JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer

Yung-Jue Bang, Seock-Ah Im, Keun-Wook Lee, Jae Yong Cho, Eun-Kee Song, Kyung Hee Lee, Yeul Hong Kim, Joon Oh Park, Hoo Geun Chun, Dae Young Zang, Anitra Fielding, Jacqui Rowbottom, Darren Hodgson, Mark J. O'Connor, Xiaolu Yin, and Woo Ho Kim

See accompanying editorial doi:10.1200/JCO.2015.62.8487

ABSTRACT

Purpose
Gastric cancer cell lines, particularly those with low levels of ataxia telangiectasia mutated (ATM), a key activator of DNA damage response, are sensitive to the poly (ADP-ribose) polymerase inhibitor olaparib. We compared the efficacy of olaparib plus paclitaxel (olaparib/paclitaxel) with paclitaxel alone in patients with recurrent or metastatic gastric cancer and assessed whether low ATM expression is predictive of improved clinical outcome for olaparib/paclitaxel.

Patients and Methods
In this phase II, double-blind study (Study 39; NCT01063517), patients were randomly assigned to oral olaparib 100 mg twice per day (tablets) plus paclitaxel (80 mg/m^2 per day intravenously on days 1, 8, and 15 of every 28-day cycle) or placebo plus paclitaxel (placebo/paclitaxel), followed by maintenance monotherapy with olaparib (200 mg twice per day) or placebo. The study population was enriched to 50% for patients with low or undetectable ATM levels (ATM$_{low}$). Primary end point was progression-free survival (PFS).

Results
One hundred twenty-three of 124 randomly assigned patients received treatment (olaparib/paclitaxel, n = 61; placebo/paclitaxel, n = 62). The screening prevalence of ATM$_{low}$ patients was 14%. Olaparib/paclitaxel did not lead to a significant improvement in PFS versus placebo/paclitaxel (overall population: hazard ratio [HR], 0.80; median PFS, 3.91 *v* 3.55 months, respectively; ATM$_{low}$ population: HR, 0.74; median PFS, 5.29 *v* 3.68 months, respectively). However, olaparib/paclitaxel significantly improved overall survival (OS) versus placebo/paclitaxel in both the overall population (HR, 0.56; 80% CI, 0.41 to 0.75; P = .005; median OS, 13.1 *v* 8.3 months, respectively) and the ATM$_{low}$ population (HR, 0.35; 80% CI, 0.22 to 0.56; P = .002; median OS, not reached *v* 8.2 months, respectively). Olaparib/paclitaxel was generally well tolerated, with no unexpected safety findings.

Conclusion
Olaparib/paclitaxel is active in the treatment of patients with metastatic gastric cancer, with a greater OS benefit in ATM$_{low}$ patients. A phase III trial in this setting is under way.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Gastric cancer is the third most common cause of cancer deaths worldwide.[1] Five-year survival rate for patients with recurrent/metastatic gastric cancer is less than 20%, with limited treatment options for those who experience progression after fluoropyrimidine and platinum–based combination chemotherapies (the current first-line therapy).[2] Paclitaxel is active after first-line failure and has become a widely used second-line therapy[3]; paclitaxel alone often fails to provide adequate efficacy, with reported response rates of 16% to 21% and median overall survival (OS) of 7.4 to 9.5 months.[3-5] Adding targeted agents to second-line paclitaxel may improve clinical benefit.

Yung-Jue Bang, Seock-Ah Im, and Woo Ho Kim, Seoul National University College of Medicine; Jae Yong Cho, Yonsei University College of Medicine, Gangnam Severance Hospital; Yeul Hong Kim, Anam Hospital, Korea University College of Medicine; Joon Oh Park, Samsung Medical Center, Sungkyunkwan University School of Medicine; Hoo Geun Chun, Seoul St Mary's Hospital, Catholic University of Korea, Seoul; Keun-Wook Lee, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam; Eun-Kee Song, Chonbuk National University Medical School, Jeonju; Kyung Hee Lee, Yeungnam University Hospital, Daegu; Dae Young Zang, Hallym University Sacred Heart Hospital, Anyang, Korea; Anitra Fielding, Jacqui Rowbottom, Darren Hodgson, and Mark J. O'Connor, AstraZeneca, Macclesfield, United Kingdom; and Xiaolu Yin, Innovation Centre, AstraZeneca, Shanghai, China.

Published online ahead of print at www.jco.org on August 17, 2015.

Supported by AstraZeneca, Wilmington, DE.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Presented, in part, at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013.

Clinical trial information: NCT01063517

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Yung-Jue Bang, MD, PhD, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, 110-744, Korea; e-mail: bangyj@snu.ac.kr.

0732-183X/15/3399-1/$20.00

DOI: 10.1200/JCO.2014.60.0320

The oral poly (ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza; AstraZeneca, London, United Kingdom) traps inactivated PARP onto single-strand DNA breaks, preventing repair and generating a potential DNA replication block, leading to double-strand DNA breaks.[6,7] Olaparib is being developed to target tumors with deficiencies in double-strand DNA break repair, such as homologous recombination repair deficiencies, including those caused by *BRCA1/2* mutations.[8-10] Consistent with this, olaparib (capsule formulation) has demonstrated significant clinical benefit in patients with *BRCA*-mutated tumors (28% to 41% at the approved dose of 400 mg twice per day) and is generally well tolerated.[11-15]

Many gastric cancer cell lines are sensitive to olaparib; this seems less well correlated with sensitivity to platinum agents, suggesting that sensitivity markers may differ from those in ovarian cancer.[16] The prevalence of *BRCA* mutations in gastric cancer is low. In a gene expression association study, using cell lines from multiple tumor types, low ataxia telangiectasia mutated (ATM) levels were associated with olaparib sensitivity; subsequently, ATM deficiency has been associated specifically with olaparib sensitivity in mantle-cell lymphoma and gastric cancer cell lines.[16-19] ATM plays an essential role in the cellular DNA damage response necessary to maintain genome stability.[20-22] Clinically, low ATM expression has been associated with microsatellite mutations in the *ATM* gene and with shorter survival in patients with gastric cancer who had undergone curative resection versus patients with high ATM expression levels.[23] A new ATM immunohistochemistry (IHC) test demonstrates that approximately 13% to 22% of tumors from patients with gastric cancer may have low or undetectable ATM expression (ATM_{low}).[24]

In patients with gastric cancer, treatment with taxane-platinum combinations has shown improved efficacy versus taxane alone.[25] There are parallels between olaparib and platinum sensitivity; for instance, homologous recombination repair–deficient tumors show increased sensitivity to both platinum-based chemotherapy and olaparib. Olaparib plus paclitaxel (olararib/paclitaxel) has previously demonstrated antitumor activity in patients with breast cancer; in a phase I trial, the response rate was greater than reported previously with olaparib or paclitaxel alone, suggesting an additive effect.[13,26,27]

Our study investigated efficacy and safety of olaparib/paclitaxel versus paclitaxel alone in patients receiving second-line treatment for recurrent or metastatic gastric cancer. ATM expression was assessed as a predictor of improved response to olaparib/paclitaxel.

