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Multicenter phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-α2b in metastatic melanoma

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Background: The addition of cytokines to chemotherapy (CT) has obtained encouraging but contradictory results in metastatic melanoma. In this phase III trial, we compared the effects of CT [cisplatin, vindesine and dacarbazine (CVD)] with those of concurrent biochemotherapy (bioCT) consisting of CVD plus interleukin-2 and interferon-α2b.
Patients and methods: A total of 151 untreated metastatic melanoma patients were randomized, 75 on arm A (cisplatin 30 mg/m^2 on days 1–3, vindesine 2.5 mg/m^2 on day 1 and dacarbazine 250 mg/m^2 on days 1–3), and 76 on arm B (same CVD scheme plus interferon-α2b on days 1–5 and interleukin-2 on days 1–5 and 8–15, both administered subcutaneously), either recycled every 3 weeks. Response was assessed every two cycles.
Results: Ten percent of the patients were alive at a median of 52 months from start of therapy. We observed a response rate (RR) of 21% on arm A versus 33% on arm B; three patients (4%) given bioCT had complete responses (CRs). Median time to progression (TTP) was identical; median overall survival (OS) time was 12 months on arm A and 11 months on arm B.
Conclusions: BioCT is not better than CT alone; the trend in favor of the bioCT in terms of RR did not translate into better TTP or OS. Therefore, bioCT cannot be recommended as standard first-line therapy for metastatic melanoma.
Key words: chemotherapy, cytokines, immunotherapy, metastatic melanoma

introduction

Melanoma is showing a rapid worldwide rise in incidence, with a yearly increase of about 5% and a frequent occurrence in young adults [1]. Even though surgery represents the cure in the early phase of disease, the prognosis in patients with metastatic melanoma remains very poor, with a median survival of about 6–9 months [2–4]. Dacarbazine is the most active single agent, with a RR of about 10%–20%. Combination chemotherapy using the 5-day or 3-day regimens consisting of cisplatin, vinblastine or vindesine, and dacarbazine (CVD), administered at 3-week intervals have produced response rates of 20%–35% [5]. However, complete response (CR) rates are low (4%) and responses are typically short lasting (median 6 months). Moreover, this and other polychemotherapy regimens were not more effective than dacarbazine alone at prolonging survival [6–9]. Cytokines such as interferons also produce clinical responses in 10%–20% of patients with metastatic melanoma [10, 11]. Globally, about 15% of patients treated with interferon-α2b (IFN-α2b) obtained tumor regression, with 5% of CRs characterized by a duration of several months and, in some cases, even years. Interleukin-2 (IL-2), also FDA approved for use in advanced melanoma, induced durable CR rates of approximately 4%. The modest clinical activity of single treatments (chemotherapy or immunotherapy) prompted use of a combined biochemotherapy or chemoimmunotherapy approach.

The rationale underlying the use of a combined biochemotherapy approach is founded on: the lack of cross-resistance; the evidence that chemotherapy could enhance macrophage activation, production of reactive oxygen intermediates in macrophages and the NK cell lytic activity; the evidence that biotherapy could synergize with chemotherapy, considering the IFN-α cytostatic mechanism of action, the action of IL-2-induced cytokines, IL-1/TNF-α, and the potential induction of the production of nitric oxide, a tumor cell killer [13]. Impressive results were obtained in

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non-randomized phase II trials using sequential and concurrent biochemotherapy (chemotherapy + IFN/IL-2), with overall RR of up to 60%, CR rate of 10%–20% and a certain improvement in terms of median time to progression (TTP) and median overall survival (OS) [14–19]. On the basis of these encouraging results, a number of randomized phase III trials were started with the aim of determining the superiority of the combined approach over the single treatment [20–27].

Therefore, in 1999 we activated a phase III prospective, randomized trial to compare the effects of concurrent biochemotherapy (bioCT) using CVD plus IFN-α2b and IL-2, both administered subcutaneously (s.c.), with those of the same CVD scheme alone (CT) in terms of clinical response, TTP and OS for patients with stage IV melanoma.

patients and methods

patient eligibility

This open-label, multicenter, randomized phase III trial was conducted by six Italian Institutions and coordinated by the Medical Oncology Unit 2 of the Istituto Nazionale per lo Studio e la Cura dei Tumori of Milan. All patients had previously undergone surgery to remove a primary cutaneous melanoma or metastatic melanoma of unknown primary site, with 41 patients having received subsequent adjuvant IFN-α2b. Eligible patients were at least 18 years of age, with histologically or cytologically confirmed measurable diagnosis of advanced, inoperable non-choroidal melanoma; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, no previous treatment for metastatic disease, adequate bone marrow [absolute neutrophil count (ANC) $\geq 1500/mm^3$, platelets $\geq 100\ 000/mm^3$], normal renal (serum creatinine ≤1.5 mg/dl) and hepatic functions; absence of brain metastases, absence of significant concomitant diseases, life expectancy of at least 4 months, absence of latent or clinically evident autoimmune diseases, verified through the absence of the antithyroglobulin antibodies; corticosteroid therapy was not allowed or, otherwise, a wash-out period of at least 3 weeks was necessary; absence of a history of other cancers (with the exception of cured basal cell skin carcinoma or *in situ* carcinoma of the uterine cervix). The study was conducted in accordance with the Declaration of Helsinki. The protocol for this multicenter study was approved by the Institutional Review Board (IRB) and Ethics Committees at each participating center. All patients gave written informed consent before randomization that was centralized by Scientific Secretary of Medical Oncology Unit 2 of the Istituto Nazionale Tumori of Milan.

treatment plan and dose adjustments

A randomization scheme stratified by previous IFN treatment in adjuvant setting and for disease site (viscera versus soft tissues) was used to assign patients to receive chemotherapy (CT, arm A) or concurrent biochemotherapy (bioCT, arm B). Arm A consisted of cisplatin at a dose of 30 mg/m^2 of body surface area on days 1–3, vindesine 2.5 mg/m^2 on day 1 only and dacarbazine 250 mg/m^2 on days 1–3. Arm B involved the same chemotherapy regimen plus IL-2 s.c. (Proleukin; Chiron) at a dosage of 9 million IU/day (flat dose) on days 1–5 and 8–15 and IFN-α2b (Intron-A; Schering-Plough) given at a dose of 5 MU/m^2 of body surface area/day s.c. on days 1–5. All patients were scheduled to receive at least two cycles of therapy. The treatment was repeated every 21 days for a maximum of six cycles or until disease progression (PD) or severe toxicity occurred. In both study arms, chemotherapy was administered on an outpatient basis for 3 consecutive days; for the arm B, in association with immunotherapy. Vials of IFN-α2b and insulin syringes with the correct dose of IL-2 were usually prepared at the Institute and given to the patient. These were then stored in the refrigerator and the cytokines were administered at home over the scheduled days (up to a maximum of 7 days). Before starting each cycle, patients underwent physical examination, toxicity assessment using NCI-CTC, and complete biochemistry and hematology tests. We sought to maintain dose and schedule intensity. If the ANC was less than 1500/μl or if the platelets were less than 100 000/μl, treatment was delayed for 1 week. If these low counts persisted, the dose of both chemotherapeutic drugs and cytokines was reduced by 25%. This dose reduction was maintained for the successive cycles. In case of persistence of neutropenia for ≥2 weeks, growth factors were used. In the presence of grade 1 renal toxicity or grade 2 hepatic toxicity, treatment was delayed for 1 week. In case of persistence of these toxicities, we forecasted a 25%–50% reduction of chemotherapy and interruption of immunotherapy, maintaining all these dose reductions for the successive cycles. In case of grade 3 toxicity (with the exception of fever and alopecia), treatment was delayed for 1 or 2 weeks. For any grade 4 toxicity, treatment was discontinued.

clinical assessments

Tumors were evaluated by radiography, computed tomography (CT) scan, nuclear magnetic resonance (NMR) imaging and photography at baseline and at 6-week intervals thereafter. All measurable and evaluable lesions were assessed by the same method used at baseline. CR was defined as the disappearance of all known disease; partial response (PR) and stable disease (SD) were defined as reduction of ≥50% and as increase of <25% of the sum of the products of the largest perpendicular diameters of all measurable lesions, respectively. No new lesions could have appeared. PD was defined as the enlargement of any measurable lesion by more than 25% or the development of new metastatic lesions. All objective responses (ORs) were to be confirmed on two separate measurements not less than 4 weeks apart.

