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ORIGINAL ARTICLE

OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer

M. E. Robson[1*], N. Tung[2], P. Conte[3], S.-A. Im[4], E. Senkus[5], B. Xu[6], N. Masuda[7], S. Delaloge[8], W. Li[9], A. Armstrong[10], W. Wu[11], C. Goessl[11], S. Runswick[12†] & S. M. Domchek[13]

[1]Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York; [2]Cancer Risk and Prevention Program, Beth Israel Deaconess Medical Center, Department of Medicine, Dana-Farber Harvard Cancer Center, Boston, USA; [3]Division of Oncology, University of Padova, Istituto Oncologico Veneto IRCCS, Padova, Italy; [4]Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [5]Center of Breast Diseases, Medical University of Gdańsk, Gdańsk, Poland; [6]Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [7]Department of Surgery, Osaka National Hospital, National Hospital Organization, Osaka, Japan; [8]Breast Oncology, Institut Gustave Roussy, Villejuif, France; [9]Department of Emergency, The First Hospital of Jilin University, Changchun, China; [10]Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester, UK; [11]Global Medicines Development, AstraZeneca, Gaithersburg, USA; [12]Global Medicines Development, AstraZeneca, Macclesfield, UK; [13]Department of Medicine, Basser Center, University of Pennsylvania, Philadelphia, USA

*Correspondence to: Dr Mark Robson, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel: +646-888-4058; E-mail: robsonm@mskcc.org

†Present address: Medorci Ltd, Macclesfield, UK.

Background: In the OlympiAD study, olaparib was shown to improve progression-free survival compared with chemotherapy treatment of physician's choice (TPC) in patients with a germline *BRCA1* and/or *BRCA2* mutation (BRCAm) and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (mBC). We now report the planned final overall survival (OS) results, and describe the most common adverse events (AEs) to better understand olaparib tolerability in this population.

Patients and methods: OlympiAD, a Phase III, randomized, controlled, open-label study (NCT02000622), enrolled patients with a germline BRCAm and HER2-negative mBC who had received ≤2 lines of chemotherapy for mBC. Patients were randomized to olaparib tablets (300 mg bid) or predeclared TPC (capecitabine, vinorelbine, or eribulin). OS and safety were secondary end points.

Results: A total of 205 patients were randomized to olaparib and 97 to TPC. At 64% data maturity, median OS was 19.3 months with olaparib versus 17.1 months with TPC (HR 0.90, 95% CI 0.66–1.23; $P = 0.513$); median follow-up was 25.3 and 26.3 months, respectively. HR for OS with olaparib versus TPC in prespecified subgroups were: prior chemotherapy for mBC [no (first-line setting): 0.51, 95% CI 0.29–0.90; yes (second/third-line): 1.13, 0.79–1.64]; receptor status (triple negative: 0.93, 0.62–1.43; hormone receptor positive: 0.86, 0.55–1.36); prior platinum (yes: 0.83, 0.49–1.45; no: 0.91, 0.64–1.33). Adverse events during olaparib treatment were generally low grade and manageable by supportive treatment or dose modification. There was a low rate of treatment discontinuation (4.9%), and the risk of developing anemia did not increase with extended olaparib exposure.

Conclusions: While there was no statistically significant improvement in OS with olaparib compared to TPC, there was the possibility of meaningful OS benefit among patients who had not received chemotherapy for metastatic disease. Olaparib was generally well-tolerated, with no evidence of cumulative toxicity during extended exposure.
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Key words: breast cancer, germline BRCA mutation, overall survival, PARP inhibitor, olaparib, tolerability

Introduction

Approximately 5% of all breast cancer patients carry a germline deleterious mutation in *BRCA1* and/or *BRCA2* (BRCAm), with higher rates among those with human epidermal growth factor receptor 2 (HER2)-negative disease [1, 2]. Germline BRCAm breast cancers tend to affect younger patients, those with a strong family history of breast cancer and Ashkenazi Jewish ancestry [1, 3].

The efficacy of the oral poly(ADP ribose) polymerase (PARP) inhibitor olaparib in patients with a germline BRCAm and HER2-negative metastatic breast cancer (mBC) was confirmed in the Phase III OlympiAD study, with a statistically significant benefit in progression-free survival compared with chemotherapy treatment of physician's choice (TPC) [4].

Here, we report findings from the prespecified final analysis of overall survival (OS) in the OlympiAD study that was conducted after 192 deaths (64% data maturity). Additionally, as real-world experience with olaparib tablets in patients with breast cancer is limited, we describe the tolerability profile in the OlympiAD study based on longer follow-up to further characterize the most common adverse events (AEs) in this population, compared to cytotoxic chemotherapy.

Methods

Study design and patients

Full details of the OlympiAD study (NCT02000622) have been reported previously [4]. In brief, this was a randomized, controlled, open-label, Phase III study in adults with a germline BRCAm and HER2-negative mBC (triple negative or hormone receptor positive) with two or fewer previous chemotherapy regimens for metastatic disease. Patients were randomized (2 : 1) to either olaparib tablets [300 mg twice daily (bid)] or predeclared single-agent chemotherapy TPC (capecitabine, eribulin, or vinorelbine). Patient randomization was stratified according to: (i) prior chemotherapy for mBC (yes versus no); (ii) hormone-receptor status (estrogen and/or progesterone receptor positive versus triple negative); and (iii) prior use of platinum therapy for breast cancer (yes versus no). Treatment was continued until disease progression or unacceptable side effects occurred. Crossover to olaparib in the study was not permitted.

