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Novartis turns to Beigene for a PD-1 blocker

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The pharma giant resorts to deal-making for a much-needed late-stage IO asset, leaving its own PD-1 agent out in the cold.

The future of Novartis's anti-PD-1 project spartalizumab was already uncertain, and it looks even shakier now. The Swiss group insists that the antibody is still in play but its deal for Beigene's rival PD-1 inhibitor tislelizumab yesterday, giving it rights to the project outside China, tells another story.

The transaction looks chunky, at $650m up front plus up to $1.55bn in milestones, but it might actually make sense for Novartis. The group has only committed $622m to ongoing clinical trials of sparta, according to *Evaluate Omnium*, which estimates that taking the project to market in all indications currently under development could cost another $3.9bn.

Beigene certainly comes off well from the agreement. The Chinese company has now been paid twice for tislelizumab – it previously had a deal with Celgene but this was terminated in 2019 following that group's takeout by Bristol Myers Squibb. Celgene gave Beigene $263m up front and also made a $150m equity investment; Beigene also got a $150m break-up fee for its trouble.

Fc gamma sparing

Perhaps this agreement is one of those rare win-win deals, as Leerink analysts describe it: Novartis gains a late-stage immuno-oncology asset while Beigene benefits from the pharma giant's global infrastructure. Still, this represents a big bet for Novartis in the context of a crowded PD-(L)1 space that has already been sewn up by Keytruda and Opdivo.

Novartis must hope it can differentiate tislelizumab, which the companies say has been designed to minimise binding to the Fc gamma receptor on macrophages. In preclinical studies, this binding has been shown to compromise the anti-tumour activity of PD-1 blockers via the elimination of cytotoxic T-cells.

The other major PD-1 blockers do not feature Fc gamma sparing, but whether this translates into better efficacy with tislelizumab is open to debate.

Either way, Novartis will have a lot to do to catch up with the market leaders, assuming tislelizumab gets approved in the US. The drug is already approved in China for third-line classical Hodgkin lymphoma and urothelial carcinoma; it is also filed there for first-line squamous and non-squamous non-small cell lung cancer and second-line hepatocellular carcinoma.

Novartis said tislelizumab's first filing outside of China is expected in 2021, but a spokesperson declined to

give details about the geography or indication. Second/third-line non-small cell lung cancer might be a good bet following the recent success of the Rationale 3 study, hailed as the first win for tislelizumab in a global pivotal trial.

However, Rationale 3 did not include any US sites, according to clinicaltrials.gov. There are several ongoing mid/late-stage studies of tislelizumab with a US presence, the table below shows.

Selected global trials of tislelizumab				
Setting	**Regimen**	**Trial ID**	**Primary completion date**	**Location(s)**
Phase III				
2L/3L NSCLC	vs docetaxel	Rationale 303, NCT03358875	Top-line win reported in November	China, Brazil, Mexico, New Zealand, Eastern Europe, Russia, Turkey
2L oesophageal squamous cell carcinoma	vs chemo	NCT03430843	Sep 2020	US, China, Europe, Japan, South Korea
1L oesophageal squamous cell carcinoma	With/out chemo	NCT03783442	Mar 2021	US, China, Europe, Japan, South Korea, Australia, Russia
Hepatocellular carcinoma	vs sorafenib	NCT03412773	Jun 2021	US, China, Europe, Japan
1L gastric	With/out chemo	NCT03777657	Aug 2022	US, China, Europe, Japan, South Korea, Russia, Turkey
Phase II				
r/r T cell and NK cell neoplasms	Monotherapy	NCT03493451	Feb 2021	US, Canada, China, Europe
Unresectable hepatocellular carcinoma	Monotherapy	NCT03419897	Apri 2021	China, Europe
r/r classical Hodgkin lymphoma	Monotherapy	Tirhol, NCT04318080	Oct 2022	US, Europe, Australia
Source: EvaluatePharma, clinicaltrials.gov.				

Currently, Chinese sales make up the bulk of tislelizumab's 2026 consensus forecast of $1.3bn, according to *EvaluatePharma*, but this is set to change given the Novartis deal. One thing to watch will be pricing outside China, where Beigene has previously said it would compete, Leerink noted.

A more immediate question is what this all means for spartalizumab, which in August failed the Combi-I trial in melanoma, its first big test (*Novartis misses in melanoma, but maybe not by much, August 24, 2020*).

Novartis will continue its ongoing studies of sparta, a spokesperson told *Evaluate Vantage,* adding that the assets were "complementary" and that the strategies for each agent were different.

In reality, however, sparta's days look numbered. If tislelizumab really is a better PD-1 inhibitor, Novartis would be better off cutting its losses sooner rather than later.

The estimated costs of spartalizumab's clinical development	
Registered trial costs*	$622m
Future trial costs**	$3.86bn
Total	$4.48bn

**Trials registered on clinicaltrials.gov; **Estimated costs of trials needed to get to market in indications currently under development. Source: Evaluate Omnium.*