mg/m² (n=7)	750 mg/m² (n=3)		
Median age	Years (range)	9 (7–13)	15 (6–20)	7 (6–17)	10 (4–16)	5 (0–19)	**7 (0–20)**
Sex, n (%)	Male	2 (66.7)	1 (33.3)	5 (71.4)	2 (66.7)	5 (38.5)	**15 (51.7)**
	Female	1 (33.3)	2 (66.7)	2 (28.6)	1 (33.3)	8 (61.5)	**14 (48.3)**
Race, n (%)	White	2 (66.7)	2 (66.7)	6 (85.7)	3 (100.0)	13 (100.0)	**26 (89.7)**
	Black/African American	1 (33.3)	1 (33.3)	1 (14.3)	0	0	**3 (10.3)**
Karnofsky/Lansky score, n (%)*	100	3 (100.0)	1 (33.3)	1 (16.7)	0	6 (46.2)	**11 (39.3)**
	90	0	1 (33.3)	4 (66.7)	2 (66.7)	3 (23.1)	**10 (35.7)**
	80	0	1 (33.3)	0	1 (33.3)	3 (23.1)	**5 (17.9)**
	70	0	0	1 (16.7)	0	1 (7.7)	**2 (7.1)**
Prior systemic therapies, n (%)	Chemotherapy	3 (100.0)	3 (100.0)	5 (71.4)	3 (100.0)	10 (76.9)	**24 (82.8)**
	Immunotherapy	0	2 (66.7)	4 (57.1)	1 (33.3)	4 (30.8)	**11 (37.9)**
	Targeted therapy**	0	2 (66.7)	1 (14.3)	0	0	**3 (10.3)**
	Monoclonal antibody	0	3 (100.0)	2 (28.6)	3 (100.0)	3 (23.1)	**11 (37.9)**
	Radiation	3 (100.0)	3 (100.0)	5 (71.4)	2 (66.7)	9 (69.2)	**22 (75.9)**

Data cut-off: October 31, 2018 *n=28; one patient excluded from 550 mg/m² phase 1 dose level due to incorrect performance score scale for age; **prior treatment with approved or investigational TRK, ROS1, or ALK inhibitors were excluded

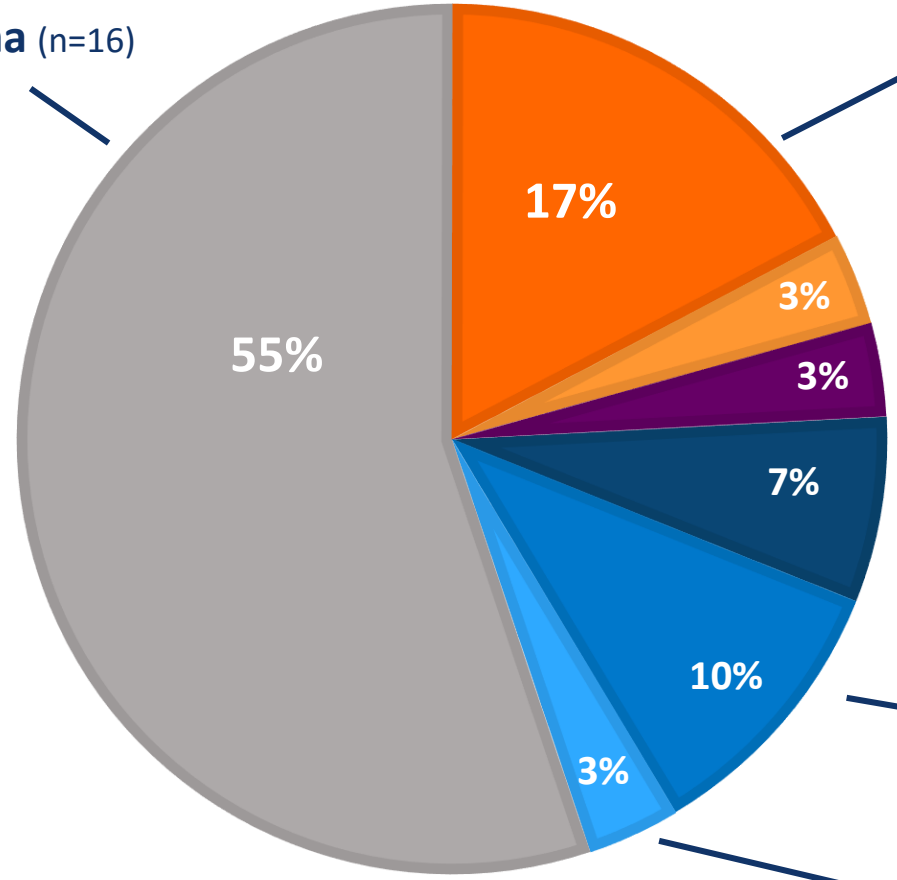
STARTRK-NG overall safety

- Most treatment-related AEs were Grade 1/2 (mild cytopenias and GI disturbances)
- Three dose-limiting toxicities (green) in the phase 1 study led to 550mg/m2 as the MTD/RP2D for phase 1b
  - were reversible upon dose interruption and/or reduction
- The treatment-related AE that continued to accumulate and result in dose reductions in the phase 1b study portion was weight gain
- There were no grade 5 treatment-related AEs

