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Asco 2022 – Merck’s follow-on immuno-oncology plan hits a myositis problem

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ILT3 blockade shows no monotherapy activity while a combo runs into toxicity issues, but Merck presses on.

Expect Immune-Onc, NGM Biopharmaceuticals and Biond Biologics to be casting a nervous eye over the data for Merck & Co’s anti-ILT3 antibody MK-0482 just presented at Asco. The results offer little reason for optimism, so the pressure is on the smaller biotechs, which are following similar approaches, to show that Merck’s problems are specific to its MAb.

The data could knock a hole in Merck’s hopes that hitting ILT3 could give it a new immuno-oncology mechanism, notwithstanding the group’s decision to press on with a Keytruda combo. MK-0482 has shown no monotherapy activity, and particularly concerning is myositis as a toxicity that led to one patient death.

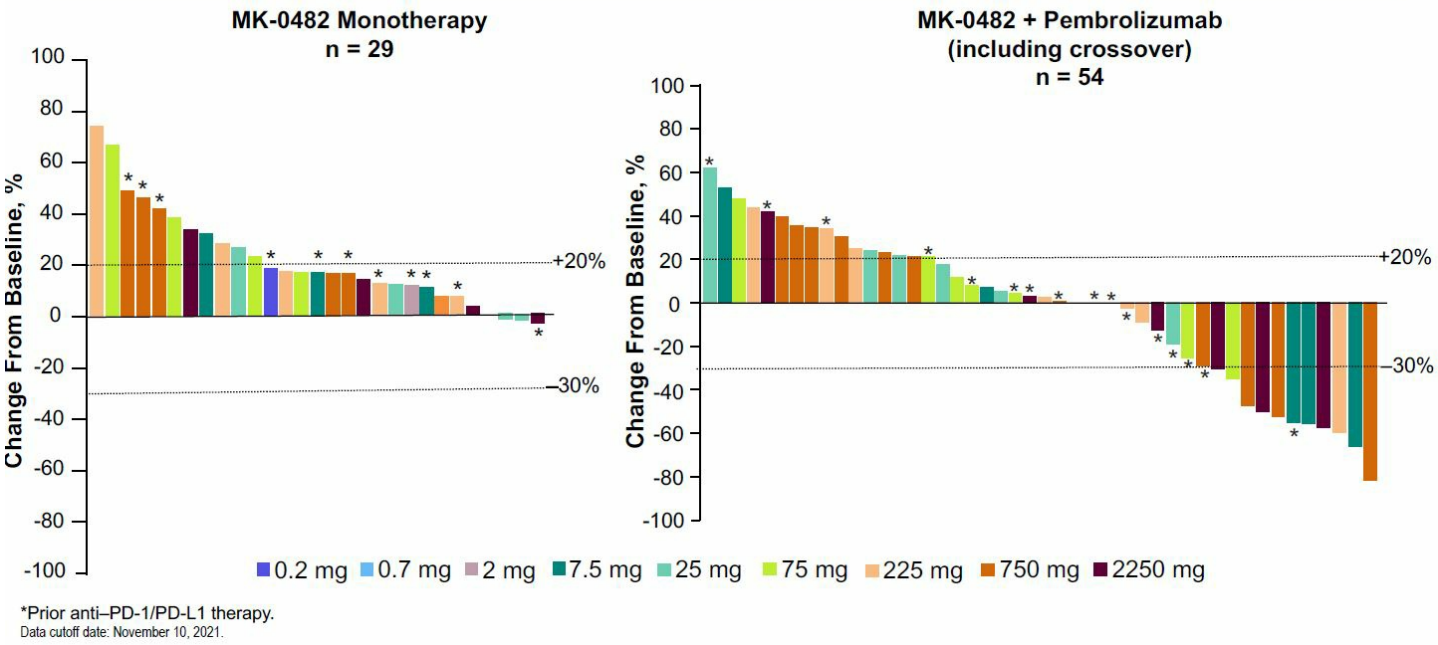
Merck cautioned that what it presented were first-in-human data from a dose-finding study. Eric Rubin, the group’s senior vice-president of early-stage oncology, called the results “promising at this stage”, and said lack of monotherapy activity was not necessarily a problem, citing Lag3 as one oncology mechanism that was relatively inactive until combined with PD-1 blockade.

