Evaluate Vantage

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Kevzara's Covid-19 setback shows need for hard evidence

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As investors continue to jump on small sparks of hope in the pandemic pipeline Sanofi and Regeneron inject a dose of reality.

A rigorous study of Sanofi and Regeron's repurposed rheumatoid arthritis drug Kevzara has found the anti-IL-6 antibody to be of little use outside the most critically ill Covid-19 patients, dashing hopes for a big impact with this mechanism. The finding reminds investors of the dangers of jumping on encouraging results from small trials of experimental interventions.

Such enthusiasm continues to boost share prices, Mesoblast being a notable beneficiary: in the last few days the company's Australia-listed shares have doubled on data in 12 coronavirus subjects treated with its allogeneic cell therapy.

Evaluate Vantage has been tracking notable Covid-19 announcements, and it is clear that the pandemic news flow is showing no sign of slowing. But as more and more clinical data emerges on biopharma's myriad attempts to identify potential treatments, the risks of drug development must not be forgotten.

The Kevzara result shows why. A small study prompted the Chinese to add Roche's Actemra treatment guidelines for Covid-19, and the initiation of bigger trials of IL-6 antibodies. One theory driving the work is that coronavirus infection prompts a surge in cytokines that IL-6 blockers can damp down (*Making sense of Covid-19 treatment approaches, March 25, 2020*).

It now seems that utility lies only in critically ill patients, meaning those requiring mechanical ventilation or high-flow oxygenation. Sanofi and Regneron said today that an ongoing phase II/III trial would continue with these subjects only, after an interim analysis found little benefit in less-severe patients. A readout expected in June, from the 600-plus phase III critical patient cohort, should give a clearer picture of any role here.

Last week's announcement from Mesoblast, on the other hand, shows little clarity on remestemcel-L's utility. The data were gathered from the allogeneic cell therapy's compassionate-use programme in the US, and while on the surface it seems encouraging that nine of 12 of patients treated came off ventilators, it is impossible to say whether remestemcel-L had anything to do with this.

The lack of any control group is only one issue. Patients were also receiving several other interventions, while Mesoblast's description of moderate to severe ARDS is puzzling, given that ventilation tends to be reserved for critical patients – of which no mention is made. A randomised phase II/III is due to start, though the company's

long history of disappointing will make many investors wary.

A selection of recent Covid-19 announcements	
Sanofi and Regeneron	Kevzara study discontined in less severe patients
Santhera	To investigate lonodelestat (hNE inhibitor) for ARDS
Redhill Pharma	Compassionate use data on opaganib
Scancell	To develop DNA vaccine
Mesoblast	Case reports on remestemcel-L treated patients
Astrazeneca	Starting ph3 Dare-19 trial of Farxiga in subjects at risk of serious complications
Johnson & Johnson	Collaboration with Emergent Biosolutions to expand vaccine manufacturing
Caldarius	To study CLBS119 (CD34+ cell therapy) for repair of lung damage, then raises $5m
Insmed	To study brensocatib (DPP1 inhibitor) in hospitalised UK patients
Lilly	LY3127804 (anti-ANG2 MAb) ph2 recently started
Biontech/Pfizer	German permission to start trial of BNT162 (4 different vaccine formats)
Pharming	Case reports from 5 subjects given Ruconest (C1 inhibitor)
Vaxart	Claims preclinical success with vaccine
Immunic	Claims preclinical success with IMU-838 (DHODH Inhibitor)
Atyr	Starts phase 2 trial of (NRP2 modulator)
Bayer	To investigate various combos, incl chloroquine and interferon beta-1b
Novartis	To start phase 3 hydroxychloroquine trial in 440 hospitalised subjects
4D Pharma	To start phase 2 trial of MRx-4DP0004 ("live biotherapeutic product"?) for cytokine storm
Redhill	To evaluate Mesupron/RHB-107 with NIAID
Alexion	To start phase 3 Ultomiris study in hospitalised patients
Progenabiome	Starts 600-subject single-arm study of 5-drug cocktail
Cyclacel	To study CDK inhibitors with Uni of Edinburgh
Biosig	To begin testing merimepodib (IMPDH inhibitor acquired from Trek Therapeutics)
Dynavax	Vaccine collaboration with Sinovac
Source: Company statements.	

Much of the data to emerge from the Covid-19 pipeline so far are from compassionate-use programmes, and Mesoblast is certainly not alone in benefiting from press releasing such early findings.

The Israeli microcap Redhill Biopharma was trading 11% higher this morning after saying that its sphingosine kinase-2 inhibitor opaganib produced measurable improvements in six subjects treated. And Pharming received a boost last week after reporting improvements in five patients given Ruconest, after these had failed to respond to standard of care.

With few rigorously gathered results available right now, investors chasing the pandemic play have little else to go on. But it is worth remembering that, even with the best intentions and an IND in hand, small companies will simply not have the cash or the capacity to run a large, confirmatory trial. Certainly not in a short time frame.

Bigger developers are not so restrained: Astrazeneca, for example, announced last week the start of a 900-patient study of Farxiga, to see if the diabetes medicine can reduce the risk of complications and death in high-

risk Covid-19 patients.

Smaller biotechs really need industry or academic partners to help fund and run the bigger studies necessary. Pharming, for example, has University Hospital Basel on board to run a 150-patient study of Ruconest in Covid-19, while Mesoblast is partnering with an arm of the NIH in the US.

But neither study seems to have started. And the travails with Gilead's remdesivir's show that, even for the most researched and probably best-funded project, nothing is certain until rigorous data emerge.