EUROPEAN UROLOGY 76 (2019) 368–380

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Education – Editor's Choice

# Safe Use of Immune Checkpoint Inhibitors in the Multidisciplinary Management of Urological Cancer: The European Association of Urology Position in 2019

*Marc-Oliver Grimm* [a,*], *Axel Bex* [b,c], *Maria De Santis* [d,e], *Börje Ljungberg* [f], *James W.F. Catto* [g], *Morgan Rouprêt* [h], *Syed A. Hussain* [i], *Joaquim Bellmunt* [j,k], *Tom Powles* [l], *Manfred Wirth* [m], *Hendrik Van Poppel* [n]

[a] *Department of Urology, Jena University Hospital, Jena, Germany;* [b] *Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust, London, UK;* [c] *UCL Division of Surgery and Interventional Science, London, UK;* [d] *Department of Urology, Campus Charité Mitte, Charité—Universitätsmedizin Berlin, Berlin, Germany;* [e] *Department of Urology, Medical University of Vienna, Austria;* [f] *Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden;* [g] *Academic Urology Unit, University of Sheffield, Sheffield, UK;* [h] *Academic Department of Urology, Sorbonne Université, GRC no. 5, ONCOTYPE-URO, Hôpital Pitié-Salpêtrière, Assistance-Publique Hôpitaux de Paris, Paris, France;* [i] *Academic Unit of Clinical Oncology, University of Sheffield, Sheffield, UK;* [j] *Harvard Medical School, Boston, MA, USA;* [k] *Hospital del Mar Medical Research Institute, Barcelona, Spain;* [l] *The Royal Free NHS Trust and Barts Cancer Institute, Queen Mary University of London, London, UK;* [m] *Department of Urology, Medical Faculty Carl Gustav Carus, Technical University of Dresden, Dresden, Germany;* [n] *Department of Urology, University Hospitals Leuven, Leuven, Belgium*

**Article info**

***Article history:***
Accepted May 30, 2019

***Associate Editor:***
Giacomo Novara

***Keywords:***
Immunotherapy
Immune checkpoint inhibitors
Immune related
Adverse events
Atezolizumab
Avelumab
Durvalumab
Ipilimumab
Nivolumab
Pembrolizumab

**Abstract**

Immune checkpoint inhibitors (ICIs) are now used routinely to treat advanced or metastatic urothelial and renal cell carcinoma, among other cancers. Furthermore, multiple trials are currently exploring their role in adjuvant, neoadjuvant, and noninvasive (eg, high-grade non-muscle-invasive bladder cancer) settings. Consequently, urologists are increasingly confronted with patients who are on, have recently received, or will be treated with ICI therapy. The care of these patients is likely to be shared between urologists and medical oncologists, with additional occasional support of other medical specialties. Therefore, it is important that urologists have good knowledge of immune-related side effects. Here, we provide advice on prevention, early diagnosis, and clinical management of the most relevant toxicities to strengthen urologists' insight and, thus, role in the multidisciplinary management in the new immunotherapy era.
***Patient summary:*** Immune therapy is a common treatment for many patients with advanced cancer. We describe common side effects of this treatment, and advise how they are best prevented and managed.



* Corresponding author. Department of Urology, Jena University Hospital, Am Klinikum 1, Jena 07747, Germany. Tel. +49 3641 9 329901; Fax: +49 3641 9 329902.
E-mail address: marc-oliver.grimm@med.uni-jena.de (M.-O. Grimm).

https://doi.org/10.1016/j.eururo.2019.05.041
0302-2838/

## 1. Introduction

Immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein (PD-1)/programmed cell death ligand (PD-L1) axis are widely used today in a growing number of cancer indications including urothelial cancer (UC) and renal cell carcinoma (RCC) [1–3]. Following their development as monotherapies, current treatment strategies use ICIs combined with other immune therapies (dual checkpoint inhibition with PD-1 and cytotoxic T-lymphocyte-associated antigen [CTLA-4] antagonists), tyrosine kinase inhibitors, or chemotherapies [1].

ICIs are being investigated in therapeutic indications usually led by multidisciplinary teams, with urologists either actively involved in or even heading such teams. Examples include the adjuvant setting in RCC or UC, or neoadjuvant treatment prior to cystectomy for bladder carcinoma as well as high-grade non-muscle-invasive bladder cancer (non-MIBC) [2,3]. Therefore, urologists need to be well informed about the basic principles, current indications, and special features of ICI therapy.

ICIs are associated with a specific spectrum of side effects, namely, immune-related adverse events (irAEs). This spectrum differs from toxicities known for kinase inhibitors or cytotoxic drugs. The incidence of irAEs varies, depending on the immune checkpoint that is targeted and the combination that is being used. As for any treatment modality, gains in efficacy must be balanced against the frequency and severity of side effects. As delays in identifying and management of side effects might result in symptom worsening and further complications, it is therefore critical that clinicians prescribing ICIs or supervising patients under or after ICI therapy must be well trained to identify irAEs promptly, monitor patients adequately, and either treat the side effects correctly or refer the patients instantly to collaborating colleagues or teams [4].

This European Association of Urology (EAU) position paper reviews the current status of ICIs in urological cancers and provides recommendations for their safe use. This work provides an overview of common and relevant irAEs that require urologists' particular attention; expert statements on the diagnosis and clinical management of irAEs are provided as well.

## 2. Patient selection

Routine clinical use of ICIs in urological tumors depends on local approval and reimbursement status. Three ICIs that act on the PD-1/PD-L1 pathway (atezolizumab, nivolumab, and pembrolizumab) are approved for the use in advanced or metastatic UC and/or RCC, as summarized in Table 1 [2,3,5]. For advanced RCC, nivolumab is also approved for use in combination with ipilimumab, an ICI-targeting CTLA-4 [6]. Detailed staging and consideration of prior treatment sequence for advanced disease are essential for deciding on patients' eligibility for ICI therapy. Additional immune biomarker testing is recommended and even required for patient selection only in specific clinical scenarios, for example, previously untreated, cisplatin-ineligible UC.

### 2.1. *Renal cell carcinoma*

#### 2.1.1. *Statement*

In advanced RCC, nivolumab monotherapy is a standard of care in patients who failed one or two prior lines of vascular endothelial growth factor (VEGF)-targeted monotherapy.

The use of nivolumab plus low-dose ipilimumab in treatment-naïve patients with advanced or metastatic clear-cell RCC of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate and poor risk is recommended by EAU guidelines [3]. ICI treatment should be prescribed only after a multidisciplinary team decision and by physicians experienced in this

**Table 1 – PD-1/PD-L1 ICIs for renal and urothelial cancer investigated in phase 3 randomized controlled trials and approved, or requests for approval filed**

| Cancer | Indication | Atezolizumab | Avelumab | Nivolumab | Pembrolizumab |
|---|---|---|---|---|---|
| RCC | Untreated patients (1st line) | | Avelumab 10 mg/kg Q2W + axitinib 5 mg BID[a] | Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W × 4 followed by Nivolumab 3 mg/kg Q2W[b] | Pembrolizumab 200 mg Q3W + axitinib 5 mg BID[a] |
| | After prior therapy | | | Nivolumab 240 mg Q2W or 480 mg Q4W | |
| UC | Untreated (1st line), cisplatin ineligible, PD-L1 positive[c] | Atezolizumab 1200 mg Q3W (IC score >5%[c]) | | | Pembrolizumab 200 mg Q3W (CPS >10[c]) |
| | After platinum-based chemotherapy | Atezolizumab 1200 mg Q3W | | Nivolumab 240 mg Q2W | Pembrolizumab 200 mg Q3W |

BI = *bis in dies* (twice per day); CPS = combined positive score; EMA = European Medicines Agency; IC = immune cell; ICI = immune checkpoint inhibitor; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; RCC = renal cell carcinoma; UC = urothelial cancer.

[a] Request for EMA approval filed.

[b] Approved for intermediate/poor-risk patients according to IMDC.

