Efficacy and Safety of Pralsetinib in Chinese Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer

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Background

- RET fusions have been reported as oncogenic drivers in approximately 1% to 2% of non-small cell lung cancer (NSCLC) patients[1-4].
- Pralsetinib is a highly potent and selective RET kinase inhibitor targeting oncogenic RET alterations, including RET fusions[5-6].
- FDA granted accelerated approval to pralsetinib for the treatment of adults with metastatic RET fusion+ NSCLC and patients with RET-altered thyroid cancers in 2020*.
- NMPA approved pralsetinib for treatment of adult with locally advanced or metastatic RET fusion+ NSCLC patients who have previously received platinum-based chemotherapy in 2021.
- A global phase I/II ARROW study (BLU-667-1101; NCT03037385) has demonstrated broad and durable antitumor activity of pralsetinib in a variety of advanced RET-altered solid tumors, including RET fusion+ NSCLC.
- Previously the primary analysis (data cutoff: May 22, 2020) has demonstrated that pralsetinib provides rapid and durable tumor responses and bears the well-tolerated safety profile in a cohort of Chinese patients with RET fusion+ NSCLC after platinum-based chemotherapy at WCLC 2020
- Here we present the main efficacy and safety results of pralsetinib in treatment naïve Chinese patients with advanced RET fusion+ NSCLC and corresponding updates for pretreatment cohort.

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ARROW study design

N~585

Phase I Dose Escalation (complete)

N=62

BOIN design
- Advance MTC, NSCLC or other solid tumor 30-600 mg (PO QD or BID)
- RET alteration required at doses 120mg QD

400 mg QD

Phase II Dose Expansion (ongoing)

G1	N~80	RET fusion NSCLC, prior platinum
G2	N~200	**RET fusion NSCLC, platinum naive**
G3	N~65	MTC, prior cabozantinib and/or vandetanib
G4	N~40	MTC, no cabozantinib or vandetanib
G5	N~100	Other RET fusion solid tumors
G6	N~20	RET-altered tumors, prior selective RET TKI
G7	N~20	Other RET-mutated solid tumors
G8	N~30*	**RET fusion NSCLC, prior platinum extension cohort（only in China）**
G9	N~30	MTC, no prior systemic therapy (except chemotherapy) extension cohort （only in China）

Endpoints

Primary:

ORR

Safety profile

Secondary:

DOR

CBR

DCR

PFS

OS

*As of 12 April 2021, 68 Chinese patients with RET fusion+ NSCLC (37 previously treated with platinum-based chemotherapies [G8] and 31 systemic treatment-naïve [G2]) received pralsetinib.
Data cut-off: April 12, 2021

Demographics and Baseline Characteristics

Characteristic	Prior platinum treatment* (n=37)	No prior systemic treatment (n=31)
Age, years, median (range)	54 (26,77)	57.0 (30,79)
Sex, male, n (%)	17 (46)	11 (35.5%)
Race, Asian, n (%)	37 (100)	31 (100%)
ECOG performance status, n (%)		
0	2 (5.4%)	1 (3.2%)
1	35 (94.6%)	30 (96.8%)
Histology type, n (%)		
Adenocarcinoma	36 (97.3%)	31 (100%)
Other	1 (2.7%)	0
Metastatic disease, n (%)		
CNS metastasis	15 (40.5%)	8 (25.8%)
Tumour stage at screening, n (%)		
Stage IIIB	0	1 (3.2%)
Stage IIIC	0	1 (3.2%)
Stage IVA	8 (21.6%)	12 (38.7%)
Stage IVB	29 (78.4%)	17 (54.8%)
Smoking history, n (%)		
Never smoked	25 (67.6%)	21 (67.7%)
Former	11 (29.7%)	10 (32.3%)
Current	1 (2.7%)	0
RET – Fusion Partner, n (%)		
KIF5B	23 (62.2%)	22 (71.0%)
CCDC6	7 (18.9%)	5 (16.1%)
Other	7 (18.9%)	4 (12.9)

