Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
26th Prioritization – 1st quarter 2016

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 26th prioritisation (March 2016), 12 drugs were filtered out of 224 identified and were sent to prioritisation. Of these, 2 drugs were ranked as ‘highly relevant’ by the expert panel, 9 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 – 26th prioritisation 1st quarter 2016	Overall category
1.	Nab-paclitaxel (Abraxane®) versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer	Relevant
2.	Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer	Relevant
3.	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	Relevant
4.	Taxanes versus S-1 (Teysuno®) as the first-line chemotherapy for metastatic breast cancer	Not relevant
5.	Cediranib in patients with relapsed platinum-sensitive ovarian cancer	Relevant
6.	Standard first-line chemotherapy with or without nintedanib (Vargatef®) for advanced ovarian cancer	Relevant
7.	Afatinib (Giotrif™) beyond progression in patients with non-small-cell lung cancer (NSCLC) following chemotherapy, erlotinib/gefitinib and afatinib	Highly relevant
8.	Apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction	Relevant
9.	Everolimus (Afinitor®) for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract	Relevant
10.	Eribulin (Halaven®) versus dacarbazine in patients with leiomyosarcoma and adipocytic sarcoma	Relevant
11.	Bendamustine (Levact®, Treanda®) plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas	Relevant
12.	Obinutuzumab (Gazyvaro®, Gazyva®) plus bendamustine versus bendamustine in relapsed/refractory indolent non-hodgkin lymphoma	Highly relevant

1 Lung cancer

1.1 Afatinib (Giotrif™) beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib

Overview

Drug Description		kinase inhibitor → ErbB-family blocker
Patient Indication		in patients who acquired resistance to erlotinib/gefitinib and progressed on afatinib after initial benefit
Incidence in Austria		4,573 newly diagnosed per year (2012), 30.5/100,000/year
Ongoing Phase III		-
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	09/2013: approved for the treatment of non-small-cell lung cancer (NSCLC) with epidermal-growth-factor-receptor (EGFR) mutation(s) 02/2016: The CHMP adopted a new indication as follows: Giotrif™ as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.
	FDA	07/2013: approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test
Costs		Giotrif™ film-coated tablets 40mg for 30 days: € 2,176.13 Paclitaxel 600mg: € 1,195.40 Patients received Giotrif™ – 40mg/day and Paclitaxel 80mg/m^2/week. For 1 month of therapy, assuming a body surface of 1.70 m^2 costs of about € 3,260 would occur.

Phase III results

Ann Oncol (2016), Issue 27: 417–423 (Schuler et al.): *"Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial"*

Background
Afatinib has demonstrated clinical benefit in patients with non-small-cell lung cancer progressing after treatment with erlotinib/gefitinib. This phase III trial prospectively assessed whether continued

irreversible ErbB-family blockade with afatinib plus paclitaxel has superior outcomes versus switching to chemotherapy alone in patients acquiring resistance to erlotinib/gefitinib and afatinib monotherapy.

Methods
Patients with relapsed/refractory disease following ≥1 line of chemotherapy, and whose tumors had progressed following initial disease control (≥12 weeks) with erlotinib/gefitinib and thereafter afatinib (50 mg/day), were randomized 2:1 to receive afatinib plus paclitaxel (40 mg/day; 80 mg/m2/week) or investigator's choice of single-agent chemotherapy. The primary end point was progression-free survival (PFS). Other end points included objective response rate (ORR), overall survival (OS), safety and patient-reported outcomes.

Results
Two hundred and two patients with progressive disease following clinical benefit from afatinib were randomized to afatinib plus paclitaxel (n = 134) or single-agent chemotherapy (n = 68). PFS (median 5.6 versus 2.8 months, hazard ratio 0.60, P = 0.003) and ORR (32.1% versus 13.2%, P = 0.005) significantly improved with afatinib plus paclitaxel. There was no difference in OS. Global health status/quality of life was maintained with afatinib plus paclitaxel over the entire treatment period. The median treatment duration was 133 and 51 days with afatinib plus paclitaxel and single-agent chemotherapy, respectively; 48.5% of patients receiving afatinib plus paclitaxel and 30.0% of patients receiving single-agent chemotherapy experienced drug-related grade 3/4 adverse events. Treatment-related adverse events were consistent with those previously reported with each agent.

Conclusion
Afatinib plus paclitaxel improved PFS and ORR compared with single-agent chemotherapy in patients who acquired resistance to erlotinib/gefitinib and progressed on afatinib after initial benefit. LUX-Lung 5 is the first prospective trial to demonstrate the benefit of continued ErbB targeting post-progression, versus switching to single-agent chemotherapy.

