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Update from the Phase 2 registrational trial of repotrectinib in TKI-pretreated patients with *ROS1+* advanced non-small cell lung cancer and with *NTRK+* advanced solid tumors (TRIDENT-1)

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Disclosures: Jessica Lin, MD

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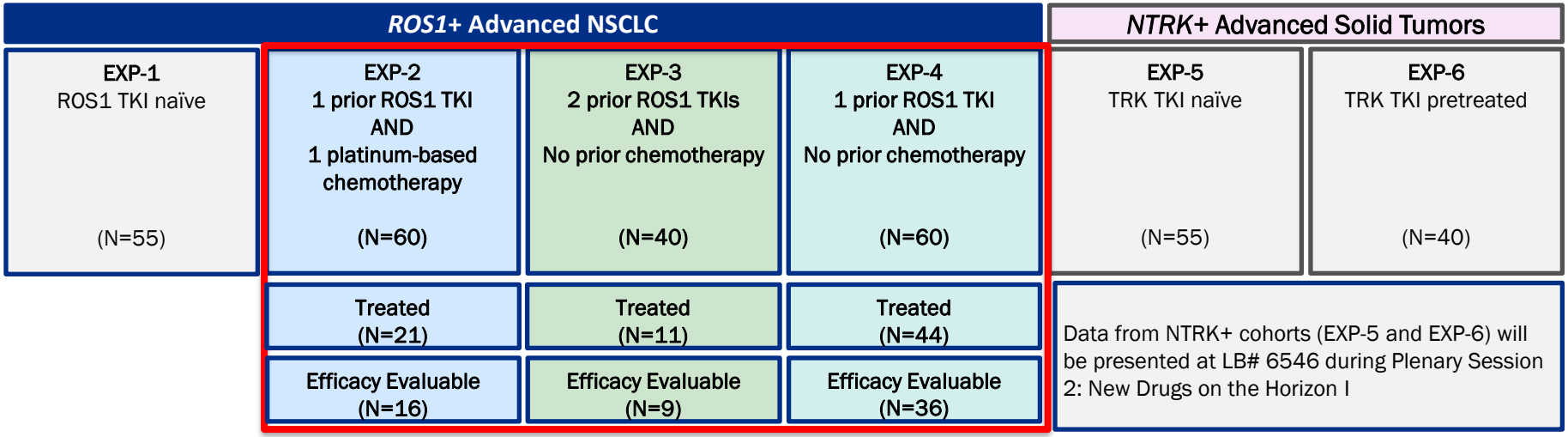
- *Repotrectinib is investigational and not approved for the treatment of any condition in any jurisdiction*

Repotrectinib: Potent ROS1 Inhibitor in TKI-Naïve and TKI-Pretreated ROS1+ NSCLC

- ROS1 fusions have been identified as oncogenic drivers in 1-2% of NSCLC[1,2]
- Crizotinib and entrectinib are FDA approved TKIs for ROS1+ NSCLC.[3] *ROS1* resistance mutations including solvent front mutations (SFMs) can emerge in up to 28% of entrectinib-treated patients and 53% of crizotinib-treated patients[4,5]
- There are currently no FDA approved targeted treatments for TKI-pretreated ROS1+ NSCLC
- Repotrectinib is a next-generation TKI with a compact macrocyclic structure that binds completely inside the ATP binding pocket even in the presence of mutations[6]
- Repotrectinib (IC_{50} < 0.2 nM) is more potent in wildtype ROS1 than crizotinib (IC_{50} 14.6 nM) and entrectinib (IC_{50} 10.5 nM), and is active against *ROS1* resistance mutations including SFM G2032R (IC_{50} 3.3 nM)[7]
- Preliminary data with repotrectinib in ROS1+ TKI-naïve NSCLC showed a cORR of 91% (N=22).[8] Repotrectinib was granted Breakthrough Therapy Designation in this setting
- Preliminary data also showed promising activity in ROS1+ TKI-pretreated NSCLC including patients with known SFMs.[7,8] Repotrectinib was granted two Fast Track Designations for ROS1+ TKI-pretreated NSCLC (with and without prior platinum-based chemotherapy)

