The efficacy and safety of Taletrectinib in patients with TKI-naïve or Crizotinib pretreated ROS1-positive Non–Small Cell Lung Cancer (NSCLC).

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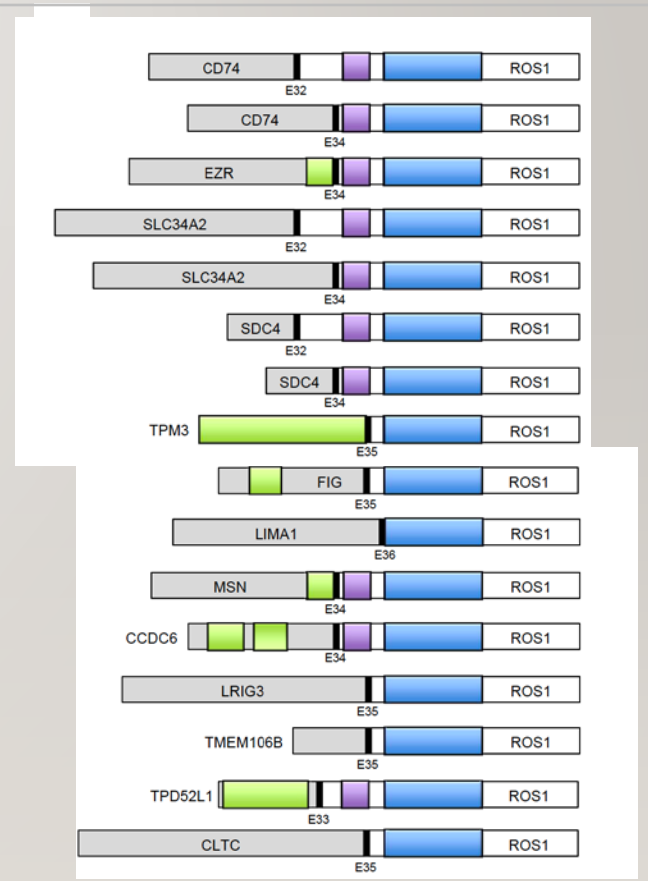
ROS 1 GENOMIC ALTERATION.

- ROS1 is an oncogene on Chromosome 6(6q22).
- ROS 1 rearrangements are seen in 22 different malignancies.
- In Non Small Cell Lung cancer(NSCLC) ROS1 rearrangements are seen in 1-2% of all cases.
- Typically seen in younger patients, never or light smokers and adenocarcinoma subtype.
- Rarely seen in large cell and squamous carcinomas too.

ROS1 REARRANGEMENTS IN NSCLC

Background

- *ROS1* rearrangements lead to fusion of a portion of ROS1, including its tyrosine kinase domain, to a variety of different partner proteins.
- ROS1 fusion kinases are constitutively activated and function as potent oncogenic drivers.
- ROS1 is phylogenetically related to ALK, resulting in sensitivity to some ALK tyrosine kinase inhibitors (TKIs).



Lin JJ, Shaw AT. *J Thorac Oncol.* 2017;12:1611–1625.

NSCLC, non-small cell lung cancer.

