Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-203-z Atezolizumab

Stand: September 2018

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

Atezolizumab
[zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms bei erwachsenen Patienten die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden]

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 „II. Zugelassene Arzneimittel im Anwendungsgebiet“* Die Liste der zugelassenen Arzneimittel im Anwendungsgebiet bezieht sich nur auf die Erstlinienbehandlung.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Pembrolizumab (Urothelkarzinom): Beschluss vom 16. März 2018 - Pembrolizumab (Urothelkarzinom, Veranlassung einer erneuten Nutzenbewertung wegen neuer wissenschaftlicher Erkenntnisse, Anpassung aufgrund Änderung der Zulassung): Beschlüsse vom 2. August 2018 - Atezolizumab (Urothelkarzinom): Beschluss vom 16. März 2018 - Atezolizumab (Urothelkarzinom, Urothelkarzinom, Veranlassung einer erneuten Nutzenbewertung wegen neuer wissenschaftlicher Erkenntnisse, Anpassung aufgrund Änderung der Zulassung): Beschlüsse vom 2. August 2018
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:	
Atezolizumab L01XC Tecentriq®	<u>Anwendungsgebiet laut Zulassung (2. Juli 2018):</u> Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC) - die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5 % aufweisen (siehe Abschnitt 5.1).
Doxorubicin L01DB01 Adrimedac®	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 L01BA 01 Methotrexat medac	Methotrexat medac 25 mg/ml Injektionslösung wird angewendet bei: Harnblasenkarzinomen - in Kombination mit anderen zytotoxischen Arzneimitteln
Pembrolizumab L01XC18 KEYTRUDA®	KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatinbasierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren, angezeigt (siehe Abschnitt 5.1).
Atezolizumab L01XC Tecentriq®	Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC) - die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5 % aufweisen (siehe Abschnitt 5.1).

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-203-z (Atezolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. September 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse events
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCG	Bacillus Calmette-Guerin
CBC	complete blood count
CCO	Cancer Care Ontario
CIS	carcinoma in situ
CMV	cisplatin, methotrexate, vinblastine
Cr	creatinine
CT	computer tomography
CUA	Canadian Urology Association
CXR	chest x-ray
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
EAU	European Association of Urology
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GCa	gemcitabine plus carboplatin
GIN	Guidelines International Network
GT	Gemcitabine
Gy	unit of radiation dose
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
k.A.	keine Angabe
MRI	magnetic resonance imaging
MVAC	methotrexate, vinblastine, adriamycin, and cisplatinum
NCCN	National Comprehensive Cancer Network

NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
ORR	Overall Remission Rate, Gesamtremissionsrate
OS	Overall Survival
PD-L1	Programe Death Ligand 1
PLND	pelvic lymph node dissection
PS	Performance Status
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
RT/RCT	Radiotherapie/Radiochemotherapie
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematisches Review
TRIP	Turn Research into Practice Database
TURBT	transurethral resection of bladder tumour
UC	urothelial cancer, Urothelkarzinom
WHO	World Health Organization

1 Indikation

Behandlung von Patienten mit lokal fortgeschrittenem oder metastasierendem Urothelkarzinom, die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden (Erstlinie).

Hinweis: Die Evidenz für die Wirkstoffe Gemcitabin und Carboplatin wird in dieser Synopse lediglich aus Leitlinien dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Urothelkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 21.08.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, IQWiG, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 730 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 15 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA-Beschlüsse / IQWiG-Berichte

G-BA, 2018 [8].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: Urothelkarzinom) vom 2. August 2018

Anwendungsgebiet

Neues Anwendungsgebiet (laut Zulassung vom 6. Juli 2018):

KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren, angezeigt

Zweckmäßige Vergleichstherapie

I. In Anlage XII werden die Feststellungen zu der Nutzenbewertung des Wirkstoffs Pembrolizumab (Urothelkarzinom) wie folgt geändert:

1. Nach Abschnitt „1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie“

werden nach den Feststellungen

„a) Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie)

Zweckmäßige Vergleichstherapie:

Eine Chemotherapie nach Maßgabe des Arztes

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.“

folgende Feststellungen eingefügt:

„Hinweis:

Das zugelassene Anwendungsgebiet von Pembrolizumab (Keytruda®) wurde mit Beschluss der EU-Kommission vom 6. Juli 2018 geändert. Diese Änderung wurde von der Europäischen Arzneimittel-Agentur (EMA) empfohlen, da sich in 2 klinischen Studien mit Atezolizumab (Tecentriq®) und Pembrolizumab (Keytruda®) ein verringertes Überleben in der Erstlinien-Therapie des Urothelkarzinoms bei Patienten mit einer geringen PD-L1-Expression zeigte.

1 Diese Änderung, nachstehend durch fette Schrift hervorgehoben, betrifft die Teilpopulation der Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie):

Neues Anwendungsgebiet (laut Zulassung vom 6. Juli 2018):

KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren, angezeigt.

Die obenstehende Aussage zum Zusatznutzen bezieht sich somit auf eine Anwendung von Pembrolizumab, die ab dem 6. Juli 2018 nicht mehr dem Zulassungsstatus des Arzneimittels entspricht, bzw. nicht mehr vom zugelassenem Anwendungsgebiet in Gänze umfasst ist.“

Fazit / Ausmaß des Zusatznutzens / Ergebnis

trifft nicht zu

G-BA, 2018 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Atezolizumab (Urothelkarzinom) vom 2. August 2018

Anwendungsgebiet

Neues Anwendungsgebiet (laut Zulassung vom 2. Juli 2018):

Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC)

• nach vorheriger platinhaltiger Chemotherapie oder

• die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5% aufweisen.

Vergleichstherapie

I. In Anlage XII werden die Feststellungen zu der Nutzenbewertung des Wirkstoffs Atezolizumab (Urothelkarzinom) wie folgt geändert:

1. Nach Abschnitt „1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie“

werden nach den Feststellungen

„a) Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie)

Zweckmäßige Vergleichstherapie:

Eine Chemotherapie nach Maßgabe des Arztes

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.“

folgende Feststellungen eingefügt:

„Hinweis:

Das zugelassene Anwendungsgebiet von Atezolizumab (Tecentriq®) wurde mit Beschluss der EU-Kommission vom 2. Juli 2018 geändert. Diese Änderung wurde von der Europäischen Arzneimittel-Agentur (EMA) empfohlen, da sich in 2 klinischen Studien mit Atezolizumab (Tecentriq®) und Pembrolizumab (Keytruda®) ein verringertes Überleben in der Erstlinien-Therapie des Urothelkarzinoms bei Patienten mit einer geringen PD-L1-Expression zeigte.

1

Diese Änderung, nachstehend durch fette Schrift hervorgehoben, betrifft die Teilpopulation der Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie):

Neues Anwendungsgebiet (laut Zulassung vom 2. Juli 2018):

Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC)

• nach vorheriger platinhaltiger Chemotherapie oder

• die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5% aufweisen.

Die obenstehende Aussage zum Zusatznutzen bezieht sich somit auf eine Anwendung von Atezolizumab, die ab dem 2. Juli 2018 nicht mehr dem Zulassungsstatus des Arzneimittels entspricht, bzw. nicht mehr vom zugelassenem Anwendungsgebiet in Gänze umfasst ist.“

Fazit / Ausmaß des Zusatznutzens / Ergebnis

trifft nicht zu

G-BA, 2018 [3].

Beschluss des Gemeinsamen Bundesausschusses über die Erteilung von Aufträgen an die Expertengruppen nach § 35c Abs. 1 SGB V (Expertengruppen Off-Label): Carboplatin in Kombination mit Gemcitabin zur Behandlung von Patienten mit inoperablem lokal-fortgeschrittenen oder metastasiertem Urothelkarzinom nach Versagen einer Chemotherapie oder wenn eine Cisplatin-Therapie nicht infrage kommt

Anwendungsgebiet

Behandlung von Patienten mit inoperablem lokal-fortgeschrittenen oder metastasiertem Urothelkarzinom nach Versagen einer Chemotherapie oder wenn eine Cisplatin-Therapie nicht infrage kommt

Vergleichstherapie

trifft nicht zu

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 19. April 2018 beschlossen, die Expertengruppen Off-Label mit folgender Bewertung zum Stand der wissenschaftlichen Erkenntnisse zu beauftragen:

Carboplatin in Kombination mit Gemcitabin zur Behandlung von Patienten mit inoperablem lokal-fortgeschrittenen oder metastasiertem Urothelkarzinom nach Versagen einer Chemotherapie oder wenn eine Cisplatin-Therapie nicht infrage kommt

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G-BA, 2018 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Atezolizumab (Urothelkarzinom) vom 16. März 2018

Anwendungsgebiet

Neues Anwendungsgebiet (laut Zulassung vom 21. September 2017):

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 (siehe Abschnitt 5.1).

Vergleichstherapie

a) Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie)

Zweckmäßige Vergleichstherapie:

Eine Chemotherapie nach Maßgabe des Arztes

b) Patienten mit vorheriger Platin-basierter Therapie

Zweckmäßige Vergleichstherapie:

a) Für Patienten mit einem Frührezidiv (≤ 6 Monate)

• Vinflunin

b) Für Patienten mit einem Spätrezidiv (> 6 – 12 Monate)

• Vinflunin

oder

• Eine erneute Cisplatin-basierte Chemotherapie (für Patienten die, abhängig von Krankheitsverlauf, Allgemeinzustand und Verträglichkeit der Erstlinientherapie, für eine solche in Frage kommen)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

a) Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

b) Patienten mit vorheriger Platin-basierter Therapie

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Vinflunin:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2018 [4].

Beschluss des Gemeinsamen Bundesausschusses über die Veranlassung einer erneuten Nutzenbewertung nach § 35a Abs. 1 i.V.m. § 3 Abs. 1 Nr. 4 AM-NutzenV und 5. Kapitel § 13 VerfO: Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Atezolizumab (Urothelkarzinom) vom 2. August 2018

Anwendungsgebiet

trifft nicht zu

Vergleichstherapie

trifft nicht zu

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 2. August 2018 beschlossen, eine erneute Nutzenbewertung des Wirkstoffes Atezolizumab (Urothelkarzinom) zu veranlassen:

I. Auf Antrag seiner Mitglieder veranlasst der G-BA eine erneute Nutzenbewertung für den Wirkstoff Atezolizumab (Urothelkarzinom).

Die Durchführung der Nutzenbewertung erfolgt mit folgenden Maßgaben:

1. Die erneute Nutzenbewertung des Wirkstoffes Atezolizumab (Urothelkarzinom) bezieht sich auf das Anwendungsgebiet:

„Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC)

• die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5% aufweisen."

2. Das Dossier ist innerhalb von drei Monaten nach Zustellung des Beschlusses durch den G-BA vorzulegen. Als Datum für die Zustellung wird der 1. Oktober 2018 bestimmt. Ausgehend von diesem Zeitpunkt ist das Dossier spätestens zum 2. Januar 2019 vorzulegen.

3. Dem pharmazeutischen Unternehmer wird hiermit bis zum 1. Oktober 2018 eine Beratung nach 5. Kapitel § 7 VerfO des G-BA angeboten.

G-BA, 2018 [9].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: Urothelkarzinom) vom 16. März 2018

Anwendungsgebiet

Neue Anwendungsgebiete (laut Zulassung vom 24. August 2017):

1. KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind, angezeigt.

2. KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms nach vorheriger Platin-basierter Therapie bei Erwachsenen angezeigt (siehe Abschnitt 5.1).

Vergleichstherapie

1. Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie)

Zweckmäßige Vergleichstherapie:

Eine Chemotherapie nach Maßgabe des Arztes

2. Patienten mit vorheriger Platin-basierter Therapie

Zweckmäßige Vergleichstherapie:

a) Für Patienten mit einem Frührezidiv (≤ 6 Monate)

• Vinflunin

b) Für Patienten mit einem Spätrezidiv (> 6 bis12 Monate)

• Vinflunin

oder

• Eine erneute Cisplatin-basierte Chemotherapie (für Patienten die, abhängig von Krankheitsverlauf, Allgemeinzustand und Verträglichkeit der Erstlinientherapie, für eine solche in Frage kommen)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

1. Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind (Erstlinie)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

2. Patienten mit vorheriger Platin-basierter Therapie

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Vinflunin:

Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2018 [5].

Beschluss des Gemeinsamen Bundesausschusses über die Veranlassung einer erneuten Nutzenbewertung nach § 35a Abs. 1 i.V.m. § 3 Abs. 1 Nr. 4 AM-NutzenV und 5. Kapitel § 13 VerfO: Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (Urothelkarzinom) vom 2. August 2018

Anwendungsgebiet

trifft nicht zu

Vergleichstherapie

trifft nicht zu

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 2. August 2018 beschlossen, eine erneute Nutzenbewertung des Wirkstoffes Pembrolizumab zu veranlassen:

I. Auf Antrag seiner Mitglieder veranlasst der G-BA eine erneute Nutzenbewertung für den Wirkstoff Pembrolizumab.

Die Durchführung der Nutzenbewertung erfolgt mit folgenden Maßgaben:

1. Die erneute Nutzenbewertung des Wirkstoffes Pembrolizumab bezieht sich auf das Anwendungsgebiet:

„KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren, angezeigt."

