Published in final edited form as:

Urol Oncol. 2017 April ; 35(4): 142–148. doi:10.1016/j.urolonc.2017.01.017.

Nivolumab treatment for advanced renal cell carcinoma: Considerations for clinical practice

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Abstract

Background: Nivolumab is an important new therapy option for patients with advanced renal cell carcinoma, and has a different mechanism of action compared with vascular endothelial growth factor -targeted therapies. It is a programmed death 1 immune checkpoint inhibitor antibody with response patterns, efficacy, and safety profiles that differ from those of conventional antiangiogenic or mammalian target of rapamycin inhibition therapy.

Methods and Purpose: This commentary discusses and evaluates the clinical experience with nivolumab from the available literature and presents practical considerations for the use of nivolumab immunotherapy in aRCC to optimize clinical management.

Keywords

Advanced renal cell carcinoma; Immune checkpoint inhibitor; Immunotherapy agents; Nivolumab; Second-line therapy; PD-1 inhibitor

1. Introduction

Nivolumab, a programmed death 1 (PD-1) checkpoint inhibitor, was recently approved by the US Food and Drug Administration and the European Commission to treat patients with advanced renal cell carcinoma (aRCC) who have received prior antiangiogenic therapy [1,2]. Approval as second-line therapy was based on superior overall survival (OS) of nivolumab in a large, international, open-label, phase III study (CheckMate 025;) that randomized patients with advanced clear cell RCC to 3 mg/kg nivolumab intravenously every 2 weeks ($n = 410$) or 10 mg everolimus orally once daily ($n = 411$) [3].

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Conflict of interest

R. W. Joseph has received consultancy/advisory fees from Bristol-Myers Squibb. G. Chatta has received honoraria, consultancy/advisory fees, and travel/accommodation fees from Bristol-Myers Squibb. U. Vaishampayan has received honoraria, research support, and consultancy/advisory fees from Bristol-Myers Squibb, Sanofi, Genentech, Novartis, Pfizer, Exelixis, Astellas, and Bayer.

Nivolumab provides an important novel therapy option for patients with aRCC, with a different mechanism of action from other targeted therapies. It is a fully human IgG4 anti-PD-1 antibody that selectively blocks interaction between PD-1, which is expressed on activated T cells, and its ligands PD-L1 and PD-L2, which are expressed on immune cells and tumor cells (Fig.) [4-6].

In contrast, targeted agents used in the treatment of aRCC, for example, tyrosine kinase inhibitors, inhibit vascular endothelial growth factor (VEGF)/VEGF receptors or mammalian target of rapamycin (mTOR)-mediated pathways to suppress angiogenesis [6,8]. Although tyrosine kinase inhibitors and agents targeting mTOR have produced robust clinical effects in aRCC, some patients are resistant to these approaches and most, if not all, acquire resistance over time, limiting the overall clinical benefit of these treatments [9]. This underlines the need for therapies with a different mechanism of action.

With their unique mechanism of action, PD-1–targeted immunotherapy agents have response patterns, efficacy, and safety profiles that differ from conventional antiangiogenic or mTOR inhibition therapy. This editorial discusses practical considerations with use of PD-1–targeted immunotherapy, with specific reference to nivolumab in aRCC, to optimize clinical management.

2. OS with nivolumab vs. other second-line therapies

Despite significant improvements in progression-free survival (PFS) with antiangiogenic therapies, significant OS benefit in aRCC in the second-line setting is just emerging with new drug therapies (Table 1) [3,10-15].

Nivolumab is the first approved immunotherapy to show a significant OS benefit in second-line aRCC treatment, with a median OS of 25.0 months (95% CI: 21.8–not reached [NR]) with nivolumab vs. 19.6 months (95% CI: 17.6–23.1) with everolimus. The hazard ratio for death with nivolumab vs. everolimus was 0.73 (98.5% CI: 0.57–0.93, $P = 0.002$) [3]. In long-term follow-up studies of nivolumab in aRCC, approximately one-third of patients are alive at 5 years in the phase I study and 3 years in the phase II study [16].

3. Subgroup analysis of OS data to identify patients who may benefit from nivolumab treatment

Nivolumab showed benefit over everolimus across patient subgroups based on baseline factors in CheckMate 025, including Heng risk group, Karnofsky performance status, prior sunitinib or pazopanib therapy, and number of prior antiangiogenic therapies (Table 2) [3,17,18].

