Frontline Approach to Metastatic BRAF-Mutant Melanoma Diagnosis, Molecular Evaluation, and Treatment Choice

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OVERVIEW

An estimated 76,100 patients will be diagnosed with invasive melanoma in the United States in 2014, and 9,710 patients will die from the disease. In almost all cases, the cause of death is related to the development of widespread metastatic disease. Although death rates from most types of cancer have steadily decreased in the United States—a 20% decrease during two decades from a peak of 215.1 deaths per 100,000 population in 1991 to 171.8 in 2010—death rates from melanoma have steadily increased during the same time, especially among males. The news regarding melanoma is far from all bad. Increases in our understanding of the human immune system have led to the development of new immunotherapeutic drugs such as ipilimumab, which has been shown to improve survival in phase III trials in metastatic melanoma, and anti-programmed death 1 (anti-PD1) antibodies, recently hailed by ASCO as one of the past year’s most noteworthy clinical cancer advances. However, no discovery has influenced and, indeed, transformed the management of metastatic melanoma more than the identification of activating mutations in the BRAF gene in the mitogen-activated protein kinase (MAPK) pathway, which occur in about half of cutaneous melanomas and can be targeted with small molecule inhibitors of the BRAF protein, the downstream MEK protein, or both. This article will address how patients with metastatic melanoma are evaluated for their mutation status and how the presence of a targetable mutation influences therapeutic decisions regarding systemic therapy and even surgery.

INITIAL WORK-UP OF METASTATIC MELANOMA

The first step in evaluating patients with known or suspected metastatic melanoma (stage IV) is to define the extent and sites of disease. A CT scan of the chest, abdomen, and pelvis is a good starting point. Some patients and physicians may be concerned about radiation exposure, in which case an abdominopelvic MRI can be substituted for the abdominopelvic CT. Although this adds expense, it decreases the overall radiation exposure from approximately 17 mSv to approximately 7 mSv. Given the risk and therapeutic significance of central nervous system metastases, it is also appropriate to obtain imaging of the brain with either MRI (preferred) or CT. Some oncologists rely on 18F-fluorodeoxyglucose (FDG) PET-CT scans to define the extent of disease and there are some studies to support this, especially in patients who are being evaluated for possible resection of oligometastatic disease. 18F-FDG PET-CT scans offer full body imaging with slightly decreased radiation exposure compared with CT.
scans of the chest/abdomen/pelvis. Clinicians should be aware, however, of certain drawbacks of 18F-FDG PET-CT scans. First, there is a substantial rate of false-negative in the lung, leading some clinicians to include a noncontrast lung CT scan with the PET scan. This results in total radiation exposures similar to that for a full body CT scan. Second, tumor dimension measurements generally cannot be made reliably from a PET scan, leading to the need to eventually perform a full body CT scan to monitor response to therapy, although newer PET-CT scanners can offer high-resolution CT images. Third, 18F-FDG PET-CT scan results do not correlate reliably with clinical effects in patients being treated with BRAF inhibitors; melanoma FDG uptake will nearly always decrease with BRAF inhibitor treatment whether or not there is substantial tumor shrinkage. Hence, PET scans should not be relied on to follow clinical response in these patients.

GENETIC EVALUATION

The next step in the work-up of metastatic melanoma involves determining whether or not the tumor harbors a BRAF mutation. This is now standard. One of the first considerations is which tumor sample should be tested. Can the primary melanoma be tested or should the genetic analysis be done on a metastasis? This raises the question of tumor heterogeneity. How often does the primary melanoma reflect the genetic changes seen in the metastases? One of the largest studies to date found that among 99 patients with paired primary and metastatic melanoma tissue available, 15% showed discordance, with the highest discordance rates observed between primary melanomas and metastases to brain or skin. It appears nearly equally likely as the converse observation between primary melanomas and metastases to lung, leading some clinicians to include a noncontrast lung CT scan with the PET scan. This results in total radiation exposures similar to that for a full body CT scan. Second, tumor dimension measurements generally cannot be made reliably from a PET scan, leading to the need to eventually perform a full body CT scan to monitor response to therapy, although newer PET-CT scanners can offer high-resolution CT images. Third, 18F-FDG PET-CT scan results do not correlate reliably with clinical effects in patients being treated with BRAF inhibitors; melanoma FDG uptake will nearly always decrease with BRAF inhibitor treatment whether or not there is substantial tumor shrinkage. Hence, PET scans should not be relied on to follow clinical response in these patients.

