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RESEARCH ARTICLE

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BRAF-mutant melanoma management: a single center retrospective analysis of patients treated with sequential therapy

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ABSTRACT

Aims: In treating patients with melanoma, the order in which therapy is administered, choosing between targeted therapy and immune checkpoint inhibition, has garnered growing interest.

Patients and Methods: We conducted a retrospective, real-world analysis of patients with advanced melanoma undergoing immunotherapy or targeted therapy as first-line at a single center.

Results: A total of 88 patients diagnosed with melanoma were identified. At 7 years, in this cohort, 68.4% (95% CI: 55.9%-83.6%) of patients were alive. In all, 47 tumors harbored BRAF mutations; 10 patients who did not receive therapy were excluded from this subgroup. Of the 37 patients with a BRAF mutation, 29 received first-line targeted therapy and 8 received first-line immunotherapy. At 2 years, 28 (76%) patients were alive and 9 (24%) had died. Of the 28 survivors, 22 received first-line targeted therapy and 6 received first-line immunotherapy. In addition, 29 patients were administered a MEK inhibitor in first line. Of these, 66.4% (95% CI: 48.3–91.2) of patients were alive at 7 years.

Conclusions: There was no significant difference between survival and first-line immunotherapy or first-line targeted therapy. Additional studies are required to establish whether front-line immunotherapy is linked to more effective long-term disease control compared to first-line targeted therapy.

HIGHLIGHTS

- In patients with melanoma, the order in which therapy and immune checkpoint inhibition are administered is receiving increased interest.
- A retrospective, single-center, real-world analysis of patients with advanced melanoma was carried.
- Patients underwent either first-line immunotherapy or first-line targeted therapy.
- A total of 88 patients diagnosed with melanoma were identified, 47 of which harbored BRAF mutations; 10 patients who did not receive therapy were excluded.
- Of these latter, 29 received first-line targeted therapy and 8 received first-line immunotherapy.
- At 2 years of the 28 survivors, 22 received first-line targeted therapy and 6 received first-line immunotherapy.
- There was no significant difference between survival and first-line immunotherapy or targeted therapy.

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Melanoma; first line; immunotherapy; targeted therapy; real-world; BRAF

1. Introduction

Melanoma arises from the transformation of melanocytes [1]. Key risk factors for cutaneous melanoma include exposure to ultraviolet radiation from the sun, sunburns, and indoor tanning [2]. Although the incidence of cutaneous melanoma varies across geographic regions, it has consistently increased in many areas worldwide

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in recent decades [3]. In the Lazio region of Italy, where the current study was conducted, the age-standardized incidence of melanoma was 22.5 per 100,000 individuals from 2008 to 2013 [4].

The diagnosis of melanoma is based on histological analysis, which helps determine the appropriate treatment course. Historically, stages I and II cutaneous melanoma are associated with favorable prognosis, with stages III and IV having poorer prognosis [5]. Nevertheless, the recent progress in targeted therapies and immune checkpoint blockade treatments represents a notable breakthrough, fundamentally altering the approach to managing individuals with high-risk melanoma [6].

A sizable proportion of melanoma patients carry an activating mutation in the proto-oncogene BRAF, a component of the RAS/MAPK signaling pathway, controlling several essential functions [7]. Indeed, approximately 40–50% of melanoma patients, the majority of whom have the BRAF V600E mutation [8]. BRAF has thus become an important therapeutic target in patients with resected stage III and IV melanoma [9]. The first drug approved for this purpose was vemurafenib, which, by inhibiting the BRAF V600E kinase, led to a significant reduction in the MAP kinase signaling pathway and decreased survival and proliferation of tumor cells [10]. Afterward, to counteract the activation of the MAP kinase pathway despite BRAF inhibition, a combination of BRAF and MEK inhibitors was implemented [11]. Currently, three common BRAF-MEK inhibitor combinations are utilized: vemurafenib and cobimetinib, dabrafenib and trametinib, and encorafenib and binimetinib. These combinations exhibit similar efficacy profiles, with differences observed in their toxicity profiles [12].

