ESMO Open
Cancer Horizons

Single-agent PARP inhibitors for the treatment of patients with *BRCA*-mutated HER2-negative metastatic breast cancer: a systematic review and meta-analysis

Francesca Poggio,[1,2] Marco Bruzzone,[3] Marcello Ceppi,[3] Benedetta Conte,[2] Samuel Martel,[4] Christian Maurer,[5] Marco Tagliamento,[2] Giulia Viglietti,[6] Lucia Del Mastro,[7] Evandro de Azambuja,[1] Matteo Lambertini[1,6]

To cite: Poggio F, Bruzzone M, Ceppi M, *et al*. Single-agent PARP inhibitors for the treatment of patients with *BRCA*-mutated HER2-negative metastatic breast cancer: a systematic review and meta-analysis. *ESMO Open* 2018;**3**:e000361. doi:10.1136/esmoopen-2018-000361

Received 20 March 2018
Accepted 29 March 2018

For numbered affiliations see end of article.

Correspondence to
Dr Matteo Lambertini; matteo.lambertini85@gmail.com

ABSTRACT

Single-agent poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) have been approved as the first targeted therapy available for patients with *BRCA*-mutated HER2-negative metastatic breast cancer. This meta-analysis aimed to better evaluate activity, efficacy and safety of single-agent PARPi in this population. A systematic search of Medline, Embase and conference proceedings up to 31 January 2018 was conducted to identify randomised controlled trials (RCTs) investigating single-agent PARPi versus monochemotherapy in patients with *BRCA*-mutated HER2-negative metastatic breast cancer. Using the random-effect model, we calculated summary risk estimates (pooled HR and OR with 95% CI) for progression-free survival (PFS), overall survival (OS), objective response rate (ORR), any grade and grade 3–4 adverse events (AEs), treatment discontinuation rate and time to deterioration in quality of life (QoL). Two RCTs (n=733) were included. As compared with monochemotherapy, single-agent PARPi significantly improved PFS (HR 0.56(95% CI 0.45 to 0.70)) and ORR (OR 4.15 (95% CI 2.82 to 6.10)), with no difference in OS (HR 0.82 (95% CI 0.64 to 1.05)). Single-agent PARPi significantly increased risk of anaemia and any grade headache, but reduced risk of neutropenia and any grade palmar-plantar erythrodysesthesia syndrome as compared with monochemotherapy. No significant differences in other AEs and treatment discontinuation rate were observed. Patients treated with PARPi experienced a significant delayed time to QoL deterioration (HR 0.40 (95% CI 0.29 to 0.54)). Single-agent PARPi showed to be an effective, well tolerated and useful treatment in maintaining QoL of patients with *BRCA*-mutated HER2-negative metastatic breast cancer.

BACKGROUND

Among unselected patients with breast cancer, approximately 10% harbour a germ line mutation in *BRCA1* or *BRCA2* genes.[1] These are tumour suppressor genes mainly involved in the maintenance of genome integrity using one of the major DNA damage repair pathways named homologous recombination.[2] Poly (ADP-ribose) polymerase (PARP) is a family of nuclear enzymes with a key role in the recognition and repair of DNA single-strand breaks.[3] In the presence of PARP inhibitors (PARPi), the PARP-dependent DNA repair system cannot be activated with consequent development of double-strand breaks. In normal cells, these breakages can be repaired through the homologous recombination pathways with subsequent retrieval of DNA integrity and cell survival. Conversely, in *BRCA*-mutated cells, homologous recombination is defective and these damages cannot be efficiently repaired resulting in cell deaths (ie, the concept of synthetic lethality).[4 5]

Preclinical studies showed that *BRCA1/2*-deficient cancer cells are sensitive to PARP inhibition, mostly due to the persistence of DNA lesions that would be ordinarily repaired by the homologous recombination pathway.[6] Based on this strong biological rationale, the study by Tutt and colleagues then provided the proof of concept for the potential clinical utility of single-agent PARPi in patients with *BRCA*-mutated metastatic breast cancer.[7] Following these results, over the past years, several clinical trials have evaluated and are currently investigating the role of different PARPi in this population.

Recently, based on the results of the phase III randomised controlled trial (RCT) OlympiAD,[8] single-agent PARPi olaparib has been approved as the first targeted therapy available for patients with *BRCA*-mutated HER2-negative metastatic breast cancer.[9] Therefore, currently, these patients are candidates to receive PARPi in the course of their metastatic disease. Hence, it would be important to have a clear overview on

potential harms and benefits with the use of these drugs in terms of expected clinical outcomes, risk of developing adverse events (AEs) and impact on quality of life (QoL). We performed a systematic review and meta-analysis to better elucidate the role of single-agent PARPi for the treatment of patients with *BRCA*-mutated HER2-negative metastatic breast cancer.

MATERIAL AND METHODS

The present study was a quantitative synthesis of RCTs aiming to assess the activity, efficacy and safety of single-agent PARPi (PARPi group) as compared with standard monochemotherapy (chemotherapy group) in patients with *BRCA*-mutated HER2-negative metastatic breast cancer.

Data sources and strategy

Eligible studies were identified by a systematic literature search of Medline and Embase databases, without language or date restriction up to 31 January 2018. Additionally, relevant reports of unpublished studies were identified through the proceedings of the annual meetings of the European Society for Medical Oncology, the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium. Finally, references of retrieved papers addressing the topic of PARPi in breast cancer were examined to identify additional relevant studies.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.[10]

Article selection and data extraction

Eligible trials had to satisfy the following criteria: (A) phase II or III RCTs with published or presented results; (B) RCTs including patients with *BRCA*-mutated HER2-negative metastatic breast cancer treated with single-agent PARPi in the experimental arm and monochemotherapy in the control arm; (C) studies with available data on progression-free survival (PFS) and/or overall survival (OS) and/or objective response rate (ORR) and/or AEs and/or QoL; (D) studies with sufficient data to estimate HR or OR and 95% CI for the study end points in the two groups of interest (PARPi vs chemotherapy group).

