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ORIGINAL ARTICLE

Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast cancer

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Background: The randomized, double-blind OlympiA trial compared 1 year of the oral poly(adenosine diphosphate-ribose) polymerase inhibitor, olaparib, to matching placebo as adjuvant therapy for patients with pathogenic or likely pathogenic variants in germline *BRCA1* or *BRCA2* (g*BRCA1/2*pv) and high-risk, human epidermal growth factor receptor 2-negative, early breast cancer (EBC). The first pre-specified interim analysis (IA) previously demonstrated statistically significant improvement in invasive disease-free survival (IDFS) and distant disease-free survival (DDFS). The olaparib group had fewer deaths than the placebo group, but the difference did not reach statistical significance for overall survival (OS). We now report the pre-specified second IA of OS with updates of IDFS, DDFS, and safety.

Patients and methods: One thousand eight hundred and thirty-six patients were randomly assigned to olaparib or placebo following (neo)adjuvant chemotherapy, surgery, and radiation therapy if indicated. Endocrine therapy was given concurrently with study medication for hormone receptor-positive cancers. Statistical significance for OS at this IA required $P < 0.015$.

Results: With a median follow-up of 3.5 years, the second IA of OS demonstrated significant improvement in the olaparib group relative to the placebo group [hazard ratio 0.68; 98.5% confidence interval (CI) 0.47-0.97; $P = 0.009$]. Four-year OS was 89.8% in the olaparib group and 86.4% in the placebo group (Δ 3.4%, 95% CI −0.1% to 6.8%). Four-year IDFS for the olaparib group versus placebo group was 82.7% versus 75.4% (Δ 7.3%, 95% CI 3.0% to 11.5%) and 4-year DDFS was 86.5% versus 79.1% (Δ 7.4%, 95% CI 3.6% to 11.3%), respectively. Subset analyses for OS, IDFS, and DDFS demonstrated benefit across major subgroups. No new safety signals were identified including no new cases of acute myeloid leukemia or myelodysplastic syndrome.

Conclusion: With 3.5 years of median follow-up, OlympiA demonstrates statistically significant improvement in OS with adjuvant olaparib compared with placebo for g*BRCA1/2*pv-associated EBC and maintained improvements in the previously reported, statistically significant endpoints of IDFS and DDFS with no new safety signals.

Key words: breast cancer, *BRCA1/2*, PARP inhibition, olaparib, adjuvant therapy

INTRODUCTION

Cancers harboring germline pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* (g*BRCA1/2*pv) are characterized by homologous recombination DNA repair deficiency following the inactivation of the wildtype allele during tumor evolution.[1] This engenders selective sensitivity to inhibition and trapping of the DNA repair enzyme, poly (adenosine diphosphate-ribose) polymerase 1 (PARP1) by exploiting the concept of synthetic lethality, as functional homologous recombination is required for cell survival when PARP1 function is inhibited and PARP1 is trapped on DNA arresting the DNA replication apparatus.[2-4] Olaparib and talazoparib both inhibit and trap PARP1 on DNA and have been approved for treating patients with g*BRCA1/2*pv and metastatic breast cancer (MBC) irrespective of hormone receptor status.[5,6]

Breast cancers associated with g*BRCA1/2*pv are characterized by high-grade disease with most g*BRCA1*pv-associated tumors being triple negative, whereas most g*BRCA2*pv-associated cancers are hormone receptor positive and human epidermal growth factor receptor 2 (HER2) negative,[7-9] and often associated with high-risk classification on RNA-based prognostic assays.[10,11] Because patients with g*BRCA1/2*pv-associated early breast cancers (EBCs) and high-risk clinico-pathological features remain at increased risk for recurrence following standard multimodality therapies, OlympiA (ClinicalTrials.gov: NCT02032823) was designed to determine whether 1 year of adjuvant olaparib could improve outcomes in this population. This phase III, double-blinded, placebo-controlled study randomized 1836 eligible patients with g*BRCA*pv-associated EBC from 2014 to 2019. Following review of the first pre-specified interim analysis (IA1) of the primary endpoint of invasive disease-free survival (IDFS), the independent data monitoring committee (IDMC) recommended full analysis, which was previously reported.[12] With a median follow-up of 2.5 years, patients

randomized to olaparib had statistically significant and clinically meaningful improvement in IDFS compared to placebo [hazard ratio (HR) 0.58; 99.5% CI 0.41-0.82; $P < 0.001$] and distant disease-free survival (DDFS) (HR 0.57; 99.5% CI 0.39-0.83; $P < 0.001$), which corresponded to absolute improvements at 3 years in IDFS of 8.8% and in DDFS of 7.1%.[12] The number of deaths in the olaparib group was fewer than in the placebo group (59 versus 86), but the difference (HR 0.68; 99% CI 0.44-1.05; $P = 0.02$) did not meet the prespecified boundary for statistical significance for overall survival (OS) ($P < 0.01$). The safety analysis was consistent with the experience in the MBC setting and provided no early evidence of increased risk of acute myeloid leukemia or myelodysplastic syndrome (AML/MDS).[12]

The second IA (IA2) of OS was pre-specified to occur when 330 IDFS events had been reported in the study population. Here we report the results of this OS analysis with updates of IDFS, DDFS, and safety information.

PATIENTS AND METHODS

Study design and patient population

Details of study design and populations for the primary and secondary efficacy endpoints and safety are described in the original manuscript.[12] The trial was conducted in accordance with the amended Declaration of Helsinki[13] and the protocol was approved by the institutional review board at each participating center. All patients provided written informed consent. Olaparib and placebo were provided by AstraZeneca.

In summary, eligible, consenting patients with g*BRCA1/2*pv determined by germline testing at the site or centrally, with high-risk, HER2-negative EBC were randomized to receive 1 year of study medication consisting of either oral olaparib 300 mg b.i.d. or matching placebo, stratified by hormone receptor status, prior neoadjuvant (NACT) versus adjuvant (ACT) chemotherapy, and platinum therapy for current breast cancer (yes versus no). Eligible patients had received at least six cycles of NACT or ACT containing a taxane, an anthracycline, or both, had completed surgery, and had completed adjuvant radiotherapy if indicated according to local standards at least 2 weeks before randomization. Patients with hormone receptor-positive cancers were to receive at least 5 years of adjuvant endocrine therapy (ET) as per local standards concurrent with study medication. Bisphosphonates and denosumab were allowed as per investigator's discretion. Patients who had received NACT could not receive postoperative chemotherapy.

Eligible patients with triple-negative breast cancer (TNBC) included those who received NACT with residual invasive cancer in the breast or axillary nodes, and those who received ACT were either node positive or node negative with a T2-T4 primary tumor at initial surgery. Following an early amendment, patients with hormone receptor-positive, HER2-negative disease became eligible with a clinical and pathological stage plus estrogen receptor and nuclear grade (CPS + EG) score of $\geq$3 following NACT[14,15] or $\geq$4 positive nodes at initial surgery.

Endpoints and assessments

In accordance with the Standardized Definitions for Efficacy End Points (STEEP) system,[16] the primary endpoint of IDFS was defined as the time from randomization until the date of first occurrence of one of the following events: ipsilateral invasive breast tumor, locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, second primary invasive cancer, or death from any cause. Patients without a documented IDFS event were censored at the date they were last known to be disease free. Secondary endpoints include DDFS, defined as time from randomization until documented evidence of first distant recurrence of breast cancer or death, and OS defined as time from the date of randomization until death due to any cause.

Efficacy analyses were based on the intention-to-treat (ITT) population. Survival functions were estimated by Kaplan—Meier method. The stratified Cox proportional hazards model was used to estimate the HR and confidence intervals (CIs), and the *P* value for the comparison of survival between treatment arms was generated by stratified log-rank test. Safety was assessed in the population who received at least one dose of study medication.

OlympiA was designed to achieve a 90% power to detect an HR of 0.70 for the primary endpoint of IDFS, assuming a two-sided 5% significance level. With a sample size of 1800 patients, the primary analysis of IDFS would be triggered by 330 IDFS events in the ITT population. Four analysis time-points were pre-planned, with a hierarchical multiple testing procedure to strongly control type 1 error across analysis time-points and endpoints (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.09.159). As previously reported,[12] the IA of IDFS in the entire ITT population was triggered when 165 IDFS events had been observed in the first 900 patients randomized (IA1). Superiority boundaries were $P < 0.005$ for IDFS, followed by $P < 0.005$ for DDFS, and $P < 0.01$ for OS (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.09.159). Superiority boundaries for both IDFS and DDFS were crossed, but not for OS.[12] The second pre-specified IA2 of OS was triggered by 330 IDFS events in the ITT population and results are presented herein. The boundary for the two-sided significance test of OS at IA2 was $P < 0.015$; thus, 98.5% CIs for OS are calculated in this analysis. Updated analyses of IDFS and DDFS were carried out with 95% CIs as these endpoint analyses are now descriptive.

RESULTS

Patients

From June 2014 through May 2019, 1836 patients were randomly assigned to receive either olaparib or placebo. IA2 was triggered on 12 July 2021; case report forms for study visits up to data cut-off for IA2 were collected and data quality controlled with database lock occurring on 17 December 2021. Median follow-up was 3.5 years [interquartile range (IQR) 2.5-4.5 years] in the ITT population, 3.6 years (IQR 2.5-4.7 years) in the TNBC cohort, and 3.4 years (IQR 2.5-4.1 years) in the hormone receptor-positive cohort.

Table 1. Demographic and baseline disease characteristics of the patients[a]

Characteristic	Olaparib (n = 921)	Placebo (n = 915)
Age, median (interquartile range), years	42 (36-49)	43 (36-50)
g*BRCA* P/LP gene—*n* (%)[b]		
BRCA1	656 (71.2)	669 (73.1)
BRCA2	260 (28.2)	238 (26.0)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
No g*BRCA* P/LP variant	2 (0.2)	3 (0.3)
Missing	1 (0.1)	0 (0.0)
Prior adjuvant/neoadjuvant chemotherapy, *n* (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Anthracycline and taxane regimen	871 (94.6)	849 (92.8)
Anthracycline regimen (without taxane)	7 (0.8)	13 (1.4)
Taxane regimen (without anthracycline)	43 (4.7)	52 (5.7)
Regimen not reported	0 (0.0)	1 (0.1)
<6 cycles of (neo)adjuvant chemotherapy	7 (0.8)	13 (1.4)
Platinum-based (neo)adjuvant therapy		
No	674 (73.2)	677 (74.0)
Yes	247 (26.8)	238 (26.0)
Concurrent hormone therapy (hormone receptor positive only), *n* (%)	146/168 (86.9)	146/157 (93.0)
Hormone receptor status, *n* (%)[c]		
Hormone receptor positive/HER2 negative[d]	168 (18.2)	157 (17.2)
Triple-negative breast cancer[e]	751 (81.5)	758 (82.8)
Menopausal status (females only), *n* (%)		
Premenopausal	572/919 (62.2)	553/911 (60.7)
Postmenopausal	347/919 (37.8)	358/911 (39.3)
Primary breast cancer surgery, *n* (%)		
Mastectomy	699 (75.9)	674 (73.7)
Conservative surgery only	222 (24.1)	239 (26.1)
Missing	0 (0.0)	2 (0.2)

HER2, human epidermal growth factor receptor 2; P/LP, pathogenic or likely pathogenic variants

[a]Further information on baseline characteristics is provided in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.09.159. Percentages may not total 100 because of rounding.

[b]For a detailed description of local and central Myriad BRCA testing in patients enrolled in the trial, see Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.09.159. Variant interpretation by Myriad Genetics (BRCAnalysis) (1649 patients) and BGI Genomics (247 patients) was carried out with the use of multiple established databases (e.g. ClinVar, ClinGen, and ENIGMA) and published and internal functional and clinical data, compliant with American College of Medical Genetics published guidelines. Eighty-five patients randomized in China had variant interpretation by both BGI Genomics and Myriad Genetics. The 24 pathogenic or likely pathogenic variants from local laboratories without central Myriad confirmation were confirmed by the OlympiA genetics advisory committee with the use of published databases as above. Discordant data are referred to in Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.09.159. Listing of pathogenic or likely pathogenic *BRCA1* and *BRCA2* variants that occurred in more than one patient have previously been reported.[12]

[c]Hormone receptor status was defined by local test results.

[d]The original protocol that was activated in 2014 was developed for HER2-negative patients but included only patients with triple-negative breast cancer after regulatory review. When the safety rationale with respect to recurrence risk relative to combination therapy with olaparib and endocrine therapy was accepted by regulators, the protocol was amended in 2015 to include patients with high-risk hormone receptor-positive disease and to increase the sample size to the current number of 1800 patients (see the protocol). The first patient with hormone receptor-positive disease was enrolled in December 2015.

