Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
32nd Prioritization – 3rd quarter 2017

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 32 prioritisation (August 2017), 10 drugs were filtered out of 366 identified and were sent to prioritisation. Of these, 5 drugs were ranked as ‘highly relevant’ by the expert panel, 5 as ‘relevant’ and none 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 – 32nd prioritisation 3rd quarter 2017	Overall category
1.	Ceritinib (Zykadia®) versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5)	Relevant
2.	Brigatinib (Alunbrig™) in patients with crizotinib-refractory anaplastic lymphoma kinase–positive non–small-cell lung cance	Relevant
3.	Cisplatin plus etoposide with or without bevacizumab (Avastin®) as first-line treatment in extensive-disease small-cell lung cancer	Relevant
4.	Bevacizumab (Avastin®) and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer	Highly relevant
5.	Adjuvant pertuzumab (Perjeta®) and trastuzumab in early HER2-positive breast cancer	Relevant
6.	Olaparib (Lynparza®) for metastatic breast cancer in patients with a germline BRCA mutation	Highly relevant
7.	Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2)	Relevant
8.	Idelalisib (Zydelig®) or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia	Highly relevant
9.	Midostaurin (Rydapt®) plus chemotherapy for acute myeloid leukemia with a FLT3 mutation	Highly relevant
10.	Abiraterone (Zytiga®) in combination with prednisone androgen-deprivation therapy in metastatic, castration-sensitive prostate cancer	Highly relevant

1 Breast cancer

1.1 Olaparib (Lynparza®) for metastatic breast cancer in patients with a germline BRCA mutation

Overview

Drug Description		a poly (ADP-ribose) polymerase (PARP) inhibitor
Patient Indication		Olaparib for the treatment of patients with germline BRCA mutation and human epidermal growth factor receptor type 2 (HER2)–negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease
Incidence in Austria		5,454 newly diagnosed per year (2014), 64.3 /100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02000622 until 12/2018
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	12/2014: as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.
	FDA	12/2014: as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.
Costs		Olaparib: 300 mg orally twice daily; ex-factory price of 22,400 mg = € 5059.29,- → € 2,845.85,- per 21 days of treatment

Phase III results

NEJM published online on June 4, 2017 (Robson et al.): *"Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation"*

Background
Olaparib is an oral poly (adenosine diphosphate–ribose) polymerase inhibitor that has promising antitumor activity in patients with metastatic breast cancer and a germline *BRCA* mutation.

Methods
We conducted a randomized, open-label, phase 3 trial in which olaparib monotherapy was compared with standard therapy in patients with a germline *BRCA* mutation and human epidermal growth factor receptor type 2 (HER2)–negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease. Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine in 21-day cycles). The

primary end point was progression-free survival, which was assessed by blinded independent central review and was analyzed on an intention-to-treat basis.

Results
Of the 302 patients who underwent randomization, 205 were assigned to receive olaparib and 97 were assigned to receive standard therapy. Median progressionfree survival was significantly longer in the olaparib group than in the standardtherapy group (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% confidence interval, 0.43 to 0.80; P<0.001). The response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group. The rate of grade 3 or higher adverse events was 36.6% in the olaparib group and 50.5% in the standard-therapy group, and the rate of treatment discontinuation due to toxic effects was 4.9% and 7.7%, respectively.

Conclusion
Among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy. (Funded by AstraZeneca; OlympiAD ClinicalTrials.gov number, NCT02000622.)

2 Leukaemia

2.1 Idelalisib (Zydelig®) or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia

Overview

Drug Description		an oral inhibitor of the delta isoform of phosphatidylinositol 3-kinase
Patient Indication		idelalisib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia
Incidence in Austria		936 newly diagnosed per year (2014), 11.3/100,000/year (European Standard Population, 2013)
Ongoing Phase II		NCT01569295 until 12/2017
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	02/2016 (+ofatumumab) & 09/2014 (+rituximab): in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies 09/2014: as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment
	FDA	07/2014: • for relapsed chronic lymphocytic leukaemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities • for relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies • for relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies
Costs		ZYDELIG 1 treatment cycle: twice-daily oral idelalisib (150 mg); ex-factory price of 60 pieces 150 mg = € 3,700,- → € 3,453,- per treatment cycle LEVACT 1 treatment cycle: 70 mg/m² intravenously on days 1 and 2 (assuming an average body surface area of 1.75 m²); ex-factory price of 500 mg = € 1,505.98,- → € 735.2,- per treatment cycle MabThera Cycle 1: 375 mg/m² on day 1 (assuming an average body surface area of 1.75 m²); ex-factory price of 500 mg = € 1,516.43,- → € 1,990.3,- per treatment cycle Cycles 2–6: 500 mg/m² on day 1 (assuming an average body surface area of 1.75 m²); ex-factory price of 500 mg = € 1,516.43,- → € 2,653.8,- per treatment cycle Total costs for combination therapy for the first treatment cycle: € 6,178.5,-

