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Combined ipilimumab and nivolumab first-line and after BRAF targeted therapy in advanced melanoma

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Abstract

Combination ipilimumab and nivolumab is a highly active systemic therapy for metastatic melanoma but can cause significant toxicity. We explore the safety and efficacy of this treatment in routine clinical practice, particularly in the setting of BRAF targeted therapy.

Consecutive patients with unresectable stage IIIC/IV melanoma commenced on ipilimumab and nivolumab across 10 tertiary melanoma institutions in Australia were identified retrospectively. Data collected included demographics, response and survival outcomes.

152 patients were included for analysis, 39% were treatment-naïve and 22% failed first-line BRAF/MEK inhibitors. Treatment-related adverse events occurred in 67% of patients, grade 3-5 in 38%. The overall objective response rate was 41%, 57% in treatment naïve and 21% in BRAF/MEK failure patients. Median progression-free survival was 4.0 months (95%CI, 3.0-6.0) in the whole cohort, 11.0 months (95%CI, 6.0-NR) in treatment-naïve, and 2.0 months (95%CI, 1.4-4.6) in BRAF/MEK failure patients.

Combination ipilimumab and nivolumab can be used safely and effectively in a real-world population. While first-line efficacy appears comparable to trial populations, BRAF-mutant patients failing prior BRAF/MEK inhibitors show less response.

Significance

Combination ipilimumab and nivolumab is arguably the most effective systemic therapy in metastatic melanoma, it is however, also associated with significant toxicity. This study demonstrates that combined immunotherapy can be used safely and effectively in a real-world population, including in patients that are pre-treated and those with adverse disease characteristics. While first-line efficacy appears comparable to that seen in trial populations, BRAF-mutant patients who have failed prior BRAF/MEK inhibitors have low response rates and short progression-free survival, supporting first-line use of combination immunotherapy in this setting.

Introduction

The therapeutic landscape in melanoma is evolving rapidly. Only seven years ago systemic therapy was ineffective for almost all patients with metastatic disease. Chemotherapy led to infrequent and short responses, while high-dose interleukin-2 and adoptive cell therapies were only suitable for a select minority (Thompson, Scolyer, & Kefford, 2005). Major breakthroughs in both targeted therapy and immunotherapy have since revolutionised melanoma treatment, improving survival for not only those with advanced disease, but also those at high risk of recurrence(Ascierto et al., 2016; Eggermont et al., 2018; Larkin et al., 2015; Long, Flaherty, et al., 2017; Long, Hauschild, et al., 2017; Schachter et al., 2017; Weber et al., 2017; Wolchok et al., 2017).

Ipilimumab, an anti-CTLA-4 antibody, was the first systemic therapy to improve overall survival in metastatic melanoma, providing durable disease control in a small subset of patients(Ascierto et al., 2017; Hodi et al., 2010). The anti-PD-1 antibodies pembrolizumab and nivolumab were subsequently shown to have higher response rates, prolonged survival and less toxicity than ipilimumab(Larkin et al., 2015; Schachter et al., 2017; Wolchok et al., 2017), replacing this as a standard of care. More recently, combination immunotherapy with ipilimumab and nivolumab has been shown to have a higher response rate and improved 3-year overall survival than nivolumab, but at the cost of significant toxicity(Larkin et al., 2015; Postow et al., 2015; Wolchok et al., 2017). Combination immunotherapy also has a higher 3-year overall survival than BRAF/MEK inhibitors, and although the studies were conducted in different time periods and the drugs have not been compared head to head, combination immunotherapy may be the most active systemic therapy for melanoma(Schadendorf et al., 2017).

At present, there are no robust biomarkers that define who requires combination immunotherapy over PD-1 monotherapy. Subgroup analyses from the CheckMate-067 trial suggest patients with BRAF-mutant melanoma, a higher Eastern Cooperative Oncology Group (ECOG) performance status,

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elevated lactate dehydrogenase (LDH) level, PD-L1 negative tumours, or mucosal melanoma appear have greater benefit from combination therapy over PD-1 monotherapy (noting that the trial was powered for a comparison between nivolumab containing arms and ipilimumab only) (Larkin et al., 2015; Postow et al., 2015; Wolchok et al., 2017), and one recent clinical trial has demonstrated a higher response rate and superior progression-free survival in patients with asymptomatic brain metastases (Long et al., 2018). There are no randomized data examining the best sequence of combination immunotherapy and targeted therapy, no data reporting the activity of combination immunotherapy after failure of BRAF/MEK inhibitors, and limited data exploring the use of combination therapy in a real-world population of patients who may have failed BRAF/MEK inhibitors or PD-1 monotherapy, have brain metastases, or have poor performance status (Bowyer et al., 2016; Hugo et al., 2015; Kakavand et al., 2015; Long et al., 2018; Tawbi et al., 2018; Wolchok et al., 2013).

