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Review

Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years?

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Abstract

Since dacarbazine was approved for treating metastatic melanoma in the 1970s, numerous studies have evaluated whether different schedules and dacarbazine-based combinations improve clinical outcomes. This evidence-based review shows that combining dacarbazine with other drugs having single-agent activity and/or hormonal or immunotherapeutic compounds fails to provide clinically meaningful improvements in survival, and may increase toxicity. In patients with metastatic melanoma, dacarbazine was previously administered in cycles of multiple consecutive daily infusions per cycle. The introduction of potent antiemetics, together with concerns relating to patient comfort and clinic utilisation time, has enabled regimens involving single-dose dacarbazine, administered at the same total dose per cycle. These appear to be as effective as multiple-dose schedules, are well tolerated, and are more straightforward to administer. Single-administration dacarbazine (850–1000 mg/m^2), once every 3 weeks, is currently the standard reference therapy in patients with advanced melanoma. New effective therapies are urgently needed for this treatment-refractory disease.

Keywords: Metastatic melanoma; Dacarbazine; DTIC

1. Introduction

Melanoma is an increasingly common disease worldwide, with an estimated 53 600 new cases and 7400 deaths from this malignancy in the United States of America (USA) in 2002 [1]. However, improved general awareness and increased diagnosis of early stage disease – which is typically surgically curable – have led to an overall stabilisation in melanoma-related mortality rates [2]. The clinical course of melanoma is determined by its dissemination and depends on thickness, ulceration, localisation and histology of the primary tumour, in addition to patient gender. Tumour stage at diagnosis is of key importance [3]. Early-stage melanoma can be readily cured by excision of the primary lesion and some 25–50% of patients with disease that has metastasised to regional lymph nodes (stage III) can be cured by surgery. However, the prognosis of patients with stage IV melanoma metastatic to distant sites is poor. Distant inoperable metastatic disease remains essentially incurable.

Interferon (IFN)-α is currently the cornerstone of adjuvant therapy in stage IIB–III disease. The evidence to date consistently demonstrates that IFN-α significantly prolongs disease-free survival, but only two prospective randomised trials – both of which employed high-dose intravenous (i.v.) and subcutaneous (s.c.) IFN-α2b – have shown significant improvements in overall survival [4,5]. Meta-analysis of published trial data demonstrate significant improvements in relapse-free survival across all doses, with borderline effects upon overall survival for high-dose therapy [6,7].

For stage IV melanoma, palliative systemic chemotherapy is the mainstay of treatment and is associated with median survival durations with combination

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regimens of 6–9 months and 5-year survival rates of approximately 6%, which are not influenced significantly by any therapy yet tested in rigorous multicentre cooperative group trials (reviewed by Brown and Kirkwood in [8]). Numerous chemotherapeutic and immunological drug combinations have been investigated in attempts to improve response rates and survival and, although a number of prognostic factors that influence response and survival have been identified, tumour stage at diagnosis remains the predominant prognostic factor [3].

The alkylating agent dacarbazine (DTIC-Dome®), which was first introduced some 30 years ago, is considered to be the reference single agent for the management of advanced melanoma, with objective tumour responses in approximately 13–20% of patients [9,10]. Nearly all of these responses are partial, although complete responses have been observed and can be durable [10,11].

Multiple alternative treatment approaches have been investigated, and numerous studies published, since the regulatory approval of dacarbazine. Thus, we considered it appropriate and useful to conduct a rigorous analysis of the current evidence for dacarbazine-based regimens. Our analysis considered peer-reviewed Phase II and III clinical trial publications spanning the past 5 years and published in English, with data from well-designed randomised, controlled trials remaining 'level 1' evidence. Selected Phase III reports currently in abstract form are also included.

1.1. The historical role of dacarbazine in metastatic melanoma

Several studies of dacarbazine in the management of metastatic melanoma were published in the early 1970s [12–14]. The first of these trials demonstrated a 19% response rate in 110 evaluable patients who received dacarbazine in 3-weekly cycles, most often at a dose of 250 mg/m^2 daily for 5 days [12]. A second study showed an overall response rate of 28% in 115 evaluable patients receiving dacarbazine 2.5 or 4.5 mg/kg daily for 10 days of a 30-day cycle [13], and another showed response rates approaching 20% with dacarbazine 150 mg/m^2 daily for 5 days of a 30-day cycle in 112 evaluable patients [14]. No clinical advantage was associated with the addition of carmustine to dacarbazine therapy in the latter study [14].

These studies were fairly robust by the standards of their time. Definitions relating to tumour response were given in all cases, although details of tumour measurement were either absent or were not as comprehensive as would be expected in a contemporary study report. Very little information was provided regarding tumour analysis and staging, which would have followed conventions of the time. Patients were not stratified or analysed according to the number of lesions, anatomical site(s) of involvement or elevated serum lactate dehydrogenase (LDH), although X-rays, bone surveys and liver scans were quoted [13,14]. However, notwithstanding the brevity of methodological details, objective tumour response rates were remarkably consistent across these studies.

2. Dacarbazine as a standard of chemotherapy in metastatic melanoma

Numerous peer-review publications have evaluated the use of dacarbazine – either alone, or in combination with other agents – in metastatic melanoma. In the past, research and resulting prescribing recommendations focused upon multiple-dose regimens, with the so-called 'Dartmouth' regimen – consisting of cisplatin, dacarbazine, carmustine and tamoxifen – having been used extensively. However, emphasis has shifted more recently to regimens in which fewer and higher individual doses of dacarbazine were administered, generally delivering a total dose of approximately 1000 mg/m^2 per cycle.

2.1. Combination therapy with standard-dose dacarbazine administered as multiple infusions

Data published over the past 5 years have called into question the widespread use of multiple low-doses of dacarbazine in combination with other agents, including those incorporated in the Dartmouth regimen. A randomised Phase III study in 184 patients has demonstrated that the inclusion of tamoxifen confers no clinically relevant advantage [15], while an additional Phase III trial in 324 patients has indicated that the addition of cisplatin to vindesine plus dacarbazine 250 mg/m^2 for 5 days every 4 weeks increases toxicity with no improvement in survival [16]. Furthermore, a four-arm Phase III study in 219 patients failed to demonstrate clinically relevant differences in terms of response rate or survival among regimens containing dacarbazine administered at variously 300 or 600 mg/m^2 for 4 days, with carmustine, vincristine, cisplatin, bleomycin and procarbazine, and suggested potentially improved tolerability of regimens containing carmustine and procarbazine, but not dacarbazine, for elderly or frail patients [17] (Table 1).

Several groups of investigators have attempted to improve response rates through the addition of immunotherapy with IFN-α and/or interleukin (IL)-2 to dacarbazine-based therapy. Phase I/II results have suggested that this approach is feasible, with some durable remissions being noted, although response rates have not been greatly enhanced relative to therapy without biological agents [18–25]. Some investigators have reported increased toxicity [23] without improvement in outcomes relative to simpler chemotherapy regimens [19].

