

Seattle disappoints Puma bulls with Cascadian takeout



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Why buy Puma for Nerlynx when you can get a company developing a similar but potentially cleaner candidate, for a lower price? This seems to be the thinking behind Seattle Genetics' acquisition of Cascadian Therapeutics for \$614m.

Cascadian's lead candidate is tucatinib, a highly selective oral kinase inhibitor against Her2, which is in a pivotal trial in metastatic breast cancer. The company hopes to avoid the diarrhoea side effect that has dogged Nerlynx, and show strong utility in patients with brain metastases, a subgroup in which previous projects have fallen short.

The deal makes Puma's valuation of \$2.5bn look even more bloated – particularly after EU regulators knocked back Nerlynx last week ([Europe blocks Nerlynx, Perjeta up next, January 24, 2018](#)).

Seattle could challenge Puma's position in this space if tucatinib turns out to be a better molecule; having only been launched in the US in July 2017, Nerlynx still has much to prove.

Active projects hitting Her2 with TKIs in breast cancer		
Product	Company	2022e sales (\$m)
<i>Marketed</i>		
Nerlynx	Puma Biotechnology	1,468
Tykerb	Novartis	92
<i>Phase II/III</i>		
Tucatinib*	Cascadian Therapeutics	233
S-222611	Shionogi	-
Varlitinib*	Aslan Pharmaceuticals	-

*Licensed from Array. Source: EvaluatePharma.

On a conference call today Seattle's chief executive, Clay Siegall, made much of tucatinib's tolerability profile – by hitting Her2 but not EGFR, the project could avoid side effects like diarrhoea and skin rash, according to Cascadian's website.

The project's promise in patients with brain metastases was obviously also a major factor in Seattle's decision to strike. Mr Siegall described the ongoing Her2Climb trial of tucatinib as the only pivotal study of a tyrokinase kinase inhibitor designed to support its use in patients with active brain metastases.

Puma has hopes for Nerlynx in brain mets too, and at last year's Asco [presented what it termed positive results](#) from an ongoing investigator-sponsored phase II trial, TBCRC 022. However, others [have described](#) the response in this study as poor.

If tucatinib becomes the first agent approved for breast cancer brain metastases, Seattle might finally achieve its goal of diversifying beyond its biggest seller, Adcetris.

Climbing

First, tucatinib has to succeed in the pivotal Her2Climb study, which is evaluating it in combination with Roche's Herceptin in patients who have failed on Herceptin, Perjeta and Kadcyca.

The study is expected to complete enrolment in 2019, but Mr Siegall was reluctant to say when results might be available, pointing out that it is an event-driven trial. Progression-free survival is the primary endpoint.

Secondary endpoints include PFS specifically in patients with brain metastases at baseline, and overall survival across the whole study population.

Mr Siegall argued that it was premature to say what kind of benefit might be needed for approval, adding that there were currently few options for patients with brain metastases. Only around 16,000 patients are on their third line of treatment, and around half of these develop brain metastases – the small addressable population is perhaps one reason why sellside hopes for tucatinib have been low.

Seattle has indicated that it hopes to expand this research, saying the project could have a role in earlier lines of metastatic breast cancer, as well as in other tumours such as colorectal cancer. In the latter, an investigator-sponsored trial, Mountaineer, is ongoing.

Cascadian's pipeline also includes two preclinical-stage projects: CASC-578, a Chk1 kinase inhibitor, and CASC-674, an anti-Tigit antibody. Seattle raised \$550m through a secondary offering today to help fund the acquisition.

Past life

It has not all been plain sailing for Cascadian – it was previously known as Oncothyreon, and pursued cancer vaccines for years without success. After licensing tucatinib from Array Biopharma in 2014 the company shifted focus and eventually changed its name in June 2016.

Mr Siegall declined to discuss the specifics of the Array deal on today's conference call, but did say that the company does not have an opt-in right.

He pre-empted any suggestion that Seattle, a company that has so far focused on antibody-drug conjugates, might not have the required expertise in small-molecule development: "Seattle is a targeted therapy company, and tucatinib is a targeted drug. We feel this fits in absolutely perfectly with our expertise."

If tucatinib lives up to his expectations Puma could soon have a new adversary.

Study	Setting	Trial ID
Her2Climb	Her2+ metastatic breast cancer	NCT02614794
Mountaineer*	Her2+ colorectal cancer	NCT03043313
Tulip*	HR+ Her2+ metastatic breast cancer	NCT03054363

*Investigator-sponsored study.

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