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## News & Views

# New era in metastatic melanoma

Janet Fricker

*In stage IV malignant melanoma four innovative new classes of treatment: immunotherapy, targeted treatments, anti angiogenesis agents and chemo ablation are transforming the landscape. The article reviews the progress reported at recent European meetings, and looks to a future where knowledge of the complete genome sequence of individual melanoma tumours may allow patients to be offered tailored treatments.*

The field of stage IV Malignant Melanoma, for long a wasteland of failed treatments, is posed to take centre stage with the advent of new therapeutic strategies. Data presented at the 3rd World Meeting of Interdisciplinary Melanoma/Skin Cancer Centres, held November 19–21, Berlin, Germany, and the joint ECCO15/ESMO34 meeting, held Berlin, 20–24 September 2009, showcased some of the innovative new approaches. The meetings highlighted results of four innovative new classes of melanoma treatments: immunotherapy, targeted treatments, anti angiogenesis agents and chemo ablation. Taken together with the publication of the entire genome of mutations relating to melanoma by the Wellcome Trust Sanger Institute in December, melanoma experts have a growing sense that we are at last on the cusp of a changing landscape that will lead to targeted treatments.



Alexander Eggermont

Alexander Eggermont, ECCO president and Professor of Surgical Oncology at the Erasmus University of Rotterdam (The Netherlands), said that the new approaches are at last

transforming melanoma “into a very exciting field instead of a graveyard”.



Steven O'Day

Steven O'Day, Chief of Research and Director of the Melanoma Program at The Angeles Clinic and Research Institute (Los Angeles, USA) agreed: “The exciting presentations reflect a significant momentum in the field of melanoma that is translating into real hope in the clinic.”



Paul Chapman

The latest advances in Melanoma research, said Paul Chapman, from Memorial Sloan-Kettering Cancer Center (New York, USA), represent one of the purest examples of bench to bedside drug development.

## 1. Dismal prognosis

Setting the scene of the situation that has existed in melanoma for the last 30 years, Eggermont said: “Metastatic melanoma has been the most desperate area in solid tumour oncology, proving to be more drug resistant than almost any other tumour we know. The field has been completely stagnant, representing one of the few areas in cancer research where there have been no real advances.”

While early detection, appropriate surgery, and in some cases adjuvant therapy have improved outcomes in melanoma, approximately 20% of patients with early-stage melanoma develop metastases. Here the prognosis has been nothing short of dismal. Patients with stage IV melanoma have a median survival of 7–9 months, with less than 5% surviving more than 5 years (Jemal et al., 2008). Furthermore, because melanoma often affects young and middle-aged adults, added O’Day, the condition has proved particularly devastating in the number of years of life lost.

The incidence of melanoma has been rising – with a three fold increase recorded between the early 1970s and 2000 for both the US and Europe. Current world-wide estimates place the number of new cases of melanoma at 160,177 each year and the number of deaths at 40,781 (Parkin et al., 2005).

### 1.1. Poverty of treatments in metastatic disease

For over 30 years the standard of care for advanced melanoma has been single-agent dacarbazine (DTIC), which in phase III trials displayed moderate response rates in the range 7–15%.

Temozolomide, an orally available analog of DTIC, often used off-label in the treatment of melanoma due to its greater potential to tackle brain metastases by penetrating the blood-brain barrier, demonstrated response and survival rates similar to DTIC.

Disappointing results with single agent chemotherapy led to the evaluation of multi-drug combination regimens in the 1980s, involving DTIC in combination with other agents (such as nitrosourea, vinka alkaloids or platinum compounds). Although response rates to combination chemotherapy could be higher, toxicity increased with use of multiple agents and no survival advantage was demonstrated over single-agent DTIC. Many vaccines have been studied, but none has to date proven to be beneficial in controlled clinical trials. Immunomodulating vaccines even demonstrated detrimental survival results in the adjuvant setting recently.

Metastatic melanoma has proved an altogether different animal from other metastatic cancers. “In breast cancer, for example, even though chemotherapy does not cure stage IV disease it can prolong life. In melanoma, unless people respond to immune type treatments, stage IV disease has proved fairly resistant to chemotherapy,” said O’Day.

Eggermont agreed: “I think it’s safe to say that the last 30 randomised phase III trials – ranging from single drugs to five strong combinations – have all failed to have an impact on overall survival. A few may have had an impact on progression free survival, but this has not panned out as a reliable

surrogate endpoint, and additionally there have been significant increases in toxicity.”