PATIENTS AND METHODS

Patients

Eligible patients were age $\geq$ 18 years and had recurrent or metastatic gastric adenocarcinoma that had progressed after first-line chemotherapy; $\geq$ one lesion (measurable and/or nonmeasurable) assessed accurately by imaging; confirmed ATM status from an archival tumor sample collected and analyzed during screening; Eastern Cooperative Oncology Group performance status $\leq$ 2; and normal hepatic, renal, and bone marrow function. This trial population was enriched for ATM_{low} patients; 50% of the overall population was ATM_{low}. ATM expression was determined by IHC analysis of a freshly cut single section from a formalin-fixed, paraffin-embedded archival biopsy or resection tumor sample, collected from the primary tumor or metastases after the original diagnosis and stored at room temperature. IHC methods followed those described in an interlaboratory concordance study.[24] Patients provided written informed consent.

Study Design

In the initial combination phase of this prospective, randomized, double-blind, multicenter phase II study (Study 39; NCT01063517), patients received olaparib (100 mg twice per day, continuous; tablet formulation) or matching placebo, in combination with paclitaxel (80 mg/m^2 per day intravenously on days 1, 8, and 15) in 4-week treatment cycles. Patients were expected to receive six to 10 paclitaxel treatment cycles. After completing paclitaxel treatment, patients entered the maintenance therapy phase, where they received olaparib (200 mg twice per day) or placebo monotherapy until objective progression or provided that they were benefiting from treatment and did not meet discontinuation criteria. Management of toxicities by olaparib and/or paclitaxel dose modifications (reductions and/or interruptions [delays]) is described in the Data Supplement. The trial protocol was reviewed and approved by the institutional review boards of the participating institutions. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca Policy on Bioethics.[28]

Random Assignment and Masking

Before starting the combination phase, patients were randomly assigned 1:1 to receive olaparib/paclitaxel or placebo plus paclitaxel (placebo/paclitaxel). The random assignment scheme was produced by computer software program (GRand; AstraZeneca Global Randomization system) that generated random numbers. Blocked random assignment was generated, with all centers using the same list to minimize imbalances in numbers of patients assigned to each arm. Random assignment was stratified by ATM status according to a prespecified threshold from an interlaboratory concordance study,[24] ensuring that the proportion of ATM_{low} patients in each arm was 50%.

Study End Points and Assessments

The primary end point was investigator-assessed progression-free survival (PFS), defined as time to objective disease progression determined by RECIST version 1.1 or death; PFS was analyzed in the overall patient population (enriched for patients with ATM_{low} status) and the ATM_{low} population. Secondary end points were OS, objective response rate (ORR), percent change in tumor size at week 8 (all assessed in the overall and ATM_{low} populations; see Data Supplement for change in tumor size results), and safety/tolerability.

Tumor assessment was performed at screening, every 8 weeks until week 40, and every 16 weeks thereafter, until objective disease progression as determined by the investigator. RECIST assessments were performed using computed tomography and magnetic resonance imaging scans of the chest, abdomen, and pelvis. Patients who had discontinued all study treatment and showed disease progression were observed for survival at 8-week intervals. Duration of follow-up was defined as the number of days from the time of random assignment to the date of death or data cutoff (May 11, 2012) in the absence of death for censored patients. Adverse events (AEs) and laboratory parameters were recorded throughout the trial and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical Analysis

This trial was sized using one-sided 10% significance levels; an outcome of $P < .1$ (one-sided) for either the overall population or the ATM_{low} population would be regarded as promising (but not definitive). The study aimed to randomly assign 120 patients, of whom 60 were to be ATM_{low}. At the time of study design, the screening prevalence for ATM_{low} tumor samples was anticipated to be 20% to 25%; therefore, once 60 ATM-positive patients had been enrolled, recruitment would be restricted to ATM_{low} patients only. PFS analysis was to be performed after approximately 99 progression events (approximately 50 events in the ATM_{low} group) and was calculated to have approximately 80% power to detect a true hazard ratio (HR) of 0.65 in the overall population (0.55 in the ATM_{low} population), based on a one-sided 10% significance level.

Efficacy was analyzed on an intent-to-treat basis in all randomly assigned patients (full analysis set), except ORR and change in tumor size, which were analyzed using an evaluable-for-response population that excluded patients

