Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
28th Prioritization – 3rd quarter 2016

General Information, efficacy and safety data

Nicole Grössmann

Claudia Wild

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 28th prioritisation (September 2016), 9 drugs were filtered out of 283 identified and were sent to prioritisation. Of these, 7 drugs were ranked as ‘highly relevant’ by the expert panel, 2 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 – 28th prioritisation 3rd quarter 2016	Overall category
1.	Oral ixazomib (MLN9708, Ninlaro®), lenalidomide, and dexamethasone for multiple myeloma	Highly relevant
2.	Daratumumab (Darzalex®), bortezomib, and dexamethasone for multiple myeloma	Highly relevant
3.	Nivolumab (Opdivo®) in classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin	Highly relevant
4.	Fulvestrant plus palbociclib (Ibrance®) versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy	Highly relevant
5.	Inotuzumab ozogamicin (CMC-544) versus standard therapy for acute lymphoblastic leukemia	Relevant
6.	Olaratumab (Lartruvo®) and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma	Highly relevant
7.	Afatinib (Giotrif®) versus methotrexate in patients with second-line recurrent and/or metastatic head and neck squamous cell carcinoma	Relevant
8.	Pembrolizumab (Keytruda®, MK-3475) versus standard treatment for recurrent or metastatic head and neck cancer	Highly relevant
9.	Nanoliposomal irinotecan (Onyvide®) with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy	Highly relevant

1 Multiple Myeloma

1.1 Oral ixazomib (MLN9708, Ninlaro®), lenalidomide, and dexamethasone for multiple myeloma

Overview

Drug Description		is a reversible proteasome inhibitor that preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome
Patient Indication		ixazomib plus lenalidomide–dexamethasone for relapsed, refractory, or relapsed and refractory multiple myeloma
Incidence in Austria		627 newly diagnosed per year (2012), 5.6 /100,000/year
Ongoing Phase III		NCT01564537 - until 05/2019
Approval status for this indication	**EMA**	On 15 September 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional1 marketing authorisation for the medicinal product ixazomib, intended for the treatment of multiple myeloma.
	FDA	11/2015: approved for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Approval status for other indications	**EMA**	Ixazomib was designated an 'orphan medicine' on 27 September 2011, for the treatment of multiple myeloma.
	FDA	01/2005: approved for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. 09/2013: approved for metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. 10/2012: approved for locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
Costs		-

Phase III results

NEJM (2016) 374:1621-1634 (Moreau et al.): *"Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma"*

Background
Ixazomib is an oral proteasome inhibitor that is currently being studied for the treatment of multiple myeloma.

Methods
In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 722 patients who had relapsed, refractory, or relapsed and refractory multiple myeloma to receive ixazomib plus lenalidomide–dexamethasone (ixazomib group) or placebo plus lenalidomide–dexamethasone (placebo group). The primary end point was progression-free survival.

Results

Progression-free survival was significantly longer in the ixazomib group than in the placebo group at a median follow-up of 14.7 months (median progression-free survival, 20.6 months vs. 14.7 months; hazard ratio for disease progression or death in the ixazomib group, 0.74; P=0.01); a benefit with respect to progression-free survival was observed with the ixazomib regimen, as compared with the placebo regimen, in all pre-specified patient subgroups, including in patients with high-risk cytogenetic abnormalities. The overall rates of response were 78% in the ixazomib group and 72% in the placebo group, and the corresponding rates of complete response plus very good partial response were 48% and 39%. The median time to response was 1.1 months in the ixazomib group and 1.9 months in the placebo group, and the corresponding median duration of response was 20.5 months and 15.0 months. At a median follow-up of approximately 23 months, the median overall survival has not been reached in either study group, and follow-up is ongoing. The rates of serious adverse events were similar in the two study groups (47% in the ixazomib group and 49% in the placebo group), as were the rates of death during the study period (4% and 6%, respectively); adverse events of at least grade 3 severity occurred in 74% and 69% of the patients, respectively. Thrombocytopenia of grade 3 and grade 4 severity occurred more frequently in the ixazomib group (12% and 7% of the patients, respectively) than in the placebo group (5% and 4% of the patients, respectively). Rash occurred more frequently in the ixazomib group than in the placebo group (36% vs. 23% of the patients), as did gastrointestinal adverse events, which were predominantly low grade. The incidence of peripheral neuropathy was 27% in the ixazomib group and 22% in the placebo group (grade 3 events occurred in 2% of the patients in each study group). Patient-reported quality of life was similar in the two study groups.