[e]Triple-negative breast cancer was defined in the eligibility criteria as estrogen receptor negative and progesterone receptor negative, as indicated by immunohistochemical (IHC) nuclear staining of <1%, and HER2 negative (not eligible for anti-HER2 therapy), as indicated by one of the following: an IHC score of 0 or 1+; an IHC score of 2+ and HER2-nonamplified disease on *in situ* hybridization (ISH) with a ratio of <2.0 and, if reported, an average HER2 copy number of <4 signals per cell; or HER2-nonamplified disease on ISH with a ratio of <2.0 and, if reported, an average HER2 copy number of <4 signals per cell (without IHC). Two patients (both in the olaparib group) were excluded from the summary of the subgroup with triple-negative breast cancer because they did not have confirmed HER2-negative status.

After randomization, 10 patients in the olaparib group and 11 in the placebo group did not receive assigned therapy (Supplementary Figure S1: Consort Diagram, available at https://doi.org/10.1016/j.annonc.2022.09.159). Baseline characteristics of the patients were balanced between the two treatment groups (Table 1, Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.09.159). Most of the patients (82.2%) had TNBC. Approximately half of them received ACT and half NACT, with the majority (93.7%) receiving both an anthracycline and a taxane. A platinum agent was also received by 26.4% of patients, primarily in the NACT setting. Germline *BRCA1*pv were present in 72.2% and g*BRCA2*pv in 27.1% of patients with even distribution between treatment groups. Seven patients had both g*BRCA1*pv and g*BRCA2*pv.

Efficacy

OS was significantly improved in the olaparib group relative to the placebo group (HR 0.68; 98.5% CI 0.47-0.97; P = 0.009) (Figure 1A). Deaths were now reported in 75 patients (8.1%) in the olaparib group and 109 (11.9%) in the placebo group, 16 and 23 more, respectively, than at the previous IA. The cause of death was breast cancer in 93.3% in the olaparib group and 94.5% in the placebo group (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.09.159). Death without a prior IDFS

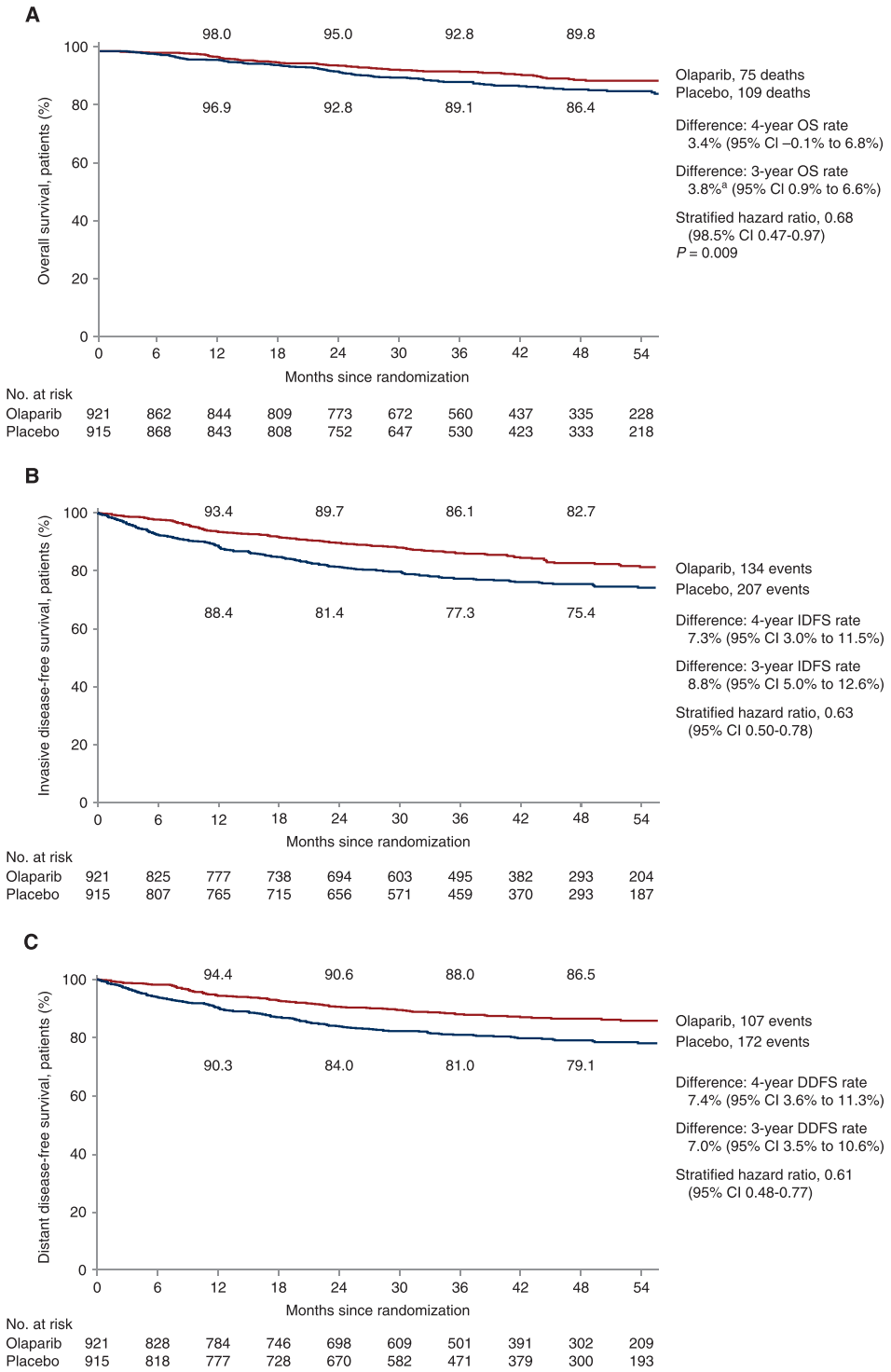


Figure 1. Kaplan-Meier Estimates of Survival. Overall survival (OS) (A) was defined as the time from the date of randomization until death due to any cause; the *P* value for the boundary for significance in this prespecified event-driven interim analysis was <0.015. In accordance with the standardized definitions for efficacy end points (STEEP) system, the primary end point of invasive disease-free survival (IDFS) (B) was defined as the time from randomization until the date of one of the following events: ipsilateral invasive breast tumor, locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, second primary invasive cancer, or death from any cause. Data for patients without a documented event of invasive disease or death were censored at the date they were last known to be disease-free. Distant disease-free survival (DDFS) (C) was defined as the time from randomization until documented evidence of first distant recurrence of breast cancer or death. Distant recurrence includes the following events: distant recurrence (metastatic breast cancer that has either been biopsy confirmed or radiologically diagnosed as recurrent invasive breast cancer); death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause; and second primary non-breast invasive cancer. Evidence of distant recurrence requires either radiologic examination or histopathological confirmation by biopsy. For IDFS and DDFS, 95% confidence intervals only are shown for the hazard ratios, as these results are descriptive. Similarly, the 98.5% confidence interval is shown for the hazard ratio for OS because a *P* value of <0.015 is required to indicate statistical significance for OS. On the basis of the pooling strategy for stratification factors described in Section 2 in the Supplementary Appendix, the primary stratified Cox proportional hazards model of IDFS, DDFS, OS, and the stratified log-rank test of OS, were based on the stratification factor of hormone receptor status only. The event-free rates at 12, 24, 36, and 48 months in each group are displayed above and below the curves. [a]Difference to 2 decimal places: 92.81-89.05 = 3.76 (rounded to 3.8).

event was reported in two patients in the olaparib group: one with cardiac arrest and one of unknown cause (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.09.159). The percentage of patients alive at 4 years from randomization was 89.8% in the olaparib group and 86.4% in the placebo group (3.4% difference: 95% CI −0.1% to 6.8%) (Figure 1A).

Planned subgroup analyses of OS demonstrated point estimates for improved OS for olaparib consistent with that of the overall population across stratification and g*BRCA1*pv or g*BRCA2*pv groups (Figure 2A). The survival benefit of olaparib was observed irrespective of g*BRCA1*pv or g*BRCA2*pv groups, hormone receptor status, prior platinum use, and ACT versus NACT context, with CIs that include the point estimate of the HR for OS in the overall population. There was no evidence of statistical heterogeneity in the treatment effect for OS across the subgroups analyzed. Consistent results were also noted in three pre-specified sensitivity analyses of OS described in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2022.09.159, and shown in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.09.159.

With ∼1 year of additional median follow-up, the improvement in the primary endpoint of IDFS observed at the initial analysis[12] was sustained with a similar treatment effect size observed: HR 0.63; 95% CI 0.50-0.78 (Figure 1B). The event frequency of all categories of IDFS events remained lower with olaparib. Distant recurrence comprised 88/134 (65.7%) of IDFS events in the olaparib group and 136/207 (65.7%) in the placebo group (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.09.159). IDFS at 4 years was 82.7% in the olaparib group and 75.4% in the placebo group (7.3% difference: 95% CI 3.0% to 11.5%) (Figure 1B). DDFS was improved in patients who received olaparib (HR 0.61; 95% CI 0.48-0.77). DDFS at 4 years was 86.5% in the olaparib group and 79.1% in the placebo group (7.4% difference: 95% CI 3.6% to 11.3%) (Figure 1C).

Subgroup analysis of IDFS across stratification and g*BRCA1*pv or g*BRCA2*pv groups revealed point estimates of treatment effect favoring olaparib over placebo consistent with that of the overall analysis population (Figure 2B). The benefit of adjuvant olaparib relative to placebo was observed irrespective of g*BRCA1*pv or g*BRCA2*pv groups, hormone receptor status, prior platinum use, and ACT versus NACT context, with CIs that include the point estimate of the HR for IDFS in the overall population. Update of previously reported detailed subgroup analyses of IDFS[12] is provided in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.09.159. Subgroup analyses of DDFS across stratification and g*BRCA1*pv or g*BRCA2*pv groups revealed similar findings (Figure 2C).

Safety

At this safety analysis all patients had completed the protocol-specified course of olaparib or placebo which included 1815 patients (911 in the olaparib group and 904 in the placebo group). The median exposure duration was 364 days on olaparib and 365 days on placebo (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2022.09.159), with median percentage of intended dose delivered being 94.5% in the olaparib group and 98.9% in the placebo group (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2022.09.159). Greater than 11 months of the planned 12 months of therapy was completed by 76.1% of patients receiving olaparib compared to 81.7% on placebo (Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2022.09.159). In the olaparib group, 228 patients (25.0%) required a dose reduction compared to 47 (5.2%) in the placebo group (Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2022.09.159). Dose interruptions lasting at least 3 days occurred in 405 (44.5%) patients in the olaparib group and 279 (30.9%) in the placebo group (Supplementary Table S11, available at https://doi.org/10.1016/j.annonc.2022.09.159). Adverse events (AEs) requiring permanent discontinuation of the trial drug occurred in 98 patients (10.8%) in the olaparib group and 42 (4.6%) in the placebo group. The most frequent AEs leading to discontinuation of olaparib were nausea (2.2%), anemia (1.8%), fatigue (1.6%), and neutrophil count decreased (1%) (Supplementary Table S12, available at https://doi.org/10.1016/j.annonc.2022.09.159).

Key AE categories are updated and summarized in Table 2 and Supplementary Table S13, available at https://doi.org/10.1016/j.annonc.2022.09.159. AEs of any grade with an incidence of ≥10% are updated in Supplementary Table S14, available at https://doi.org/10.1016/j.annonc.2022.09.159. Grade 3 or higher AEs occurring in >1% of patients were anemia (8.7%), neutropenia (4.9%), leukopenia (3.0%), fatigue (1.8%), and lymphopenia (1.3%), all in the olaparib group. Serious AEs (SAEs) occurred in 79 patients (8.7%) who received olaparib, and 78 (8.6%) who received placebo. AEs leading to death were cardiac arrest in one patient receiving olaparib, and acute myeloid leukemia (AML) and ovarian cancer each in one patient receiving placebo (Table 2). Red blood cell (RBC) transfusion requirements were previously reported[12] and final updates are provided in Supplementary Table S15A and B, available at https://doi.org/10.1016/j.annonc.2022.09.159.

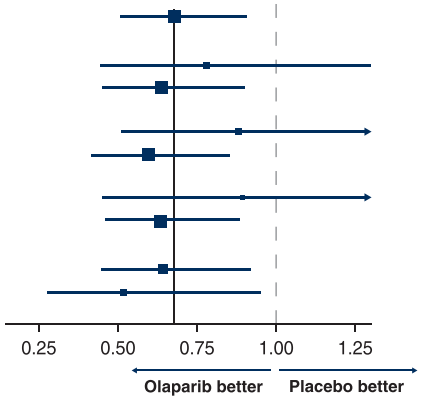
AEs of special interest (AESI) included pneumonitis, radiation pneumonitis, AML/MDS, and new primary malignancies other than AML/MDS. None of the categories had more AESI reported with olaparib relative to placebo (Supplementary Table S13, available at https://doi.org/10.1016/j.annonc.2022.09.159). As of the primary analysis, there were two cases of MDS/AML reported in the olaparib group and three in the placebo group. With additional follow-up, no additional cases of AML or MDS have been reported in either arm.

