Nivolumab (Opdivo®) in combination with cabozantinib (Cabometyx®) for the first-line treatment of patients with advanced renal cell carcinoma (RCC)

General information

Drug description [1]	Indication [2]
❖ Nivolumab is a programmed death 1 [PD-1] immune checkpoint inhibitor antibody. ❖ Cabozantinib is a small-molecule inhibitor of tyrosine kinases.	Nivolumab in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced RCC.

Current treatment [3]

The following treatment options for first-line metastatic RCC are recommended by NICE:

- ❖ Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG performance status of 0 or 1.
- ❖ Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic RCC. People who are currently being treated with bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for advanced and/or metastatic RCC should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

Regulatory status

EMA

Nivolumab (Opdivo®)

Approval status for this indication: On 25 February 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®. The CHMP adopted an extension to an existing indication as follows:

- ❖ Opdivo® in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced RCC.

Other indications: Nivolumab is indicated in

- ❖ Melanoma:
  - as monotherapy or in combination with ipilimumab 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.
- ❖ Adjuvant treatment of melanoma:
  - as monotherapy 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 cancer (NSCLC)
  - in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation.
  - as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.
- ❖ RCC:
  - as monotherapy for the treatment of advanced RCC after prior therapy in adults.
  - in combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.

FDA

Approval status for this indication: On 22 January 2021, the FDA approved the combination of nivolumab (Opdivo®) and cabozantinib (Cabometyx®) as first-line treatment for patients with advanced RCC.

Other indications:

Nivolumab is indicated for the treatment of:

- ❖ Melanoma
  - patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
  - patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- ❖ NSCLC
  - adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, as first-line treatment in combination with ipilimumab.
  - adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
- ❖ Malignant Pleural Mesothelioma
  - adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.
- ❖ RCC
  - patients with intermediate or poor risk advanced RCC, as a first-line treatment in combination with ipilimumab.
  - patients with advanced RCC who have received prior anti-angiogenic therapy.
  -

- ❖ Classical Hodgkin lymphoma (cHL)
  - as monotherapy for the treatment of adult patients with relapsed or refractory cHL after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.
- ❖ Squamous cell cancer of the head and neck (SCCHN)
  - as monotherapy for the treatment of recurrent or metastatic SCCHN in adults progressing on or after platinum-based therapy.
- ❖ Urothelial carcinoma
  - as monotherapy 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)
  - as monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.
- ❖ Malignant pleural mesothelioma (MPM)
  - in combination with ipilimumab isfor the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.
- ❖ Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)
  - in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair-deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Cabozantinib (Cabometyx®)

Approval status for this indication: On 25 February 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Cabometyx®. The CHMP adopted an extension to an existing indication as follows:

- ❖ Cabometyx® is indicated as **monotherapy** for the treatment of advanced RCC:
  - in treatment-naïve adults with intermediate or poor risk.
  - in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.
- ❖ Cabometyx®, in combination with nivolumab, is indicated for the first-line treatment of advanced RCC in adults.

Other indications: Cabozantinib is indicated in

- ❖ Hepatocellular Carcinoma (HCC):
  - as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib.

✓ **Medicine under additional monitoring**

- ❖ cHL
  - adult patients with cHL that has relapsed or progressed after (accelerated approval) :
    - o autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
    - o 3 or more lines of systemic therapy that includes autologous HSCT.
- ❖ SCCHN
  - patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy.
- ❖ Urothelial Carcinoma
  - patients with locally advanced or metastatic urothelial carcinoma who (accelerated approval):
    - o have disease progression during or following platinum-containing chemotherapy.
    - o have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- ❖ CRC
  - adult and paediatric (12 years and older) patients with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab (accelerated approval).
- ❖ HCC
  - patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab (accelerated approval).
- ❖ Oesophageal Squamous Cell Carcinoma (ESCC)
  - patients with completely resected oesophagal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).
  - patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.
- ❖ Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
  - patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and oesophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Cabozantinib (Cabometyx®) is indicated for the treatment of

- ❖ patients with advanced RCC.
- ❖ patients with HCC who have been previously treated with sorafenib.

- ✓ **Fast track review** (nivolumab application)
- ✓ **Priority review** (nivolumab and cabozantinib application)

Costs

24 ml **Opdivo®** concentrate for solution for infusion 10 mg/ml = **€ 3,432.00** (ex-factory price) [9]
30 **Cabometyx®** tablets 40 mg = **€ 5,948.80** (ex-factory price) [9]

CheckMate 9ER patients of the nivolumab-plus-cabozantinib group received nivolumab IV at a dose of 240 mg every 2 weeks plus cabozantinib (orally, 40 mg once daily); median duration of treatment was 13.3 months [1]. According to this dosing regimen, one month of treatment would cost approx. € 12,812.80.

Study characteristics [1, 10-12]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 9ER, CA2099ER NCT03141177	651	Nivolumab IV (240 mg every 2 weeks), + cabozantinib (orally, 40 mg once daily)	Sunitinib orally, 50 mg once daily for 4 weeks, followed by 2 weeks off (6-week cycle)	PFS by BICR	phase 3, randomized, open-label trial	-	Bristol Myers Squibb and others	[1]

Efficacy (I vs. C)

Median PFS (at a median follow-up for OS of 18.1 months): 16.6 months (95% CI, 12.5-24.9) vs. 8.3 months (95% CI, 7.0-9.7); HR 0.51, 95% CI, 0.41-0.64; p<0.001
Probability of PFS at 12 months: 57.6% (95% CI, 51.7-63.1) vs. 36.9% (95% CI, 31.1-42.8).
Probability of OS at 12 months: 85.7% (95% CI, 81.3-89.1) with nivolumab plus cabozantinib vs. 75.6% (95% CI, 70.5-80.0); HR for death, 0.60; 98.89% CI, 0.40-0.89; p = 0.001.
Median OS: not reached in either group
Objective response according to independent review: 55.7% (95% CI, 50.1-61.2) vs. 27.1% (95% CI, 22.4-32.3); p<0.001)
Complete response: in 8.0% vs. 4.6%
Median time to response: 2.8 months vs. 4.2 months
Median duration of response: 20.2 months vs. 11.5 months
Probability of **ongoing response at 12 months:** 71.1% vs. 40.9%
QoL:

- The mean (±SD) FKSI-19 total scores at baseline were similar in the two groups (58.7±10.6 with nivolumab plus cabozantinib and 58.4±9.9 with sunitinib);
- The percentage of patients who completed the FKSI-19 questionnaire was more than 90% in both groups at baseline, and the percentage was at least 80% at all subsequent assessments during treatment with sufficient data (≥10 patients) through at least week 91 in both groups.
- QoL was maintained over time with nivolumab plus cabozantinib, whereas a consistent deterioration from baseline was reported with sunitinib.
- Disease-related symptoms as measured by the FKSI-DRS subscale improved from baseline in patients in the nivolumab-plus-cabozantinib group, whereas patients in the sunitinib group had a decline from baseline after week 7 through week 91.
- The between-group differences were significant (p<0.05) at all time points except week 7 for the FKSI-19 total score and week 79 for the FKSI-DRS score.

Safety (I vs. C)

Grade ≥3 AEs: n=241/320 (75.3%) vs. n=226/320 (70.6%)
TRAEs grade ≥ 3: n=194/320 (60.6%) vs. n=163/320 (50.9%)
Death[1]: n=1/320 (0.3%) vs. n=2/320 (0.6%)
Discontinuation[2]: n=63/320 (19.7%) vs. n=54/320 (16.9%)

ESMO-MCBS version 1.1 [13]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	PFS: +8.3	PFS: +8.3	0.51 (0.41-0.64)	HR≤0.65 AND gain ≥1.5 months	3	-	Improved QoL	+1	4
Adapted	NC	2b	PFS: +8.3	PFS: +8.3	0.51 (0.41-0.64)	HR≤0.65 AND gain ≥1.5 months	3	-	Improved QoL	+1	4

Risk of bias (study level) [14]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	No, open-label	unclear[3]	yes[4]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, BICR=blinded independent central review, C=comparator, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRT=chemoradiotherapy, dMMR=mismatch repair deficient, ECOG=Eastern Cooperative Oncology Group, EGFR=endothelial growth factor receptor, EMA=European Medicines Agency,

[1] 1 death was considered by investigators to be treatment-related with nivolumab plus cabozantinib (small-intestine perforation), and 2 deaths were considered to be treatment-related with sunitinib (pneumonia and respiratory distress in one patient each).
[2] Discontinuation due to AE(s)
[3] CheckMate 9ER trial is ongoing until May 2024.
[4] The trial was designed by the authors in collaboration with the sponsor and partner. A medical writer employed by the sponsor assisted with the preparation of the manuscript.

ESCC=esophageal squamous cell carcinoma, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FKSI-19= National Comprehensive Cancer Network 19-item Functional Assessment of Cancer Therapy–Kidney Symptom Index, FKSI-DRS= FKSI 9-item subset of disease-related symptoms, HCC=hepatocellular carcinoma, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, Int.=intention, IV=intravenous, MG=median gain, MPM=malignant pleural mesothelioma, MSI-H= microsatellite instability-high, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, OSCC= oesophageal squamous cell carcinoma, OS=overall survival, PD-1=programmed death 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, SCCHN=squamous cell cancer of the head and neck, SD=standard deviation, ST=standard treatment, TRAE=treatment-related adverse event, VEGF=vascular endothelial growth factor

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