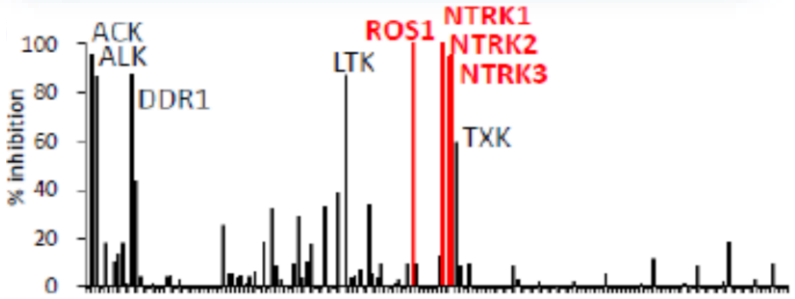
A Phase II Clinical Study to Investigate Taletrectinib in Treating Patients with ROS1 Fusion-Positive Non-Small Cell Lung Cancer

September 2021

Abbreviated English translation from the CSCO (Chinese Society of Clinical Oncology) oral presentation by Professor Caicun Zhou, Director of the Department of Oncology, Shanghai Pulmonary Hospital, Director of Cancer Institute of Tongji University Medical School, Chairman of the Oncology Department of Tongji University

Taletrectinib: A Next-Generation ROS1 Inhibitor

Kinase selectivity



Kinase inhibition

Kinase	IC50（nM）
ROS1	0.207
NTRK1	0.622
NTRK2	2.28
NTRK3	0.980

Cell Line	IC50 (nM)						
	Taletrectinib	Crizotinib	Ceritinib	Lorlatinib	Entrectinib	Brigatinib	Alectinib
Ba/F3-CD74-ROS1	0.8	3.0	11.2	<0.2	1.7	13.8	302.6
Ba/F3-CD74-ROS1^{L1951R}	4.2	86.1	598.0	1.8	3.0	766.7	616.5
Ba/F3-CD74-ROS1^{L2026M}	3.6	56.5	11.3	0.8	5.0	13.9	630.9
Ba/F3-CD74-ROS1^{G2032R}	13.5	525.2	405.7	73.6	321.1	309.1	1062.2
Ba/F3-CD74-ROS1^{D2033N}	28.3	23.2	56.3	0.4	11.2	24.2	1173.3
Ba/F3	1414.9	812.4	906.1	9959.3	1082.3	1848.6	396.1

- Highly selective and potent ROS1 inhibitor
- Effective against both solvent-front and gatekeeper mutations
- 10-fold more active against ROS1 over NTRK2, suggesting less CNS AE caused by NTRK2

Nature Communications 2019; 10:3604.

Taletrectinib Phase II Study (TRUST)

A phase II clinical study to investigate taletrectinib in treating patients with ROS1 fusion-positive non-small cell lung cancer (NSCLC)

Inclusion Criteria

- Locally advanced or metastatic NSCLC;
- Patient age ≥18 years, ECOG 0-1;
- Evidence of ROS1 fusion in tumor tissue;
- (n=106)

- Section 1 : (N=6)
  - 400mg QD, (N=3)
  - 600mg QD, (N=3)
- Section 2 :(N=100)
  - Cohort 1: never treated with any ROS1 TKI, 600mg QD (N=60)
  - Cohort 2:crizotinib failure 600mg QD (N=40)

Endpoints:

Confirmed ORR according to RECIST 1.1

Secondary endpoints :

