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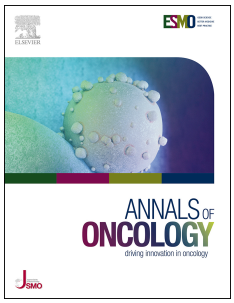

Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high risk, early breast cancer

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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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Structured Abstract

Background: The randomized, double-blind OlympiA trial compared one 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 (HER2)-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: 1,836 patients were randomly assigned to olaparib or placebo following (neo)adjuvant chemotherapy (N)ACT, 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 median follow-up of 3.5 years, the second IA of OS demonstrated significant improvement in the olaparib-group relative to the placebo-group (HR, 0.68; 98.5% CI 0.47 to 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 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 myelogenous leukemia or myelodysplastic syndrome (AML/MDS).

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.

ClinicalTrials.gov: NCT02032823

Keywords: Breast cancer, *BRCA1/2*, PARP inhibition, olaparib, adjuvant therapy

Highlights

- Adjuvant olaparib vs placebo significantly improved OS in g*BRCA1*/2pv-associated HER2-negative EBC (4-year OS 90% vs 86%)
- Adjuvant olaparib vs placebo improved 4-year IDFS (83% vs 75%) and 4-year DDFS (87% vs 79%)
- Adjuvant olaparib demonstrated benefit across major subgroups for OS, IDFS, and DDFS, including by hormone receptor status
- With 3.5 years of median follow-up there were two AML/MDS cases (0.2%) with olaparib and three (0.3%) with placebo
- With 1-year of additional follow-up, no new safety signals were identified with adjuvant olaparib compared to placebo

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), 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.[2,3,4] 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 HER2-negative,[7,8,9] 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 (EBC) and high-risk clinico-pathological features remain at increased risk for recurrence following standard multimodality therapies, OlympiA was designed to determine whether one year of adjuvant olaparib could improve outcomes in this population. This phase III, double-blinded, placebo-controlled study randomized 1,836 eligible patients with g*BRCA*pv-associated EBC from 2014-2019. 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 to 0.82; *P*<0.001) and distant-disease-free survival (DDFS) (HR, 0.57; 99.5% CI, 0.39 to 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 were fewer than in the placebo-group (59 *vs* 86), but the difference (HR, 0.68, 99% CI, 0.44 to 1.05; *P*=0.02) did not meet the pre-specified 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 myelogenous 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, human epidermal growth factor receptor 2 (HER2)-negative, EBC were randomized to receive 1 year of study medication consisting of either oral olaparib 300 mg BID or matching placebo, stratified by hormone receptor status, prior neoadjuvant versus adjuvant chemotherapy and platinum therapy for current breast cancer (yes versus no). Eligible patients had received at least 6 cycles of neoadjuvant (NACT) or adjuvant (ACT) chemotherapy 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 prior to randomization. Patients with hormone-receptor-positive cancers were to receive at least 5 years of adjuvant endocrine therapy (ET) per local standards concurrent with study medication. Bisphosphonates and denosumab were allowed per investigator discretion. Patients who had received neoadjuvant chemotherapy could not receive post-operative 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 ≥3 following NACT[14,15] or ≥4 positive nodes at initial surgery.

Endpoints and assessments

In accordance with the standardized definitions for efficacy endpoints (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 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 (CI), 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 1,800 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 timepoints and endpoints (Table S1 in supplementary appendix [SA]). 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 (Table S1 SA). 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 2-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 performed with 95% CIs as these endpoint analyses are now descriptive.

