

Immunotherapy or targeted therapy with or without stereotactic radiosurgery for patients with brain metastases from melanoma or non-small cell lung cancer – The ETOP 19-21 USZ-STRIKE study

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1. Background

Brain metastases may affect up to 30 % of patients with metastatic cancer and are a major cause for morbidity and mortality. Treatment approaches include neurosurgery, various approaches of radiotherapy, particularly radiosurgery, and systemic pharmacotherapy [1]. Encouraging response rates and response durations have been observed in patients with melanoma and non-small cell lung cancer (NSCLC) with asymptomatic or oligo-symptomatic brain metastases treated with novel systemic therapies, including immune checkpoint inhibitors and targeted therapy [2–4], challenging the need for immediate radiosurgery and introducing a change in clinical practice not supported by data from controlled clinical trials so far.

1.1. Eligibility criteria

Eligible patients must have newly diagnosed and untreated (except for surgery) asymptomatic or oligo-symptomatic brain metastases from melanoma or treatment naive non-small cell lung cancer, with indication for systemic therapy. Patients must have a Karnofsky performance status ≥ 60 and a life expectancy >12 weeks. Patients with leptomeningeal metastases, symptomatic brain metastases and prior treatment for brain metastases are excluded.

1.2. Study treatment

The treatment regimen consists of standard systemic treatment with stereotactic radiosurgery (Arm A) or without (Arm B). Systemic therapy

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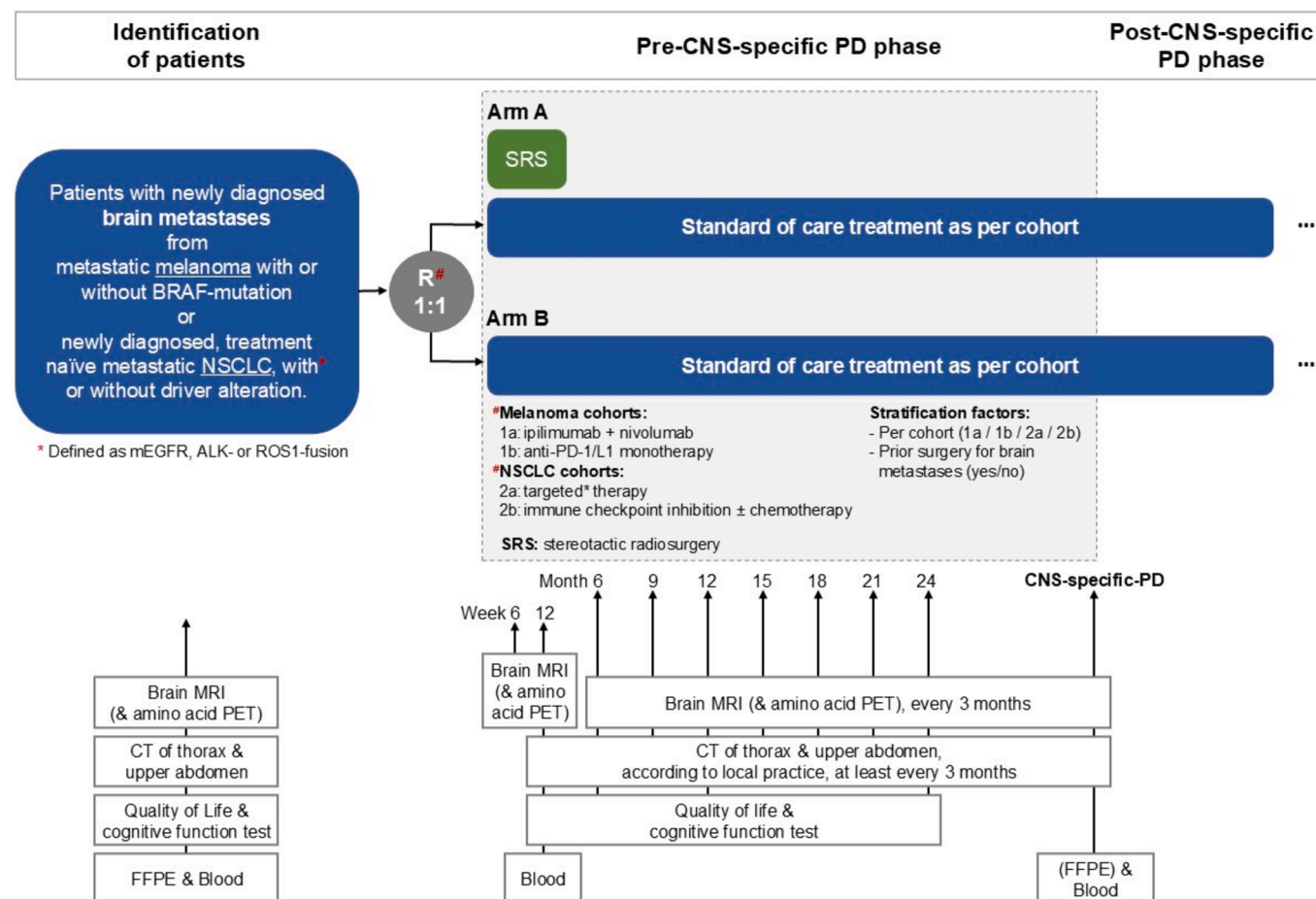
follows the current standard of care, depending on the type of the primary tumour. For patients with melanoma, systemic treatment consists of ipilimumab plus nivolumab (cohort 1a) or anti-PD-1/PD-L1 monotherapy (cohort 1b). For patients with NSCLC and a targetable oncogenic driver alteration, systemic therapy consists of EGFR-, ALK- or ROS1-targeted treatment (cohort 2a), and for patients with NSCLC without a targetable oncogenic driver alteration, immune checkpoint inhibition therapy with or without chemotherapy (cohort 2b).

