Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
35th Prioritization – 2nd quarter 2018

General Information, efficacy and safety data

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Please note:

Within this document you find general information about the drug of interest and the indication it is intended to be used for. Further we have included full text publications and conference abstracts of phase III trials, assessing the safety and efficacy of the drugs of interest.

At the very end of each chapter we have provided a table containing the prioritization criteria and a drop-down field to apply the provided criteria.

Introduction

As part of the project „Horizon Scanning in Oncology“ (further information can be found here: http://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie), 9 information sources are scanned frequently to identify emerging anticancer drugs.

Every 3 months, these anticancer therapies are filtered (i.e. in most cases defined as availability of phase III results; for orphan drugs also phase II) to identify drugs at/around the same time as the accompanying drug licensing decisions of the EMA.

An expert panel consisting of oncologists and pharmacists then applies 5 prioritisation criteria to elicit those anti-cancer therapies which might be associated with either a considerable impact on financial resources or a substantial health benefit.

For the 35th prioritisation (March 2018), eight drugs were filtered out of 404 identified and were sent to prioritisation. Of these, six drugs were ranked as ‘highly relevant’ by the expert panel, one as ‘relevant’ and one as ‘not relevant’. For ‘highly relevant’ drugs, further information including, for example, abstracts of phase III studies and licensing status is contained in this document.

The summary judgements of the expert panel for all prioritised drugs are provided in the following table.

No	Filtered Drugs – 35th prioritisation 2nd quarter 2018	Overall category
1.	Acalabrutinib (Calquence®) in relapsed or refractory mantle cell lymphoma (MCL)	Relevant
2.	Apalutamide (Erleada®) treatment and metastasis-free survival in prostate cancer	Highly relevant
3.	Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition	Not relevant
4.	Dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib (Tyverb®) plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer	Highly relevant
5.	Daratumumab (Darzalex®) plus bortezomib, melphalan, and prednisone for untreated myeloma	Highly relevant
6.	Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (NSCLC)	Highly relevant
7.	Osimertinib (Tagrisso®) in untreated EGFR-mutated advanced NSCLC	Highly relevant
8.	Rucaparib (Rubraca®) maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy	Highly relevant

1 Prostate Cancer

1.1 Apalutamide (Erleada®) treatment and metastasis-free survival in prostate cancer

Overview

Drug Description		a competitive inhibitor of the androgen receptor
Patient Indication		patients with nonmetastatic castration-resistant prostate cancer who are at high risk for the development of metastasis
Incidence in Austria		4,854 newly diagnosed per year (2015), 130.6/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02489318 until July 2022 NCT02257736 until August 2021
Approval status for this indication	**EMA**	-
	FDA	02/2018: the FDA approved apalutamide for patients with non-metastatic castration-resistant prostate cancer
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

NEJM; available online February 8, 2018 (Smith et al.): *"Apalutamide treatment and metastasis-free survival in prostate cancer"*

Background
Apalutamide, a competitive inhibitor of the androgen receptor, is under development for the treatment of prostate cancer. We evaluated the efficacy of apalutamide in men with nonmetastatic castration-resistant prostate cancer who were at high risk for the development of metastasis.

Methods
We conducted a double-blind, placebo-controlled, phase 3 trial involving men with nonmetastatic castration-resistant prostate cancer and a prostate-specific antigen doubling time of 10 months or less. Patients were randomly assigned, in a 2:1 ratio, to receive apalutamide (240 mg per day) or placebo. All the patients continued to receive androgen-deprivation therapy. The primary end point was metastasis-free survival, which was defined as the time from randomization to the first detection of distant metastasis on imaging or death.

Results
A total of 1207 men underwent randomization (806 to the apalutamide group and 401 to the placebo group). In the planned primary analysis, which was performed after 378 events had occurred, median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (hazard ratio for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; P<0.001). Time to symptomatic progression was significantly longer with apalutamide than with placebo (hazard ratio, 0.45; 95% CI, 0.32 to 0.63; P<0.001). The rate of adverse events leading to discontinuation of the trial regimen was 10.6% in the apalutamide group and 7.0% in the placebo group. The following adverse events occurred at a higher rate with apalutamide than with placebo: rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%).

