

Springworks seeks cancer win as a prelude to something bigger



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The young biotech is well placed to deliver its first pivotal win, but investor focus might lie elsewhere.

It was just four years ago that Springworks was founded to take on several assets discarded by Pfizer, and already the group faces a pivotal readout that could give it its first approved drug: the gamma secretase inhibitor nirogacestat is to yield data from a phase 3 desmoid tumours trial by the end of this year.

Investors appear to have rewarded Springworks for its strategy and for sticking to promises made at its 2019 IPO. But desmoid tumours represent a relatively small, albeit untapped, market, and nirogacestat's intellectual property position should give pause, too; indeed, the big prize might lie elsewhere.

As far as IP goes US composition patents expire in four years. Springworks cites use patents to 2039 but, barring patent extensions, should nirogacestat be approved it will surely be launched on the strength of seven years' data exclusivity. This is of course not unexpected, given that the asset had sat on the shelf at Pfizer [before Springworks picked it up](#).

Gamma secretase is a membrane-bound protein whose functions have only recently been elucidated, though its most prominent involvement, in the pathogenesis of [Alzheimer's disease, was written off as a development prospect some years ago](#).

Supporting data

Springworks' focus is oncology, and nirogacestat has shown signs of activity in desmoid tumours. In a phase 1 study run by Pfizer the project, then known as PF-03084014, yielded objective responses in five of seven patients, with median treatment duration of 49.5 months.

A subsequent phase 2 study, run by the NCI in a heavily pretreated population, showed a 29% ORR. When Springworks floated it had already begun DeFi, a registrational phase 3 study that it said would yield topline data in mid to late 2021, and it has stuck to this timeframe. The company is now worth nearly \$3bn, and is trading 220% above its listing price.

DeFi enrolled 142 subjects with desmoid tumours that are either treatment-naive or have failed one or more therapies, and is comparing nirogacestat against placebo in a blinded fashion. The primary metric is progression-free survival.

Overall survival does not even feature among the top secondary endpoints, presumably because desmoid tumours are so slow growing that it would take too long to reach an OS readout. The rare soft tissue cancer is also known as aggressive fibromatosis, and has an estimated US incidence of 1,000-1,500 patients, Springworks says.

Scientifically, binding gamma secretase is thought to block the activation of Notch receptors, whose signalling plays a role in cancer development. If nirogacestat scores in DeFi Bristol Myers Squibb will pay attention; the company's own gamma secretase inhibitor, crenigacestat, is in phase 1 cancer trials.

The real prize?

However, desmoid tumours are not the real prize. A separate function of gamma secretase is to cleave BCMA, a protein on plasma cells that serves as a target for multiple myeloma drugs like Blenrep and Car-T therapies. Blocking gamma secretase can reduce BCMA cleavage, the thinking goes, and preserve this therapeutic target.

Accordingly, Springworks has clinical trial tie-ups with Glaxosmithkline (which is also an investor), Seagen, J&J, Pfizer, Allogene and Precision Biosciences to study nirogacestat in combination with these groups' BCMA-directed therapies.

Likewise, Bristol's involvement with crenigacestat is derived from a [deal the legacy cell therapy company Juno signed with Lilly](#), and one of the project's studies is Karmma-7, where it is being combined with the Car-T therapy Abecma.

Perhaps the most important function of DeFi is to put nirogacestat on the market. One of the BCMA players can then make the next move.

Selected gamma secretase inhibitors in oncology

Project	Company	Study	Detail
Nirogacestat (PF-03084014)	Springworks (ex Pfizer)	DeFi (ph3)	Desmoid tumours, vs placebo; data H2 2021
		Dereamm-5 (ph1)	Multiple myeloma combo with Glaxo's Blenrep
		NCT04722146 (ph1)	Multiple myeloma combo with J&J's teclistamab
		Universal (ph1)	Multiple myeloma combo with Allogene's ALLO-715
		NCT04171843 (ph1)	Multiple myeloma combo with Precision's PBCAR269A
Crenigacestat (BMS-986405/ LY3039478)	Bristol Myers Squibb (ex Juno/Lilly)	NCT02836600 (ph1)	Japan solid tumours trial
		Karmma-7 (ph1)	Abecma (anti-BCMA Car-T) combinations

Source: [clinicaltrials.gov](#).

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