

**Horizon Scanning in Oncology**

**Results**

**19<sup>th</sup> Prioritisation – 2<sup>nd</sup> quarter 2014**

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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 19<sup>th</sup> prioritisation (May 2014), 11 were filtered out of 149 identified drugs and were sent to prioritisation. Of these, 6 drugs were ranked as ‘highly relevant’ by the expert panel, 3 as ‘relevant’ and 2 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 - 19 <sup>th</sup> prioritisation 2 <sup>nd</sup> quarter 2014	Overall category
1.	Pemetrexed (Alimta®) in combination with bevacizumab for the maintenance therapy of advanced non-small-cell lung cancer (NSCLC)	Highly relevant
2.	Ofatumumab, HuMax-CD20 (Arzerra®) for previously untreated CLL	Highly relevant
3.	Ibrutinib, PCI-32765 (Imbruvica®) for relapsed or refractory CLL	Highly relevant
4.	Everolimus, RAD001 (Afinitor or Votubia®) for pretreated HER2/Neu over-expressing locally advanced or metastatic breast cancer	Highly relevant
5.	Bevacizumab (Avastin®) for platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer	Highly relevant
6.	Bevacizumab (Avastin®) for stage IVB, recurrent or persistent carcinoma of the cervix	Highly relevant
7.	Ceritinib LDK378 (Zykadia®) for advanced NSCLC with previous chemotherapy (platinum doublet) and crizotinib	Relevant
8.	Rituximab (MabThera®, Rituxan®) for newly diagnosed advanced stage, asymptomatic, non-bulky follicular lymphoma	Relevant
9.	Vintafolide, EC145 (Vynfinit®) for platinum-resistant ovarian cancer	Relevant
10.	Icotinib hydrochloride, BPI-2009H (Conmana®) for advanced NSCLC previously treated with chemotherapy	Not relevant
11.	Alemtuzumab (MabCampath® or Lemtrada®) for previously untreated patients with biological high-risk CLL	Not relevant



## 1 Lung Cancer

### ***Pemetrexed (Alimta®) in combination with bevacizumab for the maintenance therapy of advanced non-small-cell lung cancer (NSCLC)***

**Drug description:** a folate analog metabolic inhibitor that exerts its action by disrupting folate dependent metabolic processes essential for cell replication.

**Incidence in Austria:** 3,500 patients

**EMA/FDA licensing for this indication:** -/-

**Phase III results:**

**Barlesi et al. *Maintenance bevacizumab–pemetrexed after first-line cisplatin–pemetrexed–bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial.* Ann Oncol. 2014; 25 (5): 1044-1052.**

#### **Background**

The randomized, phase III AVAPERL trial evaluated the safety and efficacy of bevacizumab maintenance with or without pemetrexed in nonsquamous nonsmall-cell lung cancer (nsNSCLC). PFS was significantly prolonged with bevacizumab–pemetrexed, but overall OS data were immature. In this article, we report an independent, updated analysis of survival outcomes in AVAPERL.

#### **Patients and Methods**

Patients with advanced nsNSCLC received first-line bevacizumab (7.5 mg/kg), cisplatin (75 mg/m<sup>2</sup>), and pemetrexed (500 mg/m<sup>2</sup>) every 3 weeks (q3w) for four cycles. Nonprogressing patients were randomized to maintenance bevacizumab (7.5 mg/kg) or bevacizumab–pemetrexed (500 mg/m<sup>2</sup>) q3w until progression or consent withdrawal. The primary end point of the trial was PFS; in this independent OS analysis, participating study centers were contacted to collect survival data on patients still alive at the time of the first analysis.

#### **Results**

A total of 376 patients received induction treatment. Disease control was confirmed in 71.9% of patients; 253 patients were randomized to maintenance treatment with bevacizumab (n = 125) or bevacizumab–pemetrexed (n = 128). At a median follow-up of 14.8 months, patients allocated to bevacizumab–pemetrexed had significantly improved PFS versus those on bevacizumab when measured from randomization [7.4 versus 3.7 months, hazard ratio (HR), 0.57, 95% confidence interval (CI) 0.44–0.75; P < 0.0001]. OS events occurred in 58% of all patients. OS was numerically longer with bevacizumab–pemetrexed versus bevacizumab when measured from randomization [17.1 versus 13.2 months, HR 0.87 (0.63–1.21); P = 0.29]. Second-line therapy was administered in 77% and 70% of patients in the bevacizumab and bevacizumab–pemetrexed arms, respectively. No new adverse events were reported during this updated analysis.

