Efficacy of immune checkpoint inhibitors for in-transit melanoma

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ABSTRACT
Background The efficacy of immune checkpoint inhibitors (ICI) in metastatic melanoma is well established. However, there are limited data regarding their efficacy in in-transit melanoma (ITM). This study assessed the efficacy of ICI in patients with ITM.

Methods A retrospective review of patients with ITM commenced on an ICI between March 2013 and February 2018 at three tertiary centers in Australia. Patients were excluded if they had previous or synchronous distant metastases. Overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) were based on a composite of radiological and clinical assessments.

Results Fifty-four patients were included: 27 (50%) female; median age 75 (range 26–94); 12 (22%) stage IIIB, 40 (74%) stage IIIC and 2 (4%) stage IIID; 10 (19%) male; 45 (83%), 15 (28%) partial responses; 9 (17%) stable disease; 16 (30%) progressive disease. ORR to ICI was 54%: 14 (26%) complete responses; 15 (28%) partial responses; 9 (17%) stable disease; 16 (30%) progressive disease. Thirteen (46%) responders had only one ITM lesion. ORR was 58% for single-agent anti-_PD-1 (pembrolizumab or nivolumab), 38% for single-agent anti-CTLA-4 (ipilimumab), 38% for single-agent anti-CTLA-4 and 40% for anti-PD-1/anti-CTLA-4 (ipilimumab and nivolumab or pembrolizumab) and 1 (2%) combination anti-PD-L1 (atezolizumab) and MEK inhibitor (cobimetinib). The median follow-up was 15 months (2–46).

ORR to ICI was 54%: 14 (26%) complete responses; 15 (28%) partial responses; 9 (17%) stable disease; 16 (30%) progressive disease. Thirteen (46%) responders had only one ITM lesion. ORR was 58% for single-agent anti-PD-1, 38% for single-agent anti-CTLA4 and 40% for anti-PD-1/anti-CTLA-4. The median PFS was 11.7 months (6.6–not reached). 1-year and 2-year PFS were 48% and 39%, respectively. Fourteen progressed locoregionally and 11 progressed distantly. The median OS was not reached. 1-year and 2-year OS were 85% and 63%, respectively. No clinicopathological features were associated with ORR.

Conclusions and relevance ICI produce objective responses in ITM and should be considered in patients with unresectable ITM or disease recurrence.

BACKGROUND AND RATIONALE
The advent of immune checkpoint inhibitors (ICI) and BRAF and MEK inhibitors has transformed the treatment landscape and prognosis of patients with metastatic melanoma. In seminal studies, pembrolizumab resulted in a 5-year overall survival (OS) of 34% and the combination of ipilimumab and nivolumab produced a 4-year OS rate of 53%.12 In-transit melanoma (ITM) is defined by the presence of metastases in the superficial lymphatic system more than 2 cm from the primary lesion but not beyond the regional lymph node basin. Patients with locoregional disease and ITM alone are not well represented in landmark studies.

The natural history of ITM is variable; some tumors have limited systemic metastatic potential and present with multiple locoregional recurrences over years while others rapidly develop distant metastases. Although the 5-year OS for patients with ITM exceeds that of patients with distant metastatic disease (83%, 69% and 32% for stage IIIB, IIIC and IHD disease), a significant percentage of ITM patients experience morbidity from their disease and may eventually develop distant metastases.3 4 Surgical excision has been the mainstay of treatment for ITM. However, there is limited evidence to guide therapy when ITM is either clinically or technically unresectable. Locoregional approaches including topical therapies, intralesional injections, radiotherapy, laser ablation and isolated limb infusion or perfusion (ILLI) have demonstrated efficacy.5 Intralesional injections with PV-10 (Rose Bengal) or talimogene laherparepvec (T-VEC) produce durable responses, with complete response (CR) rates of 26% and 16%, respectively, in patients with stage IIIB–IV disease.6 7 Similarly, ILLI has demonstrated a CR rate of 38% with a median duration of response of 13 months.8 However, responses in these studies should be interpreted with care as majority of were small single arm studies or case series.

Systemic therapies are increasingly used in unresectable stage III melanoma including patients with ITM. ICIs have the potential to alter the natural history of ITM by preventing the development of further locoregional or distant metastases while limiting the morbidity associated with certain
Table 1  Baseline characteristics stratified by ICI

| Characteristic                                      | Total               | Single-agent anti-PD-1 | Single-agent anti-CTLA-4 | Combination anti-PD-1/anti-CTLA-4 | Combination anti-PDL-1/MEK inhibitor |
|----------------------------------------------------|---------------------|------------------------|--------------------------|-----------------------------------|-------------------------------------|
|                                                    | n (%) or median (range) | n (%) or median (range) | n (%) or median (range) | n (%) or median (range) | n (%) or median (range) |
| Sex                                                |                     |                        |                          |                                   |                                     |
| Female                                             | 27 (50)             | 20 (50)                | 5 (63)                   | 2 (40)                            | 0                                   |
| Male                                               | 27 (50)             | 20 (50)                | 3 (38)                   | 3 (60)                            | 1 (100)                             |
| Age when commenced ICI treatment, years (range)    | 75 (26–94)          | 78 (26–94)             | 68 (34–89)               | 69 (58–79)                        | 75 (75)                             |
| Site of primary                                     |                     |                        |                          |                                   |                                     |
| Lower limb                                         | 34 (63)             | 25 (63)                | 5 (63)                   | 3 (60)                            | 1 (100)                             |
| Trunk                                              | 3 (6)               | 2 (5)                  | 1 (13)                   | 0                                 | 0                                   |
| Upper limb                                         | 3 (6)               | 3 (8)                  | 0                        | 0                                 | 0                                   |
| Head/neck                                          | 9 (17)              | 6 (15)                 | 1 (13)                   | 2 (40)                            | 0                                   |
| Unknown                                            | 5 (9)               | 4 (10)                 | 1 (13)                   | 0                                 | 0                                   |
| Primary tumor thickness, mm (range)                | 3 (0.6–40)          | 3 (0.6–40)             | 2.9 (1.2–8)              | 2.4 (1–3.9)                       | 9 (9)                               |
| Ulcerated primary tumor                            |                     |                        |                          |                                   |                                     |
| Yes                                                | 15 (28)             | 12 (30)                | 2 (25)                   | 1 (20)                            | 0                                   |
| No                                                 | 34 (63)             | 24 (60)                | 5 (63)                   | 4 (80)                            | 1 (100)                             |
| Unknown                                            | 5 (9)               | 4 (10)                 | 1 (13)                   | 0                                 | 0                                   |
| BRAF                                               |                     |                        |                          |                                   |                                     |
| Mutation                                           | 10 (19)             | 6 (15)                 | 3 (38)                   | 1 (20)                            | 0                                   |
| Wildtype                                           | 42 (78)             | 32 (80)                | 5 (63)                   | 4 (80)                            | 1 (100)                             |
| Untested                                           | 2 (4)               | 2 (5)                  | 0                        | 0                                 | 0                                   |
| NRAS                                               |                     |                        |                          |                                   |                                     |
| Mutation                                           | 15 (28)             | 10 (25)                | 3 (38)                   | 2 (40)                            | 0                                   |
| Wildtype                                           | 19 (35)             | 12 (30)                | 4 (50)                   | 2 (40)                            | 1 (100)                             |
| Untested                                           | 20 (37)             | 18 (45)                | 1 (13)                   | 1 (20)                            | 0                                   |
| AJCC 8th edition stage at time of ICI              |                     |                        |                          |                                   |                                     |
| IIIB                                               | 12 (22)             | 9 (23)                 | 3 (38)                   | 0                                 | 0                                   |
| IIIC                                               | 40 (74)             | 30 (75)                | 4 (50)                   | 5 (100)                           | 1 (100)                             |
| IIID                                               | 2 (4)               | 1 (3)                  | 1 (13)                   | 0                                 | 0                                   |
| No of lesions when treated with ICI                |                     |                        |                          |                                   |                                     |
| 1                                                  | 19 (35)             | 16 (40)                | 2 (25)                   | 1 (30)                            | 0                                   |
| 02/05/20                                           | 11 (20)             | 7 (18)                 | 1 (13)                   | 3 (60)                            | 0                                   |
| >5                                                 | 20 (37)             | 15 (38)                | 3 (38)                   | 1 (20)                            | 1 (100)                             |
| Unknown                                            | 4 (7)               | 2 (5)                  | 2 (25)                   | 1                                 | 0                                   |
| Concurrent nodal disease at time of ICI treatment   |                     |                        |                          |                                   |                                     |
| Yes                                                | 35 (65)             | 26 (65)                | 5 (63)                   | 4 (80)                            | 0                                   |
| No                                                 | 19 (35)             | 14 (35)                | 3 (38)                   | 1 (20)                            | 1 (100)                             |

