Review Article

Management of advanced melanoma in the current era: A medical oncology perspective for the Indian scenario

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ABSTRACT

Malignant melanoma is an aggressive malignancy with high recurrence rates after curative surgery and in advanced stages is characterized by resistance to conventional chemotherapy. With better understanding of the genomic landscape and mutational signature of these tumours over the past decade, there has been a paradigm shift in management of melanoma using immunotherapy (anti-PD-1 and anti-CTLA-4 antibodies) and targeted drugs against BRAF and MEK. These drugs have shown survival benefits in both adjuvant and metastatic setting with patients being eligible for immunotherapy irrespective of any biomarker. However, these drugs have varying toxicity profiles and there are no studies comparing these two classes of drugs in either the adjuvant or metastatic setting leaving the question of sequencing open to clinical judgement. Moreover, availability and cost are issues that need to be considered before use of these drugs in the Indian setting.

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INTRODUCTION

Melanoma is an uncommon malignancy with wider racial, ethnic and geographical variations in incidence than reported with any other cancer. Since we last reviewed the subject in 2010,[1] the treatment of melanoma has undergone a paradigm shift with the introduction of immunotherapy and targeted therapy. Management of metastatic melanoma is one of the biggest success stories of oncology; 5-year survival has jumped from <10% before 2011 with chemotherapy[2] to >40% with combination immunotherapy in 2019 with median overall survival (OS) of >2 years. Most of the data available are for cutaneous melanoma; practice in mucosal melanoma is based on extrapolation of that data. We summarize the evidence and rationale for various therapeutic approaches in advanced melanoma focusing on key phase 3 trials.

EPIDEMIOLOGY AND RISK FACTORS

Age-standardized incidence rates (age-adjusted rate [AAR]) of

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melanoma have increased steadily over the past two decades with the highest incidence in Australia (33/100 000/year).[3–6] India has one of the lowest AARs in the world (0.2/100 000/year). The reason for this large difference in incidence in India compared with the West is understandable because of the more wheatish/brown/black skin complexion in India and under-reporting as most localized disease presents to dermatologists/surgeons. Mucosal and acral melanoma have been reported more commonly in India compared to the West, though no concrete data on epidemiology of melanoma in India exist.[7,8] At present, melanoma is not recorded in hospital- or population-based cancer registries in India. The major risk factors for melanoma include white race and exposure to ultraviolet radiation, predominantly ultraviolet B. Intense intermittent exposure to sunlight with tendency to develop sunburns has been implicated in the pathogenesis of cutaneous melanoma.[9,10] Familial clustering is seen in 10%–15% of patients with melanoma. The most common gene associated with hereditary melanoma is CDKN2A/p16, mutation of which also leads to predisposition for pancreatic cancer; less common genes include CDK4, TERT, BAP1 and POT1.[11] Other risk factors include a personal history of melanoma, multiple naevi and atypical naevi.

CLINICAL PRESENTATION AND DIAGNOSIS

Subtypes

Six clinical subtypes of melanoma have been described and each has variable presentation, ethnic differences and prognosis (Table I).[12]

When to suspect

ABCDE approach. Patients can have multiple naevi, which may remain stable over time. Not all lesions require evaluation for suspected melanoma. However, any lesion showing the below mentioned characteristics should be considered suspicious. These are:

- **A**symmetry: if a lesion is bisected, one half is not identical to the other half
- **B**order irregularities
- **C**olour variegation with presence of multiple shades of red, blue, black, grey or white
- **D**iameter ≥6 mm
- **E**volution: a lesion that is changing in size, shape or colour, or a new lesion (most important).[13]

TABLE I. Subtypes of melanoma

Subtype	Frequency (%)	Characteristic
Superficial spreading	70	Two-thirds *de novo*, one-third arise from existing naevus, intermediate prognosis; presents as variable pigmented macule or thin plaque
Nodular	15–30	Absence of a radial growth phase, variable presentation with uniform pigmentation, poor prognosis
Lentigo maligna	10–15	Typically demonstrates slow progression, and frequently appears in sun-exposed areas (i.e. face, head, etc.) as tan brown macule in old individuals; best prognosis
Acral lentiginous	5	Has higher incidence in patients with darker skin pigmentation and frequently occurs on the palms, soles and subungual spaces; dark brown black irregular pigmented macules, patches with ulceration; poor prognosis
Amelanotic	4	Characteristic absence of pigmentation and are considered rare, worst prognosis and difficult to diagnose
Desmoplastic	<4	Rare melanoma seen in older adults as slow-growing plaque/nodule that is characterized by scant spindle cells and minimal cellular atypia, poor prognosis

Ugly duckling approach. A naevus that is different from other naevi in an individual with multiple naevi should be considered suspicious even if it does not fulfil all the ABCDE criteria.[14]

Glasgow 7-point checklist. Weighted 7-point checklist for early detection of melanoma has been shown to be more sensitive than the ABCDE criteria in clinical practice.[15]

Major features (2 points for each)
- Change in size of lesion
- Irregular pigmentation
- Irregular border

Minor features (1 point for each)
- Inflammation
- Itch
- Diameter >7 mm
- Oozing or crusting of lesion

Any lesion with a score of ≥3 should be referred to a dermatologist for evaluation.

