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Nivolumab in metastatic melanoma: good efficacy and tolerability in elderly patients

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ABSTRACT

Background Nivolumab is an anti–PD-1 antibody that restores the antitumour immune function of T cells, blocking the binding of PD-1 with its ligand PD-L1. PD-1 is expressed on T cells and interacts with PD-L1 on tumour cells. The PD-1–PD-L1 link inhibits T cell activation. In metastatic melanoma, PD-1–PD-L1 binding plays a critical role, and the advent of the immune checkpoint inhibitor nivolumab has delivered new and effective treatment options with proven clinical benefit. In the present study, we evaluated the efficacy of nivolumab in elderly patients with metastatic melanoma.

Methods The study enrolled 55 elderly patients (75 years of age and older) with a diagnosis of metastatic melanoma. Primary endpoints of the study were progression-free survival (PFS) and the objective response rate; secondary endpoints were overall survival, reduction in serum lactate dehydrogenase (LDH) from before to after treatment, and tolerability.

Results Nivolumab was well tolerated and resulted in good disease control, with a manageable toxicity profile and significant clinical benefit. The duration of PFS was 5.1 months (95% confidence interval: 3.5 months to 6.8 months). A significant correlation was observed between reduction in serum LDH and PFS: 0.60 (95% confidence interval: 0.28 to 0.86; $p = 0.002$).

Conclusions Nivolumab is an immunotherapy treatment that has proved to be an effective and well-tolerated therapeutic option in elderly patients with metastatic melanoma.

Key Words Nivolumab; melanoma, metastatic; elderly patients; immunotherapy; quality of life; clinical benefit; lactate dehydrogenase

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INTRODUCTION

Melanoma is a neoplasm of melanocytes in skin and, more rarely, in mucous membranes, associated with a poor prognosis in patients diagnosed with metastatic disease. As for many other neoplasms, the incidence of melanoma increases with age, leading to an increasing prevalence of melanoma in the older population of both sexes[1,2]. Meanwhile, thanks to prevention and new immunologic therapies, the mortality rate has declined.

Various genetic mutations are involved in the development of melanoma, with *BRAF* V600E mutation occurring in 40%–50% of cases, and *NRAS* or *c-KIT* mutations also being seen. The presence of *BRAF* V600 mutation allows for the use of drugs directed against the mutated BRAF protein and the MEK protein (downstream in the cascade), which in turn is aberrantly activated. The mutated BRAF and MEK proteins can be specifically targeted with drugs that inhibit their activity, thus interrupting melanoma cell proliferation[3,4].

The increase in melanoma rates and the lack of effective and tolerable treatments have made management of melanoma in elderly patients very difficult. Malignant melanoma is resistant to radiation therapy and cytotoxic chemotherapy. Before the advent of targeted therapies and immunotherapy, median overall survival (OS) in advanced disease was less than 1 year[5,6]. In particular, treatment with cytokines such as interleukin 2 showed limited efficacy, with severe toxicity. Recently, immune checkpoint inhibitors, with their good efficacy and tolerability profile, have revolutionized the treatment of melanoma[7-9]. They represent the most promising therapeutic options for the treatment of melanoma.

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The main classes of immune checkpoint inhibitors include the CTLA-4 inhibitors such as ipilimumab and the PD-1 inhibitors such as nivolumab and pembrolizumab[10,11]. Nivolumab is a completely human anti–PD-1 monoclonal antibody that blocks the interaction of PD-1 with its ligands PD-L1 and PD-L2 by improving the T cell response, including the antitumour response.

To protect the body physiologically from immune reactions, PD-1 inhibitors introduce a protein expressed on CD8 and CD4 activated T lymphocytes[11,12]. The interaction of PD-1 with PD-L1 and PD-L2 expressed by the tumour cell involves the inhibition of T cell proliferation and cytokine secretion. Two studies of the safety and efficacy of nivolumab for the treatment of advanced (non-operable or metastatic) melanoma have been published[13,14]. In the phase III randomized double-blind CheckMate 066 study, patients with treatment-naïve disease were randomized to receive first-line nivolumab or dacarbazine. The observed OS benefit was significantly higher in the nivolumab group (1-year survival rate: 73% vs. 42% with dacarbazine). Progression-free survival was also superior in the nivolumab arm (median: 5.1 months vs. 2.2 months), as was the objective response rate (40% vs. 14%)[13]. The phase III double-blind CheckMate 037 study randomized patients to receive treatment with nivolumab or chemotherapy (dacarbazine or carboplatin–paclitaxel). The results demonstrated the superiority of nivolumab compared with chemotherapy[7,15,16].