RESULTS

Patients

From June 2014 through May 2019, 1,836 patients were randomly assigned to receive either olaparib or placebo. IA2 was triggered on 12th July 2021; case report forms for study visits up to data cutoff for IA2 were collected and data quality controlled with database lock occurring on 17th December 2021. Median follow-up was 3.5 years (IQR:2.5, 4.5) in the ITT population, 3.6 years (IQR:2.5, 4.7) in the TNBC cohort, and 3.4 years (IQR:2.5, 4.1) in the hormone-receptor-positive cohort. After randomization, 10 patients in the olaparib-group and 11 in the placebo-group did not receive assigned therapy (Figure S1: Consort Diagram SA). Baseline characteristics of the patients were balanced between the two treatment groups (Table 1, Table S2 SA). Most of the patients (82.2%) had TNBC. Approximately half 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 to 0.97; *P*=0.009) (Fig. 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% of the olaparib-group and 94.5% in the placebo-group (Table S3 SA). Death without a prior IDFS event was reported in two patients in the olaparib-group: one with cardiac arrest and one of unknown cause (Table S4 SA). 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%) (Fig. 1a).

Planned subgroup analyses of OS demonstrated point estimates for improved OS for olaparib consistent with that of the overall population across stratification groups and g*BRCA1/2*pv (Fig. 2a). The survival benefit of olaparib was observed irrespective of g*BRCA1/2pv*, 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 Section 2 of the SA and shown in Table S5 of the SA.

With approximately one 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 to 0.78 (Fig. 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%) of the placebo-group (Table S4 SA). 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%) (Fig. 1b). DDFS was improved in patients who received olaparib (HR, 0.61; 95% CI 0.48 to 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%) (Fig. 1c).

Subgroup analysis of IDFS across stratification groups and g*BRCA1/2*pv revealed point estimates of treatment effect favoring olaparib over placebo consistent with that of the overall analysis population (Fig. 2b). The benefit of adjuvant olaparib relative to placebo was observed irrespective of g*BRCA1/2*pv, 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] are provided in Table S6 SA. Subgroup analyses of DDFS across stratification groups and g*BRCA1/2*pv revealed similar findings (Fig. 2c).

Safety

At this safety analysis, all patients had completed the protocol-specified course of olaparib or placebo which included 1,815 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 (Table S7 SA), with median percentage of intended dose delivered being 94.5% in the olaparib-group and 98.9% in the placebo-group (Table S8

SA). Greater than 11 months of the planned 12 months of therapy were completed by 76.1% of patients receiving olaparib compared to 81.7% on placebo (Table S9 SA). In the olaparib-group, 228 patients (25.0%) required a dose reduction compared to 47 (5.2%) in the placebo-group (Table S10 SA). Dose interruptions lasting at least 3 days occurred in 405 (44.5%) of the olaparib-group and 279 (30.9%) of the placebo-group (Table S11 SA). 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%) (Table S12 SA).

Key AE categories are updated and summarized in Table 2. AEs of any grade with an incidence of ≥10% are updated in Table S14 of the SA. 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 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 the SA (Tables S15A and S15B).

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 (Table S13 SA). 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 or have been reported in either arm.

Discussion

The pre-specified second IA of OS in the OlympiA trial demonstrates that one year of adjuvant olaparib relative to placebo provided a statistically significant improvement in OS (HR, 0.68; 98.5.% CI 0.47 to 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 prior to 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 *gBRCA1/2*pv-associated MBC at that time. In contrast to g*BRCA1*pv-associated breast cancers, g*BRCA2pv*-associated breast carriers are predominantly hormone-receptor positive.[7,8] Although adjuvant endocrine therapies reduce 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 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 ad hormone-receptor-positive cohorts (3.6 *vs* 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 1,509 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 (Fig. 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 (Fig. 2c). With relatively few deaths (n=33) reported among the 325 patients with hormone-receptor-positive EBC (Fig. 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 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 to >9.5 gm/dl. If recovery took more than 2 weeks, olaparib was reduced to 250 mg BID. Study therapy was discontinued if repeated RBC transfusions were required to maintain the Hgb >9.5. 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 (Table S15A SA).

