Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
24th Prioritization – 3rd 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 24th prioritisation (September 2015), 7 were filtered out of 191 identified drugs and were sent to prioritisation. Of these, 2 drugs were ranked as ‘highly relevant’ by the expert panel, 4 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 drugs are provided in the following table.

No.	Filtered Drugs – 23rd prioritisation 2nd quarter 2015	Overall category
1.	Afatinib (Giotrif®, Gilotrif®, BIBW 2992) as second-line treatment of patients with advanced squamous cell carcinoma of the lung	Relevant
2.	Necitumumab (IMC-11F8, LY3012211) as first-line therapy in patients with stage IV squamous NSCLC	Relevant
3.	Standard chemotherapy with or without bevacizumab (Avastin®) for women with newly diagnosed ovarian cancer	Highly relevant
4.	Docetaxel (Taxotere®, Docefim®) in metastatic hormone-sensitive prostate cancer	Relevant
5.	Everolimus (Afinitor®, RAD-001) as first-line treatment for patients with HER2-positive advanced breast cancer	Highly relevant
6.	Oxaliplatin (Eloxatin®) added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer	Not relevant
7.	Vosaroxin (QinprezoTM, AG-7352, SPC-595, SNS 595, Voreloxin) in patients with first relapsed or refractory acute myeloid leukaemia	Relevant

1 Ovarian Cancer

1.1 Standard chemotherapy with or without bevacizumab (Avastin®) for women with newly diagnosed ovarian cancer

Overview

Drug Description		a recombinant monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits the binding to its receptors (VEGFR-1 and VEGFR-2)
Incidence in Austria		9.0 per 100,000 women per year, 683 newly diagnosed women per year
Approval status for this indication	**EMA**	- in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer since July 2014
	FDA	-

Phase III results:

The Lancet (2015) Vol.16, Issue: 8 Pages 928-936 (Oza et al.) *Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON 7): overall survival results of a phase 3 randomised trial.*

Background
The ICON7 trial previously reported improved progression-free survival in women with ovarian cancer with the addition of bevacizumab to standard chemotherapy, with the greatest effect in patients at high risk of disease progression. We report the final overall survival results of the trial.

Methods
ICON7 was an international, phase 3, open-label, randomised trial undertaken at 263 centres in 11 countries across Europe, Canada, Australia and New Zealand. Eligible adult women with newly diagnosed ovarian cancer that was either high-risk early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I-IIa, grade 3 or clear cell histology) or more advanced disease (FIGO stage IIb-IV), with an Eastern Cooperative Oncology Group performance status of 0-2, were enrolled and randomly assigned in a 1:1 ratio to standard chemotherapy (six 3-weekly cycles of intravenous carboplatin [AUC 5 or 6] and paclitaxel 175 mg/m² of body surface area) or the same chemotherapy regimen plus bevacizumab 7·5 mg per kg bodyweight intravenously every 3 weeks, given concurrently and continued with up to 12 further 3-weekly cycles of maintenance therapy. Randomisation was done by a minimisation algorithm stratified by FIGO stage, residual disease, interval between surgery and chemotherapy, and Gynecologic Cancer InterGroup group. The primary endpoint was progression-free survival; the study was also powered to detect a difference in overall survival. Analysis was by intention to treat. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN91273375.

Results
Between Dec 18, 2006, and Feb 16, 2009, 1528 women were enrolled and randomly assigned to receive chemotherapy (n=764) or chemotherapy plus bevacizumab (n=764). Median follow-up at the end of the trial on March 31, 2013, was 48·9 months (IQR 26·6–56·2), at which point 714 patients had died (352 in the chemotherapy group and 362 in the bevacizumab group). Our results showed evidence of non-proportional hazards, so we used the difference in restricted mean survival time as the primary estimate of effect. No overall survival benefit of bevacizumab was recorded (restricted mean survival time 44·6 months [95% CI 43·2–45·9] in the standard chemotherapy group *vs.* 45·5 months [44·2–46·7] in the bevacizumab group; log-rank p=0·85). In an exploratory analysis of a predefined subgroup of 502 patients with poor prognosis disease, 332 (66%) died (174 in the standard chemotherapy group and 158 in the bevacizumab group), and a significant difference in overall survival was noted between women who received bevacizumab plus chemotherapy and those who received chemotherapy alone (restricted mean survival time 34·5 months [95% CI 32·0–37·0] with standard chemotherapy *vs.* 39·3 months [37·0–41·7] with bevacizumab; log-rank p=0·03). However, in non-high-risk patients, the restricted mean survival time did not differ significantly between the two treatment groups (49·7 months [95% CI 48·3–51·1]) in the standard chemotherapy group *vs.* 48·4 months [47·0–49·9] in the bevacizumab group; p=0·20). An updated analysis of progression-free survival showed no difference between treatment groups. During extended follow-up, one further treatment-related grade 3 event (gastrointestinal fistula in a bevacizumab-treated patient), three grade 2 treatment-related events (cardiac failure, sarcoidosis, and foot fracture, all in bevacizumab-treated patients), and one grade 1 treatment-related event (vaginal haemorrhage, in a patient treated with standard chemotherapy) were reported.

