Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial

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Summary

Background Late-line treatment options for patients with ovarian cancer are few, with the proportion of patients achieving an overall response typically less than 10%, and median overall survival after third-line therapy of 5–9 months. In this study (QUADRA), we investigated the activity of niraparib monotherapy as the fourth or later line of therapy.

Methods QUADRA was a multicentre, open-label, single-arm, phase 2 study that evaluated the safety and activity of niraparib in adult patients (≥18 years) with relapsed, high-grade serous (grade 2 or 3) epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with three or more previous chemotherapy regimens. The study was done in the USA and Canada, and 56 sites screened patients (50 sites treated at least one patient). Patients received oral niraparib 300 mg once daily continuously, beginning on day 1 and every cycle (28 days) thereafter until disease progression. The primary objective was the proportion of patients achieving an investigator-assessed confirmed overall response in patients with homologous recombination deficiency (HRD)-positive tumours (including patients with *BRCA* and without *BRCA* mutations) sensitive to their last platinum-based therapy who had received three or four previous anticancer therapy regimens (primary efficacy population). Efficacy analyses were additionally done in all dosed patients with measurable disease at baseline.

Findings Between April 1, 2015 and Nov 1, 2017, we screened 729 patients for eligibility and enrolled 463 patients, who were initiated on niraparib therapy. At the time of database lock (April 11, 2018), enrolment had closed and the study was ongoing, with 21 patients still on treatment. Patients had received a median of four (IQR 3–5) previous lines of therapy, and the median follow-up for overall survival was 12·2 months (IQR 3·7–22·1). 151 (33%) of 463 patients were resistant and 161 (35%) of 463 patients were refractory to the last administered platinum therapy. 13 (28%) of 47 patients in the primary efficacy population achieved an overall response according to RECIST (95% CI 15·6–42·6; one-sided p=0·00053). The most common drug-related grade 3 or worse treatment-emergent adverse events were anaemia (113 [24%] of 463 patients) and thrombocytopenia (95 [21%] of 463 patients). The most common treatment-emergent serious adverse events were small intestinal obstruction (34 [7%] of 463 patients), thrombocytopenia (34 [7%] of 463 patients), and vomiting (27 [6%] of 463 patients). One death due to gastric haemorrhage was considered treatment related.

Interpretation We observed clinically relevant activity of niraparib among women with heavily pretreated ovarian cancer, especially in patients with HRD-positive platinum-sensitive disease, which includes not only patients with a *BRCA* mutation but also a population with *BRCA* wild-type disease. We identified no new safety signals. Our data support expansion of the treatment indication for poly(ADP-ribose) polymerase inhibitors to include patients with HRD-positive ovarian cancer beyond those with *BRCA* mutations.

Funding Tesaro.

Introduction

Ovarian cancer is the most common cause of gynaecological cancer death in the USA, with 22 240 new cases estimated to be diagnosed in 2018.[1] Most patients with ovarian cancer present with advanced disease at diagnosis. The standard of care for front-line therapy is a combination of surgical debulking and platinum-based chemotherapy plus bevacizumab in some settings.[2] Although most patients with advanced ovarian cancer respond to initial therapy, 70% will relapse and ultimately succumb to their disease.[3]

Treatment decisions in subsequent lines of therapy are less defined. Factors that affect treatment decisions include the duration of response to the previous chemotherapy, number of lines of chemotherapy, molecular signature, histological subtype, and residual toxic effects

Research in context

Evidence before this study

We searched PubMed for studies published between Jan 1, 2010, and Sept 24, 2018, with no language restrictions, using the search terms "Poly(ADP-ribose) polymerase" or "PARP" and "ovarian cancer" and "treatment", restricting the search results to only include clinical trials. We manually excluded manuscripts concerning combination therapies, maintenance therapies, or phase 0 or phase 1 trials, and found eight manuscripts describing results from seven phase 2 trials, but identified no phase 3 trials. Most of the trials (five) were small phase 2 trials (<100 patients). The remaining large phase 2 trials comprised one trial of olaparib and one trial of rucaparib. The olaparib trial restricted enrolment to patients with germline *BRCA* mutations with platinum-sensitive or platinum-resistant disease, and the rucaparib trial enrolled platinum-sensitive patients regardless of *BRCA* mutational status.

Added value of this study

The QUADRA trial results included patients with primary or acquired platinum-resistant or platinum-refractory high-grade ovarian cancer, and *BRCA*-mutated and *BRCA* wild-type, homologous recombination deficiency (HRD)-positive and HRD-negative tumours. To our knowledge, this is the first trial to report the efficacy and safety of a poly(ADP-ribose) polymerase inhibitor in such a broad patient population. Patient demographics and baseline disease characteristics in this study are reflective of real-world patients with late-line ovarian cancer, for whom all effective treatment options have often been exhausted.

Implications of all the available evidence

Patients with late-line ovarian cancer represent a particularly challenging population to treat, with few effective treatment options. QUADRA showed that niraparib had clinical activity in patients across the spectrum of biomarkers and sensitivity to chemotherapy. Niraparib could be a meaningful treatment option and an alternative to established chemotherapy regimens for late-line treatment of patients with ovarian cancer.

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from previous therapies.[4] For patients with disease that is sensitive to first-line treatment (platinum-free interval >6 months) the standard of care for second-line therapy is currently retreatment with platinum-based chemotherapy.[2,5] Because of residual toxic effects and development of hypersensitivity, patients do not commonly receive more than three lines of platinum-based therapy, even if their disease remains platinum-sensitive.[6] Additionally, maintenance therapy following platinum-based chemotherapy has made the definition of platinum-sensitive no longer representative of the population originally described by this term. Regardless of platinum status, the proportion of patients who achieve a response, median progression-free survival, and median overall survival tend to decline with each retreatment.[7–9] The median duration of overall survival in patients who have progressed after a third line of therapy is less than 1 year.[7–9]

Poly(ADP-ribose) polymerase (PARP) inhibitors are a new treatment approach for ovarian cancer and other cancers with underlying impaired DNA repair. Inhibition of PARP leads to propagation of single-strand DNA breaks and accumulation of double-strand breaks, which require repair by homologous recombination repair mechanisms. Therefore, PARP inhibitors were initially believed to work through the concept of synthetic lethality in tumours with homologous recombination deficiency (HRD), such as *BRCA*-mutated tumours.[10] PARP inhibitors have enhanced anticancer activity in vitro in *BRCA*-mutated cancer cells, which led to initial testing of PARP inhibitors as a single-agent treatment in patients with *BRCA*-mutated cancers.[10]

Further preclinical work indicates that PARP inhibition with niraparib leads to tumour growth inhibition in patient-derived xenograft models, regardless of *BRCA* or HRD status.[11,12] These studies show that although *BRCA*-mutated and HRD-positive patient-derived xenograft tumours are more likely to achieve regression, HRD-negative tumours also achieved substantial growth inhibition.[13]

The high exposure of tumours to niraparib—driven by the high bioavailability, membrane permeability, lipophilicity, and large volume of distribution of this drug—could drive the activity shown in patient-derived xenograft models and patients with tumours not typically thought of as sensitive to PARP inhibitors, including those with *BRCA* wild-type tumours.[14] This hypothesis is consistent with the original description of non-clinical studies, which showed that cells with *BRCA* mutations had greater, but not exclusive, sensitivity to PARP inhibitors and that *BRCA* wild-type tumour cells could be killed with higher drug concentrations.[15]

A pivotal phase 3 trial[16] of niraparib (ENGOT-OV16/NOVA) showed a large benefit from niraparib maintenance therapy, which occurred along a graduated continuum. The strongest effect was observed in patients with *BRCA*-mutated tumours (hazard ratio [HR] 0·27, 95% CI 0·17–0·41), followed by patients with HRD-positive and *BRCA* wild-type tumours (0·38, 0·24–0·59) and those with HRD-negative tumours (0·58, 0·36–0·92).[16] The HRD-negative subgroup showed similar benefit to the approved drug bevacizumab in the overall recurrent platinum-sensitive ovarian cancer population.[17] The US Food and Drug Administration and European Medicines Agency approved niraparib for

maintenance treatment of all patients with recurrent ovarian cancer in complete or partial response to their last platinum-based chemotherapy, regardless of *BRCA* or HRD status.[18,19]

