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Nivolumab plus ipilimumab in melanoma patients with asymptomatic brain metastases: 7-year outcomes and quality of life from the multicenter phase III NIBIT-M2 trial☆

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ABSTRACT

Background: The primary analysis of the phase III NIBIT-M2 study showed a 41% 4-year overall survival (OS) of melanoma patients with asymptomatic brain metastases treated with ipilimumab plus nivolumab.
Methods: Here, we report the 7-year efficacy outcomes and the Health-Related Quality of Life (HRQoL) analyses of the NIBIT-M2 study.
Results: As of May 1, 2023, at a median follow-up of 67 months (mo), the median OS was 8.5 (95% CI: 6.6–10.3), 8.2 (95% CI: 2.1–14.3) and 29.2 (95% CI: 0–69.9) mo for the fotemustine (F) Arm A, ipilimumab plus fotemustine Arm B, and ipilimumab plus nivolumab Arm C, respectively. The 7-year OS rate was 10.0% (95% CI: 0–22.5) in Arm A, 10.3% (95% CI: 0–22.6) in Arm B, and 42.8% (95% CI: 23.4–62.2) in Arm C. HRQoL was preserved in all treatment arms. Most functional scales evaluated from baseline to W12 were preserved, with a lower mean score decrease for EORTC Quality of Life Questionnaire (QLQ)-C30 and an increase for EORTC QLQ-Brain neoplasm (BN20) in patients receiving ipilimumab plus nivolumab.
Conclusions: With the longest follow-up available to date in melanoma patients with asymptomatic brain metastases, the NIBIT-M2 study continues to show persistent therapeutic efficacy of I ipilimumab plus nivolumab while preserving HRQoL.

1. Introduction

Immune checkpoint inhibitors (ICI), anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) ipilimumab combined with anti-programmed death-1 (PD-1) nivolumab monoclonal antibodies (mAbs), have demonstrated to be effective in melanoma pts with

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asymptomatic brain metastases [1–5]. Two phase II studies reported that ipilimumab *plus* nivolumab induced objective intracranial responses in approximately 50% of patients [6,7], providing initial support for the combination in this hard-to-treat patient population. Furthermore, the phase III, randomized, NIBIT-M2 study, demonstrated the efficacy of ipilimumab *plus* nivolumab on the overall and long-term survival of melanoma patients with active, asymptomatic, and untreated brain metastases, with a 4-year OS rate of 41% [8]. Of note, objective clinical responses in brain metastases were paired by extra-cranial ones in most treated patients [6–8].

Due to the therapeutic efficacy of ipilimumab *plus* nivolumab in melanoma patients with brain metastases, patients reported outcomes (PROs), such as health related quality of life (HRQoL), are crucial to define pts-perceived health status. Along this line, the pivotal phase III CheckMate 067 study in metastastic melanoma patients w/o brain metastases, demonstrated that treatment with ipilimumab *plus* nivolumab maintained pts HRQoL, and no clinically meaningful deterioration was observed over time [9].

Here we report the 7-year OS results together with HRQoL data from the phase III NIBIT-M2 study.

2. Methods

2.1. Participants

Methods for the NIBIT-M2 trial (ClinicalTrials.gov. Identifier: NCT02460068; European Union Drug Regulating Authorities Clinical Trials, number 2012–004301-27) have been published elsewhere. (9, Data Supplement) Briefly, patients $\geq$ 18 years with stage IV, *BRAF* wild type or mutant melanoma with active, untreated and asymptomatic brain metastases (diameter 5–20 mm), a life expectancy $\geq$ 12 weeks (wks), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, were eligible for inclusion. Eligible patients were randomly assigned in a 1:1:1 ratio to fotemustine 100 mg/m^2 (Arm A), ipilimumab 10 mg/kg + fotemustine 100 mg/m^2 (Arm B), or ipilimumab 3 mg/kg *plus* nivolumab 1 mg/kg (Arm C). (Data Supplement [eFig. S1]). Treatment was continued until confirmed progressive disease, unacceptable toxicity, or patient refusal.

The primary endpoint was OS; among secondary were Progression Free Survival (PFS), Best Overall Response (BOR) as categorized by the World Health Organization (WHO; for Arm A), immune-related (ir) response criteria (for Arms B and C), and duration of response (DOR). HRQoL was collected at week (W) 1, 4,7, 12, 24, 36 + and at End of Treatment using the **EORTC** Quality of Life Questionnaire (QLQ)-C30 V.3, and the QLQ-Brain neoplasm (BN20).

