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Refining Sunitinib Use Extends Survival in RCC

Bernard Escudier, MD | October 10, 2014

Gene Signatures Coming Into Focus

Hello. I am Dr Bernard Escudier, head of the Genitourinary Tumor Board at Gustave-Roussy Institut in Villejuif, France. Welcome to this edition of Medscape Oncology Insights in renal cell carcinoma, from the 2014 Congress of the European Society for Medical Oncology (ESMO) in Madrid, Spain. I am going to give you a summary of what has been new in renal cancer at this meeting. I will group my summary in different domains.

The first domain is biology. An interesting presentation[1] was an update of the presentation I gave at the American Society of Clinical Oncology (ASCO) meeting, about gene signatures to characterize the risk for recurrence in localized kidney cancer.[2] At ASCO, I presented a recurrence score based on 16 genes, which was a validation study from a previous study done at the Cleveland Clinic.

We updated the study by showing that this recurrence score is adding a lot of information compared with the score we used previously (the Mayo Clinic score, also called the Leibovich score). The recurrence score adds a lot of value to the previous clinical score. This interesting gene signature will become very useful, especially if we have positive adjuvant trials in the future.

In terms of biology, we also had a symposium on gene expression in kidney cancer. Andrew Futreal[3] presented a very nice update of what we have discovered in the past 3 to 5 years in terms of gene mutation in kidney cancer. We now have very good characterization of the principal genes that are mutated in kidney cancer, especially in clear cell cancer. Of interest, all of these genes are located on chromosome 3. Outside of VHL [von Hippel-Lindau] genes, which everybody knows are abnormal in most clear cell histology, we know of at least two very important genes: One is BAP1 and the other is PBRM1, the latter being present in almost 50% of our patients with clear cell carcinoma. These genes confer different prognoses in our patients. Hopefully, these new genes will become targets for future treatment.

Following this presentation, James Larkin[4] from the United Kingdom gave a very nice presentation on precision medicine in kidney cancer. We are a long way from what we have in other tumor types, but hopefully the time is coming when we will be able to use all of this information from biology to help us direct our treatments.

Sunitinib Shines, but Combo Outlook Is Overcast

Let's move now to what has been presented outside of this biology at this meeting. I will first focus on current drugs. We had two interesting presentations on sunitinib. Sunitinib is one of the most often used drugs for first-line treatment in kidney cancer. The first was a poster discussion from Georg Bjarnason[5] from Canada, showing that we can adapt the dose of sunitinib to improve safety. By adapting the dose we can lower the toxicity, going from 4 weeks/2 weeks off to a different schedule, such as 2 weeks on/1 week off or a different schedule, and then escalate the dose in some patients without increasing toxicity. In a series of more than 60 patients, progression-free survival (PFS) was more than 1 year and the response rate exceeded 50%—one of the best response rates reported in kidney cancer. Of course, we need to have more mature data on this, but this will probably change the way we give sunitinib to our patients in the future.

Another very interesting study on sunitinib was presented by Stéphane Oudard[6] on the topic of rechallenging with sunitinib. He reported a large retrospective study from France, showing that when you give sunitinib to a cohort of patients who have at least responded or have had stable disease for a certain period of time, and then have progressed and have been given another drug (other than sunitinib), you can rechallenge in third- or fourth-line with sunitinib, resulting in a PFS exceeding 8 months. These were very interesting observations on sunitinib.

The second topic is the combination of old drugs and new drugs. We would like to find new drugs to combine with a drug we already have to improve the efficacy of our treatment. However, the studies that were presented at this meeting are negative, unfortunately. One focused on SRC inhibition, which is an attractive target, but when you combine this inhibitor with everolimus,

it doesn't seem to improve efficacy of everolimus.[7] The second trial[8] was with cediranib, which is a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI) that seems to have some interesting efficacy in kidney cancer. Unfortunately, this drug is late in the pipeline of VEGF-targeted agents in kidney cancer, and it's unlikely that this drug will go further in kidney cancer.

Nivolumab Still Promising, Alone and in Combo

The last topic in my presentation is immunotherapy. In the past 2 years immunotherapy has become the big new topic at every oncology meeting. At this meeting, it was the same for kidney cancer. We had an update on some studies that were presented at ASCO. The phase 2 nivolumab study[9] was updated with survival, which is quite attractive, at 24-25 months with nivolumab monotherapy. This at least suggests that the ongoing phase 3 trial will be positive in terms of overall survival.

We also had an update about MPDL3280A (a PD-L1 antibody, a counterpart of PD-1) from Genentech, reported by David McDermott.[10] This is another very attractive drug in kidney cancer, and it has also been studied in urothelial cancer. This drug is being combined with bevacizumab with very promising results. David McDermott showed us the first data about the combination of bevacizumab and this antibody with very promising activity. The phase 2 trial is ongoing, and very rapidly we will go to the phase 3 trial, in which the drug in combination with bevacizumab will be compared with sunitinib. This combination seems to be very safe, which is very good news for our patients. It's likely that, at least in terms of safety, this combination could become a first-line treatment in the future for kidney cancer.

We had other presentations on immunotherapy, including an update of the combination of nivolumab plus ipilimumab plus a TKI. Hans Hammers[11] gave a nice update on this combination. As we heard at ASCO,[12] the combination of nivolumab with either a TKI or ipilimumab achieves a very promising response rate of 40%-55%, which is very encouraging. The PFS data are not yet mature, although they have been updated now to almost a year.

One combination that seems to be most feasible is nivolumab 3 mg/kg with ipilimumab 1 mg/kg. Although this combination seems to be toxic, it's feasible and relatively safe, at least in expert hands. On the basis of the data that were presented at ASCO[12] and updated here, a large phase 3 trial is going to start soon, comparing the combination of ipilimumab and nivolumab with sunitinib.

One question that I have is whether we are proceeding too fast, going from 21 patients in phase 1 to a 1000-patient study. This is frightening many of us. Because we have many PD-1 and PD-L1 antibodies in development, the race to be first on the market is triggering the rapidity in moving from phase 1 to phase 3. Still, we all think that this combination is something that we'll have to get to know and look at very carefully in the future.

To summarize, immunotherapy is still promising in kidney cancer as it is in lung and other cancers. Monotherapy might not be good enough to convince people that this is going to be the major output from this drug. Nivolumab in phase 3 should be released next year, and maybe by next year's ESMO/ECCO meeting we will know whether it works in monotherapy. Combination therapy is in a race to be first to market, and the two combinations that are in competition are PD-L1 plus bevacizumab (which appears to be safe) and nivolumab plus ipilimumab (which seems to be a little more toxic), but we have very nice data from this latter combination in melanoma,[13] which suggest that this might be a very good combination for the future in renal cell carcinoma. Thank you for joining me for Medscape Oncology Insights. I am Bernard Escudier reporting from ESMO 2014.

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