The following studies were excluded from the present meta-analysis: (A) non-RCTs evaluating the role of PARPi in patients with *BRCA*-mutated HER2-negative metastatic breast cancer; (B) RCTs in which PARPi were combined with other anticancer agents in the experimental arm; (C) ongoing studies without available and/or sufficient data at the moment of the literature search.

Data extraction

The following variables were extracted independently by two authors (FP and ML) from the selected studies: name of the trial, year of publication, sample size and source of study subjects (experimental and control arms), type of PARPi used in the experimental arm, type of chemotherapy in the control arm, hormone receptor status, and number of patients previously treated with platinum-based chemotherapy. Furthermore, for the purpose of our planned analyses, study-specific rates of PFS, OS, ORR, AEs (of any grade and grade 3–4), treatment discontinuation due to AEs and time to deterioration in QoL were collected.

Study objectives

The objectives of the present meta-analysis were to compare the activity, efficacy and safety between the PARPi group and the chemotherapy group.

The activity and efficacy end points were PFS, OS and ORR in the overall population. Exploratory subgroup analyses of PFS investigated if treatment activity differed according to hormone receptor status (hormone receptor-positive cohort vs hormone receptor-negative cohort) or to prior exposure to platinum-based chemotherapy (prior platinum cohort vs no prior platinum cohort).

In terms of safety profile, the following AEs were considered: overall incidence of any grade AEs, overall incidence of grade 3–4 AEs, neutropenia and anaemia of any grade and grade 3–4, as well as fatigue, nausea, vomiting, headache, diarrhoea and palmar-plantar erythrodysesthesia of any grade. Furthermore, we investigated the rate of treatment discontinuation following AEs and the time to deterioration in QoL.

Statistical analysis

HR and 95% CI were calculated for PFS, OS and the time to deterioration in QoL. HR <1 indicates lower probability of developing EFS and OS events and delayed deterioration in QoL in the PARPi group. OR and 95% CI were calculated for the effect for ORR, AEs and treatment discontinuation. OR >1 indicates higher ORR, AEs and treatment discontinuation rates in the PARPi group.

The pooled estimates of HR and OR were calculated by means of DerSimonian and Laird random-effects model method.[11] Higgins I^2 index was obtained to measure the degree of heterogeneity of the results.[12]

All reported p values were considered statistically significant if <0.05 (two-sided). Statistical analyses were performed and forest plots were drawn with STATA software V.13.1 (StataCorp, College Station, Texas, USA).

RESULTS

Study selection

The literature search returned 183 entries: after applying all the eligibility criteria, two RCTs (the OlympiAD and EMBRACA studies) were included in the present meta-analysis (figure 1).[8 13]

A total of 733 patients was included, of whom 492 received single-agent PARPi (olaparib in the OlympiAD Trial and talazoparib in the EMBRACA Trial) and 241 physician's choice monochemotherapy (ie, capecitabine, eribulin, gemcitabine or vinorelbine).

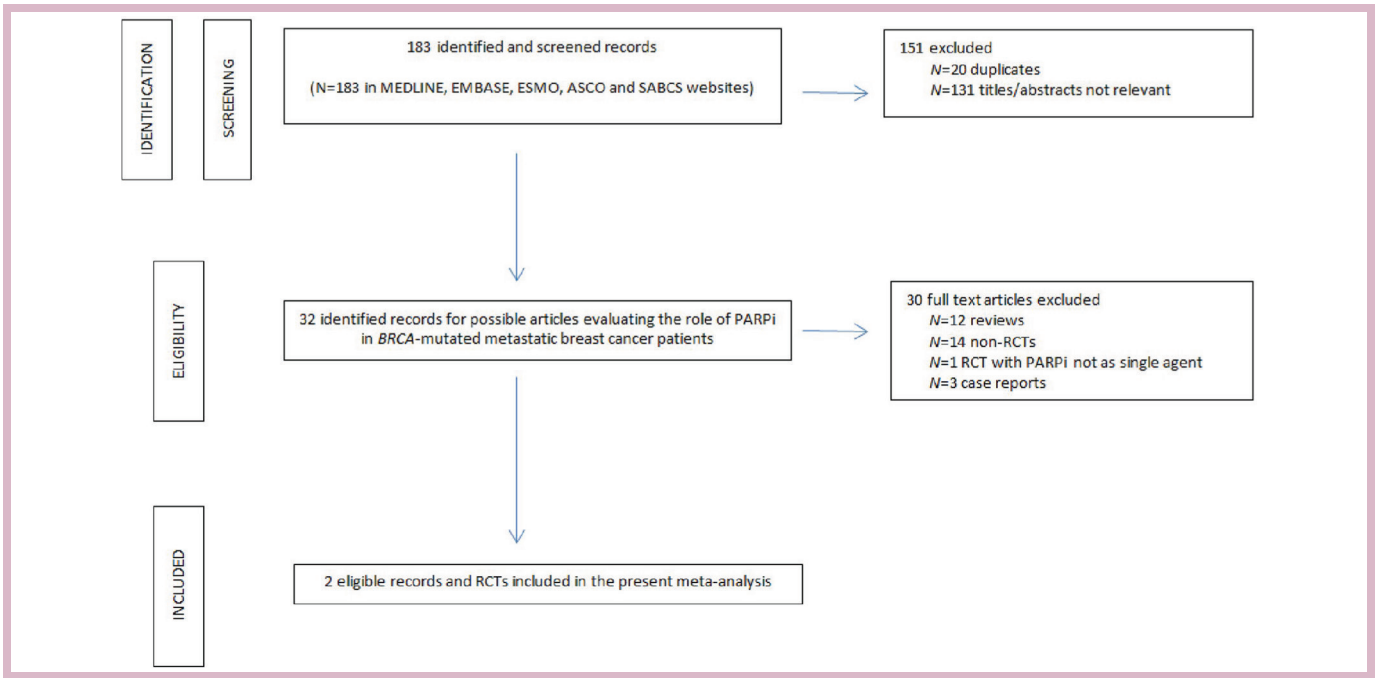

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart summarising the process for the identification of eligible studies. ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; SABCS, San Antonio Breast Cancer Symposium; PARPi, PARP inhibitor; RCT, randomised controlled trial.

