

# **Horizon Scanning in Oncology**

## **Results**

### **18<sup>th</sup> Prioritization – 1<sup>st</sup> quarter 2014**

## 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 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 18<sup>th</sup> prioritisation (March 2014), 12 were filtered out of 192 identified and were sent to prioritisation. Of these, 7 drugs were ranked as ‘highly relevant’ by the expert panel, 4 as ‘relevant’ and one 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.

An overview on all drugs sent to prioritisation and the summary judgements of the expert panel are provided in the following table.

No	Filtered Drugs - 18 <sup>th</sup> prioritisation 1 <sup>st</sup> quarter 2014	Overall category
1.	Bevacizumab (Avastin®) for the maintenance therapy of advanced non-small-cell lung cancer	Relevant
2.	Erlotinib (Tarceva®) for the first-line therapy of stage IIIB/IV non-small-cell lung cancer	Highly relevant
3.	Nintedanib (Vargatef®) for the second-line therapy of advanced or recurrent non-small-cell lung cancer	Highly relevant
4.	Bevacizumab (Avastin®) as maintenance therapy for patients with advanced colorectal carcinoma	Highly relevant
5.	Obinutuzumab afutuzumab (Gazyva®) as first line therapy for chronic lymphocytic leukaemia	Highly relevant
6.	Idelalisib (GS-1101) for relapsed chronic lymphocytic leukaemia	Highly relevant
7.	Docetaxel (Taxotere®, Docefim) for the second-line therapy of patients with relapsed oesophago-gastric adenocarcinoma	Not relevant
8.	Ramucirumab (IMC-1121B) in patients with metastatic gastric adenocarcinoma, refractory to or progressive after first-line therapy with platinum and fluoropyrimidine	Relevant
9.	Cabozantinib (Cometriq®) in patients with unresectable, locally advanced or metastatic medullary thyroid cancer (MTC)	Highly relevant
10.	Sorafenib (Nexavar®) in patients with advanced/metastatic thyroid cancer refractory to radioactive iodine treatment	Relevant
11.	Axitinib (Inlyta®) for the first-line treatment of metastatic renal cell cancer	Relevant
12.	Ibrutinib (Imbruvica®) in patients with relapsed or refractory mantle cell lymphoma	Highly relevant

# Lung Cancer

## ***Erlotinib (Tarceva®) for the first-line therapy of stage IIIB/IV Non-small cell lung cancer***

**Drug description:** An oral inhibitor of epidermal growth factor receptor tyrosine kinase.

**Incidence in Austria:** 4,200 patients, about 85% of all lung cancers belong to NSCLC

**EMA/FDA licensing:** -/-

### **Phase III results:**

Wu et al. *Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. The Lancet Oncology. 2013; 14(8):777-86.*

### **Background**

The results of FASTACT, a randomised, placebo-controlled, phase 2 study, showed that intercalated chemotherapy and erlotinib significantly prolonged progression-free survival (PFS) in patients with advanced non-small-cell lung cancer. We undertook FASTACT-2, a phase 3 study in a similar patient population.

### **Methods**

In this phase 3 trial, patients with untreated stage IIIB/IV non-small-cell lung cancer were randomly assigned in a 1:1 ratio by use of an interactive internet response system with minimisation algorithm (stratified by disease stage, tumour histology, smoking status, and chemotherapy regimen) to receive six cycles of gemcitabine (1250 mg/m<sup>2</sup> on days 1 and 8, intravenously) plus platinum (carboplatin 5 × area under the curve or cisplatin 75 mg/m<sup>2</sup> on day 1, intravenously) with intercalated erlotinib (150 mg/day on days 15–28, orally; chemotherapy plus erlotinib) or placebo orally (chemotherapy plus placebo) every 4 weeks. With the exception of an independent group responsible for monitoring data and safety monitoring board, everyone outside the interactive internet response system company was masked to treatment allocation. Patients continued to receive erlotinib or placebo until progression or unacceptable toxicity or death, and all patients in the placebo group were offered second-line erlotinib at the time of progression. The primary endpoint was PFS in the intention-to-treat population.

