Niraparib + Pembrolizumab (Pembro) Versus Placebo + Pembro 1L Maintenance Therapy in Advanced NSCLC: ZEAL-1L Phase III Study

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Background

Therapeutic area

Lung cancer is the most commonly diagnosed cancer worldwide and is the leading cancer-related cause of death in men and the second leading cause in women[1]

NSCLC accounts for approximately 85% of lung cancers and a high proportion of patients with NSCLC have advanced or metastatic disease at diagnosis[2]

- The 5-year survival rate for patients with advanced disease is approximately 30% and <6% for those with metastatic disease[3]

1L treatment for patients with advanced, unresectable, or metastatic NSCLC without actionable driver mutations generally depends on histology (squamous vs non-squamous) and PD-L1 expression levels[4,5]

- Most patients are treated with PD-(L)1 inhibitor therapy either alone or in combination with platinum-based chemotherapy, which may be followed by continuation of the PD-(L)1 inhibitor as maintenance therapy[4,5]

Although maintenance therapy has prolonged time to disease progression and improved OS in advanced/metastatic NSCLC,[6,7] there remains an unmet need for treatments that extend survival and maintain patient quality of life

1L, first line; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-(L)1, programmed cell death ligand-1.

1. Bray F, et al. *CA Cancer J Clin* 2018;68(6):394–424. 2. Lemjabbar-Alaoui H, et al. *Biochem Biophy Acta* 2015;1856:189–210. 3. National Institutes of Health, National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: lung and bronchus cancer. Available at: https://seer.cancer.gov/statfacts/html/lungb.html. Accessed November 10, 2020. 4. Postmus PE, et al. *Ann Oncol* 2017;28(suppl_4):iv1–iv21. 5. Planchard D, et al. *Ann Oncol* 2018;29(suppl_4):iv192–iv237. 6. Shan F, et al. *BioMed Res Int* 2018;2018:5839081. 7. Gadgeel S, et al. *J Clin Oncol* 2020;38:1505–17.

Background

Niraparib

Niraparib is a highly selective PARP-1/2 inhibitor with once-daily oral dosing, approved for the treatment of patients with newly diagnosed or recurrent platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer or for patients with platinum-refractory (≥3 prior chemotherapy regimens), homologous recombination deficiency-positive epithelial ovarian, fallopian tube, or primary peritoneal cancer[1,2]

Niraparib exerts antitumor activity by increasing formation of PARP-DNA complexes, leading to DNA damage, apoptosis, and cell death[1]

- 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]

Preclinical data suggest that PARP inhibitors may also activate the STING pathway, recruit T cells, and upregulate PD-L1,[4,5] suggesting that PARP inhibitors may synergize with PD-1 inhibitors

PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death receptor-1; PD-L1, programmed cell death ligand-1; STING, stimulator of interferon gene.

1. GSK. Zejula Prescribing Information. April 2020. 2. GSK. Zejula Summary of Product Characteristics. 2020. 3. Matulonis US and Monk BJ. *Ann Oncol* 2017;28:443–7. 5. Wang Z, et al. *Sci Rep* 2019;9:1853. 5. Jiao S, et al. *Clin Cancer Res* 2017;23:3711–20.

Background

Niraparib in combination with pembrolizumab

Pembrolizumab is a humanized monoclonal anti–PD-1 antibody that potentiates T-cell–mediated antitumor responses by blocking engagement of PD-1 with its ligands, PD-L1 and PD-L2, expressed in the tumor microenvironment[1]

The combination of **niraparib** and **pembrolizumab** was explored in an open-label Phase II trial as treatment in patients with TNBC and PROC (TOPACIO/KEYNOTE-162), where the combination showed promising antitumor activity and was well tolerated[2,3]

Data from the open-label Phase II JASPER trial (NCT03308942) suggested this combination is also active as 1L therapy in patients with locally advanced and metastatic NSCLC without targetable driver mutations and with high or low PD-L1 expression[4]

Notably, the safety profile of niraparib plus pembrolizumab in JASPER and TOPACIO was consistent with prior clinical experience of each agent as monotherapy or in combination, in other tumor types[2–4]

1L, first line; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death receptor-1, PD-L1/2, programmed cell death ligand-1/2; PROC, platinum-resistant ovarian cancer; TNBC, triple-negative breast cancer.

1. Keytruda Summary of Product Characteristics. July 2020. 2. Vinayak S, et al. *JAMA Oncol* 2019;5:1132–40. 3. Konstantinopoulos P, et al. *JAMA Oncol* 2019;5:1141–9. 4. Ramalingam S et al. *Ann Oncol* 2020;31(S4);S819–20.

Trial Objective

To compare the efficacy and safety of **niraparib** plus **pembrolizumab** versus placebo plus **pembrolizumab** in patients with advanced or metastatic NSCLC without known driver mutations who have SD, PR, or CR after completing 4–6 cycles of platinum-based 1L induction chemotherapy with **pembrolizumab**

