Short Communication

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Melanoma Management

Improved overall survival in dual compared to single immune checkpoint inhibitors in *BRAF* V600-negative advanced melanoma

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Aim: To evaluate the efficacy of dual versus single immune checkpoint inhibitors (ICI) in *BRAF* wild-type advanced melanoma patients. **Materials & methods:** A retrospective study of all advanced *BRAF* wild-type melanoma patients on palliative-intent ICI between 2015 and 2020 (n = 67). **Results:** Dual ICI had better overall survival (OS) when compared with single ICI in *BRAF* wild-type patients (hazard ratio: 0.204; 95% CI: 0.064–0.649; p = 0.007), but lost its statistical significance (median OSI not reached vs 20.9 months; p = 0.213; adjusted hazard ratio: 0.475; 95% CI: 0.164–1.380; p = 0.171) when only including patients treated after 2018 when dual ICI was funded in our province. Dual ICI were significantly associated with more frequent (p = 0.005) and severe (p = 0.026) immune-related adverse events, and required more immune-related adverse events-indicated systemic corticosteroid use (p < 0.001) compared with single ICI. **Conclusion:** While limited by small sample size and retrospective nature, dual ICI may have non statistically significant trend toward better OS efficacy when compared with single ICI in *BRAF* V600 wild-type advanced melanoma patients.

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Management of advanced melanoma has greatly improved since the introduction of immune checkpoint inhibitors (ICI) [1–3] and, in the event of *BRAF* V600E/K mutations, targeted therapy [4–6]. For *BRAF* V600 wild-type patients, the choices of first-line systemic treatment include either a PD-1 inhibitor monotherapy or a combination of PD-1 and CTLA-4 inhibitors. However, little is known if first-line combined ICIs offer better survival outcomes than first-line PD-1 inhibitors followed by CTLA-4 inhibitors, if progressed. Both treatment options are regarded as potential first-line therapies in various established guidelines [7–9].

Checkmate-067 is a landmark trial which randomized previously untreated advanced melanoma patients to combined PD-1 and CTLA-4 inhibitors versus PD-1 inhibitor (nivolumab) monotherapy versus CTLA-4 inhibitor (ipilimumab) monotherapy [1]. In its subgroup analysis, dual ICI was demonstrated to have superior overall survival (OS) benefit compared with ipilimumab monotherapy regardless of *BRAF* mutation status [1]. However, the Kaplan–Meier OS benefits were less apparent when evaluating dual ICI against nivolumab monotherapy in *BRAF* wild-type patients (48 vs 43%, no p-value given not formally analyzed as per protocol). It is important to note that this was based on a subset analysis, and therefore not adequately powered to detect significant results. With increased toxicities in the dual ICI group compared with nivolumab group, it would be prudent to further examine the utility of dual ICI in the *BRAF* wild-type population.

To our knowledge, there are no ongoing randomized clinical trials which evaluate the optimal first-line systemic treatment options in *BRAF* wild-type patients. Evidence is scarce from real-world population studies as well. This retrospective, real-world study aims to provide much needed insights into this important topic.

Materials & methods

This study took place in Cancer Centre of Southeastern Ontario. Research ethics board approval was obtained at our local institution prior to study commencement. We included all patients with histologically-confirmed advanced unresectable or metastatic melanoma and *BRAF* V600 wild-type who received at least one cycle of first-

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line, palliative-intent ICI between January 2015 and December 2020. Six patients with *BRAF* non-V600 mutant molecular status were excluded from this study.

In our center, *BRAF* mutation status was evaluated by Amplicon next generation sequencing. The limit of detection in our next generation sequencing was 5% in single nucleotide changes, which accounted for most of *BRAF* V600 mutations. Therefore, absence of *BRAF* V600 mutation was defined by ruling out 5% of sequenced molecules with *BRAF* V600 mutation and was validated at 400-times.

Baseline patient, tumor and treatment characteristics were collected, including age, gender, eastern cooperative oncology group (ECOG) performance status, baseline corticosteroid use (i.e., prednisone-equivalent ≥10 mg within 30 days of ICI initiation), melanoma stage, number of baseline metastasis, presence of baseline brain metastasis prior to ICI initiation, melanoma histology (cutaneous vs non cutaneous which included unknown primary, mucosal and uveal), baseline lactate dehydrogenase (LDH) level, baseline neutrophil to lymphocyte ratio (NLR ≥5), baseline platelet to lymphocyte ratio (PLR ≥200), adjuvant ICI (PD-1 inhibitor monotherapy) use and subsequent ICI (CTLA-4 inhibitor monotherapy) use.

