Evaluate Vantage

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Roche’s colon cancer failure turns the focus to other combinations

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The failure of the Imblaze-370 trial should be worrying more than just Roche and Exelixis, whose hopes of treating a sizeable portion of colorectal patients have just been dashed. The setback is another knock to tumour-sensitisation approaches, which many are pursing in an attempt to boost the effectiveness of checkpoint blockade.

A quick search of registries for trials in patients with microsatellite stable colorectal cancer – the subject of Imblaze-370 – reveals 14 active studies that involve combining an anti-PD(L)1 antibody with another mechanism. Today’s news does not mean all are destined to disappoint, of course, however it is notable that the most recently initiated study employs a cytokine targeted approach, which is very much the mechanism of the moment (see tables below).

This is being run by Merck & Co, which last month started a study recruiting patients with three types of solid tumour known not to respond to anti-PD-1 antibodies. The patients are being treated with Keytruda and navarixin, a CXC chemokine receptor 2 antagonist that has long been on the shelf, having failed in respiratory indications and psoriasis years ago.

CXCR2 is also known as IL-8 receptor B, which is up-regulated in various tumour cell types. Presumably Merck is working on a similar theory that has driven huge interest in the potential of cytokine combinations – and for which Lilly paid so richly today *(Lilly joins the cytokine gold rush with Armo deal, May 10, 2018).*

Searching for stability – actively recruiting trials in patients with MSS colorectal cancer				
Company or sponsor	**Interventions**	**Mechanisms**	**NCT ID**	**Primary completion Date****
Industry				
Array	Binimetinib; Opdivo, Yervoy	MEK inhibitor; anti-PD-1 Mab; anti-CTLA4 Mab	NCT03271047	Aug-18
Effector Therapeutics	eFT508, avelumab	MNK 1 & 2 inhibitor; anti-PD-L1 Mab	NCT03258398	May-18
Taiho	Lonsurf, Opdivo	Chemotherapy; anti-PD-1 Mab	NCT02860546	Oct-17
Novartis	PDR001 (spartalizumab); Stivarga	Anti-PD-1 Mab; multi-kinase inhibitor	NCT03081494	Aug-18
Incyte	Keytruda, epacadostat, INCB057643, INC59872, azacitidine	Anti-PD-1 Mab; IDO inhibitor, BET bromodomain inhibitor, LSD 1 inhibitor, chemo	NCT02959437 (Echo-206)*	Sep-21
Merck & Co	Navarixin, Keytruda	CXCR 2 antagonist; anti-PD-1 Mab	NCT03473925*	Aug-19
Novartis	PDR001 (spartalizumab), Avastin, mFOLFOX6	Anti-PD-1 Mab, anti-VEGFr Mab, chemo	NCT03176264	Jun-19
Novartis	NIR178, PDR001 (spartalizumab)	Adenosine A2A receptor antagonist, anti-PD-1 Mab	NCT03207867*	Jan-21
Sumitomo Dainippon	DSP-7888, Opdivo, Tecentriq	WT 1 vaccine, anti-PD-1 Mab, anti-PD-L1 Mab	NCT03311334	Oct-18
Academia				
Massachusetts Gen Hospital	Nivolumab, ipilimumab, radiation	Anti-PD-1 Mab; anti-CTLA4 Mab; radiation	NCT03104439	Oct-20
University of California	Avastin, Keytruda, capecitabine	Anti-VEGFr Mab; anti-PD-1 Mab; chemo	NCT03396926	Jan-21
Sidney Kimmel	CC - 486, Istodax, MK - 3475, Keytruda	Oral azacitidine (chemo), HDAC inhibitor, anti-PD-1 Mab	NCT02512172	Aug-18
UNC Lineberger	Panitumumab, Opdivo, Yervoy	Anti-EGFr Mab, anti-PD-1 Mab; anti-CTLA4 Mab	NCT03442569	Dec-20
M.D. Anderson	Imfinzi, Mekinist	Anti-PD-1 Mab, MAPK 1/2 inhibitor	NCT03428126	Nov-18
*Notes: * = multi-cohort trial, of which MSS is one; **as per clinicaltrials.gov; MSS = microsatellite stable; MMR = mismatch repair. Source: EvaluatePharma, clinicaltrials.gov*				

The clinical trial entry for Merck's newly commenced study predicts data later next year, though several other of the studies above are slated to read out sooner, suggesting that this is a space that could yield much data in the coming months.

All with be hoping for a better result than that unveiled by Roche and partner Exelixis this morning, though the writing was apparently on the wall for Imblaze-370 last month when Roche halted a similar study called Modul (*Quiet Modul halt puts the pressure on Exelixis, April 10, 2018).*

Imblaze-370 was a third-line study in which Roche's Tecentriq with or without Exelixis's Cotellic was pitted against Bayer's Stivarga, the standard of care. Around 90% of the patients in the trial were judged to have microsatellite stable (MSS) tumours, a cohort that tends to respond very poorly to treatment.

In healthy cells errors in microsatellites – repeated sequences of DNA – are corrected by a process called DNA mismatch repair (MMR). However when this malfunctions, microsatellite instability (MSI) occurs, a process that is particularly relevant in colon cancer.

It is thought that MSI is the most common cause of colon cancer, although paradoxically those with high levels of instability (MSI-high) actually have a better prognosis, as their tumours are less likely to metastasise. Both Keytruda and Opdivo have won approval to treat MSI-high colorectal patients.

However, these checkpoint inhibitors have shown little utility in patients with functioning mismatch repair, a

substantial cohort of patients who comprise around 80% of colorectal cancer cases. Hence the efforts by industry and academia to extend the reach of anti-PD-(L)1 antibodies, via the various combination approaches above.

The theory behind adding Cotellic, a MEK inhibitor, was that it might sensitise tumours to Tecentriq by increasing MHC I expression on tumour cells, promoting cytotoxic T cell accumulation. The failure of the combination to extend survival versus Stivarga suggests the hypothesis is a dud, although the patients in this setting were at a very advanced stage and the trial relatively small.

Ones to watch?

Exelixis shares fell 11% this morning – colorectal could have been an important new tumour type for Cotellic, which is currently approved to treat melanoma. Array, which also has MEK inhibitor being tested in this setting, shook off pre-market losses to open flat – as well as the trial listed above, binimetinib is being tested in at trial called Beacon in collaboration with Merck and Keytruda, which recruits a wider pool of colorectal patients.

The table above could well exclude other trials that are stratifying colorectal patients by MSI status – inclusion here required this being stated clearly in clinical trial registries. But these selected approaches will provide tests of various combination hypotheses in the coming months.

Incyte's Echo-206 will be one to watch, to see if anything can be salvaged from the epacadostat blow up earlier this year *(Incyte's epacadostat blow-up leaves a trail of destruction, April 6, 2018)*. And it seems that Novartis is doing a lot work in this setting, with three trials under way in MSS colorectal patients.

It is notable that all of the trials in this analysis were started within the last 18 months – this is a nascent area of drug discovery. But it is also very fast moving and perhaps the likes of Merck, Sumitomo and Effector, all of whom seem to be testing agents that activate an immune response, are the ones to watch particularly closely.

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