Case Report

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Complete Response to Anti-PD-1 Antibody Monotherapy in Metastatic Melanoma-Can Therapy be Discontinued? A Review of Current Literature

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Abstract

Newer immunotherapeutic agents such as Nivolumab and Pembrolizumab have changed the landscape of management of metastatic melanoma, with a subset of patients achieving durable responses. The ideal duration of therapy in patients who achieve a complete response with these agents has not been determined. We report a case of a 68 year old man with metastatic melanoma who progressed with Ipilimumab and BRAF-directed therapies, but achieved a complete response with Nivolumab monotherapy and continues to be in remission at almost 2 years after discontinuation of treatment. Review of the current data indicates that discontinuation of anti-PD-1 antibodies after complete response is achieved is feasible. The majority of these patients maintain their responses long-term. In those who relapse, re-treatment with the same agent is effective in most cases according to the current data. Prospective studies are necessary to determine the optimal duration of therapy and strategies to maximize the benefit of these drugs.

Keywords: Anti-PD-1, Metastatic melanoma, Nivolumab, Pembrolizumab

Introduction

Metastatic melanoma has historically been a disease with a poor prognosis, with median overall survival of less than one year [1]. However, recent advances in treatment of metastatic melanoma with targeted therapies and immune checkpoint inhibitors have changed the landscape of management of this lethal disease. Ipilimumab, a CTLA-4 antibody was approved by the FDA in 2011 for use in metastatic melanoma. Two anti-programmed death 1 (PD-1) antibodies, Pembrolizumab and Nivolumab, were approved by the United States Food and Drug Administration in 2014 for treatment of metastatic melanoma after progression with Ipilimumab or BRAF-directed therapy. Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, was first approved in July 2014 in Japan for treatment of

unresectable melanoma, hence making it the first PD-1 inhibitor to receive regulatory approval anywhere in the world. Multiple clinical trials have demonstrated the efficacy of Nivolumab and Pembrolizumab in metastatic melanoma.

We present a case of a 68 year old gentleman with recurrent metastatic melanoma who, after progression on BRAF-inhibitors and Ipilimumab, had a complete response (CR) with Nivolumab monotherapy. Nivolumab was discontinued several months after CR was confirmed, and he continues in CR a year from cessation of therapy.

Case Report

A 68 year old gentleman presented in September 2013 with complaints of a left groin lump which revealed

metastatic melanoma on excision. No other metastatic disease was identified on imaging. Previously, he had lower back midline cutaneous melanoma treated with wide local excision and negative sentinel node biopsy in May 2012. He then developed recurrent disease in the left groin in March 2014 which was excised. PET/CT scan showed bulky right para-aortic and pericaval lymphadenopathy. He had rapid progression of symptoms with abdominal pain, early satiety and weight loss. Workup revealed a pancreatic mass which was biopsied and confirmed metastatic melanoma. Testing returned positive for BRAF V6000 mutation. He was started on treatment with Dabrafenib-Trametinib combination in May 2014. CT scan in June showed interval response to treatment. However, imaging study in November the same year showed progression with new abdominal lesions. He was switched to immunotherapy with Ipilimumab, beginning in December 2014. Follow up CT scan in February 2015 showed interval progression with a moderate left pleural effusion, a soft tissue mass between the greater curvature of the stomach and spleen measuring 9.3x8.9cm, a lobulated mass in the splenic hilum measuring 8.3x4.0cm and a new 2.1cm lesion in the right hepatic lobe as seen in figure 1A. Treatment was changed to Nivolumab beginning February 2015. Follow up scan in April, shown in figure 1B, showed interval response to treatment with decreased in size of the intra-abdominal masses. CT scan in June the same year showed resolution of the pleural effusion, splenic hilar mass and the hepatic lesion, and decrease in the size of the left upper quadrant mass now measuring 2.6 × 2.0 cm, shown in figure 1C. Subsequent scans showed continued shrinkage of metastatic lesion. CT scan in April 2016, shown in figure 1D, confirmed complete resolution of the metastatic lesion and no evidence of progression. Nivolumab was continued until late December 2016. He has been followed since then with serial imaging and labs and physical examinations, most recently done in November 2018, and has sustained his excellent response. He developed intermittent diarrhea while on Nivolumab which resolved with steroid therapy. Overall, he tolerated immunotherapy well.