Most common (>10% Total) + any Grade 3/4 TRAE, n (%)	Phase 1 dose-escalation, mg/m^2 (n=16)								Phase 1b (n=13)		Total (n=29)		
	250 (n=3)		400 (n=3)		550 (n=7)		750 (n=3)						
	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	Any G
Any TRAE	3 (100)	0	2 (67)	1 (33)	7 (100)	0	1 (33)	2 (67)	11 (85)	0	**24 (83)**	**3 (10)**	**27 (93)**
Anemia	1 (33)	0	0	0	2 (29)	0	2 (67)	0	7 (54)	0	**12 (41)**	**0**	**12 (41)**
Blood creatinine increased	2 (67)	0	2 (67)	0	2 (29)*†	0	2 (67)†	0	4 (31)	0	**12 (41)†**	**0**	**12 (41)**
ALT increased	0	0	1 (33)	0	3 (43)	0	2 (67)	0	4 (31)	0	**10 (35)**	**0**	**10 (35)**
AST increased	2 (67)	0	2 (67)	0	1 (14)	0	2 (67)	0	3 (23)	0	**10 (35)**	**0**	**10 (35)**
Nausea	3 (100)	0	1 (33)	0	2 (29)	0	1 (33)	0	3 (23)	0	**10 (35)**	**0**	**10 (35)**
Neutrophil count decreased	0	0	0	1 (33)	1 (14)	0	0	1 (33)	2 (15)	3 (23)	**3 (10)**	**5 (17)**	**8 (28)**
White blood cell decreased	0	0	0	0	0	0	2 (67)	0	6 (46)	0	**8 (28)**	**0**	**8 (28)**
Weight increased	0	0	0	0	3 (43)†	0	1 (33)	0	4 (31)†	0	**8 (28)†**	**0**	**8 (28)**
Constipation	1 (33)	0	0	0	3 (43)	0	1 (33)	0	1 (8)	0	**6 (21)**	**0**	**6 (21)**
Dysgeusia	0	0	1 (33)	0	2 (29)	0	2 (67)*†	0	1 (8)	0	**6 (21)†**	**0**	**6 (21)**
Flatulence	0	0	0	0	2 (29)	0	2 (67)	0	1 (8)	0	**5 (17)**	**0**	**5 (17)**
Diarrhea	0	0	1 (33)	0	2 (29)	0	0	0	1 (8)	0	**4 (14)**	**0**	**4 (14)**
Somnolence	0	0	0	0	0	0	1 (33)	0	3 (23)	0	**4 (14)**	**0**	**4 (14)**
Hypernatremia	1 (33)	0	0	0	0	0	1 (33)	0	2 (15)	0	**4 (14)**	**0**	**4 (14)**
Muscular weakness	1 (33)	0	0	0	1 (14)	0	0	0	2 (15)	0	**4 (14)**	**0**	**4 (14)**
Platelet count decreased	0	0	0	0	0	0	1 (33)	1 (33)	1 (8)	0	**2 (7)**	**1 (3)**	**3 (10)**
Dyspnea	0	0	0	0	0	0	0	1 (33)	0	0	**0**	**1 (3)**	**1 (3)**
Pulmonary edema	0	0	0	0	0	0	0	1 (33)*†	0	0	**0**	**1 (3)**	**1 (3)**

*DLTs: 1 patient phase 1 550mg/m^2 Grade 2 increased creatinine > 7 days; 1 patient phase 1 750mg/m^2 Grade 2 dysgeusia + fatigue >7 days; 1 patient 750mg/m^2 Grade 3 pulmonary edema; †TRAEs leading to dose reduction
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event. Data relate to those AEs >10% population

Baseline characteristics by tumor type and target gene fusion



Neuroblastoma (n=16)
1 x ***ALK*** **F1174L**
15 x no *ALK/ROS1/NTRK* aberrations or unknown

High-grade glioma (n=5)
1 x ***EEF1G-ROS1***
1 x ***GOPC-ROS1***
1 x ***TPR-NTRK1***
1 x ***EML1-NTRK2***
1 x ***ETV6-NTRK3***