End points and assessments

OS was analyzed on an intention-to-treat basis. OS was assessed throughout the study until treatment was discontinued and every 8 weeks thereafter. Safety was assessed in all patients receiving at least one dose of study drug, throughout the study and a 30-day post-treatment follow-up period.

AEs were graded using the Common Terminology Criteria for Adverse Events v4.0. AEs could be managed by supportive treatment in accordance with local treatment practice guidelines, if necessary. Dose interruption was allowed for a maximum of 4 weeks, with exceptions requiring approval by the medical monitor of the study. Two dose reductions were permitted as required (250 mg bid, followed by a further reduction to 200 mg bid). No further dose reduction was allowed, and re-escalation was not permitted. Management of anemia was specified: if grade 2 [hemoglobin (Hb) 8–<10 g/dl], supportive treatment (e.g. transfusion) or dose interruption at the discretion of the investigator was required until Hb increased to ≥10 g/dl. After a second grade 2 event, along with supportive treatment, dose interruption was required with a dose reduction after recovery. If anemia was grade 3 or 4 (Hb <8 g/dl), supportive treatment and dose interruption were required with a dose reduction after recovery. The type of supportive treatment was at the discretion of the treating physician. Timing of onset, duration, and resolution of AEs were recorded for the first occurrence of nausea, vomiting, and anemia.

Statistical analysis

An interim OS analysis was conducted at the time of the primary PFS analysis. The final OS analysis was prespecified to occur when ~190 deaths had occurred (approximately 60% maturity). The OlympiAD study was sized to have 90% power to detect a hazard ratio (HR) of 0.65 for progression-free survival on olaparib compared to TPC. OS was analyzed via a hierarchical multiple-testing strategy but was not used to determine sample size. The Kaplan–Meier method was used to generate time-to-event curves, from which medians were calculated. A stratified log-rank test was used to compare treatment groups with the HR and 95% confidence intervals (CIs) estimated from the log-rank test statistics. Further methodology is presented in the supplementary material, available at *Annals of Oncology* online.

Results

Patients

In total, 302 patients were randomized to study treatment (olaparib, $n = 205$; TPC, $n = 97$). Six TPC patients declined study treatment because of treatment allocation. Overall, 41 patients received capecitabine (45%), 34 patients received eribulin (37%), and 16 patients received vinorelbine (18%; supplementary Figure S1, available at *Annals of Oncology* online). At data cut-off for the final OS analysis (25 September 2017), median follow-up for OS in censored patients was 25.3 months in the olaparib group and 26.3 months in the TPC group (18.9 versus 15.5 months overall, respectively).

Final OS

At the time of this data cut-off, 192 deaths had occurred (64% OS data maturity). Patients in the olaparib arm achieved a median OS of 19.3 months versus 17.1 months with TPC (HR = 0.90; 95% CI: 0.66–1.23; $P = 0.513$) (Figure 1). At 6 months, OS in the olaparib arm was 93.1% versus 85.8% with TPC. Slightly greater proportions of olaparib patients were alive at 12 months (72.7% olaparib versus 69.2% TPC) and at 18 months (54.1% versus 48.0%, respectively). Twenty-six patients continued to receive olaparib at the data cut-off, but no patients were receiving TPC. Of the patients who discontinued study treatment, 1.1% in the olaparib arm and 8.2% of patients in the TPC arm went on to receive subsequent therapy with a PARP inhibitor, and 43.0% and 45.4%, respectively, received subsequent platinum therapy (supplementary Table S1, available at *Annals of Oncology* online).

Final OS in the three stratification factor subgroups is shown in Figure 1. OS was consistent across predefined subgroups, with a suggested greater benefit among patients who had not received prior chemotherapy for mBC in the olaparib arm compared with TPC (first-line treatment, 22.6 versus 14.7 months; HR = 0.51; 95% CI: 0.29–0.90). Baseline characteristics for these subgroups were relatively balanced across treatment arms (supplementary Table S2, available at *Annals of Oncology* online). Forest plots of additional prespecified subgroup analyses are presented in Figure 2.

When patients who were evaluable for response were assessed by the investigator, an objective response was recorded for 95 patients in the olaparib arm (57.6%; $n = 165$) and 16 patients in the TPC arm (22.2%; $n = 72$). At the time of this data cut-off, the investigator-assessed median duration of response was 6.9 months [interquartile range (IQR) 2.8–10.1] in the olaparib arm, and 4.5 months (2.7–8.5) in the TPC arm.