[c] Restricted indication for patients with PD-L1-positive tumors as defined by either high infiltrating IC status (atezolizumab) or high CPS (pembrolizumab), both markers are correlates for PD-L1 positivity.

type of therapy. In patients who stopped an ICI due to toxicity, a rechallenge with either drug should be undertaken only with expert guidance and support from a multidisciplinary team.

#### 2.1.2. Background

For patients with advanced RCC with a clear-cell component, the EAU renal cancer guideline recommends the use of nivolumab after one or two lines of VEGF-targeted therapy in metastatic RCC, based on the results of a phase III trial [5]. Compared with everolimus, a benefit in overall survival (OS; 25.0 vs 19.6 mo, hazard ratio [HR] = 0.73 [98.5% confidence interval {CI} 0.57–0.93], $p < 0.002$), improved quality of life, and fewer grade 3 or 4 adverse events (AEs) were reported for nivolumab.

Strong evidence (grade 1B) also backs the recommendation for the European Union (EU)/US-approved use of nivolumab plus low-dose ipilimumab in treatment-naïve patients with clear-cell metastatic RCC of IMDC intermediate and poor risk [6]. A phase 3 randomized controlled trial (RCT) of atezolizumab plus bevacizumab versus sunitinib demonstrated a progression-free survival (PFS) benefit in PD-L1-positive patients. However, a later interim analysis did not show an OS benefit and the respective European Medicines Agency (EMA) application was withdrawn [7]. Recent and partly preliminary data from phase 3 RCTs comparing the combination of the VEGF receptor (VEGFR)-directed tyrosine kinase inhibitor axitinib and either the PD-L1 inhibitor avelumab [8] or the PD-1 antibody pembrolizumab [9] with the previous standard sunitinib indicated consistent gains in efficacy across the overall trial population in treatment-naïve advanced RCC with a clear-cell component. EU approval and US approval are expected for pembrolizumab and axitinib based on an OS benefit (OS benefit still to be demonstrated for avelumab plus axitinib), introducing a new era in the front-line setting of metastatic RCC in which PD-1 or PD-L1 ICIs constitute the backbone of therapy, in combination with low-dose ipilimumab or an anti-VEGFR-directed tyrosine kinase inhibitor, respectively.

### 2.2. Locally advanced unresectable/metastatic UC

#### 2.2.1. Statement

PD-1 ICIs are a standard treatment in patients after prior platinum-based chemotherapy (ie, for second-line therapy). Among the approved ICIs (pembrolizumab, atezolizumab, and nivolumab), available evidence (OS benefit) is currently favoring pembrolizumab [10].

Atezolizumab and pembrolizumab may also be used in treatment-naïve, cisplatin-ineligible patients with PD-L1-positive tumors. Patients must be properly counseled about the potential risks and benefits as well as about the lack of randomized data comparing ICIs with chemotherapy.

#### 2.2.2. Background

Checkpoint inhibition with PD-1 and PD-L1 inhibitors has shown significant antitumor activity with acceptable toxicity and durable responses in patients with locally advanced and metastatic UC. The PD-1 inhibitor pembrolizumab has shown significant prolongation of OS (10.3 vs 7.3 mo; HR = 0.73 [95% CI 0.59–0.91], $p = 0.004$) in patients who had received prior platinum-containing chemotherapy [11]. Compared with standard-of-care chemotherapy, pembrolizumab also had a favorable toxicity profile resulting in improved quality of life [12]. Atezolizumab, a PD-L1 inhibitor, similarly showed favorable efficacy and reduced toxicity compared with chemotherapy, but no OS benefit was observed [13,14]. Nivolumab is the third ICI currently approved by the EMA in platinum pretreated advanced or metastatic UC patients; its recommendation for use is based on single-arm phase II trials [15] (evidence level 1B for pembrolizumab, and 2A for atezolizumab and nivolumab according to the EAU guidelines) [8].

Based on the results from single-arm phase II trials, pembrolizumab and atezolizumab are also available in the EU for use in UC patients who are not eligible for platinum-containing first-line therapy [16,17] (evidence level 2A): up to 50% of patients with locally advanced or metastatic UC are considered “unfit” for cisplatin-based chemotherapy [18]. However, the EMA and the US Food and Drug Administration (FDA) recently restricted the use of both antibodies to patients with PD-L1-positive tumors. Different immunohistochemical evaluations (companion diagnostic tests) need to be applied to test PD-L1 positivity for each of these antibodies (see section 2.4, Biomarkers).

Recently, encouraging results on PD-1 ICIs in the neoadjuvant setting prior to cystectomy for MIBC were reported [19,20]. With surgery planned within 3 wk after the last dose, neither a delay in radical cystectomy nor more postsurgical complications were observed [19]. Ongoing phase 3 randomized trials focus on the neoadjuvant and adjuvant settings of MIBC. Furthermore, PD-1 ICIs are explored in high-grade non-MIBC, for example, for bacillus Calmette-Guérin (BCG)-refractory and BCG-naïve disease.

### 2.3. Prostate cancer

#### 2.3.1. Statement

ICIs are not recommended for prostate cancer outside of clinical trials.

#### 2.3.2. Background

In metastatic castration-resistant prostate cancer (mCRPC), results from two phase III trials investigating the use of ipilimumab were disappointing. In docetaxel-pretreated [21] as well as chemotherapy-naïve patients [22], CTLA-4 blockade did not prolong survival, but resulted in significant toxicities. However, there were signs of activity of ipilimumab, including some exceptional cases with long-term remissions [23]. Evidence for PD-1 and PD-L1 antagonists is currently limited to early clinical trials and small case series [24,25]. Several phase II but also phase III trials in mCRPC are ongoing. Combinations with second-generation nonsteroidal antiandrogens as well as combinations with various PARP inhibitors (eg, olaparib and rucaparib) or chemotherapy (docetaxel) are investigated.

### 2.4. Biomarkers

#### 2.4.1. Statement

Prior to counseling cisplatin-ineligible, treatment-naïve patients with metastatic UC about ICI treatment options, immunohistochemical PD-L1 testing shall be performed to determine the combined positive score (CPS; for pembrolizumab) and/or the tumor-infiltrating immune cell (IC) score (for atezolizumab).

For RCC or previously treated metastatic UC, upfront biomarker testing is currently not mandatory. However, additional biomarkers are under investigation, which might become important to guide treatment decisions.

#### 2.4.2. Background

Identification and validation of clinically useful biomarkers to guide therapeutic decisions for patient selection as well as for therapy monitoring of ICIs represent a critical issue across all cancer indications. PD-L1 immunohistochemistry, individual mutational analysis with The Cancer Genome Atlas (TCGA) RNA subtype correlation, determination of tumor mutational burden, tumor-infiltrating lymphocyte counts, or IC gene expression profiling have been investigated prospectively and retrospectively to identify potential biomarkers [26–29].

PD-L1 positivity, determined by PD-L1 expression with different cutoffs, is the most comprehensively studied biomarker. Its relevance as a biomarker has been highlighted by the development of several PD-L1 diagnostic tests, the use of which in the USA—foremost in non-small cell lung cancer—is either mandatorily required for certain clinical uses (eg, companion diagnostic total performance score >50% for first-line use of pembrolizumab) or at least recommended (complementary diagnostic) by the FDA to support physicians' informed decision making [30–33].

For RCC, testing of PD-L1 status yields conflicting results as a predictive factor and assessment is not mandatory. However, patients treated with the combination of nivolumab and low-dose ipilimumab having PD-L1-positive tumors appear to benefit most with regard to OS (HR 0.45 vs 0.73 for PD-L1-negative tumors) and have higher overall (58% vs 37%) and complete (16% vs 7%) response rates, respectively. Of note, no benefit in terms of PFS was observed for PD-L1-negative tumors [4]. PD-L1 status is also recorded in many ongoing ICI trials; the recently reported results from the JAVELIN Renal 101 trial [6] provide support that in advanced, clear-cell RCC, therapy outcomes are more favorable in PD-L1-positive patients treated with avelumab plus axitinib. In this trial, PFS and OS in PD-L1-positive patients were the coprimary endpoints. However, due to the so far exploratory nature of PD-L1 tumor expression, the EAU renal cancer guideline does not recommend the use of PD-L1 as a predictive biomarker. As a prognostic factor, PD-L1 status may, however, add to the IMDC prognostic criteria.

Similarly, for the second-line use of pembrolizumab, atezolizumab, and nivolumab in locally advanced or metastatic UC—the same applies for the US-registered uses of avelumab and durvalumab in this UC setting—testing of PD-L1 expression is not required. While the atezolizumab phase 2 trial indicated that response rate, PFS, and OS might be greater in patients with high PD-L1 expression, in the randomized phase 3 trial, better outcomes were also observed in the chemotherapy arm, resulting in no OS difference in the PD-L1-positive group [12,13].

However, for the first-line cisplatin-ineligible setting, on June 1, 2018, the EMA restricted the labels of pembrolizumab and atezolizumab in UC due to efficacy issues, compared with chemotherapy, identified in ongoing clinical trials, excluding patients with low PD-L1 expression from its use [34]. The US FDA had alerted health care professionals and clinical trial investigators on May 18, 2018 with the same concerns [35], which arose from interim analyses of the phase III trials, Keynote-361 and IMvigor 130 [36,37], and restricted both labels in August 2018. Therefore, treatment is limited to patients with tumors with either a combined (referring to tumor cells and ICs) positive score (CPS) of ≥10 for pembrolizumab or an IC score of ≥5% for atezolizumab.

## 3. Categorization and frequency of ICI therapy-related toxicities

### 3.1. Statement

Side effects of ICIs, namely irAEs, may affect any organ system. Symptoms are frequently nonspecific, making their attribution difficult, and the differential diagnosis between irAEs and infection (eg, pneumonitis vs pneumonia) imponderable. Urologists involved in the multidisciplinary treatment of renal, bladder, and prostate cancer should be aware of irAEs and know how to diagnose them. For the management of ICI therapy, close multidisciplinary collaboration is mandatory.

### 3.2. Background

Treatment-related toxicities of ICIs comprise two distinguishable sets of adverse drug reactions (ADRs): on the one hand, side effects generally associated with pharmacotherapy (ie, due to absorption, distribution, metabolization, and elimination processes— eg, hepatic or renal toxicities), and on the other hand, the partially novel irAEs that are well-known ICI class effects, caused by their direct impact on immune regulation.

The precise pathophysiology underlying irAEs is still unknown, but is thought to be related to the role that immune checkpoints play in immunological homeostasis [38]. It remains unknown to which extent autoantibodies, rather than autoreactive T cells, contribute to irAEs or the role of cytokines that are thought to be involved in the pathophysiology of irAEs. Current guidelines for side-effect assessment, such as Common Terminology Criteria for Adverse Events (CTCAE; CTCAE of the U.S. National Cancer Institute, V. 4.0: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf), are not specific to irAE reporting, and grading of irAEs may be challenging [39]. Currently, irAEs are described as AEs that may differ in type, frequency,

or severity from AEs caused by nonimmunotherapies: (1) which may require immunosuppression (eg, corticosteroids) as part of their management, (2) early recognition and management of which may mitigate severe toxicity, and (3) for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization [40]. An established definition of an irAE is still missing.

Differentiation of AEs (ie, whether treatment related or not, and if yes, whether immune related or not) sometimes requires a careful differential diagnosis of even nonspecific and low-grade AEs to determine whether tumor progression or organ-specific comorbidities or an ADR is the root cause of an AE. ADRs not specifically related to immune reactions dominate, by their frequency, the AE reporting for ICIs; their incidence (all grades), as summarized from the actual summaries of product characteristics (SmPCs), are listed in Table 2.

The overall incidence of AEs (all causes and grades) in clinical trials of inhibitors of the PD-1/PL-L1 axis was 67.6%; severe (grade 3–4 according to CTCAE) events occurred in 11.4% of patients, but these rates were lower than the rates in the chemotherapy control arms (82.9% and 35.7%, respectively) [41]. The most frequent ADRs are fatigue (31.8%), diarrhea (18.5%), arthralgia (12.4%), and back pain (10.9%), according to a recent meta-analysis [42]. The incidence of rash, observed with PD-1/PD-L1 inhibitors as well as with several tyrosine kinase inhibitors, reaches 10.3%—also the WHO criteria for "very common" ADRs [40]. Abnormalities in laboratory investigations are very common too: reported are increases of aspartate transaminase (AST)/alanine transaminase (ALT), hypokalemia, and hyponatremia, or increased alkaline phosphatase, creatinine, lipase, and amylase. Table 2, which lists all very common or common ADRs mentioned in current EU prescribing information text, mirrors these data from meta-analyses.

The overall incidence of treatment-related irAEs, assessed through a meta-analysis of 46 trials of PD-1/PD-L1 inhibitors reporting 13 000 patients, is 26.8%. Severe irAEs occur in 6.1% of patients; the incidence of therapy-related death is <0.2% [43]. Most frequent irAEs (of any grade) are—both common—hypothyroidism (5.6%) and pneumonitis (2.2%); colitis (0.7%), hypophysitis (0.3%), and hepatitis (0.2%) are uncommon [40]. The only common severe irAE is pneumonitis (1.4%); severe colitis (0.5%), hypophysitis (0.2%), hyperthyroidism (0.2%), and hepatitis (0.1%) are uncommon [40]. The incidences generally match those reported in the EU prescription information texts, although differences manifest, mainly due to the grouped coding of several symptoms within a given irAE. Hyperthyroidism is also considered to constitute a common irAE (incidence 1.7–3.5%). Further uncommon events (0.1–1.0%) are adrenal insufficiency, type I diabetes mellitus, pancreatitis, or nephritis; neurological ADRs such as Guillain-Barré syndrome and meningitis are uncommon too. Other irAEs such as myasthenic syndrome, encephalitis, or myocarditis occur rarely (incidence <0.1%).

Compared with ADR rates in comparator arms of clinical trials (phase II–III) of PD-1/PD-L1 inhibitors, rates of irAEs are increased for ICIs; of the more general ADRs related to immune activation, only the rates of rash and associated pruritus are significantly increased for ICIs [39,40]. Data for irAE/ADR incidences according to tumor types are inconclusive so far; however, incidences of particular irAEs vary across different cancers [41]. One review reported that arthritis and myalgia were more frequent in melanoma patients than in patients with RCC in whom pneumonitis was more prevalent [44]. Compared with PD-1 monotherapy, incidences of ADRs and irAEs are clearly augmented for PD-1/CTLA-4 combined immune checkpoint blockade (Table 2) [42,45,46]; the rates of certain irAEs (colitis, pneumonitis, increases in transaminases and lipases) augment substantially—colitis, rash, and hypophysitis are more frequent with CTLA-4 than with PD-1 monotherapy [43,44].

## 4. Clinical diagnosis and management of ICI therapy-related major toxicities

Five organ systems are frequently affected by ICI ADRs: skin with exanthema and pruritus, liver with hepatitis, colon with diarrhea/colitis, lung with pneumonitis, and the endocrine systems. In order to identify irAEs as early as possible, patients should regularly be asked for skin, bowel, and/or pulmonary symptoms. Regular laboratory analyses should include liver and pancreas enzymes as well as creatinine, since irAEs at the respective organs do not result in early symptoms. Furthermore, thyroid-stimulating hormone (TSH) should be closely monitored to identify hypo- or hyperthyroidism. In case of unspecific symptoms and/or deterioration, an irAE of the endocrine system should be ruled out by analysis of TSH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), cortisol, prolactin, and either estradiol or testosterone. The diagnosis of an irAE requires exclusion of other causes of the respective signs or symptoms, for example, by stool culture or hepatitis serology in case of diarrhea/colitis and liver ultrasound (cholestasis, progression of liver metastasis) for rising transaminases [36,43]. Early involvement of other relevant disciplines is recommended in order to facilitate optimal management of irAEs.

For the overall management of irAEs, which are predominantly inflammatory reactions, interruption of therapy or even permanent therapy discontinuation is a measure of choice. Generally, in case of grade 4 irAEs, therapy discontinuation is recommended in line with systemic corticosteroid therapy; for grade 2 irAEs, interruptions of therapy plus corticosteroid use are recommended; and for grade 1 irAEs, ICI therapy can usually be continued. Drug manufacturers' recommendations for the management of grade 3 irAEs are heterogeneous; official recommendations for the most clinically relevant (ie, frequency, severity, and complexity of event) irAEs are displayed in Fig. 1. Dose reductions/modifications are generally not recommended for ICIs.