#### **Conclusion**

In an unselected population of ns NSCLC patients achieving disease control on platinum-based induction therapy, maintenance with bevacizumab–pemetrexed was associated with a nonsignificant increase in OS over bevacizumab alone.

**Barlesi et al. *Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin and pemetrexed in advanced nonsquamous non–small-cell lung cancer: AVAPERL (MO22089)*. JCO. 2013; 31 (24): 3004-3011.**

### **Purpose**

Maintenance therapy is associated with improved survival in patients with non–small-cell lung cancer (NSCLC), but few studies have compared active agents in this setting. AVAPERL evaluated the safety and efficacy of bevacizumab with or without pemetrexed as continuation maintenance treatment.

### **Patients and Methods**

Patients with advanced nonsquamous NSCLC received first-line bevacizumab 7.5 mg/kg, cisplatin 75 mg/m<sup>2</sup>, and pemetrexed 500 mg/m<sup>2</sup> once every 3 weeks for four cycles. Those achieving response or stable disease were randomly assigned at a ratio of 1:1 to maintenance bevacizumab 7.5 mg/kg or bevacizumab 7.5 mg/kg plus pemetrexed 500 mg/m<sup>2</sup> once every 3 weeks until disease progression or unacceptable toxicity. The primary end point was progression-free survival (PFS) after random assignment.

### **Results**

In total, 376 patients received induction treatment, 71.9% achieved disease control, and 67.3% were randomly assigned to maintenance therapy, with 125 and 128 receiving single-agent bevacizumab and bevacizumab plus pemetrexed treatment, respectively. At a median follow-up of 8.1 months, PFS from random assignment was significantly improved in the bevacizumab plus pemetrexed arm (median, 3.7 v 7.4 months; hazard ratio, 0.48; 95% CI, 0.35 to 0.66; *P* < .001) per a stratified model. The PFS benefit extended across age, performance status, smoking history, and induction response (stable disease v partial response) subgroups. Any grade, grade > 3, and serious adverse events occurred more often with bevacizumab plus pemetrexed maintenance. No new safety signals were observed.

### **Conclusion**

In an unselected population of patients with nonsquamous NSCLC who had achieved disease control with platinum-based chemotherapy plus bevacizumab, bevacizumab plus pemetrexed maintenance was associated with a significant PFS benefit compared with bevacizumab alone. The combination was well tolerated.

## **2 Breast Cancer**

### ***Everolimus, RAD001 (Afinitor or Votubia®) for pretreated HER2/Neu over-expressing locally advanced or metastatic breast cancer***

**Drug description:** an orally administered inhibitor of the mammalian target of rapamycin.

**Incidence in Austria:** ~100 women HER2/neu positive mBC

**EMA/FDA licensing for this indication:** -/-

**Phase III results:**

**André et al. *Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial*. Lancet. 2014;15 (6): 580–591.**

### **Background**

Disease progression in patients with HER2-positive breast cancer receiving trastuzumab might be associated with activation of the PI3K/Akt/mTOR intracellular signalling pathway. We aimed to assess whether the addition of the mTOR inhibitor everolimus to trastuzumab might restore sensitivity to trastuzumab.

## Methods

In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited women with HER2-positive, trastuzumab-resistant, advanced breast carcinoma who had previously received taxane therapy. Eligible patients were randomly assigned (1:1) using a central patient screening and randomisation system to daily everolimus (5 mg/day) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m<sup>2</sup>) or to placebo plus trastuzumab plus vinorelbine, in 3-week cycles, stratified by previous lapatinib use. The primary endpoint was progression-free survival (PFS) by local assessment in the intention-to-treat population. We report the final analysis for PFS; overall survival follow-up is still in progress. This trial is registered with ClinicalTrials.gov, number NCT01007942.

