Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
23rd Prioritization – 2nd quarter 2015

General Information, efficacy and safety data

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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 23rd prioritisation (June 2015), 10 drugs were filtered out of 170 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 – 23rd prioritisation 2nd quarter 2015	Overall category
1.	Afatinib (BIBW-2992, Gilotrif®, Giotrif®) as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck	Relevant
2.	Neoadjuvant bevacizumab (Avastin®) for women with HER2-negative early breast cancer	Relevant
3.	Cisplatin plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer	Not relevant
4..	Ramucirumab (Cyramza®, IMC-1121B) in combination with FOLFIRI as second-line therapy for metastatic colorectal carcinoma	Highly relevant
5.	TAS-102 (= trifluridine and tipiracil hydrochloride) for refractory metastatic colorectal cancer	Relevant
6.	Elotuzumab (BMS 901608, HuLuc63) for relapsed or refractory multiple myeloma	Relevant
7.	Ipilimumab (Yervoy®, MDX-010) as adjuvant therapy for high risk stage III melanoma	Highly relevant
8.	Nivolumab (BMS-936558 / MDX1106 / ONO4538) as second-line therapy for advanced melanoma	Highly relevant
9.	Pembrolizumab (Keytruda®, MK-3475) in advanced melanoma	Highly relevant
10.	Talimogene laherparepvec (T-VEC, OncoVEXGM-CSF) in patients with advanced melanoma	Relevant

1 Colorectal cancer

1.1 Ramucirumab (Cyramza®, IMC-1121B) in combination with FOLFIRI as second-line therapy for metastatic colorectal carcinoma

Drug Description		a human vascular endothelial growth factor receptor 2-antagonist
Incidence in Austria		4,577 newly diagnosed/year (2011), 28.4/100,000/year
Approval status for this indication	**EMA**	-
	FDA	04/2015: indicated in combination with FOLFIRI for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

Phase III results:

Tabernero et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet (2015) 16: 499–508.

Background
Angiogenesis is an important therapeutic target in colorectal carcinoma. Ramucirumab is a human IgG-1 monoclonal antibody that targets the extracellular domain of VEGF receptor 2. We assessed the efficacy and safety of ramucirumab versus placebo in combination with second-line FOLFIRI (leucovorin, fluorouracil, and irinotecan) for metastatic colorectal cancer in patients with disease progression during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

Methods
Between Dec 14, 2010, and Aug 23, 2013, we enrolled patients into the multicentre, randomised, double-blind, phase 3 RAISE trial. Eligible patients had disease progression during or within 6 months of the last dose of first-line therapy. Patients were randomised (1:1) via a centralised, interactive voice-response system to receive 8 mg/kg intravenous ramucirumab plus FOLFIRI or matching placebo plus FOLFIRI every 2 weeks until disease progression, unacceptable toxic effects, or death. Randomisation was stratified by region, *KRAS* mutation status, and time to disease progression after starting first-line treatment. The primary endpoint was overall survival in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01183780.

Results
We enrolled 1072 patients (536 in each group). Median overall survival was 13·3 months (95% CI 12·4–14·5) for patients in the ramucirumab group versus 11·7 months (10·8–12·7) for the placebo group (hazard ratio 0·844 95% CI 0·730–0·976; log-rank p=0·0219). Survival benefit was consistent across subgroups of patients who received ramucirumab plus FOLFIRI. Grade 3 or worse adverse events seen in more than 5% of patients were neutropenia (203 [38%] of 529 patients in the ramucirumab group *vs.* 123 [23%] of 528 in the placebo group, with febrile neutropenia incidence of 18 [3%] *vs.* 13 [2%]), hypertension (59 [11%] *vs.* 15 [3%]), diarrhoea (57 [11%] *vs.* 51 [10%]), and fatigue (61 [12%] *vs.* 41 [8%]).

Conclusion
Ramucirumab plus FOLFIRI significantly improved overall survival compared with placebo plus FOLFIRI as second-line treatment for patients with metastatic colorectal carcinoma. No unexpected adverse events were identified and toxic effects were manageable.

