P3-1735: A phase II study of REPotrectinib in ROS1-positive non-small cell lung cancer patients with active brain mEtastasis – REPOSE

Thorsten Fuereder[1], Barbara Kiesewetter[2], Giuseppe Luigi Banna[3], Jhudit Pérez-Escuredo[4], Jose Antonio Guerrero Martinez[4], Alba Meya Molina[4], Felipe Slebe[4], Anna Grisold[5], Anna Sophie Berghoff[1], Matthias Preusser[1].

[1] Department of Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna, Vienna General Hospital, Vienna, Austria, [3]Portsmouth Hospitals University NHS Trust, Portsmouth, UK, [4]Medica Scientia Innovation Research (MEDSIR), Barcelona (Spain), Ridgewood (New Jersey, USA, [5] Department of Neurology, Medical University of Vienna, Vienna, Austria

Correspondence: matthias.preusser@meduniwien.ac.at

IASLC 2025 World Conference on Lung Cancer

SEPTEMBER 6-9, 2025 BARCELONA, SPAIN

INTRODUCTION

- A subset of patients with metastatic NSCLC (mNSCLC) harbor ROS1 rearrangements, detected in 0.9–2.6% of cases [1]. ROS1-targeted TKIs have significantly improved outcomes in this population [2]. However, brain metastasis (BMs) occur in up to 50% of patients, and treatment options remain limited, especially after resistance develops [3].
- Repotrectinib is a next-generation, highly selective ROS1 inhibitor with favorable properties for intracranial (IC) activity [4]. In the TRIDENT-1 study (NCT03093116), repotrectinib showed meaningful IC responses in patients with ROS1- or NTRK-rearranged advanced solid tumors and asymptomatic BMs [5].
- Given the limited IC treatment options, particularly for symptomatic BMs, these findings underscore the need for further research on repotrectinib's efficacy in this setting.

STATISTICS

- **Design:** single-arm, phase II trial using Simon's two-stage design (10 patients in stage 1; up to 20 total).
- **Hypotheses:** null, IC- objective response rate (ORR) ≤20%; alternative, IC-ORR ≥50%.
- **Power:** 93.8% with one-sided α = 10%.
- **Stopping rule:** futility if <2 IC responses among first 10 patients.
- **Primary endpoint met if ≥7/20 patients respond:** the study is considered positive if at least 7 out of 20 patients (≥35%) achieve an intracranial response.
- **Analysis:** Koyama & Chen method.

TRIAL ENROLLMENT

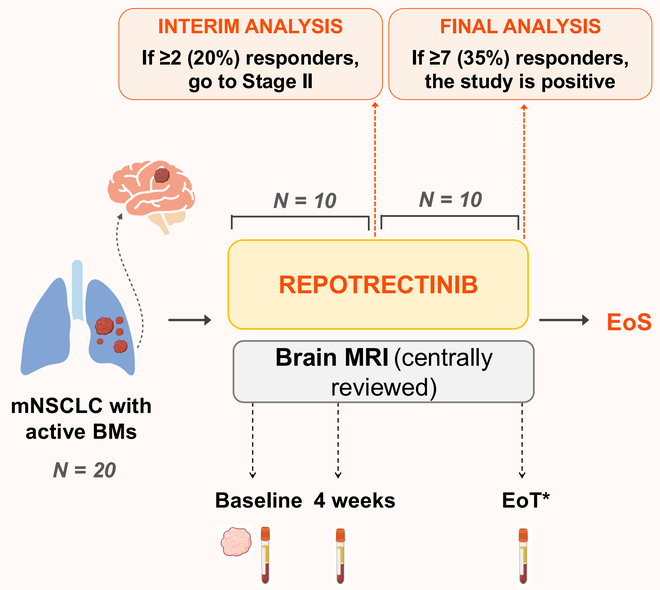
- The study includes 18 sites across Spain, Austria, and Germany. Recruitment began in Spain in April 2025 and in Austria in May 2025; site activation in Germany is expected in November 2025.