1. Bergethon K. *J Clin Oncol.* 2012;30:863–870. 2. Dugay F, et al. *Oncotarget.* 2017;8:53336-53351.

3. Davies KD, Doebele RC. *Clin Cancer Res.* 2013;19:4040–4045. 4. Lin JJ, Shaw AT. *J Thorac Oncol.* 2017;12:1611–1625.

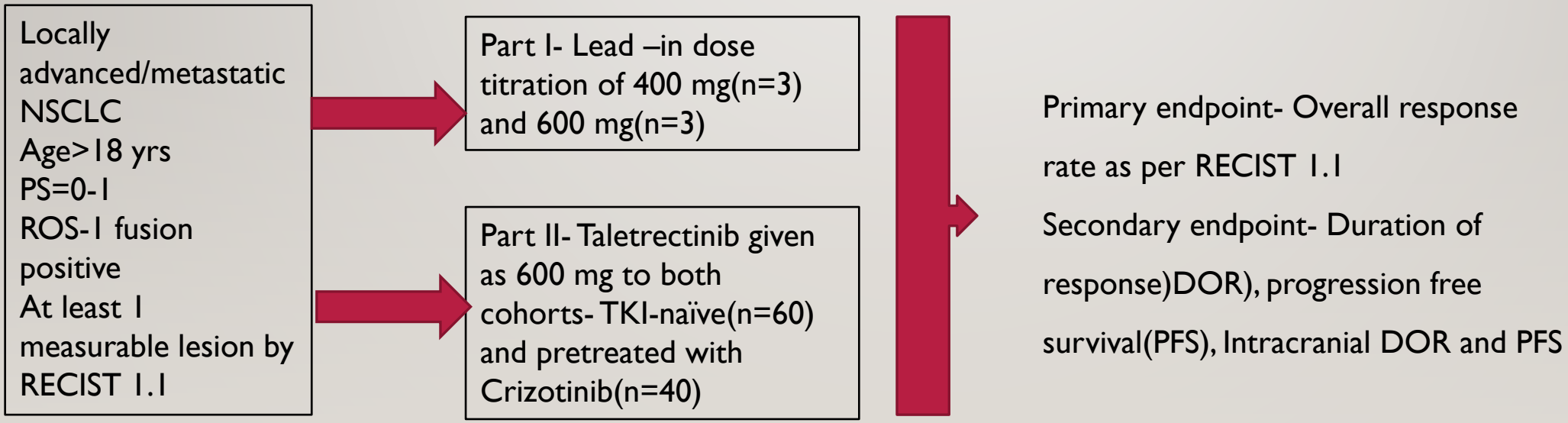
ROS POSITIVE LUNG CANCER

- The kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites. Crizotinib binds with high affinity to both ALK and ROS1.
- Crizotinib inhibits ROS cell signalling and cell vitality ***in-vitro.***
- Hence, Crizotinib was the logical first choice for ROS +ve lung cancer.
- Crizotinib has low activity in CNS.
- CNS is the first-and at times only-site of progression in ROS +ve lung cancer patients treated with Crizotinib(almost 50%)
- Hence a search for treatment with better CNS activity was ongoing.

TRUST STUDY-TALETRECTINIB

- Taletrectinib (AB-106 / DS-6051b) is a next-generation, potent, CNS- penetrant, selective ROS1 tyrosine kinase inhibitor.
- The TRUST study is a multicenter, open-label, single-arm, Phase 2 study of Taletrectinib in Chinese ROS1-positive NSCLC patients who are TKI -naïve or previously treated with Crizotinib.(n=109)

TRUST STUDY-TALETRECTINIB



Demographic and Baseline Characteristics

Category		ROS1 TKI-Naïve N=67 (%)	Crizotinib-Pretreated N=42 (%)	Total N=109 (%)
Sex	Male	28 (41.8)	16 (38.1)	44 (40.4)
	Female	39 (58.2)	26 (61.9)	65 (59.6)
Age (years)	Median (range)	54 (26, 75)	52 (31, 77)	54 (26, 77)
ECOG Performance Status	0	11 (16.4)	17 (40.5)	28 (25.7)
	1	56 (83.6)	25 (59.5)	81 (74.3)
Histological Subtype	Adenocarcinoma	64 (95.5)	38 (90.5)	102 (93.6)
	Squamous carcinoma	0	3 (7.1)	3 (2.8)
	Adenosquamous carcinoma	2 (3.0)	1 (2.4)	3 (2.8)
	NSCLC, NOS	1 (1.5)	0	1 (0.9)
Stages	Locally Advanced	8 (12.0)	2 (4.8)	10 (9.2)
	Metastatic	59 (88.1)	40 (95.2)	99 (90.8)
Prior Anti-cancer Therapy	TKI	0	42 (100.0)	42 (38.5)
	Chemo	15 (22.4)	14 (33.3)	29 (26.6)
	Other	7 (10.4)	7 (16.7)	14 (12.8)
Brain Metastasis (IRC assessed)	Yes	7 (10.4)	13 (31.0)	20 (18.3)
	No	60 (89.6)	29 (69.0)	89 (81.7)

