Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a phase 3, international, randomised, double-blind trial

Robert L Coleman, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann,* on behalf of the ARIEL3 investigators[†]*

Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler Dr., CPB6.3590 Houston, TX 77030, USA (Prof R L Coleman MD); Department of Medicine, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto M5G 2M9, Canada (Prof A M Oza MD); MITO and Gynecologic Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian, 1, 20133 Milan, Italy (D Lorusso MD); Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY, USA (C Aghajanian MD); Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), 119-129, 08035, Barcelona, Spain (A Oaknin MD); Department of Oncology, St. John of God Subiaco Hospital, 12 Salvado Rd., Subiaco, Western Australia 6008, Australia (A Dean MD); Gynecologic Cancer

Program, European Institute of Oncology and University of Milan-Bicocca, Via
 Ripamonti 435, Milan, Italy (Prof N Colombo PhD); Ottawa Hospital Research Institute,
 501 Smyth Road, Ottawa, Canada K1H 8L6 (J I Weberpals MD); Department of Medical
 Oncology, The Christie NHS Foundation Trust and University of Manchester, 550
 Wilmslow Road, Manchester, M20 4BX UK (A Clamp PhD); Gynecologic Oncology,
 Università Cattolica Roma, Largo Francesco Vito, 1, 00168 Roma, Italy (Prof G
 Scambia MD); GINECO and Gynecological Unit, Department of Medicine, Gustave
 Roussy Cancer Center and INSERM U981, 114 Rue Edouard-Vaillant, 94805, Villejuif,
 France (A Leary MD); Department of Gynecologic Oncology, Florida Hospital Cancer
 Institute, 2501 North Orange Avenue, Suite 683, Orlando, FL, USA (R W Holloway MD);
 Medical Oncology Department, Oncology Center of Galicia, Doctor Camilo Veiras, 1,
 15009 La Coruña, Spain (M Amenedo Gancedo MD); Medical Oncology Department,
 Auckland City Hospital, 2 Park Rd, Grafton, Auckland 1023, New Zealand (P C Fong
 FRACP); Department of Oncology, Cancer Care Services, Royal Brisbane and
 Women's Hospital, Level 5 Joyce Tweddell Building, Butterfield Street, Herston,
 Queensland 4029, Australia (J C Goh FRACP); Gynecologic Oncology, The Ohio State
 University, James Cancer Center, M210 Starling Loving, 320 W 10th Ave, Columbus,
 OH 43210, USA (D M O'Malley MD); The Sidney Kimmel Comprehensive Cancer
 Center at Johns Hopkins, Room 190, 1650 Orleans Street, Baltimore, MD 21287, USA
 (Prof D K Armstrong MD); HM Hospitales – Centro Integral Oncológico HM Clara
 Campal, Calle Oña, 10, Planta -1, 28050 Madrid, Spain (J Garcia-Donas MD);
 University of Washington, 1959 Northeast Pacific Street, Seattle, WA 98195, USA (Prof
 E M Swisher MD); GINECO and Institut Bergonié, 229, cours de l'Argonne, 33076

Bordeaux, France (A Floquet MD); Department of Medicine, University of California Los Angeles, 100 Medical Plaza, Los Angeles, CA 90095, USA (Prof G E Konecny MD); Institute of Cancer Sciences, University of Glasgow, 1053 Great Western Road, Glasgow, G12 0YN UK (Prof I A McNeish FCRP); Royal Melbourne Hospital, 300 Grattan Street, Parkville, Victoria, 3052, Australia (C L Scott PhD); Clovis Oncology, Inc., 5500 Flatiron Parkway, Boulder, CO 80301, USA (T Cameron MSc, L Maloney BA, J Isaacson PhD, S Goble MS, C Grace BSc, T C Harding PhD, M Raponi PhD, K K Lin PhD, H Giordano MA); Foundation Medicine, Inc., 150 Second St, Cambridge, MA, 02141, USA (J Sun PhD); UCL Cancer Institute and UCL Hospitals, 90 Tottenham Court Road, London W1T 4TJ, UK (Prof J A Ledermann MD)

*Joint lead clinical investigators.

†Members listed in the appendix.

Correspondence to: Dr Robert L Coleman, The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler Dr., CPB6.3590 Houston, TX 77030, USA; Phone: 713 745 3357; Fax: 713 792 7586; rcoleman@mdanderson.org

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Summary

Background: Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has anticancer activity in recurrent ovarian carcinoma harbouring a *BRCA* mutation or a high percentage of genome-wide loss of heterozygosity (LOH). ARIEL3 evaluated rucaparib versus placebo following response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma.

Methods: ARIEL3 is an international, randomised, double-blind, phase 3 study performed at 87 hospitals and cancer centres. Patients were randomised 2:1 to receive oral rucaparib 600 mg twice daily or placebo using a computer-generated sequence (block size of six). Patients, investigators, site staff, and study sponsor were blinded to assignments. The primary endpoint (investigator-assessed progression-free survival) was evaluated using an ordered step-down procedure for three nested cohorts: (1) *BRCA* mutant (carcinoma associated with deleterious germline or somatic *BRCA* mutation); (2) homologous recombination deficient (HRD) (*BRCA* mutant or *BRCA* wild type/LOH high); and (3) intent-to-treat population. ARIEL3 is registered with ClinicalTrials.gov, NCT01968213; enrolment is complete.

Findings: Between April 7, 2014, and July 19, 2016, 564 patients were randomised, 375 to rucaparib and 189 to placebo. Median progression-free survival in patients with a *BRCA*-mutant carcinoma (n=130, rucaparib; n=66, placebo) was 16·6 months versus 5·4 months (p<0·0001), respectively (hazard ratio [HR] 0·23; 95% confidence interval [CI] 0·16–0·34); in patients with an HRD carcinoma (n=236, rucaparib; n=118, placebo) it was 13·6 months versus 5·4 months (p<0·0001), respectively (HR 0·32; 95% CI 0·24–0·42); and in the intent-to-treat population it was 10·8 months and 5·4 months

($p < 0.0001$), respectively (HR 0.36; 95% CI 0.30–0.45). The most common grade 3 or higher adverse events in the safety population (n=372, rucaparib; n=189, placebo) were anaemia/decreased haemoglobin (70 [19%], rucaparib; one [1%], placebo) and increased alanine or aspartate aminotransferase (39 [10%], rucaparib; none, placebo).

Interpretation: Across all primary analysis groups, rucaparib significantly improved progression-free survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy.

Funding: Clovis Oncology, Inc.

Research in context

Evidence before this study

Evidence of the clinical effectiveness of poly(ADP-ribose) polymerase (PARP) inhibitors as maintenance treatment for platinum-sensitive ovarian carcinoma is limited. In a search of PubMed (conducted July 31, 2017; search term: ("PARP inhibitor" OR rucaparib OR olaparib OR niraparib OR veliparib OR talazoparib) AND (ovarian AND (cancer OR carcinoma)) AND "maintenance"), we found that data have been published in a PubMed-indexed journal for only three clinical trials, Study 19 (NCT00753545), NOVA (NCT01847274), and SOLO2 (NCT01874353). Study 19, a randomised, placebo-controlled, phase 2 study, enrolled patients with platinum-sensitive ovarian carcinoma who had received at least two prior platinum-based chemotherapies. Progression-free survival was significantly improved with olaparib maintenance treatment in the overall population, as well as in patients with a germline or somatic *BRCA* mutation. Study 19 data were published prior to the commencement of ARIEL3 and supported the investigation of rucaparib as a maintenance treatment for patients with recurrent platinum-sensitive ovarian carcinoma in ARIEL3. In late 2016, results from the NOVA trial provided additional support for the role of a PARP inhibitor as maintenance treatment. In that randomised, placebo-controlled, phase 3 study, niraparib demonstrated a significant improvement in progression-free survival when used as a maintenance treatment in patients with ovarian carcinoma with or without a germline *BRCA* mutation who had received at least two prior platinum-based chemotherapies and had no measurable disease greater than 2 cm. Results from one other phase 3 study with olaparib maintenance treatment, SOLO2, were published in

July 2017. That randomised, placebo-controlled study enrolled patients with platinum-sensitive ovarian carcinoma who had received at least two prior platinum-based chemotherapies and carried a germline mutation in *BRCA*. Similar to the results seen in Study 19, progression-free survival was significantly improved with olaparib maintenance treatment in patients enrolled in SOLO2.

Added value of this study

ARIEL3 enrolled patients with or without a germline or somatic *BRCA* mutation, and the size of residual disease was not restricted. Our results show that rucaparib maintenance treatment significantly improved progression-free survival for patients across all primary analysis groups for patients with recurrent, platinum-sensitive ovarian carcinoma who achieved a response to platinum-based therapy, including in the intent-to-treat population. We demonstrate that rucaparib maintenance treatment can provide clinical benefit not only to patients with ovarian carcinoma associated with a *BRCA* mutation, but also to those with *BRCA* wild-type ovarian carcinoma. A novel aspect of the ARIEL3 trial was the prospective validation of the tumour-based, next-generation sequencing (NGS) homologous recombination deficiency (HRD) assay that was initially utilised in the phase 2 ARIEL2 study. This NGS assay combines mutation analysis of *BRCA1* and *BRCA2* genes with measurement of the percentage of genome-wide loss of heterozygosity (LOH) in the cancer tissue as a biomarker for sensitivity to rucaparib treatment. ARIEL2 enrolled patients with measurable, recurrent ovarian carcinoma, and provided initial evidence that patients with carcinomas with high LOH benefited from rucaparib treatment. The current study (ARIEL3) validated the utility of the HRD assay overall and LOH assessment in particular in the maintenance treatment setting, where

rucaparib-treated patients with carcinomas that were *BRCA* wild type/LOH high also had improvements in progression-free survival, with a lower hazard ratio than in patients with carcinomas that were *BRCA* wild type/LOH low.

Implications of all the available evidence

Combined with the evidence from prior studies, our study supports the use of PARP inhibitors, such as rucaparib, as maintenance treatment for patients with platinum-sensitive ovarian cancer who achieved a response to platinum-based chemotherapy. ARIEL3 is the first phase 3 study to prospectively assess progression-free survival in patients with recurrent ovarian carcinoma associated with HRD as a primary endpoint, and our results demonstrate that HRD as a predictive biomarker can be an informative tool for clinicians when making treatment decisions for this patient population. In addition to PARP inhibitors, the targeted agents bevacizumab and cediranib have proven useful in extending progression-free survival for patients in this setting. Our findings strengthen the rationale for continued investigation of targeted therapies, such as PARP inhibitors, for maintenance treatment as either monotherapy or in combination with other agents, in an effort to provide the best care for patients with advanced ovarian cancer.

Introduction

Ovarian cancer is the eighth leading cause of death from cancer in women worldwide.¹ Most patients with advanced stage ovarian carcinoma initially receive platinum-based chemotherapy and achieve a clinical response; however, the majority of these patients will ultimately relapse.² The treatment for initial recurrent disease depends on many factors, including duration of initial treatment response, antecedent and persistent adverse events, performance status, histology, location and burden of disease, and, increasingly, tumour genomics such as *BRCA* mutation status.³ For patients with platinum-sensitive recurrent ovarian carcinoma, maintenance treatment with targeted agents has resulted in greater prolongation of progression-free survival.⁴⁻⁹ However, clinical benefit is typically transient, hence there is an ongoing pursuit for new therapies and tools to identify patients who may benefit most from these therapies, as well as to identify the optimal therapeutic strategy for patients.

