Nivolumab (Opdivo®) in combination with cisplatin and gemcitabine for the first-line treatment of unresectable or metastatic urothelial carcinoma

General information

Drug description [1]

Nivolumab (Opdivo®) is an antibody directed against programmed death 1 (PD-1).

Indication [2]

Nivolumab (Opdivo®) in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

Incidence [3]

In Austria, in 2022, a total of 1,247 persons were newly diagnosed with bladder cancer. The age-standardised[1] incidence rate was 22.3 per 100,000 men and 6.3 per 100,000 women.

Current treatment [4]

The Onkopedia recommendations for drug-based tumour therapy in patients with metastatic bladder cancer are displayed in the Appendix, Figure 1.

Regulatory status

EMA [2]	FDA [5, 6]
Approval status for this indication: On 25 April 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Opdivo®. The CHMP adopted a new indication as follows: ❖ Opdivo® in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. **Other indications**: Opdivo® is indicated: ❖ as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older. 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. ❖ as monotherapy for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. ❖ in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumours have no sensitising EGFR mutation or ALK translocation.	**Approval status for this indication**: On 6 March 2024, the FDA approved nivolumab (Opdivo®), in combination with cisplatin and gemcitabine for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. ✓ Priority review **Other indications**: Opdivo® is indicated for the treatment of: ❖ adult and paediatric (12 years and older) patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab. ❖ for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. ❖ adult patients with resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy. ❖ adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab. ❖ adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.

[1] European Standard Population 2013.

- as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.
- in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.
- in combination with ipilimumab for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.
- as monotherapy is indicated for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults.
- in combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.
- in combination with cabozantinib for the first-line treatment of adult patients with advanced RCC.
- as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin.
- as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy.
- as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
- as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.
- in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) after prior fluoropyrimidine-based combination chemotherapy.
- in combination with ipilimumab for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell PD-L1 expression ≥ 1%.
- in combination with fluoropyrimidine and platinum-based combination chemotherapy for the first line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD L1 expression ≥ 1%.
- as monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.
- as monotherapy for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction (GEJ) cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.
- in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative

- adult patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo®.
- adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.
- adult patients with intermediate or poor risk advanced RCC, as a first-line treatment in combination with ipilimumab.
- adult patients with advanced RCC, as a first-line treatment in combination with cabozantinib.
- adult patients with advanced RCC who have received prior anti-angiogenic therapy.
- adult patients with cHL that has relapsed or progressed after (this indication is approved under accelerated approval based on overall response rate and duration of response):
    - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
    - 3 or more lines of systemic therapy that includes autologous hematopoietic stem cell transplantation.
- adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.
- adjuvant treatment of adult patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection of urothelial carcinoma.
- adult patients with locally advanced or metastatic urothelial carcinoma who:
    - have disease progression during or following platinum-containing chemotherapy
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- adult and paediatric (12 years and older) patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab (this indication is approved under accelerated approval based on overall response rate and duration of response).
- adult patients with hepatocellular carcinoma who have been previously treated with sorafenib in combination with ipilimumab (this indication is approved under accelerated approval based on overall response rate and duration of response).
- adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy.
- adult patients with unresectable advanced or metastatic OSCC as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.
- adult patients with unresectable advanced or metastatic OSCC as first-line treatment in combination with ipilimumab.
- adult patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based chemotherapy.
- adult patients with advanced or metastatic gastric cancer, GEJ, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score ≥ 5.	

Manufacturer

Opdivo® is manufactured by Bristol-Myers Squibb.

Costs [7]

4 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 572.00 (ex-factory price)
10 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 1,430.00 (ex-factory price)

Posology [8]

- If specified in the indication, patient selection for treatment with Opdivo® based on the tumour expression of PD-L1 should be confirmed by a validated test.

