New oncology reimbursements in Belgium

P. Specenier, MD, PhD

Overview of Belgian reimbursement news.
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NIVOLUMAB (OPDIVO®)

As of January 1st, 2017, nivolumab (Opdivo®) is reimbursed for all approved indications mentioned in the Summary of Product Characteristics (SPC).[1-3] Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2 and which was already reimbursed as a single agent for the treatment of patients with **advanced melanoma.**

The new criteria now also allow the **combination with ipilimumab (Yervoy®) for patients with unresectable or metastatic melanoma**. In CheckMate 067, 945 subjects with previously untreated unresectable or metastatic melanoma were randomised to receive nivolumab 3 mg/kg every two weeks plus ipilimumab-matched placebo, nivolumab 1 mg/kg every three weeks plus ipilimumab 3 mg/kg every three weeks for four doses followed by nivolumab 3 mg/kg every two weeks, or ipilimumab 3 mg/kg for four doses nivolumab-matched placebo.[4] Co-primary endpoints were progression-free survival (PFS) and overall survival (OS). Thus far, only PFS data were published and the study remains blinded for OS. The study was not designed for a formal statistical comparison between the nivolumab group and the nivolumab-plus-ipilimumab group.

The median PFS was 6.9 months (95% confidence interval [CI] 4.3, 9.5) in the nivolumab group, 11.5 months (95% CI 8.9, 16.7) in the nivolumab-plus-ipilimumab group, and 2.9 months (95% CI 2.8, 3.4) in the ipilimumab group. Hazard ratio (HR) for PFS versus ipilimumab was 0.42 (99.5% CI 0.31, 0.57; p<0.001) for nivolumab plus ipilimumab and 0.57 (99.5% CI 0.43, 0.76; p<0.001) for single agent nivolumab. Among patients with a positive PD-L1 tumour status, the median PFS was 14.0 months (95% CI 9.1, not reached [NR]) in the nivolumab group, 14.0 months (95% CI 9.7, NR) in the nivolumab-plus-ipilimumab group, and 3.9 months (95% CI 2.8, 4.2) in the ipilimumab group. In contrast, among patients with a negative PD-L1 tumour status, the median PFS was 5.3 months (95% CI 2.8, 7.1), 11.2 months (95% CI 8.0, NR), and 2.8 months (95% CI 2.8, 3.1), in the nivolumab group, the nivolumab-plus-ipilimumab group, and the ipilimumab group, respectively. The rates of investigator-assessed objective response were 43.7% (95% CI 38.1 to 49.3) in the nivolumab group, 57.6% (95% CI 52.0, 63.2) in the nivolumab-plus-ipilimumab group, and 19.0% (95% CI 14.9, 23.8) in the ipilimumab group. The percentage of patients with a complete response was 11.5% in the nivolumab-plus ipilimumab group, 8.9% in the nivolumab group, and 2.2% in the ipilimumab group. The incidence of treatment-related adverse events of grade 3 or 4 was substantially higher in the nivolumab plus-ipilimumab group (55.0%) than in the nivolumab (16.3%) or the ipilimumab groups (27.3%). The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommends that the benefits of the combination treatment would need to be balanced against the potential increase in toxicity on a case-by-case basis in clinical practice, with a careful evaluation of the patient's demographics (e.g. age and performance status) and disease characteristics (e.g. M stage, LDH level, and *BRAF* mutation status).[2]

Department of Oncology, University Hospital Antwerp, Edegem, Belgium.

Please send all correspondence to: T. Feys, MSc, MBA, Ariez International BV, Oude Houtlei 118, 9000 Ghent, Belgium, tel: +32 479 56 78 90, email: t.feys@ariez.com.