DOR/ PFS/ TTF/ TTR according to RECIST 1.1 / Overall Survival

TRUST Phase II Study Data Overview

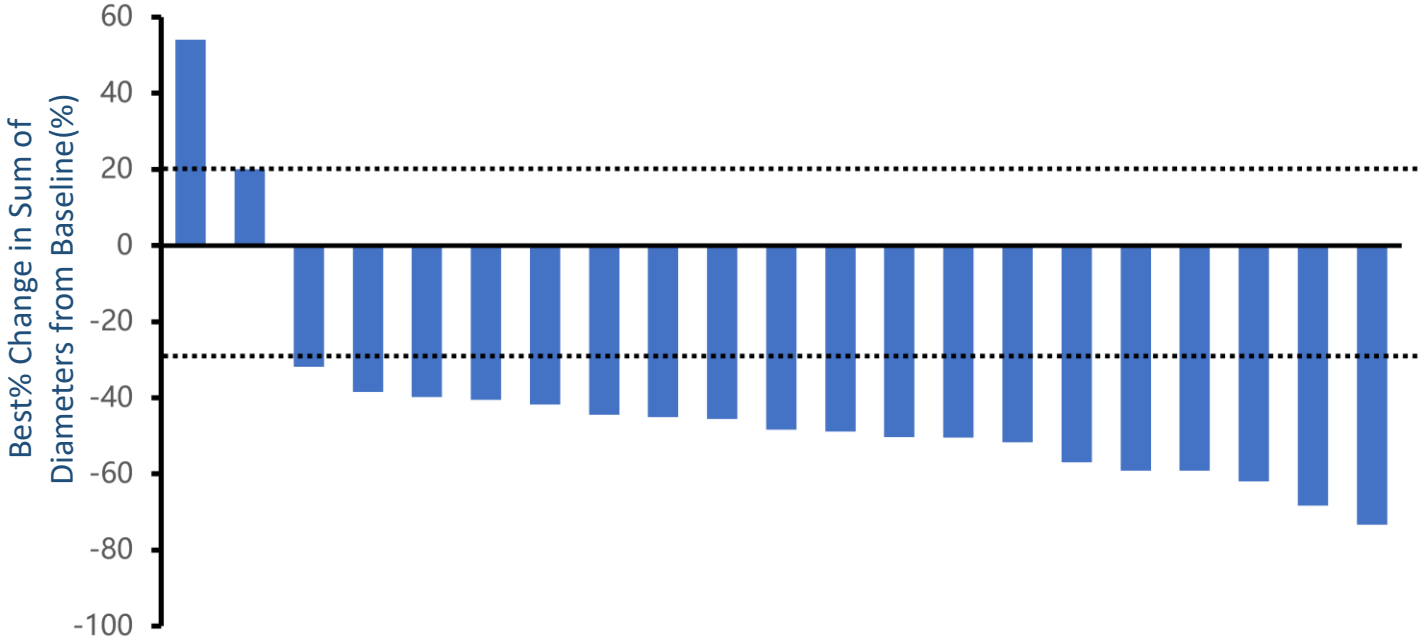
- Data cutoff date：June 16, 2021
- N=69, the patients received at least one dose taletrectinib treatment
- Investigator evaluation based on RECIST v1.1
  - ROS1 TKI Naïve：n=46, among which 21 received at least twice investigator evaluation
  - Crizotinib Failure：n=23, among which 16 received at least once investigator evaluation

Study Baseline Characteristics

Characteristics	Efficacy Evaluation（n=37）	Safety Evaluation（n=69）
Age, Median (Range), Years	53.0 (36-77)	54.0 (31-77)
Sex, N (%)		
Male	15 (40.5%)	30 (43.5%)
Female	22 (59.5%)	39 (56.5%)
ECOG, n (%)		
0	8 (21.6%)	13 (18.8%)
1	29 (78.4%)	56 (81.2%)
Staging, N (%)		
IIIb/IIIc	5 (13.5%)	11 (15.9%)
IV	32 (86.5%)	58 (84.1%)
Prior treatment, N (%)		
No prior treatment	12 (32.4%)	33 (47.8%)
Chemotherapy only	10 (27.0%)	13 (18.8%)
crizotinib only	9 (24.3%)	11 (15.9%)
Both chemotherapy and crizotinib	6 (16.2%)	12 (17.4%)