Phase III results

Lancet 2017 March, 18(3):297-311 (Zelenetz et al.) *"Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial"*

Background
Bendamustine plus rituximab is a standard of care for the management of patients with relapsed or refractory chronic lymphocytic leukaemia. New therapies are needed to improve clinically relevant outcomes in these patients. We assessed the efficacy and safety of adding idelalisib, a first-in-class targeted phosphoinositide-3-kinase δ inhibitor, to bendamustine plus rituximab in this population.

Methods
For this international, multicentre, double-blind, placebo-controlled trial, adult patients (≥18 years) with relapsed or refractory chronic lymphocytic leukaemia requiring treatment who had measurable lymphadenopathy by CT or MRI and disease progression within 36 months since their last previous therapy were enrolled. Patients were randomly assigned (1:1) by a central interactive web response system to receive bendamustine plus rituximab for a maximum of six cycles (bendamustine: 70 mg/m2 intravenously on days 1 and 2 for six 28-day cycles; rituximab: 375 mg/m2 on day 1 of cycle 1, and 500 mg/m2 on day 1 of cycles 2–6) in addition to either twice-daily oral idelalisib (150 mg) or placebo until disease progression or intolerable study drug-related toxicity. Randomisation was stratified by high-risk features (IGHV, del[17p], or TP53 mutation) and refractory versus relapsed disease. The primary endpoint was progression-free survival assessed by an independent review committee in the intention-to-treat population. This trial is ongoing and is registered with ClinicalTrials.gov, number NCT01569295.

Findings
Between June 26, 2012, and Aug 21, 2014, 416 patients were enrolled and randomly assigned to the idelalisib (n=207) and placebo (n=209) groups. At a median follow-up of 14 months (IQR 7–18), median progression-free survival was 20.8 months (95% CI 16.6–26.4) in the idelalisib group and 11.1 months (8.9–11.1) in the placebo group (hazard ratio [HR] 0.33, 95% CI 0.25–0.44; p<0.0001). The most frequent grade 3 or worse adverse events in the idelalisib group were neutropenia (124 [60%] of 207 patients) and febrile neutropenia (48 [23%]), whereas in the placebo group they were neutropenia (99 [47%] of 209) and thrombocytopenia (27 [13%]). An increased risk of infection was reported in the idelalisib group compared with the placebo group (grade ≥3 infections and infestations: 80 [39%] of 207 vs 52 [25%] of 209). Serious adverse events, including febrile neutropenia, pneumonia, and pyrexia, were more common in the idelalisib group (140 [68%] of 207 patients) than in the placebo group (92 [44%] of 209). Treatment-emergent adverse events leading to death occurred in 23 (11%) patients in the idelalisib group and 15 (7%) in the placebo group, including six deaths from infections in the idelalisib group and three from infections in the placebo group.

Interpretation
Idelalisib in combination with bendamustine plus rituximab improved progression-free survival compared with bendamustine plus rituximab alone in patients with relapsed or refractory chronic lymphocytic leukaemia. However, careful attention needs to be paid to management of serious adverse events and infections associated with this regimen during treatment selection.

2.2 Midostaurin (Rydapt®) plus chemotherapy for acute myeloid leukemia with a FLT3 mutation

Overview

Drug Description		a small molecule that inhibits multiple receptor tyrosine kinases
Patient Indication		midostaurin in combination to standard chemotherapy in patients with acute myeloid leukemia and a FLT3 mutation
Incidence in Austria		936 newly diagnosed per year (2014), 11.3/100,000/year (European Standard Population, 2013)
Ongoing Phase II		-
Approval status for this indication	**EMA**	07/2004: orphan designation was granted by the European Commission to Novartis Europharm Limited, United Kingdom, for midostaurin for the treatment of acute myeloid leukaemia.
	FDA	04/2017: for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive (FLT3+), as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.
Approval status for other indications	**EMA**	08/2010, orphan designation was granted by the European Commission to Novartis Europharm Limited, United Kingdom, for midostaurin for the treatment of mastocytosis.
	FDA	04/2017: midostaurin for the treatment of adults with aggressive systemic mastocytosis (SM), SM with associated hematological neoplasm, or mast cell leukemia.
Costs		-

Phase III results

Lancet published online June 2017, (Stone et al.) *"Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation"*

Background
Patients with acute myeloid leukemia (AML) and a *FLT3* mutation have poor outcomes. We conducted a phase 3 trial to determine whether the addition of midostaurin — an oral multitargeted kinase inhibitor that is active in patients with a *FLT3* mutation — to standard chemotherapy would prolong overall survival in this population.

