Research Article

Real life clinical management and survival in cutaneous malignant melanoma: the Italian Clinical National Melanoma Registry (CNMR) experience

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Simple Summary:

Cutaneous malignant melanoma (CMM) is one of the most aggressive types of skin cancer. The aim of this study is to investigate the oncological treatments employed in the real-life clinical management of patients with advanced CMM in several Italian centers which are part of the Clinical National Melanoma Registry (CNMR). The immunotherapy can be considered the best therapy to improve survival in a real-world-population of cutaneous malignant melanoma. In the future, the main challenge of CNMR is the identification of the best therapy that patients could benefit to improve survival.

Abstract:

Background: Cutaneous malignant melanoma (CMM) is one of the most aggressive types of skin cancer. Currently, innovative approaches such as target therapies and immunotherapies have been introduced in clinical practice for the treatment of metastatic CMM. Data of clinical trials and real life studies that evaluate the outcomes of these therapeutic associations are necessary to establish their clinical utility. The aim of this study is to investigate the types of oncological treatments employed in the real-life clinical management of patients with advanced CMM in several Italian centers which are part of the Clinical National Melanoma Registry (CNMR), and the oncological outcomes obtained.

Methods: CNMR collects data of patients with a histologically confirmed diagnosis of primary CMM treated in one of the 38 Italian institutions (hospitals, research institutes, etc.) participating in the network. Melanoma-specific survival and Overall survival were calculated. Kaplan-Meier curves and medians of OS and 95% CI are presented overall and by immunotherapy and target treatments. The Log-rank test compared curves by treatments. Multivariate Cox regression models were used to estimate the hazard ratios adjusting for confounders and other prognostic factors.

Results: The median follow-up time was 36 months (range 1.2-185.1). 787 CMM were included in the analysis with completed information about therapies. Global immunotherapy showed a significant improved survival compared with all other therapies.
(p=0.001). 75% was the highest reduction of death reached by nivolumab/pembrolizumab immunotherapy (anti-PD1 HR=0.25 95% CI 0.14-0.42), globally immunotherapy was significantly associated with improved survival, either for anti-CTL A4 monotherapy or combined with anti-PD1 (HR=0.47;95% CI 0.33-0.66 and HR=0.26; 95% CI 0.15-0.46, respectively).

Conclusions: The nivolumab/pembrolizumab and the combination of ipilimumab can be considered the best therapy to improve survival in a real-world-population. The CNMR can complement clinical registries with the intent of improving cancer management and standardizing cancer treatment.

**Keywords:** medical record systems, cutaneous malignant melanoma, survival analysis, immunotherapy

**Graphical Abstract**

| Parameter/Category | Adjusted Multivariate Analysis | HR | 95% CI | p    |
|--------------------|-------------------------------|----|-------|------|
| No Immunotherapy   |                               | 1.0 |       |      |
| Anti-PD1 (Nivolumab) |                             | 0.23 | 0.14-0.43 | <0.0001 |
| Anti-CTL A4 (Ipilimumab) |                   | 0.47 | 0.33-0.67 | <0.0001 |
| Anti-PD1 + Anti-CTL A4 |                         | 0.26 | 0.15-0.47 | <0.0001 |
1. Introduction

Cutaneous malignant melanoma (CMM) is one of the most aggressive types of skin cancer. The incidence of CMM has increased in Europe over the last years, and cohort studies suggest that the increasing trend of incidence will continue for at least the next 2 decades [1-3]. Mortality rates have also increased in the last decades, especially in men, despite a clear decrease of Breslow tumor thickness in the USA and Europe [1,4]. In the USA, the raw mortality rates per 100,000 inhabitants per year increased from 2.8 to 3.1, with an estimate of 10,130 deaths from melanoma in 2016 (they were 8650 in 2009) [1]. In Italy, 12,3000 new cases and over 2,000 deaths were estimated in 2019 [5-6].