Phase II/III randomised comparisons have failed to show any clinically meaningful improvement when IL-2

Table 1
Randomised trials of combination regimens incorporating dacarbazine 220–600 mg/m^2: in multiple infusions per cycle, in the treatment of advanced melanoma

References	Patient characteristics	Regimens (all dosages in mg/m^2 unless stated otherwise) [randomised population]	Response (ITT population unless noted otherwise)		Median survival (months)	Major toxicities (percentage of patients with grade 3–4 toxicity unless stated otherwise)
			CR (%)	PR (%)		
Comparisons involving chemotherapy with or without hormonal manipulation						
Creagan and colleagues [15] (Phase III; single-centre)	ECOG PS $\leqslant 2$; 78% measurable disease; 72.5% skin primary lesions (others primarily in eyes)	Dacarbazine 220 d1–3 q3w, carmustine 150 q6w, cisplatin 25 d1–3 q3w [$n = 92$; 72 measurable disease]	13[a]	24[a]	6.8	Severe leucopenia (40); severe thrombocytopenia (85); lethargy (9); nausea (9); vomiting (3); neuromotor (4)
		Dacarbazine 220 d1–3 q3w; carmustine 150 q6w; cisplatin 25 d1–3 q3w; tamoxifen 20 mg daily [$n = 92$; 72 measurable disease]	0[a]	32[a]	6.9	Severe leucopenia (40); severe thrombocytopenia (65); lethargy (12); nausea (10); vomiting (9); neuromotor (5)
Jelić and colleagues [17] (Phase III; single-centre)	ECOG PS $\leqslant 3$; resectable lymph node metastases excluded	Dacarbazine 300 d2–5 q4w; carmustine 60 q4w; vincristine 1.4 q4w [$n = 49$]	8	14	4.0	Leucopenia (22); thrombocytopenia (6); anaemia (10); nausea/vomiting (2)
		Dacarbazine 600 d2–5 q4w; carmustine 60 q4w; vincristine 1.4 q4w [$n = 47$]	2	17	5.0	Leucopenia (28); thrombocytopenia (17); anaemia (15); nausea/vomiting (2)
		Vindesine 3 q4w; bleomycin 7 d1–4 q4w; cisplatin 30 d5–8 q4w [$n = 63$]	3	22	6.0	Leucopenia (27); anaemia (6); nausea/vomiting (5)
		Carmustine 100 q4w; procarbazine 90 d1–10 q4w [$n = 60$]	7	8	4.0	Leucopenia (2); anaemia (5)
Jungnelius and colleagues [16] (Phase III; multicentre)	WHO PS $\leqslant 2$	Dacarbazine 250 d1–5 q28d; vindesine 3 q1w [$n = 165$]	10[b]	11[b]	6.5[bc]	Leucopenia (13); thrombocytopenia (6); anaemia (5); alopecia (19); nausea/vomiting (18)
		Dacarbazine 250 d1–5 q4w; vindesine 3 q1w; cisplatin 100 q4w [$n = 161$]	16[b]	15[b]		Leucopenia (38); thrombocytopenia (11); anaemia (11); alopecia (45); nausea/vomiting (35)
Comparisons involving immunotherapy						
Atzpodien and colleagues [26] (Phase III; multicentre)	KPS >80%; 31% uveal or unknown primary	Dacarbazine 220 d1–3 q5w; carmustine 150 q10w; cisplatin 35 d1–3 q5w; tamoxifen 20 mg daily [$n = 60$]	13	17	13.0	Thrombocytopenia (grade 4, 25% of cycles); leucopenia (grade 4, 26% of cycles) (overall)
		Dacarbazine 220 d1–3 q5w; carmustine 150 q10w; cisplatin 35 d1–3 q5w; tamoxifen 20 mg daily; IL-2 10 MU/m^2 d3–5 w4 + 5 MU/m^2 d1, 3, 5 w5; IFN-α 5 MU/m^2 d1 w4 + d1, 3, 5 w5 [$n = 64$]	11	23	12.0	Malaise (21% of cycles); anorexia (21% of cycles) (immunotherapy-related)
Bajetta and colleagues [30] (Phase II; multicentre)	PS $\leqslant 1$	Dacarbazine 800 q3w; IFN-α 3 MU 3 $\times$ /w [$n = 26$]	0[b]	7[b]	NR	NR

Table 1 (*continued*)

References	Patient characteristics	Regimens (all dosages in mg/m^2 unless stated otherwise) [randomised population]	Response (ITT population unless noted otherwise)		Median survival (months)	Major toxicities (percentage of patients with grade 3–4 toxicity unless stated otherwise)
			CR (%)	PR (%)		
		Dacarbazine 250 d1–3 q3w; cisplatin 30 d1–3 q3w; vindesine 2.5 q3w; IFN-α 3 MU 3 ×/w [$n = 24$]	13[b]	8[b]	NR	Neutropenia (20); alopecia (8); nausea/vomiting (6)
Del Vecchio and colleagues [31][d] (Phase III; multicentre)	ECOG PS $\leqslant 2$	Dacarbazine 250 d1–3 q3w; cisplatin 30 d1–3 q3w; vindesine 2.5 d1q3w [$n = 69$]		21[e]	12.0	NR
		Dacarbazine 250 d1–3 q3w; cisplatin 30 d1–3 q3w; vindesine 2.5 d1q3w; IFN-α 5 MU/m^2 d1–5 q3w; IL-2 9 MU/m^2 d1–5, 8–12 q3w [$n = 70$]		27[e]	11.0	Fever (36); asthenia (20)
Falkson and colleagues [32] (Phase III; multicentre)	PS $\leqslant 2$	Dacarbazine 200 d1–5 q4w [$n = 69$]	2[b]	8[b]	10.0	Liver (7); pulmonary (7)
		Dacarbazine 200 d22–26 q4w; IFN-α 15 MU/m^2 d1–5 × 3w, then 10 MU/m^2 3 ×/w [$n = 68$]	6[b]	8[b]	9.0	Granulocytopenia (18); leucopenia (14); fatigue (20); neuromotor (9); neuroclinical (17); nausea (9); liver (14)
		Dacarbazine 200 d1–5 q4w; tamoxifen 20 mg daily [$n = 66$]	2[b]	10[b]	8.0	Neuromotor (6); pulmonary (6)
		Dacarbazine 200 d1–5 q4w; IFN-α 15 MU/m^2 d1–5 × 3w, then 10 MU/m^2 3 ×/w; tamoxifen 20 mg daily [$n = 68$]	3[b]	10[b]	9.5	Granulocytopenia (19); leucopenia (12); fatigue (19); neuromotor (15); neuroclinical (10); liver (10); pulmonary (7)
Flaherty and colleagues [27] (Phase II; multicentre)	SWOG PS $\leqslant 1$; 32% elevated LDH[b]	Dacarbazine 250 d1–3 q4w; cisplatin 25 d1–3 q4w; IFN-α 5 MU/m^2 d6, 8, 10, 13, 15 q4w; IL-2 18 MU/m^2 d6–10, d13–15 q4w [$n = 44$]	11[b]	25[b]	10.1	Neutropenia (23% of cycles); nausea (9% of cycles); thrombocytopenia (6% of cycles)
		Dacarbazine 250 d1–3 q4w; cisplatin 25 d1–3 q4w; IFN-α 5 MU/m^2 d6, 8, 10, 13, 15 q4w; IL-2 5 MU/m^2 d6–10, d13–15 q4w [$n = 37$]	3[b]	14[b]	7.3	Neutropenia (11% of cycles); nausea (6% of cycles); thrombocytopenia (7% of cycles)
Keilholz and colleagues [28][df] (Phase III; multicentre)	41% elevated LDH	Dacarbazine 250 d1–3; cisplatin 30 d1–3; IFN-α 10 MU/m^2 d1– 5		23[e]	9.0	Higher incidence of grade 3–4 hypotension, fever, lethargy, anorexia, and diarrhoea in IL-2 arm
		Dacarbazine 250 d1–3; cisplatin 30 d1–3; IFN-α 10 MU/m^2 d1–5; IL-2 d4–9		21[e]	9.0	
Rosenberg and colleagues [29] (Phase III; single-centre)	ECOG PS $\leqslant 1$ (1 patient PS 2)	Dacarbazine 220 d2–4 q23d; cisplatin 25 d2–4 q23d; tamoxifen 40 mg d1, then 20 mg daily [$n = 52$]	8	19	15.8	29% of patients with platelet nadirs $<100\times10^9$ cells/L; WBC nadir $<3\times10^9$ cells/L in 20%