We categorized patients into two groups, depending on their systemic therapy regimen. The dual ICI group received at least one cycle of combined nivolumab and ipilimumab with or without subsequent maintenance nivolumab. The single ICI group received at least one cycle of nivolumab or pembrolizumab (PD-1 inhibitor) monotherapy. In our local institution, both dual and single ICI are available for first-line setting and treatment selection was based on discussions between physicians and patients. However, dual ICI was only funded in our province after 2018. To account for potential time bias between the two ICI groups, we conducted a sensitivity multivariable analysis by only including patients who received any ICI treatment after 2018.

The primary study outcome was OS in the total population. OS was defined as the time from ICI initiation to death from any causes or last follow-up. Secondary outcomes included objective response rate (ORR), progression free survival (PFS), patterns of subsequent therapy use and immune-related adverse events (irAEs) development/characteristics and its associated management. ORR was defined as per RECIST version 1.1 [10]. PFS was defined as the time from ICI initiation to disease progression by imaging or clinical evaluations in the absence of imaging, or death from any causes. irAEs severity was graded as per Common Terminology Criteria for Adverse Events version 5.0 [11].

Statistical analysis

All statistical analyses were conducted in IBM SPSS Statistics version 26. We conducted descriptive and univariate analyses via Fisher's Exact test or Chi-Square test to provide an overview of the baseline population characteristics and its relationships with treatment regimen. Kaplan–Meier curves were generated to examine OS and PFS. irAEs were presented as percentages. To assess for potential confounders, we used multivariable Cox proportional hazards regression model to calculate Hazard ratio (HR) and its 95% CI for OS. We set two-sided $p < 0.05$ to define statistically significant outcomes. No adjustment was made for multiple comparisons, so inferences from this data should be carefully considered.

Results

Our study included 67 patients in total. More than half were aged 65 and above (67%), male sex (66%) and had ECOG 0–1 (79%), no baseline corticosteroid use (84%), LDH ≤upper limit of normal (61%), NLR <5 (81%) and PLR <200 (75%). Regarding the melanoma characteristics, majority are cutaneous (76%), metastatic (91%), had two or less metastatic sites (72%) and had no baseline brain metastasis (85%). Univariate analysis suggested patients of younger age ($p = 0.011$), received baseline corticosteroid use ($p = 0.045$), had baseline brain metastasis ($p = 0.023$) and with non cutaneous melanoma ($p = 0.019$) were more likely to receive dual ICI than single ICI. There were no other imbalances between the two groups regarding gender ($p = 0.599$), ECOG ($p = 0.414$), melanoma stage ($p = 1.000$), baseline number of metastatic sites ($p = 0.527$), baseline liver metastasis ($p = 1.000$), baseline LDH ($p = 0.478$), baseline NLR ($p = 0.121$) or baseline PLR ($p = 0.896$). There were two patients who had adjuvant ICI prior to their first cycle of palliative-intent ICI, and both were in the dual ICI group. No p-value calculated from this perspective due to small sample size (Table 1).

The median follow-up of the overall study population, dual ICI group alone and single ICI group alone were 15.9, 22.4 and 15.1 months, respectively. Dual ICI demonstrated a non statistically significant OS (not reached vs 15.7 months; $p = 0.079$) and PFS (not reached vs 7.8 months; $p = 0.246$) improvement compared with single ICI in the study population (Figure 1A & B). However, dual ICI was not significantly associated with improved

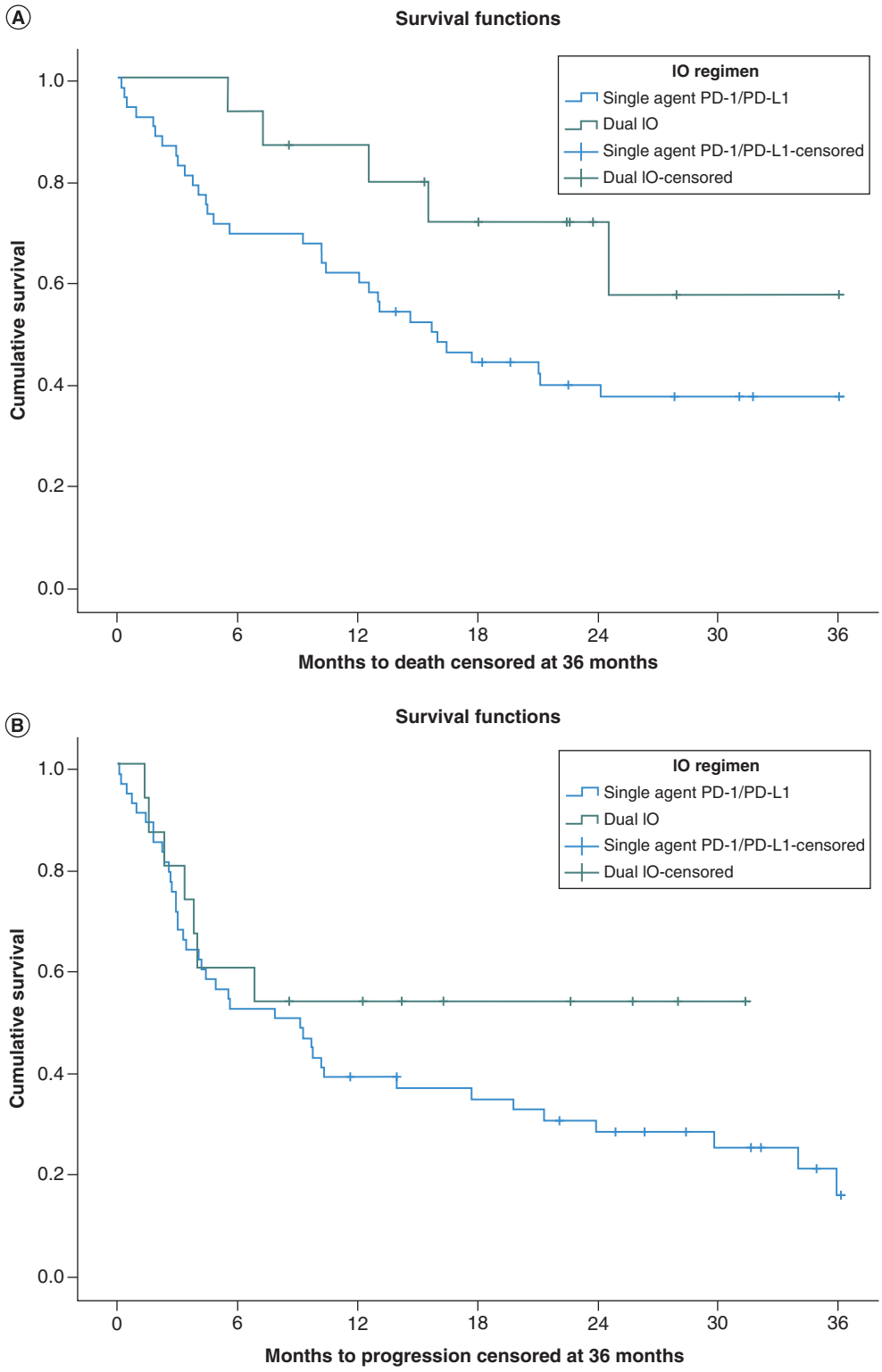

Figure 1. Survival outcomes as per treatment regimen. (A) Median overall survival as per treatment regimen (n = 67; dual ICI vs single ICI: not reached vs 15.7 months, p = 0.079). **(B)** Progression-free survival as per treatment regimen (n = 67; (dual ICI vs single ICI: not reached vs 7.8 months; p = 0.246). **(C)** ORR as per treatment regimen (n = 67; dual ICI vs single ICI: 40 vs 42%; p = 0.873). **(D)** Sensitivity analysis with excluding patients who received first-line palliative-intent ICI regimen prior to 2018 (n = 39; median overall survival not reached vs 20.9 months; p = 0.213). CR: Complete response; ICI: Immune checkpoint inhibitor; PD: Disease progression; PR: Partial response; ORR: Objective response rate.

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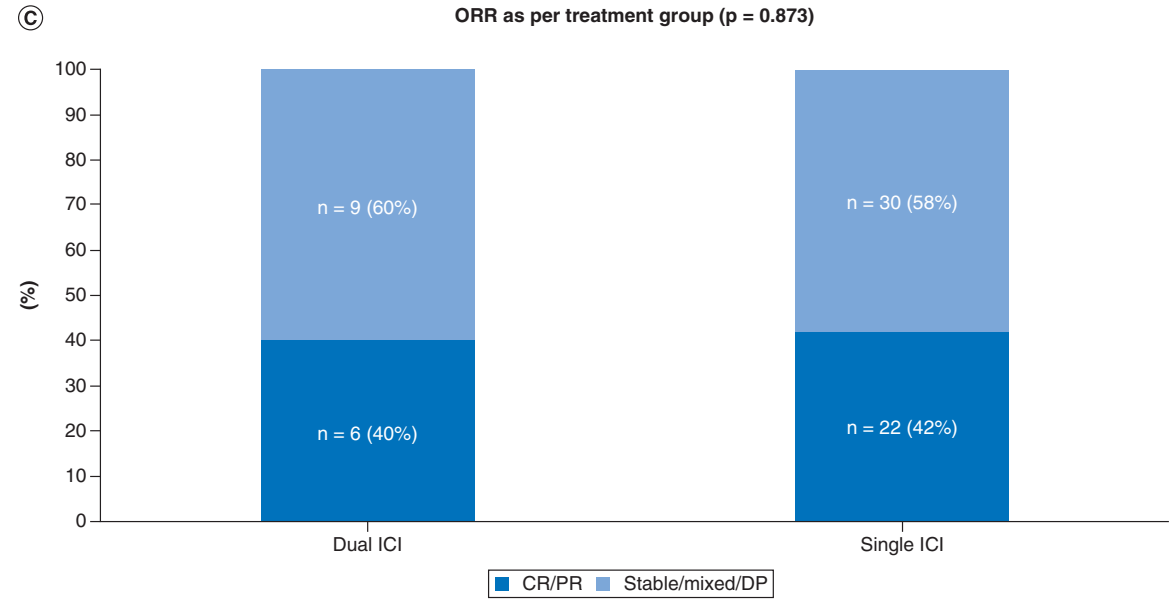

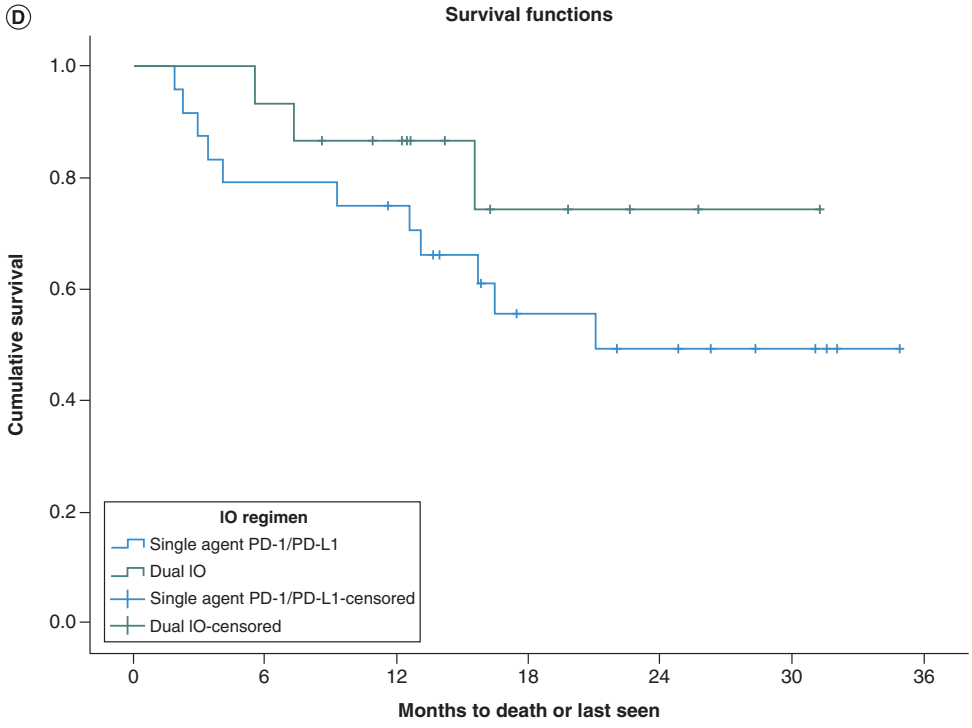

Figure 1. Survival outcomes as per treatment regimen (cont.). (A) Median overall survival as per treatment regimen (n = 67; dual ICI vs single ICI: not reached vs 15.7 months, p = 0.079). **(B)** Progression-free survival as per treatment regimen (n = 67; (dual ICI vs single ICI: not reached vs 7.8 months; p = 0.246). **(C)** ORR as per treatment regimen (n = 67; dual ICI vs single ICI: 40 vs 42%; p = 0.873). **(D)** Sensitivity analysis with excluding patients who received first-line palliative-intent ICI regimen prior to 2018 (n = 39; median overall survival not reached vs 20.9 months; p = 0.213). CR: Complete response; ICI: Immune checkpoint inhibitor; PD: Disease progression; PR: Partial response; ORR: Objective response rate.

Table 1. Baseline patient, tumor and treatment characteristics.

	Total (n, %)	Treatment regimen		
		Dual ICI (n, %)	Single ICI (n, %)	p-value
Age:				
– <65 years	22 (33)	9 (60)	13 (25)	0.011
– ≥65 years	45 (67)	6 (40)	39 (75)	
Gender:				
– Male	44 (66)	9 (60)	35 (67)	0.599
– Female	23 (34)	6 (40)	17 (33)	
ECOG:				
– 0–1	53 (79)	13 (87)	40 (77)	0.414
– ≥2	14 (21)	2 (13)	12 (23)	
Baseline corticosteroid use:				
– Yes	11 (16)	5 (33)	6 (12)	0.045
– No	56 (84)	10 (67)	46 (88)	
Melanoma histology:				
– Cutaneous	51 (76)	8 (53)	43 (83)	0.019
– Non cutaneous	16 (24)	7 (47)	9 (17)	
Of the non-cutaneous:				
– Unknown primary	6 (38)	2 (67)	4 (33)	N/A
– Ocular	2 (12)	2 (100)	0 (0)	
– Mucosal	8 (50)	3 (38)	5 (62)	
Melanoma stage:				
– Advanced unresectable	6 (9)	1 (7)	5 (10)	1.000
– Metastatic	61 (91)	14 (93)	47 (90)	
Baseline number of metastatic sites:				
– ≤2	48 (72)	12 (80)	36 (69)	0.527
– >2	19 (28)	3 (20)	16 (31)	
Presence of baseline liver metastasis:				
– Yes	18 (27)	4 (27)	14 (27)	1.000
– No	49 (73)	11 (73)	38 (73)	
Presence of baseline brain metastasis:				
– Yes	10 (15)	5 (33)	5 (10)	0.023
– No	57 (85)	10 (67)	47 (90)	
Baseline LDH:				
– >Upper limit of normal	26 (39)	7 (47)	19 (36)	0.478
– ≤Upper limit of normal	41 (61)	8 (53)	33 (64)	
Baseline NLR:				
– ≥5	13 (19)	5 (33)	8 (15)	0.121
– <5	54 (81)	10 (67)	44 (85)	
Baseline PLR:				
– ≥200	17 (25)	4 (27)	13 (25)	0.896
– <200	50 (75)	11 (73)	39 (75)	
Adjuvant ICI:				
– Yes	2 (3)	2 (13)	0 (0)	N/A
– No	65 (97)	13 (87)	52 (100)	

ECOG: Eastern cooperative oncology group; ICI: Immune checkpoint inhibitor; LDH: Lactate dehydrogenase; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

ORR (40 vs 42%; p = 0.837) (Figure 1C) when compared with single ICI in the study population. Of the 35 patients who progressed on single ICI, only six (17%) received subsequent ipilimumab, 26 (74%) died before receiving ipilimumab and three (9%) were alive at data cutoff without subsequent treatment (Figure 2). Of the six patients who received subsequent ipilimumab, all had ECOG 0–1 at baseline prior to palliative-intent first-line single ICI and none had achieved CR/PR on second-line ipilimumab (not shown in graph).

Multivariable Cox analyses demonstrated dual ICI had a statistically significant association with better OS when compared with single ICI in patients with *BRAF* V600 wild-type (HR: 0.204; 95% CI: 0.064–0.649; p = 0.007). Presence of baseline brain metastasis (HR: 6.380; 95% CI: 1.895–21.481; p = 0.003) and baseline liver metastasis (HR: 3.330; 95% CI: 1.696–6.535; p < 0.001) were also shown to be independent predictive factor for worse OS in *BRAF* V600 wild-type advanced melanoma patients. Baseline ECOG ≥2 was not significantly associated with OS in the multivariable Cox analysis (Table 2). We did not include baseline corticosteroid use in the multivariable Cox analysis due to its high collinearity with baseline brain metastasis (p < 0.001).

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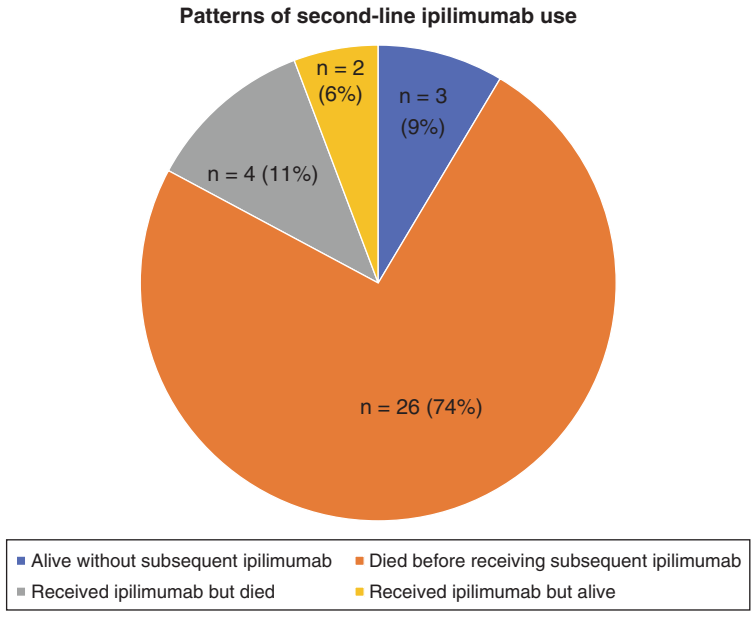

Figure 2. Patterns of subsequent ipilimumab use in single immune checkpoint inhibitor group on disease progression.

Table 2. Multivariable Cox analysis and sensitivity analysis (excluding patients who initiated treatment prior to 2018) for overall survival.

	HR	95% CI	p-value
Overall population (n = 67)			
Baseline ECOG ≥2	1.049	0.392–2.810	0.924
Baseline brain metastasis	6.380	1.895–21.481	0.003
Baseline liver metastasis	3.330	1.696–6.535	<0.001
Treatment regimen (single as reference)	0.204	0.064–0.649	0.007
Patients from 2018 to 2020 only (n = 39)			
Baseline liver metastasis	6.613	2.362–18.516	<0.001
Treatment regimen (single as reference)	0.475	0.164–1.380	0.171

ECOG: Eastern cooperative oncology group; HR: Hazard ratio.