### **Results**

From April 29, 2009, to Sept 9, 2010, 451 patients were randomly assigned to chemotherapy plus erlotinib (n=226) or chemotherapy plus placebo (n=225). PFS was significantly prolonged with chemotherapy plus erlotinib versus chemotherapy plus placebo (median PFS 7.6 months [95% CI 7.2–8.3], vs 6.0 months [5.6–7.1], hazard ratio [HR] 0.57 [0.47–0.69]; p<0.0001). Median overall survival for patients in the chemotherapy plus erlotinib and chemotherapy plus placebo groups was 18.3 months (16.3–20.8) and 15.2 months (12.7–17.5), respectively (HR 0.79 [0.64–0.99]; p=0.0420). Treatment benefit was noted only in patients with an activating EGFR gene mutation (median PFS 16.8 months [12.9–20.4] vs 6.9 months [5.3–7.6], HR 0.25 [0.16–0.39]; p<0.0001; median overall survival 31.4 months [22.2–undefined], vs 20.6 months [14.2–26.9], HR 0.48 [0.27–0.84]; p=0.0092). Serious adverse events were reported by 76 (34%) of 222 patients in the chemotherapy plus placebo group and 69 (31%) of 226 in the chemotherapy plus erlotinib group. The most common grade 3 or greater adverse events were neutropenia (65 [29%] patients and 55 [25%], respectively), thrombocytopenia (32 [14%] and 31 [14%], respectively), and anaemia (26 [12%] and 21 [9%], respectively).

### **Conclusion**

Intercalated chemotherapy and erlotinib is a viable first-line option for patients with non-small-cell lung cancer with EGFR mutation-positive disease or selected patients with unknown EGFR mutation status.

# ***Nintedanib (Vargatef®) for the second-line therapy of advanced or recurrent NSCLC***

**Drug description:** an oral triple angiokinase inhibitor

**Incidence in Austria:** 4,200 patients, about 85% of all lung cancers belong to NSCLC

**EMA/FDA licensing:** -/-

## **Phase III results:**

Reck et al. *Docetaxel plus nintedanib vs. docetaxel plus placebo in patients with previously treated NSCLC (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial.* Lancet 2014; 15 (2): 143-155.

## **Background**

The phase 3 LUME-Lung 1 study assessed the efficacy and safety of docetaxel plus nintedanib as secondline therapy for non-small-cell lung cancer (NSCLC).

## **Methods**

Patients from 211 centres in 27 countries with stage IIIB/IV recurrent NSCLC progressing after first-line chemotherapy, stratified by ECOG performance status, previous bevacizumab treatment, histology, and presence of brain metastases, were allocated (by computer-generated sequence through an interactive third-party system, in 1:1 ratio), to receive docetaxel 75 mg/m<sup>2</sup> by intravenous infusion on day 1 plus either nintedanib 200 mg orally twice daily or matching placebo on days 2–21, every 3 weeks until unacceptable adverse events or disease progression. Investigators and patients were masked to assignment. The primary endpoint was PFS by independent central review, analysed by intention to treat after 714 events in all patients. The key secondary endpoint was overall survival, analysed by intention to treat after 1121 events had occurred, in a prespecified stepwise order: first in patients with adenocarcinoma who progressed within 9 months after start of first-line therapy, then in all patients with adenocarcinoma, then in all patients.