The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved in the United States for the treatment of patients with deleterious *BRCA* mutation (germline or somatic) associated advanced ovarian carcinoma who have been treated with two or more chemotherapy regimens. Approval of rucaparib was based on the objective response rate (57 of 106 patients [54%]) observed in a pooled population of patients with *BRCA*-mutant high-grade ovarian carcinoma from the Study 10 (CO-338-10; NCT01482715) and ARIEL2 (CO-338-017; NCT01891344) clinical trials.^{10,11}

In Part 1 of the ARIEL2 trial, rucaparib treatment was found to be efficacious not only in patients with relapsed, platinum-sensitive, high-grade ovarian carcinoma with a *BRCA*

mutation, but also in patients with *BRCA* wild-type carcinomas with high genomic loss of heterozygosity (LOH),¹¹ a potential marker for homologous recombination deficiency (HRD) and thus PARP inhibitor activity.¹²⁻¹⁵ In the current phase 3, randomised, placebo-controlled study (ARIEL3), our objective was to evaluate the efficacy and safety of rucaparib versus placebo following response to second-line or later platinum-based chemotherapy in patients with high-grade, platinum-sensitive ovarian carcinoma (including fallopian tube and primary peritoneal carcinomas) and to prospectively test the genomic LOH cutoff discriminator that was optimised based on results of ARIEL2 Part 1 as a predictive biomarker for sensitivity to rucaparib treatment.

Methods

Study design and patients

ARIEL3 (NCT01968213) was a phase 3, international, randomised, placebo-controlled study conducted at 87 hospitals and cancer centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, United Kingdom, and the United States. The trial was approved by national or local institutional review boards and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. Patients provided written informed consent before participation. Per the protocol, an independent data monitoring committee monitored enrolment and reviewed the safety and efficacy of the trial approximately every 6 months, including maturity of progression-free survival events.

Eligible patients were aged 18 years or older, had platinum-sensitive (ie, documented radiologic disease progression more than 6 months following the last dose of the penultimate platinum administered), high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma and had received at least two prior platinum-based chemotherapy regimens. Prior treatment with bevacizumab was permitted, with the exception of bevacizumab maintenance treatment following the most recent platinum-based regimen. On November 4, 2014, after 91 patients had been randomised, an amendment was made to the protocol requiring that the most recent platinum-based regimen was to be administered as a chemotherapy doublet and for a minimum of four cycles. Patients must have achieved either a complete response by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST)¹⁶ or a partial response, defined as either a RECIST partial response or a serologic response per Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 (CA-125)¹⁷ response criteria, to their last platinum-based regimen. For patients who achieved a partial response, no restriction was placed on residual carcinoma size at study entry; those who had persistent lesions greater than 2 cm as defined by independent radiological review were defined as having “bulky” residual disease. Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry into ARIEL3. Additionally, CA-125 was required to be less than the upper limit of normal. Patients had Eastern Cooperative Oncology Group Performance Status of 0 to 1 and adequate organ function. Patients were ineligible if they had symptomatic/untreated central nervous system metastases, had received anticancer therapy 14 or fewer days before starting the study, or had

received prior treatment with a PARP inhibitor. A complete list of inclusion and exclusion criteria is provided in the appendix (p 6), and the full study protocol is available in the appendix.

Central testing of DNA derived from patient archival tumour tissue samples was performed to detect mutations in homologous recombination pathway genes (appendix p 8) and assess genomic LOH using Foundation Medicine's T5 NGS assay (Cambridge, MA). Based on retrospective analysis of data from ARIEL2 Part 1, a cutoff of 16% or greater was prespecified for ARIEL3 as a discriminator for high genomic LOH.¹¹ Germline mutations were identified by BRCAanalysis CDx test (Myriad Genetics, Salt Lake City, UT). Further details of the tumour tissue testing are provided in the appendix (p 2).

Randomisation and masking

Within 8 weeks of their last dose of platinum, eligible patients were randomised 2:1 to receive oral rucaparib (600 mg twice daily) or matched placebo. Randomisation was computer-generated by Almac Clinical Technologies (Souderton, PA) using a block size of six. Randomisation stratification factors included: homologous recombination repair gene mutation status (based on gene mutation only); progression-free interval following penultimate platinum-based regimen; and best response to most recent platinum-based regimen (additional details in the appendix p 3). Patients were assigned to the rucaparib arm or placebo arm in a blinded manner using Almac Clinical Technologies' interactive web and voice response system (IXRS®); patients, investigators, site staff, and the study sponsor were blinded to assignments. To ensure blinding was maintained, rucaparib and placebo tablets were manufactured to have identical appearances.

Procedures

Patients received study drug in continuous 28-day cycles until disease progression, death, or other reason for discontinuation. Dose reductions (in decrements of 120 mg) were permitted if a patient had a grade 3 or greater or persistent grade 2 adverse event (additional details in the appendix p 3). Treatment was discontinued for a toxicity-related treatment interruption lasting more than 14 consecutive days (unless otherwise agreed upon between the investigator and the study sponsor).

Disease assessments were performed at screening, every 12 weeks during treatment (and post-treatment for patients who discontinued for any reason other than disease progression), at discontinuation of treatment, and as clinically indicated. Disease progression was determined by RECIST. Patients with a complete response at study entry were only considered to have disease progression if an unequivocal new lesion was identified. Increased CA-125 levels alone were not considered to indicate disease progression unless confirmed by RECIST. All computed tomography scans and other imaging were provided to a blinded, independent central radiology review (BICR).

The National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy Ovarian Symptom Index 18 (FOSI-18)¹⁸ questionnaire was used to assess patient-reported outcomes at screening and throughout treatment. Safety was assessed by monitoring for adverse events, laboratory testing, assessing vital signs and conducting physical examinations. Adverse events were classified in accordance with the Medical Dictionary for Drug Regulatory Activities classification system version 18.1¹⁹ and graded for severity in accordance with the National Cancer Institute Common

Terminology Criteria for Adverse Events version 4-03.²⁰ Serious adverse events were classified as defined in the protocol (see appendix).

Outcomes

The primary endpoint was investigator-assessed progression-free survival, defined as time from randomisation to investigator-assessed disease progression per RECIST or death. Secondary endpoints included progression-free survival by BICR, patient-reported outcomes as evaluated by time to worsening in the FOSI-18 disease-related symptoms–physical (DRS-P) subscale (defined as ≥ 4 -point decrease) and total score (defined as ≥ 8 -point decrease), overall survival, safety, and population pharmacokinetic modelling. Additional details are available in the appendix (p 3). The secondary endpoint of population pharmacokinetic modelling will be reported separately.

