Evaluate Vantage

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Bergenbio dream lives on, despite Genmab's broken Axl

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Genmab cans its antibody-drug conjugate against Axl kinase, an approach on which Bergenbio has gone all in.

Yesterday’s discontinuation of Genmab’s enapotamab vedotin could raise further questions about the utility of targeting Axl kinase as an anticancer mechanism. Doubts had already been raised when the project disappointed in a phase I/II study presented at last year’s World Lung congress.

The most exposed stock to this approach is Bergenbio, which has gone all in on Axl kinase inhibition, chiefly via its lead small molecule, bemcentinib. The Genmab move is unlikely to derail Bergenbio’s efforts, however, especially since enapotamab used a different modality, though Bioatla and ADC Therapeutics are two companies that will not be able to make such a distinction.

Like enapotamab Bioatla’s BA3011 and ADC’s ADCT-601 are antibody-drug conjugates, though each uses a different cytotoxic payload. Bioatla has not said much about BA3011 since starting a phase I/II lung cancer trial in February 2018, though the project was one of the drivers of its $72.5m series D raise this year; the group now plans to float.

ADC, meanwhile, has struggled with ADCT-601. This had been put on hold after the US FDA demanded stability data and raised questions over its novel linker technology and trial protocol, according to the group’s IPO document. The study is now marked terminated, though ADCT-601 still appears in ADC’s pipeline.

Interestingly, ADC had licensed this asset from Bergenbio, which additionally has an anti-Axl naked antibody, tilvestamab, in phase I.

Industry projects hitting Axl kinase			
Project	**Company**	**Mechanism**	**Status**
Bemcentinib	Bergenbio	Axl kinase inhibitor	Phase 2
Dubermatinib (TP-0903)	Sumitomo Dainippon (ex Tolero)	Axl kinase inhibitor	Phase 1/2
AVB-500	Aravive	Anti-Axl kinase fusion protein	Phase 1/2 (ph3 proposed)
BA3011	Bioatla	Anti-Axl tyrosine kinase ADC	Phase 1/2
Enapotamab vedotin	Genmab/Seagen	Anti-Axl tyrosine kinase ADC	Discontinued in phase 1/2
AB-329 / DS-1205	Anheart (ex Daiichi Sankyo)	Axl kinase inhibitor	Phase 1
SLC-391	Signalchem Lifesciences	Axl kinase inhibitor	Phase 1
BPI-9016	Betta Pharmaceuticals	c-Met & Axl kinase inhibitor	Phase 1 completed
ONO-7475	Ono Pharmaceutical	Axl & Mer kinase inhibitor	Phase 1
INCB81776	Incyte	Axl & Mer kinase inhibitor	Phase 1
Tilvestamab (BGB149)	Bergenbio	Anti-Axl tyrosine kinase MAb	Phase 1 completed
ADCT-601	ADC Therapeutics (ex Bergenbio)	Anti-Axl tyrosine kinase ADC	Phase 1 terminated
Q701	Qurient Therapeutics	Axl kinase inhibitor	Preclinical
AXL Inhibitor Research Program	Vichem Chemie	Axl kinase inhibitor	Preclinical
Sym028	Servier (ex Symphogen)	Anti-Axl tyrosine kinase MAb	Preclinical
TAM Inhibitor Program	Celldex Therapeutics	Anti-Tyro3/Axl/Mer kinase MAb	Preclinical
SGI-7079	Sumitomo Dainippon (ex Tolero)	Axl kinase inhibitor	Discontinued in preclinical
Source: EvaluatePharma & company statements.			

Nevertheless, Bergenbio's focus remains mostly on bemcentinib, which it has previously argued is the only truly selective Axl inhibitor. This is in a second-line AML trial as monotherapy, while results from a phase II trial of a Keytruda combo in second-line NSCLC were presented at the SITC meeting this month.

These suggested promise, given that all patients had failed PD-(L)1 blockade, backing the theory that hitting Axl might reverse resistance to immunotherapy. Bergenbio has yet to test the hypothesis in a randomised setting with a robust control arm, however. Bergenbio's claims of selectivity notwithstanding, Genmab had also called enapotamab "Axl-targeted".

At last year's World Lung meeting a first-in-human trial showed a 42% rate of serious adverse events, and just a 19% overall response rate among 26 subjects with various cancers. Yesterday the group said expansion cohorts did not meet the criteria to continue.

Nevertheless, Axl blockade remains of interest. Just last week Aravive revealed the design of a pivotal trial of AVB-500, a fusion protein, in ovarian cancer. Should this get under way AVB-500 would overtake bemcentinib as the industry's most advanced Axl-targeting asset.

And in September Anheart Therapeutics, a private Chinese company, took over from Daiichi Sankyo rights to AB-329, describing this as a "potent, highly selective Axl inhibitor". Earlier Sumitomo Dainippon bought Tolero

for $200m, and along with it two Axl kinase inhibitors, dubermatinib and SGI-7079.

While the former is in trials for AML and solid tumours the latter, like enapotamab, is now on the industry’s scrap heap.