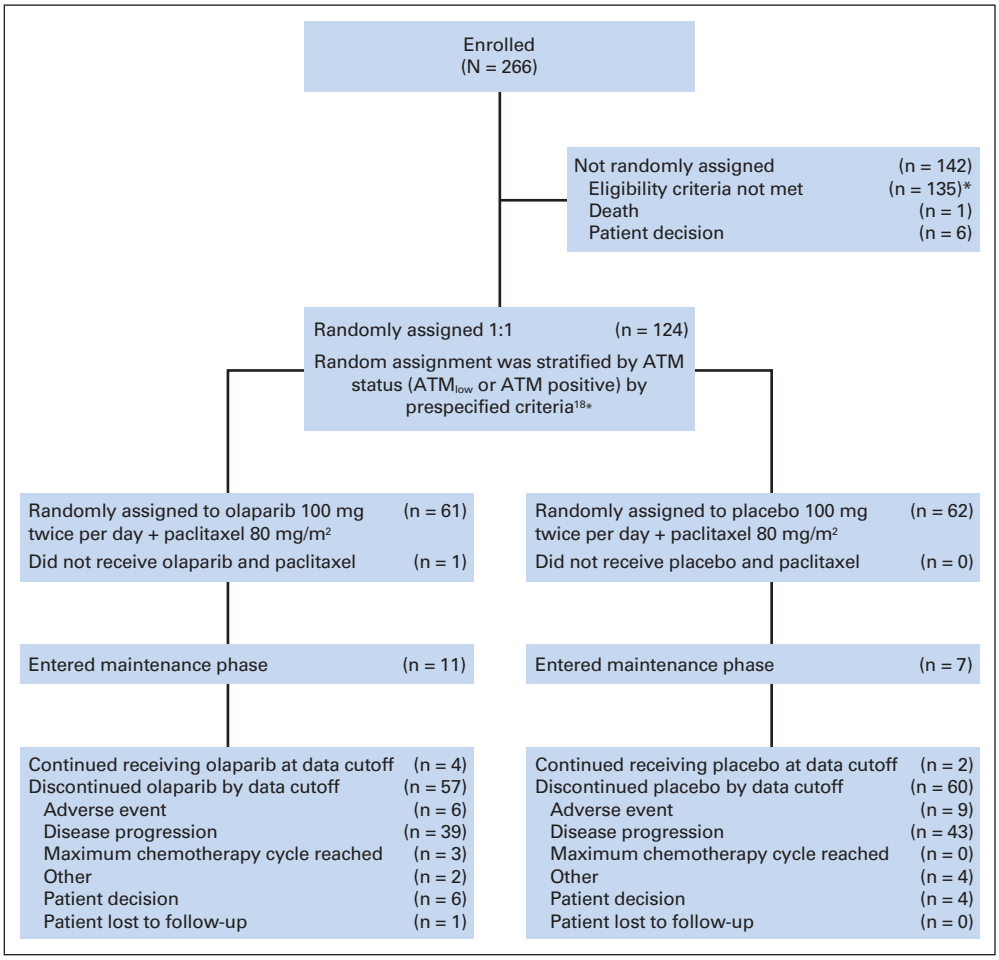

Fig 1. Trial profile, including enrollment, random assignment, and follow-up of the study patient population. (*) Once 60 patients with ataxia telangiectasia mutated (ATM) –positive tumor samples had been enrolled, recruitment was limited to ATM_{low} patients only. All 266 enrolled patients were screened for low or undetectable ATM expression (ATM_{low}) status. The full intent-to-treat analysis set included all 124 randomly assigned patients; the safety analysis set included all 123 randomly assigned patients who received study treatment. The one randomly assigned patient in the olaparib/paclitaxel arm who did not receive treatment was withdrawn as a result of a protocol deviation before receiving study treatment.

with nonmeasurable disease at baseline. The safety analysis set included all patients who received treatment with olaparib or placebo.

Cox proportional hazards regression models adjusted for ATM status (overall population only) and gastrectomy status (total, partial, or none), as prespecified in the protocol, were used to estimate PFS and OS HRs. A supportive PFS analysis was performed in which a weighted estimate of the overall HR was calculated using estimated HRs from ATM_{low} and ATM-positive populations, based on the prevalence of ATM_{low} patients at screening. In addition, a PFS subgroup analysis was performed by ATM and gastrectomy status, as described in the protocol. ORR was analyzed for both populations using a logistic regression model that included terms for the same covariates analyzed for PFS. Change in tumor size was assessed using an analysis of covariance that also included the covariates from the PFS analysis plus baseline tumor size and interaction between ATM and treatment.

RESULTS

Patients

From February 2010 to May 2012, 266 patients were enrolled at 13 sites in Korea (Fig 1). The screening prevalence of patients with ATM_{low} tumor samples was 14%. At data cutoff (May 11, 2012), six patients were ongoing and receiving olaparib/paclitaxel (n = 3), maintenance olaparib (n = 1), placebo/paclitaxel (n = 1), and maintenance placebo (n = 1).

Demographics and baseline characteristics were generally well balanced between the two treatment groups (Table 1). In both arms, approximately 90% of patients had previously received platinum plus fluoropyrimidine. The demographic characteristics of the ATM_{low} and overall populations were similar. The full intent-to-treat analysis set included all 124 patients, with the safety analysis set comprising the 123 patients who received treatment. The evaluable-for-response analysis set included 100 patients (olaparib/paclitaxel, n = 53; placebo/paclitaxel, n = 47).

Efficacy

PFS. In both the overall and ATM_{low} populations, olaparib/paclitaxel did not lead to a statistically significant improvement in PFS compared with placebo/paclitaxel, although PFS was numerically in favor of olaparib (overall population: HR, 0.80; 80% CI, 0.62 to 1.03; one-sided $P = .131$; median PFS, 3.91 *v* 3.55 months, respectively; ATM_{low}: HR, 0.74; 80% CI, 0.51 to 1.08; one-sided $P = .157$; median PFS, 5.29 *v* 3.68 months, respectively; Figs 2A and 2B). A weighted analysis of PFS in the overall population (HR, 0.87; 80% CI, 0.64 to 1.17) was consistent with the primary analysis. For PFS subgroup analyses, the global interaction test was not statistically significant ($P = .254$), suggesting that there was no evidence of significant interactions between treatment and the covariates. A trend toward greater PFS treatment benefit was observed for patients with total or partial gastrectomy compared with no gastrectomy (Appendix Fig A1, online only).

Table 1. Patient Demographics and Baseline Characteristics (full analysis set)

Characteristic	No. of Patients (%)	
	Olaparib/ Paclitaxel (n = 62)	Placebo/ Paclitaxel (n = 62)
Median age (range), years	63.0 (31–77)	60.5 (25–79)
Sex		
Female	13 (21.0)	18 (29.0)
Male	49 (79.0)	44 (71.0)
ECOG status		
0	32 (51.6)	28 (45.2)
1	30 (48.4)	32 (51.6)
2	0	2 (3.2)
Histology type		
Adenocarcinoma	54 (87.1)	54 (87.1)
Adenocarcinoma with signet ring cell carcinoma	8 (12.9)	8 (12.9)
Sites of local and metastatic disease*		
Lymph nodes	48 (77.4)	46 (74.2)
Peritoneum	26 (41.9)	27 (43.5)
Liver	19 (30.6)	24 (38.7)
GI	15 (24.2)	16 (25.8)
Prior gastrectomy		
Total	8 (12.9)	15 (24.2)
Partial	22 (35.5)	15 (24.2)
None	32 (51.6)	32 (51.6)
Prior chemotherapies†		
Cisplatin	26 (41.9)	39 (62.9)
Oxaliplatin	30 (48.4)	20 (32.3)
Fluorouracil	24 (38.7)	23 (37.1)
Capecitabine	23 (37.1)	22 (35.5)
Tegafur, gimeracil, and oteracil	21 (33.9)	23 (37.1)
Folinic acid	17 (27.4)	14 (22.6)
ATM expression‡		
Low§	31 (50.0)	32 (51.6)
Positive	31 (50.0)	30 (48.4)

Abbreviations: ATM, ataxia telangiectasia mutated; ECOG, Eastern Cooperative Oncology Group.
*All disease sites affecting ≥ 25% of the overall patient population are listed; patients may have multiple disease sites and thus may be listed in multiple categories
†All prior chemotherapies received by ≥ 25% of the overall patient population are listed; patients may have received multiple chemotherapies in combination and thus may be listed in multiple categories. In addition, before baseline, 16 patients (12.9%) had received adjuvant therapy followed by first-line therapy.
‡ATM status was defined according to prespecified criteria.[24]
§Low or undetectable protein levels by immunohistochemistry.