Data from a phase 1 study of niraparib provided the earliest evidence of a clinical continuum of benefit.[20] The proportion of patients with recurrent ovarian cancer who received niraparib in a treatment setting achieving Response Evaluation Criteria in Solid Tumors (RECIST) response was highest in those with *BRCA*-mutated platinum-sensitive disease (five [50%, 95% CI 19–81] of ten patients had an overall response). A continuum of the proportion of patients achieving a response was defined by *BRCA* status and the clinical biomarker of platinum sensitivity. The numbers of patients achieving an overall response were reported as three (33%, 95% CI 7–70) of nine patients with *BRCA*-mutated platinum-resistant disease and one (33%, 95% CI 1–91) of three patients with *BRCA* wild-type platinum-sensitive disease. One (5%, 95% CI <1–26) of 19 patients with *BRCA* wild-type, platinum-resistant disease who were given niraparib achieved an overall response, with a clinical benefit (defined as having a RECIST or CA 125 Gynecological Cancer Intergroup partial response, or disease stabilisation for longer than 16 weeks, or any combination of these three) seen in six (32%, 95% CI 13–57) of 19 patients.[20] These data support that, in addition to a molecular biomarker of *BRCA* deficiency, responsiveness or sensitivity to platinum therapy can also serve as a surrogate clinical biomarker for niraparib activity. Consistent with the ENGOT-OV16/NOVA findings,[16] data from the phase 1 study[20] showed a graduated spectrum of clinical benefit, with the greatest clinical benefit in those with *BRCA*-mutated platinum-sensitive tumours and decreased, yet clinically meaningful, benefit in platinum-resistant *BRCA* wild-type tumours.

See Online for appendix

Patients with recurrent ovarian cancer often receive multiple lines of chemotherapy before succumbing to their disease. In the late-line treatment setting, chemotherapy regimens result in responses in 5–10% of patients.[7–9] In this late-line treatment setting, the approved use of PARP inhibitors is restricted to patients with *BRCA* mutations;[21,22] however, only around 20% of patients with ovarian cancer have a *BRCA* mutation,[23] and treatments for patients without this mutation remain an unmet need.

On the basis of the early phase 1 results and the broad activity of niraparib in the maintenance setting, the QUADRA trial was designed to enable evaluation of antitumour activity and safety of niraparib in late-line recurrent ovarian cancer, regardless of platinum status and molecular biomarkers.

Methods

Study design and participants

QUADRA was a multicentre, open-label, single-arm, phase 2 study done at 56 sites in the USA and Canada (50 sites treated at least one patient). Eligible patients were adults (aged 18 years or older) with metastatic, relapsed, high-grade serous (grade 2 or 3) epithelial ovarian, fallopian tube, or primary peritoneal cancer, who had been previously treated with chemotherapy. Patients must have received three or more previous chemotherapy regimens (including, but not limited to, gemcitabine, doxorubicin, topotecan, carboplatin, oxaliplatin, cisplatin, bevacizumab, or PARP inhibitors as single agents or in combination as per standard of care). Patients were required to have measurable disease according to RECIST version 1.1, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. All patients had to undergo tumour HRD testing using the Myriad myChoice HRD test (Myriad Genetics; Salt Lake City, Utah, USA) and blood germline *BRCA*-mutated status testing. The myChoice HRD test is a central laboratory DNA-based test for HRD that quantifies genomic instability of the tumour and, in parallel, detects and classifies *BRCA1* or *BRCA2* variants.[16] The myChoice HRD test gives a three-biomarker HRD score, which along with tumour *BRCA* mutation detection is used to define HRD-positive and HRD-negative tumours. Full inclusion and exclusion criteria are listed in the protocol (appendix p 5).

All patients provided written informed consent before participation in the study. This study was done in compliance with Good Clinical Practice and all applicable local laws. Each site received institutional review board or ethics approval.

The eligibility criteria in the original study protocol did not have an upper limit on the number of previous lines of chemotherapy, patients with primary platinum-resistant and platinum-refractory disease were not excluded, and there were no restrictions on *BRCA* or HRD status. After initial enrolment of 292 patients, the study was amended (Oct 30, 2015) to restrict enrolment to patients who received three or four previous lines of chemotherapy, and who had a response to first-line platinum-based therapy lasting at least 6 months. A second study amendment (May 24, 2016) closed the study to patients with HRD-negative tumours.

Procedures

Patients received oral niraparib 300 mg once daily continuously, beginning on day 1 and every cycle (28 days) thereafter until the patient discontinued study treatment (for example, due to disease progression, unacceptable toxicity, or withdrawal of consent). Dose interruption (no longer than 28 days) and dose reductions to 200 mg once daily, and subsequently to 100 mg once daily, were done as required and according to dose modification guidelines. No further dose reductions were allowed. Dose interruption or reduction to 200 mg, then subsequently to 100 mg, was permitted at any time for any adverse event considered intolerable by the patient.

