ORIGINAL ARTICLE

Durvalumab in Combination With Olaparib Versus Durvalumab Alone as Maintenance Therapy in Metastatic NSCLC: The Phase 2 ORION Study

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ABSTRACT

Introduction: Increased DNA damage triggered through poly (ADP-ribose) polymerase inhibition may modify tumor immunogenicity, sensitizing tumors to immunotherapy. ORION (NCT03775486) evaluated the combination of olaparib with durvalumab as maintenance therapy in patients with metastatic NSCLC.

Methods: ORION is a phase 2, randomized, multicenter, double-blind, international study. Patients with metastatic NSCLC (without activating *EGFR* or *ALK* aberrations) and Eastern Cooperative Oncology Group performance status of 0 or 1 were enrolled to receive initial therapy with durvalumab (1500 mg intravenously; every 3 wk) plus platinum-based chemotherapy for four cycles. Patients without disease progression were then randomized (1:1) to maintenance durvalumab (1500 mg; every 4 wk) plus either olaparib (300 mg orally) or placebo (both twice daily); randomization was stratified by objective response during initial therapy and tumor histologic type. The primary end point was investigator-assessed progression-free survival (PFS) (Response Evaluation Criteria in Solid Tumors version 1.1).

Results: Between January 2019 and February 2020, 269 of 401 patients who received initial therapy were randomized. As of January 11, 2021 (median follow-up: 9.6 mo), median PFS was 7.2 months (95% confidence interval: 5.3–7.9) with durvalumab plus olaparib versus 5.3 months (3.7–5.8) with durvalumab plus placebo (hazard ratio = 0.76, 95% confidence interval: 0.57–1.02, $p = 0.074$). Safety findings were consistent with the known profiles of durvalumab and olaparib. Anemia was the most common adverse event (AE) with durvalumab plus olaparib (26.1% versus 8.2% with durvalumab plus placebo). The incidence of grade 3 or 4 AEs (34.3% versus 17.9%) and AEs leading to treatment discontinuation (10.4% versus 4.5%) was numerically higher with durvalumab plus olaparib versus durvalumab plus placebo.

Conclusions: Maintenance therapy with durvalumab in combination with olaparib was not associated with a statistically significant improvement in PFS versus durvalumab alone, although numerical improvement was observed.

Keywords: Durvalumab; Immunotherapy; NSCLC; Olaparib; PARP inhibition

Introduction

Immunotherapies targeting the programmed cell death (ligand)-1 (PD-[L]1) signaling pathway have transformed the treatment of patients with metastatic NSCLC (mNSCLC).[1] Several PD-(L)1 inhibitors were found to have survival benefits in this setting, both alone and in combination with chemotherapy.[1–4] On the basis of these findings, immunotherapy-based regimens have become the standard of care (SoC) for first-line treatment of patients with mNSCLC and no oncogenic driver alterations.[1,5–7] Nevertheless, median progression-free survival (PFS) typically remains less than 1 year in clinical studies, with reported 3-year survival rates in the region of 20% to 44%.[1,8–14]

New treatment combinations could yield additional efficacy benefits for patients with mNSCLC, helping to improve outcomes further. For instance, impairing tumor DNA repair through poly (ADP-ribose) polymerase (PARP) inhibition may increase tumor immunogenicity and sensitize tumors to PD-(L)1 inhibition, possibly promoting a more durable antitumor response than PD-(L)1 inhibition alone.[15,16] Preclinical data suggest that olaparib (a first-generation PARP inhibitor) may potentiate the efficacy of DNA-damaging chemotherapies, including platinum-containing agents,[17,18] and enhance antitumor activity when combined with PD-(L)1 inhibition.[15,16]

The PD-L1 inhibitor durvalumab is approved for patients with unresectable, stage III NSCLC (as consolidation therapy after platinum-based chemoradiotherapy), patients with extensive-stage SCLC (in combination with platinum-based chemotherapy as first-line therapy), and most recently for patients with mNSCLC (in combination with tremelimumab and platinum-based chemotherapy as first-line therapy).[19,20] The combination of olaparib and durvalumab was found to have antitumor responses in 5% to 63% of patients across various solid tumor types.[21–28] Treatment-related adverse events (TRAEs) for this combination have been consistent across studies and indications, with no evidence of an increase in the frequency or severity of immune-mediated adverse events (AEs).[22–25,28]

The ORION study (NCT03775486) evaluated the efficacy and safety of this combination, versus durvalumab alone, as maintenance therapy in patients with mNSCLC and no disease progression after first-line chemo-immunotherapy (with durvalumab plus SoC platinum-doublet chemotherapy). Here, we report the primary analysis of PFS and key secondary end points from ORION, including exploratory analyses of PFS according to biomarker status.

Materials and Methods

Patients

ORION was a phase 2, randomized, multicenter, double-blind, international study comprising an initial therapy phase followed by a randomized maintenance

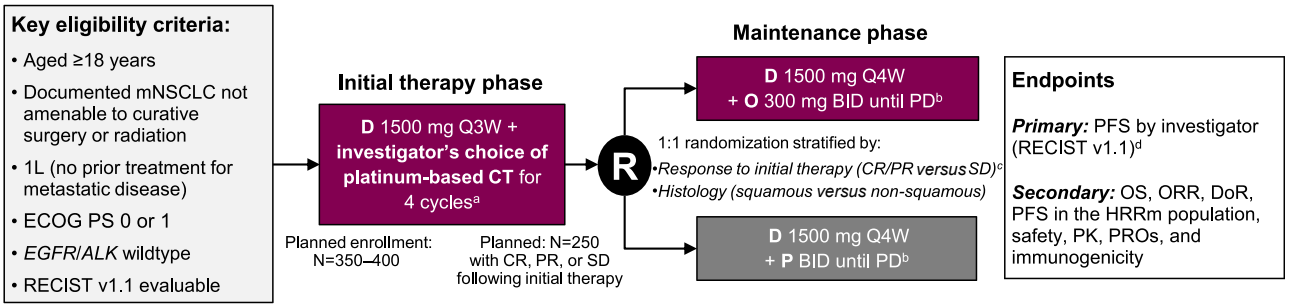

Figure 1. ORION study design. [a]Permitted platinum-doublet chemotherapy regimens were nab-paclitaxel plus carboplatin or gemcitabine plus carboplatin or cisplatin for squamous NSCLC and nab-paclitaxel plus carboplatin or pemetrexed plus carboplatin or cisplatin for nonsquamous NSCLC; pemetrexed maintenance was not allowed. [b]Patients received maintenance therapy until specific discontinuation criteria were met, including PD, unacceptable toxicity, and withdrawal of consent. [c]Obtained at the last visit before randomization (cycle 4 scan) during the initial therapy phase. [d]Defined as time from date of randomization to the date of objective radiological PD according to investigator assessment (RECIST v1.1) or death by any cause in the absence of PD. 1L, first-line therapy; BID, twice daily; CR, complete response; CT, chemotherapy; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRRm, homologous recombination repair-related gene mutation; mNSCLC, metastatic NSCLC; O, olaparib; ORR, objective response rate; OS, overall survival; P, placebo; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PROs, patient-reported outcomes; PS, performance status; QXW, every X weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

therapy phase. It was conducted in 65 centers across 12 countries (Belgium, Hungary, India, Japan, Mexico, Netherlands, Poland, South Korea, Russia, Ukraine, the United Kingdom, and the United States).