*About half (49%) had received ≥3 prior systemic regimens

CNS, Central Nervous System;
ECOG, Eastern Cooperative Oncology Group

Data cut-off: April 12, 2021

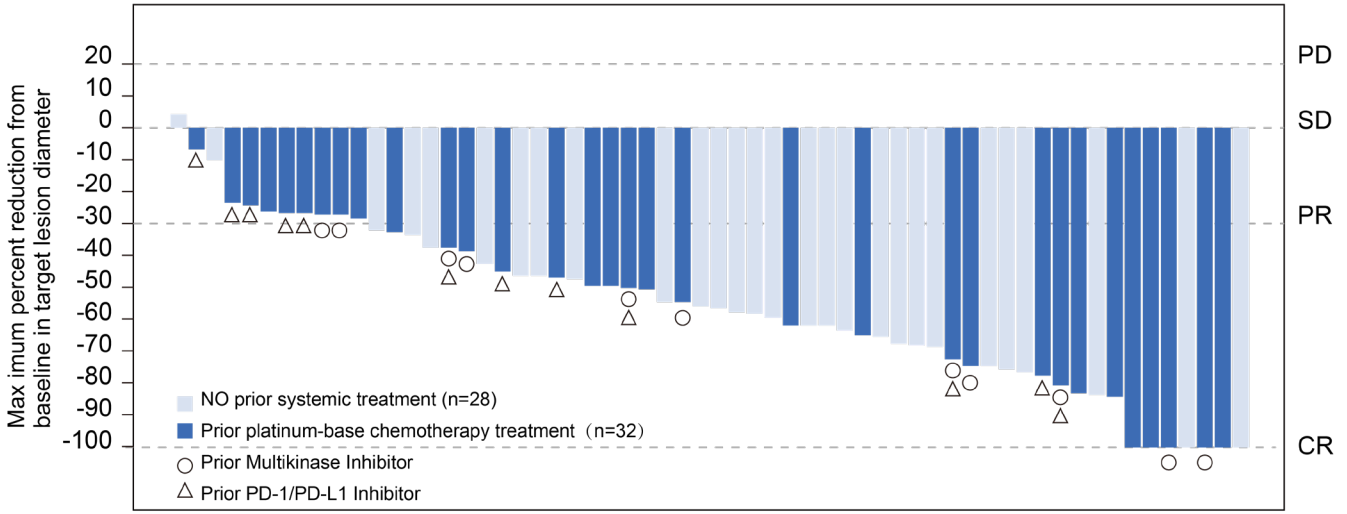
Efficacy Summary

Pralsetinib demonstrated deep response in RET-fusion positive NSCLC patients regardless of prior therapies

Response Summary of Patients with Measurable Disease at Baseline per BICR

Outcome	Prior platinum-based chemotherapy treatment (n=33)	No prior systemic treatment (n=30)
Confirmed ORR, n(%) [95% CI]	22 (66.7) [48.2-82.0]	24 (80.0) [61.4-92.3]
CR	1 (3.0)	2 (6.7)
PR	21 (63.6)	22 (73.3)
SD	9 (27.3)	2 (6.7)
PD	1 (3.0)	2 (6.7)
NE	1 (3.0)	2 (6.7)
***CBR, % (95% CI)**	84.8 (68.1-94.9)	86.7 (69.3-96.2)
DCR, % (95% CI)	93.9 (79.8-99.3)	86.7 (69.3-96.2)

Maximum Tumor Shrinkage in the Target Lesion (N= 60)**



* *60 patients have measurable disease at baseline and evaluable post-baseline response assessment per RECIST v1.1 per BICR. 3 patients did not have evaluable post-baseline disease response assessment per RECIST v1.1 per BICR.