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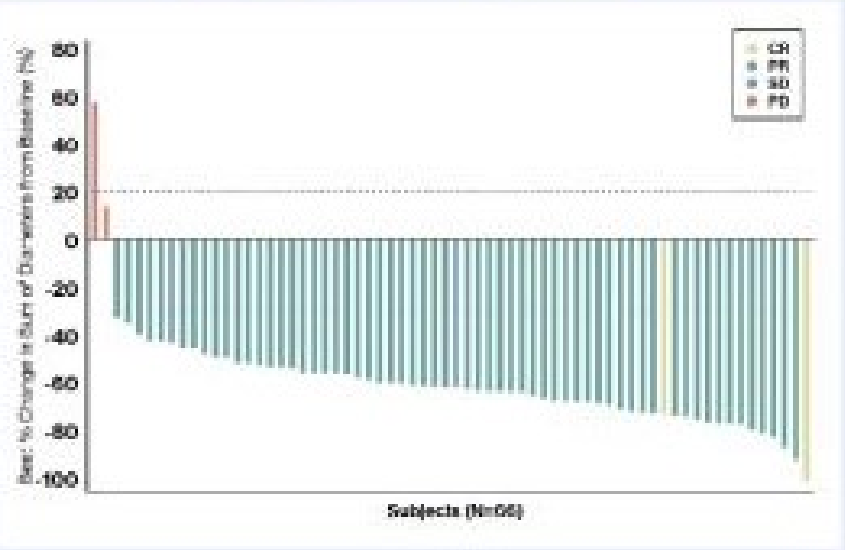
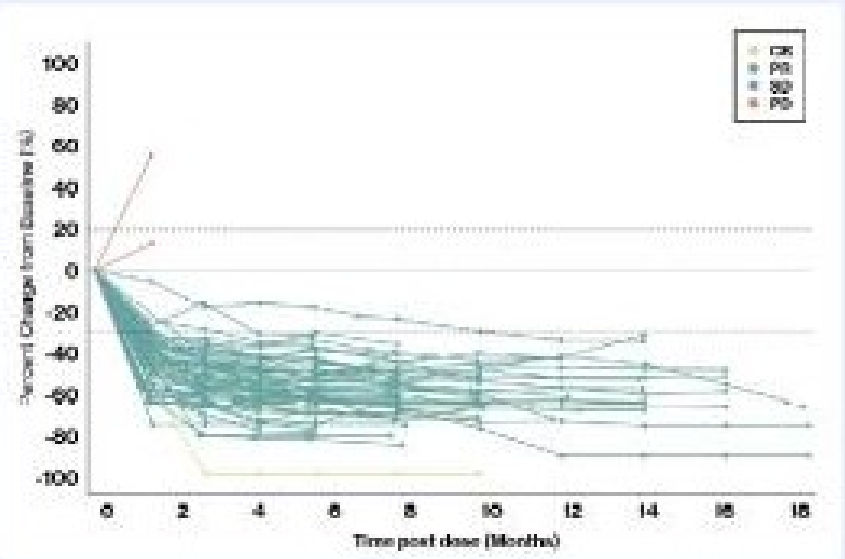
Efficacy in ROS1 TKI-Naïve Patients





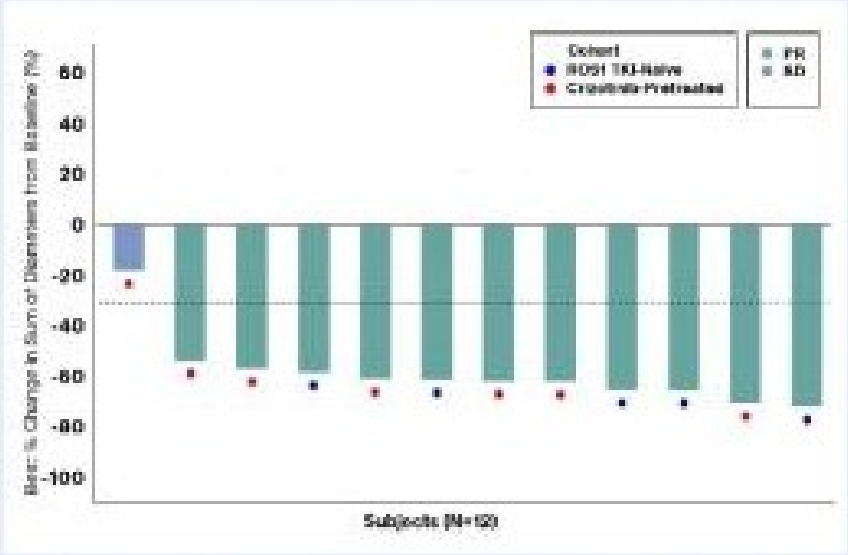
ROS1 TKI-Naïve Patients (N=67)