1. Pan Y, et al. *Lung Cancer*. 2014;84:121-126. 2. IASLC atlas of ALK and ROS1 testing in lung cancer. In: Tsao MS, Hirsch FR, Yatabe Y ed. International Association for the Study of Lung Cancer; 2016. 3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non–Small Cell Lung Cancer, Version 5.2021. 4. Doebele R, et al. ESMO 2019. Abstract LBA28. 5. Gainor JF, et al. *JCO Precis Oncol*. 2017;2017:PO.17.00063. 6. Drilon A, et al. *Cancer Discov*. 2018;8(10):1227-1236. 7. Drilon A, et al. ESMO 2019. Abstract 4536. 8. Cho BC, et al. WCLC 2020 Annual Meeting. Abstract MA11.07.

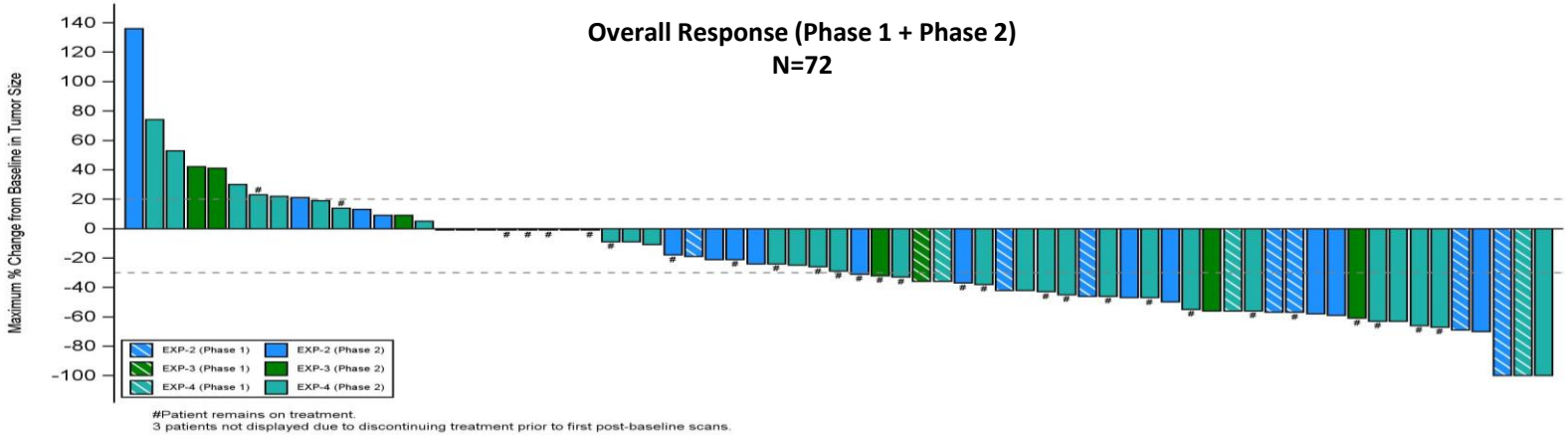
TRIDENT-1 Phase 2 Study Design



Today's presentation will focus on updated ROS1+ TKI-pretreated cohorts (EXP-2, EXP-3 and EXP-4) in a total of N=61 efficacy evaluable patients in Phase 2

Efficacy evaluable for Phase 2: patients with baseline measurable disease and ≥ 1 post-baseline scan, or off treatment prior to first post-baseline scan.
Response based on RECIST v1.1 for Phase 2 assessed by Physician Assessment with data cutoff date of 26 August 2021.