CNS embryonal tumor (n=1)
1 x ***KANK1-NTRK2***

Melanoma (n=1)
1 x ***ETV6-NTRK3***

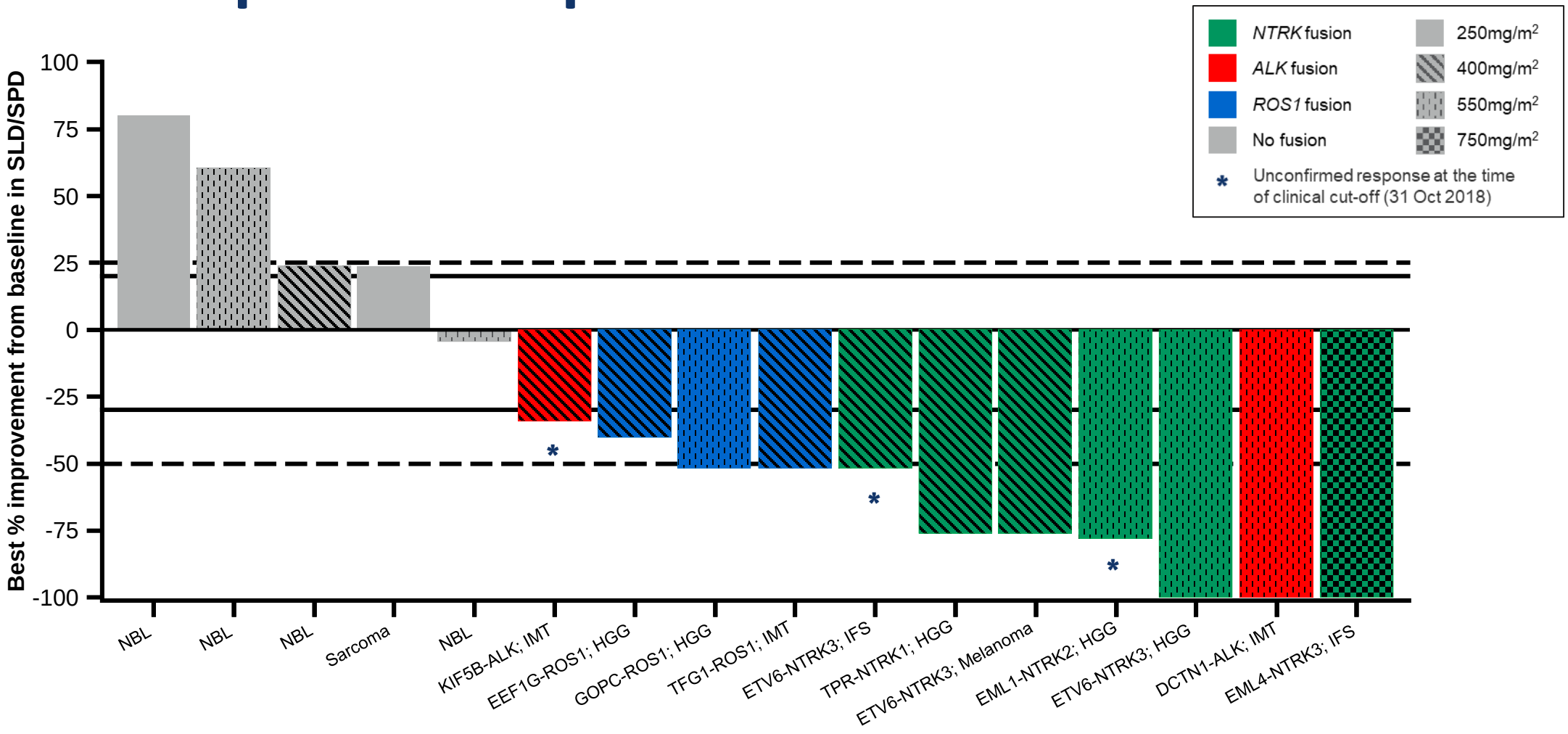
Sarcoma: IFS (n=2)
1 x ***ETV6-NTRK3***
1 x ***EML4-NTRK3***

