A Prospective Phase II Single-arm Study of Niraparib Plus Dostarlimab in Patients With Advanced Non–small-cell Lung Cancer and/or Malignant Pleural Mesothelioma, Positive for PD-L1 Expression and Germline or Somatic Mutations in the DNA Repair Genes: Rationale and Study Design

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A Prospective Phase II Single-arm Study of Niraparib Plus Dostarlimab in Patients With Advanced Non–small-cell Lung Cancer and/or Malignant Pleural Mesothelioma, Positive for PD-L1 Expression and Germline or Somatic Mutations in the DNA Repair Genes: Rationale and Study Design

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Abstract

Treatment with poly ADP ribose polymerase (PARP)1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair, thus leading to synthetic lethality. Treatment of homologous recombination deficient (HRD)-tumors with PARP inhibitors generates significant levels of DNA damage, which has the potential to further increasing tumor mutational burden, promoting neoantigen release, and upregulating both interferons and programmed death ligand-1 (PD-L1) expression, suggesting a potential complementary and synergistic role with immune checkpoint inhibitors in cancer treatment. Here we present the design and rationale of a prospective, phase II, single-arm study aiming to investigate the safety and antitumor activity of the combination of niraparib and dostarlimab in patients with HRD-positive and PD-L1 ≥ 1% advanced non-small-cell lung cancer (NSCLC) and/or malignant pleural mesothelioma (MPM). Considering the prevalence of pathogenetic germline mutations in DNA repair genes, reported to be around 5% to 10% in patients with MPM and NSCLC, a total of 700 to 1000 cases will be screened to identify 70 patients who are HRD-positive/PD-L1 ≥ 1% (N = 35 NSCLC; N = 35 MPM) to be included. Patients will receive the combination of niraparib orally once daily and dostarlimab intravenously. The primary endpoint is progression-free survival. Secondary endpoints are objective response, duration of response, overall survival, and safety. The results of this study will provide evidence on the safety and antitumor activity of niraparib and dostarlimab combination in patients with advanced, HRD-positive and PD-L1 ≥ 1% NSCLC and/or MPM.

Keywords: Homologous recombination repair deficiency; PARP inhbitors; PD-1 inhibitors; PD-L1; Treatment combinations.

Introduction

Treatment with poly ADP ribose polymerase (PARP)1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair, thus leading to synthetic lethality. An integrative clinical genomic approach based on whole-exome and -transcriptome sequencing of 500 patients with metastatic tumors revealed the presence of putative pathogenetic germline variants in 12.2%, with 75% related to defects in the DNA repair genes, including MUTYH (n = 10; 16%), BRCA2 (n = 9; 14%), CHEK2 (n = 9; 14%), and BRCA1 (n = 5; 8%).[1] A multiplatform molecular profiling of more than 53,000 solid tumors revealed the prevalence of homologous recombination deficiency (HRD) being around 13% among all tumor types, with ovarian (14.1%), breast (8%), endometrial (7.4%), prostate (7.1%), pancreas (6.5%), gastroesophageal (6.4%), colorectal (6.3%), and non–small-cell lung cancer (NSCLC) (5%), as the most common reported.[2] A DNA repair pathway defect either as a result of a germline or somatic event has been found also in a significant proportion of patients with malignant pleural mesothelioma (MPM),[3] whereas germline mutations in DNA repair genes have been associated with MPM development in asbestos-exposed subjects.[4] Clinical studies have shown PARP inhibitors to be effective in ovarian and breast cancer, and more recently also in prostate and pancreatic cancer, with clinical anticancer activity observed in both patients with and without germline BRCA mutations.[5, 6, 7, 8] However, there is increasing evidence that the presence of a deficiency in the DNA HRR genes can also predict therapeutic benefit of PARP inhibitors in cancer patients.[9,10] Therefore, the HRD status is emerging as a predictive, tumor-agnostic biomarker for PARP inhibition across different tumor types, and testing for HRD signature is currently a developing area with interesting therapeutic implications.