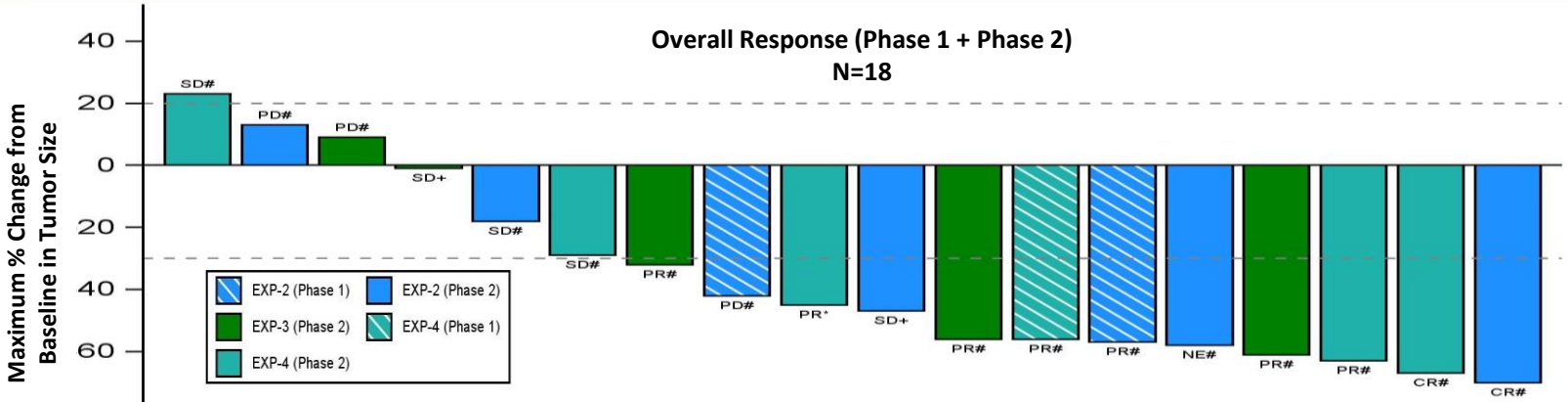
Preliminary Efficacy: Patients with ROS1+ TKI-Pretreated Advanced NSCLC



	EXP-2		EXP-3		EXP-4	
	Phase 2 (N=16)	Phase 1 + 2 (N=23)	Phase 2 (N=9)	Phase 1 + 2 (N=10)	Phase 2 (N=36)	Phase 1 + 2 (N=39)
Confirmed ORR (cORR) (95% CI)	**31%** (11 – 59)	**39%** (20 – 61)	**33%** (7 – 70)	**30%** (7 – 65)	**31%*** (16 – 48)	**33%*** (19 – 50)
Duration of Response (range in months)	1.8+ – 9.2 n=5	1.8+ – 11.1 n=9	1.9+ – 12.9+ n=3	1.9+ – 12.9+ n=3	1.7+ – 15.0+ n=11	0.8+ – 15.0+ n=13

*At time of the 26 August 2021 data cut off, 3 patients in Phase 2 EXP-4 had unconfirmed PR (uPR). One uPR has been confirmed by scans that were entered after the 26 August 2021 data cut off and is included in the cORR; the other 2 uPR patients are on treatment awaiting confirmatory scans. Phase 2: RECIST v1.1 assessed by Physician Assessment. Phase 1: RECIST v1.1 assessed by Blinded Independent Central Review (BICR) with data cutoff date of 22 July 2019 for patients with baseline measurable disease and ≥ 1 post-baseline scan. Phase 1 patients treated at or above the Phase 2 recommended dose.

Preliminary Efficacy: Patients with ROS1+ TKI-Pretreated Advanced NSCLC and Baseline *ROS1* Resistance Mutations