Discussion

Multiple clinical trials have demonstrated remarkable improvements in outcomes of metastatic melanoma patients treated with anti-PD-1 antibodies, as summarized in table 1. In the phase III CheckMate-066 trial, Nivolumab demonstrated significant improvements in overall survival (OS) and Progression-free Survival (PFS) compared to chemotherapy in previously untreated BRAF mutation-negative metastatic melanoma patients [2]. The objective

response rate was 40% in the study arm versus 13% in the chemotherapy arm. In the CheckMate-037 study [3], Nivolumab therapy resulted in an objective response rate of 31.7% versus 10.6% in the chemotherapy group in metastatic melanoma patients who had progressed after Ipilimumab, or Ipilimumab and a BRAF inhibitor if they were BRAF mutation-positive. In this study, Nivolumab demonstrated durable responses and a mean duration of response of 32 months. The overall survival difference between the groups was not statistically significant, likely due to crossover therapy in the chemotherapy group. Checkmate-172 [4] was a single arm phase II study which demonstrated a twelve-week response rate of 32% with Nivolumab in Ipilimumab-refractory patients and an OS of 19 months (17-NR). The 1 year overall survival rate was 63%.

Figure 1A: CT image in February 2015 showing intra-abdominal lesions.

Figure 1B: Scan image in April 2015 showing partial response to treatment.

Figure 1C: Significant improvement in size noted in June 2015.

Figure 1D: Complete resolution of mass in scan in April 2016.

Long term follow up data of the earlier Nivolumab studies have shown encouraging results. Data from the phase I trial (CA209-003) [5] which enrolled 107 patients with previously treated advanced melanoma showed a median survival of 17.3 months for all patients enrolled in the study, and 20.3 months for those treated with the 3 mg/kg dosage. A majority of patients had visceral metastases and a third had elevated lactate dehydrogenase, a poor prognostic factor in advanced melanoma. 34% of patients were alive at 5 years. These findings indicate that Nivolumab induces a long-term memory response that contributes to survival.

Several case reports have been published documenting durable complete responses to anti-PD-1 therapy, with

both Nivolumab and Pembrolizumab [6-8]. The optimal duration of anti-PD-1 therapy in patients with complete responses is still unclear. Few studies have evaluated this question. Outcomes of patients who discontinued anti-PD-1 therapy were reported at the ASCO 2017 meeting. This single center retrospective study [9] included patients at Memorial Sloan Kettering Cancer Center (MSKCC) who received Nivolumab monotherapy or combination immunotherapy with Ipilimumab and Nivolumab. Complete response (CR) was achieved in 10% and 16% of patients in the respective groups. For all patients who achieved CR, the median time-to-treatment failure (TTF), median PFS and median OS were not reached, with a median follow up of 28 months. These durations were calculated from the time of administration of the first dose of immunotherapy. Even patients, who responded but did not achieve a CR, demonstrated a favorable PFS, TTF and OS.

In the KEYNOTE-001 trial [10], an open-label phase 1b trial, 105 (16%) of 655 advanced melanoma patients achieved CR with pembrolizumab after a median follow up of 43 months. 92 (87.6%) of the 105 patients remained in CR after a median follow up of 30 months from first declaration of CR. Pembrolizumab was discontinued by 91 patients (86.7%), including 67 (63.8%) who elected to stop treatment after CR and proceeded to observation without additional anticancer therapy. Of these 67 patients, 4 (6%) had progressive disease, and three of the four subsequently were treated with pembrolizumab. 61 of the 67 patients (91.0%) maintained CR after a median of approximately 2 years after pembrolizumab discontinuation. It is also worth noting that the CR rate was 42.7% in PD-L1 positive tumors less than 5 cm, and less than 10% in tumors larger than 10cm in this study.

KEYNOTE-002 [11] was a phase II trial that compared Pembrolizumab versus chemotherapy in patients with Ipilimumab-refractory disease. Two doses of Pembrolizumab were studied, 2 mg/kg and 10 mg/kg and both study arms demonstrated improved PFS compared to the chemotherapy arm. At 9months, about a quarter of patients assigned to Pembrolizumab were progression free (24% and 29%) compared to 8% in the chemotherapy arm. At the time of analysis, 92% and 87% of responders in the Pembrolizumab arms remained progression free, and hence the median duration of response was not reached.

