Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-056 Erdafitinib

Stand: Mai 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Erdafitinib
[zur Behandlung des fortgeschrittenen Urothelkarzinoms nach mindestens einer vorherigen Therapielinie mit einem PD-1-Receptor- oder PD-L-1-Inhibitor]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Enfortumab Vedotin: Beschluss vom 1. Dezember 2022 • Pembrolizumab: Beschluss vom 16. März 2018, in der Fassung der Änderungsbeschlüsse vom 2. August 2018, 20. Juni 2019 und 5. März 2020 • Atezolizumab: Beschluss vom 16. März 2018, in der Fassung der Änderungsbeschlüsse vom 2. August 2018 und 20. Juni 2019 • Nivolumab: Beschluss vom 21. Dezember 2017
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Erdafitinib N.N. Balversa	<u>Anwendungsgebiet laut Beratungsanforderung:</u> Erdafitinib als Monotherapie ist indiziert zur Behandlung erwachsener Patienten mit fortgeschrittenem Urothelkarzinom, die genetische Veränderungen des Fibroblasten-Wachstumsfaktor-Rezeptors 3 (FGFR3) aufweisen und die mindestens eine vorherige Therapielinie mit einem Programmed Cell Death-1-Receptor- oder Programmed Cell Death-Ligand-1-Inhibitor erhalten haben.
Cisplatin L01XA01 Generisch	Cisplatin Teva wird angewendet zur Behandlung des: • fortgeschrittenen oder metastasierten Harnblasenkarzinoms • […]
Doxorubicin L01DB01 Generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: • Systemische Therapie des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms • […] Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Methotrexat L01BA01 Generisch	Methotrexat medac 25 mg/ml Injektionslösung wird angewendet bei: • Harnblasenkarzinomen - in Kombination mit anderen zytotoxischen Arzneimitteln • […]
Gemcitabin L01BC05 Generisch	Gemcitabin ist in Kombination mit Cisplatin zur Behandlung des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms angezeigt.
Vinflunin L01CA05	Zur Monotherapie bei fortgeschrittenem oder metastasierendem Übergangszellkarzinom des Urothels bei erwachsenen Patienten, nach Versagen einer platinhaltigen Behandlung.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Javlor	Die Wirksamkeit und Sicherheit von Vinflunin in Patienten mit einem Performance Status≥ 2 wurden nicht untersucht.
Pembrolizumab L01FF02 Keytruda	Keytruda ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms nach vorheriger Platin-basierter Therapie bei Erwachsenen angezeigt.
Atezolizumab L01FF05 Tecentriq	Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC) nach vorheriger platinhaltiger Chemotherapie oder bei erwachsenen Patienten, die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden.
Nivolumab L01FF01 Opdivo	Opdivo ist als Monotherapie zur Behandlung des lokal fortgeschrittenen nicht resezierbaren oder metastasierten Urothelkarzinoms bei Erwachsenen nach Versagen einer vorherigen platinhaltigen Therapie indiziert.
Enfortumab vedotin L01FX13 Padcev	Padcev ist als Monotherapie angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Urothelkarzinom, die zuvor eine platinhaltige Chemotherapie und einen Programmed Death Receptor-1- oder Programmed Death Ligand-1-Inhibitor erhalten haben.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-056 (Erdafitinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	5. April 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CSS	Cancer-specific survival
ECRI	Emergency Care Research Institute
EMA	European Medicines Agency
EV	Enfortumab vedotin
FDA	U.S. Food and Drug Administration
FGFR	Fibroblast growth factor receptor
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IO	Immunotherapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
la/mUC	locally advanced or metastatic urothelial cancer
LoE	Level of Evidence
mAb	monoclonal antibody
MMAE	Monomethyl auristatin E
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death-Ligand 1
RNU	Radical nephroureterectomy
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SJS	Steven-Johnson syndrome
TEN	Toxic epidermal necrolysis
TRIP	Turn Research into Practice Database
UC	Urothelial carcinoma

UTUC	Upper urinary tract urothelial carcinoma
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit fortgeschrittenem Urothelkarzinom, die bestimmte genetische Veränderungen des Fibroblasten-Wachstumsfaktor-Rezeptors 3 (FGFR3) aufweisen und die mindestens eine vorherige Therapielinie mit einem Programmed Cell Death-1-Receptor- oder Programmed Cell Death-Ligand-1-Inhibitor erhalten haben.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Urothelkarzinom durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 08.12.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1297 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf wurden insgesamt 4 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine relevanten Cochrane reviews identifiziert werden.

3.2 Systematische Reviews

Annakib S et al., 2023 [2].

