Evaluate Vantage

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Asco-GU 2019 – Bristol’s renal cancer lead looks to be short-lived

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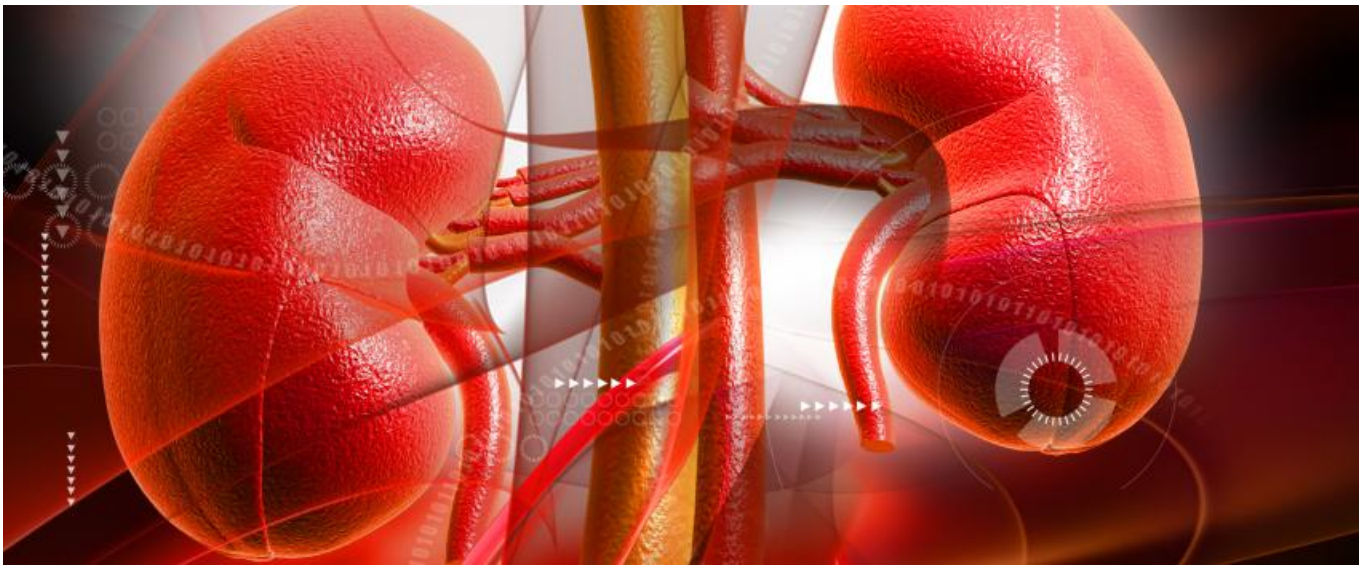


In the Keynote-426 study Merck & Co’s Keytruda looks to have blasted Opdivo out of the water, showing a 47% reduction in risk of death versus Sutent.

Bristol-Myers Squibb is probably getting tired of this, but it’s happened again. Another oncology setting in which Opdivo had seized an early foothold, in this case renal cell carcinoma, looks soon to fall to its arch-rival, Merck & Co’s Keytruda.

The first-line Keynote-426 study, in which Keytruda was combined with Pfizer's Inlyta, was already known to have hit overall and progression-free survival endpoints, but full data had been kept back until today’s abstract reveal at the Asco-Genitourinary Cancers symposium. The result looks likely also to clip the wings of Pfizer/Merck KGaA’s Bavencio, whose Inlyta combo impressed at Esmo last year.

Expectations going into today were that Merck & Co had likely trumped Pfizer/Merck KGaA’s own effort to combine an anti-PD-(L)1 antibody with a tyrosine kinase inhibitor. The latter’s Esmo presentation concerned the Javelin Renal 101 trial, though Bavencio has yet to be filed for renal cancer (*Esmo 2018 – Front-line kidney showdown now features four players, October 21, 2018*).

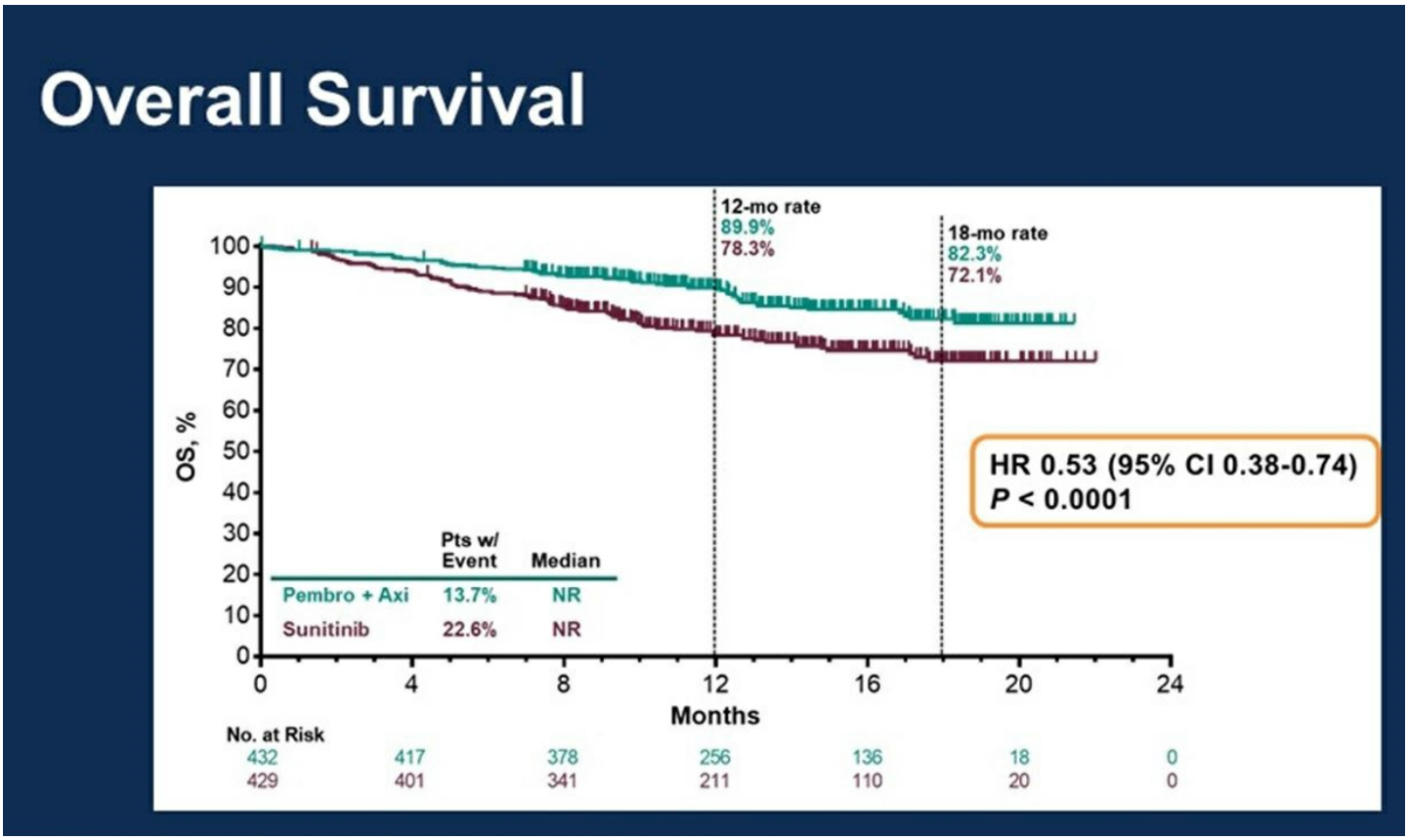
The real damage, however, seems to be to the established player, Bristol, for whose struggling Opdivo franchise renal cancer has so far been a rare bright spot. Opdivo plus Yervoy is approved for first-line use in intermediate/poor prognosis patients on the back of the Checkmate-214 trial.

Emphatic

The number for Keytruda to beat was Opdivo/Yervoy's 37% reduction in risk of death in Checkmate-214. The corresponding result in Keynote-426 is thus an emphatic victory for the Merck & Co drug: 47%, irrespective of patients’ prognosis status.

Though Keytruda’s potential in the broad population will not become apparent until subgroup analyses are revealed at Asco-GU on Saturday, today’s press call gave a clue. Describing the Keynote-426 data, Dr Thomas Powles, of Barts Health and the Royal Free NHS Trusts, said: “The benefit was seen irrespective of IMDC risk group or PD-L1 status.”

This is important, since the Checkmate-214 result was strongly driven by PD-L1-positive subjects. The Javelin Renal 101 data were said to be independent of prognosis scores and PD-L1 status, though the breakdown here has also not yet been revealed.



Overall survival in the Keynote-426 study. Source: Dr Thomas Powles & Asco-GU.

The OS result in Keynote-426 is remarkable because of the likelihood of control arm patients deriving a benefit from second-line Opdivo, which they could get on progression, something that had caused some analysts to say the hazard ratio seen in Checkmate-214 was out of reach for Keytruda. Dr Powles said he would detail patients' subsequent therapies at Asco-GU.

Another indication of the strength of the Keynote-426 data was the result for the co-primary PFS endpoint: 15.1 months for Keytruda is numerically better than the 13.8 months seen with Bavencio in Javelin Renal 101 (the OS result here is insufficiently mature for analysis).

PFS seen with Keytruda also beats the 8.6 months demonstrated by a small-molecule first-line rival, Exelixis's Cabometyx in the Cabosun study in intermediate/poor prognosis patients.

Dr Powles pointed out that 11.1 months of PFS for Sutent control in Keynote-426 was high, suggesting that the result was particularly robust.

Two of four

Keynote-426 has thus become the second of four pivotal trials combining checkpoint blockade with tyrosine kinase inhibition to read out.

Attention will now turn to Bristol's Checkmate-9ER, testing Opdivo plus Cabometyx, and Clear, a Merck & Co/Eisai study in which one cohort combines Keytruda with Lenvima; these will yield data around September 2019 and April 2020 respectively.

If Inlyta is now looking increasingly like the best drug to combine with checkpoint blockade in first-line renal cancer then overall survival data from Javelin Renal 101 remain important. Because Pfizer owns Inlyta as well as Bavencio it retains a commercial advantage, though such a bundled combo, it now seems, might come up short on efficacy even if it does come with a cost benefit.

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***	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	Said to be irrelevant	Said to be irrelevant****
Keynote-426	Keytruda + Inlyta	NR vs NR (HR=0.53)	15.1mth vs 11.1mth	Said to be irrelevant	Said to be irrelevant
Checkmate-9ER	Opdivo + Cabometyx	Secondary endpoint	Primary endpoint	Irrelevant	Irrelevant
Clear	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.*