Conclusions
The addition of ixazomib to a regimen of lenalidomide and dexamethasone was associated with significantly longer progression-free survival; the additional toxic effects with this all-oral regimen were limited. (Funded by Millennium Pharmaceuticals; TOURMALINE-MM1 ClinicalTrials.gov number, NCT01564537.)

1.2 Daratumumab (Darzalex®), bortezomib, and dexamethasone for multiple 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 in combination with bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma.
Incidence in Austria		627 newly diagnosed per year (2012), 5.6 /100,000/year
Ongoing Phase III		NCT02136134 - until 03/2017
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	05/2016: approved 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. On 17 July 2013, orphan designation was granted by the European Commission to Janssen-Cilag International N.V., Belgium, for daratumumab for the treatment of plasma-cell myeloma.
	FDA	11/2015: approved for the administration 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.

Costs	1 cycle → 21 days Dexamethasone: in one treatment cycle a dose of 20 mg was administered 8 times → total of 160 mg; 100 mg → €28.70 and for 160 mg costs of €45.92 would incur for 1 treatment cycle Bortezomib: 1.3 mg/square meter body surface administered (subcutaneously) 4 times per treatment cycle; 3.5 mg → €1,218.95 assuming a body surface of 1.70 m^2, 2.21 mg (€769.68) are needed per administration and for 1 treatment cycle costs of €3,078.7 would incur Daratumumab: 16 mg/kg/once per week (intravenously); 400 mg → €2,209.45; assuming an average body weight of 70 kg, 1,120 mg are needed per week and 3,360 mg are needed for 3 weeks; costs of €18,559.38 would incur for 1 treatment cycle Total costs of €21,684 for 1 treatment cycle of combination treatment would incur.

Phase III results

NEJM (2016) 375:754-766 (Palumbo et al.): *"Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma"*

Background
Daratumumab, a human IgGκ monoclonal antibody that targets CD38, induces direct and indirect antimyeloma activity and has shown substantial efficacy as monotherapy in heavily pre-treated patients with multiple myeloma, as well as in combination with bortezomib in patients with newly diagnosed multiple myeloma.

Methods
In this phase 3 trial, we randomly assigned 498 patients with relapsed or relapsed and refractory multiple myeloma to receive bortezomib (1.3 mg per square meter of body-surface area) and dexamethasone (20 mg) alone (control group) or in combination with daratumumab (16 mg per kilogram of body weight) (daratumumab group). The primary end point was progression-free survival.

Results
A pre-specified interim analysis showed that the rate of progression-free survival was significantly higher in the daratumumab group than in the control group; the 12-month rate of progression-free survival was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of 7.4 months, the median progression-free survival was not reached in the daratumumab group and was 7.2 months in the control group (hazard ratio for progression or death with daratumumab vs. control, 0.39; 95% confidence interval, 0.28 to 0.53; P<0.001). The rate of overall response was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, P<0.001), as were the rates of very good partial response or better (59.2% vs. 29.1%, P<0.001) and complete response or better (19.2% vs. 9.0%, P=0.001). Three of the most common grade 3 or 4 adverse events reported in the daratumumab group and the control group were thrombocytopenia (45.3% and 32.9%, respectively), anaemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively). Infusion-related reactions that were associated with daratumumab treatment were reported in 45.3% of the patients in the daratumumab group; these reactions were mostly grade 1 or 2 (grade 3 in 8.6% of the patients), and in 98.2% of these patients, they occurred during the first infusion.