DISCUSSION

The pre-specified second IA of OS in the OlympiA trial demonstrates that 1 year of adjuvant olaparib relative to placebo

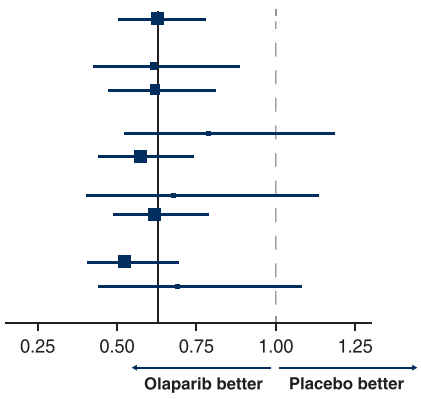
A

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	4-year overall survival		*P* value for heterogeneity
	No. of patients who died/total no.			Olaparib	Placebo	
All patients	75/921	109/915	0.678 (0.503-0.907)	89.8%	86.4%	
Prior chemo						0.543
Adjuvant	22/461	28/455	0.783 (0.444-1.365)	93.4%	93.9%	
Neoadjuvant	53/460	81/460	0.638 (0.449-0.900)	86.0%	78.5%	
Prior platinum						0.236
Yes	27/247	29/238	0.882 (0.520-1.491)	85.7%	83.9%	
No	48/674	80/677	0.601 (0.417-0.855)	91.2%	87.2%	
HR status						0.381
HR+/HER2–	16/168	17/157	0.897 (0.449-1.784)	88.1%	86.3%	
TNBC	59/751	92/758	0.640 (0.459-0.884)	90.1%	86.3%	
BRCA						0.845
BRCA1	49/579	75/588	0.643 (0.446-0.918)	89.5%	84.9%	
BRCA2	16/235	28/216	0.521 (0.276-0.951)	92.1%	85.3%	
BRCA1 and BRCA2	0/2	0/3	NC	NC	NC	



B

Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)	4-year invasive disease-free survival		*P* value for heterogeneity
	No. of patients with an invasive disease event/total no.			Olaparib	Placebo	
All patients	134/921	207/915	0.628 (0.504-0.779)	82.7%	75.4%	
Prior chemo						0.977
Adjuvant	46/461	75/455	0.618 (0.425-0.888)	88.3%	83.0%	
Neoadjuvant	88/460	132/460	0.622 (0.473-0.813)	77.0%	67.6%	
Prior platinum						0.197
Yes	42/247	51/238	0.791 (0.523-1.187)	77.8%	76.2%	
No	92/674	156/677	0.575 (0.443-0.742)	84.4%	75.2%	
HR status						0.754
HR+/HER2–	25/168	34/157	0.680 (0.402-1.134)	80.1%	76.6%	
TNBC	109/751	173/758	0.620 (0.487-0.787)	83.1%	75.2%	
BRCA						0.615
BRCA1	83/579	149/588	0.533 (0.406-0.695)	83.6%	72.4%	
BRCA2	34/235	44/216	0.693 (0.440-1.082)	80.6%	78.1%	
BRCA1 and BRCA2	0/2	0/3	NC	NC	NC	



C

Subgroup	Olaparib	Placebo	Stratified hazard ratio for distant disease-free survival (95% CI)	4-year distant disease-free survival		*P* value for heterogeneity
	No. of patients with a distant disease event/total no.			Olaparib	Placebo	
All patients	107/921	172/915	0.607 (0.476-0.771)	86.5%	79.1%	
Prior chemo						0.698
Adjuvant	33/461	59/455	0.562 (0.363-0.855)	91.9%	86.3%	
Neoadjuvant	74/460	113/460	0.623 (0.463-0.832)	81.0%	71.7%	
Prior platinum						0.132
Yes	36/247	43/238	0.812 (0.519-1.263)	82.4%	80.4%	
No	71/674	129/677	0.540 (0.403-0.719)	88.0%	78.8%	
HR status						0.608
HR+/HER2–	23/168	31/157	0.692 (0.399-1.182)	82.1%	77.7%	
TNBC	84/751	141/758	0.591 (0.450-0.772)	87.3%	79.4%	
BRCA						0.927
BRCA1	66/579	118/588	0.544 (0.400-0.732)	87.6%	77.3%	
BRCA2	28/235	41/216	0.609 (0.373-0.979)	84.5%	79.6%	
BRCA1 and BRCA2	0/2	0/3	NC	NC	NC	

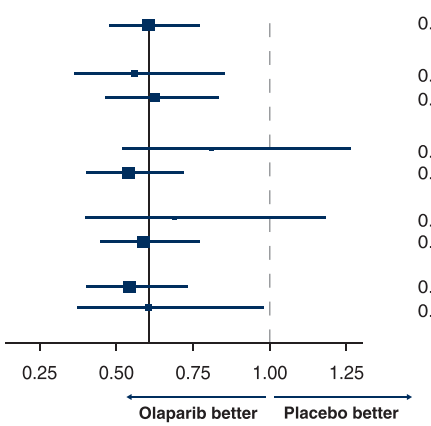


Figure 2. Subgroup analyses by stratification factors and g*BRCA1*pv or g*BRCA2*pv groups. (A-C) The solid vertical line indicates the overall hazard-ratio estimate, and the dashed vertical line indicates a hazard ratio of 1.00, as recommended by Cuzick (Cuzick J. Forest plots and the interpretation of subgroups. *Lancet* 2005; 365:1308). The size of the blue squares corresponds to the number of events contributing to the estimate of the treatment effect. Even without correcting for multiple comparisons, none of the tests for heterogeneity reached statistical significance. BRCA mutation data reflect central Myriad testing results only.
NC, not calculated.

Table 2. Summary of adverse events in the safety analysis set[a]

Adverse event, no. of patients (%)	Olaparib ($n = 911$)	Placebo ($n = 904$)
Any adverse event	836 (91.8)	758 (83.8)
Serious adverse event	79 (8.7)	78 (8.6)
Adverse event of special interest[b]	31 (3.4)	51 (5.6)
MDS/AML	2 (0.2)	3 (0.3)
Pneumonitis[c]	9 (1.0)	12 (1.3)
New primary malignancy[d]	21 (2.3)	36 (4.0)
Grade ≥3 adverse event	223 (24.5)	102 (11.3)
Grade 4 adverse event[e]	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of treatment[f]	98 (10.8)	42 (4.6)
Adverse event leading to death[g]	1 (0.1)	2 (0.2)

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

[a]Includes adverse events with an onset date on or after the first dose date and up to and including 30 days following date of the last dose of study medication.

[b]Includes adverse events of special interest with onset at any date after first dose of olaparib or placebo. One patient in the olaparib group had both pneumonitis and a new primary invasive breast cancer and is counted in both the pneumonitis and new primary cancer categories.

[c]In the olaparib group, seven patients had pneumonitis, and two patients had radiation pneumonitis. In the placebo group, eight patients had pneumonitis, and four patients had radiation pneumonitis.

[d]Detailed information on the number of patients in each group with specific new primary cancers is provided in Supplementary Table S13, available at https://doi.org/10.1016/j.annonc.2022.09.159.

[e]A total of 18 grade 4 adverse events were reported in 17 patients who received olaparib; 1 patient had both grade 4 anemia and decreased neutrophil count. In the olaparib group, grade 4 adverse events included decreased neutrophil count (in five patients), anemia (in four patients), decreased lymphocyte count (in three patients), and AML, bipolar disorder, fatigue, febrile neutropenia, abnormal hepatic function, and a suicide attempt (in one patient each). In the placebo group, grade 4 adverse events included depression (in two patients) and increased aspartate aminotransferase level and acute cholecystitis (in one patient each).

[f]The most common adverse events, occurring in at least 1% of the patients, that led to discontinuation of olaparib were nausea (2.1%), anemia (1.8%), fatigue (1.5%), and decreased neutrophil count (1.0%); there were no adverse events that occurred in at least 1% of patients that led to discontinuation of placebo.

[g]Adverse events leading to death are cardiac arrest (olaparib, $n = 1$), AML (placebo, $n = 1$), and ovarian cancer (placebo, $n = 1$).

provided a statistically significant improvement in OS (HR 0.68; 98.5% CI 0.47-0.97; $P = 0.009$) with an absolute improvement in 4-year OS of 3.4% (89.8% olaparib; 86.4% placebo) in patients with high-risk EBC and g*BRCA1/2*pv following standard-of-care chemotherapy, surgery, and radiation therapy, which if indicated had been completed at least 2 weeks before randomization. Updated descriptive analyses of IDFS and DDFS with the additional year of median follow-up demonstrated sustained absolute improvements (7.3% and 7.4%) for olaparib versus placebo in 4-year event-free rates, respectively. Safety analyses following completion of protocol therapy by all patients, including grade ≥3 AEs, SAEs, AEs leading to death, and AEs leading to discontinuation of treatment, demonstrated a favorable safety and tolerability profile consistent with the experience in the MBC setting with no substantive changes from the findings of the initial analysis. Although the key long-term safety endpoint of AML/MDS will require longer follow-up for complete assessment, the low incidence of 0.2% in the olaparib group and 0.3% in the placebo group with a median follow-up of 3.5 years coupled with the absence of new cases since the initial report is reassuring.

Breast cancers associated with g*BRCA*1/*BRCA2*pv are vulnerable to synthetic lethality caused by exposure to PARP inhibitors that inhibit catalytic activities of PARP1 and trap PARP1 on DNA, creating lesions that require functional BRCA1 and BRCA2 protein for repair.[3,4] Because this vulnerability is independent of hormone receptor status, OlympiA was designed to assess the efficacy and safety of olaparib in patients with g*BRCA1/2*pv and high-risk, HER2-negative EBC, irrespective of hormone receptor status. OlympiA was initially activated in patients with high-risk TNBC because of high unmet need for these patients in whom the residual recurrence risk following standard multimodality therapies remained sufficiently elevated to justify evaluating olaparib in the EBC setting, despite the lack of both phase III trial data and marketing authorization for olaparib in g*BRCA1/2*pv-associated MBC at that time. In contrast to g*BRCA1*pv-associated breast cancers, g*BRCA2*pv-associated breast cancers are predominantly hormone receptor positive.[7,8] Although adjuvant endocrine therapies reduce the risk of recurrence, patients presenting with larger, node-positive disease less responsive to NACT[14,15] or who have ≥4 positive axillary nodes at initial surgery have similar residual risk as patients with TNBC meeting eligibility criteria for OlympiA. Additionally, the complexities and challenges of conducting OlympiA made it unlikely that a new study specifically for patients with g*BRCA1/2*pv and hormone receptor-positive, high-risk EBC would be conducted. Therefore, once safety data on combinations of standard endocrine therapies and olaparib were available,[17] OlympiA was amended to include patients with hormone receptor-positive, HER2-negative EBC with risk of recurrence equivalent to the TNBC cohorts. Although the first patient with hormone receptor-positive disease was enrolled 18 months after start of accrual, the median follow-up was similar between the TNBC and hormone receptor-positive cohorts (3.6 versus 3.4 years).

