Evaluate Vantage

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Esmo – Exelixis basks in the Cabosun

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Exelixis revealed the detailed results of its previously toplined Cabosun trial of Cabometyx in front-line renal cell carcinoma (RCC) at Esmo earlier today, and they look good enough to prompt a change in the standard of care.

The results could help Cabometyx pull ahead of Bristol-Myers Squibb's immune checkpoint inhibitor Opdivo and Eisai's Lenvima, which are approved in the second-line setting. Exelixis and its ex-US marketing partner Ipsen intend to file for approval in first-line disease based on the Cabosun results – Cabometyx is currently used in patients with advanced RCC who have received prior anti-angiogenic therapy. This could have a knock-on effect on currently ongoing registration studies in first-line RCC (see table below).

Exelixis's stock price intially climbed on the news, but fell back after a discussant said he felt that a phase III trial would be required to confirm the overall survival benefit seen. A request for this study would not be taken well, given the competition on the horizon, though many sellside analysts continue to believe that the drug will receive an expanded label based on this phase II data.

Moment in the Cabosun

The Cabosun study showed a statistically and clinically significant 2.6-month improvement in median progression-free survival (PFS) relative to Pfizer's Sutent in intermediate and poor prognosis patients. This benefit translated into a hazard ratio (HR) of 0.69, equivalent to a 31% improvement in the relative risk of progression or death. The study also showed a large increase in objective response rate and a trend towards improved overall survival.

Cabosun's principal investigator, Dana Farber Cancer Institute's Dr Toni Choueiri, reported that the PFS benefit was independent of risk group and the presence or absence of bone metastases. The study recruited only intermediate and poor risk patients and, as a result, had a higher proportion, some 36%, of patients with bone metastases than most comparable first-line studies. The results for the control arm were also consistent with a published retrospective analysis of more than 1,000 patients showing the same median PFS of 5.6 months for Sutent.

Cabosun trial results			
	Cabometyx	**Sutent**	**Statistics**
mPFS (months)	8.2 (6.2-9.0)	5.6 (3.4-8.1)	HR=0.69 (0.48-0.99), p=0.012
ORR	46% (34-57%)	18% (10-28%)	N/A
mOS (months)	30.3 (14.6-35.6)	21.8 (16.3-27.0)	HR=0.80 (0.50-1.26)
95% confidence intervals shown in parentheses.			

Although Cabosun was a relatively small phase II study in 157 patients, Dr Choueiri considers the data to be sufficiently robust to justify Cabometyx's use in the specifically studied population of intermediate or poor risk RCC. Cabometyx is likely to receive an NCCN Compendia listing ahead of expanded approval.

Currently there are six ongoing phase III trials in first-line RCC, five of which include Sutent as the control and one in which it remains the backbone of therapy. Of course, if any of these studies are positive, they would introduce new competition.

Ongoing Phase III trials in first-line RCC					
Company	**Product**	**Study**	**Design**	**Trial ID**	**Data**
Argos	Rocapuldencel-T	Adapt	Sutent +/-	NCT01582672	Apr 2017
Pfizer/Merck KGaA	Avelumab + Inlyta	Javelin Renal 101	vs Sutent	NCT02684006	Jun 2018
Bristol-Myers Squibb	Opdivo + Yervoy	Checkmate-214	vs Sutent	NCT02231749	Jun 2019
Eisai	Lenvima/Afinitor or Lenvima/Keytuda	-	vs Sutent	NCT02811861	Oct 2019
Merck & Co	Keytruda	Keynote-426	vs Sutent	NCT02853331	Dec 2019
Roche	Tecentriq + Avastin	Immotion151	vs Sutent	NCT02420821	Jun 2020

Sutent may move up too

Another factor in that transition might be the possible movement of Sutent to earlier use in the adjuvant setting. This has been studied in the phase III S-Trac study, data for which also emerged at Esmo on Monday. Pfizer previously reported positive top-line results from S-Trac in July.

In the S-Trac study, patients with high-risk, clear cell RCC were treated for one year with Sutent or placebo immediately following nephrectory, and the outcome measured in terms of disease free survival. The primary endpoint was met, with a 1.2 year increase in median disease-free survival (6.8 vs 5.6 years with placebo). This benefit translated into a hazard ratio of 0.761, equivalent to a 24% improvement in relative risk and a p value of 0.03. The benefit was greater for higher-risk patients only, where there was a 2.2 year increase (6.2 vs 4.0 years) and a hazard ratio of 0.737.

However, despite coming from a large study, these data are likely to remain controversial as a previous study with a similar design, Assure, showed no difference in disease free survival or OS for Sutent in adjuvant RCC. Thus, the outcome of any future meta-analysis of the two studies could determine whether the change takes place.

And one other agent is being studied in the adjuvant setting: Inlyta, in the Atlas trial, which could render data next year.

The RCC therapy landscape already looks set for important changes with the Cabosun data – and there could be more to follow.

This article has been updated to include mention of the share price fall in the third paragraph.

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