There were 28 patients who initiated single ICI prior to 2018. Median follow-up duration for the post-2018 dual and single ICI groups were 22.4 and 18.9 months, respectively. When only post-2018, patients were included in our sensitivity analysis (n = 39), dual ICI maintained its non statistically significant improved OS trend compared with single ICI (mOS not reached vs 20.9 months; p = 0.213; adjusted HR: 0.475, 95% CI: 0.164–1.380; p = 0.171) (Figure 1D & Table 3). Presence of baseline liver metastasis (HR: 6.613; 95% CI: 2.362–18.516; $p < 0.001$) continued to show statistically significant worse OS in the multivariable model.

There were more irAE development in patients who received dual ICI compared with single ICI (93 vs 52%; p = 0.005). The initial irAE type differed between the two groups as well, particularly more patients in the dual ICI group developed multiple irAEs at once (36 vs 4%; p = 0.003). Dual ICI was associated with higher irAE severity than single ICI (grade 2: 50 vs 44%; grade 3–5 36 vs 7%; p = 0.026). Regarding management of the irAEs, there were more systemic corticosteroid use (93 vs 30%; $p < 0.001$) and high dose corticosteroid use (prednisone-equivalent ≥1 mg/kg) (29 vs 4%; p = 0.039) in the dual ICI group than single ICI group. There was also more subsequent irAE development in the dual ICI group than single ICI group (86 vs 48%; p = 0.041). There were no meaningful differences between the need for additional immunosuppressant use (p = 0.111), as well as subsequent irAE type (p = 1.000) and severity (p = 0.226) between the two groups (Table 3).

Discussion

Our study reported real-world evidence of dual versus single ICI on treatment outcomes and safety profile in patients with *BRAF* V600 wild-type advanced melanoma. Our study showed dual ICI had statistically significant

Table 3. Immune-related adverse events as per treatment regimen.

irAEs	Dual ICI, n (%)	Single ICI, n (%)	p-value
irAE development:			
– Yes	14 (93)	27 (52)	0.005
– No	1 (7)	24 (48)	
Initial irAE system type:			
– Endocrine	2 (14)	4 (15)	0.003
– Skin	2 (14)	15 (55)	
– Respiratory	1 (7)	1 (4)	
– Gastrointestinal	4 (29)	1 (4)	
– Rheumatology	0 (0)	2 (7)	
– Multiple	5 (36)	1 (4)	
– Other	0 (0)	3 (11)	
Initial irAE severity:			
– 1	2 (14)	13 (48)	0.026
– 2	7 (50)	12 (44)	
– 3–5	5 (36)	2 (7)	
Systemic corticosteroid use:			
– Yes	13 (93)	8 (30)	<0.001
– No	1 (7)	19 (70)	
High dose corticosteroid use:			
– Yes	4 (29)	1 (4)	0.039
– No	19 (71)	26 (96)	
Additional immunosuppressant use:			
– Yes	2 (14)	0 (0)	0.111
– No	12 (86)	27 (100)	
Subsequent irAE:			
– Yes	12 (86)	13 (48)	0.041
– No	2 (14)	14 (52)	
Same subsequent irAE type:			
– Yes	3 (25)	4 (31)	1.000
– No	9 (75)	9 (69)	
Higher subsequent irAE severity:			
– Yes	6 (50)	3 (23)	0.226
– No	6 (50)	10 (77)	

ICI: Immune checkpoint inhibitor; irAE: Immune-related adverse event.

OS improvement when compared with single ICI in *BRAF* V600 wild-type advanced melanoma patients, albeit the statistically significant OS improvement was lost when excluding patients who started treatment prior to 2018. Nevertheless, there were apparent separations between the two treatment groups in the Kaplan–Meier curves of both total population and sensitivity analyses. Larger studies with longer follow-up duration would be required to evaluate whether such separations could be sustained to reach statistical significance.

While we do not yet have long enough follow-up for 3-year OS for comparison with CheckMate-067 (53% in nivolumab + ipilimumab group vs 50% in nivolumab group) in the *BRAF* wild-type population, the dual ICI group in our study achieved a higher 2-year OS when compared with the Kaplan–Meier OS curve for *BRAF* wild type patients in Checkmate-067 (2-year OS numerical value not presented) [12]. This discrepancy may be secondary to different patient populations between the two studies. In particular, we included patients with worse ECOG ≥2, symptomatic brain metastasis, non cutaneous melanoma and baseline corticosteroid use – all of whom were excluded in Checkmate-067 trial. This might suggest that patients with less favourable clinico-pathological features may benefit from a more aggressive treatment upfront in dual ICI than single ICI. Safety analysis showed expected findings in that dual ICI were associated with more frequent and severe irAEs compared with single ICI. However, our exploratory study results need to be interpreted with cautions due to small sample size, shorter follow-up duration and retrospective nature. Future studies involving multicenters and larger sample sizes would be required to validate our findings.