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The SPC explicitly mentions that relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.[3]

Opdivo® as monotherapy has been approved by the EMA for the treatment of patients with **locally advanced or metastatic non-squamous cell non-small cell lung cancer (NSCLC)** after prior chemotherapy based on the results of CheckMate 057, in which patients were randomised to receive nivolumab 3 mg/kg every three weeks or docetaxel 75 mg/m² every three weeks.[5] Overall survival (primary endpoint) was significantly longer with nivolumab than with docetaxel. The median OS was 12.2 months (95% CI 9.7, 15.0) among 292 patients in the nivolumab group and 9.4 months (95% CI 8.1, 10.7) among 290 patients in the docetaxel group (HR 0.73; 96% CI 0.59, 0.89; p=0.002). The response rate (ORR) was 19% with nivolumab versus 12% with docetaxel (p=0.02). Although PFS did not favour nivolumab over docetaxel (median 2.3 months and 4.2 months, respectively), the PFS rate at one year was higher with nivolumab than with docetaxel (19% and 8%, respectively). Treatment-related adverse events of grade 3 or 4 were reported in 10% of the patients in the nivolumab group, as compared with 54% of those in the docetaxel group. A test for interaction suggested a strong predictive association between PD-L1 expression and clinical outcome at all expression levels for all efficacy end points. In patients with PD-L1 expression level >1%, median OS was 17 versus 9.0 months with docetaxel (HR 0.58; 95 % CI 0.43, 0.79). In contrast, in patients with PD-L1 expression level <1%, median OS was similar in both arms (10.5 months with nivolumab versus 10.1 months with docetaxel).[5]

Approval for patients with **advanced squamous NSCLC** who progressed during or after prior chemotherapy is based on the results of CheckMate 017.[6] Two hundred and seventy-two patients were randomly assigned to receive nivolumab 3 mg/kg every two weeks or docetaxel 75 mg/m² every three weeks. The median OS (primary endpoint) was 9.2 months (95% CI 7.3, 13.3) with nivolumab versus 6.0 months (95% CI 5.1, 7.3) with docetaxel (HR 0.59; 95% CI 0.44, 0.79; p<0.001). At one year, the OS rate was 42% (95% CI 34, 50) with nivolumab versus 24% (95% CI 17, 31) with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel (p=0.008). Median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR 0.62; 95% CI 0.47 to 0.81; p<0.001). The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit. Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group.[6]

The outcome of CheckMate 025 led to the approval of single agent nivolumab for patients with **advanced renal cell carcinoma after prior therapy**.[7]

In that study, 821 patients with advanced clear-cell renal-cell carcinoma for which they had received previous treatment with one or two regimens of anti-angiogenic therapy were randomly assigned to nivolumab 3 mg/kg every two weeks or everolimus 10 mg/day. The median OS (primary endpoint) was 25.0 months (95% CI 21.8, NR) with nivolumab and 19.6 months (95% CI 17.6, 23.1) with everolimus (HR 0.73; 98.5% CI 0.57, 0.93; p=0.002), which met the pre-specified criterion for superiority (p≤0.0148). The objective response rate was 25% with nivolumab versus 5% with everolimus (odds ratio [OR], 5.98; 95% CI 3.68, 9.72; p<0.001). Median PFS was 4.6 months (95% CI 3.7, 5.4) and 4.4 months (95% CI 3.7, 5.5), respectively (HR 0.88; 95% CI 0.75, 1.03; p=0.11). Grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus.[7]

Finally, on the 13th of October 2016, the CHMP also adopted a positive opinion for the treatment of adult patients with **relapsed or refractory classical Hodgkin lymphoma (cHL)** after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. In an ongoing study, 23 patients with relapsed or refractory heavily pretreated Hodgkin's lymphoma received nivolumab 3 mg/kg every two weeks. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining three patients (13%) had stable disease. The PFS rate at 24 weeks was 86%.[8]

CERITINIB (ZYKADIA®)

Ceritinib (Zykadia®) (selective inhibitor of ALK) is reimbursed as a monotherapy in patients with ALK-positive advanced NSCLC progressing during or after crizotinib treatment. ALK-positivity should be demonstrated by immunochemistry and confirmed by a validated FISH test.