Methods
We screened 3277 patients, 18 to 59 years of age, who had newly diagnosed AML for *FLT3* mutations. Patients were randomly assigned to receive standard chemotherapy (induction therapy with daunorubicin and cytarabine and consolidation therapy with high-dose cytarabine) plus either midostaurin or placebo; those who were in remission after consolidation therapy entered a maintenance phase in which they received either midostaurin or placebo. Randomization was stratified according to subtype of *FLT3* mutation: point mutation in the tyrosine kinase domain (TKD) or internal tandem duplication (ITD) mutation with either a high ratio (>0.7) or a low ratio (0.05 to 0.7) of mutant to wild-type alleles (ITD [high] and ITD [low], respectively). Allogeneic transplantation was allowed. The primary end point was overall survival.

Results
A total of 717 patients underwent randomization; 360 were assigned to the midostaurin group, and 357 to the placebo group. The *FLT3* subtype was ITD (high) in 214 patients, ITD (low) in 341 patients, and TKD in 162 patients. The treatment groups were well balanced with respect to age, race, *FLT3* subtype, cytogenetic risk, and blood counts but not with respect to sex (51.7% in the midostaurin group vs. 59.4% in the placebo group were women, P = 0.04). Overall survival was significantly longer

in the midostaurin group than in the placebo group (hazard ratio for death, 0.78; one-sided P = 0.009), as was event-free survival (hazard ratio for event or death, 0.78; one-sided P = 0.002). In both the primary analysis and an analysis in which data for patients who underwent transplantation were censored, the benefit of midostaurin was consistent across all *FLT3* subtypes. The rate of severe adverse events was similar in the two groups.

Conclusions
The addition of the multitargeted kinase inhibitor midostaurin to standard chemotherapy significantly prolonged overall and event-free survival among patients with AML and a *FLT3* mutation. (Funded by the National Cancer Institute and Novartis; ClinicalTrials.gov number, NCT00651261.)

3 Prostate caner

3.1 Abiraterone (Zytiga®) in combination with prednisone androgen-deprivation therapy in metastatic, castration-sensitive prostate cancer

Overview

Drug Description		an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17)
Patient Indication		Abiraterone in combination with prednisone androgen-deprivation therapy in metastatic, castration-sensitive prostate cancer
Incidence in Austria		4,499 newly diagnosed per year (2014), 124.0/100,000/year (European Standard Population, 2013)
Ongoing Phase II		NCT00268476 - until 09/2017 NCT01715285 until 07/2021
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	09/2011: in combination with prednisone or prednisolone the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel based chemotherapy regimen. 12/2012: in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
	FDA	04/2011: in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.
Costs		Abiraterone: 1,000 mg orally (given once daily as four 250-mg tablets); ex-factory price of 28,000 mg = € 2,895.35,- → € 2,171.51 for 21 days of treatment

Phase III results

NEJM published online June 2017 (Fizazi et al.) *"Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer"*

Background
Abiraterone acetate, a drug that blocks endogenous androgen synthesis, plus prednisone is indicated for metastatic castration-resistant prostate cancer. We evaluated the clinical benefit of abiraterone acetate plus prednisone with androgen-deprivation therapy in patients with newly diagnosed, metastatic, castration-sensitive prostate cancer.

Methods
In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 1199 patients to receive either androgen-deprivation therapy plus abiraterone acetate (1000 mg daily, given once daily as four 250-mg tablets) plus prednisone (5 mg daily) (the abiraterone group) or androgen-deprivation therapy plus dual placebos (the placebo group). The two primary end points were overall survival and radiographic progression-free survival.