statistical analysis

The primary endpoint of the study was to compare OS between the two treatment groups (CT versus bioCT). Secondary objectives included evaluation of response rates, TTP and toxicity profile. The analysis was made on an intention-to-treat (ITT) basis. With a two-sided 5% significance level, this study was designed to detect an absolute increase in 1-year OS from randomization of 20% in patients treated with bioCT: a sample size of at least 140 patients was required (log-rank model). Confidence intervals (CI) were used to determine the 95% upper and lower confidence limits of a response rate. Survival, progression analyses and graphs were performed using Kaplan–Meier methods. All analyses were performed using SAS 8.0.

results

patients

Between February 1999 and February 2003, 151 patients were accrued and randomized onto this study, including 75 in arm A (CT arm) and 76 in arm B (bioCT arm). Patients' pretreatment characteristics are summarized by treatment group in Table 1. The two arms were well balanced with respect to the stratification factors. Globally, seven (5%) patients were ineligible. In arm A, one was ineligible for presence of brain metastases, one bearing primary choroidal melanoma and one for a significant increase in transaminases. In arm B, one was ineligible for absence of the informed consent, one for HBV positiveness and two bearing primary choroidal

melanoma (Figure 1). Most patients (98%) had an ECOG PS of 0–1 and 41 patients (28%) had received interferon previously. Approximately 63% of patients had involvement of viscera with or without other metastatic sites, 13% had bone metastases ± other sites, 14% of patients showed soft tissue ± lymph node involvement, and 10% of patients had only lymph node disease. All the patients except one (unknown primary site melanoma) had previously undergone radical resection of primary cutaneous melanoma. Time to relapse following surgical resection varied from 1 to 228 months, with a median value of 14.5 months for the CT arm and 13 for the bioCT arm.

Table 1. Main patient characteristics

	Arm A, CT (n = 72)		Arm B, bioCT (n = 72)	
	n	%	*n*	%
Gender				
Male	50	69	41	57
Female	22	31	31	42
Median age (range years)	51.5	(19–70)	46.5	(19–70)
PS – ECOG				
0/1	72	100	71	99
2	–		1	1
Previous IFN treatment	20	28	21	29
High pretreatment LDH levels	19	26	15	21
Disease site				
Soft tissue ± lymph nodes	10	14	10	14
Lymph nodes only	7	10	7	10
Viscera ± other	47	65	44	61
Bone ± other	8	11	11	15
Sites of disease				
1 site	25	35	22	30
≥2 sites	47	65	50	69

treatment administration

Globally, 638 cycles were administered, 333 in arm A and 308 in arm B. The median number of cycles per patient was six in arm A: 21% of patients received one to two cycles, 18% of patients had three to four cycles while the remaining 61% of patients had five to six cycles; and five in arm B: 22% of patients received one to two cycles, 19% three to four cycles and, finally, 59% received five to six cycles.

clinical responses

Globally, 138 patients were assessable for response because six (4%) discontinued the trial after randomization or first cycle, two in arm A and four in arm B. OR data for both groups are presented in Table 2. Twenty-four patients receiving bioCT had a RR of 33% (95% CI 24% to 46%), including three CRs (4%) and 21 PRs (29%); which is superior to that produced by CT alone 21% (95% CI 13% to 31%), including 15 PRs (21%). The differential RR was consistent across prognostic groups, and the highest frequency of response was in patients with soft tissue metastases (skin, subcutaneous, lymph node), lung metastases or both (Table 3). However, we observed a greater number of responses at viscera ± other sites in arm B (75%).

To date, just one patient is alive and disease-free at 39+ months after completing treatment. The median duration of the three CRs, in arm B, was 6 months (2–39+), with the first site of relapse being the brain in two out of three patients; in one of these patients, the brain was the only site of recurrence.

The overall incidence of brain metastases at the time of this report was 38% in both treatment groups; 39% in arm A and 38% in arm B. Among these patients with CNS metastases, brain represented the first site of disease recurrence in 48% of cases in arm A and 68% in arm B, respectively.