Conclusion
Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo. (Funded by Janssen Research and Development; SPARTAN ClinicalTrials.gov number, NCT01946204.)

2 Breast Cancer

2.1 Dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib (Tyverb®) plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer

Overview

Drug Description		small molecule dual inhibitor of HER1 (ErbB1) and HER2 (ErbB2) receptor tyrosine kinases
Patient Indication		postmenopausal women with HER2-positive/HR-positive metastatic breast cancer who received prior endocrine therapy and prior neo(adjuvant)/first-line trastuzumab plus chemotherapy.
Incidence in Austria		5,390 newly diagnosed per year (2015), 63.3/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT00667251 until December 2020
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	06/2008: lapatinib (LAP) in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2) and who have received prior therapy including trastuzumab (TRAS) 02/2010: for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2); in combination with an aromatase inhibitor (AI) for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor 06/2013: indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2); in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy
	FDA	03/2007: in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab 01/2010: in combination with letrozole for the treatment of postmenopausal women with hormone-receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated
Costs		1 treatment cycle (21 days): oral 1,000 mg/day (LAP+TRAS+AI arm) or 1,500 mg/day (LAP+AI arm); ex-factory price: 84 Tyverb® tablets a 250 mg € 1,481.70 -> costs for 1 treatment cycle of lapatinib in the LAP+TRAS+AI arm: € 1,481.70 or ex-factory price: 70 Tyverb® tablets a 250 mg € 1235.07 -> costs for treatment cycle of lapatinib in the LAP+AI arm: € 2,470.14 Additional costs will incur due to the combination treatment of LAP with TRAS and and AI (letrozole, anastrozole or exemestane)

Phase III results

Journal of Clinical Oncology; available online December 15, 2017 (Johnston et al.): *"Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor–positive metastatic breast cancer: ALTERNATIVE"*

Background
Human epidermal growth factor receptor 2 (HER2) targeting plus endocrine therapy (ET) improved clinical benefit in HER2-positive, hormone receptor (HR)–positive metastatic breast cancer (MBC) versus ET alone. Dual HER2 blockade enhances clinical benefit versus single HER2 blockade. The ALTERNATIVE study evaluated the efficacy and safety of dual HER2 blockade plus aromatase inhibitor (AI) in postmenopausal women with HER2-positive/HR-positive MBC who received prior ET and prior neo(adjuvant)/first-line trastuzumab (TRAS) plus chemotherapy.

Methods
Patients were randomly assigned (1:1:1) to receive lapatinib (LAP) + TRAS + AI, TRAS + AI, or LAP + AI. Patients for whom chemotherapy was intended were excluded. The primary end point was progression-free survival (PFS; investigator assessed) with LAP + TRAS + AI versus TRAS + AI. Secondary end points were PFS (comparison of other arms), overall survival, overall response rate, clinical benefit rate, and safety.

Results
Three hundred fifty-five patients were included in this analysis: LAP + TRAS + AI (n = 120), TRAS + AI (n = 117), and LAP + AI (n = 118). Baseline characteristics were balanced. The study met its primary end point; superior PFS was observed with LAP + TRAS + AI versus TRAS + AI (median PFS, 11 v 5.7 months; hazard ratio, 0.62; 95% CI, 0.45 to 0.88; P = .0064). Consistent PFS benefit was observed in predefined subgroups. Overall response rate, clinical benefit rate, and overall survival also favored LAP + TRAS + AI. The median PFS with LAP + AI versus TRAS + AI was 8.3 versus 5.7 months (hazard ratio, 0.71; 95% CI, 0.51 to 0.98; P = .0361). Common adverse events (AEs; $\geq$15%) with LAP + TRAS + AI, TRAS + AI, and LAP + AI were diarrhea (69%, 9%, and 51%, respectively), rash (36%, 2%, and 28%, respectively), nausea (22%, 9%, and 22%, respectively), and paronychia (30%, 0%, and 15%, respectively),mostly grade 1 or 2. Serious AEs were reported similarly across the three groups, and AEs leading to discontinuation were lower with LAP + TRAS + AI.