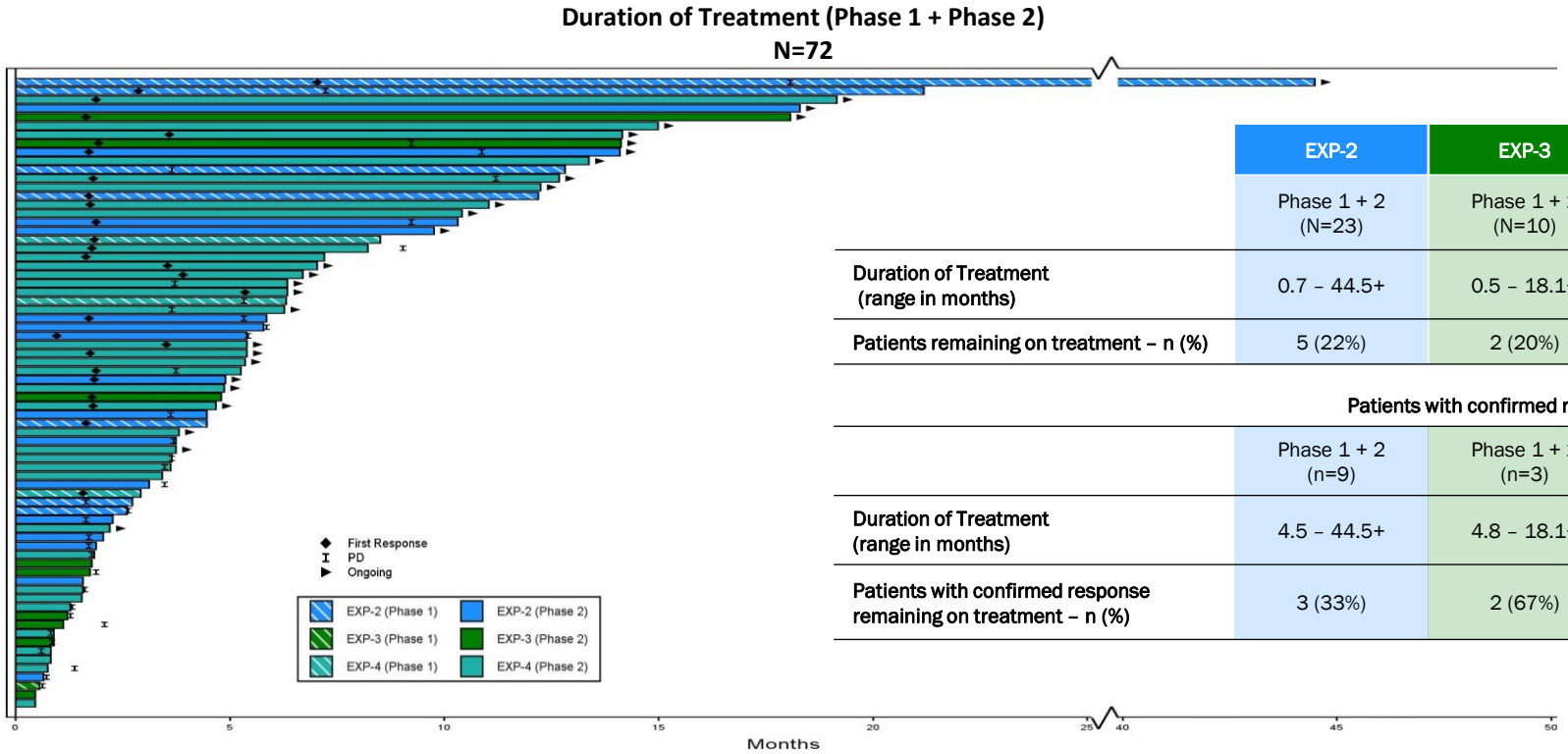


Patient with solvent front mutation
* Patient with gatekeeper mutation
+ Patient with other kinase domain mutation

	Any *ROS1* Resistance Mutation		Solvent Front Mutation (G2032R)	
	Phase 2 (N=15)	Phase 1 + 2 (N=18)	Phase 2 (N=12)	Phase 1 + 2 (N=15)
Confirmed ORR (cORR)	**47%**	**50%**	**50%**	**53%**
(95% CI)	(21 – 73)	(26 – 74)	(21 – 79)	(27 – 79)
CR	2 (13%)	2 (11%)	2 (17%)	2 (13%)
PR	5 (33%)	7 (39%)	4 (33%)	6 (40%)
Duration of Response (range in months)	*1.9+ - 15.0+* n=7	*1.9+ - 15.0+* n=9	*1.9+ - 15.0+* n=6	*1.9+ - 15.0+* n=8

15 of 18 resistance mutations were G2032R solvent front mutations; the other 3 included 1 gatekeeper (L2026M) and 2 other kinase domain mutations (F2004I and L2086F). 2 patients with CR had lymph node response and therefore not at -100% change from baseline. Data cutoff date 26 August 2021 for Phase 2 and 22 July 2019 for Phase 1.

