Safety and Preliminary Clinical Activity of Repotrectinib in Patients with Advanced *ROS1* Fusion-Positive Non-Small Cell Lung Cancer (TRIDENT-1 STUDY)

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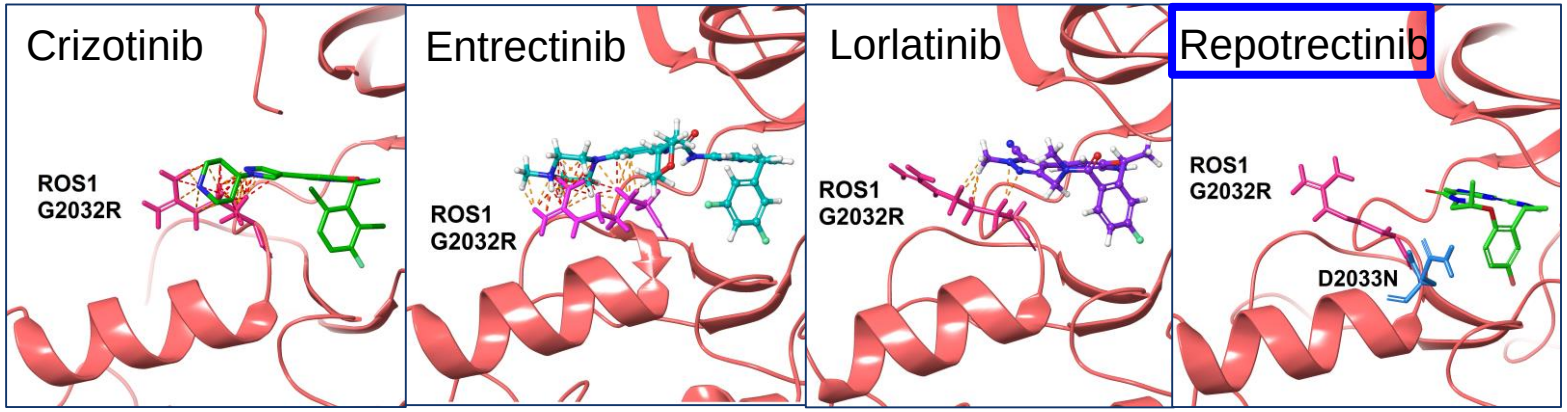
Targeting *ROS1* Fusion Positive Non-Small Cell Lung Cancer

- *ROS1* rearrangement is an oncogenic driver in 1-2% of NSCLC
- Crizotinib is the only approved targeted therapy for patients with advanced *ROS1*+ NSCLC
- G2032R is the most common *ROS1* resistance mutation after crizotinib treatment[1]
- **Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor, designed to overcome TKI resistance mutations, especially solvent front *ROS1* G2032R**[2]

Repotrectinib is a Small, Rigid Macrocycle Designed to Overcome the *ROS1* G2032R Solvent Front Mutation



CD74-ROS1 Ba/F3 Cell Proliferation IC_{50} (nM)*

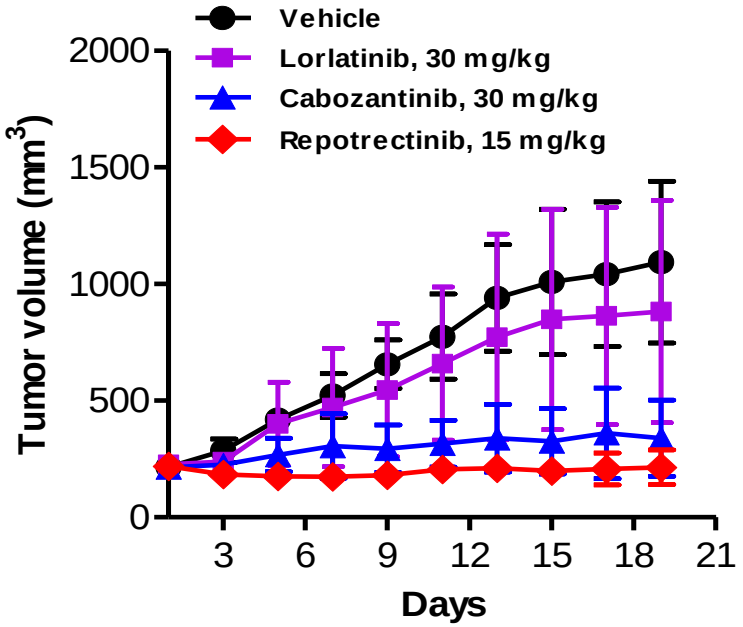
ROS1	Crizotinib	Ceritinib	Cabozantinib	Entrectinib	Lorlatinib	Repotrectinib
WT	14.6	42.8	0.5	10.5	0.2	<0.2
G2032R	**266.2**	**1391**	**11.3**	**1813**	**160.7**	**3.3**