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 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 suggests programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) 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 *gBRCA1/2*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 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, which stratified by basal *vs* non-basal subtype based on immunohistochemistry staining for cytokeratin 5/6 and epidermal growth factor receptor (EGFR). Although an HR of 0.82 (95% CI, 0.63 to 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 *vs*

platinum chemotherapy in patients with a basal subtype of TNBC determined by PAM50 analysis with ≥1 cm of residual disease following taxane-based neoadjuvant chemotherapy. 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 less than 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 more 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 to 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 patients with g*BRCA2*pv, and hormone-receptor-positive MBC may not respond as well to CDK4/6 inhibitors.[29,30,31]

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*BRCA/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 vs 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 remain 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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and other cancers, BCN/CRUK receive payments associated with a patent for the use of PARP inhibitors in DNA deficient cancers, licensee - AstraZeneca.

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.
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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. ASCO 2021;39:18s (Suppl; Abstract LBA1 ASCO Plenary) *J Clin Oncol*.
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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Figure Legends/Captions

Figure 1:

A. Overall Survival

B. Invasive disease-free survival

C. Distant disease-free survival

Figure 2: Subgroup analyses of overall survival

Figure 3: Subgroup analyses of invasive disease-free survival

~ Tables, figures, and supplementary materials provided separately ~

Appendix 1: Collaborators (participating groups, accruing institutions, and lead investigators)

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Table 1. Demographic and Baseline Disease Characteristics of the Patients.*

Characteristic	Olaparib (n=921)	Placebo (n=915)
Age, years — median (interquartile range)	42 (36–49)	43 (36–50)
g*BRCA* P/LP gene — no. (%)†		
BRCA1	656 (71.2)	669 (73.1)
BRCA2	260 (28.2)	238 (26.0)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
No *gBRCA* P/LP variant	2 (0.2)	3 (0.3)
Missing	1 (0.1)	0 (0.0)
Prior adjuvant/neoadjuvant chemotherapy — no. (%)		
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) — no. (%)	146/168 (86.9)	146/157 (93.0)
Hormone receptor status — no. (%)‡		
Hormone receptor–positive/HER2–negative§	168 (18.2)	157 (17.2)
Triple–negative breast cancer¶	751 (81.5)	758 (82.8)
Menopausal status (females only) — no. (%)		
Premenopausal	572/919 (62.2)	553/911 (60.7)
Postmenopausal	347/919 (37.8)	358/911 (39.3)
Primary breast cancer surgery — no. (%)		
Mastectomy	699 (75.9)	674 (73.7)
Conservative surgery only	222 (24.1)	239 (26.1)
Missing	0 (0.0)	2 (0.2)

P/LP pathogenic or likely pathogenic variants

* Further information on baseline characteristics is provided in Table S2 in the Supplementary Appendix. Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2.

† For a detailed description of local and central Myriad BRCA testing in patients enrolled in the trial, see Figure S2. Variant interpretation by Myriad Genetics (BRCAnalysis) (1649 patients) and BGI Genomics (247 patients) was performed 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. 85 patients randomised 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 Figure S2. Listing of pathogenic or likely pathogenic *BRCA1* and *BRCA2* variants that occurred in more than 1 patient have previously been reported[12].

‡ Hormone-receptor status was defined by local test results.

§ 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.

¶ 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 less than 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 less than 2.0 and, if reported, an average HER2 copy number of fewer than 4 signals per cell; or HER2-nonamplified disease on ISH with a ratio less of than 2.0 and, if reported, an average HER2 copy number of fewer than 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.

Table 2. Summary of adverse events in the safety analysis set.*

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†	31 (3.4)	51 (5.6)
MDS/AML	2 (0.2)	3 (0.3)
Pneumonitis ‡	9 (1.0)	12 (1.3)
New primary malignancy §	21 (2.3)	36 (4.0)
Grade ≥3 adverse event	223 (24.5)	102 (11.3)
Grade 4 adverse event §	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of treatment§	98 (10.8)	42 (4.6)
Adverse event leading to death**	1 (0.1)	2 (0.2)

* Includes adverse events with an onset date on or after the first dose date and up to and including 30 days following date of last dose of study medication. AML denotes acute myeloid leukemia; MDS myelodysplastic syndrome.