Tumor PD-L1 expression $<1\%$ was not found to be a marker of nivolumab treatment OS benefit in aRCC (Table 2) [3]. Similar results were observed among patients with PD-L1 expression $<5\%$ [3].

Although associations between tumor PD-L1 expression and improved outcomes have been observed with nivolumab treatment in other tumors (metastatic melanoma and non–small

cell lung cancer [19]), the predictive role of PD-L1 status on treatment outcomes remains to be determined [20,21]. There is currently a lack of identified biomarkers that reliably predict treatment benefit with immune PD-1 checkpoint inhibitors. This is an important area of ongoing investigation [8].

4. PFS vs. OS paradox of nivolumab

Significant improvement in median OS with nivolumab vs. everolimus was demonstrated in CheckMate 025, without significant improvement in median PFS. PFS after 6 months appeared to favor nivolumab over everolimus; however, the median PFS was similar [3]. PFS was not a surrogate predictor of OS in this study.

The exact mechanism of the PFS vs. OS paradox is not clear, with “pseudoprogression” being one potential explanation. T-cell infiltration in the tumor microenvironment after nivolumab treatment can result in the increase of lesion size and apparent progression. However, lesion size decreases after this initial increase. Additionally, there could be a delay in tumor response to treatment if there is a delay in immune system activation [22,23]. The use of traditional Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which have stringent definitions of progression, can affect PFS as related to immune-oncology treatments. For example, using RECIST 1.1 criteria, the appearance of 1 new lesion would be considered progression, even if the patient ultimately experiences clinical benefit as target tumors reduce in size or resolve [24].

Irrespective of the reason behind the PFS vs. OS discrepancy, this is a phenomenon that is being seen in patients with multiple tumor types treated with immunotherapies. Similar discrepancies were reported with ipilimumab in patients with melanoma [25], with sipuleucel-T in patients with castration-resistant prostate cancer [26], and with ibrutinib in patients with follicular lymphoma [27].

Although pseudoprogression does not occur frequently, occurrence of RECIST-defined progression should be analyzed with care in cases of treatment with immune-oncology drugs. If patients exhibit clear benefit and if clinically feasible (e.g., no clinical deterioration), immunotherapy could be continued beyond the point of progression to benefit some patients.

5. Response rate of nivolumab vs. other second-line therapies

In CheckMate 025, the objective response rate (ORR) was significantly higher with nivolumab than with everolimus (25% vs. 5%; odds ratio = 5.98 [95% CI: 3.68–9.72, $P < 0.001$]), comparing favorably with second-line VEGF-targeted therapies (Table 1). Responses were durable, with a median duration of response of 12.0 months (range: 0–27.6) [3]. The confirmed ORR is 21.5% (95% CI: 17.6–25.8) with nivolumab vs. 3.9% (95% CI: 2.2–6.2) with everolimus [1]. The ORR with nivolumab was consistent across patient subgroups based on baseline factors (Table 2).

6. Nivolumab treatment duration

The specific tumor response pattern with nivolumab treatment is different from that with targeted antiangiogenic therapies. Its immune-mediated mechanism of action means “tumor flare” may occur before the cellular immune response has a chance to affect tumor reduction, and there may be benefits in continuing nivolumab treatment beyond disease progression [23]. Tumor flare can confuse interpretation of tumor response and may result in patients discontinuing therapy before a clinical benefit can be demonstrated [22].

In a phase II study of nivolumab in patients with previously treated aRCC, 69% (25/36) of patients treated beyond initial progression (defined by RECIST) experienced subsequent tumor reduction or stabilization in target lesion size [28].

In CheckMate 025, nivolumab therapy after RECIST v.1.1 progression was permitted in patients who had investigator-assessed clinical benefit and tolerated the study drug. In total, 38% (154/406) of patients were treated beyond progression with nivolumab for 4 weeks after first progression. Of these, 140 patients had tumor measurements before and after progression, 14% of whom had 30% of tumor burden reduction from first progression [29]. This unconventional response pattern has also been observed in patients with melanoma, with a 30% of tumor burden reduction in target lesions achieved or maintained in 8.1% of patients receiving nivolumab treatment beyond progression [21].

