**Ipilimumab Prognostic Score in Progressive Metastatic Melanoma Patients. A Retrospective Analysis on Behalf of Italian Melanoma Intergroup**

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**Abstract**

**Background:** Ipilimumab is an option in Metastatic Melanoma patients in case of disease progression after antiPD1 treatment and BRAF+MEK inhibitors administration (for BRAF mutated melanoma). We evaluate the prognostic role of some relevant clinical or laboratories parameters for Ipilimumab used in late line after AntiPD1 progression to define patients that benefit most from Ipilimumab monotherapy in this setting.

**Methods:** A retrospective multicenter study was conducted in 8 Italian Oncology Centers, evaluating metastatic melanoma patients treated with Ipilimumab after AntiPD1 and / or BRAF plus Mek inhibitors progression. Endpoints were overall survival (OS) and Progression free survival (PFS), Kaplan Mayer and Cox regression were applied for survival analysis.

**Results:** Among patients that received AntiPD1 and-or Bramber inhibitors, 54 were treated with Ipilimumab monotherapy in 2nd/3rd line. Before Ipilimumab treatment, Number of metastatic sites were equal or less than 3 in 22 (40,7%) patients, ECOG Performance status was 0 in 32 (59%) patients, baseline LDH levels were within normal range in 25 (46,3%) patients, NLR (neutrophile/lymphocyte ratio) was equal or less than 0.7 in 33 (59%) patients. In Univariate analysis, ECOG PS >0 and NLR>0.7 resulted statistically significant good prognostic. In multivariate analysis for PFS, only NLR maintained statistically significance, while in multivariate analysis for OS both ECOG PS and NLR maintained a statistical significance. A score was counted for each patient considering the sum of number of negative factors associated with OS worse prognosis (ECOG PS>0, NLR more than 0.7). For patients with SCORE 0,1,2 median OS was respectively 11.4, 7.87 and 2.77 (p value<0.0001).

**Conclusions:** ECOG PS 0 and NLR<0.7 resulted prognostic factors associated with favorable OS of metastatic melanoma patients treated with Ipilimumab after AntiPD1 progression. Subgroup with all these factors has a better prognosis. These data can help treatment choice and should be evaluated prospectively.

**Keywords:** Metastatic Melanoma; Ipilimumab; prognostic score; anti-PD1; NLR ratio; immunotherapy
Introduction

Metastatic melanoma is one of the most aggressive solid tumors [1], and its management has been improved over the past few years thanks to new immune checkpoint inhibitors and targeted therapies [2-6]. Standard first line treatment of metastatic melanoma includes antibody targeting Programmed cell death protein 1 (PD1) Nivolumab or Pembrolizumab [2, 3], associated with Anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) Ipilimumab, and, in case of BRAF v600 mutation, the use of BRAF and MEK inhibitors [4-6]. In case of progression to first line treatments, one of the approved therapies that can be used is Anti-CTLA4 Ipilimumab, if not administered in first line in combination with other drugs. Ipilimumab is a recombinant human monoclonal antibody against CTLA-4 [7]. It affects the immune system by inhibiting the suppression of T-cell function. As a result, activated T-cells remain stimulated and can exert antitumor effects. In many trials, when it is used as monotherapy, Ipilimumab seems to maintain a durable clinical benefit in only about 15% of treated patients either if administered in first line [2] or second line [8], after progression to previous systemic treatments. It could be interesting to characterize the patients belonging to this 15% to optimize the use of available treatments and guarantee a long survival in this group of patients. Some patients treated with Anti-PD1 in first line show primary or acquired resistance to Anti-PD-1 therapy, and biologic modality of resistance; best treatments after progression are arguments of research [9, 10]. Several studies are currently underway to evaluate the use of multiple combinations of experimental immunomodulating drugs in case of progression to Anti-PD1, and many of these trials involve the use of drug combinations including Anti-CTLA4, investigating whether these combinations can achieve greater efficacy [11-17]. Only limited evidence is available regarding the efficacy of Ipilimumab in patients who progressed after Anti-PD-1 therapy [18-20]: it would be optimal to know in advance which patients are most likely to achieve maximum efficacy with Ipilimumab monotherapy alone. The present study is a multicenter retrospective analysis conducted in multiple Italian Centers, in which we collected data related to patients with metastatic melanoma treated with Ipilimumab after treatment with Anti-PD1 and with BRAF and MEK inhibitors if BRAF mutated: our goal is to identify clinical characteristics or routine laboratory facilities tests which may have a prognostic connotation regarding the efficacy of ipilimumab; this analysis may potentially help clinicians in choosing Ipilimumab monotherapy in this setting instead of other experimental combinations in specific subgroups of patients.

