Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
31st Prioritization – 2nd quarter 2017

General Information, efficacy and safety data

Nicole Grössmann

Sarah Wolf

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 31 prioritisation (May 2017), 10 drugs were filtered out of 302 identified and were sent to prioritisation. Of these, 4 drugs were ranked as ‘highly relevant’ by the expert panel, 5 as ‘relevant’ and 1 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 – 31st prioritisation 2st quarter 2017	Overall category
1.	Comparison of adjuvant gemcitabine and capecitabine (Xeloda®) with gemcitabine monotherapy in patients with resected pancreatic cancer	Not relevant
2.	First-line ceritinib (Zykadia®) versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer	Highly relevant
3.	Dabrafenib (Tafinlar®) plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer	Relevant
4.	Pembrolizumab (Keytruda®) as second-line therapy for advanced urothelial carcinoma	Highly relevant
5.	Pembrolizumab (Keytruda®) for platinum- and cetuximab-refractory head and neck cancer	Relevant
6.	Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma	Relevant
7.	Idelalisib (Zydelig®) or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia	Highly relevant
8.	Nivolumab (Opdivo®) for previously treated unresectable metastatic anal cancer	Relevant
9.	Mucosa-associated lymphoid tissue lymphoma: improved event-Free and progression-free survival with rituximab (MabThera®) plus chlorambucil versus either chlorambucil or rituximab monotherapy	Relevant
10.	Bortezomib (Velcade®) with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant	Highly relevant

1 Lung cancer

1.1 First-line ceritinib (Zykadia®) versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer

Overview

Drug Description		small molecule, ATP-competitive inhibitor of the tyrosine kinase anaplastic lymphoma kinase (ALK)
Patient Indication		ceritinib for untreated patients with stage IIIB/IV ALK-rearranged non-squamous 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)
Ongoing Phase II		NCT01828099 until 06/2018
Approval status for this indication	**EMA**	-
	FDA	02/2017: priority review for ALK-positive metastatic NSCLC in the first line
Approval status for other indications	**EMA**	05/2015: for advanced ALK-positive NSCLC that has been treated before with Xalkori (crizotinib)
	FDA	04/2014: for late-stage (metastatic) NSCLC after progression or intolerance to crizotinib
Costs		ZYKADIA 1 treatment cycle: 750 mg ceritinib per day for 21-days; ex-factory price of 150 mg per 150 pieces = € 5,355.30 → € 3,748.71 per treatment cycle

1.1.1 Published articles (PubMed):

Lancet (2017), published online March 12, 2017 (Soria et al.) *"First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study"*

Background
The efficacy of ceritinib in patients with untreated anaplastic lymphoma kinase (ALK)-rearranged non-small-cell lung cancer (NSCLC) is not known. We assessed the efficacy and safety of ceritinib versus platinum-based chemotherapy in these patients.

Methods
This randomised, open-label, phase 3 study in untreated patients with stage IIIB/IV ALK-rearranged non-squamous NSCLC was done in 134 centres across 28 countries. Eligible patients were assigned via interactive response technology to oral ceritinib 750 mg/day or platinum-based chemotherapy ([cisplatin 75 mg/m² or carboplatin AUC 5–6 plus pemetrexed 500 mg/m²] every 3 weeks for four cycles followed by maintenance pemetrexed); randomisation was stratified by World Health Organization performance status (0 vs 1–2), previous neoadjuvant or adjuvant chemotherapy, and presence of brain metastases as per investigator's assessment at screening. Investigators and patients were not masked to treatment assignment. The primary endpoint was blinded independent

review committee assessed progression-free survival, based on all randomly assigned patients (the full analysis set). Efficacy analyses were done based on the full analysis set. All safety analyses were done based on the safety set, which included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01828099.

Findings
Between Aug 19, 2013, and May 11, 2015, 376 patients were randomly assigned to ceritinib (n=189) or chemotherapy (n=187). Median progression-free survival (as assessed by blinded independent review committee) was 16.6 months (95% CI 12.6–27.2) in the ceritinib group and 8.1 months (5.8–11.1) in the chemotherapy group (hazard ratio 0.55 [95% CI 0.42–0.73]; p<0.00001). The most common adverse events were diarrhoea (in 160 [85%] of 189 patients), nausea (130 [69%]), vomiting (125 [66%]), and an increase in alanine aminotransferase (114 [60%]) in the ceritinib group and nausea (in 97 [55%] of 175 patients), vomiting (63 [36%]), and anaemia (62 [35%]) in the chemotherapy group.