Eligible patients were adults with histologically or cytologically documented mNSCLC not amenable to curative surgery or radiation (International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology, eighth edition[29]) with tumors that lacked activating *EGFR* or *ALK* aberrations. Key inclusion criteria were as follows: Eastern Cooperative Oncology Group performance status of 0 or 1; no prior chemotherapy or any other systemic therapy for mNSCLC; adequate organ and bone marrow function without blood transfusions in the past 28 days; at least one tumor lesion, not previously irradiated, which could be accurately measured per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); a formalin-fixed, paraffin-embedded tumor sample for tissue-based immunohistochemistry and DNA sequencing to determine homologous recombination repair-related gene mutation (HRRm) status and PD-L1 expression, among others. In addition, the ability to swallow oral medication and lack of gastrointestinal illnesses precluding absorption of olaparib were required.

Key exclusion criteria were as follows: mixed SCLC and sarcomatoid variant NSCLC; prior exposure to any chemotherapy agents for metastatic disease, PARP therapy, or immune-mediated therapy; active or prior documented autoimmune or inflammatory disorders; any contraindications to platinum-based chemotherapy; any concurrent chemotherapy, investigational product, biological, or hormonal therapy for cancer treatment; current or prior use of immunosuppressive medication less than or equal to 14 days before the first dose of investigational product; untreated central nervous system metastases or carcinomatous meningitis; and active infection. Comprehensive eligibility criteria are listed in the Supplementary Methods.

All patients provided written informed consent to participate in the study, which was approved by the relevant ethics committee or institutional review board. ORION was run in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

Study Design and Treatments

The study design is presented in Figure 1. Patients were enrolled into an initial therapy phase to receive first-line durvalumab (1500 mg intravenously [IV]; every 3 wk) plus investigator's choice of SoC platinum-doublet chemotherapy for squamous (nab-paclitaxel plus carboplatin or gemcitabine plus carboplatin or cisplatin) or nonsquamous NSCLC (nab-paclitaxel plus carboplatin or pemetrexed plus carboplatin or cisplatin) for four cycles. Patients who completed all four cycles of initial therapy and achieved and maintained complete response (CR) or partial response (PR) until the end of the initial therapy phase, or maintained stable disease throughout this phase, were randomized (1:1) to receive maintenance therapy with durvalumab (1500 mg IV; every 4 wk) plus either olaparib (300 mg) or matching placebo (given orally twice a day); maintenance pemetrexed was not permitted because of safety considerations.

A "maintenance baseline" scan was performed 14 to 28 days after cycle 4 day 1 of the initial therapy phase to determine eligibility for the maintenance phase. Randomization was stratified by tumor histologic type (squamous versus nonsquamous) and objective response during the initial therapy phase (CR or PR versus stable disease; obtained at the last visit before randomization [cycle 4 scan]). Eligible patients were randomized to maintenance therapy less than or equal to 5 weeks after cycle 4 day 1 of the initial therapy phase. Patients received maintenance therapy until specific discontinuation criteria were met, including progressive disease (PD), unacceptable toxicity, or withdrawal of consent. All patients were followed for survival until the end of the study.

End Points and Assessments

All prespecified end points relate to the randomized maintenance phase of the study. The primary end point was PFS in the intent-to-treat (ITT) population (i.e., all patients randomized to the maintenance phase); PFS was defined as time from randomization to the date of objective radiological PD according to investigator assessment (RECIST v1.1), or death by any cause in the absence of PD. The secondary end points included overall survival (OS; time from randomization to the date of death by any cause), objective response rate (ORR; RECIST v1.1), duration of response (DoR; RECIST v1.1), PFS in patients with HRRm (RECIST v1.1), and safety and tolerability (all reported here), including patient-reported outcomes, pharmacokinetics, and immunogenicity (not reported). PFS according to PD-L1 expression level was a prespecified, exploratory end point.

For efficacy assessments, tumor evaluation scans were performed every 8 weeks up to week 48 and then every 12 weeks thereafter until objective PD was documented. For assessments of safety and tolerability, AEs were graded using Common Terminology Criteria for Adverse Events version 5.

Provision of a formalin-fixed, paraffin-embedded tumor sample for biomarker testing was mandatory; tissue samples could be either newly acquired (preferred) or archival ($<$3 y old at screening). HRRm status was determined at a central reference laboratory using the FoundationOne CDx tissue-based assay; patients who did not have a sample that was adequate for the preplanned tissue-based HRRm testing underwent exploratory sequencing of circulating tumor DNA using the GuardantOMNI assay. PD-L1 expression on tumor cells was determined using the VENTANA PD-L1 (SP263) immunohistochemistry assay.

Statistical Analyses

It was estimated that approximately 350 to 400 patients needed to be enrolled into the initial therapy phase for approximately 250 patients whose disease had not progressed to be eligible for randomization to the maintenance phase. To provide strong control of the type I error rate α equals to 5% (two-sided), the testing procedure for PFS (primary end point) and OS (key secondary end point) was hierarchical. The primary analysis was planned for when approximately 163 PFS events had occurred across both maintenance arms; with 163 events (approximately 65% maturity on the basis of 250 patients being randomized) and an assumed true hazard ratio (HR) of 0.60, it was estimated that the study would have 90% power to have a statistically significant difference at the two-sided 5% significance level. An interim analysis of OS was planned to correspond with the timing of the primary analysis of PFS, when it was anticipated that 109 death events would have occurred (67% information fraction).

Medians and landmark rates for PFS, OS, and DoR were estimated using the Kaplan-Meier method. PFS and OS for the ITT population were analyzed using a log-rank test adjusted for objective response to durvalumab plus chemotherapy in the initial therapy phase (CR or PR versus stable disease) and tumor histologic type (squamous versus nonsquamous) for generation of the p value. The effect of durvalumab plus olaparib versus durvalumab plus placebo was estimated by the HR together with its 95% confidence interval (CI) calculated from a stratified Cox proportional hazards model. For analyses of PFS in the subgroups, HRs and 95% CIs were calculated from Cox proportional hazards models with treatment as the only covariate. Between-arm comparison of the ORR was analyzed using logistic regression (adjusting for response to initial therapy and tumor histologic type, the same factors used to adjust the primary PFS analysis); results were presented in terms of an OR together with its associated profile likelihood CI. SAS software version 9.4 was used for all analyses.