Sarcoma: IMT (n=3)
1 x ***DCTN1-ALK***
1 x ***KIF5B-ALK***
1 x ***TFG1-ROS1***

Sarcoma: synovial (n=1)
None

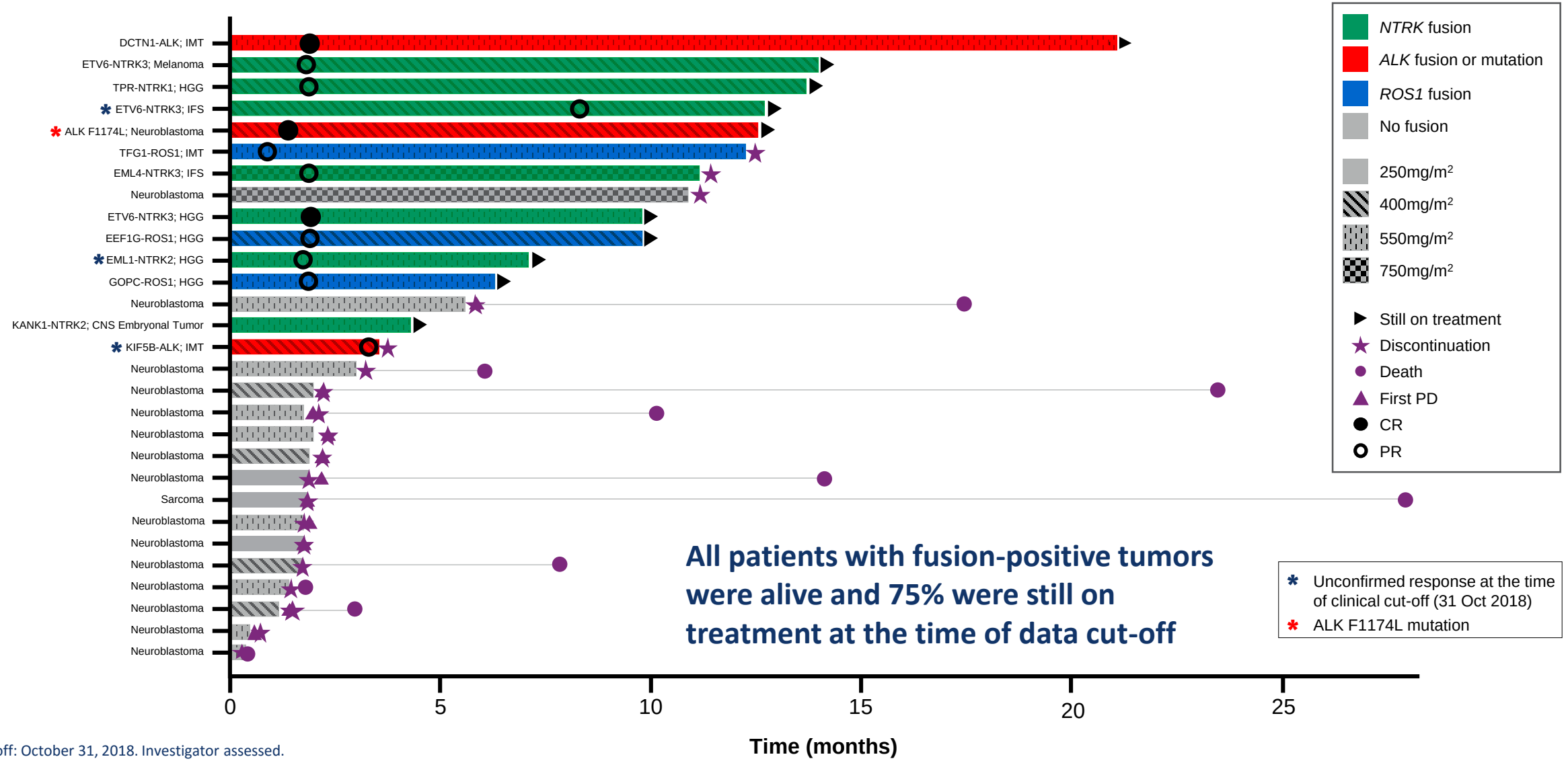
Data cut-off: October 31, 2018
IFS, infantile fibrosarcoma; IMT, inflammatory myofibroblastic tumor

Entrectinib in pediatric solid tumors: individual patient responses



Data cut-off: October 31, 2018. Investigator assessed
Includes only patients with measureable disease at baseline and tumor assessment