Safety

At the time of this data cut-off, no new safety findings were reported compared with those reported at the time of the primary

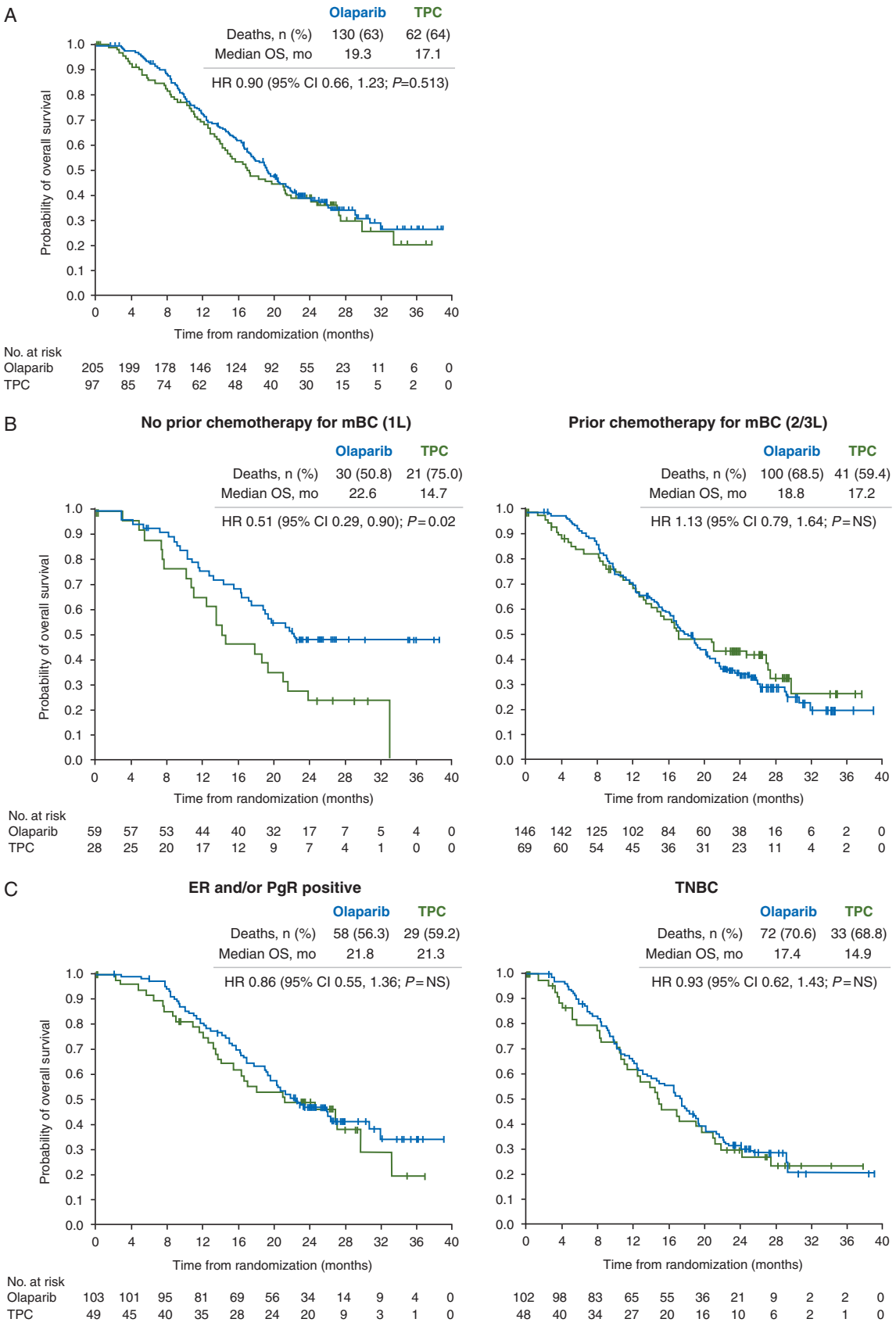

Figure 1. Kaplan–Meier estimates for overall survival in the olaparib group and the chemotherapy TPC group for (A) the overall population and for subgroup analyses stratified by (B) prior chemotherapy for metastatic breast cancer, (C) hormone-receptor status, and (D) prior platinum. Nominal *P* values were calculated using a likelihood ratio test; OS stratification factors were prespecified but not alpha controlled. ER, estrogen receptor; L, line of therapy; mBC, metastatic breast cancer; NS, not significant; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

