Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

29 June 2016

Entrectinib for the Treatment of Pediatric Cancers Harboring an Activating Alteration of *NTRK1/2/3*, *ROS1*, or *ALK*

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IGNYTA®

Outline of the Presentation

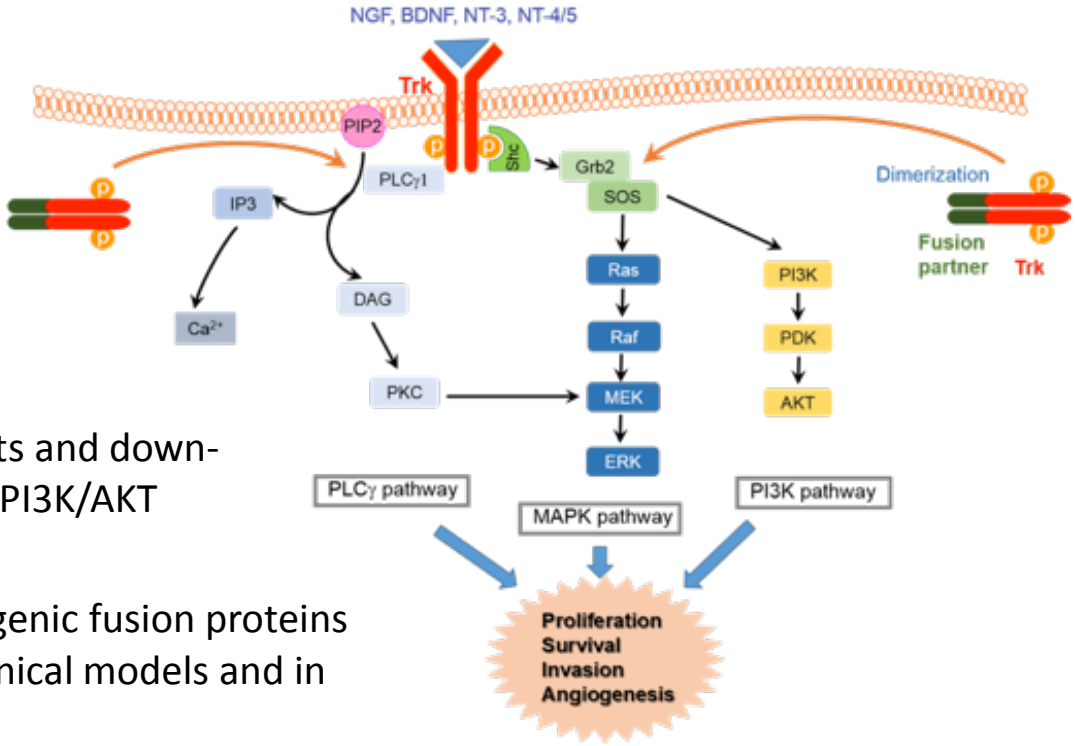
- Introduction to entrectinib (RXDX-101)
- Adult clinical development program
- Pediatric clinical development program

Mechanism of Action of Entrectinib (RXDX-101)

Highly potent, orally available TrkA/B/C, ROS1, ALK inhibitor in clinical development

Target	TrkA	TrkB	TrkC	ROS1	ALK
IC50* (nM)	1.7	0.1	0.1	0.2	1.6

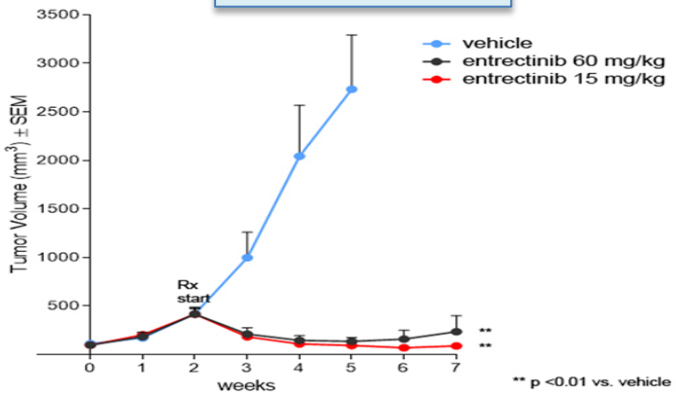
- Highly potent TrkA/B/C-, ROS1-, ALK-inhibitor with activity against most of the known Trk-resistant mutants
- Designed to cross the blood brain barrier (BBB) and address primary brain tumors as well as CNS metastases, a common complication of advanced solid tumors
- Demonstrates inhibition of its RTK targets and down-stream effectors in the PLCγ, MAPK and PI3K/AKT pathways
- Entrectinib-mediated inhibition of oncogenic fusion proteins results in rapid tumor response in preclinical models and in selected patient populations



* Biochemical kinase assay

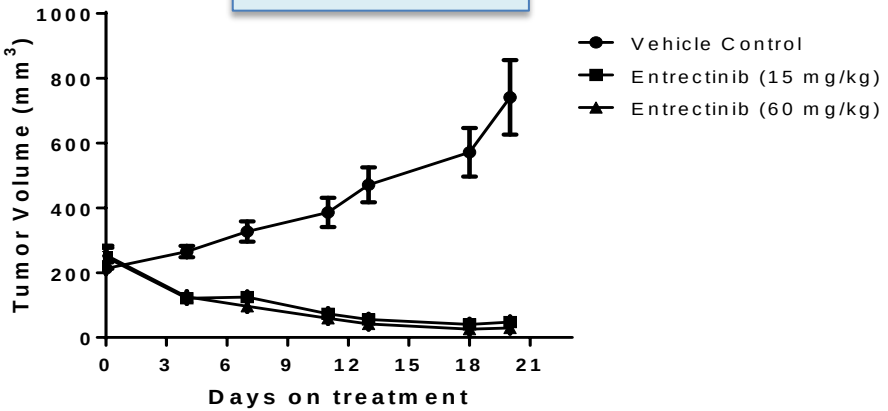
Entrectinib Demonstrates Potent *in vivo* Efficacy in Preclinical Models Driven by *NTRK*, *ROS1* or *ALK* Rearrangements

LMNA-NTRK1



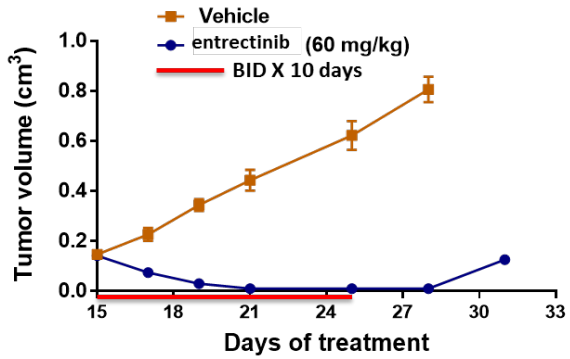
CRC PDX model est. from a pre-Rx patient in ALKA trial
Li et al. ENA 2015 abstract # A173

ETV6-NTRK3



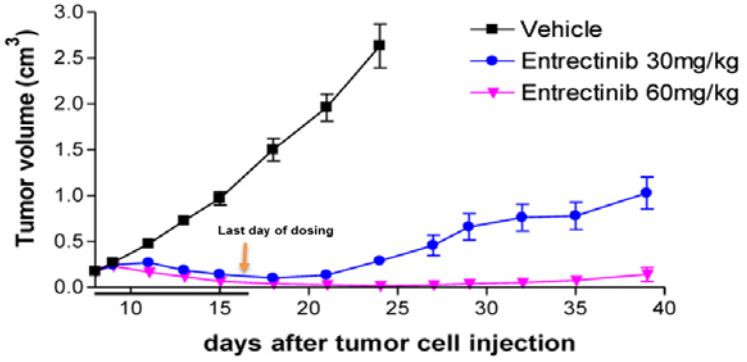
H&N PDX model est. from a met. ductal adenocarcinoma
Champions Oncology (Study 1101-001)

TEL-ROS1



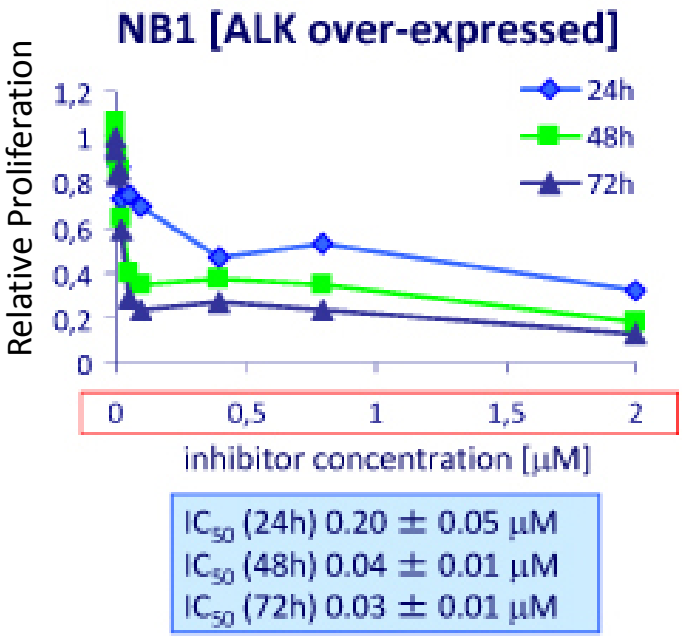
Engineered Ba/F3 allograft model driven by *TEL-ROS1*
Study N-0030001