Warnings and precautions [8]

- **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- **Assessment of PD-L1 status**
  - When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.
- **Immune-related adverse reactions**
  - When nivolumab is administered in combination, refer to the Summary of product characteristics of the other combination therapy agents prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Immune-related adverse reactions have occurred at similar frequencies when Opdivo® was administered in combination with cabozantinib relative to nivolumab monotherapy. Therefore, the guidance below for immune-related adverse reactions applies to the Opdivo® component of the combination, except where specifically noted. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications. Immune-related adverse reactions affecting more than one body system can occur simultaneously.
  - Cardiac and pulmonary adverse reactions, including pulmonary embolism have also been reported with combination therapy. Patients should be monitored continuously for cardiac and pulmonary adverse reactions, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab, should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.
  - Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.
  - An adequate evaluation should be performed for suspected immune-related adverse reactions to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1-month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.
  - Nivolumab or nivolumab combined with ipilimumab should not be resumed while the patient receives immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
  - Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.
  - For detailed information about immune-related pneumonitis, -colitis, -hepatitis, -nephritis, -endocrinopathies and -skin adverse reactions, please see Opdivo® Product Information.
- **Infusion reactions**
  - Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab. In case of a severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered.

- Patients with mild or moderate infusion reaction may receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

❖ **Disease-specific precautions[2]: Treatment of advanced urothelial carcinoma**

- Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of urothelial carcinoma. In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

❖ **Patients on controlled sodium diet**

- Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. This medicinal product contains 10 mg sodium per 4 mL vial, 25 mg sodium per 10 mL vial, 30 mg sodium per 12 mL vial or 60 mg sodium per 24 mL vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the World Health Organization recommended maximum daily intake of 2 g sodium for an adult.

❖ **Patient alert card**

- All prescribers of Opdivo® must be familiar with the physician information and management guidelines. The prescriber must discuss the risks of Opdivo® therapy with the patient. The patient will be provided with the patient alert card with each prescription.

Study characteristics [1, 9-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 901[3] NCT03036098	608 (1:1)	360 mg nivolumab IV + gemcitabine–cisplatin every 3 weeks for up to 6 cycles, followed by 480 mg nivolumab every 4 weeks for a maximum of 2 years	gemcitabine–cisplatin alone every 3 weeks for up to 6 cycles	OS + PFS	33.6 months (range, 7.4-62.4)	**ongoing[4]**, phase 3, multinational, open-label trial	PD-1	Bristol Myers Squibb and Ono Pharmaceutical	CheckMate 901 [1]

Inclusion criteria[5]	Exclusion criteria	Patient characteristics at baseline (n=304 vs. n=304)
❖ Signed written informed consent ❖ ≥18 years with histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra. Minor histologic variants (< 50% overall) are acceptable (TCC must be the dominant histology). ❖ Measurable disease by CT or MRI per RECIST 1.1 criteria. ❖ Prior systemic chemotherapy for metastatic or surgically unresectable urothelial carcinoma is not allowed.	❖ Active brain metastases or leptomeningeal metastases. ❖ There is no requirement for immunosuppressive doses of systemic corticosteroids for at least 2 weeks before study drug administration. ❖ Medical History and Concurrent Diseases ❖ Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast. ❖ Any severe or uncontrolled medical disorder that, in the investigator's opinion, may increase the risk associated with study participation or study drug administration, impair the	❖ Median age (range), years: 65 (32–86) vs. 65 (35–85) ❖ <65 years: 49.3% vs. 48.7% ❖ ≥65 years: 50.7% vs. 51.3% ❖ Female sex: 22.4% vs. 23.0% ❖ Race or ethnic group: • White: 69.4% vs. 74.0% • Asian: 24.7% vs. 20.7% • American Indian or Alaska native: 0.3% vs. 0.3% • Black: 0 vs. 0.7% • Other: 5.6% vs. 4.3%

[2] For further disease-specific precautions, please see Product Information.

[3] CheckMate 901 is performed in two parts: In the first part (results reported here), patients were assigned to receive either nivolumab plus gemcitabine–cisplatin (nivolumab combination) or gemcitabine–cisplatin alone; in the second part (ongoing), patients were assigned to receive either nivolumab plus ipilimumab or platinum-based chemotherapy. Each part of the trial had a separate determination of statistical power. Details regarding the trial design are provided in the protocol, available with the full text of this

[4] CheckMate-901 is currently ongoing; the estimated study completion date is 06/2028.