Conclusion
Among patients with relapsed or relapsed and refractory multiple myeloma, daratumumab in combination with bortezomib and dexamethasone resulted in significantly longer progression-free survival than bortezomib and dexamethasone alone and was associated with infusion-related reactions and higher rates of thrombocytopenia and neutropenia than bortezomib and dexamethasone alone. (Funded by Janssen Research and Development; ClinicalTrials.gov number, NCT02136134.)

2 Lymphoma

2.1 Nivolumab (Opdivo®) in classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin

Overview

Drug Description		humanized IgG4 anti-PD-1 monoclonal antibody
Patient Indication		nivolumab for classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin
Incidence in Austria		161 newly diagnosed per year (2012), 1.8/100,000/year
Ongoing Phase III		NCT02181738 - until 2018 NCT01822509 - until 2016
Approval status for this indication	**EMA**	-
	FDA	On May 17, 2016 nivolumab received accelerated approval for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. Based on the results of the CheckMate-205 and the CheckMate-039 trial.
Approval status for other indications	**EMA**	05/2016: approved for the treatment of advanced melanoma as a monotherapy or in combination with ipilimumab. 02/2016: approved for the treatment of non-small cell lung cancer (NSCLC) that has spread locally or to other parts of the body in patients who have previously been treated. 04/2016: nivolumab as a monotherapy for advanced renal cell carcinoma in previously treated patients.
	FDA	09/2015: approved for BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent. 09/2015: approved for BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. 09/2015: approved for resectable or metastatic melanoma, in combination with ipilimumab. 10/2015: approved for metastatic non-small cell lung cancer and progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab. 11/2015: approved for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
Costs		→ nivolumab conc. 10 mg/ml; 40 ml → €626; nivolumab conc. 10 mg/ml 100 ml: €1,517.50. The recommended dose-schedule of nivolumab is 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity; assuming an average body weight of 70 kg, a dose of 210 mg nivolumab would be needed, costing €3,186.75 per 2-week cycle and €6,373.5 per month.

Phase III results

Lancet (2016), published online July 20, 2016 (Younes et al.) *"Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial"*

Background
Malignant cells of classical Hodgkin's lymphoma are characterised by genetic alterations at the 9p24.1 locus, leading to overexpression of PD-1 ligands and evasion of immune surveillance. In a phase 1b study, nivolumab, a PD-1-blocking antibody, produced a high response in patients with relapsed and refractory classical Hodgkin's lymphoma, with an acceptable safety profile. We aimed to assess the clinical benefit and safety of nivolumab monotherapy in patients with classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin.

Methods
In this ongoing, single-arm phase 2 study, adult patients (aged ≥18 years) with recurrent classical Hodgkin's lymphoma who had failed to respond to autologous stem-cell transplantation and had either relapsed after or failed to respond to brentuximab vedotin, and with an Eastern Cooperative Oncology Group performance status score of 0 or 1, were enrolled from 34 hospitals and academic centres across Europe and North America. Patients were given nivolumab intravenously over 60 min at 3 mg/kg every 2 weeks until progression, death, unacceptable toxicity, or withdrawal from study. The primary endpoint was objective response following a pre-specified minimum follow-up period of 6 months, assessed by an independent radiological review committee (IRRC). All patients who received at least one dose of nivolumab were included in the primary and safety analyses. This trial is registered with ClinicalTrials.gov, number NCT02181738.

Findings
Among 80 treated patients recruited between Aug 26, 2014, and Feb 20, 2015, the median number of previous therapies was four (IQR 4–7). At a median follow-up of 8·9 months (IQR 7·8–9·9), 53 (66·3%, 95% CI 54·8–76·4) of 80 patients achieved an IRRC-assessed objective response. The most common drug-related adverse events (those that occurred in ≥15% of patients) included fatigue (20 [25%] patients), infusion-related reaction (16 [20%]), and rash (13 [16%]). The most common drug-related grade 3 or 4 adverse events were neutropenia (four [5%] patients) and increased lipase concentrations (four [5%]). The most common serious adverse event (any grade) was pyrexia (three [4%] patients). Three patients died during the study; none of these deaths were judged to be treatment related.