Data cutoff date: June 16, 2021

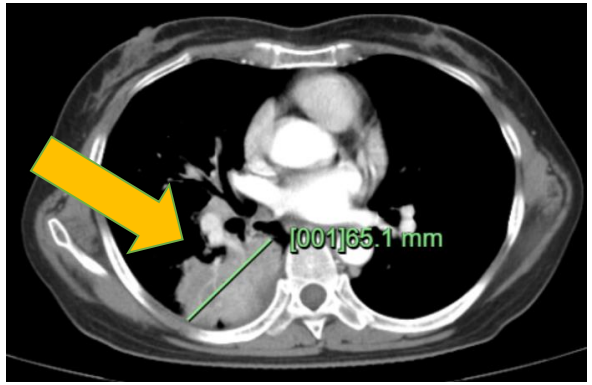
Efficacy in ROS1 TKI Naïve Patients



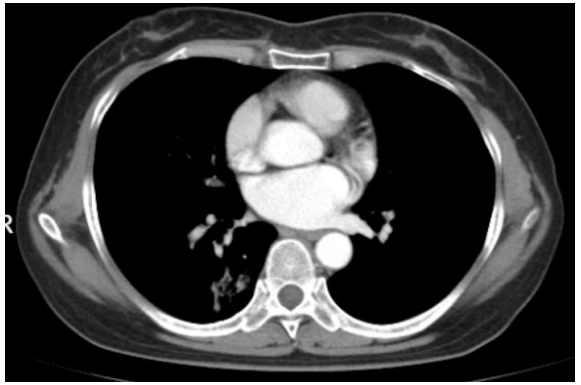
	Taletrectinib (n=21)
ORR, % (95%CI)	90.5 [69.6, 98.8]
DCR, % (95%CI)	90.5 [69.6, 98.8]
PR n (%)	19 (90.5)
PD n (%)	2 (9.5)
TTR (month), Median (95%CI)	1.4 [1.38, 1.45]
DOR (month), (Min, Max)	1.4+, 8.3+