2 Skin cancer

2.1 Ipilimumab (Yervoy®, MDX-010) as adjuvant therapy for high risk stage III melanoma

Drug Description		a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody
Incidence in Austria		1,551 newly diagnosed per year (2011), 12.2/100,000/year
Approval status for this indication	**EMA**	-
	FDA	-

Phase III results:

Eggermont et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet (2015), Issue 16: 522-530.

Background
Ipilimumab is an approved treatment for patients with advanced melanoma. We aimed to assess ipilimumab as adjuvant therapy for patients with completely resected stage III melanoma at high risk of recurrence.

Methods
We did a double-blind, phase 3 trial in patients with stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis) with adequate resection of lymph nodes (ie, the primary cutaneous melanoma must have been completely excised with adequate surgical margins) who had not received previous systemic therapy for melanoma from 91 hospitals located in 19 countries. Patients were randomly assigned (1:1), centrally by an interactive voice response system, to receive intravenous infusions of 10 mg/kg ipilimumab or placebo every 3 weeks for four doses, then every 3 months for up to 3 years. Using a minimisation technique, randomisation was stratified by disease stage and geographical region. The primary endpoint was recurrence-free survival, assessed by an independent review committee, and analysed by intention to treat. Enrollment is complete but the study is ongoing for follow-up for analysis of secondary endpoints. This trial is registered with EudraCT, number 2007-001974-10, and ClinicalTrials.gov, number NCT00636168.

Results
Between July 10, 2008, and Aug 1, 2011, 951 patients were randomly assigned to ipilimumab (n=475) or placebo (n=476), all of whom were included in the intention-to-treat analyses. At a median follow-up of 2·74 years (IQR 2·28–3·22), there were 528 recurrence-free survival events (234 in the ipilimumab group *vs.* 294 in the placebo group). Median recurrence-free survival was 26·1 months (95% CI 19·3–39·3) in the ipilimumab group versus 17·1 months (95% CI 13·4–21·6) in the

placebo group (hazard ratio 0・75; 95% CI 0・64–0・90; p=0・0013); 3-year recurrence-free survival was 46・5% (95% CI 41・5–51・3) in the ipilimumab group versus 34・8% (30・1–39・5) in the placebo group. The most common grade 3–4 immune-related adverse events in the ipilimumab group were gastrointestinal (75 [16%] *vs.* four [<1%] in the placebo group), hepatic (50 [11%] *vs.* one [<1%]), and endocrine (40 [8%] *vs.* none). Adverse events led to discontinuation of treatment in 245 (52%) of 471 patients who started ipilimumab (182 [39%] during the initial treatment period of four doses). Five patients (1%) died due to drug-related adverse events. Five (1%) participants died because of drug-related adverse events in the ipilimumab group; three patients died because of colitis (two with gastrointestinal perforation), one patient because of myocarditis, and one patient because of multiorgan failure with Guillain-Barre syndrome.

Conclusion
Adjuvant ipilimumab significantly improved recurrence-free survival for patients with completely resected high-risk stage III melanoma. The adverse event profile was consistent with that observed in advanced melanoma, but at higher incidences in particular for endocrinopathies. The risk–benefit ratio of adjuvant ipilimumab at this dose and schedule requires additional assessment based on distant metastasis-free survival and overall survival endpoints to define its definitive value.

2.2 Nivolumab (BMS-936558 / MDX1106 / ONO4538) as second-line therapy for advanced melanoma

Drug Description		a programmed death receptor-1 (PD-1) blocking antibody
Incidence in Austria		1,551 newly diagnosed per year (2011), 12.2/100,000/year
Approval status for this indication	**EMA**	06/2015: as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
	FDA	03/2015 (accelerated approval): unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Phase III results:

Weber et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet (2015) 16: 375–84.

Background
Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, can result in durable responses in patients with melanoma who have progressed after ipilimumab and BRAF inhibitors. We assessed the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma.