Subgroup analyses of IDFS, DDFS, and OS demonstrate no evidence of heterogeneity for benefit of olaparib by hormone receptor status. The HR for olaparib relative to placebo for IDFS was 0.62 in TNBC (282 IDFS events in 1509 patients) and 0.68 in hormone receptor-positive disease (59 IDFS events in 325 patients), both less than the target HR of 0.7 for the ITT population (Figure 2B). The corresponding HR for DDFS was 0.59 (225 DDFS events) in the TNBC subgroup and 0.69 (54 DDFS events) in the hormone receptor-positive subgroup (Figure 2C). With relatively few deaths ($n = 33$) reported among the 325 patients with hormone receptor-positive EBC (Figure 2A), meaningful analysis of differential treatment effect on OS is highly constrained. Therefore, based on the negative test for heterogeneity by hormone receptor status and evidence for similar efficacy in IDFS and DDFS, coupled with the safety profile and the quality-of-life data,[18] patients with high-risk, hormone receptor-positive EBC should be considered for olaparib therapy. This conclusion is further supported by the lack of mechanistic rationale for differential synthetic lethal effects of PARP inhibition in a hormone receptor-positive context, evidence of similar treatment effect for PARP inhibitor therapy in MBC irrespective of

hormone receptor status,[5,6] and reports of the randomized GeparOla study of olaparib in combination with paclitaxel, in which signals of comparative efficacy of olaparib/paclitaxel versus a carboplatin/paclitaxel regimen were stronger in the hormone receptor-positive subgroup.[19]

OlympiA was notable for a relatively high adherence rate to study medication with 76% of the olaparib group completing at least 11 months of therapy compared with 82% of the placebo group. AEs were common reasons for discontinuation and the most common AEs leading to discontinuation were nausea and anemia. Nausea tends to occur early in treatment but diminishes in prevalence and grade with continued therapy. Patients should be informed of this potential side-effect and its likely time course and should be provided anti-emetic therapy to manage symptoms should they occur. Administering olaparib after a small meal may also help mitigate early nausea and potential vomiting.[20] Management of anemia on OlympiA included holding study medication until recovery of hemoglobin (Hb) to >9.5 g/dl. If recovery took >2 weeks, olaparib was reduced to 250 mg b.i.d. Study therapy was discontinued if repeated RBC transfusions were required to maintain the Hb >9.5 g/dl. This approach, adaptable to routine care, resulted in only 53 (5.8%) patients on olaparib requiring RBC transfusions compared with 8 (0.9%) on placebo (Supplementary Table S15A, available at https://doi.org/10.1016/j.annonc.2022.09.159).

Following completion of accrual to OlympiA, KEYNOTE-522[21] demonstrated improved event-free survival (EFS) in TNBC with the addition of pembrolizumab to an NACT regimen of sequential carboplatin/paclitaxel followed by anthracycline with cyclophosphamide, followed by adjuvant pembrolizumab. Although the absolute improvement in EFS was 11% in patients without pathological complete response (pCR) with addition of pembrolizumab, 3-year EFS of this group was 67.4%, justifying consideration of additional post-surgical adjuvant therapy such as olaparib in patients with g*BRCA1/2*pv. Available safety data suggest that programmed cell death protein 1/programmed death-ligand 1 inhibitors can be co-administered with olaparib or other PARP1 inhibitors,[22,23] but this was not assessed in OlympiA.

The CREATE-X[24] study has also reported improvement in DFS (HR 0.58) and OS (HR 0.52) with adjuvant capecitabine in patients with TNBC and non-pCR following NACT that did not include platinum-based agents, which were allowed by OlympiA. A subsequent meta-analysis of 13 trials which evaluated capecitabine in EBC and included CREATE-X demonstrated improvement in DFS (HR 0.89) and OS (HR 0.83) in patients with TNBC.[25] There is an absence of safety data to support use of combination olaparib and capecitabine, so physicians and patients will need to choose between the two agents in the adjuvant setting. Although no data in EBC exist to inform the choice between the two agents, the OlympiAD MBC study in patients with g*BRCA1/2*pv demonstrated superiority of olaparib relative to mono-chemotherapy of physician's choice, in which the most common choice was capecitabine.[5] Similar findings were reported with talazoparib in the EMBRACA trial.[6] Additionally, there is evidence that patients with the basal subtype of TNBC may derive less benefit from capecitabine than their non-basal subtype affected counterparts, and patients with g*BRCA1/2*pv typically develop the basal subtype of TNBC. The most direct evidence comes from the GEICAM/CIBOMA[26] open-label trial of adjuvant capecitabine following standard (N)ACT in early TNBC, stratified by basal versus non-basal subtype based on immunohistochemistry staining for cytokeratin 5/6 and epidermal growth factor receptor. Although an HR of 0.82 (95% CI 0.63-1.06; $P = 0.136$) for the primary endpoint of DFS did not reach statistical significance, a pre-specified analysis by subtype suggested the smaller non-basal cohort (26%) derived benefit from capecitabine with a DFS HR of 0.53 compared with an HR of 0.94 in the majority basal cohort. ECOG-ACRIN EA1131[27] was a randomized trial of adjuvant capecitabine versus platinum chemotherapy in patients with a basal subtype of TNBC determined by Prediction Analysis of Microarray 50 (PAM50) with ≥1 cm of residual disease following taxane-based NACT. Accrual ended early when the IDMC determined that it was unlikely the study would demonstrate either noninferiority or superiority of platinum. Notably, 3-year IDFS in both arms was <50%, demonstrating high recurrence risks in this population despite use of either drug and the need for alternative approaches to mitigate this risk. These aggregate results, coupled with the favorable toxicity profile of olaparib in OlympiA, support the choice of olaparib in TNBC patients with g*BRCA1/2*pv.

Adjuvant therapy guidelines for high-risk, hormone receptor-positive breast cancer have been recently impacted by the monarchE trial, which demonstrated that 2 years of abemaciclib, co-administered with ET, improved 3-year IDFS from 83.4% to 88.8% (HR 0.70; 95% CI 0.59-0.82).[28] There is an absence of safety data to support the use of a combination of olaparib, abemaciclib, and ET, so physicians and patients will need to choose between which of the two agents to combine with adjuvant ET. The monarchE trial has yet to demonstrate an improvement in OS and was not designed to assess the activity in patients with g*BRCA1/2*pv. Additionally, an evolving body of evidence suggests that patients with g*BRCA2*pv and hormone receptor-positive MBC may not respond as well to cyclin-dependent kinase 4 and 6 inhibitors.[29-31]

In OlympiA, there was no evidence of statistical heterogeneity in the treatment effect for olaparib by hormone receptor status, and the similar HR for IDFS and DDFS for both hormone receptor-negative and hormone receptor-positive cohorts is consistent with a receptor-agnostic synthetic lethal targeting mechanism. The safety profile and quality-of-life data[18] from OlympiA also provide support that patients with g*BRCA1/2*pv and high recurrence risk, hormone receptor-positive EBC should be considered for combination adjuvant ET plus olaparib therapy following (N)ACT.

The pre-specified second IA of OlympiA with a median follow-up of 3.5 years demonstrates a statistically significant

improvement in OS with olaparib compared to placebo and maintenance of clinically meaningful absolute improvements in the previously reported statistically significant primary endpoint of IDFS and the secondary endpoint of DDFS. Subgroup analyses for all three endpoints demonstrate benefit irrespective of hormone receptor status, NACT versus ACT, prior use of platinum for breast cancer, and type of g*BRCA*pv with CIs that include the point estimate of the HR in the overall population for each of the endpoints. The safety and tolerability profile of olaparib in this study remains consistent with that observed in previous studies of olaparib and only two cases (0.2%) of AML/MDS have been reported in the olaparib group compared with three (0.3%) in the placebo group. The results highlight the importance of testing for g*BRCA1/2*pv in patients with newly diagnosed high-risk EBC. Blinded follow-up of patients continues to assess long-term effects on risks for recurrent breast cancer and other second malignancies including AML/MDS, as well as to fully inform future translational studies to understand mechanisms of resistance to adjuvant olaparib.

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DISCLOSURES

CEG—uncompensated advisory board member for AstraZeneca, Genentech/Roche, Daiichi Sankyo, SeaGen and as compensated advisory board member for Exact Sciences. Medical writing assistance on manuscripts from Genentech/Roche and Abbvie. Research funding from AstraZeneca, Genentech/Roche, Abbvie, Daiichi/Sankyo to institutions. Compensation for steering committee service to NSABP Foundation from Genentech/Roche. Accommodations and travel expenses from AstraZeneca, Genentech/Roche, Daiichi/Sankyo. RG—institutions have received research funding from AstraZeneca, MSD, Roche, and Novartis. MT—AstraZeneca employee and shareholder. LR—received salary support for project-related work under Agreement with Study Sponsor. PR—reports travel and accommodations by AZ. KC—employed by AstraZeneca and owns stock from AstraZeneca and BMS. AA—reports funding received by her institution as research funding from AstraZeneca, Roche/Genentech, Tesaro, Novartis, Pfizer, SERVIER, Biovica, GlaxoSmithKline, and Sanofi/Aventis, and royalties from Agendia for MammaPrint, due to the collaboration on the conduct of the MINDACT trial. GA—an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and shareholder of Merck & Co., Inc., Rahway, NJ, USA. AA—advisory board MSD and Gilead; conference fees MSD and Gilead; spousal shares AstraZeneca; institutional research funding from Astra Zeneca. MA—(during the past 3 years) has received research funding (to Gustave Roussy) from Astra Zeneca and Eli-Lilly. Received honoraria (to Gustave Roussy): Astra Zeneca (to Institut Bergonié) Astra Zeneca; honoraria (to herself): Pfizer, Gilead. Travel grant: Astra Zeneca, Daiichi Sankyo. JBa—consulting fees from Astra Zeneca and Pfizer; travel expenses by Lilly; European patent request submitted (EP17382884.9) not related to this work. JBe—has received grants from Amgen, Astra Zeneca, Bayer, Merck KGaA, Pfizer, Roche, and Sanofi-Aventis to Karolinska Institutet and/or University Hospital. No personal payments. He also receives payment from UpToDate to Asklepios Medicine HB for a chapter on breast cancer prediction. He has recently been appointed board member of Wnt Research AB. JBl—(during the past 3 years) received research funding directly to the Institute of Cancer Research from: AstraZeneca, Merck KGaA, Puma Biotechnology, Pfizer, Roche, Novartis (previously GSK), Eli Lilly, Janssen-Cilag, and Clovis Oncology. SD—institutional grant from AstraZeneca during the conduct of this study; grants, all to her institution and all outside of the submitted work, from: Sanofi, Novartis, Lilly, Puma, Myriad, Orion, Amgen, Sanofi, Genomic Health, GE, Servier, Merck KGaA, BMS, Pierre Fabre, SeaGen, Exact Sciences, Rappta, Besins, Taiho, the European Commission, the French government, Foundation ARC; and non-financial support from Pfizer; AstraZeneca, and Roche Genentech. SMD—received research funding directly to the University of Pennsylvania from AstraZeneca and has received honoraria from AstraZeneca. AE—has received research funding directly to her institution from