The phase III KEYNOTE-006 trial [12] demonstrated a CR rate of 16.6% in Ipilimumab-naïve patients with

Table 1: Clinical trials evaluating anti-PD-1 antibody therapy in metastatic melanoma.

Study/Author	Description	Number of patients	Response rates (RR) in study arm	PFS (months)	OS (months)
Robert et al. [2]	Nivolumab in treatment naïve (CHECKMATE-066); Phase III RCT.	418	40%	5.1	NR
Larkin et al. [3]	Nivolumab in Ipi-refractory (CHECKMATE-037); Phase III RCT.	405	27%	3.1	16
Schadendorf et al. [4]	Nivolumab in Ipi-refractory (CHECKMATE 172); Phase II single arm.	734	32% at 1 year	-	19
Hodi et al. [5,14]	Nivolumab in Ipi-Naïve; Phase I trial.	107	34%	-	17.3
Rosner et al. [9]	Nivolumab+/-Ipi; Retrospective single center experience.	106 in Nivo 56 in Nivo-Ipi Total 162	38.7% 60.7%	12 34	25 NR
Robert et al. [10]	Pembrolizumab in Ipi-naïve or treated (KEYNOTE-001); Phase I trial.	655	16% CR	-	23.8
Ribas et al.[11]	Pembrolizumab in Ipi-refractory (KEYNOTE-002); phase II randomized trial.	540	21% in Pem 2mg/kg 25% in Pem 10mg/kg	5.4 5.8	-
Robert et al. [12]	Pembrolizumab in Ipi-naïve (KEYNOTE-006); Phase III RCT.	834	42%	NR	50% OS rate at 33 months

Abbreviations: PFS- progression-free survival; OS- overall survival; NR- not reached; RCT- randomized controlled trial.

metastatic melanoma with Pembrolizumab therapy. In this study, patients received Pembrolizumab therapy for a pre-specified 2 years or until disease progression. Median duration of response was not reached in the Pembrolizumab arm with a median follow up of 33.9 months for the total study population. 68% of the Pembrolizumab-treated patients had a response lasting 30 months or greater. The estimated PFS was 95% in patients who had achieved CR, 91 % in those with a partial response and 83% in patients with a stable disease respectively with a median follow up of 9.7 months after completion of Pembrolizumab. Longer follow up data is awaited.

In a recent retrospective study [13], the authors analyzed their experience with 29 patients who had ceased anti-PD-1 antibody therapy with either Pembrolizumab or Nivolumab, after achieving a CR and proceeded to observation. Three of the twenty nine patients had relapsed at a median follow up of 8 months. In the MSKCC study [9], patients who had discontinued immunotherapy for CR had not reached median TTF, PFS or OS at a median follow up of 28 months. This was a

highly selected group, accounting for 9 of 106 patients in the anti-PD1 monotherapy group.

Our patient achieved CR approximately 14 months after initiation of Nivolumab and continued the therapy for another 8 months. It was subsequently discontinued as he maintained CR, confirmed with imaging.

The anti-PD-1 antibodies Nivolumab and Pembrolizumab improve progression-free and overall survival rates in treatment naïve as well as heavily pre-treated metastatic melanoma patients. About a third of patients are alive at 5 years from start of treatment with these drugs. This compares with 22% of patients achieving long term durable benefit achieved with Ipilimumab. Both Ipilimumab and PD-1 inhibitors appear to induce memory responses that lead to long-term survival.

Discontinuation of anti-PD-1 therapy appears to be feasible in patients who achieve a CR as seen in the above studies. The majority of patients with a CR who went off immunotherapy maintained the response. Those who experienced a recurrence, regained a response on

retreatment with the anti-PD1 antibody drug, as observed in the CA209-003 phase I study [5,14]. Similar results were observed in the KEYNOTE-001 trial with Pembrolizumab [10].

Clinical questions remain pertaining to the duration of anti-PD-1 therapy to achieve CR, optimal duration of anti-PD-1 treatment in metastatic melanoma after achieving CR, optimal sequencing of checkpoint blockade, and efficacy of the alternate anti-PD-1 drug on progression with one agent. Longer follow up data on current trials will help answer some of these pertinent questions. Immunotherapeutic drugs are not without adverse effects although they are better tolerated than their chemotherapeutic counterparts and cause fewer grade 3 and 4 adverse effects. In the above mentioned clinical trials, only a small percentage of patients discontinued anti-PD-1 therapy due to side effects. The question of optimal duration of therapy also has significant implications from a pharmacoeconomic perspective. Additional clinical trials are necessary to answer these questions and help optimize the benefit of immunotherapy in patients with this lethal disease.

