Evaluate Vantage

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After US approval Aveo faces a monumental task

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Aveo gets Fotivda over the line in the US, but the market celebration looks misplaced.

Anyone looking at Aveo's 89% share price surge yesterday might assume that US approval of the group's kidney cancer drug Fotivda marked a turnaround in the struggling company's commercial prospects.

Such hope is misplaced: Aveo's supporting study compared Fotivda against an obsolete drug, at best showing no overall survival advantage, and Fotivda's patent life ends soon. But the approval, 21 days before the FDA's action date, is an odd example of generosity on the part of a regulator seen recently as getting tough.

Indeed, on the same day as granting Fotivda's approval the US agency knocked back Kadmon's filing for the graft-versus-host project belumosudil, delaying its action date by three months to August 30 to allow review of additionally submitted information.

This came after the scheduling of a surprise adcom for roxadustat, a serious knockback to Nuplazid, and the withdrawal of several immuno-oncology drug uses previously approved on an accelerated basis. Such moves have caused some to suggest that the FDA was tightening its stance, a view that likely contributed to the Nasdaq biotechnology index dipping by 11% in the past month.

Third line?

No such worries for Aveo, at least from a regulatory perspective: Fotivda can now be prescribed in the US for renal cell carcinoma patients progressed after two or more systemic therapies.

Its journey was long and tortuous, and the supporting study, Tivo-3, had begun five years ago. This is crucially important, as the kidney cancer landscape has changed significantly in the meantime, seeing anti-PD-1 therapy move front line, first combined with Yervoy and then with Inlyta or Cabometyx, and older therapies relegated.

The trial was controversial. It had read out positively for its primary progression-free survival endpoint versus Nexavar, but overall survival was a different story: a first cut of the data showed a 1.12 hazard ratio for the median, meaning survival favoured Nexavar, before the final result came in at 0.97.

0.97 is clearly still unconvincing, though Aveo argues that the FDA's stance called for a PFS advantage and no detriment in OS, and Tivo-3 did show just about this. Crucially, however, median OS for Fotivda was 2.8 months shorter than for Nexavar.

In fact the very use of Nexavar as a comparator is a red flag. This drug was approved in renal cancer 16 years

ago, and is no longer routinely used; US NCCN guidelines do not recommend it in any setting, but suggest that it is “useful in some circumstances” in progressed patients.

Summary of approved renal cell carcinoma regimens (approval year, comparator in relevant trial)		
1st line*	**2nd line**	**3rd line**
Opdivo + Cabometyx (2021, Sutent)	Cabometyx (2016, Afinitor)	Fotivda (after two systemics) (2021, Nexavar)
Bavencio + Inlyta (2019, Sutent)	Lenvima + Afinitor (2016, Afinitor)	Afinitor (post Sutent or Nexavar) (2009, placebo)
Keytruda + Inlyta (2019, Sutent)	Opdivo (2015, Afinitor)	
Opdivo + Yervoy (2019, Sutent)	Inlyta (2012, Nexavar)	
Cabometyx** (2017, Sutent)	Votrient (2009, placebo)	
Avastin** (2009, interferon-α)	Sutent (2006, none)	
Torisel** (2007, interferon-α)	Nexavar** (2005, placebo)	
Sutent** (2006, interferon-α)		
*Source: drug labels & company info. *Keytruda + Lenvima read out positively vs Sutent in Keynote-581 but not yet approved; **drug no longer routinely used in this setting.*		

True, Inlyta monotherapy secured a second-line label based on a comparison versus Nexavar, but that was back in 2012. In the third-line or later setting that Fotivda might target, a more realistic comparator today might be Sutent or Afinitor, though no defined standard exists.

However, the fact combinations have taken over the first-line setting theoretically opens second-line use to Fotivda; a patient progressed on front-line Keytruda plus Inlyta, say, would therefore have already seen two systemic therapies.

Aveo stresses that Tivo-3 included patients relapsed on PD-1 inhibition, and this is clearly positive. But doctors seem likely to cycle patients from IO/IO or an IO/TKI combo, to another novel TKI, and then to Afinitor or Sutent, before Fotivda comes into play.

And then there is intellectual property: Aveo says Fotivda’s US patents start to expire next year. US approval might be surprising, but the victory will surely be short-lived.