Surgery is currently the golden standard for patients with early stage CMM, who represent only part of the global cases. The treatment of patients with advanced stage CMM is more complex, as for decades no chemotherapy regimens have been found effective in prolonging survival. Currently, innovative approaches such as target therapies and immunotherapies have been introduced in clinical practice for the treatment of metastatic CMM. Target therapies are based on the use of drugs targeting specific genetic alterations in candidate genes, blocking specific pathways implicated in the oncogenesis of melanoma [7]. BRAF mutations represent currently the main molecular targets for melanoma treatment, as they involve approximately 50% of the cases, and identify patients who may benefit from treatment with BRAF inhibitors, like vemurafenib or dabrafenib [8-10]. Recently, the combination of anti-BRAF drugs with MEK inhibitors showed improved oncological outcomes in comparison to monotherapies (70% one-year and 50% two-years survival), with a better safety profile [11-13].

Immunotherapy takes advantage of the fact that treatments indirectly affect cancer cells by stimulating the patient's immune system, particularly enhancing the immune system's T-cell response [14]. Ipilimumab, a monoclonal antibody that blocks the activity of the CTLA-4, has shown a long-term survival in about 20% of the patients treated [15-17]. Programmed death 1 (PD1) is a membrane receptor of tumor cells (its main ligand is PD-L1) that represents a powerful brake to the immune system's response, and the target of
specific inhibitors (nivolumab and pembrolizumab) which have been recently introduced into clinical practice, as they were shown more effective than ipilimumab in terms of overall survival (OS) and toxicity [18-19]. Recent studies showed that the combination of anti-CTLA-4 and anti-PD-1 is more effective than monotherapy, but a higher incidence of high-grade adverse events was found [20]. Combinations of targeted therapies and immunotherapies are currently investigated; the advantage of such combinations is that more than one anti-tumoral mechanism are employed against CMM. Data of clinical trials and real life studies that evaluate the outcomes of these therapeutic associations are necessary to establish their clinical utility.

The aim of this study is to investigate the types of oncological treatments employed in the real-life clinical management of patients with advanced CMM in several Italian centers which are part of the Clinical National Melanoma Registry (CNMR), and the oncological outcomes obtained.

2. Results

A total of 8,163 CMM cases were registered in CNMR in the period under investigation. 17% (1,401) were melanoma in situ, 63% (5,121 patients) had a stage from IA to IIC, 20% had a stage from IIIA (Table 1).

Table 1. Distribution of melanoma patients by stage in the Italian Clinical National Melanoma Registry (CNMR), 2011-2017

| Melanoma Stage | N (%)  | %  |
|----------------|--------|----|
| In situ        | 1401 (17%) | 17 |
| IA             | 2061 (25%) |    |
| IB             | 1444 (18%) |    |
| IIA            | 842 (10%)  | 63 |
| IIB            | 488 (6%)   |    |
| IIC            | 286 (4%)   |    |
| IIIA           | 229 (3%)   |    |
| IIIB           | 275 (3%)   |    |
| IIIC           | 247 (3%)   | 20 |
| IV             | 890 (11%)  |    |
| Total          | 8163     | 100|
Table 2 shows the distribution of the melanoma stage in accordance to their demographic data, geographic origin: 4,242 (52%) were males and the mean age was 58±15 years, 3,916 (48%) were females and the mean age was 54±16 years, the majority of the sample coming from northern Italian centers. Stage III counts 751 patients, but only 14% were IIIB-IIIC unresectable that were included in the analysis.

Table 2. Socio-demographic characteristics according to Stage in the Italian Clinical National Melanoma Registry (CNMR), 2011-2017

| STAGE       | In situ | I-II | III (A, B, C) | IV    |
|-------------|---------|------|---------------|-------|
| N           | (%)     | N    | (%)          | N     | (%)  | Total |
| 1401        | (17.1)  | 5121 | (62.7)       | 751   | (9.3) | 890   | (10.9) | 8163 |

Gender
- Male
  - 677 (48)
  - 2600 (51)
  - 435 (58)
  - 530 (60)
  - 4242
- Female
  - 724 (52)
  - 2521 (49)
  - 315 (41)
  - 356 (40)
  - 3916
- missing
  - 1
  - 4
  - 5

Age
- ≤40
  - 245 (18)
  - 1005 (20)
  - 105 (14)
  - 90 (10)
  - 1445
- 41-50
  - 285 (20)
  - 1134 (22)
  - 142 (19)
  - 128 (14)
  - 1689
- 51-60
  - 253 (18)
  - 1017 (20)
  - 156 (21)
  - 174 (20)
  - 1600
- 61-70
  - 310 (22)
  - 1005 (20)
  - 174 (23)
  - 214 (24)
  - 1703
- >70
  - 308 (22)
  - 960 (18)
  - 174 (23)
  - 284 (32)
  - 1726

Geographical area
- North
  - 800 (57)
  - 2584 (50)
  - 550 (73)
  - 590 (66)
  - 4524
- Center-South
  - 601 (43)
  - 2537 (50)
  - 201 (27)
  - 300 (34)
  - 3639

Patients characteristics, data on tumor and BRAF mutational status were restricted to advanced melanoma (IIIB-IIIC unresectable, IV), and the total sample counted 787 patients.