2. Das Dossier ist innerhalb von drei Monaten nach Zustellung des Beschlusses durch den G-BA vorzulegen. Als Datum für die Zustellung wird der 1. Oktober 2018 bestimmt. Ausgehend von diesem Zeitpunkt ist das Dossier spätestens zum 2. Januar 2019 vorzulegen.

3. Dem pharmazeutischen Unternehmer wird hiermit bis zum 1. Oktober 2018 eine Beratung nach 5. Kapitel § 7 VerfO des G-BA angeboten.

3.2 Cochrane Reviews

Es wurden keine Cochrane Reviews gefunden.

3.3 Systematische Reviews

Gwynn ME, DeRemer DL, 2018 [10].

The Emerging Role of PD-1/PD-L1–Targeting Immunotherapy in the Treatment of Metastatic Urothelial Carcinoma

Fragestellung

To summarize and evaluate immunotherapy agents targeting programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) recently approved for the treatment of metastatic urothelial carcinomas (UC).

Methodik

Population:

bladder cancer

Intervention:

traditional chemotherapy or immunotherapeutic agents

Komparator:

Nicht spezifiziert

Endpunkt:

•

Recherche/Suchzeitraum:

A literature review was performed using PubMed (2012 to June 2017), the American Society of Clinical Oncology (ASCO) abstract databases (2012 to June 2017 annual meetings/symposia), American Association for Cancer Research symposia (2012 to June 2017), and Cochrane Central Register of Controlled Trials (CENTER).

A search using clinicaltrials.gov was conducted to identify pertinent studies, and additional online searches were performed for guidelines and prescribing information. References cited in the identified studies, review articles, and guidelines were screened for inclusion.

English language phase I to III studies assessing PD-1 and PD-L1 in UC were incorporated.

Qualitätsbewertung der Studien:

Cochrane risk-of-bias assessment

Ergebnisse

Anzahl eingeschlossener Studien:

10

Table 1. Anti-PD-1/PD-L1 Immunotherapies in Clinical Trials.

Agent	Trial	Dose	Population	n	ORR	Notable TRAE	Reference
Atezolizumab	• Phase II • IMvigor210 • NCT02108652	1200 mg IV q3 weeks	Metastatic UC with progression following PBCT	310	15% Overall; 18% in those with PD-L1 expression ≥1%; 26% in those with PD-L1 expression≥5%	• Fatigue (30%) • Nausea (14%) • Decreased appetite (12%) • Pruritis (10%)	29
Atezolizumab	• Phase II • IMvigor210 • NCT02108652	1200 mg IV q3 weeks	Previously untreated metastatic UC and ineligible to receive cisplatin	119	23% Overall; 25% in those with PD-L1 expression ≥1%; 28% in those with PD-L1 expression≥5%	• Fatigue (30%) • Diarrhea (12%) • Pruritis (11%)	32
Avelumab	• Phase Ib • JAVELIN Solid tumor • NCT01772004	10 mg/kg IV q2 weeks	Metastatic UC that progressed after PBCT	249	17% Overall; 25% in those with PD-L1 ≥5%, 13% in those with PD-L1 <5%	• Fatigue (41%) • Infusion-related reactions (30%) • Musculoskeletal pain (25%) • Nausea (24%)	38, 39
Durvalumab	• Phase 1/2 • NCT 01693562	10 mg/kg IV q2 weeks	Metastatic UC that progressed on or ineligible for previous therapy	191	18% Overall; 28% in those with high PD-L1 expression; 5% in those with low/absent PD-L1	• Fatigue (39%) • Musculoskeletal pain (24%) • Constipation (21%) • Decreased appetite (19%)	35, 37
Nivolumab	• Phase II • CheckMate 275 • NCT02387996	3 mg/kg IV q2 weeks	Metastatic UC with progression following PBCT	265	28% Overall; 24% in those with PD-L1 expression ≥1%; 16% in those with PD-L1 expression <1%	• Fatigue (15%) • Pruritis (9%) • Decreased appetite (8%) • Hypothyroidism (8%)	41
Pembrolizumab	• Phase III • KEYNOTE-045 • NCT02256436	200 mg IV q3 weeks	Advanced UC with progression following PBCT	542	21% Pembrolizumab vs 11.4% chemotherapy (P = 0.001)	• Pruritis (20%) • Fatigue (14%) • Nausea (11%) • Diarrhea (9%)	43, 44
Pembrolizumab	• Phase II • KEYNOTE-052 • NCT02335424	200 mg IV q3 weeks	Previously untreated unresectable or metastatic UC ineligible to receive cisplatin	370	29% Overall; 47% in those with PD-L1 ≥10%	Fatigue (14%)	45

Abbreviations: IV, intravenous; ORR, objective response rate; PBCT, platinum-based chemotherapy; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; TRAE, treatment-related adverse events; UC, urothelial carcinoma.

29. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387:1909-1920.

32. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm,

multicentre, phase 2 trial. Lancet. 2017;389:67-76.

35. Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced

urothelial bladder cancer. J Clin Oncol. 2016;34:3119-3125.

37. Hahn NM, Powles T, Massard C, et al. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma. J Clin Oncol. 2017;35(suppl):abstract 4525.

38. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol. 2017;35:2117-2124.

39. Apolo AB, Ellerton JA, Infante JR, et al. Updated efficacy and safety of avelumab in metastatic urothelial carcinoma (mUC): pooled analysis from 2 cohorts of the phase 1b Javelin solid tumor study. J Clin Oncol. 2017;35(suppl):abstract 4528.

41. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy(CheckMate 275): a multicentre, single-arm, phase 2 trial.

43. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. NEngl J Med. 2017;376:1015-1026.

44. Bajorin DF, De Wit R, Vaughn DJ, et al. Planned survival analysis from KEYNOTE-045: phase 3, open-label study of pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC). J ClinOncol. 2017;35(suppl):abstract 4501.

45. O'Donnell PH, Grivas P, Balar AV, et al. Biomarker findings and mature clinical results from KEYNOTE-052: first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial

cancer (UC). J Clin Oncol. 2017;35(suppl):abstract 4502.

Qualität der Studien:

Many of the studies evaluated in this review were openlabel, single-arm trials that have a high risk of selection, performance, and detection bias.

At the time of this review, the IMvigor211 phase III study has not been published to evaluate risk of bias. Thus, the only RCT that could be formally evaluated for bias in this review was the KEYNOTE-045. There was a lack of discussion on the generation of randomization sequence, which may lead to selection bias. Also, given the open-label design of the trial, the probability of performance and detection bias was high. The use of an external data and safety monitoring, which assessed efficacy and safety, may reduce these biases. Attrition bias was low; the primary reason for discontinuation of treatment in both arms was disease progression. Reporting bias was unclear; potential involvement of the sponsor in the study design and analysis was another potential bias identified.

Studienergebnisse:

Atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab have demonstrated clinical efficacy with tolerable toxicities in patients with metastatic UC with disease progression following platinum-based chemotherapy. Anti–PD-1/PD-L1 therapies may provide overall survival advantage; these are currently being evaluated in ongoing phase 3 studies. Greater objective response rates seem to be observed in PD-L1–positive patients versus PD-L1–

negative patients, but methodologies in this assessment differ among clinical trials. The identification of biomarkers that provide greater insight into patients who positively respond to PD-1/ PD-L1 therapies are needed.

PD-L1 Inhibitors: Evaluation of Clinical Efficacy and Safety

Atezolizumab

Atezolizumab is a humanized monoclonal immunoglobulin-G1 (IgG1) antibody that targets PD-L1 found on TCs and tumor-infiltrating ICs.25,26 As an IgG1 isotype, atezolizumab has an engineered crystallizable fragment (Fc) domain modification designed to eliminate antibody-dependent cell-mediated cytotoxicity (ADCC). This was done to prevent any potential toxicity from ADCC-mediated lysis of ICs expressing PD-L1. Atezolizumab was granted accelerated approval by the FDA in May 2016 for patients with locally advanced or metastatic UC with disease progression during or following PBCT or within 12 months of neoadjuvant or adjuvant chemotherapy. In April 2017, it received an additional accelerated approval for patients not eligible to receive cisplatin-containing chemotherapy. Atezolizumab is also approved for use in metastatic non– small cell lung cancer.

Phase I studies of atezolizumab identified that a 15-mg/kg/dose, or fixed-dose equivalent of 1200 mg, administered every 3 weeks was sufficient in maintaining necessary concentrations to provide target saturation. Further pharmacokinetic simulations found no clinically meaningful

differences between the fixed versus weight-based dosing; therefore, a fixed dose of 1200 mg (equivalent to 15 mg/kg based on an average body weight of 80 kg) was selected for subsequent studies.

The IMvigor 210 trial was an open-label, multicenter, single-arm phase II study (n = 310) that evaluated the safety and efficacy of atezolizumab in patients with locally advanced or metastatic UC. Patients were enrolled in 2 cohorts: cohort 1 consisted of those who received no prior therapies and were ineligible for PBCT, and cohort 2 included patients who experienced disease progression following PBCT. Study participants received 1200 mg intravenous (IV) atezolizumab every 3 weeks on day 1 until loss of clinical benefit. Patient tumor samples were assessed for PD-1 expression with an investigational immunohistochemistry test. The PD-L1 tumor-infiltrating IC status was the percentage of PD-L1–positive ICs in the tumor microenvironment.

Patients were grouped according to percentage of PD-L1 expression as follows: IC0 (<1%), IC1 (1%-4%), and IC2/3 (≥5%). These groups were evenly matched in both cohorts. Rosenberg et al29 reported the data from cohort 2. The primary objective for the study was objective response rate (ORR) according to RECIST (Response Evaluation Criteria in Solid Tumors) compared with a historical 10% responserate. At primary analysis, the ORR was 15% (11-20; P =0.0058) for all patients, and for subgroups IC2/3, IC1/2/3, and IC0, the ORRs were 27%, 18%, and 8%, respectively. The median OS was 7.9 months for the entire cohort and was improved in the IC2/3 group (11.4 months) as compared with the IC1/2/3 and IC0 groups (8.8 and 6.5 months,respectively). Additionally, 11 of the 15 patients who experienced a complete response were in the IC2/3 group. Median progression-free survival (PFS) was comparable among all IC groups. With a higher ORR and median OS in the IC2/3 group, these results reinforce the correlation of PD-L1 expression with treatment response found in the phase I PCD4989g trial.30 Interestingly, an exploratory translational analysis showed that the median mutational load was significantly increased in responders when compared with

nonresponders (12.4 vs 6.4 per megabase, P <0.0001), supporting the association between mutational load and immunotherapy response. Additionally, greater responses to atezolizumab were associated with high expressions of chemokine ligand 9 (CXCL9; P = 0.0057) and 10 (CXCL10; P = 0.0079) as well as tumors with high CD8+ infiltration (P = 0.0265).29,31 Balar et al32 reported results from the cisplatin-ineligible study (cohort 1). The primary endpoint was ORR accordingto RECIST criteria and was 23% in all patients. Unlike cohort 2, ORR was similar across all subgroups (28%, 24%, and 21% for IC2/3, IC1/2/3, and IC0, respectively), and median OS was lower in the IC2/3 patients as compared with IC0/1 patients (12.3 vs 19.1 months, respectively). Larger studies will need to confirm the OS results seen in both cohorts of the IMvigor 210 study because it was not adequately powered for that endpoint. Ongoing phase 3 studies (IMvigor211 and IMvigor130) will continue to evaluate clinical response in relation to PD-L1 expression as well as mutational load. The IMvigor 211 trial included 931 patients with previously treated metastatic UC who progressed on or after PBCT and was intended to confirm the results seen in the IMvigor 210 study. However, a recently released report indicated that atezolizumab failed to meet the primary endpoint of improvement in OS.33 Full results from the study are expected to be presented later this year.

Atezolizumab seems to have a more favorable safety profile compared with chemotherapy; this is encouraging when considering that many patients with metastatic disease decide against receiving second-line treatment due to toxicity concerns.34 In cohort 2 of the IMvigor210 study, 69% of the 310 patients experienced any grade treatmentrelated adverse event (TRAE), 11% had grade 3/4, with fatigue being most common. The incidence of immunemediated adverse events (imAEs) was low (7%) and included pneumonitis, increased hepatic transaminases, rash, and dyspnea; however, 15 of the 23 patients (65%) who experienced an imAE had grade 3/4 events. Also, 11 patients (4%) withdrew treatment because of TRAEs, and 22% required treatment with systemic steroids.29 Rates of TRAEs were similar in cohort 1 of the IMvigor210 study; however, 1 patient died from sepsis, which was determined to be treatment related. Of the 12% of imAEs, 7% were grade 3/4; systemic steroids were necessitated in 36 (30%) patients.32

Pembrolizumab

Pembrolizumab is a humanized monoclonal IgG4, which is FDA approved in advanced melanoma, advanced non–small-cell lung cancer, recurrent head and neck squamous cell cancer, classical Hodgkin lymphoma, and UC. Recently, pembrolizumab was granted accelerated approval for the treatment of patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors who have progressed on previous treatment.