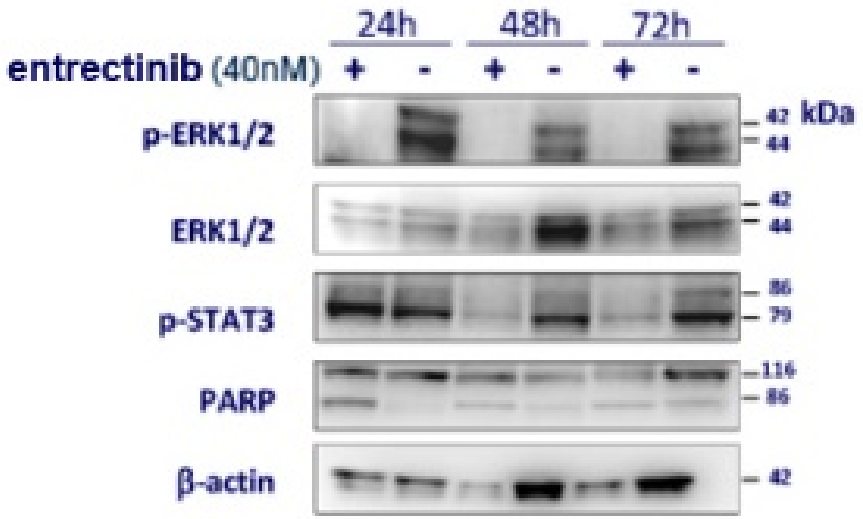
NPM-ALK



Xenograft model of ALCL cell line Karpas-299
Study N-0023595

Entrectinib Demonstrated Potent *in vitro* Efficacy in an ALK-Overexpression Driven Model of Neuroblastoma



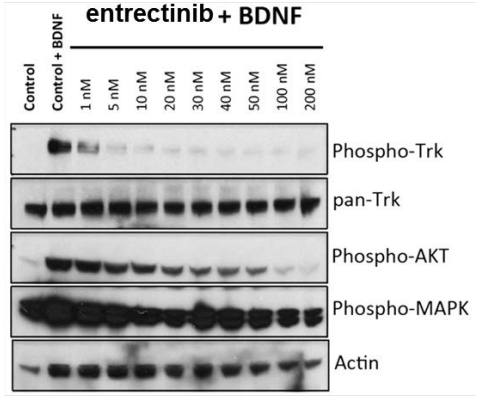


- NB1 is a neuroblastoma cell line overexpressing ALK
- The IC50 values of anti-proliferative effect of entrectinib were calculated based on MTT assay
- Entrectinib treatment (40 nM) of NB1 cells led to significant down-regulation of two main ALK kinase pathways, ERK1/2 and STAT3, and increased apoptosis (as indicated by PARP cleavage)

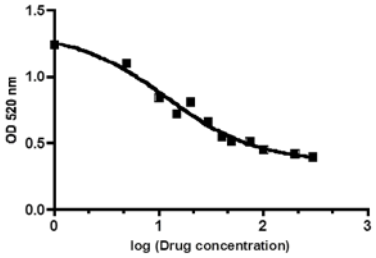
Aveic et al. Oncotarget (2016)

Entrectinib Demonstrated Potent *in vitro* and *in vivo* Efficacy in a Neuroblastoma Model Overexpressing TrkB

Results



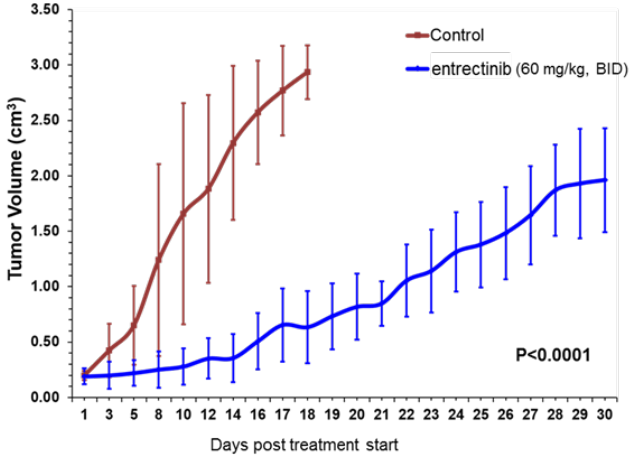
Trk phosphorylation
IC50 ~ 1 nM

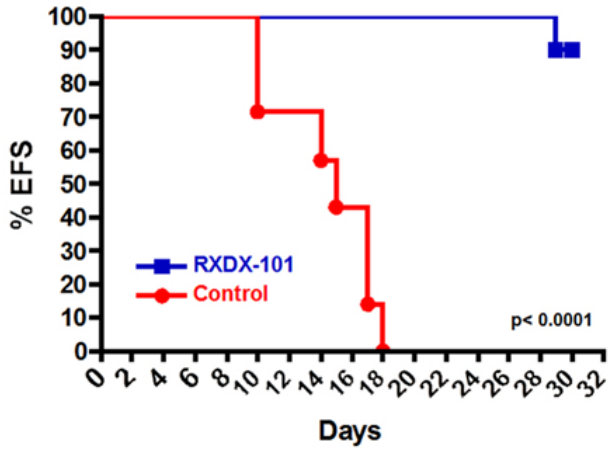


In vitro cell proliferation (72 h)
IC50 ~ 12 nM

(top) In vitro modulation of signaling pathways by entrectinib in SY5Y-TrkB neuroblastoma cell line

(bottom) 3-day *in vitro* proliferation assay





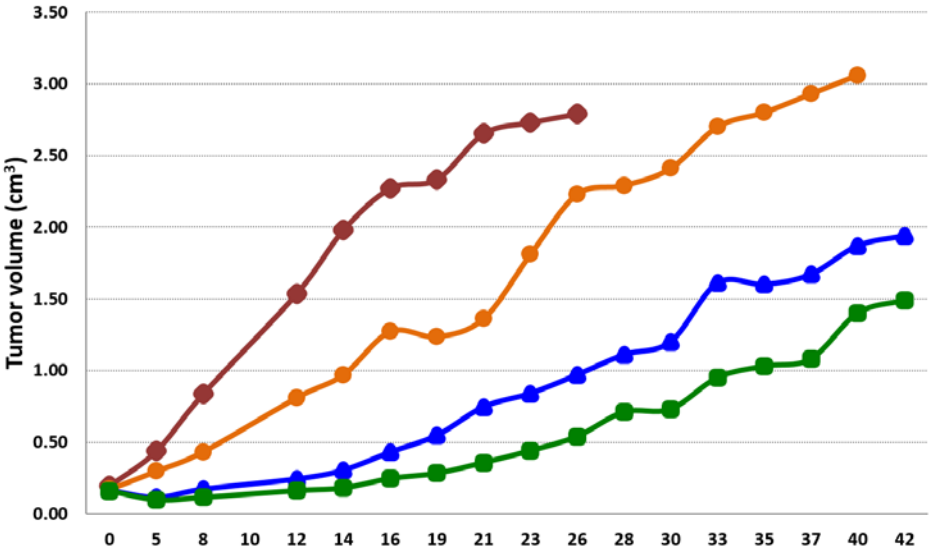
Tumor Growth Inhibition and survival benefit of entrectinib in SY5Y-TrkB xenograft model

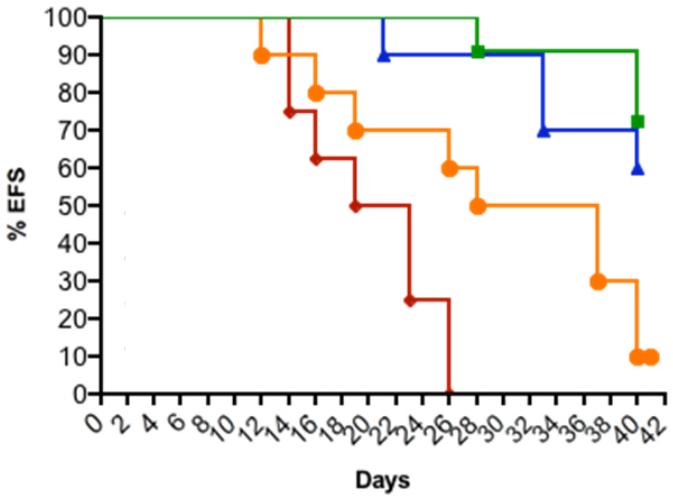
Conclusions

- Entrectinib dose-dependently inhibited TrkB phosphorylation and downstream pathways
- Entrectinib demonstrated significant *in vivo* tumor growth inhibition and improved event free survival in this model
- Similar results obtained in three other TrkB-expression driven neuroblastoma models (NLF-TrkB, NB69, NB1643)
- Entrectinib was well tolerated throughout the study

Iyer et al. Cancer Letters (2016)

Enhanced Anti-Tumor Efficacy by Combination of Entrectinib with Chemotherapy in TrkB-overexpressing Neuroblastoma Model