Table 1 (*continued*)

References	Patient characteristics	Regimens (all dosages in mg/m^2 unless stated otherwise) [randomised population]	Response (ITT population unless noted otherwise)		Median survival (months)	Major toxicities (percentage of patients with grade 3–4 toxicity unless stated otherwise)
			CR (%)	PR (%)		
		Dacarbazine 220 d2–4 q23d; cisplatin 25 d2–4 q23d; IFN-α 6 MU/m^2 d5–8 q23d; IL-2 7.2 kU/kg d5–8 q23d; tamoxifen 40 mg d1, then 20 mg daily [$n = 50$]	6	38	10.7	85% of patients with platelet nadirs $<100 \times 10^9$ cells/L; WBC nadir $<3 \times 10^9$ cells/L in 66%

Abbreviations: CR, complete response; d, day(s); ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; NR, not reported; PR, partial response; PS, performance status; q, every; SWOG, Southwestern Oncology Group; w, week(s); WBC, white blood cell; WHO, World Health Organization, IFN-α, interferon-α; IL-2, interleukin-2.

[a] Proportion of patients with measurable disease.

[b] Evaluable population.

[c] Overall population.

[d] Reported in abstract.

[e] Overall response rate.

[f] Full details of patients and cycles unavailable ($n = 363$ randomised).

and/or IFN-α were added to combination chemotherapy based on dacarbazine 220 or 250 mg/m^2 for 3 days of each cycle (Table 1) [26–31]. Rosenberg and colleagues [29] showed markedly increased haematological toxicity upon the addition of IFN-α and IL-2 to dacarbazine-based combination treatment (but without any survival benefit), while Atzpodien and colleagues [26] reported clear evidence of immunotherapy-related toxicity (grade 3–4 malaise and anorexia) in patients receiving IFN-α and IL-2 added to the Dartmouth regimen, which itself was associated with grade 4 haematological toxicity. A further four-arm Phase III trial has shown no advantage from the addition of IFN-α or tamoxifen to dacarbazine 200 mg/m^2 on Days 1–5 of a 3-week cycle [32]. Interferon (IFN) was again associated with a notable increase in toxicity, and none of the three combination regimens tested conferred longer survival than dacarbazine monotherapy.

The need for further improvements in therapy for metastatic melanoma has stimulated the development of agents directed against novel molecular targets. The chemosensitisation of melanoma with Bcl-2-targeted pro-apoptotic therapy (oblimersen sodium; Genasense^{TM}) in combination with dacarbazine 200 mg/m^2 on Days 5–9 of each cycle has been demonstrated in a Phase I–II trial [33].

2.2. Combination therapy incorporating single-doses of dacarbazine

Efforts to develop regimens with improved efficacy have involved progressively more complex regimens based on dacarbazine with the addition of other agents with minimal single-agent activity in melanoma. Unfortunately, early expectations of high response rates have not been realised, and improved survival has not been attained in randomised studies [28,34,35].

The burgeoning complexity of combination regimens has prompted research into ways in which dacarbazine-based schedules can be redesigned to facilitate administration and to improve patient comfort without the loss of efficacy. Simplification of regimens has been achieved predominantly by the replacement of dacarbazine schedules spanning several days with a single-dose of dacarbazine equivalent to the same total dose per cycle. The introduction of powerful novel antiemetic agents that significantly reduce the emetogenic effects of dacarbazine has assisted the development of these more convenient 1-day schedules.

Following indications of promising activity in early investigations, randomised studies in patients receiving combination chemotherapy based on single-dose dacarbazine have examined the addition of biological response modifiers to cytotoxic treatment. However, there is no consistent evidence that the addition of these biological response modifiers to dacarbazine-based treatment has any clinically relevant beneficial effect (Table 2) [34–42]. These regimens involve complicated administration schedules that expose the patient to additional risks of toxicity.

The addition of IFN-α and IL-2 to dacarbazine in combination with vinblastine and/or cisplatin showed no additional effect [35] or were associated with substantially increased toxicity that was felt to outweigh the increased response and borderline extended survival [37]. There was also no enhancement of efficacy with the addition of tamoxifen to a single-dose dacarbazine regimen with carboplatin [36], and no benefit of combining granulocyte-macrophage colony-stimulating factor with dacarbazine [42].

Increased response rates with complex regimens do not necessarily translate into sustained clinical

Table 2
Randomised trials of combination regimens incorporating dacarbazine 800–1000 mg/m^2, as single infusions per cycle, in the treatment of advanced melanoma