To date, pembrolizumab is the only PD-1/PD-L1 agent that has received full FDA approval for patients with locally advanced or metastatic UC with disease progression following PBCT or within 12 months of adjuvant or neoadjuvant PBC. This was granted on May 18, 2017, along with accelerated approval for use in cisplatin-ineligible patients.11 The KEYNOTE-045 was an open-label, international, nonblinded, phase 3 trial, which randomized 542 patients to pembrolizumab (200 mg IV every 3 weeks) or investigator’s choice of chemotherapy that consisted of paclitaxel, docetaxel, or vinflunine in patients with metastatic UC who progressed after PBCT. Treatment was continued until disease progression according to RECIST or unacceptable toxicity. The primary endpoints were both OS and PFS. A total of 164 patients had PD-L1 expression ≥10% (pembrolizumab, n = 74; chemotherapy, n = 90) that was

defined using a PD-L1 combined positive score (CPS), which consists of TCs and ICs. The median OS in the whole study population was significantly improved in the pembrolizumab cohort (10.3 vs 7.4 months; HR = 0.70; P < 0.001).

45. O'Donnell PH, Grivas P, Balar AV, et al. Biomarker findings and mature clinical results from KEYNOTE-052: first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol. 2017;35(suppl):abstract 4502.

Specifically in those patients who had tumor PD-L1 expression ≥10%, OS favored the pembrolizumab cohort as well (8 vs 5.2 months; HR = 0.57; P = 0.005). However, pembrolizumab demonstrated a modest benefit over chemotherapy in patients with PD-L1 <1% but lacked statistical significance. Whereas median PFS for all patients was similar between the pembrolizumab and chemotherapy groups (2.1 vs 3.3 months), the ORR was nearly doubled in those receiving pembrolizumab (21.1% vs 11.0%). Furthermore, this response continued for ≥12 months in 69% of patients in the pembrolizumab group and only 36% in the chemotherapy group.43,44

The open-label, multicenter, phase II KEYNOTE-052 trial investigated pembrolizumab as a frontline treatment in platinum-ineligible patients. The study (n = 370) evaluated pembrolizumab (200 mg IV every 3 weeks) for safety and efficacy in PBCT-ineligible patients (Eastern Cooperative Oncology Group [ECOG] performance status >2, creatinineclearance <60 mL/min, ≥grade 2 neuropathy, New York Heart Association class III heart failure). The median age of the study population was 75 years (13% ≥85 years). Preliminary data were presented at the 2017 ASCO Annual Meeting. The primary objective of the study was ORR in all patients and in PD-L1+ patients by CPS. With a median 8-month follow-up, the ORR was 24% in all patients and was improved in patients with CPS ≥10% (47%). The median duration of response has not been reached (range =1+ to 18+ months).45 Given the estimation that approximately 30% to 50% of patients with advanced UC may not be candidates for PBCT, pembrolizumab may represent a treatment paradigm shift in this vulnerable patient population, providing antitumor activity with a tolerable adverse event profile.

Overall grade 3/4 TRAEs in the KEYNOTE-045 trial were more common in the chemotherapy arm (49.8% vs 16.5%). Typical chemotherapy-associated TRAEs were identified in >90% of patients, which consisted of anemia, neutropenia, alopecia, fatigue, and peripheral neuropathy.

Pembrolizumab-associated toxicities were identified in 61.3% of patients and most commonly were pruritis, fatigue, and nausea. The treatment-related discontinuation rate was more common in the chemotherapy arm (11% vs 5.6%). The incidence of imAEs was 16.9%; pneumonitis, colitis, and nephritis were the most frequent grade ¾ imAEs. In both treatment groups, 4 patients died as a result of TRAEs. In the pembrolizumab arm, these included pneumonitis (n = 1), urinary tract obstruction (n = 1), malignant neoplasm progression (n = 1), and 1 unspecified case (n =1).43 The toxicity profile in the predominantly elderly population of the KEYNOTE-052 study was similar to the KEYNOTE-045; 65% experienced any grade TRAE, with of metrics and procedures for defining PD-L1 status could be helpful in optimizing decisions for immunotherapy treatment.

43. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. NEngl J Med. 2017;376:1015-1026.

Pembrolizumab is currently the only available agent with mature phase III data demonstrating improved OS as well as a more favorable toxicity profile compared with chemotherapy.

Anmerkung/Fazit der Autoren

Treatment options for metastatic UC have expanded to include PD-1/PD-L1 therapies. These agents should be strongly considered as second-line therapy over single-agent chemotherapy for patients who fail or progress after platinum-based treatment.

Kommentare zum Review

Hier dargestellt werden lediglich die Ergebnisse des Reviews für in Deutschland aktuell zugelassene Wirkstoffe.

3.4 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), 2016 [12].

S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms. Langversion 1.1, Stand 11.2016

Fragestellung

Ein spezifischer Schwerpunkt liegt auf einer standardisiertern Diagnostik und Therapie beim lokal fortgeschrittenen Harnblasenkarzinom sowie bei Tumorerkrankungen mit einer Fernmetastasierung. Ein besonderer Fokus liegt insbesondere in der Tumornachsorge und Rehabilitation, da bisher nur sehr fragmentierte Empfehlungen im deutschsprachigen Raum vorliegen.

Methodik

Grundlage der Leitlinie

- De-Novo-Recherche: Recherche der relevanten Literatur mit Hilfe einer systematischen Literaturrecherche in allen relevanten Datenbanken und Aufarbeitung der Evidenz in einem Evidenzbericht. Vergabe dieser resourcenintensiven Bearbeitung an externe Anbieter
- Leitlinienadaptation: Adaptation von Leitlinien nach methodischer Bewertung und Feststellung der Adaptionsmöglichkeit mit Hilfe des AGREE II Instruments
- Systematische Literaturrecherche: systematische Recherche relevanter Literatur in Medline via PubMed
- Expertenkonsens: Selektive Recherche von Literatur ("Handsuche").
- Konsensusprozess und externes Stellungnahmeverfahren wurden durchgeführt

ausführlicher Methodenreport vorhanden

Recherche/Suchzeitraum:

Die Suche umfasst den Zeitraum vom 01. Januar 2009 bis zum 09./10. Mai 2012 und Dokumente in deutscher und englischer Sprache. Bezüglich der relevanten Patientengruppen erfolgte eine Einschränkung auf erwachsene Patienten.

LoE

Tabelle 3: Schema der Evidenzgraduierung nach SIGN

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance") und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance") und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance") und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z.B. Fallberichte, Fallserien
4	Expertenmeinung

GoR

Tabelle 4: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Sonstige methodische Hinweise

Diese S3-Leitlinie ist bis zur nächsten Aktualisierung, jedoch spätestens bis September 2021 gültig. Es erfolgt eine kontinuierliche Überprüfung der Aktualität. Vorgesehen sind regelmäßige Aktualisierungen. Bei dringendem Änderungsbedarf, z.B. durch Ergebnisse relevanter Studien oder Warnhinweise, können kurzfristige und nur Teilbereiche betreffende Aktualisierungen in Form von Amendments durchgeführt werden.

Empfehlungen

9.5. Erstlinien-Chemotherapie bei Patienten mit einem metastasierten Blasenkarzinom

9.11.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Patienten mit metastasiertem Urothelkarzinom der Harnblase soll eine cisplatinhaltige Chemotherapie angeboten werden, wenn der Allgemeinzustand und die Komorbiditäten dies zulassen.
Level of Evidence **1-**	Primärrecherche: [944, 945]
	Konsens

9.12.	Evidenzbasiertes Statement
Level of Evidence **1+**	Ähnliche Wirksamkeit ergibt sich für Gemcitabin/Cisplatin, MVAC und HD-MVAC. Die Toxizität von HD-MVAC ist dabei geringer als unter konventionellem MVAC, aber höher als unter Gemcitabin/Cisplatin.
	Primärrecherche: [4, 931, 946]
	Konsens

9.13.	Evidenzbasiertes Statement
Level of Evidence **1-**	Eine Dosisintensivierung und Intervallverkürzung von Gemcitabin/Cisplatin bringt keinen Zugewinn an Effektivität.
	Primärrecherche: [947]
	Starker Konsens

9.14.	Evidenzbasiertes Statement
Level of Evidence **1+**	Die Erweiterung des Gemcitabin/Cisplatin-Schemas um Paclitaxel bringt keinen eindeutigen Vorteil bei gering erhöhter Toxizität.
	Primärrecherche: [927]
	Starker Konsens

9.16.	Konsensbasiertes Statement
EK	Bei Patienten, die für eine Cisplatin-haltige Chemotherapie geeignet sind, stellt Carboplatin keinen adäquaten Ersatz dar.
	Starker Konsens

9.6. Nicht-cisplatinbasierte Chemotherapie bei Patienten mit fortgeschrittenem und/oder metastasiertem Urothelkarzinom

9.6.1. Patientengruppe

9.17.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Patienten mit zumindest einem der folgenden 5 Parameter sollten nicht mit Cisplatin-basierter Chemotherapie behandelt werden: • WHO oder ECOG Performance Status (PS) von ≥2 oder Karnofsky PS ≤ 60-70% • Kreatinin Clearance (gerechnet oder gemessen) ≤ 40 ml/min (Bei reduzierter Kreatinin Clearance von 40-60 ml/min soll eine Dosisanpassung von Cisplatin stattfinden, siehe Empfehlung 9.18) • CTCAE Version 4, Grad 2 oder höherer Hörverlust in der Audiometrie • CTCAE Version 4, Grad 2 oder höher mit peripherer Neuropathie • NYHA Klasse III Herzinsuffizienz
Level of Evidence **3**	Primärrecherche: [951]
	Starker Konsens

9.18.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Ausgewählte Patienten mit gutem EGOC-Performance Status (0-1), mäßig eingeschränkter Nierenfunktion (GFR 40-60 ml/min) und ohne weitere Komorbiditäten können mit Cisplatin in aufgeteilten Dosen behandelt werden.
Level of Evidence **3**	Primärrecherche: [952-955]
	Starker Konsens

9.6.2. Substanzen, Substanzkombinationen und Anzahl der Therapiezyklen

9.19.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Patienten, die nicht für eine cisplatinbasierte Chemotherapie geeignet sind und einen guten EGOC-Performance Status (0-1) haben, sollten mit Gemcitabin/Carboplatin behandelt werden.
Level of Evidence **1+**	Primärrecherche: [934, 956, 957]
	Konsens

9.20.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Patienten, die nicht für eine cisplatinbasierte Chemotherapie geeignet sind und einen EGOC-Performance Status ≥2 haben, können mit einer Monochemotherapie behandelt werden.
Level of Evidence **1+**	Primärrecherche: [934, 957]
	Konsens

9.21.	Evidenzbasiertes Statement
Level of Evidence **1+**	Die vorliegende Evidenz lässt bezüglich der Frage nach der idealen oder nötigen Anzahl von Therapiezyklen bei Patienten, die für eine cisplatinhaltige Chemotherapie nicht geeignet sind, keine Empfehlung zu.
	Primärrecherche: [934, 956, 958-978]
	Konsens

934. De Santis, M., et al., Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol, 2012. 30(2): p. 191-9.

956. Culine, S., et al., Gemcitabine or gemcitabine plus oxaliplatin in the first-line treatment of patients with advanced transitional cell carcinoma of the urothelium unfit for cisplatin-based chemotherapy: a randomized phase 2 study of the French Genitourinary Tumor Group (GETUG V01). Eur Urol, 2011. 60(6): p. 1251-7.

957. De Santis, M., et al., Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. J Clin Oncol, 2009. 27(33): p. 5634-9.

Eine cisplatinhaltige Kombinations-Chemotherapie ist die Standard-Chemotherapie in der Behandlung des fortgeschrittenen und metastasierten Urothelkarzinoms (UC). Dies basiert auf randomisierten Phase-III-Studien [927, 929-931, 946, 980]. Das mediane Gesamtüberleben (OS) liegt hier zwischen 12 und 16 Monaten. Die objektiven Ansprechraten mit Methotrexat, Vinblastin, Adriamycin und Cisplatin (MVAC, high-dose [HD]-MVAC) sowie Gemcitabin und Cisplatin (GC) liegen um 50%, die Raten der Langzeitremissionen jedoch nur zwischen 15 und 20% [4].

927. Bellmunt, J., et al., Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol, 2012. 30(10): p. 1107-13.

929. Loehrer, P.J., Sr., et al., A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol, 1992. 10(7): p. 1066-73.

930. von der Maase, H., et al., Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol, 2000. 18(17): p. 3068-77.

931. Sternberg, C.N., et al., Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol, 2001. 19(10): p. 2638-46.

946. Sternberg, C.N., et al., Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer, 2006. 42(1): p. 50-4.

980. Logothetis, C.J., et al., Escalated therapy for refractory urothelial tumors: methotrexate-vinblastine-doxorubicin-cisplatin plus unglycosylated recombinant human granulocyte-macrophage colony-stimulating factor. J Natl Cancer Inst, 1990. 82(8): p. 667-72.

981. Dash, A., et al., Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer, 2006. 107(3): p. 506-13.

9.22.	Evidenzbasiertes Statement
Level of Evidence **1+**	Zur Verwendung von Monotherapien bei Patienten, die nicht geeignet für cisplatinhaltige Kombinationschemotherapien sind, lässt sich aufgrund der mangelnden Evidenz durch randomisierte Vergleichsstudien keine Empfehlung für oder gegen eine einzelne Substanz ableiten.
	Primärrecherche: [956, 979]
	Starker Konsens

Eine cisplatinhaltige Kombinations-Chemotherapie ist die Standard-Chemotherapie in der Behandlung des fortgeschrittenen und metastasierten Urothelkarzinoms (UC). Dies basiert auf randomisierten Phase-III-Studien [927, 929-931, 946, 980]. Das mediane Gesamtüberleben (OS) liegt hier zwischen 12 und 16 Monaten. Die objektiven Ansprechraten mit Methotrexat, Vinblastin, Adriamycin und Cisplatin (MVAC, high-dose [HD]-MVAC) sowie Gemcitabin und Cisplatin (GC) liegen um 50%, die Raten der Langzeitremissionen jedoch nur zwischen 15 und 20% [4].