Immunosuppression

ILT3, also known as LILRB4, is a receptor expressed on myeloid-derived suppressor cells, which are thought to be a key driver of immunosuppression in the tumour microenvironment.

MK-0482 represents one approach Merck is taking to complement the activity of Keytruda. The company also has a molecule coded MK-4830, partnered with Agenus, that targets the related ILT4 protein and is also in phase 2.

But for now the best that can be said about the ILT3 approach is that the jury is still out. The data presented at Asco showed zero remissions in 29 solid tumour subjects given MK-0482 monotherapy, while 54 receiving the MAb plus Keytruda yielded a 15% rate of responses, all partial.



Source: Dr Martin Gutierrez & Asco.

The Asco abstract had shown two cases of myositis, a rare muscle disorder, one of which was fatal. The Asco presentation revealed both to have occurred in the Keytruda combination cohort, a fact that perhaps offers Merck a ray of hope.

“Keytruda can cause myositis,” Mr Rubin told *Evaluate Vantage*. “The question is whether [MK-0482] is somehow adding to the myositis that you would see with Keytruda.”

He accepted that the toxicity was not common, but suggested that seeing two cases in a small trial like this could be down to bad luck, adding: “It’s still too early to understand whether the safety profile is really different to that of Keytruda. The other immune adverse events do not really look much different to what we would expect with Keytruda.”

Merck will now go into dose expansion in a number of solid tumours with 750mg MK-0482 plus 200mg Keytruda every three weeks, based on what the primary investigator, Dr Martin Gutierrez of Hackensack University Medical Center, called the totality of data. Another approach is to explore triple combinations that include chemo, said Mr Rubin.

Industry projects targeting immunoglobulin-like transcripts (ILTs)			
Project	**Mechanism**	**Company**	**Clinical trial**
Phase 2			
MK-4830	Anti-ILT4 MAb	Agenus/ Merck & Co	Several, including Keytruda combo trials Keymaker-U01A, B & C, & Keynote-B99
MK-0482	Anti-ILT3 MAb	Merck & Co	Keytruda combos Keymaker-U01B & C
Phase 1/2			
NGM707	Anti-ILT2 x ILT4 MAb	NGM Biopharmaceuticals	MonoRx & Keytruda combo
BND-22/ SAR444881	Anti-ILT2R MAb	Biond/ Sanofi	MonoRx & Keytruda or Erbitux combo
JTX-8064	Anti-ILT4 MAb	Jounce	MonoRx & pimivalimab combo
Phase 1			
IO-202	Anti-ILT3 MAb	Immune-Onc Therapeutics	Keytruda combo
NGM831	Anti-ILT3 MAb	NGM Biopharmaceuticals	MonoRx & Keytruda combo
IO-108	Anti-ILT4 MAb	Immune-Onc Therapeutics	MonoRx & Keytruda combo
Preclinical			
AGEN1571	Anti-ILT2 MAb	Agenus	IND cleared
CDX585	Anti-ILT4 x PD-1 MAb	Biosion	Preclinical
BND-35	Anti-ILT3 MAb	Biond Biologics	Preclinical
Source: Evaluate Pharma & clinicaltrials.gov.			

Other clinical-stage anti-ILT3 MAbs include Immune-Onc's IO-202 and NGM's NGM831, while Biond's BND-35 is still at the preclinical stage.

Merck's data will be relevant also for companies pursuing related approaches. For instance, Jounce is in the clinic with a MAb targeting ILT4, while Agenus had an anti-ILT2 MAb in addition to the anti-ILT4 it has licensed to Merck.

Previously Tolerx had worked preclinically on MAbs targeting ILT2, ILT4 and ILT5, but the company was wound up after its diabetes project failed phase 3 in 2011.