Interpretation
Dual HER2 blockade with LAP + TRAS + AI showed superior PFS benefit versus TRAS + AI in patients with HER2-positive/HR-positive MBC. This combination offers an effective and safe chemotherapy-sparing alternative treatment regimen for this patient population.

3 Multiple Myeloma

3.1 Daratumumab (Darzalex®) plus bortezomib, melphalan, and prednisone for untreated myeloma

Overview

Drug Description		human CD38-directed monoclonal antibody (CD38 is a transmembrane glycoprotein (48kDa) expressed on the surface of haematopoietic cells
Patient Indication		in combination with bortezomib, melphalan and prednisone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation
Incidence in Austria		409 newly diagnosed per year (2015), 4.9/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02252172 until November 2024 NCT03217812 until October 2022
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	07/2013: orphan designation was granted for daratumumab for the treatment of plasma-cell myeloma 05/2016: as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy 02/2017: in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
	FDA	11/2015 (accelerated approval): indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent 11/2016: in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy 06/2017: in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor
Costs		Daratumumab (1 cycle = 42 days): Cycle 1: IV 16 mg/kg/once weekly, assuming an average body weight of 70 kg, 1,120 mg/week are needed. One vial of concentrate for solution for infusion containing 400 mg costs € 2,096.0 (ex-factory price) -> €6,288.0/week x6 = € 37,728 for the first cycle Cycle 2-9: daratumumab is administered every 3 weeks, costs for one cycle: € 12,576.0 Subsequent cycles: daratumumab is administered every 4 weeks, costs for one cycle: € 9,432.0 Additionally, costs for bortezomib, melphalan, and prednisone incur; in the experimental group dexamethasone was added as well to manage infusion reactions

Phase III results

NEJM; available online December 12, 2017 (Mateos et al.): "*Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma"*

Background
The combination of bortezomib, melphalan, and prednisone is a standard treatment for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation. Daratumumab has shown efficacy in combination with standard-of-care regimens in patients with relapsed or refractory multiple myeloma.

Methods
In this phase 3 trial, we randomly assigned 706 patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation to receive nine cycles of bortezomib, melphalan, and prednisone either alone (control group) or with daratumumab (daratumumab group) until disease progression. The primary end point was progression-free survival.

Findings
At a median follow-up of 16.5 months in a prespecified interim analysis, the 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group (P<0.001), and the rate of complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001). In the daratumumab group, 22.3% of the patients were negative for minimal residual disease (at a threshold of 1 tumor cell per 105 white cells), as compared with 6.2% of those in the control group (P<0.001). The most common adverse events of grade 3 or 4 were hematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively. Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients.

Interpretation
Among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab. The daratumumab-containing regimen was associated with more grade 3 or 4 infections. (Funded by Janssen Research and Development; ALCYONE ClinicalTrials.gov number, NCT02195479.)

4 Lung Cancer

4.1 Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (NSCLC)

Overview

Drug Description		a second-generation, irreversible EGFR tyrosine kinase inhibitor
Patient Indication		first-line treatment of patients with advanced *EGFR*-mutation-positive non-small-cell lung cancer (NSCLC)
Incidence in Austria		4,860 newly diagnosed per year (2015), 57.9/100,000/year (European Standard Population, 2013), including lung, trachea and bronchial tumours
Ongoing Phase III		-
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

Lancet (2017); 18: 1454–66; available online September 2017 (Wu et al.): "*Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial"*

Background
Dacomitinib is a second-generation, irreversible EGFR tyrosine kinase inhibitor. We compared its efficacy and safety with that of the reversible EGFR tyrosine kinase inhibitor gefitinib in the first-line treatment of patients with advanced *EGFR*-mutation-positive non-small-cell lung cancer (NSCLC)

Methods
In this international, multicentre, randomised, open-label, phase 3 study (ARCHER 1050), we enrolled adults (aged ≥18 years or ≥20 years in Japan and South Korea) with newly diagnosed advanced NSCLC and one *EGFR* mutation (exon 19 deletion or Leu858Arg) at 71 academic medical centres and university hospitals in seven countries or special administrative regions. We randomly assigned participants (1:1) to receive oral dacomitinib 45 mg/day (in 28-day cycles) or oral gefitinib 250 mg/day (in 28-day cycles) until disease progression or another discontinuation criterion was met. Randomisation, stratified by race and *EGFR* mutation type, was done with a computer-generated random code assigned by a central interactive web response system. The primary endpoint was progression-free survival assessed by masked independent review in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01774721, and is ongoing but no longer recruiting patients.

