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The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma

Howard L. Kaufman, John M. Kirkwood, F. Stephen Hodi, Sanjiv Agarwala, Thomas Amatruda, Steven D. Bines, Joseph I. Clark, Brendan Curti, Marc S. Ernstoff, Thomas Gajewski, Rene Gonzalez, Laura Jane Hyde, David Lawson, Michael Lotze, Jose Lutzky, Kim Margolin, David F. McDermott, Donald Morton, Anna Pavlick, Jon M. Richards, William Sharfman, Vernon K. Sondak, Jeffrey Sosman, Susan Steel, Ahmad Tarhini, John A. Thompson, Jill Titze, Walter Urba, Richard White and Michael B. Atkins

Rush University Cancer Center, 1725 West Harrison Street, Chicago, IL 60612, USA (**H. L. Kaufman**, **S. D. Bines**, **J. Titze**). University of Pittsburgh (**J. M. Kirkwood**, **M. Lotze**, **A. Tarhini**); Dana Farber Cancer Institute (**F. S. Hodi**); St Luke's Cancer Center (**S. Agarwala**); Minnesota Oncology (**T. Amatruda**); Loyola University Medical Center (**J. I. Clark**); Providence Cancer Center (**B. Curti**, **W. Urba**); Dartmouth-Hitchcock Medical Center (**M. S. Ernstoff**); University of Chicago (**T. Gajewski**); University of Colorado (**R. Gonzalez**); Gilda's Club (**L. J. Hyde**); Emory Winship Cancer Institute (**D. Lawson**); Mount Sinai Comprehensive Cancer Center (**J. Lutzky**); University of Washington (**K. Margolin**, **J. A. Thompson**); Beth Israel Deaconess Medical Center (**D. F. McDermott**); John Wayne Cancer Institute (**D. Morton**); New York University (**A. Pavlick**); Lutheran General Hospital (**J. M. Richards**); Johns Hopkins University (**W. Sharfman**); H. Lee Moffitt Cancer Center (**V. K. Sondak**); Vanderbilt-Ingram Cancer Center (**J. Sosman**); Skin of Steel (**S. Steel**); Carolinas Medical Center (**R. White**); Georgetown-Lombardi Comprehensive Cancer Center (**M. B. Atkins**); all in USA.

Correspondence to:
H. L. Kaufman
howard_kaufman@rush.edu

Abstract | Immunotherapy is associated with durable clinical benefit in patients with melanoma. The goal of this article is to provide evidence-based consensus recommendations for the use of immunotherapy in the clinical management of patients with high-risk and advanced-stage melanoma in the USA. To achieve this goal, the Society for Immunotherapy of Cancer sponsored a panel of melanoma experts—including physicians, nurses, and patient advocates—to develop a consensus for the clinical application of tumour immunotherapy for patients with melanoma. The Institute of Medicine clinical practice guidelines were used as a basis for this consensus development. A systematic literature search was performed for high-impact studies in English between 1992 and 2012 and was supplemented as appropriate by the panel. This consensus report focuses on issues related to patient selection, toxicity management, clinical end points and sequencing or combination of therapy. The literature review and consensus panel voting and discussion were used to generate recommendations for the use of immunotherapy in patients with melanoma, and to assess and rate the strength of the supporting evidence. From the peer-reviewed literature the consensus panel identified a role for interferon-α2b, pegylated-interferon-α2b, interleukin-2 (IL-2) and ipilimumab in the clinical management of melanoma. Expert recommendations for how to incorporate these agents into the therapeutic approach to melanoma are provided in this consensus statement. Tumour immunotherapy is a useful therapeutic strategy in the management of patients with melanoma and evidence-based consensus recommendations for clinical integration are provided and will be updated as warranted.

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Introduction

The incidence of cutaneous melanoma has increased steadily since the 1970s, with over 70,000 new cases of invasive melanoma in the USA each year costing close to US$2 billion annually.[1] Early detection and wide excision is associated with 5-year survival rates of >90% and 80% for stage I and II lesions, respectively.[2] Survival decreases to 50% for patients with localized lymph-node metastases (stage III), and metastatic disease (stage IV) historically had a median survival of 8–9 months and a 3-year overall survival rate less than 15%.[3] Prior to 2011, treatment of melanoma was limited to interferon-α2b for adjuvant therapy and dacarbazine or high-dose interleukin-2 (IL-2) for metastatic disease. Since 2011, three new agents have been approved for the treatment of patients with melanoma: pegylated-interferon-α2b in the adjuvant setting, the anti-CTLA4 monoclonal antibody ipilimumab for metastatic disease and an oral BRAF inhibitor vemurafenib in patients with metastatic melanoma harbouring *BRAF*^{V600} mutations.[4–6]

Tumour immunotherapy is the clinical application of pharmacological agents that directly induce or substitute for host antitumour immunity. Melanoma can be highly sensitive to immunotherapy and of the six approved drugs highlighted above only dacarbazine and vemurafenib are not immunotherapies. The mechanism of action for most immunotherapeutic agents remains incompletely understood, but these treatments are notable for their ability to produce a durable benefit in a subset of patients.[7,8] Ipilimumab has been associated with significant improvement in overall survival in the metastatic setting.[5,9] Immunotherapy requires special attention to several caveats. Although therapeutic benefits can

Competing interests
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be durable, only a subset of patients respond.[7,8] In addition, unique adverse effects of immunotherapy, many of which relate to the induction of autoimmunity and pro-inflammatory-like states,[10] might limit eligibility or become challenges in clinical management. Recent studies suggest immunotherapy, particularly with ipilimumab and related agents, might result in tumour regression over a prolonged time, based on the kinetics of establishing an effective host antitumour immune response.[10,11] This finding has led to the development of immune-related response criteria to better monitor patients treated with immunotherapy and to determine appropriate clinical end points.[12] Availability of non-immunotherapy strategies has also resulted in the opportunity to develop combination treatment regimens for clinical evaluation and the need to better define optimal sequencing of therapy for patients with advanced-stage melanoma.

The Society for Immunotherapy of Cancer (SITC) is a non-profit professional organisation dedicated to the basic understanding and clinical applications of tumour immunotherapy. To provide guidance to practicing clinicians caring for patients with melanoma, SITC established a Melanoma Clinical Immunotherapy Guidelines panel (Supplementary Box 1 online). The panel consisted of melanoma experts, including physicians, nurses and patient advocates and considered issues related to patient selection, toxicity management, treatment cessation guidelines and current recommendations for treatment sequencing with the goal of preparing a consensus statement on clinical use of tumour immunotherapy for patients with melanoma.

Methods

Consensus statement policy

The Institute of Medicine's March 2011 Standards for Developing Trustworthy Clinical Practice Guidelines[13] served as a model for organising and preparing this consensus statement. These standards include establishing a transparent process for guideline development and funding, managing and reporting conflicts of interest, inclusion of a multidisciplinary and balanced group composition, establishing an evidence-based foundation and rating system for the strength of the evidence, reporting the results through a peer-reviewed publication and publicly available website, and having a plan for updating the statement as changes in the field warrant revisions. Convening under the umbrella of SITC (June 2011), a steering committee led a panel, which sought to develop clinical treatment guidelines considering four basic issues for each immunotherapy agent in current clinical practice: patient selection, toxicity management, assessment of response, and therapy sequencing and combinations. This consensus statement is not intended to substitute for the individual professional judgement of the treating physician. Full consensus recommendations can be found on the SITC website.[14] Owing to disparities in drug approval and availability in some countries, this panel focused solely on drugs approved by the FDA for the treatment of patients in the USA. An advance copy of this manuscript was submitted to the FDA for comment before submission for publication.

Box 1 | Evidence levels used for literature review

Level A
Significant supporting data (for example, large prospective, randomized clinical trial, sophisticated meta-analysis, and so on).

Level B
Less-convincing supporting data (for example, small prospective or single-arm phase II clinical trial, and so on).

Level C
Limited or no supporting data (for example, case series, retrospective chart reviews, and so on).

Consensus panel and conflicts of interest

Potential panel members were solicited from SITC members and non-member melanoma multidisciplinary experts, clinicians and populations in the USA expected to be affected by the development of any recommendations, including patients, patient advocates and nurses. Panel members were screened for conflicts of interest using the SITC disclosure form, which mandates full financial and other disclosures including relationships with commercial entities that might reasonably be expected to have direct regulatory or commercial impact resulting from the publication of this statement. Disclosures of potential conflicts of interest are noted in this manuscript and in detail online. No commercial funding was used in supporting the consensus panel, literature review or preparation of the manuscript.

The consensus panel convened in June 2011 in accordance with the Institute of Medicine and SITC guidelines to review results from a previously distributed questionnaire collecting information on the participants' role in the care of patients with melanoma, primary clinical focus, experience with FDA-approved agents used for immunotherapy treatments, and current practices in the use or recommendation for use of such agents. Additional questionnaires were distributed after the meeting to collect further information. The final consensus statement was made available to the entire SITC membership for open comment and these comments were considered for the final manuscript and are available in Supplementary Box 2 online.

Literature review

A search of the scientific literature (using the MEDLINE database) was conducted focusing on current therapeutic approaches in humans. The search terms were: "melanoma and interferon", "melanoma and interleukin-2", "melanoma and ipilimumab", "melanoma and vemurafenib", "melanoma and dacarbazine", and "melanoma and temozolomide"), which resulted in a 986-item (duplicates removed) bibliography (Supplementary Bibliography online) catalogued using EndNote X5.0.1. The bibliography was supplemented with additional literature identified by the panel, as appropriate. Literature was graded into three levels according to levels of evidence (Box 1).

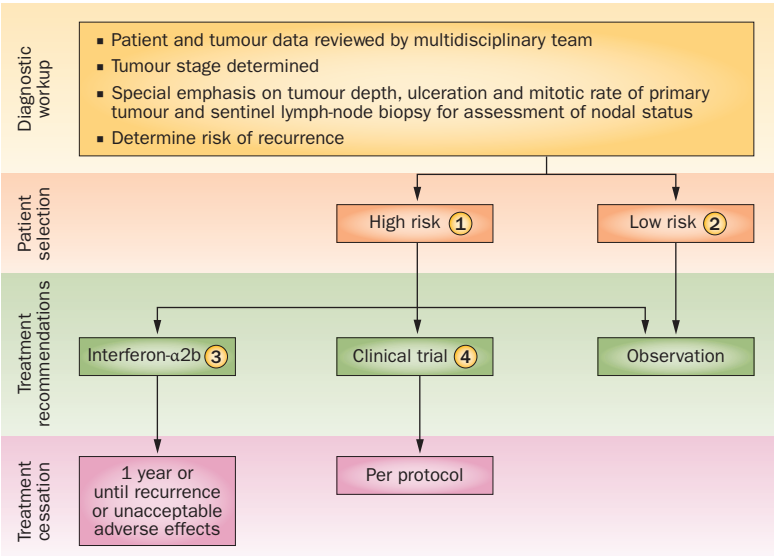

Figure 1 | Stage II melanoma immunotherapy treatment algorithm. All treatment options shown may be appropriate, and final selection of therapy should be individualized based on patient eligibility and treatment availability at the physician's discretion. These algorithms represent consensus sequencing suggestions by the panel. (1) High-risk disease is defined as tumours >4 mm in diameter, ulcerated, and/or mitotic rate ≥1 per mm^2. There is limited consensus on adjuvant therapy for this group with 43% of the panel recommending interferon-α2b, 38% recommending observation, 14% recommending clinical trial participation and no panellists recommending pegylated-interferon-α2. A minority (5%) recommended individualizing treatment for each patient. (2) There is no evidence that immunotherapy is useful in patients with low-risk stage II melanoma. (3) Patients should have a good performance status without evidence of significant depression, psychiatric history or underlying autoimmune disease to be considered for interferon-α2b. There are limited data available on interferon-α2b as treatment for stage II disease. (4) Clinical trials might be the preferred treatment recommendation for patients with stage II disease if they are available. Protocol-specific eligibility would need to be followed to appropriately select patients.

Level A represented strong supporting evidence-based data as derived from appropriately powered prospective, randomized clinical trials and meta-analyses. Level B represented moderate supporting data as derived from uncontrolled, prospective clinical trials. Level C represented weak supporting data as derived from retrospective reviews and case reports.

Consensus recommendations

Immunotherapy for stage II melanoma

Clinical question: What is the appropriate use of immunotherapy in the treatment of stage II melanoma?

Initial assessment

Patients with stage II melanoma have an excellent overall survival of 80% or better provided the tumour is treated by complete resection.[2] A subset of tumours characterized as deep (depth of >4 mm), with ulceration or possibly those with a high tumour mitotic rate (≥1 per mm^2), are considered high risk for recurrence.[15] The panel recommends that all stage II patients have a comprehensive diagnostic workup and be reviewed by a multidisciplinary team (surgical oncologist, medical oncologist and dermatopathologist) to accurately determine tumour stage and risk of melanoma recurrence. This workup should include sentinel-lymph-node biopsy, when appropriate.[3,16] There is general agreement that patients with low-risk stage II melanoma can be safely observed and do not warrant treatment (Figure 1).

Consensus management of stage II melanoma

The panel is divided on the role of immunotherapy for patients with high-risk stage II melanoma (Figure 1) and recognizes the limited level A data available to inform clinical decision-making. The majority of the panel recommends that high-risk patients be treated with standard 1-year interferon-α2b, although a minority suggest participation in clinical trials (assuming availability and eligibility to the protocol-specific patient selection criteria of the trial) or observation. A few panellists (5%) individualize treatment of patients with high-risk stage II melanoma based on the particular situation. None of the panel members recommends treatment with pegylated-interferon-α2b for patients with high-risk stage II disease. Patients with high-risk stage II melanoma who are treated with interferon-α2b should have a good performance status without evidence of significant depression or psychiatric history or underlying autoimmune disease. In addition, patients with high-risk disease receiving interferon-α2b should cease treatment when unmanageable adverse effects persist despite dose reduction of 67–75%, at the time of documented disease recurrence or after 1 year of therapy. Patients with high-risk melanoma who are enrolled in a clinical trial follow the course of treatment and treatment cessation dictated by the trial protocol.

Literature review and analysis

Limited data exist on the role of immunotherapy for low-risk stage II melanoma, but there have been several randomized clinical trials focusing on patients with high-risk stage II disease. A prospective study of 499 patients with melanoma depth >1.5 mm and without clinically detectable lymph-node metastases who were randomly assigned to 18 months of subcutaneous interferon-α2b or observation demonstrated a significant improvement in relapse-free survival ($P = 0.038$) and a clear trend toward improved overall survival ($P = 0.059$) for patients who received adjuvant interferon-α2b.[17] In another trial, 855 patients were randomly assigned to observation or 4 weeks induction interferon-α2b followed by 1 or 2 years of interferon-α2b maintenance therapy.[18] That trial reported an improvement in relapse-free survival for patients who received 1 year of maintenance interferon-α2 (hazard ratio [HR] = 0.77, 95% CI 0.63–0.96; $P = 0.034$), but no benefit in overall survival (HR = 0.91, 95% CI 0.74–1.10; $P = 0.642$). Several other prospective randomized trials examined interferon-α2b at a variety of doses and treatment schedules in patients with high-risk stage II melanoma, but none has demonstrated a survival benefit.[19–22] These studies are complicated by a lack of a standardized definition of 'high-risk',[23] different interferon-α2b doses and schedules, and in some cases include other drugs in combination.

Immunotherapy for stage III melanoma

Clinical question: What is the appropriate use of immunotherapy in the treatment of stage III melanoma?

Initial assessment

Stage III represents a heterogeneous group of patients with 5-year survival rates ranging from 30% to 80%.[3] In patients with stage lll melanoma, a diagnostic workup should be performed and reviewed by a multidisciplinary team for patient and tumour characteristics. Complete tumour staging information should be assessed, including pathological features of the primary tumour and any involved lymph nodes, whole-body imaging, serum lactate dehydrogenase (LDH) levels and performance status assessment. Nodal status should be determined based on physical examination, sentinel-lymph-node biopsy and/or lymphadenectomy status. The consensus panel identified two immunotherapy agents with potential clinical benefit in the adjuvant therapy of patients with stage III melanoma: interferon-α2b and pegylated-interferon-α2b.[4,24–27]

Consensus management of microscopic nodal disease

The panel recognized that patients with microscopically involved lymph nodes (N1a disease) might represent a different population than those with macroscopic nodal disease (N1b and N2–N3 disease). A majority (52.2%) of the panel recommends a standard 1-year course of interferon-α2b for the adjuvant therapy of microscopic nodal disease. A minority (21.7%) recommends shorter-course interferon-α2b, biochemotherapy generally consisting of cisplatin, vinblastine, dacarbazine, low-dose IL-2 and interferon-α2b (4.3%) or no further treatment (observation; 21.7%). When specifically asked, all panellists recommend that these patients consider enrolling in appropriate clinical trials, but no panellists recommend pegylated-interferon-α2b (Figure 2). There is one prospective randomized clinical trial demonstrating a benefit in relapse-free survival for patients with microscopic nodal disease treated with pegylated-interferon-α2b.[4] A *post-hoc* analysis of that trial also suggested patients with ulcerated primary tumours might derive more clinical benefit from pegylated-interferon-α2b.[28] In this analysis, patients with ulceration of their primary melanoma ($n = 849$) were compared to patients without ulceration of their primary melanoma ($n = 1{,}336$), and patients with ulceration demonstrated a significant improvement in relapse-free survival ($P = 0.02$), distant metastasis-free survival ($P < 0.001$) and overall survival ($P < 0.001$). The analysis also found that the greatest reduction in risk was seen in patients with ulcerated primary melanomas who were classified as stage IIb–III-N1, demonstrating an HR of 0.58 for overall survival benefit ($P < 0.0001$). Thus, patients with ulcerated primary tumours and those with microscopic nodal disease could consider pegylated-interferon-α2b based on level B data.

Consensus management of macroscopic nodal disease

Patients with macroscopic nodal disease (N1b and N2–N3 disease) are at increased risk for melanoma recurrence and the panel generally recommends these patients consider 1 year of interferon-α2b treatment (72.7%). A minority of the panel mentioned a shorter course of interferon-α2b (9.1%), observation (9.1%), adjuvant radiation therapy (4.5%) and biochemotherapy (4.5%). No panellists recommend pegylated-interferon-α2b for patients with resected macroscopic nodal disease. Based on the consensus and literature review, which includes several meta-analyses of clinical outcomes for interferon-α2b,[29–31] the panel considered there was level A data supporting the use of interferon-α2b in these patients (Figure 2). Participation in appropriate clinical trials was considered to be an acceptable alternative.

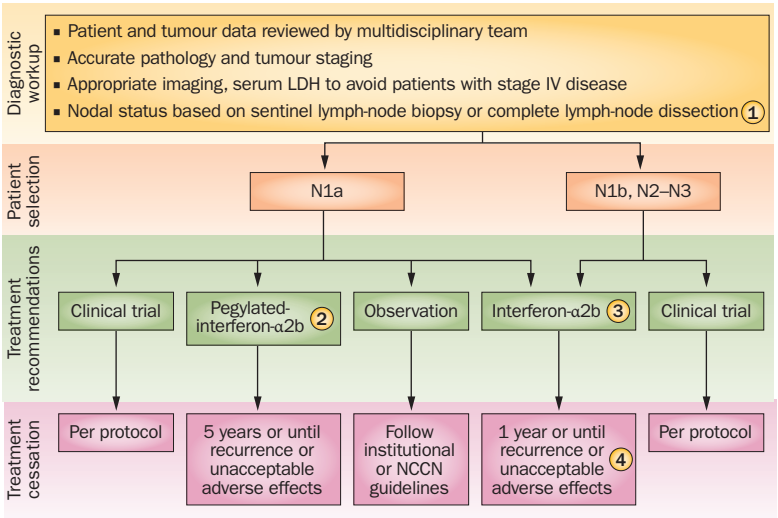

Figure 2 | Stage III melanoma immunotherapy treatment algorithm. All treatment options shown may be appropriate and final selection of therapy should be individualized based on patient eligibility and treatment availability at the physician's discretion. These algorithms represent consensus sequencing suggestions by the panel. (1) There are limited data on the role of adjuvant therapy following sentinel lymphadenectomy alone. (2) There are level B data to support a benefit in RFS for pegylated-interferon-α2b in patients with N1a disease and in patients with ulceration of the primary tumour site. The majority of the panel does not consider pegylated-interferon-α2b at all (52.4%), whereas a minority considers it for N1a disease (14.3%) or in the setting of an ulcerated primary lesion (14.3%). Some panel members will consider pegylated-interferon-α2b when patients are not willing or able to tolerate standard interferon-α2b (9.5%). (3) There are level A data that 1 year interferon-α2b is associated with improvement in RFS and it was generally recommended by the consensus panel. Abbreviations: LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network; RFS, recurrence-free survival.

Other considerations

The panel also suggests that treating physicians consider the presence of underlying depression and autoimmune disease as a potential contraindication to treatment with interferon-α2b and closely monitor such patients if interferon-α2b is used (Box 2). Practical guidelines for clinical management of interferon-α2b-related adverse effects are available.[32]

Literature review and analysis

The initial ECOG 1684 prospective randomized trial demonstrated a benefit in relapse-free and overall

Box 2 | Consensus panel recommendations for special issues in immunotherapy clinical management

Management issue: Treatment of interferon-α2b-related depression

- Can be a significant adverse effect of therapy
- Special attention to history of depression and related disorders before treatment is warranted
- Major depression is a relative contraindication to treatment
- The majority consensus opinion was to use antidepressants in selected patients who develop depression during therapy (45.5%)
- A large minority opinion suggested prophylactic antidepressants should be started at the time of treatment initiation in all patients (31.8%)
- A minority of the panel recommended referral to a psychologist before starting treatment for all patients (13.6%)
- A minority of the panel recommended selective referral to a psychologist only if and when symptoms develop (13.6%)
- Some panel members suggested both antidepressants and psychology referral should be considered

Management issue: Clinical laboratory monitoring during immunotherapy

- Immunotherapy is associated with a range of adverse effects that require routine monitoring during and after treatment
- Special attention to autoimmune and immune-related adverse effects is warranted with most immunotherapy agents
- A majority of the panel recommended routine assessment of thyroid function studies for patients receiving interferon-α2b, IL-2 and ipilimumab (100%), complete blood counts, liver enzymes and metabolic panels (100%) and serum LDH (75%)
- The majority of the panel recommended testing these factors at the following intervals: weekly during induction and then monthly until stable for interferon-α2b (70%); the panel was more divided on pegylated-interferon-α2b with 35% recommending monthly and 41% recommending weekly for 1 month and then monthly until laboratory results are stable; a majority recommend daily laboratory assessment during IL-2 treatment (76.2%) and 20% always obtain a laboratory assessment 1 week after IL-2 treatment cessation and 25% sometimes obtain post-treatment laboratory assessment. All panel members recommend laboratory assessment before ipilimumab infusion every 3 weeks (100%), but the panel was divided on long-term monitoring with 40% recommending every 3 months for 2 years and 40% recommending this be individualized to each patient
- The panel recommends additional hormone testing (TSH, free T_4, ACTH and morning cortisol) for patients who develop signs of pituitary dysfunction when receiving ipilimumab; in some patients a co-syntropin stimulation test, LH, FSH, testosterone and prolactin tests should be considered; early referral to an endocrinologist is also recommended
- The panel recognized that laboratory assessment might need to be individualized for patients who develop specific adverse effects

