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Academia–Pharma Intersect: Melanoma

Systematic Review of Medical Treatment in Melanoma: Current Status and Future Prospects

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ABSTRACT

The incidence of melanoma is increasing worldwide, and the prognosis for patients with high-risk or advanced metastatic melanoma remains poor despite advances in the field. Standard treatment for patients with thick (≥2.0 mm) primary melanoma with or without regional metastases to lymph nodes is surgery followed by adjuvant therapy or clinical trial enrollment. Adjuvant therapy with interferon-α and cancer vaccines is discussed in detail. Patients who progress to stage IV metastatic melanoma have a median survival of ≤1 year. Standard treatment with chemotherapy yields low response rates, of which few are durable. Cytokine therapy with IL-2 achieves durable benefits in a greater fraction, but it is accompanied by severe toxicities that require the patient to be hospitalized for support during treatment. A systematic literature review of treatments for advanced, metastatic disease was conducted to present the success of current treatments and the promise of those still in clinical development that may yield incremental improvements in the treatment of advanced, metastatic melanoma. ***The Oncologist*** 2011;16: 5–24

INTRODUCTION

The incidence of melanoma is increasing worldwide, with a growing fraction of patients with advanced disease for which prognosis remains poor [1]. Treatment options are limited despite advances in immunotherapy and targeted therapy. For patients with surgically resected, thick (≥2 mm) primary mel-

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anoma with or without regional lymph node metastases, the only effective adjuvant therapy is interferon-α (IFN-α) [2]. However, because of the limited benefit upon disease-free survival and the smaller potential improvement of overall survival [3, 4], the indication for IFN-α treatment remains controversial. Standard recommended therapy for patients with stage IV metastasis according to the American Joint Committee on Cancer (AJCC) is single-agent dacarbazine (Bedford Laboratories, Bedford, Ohio), but responses to this agent and its oral analogue, temozolomide (Merck & Co. Inc., Whitehouse Station, New Jersey), are $<$15% and generally transient [5]. Among other treatment options, immunotherapy with high-dose interleukin (IL)-2 achieves long-term, durable, complete responses in a small percentage of patients but has never been established in a formal, phase III, randomized comparative study [6]. Biochemotherapy increases objective response rates but has not been shown to significantly improve survival compared with chemotherapy alone and is associated with additive toxicity [7–10]. Clearly, new therapies are needed.

Adjuvant therapies for high-risk melanoma and therapies for advanced, metastatic melanoma will be discussed. This systematic literature review was performed to update a previous review of 41 randomized trials published through 2001 [11] and to identify new randomized trials that may serve to change the paradigm of melanoma treatment in the future. Thus, this review augments and provides a current analysis of randomized trials in metastatic melanoma. Additionally, clinical trial databases have been reviewed to identify and overview ongoing trials in melanoma worldwide.

METHODS

Search Strategy and Selection Criteria

A systematic search strategy was applied as used previously [11]; this review updates previous analyses. The Medline database was searched for articles published between January 1, 2002, and June 5, 2010. A combination of MeSH headings was used: "melanoma, advanced"; "melanoma, metastatic"; or "melanoma, disseminated" with the term "randomized clinical trial" for trials in advanced disease and "melanoma, adjuvant" or "melanoma, interferon" for adjuvant IFN-α trials for the trials conducted in the adjuvant setting. Searches were limited to clinical trials and publications in English, French, Italian, or German. The "related articles" feature of PubMed was used for all reports that met the requested criteria as an additional means of identifying potentially relevant investigations. The abstract databases of the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology annual congresses were searched for further up-to-date clinical trials. Textbook chapters and review articles were also consulted. Additionally, in all reports, the list of references was reviewed to find further relevant publications.

Statistical Analysis

Data derived from adjuvant trials with IFN-α were analyzed using RevMan (The Cochrane Collaboration, http://www.cc-ims.net/RevMan) software version 5.0. The standardized mean differences and 95% confidence interval (CI) were computed and displayed graphically.

Adjuvant Therapy of Melanoma

Patients with thick ($>$2.0 mm according to 2009 AJCC/International Union Against Cancer [UICC] classification) primary melanoma and regional lymph node metastases are at increased risk of recurrence and death [12]. Surgery is the standard treatment [13, 14], and surgical excision margins should be based on Breslow's tumor thickness [15, 16]. Complete lymphadenectomy is recommended for patients with involved regional nodes [13, 14]. Current recommendations for patients with stage II ($>$2.0 mm according to AJCC/UICC classification, but negative nodes) melanoma are for adjuvant therapy with IFN or enrollment in a clinical trial [13, 14]. Patients with stage III melanoma typically undergo complete lymphadenectomy followed by adjuvant therapy with IFN or enrollment in a clinical trial of adjuvant therapy [13, 14]. Over the past 25 years, adjuvant therapy for immediate-risk (stage II and IIIA) and high-risk (stage IIIB as well as resectable stage IV M1a, M1b) patients have shifted from regional radiotherapy, systemic immunostimulants such as Bacillus Calmette-Guerin (BCG) and Corynebacterium parvum, or pharmacologic immunomodulators such as levamisole, to recombinant DNA-produced biologic agents such as IFN-α, granulocyte-macrophage colony-stimulating factor, and antibodies that have immunoregulatory function such as those that block cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) [17, 18].

IFN-α

IFN-α2b (Intron A, Merck & Co. Inc., Whitehouse Station, New Jersey) was the first agent to show a significant survival benefit in patients with high-risk melanoma in a randomized, controlled trial [19]. In the Eastern Cooperative Oncology Group (ECOG) trial E1684, patients ($N = 287$) with high-risk resected cutaneous melanoma and regional lymph node metastases were randomized to standard observation or to receive IFN-α2b (20 million units [MIU]/m^2 per day) intravenously for 1 month and 10 MIU/m^2 subcutaneously 3 times per week for 48 weeks. Overall survival was significantly prolonged with IFN-α2b after a median follow-up time of 6.9 years (median overall survival 3.82

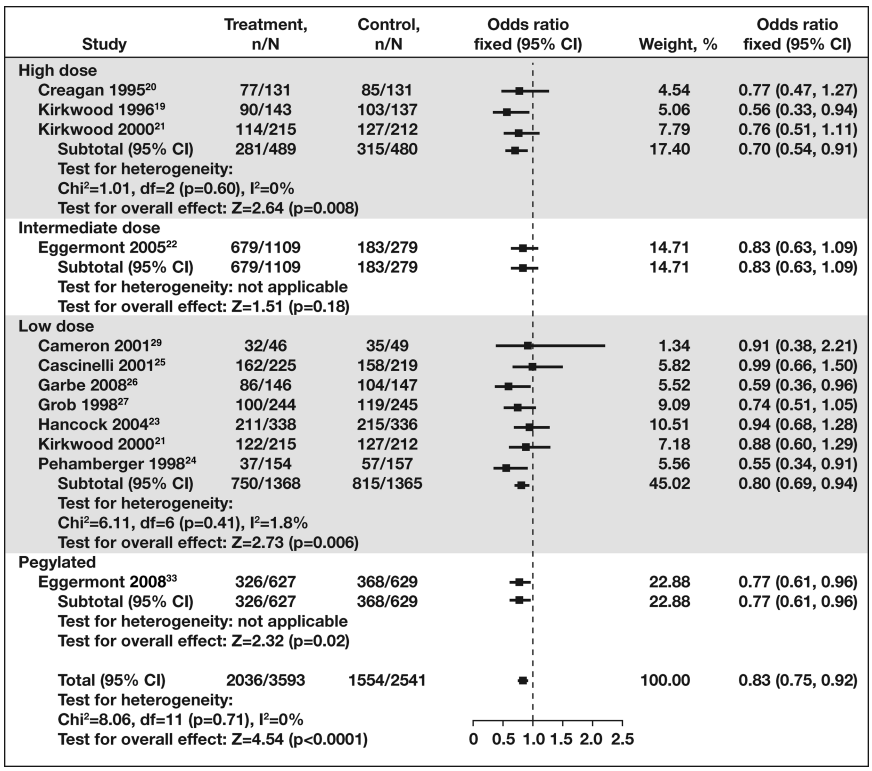

Figure 1. Forest plot of disease-free survival of patients with high-risk melanoma treated with various doses of IFN-α adjuvant therapy. Disease-free survival among patients with high-risk melanoma was improved with IFN-α adjuvant therapy compared to control ($p < .0001$; odds ratio = 0.83; 95% CI = 0.75–0.92). Treatment improved disease-free survival compared with control regardless of dose or pegylation of the adjuvant IFN. Data analysis was performed using the program RevMan (The Cochrane Collaboration).