30-50% der UC Patienten erfüllen die Kriterien für den Erhalt von Cisplatin nicht [981]. Gründe sind die Häufigkeit von Komorbiditäten in dieser Patientengruppe, bedingt durch Raucheranamnese, Alter und Probleme im Harntraktbereich.

In einem internationalen Konsensus von Experten wurden die in Tabelle 29 aufgeführten Kriterien beschrieben, die Patienten mit UC als "nicht fit" für cisplatinhältige Chemotherapie definieren [950, 951].

950. Galsky, M.D., et al., Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. Ann Oncol, 2012. 23(2): p. 406-10.

951. Galsky, M.D., et al., Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol, 2011. 29(17): p. 2432-8.

4. von der Maase, H., et al., Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol, 2005. 23(21): p. 4602-8.

Einige kleinere Studien untersuchten alternative Cisplatin-Regime auch für Patienten mit mittelgradig eingeschränkter Nierenfunktion (GFR ≥ 40 mL/min). Insbesondere kamen aufgeteilte Dosen mit 20-35mg/m² in mehreren Teilgaben pro Zyklus zur Anwendung [952-955]. Für die Anzahl der zu verabreichenden Zyklen liegen keine klaren Daten und Zahlen vor, sodass dazu auch keine eindeutige Antwort gegeben werden kann. Die Frage wurde nicht isoliert studiert. Als Anhaltspunkt können Studienprotokolle und die angestrebte Anzahl von Zyklen herangezogen werden sowie die tatsächlich in den Studien verabreichte Zyklusanzahl. In den meisten Studien wurden 6 Zyklen projektiert. Seltener war der Studienplan, bis zur Progression oder kompletten Remission plus 2 Konsolidierungszyklen zu behandeln. In 26 Studien (28 Therapiearmen) mit Kombinations- oder Monotherapien wurden zwischen 2 und 17 Zyklen verabreicht (mediane Zyklenzahl 5) (siehe Tabelle 32).

Tabelle 29: Konsensusdefinition: Kriterien für Patienten mit fortgeschrittenem Urothelkarzinom, die "nicht fit" für cisplatinbasierte Chemotherapie sind [932]

Vorliegen von zumindest einem Kriterium
- WHO oder ECOG Performance Status (PS) von 2, oder Karnofsky PS 60-70%
- Kreatinin Clearance (gerechnet oder gemessen) < 60 mL/min
- CTCAE Version 4, Grad 2 oder höherer Hörverlust in der Audiometrie
- CTCAE Version 4, Grad 2 oder höher mit peripherer Neuropathie
- NYHA Klasse III Herzinsuffizienz

Legende: WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; CTCAE, Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association

932. Bellmunt, J., et al., Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2014. 25 Suppl 3: p. iii40-8.

Für Patienten, die "nicht fit" für Cisplatin sind, wurde bisher noch keine Standardtherapie definiert.

Es liegen zwei randomisierte Studien zur Behandlung dieser Patientengruppe vor [934, 956, 957]. Die erste, größte (237 Patienten) und bislang einzige publizierte randomisierte Phase-II/III-Studie zur Chemotherapie (EORTC 30986) von "nicht fitten" Patienten mit fortgeschrittenem UC verglich Gemcitabin/Carboplatin (GCa) mit Methotrexat/Carboplatin/Vinblastin (M-CAVI). Die beiden Regime unterschieden sich nicht signifikant in ihrer Wirksamkeit (M-CAVI: medianes OS 8.1 Monate, 21% ORR; GCa: medianes OS 9.3 Monate, 36.1% ORR), jedoch war GCa weniger toxisch. "Nicht fit" wurde in dieser Studie wie folgt definiert: glomeruläre Filtrationsrate (GFR) <60 ml/Min und/oder Performance-Status 2 [934].

Patienten, die "nicht fit" für Cisplatin sind, scheinen nach den vorliegenden Daten keine einheitliche Gruppe zu sein. Jene Patienten in dieser EORTC-Studie 30986, die beide Definitionskriterien für "nicht fit" erfüllten (GFR < 60 mL/min und PS 2) oder die der Risikogruppe 2 nach Bajorin zuzuordnen waren, hatten ein medianes OS von nur 5.5 Monaten bei überdurchschnittlich hoher Toxizität [934]. Patienten mit einem ungünstigen Risikoprofil

ziehen demnach kaum Nutzen aus einer Carboplatin-Kombinationschemotherapie. Als Alternative kommt für diese Patienten eine Monochemotherapie oder "best supportive care" in Betracht [Monochemotherapie siehe Empfehlung 9.27].

Die zweite kleine randomisierte Phase II Studie von Culine verglich Gemcitabin (Gem) Monotherapie mit Gem und Oxaliplatin (GemOx) [956]. Die Studie konnte wegen mangelhafter Aktivität im Kombinationsarm keinen Therapiestandard gegenüber der Monotherapie etablieren. Insgesamt liegen mehrere kleine einarmige Phase II Studien für die sogenannte Cisplatin "nicht fitte" Patientengruppe vor mit sehr unterschiedlichen Einschlusskriterien. Dies macht auch den Vergleich zwischen den Studien schwierig. Insgesamt stehen eine eingeschränkte Nierenfunktion, Einzelniere und ein PS von > 1 als hauptsächliche Kriterien für die Auswahl einer nicht cisplatinhaltigen Chemotherapie im Vordergrund.

Widersprüchliche Ergebnisse zur Kombination von Gemcitabin und Oxaliplatin in kleinen einarmigen Phase II Studien lassen keine Empfehlung zu [956, 993].

9.7. Zweitlinientherapie bei Patienten mit metastasiertem Harnblasenkarzinom

9.7.2. Monosubstanzen, Substanzkombinationen und Anzahl der Therapiezyklen

9.25.	Konsensbasierte Empfehlung
EK	Bei Progress nach primärer Chemotherapie oder perioperativer Chemotherapie eines metastasierten Urothelzellkarzinoms kann eine Zweitlinienchemotherapie angeboten werden.
	Konsens

9.26.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	In der Zweitlinientherapie mit Gemcitabin/Paclitaxel sollen Patienten keine Erhaltungstherapie bis zum weiteren Tumorprogress erhalten.
Level of Evidence 2+	Primärrecherche: [1002]
	Starker Konsens

9.27.	Evidenzbasierte Empfehlung
Empfehlungsgrad B	Patienten mit einem metastasierten Urothelkarzinom, die eine Progression unter bzw. nach einer platinhaltigen Therapie erfahren, sollten als Zweitlinie eine Behandlung mit Vinflunin erhalten.
Level of Evidence 1-	Primärrecherche: [996, 997]
	Konsens

9.28.	Konsensbasierte Empfehlung
EK	Eine Wiederaufnahme einer platinhaltigen Primärtherapie nach einem therapiefreien Intervall (mindestens > 6 Monate) und guter Vertäglichkeit kann durchgeführt werden.
	Starker Konsens

9.29.	Evidenzbasierte Empfehlung
Empfehlungsgrad 0	Nach platinhaltiger Primärtherapie können Gemcitabin und/oder Paclitaxel ggf. auch in Kombinationen eingesetzt werden, insbesondere wenn diese nicht in der Primärtherapie enthalten waren.
Level of Evidence 1-	Primärrecherche: [1002-1004]
	Starker Konsens

Vinflunin zeigte als bislang einzige Substanz in einer Phase III-Studie zur Zweitlininentherapie nach platinhaltiger Erstlinientherapie einen signifikanten Überlebensvorteil verglichen mit „best supportive care“ (BSC). In der Studie wurden insgesamt 370 Patienten behandelt. Davon erhielten 253 Patienten Vinflunin in Kombination mit BSC, 117 Patienten wurden einer alleinigen BSC zugeführt. Insgesamt waren die beiden Behandlungsarme ausgeglichen. Obwohl die Differenz zwischen den erzielten Gesamtüberleben der beiden Behandlungsgruppen in der zu behandelnden Patientenpopulation (Intention to treat population; ITT) mehr als zwei Monate betrug, war dies nicht statistisch signifikant. In der auswertbaren Patientenpopulation (n=357) dagegen wiesen Patienten, die Vinflunin/BSC erhielten, ein signifikant längeres Gesamtüberleben von 6,9 Monaten im Vergleich zu 4,3 Monaten im Kontrollarm auf (p= 0,04). Das Risiko zu versterben konnte in dieser Patientenpopulation mit Vinflunin um 22% gesenkt werden (HR 0,78; 95% KI 0,61- 0,99). Zudem war die zusätzliche Behandlung mit Vinflunin in allen sekundären Endpunkten einer alleinigen BSC überlegen: So betrug die Gesamtansprechrate (ORR) 8,6% vs. 0% (p=0,006), der Anteil der Krankheitskontrolle (disease control rate) 41,8% vs. 24,8% (p=0,002) und das progressionsfreie Überleben (PFS) 3,0 vs. 1,5 Monate (p=0,001). Die häufigsten Grad 3/4 Nebenwirkungen der Vinflunin-Therapie umfassten Neutropenien (50%), febrile Neutropenien (6%), Anämie (19%), Fatigue (19%) und Obstipation (16%). Ein Rückgang der Lebensqualität war unter Vinflunin nicht zu verzeichnen (p=0,66). Im Gegenteil zeigte sich in Woche 18 eine positive Entwicklung der Punktzahl für globalen Gesundheitsstatus, wohingegen in der BSC-Gruppe ein kontinuierlicher Rückgang zu verzeichnen war [996, 997].

996. Bellmunt, J., et al., Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol, 2009. 27(27): p. 4454-61.

997. Bellmunt, J., et al., Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. Ann Oncol, 2013. 24(6): p. 1466-72

Ausblick Zweitlinientherapie:

Laufende Studien zu Atezolizumab, Nivolumab und Pembrolizumab, Avelumab und Durvalumab werden Aufschluss darüber geben, inwieweit eine PD-L1-bzw. PD1 gerichtete Immuntherapie in der Zweitlinie bzgl. Wirksamkeit und Verträglichkeit gegenüber den konventionellen Chemotherapeutika einzuordnen ist und ob die Wirksamkeit dieser

vielversprechenden Therapie von einer ausreichenden PD-L1/PD-1-Expression auf Tumorzellen oder tumorinfiltrierenden Immunzellen abhängt.

National Collaborating Centre for Cancer - Commissioned by the National Institute for Health and Care Excellence., 2015 [13].

Bladder cancer: diagnosis and management

Fragestellung

The scope was drafted by the GDG Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2012). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C
- inform professionals and the public about the expected content of the guideline
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategies

Methodik

Grundlage der Leitlinie

- systematische Evidenzaufbereitung und Konsensusprozesse - eigene Checklisten - Anwendung von GRADE - GoR werden durch Formulierungen wiedergegeben
- The basic steps in the process of developing this guideline:

using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline

- forming the GDG
- developing clinical questions
- identifying the health economic priorities
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- consultation and validation

Recherche/Suchzeitraum:

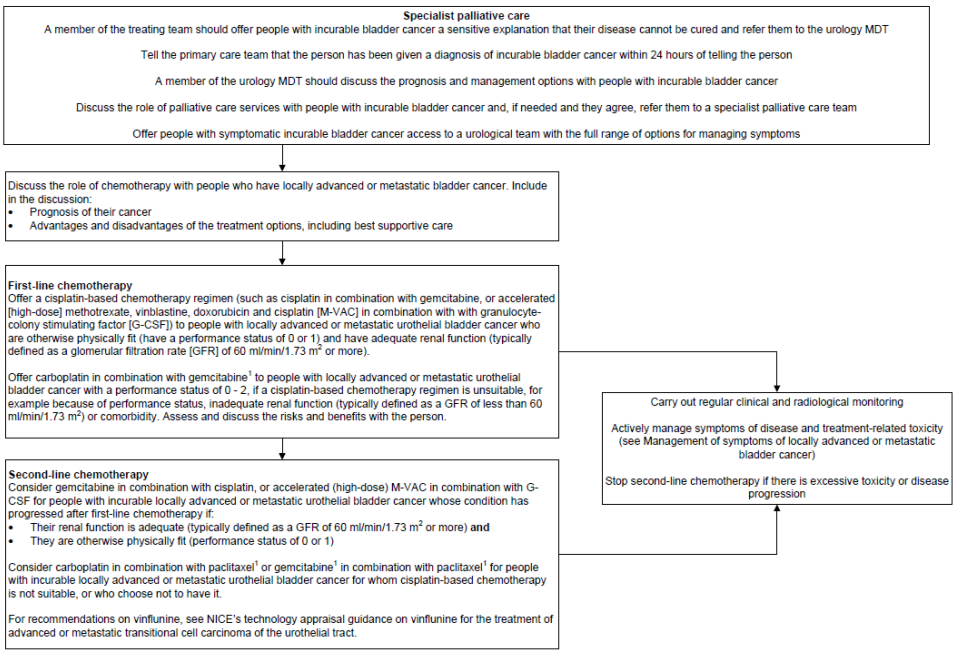
The Cochrane Library, Medline and Premedline (1946 onwards), Excerpta Medica (Embase) (1974 onwards), Web of Science (1899 onwards) and Social SciencesCitation Index (1956 onwards), Cinahl (1937 onwards), Allied & Complementary Medicine (AMED) (1985 onwards), and Psychinfo (1806 onwards) were searched in June 2014

Wording of the recommendations

- ‘Offer’ – for the vast majority of patients, an intervention will do more good than harm
- ‘Do not offer’ – the intervention will not be of benefit for most patients
- ‘Consider’ – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for an ‘offer’ recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Empfehlungen

Management of locally advanced or metastatic bladder cancer



[1] Although this use is common in UK clinical practice, at the time of publication (February 2015), this intervention did not have UK marketing authorisation for this indication. . The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

<u>Managing locally advanced or metastatic bladder cancer</u>

Chemotherapy in ‘unfit’ patients

Moderate quality evidence for overall survival and progression-free survival was provided by one phase III RCT (238 participants) comparing Gemcitabine & Carboplatin (GCarbo) with Methotrexate & Carboplatin & Vinblastine (M-CAVI) (De Santis et al., 2012) in patients unfit for cisplatin-based therapy. After a median of 4.5 years follow-up there were no differences in overall survival (HR 0.94, 95% CI 0.72 to 1.02) and progression-free survival (HR 1.04, 0.8 to 1.35) between the two treatments. GCarbo produced a lower rate of severe acute toxicity than M-CAVI (9% vs. 21%). There were no differences between treatments for changes in health-related quality of life from baseline to end of cycle 2, although mean scores were not reported and there was less than 50% response rate after the baseline assessment.