Statistical analysis

ARIEL3 was designed to enrol approximately 540 patients, including between 180 and 200 patients with a *BRCA* mutation in their carcinoma (with no more than 150 patients with a known deleterious germline *BRCA* mutation) and no more than 360 patients without a *BRCA* mutation in their carcinoma. The independent data monitoring committee surveyed enrolment of patients with a *BRCA* mutation and informed the study sponsor (Clovis Oncology, Inc.) when the target enrolment number for the *BRCA*-mutant cohort was anticipated to be reached. Once notified, patients who were in the screening process were allowed to complete screening and enrol into the study if they met all eligibility criteria. These subgroup sizes were designed to result in 90% power to determine statistical significance between rucaparib and placebo at a one-sided alpha

level of 0.025 given the following assumptions for median investigator-assessed progression-free survival for the efficacy analysis cohorts: *BRCA* mutant (carcinoma associated with a deleterious germline or somatic *BRCA* mutation), 12.0 months in the rucaparib arm versus 6.0 months in the placebo arm (hazard ratio [HR] 0.5); HRD (includes patients with a *BRCA*-mutated carcinoma and patients with *BRCA* wild-type/LOH-high carcinomas), 10.0 versus 6.0 months (HR 0.6); and intent-to-treat population (all randomised patients), 8.5 versus 6.0 months (HR 0.7).

Classification of HRD status in the carcinoma (based on *BRCA* mutation and/or LOH) for the efficacy analysis was determined before database lock and the final efficacy analysis. Per protocol, the primary analysis was to be performed after the independent data monitoring committee determined that investigator-assessed disease progression or death had occurred in at least 70% of expected patients in the *BRCA*-mutant cohort.

All efficacy analyses were performed for the intent-to-treat population. The efficacy analyses are presented separately for the nested cohorts: *BRCA* mutant, HRD, and intent-to-treat population. The primary endpoint was tested using an ordered step-down multiple comparisons procedure²¹ for the three nested cohorts: *BRCA* mutant, HRD, and the intent-to-treat population. Investigator-assessed progression-free survival in patients with a *BRCA*-mutant carcinoma was tested first at a one-sided 0.025 significance level. Analysis of investigator-assessed progression-free survival in patients with an HRD carcinoma followed by analysis in the intent-to-treat population was contingent upon a statistically significant result in the analysis of patients with a *BRCA*-mutant carcinoma. Analysis of the key secondary endpoints of patient-reported outcomes and overall survival were to follow in a similar ordered step-down procedure.

Once statistical significance was not achieved for one test, the statistical significance was not declared for all subsequent analyses in the ordered step-down procedure. Progression-free survival by BICR was evaluated as a key stand-alone secondary endpoint, separate from the step-down procedure described above. Time to progression-free survival (by investigator and by BICR) and time to worsening in the FOSI-18 DRS-P subscale were analysed using stratified Kaplan-Meier methodology where distributions between rucaparib and placebo arms were compared using a stratified log-rank test. A stratified Cox proportional hazards model was used to estimate the HR between the arms. The proportionality of hazards for the Cox proportional hazard assumption (ie, constant relative hazard) was verified graphically using log-log plots. Exploratory analyses of progression-free survival were performed in subgroups based on patient characteristics (eg, randomisation stratification factors, demographics, disease burden at baseline). For patients with measurable disease at study entry, the proportion of patients achieving a confirmed complete or partial response per RECIST as assessed by the investigator was a prespecified exploratory endpoint of ARIEL3.

Safety, including adverse events and clinical laboratory investigations, was evaluated in all patients who received at least one dose of protocol-specified treatment.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Additional details are available in the appendix (p 4).

Role of the funding source

The study was designed by the sponsor, Clovis Oncology, Inc., and the coordinating investigators (RLC and JAL). Data presented herein were collected by the investigators,

analysed by Clovis Oncology, and interpreted by all authors. All authors had access to the data and had final responsibility for the decision to submit for publication. Writing and editorial assistance were supported by the sponsor.

Results

Between April 7, 2014, and July 19, 2016, 564 patients (intent-to-treat population) were randomised, 375 to rucaparib and 189 to placebo (figure 1; appendix p 12). At the visit cutoff date (April 15, 2017), 90 (24%) and 9 (5%) patients in the rucaparib and placebo arms, respectively, were still receiving treatment. Baseline demographic and clinical characteristics were generally well balanced between the treatment arms (table 1).

Following the ordered step-down multiple comparisons procedure, the analysis of investigator-assessed progression-free survival was evaluated first in patients with a *BRCA*-mutant carcinoma (130, rucaparib; 66, placebo; appendix p 12). Median time to progression or death was 16.6 months versus 5.4 months (stratified log-rank $p < 0.0001$) in the rucaparib and placebo arms, respectively (HR 0.23; 95% confidence interval [CI] 0.16–0.34; $p < 0.0001$) (figure 2). In patients with an HRD carcinoma (236, rucaparib; 118, placebo), median progression-free survival was 13.6 months and 5.4 months (stratified log-rank $p < 0.0001$), respectively (HR 0.32; 95% CI 0.24–0.42; $p < 0.0001$). Median progression-free survival in the intent-to-treat population was 10.8 months and 5.4 months (stratified log-rank $p < 0.0001$), respectively (HR 0.36; 95% CI 0.30–0.45; $p < 0.0001$).

In a prespecified analysis of the key stand-alone, secondary endpoint of progression-free survival assessed by BICR, results were similar to those of investigator-assessed progression-free survival for the patients with a *BRCA*-mutant carcinoma (median 26.8 months vs 5.4 months; HR 0.20; 95% CI 0.13–0.32; $p<0.0001$), the patients with an HRD carcinoma (median 22.9 months vs 5.5 months; HR 0.34; 95% CI 0.24–0.47; $p<0.0001$), and the intent-to-treat population (median 13.7 months vs 5.4 months; HR 0.35; 95% CI 0.28–0.45; $p<0.0001$) (figure 2). For the three nested cohorts, the plot of the log of the cumulative hazard for each treatment arm resulted in parallel curves for both investigator-assessed and BICR-assessed progression-free survival, indicating that there was no violation of the proportionality of hazards assumption (appendix 13).