Table 1 displays the main characteristics of the included studies. In both trials, about half of the patients had triple-negative breast cancer (TNBC); around 20%–25% of the included patients were previously treated with platinum-based chemotherapy (a previous platinum-based regimen was allowed if at least 12 months occurred since the last dose in the neoadjuvant or adjuvant settings, or if there was no evidence of disease progression during the treatment for the metastatic disease).

Progression-free survival

PFS was the primary end point in both studies. In the OlympiAD and the EMBRACA trials, respectively, median PFS was 7.0 months and 8.6 months in the PARPi group versus 4.2 months and 5.6 months in the chemotherapy group.

By pooling the results of the two studies, single-agent PARPi was associated with a significantly improved PFS (HR 0.56 (95% CI 0.45 to 0.70, p<0.001)). No significant heterogeneity was observed (I^2=0%, p=0.756; figure 2A).

In the subgroup analysis according to hormone receptor status, single-agent PARPi was associated with improved PFS reaching statistical significance only in the hormone receptor-negative cohort (HR 0.51 (95% CI 0.37 to 0.71, p<0.001)) (I^2=31.5%, p=0.227; figure 3A and not in the hormone receptor-positive cohort

Table 1 Randomised trials comparing single-agent PARPi to monochemotherapy in patients with *BRCA*-mutated HER2-negative metastatic breast cancer

Study name (year)	PARPi	Comparator	Setting	Patients, n (PARPi/CT)	HR+, n (%) (PARPi/CT)	HR–, n (%) (PARPi/CT)	Previous platinum, n (%) (PARPi/CT)
OlympiAD (2017)[8]	Olaparib	Mono-CT*	Up to two prior CT regimens	302 (205/97)	103 (50.2)/49 (50.5)	102 (49.8)/48 (49.5)	60 (29.3)/26 (26.8)
EMBRACA (2017)[13]	Talazoparib	Mono-CT†	Up to three prior CT regimen	431 (287/144)	157 (54.7)/84 (58.3)	130 (45.3)/60 (41.7)	46 (16.0)/30 (21.0)

*Eribulin, capecitabine or vinorelbine (according to physician's choice).
†Eribulin, capecitabine, gemcitabine or vinorelbine (according to physician's choice).
CT, chemotherapy; HR+, hormone receptor-positive; HR–, hormone receptor-negative; PARPi, PARP inhibitor.

