Evaluate Vantage

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“Don’t eat me” competition finds Celgene discontinuation hard to digest

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Celgene’s surprise termination of a clinical trial makes for a day of soul-searching among other followers of the anti-CD47 approach.

The quiet progress made since spring on the CD47 pathway’s role in oncology hit a roadblock yesterday when it emerged that Celgene, one of the most advanced players, had terminated a phase I study of its asset, CC-90002.

The move did not even warrant a statement from Celgene, and became apparent only from a change of the company’s listing on the Clincaltrials.gov database, suggesting that not too much should be read into it. Nevertheless, the market swiftly assumed the worst: the anti-CD47 players Trillium, Forty Seven and Surface Oncology fell 9%, 8% and 4% respectively.

Apart from Celgene these three are the only listed biotechs with clinical projects targeting the CD47 pathway. As Forty Seven’s name suggests, the approach represents this group’s core focus, and the company completed a $113m flotation in June; its stock today stands 21% below the IPO price.

Don’t eat me

Academic work on CD47 has been ongoing for some time. This cytokine is a ligand for SIRPα, a protein expressed on several cells of the myeloid lineage, and this interaction inhibits destruction of the cell concerned, giving rise to this being called the “don’t eat me” mechanism.

Some cancers are thought to hijack this pathway by upregulating CD47. Pharmacologically, either CD47 or SIRPα can be inhibited to achieve a similar result, and industry approaches involve antibodies, fusion proteins and bispecifics.

CC-90002 is an anti-CD47 MAb that Celgene had licensed from the private company Inhibrx back in 2012, and subsequently put into two phase I trials. It is one of these, a study in AML and myelodysplastic syndromes, that has just had its Clinicaltrials.gov status changed to “terminated”.

The reasons stated are that preliminary monotherapy data “did not offer a sufficiently encouraging profile for further dose escalation/expansion”. A second CC-900002 trial, in combination with Rituxan in unspecified solid and haematological cancers, is continuing enrolment, with a June 2019 completion date.

Industry assets targeting the SIRPα/CD47 pathway			
Project	**Company**	**Mechanism of action**	**Note**
Phase I			
Hu5F9-G4	Forty Seven	Anti-CD47 MAb	Phase I/II Erbitux & Rituxan combo trials (NCT02953782 & NCT02953509)
CC-90002/INBRX-103	Celgene/Inhibrx	Anti-CD47 MAb	2012 deal; phase I in AML (NCT02641002) terminated in Oct 2018
TTI-621	Trillium Therapeutics	Anti-SIRPα fusion protein	Soluble decoy receptor; Rituxan and PD-(L)1 combos (NCT02663518 & NCT02890368)
ALX148	ALX Oncology	Anti-CD47 fusion protein	Keytruda, Herceptin or Rituxan combo (NCT03013218); company earlier known as Alexo
SRF231	Surface Oncology	Anti-CD47 MAb	First patient dosed (NCT03512340) in Mar 2018
TTI-622	Trillium Therapeutics	Anti-SIRPα fusion protein	Uses IgG4 Fc instead of IgG1 Fc; phase I (NCT03530683) began in May 2018
Preclinical			
TG-1801/NI-1701	Novimmune/TG Therapeutics	Anti-CD47/CD19 bispecific MAb	Effector arm (anti-CD47) and targeting arm (anti-CD19); deal signed in Jun 2018
NI-1801	Novimmune	Anti-CD47/mesothelin bispecific MAb	Effector arm (anti-CD47) and targeting arm (anti-mesothelin)
OSE-172	Boehringer Ingelheim/OSE	Anti-SIRPα MAb	Apr 4, 2018 deal worth €15m up front
IBI188	Innovent Biologics	Anti-CD47 Mab (fully human)	Permission to start US phase I trial given on Sep 30, 2018
Anti-CD47 MAb	Biocad	Anti-CD47 MAb	Russian company focused on biosimilars
AO-176	Arch Oncology	Anti-CD47 Mab (humanised)	Company previously known as Tioma (and earlier Vasculox)
CD47-SIRPα modulators	Synthon	Anti-CD47 or SIRPα MAbs	Patents licensed from Sanquin Blood Supply Foundation in Mar 2017
DSP107	Kahr Medical	Anti-CD47/4-1BB-activating bispecific MAb	Plans to be IND-ready by the end of 2019
Source: EvaluatePharma, Clinicaltrials.gov, company filings.			

Before the Celgene study's termination interest in CD47 had been growing steadily. In April, for instance, Boehringer Ingelheim became the second large company to buy into this approach, through a deal with France's OSE Immunotherapeutics (*Boehringer breathes new life into "don't eat me" approach, April 5, 2018*).

One month later Trillium put its second SIRPα-targeting fusion protein, TTI-622, into the clinic, and in June TG Therapeutics licensed Novimmune's preclinical anti-CD47/CD19 bispecific MAb NI-1701, now coded TG-1801, for an unspecified up-front payment. Last month the Chinese group Innovent Biologics got US FDA permission to begin human trials of its own anti-CD47 MAb, IBI188.

This positive sentiment has been seen in spite of doubts about the strength of the intellectual property around MAbs targeting CD47, as evidenced by a legal action between Forty Seven and Synthon. If the contagion spreads more broadly from Celgene's move, however, weak IP could be the least of the sector's worries.