Analysis of the secondary endpoint of time to worsening in the FOSI-18 DRS-P subscale score was assessed in the step-down procedure for the three nested subgroups. In patients with a *BRCA*-mutant carcinoma, there was no significant difference between arms in the time to worsening in the FOSI-18 DRS-P subscale (stratified log-rank $p=0.29$) (HR 1.24; 95% CI 0.82–1.86; $p=0.30$). As statistical significance was not reached in patients with a *BRCA*-mutant carcinoma, in accordance with the prespecified step-down procedure, statistical significance could not be determined for the remaining secondary analyses.

At the visit cutoff date (April 15, 2017), overall survival data were not mature (123 [22%] patients had died). A follow-up analysis will be performed when approximately 70% of the patients have died (≈ 395 overall survival events).

Preplanned subgroup analyses of investigator-assessed progression-free survival demonstrated that the progression-free survival benefit for rucaparib versus placebo was observed across all clinical subgroups, irrespective of presence or absence of measurable disease or bulky disease (defined as any lesion >2 cm) at baseline, response to last platinum-based regimen (complete or partial response), LOH (high, low, or indeterminate), or *BRCA* mutation (germline or somatic; *BRCA1* or *BRCA2*) (figure 3; appendix p 16). Further supporting the efficacy observed in the intent-to-treat population, in the non-nested subgroups of patients with carcinomas that were *BRCA* wild type, a progression-free survival benefit as assessed by the investigator was observed with rucaparib in patients with LOH-high carcinomas (median 9.7 months vs 5.4 months; HR 0.44; 95% CI 0.29–0.66; $p<0.0001$) and patients with LOH-low carcinomas (median 6.7 months vs 5.4 months; HR 0.58; 95% CI 0.40–0.85; $p=0.0049$) (figure 4); similar results were also observed in progression-free survival assessed by BICR (appendix p 17).

The majority of patients (374 [66%]) in ARIEL3 had achieved a partial response to the platinum-based therapy prior to randomisation. For 207 (37%) of 564 patients with measurable disease per investigator at study entry, a prespecified exploratory analysis of confirmed response was conducted. In the subgroup of patients with measurable disease at study entry with a *BRCA*-mutant carcinoma, 15 (38%) of 40 in the rucaparib arm and two (9%) of 23 in the placebo arm achieved a confirmed RECIST response (appendix p 9). In patients with an HRD carcinoma with measurable disease at baseline, the objective response was also higher in the rucaparib arm (23 [27%] of 85 patients) than the placebo arm (3 [7%] of 41 patients). A similar result was observed in

the intent-to-treat population among patients with measurable disease at baseline (26 [18%] of 141 patients in the rucaparib arm; 5 [8%] of 66 patients in the placebo arm). Complete responses were observed in the rucaparib arm in seven (18%), 10 (12%), and 10 (7%) patients with measurable disease at baseline in the nested *BRCA*-mutant and HRD cohorts, and the overall intent-to-treat population, respectively. Only one (2%) complete response was observed in the placebo arm; this occurred in the intent-to-treat population.

The safety population included 372 patients who received rucaparib (three patients were withdrawn prior to receiving rucaparib) and 189 patients who received placebo. For the safety population, the median (interquartile range) treatment duration was 8·3 (3·4–16·1) months in the rucaparib arm and 5·5 (2·8–8·3) months in the placebo arm. A treatment-emergent adverse event of any grade occurred in 372 patients (100%) in the rucaparib arm and 182 patients (96%) in the placebo arm (table 2). The most common treatment-emergent adverse events (reported in at least 35% of patients in either arm) included nausea (280 patients [75%] in the rucaparib arm and 69 patients [37%] in the placebo arm), asthenia or fatigue (258 patients [69%] and 83 patients [44%]), dysgeusia (146 patients [39%] and 13 patients [7%]), anaemia/decreased haemoglobin (139 patients [37%] and 11 patients [6%]), constipation (136 patients [37%] and 45 patients [24%]), and vomiting (136 patients [37%] and 28 patients [15%]). Treatment-emergent adverse events of grade 3 or greater were reported in 209 patients (56%) in the rucaparib arm and 28 patients (15%) in the placebo arm, the most common of which were anaemia/decreased haemoglobin (70 patients [19%] and one patient [1%]) and increase in alanine aminotransferase or aspartate aminotransferase (39 patients [10%]

and no patients). For patients in the rucaparib arm, a decline in haemoglobin level from baseline generally occurred in the first few cycles (appendix p 18). Elevations in alanine aminotransferase or aspartate aminotransferase were generally transient, self-limiting, and not associated with other signs of liver toxicity (appendix p 19). The frequency of treatment-emergent adverse events was comparable across the three nested cohorts.

One or more serious adverse events were reported in 78 patients (21%) in the rucaparib arm and 20 patients (11%) in the placebo arm. The most common serious adverse events (reported in at least 2% of patients in either arm) included anaemia (16 patients [4%] in the rucaparib arm and one patient [1%] in the placebo arm), pyrexia (six patients [2%] and no patients), vomiting (six patients [2%] and two patients [1%]), and small intestinal obstruction (three patients [1%] and three patients [2%]).

Myelodysplastic syndrome and acute myeloid leukaemia were reported in three patients (1%) in the rucaparib arm (two had a germline *BRCA*-mutant carcinoma, and one had a *BRCA* wild-type/LOH-low carcinoma). One patient died due to myelodysplastic syndrome and one due to acute myeloid leukaemia. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia in the placebo arm.

Treatment interruption due to a treatment-emergent adverse event occurred in 237 (64%) and 19 (10%) patients in the rucaparib and placebo arms, respectively (appendix p 10). Dose reduction due to a treatment-emergent adverse event occurred in 203 (55%) and eight (4%) patients in the rucaparib and placebo arms, respectively (appendix p 10). In the rucaparib and placebo arms, 117 (31%) and six (3%) patients, respectively, had both a treatment interruption due to a treatment-emergent adverse

event and a dose reduction due to a treatment-emergent adverse event. Of patients who received rucaparib, 50 (13%) discontinued due to a treatment-emergent adverse event (excluding disease progression) compared with three (2%) patients in the placebo arm (appendix p 11). As of the visit cutoff date, in the rucaparib arm there were four deaths due to adverse events considered unrelated to treatment by the investigator (two patients due to progressive disease, one due to cardiac arrest, and one due to haematophagic histiocytosis) and two deaths considered treatment related by the investigator (one due to acute myeloid leukaemia and one due to myelodysplastic syndrome). In the placebo arm, two patients died due to adverse events considered unrelated to treatment by the investigator (one due to progressive disease and one due to pulmonary embolism).