Combination immunotherapy is now approved in many countries. While it has shown impressive efficacy relative to other available therapies at present, toxicity is a major barrier. How best to integrate this into clinical practice, in real-world patients, and in BRAF-mutant melanoma, is not clear. We sought to explore the safety and efficacy of combination ipilimumab and nivolumab in such a population.

Methods

Patients and Treatment

Consecutive patients with unresectable stage IIIC/IV melanoma commenced on ipilimumab and nivolumab via an early access scheme across 10 tertiary melanoma institutions (Princess Alexandra Hospital, Greenslopes Private Hospital, Melanoma Institute Australia, Canberra Hospital, Epworth Hospital, The Alfred, St John of God, Sir Charles Gardner Hospital and Westmead Hospital) between March 2016 and June 2017 were identified retrospectively. Ipilimumab was dosed at 3mg/kg 3-weekly and nivolumab 1mg/kg during induction for 4 doses, then nivolumab maintenance was 3mg/kg 2-weekly. Patients were included if they received at least one cycle of combination therapy. Patients with clinical disease progression within 12 weeks were included, however patients with inadequate follow-up (less than 12 weeks since therapy commencement without clinical evidence of progression) were excluded. Patients with toxicities from prior treatments were not excluded. Toxicities were managed at each treating centre discretion per local policy. In general patients who developed grade 3 or higher toxicity on treatment ceased therapy however upon resolution of toxicity some patients resumed maintenance nivolumab. The study was approved by individual institution ethics committees.

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Clinical Data

Data collected included demographics, prior systemic therapy (adjuvant or metastatic), disease factors at treatment commencement (BRAF status, LDH level, ECOG performance status, American Joint Committee on Cancer [AJCC] v8 M-stage, toxicity (type and CTCAE grade [G]) and subsequent systemic therapy. Response to treatment was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al., 2009). Best response to therapy, date of progression and date of death were collected.

Statistical Analysis

Survival analyses were performed via the Kaplan Meier method and using the log-rank test. Patients with clinical disease progression within 12 weeks had best response classified as progressive disease, and the date of progression was determined by the clinician. Additional subgroup analyses of particular interest included patients who a) were treatment-naïve, b) had received first-line BRAF/MEK inhibitors prior to second-line combination immunotherapy, c) had received first-line PD1 inhibitors as monotherapy prior to second-line combination immunotherapy. One patient had received adjuvant therapy with dabrafenib and trametinib, ceased for toxicity after 3 months, and the patient later progressed, after 4 months off treatment. For analysis purposes this patient was considered treatment-naïve. A Cox proportional-hazards model was used to interrogate the treatment effect of first line therapy with Ipilimumab and Nivolumab, age, mutation status, performance status, and LDH level. Data was analysed using R version 3.4.

Results

Patients and Treatment

One hundred and seventy-three consecutive patients with unresectable stage IIIC/IV melanoma treated with combination ipilimumab and nivolumab were identified. Twenty-one patients were excluded from analysis due to inadequate follow up, leaving a total of 152 patients included for analysis. At time of analysis, 51 (34%) patients had died, and median follow-up was 6.1 months (95% CI 5.8-6.7).

Patients had a median age of 60 years (range 20-81), 68% were male, and 38% had a V600 BRAF mutation (Table 1). The cohort included 5 patients with acral melanoma, 7 patients with mucosal melanoma and 7 patients with uveal melanoma. Prior adjuvant therapy was received by 13 patients (9%), including PD-1 monotherapy ($n=4$), dabrafenib and trametinib ($n=3$), vaccine therapy ($n=3$), ipilimumab ($n=2$) and interferon ($n=1$). Ipilimumab and nivolumab was first-line therapy for advanced melanoma in 60 (39%) patients, 37% had received one prior line of therapy and 24% had received two or more previous lines of therapy. Previous treatments included BRAF and MEK inhibitors ($n=51$,

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34%), PD-1 antibody-based therapy ($n=57$, 38%), ipilimumab ($n=10$, 7%), combination immunotherapy with ipilimumab and a PD1 antibody as part of a clinical trial ($n=4$, 3%), and chemotherapy ($n=3$, 2%). Median time from last dose of prior treatment to starting combination immunotherapy was 21 days (range 1 to 440 days).