Findings
Between May 9, 2013, and March 20, 2015, 452 eligible patients were randomly assigned to receive dacomitinib (n=227) or gefitinib (n=225). Median duration of follow-up for progression-free survival was 22.1 months (95% CI 20.3‑23.9). Median progression-free survival according to masked independent review was 14.7 months (95% CI 11.1‑16.6) in the dacomitinib group and 9.2 months (9.1‑11.0) in the gefitinib group (hazard ratio 0.59, 95% CI 0.47‑0.74; p<0.0001). The most common grade 3‑4 adverse events were dermatitis acneiform (31 [14%] of 227 patients given dacomitinib *vs.* none of 224 patients given gefitinib), diarrhoea (19 [8%] *vs.* two [1%]), and raised alanine aminotransferase levels (two [1%] *vs.* 19 [8%]). Treatment-related serious adverse events were reported in 21 (9%) patients given dacomitinib and in ten (4%) patients given gefitinib. Two treatment-related deaths occurred in the dacomitinib group (one related to untreated diarrhoea and one to untreated cholelithases/liver disease) and one in the gefitinib group (related to sigmoid colon diverticulitis/rupture complicated by pneumonia).

Interpretation
Dacomitinib significantly improved progression-free survival over gefitinib in first-line treatment of patients with *EGFR*-mutation-positive NSCLC and should be considered as a new treatment option for this population.

4.2 Osimertinib (Tagrisso®) in untreated EGFR-mutated advanced NSCLC

Overview

Drug Description		irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI‑sensitizing and *EGFR* T790M resistance mutations
Patient Indication		patients with previously untreated, *EGFR* mutation‑positive advanced NSCLC
Incidence in Austria		4,860 newly diagnosed per year (2015), 57.9/100,000/year (European Standard Population, 2013), including lung, trachea and bronchial tumours
Ongoing Phase III		NCT02296125 until 06/2019
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	02/2016: for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC
	FDA	11/2015 (accelerated approval): for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC (as detected by an FDA-approved test), who have progressed on or after EGFR TKI therapy
Costs		Osimertinib dose: 80 mg/day 30 Tagrisso® tablets a 80 mg costing € 6,132.50 (ex-factory price)

Phase III results

NEJM; available online November 18, 2017 (Soria et al.): *"Osimertinib in untreated EGFR-mutated advanced non‑small-cell lung cancer"*

Background
Osimertinib is an oral, third-generation, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI‑ sensitizing and *EGFR* T790M resistance mutations. We compared osimertinib with standard EGFR-TKIs in patients with previously untreated, *EGFR* mutation‑positive advanced non‑small-cell lung cancer (NSCLC).

Methods
In this double-blind, phase 3 trial, we randomly assigned 556 patients with previously untreated, *EGFR* mutation‑positive (exon 19 deletion or L858R) advanced NSCLC in a 1:1 ratio to receive either osimertinib (at a dose of 80 mg once daily) or a standard EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily). The primary end point was investigator-assessed progression-free survival.

Findings
The median progression-free survival was significantly longer with osimertinib than with standard EGFR-TKIs (18.9 months vs. 10.2 months; hazard ratio for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001). The objective response rate was similar in the two groups: 80% with osimertinib and 76% with standard EGFR-TKIs (odds ratio, 1.27; 95% CI, 0.85 to 1.90; P = 0.24). The median duration of response was 17.2 months (95% CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95% CI, 7.3 to 9.8) with standard EGFR-TKIs. Data on overall survival were immature at the interim analysis (25% maturity). The survival rate at 18 months was 83% (95% CI, 78 to 87) with osimertinib and 71% (95% CI, 65 to 76) with standard EGFR-TKIs (hazard ratio for death, 0.63; 95% CI, 0.45 to 0.88; P = 0.007 [nonsignificant in the interim analysis]). Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% vs. 45%).