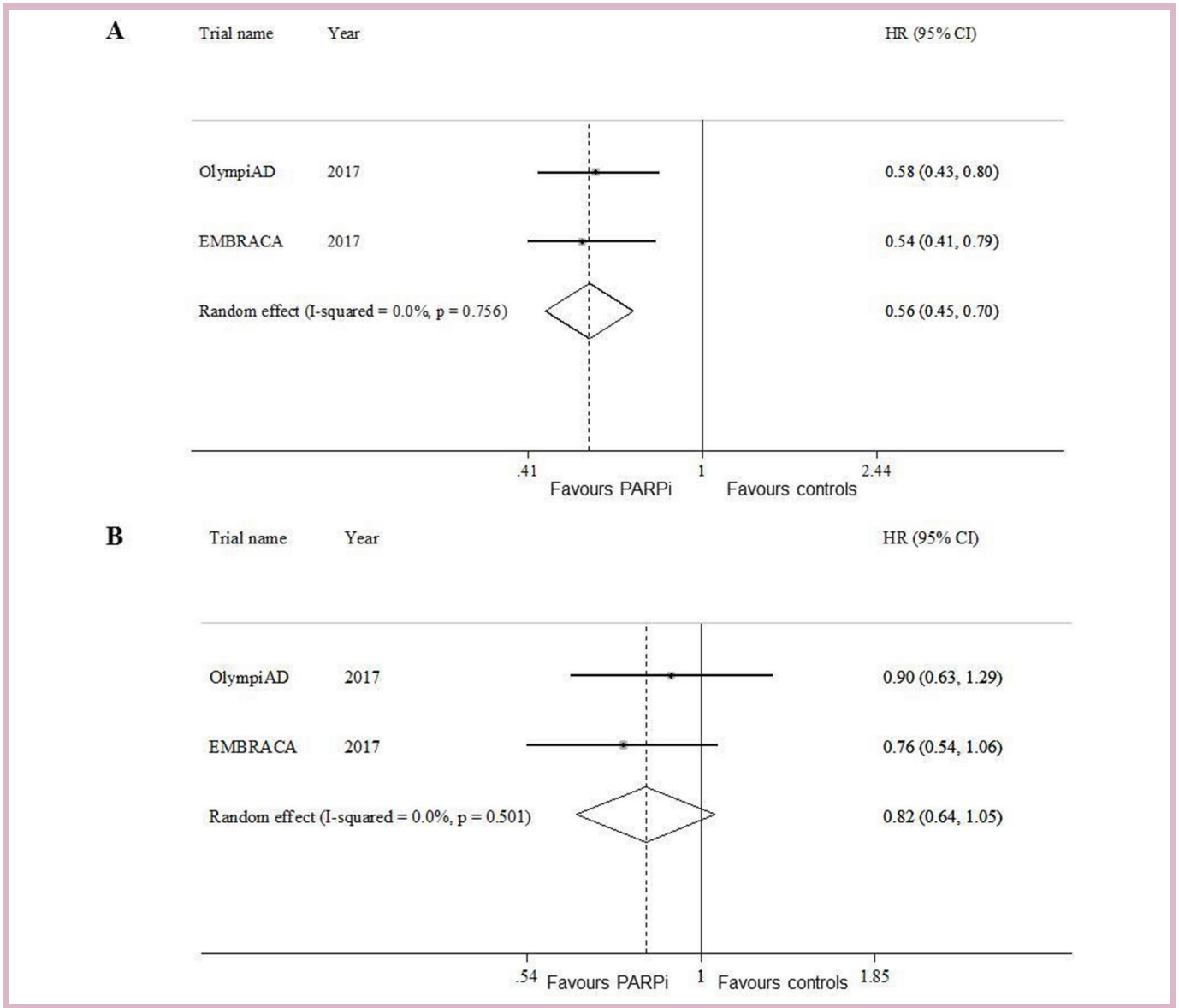

Figure 2 (A) Progression-free survival in patients with *BRCA*-mutated HER2-negative breast cancer treated with PARPi versus those treated with monochemotherapy (controls). The size of the squares is proportional to the weight of each study. (B) Overall survival in patients with *BRCA*-mutated HER2-negative breast cancer treated with PARPi versu s those treated with monochemotherapy (controls).1 The size of the squares is proportional to the weight of each study. PARPi, PARP inhibitor.

(HR 0.62 (95% CI 0.36 to 1.07, p=0.085)) (I^2=72.2%, p=0.058; figure 3B.

In the subgroup analysis according to prior exposure to platinum-based chemotherapy, the improvement in PFS with PARPi reached the statistical significance only in the no prior platinum cohort (HR 0.55 (95% CI 0.44 to 0.69, p<0.001)) (I^2=0.0%, p=0.532; figure 3C) and not in the prior platinum cohort (HR 0.70 (95% CI 0.47 to 1.05, p=0.085)) (I^2=0.0%, p=0.764; figure 3D.

Overall survival

In the OlympiAD and the EMBRACA trials, respectively, median OS was 19.3 months and 22.3 months in the PARPi group versus 19.6 months and 19.5 months in the chemotherapy group.

The meta-analysis of the two trials did not show any significant difference in OS between the two groups (HR 0.82 (95% CI 0.64 to 1.05, p=0.120)) (I^2=0%, p=0.501; figure 2B.

Objective response rate

ORR was defined as complete response plus partial response and evaluated according to RECIST criteria V.1.1 in both trials. A total of 233 (77.1%) of the 302 patients in the OlympiAD trial, and 333 (77.3%) of the 431 patients of the EMBRACA trial had measurable disease and were included in the response analysis.

ORR was 61.4% (237 of 386) in the PARPi group and 27.8% (50 of 180) in the chemotherapy group (OR 4.15 (95% CI 2.82 to 6.10, p<0.001)) (I^2=0.0%, p=0.634) (figure 4).