Results
After a median follow-up of 30.4 months at a planned interim analysis (after 406 patients had died), the median overall survival was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; P<0.001). The median length of radiographic progression-free survival was 33.0 months in the abiraterone group and 14.8 months in the placebo group (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; P<0.001). Significantly better outcomes in all secondary end points were observed in the abiraterone group, including the time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and prostatespecific antigen progression (P<0.001 for all comparisons), along with next symptomatic skeletal events (P = 0.009). These findings led to the unanimous recommendation by the independent data and safety monitoring committee that the trial be unblended and crossover be allowed for patients in the placebo group to receive abiraterone. Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group.

Conclusion
The addition of abiraterone acetate and prednisone to androgen-deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer. (Funded by Janssen Research and Development; LATITUDE ClinicalTrials.gov number, NCT01715285.)

NEJM published online June 2017 (James et al.) *"Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy"*

Background
Abiraterone acetate plus prednisolone improves survival in men with relapsed prostate cancer. We assessed the effect of this combination in men starting long-term androgen-deprivation therapy (ADT), using a multigroup, multistage trial design.

Methods
We randomly assigned patients in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1000 mg daily) and prednisolone (5 mg daily) (combination therapy). Local radiotherapy was mandated for patients with node-negative, nonmetastatic disease and encouraged for those with positive nodes. For patients with nonmetastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until radiologic, clinical, or prostate-specific antigen (PSA) progression; otherwise, treatment was to continue for 2 years or until any type of progression, whichever came first. The primary outcome measure was overall survival. The intermediate primary outcome was failure-free survival (treatment failure was defined as radiologic, clinical, or PSA progression or death from prostate cancer).

Results
A total of 1917 patients underwent randomization from November 2011 through January 2014. The median age was 67 years, and the median PSA level was 53 ng per milliliter. A total of 52% of the patients had metastatic disease, 20% had node-positive or node-indeterminate nonmetastatic disease, and 28% had node-negative, nonmetastatic disease; 95% had newly diagnosed disease. The median follow-up was 40 months. There were 184 deaths in the combination group as compared with 262 in the ADT-alone group (hazard ratio, 0.63; 95% confidence interval [CI], 0.52 to 0.76; P<0.001); the hazard ratio was 0.75 in patients with nonmetastatic disease and 0.61 in those with metastatic disease. There were 248 treatment-failure events in the combination group as compared with 535 in the ADT-alone group (hazard ratio, 0.29; 95% CI, 0.25 to 0.34; P<0.001); the hazard ratio was 0.21 in patients with nonmetastatic disease and 0.31 in those with metastatic disease. Grade 3 to 5 adverse events occurred in 47% of the patients in the combination group (with nine grade 5 events) and in 33% of the patients in the ADT-alone group (with three grade 5 events).

Conclusion
Among men with locally advanced or metastatic prostate cancer, ADT plus abiraterone and prednisolone was associated with significantly higher rates of overall and failure-free survival than ADT alone. (Funded by Cancer Research U.K. and others; STAMPEDE ClinicalTrials.gov number, NCT00268476, and Current Controlled Trials number, ISRCTN78818544.)

4 Ovarian cancer

4.1 Bevacizumab (Avastin®) and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer

Overview

Drug Description		a recombinant monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits the binding to its receptors (VEGFR-1 and VEGFR-2)
Patient Indication		bevacizumab in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab single agent for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
Incidence in Austria		635 newly diagnosed per year (2014), 13.8 /100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT00565851 until 03/2019
Approval status for this indication	**EMA**	04/2017: CHMP adopted an extension to an existing indication as follows: "Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents"
	FDA	12/2016: in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab single agent for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
Approval status for other indications	**EMA**	08/2007: in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small-cell lung cancer other than predominantly squamous cell histology. 12/2007: in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and / or metastatic renal-cell cancer. 01/2008: in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. 06/2011: in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human-epidermal-growth-factor-receptor-2 (HER2) status. 06/2011: in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine. 12/2011: in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International

		Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian-tube, or primary peritoneal cancer. 07/2014: in combination with carboplatin and gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelian-ovarian, fallopian-tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other vascular-endothelial-growth-factor (VEGF) inhibitors or VEGF-receptor-targeted agents. 03/2015: in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix. 06/2016: in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.
	FDA	02/2004: first-line treatment for patients with metastatic colorectal cancer - cancer that has spread to other parts of the body. 10/2006: in combination with carboplatin and paclitaxel, for the initial systemic treatment of patients with unresectable, locally advanced, recurrent, or metastatic, non-squamous, non-small cell lung cancer. 01:/2009: in combination with interferon alfa for the treatment of patients with metastatic renal cell carcinoma. 05/2009: single agent for patients with glioblastoma, with progressive disease following prior therapy. 01/2013: in combination with fluoropyrimidine–irinotecan- or fluoropyrimidine–oxaliplatin-based chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed while on first-line treatment with a bevacizumab-containing regimen. 08/2014: in combination with paclitaxel and either cisplatin or topotecan for the treatment of persistent, recurrent, or metastatic cervical cancer. 11/2014: in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. 12/2016: in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab single agent for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
Costs		Bevacizumab: 15 mg/kg intravenously on day 1/treatment cycle =3 weeks (assuming an average body weight of 70 kg); ex-factory price of 100 mg = € 368,- → € 3,864,- per treatment cycle