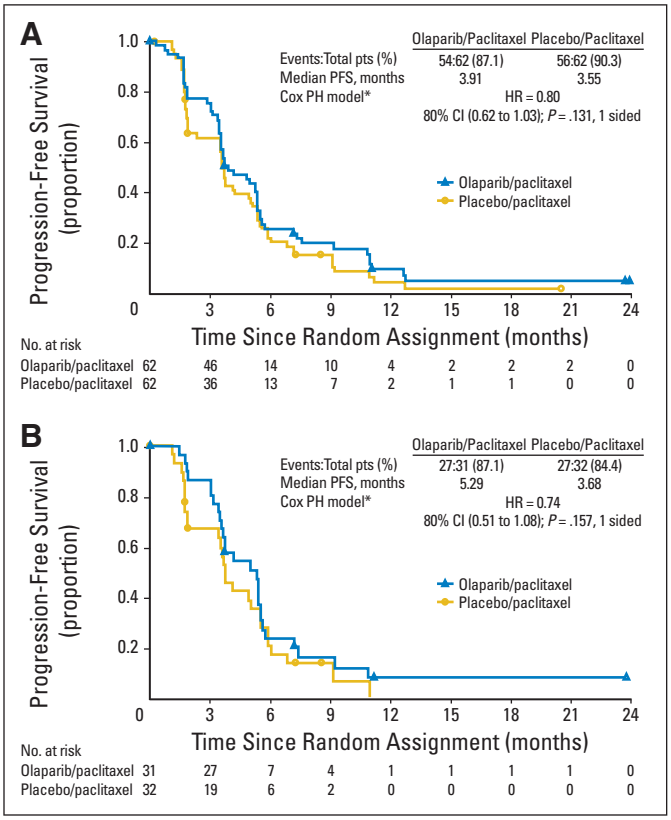

Fig 2. Progression-free survival (PFS; full analysis set). (A) PFS in overall patient population (enriched for patients with tumor samples with low or undetectable ataxia telangiectasia mutated [ATM] expression [ATM_{low}]). (*) Model with factors for treatment group, gastrectomy status (total, partial, or none), and ATM status; hazard ratio (HR) less than 1 favors olaparib/paclitaxel. (B) PFS in ATM_{low} population. (*) Model with factors for treatment group and gastrectomy status (total, partial, or none); HR less than 1 favors olaparib/paclitaxel. PH, proportional hazards.

OS. The median duration of follow-up for the overall population was 8.4 months (range, 0.3 to 26.2 months). Olaparib/paclitaxel led to a statistically significant OS improvement versus placebo/paclitaxel in the overall population (HR, 0.56; 95% CI, 0.35 to 0.87; $P = .010$; 80% CI, 0.41 to 0.75; $P = .005$; median OS, 13.1 *v* 8.3 months, respectively; Fig 3A; Appendix Fig A2, online only). Furthermore, olaparib/paclitaxel led to a greater OS benefit versus placebo/paclitaxel in the ATM_{low} population (HR, 0.35; 95% CI, 0.17 to 0.71; $P = .003$; 80% CI, 0.22 to 0.56; $P = .002$; median OS, not reached *v* 8.2 months, respectively; Fig 3B).

Objective response. There were no statistically significant differences in ORR between the arms in either population (Table 2). In the overall population, the median duration of response was 5.64 months in the olaparib/paclitaxel arm versus 3.63 months in the placebo/paclitaxel arm. A greater proportion of patients had progressive disease in the placebo/paclitaxel arm than the olaparib/paclitaxel arm.

Treatment Exposure

The majority of patients received ≥ four treatment cycles (olaparib/paclitaxel: n = 41 [67.2%]; placebo/paclitaxel: n = 32 [51.6%]), with approximately one third of patients (34.4% in olaparib/paclitaxel arm and 27.4% in placebo/paclitaxel arm) receiving ≥ six cycles and approximately 10% of patients (11.5% in olaparib/paclitaxel arm and 11.3% in placebo/paclitaxel arm) receiving ≥ nine cycles. During the combination phase, the median actual durations of treatment were 11.7 and 9.1 weeks for the olaparib/paclitaxel and placebo/paclitaxel arms, respectively. In the combination phase, the median dose-intensities of olaparib and placebo were 100% in the respective arms, but median paclitaxel dose-intensity was higher in the placebo arm (92%) than the olaparib arm (82%). The median duration of maintenance treatment was longer for olaparib/paclitaxel than placebo/paclitaxel (11.7 *v* 4.1 weeks, respectively). The proportion of patients receiving postprogression chemotherapy and the type of chemotherapy received were similar in both arms (olaparib/paclitaxel: 48.4%; placebo/paclitaxel: 43.5%; Appendix Table A1, online only).

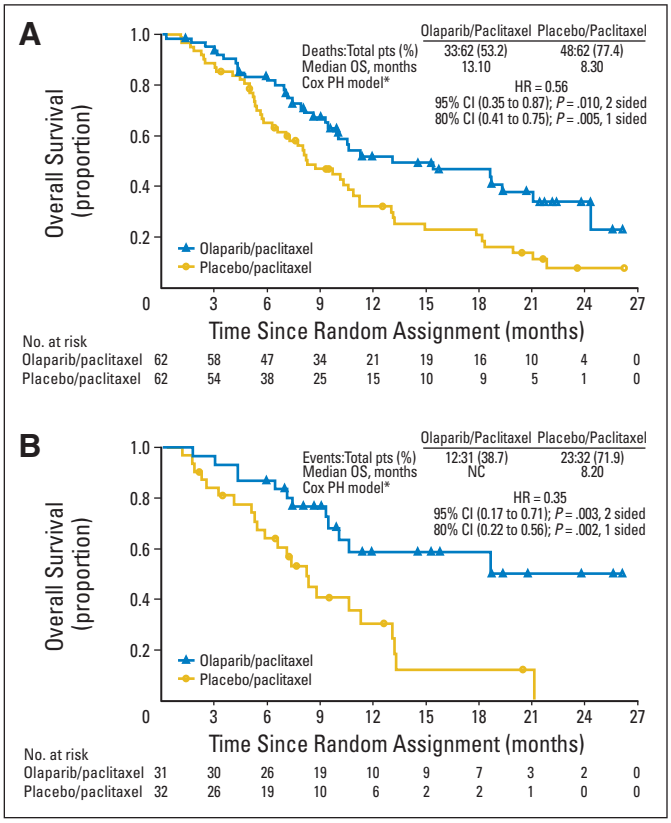

Fig 3. Overall survival (OS; full analysis set). (A) OS in overall patient population (enriched for patients with tumor samples with low or undetectable ataxia telangiectasia mutated [ATM] expression [ATM_{low}]). (*) Model with factors for treatment group, gastrectomy status (total, partial, or none), and ATM status; HR less than 1 favors olaparib/paclitaxel. (B) OS in ATM_{low} population. (*) Model with factors for treatment group and gastrectomy status (total, partial, or none). HR less than 1 favors olaparib/paclitaxel. Median OS for the olaparib/paclitaxel arm was not calculated (NC) because of lack of events. PH, proportional hazards.

