Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
25th Prioritization – 4th quarter 2015

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 25th prioritisation (December 2015), 11 drugs were filtered out of 199 identified and were sent to prioritisation. Of these, 3 drugs were ranked as ‘highly relevant’ by the expert panel, 8 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 – 25th prioritisation 4th quarter 2015	Overall category
1.	Paclitaxel (Abraxane®, Ebetaxel®, ABI-007) in chemotherapy-naïve patients with metastatic melanoma	Relevant
2.	Ipilimumab (Yervoy®, MDX-010) as adjuvant therapy for high risk stage III melanoma	Relevant
3.	Nivolumab (BMS-936558 / MDX1106 / ONO4538) versus everolimus in previously treated patients with advanced renal cell carcinoma	Relevant
4.	Cabozantinib (CometriqTM) versus everolimus for previously treated patients with advanced renal cell carcinoma	Relevant
5.	Daratumumab (DarzalexTM) as a monotherapy in patients with ≥3 lines of prior therapy or double refractory multiple myeloma	Relevant
6.	Ixazomib (MLN9708, Ninlaro®) in combination with lenalidomide and dexamethasone for patients with relapsed and/or refractory multiple myeloma	Highly relevant
7.	Pembrolizumab (Keytruda®, MK-3475) versus docetaxel in previously-treated participants with non-small cell lung cancer	Highly relevant
8.	Nedaplatin (Aqupla) plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung	Relevant
9.	Alectinib (ALECENSA®) for anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC)	Relevant
10.	Ofatumumab (Arzerra) maintenance versus observation in relapsed chronic lymphocytic leukaemia	Highly relevant
11.	Erlotinib (Tarceva®) in combination with bevacizumab for maintenance therapy in patients with unresectable metastatic colorectal cancer	Relevant

1 Multiple myeloma

1.1 Ixazomib (MLN9708, Ninlaro®) in combination with lenalidomide and dexamethasone for patients with relapsed and/or refractory multiple myeloma

Overview

Drug Description		oral proteasome inhibitor
Patient Indication		Ixazomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Incidence in Austria		627 newly diagnosed per year (2012), 5.6 /100,000/year
Approval status for this indication	**EMA**	-
	FDA	11/2015: ixazomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Phase III results: -

Other Sources: FDA

www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf (page 15-18)

2 Lung cancer

2.1 Pembrolizumab (Keytruda®, MK-3475) versus docetaxel in previously-treated participants with non-small cell lung cancer

Overview

Drug Description		a human programmed death receptor-1 (PD-1)-blocking antibody
Patient Indication		Pembrolizumab versus docetaxel in previously-treated participants with non-small cell lung cancer
Incidence in Austria		4,573 newly diagnosed per year (2012), 30.5 /100,000/year
Approval status for	**EMA**	-

this indication	**FDA**	10/2015: patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1.

Phase III results:

The Lancet, Published Online December 19, 2015 (Herbst et al.): *"Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial"*

Background

Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

Methods

We did this randomised, open-label, phase 2/3 study at 202 academic medical centres in 24 countries. Patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells were randomly assigned (1:1:1) in blocks of six per stratum with an interactive voice-response system to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2 every 3 weeks. The primary endpoints were overall survival and progression-free survival both in the total population and in patients with PD-L1 expression on at least 50% of tumour cells. We used a threshold for significance of p<0·00825 (one-sided) for the analysis of overall survival and a threshold of p<0·001 for progression-free survival. This trial is registered at ClinicalTrials.gov, number NCT01905657.

Findings

Between Aug 28, 2013, and Feb 27, 2015, we enrolled 1034 patients: 345 allocated to pembrolizumab 2 mg/kg, 346 allocated to pembrolizumab 10 mg/kg, and 343 allocated to docetaxel. By Sept 30, 2015, 521 patients had died. In the total population, median overall survival was 10·4 months with pembrolizumab 2 mg/kg, 12·7 months with pembrolizumab 10 mg/kg, and 8·5 months with docetaxel. Overall survival was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (hazard ratio [HR] 0·71, 95% CI 0·58–0·88; p=0·0008) and for pembrolizumab 10 mg/kg versus docetaxel (0·61, 0·49–0·75; p<0·0001). Median progression-free survival was 3·9 months with pembrolizumab 2 mg/kg, 4·0 months with pembrolizumab 10 mg/kg, and 4·0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel (0·88, 0·74–1·05; p=0·07) or for pembrolizumab 10 mg/kg versus docetaxel (HR 0·79, 95% CI 0·66–0·94; p=0·004). Among patients with at least 50% of tumour cells expressing PD-L1, overall survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14·9 months *vs* 8·2 months; HR 0·54, 95% CI 0·38–0·77; p=0·0002) and with pembrolizumab 10 mg/kg than with docetaxel (17·3 months *vs* 8·2 months; 0·50, 0·36–0·70; p<0·0001). Likewise, for this patient population, progression-free survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 5·0 months *vs* 4·1 months; HR 0·59, 95% CI 0·44–0·78; p=0·0001) and with pembrolizumab 10 mg/kg than with docetaxel (5·2 months *vs* 4·1 months; 0·59, 0·45–0·78; p<0·0001). Grade 3–5 treatment-related adverse events were less common with pembrolizumab than with docetaxel (43 [13%] of 339 patients given 2 mg/kg, 55 [16%] of 343 given 10 mg/kg, and 109 [35%] of 309 given docetaxel).

