Evaluate Vantage

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Esmo 2020 puts Opdivo and Cabometyx back in the game

Jacob Plieth

Full data from the Checkmate-9ER trial suggest a new combo to match Merck & Co's Keytruda plus Inlyta in first-line renal cancer.

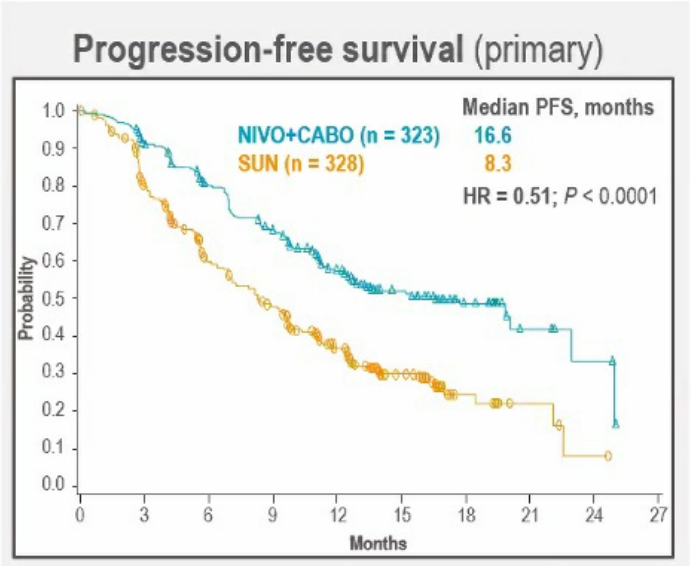
The fast-moving battle for control of first-line renal cancer had seen Opdivo and Cabometyx edged out by rival PD-(L)1/kinase inhibitor combinations, but the two could be back in the game. This is the message from full data from the Checkmate-9ER study presented today at the Esmo congress.

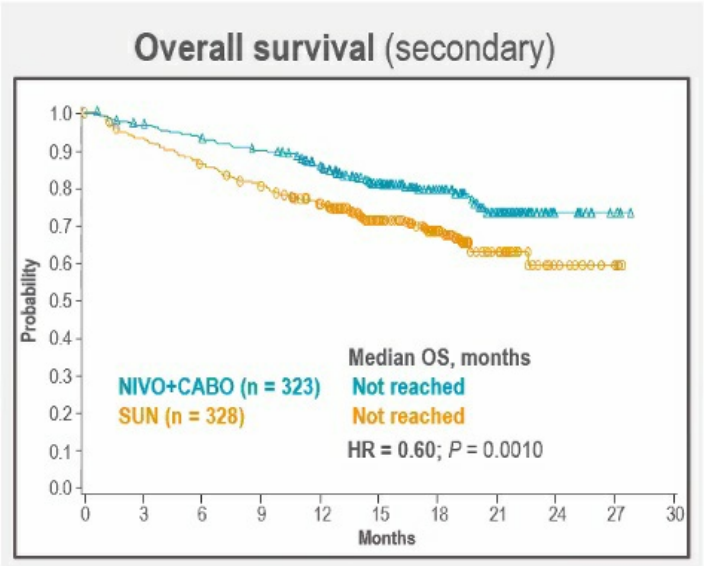
Ironically, Exelixis/Ipsen's Cabometyx and Bristol Myers Squibb's Opdivo had earlier been fierce rivals, the latter in its combination with Yervoy. But, after joining forces, they seem to have at least matched the common enemies that had threatened to consign them to the second-line setting.

The Checkmate-9ER data had been toplined in April, but nothing beyond the hazard ratios for survival had been known until now. The Esmo data showed median progression-free survival with Opdivo plus Cabometyx, '9ER's primary endpoint, of 16.8 months, versus 8.3 for Sutent control.

On a cross-trial basis the active arm's numerical benefit looks to be in line with the 17.1 months' PFS Keytruda plus Inlyta had scored in Keynote-426 – the study to beat in this setting. This benefit dashes hopes of a numerically superior median number, as the more impressive hazard ratio seen in '9ER is accounted for by Sutent's relative underperformance versus Keynote-426.

Efficacy summary in Checkmate-9ER





Source: Dr Toni Choueiri & Esmo.

Like in Keynote-426, and indeed in Merck KGaA/Pfizer's Javelin Renal 101 trial, overall survival has yet to reach a median, but the hazard ratio again shows '9ER to be competitive with the Merck & Co study.

One question is where the latest data leave Merck KGaA/Pfizer's Bavencio plus Inlyta combo. This was the first immunotherapy/kinase inhibitor combination to yield a knockout result in first-line renal cancer, but now looks to have been eclipsed: though its median overall survival has not been reached, the upper bound of its confidence interval is above 1.00.

Nevertheless, Checkmate-9ER's lead author, Dana-Farber Cancer Institute's Dr Toni Choueiri, refused to rule out any of the duelling first-line combinations. "Comparing across trials is very hard, and ... I am not sure we're going to see a phase III trial that compares all the combinations," he told an Esmo press conference.

However, he accepted that which combo to choose was now the "billion-dollar question". Varying lengths of patient follow-up currently make comparisons "unfair"; one way to level the field would be to put the studies side by side once they all had similar median follow-up.

Battle for survival in first-line kidney cancer			
	Checkmate-9ER*	**Keynote-426****	**Javelin Renal 101*****
PD-(L)1 + TKI combo	Opdivo + Cabometyx	Keytruda + Inlyta	Bavencio + Inlyta
Companies	BMS/Exelixis/Ipsen	Merck & Co/Pfizer	Merck KGaA/Pfizer
Median PFS vs control (mth)	16.6 vs 8.3	17.1 vs 11.1	13.3 vs 8.0
Hazard ratio for PFS	0.51	0.69	0.69
Median OS vs control	NR vs NR	NR vs NR	NR vs NR
Hazard ratio for OS	0.60	0.59	0.80
*Sources: *Esmo 2020; **EMA report; ***Ann Oncol, Aug 2020.*			

The discussant, Dr Dominik Berthold of Lausanne University Hospital, said Opdivo plus Cabometyx's only drawback was that the agents' mechanisms of action were not first in class: Keytruda and Bavencio's Inlyta combos are approved in the US first line.

Moreover, Cabometyx already has a first and second-line label, while Opdivo monotherapy is approved second-line, and Opdivo plus Yervoy is available first-line based on the Checkmate-214 study that caused some controversy at Esmo three years ago. The Opdivo/Cabometyx combo was filed with the US FDA last month.

"What we still need to learn is are there any patient populations that may benefit more from [the '9ER] combination," said Dr Berthold. "Cabometyx is quite a unique kinase inhibitor, which may target bone metastases better [than Inlyta], for example."

Other unanswered questions include the quality of life across the various studies, and long-term treatment discontinuations.

Still, choice is good for patients and doctors alike, and having too much is probably a nice problem to have. Referring to the multiple first-line renal cancer studies that have been upstaging one another, Dr Choueiri said: “Over the past three or four years we’ve been drinking from a hose.”