Patient Population

We conducted an institutional review board-approved, multicenter retrospective study regarding patients treated with at least one dose of Ipilimumab after prior Anti-PD-1 therapy failure, between July 2017 and January 2020. Patients were accrued in 10 referral centers in Italy, in collaboration with Italian Melanoma Intergroup scientific society. Each participating center identified patients via pharmacy databases or medical records. Patients were enrolled in data collection if the following criteria were identified: histologically-proven unresectable stage IV melanoma following American Joint Committee on Cancer (AJCC) 8th edition criteria, previous treatment with Anti-PD1 used as systemic treatment for metastatic setting, in case of patients affected by BRAF v600 mutated melanoma BRAF+MEK inhibition treatment could be administered, documented disease progression on prior anti-PD-1 therapy and BRAF+MEK inhibition if administered as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, received at least one dose of Ipilimumab as systemic treatment after Anti-PD1 progression (and after BRAF+MEK inhibition progression, if administered).

Study Design

We collected data from enrolled patient regarding the following items: baseline characteristics (demographics, age, sex, AJCC stage, BRAF mutational status, date of metastasizing, extent of metastasizing), previous systemic therapies administered in adjuvant setting, previous Anti-PD1 therapy administered in first line (date of first cycle, best response assessed, date of disease progression). The following clinical and laboratory potential prognostic factors were documented before Anti-PD1 therapy and more importantly before Ipilimumab treatment: Eastern Cooperative Oncology Group (ECOG) performance status, Neutrophile Lymphocyte Ratio (NLR), serum lactate dehydrogenase level (LDH) and presence of more than 3 metastatic sites. Ipilimumab treatment was administered at the approved dosing of 3 mg/kg every 3 weeks for four intravenous infusions. Efficacy endpoints of Ipilimumab therapy were RECIST 1.1 response, Progression Free survival (PFS) and Overall Survival (OS).

Statistical Methods

Ipilimumab response was evaluated using RECIST criteria and categorized as complete response [CR], partial response [PR] and stable disease [SD] to progression. The overall response rate (ORR) was defined as the proportion of patients with PR and CR, whereas the disease control rate (DCR) was defined as the proportion of patients with CR, PR, and SD. PFS was defined as the time from the first dose of ipilimumab to the first date of documented progression as per RECIST, or date of death, whichever came first. Patients last known to be alive and progression-free were censored at the date of last contact (all in January 2020). OS was defined as the time from the first administration of ipilimumab to death from any cause. Patients last known to be alive were censored at the date of last contact (all in January 2020). PFS and OS were estimated by the Kaplan Meier method. Log-rank tests were used to compare PFS and OS between several subgroups based on characteristics collected prior to the first cycle of Ipilimumab: ECOG (0 versus >0), LDH level (<upper limit of normal (ULN) versus > ULN), best response prior to Anti-PD1 therapy (CR/PR/SD versus progressive disease (PD)), and number of metastatic sites (<=3 versus > 3). Two-sided p-values were evaluated and a p-value of <0.05 was considered statistically significant. Analyses were carried out using SAS software, version 9.4. (Cary, NC). All categories that identified subgroups statistically significant different in terms of
Ipilimumab efficacy were considered in a multivariate analysis to identify independent factors. Independent prognostic factors that were detected by multivariate analysis were used to build up a prognostic score. To each patient was assigned a score based on the number of favorable prognostic factors. PFS and OS of different score subgroups were collected.