*Data based on evaluation of comparable proxy chemical reagents purchased from commercial sources except repotrectinib

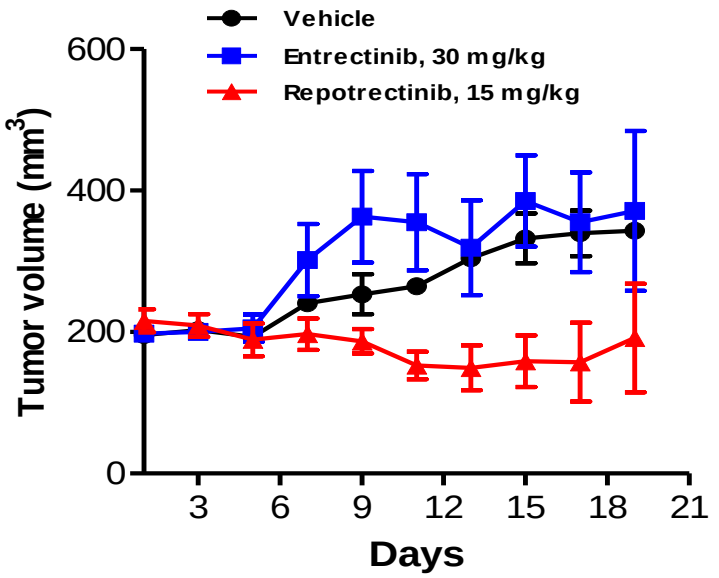
[1]Gainor JF et al., JCO Precis Oncol 2017
[2]Drilon A et al., Cancer Discov 2018

Repotrectinib is Potent Against *ROS1* G2032R Mutation and Active in Intracranial Tumor Model

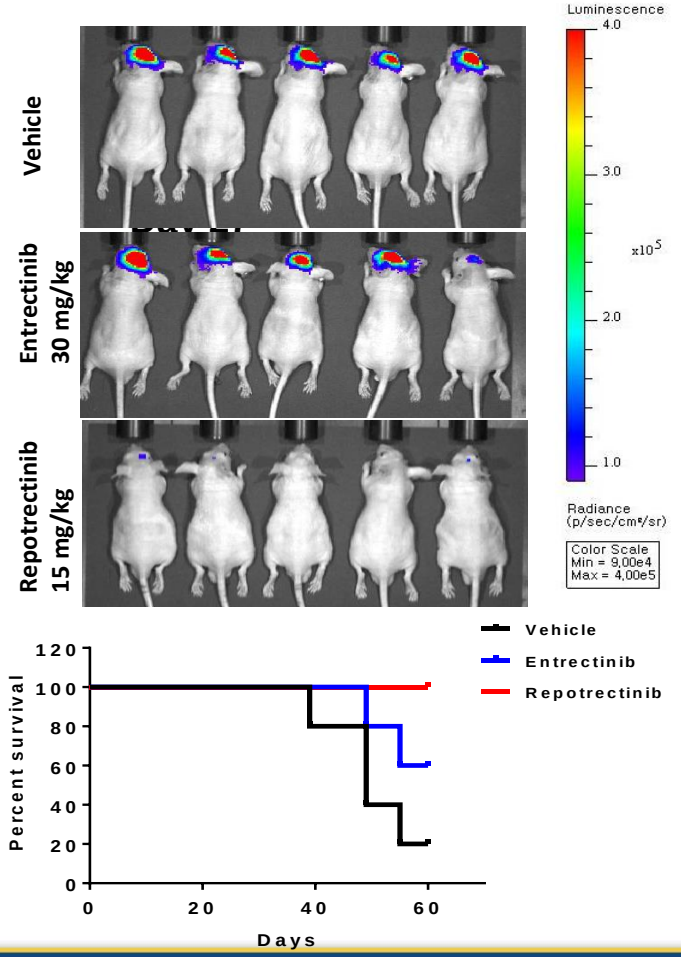
A. Antitumor activity in a NSCLC patient cell-derived mouse xenograft tumor model with CD74-*ROS1* G2032R mutation acquired after crizotinib treatment for 10 months



B. Antitumor activity in a NSCLC patient-derived xenograft mouse tumor model with CD74-*ROS1* G2032R mutation acquired after entrectinib treatment for 7 months



C. Antitumor activity in a *ROS1* fusion-driven intracranial tumor model



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TRIDENT-1: A Phase 1/2 Study of Repotrectinib

Study Design/Eligibility (Phase 1)

- Advanced solid tumors harboring *ROS1/NTRK1-3/ALK* fusions
- No limit on prior lines of therapy
- Asymptomatic CNS metastases allowed

Phase 1 Primary Objective

- Determine the MTD and RP2D

Phase 1 Secondary Objectives

- Safety and tolerability
- Preliminary objective response rate and clinical benefit rate