References	Patient characteristics	Regimens (all dosages in mg/m^2 unless stated otherwise) [randomised population]	Response (ITT population unless noted otherwise)		Median survival (months)	Major toxicities (percentage of patients with grade 3–4 toxicity unless stated otherwise)
			CR (%)	PR (%)		
Comparison involving chemotherapy with hormonal manipulation						
Agarwala and colleagues [36] (Phase III; single-centre)	ECOG PS $\leqslant 1$	Dacarbazine 1000 q4w; carboplatin 300 q4w [$n = 28$]	4	7	7.0	Leucopenia (9); thrombocytopenia (14)
		Dacarbazine 1000 q4w; carboplatin 300 q4w; tamoxifen 20 mg daily [$n = 28$]	4	11	4.6	Leucopenia (14); thrombocytopenia (17)
Studies involving chemoimmunotherapy						
Atkins and colleagues [34][a] (Phase III; multicentre)	PS 0 (66%)	Dacarbazine 800 d1 q3w; cisplatin 20 d1–4 q3w; vinblastine 1.2 d1–4 q3w [$n = 201$][b]	3	8	8.7	37% grade 4 toxicity
		Dacarbazine 800 d1 q3w; cisplatin 20 d1–4 q3w; vinblastine 1.2 d1–4 q3w; IFN-α 5 MU/m^2 d1–5, 8, 10, 12 q3w; IL-2 9 MU/m^2 d1–4 q3w [$n = 204$][b]	1	16	8.4	63% grade 4 toxicity; hypotension, metabolic abnormalities, fatigue, nausea, hepatic dysfunction, leucopenia, thrombocytopenia, anaemia and infection all more frequent in this arm versus chemotherapy alone
Eton and colleagues [37] (Phase III; single-centre)	ECOG PS $\leqslant 3$ (KPS $\geqslant 40\%$); 42% elevated LDH, 13.5% brain metastases	Dacarbazine 800 d1, 22; cisplatin 20 d1–4, 22–25; vinblastine 2 d1–4, 22–25 [$n = 92$][c]	2[c]	21[c]	9.2	Twice as many episodes of grade 3–4 thrombocytopenia and anaemia, and catheter-related sepsis with immunochemotherapy
		Dacarbazine 800 d1, 22; cisplatin 20 d1–4, 22–25; vinblastine 1.5 d1–4, 22–25; IFN-α 5 MU/m^2 d5–9, 17–21, 26–30; IL-2 9 MU/m^2 d5–8, 17–28, 26–29 [$n = 91$][c]	7[c]	37[c]	11.9	
Hauschild and colleagues [38] (Phase III; multicentre)	KPS $\geqslant 70\%$	Dacarbazine 850 q4w; IFN-α 6 MU/m^2 d1, then 3 MU/m^2 d2–5, then 5 MU/m^2 3 ×/w q4w [$n = 144$][b]	8	10	11.0	Leucopenia (10); neutropenia (6), thrombocytopenia (6); nausea/vomiting (8)
		Dacarbazine 850 q4w; IFN-α 6 MU/m^2 d1, then 3 MU/m^2 d2–5, then 5 MU/m^2 3 ×/w q4w; IL-2 4.5 MU/m^2 d3, then 9 MU/m^2 d3/4, then 4.5 MU/m^2 d4–7 q4w [$n = 137$][b]	7	9	11.0	Leucopenia (6); thrombocytopenia (6); fever/chills (11); nausea//vomiting (16)
Middleton and colleagues [39] (Phase III; multicentre)	KPS $\geqslant 50\%$	Dacarbazine 800 q3w; IFN-α 9 MU 3 ×/w [$n = 52$]	8	10	199[d]	Leucopenia (10); thrombocytopenia (8); nausea/vomiting (8); alkaline phosphataemia (8)
		Dacarbazine 220 d1–3 q3w; carmustine 150 q6w; cisplatin 25 d1–3 q3w; tamoxifen 20 mg daily [$n = 53$]	4	23	202[d]	Leucopenia (52); anaemia (24); thrombocytopenia (67); nausea/vomiting (17); infection (13); raised transaminases (9)

Table 2 (*continued*)

References	Patient characteristics	Regimens (all dosages in mg/m^2 unless stated otherwise) [randomised population]	Response (ITT population unless noted otherwise)		Median survival (months)	Major toxicities (percentage of patients with grade 3–4 toxicity unless stated otherwise)
			CR (%)	PR (%)		
Ravaud and colleagues [42] (Phase II; multicentre)	ECOG PS $\leqslant 2$	Dacarbazine 800; GM-CSF 10 μg/kg d2–19 q3w	0[c]	0[c]	7.3	Fever (40); pain (35); dyspnoea (24); anaemia (18); thrombocytopenia (12); nausea/vomiting (6)
		GM-CSF 10 μg/kg d 1–14 q3w	0[c]	0[c]	6.3	Fever (35); neurological toxicity (20); pain (6)
Ridolfi and colleagues [35] (Phase III; multicentre)	ECOG PS $\leqslant 2$; 28% adjuvant IFN-α	Dacarbazine 800 q3w; cisplatin 75 q3w; carmustine 150 q3w (optional) [$n = 89$]	3	17	9.5	Neutropenia (37); thrombocytopenia (13); nausea/vomiting (15)
		Dacarbazine 800 q3w; cisplatin 75 q3w; carmustine 150 q3w (optional); IL-2 4.5 MU d3–5, 8–12 q3w × 6, then 8 days/mo; IFN-α 3 MU d3, 5 then 3 × /w [$n = 89$]	3	22	11.0	Neutropenia (35); thrombocytopenia (20); nausea/vomiting (24); neurological (6)
Sertoli and colleagues [40] (Phase II; multicentre)	PS $\leqslant 2$	Dacarbazine 800 q3w; IL-2 9 MU d1–5, 8–12; IFN-α 3 MU 3 × /w; tamoxifen 20 mg daily [$n = 31$]	6	6	11.0	Fever (grade 3 in 6% of cycles)
		Dacarbazine 250 d1–3 q4w; vindesine 2.5 q4w; cisplatin 30 d1–3 q4w; IFN-α 3 MU 3 × /w; tamoxifen 20 mg daily [$n = 31$]	16	19	11.0	Anaemia/leucopenia (grade 3 in 1% of cycles)
		Dacarbazine 250 d1–3 q4w; vindesine 2.5 q4w; cisplatin 30 d1–3 q4w; IFN-α 3 MU 3 × /w; IL-2 5 MU d1–5, 8–12; tamoxifen 20 mg daily [$n = 30$]	20	17	11.0	Fever, asthenia, nausea/vomiting (grade 3 in 18%, 10% and 13% of cycles, respectively)
Young and colleagues [41] (Phase III; multicentre)	ECOG PS $\leqslant 2$; two prognostic groups: good = skin, lymph node metastases; poor = bone, liver, lung metastases	Dacarbazine 950 q4w [$n = 31$]	0[c]	23[c]	7.2	Haematological toxicity (all grades, 9); anorexia (16); fatigue (23)
		Dacarbazine 950 q4w; IFN-α 4.5 MU 3 × /w [$n = 30$]	0[c]	18[c]	4.8	Haematological toxicity (all grades, 19); anorexia (27); fatigue (40)

Abbreviations: CR, complete response; d, day(s); ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; ITT, intention-to-treat; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; mo, months; PR, partial response; PS, performance status; q, every; w, week(s); INF-α, interferon-α; IL-2, interleukin-2.

[a] Reported in abstract.

[b] Eligible population.

[c] Evaluable population.

[d] Days.

benefit: for example, although a Phase II randomised comparison of dacarbazine plus IL-2 versus cisplatin–vindesine–dacarbazine (CVD) versus CVD plus IL-2 yielded clinical response rates ranging from 13% to 37%, median survival was 11 months in all groups [40]. Middleton and colleagues [39] showed no significant difference in efficacy between the Dartmouth regimen and dacarbazine 800 mg/m^2 every 3 weeks plus IFN-α, whereas toxicity – particularly in terms of haematological effects – was significantly worse with the Dartmouth schedule. The authors suggested that the Dartmouth regimen, which was also associated with more time spent in hospital, should not be recommended as standard therapy, just as Chapman and colleagues [10] had earlier concluded from a US intergroup study of the Dartmouth regimen versus dacarbazine alone. Other trials

have shown increased toxicity with no clinical advantages after the addition of IFN-α or IL-2 to dacarbazine 850 or 950 mg/m^2 every 4 weeks (Table 2) [38,41].