**Results**

**Patients and efficacy of prior Anti-PD-1 therapy**

Between July 2017 and January 2010, among patients progressed after AntiPD1, 54 patients were treated with at least one dose of Ipilimumab after treatment failure to prior Anti-PD-1 therapy. Baseline patients’ characteristics before the first administration of Ipilimumab are reported in (Table 1). The median age at the time of Ipilimumab first cycle was 65 years (range 21-85); most patients were males with cutaneous primary sites. BRAF mutational status was wild type in 43 (79%) patients. Most of the patients had AJCC stage M1c; brain metastasis (M1d AJCC stage) was present in 6 (11%) patients, M1a and M1b AJCC stage was present in 5 (9%) and 10 (18%) respectively. Number of metastatic sites were equal or less than 3 in 22 (40,7%) patients. ECOG Performance status prior first Ipilimumab cycle was 0 in 32 (59%) patients. Baseline LDH levels were within normal range in 25 (46,3%) patients. NLR ratio was equal or less than 0.7 in 33 (59%) patients, and not analyzable (data not detected in medical records) in 6 (11%). All patients received Anti-PD1 prior to Ipilimumab. As described in (Table 2), the response rate of Anti-PD1 administered in first line was 41% (with 4% as Complete response) and the disease control rate was 68%.

**Table 1: Patient characteristics: characteristic documented before first ipilimumab cycle.**

| Characteristic                                      | Absolute Value | %     |
|-----------------------------------------------------|----------------|-------|
| Sex (male/female)                                   | 25 (59,5%)     | 17 (40,4%) |
| Median age (range: min-Max)                         | 65 years (21-85) |       |
| ECOG Performance status (0/1/2) prior first AntiPD1 treatment | 23 (53,4%) / 18 (41,9%) / 2 (4,6%) | - |
| BRAF mutational status (wild type/ v600E mutated/ v600K mutated/ v600d mutated) | 43 (79%) / 8 (14%) / 1 (2%) / 2 (4%) | - |
| Primary site                                         | 46 (85%) / 1 (2%) / 3 (5%) / 4 (7%) | |
| Skin /Mucosal /Uveal/Unknown primary                 |                |       |
| Baseline LDH (within normal range/ over normal range) | 25 (46,3%) / 29 (53,7%) | - |
| ECOG Performance status (0/1/2) prior first AntiPD1 treatment | 23 (53,4%) / 18 (41,9%) / 2 (4,6%) | - |
| ECOG Performance status (0/1/2) prior first ipilimumab cycle | 32 (59%) / 18 (37%) / 2 (4 %) | - |
| NLR ratio (<= 0.7 / >0,7 / NA)                      | 33 (59%) / 15 (28%) / 6 (11%) | - |
| Number of metastatic sites (<=3, >3)                | 22 (40,7%) / 32 (59,3%) | - |
| AJCC Stage IV- M1a/M1b/M1c/M1d                      | 5 (9%) / 10 (18%) / 33 (61%) / 6 (11%) | - |
| Prior systemic therapy: AntiPD1/ AntiPD1+ experimental therapy (NTKR-vaccine)/ BRAF+MEK inhibitor | 40 (74%) / 3 (5%) / 11 (20%) | - |
| Number of prior therapies                            | 40 (74%) / 12 (22%) / 2 (4%) | |

**Response rate and disease control rate.**

| Response to first line AntiPD1 | Absolute value | % | Response to Ipilimumab, after AntiPD1 | Absolute value | % |
|---------------------------------|----------------|---|---------------------------------------|----------------|---|
| CR                              | 2              | 4 |                                       | 1              | 2 |
| PR                              | 20             | 37|                                       | 6              | 11|
| SD                              | 15             | 28|                                       | 13             | 24|
| PD                              | 15             | 28|                                       | 34             | 63|
| RR (CR+PR)                      | 22             | 41|                                       | 7              | 13|
| DCR (CR+PR+SD)                  | 37             | 68|                                       | 20             | 37|

**Efficacy of Ipilimumab**

After Anti-PD-1 failure, the median follow-up for all patients after commencement of Ipilimumab was 12.1 months (range 1 to 33,2 months) (median follow-up was calculated with reverse Kaplan Meier estimation).