Control

RXDX-101 (PO, 60 mg/kg, BID, 7X/week)

Irinotecan/Temozolomide (PO, QD, 5x/week)

RXDX-101 (PO, 60 mg/kg, BID, 7X/week) + Irinotecan/Temozolomide (PO, QD, 5x/week) throughout the study

p<0.0001: combination vs. control
P<0.005: combination vs. TMZ/Irinotecan

- SY5Y-TrkB xenograft model
- When combined with Irinotecan/Temozolomide regimen, entrectinib demonstrated statistically significant improvement in tumor growth inhibition and event free survival
- Entrectinib in combination with chemotherapeutic agents was well tolerated

Irinotecan: 0.63 mg/kg/d, PO
Temozolomide: 7.5 mg/kg/d, PO

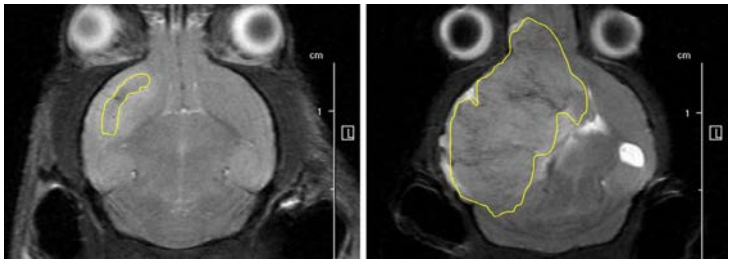
Iyer et al. Cancer Letters (2016)

Entrectinib Penetrates the CNS in Preclinical Models and Achieves Tumor Growth Inhibition

- Entrectinib designed to cross the blood-brain barrier to address CNS disease, a frequent complication of advanced solid tumors

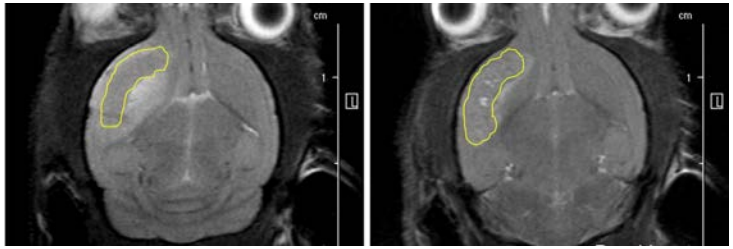
BBB penetration in three species (brain/blood ratio):
- Mouse: 0.4
- Rat: 0.6 – 1.0
- Dog: 1.4 – 2.2

- Demonstrated activity in preclinical model system of CNS tumor
  - NCI-H2228 (ALK-driven NSCLC) cells were injected intracranially;
  - Mice were treated orally with entrectinib at 120 mg/kg BID for 10 days

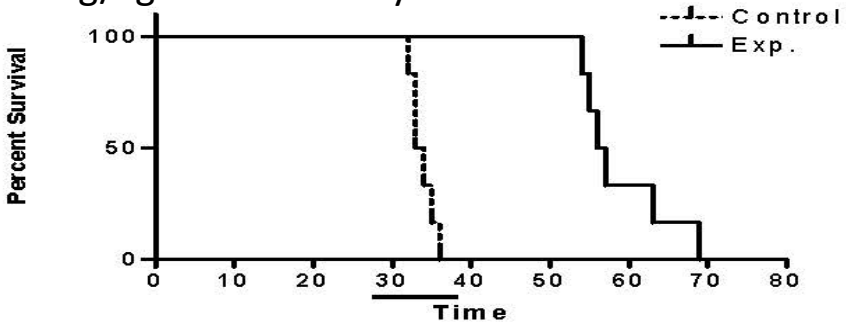


Pre-Treatment After 10 D of treatment

Vehicle



Entrectinib
120 mg/kg PO BID



	Median Survival
Control	33.5 days
Entrectinib	56.5 days
P-value:	$<5x10e^{-4}$

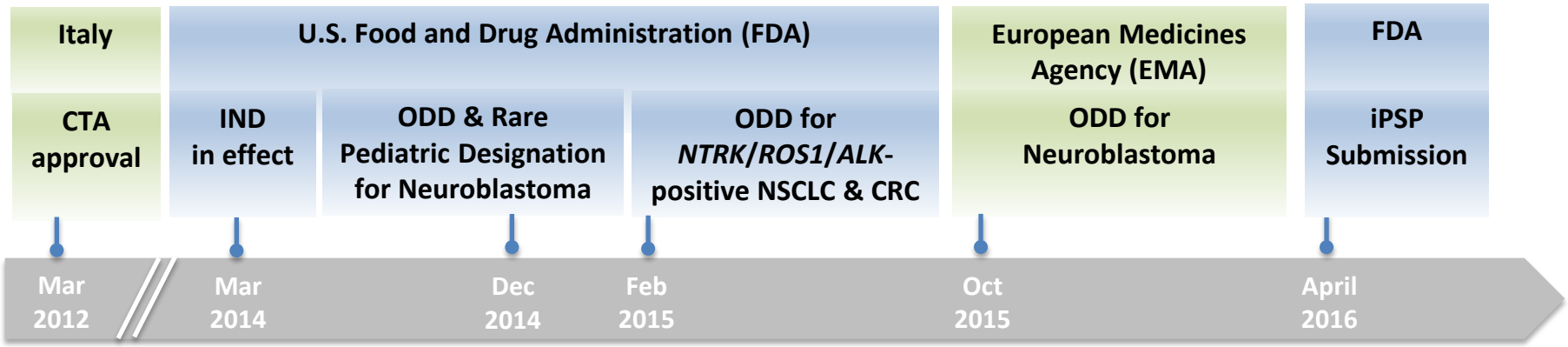
Study N-0026070

Summary of Entrectinib Nonclinical ADME & Safety Profile

- Highly plasma protein bound and partitioned to red blood cells
- Elimination is primarily through hepatic clearance
- Brain penetration detected following either single or multiple dosing in all species tested
- CNS-related effects in rats included incoordination and decreased activity. Dogs exhibited incoordination, tremors, and hypoactivity; these were reversible. No histopathological findings in the brain of either species or dorsal root ganglia in dogs
- All adverse effects observed in humans were identified in nonclinical species; no human-specific adverse effect has been observed
- Standard clinical monitoring (clinical sign, ECG and laboratory evaluations) for the identified effects is considered adequate for the adult Phase 2 clinical trial
- Preclinical safety profile supports RP2D dosing in adults

Entrectinib Milestones

Regulatory and Clinical Development Overview



Adult Phase 1 Study ALKA-372-001

Adult Phase 1 Study STARTRK-1

Adult Global Phase 2 Study STARTRK-2

Pediatric Phase 1/1b Study RXDX-101-03 (STARTRK-NG)

Adult RP2D determination

ODD=Orphan Drug Designation

Adult Phase 1 Studies

Updated data as of March 7, 2016

ALKA-372-001

- Dosing: intermittent and continuous
- TrkA/ROS1/ALK alterations by IHC/FISH
- Italy
- **54 patients**

STARTRK-1

- Dosing: continuous
- *NTRK1/2/3*, *ROS1* or *ALK* alterations by NGS
- US, EU, Asia
- **65 patients**

Total clinical experience: **119 patients**

45 patients treated at RP2D*: 600 mg PO once daily

"Phase 2-eligible population": **25 patients**

- *NTRK1/2/3*-, *ROS1*-, or *ALK*-rearranged solid tumor
- Treatment-naïve to Trk/ROS1/ALK inhibitors, as applicable
- Treated at or above RP2D*

Response Evaluation

- RECIST v1.1, locally assessed and confirmed: **24 patients**
- Volumetric assessment: **1 patient with primary brain tumor****