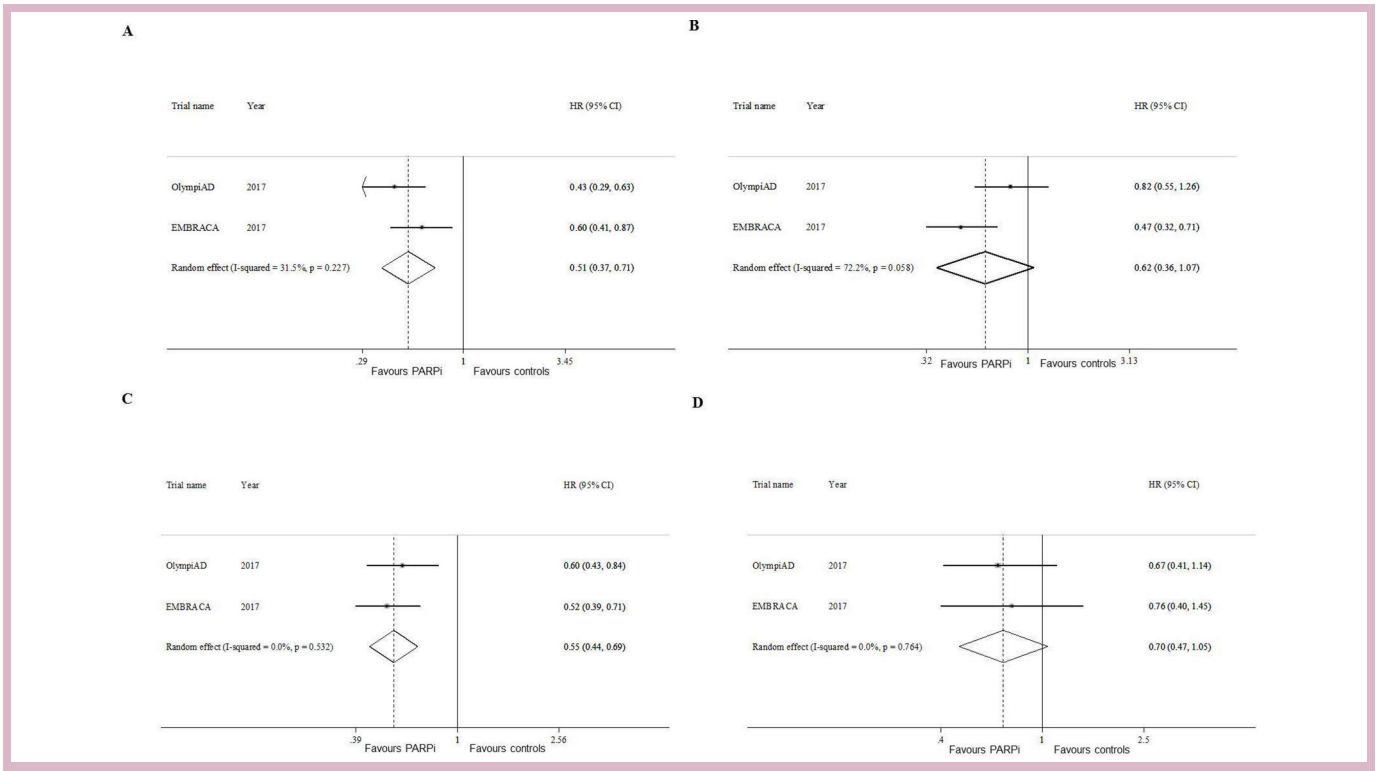

Figure 3 (A) Progression-free survival in the hormone receptor-negative cohort patients treated with PARPi versus those treated with mono chemotherapy (controls). The size of the squares is proportional to the weight of each study. (B) Progression-free survival in the hormone receptor-positive cohort of patients treated with PARPi versus those treated with mono chemotherapy (controls). The size of the squares is proportional to the weight of each study. (C) Progression-free survival in the no prior platinum cohort of patients treated with PARPi versus those treated with mono chemotherapy (controls). The size of the squares is proportional to the weight of each study. (D) Progression-free survival in the prior platinum cohort of patients treated with PARPi versus those treated with mono chemotherapy (controls). The size of the squares is proportional to the weight of each study. PARPi, PARP inhibitor.

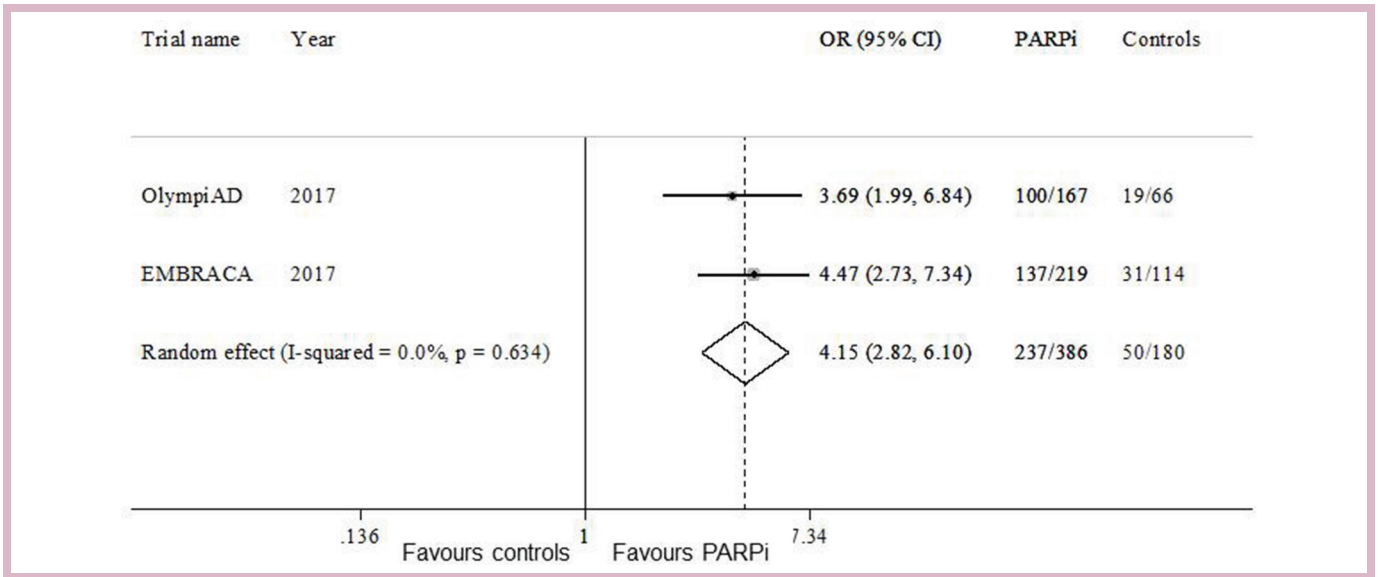

Figure 4 Objective response rate in patients with *BRCA*-mutated HER2-negative breast cancer treated with PARPi versus those treated with monochemotherapy (controls). The size of the squares is proportional to the weight of each study. PARPi, PARP inhibitor.