For the general AEs related to immune activation, consensus recommendations provide guidance in relation to the clinical management of fatigue [47,48], diarrhea [49], nausea and

**Table 2 – Very common and common ADRs of checkpoint inhibitors authorized in the EU for use in urological cancers (frequencies reported according to current SmPC[a])**

| Adverse Reaction (listed according to Standard Organ Class) | Atezolizumab | Nivolumab | Pembrolizumab | Nivolumab + ipilimumab |
|---|---|---|---|---|
| *Infections and infestations* | | | | |
| Upper respiratory tract infections/pneumonia | ○/○ | ●/◉ | ○/● | ●/● |
| *Blood and lymphatic system disorders* | | | | |
| Neutropenia | ○ | ■ | ◉ | ■ |
| Eosinophilia | ○ | ◉ | ◉ | ● |
| Anemia | ○ | ■ | ■ | ■ |
| Thrombocytopenia | ● | ■ | ● | ■ |
| *Immune system disorders* | | | | |
| Infusion-related reaction/hypersensitivity | ●/● | ●/● | ●/○ | ●/● |
| *Endocrine disorders* | | | | |
| Hypo-, hyperthyroidism/other[b,*] | ●/⊙ | ●/◉ | ■/◉ | ■/● |
| *Metabolism and nutrition disorders* | | | | |
| Decreased appetite | ■ | ● | ■ | ■ |
| Dehydration | ○ | ◉ | ○ | ● |
| Hypokalemia/hyponatremia | ●/● | ■/■ | ◉/◉ | ■/■ |
| Hyperglycemia/diabetes mellitus | ○/○ | ■/○ | ◉ | ■/● |
| *Nervous system disorders* | | | | |
| Headache | ○ | ● | ■ | ● |
| Dizziness | ○ | ● | ● | ● |
| Peripheral neuropathy | ○ | ● | ● | ● |
| *Eye disorders* | | | | |
| Uveitis[*]/blurred vision | ○/○ | ◉/◉ | ◉/○ | ◉/● |
| *Cardiac disorders* | | | | |
| Tachycardia | ○ | ◉ | ○ | ● |
| Hypertension/hypotension | ○/● | ●/○ | ●/○ | ●/○ |
| *Respiratory, thoracic, and mediastinal disorders* | | | | |
| Dyspnea/cough | ■/○ | ●/● | ■/■ | ●/● |
| Pneumonitis[*]/pulmonary embolism | ●/○ | ●/○ | ●/○ | ●/● |
| Hypoxia | ● | ○ | ○ | ○ |
| *Gastrointestinal disorders* | | | | |
| Diarrhea | ■ | ■ | ■ | ■ |
| Nausea/vomiting | ■/■ | ■/● | ■/■ | ■/■ |
| Abdominal pain | ● | ● | ■ | ● |
| Stomatitis/colitis[*]/pancreatitis[*] | ○/●/◉ | ●/●/◉ | ○/●/◉ | ●/●/● |
| Dry mouth/dysphagia | /● | ●/ | ●/ | ●/ |
| Constipation | ○ | ● | ■ | ● |
| Lipase increased/amylase increased | ◉/⊙ | ■/■ | ○/● | ■/■ |
| *Hepatobiliary disorders* | | | | |
| Hepatitis[*] | ◉ | ◉ | ◉ | ● |
| Liver transaminases increased (ALT/AST) | ●/● | ■/■ | ●/● | ■/■ |
| *Skin and subcutaneous tissue disorders* | | | | |
| Rash[*]/urticaria | ■/○ | ■/◉ | ■/○ | ■/● |
| Dry skin/pruritus | ○/■ | ●/■ | ●/■ | ●/■ |
| Vitiligo/erythema | ○/○ | ●/● | ●/● | ◉/● |
| Alopecia | ○ | ● | ● | ◉ |
| *Musculoskeletal and connective tissue disorders* | | | | |
| Arthralgia | ■ | ● | ■ | ■ |
| Myositis[*]/arthritis | | ○/◉ | ●/● | ◉/● |
| Musculoskeletal pain | ● | ● | ■ | ■ |
| *Renal and urinary disorders* | | | | |
| Renal failure (including acute kidney injury) | ○ | ◉ | ○ | ● |
| Creatinine increased | ○ | ● | ● | ● |
| *General disorders* | | | | |
| Pyrexia | ■ | ● | ■ | ■ |
| Influenza-like illness/chills | ●/● | ○/○ | ●/● | ○/○ |
| Fatigue | ■ | ■ | ■ | ■ |
| Asthenia | ■ | ○ | ■ | ○ |
| Edema | ○ | ● | ■ | ● |

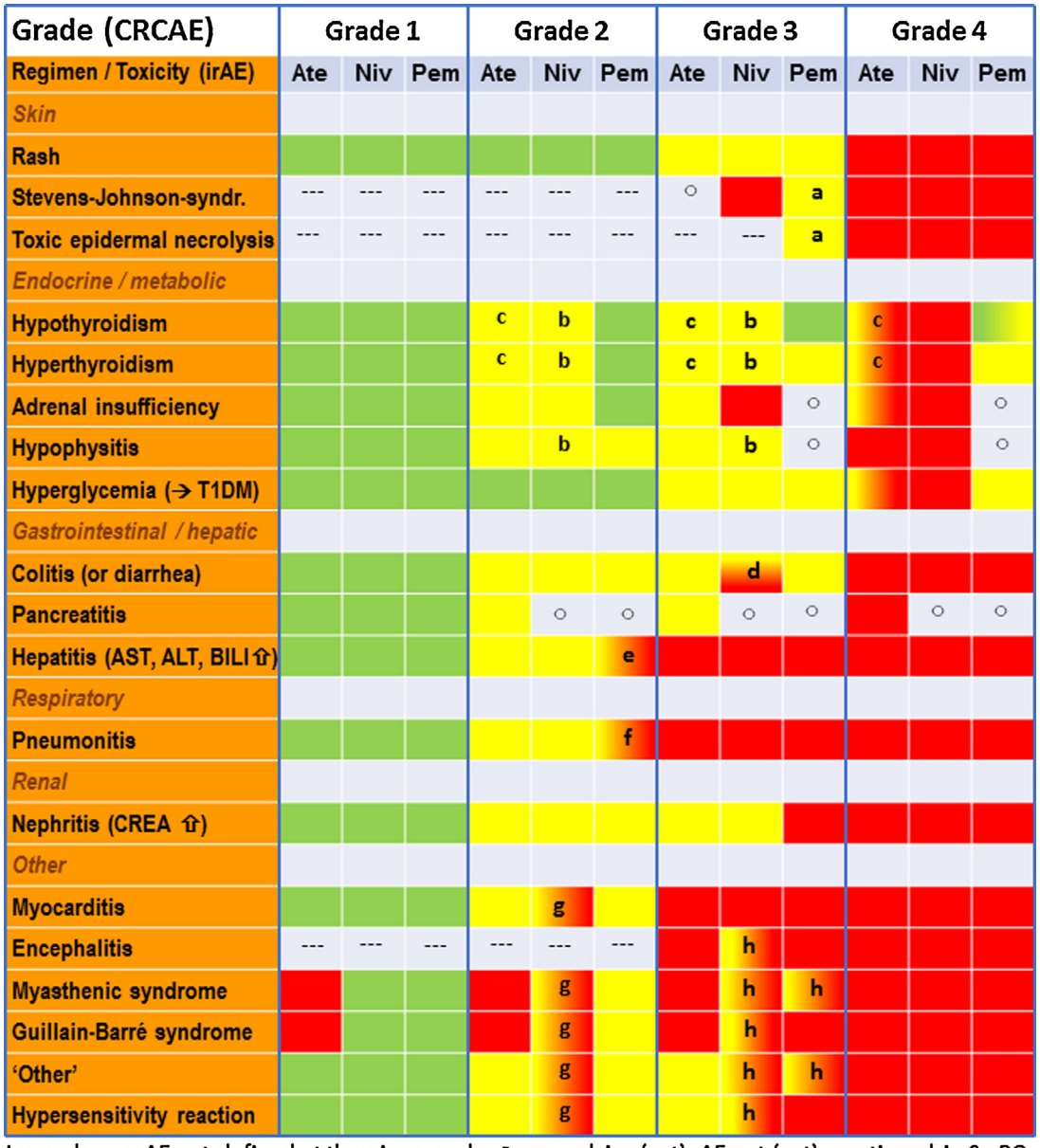
ADR = adverse drug reaction; ALT = alanine transaminase; AST = aspartate transaminase; EU = European Union; irAE = immune-related adverse event; SmPC = summary of product characteristics; ■ = very common (≥1/10 patients [≥10%]); ● = common (≥1/100 and <1/10 patients [≥1% and <10%]); ◉ = uncommon (≥1/1000 and <1/100 patients [≥0.1% and <1%]); ⊙ = rare (≥1/10 000 and <1/1000 patients [≥0.01% and <0.1%]); ○ = very rare (<1/10 000 patients [<0.01%]); ◌ = not (yet) mentioned; frequency not yet determined.

