Research Article Open Access

Secondarily, we also wanted to determine if patients achieving CR had a sustained response following discontinuation of pembrolizumab.

Between December 1st, 2015 and December 1st, 2017, patients with unresectable locally advanced and stage IV metastatic cutaneous melanoma referred to Maisonneuve-Rosemont hospital and treated with pembrolizumab were enrolled in this retrospective cohort study. Approval of the ethics committee was obtained prior to file review. Patients had to be 18 years or older with histologically confirmed cutaneous melanoma. Patients were excluded of the study if they had any other concomitant cancer within five years of the melanoma diagnosis. Metastatic lesions were identified and diagnosed on imaging (CT scan or TEP scan). Patients who presented with synchronous distant metastases at the time of initial diagnosis and those who developed metastatic disease after treatment of their primary melanoma were both included. Patients could have received prior systemic therapy or local therapy to be enrolled in this study.

The primary outcome was the evaluation of the pembrolizumab response rate. Secondary outcomes were OS, defined as the time from the first treatment after diagnosis to death or date of last follow-up, PFS, defined as the time from the initial treatment of metastatic melanoma with pembrolizumab to the earliest sign of disease progression (either radiologically or clinically) or death, and pembrolizumab related adverse events.

At the time of this study, the combination of nivolumab and ipilimumab for metastatic melanoma was not available, explaining why our cohort of patients received the single agent pembrolizumab. All patients received pembrolizumab at a dose of 2 mg/kg administered intravenously once every 3 weeks. Treatment was pursued until complete radiological response, progression of disease, severe adverse events or if the patient declined further treatment. Multiple clinicopathologic variables were collected on the primary melanoma specimen after surgical excision. Patients who received systemic treatment such as adjuvant interferon, other immunotherapy (ipilimumab, nivolumab), targebl r(er)13(e)22(a)19(t)-5(ien)19.1(ts w)-7(h6(ni)7(v)8K admiTD[(ad)12(j)l(e)-5(d p)12(r)-6(io)w)-7()-5(d p)-9(em)10(b)12(r)13(o)7(lizum)3.bles

for their metastatic disease. Two patients received pembrolizumab as second-line treatment, one after progression on ipilimumab and one after progression on dabrafenib. Four patients were treated with pembrolizumab as third line therapy and one patient received it as a fourth line treatment after progression on vemurafenib, DTIC and ipilimumab. A total of six patients (26%) received ipilimumab during their course of treatment prior to treatment with pembrolizumab. One patient received three intralesional Injections of Interleukin-2 (IL-2) for subcutaneous in transit metastases prior to pembrolizumab therapy.

The objective response rate was evaluated clinically and radiologically with FDG-PET scan as per Percist 1.0 criteria. Our patient population had an objective response rate of 52% (n=12), with a complete response rate of 48%. Our entire cohort received a median of 10 pembrolizumab cycles (range 2-45). Complete response was achieved after a median of 11 cycles of pembrolizumab (range 2-19) (Table 2). One patient presented with partial response after 9 cycles of pembrolizumab, and one patient had stable disease throughout therapy. A total of 10 patients (43%) had disease progression. These patients received a median of 6 pembrolizumab cycles before progression (range 3-25). In the subgroup of patients with a BRAF mutation, 57% received a BRAF +/- MEK inhibitor as first line therapy and 43% received pembrolizumab as first line treatment. When pembrolizumab was given in second line in those BRAF mutated patients, half of those patients presented a CR. Among the BRAF mutated patients who received pembrolizumab as first line, one patient had a CR, one had a partial response and one had progression of disease. At the time of analysis, only one patient was still on pembrolizumab. The most common reasons for treatment discontinuation were complete response and disease progression.

Therapeutic response as per PERCIST 1.0	No. of patients	Median number of cycles of pembrolizumab to achieve response-No. cycles
Complete Response (CR)	11	11
Partial Response (PR)	1	9
Stable Disease (SD)	1	45
Progressive Disease (PD)	10	6

Table 2: Response rate of pembrolizumab in locally advanced and stage IV melanoma.

The median follow-up in this cohort of patients was 27 months (range 6-46 months). Our patients with metastatic melanoma treated with pembrolizumab showed a median OS of 60 months (95% CI: 49.9-182.0). The one, three and 5-yr OS were estimated at 100%, 96% and 77%, respectively (Figure 1). The median PFS was of 29 months (95% CI: 2.8-55.2), with a one and 3-yr PFS estimated at 61% and 45%, respectively (Figure 2). Sixteen patients (70%) were alive at the time of analysis. Progression of disease was the most common cause of death. Amongst those patients, cerebral compression or hemorrhage due to brain metastases represented the most common cause of death. All 11 patients (48%) who achieved a complete response maintained their response and remained disease-free.