Recently analysed Phase III trials evaluating the efficacy of adding IFN-α and IL-2 to CVD all yielded only modest response rates and failed to show any impact on survival in a total of almost 800 randomised patients [31,34,35]. In the largest study in 416 patients, conducted by the Eastern Cooperative Oncology Group (ECOG) (trial E3695), there was no clinically relevant effect in terms of progression-free or overall survival of adding IL-2 and IFN-α to CVD (Table 2) [34]. However, toxicity was increased dramatically by the addition of immunotherapy: the incidence of grade 4 adverse events was nearly doubled. The somewhat longer progression-free survival with chemoimmunotherapy (5.3 versus 3.6 months) was counterbalanced by an increased response duration with chemotherapy alone, and by the lack of any significant differences in overall survival. The authors concluded that chemoimmunotherapy should not be considered standard therapy in patients with melanoma [34]. Similar conclusions were drawn by the authors of the Italian studies [31,35] and the large Dermatologic Cooperative Oncology Group (DeCOG) [38] and European Organisation for Research and Treatment of Cancer (EORTC) [28] trials that evaluated the addition of IL-2 to regimens incorporating dacarbazine and IFN-α, and which included 299 and 363 patients, respectively.

2.3. Single-dose dacarbazine monotherapy

The suitability of monotherapy with a single-dose of dacarbazine at the start of each treatment cycle for patients with metastatic melanoma has been demonstrated by two key randomised studies in which dacarbazine was compared with the Dartmouth regimen (Table 3) [10,42]. One trial comprised a Phase II comparison in 60 patients [43] and the other comprised a Phase III study in 240 individuals [10]. Both studies used the same basic combination of dacarbazine, cisplatin and carmustine, but there was a modification of the tamoxifen component in the Phase II trial (tamoxifen given at 160 mg daily for 7 days before chemotherapy). In addition, a 4-week cycle was used for the Dartmouth regimen in the Phase II trial versus a 3-week cycle in the Phase III study, and dacarbazine was given at a dose of 1000 mg/m^2 in one trial [10] and at 1200 mg/m^2 in the other [43].

In the Phase II randomised trial, a much higher overall tumour response rate was achieved with combination therapy than with monotherapy (24% versus 5%), but this did not translate into prolonged survival [43]. Patients with poor performance status in this study

Table 3
Phase II and III randomised comparisons of single-dose dacarbazine monotherapy with the Dartmouth regimen

References	Patient characteristics	Regimens (all dosages in mg/m^2 unless stated otherwise) [randomised population]	Response (ITT population)		Median survival (months)	Major toxicities (percentage of patients with grade 3–4 toxicity unless stated otherwise)
			CR (%)	PR (%)		
Chiarion Sileni and colleagues [43] (Phase II; single-centre)	KPS $\geqslant$ 50 (median 90); 69% visceral metastases; LDH >380U/L in 54% of combination and 84% of monotherapy patients; pretreatment in 49% of combination and 68% of monotherapy patients	Dacarbazine 220 d1–3 q4w; cisplatin 25 d1–3 q4w; carmustine 150 q8w; tamoxifen 160 mg daily for 1w prior to chemotherapy [$n = 41$]	2	22	9.0	Leucopenia (32); thrombocytopenia (28); anaemia (28); neutropenia (16); nausea/vomiting (15); alopecia (58); infection (10)[a]
		Dacarbazine 1200 q3w [$n = 19$]	0	5	7.0	Leucopenia (15); thrombocytopenia (5); anaemia (5); neutropenia (5); nausea/vomiting (9); photosensitisation (10); infection (5)[a]
Chapman and colleagues [10] (Phase III; multicentre)	PS $\geqslant$ 50 (median 90); 7.5% brain metastases	Dacarbazine 220 d1–3 q3w; cisplatin 25 d1–3 q3w; carmustine 150 q6w; tamoxifen 20 mg daily (including 1w prior to chemotherapy) [$n = 119$]	0	17	7.7	Dartmouth regimen associated with more grade 3–4 neutropenia, leucopenia, anaemia, thrombocytopenia, nausea/vomiting (all $P < 0.01$)[b]
		Dacarbazine 1000 q3w [$n = 121$]	0	10	6.3	

Abbreviations: CR, complete response; d, day(s); ITT, intention-to-treat; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; PR, partial response; PS, performance status; q, every; w, week(s).

[a] Haematological toxicities are described in Fig. 1.

[b] Toxicities are described in Fig. 2.

(Karnofsky performance status $\leqslant 80\%$) failed to respond to treatment, and the 10 responding patients (24%) in the Dartmouth group had baseline Karnofsky scores of >90% (48% of patients). Elevated serum levels of LDH at baseline were associated with poor outcomes: median survival in these patients was 8.5 months compared with 13.5 months in patients with normal serum LDH levels ($P = 0.02$).

Haematological toxicity was substantial in the combination therapy group (Table 3; Fig. 1) [43]. Two patients (5%) required platelet transfusions on four occasions, and 6 of the 11 patients with grade 3–4 anaemia needed erythrocyte transfusions. In the dacarbazine arm, 3 patients (15%) experienced grade 3–4 leucopenia versus 13 patients (32%) in the combination therapy group. Treatment delay exceeding 7 days was necessary in 17 combination therapy cycles (10%), with 13 patients (32%) requiring a dose reduction. In the monotherapy arm, three cycles (6%) were delayed in 2 patients [43].

The Phase III results of Chapman and colleagues [10] provide strong evidence that patients receiving the Dartmouth regimen fare no better in terms of the most important clinical endpoint, survival, than those receiving single-dose administration of dacarbazine, and a trend towards an improved clinical response rate in the Dartmouth group was not associated with differences in survival. Estimated 1-year survivals were 22% for the Dartmouth arm and 27% for dacarbazine ($P = 0.38$). No histologically-proven complete tumour responses were observed in this study with either regimen (in the Dartmouth arm, 2 patients with cutaneous disease with clinical complete responses were not confirmed by biopsy). Of 99 patients with disease confined to soft tissue (skin, lymph nodes or lungs), 22 responded to treatment; response rates were 14% with dacarbazine and 32% with the Dartmouth regimen ($P = 0.05$), but again there was no difference in survival in this subgroup of patients. Borderline statistical significance was also found for the difference in response rates in the dacarbazine arm between men and women (6% versus 18%; $P = 0.06$), but this also did not translate into prolonged survival.