More recently, attention has been given to the sequencing of therapy. Although targeted therapy effectively achieves prompt disease control in the majority of patients, the development of secondary resistance frequently occurs, limiting the duration of the response [13]. On the other hand, immune checkpoint inhibition may be associated with slower but more long-lasting responses at least in proportion of patients [13]. However, identification of the best therapeutic approach provided somewhat inconsistent data, although studies appear to demonstrate that BRAF/MEK inhibition before immunotherapy may reduce the efficacy of the latter. The SECOMBIT trial investigated a new therapeutic setting in patients with metastatic melanoma and BRAF V600E mutation who were randomized to either targeted therapy (encorafenib and binimetinib) or immunotherapy (ipilimumab plus nivolumab) until disease progression, after which the arm starting targeted therapy would switch to immunotherapy (arm A) and vice versa (arm B) [14]. A third arm, receiving targeted therapy for 8 weeks, was switched to immunotherapy until disease progression, and finally back to targeted therapy (arm C). The primary endpoint of overall survival (OS), at 2 years, was achieved in all three arms of the study: 65% in arm A, 73% in arm B, and 69% in arm C. The SECOMBIT trial thus suggested that immunotherapy followed by targeted therapy may be associated with better tumor control.

Herein, we present the results of a retrospective, real-world analysis in BRAF-positive patients with advanced melanoma undergoing either first-line immunotherapy or first-line targeted therapy in Southern Lazio, Latina province, Italy.

2. Materials and methods

2.1. Study design

This is a retrospective study conducted at the Unit of Dermatology of Sapienza University Polo Pontino, Latina, Italy, from February 2016 to February 2023. Eighty-eight patients diagnosed with melanoma were identified. Patient data were obtained and supplemented through the consultation of medical records to obtain updates on current health status, recurrence of disease, or death. Subsequently, the data were collected in a dedicated database. Inclusion criteria were diagnosis of metastatic melanoma or adjuvant melanoma, age 18 years, ECOG performance status of 0 or 1, and satisfactory organ function. Exclusion criteria, which were applied before considering therapies due to their status as absolute or relative contraindications to treatment in clinical routine in our country, included active, known, or suspected autoimmune disease; uncontrolled intercurrent illness (including ongoing infections or significant cardiovascular comorbidities); pregnant or breastfeeding women; inability, unwillingness, or incapacity to adhere to the study protocol; and any circumstance that, in the investigator's judgment, could compromise the participant's safety or rights. Being a retrospective chart analysis, patient consent was not needed according to Italian regulations. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with guidelines for good clinical practice.

Samples were processed as previously described [15–17]. Next-generation sequencing was performed using the Illumina platform Miseq and employing the Myriapod® NGS Cancer panel DNA (Cat. No. NG033, Diatech).

2.2. Mutational analysis

Mutational characteristics were correlated with variables including gender, age, type of therapy [immunotherapy (ipilimumab, nivolumab, pembrolizumab), and molecular targeted therapy], Breslow thickness (cut-offs examined following AJCC staging: <0.8 mm, 1–2 mm, 2–4 mm, >4 mm), histotype (NM, SSM, "A" indicating melanoma in situ, choroid, colon), ulceration (Yes/No), stage (I, II, III, IV), and death (Yes/No).

2.3. Statistical analysis

Data are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, based on their distribution and as counts and percentages for categorical variables. Overall survival (OS) was defined as the time from diagnosis to death due to any cause. Participants without documented death at the time of analysis were censored at the date of last known contact. Comparisons between treatment groups were performed using the chi-squared test. The estimate of OS obtained from the Kaplan-Meier method and displayed graphically. Differences in OS between groups were analyzed by the log-rank test. The data were analyzed using the open-source software R, version 4.3.1. A p value <0.05 was considered significant.