Quality of Life with Monoclonal Antibody Therapies for Locally Advanced or Metastatic Urothelial Carcinoma: A Systematic Review

Fragestellung

The aim of our systematic review was to describe changes in HRQoL global health and domain scores for patients with la/mUC treated with mAb therapies.

Methodik

Population:

- Patients with la/mUC treated in a metastatic setting were included

Intervention:

- Monoclonal Antibody Therapie

Komparator:

- keine Einschränkung

Endpunkte:

- HRQoL

Recherche/Suchzeitraum:

- systematic search in the MEDLINE updated on February 3, 2023

Qualitätsbewertung der Studien:

- Risk-of-Bias-2 (RoB2) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Insgesamt wurden 6 RCT eingeschlossen
- Für die Indikation der Synopse ist nur ein RCT (EV-301) und eine einarmige Studie (EV-201) relevant (und im Folgenden dargestellt).

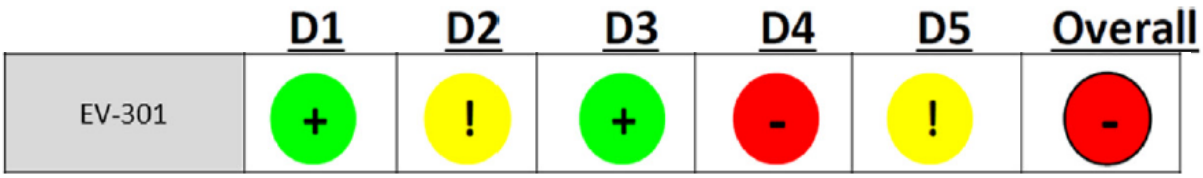
Charakteristika der Population/Studien:

Table 1 – The studies included in the review and data extracted

Study and design	Drug	CA	Pts (n)	Treatment efficacy outcomes	HRQoL tool	BTCR (%)	GHS change (SD)	Other HRQoL information
EV-201 [29,30] Phase 2, single arm	EV	NA	125	ORR 44% (95% CI 35.1–53.2%). mPFS 5.8 mo (95% CI 4.93–7.46) mOS 11.7 mo (95% CI 9.10–NR).	EORTC QLQ-C30, EQ-5D-3L	95	C3: 63 (20.8) C6: 65.2 (21.3) C9: 73.1 (16.8)	Mean score (SD) EQ-5D-3L utility: 0.80 (0.16) at BL, 0.81 (0.14) at C3, 0.83 (0.13) at C6, 0.84 (0.17) at C9 EQ-5D-VAS: 66.9 (20.5) at BL, 67.3 (19.2) at C3, 70.9 (25.0) at C9
EV-301 [6,31] Phase 3, open-label	EV	CTx	301	mPFS 5.55 mo (95% CI 5.32–5.82) mOS 12.88 mo (95% CI 10.58–15.21)	EORTC QLQ-C30	90	W12 scores: EV 2.8, CTx 5.0 (p = 0.2429)	Not reported

Atz = atezolizumab; BL = baseline; BSC = best supportive care; BTCR = baseline tool completion rate; C = cycle; CA = comparator arm; CI = confidence interval; CTx = chemotherapy; CTCAE: Common Terminology Criteria for Adverse Events; D = day; DOC = docetaxel; DSC = difference in score change; DVM = durvalumab; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Core 30; EQ-5D-5L: EuroQol-5Dimension-5Level; EQ-5D-3L: EQ-5D-3Level; EQ-5D-VAS: EQ-5D-Visual Analog Scale; EV = enfortumab vedotin; FACT-BI: Functional Assessment of Chronic Illness Therapy-Bladder; FBISI-18: Bladder Symptom Index-18; GHS = EORTC QLQ-C30 global health score; HADS: Hospital Anxiety Depression Scale; HRQoL = health-related quality of life; mOS = median overall survival; mPFS = median progression-free survival; mTTD = median time to deterioration; NA = not applicable; NR = not reached; ORR = overall response rate; PE = point estimate; Pembro = pembrolizumab; PRO-CTCAE: Patient Reported Outcomes-CTCAE; PROMIS: Patient Reported Outcomes Measurement Information System; Pts = patients; QLQ-BLM30: QLQ-Muscle Invasive Bladder Cancer-30; RMC = ramucirumab; SD = standard deviation; TCs = treatment cycles; TOI = Trial Outcome Index; W = week.

