New oncology reimbursements in Belgium

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OVERVIEW OF BELGIAN REIMBURSEMENT NEWS

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OLARATUMAB (LARTRUVO®)

Olaratumab (LARTRUVO®) is reimbursed when administered in combination with doxorubin for adult patients with soft tissue sarcoma who do not qualify for surgery or radiotherapy and who did not receive prior treatment with doxorubicin. Olaratumab is an antagonist of platelet derived growth factor receptor-α (PDGFR-α).

The efficacy and safety of olaratumab was assessed in a phase Ib/II, multi-centre study in anthracycline naïve patients advanced soft tissue sarcoma not amenable to receive surgery or radiotherapy with curative intent. Patients with gastrointestinal stromal tumours (GIST) or Kaposi sarcoma were excluded. In the phase II portion of the study, 133 patients were randomised 1:1 to receive olaratumab (15 mg/kg on day 1 and 8) plus doxorubicin (75 mg/m² on day 1) or doxorubicin (75 mg/m² on day 1) alone. Cycles were repeated every three weeks. All patients receiving more than four cycles of doxorubicin received dexrazoxane. Patients in the olaratumab plus doxorubicin arm could continue on olaratumab monotherapy until disease progression, unacceptable toxicity or any other reason for treatment discontinuation occurred. The median cumulative dose of doxorubicin was 487.6 mg/m² in the olaratumab plus doxorubicin arm and 299.6 mg/m² in the doxorubicin alone arm. Median progression-free survival (primary endpoint) was 6.6 months (95% CI 4.1-8.3) with olaratumab plus doxorubicin versus 4.1 months (95% CI 2.8-5.4) with doxorubicin with a hazard ratio of 0.672 (95% CI 0.442-1.021; p=0.0615). A statistically significant improvement in OS was seen in the olaratumab plus doxorubicin arm in comparison to treatment with doxorubicin alone in the overall population. Median overall survival was 26.5 months (95% CI 20.9-31.7) versus 14.7 months (95% CI 9.2-17.1; HR 0.463 [95% CI 0.301-0.710]; p=0.0003). Difference in objective response rate according to investigator assessment was not statistically significant (18.2 % *vs.* 11.9 %).[1]

ALECTINIB (ALECENZA®)

Alectinib (ALECENZA®) is reimbursed for patients with ALK-positive NSCLC progressing during or after crizotinib or intolerant to crizotinib. The safety and efficacy of alecenza in ALK-positive NSCLC patients pre-treated with crizotinib were studied in two phase I/II clinical trials (*Table 1*). Prior chemotherapy was allowed. Overall response rate (ORR) (primary endpoint) was 50.8% and 52.2%, respectively.[2,3]

PEGFILGRASTIM (NEULASTA®)

The reimbursement criteria for pegfilgrastim (NEULASTA®) have been thoroughly modified. Pegfilgrastim is now reimbursed for all malignancies (with the exception of chronic myeloid leukaemia and myelodysplastic syndrome) treated with cytotoxic chemotherapy, who either presented with neutropenia grade 4 in association with fever (>38°C) or with grade 4 neutropenia lasting for >5 days (secondary prevention). Primary prevention with pegfilgrastim is reimbursed in patients treated with cytotoxic chemotherapy for all malignancies (with the exception of chronic myeloid leukae-

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Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

TABLE 1. Phase I/II trials with alectinib.

		NP28673	NP28761
N		138	87
ORR (IRC)		50.8%	52.2%
	95 % CI	41.6-60.0	39.7-64.6
ORR (IRC) in patient pretreated with chemotherapy		44.8%	
	95 % CI	34.6-55.3	
DOR (IRC)	Median (months)	15.2	14.9
	95 % CI	11.2-24.9	6.9-NE
PFS (IRC)	Median (months)	8.9	8.2
	95 % CI	5.6-12.8	6.3-12.6

CI: confidence interval; IRC: independent review committee; NE: not estimable;
ORR: overall response rate; DOR: duration of response; PFS: progression-free survival.

mia and myelodysplastic syndrome) when the risk of febrile neutropenia is >20% or >10% in the presence of patient- or tumour-related risk factors, or when dose-dense or dose-intense regimens are used, or in order to avoid dose reductions or dose delays in patients treated with curative intent or with first-line treatment for metastatic disease.

RITUXIMAB (MABTHERA®)

Since January 1st, 2018, new reimbursement criteria are available for rituximab (MabThera®).

Rituximab (MabThera) is reimbursed if it is administered in the context of a serious condition that affects the life prognosis and for which the physician-specialist responsible for the treatment bases oneself on scientifically valid data that are widely recognised. Moreover, the scientific data in question can be found in international recommendations from scientific associations that explicitly accept the use of rituximab in the intended indication. New reimbursement criteria apply to the following indications:

- A hemato-oncological condition
- A serious immune disease
- Haemophilia
- A patient who has been transplanted

The reimbursement is allowed on the basis of an electronic request via the eHealth platform.