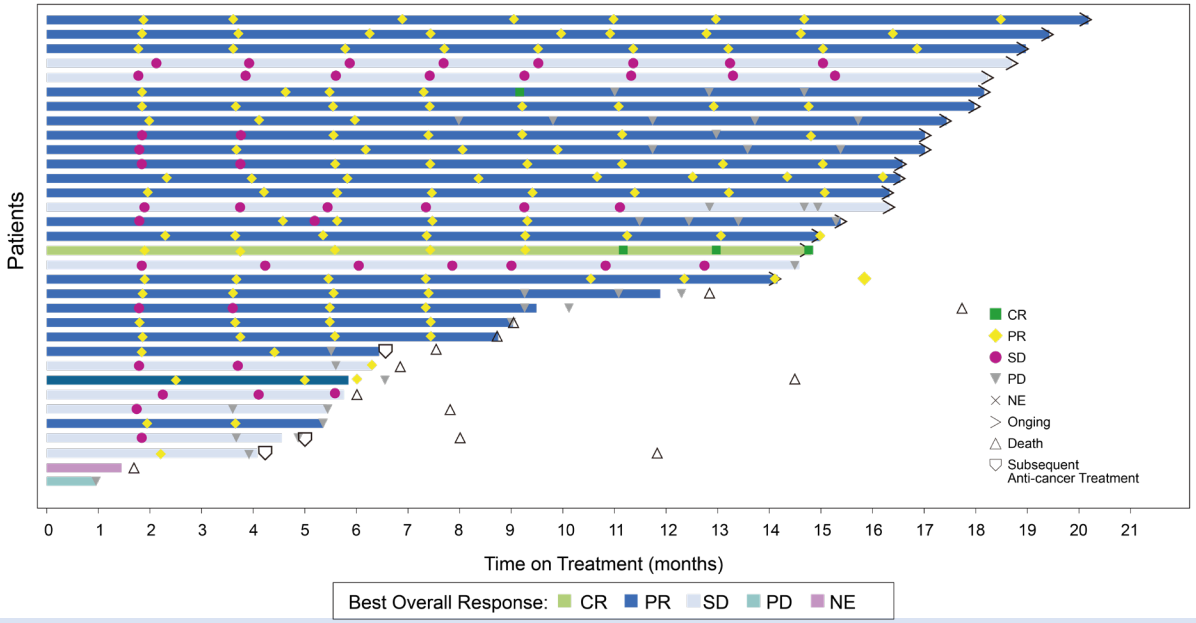
*Confirmed CR or PR or SD>=16 Weeks
BICR, Blinded Independent Centralized Review; ORR, objective response rate; CI, confidence interval; CBR, clinical benefit rate; DCR, disease control rate;

Data cut-off: April 12, 2021

Efficacy Summary

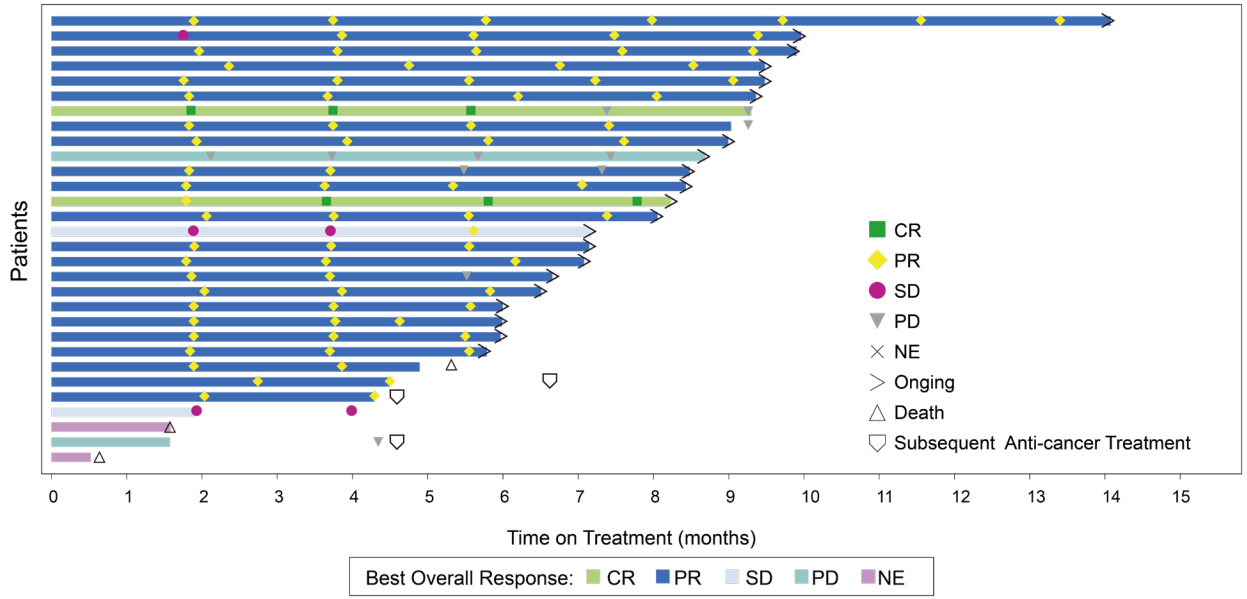
Pralsetinib induces rapid and durable response in RET Fusion+ advanced NSCLC