The Dartmouth regimen was markedly more toxic than dacarbazine monotherapy (Fig. 2), particularly in terms of bone marrow effects, and there was one treatment-related death in the Dartmouth arm [10]. In addition, 25 patients in this arm withdrew from the study because of toxicity, whereas only 3 of the dacarbazine monotherapy recipients withdrew ($P < 0.01$). The most common reasons for withdrawal were cytopenias, renal

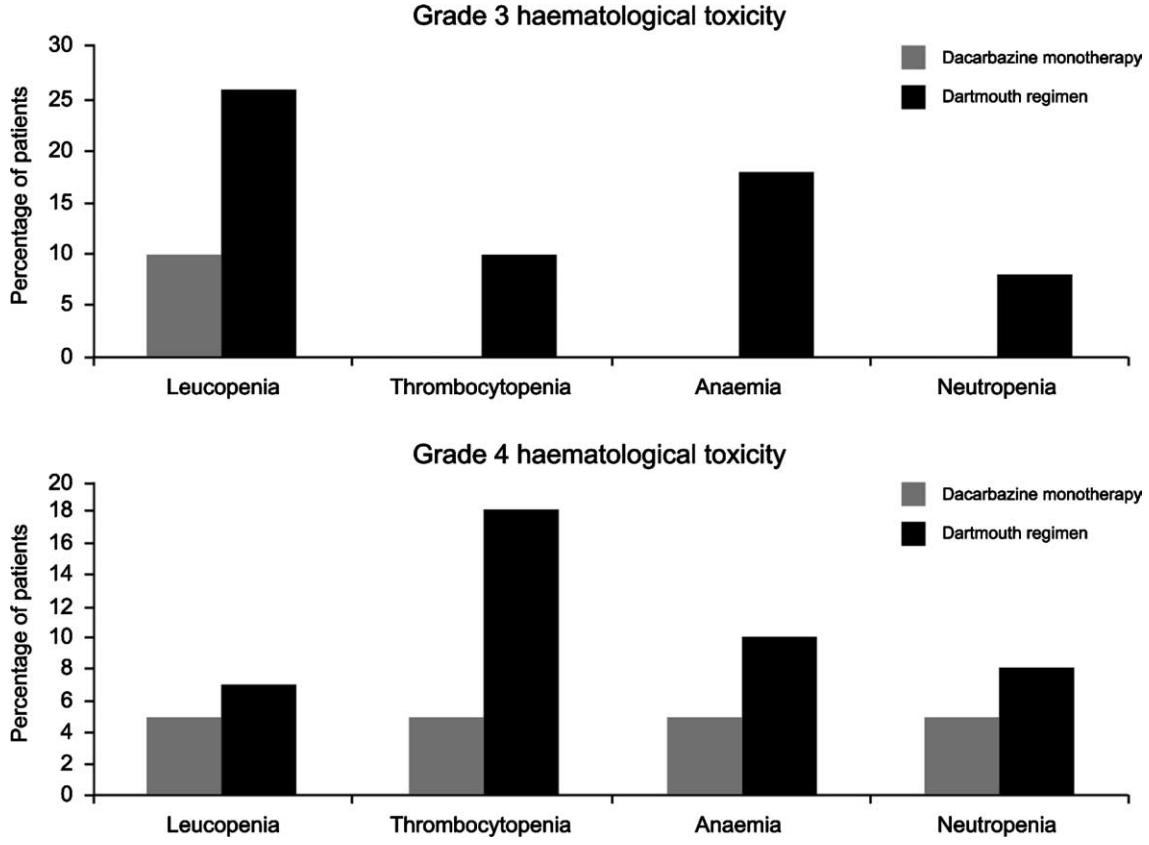

Fig. 1. Haematological toxicity after treatment with dacarbazine 1200 mg/m^2 once every 3 weeks or a modified Dartmouth combination regimen in a Phase II randomised study in 60 patients (see Table 3 for study details) [43].

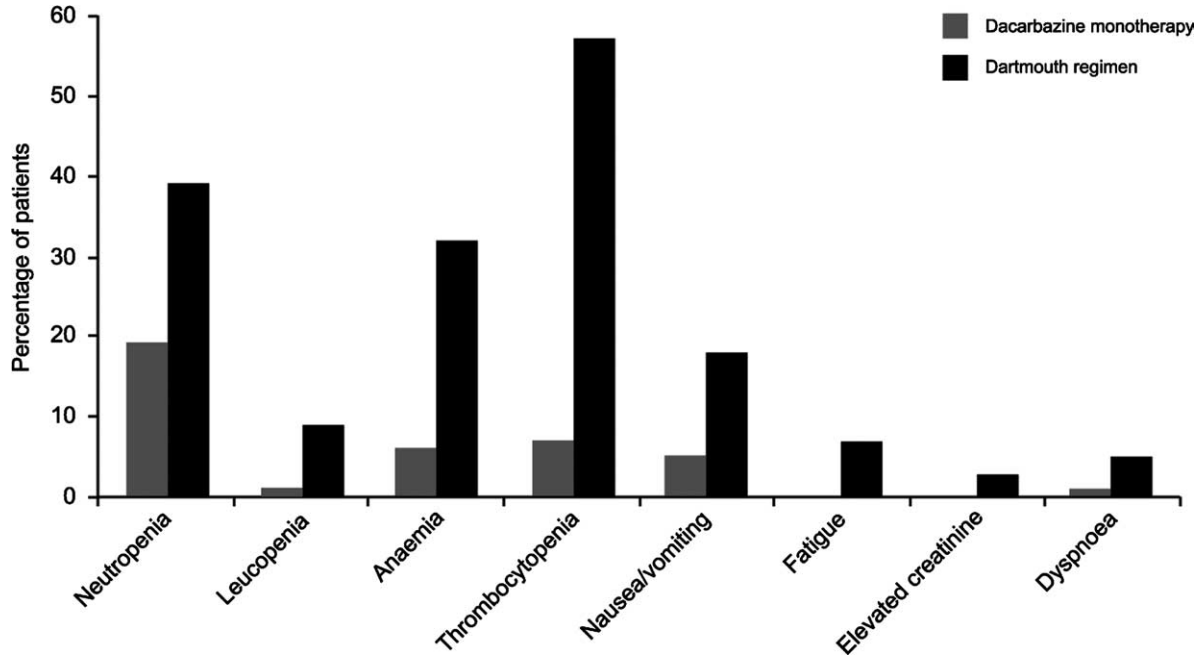

Fig. 2. Incidences of grade 3–4 toxicity after treatment with dacarbazine 1000 mg/m^2 once every 3 weeks or the Dartmouth regimen in a Phase III study in 240 patients (see Table 3 for study details) [10].

toxicity and neurotoxicity. In conclusion, the authors recommended single-agent dacarbazine 1000 mg/m^2, administered as a single-dose per cycle, as the reference standard treatment for metastatic melanoma [10].

3. Discussion and conclusions

Since the original approval of dacarbazine for the treatment of metastatic malignant melanoma, considerable effort has been expended in attempts to improve survival – the major and most meaningful endpoint in patients with any type of cancer – in patients who receive the drug for this disease. During the past two decades alone, over 30 randomised controlled trials have been conducted in which newer agents or combinations have been compared with dacarbazine monotherapy. However, both single-agent and combination therapies (most notably the Dartmouth regimen) have failed to deliver the survival improvements that were originally anticipated. In addition, the incorporation of tamoxifen in these regimens has been shown to have no consistent clinically relevant effect.