Data cutoff date: June 16, 2021

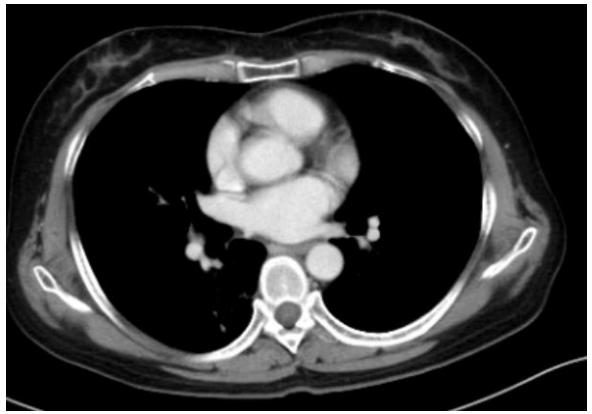
Case: ROS1 TKI Naïve Patient



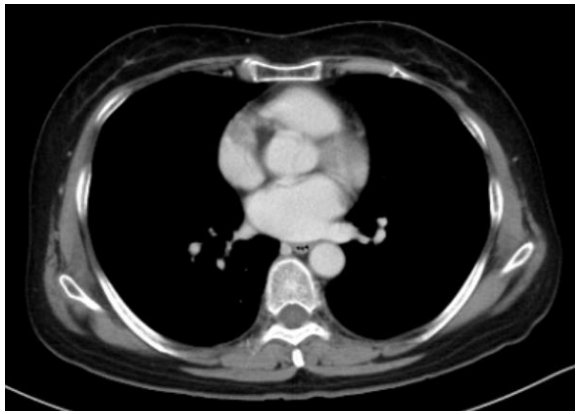
Baseline



7 W



19 W

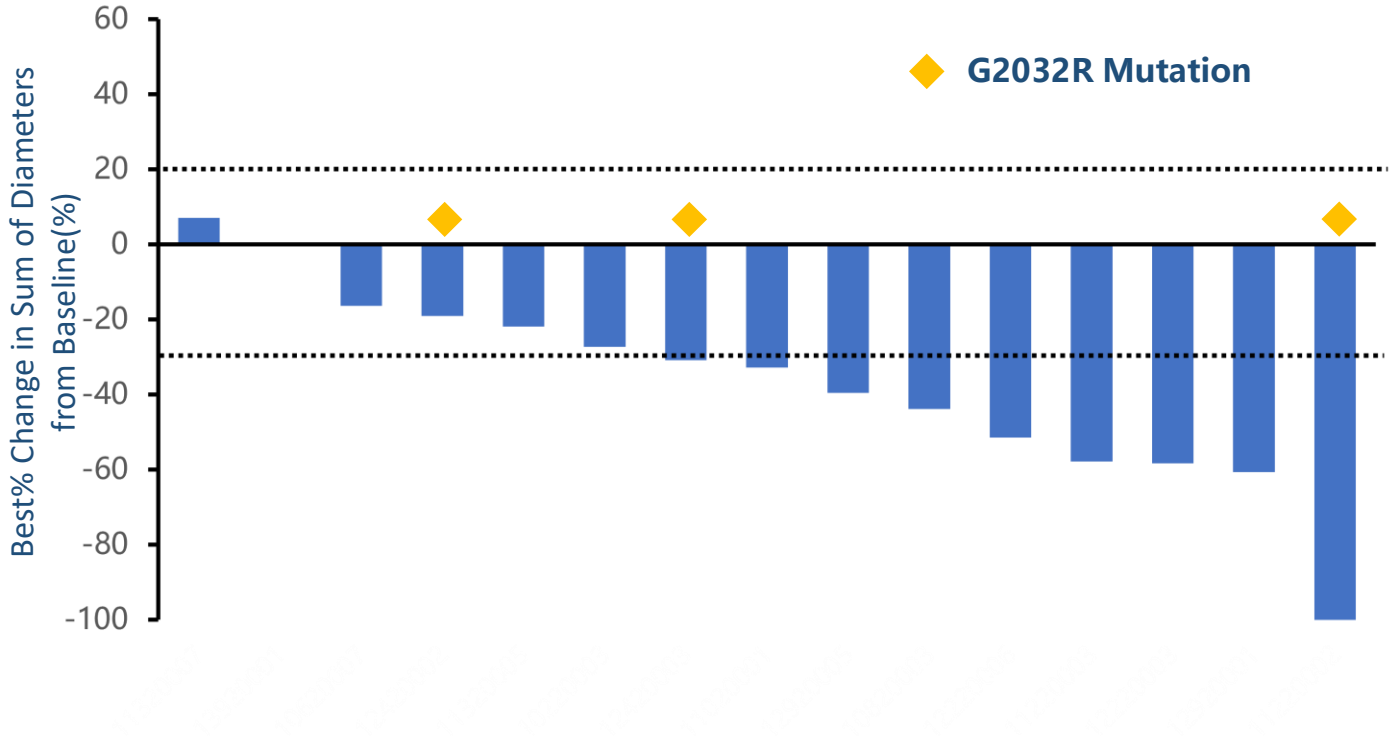


43 W

- 57-year-old female ROS1+ NSCLC, crizotinib treatment-naïve, taletrectinib 600 mg QD
- Showed a partial response on week 7 after investigator evaluation
- Remains on treatment (10 months)

Data cutoff date: June 16, 2021

Efficacy in Crizotinib Failure Patients

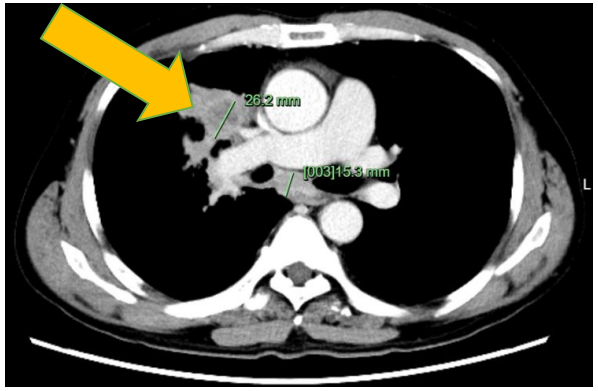


	Taletrectinib (n=16)
ORR, % (95%CI)	43.8 [19.8, 70.1]
DCR, % (95%CI)	75.0 [47.6, 92.7]
PR n (%)	7 (43.8)
SD n (%)	5 (31.3)
PD n (%)	3 (18.8)
NE* n (%)	1 (6.3)
TTR (month), Median (95%CI)	2.1 [1.38, 4.11]
DOR (month), (Min, Max)	1.3+, 2.9+