AJCC, American Joint Committee on Cancer; ICI, immune checkpoint inhibitors.

locoregional therapies. However, limited data exist ICI efficacy for ITM. Registration studies of ICI for metastatic melanoma did not prespecify ITM as a subgroup for analysis. These patients were included in the patient group with unresectable stage III disease which accounted for less than 10% of patients enrolled.$^1$ $^2$ $^3$–$^11$ Where this subgroup was analyzed retrospectively, conclusions were limited due to small patient numbers.$^1$ $^2$ $^9$–$^11$ The aim of
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Table 2 Overall response to immune checkpoint-inhibitors in patients with in-transit melanoma metastases

| Overall response | Total N (%) | Single-agent anti-PD-1 N (%) | Single-agent anti-CTLA-4 N (%) | Combination anti-PD-1/anti-CTLA-4 N (%) | Combination anti-PDL-1/MEK inhibitor N (%) |
|------------------|-------------|-----------------------------|-------------------------------|----------------------------------------|------------------------------------------|
| Overall          | 54 (100)    | 40 (100)                    | 8 (100)                      | 5 (100)                                | 1 (100)                                  |
| CR               | 14 (26)     | 12 (30)                     | 1 (13)                       | 1 (20)                                 | 0                                        |
| PR               | 15 (28)     | 11 (28)                     | 2 (25)                       | 1 (20)                                 | 1 (100)                                  |
| SD               | 9 (17)      | 4 (10)                      | 3 (38)                       | 2 (40)                                 | 0                                        |
| PD               | 16 (30)     | 13 (33)                     | 2 (25)                       | 1 (20)                                 | 0                                        |

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

The overall response rate (ORR) was defined as CR plus partial response (PR) based on a composite of radiological and clinical assessments. PR was defined as clinical disease reduction of at least 50%. ITMs are often non-evaluable by response evaluation criteria in solid tumors (RECIST). Progression-free survival (PFS) was measured from ICI commencement to radiological or clinical progression or death. OS was measured from ICI commencement to death. PFS and OS were estimated using the Kaplan-Meier method and survival distributions were compared using a log-rank test.

The association between ORR and potential clinical and pathological factors were assessed using Fisher’s exact test (two sided) if nominal variables (ulceration, BRAF status, previous intralesional/ILI therapy), Exact Cochran-Armitage Trend test (one sided) if ordinal variables (number of lesions, stage at commencement) and Wilcoxon test (two sided) if continuous variables (first disease free interval, ITM disease-free interval). Analyses were carried out using SAS (V.9.4; SAS Institute).

RESULTS

Fifty-four patients received ICI for unresectable ITM between March 2013 and February 2018. Baseline characteristics are shown in Table 1; 10 patients (19%) had BRAF mutant melanoma, 11 (20%) patients received ICI as first-line treatment for their ITM, 6 (11%) had prior ILI treatment and 17 (31%) had prior intralesional therapies (T-VEC: 2 (4%) or PV-10: 15 (28%)). Forty patients (74%) received single-agent PD-1 inhibitor (pembrolizumab or nivolumab), eight (15%) single-agent anti-CTLA-4 (ipilimumab), five (9%) combination anti-PD-1/anti-CTLA-4 (ipilimumab and nivolumab or pembrolizumab) and one (2%) combination anti-PDL-1 (atezolizumab) and MEK inhibitor (cobimetinib). Other treatment modalities were used in combination with ICI in some instances: three (6%) patient received radiotherapy, one (2%) patient had intralesional injection and one (2%) patient had topical therapy.