Qualität der Studien:



+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

Studienergebnisse:

3.4.2. Enfortumab vedotin

EV comprises an anti-NECTIN4 antibody conjugated to monomethyl auristatin E. EV-201 was a pivotal phase 2 study with two cohorts (cohort 1: EV after platinumbased chemotherapy and anti-PD-1/anti-PD-L1 treatment; cohort 2: EV after anti-PD-1/anti-PD-L1 in platinum-naïve or -ineligible patients) [29]. HRQoL in cohort 1 was evaluated using the EORTC QLQ-C30 and EQ-5D-3L instruments. A repeated-measures mixed model was used to test changes in PRO scores over time. Global health scores, the mean EQ- 5D-3L utility index, and EORTC QLQ-C30 functioning and VAS scores remained stable over time. However, the mean social functioning domain score improved from 73.5 (SD 27.8) at baseline to 86.1 (SD 21.1) at cycle 10. Symptom domain scores were stable over time. Sensitivity analyses with joint modeling accounting for missing data showed a possible improvement in global health score over time. Pain and fatigue symptom scores decreased (less symptomatic) after an objective response (post hoc analysis) [30].

EV-301, a phase 3 trial in patients previously treated with platinum salts and ICIs, assessed EV versus standard chemotherapy; the EORTC QLQ-C30 tool was administered [6,31]. Linear logistic regression models were used to analyze HRQoL scores. At week 12, the global health score was stable (mean change: 2.8 points). In the EV arm, patients reported a significant reduction in pain symptoms (EV: 5.62, standard chemotherapy: +0.11; adjusted

difference 5.73; p < 0.05) but worsening of appetite loss (EV: +8.55, standard chemotherapy: +1.26; adjusted difference 7.29; p < 0.05). Significantly more patients experienced improvements in 10 of the 15 domains, across all functioning and most symptom scores (pain, fatigue, dyspnea, constipation). Remarkably, the greatest difference in score improvement in comparison to chemotherapy was reported for pain (EV: 51.6%, standard chemotherapy: 28.8%; OR 2.76, 95% CI 1.81–4.22).

Anmerkung/Fazit der Autoren

Our review of nine studies demonstrated at least stable global health scores over time. Nevertheless, in RCTs with chemotherapy as treatment in the control arm, mAb treated patients had better HRQoL than patients treated with chemotherapy. Scores for several HRQoL symptom and function domains were improved with mAB therapy. HRQoL evolution is influenced by several factors related to treatment, tumor characteristics, and the patient's health condition. However, more research assessing HRQoL with mAb therapies for la/mUC is needed to draw strong conclusions, including well-designed real-life studies.

3.3 Leitlinien

Witjes JA et al., 2023 [4].

European Association of Urology (EAU)

EAU guidelines on muscle-invasive and metastatic bladder cancer

Zielsetzung/Fragestellung

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) have prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse werden nicht beschrieben; ein externes Begutachtungsverfahren / Review wird dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Für vorliegendes Updates der LL: Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 11th, 2021 and May 4th 2022

LoE

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

GoR

The strength rating forms draw on the guiding principles of the GRADE methodology but do not purport to be GRADE. These forms address a number of key elements namely:

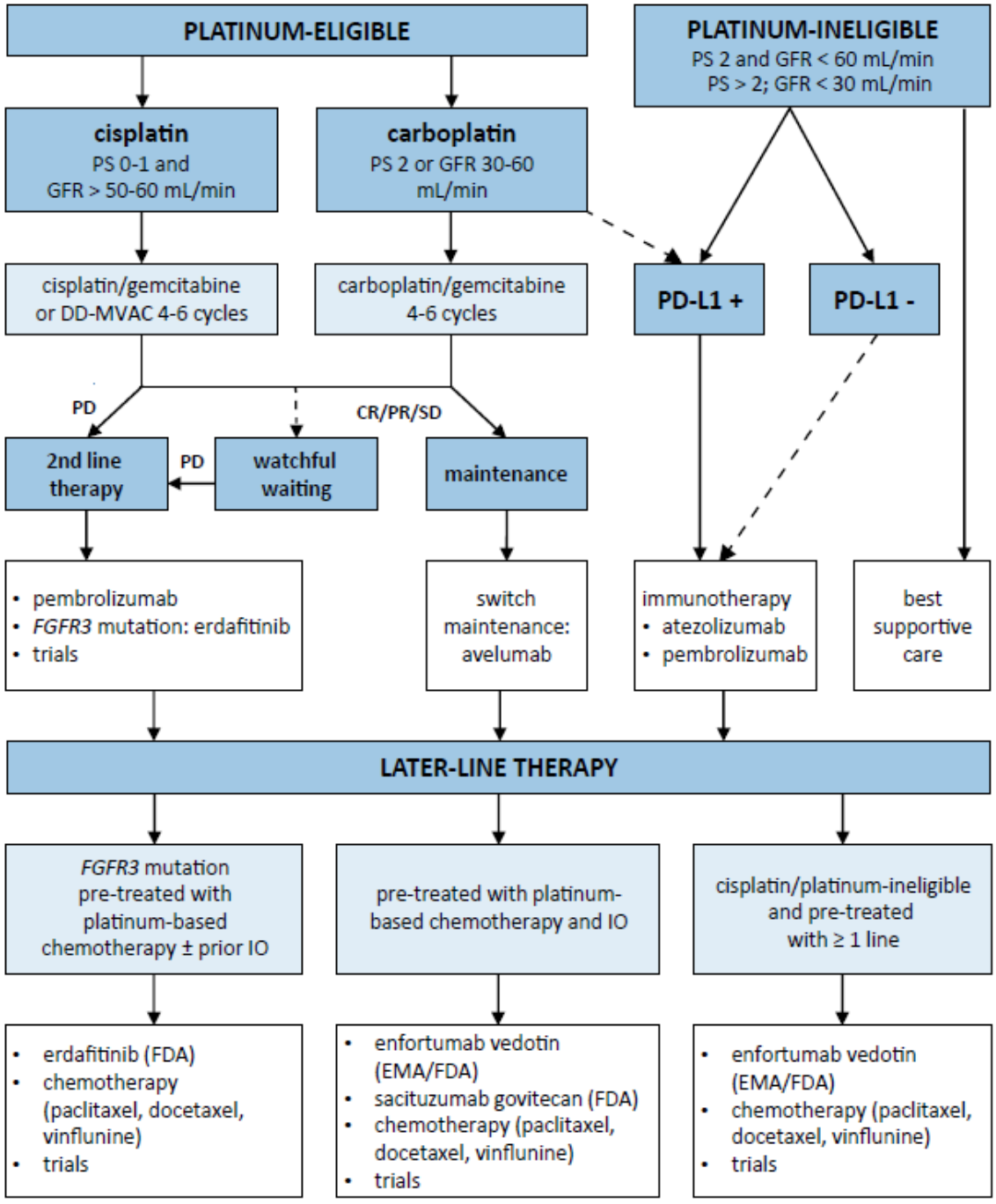
1. the overall quality of the evidence which exists for the recommendation, references used in this text are grade according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);

3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Zusammenfassung der Empfehlungen

Figure 7.2: Flow chart for the management of metastatic urothelial cancer*



**Treatment within clinical trials is highly encouraged.*
----- Dotted line: represents a treatment option which is not approved worldwide.
BSC = best supportive care; CR = complete response; DD-MVAC = dose dense methotrexate vinblastine doxorubicin cisplatin; EMA = European Medicines Agency; EV = enfortumab vedotin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PR = partial response; PS = performance status; SD = stable disease.

Recommendations	Strength rating
First-line treatment for platinum-fit patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine.	Strong
In patients achieving stable disease, or better, after first-line platinum-based chemotherapy, use maintenance treatment with PD-L1 inhibitor avelumab.	Strong
First-line treatment in patients unfit for platinum-based chemotherapy	
Consider checkpoint inhibitors pembrolizumab or atezolizumab in case of high PD-L1 expression (for definitions see text).	Weak
Second-line treatment	
Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease.	Strong
Further treatment after platinum- and immunotherapy	
Offer antibody drug conjugate enfortumab vedotin as monotherapy to patients with advanced or metastatic UC pre-treated with platinum and immunotherapy.	Strong
Offer treatment in clinical trials testing novel drugs (e.g. sacituzumab govitecan); or in case of patients with *FGFR3* alterations, *FGFR* tyrosine kinase inhibitors.	Strong
Evaluate for *FGFR2/3* genetic alterations for the potential use of erdafitinib in patients with locally-advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy).	Weak

GC = gemcitabine plus cisplatin; FGFR = fibroblast growth factor receptor; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin.

Zusammenfassung der Level of Evidenz

Summary of evidence	LE
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-L1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b
PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-L1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-L1 status).	1b
The combination of chemotherapy plus pembrolizumab or atezolizumab and the combination of durvalumab and tremelimumab have not demonstrated OS survival benefit compared to platinum-based chemotherapy alone.	1b

Hintergrund:
7.7.3.2 Second-line immunotherapy for platinum-pre-treated patients
The immune checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy and safety in patients progressing during, or after, previous platinum-based chemotherapy in phase I, II and III trials.
Pembrolizumab demonstrated a significant OS Improvement as second-line treatment in a phase III RCT leading to EMA and FDA approval. Patients (n = 542) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS with pembrolizumab was 10.3 months (95% CI: 8.0–11.8) vs. 7.4 months (95% CI: 6.1–8.3) with chemotherapy (HR 0.73, 95% CI: 0.59–0.91, p = 0.002) independent of PD-L1 expression levels [501].
Atezolizumab was the first checkpoint inhibitor approved by the FDA for metastatic UC based on the results of phase I and II trials [236, 502] The phase III RCT (IMvigor211) included 931 patients comparing