*RP2D = Recommended Phase 2 Dose

** RECIST criteria not validated in primary brain tumors (FDA-AACR Brain Tumor Endpoints Workshop 2006)

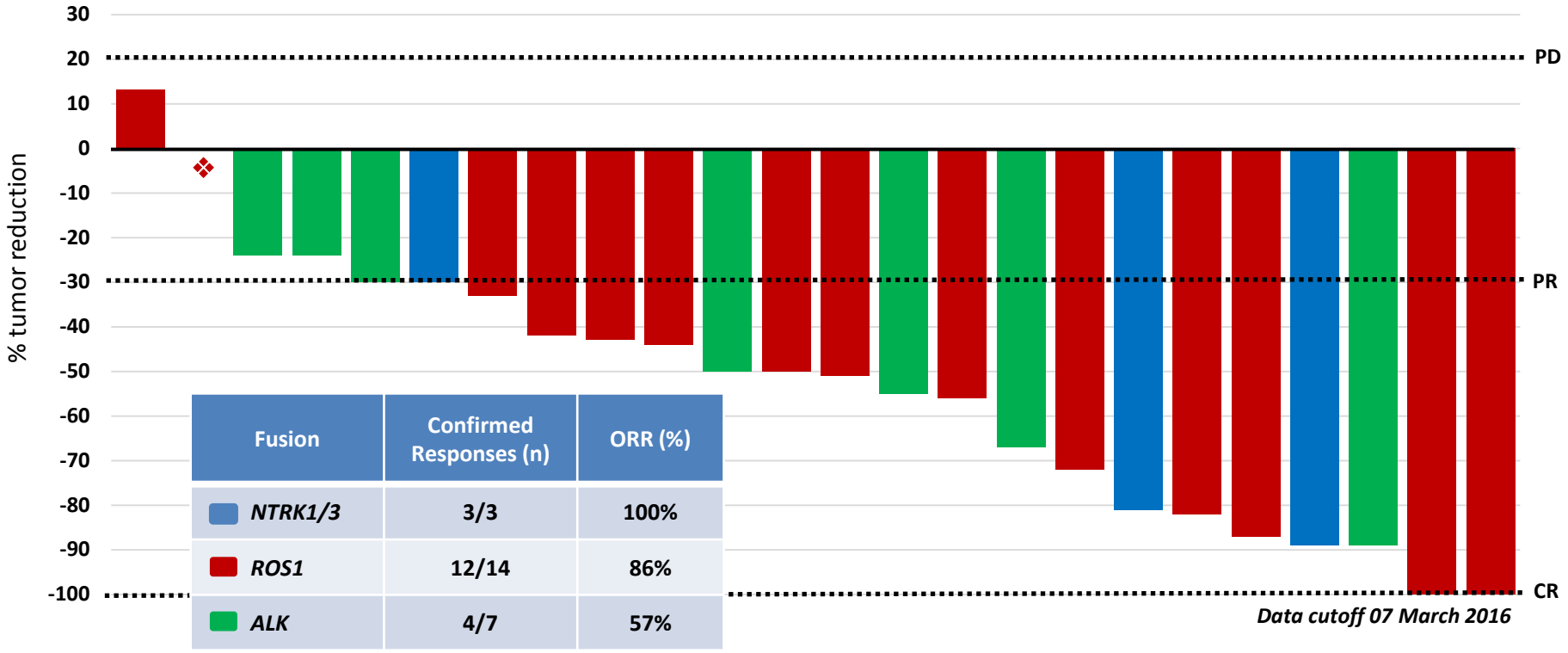
Most Common Adverse Events (n=119)

(>15% incidence all causality, as per NCI CTCAE v4.0; data cutoff 07Mar16)

- ***All dose levels tested, including > RP2D; all adverse events reversible with dose modifications***
- ***No evidence of cumulative toxicity, hepatic/renal toxicity, or QTc prolongation***
- ***Many AEs attributable to on-target Trk inhibition***

	All Causality		Treatment-Related	
Adverse Event Term, n (%)	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Fatigue/Asthenia	72 (61)	6 (5)	52 (44)	5 (4)
Dysgeusia	51 (43)		49 (41)	
Nausea	44 (37)		29 (24)	
Constipation	35 (29)		14 (12)	
Paresthesia	35 (29)		33 (28)	
Vomiting	30 (25)	1 (1)	18 (15)	
Diarrhea	29 (24)	2 (2)	23 (19)	1 (1)
Myalgia	28 (23)		26 (22)	
Dyspnea	27 (23)	6 (5)		
Dizziness	23 (19)		19 (16)	
Pyrexia	23 (19)	2 (2)		
Anemia	22 (19)	9 (8)	8 (7)	4 (3)
Arthralgia	21 (18)	1 (1)	18 (15)	1 (1)
Peripheral Edema	20 (17)		8 (7)	
Hypotension	19 (16)		7 (6)	

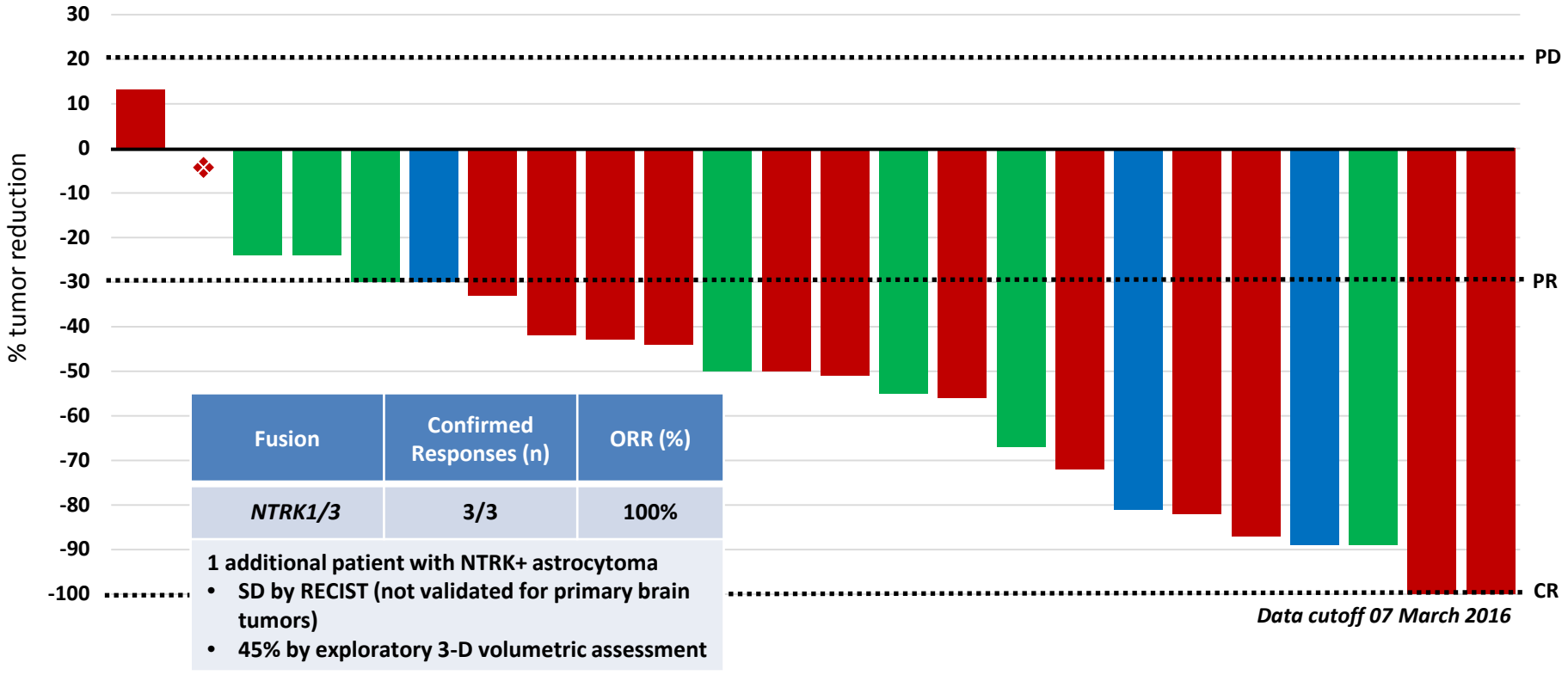
Antitumor Activity in Trk, ROS1, and ALK Inhibitor-Naïve Patients with *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements



Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%
ROS1	12/14	86%
ALK	4/7	57%

❖ 0% change (ROS1 patient)

Antitumor Activity in Trk, ROS1, and ALK Inhibitor-Naïve Patients with *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements

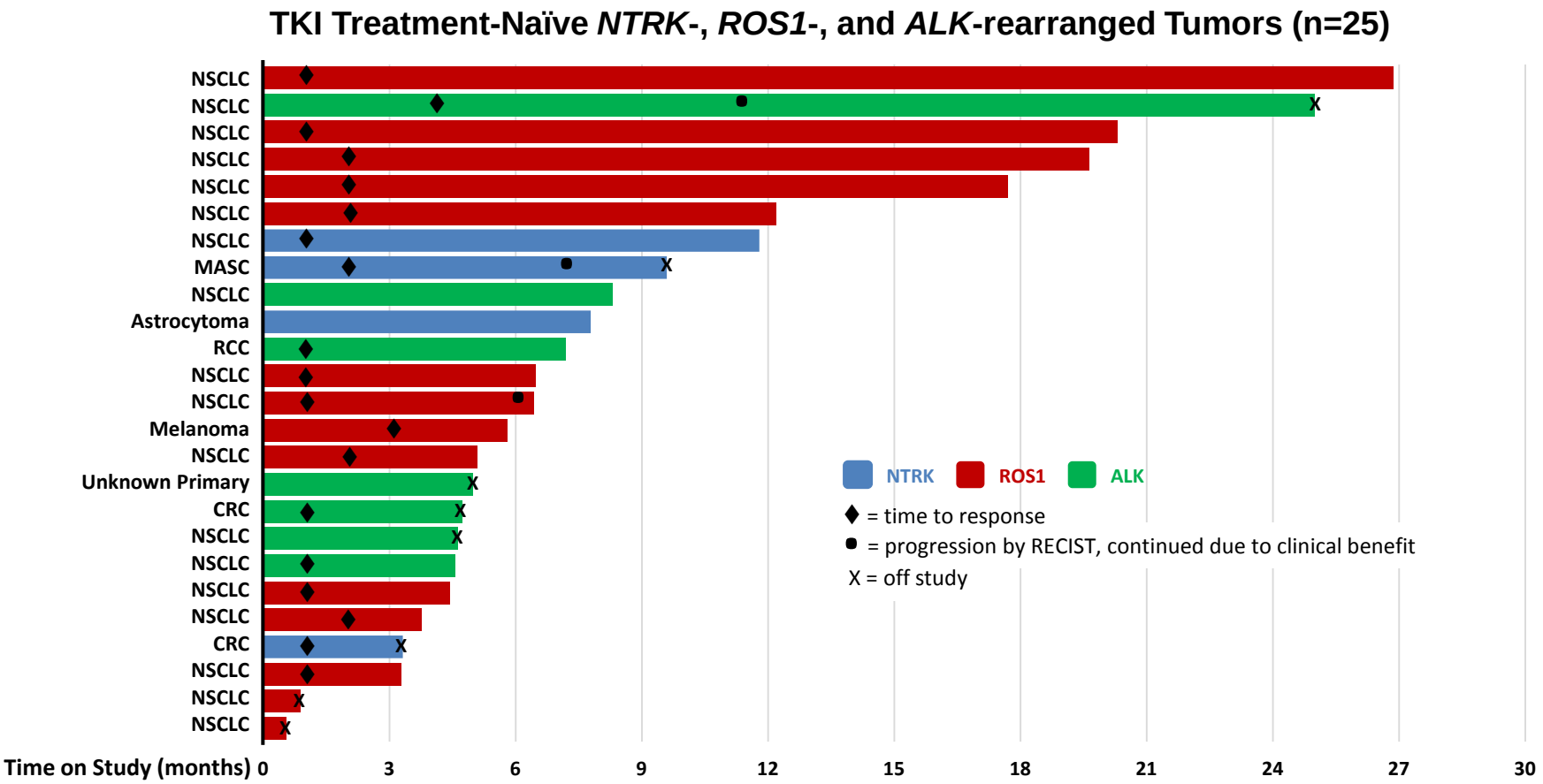


Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%

1 additional patient with NTRK+ astrocytoma
- SD by RECIST (not validated for primary brain tumors)
- 45% by exploratory 3-D volumetric assessment

❖ 0% change (ROS1 patient)

Antitumor Activity in Trk, ROS1, and ALK Inhibitor-Naïve Patients with *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements



The median duration of response has not been reached (95%CI: 6 months, NR)

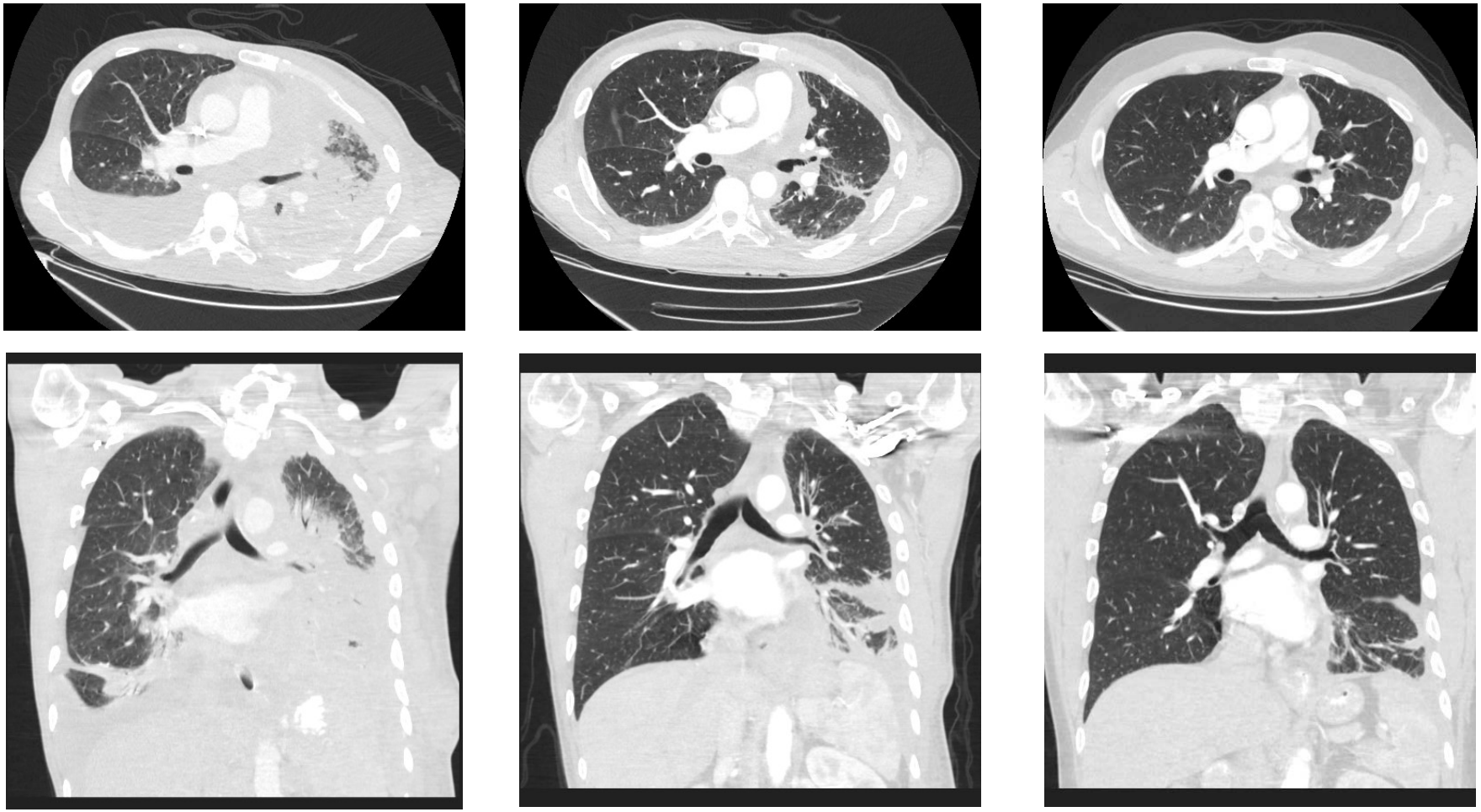
Data cutoff 07 March 2016

15

Sustained Clinical Response to Entrectinib in a 46M Patient with *NTRK1*-Rearranged NSCLC

- 4 prior therapies: carboplatin/pemetrexed, pembrolizumab, docetaxel, vinorelbine
- Poor baseline performance status (ECOG 2), on supplemental O_2, and in hospice

Baseline | **Day 26: - 47% response** | **Day 317: - 79% response**

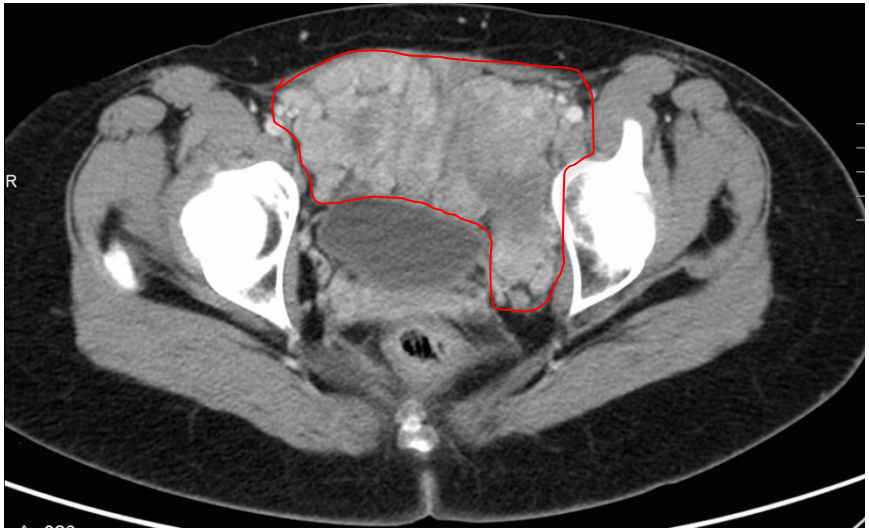


Images courtesy of A. Shaw, MD, PhD and A. Farago, MD, PhD (MGH)

Partial Response in Patient with ALK-Activated Neuroblastoma

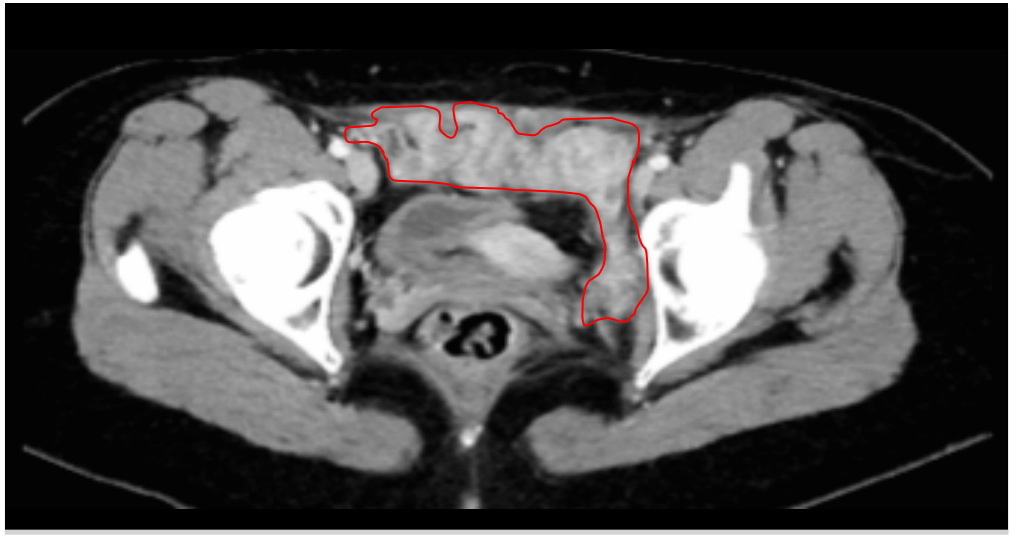
22-year old female patient with *ALK F1245V* mutation refractory to 4 prior lines of therapy, including topotecan, cyclophosphamide, adriamycin, etoposide, carboplatin, temozolomide

