

Review Article

Systemic therapy for melanoma

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ABSTRACT

Advanced melanoma is a disease with a poor prognosis. Most of the currently available chemotherapy agents are ineffective. In contrast to other cancers, immune-based and novel, targeted therapies appear to have some effect in melanoma. Exciting research in the past few years holds hope for the future. We provide an overview of the current management principles of this condition with special emphasis on the emerging options in the systemic therapy of advanced disease.

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INTRODUCTION

The incidence of melanoma in western countries has been increasing rapidly over the past few decades¹—from 1 in 1500 in 1935 to 1 in 68 in 2002.² Australia has the highest incidence of melanoma,^{3,4} (age-adjusted rate [AAR] 40.5 per 100 000 population), whereas India has one of the lowest AARs (0.2 per 100 000 population).⁵ It is possible that melanomas are under-reported in India, as many patients present with pigmented lesions of the skin in the early stages of the disease, who may be treated by dermatologists or general surgeons.

Notable risk factors for melanomas are white race and a tendency for developing sunburn, which could explain why Indians have a lower incidence. Exposure to the ultraviolet B (UV-B) component of the sun's rays has been implicated in the aetiology of melanoma. A family history is present in 10%–15% of cases. Other risk factors include a history of prior melanoma, multiple atypical moles or dysplastic nevi, and certain inherited mutations.

A majority of melanomas present with early-stage disease,⁶ but a major proportion can present with loco-regionally advanced or metastatic disease. The clinical subtypes of melanoma have been described and they vary in their mode of presentation and final prognosis (Table I).

The few therapeutic options available for advanced melanoma have limited (interferon) or no effect (dacarbazine, interleukin-2) on survival. 'Positive' phase 3 clinical trials in advanced melanoma have not been conducted so far. We discuss the principles of

management of melanoma and focus on the recent developments in the management of advanced disease.

PROGNOSTIC FACTORS AND STAGING

The depth of invasion is the most important prognostic factor of the primary tumour in melanoma (incorporated in the T stage of the TNM system), and traditional classification systems, such as Clark level⁷ and Breslow system,⁸ exploit this fact. The TNM stage⁶ is the most important prognostic factor (Table II). Ulceration increases the T stage by one level and generally indicates an adverse prognosis.⁹ The other important factors include age, growth pattern (superficial *versus* nodular), lymphovascular invasion, specific body sites (head and neck and acral melanomas have a poor prognosis), mitosis rate, negative *versus* positive margins of resection, impalpable *versus* clinically palpable regional lymph nodes, size and location of tumour in sentinel lymph nodes, extracapsular extension of the tumour in the lymph nodes, and site and size of metastases (skin-only metastasis has a better prognosis than visceral metastasis).

MANAGEMENT OF MELANOMA: AN OVERVIEW

For purposes of management, melanoma can be broadly classified as localized (stages I and II), locally advanced (stage III, lymph node involvement, satellite lesions or in-transit metastasis), and metastatic melanoma (Table III and Fig. 1). The prognosis differs widely, with survival in excess of 80% in the early stages and <10% with advanced melanomas.

Localized melanoma

These are treated by wide local excision with appropriate margins; adjuvant therapy with high-dose interferon (HDI) may be

TABLE I. Subtypes of melanoma

Subtype	Incidence (%)	Presentation	Prognosis
Superficial spreading	70	Predominantly radial spreading phase	Intermediate
Nodular melanoma	20	Early deep phase, presents in advanced T stages	Poor
Lentigo maligna melanoma	10–20	Elderly age group, long history, indolent growth	Good
Acral lentiginous	<5	Involves extremities, may be missed in early stages and may present with metastasis	Variable

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TABLE II. TNM staging of melanoma⁶ (indicating the pathological stage)

T stage (depth of invasion)		N stage (lymph node involvement or satellite lesions)		M stage	
Stage	Description	Stage	Description	Stage	Description
Tx	Primary tumour cannot be assessed	Nx	Regional LN cannot be assessed	M1a	Distant skin, subcutaneous, or nodal metastasis, with normal LDH
Tis	Melanoma <i>in situ</i>	N0	No regional LN metastasis		
T1a	≤1 mm with no ulceration, Clarke level II or III	N1a	1 LN, clinically undetectable		
T1b	≤1 mm with ulceration, or Clarke level IV or V	N1b	1 LN, clinically detectable	M1b	Lung metastasis with normal LDH
T2a	1.01–2 mm, no ulceration	N2a	2–3 LN, clinically undetectable		
T2b	1.01–2 mm with ulceration	N2b	2–3 LN, clinically detectable	M1c	All other metastases with normal LDH, or any metastases with elevated LDH
T3a	2.01–4 mm, no ulceration	N2c	No LN, in-transit or satellite lesions		
T3b	2.01–4 mm with ulceration	N3	4 or more metastatic nodes, or matted nodes, or in-transit met(s)/satellite(s) with metastatic nodes		
T4a	>4 mm, no ulceration				
T4b	>4 mm with ulceration				