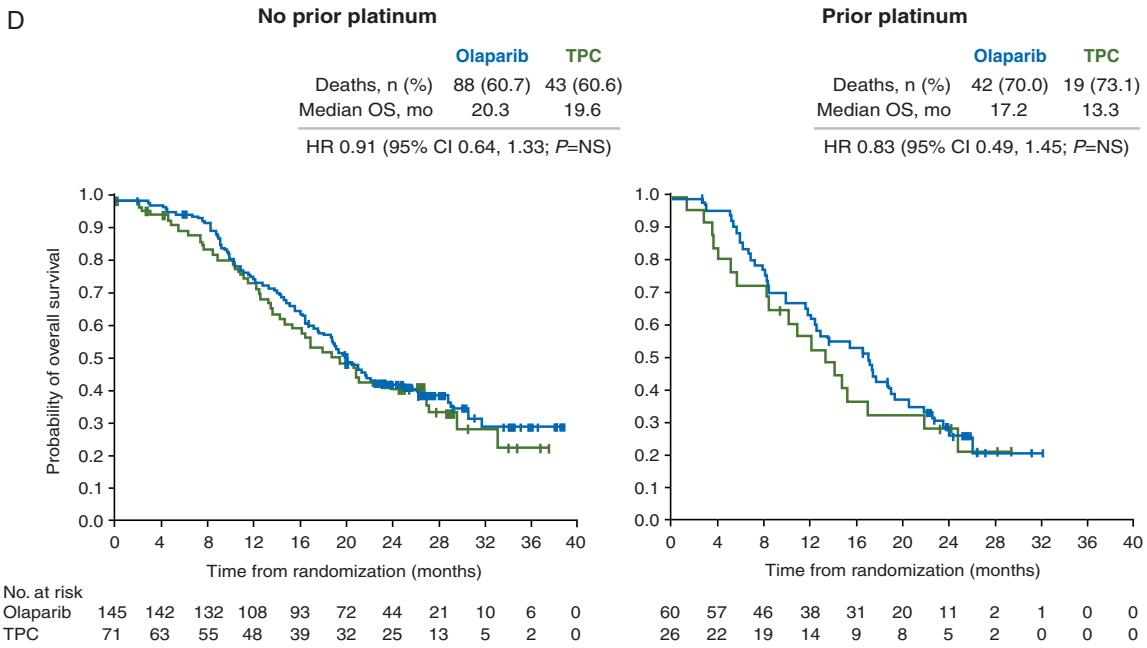

Figure 1. *continued*

data analysis [4]. Median total treatment duration was 8.2 months in the olaparib arm versus 3.4 months in the TPC arm. In the olaparib arm, median total treatment duration was similar to the actual median treatment duration (taking into account dose interruptions) of 7.5 months. Thirty-nine (19%) patients received olaparib for ≥18 months, and 18 (8.8%) patients received olaparib for ≥24 months.

The most common AEs are shown in Table 1. In the olaparib arm, these were mostly grade 1 or 2 in severity and rarely led to permanent discontinuation (supplementary Table S3, available at *Annals of Oncology* online). Nausea, anemia, vomiting, fatigue, cough, decreased appetite, back pain, and headache were reported at a relatively higher frequency (≥5%) in the olaparib arm compared with TPC. AEs of neutropenia, PPE, increased alanine aminotransferase, increased aspartate aminotransferase, and alopecia occurred at a higher frequency (≥5%) in the TPC arm compared with the olaparib arm (Table 1). The rate of alopecia during olaparib treatment was low (3.4%) and compared favorably to TPC (13.2%). Within the individual TPC groups, the most common AEs for capecitabine were PPE (43.9%), nausea (41.5%), and diarrhea (29.3%); for eribulin, neutropenia (47.1%), alopecia (29.4%), and nausea (26.5%), and for vinorelbine, anemia (62.5%), fatigue (43.8%), and neutropenia (43.8%).

The overall incidence of reported AEs of grade ≥3 was 38.0% in the olaparib arm and 49.5% in the TPC arm, with treatment-related causality suspected in 24.4% and 34.1% of patients, respectively. The most common grade ≥3 AE was anemia in the olaparib arm and neutropenia in the TPC arm (Table 1). Febrile neutropenia was not reported in the olaparib arm and occurred in three patients in the TPC arm. Exposure-adjusted AEs are shown in supplementary Table S4, available at *Annals of Oncology* online.

Overall, 10 (4.9%) and 7 (7.7%) patients discontinued treatment because of an AE in the olaparib and TPC arms, respectively (supplementary Table S3, available at *Annals of Oncology* online). Further detail is provided in the supplementary material, available at *Annals of Oncology* online.

One (0.5%) patient in the olaparib arm died after developing sepsis, which started 15 days after discontinuation of olaparib treatment. The AE was not considered by the investigator to be related to treatment. An AE with outcome of death (dyspnea) in the TPC arm was previously reported but was subsequently reassigned to disease progression by the investigator for the final data cut-off.

Timing and management of the most common AEs during olaparib treatment

Nausea and vomiting. All nausea and vomiting in the olaparib arm were grade 1–2, while in the TPC arm, a single event of grade 3 nausea (1.1%) and of vomiting (1.1%) occurred (Table 1). Dose reductions and interruptions due to nausea and vomiting occurred in ≤2% of patients in both the olaparib and TPC arms. No patients discontinued olaparib treatment because of nausea and vomiting, and one patient discontinued TPC because of vomiting (supplementary Table S3, available at *Annals of Oncology* online).

The first onset of nausea and vomiting was generally within the first month of treatment, with the majority reported as resolved (Table 2). Time to first onset of grade ≥2 vomiting was longer than for any grade for olaparib: 61 versus 27 days, but not for TPC (26 versus 27 days, respectively). Anti-emetic medications were provided at the investigator's discretion, and were used in 68 (33.2%) and 28 (30.8%) patients receiving olaparib and TPC, respectively (further detail is provided in the supplementary material, available at *Annals of Oncology* online). The prevalence of nausea in the olaparib arm reduced from 20%–30% in the first 3 months of treatment to 10%–20% from 3 months onwards,