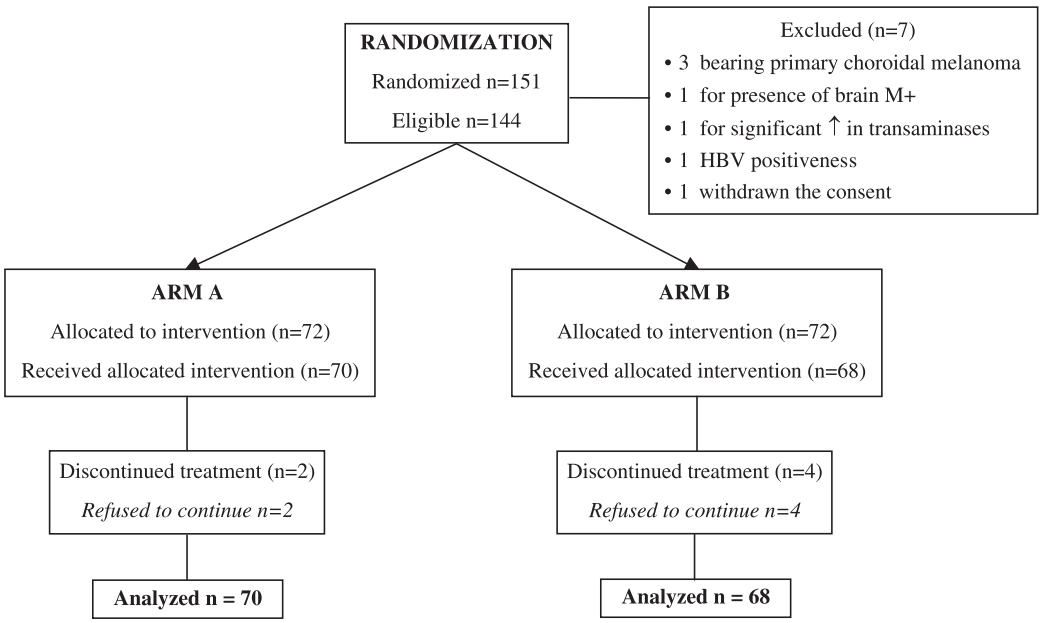

Figure 1. Patient flow chart.

Table 2. Clinical efficacy

	Arm A, CT (n = 72)			Arm B, bioCT (n = 72)		
	n	%	95% CI	n	%	95% CI
CR	0	–	–	3	4	
PR	15	21		21	29	
Objective response (CR + PR)	15	21	(13–31)	24	33	(24–46)
SD	40	55	(47–70)	19	26	(17–37)
PD	15	21	(13–31)	25	35	(26–48)
Not evaluable	2	3		4	6	
Duration of response						
CR + PR median (range)	4 months (2–25)			6 months (2–39+)		
SD median (range)	4.5 months (2–34+)			5 months (1–26)		

Table 3. Characteristics of responding patients

	Arm A, CT (n = 72)		Arm B, bioCT (n = 72)	
	n	%	n	%
Objective response (CR + PR)	15	21	24	35
Gender				
Male	10	62	11	46
Female	5	38	13	54
Median age (range years)	57.5	(32–70)	51	(29–69)
PS – ECOG				
0/1	14/1	99/1	22/1	92/4
2	0	–	1	4
Previous IFN treatment	2	13	6	25
High pretreatment LDH levels	4	27	2	8
Disease site				
Soft tissue ± lymph nodes	1	7	2	8
Lymph nodes only	3	20	2	8
Viscera ± other	10	67	18	75
Bone ± other	2	13	2	8
Sites of disease				
1 site	0	–	3	12.5
≥2 sites	15	100	21	87.5

time to progression (TTP)

In the final data no differences in the TTP were observed, with a median of 6 months for both treatment groups (Figure 2). Also, among those patients who had complete or partial response, median TTP was not different between the two treatment groups (8 months in both arms). Patients whose disease did not respond had a median TTP of 4.5 months in arm A and 3 months in arm B. The difference between non-responsive and responsive patients is more significant in patients treated with the bioCT scheme (3 versus 8 months).

survival

Enrollment in the bioCT arm did not improve median survival time over that of the CT arm (11 versus 12 months) (Figure 3). Among those who achieved OR to therapy, median survival time was 15.5 months for arm A and 19 months for arm B. Patients with PD showed median survival equal to 11 months in both treatment arms.