Pre Treatment



February 2013

Cycle 15



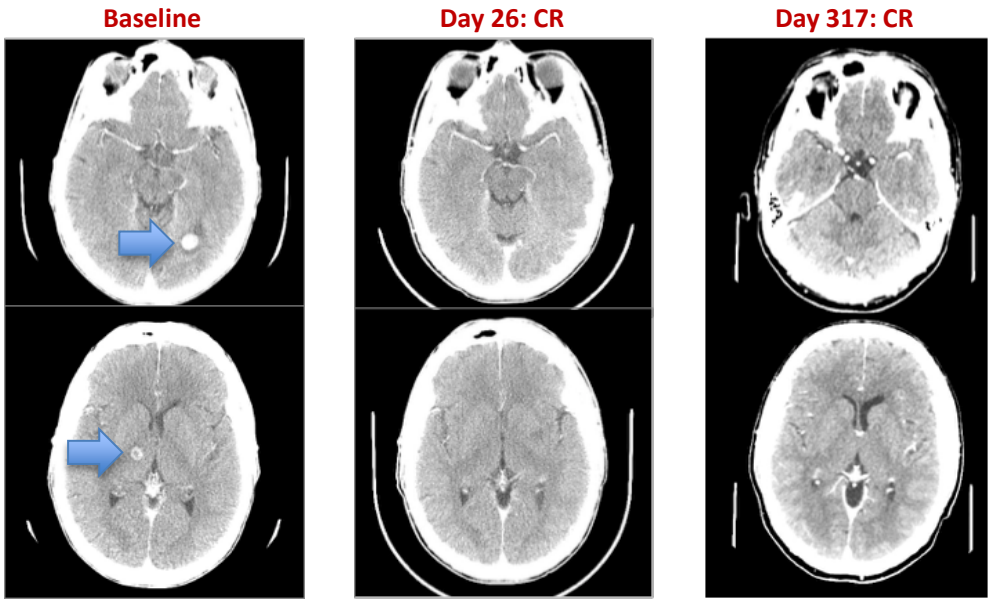
April 2014

Patient benefitted from entrectinib treatment > 3 years

Images courtesy of F. de Braud, MD (Fondazione IRCCS Istituto Nazionale dei Tumori)

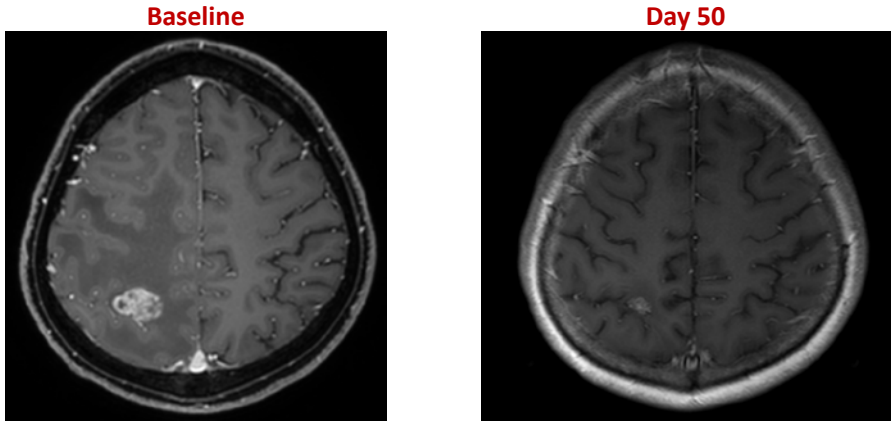
CNS Responses to Entrectinib with *NTRK1- and ROS1*-Rearranged NSCLC

- 46M *NTRK1*-rearranged NSCLC
- 4 prior therapies
- Clinically progression-free > 12 months



Images courtesy of A. Shaw, MD, PhD and A. Farago, MD, PhD (MGH)

- 53F *ROS1*-rearranged NSCLC



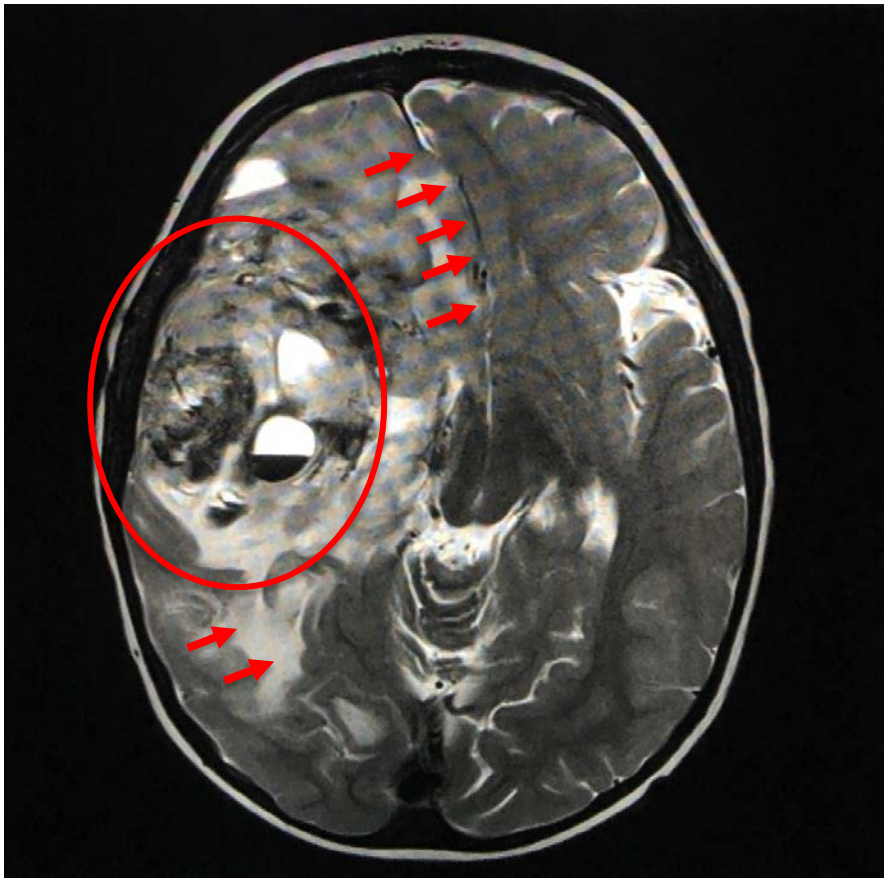
Images courtesy of MJ. Ahn, MD, Samsung Medical Center

Rapid Clinical and Radiographic Response to Entrectinib in 20 Month-Old Boy with *NTRK3*-Rearranged Infantile Fibrosarcoma

- 20 month-old boy with recurrent, metastatic infantile fibrosarcoma harboring *ETV6-NTRK3* gene rearrangement (first detected in Ignyta Diagnostic lab)
  - Presented at birth with left leg mass, requiring through-the-knee amputation
  - At age 4 months, large metastases to left lung identified → 24-weeks of chemotherapy
  - At age 12 months, large right frontal intracranial tumor identified → resected, followed by 5 cycles of salvage chemotherapy
  - Recurrent CNS disease with lesions in the right frontal and temporal lobes, as well as leptomeningeal involvement
  - On physical exam, was very sleepy but responsive to stimuli and had decreased tone and strength in the left arm
  - Baseline head CT showed large tumor mass in the right hemisphere, centering on the right temporal lobe (3.7 x 2.5cm) with massive tumor-related swelling, a 17 mm midline shift, and evidence of transtentorial herniation
  - Due to these radiographic and clinical findings, the patient's treating physician felt that: "death is likely imminent"