Discussion

In ARIEL3, rucaparib maintenance treatment versus placebo significantly improved progression-free survival in all primary analysis groups of patients with recurrent ovarian carcinoma following a complete or partial response to platinum-based therapy. The prolonged progression-free survival among patients receiving rucaparib in the intent-to-treat population (HR 0.36) demonstrates that patients with platinum-sensitive ovarian carcinoma can derive robust clinical benefit from rucaparib maintenance treatment. A similar improvement over placebo (HR 0.35) was seen in the secondary endpoint of assessment by BICR review, supporting the validity of the benefit observed with rucaparib maintenance treatment. Furthermore, the lower hazard of disease

progression or death associated with rucaparib in the study was observed across all prespecified subgroups that were analysed. Analysis of non-nested, non-overlapping patient subpopulations (ie, *BRCA* wild-type/LOH-high and *BRCA* wild-type/LOH-low patients) indicate that the statistically significant improvement in progression-free survival observed in the intent-to-treat population was not driven only by the results in the nested HRD or *BRCA*-mutant cohorts.

Patient-reported outcomes were evaluated as a secondary endpoint of ARIEL3 as part of the step-down procedure, with no significant difference in time to worsening in the FOSI-18 DRS-P subscale observed between the rucaparib and placebo arms. Further analyses of the patient-reported health outcome data gathered in ARIEL3 are planned and will be reported separately.

Overall survival data were not mature at the time of the visit cutoff, with less than 25% of the events needed for final analysis. Patient follow-up is continuing in a blinded manner and overall survival will be assessed after about 70% maturity is reached.

As reported in prior studies of rucaparib and other PARP inhibitors,^{5,6,9-11} gastrointestinal side effects, asthenia or fatigue, and myelosuppression were common treatment-emergent adverse events in the rucaparib arm. Management of adverse events included supportive care and dose modifications (including treatment interruption and/or dose reduction). Common laboratory abnormalities observed in the rucaparib arm included elevations in alanine aminotransferase, aspartate aminotransferase, and blood creatinine. Alanine aminotransferase and aspartate aminotransferase were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity, and generally resolved over time. No cases were considered to meet

Hy's law criteria for drug-induced liver injury (ie, alanine aminotransferase or aspartate aminotransferase greater than 3 times the upper limit of normal with concomitant bilirubin greater than 2 times the upper limit of normal without alkaline phosphatase elevations or another clear reason for the elevations).^{22,23} Similarly, elevations in creatinine, which have also been observed with olaparib,²⁴ were self-limiting and stabilised over time. Creatinine is secreted into urine via renal transporters (eg, MATE1, MATE2-K, OCT-1, and OCT-2), which have been shown to be inhibited in vitro by multiple PARP inhibitors, including rucaparib, olaparib, and veliparib.²⁵⁻²⁷ Patterns of elevation and stabilisation of these laboratory abnormalities similar to those reported here were observed in the treatment setting with rucaparib.^{28,29}

The results of ARIEL3 are consistent with those of other placebo-controlled studies of PARP inhibitors in the maintenance treatment setting, including NOVA (NCT01847274) with niraparib and Study 19 (NCT00753545) and SOLO2 (NCT01874353) with olaparib.^{5,6,9} However, direct comparisons with these other trials cannot be made due to differences in patient groups analysed (eg, SOLO2 only enrolled patients with a germline *BRCA* mutation), definition of HRD (eg, in NOVA, HRD included patients with somatic mutations in *BRCA*, as well as those with non-*BRCA*-related HRD), the method of primary endpoint assessment (eg, investigator vs BICR), and study design (eg, residual disease was restricted to <2 cm in NOVA).^{5,6,9,30}

Although having a CA-125 below the upper limit of normal is not a requirement of response per GCIG CA-125 criteria or a RECIST partial response, ARIEL3 required that patients have CA-125 below the upper limit of normal prior to study entry; this eligibility requirement was intended to ensure that patients had controlled disease at study entry.

Similar restrictions on CA-125 levels were included in the enrolment criteria of other studies investigating PARP inhibitors in the maintenance treatment setting, although it is unknown how many patients in these studies had CA-125 levels greater than the upper limit of normal at study entry.^{5,6,9} Furthermore, it is not known whether inclusion of patients with CA-125 levels exceeding the upper limit of normal affects the efficacy of PARP inhibitors in the maintenance treatment setting.

Although ARIEL3 extends the findings of previous studies of PARP inhibitors in this setting, there are some important differences between ARIEL3 and other studies in the maintenance treatment setting. Notably, patients in ARIEL3 with carcinomas associated with a germline or somatic *BRCA* mutation were both included in the three nested cohorts (*BRCA* mutant, HRD, and intent-to-treat population), a feature that is unique to ARIEL3 among clinical trials in this setting. In addition, ARIEL3 did not restrict enrolment based on target lesion size for patients with residual disease (partial response to prior platinum). A number of patients with measurable residual disease at study entry showed further reduction in carcinoma burden with rucaparib maintenance treatment, including conversion to a complete response per RECIST in several patients in the nested *BRCA*-mutant and HRD cohorts and the overall intent-to-treat population.

Additionally, ARIEL3 is the first phase 3 study to prospectively assess the primary endpoint of progression-free survival in patients with recurrent ovarian carcinoma associated with HRD. Preplanned analysis of progression-free survival in patients with a *BRCA* wild-type/LOH-high carcinoma, wherein patients treated with rucaparib had an increase in median progression-free survival (HR 0.44) compared with placebo, shows that the improvement observed in the HRD cohort was not driven solely by patients with

a *BRCA*-mutant carcinoma. The benefit in progression-free survival seen in patients with a *BRCA* wild-type/LOH-high carcinoma (HR 0.44) compared with patients with a *BRCA* wild-type/LOH-low carcinoma (HR 0.58) demonstrates the utility of HRD, in particular high genomic LOH as defined by Foundation Medicine's T5 assay, as a predictive biomarker for sensitivity to rucaparib treatment.

