Evaluate Vantage

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Seattle could waltz in where Astra failed

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Despite Astrazeneca stacking the odds in its favour Imfinzi's Danube trial, in first-line bladder cancer, reads out negatively.

Today's failure of Astrazeneca's Danube study marks bladder cancer as an indication where checkpoint blockade is unlikely to make major further inroads. It also underlines the huge potential of Seattle Genetics' antibody-drug conjugate Padcev as one of the hottest assets to watch in this cancer type.

It is particularly noteworthy that Astra had done everything possible to set up a positive result with Imfinzi, and yet despite this the front-line study drew a blank. This might not bode well for upcoming readouts of studies of Merck & Co's Keytruda and Bristol-Myers Squibb's Opdivo in a similar setting.

But the immediate beneficiary looks to be Seattle/Astellas's Padcev, an anti-nectin-4 drug that has already scored a second-line bladder cancer label under accelerated approval. A Keytruda combo study has shown extraordinary potential in the front-line setting, and a pivotal study, EV-302, is now under way.

For checkpoint blockade Astra's Danube result marks more uncertainty. The five major anti-PD-(L)1 drugs are all available second line, but the failure of Roche's confirmatory Imvigor-211 study raised concerns over these accelerated approvals.

Tecentriq and Keytruda are also approved first line in chemo-ineligible patients, and the Roche drug can additionally be used in those eligible for cisplatin as long as they express PD-L1 at 5% or above.

US status of anti-PD-(L)1 MAbs in urothelial bladder cancer (supporting studies in brackets)		
	1st line	**2nd line**
Tecentriq	Approved in ≥5% PD-L1+ves, & chemo-ineligible all-comers (Imvigor-210)*	Approved (Imvigor-210)**
Opdivo	Chemo combo & Yervoy combo (Checkmate-901) readout 2021	Approved (Checkmate-275)
Imfinzi	Failed as monotherapy in ≥25% PD-L1+ves & tremelimumab combo (Danube)	Approved (Study 1108)
Bavencio	OS benefit seen in 1st-line maintenance (Javelin Bladder 100)	Approved (Javelin Solid Tumor)
Keytruda	Approved in chemo-ineligible (Keynote-045 & 052); chemo combo (Keynote-361) readout imminent	Approved (Keynote-045 & 052)
**Imvigor-130 data were mixed; **failed Imvigor-211 study.*		

Danube had tested Imfinzi monotherapy or in combination with the anti-CTLA-4 MAb tremelimumab, compared against standard platinum chemo. It had been expected to read out a year ago, its primary endpoint looking at OS and PFS of the combination cohort, but was delayed as Astra made changes to increase chances of success.

These amendments focused the trial's primary endpoint on OS only, in the combo and monotherapy arms alike. For the latter a relatively narrow cut of PD-L1 expression was applied: ≥25%. Yet despite this Astra said no survival benefit versus chemo was seen.

The UK group had refocused Danube on OS along with two other first-line combo studies, Neptune in NSCLC and Kestrel in head and neck cancer. The former has already failed, while the latter looks likely to do so. And it does not need pointing out that the Danube setback marks yet another failure for a tremelimumab regimen.

Astra stresses that it has two other phase III, first-line bladder cancer studies under way: Niagara tests Imfinzi plus chemo in muscle-invasive disease, while Potomac combines Imfinzi with BCG in non-muscle-invasive bladder cancer. Keytruda monotherapy was in January approved in the latter setting in BCG-unresponsive patients.

The key two competitor front-line studies to watch are Keynote-361, which tests a chemo combo, and Checkmate-901, which combines Opdivo with chemo in one cohort and with Yervoy in another. Whatever their chances are, Padcev is now the most important drug to watch.

Selected IO phase III studies in 1st-line bladder cancer		
Study	**Primary endpoint(s)**	**Result**
Urothelial carcinoma		
Danube	OS for Imfinzi monotherapy in ≥25% PD-L1	Failed
	OS for Imfinzi + tremelimumab in all comers	
Keynote-361	PFS & OS for Keytruda monotherapy	Mid-2020
	PFS & OS for Keytruda + chemo	
Checkmate-901	PFS in cisplatin-eligible subjects	Mid-2021
	OS for Opdivo + chemo in ≥1% PD-L1	
	OS for Opdivo + Yervoy in all comers	
Muscle-invasive bladder cancer		
Niagara	PFS for Imfinzi + chemo	2025
	pCR for Imfinzi + chemo	
Keynote-992	PFS for Keytruda + chemo/radiotherapy	2026
Non-muscle invasive bladder cancer		
Potomac	PFS for Imfinzi + BCG	Late 2021
Keynote-676	CR for Keytruda + BCG	Mid-2022
Alban	PFS for Tecentriq + BCG	Mid-2022
Checkmate-7G8	PFS for Opdivo + BCG	Late 2022
Source: clinicaltrials.gov.		