3. Results

3.1. Patient cohort

A total of 88 patients diagnosed with melanoma were included in the analysis with a median age of 70.5 (IQR: 59.7–79.0) years of whom 52 (59.1%) were male (Table 1). Median age at diagnosis was 66.5 (IQR: 53.0–77.0) years and almost half of the cohort had stage IV disease (n = 42, 47.7%). In all, 47 patients (53.4%) had a mutation in BRAF, and 13 (14.8%) had another mutation. Sixty-two patients were alive (70.5%) at the time of the analysis. All cases were primary melanoma; based on histotype, primary melanomas of the in situ type, as well as those originating in the choroid and colon, were also included in the analysis, representing the entire population under examination.

The median follow-up was 4.14 years (IQR: 3.35–5.42). OS in the entire cohort is shown in Figure 1A. At 7 years, 68.4% (95% CI: 55.9%–83.6%) of patients were alive. Considering OS by tumor stage, after 7 years 96.1% (95% CI: 89.0%–1.0%) of patients were alive in those with stage 0-III disease compared to 52.6% (95% CI: 37.5%–73.7%) of those with stage IV disease (p < 0.0001; Figure 1B).

3.2. BRAF-mutated tumors

We next analyzed patients who *had* a BRAF mutation: of the 47 *BRAF*-mutated patients, 10 who did not take any therapy were excluded, leaving a cohort of 37 for the analysis. Of these latter, 8 (group 1) received first-line immunotherapy and 29 (group 2) received first-line targeted therapy. Thus, the majority of *BRAF*-positive patients (78%) received first-line targeted therapy (group 2).

At 2 years, 28 (76%) were alive, while 9 (24%) died. Of the 28 survivors, 6 belonged to group 1 (first-line immunotherapy), while 22 belonged to group 2 (first-line targeted therapy). Of the 9 who died, 2 belonged to group 1 and 7 belonged to group 2. There was no statistically significant difference between status (alive versus deceased) and therapy groups (first-line immunotherapy versus first-line targeted therapy): group 1 alive 6/8 (75%); group 2 alive 22/29 (75.8%); group 1 deceased 2/8 (25%) and group 2, deceased 7/29 (24.1%), respectively.

A total of 29 patients were also administered a MEK inhibitor in first-line (Table 2). The median age of these patients was 64.0 years (IQR: 57.0, 73.0), and most were male (n = 21, 72.4%). Twenty-eight of these patients had stage III (n = 13, 44.8%) or IV (n = 15, 51.7%) disease. Of these, at 7 years 66.4% (95% CI: 48.3–91.2) of patients were alive (Figure 2).

Table 1. Characteristics of the cohort.

Characteristic	N (%)
Total number of patients	88
Median age (years [IQR])	70.50 [59.75, 79.00]
Sex (%)	
Female	36 (40.9)
Male	52 (59.1)
Median age at diagnosis (years [IQR])	66.50 [53.00, 77.00]
Breslow (%)	
<0.8	9 (10.2)
0.8-1	2 (2.3)
2	35 (39.8)
2-4	8 (9.1)
>4	25 (28.4)
Colon	2 (2.3)
Choroid	3 (3.4)
Occult	4 (4.5)
Histotype (%)	
A	12 (13.6)
NM	38 (43.2)
SSM	38 (43.2)
Ulceration (%)	
No	63 (71.6)
Yes	25 (28.4)
Stage	
0	3 (3.4)
I	3 (3.4)
II	20 (22.7)
III	20 (22.7)
IV	42 (47.7)
Mutation (%)	
None detected	28 (31.8)
BRAF	47 (53.4)
Other	13 (14.8)
Therapy (%)	
Anti-PD-1	24 (27.3)
Anti-PD-1_Anti-CTL4	7 (8.0)
Anti-PD-1_TT	3 (3.4)
None	23 (26.1)
TT	17 (19.3)
TT_ Anti-PD-1	7 (8.0)
TT_ Anti-PD-1_antiCTL4	3 (3.4)
TT_Combo	2 (2.3)

A: in situ, choroid, colon; NM, nodular melanoma; SSM, superficial spreading melanoma; TT: targeted therapy; Combo: combination.

