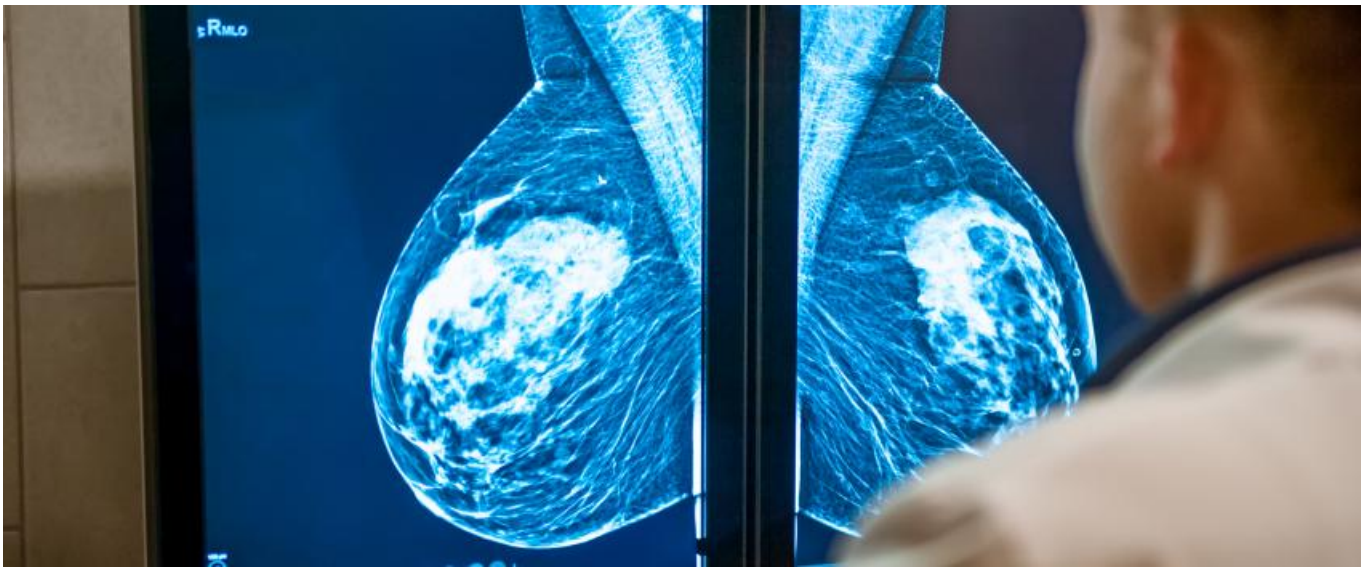
Evaluate Vantage

October 21, 2019

Vindication is sweet for Seattle

Jacob Plieth



Tucatinib yields a positive result in breast cancer, vindicating Seattle Genetics' acquisition of its originator.

Almost two years ago Seattle Genetics' investors shrugged off the group's $614m takeover of Cascadian Therapeutics. Today they found out that the deal had been a masterstroke. Cascadian's lead asset, tucatinib, has scored in a pivotal breast cancer trial, setting it up for a US filing early next year.

The success makes tucatinib two for two, after early data at the Esmo congress showed its potential in Her2-amplified colorectal cancer. The findings will make painful reading for Puma investors, who had long been told that Puma's Nerlynx was the better Her2 asset, but who have seen this drug struggle with toxicities.

Indeed, it might have seemed surprising the Seattle bought out Cascadian and not Puma (*Seattle disappoints Puma bulls with Cascadian takeout, January 31, 2018*). On the other hand, Puma was in hindsight overpriced; in January 2016 it was capitalised at $2.5bn, but since then has lost a staggering 93% of its value.

Primary endpoint

Tucatinib's Her2Climb study tested the small-molecule Her2 tyrosine kinase inhibitor in subjects who had failed Herceptin, Perjeta and Kadcyla. It compared tucatinib on top of Herceptin and capecitabine, versus Herceptin and capecitabine alone.

Seattle said it met its primary endpoint, progression-free survival, cutting risk of progression by 46% ($p<0.00001$). Two key secondaries were also met, with risk of death cut by 34% ($p=0.0048$) and risk of disease progression in subjects with brain metastases at baseline reduced by 52% ($p<0.00001$).

Tucatinib's selectivity for Her2 and not EGFR is claimed to give it a relatively clean safety profile, without the diarrhoea toxicity that has crippled Nerlynx, for instance. Her2Climb did show a 4.3-point elevation in occurrence of serious diarrhoea, but at 12.9% this pales into insignificance compared with Nerlynx, and prophylactic antidiarrhoeals were not needed.

Of more concern is tucatinib's propensity to elevate liver enzymes. Grade 3 or higher elevations in AST and ALT were respectively seen in 4.5% and 5.4% of tucatinib subjects, versus 0.5% in both cases for control patients. On an analyst call the company was asked directly whether it had seen any cases of Hy's law, but declined to comment.

Selected trials of tucatinib		
Study	**Design**	**Data**
Mountaineer	Single cohort: tucatinib + Herceptin in 40 Her2-amplified colorectal cancer subjects who had failed VEGF therapy & chemo, but were anti-Her2 naive	ORR, mPFS & mOS data from 23 evaluable subjects presented at Esmo congress Sep 2019
Her2Climb	Tucatinib + Herceptin + capecitabine vs Herceptin + capecitabine in 612 breast cancer subjects who had failed Herceptin, Perjeta & Kadcyla	mPFS & mOS data from first 480 subjects enrolled (planned analysis) toplined Oct 2019; full data at San Antonio Breast Cancer Symposium

The side effect profile reflects what was seen at Esmo: the Mountaineer trial, in Her2-amplified colorectal cancer, showed increased AST and ALT of all grades in 38.5% and 23.1% respectively, and diarrhoea in 23.1%.

That small, single-cohort trial enrolled subjects who had failed chemo but were naive to anti-Her2 therapy. In it tucatinib plus Herceptin yielded an overall remission rate, its primary efficacy measure, of 52.2%, and median PFS and overall survival of 8.1 and 18.7 months respectively.

Tucatinib is important in marking a departure from Seattle's focus on one marketed drug, Adcetris. The sellside expects tucatinib to post 2024 sales of $268m, according to *EvaluatePharma* consensus, and Seattle has a separate antibody-drug conjugate, enfortumab vedotin, awaiting a US verdict for bladder cancer by March 15.

Her2 targeting is a hot topic, with Astrazeneca/Daiichi Sankyo's ADC trastuzumab deruxtecan facing a US approval decision for Her2-positive breast cancer in the second quarter next year. However, Roche last week discontinued the phase I asset RG6148, thought to be another anti-Her2 ADC.

A separate trial, Her2Climb-02, tests tucatinib on top of Kadcyla in Her2-positive breast cancer. Tucatinib's Esmo data helped send Seattle up 18%, and this morning the company opened up another 15%, as hopes were raised that it could soon see the approval of its first small-molecule drug – though this hinges on liver toxicity being limited.

Perhaps with the benefit of hindsight Cascadian's former owners now think they let their company go too cheaply. But then, as recent events have shown, deals tend not to get done while assets are overpriced.