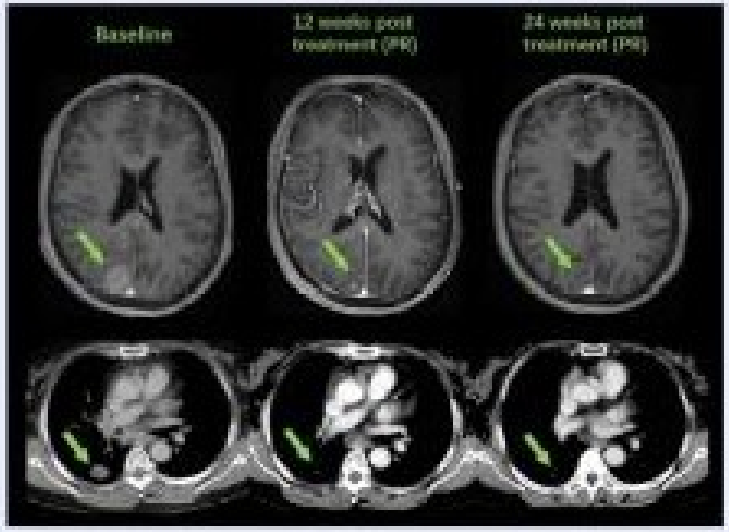
cORR (n/N) [95% CI]	92.5% (62/67) [83.4%, 97.5%]
DCR (n/N) [95% CI]	95.5% (64/67) [87.5%, 99.1%]
mDOR, month (min, max)	NR (1.3+, 16.6+)
mPFS, month (min, max)	NR (0+, 18.0+)

- The cORR was 92.5% (62/67), including 2 complete response (CR); DCR was 95.5% (64/67).
- The responses were observed mostly in the first two assessments.
- The mDOR and mPFS were not reached yet. However, in phase 1 + 2 pooled analysis[6], mDOR was 27.6 months with 95% CI of [20.7, NR] and mPFS was 33.2 months with 95% CI of [22.1, NR].

Note: One patient didn't have post-treatment tumor assessment and therefore was not included in the waterfall and spider plots.

Efficacy in Patients with Brain Metastases





ROS1-Positive NSCLC with Measurable Brain Lesions by RANO-BM (N=12)

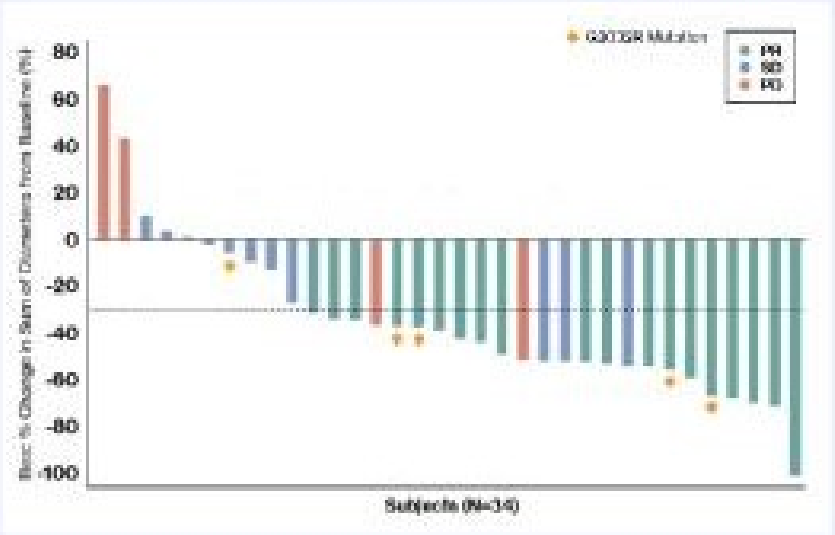
IC-ORR (n/N) [95% CI]	91.7% (11/12) [61.5%, 99.8%]
IC-DCR (n/N) [95% CI]	100% (12/12) [73.5%, 100%]