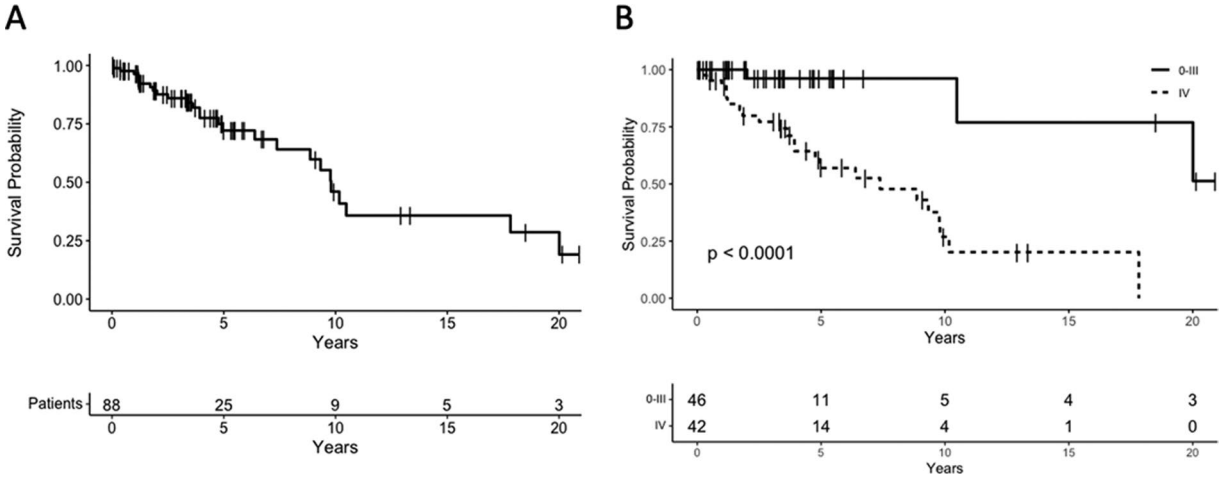

Figure 1. OS in the entire cohort (A) and OS by tumor stage (B).

4. Discussion

Systemic therapies for *BRAF*-mutant melanoma with BRAF-MEK inhibitors and immunotherapy provided an important survival benefit and have dramatically changed routine management [18]. The identification of a

Table 2. Characteristics of BRAF-positive patients who were administered a MEK inhibitor in first-line.

Characteristic	N (%)
Total number of patients	29
Median age (years [IQR])	64.00 [57.00, 73.00]
Sex (%)	
Female	8 (27.6)
Male	21 (72.4)
Median age at diagnosis (years [IQR])	60.00 [50.00, 70.00]
Breslow (%)	
<0.8	3 (10.3)
0.8-1	1 (3.4)
2	10 (34.5)
2-4	3 (10.3)
>4	11 (37.9)
Occult	1 (3.4)
Histotype (%)	
A	1 (3.4)
NM	14 (48.3)
SSM	14 (48.3)
Ulceration (%)	
No	20 (69.0)
Yes	9 (31.0)
Stage	
0	1 (3.4)
I	0 (0.0)
II	0 (0.0)
III	13 (44.8)
IV	15 (51.7)

n = 29.
A: in situ, choroid, colon; NM, nodular melanoma; SSM, superficial spreading melanoma.

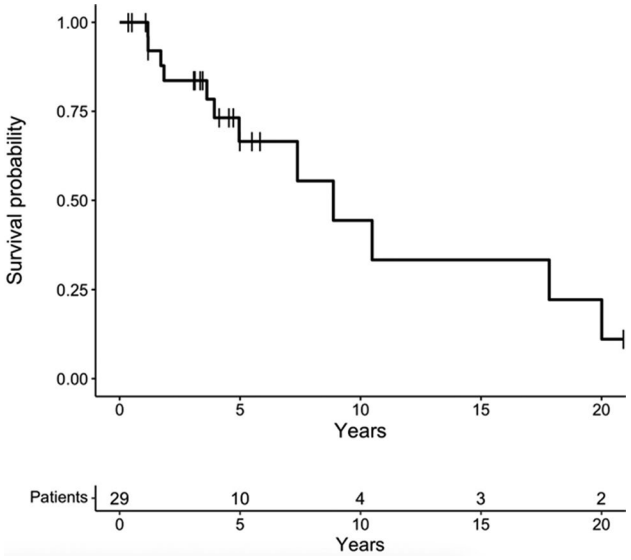

Figure 2. OS in BRAF-positive patients who were administered a MEK inhibitor in first-line (n = 29).