Abbreviations: CI, confidence interval; IFN-α, interferon-α; *N*, total number of patients per group; *n*, number of patients with disease progression.

years [95% CI = 2.34–7.08] with IFN-α2b vs. 2.78 years [95% CI = 1.83–4.03] with observation only; *p*-value = .0237) [19]. Subsequent to this first positive trial, a number of studies have attempted to identify the optimal dose, schedule, and duration of IFN-α for adjuvant therapy (Figs. 1 and 2) [20–29]. In a follow-up trial comparing patients ($N = 642$) receiving high-dose IFN-α2b (HDI) for 1 year, low-dose IFN-α2b (LDI) for 2 years, or observation, relapse-free survival (RFS) was significantly enhanced with HDI versus observation ($p = .03$), but overall survival was not improved [21]. Although LDI was associated with a greatly reduced incidence of grade 3/4 adverse events (AEs) compared with HDI (1 [0.5%] vs. 17 [8.0%] grade 4 AEs, respectively) and the early RFS benefit was equivalent to HDI after 3–4 years, LDI failed to achieve statistically significant improvement in RFS or durable impact on relapse in this trial. It is notable that this trial was conducted in part before and in part after the U.S. FDA approval of HDI, and follow-up evaluation of patients assigned to observation in the trial demonstrated that 37 patients had been treated at subsequent nodal relapse with HDI, offering an explanation for the absence of an effect upon survival in this experience. In a controlled trial of two lower doses of IFN conducted in patients ($N = 1388$) randomized to observation or to treatment with an intermediate dose of IFN-α2b (4 weeks with 10 MIU administered 5 times per week, followed by 10 MIU 3 times per week for 1 year or 5 MIU 3 times per week for 2 years) for 13 or 25 months, intermediate-dose IFNα-2b did not significantly improve distant metastasis-free interval or overall survival outcomes [22]. Low-dose IFN-α2b also failed to improve survival outcomes versus observation alone when patients were randomized to treatment with 3 MIU 2 times weekly for 6 months ($N = 95$) or 3 MIU 3 times weekly for 2 years ($N = 674$) or 3 years ($N = 444$) [23, 25, 29]. However, LDI did improve disease-free survival compared versus observation alone when patients ($N = 311$) received 3 MIU daily for 3 weeks and then 3 times weekly for 1 year ($p = .02$) and when patients ($N = 499$) were treated with 3 MIU 3 times weekly for 18 months ($p = .038$) [24, 27].

The large number of clinical trials testing variations in dosage, schedule, and duration of IFN-α administration,

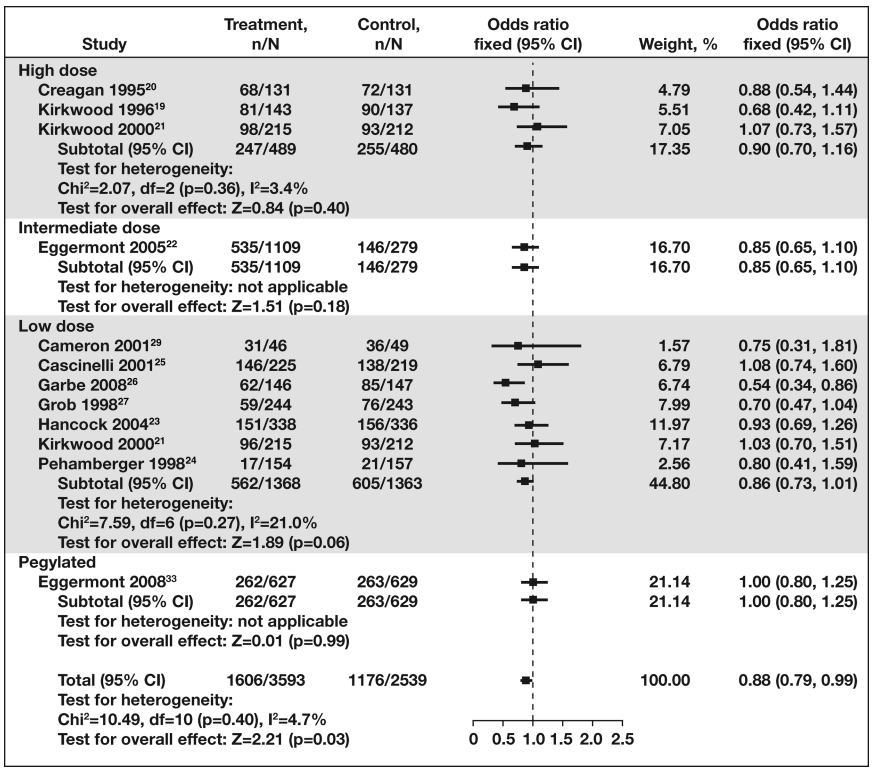

Figure 2. Forest plot of overall survival in high risk patients treated with adjuvant interferon-α (IFN-α). Overall survival among patients with high-risk melanoma was improved with IFN-α adjuvant therapy compared to control ($p < 0.03$; odds ratio = 0.88; 95% CI = 0.79–0.99). Treatment improved overall survival compared with control regardless of dose or pegylation of the adjuvant IFN.

Abbreviations: CI, confidence interval; *N*, total number of patients per group; *n*, number of patients with disease progression.

and exploring these effects in different patient populations, has prompted a number of attempts to consolidate and review the available outcome data [3, 4, 30–32]. A meta-analysis of the available published data from randomized clinical trials was reported in 2007, summarizing event-free survival and overall survival in patients with high-risk melanoma treated with IFN-α adjuvant therapy [32]. Clinical data were sorted by IFN dose: high (20 MIU/m^2), intermediate (5–10 MIU/m^2), low (3 MIU/m^2), and very low (1 MIU/m^2) doses [32]. Groups were also stratified by duration of treatment (<6 months, 12–18 months, or >24 months). Although there was a statistically significant overall survival benefit for treatment of patients with IFN-α ($p = .008$), this assimilation did not find evidence of a clear difference in overall survival with different dose levels ($p = .8$) or durations of treatment ($p = .9$) [32]. Thus, adjuvant IFN improves overall survival of patients with stage II/III melanoma, although the absolute benefit in terms of survival rate at 5 years was small (~3%, 95% CI = 1%–5%). In this review, disease-free and overall survival of patients treated with high-dose, intermediate-dose, low-dose, and pegylated IFN (PEG–IFN) were compared (Figs. 1 and 2) [19–27, 29, 33]. Similar to the meta-analysis by Wheatley et al. [32], there was a clear benefit for disease-free survival (odds ratio [OR] = 0.83; 95% CI = 0.75–0.92) and overall survival (OR = 0.88; 95% CI = 0.79–0.99) with adjuvant therapy using IFN-α, regardless of dose, schedule, duration, or formulation (pegylation).