Entrectinib in pediatric solid tumors: duration of response

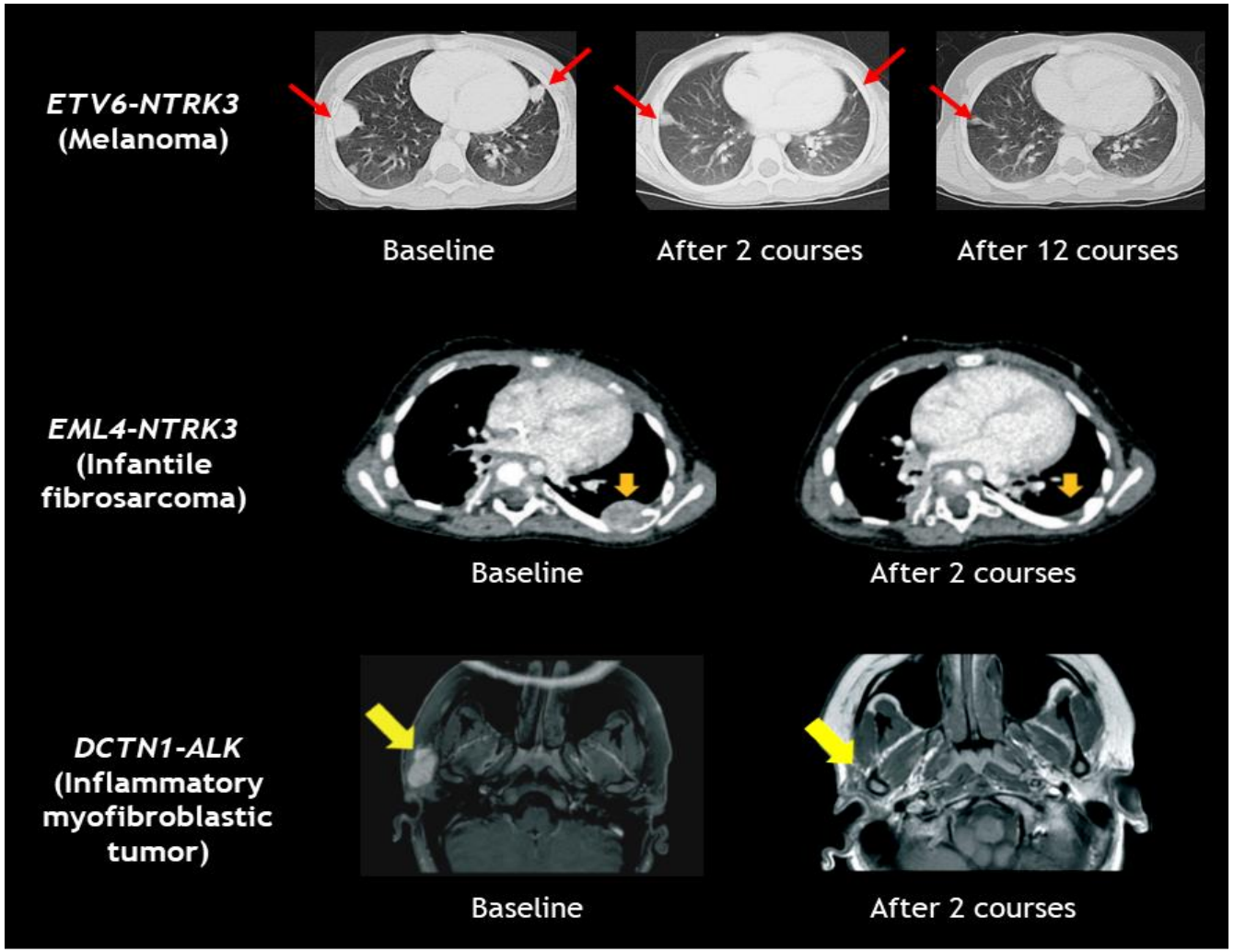


All patients with fusion-positive tumors were alive and 75% were still on treatment at the time of data cut-off

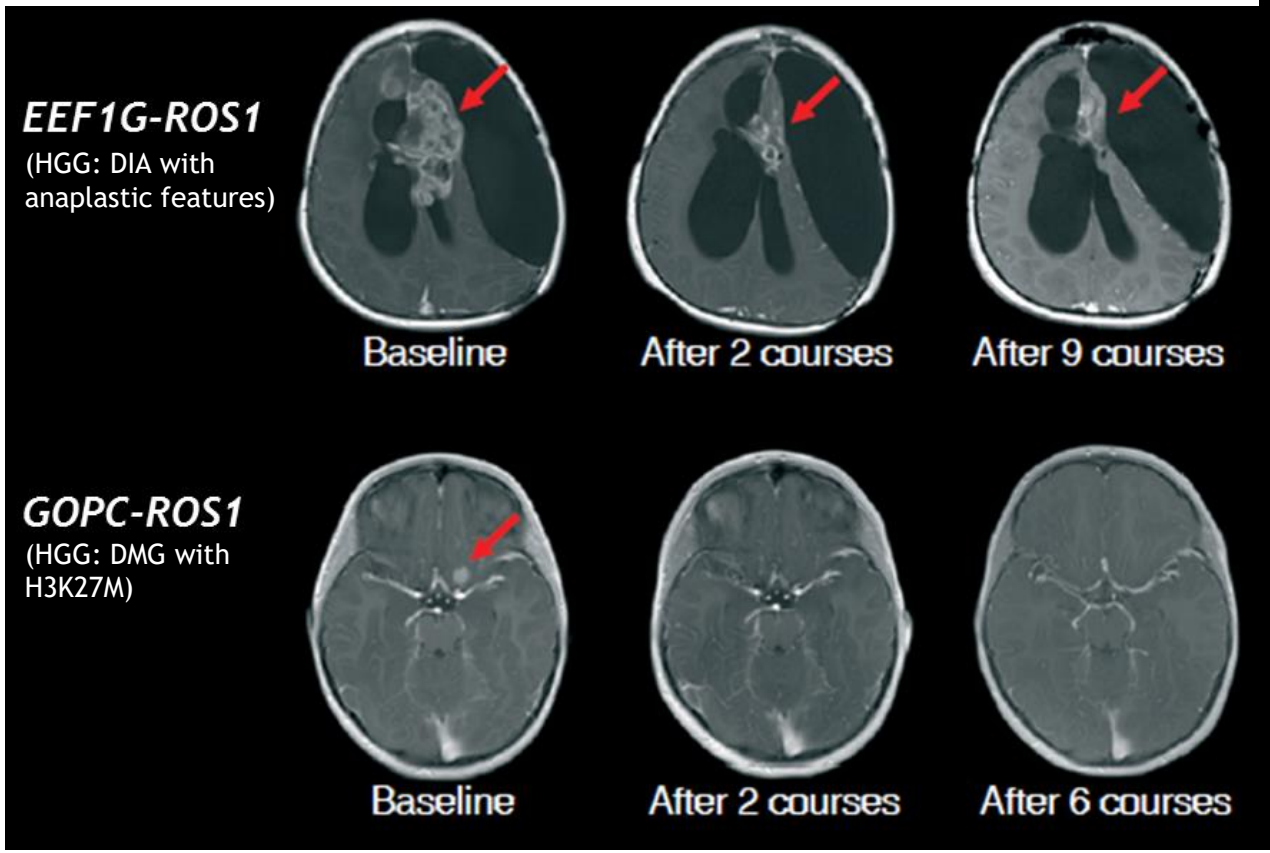
Data cut-off: October 31, 2018. Investigator assessed.
Overall duration of response: median not estimable (95% CI: NE; range 1.8 to 15.7 months). Median time to response was 57d (30–58d)
Median duration of therapy was 85 days (6–592 days) for all patients; 56 days (6–338 days) for non-responders; and 281 days (56–592 days) for responders

