New Challenges in Endpoints for Drug Development in Advanced Melanoma

Antoni Ribas¹, Peter Hersey², Mark R. Middleton³, Helen Gogas⁴, Keith T. Flaherty⁵, Vernon K. Sondak⁶, and John M. Kirkwood⁷

Abstract

During the past 3 decades, the field of clinical research for the treatment of advanced melanoma lacked significant advances. Available drugs had low antitumor activity and no proven benefit in overall survival. Recently, new drugs developed based on an in-depth understanding of the biology of this disease have shown significant benefit, with ipilimumab and vemurafenib having recently shown a positive impact in overall survival in patients with metastatic melanoma leading to approval in this indication by the U.S. Food and Drug Administration. This rapid introduction of new active agents is likely to challenge current notions on how to develop future agents for the treatment of melanoma. The strong evidence of benefit for initial agents that modulate immune regulatory checkpoints or target driver oncogenes has spurred great interest in developing other similarly acting agents. However, this will pose problems in the choice of endpoints for the future definitive clinical trials, and the hurdles for achieving these endpoints will be higher given the similar activity for comparator agents or the availability of competing agents for salvage therapy. This new reality will likely require tailoring registrational clinical trial endpoints to the patient benefits shown in early clinical testing. In this perspective article, we illustrate the challenges in the choice of endpoints for registrational trials in metastatic melanoma and that, with an improved understanding of the agent being developed, the design of the registrational programs can be informed by earlier mechanistic studies to define the assumptions for definitive clinical testing.

The Rapidly Changing Landscape of Advanced-Stage Melanoma Treatment and Its Implications for New Drug Development

For more than 30 years there has been a seemingly low hurdle for new agents to show efficacy in the treatment of unresectable stage III or IV melanoma (advanced melanoma). Yet, during this time, only 3 drugs were approved by the U.S. Food and Drug Administration (FDA) for this disease: dacarbazine, hydroxyurea, and interleukin-2 (IL-2). Of these only dacarbazine was widely used in the community and considered a standard treatment. For patients with progression after one of these agents, no second-line treatment whatsoever was agreed upon. Prospective trials involving dacarbazine had shown response rates in the 10% range, without a shown improvement in overall survival compared with supportive care. Multiple investigational agents tested during this long period of time failed to show significant benefit over dacarbazine, contributing to the widely held belief that melanoma is resistant to standard chemotherapy agents (1). This included the extensive clinical testing of combinations of immunotherapy and chemotherapy agents (so called biochemotherapy regimens), where relatively high response rates were reported without an understanding of their mechanism of action, but overall survival was repeatedly not improved over other regimens (2, 3).

Recently, advances in the molecular understanding of how the immune system can be modulated to fight melanoma, and of the oncogenic driver mutations that underlie melanoma cells, are leading to dramatic changes in how the field regards standard treatment options for patients with advanced melanoma. As melanoma oncologists, we now need to change our paradigm of therapy for the first time, and consider disease biology in relation to new agents that have shown improvement in overall survival for patients with advanced-stage melanoma. First, 2 clinical trials evaluating the immune-modulating antibody ipilimumab (previously MDX010) have shown a statistically significant improvement in survival, one in previously treated patients with metastatic melanoma.
Translational Relevance

Development of new agents in patients with metastatic melanoma has new challenges after the recent evidence of positive impact on survival with ipilimumab and vemurafenib. We argue that adapting the drug development plans to the mechanism of action of the new agent or combination, and testing mechanism of action early in the clinical testing, will help in the design and conduct of definitive studies by informing on the choice of the most favorable primary study endpoints.

compared with treatment with a peptide vaccine (4), and the other in first-line therapy in combination with dacarbazine compared with single-agent dacarbazine (5). These data led to the approval of ipilimumab by the FDA in March of 2011, the first new agent in 13 years for melanoma and the first ever based on a positive impact on overall survival. Soon thereafter, a randomized clinical trial showed that the BRAF inhibitor vemurafenib (previously PLX4032/RG7204) improved both survival and interval to progression in first-line therapy compared with dacarbazine (6), leading to the FDA approval in August 2011. Vemurafenib had previously shown unprecedented high response rates in phase I and II testing in patients with BRAFV600 mutant metastatic melanoma (7, 8). Similarly, high response rates have been observed in the phase I trial of another specific BRAF inhibitor, dabrafenib (previously GSK2118436; ref. 9; 50%–80% objective response rates in both cases). Given these changes in the standard-of-care therapies for metastatic melanoma with new agents with shown effects on overall survival, it is likely that in the next several years it will be harder to successfully show an additional benefit in overall survival of new agents compared with the recently approved ones. Therefore, the field of melanoma drug development is faced again with the question of which, if any, surrogate endpoints could be considered sufficient to show antitumor efficacy and clinical benefit in future pivotal clinical trials (Table 1).

Different Therapeutic Approaches, Different Benefit Measures

The new agents showing activity in metastatic melanoma fall into 2 broad categories: (i) immunotherapy, and in particular immune checkpoint modulating antibodies; and (ii) oncogene-targeted therapies. The lead compounds for each approach (ipilimumab and vemurafenib, respectively) are being followed by other agents with effects on the same or similar pathways, which are likely to provide similar patient benefits. The immune-modulating antibodies (anti-CTLA4, anti-PD1, anti-PDL1, anti-CD40, anti-CD137, and anti-OX40) all aim to stimulate long-lasting antitumor immune responses. The antitumor benefits are noted clinically in a variable fraction (arguably small) of the patient

### Table 1. Relative merits of different endpoints in melanoma clinical trials

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td>Gold standard</td>
<td>Quality of life not necessarily considered</td>
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<tr>
<td></td>
<td></td>
<td>Will be difficult to achieve when control groups</td>
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<td></td>
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<td>have high survival</td>
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<tr>
<td></td>
<td></td>
<td>High patient numbers then needed</td>
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<td></td>
<td></td>
<td>Symptom relief not taken into account</td>
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<td>PFS</td>
<td>Outcome more rapid and allows rapid selection of</td>
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<td></td>
<td>agents if very prolonged may be an endpoint of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>merit in its own right</td>
<td>Not necessarily related to overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quality of life not necessarily considered</td>
</tr>
<tr>
<td>Response rate</td>
<td>Valuable in single-arm studies if &quot;unprecedentedly&quot; high</td>
<td>Not necessarily a surrogate endpoint for overall survival benefit</td>
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<tr>
<td></td>
<td></td>
<td>Difficult to achieve when developing new agents</td>
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<td></td>
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<td>with similar mechanism of action with already</td>
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<td></td>
<td></td>
<td>high response rates</td>
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<tr>
<td>Quality of life</td>
<td>May be a valid endpoint irrespective of effects of other endpoints</td>
<td>No information about benefits based on time-to-event endpoints</td>
</tr>
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Abbreviation: PFS, progression-free survival.
population. For example, with the anti-CTLA4 antibody ipilimumab, the objective tumor response rate is on the order of 10% to 15%, but the reduction in the likelihood of death compared with a vaccine or dacarbazine was 34% and 28%, respectively, with the prospect of cure in some of these patients (4, 10). The long-term benefit is noted by a consistent absolute increase of approximately 10% of patients alive in the ipilimumab-containing study arms compared with the control therapy in the 2 pivotal clinical trials at the end of the study follow-up period (4, 10). This late plateau (or tail) in the survival curve is highly reminiscent of that seen with high-dose IL-2 (11), representing long-term responders who remain relapse free for years (Fig. 1). With ipilimumab having shown overall survival benefit in 2 randomized phase III trials, the development of other agents in this category of immunotherapy may involve direct comparison with this agent, perhaps with a focus on decreasing side effects while retaining survival benefits (noninferiority clinical trials). Alternatively, trials of new immunotherapy agents (or combinations of new agents with ipilimumab) may seek to show higher objective response rates while preserving or even extending the survival benefits, which will be a harder hurdle to overcome, or test concurrent or sequential therapy schemes that may improve on the tail of the survival curves obtained with ipilimumab alone.

On the opposite side of the spectrum are the dramatic initial results achieved with targeted therapies that block signaling from oncogenic driver mutations in melanoma (inhibitors of c-kit and BRAF) or downstream effectors (MEK inhibitors). The antitumor effects of these agents are restricted to subsets of melanomas that are dependent on a particular mutated oncogene or activated pathway, with minimal to no activity observed when these agents are used against tumors that do not have that oncogene or pathway "addiction." In properly selected patients, initial response rates are very high with oncogene-targeted inhibitors (7–9, 12), but in a matter of months, tumors frequently find a way to escape these drugs’ antitumor effects via a variety of molecular mechanisms of acquired resistance (13–15). The benefit of oncogene-targeted agents is noted in early improvements in the progression-free survival (PFS) and overall survival curves, because the majority of patients derive a rapid antitumor response (Fig. 1). However, the limited duration of these responses is less likely to change the slope of the tail of the survival curve than is seen with immunotherapy, based on the available data. Mature survival data are not yet available from the BRAF-targeted therapy phase III trials (6), and even once available their interpretation will likely be complicated by crossover of control arm patients to agents inhibiting the same oncogenic signaling. Therefore, it is possible that we will not have reliable overall survival curves compared with a control arm to evaluate the long-term effects of BRAF-targeted inhibitors in melanoma.

Therapeutic Benefit Measured as Improvement in Overall Survival

There is no doubt that a drug has shown objective evidence of benefit when the HR for overall survival is improved compared with a concurrent control group within an adequately designed and conducted randomized clinical trial. Survival improvement is generally agreed upon as the preeminent goal of therapeutic trials in advanced disease, such that a clinical trial that aims to improve survival frequently does not also evaluate quality of life or other patient-reported outcomes related to symptoms of the disease. Although survival benefits measured as a clinically significant improvement in HR over the new standards like ipilimumab or vemurafenib would be an obvious goal, with a higher hurdle of antitumor activity in the control arm it would be harder to show.

The recent experience in clinical trials with melanoma oncogene-targeted inhibitors using overall survival as an endpoint raises specific issues to be considered in the conduct of future randomized studies with overall survival as the primary endpoint (16). The controversies over the vemurafenib phase III clinical trial (16–18) raise the point that clinical trial endpoints and design need to be tailored to the emerging early evidence with a new therapy, and that the process needs to be dynamic as the body of knowledge increases whereas definitive trials are being planned.

When several agents with similar mechanisms of action and antitumor effects are being independently developed in the same study population, then the consideration for
unplanned crossover to a competing agent is another major problem for clinical trials with overall survival as endpoint (19). In addition, the availability of expanded access (compassionate use) programs for one agent may hamper accrual to phase III trials of another similar agent, especially if they involve open label assignment at randomization.

Overall survival is not the only clinically meaningful endpoint for a new agent in metastatic melanoma. It is hard to think that physicians would decide not to prescribe BRAF inhibitors (or other agents with similar reproducible high and rapid response rates in molecularly defined subsets of patients) for appropriate patients with bulky and symptomatic disease even if they did not show a prolongation of overall survival in a large cohort of patients followed for a long period of time. On the basis of these considerations, it is clear that overall survival in phase III randomized clinical trials can no longer be considered the only relevant clinical endpoint for new drug development in advanced melanoma. It will continue to be the preferred endpoint if the new agent has a mechanism of action significantly different from the emerging new standards (CTLA-4 and BRAF inhibitors), as long as the new agent does not provide strongly suggestive evidence of paradigm shifting antitumor activity in early single-arm clinical trials (16, 18).

**Therapeutic Benefit Measured as Objective Response Rate**

Clinical benefit is always harder to show in single-arm clinical trials. It stands to reason that clinical benefit is evident whenever a patient with a symptomatic cancer receives a treatment that leads to objective regression of the cancer according to Response Evaluation Criteria in Solid Tumors and this tumor shrinkage improves the symptoms. However, many experts in the melanoma field maintain that response rate may under- or overestimate the agent’s effects. For example, high initial response rates with highly toxic biochemotherapy have not translated into overall survival benefit (20), whereas low response rates with ipilimumab have translated into a benefit in overall survival (4). The paradigm-shifting early antitumor activity of BRAF inhibitors has led to the proposal that molecularly targeted agents may be approved immediately after a phase I trial with an expansion cohort after providing a mechanism-driven unprecedented antitumor activity (measured as response rate) in a defined population (18). For example, should acquired resistance to BRAF inhibition prove susceptible to combinations of targeted agents that block the escape mechanisms, and these combinations are highly active in the clinic and well tolerated, this may be considered sufficient evidence for definitive clinical trials.

**Therapeutic Benefit Measured as Improvement in Progression-Free Survival**

The large cooperative group clinical trial experience with very low activity agents that were tested against metastatic melanoma over the course of 3 decades has provided benchmarks for the natural history of melanoma, in what has come to be known as the Korn meta-analysis (21). PFS and overall survival benchmarks for more than 2,100 patients enrolled in 42 clinical trials were found to fall within boundaries that could be statistically defined. The authors proposed that expected time-to-event endpoints could be derived from this analysis, such that future single-arm clinical trials could be designed to show an improvement compared with this historical dataset. An example would be designing a trial to determine if a new agent has a 6-month PFS benefit that is statistically significantly better than the benchmark of 6-month PFS in the Korn meta-analysis (21). Such a design could facilitate the development of new agents by more rapidly selecting promising agents for phase III pivotal trials. However, the Korn meta-analysis has limitations as a basis for selecting benchmarks for current trials. Further study is required to determine how generalizable the results will be to current populations of patients with advanced melanoma. Indeed, it can be argued that these patients enrolled in older cooperative group trials differed in material ways from patients entered into recently conducted clinical trials. Differences could arise from improvements in the sensitivity of current screening studies and differences in the populations selected for, to give only 3 recent examples, in lactic dehydrogenase levels, specific human leukocyte antigen types, or the presence of specific mutations in the tumor. Provided that these important caveats are kept in mind, an agent developed in a single-arm, multicenter study that has a PFS well beyond what would be expected from the Korn data may provide the rationale for further development in definitive phase III trials. The more ambitious assertion that such a single-arm phase II trial showing time-to-event outcomes far outside the Korn boundaries might itself be grounds for regulatory filing does not seem warranted at this time.

The use of PFS as the primary endpoint for randomized phase III clinical trials would overcome many of the problems of using overall survival as the primary endpoint. The ethical questions of withholding a potentially active agent for the rest of the patient’s life if the patient is randomized to the control arm could be ameliorated by the possibility of crossover upon progression without affecting the primary endpoint. But the final results may be viewed as less compelling compared with an overall survival endpoint. Furthermore, biases in the evaluation of tumor progression and issues relating to the timing of imaging studies in the trial arms could erode confidence that observed PFS benefits are clinically meaningful. In addition, it is likely that clinical trial sponsors would not be keen to conduct a large study based solely on PFS improvement without the ability to also test for an overall survival improvement. An agent advanced on the basis of PFS impact could be at a commercial disadvantage compared with agents with shown overall survival benefit. Furthermore, regulatory agencies and reimbursement policies in many countries may not recognize a new agent on the basis of PFS improvement in the absence of evidence of a significant improvement in survival.
Clinical Trial Endpoints Adapted to the Clinical Effects of the New Therapeutic Approaches

With all these considerations and caveats regarding clinical trial endpoints, it is obvious that no single solution will apply to the range of new agents being developed in melanoma. An alternative to the "one-size-fits-all" approach is to generate data in early-phase clinical trials to provide information on what would be the most promising endpoints, and in which particular patient populations, to pursue the registrational program. This premise requires a careful understanding of the underlying biology of the new agent starting in the early clinical development studies, and the entry of sufficient numbers of patients to the late phase I/II clinical trials to allow solid assumptions for the design of the following pivotal trials. Mechanism-of-action studies can take advantage of highly interventional small clinical trials focused on the study of tumor biopsies. These early studies may also allow restricting of the new drug's development plans to a molecularly or clinically defined subgroup of patients in whom the benefit can be better shown and with a smaller sample size needed.

The knowledge of the general aspects of the anticipated clinical benefits of immunotherapy and targeted therapy agents developed to date in patients with advanced melanoma (Fig. 1) provides clues about improved design for future pivotal trials of these agents. If a new immunotherapeutic agent shows low response rates but these are sustained and mediated by similar intratumoral infiltration by lymphocytes, as seen with anti-CTLA4 antibodies (22–24), then it would be prudent to focus on the remarkable phenomenon of durable tumor responses as the main endpoint for pivotal trials. Similarly, if a new agent has a high response rate in a subset of the population with metastatic melanoma that is based on a good understanding of the molecular events that lead to these responses, then an endpoint that captured tumor response with a clinically meaningful duration would be an acceptable pivotal clinical trial goal (18). However, this would require a careful assessment of the risk/benefit ratio of the new approach and would only be directly applicable to highly active oncogene inhibitors. Finally, trials of combinations of targeted therapies and immunotherapies should have the goal of showing that the high frequencies of responses with targeted therapies become highly durable with the addition of immunotherapies, very likely requiring placebo-controlled randomized clinical testing.

Conclusions

Agents that are making a major impact in the treatment of metastatic melanoma have been developed based on an elegant understanding of the underlying immunobiology of this cancer and the mutations that drive its progression. It is a logical next step to adapt the clinical development plans of future agents to a deeper understanding of the mechanism of action by designing pivotal trials that focus on the strengths of the new agents and the potential benefits that may therefore be demonstrable in clinical trials. At long last, the bar has risen for the regulatory approval for drugs in melanoma, and the design of trials of new agents in clinical development will need to adapt to overcome these higher hurdles of activity. The best opportunity for positive outcomes will derive from early clinical testing that builds the knowledge of the scope of the potential benefits of the new agent, leading to the registrational trials tailored to show that benefit.

 Disclosure of Potential Conflicts of Interest

A. Ribas is a consultant and a member of the advisory board of Bristol-Myers Squibb, Roche-Genentech, Amgen, Merck, and Millennium.

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