



**Horizon Scanning in Oncology
22nd Prioritization – 1st quarter 2015**

**General information, efficacy and safety
data**

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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 22nd prioritisation (April 2015), 10 were filtered out of 180 identified drugs and were sent to prioritisation. Of these, 4 drugs were ranked as ‘highly relevant’ by the expert panel, 4 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 – 22 nd prioritisation 1 st quarter 2015	Overall category
1.	Bevacizumab (Avastin®) for recurrent, persistent, or metastatic cervical cancer	Relevant
2.	Blinatumomab (Blincyto®, MT-103) in patients with relapsed/refractory Philadelphia negative B-precursor ALL	Relevant
3.	Carfilzomib (Kyprolis®) in patients with relapsed and refractory multiple myeloma	Highly relevant
4.	Ceritinib (Zykadia®, LDK378) in patients with ALK-positive advanced non-small cell lung cancer (NSCLC)	Relevant
5.	Nab-Paclitaxel (Abraxane®, ABI-007) as first-line therapy for patients with advanced NSCLC	Highly relevant
6.	Nivolumab (Opdivo®, BMS-936558, MDX1106, ONO4538) for the second-line therapy of squamous cell/ NON-squamous cell NSCLC	Highly relevant
7.	Dinutuximab in high-risk neuroblastoma patients	Not relevant
8.	Lanreotide (Somatuline Autogel®, ITM-014) in patients with non-functioning entero-pancreatic endocrine tumour	Not relevant
9.	Lenvatinib (Lenvima®, E7080) in patients with differentiated thyroid cancer	Relevant
10.	Palbociclib (Ibrance®, PD-0332991) for the treatment of post-menopausal women with hormone receptor positive, Her2 negative advanced breast cancer	Highly relevant

1 Multiple Myeloma

1.1 Carfilzomib (Kyprolis®) in patients with relapsed and refractory multiple myeloma

Drug description: a proteasome inhibitor, targeting the 20S proteasome

Incidence in Austria: 4-5/100,000

EMA/FDA licensing for this indication: - /FDA: approved for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Phase III results:

Stewart et al. *Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma.* NEJM (2015), 372:142-52

Background

Lenalidomide plus dexamethasone is a reference treatment for relapsed multiple myeloma. The combination of the proteasome inhibitor carfilzomib with lenalidomide and dexamethasone has shown efficacy in a phase 1 and 2 study in relapsed multiple myeloma.

Methods

We randomly assigned 792 patients with relapsed multiple myeloma to carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group). The primary end point was progression-free survival.

Results

Progression-free survival was significantly improved with carfilzomib (median, 26.3 months, vs. 17.6 months in the control group; hazard ratio for progression or death, 0.69; 95% confidence interval [CI], 0.57 to 0.83; $P = 0.0001$). The median overall survival was not reached in either group at the interim analysis. The Kaplan–Meier 24-month overall survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively (hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; $P = 0.04$). The rates of overall response (partial response or better) were 87.1% and 66.7% in the carfilzomib and control groups, respectively ($P < 0.001$; 31.8% and 9.3% of patients in the respective groups had a complete response or better; 14.1% and 4.3% had a stringent complete response). Adverse events of grade 3 or higher were reported in 83.7% and 80.7% of patients in the carfilzomib and control groups, respectively; 15.3% and 17.7% of patients discontinued treatment owing to adverse events. Patients in the carfilzomib group reported superior health-related quality of life.

Conclusion

In patients with relapsed multiple myeloma, the addition of carfilzomib to lenalidomide and dexamethasone resulted in significantly improved progression-free survival at the interim analysis and had a favorable risk–benefit profile.

2. Lung cancer

2.1 Nab-Paclitaxel (Abraxane[®], ABI-007) as first-line therapy for patients with advanced NSCLC

Drug description: nab (nanoparticle albumin bound) – paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation

Incidence in Austria: 3,500 NSCLC

EMA/FDA licensing for this indication: EMA: 01/2015 CHMP adopted a new indication: Abraxane[®] in combination with carboplatin for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy
FDA: 10/2012: Locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) as first-line treatment in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy

Phase III results:

Socinski et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol (2012) 30:2055-2062

Background

This phase III trial compared the efficacy and safety of albumin-bound paclitaxel (*nab*-paclitaxel) plus carboplatin with solvent-based paclitaxel (*sb*-paclitaxel) plus carboplatin in advanced non-small-cell lung cancer (NSCLC).