† 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

‡ 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

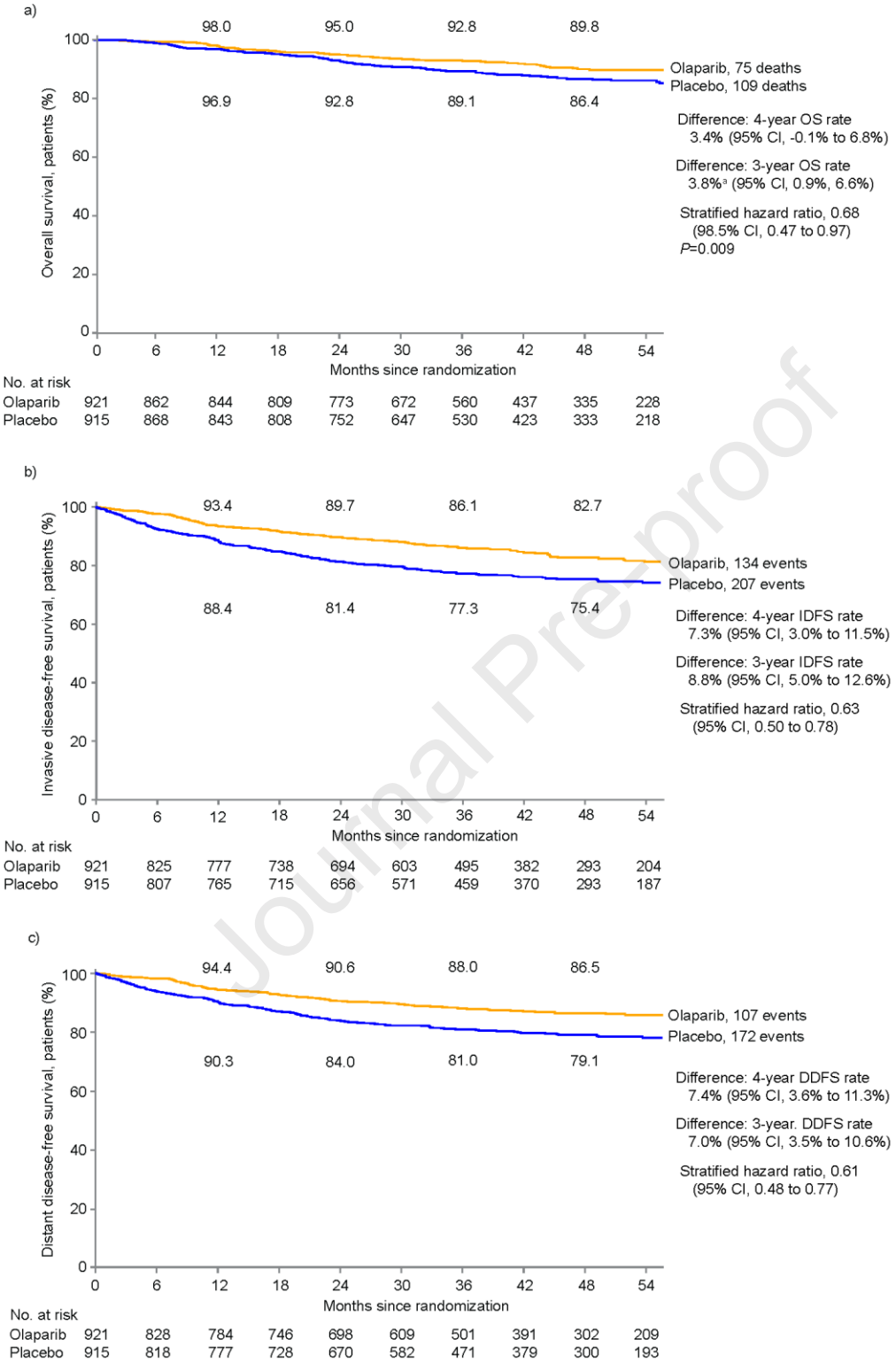
§ Detailed information on the numbers of patients in each group with specific new primary cancers is provided in Table S13.

