Evaluate Vantage

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Esmo 2021 – Astra finally sees a Wee1 signal

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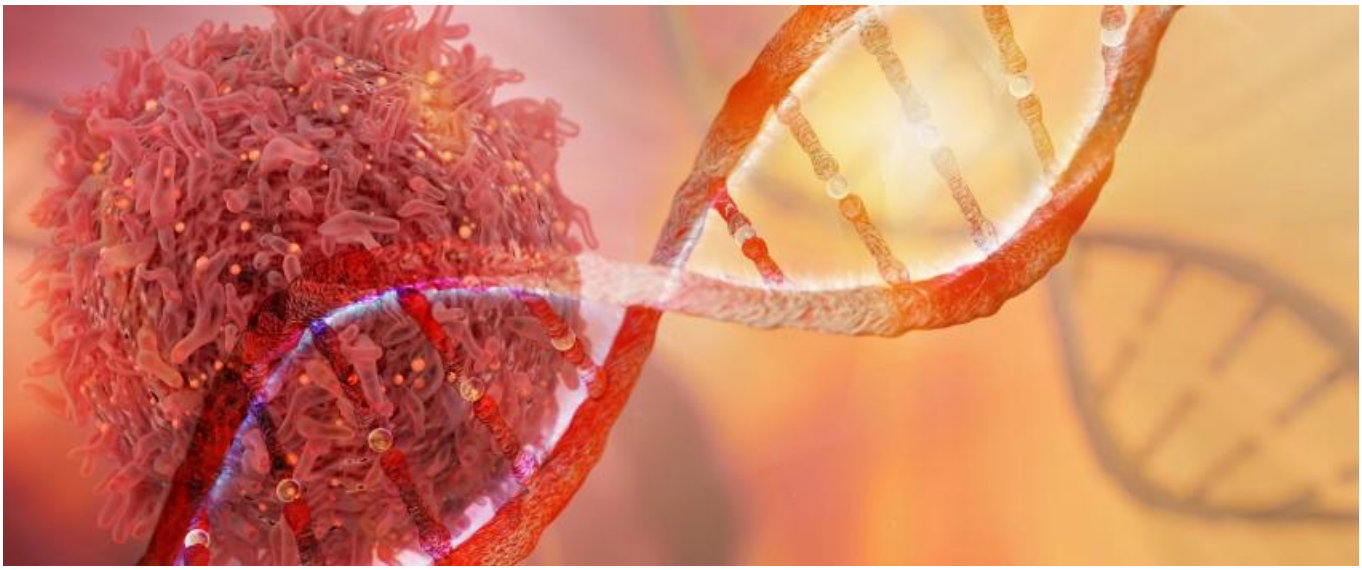

It might be too late for adavosertib, but others could benefit if a niche has finally been found for Wee1 inhibitors.

After 13 years in the clinic, and numerous clinical trials, has Astrazeneca finally found a role for Wee1 inhibition? An abstract at Esmo on the company's adavosertib suggests that this lies in tumours that carry a particular mutation, a finding that supports work being done elsewhere with this mechanism.

Adavosertib's long history and, presumably, limited patent life, means that these data could be more important for others that have put Wee1 inhibitors into the clinic more recently. This is admittedly a short list, with Zentalis having most at stake: the Wee1 inhibitor ZN-c3 is the company's lead project.

A further irony for Astrazeneca is that the study, called Focus4-C and conducted in metastatic colorectal cancer (mCRC), was run by an academic group in the UK. The pharma giant does not appear to be sponsoring any of its own work in this tumour type.

Focus4-C enrolled patients whose tumours carried Ras as well as TP53 mutations. Presence of the former is known to limit the usefulness of anti-EGFR therapies, a mainstay of mCRC treatment, while mutations in TP53 are thought to bestow resistance to chemotherapy.

Wee1 inhibitors are posited to work by interfering with a tumour's DNA repair mechanisms, and boosting the effects of chemotherapy. Wee1 is a regulator of the cell-division cycle.

The Esmo data lend some support to the theories behind this mechanism, although an impressive finding on progression-free survival is blunted somewhat by lack of an overall survival benefit. A prespecified subgroup analysis provides a further interesting finding, with a much clearer signal in left-sided colon tumours, although the small numbers involved here are a major caveat.

Focus4-C trial: newly diagnosed mCRC, Ras/TP53-mutant.			
	Adavosertib (n=44)	**Active monitoring (n=25)**	**Hazard ratio**
mPFS	3.6 mth	1.9 mth	0.35 (p=0.0022)
Left-sided tumours*			0.24
Right-sided tumours*			1.02
mOS	14.0 mth	12.8 mth	0.92 (p=0.93)
Left-sided tumours*	14.1 mth	11.3 mth	0.37
Right-sided tumours*	6.5 mth	15.5 mth	2.15
**Pre-specified subgroup. mCRC=metastatic colorectal cancer. Source: Esmo 2021 and Dr J Seligmann.*			

Numerous studies have shown that right-sided colorectal tumours are associated with aggressive disease and a worse prognosis than those found on the left. This is thought to be down to various factors including the different origins of the tumours as well as the differing physiological functions of the left and right colon; some studies have also noted genetic differences between right and left colon tumours.

Whether this explains why adavosertib appeared to work better in left-sided tumours needs to be explored in bigger studies. Disappointingly Focus4-C could have been much larger: 718 patients were registered, but in the end only 69 were randomised, owing to the outbreak of Covid-19.

Golden opportunity?

Astrazeneca has been working on adavosertib since 2013, when it paid Merck & Co $50m up front for worldwide rights; Merck put the project into the clinic in 2008. An astonishing 29 trials with the project have been listed on clinicaltrials.gov, although a couple were terminated and five were conducted by academic partners.

In the wake of this extensive effort Astra's focus settled on a rare type of endometrial cancer – uterine serous carcinoma – a tumour in which TP53 mutations are frequently found. Notably, this is Zentalis's lead indication as well.

If this mutation lies behind the efficacy seen in Focus4-C this should bode well for these readouts. Neither Astra nor Zentalis is likely to have data before the end of 2022, but the hope is that both ongoing phase 2 trials will be registrational.

Zentalis’s earlier work also includes an ovarian cancer trial testing its Wee1 agent in combination with Glaxosmithkline’s Zejula, a Parp inhibitor that also works by damaging DNA repair pathways.

Others in this space include Debiopharm, although the French firm appears to have cooled on the mechanism. This leaves the private Chinese firm Impact Therapeutics with the only other active clinical-stage Wee1 inhibitor, IMP7068. The group also has its eye on TP53: a large phase 1 basket trial in carriers of this mutation was started earlier this year.

A couple more assets are sitting in preclinical development. It would be understandable if their developers wait for data from larger clinical trials before taking the plunge.

The Wee1 pipeline		
Project	**Company**	**Details**
Adavosertib	Astrazeneca (ex Merck & Co)	2 x ph2 uterine serous carcinoma trials ongoing, plus earlier work in solid tumours (NCT04590248, NCT03668340)
ZN-c3	Zentalis	4 early/mid trials ongoing, incl ph1/2 trial in osteosarcoma started in Sep 2021 and potentially registrational USC trial
IMP7068	Impact Therapeutics	Ph1 basket trial started Feb 2021
Debio0123	Debiopharm (ex Almac)	Small ph1 solid tumour trial started 2019
SDGR2	Schrödinger	Preclinical; company plans to start clinical trials in 2022
NUV-569	Nuvation Bio	Preclinical; IND planned in next couple of years
Source: Evaluate Pharma.		