

# Trials in melanoma: Feeling the burn?

Of all the different skin cancers, melanoma is the most recalcitrant indication for new compounds. But recent research has given **Dr John Whittaker, Dr Ewan Millar and Navinder Blundell** grounds for optimism

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Cancers of the skin (basal and squamous cell carcinoma and melanoma) are the most common cancers in many parts of the world and melanoma is the most rapidly increasing tumour worldwide – the number of new cases has doubled over the past 15 years. This article will discuss the current state of some non-surgical approaches to treating melanoma, the reasons many trials have been delayed or cancelled and some other operational considerations for the successful conduct of melanoma clinical trials.

## Stages of disease and surgery

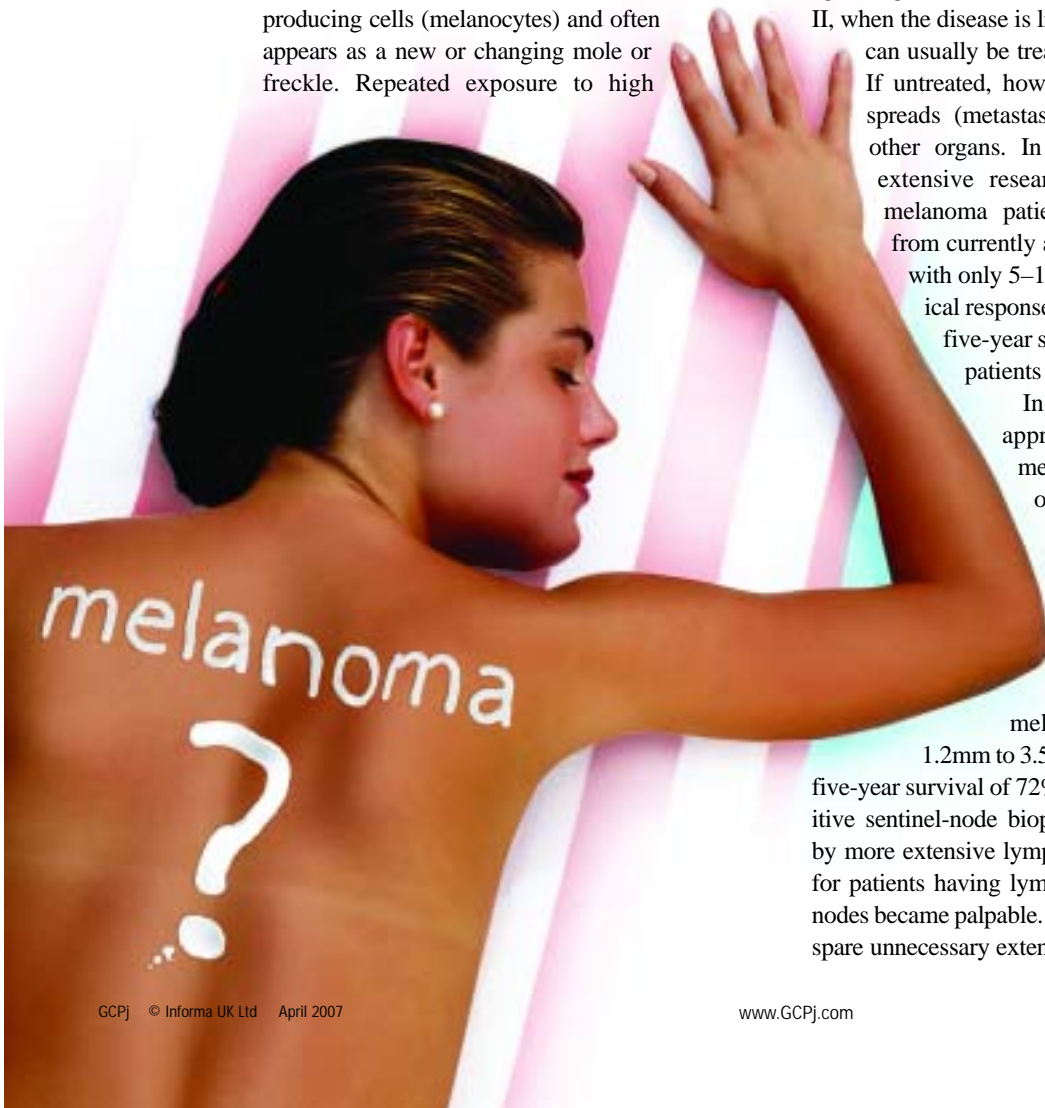
Melanoma (sometimes called cutaneous or malignant melanoma), is a tumour of melanin-producing cells (melanocytes) and often appears as a new or changing mole or freckle. Repeated exposure to high

intensity ultraviolet light (particularly UVB or Medium Wave) is the major contributory factor, with the disease being found predominantly in Caucasians who have experienced repeated sunburn. Melanoma is one of the few cancers that affect the young and is the third most common cancer in women and the fourth most common in men aged 20–34.

Worldwide, an estimated 132,000 people are diagnosed with melanoma and more than 40,000 die from the disease each year. While accounting for just 4% of skin cancer cases, it is responsible for approximately 75% of skin cancer deaths.

Treatment for melanoma varies according to factors such as the extent of the patient's disease, their age and general health. If detected during Stage I and II, when the disease is limited to one site, melanoma can usually be treated successfully by surgery. If untreated, however, the disease frequently spreads (metastasises) to lymph glands and other organs. In spite of three decades of extensive research, metastatic (Stage IV) melanoma patients benefit only modestly from currently approved systemic therapies, with only 5–10% of patients showing clinical response. No treatment has increased five-year survival to more than 20% for patients with distant metastases.

In order to select the most appropriate treatment for melanoma, accurate assessment of the extent of the disease is necessary. Recent evidence suggests that biopsy of sentinel lymph node(s), the first nodes to which cancer spreads, is advantageous in patients with melanomas – particularly of 1.2mm to 3.5mm thickness.<sup>1</sup> In this group, five-year survival of 72% has been observed if a positive sentinel-node biopsy is followed immediately by more extensive lymph node surgery, versus 52% for patients having lymph node surgery later, when nodes became palpable. Also, negative sentinel nodes spare unnecessary extensive lymph node surgery.





Changes in size, shape or colour of a mole could indicate the development of a melanoma.

### Non-surgical approaches

Listed and considered below are a selection of agents that have entered clinical trials and for which phase III data is available.

**Genasense** (oblimersen). This is a novel targeted therapy that blocks the production of Bcl-2, an anti-apoptotic protein that appears to be a fundamental cause of resistance to cancer treatment and is over-expressed in more than 80% of melanoma patients.

Marketing authorisation applications were submitted to the US FDA and more recently the European EMEA by US biopharma company Genta for Genasense, based on a two-year follow-up of patients from a pivotal Phase III trial. While there was no significant difference in median survival between the two entire groups of patients (nine months for Genasense/DTIC patients, against 7.8 months on DTIC alone), nor in patients with high lactate dehydrogenase (LDH) levels (4.5 months in both groups), nor different response rates for high LDH patients (5.7% on Genasense/DTIC and 4.6% on DTIC), the big news is that survival was enhanced for patients with normal LDH levels receiving Genasense/DTIC versus DTIC alone (11.4 months versus 9.7 months). Furthermore, 17.2% of normal LDH patients treated with Genasense/DTIC had a reduction in detectable cancer, versus 9.3% on DTIC alone.

With the company currently anticipating the EMEA's opinion on marketing approval before the end of April, Genasense is likely to be the first new agent to reach market that enhances survival in melanoma patients, albeit in a sub-group of patients with normal LDH levels.

**Nexavar** (sorafenib). Various multi-kinase inhibitors have shown early potential in the treatment of melanoma. In July 2006, the FDA granted fast-track status for the treatment of locally unresectable and metastatic forms of melanoma with Nexavar (sorafenib), an oral multi-kinase inhibitor targeting both tumour cell and tumour vasculature. However, Nexavar failed to meet its primary endpoint of enhanced progression-free survival (PFS) in a pivotal Phase III trial. There had been high expectations for this agent, as it recently became the first treatment approved for advanced renal cell carcinoma (RCC) in more than ten years. It is unclear whether trials will be pursued with this agent in any sub-groups of melanoma patients.

**M-Vax** (autologous DNP-modified tumour cells). Various therapeutic vaccines are in development for melanoma. In April 1999, Avax announced that M-Vax, an autologous (personalised) vaccine,

had received orphan drug designation from the US FDA for the treatment of melanoma. M-Vax is made from an individual patient's tumour cells conjugated to a highly immunogenic hapten (DNP, dinitrophenyl), allowing those cancer cells to be recognised more easily by the immune system.

As recently as 2006, Avax received clearance from the FDA to launch a double-blind 387-patient placebo-controlled Phase III registration trial in Stage IV melanoma under a Special Protocol Assessment. Patients on the M-Vax arm will receive an initial dose of the vaccine followed by cyclophosphamide chemotherapy and then six weekly doses of M-Vax administered with Bacillus of Calmette-Guerin. Subsequent to M-Vax (or placebo) administration, patients receive subcutaneous low-dose interleukin-2. For registration, the trial's primary endpoint of enhanced overall survival (percentage of patients surviving two years) must be met by M-Vax plus best overall anti-tumour response.

**Oncophage** (vitespen, HSPPC-96). This is an autologous vaccine made from the patient's tumour-derived heat shock protein-peptide complex. The 'antigenic fingerprint' from individual tumours reprogrammes the immune system to recognise an individual's cancer cells, not healthy tissue, avoiding side-effects associated with traditional cancer therapies. As early as February 2002, Oncophage became the first personalised cancer vaccine to receive a fast-track designation from the FDA for the treatment of metastatic melanoma, and subsequently for the treatment of RCC. By mid 2002, Oncophage was being studied in Phase III clinical trials for the treatment of malignant melanoma (and RCC) and had received orphan drug designation from the FDA for this indication. In September 2003, however, the FDA imposed a partial clinical hold on two Phase III trials, requesting additional product characterisation information. In November 2003, the FDA lifted its partial clinical hold on the trials and the developer, Antigenics, was permitted to resume enrolment.

By October 2005, preliminary results showed Oncophage improving median survival in patients with Stage IV M1a metastatic melanoma by more than half when compared with standard therapy in an open-label Phase III study. In this study, patients were stratified by American Joint Committee on Cancer (AJCC) metastatic stage of M1a, M1b or M1c. Of the 215 patients randomised to Oncophage, 133 were actually vaccinated and such patients with category M1a Stage IV melanoma experienced an extension in median survival of 20.9 months against a median survival extension of 12.8 months for patients receiving their physician's choice of treatment.

This difference was not statistically significant at that time, but more recently, Antigenics announced that patients with M1a and M1b Stage IV melanoma who received at least ten doses of Oncophage vaccine had experienced an extension in median survival of 29% compared with those who received their physician's choice. When patients with M1a,

M1b and M1c melanoma were combined, however, overall survival results were similar between the intent-to-treat Oncophage arm and the physician's choice arm. As additional Phase III studies would be needed for registration of Oncophage for use in patients with M1a melanoma, it is far from certain that Antigenics will progress commercialisation of Oncophage for melanoma patients.

**Melacine.** If more evidence of the complexity of developing drugs for this indication is required, in February 2002 the FDA's Oncology Drugs Advisory Committee (ODAC), considering a trial to evaluate Corixa's Melacine (melanoma vaccine), agreed that both overall survival and relapse-free survival (in other words, time to relapse) should be the primary endpoints in a trial of patients with intermediate thickness Stage II melanoma whose tumours were completely removed (see [www.fda.gov/ohrms/dockets/ac/02/briefing/3838b1\\_03\\_Melacine.pdf](http://www.fda.gov/ohrms/dockets/ac/02/briefing/3838b1_03_Melacine.pdf)). It was estimated that the trial would take ten years to complete!

In a previous pivotal trial, relapse-free survival had been chosen as the primary endpoint, with overall survival as a secondary endpoint. While overall survival was not significantly improved for the treatment group in the ITT analysis, further analysis found that response to Melacine correlated with patients' human leukocyte antigen (HLA) phenotype. Patients with at least two of five predefined HLA phenotypes (HLA-A2, -A28, -B44, -B45 and C3) did better statistically ( $p=0.0002$ ) than those with none or one HLA match ( $p=0.93$ ).

On the basis of these trial results, Corixa requested accelerated approval for Melacine as a treatment for A2C3+ (either HLA-A2 or HLA-C3-expressing) patients with intermediate thickness Stage II melanoma. The FDA denied this request, because the original efficacy protocol had not pre-specified looking at A2C3+ patients, and insisted that a second pivotal study be conducted, specifically to confirm the effectiveness of Melacine in A2C3+ patients.

Other well-known agents that failed to show better survival include vaccine Canvaxin, for which results were released from two Phase III trials discontinued the previous year in patients with Stage IV melanoma, and Maxim's Ceplene.

### Operational considerations in trials

It is critically important that clinical studies in this indication meet their primary endpoints for the precise patient group, or sub-group, under investigation. And as previously noted, several developers of therapeutic vaccines have incurred delays owing to regulatory authorities requiring additional product characterisation information. So what additional operational issues need to be considered to optimise the chances of success in melanoma trials?

In order to receive a timely review of study materials by regulatory and ethics committees such as institutional review boards (IRBs), the study design must be above reproach. For melanoma agent approval, pivotal Phase III registration studies often

involve evaluation of standard therapy plus or minus a study agent. A placebo control arm is only acceptable in this indication when administered on top of standard treatment. The study must be designed so that there is a good chance that the primary endpoint – likely to be enhanced survival – can be achieved.

When planning a vaccine study, adequate time must be allowed for review by regulatory authorities of the detailed product characterisation data. It is reasonable to expect that regulatory scrutiny of supporting data will limit the rate of progress for starting research programmes. Any issues that may arise from such reviews should be anticipated and supporting documentation should be ready as early as possible.

### Target patients

For trials where positive tumour antigen testing is a study entry requirement, additional patient consent may be necessary. If a trial of an innovative new agent is likely to be the patient's last hope for therapeutic success and there is a high probability that the patient's antigen test is likely to be negative for the required antigen, the IRB may decide that consenting would be unethical. To avoid raising a patient's expectations unreasonably, it is preferable for the testing to be performed without patient awareness, and with subsequent full consent only after the patient has tested positively and is therefore known to be eligible for the study. This is a contentious approach and IRB decisions are likely to vary on this subject.

Instances have already been cited of agents being developed for a broad patient group and it then being discovered during the course of pivotal registration studies that the primary endpoint will only be met for a smaller, sometimes unanticipated, sub-group of patients. One solution might be to look at innovative trial designs (such as randomised discontinuation) which enrich progressively for responding populations. It is also advantageous to ensure that all possible sub-groups are mentioned up front in trial design, even though the study may be insufficiently powered for such sub-groups. Ultimately, it may be necessary to repeat or extend trials to evaluate the desired primary endpoint in a specific sub-group.

Patients should meet study entry requirements precisely and investigational sites can avoid losing potentially eligible patients by ensuring that all site staff are fully knowledgeable about screening requirements. It is wasteful and deeply upsetting to see patients presenting too late in their disease course for a study that might have been of relevance to them had they presented earlier. Conversely, if pre-screening is particularly successful, it may become necessary to monitor screening very closely to avoid consenting more patients than are required for the study.

### Compliance with study design

Bias can be introduced into otherwise well-designed blinded placebo-controlled studies if it is possible for patients or investigators to determine who is receiving which medication. If a vaccine is known to produce a

typical reaction on injection, this may lead to a high drop-out of patients who conclude they have been allocated a placebo. An inert placebo can be replaced with one which may, for example, induce non-specific inflammation at the reaction site. Obviously, the study timelines would need to allow for full and frank discussion of this with the reviewing IRB.

Study design also needs to give due consideration to ease of patient compliance. What is considered acceptable in one patient group may be unacceptable for – for instance – patients with metastatic melanoma. Miscalculation of acceptable numbers or volumes of required laboratory samples may result in samples being missed and key data not collected at important time-points.

For melanoma, where sunlight is an important causative agent, it is important to conduct clinical trials in certain geographic locations, such as Australia and New Zealand. Not only is the disease highly prevalent in these countries, but also there is increased awareness of melanoma and many skilled professionals able to diagnose and treat the condition. Adequately trained and experienced clinical site staff and equipment are essential, but so are skills with other complex study procedures, such as (in histology/immunology departments) tumour sample preparation and antigen testing. Central histology/immunology services may provide a solution in certain geographic locations, with samples being shipped to a coordinating site or central lab for analysis. Another advantage of using coordinating centres of excellence and key opinion leaders is that they disseminate knowledge throughout the medical community and provide leadership to other investigators.

For melanoma studies, as in other areas of oncology, the handling and reading of medical images may be required to confirm patient eligibility and/or tumour response. Whole-body computerised tomography (CT) scanning is likely to be required in melanoma studies, to confirm disease staging and status of tumour metastases. Facilities for positron emission tomography (PET) and magnetic resonance imaging (MRI) scanning may also be required.

### Conclusions

Melanoma is not an easy indication in which to develop and register new agents. In terms of regulatory success, approval is likely to be contingent on meeting the primary endpoint of enhanced survival in the pivotal registration trial. Some therapeutics have been in clinical trials for a considerable time, either because this was not achieved or because effects have been seen only in an unanticipated sub-group.

Approval for a sub-group of patients must be gained via the same rigorous route as that taken for the original, wider patient group – with a pre-specified target patient group and with the study meeting its primary endpoints for the pre-specified target patient group.

The development and testing of therapeutic vaccines brings with it a host of additional challenges,

such as adequate product characterisation and manufacturing control for autologous vaccines. Various operational considerations must be considered when conducting such trials, some of which relate back to appropriate study protocol design.

There are many grounds for optimism in melanoma. Genasense has been proven to enhance patient survival in a subgroup of patients as has oncopophage vaccine. Knowledge is growing about the disease. Evidence is emerging, for example, that immune dysregulation is integral to the development and treatment of malignant melanoma. Recent data published at the 2006 meeting of the American Society for Clinical Oncology (ASCO) and in the *New England Journal of Medicine* (NEJM) last year by Gogas *et al* show that the appearance of autoantibodies or clinical evidence of autoimmunity during treatment with interferon alfa-2b predicted for improved relapse-free survival and overall survival in patients with melanoma.<sup>2</sup> The presence or absence of autoantibody response appears, with a reasonable level of certainty, to distinguish non-relapsers from those who relapsed and also with respect to survival.

These findings may well be indicative of new areas worthy of investigation with other biological agents such as anti-cytotoxic T lymphocyte associated antigen – 4 (anti-CTLA-4), IL-2 and IFN-alpha. Agents such as Medarex' anti-CTLA-4 agent, Ipilimumab (MDX-10) and ticilimumab could potentially boost natural immune responses to antigens associated with cancer (ipilimumab received FDA fast track designation recently). Better understanding of which molecular pathways are important in the development of melanoma is likely to lead to newer, better targeted therapeutics. Some early exploratory trials with demethylating agents, such as the histone deacetylase inhibitors, indicate useful activity in melanoma. Melanoma remains a challenging area for developers of therapeutics, but progress is undoubtedly being made.

### References

- 1 DL Morton, JF Thompson, AJ Cochran, *et al*. 'Sentinel-node biopsy or nodal observation in melanoma', *New England Journal of Medicine*, 355, pp1307–1317, 2006.
- 2 H Gogas, J Ioannovich, *et al*. 'Prognostic significance of autoimmunity during treatment of melanoma with Interferon', *New England Journal of Medicine*, 354, pp709–718, 2006.