ClinicalPractice

# Advances in treating solid tumors

James Larkin speaks to Laura McGuiness, Managing Commissioning Editor: Dr James Larkin, FRCP, PhD, is a Consultant Medical Oncologist specializing in the treatment of patients with cancer of the kidney and cancers of the skin, including melanoma. His research interests include the individualization of patient treatment in renal cancer and melanoma, the identification of mechanisms of sensitivity and resistance to systemic therapies and the combination of novel targeted therapies to treat these diseases. Larkin received a first in Natural Sciences from Cambridge University and undertook clinical training at Oxford University, qualifying in 1996. He underwent general medical training in London and in 2001 won a Medical Research Council Fellowship for a Clinician, carrying out laboratory research at The Institute of Cancer Research. He completed specialist training at The Royal Marsden and was appointed a Consultant in 2008. He is UK Chief Investigator for a number of clinical trials in melanoma and kidney cancer and has been awarded research grants from bodies including Cancer Research UK and the 7th European Framework Programme and the Wellcome Trust.

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**Q Why did you decide to specialize in oncology?**

It is a fairly long story as it took me while to get there. I used to want to be a neurologist when I was in medical school and as a junior doctor. However, although it is a wonderful speciality, after 6 months in neurology, I just didn't really see myself as being a consultant neurologist longer term. Then I did 6 months as a junior doctor in intensive care. But after that, even when I had passed all of my exams, I still didn't really know what to do. I had actually by chance done 3 months of oncology near the start of my training and I'd enjoyed it, so I applied for an oncology job at the Marsden. I started in the beginning of 2000 and I have been here ever since.

I suppose ultimately I've found that oncology suits my temperament, which I think is the most important thing. It is very interesting scientifically. It's rewarding in terms of looking after patients, but challenging at the same time. A lot of our patients die, so if as a doctor you didn't want to be close to that part of medicine it wouldn't be the right career for you. There is a lot of team work involved in oncology and again that might not suit everybody. With the amount of progress we've seen in treating solid tumors in the last 5–10 years, I find it genuinely exciting to be lucky enough to work in this area.

**Q How did you then go from oncology in general to focusing on the solid tumor work that you do now?**

I was actually interested in immunotherapy when I came to my interview as a junior doctor at the Marsden. At the time kidney cancer and melanoma were being treated with immunotherapy and it didn't really work and it was toxic. I ended up working with Martin Gore, who is now my colleague, in kidney cancer and melanoma. I had done my PhD in a sort of related area at the Institute of Cancer Research, although it was animal modeling, so I'd so done quite a lot of training in renal and melanoma. So in 2007 when a position came up I applied for the job. In 2007 we were beginning to develop effective drugs for kidney cancer, so people could understand why I might want to be doing kidney cancer. But at the time there was no real progress at all in melanoma, so a lot of people couldn't understand why I would want to be treating melanoma. I was lucky during my PhD to

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have met Richard Marais, a melanoma biologist who used to work at the Institute of Cancer Research and he worked a lot on *BRAF* as a therapy to target in melanoma, so based on his work I had quite a good idea that effective drugs would be developed for melanoma and that *BRAF* was a good target. Then, low and behold, in about 2009 we saw the first evidence of *BRAF*inhibitors being effective in melanoma. I would argue that melanoma is a tumor type that lots of oncologists in training would want to get into now, as there is so much happening.

**Q Do you still work on kidney cancer?**

Yes, approximately half renal cell carcinoma and half melanoma, although at the moment I am focusing more on melanoma. The reason being, kidney cancer had its therapeutic advances approximately 5 years ago with the development of new drugs, but since then there hasn't been a vast amount of progress therapeutically. We have got similar drugs but nothing really quantum leap in terms of efficacy. Where as melanoma is having its time now. There is a long list of reasons to be excited: we've got BRAF inhibitors, we've got MEK inhibitors, we've got immunotherapies, we've got different types of melanoma to consider, we've got tremendous excitement about the anti-PD1 drugs that are in trials at the moment. Melanoma is having a therapeutic explosion in terms of targeted therapies and immunotherapies. If I'm honest I'm surprised it's all happened so quickly, but I'm not complaining. We spend a lot of our time running clinical trials and we're obviously getting lots of patients being referred to us for trials, so we're very busy in melanoma at the moment, but it's a 'good' kind of busy.

**Q Your work focuses on both kidney cancers & skin cancers; are there similarities?**

The main similarity is the fact that, historically, neither cancer was sensitive to traditional cytotoxic chemotherapy. Cytoxic chemotherapy was used in hematological malignancies to start off with, for example leukemias and lymphomas. Clearly it is a good treatment for that purpose and is often curative, but it is less so in solid tumors. Some solid tumors were sensitive to cytotoxic chemotherapies, for example ovarian cancer and to some extent breast cancer. Renal and melanoma stood out because they were resistant to cytotoxic chemotherapy. I think we used immunotherapy for that reason. But historically immunotherapy was toxic and didn't really help many patients. This meant that renal cancer and melanoma were almost viewed purely as investigational diseases, where the patients' best option was often to go into clinical trials. I think that is part of the reason they were lumped together in the past. In the last 5–10 years we've seen that cytotoxic chemotherapies are the wrong way to treat the disease, and better understanding of disease biology that has, for example, led to the development of *BRAF* inhibitors in melanoma. Appropriately targeted drugs (generally kinase inhibitors) can be effective and so that's what we are seeing in both renal cancer and melanoma. Now we're seeing immunotherapies that are less toxic and benefit more patients. I hope that will improve.

At the moment with the use of anti-CTA4 antibodies, such as ipilimumab, we're talking about durable benefit with acceptable side effects in probably only 15–20% of patients. Clearly the aim is to get that 15 or 20% much higher and that is the promise of some of the new drugs that we're using in clinical trials at the moment.

**Q You said you've got a lot of clinical trials ongoing at the moment, are there any that are nearing the end stages?**

No. At the moment we're doing a number of different trials. A lot of them with anti-PD1 drugs, such as Nivolumab made by Bristol Myers Squib (NY, USA), and Merck (NJ, USA) make a similar drug referred to as MK3475. Those Phase III trials are still recruiting and I don't anticipate any results being reported in the immediate future. I hope that we'll start seeing some results towards the end of next year maybe or into 2015. We already have some results for these drugs, but they're in nonrandomized trials. They've demonstrated efficacy and acceptable toxicity, but now we are comparing these new drugs against benchmarks and obviously it takes time to do the randomized trials.

**Q What do you think are the biggest changes that you have seen since you have been in the field?**

I'd probably say BRAF inhibitors. Melanoma had been previously regarded as essentially untreatable once it had spread. Immunotherapy has been around for a long time, its just that it didn't really work initially; however, BRAF inhibitors are a very clear application of rational drug targeting based on scientific knowledge and an increased understanding of disease biology. In other words, the advance is based on the discovery that BRAF is a therapeutic target, on the crystallization of the structure of BRAF and then developing targeted drugs that are based on the crystal structure, followed by clinical trials and then the approval of drugs. It is a great example of how understanding the biology of the disease has resulted in direct patient benefit and I think it shows that by using old-fashioned cytotoxic drugs to treat melanomas we were largely barking up the wrong tree.

**Q What do you consider to be the most exciting developments in oncology at the moment?**

I think that it is all going to be about anti-PD1 in melanoma and possibly in the treatment of other tumor types as well. Anti-PD1 drugs are T-cell checkpoint inhibitors. We've already seen clear evidence of activity in early trials and so what I see happening is randomized trials in lots of different types of cancer. I wouldn't want to second guess the results of those trials, but I think in melanoma the randomized trials are likely to confirm the benefit of these drugs with acceptable toxicity. There are other immunotherapy drugs out there, which we can investigate at the early stage of the disease, so I think a lot of focus, at least in melanoma, will be on using these drugs and trying to understand who might respond and who might not respond, and then to investigate whether they work in other tumor types. I think the greatest excitement in melanoma at the moment is regarding the combination of anti-PD1 with anti-CTLA4, nivolumab and ipilimumab, and the early data for that was published in *New England Journal of Medicine* in June. For a small number of patients there has been a really spectacular level of tumor shrinkage and at the moment the Phase III trial is going on to look at that further. Another question, at least in melanoma and kidney cancer, is to find out whether using these drugs earlier in the disease course in the adjuvant setting will increase cure rate, because at the moment we don't have good adjuvant treatment for either of those diseases. We've had progress treating advanced disease, so can we translate this into higher cure rates for earlier stage disease? That will be another very important consideration moving forwards.

**Q Personalized medicine is changing oncology, what are your predictions for the next 5 years?**

I think that will carry on. I think lung cancer is a good example as we now know that there are different subsets of lung cancer. It comes down to understanding the biology better, as this means that drugs can be used more effectively. Breast cancer is a good example, with *HER2* positivity and the use of Herceptin. We are beginning to see all these examples in different cancers.

On the other hand, however, we are appreciating the limitations of targeted therapies. For example, in kidney cancer these drugs are given continuously, have side effects and, ultimately, they are not curative for advanced disease. The critical point regarding immunotherapy is that we think it can be curative for advanced disease. At European Cancer Congress 2013 in Amsterdam, The Netherlands, long-term data were presented for ipilimumab and it seems as though if you survive to 3 years after treatment, which is still only approximately 20% of people, you will probably then get to 10 years. In other words, you are probably operationally cured of the cancer, even though it is metastatic. So I think personalized targeted therapy will carry on but I think we're beginning to realize that it is not curative treatment and it does have significant implications for patients in terms of taking these drugs continuously. I think there will be greater interest in immunotherapy drugs that can potentially control cancers for years on average rather than months.

**Q What are you working on at present?**

We are interested in lots of different things, we are interested in trying to work out, in advance, who might respond or not respond to immunotherapy in both melanoma and kidney cancer and we are interested in combining these drugs together to see if we can make improvements. I suppose those would be the main headlines; we want to try to understand response and resistance to immunotherapy.

**Q What is next for you?**

I would imagine that with all of the developments at the moment and all of the clinical trials, it is going to take a few years to actually work out the place for these drugs and to understand them better. Inevitably, when we get the results of trials, this will stimulate new questions.

Some the questions, which are still unanswered, surround how we can really help the patients with very aggressive cancer biology. A lot of our treatments only work with patients who have good cancer biology in the first place. Approximately 30% of melanoma patients will have brain metastasis, and treatments for this have historically been very poor. I think that's something we need to be exploring much more. At the moment patients with brain metastasis generally can't go into clinical trials. I think there's a massive need to make progress in that area.



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