2 Lymphoma

2.1 Obinutuzumab (Gazyvaro®, Gazyva®) plus bendamustine versus bendamustine in relapsed/refractory indolent non-hodgkin lymphoma

Overview

Drug Description		A type II, glycoengineered, humanized anti-CD20 monoclonal antibody for iv administration
Patient Indication		after first-line treatment of patients with follicular lymphoma in combination with bendamustine
Incidence in Austria		1,265 newly diagnosed per year (2012), 9.0/100,000/year
Ongoing Phase III		-
Approval status for this indication	**EMA**	
	FDA	On February 26, 2016, the U. S. Food and Drug Administration approved obinutuzumab for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen.
Approval status for	**EMA**	Approved since 03/2010:

other indications		chronic lymphocytic leukaemia in patients for whom treatment with fludarabine is not appropriate. non-Hodgkin's lymphoma in patients whose cancer got worse during or following treatment containing rituximab. multiple myeloma in combination with prednisone in patients older than 65 years who are not eligible for stem-cell transplantation and cannot be treated with thalidomide or bortezomib.
	FDA	11/2013: Obinutuzumab in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia.
Costs		Gazyvaro® concentrate for solution for injection 1,000mg: € 3,668.20 The recommended dose of Gazyvaro® is 1,000mg administered as an intravenous infusion on days 1, 8, and 15 (28-days) cycle 1 → € 11,004.60 cycles 2-6: in each cycle 1,000 mg on day 1 → € 3,668.20

Abstract

ASH 2015 Annual Meeting (Pott et al.):

Background
Minimal residual disease (MRD) response after first-line treatment of follicular lymphoma (FL) is likely to predict clinical course. The prognostic relevance of MRD in relapsed/refractory (r/r) FL remains unclear. We report MRD assessment with respect to clinical outcomes in r/r FL pts in GADOLIN (NCT01059630). GADOLIN is an open-label, multicenter, randomized phase III study of pts with r/r indolent NHL (refractory to rituximab) to investigate the efficacy and safety of obinutuzumab (G) plus bendamustine (B) followed by G maintenance vs B alone. A significant improvement in PFS in the G-B arm was reported (Sehn L, et al. ASCO 2015).

Methods
MRD was analyzed by t(14;18) and/or Ig variable domain allele-specific RQ-PCR in pts with a clonal marker detectable at diagnosis in peripheral blood (PB) or bone marrow (BM) by consensus PCR. (Assessment of Ig rearrangements allows detection of a lymphoma marker in pts with a t(14;18) breakpoint not detected by generic PCR and avoids false positive signals, as a low level of the translocation can be detected in some healthy individuals.) Assays were designed with a sensitivity of 10-5 and accepted for MRD assessment when a sensitivity of ≤10-4 was reached. Results were evaluated according to ESG-MRD criteria. MRD status was analyzed at interim staging (C4, D1) and after end of induction (EOI), and defined as negative (-ve) if RQ-PCR and subsequent nested PCR produced a -ve result, i.e. achieving an MRD response. PFS was measured from the EOI date.

Results
321 of 396 randomized pts were diagnosed with FL. Baseline samples (PB and/or BM) were available for 285 of the 304 FL pts who had completed induction at the clinical cut-off date (1 Sep 2014; FL-ITT population). A clonal marker was detected in 183 (64%) of these pts; 128/183 (70%) had a RQ-PCR assay fulfilling the sensitivity criteria. EOI samples were available for 93 pts (biomarker-evaluable population) and 64 had a PB sample at mid-induction to assess MRD-response kinetics. The distribution of age, stage, and FLIPI in the biomarker-evaluable population was similar to the non-evaluable population of the B arm, while there was an enrichment of younger age, advanced-stage disease, and high risk FLIPI in the biomarker-evaluable population of the G-B arm.
MRD response was analyzed in 93 pts at EOI and was significantly higher in pts receiving G-B induction, with 42/51 (82%) achieving MRD -ve status compared with 18/42 pts (43%) in the B arm ($p<0.0001$, Chi-Squared). At mid-induction, 30/39 (77%) pts in the G-B arm achieved early MRD -ve status vs 10/25 (40%) in the B arm ($p=0.0029$; Table). MRD response was associated with clinical CR; 2/33 (6%) MRD positive (+ve) pts vs 17/60 (28%) MRD -ve pts achieved a CR. Moreover, 39/63 pts with partial remission were MRD -ve.

Pts in the G-B arm who were MRD -ve at EOI had an improved PFS at 24 mo post-EOI (74%; median PFS not reached) compared with the B arm (21%; median PFS, 7.6 mo). PFS for MRD non-responders was comparably poor in both treatment arms; all pts progressed before 24 mo with a post-EOI median PFS of 5.4 mo (G-B) and 3.0 mo (B; Figure).

Discussion

Our results suggest that G significantly contributes to the depth of response to B vs B alone during induction treatment and support the notion that MRD status at EOI treatment is a sensitive marker of efficacy in the setting of r/r FL. MRD response identifies a prognostically favorable group of pts that appear to benefit from treatment with G-B at relapse. The improved PFS outcome suggests that these pts also benefit from G maintenance. Pts without an MRD response had a very poor prognosis, irrespective of treatment arm. Future analyses will assess MRD kinetics during maintenance and follow-up.