High-dose interleukin-2 (Il-2) was approved by the FDA in the second-line setting on the basis of a single arm phase II trial yielding an objective response rate of around 16%, with prolonged responses in some patients (Atkins et al., 1999). Il-2, however, has not been licensed by the EMEA.

“The patient population responding to Il-2 is far too small to ever be detected in a randomised phase III trial, and the problem in Europe is that such phase III trials are a prerequisite for dossiers to be submitted to the EMEA,” explained Eggermont.

Additional limitations include the fact that predictive markers of response to Il-2 are not available and high toxicity (including the risk of hypotension and cardiac dysrhythmias) restricts use to carefully selected individuals and specialist treatment centres.

The paucity of treatments available for metastatic melanoma is underlined by treatment guidelines that suggest entering clinical trials is the most appropriate treatment option for patients with stage IV disease (Garbe et al., 2009). “For most stage IV tumours in other cancers guidelines include recommendations for first and second line treatments, then suggest patients enter clinical trials. For melanoma the options are so limited that guidelines say go straight into a clinical trial,” said Eggermont.



Paul Lorigan

The fundamental problem for melanoma, said Paul Lorigan from the Christie Hospital NHS Trust (Manchester, UK), is that the biology of the tumour makes it extremely resistant to treatment. “There are lots of inbuilt complexities and redundancies in the pathways, so that when you block one pathway, another is activated.”

### 1.2. Advent of targeted therapies

Many first date the sea change in stage IV melanoma treatments to a paper published in *Nature* in 2002. Richard Wooster and colleagues, from the Wellcome Trust Sanger Institute (Hinxton, UK), discovered that the somatic activating missense mutation T1796A, which results in the substitution of glutamate to valine in the kinase domain of BRAF, was found in 66% of melanomas (Davies et al., 2002). BRAF is a key player in the Ras/Raf/MAP/ERK Kinase (MEK)/Extracellular Signal Related Kinase (ERK) pathway, a mitogen-activated protein (MAP) kinase cascade, that is known to have a myriad of effects on cell growth, invasion and survival.

Heralded as the first important result to emerge from the Sanger Institutes's Cancer Genome project, the discovery opened the possibility that BRAF might represent a viable target for molecular-based therapy. "Until this paper the research community was totally focused on eliciting new immune responses. Identification of the BRAF gene gave rise to the idea that melanoma could be targeted, and launched large numbers of international researchers on projects to identify other genetic pathways" remembered O'Day.

A second significant paper appeared in the *New England Journal of Medicine*, in 2005. Boris Bastian and colleagues, from the University of California (San Francisco, USA) compared genome-wide alterations in the number of copies of DNA and mutational status of BRAF and N-RAS in 126 melanomas from four groups of patients where the degree of exposure to ultraviolet light differed: melanomas from skin with chronic sun induced damage, melanomas from skin without such damage, melanomas from palms, soles and subungual (acral) sites and mucosal melanomas (Curtin et al., 2005). The study showed there to be similar genetic alterations identified in melanomas from the same sites and the same levels of sun exposure, indicating distinct genetic pathways in the development of melanoma. "It was this paper that first enunciated the new landscape," said Chapman. "It made scientists start to think about melanoma as having distinct genetic subtypes."

For the first time, the paper showed that the way to go with melanoma was for a molecular definition, said Eggermont, rather than using traditional histopathologic criteria. "It resulted in a big shift in thinking with recognition of the need for rationale drug development to design therapies against specific mutations and targeted pathways," he added.

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## 2. PLX4032 leads the way

Taking centre stage is the new targeted agent PLX4032, which reported its latest data at the ECCO/ESMO meeting in Berlin. "The data we presented showed the highest response rates ever seen for a single agent in melanoma," said Chapman.

PLX4032, which is being co-developed by Roche and Plexxikon, is a highly selective drug that targets the BRAFV600E cancer causing mutation of the BRAF kinase gene that occurs in 50 to 60% of melanomas.

The phase 1 extension trial, (following up from data reported at the ASCO 2009 meeting that focussed on the best dose to give patients) enrolled 31 patients, median age 52 years, testing positive for the BRAFV600E mutation in the open-label, single-arm extension cohort where they were treated with PLX4032 at 960 mg twice daily (BID), with anti-tumour effects measured by RECIST (Response Evaluation Criteria in Solid Tumours) every eight weeks.

Results presented at ECCO/ESMO showed that 64% (14) of the 22 patients, who could be evaluated met the official criteria for partial response (involving the diameter of tumours shrinking by at least 30%). A further six of the 22 patients showed a response, but at time of analysis it was too early to say whether the tumours would shrink far enough to meet the response criteria. The median time to disease progression was 6 months. Describing improvements in the way patients functioned, Chapman said: "We've had patients

come off oxygen and we've had several patients who have been able to come off narcotic pain medication soon after starting treatment."

Drug-related adverse events were predominantly mild in severity and included rash, joint pain, photo sensitivity and fatigue. Serious adverse events included seven patients with cutaneous squamous cell carcinoma, that was treated by excision, while treatment with PLX4032 was continued. As has been emphasised, this is not the case of swapping one cancer for another: melanoma can be lethal, whereas squamous cell carcinomas are easily treated.

The response rate of 60% shown in the study is widely acknowledged as "orders of magnitude" higher than the response rates of up to 15% observed with DTIC.

Describing the results as "simply spectacular", Eggermont said: "The fact that you see a response rate of zero in BRAF wild type melanoma demonstrates you've touched a real nerve centre in melanoma."

"The big question is whether PLX4032 will result in differences in overall survival," said Chapman, adding that phase III trial is due to start in early 2010 where PLX4032 will be randomised against DTIC with overall survival as the primary end point.

"The next question is how durable these responses are, and what are the mechanisms of resistance so that we can produce more durable responses. Some patients appear to have short lived responses and others much longer responses with PLX4032," said O' Day.

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## 3. Tyrosine kinase inhibitors

While 60% of melanomas are BRAF mutated in the West, acral lentiginous and mucosal melanomas (found more frequently in the Far East), are more likely to display C-kit mutations. Last year in the *Journal of Clinical Oncology*, Stephen Hodi and colleagues, from Harvard Medical School (Boston, USA) reported treating a 79 year old woman suffering from an anal mucosal melanoma, found to exhibit a C-kit mutation with the tyrosine kinase inhibitor (TKI) imatinib 400 mg (Glivec<sup>®</sup>) (Hodi et al., 2008). Four weeks after initiating treatment the patient showed greater than 50% reduction in tumour volume, and 9 months later her condition remained stable. Phase II trials are currently under way to see if patients with C-kit melanomas respond to imatinib and the second generation TKI dasatinib (Sprycel<sup>®</sup>).

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## 4. BEAM study creates optimism for bevacizumab

Since the discovery that solid tumours utilize the angiogenic process to develop a vascular supply capable of sustaining continued tumour growth, numerous attempts have been made to exploit this dependence. Melanomas are known to over express VEGF receptors, which enable vessel growth through endothelial mitogenesis.

Sorafenib, with activity against both VEGF signalling and BRAF, was the initial agent of interest, with studies showing that in combination with DTIC, sorafenib doubled the

response rate from 12 to 24%. Sorafenib, however, was eventually found to have no effect on overall survival.

More recently interest has focussed on bevacizumab (Avastin<sup>®</sup>), a drug already licensed for use in breast, lung, colorectal and renal cancers.

At the ECCO/ESMO meeting Steven O'Day, presented findings from the phase II BEAM study involving 214 patients with previously untreated, advanced melanoma (stage IV, M1a/b and M1c). Randomised 2:1 to receive chemotherapy with or without bevacizumab (O'Day et al., 2009).

Results show that progression-free survival was a median of 5.6 months for patients receiving bevacizumab plus chemotherapy compared to 4.2 months for chemotherapy alone (HR 0.78,  $P = 0.14$ ).

At a median follow-up of 18 months median overall survival was 12.3 months in the bevacizumab arm versus 9.2 months in the chemotherapy arm (HR, 0.79;  $P = 0.19$ ). Furthermore, response rates were 25.5% in the bevacizumab arm versus 16.4% in the chemotherapy arm ( $P = 0.16$ ).

Despite falling short of the statistical threshold, O' Day maintained that these results provide reason for optimism. "I am hopeful because strong trends of improvement were seen across all efficacy parameters – progression-free survival, overall survival, and response," he said.

With a history of so many negative studies in melanoma, commented Lorigan, results showing even a significant trend are enough to get people excited.