Interpretation
Osimertinib showed efficacy superior to that of standard EGFR-TKIs in the first-line treatment of *EGFR* mutation‑positive advanced NSCLC, with a similar safety profile and lower rates of serious adverse events. (Funded by AstraZeneca; FLAURA ClinicalTrials.gov number, NCT02296125.)

5 Ovarian cancer

5.1 Rucarparib (Rubraca®) maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy

Overview

Drug Description		a poly(ADP-ribose) polymerase inhibitor
Patient Indication		patients with a platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma who received at least two previous platinum-based chemotherapy regimens
Incidence in Austria		659 newly diagnosed per year (2015), 14.1/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02855944 until June 2024
Approval status for this indication	**EMA**	10/2012: orphan designation was granted for the treatment of ovarian cancer
	FDA	12/2016 (accelerated approval): as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

Lancet; available online September 12, 2017 (Coleman et al.): *"Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial"*

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

Methods
In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients from 87 hospitals and cancer centres across 11 countries. Eligible patients were aged 18 years or older, had a platinum-sensitive, highgrade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, had received at least two previous platinum-based chemotherapy regimens, had achieved complete or partial response to their last platinum-based regimen, had a cancer antigen 125 concentration of less than the upper limit of normal, had a performance status of 0–1, and had adequate organ function. Patients were ineligible if they had symptomatic or untreated central nervous system metastases, had received anticancer therapy 14 days or fewer before starting the study, or had received previous treatment with a poly(ADP-ribose) polymerase inhibitor. We randomly allocated patients 2:1 to receive oral rucaparib 600 mg twice daily or placebo in 28 day cycles using a computer-generated sequence (block size of six, stratified by homologous recombination repair gene mutation status, progression-free interval after the penultimate platinum-based regimen, and best response to

the most recent platinum-based regimen). Patients, investigators, site staff, assessors, and the funder were masked to assignments. The primary outcome was investigator-assessed progression-free survival evaluated with use of an ordered step-down procedure for three nested cohorts: patients with *BRCA* mutations (carcinoma associated with deleterious germline or somatic *BRCA* mutations), patients with homologous recombination deficiencies (*BRCA* mutant or *BRCA* wild-type and high loss of heterozygosity), and the intention-to-treat population, assessed at screening and every 12 weeks thereafter. This trial is registered with ClinicalTrials.gov, number NCT01968213; enrolment is complete.

Findings

Between April 7, 2014, and July 19, 2016, we randomly allocated 564 patients: 375 (66%) to rucaparib and 189 (34%) to placebo. Median progression-free survival in patients with a *BRCA*-mutant carcinoma was 16.6 months (95% CI 13.4–22.9; 130 [35%] patients) in the rucaparib group versus 5.4 months (3.4–6.7; 66 [35%] patients) in the placebo group (hazard ratio 0.23 [95% CI 0.16–0.34]; p<0.0001). In patients with a homologous recombination deficient carcinoma (236 [63%] *vs.* 118 [62%]), it was 13.6 months (10.9–16.2) versus 5.4 months (5.1–5.6; 0.32 [0.24–0.42]; p<0.0001). In the intention-to-treat population, it was 10.8 months (8.3–11.4) versus 5.4 months (5.3–5.5; 0.36 [0.30–0.45]; p<0.0001). Treatment-emergent adverse events of grade 3 or higher in the safety population (372 [99%] patients in the rucaparib group *vs.* 189 [100%] in the placebo group) were reported in 209 (56%) patients in the rucaparib group versus 28 (15%) in the placebo group, the most common of which were anaemia or decreased haemoglobin concentration (70 [19%] *vs.* one [1%]) and increased alanine or aspartate aminotransferase concentration (39 [10%] *vs.* none).

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. ARIEL3 provides further evidence that use of a poly(ADP-ribose) polymerase inhibitor in the maintenance treatment setting versus placebo could be considered a new standard of care for women with platinum-sensitive ovarian cancer following a complete or partial response to second-line or later platinum-based chemotherapy.