Astra Zeneca, AbbVie, and RNA Diagnostics. FE—AstraZeneca employee and shareholder. LF—consulting/advisory role: Novartis, Pfizer, AstraZeneca/MSD; research funding to institution: AstraZeneca, MSD Oncology, Novartis. AF—AstraZeneca employee and AstraZeneca stockholder. JMF—has received institutional research grants from AstraZeneca, PUMA, Pfizer, Merus, Incyte, and Genentech. SF—reports support to her organization from AbbVie, AstraZeneca, Daiichi Sanko, Genentech, GlaxoSmithKline, MSD, and SeaGen. KG—advisory boards: AstraZeneca; Pfizer, Novartis, Lilly, MSD, Roche, SeaGen, Gilead, Ayala. Research funding: AstraZeneca, Pfizer, Roche, BMS. Speaker: Pfizer, Novartis, Lilly, AstraZeneca. LG—has served as compensated advisory board member for AstraZeneca, Daiichi Sankyo, and SeaGen. MG—reports personal fees/travel support from Amgen, DaiichiSankyo, AstraZeneca, EliLilly, LifeBrain, Veracyte, Novartis, PierreFabre, Merck KGaA; an immediate family member is employed by Sandoz. SH—AZ employee and shareholder. SAI—has advisory role for AstraZeneca, Bertis, Daiichi-Sankyo, Eisai, Eli Lilly, Hanmi, Idience, MSD, Novartis, Roche, Pfizer. Reports research grants from AstraZeneca, Boryung, Daewoong Pharm, Eisai, Roche, and Pfizer. SRL—institution has received honoraria for my role on the AstraZeneca International Breast Cancer Biomarker Advisory Board 2022. WJ—research grants and/or honoraria from: AstraZeneca, Celgene, Chugai, Daiichi/Sankyo, Eisai, ExactScience, GSK, Janssen, Lilly, Menarini, Merck KGaA, Novartis, Sanofi-Aventis, Roche, Pfizer, Seagen. BL—advisory boards for AZ, Pfizer, Merck KGaA, Lilly, Daiichi Sankyo, Gilead, SeaGen, and Novartis. SL—grants and honorarium to her institution from AbbVie, Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Gilead, Novartis, Pfizer, Roche; and honorarium to her institution from Bristol Myers Squibb, Eli Lilly, Eirgenix, GlaxoSmithKline, Merck KGaA, Pierre Fabre, PriME/Medscape, and Seagen; grants to her institution from Cepheid; non-financial support for medical writing from Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Novartis, Pfizer, and Roche; patents EP21152186.9, EP18209672; EP15702464.7; and EP19808852.8 pending; and licensing fees from VM Scope GmbH, all to institution; personal fees from Chugai; personal employment with GBG Forschungs GmbH; personal non-financial interest in Gilead, Novartis, Pfizer, Roche, and SeaGen (steering committees); non-financial interests from AGO Member (German Gynaeological Oncology Society), ASCO Member, DKG Member (German Cancer Society) and ESMO (Member, Chair ESMO Breast (2019-21 and Steering Committee). PCL—reports stock ownership in Amgen, speaker honorarium from Schrodinger Inc., and unreimbursed consulting for BlueSphere Bio. FM—reports other from GBG research GmbH, during the conduct of the study; personal fees from Roche, AstraZeneca, Pfizer, Tesaro, Novartis, Amgen, PharmaMar, Genomic Health, CureVac, EISAI, Clovis, Janssen-Cilag, Gilead/Immunomedics, GSK, Merck KGaA, SeaGen, Myriad, and Pierre-Fabre, outside the submitted work. RM—receives salary support for project related work under agreement with sponsors AstraZeneca, Roche, & GSK. KAP—has served as an uncompensated advisory board member for AstraZeneca. MP—scientific board member: Oncolytics; consultant/honoraria: AstraZeneca, Camel-IDS/Precirix, Gilead, Immunomedics, Lilly, Menarini, MSD, Novartis, Odonate, Pfizer, Roche-Genentech, Seattle Genetics, Immutep, Seagen, NBE Therapeutics, Frame Therapeutics; research grants to institute: AstraZeneca, Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon. GR—reports funding received by her institution as research funding from AstraZeneca, Roche/Genentech, Tesaro, Novartis, Pfizer, SERVIER, Biovica, GlaxoSmithKline, and Sanofi/Aventis, and royalties received by her institution from Agendia for MammaPrint, due to the collaboration on the conduct of the MINDACT trial. RS—grants/contracts: AstraZeneca; participation on an advisory board: AstraZeneca, MSD, Clovis Oncology. ES—reports honoraria: Amgen, AstraZeneca, Cancérodigest, Clinigen, Curio Science, Egis, Eli Lilly, Exact Sciences, Gilead, high5md, Novartis, Oncompass Medicine, Pfizer, Pierre Fabre, Roche, Sandoz, TLC Biopharmaceuticals; travel support: Amgen, AstraZeneca, Egis, Gilead, Novartis, Pfizer, Roche; clinical research: Amgen, AstraZeneca, Eli Lilly, Novartis, Pfizer, Roche, Samsung; stock: AstraZeneca, Eli Lilly, Pfizer. PS—has received consulting fee and/or honoraria from Pfizer, MSD, Gilead, Seattle Genetics, Novartis, AstraZeneca, GSK, and research support (to the institution) from Novartis, Bristol-Meyers Squibb, MSD, Gilead. CFS—travel grants and speakers' honoraria from: Novartis, Roche, AstraZeneca, Gilead Sciences, SeaGen; research grants: AstraZeneca, Novartis, Amgen, and Daiichi-Sanyko. TŠ—patient advisory board honoraria: MSD, Pfizer, Gilead Sciences. ES—honoraria: Roche, Lilly, Pfizer, Merck KGaA, AstraZeneca, Novartis, SeaGen, Daiichi Sankyo/AstraZeneca, Gilead Sciences. Consulting or advisory role: Novartis, Roche, Pfizer, Lilly, AstraZeneca, Merck KGaA. Travel, accommodations, expenses: Novartis, Roche, Pfizer, Gilead Sciences. Uncompensated relationships: German Breast Group. MT—has received honoraria for lectures or chairs from Chugai, Takeda, Pfizer, Kyowa-Kirin, Taiho, Eisai, Daiichi-Sankyo, AstraZeneca, Eli Lilly, MSD, Exact Science, Novartis, Shimadzu, Yakult, Nippon Kayaku, and Devicore Medical Japan. He has served as compensated advisory board for Kyowa-Kirin, Daiichi-Sankyo, Eli Lilly, BMS, Athenex Oncology, Bertis, Terumo, and Kansai Medical Net. His institution has received research funding from Chugai, Takeda, Pfizer, Kyowa-Kirin, Taiho, JBCRG assoc., KBCRN assoc., Eisai, Eli Lilly, Daiichi-Sankyo, AstraZeneca, Astellas, Shimadzu, Yakult, Nippon Kayaku, AFI technology, Luxonus, Shionogi, GL Science, and Sanwa Shurui. He has served as uncompensated member of the board of directors for the association of JBCRG, the association of KBCRN, and the NPO organization OOTR. TAT—has consulting honoraria from advisory boards and research support from AstraZeneca. Also, honoraria from Pfizer. GV—received honoraria and consulting fees from Roche, AstraZeneca, Daiichi Sankyo, Merck KGaA,

Agilent, and Pfizer. YHP—reports grants from Roche, AstraZeneca, Pfizer, Novartis, and MSD; personal fees from AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, MSD, Bixink, and Roche; and nonfinancial support from Pfizer and Hanmi. RY—reports consulting/advisor/honoraria: AstraZeneca, Eli Lilly, Gilead, Medison, MSD, Novartis, Pfizer, Roche, Teva; research grant: Roche. Research support: Exact Sciences. KHJ—consultancies (personal fees) from AstraZeneca, Bixink, Everest Medicine, MSD, Novartis, Pfizer, Roche, Takeda Pharmaceuticals. GSS—reports research support paid to the institution from Agendia, AstraZeneca, MSD, Roche, and SeaGen and consultancy fees paid to the institution from Biovica and SeaGen. MP—honoria/advisory board/educational events: Roche, Novartis, Pfizer, Eli Lilly, Exact Sciences, Veracyte, Pierre Fabre. MAC—reports research grant from Roche. He has served as Co-Chair of the Scientific Committee of IBCSG. MS—has received personal fees from AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, Lilly, MSD, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, Roche, and SeaGen. His institution has received research funding from AstraZeneca, BioNTech, Eisai, Genentech, German Breast Group, Novartis, Palleos, Pantarhei Bioscience, Pierre Fabre, and SeaGen. In addition, he has a patent for EP 2390370 B1 and a patent for EP 2951317 B1 issued. AMB—reports consulting/advisor/honoraria: Roche, Celgene, AstraZeneca, Seagen, Daiichi Sankyo, Athenex, Lilly, MSD, Gilead, Novartis, Eisai, Pfizer, Samsung, Lilly, GE, Coherus, Puma; research funding to the institution: Roche, AstraZeneca, MSD, Novartis, Lilly, Gilead, Puma; travel, accommodation, expenses: Pfizer, Puma, GE. DC—Aptitude Health, Roche Sweden, Pfizer Limited, Celldex Therapeutics Inc, Carnall Farrar, ELI LILLY & Company, Astra Zeneca, Roche Products Ltd, Novartis Pharma AG, Novartis Pharmaceuticals Corporation, Pfizer Limited, PFS Ltd, Novartis Pharmaceuticals UK Limited, Merck KGaA, F. Hoffmann-La Roche AG, Clovis Oncology, Daiichi Sankyo, USA, Eisai, Exact Therapeutics, G1 Therapeutics, Galapagos NV, Genentech Inc, GSK (Glaxo SmithKline), Synthon Biopharmaceuticals BV: note name change to Byondis April 2020, Seagen, SANOFI, Sapience Therapeutics Ltd, Bexon/Zymeworks Biopharmaceuticals Inc., NexGen, IQVIA. CC—received salary support for project-related work under Agreement with Study Sponsor. ANJT—reports consulting/advisor/honoraria: Pfizer, Artios, Prime Oncology, Gilead, Merck KGaA; advisory board funds to institution: Gilead, AstraZeneca; research funding to the institution: AstraZeneca, Merck KGaA; expert testimony: EM Partners; stocks: Inbiomotion. Royalty associated payments—ICR rewards to inventor's scheme payments associated with patent for the use of PARP inhibitors in DNA deficient cancers, licensee—AstraZeneca. Other, grant funded by Breast Cancer Now (BCN) and Cancer Research UK (CRUK) to study homologous recombination deficient breast and other cancers, BCN/CRUK receive payments associated with a patent for the use of PARP inhibitors in DNA deficient cancers, licensee—AstraZeneca. All other authors have declared no conflicts of interest.

PREVIOUS RELATED WORKS

Tutt ANJ, Garber J, Gelber RD, et al. Pre-specified event driven analysis of overall survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. ESMO 2022. Abstract VP1-March 2022.

Ganz PA, Bandos H, Spanic T, et al. Quality of life results from OlympiA: a phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)-adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER-2 negative early breast cancer (NSABP B-55). Presented at SABCS. December 10, 2021. Program Number: GS4-079 (Oral Abstract).

Tutt A, Garber JE, Kaufman B, et al. OlympiA: a phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo) adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer. *J Clin Oncol.* 2021;39:18s (suppl; Abstract LBA1 ASCO Plenary).

Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer. *N Engl J Med.* 2021;384(25):2394-2405.

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APPENDIX 1. COLLABORATORS (PARTICIPATING GROUPS, ACCRUING INSTITUTIONS, AND LEAD INVESTIGATORS)

ABCSG: Austrian Breast and Colorectal Cancer Study Group

Krankenhaus Hietzing, Abt. für Gynäkologie und Geburtshilfe	Austria	Paul Sevelda
KH Voecklabruck, Abt. f. Innere Medizin	Austria	Ferdinand Haslbauer
Krankenhaus der Barmherzigen Schwestern Ried	Austria	Monika Penzinger
St. Josef KH, Interne Abt.	Austria	Leopold Öhler
LKH Leoben	Austria	Christoph Tinchon
Universitätsklinikum Salzburg	Austria	Richard Greil
Klinikum Wels-Grieskirchen	Austria	Sonja Heibl
Medizinische Universität Wien, Univ. Klinik für Innere Medizin I	Austria	Rupert Bartsch
Aerztezentrum—Ordination Dr. Viktor Wette	Austria	Viktor Wette
Medizinische Universität Wien, Univ.Klinik für Frauenheilkunde	Austria	Christian F. Singer
LKH Villach, Gynaekologisch-Geburtshilfliche Abt.	Austria	Claudia Pasterk
Krankenhaus der Barmherzigen Schwestern Linz	Austria	Ruth Helfgott
LKH-Universitätsklinikum Klinikum Graz	Austria	Gunda Pristauz-Telsnigg
LKH-Universitätsklinikum Klinikum Graz	Austria	Herbert Stöger
Elisabethinen Hospital	Austria	Angsar Weltermann
Universitätsklinik Innsbruck	Austria	Daniel Egle
Ordination Dr. Irene Thiel	Austria	Irene Thiel
TumorZentrum Kepler Universitatsklinikum Linz	Austria	David Fuchs
LKH Rankweil	Austria	Holger Rumpold
Wilhelminenspital der Stadt Wien, 3. Med. Abteilung	Austria	Kathrin Strasser-Weippl

AGO-B: Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group

Universitätsklinikum Freiburg	Germany	Beate Rautenberg
Universitäts Hamburg-Eppendorf	Germany	Volkmar Müller
Universitätsmedizin Mainz	Germany	Marcus Schmidt
Klinikum rechts der Isar der TU Muenchen	Germany	Stefan Paepke
Klinikum Bremen-Mitte	Germany	Mustafa Aydogdu
Martin-Luther-Universität Halle-Wittenberg	Germany	Christoph Thomssen
Klinikum Frankfurt Höchst GmbH	Germany	Joachim Rom
Helios-Kliniken Berlin—Buch	Germany	Christine Mau
Friedrich-Alexander-Universität Erlangen-Nürnberg	Germany	Peter Fasching
Johanniter-Krankenhaus Bonn	Germany	Uwe-Jochen Göhring
Klinikum Esslingen GmbH	Germany	Thorsten Kühn
Gynäkologisch-onkologische Praxis	Germany	Stefanie Noeding
Universitätsklinikum Essen (AöR)	Germany	Sherko Kümmel
Marien Hospital Witten gGmbH	Germany	John Hackmann
Universitätsklinikum Aachen	Germany	Elmar Stickeler

BCT-ANZ: Breast Cancer Trials—Australia and New Zealand

The Townsville Hospital	Australia	Abhishek Joshi
Sir Charles Gairdner Hospital	Australia	Joanna Dewar
Prince of Wales Hospital	Australia	Michael Friedlander
Peter MacCallum Cancer Centre	Australia	Kelly-Anne Phillips
Cabrini Hospital	Australia	Yoland Antill
Mater Cancer Care Centre	Australia	Natasha Woodward

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Appendix Continued

The Tweed Hospital	Australia	Ehtesham Abdi
Gosford Hospital	Australia	Susan Tiley
Tamworth Rural Referral Hospital	Australia	Mathew George
Royal Hobart Hospital	Australia	David Boadle
Concord Repatriation General Hospital	Australia	Annabel Goodwin
Calvary Mater Newcastle	Australia	Andre van der Westhuizen
Ballarat Oncology & Haematology Services	Australia	George Kannourakis
Royal Adelaide Hospital	Australia	Nicholas Murray
ICON Cancer Care Wesley	Australia	Nicole McCarthy