REGORAFENIB (STIVARGA®)

Regorafenib (STIVARGA®) is reimbursed for the treatment of patients with a hepatocellular carcinoma progressing despite sorafenib or intolerant for sorafenib. Regorafenib has been evaluated in randomised, double-blind, placebo-controlled phase III study (RESORCE) in which 573 patients were randomly assigned 2:1 to receive either regorafenib 160 mg/day plus Best Supportive Care (BSC) or matching placebo plus BSC. The primary endpoint was OS.[4] Efficacy data are summarised in *Table 2*.

ATEZOLIZUMAB (TECENTRIQ®)

Atezolizumab (Tecentriq®) as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq.

Approval by the European Medicines Agency (EMA) for patients with UC was based on the outcome of IMvigor210 (GO29293), a single-arm trial in previously untreated UC patients who are ineligible for cisplatin therapy or have previously been treated with chemotherapy.[5]

IMvigor210 enrolled a total of 438 patients in two cohorts: 119 patients (cohort 1) who were ineligible or unfit for cisplatin-based chemotherapy or had disease progression at least twelve months after treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen and 310 patients (cohort 2) who received at least one platinum-based chemotherapy regimen for locally advanced or metastatic UC or had disease progression within twelve months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen.

The primary efficacy endpoint for cohort 1 was confirmed objective response rate (ORR) as assessed by an independent review facility (IRF) using RECIST v1.1.

The primary analysis was performed when all patients had

TABLE 2. Regorafenib in HCC.

		Regorafenib	Placebo
OS			
	median (months)	10,6	7,8
	95 % CI	9,1-12,1	6,3-8,8
	HR	0,62	
	95 % CI	0,50-0,78	
	p	< 0,0001	
PFS			
	median (months)	3,1	1,5
	95 % CI	2,8-4,2	1,4-1,6
	HR	0,45	
	95 % CI	0,37-0,56	
	p	< 0,0001	
TTP			
	median (months)	3,2	1,5
	95 % CI	2,9-4,2	1,4-1,6
	HR	0,44	
		0,36-0,54	
	p	< 0,0001	
ORR		11%	4%
	p	0,0047	
	CR	1%	0
	PR	10%	4%
	SD	54%	32%
DCR		65%	36%
	p	< 0,0001	

OS: overall survival; PFS: progression-free survival; ORR: overall response rate; TTP: time to progression; DCR: disease control rate.

at least 24 weeks of follow-up. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI 18 9.3-40.0) in patients with PD-L1 expression ≥5%, 18.8% (95% CI 10.9, 29.0) in patients with PD-L1 expression ≥1%, and 19.3% (95% CI 12.7, 27.6) in all comers. Overall survival (OS) was not mature and median OS for all patient subgroups and in all comers was 10.6 months. An updated analysis was performed with a median duration of survival follow-up of 17.2 months. Overall response rate by IRF-assessed RECIST v1.1 was 28.1% (95% CI 13.8-46.8) in patients with PD-L1 expression ≥5%, 23.8% (95% CI 15.0-34.6) in patients with PD-L1 expression ≥1%, and 22.7% (95% CI 15.5-31.3) in all comers. Medina OS was 12.3 months (95% CI 6.0-NE), 14.1 months (95% CI 9.2-NE), and 15.9 months (95% CI 10.4-NE), respectively. One-year OS was 52.4%, 54.8%, and 57.2%, respectively. In cohort 2, the co-primary efficacy endpoints were confirmed IRF-assessed ORR per RECIST v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria. At the time of analysis after a median follow-up of 21.1 months, the confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI 19.5, 37.9) in patients with PD-L1 expression ≥5%, 19.3% (95% CI 14.2- 25.4) in patients with PD-L1 expression ≥1%, and 15.8% (95% CI 11.9, 20.4) in all comers. The confirmed ORR per investigator-assessed mRECIST was 29.0% (95% CI 20.4-38.9) in patients with PD-L1 expression ≥5% 23.7% (95% CI 18.1-30.1) in patients with PD-L1 expression ≥1%, and 19.7% (95% CI 15.4-24.6) in all comers. The 1-year OS rate was 37% in all comers.[5]

In **IMvigor211** (GO29294), 931 patients were randomly assigned 1:1 to receive either atezolizumab 1200 mg every three weeks or investigator's choice chemotherapy (ICC: vinflunine 320 mg/m² every three weeks, paclitaxel 175 mg/m² every three weeks, or docetaxel 75 mg/m² every three weeks) (*Table 3*).[6]

