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Abstract CT263: Efficacy and multiomic analysis of Niraparib in relapsed mesothelioma: NERO a randomized phase II trial FREE

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Abstract

Background:

Mesothelioma is a lethal cancer caused by asbestos. Effective therapy in the relapsed setting, following standard of care treatments is lacking [1]. Inhibition of Poly-ADP ribose polymerase (PARPi) mediates synthetic lethality in cancers harboring DNA damage response gene (DDR) inactivation, notably BRCA1/2 resulting in homologous recombination deficiency (HRD), and transcription replication conflicts (TRCs). In relapsed mesothelioma PARPi was clinically active in the MIST1 phase II trial [2], warranting interrogation of underlying mechanisms and further randomized evaluation.

Methods:

NERO, NCT05455424 a multi-center, two-arm, open-label UK 2:1 randomized phase II trial compared active symptom control (ASC) with or without Niraparib (Nir). Eligibility: Relapsed mesothelioma with prior platinum doublet therapy (any line). The ASC+Nir arm received 200 or 300 mg daily in a 3-weekly cycle up to 24 weeks, with the option to continue if there was ongoing disease control. Primary endpoint: progression-free survival (PFS), one-sided α=0.1 with 80% power. In parallel, whole exome and transcriptomic analyses of the NERO, MIST1 cohort [2], primary patient derived explants (PDEs) and cell lines were conducted to understand correlates of PARPi sensitivity.

Results:

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Between 11th July 2022 and 21st December 2023, 88 patients were enrolled. Characteristics: male: n = 62 (70.5%), median age: 72 (range 33-84) years, disease site: 77 (87.5%) had pleural mesothelioma. 83 (94.3%) PFS events were observed. Median (95% CI) PFS was 4.14 months (m) (2.76, 4.73) in the ASC + Nir arm versus 2.76m (1.41, 3.02) corresponding to an unadjusted PFS HR of 0.73 (one sided 90% CI 0.99, p-value 0.091). 6m PFS rate (95% CI) was 24.6% (14.4%, 36.2%) for ASC+Nir versus 13.8% (4.4%, 28.6%) for ASC. Most common Adverse Events (>20%) in the ASC+Nir arm: Fatigue (52.6%), Constipation (45.6%) & Nausea (43.9%). Interferon (IFN) α transcription (9p21.3) but not HRD or DDR gene burden was correlated with sensitivity to PARPi in MIST1, two PDE cohorts (Niraparib and Rucaparib), and in mesothelioma cell lines treated with multiple PARPi's. Pattern recognition receptor signaling (Toll and RIG-I) positively correlated with IFNα, which in turn was associated with R-loops, a surrogate of TRCs across all models. *MTAP/IFNA* deletion at 9p21.3 inhibited PARPi activity in patients.

Conclusions:

NERO met its primary endpoint of longer PFS in patients with relapsed mesothelioma. PARPi response is predicted by IFNα transcription and 9p21.3 deletion status. Multiomic analysis of NERO is ongoing and will be presented.

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[1] Janes, Alrifai, Fennell N Engl J Med 2021 (385) p1207-1218

[2] Fennell et al, Lancet Respir Med 2021 (9) p593-600

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