Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine 4 (2018) 1−7

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

Editorial

Management of gastrointestinal adverse events induced by immune-checkpoint inhibitors

Zheng-Hang Wang, Lin Shen*

Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing 100142, China

Received 3 October 2017

Available online 13 March 2018

Keywords: Immune-checkpoint inhibitors; Treatment-related adverse event; Gastrointestinal tract; Risk factor; Management

Introduction

Cancer cells can avoid being recognized and destroyed by the immune system by activating immune checkpoints, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 (PD-1) receptor and its ligand PD-L1. Immune-checkpoint inhibitors (ICIs) have been proven effective with a long response duration in an increasing number of indications, such as melanomas and non−small-cell lung cancer (NSCLC).[1] Recently, pembrolizumab, an anti-PD-1 monoclonal antibody, has shown significant antitumor activity in microsatellite instability-high (MSI-H) or DNA mismatch repair deficient (dMMR) tumors.[2] Pembrolizumab has also been approved for use in PD-L1-positive gastric cancer.[3] Nivolumab, another anti-PD-1 monoclonal antibody, has been approved for the treatment of gastric cancer and hepatocellular carcinoma by the U.S. Food and Drug Administration (FDA) and the Japan Ministry of Health, Labor and Welfare, respectively.[4,5] Meanwhile, an increasing number of clinical trials are ongoing to evaluate the efficacy of ICIs with the goal of expanding the application of ICIs in advanced cancers.

Along with potential benefits, clinical safety is another major concern when applying check-point blockade therapy. With more cancer patients being treated with ICIs, more adverse events (AEs) are being recognized. Treatment-related AEs may involve any organ or system, and some of them are considered to be caused by a dysfunctional immune system.[6]

Disorders of the gastrointestinal (GI) tract are some of the most common AEs, which may be difficult to deal with and lead to discontinuation of ICIs.[1,7] GI toxicity involves both upper and lower GI AEs. Only colitis and diarrhea, two types of lower GI AEs, have been investigated, and we know little about the epidemiology, pathogenesis, clinical features, and management of other GI AEs. Herein, we have reviewed the currently available literature on GI toxicity induced by ICIs and have shared our experience in managing treatment-related GI AEs based on our immunotherapy clinical practice.

* Corresponding author.
E-mail address: linshenpku@163.com (L. Shen).

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.cdtm.2017.12.001

Upper GI AEs

Incidence

The upper GI toxicity has drawn little attention from oncologists. The most common manifestations are decreased appetite and nausea. With anti-PD-1 antibody, the incidences of decreased appetite and nausea were 2.5%−13.6% and 7.0%−16.5%, respectively, in non-upper-GI cancers,[8−21] 4.8%−15.3% and 4.2%−16.4%, respectively, in the upper GI cancers[22−28]. Following treatment with anti-CTLA4 antibody, 25.0%−26.7% and 35.1%−36.1% of patients with melanoma presented with loss of appetite and nausea/vomiting, respectively,[29,30] while 16.7% of upper GI cancer patients presented with nausea.[31] Compared to monotherapy, combination immunotherapy (blockade of both PD-1/PD-L1 and CTLA4) was associated with similar incidences of decreased appetite and nausea. Table 1 summarized the incidence of ICI treatment-related AEs in GI cancer.[21−28,31−34]

Other reported upper GI AEs included stomatitis, esophagitis, dysphagia, gastritis, vomiting and gastro-esophageal reflux disease.[21,26,32,33] Recently, gastric hemorrhage was reported in patients with GI stromal tumors (GIST) receiving dasatinib plus ipilimumab in a phase Ib study.[35] The AE incidences might be underestimated for the upper GI cancer patients because some AEs are considered tumor-related rather than treatment-related.

Potential risk models

No risk factor has been identified for upper GI AEs. The primary tumor does not influence the occurrence of upper GI AEs of any grade as their incidences were comparable between the upper and non-upper-GI cancer patients.[6] However, severe hemorrhage has not been described in non-upper-GI cancers, indicating that the primary tumor may be a predictive factor for severe AEs. Radiation exposure of the upper GI tract may be another potential risk factor, as hemorrhage was observed in one patient who received radiotherapy for the primary tumor in our center. Moreover, one gastric cancer patient treated with anti-CTLA4 plus anti-PD-1 antibody in our center and three GIST patients treated with dasatinib plus ipilimumab developed severe gastric bleeding,[35] indicating that combination therapy can increase the incidence of severe AEs such as upper GI hemorrhage. Chronic inflammation and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) may also increase the susceptibility to upper GI toxicity.

Management

There are no available management guidelines for upper GI AEs. Literature review and our experience shows that most AEs are primarily mild and can be resolved with symptomatic treatments alone. For severe AEs, a comprehensive workup should be performed in order to clarify the etiology (treatment-related or tumor-related) and evaluate the AE severity, which should include a complete blood count, serum electrolyte profile, stool occult blood test, abdominal CT scan, gastroscopy, and histopathology examinations.

For upper GI bleeding caused by gastritis (including positive fecal occult blood), which is potentially immune-mediated, we do not advocate glucocorticoids to be used due to their potential to result in upper GI ulcerations and aggravate hemorrhage. In our center, all cases of upper GI bleeding were resolved with routine non-surgical approaches, including proton pump inhibitors (PPI), octreotide, and hemostatic drugs. Elective resection of the primary tumor should also be considered to avoid hemorrhage recurrence in upper GI cancer patients.

For severe AEs except for bleeding, best supportive care and symptomatic treatments can offer great benefit. If dysfunction of the immune system is suspected to be the etiology, high-dose glucocorticoids should be used according to the principles of the current guidelines.[1] However, it should be noted that glucocorticoids are not recommended for autoimmune gastritis and have not yet been investigated in ICI-induced upper GI AEs.[36] Therefore, a multidisciplinary team (MDT) should determine whether to initiate treatment with glucocorticoids. PPIs and gastric mucosa protectants should be used along with glucocorticoids to prevent the occurrence of upper GI bleeding.

Lower GI AEs

Incidence

Clinical manifestations of lower GI complications mainly involve colitis and diarrhea. A meta-analysis involving 10 clinical trials showed that ICIs were more likely to induce colitis and diarrhea compared to the control.[37] Patients treated with CTLA4 blockade therapy had higher rates of lower GI AEs than those treated with PD-1 blockade therapy.[1,6] In GI cancers, colitis occurred in 0.6%−5.6% of the patients receiving monotherapy (anti-PD-1 or anti-CTLA4 antibody). The incidences of diarrhea were 6.6%−27.8% among patients receiving monotherapy and

Table 1
The incidence of ICI treatment-related AEs in GI cancers.

Study	ICIs	Cancer type	Decreased appetite (%)	Nausea (%)	Diarrhea (%)	Colitis (%)	Others (%)
CheckMate 142[21]	Nivo (3)[a], $n = 74$	CRC	−	9.5	21.6	1.4	4.1 (Stomatitis) 2.7 (Abdominal pain) 1.4 (Esophagitis) 1.4 (Gastritis)
KEYNOTE-012[22]	Pembro, $n = 39$	GC	12.8	−	−	−	−
KEYNOTE-059 cohort 1[23]	Pembro, $n = 259$	GC	7.3	6.9	6.6	2.3	−
ATTRACTION-2[24]	Nivo, $n = 330$	GC, EGJ	4.8	4.2	7.0	0.6	−
	Placebo, $n = 163$		4.3	2.5	1.9	0.0	−
CheckMate 032[25]	Nivo (3)[a], $n = 59$	GC, EC, EGJ	15.3	−	15.3	−	−
	Nivo (3)[a] + Ipi (1)[a], $n = 52$		5.8	−	9.6	−	−
	Nivo (1)[a] + Ipi (3)[a], $n = 49$		10.2	−	30.6	−	−
Desai et al 2017[26]	BGB-A317, $n = 55$	GC, EC	−	16.4	−	1.8	14.5 (Dysphagia)
KEYNOTE-028[27]	Pembro, $n = 23$	EC	13.0	−	−	−	−
Kudo et al 2017[28]	Nivo, $n = 65$	ESCC	9.2	−	13.8	−	1.5 (Constipation)
Ralph et al 2010[31]	Treme, $n = 18$	GC, EAC	−	16.7	27.8	5.6	−
KEYNOTE-059 cohort 2[32]	Pembro+5-FU/ CAPE + CDDP, $n = 25$	GC	−	−	−	4.0	−
Moehler et al 2016[33]	Ipi, $n = 57$	GC, EGJ	−	−	24.6	−	−
CheckMate 142[34]	Nivo (3)[a] + Ipi (1)[a], $n = 30$	CRC	−	20.0	43.3	−	−
	Nivo (3)[a] + Ipi (1)[a], $n = 10$		−	20.0	20.0	−	10.0 (Vomiting)
	Nivo (1)[a] + Ipi (3)[a], $n = 10$		−	30.0	40.0	−	30.0 (Vomiting)

ICI: immune-checkpoint inhibitor; AE: adverse event; GI: gastrointestinal; Pembro: pembrolizumab; Nivo: nivolumab; Ipi: ipilimumab; Treme: tremelimumab; 5-FU: 5-fluorouracil; CAPE: capecitabine; CDDP: cisplatin; CRC: colorectal cancer; GC: gastric cancer; EGJ: esophagogastric junction; EC: esophageal carcinoma; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous-cell carcinoma; −: not applicable.
[a] The number in the parenthesis indicated the dose of Nivo or Ipi: "3" represented "3 mg/kg" and "1" represented "1 mg/kg".

9.6%−43.3% among those receiving combination therapy (Table 1).[21−28,31−33] These data were comparable to those from non-GI cancers.[6,38] Panenteritis,[39] celiac disease[40] and constipation[15] have also been reported, and paralytic bowel obstruction has been observed in our center.

Potential risk models

Identifying patients prone to treatment-related AEs before starting ICI therapy can help optimize the follow-up strategy and determine the treatment intensity. Underlying diseases, previous treatments, positive baseline biomarkers and intensive treatment of ICIs may favor the emergence of colitis.[41−52] However, we know little about risk factors for other lower GI AEs.

Whether underlying immune disorders increase the likelihood of colitis, is controversial.[41] Among patients with prior ipilimumab-induced colitis, recurrence of colitis following anti-PD-1 therapy was rare.[42,43] However, 3 out of 13 patients (23.1%) with preexisting Crohn's disease or ulcerative colitis experienced disease flares or newly emerged colitis (Table 2),[42−44] which was much higher than the rate of 5%−8% reported in melanoma patients in another study.[38] Larger studies are warranted to clarify the impact of underlying immune disorders on the development of colitis.

Some previous treatments increased the likelihood of lower GI AEs. Prescribed NSAIDs were associated with a higher susceptibility to enterocolitis.[41] Existing evidence shows that previous thoracic and brain radiotherapy is associated with increased incidences of pulmonary toxicity and hypophysitis, respectively.[53,54] We presume that radiation exposure of the colorectum can increase the possibility of developing colitis as well. One patient with severe colitis in our center was rectally exposed to radiation. Similarly, in prostate cancer, the incidence of diarrhea was numerically higher in patients who received pelvic radiotherapy before ICI therapy than those who did not.[45] The relationship between radiation exposure of the colorectum and colitis should be investigated in prospective clinical trials.

The presence of baseline gut microbiota enriched with Firmicutes was associated with the more frequent occurrence of colitis, whereas patients with Bacteroidetes bacteria enrichment were resistant to colitis.[46,47] The use of antibiotics can alter the gut

Table 2
The incidence of ICI-induced AEs or flare of preexisting diseases in patients with prior AEs or preexisting autoimmune diseases.

Study	Cancer	ICIs	Ipi-induced immune-related AEs		Preexisting autoimmune diseases	
			Colitis	Non-colitis	Crohn's disease or ulcerative colitis	Non-GI disorders
Johnson et al 2016[44]	Melanoma	CTLA4	−	−	33.3% (2/6, 1 flare and 1 colitis)	25.0% (4/24)
Gutzmer et al 2017[42]	Melanoma	PD-1	0 (0/11)	0 (0/11)	100.0% (1/1, 1 colitis)	0 (0/18)
Menzies et al 2017[43]	Melanoma	PD-1	2.1% (1/47)	40.0% (8/20)	0 (0/6)	≥2.2% (≥1/46)

AE: adverse event; ICI: immune-checkpoint inhibitor; Ipi: ipilimumab; GI: gastrointestinal; CTLA4: cytotoxic T lymphocyte-associated antigen 4; PD-1: programmed death-1.

microbiota. However, it did not influence the occurrence of colitis.[41] Pretreatment serum IL-17 levels were significantly associated with the development of grade 3 diarrhea or colitis, but not with all grades of colitis.[48] Increase in expression of two neutrophil-activation markers, CD177 and carcino-embryonic antigen related cellular adhesion molecule1 (CEACAM1),[49] and any abnormal histologic finding after ICI initiation[50] predicted the emergence of lower GI AEs. However, these biomarkers need further verification in clinical practice and are not recommended to predict lower GI AEs currently.

In terms of treatment intensity, the incidence of colitis did not increase in the patients receiving high doses of ipilimumab only.[41] However, it was much higher in patients receiving combination immunotherapy compared to those receiving monotherapy,[6,51] and combining immunotherapy with conventional therapies may induce more treatment-related AEs.[52]

Management

Once treatment with an ICI is started, patients should be followed up regularly as the majority of any-grade AEs and all grades 3−5 AEs occurred within the first 12−16 weeks.[7,55] Patients should be told to report any discomfort and oncologists should always keep treatment-related AEs in mind. The proposal of prophylactic approaches to prevent treatment-related AEs is attractive. Nevertheless, prophylactic budesonide did not reduce the incidence of colitis.[50,56]

Most cases of mild diarrhea and colitis (grade 1−2) were treated successfully under the guidance of detailed algorithms.[1] However, for severe lower GI AEs, most of them are graded only based on symptoms, which might lead to an inaccurate evaluation of the condition and inappropriate treatment. Radiological and histopathologic examinations should be integrated into a comprehensive assessment plan for severe colitis.[57,58] Kim et al[58] reviewed radiological images of 16 patients with ipilimumab-associated colitis and identified two distinct CT patterns: the diffuse colitis pattern and the segmental colitis associated with diverticulosis (SCAD) pattern. The diffuse colitis pattern was characterized by mesenteric vessel engorgement, mild diffuse bowel wall thickening, and fluid-filled distended colon, and the SCAD pattern had the features of segmental moderate wall thickening and pericolic fat stranding in a segment of preexisting diverticulosis. Patients with the SCAD pattern presented with more severe symptoms such as mixed watery and bloody diarrhea and cramping pain and were recommended to be treated with both glucocorticoids and antibiotics. Endoscopy and histopathological evaluation should be performed if there is no contradiction. Oncologists should confirm the etiology of diarrhea (ICI-induced colitis or inflammatory bowel disease) and evaluate the severity of colitis.[59] One patient with grade 3 colitis in our center was treated with low dosage of methylprednisolone ($0.5-1\ mg\cdot kg^{-1}\cdot d^{-1}$) mainly because only mild inflammation was observed pathologically, and he responded well. Therefore, we need to investigate the additional role of radiological and histopathological findings in guiding treatments. Glucocorticoids are the first-line therapy for severe colitis or diarrhea, with other immunosuppressive drugs as salvage therapies such as infliximab.[1] It should be kept in mind that approximately 50% of the colitis patients undergoing upper GI endoscopy had gastritis or duodenitis.[59,60] Therefore, oncologists must pay more attention to potential upper GI bleeding, and prophylactic PPI may be beneficial.

Besides diarrhea and colitis, constipation may occur in a small number of patients and paralytic bowel obstruction in rare cases. These AEs may represent another type of lower GI disorders, namely dysfunction of bowel movements probably mediated by enteric neuropathy. These symptoms can be considered ICI-induced only after excluding mechanical obstruction due to the primary tumor, peritoneal metastasis, and weak bowel movements caused by decreased appetite or poor performance status, which were rather common in advanced cancers, especially GI cancers. Medications facilitating the digestive tract force, such as

anticholinesterase drugs and mosapride, may be sufficient. The therapeutic value of glucocorticoids needs to be further clarified.

Future directions

Immunotherapy has been proven promising in a wide range of cancers. Combining immunotherapy with conventional treatments often offers a therapeutic advantage,[61] but it can increase the incidence of rare and severe AEs.[52] Currently, our knowledge of these AEs is rather limited.

Identifying risk factors can help select high-risk patients to be followed up intensively and be given prophylactic treatments. For treatment-related GI AEs, although oral budesonide failed to decrease the frequency of colitis,[50,56] it remained unclear whether budesonide was beneficial in a high-risk population. PPI or histamine H2-receptor antagonists may be used for preventing gastritis and upper GI hemorrhage, but this needs further confirmation in clinical trials.

When GI symptoms appear in advanced cancer patients, especially in patients with GI cancers, one major challenge is to identify whether these symptoms are manifestations of the ICI-associated AEs, primary or metastatic tumor or a potential infection. However, the clinical, radiological and pathological characteristics have not been well described for most GI AEs, thus making differential diagnosis difficult. If patients who had tumor progression or an infection were misdiagnosed with GI AEs and treated with glucocorticoids, the symptoms could worsen or even turn fatal. Therefore, further studies should investigate the characteristics of GI AEs.

Another challenge lies in finding appropriate treatments for severe GI AEs. Overall, there is no high-level evidence supporting the current recommendations from guidelines. Well-designed prospective randomized clinical trials need to be conducted to investigate the most optimal treatments. According to the current guidelines, glucocorticoids are recommended for severe colitis and diarrhea, but one-third to two-thirds of the patients either do not respond to standard glucocorticoids or have a relapse during glucocorticoid tapering,[1] indicating that glucocorticoids are not the best choice in some cases, where infliximab seems to be more appropriate. Moreover, the role of other immunomodulators (e.g., tacrolimus, cyclosporine, and mycophenolate mofetil) has not been clarified. Further studies are warranted to predict glucocorticoid resistance and to evaluate the efficacy of non-glucocorticoid regimens in colitis patients. In addition, an increasing number of rare GI AEs have been observed with no available treatment recommendations, such as upper GI bleeding and paralytic bowel obstruction. Our experiences described here have been helpful and should be considered in clinical trials. A multidisciplinary team (MDT) involving oncologists, rheumatologists, gastroenterologists, radiologists, and pathologists should be built to evaluate all aspects of the AEs and provide personalized treatments. Oncologists worldwide are encouraged to share their experiences in dealing with these challenging situations.

Conclusions

Immunotherapy has shown great promise for advanced cancers, and a growing number of new ICIs targeting PD-1/PD-L1 and CTLA4 are being evaluated in early-phase clinical trials. However, these drugs are associated with AEs affecting almost every system. Upper GI AEs have been poorly investigated, and gastric bleeding has been observed in GI cancer patients. Glucocorticoids are not recommended for upper GI bleeding and should be carefully used for cases without bleeding. Diarrhea and colitis are the most common lower GI AEs, where high dosage of glucocorticoids and timely addition of other immunomodulators are important. Constipation and paralytic bowel obstruction, caused by GI tract dysfunction, represent other types of lower GI AEs and can be resolved with medications promoting bowel movements. The MDT approach should be considered in every severe or rare case of AEs. Further research is warranted to establish risk models for the development of GI AEs and to investigate the radiological and pathological characteristics to optimize treatments for severe cases.

Conflicts of interest

No potential conflicts of interest were disclosed.

Acknowledgement

This work was supported by the National Key Research and Development Program of China (No. 2017YFC1308900).

References

1. 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.* 2017;28(suppl 4):iv119−iv142.

2. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357:409−413.
3. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for advanced gastric cancer. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm577093.htm. Accessed September 22, 2017.
4. U.S. Food and Drug Administration. FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm577166.htm. Accessed September 25, 2017.
5. Bsistol-Myers Squibb. Japan Ministry of Health, Labor and Welfare Approves Opdivo (nivolumab) for the Treatment of Patients with Unresectable Advanced or Recurrent Gastric Cancer Which Has Progressed After Chemotherapy. https://news.bms.com/press-release/corporatefinancial-news/japan-ministry-health-labor-and-welfare-approves-opdivo-nivolu. Accessed September 22, 2017.
6. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13:473−486.
7. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol*. 2017;35:785−792.
8. Chow LQM, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol*. 2016;34:3838−3845.
9. Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856−1867.
10. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18:312−322.
11. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803−1813.
12. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol*. 2016;34:3733−3739.
13. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol*. 2016;17:1283−1294.
14. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372:320−330.
15. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16:375−384.
16. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627−1639.
17. 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;373:123−135.
18. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018−2028.
19. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823−1833.
20. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540−1550.
21. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18:1182−1191.
22. Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol*. 2016;17:717−726.
23. Fuchs CS, Doi T, Jang RWJ, et al. KEYNOTE-059 cohort 1: efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer. *J Clin Oncol*. 2017;35(suppl 15):abstr 4003.
24. Kang YK, Satoh T, Ryu MH, et al. Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): a double-blinded, randomized, phase III trial. *J Clin Oncol*. 2017;35(suppl 4):abstr 2.
25. Janjigian YY, Ott PA, Calvo E, et al. Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study. *J Clin Oncol*. 2017;35(suppl 15):abstr 4014.
26. Desai J, Millward M, Chao Y, et al. Preliminary results from subsets of patients (pts) with advanced gastric cancer (GC) and esophageal carcinoma (EC) in a dose-escalation/expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb). *Ann Oncol*. 2017;28(suppl 5):abstr 387P.
27. Doi T, Piha-Paul SA, Jalal SI, et al. Updated results for the advanced esophageal carcinoma cohort of the phase Ib KEYNOTE-028 study of pembrolizumab (MK-3475). *J Clin Oncol*. 2016;34(suppl 4):abstr 7.
28. Kudo T, Hamamoto Y, Kato K, et al. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. *Lancet Oncol*. 2017;18:631−639.
29. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012;13:459−465.
30. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711−723.
31. Ralph C, Elkord E, Burt DJ, et al. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. *Clin Cancer Res*. 2010;16:1662−1672.
32. Bang YJ, Muro K, Fuchs CS, et al. KEYNOTE-059 cohort 2: safety and efficacy of pembrolizumab (pembro) plus 5-fluorouracil (5-FU) and cisplatin for first-line (1L) treatment of advanced gastric cancer. *J Clin Oncol*. 2017;35(suppl 15):abstr 4012.
33. Moehler MH, Cho JY, Kim YH, et al. A randomized, open-label, two-arm phase II trial comparing the efficacy of sequential ipilimumab (ipi) versus best supportive care (BSC) following first-

line (1L) chemotherapy in patients with unresectable, locally advanced/metastatic (A/M) gastric or gastro-esophageal junction (G/GEJ) cancer. *J Clin Oncol*. 2016;34(suppl 15):abstr 4011.
34. Overman MJ, Kopetz S, McDermott RS, et al. Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results. *J Clin Oncol*. 2016;34(suppl 15):abstr 3501.
35. D'Angelo SP, Shoushtari AN, Keohan ML, et al. Combined KIT and CTLA-4 blockade in patients with refractory GIST and other advanced sarcomas: a phase Ib study of dasatinib plus ipilimumab. *Clin Cancer Res*. 2017;23:2972−2980.
36. Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. *Clin Exp Gastroenterol*. 2017;10:19−27.
37. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of gastrointestinal complications in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Immunotherapy*. 2015;7:1213−1227.
38. Gupta A, De Felice KM, Loftus Jr EV, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. *Aliment Pharmacol Ther*. 2015;42:406−417.
39. Oble DA, Mino-Kenudson M, Goldsmith J, et al. Alpha-CTLA-4 mAb-associated panenteritis: a histologic and immunohistochemical analysis. *Am J Surg Pathol*. 2008;32:1130−1137.
40. Gentile NM, D'Souza A, Fujii LL, Wu TT, Murray JA. Association between ipilimumab and celiac disease. *Mayo Clin Proc*. 2013;88:414−417.
41. Marthey L, Mateus C, Mussini C, et al. Cancer immunotherapy with anti-CTLA-4 monoclonal antibodies induces an inflammatory bowel disease. *J Crohns Colitis*. 2016;10:395−401.
42. Gutzmer R, Koop A, Meier F, et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. *Eur J Cancer*. 2017;75:24−32.
43. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol*. 2017;28:368−376.
44. Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol*. 2016;2:234−240.
45. 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;15:700−712.
46. Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol*. 2017;28:1368−1379.
47. Dubin K, Callahan MK, Ren B, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. *Nat Commun*. 2016;7:10391.
48. Tarhini AA, Zahoor H, Lin Y, et al. Baseline circulating IL-17 predicts toxicity while TGF-β1 and IL-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. *J Immunother Cancer*. 2015;3:39.
49. Shahabi V, Berman D, Chasalow SD, et al. Gene expression profiling of whole blood in ipilimumab-treated patients for identification of potential biomarkers of immune-related gastrointestinal adverse events. *J Transl Med*. 2013;11:75.
50. Berman D, Parker SM, Siegel J, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. *Cancer Immun*. 2010;10:11.
51. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:23−34.
52. U.S. Food and Drug Administration. *FDA Alerts Healthcare Professionals and Oncology Clinical Investigators About Two Clinical Trials on Hold Evaluating KEYTRUDA® (pembrolizumab) in Patients With Multiple Myeloma*. https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm. Accessed September 20, 2017.
53. Min L, Hodi FS, Giobbie-Hurder A, et al. Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. *Clin Cancer Res*. 2015;21:749−755.
54. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol*. 2017;18:895−903.
55. Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS; MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer*. 2013;119:1675−1682.
56. Weber J, Thompson JA, Hamid O, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin Cancer Res*. 2009;15:5591−5598.
57. Beck KE, Blansfield JA, Tran KQ, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol*. 2006;24:2283−2289.
58. Kim KW, Ramaiya NH, Krajewski KM, et al. Ipilimumab-associated colitis: CT findings. *AJR Am J Roentgenol*. 2013;200:W468−W474.
59. Cramer P, Bresalier RS. Gastrointestinal and hepatic complications of immune checkpoint inhibitors. *Curr Gastroenterol Rep*. 2017;19:3.
60. Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM, Shi C. PD-1 inhibitor gastroenterocolitis: case series and appraisal of 'immunomodulatory gastroenterocolitis'. *Histopathology*. 2017;70:558−567.
61. Coussens LM, Zitvogel L, Palucka AK. Neutralizing tumor-promoting chronic inflammation: a magic bullet. *Science*. 2013;339:286−291.

Edited by Pei-Fang Wei