atezolizumab with second-line chemotherapy (paclitaxel, docetaxel or vinflunine) did not meet its primary endpoint of improved OS for patients with high PD-L1 expression with 11.1 months (atezolizumab) vs. 10.6 (chemotherapy) months (stratified HR: 0.87, 95% CI: 0.63–1.21, p = 0.41) [503].
The PD-1 inhibitor nivolumab was approved by the FDA based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pre-treated patients. The primary endpoint of ORR was 19.6%, and OS was 8.74 months for the entire group [504].
Based on level 1 evidence from a RCT, pembrolizumab has emerged in clinic as the preferred standard of care immunotherapy in the second-line setting.

7.7.4.1 Antibody drug conjugates

The first antibody drug conjugate to report encouraging data was enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, a cell adhesion molecule which is highly expressed in UC conjugated to monomethyl auristatin E (MMAE). A phase-II single-arm study (EV-201) in 125 patients previously treated with platinum chemotherapy and checkpoint inhibition showed a confirmed objective response rate of 44%, including 12% complete responses [508]. This data led to accelerated FDA and EMA approval for enfortumab vedotin in locally-advanced or metastatic UC patients who previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, as well as for cisplatin-ineligible patients who received one or more prior lines of therapy [509, 510]. Another cohort of the same EV-201 trial demonstrated similar promising results in a cohort of 91 patients that were cisplatin-ineligible and had received prior IO [511]. A phase III RCT (n = 608) comparing enfortumab vedotin with single-agent chemotherapy after prior platinum chemotherapy and checkpoint inhibitor immunotherapy demonstrated significant survival benefit of almost 4 months (12.88 months vs. 8.97 months; HR 0.7, 95% CI: 0.56–0.89) [512]. The most common treatment-related AEs included alopecia (45%), peripheral neuropathy (34%), fatigue (31%, 7.4% > grade 3), decreased appetite (31%), diarrhoea (24%), nausea (23%) and skin rash (16%, 7.4% > grade 3).

7.7.4.2 FGFR inhibition

Genomic profiling of UC has revealed common potentially actionable genomic alterations including alterations in *FGFR* [515]. Erdafitinib is a pan-*FGFR* tyrosine kinase inhibitor and the first FDA-approved targeted therapy for mUC with susceptible *FGFR2/3* alterations following platinum-containing chemotherapy. The phase II trial of erdafitinib included 99 patients whose tumour harboured an *FGFR3* mutation or *FGFR2/3* fusion and who had disease progression following chemotherapy [234]. The confirmed ORR was 40% and an additional 39% of patients had stable disease. A total of 22 patients had previously received immunotherapy with only one patient achieving a response, yet the response rate for erdafitinib for this subgroup was 59%. At a median follow-up of 24 months, the median PFS was 5.5 months (95% CI: 4.0‑6.0) and the median OS was 11.3 months (95% CI: 9.7‑15.2) [234]. Treatment-related AEs of > grade 3 occurred in 46% of patients. Common AEs of > grade 3 were hyponatraemia (11%), stomatitis (10%), and asthenia (7%) and 13 patients discontinued erdafitinib due to AEs, including retinal pigment epithelial detachment, hand-foot syndrome, dry mouth, and skin/nail events. In addition to erdafitinib, several other *FGFR* inhibitors are being evaluated including infigratinib which has demonstrated promising activity [235]. In the recently published long-term follow up, the efficacy and safety profile remained similar with no new safety signals with longer follow-up [516]. The increased identification of *FGFR*3 mutations/fusion has led to several ongoing trials with different agents and combinations in different disease settings.

7.7.8 Summary: treatment algorithm for metastatic urothelial cancer update 2021

Patients with FGFR3 mutations are candidates for FGFR inhibitor treatment. Enfortumab vedotin therapy is the new standard in case of progression after platinum chemotherapy and IO but has not yet been approved in Europe.

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European Association of Urology (EAU)

EAU guidelines on upper urinary tract urothelial carcinoma

Zielsetzung/Fragestellung

The European Association of Urology (EAU) Non-muscle-invasive Bladder Cancer (NMIBC) Guidelines Panel has compiled these clinical guidelines to provide clinicians with evidence-based information and recommendations for the management of upper urinary tract urothelial carcinoma (UTUC).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse werden nicht beschrieben; ein externes Begutachtungsverfahren / Review wird dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Für vorliegendes Updates der LL: Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 11th, 2021 and May 4th 2022

LoE

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

GoR

The strength rating forms draw on the guiding principles of the GRADE methodology but do not purport to be GRADE. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are grade according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Zusammenfassung der Empfehlungen

Recommendations	Strength rating
First-line treatment for platinum-eligible patients	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients.	Strong
Offer maintenance avelumab to patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin/carboplatin.	Strong
First-line treatment in patients ineligible for cisplatin or carboplatin	
Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer enfortumab vedotin to patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	Strong
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-line treatment.	Strong
Offer erdafitinib as subsequent-line therapy to platinum-refractory patients with *FGFR* DNA genomic alterations (*FGFR2/3* mutations or *FGFR3* fusions).	Weak
Offer nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally-advanced tumours.	Weak

DNA = deoxyribonucleic acid; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1.