Safety

Table 3 lists the most commonly reported AEs. A similar proportion of patients in both arms reported Common Terminology Criteria for Adverse Events grade ≥ 3 AEs (olaparib/paclitaxel: n = 46, 75.4%; placebo/paclitaxel: n = 46, 74.2%). A higher proportion of patients reported serious AEs (SAEs) in the placebo/paclitaxel arm (n = 23, 37.1%) than the olaparib/paclitaxel arm (n = 17, 27.9%); pneumonia was the most common SAE (olaparib/paclitaxel: n = 3, 4.9%; placebo/paclitaxel: n = 6, 9.7%).

No SAEs were considered causally related to olaparib, whereas 19 patients had SAEs considered related to paclitaxel (olaparib/paclitaxel: n = 7, 11.5%; placebo/paclitaxel: n = 12, 19.4%). There were no drug-related deaths during the study, but six patients discontinued study treatment as a result of AEs (olaparib/paclitaxel: n = 1, peripheral neuropathy; placebo/paclitaxel: n = 1 each, cerebral infarction, pneumonia, hepatotoxicity, herpes zoster, pneumonitis). AEs leading to dose modification occurred in 46 patients (75.4%) receiving olaparib/paclitaxel and 42 patients (67.7%) receiving placebo/paclitaxel, with neutropenia the most frequent AE leading to dose modification (olaparib/paclitaxel: n = 33, 54.1%; placebo/paclitaxel: n = 23, 37.1%). AEs leading to dose reduction were more common in the olaparib/paclitaxel arm than the placebo/paclitaxel arm (n = 25 [41%] *v* n = 10 [16.1%], respectively); neutropenia (n = 19 [31.1%] *v* n = 9 [14.5%], respectively) was the only AE leading to dose reduction reported by more than one patient in either arm. No changes of significant clinical impact in any clinical chemistry parameter were reported.

DISCUSSION

In this randomized phase II study in patients with recurrent/metastatic gastric cancer, it was hypothesized that all patients would benefit from olaparib and that patients with DNA repair–deficient tumors through loss of ATM expression might receive greater benefit. Our results showed a statistically significant and clinically meaningful OS improvement for olaparib/paclitaxel compared with paclitaxel alone. A greater OS benefit was observed in patients with ATM_{low} tumors than in the overall population (enriched for ATM_{low} patients), suggesting that ATM status may be predictive of improved outcome to olaparib/paclitaxel. Compared with paclitaxel alone, olaparib/paclitaxel did not lead to a statistically significant improvement in the primary end point of PFS in either the overall or ATM_{low} population, but PFS favored olaparib numerically in both populations, particularly the ATM_{low} population (HR., 0.74; median PFS, 5.29 *v* 3.68

Table 2. Best Objective Response (evaluable-for-response analysis set)

	No. of Patients (%)			
	Overall Population		ATM_{low} Population	
Best Response	Olaparib/Paclitaxel (n = 53)	Placebo/Paclitaxel (n = 47)	Olaparib/Paclitaxel (n = 26)	Placebo/Paclitaxel (n = 23)
ORR*	14 (26.4)	9 (19.1)	9 (34.6)	6 (26.1)
DCR	38 (71.7)	26 (55.3)	22 (84.6)	15 (65.2)
CR	3 (5.7)	1 (2.1)	2 (7.7)	1 (4.3)
PR	11 (20.8)	8 (17.0)	7 (26.9)	5 (21.7)
SD	24 (45.3)	17 (36.2)	13 (50.0)	9 (39.1)
PD	14 (26.4)	21 (44.7)	4 (15.4)	8 (34.8)
NE	1 (1.9)	0	0	0

Abbreviations: ATM_{low}, low or undetectable expression of ataxia telangiectasia mutated; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*The odds ratio (OR) for ORR was 1.65 (80% CI, 0.86 to 3.23; $P = .162$) in the overall population and 1.76 (80% CI, 0.76 to 4.21; $P = .195$) in the ATM_{low} population. OR greater than 1 favors olaparib.

Table 3. AEs (any grade) Reported in > 20% of Patients Overall or Grade ≥ 3 AEs Reported in > 5% of Patients Overall, Arranged by MedDRA Preferred Term

	No. (%)							
	Combination Phase				Maintenance Phase			
	Olaparib/Paclitaxel (n = 61)		Placebo/Paclitaxel (n = 62)		Olaparib/Paclitaxel (n = 11)		Placebo/Paclitaxel (n = 7)	
AE	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hematologic AEs								
Anemia	11 (18)	7 (11)	12 (19)	7 (11)	0	0	2 (29)	1 (14)
Neutropenia*	46 (75)	34 (56)	40 (65)	24 (39)	1 (9)	1 (9)	0	0
Nonhematologic AEs								
Alopecia	30 (49)	0	29 (47)	0	0	0	0	0
Decreased appetite	23 (38)	0	26 (42)	0	2 (18)	0	1 (14)	0
Neuropathy peripheral	22 (36)	3 (5)	13 (21)	1 (2)	0	0	0	0
Nausea	20 (33)	0	25 (40)	0	1 (9)	0	1 (14)	0
Asthenia	19 (31)	2 (3)	17 (27)	6 (10)	1 (9)	0	0	0
Diarrhea	19 (31)	2 (3)	17 (27)	1 (2)	2 (18)	0	0	0
Abdominal pain	15 (25)	0	15 (24)	2 (3)	1 (9)	0	1 (14)	0
Fatigue	15 (25)	1 (2)	20 (32)	2 (3)	1 (9)	1 (9)	0	0
Myalgia	10 (16)	0	22 (36)	0	0	0	0	0
Pneumonia	4 (7)	2 (3)	6 (10)	5 (8)	0	0	0	0

Abbreviations: AE, adverse event; –MedDRA, Medical Dictionary for Regulatory Activities.
*In addition to the cases of neutropenia, two patients experienced adverse events of febrile neutropenia. Both events occurred in the olaparib/paclitaxel arm during the combination phase; one event was grade 3 by Common Terminology Criteria for Adverse Events (the other was grade 2) and led to dose modification.

months). The observed PFS and OS results with paclitaxel alone are consistent with phase III studies involving paclitaxel as second-line chemotherapy for advanced gastric cancer.[3,5]

The validity of PFS as a surrogate end point for OS in gastric cancer was evaluated in a recent meta-analysis, which demonstrated only a modest correlation between PFS and OS treatment effects; this supports the observed disparity in the current study.[29] The difference between our PFS and OS results probably results from the relatively small sample size and the exploratory nature of this phase II trial, which was powered to determine whether olaparib/paclitaxel was sufficiently active to warrant assessment in a phase III trial. The sample size was calculated to detect a promising, but not definitive, benefit. The PFS HRs of 0.80 and 0.74 in the overall and ATM_{low} populations, respectively, are considered quite promising for further exploration in a phase III trial. Although OS was nominated as a secondary end point, it is recognized as a gold standard, providing a direct measure of clinical benefit.[30] Overall, our results provide strong evidence of a treatment effect for olaparib/paclitaxel in this setting, and the clinical signals justify further investigation of this combination in a phase III trial.

