Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced *RET* Fusion+ Non-Small Cell Lung Cancer (NSCLC)

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Background and methods

- The advent of targeted therapies for molecularly defined subtypes has revolutionized treatment of NSCLC[1]
- Oncogenic fusions in the proto-oncogene *RET*, which encodes a receptor tyrosine kinase, are present in 1%–2% of NSCLC[2–5]
- Pralsetinib is an investigational, highly potent, oral, selective RET kinase inhibitor that targets oncogenic *RET* alterations, including *RET* fusions[6,7]
- ARROW (NCT0307385) is an ongoing global phase 1/2 registrational study of pralsetinib in patients with advanced solid tumors and *RET* alterations, including *RET* fusion+ NSCLC

ARROW study design

Eligibility criteria
- Age ≥18 years
- Unresectable locally advanced or metastatic solid tumor
- Documented *RET* fusion or mutation (local testing)
- Measurable disease per RECIST v1.1
- ECOG PS 0–1

Phase 1 dose escalation (completed)
Phase 2 dose determined:
400 mg once daily (QD)

Phase 2 dose expansion (ongoing)
Groups defined by disease type and prior therapy, treated at phase 2 dose

1º endpoints:
- ORR (BICR per RECIST v1.1)
- Safety

Key 2º endpoints:
- DOR
- CBR*
- DCR

*Complete or partial response or stable disease of ≥16 weeks; BICR, Blinded Independent Centralized Review; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, overall response rate; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection.

Results

Patient disposition / analysis populations

Safety population, N=354
Patients[a] who initiated pralsetinib at the RP2D of 400 mg QD

RET fusion+ NSCLC n=179

Other *RET*-altered solid tumors n=175

RET fusion+ NSCLC intent-to-treat efficacy population, n=132
Initiated pralsetinib by July 11, 2019[b]

16 not response evaluable
1 alternate driver mutation
1 insufficient evidence of RET fusion
2 incomplete baseline imaging
7 without measurable disease per BICR
5 without post-treatment disease assessment[c]

RET fusion+ NSCLC response-evaluable population, n=116
Measurable disease by BICR, ≥1 evaluable post-baseline scan, no major protocol violations

Data cut-off date was November 18, 2019

[a]Includes all patients enrolled in dose escalation (phase 1) and dose expansion (phase 2) who initiated 400 mg once daily pralsetinib with any tumor type. [b]To provide sufficient time for ≥2 post-baseline scans. [c]3 patients died due to unrelated AE, 1 withdrew consent, 1 withdrew due to symptomatic deterioration; AE, adverse event; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose

Baseline characteristics (efficacy population)

	All NSCLC (n=132)*	Prior platinum (n=92)	Treatment naïve (n=29)
Median age (range), years	60 (28–87)	60 (28–85)	65 (30–87)
Male	48%	50%	48%
Race			
White	57%	53%	59%
Asian	33%	35%	34%
Other/unknown	11%	12%	7%
Smoking history			
Current/former	36%	35%	45%
Never	62%	63%	52%
ECOG PS			
0	38%	37%	38%
1	58%	58%	59%
2†	5%	5%	3%
Brain metastases‡	42%	41%	41%
***RET* fusion partner**			
KIF5B	71%	74%	69%
CCDC6	17%	17%	10%
Other§	2%	2%	0%
Unknown‖	11%	7%	21%
Prior therapy type			
Chemotherapy	71%	100%	0%
PD-(L)1 inhibitor	36%	45%	0%
Chemotherapy + PD-(L)1 inhibitor	31%	45%	0%

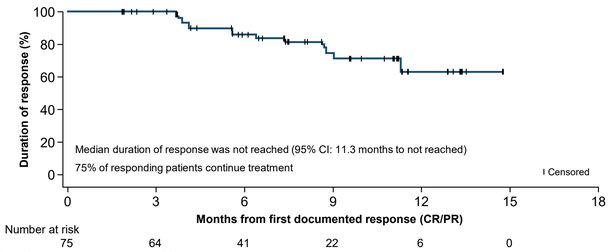
*Includes 11 patients with prior treatment other than platinum. †ECOG PS of 2 was permitted prior to a protocol amendment.
‡History of or current. §EML4 or DOCK1. ‖Fusion present but specific partner unknown
DOK1, dedicator of cytokinesis 1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EML4, echinoderm microtubule-associated protein-like 4; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death/programmed cell death ligand-1

Efficacy summary (Blinded Independent Centralized Review)

	Intent-to-treat efficacy population			Response-evaluable population		
	All NSCLC (n=132)*	Prior platinum (n=92)	Treatment naïve (n=29)	All NSCLC (n=116)†	Prior platinum (n=80)	Treatment naïve (n=26)
Overall response rate	**58%‡**	**55%‡**	**66%**	**65%‡**	**61%‡**	**73%**
95% CI	49–67%	45–66%	46-82%	55–73%	50–72%	52–88%
Best overall response						
CR	6%	5%	10%	6%	5%	12%
PR	52%‡	50%‡	55%	59%‡	56%‡	62%
SD	30%	35%	14%	28%	34%	15%
PD	8%	4%	17%	7%	5%	12%
NE	5%	5%	3%	0%	0%	0%
Disease control rate (95% CI)	88% (81–93)	90% (82–85)	79% (60–92)	93% (87–97)	95% (88–99)	88% (70–98)
Clinical benefit rate (95% CI)§	68% (60–76)	70% (59–79)	66% (46–82)	72% (62–80)	71% (60–81)	73% (52–88)