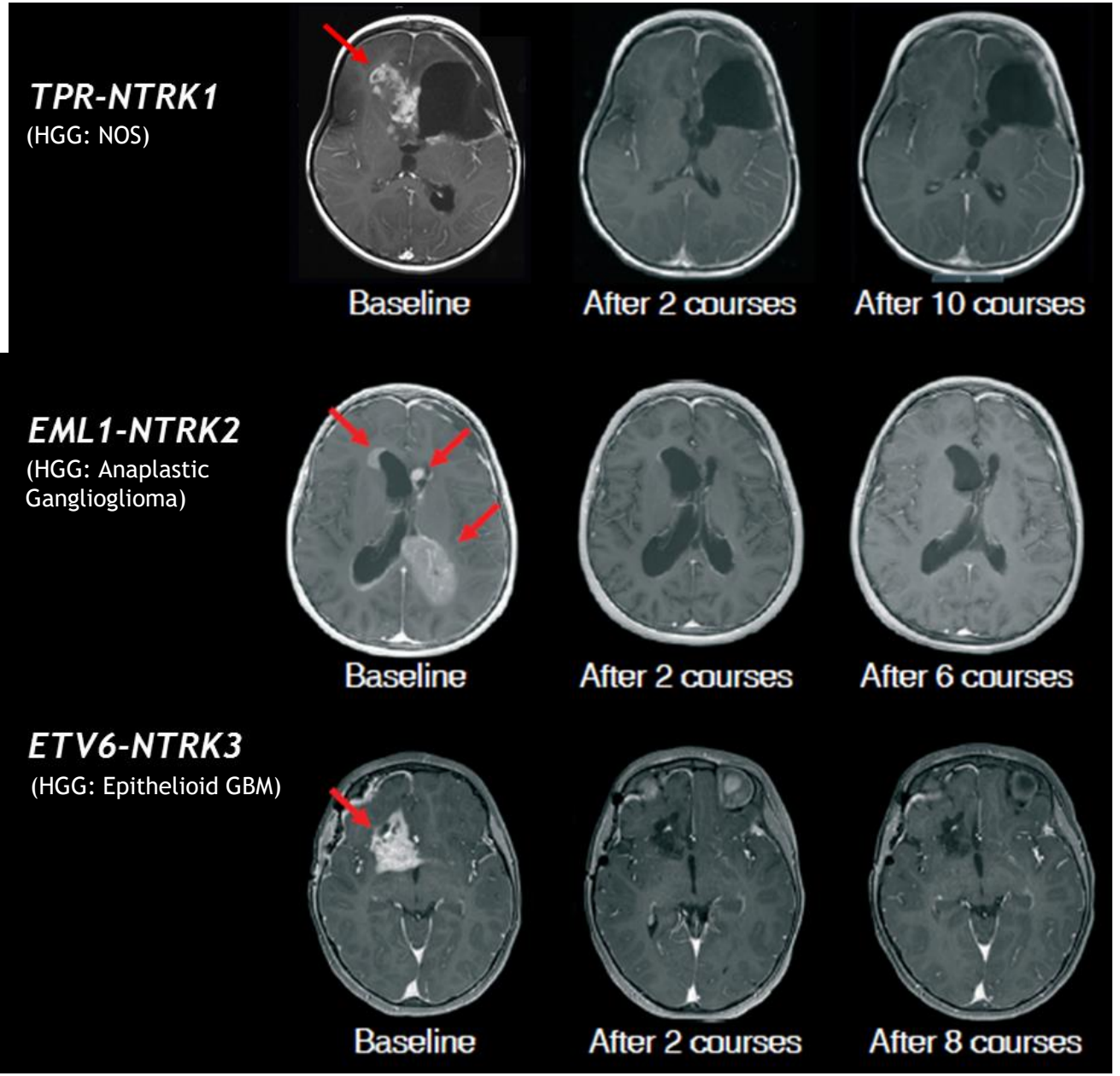
All patients (N=29)