At commencement of combination therapy, the majority of patients had a high AJCC M stage (63% M1c, 26% M1d), while 39% were ECOG ≥ 1 , and 55% had an elevated LDH level. In the subgroups of interest; a) 60 treatment-naïve patients had similar adverse prognostic factors (65% AJCC M1c, 25% M1d, 32% ECOG ≥ 1 , and 55% elevated LDH), as did b) 33 patients who received first-line BRAF/MEK inhibitors only (an additional 18 patients were treated with BRAF/MEK inhibitors but received additional therapies on progression) prior to combination therapy second-line (52% M1c, 48% M1d, 61% ECOG ≥ 1 , and 55% elevated LDH), and d) of the 57 patients previously treated with PD1 inhibitors, 22 patients received first-line PD1 monotherapy only (others receiving additional prior treatment with therapies such as ipilimumab or other investigational agents) prior to combination immunotherapy second-line (68% M1c, 9% M1d, 55% ECOG ≥ 1 , and 68% elevated LDH). For the latter cohort, 3 patients included had received adjuvant treatment: 2 developing distant disease on treatment and 1 within 3 months of cessation of adjuvant PD-1. Within the treatment-naïve cohort, the five BRAF mutant patients had similar baseline staging to the groups above however, better baseline performance status (60% M1c, 20% M1d, 80% ECOG 0, and 20% elevated LDH). The median duration of PD-1 therapy was 2.5 months, 2 patients had ceased for toxicity and remained off treatment for 10 and 15 months respectively before disease progression and commencing combination therapy. 1 patient stopped for unspecified reasons after one cycle of PD-1 therapy and immediately commenced combination therapy, and the rest stopped for progressive disease. The median interval from last cycle of PD-1 treatment to commencement of combination therapy was 9 days.

Following cessation of combination ipilimumab and nivolumab or nivolumab maintenance, 13% of patients went on to receive further systemic treatment. Median time from last dose of therapy to subsequent therapy was 44 days (range 17-113 days). Subsequent treatments included clinical trials ($n=7$), chemotherapy ($n=5$), PD-1 antibody-based therapy (including combinations of PD1 with chemotherapy or targeted therapy) ($n=3$), targeted therapy ($n=3$), ipilimumab ($n=1$), and one patient was retreated with further ipilimumab and nivolumab after progression on maintenance nivolumab.

Safety

Treatment-related adverse events occurred in 102 (67%) patients, and in 38% they were grade 3-5. Toxicity rates were higher in treatment naïve compared to pre-treated patients (78% vs 60%, $p=0.022$), and a higher prevalence of grade 3/4 toxicity was also noted (47% vs 26%). Colitis was seen in 31

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(20%) of patients, and was grade 3/4 in 13%. Hepatitis occurred in 38 (25%) patients, and was grade 3/4 in 15%. Other significant toxicities included pneumonitis (22%, with 5% G3/4), significant rash (3% G3), nephritis (1%), and fevers (<1%). Neurotoxicity was seen in two (1%) patients, grade 1/2 and resolved with oral steroids. One patient died from immune myocarditis. Treatment was discontinued for toxicity in 34 (22%) patients, mainly during the induction phase (n=25).

Efficacy

The objective response rate (ORR) in the whole cohort was 41% (Table 2). In the treatment naïve group the ORR was 57% (17% complete) and the disease control rate (DCR) 65%. In the five treatment-naïve BRAF-mutant patients the ORR was 60%. The ORR in the 33 patients that had received first-line BRAF/MEK inhibitors and second-line combination therapy was 21%. From the group of 57 patients treated with prior PD1 inhibitors, the 22 patients that received first-line PD1 monotherapy and second-line combination, the ORR was 41%.