[5] For detailed in- and exclusion criteria, please see trial protocol.

❖ Participants ineligible for cisplatin-based chemotherapy will be defined by any one of the following criteria: • Impaired renal function (GFR > 30 but < 60 mL/min); • CTCAE version 4, ≥ Grade 2 hearing loss • CTCAE version 4, ≥ Grade 2 peripheral neuropathy • Cisplatin-ineligible patients will receive gemcitabine-carboplatin treatment. ❖ Participants eligible for cisplatin-based chemotherapy must exhibit adequate renal function as follows: • Serum creatinine ≤ 1.5 × ULN or GFR ≥ 30 mL/min or, if not available, by calculation using the Cockcroft-Gault formula. ❖ Participants must provide a fresh tumour biopsy from the disease site. ❖ ECOG PS 0 or 1 ❖ Adequate hematologic and liver function (using CTCAE v. 4) ❖ Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 24 hours prior to the start of study treatment and must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus 5 half-lives of study treatment, plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion. ❖ Women must not be breastfeeding. ❖ Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus 5 half-lives of the study treatment plus 90 days for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.	ability of the participant to receive protocol therapy, or interfere with the interpretation of study results. ❖ Participants must have recovered from the effects of major surgery requiring general anaesthetic or significant traumatic injury at least 14 days before randomisation or treatment assignment. ❖ Active, known or suspected autoimmune disease. ❖ Participants with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration. ❖ Uncontrolled adrenal insufficiency. ❖ NYHA Functional Classification of Heart Failure: Class III or Class IV ❖ ECOG PS ≥ 2 ❖ All toxicities attributed to prior anticancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. ❖ Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or completing QoL questionnaire. ❖ Known history of positive test for HIV or known AIDS. ❖ Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements. ❖ History of acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation. ❖ Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. ❖ Positive test for HBV sAg or hepatitis C virus RNA or hepatitis C antibody indicating acute or chronic infection. ❖ Allergies and Adverse Drug Reaction ❖ History of allergy or hypersensitivity to study drug components	❖ Geographic region: • United States: 6.2% vs. 6.9% • Europe: 44.1% vs. 46.7% • Asia: 23.7% vs. 20.1% • Other region: 26.0% vs. 26.3% ❖ ECOG PS score: • 0: 53.3% vs. 53.3% • 1: 46.1% vs. 46.7% • >1: 0.7% vs. 0 ❖ Tumour type at initial diagnosis: • Urinary bladder: 77.3% vs. 72.0% • Renal pelvis: 10.9% vs. 14.5% • Other: 11.8% vs. 13.5% ❖ Time from initial diagnosis: • Median (range); years: 0.51 (0–27.8) vs. 0.36 (0–23.9) • Distribution o <1 yr: 58.9% vs. 65.5% o ≥1 yr: 41.1% vs. 34.5% ❖ Histologic variant • None: 49.3% vs. 46.7% • Adenocarcinoma: 17.4% vs. 16.4% • Squamous-cell carcinoma: 6.6% vs. 7.6% • Micropapillary: 5.6% vs. 5.3% • Other: 20.4% vs. 23.4% • Not reported: 0.7% vs. 0.7% ❖ Disease stage: • Metastatic: 85.9% vs. 88.5% • Locally unresectable or nonmetastatic: 13.5% vs. 10.9% • Not reported: 0.7% vs. 0.7% ❖ Tumour PD-L1 expression: • ≥1%: 36.5% vs. 36.2% • <1%: 63.5% vs. 63.8% ❖ Liver metastasis: • Yes: 21.1% vs. 21.1% • No: 78.9% vs. 78.9%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Final analysis of the first part of CheckMate-901; median follow-up: 33.6 months:</u> **OS**: HR for death 0.78 (95% CI, 0.63-0.96; p=0.02)	**AEs of any cause**: 99.7% vs. 98.6% **AEs of grade ≥3**: 76.6% vs. 67.7%