G8 (Prior platinum-based chemotherapy treated NSCLC): Duration of Treatment and Response (N = 33)



- The median treatment duration was 14.65 (range: 0.9-20.0) months as of the data cut-off.
- 68.18% (15/22) of responding patients remain on treatment as of the data cut-off.
- The median time to first response among the 22 patients with measurable disease at baseline and a confirmed response was 1.89 (1.7-5.6) months.
- Median duration of response (DOR) was 8.6 (6.9, -)months; 6-month DOR rate was 77.3 (95% CI: 59.8 - 94.8)and 9-month DOR was 50.0 (29.1 – 70.9) as of the data cut-off.

G2 (First-line NSCLC): Duration of Treatment and Response (N = 30)



- The median treatment duration was 7.13 (range: 0.5-14.0) months as of the data cut-off.
- 79.17% (19/24) of responding patients remain on treatment as of the data cut-off.
- The median time to first response among the 24 patients with measurable disease at baseline and a confirmed response was 1.87 (1.7-3.8) months.
- Median duration of response (DOR) was 7.5 (7.5, -) months; 6-month DOR rate was 76.7 (95% CI: 55.6 - 97.8) and 9-month DOR was 38.3 (0.0 – 92.5) as of the data cut-off.

Data cut-off: April 12, 2021

Safety Profile

Pralsetinib safety profile in Chinese NSCLC patients is manageable

Treatment-Related AEs in ≥ 20% of Patients

Preferred Term	Overall (N=68)	
	Any grade, n (%)	Grade 3-4, n (%)
Aspartate aminotransferase increased	55 (80.9)	3 (4.4)
Neutrophil count decreased	54 (79.4)	23 (33.8)
Anaemia	46 (67.6)	22 (32.4)
White blood cell count decreased	41 (60.3)	9 (13.2)
Alanine aminotransferase increased	39 (57.4)	3 (4.4)
Blood creatine phosphokinase increased	31 (45.6)	12 (17.6)
Hypertension	24 (35.3)	8 (11.8)
Platelet count decreased	21 (30.9)	6 (8.8)
Blood creatinine increased	20 (29.4)	1 (1.5)
Bilirubin conjugated increased	19 (27.9)	0
Constipation	19 (27.9)	0
Gamma-glutamyltransferase increased	19 (27.9)	4 (5.9)
Blood alkaline phosphatase increased	18 (26.5)	2 (2.9)
Malaise	17 (25.0)	0
Blood bilirubin increased	16 (23.5)	1 (1.5)
Hypocalcaemia	14 (20.6)	1 (1.5)

- All 68 patients experienced at least one treatment emergent adverse event (TEAE), among whom 67 (98.5%) experienced pralsetinib-related AEs.
- 10.3% (7/68) patients discontinued from treatment due to pralsetinib related TEAEs.
- 2.9%(2/68) patients death due to pralsetinib related TEAEs.

Additional grade 3-4 treatment-related AEs (≥5%): Lymphocyte count decreased (5.9%%)、 Leukopenia (5.9%)、 Hypophosphataemia (11.8%).

Data cut-off: April 12, 2021

Conclusions

- Pralsetinib is a promising targeted therapy with rapid and deep clinical activity in RET fusion+ NSCLC Chinese patients regardless of prior therapies.
- Pralsetinib safety profile in Chinese patients is manageable, with no new safety signals detected.
- Efficacy results are consistent with previously reported data from the global population in the ARROW trial.
- Pralsetinib shows a favorable benefit-risk profile, offering a transformative medicine to Chinese RET-fusion driven advanced NSCLC patients.

Data cut-off: April 12, 2021

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