Evaluate Vantage

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The joker in Exelixis and Bristol's kidney cancer pack

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The first-line Checkmate-9ER study will read out soon, and could show whether two arch rivals can together defeat a common enemy.

Do Bristol-Myers Squibb's Opdivo and Exelixis's Cabometyx have a bright future in first-line treatment of kidney cancer? The two have fought fiercely over this space, only to be outmanoeuvred by Merck & Co's Keytruda, but now a single study could give them both a second wind.

That study is Checkmate-9ER, which tests a combination of Opdivo and Cabometyx and is due to be completed this month. It would be a huge surprise to see this trial fail given that in Pfizer's Sutent it has a low bar to clear; much more relevant will be the extent to which the combination is able to extend survival over Sutent.

This is because in Keynote-426 Keytruda plus Inlyta reduced risk of death by 47% versus Sutent in this setting, generating what at present looks like the strongest dataset in the front-line all-comers setting.

Moving quickly

Leadership in renal cancer treatment has been changing fast. Cabometyx had initially shown great first-line promise as monotherapy, thanks to the Cabosun study, but was quickly outflanked by Bristol's controversial Checkmate-214 trial of Opdivo plus Yervoy (*Many questions and few answers after Esmo's Checkmate debacle, September 20, 2017*).

The polemics over patient subgroups quickly became irrelevant when Pfizer/Merck KGaA's Bavencio in combination with Inlyta scored an impressive all-comers benefit in the Javelin Renal 101 trial. But soon afterwards Merck & Co blew even these data out of the water with the Keynote-426 readout.

All four regimens now carry first-line renal cancer labels.

Perhaps the most important aspect of the last two datasets is that they showed the clear promise of combining checkpoint blockade with VEGF inhibition. Checkmate-9ER plays to this strength, as Cabometyx, like Inlyta, is an inhibitor of several VEGFR tyrosine kinases.

The study has undergone several changes. It had initially included an additional Opdivo/Yervoy/Cabometyx triplet, but this was removed two years ago, citing the need to accelerate the Opdivo/Cabometyx doublet and reflect changing clinical practice. Exelixis denied that this move was due to fears over Yervoy's toxicity.

Then the remaining two cohorts were slightly enlarged, from 630 to around 650 subjects, to improve powering, delaying completion from September 2019 to this month. Enrolment was completed last April, and results are due early in the first half of 2020.

Selected first-line renal cell carcinoma trials					
Study	**Design vs Sutent**	**mOS**	**mPFS**	**Patient prognosis**	**PD-L1 status**
Cabosun	Cabometyx	Not stat sig*	8.6mth vs 5.3mth	Irrelevant, per US label***	Irrelevant
Checkmate-214	Opdivo + Yervoy	NR vs 25.9mth (HR=0.63)	Not stat sig**	Intermediate/poor	Result driven by PD-L1 +ves
Javelin Renal 101	Bavencio + Inlyta	Immature	13.8mth vs 8.4mth	Irrelevant	Irrelevant****
Keynote-426	Keytruda + Inlyta	NR vs NR (HR=0.53)	15.1mth vs 11.1mth	Irrelevant	Irrelevant
Checkmate-9ER	Opdivo + Cabometyx	Secondary endpoint	Primary endpoint	Irrelevant	Irrelevant
Clear/Keynote-581	Lenvima +/- Ketyruda	Secondary endpoint	Primary endpoint	Irrelevant	Irrelevant

*Note: *26.6mth vs 21.2mth; **11.6mth vs 8.4mth; ***pivotal Cabosun study tested only intermediate/poor prognosis subjects; ****primary analysis was in PD-L1 +ves. NR=not reached. HR=hazard ratio. Source: US labels & trial reports.*

While the chances of success seem high, investors hoping for a knockout result might be disappointed. For one thing, Checkmate-9ER's primary efficacy measure is progression-free survival and, if this is the only result toplined, the data could underwhelm given the strong overall survival benchmark set by Keynote-426.

And a subsequent effect on OS could be difficult to parse, given that subjects in the Sutent control arm who progress can go on to receive immunotherapy, from which they should derive a benefit. However, in Javelin Renal 101 only 30% of control cohort progressers got second-line immunotherapy.

Finally, Merck & Co still has its own joker in the pack, in the form of the Clear/Keynote-581 trial, which tests Eisai's VEGFR-targeting drug Lenvima with and without Keytruda and should read out later this year.

It seems that Exelixis and Bristol have a chance to claw back some lost ground, but the tectonic plates here will continue to shift.