Evaluate Vantage

July 26, 2022

Padcev has the front line in its sights

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But the main question for deal-hungry investors will be what this means for the chances of Merck & Co buying out Seagen.

The 12-arm EV-103 trial of Seagen/Astellas's Padcev is certainly convoluted, but for investors the message is clear: its cohort K, toplined positive this morning, positions Padcev's Keytruda combo for approval in first-line urothelial cancer, potentially securing $1bn of US sales.

The bigger question is whether this will embolden Merck & Co to pull the trigger on a widely expected takeover of Seagen. Clearly the bigger Padcev becomes the higher Seagen's valuation will go, but the threat of antitrust concerns cannot be ignored, and the outcome of arbitration between Seagen and Daiichi Sankyo must surely be known before any bid is made.

These stumbling blocks to valuing Seagen have already been widely aired by Evercore ISI and *Evaluate Vantage*. The Wall Street Journal, which had initially speculated that a deal was imminent, recently rowed back, citing the Daiichi arbitration and upcoming clinical readouts as reasons why the deal timeline had "slowed".

Cohort K

The most important of these data catalysts was cohort K of the EV-103/Keynote-869 trial. Padcev is available for third-line urothelial cancer after PD-(L)1 blockade and platinum chemo, and second line in cisplatin chemo-ineligible patients, and EV-103 could provide a path to front-line approval.

Two years ago Seagen and Astellas said the FDA had indicated that randomised results from cohort K, along with other data from EV-103, could back an accelerated approval, to be confirmed by the phase 3 EV-302 trial. EV-103 tests Padcev in various combinations, and cohort K compared a Keytruda combo against Padcev monotherapy in cisplatin-ineligible patients.

This morning Seagen/Astellas said the combo had yielded a 65% overall remission rate by independent review in cohort K, with median duration of response not reached. No data for Padcev monotherapy were provided. Keytruda itself had yielded a 24% ORR in the Keynote-052 study in first-line, cisplatin-ineligible patients.

As such there appears to be some backing for the additive effect of the combo, and the companies said they would discuss the results with regulators. Still, failure to say how Padcev monotherapy did should raise eyebrows, since this drug carries a 51% ORR on its label in second-line, cisplatin-ineligible patients.

Cohort K backs up the result of EV-103's cohort A, where an uncontrolled Padcev/Keytruda combo yielded a

73% ORR by investigator review, including 85% in PD-L1-high and 67% in PD-L1-low patients, according to data presented at Asco-GU in 2020.

Evercore ISI analysts say the first-line opportunity could account for over $1bn of sales for Padcev, an anti-nectin-4 antibody-drug conjugate reckoned to sell $4.7bn in 2028, according to *Evaluate Pharma* sellside consensus.

Selected Padcev trials in urothelial bladder cancer			
Setting	**Status**	**Supporting study**	**Key data**
3L (post PD-(L)1 + platinum chemo)	Accelerated approval Dec 2019	EV-201 cohort 1	ORR 44.0%, mDoR 7.6mth
	Full approval Jul 2021	EV-301	OS 12.9mth vs 9.0mth for chemo (HR 0.70, p=0.0014)
2L (cisplatin-ineligible)	Full approval Jul 2021	EV-201 cohort 2	ORR 50.6%, mDoR 13.8mth
1L Keytruda combo (cisplatin-ineligible)	Data at Asco-GU 2020	EV-103 cohort A	ORR 73.3%
Neoadjuvant monoRx (MIBC)	Data at Asco-GU 2022	EV-103 cohort H	pCR rate 36.4%
1L Keytruda combo vs monoRx (cisplatin-ineligible)	Toplined Jul 2022	EV-103 cohort K	ORR 64.5% for combo
1L chemo +/-Keytruda combos	Enrolling	EV-103 cohorts D, E, F & G	None
Adjuvant monoRx & neoadjuvant Keytruda combo (MIBC)	Enrolling	EV-103 cohorts J & L	None
1L Keytruda combo vs chemo	Enrolling	EV-302	Confirmatory trial, reads out 2023
Note: EV-103 is technically a 10-cohort trial with 12 arms, including the two arms of cohort K and a dose escalation. MIBC=muscle-invasive bladder cancer. Source: company statements, Asco & clinicaltrials.gov.			

Assuming that Merck is seriously looking at buying out Seagen the result of cohort K should at least help crystallise the Padcev opportunity. Keytruda already has front-line urothelial bladder cancer on its US label, and Merck will be especially keen to bolster its presence given the failure of a Keytruda/Lenvima combo in the Leap-011 trial at this year's Asco-GU.

However, an increasingly vigilant US FTC might see other antitrust concerns, and the outcome of arbitration between Seagen and Daiichi Sankyo over the former's ADC technology looms large. Seagen has already secured $42m in a patent infringement case, but far more hangs on separate arbitration proceedings, expected to conclude shortly.

By chance Merck and Seagen both report second-quarter earnings on Thursday, but investors should probably not hold their breath for news of a takeover.

This story has been amended to add detail about the design of EV-103.

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