Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
34th Prioritization – 1st 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 34 prioritisation (January 2018), 15 drugs were filtered out of 405 identified and were sent to prioritisation. Of these, seven drugs were ranked as ‘highly relevant’ by the expert panel, seven 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 – 34th prioritisation 1st quarter 2018	Overall category
1.	Lomustine and bevacizumab (Avastin®) in progressive glioblastoma	Not relevant
2.	Nintedanib (Vargatef®) plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma	Relevant
3.	Nivolumab (Opdivo®) in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens	Relevant
4.	Bosutinib (Bosulif®) versus imatinib for newly diagnosed chronic myeloid leukemia	Relevant
5.	Incorporation of brentuximab vedotin (Adcetris®) into first-line treatment of advanced classical Hodgkin’s lymphoma	Relevant
6.	Brentuximab vedotin (Adcetris®) with chemotherapy for stage III or IV Hodgkin’s lymphoma	Relevant
7.	Rituximab (MabThera®) after autologous stem-cell transplantation in mantle-Cell lymphoma	Highly relevant
8.	Daratumumab (Darzalex®) plus bortezomib, melphalan, and prednisone for untreated myeloma	Highly relevant
9.	Abemaciclib (Verzenio™) as initial therapy for advanced breast cancer	Highly relevant
10.	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
11.	Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer	Highly relevant
12.	First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma	Relevant
13.	Osimertinib (Tagrisso®) in untreated EGFR-mutated advanced non–small-cell lung cancer	Highly relevant
14.	Ramucirumab (Cyramza®) plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy	Relevant
15.	Rucaparib (Rubraca®) maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy	Highly relevant

1 Lymphoma

1.1 Rituximab (MabThera®) after autologous stem-cell transplantation in mantle-cell lymphoma

Overview

Drug Description		a monoclonal antibody targeting CD20
Patient Indication		rituximab as maintenance therapy in patients with mantle-cell lymphoma who had undergone autologous stem-cell transplantation
Incidence in Austria		936 newly diagnosed per year (2014), 11.3/100,000/year (European Standard Population, 2013)
Ongoing Phase III		-
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	07/2009: in combination with CHOP chemotherapy in non-Hodgkin' s Lymphoma (follicular lymphoma and diffuse large B-cell lymphoma) and as first-line in chronic lymphocytic leukaemia 07/2011: in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia 03/2013: in combination with glucocorticoids for the induction of remission in patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)
	FDA	02/2006: for first-line treatment of patients with diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or other anthracycline-based chemotherapy regimens 09/2006: for first-line treatment of patients with low grade or follicular B-cell, CD20-positive non-Hodgkin's lymphoma 02/2010: in combination with fludarabine and cyclophosphamide (FC), for the treatment of both previously untreated and previously treated patients with chronic lymphocytic leukaemia (CLL) 01/2011: for maintenance therapy for patients with previously untreated follicular CD-20 positive B-cell non-Hodgkin lymphoma (NHL) who achieve a response to rituximab in combination with chemotherapy 10/2012: for second-line treatment in patients with NHL who did not experience a grade 3 or 4 infusion-related adverse reaction during cycle 1
Costs		Rituximab: Maintenance therapy: IV 375 mg/m² body surface area (BSA) every 2 months for 3 years (assuming an average BSA of 1,73 m²); ex-factory price of 375 mg = € 1,150.22 → € 1,989.88 per treatment

Phase III results

NEJM; available online 28 September 2017 (Le Gouill et al.): *"Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma"*

Background
Mantle-cell lymphoma is generally incurable. Despite high rates of complete response after initial immune chemotherapy followed by autologous stem-cell transplantation, patients have relapses. We investigated whether rituximab maintenance therapy at a dose of 375 mg per square meter of body-surface area administered every 2 months for 3 years after transplantation would prolong the duration of response.

Methods
In a phase 3 trial involving 299 patients who were younger than 66 years of age at diagnosis, we randomly assigned 240 patients to receive rituximab maintenance therapy or to undergo observation after autologous stem-cell transplantation (120 patients per group); 59 patients did not undergo randomization. The primary endpoint was event-free survival (with an event defined as disease progression, relapse, death, allergy to rituximab, or severe infection) after transplantation among patients who underwent randomization.