Current trials are assessing the tolerability and efficacy of more intense but shorter regimens of dosing with IFN-α2b [34] or PEG–IFN-α2a and PEG–IFN-α2b [35, 36]. A fundamental question has been posed regarding whether the benefit of IFNs occurs through durable immunologic, antiangiogenic, or other antitumor mechanisms that would require prolonged, and perhaps indefinite, exposure to IFN. A recent phase III European Organization for Research and Treatment of Cancer (EORTC) study ($N = 1256$) showed that prolonged treatment with PEG–IFN-α2b (for up to 5 years) significantly improved recurrence-free survival compared with observation in patients with resected stage III melanoma (328 events compared with 368 events; hazard ratio (HR) = 0.82, 95% CI = 0.71–0.96; $p = .01$) [33]. This effect is remarkably consistent with the aggregate assessment of IFN effects on relapse in melanoma [3]. In the EORTC trial, both gross nodal disease and microscopic nodal disease were included, but the benefit of therapy ap-

peared to be confined to the subset of patients with microscopic metastatic disease [33]. The magnitude of this effect appears to be less than the magnitude of the HDI effect, and there is no hint of a survival benefit with this regimen (HR = 0.99). Many patients in the PEG–IFN-α2b arm (191 of 627; 31%) discontinued therapy because of toxicities [33]. The median duration of dosage, despite the initial goals of this trial, was 12 months. A trial of the European Association of Dermatologic Oncology investigated adjuvant treatment efficacy of low-dose PEG–IFN-α2b (100 μg/wk) for 36 months in comparison to classic LDI for 18 months and did not find differences in disease-free or overall survival [37].

Other studies have investigated the benefit of derivative components of the approved regimen of HDI, and specifically the benefit of intravenous high-dose induction therapy alone. A randomized phase III trial by the Hellenic Cooperative Oncology Group tested a modified HDI regimen versus a modified HDI induction regimen and showed that 1 month of modified intravenous IFN-α2b induction was not inferior to 1 year of modified HDI therapy [38]. The current U.S. intergroup trial tests the IV HDI induction regimen versus observation. An early report on a study of DeCOG has found that 1 month of HDI induction therapy adds no benefit to LDI given for 2 years [39].

To date, the mechanism of the therapeutic effects of IFN-α is not completely known. A neoadjuvant trial with HDI applied for 4 weeks before complete lymphadenectomy in patients with macrometastatic lymph node metastases and histologic comparison of pre- and post-treatment specimens implicated an indirect immunomodulatory mechanism [40]. In this trial, 20 patients who had bulky nodal disease at presentation or recurrence were enrolled. Remarkably, 55% of patients demonstrated objective clinical response after only 20 doses of HDI, including 3 with a complete response demonstrated pathologically. The examination of the nodal tumor tissue taken before and after 20 doses of IFN revealed increased infiltration of the tumor tissue by dendritic cells (DCs) marked by CD11a; T cells positive for CD3, CD4, and CD8; and striking ablation of the STAT3 expression that is typically constitutively active in melanoma. These findings argue that HDI has an immunologic mechanism of action. Additional data from Yurkovetsky et al. [41] revealed significant decreases of serum levels of immunosuppressive and tumor angiogenic/growth stimulatory factors and increased levels of antiangiogenic IFN-γ inducible protein 10 under IFN-α treatment. This study also demonstrates a profile of pro-inflammatory cytokines that may serve to predict response to therapy.

Treatment benefits with IFN-α, however, remain suboptimal, and the balance of this benefit weighed against the toxicity and cost of therapy has led to differences in the therapy pursued in different countries. In all western nations, HDI has received regulatory approval for stage III melanoma. In the United States, where three randomized controlled trials have shown this regimen to be superior to observation, as well as superior to LDI and a ganglioside vaccine, most physicians offer this treatment to patients. In Europe, LDI has also been approved for stage II melanoma, and this treatment is offered to patients. However, despite regulatory approval, many countries (e.g., United Kingdom, Scandinavian countries, Australia, etc.) do not have financial support for treatment with HDI and do not routinely offer HDI to patients.

Cancer Vaccines and Immunotherapies

Cancer vaccines have been pursued in hopes of enhancing immune recognition and effector antitumor immune responses through improved antigen presentation and the ability to elicit effector memory T-cell responses that are durable [42]. Increased knowledge of the relevant antigenic epitopes capable of eliciting antitumor immunity has prompted a variety of vaccine approaches. Although vaccines are well tolerated, they rarely have been monitored with methods that are now recognized to be critical to detect whether or not the vaccine induced an immune response. Not surprisingly, the large phase III trials of older crude tumor cell vaccines have not demonstrated robust clinical evidence of antitumor activity either in advanced disease or in the adjuvant setting [43]. A randomized, phase III study (ECOG 1694) compared HDI with the ganglioside vaccine GMK (ganglioside conjugate [GM2] coupled to keyhole limpet hemocyanin and formulated with adjuvant QS-21 [Progenics Pharmaceuticals, Tarrytown, New York]) as adjuvant therapies for patients with high-risk melanoma [44]. The GMK vaccination induces antibodies against GM2 capable of specifically binding GM2 and killing melanoma cells in vitro through complement or antibody-dependent cell-mediated cytotoxicity. Patients were documented to have generated robust antibody immune responses to GM2 in this trial, and those who had immunity to GM2 with these antibodies had a trend to an improved survival. However, the study was terminated early when interim analyses demonstrated a markedly inferior relapse-free and overall survival among patients who received GMK vaccine compared with patients who received HDI [44]. Subsequent analyses comparing pre- and post-treatment patient sera found that GMK had induced persistent (for at least 1 year) antibodies in ~80% of vaccinated patients [45], so these results were not explained by a lack of immune activation. In two other randomized, phase III trials, postoperative adjuvant therapy with BCG alone or in combination

with an allogeneic melanoma vaccine (Canvaxin; Micromet, Munich, Germany) tested as adjuvant treatment for patients with resected stage III ($n = 1160$) or stage IV ($n = 496$) melanoma was terminated because of the statistically inferior relapse-free and overall survival of patients (stage III) who received Canvaxin plus BCG, as well as the futility of the original hypothesis that Canvaxin would show an improvement in relapse-free and overall survival [46]. The fact that relapse-free and overall survival was shorter among patients who received BCG plus vaccine suggests that the vaccine may have induced tolerance to tumor antigens rather than effector immunity. This question also arises in the context of another large adjuvant vaccine trial in patients with high-risk melanoma. The EORTC 18961 trial ($N = 1314$) in patients with stage II melanoma compared vaccination with a synthetic GM2 vaccine and observation. This trial was prematurely halted after the second interim analysis (267 recurrences, median follow-up of 1.8 years) because, for the primary endpoint (RFS), the criteria for stopping for futility were met. For distant metastasis-free and overall survival, the results suggested no advantageous effects of the vaccine cohort (143 vs. 152 events, $p = .36$; 112 vs. 124 events, $p = .25$) [47].

Currently, a large phase III vaccine trial is ongoing in patients with stage IIIB/C melanoma whose tumors express MAGE-A3 antigen in lymph node metastases [48]. This vaccine is conceptually quite different from the previously described vaccines because it targets a cancer germline family antigen that has been considerably better defined than the crude Canvaxin preparation, and it induces effector T-cell responses rather than antibody responses.

Peptide vaccines are another category of vaccine that has been studied in large multicenter ECOG trials in the United States. These studies in patients with advanced metastatic melanoma revealed the induction of immune responses; more than one-third of vaccinated patients had increased T-cell production of IFN gamma as detected by ELISPOT. Of interest, those patients who demonstrated immune response to any of the three peptides studied (gp100, MART-1/Melan-A, and tyrosinase HLA-A2 epitopes) had significantly improved survival that was nearly double that of patients who did not develop immunity to 1 or more of the peptide vaccine epitopes. This triple vaccine has now also been evaluated in the placebo-controlled E4697 intergroup adjuvant trial ($N = 815$), for which results are pending final evaluation [49].

In contrast to the various vaccines discussed above, antibodies to immunoregulatory checkpoint molecules such as CTLA-4 (for details, see below) have been shown to elicit a broader stimulation of the immune system, with autoimmune toxicities that are reminiscent of IL-2 [6] (details below), and the clinical and serologic evidence of autoimmunity associated with IFN-α2b [50]. An adjuvant therapy with CTLA-4–blocking antibodies compared against placebo is presently being conducted by the EORTC, whereasthe ECOG and U.S. Intergroup are conducting studies of these antibodies compared with HDI [51].