Recent therapeutic advances and discoveries have revolutionized the treatment of metastatic melanoma, but in elderly patients with advanced melanoma, data about efficacy, safety, and tolerability are still lacking[17]. Most studies have not performed subgroup analyses based on age groups, and patients more than 75 years of age are rarely included. The current therapeutic approach for elderly patients with metastatic melanoma therefore closely resembles that for younger patients[18]. A comprehensive geriatric assessment is useful for determining which older adults are able to undergo the various systemic treatments available[19,20]. The recommendations of the International Society of Geriatric Oncology related to the updated (2014) geriatric evaluation[21] indicate an association of assessment with survival and provide comparisons between the methods of selection, both physical and psychological, for elderly patients who can better respond to cancer treatment. In our retrospective study, we set out to evaluate the safety and efficacy of nivolumab in elderly patients diagnosed with metastatic melanoma.

METHODS

Study Design

In this observational study, information from the medical records of elderly patients with metastatic melanoma were retrospectively collected and analyzed to evaluate the efficacy and tolerability of nivolumab as frontline therapy. The primary endpoints analyzed were PFS and the objective response rate. Secondary endpoints were OS, decline in serum LDH from before to after treatment, and tolerability. The trial was performed in accordance with the provisions of the Declaration of Helsinki and guidelines for good clinical practice.

Patient Selection

The study enrolled 55 patients more than 75 years of age who were diagnosed with metastatic melanoma between January 2013 and January 2018 in the medical oncology unit of the University of Palermo and ARNAS Ospedali Civico in Palermo, Italy. Evaluation of *BRAF* mutational status showed 21 patients with wild-type and 34 patients with mutated *BRAF*. These elderly patients with advanced melanoma had not previously been treated.

All patients had to meet these inclusion criteria:

- Histologic and cytologic diagnosis of melanoma, unresectable, stage III or IV
- Age greater than 75 years
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1
- Clinical or radiologic evidence of measurable metastatic disease (1 or more lesions) by spiral computed tomography imaging or magnetic resonance imaging, in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1[22]
- Laboratory results within these parameters: neutrophils greater than 2.0×10^9/L, platelets greater than 100×10^9/L, hemoglobin greater than 10 g/dL, creatinine less than 1 mg/dL [the upper limit of normal (ULN)], creatinine clearance greater than 60 mL/min if creatinine was above the ULN, bilirubin less than 1×ULN, aspartate transaminase and alanine transaminase both less than 5×ULN, and alkaline phosphatase less than 5×ULN, except in the presence of bone metastasis

In accordance with previous studies[23,24], we excluded patients from the study if they

- were hypersensitive to nivolumab and its excipients, or to other components of the formulation.
- had ocular and uveal melanoma only.
- had active brain metastases or leptomeningeal metastases.
- had an active autoimmune disease or a condition requiring corticosteroids or immunosuppressive medication within 14 days of study drug administration.
- had been diagnosed and treated for other malignancies, with the exception of basal cell carcinoma of the skin.
- had severe inadequately controlled comorbidities.

Furthermore, before patients started treatment, use of systemic corticosteroids and other immunosuppressants was avoided because of their potential interference with pharmacodynamic activity.

Study Assessments

Evaluation of Response and Toxicity

The evaluation of response rates in terms of reduction of measurable pathology, according to the Response Criteria of Solid Tumor Response, version 1.1[22], was conducted at the beginning of treatment and then every 3 months until disease progression. Furthermore, during evaluation of the response, the delayed effect of 2 or 3 months for nivolumab

compared with chemotherapy was taken into account in patients experiencing rapid disease progression. Spiral computed tomography imaging was performed in every patient before treatment start and then every 3 months on average or coinciding with presumed progression. Positron-emission tomography was performed in selected cases at the discretion of the physician. In the case of brain metastasis, magnetic resonance imaging was performed every 6–12 weeks.

Dose escalation or reduction was not allowed. Dose interruptions were permitted to manage treatment-related adverse events. Patients were assessed for safety if they received any study treatment. At baseline, local laboratory assessments were conducted 14 days before randomization, and safety assessments were conducted throughout the treatment phase. Drug-related toxicities were graded in accordance with the *Common Terminology Criteria for Adverse Events,* version 4.0[25].

Treatment continued until clinical benefit was observed or until treatment was no longer tolerated. Furthermore, the response percentage (in terms of serum LDH enzyme reduction) was evaluated by comparing the mean scores for serum LDH before and at the end of treatment. An increase in LDH was defined an increase of 25% or more compared with baseline values in patients who did not experience a significant reduction (≥50%) in serum LDH during treatment, or an increase of 50% or more from the lowest level observed in patients who achieved a significant reduction (≥50%) in serum LDH during treatment.