Table 112: GRADE evidence profile: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer? Comparison: Gemcitabine & Carboplatin (GCarbo) versus Methotrexate, Carboplatin & Vinblastine (M-CAVI) in patients unfit for cisplatin

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	GCarbo	M-CAVI	Relative (95% CI)	Absolute	Quality
Overall survival (mortality rate, follow-up median 4.5 years, maximum 7.8 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	110/119 (92.4%)	108/119 (90.8%)	HR 0.94 (0.72 to 1.02)	Median OS, 9.3 vs. 8.1 mo	MODERATE
Progression-free survival (progression or death rate, follow-up median 4.5 years, maximum 7.8 years)											
1[1]	randomised trials	none	none	none	serious[2]	none	115/119 (96.6%)	113/119 (95%)	HR 1.04 (0.8 to 1.35)	Median PFS, 5.8 vs. 4.2 mo	MODERATE
Severe Acute Toxicity (SAT) (follow-up median 4.5 years; NCI-Common Toxicity Criteria)											
1[1]	randomised trials	none	none	none	serious[2]	none	11/118 (9.3%)	25/118 (21.2%)	RR 0.44 (0.23 to 0.85)	119 fewer per 1000 (from 32 fewer to 163 fewer)	MODERATE
Treatment-related mortality (follow-up median 4.5 years)											
1[1]	randomised trials	none	none	none	Serious[3]	none	3/119 (2.5%)	4/119 (3.4%)	RR 0.75 (0.17 to 3.28)	8 fewer per 1000 (from 28 fewer to 77 more)	MODERATE
Health-related quality of life (measured with: EORTC Quality of life questionnaire C30, measured until end of treatment; Better indicated by higher values)											
1[1]	randomised trials	none	none	none	Serious[4]	none	0	0	-	MD 0 higher (0 to 0 higher)[5]	MODERATE

[1] De Santis et al. (2012); [2] Low number of events limit precision; [3] Wide confidence intervals and low number of events suggest imprecise results; [4] Low compliance (90% at baseline and less than 50% afterward) limits the precision of this outcome. Mean scores for each arm across time not reported; [5] Authors state there were no differences between the two treatment arms for changes in primary scale global health status/QoL from baseline to end of cycle 2.

De Santis, M et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. Journal of Clinical Oncology 2012; 30(2): 191-199.

Alberta Health Services, 2013 [1].

Muscle invasive and locally advanced/ metastatic bladder cancer

Leitlinienorganisation/Fragestellung

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists.

Fragestellung: What is the appropriate stage-specific treatment (i.e., surgery, systemic therapy, radiotherapy) for patients with bladder cancer?

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Suchzeitraum der syst. Literaturrecherche: bis März 2013 (The original guideline, which was developed in 2005 and updated in 2009, 2010, and 2011, was divided into two distinct documents during the 2013 update: a guideline on noninvasive bladder cancer and a guideline on muscle-invasive and locally advanced or unresectable/metastatic disease.)

LoE

Keine Angabe

GoR

Keine Angabe

Empfehlungen

Management of Advanced Unresectable or Metastatic Disease (T4b, N1-3, M1)

Unresectable metastatic disease (T4b, N1-3, M1) should be treated primarily with systemic chemotherapy. Cisplatinum in combination with gemcitabine (six cycles) is the standard regimen; 18,66-68 however, if clinically indicated, carboplatin can be substituted for cisplatin. 69,70 Single agent gemcitabine can be considered for poor performance status patients who are not eligible for platinum-based chemotherapy. MVAC has also been investigated. 71-74 For patients with good performance status, paclitaxel in combination with a platinum agent can be considered for second line therapy. 75-83 The EORTC 30987 trial compared cisplatin/gemcitabine combination therapy with or without paclitaxel in 513 patients with locally advanced or metastatic urothelial cancer. Median overall survival was longer in the paclitaxel group (15.9 months vs. 11.9 months; HR 0.80; p=.025); however progression-free survival was not different (8.3 months vs. 7.6 months (HR 0.87; p=.113). 84 Although both treatments were well tolerated, there was more thrombocytopenia and bleeding on cisplatin/gemcitabine regimen than the paclitaxel combination.
(11.4% vs. 6.8%; p=.05) and more febrile neutropenia on the paclitaxel combination than the cisplatin/gemcitabine regimen (13.2% vs. 4.3%; p<.001). 84

Radiotherapy alone or in combination with a platinum can be considered for palliation or to reduce the risk of local recurrence. 18 In patients who fail first-line platinum-based combination chemotherapy within six months, CMV (cisplatin, methotrexate, vinblastine) or MVAC (methotrexate, vinblastine, adriamycin, and cisplatinum) can be considered. 70-73 Patients with urothelial carcinoma (n=255) who were treated with combination chemotherapy (e.g. MVAC) every 28 days (versus cisplatin alone) experienced superior overall survival (6.8 vs. 1.6%; P=.00015); however, only 3.7% of patients treated with MVAC were alive and continuously disease-free at six years follow-up. 72 A phase III randomized controlled trial (AUO AB 20/99) comparing short-term gemcitabine and paclitaxel (GP) with long-term GP in patients with metastatic disease who had failed 1st line treatment with cisplatin-based chemotherapy found no difference in median overall survival (7.8 months vs. 8.0 months, respectively) or progression-free survival (4.0 months vs. 3.1 months, respectively). However, severe grade III/IV anemia was less in the short-term group (6.7% vs. 26.7%; p=.011). 85 Failures that occur after six months may be treated with the original regimen, CMV or MVAC, or a platinum-paclitaxel combination.

Witjes JA et al., 2018 [15].

European Association of Urology (EAU)

EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer

Leitlinienorganisation/Fragestellung

The European Association of Urology (EAU) Muscleinvasive and Metastatic Bladder Cancer (MIBC) Guidelines are updated yearly and provides information to optimise diagnosis, treatment, and follow-up of this patient population.

Methodik

Grundlage der Leitlinie

The EAU published its first guidelines on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC Guidelines in 2004. This 2018 document presents a limited update of the 2017 version.

Recherche/Suchzeitraum:

A comprehensive literature search, covering all sections of the MIBC Guidelines, was performed. The search was limited to English-language publications excluding conference abstracts. Databases searched included Medline, Embase, and the Cochrane Libraries between April 1, 2014, and July 21, 2015. A total of 2770 unique records were identified, retrieved, and screened for relevance to change or augment the 2015 guidelines.

LoE /GoR

Search results were reviewed and discussed by the panel members and an expert external consultant, and finally used to provide levels of evidence (LEs) and grades of recommendation (GRs) according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence [1]. The link between LE and GR is not always linear.

Sonstige methodische Hinweise

Die Leitlinie entspricht nicht einer S3-Leitlinie (z.B. fehlende Dokumentation des Konsentierungsprozesses, nicht dargelegte Verknüpfungsregeln von Evidenz und Empfehlungen), wurde aufgrund der insgesamt geringen Evidenzlage deshalb hier ausnahmsweise aufgenommen.

Die Leitlinie in der Fassung von 2018 ist nur online im Internet verfügbar.

Empfehlungen

7.8.11.Summary of evidence and guidelines for metastatic disease

Summary of evidence	LE
In a first-line setting, performance status (PS) and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings.	2a
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer (UC).	2b
Vinflunine reaches the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival in selected patients.	3
Zoledronic acid and denosumab have been approved for all cancer types including UC, because they reduce and delay skeletal related events in metastatic bone disease.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase-II trial.	2a
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
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase-II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase-II trial.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase-II trial.	2a

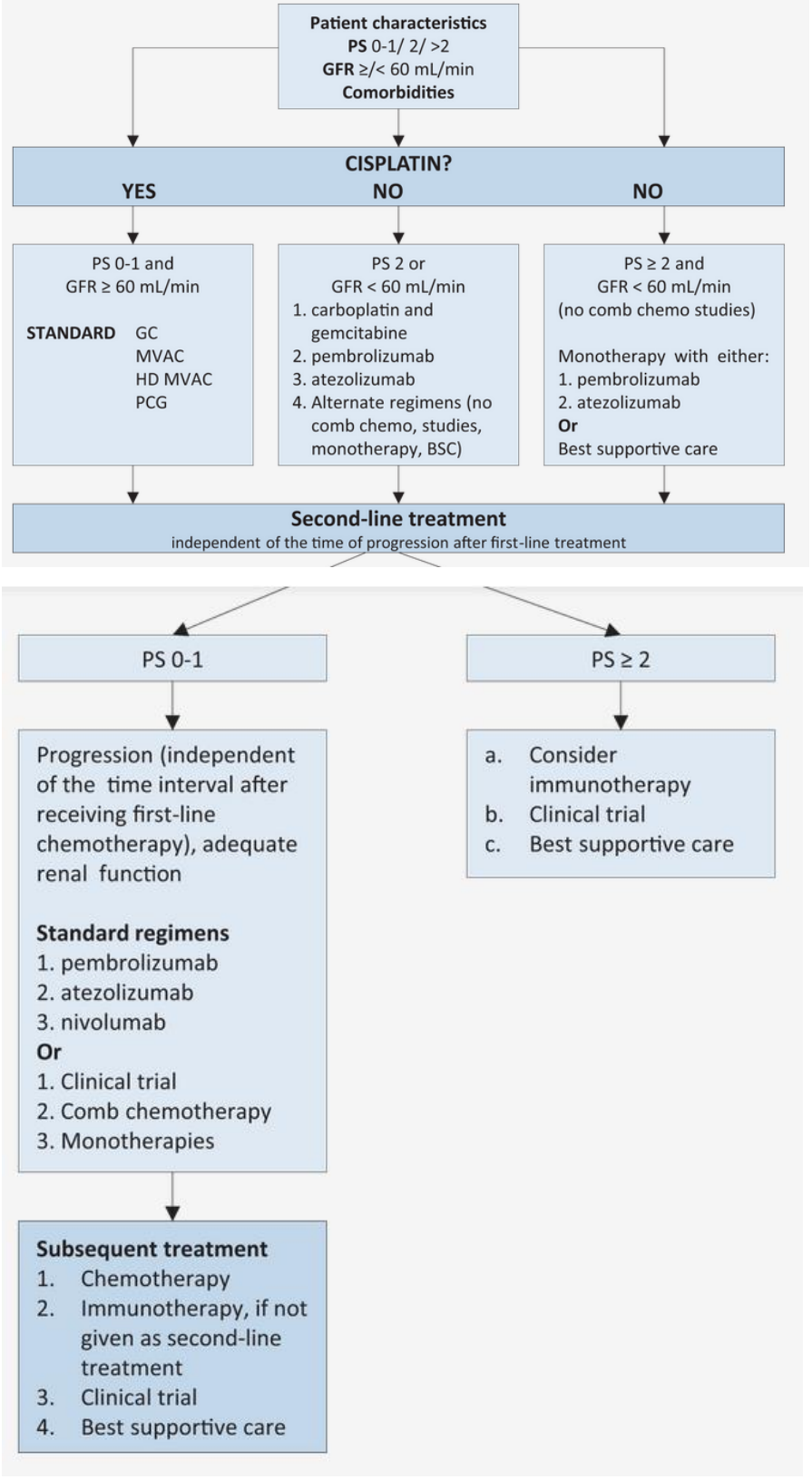
Recommendations	Strength rating
First-line treatment for fit patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not use carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients ineligible (unfit) for cisplatin:	
Use checkpoint inhibitors pembrolizumab or atezolizumab.	Strong
Use carboplatin combination chemotherapy.	Weak
Second-line treatment:	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients progressing during or after platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Offer checkpoint inhibitor nivolumab to patients progressing during or after platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Offer zoledronic acid or denosumab to treat bone metastases.	Weak
Second-line treatment:	
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as subsequent treatment line, or offer treatment within a clinical trial setting or best supportive care.	Weak

GC=gemcitabine plus cisplatin; G-CSF=granulocyte colony-stimulating factor; HD-MVAC=high-dose

7.8.12.1.Recommendation for the use of biomarkers

Recommendation	Strength rating
Do not use biomarkers in daily clinical practice since they have no impact on predicting outcome, treatment decisions, or monitoring therapy in muscle-invasive bladder cancer.	Strong

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



7.8.6.Chemotherapy in patients unfit for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [458]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit [456]. The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group [456]. Phase III data have confirmed these results [448].