As described in (Table 2), with Ipilimumab treatment DCR was 37%, ORR was 13%. Thirty-three patients (61%) in the Ipilimumab group received all four doses of ipilimumab, 16 patients (29%) stopped treatment before third cycle due to tumor progression and/or clinical deterioration. None of the patient is still on treatment.
Median PFS in total population of patients treated with ipilimumab was 3.3 months, with 1- and 2-year PFS rate of 24% (95%CI 14-38%) and 24% (95%CI 14-38%) respectively. Median OS in total population was 9.4 months, with 1- and 2-year OS rate of 32.2% (95%CI 17.9-47.2%) and 24.2% (95%CI 9.2-42.9%). Considering subgroups, median PFS was higher in ECOG 0 patients compared to patients with ECOG 1 and 2 (3.97 months versus 2.97 months, HR 0.482, 95% CI of ratio 0.246 to 0.946, p 0.0339, (Figure 2a); in patients with less than three metastatic sites compared to patients with more than three metastatic sites (3.5 months versus 3.27 months, HR 0.524 95% Cl of ratio 0.279 to 0.964, p 0.0445, (Figure 2c); in NLR <0.7 patients compared to patients with NLR > 0.7 (4.77 months versus 2.43 months, HR 0.223 95% CI of ratio 0.093 to 0.535, p 0.0008, (Figure 2d). LDH prior to Ipilimumab therapy, and best response to prior anti-PD-1 therapy were not associated with PFS (figure 2b, 2e). Median OS was higher in ECOG 0 patients compared to patients with ECOG 1 or 2 (11.4 months versus 4.07 months, HR 0.301 95% CI of ratio 0.141 to 0.644, p 0.002 (Figure 3a), in NLR <0.7 patients compared to patients with NLR > 0.7 (11.17 months versus 3.63 months, HR 0.161 95%CI of ratio 0.058 to 0.460, p 0.0006, (Figure 3d). LDH prior to ipilimumab therapy, best response to prior anti-PD-1 therapy and number of metastatic sites were not associated with OS (figure 3b, 3c, 3e).
Multivariate analyses were conducted considering factors that resulted statistically significant in previous univariate analysis. In table 3a multivariate analysis for PFS is reported: between all factors that resulted statistically significant in univariate analysis only NLR maintained statistically significance in multivariate analysis. In table 3b multivariate analysis for OS is reported: both ECOG

Figure 3: OS in Subgroup.

Figure 4: Based on Score.
Table 3 (a): Multivariate analysis for PFS.

| Variable          | Univariate | Multivariate |
|-------------------|------------|--------------|
| ECOG PS (0; >0)   | 0.037      | 1.488        |
| NLR (≤0.7; >0.7)  | 0.0014     | 3.07         |
| N° MTS (≤3; >3)   | 0.049      | 1.843        |

Table 3 (b): Multivariate analysis for OS.

| Variable          | Univariate | Multivariate |
|-------------------|------------|--------------|
| ECOG PS (0; >0)   | 0.0031     | 2.924        |
| NLR (≤0.7; >0.7)  | 0.0014     | 3.508        |

Discussion

The treatment algorithm for patients suffering from affected by metastatic melanoma is constantly evolving. Although much debate has been focused on the optimal choice of first-line systemic treatment, many options are also available regarding subsequent lines of treatment and clinicians must choose which drug to administer in case of progression after using Anti-PD1 in the metastatic setting [2-6]. Our study investigates patients with metastatic melanoma who progressed to Anti-PD1 and eventually to BRAF and MEK inhibitors if BRAF v600 mutated: in this setting the standard treatment is Ipilimumab at a dose of 3 mg/kg every 21 days for 4 total cycles; further alternatives are chemotherapeutic treatments; finally, experimental drugs are investigated within ongoing clinical trials. Among these options, chemotherapy has limited activity. Experimental treatments often consist in combination regimens of several drugs; often these regimens are associated with a higher incidence of toxicity compared to monotherapies: now, however, these combinations are the topic of ongoing trials and they can be only administered among enrollment in experimental protocols [11-17]. In this setting it is therefore further useful to be able to identify those patients with a high probability of obtaining good disease control using Ipilimumab. Treatment with Ipilimumab is associated with several advantages: its use is now well established, and clinicians are experienced in the management of its toxicity, in case of efficacy after a total of 4 cycles the patients continue with only follow-up. In patients who get disease control for 3 years, we can reasonably expect to have disease control that will last over time. Unfortunately, in each study reported in literature only about 15% of the patients treated with Ipilimumab shows good disease control: the great difficulty for the scientific community is to identify these patients. Even in the setting of Anti-PD1 progressed patients, the knowledge of clinical or laboratory prognostic factors connoting Ipilimumab responders could help clinicians to choose more easily the treatment to use among the available drugs.