Results
After four courses of immune chemotherapy induction (rituximab, dexamethasone, cytarabine, and a platinum derivative [R-DHAP]), the overall response rate was 89%, and the complete response rate 77%. Transplantation was performed in 257 patients. The median follow-up from randomization after transplantation was 50.2 months (range, 46.4 to 54.2). Starting from randomization, the rate of event-free survival at 4 years was 79% (95% confidence interval [CI], 70 to 86) in the rituximab group versus 61% (95% CI, 51 to 70) in the observation group ($p = 0.001$). The rate of progression-free survival at 4 years was 83% (95% CI, 73 to 88) in the rituximab group versus 64% (95% CI, 55 to 73) in the observation group ($p<0.001$). The rate of overall survival was 89% (95% CI, 81 to 94) in the rituximab group versus 80% (95% CI, 72 to 88) in the observation group ($p = 0.04$). According to a Cox regression unadjusted analysis, the rate of overall survival at 4 years was higher in the rituximab group than in the observation group (hazard ratio for death, 0.50; 95% CI, 0.26 to 0.99; $p = 0.04$).

Conclusions
Rituximab maintenance therapy after transplantation prolonged event-free survival, progression-free survival, and overall survival among patients with mantle-cell lymphoma who were younger than 66 years of age at diagnosis. (Funded by Roche and Amgen; LyMa ClinicalTrials.gov number, NCT00921414.)

2 Multiple Myeloma

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

Overview

Drug Description		human CD38-directed monoclonal antibody (CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells)
Patient Indication		daratumumab plus bortezomib, melphalan, and prednisone for newly diagnosed multiple myeloma patients who were ineligible for autologous stem-cell transplantation
Incidence in Austria		382 newly diagnosed per year (2014), 4.3/100,000/year (European Standard Population, 2013)
Ongoing Phase II		-
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	05/2016: as a 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: as a single agent 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: IV 16 mg/kg/once per week in cycle 1;400 mg → € 2,209.45; assuming an average body weight of 70 kg, 1,120 mg/week are needed and 3,360 mg/3 weeks are needed; costs of €18,559.38 would incur for treatment cycle 1 (in cycles 2-9 daratumumab is administered every 3 weeks)

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 endpoint was progression-free survival.

Results
At a median follow-up of 16.5 months in a pre-specified 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 tumour 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 anaemia (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.

Conclusion
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.)

3 Breast cancer

3.1 Abemaciclib (Verzenio™) as initial therapy for advanced breast cancer

Overview

Drug Description		inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6)
Patient Indication		abemaciclib as initial therapy for advanced HR-positive, HER2-negative breast cancer
Incidence in Austria		5,454 newly diagnosed per year (2014), 64.3 /100,000/year (European Standard Population, 2013)
Ongoing Phase II		NCT02246621 until 07/2021
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	-
	FDA	09/2017: in combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy 09/2017: as monotherapy for women and men with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
Costs		-

Phase III results

JCO; available online October 2017: 35:32, 3638-3646 (Goetz et al.): *"MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer"*

Purpose
Abemaciclib, a cyclin-dependent kinase 4 and 6 inhibitor, demonstrated efficacy as monotherapy and in combination with fulvestrant in women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer previously treated with endocrine therapy.

Methods
MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole, daily. The primary objective was investigator-assessed progression-free survival. Secondary objectives included response evaluation and safety. A planned interim analysis occurred after 189 events.

Results
Median progression-free survival was significantly prolonged in the abemaciclib arm (hazard ratio, 0.54; 95% CI, 0.41 to 0.72; P = .000021; median: not reached in the abemaciclib arm, 14.7 months in

the placebo arm). In patients with measurable disease, the objective response rate was 59% in the abemaciclib arm and 44% in the placebo arm (P = .004). In the abemaciclib arm, diarrhoea was the most frequent adverse effect (81.3%) but was mainly grade 1 (44.6%). Comparing abemaciclib and placebo, the most frequent grade 3 or 4 adverse events were neutropenia (21.1% v 1.2%), diarrhoea (9.5% v 1.2%), and leukopenia (7.6% v 0.6%).

