Evaluate Vantage

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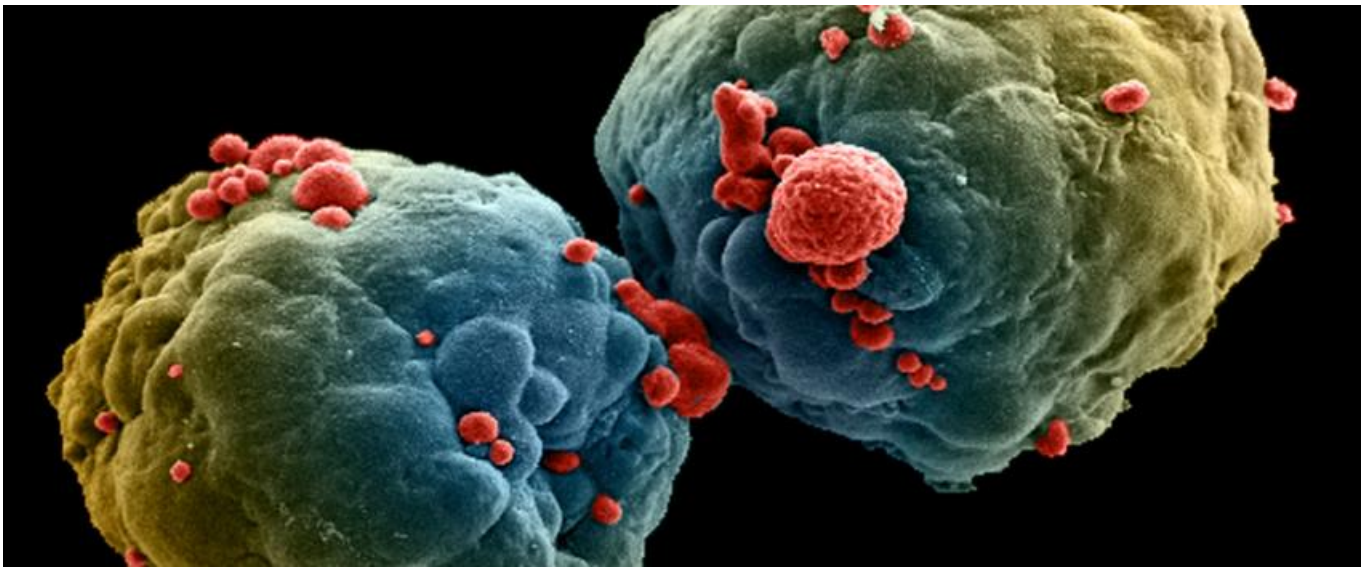
Asco 2018 – Toll like receptors join the immuno-oncology combo parade

Jonathan Gardner



As investigators scrabble to find new cancer combos toll like receptor agonists come back into fashion.

Biopharma's hunger for new agents to plug into immuno-oncology combinations has given new life to a mostly forgotten mechanism of action – toll like receptor (TLR) agonists.

Asco heard promising mid-stage data from two TLR9 agonists, Idera's IMO-2125 and Dynavax's SD-101, in melanoma. With response rates that compare favourably with those seen with PD-1 agents in first-line disease, the data appear strong enough to justify phase III trials. But investors are treating immuno-oncology combinations with more caution since IDO inhibition imploded earlier this year, and there were criticisms of both Idera's and Dynavax's trials, including their small size and lack of control arms.

Selling on the news

Shares in both companies slumped 4% yesterday in a trading session that weighed heavily on immuno-oncology due also to Nektar's deflation. The next catalysts for investors trading on TLR9 news from these two companies is months away at best, as Idera's phase III trial has a completion date of 2021 and Dynavax has said that it plans to start a pivotal trial in melanoma by the end of 2018, and in head and neck cancer early next year.

Stimulating TLR9 is one of the many ways drug developers are trying to "turn cold tumours hot" and make them responsive to treatment with an immuno-oncology agent. For example, in patients treated with 2mg or less of SD-101 along with Keytruda, seven of nine patients expressing no PD-L1 whatsoever at baseline achieved a complete or partial response.

Numerically speaking, Dynavax's TLR9 looks slightly better than Idera's, though Dynavax's trial included patients who had never been treated, as well as those who had progressed after treatment.

At the 2mg dose injected in up to four lesions, which Dynavax has selected as the phase III therapy, SD-101 achieved a 70% overall response rate, which translated into a six-month progression free survival rate of 76%. An 8mg dose had a lower response rate of 38%, raising concerns about the unusual dose response – however, that was only injected into a single lesion.

Idera's IMO-2125, now called tilsotolimod, was combined with Yervoy in patients who had progressed on a PD-

1 agent. It achieved a 38% overall response rate, which researchers point out is numerically above the historical 13% response seen with Yervoy alone in the refractory population.

The market's response yesterday suggests that investors are less trusting of single-arm trials than they might have been previously.

Extending response

While the entry of the PD-1s, first Opdivo and then Keytruda, transformed the treatment of melanoma, 70% of patients will progress, said Alexander Menzies of the University of Sydney. Finding ways to delay progression should be a priority, he said: "We want to lift the bar, so people respond and continue to respond."

Administration via intratumoural injection will, of course, limit the commercial promise of both of these agents. This is also the case with another TLR agent, Immune Design's TLR4 G100, now in mid-stage trials in lymphoma. Imlygic, an oncolytic virus approved in melanoma, is injected into tumours and that is likely one factor in its rather modest sales outlook.

Enthusiasm for immuno-oncology combinations has waned this year since epacadostat's blow-up, with investors wanting clearer signs that biopharma companies are not rushing into late-stage trials on thin data. Results seen with TLR9s are reason to continue to study them, but care will be needed to give them the best chance of success.