As illustrated in figure 4, OS was significantly higher in patient with score 0 then patient with score 1 or 2. Median OS for patient with score 0, 1 or 2 were respectively 11.4, 7.87 and 2.77 respectively (p value < 0.0001) (Figure 4)
conversely an inactivity of Ipilimumab in those who have had a low efficacy of AntiPD1 does not seem obvious. On the other hand, it is the current characteristics at the time of undertaking the next treatment line with Ipilimumab that prognostically characterize patient’s prognosis.

Recently, some studies have tried to investigate the efficacy and activity of the combination of Ipilimumab with Anti-PD1 on progression after Anti-PD1. In the retrospective study by Zimmer et al, this combination was compared with the use of Ipilimumab alone and no data of efficacy of the combination emerged compared to ipilimumab monotherapy, in the face of greater toxicity of the combination [8]. Other trials were recently presented at the American Society of Clinical Oncology 2020 conference evaluating the use of antiPD1 plus Ipilimumab in progression after antiPD1. In the phase II study of Olson et al, Pembrolizumab at 200 mg combined with Ipilimumab 1 mg / kg every 21 days was administered [11]. Data show a median PFS of 5 months and a median OS of approximately 24.7 months comparable to what was obtained in our study in the subgroup at score 0. Da Silva presented the results of a study in which patients who progressed to Anti-PD1 received Ipilimumab alone or in combination with Anti-PD1 [12]; from the comparison it would seem to highlight an advantage in terms of OS and PFS for the combination, but the population investigated in this study also included patients progressing to AntiPD1 used in the adjuvant setting, and it is not possible to evaluate how much this component of the population affected the results.

In any case, if we compare the results of these trial to our casuistic, in the 0-score population of our study, we observed a relationship between efficacy and toxicity profile that is competitive when compared to the more much toxic AntiCTLA4 plus AntiPD1 combination regimen. Further studies to identify which subgroups benefit most from Anti-CTLA4 monotherapy or the combination of Anti-CTLA4 and Anti-PD1 are required. Our study has some limitations. First, it is a retrospective study, and therefore it presents the typical biases of all retrospective studies. Follow-up is not comparable to that of first-line Ipilimumab studies, but we believe that the setting (second line after Anti-PD1 and BRAF-MEK inhibitors) may justify shorter follow-up times for conducting analyzes. The use of Ipilimumab in combination with Anti-PD1 in the first line is becoming increasingly widespread, therefore the population investigated (treated with Anti-PD1 or BRAF and MEK inhibitors in sequence) in the current population of patients with metastatic melanoma and progressed to previous lines will be a minority, as more and more patients will have already been treated with Ipilimumab in combination with other immunotherapy: however we believe that in the near future there will always be a space for the use of Ipilimumab in the second line, because there will be still patients treated in first line with Anti-PD1 monotherapy or AntiPD1 in combination with drugs other than Ipilimumab: for such patients the disquisitions of this study may possibly be applicable and useful for the choice of undertaking Ipilimumab monotherapy or not. In conclusion, in our multicenter retrospective study, metastatic melanoma patients previously treated with Anti-PD1 inhibitors and treated with Ipilimumab have a better prognosis in the presence of ECOG PS 0, NLR <0.7 at the time of Ipilimumab first cycle; we do not recommend its use in the total absence of these parameters, preferring in such cases any therapeutic alternatives.

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