STUDY DESIGN

REPOSE is an international, multicenter, open-label, single-arm phase II trial (NCT06315010) using Simon's two-stage design

KEY INCLUSION CRITERIA

- Age ≥ 18 years.
- Histologically documented mNSCLC.
- Presence of active BMs, defined as measurable parenchymal brain lesions (per RANO-BM), regardless of neurological symptoms, not requiring immediate local therapy (e.g., neurosurgery or brain radiotherapy) as judged by the investigator.
- Type II leptomeningeal disease per ESMO-EANO guidelines are allowed.
- Patients must have known tumoral ROS1 rearrangement locally determined prior to study entry.
- ROS1 TKI-naïve patients.
- No limit to the number of prior chemotherapies, immunotherapy or other non-ROS1 TKI regimens.
- *De novo* patients can be included.
- ECOG PS ≤ 2.
- Life expectancy ≥ 6 weeks.
- LVEF ≥ 50% by ECHO or MUGA scan.
- Optional collection of tumor biopsy sample at baseline (FFPE of primary tissue or any metastatic site).



Treatment regimen:

Repotrectinib: 160 mg PO QD x 14 days followed by 160 mg PO BID.

***EoT:** until disease progression, patient's consensus withdrawal, discontinuation for any reason or death

PRIMARY ENDPOINT

- **IC-ORR** at any timepoint, per best CNS response (RANO-BM), assessed by investigator.

SECONDARY ENDPOINTS

- **Extracranial (EC)-ORR and bicompartmental-ORR** according to RECIST v1.1.
- CBR, DCR, DoR, TTR, PFS according to RANO-BM for IC lesions and to RECIST v1.1 for EC and overall lesions; and OS.
- **Best percentage of change in tumor burden** according to RANO-BM for IC lesions, and to RECIST v1.1 for EC and overall lesions.
- **Safety and tolerability** (CTCAE v.5.0)
- **QoL and neurocognitive function** (EORTC QLQ-C30 and QLQ-BN20)
- **Neurologic function** (NANO scale).

EXPLORATORY ENDPOINTS

- Efficacy according to biomarkers analyzed in tumor tissue samples and/or blood samples.
- Evaluation of treatment efficacy correlations with radiological imaging.

REFERENCES

1. Gendarme S. et al. Current Oncology. 2022; 28;29(2):641–58.
2. Shaw AT. et al. JCO. 2012: 20;30(15_suppl):7508–7508.
3. Wasilewski D. et al. JAMA New Open. 2022; 29;5(4):e229553.
4. Yun MR. et al. Clinical Cancer Research. 2020; 1;26(13):3287–95.
5. Cho BC. et al. Journal of Thoracic Oncology. 2021;16(3):S174–5.

ACKNOWLEDGEMENTS

The REPOSE team wants to thank all the patients and their families who will be involved in this study, as well as the trial teams of the participating sites. We also thank Bristol-Myers Squibb for funding this trial.

***ABBREVIATIONS** : **BICR:** Blinded Independent Central Review; **BID:** twice a day; **BM**: brain metastases; **CBR**: clinical benefit rate; **CNS:** Central Nervous System; **CTCAE:** Common Terminology Criteria for Adverse Events; **DCR:** Disease control rate; **DoR**: Duration of Response; **EANO:** European Association of Neuro-Oncology; **EC:** extracranial; **ECHO:** echocardiogram; **ECOG PS**: Eastern Cooperative Oncology Group Performance Status; **EORTC**: European Organization For Research And Treatment Of Cancer; **EoS**: End of Study; **EoT:** End of Treatment; **ESMO:** European Society for Medical Oncology; **FFPE:** Formalin-fixed paraffin-embedded; **IC:** intracranial; **LVEF:** Left ventricular ejection fraction; **mNSCLC**: metastatic non-small cell lung cancer **MUGA:** multigated acquisition; **MRI**: magnetic resonance imaging; **N:** number of patients; **NANO:** Neurologic Assessment in Neuro-Oncology; **NTRK**: Neurotrophic Receptor Tyrosine Kinase 1; **ORR**: overall response rate; **OS**: overall survival; **PFS**: progression-free survival; **PO:** orally; **QLQ-C30:** quality of life questionnaire – Core 30; **QLQ-BN20;** quality of life questionnaire – Brain Neoplasm 20; **QD:** every day; **QoL**: Quality of Life; **RANO-BM:** Response Assessment in Neuro-Oncology Brain Metastases; **RECIST v1.1**: Response Evaluation Criteria in Solid Tumors version 1.1; **ROS1(+):** ROS1 receptor tyrosine kinase encoded (mutation); **TKI**: tyrosine kinase inhibitor; **TTR**: Time to Response*

Scan here to view the lay language summary of this trial in progress.

Scan here to view a PDF version of this poster. Copies obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® or the authors of this poster.