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

Suresh S Ramalingam¹, Sujata Arora², Melissa Whipple Neibauer², Jiangxiu Zhou², Sebastien Hazard³, Tara Frenkl², Alexander Stojadinovic², Solange Peters⁴

¹Emory University, Winship Cancer Institute, Atlanta, GA, USA; ²GlaxoSmithKline, Philadelphia, PA, USA; ³GlaxoSmithKline, Waltham, MA, USA; ⁴Oncology Department, Lausanne University, Lausanne, Switzerland
DISCLOSURES

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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.

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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.
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.

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.

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.

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.
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.
The ZEAL-1L study (NCT04475939) is:

- Phase III
- Randomized
- Double-blind
- Placebo-controlled
- Global multicenter
Study Design

Patients
Approximately 650 with stage IIIB/IV NSCLC

Randomization (1:1)
Stratification
• NSQ vs SQ
• PD-L1 <1% vs ≥1%
• CR/PR vs SD

Treatment period
Day 1 to disease progression, unacceptable toxicity, or death

Niraparib
(200 or 300 mg, orally, daily)
+ pembrolizumab
(200 mg IV on Day 1 of each 21-day cycle)

Placebo
+ pembrolizumab
(200 mg IV on Day 1 of each 21-day cycle)

Induction period
4–6 cycles of 1L platinum-based chemotherapy + pembrolizumab

Pre-screening
Day -42 to -22
Screening
Day -21 to -1

Disease assessments
Imaging Q6W from date of randomization for 48 weeks or until PD; Q12W for patients who remain on treatment thereafter

Safety follow-up
30 and 90 (±3) days after last dose

Survival assessment
Every 90 (±14) days after last dose

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

**Secondary endpoints**

- Investigator-assessed PFS per RECIST v1.1 criteria
- PFS\(^*\) and OS\(^†\) by PD-L1 status (TC <1% vs ≥1%)

**Key secondary endpoint**

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

**Exploratory endpoints**

- PFS\(^*\)\(^§\)
- 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
- Safety and tolerability in patients treated with niraparib plus pembrolizumab versus placebo plus pembrolizumab

*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; PFS\(^*\)\(^§\), progression-free survival \(^†\)\(^§\); PRD, 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

- **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

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Presenting author email: ssramal@emory.edu