A particularly interesting observation, added O'Day, was that patients who typically do worst with visceral tumour involvement and elevated lactate dehydrogenase (LDH) did particularly well with bevacizumab. "It may be that VEGF is more important for patients with advanced disease and this may represent an opportunity to target a group of patients who traditionally have little or no other options," he said.

"Since bevacizumab is not as targeted as PLX4032 you would not expect it to be as effective. Ultimately it's likely that such drugs will have additional roles in second line treatment of melanoma when people have failed drugs targeting specific mutations," commented Eggermont.

## 5. Ipilimumab leads the way for immunotherapy

Immunotherapy, an approach where the body's immune system is harnessed to fight disease, was represented at ECCO/ESMO with new data from ipilimumab. Ipilimumab is an antibody that activates the body's immune system to fight melanoma by inhibiting the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) molecule, found on T cells.

CTLA-4 is characterized as a 'brake' that binds to co-stimulatory molecules on antigen-presenting cells, preventing their interaction with CD28 on T cells and thereby generating an inhibitory signal that prevents further T cell activation. This reaction is necessary to prevent hyperstimulation of T cells that could result in harmful autoimmunity reactions. The most commonly used analogy is that with CTLA4 inhibition you are "disconnecting the brake and allowing the accelerator to work unchecked".

After such interactions were first characterised in 1995 by James P Allison, from Memorial Sloan-Kettering Cancer

Centre, it was hypothesised that inhibition of CTLA-4 would lead to more robust T cell activation in cancer. To date, two human monoclonal antibodies designed to block CTLA-4 have been used in melanoma clinical trials: tremelimumab, an IgG2a antibody developed by Pfizer and ipilimumab, a IgG1 antibody being jointly developed by Medarex and Bristol-Myers Squibb.

A phase III trial of tremelimumab versus DTIC/temozolomide reported at ASCO 2008 by Antoni Ribas, from the University of California at Los Angeles Medical Center showed no detectable survival advantage between the two arms. "One possible explanation for the failure of this trial was that the large majority of patients only got tremelimumab injected once, and there are indications that much higher doses are needed to achieve a response," said Eggermont.

Of much greater promise was the ipilimumab data presented at ECCO/ESMO. Altogether 487 patients with Stage III – Stage IV unresectable metastatic melanoma, some pretreated with other drugs, were enrolled into the three separate phase II studies (Trial 008, 022, and 007), and treated with 0.3 mg/kg, 3.0 mg/kg or 10 mg/kg of ipilimumab (Maio et al., 2009). For the current analysis only data in the 10 mg/kg arm were used.

In Trial 008, an open-label, single arm trial evaluating 155 previously treated patients who had progressed while on or after receiving standard treatment, results showed 18 month survival rates of 39% and 24 month survival rates of 33%.

Trial 022, evaluating the efficacy of three dose levels of ipilimumab in 217 previously treated patients who had either relapsed or failed to respond to experimental treatment or who were unable to tolerate currently approved therapies, showed 18 month survival rates of 34.5% for the 10 mg/kg dose, and 2 year survival rates of 29.8%.

In trial 007 (designed primarily to evaluate grade two diarrhoea), 32 treatment naïve patients receiving ipilimumab (with or without prophylactic oral budesonide) showed 18 month survival rates of 61% and 2 year survival rates of 56.6%.

"To reach 2 years and have 56% of treatment naïve metastatic melanoma patients surviving is nothing short of extraordinary, and never seen before in metastatic melanoma," said Eggermont, adding that historically most patients have died between 12 and 18 months, "Such data points to ipilimumab as being a drug with a very interesting future."

Emergence of ipilimumab toxicities (such as diarrhoea, rash, pituitary and liver abnormalities), appear to correlate with long-term benefit. Pooled data from studies has indeed shown that median overall survival for patients who experienced any immune-related adverse events within 12 weeks of starting treatment was almost double that of patients who did not experience such events.

"When you see these events, it means that the antibody is working – a clear signal that it is hitting its target," said Eggermont, adding that once identified such toxicities can be managed with corticosteroids.

Another intriguing observation in ipilimumab is that tumour lesions may initially increase in size following treatment before regression. "For a partial response to translate into a complete response can take up 26 weeks. But when patients are in CR, they generally remain in CR for a long time," said Eggermont.

The results of the definitive randomised phase III trial of DTIC versus DTIC plus ipilimumab are expected mid 2010.

Ultimately, many believe that it is immunomodulatory drugs, such as ipilimumab, that will salvage the field of vaccine development in melanoma. “With vaccination you get a T cell response that tapers off, with recent data suggesting that vaccination may even preferentially enhance the tapering effect. Ipilimumab has the potential to restore immunity and make vaccines work,” said Eggermont.

## 6. Pro-apoptotic treatments prove disappointing

Undoubtedly less progress has been made in the realm of pro-apoptotic treatments, with recent disappointment the AGENDA trial results, presented at the 3rd World Meeting of Interdisciplinary Melanoma/Skin Cancer Centres. The long anticipated results of the phase III trial in patients with advanced melanoma did not show a statistically significant benefit for progression free survival, overall response or disease control between patients randomised to oblimersen and DTIC and those just receiving DTIC. This was despite the fact that the study had been undertaken in patients with low levels of serum lactate dehydrogenase (LDL levels), the subgroup predicted from earlier studies to show the most beneficial response.

Oblimersen sodium, developed by Genta, is an anti-sense oligonucleotide that targets the initiation codon region of mRNA for the Bcl-2 protein. The protein is known to be a potent inhibitor of apoptosis.



Claus Garbe

“The rationale behind treatment is that by reducing the amount of Bcl-2 protein in cancer cells, apoptosis will become more effective and oblimersen may enhance the effectiveness of conventional anticancer treatments given with it,” explained Claus Garbe, the European Principal Investigator of AGENDA, from the Eberhard-Karls University (Tuebingen, Germany).

The earlier GM301 study, which at the time represented the largest study ever conducted in advanced melanoma to date, randomised 771 patients to oblimersen and DTIC or just DTIC. Results for the 760 patients for whom baseline serum levels had been recorded showed a strong linear correlation between overall survival and levels of LDL, favouring those with the lowest levels (Bedikian et al., 2006).

The latest AGENDA trial, presented at the November Berlin meeting, therefore, set out to randomise patients with the most beneficial serum levels of LDL (defined as 0.8 of the normal) to receive oblimersen and DTIC ( $n = 157$ ) or DTIC and placebo ( $n = 157$ ). Results show that progression free survival was 2.8 months for the group taking oblimersen/DTIC compared to

2.7 months for the group taking DTIC alone (HR 0.85,  $P = 0.23$ ). Additionally overall response was 17% for OBL/DTIC versus 12% for DTIC ( $P = 0.19$ ), while the disease control rate was 42% for oblimersen/DTIC versus 36% for DTIC ( $P = 0.3$ ).



Sanjiv Agarwala

“It’s possible that the second AGENDA trial was too small to show an effect, or that oblimersen might work better with taxanes,” said Sanjiv Agarwala, from St. Luke’s Cancer Centre (Bethlehem, PA, USA), who presented the data.

Following a futility analysis, Genta decided to continue the trial to completion to get the information on overall survival, with the study remaining blind. “But if a trial has failed progression free survival it’s highly unlikely to ever have a beneficial effect on overall survival,” cautioned Garbe.

Molecules, such as the MCL1 protein, he believes, may display stronger anti-apoptotic effects than Bcl-2, and ultimately provide more appropriate drug targets. “Knowledge about apoptotic regulation in melanoma is still at an early stage,” said Garbe. “It’s my feeling that before undertaking clinical trials in this area there needs to be greater preclinical testing, with more evaluation in cell culture and animal models. Ultimately for any real success we are likely to need a combined approach that blocks several pathways. In reality it’s likely that when one of these pathways is blocked the others take over and are up regulated.”

## 7. Fluorescent stain delivers intriguing chemoablation data

At the 3rd World Meeting of Interdisciplinary Melanoma/Skin Cancer Centres, a phase 2 trial injecting cutaneous metastatic melanoma lesions with the Rose Bengal Staining compound, stimulated “intrigue and interest” among delegates.

Rose Bengal, a derivative of fluorescein used for over 80 years in medicine to stain necrotic tissue in the cornea and as an IV diagnostic of liver impairment, has recently been found to be selectively toxic to cancer cells via chemoablation, a process where cells undergo a form of cell death mimicking necrosis and apoptosis. Of particular note, said Agarwala, a principal investigator of the Phase 2 study, has been a “by-stander effect” where the agent also elicits spontaneous regression of nearby melanoma tumours that have not been injected. “Immune cells appear to be recruited following cell damage, that we believe circulate in the system and influence distant tumours,” said Agarwala.

Provectus Pharmaceuticals Inc. (Knoxville, Tennessee, USA), a development phase company, discovered the novel

use for Rose Bengal while exploring different formulations for use in photodynamic cancer therapy. By serendipity the company discovered that PV-10, a formulation developed to be administered directly into solid tumours, destroyed tumours without need for light activation.

“In melanoma the overall effect appears similar to that of recent melanoma vaccines with the important additional features that PV-10 reduces overall disease burden by destroying the injected lesion,” explained Eric Wachter, from Provectus. “The process occurs insitu so the patient’s specific melanoma antigens are presented in the proper immunologic context.”

At the meeting 1-year follow-up data was presented for the first 20 subjects in the phase 2 open label single arm trial that plans to enrol 80 subjects with stage III/IV metastatic cutaneous melanoma. Results, presented by Professor John F. Thompson, from the University of Sydney (Australia), showed that patients who were responsive (i.e. those who had achieved a complete or partial response to PV-10) had a mean overall survival of 11.8 months, compared to 9.9 months for those who did not achieve a robust response (defined as progressive disease and stable disease). Furthermore, two of five subjects displayed bystander effects with regression of visceral or nodal metastases that had not been injected.

Extended survival data from the phase 1 study, which tested 20 subjects, showed median disease specific survivals of 44 months for responsive subjects versus 14.6 months for non responsive subjects.

While accepting that PV-10 is unlikely to have a role in patients with widespread organ involvement, Agarwala believes it offers the possibility to intervene early in the metastatic process. “It’s likely to have a role in around one third of metastatic melanoma patients whose disease is predominantly on the surface,” he said. “Furthermore, because melanoma often metastasises to areas that are difficult to treat, such as the head and neck the bystander effect could dramatically improve prognosis.”

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## 8. Future points way to combination treatments

Combinations of new agents, most experts believe, will be necessary to progress overall survival in melanoma. The move towards a renal cancer situation, where there are now five or six FDA approved treatments for metastatic cancer, is seen as the most likely step forward. “A realistic view for melanoma over the next 10–20 years would be to become more of a chronic disease, where patients will receive treatments based on the genetics of their individual tumours,” predicts O’Day.

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## 9. Melanoma provides first genome catalogue

The field has already taken a major step with the publication in December 2009 of a paper in *Nature* from the same Wellcome Trust Sanger Institute team who discovered the BRAF mutation (Pleasant et al., 2009). Using the *Illumina* DNA sequencing technology to decode the genome of both tumour tissue and normal tissue taken from the same patient with

malignant melanoma, Mike Stratton and colleagues have identified 33,000 separate mutations in the cancer sample.



Mike Stratton

“Although sounding a lot, only a small number (we estimate around five) will be the driver mutations that deliver a competitive advantage to the cell resulting in the development of cancer. The remaining mutations are passengers there for the ride. The key for future melanoma drug development will be to identify these driver genes,” explained Stratton.

The next step, he said, will be to repeat the process with a further 500 different individuals with malignant melanoma. “The mutations that continually recur in large numbers of individuals will be likely candidates for the driver genes,” said Stratton, who estimates the project will take 8–10 years to complete and cost around \$20 million.

Once identified the mutated driver genes will offer potential targets for drug development, with the data being freely available to all.

Looking to the distant future, said Stratton, it may be possible to undertake a complete genome sequence of all melanoma patients coming into the clinic, so that their individual “driver” mutations can be identified, and bespoke treatments offered. Another potential spin-off from the project, said Stratton, is that the presence of driver mutations in blood samples, might be used as “signatures” of the tumour. “This could be used to monitor the effectiveness of therapy and whether we may need to switch treatment,” he added.

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## 10. Treatment paradigms with ever increasing complexity

With so many new possibilities for agents there will undoubtedly be issues over whether the drugs should be used concurrently or sequentially, with the ever present issue of toxicity. “We’re talking about incredibly complex new treatment paradigms that will take a long time to tease out,” said Lorigan.

Such increasing complexity will require oncologists who are solely dedicated to melanoma, commented O’Day. “It will be virtually impossible for general oncologists to keep up with such continually evolving intricate recipes,” he added.

But all are agreed we are entering exciting times for melanoma specialists “I’d have no reservations in recommending the melanoma field to talented young medical oncologists because this is where the action is now,” said

Eggermont, adding that one oncologist had commented to him that the extension to life being provided by new melanoma treatments meant for the first time that he had the opportunity to get to know his patients.

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