Treatment of Metastatic Melanoma

Among patients with AJCC stage IV metastatic melanoma, median survival time is estimated to be ~8 months (±2 months), and only ~10% patients survive >5 years from diagnosis of metastatic melanoma [12]. In the United States, there are only two agents approved for treatment of patients with metastatic melanoma: dacarbazine and high-dose IL-2. Current consensus is that there is no single standard therapy for metastatic melanoma [13, 14], and single agents are not likely to prove to be effective. Neither of the FDA-approved systemic therapies has been ever been shown to significantly prolong survival in phase III trials in patients with advanced stage IV melanoma [14].

Chemotherapy

Chemotherapy is an accepted palliative therapy for stage IV metastatic disease (Table 1) [7, 9, 52–69], and dacarbazine is the most widely used single chemotherapeutic agent for the treatment of metastatic melanoma [70]. Dacarbazine was originally reported to yield objective responses in up to 25% of patients in older phase II trials, but current trials in more rigorous, large-scale, cooperative group settings have shown response rates of 5%–12% [52, 54, 55]. Unfortunately, most responses to this agent and its oral analogue temozolomide are transient; only 1%–2% of patients achieve a durable long-term response to chemotherapy [11]. Temozolomide, an oral prodrug that yields the same active intermediate (3-methyl-[triazen-1-yl]imidazole-4-carboxamide) as dacarbazine, has been demonstrated to be as effective as dacarbazine in phase III studies and is an oral, although more expensive, alternative to dacarbazine [71]. For symptomatic patients, or patients who are not eligible for current investigational trials, chemotherapy with one of these agents remains a reasonable palliative option; for novel agents being tested in clinical trials, chemotherapy is an accepted comparator (Table 1) [9, 52–69]. Other chemotherapies that have been explored include fotemustine (Servier, Gidy, France), a chloroethyl nitrosourea that has significantly improved the objective response rate (15.2% vs. 6.8% in the intent-to-treat populations; $p = .043$) and prolonged median overall survival, although not significantly (7.3 vs. 5.6 months; $p = .067$), when compared with dacarbazine in a phase III trial [52].

The antitumor activity of combinations of chemothera-

Table 1. Studies of different regimens of chemotherapies used as a single agent or in combination with other therapeutic agents (final data published)

Author	Treatment schedule	*n*[a]	CR (%)	PR (%)	Response *p*-value	Median OS, mo	OS *p*-value
Chemotherapy or multiple agent therapy compared with dacarbazine or temozolomide as single agent							
Avril et al. 2004 [52]	Induction phase	112	2.7	12.5		7.3	
	Fotemustine: 100 mg/m^2 IV d 1,8,15; 5-wk rest period						
	Maintenance phase						
	Fotemustine: 100 mg/m^2 IV d1, q21d						
	vs.				0.043		0.067
	Dacarbazine (DTIC): 250 mg/m^2 d1–5, q28d	117	0.9	6.0		5.6	
Middleton et al. 2007 [53]	Histamine dihydrochloride: 1 mg bid SC d1–5	119	2.5	11.5		9.0	
	IL-2: 2.4 MIU/m^2 BID SC d1–5, 8–12, q28d						
	IFN-α2b: 3 MIU SC daily						
	vs.				NS		0.94
	DTIC 850 mg/m^2 IV d1, q21d	122	2.5	10.1		7.7	
Bedikian et al. 2006 [54]	Oblimersen: 7 mg/kg/d IV (continuous) d1–5	386	2.8	10.6		9.0	
	DTIC: 1,000 mg/m^2 IV d5, q21d						
	vs.				0.007		0.077
	DTIC: 1,000 mg/m^2 IV d1, q21d	385	0.8	6.8		7.8	
Schadendorf et al. 2006 [55]	Autologous peptide-loaded dendritic cell vaccination: SC d1, q14d (first 5 cycles), thereafter q28d	53	0	3.8		9.3	
	vs.				NS		0.48
	DTIC: 850 mg/m^2 IV d1, q28d	55	0	5.5		11.6	
Ranson et al. 2007 [56]	Lomeguatrib: 40/60/80 mg/d PO d1–5	52	1.9	11.5		7.6	
	Temozolomide: 125 mg/m^2/d PO d1–5, q28d						
	vs.				NS		NS
	Temozolomide: 200 mg/m^2/d PO d1–5, q28d	52	3.8	13.4		7.7	
Kaufmann et al. 2005 [57]	Temozolomide: 200 mg/m^2/d PO d1–5, q28d	137	8.0	16.1		9.7	
	IFN-α2b: 5.0 MIU/m^2 SC 3/wk						
	vs.				0.036		0.16
	Temozolomide: 200 mg/m^2/d PO d1–5, q28d	134	2.2	11.2		8.4	
Bafaloukos et al 2005 [58]	Temozolomide: 200 mg/m^2/d PO d1–5,	65	10.8	18.5		12	
	Cisplatin: 75 mg/m^2 IV d1, q28d						
	vs.				0.695		0.9
	Temozolomide: 200 mg/m^2/d PO d1–5, q28d	62	8.1	17.7		11.5	
Danson et al. 2003 [59]	Temozolomide: 150 mg/m^2/d PO d1–5,	60	3.3	11.7		7.3	
	Thalidomide: 100 mg/d PO daily, q28d						
	vs.				NS		NS
	Temozolomide: 200 mg/m^2/d PO d1–5, q28d	62	3.2	14.5		7.7	
	IFN-α2b: 5.0 MIU/m^2 SC 3/wk						
	vs.						
	Temozolomide: 200 mg/m^2 PO every 8 h for 5 doses, q28d	55	0	9.1		5.3	
McDermott et al. 2008 [60]	DTIC: 1,000 mg/m^2 d1, q21d	51	0	24		11.4	
	Sorafenib: 800 mg/d						
	vs.				0.194		0.93
	DTIC: 1,000 mg/m^2, q21d	50	0	12		12.8	

(continued)

Table 1. (continued)

Author	Treatment schedule	*n*[a]	CR (%)	PR (%)	Response *p*-value	Median OS, mo	OS *p*-value
Biochemotherapy compared with polychemotherapy							
Atkins et al. 2008 [9]	Cisplatin: 20 mg/m^2 IV d1–4 Vindesine: 1.2 mg/m^2 IV d1–4 DTIC: 800 mg/m^2 d1 IL-2: 9 × 10^6 IU/m^2/24-h IV IFN-α2b: 5 × 10^6 IU/m^2 SC d1–5, 8, 10, 12 GM-CSF: 5 g/kg SC d7–16 q21d	210	2.5	18.5		9.0	
	vs.				0.14		0.64
	Cisplatin: 20 mg/m^2 IV d1–4 Vindesine: 1.2 mg/m^2 IV d1–4 DTIC: 800 mg/m^2 d1 q21d	206	4.6	9.7		8.7	
Atzpodien et al. 2002 [61]	Cisplatin: 35 mg/m^2, d 1–3 Carmustine: 150 mg/m^2, d1, cycles 1 & 3 only DTIC: 220 mg/m^2, d1–3 Tamoxifen: 20 mg/m^2, daily IL-2: SC 10 × 10^6 IU/m^2, d3–5 wk 4 5 × 10^6 IU /m^2, d1,3,5 wk 5 IFN-α: SC 5 × 10^6 IU/m^2, d1 wk 4 5 × 10^6 IU/m^2 d1,3,5 wk 5 q35d	60	13.3	16.6		12	
	vs.				NS		0.79
	Cisplatin: 35 mg/m^2 IV, d1–3 Carmustine: 150 mg/m^2 IV, d1, cycles 1 & 3 DTIC: 220 mg/m^2 IV, d1–3 Tamoxifen: 20 mg/m^2 IV, daily q35d	64	11.9	23.4		13	
Keilholz et al. 2005 [62]	DTIC: 250 mg/m^2 IV Cisplatin: 30 mg/m^2 IV d1–3 IFN-α2b: 10 × 10^6 IU/m^2 SC d1–5 IL-2: 18 × 10^6 IU/m^2/6 h IV d5 18 × 10^6 IU/m^2/12 h IV d6 18 × 10^6 IU/m^2/24 h IV d7 4.5 × 10^6 IU/m^2/24 h IV d8–10 q28d	183	3.3	17.5		9.0	
	vs.				0.74		0.31
	DTIC: 250 mg/m^2 IV Cisplatin: 30 mg/m^2 IV d1–3 IFN-α-2b: 10 × 10^6 IU/m^2 SC d1–5 q28d	180	3.9	18.9		9.0	
Bajetta et al. 2006 [7]	Cisplatin: 30 mg/m^2 IV d1–3 Vindesine: 2.5 mg/m^2 IV d1 DTIC: 250 mg/m^2 IV d1–3 IL-2: 9 × 10^6 IU SC d1–5, 8–15 IFN-α2b: 5 × 10^6 IU/m^2 SC d1–5 q21d	72	4.2	29.2		11	
	vs.				Not reported		NS
	Cisplatin: 30 mg/m^2 IV d1–3 Vindesine: 2.5 mg/m^2 IV d1 DTIC: 250 mg/m^2 d1–3	72	0	20.8		12	

(continued)

Table 1. (continued)

Author	Treatment schedule	*n*[a]	CR (%)	PR (%)	Response *p*-value	Median OS, mo	OS *p*-value
Further therapeutic schedules							
Punt et al. 2006 [63]	Cisplatin: 30 mg/m^2 IV d1–3	45	2.2	20		9.5	
	DTIC: 250 mg/m^2 IV d1–3						
	IFN-α: 10 $\times$ 10^6 IU/m^2 SC d1–5						
	IL-2: IV						
	1 mg/m^2/6 h d4;						
	1 mg/m^2/12 h d5;						
	1 mg/m^2/24 h d6;						
	0.25 mg/m^2/24 h d7–9						
	q28d						
	vs.				NS		NS
	DTIC: 850 mg/m^2 IV d1, q21d for 2 cycles followed by	44	4.5	11.4		10.5	
	Cisplatin: 30 mg/m^2 IV d1–3						
	DTIC: 250 mg/m^2 IV d1–3						
	IFN-α: 10 $\times$ 10^6 IU/m^2 SC d1–5						
	IL-2: IV						
	1 mg/m^2/6 h d4;						
	1 mg/m^2/12 h d5;						
	1 mg/m^2/24 h d6,						
	0.25 mg/m^2/24 h d7–9						
Richtig et al. 2004 [64]	Temozolomide: 150 mg/m^2 PO d1–5	20	5	30		14.5 for the whole group of patients	
	IFN-α2b: 10 $\times$ 10^6 IU/m^2 SC every other day d6–27						
	q28d						
	vs.				0.35		NS
	Temozolomide: 150 mg/m^2 PO d1–5	27	14.8	7.4			
	IFN-α2b: 10 $\times$ 10^6 IU flat dose SC every other day d6–27						
	q28d						
Glover et al. 2003 [65]	Cisplatin: 150 mg/m^2 SC	49	2	18.4		7.52	
	WR-2721: 910 mg/m^2						
	q21d						
	vs.				NS		NS
	Cisplatin: 120 mg/m^2 IV q21d	45	0	15.6		7.58	
Vuoristo et al. 2005 [66]	DTIC: 200 mg/m^2 IV d1–5	31	10	3		9.8	
	Vincristine: 1 mg/m^2 (max 2 mg) IV d1–4,						
	Bleomycin: 15 mg IV d2,5						
	CCNU: 80 mg PO d1						
	q28d						
	nIFN-α: 3 $\times$ 10^6 IU SC/d8–50, following 6 $\times$ 10^6 IU 3/wk						
	vs.				0.82		0.62
	DTIC: 200 mg/m^2 IV d1–5	25	12	12		7.5	
	Vincristine: 1 mg/m^2 (max. 2 mg) IV d1–4,						
	Bleomycin: 15 mg IV d2,5						
	CCNU: 80 mg PO d1						
	q28d						
	rIFN-α2b: 3 $\times$ 10^6 IU SC/d8–50, following 6 $\times$ 10^6 IU 3/wk						
	vs.						

(continued)

Table 1. (continued)

Author	Treatment schedule	*n*[a]	CR (%)	PR (%)	Response *p*-value	Median OS, mo	OS *p*-value
	DTIC: 250 mg/m2 IV d1–5, q28d	25	4	4		11.1	
	nIFN-α: 3×10^6 IU SC/d8–50, following 6×10^6 IU 3/wk						
	vs.						
	DTIC: 250 mg/m^2 IV d1–5, q28d	25	4	8		9.1	
	rIFN-α2b: 3×10^6 IU SC/d8–50, following 6×10^6 IU 3×/wk						
Reichle et al. 2007 [67]	Trofosfamide: 50 mg orally 3 times daily	32				8.2	
	vs.						0.045
	Trofosfamide: 50 mg orally 3 times daily	35				18.8	
	Rofecoxib: 25 mg orally d1+						
	Pioglitazone: 60 mg orally d1+						
Hauschild et al. 2009 [68]	Paclitaxel: 225 mg/m^2 IV d1	135	0	15		10.5	
	Carboplatin AUC 6 IV d1 q21d						
	vs.				1.00		0.92
	Paclitaxel: 225 mg/m^2 IV d1	135	0	16		10.5	
	Carboplatin AUC 6 IV d1						
	Sorafenib 400 mg PO 2 times daily q21d						
Maio et al. 2010 [69]	DTIC 800 mg/m^2 IV d1	97	2	5		9.3	
	IFN-α: 3×10^6 IU/m^2 SC d11–15						
	Thymosin-α1 1.6 mg SC d8–11;15–18						
	q28d						
	vs.						
	DTIC 800 mg/m^2 IV d1	97	3	7	NS	8.6	0.08
	IFN-α: 3×10^6 IU/m^2 SC d11–15						
	Thymosin-α1 3.2mg SC d8–11;15–18						
	q28d						
	vs.						
	DTIC 800 mg/m^2 IV d1	98	2	4		10.3	
	IFN-α: 3×10^6 IU/m^2 SC d11–15						
	Thymosin-α1 6.4mg SC d8–11,15–18						
	q28d						
	vs.						
	DTIC 800 mg/m^2 IV d1	99	2	10		9.3	
	Thymosin-α1 3.2 mg d 8–11,15–18						
	q28d						
	vs.						
	DTIC 800 mg/m^2 IV d1	97	0	4		6.6	
	IFN-α: 3×10^6 IU/m^2 SC d11–15						
	q28d						
Hodi et al. 2010 [87]	Ipilimumab 3 mg/kg IV d1	403	0.2	5.5	0.04[b]	10.0	<0.001
	gp100 peptide vaccine SC q21d						
	vs.						
	Ipilimumab 3 mg/kg IV d1 q21d	137	1.5	9.5	0.001[b]	10.1	0.003
	vs.						
	gp100 peptide vaccine SC q21d	136	0	1.5		6.4	

[a]Evaluable patients.
[b]Best overall response rate.
Abbreviations: AUC, area under the concentration–time curve; bid, twice daily; CCNU, Lomustine; CR, complete response; d, day; GM-CSF, granulocyte-macrophage colony stimulating factor; h, hour; IFN, interferon; IL, interleukin; IU, international units; IV, intravenously; MIU, million international units; nIFN-α, natural interferon alfa; NS, not shown; OS, overall survival; PO, by mouth; PR, partial response; q, every; rIFN-α2b, recombinant interferon alfa 2b; SC, subcutaneously; wk, week.

