Combination or single-agent ipilimumab as immunotherapy of advanced melanoma: a critical review

Omar Abdel-Rahman*

Practice points

Background

- A pooled analysis of the efficacy and toxicity of doublet immunotherapy versus single-agent ipilimumab in the management of advanced melanoma has been conducted.

Methods

- Eligible studies included studies evaluating ipilimumab-based doublet immunotherapy versus ipilimumab monotherapy for the management of advanced melanoma.

Results

- After exclusion of ineligible studies, four studies were included in the quantitative synthesis of the analysis. Nivolumab/ipilimumab combination strategy is associated with a significant improvement in objective response rate (odds ratio: 7.38; 95% CI: 3.71–14.67; $p < 0.00001$) and progression-free survival (hazard ratio: 0.42; 95% CI: 0.34–0.52; $p < 0.00001$) as well as a higher relative risk for high-grade elevated alanine aminotransferase (relative risk: 5.58; 95% CI: 2.28–13.67; $p = 0.0002$).

Aim: A pooled analysis of the efficacy and toxicity of combination immunotherapy versus single-agent ipilimumab in the management of advanced melanoma has been conducted.

Methodology: Eligible studies included randomized controlled studies evaluating ipilimumab-based doublet immunotherapy versus ipilimumab monotherapy for the management of unresectable melanoma. **Results:** Nivolumab/ipilimumab combination strategy is associated with a significant improvement in objective response rate (odds ratio: 7.38; 95% CI: 3.71–14.67; $p < 0.00001$) and progression-free survival (0.42; 95% CI: 0.34–0.52; $p < 0.00001$) as well as a higher relative risk for high-grade elevated alanine aminotransferase (5.58; 95% CI: 2.28–13.67; $p = 0.0002$). **Conclusion:** This analysis demonstrated that nivolumab/ipilimumab combination is associated with a higher objective response rate and progression-free survival in the management of advanced melanoma.

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Background

Malignant melanoma is the most lethal skin malignancy, with an average incidence rate of 21.6/100,000 population according to the SEER database [1]. Many hereditary and environmental factors have been proposed as contributors in the development of melanoma; however, proper understanding of melanoma biogenesis is still at its infancy [2]. Moreover, significant variation in the incidence and prognosis of melanoma has been noted among different geographical areas and ethnic groups [3].

KEYWORDS

- immunotherapy
- ipilimumab • melanoma
- nivolumab

*Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Lotfy Elsayed Street, Cairo 11665, Egypt; Fax: +20 33028656; omar.abdelrhman@med.asu.edu.eg

For resectable melanoma, radical surgical resection remains the standard of care, high-risk patients are considered for adjuvant therapy with active research to determine the best agent for this [4]. For advanced/unresectable melanoma, the prognosis until recently was very poor and treating physicians had limited effective therapeutic options. Following a better understanding of melanoma biology and an assessment of potential oncogenic drivers, a plethora of targeted therapies have joined the therapeutic armamentarium of this disease. These include; BRAF inhibitors (vemurafenib/dabrafenib), MEK inhibitors (trametinib/sleumetinib) and various combinations of these agents with each other [5,6]. Moreover, the introduction of immune checkpoint inhibitors has greatly advanced the field of melanoma therapy. Following a number of successful Phase III studies, ipilimumab

was approved for the management of this disease [7]. This has been followed by approval of two anti-PD1 agents, pembrolizumab and nivolumab. More recently, ipilimumab-based doublet immunotherapy regimens have been evaluated in clinical studies. We are trying to evaluate such combinations as a potential new therapeutic option.

Biological rationale of combination immunotherapy in melanoma

The basic rationale behind the use of immune check point inhibitors in cancer therapy stems from the orchestrating role played by T lymphocytes within the immune system. However, this role of T lymphocytes to combat invading organisms/malignant cells has to be counteracted by checkpoints that prevent normal tissue self-targeting [8,9]. Selective inhibition

Figure 1. Flowchart of study selection procedure.