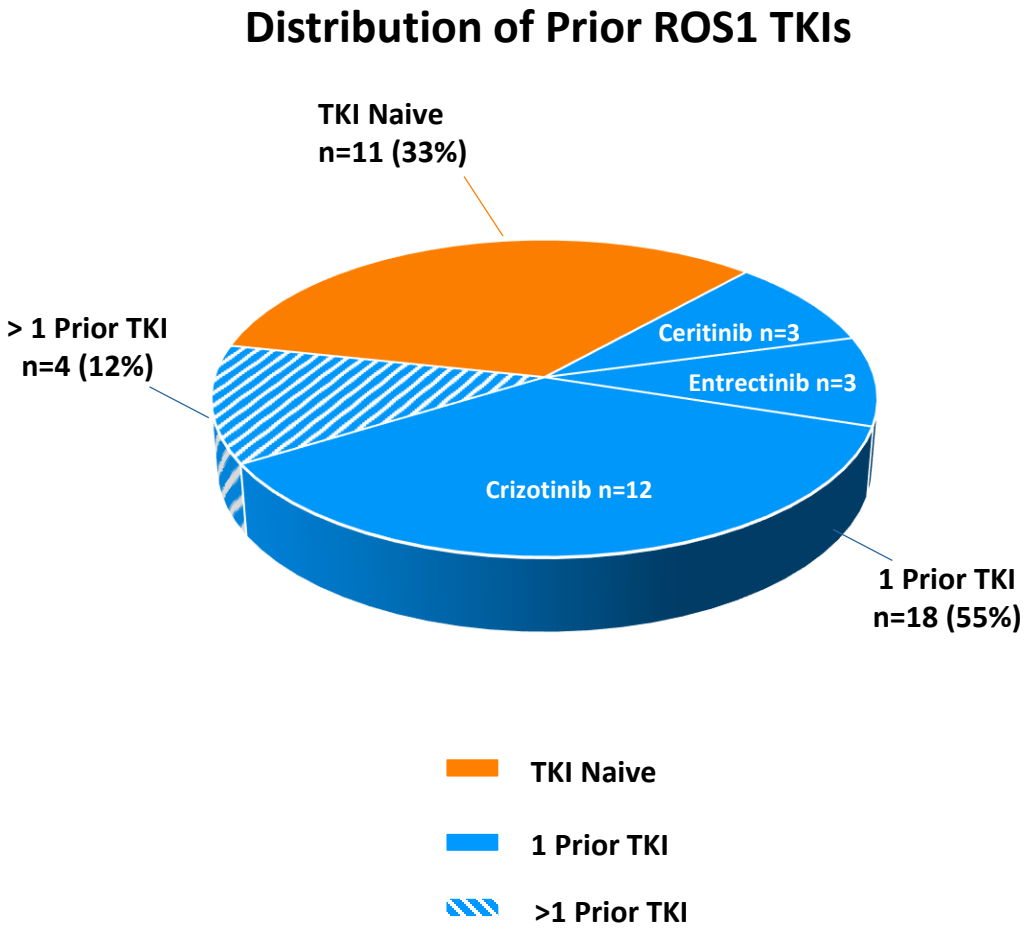
	Number of patients per dose cohort									
	40 mg QD	80 mg QD	160 mg QD	240 mg QD	160 mg BID	200 mg BID[1]	120 mg QD w/ Food	160 mg QD w/ Food	160 mg QD/BID w/Food[2]	Total
Safety population (*ROS1+, NTRK1-3+, ALK+* solid tumors)	13	12	23	10	12	2	3	5	3	83**
Efficacy population (*ROS1*+ NSCLC)	5	5	10	2	6	0	2	3	0*	33

[1] 2 ALK patients enrolled
[2] 160 mg QD for one week followed by 160 mg BID
* Not yet evaluable for efficacy by BICR
** N=83 patients: 31 were *ALK*+, 9 were *NTRK*+, and 43 were *ROS1*+ (of which 33 *ROS1*+ NSCLC were evaluable for efficacy by BICR)
BICR: Blinded Independent Central Review

TRIDENT-1: *ROS1*+ NSCLC Patient Demographics

Characteristics	N=33
Age, median (range)	57 (30, 79)
Sex, female n (%)	23 (70)
Race, Asian n (%)	20 (61)
Median lines of prior systemic therapy (range)	2 (1, 8)
Prior chemotherapy, n (%)	28 (85)
CNS metastases at baseline n (%)*	18 (55)
Median # of prior ROS1 TKIs (range)	1 (0, 3)
TKI Naive, n (%)	11 (33)
TKI Pretreated, n (%)	22 (67)
1 prior TKI	18 (55)
Crizotinib only	12 (67)
Ceritinib or entrectinib	6 (33)
>1 prior TKI	4 (12)