Management issue: Imaging during and after immunotherapy

- Disease response might be more challenging to document in patients treated with immunotherapy than chemotherapy or targeted therapy owing to the kinetics of response and induction of local inflammation
- A majority of the panel recommended whole-body imaging before and after treatment with all immunotherapy agents (100%)
- A majority of the panel recommended CT scans of the chest, abdomen and pelvis (95.8%)
- A majority of the panel recommended the routine use of MRI of the brain (66.7%)
- A minority of the panel recommended routine PET scans (17.4%) or whole-body PET–CT scans (21.7%)
- Routine ultrasound imaging was not recommended and a minority of the panel suggested routine chest X-rays (39.1%)
- The frequency of imaging was more controversial. For patients with stage III disease, the panel recommended imaging be performed every 3 months (14.3%), every 6 months (28.6%), annually (23.8%) or at a range of other intervals (33.3%); for patients with stage IV disease, the majority of the panel (95%) recommended imaging, with 55% suggesting every 3 months for 2 years, then every 6 months for 3 years with no further imaging at 5 years unless there is evidence of disease progression, and 40% suggested the imaging frequency should be individualized to each patient

Management issue: Immunotherapy treatment cessation

- The kinetics of response with immunotherapy might be delayed, making decisions regarding continuation or cessation of treatment challenging
- The panel recommended stopping any treatment for serious adverse effects or for unequivocal evidence of disease progression
- The appearance of new disease or significant growth of established disease should result in cessation of interferon-α2b and IL-2
- The panel recommended more caution in stopping ipilimumab in the face of new lesions or asymptomatic progression
- Repeat imaging within 1–2 months was generally recommended for patients receiving ipilimumab who had asymptomatic disease progression by imaging at the first follow-up
- A minority of the panel recommended continuing treatment with ipilimumab (39.1%) in the face of new lesions or progressive disease
- No panel members recommended continuing interferon-α2b or IL-2 in the face of new lesions or progressive disease
- A minority of the panel suggested that surgical resection be considered for all patients with a mixed response (8.7% after ipilimumab and 9.1% after IL-2)
- A minority of the panel recommended routine biopsy of new or progressing disease before making further treatment decisions (8.7% after ipilimumab and 9.1% after IL-2)

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; IL, interleukin; LDH, lactate dehydrogenase; LH, luteinizing hormone; T_4, tetraiodothyronine; TSH, thyroid-stimulating hormone.

survival for patients with stage III melanoma treated with a 1-year course of interferon-α2b.[24] Long-term follow-up studies confirmed a benefit in relapse-free survival, but failed to show an overall survival benefit.[26] Subsequent randomized studies confirmed a benefit in relapse-free survival, but results indicating an overall survival benefit were inconsistent.[25,33] Several meta-analyses evaluated the clinical benefits of interferon-α2b and indicate a benefit in relapse-free survival and a trend toward improved overall survival.[29–31] The panel generally considered the data to provide level A evidence for a benefit in relapse-free survival with level B support for an improvement in overall survival from treatment with interferon-α2b. Pegylated-interferon-α2b was approved by the FDA based on improvement in relapse-free survival in patients with microscopic nodal disease.[4] A *post-hoc* analysis also suggested that primary tumours harbouring ulceration were more likely to benefit from pegylated-interferon-α2b.[28] The panel considered this to be level B data in support of pegylated-interferon-α2b.

Immunotherapy in stage IV melanoma

Clinical question: What is the appropriate use of immunotherapy in stage IV melanoma?

Initial assessment

In patients with stage lV melanoma, a diagnostic workup that includes a multidisciplinary team review of clinical and tumour data should be conducted. Staging should be confirmed via pathological evaluation, whole-body imaging, and serum LDH analysis. Genetic mutation analysis of the tumour should also be performed. Special emphasis should be placed on central nervous system (CNS) assessment and surgical evaluation by a qualified surgical oncologist for possible metastasectomy. If complete resection of all metastatic disease is possible, patients should consider metastasectomy as first-line treatment; this is supported by level B retrospective outcome studies, especially when a solitary metastasis is present (Figure 3).[34–37] Following immunotherapy, patients who achieve partial or stable disease responses should be re-assessed for resection.[38,39] The panel recognizes several systemic treatment options for unresectable stage IV melanoma, including high-dose IL-2 (where available), ipilimumab, vemurafenib, dabrafenib and trametinib for patients with *BRAF* mutated tumours, clinical trial participation and cytotoxic chemotherapy.

Consensus management of stage IV melanoma with good clinical performance and BRAF-mutated tumours

The treatment approach for patients with stage IV melanoma who are not surgical candidates should include an assessment of *BRAF* mutation status (and/or other high priority molecular targets with drugs in development, such as *KIT*), performance status and complete evaluation for CNS disease before treatment selection. A panel majority recommends patients whose tumours harbour a *BRAF* mutation with a good performance status and no CNS disease be treated with IL-2 as first-line therapy, provided they meet IL-2 eligibility, and a BRAF inhibitor

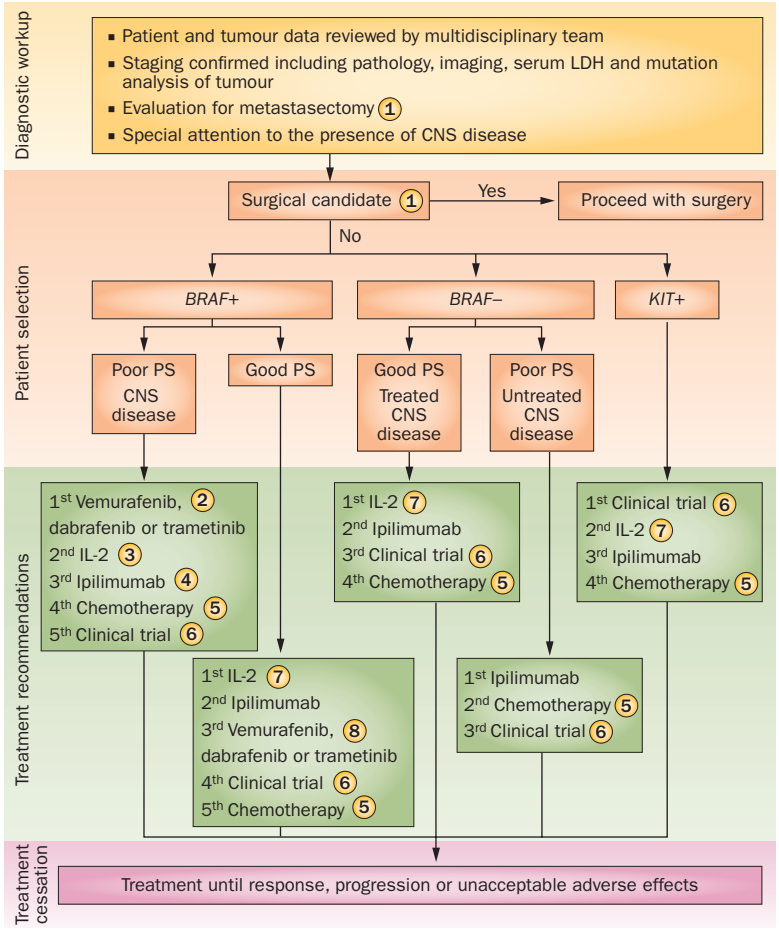

Figure 3 | Stage IV melanoma immunotherapy treatment algorithm. All treatment options shown may be appropriate and final selection of therapy should be individualized based on patient eligibility and treatment availability at the physician's discretion. These algorithms represent consensus sequencing suggestions by the panel. (1) All patients should be evaluated for surgical resection before and after immunotherapy treatment. There was level B data for a clinical benefit with surgical resection of completely resectable lesions and first-line surgical resection was a minority opinion (9%) of the consensus panel. (2) The panel recommended a BRAF inhibitor for patients with *BRAF*-mutated melanoma with poor PS, who have untreated CNS disease and who are not candidates for clinical trials. (3) The panel recommended that immunotherapy be considered in patients with *BRAF*-mutated melanoma who have been treated with a BRAF inhibitor if their PS improved with treatment and CNS disease is controlled. IL-2 can be considered in those patients who have a good PS and otherwise qualify for IL-2 administration as per local institutional guidelines. (4) The panel recommended that ipilimumab be considered for patients with *BRAF*-mutated melanoma with an initial poor PS who respond to a BRAF inhibitor and who are not candidates for IL-2 treatment or clinical trials. (5) The panel recommended that chemotherapy be considered in patients who have disease progression on a BRAF inhibitor and immunotherapy or who are not candidates for immunotherapy or clinical trials. (6) The panel was generally enthusiastic about recommending appropriate clinical trials for patients with melanoma. In most cases individual clinical trials should be considered pending patient eligibility and interest. (7) The panel recommended that IL-2 be considered first, provided that patients have a good PS and otherwise meet local institutional guidelines for IL-2 administration. Patients who are not candidates for IL-2 therapy should consider ipilimumab. (8) The panel recommended that patients with *BRAF*-mutated melanoma and a good PS with no evidence of CNS disease, or with treated CNS disease, consider immunotherapy first and delay a BRAF inhibitor until there is unequivocal evidence of disease progression. Abbreviations: *BRAF*+, positive for actionable *BRAF* mutations; *BRAF*–, negative for actionable *BRAF* mutations; CNS, central nervous system; IL, interleukin; *KIT*+, positive for actionable *KIT* mutations; LDH, lactate dehydrogenase; PS, performance status.

should be reserved for later treatment stages (Figure 3). Panel members recommend targeted therapy or ipilimumab as second-line or third-line therapy in these patients. There was general consensus that immunotherapy should be used first owing to the durable response rates observed, and a BRAF inhibitor should be considered when the disease is progressing rapidly or when performance status is poor.

Consensus management of stage IV melanoma with poor clinical performance and BRAF-mutated tumours

In patients whose melanoma harbours a *BRAF* mutation, but who have a poor performance status or uncontrolled CNS disease, vemurafenib, dabrafenib and/or trametinib should be considered to be the first-line therapy. The panel recommends that ipilimumab or chemotherapy be considered as second-line treatment in these patients. The panel recommends several options for third-line therapy in patients with these characteristics, including single-agent chemotherapy, palliative care, combination chemotherapy, clinical trials or IL-2, if performance status improves and/or CNS disease is controlled.

Consensus management of stage IV melanoma with good clinical performance and BRAF wild-type tumours

In patients with wild-type *BRAF* melanoma who have good performance status and no evidence of CNS disease, the panel recommends IL-2 as first-line therapy with a minority considering ipilimumab, clinical trials, chemotherapy or other regimens. The panel recognized that there is limited to no data on drug sequencing or possible untoward reactions between the available agents. Although the panel accepted that IL-2 and ipilimumab are acceptable agents for these patients, it is often challenging to administer high-dose IL-2 in patients with rapidly progressive disease or a declining performance status and there are no data documenting the safety of IL-2 after treatment with ipilimumab. These reasons led the panel to recommend IL-2 first. The panel generally agrees that patients who did not respond to IL-2 should receive ipilimumab as second-line treatment and then consider clinical trials or chemotherapy as third-line options. The delayed kinetics of antitumour activity with ipilimumab also suggests that patients should have a good performance status and have time to receive and respond to treatment before starting therapy.

Consensus management of stage IV melanoma with poor clinical performance and BRAF wild-type tumours

In patients with a wild-type *BRAF* melanoma with poor performance status or in the presence of uncontrolled CNS metastasis, the first-line treatment should consist of ipilimumab, clinical trial participation or chemotherapy. These patients often require individualized management with attention given to the control of CNS disease through resection or radiation therapy and careful consideration to the performance status, tempo of disease progression and realistic assessment of life expectancy.

Consensus management of KIT mutated melanoma

In the special situation where a patient has a melanoma with a known *KIT* mutation, the panel recommends participation in a clinical trial of a KIT inhibitor. Secondary treatment recommendations include IL-2, ipilimumab and chemotherapy.

Consensus management of clinical response

All patients should continue their designated treatment until maximum response is reached or confirmed progression or unacceptable adverse effects occur. The assessment of response might be particularly difficult in patients receiving ipilimumab, because delayed responses have been reported.[12,40,41] These patients should be followed after treatment until evidence of clinical deterioration or confirmation of tumour progression by follow-up imaging at least 4 weeks after progression is first noted.

Literature review and analysis

There is data supporting a role for high-dose IL-2, ipilimumab and targeted therapy in the treatment of patients with stage IV melanoma. Early single-institutional and multi-institutional single-arm clinical trials of high-dose IL-2 in patients with metastatic melanoma revealed objective response rates of 16–17%, including a 6–7% complete response rate.[42,43] Further follow-up has shown 80–90% of complete responders remain alive 10–15 years later.[7] Durability and consistency of responses led to the FDA approval of IL-2 for metastatic melanoma in 1998. Ipilimumab has been evaluated in several phase I and II clinical trials and demonstrated an improvement in overall survival in patients with metastatic melanoma in two large prospective randomized phase III trials.[5,9,44,45] In a double-blind, randomized phase III trial, 676 patients with advanced-stage melanoma who expressed the HLA-A2 haplotype were treated with ipilimumab (3 mg/kg), ipilimumab (3 mg/kg) and an HLA-A2-restricted modified gp100 peptide vaccine, or vaccine alone. Patients who received ipilimumab in either treatment arm had improved overall survival compared to patients receiving vaccine alone (10 months versus 6 months; $P = 0.0026$).[5] A second randomized trial assessed 502 patients with previously untreated metastatic melanoma who were randomly assigned to receive ipilimumab (10 mg/kg) and dacarbazine (850 mg/m^2 body-surface area) or dacarbazine (850 mg/m^2) and placebo.[9] In that trial, overall survival was increased in patients who received ipilimumab (11.2 months versus 9.1 months; $P < 0.001$). The 3-year survival was also higher in patients receiving ipilimumab (20.8% versus 12.2%; hazard ratio for death, 0.72; $P < 0.001$). Ipilimumab has also been shown to have activity against CNS metastases in a phase II clinical trial.[46]

Vemurafenib was evaluated in a prospective, randomized phase III study in 675 previously untreated patients with metastatic melanoma harbouring a *BRAF*^{V600E} mutation. In that study patients were randomly assigned to vemurafenib (960 mg twice daily) or dacarbazine (1,000 mg/m^2 body-surface area every 3 weeks). A significant improvement in overall survival (hazard ratio 0.37,

P <0.001) and progression-free survival (5.3 months versus 1.6 months; hazard ratio 0.26, P <0.001) favouring vemurafenib led to FDA approval in late 2011.[6] Although combinations of the above agents are planned, there are currently no prospective data on clinical outcomes with concurrent or sequential combinations. The panel concluded there are level A and level B data supporting each drug, but no data are available to promote specific combinations or sequencing of drugs at this time.

Special issues

Clinical question: What are the special issues and clinical management recommendations in the use of immunotherapy for the treatment of melanoma?

There are a number of special issues related to clinical management of patients receiving immunotherapy. Almost all forms of immunotherapy have been associated with the development of autoimmune adverse effects.[47–58] These effects can range from asymptomatic vitiligo or autoimmune thyroiditis, to symptomatic skin, gastrointestinal, hepatic and endocrine immune-related toxic effects, as seen with ipilimumab.[47–58] The development of autoimmunity might be associated with clinical response, as a report demonstrated an association between autoimmune thyroid dysfunction and improved relapse-free and overall survival in patients with melanoma who were treated with adjuvant interferon-α2b or IL-2.[58,59] Although the panel recognizes published guidelines for the treatment of patients with interferon-α2b,[32] IL-2[60] and ipilimumab,[10] four special-issue topics were identified where there are not significant level A or level B data to guide clinical recommendations. These issues include the management of interferon-related depression, frequency of clinical laboratory monitoring and imaging during treatment and how to determine when to stop therapy (Box 2).

Consensus management of interferon-related depression

Depression and related constitutional symptoms, such as fatigue, anorexia and anxiety can be a major treatment management challenge during interferon-α2b therapy. Depression can be profound and has been associated with suicidal ideation and attempts.[61] The panel generally recommends a significant history of major depression or related psychiatric conditions be considered to be a relative contraindication to any form of interferon treatment. The majority panel opinion is to selectively use antidepressants in patients who develop depressive symptoms during treatment, which commonly occurs around 5–6 months into treatment.[61,62] A panel minority recommends prophylactic use of antidepressants before initiating treatment with interferon-α2b and some panellists suggest early referral to a psychologist or psychiatrist.

Consensus management of autoimmune-related toxic effects

Immunotherapy is associated with a range of cell and metabolic toxic effects that need to be carefully monitored during and after treatment. Special attention to the development of autoimmune-like symptoms is particularly important and these have been reported with interferon-α2b,[32,55] IL-2[57,60] and ipilimumab.[10] The panel recommends all patients be routinely assessed with thyroid function studies, complete blood counts, liver function and metabolic panels, and serum LDH tests. The majority opinion is that baseline laboratory data should be obtained on all patients treated with any immunotherapy and then weekly during induction and monthly for patients on standard high-dose interferon-α2b therapy. The panel is divided on recommendations for pegylated-interferon-α2b with two minority opinions: some panellists recommend monthly analysis and others recommend weekly for 1 month and then monthly until stable. Most panellists recommend daily laboratory analysis during IL-2 treatment and some panellists also get tests 1 week after stopping treatment. All panellists agree laboratory reports should be obtained before each ipilimumab infusion, but are divided on long-term follow-up, with some members recommending repeat laboratory analysis every 3 months for 2 years and some recommending the frequency based on individual response and side effects (Box 2).

Consensus management of imaging for patients receiving immunotherapy

The type and frequency of imaging for patients with melanoma is controversial. Since clinical responses can be delayed with some forms of immunotherapy, appropriate imaging becomes increasingly important to assure potential therapeutic benefit is confirmed. All panellists recommend whole-body imaging before all immunotherapy with a majority recommending CT scans of the chest, abdomen and pelvis and MRI of the brain. This brain imaging is particularly important as IL-2 might increase neurological sequelae in patients with CNS lesions and ipilimumab has demonstrated activity in treating CNS disease. A panel minority recommends whole-body PET or PET–CT scans. The false-positive rate for PET and difficulty providing definitive lesion measurements were reasons cited for preferring CT and MRI imaging. The panel recognizes the absence of level A data to support imaging, but the consensus of the panel was to recommend post-treatment imaging in all patients although there was a range of opinion related to frequency. For patients with stage III melanoma, re-imaging is recommended every 3 to 12 months depending on the disease-free period from diagnosis and as clinically indicated (Box 2). For stage IV patients, nearly all panellists recommend re-imaging with the majority recommending every 3 months for a 2-year period and then every 6 months until 5 years post-treatment unless there is evidence of disease progression. A minority opinion suggests imaging should be individualized to each patient.

Consensus management of clinical end points for patients receiving immunotherapy

The kinetics of response with immunotherapy might be such that delayed clinical responses can occur after treatment, and this has been documented for ipilimumab in

particular.[40,63] Some patients can demonstrate tumour growth or even the appearance of new lesions before the onset of tumour regression; therefore, some immunotherapists have suggested new clinical outcome guidelines.[11,12] These guidelines are generally endorsed by the panel; they recommend treatment with immunotherapy be stopped only after significant toxic effects occur or unequivocal evidence of disease progression. The appearance of new lesions or significant increase in tumour burden should be indicators to stop treatment with interferon or IL-2, but more caution is needed when evaluating clinical response to ipilimumab. Most panellists agree re-imaging within 1–2 months is indicated for patients with asymptomatic apparent disease progression 3 months following initiation of therapy with ipilimumab. The panel also suggests patients be considered for resection in situations where responses are mixed or incomplete following immunotherapy with some members further recommending biopsy in ambiguous cases.

Literature review and analysis

Although depression is a recognized side effect of interferon and IL-2 treatment, there are few level A data addressing the role of either pharmacological or psychoanalytical management of this condition.[3,61,62] Depressive symptoms can be dose-dependent and various mechanisms have been proposed, including decreased tryptophan levels (a precursor of 5-hydroxytryptamine), alterations in corticotropin-releasing factors, release of soluble ICAM-1, and secondary increase in permeability of the blood–brain barrier.[64–66] These hypotheses have not been confirmed.[67] A small randomized trial evaluated the non-steroidal anti-inflammatory drug indomethacin and reported no difference in depression frequency between patients who received indomethacin and placebo.[68] In a double-blind, randomized phase II trial of 40 patients undergoing interferon-α2b treatment for melanoma, the selective 5-hydroxytryptamine reuptake inhibitor paroxetine significantly decreased depression and increased the likelihood that patients completed the course of treatment as compared to patients receiving placebo.[69] The panel considers there to be level B data supporting prophylactic anti-depressant use.

There are no prospective randomized trials evaluating the role of routine laboratory monitoring or clinical imaging in patients with melanoma. Thus, only level C data are available and this has been cited as an important area for increased evidence-based research in oncology.[70] The delayed kinetics of clinical response has been documented in patients with metastatic melanoma treated with ipilimumab.[40,63] New immune-related response criteria have been developed, but require further validation.[11,12] Thus, limited level C data were considered to be available for clinical monitoring and end point assessment.

Future perspectives

The success of immunotherapy in the treatment of melanoma is expected to result in the approval and development of additional agents over the next several years. There is considerable excitement in the field for T-cell checkpoint inhibitors for cancer therapy. Programmed death 1 (PD-1) is a T-cell checkpoint molecule that is expressed on activated T cells in a manner similar to CTLA-4, the major target of ipilimumab.[71] PD-1 binds to several ligands, including the programmed death ligand 1 (PD-L1) and PD-L2. When PD-1 is engaged by its receptors, T-cell activity is suppressed and blockade of both PD-1 and PD-L1 seems to be promising for cancer immunotherapy. Early phase clinical trials of two distinct monoclonal antibodies targeting PD-1 have shown impressive clinical responses in melanoma and other cancer types, including renal cell, non-small-cell lung and ovarian cancers.[71,72] An antibody targeting PD-L1 has also shown therapeutic benefit in early clinical trials.[73] These early phase clinical studies also suggested that local PD-L1 expressed on tumour cells and on other cells within the tumour microenvironment might be part of a more-general mechanism through which PD-1-positive T cells are eliminated by established tumours; therefore, PD-L1 expression might be a potential biomarker of immunotherapy response, although this requires further prospective validation.[74] Results from a clinical trial also demonstrate that the combination of immunotherapy using an anti-CTLA-4 and anti-PD-1 antibody together resulted in a 53% objective response rate in patients with melanoma, suggesting that combinations of immunotherapy may be an important area for future investigation.[75]

In addition, there are several reports of a potent abscopal effect when ipilimumab and IL-2 were used after localized radiotherapy, suggesting that combinations of immunotherapy and standard radiation treatment might also be a possible therapeutic strategy.[76,77] Another immunotherapeutic strategy demonstrating promise is the use of an oncolytic herpes virus encoding granulocyte-macrophage colony-stimulating factor for the treatment of melanoma, and results of a randomized phase III clinical trial are awaited.[78] Another approach is to use T cells expressing modified T-cell receptors capable of recognizing tumour-associated antigens while providing T-cell activation signals upon antigen recognition. Chimeric antigen receptor T cells targeting CD19 have been tested in patients with leukaemia with promising initial results and similar trials are anticipated in melanoma.[79,80] There are other agents in clinical development and it is anticipated that more such immunotherapy strategies will be entering clinical trials in the near future.

Conclusions

Immunotherapy is an established modality for treating patients with melanoma with selected patients achieving durable therapeutic responses. These agents have unique mechanisms of action and toxicity profiles that require careful patient selection and clinical management. SITC has provided a consensus statement by a panel of immunotherapy experts and patient advocates for integrating immunotherapy into the clinical management of melanoma. The appropriate use of tumour immunotherapy can provide meaningful benefit to patients with melanoma.

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Author contributions

H. L. Kaufman, J. M. Kirkwood, F. S. Hodi and M. B. Atkins researched the data for the article and wrote the manuscript. All authors made a substantial contribution to the discussion of the content and reviewed the article prior to submission.

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