Conclusion
Abemaciclib plus a nonsteroidal aromatase inhibitor was effective as initial therapy, significantly improving progression-free survival and objective response rate and demonstrating a tolerable safety profile in women with HR-positive, HER2-negative advanced breast cancer.

3.2 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		lapatinib in postmenopausal women with HER2-positive/HR-positive metastatic breast (MBC) cancer who received prior endocrine therapy (ET) and prior neo(adjuvant)/first-line trastuzumab (TRAS) plus chemotherapy
Incidence in Austria		5,454 newly diagnosed per year (2014), 64.3/100,000/year (European Standard Population, 2013)
Ongoing Phase III		-
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	06/2008: in combination with capecitabine for the treatment of patients with advanced or MCB whose tumours overexpress ErbB2 (HER2) 06/2011: in combination with an aromatase in women who have been through the menopause, when the cancer is metastatic and responds to hormones 06/2013: in combination with trastuzumab for the treatment of patients with hormone receptor (HR)-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 MCB whose tumours overexpress HER2 and who have received prior therapy including an anthracycline, taxane, and trastuzumab 01/2010: in combination with letrozole for the treatment of postmenopausal women with HR-positive MBC that overexpresses the HER2 receptor and for whom hormonal therapy is indicated
Costs		Lapatinib: 1 treatment cycle (21 days): oral 1,000 mg/day or 1,500 mg/day; ex-factory price of 1,000 mg = € 70.58 → € 1,482.18 per treatment cycle OR ex-factory price of 1,500 mg = € 105.86 → € 2,223.06 per treatment cycle; Additional costs will occur due to the combination treatment of lapatinib with trastuzumab and an aromatase inhibitor (letrozole, anastrozole or exemestane).

Phase III results

JCO: available online 15 December 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"*

Purpose
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 endpoint was progression-free survival (PFS; investigator assessed) with LAP + TRAS + AI versus TRAS + AI. Secondary endpoints were PFS (comparison of other arms), overall survival, overall response rate, clinical benefit rate, and safety.

Findings
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 endpoint; 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 favoured 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 ≥ 15%) with LAP + TRAS + AI, TRAS + AI, and LAP + AI were diarrhoea (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.

Conclusion
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.

4 Lung cancer

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

Overview

Drug Description		second-generation, irreversible EGFR tyrosine kinase inhibitor
Patient Indication		dacomitinib for the first-line treatment of patients with advanced EGFR-mutation-positive non-small-cell lung cancer
Incidence in Austria		4,716 newly diagnosed per year (2014), 56.9/100,000/year (European Standard Population, 2013) (including: lung, trachea and bronchial tumours)
Ongoing Phase II		-
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

Lancet; available online September 2017: 18:11, 1454-1466 (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 non–small-cell lung cancer

Overview

Drug Description		irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitising and EGFR T790M resistance mutations
Patient Indication		osimertinib in patients with previously untreated, epidermal growth factor receptor (EGFR) mutation–positive advanced non–small-cell lung cancer (NSCLC)
Incidence in Austria		4,716 newly diagnosed per year (2014), 56.9/100,000/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 in patients with NSCLC, that is advanced or has spread and who have EGFR T790M mutation
	FDA	03/2017: for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy
Costs		Osimertinib: Dose: 80 mg/day; ex-factory price of 80 mg/30 days → € 6,132.50 of 30 days of treatment

Phase III results

NEJM; available online 18 November 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 endpoint was investigator-assessed progression-free survival.

Results
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 [non-significant in the interim analysis]). Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% versus 45%).

Conclusions
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 carcinoma

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

Overview

Drug Description		a poly(ADP-ribose) polymerase inhibitor,
Patient Indication		rucaparib in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma
Incidence in Austria		635 newly diagnosed per year (2014), 13.8/100,000/year (European Standard Population, 2013)
Ongoing Phase III		-
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	10/2012: orphan designation (EU/3/12/1049) was granted for the treatment of ovarian cancer
	FDA	12/2016: women with advanced ovarian cancer who have been treated with two or more chemotherapies and whose tumours have a specific gene mutation (deleterious BRCA)
Costs		-

Phase III results

Lancet; available online 28 October 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, high-grade 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%] versus 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 versus 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%] versus 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.