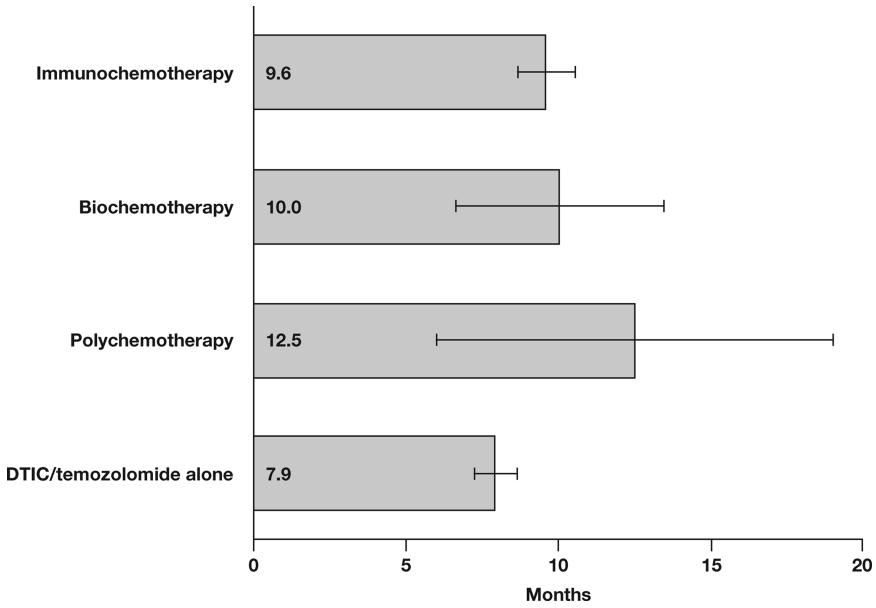

Figure 3. Overall survival of patients treated with different therapies for melanoma. The data analyzed are listed in Table 1. On this figure, the error bars represent the 95% confidence interval. Abbreviation: DTIC, dacarbazine.

peutic agents has been evaluated as a consequence of the increasingly frequently held belief that single agents are unlikely to improve the outcome of patients with advanced metastatic melanoma (Table 1 and Fig. 3) [7, 9, 52–69]. Other polychemotherapies tested in phase III trials (e.g., Dartmouth regimen: cisplatin/vinblastine/dacarbazine/tamoxifen) have failed to demonstrate a survival benefit compared with dacarbazine alone [9].

IL-2 and Other Immunotherapies

High-dose recombinant IL-2 (aldesleukin, Proleukin; Prometheus Laboratories Inc., San Diego, California) received U.S. FDA approval for the treatment of patients with metastatic melanoma in 1998. An objective response rate of ~16% was observed in the collected set of phase II trials in patients ($N = 47$) with metastatic melanoma presented for regulatory review. Single-agent therapy was administered using the inpatient high-dose regimen of 600,000 U/kg IL-2 every 8 hours for up to 14 doses [72]. A small percentage of patients (~5%) [73] experienced long-term, durable complete responses with IL-2, which has been interpreted as a potential cure. However, this therapy has not been shown to improve overall survival in the patient population and has never been evaluated in a phase III setting [74, 75]. In addition, IL-2 treatment-related toxicity is severe [72] and requires inpatient intensive care [76, 77]. Common dose-limiting toxicities include hemodynamic toxicity (e.g., hypotension, edema, weight gain, decreased renal function), respiratory insufficiency, and neurotoxicity [76, 77]. High-dose recombinant IL-2 treatment is the first immunotherapy of metastatic melanoma that induces a low percentage of long-term cancer remissions. Such long-term cancer remissions have not been convincingly demonstrated after chemotherapy. High-dose recombinant IL-2 has not been approved in Europe and is offered only in specialized cancer centers in the United States.

Furthermore, a recent multicenter study ($N = 185$) conducted by Schwartzentruber and colleagues [78] has built upon high-dose IL-2, evaluating the adding benefit of a peptide vaccine (gp100: 209–217[210M]). The remarkable finding that emerged from this trial was that peptide vaccination added significantly to the benefit of high-dose IL-2, improving response rates (22.1% vs. 9.7%, $p = .02$) and prolonging progression-free survival (1.6 vs. 2.9 months, $p = .0101$) significantly. Overall survival was also prolonged in the combination arm (17.6 vs. 12.8 months, $p = .09$) but did not reach significance. One ongoing study ($N = 387$) will determine whether the combination of IL-2 and vaccination with autologous melanoma cells can improve antitumor responses and overall survival compared with IL-2 alone (Table 2) [79]. Another vaccine currently under investigation in phase III is a DNA/lipid complex (allovectin) that enhances the expression of the major histocompatibility complex protein HLA-B7 and induces a fraction of antitumor responses (Table 2) [80].

An area of great research interest focuses on the role of DCs that are recognized as the natural source of antigen presentation. The only randomized trial of a vaccine using DCs and melanoma peptides did not show any clinical benefit compared with chemotherapy (dacarbazine) [55], but

newer, more highly polarized and immunogenic forms of DCs are now available and will doubtless be evaluated in the future (Table 1).

Biochemotherapy

Biochemotherapy (e.g., cisplatin, vinblastine, and dacarbazine combined with IFN-$\alpha \pm$ IL-2) increases response rates but has not been shown to significantly improve survival compared with chemotherapy alone in randomized phase II and III trials [7, 8, 63]. In a systematic review of 41 randomized clinical trials of patients receiving various treatment schedules, including biochemotherapy regimens, none of them improved progression-free survival (PFS) or overall survival (Fig. 3) [11]. Similarly, objective response to polychemotherapy with cisplatin, carmustine, dacarbazine, and tamoxifen was also improved with the addition of subcutaneous IL-2 and IFN-α in a randomized study, but this did not result in significantly improved PFS or overall survival (Table 1) [61]. Furthermore, the addition of IL-2 does not significantly enhance the efficacy of dacarbazine/IFN [81] or dacarbazine/cisplatin/IFN-α2b (Table 1) [62]. Combinations with temozolomide have not been more successful than those with dacarbazine. In a phase III, randomized study, the addition of IFN-α to temozolomide improved the objective response rate but not overall survival compared with temozolomide alone (Table 1) [57]. A phase II study compared combinations of temozolomide with either thalidomide or IFN-α to treatment with temozolomide alone, but neither combination significantly improved objective response rate or median overall survival (Table 1) [59]. Another randomized phase II study analyzed the efficacy and tolerability of bleomycin, vincristine, lomustine, and dacarbazine (BOLD) combined with natural IFN-α or recombinant IFN-α2b (nIFN-α or rIFN-α2b, respectively) [66]. Treatment groups included dacarbazine plus nIFN-α, BOLD plus nIFN-α, dacarbazine plus rIFN-α2b, and BOLD plus rIFN-α2b. There were no significant differences in objective response rate or overall survival among these four treatments.

Although a recent meta-analysis of 18 trials and nearly 2,500 patients with metastatic melanoma suggested a benefit of biochemotherapy in terms of objective response, no benefit in terms of overall survival was found ($p = .9$) [82]. A similar pattern was observed in a phase III ECOG-led intergroup U.S. study comparing polychemotherapy treatment with cisplatin, vinblastine, and dacarbazine (CVD, $n = 195$) alone or given in combination with IL-2 and IFN-α2b (BCT, $n = 200$) administered as first-line treatment of patients with metastatic melanoma [9]. The objective response rate was slightly higher in the BCT arm than in the CVD arm (19.5% vs. 13.8%, respectively; $p = .140$); median PFS was significantly longer in the BCT arm than in the CVD arm (4.8 vs. 2.9 months; $p = .015$). However, the addition of IL-2 and IFN-α2b to chemotherapy was associated with greater toxicity and no improvements in overall survival or durable responses; the BCT regimen cannot be recommended for patients with metastatic melanoma [9]. An interesting observation has been reported by O'Day and colleagues from a study with 133 metastasized melanoma patients treated first line with a biochemotherapy induction regimen including CVD, IL-2, IFN-α, and granulocyte macrophage colony-stimulating factor (GM-CSF) [83]. Patients not experiencing disease progression received maintenance biotherapy with low-dose IL-2 and GM-CSF followed by intermittent pulses of decrescendo IL-2 over 12 months. The median survival time in this trial was 13.5 months, and the 12- and 24-month survival rates were 57% and 23%, respectively. It has been suggested that this promising regimen should be studied in a randomized clinical trial.