Phase III results

Lancet 2017, 18:6, 779–791, (Coleman et al.): *"Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial"*

Background
Platinum-based chemotherapy doublets are a standard of care for women with ovarian cancer recurring 6 months after completion of initial therapy. In this study, we aimed to explore the roles of secondary surgical cytoreduction and bevacizumab in this population, and report the results of the bevacizumab component here.

Methods
The multicentre, open-label, randomised phase 3 GOG-0213 trial was done in 67 predominantly academic centres in the USA (65 centres), Japan (one centre), and South Korea (one centre). Eligible patients were adult women (aged ≥18 years) with recurrent measurable or evaluable epithelial ovarian, primary peritoneal, or fallopian tube cancer, and a clinical complete response to primary platinum-based chemotherapy, who had been disease-free for at least 6 months following last infused cycle of platinum. Patients were randomly assigned (1:1) to standard chemotherapy (six 3-weekly cycles of paclitaxel [175 mg/m2 of body surface area] and carboplatin [area under the curve 5]) or the same chemotherapy regimen plus bevacizumab (15 mg/kg of bodyweight) every 3 weeks and continued as maintenance every 3 weeks until disease progression or unacceptable toxicity. Individuals who participated in both the bevacizumab objective and surgical objective (which is ongoing) were randomly assigned (1:1:1:1) to receive either of these two chemotherapy regimens with or without prior secondary cytoreductive surgery. Randomisation for the bevacizumab objective was stratified by treatment-free interval and participation in the surgical objective. The primary endpoint was overall survival, analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00565851.

Findings
Between Dec 10, 2007, and Aug 26, 2011, 674 women were enrolled and randomly assigned to standard chemotherapy (n=337) or chemotherapy plus bevacizumab (n=377). Median follow-up at the end of the trial on Nov 5, 2014, was 49·6 months in each treatment group (IQR 41·5–62·2 for chemotherapy plus bevacizumab; IQR 40·8–59·3 for chemotherapy), at which point 415 patients had died (214 in the chemotherapy group and 201 in the chemotherapy plus bevacizumab group). Based on pretreatment stratification data, median overall survival in the chemotherapy plus bevacizumab group was 42·2 months (95% CI 37·7–46·2) versus 37·3 months (32·6–39·7) in the chemotherapy group (hazard ratio [HR] 0·829; 95% CI 0·683–1·005; p=0·056). We identified incorrect treatment-free interval stratification data for 45 (7%) patients (equally balanced between treatment groups); a sensitivity analysis of overall survival based on the audited treatment-free interval stratification data gave an adjusted HR of 0·823 (95% CI 0·680–0·996; p=0·0447). In the safety population (all patients who initiated treatment), 317 (96%) of 325 patients in the chemotherapy plus bevacizumab group had at least one grade 3 or worse adverse event compared with 282 (86%) of 332 in the chemotherapy group; the most frequently reported of these in the chemotherapy plus bevacizumab group compared with the chemotherapy group were hypertension (39 [12%] vs two [1%]), fatigue (27 [8%] vs eight [2%]), and proteinuria (27 [8%] vs none). Two (1%) treatment-related deaths occurred in the chemotherapy group (infection [n=1] and myelodysplastic syndrome [n=1]) compared with nine (3%) in the chemotherapy plus bevacizumab group (infection [n=1], febrile neutropenia [n=1], myelodysplastic syndrome [n=1], secondary malignancy [n=1]; deaths not classified with CTCAE terms: disease progression [n=3], sudden death [n=1], and not specified [n=1]).

Interpretation
The addition of bevacizumab to standard chemotherapy, followed by maintenance therapy until progression, improved the median overall survival in patients with platinum-sensitive recurrent ovarian cancer. Although the intention-to-treat analysis for overall survival was not significant, our sensitivity analysis based on corrected treatment-free interval stratification indicates that this strategy might be an important addition to the therapeutic armamentarium in these patients.