The study was done in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. The protocol was approved by appropriate independent ethics committees of participating Institutions. All participants or their legal representatives provided written informed consent before enrolment.

2.2. Statistical analysis

Analyses of efficacy endpoints were performed on all randomized subjects who received at least one dose of fotemustine, ipilimumab *plus* fotemustine, or ipilimumab *plus* nivolumab. Secondary efficacy endpoints were evaluated with an exploratory intent and no formal hypothesis testing was planned. For the proportion endpoint ORR, exact two-sided 95% CIs were calculated using the binomial method. Immune-related DOR was estimated only for patients with a confirmed BOR of ir-complete or -partial response. Median follow-up was estimated with the reverse Kaplan-Meier method. All statistical analyses used IBM-SPSS statistical software, version 21.0.

HRQoL outcomes were evaluated in all patients who completed the questionnaire from baseline to W12. A questionnaire was considered complete if data were available for at least 50% of its scales, as per scale instructions [10]. HRQoL items, once scored according to guidelines, were summarized as mean and standard deviation; number of patientswith an absolute variation of more than 10 points (clinically meaningful value) in Global health Score (GhS) was also reported.

3. Results

Eighty melanoma patients with active, asymptomatic brain metastases were enrolled in the NIBIT-M2 study between January 24, 2013 to September 4, 2018, and 76 were randomly assigned to the 3 study Arms (27 to fotemustine, 26 to ipilimumab *plus* fotemustine, and 27 to ipilimumab *plus* nivolumab). Patient characteristics were well balanced (Table 1), as previously reported [9].

At data cutoff of May 1, 2023, the minimum follow-up was 56 months (mo), and the median follow-up was 48, 69, and 69 mo in the fotemustine, ipilimumab *plus* fotemustine, or ipilimumab *plus* nivolumab Arms, respectively. Most patients were off study therapy while 3 were still on treatment (1 in the ipilimumab *plus* fotemustine and 2 in the ipilimumab *plus* nivolumab Arms). With a median follow-up of 67 mo (IQR 42–79), median OS was 8.5 (95% CI: 4.8–12.2), 8.2 (95% CI: 2.2–14.3), and 29.2 (95% CI: 0–69.9) mo for Arm A, B, and C, respectively. The 7-year OS rate was 10.9% (95% CI: 0–24.4) in Arm A, 10.3% (95% CI: 0–22.6) in Arm B, and 42.8% (95% CI: 23.4–62.2) in Arm C, and it was significantly higher for ipilimumab *plus* nivolumab Arm compared to the fotemustine Arm ($p = 0.011$). (Fig. 1) The combination of ipilimumab *plus* nivolumab induced a 57% reduction in risk of death compared with F (HR 0.43, 95% CI: 0.22–0.86; $p = 0.016$), while risk of death did not differ between the ipilimumab *plus* fotemustine and the fotemustine Arms (HR 1.07, 95% CI 0.59–1.96.; $p = 0.82$) (Fig. 1).

The 7-year response rates are detailed in eTable S1. Briefly, intracranial and global ORR remained unchanged compared to the primary analysis of the study, with an intracranial ORR of 0%, 19.2% (95% CI: 4·1–34·4), and 44.4% (95% CI: 25·7–63·2) with fotemustine, ipilimumab *plus* fotemustine, and Iipilimumab *plus* nivolumab, respectively. Median intracranial DoR was 13.8 mo (10.5–17.2) and 49.0 (NE) mo in the ipilimumab *plus* fotemustineand ipilimumab *plus* nivolumab Arms. Median global and intracranial PFS was 3.0 (95% CI: 2.3–3.6), 3.3 (95% CI: 1.2–5.4), and 8.7 (95% CI: 0–19.9) for Arm A, B, and C, respectively. The 7-year intracranial PFS rate was 4.3% (95% CI: 0–12.7) in Arm A, 11.5% (95% CI: 0–23.8) in Arm B, and 43.5% (95% CI: 24.5–62.5) in Arm C. (eTable S1; Fig. 2).