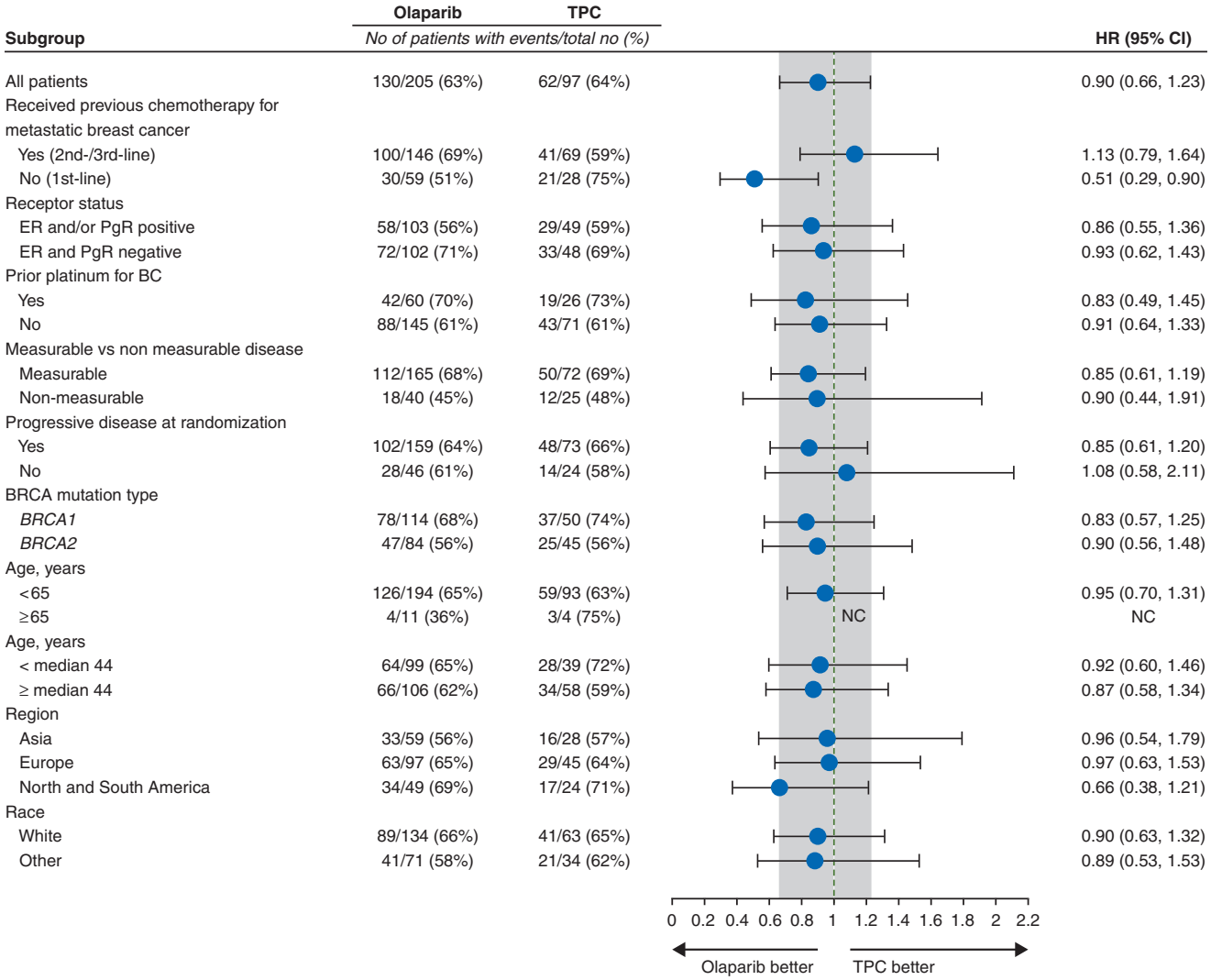

Figure 2. Forest plots of final OS overall population and all subgroup analyses. BC, breast cancer; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; NC, not calculated; PgR, progesterone receptor; TPC, treatment of physician's choice.

being almost negligible after 24 months among the small number of patients continuing treatment (Figure 3A). The prevalence of vomiting was approximately 5% with olaparib for most of the study (Figure 3B).

Anemia. Anemia was reported in 40.0% of patients in the olaparib arm and 26.4% of patients in the TPC arm, of which 16.1% and 4.4% were grade ≥3, respectively (Table 1). Dose interruptions (15.1%) and reductions (13.7%) were more frequently used in patients receiving olaparib than TPC (2.2% and 1.1%, respectively; supplementary Table S3, available at *Annals of Oncology* online). The first onset of anemia was typically in the first 3 months of starting olaparib. The prevalence of all grades of anemia was stable over time, while the risk of grade ≥3 anemia was low in the patients who continued treatment beyond 24 months (Figure 3C). Detail about anemia and treatment history is provided in the supplementary material, available at *Annals of Oncology* online.