KEY POINTS

- Dramatic recent advances in the management of metastatic BRAF-mutant melanoma have significantly improved outcomes for patients with the disease.
- For now, the best approach begins with a thorough evaluation the extent and resectability of the patient’s metastatic disease and involves a multidisciplinary decision-making process that takes into account the disease burden and symptomatology, the kinetics of tumor progression, and, above all, patient preferences.
- Not every patient with unresectable metastatic BRAF-mutant melanoma will initially receive kinase inhibitor therapy when that approach is used in today’s environment.
- During the next few years we are likely to see changes in how frequently surgery and immunologic therapies are used in front-line management of metastatic BRAF-mutant melanoma.
**Immunohistochemistry.** BRAF V600E mutant protein can be detected by immunohistochemical staining using the VE1 antibody. The advantages of this method are that only two slides are needed (one for staining and one for hematoxylin and eosin), turn-around time is extremely rapid, no specialized equipment is needed, and the analysis can be done on fine-needle aspirates. Sensitivity and specificity for the BRAF V600E mutation were reported to be high, 97% and 98%, respectively, and even found some mutant cases that had been missed by standard testing. Two disadvantages are that the assay is not yet FDA-approved and the VE1 antibody is highly specific for the V600E mutant protein. Other clinically relevant BRAF mutations are not detected.

**Future genetic tests.** Plasma from patients with melanoma contains low levels of circulating tumor-derived DNA, and BRAF V600E mutations can be detected in blood samples using current PCR technology. This approach may provide insights about genetic changes occurring as a result of therapy, and may provide a biomarker of tumor burden. New technologies are being developed to carry out detailed genetic analyses on single cells. This may allow the use of circulating tumor cells for genetic analyses and provide true “liquid biopsies.”

**PROGNOSTIC SIGNIFICANCE OF BRAF MUTATION IN METASTATIC MELANOMA**

BRAF mutation status is an extraordinarily powerful predictive factor for BRAF inhibitor treatment of metastatic melanoma, given the high response rates for patients whose metastases harbor BRAF V600E mutations, the absence of response and possibility of stimulating tumor growth among patients whose metastases possess wild-type BRAF genes, and the intermediate situation (some responses but generally at a lower frequency) for patients whose metastases harbor BRAF mutations other than the most common V600E mutation. The actual prognostic significance of BRAF mutation status in localized or metastatic melanoma is less clear, and to date largely assessed only in retrospective studies. Several important biases can influence such retrospective attempts to evaluate a biomarker like mutation status, such as the fact that very small tumors (which likely have the best prognosis) may not yield enough tumor DNA to obtain accurate mutation data whereas larger, higher-risk tumors are readily analyzed. Hence, it is not surprising that available data on this topic are inconsistent but suggest a possible adverse prognostic effect for tumors harboring BRAF mutations, whether localized primary tumors, regionally metastatic cases or distant metastases are considered.

Further research on the topic is clearly warranted, ideally in the setting of prospective evaluations. At present, it seems premature to base decisions about prognosis solely based on BRAF mutation status.

**FRONTLINE TREATMENT OPTIONS FOR UNRESECTABLE METASTATIC BRAF-MUTANT MELANOMA**

Once a patient is identified as having metastatic melanoma that harbors a BRAF V600 mutation, additional information is required before deciding on the best course of front-line treatment. Patients with solitary or limited metastasis should be evaluated for resection. Immunotherapy, whether with interleukin-2 (IL-2), ipilimumab, or on clinical trials involving anti-PD1 antibodies, may be the appropriate first course of treatment for some cases of BRAF-mutant melanoma, whereas kinase inhibitors as single agents or in combination would be ideal for others. With the availability of more therapeutic options, treatment decisions are becoming more complex and continue to evolve.

**ADVANTAGES AND DISADVANTAGES OF KINASE INHIBITORS AS FRONTLINE TREATMENT FOR UNRESECTABLE METASTATIC BRAF-MUTANT MELANOMA**

The BRAF inhibitor vemurafenib was the first approved targeted therapy for melanoma. Recently, dabrafenib received approval both from the FDA as well as the European Medical Agencies. The FDA approved the MEK inhibitor trametinib as single-agent treatment in June 2013 and, subsequently, the combination of dabrafenib and trametinib in January 2014. The clearest advantage of BRAF inhibitors is their high objective response rate, which is in the range of 50% for either vemurafenib or dabrafenib. Both drugs provided a progression-free survival (PFS) of 6.9 months in updated phase III randomized trials, which was far better than PFS expectations for dacarbazine (DTIC) chemotherapy. Another obvious advantage of selective BRAF inhibitors is the rapid onset of response. The first signs of response are frequently seen after just one or two weeks. Before responses become evident by conventional cross-sectional imaging (MRI or CT), a dramatic decrease of tumor metabolic activity is observed by PET.

Both approved BRAF inhibitors appear to improve overall survival compared with chemotherapy. In the BRIM-3 randomized trial, the median survival was 13.6 months for patients randomly assigned to vemurafenib, which was a statistically significant better overall survival than seen with dacarbazine. In the BREAK-3 randomized trial the median survival for patients randomly assigned to dabrafenib was 18.2 months; however, the trial was not powered to detect an improvement in overall survival. It is difficult therefore to use these trials to compare the two BRAF inhibitors. Of interest, 69% of patients assigned to dacarbazine (the control arm) in the BREAK-3 trial crossed over to receive a BRAF inhibitor (59% dabrafenib, 10% vemurafenib). This led to a survival time of 15.6 months for these patients. These results, as well those of the nonrandomized BRIM-2 trial, which demonstrated an overall survival of 15.9 months for patients treated initially with chemotherapy or IL-2 followed by vemurafenib, indicate that BRAF inhibi-
tors may not only have a role in first-line treatment but also in second-line treatment of unresectable metastatic melanoma. This ability of BRAF inhibitors to induce antitumor response in almost every line of treatment emphasizes the need for thoughtful decision-making about when these drugs are actually recommended. BRAF inhibitors as single-agents are well tolerated: Only 3% of patients on BREAK-3 discontinued treatment because of toxicity. Life-threatening adverse events are rare and treatment-related deaths were not reported in these two trials. Nonetheless, development of second primary cutaneous neoplasms, notably keratoacanthoma-type squamous cell carcinomas, but also some BRAF wild-type melanomas, has been a non-life-threatening but troublesome consequence of BRAF inhibitor therapy. More concerning is the potential for BRAF inhibitors to accelerate the progression of other coexisting malignancies, particularly those with RAS mutations.

A clear disadvantage of treatment with BRAF inhibitors is the eventual development of resistance in a high percentage of cases. Little is known about long-term survival after BRAF inhibitor therapy, and, therefore, it remains uncertain how often single-agent BRAF inhibitors induce long-term survival, and if any patients are cured by this treatment. The number of patients with complete response is low. For either BRAF inhibitor, complete responses were initially reported in roughly 1% to 3% of cases; this improved with longer follow-up to 5% to 7%. Many feel that the BRAF inhibitors represent drugs with great potential to delay progression of metastatic melanoma, but that the chance for cure is small. It remains to be seen whether the probability of long-term disease control is better if the drugs are introduced in frontline treatment (i.e., whether more resistance to BRAF inhibition emerges when patients are treated unsuccessfully with other agents first).

Resistance to BRAF inhibition generally arises in conjunction with reactivation of the MAPK pathway, often via signaling through the downstream MEK protein kinase. Trametinib mediates blockade of MEK and has been associated with improved PFS and overall survival in patients with BRAF V600 (V600E or V600K) mutant melanoma. Other MEK inhibitors, such as cobimetinib, selumetinib and MEK162, also appear to have clinical activity in BRAF-mutant melanoma. Overall, however, the activity of single-agent therapy with MEK inhibitors appears to be less than seen with vemurafenib and dabrafenib, and their use as a single agent in patients with BRAF-mutant melanoma appears to be limited to patients who are intolerant to both available BRAF inhibitors.

Although the role for single-agent MEK inhibitor therapy may be limited in BRAF-mutant melanoma, the potential exists that combining BRAF and MEK inhibitors could lead to more effective blockade of the MAPK pathway, and/or delay the onset of resistance from pathway reactivation. In fact, the combinations of dabrafenib and trametinib and of vemurafenib and cobimetinib have both shown promising results in early-phase clinical trials.

In a randomized phase II trial in which two doses of trametinib combined with dabrafenib were compared with dabrafenib alone, it was found that the median PFS for patients assigned to dabrafenib 150 mg twice daily and trametinib 2 mg daily was 9.4 months, as compared with 5.8 months for those assigned to dabrafenib 150 mg twice daily monotherapy (hazard ratio for progression or death 0.39; 95% confidence interval [CI] 0.25–0.62; \( p < 0.001 \)). When assessed by an independent review committee, the PFS improvement was less pronounced but still quite dramatic and significant (HR 0.55; 95% CI 0.33–0.93; \( p = 0.02 \)). The combination of dabrafenib with trametinib 2 mg daily was superior to monotherapy with dabrafenib in terms of other study endpoints as well: the objective response rate was 76% versus 54% for monotherapy (\( p = 0.03 \)), and median duration of response was 10.5 months (95% CI 7.4–14.9) versus 5.6 months (95% CI 4.5–7.4), respectively. The percentage of patients who were alive at 12 months post-study entry was 79% in the 150/2 mg combination arm compared with 70% in the monotherapy arm, even though 80% of patients in the monotherapy arm crossed over to the 150/2 mg combination at disease progression. Patients in the 150/2 mg combination arm developed fewer secondary cutaneous squamous cell carcinomas than those on the monotherapy arm, at the expense of a markedly higher incidence of pyrexia (approximately 70% for the combination vs. 26% for dabrafenib monotherapy, including grade 3 and 4 febrile events for the combination arm). Of note, the combination of dabrafenib and trametinib was clearly more effective when used as the first-line inhibitor therapy; the results were not nearly as impressive when the combination was used in patients who had already progressed on single-agent BRAF inhibitor treatment.

Taken together, these results on the combination of BRAF and MEK inhibitors led to accelerated FDA approval of the combination of dabrafenib 150 mg twice daily and trametinib 2 mg daily earlier this year. Whether combination regimens including both BRAF and MEK inhibitors will lead to significant improvements in overall survival compared with BRAF inhibitor monotherapy, however, needs to be determined in phase III trials. In all, three different randomized phase III trials of combination BRAF-MEK inhibition compared with BRAF inhibitor monotherapy have now completed accrual of patients with unresectable metastatic melanoma. The results are eagerly awaited, and will also help us understand whether combined BRAF and MEK inhibition merely delays the time to development of drug resistance or is actually able to prevent resistance from developing entirely in a subset of patients. Regardless, it seems likely that if the advantages already seen in phase I and II trials of combined BRAF and MEK inhibition are sustained in the phase III experience, then combination therapy will supplant monotherapy as the preferred approach to kinase inhibition in patients with BRAF-mutant unresectable metastatic melanoma.
ADVANTAGES AND DISADVANTAGES OF IMMUNOTHERAPY AS FRONTLINE TREATMENT FOR UNRESECTABLE METASTATIC BRAF-MUTANT MELANOMA

Notwithstanding the excellent results for kinase inhibitor therapy in BRAF-mutant melanoma, immunotherapy continues to have a role in the treatment of these patients. This is because of the documented potential of immunologic agents to induce long-lasting complete responses in a limited number of patients, to the point where the question of “cure” in these cases must be entertained. For a long time, IL-2 was the only available approved immunotherapy for stage IV melanoma in the United States. But even before BRAF inhibitor therapy was introduced, IL-2 was used only in selected centers in highly selected patients. In 2011, the anti-cytotoxic T lymphocyte antigen (CTLA) 4 antibody ipilimumab, an immune checkpoint regulator, was approved in both the United States and Europe. In the pivotal phase III trial that led to initial approval, ipilimumab was used in second-line therapy and showed an improvement in overall survival for the first time in any metastatic melanoma phase III trial.\(^2\) Subsequently, a phase III trial evaluating DTIC with and without ipilimumab confirmed an overall survival benefit in the first-line setting as well.\(^3\) The approved indication for ipilimumab was initially broader in the United States than in Europe, but since October 2013 the European indication was extended to include the first-line treatment of patients with advanced melanoma as well.

Advantages of ipilimumab treatment as the front-line approach for patients with unresectable metastatic BRAF-mutant melanoma, instead of beginning with kinase inhibitor treatment, are related mainly to the longer response duration (about 14 months) compared with what can be achieved with BRAF inhibitors alone or with MEK inhibitors. However, the number of objective responses seen is relatively low, in the range of 10% to 15%. In an updated survival analysis of pooled clinical trials in front-line patients (regardless of BRAF mutation status), a median overall survival of 13.5 months was demonstrated. After one, two and three years, 54%, 32%, and 24% of patients were alive, respectively.\(^4,5\)

Disadvantages of front-line ipilimumab treatment compared with kinase inhibitor therapy are the rather low response rate, an unimpressive PFS of about two months, and a substantial frequency of so-called immune-related adverse events. Since ipilimumab targets the immune system, rather than directly targeting the tumor, this agent can be associated with serious immune-related adverse events such as colitis, hypophysitis and hepatitis. Typically, these adverse events are manageable when using established guidelines that emphasize vigilance and prompt intervention,\(^4,5\) but treatment-related deaths have been seen. Another disadvantage is the prolonged time to response typical of immune-mediated tumor regression. Unlike the rapidly evolving responses seen with BRAF inhibitors, ipilimumab responses generally take much longer to unfold—often occurring two to three months after the end of treatment, and in some cases even later. This emphasizes that patients should have a reasonable life expectancy when treated with ipilimumab and that the kinetics of tumor growth should be taken into consideration when deciding whether patients with BRAF-mutant melanoma are treated with ipilimumab or kinase inhibitors.\(^4,5\)

Another class of immune checkpoint regulators, the anti-PD1 antibodies, are of great hope for patients with metastatic melanoma.\(^6\) Like ipilimumab, the antitumor activity of these antibodies is not restricted only to patients whose tumors harbor BRAF mutations, so they can be used in front-line therapy or after failure of kinase inhibitors. Two anti-PD1 antibodies are already being tested in phase III trials in metastatic melanoma: nivolumab and MK-3475 (formerly known as lambrolizumab). Both of these antibodies have demonstrated high response rates of 25% to 38% in phase I and II trials in patients with metastatic melanoma (with even higher responses reported in some subsets of patients),\(^4,5,45\) indicating a remarkable contrast to ipilimumab. The reported response durations—with most responses lasting in excess of 12 months—and PFS data are also impressive. Another advantage of anti-PD1 antibodies relative to ipilimumab is the shorter time to response, with responses often seen relatively promptly, in some cases after only two to four weeks of treatment. Even patients with a high tumor burden and rapidly growing tumors can benefit, according to the available data from publications and presentations. For single-agent anti-PD1 antibodies, grade 3/4 toxicities in a range of 13% to 14%,\(^4,5\) almost all immune-related, have been reported, and patients who had significant toxicity from ipilimumab can, in many cases, tolerate anti-PD1 antibody therapy.\(^4,5\) Hence, the toxicity of anti-PD1 antibody therapy seems to be substantially lower than that seen with ipilimumab. However, some patients have died from pneumonitis,\(^4,5\) a toxicity that appears to be associated with anti-PD1 antibody therapy more commonly than with ipilimumab. The anti-PD1 antibodies offer very promising new treatment alternatives,\(^6\) but currently they are only available in clinical trials.

The efficacy, mechanism of action and relatively limited toxicity of anti-PD1 antibody therapy suggest the potential for combining these agents with ipilimumab. Indeed, combination treatment using ipilimumab plus nivolumab appears to be feasible and highly active. A phase I/II trial showed a promising response rate: At the doses of nivolumab 1 mg/kg and ipilimumab 3 mg/kg, 53% of 17 treated patients had an objective response, all with tumor reduction of 80% or more, at the cost of increased toxicity. In all, 53% of patients treated with concurrent nivolumab and ipilimumab experienced grade 3/4 adverse events, although many were asymptomatic laboratory abnormalities.\(^4,6\) In this clinical trial, the numbers of complete responders was higher than anticipated for ipilimumab alone and the speed of response was impressive. Ongoing phase II and III trials will help determine if the efficacy of this combination is sufficiently greater than single-agent therapy to justify the additional toxicity.
Biomarkers to Help Determine Frontline Treatment for Unresectable Metastatic BRAF-Mutant Melanoma

Regardless of whether phase III trials indicate that the optimum immunotherapeutic regimen for frontline treatment of unresectable metastatic melanoma is anti-PD1 antibody, anti-CTLA4 antibody, or a combination of both, it is clear that the advantages of immunotherapy are such that at least some patients with BRAF-mutant metastatic melanoma should be considered for immunotherapy before attempting kinase inhibitor therapy. However, our ability to determine in advance which patients will respond to immunotherapy is very limited. Some physicians would consider ipilimumab as the frontline treatment only for those patients with BRAF-mutant metastatic melanoma who are asymptomatic and with relatively limited disease burden, but this logic might not apply to anti-PD1 therapy alone or combined with ipilimumab. Conversely, the benefits of combined BRAF and MEK inhibitor therapy might be sufficiently great that even patients with asymptomatic, limited disease burden should receive this approach as frontline therapy. There is clearly an unmet need for biomarkers that can help identify patients more or less likely to respond to either immunologic or kinase inhibitor therapies to assist in personalizing treatment for each individual patient. Already, there are suggestions that immunologic "signatures" might predict which patients are most likely to respond or fail to respond to specific vaccines or immunotherapy in general. There is also substantial reason to think that additional genetic aberrations within melanoma cells, besides those in the BRAF gene itself, may influence the likelihood a given tumor will respond to kinase inhibitor therapy. Therefore, in the future, it is likely that decision-making regarding frontline treatment of patients with BRAF-mutant metastatic melanoma will become more rational and personalized, but, for now, clinical judgment remains of paramount importance.

Incidence of Resectable Metastatic BRAF-Mutant Melanoma

The frequency with which patients present with limited metastatic disease potentially amenable to resection is poorly understood, and there is no available information at present regarding whether BRAF mutation status influences the likelihood of resectability at presentation. Some evidence suggests that presentation with oligometastatic disease amenable to resection may be more common than most oncologists would surmise. Of 291 patients who developed stage IV melanoma after enrolling onto a prospective, randomized trial evaluating sentinel lymph node biopsy (MSLT-1) in whom complete data regarding postrecurrence treatment was available, 161 (55%) underwent surgery alone or with systemic medical therapy as a component of that treatment. In contrast to this high rate of surgical utilization on recurrence in a selected population of patients who initially presented with clinically node-negative melanoma and were being closely followed by surgical oncologists, a review of 70 consecutive patients presenting with metastatic melanoma to a European center over a recent 18-month period showed that most patients (n = 55, 78.6%) were ineligible for complete resection. The majority had seven or more metastases at presentation; whereas, only 13 patients (18.6%) presented with a solitary metastasis. Even fewer patients (six patients, or 8.6% of the total group) underwent complete surgery as initial stage IV treatment, while in another nine patients incomplete surgery was performed. This latter experience would seem to be much more representative of what a modern, multidisciplinary melanoma team would encounter, but it still indicates a substantial role for surgery in the frontline management of stage IV melanoma.
OUTCOMES WITH SURGERY

For the cohort of MSLT-1 patients who developed stage IV melanoma, the median survival was 15.8 months in the selected group of patients receiving surgery with or without systemic medical therapy compared with 6.9 months for those receiving systemic therapy alone.\(^5\) Survival at four years was 69.3%. Surgery was associated with better survival for patients regardless of M substage (M1a, median >60 months vs. 12.4 months (p = 0.01); M1b, median 17.9 months vs. 9.1 months (p = 0.11); and M1c, median 15.0 months vs. 6.3 months (p < 0.0001).\(^5\) The results in this surgically treated cohort represent a highly selected subpopulation of patients. Hence, they must be considered as “best case” results for what can be achieved with surgery in stage IV melanoma.

To date, there has only been one prospective (albeit non-randomized) evaluation of surgery for stage IV melanoma, conducted by the Southwest Oncology Group (SWOG)\(^5\). In this trial, patients with stage IV melanoma were enrolled before undergoing surgery, as soon as the determination of potential resectability was made, allowing for an estimation of resectability rate as well as relapse-free and overall survival after complete resection. During a 10-year period ending in late 2005, 77 patients were enrolled. Although this could reflect unique constraints of conducting this research in the cooperative group setting, it certainly suggests that potentially resectable metastases are not likely to be found in the majority of otherwise unselected stage IV patients with melanoma! Among these 77 patients, two had only stage III disease and were hence ineligible, and three had no melanoma within the resected specimen (the suspected metastatic deposit was either benign or a second primary malignancy). An additional eight eligible patients were not able to have all gross disease completely resected. Therefore, 64 patients (88.9% of eligible stage IV patients with melanoma) who were felt to be resectable were in fact resected to a disease-free state. Among these 64 patients, after a median follow-up of five years, all but six (9.4%) have manifest disease recurrence, with a median relapse-free survival of approximately five months. Overall survival was considerably longer than relapse-free survival, at a median of 21 months, with an estimated 12-month survival of 75%. Survival at four years was 31%.\(^5\) By virtue of being prospectively derived from otherwise unselected patient populations, these resectability and survival rates can be considered as the most representative data available for comparing surgical and nonsurgical approaches to stage IV melanoma. So how do the results compare? Once again, we must acknowledge the absence of data regarding BRAF mutation status in these surgically treated cohorts, but if we assume that the available reflect what could be expected for selected patients with resectable metastatic BRAF-mutant melanoma, some relevant points of comparison emerge.

Comparison of Outcomes

Complete response rate and duration of response. By definition, patients who are rendered free of disease after surgery have immediately achieved a complete response, and the SWOG data indicated that about 90% of the highly selected group of patients who were deemed surgical candidates in fact achieved that complete response, with a median “response duration” (relapse-free survival) of five months.\(^5\) No available systemic therapy or combination of therapies can come anywhere close to achieving a complete response, even in highly selected cases, in such a high percentage of treated individuals. Although the duration of “response” is relatively low at five months median, about half of relapsing patients can be “reinduced” into another complete response with a second or subsequent surgeries.\(^5,\)\(^5\)

Progression-free survival. In the two phase III randomized trials of single-agent BRAF inhibitors, the median PFS was five months,\(^17,18\) basically identical to the median relapse-free survival after surgery in the SWOG study.\(^5\) This rate is much longer than the PFS associated with ipilimumab,\(^5,3\) but shorter than the PFS seen in the early phase trials with anti-PD1 antibody therapy (7 months for MK-3475)\(^5\) or with combined BRAF and MEK inhibitors (9.4 months)\(^40\) in unselected (and clearly less favorable) patients.

Overall survival. In part because of the ability of repeat resection to salvage many patients who develop recurrence after initial surgery, survival times for highly selected patients with stage IV melanoma subjected to surgery (median 15.8 months and 21 months)\(^5,\)\(^5\) have been longer, with more patients alive at one year, than seen among unselected patients given pre-2011 systemic therapies.\(^5\) For the first time, however, overall survival values for patients treated with BRAF and MEK inhibitors\(^45\) or anti-PD1 antibodies alone\(^5\) or with ipilimumab\(^46\) appear to be approaching or even exceeding the best results seen with surgery.

THE ROLE OF NEOADJUVANT OR PREOPERATIVE SYSTEMIC THERAPY

It may be that new therapeutic approaches to metastatic BRAF-mutant melanoma are becoming so effective that a reconsideration of the role of surgery in front-line management is appropriate. If phase III results with BRAF and MEK inhibitors or anti-PD1 antibodies alone or with ipilimumab match or exceed the outcomes seen in phase I and II trials, then that will certainly be the case. For now, the extremely high rate of achieving complete eradication of all known disease continues to argue in favor of surgery when feasible. The role of adjuvant systemic therapy after metastasectomy remains to be defined, and is the focus of ongoing studies with immunomodulatory drugs and other agents.\(^5\) Neoadjuvant therapy is the preoperative use of systemic therapy either to facilitate tumor shrinkage and enhance resectability or to improve outcomes by eliminating unresected foci of disease, and its use in metastatic BRAF-mutant melanoma is still in its infancy.\(^6\) Given the high response rate and rapid time to response associated with BRAF inhibitor therapy, alone or along with MEK inhibition, patients whose metastatic BRAF-mutant melanoma is considered “borderline” resectable or in
whom unfavorable clinicopathologic characteristics argue against surgery (e.g., those with multiple metastases and a very short disease-free interval and/or an elevated serum lactate dehydrogenase level) should be offered initial treatment with kinase inhibitors and subsequently re-evaluated for resectability. When single-agent BRAF inhibitors are used, we tend to re-evaluate patients after about four months on therapy, with the hope of intervening surgically at the nadir of tumor size and before resistant clones lead to clinically evident tumor progression. Use of combined BRAF and MEK inhibitors could allow for a longer time on therapy, and, perhaps, result in some complete responses that obviate the need for surgery altogether. In patients who have undergone successful resection after kinase inhibitor treatment, it is unclear whether maintenance BRAF inhibition is of value as compared with reserving further systemic therapy for subsequent unresectable recurrence. Individualized decision-making is appropriate in this scenario, recognizing that a minority of patients (approximately 10% in the SWOG experience) are long-term survivors after surgery without any additional systemic treatment.

**SUMMARY AND CONCLUSIONS**

Dramatic recent advances in the management of metastatic BRAF-mutant melanoma have improved outcomes so substantially compared with expectations from just a few years ago that it is appropriate to question what the optimum front-line management of these patients should be. Eagerly awaited results from phase III trials of combinations of targeted or immunologic agents will likely change our paradigms even further in the future. For now, the best approach begins with a thorough evaluation of the extent and resectability of the patient’s metastatic disease and involves a multidisciplinary decision-making process that takes into account the disease burden and symptomatology, the kinetics of tumor progression, and, above all, patient preferences. Not every patient with unresectable metastatic BRAF-mutant melanoma will initially receive kinase inhibitor therapy when that approach is used in today’s environment. During the next few years we are likely to see changes in how frequently surgery and immunologic therapies are used in front-line management of metastatic BRAF-mutant melanoma.

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