The nature of PARP inhibition may have contributed to the apparent exacerbation of the treatment effect with OS compared with PFS, with preclinical data suggesting that the activity of PARP inhibitors observed from long-term colony formation assays is more prominent than from short-term MTT assays. Furthermore, in a preclinical study in which olaparib and the topoisomerase inhibitor irinotecan were shown to act synergistically, an antitumor effect was observed even after discontinuation of therapy.[31] Because a third of patients in the current trial received an irinotecan-containing regimen after discontinuation of study treatment, it is possible that a similar olaparib carryover effect occurred, causing postprogression synergism with irinotecan.

A randomized and comparative design was adopted for this phase II study to reduce selection bias and to detect significant treatment differences that would identify an active treatment for further investigation.[32] The study was well conducted, and data were sufficiently mature (88.7% progression events in the overall population) to allow PFS analysis in accordance with the original objectives. The study population was enriched to 50% with patients classified as ATM_{low}; however, the actual screening prevalence rate (14%) was lower than expected based on unpublished data (25%). Although subgroup analyses suggested that the PFS treatment effect of olaparib/paclitaxel versus paclitaxel alone may be greater in patients with a total gastrectomy, these results should be interpreted with caution because of the relatively small number of patients within these subgroups and because patients with a total or partial gastrectomy were more likely to be ATM_{low} compared with the overall population, potentially confounding the analysis.

During the current study, Kim et al[24] reported that ATM IHC results were reproducible in different laboratories using the methods they described. *ATM* mutations have been linked to olaparib response in patients with advanced castration-resistant prostate cancer[33]; the same ATM antibody has also been used to identify patients with pancreatic cancer with an ATM deficiency.[34]

Cytotoxicity induced by PARP inhibitors in DNA repair–deficient cells has been associated with chromosomal aberrations such as complex chromatid rearrangements and chromatid breaks[8]; it is reasonable to hypothesize that these effects may be enhanced further by the mitotic stress generated by paclitaxel. Emerging data from studies investigating the combination of olaparib with paclitaxel in metastatic triple-negative breast cancer[26] and advanced solid tumors[35] may provide additional data.

The combination of olaparib with weekly paclitaxel, at doses selected based on safety data from a previous trial,[35] was generally well tolerated, with no unexpected safety findings. The most common AE in both arms was neutropenia, which contributed to more dose modifications in the olaparib/paclitaxel arm than the placebo/paclitaxel arm, leading to a lower median dose-intensity of paclitaxel in the

olaparib/paclitaxel arm. The higher incidence of neutropenia in the olaparib/paclitaxel arm was apparent as early as the first treatment cycle and remained higher throughout the course of treatment. However, few patients experienced febrile neutropenia or neutropenia that lasted more than 2 weeks. A higher than expected incidence of neutropenia has previously been reported in a phase I/II multicenter trial of olaparib plus paclitaxel for first- or second-line treatment of patients with metastatic triple-negative breast cancer.[26] Studies in which olaparib has been combined with other chemotherapeutic agents also reported hematologic toxicities.[36-38]