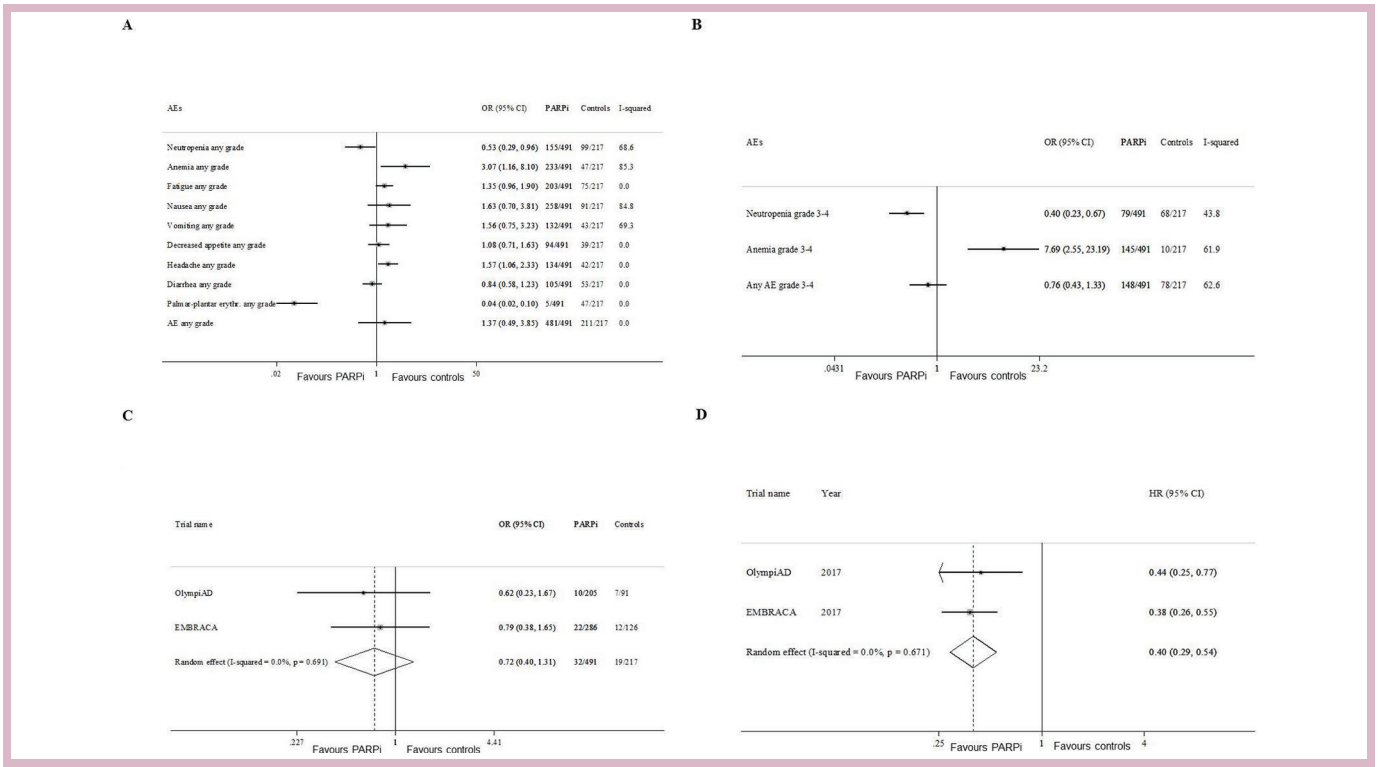

Figure 5 (A) Safety profile overview. Any grade neutropenia, any grade anaemia, any grade fatigue, any grade nausea, any grade vomiting, any grade decreased appetite, any grade headache, any grade diarrhoea and any grade palmar-plantar erythrodysesthesia in patients with *BRCA*-mutated HER2-negative breast cancer treated with PARPi versus those treated with monochemotherapy (controls). (B) Safety profile overview. Grade 3–4 neutropenia and grade 3–4 anaemia in *BRCA*-mutated HER2-negative patients treated with PARPi versus those treated with monochemotherapy (controls). (C) Treatment discontinuation rate in *BRCA*-mutated HER2-negative patients treated with PARPi versus those treated with monochemotherapy (controls). The size of the squares is proportional to the weight of each study. (D) Time to clinically meaningful deterioration in quality of life in patients with *BRCA*-mutated HER2-negative metastatic breast cancer treated with PARPi versus those treated with monochemotherapy (controls). The size of the squares is proportional to the weight of each study. PARPi, PARP inhibitors.

Adverse events of any grade

Figure 5A summarises the comparative safety profile in terms of AEs of any grade in the PARPi group versus chemotherapy group. Overall, 481 of 491 patients (98.0%) in the PARPi group and 211 of 217 (97.2%) in the chemotherapy group presented AEs of any grade (OR 1.37 (95% CI 0.49 to 3.85, p=0.546)) (I^2=0.0%, p=0.691).

Neutropenia

Neutropenia of any grade was reported in 155 of 491 patients (31.6%) in the PARPi group and in 99 of 217 (45.6%) in the chemotherapy group (OR 0.53 (95% CI 0.29 to 0.96, p=0.036)) (I^2=68.6%, p=0.075).

Anaemia

Anaemia of any grade was reported in 233 of 491 patients (47.5%) in the PARPi group and 47 of 217 (21.7%) in the chemotherapy group (OR 3.07, 95% CI 1.16 to 8.10, p=0.024)) (I^2=85.3%, p=0.009).

Fatigue

Fatigue of any grade was reported in 203 of 491 patients (41.3%) in the PARPi group and 75 of 217 (34.6%) in the chemotherapy group (OR 1.35 (95% CI 0.96 to 1.90, p=0.083)) (I^2=0.0%, p=0.992).

Nausea

Nausea of any grade was reported in 258 of 491 patients (52.5%) in the PARPi group and 91 of 217 (41.9%) in the chemotherapy group (OR 1.63 (95% CI 0.70 to 3.81, p=0.256)) (I^2=84.8%, p=0.010).

Vomiting

Vomiting of any grade was reported in 132 of 491 patients (26.9%) in the PARPi group and 43 of 217 (19.8%) in the chemotherapy group (OR 1.56 (95% CI 0.75 to 3.23, p=0.234)) (I^2=69.3%, p=0.071).

Decreased appetite

Decreased appetite of any grade was reported in 94 of 491 patients (19.1%) in the PARPi group and 39 of 217 (18.0%) in the chemotherapy group (OR 1.08 (95% CI 0.71 to 1.63, p=0.734)) (I^2=0.0%, p=0.396).

Headache

Headache of any grade was reported in 134 of 491 patients (27.3%) in the PARPi group and 42 of 217 (19.4%) in

the chemotherapy group (OR 1.57 (95% CI 1.06 to 2.33, p=0.024)) (I^2=0.0, p=0.627).