*Assessed by Investigator



Preliminary Efficacy of Repotrectinib in TKI Naive *ROS1*+ NSCLC by BICR

	TKI Naive (N=11)
Confirmed ORR, n/N (%)	**9/11 (82%)**
95% CI (%)	(48 – 98)
ORR at 160mg QD or above	**5/6 (83%)**
Duration of response (DOR), months	
Median	**Not reached**
Range	5.6 – 17.7+
Intracranial ORR (IC-ORR)[1], n/N (%)	**3/3 (100%)**
95% CI (%)	(29 – 100)
Clinical benefit rate, n/N (%)	**11/11 (100%)**
95% CI (%)	(72 – 100)
Median follow-up time, months	**16.4**
Range	3.5+ – 19.4+

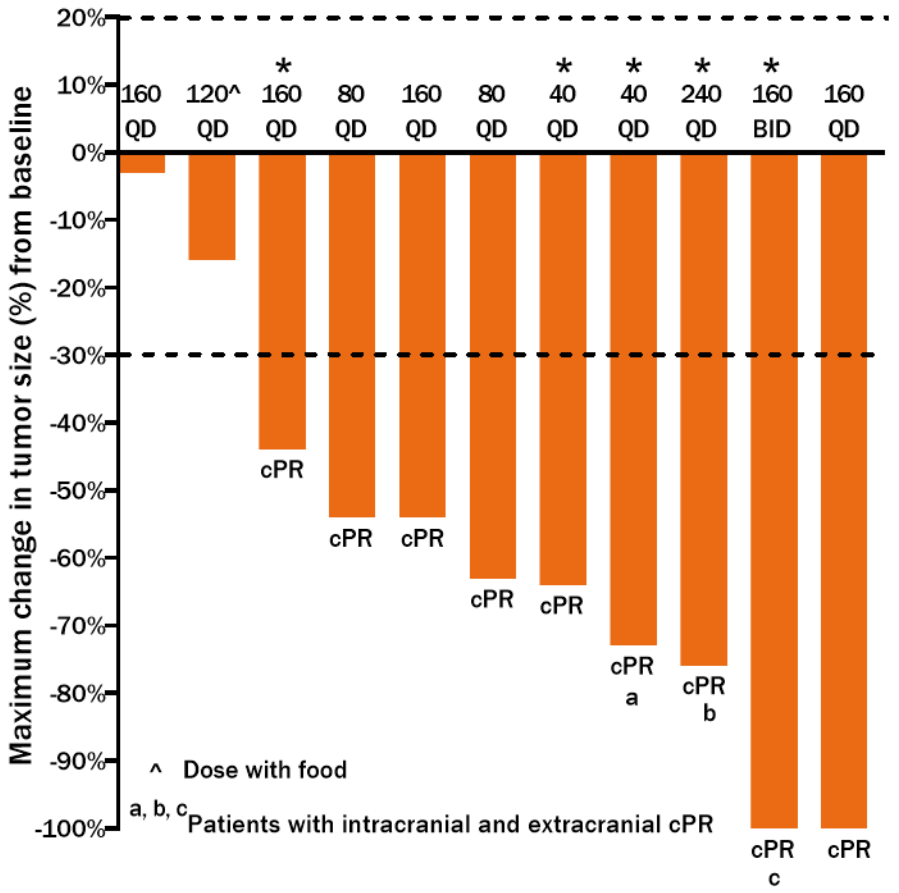
***5 of 9 patients remain in cPR from 10.9+ to 17.7+ months. 3 patients with IC-ORR remain in cPR for 10.9+, 12.1+, and 17.6+ months.**

[1] For patients with CNS measurable disease at baseline

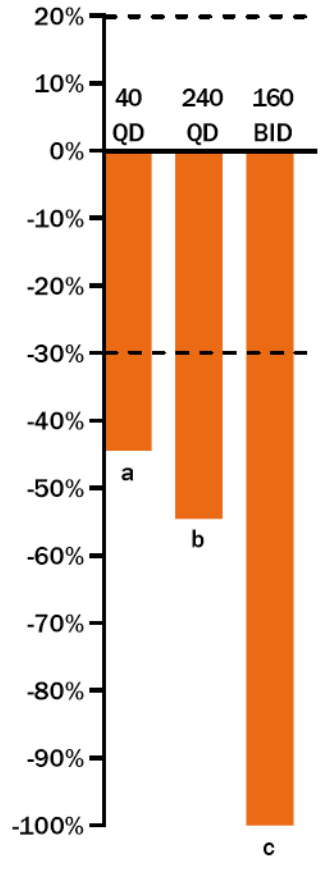
BICR: Blinded Independent Central Review

Clinical Benefit Rate: CR + PR + SD ≥ 2 Cycles

Overall Response (N=11)



Intracranial Response (N=3)



