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First-line (1L) Maintenance Therapy With Niraparib (nira) + Pembrolizumab (pembro) vs Placebo + Pembro in Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC): Phase 3 ZEAL-1L Study

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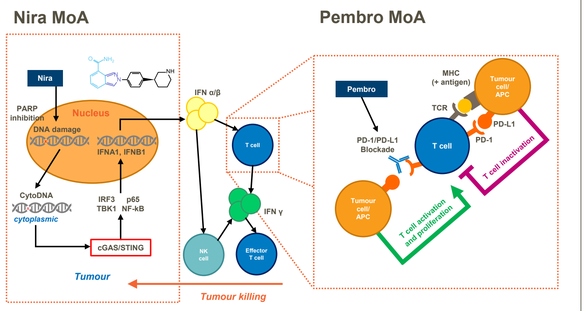
Introduction

- NSCLC accounts for approximately 85% of lung cancers and a high proportion of patients with NSCLC have advanced or metastatic disease at diagnosis.[1]
- Pembro, a PD-1 inhibitor, maintained until disease progression with or without platinum-based chemotherapy, is a standard 1L treatment for advanced/metastatic NSCLC.[2]
- However, durable long-term benefit is limited to a small subset of patients.
- There remains an unmet need for treatments that extend survival and maintain quality of life in patients with NSCLC.
- Platinum-based chemotherapy induces DNA double-strand breaks, leading to cytotoxicity, which may be further increased by impairment of DNA damage repair via PARP inhibition.[3]
- Nira, a PARP inhibitor, promotes PARP trapping, activates the STING pathway, recruits T cells, and upregulates PD-L1, making it a promising partner for PD-1 inhibitors.[4,5]
- Nira crosses the blood–brain barrier in animal models with 34-fold higher brain tissue exposure than other PARPi, suggesting it may reduce risk/progression of BM.[6]
- Nira + pembro has shown antitumour activity and acceptable safety in triple-negative breast cancer and platinum-resistant ovarian cancer (TOPACIO/KEYNOTE-162), and as 1L therapy in advanced/metastatic NSCLC (JASPER).[7,8]

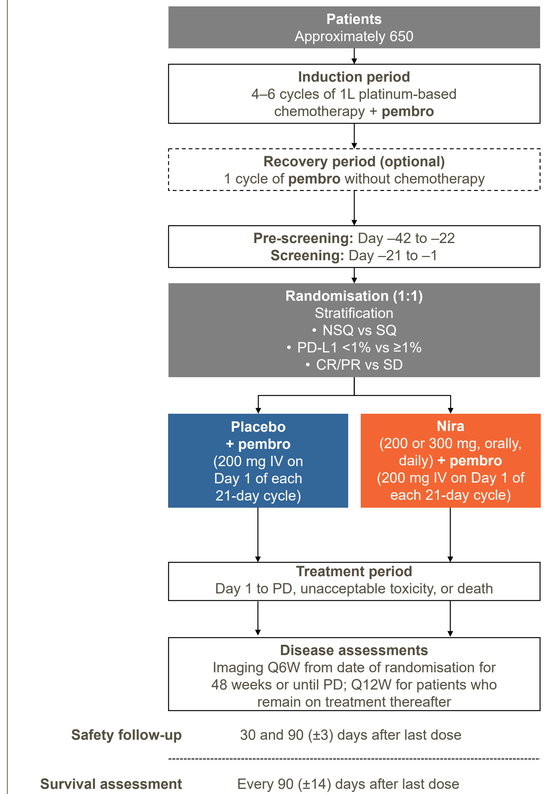
Objective

- ZEAL-1L (NCT04475939) is a Phase 3, randomised, double-blind trial in patients with advanced or metastatic NSCLC without known driver mutations that will compare efficacy and safety of nira + pembro with placebo + pembro.