Overall, at the time of approval by the EMA, 515 ALK-positive NSCLC patients had been treated with ceritinib 750 mg (83 ALK inhibitor naïve and 163 ALK inhibitor pretreated patients in study X2101; 140 ALK inhibitor pretreated patients in study A2201 and 124

ALK inhibitor naïve patients in study A2203; five additional patients have been treated at the proposed dose in study X1101). The ALK inhibitor pretreated patients comprise a heavily pretreated patient population, with more than half of the patients having received at least three prior regimens, including crizotinib. The ORR (56.4% in study X2101 and 37.1% in study A2201) seen in these patients exceeded that expected with chemotherapy.[9]

For the ALK inhibitor naïve population, the majority of the patients had received at least a platinum agent or a platinum doublet. The overall response rate in that population was 72.3%.[9,10] Since the EMA approval for ceritinib, positive data from randomised trials in both crizotinib treated and treatment naïve patients have been presented.[21,22]

OSIMERTINIB (TAGRISSO®)

Osimertinib (Tagrisso®) is an irreversible inhibitor of Epidermal Growth Factor Receptors (EGFR) harbouring sensitising-mutations and tyrosine kinase resistance (TKI)-resistance mutation T790M. Osimertinib (Tagrisso®) is reimbursed as a single agent for the treatment of patients with locally advanced or metastatic NSCLC harbouring an EGFR T790M mutation, progressing during or after prior treatment with an EGFR-directed TKI.

Approval and reimbursement were based on the results of the AURA phase I/II studies showing an ORR of 66% and a median response duration (DOR) of 8.5 months and a median PFS of 9.7 months, which is considerably superior to historical results obtained with chemotherapy or TKI re-challenge.[11,12]

AFATINIB (GIOTRIF®)

The reimbursement criteria of afatinib (Giotrif®) (ErbB Family Blocker) have been slightly modified. Giotrif® is now reimbursed for the treatment of patients with a locally advanced or metastatic NSCLC harbouring an activating EGFR tyrosine kinase mutation, who have not been previously treated with an EGFR tyrosine kinase inhibitor.

In the 1200.32/LUX-Lung 3 study, 325 previously untreated patients with stage IIIB or IV adenocarcinoma of the lung, harbouring an EGFR-activating mutation were randomised, in a 2:1 ratio, to receive afatinib 40 mg/day or pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2 on day 1 of each 21-day treatment course. Median PFS (primary endpoint) was 11.1 months (95 % CI 9.6, 13.6) with afatinib and 6.9 months (95 % CI 5.4, 8.2) with chemotherapy with a hazard ratio of 0.58 (95 % CI 0.43, 0.78; p=0.0004).[13,14]

PANOBINOSTAT (FARYDAK®)

Panobinostat (Farydak®) is a histone deacetylase (HDAC) inhibitor which is now reimbursed in combination with bortezomib and dexamethasone in patients with recurrent or refractory multiple myeloma after at least two prior regimens including an immunomodulatory drug and a proteasome inhibitor.

In the PANORAMA 1 study, 768 patients with relapsed or relapsed/refractory multiple myeloma were randomised to receive bortezomib and dexamethasone with either panobinostat or placebo.[15,16]

Median PFS (primary endpoint) was 12 months (95 % CI 10.32, 12.94) with bortezomib and dexamethasone plus panobinostat versus 8.1 months (95 % CI 7.56, 9.23) with bortezomib and dexamethasone plus placebo (hazard ratio [HR] 0.63; 95 % CI 0.52, 0.76; p<0.0001).

At the time of the second interim analysis, median OS was 38.2 months and 35.4 months, in the bortezomib and dexamethasone plus panobinostat and bortezomib and dexamethasone plus placebo arms, respectively (HR 0.87; 95% CI 0.70, 1.07; p=0.18).[16]

CARFILZOMIB (KYPROLIS®)

Carfilzomib (Kyprolis®) is a proteasome inhibitor which is now reimbursed in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma progressing after at least one prior therapy including a hematopoietic stem cell transplant, except in patients who do not qualify for a transplant.