Preliminary Efficacy of Repotrectinib in TKI Pretreated *ROS1+* NSCLC by BICR

Pretreated with 1 TKI (N=18**)	
Confirmed ORR, n/N (%)	**7/18 (39%)**
95% CI (%)	(17 – 64)
ORR at 160 mg QD or above	**6/11 (55%)**
• **Crizotinib as ONLY prior TKI**	**4/7 (57%)**
IC-ORR[1], n/N (%)	**3/4 (75%)**
95% CI (%)	(19 – 99)
Clinical benefit rate, n/N (%)	**14/18 (78%)**
95% CI (%)	(52 – 94)
Median follow-up time, months	**14.6**
Range	1.4 – 14.6+

***3 of 7 patients remain in cPR from 1.0+ to 7.6+ months**

** 4 patients treated with > 1 prior TKI not included (3 of 4 had tumor regressions)

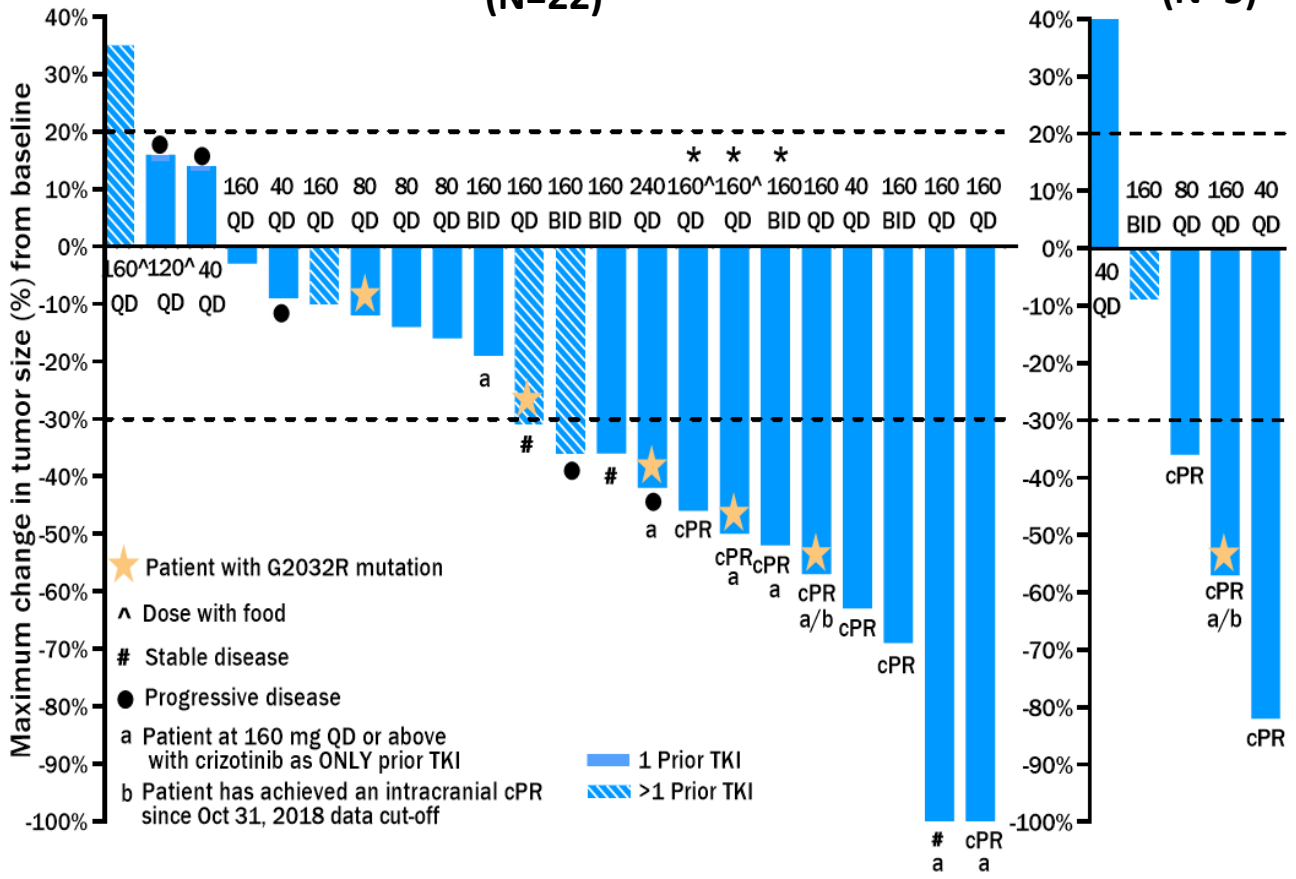
[1] For patients with CNS measurable disease at baseline