Seventy-two patients (compliance 95%) and 34 patients (compliance 45%), and 67 patients (compliance 88%) and 32 (compliance 42%) patients completed the QLQ-C30 and -BN20 assessment at baseline and W12 respectively. The median (IQR) number of wks for which patients had completed questionnaires after baseline was 12 [7–12], 24 [7–60] and 96 (12−228) in Arm A, B and C, respectively. Due to the decrease in the proportion of responding patients in all treatment arms over time, the HRQoL analysis was limited up to W12. HRQoL was preserved in all treatment arms; no significant differences were observed in GhS. Mean baseline GhS was 73.0 (SD=18.4), 65.7 (SD=27.8) and 78.3 (SD=16.1) for Arm A, B and C, respectively; when assessing as clinically meaningful a variation in GhS of 10-point, a worsening $\geq$ 10-point was observed in 44% of pts for Arm A and B, and in 29% for Arm C. (Fig. 3) Most functional scales evaluated were preserved from baseline to W12, with a lower mean score decrease for QLQ-C30, and an increase for BN20 in patients receiving ipilimumab *plus* nivolumab (data not shown).

Neither new and long-term side effects nor treatment-related deaths were observed in all treatment Arms, except for 1 patient who was discontinued after 69 mo of therapy in the ipilimumab *plus* nivolumab Arm due to a ir G4 lipase, amylase increase (Table 2).

4. Discussion

To our knowledge, the 7-year results of the phase 3 NIBIT-M2 study

Table 1
Baseline characteristics.

	Fotemustine (n=23)[a]	ipilimumab plus fotemustine (n=26)	Ipilimumab plus nivolumab (n=27)
SexMaleFemale	15 (65%)[b]8 (35%)	16 (62%)10 (38%)	17 (63%)10 (37%)
Age (years)	57 [20–80][c]	60 [31–74]	56 [25–79]
ECOG performance status01	21 (91%)2 (9%)	18 (69%)8 (31%)	22 (81%)5 (19%)
Number of brain lesions123 > 3	5 (22%)3 (13%)5 (22%)10 (43%)	12 (46%)8 (31%)1 (4%)5 (19%)	7 (26%)8 (30%)3 (11%)9 (33%)
Target brain lesion diameters (mm)5×55–20	6 (26%)17 (74%)	4 (15%)22 (85%)	5 (19%)22 (81%)
Previous local treatments for brain metastasesSurgeryStereotactic radiosurgeryWhole brain radiotherapy	4 (17%)2 (9%)1 (4%)	5 (19%)00	7 (26%)00
BRAF statusMutated (*BRAF*-V600)Wild typeUnknown	8 (35%)13 (57%)2 (9%)	11 (42%)15 (58%)0	11 (41%)15 (56%)1 (4%)
Serum lactate dehydrogenaseElevatedNormal	3 (13%)20 (87%)	13 (50%)13 (50%)	7 (26%)20 (74%)

Abbreviations: ECOG=Eastern Cooperative Oncology Group.
a Number of treated patients per Arm;
b n (%);
[c] Median (range).

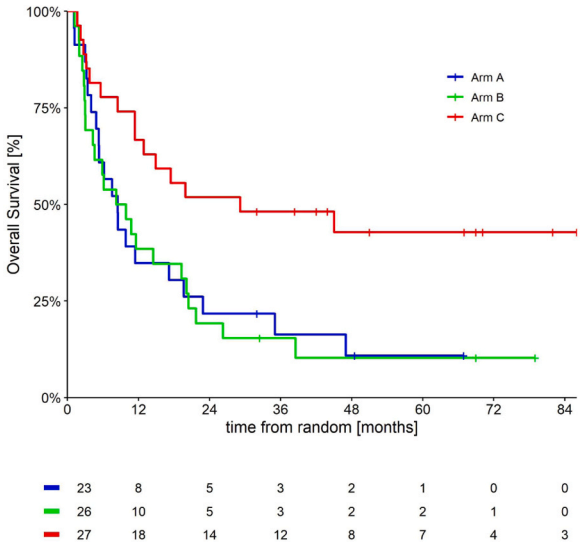

Fig. 1. Kaplan-Meier plots of overall survival of all treated patients. Vertical lines indicate censoring. CI=confidence interval. HR=hazard ratio.

