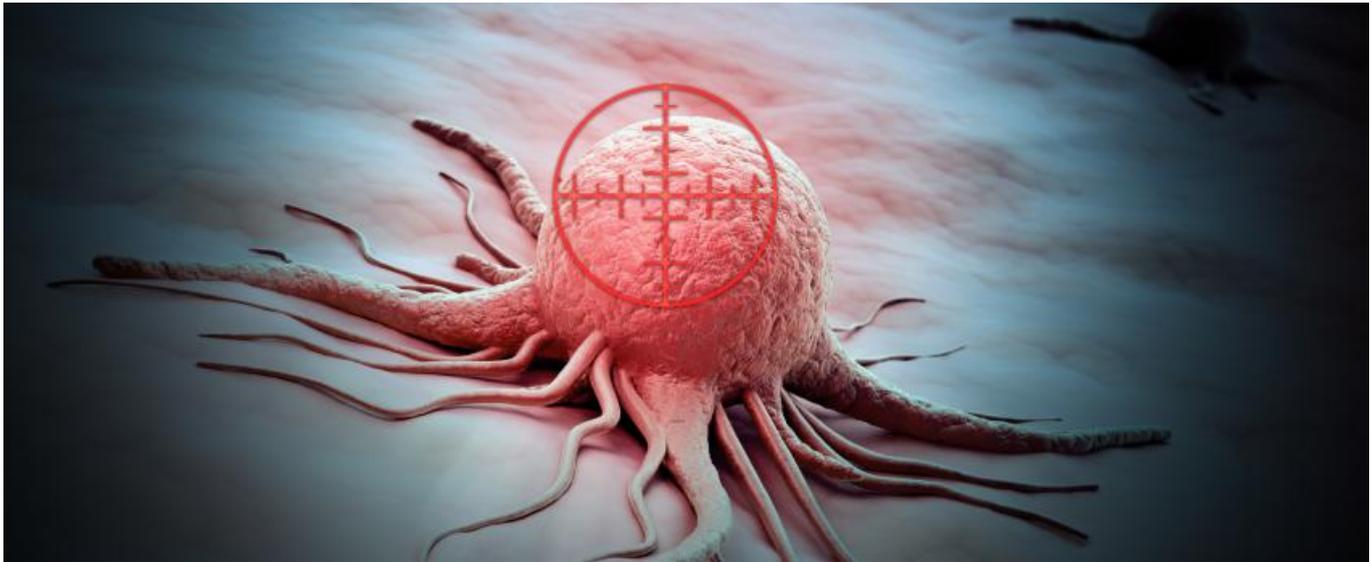


Astra turns to bispecifics to solve the tremelimumab problem



[Amy Brown](#)



Astrazeneca reckons a bispecific approach can unlock the potential of CTLA-4 inhibition, and is to start a large phase II programme this year.

The heavy toxicity burden of CTLA-4 inhibitors like Bristol-Myers Squibb's Yervoy and Astrazeneca's tremelimumab has always been a major drawback; it is still not clear whether the latter will ever make it to market. But Astra remains convinced that this mechanism holds much potential in several tumour types, and today revealed plans for a large phase II programme with a bispecific approach.

MEDI5752 hits both CTLA-4 and PD-1, and has been designed to target lymphocytes in the tumour bed that express both of these immune checkpoints. José Baselga, Astra's head of oncology R&D, told *Vantage* that early studies had shown the bispecific achieving substantially higher inhibition of CTLA-4 with a big reduction in toxicity, persuading the company to push on.

Astra has figured out the optimal dose of MEDI5752 and is expanding an ongoing phase I trial, but is also preparing to launch phase II studies, according to Mr Baselga.

"We will be moving ahead very quickly in indications that are CTLA-4 dependent - renal cell carcinoma, melanoma, hepatocellular - but we also feel incredibly excited about lung cancer and hope to launch a very aggressive programme," he said, speaking to *Vantage* after the company released its annual results today.

A fledgling field: bispecifics against anti-CTLA4 and PD1

Project	Company	Setting	Notes
KN046	Alphamab	NSCLC, TBNC, pancreatic	Phase I/II in China & Australia; early Asco 2019 data
AK104	Akeso	Starting ph2 this year (China only) in nasopharyngeal carcinoma	First-in-human data at SITC 2019; 24% ORR in solid tumours, 15% treatment-related serious AEs
XmAb20717	Xencor	Solid tumours	Phase I Duet-2 study (NCT03517488; no clinical data)
MEDI5752	Astrazeneca	Basket study in several tumours, incl renal cell and lung	Phase I (NCT03530397; no clinical data)
MDG019	Macrogenics	Solid tumours	Phase I (NCT03761017)
CN104974253A	Shanghai CITIC Guojian Pharmaceutical	NA	Patent only

Sources: EvaluatePharma, [clinicaltrials.gov](#) & proprietary research.

This progress would make Astra the leading developer in this space, in the west at least: Alphamab Oncology has a broad early/mid-stage clinical programme under way with KN046, although this is only recruiting patients in China and Australia for now. Xencor has an 87-patient study with its candidate ongoing in the US; Astra's burgeoning investment could focus attention on these smaller players' progress.

Still, Mr Baselga maintains that MEDI5752 has an advantage over these projects thanks to variability in binding affinity.

"Ours is different because it changes the binding affinity to CTLA-4 upon binding to PD-1. Other bispecifics are not that different to giving two separate molecules," he says.

This is important because the toxicity seen with agents like tremelimumab is caused by binding to non-tumour related CTLA-4 receptors. Some [preclinical studies have shown that](#), unlike lymphocytes in the periphery, tumour-infiltrating lymphocytes (TILs) co-express these receptors, and that these same TILs might be resistant to single checkpoint blockade.

"By creating an antibody that does not bind well to CTLA-4 alone, that requires PD-1 to be there, you are preventing binding to the lymphocytes that are not in the tumour, and preventing a lot of the side effects seen with CTLA-4," he says.

Judgement time?

Of course this all remains to be proven, and very little clinical data are available on any of these projects. Mr Baselga says Astra hopes to present phase I results in the coming months.

Success here would presumably help mitigate disappointment with tremelimumab, which [failed to add anything to Imfinzi in the Neptune study](#) and is increasingly suspected to be a dud ([Tremelimumab's deprioritisation laid bare, February 13, 2020](#)).

Important readouts for the project include the bladder cancer study [Danube](#), which could report in the coming months; the liver cancer study [Himalaya](#), due to report in the second half; and the [final](#) survival readout from [Poseidon](#), due next year.

Dave Fredrickson, head of Astra's oncology unit, said results from these three trials would help determine treme's future. But it seems that in MEDI5752 the company already has its pivot in place.

This story has been updated to add the Macrogenics project.