BICR: Blinded Independent Central Review

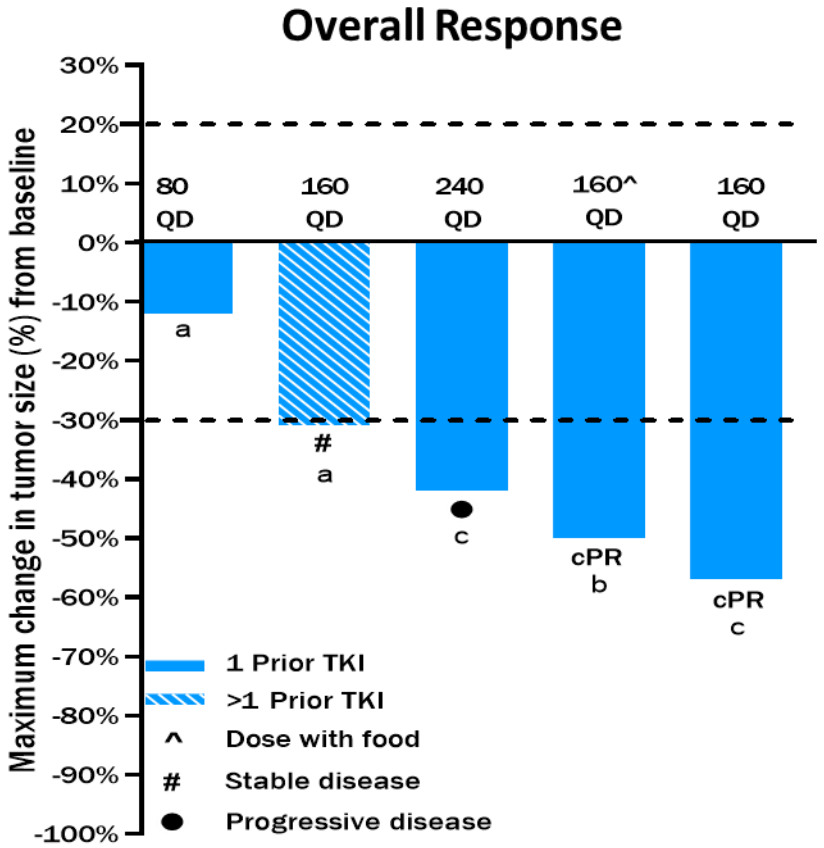
Clinical Benefit Rate: CR + PR + SD ≥ 2 Cycles

Overall Response (N=22)

Intracranial Response (N=5)



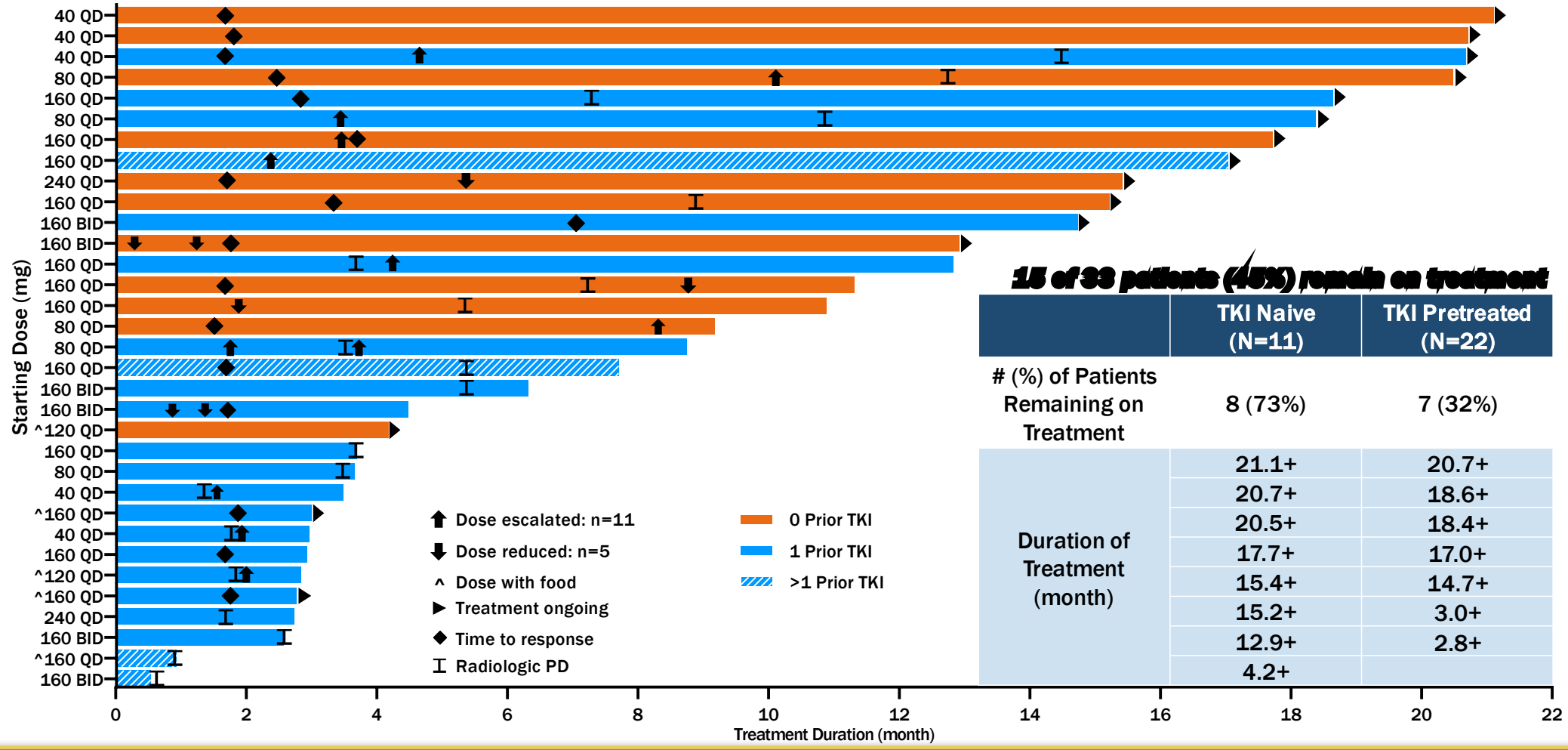
Preliminary Clinical Activity of Repotrectinib Against *ROS1* G2032R Solvent Front Mutation