LDH lactate dehydrogenase LN lymph node

TABLE III. Pathological stage grouping, prognosis and broad management principles

Stages I and II <i>Localized melanoma</i>			Stage III <i>Locally advanced melanoma</i>			Stage IV <i>Metastatic melanoma</i>		
Stage	Description	5YS (%)	Stage	Description	5YS (%)	Stage	Description	5YS (%)
0	pTis N0 M0	>99	IIIA	pT1a-pT4a N1a M0	70	IV	Any T Any N M1a	19
IA	pT1a N0 M0	95	IIIA	pT1a-pT4a N2a M0	63	IV	Any T Any N M1b	7
IB	pT1b N0 M0	89	IIIB	pT1b-pT4b N1a M0	53	IV	Any T Any N M1c	5–10
	pT2a N0 M0							
IIA	pT2b-pT3a N0 M0	77–79	IIIB	pT1b-pT4b N2a M0	50			
IIIB	pT3b-pT4a N0 M0	63–67	IIIB	pT1a-pT4b N1a/N2a M0	46–59			
				pT1a-pT4a N1b/N2b M0				
				pT1a-pT4a/b N2c M0				
IIC	pT4b N0 M0	45	IIIC	pT1b-pT4b N1b or N2b M0 or any T with N3	24–29			

Intent: Curative
Local site: Wide local excision of primary with appropriate margins +/- sentinel or complete lymph node dissection
Adjuvant therapy: Consider HDI for T3b and T4

Intent: Curative if radical lymph node dissection is possible
Local site: Surgery and radical lymph node dissection
Adjuvant therapy: Consider HDI. Consider radiotherapy to lymph node sites

Intent: Palliative systemic therapy only
 No therapy has been shown to improve survival in phase 3 trials so far

5YS 5-year survival HDI high-dose interferen

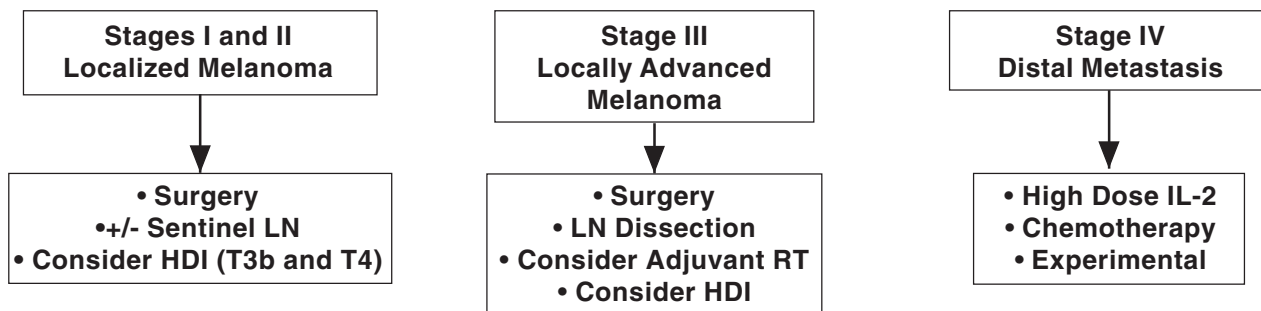


FIG 1. Management of melanoma: An overview LN lymph node HDI high-dose interferen

considered in deeply infiltrating or ulcerated lesions (T3b and T4).¹⁰

Regional disease

Whenever feasible, regional disease is resected with the intent to cure. Adjuvant therapy is given because of the high chance of local and systemic relapse of regional melanomas.¹⁰ Unresectable regional disease is treated systemically, chiefly for palliation. In some cases, surgery may be possible after systemic therapy. Radiotherapy has a limited role in regional disease; while improving local control it does not affect the overall survival. A recent trial comparing regional radiotherapy *versus* observation in localized melanoma after regional lymphadenectomy did not show a survival advantage for adjuvant radiotherapy.¹¹ Systemic therapy for melanoma might be useful in the adjuvant setting in resected deeply infiltrating or 'thick' melanomas, and in melanomas with regional spread.