Interestingly, patients with baseline ECOG ≥2 did not confer a worse OS compared with patients with baseline ECOG 0–1 in the multivariable Cox models. While dual or single ICI use did not differ between the ECOG groups, 74% of patients died from disease progression prior to receiving subsequent ipilimumab use and none with poor baseline performance status had received subsequent ipilimumab. Additionally, there were no CR/PR achieved in patients who received second-line ipilimumab, although this interpretation is limited by its small sample size.

Contrary to conventional systemic therapy whereby clinicians may avoid more aggressive therapy in patients with poor performance status, our study showed paradoxical findings in that dual ICI might be considered in patients with baseline ECOG 2, given its potential superior efficacy over single ICI and that only a small proportion of such patients were eligible for subsequent treatment with limited efficacy.

Our multivariable analysis indicated presence of baseline liver metastasis was independently associated with poorer OS outcome. This was consistent with the latest 6.5-year update from CheckMate-067 whereby patients with baseline liver metastasis had shorter median OS than those without baseline liver metastasis regardless of ICI regimen (dual ICI: 28.2 months vs not reached; single ICI: 18.2 vs 52.7 months). Other retrospective analyses also demonstrated similar findings of baseline liver metastasis being an independent poor predictor for OS in advanced melanoma patients on ICI regimen [13,14]. Within the limitation of subgroup-analysis, Checkmate-067 demonstrated dual ICI to have improved OS trend compared with nivolumab alone in patients with (HR: 0.81; 95% CI: 0.56–1.16) or without (HR: 0.84; 95% CI: 0.64–1.09) baseline liver metastasis. It would be important to further improve therapeutic options (local and/or systemic) for such patient population with nonfavorable prognostic factor.

In relation to baseline brain metastasis, our study indicated that this subgroup of patients had worse prognosis compared with non brain metastasis group, even when patients received dual ICI. Previous multicenters phase II trial evaluated the intracranial efficacy of combined ipilimumab and nivolumab in patient with metastatic melanoma and asymptomatic, irradiated, no more than 3 cm brain metastasis. The study demonstrated 57% of enrolled patients achieved complete or partial intracranial response for at least 6 months [15]. Unfortunately, our study only had ten patients with baseline brain metastasis, and therefore not equipped to conduct further analysis from this perspective.

Our study was also not able to incorporate systemic corticosteroid use into the multivariable Cox model due to its high collinearity with baseline brain metastasis. This is an important potential prognosticating variable, given that systemic corticosteroid use has been previously correlated with immunosuppression [16,17], further drawing concerns of impairing ICI efficacy in advanced cancer patients. Multiple studies reported early corticosteroid use prior to ICI may be linked with decreased efficacy in various advanced cancer settings [18–22], particularly if indicated for cancer symptom relief [20], as well as higher dose [21] and prolonged use of corticosteroid [22]. Nevertheless, these studies evaluated single ICI rather than dual ICI. It is expected that the concurrent PD-1 and CTLA-4 inhibition would lead to not only better recognition between tumor cells and T cells, but also priming of the T cells via antigen presenting cells, thereby reducing the effect of corticosteroid inducing T cells energy. Future studies from this perspective, particularly in the setting of systemic corticosteroid use for non brain metastatic indications, would be important to further evaluate the effect of baseline corticosteroid on dual ICI efficacy.

There are several limitations warrant attentions. First, our study is limited through its retrospective nature and unable to determine causal–effect relationships. Second, follow-up duration for dual ICI is likely limited for mature OS analysis. However, the Kaplan–Meier curves separation between the two groups were apparent at the 1-year mark, with only two patients being censored at the time. Third, our study results should be interpreted with cautions due to small sample size. At last, our study did not capture the pattern of disease progression (oligometastasis vs diffuse) and its subsequent local therapy (e.g., radiation therapy or surgery), which might impact on post progression survivals or OS. Nevertheless, our study accounted for subsequent systemic immunotherapy use upon disease progression. Overall, our study provides valuable real-world evidence in an understudied yet important topic. Future multicenter studies with larger sample sizes would be required to validate our findings.

Conclusion

In this real-word study, we reported dual ICI may have non statistically significant trend toward better OS efficacy when compared with single ICI in *BRAF* V600 wild-type advanced melanoma patients. Dual ICI was also associated with more frequent and severe irAEs necessitating systemic corticosteroid use than single ICI. However, our study was limited by its small sample size, relatively shorter follow-up duration and retrospective nature. Future studies on better patient selection for dual ICI would be required to achieving optimal survival benefit while minimizing toxicities.