How to confirm?
A complete full-thickness excisional biopsy of suspicious lesions with 1–3 mm margin of normal skin and part of the subcutaneous fat should be performed whenever possible. Partial incisional biopsy may be acceptable if the excision of the entire lesion is not feasible.[16]

Staging work-up (Table II)
Work-up for metastasis is not indicated in stages I and II melanoma with no clinical symptoms. In patients with stage III melanoma with occult lymph node metastasis, the role of metastatic work-up is controversial. Various studies have reported detection

TABLE II. Evaluation of a suspected case of melanoma

Clinical examination

ABCDE approach: Observe asymmetry, border, colour, diameter >6 mm and evolution of lesion

Ugly duckling approach: Biopsy any lesion that stands out if many naevi present

Glasgow 7-point checklist: Biopsy any lesion with score ≥3

Dermatologist referral for dermoscopy/confocal microscopy

Confirmation of diagnosis

Full thickness excision biopsy with 1–3 mm margin-best

Incisional biopsy adequate if above not possible

Staging work-up

Stage I, II melanoma: Chest X-ray and sentinel node biopsy

Stage III

Clinically occult: Sentinel node mapping plus whole body FDG-PET/CT for distant metastasis; MRI brain if suspicion high for brain metastasis

Clinically palpable nodes: Whole-body PET-CT plus contrast enhanced MRI brain

Stage IV (clinical)

Whole-body PET-CT for sites of metastasis, CEMRI brain

Serum LDH for prognostic information in all patients

FDG fluorodeoxyglucose   PET positron emission tomography
CT computed tomography   MRI magnetic resonance imaging
CEMRI contrast-enhanced MRI   LDH lactate dehydrogenase

of distant metastasis in 3%–4% of such patients.[17–19] However, detection of metastasis has a major impact on the intent of therapy; hence, we suggest complete work-up for all such patients. For patients who have clinically palpable lymph nodes or evidence of metastasis, imaging is indicated to document sites of disease. These include magnetic resonance imaging (MRI) of the brain with contrast and fluorodeoxyglucose-positron emission tomography-computed tomography (PET-CT) of the whole body; if unavailable contrast-enhanced CT of the chest, abdomen and pelvis can be done. Although PET-CT can be false-positive and -negative, it is rapidly replacing other modalities for metastatic work-up. In a meta-analysis the median sensitivity of PET-CT for staging was 86% and specificity was 91%, whereas those for CT only were 63% and 78%, respectively.[20]

PROGNOSTIC FACTORS

First described by Clark *et al.*[21] and Breslow *et al.*,[22] the depth of invasion of the primary tumour has been the most important prognostic factor in localized cutaneous melanoma, in traditional staging systems.[23] In a large multicentre analysis of over 2000 patients with melanoma, it was found that Breslow thickness, mitotic rate, ulceration and sentinel lymph node status were associated with survival.[24] Tumour node metastasis (TNM) stage has important prognostic implications and co-relates directly with survival.[25] Other important prognostic factors include advanced age, sex (females have a better prognosis), anatomical location (upper extremity and face have a better prognosis than head and neck, trunk and lower extremity), growth pattern (nodular has a worse prognosis than superficial spreading), extracapsular nodal extension, pre-existing naevi (better prognosis), margins of resection, site and size of metastasis (skin only have a better prognosis than visceral metastasis) and lymphovascular invasion.[26–30] Elevated lactate dehydrogenase (LDH) is an important marker for poor prognosis and has been shown, in a meta-analysis, to be a predictive marker of benefit from immunotherapy and targeted therapies.[31]

MUTATION TESTING IN MELANOMA

Mutations in the BRAF gene leading to MAP kinase pathway activation are the most common driver mutations seen in 40%–60% of all cases of melanoma.[32] The mutations most often seen in the BRAF gene are V600E (70%–80%) and V600K (20%).[32] BRAF is also the most common targetable mutation in metastatic melanoma. Real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR) is the method of choice for biomarker testing. For BRAF, both V600E and V600K should be tested as both are sensitive to BRAF inhibitors.

Other important targetable mutation in melanoma is c-KIT, which is seen in 15%–40% of cases of acral melanoma, mucosal melanoma and melanoma arising from chronically sun-damaged skin but is rare in other types.[33] Since acral melanoma is more common in Asian countries, especially India, c-KIT is an important target for our population. For c-KIT mutated melanoma, mutations in exon 11 are more common than exon 9, 13, 17 and 18.[34,35] Preferential testing for exon 11 and 9 should be done if tissue quantity is the limiting factor. Either direct sequencing or RT-qPCR can be used with the latter being the preferred method. Excluding c-KIT mutations based on immunohistochemistry for CD117 is unreliable and should not be done.[36]

At present, guidelines recommend testing for BRAF mutation in all advanced melanoma and c-KIT testing for acral and mucosal melanomas.[37] If BRAF mutation is negative, further molecular testing for *NRAS, GNA11* or *GNAQ* (uveal primary) can be considered as patients with NRAS mutations have responded to MEK inhibitors in phase 2 trials.[38] An algorithm for mutation testing is presented in Fig. 1 and key genetic alterations are given in Table III.

ADJUVANT THERAPY IN RESECTED MELANOMA

Indications for adjuvant therapy

All patients with localized melanoma should undergo wide local excision. Management of occult lymph nodes is controversial and the role of extensive surgery in the era of adjuvant immunotherapy is not well defined. While regional lymph-adenectomy is standard for clinically positive nodes, the role of completion surgery in sentinel lymph node biopsy (SLNB) positive patients is controversial with many randomized trials not showing survival benefit.[39,40] However, SLNB should be done for clinically negative nodes as it provides prognostic information and is necessary for entry into clinical trials for adjuvant therapy.[41]

At present, all patients with lymph nodal involvement (including satellite/in-transit metastasis) warrant adjuvant immune/targeted therapy after surgery including those who have clinically negative lymph nodes but positive SLNB,
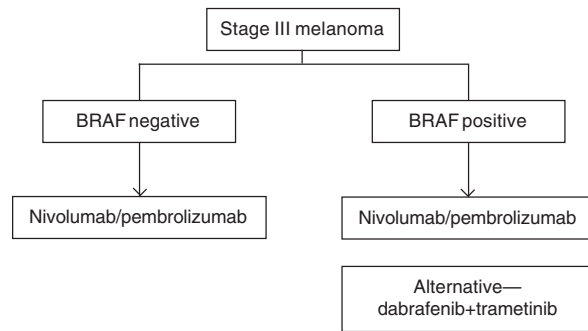

FIG 1. Mutation testing algorithm in melanoma

TABLE III. Key genetic alterations in advanced melanoma

Gene	Gene alterations	Histological subtypes
BRAF	Point mutation	Superficial spreading melanoma Nodular melanoma
KIT	Point mutation	Mucosal (10%) Acral lentiginous (10%)
NRAS	Point mutation	Superficial spreading melanoma Nodular melanoma
GNAQ	Point mutation	Uveal melanoma (40%)
GNA11	Point mutation	Uveal melanoma (40%)
PTEN	50–60 point mutations or deletions	All types

BRAF v-Raf murine sarcoma viral oncogene homolog B   KIT stem cell growth factor receptor   NRAS neuroblastoma   RAS viral oncogene homolog   PTEN phosphatase and tensin homolog   GNAQ G protein subunit alpha Q   GNA11 G protein subunit alpha 11

irrespective of the size of the deposit. The best agents, toxicities and optimal duration of therapy are described in Table IV.

Immunotherapy

Ipilimumab. Ipilimumab is an anti-CTLA-4 antibody which improved recurrence-free survival (RFS), metastasis-free survival and OS in phase 3 EORTC 18 071 trial in the adjuvant setting compared to placebo; the dose was 10 mg/kg and the duration of therapy was 3 years.[42,43] However, 54% of patients experienced grades 3–4 adverse effects with treatment discontinuation rates of 41.6%. Five patients (1.1%) died during treatment. Notably, the accepted dose of ipilimumab in metastatic setting is 3 mg/kg,[44] and hence the higher dose used in this trial could explain the higher toxicity.[42] Ipilimumab has been replaced by other immuno-oncology drugs in the adjuvant setting due to its unacceptable toxicity profile.

Nivolumab. Nivolumab is an anti-programmed cell death

TABLE IV. Landmark trials in stage III cutaneous melanoma

Trial	n	Stage of patients	Treatment arms	HR for for RFS	p value RFS	HR OS	p value OS	Grades 3–4 toxicity (%)
EORTC 18071[41,42]	951	Stage III (lymph node metastasis >1 mm)	Ipilimumab (10 mg/kg) *v.* placebo	0.76	<0.001	0.72	<0.001	54
CheckMate 238[44,45]	906	All stage III	Nivolumab 3 mg/kg 2 weekly for 1 year *v.* ipilimumab	0.66	<0.001	NR	NR	14
KEYNOTE 054[46]	1019	Resected stage III	Pembrolizumab 200 mg 3 weekly 18 doses *v.* placebo	0.57	<0.001	NR	NR	15
Combi-AD trial[47,48]	870	BRAF+resected stage III	Dabrafenib and trametinib for 1 year *v.* placebo	0.47	<0.001	0.57	0.0006	41

BRAF v-Raf murine sarcoma viral oncogene homologue B   RFS recurrence-free survival   OS overall survival   NR not reached   HR hazard ratio

protein 1 (PD-1) inhibitor which improved RFS and OS in resected melanoma compared with ipilimumab in CheckMate 238 trial (hazard ratio [HR] for disease recurrence or death, 0.66; 95% CI 0.54–0.81) at a dose of 3 mg/kg every 2 weeks for 1 year; grades 3–4 toxicity was 14.4% in nivolumab compared to 45.9% in ipilimumab with no treatment-related deaths; treatment discontinuation was 4% with nivolumab compared to 30% with ipilimumab; and all major pre-specified subgroups had same degree of benefit.[45,46] Approximately 42% of patients in this trial had BRAF mutation, demonstrating efficacy of nivolumab in this subset. This trial established nivolumab at 3 mg/kg for 1 year as standard adjuvant therapy for resected stage III melanoma.

Pembrolizumab. Pembrolizumab is also an anti PD-1 antibody similar to nivolumab. It was approved for adjuvant therapy in resected stage III melanoma based on KEYNOTE-054 trial in which pembrolizumab at 200 mg thrice weekly for 18 doses significantly improved RFS compared to placebo (HR 0.57, 98.4% CI 0.43–0.74).[47] As in CheckMate 238 trial of nivolumab, PD-L1 positivity was not a predictor of response. Adverse event profile was similar to nivolumab.

BRAF inhibitors in adjuvant setting
BRAF mutation is the most common driver mutation in advanced melanoma.[32] As in metastatic melanoma, combinations of BRAF and MEK inhibitors have been tested in adjuvant setting. In the phase 3 randomized trial Combi-AD,[48,49] dabrafenib and trametinib for 1 year improved RFS and OS with an estimated 54% cure rate (HR 0.49 for RFS and 0.57 for OS); treatment benefits were observed irrespective of baseline factors. Grade 3–4 adverse events occurred in 41% of patients, the most common being fatigue and pyrexia; the rate of new squamous cell skin cancers was similar between the two arms. Twenty-six per cent patients discontinued trial drug. Another phase 3 trial of BRAF inhibitor vemurafenib failed to meet its primary end-point of disease-free survival.[50] If data from immunotherapy trials and combi-AD are compared, 2-year RFS rates are around 60% in both, with higher toxicity in the combi-AD trial compared to nivolumab/ pembrolizumab. However, the combination seems to be better tolerated than ipilimumab with benefit of adjuvant therapy extending to all subgroups including stage IIIA melanoma.

Which agent to choose?
Given the evidence, both nivolumab and pembrolizumab are first-line options for adjuvant treatment irrespective of PDL-1 and BRAF mutation status. In our view, ipilimumab can be considered a second-line option for patients who progress on nivolumab/pembrolizumab. However, its major toxicity and dose consideration need to be kept in mind. BRAF plus MEK inhibitors remain an option in BRAF mutant patients keeping in mind their adverse event profile. The optimal duration of therapy is 1 year. Patients with stage IIIA melanoma especially with sentinel node deposit <1 mm have a 91% 5-year RFS and observation can be considered a valid treatment option for this subset of patients.[51] The benefit of using nivolumab/ pembrolizumab after progression on either agent is a pertinent research question (Fig. 2)

METASTATIC MELANOMA: WHERE DO WE STAND?
Immunotherapy in metastatic melanoma
Ipilimumab. Ipilimumab in combination with dacarbazine improved OS in treatment naïve patients compared to dacarbazine alone with 5-year survival approaching 20% with ipilimumab.[52,53]


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┌─────────────────────────────────────────────┐
│         Mutation testing in melanoma          │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│ BRAF V600E and V600K in all melanomas         │
│ (stage III and IV)                            │
│ Method of choice qRT-PCR                      │
└─────────────────────────────────────────────┘
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┌─────────────────────────────────────────────┐
│ c-KIT especially in acral and sun-damaged     │
│ skin melanoma                                 │
│ (consider in all Indians patients)            │
│ Preferential exon 11 testing if tissue        │
│ insufficient                                  │
│ Method: qRT-PCR or sequencing CD117 IHC—      │
│ unreliable                                    │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│ If BRAF positive—BRAF plus MEK inhibitors     │
│ If c-KIT positive—imatinib/sunitinib          │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│ If both negative—consider NRAS testing by     │
│ qRT–PCR;                                       │
│ may respond to binimetinib                    │
│ GNAG testing if uveal primary                 │
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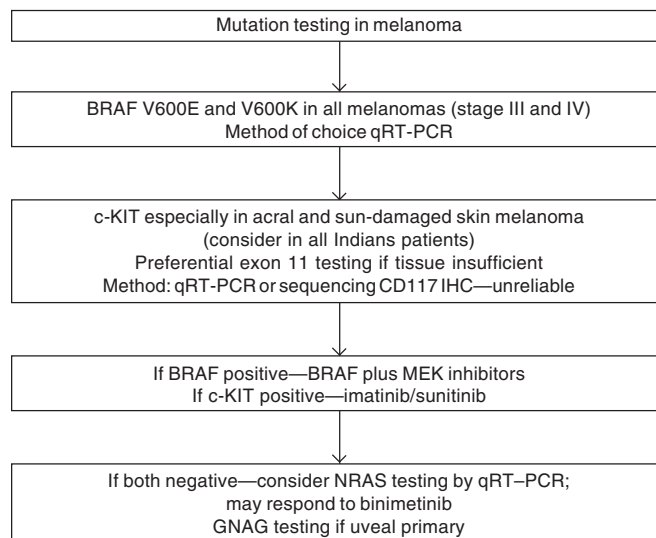
FIG 2. Adjuvant therapy in stage III melanoma

The dose used in this trial was 10 mg/kg and resulted in 56% of patients having grades 3–4 adverse events. The responses obtained with ipilimumab were durable with a plateau in survival curve after 3 years.[54] Another randomized trial which compared a dose of 10 mg/kg versus 3 mg/kg in unresectable/metastatic setting had improved survival with higher dose albeit at much higher toxicity.[44]

Pembrolizumab
Ipilimumab refractory disease. Pembrolizumab at doses of 2 mg/kg/3 weekly, 10 mg/kg/3 weekly improved progression-free survival (PFS) compared to chemotherapy in ipilimumab refractory patients (KEYNOTE-002 trial) with significantly less toxicity.[55] Both pembrolizumab arms had similar outcomes. The trial showed only a trend towards superior OS likely due to heavy crossover.[56]

Immunotherapy naïve patients. KEYNOTE-006 phase 3 trial compared two doses of pembrolizumab (10 mg/kg/2 weekly and 10 mg/kg/3 weekly) versus ipilimumab (3 mg/kg/3 weeks for 4 doses). Pembrolizumab was given for a fixed interval of 2 years. Around 35% of these patients were BRAF-positive and had received prior targeted therapy. Pembrolizumab improved response rates (42% v. 17%), PFS (2 year: 30% v. 14%) and OS (4 year: 41% v. 34%) with no difference between the two pembrolizumab arms.[57,58] Grades 3–4 adverse events were reported in 14%–17% of patients in the pembrolizumab group and 20% of patients in the ipilimumab group. Patterns of toxicity differed with colitis being more common with ipilimumab (7%–8%; grades 3–4) whereas thyroid dysfunction (10%) and pneumonitis (2%) were more common with pembrolizumab.

Nivolumab. Initial phase 3 trials with nivolumab in treatment-naïve patients without BRAF mutation provided evidence of its superiority over chemotherapy (median OS 38 v. 11 months, overall response rate 40% v. 14% and PFS 5.1 v. 2.2 months; CheckMate 066 trial).[59,60] In patients who had received prior ipilimumab, nivolumab compared with chemotherapy improved response rates and duration of response. However, in this trial there was no survival difference which can be due to poor compliance in the chemotherapy arm and severe imbalance of poor prognostic factors in the nivolumab arm which had more patients with brain metastasis and elevated LDH. Based on

these data, the US Food and Drug Administration approved nivolumab for metastatic melanoma at 3 mg/kg/2 weekly;[61] later a flat dose of 240 mg/2 weekly or 480 mg/4 weekly was also approved. The adverse event profile of nivolumab was similar to that seen in the adjuvant setting.

Combination immunotherapy. To further improve outcomes, combination immunotherapy was tested in the landmark phase 3 trial—CheckMate 067.[62] In this trial, a combination of nivolumab and ipilimumab (induction for 4 cycles, nivolumab dose 1 mg/kg and ipilimumab dose 3 mg/kg) was tested against nivolumab single agent (3 mg/kg/2 weekly) and ipilimumab single agent (3 mg/kg/2 weekly 4 doses) with maintenance nivolumab in the first two arms. The combination and single agent nivolumab arm did better in all end-points including response rates (58%, 44% and 19%), PFS and OS compared to ipilimumab. Three-year PFS was 39%, 32% and 10%, respectively. Three-year OS was 58%, 52% and 34% (HR for the combination *v.* ipilimumab 0.55, 95% CI 0.45–0.69, and HR for nivolumab alone *v.* ipilimumab 0.65, 95% CI 0.53–0.80). Although PFS was better with combination than with single agent nivolumab, it was marginal and the trial was not adequately powered to detect this difference.[63] Compared to patients without BRAF mutation, those with mutation had better PFS and OS than patients with combination immunotherapy providing a statistically significant PFS benefit over single agent nivolumab in this subset. Around 59% of patients receiving combination therapy had grades 3–4 adverse events compared to 21% with nivolumab alone and 28% with ipilimumab alone. Treatment had to be discontinued in 39% in the combination arm due to toxicity compared to 12% in the nivolumab arm. The lower dose of the combination was tested in the CheckMate 511 trial (ipilimumab (1 mg/kg) with nivolumab at 3 mg/kg); although grades 3–4 adverse events decreased (34% in this trial *v.* 48% in the original trial), they were still significant and the trial was not adequately powered to ascertain non-inferiority.[64]

Stopping immunotherapy?
In the KEYNOTE 006 trial the duration of therapy was fixed at 2 years and it was observed that around 20% of patients who completed planned pembrolizumab treatment discontinued therapy after 2 years and 86% of those remained disease-free on long-term follow-up (median 20 months) suggesting a potential cure and durable response.[65,66] This trial also highlighted that the initial response to immunotherapy can be a surrogate for survival as 28% of patients who had complete response with pembrolizumab had PFS rate of 96% at 18 months. For patients who progressed, around 50% responded to a re-challenge suggesting that the initial good response can be used as a pointer to subsequent response on progression. A similar phase 1B KEYNOTE 001 trial showed feasibility of stopping pembrolizumab after a minimum of 6 months or 2 cycles after CR whichever was later.[67] Tumour size, PD-L1 status and LDH were predictors of response to immunotherapy; however, their validation requires larger trials. Similar trials for nivolumab and combination immunotherapy are under way. Based on this data, 2 years of immunotherapy may be considered standard in responding patients.

What is the best frontline therapy?
Based on the above data, although combination immunotherapy provides better response rates and PFS rates compared to single agent immunotherapy, single agent nivolumab and pembrolizumab fare well in terms of all end-points with no significant difference in OS compared to a combination with a favourable side-effect profile. Effectiveness is maintained in BRAF mutated tumours also. In our setting where cost is a major issue, single agent nivolumab is probably the best frontline option. As shown for pembrolizumab in the KEYNOTE 006 trial, patients with CR or those who have maintained response for 2 years can discontinue therapy without losing effectiveness. Though this approach has not been tested for nivolumab, conceptually it should be valid. Best treatment after progression on first-line immunotherapy with nivolumab and pembrolizumab is uncertain; combination immunotherapy or single agent ipilimumab can be considered in this setting. Better response rates and OS have been demonstrated in nivolumab to ipilimumab sequence than reverse but toxicity was similar to that for the combination.[68] A comparison of various trials of immunotherapy in metastatic disease is summarized in Table V.

Immune-related adverse events (irAEs)
irAEs are a unique spectrum of side-effects associated with immune checkpoint inhibition. In various clinical trials, ipilimumab was consistently more toxic than nivolumab/pembrolizumab with grades 3–4 adverse events seen in 50% of patients with ipilimumab and 15% with nivolumab/pembrolizumab. irAEs require strict monitoring and are treatable with steroids if detected early. The spectrum of irAEs seen with anti-CTLA-4 and anti-PD-1 antibodies is different. Endocrinopathies (thyroiditis, hypophysitis, adrenal insufficiency) and colitis are more frequent with anti-CTLA-4 and pneumonitis and hepatitis seen more commonly with anti-PD-1. Appearance of irAEs is unpredictable and does not corelate with the cumulative dose.[69]

Management of irAEs depends on the grade of the adverse event. Temporary discontinuation of immunotherapy is required for a grade 2 event, steroids may be added at 0.5 mg/kg if symptoms do not resolve within a week. The drug should be restarted once symptoms are grade 1 or less. Immunotherapy should be permanently discontinued for grades 3–4 adverse events and management requires high dose steroids (1–2 mg/kg) with refractory cases requiring infliximab. Steroids can be tapered slowly once symptoms decrease to grade 1 or less.[69]

BRAF and MEK inhibitors: Two better than one?
Concept of dual inhibition. Targeted therapy against BRAF and MEK is an important treatment option for patients with BRAF/NRAS mutated tumours. There are no data from randomized trials comparing BRAF/MEK inhibitors with immunotherapy in BRAF mutated melanoma and optimal sequencing is unknown.

Both dabrafenib and vemurafenib improved response rates, PFS and OS in pivotal phase 3 trials when compared with dacarbazine.[70–73] However, single agent BRAF inhibitors caused keratoacanthomas and new squamous cell carcinomas in 20%–25% of patients[74] and new melanomas in around 2%. The accepted hypothesis implicates BRAF independent downstream activation of MAP kinase pathway as a possible mechanism for this toxicity and that a second step inhibition with MEK inhibitors might circumvent this complication. Based on the above hypothesis, combinations of BRAF inhibitors with MEK inhibitors have been tested in melanoma.

TABLE V. Landmark trials of immunotherapy in metastatic melanoma

Study	Design	Treatment groups and regimen	ORR	Median DOR	PFS (months)	OS (months)
Robert et al.[52] (2011)	Untreated patients; double-blind, phase 3 trial	Ipilimumab 10 mg/kg and dacarbazine (n=250) v. placebo and dacarbazine (n=252)	15.2% v. 10.3%, p=0.09	19.3 months v. 8.1 months, p=0.03	Median survival in both groups similar, HR 0.76, p<0.006 in favour of ipilimumab and dacarbazine	11.2 v. 9.1 months, HR 0.72, p<0.001
Robert et al.[59] (2015)	Untreated patients (with melanoma without BRAF mutation); double-blind, phase 3 trial (CheckMate 66)	Nivolumab (n=210) v. dacarbazine (n=208)	40.0% v. 13.9%, p<0.001	NR v. 6.0 months	5.1 v. 2.2 months, HR 0.43, p<0.001	NR v. 10.8 months, HR 0.42, p<0.001
Weber et al.[61] (2015)	Patients pre-treated with ipilimumab and BRAF inhibitor; open-label, phase 3 trial (CheckMate 37)	Nivolumab (n=272) v. chemotherapy (n=133)	27% v. 10%	31.9 v. 12.8 months	3.1 v. 3.7 months, HR 1.0	15.7 v. 14.4 months, HR 0.95
Weber et al.[68] (2016)	Untreated and pre-treated patients; open-label, phase 2 trial (CheckMate 64)	Nivolumab followed by ipilimumab (n=68) v. ipilimumab followed by nivolumab (n=70)	56% v. 31%	NR v. NR	–	NR v. 16.9 months, HR 0.48
Larkin et al.[62] (2015) and Wolchok et al.[63] (2017)	Untreated patients; double-blind, phase trial (CheckMate 67)	Nivolumab+ ipilimumab (A) (n=314) v. nivolumab (B) (n=316) v. ipilimumab (C) (n=315)	58% (A) v. 44% (B) v. 19% (C)	NR v. NR v. 19.3 months	11.5 months nivolumab+ ipilimumab, nivolumab 6.9 months ipilimumab 2.9 months (Nivolumab+ ipilimumab significant compared to nivolumab and ipilimumab, nivolumab significant compared to ipilimumab)	Nivolumab+ ipilimumab NR nivolumab 37.6 months ipilimumab 19.9 months (nivolumab+ ipilimumab significant compared to ipilimumab, not significant compared to nivolumab, nivolumab significant compared to ipilimumab)
Ribas et al.[55] (2015) and Hamid et al.[56] (2017)	Patients pre-treated with ipilimumab and BRAF inhibitor; open-label, phase 2 trial (KEYNOTE 002)	Pembrolizumab 2 mg/kg (n=180) v. pembrolizumab 10 mg/kg (n=181) v. chemotherapy (n=179)	22% v. 28% v. 4%, p<0.0001	22.8 months v. NR v. 6.8 months	Pembrolizumab (2 mg/kg) 2.9 months (HR v. chemotherapy 0.57, p<0.0001); pembrolizumab (10 mg/kg) 2.9 months (HR v. chemotherapy 0.50, p<0.0001); chemotherapy 2.7 months	Crossover allowed; pembrolizumab (2 mg/kg) 13.4 months (HR v. chemotherapy 0.86, p=0.117); pembrolizumab (10 mg/kg) 14.7 months (HR 0.74, p=0.011); chemotherapy 11.0 months
Hamid et al.[56] (2017) and Robert et al.[57] (2015)	Untreated and pre-treated patients; double-blind, phase 3 trial (KEYNOTE 006)	Pembrolizumab once every 2 weeks (n=279) v. pembrolizumab once every 3 weeks (n=277) v. ipilimumab (n=278)	37% v. 36% v. 13%	NR v. NR v. NR	5.6 v. 4.1 v. 2.8 months; pooled pembrolizumab groups v. ipilimumab HR 0.61, p<0.0001	Pembrolizumab once every 2 weeks NR (HR v. ipilimumab 0.68, p=0.0009); pembrolizumab once every 3 weeks NR (HR v. ipilimumab 0.68, p=0.0008); ipilimumab 16.0 months

ORR overall response rate   NR not reached   HR hazard ratio   DOR duration of response   PFS progression-free survival   OS overall survival

SUPPORTING EVIDENCE

The first combination tried was dabrafenib with trametinib in two randomized trials. In the Combi-AD study, a combination of dabrafenib and trametinib was compared to dabrafenib alone; the combination arm showed unprecedented response rates (68% *v.* 55%), median PFS (11 *v.* 8.8 months, HR 0.67, 95% CI 0.53–0.84) and OS (median 25.1 *v.* 18.7 months, HR 0.71, 95% CI 0.55–0.92). Around 20% of patients treated with the combination maintained disease control on long-term follow-up compared to 6% in dabrafenib alone.[75,76] Cutaneous toxicity was decreased with the combination with squamous cell carcinoma seen in 9% with dabrafenib alone and 3% with the combination. Pyrexia, chills and gastrointestinal toxicity was more in the combination leading to higher discontinuation rates (11% *v.* 7%). Similar results were seen when the above combination was compared with vemurafenib in a phase 3 trial.[77] These trials showed a median PFS of 11 months and median OS of 25 months; patients having less than three sites of metastasis and normal LDH had significantly better outcomes.[78]

A combination of vemurafenib and cobimetinib tested in a phase 3 trial showed similar results to dabrafenib and trametinib with similar toxicity.[79]

In the phase 3 COLUMBUS trial,[80,81] a combination of encorafenib and binimetinib showed prolonged PFS and OS compared to vemurafenib alone or encorafenib alone (PFS 14.3 *v.* 9.7 months, OS 33.6 *v.* 23.5 months). Numerically this trial had the longest median PFS and OS, but none of these combinations have been directly compared and cross-trial comparisons should be interpreted cautiously. A combination of dabrafenib and trametinib has shown great efficacy in brain metastasis with response rates of 55%. Binimetinib has also shown activity in NRAS mutated tumours and can be used in this subset of patients; however, it is not currently approved for this indication.[82]

WHEN TO USE?

To summarize, a combination of BRAF and MEK inhibitors is an important treatment option in BRAF mutant melanoma with best results so far for the encorafenib and binimetinib combination. However, there are no direct comparisons between various BRAF and MEK inhibitors and between these targeted therapy and immunotherapy. Moreover, pembrolizumab showed excellent response and survival in BRAF mutated tumours, making it a reasonable first-line choice in this subset. Also, BRAF and MEK inhibitors, although approved by DCGI, they are not currently available in India making targeted therapy a second-line option in BRAF mutated melanoma (Fig. 3).

C-KIT AND IMATINIB: VALUE IN THE INDIAN SETTING

Mutations in c-KIT are more often seen in acral and mucosal melanomas; since acral melanoma is more common in India compared to the West, targeting c-KIT with tyrosine kinase inhibitors is a valid treatment option. Three phase 2 trials have tested imatinib in c-KIT mutant melanoma; results are variable with partial responses seen in 23%–54% of patients.[34,83,84] Interestingly, only patients with exon 11 (L576P) and exon 13 (K642E) responded; patients with KIT amplification without mutation did not respond. Similar activity has been observed with nilotinib in previously treated patients with imatinib and treatment-naïve patients,[85,86] dasatanib,[87] sorafenib[88] and sunitinib.[89]

DOES CHEMOTHERAPY HAVE A ROLE IN THE CURRENT SCENARIO?

Chemotherapy in metastatic melanoma has been disappointing. A number of agents have been tried alone and in combination with disappointing results. Dacarbazine has been the traditional comparator arm for most immunotherapy trials and is considered the most active chemotherapeutic drug in melanoma. Other drugs such as temozolomide, platinum compounds and taxanes have been tested without much benefit. Addition of interleukin 2 has not shown survival benefit in any trial. In the present scenario, chemotherapy may be considered for patients who are not eligible or have progressed on immunotherapy and are not eligible for clinical trials as a last resort. The major chemotherapy trials are summarized in Table VI.

FUTURE PERSPECTIVES

Patients with high-risk early-stage disease (>4 mm thickness without ulceration and >2 mm thickness with ulceration but negative nodes) have higher relapse risk, but they have not been evaluated in phase 3 trials involving adjuvant immunotherapy or targeted therapy. Trials in this population is an unmet need but they do not merit adjuvant therapy outside of a trial setting at present. Adequately powered trials comparing combination immunotherapy with single agent nivolumab are required to answer the question of best frontline option in metastatic melanoma. Since no direct comparisons of immunotherapy and targeted therapy are available, trials to answer that question in BRAF mutated melanoma are also anticipated. Although preliminary evidence indicates that immunotherapy can be discontinued after 2 years in metastatic melanoma, concrete evidence to this effect is lacking.
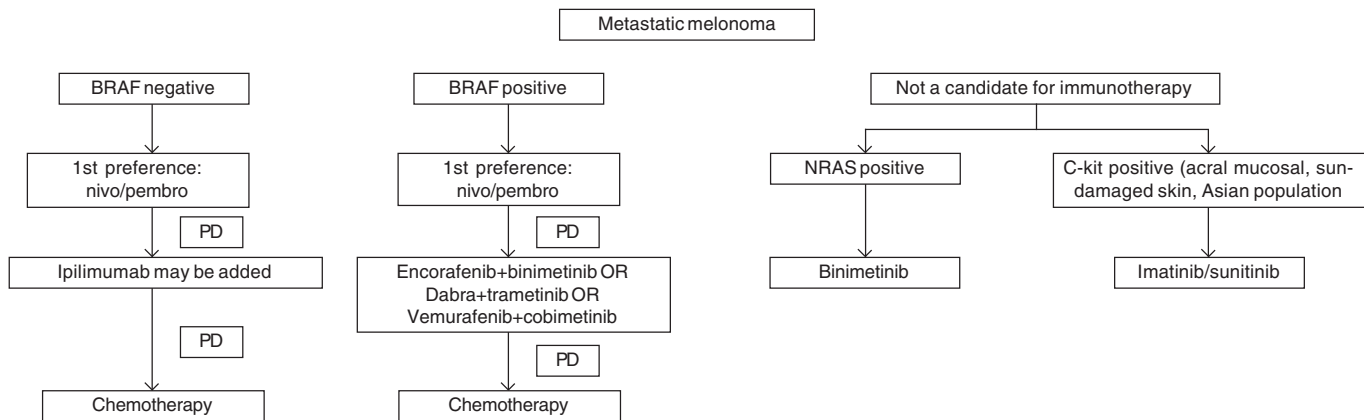

FIG 3. Management algorithm for metastatic melanoma

TABLE VI. Cytotoxic chemotherapy in melanoma

Trial	n	Treatment arms	Main findings
Middleton et al.[90]	305	Temozolomide v. dacarbazine (DTIC)	Median survival 7.7 months for temozolomide and 6.4 months for DTIC
Legha et al.[91]	52	CVD chemotherapy (cisplatin, vinblastine and DTIC)	ORR 40% (2 patients had complete response), median survival was 12 months
Luikart et al.[92]	57	DTIC v. vincristine, bleomycin, DTIC (VBD)	VBD was not superior to DTIC
Chapman et al.[93]	240	DTIC v. Dartmouth regimen (DTIC, cisplatin)	Median survival 7 months, similar in both arms; response rate slightly higher in combination arm (18% v. 10%)
Eton et al.[94]	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 et al.[95]	416	CVD alone v. CVD followed by IFN and IL-2	Biochemotherapy had an inferior PFS and OS
EORTC 18951[96]	363	Cisplatin, DTIC and IFN alpha+high dose IL-2 v. IL2 alone	Improved responses but no difference in survival

IFN interferon　　　IL-2 interleukin-2　　　ORR overall response rate　　　PFS progression-free survival　　　OS overall survival

To conclude, based on the results with the present-day immunotherapy and targeted therapy in melanoma, it appears that the intent of treatment in metastatic setting may be considered as curative as more than half the patients have long-term survival with many patients able to discontinue treatment without losing response.

Conflicts of interest. Nil

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