990P Osimertinib for RT-naïve CNS Metastasis of EGFR mutation positive NSCLC: phase II OCEAN Study (LOGIK 1603/WJOG 9116L), Part of the first-line cohort.

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Background

- Non-small cell lung cancer (NSCLC) with *EGFR* mutations exhibits a higher incidence (15–30%) of central nervous system (CNS) metastasis[1-2].
- Although radiotherapy (RT) is a standard treatment for CNS metastasis, it delays the start of systemic chemotherapy, and whole brain RT carries a risk of cognitive dysfunction[3, 4].
- Osimertinib is an irreversible EGFR-TKI that selectively inhibits both *EGFR*-sensitizing and T790M mutation.
- Osimertinib achieved greater penetration into the brain in a preclinical model[5].
- The aim of the study was to assess osimertinib for patients with RT-naïve CNS metastasis of *EGFR* mutations positive NSCLC.
- We previously reported the results of *T790M* cohort[6], here we show the results of first-line cohort.

Methods

Study design

Single-arm phase II trial sponsored by AstraZeneca.

- **≥ 20 years old**
- **ECOG PS 0–2**
- **NSCLC**
- ***EGFR* Del19 or L858R (+)**
- **brain metastasis (BM) ≥5 mm long axis**
- **No prior RT for BM**

→ ***T790M* cohort (n = 40)**
✓Pretreated with EGFR-TKI
✓*EGFR* T790M-positive

→ **First-line cohort (n = 25)**
✓Not treated with EGFR-TKI
✓Stage IV / postoperative relapse

→ **Osimertinib** 80 mg once daily → until PD, death, withdrawal of consent

- Brain MRI and chest/abdomen CT were performed every 6 weeks in the first year and every 3 months thereafter.

Primary endpoint

- Response rate of brain metastasis (**BMRR**) assessed by **PAREXEL criteria**[7]

Cohort	Threshold value	Expected value	one sided α	power	n
T790M	50%	70%	0.05	0.8	40
First-line	**55%**	**80%**	**0.05**	**0.8**	**25**

※We set a threshold and an expected value at 50% and 70%, respectively, on the basis of the AURA trial (BMRR 61%, 95% CI = 52-70%)[8] in *T790M* cohort. In the first line cohort, we set a threshold and an expected value at 55% and 80%, respectively.

Secondary endpoint

- BMRR (RECIST), PFS of BM, ORR, safety, PFS, OS
- BMRR (PAREXEL criteria), PFS, OS in the first- line cohort

Exploratory endpoints

- plasma concentration (in a steady state, day22) of osimertinib
- CSF penetration of osimertinib
- *EGFR* mutation analysis in plasma

PAREXEL criteria

- A tool for assessing BM used in several recent trials.
- BM response is assessed more closely than the RECIST criteria.

criteria	Slice Thickness of MRI or CT	Target lesion		non-target lesion
		Size	maximum number	Size
PAREXEL	**≤3mm (MRI)**	**≥5mm**	**5**	**<5mm**
RECIST	≤5mm (CT or MRI)	≥10mm	2 (one organ)	<10mm

Key exclusion criteria

- Symptomatic BM requiring radiotherapy or surgical resection.
- BM requiring emergent therapy.
- Prior treatment with anti-PD-1/PD-L1/CD137/CTLA-4 antibody.
- History of interstitial lung disease (ILD), drug-induced ILD, and radiation pneumonitis requiring steroid.

Conclusions

- **The OCEAN study met the endpoint in the first-line cohort in addition to *T790M* cohort.**
- **Osimertinib can be a treatment option for patients harboring EGFR mutations with RT-naive CNS metastasis.**

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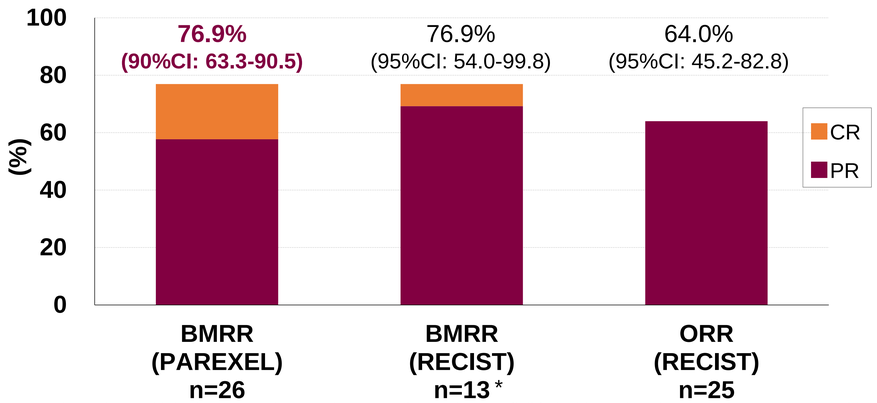
Results