## Results

Between Oct 26, 2009, and May 23, 2012, 569 patients were randomly assigned to everolimus (n=284) or placebo (n=285). Median follow-up at the time of analysis was 20.2 months (IQR 15.0—27.1). Median PFS was 7.00 months (95% CI 6.74—8.18) with everolimus and 5.78 months (5.49—6.90) with placebo (hazard ratio 0.78 [95% CI 0.65—0.95]; p=0.0067). The most common grade 3—4 adverse events were neutropenia (204 [73%] of 280 patients in the everolimus group vs 175 [62%] of 282 patients in the placebo group), leucopenia (106 [38%] vs 82 [29%]), anaemia (53 [19%] vs 17 [6%]), febrile neutropenia (44 [16%] vs ten [4%]), stomatitis (37 [13%] vs four [1%]), and fatigue (34 [12%] vs 11 [4%]). Serious adverse events were reported in 117 (42%) patients in the everolimus group and 55 (20%) in the placebo group; two on-treatment deaths due to adverse events occurred in each group.

## Conclusion

The addition of everolimus to trastuzumab plus vinorelbine significantly prolongs PFS in patients with trastuzumab-resistant and taxane-pretreated, HER2-positive, advanced breast cancer. The clinical benefit should be considered in the context of the adverse event profile in this population.

## 3 Chronic lymphocytic leukaemia (CLL)

### 3.1 Ofatumumab, HuMax-CD20 (Arzerra®) for previously untreated CLL

**Drug description:** a fully humanised, high affinity monoclonal antibody targeted against the CD20 cell surface antigen of B-cell membranes.

**Incidence in Austria:** 350 patients

**EMA/FDA licensing for this indication:** 05/2014: EMA- CHMP positive opinion: Previously untreated CLL: Arzerra® in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.

04/2014: FDA approval for ofatumumab in combination with chlorambucil, for the treatment of previously untreated patients with CLL, for whom fludarabine-based therapy is considered inappropriate

**Phase III results:** None (FDA licensing document at: <http://tinyurl.com/pto32wn> ;p 16-18)

### 3.2 Ibrutinib, PCI-32765 (Imbruvica®) for relapsed or refractory CLL

**Drug description:** covalently binds to, and irreversibly inhibits, Bruton's Tyrosine Kinase (BTK), resulting in the inhibition of B-cell proliferation and survival as well as inhibition of B-cell migration and homing.

**Incidence in Austria:** 350 patients

**EMA/FDA licensing for this indication:** - /February 2014: FDA approved for the treatment of patients with CLL who have received at least one prior therapy

**Phase III results:** None (FDA licensing document at: <http://tinyurl.com/nd3ya8g> ;p 15)

## 4 Ovarian Cancer

### ***Bevacizumab (Avastin®) for platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer***

**Drug description:** an i.v., anti-VEGF monoclonal antibody consisting of humanized murine antibody with antigen-binding, complementary-determining regions from murine VEGF

**Incidence in Austria:** 640 patients

**EMA/FDA licensing for this indication:** -/-

**Phase III results:**

**Pujade-Lauraine et al. *Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial*. JCO. 2014; 32 (13): 1302-1308.**

#### **Background**

In platinum-resistant ovarian cancer (OC), single-agent chemotherapy is standard. Bevacizumab is active alone and in combination. AURELIA is the first randomized phase III trial to our knowledge combining bevacizumab with chemotherapy in platinum-resistant OC.

#### **Patients and Methods**

Eligible patients had measurable/assessable OC that had progressed < 6 months after completing platinum-based therapy. Patients with refractory disease, history of bowel obstruction, or > two prior anticancer regimens were ineligible. After investigators selected chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), patients were randomly assigned to single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity, or consent withdrawal. Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone. The primary end point was progression-free survival (PFS) by RECIST. Secondary end points included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes

#### **Results**

The PFS hazard ratio (HR) after PFS events in 301 of 361 patients was 0.48 (95% CI, 0.38 to 0.60; unstratified log-rank  $P < .001$ ). Median PFS was 3.4 months with chemotherapy alone versus 6.7 months with bevacizumab-containing therapy. RECIST ORR was 11.8% versus 27.3%, respectively ( $P = .001$ ). The OS HR was 0.85 (95% CI, 0.66 to 1.08;  $P < .174$ ; median OS, 13.3 v 16.6 months, respectively). Grade  $\geq 2$  hypertension and proteinuria were more common with bevacizumab. GI perforation occurred in 2.2% of bevacizumab-treated patients

#### **Conclusion**

Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant. No new safety signals were observed.

