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CORRESPONDENCE

Maintenance therapy with a poly (ADP-ribose) polymerase inhibitor in patients with newly diagnosed advanced epithelial ovarian cancer: updated individual patient data and trial-level meta-analysis

We have recently published an extracted individual patient data (IPD) meta-analysis on the efficacy of maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) in patients with newly diagnosed epithelial ovarian cancer in ESMO Open.[1] We now report an updated IPD meta-analysis after inclusion of extracted data (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100632 and Supplementary Figures S1-S5, available at https://doi.org/10.1016/j.esmoop.2022.100632) from the recently published ATHENA-MONO trial, which was published after our report.[2]

In the combined patient population from ATHENA-MONO and three other randomized trials,[3-5] excluding the SOLO-1 trial,[6] which only included patients with germline *BRCA1* or *BRCA2* mutations, there were 2834 patients with 1596 events. The progression-free survival (PFS) was significantly longer in the PARPi group [median 20.3 months; 95% confidence interval (CI) 18.6-21.9 months] versus the placebo group (median 14.4 months; 95% CI 13.2-15.7 months) with a hazard ratio (HR) of 0.66 (95% CI 0.60-0.73; $P < 0.001$), as shown in Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2022.100632. In subgroup analyses, after including the ATHENA-MONO data, the benefit of PARPi versus placebo continued to be substantial in the somatic or germline *BRCA*-mutated subgroup