Listed in the table are adverse reactions that are classified as "very common" or "common" for at least one drug regimen approved for use.

[a] SmPC versions: as of April 30, 2019.

[b] Includes (mainly): adrenal insufficiency, hypophysitis, and thyroiditis.

[*] Classified as irAE also.




Legend: --- = AE not defined at the given grade; ○ = no advice (yet), AE not (yet) mentioned in SmPC

[a] withhold, if ADR is suspected
[b] if symptomatic; therapy to be restarted once symptoms resolved (in presence of hormone replacement therapy)
[c] therapy might be resumed if symptoms are controlled & TSH levels decrease (hypothyroidism) / thyroid function improves (hyperthyroidism)
[d] nivolumab monotherapy: withhold; nivolumab + ipilimumab: permanently discontinue
[e] permanently discontinue in case of liver metastasis with baseline grade 2 elevation of AST/ALT or lasting AST/ALT
[f] permanently discontinue therapy, if recurrent grade 2
[g] permanently discontinue therapy, if persisting grade 2
[h] permanently discontinue if recurrent grade 3

**Fig. 1 – Recommendations dependent on irAE type/severity for treatment modifications of ICI therapy. Various colors indicate that treatment may be continued (green), should be interrupted (yellow), or should be discontinued permanently (red; assessment based on drug manufacturers' current prescribing information text according to Table 2). ADR = adverse drug reaction; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase Ate = atezolizumab; BILI = bilirubin; CREA = creatinine; CTCAE = Common Terminology Criteria for Adverse Events; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; Niv = nivolumab; Pem = pembrolizumab; SmPC = summaries of product characteristics; syndr. = syndrome; TSH = thyroid-stimulating hormone.**

vomiting [50], infusion-related reactions [51], pain [52], or cardiotoxicities [53,54]. More specific recommendations for the management of immunotherapy-induced toxicities are provided in a specific, novel European Society for Medical Oncology Clinical Practice Guideline [55]; for the USA, similar guidance has been provided by the American Society of Clinical

Oncology [56]. For the most relevant irAEs, specific recommendations for their diagnosis and clinical management are given in the subsequent text chapters.

### 4.1. Skin and mucosal toxicity

#### 4.1.1. Statement

Rash and pruritus are the clinically most relevant dermatological side effects, which are reversible and clinically well manageable; their predictive value for response/survival requires clarification in larger studies. For CTCAE grading, the affected body surface area is estimated using the "rule of nine" (known from burns). Urologists should consult a dermatologist in case of persisting or recurrent grade 3 (>30% of body surface area affected) toxicity.

#### 4.1.2. Background

Very common skin toxicities include itching (pruritus) and associated rash, often in maculopapular form, and vitiligo (Table 2), most often in melanoma patients [57]. Widespread rash (exanthema) may occur at the trunk and/or extremities; treatment modalities include the use of topical corticosteroids (eg, hydrocortisone creams 1%) or moisturizing creams or lotions containing urea or glycerine. For continued itching, oral, nonsedative, systematic H1-antihistamines might be used. Regular examinations prior to and during ICI therapy should rule out skin problems of other etiology, such as an infection, vasculitis, or contact dermatitis. The association of dermatological AEs and ICI response or survival has been investigated, but its predictive value remains uncertain [58].

For severe rash, treatment interruption (grade 3) or permanent discontinuation (grade 4) of ICI therapy is recommended (Fig. 1), and patients should immediately be placed under a dermatologist's supervision: this applies particularly if severe skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, are suspected or clinically manifest. Treatment consists of intravenous (i.v.) (methyl)prednisolone 1–2 mg/kg, with slow tapering and switching to oral therapy when toxicity resolves to normal [53].

### 4.2. Endocrinological and metabolic toxicities

#### 4.2.1. Statement

Thyroid gland disorders are common side effects of ICIs, with 5–10% of all patients being affected. Narrow monitoring of TSH and a detailed hormone analysis (ACTH, LH, FSH, prolactin, cortisol, and estradiol/testosterone) for otherwise unspecific symptoms or deterioration are required. The onset of immune-related endocrinopathies is slow; their resolution may last for weeks and is not always reversible. Patients should be informed adequately prior to the initiation of treatment that occurrence of endocrinopathies may result in long-lasting or even permanent hormone replacement therapy. In case of suspected endocrinopathy other than hypo-/hyperthyreosis, the patient should be referred early to a specialist with experience in the management of immune-related endocrinopathies.

#### 4.2.2. Background

ICI-related immune endocrinopathies commonly include thyroid gland disorders (hypothyroidism, and less frequently hyperthyroidism or thyroiditis). Adrenal insufficiency is a common disorder too, while hypophysitis is a rather rare event (Table 2). Compared with PD-1 ICI monotherapy, endocrine toxicities are more frequent under combined immune checkpoint blockade [43]. Owing to their unspecific and often complex symptoms, the diagnostic approach might be challenging [59].

The pathogenesis of thyroid disorders arising from ICI therapy is not yet well understood [36,53]. Regular control of TSH—if repeatedly elevated or decreased TSH or if a thyroid dysfunction is suspected, fT3, fT4, and cortisol should be measured as well—is helpful to diagnose hypo- or hyperthyroidism: these toxicities occur rather late after the start of therapy and resolve more slowly than other immune-related toxicities [43,60]. Substitution with thyroid hormone (L-thyroxin, starting dose 50 mg) should be considered if hypothyroidism is diagnosed. Mild and asymptomatic hyperthyroidism may be initially observed and might eventually turn into hypothyroidism. However, in symptomatic patients, beta-blockers might be started [53]; interruption of ICI therapy until recovery from symptoms is generally SmPCs recommended for CTCAE of grade 3 (Fig. 1).

Adrenal insufficiency may manifest with diffuse symptoms including signs of dehydration, electrolyte abnormalities (hyperkalemia and hyponatremia), hypotension, and/or shock, sometimes mild to moderate but occasionally leading to an adrenal crisis [61]. The disorder might also develop following (partial) insufficiency of the pituitary gland and therefore requires a differential diagnosis: whether the adrenal gland is affected or a hypophyseal insufficiency is suspected. Corticosteroid replacement may be sufficient in patients with moderate symptoms (grade 2), but high-dose steroids are required in more severe cases (grade 3–4). When symptoms ameliorate, the use of hydrocortisone has been recommended to avoid the additional use of fludrocortisone as mineral corticoid replacement [62]. An endocrinologist should be consulted to supervise/optimize substitution.

