Long-term survival as a treatment benchmark in melanoma: latest results and clinical implications

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Abstract: Historically, stage III–IV melanoma patients have had few options to achieve long-term survival. For patients with stage III disease, surgery alone may be curative for approximately 50%. Adjuvant treatment with a slightly greater impact on relapse-free survival at the cost of substantial toxicity, and studies are ongoing to test the adjuvant benefit of other immunotherapies that appear more active and less toxic in advanced melanoma. Achieving long term survival for stage IV patients had been rare until recently and progress was painfully slow with traditional cytotoxic chemotherapy; review of multiple phase II studies showed universally poor results. Fortunately, since the approval by the US Food and Drug Administration of agents targeting the cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor, as well as those targeting B-raf and mitogen-activated protein kinase kinase (MEK) in the mitogen-activated protein kinase (MAPK) pathway for patients whose melanoma is ‘driven’ by a BRAF mutation, long-term survival of stage IV melanoma is increasing substantially. Here we review the examples of studies documenting potentially curative approaches to melanoma and propose suggestions for the use of various treatments in achieving this important goal.

Keywords: melanoma, immunotherapy, targeted therapy, b-raf, ipilimumab, nivolumab, pembrolizumab, vemurafenib, dabrafenib, trametinib

Historical background

Starting in the 1980s, highly selected patients treated with high-dose interleukin-2 (IL-2) could achieve durable remissions, and combinations of IL-2, interferon- α (IFN- α) and cisplatin-based combination chemotherapies showed high overall response rates with some durable remissions [Atkins *et al.* 1999; Bedikian *et al.* 2008]. Unfortunately, the therapeutic index of both approaches is poor, and in particular, biochemotherapy has proven less active than originally reported [Atkins *et al.* 2008]. While high-dose IL-2 is still used in some centers and current series suggest selected clinical factors associated with more favorable outcomes [Payne *et al.* 2014], IL-2 as a single agent has for the most part been replaced by other forms of immunotherapy with a more favorable therapeutic index. Multiple phase II studies have been conducted in search of other active agents for melanoma during this era, but produced disappointing results (Korn *et al.* 2008). Surgery for oligometastatic stage IV disease does provide durable disease control in a fraction of

patients, but identifying patients prospectively for enhanced surveillance based on risk factors with the goal of early detection of metastatic lesions resectable for curative intent is another challenge requiring further investigation. Furthermore, it may eventually be possible to identify different markers of risk that lead to different approaches. For example, frequent scanning to identify surgically resectable disease *versus* the use of a circulating biomarker that identifies patients more likely to benefit from adjuvant or systemic interventions before the development of more overt signs of metastatic disease.

Adjuvant treatment may represent the best opportunity to cure patients after surgery and to prevent morbidity from progression

Following surgery for melanoma with a high risk of relapse and death [many patients from stage IIB (>4 mm Breslow depth) and most from IIIA through IIIC], melanoma patients currently have two treatment options approved by the US Food

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and Drug Administration: high-dose IFN- α (HDI) and pegylated IFN (PEG-IFN) (PEG-IFN is approved for patients with nodal metastasis only). The patterns of relapse in this population show that 51% of the relapses occur at distant sites [Romano *et al.* 2010], so treatment to delay relapse can be a significant benefit to patients, even if the therapy does not increase long-term overall survival (OS). Curing patients in this population at high risk for relapse and death ideally would require the pretreatment ability to identify which patients are destined for relapse (prognostic information) and, among those at highest risk, who will benefit from a particular adjuvant intervention (predictive characteristics) which may relate to patient, tumor and therapy.

To answer the first question, years of work have been devoted to evaluating clinical and pathologic risk factors related to the primary melanoma, and the presence or absence of tumor in draining lymph nodes, which is the single most important determinant of survival. The current American Joint Committee on Cancer (AJCC) staging system recognizes the importance of ulceration of the primary tumor, mitotic rate, and the number and size of tumor bearing lymph nodes [Balch *et al.* 2009, 2010]. Further refinement of this system is needed, because even with a full knowledge of all of these factors, many patients defined as high risk by AJCC criteria are likely cured by surgery and may be receiving adjuvant therapy for no benefit.