Table 1. Efficacy outcomes in the included studies.					
Study (year)	Study type	Treatment regimen	ORR	PFS	OS
Nivolumab plus ipilimumab					
Postow <i>et al.</i> (2015)	Randomized Phase II	142 patients were randomized in a 2:1 fashion into: – Ipilimumab (3 mg/kg) combined with nivolumab (1 mg/kg); – Ipilimumab (3 mg/kg) combined with placebo	61 vs 11% (odds ratio 12.96%; $p < 0.001$)	Not reached with the combination therapy and was 4.4 months with ipilimumab monotherapy (HR: 0.40; 95% CI: 0.23–0.68; $p < 0.001$)	N/R [18]
Larkin <i>et al.</i> (2015)	Phase III	945 patients were randomized in a 1:1:1 fashion into: – Nivolumab 3 mg/kg combined with placebo; – Ipilimumab (3 mg/kg) combined with nivolumab (1 mg/kg); – Ipilimumab (3 mg/kg) combined with placebo	43.7 vs 57.6 vs 19% ($p = 0.001$)	6.9 vs 11.5 vs 2.9 months (HR for combination vs ipilimumab: 0.42; $p = 0.001$)	N/R [17]
Wolchok <i>et al.</i> (2013)	Phase I	All 53 patients received nivolumab plus ipilimumab in successive cohorts of patients with escalating doses	Across all cohorts: 40%	N/R	N/R [14]
Immunomodulatory agent plus ipilimumab					
Hodi <i>et al.</i> (2014)	Randomized Phase II	Ipilimumab, 10 mg/kg, intravenously on day 1 plus sargramostim, 250 µg subcutaneously, on days 1–14 of a 21-day cycle ($n = 123$) Ipilimumab alone ($n = 122$)	16.3 vs 18.9% ($p = 0.88$)	3.1 months (95% CI: 2.9–4.6) vs 3.1 months (95% CI: 2.9–4.0); $p = 0.37$ HR: 0.87	17.5 months (95% CI: 14.9–not reached) vs 12.7 months (95% CI: 10.0–not reached); $p = 0.01$ HR: 0.64 [19]
Hodi <i>et al.</i> (2010)	Phase III	676 patients were randomized in a 3:1:1 fashion into: – Ipilimumab (3 mg/kg) plus gp100; – Ipilimumab (3 mg/kg) alone gp100 alone	5.7 vs 10.9 vs 1.5%	HR for doublet vs ipilimumab monotherapy: 1.25; $p = 0.04$	10 vs 10.1 vs 6.4 months (HR for doublet vs ipilimumab monotherapy: 1.04; $p = 0.74$) [7]
Maker <i>et al.</i> (2005)	Phase I/II	36 patients received CTLA-4 blockade (MDX-010) in combination with IL-2	Eight patients (22%) experienced objective tumor regression (three complete and five partial)	N/R	N/R [20]

HR: Hazard ratio; N/R: Not reported; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

of these checkpoints may thus lead to restoration of the activity of T lymphocytes and thus promote stronger antitumor responses [10,11]. Given the single-agent preclinical and clinical activity of immune check point inhibition in melanoma [12,13]; and in addition to preclinical data suggesting synergistic action of checkpoint molecules to promote tumor immune evasion, it seems logical to assess whether combination checkpoint inhibitors will improve activity, compared with single agent use [14]. Of particular interest is the combination of CTLA-4 – targeting agents such as ipilimumab with PD-1/PDL-1 targeting agents because these checkpoints work physiologically at different molecular levels (priming phase vs effector phase); thus, nonresponsiveness to single-agent use could be overcome by combination therapies.

Objective of the systematic review

The aim of this review is to provide a comparative assessment of the efficacy and toxicity of combination or single-agent ipilimumab as immunotherapy of advanced melanoma.

Methodology

• Search strategy

A comprehensive search for literature published in English was performed in the following databases: PubMed/MEDLINE, the Cochrane Controlled

Trials Register and Google Scholar in order to identify all relevant citations; the start date of the search was 1 July 2005 and the date of the last search was 1 July 2015 for all databases. Meeting abstracts including American Society of Clinical Oncology and European Society of Medical Oncology were also reviewed. Additional supplementary approaches have been employed to identify studies including hand searching of journals, checking reference lists and searching trials registries. Citations with the following words in their titles or abstracts were examined: ‘melanoma’ and ‘ipilimumab’ or ‘nivolumab’. References of relevant citations were also checked for possible cross-references. The search was developed and conducted by the review author.