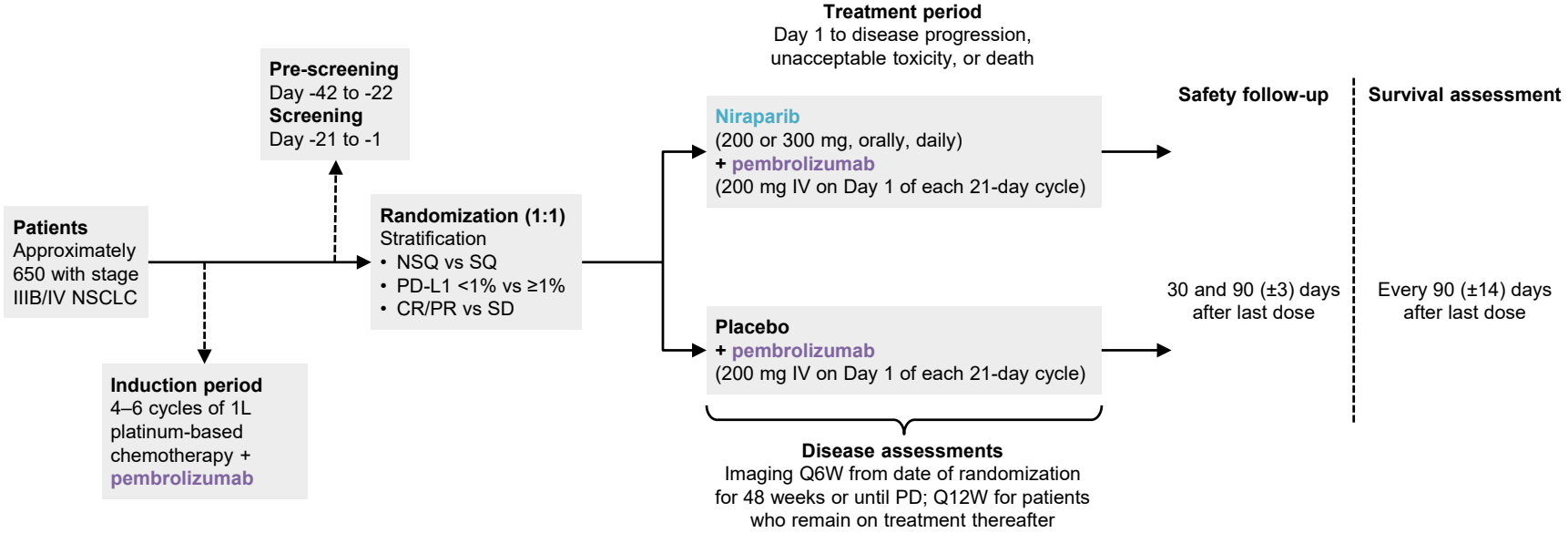
1L, first line; CR, complete response; NSCLC, non-small-cell lung cancer; PR, partial response; SD, stable disease.

Methods

The ZEAL-1L study (NCT04475939) is:

- 3 — Phase III
- Randomized
- Double-blind
- Placebo-controlled
- Global multicenter

Study Design



1L, first line; CR, complete response; IV, intravenous; NSQ, non-squamous; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; Q6W, every 6 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SQ, squamous.

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 metastatic (stage IV) NSCLC
- Completed 4–6 cycles of standard-of-care platinum-based 1L induction chemotherapy plus **pembrolizumab**
- SD, PR, or CR after 4–6 cycles of platinum-based 1L induction chemotherapy plus **pembrolizumab**
- ECOG PS 0 or 1

Key exclusion criteria

- Mixed SCLC or sarcomatoid variant NSCLC
- Prior treatment with PARP inhibitor(s)
- Leptomeningeal disease, carcinomatous meningitis, symptomatic brain metastases, or radiologic signs of CNS hemorrhage (asymptomatic brain metastases permitted if patient is off corticosteroids and anticonvulsants for ≥7 days)
- Active/prior autoimmune or inflammatory disorder

1L, first line; CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer; PARP, poly(ADP-ribose) polymerase; PR, partial response; SD, stable disease.

Study Endpoints

Dual primary endpoints

PFS* and OS† of patients treated with niraparib plus pembrolizumab versus placebo plus pembrolizumab

Key secondary endpoint

TTP in the CNS assessed by BICR per RANO-BM criteria

Secondary endpoints

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 in patients treated with niraparib plus pembrolizumab versus placebo plus pembrolizumab

Population PK of niraparib plus pembrolizumab

Exploratory endpoints

PFS2§

PFS* and OS† by HRd status (positive/negative)

PFS* and OS† by TMB status (high/low)

Change from baseline in overall symptom severity per PGIS/PGIC

PROs, including PRO-CTCAE, FACT-GP5, EQ-5D-3L

Impact of niraparib exposure on efficacy/safety endpoints

*Assessed by BICR per RECIST v1.1 criteria. †Defined as time from randomization to date of death due to any cause. ‡Time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from EORTC QLQ-LC13. §Time from randomization to progression or death from any cause in the absence of progression (whichever comes first) on subsequent anticancer treatment after maintenance therapy.

BICR, blinded independent central review; CNS, central nervous system; 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; HRd, homologous recombination deficiency; HRQoL, health-related quality of life; OS, overall survival; PD-L1, programmed cell death ligand-1; PGIS/PGIC, Patient Global Impression of Severity/Change; PK, pharmacokinetics; PFS, progression-free survival; PFS2, progression-free survival 2; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cells; TMB, tumor mutational burden; TTD, time to deterioration; TTP, time to progression.

Current Status and Key Points

Current status

- Active, recruiting

Key points

- Ongoing research to address the unmet need for patients with advanced/metastatic NSCLC is crucial
- PARP inhibitors such as **niraparib**, when combined with PD-1 inhibitors like **pembrolizumab**, may have the potential to prolong responses after 1L chemotherapy
- Patients with advanced NSCLC frequently develop brain metastasis over the course of disease. **Niraparib** crosses the blood–brain barrier and may decrease the risk of occurrence or progression of CNS metastasis; this is a key differentiator from KEYLYNK NSCLC studies

1L, first line; CNS, central nervous system; NSCLC, non-small-cell lung cancer; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death receptor-1.

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Other Author Disclosures

SA, **JZ**, and **AS**: employees of and stockholders in GlaxoSmithKline.

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MWN and TF: employees of GlaxoSmithKline; stockholders in GlaxoSmithKline and Merck.

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