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Bristol failure makes small dent in CXCR4-blocking approach

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Bristol-Myers Squibb's discontinuation of a phase I/II study of ulocuplumab highlights an unusual mechanism of action – CXCR4 inhibition – that has quietly been pursued as part of several companies' oncology strategies.

Biolinerx and Polyphor have similarly acting agents as lead projects, while Lilly is relying on one as potentially its fifth-most lucrative pipeline asset. The approach aims to trigger stem cell mobilisation, and while the Bristol failure raises obvious doubts at least one other group, X4 Pharmaceuticals, is entirely focused on exploring the CXCR4 pathway (see table below).

Still, the discontinued Bristol trial specifically combined ulocuplumab with Opdivo, and included pancreatic cancer, a notoriously hard to treat and immunologically cold cancer. If the mechanistic logic behind it was to make the tumour more immunogenic then the study's halt might only affect this type of combinatorial approach.

After all, it is in liquid cancers that CXCR4 inhibition seems to hold most promise. The idea here is that antagonising CXCR4, a chemokine receptor, blocks its interaction with the ligand SDF-1 and mobilises stem cells from the bone marrow into peripheral blood; if such cells are responsible for a leukaemia, for instance, once in peripheral blood they could become vulnerable to chemotherapy.

Indeed, in AML ulocuplumab generated an impressive 51% complete remission rate in a study presented at the 2014 Ash meeting. The MAb remains in a separate trial in AML in which it is being added on top of cytarabine.

Lack of efficacy

There has been no announcement from Bristol, but the combo study's Clinicaltrials.gov entry states that it was terminated for lack of efficacy.

The most obvious readacross here is to a study Lilly is running combining its own CXCR4 inhibitor, LY2510924, with Astrazeneca's durvalumab. LY2510924 is separately being studied for AML, added on top of idarubicin and cytarabine chemo.

Rather than being a MAb like ulocuplumab, LY2510924 has a smaller, peptide structure, in common with various other CXCR4-targeting agents. The only other MAb in clinical development appears to be Pfizer's PF-06747143, in phase I for AML, either alone or combined with chemotherapy.

Targeting CXCR4 could also be used outside the cancer arena, where cell mobilisation might be used for instance to aid apheresis in stem cell transplantation, or for tissue repair, though these indications are not considered here. One anti-CXCR4 agent, Sanofi's Mozobil, is marketed for the former use.

Sanofi had acquired it along with Genzyme, and subsequently a separate portfolio of small-molecule CXCR4 antagonists was spun out by the former Genzyme team into a new private business, X4 Pharmaceuticals. X4 has one clinical asset, X4P-001, in development for WHIM syndrome, an immunodeficiency disease, and solid tumours.

Selected clinical-stage CXCR4 antagonists in oncology			
Project	**Type**	**Company**	**Trial ID**
Phase II			
Ulocuplumab	MAb	Bristol-Myers Squibb	NCT02305563
BL-8040	Peptide	Biolinerx	NCT02502968
LY2510924	Cyclic peptide	Lilly	NCT02737072
USL311	Small molecule	Upsher-Smith	NCT02765165
Phase I			
PF-06747143	MAb	Pfizer	NCT02954653
POL6326	Peptide	Polyphor	NCT01837095
GMI-1359*	Small molecule	Glycomimetics	NCT02931214
X4P-001	Small molecule	X4 Pharmaceuticals	NCT02823405
Abandoned in clinical trials			
CTCE-9908	Peptide	British Canadian Biosciences	–
ALX-0651	Single-domain Ab	Ablynx	NCT01374503
MSX-122	Small molecule	Altiris Therapeutics	NCT00591682
*Note: *CXCR4 & E-selectin antagonist.*			

The small-molecule approach seems to have a simpler basis, being founded merely on the view that CXCR4 is overexpressed in some cancers, and that its activation plays a role in tumour metastasis. Another oral small molecule, Upsher-Smith's USL311, originated by the UK firm Proximagen, entered phase I in solid tumours last year, with a possible focus on glioblastoma.

Meanwhile, Biolinerx and Polyphor's lead assets, BL-8040 and POL6326 respectively, are both peptide-based CXCR4 antagonists. The former's lead indication is AML, while the latter has three potential applications, its originator says: breast cancer in combination with chemo, stem cell transplantation and tissue repair in acute myocardial infarction.

Interestingly, BL-8040 is also being studied as part of an immuno-oncology combination – the Keynote-202 trial tests it together with Keytruda against pancreatic cancer.

As in the case of Lilly, the signs from Bristol's study for Keynote-202 are not good. However, Biolinerx and others can at least look forward to various further applications of the CXCR4 approach.

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