The median progression-free survival (PFS) for all patients was 4.0 months (95% CI, 3.0 to 6.0) (Table 2, Figure 1a). Treatment naïve patients had a median PFS of 11.0 months (95% CI, 6.0 - NR) (Figure 2a). BRAF-mutant patients who had failed first-line BRAF/MEK inhibitors had a median PFS of 2.0 months (95% CI, 1.4 - 4.6), with less than 20% progression-free beyond six months. Of the five BRAF-mutant patients who received combination immunotherapy first-line, the median PFS was 14.2 months (95% CI, NR – NR), and only one patient had progressed at last follow up, at 6.1 months. Ongoing disease control was seen in the other four patients with a median of 9.7 months follow up. Patients who failed first-line PD1 monotherapy who received combination second-line had a median PFS of 4.6 months (95% CI, 2.7 – NR).

The median overall survival (OS) for all patients was 13.8 months (95% CI, 8.0 – NR) (Figure 1b). Treatment-naïve patients had a median OS of 14.2 months (95% CI, 8.0 - NR) (Figure 2b). Patients who had failed first-line BRAF/MEK inhibitors had a median OS of only 3.6 months (95% CI, 1.6 - NR) compared to the five BRAF mutant patients treated with first-line ipilimumab and nivolumab with a median OS of 14.2 months (95% CI, NR – NR) (Figure 2b). Patients failing first-line PD1 inhibitors as their only prior line of therapy had a median OS of 9.6 months (95% CI, 6.7 - NR).

Discussion

While combination ipilimumab and nivolumab is arguably the most effective systemic therapy in metastatic melanoma, it is also the most toxic. Safety and efficacy have been demonstrated in only a few clinical trials, largely in well patients who had not received prior systemic therapy (Larkin et al., 2015; Postow et al., 2015). Incorporating this therapy into routine clinical practice is therefore not

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straightforward, and real-world data are needed to assist best management. This study describes a real-world experience of the use of combination ipilimumab and nivolumab in advanced melanoma and demonstrates that efficacy and toxicity in treatment-naïve patients is similar to that seen in trials, but the efficacy after failure of targeted therapy is poor.

This retrospective study has several limitations. The study only included patients whom clinicians deemed necessary for combination treatment, thus most patients had adverse disease characteristics (AJCC stage M1c/d, elevated LDH, ECOG ≥ 1). Most patients received prior systemic treatment for advanced disease, largely BRAF/MEK inhibitors (34%) or PD-1 antibodies (38%). While this may not necessarily reflect current clinical practice, a sizeable subgroup of patients were treatment-naïve (with more adverse prognostic factors than trial populations), and prospective clinical trial data in the treatment refractory setting is lacking. Furthermore, patients were treated in a clinical environment in Australia where dabrafenib and trametinib was only funded when given first-line in BRAF-mutant melanoma patients. That is, if BRAF-mutant patients accessed immunotherapy first-line, they could not guarantee access to targeted therapy in the event of immunotherapy failure. As such, almost all BRAF-mutant patients (88%) had received BRAF/MEK inhibitors prior to ipilimumab and nivolumab and comparative analysis with the small population of BRAF mutant patients treated with first line ipilimumab and nivolumab is limited by a very small sample size ($n=5$). Further analysis with longer follow up of the BRAF mutant cohort from the Checkmate 067 clinical trial evaluating the efficacy of nivolumab treatment arm compared to ipilimumab and nivolumab arm may help to discriminate these findings. There is likely significant bias in the activity of combination therapy in the PD-1 monotherapy only pre-treated cohort as a result of the small sample size of 22 patients, the inclusion of 3 patients progressing during and shortly after adjuvant PD-1 inhibitors and a short duration of PD-1 therapy and rapid sequence to combination therapy suggestive of a possible pre-emptive switch to combination therapy before overt disease progression. Finally, follow-up was short (median 6.1 months) and thus longer-term survival outcomes remain unknown.

The toxicity seen with combination treatment in this cohort was similar to that noted in clinical trials, with a comparable rate of grade 3/4 events. Despite the fact that the median interval from last prior therapy to combination therapy in pre-treated patients was three weeks, there did not appear to be a higher rate of toxicity in this cohort, suggesting that sequencing from BRAF/MEK inhibitors or anti-PD-1 monotherapy to combination may be considered with a narrow washout window, where necessary.

Consistent with the adverse prognostic features and pre-treatment received, in the whole population, the response rate to combination immunotherapy was lower than clinical trial populations (41% vs

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approximately 60%), however clinically meaningful. Treatment-naïve patients demonstrated a RECIST response rate of 57%, near identical to that seen in the CheckMate-067 trial, despite having more aggressive disease characteristics. This patient cohort had a higher rate of M1c/d disease (90% vs 58%), poorer performance status (ECOG 2/3 7% vs 0%) and higher rates of elevated LDH (55% vs 36%) (Larkin et al., 2015; Wolchok et al., 2017). Progression-free survival was similarly comparable to trial populations, with a median of 11.0 months in this cohort compared to 11.5 months seen in the Phase 3 trial setting (Larkin et al., 2015).

In contrast, the use of ipilimumab and nivolumab in the second- or later line settings demonstrated reduced efficacy. BRAF-mutant patients refractory to first-line BRAF/MEK inhibitors had a high proportion of brain metastases (47%), a common site of targeted therapy failure which often contributes to death. This cohort had higher rates of poor prognostic features (M1c/d disease 100%, elevated LDH 56%, ECOG 2/3 9%). Here, a response rate of only 21% was seen, with only a small proportion of patients (<20%) progression-free beyond six months. In the small subset of BRAF-mutant patients treated with first-line combination immunotherapy the response rate was 60%, similar to the CheckMate-067 clinical trial data, with only one patient having progressed at a median of 5.8 months follow-up. Despite the lack of randomized trial data, translational evidence suggests that an immuno-resistant phenotype emerges on progression after targeted therapy (Hugo et al., 2015; Kakavand et al., 2015). Subgroup analyses from the CheckMate-067 clinical trial and data from two clinical trials of patients with asymptomatic brain metastases, in addition to this study, provide evocative evidence that for most BRAF-mutant patients, combination ipilimumab and nivolumab is an appropriate treatment choice, particularly in the first-line setting, prior to BRAF/MEK inhibitors (Larkin et al., 2015; Long et al., 2018; Postow et al., 2015; Tawbi et al., 2018; Wolchok et al., 2017). Upcoming analysis of the Checkmate-067 clinical trial will be of significant interest and may distinguish the best first line treatment option for BRAF mutant disease and the role of ipilimumab and nivolumab combination therapy.

Patients with BRAF wild-type melanoma failing first line PD-1 monotherapy currently have limited options. Three retrospective studies and early data from one clinical trial suggest some benefit with either ipilimumab alone or combination immunotherapy, with response rates ranging from 10 - 47% (Bowyer et al., 2016; Olson et al., 2018; Tetu et al., 2018; Zimmer et al., 2017). While it is not yet clear which strategy is better, the use of second-line combination ipilimumab and nivolumab in selected patients appears safe, but requires further research.

In conclusion, this study demonstrates that combined immunotherapy can be used safely and effectively in a real-world population, including in patients that are pre-treated and those with adverse

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disease characteristics. While first-line efficacy appears comparable to that seen in trial populations, BRAF-mutant patients who have failed prior BRAF/MEK inhibitors have low response rates and short progression-free survival, supporting first-line use of combination immunotherapy in this setting.

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Conflict of interest statement

RM has reported travel and expenses support by Bristol-Myers Squibb. HD and LW have reported travel, and expenses support by MSD. JSO has reported travel and expenses support by Pfizer. MR has reported travel and expenses support by Merck. TM has reported honoraria and consultancy for AstraZeneca/MedImmune, research funding by Incyte, BeiGene, AstraZeneca/MedImmune, Regeneron, Bayer, Roche/Genentech, Bristol Myers Squibbs, Merck Serono Ltd, and travel and expenses support by Roche/Genentech. AG has reported consultancy for Roche, Regeneron, Eisai, Sun Pharma, Bristol Myers Squibbs and travel and expenses support by Sun Pharma, Bristol Myers Squibbs. SA has reported honoraria and consultancy from Bristol Myers Squibbs. AMH has reported consultancy for Novartis. GVL has reported consultancy for Bristol-Myers Squibb, Roche/Genentech, Amgen, Merck, Novartis, Array BioPharma, Pierre Fabre, Incyte, and honoraria from Bristol-Myers Squibb, Merck, Roche, Novartis, and Incyte. MSC has reported consultancy for Bristol-Myers Squibb, MSD, Amgen, Novartis, Pierre Fabre and honoraria from Bristol-Myers Squibb, MSD, Novartis. MM has reported consultancy for AstraZeneca, MSD, Roche, and Bristol Myers Squibbs and travel and expenses support from Roche, MSD, and Bristol Myers Squibbs. VA has reported honoraria from Novartis, Bristol Myers Squibbs, consultancy for Novartis, Pierre Fabre, Bristol Myers Squibbs, Merck Serono Ltd, MSD and travel and expenses support from Bristol Myers Squibbs. AMM has reported consultancy for MSD, Novartis, Pierre Fabre, Bristol-Myers Squibb, Roche; and travel, and expenses support from Bristol-Myers Squibb. The remaining authors have declared no conflicts of interest.