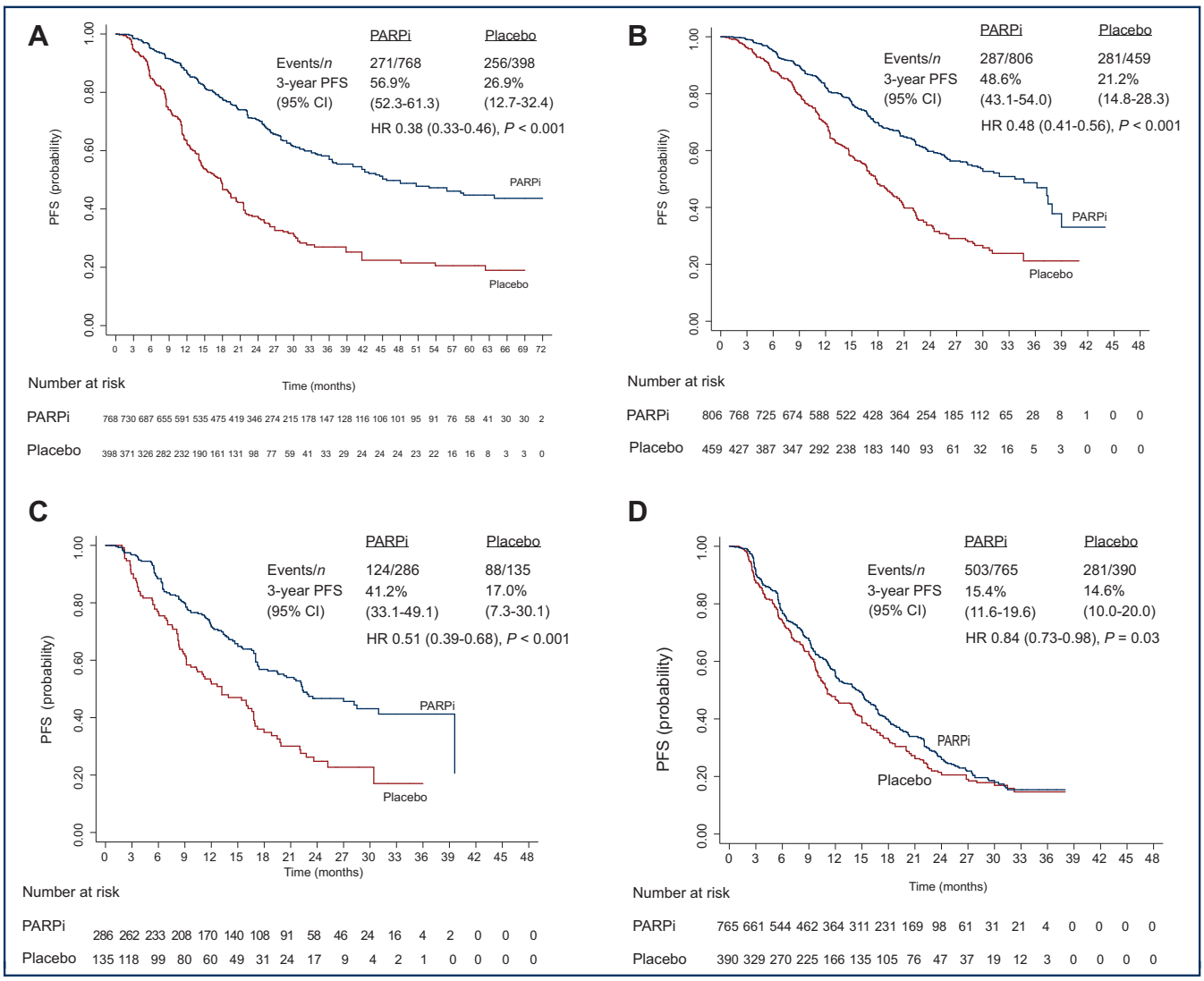

Figure 1. Progression-free survival (PFS) curves comparing poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) versus placebo in the BRCA/HRD subgroups with combined extracted individual patient data from five randomized controlled trials (RCTs).
(A) Germline and/or tumor BRCA-mutated, (B) HRD-positive including BRCA-mutated, (C) HRD-positive excluding BRCA-mutated, (D) HRD-negative, and (E) forest plots of individual patient data from five RCTs. HR, hazard ratio; HRD, homologous recombination deficiency.