Duration of Treatment: Patients with ROS1+ TKI-Pretreated Advanced NSCLC



	EXP-2	EXP-3	EXP-4
	Phase 1 + 2 (N=23)	Phase 1 + 2 (N=10)	Phase 1 + 2 (N=39)
Duration of Treatment (range in months)	0.7 – 44.5+	0.5 – 18.1+	0.5 – 19.2+
Patients remaining on treatment – n (%)	5 (22%)	2 (20%)	21 (54%)

Patients with confirmed response

	Phase 1 + 2 (n=9)	Phase 1 + 2 (n=3)	Phase 1 + 2 (n=13)
Duration of Treatment (range in months)	4.5 – 44.5+	4.8 – 18.1+	2.9 – 19.2+
Patients with confirmed response remaining on treatment – n (%)	3 (33%)	2 (67%)	8 (62%)

Phase 2 data cutoff date 26 August 2021 (responses confirmed by Physician Assessment).
Phase 1 data cutoff date 22 July 2019 for responses confirmed by BICR and 26 August 2021 for duration of treatment.

Safety Summary: Phase 1 and Phase 2 Combined

All Treated Patients (N=301)					
	TEAEs (≥15% of patients)			TRAEs	
Adverse Events	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Dizziness	181 (60.1)	7 (2.3)	0	7 (2.3)	0
Dysgeusia	132 (43.9)	1 (0.3)	0	1 (0.3)	0
Constipation	101 (33.6)	1 (0.3)	0	0	0
Paraesthesia	87 (28.9)	3 (1.0)	0	3 (1.0)	0
Dyspnoea[a]	84 (27.9)	18 (6.0)	3 (1.0)	1 (0.3)	0
Anaemia	82 (27.2)	24 (8.0)	1 (0.3)	10 (3.3)	0
Fatigue	73 (24.3)	5 (1.7)	0	2 (0.7)	0
Nausea	62 (20.6)	3 (1.0)	0	0	0
Muscular weakness	57 (18.9)	5 (1.7)	0	3 (1.0)	0
Ataxia	51 (16.9)	0	0	0	0

- Repotrectinib was generally well tolerated
- Most TRAEs were Grade 1 or 2
- The most commonly-reported TEAE remains low-grade dizziness (60%)
  - 76% (138/181) were Grade 1
  - 11 (4%) patients reported ataxia in the absence of dizziness
  - No events of dizziness or ataxia led to treatment discontinuation
- Dose modifications due to TEAEs:
  - 27% with TEAEs that led to dose reduction
  - 11% with TEAEs that led to drug discontinuation

[a] One patient reported Grade 5 dyspnoea.
Note: 2 Grade 4 TRAEs of transient CPK increase and no Grade 5 TRAEs. TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event. Data cutoff date 26 August 2021.

Conclusions

- Repotrectinib is a next-generation ROS1/TRK inhibitor
- In the setting of ROS1+ TKI pretreated advanced NSCLC with limited treatment options, repotrectinib demonstrated clinical activity in Phase 1 and Phase 2
  - EXP-2: N=23, cORR 39% (95% CI: 20 – 61)
  - EXP-3: N=10, cORR 30% (95% CI: 7 – 65)
  - EXP-4: N=39, cORR 33% (95% CI: 19 – 50)
  - In TKI-pretreated NSCLC and *ROS1* G2032R SFM (N=15): cORR 53% (95% CI: 27 – 79)
- Repotrectinib was generally well-tolerated
- Enrollment is ongoing in the registrational Phase 2 TRIDENT-1 study evaluating repotrectinib for the treatment of TKI-naive and TKI-pretreated patients with ROS1+ advanced NSCLC and NTRK+ advanced solid tumors
- Data for NTRK+ cohorts (EXP-5 and EXP-6) will be presented at LB# 6546 during Plenary Session 2: New Drugs on the Horizon I

Acknowledgments

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For further questions please contact: jjlin1@partners.org