Interpretation
Nivolumab resulted in frequent responses with an acceptable safety profile in patients with classical Hodgkin's lymphoma who progressed after autologous stem-cell transplantation and brentuximab vedotin. Therefore, nivolumab might be a new treatment option for a patient population with a high unmet need. Ongoing follow-up will help to assess the durability of response.

3 Breast cancer

3.1 Fulvestrant plus palbociclib (Ibrance®) versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy

Overview

Drug Description		selective, small molecule inhibitor of cyclin-dependent kinases 4 and 6
Patient Indication		palbociclib and fulvestrant in patients with hormone-receptor-positive, HER2-negative metastatic breast cancer
Incidence in Austria		5,594 newly diagnosed per year (2012), 40.3/100,000/year
Ongoing Phase III		NCT01942135 – until January 2017
Approval status for this indication	**EMA**	On 15 September 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product palbociclib, intended for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer: -in combination with an aromatase inhibitor; -in combination with fulvestrant in women who have received prior endocrine therapy.
	FDA	02/2016: The FDA approved palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy.
Approval status for other indications	**EMA**	-
	FDA	02/2015: approved for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with letrozole as initial endocrine based therapy in postmenopausal women.
Costs		-

Phase III results

Lancet (2016), published online March 2, 2016 (Cristofanilli & Turner et al.): "*Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial"*

Background
In the PALOMA-3 study, the combination of the CDK4 and CDK6 inhibitor palbociclib and fulvestrant was associated with significant improvements in progression-free survival compared with fulvestrant plus placebo in patients with metastatic breast cancer. Identification of patients most suitable for the addition of palbociclib to endocrine therapy after tumour recurrence is crucial for treatment optimisation in metastatic breast cancer. We aimed to confirm our earlier findings with this extended follow-up and show our results for subgroup and biomarker analyses.

Methods
In this multicentre, double-blind, randomised phase 3 study, women aged 18 years or older with hormone-receptor-positive, HER2-negative metastatic breast cancer that had progressed on previous

endocrine therapy were stratified by sensitivity to previous hormonal therapy, menopausal status, and presence of visceral metastasis at 144 centres in 17 countries. Eligible patients—ie, any menopausal status, Eastern Cooperative Oncology Group performance status 0–1, measurable disease or bone disease only, and disease relapse or progression after previous endocrine therapy for advanced disease during treatment or within 12 months of completion of adjuvant therapy—were randomly assigned (2:1) via a centralised interactive web-based and voice-based randomization system to receive oral palbociclib (125 mg daily for 3 weeks followed by a week off over 28-day cycles) plus 500 mg fulvestrant (intramuscular injection on days 1 and 15 of cycle 1; then on day 1 of subsequent 28-day cycles) or placebo plus fulvestrant. The primary endpoint was investigator-assessed progression-free survival. Analysis was by intention to treat. We also assessed endocrine therapy resistance by clinical parameters, quantitative hormone-receptor expression, and tumour PIK3CA mutational status in circulating DNA at baseline. This study is registered with ClinicalTrials.gov, NCT01942135.

Results

Between Oct 7, 2013, and Aug 26, 2014, 521 patients were randomly assigned, 347 to fulvestrant plus palbociclib and 174 to fulvestrant plus placebo. Study enrolment is closed and overall survival follow-up is in progress. By March 16, 2015, 259 progression-free-survival events had occurred (145 in the fulvestrant plus palbociclib group and 114 in the fulvestrant plus placebo group); median follow-up was 8·9 months (IQR 8·7–9·2). Median progression-free survival was 9·5 months (95% CI 9·2–11·0) in the fulvestrant plus palbociclib group and 4·6 months (3·5–5·6) in the fulvestrant plus placebo group (hazard ratio 0·46, 95% CI 0·36–0·59, p<0·0001). Grade 3 or 4 adverse events occurred in 251 (73%) of 345 patients in the fulvestrant plus palbociclib group and 38 (22%) of 172 patients in the fulvestrant plus placebo group. The most common grade 3 or 4 adverse events were neutropenia (223 [65%] in the fulvestrant plus palbociclib group and one [1%] in the fulvestrant plus placebo group), anaemia (ten [3%] and three [2%]), and leucopenia (95 [28%] and two [1%]). Serious adverse events (all causalities) occurred in 44 patients (13%) of 345 in the fulvestrant plus palbociclib group and 30 (17%) of 172 patients in the fulvestrant plus placebo group. PIK3CA mutation was detected in the plasma DNA of 129 (33%) of 395 patients for whom these data were available. Neither PIK3CA status nor hormone-receptor expression level significantly affected treatment response.