provide the longest evidence of the efficacy of ipilimumab *plus* nivolumab in melanoma patients with active, untreated, asymptomatic brain metastases The 4-year primary analysis of the NIBIT-M2 study demonstrated that treatment with ipilimumab *plus* nivolumab induced an intriguing 41% OS rate in melanoma patients with brain metastases [8]; of note, results from the Checkmate 204 trial showed a 3-year OS rate of 71% [11], while the ABC trial demonstrated a 50% OS rate at 5-years [7]. The initial findings of the NIBIT-M2 study are now corroborated by its 7-year results that continue to show a persistent therapeutic efficacy of the ipilimumab *plus* nivolumab regimen, with a 43% OS rate. The long-term efficacy of the ipilimumab *plus* nivolumab combination, seems to be also enforced by the finding that the largest

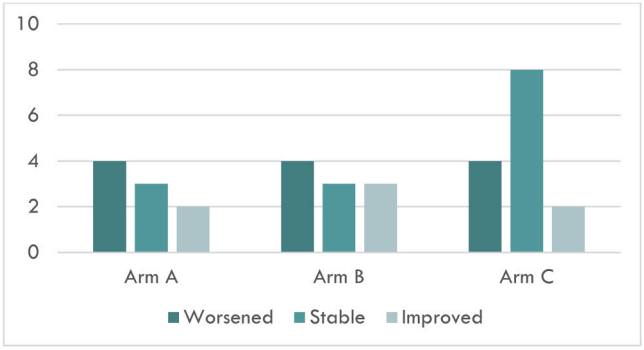

Fig. 3. Changes in Global QoL scores from baseline to week 12. Worsened: absolute change > 10 in negative; Stable: absolute change between − 10 and + 10; Improved: absolute change > 10 in positive.

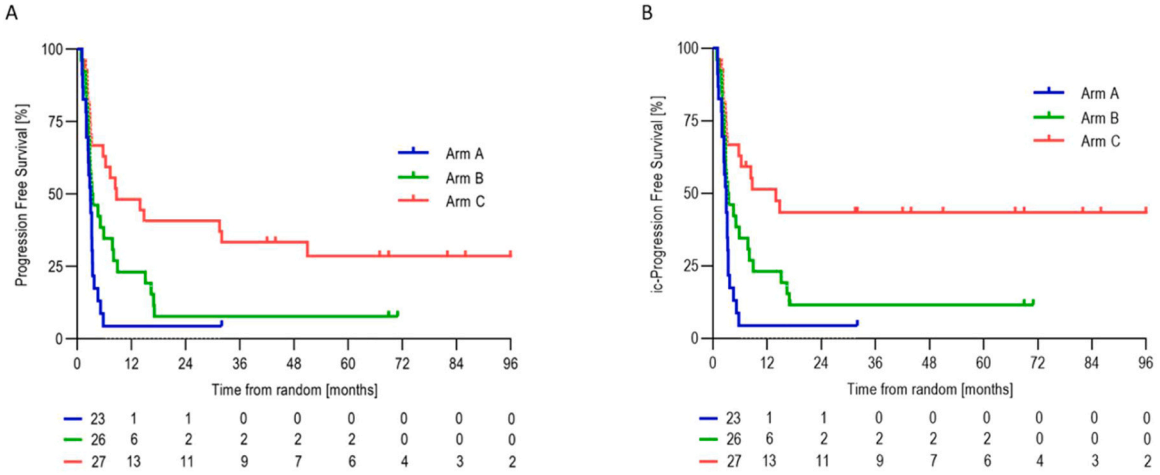

Fig. 2. Kaplan-Meier plots of (A) global and (B) Intracranial progression-free survival of all treated patients. Vertical lines indicate censoring. CI=confidence interval. HR=hazard ratio.

Table 2
Summary of adverse events occurring in the study population.