Conclusion
Bevacizumab, added to platinum-based chemotherapy, did not increase overall survival in the study population as a whole. However, an overall survival benefit was recorded in poor-prognosis patients, which is concordant with the progression-free survival results from ICON7 and GOG-218, and provides further evidence towards the optimum use of bevacizumab in the treatment of ovarian cancer.

2 Breast Cancer

2.1 Everolimus (Afinitor®, RAD-001) as first-line treatment for patients with HER2-positive advanced breast cancer

Overview

Drug Description		an inhibitor of the mammalian target of rapamycin (mTOR) protein
Incidence in Austria		76.2 per 100,000 women per year; 5,423 newly diagnosed women per year
Approval status for this indication	**EMA**	-
	FDA	-

Phase III results:

The Lancet (2015) Vol.16, Issue: 7, Pages 816-829 (Hurvitz et al.) *Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial*

Background
mTOR inhibition reverses trastuzumab resistance via the hyperactivated PIK/AKT/mTOR pathway due to PTEN loss, by sensitising PTEN-deficient tumours to trastuzumab. The BOLERO-1 study assessed the efficacy and safety of adding everolimus to trastuzumab and paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer.

Methods
In this phase 3, randomised, double-blind trial, patients were enrolled across 141 sites in 28 countries. Eligible patients were aged 18 years or older, with locally assessed HER2-positive advanced breast cancer, with Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, who had not received previous trastuzumab or chemotherapy for advanced breast cancer within 12 months of randomisation, had measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) or bone lesions in the absence of measurable disease, without previous systemic treatment for advanced disease except endocrine therapy. Patients were randomly assigned (2:1) with an interactive voice and web response system to receive either 10 mg everolimus once a day orally or placebo plus weekly trastuzumab intravenously at 4 mg/kg loading dose on day 1 with subsequent weekly doses of 2 mg/kg of each 4 week cycle plus paclitaxel intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of each 4 week cycle. Randomisation was stratified according to previous use of trastuzumab and visceral metastasis. Patients and investigators were masked to the assigned treatments. Identity of experimental treatments was concealed by use of everolimus and placebo that were identical in packaging, labelling, appearance, and administration schedule. The two primary objectives were investigator-assessed progression-free survival in the full study population and in the subset of patients with hormone receptor-negative breast cancer at baseline; the latter was added during the course of the study, before unmasking based on new clinical and biological findings from other studies. All efficacy analyses were based on the intention-to-treat population. Enrolment for this trial is closed and results of the final progression-free survival analyses are presented here. This trial is registered with ClinicalTrials.gov, number NCT00876395.

Results
Between Sept 10, 2009, and Dec 16, 2012, 719 patients were randomly assigned to receive everolimus (n=480) or placebo (n=239). Median follow-up was 41·3 months (IQR 35·4–46·6). In the full population, median progression-free survival was 14·95 months (95% CI 14·55–17·91) with everolimus versus 14·49 months (12·29–17·08) with placebo (hazard ratio 0·89, 95% CI 0·73–1·08; p=0·1166). In the HR-negative subpopulation (n=311), median progression-free survival with everolimus was 20·27 months (95% CI 14·95–24·08) versus 13·08 months (10·05–16·56) with placebo (hazard ratio 0·66, 95% CI 0·48–0·91; p=0·0049); however, the protocol-specified significance threshold (p=0·0044) was not crossed. The most common adverse events with everolimus were stomatitis (314 [67%] of 472 patients in the everolimus group *vs.* 77 [32%] of 238 patients in the placebo group), diarrhoea (267 [57%] *vs.* 111 [47%] patients), and alopecia (221 [47%] *vs.* 125 [53%]). The most frequently reported grade 3 or 4 adverse events in the everolimus group versus the placebo group were neutropenia (117 [25%] *vs.* 35 [15%]), stomatitis (59 [13%] *vs.* three [1%]), anaemia (46 [10%] *vs.* six [3%]) and diarrhoea (43 [9%] *vs.* 10 [4%]) On-treatment adverse event-related deaths were reported in 17 (4%) patients in the everolimus group and none in the placebo group.

Conclusion
Although progression-free survival was not significantly different between groups in the full analysis population, the 7·2 months prolongation we noted with the addition of everolimus in the HR-negative, HER2-positive population warrants further investigation, even if it did not meet prespecified criteria for significance. The safety profile was generally consistent with what was previously reported in BOLERO-3. Proactive monitoring and early management of adverse events in patients given everolimus and chemotherapy is crucial.