Conclusion

Fulvestrant plus palbociclib was associated with significant and consistent improvement in progression-free survival compared with fulvestrant plus placebo, irrespective of the degree of endocrine resistance, hormone-receptor expression level, and PIK3CA mutational status. The combination could be considered as a therapeutic option for patients with recurrent hormone-receptor-positive, HER2-negative metastatic breast cancer that has progressed on previous endocrine therapy.

4 Soft-tissue sarcoma

4.1 Olaratumab (Lartruvo®) and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma

Overview

Drug Description		is a fully human IgG1 monoclonal antibody that targets platelet-derived growth factor receptor alpha (PDGFRα)
Patient Indication		olaratumab plus doxorubicin in patients with advanced or metastatic soft-tissue sarcoma
Incidence in Austria		Austria: 2.4/100,000/year; 11,000 newly diagnosed per year in Europe
Ongoing Phase III		NCT01185964 - until March 2016
Approval status for this indication	**EMA**	On 15 September 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional1 marketing authorisation for the medicinal product olaratumab, intended for the treatment of advanced soft tissue sarcoma. olaratumab was designated as an orphan medicinal product on 12 February 2015.
	FDA	-
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

Lancet (2016), published online: 09 June 2016 (Tap et al.): *"Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial"*

Background
Treatment with doxorubicin is a present standard of care for patients with metastatic soft-tissue sarcoma and median overall survival for those treated is 12–16 months, but few, if any, novel treatments or chemotherapy combinations have been able to improve these poor outcomes. Olaratumab is a human antiplatelet-derived growth factor receptor α monoclonal antibody that has antitumor activity in human sarcoma xenografts. We aimed to assess the efficacy of olaratumab plus doxorubicin in patients with advanced or metastatic soft-tissue sarcoma.

Methods
We did an open-label phase 1b and randomised phase 2 study of doxorubicin plus olaratumab treatment in patients with unresectable or metastatic soft-tissue sarcoma at 16 clinical sites in the USA. For both the phase 1b and phase 2 parts of the study, eligible patients were aged 18 years or older and had a histologically confirmed diagnosis of locally advanced or metastatic soft-tissue sarcoma not previously treated with an anthracycline, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and available tumour tissue to determine PDGFRα expression by immunohistochemistry. In the phase 2 part of the study, patients were randomly assigned in a 1:1 ratio to receive either olaratumab (15 mg/kg) intravenously on day 1 and day 8 plus doxorubicin (75 mg/m2) or doxorubicin alone (75 mg/m2) on day 1 of each 21-day cycle for up to eight cycles. Randomisation was dynamic and used the minimisation randomisation technique. The phase 1b primary endpoint was

safety and the phase 2 primary endpoint was progression-free survival using a two-sided α level of 0·2 and statistical power of 0·8. This study was registered with ClinicalTrials.gov, number NCT01185964.