In the ASPIRE trial, 792 patients with relapsed multiple myeloma were randomly assigned to carfilzomib, lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group).[17] Progression-free survival (primary endpoint) was significantly improved with carfilzomib (median, 26.3 months, versus 17.6 months in the control group; HR, 0.69; 95% CI, 0.57 to 0.83; p=0.0001).[17]

TRAMETINIB (MEKINIST®)

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity.[18-20]

From February 1st, 2017, trametinib (Mekinist®) will be reimbursed for the treatment of patients with advanced *BRAF*v600-mutated melanoma. Reimbursement is re-

stricted to the combination with dabrafenib (Tafinlar®). Although trametinib is also approved as a single agent by the EMA, the Market Authorisation Holder did not request reimbursement for trametinib administered as a single agent.

Combi-d (MEK115306) is a phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo as first-line therapy in 423 subjects with unresectable (stage IIIC) or metastatic (stage IV) *BRAF* v600E/K mutation-positive cutaneous melanoma.[19] Median PFS (primary endpoint) for the combination therapy arm was 11.0 (95 % CI 8.0, 13.9) months compared with 8.8 (95 % CI 5.9, 9.3) months for the dabrafenib monotherapy arm with a HR of 0.67 (95% CI 0.53, 0.84; p<0.001). At the time of the final OS analysis, a statistically significant reduction in risk of death for the combination therapy arm compared with the dabrafenib monotherapy arm was reported (HR 0.71, 95% CI 0.55, 0.92; p=0.011). The median OS was 25.1 months for the combination therapy arm and 18.7 months for the dabrafenib monotherapy arm.[19]

Combi-v (MEK116513) (20) is a phase III, randomised, open-label study comparing the combination of the dabrafenib and trametinib to vemurafenib in 704 subjects with unresectable (stage IIIc) or metastatic (stage IV) *BRAF*v600E/K mutation positive cutaneous melanoma. The study was stopped early by the independent data monitoring committee at the interim analysis as the adjusted stopping boundary for efficacy (p<0.0214) was crossed. Median OS (primary endpoint) had not been reached (95 % CI 18.3, not reached [NR]) in the combination therapy arm and was 17.2 (95% CI 16.4, NR) months in the vemurafenib monotherapy arm with a HR of 0.69 (95% CI 0.53, 0.89; p=0.005).[20]

REFERENCES

1. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003985/WC500209378.pdf

2. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf

3. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/003985/WC500214219.pdf

4. Larkin J et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373:23-34.

5. Borghaei H et al. Nivolumab versus Docetaxel in Advanced Non-squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 373(17):1627-39.

6. Brahmer J et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123-35.

7. Motzer RJ et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1803-13.

8. Ansell SM et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311-9.

9. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003819/WC500187506.pdf

10. Kim DW et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol. 2016;17(4):452-63.

11. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004124/WC500202024.pdf

12. Goss G et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA 2): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2016;17(12):1643-52.

13. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002280/WC500152394.pdf

14. Sequist LV et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-34.

15. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003725/WC500193300.pdf

16. San-Miguel JF et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. Lancet Haematol. 2016;3(11):e506-e515.

17. Stewart AK et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142-52.

18. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002643/WC500196317.pdf

19. Long GV et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-51.

20. Grob JJ et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol. 2015;16:1289-99.

21. Scagliotti G et al. Ceritinib vs chemotherapy (CT) in patients with advanced ALK-rearranged NSCLC previously treated with CT and crizotinib: results from the confirmatory phase 3 ASCEND-5 study. Presented at ESMO 2016, Abstract LBA42_PR.

22. De Castro G et al. First-line ceritinib versus chemotherapy in patients with ALK-rearranged (ALK+) NSCLC: a randomized phase 3 study (ASCEND-4). Presented at WCLC 2016, abstract PL03.07.