A recently published randomised, multinational phase-II trial (JASINT1) assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine-gemcitabine vs. vinflunine-carboplatin). Both regimens showed equal ORR and OS with less haematologic toxicity for the combination vinflunine-gemcitabine [481].

458.Galsky, M.D., et al. Treatment of patients with metastatic urothelial cancer “unfit” for Cisplatin-based chemotherapy. J Clin Oncol, 2011. 29: 2432.

456.De Santis, M., et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer “unfit” for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. J Clin Oncol, 2009. 27: 5634.

448.De Santis, M., et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol, 2012. 30: 191.

481.De Santis, M., et al. Vinflunine-gemcitabine versus vinflunine-carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: results of an international randomized phase II trial (JASINT1). Ann Oncol, 2016. 27: 449.

7.8.10.Role of immunotherapy

Immunomodulatory therapies using checkpoint inhibition, particularly with antibodies directed against the programmed cell death-1 (PD-1) protein, its ligand (PD-L1) or the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-pathway have shown significant anti-tumour activity with tolerable safety profiles and durable responses in patients with locally advanced and metastatic UC. Trials currently investigate immunotherapy agents; either as monotherapy or in combination with other immune-enhancing agents in a first-line or subsequent management setting. Pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy in patients progressing during, or after, standard platinum-based chemotherapy.

7.8.10.1.First-line immunotherapy for patients not eligible for standard cisplatin chemotherapy

A phase-II trial assessed the PD-1 inhibitor pembrolizumab in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [513]. With the PD-L1 inhibitor atezolizumab, a second agent was evaluated in this patient population. A two-cohort phase-II trial (n=119) included patients unfit for cisplatin (cohort 1). The ORR was 29%; 9% of patients presented with a CR and median OS was 15.9 months [514].

The toxicity profile was favourable for pembrolizumab as well as for atezolizumab. Since 2017 both drugs are U.S. Food and Drug Administration (FDA) and EMA approved for first-line treatment in cisplatin-ineligible patients.

513.O'Donnell, P.H., et al. Pembrolizumab (Pembro; MK-3475) for advanced urothelial cancer: Results of a phase IB study. J Clin Oncol 2015. 33: 296.

514.Balar, A.V., et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet, 2017. 389: 67.

1.4.2.Summary of changes

7.8.11 Summary of evidence and guidelines for metastatic disease

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
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase-II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase-II trial.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase-II trial.	2a

Recommendations	Strength rating
First-line treatment in patients ineligible (unfit) for cisplatin:	
Use checkpoint inhibitors pembrolizumab or atezolizumab.	Strong
Use carboplatin combination chemotherapy.	Weak
Second-line treatment	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Offer checkpoint inhibitor nivolumab to patients progressing during or after platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Subsequent treatment	
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as subsequent treatment line, or offer treatment within a clinical trial setting or best supportive care.	Weak

National Comprehensive Cancer Network (NCCN), 2018 [14].

NCCN clinical practice guidelines in oncology: Bladder cancer, Version 5.2018 – July 3, 2018

Leitlinienorganisation/Fragestellung

Methodik

- Grundlage der Leitlinie
- Leitlinien-Update von 2017

Recherche/Suchzeitraum:

- bis 2018

LoE/ GoR

- Category 1 Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2A Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2B Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- Category 3 Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

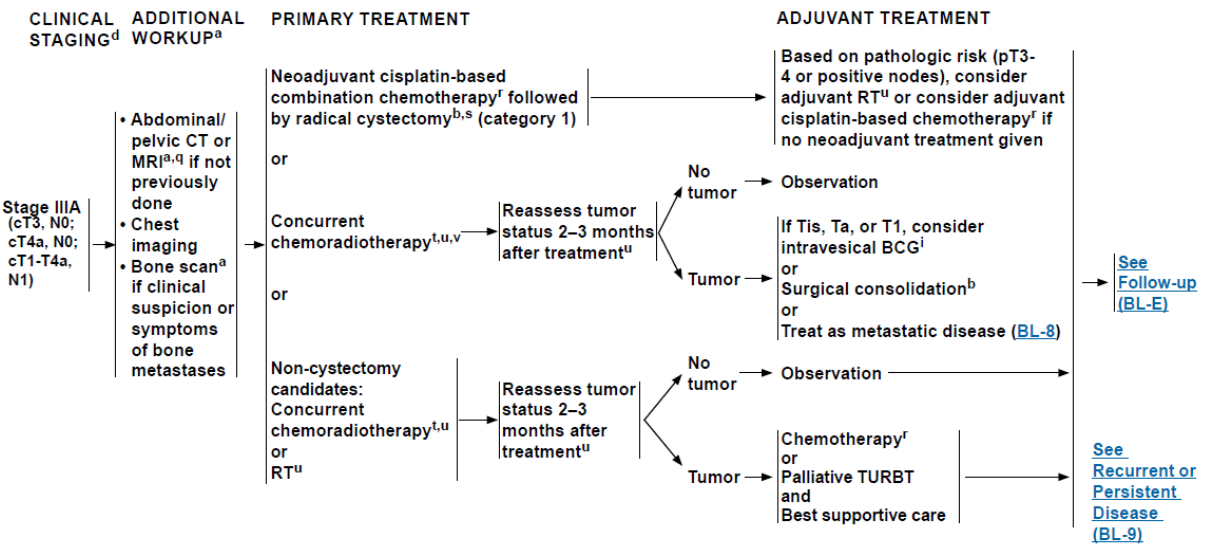
Note: All recommendations are category 2A unless otherwise indicated.

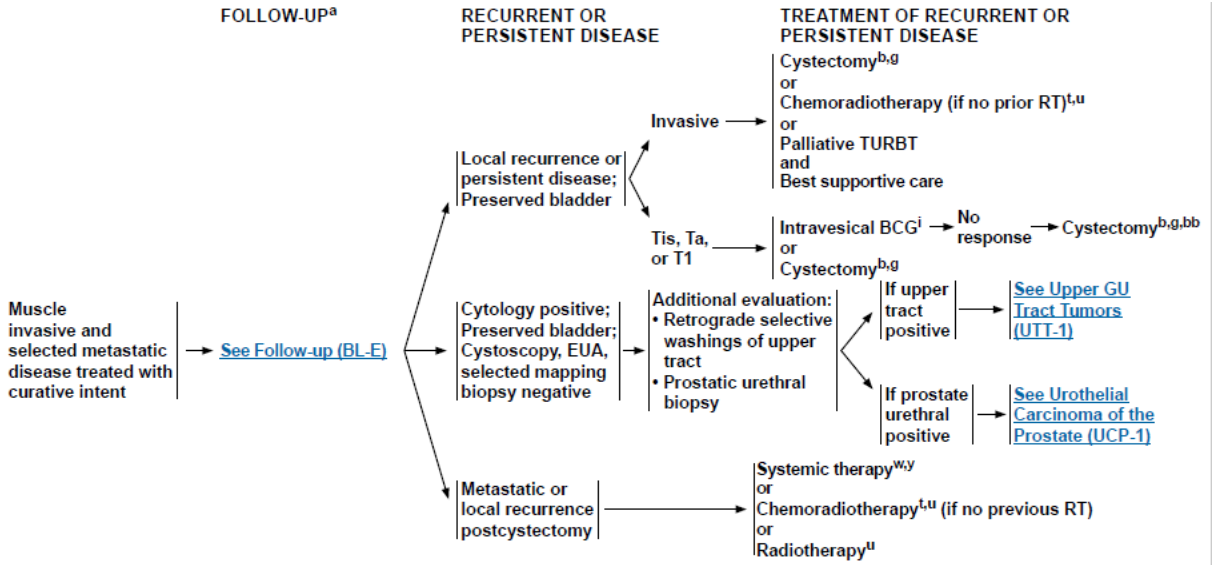
Sonstige methodische Hinweise

Der Methodenreport der NCCN-Leitlinie beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - eigenes Graduierungssystem - industriefinanziert

Die Leitlinie entspricht nicht einer S3-Leitlinie (z.B. fehlende Dokumentation des Konsentierungsprozesses, nicht dargelegte Verknüpfungsregeln von Evidenz und Empfehlungen), wurde aufgrund der insgesamt geringen Evidenzlage und ihrer hohen Aktualität hier ausnahmsweise aufgenommen.

Empfehlungen





[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See Principles of Surgical Management (BL-B).
[g] See Follow-Up (BL-E).
[i] See Principles of Intravesical Treatment (BL-F).
[t] See Principles of Systemic Therapy (BL-G 4 of 5).
[u] See Principles of Radiation Management of Invasive Disease (BL-H).
[w] See Principles of Systemic Therapy (BL-G 2 of 5).
[y] See Principles of Systemic Therapy (BL-G 3 of 5).
[bb] If not a cystectomy candidate, consider concurrent chemoradiotherapy (See BL-G 4 of 5) (if no prior RT), change in intravesical agent, or a clinical trial.

PRINCIPLES OF SYSTEMIC THERAPY

First-line systemic therapy for locally advanced or metastatic disease (Stage IV)	
Cisplatin eligible	Preferred regimens • Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]
Cisplatin ineligible	Preferred regimens • Gemcitabine and carboplatin[11] • Atezolizumab[12] (only for patients whose tumors express PD-L1[a] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) Other recommended regimens • Gemcitabine[14] • Gemcitabine and paclitaxel[15] Useful under certain circumstances • Ifosfamide, doxorubicin, and gemcitabine[16] (for patients with good kidney function and good PS)

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[17]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

See Evidence Blocks on BL-G EB-2

EVIDENCE BLOCKS FOR FIRST-LINE SYSTEMIC THERAPY FOR LOCALLY ADVANCED OR METASTATIC DISEASE

Cisplatin-Eligible Patients

Gemcitabine and cisplatin	
DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support	

Cisplatin-Ineligible Patients

Gemcitabine and carboplatin	
Atezolizumab	
Pembrolizumab	
Gemcitabine	
Gemcitabine and paclitaxel	
Ifosfamide, doxorubicin, and gemcitabine	

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1)[18]	Other recommended regimens • Nab-paclitaxel[26] • Paclitaxel or docetaxel[24] • Gemcitabine[14] • Pemetrexed[25]
Alternative preferred regimens • Atezolizumab[19] • Nivolumab[20] • Durvalumab[21] • Avelumab[22,23]	Useful in certain circumstances based on prior medical therapy • Ifosfamide[27] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimen for cisplatin ineligible, chemotherapy naïve • Gemcitabine/carboplatin	Other recommended regimens • Nab-paclitaxel[26] • Paclitaxel or docetaxel[24] • Gemcitabine[14] • Pemetrexed[25]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	Useful in certain circumstances based on prior medical therapy • Ifosfamide[27] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15]

See Evidence Blocks o

EVIDENCE BLOCKS FOR SUBSEQUENT SYSTEMIC THERAPY FOR LOCALLY ADVANCED OR METASTATIC DISEASE (STAGE IV)

	Post-Platinum	Post-Checkpoint Inhibitor	
		Platinum-Ineligible	Platinum-Eligible
Pembrolizumab	▦	—	—
Atezolizumab	▦	—	—
Nivolumab	▦	—	—
Durvalumab	▦	—	—
Avelumab	▦	—	—
Nab-paclitaxel	▦	▦	▦
Paclitaxel	▦	▦	▦
Docetaxel	▦	▦	▦
Gemcitabine	▦	▦	▦
Pemetrexed	▦	▦	▦
Ifosfamide	▦	▦	▦
Methotrexate	▦	▦	▦
Ifosfamide, doxorubicin, and gemcitabine	▦	▦	▦
Gemcitabine and carboplatin	—	▦	—
Gemcitabine and cisplatin	▦	—	▦
Gemcitabine and paclitaxel	▦	▦	▦
DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support	▦	—	▦

Chemotherapy for Metastatic Disease

The specific chemotherapy regimen recommended partially depends on the presence or absence of medical comorbidities, such as cardiac disease and renal dysfunction, along with the risk classification of the patient based on disease extent. In general, long-term survival with combination chemotherapy alone has been reported only in good-risk patients, defined as those with good performance status, no visceral (ie, liver, lung) or bone disease, and normal alkaline phosphatase or lactic dehydrogenase levels. Poor-risk patients, defined as those with poor performance status or visceral disease, have consistently shown very poor tolerance to multiagent combination programs and few complete remissions, which are prerequisites for cure.