Disclosure

The author reports no conflicts of interest in this work.

References

- Agarwala SS. Current systemic therapy for metastatic melanoma. *Expert Rev Anticancer Ther.* 2009;9(5):587-595. Doi: <http://dx.doi.org/10.1586/era.09.25>
- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372(4):320-330. Doi: <http://dx.doi.org/10.1056/NEJMoa1412082>
- Larkin J, Minor D, D'Angelo S, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. *J Clin Oncol.* 2018;36(4):383-390. Doi: <http://dx.doi.org/10.1200/JCO.2016.71.8023>
- Dirk S, Paolo Antonio A, John BAGH, et al. Efficacy and safety of nivolumab (NIVO) in patients with advanced melanoma (MEL) and poor prognostic factors who progressed on or after ipilimumab (IPI): Results from a phase II study (CheckMate 172). *J Clin Oncol.* 35(15_suppl). Doi: http://dx.doi.org/http://ascopubs.org/Doi/abs/10.1200/JCO.2017.35.15_suppl.9524
- "OASIS," <http://www.abstractsonline.com/Plan/> *J Cancer Biol Therap,* 5(1): 217-222 (2019)
- ViewAbstract.aspx?mID=4017&sKey=371fa616-a0cf-4bf8-993d-ce424853b52c&cKey=616f965e-a236-4bd2-9f7a-6399bd6f3f6c&mKey=1d10d749-4b6a-4ab3-bcd4-f80fb1922267.
- Ascierto PA, Vanella V, Grimaldi AM, et al. Complete response to nivolumab monotherapy in a treatment-naive, BRAF wild-type patient with advanced mucosal melanoma and elevated lactate dehydrogenase: a case report from a phase III trial. *Cancer Immunol Immunother.* 2016;65(11):1395-1400. Doi: <http://dx.doi.org/10.1007/s00262-016-1898-2>
- Lipson EJ, Sharfman WH, Drake CG, et al. Durable cancer regression off-treatment and effective reinduction therapy with an Anti-PD-1 antibody. *Clin Cancer Res.* 2013;19(2):462-468. Doi: <http://dx.doi.org/10.1158/1078-0432.CCR-12-2625>
- Wyluda EJ, Cheng J, Schell TD, et al. Durable complete responses off all treatment in patients with metastatic malignant melanoma after sequential immunotherapy followed by a finite course of BRAF inhibitor therapy. *Cancer Biol Ther.* 2015;16(5):662-670. Doi: <http://dx.doi.org/10.1080/15384047.2015.1026507>
- Meeting Library | Meeting Library. <https://meetinglibrary.asco.org/record/149306/abstract>
- Robert C, Ribas A, Hamid O, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. *J Clin Oncol.* 2018;36(17):1668-1674. Doi: <http://dx.doi.org/10.1200/JCO.2017.75.6270>
- Daud A, Kang SP, Ebbinghaus S, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol.* 2015;16(8):908-918. Doi: [http://dx.doi.org/10.1016/S1470-2045\(15\)00083-2](http://dx.doi.org/10.1016/S1470-2045(15)00083-2)
- Robert C, Long GV, Schachter J, et al. Long-term outcomes in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab (pembro) treatment. *J Clin Oncol.* 2017;35(15_suppl):9504-9504. Doi: http://dx.doi.org/10.1200/JCO.2017.35.15_suppl.9504
- Ladwa R, Atkinson V. The cessation of anti-PD-1 antibodies of complete responders in metastatic melanoma: *Melanoma Research.* 2017;27(2):168-170. Doi: <http://dx.doi.org/10.1097/CMR.0000000000000336>
- One-Third of patients with advanced melanoma

survive at least 5 years after nivolumab treatment
- the ASCO post. <http://www.ascopost.com/issues/may-10-2016/one-third-of-patients-with-advanced-melanoma-survive-at-least-5-years-after-nivolumab-treatment>.

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