Median OS: 21.7 months (95% CI, 18.6-26.4) vs. 18.9 months (95% CI, 14.7-22.4) **OS at 12 months**: 70.2% vs. 62.7% **OS at 24 months**: 46.9% vs. 40.7% **PFS according to central review**: HR for progression or death 0.72 (95% CI, 0.59-0.88; p=0.001) **Median PFS according to central review**: 7.9 months (95% CI, 7.6-9.5) vs. 7.6 months (95% CI, 6.1-7.8) **PFS at 12 months**: 34.2% vs. 21.8%, **PFS at 24 months**: 23.5% vs. 9.6% **PFS according to investigator assessment**: HR 0.70 (95% CI, 0.57-0.85) **Censoring of data for PFS because of subsequent anticancer therapy before disease progression**: 7.9% vs. 24.3% **Objective response according to central review**: 57.6% vs. 43.1% **Complete response**: 21.7% vs. 11.8% **Median time until either an objective response or a complete response**: 2.1 months in each treatment group **Median duration of response according to central review**: 9.5 months (95% CI, 7.6-15.1) vs. 7.3 months (95% CI, 5.7-8.9) **Median duration of complete response:** 37.1 months (95% CI, 18.1 to not estimable) vs. 13.2 months (95% CI, 7.3-18.4) **Subsequent systemic therapy administered**: 35.5% vs. 51.3%	**AEs of any grade that were deemed by the investigator to be related to a trial treatment**: 97.4% vs. 92.7% **AEs of grade ≥3 that were deemed by the investigator to be related to a trial treatment**: 61.8% and 51.7% **TRAE of grade 5 treatment-related adverse event**: n=1 (sepsis) vs. n=1 (acute kidney injury) **TRAEs of any grade leading to discontinuation**: 21.1% vs. 17.4% **TRAEs of grade ≥3 leading to discontinuation**: 11.2% vs. 7.6% **Any immune-mediated AE of any grade**: 29.3% vs. 0.7% **Any immune-mediated AE of grade ≥3**: 6.6% vs. 0

Patient-reported outcomes

- The change from baseline in HRQol was assessed according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) Global Health Status score.
- More than 90% of the patients in the two groups completed the EORTC QLQ-C30 survey at baseline.
- In the two groups, completion ranged from 78 to 86% through week 10, after which completion decreased to 40% in the nivolumab-combination group and to 66% in the gemcitabine–cisplatin group.
- The EORTC QLQ-C30 global health status was stable in the two groups with no change of more than 10 points in either direction through week 16.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	>12 months ≤24 months	OS: +2.8 months	0.78 (0.63-0.96)	HR 0.70 AND gain 1.5-<3 months	2	-	No significant benefit	-	2
Adapted	NC	2A	>12 months ≤24 months	OS: +2.8 months	0.78 (0.63-0.96)	HR >0.75 OR gain <1.5 months	1	+10.1% AEs of grade ≥3 that were deemed by the investigator to be related to a trial treatment	No significant benefit	-1[6]	0

Risk of bias (RCT) [13]

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 high risk	-	no high risk	unclear[7] unclear risk	yes[8] high risk	unclear

Ongoing trials [14]

[6] Toxicity adjustment.
[7] The CheckMate-901 trial is currently ongoing.
[8] The sponsors funded the trial, provided the trial drugs, and collaborated with the academic authors on the trial design and on the collection, analysis, and interpretation of the data. Medical writing support was funded by the sponsor.

NCT number/trial name	Description	Estimated study completion date
NCT03036098 / CheckMate 901	Please see above.	06/2026
NCT04637594 / IMAGINE	Duration of immune checkpoint therapy in locally advanced or metastatic urothelial carcinoma: A randomised phase 3 non-inferiority trial.	09/2030

Available assessments

- No assessments were identified via NICE, CDA-AMC, ICER, G-BA or NIHR.