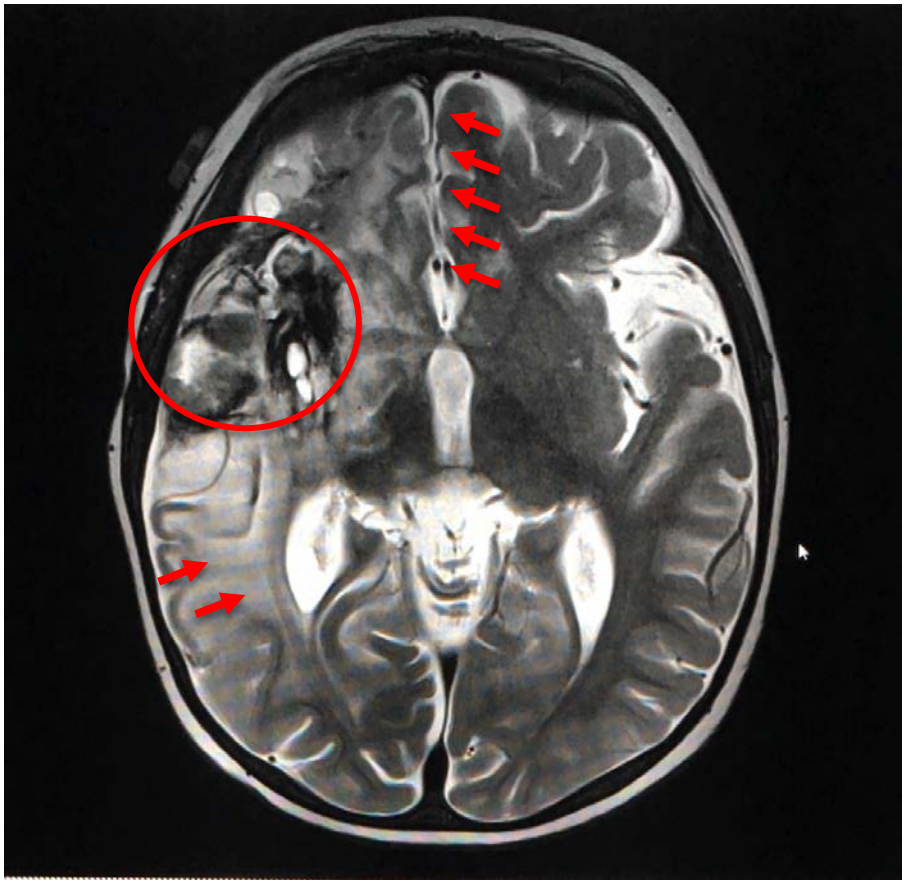
Rapid Clinical and Radiographic Response to Entrectinib in 20 Month-Old Boy with *NTRK3*-Rearranged Infantile Fibrosarcoma

Baseline



Patient not eating, progressively less active and more sleepy

Day 35



Patient eating, mobile (crawling), more alert

Images courtesy of K. Heym, MD, Cook Children's, Fort Worth, TX

Conclusions from Phase 1 Clinical Experience

- Entrectinib continues to be well tolerated in patients with relapsed or refractory metastatic cancers harboring *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations
  - 119 patients have been treated, 45 at the RP2D
  - 19 patients > 6 months; of those, 11 patients > 1 year, including 3 patients > 2 years
- Confirmed responses observed in 19/24 (79%) patients with extracranial solid tumors; in addition, evidence of tumor shrinkage observed in a patient with *NTRK* positive astrocytoma
  - As early as after 4 weeks of treatment
  - Durable for up to 27+ months
  - As many as 6 distinct histologies
- Complete and durable CNS responses have been observed

Pediatric Clinical Development

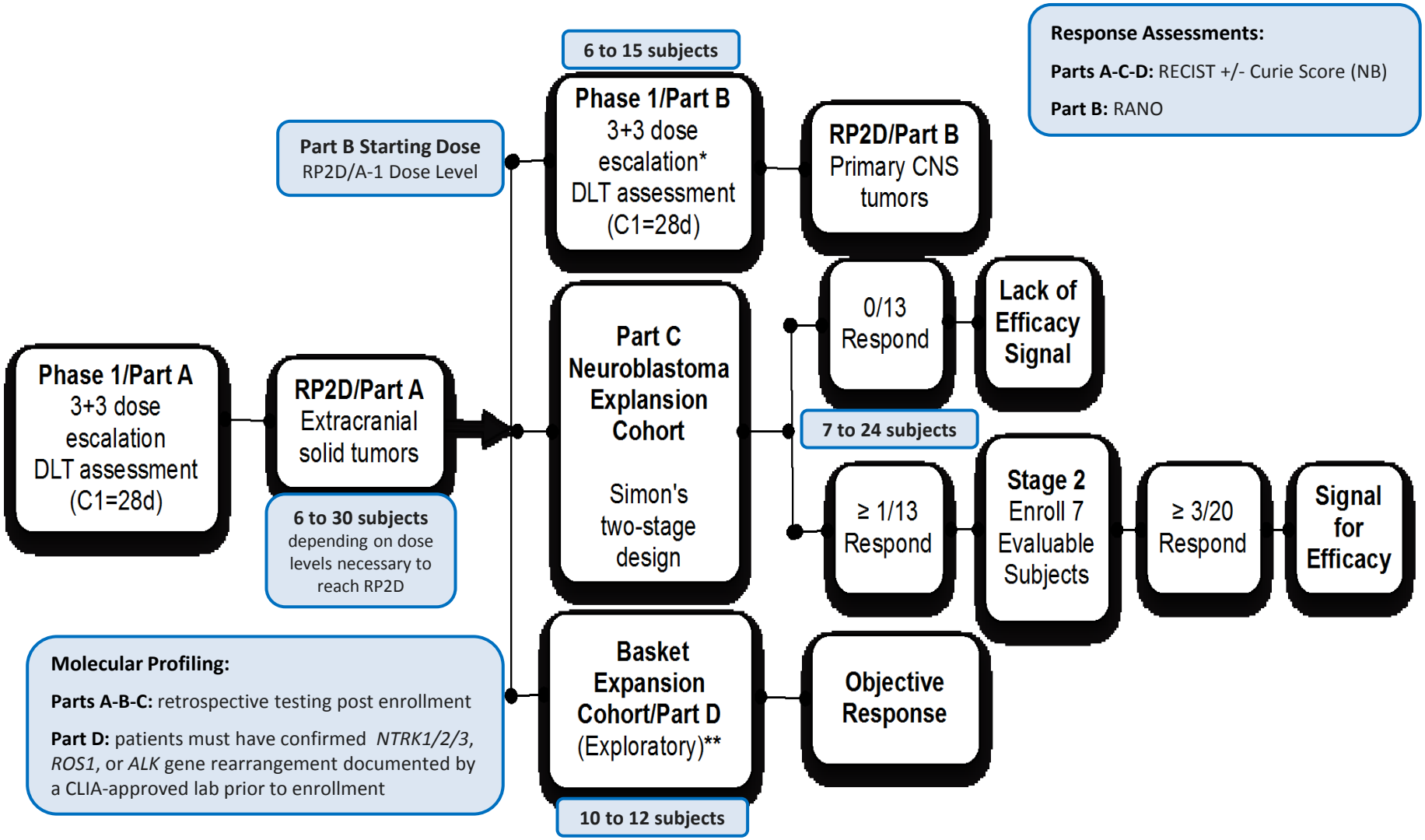
Many pediatric cancers have genomic alterations that are potentially targetable by entrectinib

Pediatric cancer	TrkA	TrkB	TrkC	ROS1	ALK	Alteration
Congenital fibrosarcoma Lipofibromatosis-like neural tumors	✓		✓	✓	✓	*TPR-NTRK1* *TPM3-NTRK1* *LMNA-NTRK1* *ETV6-NTRK3* *ROS1 OE*
Inflammatory myofibroblastic tumor				✓	✓	*TFG-ROS1* *EML4-ALK*
Ewing sarcoma	✓	✓	✓			*EWS-FLI1* fusion leads to Trk overexpression
Glial tumors	✓	✓	✓		✓	*TPM3-NTRK1* *ETV6-NTRK1* *NFASC-NTRK1* *BCAN-NTRK1* *VCL-NTRK2* *QK1-NTRK2* *AGBL4-NTRK2* *BTBD1-NTRK3* *PPP1CB-ALK*
Neuroblastoma	✓	✓	✓		✓	Autocrine activation of the TrkB/BDNF pathways in 50-60% high risk NB *BEND5-ALK* *ALK* activating mutations: R1275Q, F1174L, G1128A, I1171N, R1192P, F1245C
Medulloblastoma	✓	✓	✓			TrkA/B/C overexpression
Mesoblastic nephroma			✓			*ETV6-NTRK3*
Papillary thyroid cancer	✓		✓			*TPR-NTRK1* *ETV6-NTRK3*
Retinoblastoma	✓	✓	✓			TrkA/B/C overexpression
Secretory breast carcinoma			✓			*ETV6-NTRK3*
Wilms tumor (anaplastic)	✓	✓	✓			Autocrine/paracrine activation of neurotophin receptors (TrkA/B/C)