A multidisciplinary geriatric assessment performed by the geriatricians evaluated somatic comorbidity, functional status and level of autonomy, cognitive functioning, and depressive symptoms. The evaluation was performed during the clinical interview with the patient and family, using validated tests and scales that allowed for an objective evaluation of age-related clinical problems.

Nivolumab Administration

Nivolumab was administered intravenously for a period of 60 minutes at a dose of 3 mg/kg every 2 weeks. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Patients with progressive disease were started on a new line of treatment. In cases of suspected immune-related adverse reactions, an appropriate clinical evaluation was performed to confirm the cause and to rule out non-immune-related causes. Based on the severity of the adverse reaction, nivolumab was discontinued and corticosteroids (prednisone, dexamethasone, methylprednisolone) were administered for at least 1 month and then gradually tapered. If symptoms were worsening, non-corticosteroid immunosuppressive therapy was added. Antibiotic prophylaxis was used to prevent infections. During the entire treatment period, the patient was advised to maintain adequate hydration to prevent complications such as renal failure. Before starting nivolumab treatment and periodically, patients also received instrumental and hematochemical controls for thyroid (thyroid stimulating hormone, free T3 and T4), adrenal gland (cortisol, adrenocorticotropic hormone), kidney, and pancreas.

Under clinical practice procedures, a neutrophil count less than 1.5×10^9/L, a platelet count less than 100×10^9/L, a hemoglobin level less than 8.5 g/dL, and a bilirubin or transaminase level greater than 1.5×ULN triggered postponement of therapy for up to 2 weeks. In the case of neutropenia (grades 2–3), granulocyte colony–stimulating factor was administered subcutaneously. In the case of anemia, blood transfusions were performed (grades 3–4) or erythropoietin was administered subcutaneously (grade 2). Finally, in the case of thrombocytopenia, platelet infusions were administered intravenously. In severe cases of thrombocytopenia (grade 4), cortisone was administered for immune-related toxicity. Most immune-related adverse reactions improved or resolved with appropriate measures (corticosteroid administration or treatment change).

Statistical Analysis

Descriptive statistics provide a sociodemographic representation of the study cohort and explore the distribution of the variables being evaluated. Normality of the distribution was verified using univariate kurtosis and asymmetry indices with an acceptance threshold of 1. No variance violated the normality indices.

Inferential statistical analyses were performed to detect the existence of significant associations between the variables being evaluated. Disease control was defined as the proportion of patients achieving an objective response or stabilization of disease overall or over 6 months. The PFS was calculated by the Kaplan–Meier method from the start of treatment to disease progression, death from any cause, or the date of the last PFS follow-up. The study end date was December 2018.

Serum LDH before and after treatment was compared by the paired-samples *t*-test. Reduction in serum LDH was considered clinically relevant if at least a 25% decline was reached compared with baseline, with an alpha of 5% and a statistical power of 80%. In addition, the Bravais–Pearson linear correlation index *(r)* was used to measure the intensity of the relation between PFS and LDH, with a 95% confidence interval (CI). Considering the sample amplitude, parametric statistics were used, and a threshold value of 0.05 was considered to indicate significance. All statistical analyses were carried out in the IBM SPSS Statistics software application (version 24.0: IBM, Armonk, NY, U.S.A.).

RESULTS

Treatment Exposure and Follow-Up

At the time of diagnosis, patients were more than 75 years of age (mean: 78 years), with 68% being women, and 32% being men. All were white. All patients has metastatic disease, and the primary melanoma sites were mucosal ($n = 2$) and cutaneous ($n = 53$). Before immunotherapy, metastatic site involvement included lymph nodes ($n = 54$), viscera ($n = 16$), and central nervous system ($n = 1$). The ECOG PS was 0 in 64% of the patients and 1 in 36% (Table I).

All enrolled patients underwent surgery for the primary tumour or for sentinel lymph node biopsy. No patient died from treatment-related adverse events. Efficacy was assessed considering that the onset of therapeutic effect is delayed (equivalent to the effect of 2–3 months of chemotherapy). After an average follow-up of 12.1 months (range: 3–18 months), 35% of the patients achieved a partial

TABLE I Baseline demographic and clinical characteristics for 55 elderly patients

Characteristic	Value
Age (years)	
Mean	78
Range	75–84
Sex (%)	
Men	32
Women	68
Tumour site *(n)*	
Cutaneous	53
Mucosal	2
ECOG PS (%)	
0	64
1	36
Serum LDH (ng/mL)	
Median	450
Range	200–2057
Relative to ULN (%)	
Exceeds	86
Less than or within	14
Metastatic site or sites *(n)*	
Central nervous system	1
Visceral	16
Lymph nodes	54
BRAF status *(n)*	
Wild type	21
Mutant	34

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; ULN = upper limit of normal.

response, 13% achieved a complete response, and 15% showed disease stabilization. The remaining 37% experienced disease progression. Nivolumab treatment was well tolerated and was associated with a good level of disease control (partial response + complete response + stable disease > 50%). Median time to response was 3.8 months (95% CI: 1.7 months to 7.2 months), with significant clinical benefit [objective response rate (partial response + complete response): 48%].