Along with having high mutational loads, HRD-positive tumors also display unique immunologic characteristics, characterized by high levels of tumor-infiltrating lymphocytes, increased secretion of lymphocyte attractants as CXCL10, and upregulation of immune suppressive ligands.[11,12] Treatment of HRD-positive tumors with PARP inhibitors generates significant levels of DNA damage, which has the potential to further increase tumor mutational burden, promoting neoantigen release, and upregulating both interferons and programmed death-ligand 1 (PD-L1) expression within the tumor microenvironment. Finally, mutations in DNA repair genes such as POLD1, POLE, BRCA1-2, PRKDC, MSH2, RAD51C, LIG3, and RAD17 were frequently identified in NSCLC with high mutational burden, and have been frequently associated with clinical response to pembrolizumab.[13] Overall, these data suggest that PARP and immune checkpoint inhibitors have different therapeutic effects with complementary and synergistic roles in cancer treatment, providing an intriguing rational for combination strategies in molecularly defined subsets of patients. Preliminary results of early phase clinical studies have recently demonstrated promising activity of PARP inhibition plus immunotherapy for patients with metastatic breast, ovarian, and prostate cancer, predominantly in BRCA-mutant subgroups.[14] An open-label phase I trial (Study 3000-01-002) has been initiated to investigate the safety and antitumor activity of the combination of dostarlimab plus niraparib in participants with selected advanced solid tumors. The combination proved to be safe, with the majority of subjects reporting at least 1 treatment-related adverse event, including nausea, decreased appetite, fatigue and dyspnoea among the most common. On these bases, considering the prevalence of pathogenetic germline mutations in the DNA repair genes, in both MPM[15] and NSCLC,[16] we hypothesized that combining niraparib with dostarlimab may be synergistic, with the potential to prolong survival outcomes and increase tumor response in molecularly selected patients, with HRD- and PD-L1–positive, advanced NSCLC and/or MPM.

Objectives

The primary objective of the study is to evaluate the progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) of the combination of niraparib and dostarlimab in patients with HRD-positive and PD-L1-positive advanced NSCLC and/or MPM.

The secondary objectives are: to evaluate the objective response rate (ORR) and the duration of response (DOR) according to RECIST 1.1; and to evaluate the overall survival (OS), the safety, and the tolerability of the combination of niraparib and dostarlimab in patients with HRD-positive and PD-L1-positive advanced NSCLC and/or MPM.

Patients and Methods

Eligibility Criteria

Study entry is limited to patients with histologically or cytologically proven diagnosis of advanced NSCLC without known EGFR/ALK/ROS1 alterations, or with histologically proven diagnosis of metastatic MPM (according to the Eighth Edition of the Union for International Cancer Control TNM Classification). Participant must have centrally confirmed positivity for germline or somatic HRD status and tumor PD-L1 expression (tumor proportion score ≥ 1%) and must have experienced disease progression or recurrence during or after at least 1 systemic therapy for advanced metastatic disease. The inclusion of patients receiving first-line PD-1/PD-L1 inhibitors eiher as single agent or in combination with chemotherapy is allowed. Patients are excluded if they received prior treatment with a known PARP inhibitor or experienced ≥ grade 3 immune-related adverse events with prior immunotherapy, or ≥ grade 3 anemia, neutropenia, or thrombocytopenia to prior chemotherapy that persisted > 4 weeks. Participant with any known history of myelodysplastic syndrome or acute myeloid leukemia are also excluded. Participants with a diagnosis of immunodeficiency, a known active hepatitis B/C, or an active autoimmune disease that has required systemic treatment in the past 2 years may not be included as well as patients with known, symptomatic brain or leptomeningeal metastases or a known history of interstitial lung disease or drug-related or radiation pneumonitis.

Study Design and Treatments

This is a single-arm, prospective, interventional, phase II study of the combination of niraparib and dostarlimab in patients with advanced NSCLC and/or MPM, positive for PD-L1 expression (tumor proportion score ≥ 1%) and germline or somatic mutations in the DNA HRR genes (Figure 1).

Approximately 70 eligible patients with previously treated advanced disease will be included in this study and grouped as follows: (1) HRD-positive and PD-L1-positive advanced NSCLC, referred to as Cohort A (n = 35) and (2) HRD-positive and PD-L1-positive advanced MPM, referred to as Cohort B (n = 35).

Mandatory archival or fresh tumor tissue and blood specimens will be collected for central assessment of both HRD and PD-L1 status before the treatment period. Considering that the prevalence of pathogenetic germline mutations in DNA repair genes is reported to be around 5% to 10% in patients with MPM[15] and NSCLC,[16] a total of 700 to 1000 cases will be screened to select the HRD-positive target population.

Patients will receive the combination of niraparib 300 mg (≥ 77 kg and a platelet count ≥ 150,000 μL) or 200 mg (< 77 kg or a platelet count < 150,000 μL) orally once daily, and dostarlimab via a 30-minute intravenous infusion on day 1 of every 21-day cycle at 500 mg for the first 4 doses, followed by 1000 mg on day 1 of every 42-day cycle thereafter, until the patient discontinues study treatment.