Metastatic melanoma

Systemic therapy is administered for metastatic melanomas with palliative intent. The role of surgery is well defined in metastatic melanoma¹² (Table IV). Surgery with curative intent is possible in some cases, such as solitary metastases in the lung, liver or brain. The currently available systemic therapy for metastatic melanoma

TABLE IV. Role of surgery in metastatic melanoma

Benefit of surgery is clear	Benefit of surgery is likely
<ul style="list-style-type: none"> Anaemia due to occult bleeding from intestinal metastasis Bowel obstruction due to small bowel metastasis Cutaneous or subcutaneous metastasis or metastases with ulceration, pain or impending ulceration Lymph node metastasis with neurological symptoms Symptomatic brain metastasis Life-threatening haemorrhage from metastasis 	<ul style="list-style-type: none"> Solitary asymptomatic visceral metastasis resectable with minimal morbidity Bony metastasis with pain or joint involvement, non-responsive to radiation Solitary brain metastasis without symptoms Large nodal metastasis in the absence of symptoms and with concurrent low-volume systemic disease Extensive skin and soft tissue metastases in the absence of visceral metastases Isolated growing metastasis in the setting of stable or regressing metastases after systemic therapy

Modified from Slingluff *et al.*¹²

has a curative potential of <10% and hence consideration must be given to the possibility of surgical resection of metastasis wherever feasible.

SYSTEMIC THERAPY

Adjuvant setting

Deep and regionally advanced melanomas have long term survival ranging from 30% to 70% (Table III). Many of these recur after surgery alone and might benefit from some form of adjuvant therapy.

Chemotherapy as adjuvant therapy in melanoma. Extrapolating from the response to chemotherapeutic agents when tried in the metastatic setting, drugs, such as dacarbazine, cisplatin, temozolomide and taxanes, have been tried as single agents or in combination in resected melanomas. Unfortunately, no drug has been beneficial in this setting.^{13,14}

High-dose interferon (HDI). HDI was tried in phase 2 trials of patients with metastatic melanoma and was found to be active, prompting trials in the adjuvant setting. Interferon acts by direct anti-proliferative and cytotoxic effects, potentiation of NK-, T- and B-cell responses, and induction of autoimmunity.^{12,15} The first randomized trial (E1684) demonstrated an absolute 1-year survival difference between the interferon and placebo arms.¹⁶ Subsequent phase 3 trials, though demonstrating disease-free survival advantage with HDI, have not shown a benefit in overall survival (Table V).¹⁷⁻²³ Combined analyses of the Eastern Cooperative Oncology Group (ECOG) trials showed that HDI therapy provides improvement in relapse-free survival for patients with high risk disease.^{18,19} Similarly, subgroup analysis from the European Organization for Research and Treatment of Cancer (EORTC) trials^{20,21} have suggested benefits restricted to high risk categories (IIb-III and ulcerated melanomas).²²

The appropriate post-surgical management strategies for stage IIb-III melanoma include enrolment in a clinical trial, HDI, or observation and follow up alone.²⁴ Thus, after discussing the costs and benefits of adjuvant HDI, it may be offered to selected patients with stage IIb-III melanoma who have no serious comorbid conditions and have a good performance status.^{6,10}

The toxicity of HDI can be significant, with up to 67% of patients experiencing some grade III/IV side-effects. The commonly experienced problems are flu-like syndromes, myelosuppression, especially thrombocytopenia, hepatotoxicity, and neuropsychiatric problems, including suicidal ideations and depression.^{16,17,19} Efforts to decrease the dose, and hence the side-effects of this treatment, have been unsuccessful. The other limiting factor is the cost of therapy (Rs 500 000–1 000 000 for

TABLE V. Trials of adjuvant high-dose interferon in melanoma

Trial	n	Treatment arms	Stage	Chief findings
ECOG 1684 ¹⁶	280	HDI for 1 year and Observation	IIB or III	HDI improved both RFS and OS
ECOG 1690 ¹⁷	642	HDI for 1–2 years and Observation	IIB or III	HDI improved RFS but not OS
EORTC 18952 ²⁰	1388	HDI for 1–2 years and Observation	IIB or III	HDI for 2 years improved RFS but not OS. No benefit in RFS or OS in the 1-year arm
EORTC 18991 ²¹	1256	HDI (peg-interferon) for 5 years and observation	III	HDI improved RFS but not OS
Sunbelt Melanoma Trial ²³	774	HDI ± CLND and observation for positive SLNB	III	No benefit of HDI in those with a single positive lymph node
HDI high-dose interferon		CLND completion lymph node dissection	SLNB sentinel lymph node biopsy	
RFS relapse-free survival		OS overall survival		

1-year), which can be prohibitive in resource-limited countries, such as India.