Diarrhoea

Diarrhoea of any grade was reported in 105 of 491 patients (21.3%) in the PARPi group and 53 of 217 (24.4%) in the chemotherapy group (OR 0.84 (95% CI 0.58 to 1.23, p=0.369)) (I^2=0.0, p=0.725).

Palmar-plantar erythrodysesthesia syndrome

Palmar-plantar erythrodysesthesia syndrome of any grade was reported in 5 of 491 patients (1.0%) in the PARPi group and 47 of 217 (21.7%) in the chemotherapy group (OR 0.04 (95% CI 0.02 to 0.10, p<0.001)) (I^2=0.0, p=0.393).

Grade 3–4 adverse events

Figure 5B summarises the comparative safety profile for grade 3–4 AEs in the PARPi group versus chemotherapy group. Overall, 148 of 491 (30.1%) patients in the PARPi group and 78 of 217 (35.9%) in the chemotherapy group presented any grade 3–4 AEs (OR 0.76 (95% CI 0.43 to 1.33, p=0.336)) (I^2=62.6%, p=0.102).

Neutropenia

Grade 3–4 neutropenia was reported in 79 of 491 patients (16.1%) in the PARPi group and 68 of 217 (31.3%) in the chemotherapy group (OR 0.40 (95% CI 0.23 to 0.67, p=0.001)) (I^2=43.8%, p=0.182).

Anaemia

Grade 3–4 anaemia was reported in 145 of 491 patients (29.5%) in the PARPi group and 10 of 217 (4.6%) in the chemotherapy group (OR 7.69 (95% CI 2.55 to 23.19, p<0.001)) (I^2=61.9%, p=0.105).

Treatment discontinuation rate and time to deterioration in QoL

Overall, 32 of 491 patients (6.5%) in the PARPi group and 19 of 217 (8.8%) in the chemotherapy group discontinued the treatment due to AEs (OR 0.72 (95% CI 0.40 to 1.31, p=0.287)) (I^2=0.0%, p=0.691) (figure 5C).

The 30-item EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) Score was used to assess patients' health-related QoL in both trials; an increase or decrease of at least 10 points was considered a clinically meaningful variation.

In the OlympiAD and EMBRACA trials, respectively, the median time to a clinically meaningful deterioration in QoL was not reached and was 24.3 months in the PARPi group versus 15.3 months and 6.3 months in the chemotherapy group.

As compared with monochemotherapy, single-agent PARPi was associated with a significant delayed time to clinically meaningful deterioration in QoL (HR 0.40 (95% CI 0.29 to 0.54, p<0.001)) (I^2=0.0%, p=0.671) (figure 5D).

DISCUSSION

This meta-analysis assessed the activity, efficacy and safety of single-agent PARPi in patients with *BRCA*-mutated HER2-negative metastatic breast cancer. In comparison to standard monochemotherapy, single-agent PARPi was associated with a significantly improved PFS and ORR and no difference in OS. Use of single-agent PARPi was associated with a significantly increased risk of anaemia and any grade headache, but a reduced risk of neutropenia and any grade palmar-plantar erythrodysesthesia syndrome, as compared with monochemotherapy. Notably, use of single-agent PARPi significantly delayed time to clinically meaningful QoL deterioration.

Overall, treatment with single-agent PARPi showed significant activity over standard monochemotherapy by halving the probability of developing disease progression (HR 0.56 (95% CI 0.45 to 0.70, p<0.001)) and by inducing a fourfold increased chance of tumour response (OR 4.15 (95% CI 2.82 to 6.10, p<0.001)). The significantly increased tumour shrinkage with single-agent PARPi suggests that this treatment can also be a feasible option in patients with visceral symptomatic or rapidly progressing disease. Although no significant benefit was observed in terms of OS, both trials were not powered to detect differences in this end point.

While the majority of women with mutated *BRCA1* are at risk of developing triple-negative breast cancer, tumours arising in those carrying a *BRCA2* mutation more commonly express the hormone receptors.[14] Both patients were included in a similar proportion in the OlympiAD and EMBRACA trials. With an exploratory analysis assessing the activity of single-agent PARPi according to hormone receptor status, the improvement in PFS reached statistical significance only for patients with TNBC (HR 0.51 (95% CI 0.37 to 0.71, p<0.001)) and not for those with hormone receptor-positive tumours (HR 0.62 (95% CI 0.36 to 1.07, p=0.085)). Therefore, given also the poor prognosis and the limited treatment options, the benefit derived from single-agent PARPi may be particularly relevant for the management of the TNBC population.

Importantly, it is still unclear which is the best sequencing of treatments for patients with *BRCA*-mutated HER2-negative metastatic breast cancer. According to recent guidelines, platinum-based chemotherapy is the preferred treatment option for these patients.[15 16] Based on the TNT study results, among the 48 patients with *BRCA*-mutated (any hormone receptor and HER2 status) metastatic breast cancer, treatment with carboplatin significantly increased ORR (68% vs 33.3%, p=0.03) and PFS (6.8 months vs 4.4 months, p=0.002) as compared with docetaxel.[17] Hence, a growing proportion of patients with newly diagnosed *BRCA*-mutated HER2-negative metastatic breast cancer is expected to receive treatment with platinum agents. In the OlympiAD and EMBRACA trials, a total of 162 (22.1%) patients had prior exposure to platinum-based regimens. In the present meta-analysis

no significant difference in PFS between the PARPi and chemotherapy groups in the prior platinum cohort (HR 0.70 (95% CI 0.47 to 1.05, p=0.085)) was observed, while the benefit from the use of single-agent PARPi became clearer in the no prior platinum cohort (HR 0.55 (95% CI 0.44 to 0.69, p<0.001)). Noteworthy, the comparator arm in both the OlympiAD and EMBRACA trials was composed of a platinum-free regimen.