## **Results**

Between Dec 23, 2008, and Feb 9, 2011, 655 patients were randomly assigned to receive docetaxel plus nintedanib and 659 to receive docetaxel plus placebo. The primary analysis was done after a median follow-up of 7.1 months (IQR 3.8–11.0). PFS was significantly improved in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group (median 3.4 months [95% CI 2.9–3.9] vs 2.7 months [2.6–2.8]; hazard ratio [HR] 0.79 [95% CI 0.68–0.92], p=0.0019). After a median follow-up of 31.7 months (IQR 27.8–36.1), overall survival was significantly improved for patients with adenocarcinoma histology who progressed within 9 months after start of first-line treatment in the docetaxel plus nintedanib group (206 patients) compared with those in the docetaxel plus placebo group (199 patients; median 10.9 months [95% CI 8.5–12.6] vs 7.9 months [6.7–9.1]; HR 0.75 [95% CI 0.60–0.92], p=0.0073). Similar results were noted for all patients with adenocarcinoma histology (322 patients in the docetaxel plus nintedanib group and 336 in the docetaxel plus placebo group; median overall survival 12.6 months [95% CI 10.6–15.1] vs 10.3 months [95% CI 8.6–12.2]; HR 0.83 [95% CI 0.70–0.99], p=0.0359), but not in the total study population (median 10.1 months [95% CI 8.8–11.2] vs 9.1 months [8.4–10.4]; HR 0.94, 95% CI 0.83–1.05, p=0.2720). Grade 3 or worse adverse events that were more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group were diarrhoea (43 [6.6%] of 652 vs 17 [2.6%] of 655), reversible increases in alanine aminotransferase (51 [7.8%] vs six [0.9%]). 35 patients in the docetaxel plus nintedanib group and 25 in the docetaxel plus placebo group died of adverse events possibly unrelated to disease progression; the most common of these events were sepsis (five with docetaxel plus nintedanib vs one with docetaxel plus placebo), pneumonia (two vs seven), respiratory failure (four vs none), and pulmonary embolism (none vs three).

## **Conclusion**

Nintedanib in combination with docetaxel is an effective second-line option for patients with advanced NSCLC previously treated with one line of platinum-based therapy, especially for patients with adenocarcinoma.

# Colorectal Cancer

## ***Bevacizumab (Avastin®) as maintenance therapy for patients with advanced colorectal carcinoma***

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

**Incidence in Austria:** metastatic colorectal cancer: 2,230

**EMA/FDA licensing:** -/January 2013: FDA approval for bevacizumab for use in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed on a first-line bevacizumab-containing regimen.

### **Phase III results:**

Bennouna et al. *Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial.* Lancet 2013;14: 29–37

### **Background**

Bevacizumab plus fluoropyrimidine-based chemotherapy is standard treatment for first-line and bevacizumab-naïve second-line metastatic colorectal cancer. We assessed continued use of bevacizumab plus standard second-line chemotherapy in patients with metastatic colorectal cancer progressing after standard first-line bevacizumab-based treatment.

### **Methods**

In an open-label, phase 3 study in 220 centres in Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, the Netherlands, Norway, Portugal, Saudi Arabia, Spain, Sweden, and Switzerland, patients (aged ≥18 years) with unresectable, histologically confirmed metastatic colorectal cancer progressing up to 3 months after discontinuing first-line bevacizumab plus chemotherapy were randomly assigned in a 1:1 ratio to second-line chemotherapy with or without bevacizumab 2.5 mg/kg per week equivalent (either 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks, intravenously). The choice between oxaliplatin-based or irinotecan-based second-line chemotherapy depended on the first-line regimen (switch of chemotherapy). A combination of a permuted block design and the Pocock and Simon minimisation algorithm was used for the randomisation. The primary endpoint was overall survival, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00700102.

### **Results**

Between Feb 1, 2006, and June 9, 2010, 409 (50%) patients were assigned to bevacizumab plus chemotherapy and 411 (50%) to chemotherapy alone. Median follow-up was 11.1 months (IQR 6.4–15.6) in the bevacizumab plus chemotherapy group and 9.6 months (5.4–13.9) in the chemotherapy alone group. Median overall survival was 11.2 months (95% CI 10.4–12.2) for bevacizumab plus chemotherapy and 9.8 months (8.9–10.7) for chemotherapy alone (hazard ratio 0.81, 95% CI 0.69–0.94; unstratified log-rank test  $p=0.0062$ ). Grade 3–5 bleeding or haemorrhage (eight [2%] vs one [ $<1\%$ ]), gastrointestinal perforation (seven [2%] vs three [ $<1\%$ ]), and venous thromboembolisms (19 [5%] vs 12 [3%]) were more common in the bevacizumab plus chemotherapy group than in the chemotherapy alone group. The most frequently reported grade 3–5 adverse events were neutropenia (65 [16%] in the bevacizumab and chemotherapy group vs 52 [13%] in the chemotherapy alone group), diarrhoea (40 [10%] vs 34 [8%], respectively), and asthenia (23 [6%] vs 17 [4%], respectively). Treatment-related deaths were reported for four patients in the bevacizumab plus chemotherapy group and three in the chemotherapy alone group.