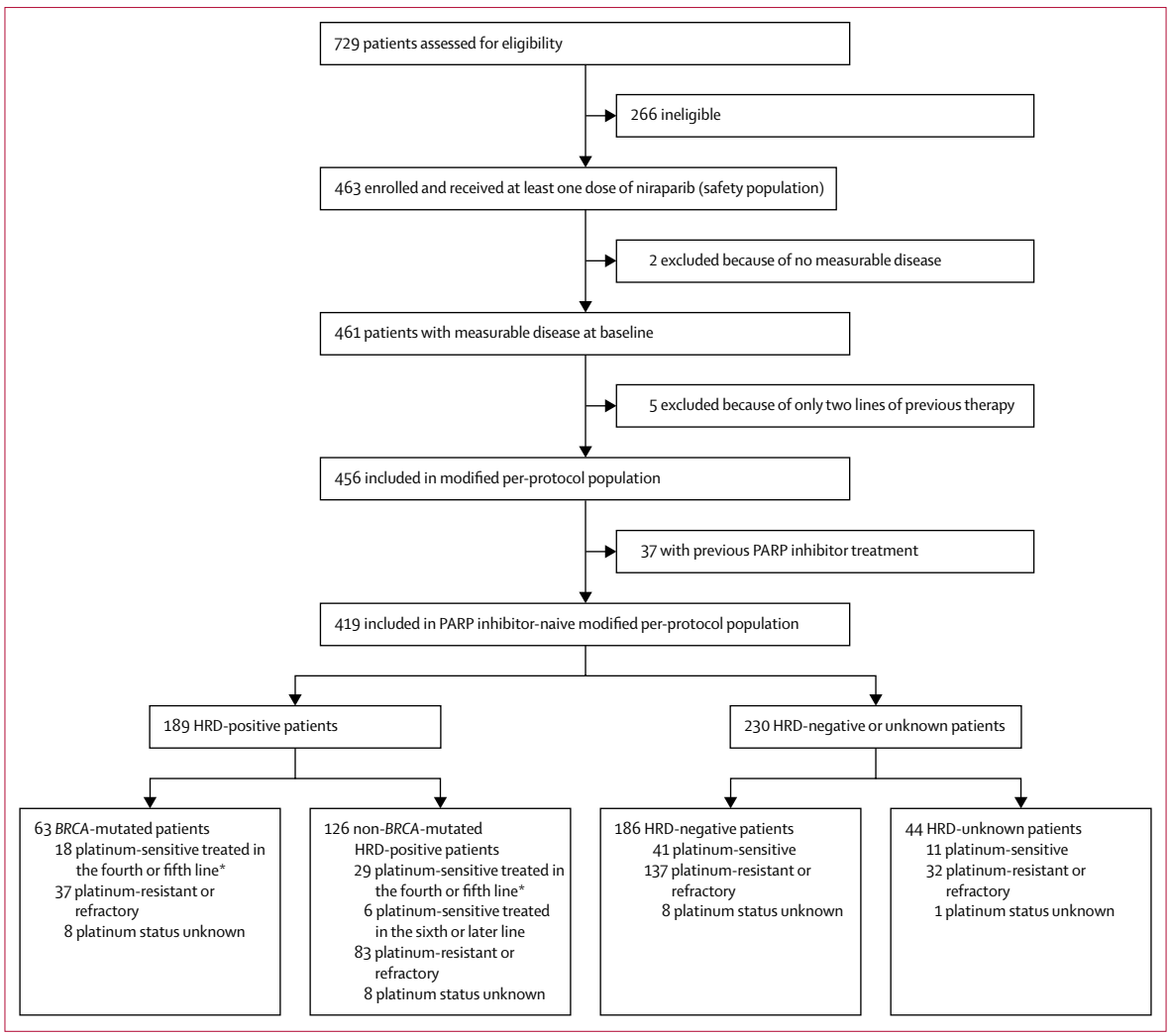

Figure 1: **Trial profile**
HRD=homologous recombination deficiency. PARP=poly(ADP-ribose) polymerase. *Included in the 47 patients in the primary efficacy population.

RECIST version 1.1 tumour assessment via CT or MRI of the abdomen and pelvis and clinically indicated areas was required every 8 weeks (±7 days) from cycle 1, day 1 for 6 months, and then every 12 weeks until progression. Safety monitoring was done weekly during the first cycle and then every 4 weeks for subsequent cycles.

After treatment was discontinued, tumour assessments and safety monitoring were done every 12 weeks until loss to follow-up or death.

All adverse events were classified using the Medical Dictionary for Regulatory Activities version 20.0 or later. The severity of the toxic effects was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. All adverse events and serious adverse events were collected and recorded for each patient from the day of signing the informed consent form until the end of treatment visit. New serious adverse events (including deaths) were collected for 30 days after the last dose of study treatment. Adverse events of special interest and serious adverse events assessed as related to study treatment were reported throughout the study and post-treatment assessments. If an investigator became aware of a serious adverse event after the 30-day follow-up period after treatment discontinuation and considered it related to the investigational product, the investigator should have reported the serious adverse event to the study sponsor.

Outcomes

The prespecified primary endpoint was the proportion of patients achieving an investigator-assessed confirmed overall response. We tested this endpoint hierarchically, first in patients with HRD-positive tumours sensitive to the last platinum-based therapy (primary efficacy population following the ENGOT-OV16/NOVA study[16] results, which showed an expansion of niraparib activity

	Safety population (n=463)
Age (years)	65 (29–91; 58–71)
Age category (years)	
18–64	231 (50%)
65–74	170 (37%)
≥75	62 (13%)
Race	
White	394 (85%)
Black	20 (4%)
Asian	16 (3%)
Other or unknown	33 (7%)
Time from diagnosis (years)	4·0 (2·8–5·8)
Tumour site	
Ovarian	367 (79%)
Primary peritoneal	47 (10%)
Fallopian tube	49 (11%)
Weight (kg)	70 (36–147; 58–82)
Eastern Cooperative Oncology Group performance status	
0	267 (58%)
1	196 (42%)
HRD status	
HRD-positive	222 (48%)
BRCA-mutated	87 (19%)
BRCA-wild type or *BRCA*-unknown and HRD-positive	135 (29%)
HRD-negative	195 (42%)
HRD-unknown	46 (10%)
BRCA status	
Germline *BRCA*-mutated	58 (13%)
Somatic *BRCA*-mutated	29 (6%)
Number of previous lines of therapy	
2	5 (1%)
3	188 (41%)
4	144 (31%)
≥5	126 (27%)
Time from last chemotherapy to first dose (months)	2 (1–73; 1–4)
Previous platinum courses	463 (100%)
1	37 (8%)
2	235 (51%)
3	147 (32%)
4	37 (8%)
≥5	7 (2%)
Patients with previous taxane treatment	461 (>99%)
Patients with previous liposomal doxorubicin treatment	325 (70%)
Patients with previous bevacizumab treatment	288 (62%)
Patients with previous gemcitabine treatment	271 (59%)
Platinum status	
Platinum-sensitive (platinum-free interval >6 months after most recent previous platinum-based therapy)	120 (26%)
Platinum-resistant (platinum-free interval 1–6 months)	151 (33%)
Platinum-refractory (platinum-free interval <28 days)	161 (35%)
Platinum-unknown	31 (7%)

Data are median (range; IQR), median (IQR), or n (%). Platinum-free interval defined as time from last platinum administration until the next documented disease progression. HRD=homologous recombination deficiency.

Table 1: **Patient demographics and baseline characteristics**

beyond the *BRCA*-mutated subgroup) who had received three or four previous anticancer therapies, followed by patients in broader groups to include all those with platinum-sensitive tumours who had received three or four previous lines of therapy (key secondary endpoint 1), those with platinum-sensitive or platinum-resistant tumours who had received three or four previous lines of therapy (key secondary endpoint 2), and all patients treated in the study, including those with HRD-negative or HRD-unknown tumours (key secondary endpoint 3). Other secondary endpoints were the proportion of patients who achieved an overall response, duration of response, the proportion of patients with disease control, progression-free survival, time to first subsequent treatment, and overall survival in all patients who had received three or four previous lines of anticancer therapy and in all patients regardless of previous lines of anticancer therapy, and safety. The secondary endpoint of time to first subsequent treatment will be analysed and reported separately. We did prespecified exploratory subgroup analyses by *BRCA* and HRD biomarker status and response to previous platinum-based therapy.

Statistical analysis

With at least 45 patients enrolled in the primary efficacy population (patients with HRD-positive tumours who had received three or four previous lines of anticancer therapy and were sensitive to the last platinum-based therapy), this study was designed to have at least 90% power at a one-sided significance level of 2·5% to reject the null hypothesis of a proportion of patients with an overall response of 10% or less in this population, assuming a true proportion of 30% of patients achieving a response. We calculated the proportion of patients achieving a response and 95% CIs with a one-sided p value for testing the null hypothesis on the basis of the binomial distribution.

We used a hierarchical testing procedure to control the overall significance level (one-sided 2·5%) from the primary endpoint sequentially through the key secondary endpoints. We calculated binary endpoints (proportion of patients achieving an overall response and proportion of patients with disease control) and 95% CIs using the exact method based on the binomial distribution. We measured time-to-event endpoints (duration of response,

