Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology

Results
20th Prioritisation – 3rd 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 20th prioritisation (September 2014), 7 were filtered out of 145 identified drugs and were sent to prioritisation. Of these, 4 drugs were ranked as ‘highly relevant’ by the expert panel, 3 as ‘relevant’ and none 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 - 20th prioritisation 3rd quarter 2014	Overall category
1.	Ramucirumab (Cyramza®) for the second-line therapy of stage IV NSCLC	Relevant
2.	Exemestane (Aromasin®) for premenopausal women with endocrine responsive breast cance	Relevant
3.	Idelalisib (GS-1101) for relapsed chronic lymphocytic leukaemia	Highly relevant
4.	Lenalidomide (Revlimid™) induction/maintenance therapy in patients with newly diagnosed multiple myeloma	Highly relevant
5.	Lenalidomide (Revlimid™) for first line therapy in transplant-ineligible patients with multiple myeloma	Highly relevant
6.	Trebananib (AMG 386) for recurrent epithelial ovarian, primary peritoneal or fallopian tube cancers	Relevant
7.	Enzalutamide, MDV3100 (Xtandi®) in chemotherapy-naive patients with castration resistant prostate cancer	Highly relevant

1 Chronic lymphocytic leukaemia

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 for this indication: positive decision by European Medicines Agency's Committee for Medicinal Products for Human Use in July 2014 /-

Phase III results:

Furman et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. NEJM (2014); 1–11.

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.

2 Multiple Myeloma

Lenalidomide (Revlimid™) induction/maintenance therapy in patients with newly diagnosed multiple myeloma

Drug description: an orally administered thalidomide analogue
Incidence in Austria: ~ 600 patients newly diagnosed/year
EMA/FDA licensing for this indication: -/-
Phase III results:

Palumbo et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. NEJM (2014); 371: 895-905.

Background
This open-label, randomized, phase 3 study compared melphalan at a dose of 200 mg per square meter of body-surface area plus autologous stem-cell transplantation with melphalan–prednisone–lenalidomide (MPR) and compared lenalidomide maintenance therapy with no maintenance therapy in patients with newly diagnosed multiple myeloma.

Methods
We randomly assigned 273 patients 65 years of age or younger to high-dose melphalan plus stem-cell transplantation or MPR consolidation therapy after induction, and 251 patients to lenalidomide maintenance therapy or no maintenance therapy. The primary end point was progression-free survival.

Results
The median follow-up period was 51.2 months. Both progression-free and overall survival were significantly longer with high-dose melphalan plus stem-cell transplantation than with MPR (median progression-free survival, 43.0 months vs. 22.4 months; hazard ratio for progression or death, 0.44; 95% confidence interval [CI], 0.32 to 0.61; P<0.001; and 4-year overall survival, 81.6% vs. 65.3%; hazard ratio for death, 0.55; 95% CI, 0.32 to 0.93; P=0.02). Median progression-free survival was significantly longer with lenalidomide maintenance than with no maintenance (41.9 months vs. 21.6 months; hazard ratio for progression or death, 0.47; 95% CI, 0.33 to 0.65; P<0.001), but 3-year overall survival was not significantly prolonged (88.0% vs. 79.2%; hazard ratio for death, 0.64; 95% CI, 0.36 to 1.15; P=0.14). Grade 3 or 4 neutropenia was significantly more frequent with high-dose melphalan than with MPR (94.3% vs. 51.5%), as were gastrointestinal adverse events (18.4% vs. 0%) and infections (16.3% vs. 0.8%); neutropenia and dermatologic toxic effects were more frequent with lenalidomide maintenance than with no maintenance (23.3% vs. 0% and 4.3% vs. 0%, respectively).

Conclusions
Consolidation therapy with high-dose melphalan plus stem-cell transplantation, as compared with MPR, significantly prolonged progression-free and overall survival among patients with multiple myeloma who were 65 years of age or younger. Lenalidomide maintenance, as compared with no maintenance, significantly prolonged progression-free survival.

Lenalidomide (Revlimid™) for first line therapy in transplant-ineligible patients with multiple myeloma

Drug description: an orally administered thalidomide analogue
Incidence in Austria: ~ 600 patients newly diagnosed/year
EMA/FDA licensing for this indication: -/-
Phase III results:

Benboubker et al. Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma. NEJM (2014); 371: 906-917.

Background
The combination melphalan–prednisone–thalidomide (MPT) is considered a standard therapy for patients with myeloma who are ineligible for stem-cell transplantation. However, emerging data on the use of lenalidomide and low-dose dexamethasone warrant a prospective comparison of the two approaches.

Methods
We randomly assigned 1623 patients to lenalidomide and dexamethasone in 28-day cycles until disease progression (535 patients), to the same combination for 72 weeks (18 cycles; 541 patients), or to MPT for 72 weeks (547 patients). The primary end point was progression-free survival with continuous lenalidomide–dexamethasone versus MPT.

Results
The median progression-free survival was 25.5 months with continuous lenalidomide–dexamethasone, 20.7 months with 18 cycles of lenalidomide–dexamethasone, and 21.2 months with MPT (hazard ratio for the risk of progression or death, 0.72 for continuous lenalidomide–dexamethasone vs. MPT and 0.70 for continuous lenalidomide–dexamethasone vs. 18 cycles of lenalidomide–dexamethasone; P<0.001 for both comparisons). Continuous lenalidomide–dexamethasone was superior to MPT for all secondary efficacy end points, including overall survival (at the interim analysis). Overall survival at 4 years was 59% with continuous lenalidomide–dexamethasone, 56% with 18 cycles of lenalidomide–dexamethasone, and 51% with MPT. Grade 3 or 4 adverse events were somewhat less frequent with continuous lenalidomide–dexamethasone than with MPT (70% vs. 78%). As compared with MPT, continuous lenalidomide–dexamethasone was associated with fewer hematologic and neurologic toxic events, a moderate increase in infections, and fewer second primary hematologic cancers.

Interpretation
IAs compared with MPT, continuous lenalidomide–dexamethasone given until disease progression was associated with a significant improvement in progression-free survival, with an overall survival benefit at the interim analysis, among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation.

3 Prostate Cancer

Enzalutamide, MDV3100 (Xtandi®) in chemotherapy-naive patients with castration resistant prostate cancer

Drug description: first oral androgen receptor signalling inhibitor (ARSI)
Incidence in Austria: 4,800 men/year newly diagnosed with prostate cancer
EMA/FDA licensing for this indication: -/-
Phase III results:

Beer et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy NEJM (2014); 371: 424-433.

Background
Enzalutamide is an oral androgen-receptor inhibitor that prolongs survival in men with metastatic castration-resistant prostate cancer in whom the disease has progressed after chemotherapy. New treatment options are needed for patients with metastatic prostate cancer who have not received chemotherapy, in whom the disease has progressed despite androgen-deprivation therapy

Methods
In this double-blind, phase 3 study, we randomly assigned 1717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The coprimary end points were radiographic progression-free survival and overall survival.

Results
The study was stopped after a planned interim analysis, conducted when 540 deaths had been reported, showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% confidence interval [CI], 0.15 to 0.23; P<0.001). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P<0.001). The benefit of enzalutamide was shown with respect to all secondary end points, including the time until the initiation of cytotoxic chemotherapy (hazard ratio, 0.35), the time until the first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), the time until prostate-specific antigen (PSA) progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) (P<0.001 for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment.

Conclusion
Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer.