New oncology reimbursements in Belgium

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OVERVIEW OF BELGIAN REIMBURSEMENT NEWS

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Thus far, the anti-PD-(L)1 monoclonal antibodies are reimbursed upon approval by the European Medicines Agency (EMA) with the exception of KYETRUDA® for the indication "monotherapy in patients with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy", and LIBTAYO®, for which the procedure potentially leading to reimbursement is still ongoing. For some combinations, the companion drug (i.e. bevacizumab, nab-paclitaxel) is not reimbursed in Belgium.

Multiple new indications have been recently approved and reimbursed. We aim to summarise reimbursed indications for each anti-PD-(L)1 as of February 1st, 2021. Recently reimbursed indications include first-line treatment of adults with advanced renal cell carcinoma (RCC) in combination with axitinib (avelumab and pembrolizumab) and first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC) (atezolizumab and durvalumab).

BAVENCIO® (AVELUMAB)

MERCKEL CELL CARCINOMA

BAVENCIO is indicated as monotherapy for the treatment of adult patients with metastatic Merckel cell carcinoma (MCC).

RENAL CELL CARCINOMA (RCC)

BAVENCIO is indicated in combination with axitinib for the first-line treatment of adult patients with advanced RCC. The efficacy and safety of avelumab in combination with axitinib was demonstrated in a randomised, multicentre, open-label study in 886 patients with untreated advanced or metastatic RCC with a clear-cell component. Patients were randomised (1:1) to either avelumab 10 mg/kg every two weeks in combination with axitinib 5 mg, orally, twice daily (N=442), or sunitinib 50 mg once daily orally for four weeks followed by two weeks off (N=444).

The primary efficacy endpoints were progression-free survival (PFS), as assessed by Blinded Independent Central Review (BICR) using RECIST v1.1 and overall survival (OS) in who have PD-L1-positive tumours (PD-L1 expression level ≥ 1%). Efficacy data is summarised in *Table 1*.

With a median OS follow-up of nineteen months, OS data were immature. The observed hazard ratio (HR) for OS was 0.80 (95% CI: 0.616, 1.027) for avelumab in combination with axitinib compared to sunitinib.[1]

IMFINZI® (DURVALUMAB)

NON-SMALL CELL LUNG CARCINOMA (NSCLC)

IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

SMALL CELL LUNG CANCER

IMFINZI in combination with etoposide and either carbo-

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TABLE 1. First line treatment advanced RCC

		JAVELIN RENAL 101		KEYNOTE 426	
		sunitinib	axitinib + avelumab	axitinib + pembrolizumab	sunitinib
FU	median (months)	19		12,8	
PFS*	median (months)	8	13,3	15,1	11
	95 % CI	6.7-9.8	11.1-16.3	12.6-17.7	8.7-12.5
	HR	0,69		0,69	
	95 % CI	0.574-0.825		0.56-0.84	
	p	<0.0001		0,00012	
	12-month	39,2%	52,4%		
	95 % CI	34.1-44.2	47.4-57.2		
	24-month	29,3%	43,9%		
	95 % CI	24.2-34.6	38.8-49.0		
OS*	median (months)	immature		NR	
	95 % CI			NE-NE	NE-NE
	HR	0,8		0,53	
	95 % CI	0.616-1.027		0.38-0.74	
ORR		27,3%	52,5%	59%	36%
	95 % CI	23.2-31.6	47.7-57.2	54-64	31-40
	CR	2,0	3,8%	6%	2%
	p			<0.0001	
DOR	median (months)	NE	18,5	NR	15,2
	95 % CI	16.4-NE	17.8-NE	1.4+-18.2+	1.1+-15.4+

ORR: overall response rate; CI: confidence interval; DOR: duration of response; FU: follow-up; CR: complete response; NE: not estImable; OS: overall survival; NR: not reached; *: (co)-primary endpoint.

platin or cisplatin is indicated for the first-line treatment of adults with ES-SCLC. CASPIAN was a randomised, open label, multicentre study designed to evaluate the efficacy of IMFINZI with or without tremelimumab in combination with etoposide and either carboplatin or cisplatin. In total, 805 treatment naïve ES-SCLC patients were randomised 1:1:1 to receive:

- Arm 1: IMFINZI 1500 mg + tremelimumab 75 mg plus etoposide and either carboplatin or cisplatin
- Arm 2: IMFINZI 1500 mg plus etoposide and either carboplatin or cisplatin
- Arm 3: Either carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m^2) on day 1 and etoposide (80-100 mg/m^2) on days 1, 2, and 3 of each 21-day cycle for 4-6 cycles.

