Evaluate Vantage

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Upcoming events – Aveo awaits tivo's death sentence and Glaxo goes long

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Aveo will soon find out whether Fotivda has a future, while Glaxo awaits data with an even longer-lasting HIV doublet.

Welcome to your weekly digest of approaching clinical readouts, which most companies face with a sense of nervous excitement at the possibilities that they might open. Not so Aveo, for whom tivozanib's pivotal Tivo-3 study, due to yield final survival results next month, hangs like the sword of Damocles and will determine whether this drug is pulled from the EU market.

True, positive results could also result in a US filing, but the omens are not good. The study, in third-line renal cancer, tests progression-free survival as primary endpoint, but overall survival is the all-important secondary measure.

It was a preliminary OS analysis, showing a numerical 12% increase of risk of death for tivozanib subjects versus Nexavar control, that led the FDA in January to advise Aveo not to file for approval. Three months later the EMA said "regulatory action should be considered" if Tivo-3's mature OS analysis confirmed the negative trend.

Given tivozanib's controversial history, including a 2013 US complete response letter, it is remarkable that the drug has an EU label at all. This was granted two years ago, with the brand name Fotivda, for first-line renal cancer and in VEGFR and mTOR pathway inhibitor-naive second-line patients, backed by progression-free survival seen in Tivo-1, a trial that was also negative for OS.

At one stage tivozanib was seen as a US dark horse in late-line renal cancer, but the landscape is changing fast, with Merck & Co's Keytruda and Pfizer/Merck KGaA's Bavencio, both combined with Inlyta, recently being approved first line. And EU sales by Aveo's partner Eusa Pharma have been negligible. The market might consign tivozanib to the scrapheap even if the regulator does not step in.

Trial	Setting	Preliminary PFS (primary endpoint)	Preliminary OS
Tivo-3 (NCT02627963)	3rd-line renal cancer, vs Nexavar	Hazard ratio=0.74	Hazard ratio=1.12

Meanwhile, Glaxosmithkline still has some way to go to justify its faith in two-drug combos for HIV, but it is set

for more data here, this time with a long-acting doublet, cabotegravir plus rilpivirine.

The company's HIV joint venture, Viiv, is already seeking US FDA approval for once-monthly dosing of the injectable project, but it hopes to push the envelope further with dosing every two months. Data from the Atlas 2M trial, due this quarter, will show whether this quest for greater convenience can be matched by solid efficacy.

Atlas 2M aims to show that cabotegravir/rilpivirine given every two months is noninferior to once-monthly dosing of the same combo. The primary endpoint measures viral suppression, specifically the proportion of patients with plasma HIV RNA of 50 copies/ml or greater, at week 48. Glaxo will want this number to be at least as low as that seen in the once-monthly group.

However, a more relevant comparator would have been an HIV triplet, with three-drug regimens representing the current standard of care. Indeed, none of the Viiv doublets is expected to challenge Gilead's dominance in HIV, with the latter's oral once-daily triplet Biktarvy set to bring in $7.6bn by 2024, according to *EvaluatePharma* consensus.

Viiv's HIV doublets

			Sales ($m)	
Product	**Status**	**Note**	**2019e**	**2024e**
Juluca (dolutegravir & rilpivirine)	US approval Nov 2017; EU approval May 2018	Oral once daily, stable treated patients only	427	847
Dovato (dolutegravir & lamivudine)	US approval Apr 2019; EU approval Jul 2019	Oral once daily, includes treatment-naive patients	90	1,153
Cabotegravir & rilpivirine	Filed in US; EU filing planned Q3 2019	Injectable once monthly or less frequently	-	489

Source: EvaluatePharma.

Patients in Atlas 2M had previously been receiving either standard of care – presumably triplets – or monthly cabotegravir/rilpivirine.

Worries about two-drug regimens include resistance seen in an investigator-led study of Viiv's most recently approved doublet, dolutegravir plus lamivudine, now trademarked Dovato (*Glaxo runs into double trouble in HIV, July 27, 2017*).

Glaxo stressed on Wednesday that it had not seen any resistance in its own studies of the drug, and said Dovato's launch was going well. But sales came in at just £5m ($6.2m) in the second quarter, and the group will need a quick ramp-up to hit 2019 expectations.