Immunological Agents Used in Cancer Treatment

Melih Simsek, Salim Basol Tekin, Mehmet Bilici

ABSTRACT

Immune checkpoint inhibitors (ICI) are monoclonal antibodies targeting cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), or PD-1 ligand (PD-L1). ICI are approved for the treatment of malign melanoma, non-small cell lung cancer, classical Hodgkin lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, and renal cell carcinoma. They can lead to long-term anti-tumor responses by deactivating the brake mechanism in the immune system. Ipilimumab, tremelimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab are examples of ICI. CTLA-4 is a brake mechanism in immune response. Ipilimumab and tremelimumab are antibodies against CTLA-4. PD-1 is another important immune checkpoint co-inhibitor receptor that is expressed by activated T cells in the peripheral tissue. As a result of blockage of the PD-1/PD-L1 pathway, local tumor-specific immune response augments, and long-term tumor control can be achieved. In recent years, ICI are approved for the treatment of various malignities. They may be responsible for specific toxicities called immune-related adverse events (irAEs). irAEs are a consequence infiltration of normal tissues by activated T lymphocytes that are responsible for autoimmunity. Corticosteroids and anti-tumor necrosis factor agents, such as infliximab and mycophenolate mofetil, are effective in the treatment of irAEs. Immune checkpoint inhibition with monoclonal antibodies against CTLA-4 and/or PD-1/PD-L1 by single agent or combination treatments became a new option in various solid tumors. However, ICI have unique adverse events, and these adverse events should be considered in any new onset clinical situation and should be managed properly. Future prospective randomized clinical trials will clarify recent questions.

Keywords: Immunotherapy, cancer, checkpoint inhibition

Introduction

Immune checkpoint inhibitors (ICI) in monoclonal antibody form targeting cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), or PD-1 ligand (PD-L1) are promising anti-cancer agents for various malignancies. Significant and long-term clinical responses were achieved with these agents. Different from chemotherapy, immunotherapeutic effect emerges lately. Recently, different treatment options are developed, such as discovery of new immunotherapy agents, combination with another immunotherapeutic agent, and combination with a targeted therapy, combination with chemotherapeutic agents, or radiotherapy.

Receptors of CTLA-4 and PD-1 are expressed on T cells, whereas PD-L1 is expressed in many cell subtypes including tumor cells. Cancer immunotherapy which is succeeded by immune checkpoint blockade is different from cytotoxic treatments and inhibits cell proliferation by constituting tumor-related immune response [1-4]. T cells play important roles in immune defense mechanisms against cancer. They recognize tumor antigens, thus they are activated and extensively eliminate tumor cells [1-4].

Immune checkpoint inhibitors are approved for the treatment of patients diagnosed with malign melanoma, non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma (cHL), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, and renal cell carcinoma (RCCa) [5-7]. Continuing reports of high response rates with these agents in different cancer subtypes may increase the number of indications for them. Small cell lung cancer (15% overall response rate (ORR)) [8], urothelial cancer (25% ORR) [9], HNSCC (12%-25% ORR) [10, 11], gastric cancer (20% ORR) [12], hepatocellular carcinoma (20% ORR) [13], ovarian cancer

Cite this article as: *Simsek M, Tekin SB, Bilici M. Immunological Agents Used in Cancer Treatment. Eurasian J Med 2018. DOI: 10.5152/eurasianjmed.2018.18194.*

ORCID IDs of the authors:
M.S. 0000-0003-0633-8558
S.B. 0000-0002-0974-3412
M.B. 0000-0003-1306-2238

Department of Medical Oncology, Atatürk University School of Medicine, Erzurum, Turkey

Received: May 17, 2018
Accepted: July 26, 2018
Available Online Date: November 30, 2018

Correspondence to: Melih Simsek
E-mail: mdmelih@gmail.com

DOI 10.5152/eurasianjmed.2018.18194

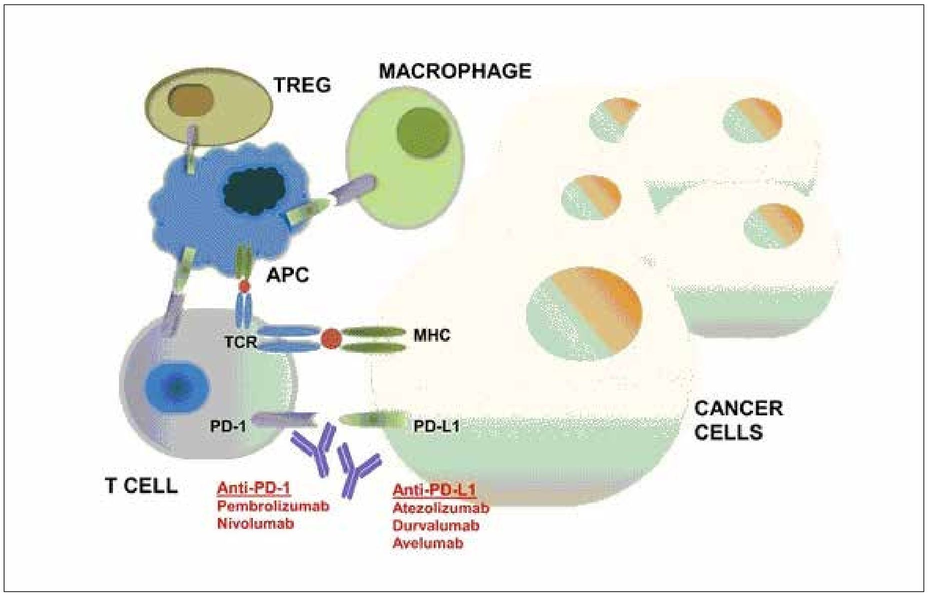

Figure 1. Interaction between PD-1 and PD-L1

(15% ORR) [14, 15], triple negative breast cancer (20% ORR) [16], mismatch repair deficient (dMMR) colorectal cancer (60% ORR) [17], and cHL (65%-85% ORR) [18, 19] are examples of these good responses. ICI can lead to long-term anti-tumor responses by deactivating the brake mechanism in the immune system [20].

Clinical and Research Consequences

Cytotoxic T lymphocyte antigen-4 reverses the activity of the T cell co-stimulator receptor called CD28. CD28 and CTLA-4 share similar ligands called CD80 (B7.1) and CD86 (B7.2). CTLA-4 has a much higher affinity to both ligands. It is expressed on activated CD4+ and CD8+ T cells and on regulatory T (Treg) cells [21]. While the activation of CTLA-4 reinforces the inhibitor function of Treg cells, interleukin-2 production and receptor expression decline. Therefore, CTLA-4 blockage increases cytotoxic T cell activation and inhibits Treg cell-dependent immune suppression, thus showing anti-tumor activity.

Ipilimumab is a fully human IgG1 monoclonal antibody [22]. It prevents the interaction between CTLA-4 and CD80/CD86. In this way, it enhances the activation and proliferation of T cells and increases anti-tumor immunity [23]. The results of studies that evaluated the efficacy of ipilimumab in patients diagnosed with advanced malign melanoma were revealed in 2010 [2-4, 21, 24]. It is the first agent that showed an overall survival (OS) advantage in a phase III study conducted in a patient population diagnosed with malign melanoma and who had prior therapy history [24]. It was reported in two randomized phase III studies conducted in patients diagnosed with advanced malign melanoma that adverse events are manageable [24, 25]. Ipilimumab of 3 mg/kg every 3 weeks was approved in the USA in 2011 as a monotherapy for the treatment of patients diagnosed with unresectable or metastatic malign melanoma. It was determined after the evaluation of 4800 patients that 20% of the patients who were alive at year 3 were still alive at year 10, and it was observed that this was a clear evidence of the long-term activity of immunotherapy [20].

Tremelimumab is a fully human IgG2 monoclonal antibody against CTLA-4. It could not show any OS advantage in a phase III study conducted in patients diagnosed with unresectable stage III-IV malign melanoma [26].

PD-1 is another important immune checkpoint co-inhibitor receptor that is expressed by activated T cells in the peripheral tissue (Figure 1). It interacts with PD-L1 (B7H1) and PD-L2 (B7DC). These ligands are expressed on antigen-presenting cells, cancer cells, and tumor microenvironment [21, 27]. Thus, PD-1 ligand expression constitutes an immune suppressive environment. This immune escape mechanism can be activated by the intrinsic basic oncogenic signaling pathway or emerges by activated anti-tumor immune response that produces inflammatory signals [21, 28, 29]. PD-L1 expression is defined in various histological cancer subtypes. PD-1 inhibitors intercept the interaction between PD-1 and PD-L1 and PD-L2. PD-L1 inhibitors directly bind to PD-L1 and deactivate this brake mechanism. As a result of blockage of the PD-1/PD-L1 pathway, local tumor-specific immune response augments, and long-term tumor control can be achieved. In recent years, nivolumab is approved for the treatment of malign melanoma, NSCLC, RCCa, and cHL. Pembrolizumab is approved for the treatment of malign melanoma, NSCLC, cHL, and HNSCC. Atezolizumab is approved for the treatment of urothelial carcinoma and NSCLC.

Nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab are ICI that showed efficacy in the treatment of lung cancer. Chemotherapy was compared with monotherapies with antibodies against PD-1 or PD-L1 in phase II and III randomized five studies including patients who received prior therapy for advanced NSCLC. A significant improvement was observed in OS independent from histological features (9.2-13.8 months vs. 6-9.7 months; HR for death 0.59 vs. 0.73). It was also reported that safety and adverse event profile were better [30-34].

Nivolumab is a fully human IgG4 monoclonal antibody against PD-1 receptor and prevents PD-1 from contact with PD-L1 and PD-L2. In a phase III study, efficacy and tolerability of nivolumab in second-line treatment of patients with NSCLC after platinum-based doublet chemotherapy were evaluated [30]. OS was better in the nivolumab arm than in the docetaxel arm. The median OS was 12.2 months in the nivolumab group (95% CI, 9.7-15.0) and 9.4 months in the docetaxel group (95% CI, 8.1-10.7) (HR for death 0.73; 96% CI, 0.59-0.89; P=0.002). The 1-year survival rates were 51% for nivolumab (95% CI, 45-56) and 39% for docetaxel (95% CI, 33-45). However, in a study conducted in patients diagnosed with advanced NSCLC, who had no prior therapy history for NSCLC, and who had low PD-L1 expression in tumor cells (≥5%), nivolumab was compared with chemotherapy, and no progression-free survival (PFS) difference was observed (median PFS 4.2 months vs. 5.9 months; p=0.25) [35].

In a phase III randomized study conducted in patients with advanced RCCa, a 27% decrease in death risk with nivolumab compared with everolimus was reported [36]. In 384 (39%) patients aged >65 years, the risk reduction was 36% (HR 0.64; 0.45-0.91).

Pembrolizumab is a human IgG4 monoclonal antibody against PD-1. In a phase III study conducted in patients with advanced malign melanoma, pembrolizumab (10 mg/kg every 2 to 3 weeks) was compared with four doses of ipilimumab (3 mg/kg every 3 weeks) [37]. Of the 834 patients, 279 were randomized to the arm that pembrolizumab was administered every 2 weeks, 277 were randomized to the arm that pembroli-

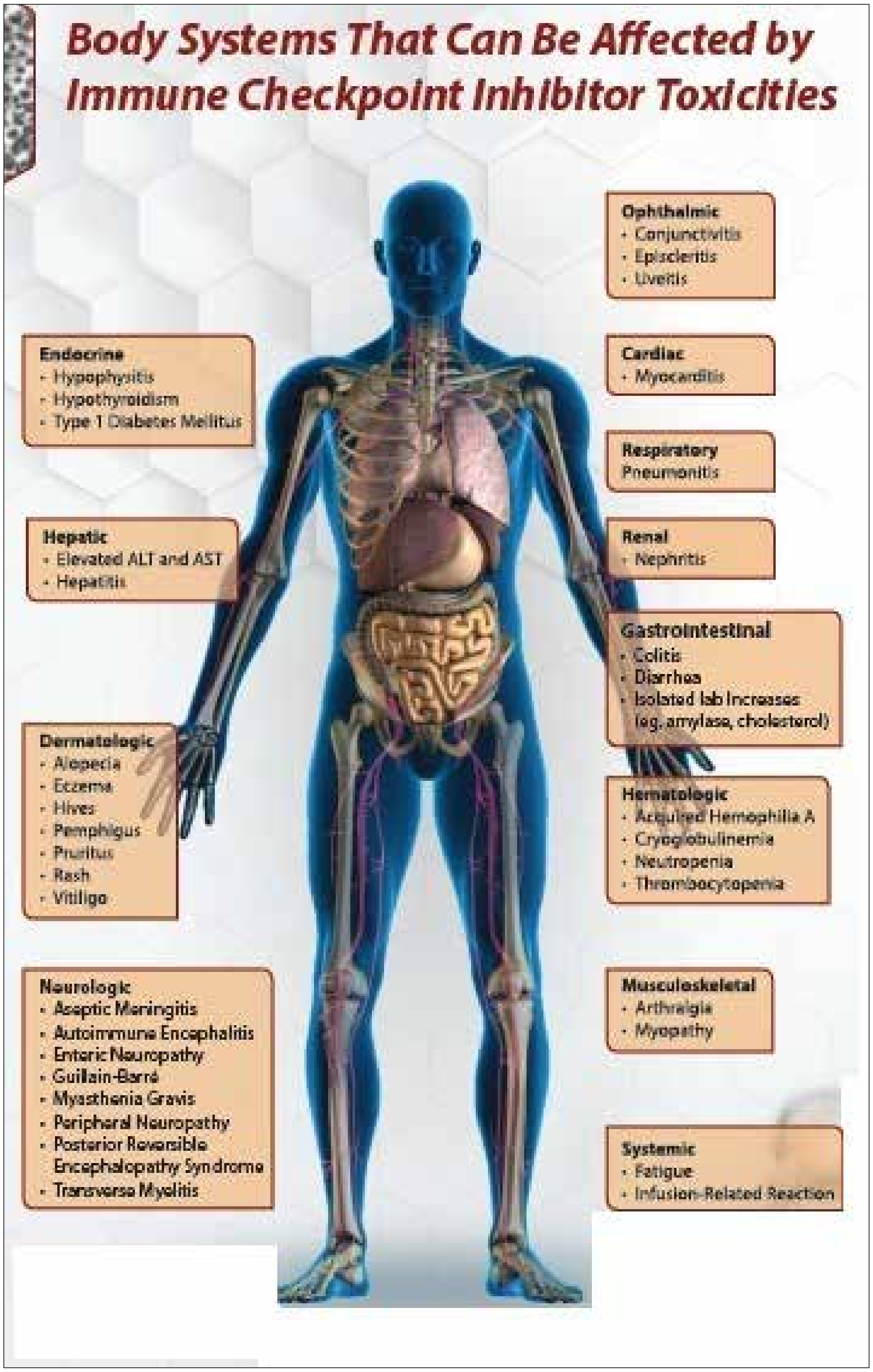

Figure 2. Summary of irAEs

zumab was administered every 3 weeks, and 278 were randomized to the ipilimumab arm. The 1-year OS rates were reported as 74.1% (HR for death compared with the ipilimumab arm 0.63; 95% CI, 0.47-0.83; P<0.0005) for the pembrolizumab arm every 2 weeks, 68.4% (HR for death compared with the ipilimumab arm 0.69; 95% CI, 0.52-0.90; p=0.004) for the pembrolizumab arm every 3 weeks, and 58.2% for the ipilimumab arm.

In the KEYNOTE-024 study, patients diagnosed with advanced NSCLC (adenocarcinoma and squamous cell carcinoma), who had no prior therapy history for NSCLC, and who had high PD-L1 expression in tumor cells (≥50%) were randomized to the pembrolizumab or platinum-based chemotherapy arms. Cross-over from the chemotherapy arm to the pembrolizumab arm was allowed in case of progression. A significant improvement in PFS (median 10.3 months vs. 6 months; p<0.001) and OS (HR for death 0.6; p=0.005) with a higher response rate (44.8% vs. 27.8%) and lower treatment-related grade 3-4 adverse event rate (26.6% vs. 53.5%) was observed in the pembrolizumab arm [38]. ORR was reported as 45% in the pembrolizumab arm and 28% in the chemotherapy arm (p=0.011).

In the KEYNOTE-021 study, first-line pembrolizumab plus chemotherapy was compared with chemotherapy alone. ORR was reported as 55% for the pembrolizumab plus chemotherapy arm and 29% for the chemotherapy alone arm (p=0.0016) [39]. The 6-month PFS was found as 77% in the pembrolizumab plus chemotherapy arm and 63% for the chemotherapy arm (p=0.102).

Nivolumab and pembrolizumab were approved by the Food and Drug Administration for second- or third-line treatment of patients with advanced or metastatic stage colorectal cancer who had dMMR/microsatellite instability high (MSI-H) tumors after progression with treatment including fluoropyrimidine, oxaliplatin, and irinotecan [40]. In an ongoing phase III KEYNOTE-177 study, standard treatment with pembrolizumab in first-line treatment of MSI-H colorectal cancers is compared. There is an ongoing phase III study in patients with stage III MSI-H colorectal cancer evaluating adjuvant treatment with atezolizumab plus FOLFOX regimen.

Atezolizumab is a human IgG4 monoclonal antibody against PD-L1, and durvalumab and avelumab are fully human IgG1 monoclonal antibodies against PD-L1. Atezolizumab was approved for second-line treatment of lung cancer.

Immune checkpoint inhibitors cause specific toxicities called immune-related adverse events (irAEs) (Figure 2). irAEs are a consequence of invasion of normal tissues by activated T lymphocytes. Immune checkpoints play important physiological role and are expressed in many cells including tumor cells. Thus, ICI may enrich a present immune response and may affect all organs of the patient. Unfortunately, to our knowledge, there are no any prospective randomized studies regarding the management of irAEs. However, when irAEs occur, immunotherapy should be interrupted or discontinued on the basis of severity.

As reported in previous studies [5-7, 41], irAEs may affect the skin (maculopapular rash, vitiligo, psoriasis, Lyell's syndrome, and drug reaction with eosinophilia and systemic symptoms), gastrointestinal tract (enterocolitis, gastritis, pancreatitis, and celiac disease), endocrine glands (hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, and diabetes), lung (pneumonitis, pleural effusion, and sarcoidosis), nerve system (peripheral neuropathy, aseptic meningitis, Guillain-Barré syndrome, encephalopathy, myelitis, meningo-radicular-neuritis, and myasthenia), liver (hepatitis), kidney (granulomatous interstitial nephritis and lupus-like glomerulonephritis), hematological cells (hemolytic anemia, thrombocytopenia, neutropenia, and pancytopenia), muscle-articular system (arthritis and myopathies), heart (pericarditis and cardiomyopathy), and eyes (uveitis, conjunctivitis, retinitis, blepharitis, choroiditis, and orbital myositis). Fortunately, most irAEs are rare (<1%) [5-7].

While toxicities with anti-CTLA-4 or PD-1/PD-L1 agents are similar, frequencies are different [37, 42, 43]. While grade 3-4 toxicities with anti-CTLA-4 agents are reported at a rate of 20%-30%, the rate is 10%-15% with anti-PD-1 agents. The most common toxicities (>10% of the cases) with anti-CTLA-4 agents are diarrhea, rash, pruritus, fatigue, nausea, vomiting, anorexia, and abdominal pain [5]. The most common toxicities (>10% of the cases) with anti-PD-1 agents are fatigue, rash, pruritus, diarrhea, nausea, and arthralgia [6, 7].

Serious irAEs are rarely observed (~10% of the cases receiving monotherapy), but they may be life-threatening if they are not recognized and treated properly. The most important life-threatening toxicities of ICI are immune-related colitis (more common with anti-CTLA-4 agents) and interstitial pneumonitis (for anti-PD-1 agents). Other serious toxicities including infusion reactions are Guillain-Barré syndrome, type I diabetes with ketoacidosis, Stevens-Johnson syndrome, or bleeding complications with autoimmune anemia and thrombocytopenia. The severity of irAEs can be avoided by early diagnosis and treatment. According to the severity of irAEs, close follow-up, interruption or discontinuation of ICI treatment, initiation of corticosteroid treatment, and, in some cases, more immunosuppression with anti-tumor necrosis factor agents (infliximab and mycophenolate mofetil) can be administered. Various guidelines are present for the management of irAEs [41, 44-46].

Most irAEs occur in the first 4 weeks of ICI treatment [47]. However, irAEs may occur at the beginning of treatment, during treatment, or even a few months after the completion of treatment. Grade 3-4 toxicities are reported in 58% of patients diagnosed with lung cancer who received chemotherapy and ipilimumab combination [48]. Similarly, a combination of ICI increases irAEs. For example, fatigue is reported in 2% of cases receiving nivolumab alone, whereas it is 13% in patients receiving a combination of ipilimumab and nivolumab. In addition, grade 3-4 irAEs are reported as 55% with a combination of ipilimumab and nivolumab [42]. When suspected for diagnosis of irAEs, referral to the National Cancer Institute-Common Terminology Criteria for Adverse Events is recommended [49].

It is very important to investigate personal or familial autoimmune diseases or viral infections before the initiation of ICI treatment in the prevention of irAEs. The most important points in determining early symptoms associated with irAEs are information of the patient, family of the patient, and the caregivers about irAEs. When new symptoms occur or present symptoms increase, irAEs should be considered. Especially, respiratory (cough and dyspnea), gastrointestinal (diarrhea), or skin (rash and itching) symptoms should be kept in mind. Laboratory tests should be evaluated for hematological (anemia, thrombocytopenia, and neutropenia), hepatic (elevation of transaminase levels), or renal (elevation of serum creatinine levels) toxicities. Thyroid-stimulating hormone levels should be assessed every 2-3 months. Clinical and laboratory evaluation should be repeated after the completion of treatment.

Corticosteroids are very important in the treatment of irAEs and should be initiated immediately. Colitis, pneumonitis, hepatitis, and pancreatitis are the most potentially serious irAEs. After recovery of symptoms, corticosteroid treatment should be terminated through slowly tapering (generally >1 month). However, it should not be forgotten that many irAEs may recover by only symptomatic treatment. When ICI were initiated again, of the cases, 24% with the same irAE and 26% with a new irAE were reported, and no irAE was reported in 50%. Another ICI inhibiting the same pathway or dose reduction of ICI is not recommended. Long-term hormonal replacement is frequently needed in endocrine insufficiencies [31, 42, 50].

In conclusion, immune checkpoint inhibition with monoclonal antibodies against CTLA-4 and/or PD-1/PD-L1 by single agent or combination treatments became a new option in various solid tumors. However, along with being a new and efficient treatment option, immune checkpoint inhibition has unique adverse events. Owing to this, adverse events should be considered in any new onset clinical situation and should be managed properly. In the future, new prospective randomized trials will answer many questions present today.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.B.T.; Design – M.S.; Supervision – S.B.T.; Resource – M.S.; Materials – M.B.; Data Collection and/or Processing – M.S.; Analysis and /or Interpretation – M.B.; Literature Search – M.S.; Writing – M.S.; Critical Reviews – S.B.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. Annu Rev Immunol 1996; 14: 233-58. [CrossRef]
2. Ott PA, Hodi FS, Robert C. CTLA 4 and PD 1/ PD L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. Clin Cancer Res 2013; 19: 5300-9. [CrossRef]
3. Nishino M, Jagannathan JP, Krajewski KM, et al. Personalized tumor response assessment in the era of molecular medicine: cancer-specific and therapy-specific response criteria to complement pitfalls of RECIST. AJR Am J Roentgenol 2012; 198: 737-45. [CrossRef]
4. Nishino M, Tirumani SH, Ramaiya NH, Hodi FS. Cancer immunotherapy and immune-related response assessment: the role of radiologists in the new arena of cancer treatment. Eur J Radiol 2015; 84: 1259-68. [CrossRef]
5. European Medicines Agency: EMEA/H/C/002213-PSUSA/00009200/201409 - ipilimumab product information. August 2015. Available From: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002213/WC500109299.pdf.
6. European Medicines Agency: EMEA/H/C/003985 - nivolumab product information. July 2015. Available From: URL: http://www.ema.europa. eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf.
7. European Medicines Agency: EMEA/H/C/003820 - pembrolizumab product information. July 2015. Available From: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf.
8. Antonia SJ, Bendell JC, Taylor MH, et al. Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. J Immunother Cancer 2015; 3(Suppl 2): P376.
9. Plimack ER, Bellmunt J, Gupta S, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol 2017; 18: 212-20. [CrossRef]

10. 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: 3838-45. [CrossRef]
11. Segal NH, Ou AI, Balmanoukian AS, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. Ann Oncol 2016; 27(Suppl 6): 949O.
12. Muro K, Chung H, 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: 717-26. [CrossRef]
13. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017; 389: 2492-502. [CrossRef]
14. Hamanishi J, Mandai M, Ikeda T, et al. Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. J Clin Oncol 2015; 33: 4015-22. [CrossRef]
15. Varga A, Piha-Paul A, Ott PA, et al. Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: interim results from a phase Ib study. ASCO 2015, Vol. 33. J Clin Oncol; 2015: 33(Suppl 15): 5510.
16. Emens LA, Braiteh FS, Cassier P, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer (TNBC). 2015 AACR Annual Meeting; 2015 April 18-22; Philadelphia, USA. PA: American Association for Cancer Research 2015. [Abstract 6317].
17. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372: 2509-20. [CrossRef]
18. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015; 372: 311-9. [CrossRef]
19. Armand P, Shipp MA, Ribrag V, et al. Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After BrentuximabVedotin Failure. J Clin Oncol 2016; 34: 3733-9. [CrossRef]
20. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 2015; 33: 1889-94. [CrossRef]
21. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12: 252-64. [CrossRef]
22. Hoos A, Ibrahim R, Korman A, et al. Development of ipilimumab: contribution to a new paradigm for cancer immunotherapy. Semin Oncol 2010; 37: 533-46. [CrossRef]
23. Lipson EJ, Drake CG. Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma. Clin Cancer Res 2011; 17: 6958-62. [CrossRef]
24. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363:711-23. [CrossRef]
25. Robert C, Thomas L, Bondarenko I, et al. 2011. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364: 2517-26. [CrossRef]
26. Ribas A, Kefford R, Marshall MA, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013; 31: 616-22. [CrossRef]
27. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy-inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012; 18: 6580-7. [CrossRef]
28. Crane CA, Panner A, Murray JC, et al. PI(3) kinase is associated with a mechanism of immunoresistance in breast and prostate cancer. Oncogene 2009; 28: 306-12. [CrossRef]
29. Parsa AT, Waldron JS, Panner A, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. Nat Med 2007; 13: 84-8. [CrossRef]
30. 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: 1627-39. [CrossRef]
31. 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. [CrossRef]
32. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-smallcell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016; 387: 1837-46. [CrossRef]
33. 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: 1540-50. [CrossRef]
34. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated nonsmall-cell lung cancer (OAK): a phase 3, open-label, multicentrerandomised controlled trial. Lancet 2017; 389: 255-65. [CrossRef]
35. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med 2017; 376: 2415-26. [CrossRef]
36. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373: 1803-13. [CrossRef]
37. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372: 2521-32. [CrossRef]
38. 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: 1823-33. [CrossRef]
39. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, nonsquamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open label KEYNOTE-021 study. Lancet Oncol 2016; 17: 1497-508. [CrossRef]
40. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. Available from: URL: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm
41. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol 2015; 27: 559-74. [CrossRef]
42. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373: 1270-1. [CrossRef]
43. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015; 372: 2006-17. [CrossRef]
44. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012; 30: 2691-7. [CrossRef]
45. Kähler KC, Hauschild A. Treatment and side effectmanagement of CTLA-4 antibody therapy in metastatic melanoma. J Dtsch Dermatol Ges 2011; 9: 277-86. [CrossRef]
46. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2016; 27: 1362. [CrossRef]
47. 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: 785-92. [CrossRef]
48. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012; 30: 2046-54. [CrossRef]
49. Common Terminology Criteria for Adverse Events (CTCAE; Version 4.0). US Department of Health and Human Services website. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Published May 28, 2009. Accessed July 2017.
50. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372: 320-30. [CrossRef]