Evaluate Vantage

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Asco-GU – Roche's renal success spells danger for all-comer studies

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Patient selection by PD-L1 status could be necessary for developing checkpoint inhibitors in first-line renal cell carcinoma, if data from Roche's phase II Immotion-150 study presented at Asco-GU over the weekend have a read-across to similarly acting agents.

The results show that Tecentriq plus Avastin only beat Sutent in PD-L1 expressers, and fortuitously Roche is recruiting exactly the same patient group into its large registration trial. Not so Pfizer/Merck KGaA and Merck & Co, neither of whose pivotal studies in this setting requires patients to show PD-L1 expression – a fact that spells fresh risk for these rival trials (see table below).

In Roche's Immotion-150 trial, in PD-L1 expressers the two-drug combo reduced risk of progression by 36% versus Sutent. There was no advantage over this long-standing standard of care for metastatic renal cell carcinoma (RCC) with Tecentriq alone – either in PD-L1 expressers, defined at 1% or above, or for the combination in all comers.

Expressing its immotions

This is important because Immotion-151, Roche's large registration study of the Tecentriq/Avastin combo in first-line RCC, recruits the same 1% PD-L1 expression group.

While this is well behind Pfizer/Merck KGaA and Merck & Co's rival studies of avelumab and Keytruda respectively, neither requires patients to show PD-L1 expression on entry. Both these trials might now be perceived as risky – or, if successful, could offer only a short-lived advantage – if PD-L1 status is found to be important in determining response in RCC.

If PD-L1 expression does play an important role here it would put RCC on a similar footing as first-line lung cancer, where Bristol-Myers Squibb's unfortunate decisions in study design caused Opdivo to fall behind Keytruda, which had been studied in a PD-L1-expressing population.

The new risk could be a factor in Merck's strategic thinking, given that it recently started two separate phase II RCC studies that examine Keytruda with Votrient (Keynote-018) and with pegylated-interferon or Yervoy (Keynote-029).

Moreover, PD-L1 status could also become important in the second line setting, where Opdivo is the only approved agent, despite the fact that its approval is independent of patients' PD-L1 status. Bristol is, of course, unlikely to examine this hypothesis and is instead focused on showing an advantage for Opdivo combined with its anti-CTLA4 checkpoint inhibitor, Yervoy, in the same way as was done in melanoma.

A phase I study testing two Opdivo/Yervoy combinations in this setting was published at ESMO last year. The more successful of the regimens tested, 3mgkg + 1mg/kg – now being used in Checkmate-214 – showed overall remission of 40%. This would seem to be in the same range as the 46% seen for Tecentriq/Avastin in the PD-L1 expressers in Immotion-150.

Bristol is also conducting Checkmate-800, a phase II trial of sequential versus simultaneous administration of Opdivo and Yervoy in first-line RCC. However, it is Fraction-RCC that could give more insight into its longer-term strategy: this effectively tests Opdivo with Bristol's anti-Lag-3 antibody, BMS-986016, against Opdivo/Yervoy.

The disclosed inclusion/exclusion criteria for this study do not show whether it recruits only first-line patients, although in practice it would probably have to.

Selected first-line renal cell carcinoma studies					
Sponsors	**Project(s)**	**Acronym**	**Enrolment**	**Trial ID**	**Data**
Phase III					
Pfizer/Merck KGaA	Avelumab + Inlyta	Javelin Renal 101	583	NCT02684006	Jun 2018
Bristol-Myers Squibb	Opdivo + Yervoy	Checkmate-214	1,099	NCT02231749	Jun 2019
Merck & Co	Keytruda + Inlyta	Keynote-426	840	NCT02853331	Jan 2020
Roche	Tecentriq + Avastin	Immotion-151	900	NCT02420821	Jul 2020
Eisai	Lenvima + Afinitor; Lenvima + Keytruda	Clear	735	NCT02811861	Oct 2019
Phase II					
Bristol-Myers Squibb	Opdivo + Yervoy	Checkmate-800	100	NCT03029780	Feb 2018
Merck/Novartis	Keytruda + Votrient	Keynote-18	248	NCT02014636	Dec 2018
Merck & Co	Keytruda +peg-IFN	Keynote-029	293	NCT02089685	Apr 2020
Bristol-Myers Squibb	Opdivo + BMS-986016	Fraction-RCC	650	NCT02996110	Jan 2022
All studies have Sutent as control except Keynote-029 (Keytruda + Yervoy) and Fraction-RCC (Opdivo + Yervoy).					

While checkpoint inhibitors have come to dominate later-stage approaches in first-line RCC, it is worth noting that Exelixis's kinase inhibitor Cabometyx, which was approved last year as a second-line agent, will shortly be filed for first-line use based on the results of the phase II Cabosun study (*Esmo – Exelixis basks in the Cabosun, October 10, 2016*).

If Cabosun succeeds this drug could become the preferred choice, as Cabosun showed a solid survival advantage for Cabometyx over Sutent.

KOLs in the field have expressed interest in seeing a study of Opdivo and Cometriq in first-line RCC. While such a trial has yet to materialise, the NCI is studying this doublet, and indeed a triple combo with Yervoy, in a variety of genitourinary cancers, including RCC, that could read out in 2018.

Another kinase inhibitor is Lenvima, which was approved for second-line RCC in combination with Afinitor, and which Eisai is testing in a three-arm study that examines combos with Afinitor and Keytruda versus Sutent. On the other hand, the competition thinned with today's failure for futility of the long-running Adapt study of Argos Therapeutics' autologous cell-based therapy vaccine rocapuldencel-T.

RCC remains one of the most important indications for checkpoint inhibitors after NSCLC and there is much to play for with the first-line setting still wide open. The results of trials over the next couple of years will reveal the importance of patient selection, and help determine how the market splits between the various agents.

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