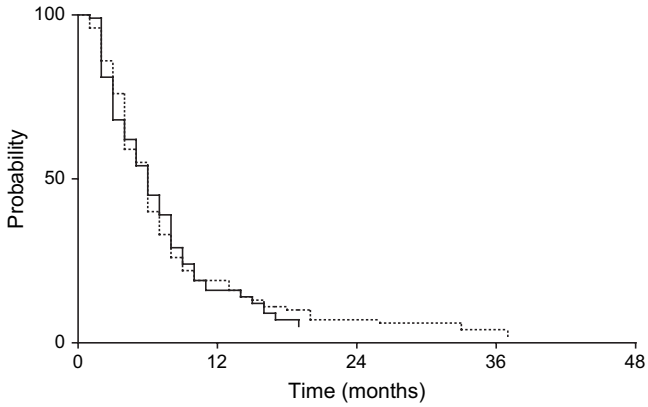

Figure 2. Kaplan–Meier estimates of TTP in the two treatment groups: arm A, CT (dashed line); arm B, bioCT (solid line).

We obtained an OS rate compatible with literature data. In our trial, the 1-year survival rate was 49.8% for the CT arm and 43.4% for the bioCT arm; therefore, the trial could not be considered positive.

Twenty-four percent of the patients treated in the CT arm were subsequently crossed over to receive IL-2 and IFN-based immunotherapy after PD. Obviously this could introduce a bias, causing overestimation of the OS data in the CT arm. However, this issue could have an influence on OS, not on RR, and it is a drawback of any such study.

toxic effects

Frequency of grade 3 or 4 toxic effects was not significantly higher in the bioCT arm than in the CT arm (Table 4), an interesting finding considering the number of responses and the performance of the IL-2/IFN-based immunotherapy on outpatient setting. Nevertheless, nearly all of the toxic effects associated with bioCT were expected and were reversible with cessation of treatment.

In arm B, the episodes of grade 3/4 anemia were almost three times more than in arm A (11.1% versus 4.1%); grade 3/4 leukopenia and thrombocytopenia had practically the same

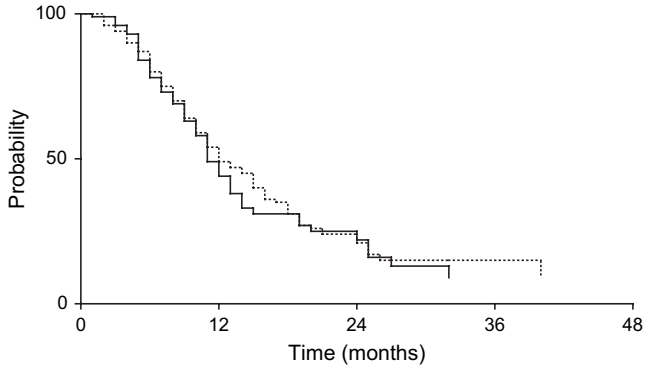

Figure 3. Kaplan–Meier estimates of OS in the two treatment groups: arm A, CT (dashed line); arm B, bioCT (solid line). One-year survival rate was 49.8% for arm A (CT), and 43.4% for arm B (bioCT).

Table 4. Toxicity profile (only grade 3–4)

Adverse event	Arm A, CT (n = 72)		Arm B, bioCT (n = 72)	
	n	%	n	%
Non-hematologic toxicity				
Flu-like syndrome				
Fever	0	–	26	36.1
Asthenia/fatigue	6	8.3	14	19
Headache	0	–	1	1.4
Nausea/vomiting	9	12.5	22	30
Constipation	1	1.4	0	–
Skin rashes	0	–	2	2.7
Hematologic toxicity				
Anemia	3	4.1	8	11.1
Neutropenia	9	12.5	11	15.2
Leukopenia	3	4.1	4	5.5
Thrombocytopenia	7	9.7	6	8.3
Liver toxicity	0	–	3	4.1

frequency in the two treatment arms. Just three cases of grade 3 liver toxicity, without significant sequelae, were observed in the bioCT arm. Grade 3/4 flu-like syndrome, totally manageable in the outpatient setting, was observed in 36.1% of patients treated with bioCT; therefore, the constitutional symptoms were greater but the overall toxicity was overlapping, if compared with CT alone. No treatment-related deaths occurred.

discussion

All previous phase III clinical trials failed to demonstrate a clear superiority of a combined biochemotherapy approach over either chemotherapy or immunotherapy alone [20–27].