Regarding to stage 12% had an initial diagnosis of in situ, 38% had an early diagnosis (IA-IIC), 37% stage III and 13% had a confirmed advanced melanoma stage (IV). 76% was the percentage of BRAF executed in our sample and the incidence of BRAF mutations was slightly greater than 50%; most cases were analyzed after the year 2013 when target
therapies were diffusely employed in clinical practice; in addition, more cases among those analyzed harbored stage IV tumors rather than stage IIIB-IIIC melanomas. (Table3)

Table 3: Tumor characteristics for Advanced Stage (IIIB-IIIC unresectable, IV)

| ADVANCED STAGE | IIIB-IIIC (unresectable), IV | N=787 |
|----------------|-----------------------------|-------|
| Gender         |                             |       |
| Male           | 476 (61)                    |       |
| Female         | 307 (39)                    |       |
| Age            |                             |       |
| ≤60 yrs        | 355 (45)                    |       |
| >60 yrs        | 432 (55)                    |       |
| BMI            |                             |       |
| <25            | 315 (40)                    |       |
| ≥25            | 386 (49)                    |       |
| missing        | 86 (11)                     |       |
| LDH            |                             |       |
| Normal         | 479 (61)                    |       |
| Abnormal       | 43 (5)                      |       |
| Unknown        | 265 (34)                    |       |
| Initial Stage  |                             |       |
| In situ        | 98 (12)                     |       |
| Stage I-II     | 297 (38)                    |       |
| Stage III      | 291 (37)                    |       |
| Stage IV       | 101 (13)                    |       |
| BRAF executed  |                             |       |
| No             | 120 (15)                    |       |
| Yes            | 594 (76)                    |       |
| Not applicable | 73 (9)                      |       |
| Mutational status |                         |       |
| Mutant         | 322 (54)                    |       |
| Wild Type      | 269 (45.5)                  |       |
| unknown        | 3 (0.5)                     |       |
| Year BRAF executed |                     |       |
| <2013          | 498 (63)                    |       |
| ≥2013          | 289 (37)                    |       |

*4 patients did not report the gender
The median follow-up time was 36 months (range 1.2-185.1). Observed patients and percentage according to type of treatment were reported in Table 4; total death events (for all causes and deaths for the diseases) were reported and median Melanoma-specific survival (M-s S) was calculated. As first line of treatment (choice), 41% of patients (n=319) received immunotherapy, 36% received BRAF-targeted therapies (n=285), 35% received chemotherapy (n=275), 35% received local therapy (electrochemotherapy) (n=275). In details, among immunotherapy: 62% received ipilimumab (anti-CTL A4), 25% nivolumab/pebrolizumab (anti PD1), 13% the two combined. Among BRAF therapy: 69% received BRAF monotherapy (vemurafenib/dabrafenib), about 31% received BRAF+MEK combination therapy (vemurafenib/dabrafenib + cobimetinib/trametinib). In the entire cohort the median overall melanoma-specific survival was 47 months (95% CI: 40-53), the lowest median survival was detected by patients treated by chemotherapy (33 months, 95% CI 27-38) as first option. Among immunotherapy the M-s S globally was 50 months (95% CI 43-57), it varied from 47 months (95% CI 37-56) for ipilimumab (anti-CTL A4) to 70 months (95% CI 39-101) for nivolumab/pebrolizumab (anti-PD 1). Target therapy globally produced M-s S of 44 months (95% CI 38-50), it varied from 40 months (95% CI 34-45) for Vemurafenib/Dabrafenib single agent (anti-BRAF) to 55 months (95% CI 49-61) for and the addition of Cobimetinid/Trametinib (anti-MEK).

Table 4. Results of the performance indicators on the quality of metastatic melanoma care – Univariate Analysis

| Indicator | Advanced melanoma patients | Patients eligible for analysis |
|-----------|-----------------------------|--------------------------------|
|            | Observed patients (n) (%)   | (%)                           |
| Advanced melanoma patients | 966 (81.5)                  | 787 (100)                     |
| Patients excluded from the analysis for missing therapies | 179 (18.5)                  |                                |
| Patients with local therapy | 275 (35)                    |                                |
| Patients with systemic therapy: chemotherapy | 275 (35)                    |                                |
| Patients with systemic therapy: immunotherapy | 319 (41)                    |                                |
| Immunotherapy: ANTI-PD 1 (Nivolumab/Pebrolizumab) | 80 (25.1)                   |                                |
| Immunotherapy: ANTI-CTL A4 (Ipilimumab) | 198 (62.1)                  |                                |
Immunotherapy showed an improved survival compared with all other therapies (p=0.001) (Fig. 2, A); for Ipilimumab and combined target therapy compared with all other therapies a slight significance were observed (p=0.05) (see Fig. 2B). The highest survival (70 months; 95% CI 45-96) was reached by patients treated with Nivolumab/Pembrolizumab compared with combined target therapy and all other therapies (p=0.001) (see Fig. 2 C); Immunotherapy across strata showed an improved survival for anti-PD1 and combined anti-PD 1 + anti-CTL A4 compared with Ipilimumab and all other therapies (p<0.0001) (see Fig. 2 D). The treatment-sequence did not show any significant difference (Immuno in 1st and Target in 2nd vs. Target in 1st and Immuno in 2nd line ) (p=0.5) (see Fig. 2 E). A significant difference was observed between BRAF vs. BRAF with the addition of Cobimetinid/Trametinib (anti-MEK) (p=0.03) (see Fig. 2F).
Figure 2. Overall Survival (OS) in patients with IIIB-IIIC (UNRESECTABLE), IV by Therapy (A, B, C, D, E, F)

Multivariate Cox model hazard ratios were reported in Table 5: a significant increased risk of death was observed for abnormal LDH compared to normal (HR=1.94 95% CI 1.23-3.06); among the Target therapy a significant protective effect was observed for target therapy with the addition of Cobimetinid/Trametinib (BRAF+MEK) (HR=0.63 95% CI 0.42-0.94). All immunotherapy categories were significantly associated with a reduction of death: anti-PD1 HR=0.25 (95% CI 0.15-0.43), anti-CTL A4 HR=0.47 (95% CI 0.33-0.67) and combined anti-PD1+ anti-CTL A4 HR=0.26 (95% CI 0.13-0.53).
CI 0.15-0.47), respectively. The treatment-sequence was not associated to the risk of death (p=0.3).

Table 5. Univariate and multivariate Cox regression models for death

| Parameter / Category               | Adjusted Multivariate Analysis† | HR    | 95% CI           | p     |
|----------------------------------|---------------------------------|-------|-----------------|-------|
| LDH                              |                                 |       |                 |       |
| Normal                           |                                 | 1.0†  |                 |       |
| Abnormal                         |                                 | 1.95  | 1.24-3.01       | 0.004 |
| Unknown                          |                                 | 0.97  | 0.95-1.53       | 0.09  |
| Target therapy                   |                                 |       |                 |       |
| No Target and No Immuno therapy  |                                 | 1.0†  |                 |       |
| BRAF                             |                                 | 1.14  | 0.85-1.53       | 0.4   |
| BRAF+MEK                         |                                 | 0.623 | 0.42-0.94       | 0.02  |
| Immunotherapy                    |                                 |       |                 |       |
| No Immuno and No Target therapy  |                                 | 1.0†  |                 |       |
| ANTI-PD 1 (Nivolumab/Pebrolizumab)|                                 | 0.25  | 0.147-0.43      | <0.0001 |
| ANTI-CTL A4 (Ipilimumab)         |                                 | 0.47  | 0.33-0.67       | <0.0001 |
| ANTI-PD 1+ ANTI-CTL A4           |                                 | 0.26  | 0.15-0.47       | <0.0001 |
| Treatment Sequence               |                                 |       |                 |       |
| Immuno 1st and Target 2nd        |                                 | 1.0†  |                 |       |
| Target 1st and Immuno 2nd        |                                 | 1.64  | 0.65-4.12       | 0.3   |