Findings
15 patients were enrolled and treated with olaratumab plus doxorubicin in the phase 1b study, and 133 patients were randomised (66 to olaratumab plus doxorubicin; 67 to doxorubicin alone) in the phase 2 trial, 129 (97%) of whom received at least one dose of study treatment (64 received olaratumab plus doxorubicin, 65 received doxorubicin). Median progression-free survival in phase 2 was 6·6 months (95% CI 4·1–8·3) with olaratumab plus doxorubicin and 4·1 months (2·8–5·4) with doxorubicin (stratified hazard ratio [HR] 0·67; 0·44–1·02, p=0·0615). Median overall survival was 26·5 months (20·9–31·7) with olaratumab plus doxorubicin and 14·7 months (9·2–17·1) with doxorubicin (stratified HR 0·46, 0·30–0·71, p=0·0003). The objective response rate was 18·2% (9·8–29·6) with olaratumab plus doxorubicin and 11·9% (5·3–22·2) with doxorubicin (p=0·3421). Steady state olaratumab serum concentrations were reached during cycle 3 with mean maximum and trough concentrations ranging from 419 μg/mL (geometric coefficient of variation in percentage [CV%] 26·2) to 487 μg/mL (CV% 33·0) and from 123 μg/mL (CV% 31·2) to 156 μg/mL (CV% 38·0), respectively. Adverse events that were more frequent with olaratumab plus doxorubicin versus doxorubicin alone included neutropenia (37 [58%] vs 23 [35%]), mucositis (34 [53%] vs 23 [35%]), nausea (47 [73%] vs 34 [52%]), vomiting (29 [45%] vs 12 [18%]), and diarrhoea (22 [34%] vs 15 [23%]). Febrile neutropenia of grade 3 or higher was similar in both groups (olaratumab plus doxorubicin: eight [13%] of 64 patients vs doxorubicin: nine [14%] of 65 patients).

Interpretation
This study of olaratumab with doxorubicin in patients with advanced soft-tissue sarcoma met its predefined primary endpoint for progression-free survival and achieved a highly significant improvement of 11·8 months in median overall survival, suggesting a potential shift in the treatment of soft-tissue sarcoma.

5 Head and neck squamous cell carcinoma

5.1 Pembrolizumab (Keytruda®, MK-3475) versus standard treatment for recurrent or metastatic head and neck cancer

Overview

Drug Description		a human programmed death receptor-1 (PD-1)-blocking antibody
Patient Indication		pembrolizumab for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
Incidence in Austria		1,085 newly diagnosed per year (2012), 7.9/100,000/year
Ongoing Phase III		NCT02252042 - until 05/2017
Approval status for this indication	**EMA**	-
	FDA	On August 5, 2016, the U. S. Food and Drug Administration granted accelerated approval to pembrolizumab for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.
Approval status for other indications	**EMA**	07/2016: approved for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab. 07/2015: pembrolizumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
	FDA	10/2015: approved for the treatment of patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumours that express a protein called PD-L1. 09/2014: approved for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
Costs		pembrolizumab 50 mg: € 1,812.55 - patients received 200 mg every 3 weeks (€7,250.2)

Abstracts

- 2015 ASCO Annual Meeting; Board #407b (Cohen et al.)

Background
Prognosis of patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is poor, with limited treatment options and survival rates of 6-9 months following standard-of-care (SOC) therapies. Pembrolizumab, a humanized IgG4 monoclonal antibody against PD-1 designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2, has demonstrated clinical efficacy by investigator review (confirmed and unconfirmed responses) in a phase I study of R/M HNSCC. Preliminary PD-L1 biomarker data suggest that response rate may be greater in PD-L1–positive patients.

Methods

In this global open-label, phase III KEYNOTE-040 (NCT02252042) trial, 466 subjects with recurrent or metastatic HNSCC that have failed prior platinum therapy will be randomized (1:1) to pembrolizumab (200 mg Q3W) vs investigator's choice SOC (single-agent methotrexate, docetaxel, or cetuximab). Randomization will be stratified by ECOG PS (0 vs 1), human papillomavirus (HPV) status in oropharyngeal cancer by p16 immunohistochemistry testing (positive vs negative), and centralized PD-L1 status (positive vs negative). Pembrolizumab will be given for ≤ 24 months or until disease progression, unacceptable toxicity, or investigator decision. AEs will be assessed according to NCI CTCAE, v4.0. Imaging will occur per RECIST v1.1 at 9 weeks and every 6 weeks thereafter. Modified RECIST, which allows for continued treatment after initial radiographic progression until confirmation imaging ≥ 4 weeks, will be used to account for unique responses seen with pembrolizumab. Radiographic responses will be confirmed by independent central review by RECIST v1.1 and modified RECIST and analysed in real time for verification of progressive disease by RECIST v1.1. Survival follow-up will occur every 12 weeks. Primary end points are progression free survival (PFS) and overall survival (OS); secondary end points include ORR, DOR and PFS, OS, and ORR in PD-L1+ patients. Treatment differences in PFS and OS will be assessed using stratified log-rank test; Hazard ratios with 95% confidence intervals will be estimated using stratified Cox proportional hazard models. Clinical trial information: NCT02252042