Until today, biochemotherapy has not demonstrated significant clinical benefit in adjuvant trials nor in randomized prospective studies in the metastatic setting, but it is associated with additive toxicity. The addition of maintenance biotherapy may be suitable to prolong overall survival. Presently, biochemotherapy regimens cannot be regarded as standard clinical practice and should be further evaluated in clinical trials.

Emerging Therapies for Patients with Metastatic Melanoma

An increased understanding of tumor biology and the complexity of immune antitumor response and immune regulation has led to the development of novel agents. Several approaches to overcoming tolerance that appear promising in clinical trials include blockade of inhibitory immune receptors, inhibition of oncogenic kinase pathways, downregulation of antiapoptotic proteins, and adoptive cell therapy after nonmyeloablative lymphodepletion (Table 2) [79, 80, 84–92].

Antibody Blockade of Cytotoxic T-Lymphocyte–Associated Antigen 4

Full T-cell activation requires stimulation through the T-cell receptor as well as a costimulatory signal provided by the binding of B7 on the antigen-presenting cell (e.g., dendritic cell) to CD28 on the T cell. Cytotoxic T-lymphocyte–associated antigen 4 is a homologue of CD28 and is an inhibitory T-cell receptor that is upregulated following T-cell activation. The normal function of CTLA4 is to compete with CD28 to bind B7 to downregulate T-cell activation, acting as a natural "brake" by removing the co-

Table 2. Recent phase III trials in patients with metastatic melanoma

Sponsor	Study and treatment schedule	Stage[a]	*N*[b]	Primary endpoint
Fully recruited, interim data available				
Pfizer [92]	Tremelimumab vs. DTIC or temozolomide	Stage IV or unresectable stage IIIC with N3 status for regional lymph nodes and in-transit or satellite lesions	655	OS (not achieved)
EORTC [71]	Temozolomide vs. DTIC	Unresectable stage III or stage IV	859	OS (not achieved)
Synta (Symmetry trial) [123][c]	Elesclomol (STA-4783) and paclitaxel vs. Paclitaxel	Stage IV	630	PFS (not achieved)
Genta (AGENDA trial) [124]	DTIC and oblimersen vs. DTIC and placebo	Unresectable stage III or stage IV (low-normal LDH, defined as 0.8 times the upper limit of normal)	300	PFS (not achieved) OS
ECOG/SWOG [105]	Carboplatin and paclitaxel and sorafenib vs. Carboplatin and paclitaxel	Unresectable stage III or stage IV	834	OS (not achieved)
Fully recruited, under evaluation, no interim data available				
BMS/Medarex [84]	DTIC and Ipilimumab vs. DTIC and placebo	Unresectable stage III or stage IV	500	PFS
ECOG/SWOG [105]	Carboplatin and paclitaxel and sorafenib vs. Carboplatin and paclitaxel	Unresectable stage III or stage IV	800	OS
Vical [80]	Allovectin and DTIC vs. DTIC	Unresectable stage III or stage IV	280	Median TTP
Currently recruiting				
GSK [48]	GSK 2132231A vaccine vs. placebo	MAGE-A3–positive, resected stage III	1300	Disease-free survival
BMS [51]	Ipilimumab vs. placebo	High-risk resected stage III	950	Recurrence-free survival
Cambridge University Hospitals NHS Foundation Trust [125]	Bevacizumab vs. placebo	Resected stage IIb–III	1320	OS
Hoffmann-La Roche [89]	RG7204 vs. DTIC	Unresectable stage III or stage IV	896	OS
Eli Lilly and Company [90]	Tasisulam vs. Paclitaxel	Stage IV	800	OS
Abraxis [91]	ABI-007 vs. DTIC	Stage IV	514	PFS
AVAX technologies [79]	IL-2 and M-Vax vs. IL-2 and placebo	Stage IV	387	Best overall antitumor response OS (%) at 2 years
BioVex Limited [126]	OncoVEXGM-CSF vs. GM-CSF	Unresectable Stage IIIb, IIIc, or IV	430	Durable response rate

[a]Disease stage by AJCC/UICC criteria.
[b]Required, planned number of patients.
[c]This study was halted for safety reasons by an independent Data Monitoring Committee; there was also an imbalance in the outcome of patients treated in the different cohorts.
Abbreviations: AJCC, American Joint Committee on Cancer; DTIC, dacarbazine; EORTC, European Organization for Research and Treatment of Cancer; IL, interleukin; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; TTP, time to progression; UICC, International Union Against Cancer.

stimulatory signal. The CTLA4–B7 interaction can be blocked with an anti-CTLA4 monoclonal antibody (mAb), which has a higher affinity for CTLA4 than B7. Thus, the inhibitory signal is prevented and the "brake" on T-cell activation is released. Two fully human anti-CTLA4 mAb's are currently in clinical development: tremelimumab (CP-675,206; Pfizer Inc., New York) and ipilimumab (MDX-010; Medarex, Inc./Bristol-Myers Squibb, New York). Objective response rates of patients with metastatic melanoma treated with either of the two anti-CLTA4 mAb's as single agents are similar (~7%–10%) [92–100] and resemble the response rate found in patients treated with high-dose IL-2. Responses to anti-CTLA4 mAb's are durable (as much as 70%) [87, 92] but may take as long as 12 weeks or even longer to develop [98, 101], and late-onset objective responses are sometimes preceded by months of stable disease or even transient disease progression [101]. Side effects with CTLA4 blockade are autoimmune-related but less acute than those observed with exogenous cytokine therapy and are manageable. Commonly reported AEs include diarrhea and rash [87, 92]. Several randomized studies are ongoing to assess whether these early observations of durable responses will translate into an overall survival benefit (Table 2) [84, 87, 92]. In a phase III randomized study of tremelimumab (15 mg/kg administered once every 3 months, $n = 328$) and chemotherapy ($n = 327$) with dacarbazine or temozolomide in treatment-naive patients, median survival was longer (11.76 months) in patients treated with tremelimumab compared with chemotherapy (10.71 months) [92]. However, the difference was not statistically significant (HR chemotherapy/tremelimumab 1.04; $p = .729$), and the trial was halted at the second interim analysis. However, patients with clinical benefit from tremelimumab treatment are continuing on study, and more mature survival and response data are anticipated. Ipilimumab is also currently being investigated in a large phase III trial in patients with metastatic melanoma (Table 2) [84]. The results of a randomized phase III trial for single ipilimumab treatment versus gp100 vaccination and versus the combination of ipilimumab and gp100 vaccination have been recently published, showing improved overall survival of a median duration of 10.1 and 10.0 months in the ipilimumab arm and the combined arm, respectively, in comparison to 6.4 months in the vaccination alone arm. Although objective response rates were rather low with 10.9% in the ipilimumab alone arm and 5.7% in the combined ipilimumab and vaccination arm versus 1.5% in the gp100 vaccination alone arm, highly significant differences in hazard rates for overall survival resulted were detected between ipilimumab alone versus vaccination alone (0.66; 95% CI = 0.51–0.87; $p = .003$) and between the combined arm versus vaccination alone (0.68; 95% CI = 0.55–0.85; $p < .001$) [87]. This observation may result in approval of ipilimumab by health authorities for the treatment of advanced melanoma.

Inhibitors of the Mitogen-Activated Protein Kinase Pathway

The most frequently (60%–70%) mutated oncogene identified to date in melanoma is BRAF, an upstream mediator of the mitogen-activated protein kinase (MAPK) pathway [102]. Increased activation of the MAPK pathway is implicated in melanoma tumorigenesis and is enhanced in advanced-stage melanoma [103]. Sorafenib (Nexavar, BAY 43–9006; Bayer HealthCare Pharmaceuticals Inc., Wayne, New Jersey, and Onyx Pharmaceuticals, Inc., Emeryville, California) is an oral multikinase BRAF inhibitor that has been widely investigated. Unfortunately, the majority of published clinical studies have failed to show any benefit associated with the addition of sorafenib to standard chemotherapy [60, 68, 104–106].