Although the primary end point of PFS was not achieved in this study, olaparib plus paclitaxel resulted in a statistically significant and clinically meaningful OS improvement in patients with recurrent or metastatic gastric cancer. To our knowledge, this is the first phase II study to investigate the olaparib tablet formulation being used in phase III trials. Overall, olaparib 100 mg twice per day plus weekly paclitaxel 80 mg/m^2 was generally well tolerated. Our results suggest that, in the subset of patients with advanced gastric cancer who have ATM_{low} tumors and are enriched for functionally compromised ATM protein, olaparib plus weekly paclitaxel may be an effective targeted treatment. Further evaluation of this combination in a phase III trial in advanced gastric cancer is ongoing (NCT01924533). The relevance of an ATM_{low} patient subset in Asia will also be explored because gastric cancer is particularly common in Asian countries[39] and represents an enormous unmet need.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Yung-Jue Bang, Seock-Ah Im, Hoo Geun Chun, Darren Hodgson, Mark J. O'Connor
Administrative support: Seock-Ah Im
Provision of study materials or patients: Yung-Jue Bang, Seock-Ah Im
Collection and assembly of data: Yung-Jue Bang, Seock-Ah Im, Keun-Wook Lee, Jae Yong Cho, Eun-Kee Song, Kyung Hee Lee, Yeul Hong Kim, Joon Oh Park, Dae Young Zang, Anitra Fielding, Jacqui Rowbottom, Woo Ho Kim
Data analysis and interpretation: Yung-Jue Bang, Seock-Ah Im, Joon Oh Park, Anitra Fielding, Jacqui Rowbottom, Darren Hodgson, Mark J. O'Connor, Xiaolu Yin
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. International Agency for Research on Cancer: GLOBOCAN statistics, 2012. http://globocan.iarc.fr/.
2. Price TJ, Shapiro JD, Segelov E, et al: Management of advanced gastric cancer. Expert Rev Gastroenterol Hepatol 6:199-208, 2012
3. Hironaka S, Ueda S, Yasui H, et al: Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 31:4438-4444, 2013
4. Kodera Y, Ito S, Mochizuki Y, et al: A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 study). Anticancer Res 27:2667-2671, 2007
5. Wilke H, Muro K, Van Cutsem E, et al: Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol 15:1224-1235, 2014
6. Murai J, Huang SY, Das BB, et al: Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res 72:5588-5599, 2012
7. Helleday T: The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. Mol Oncol 5:387-393, 2011
8. Farmer H, McCabe N, Lord CJ, et al: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917-921, 2005
9. Ashworth A: A synthetic lethal therapeutic approach: Poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 26:3785-3790, 2008
10. McCabe N, Turner NC, Lord CJ, et al: Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res 66:8109-8115, 2006
11. Audeh MW, Carmichael J, Penson RT, et al: Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: A proof-of-concept trial. Lancet 376:245-251, 2010
12. Tutt A, Robson M, Garber JE, et al: Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial. Lancet 376:235-244, 2010
13. Gelmon KA, Tischkowitz M, Mackay H, et al: Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: A phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 12:852-861, 2011
14. Kaye SB, Lubinski J, Matulonis U, et al: Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol 30:372-379, 2012
15. Ledermann J, Harter P, Gourley C, et al: Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 15:852-861, 2014
16. Hodgson D, Mason H, Oplustilova L, et al: Activity of the PARP inhibitor olaparib in ATM-deficient gastric cancer: From preclinical models to the clinic. Proc Am Assoc Cancer Res 2014:2398, 2014 (abstr)
17. Williamson CT, Muzik H, Turhan AG, et al: ATM deficiency sensitizes mantle cell lymphoma cells to poly(ADP-ribose) polymerase-1 inhibitors. Mol Cancer Ther 9:347-357, 2010
18. Guo X, Shen D, Cheng W, et al: ATM deficiency sensitizes gastric cancer cells to the PARP inhibitor olaparib. Mol Cancer Ther 8:B42, 2009 (suppl 12)
19. Kubota E, Williamson CT, Ye R, et al: Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines. Cell Cycle 13:2129-2137, 2014
20. Shiloh Y: ATM and related protein kinases: Safeguarding genome integrity. Nat Rev Cancer 3:155-168, 2003
21. Kurz EU, Lees-Miller SP: DNA damage-induced activation of ATM and ATM-dependent signaling pathways. DNA Repair (Amst) 3:889-900, 2004
22. Goodarzi AA, Jeggo PA: The heterochromatic barrier to DNA double strand break repair: How to get the entry visa. Int J Mol Sci 13:11844-11860, 2012
23. Kim JW, Im SA, Kim MA, et al: Ataxia-telangiectasia mutated protein expression with microsatellite instability in gastric cancer as prognostic marker. Int J Cancer 134:72-80, 2014
24. Kim HS, Kim MA, Hodgson D, et al: Concordance of ATM (ataxia telangiectasia mutated) immunohistochemistry between biopsy or metastatic tumor samples and primary tumors in gastric cancer patients. Pathobiology 80:127-137, 2013
25. Sakamoto J, Matsui T, Kodera Y: Paclitaxel chemotherapy for the treatment of gastric cancer. Gastric Cancer 12:69-78, 2009
26. Dent RA, Lindeman GJ, Clemons M, et al: Phase I trial of the oral PARP inhibitor olaparib in combination with paclitaxel for first- or second-line treatment of patients with metastatic triple-negative breast cancer. Breast Cancer Res 15:R88, 2013
27. Perez EA, Vogel CL, Irwin DH, et al: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 19:4216-4223, 2001
28. AstraZeneca: Global policy: Bioethics, 2015. http://www.astrazeneca.com/Responsibility/Code-policies-standards/Our-global-policies

29. Paoletti X, Oba K, Bang YJ, et al: Progression-free survival as a surrogate for overall survival in advanced/recurrent gastric cancer trials: A meta-analysis. J Natl Cancer Inst 105:1667-1670, 2013

30. Matulonis UA, Oza AM, Ho TW, et al: Intermediate clinical endpoints: A bridge between progression-free survival and overall survival in ovarian cancer trials. Cancer 121:1737-1746, 2015

31. Min A, Im SA, Yoon YK, et al: RAD51C-deficient cancer cells are highly sensitive to the PARP inhibitor olaparib. Mol Cancer Ther 12:865-877, 2013

32. Wieand HS: Randomized phase II trials: What does randomization gain? J Clin Oncol 23:1794-1795, 2005

33. Mateo J, Hall E, Sandhu S, et al: Antitumour activity of the PARP inhibitor olaparib in unselected sporadic castration-resistant prostate cancer (CRPC) in the TOPARP trial. Ann Oncol 25:LBA20, 2014 (suppl 4)

34. Kim H, Saka B, Knight S, et al: Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poorer prognosis. Clin Cancer Res 20:1865-1872, 2014

35. van der Noll R, Ang JE, Jager A, et al: Phase I study of olaparib in combination with carboplatin and/or paclitaxel in patients with advanced solid tumors. J Clin Oncol 31, 2013 (suppl 15; abstr 2579)

36. Samol J, Ranson M, Scott E, et al: Safety and tolerability of the poly(ADP-ribose) polymerase (PARP) inhibitor, olaparib (AZD2281) in combination with topotecan for the treatment of patients with advanced solid tumors: A phase I study. Invest New Drugs 30:1493-1500, 2012

37. Giaccone G, Rajan A, Kelly RJ, et al: A phase I combination study of olaparib (AZD2281; KU-0059436) and cisplatin (C) plus gemcitabine (G) in adults with solid tumors. J Clin Oncol 28, 2010 (suppl 15; abstr 3027)

38. Khan OA, Gore M, Lorigan P, et al: A phase I study of the safety and tolerability of olaparib (AZD2281, KU0059436) and dacarbazine in patients with advanced solid tumours. Br J Cancer 104:750-755, 2011

39. Jung KW, Won YJ, Kong HJ, et al: Cancer statistics in Korea: Incidence, mortality, survival, and prevalence in 2011. Cancer Res Treat 46:109-123, 2014

GLOSSARY TERMS

ATM (ataxia telangiectasia mutated): the protein, encoded by the ATM gene; a kinase that coordinates DNA repair by activating other proteins.

homologous recombination: genetic recombination whereby nucleotide sequences are exchanged between two similar or identical strands of DNA to facilitate accurate repair of DNA double-strand breaks.

maintenance therapy: therapy intended to prolong the benefit (eg, disease remission) experienced by a patient from a prior primary treatment (eg, chemotherapy).

overall survival: the duration between random assignment and death.

poly (ADP-ribose) polymerase (PARP): a family of nuclear enzymes that facilitate DNA repair via poly (ADP-ribose)ylation of histones and DNA repair enzymes.

progression-free survival: time from random assignment until death or first documented relapse, categorized as either locoregional (primary site or regional nodes) failure or distant metastasis or death.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Yung-Jue Bang
Honoraria: AstraZeneca
Consulting or Advisory Role: AstraZeneca
Research Funding: AstraZeneca (Inst)

Seock-Ah Im
Research Funding: AstraZeneca (Inst)

Keun-Wook Lee
Research Funding: AstraZeneca (Inst)

Jae Yong Cho
No relationship to disclose

Eun-Kee Song
No relationship to disclose

Kyung Hee Lee
No relationship to disclose

Yeul Hong Kim
Research Funding: AstraZeneca (Inst)

Joon Oh Park
Research Funding: AstraZeneca

Hoo Geun Chun
Research Funding: AstraZeneca (Inst)

Dae Young Zang
No relationship to disclose

Anitra Fielding
Employment: AstraZeneca
Stock or Other Ownership: AstraZeneca

Jacqui Rowbottom
Employment: AstraZeneca
Stock or Other Ownership: AstraZeneca

Darren Hodgson
Employment: AstraZeneca
Stock or Other Ownership: AstraZeneca

Mark J. O'Connor
Employment: AstraZeneca
Stock or Other Ownership: AstraZeneca

Xiaolu Yin
Employment: AstraZeneca
Stock or Other Ownership: AstraZeneca

Woo Ho Kim
No relationship to disclose

Acknowledgment

We thank Ben Clarke from Mudskipper Business, who provided medical writing assistance funded by AstraZeneca.