There are currently no widely accepted guidelines or biomarkers to distinguish actual disease progression from pseudoprogression. However, we suggest that to differentiate between the 2, patients with RECIST-defined disease progression, who are either asymptomatic or show stable performance status, no significant deterioration of laboratory values, moderate growth on physical examination or radiographic imaging, or a symptomatic improvement in association with a mixed response, should be considered for repeat confirmation scans before true progressive disease is determined and immunotherapy is discontinued. Evaluation of disease characteristics at first progression, less deterioration in Karnofsky performance status, less small-to-bulky transition in tumor burden, higher ORR, shorter time to response, lower incidence of new bone lesions, and improved health-related quality of life (HRQoL) may provide guidance as to whether treatment beyond progression with nivolumab is likely to be beneficial [29].

7. Quality of life benefits with nivolumab treatment

Median changes from baseline in Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms (FKSI-DRS) questionnaires from CheckMate 025 showed rapid, significant, and sustained HRQoL improvement with nivolumab vs. everolimus [3]. The mean difference in FKSI-DRS scores between the nivolumab and everolimus groups was 1.6 (95% CI: 1.4–1.9, $P < 0.0001$), with clinically meaningful HRQoL improvement better with nivolumab (55%) vs. everolimus (37%, $P < 0.0001$). Median time to HRQoL improvement was shorter with nivolumab (4.7 mo, 95% CI: 3.7–7.5) vs. everolimus (median not reached, NR–NR) [30].

8. Nivolumab-related toxicities and appropriate management

Nivolumab had a favorable toxicity profile vs. everolimus in CheckMate 025. Treatment-related adverse events (AEs) of any grade occurred in 79% (319/406) of patients treated with nivolumab and in 88% (349/397) treated with everolimus. Grade 3 or 4 AEs occurred in 19% (76/406) with nivolumab and 37% (145/397) with everolimus. The most common AEs during nivolumab therapy were fatigue (33%; 134/406), nausea (14%; 57/406), and pruritus (14%; 57/406). The most common grade 3 or 4 AE was fatigue (2%, 10/406). No treatment-related deaths occurred with nivolumab [3].

Immune checkpoint inhibition is associated with a unique spectrum of side effects termed immune-related AEs (irAEs), for example, endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash [1,2]. These are typically transient, but occasionally can be moderate or severe. The incidence of irAEs can be unpredictable, and continuous vigilance for symptoms suggestive of irAEs is recommended. In general, many toxicities can be detected by routine bloodwork, and in particular, liver, kidney, and thyroid functions should be closely monitored. Management of irAEs can include either the use of corticosteroid immunosuppression or interruption of the checkpoint inhibitor (Table 3) [31].

9. Cost considerations

The cost of cancer therapy is substantial and is a key factor for many clinicians. Cost-effectiveness data were calculated for nivolumab and compared with those for everolimus based on the superior efficacy/tolerability demonstrated in CheckMate 025; the monthly cost per responder in the United States was significantly lower for nivolumab (\$54,315) vs. everolimus (\$224,711; $P=0.001$) [32]. Furthermore, nivolumab treatment had a favorable toxicity profile and provided superior improvement in HRQoL compared with everolimus, both previously associated with increased drug value [33].

10. Summary

Nivolumab is currently approved for use as a second-line therapy for patients with aRCC. Although ~25% of patients achieve an ORR by RECIST v.1.1, some patients treated with nivolumab beyond progression have tumor shrinkage, increasing the overall percentage of patients with aRCC who experience some degree of benefit. In addition to the substantial benefit nivolumab provides, only a minority of patients experience significant toxicities, providing nivolumab with a favorable efficacy-to-toxicity therapeutic ratio. Questions remain on how to optimize nivolumab treatment in patients with aRCC, including improving patient selection, exploring nivolumab in earlier lines of therapy, and defining optimal duration of therapy. Many of these questions will be answered in future studies.

Acknowledgment

All authors participated equally in manuscript inception, development, editing, and approval. Professional medical writing assistance was provided by Pam Milner, PhD, of PPSI (a PAREXEL company), funded by Bristol-Myers Squibb.