TABEL 3: Randomised phase III trials with anti-PD(L)1 in urothelial cancer

			KEYNOTE-045		IMvigor211			
					ITT		IC2/3	
			Pembrolizumab	ICC	Atezolizumab	ICC	Atezolizumab	ICC
N			270	272	467	464	116	118
n	paclitaxel		NA	31%	NA	33%		
	docetaxel		NA	31%	NA	12%		
	vinflunine		NA	32%	NA	55%		
Age	median		67	65	67	67	67	67
	range		29-88	26-84	33-88	31-84	43-88	36-84
Male			74.1%	74.3%	76%	78%	70%	81%
ECOG	0		44.1%		47%	45%	53%	48%
	1		53.0%	39.0%	53%	55%	47%	52%
	2		0.7%	1.5%				
Interval since last treatment < 3 months			38.3%	38.4%	34%	34%	30%	36%
Visceral metastases					77%	77%	67%	69%
Liver metastases					30%	28%	24%	25%
HB< 10g/dl			16.4%	16.5%	14%	16%	15%	16%
Risk factors								
	0				31%	30%	38%	35%
	1				46%	45%	43%	41%
	2				18%	21%	14%	21%
	≥3		16.7%	16.5%	5%	4%	5%	3%
Never smoker			38.7%	30.9%	30%	26%	30%	27%
Most recent prior therapy								
	(Neo)adjuvant		11.5%	19.5%	28%	26%	37%	35%
	First line		67.8%	57.7%	53%	56%	47%	50%
	Second line		20.4%	22.1%	17%	16%	16%	15%
PD-L1 CPS,I								
	≤ IC2/3				74.6%	75.2%	NA	NA
	< 10 %		68.9%	64.7%			NA	NA
Median FU			14.1 months		17 months			
Overall survival								
	median		10.3*	7.4*	8.6	8.0	11.1*	10.6*
	95 % CI		8.0-11.8	6.1-8.3	7.8-9.6	7.2-8.6	8.6-15.5	8.4-12.2
	HR		0.73		0.85		0.87	
		95 % CI	0.59-0.91		0.73-0.99		0.63-1.21	
	p		0.002		0.0378		0.41	
	12-month		43.9%	30.7%	39.2%	32.4%		
Progression-free survival								
	median		2.1	3.3	2.1	4.0	2.4	4.2
	95 %CI		2.0-2.2	2.3-3.5	2.1-2.2	3.4-4.2	2.1-4.2	3.7-5.0
	HR		0.98					
		95% CI	0.81-1.19					
		p	0.42					
ORR								
	%	21.1%	11.4%		13.4%	13.4%	23.0%	21.6%
	95 %CI	16.5-26.5	7.9-15.8		10.5-16.9	10.5-16.9	15.6-31.9	14.5-30.2
	p	0.001						
Duration of response								
	median				21.7	7.4	15.9	8.3
	95 % CI				13.0-21.7	6.1-10.3	10.4-NE	5.6-13.2

Pembrolizumab 200 mg every 3 weeks

ICC: paclitaxel 175 mg/m², docetaxel 75 mg/m², or vinflunine 320 mg/m² every 3 weeks

N: number of patients; ORR: overall response rate; FU: follow-up; CI: confidence interval

Atezolizumab 1200 mg every 3 weeks

At the time of analysis, median follow-up was seventeen months. IMvigor211 failed to meet its primary endpoint (OS). Atezolizumab did not demonstrate a statistically significant survival benefit compared to ICC in patients with previously treated, locally advanced or metastatic UC. Per the pre-specified hierarchical testing order, the IC2/3 population was tested first, with an OS HR of 0.87 (95% CI 0.63-1.21; median OS of 11.1 *vs.* 10.6 months for atezolizumab and ICC, respectively) and a stratified log-rank p-value of 0.41.

As a consequence, no formal tests of statistical significance could be performed for OS in the IC1/2/3 or all comer populations, and results of those analyses should be considered exploratory. In the all comer population, median OS was 8.6 months (95% CI 7.8-9.6) with atezolizumab versus 8.0 months (95% CI 7.2-8.6) with a HR of 0.85 (95% CI 0.73-0.99; p=0.0378). One-year OS rates were 39.2% and 32.4%, respectively.

Median investigator-assessed PFS (RECIST v1.1) was 2.1 months (95% CI 2.1-2.2) with atezolizumab versus 4.0 months (95% CI 3.4-4.2) with a HR of 1.1 (95% CI 0.95-1.26). Investigator-assessed ORR (RECIST v1.1) was 13.4% in both treatment arms. Median duration of response was 21.7 months (95% CI 13.0-21.7) and 7.4 months (95% CI 6.1-10.3), respectively.[6]

Approval for NSCLC is based on the results of **OAK (GO28915)** in which 1,225 patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen were randomly assigned 1:1 to receive either atezolizumab 1200 mg fixed dose or docetaxel 75 mg/m² administered every three weeks.