Immune-related inflammation of the pituitary gland may lead to local swelling and hormone dysfunction most commonly presenting as central adrenal insufficiency. Thus, hypophysitis is diagnosed by the detection of decreased ACTH, LH, FSH, TSH, and prolactin, as well as subsequently decreased cortisol and gender-dependent estradiol or testosterone; magnetic resonance tomography (MRT) of the brain might confirm a swollen or enlarged pituitary gland. Symptoms of hypophysitis are generally unspecific and include those of adrenal insufficiency (see above) as well as headache, impaired vision, and dizziness. High-dose corticosteroids should be given at least in cases with severe symptoms (grade 3–4); ICI therapy should be interrupted in grade 2–3 cases and discontinued for grade 4 cases (Fig. 1): this irAE may result in continuous hormone (hydrocortisone) replacement therapy [63].

Endocrine side effects are reversible in approximately half of all the patients with thyroid or pituitary gland side

effects, often requiring long-lasting hormone replacement therapy. Therefore, all patients should be informed upfront about this potential, aggravating consequence of ICI therapy.

Type I diabetes mellitus and also diabetes insipidus are uncommon to rare side effects; advice is given to regularly monitor blood glucose levels, particularly if patients report polydipsia or polyuria [43,53]. In severe cases, patients may develop ketoacidosis [64] that should be treated according to established guidelines. Patients developing diabetes may require insulin substitution; in metabolically stable patients, ICI therapy may be restarted [53,65].

### 4.3. Gastrointestinal and hepatic toxicities

#### 4.3.1. Statement

To detect toxicities early, urologists should train and advise their patients to report any suspicious gastrointestinal and bowel symptoms directly to them; regarding hepatic irAEs, close monitoring of liver transaminases and bilirubin is a key prerequisite.

#### 4.3.2. Background

Similar to skin and endocrine toxicities, certain gastrointestinal side effects (diarrhea, nausea, and vomiting) are very common. Therapy-induced inflammation reactions under monotherapy vary from being common to uncommon side effects (Table 2); routine monitoring should encompass events such as stomatitis, colitis, and pancreatitis as well as hepatitis [66]. Diarrhea, although a rather unspecific adverse reaction, and very frequently observed with chemotherapy or tyrosine kinase inhibitor therapy, is however categorized as an irAE: its onset and resolution are equated in the official prescribing information with the onset and resolution of colitis, the most frequent severe gastrointestinal ADR of ICI therapy. Diagnostic workup of colitis symptoms such as diarrhea, mucus or blood in stool, abdominal pain, or change in bowel habits should include microbiological examination of stool to exclude pathological intestinal germs.

Therapy of mild to moderate symptoms of colitis include withholding the ICI treatment beginning at CTCAE grade 2 and start of oral corticosteroid therapy: from grade 2 symptoms upward, a colonoscopy should be considered. For combined immune checkpoint blockade, permanent therapy discontinuation is recommended for grade 3 or higher cases (Fig. 1); similarly, ICI monotherapy should be stopped after a first episode of grade 4 colitis and/or diarrhea. In case of grade 3 diarrhea or colitis, or in case of remaining symptoms after ICI withdrawal, the i.v. application of corticosteroids is recommended without further delay. Diarrhea and colitis are more frequent and occur earlier with CTLA-4 antibodies than with PD-1 or PD-L1 therapy [42]. In case i.v. administration of corticosteroids does not improve symptoms of a (moderate to) severe colitis, immune suppression should be escalated by using infliximab in cases that are refractory to steroids after 3–5 d [53,58].

Increased lipase and amylase as well as bowel pain or vomiting may indicate moderate to severe forms of pancreatitis, which is commonly seen with combined anti-CTLA-4 plus PD-1 ICI therapy (Table 2). Pancreatitis as well as small bowel enterocolitis may be visible through computer tomography (CT): if confirmed, discontinuation of ICI therapy and initiation of immunosuppression treatment is recommended in symptomatic patients with severe inflammation reactions (Fig. 1) [53]. However, treatment may be continued in cases of asymptomatic increases of amylase and lipase up to grade 3.

Narrow monitoring of serum transaminases (AST and ALT) and bilirubin is the key to detect immune-related hepatitis and should be carried out prior to each treatment cycle [67]. Loss of appetite, nausea and vomiting, fatigue, icterus, and frequent hematomas are other unspecific events. As hepatitis is a diagnosis by exclusion, other causalities—particularly infections including viral hepatitis—must be ruled out [53,63]. Liver sonography to exclude cholestasis or tumor progression and liver biopsy may be considered in assisting in the differential diagnosis of more severe hepatic side effects [58]. Treatment of hepatitis includes the use of corticosteroids and, depending on severity, additive immunosuppressant agents, for example, mycophenolate mofetil (as infliximab is hepatotoxic), if there is no response to corticosteroids within 2–3 d. ICI therapy should be withheld if transaminases or bilirubin reach CTCAE grade 2: this has been recommended already (Fig. 1). For hepatitis grade 3, all drug manufacturers recommend permanent discontinuation of ICI therapy.

### 4.4. Pulmonary toxicity

#### 4.4.1. Statement

Pneumonitis, the only severe irAE of common frequency in PD-1 ICI monotherapy (ie, in >1% of patients), has been the ADR associated with the highest number of fatal outcomes in clinical trials and routine use. Treating physicians should carefully monitor any pulmonary symptoms during or after ICI therapy and start differential diagnostic workup (eg, high-resolution thoracic CT) immediately in case of suspected pulmonary inflammation reactions.

#### 4.4.2. Background

Pneumonitis is one of the most common irAEs and the only severe irAE of common frequency (1.4%) [40]; numerous cases with a fatal outcome are reported (Table 1) [68,69]. Hence, any pulmonary symptoms during ICI therapy should be monitored carefully: in case of upper airway infections, cough, hypoxia or dyspnea, use of high-resolution thoracic CT shall be considered to exclude pneumonitis. Ideally, an infection should be ruled out by bronchoscopy, especially in case of suspected pneumonitis of grade 2 or higher.

After diagnosis, corticosteroid therapy should be started immediately with close lung function and blood gas control; thoracic X-ray is required in short intervals to control the clinical course of pneumonitis. Exclusion of infection allows introduction of immunosuppressive therapy more safely, as such medication increases the chance of opportunistic infections [53]. However, if the differential diagnosis

between pneumonitis and pneumonia remains uncertain, high-dose corticosteroids and antibiotics should be applied simultaneously.

Higher-grade pneumonitis leads to permanent discontinuation of ICI therapy; one drug manufacturer has already recommended therapy discontinuation in case of recurrent grade 2 pneumonitis (Fig. 1). In severe cases, additional nonsteroidal immune suppression, for example, with mycophenolate mofetil, should be considered. Corticosteroids should be tapered over 4–6 wk (or even more slowly) after recovery. For prophylaxis of opportunistic infections during this time, use of trimethoprim and sulfamethoxazole (eg, 3× weekly) has been recommended [53,63].

### 4.5. Renal toxicity

#### 4.5.1. Statement

Routine clinical chemistry (serum sodium, potassium, creatinine, and urea) should be monitored during and after ICI therapy to monitor for renal dysfunctions.

#### 4.5.2. Background

Cases of renal dysfunction are common under ICI therapy, usually indicated by an asymptomatic increase in creatinine: the incidence is higher with the combination of nivolumab and ipilimumab (Table 2) [4,53]. Diagnostically, serum sodium, potassium, creatinine, and urea should be monitored during ICI therapy, and urinalysis (eg, proteinuria) should be performed in case of creatinine rise [70,71]. However, histologically proven cases with nephritis are rare. Therefore, other causes of renal function deterioration (eg, exsiccosis) should be excluded and renal biopsy should be considered prior to start of corticosteroid therapy for potential immune-related renal inflammation or damage. Beginning with creatinine elevations of grade 2 or higher, therapy should be withheld; for a grade 3 increase, certain drug manufacturers recommend stopping ICI therapy permanently (Fig. 1).

### 4.6. Cardiac toxicity

#### 4.6.1. Statement

One should be aware of the rare, but potentially life-threatening, cardiac irAEs that may result from ICIs. In case of doubt, consult a cardiologist early.

#### 4.6.2. Background

Immune-related cardiovascular toxicities are rare, but higher, with the combination of nivolumab plus ipilimumab. Cardiovascular toxicities can be life threatening and have caused fatalities; they deserve special attention and early consultation with a cardiologist [43]. Onset of cardiotoxicity may occur early during treatment, with nonspecific symptoms such as fatigue or hypotension, or may occur as acute heart failure directly. Clinical symptoms and elevated creatinine kinase should prompt further diagnostic modalities, including echocardiography or cardiac MRT, as well as cardiac biopsy. High-dose corticosteroids were successful in some patients, but the course was fatal in others [53]. Drug manufacturers recommend permanently discontinuation of ICI therapy in case of myocarditis with CTCAE grade ≥3 and even in case of persisting grade 2 toxicity (Fig. 1).

### 4.7. Neurological toxicity

#### 4.7.1. Statement

Neurological side effects are rare but might result in serious outcomes for patients; in case of onset, early therapy interruption and permanent discontinuation for all severe events (grade 3 and higher) are recommended.

#### 4.7.2. Background

Neurological events are rare and may present in the form of encephalitis, Guillain-Barré syndrome, myasthenic syndrome, or myasthenia gravis [72–74], or other very rare events [43]; some were recently identified through EMA routine pharmacovigilance activities. Brain metastasis should be excluded by MRT in case of neurological symptoms. As laboratory and other examinations might differ from classical diagnostic procedures, a neurologist should be consulted in case of a suspected neurological irAE. Treatment should include high-dose steroids as oral or i.v. prednisolone (1–2 mg/kg) and might be intensified through additional immunosuppressive measures. Permanent discontinuation of ICI therapy is generally recommended for grade 3 or higher neurological toxicities (Fig. 1).

## 5. Conclusions

Immunotherapy using ICIs plays an important role in the treatment of patients with advanced urological cancers. In order to manage patients with ICI treatment safely, urologists should be aware of the nature, diagnosis, and treatment of immune-related AEs. Most toxicities affect the skin with rash and pruritus, the gastrointestinal tract with hepatitis and colitis/diarrhea, the endocrine system with thyroid gland disorders, and the lung with pneumonitis. However, immune-related AEs may affect any organ system, and should be considered in each patient with current or prior ICI treatment. Immune-related AEs should be graded according to CTCAE in order to decide about treatment interruption or discontinuation as well as the initiation of corticosteroid therapy. For urologists inexperienced in immunotherapy, early referral for suspected irAEs to specialist care is strongly recommended. For the safe use of ICI therapy, early identification, and management of toxicity, close multidisciplinary collaboration is mandatory.

***Author contributions:*** Marc-Oliver Grimm had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Grimm, Van Poppel, Wirth.
*Acquisition of data:* Grimm.
*Analysis and interpretation of data:* Grimm, Bex, De Santis, Ljunberg, Catto, Rouprêt, Hussain, Bellmunt, Powles, Wirth, Van Poppel.
*Drafting of the manuscript:* Grimm.
*Critical revision of the manuscript for important intellectual content:* Grimm, Bex, De Santis, Ljunberg, Catto, Rouprêt, Hussain, Bellmunt, Powles, Wirth, Van Poppel.

*Statistical analysis:* None.
*Obtaining funding:* None.
*Administrative, technical, or material support:* None.
*Supervision:* Grimm, Bex, De Santis, Ljunberg, Catto, Rouprêt, Hussain, Bellmunt, Powles, Wirth, Van Poppel.
*Other:* None.

***Financial disclosures:*** Marc-Oliver Grimm certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Axel Bex reports participation in advisory boards of Pfizer, BMS, Novartis, Ipsen, and Eusa; fees were paid to an institutional account for participation in the CheckMate 914 and IMmotion 010 adjuvant trials; research grants were received from Pfizer for a neoadjuvant phase 2 trial of avelumab and axitinib in high-risk. Börje Ljunberg has received company speaker honoraria from GlaxoSmithKline, Roche, Pfizer, and Novartis; has participated in trials for GlaxoSmithKline, Medivation, Pfizer, and Janssen R&D; and has been on advisory boards for Pfizer and GlaxoSmithKline. Hendrik Van Poppel has no conflicts of interest to declare. Joaquim Bellmunt declares payments for advisory boards by Genentech, MSD, Pfizer, BMS, Pierre-Fabre, and Janssen; lecture fees by Genentech, MSD, Pfizer, BMS, Pierre-Fabre, and Janssen; and research funding by Takeda and Pfizer. James Catto has been paid to lecture by Roche, MSD, Nucleix, Roche, BMS, and Astra Zeneca; and has received payment for advisory boards and consultancy from Astra Zeneca, Astellas, and Steba Biotech. Maria De Santis reports personal financial interests for Amgen, Astellas, AstraZeneca, Bayer, Bioclin, BMS, EISAI, ESSA, Ferring, Ipsen, Janssen, MSD, Merck, Novartis, OncoGenex, Pfizer, Pierre Fabre Oncology, Roche, Sandoz, Sanofi, SeaGen, Synthon, and Takeda; and institutional financial interests for Amgen, Astellas, AstraZeneca, Bayer, Bioclin, BMS, EISAI, ESSA, Ferring, Ipsen, Janssen, MSD, Merck, Novartis, OncoGenex, Pfizer, Pierre Fabre Oncology, Roche, Sandoz, Sanofi, SeaGen, and Takeda. Marc-Oliver Grimm reports payments for advisory boards and consultancy from Astellas, AstraZeneca, Bayer Healthcare, BMS, Intuitive Surgical, Ipsen, Janssen Cilag, Merck Darmstadt, MSD, Novartis, Pfizer, and Sanofi Aventis; and payment for lectures by Apogepha, Astellas, AstraZeneca, Bayer Healthcare, BMS, GlaxoSmithKline, Ipsen, Janssen Cilag, MSD, Novartis, ONO Pharma, and Pfizer. Morgan Rouprêt reports participation in advisory boards of MSD, Ferring, Janssen, and Roche; and institutional support from Roche. Manfred Wirth reports personal fees from Amgen, ABX Advanced Biochemical Compounds, Apogepha, Astellas, Bayer Vital, Janssen-Cilag, MSD Sharp & Dohme, Novartis, and Pierre Fabre. Syed A. Hussain has been paid to lecture by Roche, MSD, AstraZeneca, BMS, Sotio, Janssen, Pierre Fabre, and Pfizer; and has received payment for advisory boards and consultancy from Roche, MSD, Astra Zeneca, Astellas, BMS, Pierre Fabre, Janssen, Pfizer, and Bayer. Tom Powles reports lecture fees of Genentech, MSD, Pfizer, BMS, AZ, Janssen, and Novartis; research funding by AZ Roche; and payments for advisory boards by Genentech, MSD, Pfizer, BMS, and AZ.

***Funding/Support and role of the sponsor:*** None.

***Acknowledgments:*** The authors thank Dr. Markus Hartmann for editorial assistance.

## References

[1] Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol 2016;39:98–106.
[2] Hahn NM, Necchi A, Loriot Y, et al. Role of checkpoint inhibition in localized bladder cancer. Eur Urol Oncol 2018;1:190–8.
[3] Ljunberg B, Albiges L, Bensalah K, et al. EAU guidelines on renal cell carcinoma. EAU; 2019.
[4] Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. In press. http://dx.doi.drg/10.1038/s41571-019-0218-0.
[5] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.
[6] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.
[7] European Medicines Agency. Withdrawal of application for a change to the marketing authorization for Tecentriq (atezolizumab). EMA/798527/2018. https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-withdrawal-application-change-marketing-authorisation-tecentriq-atezolizumab_en.pdf.
[8] Motzer RJ, Penkov K, Haanen JB, et al. Avelumab plus axitinib versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2019;380:1103–15.
[9] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2019;380:1116–27.
[10] Witjes JA, Bruins M, Cathomas R, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer. EAU; 2019.
[11] Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.
[12] Vaughn DJ, Bellmunt J, Fradet Y, et al. Health-related quality-of-life analysis from KEYNOTE-045: a phase III study of pembrolizumab versus chemotherapy for previously treated advanced urothelial cancer. J Clin Oncol 2018;36:1579–87.
[13] 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;387:1909–20.
[14] Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748–57.
[15] Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicenter, single-arm, phase 2 trial. Lancet Oncol 2017;388:312–22.
[16] Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017;18:1483–92.
[17] 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.
[18] Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432–8.
[19] Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. J Clin Oncol 2018;36:3353–60.
[20] Castellano D, Duran Martinez I, Rodríguez-Vida A, et al. A phase II study investigating the safety and efficacy of neoadjuvant

atezolizumab in muscle invasive bladder cancer (ABACUS). Ann Oncol 2018;29(Suppl. 8):viii303–3.
[21] Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:700–12.
[22] Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. J Clin Oncol 2017;35:40–7.
[23] Cabel L, Loir E, Gravis G, et al. Long-term complete remission with Ipilimumab in metastatic castrate-resistant prostate cancer: case report of two patients. J Immunother Cancer 2017;5:31.
[24] Graff JN, Alumkal JJ, Drake CG, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget 2016;7:52810–7.
[25] Redman JM, Steinberg SM, Gulley JL. Quick efficacy seeking trial (QuEST1): a novel combination immunotherapy study designed for rapid clinical signal assessment metastatic castration-resistant prostate cancer. J Immunother Cancer 2018;6:91.
[26] Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer 2016;16:275–87.
[27] Patil PD, Burotto M, Velcheti V. Biomarkers for immune-related toxicities of checkpoint inhibitors: current progress and the road ahead. Expert Rev Mol Diagn 2018;18:297–305.
[28] Zhu J, Armstrong AJ, Friedlander TW, et al. Biomarkers of immunotherapy in urothelial and renal cell carcinoma: PD-L1, tumor mutational burden, and beyond. J Immunother Cancer 2018;6:4.
[29] Melosky B, Chu Q, Juergens RA, et al. Breaking the biomarker code: PD-L1 expression and checkpoint inhibition in advanced NSCLC. Cancer Treat Rev 2018;65:65–77.
[30] Udall M, Rizzo M, Kenny J, et al. PD-L1 diagnostic tests: a systematic literature review of scoring algorithms and test-validation metrics. Diagn Pathol 2018;13:12.
[31] Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. J Thorac Oncol 2017;12:208–22.
[32] Tsao MS, Kerr KM, Kockx M, et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of blueprint phase 2 project J Thorac Oncol 2018;13:1302–11.
[33] Rimm DL, Han G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer. JAMA Oncol 2017;3:1051–8.
[34] European Medicines Agency. EMA restricts use of keytruda and tecentriq in bladder cancer. EMA press release; EMA/364553/2018; 1 June 2018.
[35] FDA. FDA drug safety and availability alerts. FDA alerts health care professionals and oncology clinical investigators about an efficacy issue identified in clinical trials for some patients taking keytruda (pembrolizumab) or tecentriq (atezolizumab) as monotherapy to treat urothelial cancer with low expression of PD-L1. Alert 18 May 2018; update 20 June 2018.
[36] Powles T, Geschwend JE, Loriot Y, et al. Phase 3 KEYNOTE-361 trial: Pembrolizumab (pembro) with or without chemotherapy versus chemotherapy alone in advanced urothelial cancer. J Clin Oncol 2017;35(Suppl.):TPS4590.
[37] Galsky MD, Grande E, Davis ID, et al. IMvigor130: a randomized, phase III study evaluating first-line (1L) atezolizumab (atezo) as monotherapy and in combination with platinum-based chemotherapy (chemo) in patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC). J Clin Oncol 2018;36 (Suppl.):TPS4589.
[38] Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68.
[39] Chen TW, Razak AR, Bedard PL, Siu LL, Hansen AR. A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors. Ann Oncol 2015;26:1824–9.
[40] European Medicines Agency. Assessment report Opdivo (nivolumab). EMA/682492/2015, September 24, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003985/WC500197950.pdf.
[41] Nishijima TF, Shachar SS, Nyrop KA, Muss HB. Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy in patients with advanced cancer: a meta-analysis. Oncologist 2017;22:470–9.
[42] Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2018;360:k793.
[43] Wang PF, Chen Y, Song SY, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. Front Pharmacol 2017;8:730.
[44] Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol 2017;28:2377–85.
[45] Hassel JC, Heinzerling L, Aberle J, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): evaluation and management of adverse drug reactions. Cancer Treat Rev 2017;57:36–49.
[46] El Osta B, Hu F, Sadek R, Chintalapally R, Tang SC. Not all immune-checkpoint inhibitors are created equal: meta-analysis and systematic review of immune-related adverse events in cancer trials. Crit Rev Oncol Hematol 2017;119:1–12.
[47] Ripamonti CI, Antonuzzo A, Bossi P, Cavalieri S, Roila F, Fatigoni S. Fatigue, a major still underestimated issue. Curr Opin Oncol 2018;30:219–25.
[48] Pearson EJ, Morris ME, McKinstry CE. Cancer-related fatigue: appraising evidence-based guidelines for screening, assessment and management. Support Care Cancer 2016;24:3935–42.
[49] Bossi P, Antonuzzo A, Cherny NI, et al. Diarrhea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29 (Suppl. 4):iv126–42.
[50] Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016;27(Suppl. 5):v119–33.
[51] Roselló S, Blasco I, García Fabregat L, Cervantes A, Jordan K, ESMO Guidelines Committee. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29(Suppl. 4), iv260.
[52] Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F, ESMO Guidelines. Management of cancer pain: ESMO Clinical Practice Guidelines Working Group. Ann Oncol 2012;23(Suppl. 7):vii139–5.
[53] Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2768–801.
[54] Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23(Suppl. 7): vii155–6.

[55] Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl. 4): iv264–6.
[56] Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714–68.
[57] Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer 2016;60:12–25.
[58] Hopkins AM, Rowland A, Kichenadasse G, et al. Predicting response and toxicity to immune checkpoint inhibitors using routinely available blood and clinical markers. Br J Cancer 2017;117:913–20.
[59] Sznol M, Postow MA, Davies MJ, et al. Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. Cancer Treat Rev 2017;58:70–6.
[60] Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev 2016;45:7–18.
[61] Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2016;101:364–89.
[62] Grimm MO, Oppel-Heuchel H, Foller S. Treatment with PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors: immune-mediated side effects. Urologe A 2018;57:543–51.
[63] Solinas C, Porcu M, De Silva P, et al. Cancer immunotherapy-associated hypophysitis. Semin Oncol 2018;45:181–6.
[64] Gauci ML, Laly P, Vidal-Trecan T, et al. Autoimmune diabetes induced by PD-1 inhibitor-retrospective analysis and pathogenesis: a case report and literature review. Cancer Immunol Immunother 2017;66:1399–410.
[65] Foller S, Oppel-Heuchel H, Fetter I, Winkler Y, Grimm MO. Adverse events of immune checkpoint inhibitors. Urologe A 2017;56:486–91.
[66] Samaan MA, Pavlidis P, Papa S, Powell N, Irving PM. Gastrointestinal toxicity of immune checkpoint inhibitors: from mechanisms to management. Nat Rev Gastroenterol Hepatol 2018;15:222–34.
[67] Suzman DL, Pelosof L, Rosenberg A, Avigan MI. Hepatotoxicity of immune checkpoint inhibitors: an evolving picture of risk associated with a vital class of immunotherapy agents. Liver Int 2018;38:976–87.
[68] Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of Programmed Death 1 and Programmed Death-Ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. Chest 2017;152:271–81.
[69] Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol 2016;2:1607–16.
[70] Wanchoo R, Karam S, Uppal NN, et al. Adverse renal effects of immune checkpoint inhibitors: a narrative review. Am J Nephrol 2017;45:160–9.
[71] Rassy EE, Kourie HR, Rizkallah J, et al. Immune checkpoint inhibitors renal side effects and management. Immunotherapy 2016;8:1417–25.
[72] Fellner A, Makranz C, Lotem M, et al. Neurologic complications of immune checkpoint inhibitors. J Neurooncol 2018;137:601–9.
[73] Eldar AH, Chapman J. Guillain Barré syndrome and other immune mediated neuropathies: diagnosis and classification. Autoimmun Rev 2014;13:525–30.
[74] Makarious D, Horwood K, Coward JIG. Myasthenia gravis: an emerging toxicity of immune checkpoint inhibitors. Eur J Cancer 2017;82:128–36.