References

- [1]. Opdivo (nivolumab) injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Co; 2016.
- [2]. Opdivo [summary of product characteristics]. Uxbridge, UK: Bristol-Myers Squibb Pharma EEIG; 2015.
- [3]. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803–13. [PubMed: 26406148]
- [4]. Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory B7-H1 in renal cell carcinoma patients: indicator of tumor aggressiveness and potential therapeutic target. *Proc Natl Acad Sci U S A* 2004;101:17174–17179. [PubMed: 15569934]
- [5]. Thompson RH, Dong H, Lohse CM, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin Cancer Res* 2007;13:1757–61. [PubMed: 17363529]
- [6]. Raman R, Vaena D. Immunotherapy in metastatic renal cell carcinoma: a comprehensive review. *Biomed Res Int* 2015;2015:367354. [PubMed: 26161397]
- [7]. Brahmer JR, Hammers H, Lipson EJ. Nivolumab: targeting PD-1 to bolster antitumor immunity. *Future Oncol* 2015;11:1307–26. [PubMed: 25798726]
- [8]. Xu KY, Wu S. Update on the treatment of metastatic clear cell and non-clear cell renal cell carcinoma. *Biomark Res* 2015;3:5. [PubMed: 25734007]
- [9]. Rini BI, Atkins MB. Resistance to targeted therapy in renal-cell carcinoma. *Lancet Oncol* 2009;10:992–1000. [PubMed: 19796751]
- [10]. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010;116:4256–65. [PubMed: 20549832]
- [11]. Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2014;32:760–7. [PubMed: 24297950]
- [12]. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol* 2013;14:552–62. [PubMed: 23598172]
- [13]. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;378:1931–9. [PubMed: 22056247]
- [14]. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1814–23. [PubMed: 26406150]
- [15]. Quinn DI, Lara PN Jr. Renal-cell cancer-targeting an immune checkpoint or multiple kinases. *N Engl J Med* 2015;373:1872–4. [PubMed: 26406149]
- [16]. McDermott DF, Motzer RJ, Atkins MB, et al. Long-term overall survival (OS) with nivolumab in previously treated patients with advanced renal cell carcinoma (aRCC) from phase I and II studies [ASCO abstract 4507] [abstract]. *J Clin Oncol* 2016;34(15 Suppl).
- [17]. Motzer RJ, Sharma P, McDermott DF, et al. CheckMate 025 phase III trial: outcomes by key baseline factors and prior therapy for nivolumab (NIVO) vs everolimus (EVE) in advanced renal cell carcinoma (RCC) [Genitourinary Cancers Symposium abstract 498] [abstract]. *J Clin Oncol* 2016;34(Suppl 2).
- [18]. Motzer RJ, Escudier B, Choueiri TK. Treatment of advanced renal-cell carcinoma. *N Engl J Med* 2016;374:889–90. [PubMed: 26962911]
- [19]. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54. [PubMed: 22658127]
- [20]. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123–35. [PubMed: 26028407]
- [21]. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30. [PubMed: 25399552]

- [22]. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. *J Clin Oncol* 2015;33:3541–3. [PubMed: 26261262]
- [23]. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412–20. [PubMed: 19934295]
- [24]. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47. [PubMed: 19097774]
- [25]. Di Giacomo AM, Danielli R, Guidoboni M, et al. Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer Immunol Immunother* 2009;58:1297–306. [PubMed: 19139884]
- [26]. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22. [PubMed: 20818862]
- [27]. Salles GA, Trotman J, Lill M, et al. Pseudo-progression among patients with follicular lymphoma treated with ibrutinib in the phase 2 DAWN study [abstract]. *Blood* 2016;128:2980.
- [28]. George S, Motzer RJ, Hammers HJ, et al. Safety and efficacy of nivolumab in patients with metastatic renal cell carcinoma treated beyond progression: a subgroup analysis of a randomized clinical trial. *JAMA Oncol* 2016;2:1179–86. [PubMed: 27243803]
- [29]. Escudier B, Motzer RJ, Sharma P, et al. Treatment beyond progression with nivolumab (nivo) in patients (pts) with advanced renal cell carcinoma (aRCC) in the phase III CheckMate 025 study [ASCO abstract 4509] [abstract]. *J Clin Oncol* 2016;34(15 Suppl).
- [30]. Cella D, Grünwald V, Nathan P, et al. Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial. *Lancet Oncol* 2016;17:994–1003. [PubMed: 27283863]
- [31]. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015;26:2375–91. [PubMed: 26371282]
- [32]. Liu JS, Bell J, Rao S. Cost per responder analysis from the CheckMate 025 phase III study of nivolumab versus everolimus in previously treated patients with advanced renal cell carcinoma [abstract]. Presented at: Annual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Meeting; May 21–25, 2016; Washington, DC.
- [33]. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: revisions and reflections in response to comments received. *J Clin Oncol* 2016;34:2925–34. [PubMed: 27247218]

Fig.

Mechanism of action of nivolumab [7]. Interaction between PD-1 and PD-L1 or PD-L2 normally results in inhibition of the cellular immune response, and tumors with increased PD-L1 expression are associated with poor prognosis in renal cell carcinoma [4,5]. By disrupting PD-1/PD-L1-mediated signaling, nivolumab is thought to restore the immune response and antitumor immunity [6]. IFN = interferon; MHC = major histocompatibility complex. (Republished with permission of Future Medicine Ltd, from Brahmer et al. [7]; permission conveyed through Copyright Clearance Center, Inc.) (Color version of figure is available online).

Efficacy end points from recent phase III trials of previously treated aRCC (Adapted with permission from Quinn et al. [15])

Table 1

Trial and treatment	ORR, %	PFS		OS		
		Median, mo	HR (95% CI)	P	Median, mo	HR (95% CI) P
RECORD-1 [10]						
Best supportive care	0	1.9	0.33 (0.25–0.43)	0.001	14.4	0.87 (0.65–1.15) 0.162
Everolimus	2	4.9			14.8	
INTORSECT [11]						
Sorafenib	8	3.9	0.87 (0.71–1.07)	0.19	16.6	1.31 (1.05–1.63) 0.01
Temsirolimus	8	4.3			12.3	
AXIS [12,13]						
Sorafenib	9	4.7	0.67 (0.54–0.81)	<0.0001	19.2	0.97 (0.8–1.17) 0.37
Axitinib	19	6.7			20.1	
METEOR [14]						
Everolimus	5	3.8	0.58 (0.45–0.75)	<0.001	NR	0.67 (0.51–0.89) 0.005
Cabozantinib	21	7.4			NR	
CheckMate 025 [3]						
Everolimus	5	4.4	0.88 (0.75–1.03)	0.11	19.6	HR (98.5% CI) 0.73 (0.57–0.93) 0.002
Nivolumab	25	4.6			25.0	

HR = hazard ratio; NR = not reached.

Bold value represents HR (98.5% CI).

Table 2

Median OS and ORR by baseline subgroup characteristics in CheckMate 025 [3,17,18]

Subgroup	Median OS, mo (95% CI)		ORR, % (95% CI)	
	Nivolumab	Everolimus	Nivolumab	Everolimus
Heng risk group				
Favorable	NR (NR–NR)	29.0 (24.7–NR)	23.6 (13.2–37.0)	7.1 (2.4–15.9)
Intermediate	NR (21.4–NR)	19.9 (17.7–26.2)	24.4 (19.1–30.3)	5.0 (2.6–8.5)
Poor	15.3 (10.6–20.4)	8.4 (5.9–11.4)	30.2 (21.3–40.4)	4.8 (1.3–11.9)
KPS, %				
90–100	NR (26.7–NR)	29.0 (24.3–NR)	26.1 (21.0–31.7)	6.8 (4.1–10.6)
< 90	18.1 (14.3–22.2)	10.1 (7.9–12.8)	23.1 (16.3–31.2)	2.7 (0.7–6.8)
Prior antiangiogenic therapies				
1	23.6 (20.8–NR)	19.9 (17.7–24.7)	24.3 (19.7–29.4)	5.4 (3.2–8.6)
2	NR (18.1–NR)	18.4 (14.0–NR)	27.8 (18.9–38.2)	5.1 (1.7–11.4)
Prior therapy				
Sunitinib	23.6 (20.4–28.1)	–	23 (18–28)	–
Pazopanib	NR (19.7–NR)	–	28 (20–37)	–
Tumor PD-L1 expression				
1%	21.8 (16.5–28.1)	18.8 (11.9–19.9)	–	–
<1%	27.4 (21.4–NR)	21.2 (17.7–26.2)	–	–

Management of irAEs with immune checkpoint inhibitors (Republished with permission of Oxford University Press, from Naidoo et al. [31]; permission conveyed through Copyright Clearance Center, Inc.)