Experience has also shown that immunotherapeutic agents – notably the IFNs and ILs – confer no lasting added benefit in terms of survival in the treatment of advanced melanoma. The recent authoritative findings of ECOG trial E3695 [34] and EORTC trial 18951 [28] may settle this issue by showing definitively that there is no clinical advantage to be gained by adding cocktails of inactive dosages of immunotherapeutic agents to chemotherapy with dacarbazine. Indeed, it appears that patients who receive immunotherapy in addition to their chemotherapy simply suffer additional and more severe adverse effects of treatment, and that chemoimmunotherapy is in fact not to be recommended. It is also becoming apparent that the addition of hormonal treatment to chemotherapy regimens for advanced melanoma may not deliver the clinical benefits that were originally believed to accrue from this type of intervention.

Few data regarding quality of life are currently available, but the literature implies that a convenient single-dose regimen is preferable. This is suggested by a comparison of dacarbazine with temozolomide [44] and a subsequent economic analysis [45], both of which indicate an advantage for orally administered temozolomide. It is noteworthy that the conclusions of Middleton and colleagues [44] are based on the comparison of a multiple-dose regimen of i.v. dacarbazine 250 mg/m^2 for 5 days per cycle versus oral (p.o.) temozolomide 250 mg/m^2 for 5 days. Patients and physicians are likely to prefer the convenience and comfort of a single-dose of dacarbazine to the multiple i.v. infusions used in this study, which involve the need for repeated visits to the clinic during the course of a treatment week. The analysis of Hillner and colleagues [45] was similarly sensitive to the practice style of dacarbazine delivery, which was administered at 250 mg/m^2 for 5 days per cycle. The authors comment that lost wages and the time of companions to accommodate patients for i.v. therapy on several consecutive days impact up on the patient's perspective. Quality of life assessments involving single-

dose regimens of dacarbazine would be of interest, particularly if they measured the effects of treatment on daily living.

In conclusion, data gathered over the past 30 years, and in the past 5 years in particular, clearly show that dacarbazine monotherapy is equivalent in terms of antitumour efficacy and survival to combinations of dacarbazine with other currently available chemotherapeutic drugs and/or biological agents. Although several studies have shown higher tumour response rates with combination therapy, such treatment has not made any clinically relevant difference in terms of survival times, and the higher rates of apparent tumour regression have been invariably accompanied by substantially increased and potentially hazardous toxicity. In addition, single-doses of dacarbazine (850–1000 mg/m^2) have been shown to be well tolerated, and appear to deliver clinical improvements similar to those seen with multiple-doses that provide the same total dose per cycle. Notwithstanding the lack of comparative data, there is no evidence of a significant difference in toxicity between the 850 and 1000 mg/m^2 doses. When viewed in light of the quality of life and patient comfort issues that should be considered when treating patients undergoing essentially palliative therapy, the simplest regimens available are best used if research has indicated no clinically relevant advantage to be associated with more complex schedules. The evidence to date shows this to be the case in patients with advanced melanoma who undergo treatment with dacarbazine, and indicate that a single-dose of 850–1000 mg/m^2 administered once per cycle is a reference standard for therapy trials. This is not to say that well-designed studies evaluating newer molecular interventions should not embrace other drugs, and it is hoped that ongoing efforts investigating new and novel treatment approaches in metastatic melanoma will soon enable improve patient outcomes in this notoriously treatment-refractory disease.

References

1. Jemal A, Thomas A, Taylor M, Thun M. Cancer statistics, 2002. *CA-Cancer J Clin* 2002, **52**, 23–47.
2. Howe HL, Wingo PA, Thun MJ, *et al*. Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. *J Natl Cancer I* 2001, **93**, 824–842.
3. Lotze MT, Dallal RM, Kirkwood JM, *et al*. Cutaneous melanoma. In DeVita Jr VT, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. sixth ed. Philadelphia, Lippincott, Williams & Wilkens, 2001, pp 2012–2069.
4. Kirkwood JM, Ibrahim JG, Sosman JA, *et al*. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB–III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol* 2001, **19**, 2370–2380.
5. Kirkwood JM, Strawderman MH, Ernstoff MS, *et al*. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996, **14**, 7–17.
6. Eggermont A, Punt C. Does adjuvant systemic therapy with interferon-alpha for stage II–III melanoma prolong survival? *Am J Clin Dermatol* 2003, **4**, 531–536.
7. Wheatley K, Ives N, Hancock B, *et al*. Does adjuvant interferon-alpha for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. *Cancer Treat Rev* 2003, **29**, 241–252.
8. Brown CK, Kirkwood JM. Medical management of melanoma. *Surg Clin N Am* 2003, **83**, 283–322.
9. Luikart SD, Kennealey GT, Kirkwood JM. Randomized phase III trial of vinblastine, bleomycin, and cis-dichlorodiammine-platinum versus dacarbazine in malignant melanoma. *J Clin Oncol* 1984, **2**, 164–168.
10. Chapman PB, Einhorn LH, Meyers ML, *et al*. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999, **17**, 2745–2751.
11. Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials. *Melanoma Res* 2001, **11**, 75–81.
12. Luce JK, Thurman WG, Isaacs BL, Talley RW. Clinical trials with the antitumor agent 5-(3,3-dimethyl-1-triazeno) imidazole-4-carboxamide (NSC 45388). *Cancer Chemoth Rep* 1970, **54**, 119–124.
13. Nathanson L, Wolter J, Horton J, *et al*. Characteristics of prognosis and response to an imidazole carboxamide in malignant melanoma. *Clin Pharmacol Ther* 1971, **12**, 955–962.
14. Costanza ME, Nathanson L, Lenhard R, *et al*. Therapy of malignant melanoma with an imidazole carboxamide and bischloroethyl nitrosurea. *Cancer* 1972, **30**, 1457–1461.
15. Creagan ET, Suman VJ, Dalton RJ, *et al*. Phase III clinical trial of the combination of cisplatin, dacarbazine and carmustine with or without tamoxifen in patients with advanced malignant melanoma. *J Clin Oncol* 1999, **17**, 1884–1890.
16. Jungnelius U, Ringborg U, Aamdal S, *et al*. Dacarbazine–vindesine versus dacarbazine–vindesine–cisplatin in disseminated malignant melanoma. A randomised phase III trial. *Eur J Cancer* 1998, **34**, 1368–1374.
17. Jelić S, Babovic N, Kovcin V, *et al*. Comparison of the efficacy of two different dosage dacarbazine regimens and two regimens without dacarbazine in metastatic melanoma: a single-centre randomized four-arm study. *Melanoma Res* 2002, **12**, 91–98.
18. Andersson R, Ake Hofer P, Riklund-Ahlstrom K, Henriksson R. Effects of interferon-alpha, verapamil and dacarbazine in the treatment of advanced malignant melanoma. *Melanoma Res* 2003, **13**, 87–91.
19. Dillman RO, Soori G, Wiemann MC, *et al*. Phase II trial of subcutaneous interleukin-2, subcutaneous interferon-α, intravenous combination chemotherapy, and oral tamoxifen in the treatment of metastatic melanoma: final results of Cancer Biotherapy Study Group 94–11. *Cancer Biother Radio* 2000, **15**, 487–494.
20. Hoffmann R, Muller I, Neuber K, *et al*. Risk and outcome in metastatic melanoma patients receiving DTIC, cisplatin, BCNU and tamoxifen followed by immunotherapy with interleukin 2 and interferon α_{2a}. *Br J Cancer* 1998, **78**, 1076–1080.
21. Kashani-Sabet M, Sagebiel RW, Collins HE, *et al*. Outpatient combination chemoimmunotherapy for patients with metastatic melanoma: results of a phase I/II trial. *Cancer* 1999, **86**, 2160–2165.