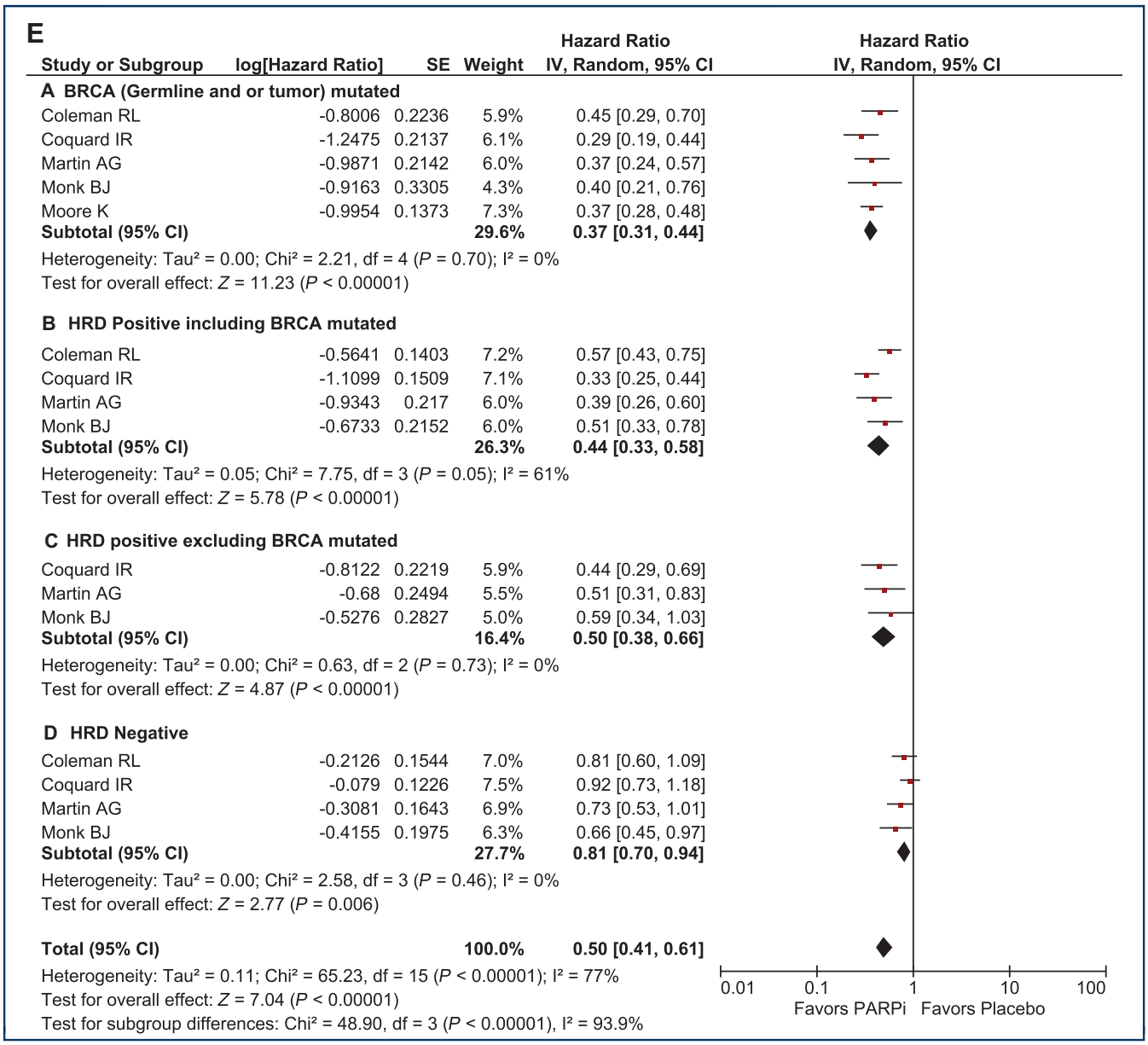

Figure 1. Continued.

(including the data from the SOLO-1 trial), with a median PFS of 45.7 months (95% CI 40.0-63.8 months) versus 17.7 months (95% CI 14.4-19.3 months), respectively (HR 0.38, 95% CI 0.32-0.46; $P < 0.001$); the homologous recombination deficiency (HRD)-positive (including *BRCA* mutated) subgroup, with a median PFS of 34.6 months (95% CI 29.4-37.9 months) versus 17.6 months (95% CI 16.6-19.3 months), respectively (HR 0.48, 95% CI 0.41-0.56; $P < 0.001$); and the HRD-positive (excluding *BRCA* mutated) subgroup, with a median PFS of 22.3 months (95% CI 18.4-30.9 months) versus 13.1 months (95% CI 9.1-16.8 months), respectively (HR 0.51, 95% CI 0.39-0.68; $P < 0.001$). However, even after combining the ATHENA-MONO data, there is a lack of substantial benefit of PARPi versus placebo in patients with HRD-negative tumors with a median PFS of 14.5 months (95% CI 12.4-15.7 months) versus 11.0 months (95% CI 10.0-13.8 months), respectively (HR 0.84, 95% CI 0.73-0.98; $P = 0.03$). The PFS in various subgroups after including the ATHENA-MONO data are shown in Figure 1.

The ATHENA-MONO trial has several features that make its results, including in the HRD-negative subgroup, less definitive. These include a different assay [a percentage loss of heterozygosity (LOH) score] for measuring HRD and the highly imbalanced (4 : 1) randomization, which reduced the number of patients in the placebo arm. Notably, in the HRD-negative (BRCA wild type/LOH low) subgroup there were only 189 patients on rucaparib and 49 patients on placebo, which makes the reported PFS benefit of rucaparib (median 12.1 versus 9.1 months, HR 0.65, 95% CI 0.45-0.95) in this subgroup less precise. Our IPD meta-analysis also suggests that there is only a 3.5-month absolute PFS benefit of PARPi in the BRCA wild-type/HRD-negative subgroup, which is a relatively small gain in the context of newly diagnosed ovarian cancer.

In summary, our updated IPD meta-analysis suggests that there is substantial PFS benefit of maintenance therapy with PARPi in patients with BRCA-mutated or HRD-positive tumors but not in those with HRD-negative tumors.

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Available online 7 November 2022

https://doi.org/10.1016/j.esmoop.2022.100632
DOI of original article: https://doi.org/10.1016/j.esmoop.2022.100558

FUNDING

None declared.

DISCLOSURE

SGul has declared institutional financial interest for the conducted research from Eli Lilly, Pfizer Inc, Celltrion, Kendle India Pvt Ltd, and Zydus; reports nonremunerated activities; serves on the advisory board: Novartis and Eisai. SGup has participated in lectures, presentations, speaking assignments (honoraria to author's institution) for Seoul National University Hospital, Lupin Limited, Roche, Novartis, Eli Lilly, Nag Foundation, Eisai, Omnicuris, Cipla, Cadila Pharmaceuticals, and Intas Pharmaceuticals; serves on the advisory boards (honoraria to author's institution) of Novartis, AstraZeneca, and Eli Lilly; is a member on the national committee (honorarium to author), including the Indian Council of Medical Research, Government of India; Council of Scientific and Industrial Research, Government of India; Department of Biotechnology, Government of India; India Alliance; is a site PI in clinical trials (institutional funding) sponsored by F. Hoffmann-La Roche Ltd, EirGenix Inc., Novartis Healthcare Pvt. Ltd., AstraZeneca Pharma India Limited, Glenmark Pharmaceuticals Ltd., Roche Products (India) Pvt. Ltd., HLL Lifecare Limited (a Government of India Enterprise), and Intas Pharmaceuticals Ltd. SK has declared no conflicts of interest.

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