LETTER TO THE EDITOR

Sorting through the many opportunities for melanoma therapy

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Dear Editor,

The melanoma field has made unprecedented advances in the therapy of Stage IV disease, which were the highlight of the 2011 ASCO meeting. Two new drugs have been recently approved, one stimulating the immune response, the other targeting the oncogene BRAF that is mutated in 50% of all melanomas. However, neither drug cures patients underscoring the need for further improvements of current treatments. Likely, the key to further success in therapy lies in combination therapies, in which two or more drugs that synergize in their activity are combined. This approach adapts many of the elements of current AIDS combination therapies that do not cure but allow patients to maintain productive lives. Thus, even if we cannot cure melanoma in all cases, our goal is to achieve chronic disease states with relatively high quality of life. Assessing optimal combination therapies for melanoma in clinical trials is slow, expensive, and potentially frustrating because so many avenues may end in failure. Some combinations of drugs may result in worse clinical response than the same drugs as single agents.

For both targeted and immunotherapies, the melanoma field is confronted with the ‘troubles of the riches’ as pharmaceutical companies have developed in the last five years a large portfolio of drugs that are candidates for treatment of this disease. These drugs are being tested initially as single agents, but increasingly as part of a cocktail of two or more drugs. Given the critical role of the MAPK pathway for melanoma signaling, not only in those tumors addicted to mutant BRAF or NRAS oncogenes but also in wildtype/wildtype tumors, i.e., those without RAF, RAS, or c-kit gene mutations, numerous drugs are in clinical trials targeting BRAF, CRAF, MEK, and ERK. Scattered in vitro and in vivo experiments point to the potential synergisms of BRAF, MEK, and ERK inhibitors with those against receptor tyrosine kinases (RTK) such as FGFR, IGFR, c-kit, c-met, PDGFR, or EGFR as well as with inhibitors of PI3K and AKT. None of the inhibitors for RTK or the PI3K pathway show impressive results as single agents against melanoma; however, they are prime candidates for combination therapies due to their potential synergistic activities. The numbers of inhibitors available for clinical trials are staggering. While only two inhibitors against mutant BRAF are in advanced clinical trials, additional eight or more are in early Phase I trials or late preclinical studies. Similar number of drugs against MEK, PI3K and AKT are winding their way towards potential
approval, if not as single agents then as part of a combination. Not all drugs against the same target are the same. Even if not factoring in differences in solubility, pharmacokinetics or pharmacodynamics, specificities for those drugs targeting the same molecules may not be completely overlapping resulting in potential differences in activity. One clear example is Sorafenib, the first ‘RAF inhibitor’ to be tested in clinical trials for melanoma. Sorafenib was not very effective inhibiting the MAPK pathway and had inadequate clinical efficacy as a single agent in melanoma. Even though these results led to some skepticism and questioning on whether BRAF was a good target for melanoma therapy, it became clear that the lack of selectivity of this compound and the low potency against BRAF limited the dose that could be achieved in patients. Additionally, differences in efficacies of the anti-BRAF selective drugs were observed among melanoma, colorectal carcinoma or thyroid carcinoma patients, with melanomas being the most responsive, thus making it difficult to predict response in melanoma patients based on clinical studies in other cancers. In summary, there are at least thirty small molecule inhibitors against molecular targets in the clinical pipeline that can be tested in the next two years in melanoma patients in phase I/II clinical trials. Considering the history over the last twenty years of ‘never ending’ series of clinical trials for interferon, the prospects for rapid progress in the emerging field of targeted therapy will be diminished unless we become more efficient in handling the unprecedented avalanche of new drugs. While each drug requires a Phase I clinical trial (not restricted to melanoma) to determine the maximally tolerated dose, pharmacokinetics, and also collect information on target inactivation, any combination will require a Phase II trial with increased number of patients and resources. Although the FDA has recently issued new guidelines to accelerate co-development of unmarketed drugs, it is unrealistic to expect that clinical trials will sort out the best drugs for each target and the best combination of drugs inhibiting different targets in the foreseeable future.

The prospects for combining targeted therapy with immunotherapy are exciting but the number of combinations are similarly staggering further taxing the resources in the field. How has the melanoma field coped with this dilemma in the past? There were far fewer opportunities due to the scarcity of new drugs. Decisions on protocols were made based on scant preclinical data mostly provided by companies and predominantly from correlative information in other cancers or from previous melanoma trials; thus, progress was slow with the history of interferon’s clinical trials being a case in point.
As we move forward, we cannot expect that our clinical colleagues will sort out different drugs for each target, nor determine how to best combine each with others. Unfortunately, a large number of combination trials are already in the active planning phase without having a foundation of preclinical data that would provide a strong rationale. We have to do better in the future through increased reliance on preclinical studies, both in vitro and in vivo, using models that mimic the disease as closely as possible. There is not one model that reflects all melanomas but each model has specific strengths and weaknesses that have to be explored in the context of therapy (discussed in Herlyn and Fukunaga, 2010). Preclinical models should reflect the complex genetics of melanoma and phenotypic characteristics including patterns of invasion and metastasis as in the human disease. When discounting outdated models such as B16, there are two basic models available: human xenografts and murine genetic models.

Cells derived from these models can also be used for in vitro testing, particularly if cells are embedded in a three-dimensional tissue-like matrix. For human tumor cell lines our laboratories and others have established six groups of three to ten cell lines, each representing unique genetic sub-groups. We also expect that in the fall of 2011 the Tyr::CreER; BrafCA; Ptenlox/lox mouse genetic model, backcrossed to homozygosity in C57Bl6 mice, will be ready for immunological studies (D. Herlyn, M. McMahon, M. Bosenberg, personal communication).

A systematic comparison of the same drugs in the different in vitro and in vivo models has not been done. Studies assessing the suitability of models for therapy are overdue but have been hampered by lack of funding. NIH study sections generally scoff at such experiments because they are not ‘hypothesis driven’. In addition, the preclinical research community has only a scant record of active collaborations – unlike the clinical community, which has a long history of productive collaborations. As a case in point, the recent formation of the MRF BC (Melanoma Research Foundation Breakthrough Consortium), represents a culmination of successful collaborations among oncologists. In this consortium, the MRF acts as an ‘honest broker’ between academic institutions and pharmaceutical companies by providing organizational infrastructure and legal support. Preclinical and biomarker studies could become part this consortium, if funding allows.
Can we realistically expect that companies will allow us to compare in preclinical (or clinical) settings different MEK, BRAF, etc inhibitors? Doubtful or never, depending on who you ask. Even if the NIH has a drug in its Cancer Therapy Evaluation Program (CTEP) portfolio, any use in combination with a drug from another company needs approval. Proposals for such combination studies are usually denied mainly because of the many legal issues involved when combining two non-approved drugs from two different companies. Can we wait until each of the candidate drugs is approved allowing us only then to mix and match? Clearly not because we would need to wait five or ten more years with many drugs falling by the way side where we, the academic community, may have found a niche. At this time, we generally have to rely on the companies for finding the best dose, scheduling, and response evaluation but industry often lacks the sophisticated preclinical models that the academic community has. Most large pharmaceutical companies have inhibitors for each member of the MAPK or PI3K pathway, but how do we know whether those are the best without direct comparison? We would need to rely on information provided by the companies but this is likely biased. How do pharmaceutical companies become knowledgeable about an inhibitor from another company that recognizes the same target? As soon as the structure of a compound is in the public domain, their chemists synthesize it for internal use. Could academic scientists follow industry’s example and have compounds synthesized by contract companies for research purposes? By using this approach approximately fifty percent of the hottest compounds could be obtained allowing us to begin sorting through the best combinations with approved or unmarketed drugs.

Before conducting any in vivo experiments, compounds should be extensively studied in vitro using human and mouse model cell lines in the most suitable assay systems. Initial in vitro studies can also help define not only drug properties but also to prioritize the most selective and potent compounds that can then move into combinations. We have found that conventional two-dimensional cultures are the most sensitive and can be used for initial screening but many compounds do not show activity when cells are maintained in a three-dimensional tumor-like environment. Those compounds are also expected to fare poorly in vivo. Using these models we have shown that while BRAF inhibitors can induce cytotoxic effects in 2D-, 3D-cultures, and in vivo, MEK inhibitors like AZD6244 had only cytostatic effects in 3D-cultures and in vivo (Haass et al. 2008). These data are consistent with clinical experience where RAF inhibitors induce tumor
shrinkage, while MEK inhibitors tend to cause tumor stabilization at best. Compounds like Sorafenib, PD325901, and Cl-1040, which show activity in 2D in preclinical studies, but were not tested in 3D models, failed to show clinical activity against BRAFV600E tumors. Since both two- and three-dimensional cultures can be tested in high-throughput settings, there should be no limitations in testing all compounds against each other at various concentrations. Thus much of the sorting processes can be done in vitro leaving the in vivo studies for validation only. As cell lines can be readily generated from genetically engineered mouse (GEM) models, they can be promptly used for preclinical studies to save time and cost and increase reproducibility. Finally, patient-derived xenografts and GEM models could be used not only to test the efficacy but also possible toxicities of the combinations. Although there are not yet precedents in mouse models of melanoma, based on experience with models of lung, breast, and pancreatic cancer, we expect that preclinical trials in GEM and relevant xenograft models could guide the development of effective drug combinations. All this work could be followed by extensive ‘omics’ studies to discover new biomarkers for model selection and therapy response. These preclinical data will need to be validated in future clinical trials. Such preclinical and biomarker studies cannot be easily done by a single laboratory but within a consortium modeled after those for clinical trials. The preclinical community has to learn to work closely together. How can the clinical trialists use the new information for planning of future clinical trials? Will companies cooperate and allow novel combination trials? We need to try and work hard to convince them. We cannot miss a single opportunity for new treatments that could potentially lead towards cures and together we have to rise to the challenge.

References