BOOG: Borstkanker Onderzoek Groep

Leids Universitair Medisch Centrum	The Netherlands	Judith Kroep
Maastricht Universitair Medisch Centrum	The Netherlands	Maaike de Boer
Amphia Ziekenhuis	The Netherlands	Joan Heijns
Dutch Breast Cancer Research Group, Utrecht, The Netherlands	The Netherlands	Agnes Jager
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Zaans Medisch Centrum	The Netherlands	Sandra Bakker
Nederlands Kanker Instituut Antoni van Leeuwenhoek Ziekenhuis	The Netherlands	Gabe S. Sonke

CCTG: Canadian Cancer Trials Group

Saskatchewan Cancer Agency	Canada	Amer Sami
Cross Cancer Institute	Canada	John Mackey
CISSSMC—Hospital Charles Le Moyne	Canada	Catherine Prady
Odette Cancer Centre, University of Toronto	Canada	Andrea Eisen
CHAUQ Hopital du St-Sacrement	Canada	Christine Desbiens
Centre Hospitalier de l'Universite de Montreal	Canada	Erica Patocskai
Hopital General Juif	Canada	Cristiano Ferrario
BC—Vancouver Centre	Canada	Karen Gelmon
Juravinski Cancer Centre	Canada	Louise Bordeleau
Allan Blair Cancer Centre	Canada	Haji Chalchal
CancerCare Manitoba	Canada	Saroj Niraula

CEEOG: Central and East European Oncology Group

Tel Aviv Sourasky Medical Center Ichilov	Israel	Ido Wolf
Uniwersyteckie Centrum Kliniczne w Gdańsku	Poland	Elżbieta Senkus

EORTC: European Organisation for Research and Treatment of Cancer

Cliniques Universitaires Saint-Luc	Belgium	François Duhoux
A.Z. Damiaan	Belgium	Randal d'Hondt
Cliniques universitaires de Bruxelles—Hôpital Érasme	Belgium	Sylvie Luce
Institut Jules Bordet	Belgium	Daphné t'Kint de Roodenbeke
Universitair Ziekenhuis Antwerpen (UZA)	Belgium	Konstantinos Papadimitriou
AZ Groeninge	Belgium	Marleen Borms
CHU UCL Namur	Belgium	Claire Quaghebeur
Institut du Cancer de Montpellier Val d'Aurelle	France	William Jacot
Institut Curie—Hôpital René Huguenin	France	Etienne Brain

Continued

Appendix Continued		
CHU de Limoges—Hôpital Dupuytren	France	Laurence Venat-Bouvet
Hôpital Privé du Confluent	France	Alain Lortholary
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie	Poland	Zbigniew Nowecki
Centro Clínico Champalimaud	Portugal	Fátima Cardoso
Western General Hospital	UK	Richard Hayward

GAICO: Grupo Argentino De Investigación Clinica En Oncologia

Clinica Universitaria Privada Reina Fabiola	Argentina	Santiago Bella
Centro Oncologico de Integracion Regional	Argentina	Mauricio Fernández Lazzaro
Clínica Privada Colombo	Argentina	Norma Pilnik
Instituto de Oncología de Rosario	Argentina	Luis E. Fein
Clinica ISIS	Argentina	Cesar Blajman
CENIT Centro Medico de Neuro, Investigacion y Tratamiento	Argentina	Guillermo Lerzo
Centro de Oncologia e Investigacion en Buenos Aires	Argentina	Mirta Varela
Centro Medico San Roque	Argentina	Juan Jose Zarba
Centro Oncologico Riojano Integral (Cori)	Argentina	Diego Kaen
Instituto Medico Especializado Alexander Fleming	Argentina	Maria Victoria Constanzo

GBG: German Breast Group

Universitätsklinikum Münster	Germany	Joke Tio
Henriettenstiftung, Hannover	Germany	Wulf Siggelkow
Klinikum Offenbach	Germany	Christian Jackisch
Klinikum der Eberhard-Karls-Universität Tübingen	Germany	Eva Maria Grischke
Wald-Klinikum Gera	Germany	Dirk Zahm
DONAUISAR Klinikum Deggendorf	Germany	Sara Tato-Varela
Elisabeth-Krankenhaus Kassel	Germany	Sabine Schmatloch
Praxisklinik Berlin	Germany	Peter Klare
Johanniter-Krankenhaus der Altmark Stendal	Germany	Andrea Stefek
Universitätsklinikum Köln	Germany	Kerstin Rhiem
Universitätsklinikum Essen (AöR)	Germany	Oliver Hoffmann
Kliniken Essen-Mitte	Germany	Sherko Kümmel
Caritasklinik St. Theresia, Saarbrücken	Germany	Mustafa Deryal
Praxis und Tagesklinik, Ebersberg	Germany	Isolde Gröll
Städtisches Klinikum Brandenburg	Germany	Peter Ledwon
Gemeinschaftspraxis, Hildesheim	Germany	Christoph Uleer
Klinikum Chemnitz	Germany	Petra Krabisch
Ev. Waldkrankenhaus Spandau, Berlin	Germany	Jochem Potenberg
Luisenkrankenhaus GmbH&Co.KG Düsseldorf	Germany	Maren Darsow
Medizinische Hochschule Hannover	Germany	Tjoung-Won Park-Simon
MVZ Osthessen GmbH, Fulda	Germany	Heinz-Gert Höffkes
Oncologianova GmbH, Recklinghausen	Germany	Till-Oliver Emde
Studienzentrum Zehlendorf, Berlin	Germany	Gerd Graffunder
St.-Vincentius Kliniken gAG Karlsruhe	Germany	Oliver Tomé
Universitätsklinikum Leipzig AöR	Germany	Dirk Forstmeyer
Praxis Dr. med. Jürgen Terhaag, Eggenfelden	Germany	Jürgen Terhaag
Rotkreuzklinikum Munich	Germany	Christoph Salat
Universitätsklinikum Carl Gustav Carus der TU Dresden	Germany	Karin Kast
Gemeinschaftspraxis für Hämatologie und Onkologie, Erfurt	Germany	Steffi Weniger
Onkologisch Hämatologische Schwerpunktpraxis, Bremen	Germany	Carsten Schreiber
Gemeinschaftspraxis, Augsburg	Germany	Bernhard Heinrich
Klinikum Südstadt, Rostock	Germany	Max Dieterich
St. Vincenz Krankenhaus, Karlsruhe	Germany	Michaela Penelope Wüllner

GEICAM: Spanish Breast Cancer Group

Hospital Clinico Universitario Lozano Blesa	Spain	Raquel Andrés Conejero
Hospital Clinico Universitario San Carlos	Spain	José Ángel García Sáenz
Complejo Hospitalario Universitario A Coruña	Spain	Lourdes Calvo Martinez
Consorci Sanitari de Terrassa	Spain	Angels Arcusa Lanza
Hospital Arnau de Vilanova (Lleida)	Spain	Serafín Morales Murillo
Hospital Universitario Virgen Macarena	Spain	Fernando Henao Carrasco
Fundación Instituto Valenciano de Oncología (IVO)	Spain	Salvador Blanch Tormo
Hospital Universitario de Donostia	Spain	Isabel Álvarez López
Hospital Infanta Cristina	Spain	Juan Ignacio Delgado Mingorance
Hospital Lucus Augusti de Lugo	Spain	Elena Álvarez Gomez
Clínica Universitaria de Navarra	Spain	Marta Santisteban
Hospital Universitario de Canarias (Tenerife)	Spain	Josefina Cruz Jurado
Hospital Germans Trias i Pujol	Spain	Vanesa Quiroga
Hospital Universitario Virgen del Rocio	Spain	Manuel Ruiz Borrego
Hospital Provincial Centre de Castello	Spain	Eduardo Martínez de Dueñas
Complejo Asistencial de Avila	Spain	Jose Enrique Alés Martínez
Hospital Universitario Reina Sofía	Spain	Juan De la Haba
Hospital Universitario Ramón y Cajal	Spain	Noelia Martínez Jañez
Hospital General Universitario de Elche	Spain	Álvaro Rodríguez Lescure
Hospital Miguel Servet	Spain	Antonio Antón Torres
Corporació Sanitària Parc Taulí	Spain	Gema Llort Crusades
Hospital San Pedro de Alcántara	Spain	Santiago González-Santiago
Hospital Clínico Univ. Virgen de la Victoria	Spain	Antonia Marquez Aragones
Complejo Hospitalario de Jaen	Spain	Ana Laura Ortega
Hospital de la Santa Creu i Sant Pau	Spain	Agusti Barnadas Molins
Toledo, H. V. de la Salud, Oncología	Spain	José Ignacio Chacón López-Muñiz
Hospital General Universitario Gregorio Marañón	Spain	Miguel Martín Jiménez
Hospital Universitari i Politècnic La Fe	Spain	Ana Santaballa Bertrán
Hospital Clínico Universitario de Salamanca	Spain	César Rodríguez
Hospital Quiron de Madrid	Spain	Lucía González Cortijo

GOIRC: Italian Oncology Group for Clinical Research

Ospedale Generale Regionale Bolzano Boheler Lorenz	Italy	Elisabetta Cretella
Azienda Ospedaliera Policlinico di Modena	Italy	Laura Cortesi
Ospedale di Belcolle	Italy	Enzo Maria Ruggeri
AO Busto Arsizio—Presidio di Saronno—SC Oncologia Medica	Italy	Claudio Verusio
Ospedale Sacro Cuore	Italy	Stefania Gori
Azienda Ospedaliera "Mater Salutis"/Aulss 9	Italy	Andrea Bonetti
Ospedale S.Maria della Misericordia	Italy	Anna Maria Mosconi

IBCG: Icelandic Breast Cancer Group

Landspitali, University Hospital	Iceland	Oskar Johannsson

IBCSG: International Breast Cancer Study Group

CHU de Liège	Belgium	Guy Jerusalem
UZ Leuven	Belgium	Patrick Neven
Országos Onkológiai Intézet Chemotherapy Department "B"	Hungary	Tünde Nagy

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Appendix Continued		
A. O. Ospedale di Circolo e Fondazione MACCHI	Italy	Graziella Pinotti
European Institute of Oncology	Italy	Marco A. Colleoni
Fondazione S. Maugeri	Italy	Antonio Bernardo
Ospedale Infermi—Rimini, AUSL della Romagna	Italy	Lorenzo Gianni
Multimedica Castellanza	Italy	Eraldo Bucci
Ospedale Misericordia e Dolce	Italy	Laura Biganzoli
University Hospital of Zurich	Switzerland	Konstantin Dedes
Inselspital Bern	Switzerland	Urban Novak
Centre Hospitalier Universitaire Vaudois	Switzerland	Khalil Zaman

ICR CTSU: Institute of Cancer Research—Clinical Trials and Statistics Unit

Bristol Royal Infirmary, Dept of Oncology	UK	Jeremy Braybrooke
Weston Park Hospital, Oncology	UK	Matthew Winter
Queen Elizabeth Hospital	UK	Daniel Rea
St Georges Hospital, Dept of Oncology	UK	Muireann Kelleher
The Beatson West of Scotland Cancer Centre	UK	Sophie Barrett
Nottingham City Hospital	UK	Stephen Chan
Royal Bournemouth Hospital	UK	Tamas Hickish
Belfast City Hospital	UK	Jane Hurwitz
St Bartholomew's Hospital	UK	John Conibear
CNS/Manager for Cancer and Haematology Clinical Trials	UK	Apurna Jegannathen
Royal Marsden Hospital	UK	Marina Parton
Guys And St Thomas Hospital	UK	Andrew Tutt
Russells Hall Hospital	UK	Rozenn Allerton
Velindre Cancer Centre	UK	Annabel Borley
The Christie Hospital NHS Foundation Trust	UK	Anne Armstrong
Southampton General Hospital	UK	Ellen Copson
Churchill Hospital	UK	Nicola Levitt
Addenbrooke's Hospital	UK	Jean Abraham
St James' University Hospital	UK	Timothy Perren
University College Hospitals London	UK	Rebecca Roylance