Other aspects and conclusions

- In April 2024, the **CHMP adopted a new indication** for Opdivo® in combination with cisplatin and gemcitabine for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. In March 2024, the **FDA approved Opdivo®**, in combination with cisplatin and gemcitabine for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.
- **CheckMate 901 (NCT03036098)** is a phase 3, international, open-label, randomised trial (performed in two parts), assessing the efficacy, safety and patient-reported outcomes of adding nivolumab to gemcitabine-cisplatin in patients with advanced urothelial carcinoma. Patients with histologically confirmed unresectable or metastatic urothelial carcinoma involving the renal pelvis, ureter, bladder, or urethra, measurable disease according to RECIST version 1.1, and an ECOG PS score of 0 or 1 were eligible. Previous systemic chemotherapy for unresectable or metastatic urothelial carcinoma was not permitted.
- The primary outcomes of CheckMate 901 were OS and PFS; **OS was longer with nivolumab-combination** therapy than with gemcitabine–cisplatin alone (HR for death 0.78; 95% CI, 0.63 to 0.96; p= 0.02) and the median OS was 21.7 months vs. 18.9 months. **PFS was also longer with nivolumab-combination** therapy than with gemcitabine–cisplatin alone (HR for progression or death 0.72; 95% CI, 0.59 -0.88; p= 0.001).
- Patient-reported outcomes were evaluated, showing that **EORTC QLQ-C30 global health status was stable** in the two groups with no change of more than 10 points in either direction through week 16.
- The **original and adapted ESMO-MCBS** was applied, resulting in a **final adjusted magnitude of clinical benefit grade 2 and 1**, respectively.
- Due to the ongoing status of the trial, the **risk of bias was considered unclear**. However, the risk is increased by the open-label trial design and the involvement of the sponsor in trial design, collection, analysis and interpretation of the data.
- Beside CheckMate 901, one further phase 3 trial with nivolumab administration in patients with locally advanced or metastatic urothelial carcinoma was identified; this trial aims to find the correct duration of immune checkpoint therapy.
- More robust phase 3 data from a more homogenous patient population is required to determine the role of nivolumab addition t platinum-based chemotherapy in patients with advanced urothelial carcinoma.

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Abbreviations: AE=adverse event, AIDS=acquired immunodeficiency syndrome AJ=adjustment, ALK=anaplastic lymphoma kinase, C=comparator, CDA-AMC=Canada's Drug Agency, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CT=computed tomography, CTCAE= Common Terminology Criteria for Adverse Events, CRC=colorectal carcinoma, dMMR=deficient mismatch repair, ECOG PS= Eastern Cooperative Oncology Group performance-status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GEJ=gastroesophageal junction, GFR= glomerular filtration rate, HBV sAG=hepatitis B virus surface antigen, HER2= human epidermal growth factor receptor 2, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, IV=intravenous, MIUC=muscle invasive urothelial carcinoma, MRI=magnetic resonance imaging, MSI-H=microsatellite instability-high, n=number of patients, NICE=National Institute for Health Care Excellence, WOCBP=women of childbearing potential, NSCLC=non-small cell lung cancer, NYHA=New York Heart Association, OSCC=oesophageal squamous cell carcinoma, OS=overall survival, PD-1= programmed death 1, PD-L1=programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RCC=renal cell carcinoma, RECIST= Response Evaluation Criteria in Solid Tumors, RNA=ribonucleic acid, SAE=serious adverse event, SCCHN=squamous cell carcinoma of head and neck, ST=standard treatment, TCC= transitional cell carcinoma, TRAE=treatment-related adverse event