The results of the present retrospective analysis suggest that efficacy and safety results for nivolumab are similar whether elderly patients have wild-type or mutant *BRAF*.

LDH Reduction

During treatment in this cohort of patients, serum LDH declined to the normal range. Analysis of serum LDH showed that, after nivolumab treatment, more than 50% of the patients experienced a reduction from the baseline level of this enzyme—results that were linked to better response to nivolumab. Specifically, the average reduction was 50% (95% CI: 49.50% to 60.9%). To evaluate the LDH response, a paired-samples *t*-test was used to analyze mean serum LDH before and after nivolumab treatment, and LDH was significantly lower after treatment ($t = 13.84$, $p < 0.01$, Table II).

OS Rate Analysis

The median OS could not be calculated because only 24% of the patients had died at the time of the interim survival analysis (last follow-up in December 2018). We then proceeded with an analysis of the OS rate, which yielded a 1-year survival rate of 68%.

PFS Analysis

The median PFS was 5.1 months (95% CI: 3.5 months to 6.1 months; Figure 1), and a positive association of PFS with LDH was observed. In fact, the Bravais–Pearson index demonstrated good correlation between those two variables at 0.60 (95% CI: 0.28 to 0.86; $p = 0.002$; Table II).

Tolerability

In terms of treatment-related toxicity, nivolumab was well tolerated, and after each course of therapy, adverse events were evaluated and reported in accordance with the *Common Terminology Criteria for Adverse Events*, version 4.0[25]. All patients continued treatment until progression or unacceptable toxicity. No patient died from treatment-related adverse events. Most of the adverse reactions related to the immune system were resolved with the application of

TABLE II Average serum lactate dehydrogenase (LDH) in 55 elderly patients before and after treatment with nivolumab

Time of testing	Serum LDH		
	Mean	*t*[a]	*p* Value[a]
Before treatment	460±78.98	13.84	0.006
After treatment	200±6.17		

[a] By paired samples *t*-test.

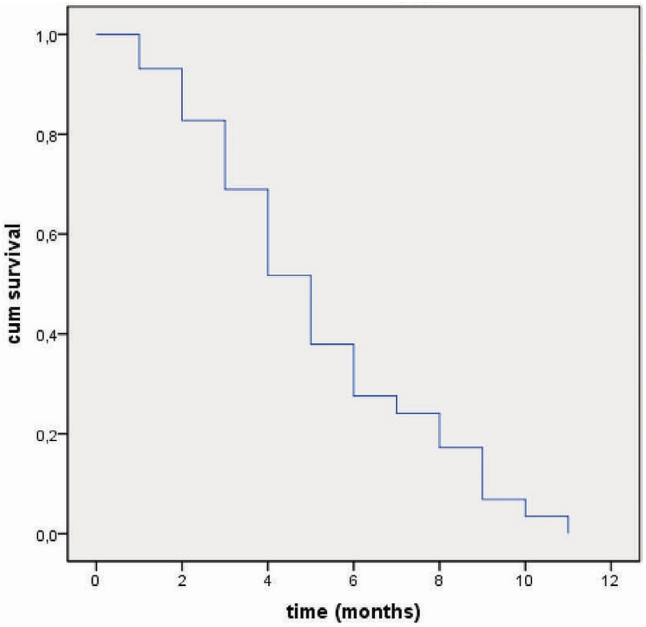

FIGURE 1 Kaplan–Meier plot of median progression-free survival (5.1 months; 95% confidence interval: 3.5 to 6.1 months) for 55 elderly patients (interim analysis).

established safety guidelines. All immune-related toxicities were successfully treated with immediate discontinuation of nivolumab and the administration of cortisone in doses that gradually increased as necessary.

