State-of-the-art treatment for advanced melanoma

Progress in treating melanoma has lagged behind many other cancers for decades. But a number of novel approaches, based on better understanding of the role of the immune system, better selection of patients and the identification of targetable mutations, is now offering a glimmer of hope.

Before 2010, advanced melanoma was considered a disease with very poor prognosis. Mortality was increasing compared to other cancers, and median survival remained at only six to nine months in most studies. There were few, if any, effective therapies. Interferon (IFN) had limited effect, and dacarbazine (DTIC) and high-dose interleukin-2 (IL-2) had no confirmed effect on overall survival. High-dose IL-2, which was a standard in the US, had significant toxicity. There were no positive phase III trials for overall survival.

For cytotoxic chemotherapy, there is currently no evidence that single agents, combination chemotherapy or the addition of tamoxifen or IFN to DTIC is superior to DTIC alone. Although some data suggest that the combination of carboplatin and paclitaxel might be superior to DTIC alone, these treatment approaches have not been formally compared.

High-dose IL-2 therapy became the standard in the US in 1998, based on data showing a response rate of about 16%. Some responses

European School of Oncology
e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Michael B. Atkins, from the Beth Israel Deaconess Medical Center, Dana Farber/Harvard Cancer Center and Harvard Medical School, Boston, USA, provides an update on the latest developments in treating patients with advanced melanoma, and looks at what the future may bring.

Daniel Helbling, Onkozentrum Zurich, Switzerland, poses questions sent in by participants during the e-grandround live presentation, which is summarised here by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

were very durable, with the median duration of response being 8.9 months and the median not being reached for complete responders. There was limited impact on overall survival, but among responders, any patient who was still responding at 30 months has remained in response for more than 10 years (*JCO* 17: 2105–16, *Cancer J Sci Am* 6 [suppl 1]:S11–S14).

High-dose IL-2 appears to be useful and we still use it in the US, but it is toxic and requires inpatient treatment, making it expensive and impractical. Therefore, its use is limited to selected patients treated at experienced centres. Efforts to better select patients who might benefit from IL-2 therapy are warranted and we are currently actively investigating this.

The therapeutic landscape in 2010

Looking at the therapeutic landscape in 2010, results may be improving a little bit for non-specific reasons: earlier treatment, better patient selection, improved treatment of brain metastases and better systemic therapy. But new approaches are clearly necessary. Unless new approaches are unquestionably active, it is likely that they will need to be studied in phase III trials.

Question: *Is there a predictive tool in metastatic melanoma to select on the basis of genetic profile?*

Answer: *There are mutations that help select therapies, particularly for therapies that target protein products of C-KIT or B-RAF mutations. But these mutations may also help us select for who might respond to immunotherapy. We may also need to come up with therapies for patients whose tumours don't have those mutations.*

Promising therapeutic approaches

Immunotherapy

The benefit from immunotherapy may be limited by the ability of T cells to infiltrate a tumour. Melanomas may vary in their degree of immune infiltration, with about 24% of tumours having a high degree of immune infiltration and 40% having very little T cell infiltration. The higher the degree of immune infiltration, the better the outcome. This is particularly true if the infiltrating cells are CD8+ T cells.

Using an immune signature based on gene expression profiling, we have found that patients whose tumours have this signature are more likely to respond to high-dose IL-2 and have a significantly longer median progression-free survival, of 19.4 months for the class 2 immune versus 2.5 months for class 1 antigenic gene expression signatures, respectively (*JCO* 27:15S, abstract 9003).

Another factor potentially associated with response to high-dose IL-2, which may be worth investigating with novel immunotherapies, is mutational status. A significantly larger proportion of patients with *B-RAF* and, particularly *N-RAS*, mutations are likely to respond to high-dose IL-2 compared to those with wildtype tumours (*JCO* 28:15S, abstract 8597). More data are needed on this.

Elevated lactate dehydrogenase (LDH) status is a negative predictor for response to high-dose IL-2. If the patient has a high level of LDH released from the tumour, which is a poor prognostic finding, he/she will be less likely to respond to high-dose IL-2 therapy, with a response rate of 6% and no complete responses.

It is becoming clear that LDH regulation is associated with hypoxia. Other hypoxia-related genes such as *VEGF* (*JCO* 27:2645–52) are also inversely associated with likelihood of benefiting from high-dose IL-2 therapy.

In summary, with regard to high-dose IL-2 tissue-based predictive biomarkers, a novel immune-based gene expression profile appears to predict for better progression-free survival and, possibly, response to high-dose IL-2. The association of clinical benefit with immune response signature suggests a possible mechanism for high-dose IL-2 anti-tumour effect based on immune cells that are already present in the tumour and blocked for a particular reason.

This is part of the reason we were so excited about some of the novel immunotherapies. The fact that both *B-RAF* and *N-RAS* mutational status may predict for favourable response to high-dose IL-2 suggests opportunities for combination studies. An elevated LDH or *VEGF* may predict for lack of response to high-dose IL-2, so different treatments may be necessary for those patients.

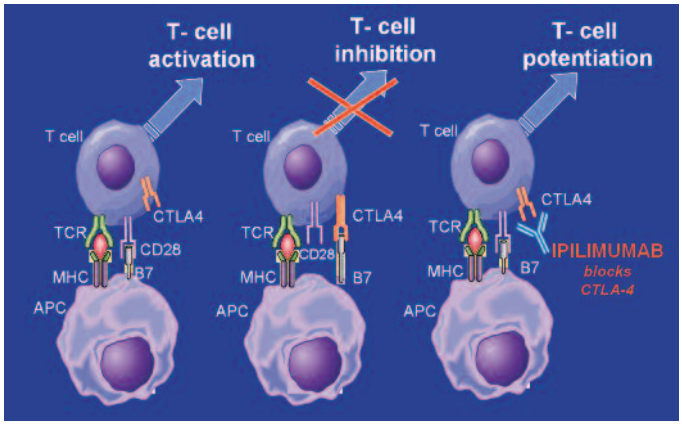
Question: *Which patients do you treat with high-dose IL-2? How do you select these patients?*

Answer: *In the US, we treat patients who have good performance status (0–1), good heart and lung function, no CNS metastases and, based on the data I have just described, normal LDH. We are not yet selecting patients based on mutational status of their tumours, but we are carrying out a prospective trial to see whether factors including mutational status and immune signature will predict which patients benefit from IL-2 based therapy.*

Novel immunotherapy

Ipilimumab is a novel type of immunotherapy. When the immune system recognises an antigen on an antigen-presenting cell (APC), binding occurs between a Tcell receptor (TCR) and a co-stimulatory molecule, CD28.

IPILIMUMAB TAKES THE BRAKES OFF THE IMMUNE SYSTEM



By blocking the binding between CTLA4 and B7, this new type of drug allows the immune system to do its job

Source: Adapted from Lebbe et al, oral presentation 769O at ESMO 2008

When this binding takes place, CTLA4 is upregulated on the surface of the T cell. This out-competes CD28 for binding to be severed on the antigen-presenting cell, which leads to a shutting off of T cell function. CTLA4 antibodies such as ipilimumab block binding between CTLA4 and B7 and allow for that brake on the immune system to be removed, and for the immune system to continue to expand (see figure *above*).

The two antibodies blocking CTLA4 that have been studied extensively – ipilimumab and tremilimumab – both produce responses in 8–15% of patients with refractory melanoma. These responses are associated with autoimmunity, because taking the brakes off the immune system happens not just within the tumour but also within organs that are protected from autoimmunity by CTLA4. Responses are durable in many patients, with the majority lasting longer than two years: 20–30% of patients have durable disease control longer than three years.

In contrast to IL-2, activity is seen in the central nervous system and is not prevented by steroid co-administration. Responses are delayed at onset and can show tumour flare before response.

The CT scan in the figure below shows extensive disease on the patient's abdominal wall at baseline, which gets worse three weeks into therapy, but has completely disappeared by four months. This pattern is seen in about 10-20% of patients who respond to ipilimumab. It calls into question the standard RECIST criteria for disease progression, and may have confounded the interpretation of some of the early studies with ipilimumab.

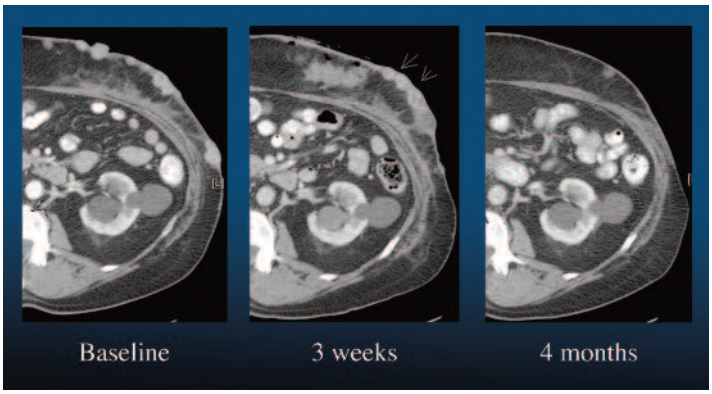
Pivotal trials with ipilimumab

A trial presented at ASCO last year (2010) by Steve Hodi (*NEJM* 363:711–723) randomised patients who were originally HLA (human leukocyte antigen) A2+ to a low dose of ipilimumab (3 mg/kg), either alone or in combination with gp100 peptide vaccine, or to gp100 vaccine alone. Results showed an overall survival advantage for the ipilimumab-containing arms but no advantage for the vaccine, either alone or when added to ipilimumab.

A pivotal phase III trial with DTIC +/- ipilimumab (10 mg/kg) completed accrual a couple of years ago and the required events have just been achieved. Positive results showing an improvement in overall survival for the DTIC + ipilimumab arm relative to DTIC alone were recently reported (*NEJM* 364:2517–26). The Cytokine Working Group has looked at ipilimumab in patients with CNS metastases and we have seen similar activity to that seen in systemic disease.

Adjuvant studies are currently ongoing in patients with stage III disease: one in Europe comparing ipilimumab to observation, which is nearing completion, and a second that

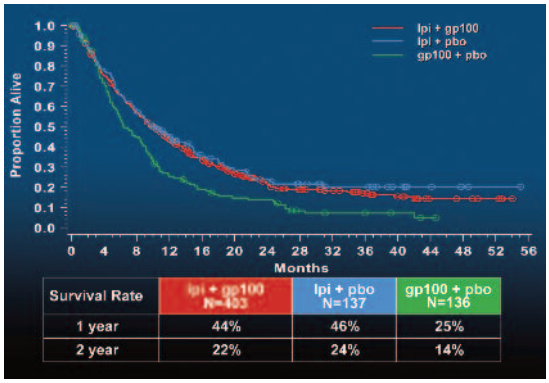
CTLA4 BLOCKERS: IT CAN GET WORSE BEFORE IT GETS BETTER



This typical pattern of a flare up followed by response must be borne in mind when evaluating response to treatment

Source: Courtesy of Michael B Atkins

IPILIMUMAB: SURVIVAL ANALYSIS



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Kaplan-Meier analysis shows a clear survival advantage for both ipilimumab arms in this trial for use as a second-line therapy

Source: FS Hodi et al. *NEJM* (2010) 19:363:711–723. Printed by permission from Massachusetts Medical Society

has just opened in the US, comparing ipilimumab to interferon.

The second-line phase III trial presented at ASCO in 2010 randomised patients with pretreated metastatic melanoma to ipilimumab plus gp100 (60%), ipilimumab plus placebo (20%) or gp100 plus placebo (20%). Both the ipilimumab arms showed superior overall survival to gp100 alone, with 44–46% of patients alive at one year, compared with 25% with placebo alone (see figure *above*). Twice as many patients treated with ipilimumab were alive at two years compared to those given placebo alone.

There was a fair amount of toxicity related to ipilimumab. This was primarily autoimmune toxicity, including dermatologic side-effects, gastrointestinal side-effects such as colitis, and a small percentage of patients with endocrine or hepatic side-effects. These are the major side-effects related to ipilimumab, which need to be kept in mind and treated aggressively with steroids if they occur.

Summing up, it appears that CTLA4 antibody enables immune responses and anti-tumour responses in some individuals. Tumour expression of PD-1 ligand may prevent immune response even with CTLA4 blockade by inducing T cell death, serving as 'barbed wire' to those immune cells that may be in the tumour. Given that melanoma cells have been shown to express PD-1 ligand, CTLA4 antibody effects might be augmented by antibodies that inhibit the PD-1 pathway. Controlling immune regulation may provide a way forward for immunotherapy of patients with melanoma.

Question: *Auto-immunity is a major concern. My first impression was that ipilimumab is not very targeted, because it releases the immune system to fight against anything it finds. Do you think it is really a targeted approach for melanoma patients? Are you not particularly concerned about auto-immunity?*

Answer: *I think people should have a healthy respect for auto-immunity. Patients can get into very serious trouble if the auto-immune side-effects are not treated quickly with steroids and, if necessary, infliximab. It is interesting that treating the auto-immune side-effects can control them without preventing the anti-tumour response, so you do not have to be worried about giving immunosuppressants the way you might be with other immunotherapies. If you delay treating auto-immunity, the effects can be severe. But if you are attuned to the problem and react quickly, you can provide this therapy safely in an outpatient setting and patients can achieve the benefit. Nonetheless, it is not as targeted to the tumour as we would like.*

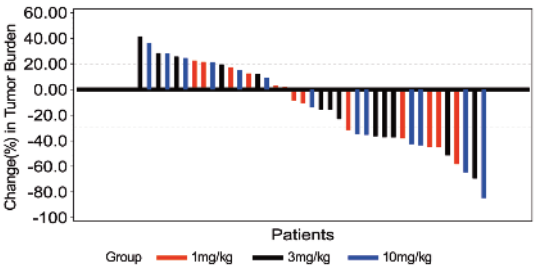
Question: *Can ipilimumab be used as a neoadjuvant therapy in patients who are potentially resectable?*

Answer: *I think that is a potentially useful research tool and ongoing studies are using ipilimumab as neoadjuvant therapy. However, fewer than one-third of patients show responses. I would not advise this outside a research study, as the toxicity might complicate surgery.*

Question: *Are auto-immunity and side-effects related to response – can they be surrogate markers?*

Answer: *Yes, it appears that auto-immunity is related to response. The response rate in patients who get auto-immune side-effects is 40–50%, while it is closer to 5% in those who do not. This tells us that the mechanism of the response is probably unleashing latent auto-immunity against the tumour cell. At the same time, those patients who*

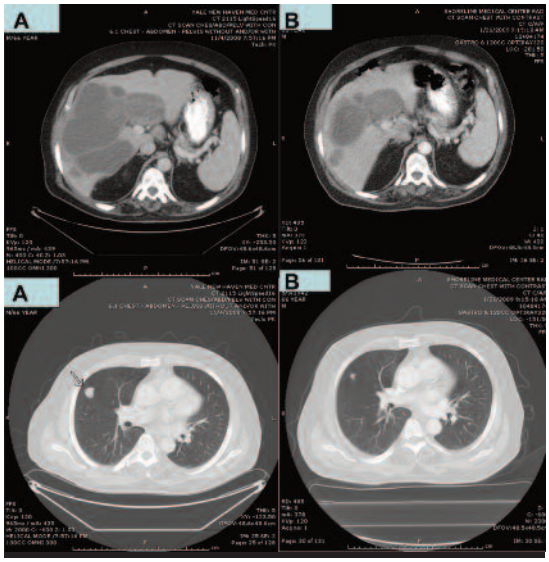
PD-1 ANTIBODY: CHANGE IN TUMOUR BURDEN



Tumour shrinkage occurred in more than 50% of patients treated with various doses of a PD-1 antibody in this phase I trial

Source: M Sznol et al ASCO 2010 presentation, abstract 2506

PD-1 ANTIBODY: OBJECTIVE RESPONSE



Response to PD-1 antibody (1 mg/kg) of liver (*upper*) and lung (*lower*) metastases in a 66-year-old male patient with melanoma, who had progressed on high-dose IL-2. *A* shows the baseline and *B* shows after one cycle of treatment. The patient met the partial response criteria after three cycles of treatment, and the response was still continuing at 12+ months

Source: Courtesy of M Sznol, Yale University

develop immune reactions against their tumours probably also have some sort of defect in their immune regulation that allows them to also develop reactions against their colon, their skin or their liver.

PD-1 antibodies and inhibitors

PD-1 antibodies, or PD-1 inhibitors, may provide more tumour-specific immune suppression. When T cells are exposed to the tumour, they up regulate PD-1 on their surface. PD-1 is a member of the CD28 family involved in T cell regulation. When it binds to tumour or antigen that is expressing PD-L1, this causes apoptosis or exhaustion of the immune cells. This happens primarily in the tumour or in chronic inflammatory situations. If you could block the interaction you might be able to restore the activity of the immune system selectively within tumours.

A phase I study of an antibody to PD-1 presented at ASCO in 2010 (*JCO* 28:15S, abstract 2506) treated 46 patients with melanoma with three different doses. Almost 33% (15/46) exhibited tumour responses. All of these responses were ongoing (with the longest >18 months) when the results were reported. More than 50% of patients had tumour shrinkage on a waterfall plot at different dose levels (see figure *opposite page, below*).

The figure (*this page, top left*) gives an example of response in a patient with very extensive liver metastases as well as some lung metastases that reduced dramatically within two cycles of treatment with PD-1 antibody, even at the 1 mg/kg dose.

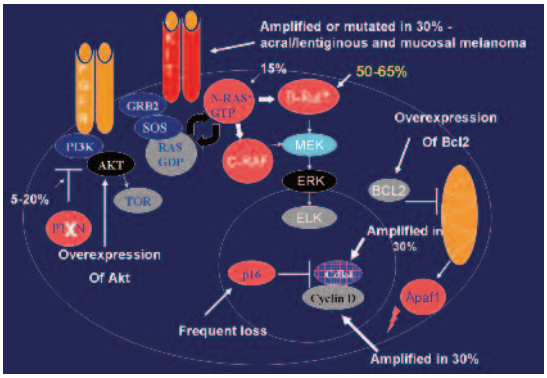
Early trials show tumour response in more than 30% of heavily pretreated patients with advanced melanoma (*JCO* 28:15S, abstract 2506), which is very exciting. Responses have also been seen in other cancers, including lung, colon and kidney cancer, which are durable to date. The toxicity seen so far has been relatively mild, without the degree of auto-immunity seen with ipilimumab. Combination studies with ipilimumab and PD-1 antibody are now underway, and other studies are being considered. Overall, it is possible that the PD-1 antibody may offer even more tumour-specific targeted immunotherapy.

Targeting molecular alterations in melanoma

Around 50–60% of melanomas have mutations in a very specific area, V600E or K mutations in *B-RAF*. A complementary 15% of tumours have mutations in *N-RAS* and about 30% of patients with mucosal or acral/lentiginous melanomas have amplifications or mutations in *C-KIT* (see figure *below*).

These mutations are not distributed randomly across melanomas. Tumours in moles or in non-chronic sun-damaged skin are more likely to have *B-RAF* mutations, but rarely have *C-KIT* mutations. Tumours in chronic sun-damaged skin, acral/lentiginous or mucosal areas are more likely to have *C-KIT* amplification or mutations. Tumours that have *C-KIT* mutations are very sensitive to inhibitors of *C-KIT* such as imatinib. The figure overleaf shows a PET scan before and after four weeks of treatment, with dramatic reduction in the PET uptake of multiple tumour metastases (*JCO* 26:2046–51).

MOLECULAR ALTERATIONS IN MELANOMA



Experience with *C-KIT* inhibitors

C-KIT inhibitors have dramatic effects in patients with melanomas containing a variety of *C-KIT* mutations. However, these mutations occur in less than 1% of all melanomas. The role of *C-KIT* inhibition in *C-KIT* amplified tumours is yet to be fully established and it is possible that those with amplifications in *C-KIT* may be less responsive than those with mutations in *C-KIT* or not responsive at all.

Despite being rare tumours in Europe and the US, mucosal melanomas make up the majority of melanomas in Asia, particularly in India and China. *C-KIT* mutated tumours are, therefore, much more prevalent. Multiple studies are currently underway with imatinib, sunitinib, dasatinib and nilotinib, including an international phase III trial comparing nilotinib versus DTIC in patients with *C-KIT* mutated mucosal melanomas. This is all very exciting, and provides a proof of principle, but it is not the answer for the majority of patients with melanoma.

B-RAF inhibitors in melanoma

Initial studies to determine whether *B-RAF* inhibitors had activity in melanoma did not select by mutational status and used sorafenib, which is a very poor *B-RAF* inhibitor. Studies showed limited or no activity with single-agent sorafenib. A phase II trial of sorafenib combined with DTIC showed some improvement in progression-free survival (*JCO* 26:2178–85). But there was no additional benefit when combined with carboplatin/paclitaxel (E2603, PRISM), either in a first-line co-operative group trial or a second-line industry-sponsored trial.

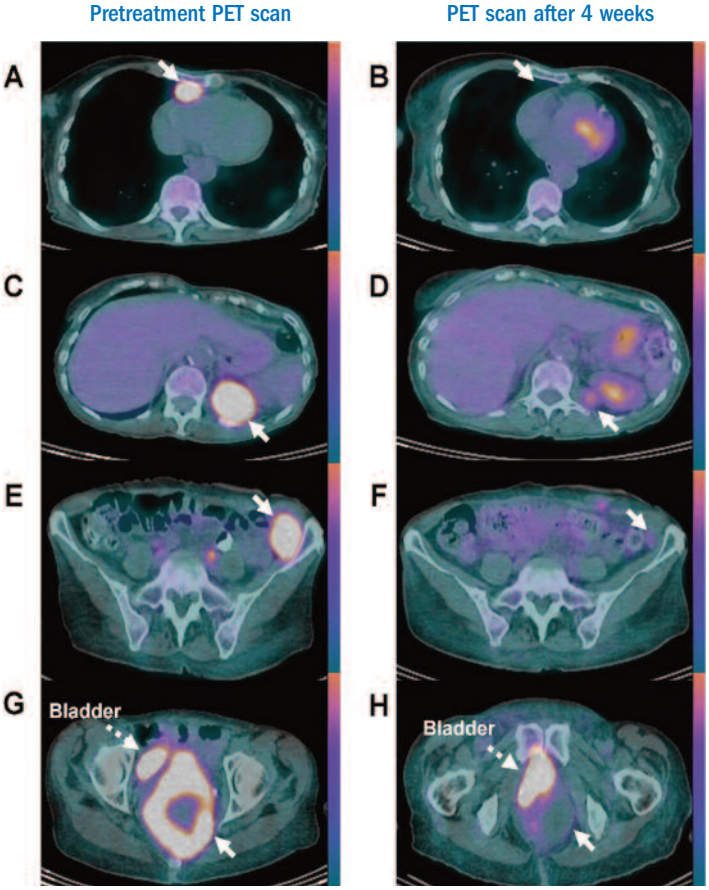
We did not know whether the poor response was because sorafenib was a poor *B-RAF* inhibitor or because *B-RAF* was not an important target in melanoma. We needed better tools to answer these questions, and two of these have now come along: PLX 4032/RG7204, which is a more selective inhibitor of mutant *B-RAF* (*NEJM* 363:809–819); and GSK 2118436, also a selective inhibitor of *B-RAF* (*JCO* 28:15S abstract 8503). Both of these have shown promising data.

Studies show that PLX4720 inhibits tumour growth in *B-RAF* mutant tumours but has no activity in wildtype tumours. Results from a phase I trial of PLX4032 in patients with mutant *B-RAF* tumours (*NEJM* 363:809–819) showed tumour response in 70% of patients, including one complete response, even though many had M1c disease (metastases involving visceral sites beyond lung and/or an elevated LDH) (see bar-chart *opposite*). A dramatic response was seen on PET scan within 15 days, showing very significant reduction in glucose uptake in disease in the lungs (see scans *opposite*).

Although this was not a randomised study, survival curves from this phase I study show significant prolongation in progression-free survival, with a median progression-free survival of around eight months in patients with V600E mutations treated at the optimal dose (see graph *opposite, lower*).

This treatment is associated with some toxicity, including arthralgia, photosensitivity, rash, fatigue, pruritus and palmar-plantar dysaesthesia, although mostly not serious (grade I and II) (*NEJM* 10:363:809–819). The most troubling side-effect is cutaneous

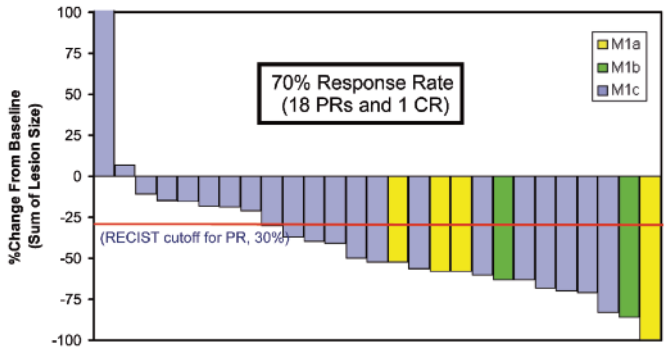
C-KIT INHIBITOR IN PATIENT WITH *KIT*-MUTANT MELANOMA



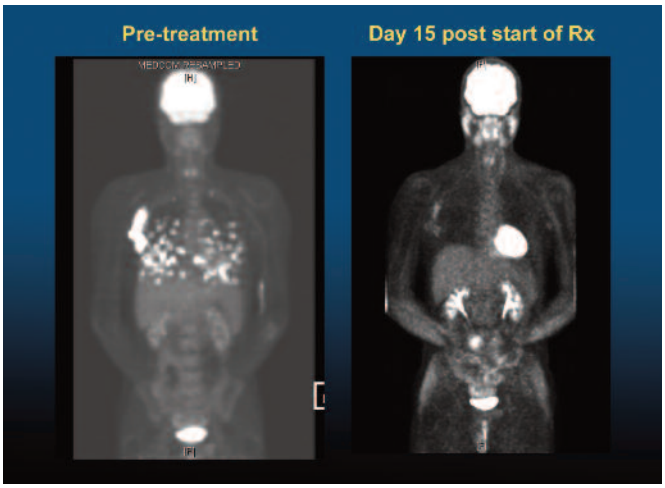
Source: S Hodi (2008) *JCO* 26:2046–51, reprinted with permission © American Society of Clinical Oncology. All rights reserved

PHASE 1 TRIAL OF PLX4032 IN *B-RAF* MUTANT MELANOMA PATIENTS

Interim best overall response



Reduced glucose uptake by day 15



Above: Interim results for the maximum tumour shrinkage for patients involved in the study show a 70% response rate

Right: These PET scans show a dramatic response to the *B-RAF* inhibitor

Source: Bar chart – K Flaherty et al. (2010) *NEJM* 363:809-819; Scans courtesy of Jeff Sosman, Vanderbilt University

malignancies, which look like squamous cell cancers. They occur in about one-quarter of patients and require follow-up with a dermatologist.

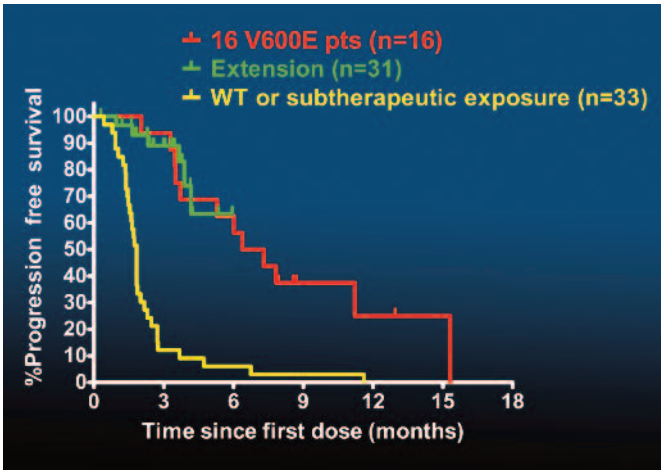
Conclusions from the phase I study are that PLX4032 is tolerable and highly effective, even in patients with extensive prior treatment. Results provide proof of concept that *B-RAF* mutations are critical oncogenic drivers in *B-RAF* mutant melanoma.

There is a lot of excitement around this therapy, which is justified, but its true efficacy will depend on the durability of response and the ability to impact on overall survival.

Larger phase II and randomised phase III studies are necessary to confirm this benefit. These trials have been completed and the results were reported at ASCO 2010. The phase II trial confirmed the efficacy of PLX4032 (vemurafenib) in patients with *B-RAF* mutant melanoma (*JCO* 29[15S)]:abstract 8509), and the phase III trial showed a significant improvement in overall survival for treatment-naïve patients receiving vemurafenib compared to DTIC (*NEJM* 364:2507–16).

Findings with *B-RAF* inhibitors have implications for how we select patients for various therapies. In the future, I think that melanoma studies will divide patients into three classifications: V600 mutant tumours; V600 wildtype tumours and V600 mutant tumours that have progressed after selective *B-RAF* inhibitor therapy. It is very important to carry out studies designed to enhance the efficacy of selective *B-RAF* inhibitors, such as studies combining them with *MEK* inhibitors, with other agents

INTERIM PFS FOR PLX4032



This plot of interim phase 1 data show that patients with the V600 mutation on *B-RAF* show a much better progression-free survival in response to PLX4032 than those with wildtype (WT) *B-RAF*

Source: Courtesy of Keith Flaherty, Massachusetts General Hospital

that might inhibit the development of resistance, and in combination with immunotherapy.

Question: *If you have a patient with metastatic melanoma, do you always test for B-RAF and C-KIT now? Is this standard?*
Answer: *We test B-RAF status in patients who develop metastatic disease or in those with very high-risk stage III disease with intransit metastases. We then incorporate the result into decision making on which the treatments to offer them. We do not test patients who only have sentinel node involvement or who only have primary tumours as there is, as yet, no role established for B-RAF inhibitors in the adjuvant setting.*

What can be done for patients who have elevated LDH?

We are reluctant to give immunotherapy to patients with elevated LDH or with *B-RAF* wildtype tumours. One thing that is becoming clear is that patients who have elevated LDH may be the same as those with elevated *VEGF*, and elevated *VEGF* levels within tumours correlates with poor outcome.

The phase II BEAM study randomised 200 patients treated with carboplatin/paclitaxel in a 2:1 ratio to bevacizumab-containing therapy versus placebo (*Advanced Melanoma: Eur J Cancer Suppls* 7[3]:13).

Survival curves at one year showed a significant, or nearly significant, improvement in overall survival (52% for the bevacizumab-containing arm, compared to 39% for the placebo arm). This was particularly true for patients with M1c disease or those with M1c disease and elevated LDH, with significant benefit for those patients receiving bevacizumab.

This has led to a trial proposed in the US Intergroup by Ryan Sullivan taking patients who have primarily *B-RAF* wildtype tumours or potentially those with tumours containing *B-RAF* mutations who are resistant to *B-RAF* inhibitors, and randomising them to either carboplatin/paclitaxel + bevacizumab or carboplatin/paclitaxel + placebo.

Where are we in 2011?

We are beginning to see a glimmer of hope on the horizon, with novel immunotherapies, some specific and highly active tumour-targeted therapies, antiangiogenic therapies, and the potential ability to select patients for particular tumour types based on molecular profiling.

Question: *There has been very little change in adjuvant therapy over the past years. Which patients do you treat with adjuvant therapy? Do you think those new promises will also translate into benefits in the adjuvant setting?*
Answer: *We still use the standard high-dose interferon regimen for patients with stage IIB and stage III melanoma who are not eligible for research protocols, but who are physiologically 70 years or less, and able to tolerate interferon. We do not yet know whether the new agents that are showing activity in the metastatic setting will be active and tolerable in the adjuvant setting.*

The study carried out in Europe comparing ipilimumab to control in patients with stage III disease has had some difficulty with toxicity. So it remains to be seen whether any benefit seen, or the number cured, is sufficient to justify the toxicity that patients may have to undergo. A trial in the US comparing ipilimumab to interferon will be a truer test as patients in the US may be reluctant to take a placebo.

Whether the B-RAF *inhibitors will have a role in the adjuvant setting is unclear because, at the moment, in contrast to immunotherapy, they are primarily palliative. They cause dramatic tumour shrinkage, but do not appear to be causing durable complete responses. Whether this type of activity in the metastatic setting will translate into eliminating tumour cells, which is what we would like to see in the adjuvant setting, requires investigation.*
Question: *For practical purposes, how do you use interferon? Do you think it can be replaced by Pegintron [peginterferon alpha-2b], because that is better tolerated, or do you give one month of high-dose interferon followed by low-dose for the rest of the 11 months?*
Answer: *In the US, we believe that the high-dose, four-week induction period is the most important component of interferon treatment, so we are reluctant to adjust that in any way. We have a lower threshold for reducing or stopping therapy, because we think that most of the benefit of interferon happens within the first 4–12 weeks. If we are going to modify the treatment, it is more likely in the last nine months of therapy, either using a lower dose or even omitting it, rather than modifying the four-week induction period. Therefore, we have not moved towards Pegintron, at least in our patient population.*
Question: *Are* B-RAF *inhibitors active in patients who have* B-RAF *mutations in their melanoma and who also have CNS metastasis?*
Answer: *PLX4032 has not been formally studied in patients with brain metastases as these patients have been excluded from the trials. But the GSK B-RAF inhibitor has been studied in some patients with CNS disease. A study reported at ECCO in 2010 (*Advanced Melanoma: Eur J Cancer Suppls, *8[3]) showed activity in the central nervous system. We will see more studies including these patients in the future.*