Appendix

Table A1. Postprogression Chemotherapy Received by Patients in the Overall Population and in the ATM_{low} Population

Chemotherapy Post-Treatment Discontinuation*	No. of Patients (%)			
	Overall Population		ATM_{low} Population	
	Olaparib/Paclitaxel (n = 62)	Placebo/Paclitaxel (n = 62)	Olaparib/Paclitaxel (n = 31)	Placebo/Paclitaxel (n = 32)
Fluorouracil	19 (30.6)	22 (35.5)	9 (29.0)	10 (31.3)
Irinotecan	18 (29.0)	21 (33.9)	7 (22.6)	10 (31.3)
Folinic acid	14 (22.6)	16 (25.8)	8 (25.8)	9 (28.1)
Oxaliplatin	5 (8.1)	6 (9.7)	2 (6.5)	3 (9.4)

Abbreviation: ATM_{low}, low or undetectable expression of ataxia telangiectasia mutated.
*All chemotherapies received by ≥ 5% of the overall patient population or the ATM_{low} population are listed; patients may have received multiple chemotherapies in combination and thus may be listed in multiple categories.

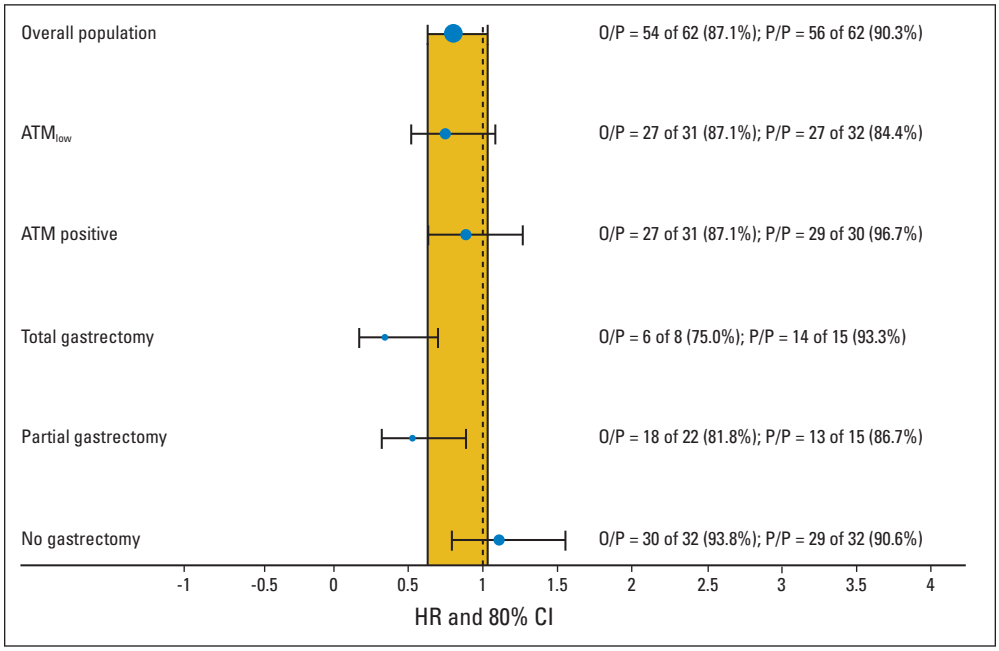

Fig A1. Subgroup analysis of progression-free survival (full analysis set). Hazard ratio (HR) < 1 favors olaparib/paclitaxel (O/P). Colored band represents the 80% CI for the HR for the overall population. Circle size is proportional to the number of events in the group. ATM, ataxia telangiectasia mutated; ATM_{low}, low or undetectable ATM expression; P/P, placebo/paclitaxel.

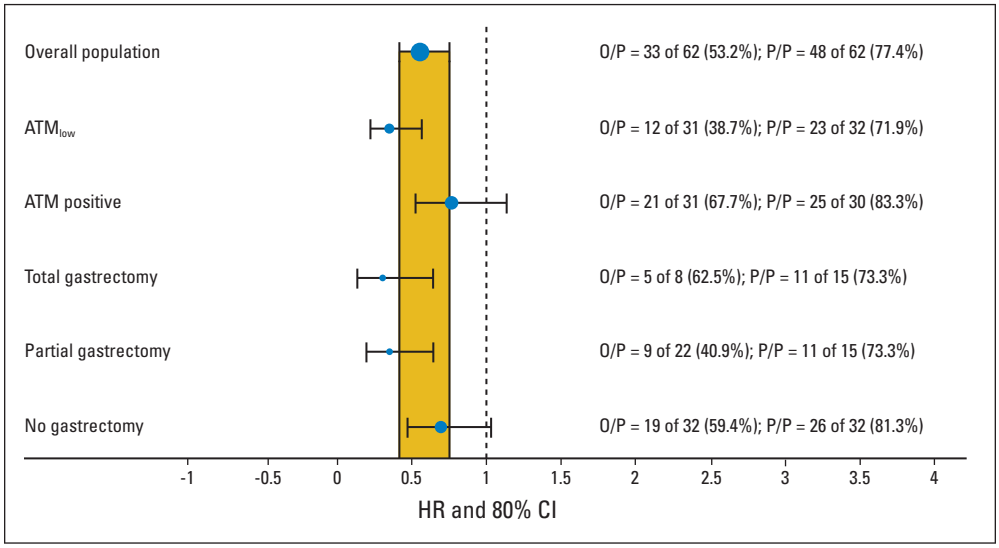

Fig A2. Subgroup analysis of overall survival (full analysis set). Hazard ratio (HR) < 1 favors olaparib/paclitaxel (O/P). Colored band represents the 80% CI for the HR for the overall population. Circle size is proportional to the number of events in the group. ATM, ataxia telangiectasia mutated; ATM$_{low}$, low or undetectable ATM expression; P/P, placebo/paclitaxel.