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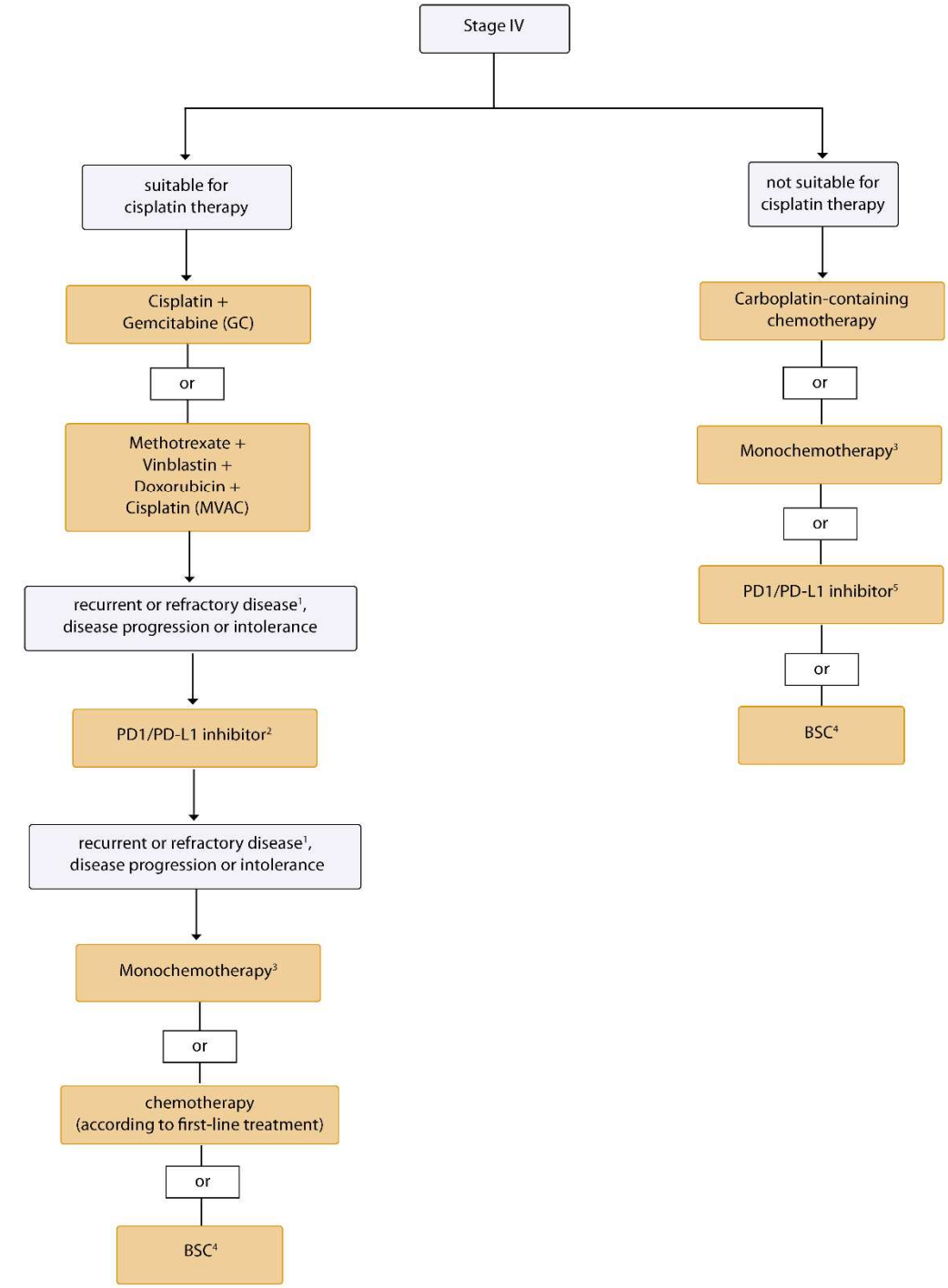
Appendix – Figure 1: Drug-based tumour therapy for patients with metastatic bladder cancer



Legend:

curative intention; palliative intention;

[1] If duration of remission is >6 months, repetition of first-line therapy provides an option, depending on tolerability.
[2] PD1/PD-L1 inhibitor: approved are atezolizumab, nivolumab, pembrolizumab
[3] Monochemotherapy: vinflunine, carboplatin, docetaxel, gemcitabine, paclitaxel
[4] BSC - Best Supportive Care
[5] PD1/PD-L1 inhibitor: if PD-L1 expression is positive (combined positive score, CPS): approved are pembrolizumab CPS ≥10%, atezolizumab PD-L1 ≥5%.