Interpretation
First-line ceritinib showed a statistically significant and clinically meaningful improvement in progression-free survival versus chemotherapy in patients with advanced ALK-rearranged NSCLC.

2 Urothelial carcinoma

2.1 Pembrolizumab (Keytruda®) as second-line therapy for advanced urothelial carcinoma

Overview

Drug Description		human programmed death receptor-1 (PD-1)-blocking antibody
Patient Indication		pembrolizumab for patients with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy
Incidence in Austria		1,427 newly diagnosed per year (2014), 17.3/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02256436 - until 01/2017
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	07/2015: as monotherapy for advanced (unresectable or metastatic) melanoma in adults 07/2016: for locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adultswhose 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 01/2017: as monotherapy for metastatic NSCLC in the first line in adultswhose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
	FDA	09/2014: for unresectable or metastatic melanoma, after disease progression following ipilimumab and if positive BRAF V600 mutation 10/2016: • for metastatic NSCLC in patients whose tumours have high PD-L1

Approval status for other indications		expression (Tumour Proportion Score [TPS] greater than or equal to 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC • for metastatic NSCLC in patients whose tumours express PD-L1 (TPS greater than or equal to 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab 08/2016: for recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy 10/2016: for metastatic non-small cell carcinoma in the first line
Costs		KEYTRUDA 1 treatment cycle: 200 mg pembrolizumab every three weeks; ex-factory price of 25 mg/ml 4ml = € 3,428,- → € 6,856,- per treatment cycle

2.1.1 Published articles (PubMed):

NEJM (2017), published online February 17, (Bellmunt et al.) *"Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma"*

Background
Patients with advanced urothelial carcinoma that progresses after platinum-based chemotherapy have a poor prognosis and limited treatment options.

Methods
In this open-label, international, phase 3 trial, we randomly assigned 542 patients with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy to receive pembrolizumab (a highly selective, humanized monoclonal IgG4κ isotype antibody against programmed death 1 [PD-1]) at a dose of 200 mg every 3 weeks or the investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine. The co-primary end points were overall survival and progression-free survival, which were assessed among all patients and among patients who had a tumour PD-1 ligand (PD-L1) combined positive score (the percentage of PD-L1–expressing tumour and infiltrating immune cells relative to the total number of tumour cells) of 10% or more.

Results
The median overall survival in the total population was 10.3 months (95% confidence interval [CI], 8.0 to 11.8) in the pembrolizumab group, as compared with 7.4 months (95% CI, 6.1 to 8.3) in the chemotherapy group (hazard ratio for death, 0.73; 95% CI, 0.59 to 0.91; P = 0.002). The median overall survival among patients who had a tumour PD-L1 combined positive score of 10% or more was 8.0 months (95% CI, 5.0 to 12.3) in the pembrolizumab group, as compared with 5.2 months (95% CI, 4.0 to 7.4) in the chemotherapy group (hazard ratio, 0.57; 95% CI, 0.37 to 0.88; P = 0.005). There was no significant between-group difference in the duration of progression-free survival in the total population (hazard ratio for death or disease progression, 0.98; 95% CI, 0.81 to 1.19; P = 0.42) or among patients who had a tumour PD-L1 combined positive score of 10% or more (hazard ratio, 0.89; 95% CI, 0.61 to 1.28; P = 0.24). Fewer treatment-related adverse events of any grade were reported in the pembrolizumab group than in the chemotherapy group (60.9% vs. 90.2%); there were also fewer events of grade 3, 4, or 5 severity reported in the pembrolizumab group than in the chemotherapy group (15.0% vs. 49.4%).

Conclusion
Pembrolizumab was associated with significantly longer overall survival (by approximately 3 months) and with a lower rate of treatment-related adverse events than chemotherapy as second-line therapy for platinum-refractory advanced urothelial carcinoma. (Funded by Merck; KEYNOTE-045 ClinicalTrials.gov number, NCT02256436.)

3 Leukaemia

3.1 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,-.

3.1.1 Published articles (PubMed):

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.

