Evaluate Vantage

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Vantage Point - Swelling TKI field prompts calls for new approaches in kidney cancer

Amy Brown

Where it is reimbursed, Pfizer's Sutent is normally the first drug to be used in patients with advanced renal cell carcinoma. Approved for front line use in 2007, the tyrosine kinase inhibitor (TKI) has retained this primary go-to status and grown market share even with the arrival of other targeted agents in the meantime – but the threats to its position are growing.

Pfizer's own axitinib, Aveo Pharmaceuticals' tivozanib and GlaxoSmithKline's Votrient are potentially keen competitors – all are described as more potent inhibitors of the VEGF signalling pathway that drives most kidney cancers and the fight for market share in the future will be fiercely fought. Oncologists will of course welcome new agents that offer greater efficacy and fewer side effects. But at this year's Asco, where the first pivotal data on axitinib were presented, calls were also made for new mechanisms to treat what remains a deadly disease for most patients, questioning the benefit of adding more agents to the increasingly crowded TKI space.

Reference or reasonable?

Pfizer was eager to promote the first pivotal data to emerge from axitinib at Asco. In a trial called Agile 1032, axitinib was pitted against Nexavar in a second-line setting in 723 patients. Progression free survival was significantly longer in the axitinib arm - 6.7 months versus 4.7 months. The company also believes the drug has a more favourable tolerability profile.

Dr Brian Rini of the Cleveland Clinic, and lead investigator of the trial, concludes that axitinib should be considered a "reference" second-line treatment for advanced RCC.

A review of the study given at Asco by Dr Bruce Redman, professor of medicine at the University of Michigan, was less effusive. Pointing to trials with Sutent and Votrient, he said in patients previously treated with cytokine therapy – the immunotherapies interleukin or IL-2 that were standard of care before the arrival of TKIs – axitinib may be more effective in a second line setting. In patients refractory to other TKIs or mTOR inhibitors, the picture is less clear, he believes.

So while axitinib is a "valid option" after prior IL-2 – which is not used first line in the US anymore – it is only a "reasonable" second line option after a patient has relapsed on TKIs, he concludes.

Dr Redman believes axitinib appears no less tolerable than Sutent. But he also points out that quality of life improves significantly after these "tolerable agents" are discontinued, even when it is due to disease progression. Evidence exists that these agents are taken for much shorter periods in clinical practice, outside of controlled trials.

"Quality of life is the goal of palliative therapy," he says.

More of the same?

Another question occupying Dr Redman is whether kidney cancer needs more of the same agents. Should tivoazanib and axitinib reach the market, doctors will be faced with five TKIs, two mTOR inhibitors - Pfizer's Torisel and Novartis' Afinitor – and Avastin. Like the TKIs, the Roche antibody works by blocking the VEGF signalling pathway.

"After progression on a good TKI, what is the role of a second "good" TKI? Do we need more TKIs or mTOR inhibitors or do we want a new target?" he asks.

This sentiment is echoed by other doctors working with kidney cancer patients.

"We haven't had the home run (in kidney cancer) we've wanted, we haven't seen anything that doubles or triples survival, it's all been incremental," says Dr Nicholas Vogelzang, of US Oncology Research. "We would obviously now like to see an agent that targets the stem cell of kidney cancer."

Despite a number of novel approaches moving through the clinic, that hope seems some way from being realised. However, Dr Vogelzang believes these newer kinase inhibitors do hold promise, and that for some patients, several lines of existing targeted agents can have an impact.

“I have a patient on sixth line Votrient. He’s been benefiting for a year. I don’t discount the possibility of recycling these drugs, to keep the [tumour] rocking on its feet – hitting it again and again,” he says.

First line choice

Unfortunately these patients are the minority. Five year survival for advanced renal cell carcinoma is approximately 25%, and although the kinase inhibitors have substantially extended life expectancy over cytokine therapies, there is substantial room for improvement.

In the meantime, however, doctors are faced with decisions about which targeted agents to use first, second and in later rounds of therapy – a decision that will become harder should axitinib and tivozanib reach the market.

Although European regulators have been more specific in their labelling advice, in the US the FDA has granted a broad label to all the TKIs, leaving the decision in the hands of the physicians.

Dr Vogelzang says Sutent is used first over rival kinase inhibitor Nexavar due to a perceived longer duration of response, and that Nexavar is often used behind the mTor inhibitors.

Head to head

The newest approval in the TKI space, Glaxo’s Votrient, appears to hold more potential to grab first-line patients from Sutent than Nexavar. Both have shown similar prolongations of progression free survival, around 11 months, and Votrient is suspected to have a more benign safety profile.

Glaxo has boldly chosen to run a head-to-head trial of the two agents in first line use in an attempt to win more treatment naïve patients. Called Comparz, the study should generate data next year, according to Dr Lini Pandite, pazopanib project leader for Glaxo and a vice president in the company’s oncology division.

“We were coming into the market after other agents, and we as a company have always believed we need to do the right study to inform the prescriber and the payer as to the benefit of our drug,” she says. “Our positioning is first line and we are already making inroads here.”

The non-inferiority trial measures progression free survival and other tolerability aspects, and these read outs will be crucial in convincing doctors to reach for Votrient first.

“Patients would benefit from a more tolerable drug. These agents are given continuously so the more tolerable the drug, the easier for patients,” she says.

Pushing the paradigm

Unsurprisingly, Pfizer has no plans to run a head-to-head with axitinib and Sutent in the first line setting, although a second and ongoing pivotal study – Agile 1051 – does have an arm recruiting treatment naïve patients.

Also due next year, these data and a read out of Comparz will help determine how much competition Sutent is facing for these front line patients.

Further behind but still creating considerable excitement is Aveo with tivozanib. The highly potent inhibitor of VEGF has demonstrated comparable efficacy to Sutent in phase II and some believe it could do even better. Pivotal data due towards the end of this year are keenly awaited (*Event – Aveo hoping for game-changing data from tivozanib, April 28, 2011*).

Aside from axitinib and tivozanib, the phase III pipeline is free of new TKIs or mTORs, although other targeted therapies are being investigated.

“I don’t think the paradigm is exhausted. There are lots of targets worth pursuing,” says Dr Vogelzang.

He believes Novartis’ dovitinib, which targets FGF and VEGF, and Exelixis’ CMET and VEGF inhibitor cabozantinib as having the potential to “push the paradigm path.”

Crux of the issue

However, agents that target the metabolism of the cancer cell are the ultimate goal, but for now remain elusive.

“Pharma is now beginning to realise they are only going to go so far with these targeted agents,” Dr Vogelzang says. “They aren’t hitting the cancer - they are hitting the stroma, the blood cells supporting the cancer. And

stroma adapts. The crux of the issue is we don’t have a drug that hits the cancer itself”.

Dr Vogelzang believes a potential answer lies in targeting a driver mutation for kidney cancer, VHL, which signals through the VEGF pathway.

Until such agents can be found, however, it seems doctors’ armamentarium will include a swelling number of TKIs. But even the developers of this class recognise the need for more options.

“As a physician, I would definitely say we need new agents,” says Dr Pandite. “What we really need to be looking at is the biology of kidney cancer.”

The advent of the TKIs doubled median survival for advanced kidney cancer patients to about 20 months or more, compared to interferon therapy. For another advance of that magnitude, progress outside the kinase inhibitor field is needed.