22. Richards JM, Gale D, Mehta N, Lestingi T. Combination of chemotherapy with interleukin-2 and interferon α for the treatment of metastatic melanoma. *J Clin Oncol* 1999, **17**, 651–657.
23. Stark JJ, Dillman RO, Schulof R, *et al*. Interferon-α and chemohormonal therapy for patients with advanced melanoma: final results of a phase I–II study of the Cancer Biotherapy Research Group and the Mid-Atlantic Oncology Program. *Cancer* 1998, **82**, 1677–1681.
24. Stein ME, Bernstein Z, Drumea K, *et al*. Sustained complete remission after chemobiohormonal therapy for metastatic melanoma. *Am J Clin Oncol* 1999, **22**, 62–64.
25. Vaughan MM, Moore J, Riches PG, *et al*. GM-CSF with biochemotherapy (cisplatin, DTIC, tamoxifen, IL-2 and interferon-α): a phase I trial in melanoma. *Ann Oncol* 2000, **11**, 1183–1189.
26. Atzpodien J, Neuber K, Kamanabrou D, *et al*. Combination chemotherapy with or without s.c. IL-2 and IFN-α : results of a prospectively randomized trial of the Cooperative Advanced Malignant Melanoma Chemoimmunotherapy Group (ACIMM). *Br J Cancer* 2002, **86**, 179–184.
27. Flaherty LE, Atkins M, Sosman J, *et al*. Outpatient biochemotherapy with interleukin-2 and interferon alfa-2b in patients with metastatic malignant melanoma: results of two phase II Cytokine Working Group trials. *J Clin Oncol* 2001, **19**, 3194–3202.
28. Keilholz U, Punt CJ, Gore M, *et al*. Dacarbazine, cisplatin and IFN-α 2b with or without IL-2 in advanced melanoma: final analysis of EORTC randomized phase III trial 18951. *Proc Am Soc Clin Oncol* 2003, **22**, 708, Abstract 2848.
29. Rosenberg SA, Yang JC, Schwarzentruber DJ, *et al*. Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alfa-2b. *J Clin Oncol* 1999, **17**, 968–975.
30. Bajetta E, Del Vecchio M, Vitali M, *et al*. A feasibility study using polychemotherapy (cisplatin + vindesine + dacarbazine) plus interferon-alpha or monochemotherapy with dacarbazine plus interferon-alpha in metastatic melanoma. *Tumori* 2001, **87**, 219–222.
31. Del Vecchio M, Bajetta E, Vitali M, *et al*. Multicenter phase III randomized trial of cisplatin, vindesine and dacarbazine (CVD) versus CVD plus subcutaneous interleukin-2 and interferon-alpha-2b in metastatic melanoma patients. *Proc Am Soc Clin Oncol* 2003, **22**, 709, Abstract 2849.
32. Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with interferon α-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon α-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1998, **16**, 1743–1751.
33. Jansen B, Wacheck V, Heere-Ress E, *et al*. Chemosensitisation of malignant melanoma by *BCL2* antisense therapy. *Lancet* 2000, **356**, 1728–1733.
34. Atkins MB, Lee S, Flaherty LE, Sosman JA, Sondak VK, Kirkwood JM. A prospective randomized phase III trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine (CVD), IL-2 and interferon alpha-2b versus CVD alone in patients with metastatic melanoma (E3695): an ECOG-coordinated intergroup trial. *Proc Am Soc Clin Oncol* 2003, **22**, 708, Abstr. 2847.
35. Ridolfi R, Chiarion-Sileni V, Guida M et al., for the Italian Melanoma Intergroup. Cisplatin, dacarbazine with or without subcutaneous interleukin-2, and interferon alfa-2b in advanced melanoma outpatients: results from an Italian multicenter phase III randomized clinical trial. *J Clin Oncol* 2002, **20**, 1600–1607.
36. Agarwala SS, Ferri W, Gooding W, Kirkwood JM. A phase III randomized trial of dacarbazine and carboplatin with and without tamoxifen in the treatment of patients with metastatic melanoma. *Cancer* 1999, **85**, 1979–1984.
37. Eton O, Legha SS, Bedikian AY, *et al*. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. *J Clin Oncol* 2002, **20**, 2045–2052.
38. Hauschild A, Garbe C, Stolz W, *et al*. Dacarbazine and interferon α with or without interleukin 2 in metastatic melanoma: a randomized phase III multicentre trial of the Dermatologic Cooperative Oncology Group (DeCOG). *Br J Cancer* 2001, **84**, 1036–1042.
39. Middleton MR, Lorigan P, Owen J, *et al*. A randomized phase III study comparing dacarbazine, BCNU, cisplatin and tamoxifen with dacarbazine and interferon in advanced melanoma. *Br J Cancer* 2000, **82**, 1158–1162.
40. Sertoli MR, Queirolo P, Bajetta E, *et al*. Multi-institutional phase II randomized trial of integrated therapy with cisplatin, dacarbazine, vindesine, subcutaneous interleukin-2, interferon α2a and tamoxifen in metastatic melanoma. *Melanoma Res* 1999, **9**, 503–509.
41. Young AM, Marsden J, Goodman A, Burton A, Dunn JA. Prospective randomized comparison of dacarbazine (DTIC) versus DTIC plus interferon-alpha (IFN-α) in metastatic melanoma. *Clin Oncol* 2001, **13**, 458–465.
42. Ravaud A, Delaunay M, Chevreau C, *et al*. Granulocyte-macrophage colony-stimulating factor alone or with dacarbazine in metastatic melanoma: a randomized phase II trial. *Br J Cancer* 2001, **85**, 1467–1471.
43. Chiarion Sileni V, Nortilli R, Aversa SML, *et al*. Phase II randomized study of dacarbazine, carmustine, cisplatin and tamoxifen versus dacarbazine alone in advanced melanoma patients. *Melanoma Res* 2001, **11**, 189–196.
44. Middleton MR, Grob JJ, Aaronson N, *et al*. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic melanoma. *J Clin Oncol* 2000, **18**, 158–166.
45. Hillner BE, Agarwala S, Middleton MR. Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma. *J Clin Oncol* 2000, **18**, 1474–1480.