GC[146,147] and ddMVAC[92,104] are commonly used in combinations that have shown clinical benefit. A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard (28-day) MVAC.[106] At a median follow-up of 19 months, OS and time to progression were similar in the two arms. Fewer toxic deaths were recorded among patients receiving GC compared to MVAC (1% vs. 3%), although this did not reach statistical significance. A 5-year update analysis confirmed that GC was not superior to MVAC in terms of survival (OS, 13.0% vs. 15.3%; progression-free survival [PFS], 9.8% vs. 11.3%, respectively).[147] Another large, randomized, phase III trial compared ddMVAC to standard (28-day) MVAC.[92,104] At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. There was one toxic death in each arm, but less overall toxicity was seen in the dose-dense group. From these data, ddMVAC had improved toxicity and efficacy as compared to standard MVAC; therefore, standard (28-day) MVAC is no longer used. Both GC and ddMVAC with growth factor support are category 1 recommendations for metastatic disease.

Alternative first-line regimens also include carboplatin or taxane-based regimens (category 2B) or single-agent chemotherapy (category 2B).

The performance status of the patient is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients who are not cisplatin-eligible and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy, atezolizumab or pembrolizumab are appropriate first-line options (see *Targeted Therapies* in the discussion). Alternatively, carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2).[148] The overall response rate was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR <60 mL/min).

Taxanes have been shown to be active as both front-line and palliative therapies. Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin, as initial therapy. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer.[149] The addition of paclitaxel to GC resulted in higher response rates and a borderline OS advantage, which was not statistically significant in the intent-to-treat analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the 3-drug regimen ($P = .03$). There was no difference in PFS. The incidence of neutropenic fever was substantially higher with the 3-drug combination (13.2% vs. 4.3%; $P < .001$). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial. The alternative regimens, including cisplatin/paclitaxel,[150] gemcitabine/paclitaxel,[151] cisplatin/gemcitabine/paclitaxel,[152] carboplatin/gemcitabine/paclitaxel,[153] and cisplatin/gemcitabine/docetaxel,[154] have shown modest activity in patients with bladder cancer in phase I-II trials. Category 1 level evidence now supports the use of checkpoint inhibitors in patients with advanced disease previously treated with a platinum-containing regimen (see *Targeted Therapies* in the discussion).

Although current data are insufficient to recommend the above alternative regimens as routine first-line options, non-cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin because of renal impairment or other comorbidities (see *Principles of Systemic Therapy* in the algorithm). Additionally, two checkpoint inhibitors, atezolizumab and pembrolizumab, have been FDA approved for use as a first-line therapy in certain patients. Consideration of checkpoint inhibitors must be integrated into the therapeutic planning for all patients with locally advanced and metastatic disease (see *Targeted Therapies* in the discussion). The NCCN Panel recommends enrollment in clinical trials of potentially less toxic therapies.

Independent of the specific regimen used, patients with metastatic disease are re-evaluated after 2 to 3 cycles of chemotherapy, and treatment is continued for 2 more cycles in patients whose disease responds or remains stable. Chemotherapy may be continued for a maximum of 6 cycles, depending on response. If no response is noted after 2 cycles or if significant morbidities are encountered, a change in therapy is advised, taking into account the patient's current performance status, extent of disease, and specific prior therapy. A change in therapy is also advised for patients who experience systemic relapse after adjuvant chemotherapy.

Studies have shown that surgery or radiotherapy may be feasible in highly select cases for patients who show a major partial response in a previously unresectable primary tumor or who have a solitary site of residual disease that is resectable after chemotherapy. In selected series, this approach has been shown to afford a survival benefit. If disease is completely resected, 2 additional cycles of chemotherapy can be considered, depending on patient tolerance.

Clinical trial enrollment is recommended by the NCCN Panel for all patients when appropriate, but is strongly recommended for subsequent-line therapy since data for locally advanced or metastatic disease treated with subsequent-line therapy are highly variable. The available options depend on what was given as first line. Regimens used in this setting include checkpoint inhibitors, and the following chemotherapies: docetaxel, paclitaxel, gemcitabine, or pemetrexed monotherapy.[155-158] Other options include nab-paclitaxel; ifosfamide; methotrexate; ifosfamide, doxorubicin, and gemcitabine; gemcitabine and paclitaxel; GC; and ddMVAC.

Targeted Therapies

Platinum-based chemotherapy has been the standard of care in patients with metastatic disease with an OS of 9 to 15 months.[147,159] However, in patients with disease that relapses after this type of chemotherapy, the median survival is reduced to 5 to 7 months.[160] Several new agents, notably checkpoint inhibitors for the treatment of metastatic urothelial carcinoma, have data supporting improved outcomes compared to standard therapies. Cancers with higher rates of somatic mutations have been shown to respond better to checkpoint inhibitors.[161-166] Data from the Cancer Genome Atlas rank bladder cancer as the third highest mutated cancer,[167,168] suggesting that checkpoint inhibitors may have a substantial impact as a treatment option for this cancer.

The FDA has approved the PD-L1 inhibitors atezolizumab, durvalumab, and avelumab as well as the PD-1 inhibitors nivolumab and pembrolizumab for patients with urothelial carcinoma. Pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab are approved for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels. Additionally, atezolizumab and pembrolizumab are approved as a first-line treatment option for patients with locally advanced or metastatic urothelial cell carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression. All of these approvals have been based on category 2 level evidence with the exception of pembrolizumab as a subsequent treatment option, which has category 1 level evidence supporting the approval.

Pembrolizumab is a PD-1 inhibitor that has been evaluated as second-line therapy for patients with bladder cancer who previously received platinum-based therapy and subsequently progressed or metastasized.[169] An open-label, randomized, phase III trial compared pembrolizumab to chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy. Data from this trial

showed a longer median OS for patients treated with pembrolizumab compared to chemotherapy (10.3 months vs. 7.4 months; $P = .002$). In addition, fewer grade 3, 4, or 5 treatment-related AEs occurred in the pembrolizumab-treated patients compared to those treated with chemotherapy (15.0% vs. 49.4%).[170] Results from this phase 3 trial have lead the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy. A single-arm, phase II trial evaluated pembrolizumab as a first-line therapy in 370 patients with advanced urothelial carcinoma who were ineligible for cisplatin-based therapy. Data from this study showed an overall response rate of 24%, with 5% of patients achieving a complete response. Grade 3 or higher treatment-related AEs occurred in 16% of patients treated with pembrolizumab at the time of data cutoff.[171] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab which warned that early reviews of data from 2 ongoing clinical trials (KEYNOTE-361 and IMvigor-130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[172] Based on these data, the pembrolizumab prescribing information was subsequently amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by a combined positive score (CPS) of at least 10 or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[173]

Data from a two-cohort, multicenter, phase II trial evaluated atezolizumab in patients with metastatic disease. Cohort 2 of the trial enrolled 310 patients with metastatic urothelial carcinoma post-platinum treatment and showed a significantly improved overall response rate compared to historical controls (15% vs. 10%; $P = .0058$).[174] Follow-up to date suggests these responses may be durable with ongoing responses recorded in 38 (84%) of 45 responders with a median follow-up of 11.7 months. Although a similar response rate was seen regardless of PD-L1 status of tumor cells, a greater response was associated with increased PD-L1 expression status on infiltrating immune cells in the tumor microenvironment. Grade 3 or 4 treatment-related or immune-mediated AEs occurred in 16% and 5% of patients, respectively. Furthermore, there were no treatment-related deaths in this trial, which suggests good tolerability. In cohort 1 of the same phase II trial, atezolizumab was evaluated as a first-line therapy in 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin. Data from this study showed an objective response rate (ORR) of 23% with 9% of patients showing a complete response. Median OS was 15.9 months. Grade 3 or 4 treatment-related AEs occurred in 16% of patients.[175] The multicenter, randomized, controlled, phase III IMvigor211 study compared atezolizumab to chemotherapy (vinflunine, paclitaxel, or docetaxel) in 931 patients with locally advanced or metastatic urothelial carcinoma following progression with platinum-based chemotherapy.[176] The primary endpoint of this study, median OS in patients with IC2/3 PD-L1 expression levels (n = 234), showed no significant difference between atezolizumab and chemotherapy (11.1 months vs. 10.6 months; $P = 0.41$). Likewise, confirmed ORR was similar between atezolizumab and chemotherapy treatments in this group of patients (23% vs. 22%). While atezolizumab was not associated with significantly longer OS compared to chemotherapy, the safety profile of atezolizumab was favorable, with 20% of patients experiencing grade 3 or 4 adverse effects compared to 43% with chemotherapy. Atezolizumab was also associated with a longer duration of response than chemotherapy, including durable responses, consistent with the observations in the previous phase II study.[176] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab which warned that early reviews of data from 2 ongoing clinical trials (KEYNOTE-361 and IMvigor-130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[172] Based on these data, the atezolizumab prescribing information was subsequently amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by PD-L1 stained tumor-infiltrating immune cells covering at least 5% of the tumor area or 2) are not eligible for any platinum-containing chemotherapy regardless of the level of tumor PD-L1 expression.[177]

Data from a phase II trial in patients with locally advanced or metastatic urothelial carcinoma who progressed after at least one platinum-containing regimen, reported an overall objective response in 52 of 265 patients (19.6%; 95% CI, 15.0–24.9) following treatment with nivolumab that was unaffected by PD-1 tumor status.[178] Out of the 270 patients enrolled in the study, grade 3 or 4 treatment-related AEs were reported in 18% of patients. Three patient deaths were the result of treatment.[178] The median OS was 8.74 months (95% CI, 6.05–not yet reached). Based on PD-L1 expression of less than 1% and 1% or greater, OS was 5.95 months to 11.3 months, respectively. These data are comparable to the phase I/II data that reported an ORR of 24.4% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status. Out of the 78 patients enrolled in this study, 2 experienced grade 5 treatment-related AEs, and grade 3 or 4 treatment-related AEs were reported in 22% of patients.[179]

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer who have tumor that has progressed during or after one standard platinum-based regimen showed that 46.4% of patients who were PD-L1 positive had disease that responded to treatment; no response was seen in patients who were PD-L1 negative.[180] A 2017 update on this study (N = 191) showed an ORR of 17.8% (27.6% ORR for PD-L1-high disease and a 5.1% ORR for PD-L1-low or -negative disease). Median OS was 18.2 months, with 55% of patients surviving at 1 year. Median duration of response was not yet reached at time of data cutoff. Grade 3 or 4 treatment-related AEs occurred in 6.8% of treated patients and 4 patients had a grade 3 or 4 immune-mediated AE.[181]

Avelumab is another PD-L1 inhibitor currently in clinical trials to evaluate its activity in the treatment of bladder cancer. Results from the phase 1b trial for 44 patients with platinum-refractory disease demonstrated an ORR of 18.2% that consisted of 5 complete responses and 3 partial responses following treatment with avelumab. The median PFS was 11.6 weeks and the median OS was 13.7 months with a 54.3% OS rate at 12 months. Grade 3 or 4 treatment-related AEs occurred in 6.8% of patients treated with avelumab.[182] A pooled analysis of two expansion cohorts of the same trial reported results for 249 patients with platinum-refractory metastatic urothelial carcinoma or who are ineligible for cisplatin based chemotherapy. Of the 161 post-platinum patients with at least 6 months of follow-up, the ORR as determined by independent review was 17%, with 6% reporting complete responses and 11% reporting partial responses. Grade 3 or 4 treatment-related AEs occurred in 8% of patients and, likewise, 8% of patients had a serious AE related to treatment with avelumab.[183]

The value of checkpoint inhibitors is reflected in the unanimous decision by the NCCN Panel to include pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab as second-line systemic therapy

options after platinum-based therapy (and in the case of atezolizumab and pembrolizumab, as first-line therapy options for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) for locally advanced or metastatic disease (see *Systemic Therapy* in the algorithm). With the exception of pembrolizumab as a subsequent treatment option (category 1), the use of checkpoint inhibitors are all category 2A recommendations.

Non-Urothelial Carcinomas of the Bladder

Approximately 10% of bladder tumors are non-urothelial (non-transitional cell) carcinoma. These pathologic entities include mixed histology, pure squamous, adenocarcinoma, small cell tumors, urachal carcinoma, or primary bladder sarcoma. Depending on the pathologic findings, adjuvant chemotherapy may or may not be recommended. The regimens effective for urothelial carcinoma histologies have limited efficacy for patients with non-urothelial carcinomas.

These individuals are often treated based on the identified histology. In general, patients with non-urothelial invasive disease are treated with cystectomy, although those with certain urachal tumors require complete urachal resection (en bloc resection of the urachal ligament with the umbilicus) or may be appropriately treated with partial cystectomy. For example, adenocarcinomas are managed surgically with radical or partial cystectomy and with individualized adjuvant chemotherapy and radiotherapy for maximum benefit. Pure squamous cell tumors are treated by cystectomy, radiation therapy, or agents commonly used for squamous cell carcinoma of other sites such as 5-FU or taxanes. However, overall experience with chemotherapy in non-urothelial carcinomas is limited.

Data are limited to support perioperative chemotherapy for non-urothelial carcinomas; however, neoadjuvant chemotherapy may have benefit in patients with small cell carcinoma of the bladder and is recommended by the panel for any patient with small-cell component histology with localized disease regardless of stage.[184-188] In addition, a retrospective analysis has shown that neoadjuvant chemotherapy may have a modest benefit for other variant histologies.[189] In patients with non-urothelial carcinomas of any stage, no data support the use of adjuvant chemotherapy, although the risk for relapse may be high. Some of the general principles of management applicable to urothelial carcinomas are appropriate with minor variations.

