Evaluate Vantage

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Therapy focus – Fibrogen and Galapagos raise lung disease hopes

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Important new data on novel idiopathic pulmonary fibrosis candidates look set to continue to emerge in the wake of two encouraging reports in the past couple of weeks. Biogen, Promedior, Sanofi and Roche are all due to unveil fresh information from mid-stage candidates before the end of the year.

These projects will follow updates from Fibrogen and Galapagos, both of which raised hopes for new mechanisms in this field. To date no drug has managed to completely arrest the inevitable decline in lung function that is the hallmark of this devastating disease, so the bar to success remains very high, but with several shots on goal looming there is some cause for optimism (see table below).

However, any optimism must be tempered with caution, as both the Fibrogen and Galapagos data came from relatively small trials (*Pamrevlumab comes off the bench to deliver for Fibrogen, August 8, 2017*). And neither can Biogen's silence on BG00011 be an encouraging sign.

Biogen had bought Stromedix for this anti-avb6 integrin antibody, and, while a phase II study ended in March, according to Clinicaltrials.gov, it has yet to reveal an update; Stromedix fetched $75m up front in 2012, and its private backers will hope to see a bit more of the $488m in milestones heading their way.

Biogen did not respond to an emailed request for an update. Glaxosmithkline has an asset in phase I targeting the same pharmacology, but the industry's idiopathic pulmonary fibrosis (IPF) pipeline is in fact characterised by a remarkable breadth of mechanistic approaches.

Cytokines

Two agents targeting the IL-13 and IL-4 cytokines should yield data towards the end of the year. Sanofi is testing its bispecific antibody in the large Estair study, while Roche has lebrikuzumab in a very expansive phase II trial, which includes Esbriet combination arms.

Presumably Roche's Esbriet and Boehringer Ingelheim's Ofev are considered standard of care now, at least where payers are able to support them, so surely novel molecules will have to be tested in combination with them. However, it is notable that few companies are attempting to do this, possibly because the standards are still not considered disease modifying.

Still, with current treatments costing close to $100,000 a year, anything proposed as a combination therapy could come under pressure. Roche's dominance here will allow it more flexibility, and should lebrikizumab succeed the Swiss group will be the force to be reckoned with here.

But caution is again warranted: tralokinumab and QAX576, IL-13 antibodies from Astrazeneca and Novartis respectively, have been abandoned in IPF.

Meanwhile, Bristol has dibs on Promedior's PRM-151, a recombinant form of human pentraxin-2, in the form of a buyout option for the whole company for $150m initially and up to $1.25bn in future earnouts. Phase II trials completed enrolment at the end of last year, so results in both IPF and myelofibrosis should be in house, though no news has emerged.

Ones to watch in the IPF space					
Project	**Mechanism**	**Company**	**Data due***	**Enrolment**	**Trial ID**
Phase II completed					
GLPG1690	Autotaxin inhibitor	Galapagos	Reported	23	NCT02738801
Pamrevlumab	Anti-CTGF MAb	Fibrogen	Reported	160	NCT01890265
TD139	Galectin-3 inhibitor	Galecto Biotech	Reported	60	NCT02257177
PBI-4050	Anti-inflammatory & anti-fibrotic	Prometic Life Sciences	Reported	41	NCT02538536
BG00011	Anti-alpha 5 beta 6 integrin MAb	Biogen (via Stromedix buyout)	?	43	NCT01371305
Phase II ongoing					
PRM-151 (pentraxin-2)	MREG differentiation inducer	Promedior (Bristol-Myers option)	Mar 2017	117	NCT02550873
SAR156597	Anti-IL-4 & IL-13 bispecific MAb	Sanofi	Aug 2017	300	NCT02345070 (Estair)
Lebrikizumab	Anti-IL-13 MAb	Roche	Nov 2017	507	NCT01872689
KD025	ROCK 2 inhibitor	Kadmon	Q4 2017*	36	NCT02688647
GBT440	HbS polymerisation inhibitor	Global Blood Therapeutics	Q4 2017*	30; 16	NCT02846324; NCT02989168 (Zephyr)
MN-001	Leukotriene, PDE 3 & 4 & 5-LO inhibitor	Medicinova	Dec 2017	15	NCT02503657
CC-90001	JNK 1 inhibitor	Celgene	May 2020	135	NCT03142191^
Phase I					
GSK3008348	Alpha 5 beta 6 integrin inhibitor	Glaxosmithkline	Jan 2019	17	NCT03069989
Moving into the clinic?					
Autotaxin inhibitor program	Autotaxin inhibitor	Pharmakea (Celgene option)	First clinical trials targeted to start in 2017**		
*Notes: *according to clinicaltrials.gov; **based on company guidance; ^not yet recruiting, according to clinicaltrials.gov.*					

This is not Bristol's only involvement in IPF – and fibrotic disease more widely – though its efforts so far have come to naught. An asset licensed from Amira, an LPA 1 receptor antagonist, failed to progress beyond early trials, while an option to buy Galecto on the basis of phase Ib results from its galectin-3 inhibitor TD139 has presumably lapsed.

Small comfort for Bristol could come from royalties on Fibrogen's pamrevlumab, which a very long time ago was created with antibody technology from Medarex, which is now owned by Bristol.

Notably, the Amira asset targeted the same pathway as the autotaxin approach that Galapagos highlighted last week with GLPG1690 with data in only 23 patients. Inhibition of ATX leads to a reduction in lysophosphatidic acid production, which blocks signalling cascades that ultimately drive the development of fibrosis.

Not the big story?

Also gearing up to release results, in the fourth quarter from three trials, is Global Blood Therapeutics; hopes are high for GBT440's ability to enhance oxygen saturation, which would prompt a decision to move into phase IIb. IPF is not considered a big part of the GBT story, much like Galapagos, so strong results could generate an equally positive share price reaction.

Meanwhile, Prometic is pushing into phase II/III on the back of data from an open-label, 40-patient phase II trial of PBI-4050 earlier this year – patients treated with the asset appeared to demonstrate a stabilisation of disease progression. Two placebo-controlled phase II/III trials, testing the agent as a monotherapy and in combination with Ofev, have been approved by the FDA.

And Celgene has a collaboration with Pharmakea that at the end of 2016 was looking to put an autotaxin inhibitor into the clinic this year. Later in 2017 Celgene also plans to start a phase IIa trial with CC-90001, an internally originated compound.

Celgene might be behind the leaders, but it neither it nor any of the other big hitters like Roche and Bristol should be underestimated.

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