	Fotemustine (n=23)[a]		Ipilimumab plus fotemustine (n=26)		Ipilimumab plus nivolumab (n=27)	
	Any Grade	G3-G4	Any Grade	G3-G4	Any Grade	G3-G4
Any adverse event[b]	**23 (100%)[c]**	**16 (70%)**	**23 (88%)**	**22 (85%)**	**23(85%)**	**14 (52%)**
Treatment-related adverse events	**19 (83%)**	**11 (48%)**	**21 (81%)**	**18 (69%)**	**21 (78%)**	**9 (33%)**
Nausea	3 (13%)	0	3 (12%)	0	3 (11%)	0
Vomiting	0	0	1 (4%)	0	1 (4%)	0
MyelotoxicityAnaemiaThrombocytopeniaNeutropeniaLeukopenia	5 (22%)11 (48%) 10 (43%)10 (43%)	04 (17%)7 (30%)3 (13%)	3 (12%)14 (54%)10 (38%) 2 (8%)	1 (4%)10 (38%) 6 (23%)2 (8%)	0000	0000
Other (fever, fatigue, liver)	10 (43%)	3 (13%)	8 (31%)	1 (4%)	12(44%)	0
Any immune-related adverse events	**0**	**0**	**15 (58%)**	**10 (38%)**	**19 (70%)**	**9 (33%)**
SkinRash PruritusTEN	000	000	9 (35%)5 (19%) 0	3(11.5%)00	10(37%)6 (22%)1 (4%)	1(4%)01 (4%)
HepaticALT increaseAST increaseBilirubin increaseHepatic failure	000	000	8 (31%)9 (35%) 2 (8%)1 (4%)	7 (27%)3 (12%) 01 (4%)	10 (37%)8 (30%)01 (4%)	5 (19%)3 (11%)01 (4%)
Gastrointestinal (diarrhoea or colitis)	0	0	5 (19%)	2 (8%)	7 (26%)	2 (7%)
EndocrineHyperthyroidismHypothyroidismHypophysitis	000	000	3 (12%)3 (12%) 0	2 (8%)00	3 (11%)4 (15%)1 (4%)	000
Other (amylase or lipase increase)	0	0	0	0	3 (11%)	1 (4%)

Abbreviations: ALT=alanine aminotransferase. AST=aspartate aminotransferase. G=grade. TEN=toxic epidermal necrolysis.
All reported treatment-related and immune-related adverse events are shown.
a Number of treated patients per cohort;
b AEs were graded using the NCI Common Terminology Criteria for Adverse Events (version 4.0);
c n (%).

proportion (67%) of pts who were alive at 7-years (i.e., 12 out of the 27 enrolled pts) in the ipilimumab *plus* nivolumab Arm of the NIBIT-M2 study were also treatment-free. Additionally, among patients who were alive at 7-years and who received subsequent treatment (33%) in the ipilimumab *plus* nivolumab Arm, none had progressed in the brain. Altogether, these findings, though generated in a limited number of patients in all available studies, contribute to break the dogma that the blood-brain barrier limits the efficacy of ICI therapy in melanoma patients [1]. Additionally, treatment with ipilimumab *plus* nivolumab seems to provide both an effective regimen in the presence of asymptomatic melanoma brain metastases but also to protect from long-term disease recurrence in the brain [7,8].

In addition to its therapeutic efficacy, the HRQoL assessment performed in the NIBIT-M2 study showed that treatment with ipilimumab *plus* nivolumab did not significantly impair the quality of life of treated pts. Indeed, a lower decrease in the mean QLQ-C30 scores and a lower increase in BN20 scores was observed in the ipilimumab *plus* nivolumab Arm as compared to the fotemustine and ipilimumab *plus* fotemustine Arms. This evidence, despite limited by the small number of pts, finds support in the recent results from the phase II ABC study, showing that ipilimumab *plus* nivolumab -treated patients did not report a significant deterioration in HRQoL within the initial 18 wks of therapy [12].

From the daily practice viewpoint, an additional relevant finding of the 7-year follow-up of the NIBIT-M2 study seems to derive from the lack of long-term immune-mediated brain AEs, possibly due to ipilimumab *plus* nivolumab therapy. Consistent with these results the Checkmate 204 trial reported 7% G 3–4 neurological treatment-related AEs, at 3-year follow-up [11].

5. Conclusions

Treatment with ipilimumab *plus* nivolumab has become the standard of care first-line regimen of melanoma patients with asymptomatic brain metastases. The 7-year results of the NIBIT-M2 study, together with the evidence that clinical responses to ipilimumab *plus* nivolumab in the brain are paired with extra-cranial ones, seem to enforce the notion that a meaningful percentage of these hard-to-treat patients may indeed achieve a cure from ipilimumab *plus* nivolumab therapy.