Zusammenfassung der Level of Evidenz

Summary of evidence	LE
PD-1 inhibitor pembrolizumab has been approved for patients who have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients whose disease has progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial, but use of atezolizumab is restricted to PD-L1 positive patients.	2a
Erdafitinib was associated with radiological response in platinum-refractory patients with locally-advanced or metastatic UC and *FGFR* DNA genomic alterations (*FGFR2/3* mutations or *FGFR3* fusions).	2a
Enfortumab vedotin was associated with OS benefit in patients who had previously received platinum-containing chemotherapy and experienced disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	1b
Palliative nephroureterectomy can improve quality of life by controlling symptomatic disease.	3
RNU can confer a survival benefit in highly selected patients.	4

Hintergrund

7.3.2.1.2 Second-line setting

7.3.2.1.2.1 Immunotherapy

A phase III RCT including 542 patients who received prior platinum-based chemotherapy for advanced UC showed that pembrolizumab decreased the risk of death compared to second-line chemotherapy (the investigator's choice of paclitaxel, docetaxel, or vinflunine); median OS: 10.3 months for pembrolizumab and 7.4 months for chemotherapy (HR: 0.73; 95% CI: 0.59–0.91) [290]. Responses were more frequent and durable for pembrolizumab compared with chemotherapy (21% vs. 11%). In the UTUC subgroup (n = 75/13.8%), the OS benefit seemed larger (50%).

The IMVigor211 trial explored atezolizumab in PD-L1 biomarker-positive tumours in patients with tumours which relapsed after platinum-based chemotherapy and failed to show a significant OS advantage [291]. Other immunotherapies such as nivolumab [292], avelumab [293, 294] and durvalumab [295] have shown objective response rates ranging from 17.8% [295] to 19.6% [292] and median OS ranging from 7.7 months to 18.2 months in patients with platinum-resistant metastatic UC. These results were obtained from singlearm phase I or II trials only and the number of UTUC patients included in these studies was only specified for avelumab (n = 7/15.9%) without any subgroup analysis based on primary tumour location [294].

The immunotherapy combination of nivolumab plus ipilimumab has shown significant anti-tumour activity with objective response rate up to 38% in a phase I/II multicentre trial including 78 patients with metastatic UC progressing after platinum-based chemotherapy [296]. Although UTUC patients were included in this trial, no subgroup analysis was available. Other immunotherapy combinations may be effective in the second-line setting but data are currently limited [297].

7.3.2.1.2.2 Novel agents

7.3.2.1.2.2.1 Fibroblast growth factor receptors (FGFR) inhibition

Erdafitinib, a pan-FGFR tyrosine kinase inhibitor of FGFR1–4, was associated with a 40% radiological response rate (RECIST) in a phase II trial of 99 patients with locally-advanced or metastatic UC who progressed after first-line chemotherapy and harboured a FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 fusions) [298]. This study included 23 UTUC patients with visceral metastases showing a 43% radiological response rate. No OS data are available to date.

7.3.2.1.2.2.2 Antibody drug conjugates (ADC)

A phase II study enrolled 89 patients (of whom 43% had UTUC) with cisplatin-unfit metastatic UC progressing after therapy with PD-1 or PD-L1 inhibitors. All patients received the antibody–drug conjugate

enfortumab vedotin. The objective radiological response rate (RECIST) was 52% of which 20% of patients achieved complete response [299]. In a phase III trial of enfortumab vedotin for the treatment of patients with locallyadvanced or metastatic UC who had previously received platinum-containing chemotherapy and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor, enfortumab vedotin significantly prolonged survival as compared with standard chemotherapy (median OS 12.88 vs. 8.97 months) [300].

7.3.2.2 Surgery

7.3.2.2.1 Radical nephroureterectomy (RNU)

Data regarding RNU in the metastatic setting are lacking with mainly retrospective observational studies [303-305]. Although evidence remains very limited, RNU may be associated with CSS [304, 306, 307] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [303, 304]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [304]. Nonetheless, given the high risk of bias of the observational studies addressing RNU for metastatic UTUC, indications for RNU in this setting should mainly be reserved for palliative patients, aimed at controlling symptomatic disease [20, 118] (LE: 3).

