Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. N Engl J Med 2019;381:317-27. DOI: 10.1056/NEJMoa1903387

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

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Supplement to: Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer.

CONTENTS

POLO INVESTIGATORS

The table below lists the principal investigator for each site who participated in the study.

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METHODS

MODIFIED RECIST v1.1 CRITERIA

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria were modified to allow for assessment of disease progression due to new lesions in patients with no evidence of disease at baseline. Patients with no evidence of disease following platinum-based chemotherapy were deemed to have disease progression if new lesions were detected.

PFS SENSITIVITY ANALYSES

A prespecified sensitivity analysis of progression-free survival (PFS) was performed in the subgroup of patients with a germline *BRCA1* and/or *BRCA2* mutation (gBRCAm) confirmed by BRACAnalysis CDx® (Myriad Genetics Laboratories, Inc) testing, in case of discrepancies between BRACAnalysis CDx® and unconfirmed local testing results. The same methodology as for the primary analysis was used.

A prespecified sensitivity analysis was also performed based on investigator assessments of PFS using modified RECIST v1.1 criteria, to assess ascertainment bias.

In the primary analysis of PFS by blinded independent central review, patients who had not had a progression event or died, or who had a progression event or died after two or more missed visits, were censored at the date of their last evaluable tumor assessment. To assess attrition bias, a prespecified sensitivity analysis was carried out using the actual PFS event time for patients whose disease progressed or who died in the absence of progression (as assessed by blinded independent central review) immediately following two or more non-evaluable tumor assessments.

POPULATIONS FOR ANALYSES

Full analysis set

The primary statistical analysis of the efficacy of olaparib included all randomized patients and compared treatment groups on the basis of randomized treatment, regardless of the treatment actually received, or discrepancy between local and Myriad gBRCAm test results. Patients who were randomized but did not subsequently go on to receive study treatment were included in the full analysis set. Therefore, all efficacy endpoints were summarized and analyzed using the full analysis set on an intention-to-treat basis. In addition, a key sensitivity analysis of PFS was performed in the subgroup of patients in the full analysis set with a gBRCAm confirmed by Myriad test.

Safety analysis set

Safety data were analyzed in all patients who received at least one dose of investigational product.

Patient-reported outcome analysis set

Health-related quality of life (HRQoL) data were analyzed in the subset of patients in the intention-to-treat population who had evaluable baseline 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and/or 26-item Pancreatic Cancer Quality of Life Questionnaire (EORTC QLQ-PAN26)

forms. An evaluable form was defined as one on which at least one subscale baseline score could be determined. For the adjusted mean change from baseline in global EORTC QLQ-C30 HRQoL score analysis, only visits with at least 25% non-missing values in each treatment arm were included. The study treatment discontinuation and 30 days following last dose of study treatment visits were excluded from this analysis.

MIXED MODEL FOR REPEATED MEASURES ANALYSIS APPLIED TO HEALTH-RELATED QUALITY OF LIFE

Restricted maximum likelihood (REML) estimation was used. The model included randomized treatment group, visit and treatment by visit interaction as explanatory variables and the baseline EORTC QLQ-C30 global HRQoL score as a covariate along with a baseline EORTC QLQ-C30 global HRQoL score by visit interaction. Treatment, visit and treatment by visit interaction were included as fixed effects in the model. The treatment by visit interaction remained in the model regardless of significance. An unstructured covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used to estimate the degrees of freedom.

RESULTS

PATIENTS WITH A gBRCAm NOT CONFIRMED BY BRACAnalysis CDx®

Four patients randomized on the basis of a local gBRCAm test result did not have a confirmatory BRACAnalysis CDx® test as part of the study. Local testing for two of these patients was carried out using BRACAnalysis CDx®. The remaining two patients were found to have deleterious deletions upon review of their local test reports.

MULTIVARIATE ANALYSIS OF PFS

A multivariate analysis of PFS was carried out to assess possible bias caused by baseline imbalances between treatment groups. Comparison of the unadjusted result with a multivariate analysis adjusted for key baseline prognostic factors showed that imbalances between arms did not impact on treatment effect (Table S4).

DOSE INTENSITY

The median (range) relative dose intensity was 99.3% (45 to 100) in the olaparib group and 100% (35 to 100) in the placebo group.

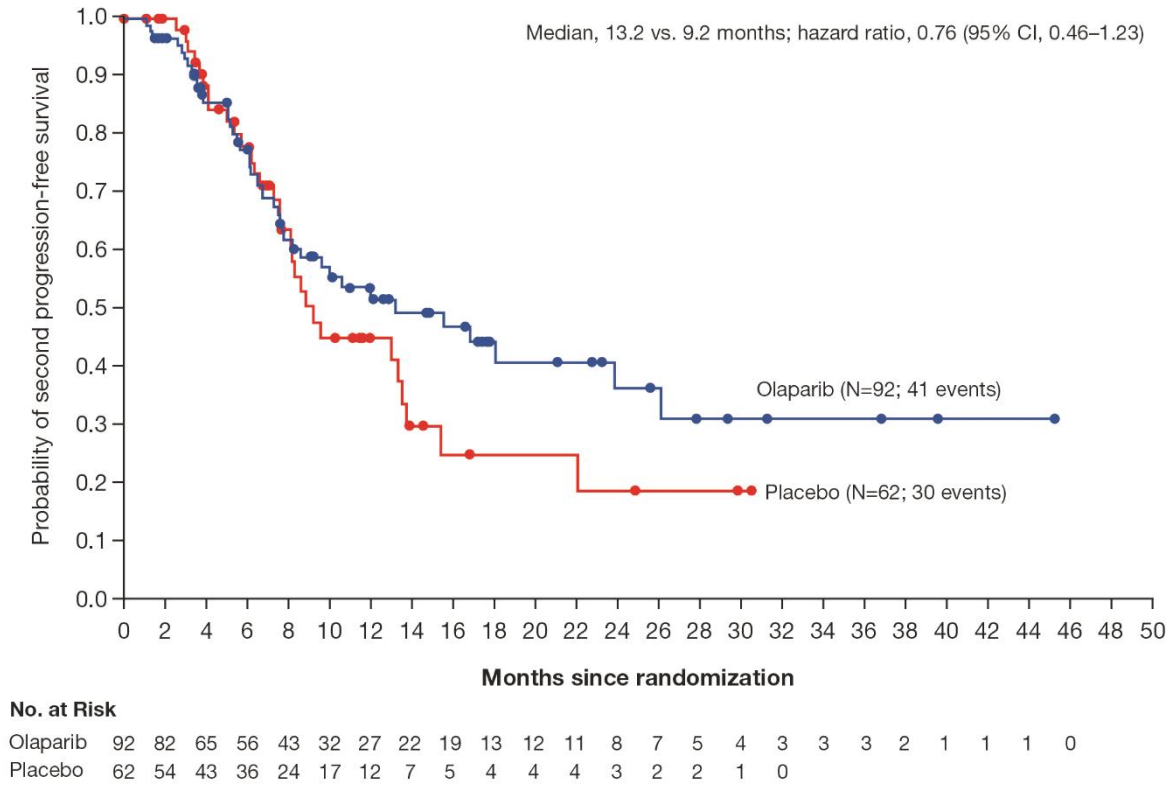
PNEUMONITIS

The one case of pneumonitis, in a patient in the olaparib group, was of grade 1 severity and was not considered to be causally related to study treatment. The adverse event was not serious, and the treatment dose was not changed as a result of pneumonitis. The adverse event was not resolved at the data cut-off for this analysis.

ADVERSE EVENT LEADING TO DEATH

One patient in the olaparib arm had an adverse event of duodenal perforation (in association with a stent) that began 15 days after the last dose of study treatment and became a grade 5 adverse event after the data cut-off for this analysis (January 15, 2019) and after the end of the 30 days from discontinuation of study treatment follow-up period. The patient received olaparib for 3.8 months and discontinued treatment due to an adverse event of gastric fistula (grade 1). The patient had a history of duodenal perforation prior to randomization in the POLO study.

Figure S1. Kaplan–Meier Estimate of PFS2 by Investigator Assessment*



*Overall survival (OS) data in POLO are immature and likely to be confounded by subsequent therapies. The time from randomization to second progression or death (PFS2) analysis was carried out as a surrogate for OS, and results at 46% maturity show a trend towards benefit for olaparib-arm patients. This could suggest that treatment with olaparib preserved the benefit of second-line therapy, which was received by 49% and 74% of patients in the olaparib and placebo arms, respectively.

Table S1. Patients Randomized in the POLO Study, by Country

Country — no. (%)	Olaparib (N = 92)	Placebo (N = 62)	Total (N=154)
United States	19 (20.7)	13 (21.0)	32 (20.8)
France	15 (16.3)	9 (14.5)	24 (15.6)
Israel	16 (17.4)	7 (11.3)	23 (14.9)
Germany	11 (12.0)	9 (14.5)	20 (13.0)
Italy	7 (7.6)	9 (14.5)	16 (10.4)
Spain	6 (6.5)	5 (8.1)	11 (7.1)
United Kingdom	3 (3.3)	6 (9.7)	9 (5.8)
Republic of Korea	4 (4.3)	2 (3.2)	6 (3.9)
Belgium	5 (5.4)	0	5 (3.2)
Canada	3 (3.3)	0	3 (1.9)
The Netherlands	2 (2.2)	1 (1.6)	3 (1.9)
Australia	1 (1.1)	1 (1.6)	2 (1.3)

Table S2. Additional Characteristics of the Randomized Patients at Baseline*

Characteristic	Olaparib (N = 92)	Placebo (N = 62)
Race — no. (%)		
White	82 (89.1)	59 (95.2)
Black or African American	5 (5.4)	0
Asian	4 (4.3)	2 (3.2)
Other†	1 (1.1)	1 (1.6)
Biliary stent present — no. (%)	1 (1.1)	4 (6.5)
Location of primary tumor in pancreas — no. (%)‡		
Head	46 (50.0)	34 (54.8)
Body	41 (44.6)	17 (27.4)
Tail	29 (31.5)	22 (35.5)
Missing	2 (2.2)	1 (1.6)
Site of metastases prior to chemotherapy — no. (%)‡		
Liver	61 (66.3)	48 (77.4)
Lung	10 (10.9)	5 (8.1)
Peritoneum	10 (10.9)	5 (8.1)
Other	14 (15.2)	8 (12.9)
Disease status following platinum-based chemotherapy — no. (%)		
Measurable	78 (84.8)	52 (83.9)
Non-measurable or no evidence of disease	13 (14.1)	6 (9.7)
Missing	1 (1.1)	4 (6.5)
Median albumin concentration, g/L (range)	41.0 (32–48)	40.0 (34–50)

*Percentages may not total 100 because of rounding. †Other race includes American Indian or Alaskan Native (olaparib-arm patient) and unknown race (placebo-arm patient). ‡Patients may be counted in more than one category.

Table S3. Germline BRCA Mutation Status at Baseline by BRACAnalysis CDx® (Myriad Genetics Laboratories, Inc.)

Germline BRCA mutation status — no. (%)	Olaparib group (N = 92)	Placebo group (N = 62)
Germline BRCA mutation	89 (96.7)	61 (98.4)
BRCA1	29 (31.5)	16 (25.8)
BRCA2	59 (64.1)	45 (72.6)
Both *BRCA1* and *BRCA2*	1 (1.1)	0
Missing	3 (3.3)	1 (1.6)

Table S4. First-Line Platinum-Based Chemotherapy Received by Patients Immediately Prior to Randomization in POLO

Prior chemotherapy — no. (%)	Olaparib (N = 92)	Placebo (N = 62)
FOLFIRINOX	73 (79.3)	44 (71.0)
FOLFOX	4 (4.3)	5 (8.1)
GEMOX	5 (5.4)	1 (1.6)
Gemcitabine/cisplatin	2 (2.2)	3 (4.8)
Gemcitabine/nab-paclitaxel/capecitabine/cisplatin	2 (2.2)	2 (3.2)
XELOX	2 (2.2)	1 (1.6)
Oxaliplatin	1 (1.1)	1 (1.6)
Gemcitabine/epirubicin/capecitabine/cisplatin	0	2 (3.2)
FOLFIRI/cisplatin	0	1 (1.6)
FOLFOX/nab-paclitaxel	0	1 (1.6)
5-fluorouracil/carboplatin	1 (1.1)	0
FOLF/cisplatin	1 (1.1)	0

Table S5. Sensitivity Analyses of PFS

PFS sensitivity analysis		Olaparib	Placebo	Between-group difference	HR (95% CI)
By investigator assessment	n	92	62		0.51
	Median PFS, months	6.3	3.7	2.6	(0.34 to 0.78)
In patients with a Myriad-confirmed gBRCAm	n	89	61		0.55
	Median PFS, months	7.4	3.8	3.6	(0.36 to 0.84)
Assessment of attrition bias*	n	92	62		0.51
	Median PFS, months	7.5	3.8	3.7	(0.33 to 0.78)

*This analysis uses actual PFS event times for patients whose disease progressed or who died in the absence of progression (as assessed by blinded independent central review) immediately following two or more non-evaluable tumor assessments. In the primary PFS analysis, one olaparib group and three placebo group patients were censored as a result of having two or more non-evaluable tumor assessments.

Table S6. Multivariate Analysis of PFS

Model	Olaparib (N = 92)	Placebo (N = 62)
Unadjusted model*		
n	92	62
HR (95% CI)	0.56 (0.37 to 0.83)	
Adjusted model†		
n	85	59
HR (95% CI)	0.61 (0.40 to 0.92)	

*Cox proportional hazards model including only randomized treatment group (olaparib vs. *placebo*) as a factor. †Cox proportional hazards model including treatment group (olaparib vs. *placebo*) and the following baseline covariates: best response to first-line treatment (*complete/partial response* vs. stable disease); time on first-line treatment (*≤6 months* vs. >6 months); age group (*<65 years* vs. ≥65 years); ECOG performance status (*0, normal activity* vs. 1, restricted activity); type of previous chemotherapy (*FOLFIRINOX* vs. gemcitabine/cisplatin vs. other); type of previous chemotherapy (doublets vs. *triplets* vs. other); site of metastases prior to chemotherapy (*liver* vs. other). Italicized text indicates which factor level was included in the model as the reference level. n, number of evaluable patients.

Table S7. Treatments Received by Patients Following Discontinuation of Study Treatment*

Subsequent therapy — no. (%)	Olaparib (N = 92)	Placebo (N = 62)
Continuing study treatment	30 (32.6)	8 (12.9)
Any subsequent therapy†	45 (48.9)	46 (74.2)
Platinum-based chemotherapy	20 (21.7)	18 (29.0)
Carboplatin	4 (4.3)	4 (6.5)
Cisplatin	10 (10.9)	12 (19.4)
Oxaliplatin	9 (9.8)	4 (6.5)
PARP inhibitor	1 (1.1)	9 (14.5)
Olaparib	0	7 (11.3)
Rucaparib	1 (1.1)	1 (1.6)
Veliparib	0	1 (1.6)
Other chemotherapy regimen‡	45 (48.9)	45 (72.6)
Gemcitabine/cisplatin	1 (1.1)	1 (1.6)
GEMOX	1 (1.1)	0
FOLFIRINOX	17 (18.5)	18 (29.0)
FOLFOX	2 (2.2)	5 (8.1)

*Patients may be counted in more than one category. †Subsequent therapies may be reported as regimens or as individual drugs and in some cases are reported both ways. ‡'Other chemotherapy regimen' includes platinum-based combinations (listed) and non-platinum-containing chemotherapy regimens.

Table S8. Adverse Events Leading to Treatment Discontinuation*

Adverse event leading to discontinuation — no. (%)	Olaparib (N = 91)	Placebo (N = 60)
Any	5 (5.5)	1 (1.7)
Fatigue/asthenia†,‡	2 (2.2)	0
Arthralgia†	1 (1.1)	0
Decreased appetite‡	1 (1.1)	0
Gastric fistula	1 (1.1)	0
Proteinuria	1 (1.1)	0
Myalgia†	1 (1.1)	0
Vomiting	1 (1.1)	0
Pyrexia	0	1 (1.7)

*Patients could have had more than one adverse event leading to treatment discontinuation. †One patient discontinued olaparib due to fatigue/asthenia, arthralgia and myalgia. ‡One patient discontinued olaparib due to decreased appetite and fatigue/asthenia.