Table 3

Symptom	Grade/ severity	Management	Follow-up
Skin rash	1	Continue immunotherapy Administer topical corticosteroids Oral antihistamines for pruritus	If symptoms develop, treat as higher grade
	2	Administer oral prednisone 1 mg/kg/d or equivalent Oral antihistamines for pruritus	If symptoms improve, taper steroids over 1 mo If rash does not improve after 12 wk from last dose of therapy, discontinue immunotherapy
	3/4	Withhold immunotherapy (grade 3) or permanently discontinue (grade 4) Oral prednisone 1–2 mg/kg/d or equivalent Oral antihistamines for pruritus	If worsens in 48 h, consider additional immunosuppression or supportive measures If no improvement 12 wk from last dose of therapy discontinue immunotherapy
Hepatitis	1	Continue immunotherapy if asymptomatic Monitor liver function tests until resolution	If liver function tests worsen or symptoms develop, treat as higher grade
	2	Withhold immunotherapy Oral prednisone 1 mg/kg/d or equivalent Monitor liver function tests daily	If liver function tests worsen, treat as higher grade
Pneumonitis	3/4	Permanently discontinue therapy IV methylprednisolone 2–4 mg/kg/d or equivalent Monitor liver function tests daily	If no response within 3 d, consider additional immunosuppression such as anti-TNF therapy
	1	Continue immunotherapy Monitor for symptoms every 3 d	If symptoms develop, treat as higher grade
	2	Withhold immunotherapy until resolution Monitor for symptoms daily Oral prednisone 1–2 g/kg/d or equivalent, followed by corticosteroid taper	If persistent beyond 3 d discontinue immunotherapy
Diarrhea/colitis	3	Permanently discontinue immunotherapy Hospitalization methylprednisolone 2–4 mg/kg/d or equivalent Prophylactic antibiotics	If symptoms worsen in 48 h, consider additional immunosuppression such as anti-TNF therapy
	1	Follow American Dietary Association's colitis diet and antidiarrheal medications	If symptoms worsen or persist for 3 d, rule out infectious cause, withhold immunotherapy, antidiarrheal medications, intervention with oral corticosteroids; perform endoscopic or radiologic evaluation to confirm the diagnosis
	2	For colitis of 5 d duration or that recurs, administer corticosteroids at a dose of 0.5–1 mg/kg/d prednisone equivalents followed by corticosteroid taper Withhold immunotherapy	If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1–2 mg/kg/d prednisone equivalents
3	3	Hospitalize for IV corticosteroids (methylprednisolone 1–2 mg/kg total daily dose) followed by steroid taper and additional immunosuppression with anti-TNF therapy	If IV corticosteroids are not effective within the first 3 d, consider infliximab
		Withhold immunotherapy (single-agent immunotherapy) or permanently discontinue (combination with checkpoint inhibitor)	
4	4	Permanently discontinue immunotherapy	If symptoms persist, infliximab may be repeated 2 wk after the initial dose

Symptom	Grade/ severity	Management	Follow-up
Administer corticosteroids at a dose of 1–2 mg/kg/d prednisone equivalents followed by corticosteroid taper			
Endocrinopathies			
Hypophysitis	2/3	Administer corticosteroids at a dose of 1 mg/kg/d prednisone equivalents and hormone replacement therapy, as clinically needed Withhold immunotherapy	
	4	Administer corticosteroids at a dose of 1 mg/kg/d prednisone equivalents for moderate to severe cases Permanently discontinue immunotherapy	
Adrenocortical insufficiency ^a	1	Initiate glucocorticoid replacement	Immunotherapy need not be withheld
	2	Withhold immunotherapy	
	3/4	Administer corticosteroids at a dose of 1–2 mg/kg/d prednisone equivalents Permanently discontinue immunotherapy	Endocrinology consultation, IV corticosteroid replacement, aggressive fluid, and electrolyte replacement may be required
Thyroid dysfunction	–	Hypothyroidism: administer thyroid hormone replacement Hyperthyroidism: initiate antithyroid pharmacotherapy Thyroiditis: hyperthyroidism treated with β -blockers initially in symptomatic cases, and subsequent hypothyroidism with thyroid hormone replacement	–

IV = intravenous; TNF = tumor necrosis factor.

^a Adrenocortical insufficiency may potentially be induced secondary to autoimmune hypophysitis.