

Improved melanoma survival at last! Ipilimumab and a paradigm shift for immunotherapy

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Most melanomas express antigens that can be recognized by T cells of the host immune system. However, by the time a tumor has become manifest, immune escape must have occurred to allow tumor outgrowth. It had been reasoned that this putative immune escape would likely be at the level of failed T cell priming, which led to the empiric development of various melanoma vaccine strategies. However, more recent data has suggested that a major mechanism of tumor escape from immune destruction is via dominant negative regulatory pathways that impart a state of peripheral T cell tolerance. These inhibitory pathways can be in the form of cytokines (e.g. TGF- β and IL-10), suppressive cell populations (e.g. Tregs and myeloid-derived suppressor cells), amino acid-catabolizing enzymes (e.g. indoleamine-2,3-dioxygenase (IDO) and arginase), and ligation of inhibitory receptors on activated T cells (e.g. CTLA-4 and PD-1), among others (Gajewski et al., 2006). These notions have led to active clinical development of strategies to block specific negative regulatory pathways that may potentiate anti-tumor immune responses and thus lead to improved tumor control.

Monoclonal antibodies (mAbs) against CTLA-4 are the farthest along in development. Two fully human anti-CTLA-4 mAbs, Ipilimumab (developed by Medarex and BMS) and Tremelimumab (developed by Pfizer) have shown single agent activity in patients with metastatic melanoma (Camacho et al., 2009; O'Day et al., 2010). Importantly, results of a positive phase III clinical trial of Ipilimumab were recently reported at the ASCO 2010 annual meeting and published in the *New England Journal of Medicine* (Hodi et al., 2010). In the recently published study by Hodi and colleagues, 676 patients with previously

treated advanced melanoma were randomized to be treated with either a gp100 peptide vaccine, Ipilimumab, or a combination of the gp100 vaccine and Ipilimumab. The median survival for the Ipilimumab alone group was 10.1 months compared to 6.4 months for the gp100 vaccine alone ($P < 0.001$). The combination arm showed a similar outcome to Ipilimumab alone. Grade 3–4 adverse events occurred in around 15% of patients treated with Ipilimumab, most of which were immune-related, and this included seven patient deaths that were associated with Ipilimumab treatment. Such immune-related adverse events are consistent with what had been observed in phase II studies of the drug.

These results are noteworthy and paradigm-shifting for several reasons. First, they represent the first positive randomized clinical trial ever reported in patients with metastatic melanoma. The two established FDA-approved drugs for this disease, the chemotherapeutic agent dacarbazine and the immune-stimulating agent IL-2, were approved without phase III clinical trial data. Second, they are the first bona fide positive data showing a beneficial effect of a melanoma treatment in the second line setting. Third, they demonstrate that clinical benefit can be derived from an immunotherapeutic approach for cancer without immediate frank tumor shrinkage. Although the response rate by RECIST criteria was only 11%, the one- and 2 yr survival rates with Ipilimumab were 46 and 24%, respectively. Forth, and most importantly, they represent the first example of blockade of an immune inhibitory pathway as a cancer therapeutic. These results should fuel accelerated development and clinical trial testing of agents that block the effects of other negative regulatory pathways postulated to restrain anti-tumor immune responses.

The study by Hodi et al. has some limitations. First, the gp100 peptide-based vaccine used as the control arm is not an established second-line therapy for melanoma. However, there is arguably no standard second-line treatment for this disease, so it is hard to

envison a better reference point for comparison. Second, it has been suggested that some melanoma vaccine platforms may have a detrimental effect on patient outcome, and so it is theoretically possible that the vaccine arm may have done worse than expected. While those reported effects from other studies are weak, they regardless are probably not relevant to this study. The same gp100 vaccine used in this study showed positive results when combined with high-dose IL-2, as presented at the ASCO 2009 annual meeting. In addition, the 6.4 month median survival reported in the current study is not worse than what has been seen in other large melanoma clinical trials.

How should these Ipilimumab data be integrated into continued optimization of therapies for melanoma into the future? First, not all patients show clinical benefit to the agent. There is likely inter-patient heterogeneity, either at the level of somatic differences of the tumor or at the level of germline polymorphisms in immune regulatory genes. Recent results have suggested that a subset of melanoma patients display an inflamed tumor microenvironment (Harlin et al., 2009), and it is tempting to speculate that the patients gaining clinical benefit from this agent are among those who have an ongoing smoldering interaction between the tumor and the host immune system. Identifying predictive biomarkers associated with benefit from Ipilimumab should receive increased attention, to enrich for a subset of patients likely to respond and to spare other patients from unnecessary toxicity. Second, it seems likely that combination treatments will have a greater clinical impact. Preclinical data have indicated that anti-CTLA-4 mAb can show synergistic effects with several positive immune stimulators (e.g. selected cancer vaccines) and interference with other negative immune regulators (e.g. regulatory T cells). Thus, the field should look forward to logical combinations to pursue in the clinic based on sound animal data. Third, evaluation of inhibitors of other immune inhibitory pathways as a cancer therapeutic strategy should proceed at an accelerated pace. Agents

Coverage on: Hodi, F.S., O'Day, S.J., McDermott, D.F. et al. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* doi: 10.1056/NEJMoa1003466.

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are already in clinical testing to interfere with TGF- β signaling, PD-1, Tregs, and IDO, and it is not difficult to envision combination studies to block two or more pathways in concert, in the near future. Finally, signal transduction inhibitors that block the activity of specific mutated kinases in melanoma, including B-Raf and c-kit, have shown high rates of clinical activity in patients bearing melanomas with the relevant mutations. Agents that target other pathways are also in clinical development. As many of the clinical responses to these agents appear to be of short duration, integrating an immunotherapeutic strategy in combination is logical to consider, perhaps to capitalize on the rapid tumor cell death that occurs that could deliver

tumor-derived antigens to the host immune system.

It is indeed exciting to have a spectrum of active agents in clinical development for melanoma. A thoughtful path forward is likely to improve the outcome of patients with this disease, while catering therapeutic choices to specific biologic properties of the tumors in individual patients.

References

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TRP-ing off the p53 apoptotic switch

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Sustained angiogenesis is a common hallmark of many tumours and contributes significantly to the invasion and metastatic potential of tumour cells. The hypoxia inducible factor (HIF) is a key transcription factor responsible for maintaining oxygen homeostasis and regulating angiogenesis (Bertout et al., 2008; Kaelin and Ratcliffe, 2008). HIF is deregulated across a broad range of cancers and is associated with increased mortality and treatment failure (Semenza, 2010). Previous studies have demonstrated that HIF- α , the regulatory subunit of HIF, is not only involved in cellular adaptation to oxidative stress, but also has an important function in regulating p53-dependent cell death responses (Carmeliet et al., 1998). Tumour cells that adapt to evade cell death and induce angiogenesis in response to changes in the tumour microenvironment are generally more aggressive and metastatic. However, precisely how HIF and p53 co-operate to maintain cellular

integrity is unclear and many avenues of HIF-p53 regulation and interaction are yet to be explored.

A recent study by Sandoel and colleagues has utilized the nematode *Caenorhabditis elegans* to provide novel insights into mechanisms linking HIF and apoptosis (Sandoel et al., 2010). Both HIF and the apoptotic machinery are evolutionarily conserved and well characterised in *C. elegans*. Irradiation induced DNA damage and cell death in the germ line of *C. elegans* is regulated by Cep-1 (the *C. elegans* homologue of p53). Intriguingly, Sandoel and colleagues identify a mechanism by which Cep-1 is transcriptionally repressed by HIF-1 (Sandoel et al., 2010). Sandoel and colleagues begin their investigation by demonstrating that in wildtype *C. elegans*, DNA damage induced by ionizing radiation (IR) increases germ cell apoptosis. However, in *C. elegans* that overexpress HIF-1 due to *vhl-1* (von-Hippel Lindau) mutation [*vhl-1(ok161)*], apoptosis is significantly impaired. HIF-1 is subsequently shown to protect *C. elegans* against apoptosis by targeting Cep-1 specifically (Sandoel et al., 2010). In contrast to these findings, a previous report has shown that HIF-1 α binds and stabilizes p53, thus promoting p53-mediated activation (An et al., 1998). Other studies have shown that p53 activation inhibits HIF-

1 α -mediated responses in tumour cells (Yang et al., 2009).

Sandoel and colleagues now present a novel mechanism for Cep-1 inhibition by HIF-1 that involves transcriptional upregulation of the tyrosinase family member tyrosinase-related protein 2 (TYR-2). Tyrosinases are specific enzymes involved in catalysing production of the pigment melanin in melanocytes. TYR-2 expression is induced by stabilised HIF-1 α in *vhl* mutant *C. elegans* and this occurs specifically in ASJ neurons present in the head of *C. elegans*. TYR-2 is secreted by the ASJ neurons and is taken up by endocytosis to inhibit apoptosis specifically in germ cells, in a non-autonomous fashion. The dependency of this effect on TYR-2 was confirmed by Sandoel and colleagues using RNAi to knock down TYR-2 which restored sensitivity to IR-induced apoptosis in the germ cells of *vhl-1* mutant *C. elegans* (Sandoel et al., 2010). The fascinating model proposed by Sandoel and colleagues in which neurons are able to regulate HIF transcription and transmit a long range signal to protect distant tissues from DNA damage and stress is summarised in Figure 1A.

The anti-apoptotic functions of TYR-2 in *C. elegans* appear to translate to human cells: Sandoel and colleagues found that shRNA inhibition of human

Coverage on: Sandoel, A., Kohler, I., Fellmann, C., Lowe, S.W., and Hengartner, M.O. (2010). HIF-1 antagonizes p53-mediated apoptosis through a secreted neuronal tyrosinase. *Nature* 465, 577–583.

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