In 1999, Rosenberg prematurely closed his phase III trial comparing CT (CDDP, DTIC, TAM) with the same scheme plus IFN-α2b and high-dose bolus IL-2, following a higher OS in patients treated with CT alone [22]. In another randomized phase III trial, Eton et al. [24] compared CT alone (CDDP, DTIC, Vinblastine) with the same regimen in association with IFN-α2b and IL-2 given in continuous i.v. infusion. The authors practically observed a doubling of the RR (48% versus 25%) and TTP (4.9 versus 2.4 months), with an improvement of the OS reaching borderline statistical significance. In this case, the biotherapy was completely administered in the inpatient setting.

The preliminary data of the Intergroup E-3695 trial, comparing a modified version of the concurrent biochemotherapy regimen using CVD-based chemotherapy on 416 patients, have indicated a slightly higher response rate (17.1 versus 11.4%) and PFS (5.3 versus 3.6 months) in favor of the combined approach [26]. However, no improvement in either quality of response or OS (8.4 versus 8.7 months) was observed despite a significant increase of the global toxicity (hypotension, metabolic abnormalities, fatigue, hepatic dysfunction and myelotoxicity) and costs.

Virtually identical response, TTP and OS rates were observed in the report by Keilholz et al. [27] on the EORTC 18951 randomized phase III trial comparing DTIC+CDDP+IFN-α versus the same regimen + intravenous IL-2 in 363 patients.

In our trial we found that concurrent bioCT, based on the subcutaneous administration of both cytokines, was able to induce an improvement in terms of RR and CR rate, whereas no differences on the median TTP and OS were observed. The durable CRs for the tested regimen (4%) were few, considering the favorable patients characteristics profile in terms of PS, pretreatment LDH levels and absence of brain metastases. One of the possible reasons could be, at least in part, the high number of patients with the involvement of multiple visceral organs (Table 3).

No conclusion can be made regarding the impact of previous adjuvant interferon therapy on the durable response rate and on the global response rate to bioCT because fewer than 21 patients (29%) received such therapy in either arm.

There are other potential causes for the small number of the CRs observed, such as the schedules of the cytokines used. In our trial we decided to use a concurrent bioCT regimen, according to Legha's finding, that it is easier to administer and better tolerated than sequential bioCT. In Legha's phase III trial a trend in terms of improved OS in favor of the combined therapy was shown, in spite of the fact that 51% of the patients treated with chemotherapy alone were subsequently crossed over to receive IL-2 and/or IFN-α2b [24]. In their conclusion, the authors stated that the absolute results could have been more impressive if the eligibility criteria had been more selective, considering that the greatest clinical impact was observed in patients with good PS, soft tissue and/or lung metastases only, without evidence of brain metastases.

In our trial we confirm these data; nevertheless, we observed a greater number of responses at viscera ± other sites (75%). This is important, considering that viscera and particularly liver are, characteristically, sites refractory to chemotherapy and biological therapies in general. Thus, a trend in favor of bioCT in terms of RR and CR rate is evident, moreover, in the absence of severe toxicity generally associated with the use of high-dose IL-2 administered intravenously.

These last considerations are intriguing considering that the advance, represented by the addition of cytokines in terms of clinical activity on a historically chemoresistant tumor,

is usually tempered by the considerable toxicity. In our regimen, the immunotherapy is completely manageable in an outpatient setting with a consequent favorable impact on the patients' quality of life and acceptability of the treatment. An important future issue should be the identification of a specific subset of patients for whom the addition of a biotherapy is likely to be more useful.

A recent report has demonstrated that circulating DNA markers (microsatellites) may be useful, as molecular determinants, in assessing the response of advanced melanoma patients to bioCT [28]. The presence of loss of heterozygosity (LOH) in the serum of patients with advanced/metastatic melanoma was associated, in a statistically significant way, with a poorer response to induction bioCT and, independently, with patient outcome. More recently, some authors have used circulating DNA with allelic imbalance on 12q22-23 in serum as a surrogate marker to predict bioCT responsiveness, observing a significantly lower frequency of such an allelic imbalance in bioCT responders [29]. Also in our trial, brain represented the most frequent site of disease relapse independently of the treatment arm, thus raising considerations of including agents able to cross the blood–brain barrier, such as temozolomide or fotemustine [30]. In conclusion, chemoimmunotherapy does not represent the standard first-line medical treatment of stage IV melanoma patients at the moment; in fact, our trial also failed to demonstrate a survival advantage using the combined approach.

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