¶ A total of 18 grade 4 adverse events were reported in 17 patients who received olaparib; one patient had both grade 4 anemia and decreased neutrophil count. In the olaparib group, grade 4 adverse events included decreased neutrophil count (in 5 patients), anemia (in 4 patients), decreased lymphocyte count (in 3 patients), and AML, bipolar disorder, fatigue, febrile neutropenia, abnormal hepatic function, and a suicide attempt (in 1 patient each). In the placebo group, grade 4 adverse events included depression (in 2 patients) and increased aspartate aminotransferase level and acute cholecystitis (in 1 patient each).

§ 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.

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

Figure 1



Footnote

figure 1a

[*] Difference to 2 decimal places: 92.81 – 89.05 = 3.76 (rounded to 3.8)

Figure legends

Legend KM curves

Overall survival (FIG 1A) 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 less than 0.015.

In accordance with the standardized definitions for efficacy end points (STEEP) system, the primary end point of invasive disease–free survival (FIG 1B) 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 (FIG 1C) 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 invasive disease–free survival and distant disease–free survival, 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 overall survival because a P value of less than 0.015 is required to indicate statistical significance for overall survival.

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 and 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.

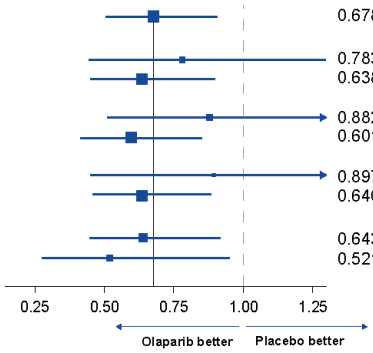
Legend all forest plots

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.

Figure 2

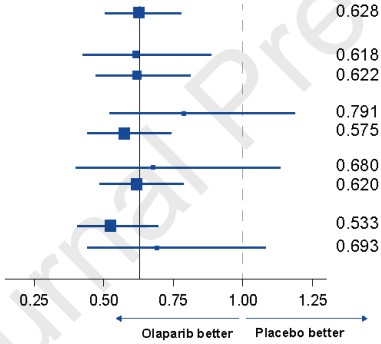
a)

Subgroup	Olaparib (No. of patients who died/total no.)	Placebo (No. of patients who died/total no.)	Stratified hazard ratio for overall survival (95% CI)	4-year overall survival: Olaparib	4-year overall survival: Placebo	*P* value for heterogeneity
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	



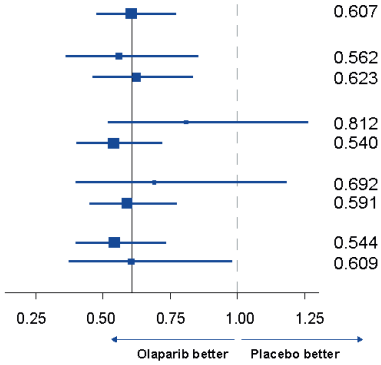
b)

Subgroup	Olaparib (No. of patients with an invasive disease event/total no.)	Placebo (No. of patients with an invasive disease event/total no.)	Stratified hazard ratio for invasive disease-free survival (95% CI)	4-year invasive disease-free survival: Olaparib	4-year invasive disease-free survival: Placebo	*P* value for heterogeneity
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 (No. of patients with a distant disease event/total no.)	Placebo (No. of patients with a distant disease event/total no.)	Stratified hazard ratio for distant disease-free survival (95% CI)	4-year distant disease-free survival: Olaparib	4-year distant disease-free survival: Placebo	*P* value for heterogeneity
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	



Footnote figure 2a/b/c

NC, not calculated

Figure legends

Legend KM curves

For invasive disease–free survival and distant disease–free survival, 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 overall survival because a P value of less than 0.015 is required to indicate statistical significance for overall survival.

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 and 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.

Legend all forest plots

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.