G2032R identified in (a) plasma cfDNA; (b) tumor tissue; (c) plasma cfDNA and tumor tissue

- *ROS1* G2032R identified by plasma cfDNA or tissue NGS test in 5 patients who had prior crizotinib treatment
- All 5 patients experienced tumor regressions on repotrectinib
- **<u>Confirmed ORR</u>: 2/5 (40%)**
  - 2/3 (67%) for 160 mg QD and above with 1 prior TKI
    - 1 cPR at 160 mg QD with food (DOR 1.0+ months and remains on treatment at 3.0+ months)
    - 1 cPR at 160 mg QD (DOR 4.4 months and remains on treatment at 18.6+ months)

Duration of Repotrectinib Treatment in N=33 *ROS1*+ NSCLC by BICR



15 of 33 patients (45%) remain on treatment

	TKI Naive (N=11)	TKI Pretreated (N=22)
# (%) of Patients Remaining on Treatment	8 (73%)	7 (32%)
Duration of Treatment (month)	21.1+	20.7+
	20.7+	18.6+
	20.5+	18.4+
	17.7+	17.0+
	15.4+	14.7+
	15.2+	3.0+
	12.9+	2.8+
	4.2+	

Safety Summary: Treatment-Emergent and Treatment-Related AEs

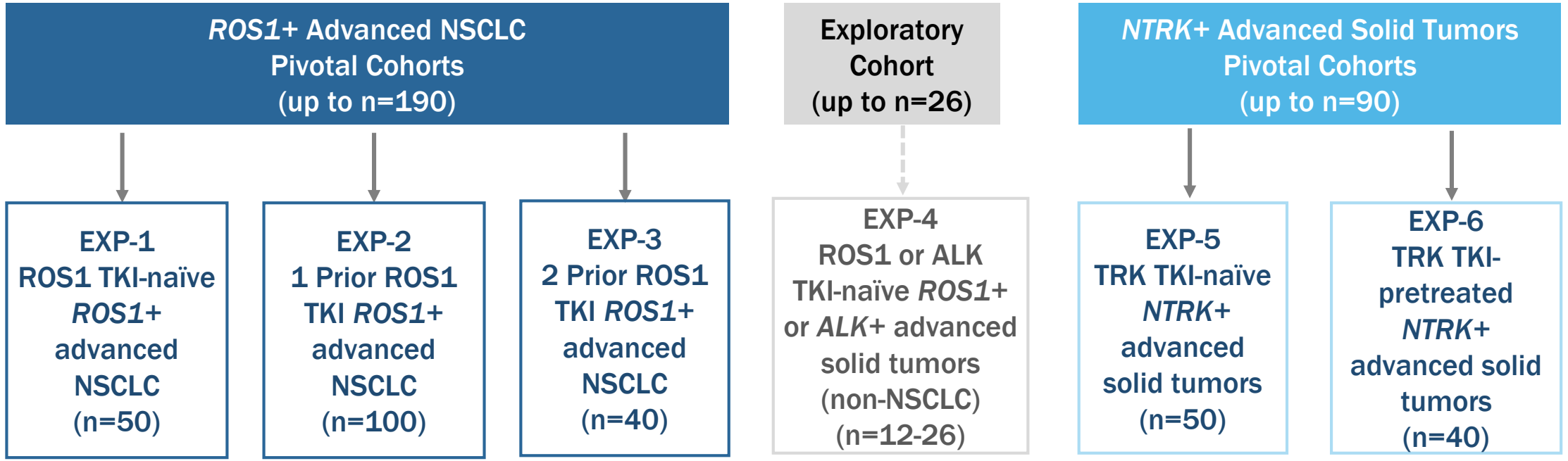
Adverse Event	All Treated Patients (N=83)				
	TEAEs (≥10% of patients)			TRAEs	
	All Grades n(%)	Grade 3 n(%)	Grade 4* n(%)	Grade 3 n(%)	Grade 4 n(%)
Dizziness	47 (56.6)	2 (2.4)	---	2 (2.4)	---
Dysgeusia	42 (50.6)	---	---	---	---
Dyspnea	25 (30.1)	5 (6.0)	1 (1.3)	1 (1.2)	---
Fatigue	25 (30.1)	2 (2.4)	---	---	---
Constipation	24 (28.9)	---	---	---	---
Paresthesia	24 (28.9)	---	---	---	---
Anemia	23 (27.7)	10 (12.0)	---	3 (3.6)	---
Nausea	19 (22.9)	2 (2.4)	---	---	---
Cough	17 (20.5)	---	---	---	---
Pyrexia	16 (19.3)	---	---	---	---
Headache	14 (16.9)	1 (1.2)	---	---	---
Vomiting	13 (15.7)	---	---	---	---
Upper respiratory tract infection	11 (13.3)	---	---	---	---
Ataxia	10 (12.0)	---	---	---	---
Pain in extremity	10 (12.0)	1 (1.2)	---	---	---
Abdominal pain	9 (10.8)	---	---	---	---
Muscular weakness	9 (10.8)	1 (1.2)	---	---	---