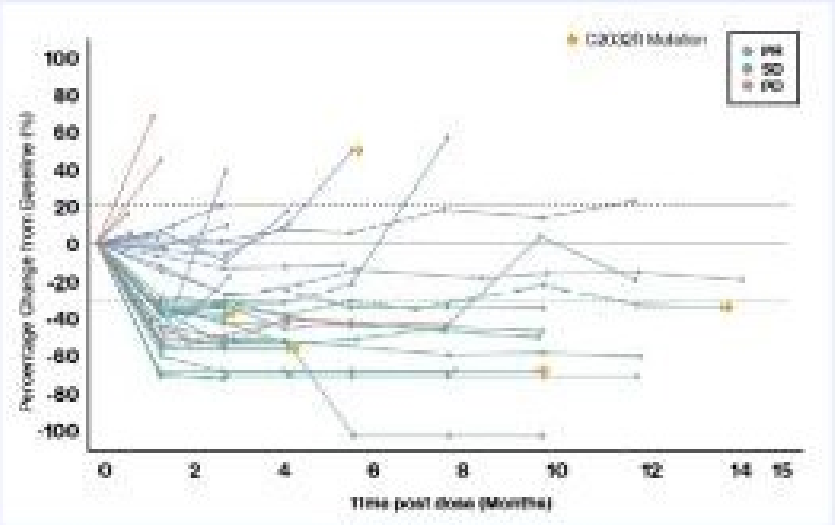
- 12 patients had measurable brain lesions and the IC-ORR and IC-DCR were 91.7% and 100%, respectively.

Patient Case:

- A patient with ROS1-positive NSCLC and brain metastasis with measurable brain lesions, no prior ROS1 TKI treatment.
- Near-complete disappearance of target lesions in brain and lung after 12 weeks of taletrectinib 600mg QD.
- Continues to receive treatment with confirmed PR.

Efficacy in Crizotinib-Pretreated Patients





Crizotinib-Pretreated Patients (N=38)

cORR (n/N) [95% CI]	50.0% (19/38) [33.4%, 66.6%]
DCR (n/N) [95% CI]	78.9% (30/38) [62.7%, 90.4%]
mDOR, month (min, max)	NR (1.4+, 12.3+)
mPFS, month (min, max)	NR (0+, 13.6+)

- The cORR was 50% (19/38), DCR was 78.9% (30/38).
- 5 patients had ROS1 G2032R mutation, 4/5 achieved PR, and 1/5 achieved SD, the cORR was 80%.
- The mDOR and mPFS were not reached yet.

Note: Four patients didn't have post-treatment tumor assessment results and therefore were not included in the waterfall and spider plots.

Safety Profile (Pooled Data)

The Most Common (≥15%) TEAEs (N=190)

Adverse Event (Preferred Term)	TEAE Any Grade (%)	TEAE Grade 3 (%)	TEAE Grade 4 (%)	TRAE (%)
Diarrhea	117 (61.6)	8 (4.2)	0	107 (56.3)
AST increased	106 (55.8)	14 (7.4)	0	102 (53.7)
ALT increased	94 (49.5)	12 (6.3)	0	94 (49.5)
Nausea	90 (47.4)	2 (1.1)	0	82 (43.2)
Vomiting	86 (45.3)	1 (0.5)	0	77 (40.5)
Anemia	52 (27.4)	6 (3.2)	0	41 (21.6)
Dizziness	35 (18.4)	0	0	27 (14.2)
Decreased appetite	33 (17.4)	1 (0.5)	0	30 (15.8)
WBC decreased	29 (15.3)	4 (2.1)	0	28 (14.7)

Dose reduction- in 14.2%

Dose discontinuation-5.3%

SUMMARY

- Taletrectinib has an impressive overall response rate both in naïve and Crizotinib pretreated patients with ROS1 rearrangement.
- It showed efficacy against Crizotinib resistant mutations viz. G2032R solvent front mutation.
- Intracranial disease control rate is 100% making it a very important drug for patients with CNS disease/progression.
- Taletrectinib has highly selective ROS 1 inhibition, hence systemic side effects are significantly less and mild.
- Global Phase II study underway- will be interesting to see its efficacy and safety in a large diverse population.