Summary points

- Both first-line combined PD-1 and CTLA-4 inhibitors (dual immune checkpoint inhibitors [ICI]), as well as first-line PD-1 inhibitor followed by CTLA-4 inhibitors if progressed (single ICI), are available options for *BRAF* V600 wild-type advanced melanoma patients.
- This retrospective, real-world study evaluated the efficacy of dual versus single ICI in patients with *BRAF* wild-type advanced melanoma.
- Our study showed dual ICI had statistically significant OS improvement (HR: 0.204; 95% CI: 0.064–0.649; p = 0.007) when compared with single ICI in *BRAF* V600 wild-type advanced melanoma patients.
- In contrary to Checkmate-067, the discrepancy may be secondary to different patient populations between the two studies. We included patients with worse ECOG ≥2, symptomatic brain metastasis, non cutaneous melanoma and baseline corticosteroid use – all of whom were excluded in Checkmate-067 trial.
- However, dual ICI lost its statistically significant OS benefit (mOS not reached vs 20.9 months; p = 0.213; adjusted HR: 0.475; 95% CI: 0.164–1.380; p = 0.171) on our sensitivity analysis which included only patients who were initiated on ICI post-2018 when dual ICI was funded in our province.
- Safety analysis showed expected findings in that dual ICI were associated with more frequent and severe immune-related adverse events compared with single ICI.
- Our results need to be interpreted with great caution due to low sample size, shorter follow-up duration and retrospective nature.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

1. Wolchok JD, Chiarion-Sileni V, Gonzalez R *et al.* Long-term outcomes with nivolumabplus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *J. Clin. Oncol.* 40, 127–137 (2022).
2. Robert C, Ribas A, Schachter J *et al.* Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicenter, randomized, controlled, Phase III study. *Lancet Oncol.* 20, 1239–1251 (2019).
3. Robert C, Thomas L, Bondarenko I *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N. Eng. J. Med.* 364, 2517–2526 (2011).
4. Robert C, Grob JJ, Stroyakovskiy D *et al.* Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N. Eng. J. Med.* 38, 626–636 (2019).
5. Dreno B, Ascierto PA, McArthur GA *et al.* Efficacy and safety of cobimetinib (C) combined with vemurafenib (V) in patients (pts) with BRAF V600 mutation-positive metastatic melanoma: analysis from the 4-year extended follow-up of the Phase III coBRIM study. *J. Clin. Oncol.* 36(Suppl. 15), 9522 (2018).
6. Dummer R, Ascierto PA, Gogas HJ *et al.* Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicenter, open-label, randomized Phase III trial. *Lancet Oncol.* 19, 603–615 (2018).
7. National Comprehensive Cancer Network. Cutaneous melanoma (Version 3.2020). https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
8. Seth R, Messersmith H, Kaur V *et al.* Systemic therapy for melanoma: ASCO guideline. *J. Clin. Oncol.* 38, 3947–3970 (2020).
9. Keilholz U, Ascierto PA, Dummer R *et al.* ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO guidelines committee. *Ann.Oncol.* 31, 1435–1448 (2020).

10. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45, 228–247 (2009).
11. Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
12. Wolchok JD, Chiarion-Sileni V, Gonzalez R *et al.* Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N. Eng. J. Med.* 377, 1345–1356 (2017).
13. Tumeh PC, Hellmann MD, Hamid O *et al.* Liver metastasis and treatment outcome with anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. *Cancer Immunol. Res.* 5, 417–424 (2017).
14. Wang X, Ji Q, Yan X *et al.* The impact of liver metastasis on anti-PD-1 monoclonal antibody monotherapy in advanced melanoma: analysis of five clinical studies. *Front. Oncol.* 10, 546604 (2020).
15. Tawbi HA, Forsyth PA, Algazi A *et al.* Combined nivolumab and ipilimumab in melanoma metastatic to brain. *N. Eng. J. Med.* 379, 722–730 (2018).
16. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev. Infect. Dis.* 11, 954–963 (1989).
17. Libert C, Dejager L. How steroids steer T cells. *Cell Rep.* 7, 938–939 (2014).
18. Arbour KC, Mezquita L, Long N *et al.* Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J. Clin. Oncol.* 36, 2872–2878 (2018).
19. Scott SC, Pennell NA. Early use of systemic corticosteroids in patients with advanced NSCLC treated with nivolumab. *J. Thorac. Oncol.* 13, 1771–1775 (2018).
20. Ricciuti B, Dahlberg SE, Adeni A *et al.* Receiving baseline corticosteroids for palliative versus nonpalliative indication. *J. Clin. Oncol.* 37, 1927–1934 (2019).
21. Kartolo A, Deluce J, Holstead R *et al.* Impact of baseline corticosteroids on immunotherapy efficacy in patients with advanced melanoma. *J. Immunother.* 44, 167–174 (2021).
22. Pan EY, Merl MY, Lin K. The impact of corticosteroid use during anti-PD1 treatment. *J. Oncol. Pharm. Pract.* 26, 814–822 (2020).