• Selection criteria

Inclusion criteria

- Clinical trials that compared ipilimumab monotherapy versus doublet immunotherapeutic agents for the treatment of adult patients with advanced melanoma (unresectable stage III and IV disease);

- Efficacy measures and/or toxicities were reported.

Exclusion criteria

- Non-English language records were excluded.

Table 2. All grade immune-related adverse events in the included studies.

Study (year)	Endocrinopathy	Hepatic	Cutaneous	Gastrointestinal	Ref.
Nivolumab plus ipilimumab					
Postow <i>et al.</i> (2015)	Hypothyroidism: 15 (16%) vs 7 (15%) Hypophysitis: 11(12%) vs 3 (7%)	Elevated ALT: 21 (22%) vs 2 (4%) Elevated AST: 20 (21%) vs 2 (4%)	Rash: 39 (41%) vs 12 (26%) Vitiligo: 10 (11%) vs 4 (9%)	Diarrhea: 42 (45%) vs 17 (37%) Colitis: 22 (23%) vs 6 (13%)	[18]
Larkin <i>et al.</i> (2015)	Hypothyroidism: 27 (8.6%) vs 47(15%) vs 13 (4.2%)	Elevated ALT: 12 (3.8%) vs 55 (17.6%) vs 12 (3.9%) Elevated AST: 12 (3.8%) vs 48 (15.3%) vs 11 (3.5%)	Rash: 81 (25.9%) vs 126 (40.3%) vs 102(32.8%)	Diarrhea: 60 (19.2%) vs 138 (44.1%) vs 103 (33.1%) Colitis: 4 (1.3%) vs 37 (11.8%) vs 36 (11.6%)	[17]
Wolchok <i>et al.</i> (2013)	Hypothyroidism: 2 (4%) Hypophysitis: 1 (2%)	Elevated ALT: 11 (21%) Elevated AST: 11 (21%)	Rash: 37 (70%)	Diarrhea: 18 (34%) Colitis: 5 (9%)	[14]
Immunomodulatory agent plus ipilimumab					
Hodi <i>et al.</i> (2014)	N/R				[19]
Hodi <i>et al.</i> (2010)	Hypothyroidism: 6 (1.6%) vs 2 (1.5%) vs 2 (1.5%) Hypophysitis: 2 (0.5%) vs 2 (1.5%) vs 0	Elevated ALT: 3 (0.8%) vs 2 (1.5%) vs 3 (2.3%) Elevated AST: 4 (1.1%) vs 1 (0.8%) vs 2 (1.5%)	Rash: 67 (17.6%) vs 25 (19.1%) vs 6 (4.5%) Vitiligo: 14 (3.7%) vs 3 (2.3%) vs 1 (0.8%)	Diarrhea: 115 (30.3%) vs 36 (27.5%) vs 18 (13.6%) Colitis: 20 (5.3%) vs 10 (7.6%) vs 1 (0.8%)	[7]

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Table 3. High-grade (grade 3–5) immune-related adverse events in the included studies.

Study (year)	Endocrinopathy	Hepatic	Cutaneous	Gastrointestinal	Ref.
<i>Nivolumab plus ipilimumab</i>					
Postow <i>et al.</i> (2015)	Hypothyroidism: 0 vs 0 Hypophysitis: 2 (2%) vs 2 (4%)	Elevated ALT: 10 (11%) vs 0 Elevated AST: 7 (7%) vs 0	Rash: 5 (5%) vs 0 Vitiligo: 0 vs 0	Diarrhea: 10 (11%) vs 5 (11%) Colitis: 16 (17%) vs 3 (7%)	[18]
Larkin <i>et al.</i> (2015)	Hypothyroidism: 0 vs 1 (0.3%) vs 0	Elevated ALT: 4 (1.3%) vs 26 (8.3%) vs 5 (1.6%) Elevated AST: 3 (1%) vs 19 (6.1%) vs 2 (0.6%)	Rash: 2 (0.6%) vs 15 (4.8%) vs 6 (1.9%)	Diarrhea: 7 (2.2%) vs 29 (9.3%) vs 19 (6.1%) Colitis: 2 (0.6%) vs 24 (7.7%) vs 27 (8.7%)	[17]
Wolchok <i>et al.</i> (2013)	Hypothyroidism: 1(2%) Hypophysitis: 0	Elevated ALT: 8 (15%) Elevated AST: 6 (11%)	Rash: 2(4%)	Diarrhea: 18 (34%) Colitis: 2 (4%)	[14]
<i>Immunomodulatory agent plus ipilimumab</i>					
Hodi <i>et al.</i> (2014)	4(3.4%) vs 9 (7.5%)	Elevated ALT: 6 (5.1%) vs 7 (5.8%) Elevated AST: 5 (4.2%) vs 9 (7.5%)	Rash: 11(9.3%) vs 11 (9.2%)	Diarrhea: 15 (12.7%) vs 16 (13.3%) Colitis: 7 (5.9%) vs 10 (8.3%)	[19]
Hodi <i>et al.</i> (2010)	Hypothyroidism: 1 (0.3%) vs 0 vs 0 Hypophysitis: 2 (0.5%) vs 2 (1.5%) vs 0	Elevated ALT: 2 (0.5%) vs 0 vs 0 Elevated AST: 1 (0.3%) vs 0 vs 0	Rash: 5 (1.3%) vs 1 (0.8%) vs 0 Vitiligo: 0 vs 0 vs 0	Diarrhea: 22 (6%) vs 10 (7.6%) vs 1 (0.8%) Colitis: 12 (3.2%) vs 5 (5.3%) vs 0	[7]

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

• Data extraction

Data were extracted by two independent review author. All eligible articles underwent initial assessment for relevance. The following set of data has been extracted from each of the included studies (where available): study author and year of publication; treatment regimen and schedule, number of patients, objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and the incidence of immune-related adverse events (IRAEs). IRAEs evaluated in this analysis included gastrointestinal (diarrhea and colitis), hepatic (elevated alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), cutaneous (skin rash and vitiligo) and endocrine (hypothyroidism and hypophysitis).

• Outcome measures

The outcome measures of interest were median PFS, median OS, ORR and IRAEs. Response was assessed using Response Evaluation Criteria in Solid Tumors v 1.1 and toxicities were assessed using National Cancer Institute-Common Terminology Criteria. The main outcome measures are summarized using descriptive statistics. This systematic review adheres to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report (PRISMA Statement) [15].

• Data analysis

For efficacy analysis, odds ratio (OR) and CIs have been calculated for ORR evaluating ipilimumab monotherapy versus doublet immunotherapy. Hazard ratios (HRs) were extracted for PFS and OS from each study and then the log of HRs and CIs were derived. A meta-analysis of both HRs and ORs were then conducted and random effects model was used because of the observed heterogeneity among different studies. The calculation of the random effects model was done using the DerSimonian method [16]. An OR of more than one and an HR of less than one means a benefit for patients receiving doublet immunotherapy.

For toxicity analysis, the principal measures were relative risk (RR) and corresponding 95% CIs of all grade (grade 1–5) and high-grade (grade 3–5) IRAEs. For all calculations of RRs and CIs, data extracted only from randomized studies have been used, comparing the incidence of each adverse event in patients assigned to doublet immunotherapy versus those allocated to ipilimumab monotherapy. The random effects model using the DerSimonian method was also used in toxicity analysis.

Subgroup analysis was performed according to the different companion drugs plus ipilimumab and publication bias was assessed using funnel plots. All statistical analyses were conducted using the program RevMan 5.3 (Copenhagen, Denmark).

Results

• Search results

Figure 1 summarizes the PRISMA diagram for study selection procedure; 125 results were obtained from the searches in Pub Med (n = 80 studies) and other databases (n = 45). Of these results, 33 were duplicates and 82 did not meet the eligibility criteria and were

therefore excluded. Of the ten studies which appeared to be eligible after the initial screening, a full text search was performed. Four studies were removed after the full text search; thus, six studies were included in the final qualitative analysis; two Phase III studies, two randomized Phase II studies and two Phase I study (**Tables 1–3**). Among the included studies,

Figure 2. Efficacy outcomes. (A) Forest plots of odds ratio of objective response rate associated with doublet immunotherapy versus ipilimumab monotherapy; **(B)** Forest plots of hazard ratio of progression-free survival associated with doublet immunotherapy versus ipilimumab monotherapy; the size of squares corresponds to the weight of the study in the meta-analysis.
df: Degree of freedom; SE: Standard error.

Table 4. Summary of relative risk of selected immune-related side effects (for doublet immunotherapy vs ipilimumab monotherapy).

Toxicity	Group I studies	Group II studies
High-grade diarrhea	1.38 (95% CI: 0.85–2.25); p = 0.2	0.83 (95% CI: 0.51–1.36); p = 0.47
High-grade colitis	1.34 (95% CI: 0.47–3.80); p = 0.58	0.74 (95% CI: 0.37–1.48); p = 0.39
High-grade rash	2.70 (95% CI: 1.11–6.55); p = 0.03	1.06 (95% CI: 0.50–2.23); p = 0.88
High-grade elevated ALT	5.58 (95% CI: 2.28–13.67); p = 0.0002	0.92 (95% CI: 0.34–2.49); p = 0.86
High-grade elevated AST	9.05 (95% CI: 2.49–32.89); p = 0.0008	0.59 (95% CI: 0.21–1.61); p = 0.3

Group I: Nivolumab/ipilimumab combination; Group II: immunomodulators/ipilimumab combination; High-grade: Grade 3–5.
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

three studies evaluated nivolumab/ipilimumab combination [14,17,18], one study evaluated ipilimumab plus sargamostim (granulocyte macrophage colony stimulating factor; GM-CSF) combination [19], one study evaluated ipilimumab plus IL-2 [20] and one study evaluated ipilimumab plus gp100 (tumor vaccine) combination [7]. For the quantitative analysis, the two Phase I studies were excluded and four studies only were included. For the sake of the analysis, the studies in the quantitative synthesis have been categorized into two groups; group I which includes the nivolumab/ipilimumab studies (two studies) and group II which includes the immunomodulators/ipilimumab studies (two studies). Each of these groups has been analyzed independently.

• Population characteristics

A total of 2061 patients were included in the analysis, most patients have an Eastern Cooperative Oncology Group performance score between 0 and 1 in addition to adequate hematological, hepatic and renal functions. The baseline characteristics and the relevant outcomes in each trial have been summarized in [Tables 1–3](#). Funnel plots did not reveal any evidence of a publication bias among the examined outcomes (data not shown).

• Efficacy outcomes

Objective response rate

The OR for group I studies was 7.38 (95% CI: 3.71–14.67; p < 0.00001) while the OR for group II studies was 0.67 (95% CI: 0.41–1.08; p = 0.1) ([Figure 2A](#)).

Progression-free survival

The HR for group I studies was 0.42 (95% CI: 0.34–0.52; p = 0.00001) while the HR for group II studies was 1.06 (95% CI: 0.74–1.51; p = 0.76) ([Figure 2B](#)).

Overall survival

OS was not reported for group I studies; however, for group II studies, the HR is 0.89 (95% CI: 0.73–1.09; p = 0.26) (data not shown).

Thus, the available efficacy analyses demonstrate that nivolumab/ipilimumab combination strategy is associated with a statistically significant improvement in ORR and PFS. On the other hand, the same improvement is not seen with the other group of studies.

• Toxicities (IRAEs)

Gastrointestinal toxicities

The RR of high-grade diarrhea for group I was 1.38 (95% CI: 0.85–2.25; p = 0.2) while for group II it was 0.83 (95% CI: 0.51–1.36; p = 0.47).

The RR of high-grade colitis for group I was 1.34 (95% CI: 0.47–3.80; p = 0.58) while for group II it was 0.74 (95% CI: 0.37–1.48; p = 0.39) ([Figure 3](#)).

Hepatic toxicities

The RR of high-grade elevated ALT for group I was 5.58 (95% CI: 2.28–13.67; p = 0.0002) while for group II studies it was 0.92 (95% CI: 0.34–2.49; p = 0.86).

The RR of high-grade elevated AST for group I was 9.05 (95% CI: 2.49–32.89; p = 0.0008) while for group II it was 0.59 (95% CI: 0.21–1.61; p = 0.3) ([Figure 4 & Table 4](#)).

Cutaneous toxicities

The RR of high-grade skin rash for group I was 2.70 (95% CI: 1.11–6.55; p = 0.03) while for group II it was 1.06 (95% CI: 0.50–2.23; p = 0.88) ([Figure 5](#)).

Thus, the nivolumab/ipilimumab combination is associated with a significantly higher RR for high-grade elevated ALT, elevated AST and skin rash. On the other hand, the other group of studies did not show increased risk of

these toxicities. Endocrine toxicities (including hypothyroidism and hypophysitis) were not adequately reported to enable the calculation of a meta-analysis.

Discussion
To the best of knowledge, this is the most updated pooled analysis to provide a comparative assessment of the efficacy and toxicity

Figure 3. Gastrointestinal toxicities. (A) Forest plots of relative risk of high-grade diarrhea associated with doublet immunotherapy versus ipilimumab monotherapy; (B) Forest plots of relative risk of high-grade colitis associated with doublet immunotherapy versus ipilimumab monotherapy.
df: Degree of freedom; M-H: Mantel-Haenszel test.

Figure 4. Hepatic toxicities. (A) Forest plots of relative risk of high-grade elevated alanine aminotransferase associated with doublet immunotherapy versus ipilimumab monotherapy; (B) Forest plots of relative risk of high-grade elevated aspartate aminotransferase associated with doublet immunotherapy versus ipilimumab monotherapy.
df: Degree of freedom; M-H: Mantel-Haenszel test.

of doublet immunotherapy compared with single-agent ipilimumab in the management of advanced melanoma. This analysis of data demonstrated that nivolumab/ipilimumab

combination strategy is associated with a statistically significant improvement in ORR and PFS. Moreover, the increased benefit of nivolumab/ipilimumab combination comes

Figure 5. Forest plots of relative risk of high-grade skin rash associated with doublet immunotherapy versus ipilimumab monotherapy.
df: Degree of freedom; M-H: Mantel-Haenszel test.

at the expense of a higher risk of high-grade toxicities such as high-grade elevation in ALT, AST and high-grade skin rash compared with ipilimumab monotherapy.

Immune check point inhibitors have been considered a practice-changing intervention in the management of advanced melanoma converting this lethal disease into a rather chronic, potentially treatable/controllable disease. Ipilimumab has been the first agent of this group to be approved in this indication [21]; this has been followed more recently by the approval of nivolumab and pembrolizumab in this indication also [22,23]. Tremelimumab is another immune checkpoint inhibitor that has been evaluated in this indication also [24]. In terms of the mechanism of action, these agents can be classified into two groups; namely, CTLA-4-targeting agents and PD-1-targeting agents [25]. Among the first group comes ipilimumab and tremelimumab while among the second group comes nivolumab and pembrolizumab. Knowledge of these different mechanisms of action is relevant in terms of designing appropriate combination of agents as well as in terms of interpreting the different toxicity profiles of these agents.

The initial success of single agent immune check point inhibitor has paved the way into

evaluating dual immunotherapy strategies with the aim of achieving more profound and durable therapeutic effect.

Nivolumab has been evaluated with or without peptide vaccine in ipilimumab-naïve or refractory melanoma in a Phase I trial. In this study, nivolumab induced responses in ipilimumab-refractory patients and the reverse was also true, in other words, ipilimumab was effective after failure on nivolumab [26]. These results have been confirmed in another study (CheckMate 037) which showed higher ORR and less toxicity with nivolumab versus chemotherapy in the post ipilimumab setting [27]. Such responses led to the evaluation of the combination strategies of nivolumab/ipilimumab.

The marked success of these agents comes at the cost of a completely new set of toxicities that were not usually encountered by the practicing oncologists with traditional anticancer agents. These characteristic toxicities come out of the novel mechanism of action of these agents thus it has been collectively termed as irAEs. These toxicities include gastrointestinal toxicities (principally diarrhea and colitis) [28]; hepatic toxicities (principally elevated transaminases and clinical hepatitis) [29]; cutaneous toxicities (principally skin rash and vitiligo) [30] and endocrine toxicities (mainly thyroid, pituitary and adrenal

disorders) [31]. Rarer IRAEs reported with these agents include pneumonitis, neuropathy and retinopathy [32]. Moreover, ipilimumab IRAEs including (colitis, hypophysitis, thyroiditis and dermatitis) have been linked to a higher response rate in some clinical studies [33]. Whether this is equally applicable to nivolumab/ipilimumab combination needs further evaluation.