Methods
In this randomised, controlled, open-label, phase 3 trial, we recruited patients at 90 sites in 14 countries. Eligible patients were 18 years or older, had unresectable or metastatic melanoma, and progressed after ipilimumab, or ipilimumab and a BRAF inhibitor if they were *BRAF*^{V600} mutation-

positive. Participating investigators randomly assigned (with an interactive voice response system) patients 2:1 to receive an intravenous infusion of nivolumab 3 mg/kg every 2 weeks or ICC (dacarbazine 1000 mg/m2 every 3 weeks or paclitaxel 175 mg/m2 combined with carboplatin area under the curve 6 every 3 weeks) until progression or unacceptable toxic effects. We stratified randomisation by *BRAF* mutation status, tumour expression of PD-L1, and previous best overall response to ipilimumab. We used permuted blocks (block size of six) within each stratum. Primary endpoints were the proportion of patients who had an objective response and overall survival. Treatment was given open-label, but those doing tumour assessments were masked to treatment assignment. We assessed objective responses per-protocol after 120 patients had been treated with nivolumab and had a minimum follow-up of 24 weeks, and safety in all patients who had had at least one dose of treatment. The trial is closed and this is the first interim analysis, reporting the objective response primary endpoint. This study is registered with ClinicalTrials.gov, number NCT01721746.

Results
Between Dec 21, 2012, and Jan 10, 2014, we screened 631 patients, randomly allocating 272 patients to nivolumab and 133 to ICC. Confirmed objective responses were reported in 38 (31・7%, 95% CI 23・5–40・8) of the first 120 patients in the nivolumab group versus five (10・6%, 3・5–23・1) of 47 patients in the ICC group. Grade 3–4 adverse events related to nivolumab included increased lipase (three [1%] of 268 patients), increased alanine aminotransferase, anaemia, and fatigue (two [1%] each); for ICC, these included neutropenia (14 [14%] of 102), thrombocytopenia (six [6%]), and anaemia (five [5%]). We noted grade 3–4 drug-related serious adverse events in 12 (5%) nivolumab treated patients and nine (9%) patients in the ICC group. No treatment-related deaths occurred.

Conclusion
Nivolumab led to a greater proportion of patients achieving an objective response and fewer toxic effects than with alternative available chemotherapy regimens for patients with advanced melanoma that has progressed after ipilimumab or ipilimumab and a BRAF inhibitor. Nivolumab represents a new treatment option with clinically meaningful durable objective responses in a population of high unmet need.

2.3 Pembrolizumab (Keytruda®, MK-3475) in advanced melanoma

Drug Description		a human programmed death receptor-1 (PD-1)-blocking antibody
Incidence in Austria		1,551 newly diagnosed per year (2011), 12.2/100,000/year
Approval status for this indication	**EMA**	07/2015: as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
	FDA	09/2014: indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Phase III results:

Robert et al. Pembrolizumab versus ipilimumab in advanced melanoma. NEJM (2015) 372:2521-32.

Background

The immune checkpoint inhibitor ipilimumab is the standard-of-care treatment for patients with advanced melanoma. Pembrolizumab inhibits the programmed cell death 1 (PD-1) immune checkpoint and has antitumor activity in patients with advanced melanoma.

Methods
In this randomized, controlled, phase 3 study, we assigned 834 patients with advanced melanoma in a 1:1:1 ratio to receive pembrolizumab (at a dose of 10 mg per kilogram of body weight) every 2 weeks or every 3 weeks or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks. Primary end points were progression-free and overall survival.

Results
The estimated 6-month progression-free-survival rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (hazard ratio for disease progression, 0.58; P<0.001 for both pembrolizumab regimens versus ipilimumab; 95% confidence intervals [CIs], 0.46 to 0.72 and 0.47 to 0.72, respectively). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively (hazard ratio for death for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 to 0.83; P = 0.0005; hazard ratio for pembrolizumab every 3 weeks, 0.69; 95% CI, 0.52 to 0.90; P = 0.0036). The response rate was improved with Pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (P<0.001 for both comparisons). Responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, respectively, after a median follow-up of 7.9 months. Efficacy was similar in the two pembrolizumab groups. Rates of treatment-related adverse events of grade 3 to 5 severity were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%).

Conclusion
The anti–PD-1 antibody pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity than did ipilimumab in patients with advanced melanoma. (Funded by Merck Sharp & Dohme; KEYNOTE-006 ClinicalTrials.gov number, NCT01866319.)