Results

Patients and Treatment

A total of 594 patients were enrolled between January 2019 and February 2020, 401 (67.5%) of whom received durvalumab and chemotherapy during the initial therapy phase ($\geq$1 dose of each medication). Reasons for discontinuing durvalumab and chemotherapy during the initial therapy phase are listed in the Consolidated Standards of Reporting Trials diagram (Supplementary Fig. 1). After initial therapy, 269 of 401 patients (67.1%) were randomized to the maintenance phase; 134 were assigned to durvalumab plus olaparib and 135 were assigned to durvalumab plus placebo (Supplementary Fig. 1).

Patients who underwent randomization had a median age of 65 (range: 24–84) years, 72.5% were male,

Table 1. Baseline Demographics and Disease Characteristics (ITT Population)

Characteristics		Durvalumab Plus Olaparib (n = 134)	Durvalumab Plus Placebo (n = 135)	Total (N = 269)
Median age at study entry, y (range)		67 (24-84)	64 (30-80)	65 (24-84)
Age category, n (%)	<50 y	7 (5.2)	14 (10.4)	21 (7.8)
	≥50 to <65 y	49 (36.6)	55 (40.7)	104 (38.7)
	≥65 to <75 y	54 (40.3)	54 (40.0)	108 (40.1)
	≥75 y	24 (17.9)	12 (8.9)	36 (13.4)
Sex, n (%)	Male	98 (73.1)	97 (71.9)	195 (72.5)
	Female	36 (26.9)	38 (28.1)	74 (27.5)
Race, n (%)[a]	White	96 (71.6)	89 (65.9)	185 (68.8)
	Asian	37 (27.6)	45 (33.3)	82 (30.5)
Smoking status, n (%)	Current or former	109 (81.3)	103 (76.3)	212 (78.8)
	Never	25 (18.7)	32 (23.7)	57 (21.2)
ECOG PS, n (%)[b]	0	52 (38.8)	54 (40.0)	106 (39.4)
	1	81 (60.4)	80 (59.3)	161 (59.9)
	2	1 (0.7)	1 (0.7)	2 (0.7)[c]
IASLC disease stage at initial diagnosis, n (%)	I-III	13 (9.7)	13 (9.6)	26 (9.7)
	IVA	76 (56.7)	77 (57.0)	153 (56.9)
	IVB	45 (33.6)	45 (33.3)	90 (33.5)
Histologic subtype, n (%)	Squamous	58 (43.3)	59 (43.7)	117 (43.5)
	Nonsquamous	76 (56.7)	76 (56.3)	152 (56.5)
HRRm status, n (%)[d]	Mutant	11 (8.2)	17 (12.6)	28 (10.4)
	Wildtype	119 (88.8)	113 (83.7)	232 (86.2)
	Unknown[e]	4 (3.0)	5 (3.7)	9 (3.3)
PD-L1 expression level, n (%)	<1%	43 (32.1)	56 (41.5)	99 (36.8)
	1%-49%	34 (25.4)	25 (18.5)	59 (21.9)
	≥50%	24 (17.9)	19 (14.1)	43 (16.0)
	Unknown[e]	33 (24.6)	35 (25.9)	68 (25.3)
Objective tumor response to initial therapy with durvalumab plus CT, n (%)[f]	CR or PR	63 (47.0)	68 (50.4)	131 (48.7)
	Stable disease	70 (52.2)	67 (49.6)	137 (50.9)

[a]Two patients were Black or African American (one in each arm).
[b]Determined at baseline before randomization.
[c]Two patients had ECOG PS 2 at baseline (one per arm); both had PS 1 at screening.
[d]HRRm status summary on the basis of test result data from patients profiled using the FoundationOne CDx tissue-based assay (the preplanned method; n = 181) and the GuardantOMNI assay (n = 81); two patients were profiled with both assays. The HRRm subgroup was defined by the presence of functional mutations in the following genes: *BRCA1*, *BRCA2*, *ATM*, *RAD51B*, *RAD51C*, *RAD54L*, *RAD51D*, *BRIP1*, *FANCI*, *FANCL*, *PALB2*, *BARD1*, *CHEK1*, *CHEK2*, and *CDK12*.
[e]Sample could not be tested due to an inadequate quality sample or insufficient sample being available.
[f]Response collected 14 to 28 days after cycle 4 day 1 of the initial therapy phase. Reported per investigator responses on the case report form; no patient had CR and one (allocated to the durvalumab plus olaparib arm) had PD (reported as a protocol deviation).
CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HRRm, homologous recombination repair-related gene mutation; IASLC, International Association for the Study of Lung Cancer; ITT, intent-to-treat; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; PS, performance status.

68.8% were White, and 78.8% had a history of smoking. Most had stage IVA disease (56.9%) and nonsquamous tumor histologic type (56.5%) at initial diagnosis (Table 1). Baseline characteristics were generally well balanced between the two arms; however, a higher proportion of patients were aged 75 years or above in the durvalumab plus olaparib arm (17.9%) versus the durvalumab plus placebo arm (8.9%). Use of palliative radiotherapy (administered before initial study therapy) was similar between the durvalumab plus olaparib (6.0%) and durvalumab plus placebo (6.7%) arms.

At the data cutoff for the final analysis of PFS (January 11, 2021), 92 patients remained on maintenance therapy (comprising 38.1% and 30.6% of patients who received durvalumab in the durvalumab plus olaparib and durvalumab plus placebo arms, respectively) and 155 were ongoing in the study (57.5% and 57.8% of patients randomized to each arm, respectively). The most common reasons for discontinuing durvalumab were PD (66 [49.3%] in the durvalumab plus olaparib arm versus 81 [60.4%] in the durvalumab plus placebo arm), AEs (9 [6.7%] versus 7 [5.2%], respectively), and patient decision (7 [5.2%] versus 6 [4.5%], respectively).