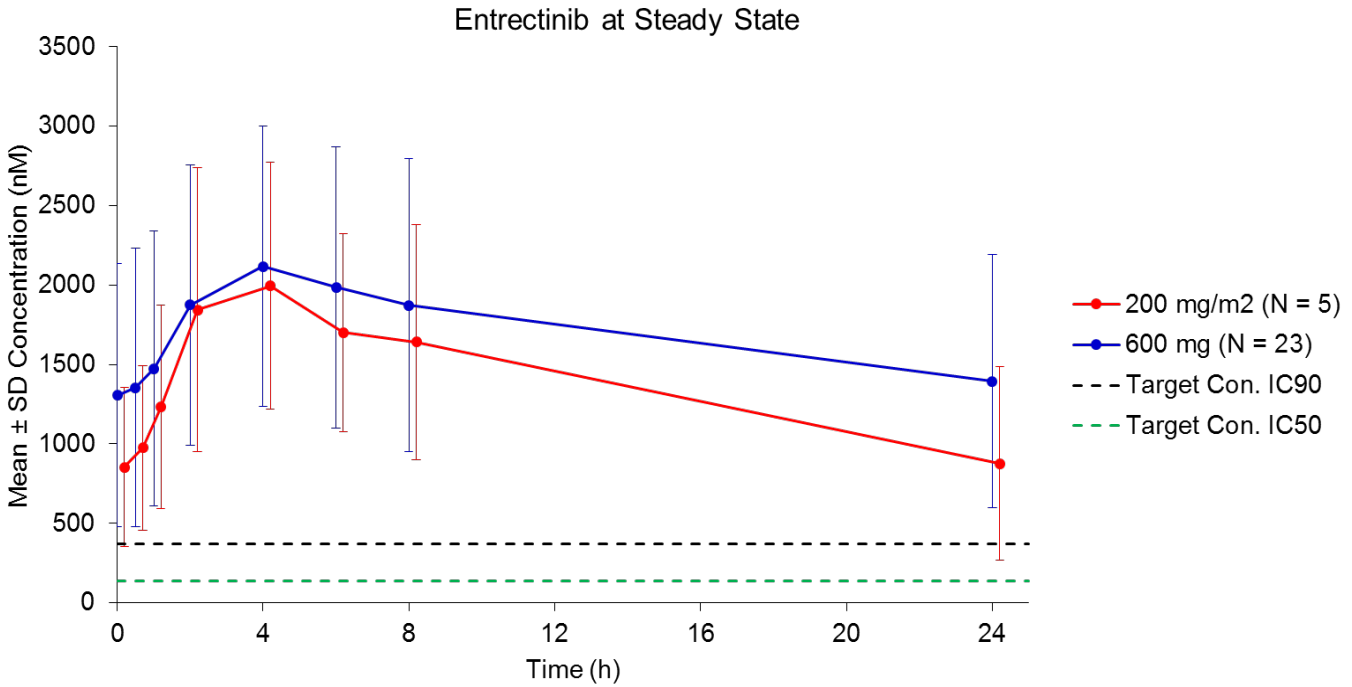
Pediatric Clinical Development

- Ignyta initiated in December 2015 STARTRK-Next Generation (STARTRK-NG), a Phase 1/1b study
  - Relapsed or refractory neuroblastoma
  - Extracranial solid tumors (non-neuroblastoma) with or without *NTRK1/2/3*, *ROS1* or *ALK* gene rearrangements
  - Primary CNS tumors
- Starting pediatric dose selected to achieve potential therapeutic exposure
- Clinical formulations for pediatric use
  - Capsules (100 mg and 200 mg strength)
  - Granules (meant to be sprinkled over soft food)
  - [Liquid formulations evaluated but not feasible]

Study RXDX-101-03 (STARTRK-NG)



Pediatric Starting Dose Selected Based Upon Adult Therapeutic Exposure



- Plasma half-life in adult patients is ~ 20-24 hours → compatible with QD dosing
- At adult RP2D (600 mg QD) and at 200 mg/m^2, the plasma protein binding corrected mean C_{trough} is continuously above the IC_{90}, which is correlated with complete tumor growth inhibition in Trk-driven xenograft models
- Based on adult data and PBPK modeling, pediatric starting dose of 250 mg/m^2 was selected to achieve therapeutic exposures

STARTRK-NG: Dose Escalation

Part A: Dose escalation based on nomogram and BSA

Dose Level	
1A	250 mg/m^2 (starting dose) *(60% of Adult RP2D)*
2A	400 mg/m^2 once daily *(BSA-based Adult RP2D)*
3A	550 mg/m^2 once daily
4A	750 mg/m^2 once daily

Part B: Starting dose Part A -1 dose level

Dose Level	
1B	RP2D/Part A-1 (starting dose)
2B	RP2D/Part A

Parts C and D: RP2D determined in Part A

STARTRK-NG: Study Objectives

- Primary Objectives
  - Determine the MTD or recommended phase 2 dose (RP2D) of entrectinib in pediatric subjects (children and adolescents) with relapsed or refractory extracranial solid tumors
  - Determine the MTD or RP2D of entrectinib in pediatric subjects with relapsed or refractory primary CNS tumors
- Secondary Objectives
  - Safety and PK profile
  - Objective Response Rate (ORR)
  - Progression-free survival (PFS)

STARTRK-NG: Key Eligibility Criteria

- Histologic/molecular diagnosis of malignancy at diagnosis or time of relapse
- Archival tumor tissue from diagnosis or preferably, at relapse
- **Parts A, B and C:** Measurable or evaluable disease
- **Part D:** Measurable disease **and** documented gene rearrangement, determined by a CLIA-approved lab for *NTRK1*/2/3, *ROS1*, or *ALK* gene rearrangements
- Performance Status: Lansky or Karnofsky score ≥ 60%
- Body surface area (BSA) ≥ 0.45 m^2

STARTRK-NG: Safety Monitoring

- To date, based on the ongoing Phase 1 adult studies (> 120 patients), there is no evidence of cumulative toxicity, hepatic/renal toxicity, or QTc prolongation
- Many AEs are attributable to on-target Trk inhibition, e.g., central and peripheral neurologic effects, increased appetite and weight gain
- During the dose escalation (Parts A and B), patients will be monitored for dose-limiting toxicities
- In general, for AEs Grade ≥ 3, entrectinib will be interrupted and toxicities must resolve to Grade ≤ 2 or baseline before resuming treatment (with dose reduction, as appropriate)
- Specific to this pediatric study, for **somnolence or cognitive disturbance**, toxicity must resolve to Grade **≤ 1** or baseline before resuming treatment (with dose reduction, as appropriate)

STARTRK-NG: Pharmacokinetics/Pharmacodynamics

PHARMACOKINETICS

- Parts A and B
  - Cycle 1 Day 1: pre-dose, 1, 2, 4, 6, and 24 hours post-dose
  - Cycle 1 Days 8, 15, 22: pre-dose
  - Cycle 2 Day 1: pre-dose, 1, 2, 4, 6, and 24 hours post-dose
- Parts C and D
  - Cycle 1 Day 1: pre-dose and 4 hours post-dose
  - Cycle 1 Day 15: pre-dose
  - Cycle 1 Day 22: pre-dose

PHARMACODYNAMICS

- All patients
  - Archival tissue will be collected at baseline for molecular testing at Ignyta's CLIA laboratory
- Phase 1b patients
  - Additional tissue at the time of progression will be collected (if clinically feasible) to identify molecular alterations that may predict activity of entrectinib and/or to gain insights into potential mechanisms of resistance

Biomarker Approach for Mechanistic Understanding and Potential Patient Selection

- Ignyta has a fully integrated capability to screen patients in its in-house CAP/CLIA diagnostic lab, which enables comprehensive genomic biomarker analysis
- RNA-based multiplex NGS assay (Trailblaze Pharos™) performed to assess gene rearrangements, overexpression, insertions, deletions and splice variants of NTRK1, NTRK2, NTRK3, ROS1 and ALK

- Trailblaze Pharos will be deployed in STARTRK-NG Phase 1 to help guide patient selection strategy in Phase 1b, and/or in future pediatric studies
  - Retrospective tumor genomic profiling to be conducted in all patients to assess if activating alterations (e.g., TrkB overexpression) predict response
  - Condition for enrollment into cohort of patient populations with tumors harboring target gene rearrangements (Part D)
    - Can be assessed either by Trailblaze Pharos or by local methods (e.g., Foundation Medicine)

Representative US Diagnostic Testing for NTRK and ROS1

All Major Molecular Reference Labs and IVD Manufacturers Cover NTRK and ROS1 on Their NGS Panels

Reference Labs

FOUNDATION MEDICINE®

Knight Diagnostic Laboratories (OHSU)

CARIS LIFE SCIENCES

NeoGenomics Laboratories — Time Matters. Results Count.

PathGroup — Physician Centered. Patient Focused.

Liquid Bx Labs

PGD — Personal Genome Diagnostics

GUARDANT360

Cooperative Group Studies

NCI National Clinical Trials Network — a National Cancer Institute program

OEM/IVDs

illumina®

ThermoFisher SCIENTIFIC

ARCHER™

HTG Molecular

Conclusions

- Entrectinib is a potent TrkA/B/C, ROS1, and ALK inhibitor
- Compelling preliminary efficacy (including CNS antitumor activity) with manageable safety profile in adults with solid tumors harboring an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement
- Adult global Phase 2 study ongoing
- Strong scientific rationale for pediatric development
  - Many pediatric cancers have genomic alterations that are potentially targetable by entrectinib
  - Nonclinical evidence of efficacy in a neuroblastoma model overexpressing TrkB
- Pediatric Phase 1 study STARTRK-NG ongoing
- Seeking a Written Request from the FDA for STARTRK-NG