For patients randomised to Arm 1 and 2, chemotherapy was limited to four cycles and IMFINZI monotherapy continued every four weeks until disease progression or unacceptable toxicity.

The primary endpoints of the study were OS for Arm 2 *vs.* Arm 3 and for Arm 1 *vs.* Arm 3.

At a planned interim (primary) analysis the study demonstrated a statistically significant improvement in OS with IMFINZI + etoposide + platinum (Arm 2) *vs.* etoposide + platinum alone (Arm 3) [HR=0.73 (95% CI: 0.591, 0.909), p=0.0047]. Although not formally tested for significance,

TABLE 2. First line treatment ES-SCLCadvanced RCC

		CASPIAN		IMpower133	
		durvalumab + chemotherapy	chemotherapy	placebo + chemotherapy	atezolizumab + chemotherapy
FU	median (months)	25,1		22,9	
OS*	median (months)	12,9	10,5	10,3	12,3
	95 % CI	11.3-14.7	9.3-11.2	10.8-15.8	9.3-11.3
	HR	0,75		0,76	
	95 % CI	0.625-0.910		0.60-0.95	
	p	0,0032		0,0154	
	12-month			51,9%	39,0%
	18-month	32,0%	24,8%		
	95 % CI	26.5-37.7	19.7-30.1		

IMFINZI + etoposide + platinum demonstrated an improvement in PFS *vs.* etoposide + platinum alone [HR=0.78 (95% CI: 0.645, 0.936)]. In the planned follow-up analysis (median: 25.1 months), IMFINZI + etoposide + platinum (Arm 2) *vs.* etoposide + platinum (Arm 3) continued to demonstrate improved OS. Median OS was 12.9 months (95% CI 11.3-17.7) with IMFINZI + chemotherapy and 10.5 months (95% CI 9.3-11.2) with chemotherapy. Overall survival at eighteen months was 32.0 % (95% CI 26.5-37.7) and 24.8% (95% CI 19.7-30.1), respectively, with a HR of 0.75 (95% CI 0.625-0.910; p=0.0032) (*Table 2*).[2]

KEYTRUDA® (PEMBROLIZUMAB)

MELANOMA

KEYTRUDA as monotherapy is indicated:

- for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.

NON-SMALL CELL LUNG CARCINOMA (NSCLC)

KEYTRUDA as monotherapy is indicated:

- for the first-line treatment of metastatic NSCLC adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

KEYTRUDA, in combination:

- with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults. ***However, nab-paclitaxel is not reimbursed for this indication.***

CLASSICAL HODKIN LYMPHOMA (CHL)

KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

UROTHELIAL CARCINOMA

KEYTRUDA as monotherapy is indicated:

- for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

HEAD AND NECK SQAMOUS CELL CARCINOMA (HNSCC)

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1.

KEYTRUDA as monotherapy is also approved for the treatment of recurrent or metastatic (R/M) HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. ***However, the Marketing Authorisation Holder (MAH) elected not to request reimbursement for the latter indication.***

RENAL CELL CARCINOMA (RCC)

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced RCC in adults. The efficacy of pembrolizumab in combination with axitinib was investigated in KEYNOTE-426, a randomised, multicentre, open-label, active-controlled study conducted in 861 patients with advanced RCC with clear cell component, regardless of PD-L1 tumour expression status and International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were randomised (1:1) to either pembrolizumab 200 mg every three weeks in combination with axitinib 5 mg orally, twice daily (N= 432), or sunitinib 50 mg orally, once daily for four weeks and then off treatment for two weeks (N= 429). The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1).

