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Therapy focus – New kidney cancer data emerge in time for Asco

Robin Davison

Yesterday's positive topline result with Cabometyx in first-line renal cell carcinoma could hardly have come at a more opportune moment for Exelixis, arriving just days before Asco, the world's largest cancer conference. The result from the Cabosun phase II trial could tip the balance in its favour against Bristol-Myers Squibb's anti-PD1 juggernaut Opdivo, which was launched several months before Cabometyx in this indication (see table below).

Physicians can now speculate over whether the still unknown but apparently statistically and clinically significant progression-free survival advantage over Sutent justifies Cabometyx's move into first-line use. Sutent has been the de facto first-line standard of care since 2006. Exelixis plans to disclose the Cabosun data at a future scientific meeting.

The announcement also gives Exelixis something with which to make a splash at Asco, having had the chance to reveal mature overall survival results from its pivotal Meteor study of Cabometyx thwarted. The FDA's earlier-than-expected approval meant that data emerged on the package insert last month.

Moment in the Cabosun

Whether Exelixis can allude to the Cabosun result at Asco or not, the conference should provide a forum for a lively debate on the relative merits of Cabometyx and Opdivo in the approved second-line indication.

Doctors will also be able to consider the role for the other new agent that has just entered the RCC field, namely Eisai's Lenvima, which won a rapid approval – based on a phase II study – for use in combination with Afinitor in second-line patients.

Thus there are now three new choices for second-line RCC: Opdivo and Cabometyx as monotherapies, and Lenvima/Afinitor in combination. A side-by-side comparison of the pivotal data suggests that Cabometyx offers a 4.9-month, Opdivo a 5.4-month and the Lenvima/Afinitor combo a 10.1-month OS benefit.

However, the cross-trial comparison is compromised by the fact that Opdivo recruited better-prognosis patients, as seen by the control arm performance, and that Eisai's data came from a smaller phase II study. The control arm is, however, the same in all three cases: Afinitor alone. Moreover, the relative improvement in survival, as shown by hazard ratio, was greatest for Cabometyx, albeit by a small margin over Lenvima/Afinitor.

Cross-trial data comparison: new second-line RCC therapies

Drug	Cabometyx	Opdivo	Lenvima/Afinitor
PFS	7.4 vs 3.8mths (HR=0.58, p<0.0001)	4.6 vs 4.4mths (HR=0.88, p=0.1135)	14.6 vs 5.5mths (HR=0.37)
OS	21.4 vs 16.5mths, (HR=0.66, p=0.0003)	25.0 vs 19.6mths (HR =0.73, p=0.0018)	25.5 vs 15.4mths (HR=0.67)
ORR	21% vs 5% (p<0.0001)	25% vs 5% (odds ratio=6.05, p<0.001)	37% vs 6%

Before the Cabosun trial outcome sellside analysts had assumed that doctors would probably mostly use an immune checkpoint inhibitor ahead of a tyrosine kinase inhibitor, which meant that most of Cabometyx's sales would come in what is effectively the new third-line setting, after Sutent and Opdivo. But this could now change if the Cabosun data demonstrate a significant advantage from its earlier use.

But Cometriq might not be the only drug moving up the therapy lines shortly. The outcome, due imminently, of

the S-trac study could position Sutent in the adjuvant setting in patients at high risk of recurrence. This study could make the Pfizer drug suitable for immediate post-nephrectomy use.

If Cabosun does establish Cabometyx as the first-line agent of choice it could have some implications for several ongoing phase III studies that use Sutent as control. These include the three combination studies involving checkpoint inhibitors: Javelin-Renal-101 of avelumab plus Inlyta, CheckMate-214 of Opdivo and Yervoy, and Immotion151 of Tecentriq plus Avastin.

Company	Product(s)	Study	n	Design	Setting	Trial ID	Data
Phase III							
Pfizer	Sutent	S-TRAC	720	vs placebo	Adjuvant	NCT00375674	Apr 2016
Argos	rocapuldencel-T	ADAPT	450	Sutent +/-	1L	NCT01582672	Apr 2017
Pfizer	Inlyta	ATLAS	700	vs placebo	Adjuvant	NCT01599754	Jun 2017
AVEO	Tivozanib	TIVO-3	322	vs Nexavar	>3L	NCT02627963	Mar 2018
Pfizer	Avelumab + Inlyta	JAVELIN Renal 101	583	vs Sutent	1L	NCT02684006	Jun 2018
Bristol-Myers Squibb	Opdivo + Yervoy	CheckMate 214	1,099	vs Sutent	1L	NCT02231749	Jun 2019
Roche	Tecentriq + Avastin	Immotion151	830	vs Sutent	1L	NCT02420821	Jun 2020
Phase II (selected)							
Tracon	TRC105	-	168	Inlyta +/-	2-3L	NCT01806064	Jul 2016
Cerulean Pharma	CRLX101	-	110	vs SoC	3-4L	NCT02187302	Sep 2016
Roche	Tecentriq +/- Avastin	IMmotion150	305	vs Sutent	1L	NCT01984242	2016
Boehringer Ingelheim	Vargatef	-	99	vs Sutent	1L	NCT01024920	Feb 2017
Takeda	MLN0128 +/- MLN1117	-	189	vs Afinitor	1L	NCT02724020	May 2017
Acceleron	Dalantercept	-	174	Inlyta +/-	3L	NCT01727336	Dec 2017
Agensys	AGS-16C3F	-	134		>3L	NCT02639182	Jan 2018

While the introduction of new agents should represent welcome improvements in the treatment of RCC, it is clear that that there will have to be more scientific debate on the merits of these drugs.

Key RCC data from Cabometyx, Opdivo and Lenvima at Asco		
Abstract	**Detail**	**Date/time/location**
4506	OS data from Meteor study of Cometriq	Oral abstract: Jun 5, 10:12-10:24am. Hall D2
4558	Sub-group of Meteor study with bone metastases	Poster board: #180 Jun 6, 1:00-4:30pm. Hall A
4547	Outcomes based on prior VEGFR TKI and PD-1 therapy in Meteor study	Poster board: #179 Jun 6, 1:00-4:30pm. Hall A
4552	Correlation of response with OS from CheckMate 025 study of Opdivo	Poster board: #174 Jun 6, 1:00-4:30pm. Hall A
4507	Long-term OS in previously treated patients with advanced RCC from 010/003 Opdivo phase I and II studies	Oral abstract: Jun 5, 10:24-10:36am. Hall D2
4508/4509	Analyses of treatment beyond disease progression from CheckMate-025 study	Poster boards: #131 and 132, Jun 6, 1:00-4:30pm. Hall A. Discussed at 4:45-6:00pm, Arie Crown Theater.
4553	Subgroup analyses and updated overall survival from the phase II trial of Lenvima	Poster board: #175. Jun 6, 1;00-4.30pm. Hall A

The author will be reporting live from Asco, which begins on June 3. To contact the writer of this story email Robin Davison at news@epvantage.com or follow @RobinDavison2 on Twitter