In our cohort of 23 patients, 65% (n=15) of patients experienced adverse events. The most common adverse events were fatigue (22%), pruritus (26%), isolated hypothyroidism (17%), diarrhea (17%), and persistent cough (17%). Two patients reported cutaneous rashes (8%) and one patient presented nausea (4%), all of which were identified as grade 1 or 2 adverse events. Overall, grade 3 and 4 adverse events occurred in 3 patients (13%), all of which were autoimmune related events (Table 3). These adverse events included pancreatitis, colitis, interstitial nephritis, pneumonitis and heart failure. Those immune-mediated adverse events were treated with discontinuation of pembrolizumab, high dose corticosteroids and supportive care. Two patients required hospitalization. All three patients had CR with pembrolizumab. There were no reported treatment-related deaths in our cohort of patients.

Cough	4 (17,4)	4 (17,4)	0	0
Pancreatitis	2 (8,7)	0	1 (4,3)	1 (4,3)
Skin rash	2 (8,7)	2 (8,7)	0	0
Xerostomia	2 (8,7)	2 (8,7)	0	0
Peripheral neuropathy	2 (8,7)	2(8,7)	0	0
Thyroiditis	1 (4,3)	0	1 (4,3)	0
Nephritis	1 (4,3)	0	0	1 (4,3)
Adrenal dysfonction	1 (4,3)	0	1 (4,3)	0
Pneumonia	1 (4,3)	1 (4,3)	0	0
Pneumonitis	1 (4,3)	0	0	1 (4,3)
Colitis	1 (4,3)	0	0	1 (4,3)
Heart failure	1 (4,3)	0	0	1 (4,3)
Arthritis	1 (4,3)	1 (4,3)	0	0
Nausea	1 (4,3)	1 (4,3)	0	0
Alopecia	1 (4,3)	1 (4,3)	0	0

*Calculations were based on 23 patients who received at least one dose of Pembrolizumab. Above are listed the adverse events reported between the first dose and 30 days after the last treatment dose. For serious immune related adverse events, a cutof period of 90 days after the last treatment dose was used. The severity of adverse events was graded according to the CTCAE, version 5.0

Table 3: Pembrolizumab related adverse events.

The Objective Response Rate (ORR) in our cohort of patients was 52% and Complete Response Rate (CRR) was 48% after a median of 11 cycles of pembrolizumab. At the time of data collection, all 11 patients with complete response remained disease free. Our study showed a median OS and PFS of 60 months and 29 months, respectively. When comparing to the oncologic outcomes of the pembrolizumab group in KEYNOTE-006, the results reported in our study showed a higher response rate with longer OS and PFS. KEYNOTE-006 demonstrated an ORR of 36% and a CRR of 13% [11]. The estimated PFS of our population was 29 months compared to 5.6 months in the KEYNOTE-006 cohort. Multiple factors can explain the overall favorable results reported in this study. First, our cohort of patients was evaluated using FDG-PET scan with the PERCIST criteria, which could overestimate the response rate [15-17]. Using FDG-PET scan and PERCIST criteria instead of computed tomography imaging and RECIST criteria, as used in the KEYNOTE trial, can explain the higher number of complete responders as well as our improved overall response rate. Although our cohort of patients had similar baseline demographic and clinical characteristics as patients enrolled in the KEYNOTE-006 trial, the small cohort size remains a major limitation of this study and limits the direct comparison and generalization of our statistical results.

The favorable safety profile of pembrolizumab observed in this study is consistent with the toxicity that had already been described in the literature [9-11]. Most patients (65%) developed adverse reactions during the treatment period, with a majority of self-limited grade 1 and 2 toxicities. Grade 3 and 4 adverse reactions were reported in 13%. They were all autoimmune related events which were managed medication and discontinuation of treatment with no long-term consequences.

In terms of duration of treatment, patients with complete

10. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, et al. (2017) Pembrolizumab versus ipilimumab for advanced melanoma: Final overall survival results of a multicentre, randomised, open-label phase 3 study. Lancet 390: 1853-1862.

11. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, et al. (2019) Pembrolizumab versus ipilimumab in advanced melanoma: Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 20: 1239-1251.

12. Eisenhauer EA, Therasseb P, Bogaerts J, Schwartzd LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guidelines Eur J Cancer 45: 228-247.

13. Hyun O J, Lodge MA, Wahl, RL (2016) Practical PERCIST: A simplifed guide to pet response criteria in solid tumors 1.0. Radiology 280: 576-584.

14. Common terminology criteria for adverse events. (2017) National Cancer Institute.

15. Adkins D, Ley J, Dehdashti F, Siegel MJ, Wildes TM, et al. (2014) A prospective trial comparing FDG-PET/CT and CT to assess tumor response to cetuximab in patients with incurable squamous cell carcinoma of the head and neck. Cancer Med 3: 1493-1501.

16. Cho SY, Lipson EJ, Im HJ, Rowe SP, Gonzalez EM, et al. (2017). Prediction of response to immune checkpoint inhibitor therapy using early-time-point 18F-FDG PET/CT Imaging in Patients with Advanced Melanoma. J. Nucl. Med 58: 1421-1428.

17. Schwenck J, Schörg B, Fiz F, Sonanini D, Forschner A, et al. (2020) Cancer immunotherapy is accompanied by distinct metabolic patterns in primary and secondary lymphoid organs observed by non-invasive in vivo 18F-FDG-PET. Theranostics, 10: 925-937.