### **Conclusion**

Maintenance of VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in patients with metastatic colorectal cancer. This approach is also being investigated in other tumours, including metastatic breast and non-small cell lung cancers.

# Chronic lymphocytic leukaemia

## ***Obinutuzumab afutuzumab (Gazyva®) as first line therapy for chronic lymphocytic leukaemia***

**Drug description:** A glycoengineered, fully humanized IgG1 monoclonal antibody with potential antineoplastic activity. Obinutuzumab, a third generation type II anti-CD20 antibody, selectively binds to the extracellular domain of the human CD20 antigen on malignant human B cells. iv administration.

**Incidence in Austria:** ~ 350 patients newly diagnosed/year

**EMA/FDA licensing status:** -/November 2013: FDA approved obinutuzumab for use in combination with chlorambucil for the treatment of patients with previously untreated CLL.

### **Phase III results:**

Goede et al. *Obinutuzumab plus Chlorambucil in patients with CLL and coexisting conditions. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.* The New England journal of medicine. 2014; 370(12):1101-10.

### **Background**

The monoclonal anti-CD20 antibody rituximab, combined with chemotherapeutic agents, has been shown to prolong overall survival in physically fit patients with previously untreated chronic lymphocytic leukemia (CLL) but not in those with coexisting conditions. We investigated the benefit of the type 2, glycoengineered antibody obinutuzumab (also known as GA101) as compared with that of rituximab, each combined with chlorambucil, in patients with previously untreated CLL and coexisting conditions.

### **Methods**

We randomly assigned 781 patients with previously untreated CLL and a score higher than 6 on the Cumulative Illness Rating Scale (CIRS) (range, 0 to 56, with higher scores indicating worse health status) or an estimated creatinine clearance of 30 to 69 ml per minute to receive chlorambucil, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil. The primary end point was investigator-assessed progression-free survival.

### **Results**

The patients had a median age of 73 years, creatinine clearance of 62 ml per minute, and CIRS score of 8 at baseline. Treatment with obinutuzumab–chlorambucil or rituximab–chlorambucil, as compared with chlorambucil monotherapy, increased response rates and prolonged progression-free survival (median progression-free survival, 26.7 months with obinutuzumab–chlorambucil vs. 11.1 months with chlorambucil alone; hazard ratio for progression or death, 0.18; 95% confidence interval [CI], 0.13 to 0.24;  $P < 0.001$ ; and 16.3 months with rituximab–chlorambucil vs. 11.1 months with chlorambucil alone; hazard ratio, 0.44; 95% CI, 0.34 to 0.57;  $P < 0.001$ ). Treatment with obinutuzumab–chlorambucil, as compared with chlorambucil alone, prolonged overall survival (hazard ratio for death, 0.41; 95% CI, 0.23 to 0.74;  $P = 0.002$ ). Treatment with obinutuzumab–chlorambucil, as compared with rituximab–chlorambucil, resulted in prolongation of progression-free survival (hazard ratio, 0.39; 95% CI, 0.31 to 0.49;  $P < 0.001$ ) and higher rates of complete response (20.7% vs. 7.0%) and molecular response. Infusion-related reactions and neutropenia were more common with obinutuzumab–chlorambucil than with rituximab–chlorambucil, but the risk of infection was not increased.

### **Conclusion**

Combining an anti-CD20 antibody with chemotherapy improved outcomes in patients with CLL and coexisting conditions. In this patient population, obinutuzumab was superior to rituximab when each was combined with chlorambucil.

## ***Idelalisib (GS-1101) for relapsed chronic lymphocytic leukaemia***

**Drug description:** an oral inhibitor of the delta isoform of phosphatidylinositol 3-kinase

**Incidence in Austria:** ~ 350 CLL patients newly diagnosed/year

**EMA/FDA licensing approval status:** -/-

### **Phase III results:**

Furman RR, et al. *Idelalisib and rituximab in relapsed chronic lymphocytic leukemia*. The New England journal of medicine. 2014;370(11):997-1007.