Measureable and durable responses in extracranial solid tumors

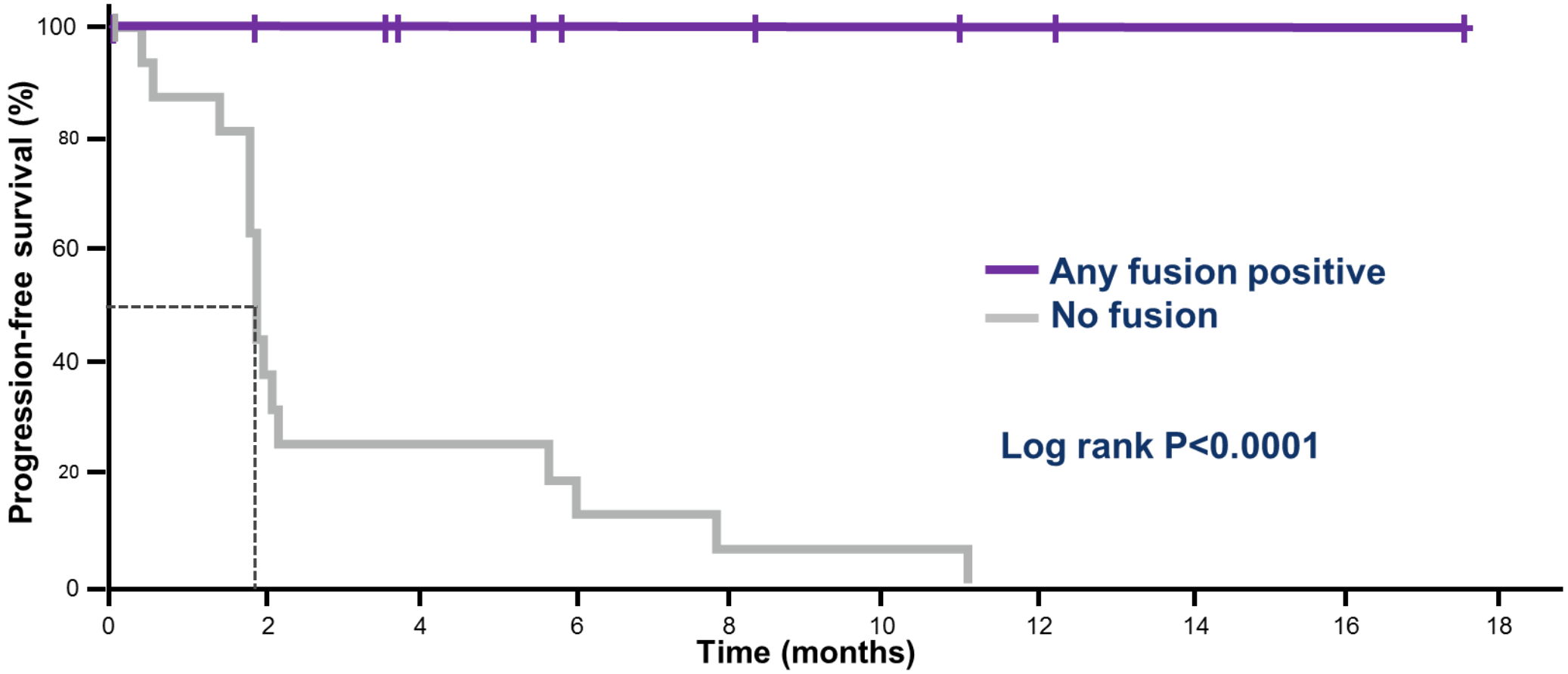


Measureable and durable responses in CNS tumors





PFS: patients with and without gene fusions



No. at Risk								
Any fusion positive	12	10	8	6	6	3	2	1	1
No fusion	17	6	4	3	1	1			

Data cut-off: October 31, 2018. Investigator assessed

A NBL patient with ALK F1174L point mutation was censored from day 1 as no further tumor assessment as per RECIST/RANO has been recorded. Patient has been assessed as per Curie criteria

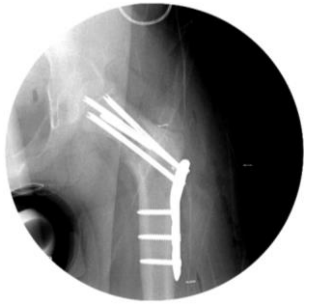
STARTRK-NG summary of safety: Dose discontinuations, reductions, and adverse events

- Discontinuations:
  - 2 patients (6.9%) discontinued drug
    - One treatment-related AE (pulmonary edema)
    - One event not related to treatment (dyspnea)

- Reductions:
  - 11 patients (39.7%) were dose reduced for treatment-related AE – see table

AE leading to dose reductions by patient	
Phase 1 dose escalation (n=5/16)	**Phase 1b (n=6/13)**
Increased blood creatinine	Weight gain
Weight gain (2 episodes)	Ataxia
Dysgeusia	Intermittent falling episodes
Pulmonary edema (3 episodes)	Weight gain
Increased blood creatinine	Headache
	Prolonged QT interval

- Notable adverse events:
  - **Elevated Creatinine**
    - 41% of all patients – all G1/G2
    - May not reflect true renal clearance since Entrectinib inhibits the MATE1 transporter which is involved in creatinine excretion.[1]
  - **Weight gain**
    - Possible **on-target effect** (hyperphagia, obesity) [1-4]
    - Most common reason for dose reduction
    - More common in patients on the drug for prolonged period (i.e. responders)
    - 2 patients have experienced **bilateral femoral neck fractures** possibly related to study drug, rapid weight gain, and steroid use.
  - **Dysgeusia/Ataxia/Falling**
    - Also possible on-target effects [1-4]
    - Sensory impairments from TRK protein inhibition?
    - Dysgeusia 21% total - G1/G2
    - Ataxia and falling < 10% total