Anemia was subsequently reported as resolved in 78% of olaparib patients who experienced the AE ($n = 64$), either with supportive care or dose modification (supplementary Table S3, available at *Annals of Oncology* online and Table 2). Four olaparib patients (2.0%) and two TPC patients (2.2%) discontinued study treatment due to anemia. Supportive treatment was provided for 46.3% of the olaparib patients who experienced anemia (Table 2). More patients in the olaparib arm ($n = 37$; 18.0%) than in the TPC arm ($n = 5$; 5.5%) received at least one blood transfusion. In total, 20 patients in the olaparib arm had one transfusion, nine patients had two transfusions, seven patients had three transfusions each, and one patient had four transfusions. For patients with a blood transfusion that was reported as related to anemia, 6/33 (18.2%) olaparib patients were transfused for grade 2 anemia, and one olaparib patient was transfused for grade 1 anemia. All other anemia-related blood transfusions in the olaparib arm were for grade ≥3 anemia.

Anti-anemic preparations were used at the investigator's discretion in 43 (21.0%) olaparib patients and 12 (13.2%) TPC patients.

Table 1. Incidence of the most common AEs occurring in >10% of patients in either treatment arm, by maximum reported CTCAE grade[a]

	Olaparib (N = 205)				Chemotherapy TPC (N = 91)			
	All grades	Grade 1	Grade 2	Grade ≥3	All grades	Grade 1	Grade 2	Grade ≥3
Any AE	200 (97.6)	33 (16.1)	89 (43.4)	78 (38.0)	87 (95.6)	6 (6.6)	36 (39.6)	45 (49.5)
Nausea	119 (58.0)	92 (44.9)	27 (13.2)	0	32 (35.2)	26 (28.6)	5 (5.5)	1 (1.1)
Anemia	82 (40.0)	19 (9.3)	30 (14.6)	33 (16.1)	24 (26.4)	9 (9.9)	11 (12.1)	4 (4.4)
Neutropenia	56 (27.3)	12 (5.9)	25 (12.2)	19 (9.3)	45 (49.5)	4 (4.4)	17 (18.7)	24 (26.4)
Vomiting	66 (32.2)	49 (23.9)	17 (8.3)	0	14 (15.4)	12 (13.2)	1 (1.1)	1 (1.1)
Fatigue	61 (29.8)	40 (19.5)	14 (6.8)	7 (3.4)	22 (24.2)	6 (6.6)	15 (16.5)	1 (1.1)
Diarrhea	42 (20.5)	33 (16.1)	8 (3.9)	1 (0.5)	20 (22.0)	13 (14.3)	7 (7.7)	0
PPE	1 (0.5)	1 (0.5)	0	0	19 (20.9)	8 (8.8)	9 (9.9)	2 (2.2)
Decreased WBC	33 (16.1)	13 (6.3)	13 (6.3)	7 (3.4)	19 (20.9)	3 (3.3)	7 (7.7)	9 (9.9)
Headache	42 (20.5)	28 (13.7)	12 (5.9)	2 (1.0)	14 (15.4)	8 (8.8)	4 (4.4)	2 (2.2)
Pyrexia	30 (14.6)	25 (12.2)	5 (2.4)	0	16 (17.6)	10 (11.0)	6 (6.6)	0
Increased ALT	24 (11.7)	15 (7.3)	6 (2.9)	3 (1.5)	16 (17.6)	8 (8.8)	7 (7.7)	1 (1.1)
Cough	35 (17.1)	24 (11.7)	11 (5.4)	0	6 (6.6)	5 (5.5)	1 (1.1)	0
Increased AST	20 (9.8)	11 (5.4)	4 (2.0)	5 (2.4)	15 (16.5)	11 (12.1)	4 (4.4)	0
Decreased appetite	35 (17.1)	26 (12.7)	9 (4.4)	0	11 (12.1)	9 (9.9)	2 (2.2)	0
Constipation	26 (12.7)	19 (9.3)	6 (2.9)	1 (0.5)	12 (13.2)	9 (9.9)	3 (3.3)	0
Asthenia	19 (9.3)	11 (5.4)	6 (2.9)	2 (1.0)	12 (13.2)	6 (6.6)	6 (6.6)	0
Alopecia	7 (3.4)	6 (2.9)	1 (0.5)	0	12 (13.2)	7 (7.7)	5 (5.5)	0
URTI	27 (13.2)	17 (8.3)	9 (4.4)	1 (0.5)	9 (9.9)	4 (4.4)	5 (5.5)	0
Back pain	30 (14.6)	15 (7.3)	11 (5.4)	4 (2.0)	8 (8.8)	5 (5.5)	2 (2.2)	1 (1.1)
Stomatitis	16 (7.8)	14 (6.8)	2 (1.0)	0	10 (11.0)	6 (6.6)	4 (4.4)	0
Arthralgia	23 (11.2)	20 (9.8)	2 (1.0)	1 (0.5)	9 (9.9)	6 (6.6)	2 (2.2)	1 (1.1)
Leukopenia	23 (11.2)	4 (2.0)	14 (6.8)	5 (2.4)	9 (9.9)	3 (3.3)	3 (3.3)	3 (3.3)

[a]AEs of any cause; MedDRA-preferred terms are grouped for anemia (anemia, decreased Hb level, decreased hematocrit, decreased red blood cell count, and erythropenia) and neutropenia (febrile neutropenia, granulocytopenia, decreased granulocyte count, neutropenia, neutropenic sepsis, decreased neutrophil count, and neutropenic infection).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PPE, palmar plantar erythrodysesthesia; TPC, treatment of physician's choice; URTI, upper respiratory tract infection; WBC, white blood cells.