Statistical Analyses

The sample size is based on the primary endpoint of PFS, defined as the time since the date of enrollment to the date of disease progression, or to the date of death of any cause, whichever occurs earlier. Assuming a median PFS of 4 months associated with single-agent immune checkpoint inhibitors as second-line treatment of both PD-L1–positive advanced NSCLC and MPM, based on historical data, a minimum of 59 events is required to detect an improvement in median PFS from 4 months to 7 months with 90% power and a 1-sided alpha of 0.05. With an accrual duration of 24 months, and additional 10 months of follow-up after the completion of recruitment, 67 patients are needed to obtain the 59 events requested.[17] Considering that approximately 5% of patients will be lost during follow-up, 3 additional patients will be included for a total of 70 patients. Among the 70 patients enrolled in this study, 35 patients will have a diagnosis of advanced NSCLC (Cohort A) and 35 patients of metastatic MPM (Cohort B). ORR is defined as the proportion of participants who have a best overall response of either complete response or partial response as assessed by investigator's review according to RECIST 1.1. The observed ORR per RECIST 1.1 will be summarized by a binomial response rate, and its corresponding exact 2-sided 95% confidence interval will be calculated using the Clopper-Pearson method. DOR is defined as the time from the date a response was first documented until either disease progression or death owing to any cause, whichever occurs first, whereas OS is defined as the time from the date of the first dose to death owing to any cause. The PFS, DOR, and OS analysis will be

separately performed for the NSCLC and MPM cohorts, by using Kaplan-Meier methods. Medians and 2-sided 95% confidence intervals will be calculated, and Kaplan-Meier plots will be provided as appropriate. Treatment-emergent adverse events occurring on or after treatment on cycle 1, day 1 will be summarized by mapped term, appropriate thesaurus level, and National Cancer Institute Common Terminology Criteria for Adverse Events v5.00 grade.

Conclusion

The results of this prospective phase II study will provide evidence on the safety and antitumor activity of niraparib and dostarlimab combination in patients with advanced NSCLC and/or MPM, positive for PD-L1 expression and germline or somatic mutations in the HRR genes.

Disclosure

Francesco Passiglia declared consultant's fee from MSD and Astra Zeneca; Paolo Bironzo declared consultant's fee from MSD , BMS, Astra Zeneca, and Roche; Luisella Righi declared consultant's fee from Astra Zeneca, Novartis, and Boehringer Ingelheim; Silvia Novello declared speaker bureau/advisor's fee from: Eli Lilly, MSD, Roche, BMS, Takeda, Pfizer, Astra Zeneca and Boehringer Ingelheim; Giorgio Scagliotti declared speaker bureau/advisor's fee from: Eli Lilly, MSD, Roche, BMS, Clovis Pfizer, Novartis, and Astra Zeneca. The other authors have nothing to declare.

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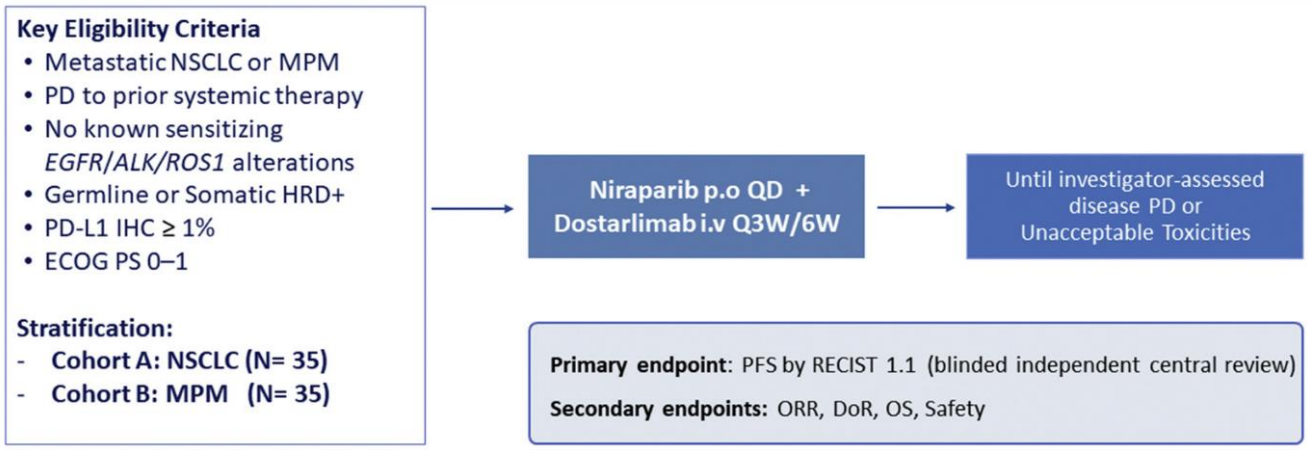
FIGURE 1. Study Design



Abbreviations: DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; HRD = homologous recombination deficiency; IHC = immunohistochemistry; i.v. = intravenously; MPM = malignant pleural mesothelioma; NSCLC = non–small-cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; p.o. = orally; QD = daily; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors.