Journal of Oncological Sciences 4 (2018) 125–129

Contents lists available at ScienceDirect

Journal of Oncological Sciences

journal homepage: https://www.elsevier.com/locate/jons

Original Article

# Experience from Turkish centers participating in the Early Access Program (EAP): Preliminary real-world safety data of nivolumab (nivo) combined with ipilimumab (ipi) in pre-treated advanced melanoma patients

Nuri Karadurmus [a, *], Mehmet Ali Nahit Sendur [b], Burcak Karaca [c], Omer Fatih Olmez [d], Ilhan Hacibekiroglu [e], Hasan Senol Coskun [f], Serkan Degirmencioglu [g], Yasemin Kemal [h], Saadettin Kilickap [i], Ahmet Taner Sumbul [j], Burc Aydin [k], Hande Turna [l], Muhammet Ali Kaplan [m], Nalan Babacan [n], Umut Demirci [o], Alper Ata [p], Dilek Erdem [q], Ahmet Ozet [r], Huseyin Abali [s]

[a] Health Sciences University, Gulhane Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey
[b] Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey
[c] Ege University, Faculty of Medicine, Department of Medical Oncology, Izmir, Turkey
[d] Medipol Mega Hospitals Complex, Faculty of Medicine, Department of Medical Oncology, İstanbul, Turkey
[e] Sakarya University, Faculty of Medicine, Department of Medical Oncology, Sakarya, Turkey
[f] Akdeniz University, Faculty of Medicine, Department of Medical Oncology, Antalya, Turkey
[g] Pamukkale University, Faculty of Medicine, Department of Medical Oncology, Denizli, Turkey
[h] Ondokuz Mayıs University, Faculty of Medicine, Department of Medical Oncology, Samsun, Turkey
[i] Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara, Turkey
[j] Baskent University Faculty of Medicine, Department of Medical Oncology, Adana, Turkey
[k] Medical Science Liaison, Bristol Myers Squib, İstanbul, Turkey
[l] Istanbul Cerrahpasa University, Faculty of Medicine, Department of Medical Oncology, İstanbul, Turkey
[m] Dicle University, Faculty of Medicine, Department of Medical Oncology, Diyarbakır, Turkey
[n] MarmaraUniversity, Faculty of Medicine, Department of Medical Oncology, İstanbul, Turkey
[o] University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey
[p] Medical Park Tarsus Hospital, Department of Medical Oncology, Mersin, Turkey
[q] Medical Park Samsun Hospital, Department of Medical Oncology, Samsun, Turkey
[r] Gazi University, Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey
[s] Acıbadem University, Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey

ARTICLE INFO

*Article history:*
Received 2 August 2018
Received in revised form
29 September 2018
Accepted 7 October 2018
Available online 13 November 2018

*Keywords:*
Nivolumab
Ipilimumab
Immunotherapy
Melanoma

ABSTRACT

*Objective:* We aimed to evaluate the safety of nivolumab + ipilimumab (nivo + ipi) in advanced melanoma patients who had relapsed after ≥1 line of systemic treatment in a real-world setting.
*Methods:* Adult patients with advanced melanoma who had progressed after ≥1 line of systemic treatment were eligible for nivo 1 mg/kg + ipi 3 mg/kg Q3W × 4, followed by nivo 3 mg/kg Q2W until progression, or unacceptable toxicity for up to 24 months in the Early Access Program (EAP) in Turkey. Treatment-related adverse events (TRAEs) were recorded and analyzed.
*Results:* Forty patients who received at least one dose of nivo + ipi were included. Median number of doses (Nivo + ipi and nivo alone) were 4 with a median follow-up of 19 weeks. Thirty patients (75%) were alive and 24 patients (60%) were on treatment. TRAEs of any grade and grade 3–4 occurred in 53% and 20% of the patients, respectively. One patient died due to TRAEs (colitis and diarrhea) after the second dose of nivo + ipi. Median times to onset and resolution of TRAEs were 6 and 3 weeks, respectively. Eleven patients (28%) discontinued treatment for reasons other than TRAEs. TRAEs of any grade led to discontinuation in 5 patients (13%). Most of the TRAEs were reversible when managed with available guidelines.

* Corresponding author. Gulhane Military Medical Academy, Department of Medical Oncology, Ankara, Turkey.
*E-mail address:* drnkaradurmus@yahoo.com (N. Karadurmus).
Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2018.10.001

*Discussion:* Safety profile of N + I was found to be consistent with early reports. Increased experience with the management of TRAEs of immunotherapies, short follow-up and ≥2 line real-world setting may account for lower TRAEs rates. Long-term follow is needed.


## 1. Introduction

Until the last decade, the response rate was less than 20%, and the overall survival (OS) was less than 10 months with cytotoxic chemotherapeutic agents used in metastatic melanoma as first-line or second-line therapies.[1–5] Checkpoint inhibition by monoclonal antibodies targeting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and/or programmed cell death-1 (PD-1)/PD-L1 is now one of the most promising therapy to achieve long-term benefit in patients with metastatic melanoma. CTLA-4, immune checkpoint molecule that down-regulates pathways of T-cell activation, is a negative regulator of the immune system.[6] Being highly expressed on T cells from patients with malignancies, PD-1 is located on T cells, pro-B cells and NK cells and interacts with its ligands PD-L1 and PD-L2 to inhibit T cell activation, proliferation, tumor cell apoptosis and causes tumor-related immune suppression. Immunotherapy can be effective. The efficacy of immunotherapy has been demonstrated in diseases such as malignant melanoma, head and neck cancer, non-small cell lung cancer and renal cell carcinoma.[7–11]

Ipilimumab (ipi), which blocks CTLA-4, was the first monoclonal antibody to improve OS in a randomized controlled, phase 3 trial of patients with previously treated metastatic melanoma compared to gp100 alone arm.[12] In this trial, the median OS was 10.1 months among patients receiving ipi, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio (HR) for death, 0.66; $P = 0.003$). In the longer follow-up, 3-year OS rate in patients treated with ipi alone was 25%.[13] In another randomized, phase III trial, adding ipi 10 mg per kilogram to dacarbazine every 3 weeks for four doses followed by dacarbazine alone every 3 weeks through week 22 significantly improved OS from 9.1 months to 11.2 months (HR, 0.72; $P < 0.001$).[14] In a pooled OS analysis for 1861 patients from 10 prospective and two retrospective studies of ipi, including phase II and III trials, median OS was 11.4 months and 3-year OS rates were 22% and 26% for all patients and treatment-naive patients, respectively.[15]

Checkpoint inhibition by the interaction of PD-1 with PD-L1 on tumor cells has emerged as an effective treatment strategy for various cancers including metastatic melanoma. Newer monoclonal antibodies, which block PD-1, include nivolumab (nivo) and pembrolizumab led to a greater proportion of patients achieving an objective response rate (ORR) and less toxicity compared to ipi and chemotherapeutic agents in patients with metastatic melanoma.[16–19] In the randomized controlled phase III KEYNOTE-006 study, the primary endpoints of progression-free survival (PFS) and OS were significantly improved with less toxicity in both pembrolizumab arms (10 mg per kilogram every 2 or 3 weeks) than ipi in patients with advanced melanoma who had received no more than one previous systemic therapy for advanced disease.[17] In the randomized phase III Checkmate 066 trial nivo monotherapy significantly improved OS, PFS and ORR compared to dacarbazine arm among previously untreated patients who had metastatic melanoma without a BRAF mutation.[20]

PD-1/PD-L1 interaction appears to be more effective on immunosuppression due to the regularly found PD-L1 expression on tumor cells shaping the T cell effector functions, whereas CTLA-4 may play a lesser role, due to the absence of B7 family ligands on tumor cells.[21] Combined inhibition of CTLA-4 and PD-1 checkpoints increase antitumor immunity with complementary and synergistic mechanisms.[22] In a double-blind phase II Checkmate 69 trial on patients with BRAF V600 wild-type tumors, the primary endpoint ORR was 61% in combination nivo plus ipi arm, whereas it was only 11% in ipi arm (odds ratio, 12.96; $P < 0.001$).[23] At a median 24.5 months follow-up of, 2-year OS rate was 63.8% in the combination arm and 53.6% in ipi arm.[24] In phase III Checkmate 67 trial, 945 patients with treatment-naive advanced staged melanoma randomized to nivo alone, nivo + ipi or ipi arms.[19] In this trial nivo alone or combination with ipi significantly improved coprimary endpoints PFS and OS than ipi alone.[19–25] Two-year OS rates were 64% for nivo plus ipi combination, 59% for nivo arm and 45% for ipi arms (nivo plus ipi versus ipi HR; 0.55, $P < 0.0001$, nivo versus ipi HR; 0.63, $P < 0.0001$). In Checkmate 67 trial, grade 3 and 4 adverse events were reported in 58.5%, 20.8% and 27.7% of patients with advanced melanoma treated with ipilimumab plus nivo combination, nivo or ipi, respectively.[25]

Both ipi and ipi are approved by Food and Drug Administration (FDA) for the treatment of advanced melanoma.[12–26] As an Early Access Program (EAP), nivo was given in combination with ipi in Turkey. The aim of this study was to evaluate the safety of nivo plus ipi in advanced melanoma patients who had relapsed after ≥1 line of systemic treatment in a real-world setting.

## 2. Methods

Patients aged ≥18 years with advanced melanoma who had relapsed after at least one line of systemic treatment were eligible for nivo and ipi combination treatment upon physicians' request through the updated nivo EAP in 2016, following the approval of nivo and ipi combination for the treatment of advanced melanoma across BRAF status in the United States. Key inclusion criteria were histologically confirmed, pre-treated unresectable American Joint Committee on Cancer stage III or stage IV melanoma and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, whereas key exclusion criteria included active brain metastases and the use of corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. Patients were to be treated with 1 mg/kg nivo plus 3 mg/kg ipi every 3 weeks for 4 doses, followed by 3 mg/kg nivo every 2 weeks until progression or unacceptable toxicity for up to 24 months. EAP protocols were approved by the Turkish Medicines and Medical Devices Agency and all patients provided written informed consent for EAP enrollment.

## 3. Study design, data collection, and statistical analysis

A retrospective safety analysis was conducted with participating centers by reviewing anonymous EAP forms and related AE reports. A data collection sheet was also used to collect additional treatment information and treatment-related adverse events (TRAEs) characteristics. The study population included patients who had received at least one dose of nivo plus ipi. TRAEs were recorded and

graded according to the Common Terminology Criteria for Adverse Events, version 3.0. Data were analyzed using descriptive statistics. Overall survival data were immature. The local ethics committee approved this study.

## 4. Results

Between July 2014 to December 2016, 837 adult patients with pre-treated advanced cancers (245 non-squamous non-small cell lung cancer [NSCLC], 20 squamous NSCLC, 166 melanoma, 275 renal cell carcinoma, and 131 classical Hodgkin's lymphoma patients) participated in the nivo EAP in Turkey and received at least one dose of nivo. Of the melanoma patients, 40 were enrolled in 23 Turkish centers for nivo and ipi combination treatment and received at least one dose of nivo plus ipi. All patients had stage IV melanoma. Patient and disease characteristics are presented in Table 1.

The dataset was locked for analysis on April 15, 2017. At a median follow-up of 19 weeks (range, 10–39), 30 patients (75%) were alive, and 24 patients (60%) were continuing treatment. The median number of doses administered (nivo plus ipi and nivo alone) was 4 (range, 1–14). Five patients (13%) discontinued treatment due to any TRAEs, of whom 4 (10%) had grade 3 or higher TRAEs. Eleven patients (28%) discontinued treatment for any reason except TRAEs (1 patient was lost to follow-up, 3 patients had progressive disease, and 7 patients died due to disease progression or other medical conditions).

TRAEs of any grade and grade 3 or 4 occurred in 21 patients (53%) and 8 patients (20%), respectively. The most common TRAEs were fatigue, rash, pruritus, diarrhea, an increase in alanine aminotransferase and/or aspartate aminotransferase levels (10% each) (Table 2).

**Table 1**
Patient and disease characteristics.

| | All patients (n = 40) |
|---|---|
| Age (years) | 58 (21–77) |
| Sex | |
| Male | 24 (60%) |
| Female | 16 (40%) |
| Weight (kg)[a] | 76 (44–103) |
| ECOG performance status | |
| 0 | 22 (55%) |
| 1 | 18 (45%) |
| History of medical comorbidities | 10 (25%) |
| Melanoma type | |
| Cutaneous | 28 (70%) |
| Mucosal | 4 (10%) |
| Ocular | 2 (5%) |
| Unknown | 6 (15%) |
| History of brain metastasis | 11 (28%) |
| History of cranial radiotherapy | 6 (15%) |
| History of liver metastasis | 20 (50%) |
| History of adjuvant IFN for AJCC stage 3 disease | 9 (23%) |
| Number of previous systemic treatments[b] | |
| 1 | 35 (87%) |
| 2 | 4 (10%) |
| 3 | 1 (3%) |
| Type of previous treatment[b] | |
| Temozolamide | 26 (65%) |
| BRAF ± MEK inhibitor | 11 (28%) |
| IFN | 6 (15%) |
| Other chemotherapy | 6 (15%) |
| Duration of previous systemic treatments (weeks)[b] | 25 (0–230) |
| BRAF mutant[c] | 12 (30%) |

Data are median (range) or n (%). IFN = interferon. ECOG = Eastern Cooperative Oncology Group. AJCC = American Joint Committee on Cancer.
[a] Unknown for 4 patients.
[b] In metastatic disease setting.
[c] Unknown for 3 patients.

The median time to onset of any TRAEs was 6 weeks (range, 1–20). The median time to resolution of any TRAEs from the onset was 3 weeks (range, 1-not resolved). Four TRAEs (14%) did not resolve by the time of the database lock (one grade 1 fatigue, one grade 3 alanine aminotransferase and/or aspartate aminotransferase increase, one grade 5 colitis, and one grade 5 diarrhea). Patterns of TRAEs by organ system are summarised in Table 3.

Of the 21 patients who developed TRAEs, 11 patients (52%) were treated with systemic corticosteroids. One patient (5%) received mycophenolate mofetil, too. Three patients (14%) required hormone replacement or antithyroid treatments. Seven patients (33%) were hospitalized for the management of TRAEs. The median duration of hospitalization was 7 days (range, 4–19 days).

One patient (3%) was lost to follow-up after the second cycle of nivo plus ipi and reported to have died due to TRAEs of diarrhea and colitis despite management in the intensive care unit. The patient received supportive care and was not treated with corticosteroids or other immunosuppressive medications.

## 5. Discussion

In our study, 40 EAP patients who received at least one dose of nivo plus ipi enrolled to the safety analysis. In our study, any grade adverse events and grade 3-4 adverse events occurred in 53% and 20% of the patients, respectively. Only one patient died due to TRAEs (colitis and diarrhea) after the second dose of combination regimen. The most common TRAEs were fatigue, rash, pruritus, diarrhea, and alanine aminotransferase/aspartate aminotransferase elevation.

Although crucial clinical OS, PFS and ORR benefits were associated with single or dual checkpoint inhibition, a unique spectrum of side effects termed immune-related adverse events (irAEs) should be managed with special interest. Immune-related adverse events include mostly dermatologic and gastrointestinal system than endocrine, hepatic, and other less common inflammatory events such as pneumonitis, hypophysitis, neurological disorders and others respectively.[27,28] Any grade 3 and 4 adverse events were largely immune-related with ipi and nivo. Grade 3 and 4 adverse events were reported up to 45% of patients treated with ipi and irAEs with ipi, occurring mainly in the skin and gastrointestinal tract, with 15%–22%.[12,29] Grade 3 and 4 adverse events were reported in from 5% up to 20% of patients treated with nivo alone for advanced stage malign melanoma.[14,20,25] The most common grade 3 and 4 adverse events with ipi and nivo monotherapies or combination regimen were diarrhea and colitis.[19]

In phase II Checkmate 69 trial, grade 3 and 4 TRAEs were

**Table 2**
Treatment-related adverse events.

| Event | All patients (n = 40) | |
|---|---|---|
| | Any graden (%)[a] | Grade 3 or highern (%)[a] |
| Any adverse event | 21 (53) | 8 (20) |
| Fatigue | 4 (10) | 1 (3) |
| Rash | 4 (10) | 0 |
| Pruritus | 4 (10) | 0 |
| Diarrhea | 4 (10) | 3 (8) |
| ALT/AST increase | 4 (10) | 3 (8) |
| Hypothyroidism | 2 (5) | 1 (3) |
| Hyperthyroidism | 2 (5) | 0 |
| Thyroiditis | 1 (3) | 1 (3) |
| Hypophysitis | 1 (3) | 0 |
| Colitis | 1 (3) | 1 (3) |
| Nausea | 1 (3) | 0 |
| Thrombocytopenia | 1 (3) | 0 |

[a] Five patients developed more than one event. One patient deceased due to treatment-related adverse events (diarrhea and colitis).

**Table 3**
Patterns of treatment-related select adverse events by organ system.

| Event by type[a] | All patients (n = 40) | | Time to onset, median week (range) | Time to resolution from the onset, median week (range) |
|---|---|---|---|---|
| | Any grade n (%) | Grade 3 or higher n (%) | | |
| Skin | 6 (15) | 0 | 4 (2–7) | 1 (1–4) |
| Endocrine | 6 (15) | 2 (5) | 9.5 (1–20) | 3.5 (1–5) |
| Gastrointestinal | 4 (10) | 3 (8) | 4 (1–12) | 2 (1-not resolved) |
| Hepatic | 4 (10) | 3 (8) | 10 (6–12) | 5 (4-not resolved) |
| Hematologic | 1 (3) | 0 | 8 (NA) | 1 (NA) |

[a] Four patients developed more than one event by type. One patient deceased due to treatment-related gastrointestinal adverse events (diarrhea and colitis).

reported in 54% and 24% of patients treated with ipi plus nivo and ipi treatment arms, respectively.[23] Most common grade 3 and 4 TRAEs were colitis (17%), diarrhea (11%) and alanine aminotransferase and/or aspartate aminotransferase increase (11%) with combination regimen. Three deaths (3.1%) were attributed to the combination therapy according to the investigator assessment.

In phase III Checkmate 67 trial, grade 3 and 4 TRAEs were reported in 58.5%, 20.8% and 27.7% of patients with advanced melanoma treated with ipi plus nivo combination, nivo or ipi, respectively.[19,25] The most common grade 3 and 4 TRAEs in the nivo plus ipi combination arm were diarrhea (9.3%), alanine aminotransferase and/or aspartate aminotransferase increase (8.3%) and colitis (7.7%). Treatment discontinuation were reported in the 36.4% of patients treated with the nivo plus ipi combination arm due to TRAEs, whereas treatment discontinuation was occurred only in 7.7% of the patients in the nivo arm and 14.8% of the patients the ipi arm due to TRAEs. Two deaths (0.6%) were attributed to the combination therapy.[25] Similar safety outcomes were reported from North American expanded access program of nivo plus ipi in advanced melanoma. TRAEs of any grade and grade 3 or 4 occurred in 91–94% and 50–59% of these patients, respectively.[30,31]

In our study, TRAEs of any grade and grade 3 or 4 occurred in 53% and 20%, respectively with a median 19 weeks follow up. In Checkmate 67 and 69 trials grade 3 and 4 TRAEs were reported in more than %50 of patients treated with nivo plus ipi combination but in our study grade 3 and 4 TRAEs were only %20.[23,25] Only one patient death (2.5%) was attributed to the nivo plus ipi combination is consistent with the literature. TRAEs of any grade led to discontinuation in 13% of patients treated with nivo plus ipi combination regimen in our study is lower compared to Checkmate 67 trial where 36.4% of patients treated with the nivo plus ipi combination arm led to treatment discontinuation due to TRAEs.[24] Increased experience with the management of TRAEs of immunotherapies, short follow-up and ≥2 lines real-world setting may account for lower TRAE rates in our study. Retrospective nature of our study might have resulted in under-reporting as well. The most common TRAEs were fatigue, rash, pruritus, diarrhea, and increase in alanine aminotransferase and/or aspartate aminotransferase levels (10% each) which are consistent with the reported adverse events in the literature. Most of the TRAEs were reversible when managed with available guidelines. In our study, median times to onset and resolution of TRAEs were 6 and 3 weeks, respectively are consistent with the literature.[12,26,27]

## 6. Conlusion

The combination of nivo plus ipi was safe and consistent with early reports in advanced melanoma patients who had relapsed after ≥1 line of systemic treatment in a real-world setting. Immune-related adverse events were manageable and generally reversible with corticosteroids.

## References


1. Serrone L, Zeuli M, Sega FM, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. *J Exp Clin Canc Res*. 2000;19:21–34.
2. Keilholz U, Punt CJ, Gore M, et al. Dacarbazine, cisplatin, and interferon-alfa-2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol*. 2005;3:6747–6755.
3. Atkins MB, Hsu J, Lee S, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2008;26:5748–5754.
4. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol*. 2000;18:158–166.
5. Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. *Cancer*. 2006;106:375–382.
6. Wang CJ, Schmidt EM, Attridge K, et al. Immune regulation by CTLA-4–relevance to autoimmune diabetes in a transgenic mouse model. *Diabetes Metab Res Rev*. 2011;27:946–950.
7. Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med*. 2009;206:3015–3029.
8. Amarnath S, Mangus CW, Wang JC, et al. The PDL1-PD1 axis converts human TH1 cells into regulatory T cells. *Sci Transl Med*. 2011;3:111–120.
9. Keir ME, Liang SC, Guleria I, et al. Tissue expression of PD-L1 mediates peripheral T cell tolerance. *J Exp Med*. 2006;203:883–895.
10. Karadurmus Nuri, Ertürk Ismail. Which is the best for cancer treatment? Surgery or chemotherapy. *J Oncol Sci*. 2017;3:32–33.
11. Birol Yildiz, İsmail Ertürk, Nuri Karadurmuş. "Baş-Boyun kanserlerinde İmmünoterapi Yaklaşımları". *Turkiye Klinikleri Journal of Medical Oncology Special Topics*. 2018;11:195–198.
12. 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.
13. Mcdermott D, Haanen J, Chen TT, Lorigan P, O'day S, Investigators MDX. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). *Ann Oncol*. 2013;24:2694–2698.
14. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364:2517–2526.
15. 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;33:1889–1894.
16. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16:908–918.
17. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521–2532.
18. 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.
19. 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.
20. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372:320–330.
21. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A*. 2010;107:4275–4280.
22. Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. *Nat Immunol*. 2013;14:1212–1218.
23. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372:2006–2017.

24. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol*. 2016;17:1558–1568.
25. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Overall survival results from a phase III trial of nivolumab combined with ipilimumab in treatment-naïve patients with advanced melanoma (CheckMate 067). *AACR Annual Meeting*. 2017. Abstract CT075. (2017).
26. Khoja L, Atenafu EG, Ye Q, et al. Real-world efficacy, toxicity and clinical management of ipilimumab treatment in metastatic melanoma. *Oncol Lett*. 2016;11:1581–1585.
27. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Canc*. 2016;60:210–225.
28. 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;26:1824–1829.
29. O'day SJ, Maio M, Chiarion-Sileni V, et al. Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study. *Ann Oncol*. 2010;21:1712–1717.
30. Hogg D, Chapman PB, Sznol M, et al. Overall survival (OS) analysis from an expanded access program (EAP) of nivolumab (NIVO) in combination with ipilimumab (IPI) in patients with advanced melanoma (MEL). *J Clin Oncol*. 2017;35:9522, 9522.
31. Shoushtari AN, Friedman CF, Navid-Azarbaijani P, et al. Measuring toxic effects and time to treatment failure for nivolumab plus ipilimumab in melanoma. *JAMA Oncol doi*. 2017. https://doi.org/10.1001/jamaoncol.2017.2391.