**Stockler et al. *Patient-Reported Outcome Results From the Open-Label Phase III AURELIA Trial Evaluating Bevacizumab-Containing Therapy for Platinum-Resistant Ovarian Cancer*. JCO. 2014; 32 (13): 1309-1316.**

## Background

To determine the effects of bevacizumab on patient-reported outcomes (PROs; secondary end point) in the AURELIA trial.

## Patients and Methods

Patients with platinum-resistant ovarian cancer were randomly assigned to chemotherapy alone (CT) or with bevacizumab (BEV-CT). PROs were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Ovarian Cancer Module 28 (EORTC QLQ-OV28) and Functional Assessment of Cancer Therapy–Ovarian Cancer symptom index (FOSI) at baseline and every two or three cycles (8/9 weeks) until disease progression. The primary PRO hypothesis was that more patients receiving BEV-CT than CT would achieve at least a 15% ( $\geq 15$ -point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale (items 31-36) at week 8/9. Patients with missing week 8/9 questionnaires were included as unimproved. Questionnaires from all assessments until disease progression were analyzed using mixed-model repeated-measures (MMRM) analysis. Sensitivity analyses were used to determine the effects of differing assumptions and methods for missing data.

## Results

Baseline questionnaires were available from 89% of 361 randomly assigned patients. More BEV-CT than CT patients achieved a  $\geq 15\%$  improvement in abdominal/GI symptoms at week 8/9 (primary PRO end point, 21.9% v 9.3%; difference, 12.7%; 95% CI, 4.4 to 20.9;  $P = .002$ ). MMRM analysis covering all time points also favored BEV-CT (difference, 6.4 points; 95% CI, 1.3 to 11.6;  $P = .015$ ). More BEV-CT than CT patients achieved  $\geq 15\%$  improvement in FOSI at week 8/9 (12.2% v 3.1%; difference, 9.0%; 95% CI, 2.9% to 15.2%;  $P = .003$ ). Sensitivity analyses gave similar results and conclusions.

## Conclusion

Bevacizumab increased the proportion of patients achieving a 15% improvement in patient-reported abdominal/GI symptoms during chemotherapy for platinum-resistant ovarian cancer.

## 5 Cervix cancer

### ***Bevacizumab (Avastin®) for stage IVB, recurrent or persistent carcinoma of the cervix***

**Drug description:** an i.v., anti-VEGF monoclonal antibody consisting of humanized murine antibody with antigen-binding, complementary-determining regions from murine VEGF

**Incidence in Austria:** 390 patients

**EMA/FDA licensing for this indication:** -/-

**Phase III results:**

**Tewari et al. *Improved Survival with Bevacizumab in Advanced Cervical Cancer*. N Engl J Med. 2014; 37: 734-743.**

## Background

Vascular endothelial growth factor (VEGF) promotes angiogenesis, a mediator of disease progression in cervical cancer. Bevacizumab, a humanized anti-VEGF monoclonal antibody, has single-agent activity in previously treated, recurrent disease. Most patients in whom recurrent cervical cancer develops have previously received cisplatin with radiation therapy, which reduces the effectiveness of cisplatin at the time of recurrence. We evaluated the effectiveness of bevacizumab and nonplatinum combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer.

## Methods

Using a 2-by-2 factorial design, we randomly assigned 452 patients to chemotherapy with or without bevacizumab at a dose of 15 mg per kilogram of body weight. Chemotherapy consisted of cisplatin at a dose of 50 mg per square meter of body-surface area, plus paclitaxel at a dose of 135 or 175 mg per square meter or topotecan at a dose of 0.75 mg per square meter on days 1 to 3, plus paclitaxel at a dose of 175 mg per square meter on day 1. Cycles were repeated every 21 days until disease progression, the development of unacceptable toxic effects, or a complete response was documented. The primary end point was overall survival; a reduction of 30% in the hazard ratio for death was considered clinically important

### **Results**

Groups were well balanced with respect to age, histologic findings, performance status, previous use or nonuse of a radiosensitizing platinum agent, and disease status. Topotecan–paclitaxel was not superior to cisplatin–paclitaxel (hazard ratio for death, 1.20). With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased overall survival (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% confidence interval, 0.54 to 0.95;  $P=0.004$  in a one-sided test) and higher response rates (48% vs. 36%,  $P=0.008$ ). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%).

### **Conclusion**

The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival.