

## **SMR News Piece: Why no new approved therapies for melanoma?**

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A contentious session of the last year's ASCO annual meeting focused upon the dearth of new drugs for melanoma, and questioned whether the absence of new inroads to effective therapy for melanoma is related to bad drugs, bad trial designs, or a bad disease? In fact, after 35 years of work upon this disease, it appears that the finger of blame for the stalled efforts in melanoma can be pointed at many components of the scientific chain of development for understanding of the biology, immunology and therapy of melanoma. This short discussion, from a pair of medical and surgical specialists who have worked for over 20 years to develop more effective therapies for melanoma, will conclude that we have a rare opportunity to understand this disease and its molecular and immunological origins. However, melanoma has not enjoyed the level of systematic support that many other solid tumors have received, and it is apparent that we have devoted fewer resources than would seem appropriate to the understanding and clinical investigation of melanoma than to many other cancers.

The funds lavished upon development and investigation of new agents for breast, prostate, lung, colorectal and ovarian cancers far exceed what has been devoted to melanoma. At the level of public information and congressional lobbying, we have had a small and thus far splintered constituency that has not mobilized governmental sponsorship nor generated a high level of interest from most of the pharmaceutical industry in this disease. Finally, inadequate communication among the clinical and basic scientific members of our community in academia, government and industry has led to widening gaps in the support of melanoma research. While there are regularly convened NCI supported Progress Review Groups (PRGs) for many other solid tumors, there is none for melanoma—and at the first (and only) State of the Science meeting for melanoma three years ago, it was made clear that no options for a new melanoma PRG exist in the near-term.

With only one cytotoxic drug and one biological agent approved and currently used for the treatment of advanced melanoma (hydroxyurea was approved for use in advanced melanoma but today is considered essentially devoid of activity in this disease), neither of which has ever been shown to convey an overall survival benefit, there is no question that melanoma therapy lags seriously behind other major solid tumors. The failures of several new bids for approval of new agents and combinations may be attributed to the small increment in response, and its lack of significance—but here the focus upon response rates for evaluation of therapeutic impact may be misguided. Little data exists to support the contention that response rate increments correlate with survival increments in melanoma. Even doubling of response rates in our trials has not been sufficient to move survival endpoints. In the one situation in which survival has been documented to be improved in this disease, the adjuvant therapy of high-risk melanoma with high-dose IFN $\alpha$ , the lack of consistency among three cooperative group trials, combined with

diminished survival impact past 10 years in the most mature study, has caused existential doubts for our field at large.

For melanoma, prevailing attitude has been that only clinically meaningful and statistically significant benefits upon survival would be unequivocal tickets to approval for new agents and/or combinations. But perhaps the endpoint of survival is one that ought not be the initial focus of new trials in advanced disease: progression-free survival has been accepted by the FDA in principle, and progression-free survival at 4 or 6 months appears to be of use in other diseases for the assessment of new therapeutic interventions. For other malignancies, small increments in time to progression or in symptom scores have served as the basis for approval of new therapies. In the most recent FDA deliberations relating to melanoma, we have seen openness to consider progression free survival as an approvable endpoint for melanoma trials. What this increment in progression free survival would need to be has yet to be argued, but this is a most encouraging turn of opinion. Within the cooperative groups, we wonder whether the long and arduous experience to date can be examined to define outcome endpoints that would be so consistent that one might, in the setting of a multicenter trial conducted in similar cooperative group institutions, be able to argue from observations made even in single arm studies. We need to ask what the impact upon progression free survival would be sufficient to be credible? We need rigor in our trials, and open paths to more rapid drug discovery through definition of more relevant and rapidly ascertained intermediate endpoints for our therapeutic trials in advanced disease—such as progression free survival rates at, say, 4, 6 or 12 months. If these are correlated to improved overall survival, or to meaningful improvements in patient quality of life, the rate of progress will be accelerated and the options to examine many more of the promising new agents before us will be increased.

More to the point, we may need to look earlier in the progression of disease to evaluate new therapies: studies in advanced inoperable disease may be the least susceptible to therapeutic alteration, and earlier intervention in the adjuvant setting, or better yet, the prevention arena, may hold the greatest promise. There has not been an active trial in the group of patients with a single lymph node involved with microscopic tumor since the closure of the E1694 trial in 2001—and no prospective trial of an agent for prevention (chemoprevention) has yet been conducted for melanoma. The field needs to develop these areas of opportunity, since it is likely here that the options are brightest for a new agent to demonstrate a therapeutic benefit.