Table 2. Median time to onset, duration, resolution, and supportive care used for the most common AEs during olaparib treatment, for patients who experienced the event

	Nausea		Vomiting		Anemia	
	Olaparib (n = 119)	TPC (n = 32)	Olaparib (n = 66)	TPC (n = 14)	Olaparib (n = 82)	TPC (n = 24)
Median time to first onset, days						
All grades	5	5	27	27	44	16
Grade ≥2 or ≥3[a]	4	47	61	26	62	59
Median duration of first event, days						
All grades	34	20	2	5	41	53
Grade ≥2 or ≥3[a]	43	20	4	33	80	38
Supportive treatment, *n* (%)	63 (52.9)	17 (53.1)	22 (33.3)	3 (21.4)	38 (46.3)	7 (29.2)
Transfusion for all-grade anemia[b]	–	–	–	–	33 (40.2)	4 (16.7)
Transfusion for grade ≥3 anemia[b]	–	–	–	–	26/33 (78.8)	2/4 (50.0)
Resolved, *n* (%)[c]						
All grades	109 (91.6)	26 (81.3)	63 (95.5)	12 (85.7)	64 (78.0)	15 (62.5)
Grade ≥2 or ≥3[a]	23/27 (85.2)	2/6 (33.3)	17/17 (100)	1/2 (50.0)	26/33 (78.8)	2/4 (50.0)

[a]Grade ≥2 for nausea and vomiting and grade ≥3 for anemia.

[b]Reported as related to anemia.

[c]Patients in whom the event resolved as a percentage of all patients experiencing the AE.

AE, adverse event; TPC, treatment of physician's choice.

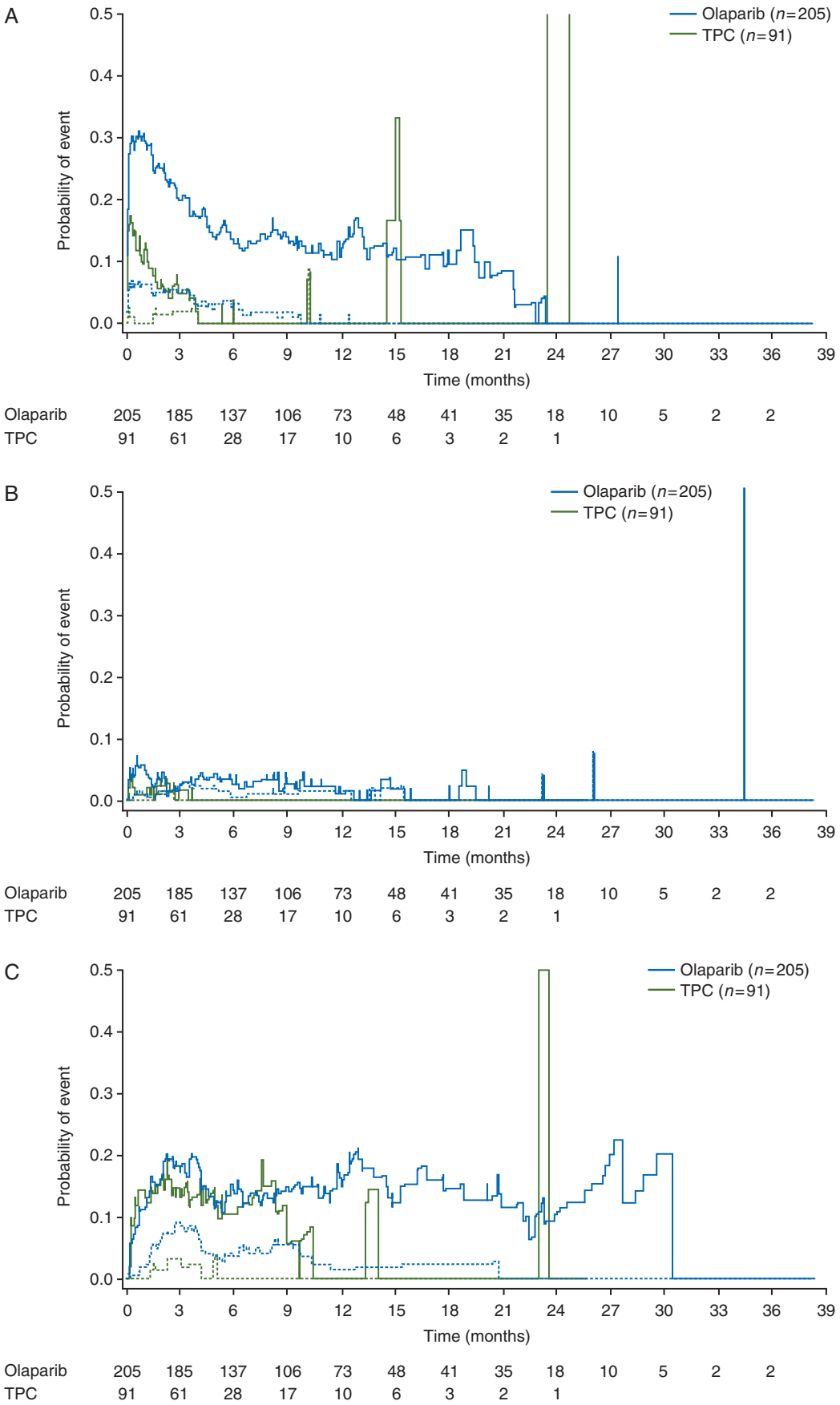

Figure 3. Prevalence of all (solid lines) and grade ≥2 (dotted lines) (A) nausea* and (B) vomiting, and (C) all (solid lines) and grade ≥3 (dotted lines) anemia, during the OlympiAD study. *The probability of event in the TPC arm was 1.0 at 24 months.