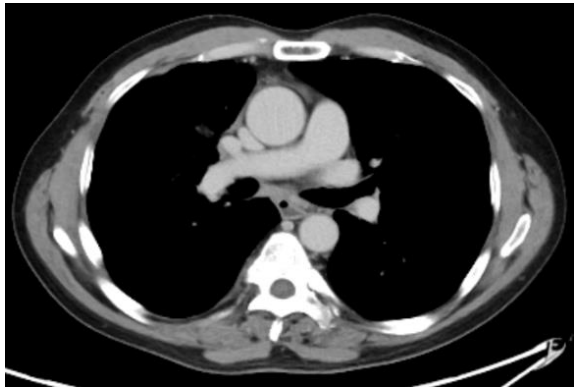
* Waterfall plot doesn't include the NE

Data cutoff date: June 16, 2021

Case: Crizotinib Failure Patient



Baseline



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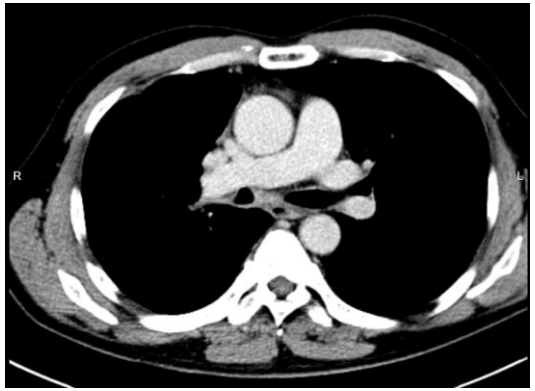
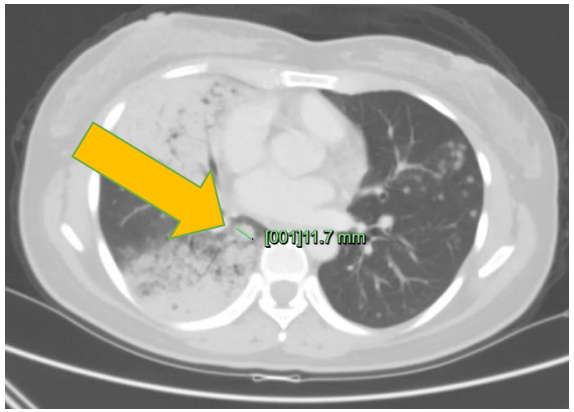


19 W

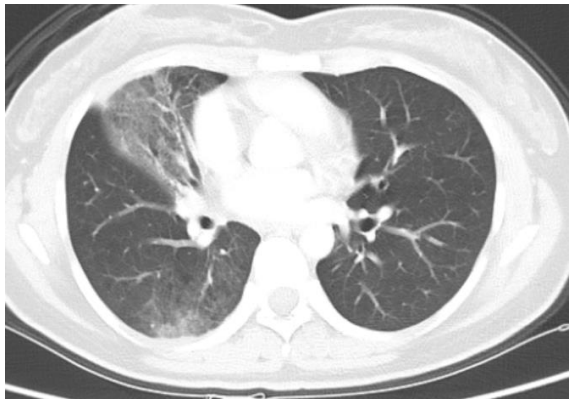
- 47-year-old male ROS1 + NSCLC
- Crizotinib failure
- Showed a partial response on week 13 after investigator evaluation
- Remains on treatment (8 months)

Data cutoff date: June 16, 2021

Case: Crizotinib Failure Patient with ROS1 G2032R mutation



Baseline



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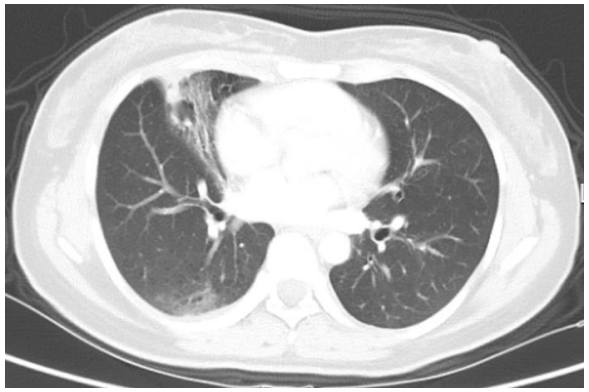
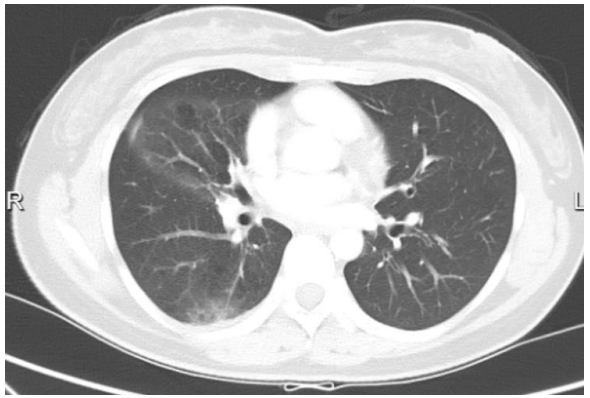