4 Multiple myeloma

4.1 Bortezomib (Velcade®) with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant

Overview

Drug Description		a first-in-class proteasome inhibitor
Patient Indication		bortezomib with lenalidomide and dexamethasone for untreated multiple myeloma who were not planned for immediate autologous stem-cell transplant
Incidence in Austria		382 newly diagnosed per year (2014), 4.3/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02136134 - until 03/2017
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	12/2013: as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. 08/2008: in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high dose chemotherapy with haematopoietic stem cell transplantation. 06/2013: in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation. 01/2015: in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.
	FDA	06/2003: for the treatment of patients with multiple myeloma 12/2006: for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Costs		VELCADE <u>Dexamethasone:</u> in one treatment cycle a dosis 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 <u>Bortezomib</u>: 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 <u>Lenalidomide:</u> 1 cycle: 25 mg daily on days 1–14; 21 pieces → € 6,696.10 and for 1 treatment cycle (14 pieces) € 4,464.1 would incur Total costs of € 7,588.72 for 1 treatment cycle (21-days) of combination treatment would incur

4.1.1 Published articles (PubMed):

Lancet (2016) published online December 22, (Durie et al.): *"Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial"*

Background
Lenalidomide plus dexamethasone is a reference treatment for patients with newly diagnosed myeloma. The combination of the proteasome inhibitor bortezomib with lenalidomide and dexamethasone has shown significant efficacy in the setting of newly diagnosed myeloma. We aimed to study whether the addition of bortezomib to lenalidomide and dexamethasone would improve progression-free survival and provide better response rates in patients with previously untreated multiple myeloma, who were not planned for immediate autologous stem-cell transplant.

Methods
In this randomised, open-label, phase 3 trial, we recruited patients with newly diagnosed multiple myeloma aged 18 years and older from participating Southwest Oncology Group (SWOG) and National Clinical Trial Network (NCTN) institutions (both inpatient and outpatient settings). Key inclusion criteria were presence of CRAB (C=calcium elevation; R=renal impairment; A=anaemia; B=bone involvement) criteria with measurable disease (measured by assessment of free light chains), Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, haemoglobin concentration 9 g/dL or higher, absolute neutrophil count 1 × 103 cells per mm3 or higher, and a platelet count of 80 000/mm3 or higher. We randomly assigned (1:1) patients to receive either an initial treatment of bortezomib with lenalidomide and dexamethasone (VRd group) or lenalidomide and dexamethasone alone (Rd group). Randomisation was stratified based on International Staging System stage (I, II, or III) and intent to transplant (yes vs no). The VRd regimen was given as eight 21-day cycles. Bortezomib was given at 1·3 mg/m2 intravenously on days 1, 4, 8, and 11, combined with oral lenalidomide 25 mg daily on days 1–14 plus oral dexamethasone 20 mg daily on days 1, 2, 4, 5, 8, 9, 11, and 12. The Rd regimen was given as six 28-day cycles. The standard Rd regimen consisted of 25 mg oral lenalidomide once a day for days 1–21 plus 40 mg oral dexamethasone once a day on days 1, 8, 15, and 22. The primary endpoint was progression-free survival using a pre-specified one-sided stratified log rank test at a significance level of 0·02. Analyses were intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00644228.

Findings
Between April, 2008, and February, 2012, we randomly assigned 525 patients at 139 participating institutions (264 to VRd and 261 to Rd). In the randomly assigned patients, 21 patients in the VRd group and 31 in the Rd group were deemed ineligible based mainly on missing, insufficient, or early or late baseline laboratory data. Median progression-free survival was significantly improved in the VRd group (43 months vs 30 months in the Rd group; stratified hazard ratio [HR] 0.712, 96% CI 0.56–0.906; one-sided p value 0.0018). The median overall survival was also significantly improved in the VRd group (75 months vs 64 months in the Rd group, HR 0.709, 95% CI 0.524–0.959; two-sided p value 0.025). The rates of overall response (partial response or better) were 82% (176/216) in the VRd group and 72% (153/214) in the Rd group, and 16% (34/216) and 8% (18/214) of patients who were assessable for response in these respective groups had a complete response or better. Adverse events of grade 3 or higher were reported in 198 (82%) of 241 patients in the VRd group and 169 (75%) of 226 patients in the Rd group; 55 (23%) and 22 (10%) patients discontinued induction treatment because of adverse events, respectively. There were no treatment-related deaths in the Rd group, and two in the VRd group.

Interpretation
In patients with newly diagnosed myeloma, the addition of bortezomib to lenalidomide and dexamethasone resulted in significantly improved progression-free and overall survival and had an acceptable risk-benefit profile.