Recently, the phase II trial BROCADE showed that the addition of veliparib to carboplatin/paclitaxel was associated with a numerically although not statistically significantly increased PFS (14.1 months vs 12.3 months, HR 0.79 (95% CI 0.54 to 1.16, p=0.227)) and OS (28.3 months vs 25.9 months, HR 0.75 (95% CI 0.5 to 1.12, p=0.156));[18] as in the neoadjuvant setting, this combination does not seem to be a promising option.[19] Similarly, patients receiving veliparib and temozolomide experienced significantly lower PFS, OS and ORR as compared with those treated with carboplatin/paclitaxel, confirming the limited activity of temozolomide in metastatic breast cancer, even with the addition of a PARPi.[18 20] Although the combination with chemotherapy does not seem to be a strategy of particular interest, it would be important to have a head-to head comparison between PARPi and the platinum-based regimen as well as to further investigate the activity of PARPi in platinum-exposed patients in order to better clarify the optimal sequence of treatment in patients with *BRCA*-mutated HER2-negative metastatic breast cancer.

As recently shown in the phase I/II trial MEDIOLA, the combination of PARPi and immune checkpoint inhibitors appears to be a promising combination for these patients.[21] These results, together with the enhanced immunogenicity of *BRCA*-mutated cancers, provide strong scientific rationale to further explore this strategy to potentiate the activity of PARPi.[22] Results of several ongoing trials exploring this combination are awaited.

Our meta-analysis also provides an overview of the expected safety and tolerance of single-agent PARPi that can be of value to discuss treatment risk and benefit ratio with patients. Single-agent PARPi significantly reduced the risk of developing some of the most common side effects of chemotherapy such as neutropenia (OR 0.53 (95% CI 0.29 to 0.96)) and any grade palmar-plantar erythrodysesthesia syndrome (OR 0.04 (95% CI 0.02 to 0.10)); however, this treatment was associated with an increased risk of anaemia (OR 3.07 (95% CI 1.16 to 8.10)) and any grade headache (OR 1.57 (95% CI 1.06 to 2.33)). As shown in an exploratory analysis within the OlympiAD Study, the onset of anaemia during treatment with olaparib occurs early and rarely leads to treatment discontinuation. Unlike anaemia related to cytotoxic chemotherapy, it remains fairly constant throughout exposure to olaparib, not increasing transfusion requirements with time.[23]

Importantly, treatment with single-agent PARPi significantly delayed time to clinically meaningful deterioration in QoL (HR 0.40 (95% CI 0.29 to 0.54)) as compared with monochemotherapy. In the last years, the evaluation of QoL and the use of patient-reported outcomes (PROs) has been implemented in the trials conducted in the metastatic setting, where the maintenance of QoL is a crucial goal to be accomplished.[24] The integration of PROs into routine care has recently demonstrated to also improve the survival outcomes of patients with metastatic cancer.[25] This further highlights that, in addition to physician's reporting, patient's assessment of AEs severity provides additional important information to better estimate the overall risk and benefit ratio of a given anticancer treatment.[26] The findings that single-agent PARPi was well tolerated and also the delayed time to clinically meaningful QoL deterioration supports the prominent role of these oral agents in the management of patients with *BRCA*-mutated HER2-negative metastatic breast cancer; this also extends the time until chemotherapy is necessary.

Some limitations of the present meta-analysis should be acknowledged. Only two RCTs were included, and one was available only in abstract form. Moreover, this meta-analysis is based on abstracted data and not on individual patient-level data. Nevertheless, we believe that all the analyses performed may help in giving a point estimate on the role of single-agent PARPi in the management of patients with *BRCA*-mutated HER2-negative metastatic breast cancer.

In conclusion, single-agent PARPi showed to be an effective, well tolerated and useful treatment in maintaining QoL of patients with *BRCA*-mutated HER2-negative metastatic breast cancer. Although the optimal sequence as well as the possible combination strategies are not still determined, this treatment can now be regarded as a clinically relevant additional option in the therapeutic armamentarium of these patients.

Author affiliations
[1]Department of Medical Oncology, Institut Jules Bordet, Université Libre de Bruxelles (U.L.B.), Bruxelles, Belgium
[2]Department of Medical Oncology, Oncologia Medica 2, Ospedale Policlinico San Martino, Genova, Italy
[3]Unit of Clinical Epidemiology, Ospedale Policlinico San Martino, Genova, Italy
[4]Department of Hemato-Oncology, CISSS Montérégie-Centre/Hôpital Charles-Le Moyne, centre affilié de l'Université de Sherbrooke, Quebec, Canada
[5]Department I of Internal Medicine, Center of Integrated Oncology Cologne Bonn, University of Cologne, Cologne, Germany
[6]Breast Cancer Translational Research Laboratory, Institute Jules Bordet, Université Libre de Bruxelles (U.L.B.), Bruxelles, Belgium
[7]Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, Ospedale Policlinico San Martino, Department of Internal Medicine and Medical Specialties (DIMI), University of Genova, Genova, Italy

Acknowledgements ML thanks the European Society for Medical Oncology (ESMO) for support in the form of a Translational Research Fellowship at the Institut Jules Bordet (Brussels, Belgium).

Contributors All the authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data, giving final approval of the version to be submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests LDM received personal fees from Novartis Pharma AG, Roche-Genentech, Ipsen, Astrazeneca, Takeda, Eli Lilly outside the submitted work. EdA received honoraria from Roche-Genentech, research grant from Roche-Genentech (to the institution) and travel grants from Roche-Genentech and GlaxoSmithKline outside the submitted work. ML served as a consultant for Teva outside the submitted work.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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