Interpretation

Pembrolizumab prolongs overall survival and has a favourable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. These data establish pembrolizumab as a new treatment option for this population and validate the use of PD-L1 selection.

3 Leukemia

3.1 Ofatumumab (Arzerra) maintenance versus observation in relapsed chronic lymphocytic leukaemia

Overview

Drug Description		CD20-directed cytolytic monoclonal antibody
Patient Indication		maintenance treatment versus observation for patients in remission after re-induction treatment for relapsed chronic lymphocytic leukaemia
Incidence in Austria		1,083 newly diagnosed per year (2012), 8.1 /100,000/year
Approval status for this indication	**EMA**	-
	FDA	-

Phase III results:

The Lancet (2015) Volume 16, Issue: 13 Pages 1370–1379 (H J van Oers et al.): *"Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study"*

→ **PDF-file**: ofatumumab_leukemia_H J van Oers_2015_LANCET.pdf

Background
Ofatumumab is a human anti-CD20 monoclonal antibody that has proven efficacy as monotherapy in refractory chronic lymphocytic leukaemia. We assessed the efficacy and safety of ofatumumab maintenance treatment versus observation for patients in remission after re-induction treatment for relapsed chronic lymphocytic leukaemia.

Methods
This open-label, multicentre, randomised phase 3 study enrolled patients aged 18 years or older from 130 centres in 24 countries who had chronic lymphocytic leukaemia in complete or partial remission after second-line or third-line treatment. Eligible patients had a WHO performance status of 0–2, had a response assessment within the previous 3 months, did not have refractory disease, autoimmune haemolytic anaemia requiring treatment, chronic or active infection requiring treatment, and had not previously received maintenance treatment or autologous or allogeneic stem-cell transplant. Using a randomisation list generated by a central computerised system and an interactive voice recognition system, we randomly assigned (1:1) patients to receive ofatumumab (300 mg followed by 1000 mg 1 week later and every 8 weeks for up to 2 years) or undergo observation. Randomisation was stratified by number and type of previous treatment and remission status after induction treatment (block size of four). Treatment assignment was open label. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. We report the results of a prespecified interim analysis after two-thirds of the planned study events (disease progression or death) had happened. This trial is closed to accrual but follow-up is ongoing. This trial is registered with ClinicalTrials.gov, number NCT00802737.

Findings

Between May 6, 2010, and June 19, 2014, we enrolled 474 patients: 238 patients were randomly assigned to receive ofatumumab maintenance treatment and 236 to undergo observation. One (<1%) patient in the ofatumumab group did not receive the allocated intervention (withdrawal of consent). The median follow-up was 19·1 months (IQR 10·3–28·8). Progression-free survival was improved in patients assigned to the ofatumumab group (29·4 months, 95% CI 26·2–34·2) compared with those assigned to observation (15·2 months, 11·8–18·8; hazard ratio 0·50, 95% CI 0·38–0·66; p<0·0001). The most common grade 3 or higher adverse events up to 60 days after last treatment were neutropenia (56 [24%] of 237 patients in the ofatumumab group *vs* 23 [10%] of 237 in the observation group) and infections (31 [13%] *vs* 20 [8%]). 20 (8%) of 237 patients in the ofatumumab group and three (1%) of 237 patients in the observation group had adverse events that led to permanent discontinuation of treatment. Up to 60 days after last treatment, two deaths related to adverse events occurred in the ofatumumab treatment group and five deaths related to adverse events occurred in the observation group; no deaths were attributed to the study drug.

Interpretation

These data are important for the development of optimum maintenance strategies in patients with relapsed chronic lymphocytic leukaemia, notably in the present era of targeted drugs, many of which are to be used until progression.