### **Background**

Patients with relapsed chronic lymphocytic leukemia (CLL) who have clinically significant coexisting medical conditions are less able to undergo standard chemotherapy. Effective therapies with acceptable side-effect profiles are needed for this patient population.

### **Methods**

In this multicenter, randomized, double-blind, placebo-controlled, phase 3 study, we assessed the efficacy and safety of idelalisib, an oral inhibitor of the delta isoform of phosphatidylinositol 3-kinase, in combination with rituximab versus rituximab plus placebo. We randomly assigned 220 patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses to receive rituximab and either idelalisib (at a dose of 150 mg) or placebo twice daily. The primary end point was progression-free survival. At the first prespecified interim analysis, the study was stopped early on the recommendation of the data and safety monitoring board owing to overwhelming efficacy.

### **Results**

The median progression-free survival was 5.5 months in the placebo group and was not reached in the idelalisib group (hazard ratio for progression or death in the idelalisib group, 0.15;  $P < 0.001$ ). Patients receiving idelalisib versus those receiving placebo had improved rates of overall response (81% vs. 13%; odds ratio, 29.92;  $P < 0.001$ ) and overall survival at 12 months (92% vs. 80%; hazard ratio for death, 0.28;  $P = 0.02$ ). Serious adverse events occurred in 40% of the patients receiving idelalisib and rituximab and in 35% of those receiving placebo and rituximab.

### **Conclusion**

The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy.

## **Thyroid cancer**

### ***Cabozantinib (Cometriq®) in patients with unresectable, locally advanced or metastatic medullary thyroid cancer (MTC)***

**Drug description:** a potent dual inhibitor of the MET and VEGF pathways designed to block MET driven tumor escape, oral administration

**Incidence in Austria:** ~ 70 patients

**EMA/FDA licensing:** -/11/2012: approval of cabozantinib for the treatment of patients with progressive metastatic MTC

### **Phase III results:**

Elisei et al. *Cabozantinib in progressive medullary thyroid cancer*. Official journal of the American Society of Clinical Oncology. 2013;31(29):3639-46.

#### **Purpose**

Cabozantinib, a tyrosine kinase inhibitor (TKI) of hepatocyte growth factor receptor (MET), vascular endothelial growth factor receptor 2, and rearranged during transfection (RET), demonstrated clinical activity in patients with medullary thyroid cancer (MTC) in phase I.

#### **Patients and Methods**

We conducted a double-blind, phase III trial comparing cabozantinib with placebo in 330 patients with documented radiographic progression of metastatic MTC. Patients were randomly assigned (2:1) to cabozantinib (140 mg per day) or placebo. The primary end point was progression-free survival (PFS). Additional outcome measures included tumor response rate, overall survival and safety.

#### **Results**

The estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40;  $P < .001$ ). Prolonged PFS with cabozantinib was observed across all subgroups including by age, prior TKI treatment, and *RET* mutation status (hereditary or sporadic). Response rate was 28% for cabozantinib and 0% for placebo; responses were seen regardless of *RET* mutation status. Kaplan-Meier estimates of patients alive and progression-free at 1 year are 47.3% for cabozantinib and 7.2% for placebo. Common cabozantinib-associated adverse events included diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue and resulted in dose reductions in 79% and holds in 65% of patients. Adverse events led to treatment discontinuation in 16% of cabozantinib-treated patients and in 8% of placebo-treated patients.

#### **Conclusion**

Cabozantinib (140 mg per day) achieved a statistically significant improvement of PFS in patients with progressive metastatic MTC and represents an important new treatment option for patients with this rare disease. This dose of cabozantinib was associated with significant but manageable toxicity.

## **Mantle cell carcinoma**

### ***Ibrutinib (Imbruvica®) in patients with relapsed or refractory mantle cell lymphoma***

**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. oral administration

**Incidence in Austria:** ~50 – 100 patients/year

**EMA/FDA licensing:** -/November 2013: FDA approved ibrutinib for Mantle cell lymphoma (MCL) who have received at least one prior therapy

**Phase III results:** None