JBCRG: Japan Breast Cancer Research Group

Iwate Medical University Hospital	Japan	Kazushige Ishida
Nagoya City University Hospital	Japan	Tatsuya Toyama
National Hospital Organization Osaka National Hospital	Japan	Norikazu Masuda
Shizuoka Cancer Center	Japan	Junichiro Watanabe
National Hospital Organization Kyushu Cancer Center	Japan	Eriko Tokunaga
National Cancer Center Hospital	Japan	Takayuki Kinoshita
Hakuaikai Sagara Hospital	Japan	Yoshiaki Rai
Kyoto University Hospital	Japan	Masahiro Takada
Gunma Prefectural Cancer Center	Japan	Yasuhiro Yanagita
Chiba Cancer Center	Japan	Rikiya Nakamura
Osaka International Cancer Institute	Japan	Takahiro Nakayama
Osaka University Hospital	Japan	Yasuto Naoi
Aichi Cancer Center Hospital	Japan	Hiroji Iwata
Showa University Hospital	Japan	Seigo Nakamura
National Hospital Organization Hokkaido Cancer Center	Japan	Masato Takahashi
	Japan	Kenjiro Aogi

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National Hospital Organization Shikoku Cancer Center		
St Marianna University School of Medicine	Japan	Koichiro Tsugawa
National Cancer Center Hospital East	Japan	Hirofumi Mukai
The Cancer Institute Hospital of JFCR	Japan	Toshimi Takano
Saitama Medical University International Medical Center	Japan	Akihiko Osaki
Niigata Cancer Center Hospital	Japan	Nobuaki Sato
St. Luke's International Hospital	Japan	Hideko Yamauchi
Tokai University Hospital	Japan	Yutaka Tokuda
Hiroshima City Hospital	Japan	Mitsuya Ito
Kochi Medical School Hospital	Japan	Takeki Sugimoto

NCI National Clinical Trials Network: Comprised of NRG Oncology, Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group and Southwest Oncology Group

Banner MD Anderson Cancer Center	USA	Shakeela W. Bahadur
UCLA/Jonsson Comprehensive Cancer Center	USA	Patricia A. Ganz
USC/Norris Comprehensive Cancer Center	USA	Min J. Lu
Los Angeles County-USC Medical Center	USA	Min J. Lu
Cedars-Sinai Medical Center	USA	Monica M. Mita
City of Hope Comprehensive Cancer Center	USA	James Waisman
Kaiser Permanente—Fontana	USA	Jonathan A. Polikoff
Stanford Cancer Institute Palo Alto	USA	Melinda L. Telli
Kaiser Permanente San Leandro	USA	Samantha A. Seaward
Kaiser Permanente—Vallejo	USA	J. Marie Suga
Kaiser Permanente—Northern California	USA	Samantha A. Seaward
Kaiser Permanente Oncology Clinical Trials—Northern California	USA	J. Marie Suga
Kaiser Permanente—Southern California	USA	Lara N. Durna
Kaiser Permanente—Hawaii	USA	Jennifer Fu Carney
Kaiser Permanente—Colorado	USA	Alex Menter
Kaiser Permanente—Santa Teresa-San Jose	USA	J. Marie Suga
Saint Joseph's Medical Center	USA	Ajithkumar Puthillath
Kaiser Permanente Los Angeles Medical Center	USA	Jonathan A. Polikoff
Kaiser Permanente—Fresno	USA	J. Marie Suga
Sutter Cancer Research Consortium—Sacramento	USA	Nitin Rohatgi
Kaiser Permanente—Santa Rosa	USA	J. Marie Suga
Kaiser Permanente—Woodland Hills	USA	Jonathan A. Polikoff
Kaiser Permanente—Baldwin Park	USA	Jonathan A. Polikoff
Contra Costa Regional Medical Center	USA	James H. Feusner
Sutter Cancer Research Consortium—Roseville	USA	Kristie A Bobolis
Kaiser Permanente West Los Angeles	USA	Jonathan A. Polikoff
Marin Cancer Care Inc	USA	Peter D. Eisenberg
Kaiser Permanente Medical Center—Vacaville	USA	J. Marie Suga
Kaiser Permanente—San Marcos	USA	Jonathan A. Polikoff
Palo Alto Medical Foundation—Sunnyvale	USA	Derrick Wong
University of Colorado Cancer Center	USA	Virginia F. Borges
Shaw Cancer Center	USA	Alexander T. Urquhart
Yale University	USA	Erin W. Hofstatter
Smilow Cancer Hospital Care Center—Trumbull	USA	Erin W. Hofstatter
Smilow Cancer Hospital-Waterbury Care Center	USA	Erin W. Hofstatter
Medstar Franklin Square Medical Center/Weinberg Cancer Institute	USA	Edward C. McCarron
MedStar Georgetown University Hospital	USA	Claudine Isaacs

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MedStar Washington Hospital Center	USA	Pia Herbolsheimer
ChristianaCare Oncology Hematology at the Helen F. Graham Cancer Center & Research Institute	USA	Ramya Varadarajan
Helen F Graham Cancer Center & Research Institute	USA	Adam Raben
Halifax Health Medical Center-Centers for Oncology	USA	Ruby Anne E. Deveras
University of Miami Miller School of Medicine—Sylvester Cancer Center	USA	Frances Valdes-Albini
UM Sylvester Comprehensive Cancer Center at Deerfield Beach	USA	Reshma L. Mahtani
UM Sylvester Comprehensive Cancer Center at Plantation	USA	Reshma L. Mahtani
Emory University Hospital/Winship Cancer Institute	USA	Jane L. Meisel
Medical Center of Central Georgia	USA	Bradley T. Sumrall
Northside Hospital, Georgia NCORP	USA	Cheryl F. Jones
South Georgia Medical Center/Pearlman Cancer Center	USA	Samuel N. Ofori
Straub Clinic and Hospital	USA	Kenneth N.M. Sumida
Pali Momi Medical Center	USA	Kenneth N.M. Sumida
University of Iowa/Holden Comprehensive Cancer Center	USA	Mark Karwal
Oncology Associates at Mercy Medical Center	USA	Deborah W. Wilbur
Mercy Medical Center—North Iowa	USA	Joginder (Joe) Singh
Genesis Medical Center—East Campus	USA	David M. Spector
Kootenai Cancer Center	USA	John Schallenkamp
NorthShore University HealthSystem-Highland Park Hospital	USA	Douglas E. Merkel
Loyola University Medical Center	USA	Shelly S. Lo
Mount Sinai Hospital Medical Center	USA	Pam G. Khosla
Northwestern University	USA	Massimo Cristofanilli
Northwestern Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University	USA	Lisa Flaum
University of Illinois	USA	Kent F. Hoskins
Rush University Medical Center	USA	Melody A. Cobleigh
Swedish Covenant Hospital	USA	Elyse A. Lambiase
University of Chicago Comprehensive Cancer Center	USA	Olwen M. Hahn
Presence Saint Joseph Hospital—Chicago	USA	Ira A. Oliff
Missouri Baptist Cancer Center	USA	Bryan A. Faller
Illinois CancerCare—Peoria	USA	James L. Wade
Joliet Oncology-Hematology Associates Limited	USA	Nafisa D. Burhani
Cancer Care Specialists of Illinois—Decatur	USA	James L. Wade
Elmhurst Memorial Hospital	USA	Amaryllis Gil
SwedishAmerican Regional Cancer Center	USA	Harvey E. Einhorn
Indiana University School of Medicine/Melvin and Bren Simon Cancer Center	USA	Anna M.V. Storniolo
Parkview Hospital Randallia	USA	Brian K. Chang
IU Health Ball Memorial Hospital	USA	Maitri Kalra
The Community Hospital	USA	Erwin L. Robin
Michiana Hematology Oncology PC—Mishawaka	USA	Bilal Ansari
Department of Internal Medicine, Division Medical Oncology, University of Kansas Medical Center	USA	Priyanka Sharma
Cancer Center of Kansas—Wichita	USA	Shaker R. Dakhil
Cancer Center of Kansas-Wichita Medical Arts Tower	USA	Shaker R. Dakhil
Saint Joseph Hospital East	USA	Richard L. Deming
Ochsner Medical Center Jefferson	USA	John T. Cole
CHRISTUS Highland Medical Center	USA	John T. Cole
Ochsner Health Center—Summa	USA	John T. Cole
Our Lady of the Lake Physician Group	USA	David S. Hanson
Louisiana Hematology Oncology Associates LLC	USA	Augusto C. Ochoa
Ochsner Medical Center Kenner	USA	John T. Cole
Mary Bird Perkins Cancer Center—Covington	USA	Augusto C. Ochoa

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Dana-Farber/Harvard Cancer Center	USA	Judy E. Garber
Beth Israel Deaconess Medical Center	USA	Judy E. Garber
Berkshire Medical Center—Cancer Center	USA	Harvey Zimbler
Suburban Hospital	USA	Deborah K. Armstrong
University of Maryland/Greenebaum Cancer Center	USA	Katherine H.R. Tkaczuk
Mercy Medical Center	USA	David A. Riseberg
Johns Hopkins University/Sidney Kimmel Cancer Center	USA	Deborah K. Armstrong
Frederick Memorial Hospital	USA	Brian M. O'Connor
Eastern Maine Medical Center	USA	Thomas H. Openshaw
Penobscot Bay Medical Center	USA	Thomas H. Openshaw
Harold Alfond Center for Cancer Care	USA	Thomas H. Openshaw
William Beaumont Hospital—Royal Oak	USA	Dana Zakalik
Ascension Providence Hospitals—Southfield	USA	Cynthia M. Vakhariya
University of Michigan Rogel Cancer Center	USA	Anne F. Schott
Wayne State University/Karmanos Cancer Institute	USA	Michael S. Simon
Henry Ford Hospital	USA	Thomas J. Doyle
Trinity Health Ann Arbor Hospital, Michigan Cancer Research Consortium (NCORP)	USA	Tareq Al Baghdadi
Cancer Research Consortium of West Michigan, Spectrum Health at Butterworth Campus	USA	Amy VanderWoude
Regions Hospital	USA	Patrick J. Flynn
Mercy Hospital	USA	Richard T. Zera
Essentia Health Cancer Center	USA	Bret E.B. Friday
Mayo Clinic	USA	Kathryn J. Ruddy
Saint Francis Regional Medical Center	USA	Richard T. Zera
Mayo Clinic Health Systems—Mankato	USA	Ron Smith
Fairview Clinics and Surgery Center Maple Grove	USA	Patrick J. Flynn
Washington University School of Medicine	USA	Foluso Olabisi Ademuyiwa
CoxHealth South Hospital	USA	Robert Ellis
Mercy Hospital Springfield	USA	Jay W. Carlson
Saint Louis Cancer and Breast Institute—South City	USA	Jay W. Carlson
Kalispell Regional Medical Center	USA	Marchello, Benjamin T.
Atrium—Wake Forest University Health Sciences	USA	Edward A. Levine
Duke University Medical Center	USA	Paul K. Marcom
Mission Hospital	USA	Cameron B. Harkness
Levine Cancer Institute, Atrium Health	USA	Antoinette R. Tan
CaroMont Regional Medical Center	USA	William J. Charles
FirstHealth of the Carolinas—Pinehurst	USA	Charles S. Kuzma
Southeastern Medical Oncology Center—Jacksonville	USA	Shonda Asaad
Margaret R Pardee Memorial Hospital	USA	James E. Radford
Sanford Roger Maris Cancer Center	USA	Preston D. Steen
Trinity Cancer Care Center	USA	Madhu Unnikrishnan
Altru Cancer Center	USA	Grant R. Seeger
Nebraska Methodist Hospital	USA	Kirsten M.H. Leu
CHI Health Saint Francis	USA	Mehmet S. Copur
Southeast Nebraska Cancer Center—68th Street Place	USA	Ralph J. Hauke
Nebraska Hematology and Oncology	USA	Gamini S. Soori
Faith Regional Health Services Carson Cancer Center	USA	Ralph J. Hauke
Dartmouth-Hitchcock Medical Center/Norris Cotton Cancer Center	USA	Bradley A. Arrick
Morristown Medical Center	USA	Jennifer G. Reeder
Rutgers Cancer Institute of New Jersey	USA	Deborah L. Toppmeyer
University of New Mexico Comprehensive Cancer Center (NM MU-NCORP)	USA	Zoneddy R. Dayao
Laura and Isaac Perlmutter Cancer Center at NYU Langone	USA	Sylvia Adams