A recent publication comparing the use of induction interferon for 1 month with 1 year of adjuvant interferon found no significant difference between these 2 schedules.²⁵ Although this trial used inadequate doses of interferon in the standard arm, the use of the 1-month schedule could save costs and decrease side-effects. This thought-provoking concept is currently being explored in a multi-centre randomized trial (ECOG 1697; www.clinicaltrials.gov ID: NCT00003641).

Other agents. Various combinations of chemotherapy and interferons and interleukins (biochemotherapy) have been tried on melanomas, but without much success. Adjuvant granulocyte-monocyte colony stimulating factor was found to be useful in phase 2 trials; the results of phase 3 trials are awaited.^{26,27}

Metastatic setting: Chemotherapy, immunotherapy and 'targeted' therapy

Chemotherapy. Chemotherapy with single-agent dacarbazine or temozolomide is often used in metastatic melanoma in both the clinic and in the trial setting as the comparator arm. Unfortunately, neither dacarbazine nor temozolomide have been tested against a placebo and been proven to be superior.

The initial demonstration that the tumours respond to many of the conventional chemotherapeutic agents has been the basis for trials that have used several of these agents in combination with each other and with interferon and interleukin. None of the agents have shown a clear advantage and despite 3 decades of research, the median survival in patients with disseminated disease continues to remain a disappointing 8–9 months in the most recent phase 3 trials (Table VI).^{28–34}

Immunotherapy and the limited success of interleukin-2. High-dose interleukin-2 (IL-2) is the only therapy which has shown benefit in advanced metastatic melanoma.^{35–37} Its unique feature is the dosing, which is done 'to tolerance', i.e. a high dose of 600 000–720 000 IU/kg is administered every 8 hours (maximum of 14 doses) until grade III/IV side-effects occur. The side-effects include capillary leak syndrome causing severe hypotension, which requires inotropic support, fever with chills, dyspnoea, weight gain and oliguria—which may even lead to early mortality in some patients. Intensive care unit monitoring may be required in patients who develop haemodynamic and pulmonary complications. Studies have suggested a definite learning curve, with outcomes improving in centres with more experience.³⁸

IL-2 therapy had a 16% response rate (6% complete and 10%

partial) with >80% complete responders having excellent long term outcomes and even cure.³⁵ The drawback of this treatment was the lack of overall survival benefit for the entire cohort of patients who were treated; only a small subset of patients (who cannot be identified prospectively) benefit. The responses are best in those with only cutaneous metastasis³⁶ compared with other sites. The high cost (estimated cost of the drug alone is approximately Rs 500 000–700 000 for the entire course) and the high toxicity means that this type of therapy is out of the reach of most patients in India. The alternative patterns of administration of IL-2 (subcutaneous, lower doses with or without interferons), though less toxic, have not been shown to be efficacious.

Biochemotherapy. Considering the toxicity of higher doses of interferon and IL-2, modified doses of both were tried in combination with various chemotherapeutic agents. Although the response rates were higher in all these trials compared with single agent chemotherapy or immunotherapy alone, no phase 3 trial has demonstrated a disease-free or overall survival advantage.^{36–38}

Both chemotherapy and biochemotherapy results have been disappointing. The only therapy that works is high-dose IL-2, but it benefits <10% of the patients and is limited by cost and toxicity issues. Thus, it can be considered only in a few patients selected on the basis of age, absence of co-existing medical conditions, and absent or controlled brain metastases.³⁹ Hence, recent research has focused on novel drugs.

NOVEL AND TARGETED THERAPY

B-Raf inhibitors

The single most important molecular alteration in melanoma is in the B-Raf protein, which is involved in downstream signalling of the ras-raf-mek pathway.⁴⁰ This protein is activated in 50%–65% of all melanomas. However, studies with sorafenib (a B-raf inhibitor) as a second-line agent have been disappointing.⁴¹ More recent studies with PLX4032, a selective inhibitor of the oncogenic V600E mutation in the B-Raf kinase, have shown promise. Five of seven patients with B-Raf V600E+ showed a response in a phase 1 study.⁴²

Imatinib and dasatinib

The molecular target of imatinib is C-kit, which is activated in 30% of acral lentiginous and mucosal melanomas. Because of the success of imatinib in targeting these melanomas in a small groups of patients⁴³ (3% of all melanomas), imatinib or dasatinib could play a key role in their treatment.^{44,45}

TABLE VI. Chemotherapy and biochemotherapy trials in metastatic melanoma

Trial	n	Treatment arms	Chief findings
Middleton <i>et al.</i> ²⁸	305	Temozolomide v. DTIC	Median survival 7.7 months for temozolomide and 6.4 months for DTIC
Legha <i>et al.</i> ²⁹	52	CVD chemotherapy (cisplatin, vinblastine and DTIC)	Overall response rate 40% (2 patients had complete response), median survival was 12 months
Luikart <i>et al.</i> ³⁰	57	DTIC v. Vincristine, bleomycin, DTIC (VBD)	VBD was not superior to DTIC
Chapman <i>et al.</i> ³¹	240	DTIC v. Dartmouth regimen (DTIC, cisplatin, BCNU, tamoxifen)	Median survival 7 months, similar in both arms; response rate was slightly higher in combination arm (18.5% v. 10%)
Eton <i>et al.</i> ³²	190	CVD alone v. CVD followed by IFN and IL-2	Improved response rate and PFS with biochemotherapy but no significant difference in OS
Atkins <i>et al.</i> ³³	416	CVD alone v. CVD followed by IFN and IL-2	Biochemotherapy had an inferior PFS and OS
EORTC 18951 ³⁴	363	Cisplatin, DTIC and IFN alpha + high-dose IL-2 v. high-dose IL-2 alone	Improved responses but no difference in survival
OS overall survival		DTIC dacarbazine BCNU carmustine PFS progression-free survival	

Anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) mediated therapy

CTLA-4 is expressed in activated T cells and suppresses their function and decreases autoimmunity and over activation of the immune system. Blocking this molecule leads to stimulation of the T cells whereby they could possibly mount anti-tumour immune responses.⁴⁶ As a melanoma has exhibited responses to immune-based therapies, anti-CTLA-4 antibodies were tried as therapeutic agents. The autoimmune toxicities observed with anti-CTLA-4 antibodies include dermatitis, enterocolitis, hypophysitis, uveitis, hepatitis and nephritis. Ipilimumab and tremelimumab block the CTLA-4 molecule on the T-cell surface and have shown promising activity in phase 1 and 2 trials.^{47,48} However, a phase 3 trial of tremelimumab, in combination with interferon in stage III or IV melanomas, was disappointing, though a subset of patients benefited.⁴⁹ A trial combining ipilimumab and dacarbazine (DTIC) *versus* DTIC alone has also been completed (www.clinicaltrials.gov ID:NCT00324155) and the results are likely to be available in 2010.

Adoptive immunotherapy and vaccines

Trials of vaccines in melanoma have been disappointing⁵⁰⁻⁵² and some trials of vaccine-based therapy showed decreased survival (as in the GM2-KLH vaccine in E1694⁵² and the EORTC 18961 trials).⁵¹ The first successful vaccine therapy for melanoma was presented at the American Society of Clinical Oncology (ASCO) 2009 meeting; a combination of IL-2 and a peptide vaccine showed significant improvement in response rates (22.1% *v.* 9.7%) and progression-free survival (2.9 *v.* 1.6 months). The median overall survival improved in the vaccine arm (17.6 *v.* 12.8 months) with a trend towards significance ($p=0.0964$).⁵³

Another novel vaccine strategy is the introduction of tyrosinase DNA (tyrosinase being an enzyme expressed in melanoma cells) to stimulate cytotoxic T cells against melanoma cells. This has shown promise in a phase 1 study.⁵⁴

Anti-angiogenic therapy

Axitinib, a multi-targeted antagonist of vascular endothelial growth factor receptors (VEGFR-1, 2 and 3) demonstrated an impressive 19% response rate in highly pre-treated patients in a phase 2

study.⁵⁵ Bevacizumab, a humanized monoclonal antibody inhibitor of the VEGF, was tried along with paclitaxel and carboplatin in a phase 2 trial and the combination showed improved progression and overall survival (BEAM trial) although the results were not statistically significant.⁵⁶

Anti-BCL2 antisense oligonucleotide

BCL2 is an anti-apoptotic molecule, which is overexpressed in melanoma cells and confers resistance to cell kill by various chemotherapeutic agents. Oblimersen sodium, an anti-BCL2 antisense oligonucleotide showed promising results in combination with DTIC in phase 2 trials. A phase 3 trial in combination with DTIC, however, did not demonstrate a statistically significant improvement in overall survival compared with DTIC alone (9.1 *v.* 7.9 months), but response rates and progression-free survival improved. This demonstration of overall survival benefits in subgroups of patients with LDH values ≤ 2 times the upper limit of normal have prompted further studies of oblimersen in melanoma.⁵⁷

Other attempts at treatment of melanoma include strategies using molecules starting the Map-kinase, MEK pathways and the Ras pathway (farnesyl transferase inhibitors),⁵⁸ and gene therapy using Allovectin-7 (a plasmid encoding HLA-B7 and beta-2 microglobulin, delivered intra-lesionally in a lipid system and thereby stimulating a localized inflammatory response). The latter has shown promise in a phase 2 trial and is currently undergoing phase 3 testing.⁵⁹

SUMMARY AND CONCLUSIONS

Table VII summarizes the various treatment approaches and their current status in the treatment of melanoma. At our institution, melanomas in early stages are managed with surgical resection. Radiotherapy is offered to all regionally advanced melanomas (positive lymph node metastasis). Interferons are not being used routinely. For metastatic disease, we use single-agent DTIC or temozolomide if the patients have a good performance status. For others, only supportive treatment is offered. High-dose IL-2 is offered in selected tertiary centres in India, but data on outcomes are not available.

Extensive research in the past 2 decades has not produced

TABLE VII. Therapeutic approaches in melanoma and their current status

Approach	Status
Surgery	Standard of care for early-stage disease. Has a definite role in advanced stages, including limited metastatic disease (Table IV).
Radiotherapy	Helps in loco-regional control into lymph node disease metastatic but no impact on overall survival has been shown. Localized radiation may be used to palliate.
Interferon	Adjuvant therapy with high-dose interferon improves disease-free survival in T3, T4 and lymph node metastatic disease; conflicting data on overall survival; no role for interferon in metastatic disease.
Interleukin-2	High-dose IL-2 is the only therapy that has shown prolonged survival in metastatic melanoma; particular benefit in patients with disease metastatic to skin only. Limited by cost and high toxicity and the small number of patients who actually benefit (<10%).
Chemotherapy (single agent, combinations)	No survival benefit demonstrated with any chemotherapy-based options either in adjuvant or metastatic disease setting. Most active agents are DTIC and temozolomide.
Biochemotherapy	Combinations of conventional chemotherapy agents with IL-2 or IFN have higher response rates but none have demonstrated survival advantage in phase 3 trials.
Melanoma vaccine	All phase 3 trials, except one, have not shown benefit of vaccine-based approaches.
Targeted therapies	Novel drugs targeting the B-Raf pathway, c-kit pathway, CTLA-4 antibody, VEGFR have shown promise in phase 1 and 2 studies; hold promise for future treatment strategies in melanoma.
DTIC dacarbazine	IL-2 interleukin-2 IFN interferon CTLA cytotoxic T-lymphocyte associated VEGFR vascular endothelial growth factor receptors

improved survivals in advanced melanoma, but there has been an explosion in knowledge on the biology of the disease. Multiple trials have exposed the futility of conventional chemotherapy. Immune therapy is effective but benefits a minority of patients. Targeted and novel therapeutic agents, painstakingly developed by extrapolation from molecular studies, hold promise for the future in tackling this disease.