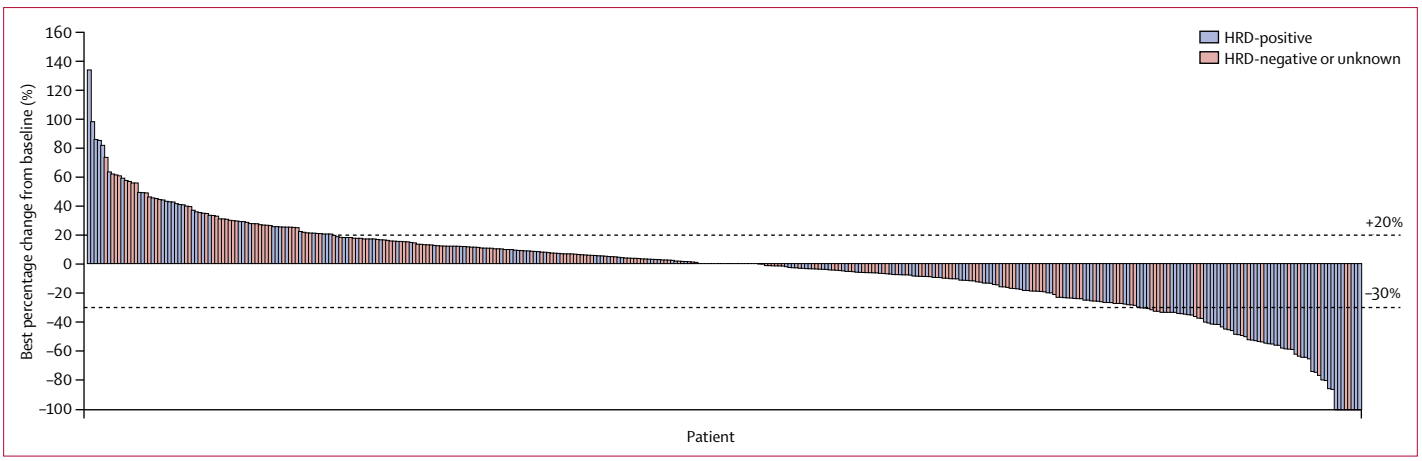

Figure 2: **Tumour response in the modified per-protocol population**
All patients with at least one evaluable post-baseline tumour assessment in the modified per-protocol population (n=380). Best response for target lesions by each patient is based on the maximal percentage of reduction in the sum of diameters from baseline. Horizontal dotted lines represent +20% (progressive disease: at least a 20% increase in the sum of diameters of target lesions) and –30% (partial response: at least a 30% decrease in the sum of diameters of target lesions). HRD=homologous recombination deficiency.

overall survival, and progression-free survival) from study treatment initiation and calculated medians and accompanying 95% CIs with the Kaplan-Meier method.

Activity analyses were primarily done in all dosed patients with measurable disease at baseline. We also did analyses in the response-evaluable population, defined as all patients with at least one evaluable post-baseline tumour scan. A modified per-protocol population was derived by excluding five patients who had received only two previous lines of therapy. The PARP inhibitor-naive modified per-protocol population excluded 37 patients who had received a PARP inhibitor as a previous therapy (figure 1).

We did post-hoc analyses to describe clinically meaningful disease stabilisation in this late-line treatment population. The proportion of patients with clinical benefit has been positively associated with overall survival,[24,25] particularly when patients remain progression free for 6 months or longer.[26] Therefore, we assessed the proportion of patients achieving clinical benefit at 16 and 24 weeks, defined as the proportion of patients with a complete or partial response or patients with stable disease with a duration of at least 16 and 24 weeks.

We did further post-hoc exploratory analyses to assess whether niraparib treatment contributed to disease stabilisation beyond the natural history of a patient's disease. Each individual patient's time to progression on the most recent previous therapy was compared with time to progression with niraparib treatment, and a progression-free survival ratio was defined for each patient as:

$$\text{Progression-free survival ratio} = \frac{\text{Progression-free survival on study with investigational niraparib monotherapy}}{\text{Progression-free survival on therapy immediately before study entry}}$$

Progression-free survival on therapy immediately before study entry was calculated in days as (documented disease progression date before study entry – most recent previous therapy start date + 1); if the disease progression date was missing, the first dose date in QUADRA was used as a proxy for progression.

The natural history of ovarian cancer suggests an expected decrease in the proportion of patients achieving a response and the duration of response with each subsequent line of therapy, which would result in a progression-free survival ratio of less than 1·0.[7,9] A progression-free survival ratio greater than 1·3 has been used as a conservative estimate of treatment benefit in clinical trials of targeted therapy in order to capture clinically meaningful benefit beyond formal partial response and complete response criteria.[27,28]

All statistical analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, number NCT02354586.

Role of the funding source

This study was designed by the sponsor and the study investigators. Data were collected by the investigators and analysed by the sponsor. All authors, including those employed by the sponsor of the study, contributed to the interpretation of the data and the writing of the manuscript. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between April 1, 2015, and Nov 1, 2017, 729 patients were assessed for eligibility, of whom 463 patients were enrolled and received at least one dose of niraparib (safety population; figure 1). At the time of database lock (April 11, 2018), enrolment had closed and the study was

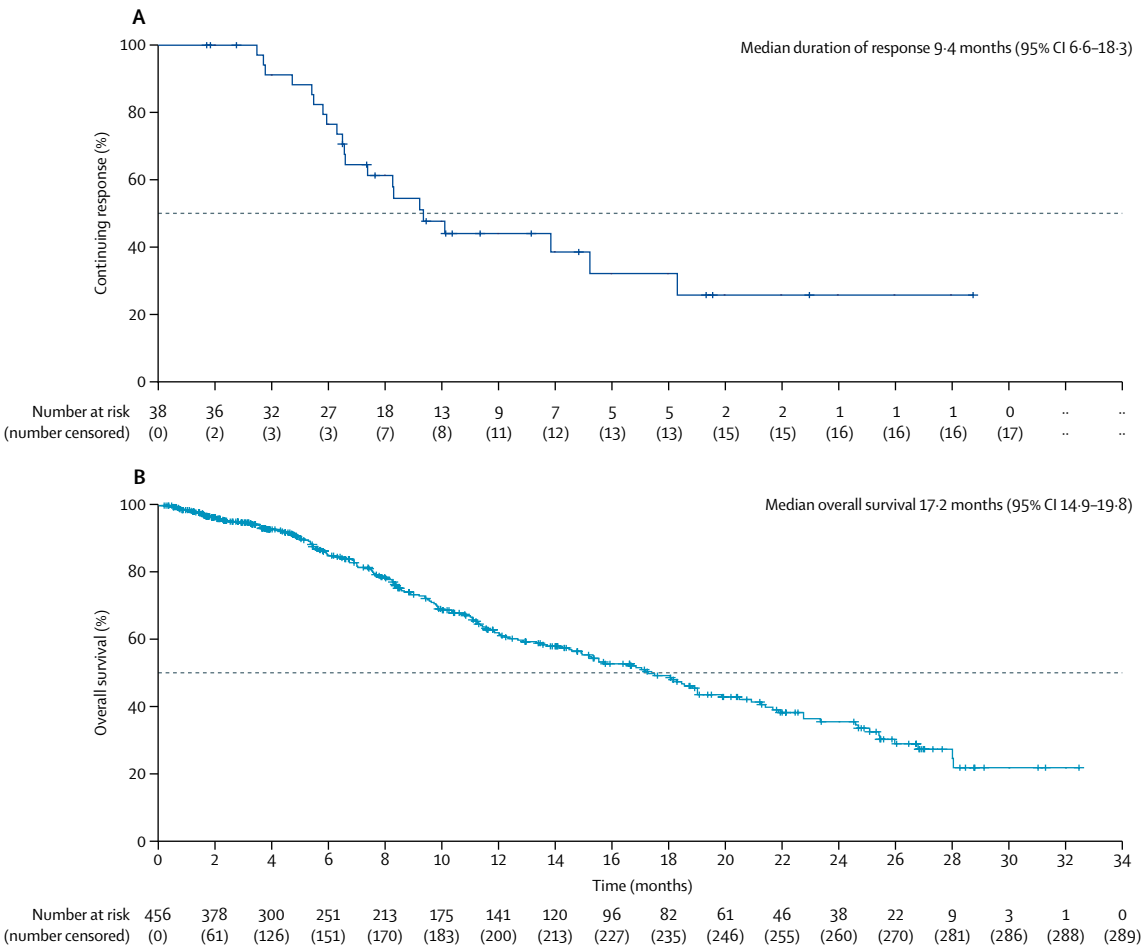

Figure 3: **Kaplan-Meier graphs of duration of response (A) and overall survival (B) in the modified per-protocol population**
Horizontal dashed lines represent 50% (the median).