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1.4. Trial organisation

USZ-STRIKE is an academic study sponsored and coordinated by the ETOP IBCSG Partners Foundation, with substantial funding from a philanthropic grant from the USZ Foundation.

The study is being conducted in 14 centres in Switzerland, Italy, The Netherlands, Spain and the United Kingdom. The study was activated in September 2022 and the first patient was randomised on 31 March 2023



1.3. Statistical considerations and sample size

ETOP 19-21 USZ-STRIKE is a randomised phase III study. The primary endpoint is CNS-specific progression-free survival (PFS), locally assessed according to RANO criteria [5,6]. Secondary endpoints include CNS-specific PFS per tumour cohort, objective CNS response rate, duration of CNS response, pattern of CNS-specific progression, extra-CNS progression, incidence of radionecrosis and pseudo-progression, overall survival, neurocognitive function, quality of life and functional independence, and toxicity.

We expect that the addition of radiosurgery to systemic treatment will decrease the risk of a CNS-specific PFS event by 38 % (HR = 0.62), assuming a median of 4 months for melanoma and 8 months for NSCLC with systemic treatment alone. Using the log-rank test at 5 % one-sided significance level, 138 events are required to detect with 88 % power the targeted benefit. A total of 190 patients need to be randomised and followed for an expected study duration of 34 months to observe the required events. An interim efficacy analysis is planned at 50 %

in Siena, Italy. The accrual as of 02.10.2024 is 23 patients.

The study is registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05522660): NCT05522660.

CRediT authorship contribution statement

Michael Weller: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft. **Emilie Le Rhun:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **Lydia Tsamtsouri:** Writing – review & editing. **Reinhard Dummer:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Matthias Guckenberger:** Conceptualization, Writing – review & editing. **Karin Ribi:** Conceptualization, Writing – review & editing. **Anna Maria di Giacomo:** Investigation, Writing – review & editing. **Gabriele Minuti:** Investigation, Writing – review & editing. **Ana Collazo-Lorduy:** Investigation, Writing – review & editing. **Dieta Brandsma:** Investigation, Writing – review & editing. **Mary O'Brien:** Investigation, Writing – review & editing. **Ekin Ermis:** Investigation, Writing – review & editing. **Natalie Fischer:**

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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