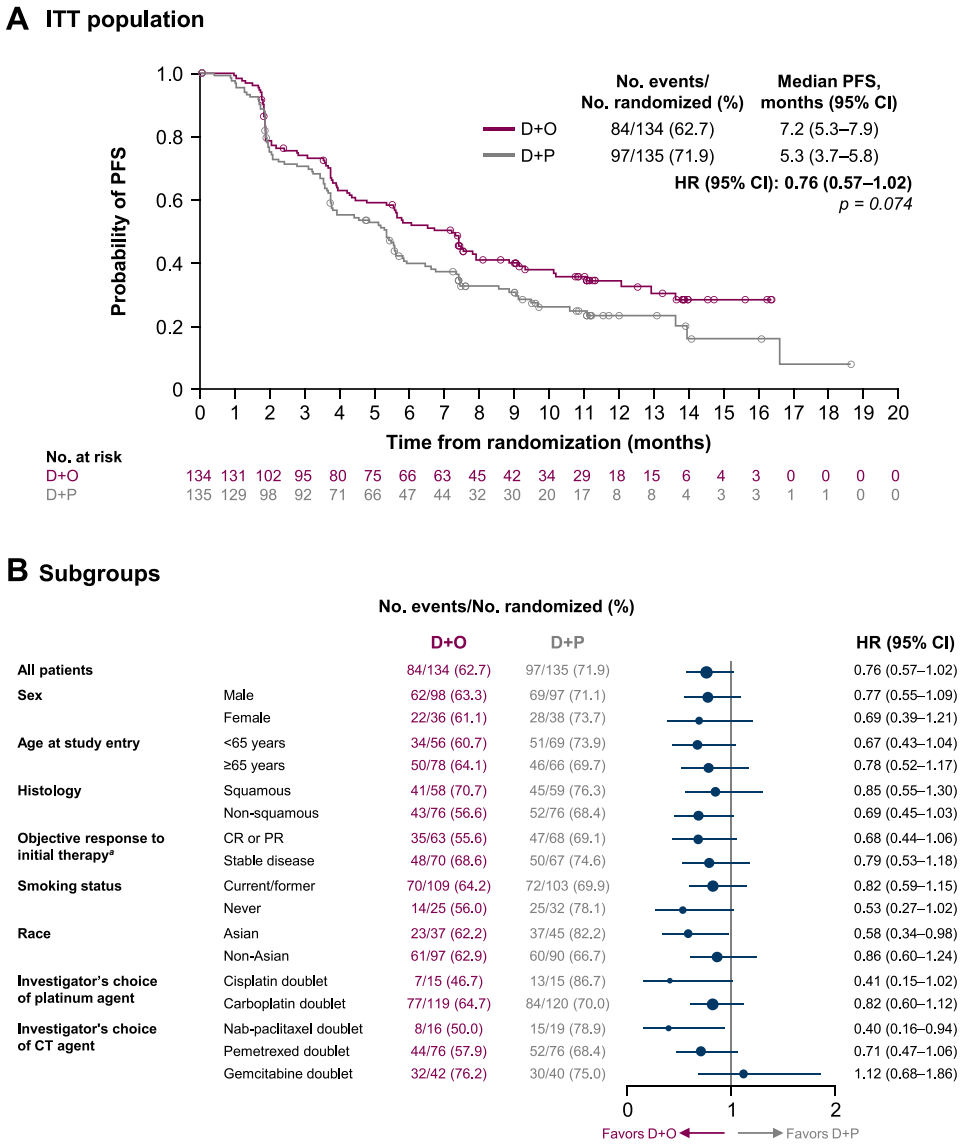

Figure 2. Investigator-assessed PFS (maintenance phase) in (*A*) the ITT population and (*B*) exploratory subgroups. Patients who did not progress or die, or who progressed or died after two or more missed visits, were censored at the latest evaluable RECIST assessment, or at day 1 if there were no evaluable visits. [a]Based on actual values recorded on the case report form as assessed by the investigator. Excludes one patient allocated to the durvalumab plus placebo arm who had PD at the end of initial therapy (reported as a protocol deviation). CI, confidence interval; CT, chemotherapy; D+O, durvalumab plus olaparib; D+P, durvalumab plus placebo; HR, hazard ratio; ITT, intent-to-treat; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

The most common reasons for discontinuing olaparib or placebo were PD (59 [46.1%] in the durvalumab plus olaparib arm versus 76 [59.4%] in the durvalumab plus placebo arm), AEs (13 [10.2%] versus 5 [3.9%], respectively), and patient decision (5 [3.9%] versus 5 [3.9%], respectively).

Patients received a median of six cycles of durvalumab as maintenance treatment in both the durvalumab plus olaparib (range: 1–21 cycles) and durvalumab plus placebo (range: 1–22 cycles) arms; the median total duration of maintenance treatment with durvalumab was 210.5 (range: 28–582) days and 168.0 (range: 11–615) days in each arm, respectively. The median total duration of maintenance treatment with olaparib and placebo was 199.0 (range: 1–545) days and 168.5 (range: 15–615) days, respectively.

Efficacy

Primary End Point. At the data cutoff, 181 of 269 (67.3%) randomized patients had experienced PFS events, including 84 of 134 patients (62.7%) in the durvalumab plus olaparib arm and 97 of 135 patients

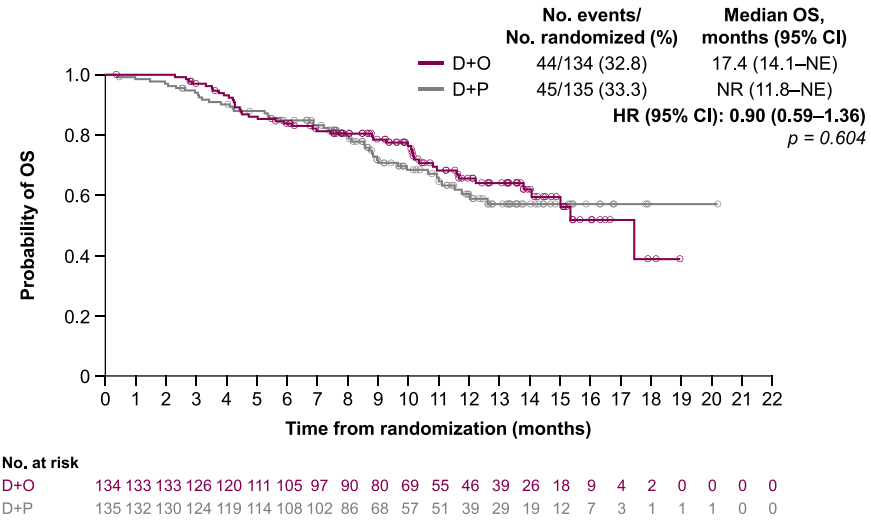

Figure 3. OS (maintenance phase; ITT population). CI, confidence interval; D+O, durvalumab plus olaparib; D+P, durvalumab plus placebo; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; OS, overall survival.

(71.9%) in the durvalumab plus placebo arm. Summaries of the specific types of PFS events and the incidence of new lesions according to anatomical site are provided (Supplementary Tables 1 and 2). The median duration of follow-up in censored patients (from randomization) was 9.6 (range: 0–18.6) months. Investigator-assessed PFS (from randomization) was numerically longer with durvalumab plus olaparib (median: 7.2 mo, 95% CI: 5.3–7.9) versus durvalumab plus placebo (median: 5.3 mo, 95% CI: 3.7–5.8) (Fig. 2*A*); however, the difference was not statistically significant (stratified HR = 0.76, 95% CI: 0.57–1.02, $p = 0.074$). To assess possible evaluation bias, the treatment effect for PFS was estimated using results determined by blinded independent central review; the result was consistent with the primary analysis (stratified HR = 0.75, 95% CI: 0.56–1.01).