Ipilimumab-based doublet immunotherapy has been evaluated in a number of other solid tumor indications. Le and coworkers presented data of ipilimumab (10 mg/kg) with or without allogeneic pancreatic tumor cells transfected with a GM-CSF gene (*GVAX*) in previously treated pancreatic cancer. The median OS and 1 year OS rate favored the combination therapy arm [34]. Another study by Fong and coworkers evaluated ipilimumab in combination with subcutaneous injection of GM-CSF for castrate-resistant prostate cancer. They found that this combination can induce responses against important tumor antigens such as NY-ESO-1 and thus can induce stronger antitumor responses [35]. An additional study has evaluated ipilimumab and a poxviral vaccine targeting prostate-specific antigen in castrate-resistant prostate cancer [36]. Consistent with the studies in melanoma, combining ipilimumab with either cancer vaccines or GM-CSF did not exacerbate the previously known IRAEs (on the contrary, the ipilimumab/sargamostim study revealed lower toxicity in the combination arm vs the ipilimumab monotherapy arm).

Interpretation of the results of this analysis has to take into account the data of KEYNOTE-006 study which showed clear superiority and better

tolerability of pembrolizumab monotherapy versus ipilimumab monotherapy [37]. Thus, integration of nivolumab/ipilimumab combination versus other options into the treatment armamentarium of advanced melanoma has to be evaluated cautiously in terms of cost effectiveness.

Pembrolizumab/low-dose ipilimumab combination has been evaluated in a Phase I study (KEYNOTE-029) by Atkins and coworkers that has been presented in American Society of Clinical Oncology meeting 2015. The safety profile of this combination was acceptable and this suggests that low-dose ipilimumab may be better tolerated than full dose ipilimumab if used in combination with other immune checkpoint inhibitors [38]. This study was not included in this review because the results were reported as preliminary results in an abstract form with unclear efficacy and toxicity data.

A number of ongoing studies are currently evaluating different combinatorial approaches and they are summarized in [Table 5](#).

Among the potential weaknesses of this analysis is the heterogeneity of included studies; however, different groups of studies have been analyzed independently and random effects model has been employed to avoid misleading results.

Conclusion & future perspective

This analysis has demonstrated that nivolumab/ipilimumab combination is associated with higher ORR and PFS. However, this comes at the expense of a higher risk of high-grade

Table 5. Ongoing studies evaluating combinatorial immunotherapy approaches for advanced melanoma.

Study	Title	Status	Primary completion date
NCT02608437	A study investigating SGI-110 in combination with ipilimumab in unresectable or metastatic melanoma patients (NIBIT-M4)	Ongoing	October 2016
NCT02009397	Phase I/II open-label study of ipilimumab and GM-CSF administered to unresectable stage IIIC and stage IV melanoma patients	Ongoing	December 2017
NCT02186249	Expanded access program with nivolumab (BMS-936558) in combination with ipilimumab (Yervoy®) in subjects with unresectable or metastatic melanoma (CheckMate 218)	Ongoing	N/R
NCT02320058	A multicenter Phase II open-label study to evaluate safety and efficacy in subjects with melanoma metastatic to the brain treated with nivolumab in combination with ipilimumab followed by nivolumab monotherapy (CheckMate 204)	Ongoing	June 2018
NCT02174172	A study to assess the safety and tolerability of MPDL3280A in combination with other immune-modulating therapies in patients with locally advanced or metastatic solid tumors	Ongoing	February 2018

GM-CSF: Granulocyte macrophage colony stimulating factor; N/R: Not reported.

toxicities such as high-grade elevation in ALT, AST and high-grade skin rash compared with ipilimumab monotherapy. Further research will focus on comparing the combination strategy with newer immunotherapies (particularly pembrolizumab and atezolizumab) for advanced melanoma. Moreover, additional research will focus on potential predictive and prognostic markers that may help direct our best choice of systemic therapy in this setting.

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Papers of special note have been highlighted as:
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