combination strategy for the use targeted and immunotherapy appears to be promising for management of patients with BRAF-mutant melanoma. Immunotherapy alone is associated with a slow but durable response, while BRAF plus MEK inhibition yields early response that is, however, followed by a rapid onset of resistance and a short duration of response [19]. Thus, the optimal sequencing strategy remains to be defined. The SECOMBIT trial highlighted that combination therapy for metastatic *BRAF*-mutant melanoma can improve progression-free survival (PFS) and OS [14]. More specifically, the combination of immune checkpoint inhibitors (ipilimumab + nivolumab) prior to administration of BRAF inhibitors (encorafenib + binimetinib) showed a benefit for both PFS and OS compared to the reverse sequence (53% vs. 41% for PFS and 62% vs. 54% for OS) [14].

Additional evidence in support of sequential therapy comes from the DREAMSeq real-world analysis where patients receiving first-line immunotherapy had better survival compared to those receiving first-line BRAF-MEK

inhibition [20]. In fact, at a mean follow-up of 15–16 months, 64% of patients receiving nivolumab-ipilimumab first-line were alive, compared to 43% of BRAF-MEK inhibition first-line were alive. The ImmunoCobiVem trial assessed if a switch to atezolizumab after achieving tumor control during first-line vemurafenib+cobimetinib benefited PFS and OS vs. continuation of targeted therapy [21]. The authors reported that 2-year OS was higher in those switched atezolizumab to compared to continued targeted therapy (67% vs 58%, respectively). In our analysis, no differences have been revealed in survival concerning the choice of first-line treatment, whether it was immunotherapy or targeted therapy. However, the present analysis has some limitations. First is the relatively small number of patients which can potentially limit the overall interpretation of the results. In addition, this was a retrospective chart review, and the majority of BRAF-positive patients had received first-line targeted therapy since this had an indication in patients with mutated BRAF V600E, in contrast to immunotherapy. It should also be noted that the overall duration of follow-up was rather short. Lastly, 4 of 5 BRAF-positive patients received first-line targeted therapy, which is likely because this has an indication exclusively in patients with mutated BRAF V600E, while immunotherapy can be used either in patients wild-type for BRAF or with mutations other than BRAF V600E.

5. Conclusion

At present, the available data in the literature encourage use of therapy to metastatic BRAF-mutated melanoma patients after first-line failure [13]. While sequential therapy is advocated in current guidelines by the EORTC, the preferred strategy is not, even though it is noted that literature data support immunotherapy followed by targeted therapy [22]. In our center, data on the use of first-line immunotherapy encourage us to start with nivolumab/ipilimumab in patients with mutated BRAF, since it has been demonstrated a more durable response than BRAF inhibitors in first-line [13]. Notwithstanding, inconsistent data have been obtained and larger series are needed to confirm that front-line immunotherapy is associated with better control of disease in the long-term than first-line targeted therapy.

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Author contributions

Conceptualization, Ilaria Proietti and Concetta Potenza; Data curation, Elena De Falco, Luca Pacini, Giorgio Mangino, Giovanna Romeo, Paolo Rosa, and Antonella Calogero; Formal analysis, Elena De Falco, Luca Pacini, Alessandra Spagnoli, Velia Melone, Giorgio Mangino, Giovanna Romeo, Paolo Rosa, and Antonella Calogero; Investigation, Vincenzo Petrozza, Claudio Di Cristofano, and Concetta Potenza; Methodology, Concetta Potenza; Project administration, Ilaria Proietti; Validation, Ilaria Proietti; Writing – original draft, Ilaria Proietti and Concetta Potenza.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Sapienza University of Rome-Polo Pontino (n. 0027005/2020 -12/02/2022).

Consent form

Informed consent was obtained from all subjects involved in the study.

Disclosure statement

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Data availability statement

Data are available upon request to the corresponding author.

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*Update of European Guidelines