6 Pancreatic cancer

6.1 Nanoliposomal irinotecan (Onyvide®) with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy

Overview

Drug Description		is a nanoliposomal formulation of irinotecan hydrochloride (CPT-11), a topoisomerase I inhibitor
Patient Indication		nanoliposomal irinotecan in combination with fluorouracil and folinic acid, compared with a common control (fluorouracil and folinic acid), for patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine based therapy
Incidence in Austria		1,583 newly diagnosed per year (2012), 9.6 /100,000/year
Ongoing Phase III		-
Approval status for this indication	**EMA**	On 21 July 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product nanoliposomal irinotecan, intended for the treatment of metastatic adenocarcinoma of the pancreas. nanoliposomal irinotecan was designated as an orphan medicinal product on 9 December 2011.
	FDA	10/2015: nanoliposomal irinotecan (irinotecan liposome injection), in combination with fluorouracil and leucovorin is approved to treat patients with advanced (metastatic) pancreatic cancer who have been previously treated with gemcitabine-based chemotherapy.
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

Lancet (2016), published online 22 November 2015 (Wang-Gillam et al.): *"Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial"*

Background
Nanoliposomal irinotecan showed activity in a phase 2 study in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapies. We assessed the effect of nanoliposomal irinotecan alone or combined with fluorouracil and folinic acid in a phase 3 trial in this population.

Methods
We did a global, phase 3, randomised, open-label trial at 76 sites in 14 countries. Eligible patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy were randomly assigned (1:1) using an interactive web response system at a central location to receive either nanoliposomal irinotecan monotherapy (120 mg/m2 every 3 weeks, equivalent to 100 mg/m2 of irinotecan base) or fluorouracil and folinic acid. A third arm consisting of nanoliposomal irinotecan (80 mg/m2, equivalent to 70 mg/m2 of irinotecan base) with fluorouracil and folinic acid every 2 weeks was added later (1:1:1), in a protocol amendment. Randomisation was stratified by baseline albumin, Karnofsky performance status, and ethnic origin. Treatment was continued until disease progression or intolerable toxic effects. The primary endpoint was overall survival, assessed in the intention-to-treat

population. The primary analysis was planned after 305 events. Safety was assessed in all patients who had received study drug. This trial is registered at ClinicalTrials.gov, number NCT01494506.

Findings
Between Jan 11, 2012, and Sept 11, 2013, 417 patients were randomly assigned either nanoliposomal irinotecan plus fluorouracil and folinic acid (n=117), nanoliposomal irinotecan monotherapy (n=151), or fluorouracil and folinic acid (n=149). After 313 events, median overall survival in patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid was 6·1 months (95% CI 4·8–8·9) vs 4·2 months (3·3–5·3) with fluorouracil and folinic acid (hazard ratio 0·67, 95% CI 0·49–0·92; p=0·012). Median overall survival did not differ between patients assigned nanoliposomal irinotecan monotherapy and those allocated fluorouracil and folinic acid (4·9 months [4·2–5·6] vs 4·2 months [3·6–4·9]; 0·99, 0·77–1·28; p=0·94). The grade 3 or 4 adverse events that occurred most frequently in the 117 patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid were neutropenia (32 [27%]), diarrhoea (15 [13%]), vomiting (13 [11%]), and fatigue (16 [14%]).

Interpretation
Nanoliposomal irinotecan in combination with fluorouracil and folinic acid extends survival with a manageable safety profile in patients with metastatic pancreatic ductal adenocarcinoma who previously received gemcitabine-based therapy. This agent represents a new treatment option for this population.