Patients with small cell carcinoma of the bladder are best treated with initial chemotherapy (see NCCN Guidelines for Small Cell Lung Cancer) followed by either radiation therapy or cystectomy as consolidation, if there is no metastatic disease. Primary bladder sarcomas are treated as per the NCCN Guidelines for Soft Tissue Sarcoma.

Upper Tract Urothelial Carcinoma (UTUC)

Upper tract tumors, including those that originate in the renal pelvis or in the ureter, are relatively uncommon. The treatment recommendations discussed in this section are based on the most common histology of upper tract tumors, urothelial carcinoma.

Renal Pelvis Tumors

Tumors that develop in the renal pelvis may be identified during evaluation of hematuria or a renal mass. In the latter case, renal pelvic tumors must be distinguished from the more typical adenocarcinomas

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Chang SS et al., 2017 [2].

American Urological Association (AUA) / American Society of Clinical Oncology (ASCO) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO)

Treatment of non-metastatic muscle-invasive bladder cancer: AUA/SUO guideline

Leitlinienorganisation/Fragestellung

This guideline provides a risk-stratified clinical framework for the management of muscle-invasive urothelial bladder cancer and is designed to be used in conjunction with the associated treatment algorithm.

Methodik

Grundlage der Leitlinie

The systematic review utilized to inform this guideline was conducted by a methodology team at the Pacific Northwest Evidence-based Practice Center. The original review was funded by the Agency for Healthcare Research and Quality (AHRQ), and a subsequent supplemental report was funded by the AUA to address additional key questions and more recently published literature.

The methodology team assessed the risk of bias for randomized controlled trials (RCTs) and observational studies using criteria adapted from those developed by the U.S. Preventive Services Task Force. These criteria were applied in conjunction with the approach recommended in the AHRQ Methods Guide for medical interventions. Two investigators independently assessed the risk of bias of each study. Discrepancies were resolved through discussion and consensus. Each study was rated as low, medium, or high risk of bias.

Recherche/Suchzeitraum:

- 1990 – 3. Quartal 2014
- A supplemental search of Ovid MEDLINE and Cochrane Central Register of Controlled Trials was conducted to capture additional published literature through February 2, 2016.

LoE/ GoR

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

Empfehlungen

VARIANT HISTOLOGY

35. In patients diagnosed with variant histology, clinicians should consider unique clinical characteristics that may require divergence from standard evaluation and management for urothelial carcinoma. (Expert Opinion)

As variant histologies become recognized, the most appropriate care and evaluation may also become better understood as well as increasingly defined. Importantly, treatment recommendations previously outlined may NOT apply to these patients who represent a small but significant number.

Multiple retrospective and small prospective single-arm studies support the use of systemic chemotherapy in patients with small cell/high-grade neuroendocrine MIBC, although the optimal regimen remains undefined.265-269 Regimens optimized for small cell lung carcinoma, such as cisplatin and etoposide, are preferred. Due to the early systemic spread of small cell carcinoma, some experts administer carboplatin-based regimens (e.g. carboplatin-etoposide) in patients not eligible for cisplatin. For this histologic subtype, NAC is preferred over AC.270 Platinum-based chemoradiation using chemotherapy regimens similar to small cell lung cancer may also be considered as there is no standard modality for local control of this rare entity.271-274

265. Siefker-Radtke AO, Kamat AM, Grossman HB et al: Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. J Clin Oncol 2009; 27: 2592.

266. Patel SG, Stimson CH, Zaid HB et al: Locoregional small cell carcinoma of the bladder: clinical characteristics and treatment patterns. J Urol 2014; 191: 329.

267. Choong NW, Quevedo JF and Kaur JS: Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer 2005; 103: 1172.

268. Quek ML, Nichols PW, Yamzon J et al: Radical cystectomy for primary neuroendocrine tumors of the bladder: the university of southern California experience. J Urol 2005; 174: 93.

269. Kaushik D, Frank I, Boorjian SA et al: Long-term results of radical cystectomy and role of adjuvant chemotherapy for small cell carcinoma of the bladder. Int J Urol 2015; 22: 549.

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273. Meijer RP, Meinhardt W, van der Poel HG et al: Local control rate and prognosis after sequential chemoradiation for small cell carcinoma of the bladder. Int J Urol 2013; 20:778.

274. Bryant CM, Dang LH, Stechmiller BK et al: Treatment of small cell carcinoma of the bladder with chemotherapy and radiation after transurethral resection of a bladder tumor. Am J Clin Oncol 2016; 39: 69.

FUTURE RESEARCH

Several key areas of future research need emphasis to improve clinical care and provide a path to better patient outcomes with invasive bladder cancer.

Detection and markers. Enhanced detection of bladder cancer cells via imaging technology or other means is needed to identify patients with high-risk disease and advanced disease. This includes cystocopic and radiographic imaging of local disease and more effective and accurate evaluation techniques of regional lymphatics and distant sites. Defining the role of PET imaging

and the best PET imaging agent as well as the investigation and validation of other novel technologies are deemed high-priority.

Urine cytology can be used to monitor for recurrence after TURBT and cystectomy, but difficulties with interpretation after urinary diversion have limited its usefulness after bladder removal. Radiation therapy can alter the appearance of shed cells and oftentimes result in atypical results. Current urinary markers have a limited role in the routine monitoring for recurrence of urothelial carcinoma after radical cystectomy due to false positive rate. Future studies should focus on the development of urinary and serum based markers that can be used to identify early urothelial based and/or distant recurrences.

Increased knowledge gained from comprehensive genetic studies of invasive bladder cancer should be exploited to identify and validate markers that could be used to guide diagnosis and therapeutic decision making. This would include the identification of prognostic markers capable of stratifying patients at risk for advanced disease, predictive markers for the response to chemotherapeutic/immunotherapeutic agents as well as radiation-based therapies. In addition, further studies are needed to evaluate and validate the prognostic and predictive information obtained from novel molecular classifications of bladder cancer Therapy. The rapid introduction of novel immunotherapeutic agents into the therapeutic armamentarium for treatment of bladder cancer has begun to show promise. Phase II and III studies have now demonstrated significant antitumor activity of the anti-PD-1 and anti-PDL-1 antibodies in the metastatic setting. A myriad of studies are needed to further define the role of these agents alone or in combination with other therapies for all stages of bladder cancer.

Kamat AM et al., 2017 [11].

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma

Leitlinienorganisation/Fragestellung

Following the standard approach established by the Society for other cancers, a systematic literature review and analysis of data, combined with consensus voting was used to generate guidelines. Here, we provide a consensus statement for the use of immunotherapy in patients with bladder cancer, with plans to update these recommendations as the field progresses.

Methodik

Grundlage der Leitlinie

Consensus statement policy

This consensus statement utilized the National Academy of Medicine's (NAM, formerly the Institute of Medicine) Standards for Developing Trustworthy Clinical Practice Guidelines reported in March 2011 [21]. In addition, the previously released SITC consensus guidelines were used as a model to develop and organize this manuscript as previously described.

To develop these guidelines, SITC sponsored a panel led by a steering committee of bladder cancer experts who met in December 2014 in person. To discuss updates to the field, the panel subsequently communicated via email. The meeting and follow-up discussions were guided with the goal of developing clinical treatment guidelines specifically for immunotherapy in bladder cancer patients. This consensus statement is only intended to provide guidance; it is not to be used as a substitute for the individual professional judgment of the treating

physician. The full version of this consensus report and others can be found on the SITC website.

The Task Force consisted of 17 participants, including 8 medical oncologists, 7 urologists, 1 nurse, and 1 patient representative.

Recherche/Suchzeitraum:

- 2006- 2017 (in einigen Datenbanken kürzer)

LoE

Using the previously established grading system, the supporting literature was graded into three levels [22]. To summarize, Level A was defined as strong, evidence-based data derived from prospective, randomized clinical trials and meta-analyses. Level B literature consisted of moderately supported data from uncontrolled, prospective clinical trials. Level C represented weak supporting data derived from reviews and case reports.

22. Kaufman HL, et al. The Society for Immunotherapy of Cancer Consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. Nat Rev Clin Oncol. 2013;10(10):588–98.

GoR

Keine Angabe

Empfehlungen

Consensus recommendations

- Atezolizumab, durvalumab, avelumab, pembrolizumab and nivolumab are all currently FDA-approved and recommended for treatment of patients with locally advanced or metastatic urothelial carcinoma previously treated with platinumbased chemotherapy or relapsed within 12 months of perioperative platinum-based chemotherapy. Pembrolizumab demonstrated improved survival and is the only agent with Level A evidence at this time. There are currently no evident reasons to select one agent over the others, other than the practical matters of dosing and convenience. Atezolizumab and pembrolizumab are also recommended as first-line therapy in cisplastin-ineligible patients (Fig. 3). Finally, pembrolizumab is an appropriate choice of treatment in any patient whose tumor has the MSI-H biomarker and whose disease has progressed following prior treatment, with no satisfactory alternative treatment options.
- Currently, the data do not support using PD-L1 immunohistochemistry to select patients for treatment. However, the FDA has approved complementary assays for evaluating PD-L1 expression when considering treatment with atezolizumab (Ventana PD-L1 SP142) and durvalumab (Ventana PD-L1 SP263) in urothelial carcinoma. This will lead to ongoing evaluation of this aspect of patient selection.

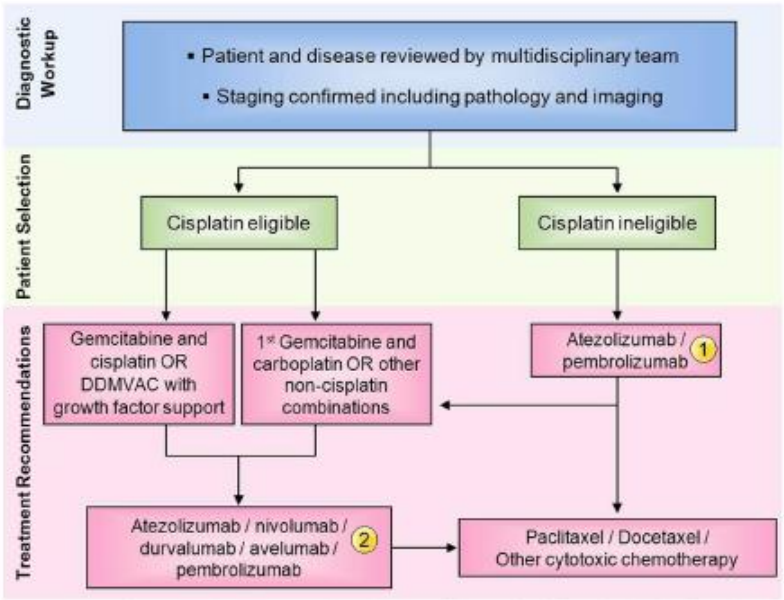

Fig. 3 All of the treatment options shown may be appropriate. The selection of therapy should be individualized based on patient eligibility and the availability of therapy, at the discretion of the treating physician. These algorithms represent the consensus recommendations of the Task Force. (1) Atezolizumab and pembrolizumab are FDA approved for patients with metastatic urothelial carcinoma who are ineligible to receive cisplatin. (2) Atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab are FDA approved for advanced disease that has worsened on platinum containing regimens or within 12 months of receiving a platinum-containing regimen before (neoadjuvant) or after surgery (adjuvant). Abbreviations: dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (DDMVAC)

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Es wurden keine relevanten Dokumente gefunden.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 8 of 12, August 2018) am 17.08.2018

#	Suchfrage
1	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
2	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
3	(urotheli* or transitional or bladder):ti,ab,kw
4	(tumor* or tumour* or carcinoma* or cancer* or neoplasm*):ti,ab,kw (Word variations have been searched)
5	#3 and #4
6	#1 or #2 or #7
7	#6 with Cochrane Library publication date from Aug 2013 to Aug 2018

Systematic Reviews in Medline (PubMed) am 20.08.2018

#	Suchfrage
1	((urotheli*[tiab]) OR transitional[tiab]) OR bladder[tiab]
2	(((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR neoplasm*[tiab]) OR cancer*[tiab]
3	((#1) AND #2)
4	(#3) AND ((((advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab])
5	((((((((((treatment*[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 treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]
6	(#4) AND #5
7	((("carcinoma, transitional cell/drug therapy"[mh]) OR "carcinoma, transitional cell/radiotherapy"[mh]) OR "carcinoma, transitional cell/surgery"[mh]) OR "carcinoma, transitional cell/therapy"[mh]
8	((("urinary bladder neoplasms/drug therapy"[mh]) OR "urinary bladder neoplasms/radiotherapy"[mh]) OR "urinary bladder neoplasms/surgery"[mh]) OR "urinary bladder neoplasms/therapy"[mh]
9	(#6 OR #7 OR #8)
10	(#9) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
11	(#10) AND ("2013/08/01"[PDAT] : "3000"[PDAT])

Leitlinien in Medline (PubMed) am 20.08.2018

#	Suchfrage
1	"carcinoma, transitional cell"[mh]

2	urinary bladder neoplasms[mh]
3	((urotheli*[tiab]) OR transitional[tiab]) OR bladder[tiab]
4	(((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR neoplasm*[tiab]) OR cancer*[tiab]
5	(#3) AND #4
6	((#1) OR #2) OR #5
7	(#6) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
8	(#7) AND ("2013/08/01"[PDAT] : "3000"[PDAT])

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