Findings across exploratory subgroups were generally consistent with the ITT analysis (Fig. 2*B*); however, PFS favored durvalumab plus placebo versus durvalumab plus olaparib among patients who received a gemcitabine-doublet chemotherapy regimen during initial therapy (HR = 1.12, 95% CI: 0.68–1.86). In addition, the treatment effect for PFS with durvalumab plus olaparib, relative to durvalumab plus placebo, was more pronounced among the following: Asians (HR = 0.58, 95% CI: 0.34–0.98) compared with non-Asians (HR = 0.86, 95% CI: 0.60–1.24); never smokers (HR = 0.53, 95% CI: 0.27–1.02) compared with current or former smokers (HR = 0.82, 95% CI: 0.59–1.15); patients with nonsquamous tumor histologic type (HR = 0.69, 95% CI: 0.45–1.03) compared with those with squamous tumor histologic type (HR = 0.85, 95% CI: 0.55–1.30); and patients who received cisplatin-based chemotherapy (HR = 0.41, 95% CI: 0.15–1.02) compared with those with carboplatin-based chemotherapy (HR = 0.82, 95% CI: 0.60–1.12) during initial therapy. Kaplan-Meier distributions of PFS according to tumor histologic type are provided (Supplementary Fig. 2).

Secondary End Points. OS data were immature: 89 of 269 (33.1%) randomized patients had died at the data cutoff (44 in the durvalumab plus olaparib arm and 45 in the durvalumab plus placebo arm). Median OS was 17.4 months (95% CI: 14.1–not estimable) in the durvalumab plus olaparib arm and was not reached (95% CI: 11.8–not estimable) in the durvalumab plus placebo arm; the 12-month OS rates were 65.6% (95% CI: 55.4–73.9) and 60.4% (95% CI: 49.9–69.3), respectively (stratified HR = 0.90, 95% CI: 0.59–1.36, $p = 0.604$) (Fig. 3).

The ORR (including unconfirmed responses) was numerically higher in the durvalumab plus olaparib arm (17.1%) compared with the durvalumab plus placebo arm (13.7%) (OR = 1.29; 95% CI: 0.66–2.57) (Supplementary Table 3). Two patients in the durvalumab plus olaparib arm had CR as their best objective response; no patient in the durvalumab plus placebo arm had a CR. Confirmed CR or PR was reported for 14.7% and 9.2% of patients in each arm, respectively. Median DoR was not reached in either arm (Supplementary Table 1). An estimated 79.1% and 65.7% of patients in the durvalumab plus olaparib and durvalumab plus placebo arms, respectively, remained in response at 6 months (and 69.2% and 65.7%, respectively, remained in response at 12 mo).

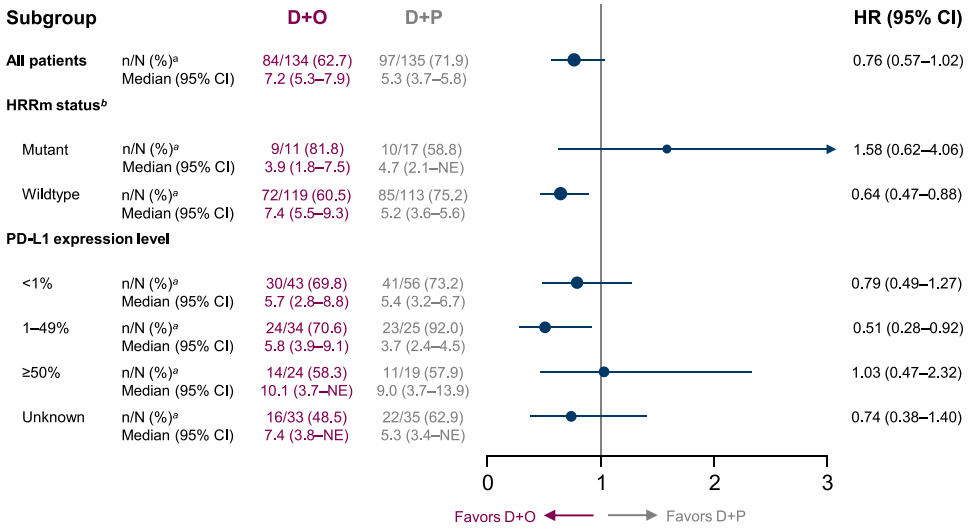

Figure 4. Investigator-assessed PFS by biomarker status (maintenance phase; biomarker-evaluable population). [a]No. of events (n)/no. of patients randomized (N). [b]HRRm status was defined by the presence of functional mutations in the following genes: *BRCA1*, *BRCA2*, *ATM*, *RAD51B*, *RAD51C*, *RAD54L*, *RAD51D*, *BRIP1*, *FANCI*, *FANCL*, *PALB2*, *BARD1*, *CHEK1*, *CHEK2*, and *CDK12*. Overall, 181 patients had HRRm status determined using the FoundationOne CDx tissue-based assay (the preplanned method) and 81 patients underwent sequencing of ctDNA using the GuardantOMNI assay (two patients were profiled with both assays); nine patients had unknown HRRm status (D+O, n = 4; D+P, n = 5). Although PFS in the HRRm population was a secondary end point, the analysis presented here is exploratory as ctDNA sequencing was performed to determine HRRm status in patients who were unable to provide a sample adequate for the preplanned HRRm tissue-based testing. CDx, companion diagnostic; CI, confidence interval; ctDNA, circulating tumor DNA; D+O, durvalumab plus olaparib; D+P, durvalumab plus placebo; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; NE, not estimable; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Exploratory Analyses of PFS According to Biomarker Status

HRRm status was assessed by preplanned tissue-based testing (FoundationOne CDx assay. Tumors were considered HRRm positive if a functional mutation was detected in one of 15 genes (*BRCA1*, *BRCA2*, *ATM*, *RAD51B*, *RAD51C*, *RAD54L*, *RAD51D*, *BRIP1*, *FANCI*, *FANCL*, *PALB2*, *BARD1*, *CHEK1*, *CHEK2*, and *CDK12*); this subgroup defines one of the populations eligible for olaparib based on its ability to enrich for clinical activity with olaparib in the context of the PROfound study.[30] In all, 14 of 269 (5.2%) randomized patients had positive HRRm status. HRRm status could not be determined for 32.7% of patients due to their tissue sample being of inadequate quality, or insufficient sample being available. The small number of patients with HRRm-positive tumors determined through tissue-based testing precluded meaningful analysis of PFS. Therefore, the HRRm biomarker-evaluable population (BEP) was enlarged to make an analysis of PFS feasible; patients for whom tissue-based testing was unsuccessful had HRRm status determined through sequencing of circulating tumor DNA (GuardantOMNI assay). The final (aggregated) HRRm BEP included 260 of 269 (96.7%) randomized patients; 28 of 260 (10.8%) had HRRm-positive tumors (Fig. 4). Consistent with the ITT analysis, PFS favored durvalumab plus olaparib versus durvalumab plus placebo among patients with HRR-wildtype tumors (HR = 0.64, 95% CI: 0.47–0.88). In contrast, no improved activity for durvalumab plus olaparib versus durvalumab plus placebo was observed among patients with HRRm-positive tumors (HR = 1.58, 95% CI: 0.62–4.06). Moreover, positive HRRm status did not enrich for activity with olaparib: within the durvalumab plus olaparib arm, median PFS was shorter among patients with HRRm-positive (3.9 mo, 95% CI: 1.8–7.5) versus HRR-wildtype (7.4 mo, 95% CI: 5.5–9.3) tumors.

The PD-L1 BEP included 201 of 269 (74.7%) randomized patients; 49.3%, 29.4%, and 21.4% of patients in the BEP had a PD-L1 expression level of less than 1%, 1% to 49%, and 50% or more, respectively. Consistent with the ITT analysis, PFS trends favored durvalumab plus olaparib versus durvalumab plus placebo in the PD-L1 less than 1% (HR = 0.79, 95% CI: 0.49–1.27) and 1% to 49% (HR = 0.51, 95% CI: 0.28–0.92) subgroups (Fig. 4). Meanwhile, PFS in the PD-L1 50% or more subgroup did not differ between the two arms (HR = 1.03, 95% CI: 0.47–2.32); median PFS in both arms was numerically longer in the PD-L1 50% or more subgroup compared with the less than 1% and 1% to 49% subgroups.

Table 2. Summary of AEs by Category and by Preferred Term (Maintenance Phase; Safety Analysis Set)

AE Category	Durvalumab Plus Olaparib, n (%) (n = 134)	Durvalumab Plus Placebo, n (%) (n = 134)[a]
Any AE	116 (86.6)	104 (77.6)
TRAE[b]	83 (61.9)	54 (40.3)
Any AE of grade 3 or 4	46 (34.3)	24 (17.9)
TRAE of grade 3 or 4[b]	25 (18.7)	6 (4.5)
Any AE with outcome of death[c]	5 (3.7)	7 (5.2)
TRAE with outcome of death[b]	0	1 (0.7)
Any Serious AE	25 (18.7)	19 (14.2)
Serious TRAE[b]	10 (7.5)	3 (2.2)
Any AE leading to treatment discontinuation[d]	14 (10.4)	6 (4.5)
TRAE leading to treatment discontinuation[b,d]	8 (6.0)	2 (1.5)
AEs of any cause by preferred term (≥5% total incidence)[e]		
Anemia	35 (26.1)	11 (8.2)
Nausea	19 (14.2)	10 (7.5)
Decreased appetite	16 (11.9)	9 (6.7)
Fatigue	15 (11.2)	9 (6.7)
Arthralgia	13 (9.7)	8 (6.0)
Hypothyroidism	8 (6.0)	13 (9.7)
Asthenia	8 (6.0)	10 (7.5)
Vomiting	15 (11.2)	3 (2.2)
Weight decreased	12 (9.0)	6 (4.5)
Alanine aminotransferase increased	6 (4.5)	11 (8.2)
Diarrhea	11 (8.2)	6 (4.5)
Dyspnea	10 (7.5)	4 (3.0)
Pneumonia	8 (6.0)	6 (4.5)

Note: Includes AEs with an onset or worsening date on or after the first dose in the maintenance phase and up to and including the end of the follow-up period but before initiation of subsequent therapy.
[a]One patient randomized to the durvalumab plus placebo arm did not receive maintenance therapy and was excluded from the safety analysis set.
[b]Possible causal relationship between AEs and any of the study treatments (i.e., durvalumab or olaparib/placebo) was according to investigator assessment.
[c]AEs with outcome of death in the durvalumab plus olaparib arm were pneumonia, endocarditis, cardiovascular insufficiency, pulmonary hemorrhage, and death (n = 1 for each). AEs with outcome of death in the durvalumab plus placebo arm were disease progression (n = 2), pneumonia (n = 1), depressed level of consciousness and seizure (n = 1), cardiac failure acute (n = 1), cardiopulmonary failure (n = 1), and general physical health deterioration (n = 1).
[d]Includes patients who permanently discontinued any of the study treatments.
[e]Sorted in decreasing order of frequency (total across arms).
AE, adverse event; TRAE, treatment-related adverse event.

Safety

During the maintenance phase, 86.6% and 77.6% of patients who received durvalumab plus olaparib and durvalumab plus placebo, respectively, experienced AEs of any cause and severity grade. The most frequently reported AEs of any cause and severity grade are listed in Table 2; anemia was the most frequently reported AE with durvalumab plus olaparib (26.1%), followed by nausea (14.2%). A majority of the most frequent AEs occurred with a numerically higher incidence in the durvalumab plus olaparib arm versus the durvalumab plus placebo arm, with the greatest between-arm differences observed for anemia (26.1% versus 8.2%), vomiting (11.2% versus 2.2%), and nausea (14.2% versus 7.5%). The incidence of grade 3 or 4 AEs (34.3% versus 17.9%) and AEs leading to discontinuation of either study treatment (10.4% versus 4.5%) was also numerically higher with durvalumab plus olaparib versus durvalumab plus placebo; anemia was the most common grade 3 or 4 AE and was reported with a numerically higher incidence among patients who received durvalumab plus olaparib (12.7%) versus durvalumab plus placebo (2.2%) (Supplementary Table 4). The incidence of grade 5 AEs was comparable between the arms (3.7% versus 5.2%, respectively).

Overall, 61.9% and 40.3% of patients who received durvalumab plus olaparib and durvalumab plus placebo, respectively, experienced any-grade AEs possibly related to either study treatment ("TRAEs") (Table 2). The most common TRAEs of any grade (incidence ≥5% in either arm) were anemia (reported in 15.7% of patients in the durvalumab plus olaparib arm versus 3.0% in the durvalumab plus placebo arm), followed by nausea (11.9% versus 5.2%), hypothyroidism (5.2% versus 7.5%), alanine aminotransferase increased (3.0% versus 5.2%), fatigue (6.0% versus 2.2%), asthenia (2.2% versus 5.2%), vomiting (6.7% versus

0.7%), and decreased appetite (5.2% versus 0.7%). The incidence of grade 3 or 4 TRAEs (18.7% versus 4.5%), serious TRAEs (7.5% versus 2.2%), and TRAEs leading to discontinuation of either study treatment (6.0% versus 1.5%) was numerically higher with durvalumab plus olaparib versus durvalumab plus placebo (Table 2); no patient experienced grade 5 TRAEs with durvalumab plus olaparib, whereas one patient (0.7%) had a grade 5 TRAE with durvalumab plus placebo (pneumonia).

Predefined AEs of special interest for olaparib were reported in 3.7% of patients in both arms. Meanwhile, predefined AEs of special or potential interest for durvalumab were reported in 41.0% of patients in both arms; overall, 6.0% of patients in each arm had grade 3 or 4 AEs of special or potential interest for durvalumab. Immune-mediated AEs were reported in 13.4% and 14.9% of patients who received durvalumab plus olaparib and durvalumab plus placebo, respectively (Supplementary Table 5). Most immune-mediated AEs were grade 1 or 2; grade 3 or 4 events were reported in three patients (2.2%) who received durvalumab plus olaparib and one patient (0.7%) who received durvalumab plus placebo.

Discussion

The primary end point of PFS was not met in this preplanned analysis from ORION. Although the combination of durvalumab and olaparib was associated with a numerical improvement in PFS versus durvalumab alone, the difference was not statistically significant (HR = 0.76, 95% CI: 0.57–1.02, $p = 0.074$). OS data were immature at the data cutoff (33.1% maturity).

Safety findings were consistent with the known profiles of durvalumab and olaparib, administered alone and in combination,[19,21,23,27,28,31] and no new safety signals were identified. Administration of olaparib alongside durvalumab was generally well tolerated after four cycles of durvalumab plus SoC chemotherapy; however, the incidence of any-grade anemia, vomiting, and nausea, including the overall incidence of grade 3 or 4 AEs and AEs leading to discontinuation, was numerically higher with the combination versus durvalumab alone. Reassuringly, the combination was not associated with a greater frequency or severity of immune-mediated AEs.

To the best of our knowledge, ORION is the first randomized study to investigate the combination of PARP inhibition and immunotherapy as maintenance therapy in the mNSCLC setting. Previous studies across various solid tumor indications have revealed that a subset of patients can achieve durable responses with the combination of durvalumab and olaparib.[22–25,27,28] Theoretically, patients who achieve at least stable disease with chemo-immunotherapy are likely to be sensitive to DNA-damaging agents (e.g., platinum); therefore, they should have the most to gain from the addition of a PARP inhibitor such as olaparib to their treatment regimen. Despite this, the combination of olaparib and durvalumab did not yield a meaningful improvement in the ORR in ORION (OR = 1.29, 95% CI: 0.66–2.57). The reasons for this are unclear.

Baseline characteristics in ORION were broadly representative of a typical patient population with mNSCLC. Patients with nonsquamous tumor histologic type made up a lower proportion of the population that was randomized to maintenance therapy than may have been expected for this disease setting, possibly because the ORION protocol did not permit use of maintenance pemetrexed (an option for these patients[32]). Notably, findings from the exploratory subgroups analysis suggest that patients with nonsquamous tumor histologic type may derive more PFS benefit from the addition of a PARP inhibitor alongside anti–PD-(L)1 therapy (HR = 0.69, 95% CI: 0.45–1.03) when compared with patients with squamous tumor histologic type (HR = 0.85, 95% CI: 0.55–1.30). Ongoing phase 3 studies are evaluating the combination of PD-(L)1 and PARP inhibition as maintenance therapy (after first-line chemo-immunotherapy) exclusively in patients with (1) nonsquamous mNSCLC (KEYLYNK-006; NCT03976323) and (2) squamous mNSCLC (KEYLYNK-008; NCT03976362),[33,34] and should provide more definitive conclusions regarding the benefit of the combination in each of these populations. Findings from the subgroups analysis also suggest that patients who receive cisplatin-based chemotherapy regimens during initial therapy may derive more PFS benefit from the combination compared with those who receive carboplatin-based regimens; however, interpretation is limited by the small number of randomized patients who received cisplatin-based regimens (n = 30).

Previous studies of PARP inhibitors (alone or in combination with durvalumab) across various solid tumor indications have established that patients harboring mutations in the HRR pathway are more likely to benefit from PARP inhibition.[27,35–37] In ORION, patients with HRR wildtype tumors seemed to derive benefit from the combination of durvalumab and olaparib, whereas (counterintuitively) HRRm-positive status did not correlate with improved PFS outcomes with this combination. This suggests that HRRm status may not be a useful predictive biomarker for response to PARP inhibitors in patients with mNSCLC, at least when used in combination with immunotherapy in the maintenance setting. Nevertheless, relatively few patients harbored HRR gene mutations in ORION (n = 28)

and HRRm status was not used as a trial stratification factor, limiting interpretation. The prevalence of HRRm in ORION (10.8%) was similar to the prevalence observed in a large sample of patients with lung cancer (12.7%).[38]

Findings from ORION suggest that the benefit of combining inhibitors of PD-(L)1 and PARP may be limited to patients with lower PD-L1 expression levels. In the PD-L1 50% or more subgroup, median PFS was numerically longer for both maintenance arms versus the PD-L1 less than 50% subgroups (as expected given that PD-L1 is a predictive biomarker for response to immunotherapy); however, the PFS HR was 1.03, suggesting that patients with PD-L1 expression of 50% or more, who are more likely to benefit from immunotherapy alone, may not benefit further from the addition of a PARP inhibitor. Nevertheless, interpretation of this exploratory analysis is limited by the overlapping 95% CIs for HRs across the subgroups, the large proportion of patients for whom PD-L1 expression was unknown, small subgroup sizes, and PD-L1 expression level not being used as a trial stratification factor.

Treatment regimens comprising combinations of next-generation PARP inhibitors and PD-(L)1 inhibitors represent a possible avenue for future research. AZD5305 is a highly selective PARP1 inhibitor currently in phase 1 development (NCT04644068)[39,40]; targeting PARP1 specifically could retain the therapeutic benefit of dual PARP inhibitors (which inhibit PARP1 and PARP2 [e.g., olaparib]), while also reducing the risk of hematologic toxicity. The potential for an improved therapeutic index with selective PARP1 inhibitors could improve the tolerability of combination regimens, possibly opening new therapeutic opportunities for patients with solid tumors, including NSCLC.

In conclusion, maintenance therapy with durvalumab in combination with olaparib was not associated with a statistically significant improvement in PFS compared with durvalumab alone, although numerical improvement was observed. The combination was generally well tolerated after four cycles of initial chemoimmunotherapy, with no new safety concerns. Contrary to expectations, no improved activity for the combination was observed among patients with HRRm-positive tumors, although the small size of this subgroup prevents robust conclusions. Selected patients with mNSCLC may benefit from combined therapy incorporating PD-(L)1 and PARP inhibitors. Additional studies are ongoing to evaluate the possible role of this combination as maintenance therapy for patients with nonsquamous (KEYLYNK-006) and squamous (KEYLYNK-008) mNSCLC. Further research is needed to identify biomarkers that can predict response to PARP inhibitors in this disease setting.

CRediT Authorship Contribution Statement

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Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at: www.vivli.org. Data for

studies not listed on Vivli could be requested through Vivli at: https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.06.013.

References

1. Shields MD, Marin-Acevedo JA, Pellini B. Immunotherapy for advanced non-small cell lung cancer: a decade of progress. *Am Soc Clin Oncol Educ Book*. 2021;41:e105-e127.
2. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
3. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819-1830.
4. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.
5. Alexander M, Kim SY, Cheng H. Update 2020: Management of non-small cell lung cancer. *Lung*. 2020;198:897-907.
6. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv192-iv237.
7. Singh N, Temin S, Baker S Jr, et al. Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO living guideline. *J Clin Oncol*. 2022;40:3323-3343.
8. Brahmer JR, Lee JS, Ciuleanu TE, et al. Five-year survival outcomes with nivolumab plus ipilimumab versus chemotherapy as first-line treatment for metastatic non-small cell lung cancer in CheckMate 227. *J Clin Oncol*. 2023;41:1200-1212.
9. Cho BC, Wu Y, Lopes G, et al. FP13.04 KEYNOTE-042 3-year survival update: 1L pembrolizumab vs platinum-based chemotherapy for PD-L1+ locally advanced/metastatic NSCLC. *J Thorac Oncol*. 2021;16(suppl):S225-S226.
10. Gray J, Rodríguez-Abreu D, Powell SF, et al. FP13.02 Pembrolizumab + pemetrexed-platinum vs pemetrexed-platinum for metastatic NSCLC: 4-year follow-up from KEYNOTE-189. *J Thorac Oncol*. 2021;16(suppl):S224.
11. Paz-Ares LG, Ciuleanu T-E, Cobo-Dols M, et al. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients (pts) with metastatic non-small cell lung cancer (NSCLC): 3-year update from CheckMate 9LA. *J Clin Oncol*. 2022;40(suppl 17):LBA9026.
12. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50. *J Clin Oncol*. 2021;39:2339-2349.
13. Robinson AG, Vicente D, Tafreshi A, et al. 97O First-line pembrolizumab plus chemotherapy for patients with advanced squamous NSCLC: 3-year follow-up from KEYNOTE-407. *J Thorac Oncol*. 2021;16(suppl):S748-S749.
14. Socinski MA, Nishio M, Jotte RM, et al. IMpower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. *J Thorac Oncol*. 2021;16:1909-1924.
15. Ding L, Kim HJ, Wang Q, et al. PARP inhibition elicits STING-dependent antitumor immunity in BRCA1-deficient ovarian cancer. *Cell Rep*. 2018;25:2972-2980.e5.
16. Stewart RA, Pilié PG, Yap TA. Development of PARP and immune-checkpoint inhibitor combinations. *Cancer Res*. 2018;78:6717-6725.
17. Evers B, Drost R, Schut E, et al. Selective inhibition of BRCA2-deficient mammary tumor cell growth by AZD2281 and cisplatin. *Clin Cancer Res*. 2008;14:3916-3925.
18. Rottenberg S, Jaspers JE, Kersbergen A, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci USA*. 2008;105:17079-17084.
19. Food and Drug Administration (FDA). Durvalumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s033lbl.pdf. Accessed February 2023.
20. European Medicines Agency (EMA). Imfinzi (durvalumab) summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf. Accessed October 2022.
21. Besse B, Awad MM, Forde PM, et al. OA15.05 Hudson: an open-label, multi-drug, biomarker-directed phase 2 study in NSCLC patients who progressed on anti-PD-(L)1 therapy. *J Thorac Oncol*. 2022;17(suppl):S41-S42.
22. Desmond D, Vilimas R, Mullenix C, et al. Durvalumab (D) in combination with olaparib (O) for advanced, previously treated non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2022;40:e21153.
23. Domchek SM, Postel-Vinay S, Im SA, et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. *Lancet Oncol*. 2020;21:1155-1164.
24. Karzai F, VanderWeele D, Madan RA, et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. *J Immunother Cancer*. 2018;6:141.
25. Lee JM, Cimino-Mathews A, Peer CJ, et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-ribose) polymerase inhibitor olaparib or vascular

endothelial growth factor receptor 1–3 inhibitor cediranib in women's cancers: a dose-escalation, phase I study. *J Clin Oncol*. 2017;35:2193–2202.
26. Post CCB, Westermann AM, Boere IA, et al. Efficacy and safety of durvalumab with olaparib in metastatic or recurrent endometrial cancer (phase II DOMEC trial). *Gynecol Oncol*. 2022;165:223–229.
27. Rosenberg JE, Park SH, Kozlov V, et al. Durvalumab plus olaparib in previously untreated, platinum-ineligible patients with metastatic urothelial carcinoma: a multicenter, randomized, phase II trial (BAYOU). *J Clin Oncol*. 2023;41:43–53.
28. Thomas A, Vilimas R, Trindade C, et al. Durvalumab in combination with olaparib in patients with relapsed SCLC: results from a phase II study. *J Thorac Oncol*. 2019;14:1447–1457.
29. International Association for the Study of Lung Cancer (IASLC). *Staging Manual in Thoracic Oncology*. 2nd ed. North Fort Myers, FL: Editorial Rx Press; 2016.
30. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091–2102.
31. Food and Drug Administration (FDA). Lynparza prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf. Accessed February 2023.
32. Food and Drug Administration (FDA). Alimta prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021462s021lbl.pdf. Accessed October 2022.
33. Gray JE, Owonikoko TK, Kato T, et al. 1418TiP Randomized, placebo-controlled phase III study of 1L pembrolizumab (Pembro) plus carboplatin/taxane followed by pembro with or without maintenance olaparib in patients (Pts) with metastatic squamous non-small cell lung cancer (sqNSCLC): KEYLYNK-008. *Ann Oncol*. 2020;31(suppl 4):S896.
34. Gray JE, Owonikoko TK, Kato T, et al. Randomized phase III study of first-line pembrolizumab plus pemetrexed/platinum followed by pembrolizumab and maintenance olaparib versus pemetrexed in patients with metastatic nonsquamous non-small cell lung cancer (NSCLC): KEYLYNK-006. *J Clin Oncol*. 2020;38(suppl 15):TPS9632.
35. Chi KN, Rathkopf DE, Smith MR, et al. Phase 3 MAGNITUDE study: first results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. *J Clin Oncol*. 2022;40:12.
36. Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. *Eur J Cancer*. 2016;60:49–58.
37. Poveda A, Lheureux S, Colombo N, et al. Olaparib maintenance monotherapy in platinum-sensitive relapsed ovarian cancer patients without a germline BRCA1/BRCA2 mutation: OPINION primary analysis. *Gynecol Oncol*. 2022;164:498–504.
38. Lai Z, Brosnan M, Sokol ES, et al. Landscape of homologous recombination deficiencies in solid tumours: analyses of two independent genomic datasets. *BMC Cancer*. 2022;22:13.
39. Illuzzi G, Staniszewska AD, Gill SJ, et al. Preclinical characterization of AZD5305, a next-generation, highly selective PARP1 inhibitor and trapper. *Clin Cancer Res*. 2022;28:4724–4736.
40. Johannes JW, Balazs A, Barratt D, et al. Discovery of 5-{4-[(7-ethyl-6-oxo-5,6-dihydro-1,5-naphthyridin-3-yl) methyl]piperazin-1-yl}-N-methylpyridine-2-carboxamide (AZD5305): a PARP1-DNA trapper with high selectivity for PARP1 over PARP2 and other PARPs. *J Med Chem*. 2021;64:14498–14512.