Response

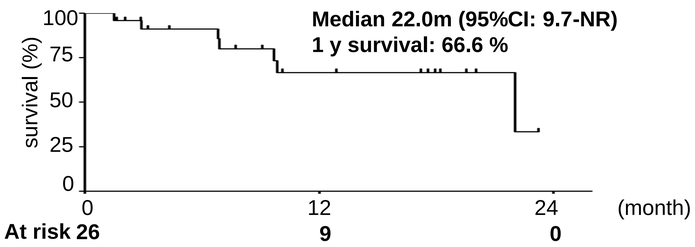


* The patients with brain metastasis more than 5 mm long axis was eligible in this study. Whereas only 13 patients could be evaluated for the RECIST criteria which require the lesion a size of at least 1 cm, because of insufficient size.

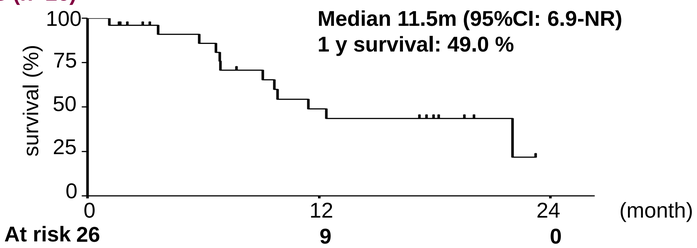
Patients Characteristics

		n=26
Age, years	Median (Range)	72 (55 – 82)
Gender	Male / Female	5 (19.2%) / 21 (80.8%)
Stage	IV / Postoperative	19 (73.1%) / 7 (26.9%)
ECOG PS	0 / 1 / 2	9 (34.6%) / 15 (57.7%) / 2 (7.7%)
Histologic type	Adenocarcinoma/other	24 (92.3%) / 2 (7.7%)
Smoking history	Current or Former / Never	9 (34.6%) / 17 (65.5%)
EGFR mutation type	Del 19 / L858R	15 (57.7%) / 11 (42.3%)
CNS lesion	Single / multiple	6 (23.1%) / 20 (76.9%)
Symptomatic BM	Present / Absent / ND	4 (15.4%) / 21 (80.8%) / 1 (3.8%)

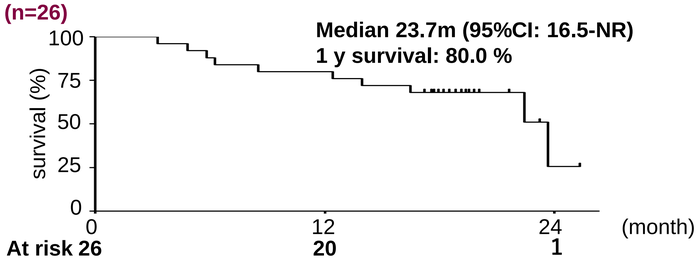
PFS of BM (n=26)



PFS (n=26)



OS (n=26)



Toxicity (n=26)

event	Any grade	Grade 3 + 4
Neutropenia	6 (23.1%)	1 (3.9%)
Anemia	15 (57.7%)	0 (0%)
Platelet decreased	12 (46.2%)	0 (0%)
AST increased	11 (42.3%)	0 (0%)
ALT increased	8 (25.0%)	1 (3.9%)
Rash acneiform	9 (34.6%)	0 (0%)
Pruritus	6 (23.1%)	1 (3.9%)
Dry skin	8 (25.0%)	0 (0%)
Diarrhea	12 (46.2%)	1 (3.9%)
Mucositis	12 (46.2%)	2 (7.7%)
Pneumonitis	5 (19.2%)	0 (0%)

- No treatment related death
- Pneumonitis was observed in five patients (19.2%) and all cases are grade 1-2. The frequency is higher than global trials, however, similar to recent reports in Japanese patients[9, 10].

Reference

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Disclosure (presenter)

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