† Reference category; † Multivariate Cox model adjusted for gender (male, female); age (≤60, >60); geographical area (North, Central-South); Year BRAF executed (≤2013, >2013); N. of therapies (1, 2, ≥3); Other therapies: Chemotherapy; Local and systemic therapy whenever.
3. Discussion

In this study, we examined data of advanced melanoma in the Italian Clinical National Melanoma Registry (CNMR). CNMR does not have the typical aim of cancer registries to estimate incidence data, but as a clinical registry may collect data from the real world experience which is different from that coming from clinical studies which included selected patients. [22-23]. Indeed, much of the existing research on advanced melanoma patients has been conducted in clinical trials settings among patients who meet stringent inclusion and exclusion criteria.

The analysis of the 787 patients from the advanced cohort showed some interesting results. As first, looking at the advanced patients’ characteristics, a good percentage of them come from the initial stages more than from the high risk conditions. Indeed, 50% of advanced melanoma had an initial diagnosis of early stage that then developed into advanced one.

Interestingly, the BRAF mutational status was not evaluated in all patients; indeed, the BRAF status has been documented in as much as 76% of these patients. An important consideration is that the CNMR collected data from December 2011 and the most important drug in the field of melanoma, like BRAF inhibitors, anti-CTLA4, anti-PD1 were approved in the following years. Specifically, ipilimumab was the first treatment to be approved, on February 2013, by AIFA. Vemurafenib and dabrafenib received approval on May 2013 and on October 2014 respectively as monotherapy, and on September 2016 and on January 2017 in combination with cobimetinib and trametinib respectively. Pembrolizumab was approved on May 2016 while nivolumab on 24 March 2016(24). Moreover, the possibility to ask for the BRAF mutational status was probably related only to the centers which were participating to clinical studies or expanded access programs with such drugs.

Another important analysis is that related to the OS. With all the limitation of the analysis due mainly to the time of collection of such data (before the largely use of anti-PD-1 and BRAF/MEK inhibitors, and the small number of patients considered), there are still some interesting findings. It is evident that the new therapies available had an important impact on the survival of these patients. Indeed, patients who practiced immunotherapy or target
therapy performed better in terms of median survival than those who practiced local therapy and/or chemotherapy, considered for a long time the only standard of treatment for metastatic melanoma. The addition of the MEK inhibitor to the BRAF inhibitor significantly improved patient OS.

It seems that the greater advantage in terms of OS is in those patients who have performed immunotherapy lines, even compared to those who have performed target therapies. This finding could be explained by the fact that many patients received BRAF inhibitor therapy as single agent (69.5%), and only a minority had benefit from the addition of the MEK inhibitor. Indeed, we learned that disease progression during therapy with the BRAF inhibitor alone was often rapid and unresponsive to subsequent treatments [25]; with the addition of MEK inhibitors, the fast progression from target therapy was reduced.

The data on the combination nivolumab + ipilimumab also appears intriguing, especially in terms of long survival; however, the low number of patients does not allow us to give definitive conclusions.

The correlation between survival and the LDH value is also consistent with the literature data. Analyzing the LDH values, there is an increased risk of death for patients with high LDH, compared to those with normal LDH, especially in the group of patients who received immunotherapy (HR = 2.45, p = 0.01).

We found that immunotherapy allows better results in terms of overall survival in patients with advanced melanoma, however in our analysis there is no statistically significant benefit of the treatment-sequence variable (Immuno in 1st and Target in 2nd vs. Target in 1st and Immuno in 2nd line). In consideration of the retrospective analysis, the small number of patients who started with anti-PD-1, and the lack of patients who received the dual MAPK blockade, definitive conclusions cannot be made.

At the moment several combination studies of target and immunotherapies as well as protocols to establish the best sequential therapy are ongoing. [26]. Our study has several limitations. In fact, most patients received chemotherapy as a first systemic treatment for
advanced disease, because more effective drugs such as BRAF/MEK inhibitors, anti-CTLA4 and anti-PD1 inhibitors were approved subsequently in different years. In addition, many centers did not test all patients for BRAF, especially at the beginning.