13 W

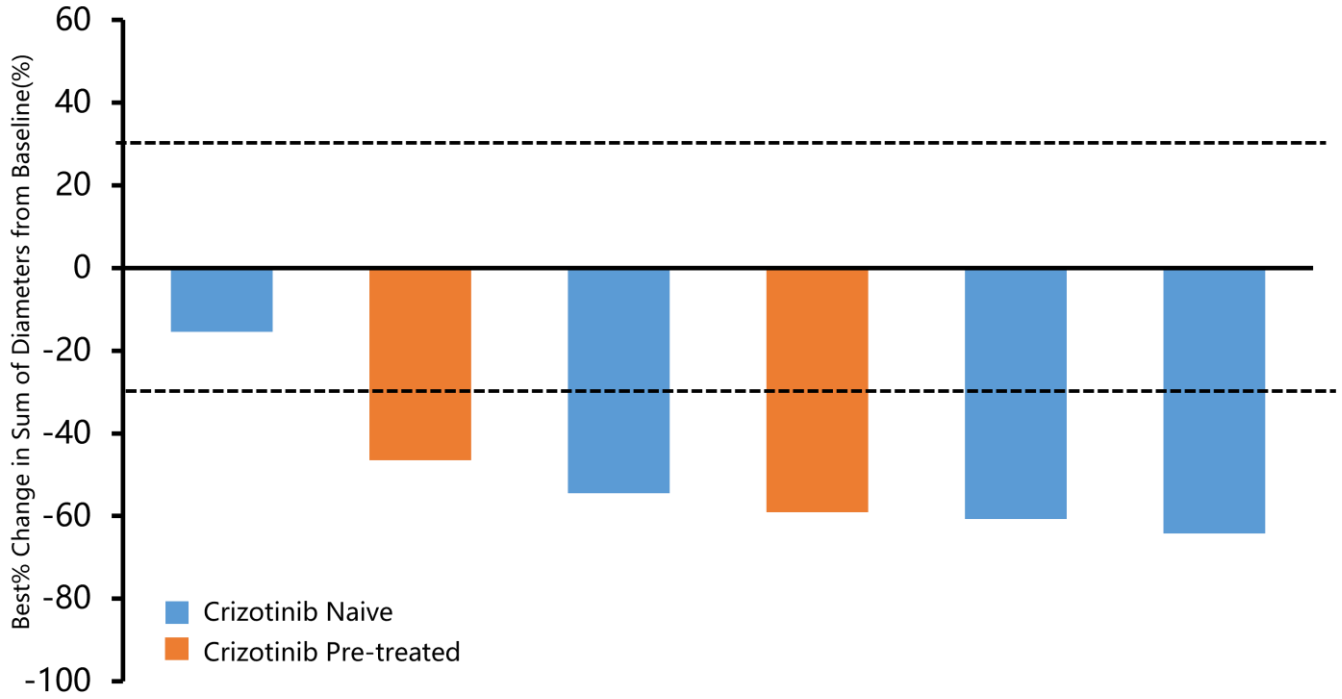


19 W

- 38-year-old female ROS1 + NSCLC
- Two prior systematic regiment: chemotherapy and crizotinib
- Acquired ROS1 G2032R resistant mutation post-crizotinib therapy
- Received taletrectinib 600 mg QD
- Achieved PR by investigator evaluation at week 7
- Remains on treatment (7 months)