7.3.2.2.2 Metastasectomy

There is no UTUC-specific study supporting the role of metastasectomy in patients with advanced disease. Reports suggesting that resection of metastatic lesions could be safe and oncologically beneficial in selected patients should be interpreted with caution [308-312]. In the absence of data from RCTs, patients should be evaluated on an individual basis and the decision to perform a metastasectomy (surgically) should be made following a shared decision-making process with the patient (LE: 3).

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Locally advanced/metastatic bladder cancer (T4bNxM0, TxN2-3M0, TxNxM1)

Zielsetzung/Fragestellung

The objective of this guideline is to provide physicians with the latest, evidence-based management strategies for locally advanced/metastatic bladder cancer in Alberta.

Methodik

Grundlage der Leitlinie

- Repräsentativität des Gremiums unklar, Patientenbeteiligung wird nicht berichtet;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Im Handbuch zur Leitlinienentwicklungen werden allgemein die Möglichkeit von informellen und formale Konsensusprozessen beschrieben. Das exakte Vorgehen für die Vorliegende Leitlinie ist unklar. Ein externes Begutachtungsverfahren wird dargelegt.
- Empfehlungen der Leitlinie sind eindeutig, zugrundeliegenden Evidenz wird separat diskutiert;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Systematische Suche in Pubmed im März 2020

LoE / GoR

Im Handbuch werden Angaben zur Graduierung des LoE und GoR, jedoch ist in der Leitlinie keine Graduierung ersichtlich.

Sonstige methodische Hinweise

- Es handelt sich um eine Leitlinie mit systematischer Recherche und systematischer Evidenzauswahl. Es wurden keine ausreichenden Angaben zu Art und Umfang der Qualitätsbewertung der eingeschlossenen Studien vorgenommen. Die im Handbuch

erwähnte Graduierung der Evidenz und Empfehlungen ist in der Leitlinie nicht ersichtlich.

Management of Metastatic Disease (TxNxM1)

4. Second-line therapy:

A. In eligible patients, pembrolizumab should be considered for patients who progress on or after 1st line platinum-based chemotherapy, or in those who have recurred/progressed within 12 months of receiving platinum-based chemotherapy in the (neo)adjuvant setting.6 Standard dosing of pembrolizumab is as follows:

i. Pembrolizumab (21-day cycle): 2mg/kg up to maximum of 200 mg IV day 1

B. Retreatment with platinum-based regimens can be considered if initial progression-free interval to platinum was > 12 months.

C. Pembrolizumab is NOT indicated for patients who have progressed on avelumab maintenance therapy.

D. For patients who received immunotherapy alone in the first-line setting as part of a clinical trial, platinum-based chemotherapy is recommended as per first-line therapy above if the patient is eligible and has not previously received platinum-based treatment. If prior platinum-based therapy has been received (with <12 month treatment-free interval) and/or the patient is ineligible, second-line options are as per third-line therapy and beyond (see below).

5. Third-line therapy:

A. Enfortumab Vedotin is a nectin-4 directed antibody microtubule inhibitor drug conjugate. It is recommended for eligible patients who have progressed after platinum-based 1st line chemotherapy and immunotherapy (maintenance or 2nd line).

B. Erdafitinib is a treatment option in patients with selected FGFR mutations and fusions. The phase II BLC 2001 study enrolled patients with advanced urothelial carcinoma with prespecified FGFR alterations demonstrating a ORR of 40%. Patients had all been previously treated with platinum-based chemotherapy and some with immunotherapy.

ii. Currently there is no level I evidence to guide sequencing of therapies after 1st-line chemotherapy in patients with FGFR mutations and fusions.

6. Fourth-line therapy and beyond:

A. Taxane-based chemotherapy can be considered post-progression on platinum-based chemotherapy and immunotherapy and enfortumab vedotin. Commonly used agents are single-agent paclitaxel or docetaxel.

7. Palliative local therapies

A. Palliative local therapies (i.e. TURBT, cystectomy, radiation) may be considered for patients experiencing intolerable pain/voiding symptoms or recurrent/refractory hematuria.

B. RT or surgery should be considered in patients with symptomatic sites of bony metastases and/or with impending fracture/complication.