In contrast to nonselective multikinase inhibitors, RG7204, formerly PLX4032 (Hoffmann-La Roche, Basel, Switzerland/Plexxikon, Inc., Berkeley, California), is a novel selective inhibitor of the oncogenic V600E mutant BRAF kinase. A phase I dose-escalation study in patients with solid tumors carrying the V600E mutation was reported at ASCO 2009 and showed objective responses in ~70% of patients treated with RG7204 [107]. At ASCO 2010, data from an international multicenter phase I study were reported showing an objective fluorodeoxyglucose positron emission tomography response in all 22 treated patients. The best overall response was determined by conventional assessment using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and an objective response rate of 86% has been described. No relationship was found between reduction in target lesions, maximum standardized uptake value (SUVmax) and response by RECIST, PFS, and time to achieve RECIST partial response [108]. A consecutive phase III study comparing RG7204 versus dacarbazine is currently recruiting patients worldwide (Table 2) [89]. Other BRAF inhibitors such as GSK2118436 (GlaxoSmithKline PLC, Brentford, U.K.) and RAF265 (Novartis, Basel, Switzerland) are likewise in first clinical trials [109, 110]. For GSK2118436 a clinical objective response rate of 66% has recently been reported in V600 mutant melanoma patients treated with >150 mg 2 times daily (b.i.d.) [111].

AZD6244 (ARRY-142886; AstraZeneca, Wilmington, Delaware) is a potent, selective inhibitor of MEK 1/2 kinase [112]. Its therapeutic target is downstream but in the same signaling pathway as the kinase targeted by the BRAF inhibitors. First results of AZD6244 antitumor activity were

presented at the ASCO 2008 annual meeting [113], indicating partial responses in mainly BRAF-mutated patients. AZD6244 is currently being tested in a phase II, multicenter, open-label, randomized study comparing its antitumor activity in combination with dacarbazine versus dacarbazine alone for patients with stage III or IV malignant melanoma [114]. First clinical results have also been reported for the MEK inhibitor GSK1120212 in 20 patients with BRAF mutant melanoma showing six partial responses and two complete responses (40% OR). Interestingly, two partial responses have likewise been observed in 22 BRAF wild-type melanoma patients [115].

Tasisulam

Tasisulam (Eli Lilly and Company, Indianapolis) is a novel antiproliferative and cytotoxic drug that induces apoptosis through the mitochondrial cell death pathway. In addition to the apoptotic activity, a loss of mitochondrial membrane potential and the induction of reactive oxygen species appear to be the relevant anticancer mechanisms. Interim data of a phase II trial showed an overall response rate of 12% and disease stabilization in an additional 35% of patients [116]. Recently, a phase III trial comparing tasisulam versus paclitaxel alone was initiated, recruiting 800 patients worldwide [90].

ABI-007 (Abraxane)

ABI-007 (Abraxane, Abraxis BioScience Inc., Los Angeles) is an albumin-bound paclitaxel that is approved for the treatment of metastatic breast cancer and is now being investigated in phase III compared with dacarbazine in previously untreated patients with advanced melanoma. Abraxane has important tolerance benefits compared to solvent-based paclitaxel, which has a high risk of Cremophor EL-related hypersensitivity reactions [91].

Adoptive Cell Therapy

To date, adoptive cell therapy that has been developed by Rosenberg and colleagues has yielded some of the most dramatic responses among patients with metastatic melanoma. Objective response rates in highly selected patients enrolled in this series have been stated to range between 49% and 72%. Adoptive cell therapy as undertaken by this group based at the National Cancer Institute is complex and costly, involving multiple steps: first, specifically sensitized antitumor lymphocytes must be isolated from the patient's tumor or stimulated in vitro with autologous melanoma cells. For this purpose, tumor-infiltrating lymphocytes are cultured in vitro. These are grown in IL-2, exhibiting major histocompatibility complex–restricted recognition of the autologous melanoma cells. Second, the antitumor lymphocytes have to be expanded in vitro to large numbers. The efficacy of adoptive cell therapy depends on the presence of large numbers of antitumor lymphocytes capable of recognizing the melanoma cells and destroying the cancer cells in vivo. The ideal number for the adoptive transfer is $>10^{11}$ cells. Objective clinical responses were associated with cells that were cultured for shorter time periods, and a protocol for rapid expansion has therefore been developed. The in vitro expansion was performed with use of IL-2 and anti-CD3-antibodies in the presence of irradiated allogeneic feeder cells. Cells were harvested 14 days after in vitro expansion [117]. Third, lymphodepletion has been performed as preparation of the host before adoptive cell transfer. Seven days before adoptive transfer, a nonmyeloablative lymphodepleting regimen consisting of cyclophosphamide and fludarabine has been applied. It has been suggested that this has to be supplemented by total body irradiation in single fractions of 2 Gy or with 12 Gy administered as 2 Gy b.i.d. for 3 days. Fourth, the adoptive cell transfer accompanied by a high-dose treatment with IL-2 for 3 days is performed. The tumor-infiltrating lymphocytes were applied as a bolus intravenous infusion over 0.5–1 hours, and the high-dose IL-2 treatment was started within 24 hours. Patients who received total body irradiation additionally received autologous purified cryopreserved $CD34^+$ hematopoietic stem cells from a granulocyte colony-stimulating factor-mobilized pheresis [118]. After nonmyeloablative but lymphodepleting chemotherapy, adoptive cell transfer therapy ($N = 35$) resulted in objective response rates of 51% [119]. By intensifying the lymphodepleting therapy ($N = 25$) through the addition of total body irradiation with a total dose of 12 Gy, the response rate could be increased to 72% [118].

It is important to mention that this therapeutic approach is in general not available for metastatic melanoma patients. First, this particular therapeutic approach has exclusively been established at the surgery branch, National Cancer Institute in Bethesda, Maryland. There are very few groups worldwide that developed therapeutic approaches with lymphodepletion and adoptive cell transfer [120–122]. Second, this procedure is very complex and has several critical steps, such as the isolation of the tumor-infiltrating lymphocytes and their in vitro expansion, which is labor-intensive as well as costly. Third, the selected patients must have an excellent performance status with no other severe concomitant disease. Therefore, only a few patients per year have been included in phase II studies, and to date, no phase III study has been initiated. Nevertheless, tumor remissions accomplished by such a strategy seem to be durable and may result in cancer cure.

CONCLUSIONS

Despite decades of clinical research, patients with advanced melanoma continue to have a poor prognosis, and no agents have shown statistically significant improvement in overall survival in a phase III trial in patients with metastatic melanoma. For high-risk, resected disease, adjuvant therapy with IFN-α has been shown to consistently increase relapse-free survival, as well as overall survival in some studies. Standard off-protocol treatment for patients with metastatic melanoma is evolving, and where mutations can be documented in BRAF (V600E) or the c-Kit gene, there exist promising new approaches to targeted therapy that have altered the paradigm of systemic therapy. Apart from these, or for patients who are symptomatic and unable to consider the pursuit of new investigational trials, chemotherapy offers transient, palliative efficacy. Advances in the understanding of the mechanism of chemotherapy resistance offer the hope for improved results with chemotherapy, and the triumvirate of more effective chemotherapy, immunotherapy, and targeted therapy are likely to be combined with one another for significant advances in melanoma over the coming few years. Because of the potential benefits of new targeted drugs and of immunotherapies, treatment guidelines for melanoma recommend the inclusion of patients with metastatic melanoma in clinical trials.

Several new immunotherapies have demonstrated promising antitumor activity with manageable side effects in patients with advanced melanoma. These include the anti-CTLA4 mAb's tremelimumab and ipilimumab, and the targeted agents RG7204 (BRAF V600E), AZD6244 (BRAF V600E), and the novel proapoptotic agent tasisulam. Although early clinical trials have not indicated that any of these offers a "breakthrough" in terms of antitumor activity for all patients, each will likely offer incremental improvements over standard care. Complex immunotherapies with adoptive T-cell transfer after nonmyeloablative lymphodepletion suggest response rates that are extraordinary, but we must remember that these results are derived from highly selected patient samples, without large multicenter phase III trials to date. Ongoing clinical trials will hopefully elucidate the therapeutic mechanisms of these approaches and provide survival benefit to patients with melanoma.

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