REFERENCES

- Lee KC, Weinstock MA. Melanoma is up: Are we up to this challenge? *Invest Dermatol* 2009;**129**:1604–6.
- Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics 2007. *CA Cancer J Clin* 2007;**57**:43–66.
- Mack TM, Floderus B. Malignant melanoma risk by nativity, place of residence at diagnosis, and age at migration. *Cancer Causes Control* 1991;**2**:401–11.
- Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist* 2007;**12**:20–37.
- Raina V, Tyagi BB, Manoharan N. *Cancer incidence and mortality in Delhi UT, Urban—2002 and 2003*. Delhi: Delhi Cancer Registry; 2007.
- American Joint Committee on Cancer. In: *AJCC Cancer Staging Manual*. 6th ed. New York: Springer-Verlag; 2002:157–64.
- Clark WH Jr, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res* 1969;**29**:705–27.
- Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970;**172**:902–8.
- Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: Validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2001;**19**:3622–34.
- Dummer R, Hauschild A, Pentheroudakis G. Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;**20** (Suppl 4):129–31.
- Henderson MA, Burmeister B, Thompson JF, Di Iulio J, Fisher R, Hong A. Adjuvant radiotherapy and regional lymph node field control in melanoma patients after lymphadenectomy: Results of an intergroup randomized trial (ANZMTG 01.02/TROG 02.01). *J Clin Oncol* 2009;**27** (Suppl):abstr LBA9084.
- Slingluff CL, Flaherty K, Rosenberg SA, Read PW. Cutaneous melanoma. In: DeVita Jr VT, Lawrence TS, Rosenberg SA, DePinto RA, Weinberg RA. *DeVita, Hellman, and Rosenberg's Cancer: Principles and practice of oncology*. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2008:1899–965.
- Karakousis C, Blumenson L. Adjuvant chemotherapy with a nitrosourea-based protocol in advanced malignant melanoma. *Eur J Cancer* 1993;**29A**:1831–5.
- Veronesi U, Adamus J, Aubert C, Bajetta E, Beretta G, Bonadonna G, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 1982;**307**:913–16.
- Gogas H, Ioannovich J, Dafni U, Stavropoulou-Giokas C, Frangia K, Tsoutsos D, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *N Engl J Med* 2006;**354**:709–18.
- Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. 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.
- Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: First analysis of intergroup trial E1690/S9111/C9190. *J Clin Oncol* 2000;**18**:2444–58.
- Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U; Eastern Cooperative Oncology Group. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res* 2004;**10**:1670–7.
- Lens MB, Dawes M. Interferon alfa therapy for malignant melanoma: A systematic review of randomized controlled trials. *J Clin Oncol* 2002;**20**:1818–25.
- Eggermont AM, Suci S, MacKie R, Ruka W, Testori A, Kruit W, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): Randomised controlled trial. *Lancet* 2005;**366**:1189–96.
- Eggermont AM, Suci S, Santinami M, Testori A, Kruit WH, Marsden J, et al.; EORTC Melanoma Group. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: Final results of EORTC 18991, a randomised phase III trial. *Lancet* 2008;**372**:117–26.
- Eggermont AM, Suci S, Testori A, Patel P, Spatz A, EORTC Melanoma Group; Ulceration of primary melanoma and responsiveness to adjuvant interferon therapy: Analysis of the adjuvant trials EORTC 18952 and EORTC 18991 in 2,644 patients. *J Clin Oncol* 2009;**27** (Suppl):15S, abstr. 9007.
- McMasters KM, Ross I, Reintgen DS, Edwards MJ, Noyes RD, Urist M. Final results of the Sunbelt Melanoma Trial. *J Clin Oncol* 2008;**26** (Suppl):Abstr 9003.
- National Comprehensive Cancer Network (NCCN). *Clinical Practice Guidelines in Oncology*.v.2.2009. Available at www.nccn.org (accessed on 5 November 2009).
- Pectasides D, Dafni U, Bafaloukos D, Skarlos D, Polyzos A, Tsoutsos D, et al. Randomized phase III study of 1 month versus 1 year of adjuvant high-dose interferon alfa-2b in patients with resected high-risk melanoma. *J Clin Oncol* 2009;**27**:939–44.
- Spitler LE, Grossbard ML, Ernstoff MS, Silver G, Jacobs M, Hayes FA, et al. Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophage colony-stimulating factor. *J Clin Oncol* 2000;**18**:1614–21.
- Spitler LE, Weber RW, Allen RE, Meyer J, Cruickshank S, Garbe E, et al. Recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) administered for 3 years as adjuvant therapy of stages II(T4), III, and IV melanoma. *J Immunother* 2009;**32**:632–7.
- Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000;**18**:158–66.
- Legha SS, Ring S, Papadopoulos N, Plager C, Chawla S, Benjamin R. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. *Cancer* 1989;**64**:2024–9.
- 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**:164–8.
- Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999;**17**:2745–51.
- Eton O, Legha SS, Bedikian AY, Lee JJ, Buzaid AC, Hodges C, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: Results from a phase III randomized trial. *J Clin Oncol* 2002;**20**:2045–52.
- Atkins MB, Hsu J, Lee S, Cohen GI, Flaherty LE, Sosman JA. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): A trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2008;**26**:5748–54.
- Keilholz U, Punt CJ, Gore M, Kruit W, Patel P, Lienard D, et al. Dacarbazine, cisplatin, and interferon-alfa-2b with or without interleukin-2 in metastatic melanoma: A randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol* 2005;**23**:6747–55.
- Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999;**17**:2105–16.
- Tarhini AA, Kirkwood JM, Gooding WE, Cai C, Agarwala SS. Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy. *J Clin Oncol* 2007;**25**:3802–7.
- Phan GQ, Attia P, Steinberg SM, White DE, Rosenberg SA. Factors associated with response to high-dose interleukin-2 in patients with metastatic melanoma. *J Clin Oncol* 2001;**19**:3477–82.
- Kammula US, White DE, Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. *Cancer* 1998;**83**:797–805.
- McDermott DF, Atkins MB. More support for the judicious use of high-dose interleukin-2 in patients with advanced melanoma. *J Clin Oncol* 2007;**25**:3791–3.
- Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005;**353**:2135–47.
- Hauschild A, Agarwala SS, Trefzer U, Hogg D, Robert C, Hersey P, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J Clin Oncol* 2009;**27**:2823–30.
- Flaherty K, Puzanov I, Sosman J, Kim K, Ribas A, McArthur G, et al. Phase I study of PLX4032: Proof of concept for V600E BRAF mutation as a therapeutic target in human cancer. *J Clin Oncol* 2009;**27** (Suppl):abstr 9000.
- Hodi FS, Friedlander P, Corless CL, Heinrich MC, MacRae S, Kruse A, et al. Major response to imatinib mesylate in KIT-mutated melanoma. *J Clin Oncol* 2008;**26**:2046–51.
- Kluger HM, Dudek A, McCann C, Rink L, Ritacco J, Adrada CA. A phase II trial of dasatinib in advanced melanoma. *J Clin Oncol* 2009;**27**s:abstr. 9010.
- Woodman SE, Trent JC, Stemke-Hale K, Lazar A, Priol S, Pavan GM. Selective activity of dasatinib for the most common KIT mutation in melanoma (L576P). *J Clin Oncol* 2009;**27** (Suppl):abstr. 9019.
- Ribas A, Camacho LH, Lopez-Berestein G, Pavlov D, Bulanhagui CA, Millham R, et al. Antitumor activity in melanoma and anti-self responses in a phase I trial with the anti-cytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody CP-675,206. *Clin Oncol* 2005;**23**:8968–77.
- Tarhini AA, Moschos SS, Schlesselman JJ, Shope-Spotloe J, Demark M, Kirkwood JM. Phase II trial of combination biotherapy of high-dose interferon alfa-2b and tremelimumab for recurrent inoperable stage III or stage IV melanoma. *J Clin Oncol* 2008;**26**s:abstr 9009.
- Weber JS, Berman D, Siegel J, Minor D, Amin A, Thompson JA. Safety and efficacy of ipilimumab with or without prophylactic budesonide in treatment-naïve and previously treated patients with advanced melanoma. *J Clin Oncol* 2008;**26**s:abstr 9010.

- 49 Ribas A, Hauschild A, Kefford R, Punt CJ, Haanen JB, Marmol M, *et al.* Phase III, open-label, randomized, comparative study of tremelimumab (CP-675,206) and chemotherapy (temozolomide [TMZ] or dacarbazine [DTIC]) in patients with advanced melanoma. *J Clin Oncol* 2008;**26s**:abstr LBA9011.
- 50 Morton DL, Mozzillo N, Thompson JF, Kelley MC, Faries M, Wagner J, *et al.* An international, randomized, phase III trial of bacillus Calmette-Guerin (BCG) plus allogeneic melanoma vaccine (MCV) or placebo after complete resection of melanoma metastatic to regional or distant sites. *J Clin Oncol* 2007;**18s**:8508.
- 51 Eggermont AM, Suci S, Ruka W, Marsden J, Testori A, Corrie P, *et al.* EORTC 18961: Post-operative adjuvant ganglioside GM2-KLH21 vaccination treatment vs observation in stage II (T3-T4N0M0) melanoma: 2nd interim analysis led to an early disclosure of the results. *J Clin Oncol* 2008;**26s**:abstr 9004.
- 52 Kirkwood JM, Ibrahim JG, Sosman JA, Sondak VK, Agarwala SS, Ernstoff MS, *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**:2370-80.
- 53 Schwartzentruber DJ, Lawson D, Richards J, Conry RM, Miller D, Triesman J, *et al.* A phase III multi-institutional randomized study of immunization with gp 100:209-217 (210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma. *J Clin Oncol* 2009;**27s**:abstr 9011.
- 54 Wolchok JD, Yuan J, Houghton AN, Gallardo HF, Rasalan TS, Wang J, *et al.* Safety and immunogenicity of tyrosinase DNA vaccines in patients with melanoma. *Mol Ther* 2007;**15**:2044-50.
- 55 Fruehauf JP, Lutzky J, McDermott DF, Brown CK, Pithavala YK, Bycott PW, *et al.* Axitinib (AG-013736) in patients with metastatic melanoma: A phase II study. *J Clin Oncol* 2008;**26**:2008 (May 20 suppl; abstr 9006).
- 56 O'Day SJ, Kim KB, Sosman JA, Peterson AC, Feng S, Minor DR, *et al.* 23LBA BEAM: A randomized phase II study evaluating the activity of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced melanoma. *Eur J Cancer Suppl* 2009;**7**:13s.
- 57 Bedikian AY, Millward M, Pehamberger H, Conry R, Gore M, Trefzer U, *et al.* Bel-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: The Oblimersen Melanoma Study Group. *J Clin Oncol* 2006;**24**:4738-45.
- 58 Katipamula R, Markovic SN. Emerging therapies for melanoma. *Expert Rev Anticancer Ther* 2008;**8**:553-60.
- 59 Richards JM, Bedikian A, Gonzalez R, Atkins MB, Whitman E, Lutzky J, *et al.* High-dose Allovectin-7 in patients with advanced metastatic melanoma: Final Phase 2 data and design of Phase 3 registration trial. *J Clin Oncol* 2005;**23s**:abstr 7543.

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