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CRediT authorship contribution statement

Mandalà Mario: Data curation, Investigation, Supervision, Writing – review & editing. **Ferrucci Pier Francesco:** Data curation, Investigation, Supervision, Writing – review & editing. **Valente Monica:** Data curation, Investigation, Validation, Writing – review & editing. **Del Vecchio Michele:** Data curation, Investigation, Supervision, Writing – review & editing. **Guida Michele:** Data curation, Investigation, Supervision, Writing – review & editing. **Maio Michele:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Writing – original draft, Validation, Writing – review & editing. **Guidoboni Massimo:** Data curation, Investigation, Supervision, Writing – review & editing. **Calabrò Luana:** Data curation, Investigation, Validation, Writing – review & editing. **Quaglino Pietro:** Data curation, Investigation, Supervision, Writing – review & editing. **Simonetti Elena:** Data curation, Investigation, Visualization, Writing – review & editing. **Marchetti Paolo:** Data curation, Investigation, Supervision, Writing – review & editing. **Amato Giovanni:** Data curation, Methodology, Validation, Visualization, Writing – review & editing. **Santangelo Federica:** Data curation, Investigation, Visualization, Writing – review & editing. **Camerini Roberto:** Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. **Chiarion-Sileni Vanna:** Data curation, Investigation, Validation, Writing – review & editing. **Covre Alessia:** Data curation, Methodology, Validation, Writing – review & editing. **Di Giacomo Anna Maria:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Giannarelli Diana:** Formal analysis, Methodology, Software, Validation, Writing – review & editing.

Declaration of Competing Interest

AMDG has served as a consultant and/or advisor to Incyte, Pierre Fabre, Glaxo Smith Kline, Bristol-Myers Squibb, Merck Sharp Dohme, Sunpharma, Immunocore and Sanofi and has received compensated educational activities from Bristol Myers Squibb, Merck Sharp Dohme, Pierre Fabre and Sanofi; VCS has served as advisor to Merk Serono, Novartis, and Pierre Fabre and has received travel accommodation from Bristol-Myers Squibb, and Pierre Fabre and has received personal fees as invited speaker from Sanofi, Merck Sharp Dohme, and Pierre Fabre; MDV has served as consultant and/or advisor to Bristol-Myers Squibb, Merck Sharp Dohme, Novartis, Pierre Fabre, Sanofi, and Roche; PFF has served as consultant and/or advisor to Bristol-Myers Squibb, Pierre Fabre, Merck Sharp Dohme, Roche and Novartis; MG has served as a consultant and/or advisor to Bristol-Myers Squibb, Merck Sharp Dohme, and Novartis; PQ has served as consultant and/or advisor to Bristol-Myers Squibb, Merck Sharp Dohme, Novartis, Roche, Pierre Fabre, and Igea and has received personal fees as invited speaker from Bristol-Myers Squibb, Merck Sharp Dohme, Novartis, Roche, Pierre Fabre, and Igea; M Guidoboni has served as consultant and/or advisor to Bristol-Myers Squibb, Merck Sharp Dohme, Novartis, Pierre Fabre and has received grant support from Merck Sharp Dohme; PM has served as a consultant and/or advisor to Roche, Bristol-Myers Squibb, Novartis, Pfizer, Merck Sharp Dohme, AstraZeneca and has received research funding from Bristol-Myers Squibb, Novartis, Pfizer, Merck Sharp Dohme, AstraZeneca, Boehringer, Celgene, and Roche; LC has served as consultant and/or advisor to Bristol-Myers Squibb, Roche, and Merck Sharp Dohme, and has received compensated educational activities from Bristol Myers Squibb, AstraZeneca and Sanofi; RD has served as a consultant and/or advisor to Merck Serono, Sciclone Pharmaceuticals, and has received compensated educational activities from Bristol Myers Squibb, Merck Sharp Dohme, Pierre Fabre; MM has served as consultant and/or advisor to Bristol-Myers Squibb, Pierre Fabre, Merck Serono, Sanofi Aventis and Novartis, and has received grant support from Novartis; M Maio has served as a consultant and/or advisor to Roche, Bristol-Myers Squibb, Merck Sharp Dohme, Incyte, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, Glaxo Smith Kline, Sciclone, Sanofi, Alfasigma, and Merck Serono; M Maio, RC, and AC own shares in Epigen Therapeutics, Srl. The other authors declare no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113531.

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