Data cutoff date: June 16, 2021

Efficacy in Patients with Brain Metastases

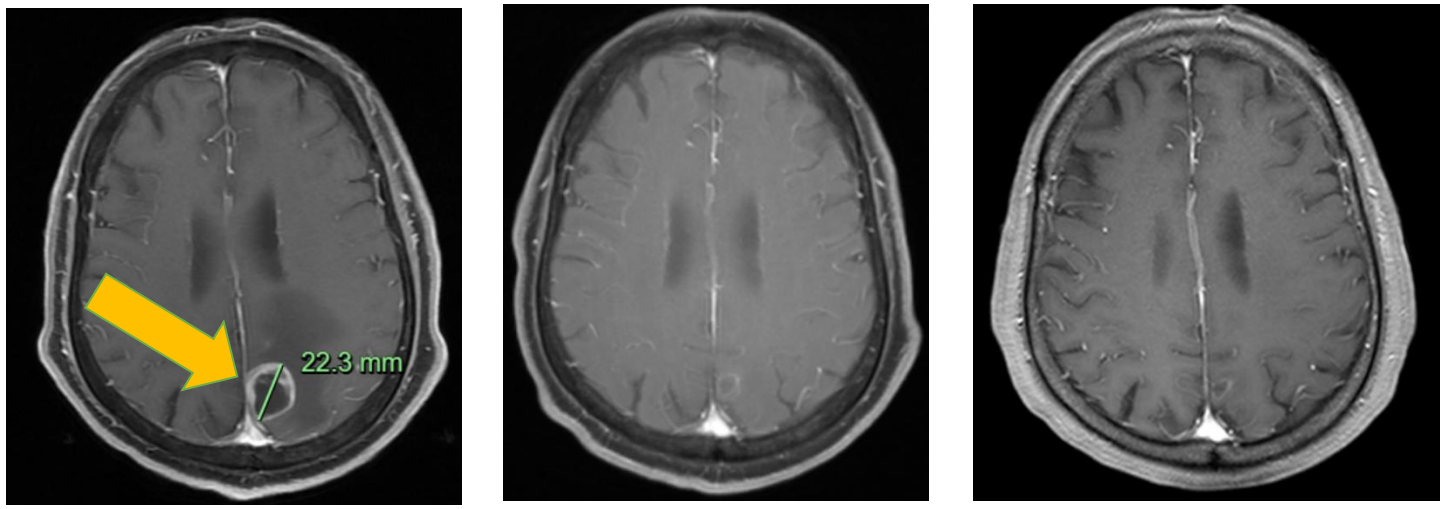


	Taletrectinib (n=6*)
iORR, % (95% CI)	83.3 [35.9, 99.6]
iDOR, %(95% CI)	100.0 [54.1, 100.0]
PR n (%)	5 (83.3)
SD n (%)	1 (16.7)

* Six patients have measurable brain lesions according to RANO-BM.

Data cutoff date: June 16, 2021

Case: Patient with Brain Metastases



Baseline 7 W 13 W

- 71-year-old female ROS1 + NSCLC, brain metastases
- Received taletrectinib 600 mg QD
- Achieved PR by investigator evaluation at week 7
- Remains on treatment (5 months)

Data cutoff date: June 16, 2021

Safety Profile

TRAE, N(%)	All Grade	≥ Grade 3
Any TRAE	56 (81.2%)	8 (11.6%)
Diarrhea	33 (47.8%)	0
Nausea	22 (31.9%)	0
Vomiting	23 (33.3%)	0
Aspartate Aminotransferase Increase	44 (63.8%)	7 (10.1%)
Alanine Aminotransferase Increase	42 (60.9%)	6 (8.7%)
Anemia	13 (18.8%)	0
Neutropenia	10 (14.5%)	1 (1.4%)
Prolonged QTc	9 (13.0%)	0
Dizziness	7 (10.1%)	0

Data cutoff date: June 16, 2021

Summary: Taletrectinib Is A Best-in-Class Next-Generation ROS1 Inhibitor

- The ORRs in ROS1 TKI naïve and crizotinib failure patients are 90.5% (19/21) and 43.8% (7/16), respectively
- Effective against crizotinib resistance mutations including G2032R mutation
- Effective in brain metastatic patients: intracranial ORR 83.3% (5/6)
- Shows good safety profile with few CNS adverse events