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NYP/Weill Cornell Medical Center	USA	Eleni Andreopoulou
University of Rochester	USA	Magnuson Allison
Montefiore Medical Center—Einstein Campus	USA	Jesus D. Anampa Mesias
Northwell Health Cancer Institute	USA	Ruby Sharma
Ohio State University Comprehensive Cancer Center	USA	Bhuvaneswari Ramaswamy
Cleveland Clinic Foundation	USA	Aaron T. Gerds
UH Seidman Cancer Center at Southwest General Hospital	USA	Robert R. Shenk
Kettering Medical Center	USA	Howard M. Gross
Aultman Health Foundation	USA	Shruti Trehan
Miami Valley Hospital North	USA	Howard M. Gross
Blanchard Valley Hospital	USA	Howard M. Gross
Dayton Physician LLC-Miami Valley Hospital North	USA	Howard M. Gross
UHHS-Chagrin Highlands Medical Center	USA	Robert R. Shenk
Springfield Regional Cancer Center	USA	Howard M. Gross
Mercy Cancer Center-Elyria	USA	Robert R. Shenk
Stephenson Cancer Center, University of Oklahoma Health Sciences Center	USA	Wajeeha Razaq
Kaiser Permanente Northwest	USA	Abdul H. Mansoor
Allegheny Health Network	USA	Christie J. Hilton
UPMC Hillman Cancer Center	USA	Adam M. Brufsky
WellSpan Health	USA	Chanh Huynh
Delaware County Memorial Hospital	USA	Nabila Chowdhury
Basser Center for BRCA at the Abramson Cancer Center, University of Pennsylvania	USA	Susan M. Domchek
Fox Chase Cancer Center	USA	Elin R. Sigurdson
Reading Hospital	USA	Terrence P. Cescon
Penn State Health Saint Joseph Medical Center	USA	Marc A. Rovito
Lankenau Medical Center	USA	Albert S. DeNittis
Geisinger Wyoming Valley/Henry Cancer Center	USA	Victor G. Vogel
Jefferson Hospital	USA	Thomas B. Julian
Adams Cancer Center	USA	L. E. Boyle
San Juan City Hospital	USA	Luis Baez-Diaz
Medical University of South Carolina	USA	Frank J. Brescia
AnMed Health Cancer Center	USA	John E. Doster
Saint Francis Cancer Center	USA	Robert D. Siegel
Scott and White Memorial Hospital	USA	Lucas Wong
Houston Methodist Hospital	USA	Tejal Patel
Baylor College of Medicine/Dan L Duncan Comprehensive Cancer Center	USA	Julie R. Nangia
Texas Tech University Health Sciences Center—Lubbock	USA	Catherine A. Jones
McKay-Dee Hospital Center	USA	George M. Cannon
Utah Valley Regional Medical Center	USA	George M. Cannon
Virginia Commonwealth University/Massey Cancer Center	USA	Harry D. Bear
Virginia Commonwealth University/Massey Cancer Center	USA	Hetal Vachhani
Inova Schar Cancer Institute	USA	Mary Wilkinson
University of Vermont and State Agricultural College	USA	Marie E. Wood
Central Vermont Medical Center	USA	Marie E. Wood
Swedish Medical Center—First Hill	USA	Fengting Yan
Providence Regional Cancer System—Centralia	USA	Xingwei Sui
University of Washington School of Medicine, Division of Oncology Fred Hutch/University of Washington Cancer Consortium	USA	Carol M. van Haelst
University of Washington School of Medicine, Division of Oncology Fred Hutch/University of Washington Cancer Consortium	USA	Jennifer M. Specht
Kadlec Clinic Hematology and Oncology	USA	Ying Zhuo
Aurora Saint Luke's Medical Center	USA	Rubina Qamar
Saint Vincent Hospital Cancer Center at Saint Mary's	USA	Matthew L. Ryan
Mayo Clinic Health System-Franciscan Healthcare	USA	Abigail Stockham

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Aurora Cancer Care-Southern Lakes VLCC	USA	Shamsuddin Virani
Aurora BayCare Medical Center	USA	Rubina Qamar
Marshfield Medical Center—Weston	USA	Arlene A. Gayle
Aurora Cancer Care—Grafton	USA	Rubina Qamar
Aurora Health Center—Fond du Lac	USA	Rubina Qamar
Charleston Area Medical Center, David Lee Cancer Center	USA	Steven J. Jubelirer
West Virginia University Cancer Institute	USA	Sobha Kurian
West Virginia University Healthcare	USA	Mohamad A. Salkeni

SABO: Swedish Association of Breast Oncologists

Skånes Universitetssjukhus Lund/Skåne/Lund University Hospital, Department of Oncology, Malmö	Sweden	Niklas Loman
Sahlgrenska Universitetssjukhuset, Gothenburg	Sweden	Barbro Linderholm
Norrlands Universitetssjukhus, Umeå	Sweden	Gustav Silander
Linköpings Universitetssjukhus, Linköping	Sweden	Anna-Lotta Hallbeck
Södersjukhuset, Stockholm	Sweden	Anna von Wachenfeldt Väppling

SOLTI

Hôpital Jean Minjoz	France	Elsa Curtit
IPO Lisboa, Serviço de Oncologia Médica 2	Portugal	Catarina Cardoso
Hospital CUF Descobertas	Portugal	Sofia Braga
IPO Porto, Serviço de Oncologia Médica	Portugal	Miguel Abreu
Hospital Beatriz Ângelo, Hospital de Dia Oncologia	Portugal	Mafalda Casa-Nova
Hospital da Luz	Portugal	Mónica Nave
Hospital Universitario 12 de Octubre	Spain	Eva María Ciruelos Gil
Hospital Vall d'Hebron	Spain	Judith Balmaña Gelpi
Institut Catala d'Oncologia Hospitalet	Spain	Adela Fernández Ortega
Hospital San Joan de Reus	Spain	Josep Gumà Padró
Hospital Clínico Universitario de Valencia	Spain	Begoña Bermejo de las Heras
Usp Institut Universitari Dexeus	Spain	María González Cao
Complejo Hospitalario Universitario de Santiago (CHUS)	Spain	Juan Cueva Bañuelos
Hospital Universitario Son Espases	Spain	Jesús Alarcon Company
Hospital Josep Trueta	Spain	Gemma Viñas Villaró
MD Anderson Cancer Center	Spain	Laura García Estevez

SUCCESS

Universitätsklinikum Ulm	Germany	Jens Huober
Brustzentrum Mittelthüringen	Germany	Steffi Busch
Universitätsklinikum Düsseldorf	Germany	Tanja Fehm
Stadtklinik Baden-Baden	Germany	Antje Hahn
Südharz-Krankenhaus Nordhausen gGmbH	Germany	Andrea Grafe
Kreiskrankenhaus Hameln	Germany	Thomas Noesselt
Klinikum Gifhorn GmbH	Germany	Thomas Dewitz
Gemeinschaftspraxis Drs. med. Wilke/Wagner	Germany	Harald Wagner
Klinikum Memmingen	Germany	Christina Bechtner
Leopoldina-Krankenhaus der Stadt Schweinfurt	Germany	Michael Weigel
Marienhospital Bottrop gGmbH	Germany	Hans-Christian Kolberg
Onkologie Ravensburg	Germany	Thomas Decker

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Institut für Versorgungsforschung in der Onkologie	Germany	Jörg Thomalla
Diakoniekrankenhaus Rotenburg (Wümme) gGmbH	Germany	Tobias Hesse
Klinikum der Ludwig-Maximillians-Universität München	Germany	Nadia Harbeck
Onkologische Schwerpunktpraxis Mülheim	Germany	Jan Schröder
Charité—Universitätsmedizin Berlin	Germany	Jens-Uwe Blohmer
Universitätsklinikum Mannheim	Germany	Marc Wolf Sütterlin
SweBCG Swedish Breast Cancer Group		
Karolinska Universitetssjukhuset, Solna	Sweden	Renske Altena

TCOG: Taiwan Cooperative Oncology Group

China Medical University Hospital	Taiwan	Chang-Fang Chiu
Chang-Gung Medical Foundation Linkou	Taiwan	Shin-Cheh Chen
Kaohsiung Medical University Chung-Ho Memorial Hospital	Taiwan	Ming-Feng Hou
Mackay Memorial Hospital	Taiwan	Yuan-Ching Chang
Chi Mei Hospital-Liou Yin	Taiwan	Shang-Hung Chen
Changhua Christian Hospital	Taiwan	Shou-Tung Chen
National Taiwan University Hospital	Taiwan	Chiun-Sheng Huang
Veterans General Hospital Taichung	Taiwan	Dah-Cherng Yeh
Triple Service General Hospital	Taiwan	Jyh-Cherng Yu
Veteran General Hospital Taipei	Taiwan	Ling-Ming Tseng
National Cheng Kung University (NCKU) Hosptial	Taiwan	Wei-Pang Chung

UCBG: Unicancer Breast Group

Centre Oscar Lambret	France	Audrey Mailliez
Centre Paul Strauss	France	Thierry Petit
Institut Gustave Roussy	France	Suzette DELALOGE
Centre François Baclesse	France	Christelle Lévy
Hôpital Européen de Marseille	France	Philippe Dalivoust
Institut Paoli Calmettes	France	Jean-Marc Extra
Centre Jean Perrin	France	Marie-Ange Mouret-Reynier
Centre CARIO-HPCA	France	Anne-Claire Hardy-Bessard
CHU Morvan-Institut de Cancerologie et d'Hematologie	France	Hélène Simon
Centre Hospitaliser Départemental Les Oudairies	France	Tiffenn L'Haridon
Institut Sainte Catherine	France	Alice Mege
Hôpital Saint Louis	France	Sylvie Giacchetti
Institut Bergonié	France	Camille Chakiba-Brugere
Clinique Pasteur	France	Alain Gratet
Centre Léonard de Vinci	France	Virginie Pottier
Centre Antoine Lacassagne	France	Jean-Marc FERRERO
Centre Henri Becquerel	France	Isabelle Tennevet
Centre Eugène Marquis	France	Christophe Perrin

Independent Sites

Grand Hôpital de Charleroi (GHdC)	Belgium	Jean-Luc Canon
Universitair Ziekenhuis Brussel	Belgium	Sofie Joris
Fudan University Shanghai Cancer Center	China	Zhimin Shao
Cancer Hospital, CAMS&PUMC	China	Binghe Xu
PLA 307 hospital	China	ZeFei Jiang
Peking Union Medical College Hospital	China	Qiang Sun
Ruijin hospital Shanghai Jiaotong University of medicine	China	Kunwei Shen
Harbin Medical University Cancer Hospital	China	Da Pang
Tianjin Medical University Cancer Institute and Hospital	China	Jin Zhang
Jiangsu Province Hospital	China	Shui Wang
The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences.	China	Hongjian Yang
Guangdong Provincial People's Hospital	China	Ning Liao
West China Hospital, Sichuan University	China	Hong Zheng
The 1st Affiliated Hospital of Medical School of Zhejiang Un	China	Peifen Fu
The Union Hospital affiliated to Fujian Medical University	China	Chuangui Song
ShanDong Cancer Hospital	China	Yongsheng Wang
The First Hospital of Jilin University	China	Zhimin Fan
Hebei Medical University Fourth Hospital	China	Cuizhi Geng
Centre Léon Bérard	France	Olivier Tredan
Uzsoki utcai Kórház	Hungary	László Landherr
Chaim Sheba Medical Centre at Tel Hashomer	Israel	Bella Kaufman[a]
Institute of Oncology, Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petach Tikva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv	Israel	Rinat Yerushalmi
Hadassah Hebrew University Medical Center	Israel	Beatrice Uziely
Istituto Oncologico Veneto	Italy	Pierfranco Conte
A.O.U. di Bologna—Policlinico Sant'Orsola-Malpighi	Italy	Claudio Zamagni
Ospedale S. Raffaele—Milano	Italy	Giampaolo Bianchini
Istituto Nazionale Tumori Fondazione Pascale IRCCS	Italy	Michelino De Laurentiis
Ospedali Riuniti—Azienda Ospedaliera Papa Giovanni XXIII	Italy	Carlo Tondini
La Maddalena Clinic For Cancer University Of Palermo	Italy	Vittorio Gebbia
Azienda Ospedaliera Vito Fazzi	Italy	Mariangela Ciccarese
Magodent Szpital Elbląska	Poland	Tomasz Sarosiek
Med Polonia Sp.Z.o.o NSZOZ	Poland	Jacek Mackiewicz
SPZOZ MSWiA z Warmińsko-Mazurskim Centrum Onkologii	Poland	Anna Słowińska
Instytut Centrum Zdrowia Matki Polki	Poland	Ewa Kalinka
Niepubliczny Zakład Opieki Zdrowotnej Innowacyjna Medycyna	Poland	Tomasz Huzarski
Seoul National University Hospital	Republic of Korea	Seock-Ah Im
Asan Medical Center	Republic of Korea	Kyung Hae Jung
Yonsei University Severance Hospital	Republic of Korea	Joo Hyuk Sohn
Seoul National University Bundang Hospital	Republic of Korea	Jee Hyun Kim
National Cancer Center	Republic of Korea	Keun Seok Lee
Samsung Medical Center	Republic of Korea	Yeon Hee Park
Ewha Womans University Mokdong Hospital	Republic of Korea	Kyoung Eun Lee
Chilgok Kyungpook National University Medical Center	Republic of Korea	Yee Soo Chae
Gachon University Gil Hospital	Republic of Korea	Eun Kyung Cho

[a]Deceased.