Based on our findings, HRD assessment may be an informative tool for clinicians making treatment decisions for patients with *BRCA* wild-type associated platinum-sensitive ovarian carcinoma. ARIEL2 Part 1 demonstrated that HRD assessment in platinum-sensitive patients with ovarian carcinoma who received 1 or 2 prior lines of chemotherapy helped discriminate which patients benefited from rucaparib; however, HRD assessment did not do so completely because some patients with carcinomas that were *BRCA* wild type/LOH low responded to rucaparib.¹¹ Similarly, in ARIEL3 response to rucaparib was also clearly observed in the cohort of patients with carcinomas that were *BRCA* wild type/LOH low, with more than 30% of patients in the rucaparib arm achieving benefit of more than a year's duration compared with less than 10% in the placebo arm. Therefore, the biomarker does not appear to be sufficiently precise to predict lack of benefit on an individual basis. As next-generation sequencing-based assays become more common in routine clinical practice, the cost-benefit ratio of using these assays will need to be evaluated in the context of optimal response to preceding platinum therapy, the cost of maintenance therapy, and the potential magnitude of clinical benefit in a particular subgroup.

In summary, rucaparib improved progression-free survival in women with platinum-sensitive ovarian carcinoma following a complete or partial response to second-line or

later platinum-based chemotherapy. Treatment-emergent adverse events in the rucaparib arm were generally managed with dose modifications and were not associated with increased mortality or morbidity compared with the placebo arm.

Contributors

RLC, JI, KKL, HG, and JAL were responsible for the study design. RLC, AMO, DL, CA, AO, AD, NC, JIW, AC, GS, AL, RWH, MAG, PCF, JCG, DMO, DKA, JGD, EMS, AF, GEK, IAM, CLS, and JAL treated patients. RLC, AMO, DL, CA, AO, AD, NC, JIW, AC, GS, CA, AL, RWH, MAG, PCF, JCG, DMO, DKA, JGD, EMS, AF, GEK, IAM, CLS, KKL, and JAL acquired the data. RLC, TC, LM, JI, SG, CG, TCH, MR, JS, KKL, HG, and JAL interpreted the data. All authors were responsible for writing the manuscript, and reviewed draft and final versions of the manuscript.

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Figure legends

Figure 1: CONSORT diagram

*A full description of protocol deviations is provided in the appendix (p 5); these protocol deviations are reported as of the visit cutoff date (April 15, 2017) and did not result in the exclusion of patients or data from any efficacy or safety analyses in the study.

Figure 2: Investigator-assessed and blinded independent central radiology review–assessed progression-free survival

Kaplan-Meier estimates of progression-free survival as assessed by the investigator (A–C) and by BICR (D–F) in the rucaparib (blue) and placebo (red) arms for patients with a *BRCA*-mutant carcinoma (A, D), patients with an HRD carcinoma (B, E), and the intent-to-treat population (C, F). BICR=blinded independent central radiology review.

CI=confidence interval. HR=hazard ratio. HRD=homologous recombination deficient.

NR=not reached.

Figure 3: Investigator-assessed progression-free survival in subgroups of the intent-to-treat population

CA-125=cancer antigen 125. CI=confidence interval. CR=complete response.

GCIG=Gynecologic Cancer InterGroup. HR=hazard ratio. LOH=loss of heterozygosity.

PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors version

1.1. *By local germline test, central germline test, or tumour testing. †Tumour sample

was not evaluable for percent of genomic LOH due to low tumour content or low

aneuploidy. †Prior treatment with bevacizumab was permitted as part of penultimate or earlier treatment.

Figure 4: Investigator-assessed progression-free survival in patients with a *BRCA* wild-type carcinoma

Kaplan-Meier estimates of progression-free survival as assessed by the investigator in the rucaparib (blue) and placebo (red) arms for patients with a *BRCA* wild-type carcinoma with LOH high (A) and LOH low (B). CI=confidence interval. HR=hazard ratio. LOH=loss of heterozygosity.

Table 1: Baseline patient and disease characteristics in the intent-to-treat population

Characteristic	Rucaparib (n=375)	Placebo (n=189)
Age (years)	61.0 (53.0–67.0)	62.0 (53.0–68.0)
Race		
White	302 (81%)	149 (79%)
Non-white	26 (7%)	13 (7%)
Unknown	47 (13%)	27 (14%)
ECOG Performance Status		
0	280 (75%)	136 (72%)
1	95 (25%)	53 (28%)
Diagnosis		
Epithelial ovarian cancer	312 (83%)	159 (84%)
Fallopian tube cancer	32 (9%)	10 (5%)
Primary peritoneal cancer	31 (8%)	19 (10%)
High-grade serous adenocarcinoma*	0	1 (1%)
Histology		
Serous	357 (95%)	179 (95%)
Endometrioid	16 (4%)	7 (4%)
Mixed	1 (<1%)	3 (2%)
Transitional	1 (<1%)	0
BRCA mutation in the carcinoma		
BRCA mutant	130 (35%)	66 (35%)
BRCA1	80 (21%)	37 (20%)
BRCA2	50 (13%)	29 (15%)
Germline	82 (22%)	48 (25%)
Somatic	40 (11%)	16 (8%)
Unknown†	8 (2%)	2 (1%)
BRCA wild type	245 (65%)	123 (65%)
LOH high	106 (28%)	52 (28%)
LOH low	107 (29%)	54 (29%)
LOH indeterminate‡	32 (9%)	17 (9%)
Number of prior chemotherapy regimens	2 (2–3)	2 (2–3)
2	231 (62%)	124 (66%)
≥3	144 (38%)	65 (34%)
Prior bevacizumab use§	83 (22%)	43 (23%)
Number of platinum-based regimens	2 (2–3)	2 (2–3)
2	236 (63%)	126 (67%)
≥3	139 (37%)	63 (33%)
Measurable disease at baseline (per investigator)	141 (38%)	66 (35%)
Bulky disease (any lesion >2 cm) at baseline (per independent radiological review)	71 (19%)	29 (15%)
Randomisation stratification factors		

