Evaluate Vantage

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Opinions split on Ox40

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Just a couple of years ago Ox40 was billed as one of the most promising targets in a new wave of immuno-oncology projects. But subsequent clinical data have been anything but overwhelming, and last week more evidence emerged that opinion has split on the utility of this target.

In a week that saw major pipeline culls from Lilly, Glaxosmithkline and Roche, the last of these revealed that it was scrapping its Ox40 project RG7888; it thus joins Astrazeneca, which recently ditched two such assets. The industry's oncology pipeline now stands at just five active Ox40-targeting assets.

However, Roche's move contrasted with an announcement by Glaxo just one day earlier. On July 26 the UK group picked out its own Ox40 agonist MAb GSK3174998 as one of five oncology projects whose development it was prioritising (*Glaxo gets out the axe, July 26, 2017*).

It must be stressed that Astra, too, is not giving up on Ox40, a target its chief medical officer, Sean Bohen, mentioned in Thursday's pipeline update.

As such, Astra's Ox40 cull has to be seen as the focusing of a pipeline that had at one stage included no fewer than three Ox40-targeting assets: the murine MAb MEDI6469, humanised MEDI0562, and MEDI6383, a fusion protein. All three remain in the clinic, according to Clinicaltrials.gov, but Astra now lists only the humanised MAb in its pipeline.

Oncology projects targeting Ox40			
Project	**Company**	**Trial ID**	**Comment**
Clinical-stage assets			
BMS-986178	Bristol-Myers Squibb	NCT02737475	Monotherapy or Opdivo or Yervoy combo in metastatic cancers
PF-04518600	Pfizer	NCT02554812	One of several agents combined with Imfinzi
INCAGN1949	Incyte /Agenus	NCT02923349	Dose-escalation trial
GSK3174998	Glaxosmithkline	NCT02528357	Keytruda combo
MEDI0562	Astrazeneca	NCT02705482	Humanised MAb; Imfinzi + tremelimumab combo
RG7888	Roche	NCT03029832, NCT02410512	Monotherapy and Tecentriq combo in solid tumours; discontinued by Roche 27 Jul 2017
MEDI6469	Astrazeneca	NCT01862900, NCT01303705	Murine MAb; breast and prostate cancers; no longer appears in Astra's pipeline
Efizonerimod (MEDI6383)	Astrazeneca	NCT02221960	Fusion protein; no longer appears in Astra's pipeline
Selected preclinical assets			
ATOR-1015	Alligator Bioscience	–	CTLA4 + Ox40 bispecific; clinical trial expected mid-2019
mRNA-2416	Moderna Therapeutics	–	mRNA coding for Ox40L
OX40 agonist	Apogenix	–	–
JNJ-6892	Johnson & Johnson	–	–
ENUM004	Enumeral Biomedical Holdings	–	–
Ox40 agonist	Abbvie	–	Rumoured to be ABBV-368
Source: EvaluatePharma, Clinicaltrials.gov.			

Unlike PD-(L)1, which is an inhibitory checkpoint, Ox40 is an activating molecule, and its normal role is as a secondary co-stimulator of T cells. Hitting it with an activating MAb could help promote T cells' anticancer activity.

Conversely, there is also a role for Ox40 antagonists, and these include Kyowa Hakko Kirin's KHK4083 and Kymab's KY1005, which are thought to have potential in ulcerative colitis and graft-versus-host disease respectively.

Theories aside, clinical data with Ox40 agonists have disappointed. At last year's Esmo meeting results were revealed from a first-in-human trial of Pfizer's PF-04518600, showing just one partial remission in 25 patients, while Astra's MEDI0562 showed one partial response in 19 evaluable patients.

Scientifically there might be two reasons for Ox40's underwhelming performance: it might be that without first activating the co-stimulatory molecule CD28 hitting Ox40 is insufficient to turn on T cells, or that additional release of an immune system brake might be needed for activity.

The latter is clearly the theory behind several Ox40 agonists being combined with anti-PD-1 and/or anti-CTLA4 MAbs. However, these represent no more than a few assets jostling for attention in what is a tidal wave of immuno-oncology combination trials now under way.

A special EP Vantage report on anti-PD-(L)1 combination trials is available on free download.

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