The ORR to ICI was 54%: 14 (26%) CR; 15 (28%) PR; 9 (17%) stable disease (SD); 16 (30%) progressive disease (PD). The ORR was 58% for single agent anti PD-1, 38% for single-agent anti-CTLA-4 and 40% for anti-PD-1/anti-CTLA-4 (Table 2). Ulceration, BRAF status, number of lesions, prior treatments (ILI or intralesional injection) and stage also had no significant association with ORR.

The median duration of follow-up was 15.1 months (95% CI 2 to 46). Twenty-five patients progressed (48%): 14 (56%) progressed locoregionally and 11 (44%) developed distant metastases. The median PFS was 11.7 months (6.3-not reached). One-year and 2-year PFS were...
48% (95% CI 33% to 61%) and 39% (95% CI 23% to 55%), respectively (figure 1). Further 2-year PFS for anti-PD-1, anti-CTLA-4 and anti-PD-1/anti-CTLA-4 was 30%, 50% and 80%, respectively.

The median OS was not reached, three (6%) patients died. One-year and 2-year OS rate were 85% (95% CI 71% to 93) and 63% (95% CI 43% to 77%), respectively. At 2 years, the OS for patients with an overall response was 85% (95% CI 50% to 96%) compared with 40% (95% CI 16% to 64%) in those who did not.

DISCUSSION

This study demonstrates that single agent and combination ICI produces durable responses in ITM similar to rates seen in patients with stage IV melanoma. The 2-year PFS of 39% and 2-year OS of 63% are consistent with landmark survival data from registration studies for ICI in unresectable stage III and stage IV melanoma (pembrolizumab resulted in a 5-year OS of 34% study and ipilimumab/nivolumab a 4-year OS rate of 53%).

Objective measurements of responses are challenging in the ITM population as the majority of patients have disease which is non-evaluable by RECIST. Thus, this study relied on subjective clinician assessed responses as well as radiological responses, a significant limitation.

The lower than expected response rate in the anti-PD-1/anti-CTLA-4 group may be due to the small sample size and higher relative disease burden.

While ICI is clearly an effective treatment for ITM, there is minimal data to guide how ICI could be optimally integrated with other commonly used locoregional therapies for ITM. For patients with slowly progressing, isolated or low volume ITM, surgical resection remains a standard of care, however, for patients with rapidly progressive disease the selection of locoregional therapies, ICI or a combination of both is unclear. A phase I/2 study evaluating the combination of PV-10 and pembrolizumab in 25 patients with stage IIIIB–IV M1c melanoma demonstrated a CR rate of 77%. Further, a phase II study of 18 patients with stage IIIB–IV melanoma (previous treatment not reported) examined the efficacy of ILI in combination with ipilimumab. This study demonstrated a CR rate of 65% and a 1-year PFS of 57%. Therefore, combinations of locoregional therapy and ICI may produce higher ORR and more durable responses than either treatment in isolation and warrants further examination in larger studies; such as MASTERKEY-265 comparing pembrolizumab with or without T-VEC (NCT02263508). In our retrospective analysis, prior treatment with ICI or intraleisonal injections was not associated with higher response rates to subsequent ICI therapy.

CONCLUSION

This multi-institutional study provides the largest evidence base of durable responses to ICI in patients with ITM, demonstrating this to be an effective treatment in patients with unresectable ITM or disease recurrence despite locoregional therapies. Prospective studies specifically targeting this unique population are needed to confirm the efficacy of ICI and to determine optimal sequencing of treatment and potential locoregional combinations.
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Correction: Efficacy of immune checkpoint inhibitors for in-transit melanoma

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Since the online publication of this article, the authors noticed that the middle initial for author ‘Georgina V Long’ was missing. This has now been corrected.

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