	BRCA-mutated (n=63)	HRD-positive* (n=189)	HRD-negative or unknown (n=230)
Platinum-sensitive to most recent line of platinum therapy	7/18 (39%)	14/53 (26%)	2/52 (4%)
Platinum-resistant or refractory	10/37 (27%)	12/120 (10%)	5/169 (3%)
Platinum status unknown	1/8 (13%)	3/16 (19%)	1/9 (11%)
All	18/63 (29%)	29/189 (15%)	8/230 (3%)

Data are n/N (%). The table shows patients in the modified per-protocol population who were poly(ADP-ribose) polymerase inhibitor naive. HRD=homologous recombination deficiency. *Includes patients with *BRCA*-mutated and non-*BRCA*-mutated tumours.

Table 2: **Proportion of patients with a confirmed overall response by molecular biomarker and platinum status**

ongoing, with 21 patients still on treatment, and the median follow-up for overall survival was 12·2 months (IQR 3·7–22·1). The population of patients with measurable disease at baseline comprised 461 patients, and 391 patients were evaluable for response. After enrolment, we found that five patients had only two previous lines of therapy; therefore, we used a modified per-protocol population excluding these patients for further analyses (456 patients; figure 1).

The median age of all 463 treated patients was 65 years (IQR 58–71; table 1). The median time from diagnosis was 4·0 years (IQR 2·8–5·8). Molecular biomarker composition was consistent with that in the overall ovarian cancer population, with 222 (48%) of 463 patients having HRD-positive tumours (including germline *BRCA*-mutated, somatic *BRCA*-mutated, and non-*BRCA*-mutated and HRD-positive) and 87 (19%) of 463 patients having a germline or somatic *BRCA* mutation.

Patients had received a median of four (IQR 3–5) previous lines of therapy and 126 (27%) of 463 patients were treated in the fifth or later line (table 1). All patients had at least one previous line of platinum-based therapy, with 235 (51%) of 463 patients receiving two previous lines and 147 (32%) receiving three previous lines (table 1). 151 (33%) patients had platinum-resistant disease and 161 (35%) had platinum-refractory disease (table 1). Although 120 (26%) of 463 patients were found to have disease sensitive to the most recent previous line

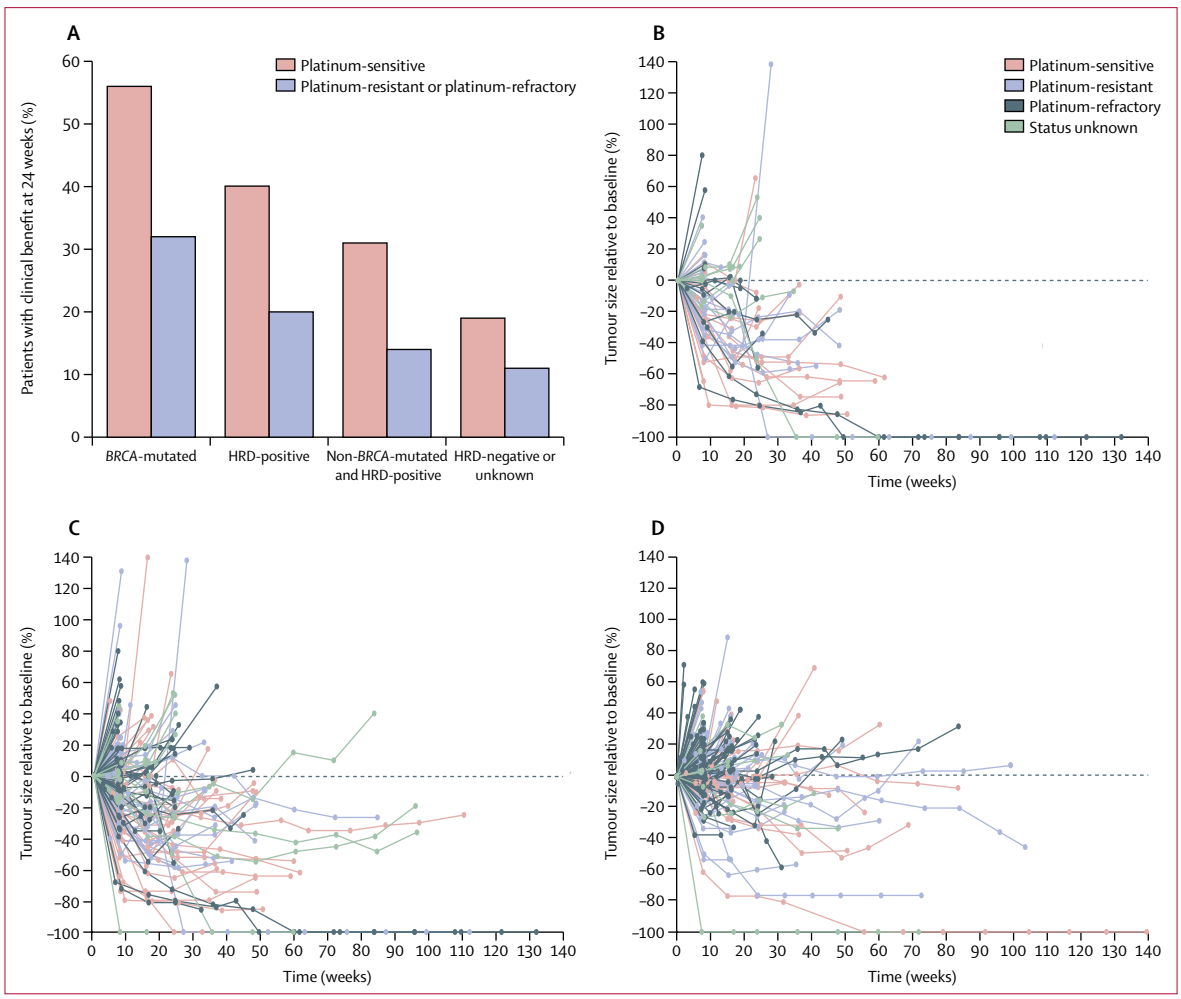

Figure 4: **Clinical activity in biomarker-defined subgroups**
The proportion of patients with clinical benefit at 24 weeks in subgroups defined by clinical (platinum status) and molecular biomarkers (n=419) (A). Spider plots of responses in patients with *BRCA*-mutated tumours (n=54) (B), HRD-positive tumours (n=160) (C), and HRD-negative or unknown HRD status tumours (n=220) (D). Patients in the modified per-protocol population who were poly(ADP-ribose) polymerase inhibitor naive were included. Horizontal dotted lines represent 0 (no change from baseline). HRD=homologous recombination deficiency.

of platinum therapy, only 35 (8%) of 463 patients received platinum immediately before entering the study and were platinum sensitive. 42 (9%) patients with primary platinum-resistant disease and 41 (9%) patients with primary platinum-refractory disease were enrolled. The median time from the last dose of previous chemotherapy to the first dose on study treatment was 2 months (IQR 1–4; table 1).

The study met the primary endpoint, with 13 (28%) of 47 patients who received three or four previous anticancer therapies with HRD-positive tumours that were sensitive to the most recent platinum-based therapy and were PARP inhibitor naive (primary efficacy population) achieving an overall response (95% CI 15·6–42·6, one-sided p=0·00053). The median duration of progression-free survival in this population was 5·5 months (95% CI 3·5–8·2) and median duration of response was 9·2 months (5·9–not estimable). 32 (68%) of 47 patients achieved disease control (95% CI 53–81).

38 (10%) of 387 response-evaluable patients and 38 (8%) of 456 patients in the modified per-protocol population achieved an overall response. We observed a clinically meaningful benefit in terms of best response in the modified per-protocol population (figure 2). Responses were durable, with a median duration of response of 9·4 months (95% CI 6·6–18·3; figure 3). The observed median overall survival in the modified per-protocol population was 17·2 months (95% CI 14·9–19·8; figure 3).

Prespecified exploratory analyses assessed outcomes according to biomarker status and platinum status. The proportion of patients achieving an overall response by molecular biomarker and platinum status is shown in table 2. The median duration of response in the modified per-protocol population was 9·4 months (95% CI

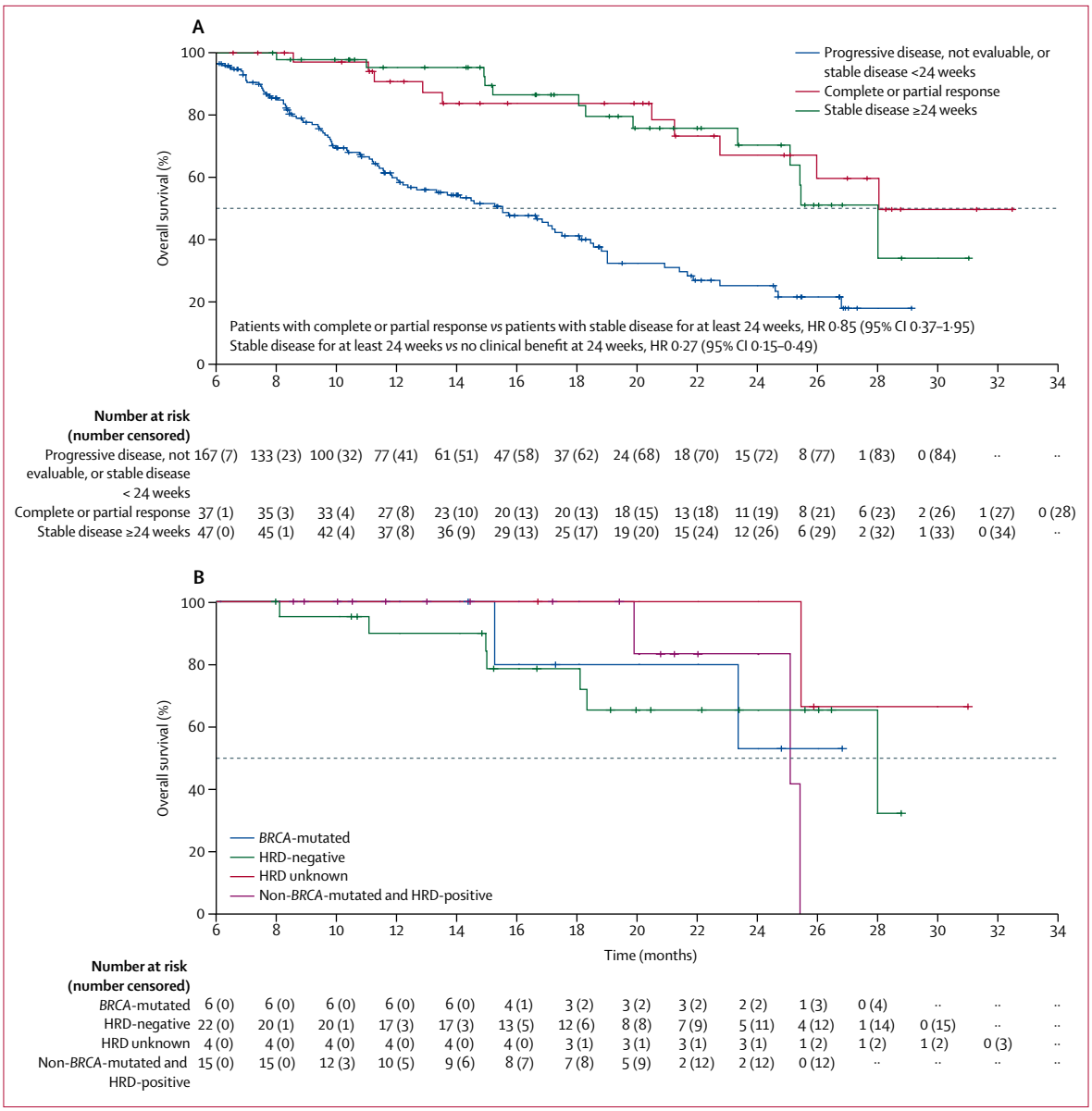

Figure 5: **Kaplan-Meier estimates of overall survival based on the proportion of patients with clinical benefit at 24 weeks**
Landmark analyses are included for patients at risk at 24 weeks—patients who died or were censored before the week 24 landmark were not included. Overall survival among patients with stable disease (A) and clinical benefit at 24 weeks by molecular biomarkers (B). Horizontal dashed lines represent 50% (the median). HR=hazard ratio. HRD=homologous recombination deficiency.

6·6–18·3) and was similar for all biomarker subgroups, including *BRCA*-mutated (9·2 months, 7·4–not estimable), HRD-positive (9·2 months, 6·6–15·2), and HRD-negative (10·1 months, 6·3–not estimable).

Median overall survival was 26·0 months (95% CI 18·1–not estimable) in the *BRCA*-mutated population, 19·0 months (14·5–24·6) in the HRD-positive population, and 15·5 months (11·6–19·0) in the HRD-negative population.

134 (29%) of 456 patients achieved clinical benefit at 16 weeks, and 85 (19%) of 456 patients achieved clinical benefit at 24 weeks. We observed a graduated spectrum of clinical benefit across subgroups (figure 4). The proportion of patients achieving an overall response was highest in those with *BRCA*-mutated and HRD-positive tumours. Although a low proportion of patients achieving an overall response was observed in the absence of a molecular biomarker, 44 (24%) of 186 patients had clinical benefit at 16 weeks and 26 (14%) of 186 patients had clinical benefit at 24 weeks in a post-hoc analysis. Post-hoc analysis of extended clinical benefit for individual patients over time is shown for patients in various biomarker subgroups in figure 4.

Disease stabilisation, as observed in this study, provided evidence of meaningful clinical activity. A post-hoc analysis of overall survival by the proportion of patients achieving clinical benefit at 16 weeks and 24 weeks in the entire modified per-protocol population, and an analysis of patients at risk at 16 weeks and 24 weeks (to address potential guarantee-time bias) are shown in the appendix (pp 1–2). Patients with a RECIST response of stable disease for 24 weeks or more had a median overall survival similar to that of patients achieving a partial response or complete response (median overall survival of 28 months for both; figure 5). Furthermore, median overall survival did not appear to be driven by patients with *BRCA*-mutated tumours (six patients), and survival curves for all biomarker subgroups were similar (figure 5) among these patients, with stable disease for 24 weeks or more.

65 (35%) of 187 patients treated in the fourth line or later with the best overall response of stable disease had a progression-free survival ratio greater than 1·3, with a mean increase of 4·1 months compared with progression-free survival achieved with the preceding line of therapy, and 82 (44%) of 187 patients had a progression-free survival ratio greater than 1·0. A similar proportion of patients had a progression-free survival ratio greater than 1·3 regardless of molecular biomarker status (table 3).

The most common grade 3 or worse drug-related treatment-emergent adverse events were haematological toxicities of anaemia (113 [24%] of 463 patients) and thrombocytopenia (95 [21%] of 463 patients; table 4). The most commonly reported all grade drug-related treatment-emergent adverse events were consistent with previous clinical findings and included gastrointestinal disorders, including nausea (269 [58%] of 463 patients), vomiting (150 [32%] of 463 patients), and constipation (79 [17%] of 463 patients); haematological toxicities, including anaemia (206 [44%] of 463 patients), thrombocytopenia (153 [33%] of 463 patients), and decreased platelet count (98 [21%] of 463 patients); and general disorders, including fatigue (190 [41%] of 463 patients). Treatment-emergent adverse events led to dose interruption in 288 (62%) of 463 patients, dose reduction in 218 (47%) patients, and treatment discontinuation in 98 (21%) patients (appendix p 4). Serious treatment-emergent adverse events were observed in 197 (43%) of 463 patients, and those reported in at least 5% of patients were small intestinal obstruction in 34 (7%) of 463 patients, thrombocytopenia in 34 (7%) patients, and vomiting in 27 (6%) patients. One treatment-related death due to gastric haemorrhage was reported. We detected no new safety signals.

