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Phase II study of brigatinib in patients with tyrosine kinase inhibitor-naïve ROS1-rearranged advanced non-small cell lung cancer: Barossa cohort 1.

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Background

- The ROS1 protein is a proto-oncogene receptor tyrosine kinase involved in proliferation and differentiation of cells.
- ROS1 rearrangements occur in approximately 1% of patients with non-small cell lung cancer (NSCLC) and other solid tumors.
- Crizotinib is the first drug approved for the treatment of ROS1 fusion-positive NSCLC.
- Brigatinib is a next-generation tyrosine kinase inhibitor targeting ALK and ROS1.
- Barossa is a multicenter, phase II basket study of brigatinib in patients with ROS1-positive solid tumors.

Methods

Study design

- Unblinded, single arm, multicenter basket trial

- **Advanced solid tumor**
- **ROS1 fusion positive**
- **20 years or older**
- **ECOG PS 0-2**
- **Measurable lesion according to RECIST1.1**

Enroll

Brigatinib 180 mg/day, once daily
(lead-in: 90 mg/day for 7 days)
28 days cycle
Until PD or unacceptable toxicities

Cohort 1: Crizotinib-naïve ROS1+ NSCLC (n=28)
Cohort 2: Crizotinib-treated ROS1+ NSCLC (n=19)
Cohort 3: ROS1+ solid tumor other than lung cancer (n≤5)

Primary endpoint: Overall response rate (ORR)
Secondary endpoints: Overall survival (OS), Progression-free survival (PFS), intracranial ORR, intracranial PFS, time to intracranial progression, safety

- The sample size was set at 28 subjects, with a one-sided alpha of 0.05, a beta of 0.2, and threshold and expected values for the primary endpoints of 50% and 75% in the cohort 1.
- Clinical trial information: JapicCTI-194851

Patient eligibility

Key inclusion criteria (cohort 1):
- Advanced or recurrent NSCLC with ROS1 fusion which was determined by a validated RT/PCR or NGS using tissues or blood
- ROS1-tyrosine kinase inhibitor (TKI)-naïve
- Age ≥ 20 years
- ECOG performance status (PS) of 0-2
- Adequate organ function
- Written informed consent

Key exclusion criteria
- ALK fusion gene positive
- Symptomatic brain metastases
- Interstitial fibrosis or interstitial lung disease

Results

- Twenty-eight patients were enrolled from 9 institutions between Sep 2019 and May 2021.
- Data cutoff: 31 Nov 2021
- Median follow-up time: 9.3 months

Patient characteristics (n=28)

		No.	(%)
Age (years)	Median (range)	65	(38-81)
Gender	Male	10	(36)
	Female	18	(64)
PS	0-1	28	(100)
	2	0	(0)
Smoking status	Never smoker	16	(57)
	Current / ex-smoker	12	(43)
Histological type	Adenocarcinoma	27	(96)
	NSCLC-NOS	1	(4)
Brain metastasis		8	(29)
Prior cytotoxic chemotherapy		6	(21)
Prior surgery		5	(18)

Treatment-related adverse events

No. (%)	G1	G2	G3	G4
Hypertension	0	4 (14)	6 (21)	0
Diarrhea	6 (21)	1 (4)	0	0
Constipation	4 (14)	0	0	0
Mucositis oral	4 (14)	1 (4)	0	0
Anorexia	4 (14)	0	1 (4)	0
Vomiting	3 (11)	1 (4)	0	0
Dry skin	5 (18)	1 (4)	0	0
Fever	2 (7)	1 (4)	0	0
Headache	3 (11)	0	0	0
Muscle pain	3 (11)	0	0	0
Pneumonitis	0	1 (4)	3 (11)	0
CPK increased	5 (18)	7 (25)	8 (29)	0
AST increased	12 (43)	0	2 (7)	0
ALT increased	8 (29)	1 (4)	2 (7)	1 (4)
Amylase increased	6 (21)	3 (11)	0	0
Lipase increased	2 (7)	8 (29)	0	0
ALP increased	6 (21)	1 (4)	0	0
GGT increased	1 (4)	0	2 (7)	0

- No grade 5 treatment-related adverse event was found.
- Grade 3 of pneumonitis was developed on day 4, 20, and 51 in 3 patients. Those 3 patients terminated the study treatment.

Response

PR	SD	PD	NE
19	3	5	1

ORR: 67.9% (90%CI, 50.6-82.1)
(95%CI, 47.6-84.1)
DCR: 78.6% (95%CI, 50.9-91.7)

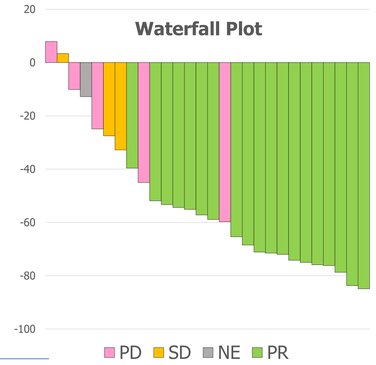
- The lower limit of 90% CI of ORR was significantly higher than the threshold value of 50% (p=0.0436).

Treatment delivery

	No. (%)
Median duration of treatment (days) (range)	249 (6-787)
Dose reduction	12 (43)
-1 dose level (120 mg/day)	6
-2 dose level (90 mg/day)	4
-3 dose level (60 mg/day)	2
Treatment interruption	23 (82)
Median duration of interruption (days) (range)	13 (1-124)
Treatment termination	14 (50)

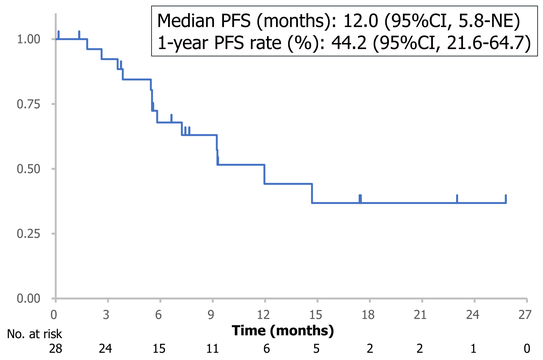
Reasons for treatment termination

	No. (%)
Progressive disease	9 (32)
Toxicities (pneumonitis)	3 (27)
Others (investigators' judgment; ALT increased G3, CEA elevation)	2 (18)

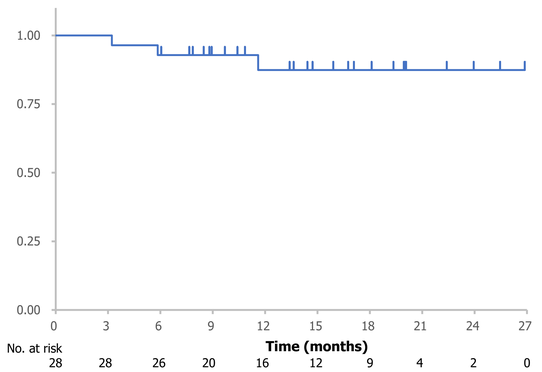


PFS and OS

PFS assessed by independent review



OS



Conclusions

- Brigatinib demonstrated encouraging antitumor activity in patients with TKI-naïve ROS1-rearranged advanced NSCLC.
- The safety profile of brigatinib was consistent with previous studies.

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