

Therapeutic focus - Roche and AstraZeneca take interferon approach to lupus



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Roche's decision to advance rontalizumab into phase III studies highlights a little-exploited approach to treating at least one subset of patients with systemic lupus erythematosus.

Rontalizumab, like AstraZeneca's sifalimumab, targets interferon alpha, and while this strategy counts just a handful of lupus projects the involvement of big pharma could give it credibility (see table). The disease has generated interest of late thanks to GlaxoSmithKline's Benlysta, which became the first lupus drug to reach the market for over 50 years; however, its sales have so far disappointed, necessitating numerous mechanistic approaches to treat this complex autoimmune disease.

Although the way the immune system becomes dysregulated in lupus is still relatively poorly understood, it is known to involve numerous components. Several genes in the interferon pathway are associated with risk of developing the disease, and increased levels of the cytokine are often found in people with lupus, suggesting a way to target it.

EvaluatePharma identifies only five interferon alpha-based lupus projects, although this is perhaps not too bad for a disease that has suffered more than its share of development failures ([Therapeutic focus - Late stage lupus pipeline sparse but potentially valuable, July 5, 2012](#)).

Interferon alpha-targeting projects for treating lupus

Product	Company	Status	Notes	Trial ID
sifalimumab	AstraZeneca	phase II	544-patient trial due to end in 2014	NCT01283139
rontalizumab	Roche	phase II	Phase III "go" decision has been made	NCT00962832
IFNalpha kinoid	Neovacs	phase I/II	28-patient safety trial	NCT01058343
AGS-009	Argos Therapeutics	phase I	13-patient safety trial	NCT00960362
RSLV-125	Resolve Therapeutics	preclinical	-	-

Mixed data

Roche said at its recent R&D day that it had made a "go" decision to take rontalizumab into phase III, a move that would make the project the first anti-interferon alpha to enter pivotal lupus studies. But data so far have been mixed.

A recently completed phase II study in 238 lupus patients missed its primary endpoint, showing no difference in response rates between active and placebo groups, but did hit statistical significance in a pre-specified secondary analysis - response rate in ISM-low subjects. Full results from this trial are to be presented at the American College of Rheumatology meeting next month.

ISM is the interferon signature metric, which measures the expression of certain genes. It is not yet known whether phase III will focus on this biomarker-defined ISM-low subgroup, or how many patients will be recruited, but Roche says it will make a formal announcement regarding phase III in due course.

A much bigger phase II trial - in 544 patients - is underway with AstraZeneca's sifalimumab. This will measure the proportion of subjects achieving a response after a year's treatment, but will not read out until mid-2014.

AstraZeneca acquired sifalimumab, previously known as MEDI-545, through its \$15.6bn takeover of Medimmune, and *EvaluatePharma's* clinical trials module says a total of 1,083 patients have been enrolled into completed and ongoing studies.

While the Roche and AstraZeneca projects are both anti-interferon antibodies, a slightly different approach is being pursued by Neovacs, a tiny French biotech firm focusing on what it terms a “kinoid”. This consists of an inactivated form of interferon alpha combined with a carrier immunogenic protein, and is thought to confer some advantages over monoclonal antibodies.

A phase I/II trial demonstrated good tolerability and the production of antibodies to interferon alpha, and a phase IIb study is planned, although a partner is likely to be needed. Neovacs’s share price has risen 30% since a note from Edison Investment Research on October 8 highlighted Roche’s phase III “go” decision on rontalizumab.

Earlier-stage projects include Argos Therapeutics’ AGS-009 – this completed a phase I safety study last December, with data yet to be published – while Resolve Therapeutics has done preclinical work on what it calls a new approach to inhibiting the interferon pathway. Another interferon alpha monoclonal had been in development by Theraclone Sciences, but was discontinued in preclinical studies.

Consensus sales data are not available for any of these projects and they do not appear in most analysts’ financial models – understandable given the uncertain phase II results with rontalizumab.

Still, Roche’s confidence must count for something, and future positive data could breathe new life into the interferon alpha-targeting approach.

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