Evaluate Vantage

May 22, 2023

Here come the PD-1 agonists

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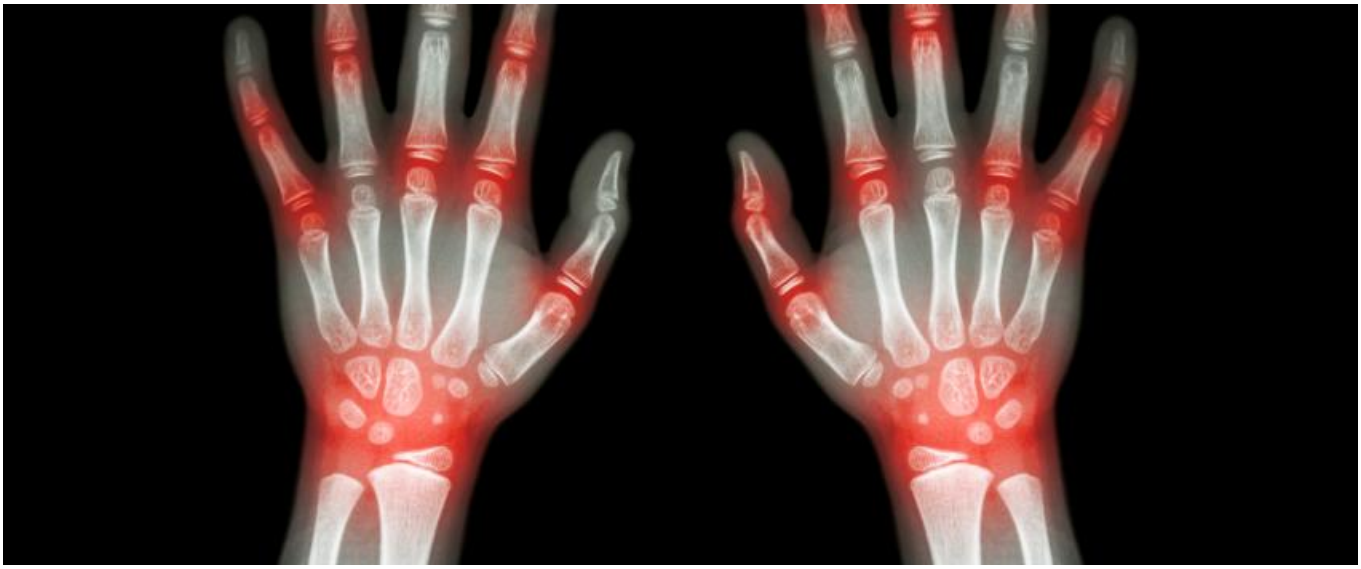

Lilly shows that peresolimab is a goer, and others are not far behind; but what about the cancer risk?

If blocking PD-1 on T cells can release a brake on the immune system and revolutionise cancer treatment, the reverse could damp down immune response and have use in autoimmune diseases. This idea has been around for some time, and phase 2 data with Lilly's peresolimab have provided evidence that the strategy could work in rheumatoid arthritis.

Next up are several rival PD-1 agonist projects that will test this theory and attempt to repeat Lilly's success, most notably Anaptysbio's rosnilimab. The space has seen takeover activity, though one key question is whether such a mechanistic approach could provide tumours with a way to bypass the immune system, and thus raise a patient's cancer risk.

This issue was tackled in an NEJM editorial last week that discussed Lilly's peresolimab data, also published in full in that journal. "Because this therapeutic approach is not antigen-specific one of the biggest concerns about the treatment relates to the development of cancer," the editorialists wrote, adding that such a risk "probably would not have been identified during the short timeframe of the trial".

The phase 2 study in question primarily concerned a 12-week endpoint, namely change in a disease activity score called DAS28-hsCRP. As had already been presented at last year's American College of Rheumatology meeting, the 700mg peresolimab dose met this endpoint versus placebo, and an exploratory analysis of 300mg also appeared positive.

Adverse events seemed consistent across the three trial cohorts, with similar rates of mild and moderate events, and no severe toxicities. However, if there is an increased risk that a neoplasm could evade the immune system – a theoretical concern with any immune system-suppressing therapy – this would logically take much longer than 12 weeks to materialise.

The NEJM editorialists did not provide an answer, and said many other questions remained, including whether PD-1 agonism could "reset the immune response" and so provide a longer-term treatment than current RA drugs, whose effects typically wane after they are withdrawn.

Next up

Next to shed light on this mechanism could be Anaptysbio, whose rosnilimab is to enter phase 2 for RA in the third quarter. In 2021 a phase 1 study showed rosnilimab's sustained PD-1 receptor occupancy and "favourable safety and tolerability", and Anaptysbio then started phase 2 in alopecia areata.

However, alopecia drew a blank, and Anaptysbio switched to RA based on the claim that PD-1-positive T cells were clinically validated drivers of disease in RA; the Lilly data appear to back this. Anaptysbio also has a separate PD-1 agonist asset, CC-90006, originally partnered with Celgene, but Bristol Myers Squibb appears to have discontinued this after phase 1.

Also boasting two assets is Merck & Co, courtesy of its $1.9bn takeout of Pandion, which brought with it the PD-1 agonists PT627 and PT001. The former has systemic activity while the latter carries a MAdCAM tether for gut and liver targeting. Though Merck has not said much about the Pandion assets it has put PT101, now known as MK-6194, into phase 1.

Two other takeovers featured PD-1 agonists: Gilead's $405m acquisition of Mirobio last August brought MB151, while Ibio's $1m move on Rubryc included rights to RTX-002; both are preclinical.

PD-1 agonists in development		
Project	**Company**	**Status**
Peresolimab	Lilly	Ph2 in rheumatoid arthritis
Rosnilimab (ANB030)	Anaptysbio	Ph2 in alopecia areata not being pursued; ph2 RA trial starts Q3 2022
MK-6194 (PT101)	Merck & Co (ex Pandion)	Ph1 in ulcerative colitis (GI/liver tethered project)
CC-90006	Anaptysbio/ Bristol Myers Squibb (ex Celgene)	Ph1 in psoriasis completed (likely discontinued)
PT627	Merck & Co (ex Pandion)	Preclinical (systemically acting)
MB151	Gilead (ex Mirobio)	Preclinical
RTX-002	Ibio (ex Rubryc)	Preclinical
Unnamed	Meiji Holdings	Preclinical
Source: Evaluate Pharma & clinicaltrials.gov.		

It is also worth mentioning a curious approach to autoimmune disease, namely Ono's ONO-4685. This is not a PD-1 agonist but an anti-PD-1 x CD3 bispecific MAb, designed to reduce autoimmunity by eliminating T cells through fratricide.

However, a phase 1 study in plaque psoriasis is suspended, presumably owing to toxicity concerns. A separate trial in T-cell lymphoma – an apparently more logical setting for such an indiscriminate approach – continues.

Tox worries for PD-1 agonists are unlikely to abate any time soon, though Lilly has already put peresolimab into a large phase 2 RA study, Resolution-1, testing three doses against placebo on the primary endpoint of ACR20 response. In the NEJM paper 71% of 700mg recipients had ACR20 responses, versus 44% and 42% of 300mg and placebo patients respectively.

It will be up to the FDA to determine the follow-up necessary to give sufficient confidence over safety.