All authors made a significant contribution to this work in either: trial design, data collection and analysis, or manuscript preparation and editing.

Tables:

Table 1: Patient characteristics

Table 2: Efficacy of combination nivolumab and ipilimumab

Figures:

Figure 1(a): Progression free survival of all patients treated with combination nivolumab and ipilimumab

Figure 1(b): Overall survival of all patients treated with combination nivolumab and ipilimumab

Figure 2(a): Progression free survival of patients treated with combination nivolumab and ipilimumab in the treatment naïve setting (blue) or following BRAF/MEK inhibitors (red)

Figure 2(b): Overall survival of patients treated with combination nivolumab and ipilimumab in the treatment naïve setting (blue) or following BRAF/MEK inhibitors (red)

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Tables and Figures

Table 1: Patient Characteristics

	All patients	Treatment naïve			Patients refractory to first-line BRAF/MEK inhibitors	Patients Treated with prior PD-1 inhibitors
		All patients	BRAF-wildtype	BRAF-mutant		
No. of patients (%)	152	60 (39)	55 (36)	5 (3)	33 (22)	57
Med age (range) -yrs	60 (20-81)	60 (33-78)	60 (35-78)	58 (33-69)	56 (20-81)	60 (24-79)
Male sex no. (%)	104 (68)	41 (68)	36 (65)	5 (100)	23 (70)	40 (66)
BRAF mutation no. (%)	58 (38)	5 (8)	0	5 (100)	33 (100)	20 (35%)
Stage no. (%)						
3c unresectable	2 (1)	0	0	0	0	2 (3)
M1a	6 (4)	4 (7)	3 (5)	1 (20)	0	2 (3)
M1b	9 (6)	2 (3)	2 (4)	0	0	7 (12)
M1c	95 (63)	39 (65)	36 (65)	3 (60)	17 (52)	37 (65)
M1d	40 (26)	15 (25)	14 (25)	1 (20)	16 (48)	9 (16)
Elevated LDH no. (%)	84 (55)	33(55)	32 (58)	4 (80)	18 (55)	32 (56)
ECOG no (%)						
0	92 (61)	41 (68)	36 (65)	5 (100)	13 (39)	36 (63)
1	49 (32)	15 (25)	15 (27)	0	17 (52)	17 (30)
2+	11 (7)	4(7)	4 (7)	0	3 (9)	4 (7)

Table 2: Efficacy of combination ipilimumab and nivolumab

	All patients	Treatment naive			Refractory to first-line BRAF therapy	Prior PD- 1 inhibitor therapy
		All patients	BRAF- wildtype	BRAF- mutant		
No of patients	152	60	55	5	33	57
Best Response no. (%)						
Complete response	14 (9%)	10 (17%)	9 (16%)	1 (20%)	1 (3%)	3 (5%)
Partial response	48 (32%)	24 (40%)	22 (40%)	2 (40%)	6 (18%)	16 (28%)
Stable disease	14 (9%)	5 (8%)	4 (7%)	1 (20%)	1 (3%)	8 (14%)
Progressive disease	75 (49%)	20 (33%)	19 (35%)	1 (20%)	25 (76%)	30 (53%)
Unknown	1 (1%)	1 (2%)	1 (2%)	0	0	0
Objective response rate	41%	57%	56%	60%	21%	33%
Disease control rate	50%	65%	63%	62%	24%	47%
PFS months, median (95% CI)	4.0 (3.0 - 6.0)	11.0 (6.0 - NR)			2.0 (1.4 – 3.6)	4.0 (2.8-NR)
6-month PFS (95% CI)	40% (32 – 49)	56% (44 – 71)			17% (7 – 41)	
OS months, median	13.8 (8.0 - NR)	14.2 (8.0 - NR)			3.6 (1.6 - NR)	9.6 (7.8–NR)

(95% CI)						
12-month OS (95% CI)	56% (46 - 69)	65% (49 - 86)			41% (26 – 65)

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