Methods

In all, 1,052 untreated patients with stage IIIB to IV NSCLC were randomly assigned 1:1 to receive 100 mg/m² *nab*-paclitaxel weekly and carboplatin at area under the concentration-time curve (AUC) 6 once every 3 weeks (*nab*-PC) or 200 mg/m² *sb*-paclitaxel plus carboplatin AUC 6 once every 3 weeks (*sb*-PC). The primary end point was objective overall response rate (ORR).

Results

On the basis of independent assessment, *nab*-PC demonstrated a significantly higher ORR than *sb*-PC (33% v 25%; response rate ratio, 1.313; 95% CI, 1.082 to 1.593; *P* = .005) and in patients with squamous histology (41% v 24%; response rate ratio, 1.680; 95% CI, 1.271 to 2.221; *P* = .001). *nab*-PC was as effective as *sb*-PC in patients with nonsquamous histology (ORR, 26% v 25%; *P* = .808). There was an approximately 10% improvement in progression-free survival (median, 6.3 v 5.8 months; hazard ratio [HR], 0.902; 95% CI, 0.767 to 1.060; *P* = .214) and overall survival (OS; median, 12.1 v 11.2 months; HR, 0.922; 95% CI, 0.797 to 1.066; *P* = .271) in the *nab*-PC arm versus the *sb*-PC arm, respectively. Patients ≥ 70 years old and those enrolled in North America showed a significantly increased OS with *nab*-PC versus *sb*-PC. Significantly less grade ≥ 3 neuropathy, neutropenia, arthralgia, and myalgia occurred in the *nab*-PC arm, and less thrombocytopenia and anemia occurred in the *sb*-PC arm.

Conclusion

The administration of *nab*-PC as first-line therapy in patients with advanced NSCLC was efficacious and resulted in a significantly improved ORR versus *sb*-PC, achieving the primary end point. *nab*-PC produced less neuropathy than *sb*-PC.

Socinski et al. Safety and efficacy analysis by histology of weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer. Annals of Oncology (2013); 24: 2390–2396;

Background:

This analysis compared the efficacy and safety outcomes by histology of nab-paclitaxel (nab-P) plus carboplatin (C) versus solvent-based paclitaxel (sb-P) plus C in patients with advanced non-small-cell lung cancer (NSCLC) based on preplanned stratification factors specified in the phase III trial protocol.

Patients and methods:

Patients with untreated stage III/IV NSCLC received 100 mg/m² nab-P weekly and C (area under the curve, AUC = 6) every 3 weeks (q3w) or 200 mg/m² sb-P plus C (AUC = 6) q3w. Primary end point was objective overall response rate (ORR).

Results:

nab-P/C versus sb-P/C produced a significantly higher ORR (41% versus 24%; response rate ratio [RRR] 1.680; P < 0.001) in patients with squamous cell (SCC) NSCLC. For nab-P/C versus sb-P/C, ORRs were 26% versus 27% (RRR 0.966; P = 0.814) in patients with adenocarcinoma, 33% versus 15% (RRR 2.167; P = 0.323) in patients with large cell carcinoma (LC), and 24% versus 15% (RRR 1.593; P = 0.372) in patients with not otherwise specified histology. Median overall survival for nab-P/C versus sb-P/C in patients with SCC was 10.7 versus 9.5 months (HR 0.890; P = 0.310), and 12.4 versus 10.6 months (HR 1.208; P = 0.721) for patients with LC. nab-P/C produced significantly (P < 0.05) less grade 3/4 neuropathy and arthralgia, whereas sb-P/C produced less thrombocytopenia and anemia.

Conclusion(s):

First-line nab-P/C demonstrated a favorable risk-benefit profile in patients with NSCLC regardless of histology.

2.2 Nivolumab (Opdivo[®], BMS-936558, MDX1106, ONO4538) for the second-line therapy of squamous cell/ NON-squamous cell NSCLC

Drug description: a human programmed death receptor-1 (PD-1) blocking antibody

Incidence in Austria: 3,500 NSCLC

EMA/FDA licensing for this indication: -/FDA: 03/2015: approved for metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy

Phase III results: -

Other sources: FDA:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125527s000lbl.pdf, p 19ff

3. Breast cancer

3.1 *Palbociclib (Ibrance® , PD-0332991) for the treatment of post-menopausal women with hormone receptor positive, Her2 negative advanced breast cancer*

Drug description: orally available cyclin-dependent kinase (CDK) inhibitor (targets CDK4 and CDK6)

Incidence in Austria: 5,400 breast cancer patients

EMA/FDA licensing for this indication: -/FDA: 02/2015: accelerated approval, indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2) - negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease

Phase III results:-

Other Sources:

Finn et al. *The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.* *Lancet Oncol.* (2015) Jan;16(1):25-35

Background

Palbociclib (PD-0332991) is an oral, small-molecule inhibitor of cyclin-dependent kinases (CDKs) 4 and 6 with preclinical evidence of growth-inhibitory activity in oestrogen receptor-positive breast cancer cells and synergy with anti-oestrogens. We aimed to assess the safety and efficacy of palbociclib in combination with letrozole as first-line treatment of patients with advanced, oestrogen receptor-positive, HER2-negative breast cancer.

Methods

In this open-label, randomised phase 2 study, postmenopausal women with advanced oestrogen receptor-positive and HER2-negative breast cancer who had not received any systemic treatment for their advanced disease were eligible to participate. Patients were enrolled in two separate cohorts that accrued sequentially: in cohort 1, patients were enrolled on the basis of their oestrogen receptor-positive and HER2-negative biomarker status alone, whereas in cohort 2 they were also required to have cancers with amplification of cyclin D1 (CCND1), loss of p16 (INK4A or CDKN2A), or both. In both cohorts, patients were randomly assigned 1:1 via an interactive web-based randomisation system, stratified by disease site and disease-free interval, to receive continuous oral letrozole 2.5 mg daily or continuous oral letrozole 2.5 mg daily plus oral palbociclib 125 mg, given once daily for 3 weeks followed by 1 week off over 28-day cycles. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. Accrual to cohort 2 was stopped after an unplanned interim analysis of cohort 1 and the statistical analysis plan for the primary endpoint was amended to a combined analysis of cohorts 1 and 2 (instead of cohort 2 alone). The study is ongoing but closed to accrual; these are the results of the final analysis of progression-free survival.

Results

Between Dec 22, 2009, and May 12, 2012, we randomly assigned 165 patients, 84 to palbociclib plus letrozole and 81 to letrozole alone. At the time of the final analysis for progression-free survival (median follow-up 29.6 months [95% CI 27.9-36.0] for the palbociclib plus letrozole group and 27.9 months [25.5-31.1] for the letrozole group), 41 progression-free survival events had occurred in the palbociclib plus letrozole group and 59 in the letrozole group. Median progression-free survival was 10.2 months (95% CI 5.7-12.6) for the letrozole group and 20.2 months (13.8-27.5) for the palbociclib plus letrozole group (HR 0.488, 95% CI 0.319-0.748; one-sided $p=0.0004$). In cohort 1 ($n=66$), median progression-free survival was 5.7 months (2.6-10.5) for the letrozole group and 26.1 months (11.2-not estimable) for the palbociclib plus letrozole group (HR 0.299, 0.156-0.572; one-sided $p<0.0001$); in

cohort 2 (n=99), median progression-free survival was 11.1 months (7.1-16.4) for the letrozole group and 18.1 months (13.1-27.5) for the palbociclib plus letrozole group (HR 0.508, 0.303-0.853; one-sided p=0.0046). Grade 3-4 neutropenia was reported in 45 (54%) of 83 patients in the palbociclib plus letrozole group versus one (1%) of 77 patients in the letrozole group, leucopenia in 16 (19%) versus none, and fatigue in four (4%) versus one (1%). Serious adverse events that occurred in more than one patient in the palbociclib plus letrozole group were pulmonary embolism (three [4%] patients), back pain (two [2%]), and diarrhoea (two [2%]). No cases of febrile neutropenia or neutropenia-related infections were reported during the study. 11 (13%) patients in the palbociclib plus letrozole group and two (2%) in the letrozole group discontinued the study because of adverse events.

Conclusion

The addition of palbociclib to letrozole in this phase 2 study significantly improved progression-free survival in women with advanced oestrogen receptor-positive and HER2-negative breast cancer. A phase 3 trial is currently underway.