HRR gene mutation status		
<i>BRCA</i> mutant	130 (35%)	66 (35%)
Mutation in other, non- <i>BRCA</i> HRR gene	28 (7%)	15 (8%)
No mutation detected in <i>BRCA</i> or HRR gene	217 (58%)	108 (57%)
Time to progression with penultimate platinum (months)	13·8 (10·0–22·3)	14·6 (10·7–24·0)
6 to <12 months	151 (40%)	76 (40%)
≥12 months	224 (60%)	113 (60%)
Response to last platinum		
CR per RECIST	126 (34%)	64 (34%)
PR per RECIST or serologic response per GCIG CA-125 criteria	249 (66%)	125 (66%)
<p>Data are median (interquartile range) or n (%). CA-125=cancer antigen 125. CR=complete response. ECOG=Eastern Cooperative Oncology Group. GCIG=Gynecologic Cancer InterGroup. HRR=homologous recombination repair. LOH=loss of heterozygosity. PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors version 1·1. *Per patient records, origin was fallopian tube and/or ovary. †Tumour sample was <i>BRCA</i> mutant by Foundation Medicine's T5 next-generation sequencing assay, but a blood sample was not available for central germline testing. ‡Tumour sample was not evaluable for percent of genomic LOH due to low tumour content or low aneuploidy. §Prior treatment with bevacizumab was permitted as part of penultimate or earlier treatment.</p>		

Table 2: Treatment emergent adverse events of any grade reported in ≥10% of patients in either arm in the safety population

	Rucaparib (n=372)				Placebo (n=189)			
	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4
At least one AE	372 (100%)*	163 (44%)	179 (48%)	24 (6%)	182 (96%)†	154 (81%)	24 (13%)	2 (1%)
Blood and lymphatic system disorders								
Anaemia; decreased haemoglobin	139 (37%)	69 (19%)	67 (18%)	3 (1%)	11 (6%)	10 (5%)	0	1 (1%)
Neutropenia; neutrophil count decreased	67 (18%)	42 (11%)	19 (5%)	6 (2%)	9 (5%)	7 (4%)	1 (1%)	1 (1%)
Thrombocytopenia; platelet count decreased	104 (28%)	85 (23%)	13 (3%)	6 (2%)	5 (3%)	5 (3%)	0	0
Gastrointestinal disorders								
Abdominal distension	41 (11%)	41 (11%)	0	0	22 (12%)	22 (12%)	0	0
Abdominal pain	111 (30%)	102 (27%)	9 (2%)	0	49 (26%)	48 (25%)	1 (1%)	0
Abdominal pain (upper)	52 (14%)	50 (13%)	2 (1%)	0	10 (5%)	10 (5%)	0	0
Constipation	136 (37%)	129 (35%)	7 (2%)	0	45 (24%)	43 (23%)	2 (1%)	0
Diarrhoea	118 (32%)	116 (31%)	2 (1%)	0	41 (22%)	39 (21%)	2 (1%)	0
Dyspepsia	54 (15%)	53 (14%)	1 (<1%)	0	9 (5%)	9 (5%)	0	0
Nausea	280 (75%)	266 (72%)	14 (4%)	0	69 (37%)	68 (36%)	1 (1%)	0
Vomiting	136 (37%)	121 (33%)	15 (4%)	0	28 (15%)	26 (14%)	2 (1%)	0
General disorders and administration site conditions								
Asthenia; fatigue	258 (69%)	233 (63%)	25 (7%)	0	83 (44%)	78 (41%)	5 (3%)	0
Oedema peripheral	39 (10%)	38 (10%)	1 (<1%)	0	14 (7%)	14 (7%)	0	0
Pyrexia	44 (12%)	44 (12%)	0	0	8 (4%)	8 (4%)	0	0
Infections and infestations								
Upper respiratory tract infection	41 (11%)	41 (11%)	0	0	6 (3%)	4 (2%)	2 (1%)	0
Investigations								
Increase in alanine aminotransferase or aspartate aminotransferase [‡]	126 (34%)	87 (23%)	39 (10%)	0	7 (4%)	7 (4%)	0	0
Increase in blood creatinine	57 (15%)	56 (15%)	1 (<1%)	0	3 (2%)	3 (2%)	0	0
Metabolism and nutrition disorders								
Decreased appetite	87 (23%)	85 (23%)	2 (1%)	0	26 (14%)	26 (14%)	0	0
Hypomagnesaemia	40 (11%)	39 (10%)	1 (<1%)	0	11 (6%)	11 (6%)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	57 (15%)	55 (15%)	2 (1%)	0	24 (13%)	24 (13%)	0	0
Back pain	45 (12%)	45 (12%)	0	0	28 (15%)	28 (15%)	0	0
Nervous system disorders								
Dizziness	54 (15%)	54 (15%)	0	0	15 (8%)	14 (7%)	1 (1%)	0
Dysgeusia	146 (39%)	146 (39%)	0	0	13 (7%)	13 (7%)	0	0
Headache	67 (18%)	66 (18%)	1 (<1%)	0	30 (16%)	29 (15%)	1 (1%)	0
Psychiatric disorders								
Insomnia	53 (14%)	53 (14%)	0	0	15 (8%)	15 (8%)	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	54 (15%)	54 (15%)	0	0	25 (13%)	25 (13%)	0	0
Dyspnoea	50 (13%)	50 (13%)	0	0	14 (7%)	14 (7%)	0	0
Skin and subcutaneous tissue disorders								
Photosensitivity reaction	64 (17%)	62 (17%)	2 (1%)	0	1 (1%)	1 (1%)	0	0
Pruritus	47 (13%)	47 (13%)	0	0	19 (10%)	19 (10%)	0	0
Rash	46 (12%)	45 (12%)	1 (<1%)	0	17 (9%)	17 (9%)	0	0

Data are n (%); the safety population includes all patients who received at least one dose of protocol-specified treatment. AE=adverse event. *Includes six patients with a grade 5 treatment-emergent adverse event. †Includes two patients with a grade 5 treatment-emergent adverse event. ‡Elevations were transient, self-limiting, and not associated with other signs of liver toxicity.