Data cut-off: October 31, 2018. AE, adverse event; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

1. Entrectinib – Investigator Brochure v8; 2. Drilon, et al. Cancer Discov 2017
3. Drilon, et al. NEJM 2018; 4. Cocco, et al. Nat Rev Clin Oncol. 2018

Conclusions

- Entrectinib was generally well tolerated; the recommended dose of the clinical trial formulation in children is 550 mg/m^2 daily
  - dose-limiting toxicities were elevated creatinine, dysgeusia, fatigue and pulmonary edema
  - other adverse events that resulted in dose reductions included weight gain and sensory impairments (dysgeusia, ataxia) and these still need to be followed closely (on-target effects)
- Entrectinib produced striking, rapid and durable objective responses in children with refractory CNS and solid tumors harboring *NTRK1/2/3*, *ROS1* or *ALK* fusions (11/11) as well as in a patient with *ALK* mutation-positive neuroblastoma
- No responses were seen in tumors lacking aberrations in target kinases
- Entrectinib has very promising anti-tumor activity and PFS in patients with target gene fusions, especially malignant CNS tumors
  - as a result the study remains open to accrual for patients with target gene fusions

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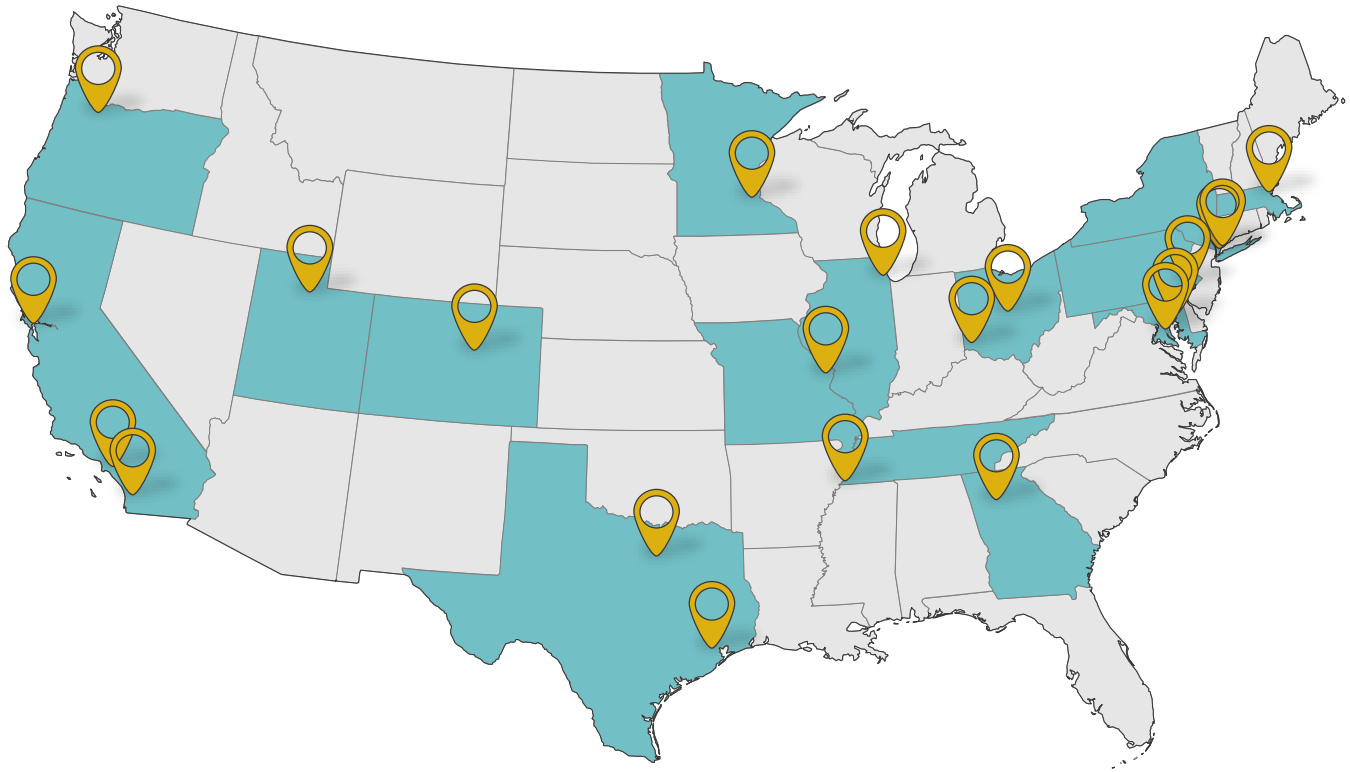
STARTRK-NG study sites



North America

Children's Hospital Colorado, Aurora
Children's Hospital of Orange County
Children's Hospital of Philadelphia
Children's National Medical Center, Washington DC
Cincinnati Children's Hospital
Columbia University Medical Center, New York
Cook Children's Medical Center, Fort Worth
Dana Farber Cancer Institute, Boston
Egleston Children's Hospital, Atlanta
Johns Hopkins University, Baltimore
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