In 1 patient, only a single administration of nivolumab was delivered because, when three quarters of the infusion was complete, he experienced an adverse reaction, with tachypnea, cough, and hypertension. In 3 patients, grades 2–3 skin lesions appeared, and in 1 case of grade 4 lesions, administration of antihistamine and steroids was required. The immune-related endocrine toxicities were statistically the most significant. Thyroid dysfunction in 3 patients was treated by the endocrinologist with levothyroxine, and grade 2 adrenal insufficiency occurred in 1 patient. In 2 patients, grades 2–3 immune-related colitis was refractory to steroids, rifaximin, and loperamide, and electrolyte infusion therapies were required. An initial presentation of abdominal pain and diarrhea in 1 patient was treated with loperamide, rifaximin, and prednisone. After aggravation of those symptoms, together with the appearance of blood in the stool, intravenous methylprednisolone 125 mg was administered, with resolution of the symptoms (Table III).

Clinical benefit of nivolumab therapy was assessed based on PS (obtained at treatment start and every 3 weeks thereafter), pain index, weight, analgesic consumption, and use of palliative radiotherapy. In patients who required a comprehensive geriatric assessment, results showed no physical and psychological limitations or contraindications to nivolumab treatment. The assessment was undertaken in 40% of patients, revealing a mean score on the screening tool of 11.5 ± 1.98 (range: 2.5–16.0). The results of a pain assessment on a visual analog scale administered by the geriatric team showed reduction in pain in 54% of patients and a reduction in the use of analgesics. Moderate cognitive impairment and depressive symptoms were observed in 24% and 20% of patients respectively.

DISCUSSION

The prevalence of melanoma in elderly patients is on the rise because of an increasing incidence in the general population and improved population life expectancy[19,26]. The introduction of immunotherapy is increasing the percentage survival in elderly patients as well as in the cohort of patients with melanoma overall. The literature confirms that monotherapy with nivolumab leads to an OS and PFS benefit overall and also for elderly patients[6]. In our study, treatment continued until clinical benefit was observed or nivolumab was no longer tolerated. The most frequent and serious adverse reactions during nivolumab treatment were predominantly immune-related and were resolved with treatment discontinuation and administration of corticosteroids, in accordance with published data from the CheckMate 066 and 037 studies[13,14].

Our analysis shows that nivolumab treatment was well tolerated and was associated with a good objective response rate. Above all, it had a very positive effect on quality of life. Specifically, we noted that clinical benefit and quality of life were better when a good response to treatment in terms of increased PFS was observed. *BRAF* gene mutation was observed less frequently in the present study's elderly patients than in the literature's younger patients (18% vs. 40%–60% in patients with cutaneous melanoma regardless of age). Furthermore, the results indicate that efficacy and safety outcomes with nivolumab were similar whether patients had wild-type or mutant *BRAF*[27]. Those data are consistent with data in previous studies that showed a different molecular profile of melanoma in elderly compared with younger people[20,28]. Using a descriptive analysis, we monitored serum LDH in our patients and found a reduction in LDH enzyme levels in patients who responded to treatment and an increase in those who were experiencing progressive disease. That observation suggests that serum LDH response could be an important predictor of treatment response and method of monitoring treatment. However, we realize that more clinical trials must be conducted to validate that hypothesis.

TABLE III Adverse events[a] in 55 elderly patients

Event	Pts *(n)*
Skin reactions	
Grades 2–3	3
Grade 4	1
Diarrhea (grades 1–2)	1
Colitis (grades 2–3)	2
Pneumonitis (grades 2–3)	3
Endocrine	4

[a] Graded according to the *Common Terminology Criteria for Adverse Events,* version 4.0.

Pts = patients.

CONCLUSIONS

Immune checkpoint inhibitors significantly improve the treatment of metastatic melanoma, with a good efficacy and tolerability profile. Our study suggests that nivolumab monotherapy is effective and well-tolerated in elderly patients with melanoma. Our experience confirms the good efficacy and safety of nivolumab for metastatic melanoma in elderly patients, with no significant increase in toxicity rates compared with a younger population.

Based on the foregoing results, we conclude that nivolumab every 2 weeks is a valuable regimen for metastatic melanoma in elderly patients. Until a few years ago, not many therapeutic options were available for metastatic melanoma, and so the use of nivolumab, as demonstrated in the present work, remains a valid therapeutic option awaiting new studies.

Despite a retrospective study design and a limited number of patients, our results agree with the clinical evidence reported in the literature[29]. We made an effort to collect all the available information from medical records. Not all patients underwent a geriatric evaluation before treatment start, and as has been already shown in various studies, PS by the ECOG and Karnofsky methods is not a good estimator of treatment response in the elderly population. Future studies should conduct a comprehensive geriatric assessment using validated tools such as the Geriatric 8 in

older patients, and such an assessment is highly recommended before immunotherapy start.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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