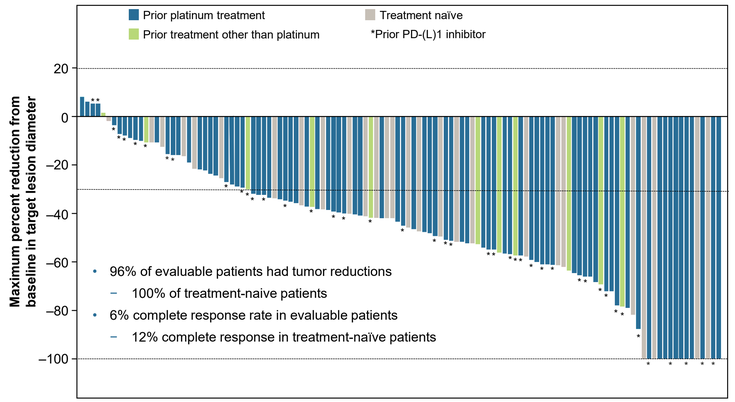
*Includes 11 patients with prior treatment other than platinum. †Includes 10 patients with prior treatment other than platinum. ‡ Includes 2 patients still on treatment with PRs pending confirmation. §CR or PR or SD of ≥16 weeks; CI, confidence interval; CR, complete response; NE, not evaluable; NSCLC, non-small-cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease

Duration of response (Blinded Independent Centralized Review)



CI, confidence interval; CR, complete response; PR, partial response

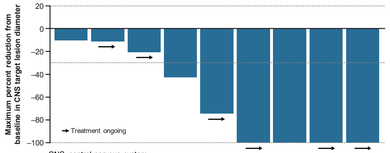
Tumor shrinkage (Blinded Independent Centralized Review)



PD-(L)1, programmed cell death/programmed cell death ligand-1

CNS activity (Blinded Independent Centralized Review)

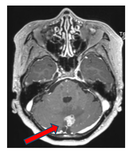
- Intracranial overall response rate in 9 patients with measurable CNS metastases at baseline was 56%
- Three patients (33%) with intracranial complete response

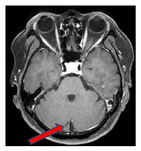



Baseline


After 8 months

71 year-old female previous smoker with *RET-CCDC6* fusion-positive metastatic NSCLC. No response and disease progression at 6 months on prior pembrolizumab monotherapy. Metastatic disease in brain, bone, adrenal gland, and lymph nodes at study entry. Complete resolution of a 12.6 mm brain target lesion observed at 1.6 months on pralsetinib. As of May 1, 2020, continues pralsetinib for 10+ months with ongoing overall partial response. (Courtesy of G. Curigliano)


Baseline


After 16 months

56 year-old female never smoker with *RET-KIF5B* fusion-positive NSCLC. Previously received adjuvant therapy with carboplatin/paclitaxel. Metastatic disease in brain, pleura, lymph nodes at study entry. 20 mm brain target lesion with rapid shrinkage and complete resolution by 7.5 months on pralsetinib As of May 1, 2020, continues pralsetinib for 16+ months with ongoing overall partial response. (Courtesy of D.W Kim)

Safety

- Pralsetinib 400 mg once daily treatment was well-tolerated with treatment duration between 0.1–22.3 months and median (range) dose intensity of 92% (18–100)
- Only 4% of patients discontinued due to treatment-related adverse events

Treatment-related adverse events in ≥10% of patients (N=354, all tumor types)

AE preferred term	All patients (n=354)	
	Any grade	Grade ≥3
AST increased	31%	2%
Anemia	22%	8%
ALT increased	21%	1%
Constipation	21%	1%
Hypertension	20%	10%
Neutropenia	19%	10%
Diarrhea	14%	1%
White blood cell count decreased	14%	3%
Dysgeusia	13%	0%
Blood creatinine increased	12%	0%
Fatigue	12%	1%
Neutrophil count decreased	12%	4%
Dry mouth	11%	0%
Hyperphosphatemia	11%	<1%
Asthenia	10%	1%

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Conclusions

- In this pivotal phase 1/2 study, once daily oral treatment of pralsetinib provides rapid and durable tumor responses
- 65% overall response rate, including 6% complete responses, in all response evaluable patients with *RET* fusion+ NSCLC
- Antitumor activity demonstrated regardless of *RET* fusion genotype or prior therapies
- Pralsetinib has robust intracranial activity
- Pralsetinib is well-tolerated across tumor types, with predominantly grade 1–2 treatment-related adverse events
- Pralsetinib has the potential to change standard of care for the treatment of patients with *RET* fusion+ NSCLC

References

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