Rationale for combination therapy



Study design



Study population

Key inclusion criteria

- Histologically/cytologically confirmed diagnosis of NSCLC without known targetable driver mutations (non-squamous, squamous or mixed histology allowed)
- Advanced (stage IIIB not amenable to definitive chemoradiotherapy or stage IIIC) or metastatic (stage IV) NSCLC
- Completed 4–6 cycles of standard-of-care platinum-based 1L induction chemotherapy plus **pembro**
- SD, PR or CR after 4–6 cycles of platinum-based 1L induction chemotherapy plus **pembro**
- ECOG PS 0 or 1

Key exclusion criteria

- Mixed SCLC or sarcomatoid variant NSCLC
- Prior treatment with PARP inhibitor(s)
- Systolic BP >140 mmHg or diastolic BP >90 mmHg
- Leptomeningeal disease, carcinomatous meningitis, symptomatic BM, or radiologic signs of CNS haemorrhage (asymptomatic BM permitted if patient is off corticosteroids and anticonvulsants for ≥7 days)
- Active/prior autoimmune or inflammatory disorder

Study endpoints

Dual primary endpoints

PFS* and OS† of patients treated with nira + pembro versus placebo + pembro

Secondary endpoints

- TTP in the CNS assessed by BICR per RANO-BM criteria
- Investigator-assessed PFS per RECIST v1.1 criteria
- PFS* and OS† by PD-L1 status (TC <1% vs ≥1%)
- TTD in lung symptoms‡
- Change from baseline in HRQoL per EORTC QLQ-C30 and EORTC QLQ-LC13
- Safety and tolerability of nira + pembro vs placebo + pembro
- Plasma concentrations of nira over time

*Assessed by BICR per RECIST v1.1 criteria. †Defined as time from randomisation to date of death due to any cause. ‡Time from randomisation to meaningful deterioration on a composite endpoint of dyspnoea, chest pain and cough, from EORTC QLQ-LC13.

Current status and key points

- The Phase 3 ZEAL-1L study is registered at clinicaltrials.gov (NCT04475939) and is currently active and recruiting.
- Recruitment began in November 2020.
- Ongoing research to address the unmet need for patients with advanced/metastatic NSCLC is crucial.
- PARP inhibitors such as nira, when combined with PD-1 inhibitors like pembro, may have the potential to prolong responses after 1L chemotherapy.

Abbreviations

1L, first line; APC, antigen-presenting cell; BICR, blinded independent central review; BM, brain metastases; BP, blood pressure; cGAS, cyclic GMP-AMP synthase; CNS, central nervous system; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module; EQ-5D-3L, European Quality of Life 5-Dimensions 3-Level Scale; FACT-GP5, Functional Assessment of Cancer Therapy – General Population item 5; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; IFNA1, interferon alpha 1; IFNB, interferon beta1; IFNα/β, interferon alpha/beta; IFNγ, interferon gamma; IRF3, interferon regulatory factor 3; IV, intravenous; MHC, major histocompatibility complex; MoA, mechanism of action; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nira, niraparib; NK, natural killer; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, overall response rate; OS, overall survival; p65, transcription factor 65; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; Pembro, pembrolizumab; PGIS/PGIC, Patient Global Impression of Severity/Change; PK, pharmacokinetics; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; Q6W, every 6 weeks; Q12W, every 12 weeks; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumours; SCLC, small cell lung cancer; SD, stable disease; SQ, squamous; STING, stimulator of interferon gene; T, thymus; TBK1, tank-binding kinase; TC, tumour cells; TCR, T-cell receptor; TMB, tumour mutational burden; TTD, time to deterioration; TTP, time to progression.

References

1. Lemjabbar-Alaoui H et al. *Biochem Biophy Acta.* 2015;1856:189–210.
2. Keytruda Summary of Product Characteristics. Accessed July 2021. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/Keytruda.
3. Matulonis US, Monk BJ. *Ann Oncol.* 2017;28:443–447.
4. Wang Z et al. *Sci Rep.* 2019;9:1853.
5. Jiao S et al. *Clin Cancer Res.* 2017;23:3711–3720.
6. Sun K et al. *Oncotarget.* 2018;9:37080–37096.
7. Vinayak S et al. *JAMA Oncol.* 2019;5:1132–1140.
8. Ramalingham S et al. *Ann Oncol.* 2020;31:S819–S820.

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