Evaluate Vantage

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Pincer movement squeezes Exelixis in kidney cancer

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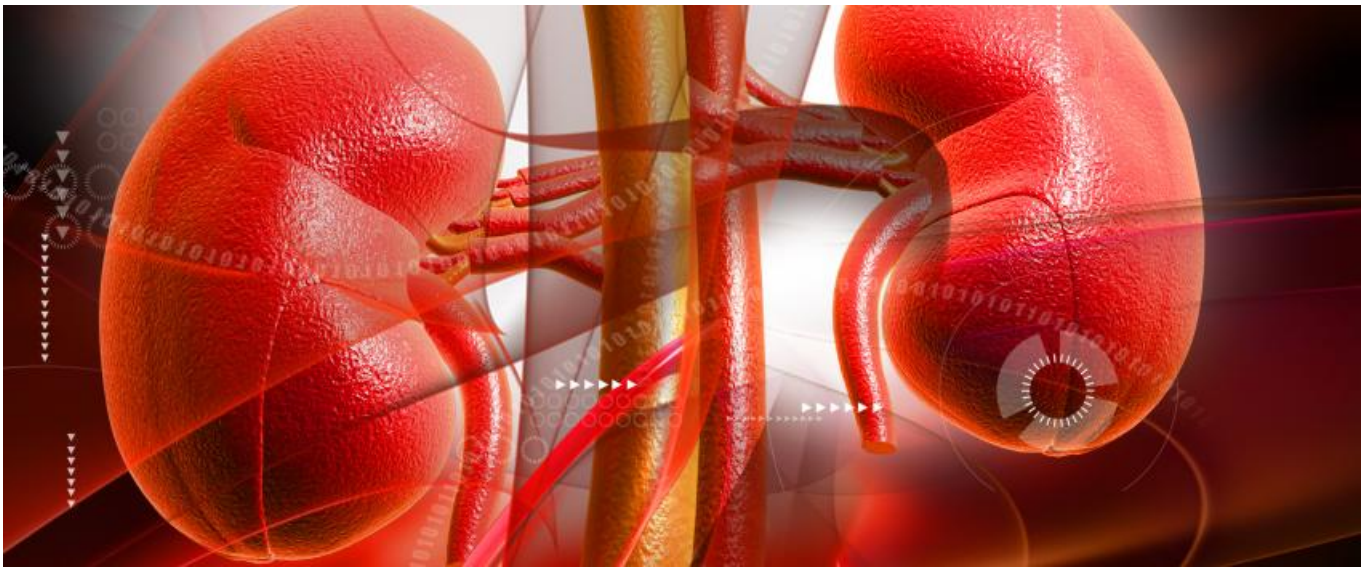

Pfizer hedging its bets in the Javelin Renal 101 study makes no difference as the trial reads out positively anyway

Pity poor Exelixis. In first-line renal cancer the company's Cabometyx was first hit by controversially broad approval of Bristol-Myers Squibb's Opdivo plus Yervoy, and now it has to contend with surprisingly strong results backing Pfizer/Merck KGaA's Bavencio plus Inlyta.

There are numerous intriguing aspects to the data, toplined yesterday from the Javelin Renal 101 study, most notably that an effect has been seen in all-comers despite the trial being refocused on PD-L1-positive patients. The extent of the benefit across subgroups – a key sticking point – will not become clear until the full data are unveiled, perhaps at next month's Esmo meeting.

It was at Esmo 2017 that debate raged over Bristol's corresponding Checkmate-214 trial, with Opdivo/Yervoy's effect driven by intermediate or poor-risk patients who were PD-L1 positive (*Medical disclosure farrago hits Esmo 2017, September 15, 2017*).

For now the only thing Bavencio followers have to go on in comparison is that Javelin Renal 101 recruited patients from all risk groups. And across this population an interim analysis revealed a positive progression-free survival benefit favouring the Bavencio and Inlyta combo irrespective of subjects' PD-L1 status.

This was taken as an immediate threat to Cabometyx, approved broadly for first-line renal cancer in December, and sent Exelixis's stock down 8% yesterday.

Cabometyx was first hit in April by US approval of Opdivo plus Yervoy in intermediate/poor-risk patients – controversially with no precondition for patients to have high PD-L1 status. Bavencio plus Inlyta, if approved on the strength of the latest trial, would put more pressure on the Cabometyx franchise.

Questions remain

Still, much data unpicking remains to be done from Javelin Renal 101. Did poor progressors and/or high PD-L1 expressers drive the PFS benefit? Can the study show its co-primary overall survival benefit given that progressing patients might have received Opdivo second line, according to its label? Will this confounding effect matter?

It is certainly an unexpected outcome that Bavencio/Inlyta hit a PFS benefit irrespective of PD-L1 status. Pfizer

had gone out of its way to redesign Javelin Renal 101, increasing enrolment from 583 to 830 patients, and analysing PD-L1 expressers before looking at all comers.

The group was presumably moved to make such changes after Roche's Immotion-150 trial showed a strong bias for Tecentriq in PD-L1-expressing first-line subjects. Roche's Immotion-151 study read out positively for PFS in December, but only in patients expressing PD-L1.

Now that Javelin Renal 101 has become what Pfizer termed the first phase III trial of immunotherapy combined with a tyrosine kinase inhibitor to read out positively in any tumour type, attention will turn to combos of Merck & Co's Keytruda with Inlyta (Keynote-426) and with Lenvima (Clear).

Perhaps most intriguing of all is Checkmate-9ER, which combines Cabometyx with its arch rival Opdivo, and should read out next year. This study could underscore Cabometyx's importance, but by then much of Exelixis's first-line first-mover advantage might have been lost.

Bristol's ability to secure a broad first-line label was a major coup, enabling Opdivo/Yervoy to fit right into a prescribing environment where there was no requirement for PD-L1 testing. Bavencio/Inlyta's all-comers success only reinforces the threat.

Selected phase III immuno-oncology studies in first-line renal cell carcinoma

Sponsors	Products	Study	Enrolment	Primary endpoint	Trial ID	Data
Pfizer/Merck KGaA	Bavencio + Inlyta	Javelin Renal 101	830	PFS/OS in PD-L1+	NCT02684006	Toplined Sep 2018
Merck & Co	Keytruda + Inlyta	Keynote-426	826	PFS/OS	NCT02853331	Jan 2020
Bristol-Myers Squibb/Exelixis	Opdivo + Cabometyx	Checkmate-9ER	630*	PFS	NCT03141177	Sep 2019
Eisai	Lenvima + Afinitor; Lenvima + Keytruda	Clear	735	PFS	NCT02811861	Oct 2019

*Note: all studies have Sutent as control; *cut from 1,014 subjects, eliminating a Yervoy-containing triplet cohort, in Aug 2017.*

This story was corrected to reflect changes to the design of Checkmate-9ER.