These included erythropoietin-stimulating agents in 5.9% and 1.1% of patients; iron-containing preparations and vitamin B12 were also used. Patients may have received more than one preparation, and administration was at the discretion of the investigator.

As reported at the time of the primary data analysis, there were no cases of myelodysplastic syndrome or acute myeloid leukemia, no cases of pneumonitis, and the incidence of new primary malignancies was low (one patient in the olaparib arm with a nonserious event of melanoma *in situ* which was reported previously) [4].

Discussion

Once cure is no longer feasible, OS is the most desirable goal of cancer treatment. Findings from this final prespecified analysis of the Phase III OlympiAD study of olaparib monotherapy compared with TPC in patients with a germline BRCAm and HER2-negative mBC show that there was no statistically significant difference in OS between treatment arms, although the study was not powered to identify a difference in this end point. Analyses in clinical trials may also be confounded by lack of control over crossover treatment once the study drug has been discontinued [5]. OS was consistent among the predefined subgroups. The observation that olaparib patients who had not received prior chemotherapy for mBC achieved a 7.9-month longer median OS compared with TPC was provocative. These findings support earlier observations by Kaufman et al. [6], in which olaparib efficacy was greatest in patients who were less heavily pretreated. The subset analyses were preplanned and clinical prognostic factors were generally well-balanced between arms in the subsets; however, the sample sizes are small and confounding cannot be excluded. Therefore, it would be ideal if the potential for a clinically meaningful survival benefit for olaparib in first-line treatment for metastatic disease could be confirmed in further studies, such as those employing real-world evidence.

The safety profile of olaparib was consistent with the primary analysis. There was no evident cumulative toxicity with extended exposure. The median duration of treatment with olaparib was more than double that with TPC. Dose interruptions did not have a significant impact on actual olaparib treatment duration, indicating that most patients were able to receive their assigned treatment. The rate of discontinuation from olaparib treatment due to AEs was low (<5%), showing that supportive treatment, dose interruptions, and dose reductions can be used effectively to manage tolerability while ensuring that patients remain on treatment for as long as they are receiving benefit.

Nausea and vomiting were both low-grade, early events for olaparib, and prevalence decreased over time. Dose modifications for nausea and vomiting were infrequent, with supportive care provided to approximately half and one-third of patients, respectively. There was no evidence of a cumulative effect on the risk of developing anemia with increasing treatment duration, and the risk of discontinuation due to anemia was low. Anemia was managed at the investigator's discretion with blood transfusions and/or antianemic preparations, and a hemoglobin level of 10 mg/dl was required to continue uninterrupted full-dose therapy with olaparib. In clinical practice, the management of asymptomatic anemia may be less likely to warrant a blood transfusion than that specified in the OlympiAD study protocol. Approximately 20% (7/33) of the olaparib patients who were transfused for anemia received blood for grade 1 or 2 anemia, a level that would not usually indicate transfusion in clinical practice.

The rate of alopecia during olaparib treatment was low (3.4%) and compared favorably to TPC (13.2%).

Myelosuppression appears to be a class effect of PARP inhibitors in the treatment of both breast and ovarian cancer. In the recently reported EMBRACA trial comparing talazoparib to TPC in a similar population to the OlympiAD study, 39.2% of patients experienced grade ≥3 anemia, with grade ≥3 neutropenia in 21.0% and grade ≥3 thrombocytopenia in 14.7% of patients [7]. The mechanism of and risk factors for myelosuppression with PARP inhibitors are not well-defined, and further research will be necessary to predict and mitigate these side effects.

Limitations of the OlympiAD study have been reported previously [4] and include the open-label trial design required to accommodate the TPC arm, and the heterogeneity of the study population in terms of treatment history and hormone-receptor status. However, including a broad patient population in the OlympiAD study does provide evidence of olaparib efficacy and safety in a patient population that is relevant to daily clinical practice. In addition, the lack of a platinum-based chemotherapy option leaves open the question of the best initial treatment for patients with BRCA mutation-associated breast cancer. While one might hypothesize that olaparib would provide better quality of life than platinum-based chemotherapy, the relative benefits of these two treatment approaches can only be addressed through a specific clinical trial.

OS, a secondary end point, was not significantly different between olaparib and TPC. Preplanned subgroup analyses raise the possibility of a meaningful OS benefit for olaparib in patients who had not received chemotherapy for metastatic disease. Gastrointestinal toxicity and anemia were the most common AEs during olaparib treatment and were generally of low grade, transient, and manageable by supportive treatment, dose interruption, or dose reduction. The safety profile of olaparib was consistent with the primary analysis, indicating no relevant cumulative toxicity with extended exposure.

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