- **Repotrectinib was generally well tolerated**
- **Majority of treatment emergent adverse events (TEAEs) were Grade 1 or Grade 2**
  - No Grade 3 or Grade 4 ALT or AST elevations
  - No cases of dizziness have led to treatment discontinuation
- **Four DLT events**:
  - Grade 2 or 3 dizziness
    - 160 mg BID (n=2)
    - 240 mg QD (n=1)
  - Grade 3 dyspnea and hypoxia
    - 160 mg BID (n=1)
- **Four TEAE Grade 5 events^**
- **Treatment related adverse events (TRAEs) leading to dose modifications**
  - Dose reduction: n=8 (9.6%)
  - Dose interruption: n=2 (2.4%)
  - Drug discontinuation: n=2 (2.4%)

**Add'l Grade 4 TEAEs: cerebrovascular accident, dyspnea, influenza, hyperkalemia, bacterial pneumonia (n=1 each), respiratory failure (n=2); None were determined to be related to treatment*

^ Grade 5 TEAEs: respiratory failure (n=2), sepsis, sudden death (n=1 each); Only the case of sudden death was determined to be possibly related to treatment

Pivotal Phase 2 Portion of TRIDENT-1: Plan to Initiate in 2H 2019



- **Phase 2 Primary Objective**
  - cORR by BICR in each expansion cohort
- **Phase 2 Secondary Objectives**
  - DOR, PFS, and OS
  - IC-ORR and CNS-PFS

Conclusions

- **TRIDENT-1 Phase 1 data support repotrectinib as a potential best-in-class *ROS1* agent in advanced NSCLC**
- **Preliminary clinical activity demonstrated across 7 dose cohorts in *ROS1+* NSCLC patients**
  - TKI-naive:
    - cORR 82% (9/11); median DOR not yet reached
  - TKI-pretreated:
    - 1 prior TKI: cORR 39% (7/18)
      - cORR 57% (4/7) in crizotinib-pretreated patients at 160 mg QD and above
  - CNS activity observed in both TKI-naïve and TKI-pretreated patients
- **Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor designed to overcome TKI resistant mutations**
  - All 5 *ROS1+* NSCLC patients with the G2032R SFM experienced tumor regressions with a cORR of 40%
- **Repotrectinib was well tolerated with a manageable safety profile**
  - Dizziness is an on-target AE associated with TRK inhibition and manageable
  - Most AEs managed without dose modification and rarely led to discontinuation
- **Pivotal Phase 2 portion of TRIDENT-1 planned to initiate in 2H 2019**

Thank you to the patients, their families and caregivers and participating clinical sites

United States:

- **Memorial Sloan Kettering Cancer Center**
  Alexander Drilon, MD - Principal Investigator

- **Massachusetts General Hospital**
  Alice Shaw, MD - Principal Investigator
  Jessica Lin, MD - Sub-Investigator

- **University of Colorado**
  Robert Doebele, MD - Principal Investigator
  Ross Camidge, MD - Sub-Investigator

- **University of California Irvine**
  Samuel Ejadi, MD - Principal Investigator
  Viola Zhu, MD - Sub-Investigator

South Korea:

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  You Jin Chun, MD – Sub-Investigator
  Hye Ryun Kim, MD - Sub-Investigator

- **Seoul National University Hospital**
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