Evaluate Vantage

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Immunogen fails to leap Forward

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As doubts grow about targeting the folate receptor, Immunogen's decision to press on with mirvetuximab soravtansine looks desperate.

If at first you don't succeed, try a patient subgroup. Immunogen became the latest company to take a leaf out of the standard biotech playbook today, refusing to give up on its lead antibody-drug conjugate, mirvetuximab soravtansine, despite the failure of the pivotal Forward I trial in ovarian cancer.

The company has found a population to home in on: patients with high folate receptor alpha expression. But with mirvetuximab the third folate-targeting agent to fail in recent years, the evidence against this approach is mounting.

Immunogen might be better off cutting its losses to focus on the rest of its pipeline. But its next most promising asset takes aim at another troubled target, CD123, so could also run into problems.

Mono or combo?

Immunogen's choice appears to boil down to carrying out another monotherapy trial in high folate receptor alpha (FRα) expressers only, or switching focus to a combination of mirvetuximab soravtansine with one or more other agents.

As luck would have it, Immunogen already has a combo trial ongoing, called Forward II. That tests mirvetuximab soravtansine in doublets with Keytruda, Avastin or carboplatin, as well as in a triplet alongside Avastin and carboplatin. Initial data with the triple combo should emerge this year.

Forward I, in platinum-resistant ovarian cancer patients who had already received up to three prior therapies, failed to meet its primary endpoint, progression-free survival. Immunogen's stock fell 48% this morning, having already lost 20% on Wednesday.

Immunogen had two bites at the cherry here, as the Forward I study looked at PFS in both the entire patient population and a prespecified subset of patients with high FRα expression.

In the broad trial population Forward I was a resounding failure, with no PFS benefit favouring mirvetuximab soravtansine, hazard ratio of 0.98 and a p value of 0.897.

Results were more promising in the FRα-high subgroup, which returned a hazard ratio of 0.69 and a p value of 0.049. However, this was not significant because of the statistical analysis plan that Immunogen used.

Definite signal?

Despite the result, Immunogen's chief medical officer, Anna Berkenblit, said on the conference call today that there was "definitely" a signal in the FRα-high subgroup.

She added that the proportion of high expressers in the trial had been slightly lower, at 60%, than the 66% Immunogen had anticipated. An obvious question is why, if the company had expected these patients to drive the benefit, it did not focus on this group in the first place.

As it stands, Immunogen now faces the prospect of paying for another phase III trial. The group has around $295m in the bank and could soon start cutting costs to try and make this go further – its chief executive, Mark Enyedy, said on the call that it would carry out an operational review.

As for Immunogen's next most promising project, he highlighted IMGN632, a CD123-targeting asset that yielded promising phase I data at last year's Ash meeting (*Ash 2018 – Immunogen makes its case for a Jazz gig, December 1, 2018*). However, other projects targeting CD123 have run into safety problems, most recently Xencor's bispecific antibody XmAb14045.

Immunogen's pipeline			
Project	**Target**	**Setting**	**Status**
Mirvetuximab soravtansine	Folate receptor α	Ovarian cancer monotherapy	Failed phase III
		Ovarian cancer combo therapy	Phase II
IMGN632*	CD123	Haematologic malignancies	Phase I
IMGN779*	CD33	Acute myeloid leukaemia	Phase I
IMGC936**	ADAM9	Solid tumours	Preclinical
**Optioned to Jazz; **partnered with Macrogenics; Source: EvaluatePharma, company website.*			

As for the folate receptor, this now looks like a dead end as a target. Mirvetuximab soravtansine is the third failure in this field, following in the footsteps of Eisai's monoclonal antibody farletuzumab and Endocyte's small-molecule drug conjugate vintafolide.

There is still plenty of activity here, however, with various companies developing folate-targeting candidates, including the UK's Igem Therapeutics and Carrick Therapeutics and the public US groups Marker Therapeutics and Sutro Biopharma.

Perhaps investors in these players should now be getting nervous. As for Immunogen, its only hope of getting out of the doldrums in the near term could be stellar data with a mirvetuximab soravtansine combo or a full deal with Jazz.

Efforts to target folate receptor α (FRα)			
Project	**Mechanism**	**Company**	**Status**
Farletuzumab	Anti-FRα MAb	Eisai (ex-Morphotek)	Failed in phase III
Vintafolide	Anti-FRα small-molecule conjugate	Endocyte	Failed in phase II
Mirvetuximab soravtansine	Anti-FRα MAb-drug conjugate	Immunogen	Failed in phase III
STRO-002	Anti-FRα MAb-drug conjugate	Sutro Biopharma	Phase I
TPIV200	Anti-FRα cancer vaccine	Marker Therapeutics	Phase I
IGEM-F/MOv18 IgE	Anti-FRα MAb	Igem Therapeutics	Phase I
CT900/BTG945	Anti-FRα thymidylate synthase inhibitor	Carrick Therapeutics (ex-BTG)	Phase I
MOv19-BBz	Anti-FRα CAR-T therapy	Uni of Pennsylvania	Phase I
Source: company documents & clinicaltrials.gov.			