The primary efficacy endpoint was OS. At the time of analysis, median follow-up was 21 months. Median OS was 13.8 months (95% CI 11.8-15.7) with atezolizumab and 9.6 months (95% CI8.6-11.2) with docetaxel. The hazard ratio was 0.73 (95% CI 0.62-0.87; p=0.0003). Survival rates at twelve and eighteen months were 55% and 40% with atezolizumab and 41% and 27% with docetaxel, respectively. Median investigator-assessed PFS (RECIST v1.1) was 2.8 months (95% 2.6-3.0) with atezolizumab and 4.0 months (95% CI 3.3-4.2) with docetaxel, respectively with a HR of 0.95 (95% CI 0.82-1.1. Investigator-assessed ORR (RECIST v1.1) was 14% (95% CI 10.5-17.3) and 13% (10.3-17.0), respectively. Median duration of response was 16.3 months (95 % CI 10.0-NE) and 6.2 months (95% CI 4.9-7.6), respectively.[7]

POPLAR (GO28753) is a randomised phase II trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy in which 287 were randomised 1:1 to receive either 1200 mg fixed dose or docetaxel 75 mg/m² administered every three weeks. After a median follow-up of 22 months, median OS was 12.6 months in patients treated with atezolizumab versus 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI 0.52, 0.92). ORR was 15.3% *vs.* 14.7% and median DOR was 18.6 months *vs.* 7.2 months for atezolizumab *vs.* docetaxel, respectively.[8]

PALBOCICLIB (IBRANCE®)

Palbociclib (Ibrance®) is reimbursed in combination

> with a non-steroidal aromatase inhibitor in women

- with hormone receptor positive, HER2-negative locally advanced or metastatic breast cancer after prior adjuvant hormonal treatment with tamoxifen and who present with a recurrence during or within twelve months after adjuvant therapy,
- with symptomatic hormone receptor positive, HER2-negative locally advanced or metastatic breast cancer, who received prior adjuvant hormonal treatment and present with a recurrence after at least twelve months after adjuvant therapy and
- with *de novo* symptomatic hormone receptor positive, HER2-negative locally advanced or metastatic breast cancer.

> in combination with fulvestrant in women with a non-steroidal aromatase inhibitor in women

- with hormone receptor positive, HER2-negative locally advanced or metastatic breast cancer who have received prior hormonal therapy for locally advanced or metastatic disease and
- with hormone receptor positive, HER2-negative locally advanced or metastatic breast cancer who received prior adjuvant treatment with an aromatase inhibitor presenting with a recurrence during or within twelve months after adjuvant therapy.

Approval and reimbursement for the combination of palbociclib and a non-steroidal aromatase inhibitor are based on the outcome of the PALOMA-2 trial (BJMO 2018;12:34).

Approval and reimbursement for the association of palbociclib and fulvestrant are based on the outcome of PALOMA-3 in which 521 patients were randomised 2:1 to palbociclib plus fulvestrant or placebo plus fulvestrant. The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST 1.1. The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events; the results crossed the pre-specified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. Median PFS was 11.2 months (95% CI 9.5-12.9) with pal-

bociclib and 4.6 months (95% CI 3.5-5.6) with placebo (HR .497; 95% CI 0.398-0.620; p<0.000001). Overall response rates were 26.2% (95% CI 21.7-31.2) and 13.8% (95% CI 9.0-19.8), respectively.[9]

ANTI-PD(L)1 AS OF MARCH 1ST, 2018

Nivolumab (Opdivo®) is reimbursed for the treatment of

- advanced (unresectable or metastatic) melanoma (as monotherapy or in combination with ipilimumab)
- locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults
- advanced renal cell carcinoma after prior therapy in adults
- relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin
- Squamous Cell Cancer of the Head and Neck (SCCHN) in adults progressing on or after platinum-based therapy
- locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Atezolizmab (Tecentriq®) is reimbursed as monotherapy for patients with

- locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible
- locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy.

Pembrolizumab (Keytruda®) is reimbursed as monotherapy

- for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in 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
- for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy or who are not eligible for cisplatin-containing chemotherapy.

BEVACIZUMAB (AVASTIN®)

The reimbursement criteria for bevacizumab (Avastin®) in colorectal cancer have been thoroughly modified. Avastin is now reimbursed in patients with metastatic colorectal cancer when is administered in association with a 5-fluorouracel or capecitabine containing regimen and when it is used according to the summary of product characteristics.

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