Hintergrundinformationen:

Recommended second-line therapy for patients progressing on first-line platinum-based chemotherapy is pembrolizumab. This is based on the KEYNOTE-045 phase III RCT which demonstrated higher response rates (21% vs 11%) and improved OS (10.1 vs 7.3 months, HR 0.70, p=0.002) with pembrolizumab versus chemotherapy in the second-line.[17]

Erdafitinib is currently under investigation in the phase III setting (NCT03390504), however, phase II data has shown great promise in locally advanced and uresectable or metastatic urothelial carcinoma patients with prespecified FGFR alterations. In the trial all patients had disease progression after at least one course of chemotherapy or within 12 months after neoadjuvant or adjuvant chemotherapy (prior immunotherapy was allowed). A total of n=99 patients were evaluated in an open-label, phase 2 design. The rate of confirmed response to erdafitinib therapy was 40% (3% complete response, 37% partial response). Among n=22 patients who underwent previous immunotherapy, the confirmed response rate was 59%. The median duration for progression-free survival was 5.5 months, and the median duration for overall survival was 13.8 months. Grade 3 or higher adverse events were managed mainly by dose adjustments, and 13% of patients discontinued treatment because of adverse event.[18]

Enfortumab Vedotin was evaluated in a phase III clinical trial (EV-301)[19] of 608 patients with locally advanced unresectable or metastatic urothelial carcinoma (including those with squamous differentiation or mixed cell types) previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitor. Patients were randomly assigned to either enfortumab vedotin or investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). At median follow-up of approximately 11 months, compared with chemotherapy, enfortumab vedotin improved OS (median 13 versus 9 months, HR 0.70, 95% CI 0.56-0.89), PFS (median 6 versus 4 months, HR 0.62, 95% CI 0.51-0.75) and overall response rates (41 versus 18 percent). Grade ≥3 toxicity rates for any adverse event were similar between the two treatment arms (51 versus 50 percent). Grade ≥3 toxicities specifically associated with enfortumab vedotin included rash (15 percent), peripheral neuropathy (5 percent), and hyperglycemia (4 percent). Ocular toxicities, pneumonitis (eg, interstitial lung disease), and severe cutaneous adverse reactions, including cases of Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have also been reported with this agent.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2023) am 08.12.2023

#	Suchfrage
1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
2	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
3	(bladder OR urotheli* OR transitional):ti,ab,kw
4	(tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR neoplas* OR cancer*):ti,ab,kw
5	#1 OR #2 OR (#3 AND #4)
6	#5 with Cochrane Library publication date from Dec 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 08.12.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"urinary bladder neoplasms/therapy"[mh]
2	"carcinoma, transitional cell/therapy"[mh]
3	bladder[ti] OR urotheli*[ti] OR transitional[ti]
4	tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR cancer*[ti]
5	urologic*[ti] OR urinary[ti] OR genitourinary[ti] OR urogenital[ti]
6	bladder[tiab] OR urotheli*[tiab] OR transitional[tiab]
7	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR cancer*[tiab]
8	treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab] OR chemotherap*[tiab] OR immunotherap*[tiab] OR radiotherap*[tiab]
9	#3 AND #4 AND #8
10	#5 AND #6 AND #7 AND #8
11	(#6 AND #7 AND #8) NOT medline[sb]
12	#1 OR #2 OR #9 OR #10 OR #11
13	(#12) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR

#	Suchfrage
	meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
14	(#13) AND ("2018/12/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT "The Cochrane database of systematic reviews"[Journal]
16	(#15) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 08.12.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	urinary bladder neoplasms[mh]
2	carcinoma, transitional cell[mh]
3	bladder[ti] OR urotheli*[ti] OR transitional[ti]
4	tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR cancer*[ti]
5	#1 OR #2 OR (#3 AND #4)
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2018/12/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 08.12.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Alberta Health Services (AHS).** Locally advanced/metastatic bladder cancer (T4bNxM0, TxN2-3M0, TxNxM1) [online]. Edmonton (CAN): AHS; 2023. [Zugriff: 08.12.2023]. (Clinical Practice Guideline; Band GU-014 Version 3). URL: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gu014-ambc.pdf.

2. **Annakib S, Fiteni F, Houédé N.** Quality of life with monoclonal antibody therapies for locally advanced or metastatic urothelial carcinoma: a systematic review. Eur Urol Oncol 2023;6(5):467-476.

3. **Rouprêt M, Gontero P, Birtle A, Compérat E, Dominguez Escrig JL, Liedberg F, et al.** EAU guidelines on upper urinary tract urothelial carcinoma [online]. Arnhem (NED): European Association of Urology (EAU); 2023. [Zugriff: 08.12.2023]. URL: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Upper-Urinary-Tract-Urothelial-Carcinoma-2023.pdf.

4. **Witjes JA, Bruins HM, Carrion A, Cathomas R, Comperat E, Efstathiou JA, et al.** EAU guidelines on muscle-invasive and metastatic bladder cancer [online]. Arnhem (NED): European Association of Urology (EAU); 2023. [Zugriff: 08.12.2023]. URL: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Muscle-Invasive-Bladder-Cancer-2023_2023-03-14-145913_jsen.pdf.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO