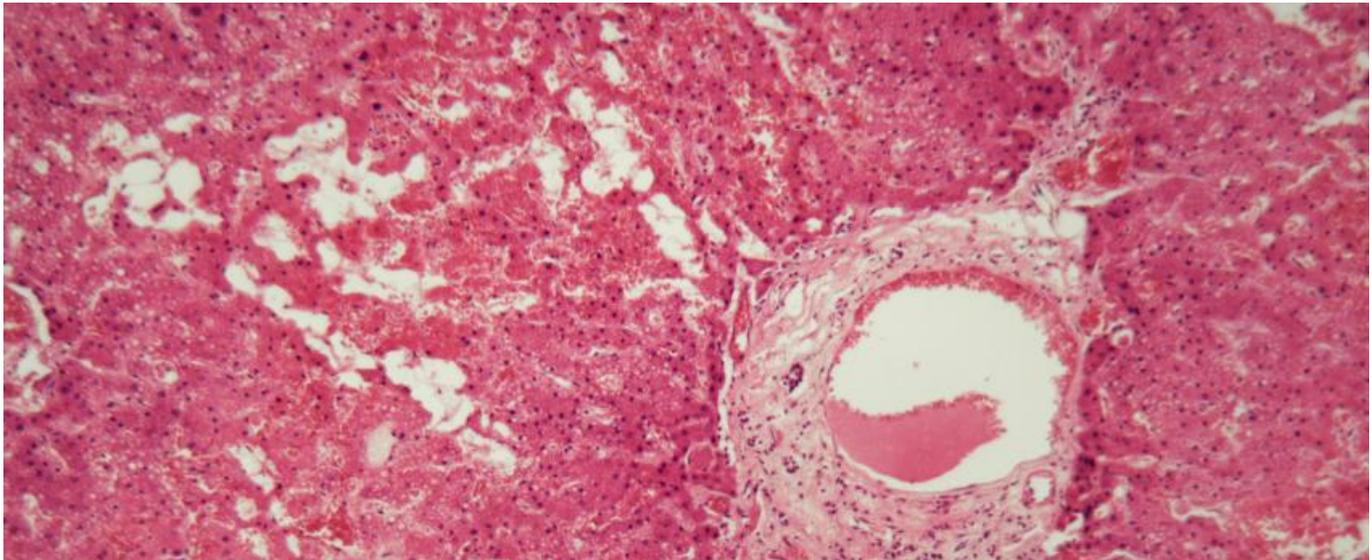


Non-genetic amyloidosis lives again, thanks to Darzalex and Astra



Jacob Plieth



Interest in AL amyloidosis has been piqued by January's approval of Darzalex, and today AstraZeneca bought out a company with a phase 3 asset.

AstraZeneca's exercise of a legacy takeover option over Caelum Biosciences will remind investors that interest in AL amyloidosis has quietly been growing. Caelum's CAEL-101 had two years ago been mired in an obscure investigator-sponsored trial, but is today the subject of two registrational studies in the disease.

Interest might have been piqued by this year's approval of Johnson & Johnson/Genmab's blockbuster Darzalex. Despite the obvious scientific rationale behind using multiple myeloma drugs like Darzalex in AL amyloidosis, though, clinical successes have been scarce, and the pipeline of industry-sponsored trials remains fairly modest.

Symptoms vs cause

Apart from CAEL-101 the only other phase 3 asset appears to be Prothena's birtamimab, an antibody that aims not to target the disease's underlying cause - malfunctioning plasma cells - but instead to clear the resulting damaging amyloid deposits.

This in itself is remarkable: birtamimab had in 2018 failed the phase 2 Pronto trial in AL amyloidosis, prompting discontinuation of its phase 3 study, Vital. However, [this year Prothena claimed to have seen a survival benefit in Vital patients at high risk of early mortality](#), and started a new pivotal trial, Affirm-AL, in this population.

Meanwhile, [Darzalex's January approval](#) was based on haematologic complete response rates in the Andromeda study. As Darzalex targets plasma cells - the antibody-producing cells that cause multiple myeloma - it can be said to hit the underlying cause of AL amyloidosis. The disease is also called light-chain amyloidosis, and is quite distinct from familial amyloidosis.

Other multiple myeloma drugs have fared less well in AL amyloidosis. Kyprolis completed phase 1 years ago with no further work by Amgen, while [Takeda's Ninlaro failed the Tourmaline-AL1 study in 2019](#). Numerous studies with Revlimid, Pomalyst and others continue in academic hands, but pharma's involvement with multiple myeloma drugs in AL amyloidosis is limited to [Oncopeptides' Pepaxto](#), Sanofi's Sarclisa and Karyopharm's Xpovio.

The AL (light-chain) amyloidosis pipeline

Project	Mechanism	Sponsor	Status	Trial
Darzalex	Anti-CD38 MAb	Johnson & Johnson	Approved	Andromeda
CAEL-101	Fibril-reactive MAb	Astrazeneca (ex Caelum (Fortress Bio))	Phase 3	NCT04512235 (stage IIIa disease)
				NCT04504825 (stage IIIb disease)
Birtamimab	Anti-beta-amyloid MAb	Prothena	Phase 3	Affirm-AL
				Vital (terminated after ph2 failure)
APG-2575	Bcl-2 inhibitor	Ascentage Pharma	Phase 1/2	NCT04942067
STI-6129	Anti-CD38 MAb	Sorrento	Phase 1	NCT04316442
Pepaxto	Anti-aminopeptidase chemo	Oncopeptides	Ph1/2 on hold after survival imbalance in separate trial	Ascent
Sarclisa	Anti-CD38 MAb	Sanofi	Ph2 not yet recruiting	NCT04943302
Xpovio	XPO1 inhibitor	Karyopharm	Ph1 not yet recruiting	NCT04984330
Kyprolis	Proteasome inhibitor	Amgen	Ph1 completed	NCT01789242
Ninlaro	Proteasome inhibitor	Takeda	Failed ph3	Tourmaline-AL1
GSK2315698 + GSK2398852	SAP depleter + anti-SAP MAb	Glaxosmithkline	Ph2 terminated	NCT03044353
Zydelig	PI3k delta inhibitor	Gilead	Ph2 terminated	NCT02590588
Venclexta	Bcl-2 inhibitor	Tufts Medical Center	Ph1 terminated	NCT03000660

Source: [clinicaltrials.gov](#) & company announcements.

For its part CAEL-101 also targets AL amyloidosis symptoms rather than its cause, being a fibril-reactive MAb that binds to misfolded kappa and lambda light chain proteins and amyloid.

In June Caelum, a Fortress Bio subsidiary, reported data at the European Hematology Association Congress that it said supported CAEL-101's phase 3 studies. Phase 2 had yielded 1,000mg/m² as the phase 3 dose of the MAb, and combination with cyclophosphamide, Velcade, dexamethasone and Darzalex was said to raise no new toxicity signals or alter pharmacokinetics.

Today's takeover of Caelum by Astra dates back to early 2019, when Alexion, now owned by the UK company, paid \$30m in stock for a 19.9% stake with an option to buy the remainder on the basis of phase 2 data. This has now been exercised, with Astra paying \$150m to Caelum, some \$64m of which will accrue to Fortress.

Other industry work in AL amyloidosis includes Sorrento's STI-6129, like Darzalex and Sarclisa an anti-CD39 MAb, and Ascentage's Bcl-2 inhibitor APG-2575. An academic trial of Abbvie/Roche's marketed Bcl-2 inhibitor, Venclexta, was terminated after being put on FDA hold.

After Darzalex CAEL-101 looks like the most-advanced industry project: its two phase 3 studies are slated to complete next August.

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