Discussion

In the QUADRA study, we assessed the clinical benefit of niraparib monotherapy in an extended late-line treatment setting. The broad patient population and baseline disease characteristics in this study are reflective of real-world patients receiving late-line treatment for ovarian

	BRCA-mutated (n=63)	HRD-positive* (N=189)	HRD-negative or unknown (n=230)
Platinum-sensitive to most recent line of platinum therapy	10/18 (56%)	21/53 (40%)	10/52 (19%)
Platinum-resistant or refractory	12/37 (32%)	24/120 (20%)	18/169 (11%)
Platinum status unknown	2/8 (25%)	5/16 (31%)	5/9 (56%)
All	24/63 (38%)	50/189 (26%)	33/230 (14%)
Patients with stable disease with progression-free survival ratio >1·3	9/25 (36%)	23/72 (32%)	39/103 (38%)
Patients with stable disease with progression-free survival ratio >1·0	11/25 (44%)	30/72 (42%)	47/103 (46%)

Data are n/N (%). The table shows patients in the modified per-protocol population who were poly(ADP-ribose) polymerase inhibitor naive. HRD=homologous recombination deficiency. *Includes patients with *BRCA*-mutated and non-*BRCA*-mutated tumours.

Table 3: **Proportion of patients achieving clinical benefit at 24 weeks by platinum status and biomarker, and progression-free survival ratio in patients with stable disease by biomarker**

	Grade 1–2	Grade 3	Grade 4	Grade 5
Any drug-related treatment-emergent adverse event	416 (90%)	257 (56%)	93 (20%)	1 (<1%)
Nausea	261 (56%)	20 (4%)	0	0
Fatigue	185 (40%)	20 (4%)	1 (<1%)	0
Anaemia	176 (38%)	112 (24%)	1 (<1%)	0
Vomiting	139 (30%)	19 (4%)	0	0
Thrombocytopenia	136 (29%)	76 (16%)	58 (13%)	0
Decreased platelet count	91 (20%)	35 (8%)	22 (5%)	0
Decreased appetite	85 (18%)	4 (1%)	0	0
Constipation	76 (16%)	5 (1%)	0	0
Insomnia	55 (12%)	3 (1%)	0	0
Headache	52 (11%)	1 (<1%)	0	0
Decreased white blood cell count	48 (10%)	17 (4%)	2 (<1%)	0
Neutropenia	32 (7%)	29 (6%)	21 (5%)	0
Decreased neutrophil count	28 (6%)	20 (4%)	4 (1%)	0
Leucopenia	23 (5%)	11 (2%)	5 (1%)	0
Decreased lymphocyte count	17 (4%)	11 (2%)	0	0
Hypertension	8 (2%)	8 (2%)	0	0
Lymphopenia	9 (2%)	8 (2%)	0	0
Abdominal pain	14 (3%)	6 (1%)	0	0
Decreased haemoglobin	5 (1%)	5 (1%)	1 (<1%)	0
Asthenia	14 (3%)	4 (1%)	0	0
Prolonged electrocardiogram QT	14 (3%)	3 (1%)	0	0
Increased γ-glutamyltransferase	8 (2%)	3 (1%)	0	0
Hyponatraemia	13 (3%)	3 (1%)	0	0
Dehydration	11 (2%)	2 (<1%)	1 (<1%)	0
Increased amylase	8 (2%)	2 (<1%)	0	0
Dyspnoea	18 (4%)	2 (<1%)	0	0
Electrolyte imbalance	0	2 (<1%)	0	0
Hyperglycaemia	4 (1%)	2 (<1%)	0	0
Hypokalaemia	7 (2%)	2 (<1%)	0	0
Decreased weight	25 (5%)	2 (<1%)	0	0
Pancytopenia	1 (<1%)	1 (<1%)	1 (<1%)	0
Arthralgia	3 (1%)	1 (<1%)	0	0
Increased blood alkaline phosphatase	17 (4%)	1 (<1%)	0	0

(Table 4 continues on next page)

	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)				
Increased blood bilirubin	0	1 (<1%)	0	0
Chronic kidney disease	1 (<1%)	1 (<1%)	0	0
Colitis	0	1 (<1%)	0	0
Diarrhoea	40 (9%)	1 (<1%)	0	0
Dysphagia	3 (1%)	1 (<1%)	0	0
Eastern Cooperative Oncology Group performance status worsened	0	1 (<1%)	0	0
Epistaxis	14 (3%)	1 (<1%)	0	0
Gastritis	0	1 (<1%)	0	0
Gastrointestinal fistula	0	1 (<1%)	0	0
Hypoxia	0	1 (<1%)	0	0
Mucosal inflammation	12 (3%)	1 (<1%)	0	0
Musculoskeletal chest pain	0	1 (<1%)	0	0
Myocardial infarction	0	1 (<1%)	0	0
Oesophagitis	2 (<1%)	1 (<1%)	0	0
Palpitations	20 (4%)	1 (<1%)	0	0
Proteinuria	5 (1%)	1 (<1%)	0	0
Pyrexia	2 (<1%)	1 (<1%)	0	0
Maculopapular rash	3 (1%)	1 (<1%)	0	0
Rectal haemorrhage	3 (1%)	1 (<1%)	0	0
Skin exfoliation	0	1 (<1%)	0	0
Small intestinal obstruction	0	1 (<1%)	0	0
Stomatitis	30 (6%)	1 (<1%)	0	0
Syncope	0	1 (<1%)	0	0
Sepsis	0	0	2 (<1%)	0
Bone marrow failure	0	0	1 (<1%)	0
Acute myeloid leukaemia	0	0	1 (<1%)	0
Hyperuricaemia	0	0	1 (<1%)	0
Myelodysplastic syndrome	0	0	1 (<1%)	0
Gastric haemorrhage	0	0	0	1 (<1%)

Data are n (%). A patient can be counted in more than one grade for a given adverse event.

Table 4: **Drug-related treatment-emergent adverse events (n=463)**

cancer, who have often exhausted all effective treatment options. Consistent with the phase 1 and ENGOT-OV16/NOVA phase 3 trials of niraparib,[16,20] the results of QUADRA support a continuum of clinical benefit—manifested here as the proportion of patients achieving an overall response and overall survival—with niraparib therapy in subgroups defined by clinical and molecular biomarkers.

Previous studies have shown that PARP inhibitors are a treatment option for patients with *BRCA*-mutated, advanced ovarian cancer. This study extends this finding to a broad patient population with late-line ovarian cancer.

34% (95% CI 26–42) of PARP inhibitor naive patients with germline *BRCA*-mutated tumours treated with olaparib, who had received three or more previous lines of therapy, were reported as having an overall response, with a median duration of response of 7·9 months (95% CI 5·6–9·6).[21] In a pooled analysis of data from rucaparib studies,[29] 45% (95% CI 32–58) of PARP inhibitor naive patients with *BRCA*-mutated tumours who received three or more previous lines of therapy achieved an overall response; however, this patient population mostly comprised patients with platinum-sensitive disease.[29] We previously reported that 29% (95% CI 18–41) of patients with *BRCA*-mutated (germline or somatic) tumours treated with niraparib achieved a response, with a median duration of response of 9·2 months (95% CI 7–not estimable) and median overall survival of 26 months (95% CI 18–not estimable), with meaningful activity observed among patients with platinum-resistant (33% of patients had an overall reponse, 95% CI 15–57) and platinum-refractory disease (19% of patients had an overall response, 95% CI 4–46).[30]

Although the efficacy of PARP inhibitors in *BRCA*-mutated tumours represents a clinically meaningful benefit and treatment advancement, only around 20% of patients with ovarian cancer have a *BRCA* mutation,[23] and for the remaining 80% of patients, the activity of available therapy remains insufficient.

Patients with late-line ovarian cancer are a particularly challenging population to treat, with few effective treatment options. Historically, the expected overall survival has been less than 1 year for patients treated in the fourth or later line.[7,9] Survivorship, including palliation of both treatment-related and disease-related symptoms, is prioritised in this setting, and as such, there is an increasing focus on minimisation of toxic effects and spending more time outside the hospital or clinic.[31,32] Therefore, disease stabilisation with preserved quality of life and the ability for patients to take their treatment at home might represent meaningful achievements to the patient.[32] In this context, capturing clinically meaningful disease stabilisation is an important descriptor of treatment efficacy. Furthermore, in post-hoc analyses, we showed that achieving clinical benefit at 24 weeks correlated with increased overall survival, such that patients achieving partial response, complete response, or stable disease for 24 weeks had an expected median overall survival of 28 months on niraparib therapy.

There are some limitations of this study. This was a single-arm, non-randomised study. We did an exploratory analysis to investigate whether patients had a substantially improved disease stabilisation on niraparib treatment compared with the treatment they received immediately before enrolment in QUADRA. About a third of patients achieving stable disease had disease stabilisation on niraparib for around 4 months longer than on their previous therapy, suggesting niraparib treatment had an effect on their disease. Although the study was powered for the primary outcome, the study was not powered for other subgroup analyses.

The safety profile reported here was based on a niraparib starting dose of 300 mg once daily, with the requirement to initiate dose reductions following treatment-emergent adverse events. A 2018 analysis[33] of

the safety data from ENGOT-OV16/NOVA, which used a similar dosing schedule to this study, showed that a starting dose of 200 mg in patients with low bodyweight or low baseline platelet count reduced the incidence of treatment-emergent adverse events, with no reduction in efficacy. Indeed, the incidence of haematological adverse events decreased substantially after initial dose modification in QUADRA. Ongoing trials of niraparib have implemented dosing whereby patients with a baseline weight lower than 77 kg or baseline platelet count less than 150 000 cells per µL receive a 200 mg starting dose, whereas patients with a baseline weight of 77 kg or greater and baseline platelet count of 150 000 cells per µL or more receive a 300 mg starting dose.

As a single-arm study, QUADRA was not designed to collect formal patient-reported outcome endpoints. However, the double-blind randomised placebo-controlled ENGOT-OV16/NOVA trial assessed patient quality of life on niraparib compared with placebo.[34] The safety profile of niraparib in the QUADRA treatment study was consistent with the safety profile observed in the ENGOT-OV16/NOVA trial maintenance population, despite higher tumour burden and a more heavily pretreated population in QUADRA.

In this study, patients derived clinical benefit from niraparib treatment beyond what could be described by the proportion of patients achieving an overall response. Disease stabilisation for 24 weeks, along with an improved progression-free survival compared with last-line therapy among patients with stable disease, and improved median overall survival relative to those previously reported, suggest a benefit of niraparib in the late-line treatment setting, regardless of biomarker status. These data suggest the proportion of patients with clinical benefit at 24 weeks could be a relevant outcome and might explain why the observed survival benefit extended to all biomarker subgroups, including patients with *BRCA* wild-type and HRD-negative disease.

To our knowledge, QUADRA is the largest clinical trial ever done to evaluate the activity of a single-agent PARP inhibitor in the late-line treatment setting and is notable for its comparability with a real-world patient population. Consistent with previous studies of niraparib (PN001[20] and ENGOT-OV16/NOVA[16]), QUADRA showed a continuum of clinical benefit in subgroups defined by clinical and molecular biomarkers. We identified no new safety signals, and haematological toxicity was well managed by dose modification. Niraparib could represent a meaningful treatment option and be considered an alternative to established chemotherapy regimens for late-line treatment of patients with ovarian cancer on the basis of the current treatment landscape in this area of high unmet need.

Contributors

All authors contributed to the design of the study and interpreted the data. KNM, AAS, MAG, DSM, NC, GFF, AEWH, MA, PD, AMO, MC, JSB, JKC, UAM, BJM, BJR, and DEM collected the data. YL compiled the data and did the statistical analysis. KNM and KL prepared the manuscript with input from all authors. KNM, PD, JSB, UAM, and BJM are members of the trial management group.

Declaration of interests

KNM reports honoraria or advisory board fees from Tesaro, Genentech, Roche, Clovis Oncology, AstraZeneca, ImmunoGen, VBL Therapeutics, and Janssen, outside the submitted work. AAS reports research funding and honoraria or advisory board fees from Tesaro during the conduct of the study; and research funding from AbbVie, Amgen, Astex Pharmaceuticals, AstraZeneca, Clovis, Astellas Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Endocyte, Exelixis, Incyte, Merck, PharmaMar, Immutep, Roche, Genentech, Seattle Genetics, and TapImmune, and honoraria or advisory board fees from Alexion, Aravive, Astex Pharmaceuticals, AstraZeneca, Clovis, Janssen, Johnson & Johnson, Merck, Mersana, Myriad, Oncoquest, Roche, and Genentech, outside the submitted work. MAG reports consulting fees, speaker's bureau fees, and research funding from Tesaro, outside the submitted work. DSM reports consulting fees, speakers' bureau fees, and research funding from Genentech; consulting fees and research funding from Tesaro, ImmunoGen, and AstraZeneca; consulting and speakers' bureau fees from Clovis Oncology; consulting fees from Eisai, Guardant Health, and Alexion Pharmaceuticals; and research funding from TRACON Pharmaceuticals, Janssen, Aeterna Zentaris, Pfizer, Aprea Therapeutics, Takeda, and Xenetic Biosciences, all outside the submitted work. NC reports research funding from Tesaro, and employment by Texas Oncology, outside the submitted work. GFF reports financial relationships with Aeterna Zentaris outside the submitted work. PD reports consulting fees and research funding from Tesaro and AstraZeneca, and research funding from AbbVie, Genentech, Roche, and Janssen, outside the submitted work. AMO reports consulting and advisory fees from Clovis Oncology; honoraria from WebRX and Intas Oncology, and travel and expenses payments from AstraZeneca, outside the submitted work. MC reports research funding from TrovaGene outside the submitted work. JKC reports consulting fees, speakers' bureau fees, and honoraria from Genentech, Roche, AstraZeneca, and Tesaro; speakers' bureau fees and honoraria from Clovis Oncology; and consulting for Janssen Oncology, Mateon Therapeutics, and Biodesix, all outside the submitted work. BJR reports advisory board participation with Tesaro, AstraZeneca, Genentech, and Clovis Oncology outside the submitted work. DEM reports personal fees from AstraZeneca, Roche, Tesaro, The European Commission, Clovis, and Astex, outside the submitted work. YL, KS, and KL are employees and stockholders of Tesaro. UAM reports consulting and advisory fees from Merck, Clovis Oncology, Geneos, Eli Lilly, and 2X Oncology outside the submitted work. BJM reports honoraria, and consultancy and speaker fees from AstraZeneca, Clovis Oncology, Janssen, Johnson & Johnson, Roche, Genentech, and Tesaro; honoraria and consultancy fees from AbbVie, Advaxis, Amgen, Biodesix, Genmab, Gradalis, ImmunoGen, Immunomedics, Incyte, Mateon (formerly Oxigene), Merck, Myriad, Perthera, Pfizer, Precision Oncology, Puma Biotechnology, Samumed, Takeda, and VBL Therapeutics, all outside the submitted work. All other authors report no competing interests.

Data sharing

Tesaro has shared the redacted QUADRA study protocol in the online appendix of this Article. De-identified individual participant data that underlie the results (text, tables, figures, and appendices) reported in this Article are available upon request at tesaropublications@tesarobio.com to qualified scientific and medical researchers who provide an approved methodologically sound proposal, upon researcher's request, and upon signing a data access agreement. Data will be available as soon as possible but no later than within 1 year of the acceptance of this Article for publication, and for 3 years following Article publication. Provision of data will be completed without external investigator support. Tesaro will not share identified participant data or a data dictionary.

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