The potential for using molecular classifications to define risk is best exemplified in uveal melanoma based on gene expression profile data, where 459 patients were followed prospectively after surgery. Gene expression profiling segregated tumors into class 1 with a very low 1.1% incidence of developing distant metastasis at a mean follow up of 18 months, compared with patients with a class 2 tumor who experienced a relapse rate of 25.9% over the same time interval [Onken *et al.* 2012]. Surveillance of these patients included blood testing of liver functions every 6 months and liver imaging [usually computerized tomography (CT) with contrast] at 1 year intervals, but the contribution of surveillance to OS is not clear, since therapy for uveal melanoma with distant relapse has rarely been associated with prolonged survival. Several groups are further developing expression assays in cutaneous melanoma, which may soon prove to be useful tools in addition to the AJCC risk stratification presently in use.

With regard to which characteristics will identify patients most likely to benefit from treatment, a predictive biomarker is presently lacking for FDA approved treatment options. High dose IFN- α is the best studied treatment for patients with high risk resected melanoma with three completed multicenter US intergroup trials: E 1684 [Kirkwood *et al.* 1996]; E1690 [Kirkwood *et al.* 2000]; and E1694 [Kirkwood *et al.* 2001]. These studies showed a consistent benefit in relapse-free survival (RFS), and two of the three studies showed an OS benefit when compared with an inactive control (1684 *versus* observation, and 1694 *versus* a ganglioside vaccine). Other dosing regimens of IFN- α -2b have also been studied, and in a meta-analysis of data from over 10,000 patients who participated in studies of adjuvant IFN- α with a 'no treatment' comparator cohort, a RFS benefit [hazard ratio (HR) 0.83 (0.78–0.87)] and OS benefit [HR 0.91 (0.85–0.97)] were reported [Mocellin *et al.* 2013].

Polyethylene glycol-conjugated PEG-IFN- α has also been studied in the adjuvant setting and received FDA approval for stage III melanoma following report of the European Organisation for Research and Treatment of Cancer (EORTC) trial demonstrating a relapse free survival benefit [HR = 0.82 (0.71–0.96) at 3.8 years follow up, and HR = 0.87 (0.76–1.00) at 7.6 years follow up] without OS benefit [Eggermont *et al.* 2008, 2012]. However, retrospective subset analysis revealed that patients who had ulcerated primary lesions and microscopic nodal disease derived the most benefit, including significantly improved survival [Eggermont *et al.* 2012], and a subsequent study [ClinicalTrials.gov identifier: NCT01502696] was designed to confirm those findings. Confirmation about whether ulceration is also useful as a predictive marker for high-dose IFN- α may come from the ongoing intergroup study investigating IFN in comparison with ipilimumab (E1609) [ClinicalTrials.gov identifier: NCT01274338]. While retrospective subgroup analyses do not provide sufficiently robust data for the identification of predictive biomarkers of benefit, they often provide hypothesis-generating data that can then be tested prospectively in confirmatory trials.

Other recent adjuvant trials for high risk melanoma include the US cooperative group study of biochemotherapy *versus* high-dose IFN- α (S0008); an earlier US cooperative group trial (E4697) investigating the immunomodulatory

effects of granulocyte-monocyte colony-stimulating factor (GM-CSF); a melanoma antigen (gp-100)-derived peptide vaccine (this study included patients with fully-resected oligometastatic melanoma); and most recently, a placebo-controlled trial of a different melanoma antigen (MAGE-A3, GDK-2132231A) [ClinicalTrials.gov identifier: NCT00796445]. The vaccine trials and the GM-CSF study have thus far failed to produce a meaningful benefit. However, the biochemotherapy study did show some intriguing results. Biochemotherapy was selected as a potentially better option for eradicating micrometastatic disease owing to its higher response rate in stage IV cancer (30–50% *versus* 15% for HDI). The RFS advantage of 2 years median for biochemotherapy in comparison with HDI does corroborate that extrapolation, but the lack of OS benefit similarly mirrors the experience in advanced melanoma, where the pooled data demonstrate that increasing the objective response rate fails to enhance survival [Atkins *et al.* 2008].

The most recently reported data were from a global adjuvant trial of ipilimumab *versus* placebo which remarkably mirrored the PEG-IFN- α data in demonstrating an overall RFS advantage and a strong association of benefit with ulceration of the primary melanoma [Eggermont *et al.* 2014]. Further investigation of the immunologic correlates of ulceration that explain this association with favorable adjuvant therapy outcomes may lead to better patient selection for individual types of adjuvant therapy and, importantly, for those who cannot benefit or who do not need adjuvant therapy. The potential for long-term OS benefit will also require both longer follow up and a careful assessment of the effects of subsequent therapy on patients who relapse. However, rapid developments in the field of immune checkpoint blockade for melanoma have already permitted the development of the next important adjuvant trial, which will compare the PD-1 blocking antibody, pembrolizumab, with HDI for patients with resected melanoma at high risk of relapse (S1404). In parallel, the molecularly-targeted agents that have shown important activity in advanced disease are also under evaluation in the adjuvant setting for patients with BRAF-mutated melanoma; due to their distinct mechanisms of action and toxicities, these agents are being compared to placebo rather than IFN (vemurafenib *versus* placebo [ClinicalTrials.gov identifier: NCT01667418] and dabrafenib plus trametinib *versus* placebo [ClinicalTrials.gov identifier: NCT01682083]).

Ipilimumab

Ipilimumab is the first drug in the history of systemic therapy for melanoma to demonstrate an OS advantage in a randomized controlled trial in patients with metastatic melanoma [Hodi *et al.* 2010]. The toxicity of the drug, although significant, has well-established management algorithms, making it a generally safe and effective front-line treatment for stage IV melanoma [Weber *et al.* 2012]. Response rates to the drug have been modest (10–15%), but the achievement of long-term progression-free survival (PFS) among patients whose best response is stable disease rather than objective response has led to the concept of a ‘disease control rate’ based on the sum of the rate of objective response plus stable disease at the time of first post-therapy assessment and beyond [Wolchok *et al.* 2009]. Long-term follow-up data of the patients treated in the phase II program of ipilimumab demonstrate that, in treatment-naïve patients treated at the highest dose of ipilimumab (10 mg/kg), 37.7–49.5% of patients were living 4 years or longer [Wolchok *et al.* 2013b]. Experience with the drug in 833 patients in the Italian expanded access program, which was less stringent in terms of patient eligibility, showed that although the median PFS and OS were 3.7 and 7.2 months, respectively [Ascierto *et al.* 2014b], a very encouraging long RFS plateau around 20% was reported. This important benchmark appears to be a plateau in the PFS curve, suggesting that patients who achieve PFS at the inflection point of 2.5–3.0 years may not relapse and may effectively be cured of their melanoma. While there remains a possibility that aftertherapies such as surgery for residual oligometastases contributed to durable control, the role of ipilimumab seems incontrovertible in the ultimate success of preventing these patients’ death from advanced melanoma.

Although clearly exciting, the low overall clinical benefit rate and the notoriously slow or delayed regressions of metastatic melanoma in patients treated with ipilimumab, together with the advent of mutation-directed molecularly targeted agents, have led to the development of combination regimens designed to exploit both immunologic and molecularly directed mechanisms of antitumor activity. Unfortunately, the toxicity of ipilimumab has made it difficult to combine with the B-raf inhibitor vemurafenib [Ribas *et al.* 2013] or with the cytotoxic agent dacarbazine [Robert *et al.* 2011]. In both cases, there was an increase in the frequency of high-grade hepatotoxicity, which is a

very low frequency event with any of the single agents. Furthermore, the addition of dacarbazine did not appear to increase the activity of ipilimumab or downmodulate any of the other toxicities, making this an unattractive combination. Combining molecularly targeted drugs with other immunomodulators for advanced disease continues to be an active area of investigation: dabrafenib +/- trametinib plus ipilimumab [ClinicalTrials.gov identifiers: NCT01767454, NCT01940809, NCT02200562]; and vemurafenib plus IL-2 [ClinicalTrials.gov identifiers: NCT01683188, NCT01754376].

Long-term survival on targeted therapy

Approximately half of cutaneous melanomas (40–60%) harbor a B-raf mutation [Davies and Samuels, 2010]. In the first reports of clinical activity, response rates were impressive for both vemurafenib (FDA approved in 2011) [Flaherty *et al.* 2010; Sosman *et al.* 2012], and dabrafenib (approved in 2013) [Ascierto *et al.* 2013]. Longer term follow-up data are maturing for the randomized trial comparing vemurafenib with dacarbazine in patients with unresectable stage IIIC or IV melanoma with a *B-raf* mutation. The first report of this trial showed significant improvements for both OS and PFS [Chapman *et al.* 2011]. Given the 44% crossover from dacarbazine to vemurafenib, longer term follow up was needed to estimate the impact of this effect. Uncensored data show that the 18 month OS was 39% [95% confidence interval (CI) 33–45] in the vemurafenib group and 34% (95% CI 29–40) in the dacarbazine group [McArthur *et al.* 2014]. Although the difference seen in this subset analysis small, it is statistically significant (HR 0.76, 95% CI 0.63–0.93, $p = 0.0068$).

This crossover impact suggests that patients can be rescued with highly active treatment following progression, but the lower OS associated with this sequencing, together with the likely morbidity of progression events, toxicities and time to recover from cytotoxic therapy before targeted therapy, makes targeted therapy a better first choice in strategies to achieve long-term survival. What is very encouraging about the longer term follow up is that there appears to be a subset of patients who are surviving out to 2 years (>20%). The characteristics of these long-term survivors are not known yet, but are under intense investigation focused on characteristics of patient, tumor and

treatment, including the contribution of post progression therapies to long-term survival.

One concern about the use of single agent B-raf blockade is the multitude of resistance mechanisms that evolve on therapy [Bucheit and Davies, 2014]. This leads to PFS times for vemurafenib and dabrafenib of approximately 6 months [Chapman *et al.* 2011; Hauschild *et al.* 2012]. Combining B-raf and mitogen-activated protein kinase kinase (MEK) blockade, using the oral agent trametinib has led to improved PFS and OS in a randomized trials; PFS 9.4 months with combination dabrafenib/trametinib, *versus* 5.8 months in the dabrafenib monotherapy group, and OS at 12 months 72% combination *versus* 65% vemurafenib alone (HR 0.69; 95% CI 0.53–0.89) [Flaherty *et al.* 2012; Robert *et al.* 2015a]. A recently completed phase III placebo-controlled randomized trial also showed an improved PFS (HR 0.75, $p = 0.035$) in favor of dabrafenib plus trametinib in comparison with dabrafenib alone as first-line therapy [Long *et al.* 2014]. The combination of dabrafenib and trametinib were granted accelerated approval for the use in patients with advanced B-raf V600 mutated melanoma in January 2014. Similar results have been seen with vemurafenib and cobimetinib (a second MEK inhibitor) combinations that have similar mechanisms but a slightly different toxicity spectrum; PFS 9.9 months combination *versus* 6.2 months vemurafenib; OS 9 month OS 81% *versus* 73% (HR = 0.65; 95% CI 0.42–1.00) [Larkin *et al.* 2014]. There are also newer investigational agents undergoing testing to overcome mechanisms of resistance and the emergence of a successful regimen from these studies is likely to provide further survival benefits to selected patients.

PD-1 blockade

Patients treated with targeted drugs first, followed by immunotherapy upon disease progression, appeared to benefit to a lesser extent and to experience greater toxicities than those receiving immunotherapy as their first treatment. The data demonstrating this phenomenon [Ackerman *et al.* 2014; Ascierto *et al.* 2014a] may reflect a bias in the assignment of patients with more aggressive disease to initial targeted therapy due to its high response rate and rapid action. Immunotherapies that have been available so far (high-dose IL-2 and ipilimumab) benefit only a small fraction of patients and have a very unfavorable (IL-2) or moderately unfavorable (ipilimumab) therapeutic index.

However, recent advances in the understanding of immune checkpoint blockade have led to the development of a class of fully human or humanized antibodies that interrupt a different, more tumor-specific checkpoint. So far, these agents, which block either programmed death-1 (PD-1) mediated negative signaling on 'exhausted' T cells or its main ligand, PD-1 ligand (PD-L1) on tumor and/or stroma, appear to have higher activity, lower toxicity and the potential for synergy with cytotoxic T lymphocyte antigen-4 (CTLA4) blocking antibodies.

Nivolumab, targeting PD-1, has provided objective response rates of approximately 30% in stage IV melanoma [Topalian *et al.* 2012]. When used in the front-line setting, it has also shown an improvement in OS in comparison with dacarbazine in B-raf wildtype patients (HR 0.42, $p < 0.001$) [Robert *et al.* 2015b]. A second PD-1 antibody, pembrolizumab, has also shown similar results with a response rate of 38% across all dose levels in a phase I study focusing on melanoma patients [Hamid *et al.* 2013]. It was data from this large phase I study ($n = 411$) that led to the FDA approval of pembrolizumab in patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if B-raf V600 mutation positive, a B-raf inhibitor. Recent updates have confirmed the response rate and durability of pembrolizumab with 1 year OS being reached in 71% of all patients enrolled [Ribas *et al.* 2014]. Nivolumab shows similarly encouraging longer term follow-up data with 2 and 3 year OS rates of 48 and 41%, respectively [Hodi *et al.* 2014]. Nivolumab was also granted FDA approval in December 2014 for the same indication as pembrolizumab (see above).

In these landmark studies, the antitumor response also appears more quickly following initiation of therapy than has been observed with CTLA4 blockade, which often takes 12–24 weeks before tumor regression or confirmed stabilization is achieved; furthermore some patients will experience tumor progression prior to responding to ipilimumab [Wolchok *et al.* 2009] and only with delayed follow up will demonstrate tumor regression – a problem in both assessing the activity of the agent using traditional criteria and in the clinical management of such patients. With nivolumab and pembrolizumab, most responses are apparent within 6–8 weeks, and most responding patients remain free of progression beyond 1 year; 13 of 18 responses to nivolumab were ongoing at 1

year, while among the patients responding to pembrolizumab, a median response duration had not been reached at 11 months' follow up. Importantly, over half of the patients whose disease had progressed on prior ipilimumab experienced clinical benefit (objective response or disease stabilization) with pembrolizumab (21/29 patients). Both reagents have similarly favorable toxicity profiles with <12% Gr3/4 adverse event (AE) rates, which supports the safety and feasibility of combining PD-1 blockade with other agents and suggests that these combinations will be safer and more effective than ipilimumab-based combinations. Results of combining ipilimumab with nivolumab have shown high response rates (53%), but high-grade toxicities, generally inflammatory/autoimmune in nature, have also emerged in about half of the patients treated with the doses that provided the highest disease control rates [Wolchok *et al.* 2013a]. Longer follow up from large ongoing and other planned trials will better demonstrate the contribution of PD-1 blockade to long-term survival of melanoma patients and where this form of therapy best fits in the treatment algorithm.

High-dose IL-2

High-dose IL-2 remains an important treatment option for patients with stage IV melanoma that has been available for many years to selected patients at experienced centers. The most recently published update on the activity of IL-2 from a multicenter experience showed that in melanoma, the response rate was about 16%, with long-term survival in approximately 10% of the patient population [Atkins *et al.* 1999]. Patients with melanoma and residual single lesions of unknown nature have often undergone excision, which may have contributed to long-term RFS, and while a few patients relapse from radiologic complete response, there are additional patients with radiologic partial response who never relapse. A recently published single institution experience with 314 melanoma patients among the 500 total (the others had renal clear cell cancer) reported 23% of patients alive at least 5 years beyond treatment with high-dose IL-2 [Payne *et al.* 2014]. Unfortunately there is, to date, no biomarker or group of parameters that can help to select patients for a higher therapeutic index (either more likely to benefit or less likely to experience toxicities), although a recently completed 170 patient Cytokine Working Group protocol to identify such factors is likely to provide important insights in 2015.

Table 1. Update of current melanoma treatment options for adjuvant therapy and metastatic disease.

	Practice impacting	Trial design consideration-control arm	Endpoint RFS/PFS versus OS	Capable of impacting long-term survival
Adjuvant therapy				
High dose IFN	Yes for stage III	Yes	RFS and OS seen consistently in stage IIB–III	Yes
PEG-IFN	Yes for stage III	Yes	RFS benefit maintains relevance considering prevention of morbidity from relapses in node positive patients	No
Metastatic disease				
Ipilimumab	Yes	Yes, will be good control arm for second line studies following approval of PD-1	Durable OS benefitPFS benefit	Yes
High dose IL-2	Yes	Phase II combination studies needed to improve response rate	Durable OS benefitQuestionable PFS benefit	Yes
TIL (tumor infiltrating lymphocytes)	Yes	Not a good control arm, Further work to decrease toxicity necessary	PFS benefit modestDurable OS benefit likely	Single institution studies suggest yes, accessibility remains a problem
PD-1 blockade	Yes	Yes, should be new control arm for front line phase III trials for stage IV patients, and will likely be impactful experimental arm in Stage III patients	Significant PFS and OS benefit seen	Yes, significant, should become the new standard front-line therapy for melanoma patients upon FDA approval
Targeted therapy #vemurafenib #dabrafenib #combination	Yes	Yes, but must establish whether this is best prior to or after immune therapy	PFS and OS both positive	Probably, but longer term follow-up data needed.
Carboplatin/paclitaxel	Yes	No	Unknown	Unlikely
DTIC/ temozolomide	Yes, but more recent data less compelling	No	Unknown	Unlikely
DTIC, dacarbazine; FDA, US Food and Drug Administration; IFN, interferon; OS, overall survival; PD-1, programmed death 1; PEG-IFN, pegylated interferon; PFS, progression-free survival; RFS, relapse-free survival.				

Surgery for resectable melanoma

Surgery remains the most well established treatment for patients with melanoma up to stage III disease and may even be appropriate for selected patients with oligometastatic disease. No treatment presently available should replace surgical resection as the first, curative-intent therapy for

locoregional disease eradication (Table 1). Surgery alone for stage IV melanoma patients in an era with few systemic options has been reported to provide long-term survival in a substantial fraction of patients. Ollila reviewed the data from previously published single-institution series and concluded that 5 year survival following resection

for stage IV melanoma could be achieved in 5–38% of patients with skin, soft tissue and lymph node metastasis, 4.5–27% of patients with pulmonary metastasis, and 28–41% of patients with metastatic disease to the GI tract [Ollila, 2006]. Interpreting these data is difficult given the following issues: (1) patient selection bias and for the institutional variations in surgical procedures and postsurgical surveillance methods and timing; (2) the lack of a method to control for nonsurgical treatments received prior to and after surgery; and (3) no nonsurgical comparator series in which some patients were randomized to receive nonsurgical therapy, which in some eras could have ranged from best supportive care or single-agent chemotherapy to aggressive biochemotherapy or high-dose IL-2, and in the present era could include any one or more of the wide variety of systemic therapies detailed above.

The first efforts at controlling for at least some of these variables were demonstrated in the report of the multicenter controlled study SWOG 9430, in which 77 patients were entered prospectively and described in detail [Sosman *et al.* 2011]. Reported characteristics included presurgery performance status, use of systemic therapy and radiation, and standardized staging techniques. Patients enrolled in S9430 had a median OS of 21 months, and at 4 years, 31% of the patients were alive. These results were achieved in a population which was uniquely favorable in having predominantly non-visceral sites of metastasis (69%).

Another retrospective study in the relatively recent era reported the long-term survival of patients originally participating in the Multicenter Sentinel Lymph Node Trial-1, which randomized patients 3:2 to undergo sentinel lymph node biopsy or observation following primary melanoma excision [Howard *et al.* 2012]. Among the 291 patients who relapsed at a distant site, approximately half (161) underwent surgical resection to no evidence of disease (NED) status, with or without additional systemic therapy. This subset of patients enjoyed a significantly higher 4 year survival (21%) than those who received only systemic therapy without further surgery (7%). While the original study population had surgery in a prospectively randomized assignment, the decision to pursue surgery in this subsequent group of relapsers was based on operability as well as a number of other clinical factors, thus invalidating any direct comparison between the surgical and nonsurgical groups. However, the value of this report remains high since the surgical

subset from this series may turn out to be the last and largest multicenter dataset available to inform understanding of the impact of surgery outside the setting of modern effective systemic therapy.

Surgery as the first option for treatment of oligometastatic melanoma is still worthy of consideration, even with modern systemic therapies. In their review, Sondak and Gibney point out that the complete response rate to surgery in stage IV cancer is 90% (the highest complete response rate in any stage IV trial) [Sondak and Gibney, 2014]. However, the average PFS is only 5 months in the SWOG series, which prospectively identified patients who on clinical grounds were felt *most likely* to achieve a status of NED following surgery. This observation was a further grim reminder that any pattern of metastasis in stage IV melanoma patients is likely to be hematogenously spread and rarely amenable to cure by resecting all detectable macroscopic metastases.

It seems likely that for those who have prolonged PFS following surgery, tumor biology is in their favor; they must have tumors that metastasize once, but do not maintain metastatic potential beyond their final resting place. Debulking surgery may have OS impact but no PFS benefit if an alternate model of tumor spread is considered, i.e. metastasis begets more metastasis. In this patient, removal of a perpetually seeding clone of tumor may offer long-term survival benefit.

Many scenarios now occur where front-line therapy for responding patients eradicates all but a few disease sites. Furthermore, some patients experienced so-called mixed responses featuring different progression in one or more sites while responding at all other sites of metastatic disease, making surgery to remove the resistant and relapsing clones an attractive option to consider. Proof of principle for this practice may come from the data on longer term follow up of completed [Koers *et al.* 2013], ongoing, and proposed neoadjuvant studies investigating modern systemic treatment where patients are resected to NED for advanced melanoma. Until these studies mature, surgery remains a highly valuable modality, although the precise clinical settings in which oligometastatic disease should be considered for resection remain without rigorous evidence-based guidelines.

Other important therapeutic considerations and future directions

As our systemic therapies advance in their disease control rates, the late appearance of brain

metastasis has become an increasing problem. Metastasis to the brain, and more rarely to the leptomeninges, not uncommonly ends a remission [Mitchell, 1989], and the biological mechanisms for this CNS escape remain under investigation. Long-term survival for patients with brain metastasis is achievable but requires a multidisciplinary approach that may include radiation (especially stereotactic forms of radiosurgery) and surgery [Long and Margolin, 2013; Ramakrishna and Margolin, 2013]. Although many of the drugs and antibodies described in this review may not cross an intact blood–brain barrier with great efficiency, responses of melanoma brain metastases have been reported with both the BRAF inhibitors [Long *et al.* 2012] and ipilimumab [Margolin *et al.* 2012] at frequencies similar to their activity in extracranial disease.

For ipilimumab, several important studies are reported: (1) an open-label phase II trial with two cohorts, one requiring steroids for symptom control ($n = 21$), the other not ($n = 51$); (2) a subset analysis of the US expanded access study for patients with asymptomatic brain metastasis ($n = 165$) [Heller *et al.* 2011]; and (3) a subset analysis of the Italian expanded access program for patients with asymptomatic brain metastasis ($n = 146$) [Queirolo *et al.* 2014]. For patients requiring no steroids at study entry, it is encouraging to note that 1 and 2 year OS rates were 31% and 26%, respectively. For patients on the US expanded access protocol, OS rate at 1 year was 20%, which was similar to the Italian experience (1 year OS = 20%).

Combining ipilimumab with drugs known to cross the blood–brain barrier such as temozolomide [ClinicalTrials.gov identifier: NCT01119508; accrual complete, final results pending] or fotemustine [Di Giacomo *et al.* 2012] have also been studied in melanoma. Fotemustine plus ipilimumab demonstrated a reasonable safety profile in the 20-patient subset of the 86-patient Italian multicenter trial NIBIT-M1, as well as showing at least stable or reduced central nervous system (CNS) disease from baseline imaging (50%, 95% CI 27.2–72.8) among 10 of the 20 patients with asymptomatic brain metastasis [Di Giacomo *et al.* 2012]. The ipilimumab and fotemustine combination is presently being further studied in a randomized phase III trial for patients with brain metastasis which was designed to compare fotemustine alone with the combination of ipilimumab and fotemustine, but has now added another treatment cohort

treated with ipilimumab plus nivolumab [EudraCT Number: 2012-004301-27].

Regarding the mechanisms for brain metastasis control by agents not expected to cross the physiologic blood–brain barrier, two principles are likely at work. First, tumor directed lymphocytes may transit from the circulation into the brain. Second, the blood–brain barrier may be focally disrupted at the site of the tumor, or be disrupted by the use of radiation allowing better access of drugs into the brain–metastasis microenvironment. Better guidelines for managing this critical disease site require well-designed studies focused on patients with CNS disease. In addition to the encouraging results from the trials mentioned above, several other studies are ongoing or in development that include further investigation of both the molecularly targeted agents and current immunotherapeutic agents.

For treatment of patients who do not achieve durable remission from any of the strategies outlined earlier or from other investigational therapies, it is unlikely that available, approved agents will provide long-term disease control. However, one of the most promising strategies has been the use of adoptive cell therapies derived from tumor infiltrating lymphocytes (TIL), which have shown gratifying activity in patients with melanoma refractory to one or more of the standard or other investigational therapies. Although this form of autologous adoptive T-cell therapy has been under investigation since the 1980s [Lizee *et al.* 2013; Weber, 2014]), it was almost exclusively provided at the Surgery Branch of the US National Cancer Institute and thus limited to a very small number of patients. However, improvements over the succeeding years and the recent development of similar programs at select other US centers (National Institutes of Health, Moffitt and the MD Anderson Cancer Center), as well as in Israel and Denmark, have led to reports of objective responses in up to half of all patients receiving treatment, and many of these responses are continuing beyond one year of follow up [Weber, 2014]. To take this technology to the next level would require expansion of the treatment to more investigative centers to perfect and extend the techniques or to utilize a commercial supplier for TIL that are produced and quality controlled centrally from a carefully handled portion of resected tumor and then shipped back to be administered at a center closer to the patient's home where the treating team has experience in

the management of high-dose chemotherapy, therapeutic immune cell infusions and a course of high-dose IL-2.

It is truly exciting to be treating melanoma in the year 2014 with therapies now capable of reliably offering long-term survival as an outcome. With promising new drugs approved, and many more on the near horizon, it is not unreasonable to expect as many as half of all patients with stage IV melanoma to be cured, so that efforts can be increased to understand and overcome the obstacles to cure of the remaining patients.

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