4. Materials and Methods

4.1 Patients and data collection

CNMR is the first clinical registry established in Italy in 2010. It collects data from a wide network of melanoma centers throughout the country with the aim to carry out clinical and therapeutic evaluations investigating geographical and policy differences and instruments for planning specific health interventions in different populations and areas, in order to optimize the clinical management and survival of CMM patients. CNMR collects data of patients with a histologically confirmed diagnosis of primary CMM treated in 38 Italian institutions (hospitals, research institutes, ecc.) participating in the network, as previously described [21]. For the purposes of the present study, data of consecutive patients enrolled from January 2011 to December 2018 were considered (CNMR established in 2010 but the first year was spent for administrative approvement and ethical comette in each centres).

A diagram of the CNMR’s organizational structure can be found in Figure 1.

**Organizational structure of Clinical National Melanoma Registry (CNMR)**
Data were collected via an electronic Case Report Form (eCRF), which was developed by the Clinical Research Technology S.r.l. group (Salerno, Italy) on its clinical platform ‘eClinical’. ‘eClinical’ assigned an identification (ID) number to all the patients screened. The quality of the electronic data was verified through onsite clinical visits, undertaken periodically during the study. The eCRF was designed to collect information on sociodemographic, clinical, pathological and treatment variables. The type of therapy was registered in all cases: local therapy (radiotherapy and electro-chemotherapy), systemic chemotherapy (platinum salts, dacarbazine, fotemustine), targeted therapy (anti-BRAF: vemurafenib/dabrafenib; BRAF+MEK: cobimetinib/trametinib), and immunotherapy (anti-CTLA4: ipilimumab, anti-PD1: nivolumab/pembrolizumab; and anti-CTLA4 + anti-PD1). Further information regarding the date of diagnosis, the duration of therapy, the date of the last follow-up, and the clinical status of the patients were also registered.

### 4.2 Statistical analysis

Descriptive statistics for the categorical data were reported. Pearson’s Chi-squared was used to compare categorical variables. Eligible patients for the survival analysis had histologically confirmed, unresectable stage III or stage IV metastatic melanoma (stage IIIB-IV) with an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and known BRAF mutation status. All patients were followed until 31 December 2018 or until the date of last visit, or death, whichever came first.

Melanoma-specific survival (M-s S) was calculated from the date of initial adjuvant treatment to death for the disease and Overall survival (OS) until date of death from any cause. Patients who did not die were censored for OS on the last visit date available in the database. When the date of diagnosis was antecedent the beginning of the Melanoma Registry or the initial diagnosis was an early melanoma we considered the M-s Survival from the date of initial adjuvant treatment.
Kaplan-Meier curves and medians of OS and 95% CI are presented overall and by immunotherapy and target treatments. The Log-rank test compared curves by treatments (immunotherapy: anti-CTLA4, anti-PD1 vs. no immunotherapy and no target therapy; BRAF: anti-BRAF, BRAF+MEK vs. no immunotherapy and no target therapy). Univariate and multivariable Cox regression models were used to estimate the hazard ratios adjusting for confounders and other prognostic factors.

All statistical tests were two-sided. P-values < 0.05 were considered significant. Statistical analyses were performed using statistical software SAS (version 9.02 for Windows), and Statistical Package for Social Science (SPSS) version 25 (SPSS inc., Chicago IL, USA).

5. Conclusions

Finally, this study shows that immunotherapy improves survival in advanced melanoma in a real-world population. The CNMR represents a set of data useful not only to plan the appropriate prevention measures but to better understand the effectiveness of anti-cancer treatments in a large unselected population from a real world experience. Furthermore, qualified data is essential and it is important that this information is constantly updated in order to maintain high levels of evidence.

The nivolumab/pembrolizumab and the combination of ipilimumab can be considered the best therapy to improve survival in a real-world-population. The CNMR can complement clinical registries with the intent of improving cancer management and standardizing cancer treatment.

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Ethics approval
This study was approved by the ethics committee of the National Cancer Institute “Fondazione Giovanni Pascale” in Naples, with the protocol number 537/10 registration date October 27, 2010.

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**Conflicts of Interest:** Paolo A. Ascierto has/had a consultant/advisory role for Bristol Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Array, Merck Serono, Pierre-Fabre, Incyte, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimova, Sandoz, Immunocore, 4SC, Alkermes, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Oncosec, Pfizer. He also received research funding from Bristol Myers Squibb, Roche-Genentech, Array and travel support from MSD.

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