After a median follow up of 12.8 months, pembrolizumab plus axitinib significantly improved OS and PFS (*Table 1*). An updated OS analysis was performed when patients had a median follow-up of 16.6 months (range: 0.1 to 26.3 months). At the time of this analysis, the HR (95% CI) was 0.59 (0.45-0.78) with 19.4% events in the combination arm and 28.4% events in the sunitinib arm. The twelve-month OS rate was 89.5% (95% CI 86.2-92.1) for pembrolizumab in combination with axitinib and 78.8% (95% CI 74.7-82.4) for sunitinib. The eighteen-month OS rate was 81.0% (95% CI 76.7-84.6) for pembrolizumab in combination with axitinib and 70.7% (95% CI 65.8-75.1) for sunitinib.[3]

COLORECTAL CANCER (CRC)

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

LIBTAYO® (CEMIPLIMAB)

LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation.[4] ***The procedure potentially leading to reimbursement is still ongoing.***

OPDIVO® (NIVOLUMAB)

MELANOMA

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in PFS and OS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

NON-SMALL CELL LUNG CARCINOMA (NSCLC)

OPDIVO in combination with ipilimumab and two cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.

RENAL CELL CARCINOMA (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced RCC after prior therapy in adults.

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.

CLASSICAL HODKIN LYMPHOMA (CHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with BV.

HEAD AND NECK SQAMOUS CELL CARCINOMA (HNSCC)

OPDIVO as monotherapy is indicated for the treatment of R/M HNSCC in adults progressing on or after platinum-based therapy.

UROTHELIAL CARCINOMA

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

OESOPHAGEAL SQUAMOUS CELL CARCINOMA (OSCC)

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, R/M OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.[5]

TECENTRIQ® (ATEZOLIZUMAB)

UROTHELIAL CARCINOMA

TECENTRIQ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

- after prior platinum containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.

NON-SMALL CELL LUNG CARCINOMA (NSCLC)

TECENTRIQ, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, TECENTRIQ, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies. However, reimbursement for bevacizumab is restricted to patients with EGFR mutated or ALK positive tumours or with liver metastases.

TECENTRIQ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving TECENTRIQ, in combination with nab-paclitaxel and carboplatin, is indicated for the first line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK positive NSCLC. ***However, nab-paclitaxel is not reimbursed for this indication.***

SMALL CELL LUNG CANCER

TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with ES-SCLC. IMpower 133 is a randomised, multicentre, double-blind, placebo-controlled study, in which 403 patients were randomised (1:1) to receive carboplatin (AUC 5) on day 1 plus etoposide 100 mg/m^2 on day 1, 2, and 3 plus either atezolizumab 1200 mg or placebo on day 1 of each 21-day cycle. Atezolizumab or placebo were administered until loss of clinical benefit as assessed by investigator. Carboplatin and etoposide were administered until completion of four cycles, or progressive disease or unacceptable toxicity, whichever occurred first. Co-primary endpoints were OS and investigator-assessed PFS (RECIST v1.1). At the time of the primary analysis, patients had a median survival follow up time of 13.9 months. A statistically significant improvement in OS was observed with atezolizumab in combination with carboplatin and etoposide compared to the control arm (HR of 0.70, 95% CI: 0.54-0.91; median OS of 12.3 months *vs.* 10.3 months) (*Table 2*).[6]

HEPATOCELLULAR CARCINOMA

TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy. ***However, bevacizumab is not reimbursed for this indication.***

TRIPLE NEGATIVE BREAST CANCER

TECENTRIQ in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease. ***The procedure potentially leading to reimbursement for this indication is ongoing. Nab-Paclitaxel is not reimbursed for this indication***. Nab-Paclitaxel is approved by EMA as *monotherapy* for the treatment of metastatic breast cancer in adult patients who *have failed first-line treatment* for metastatic disease and for whom standard, anthracycline-containing therapy is not indicated. In a recent communication, EMA is reminding physicians to use TECENTRIQ only in combination with nab-paclitaxel and not with conventional paclitaxel when treating patients with locally advanced or metastatic TNBC that cannot be surgically removed. EMA's advice follows the release of results from IMpassion131, which did not show that combining Tecentriq with conventional paclitaxel improved PFS in these patients.[7]

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