Evaluate Vantage

October 12, 2022

Kinnate is the latest Raf player to trip up

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The company's attempt to segment Braf-mutant cancers further isn't going smoothly.

Kinnate Biopharma floated two years ago on the promise of novel small molecules able to hit mutations other kinase inhibitors could not, but it is finding the going tough. Yesterday brought news of a second delay to its lead project, KIN-2787, and some analysts fear the worst.

However, the problem might not lie in the logic of what Kinnate is trying to do; KIN-2787 is a Raf kinase inhibitor with activity in class 2 and 3 Braf alterations, and thus said to work beyond Tafinlar's class 1-restricted label. Rather, Kinnate might have designed the phase 1 study badly or recruited the wrong patients, or its molecule lacks potency.

Whatever the reason, the markets did not take kindly to the delay, which will see initial phase 1 data pushed into 2023; results had first been expected in the third and then the fourth quarter of this year. Kinnate was yesterday trading just above half its IPO price, and today the shares fell 27%.

Raf inhibitors approved for cancers with Braf class 1 (V600) mutations

			Sales ($m)	
Product	**Company**	**Approved uses**	**2021**	**2028e**
Tafinlar (dabrafenib)	Novartis (ex GSK)	Melanoma (incl adjuvant), NSCLC & anaplastic thyroid cancer	1,693	1,875
Braftovi (encorafenib)	Pfizer (ex Array)	Melanoma & colorectal cancer	231	576
Zelboraf (venmurafenib)	Roche	Melanoma & Erdheim-Chester disease	86*	83

*Note: *estimate as Roche has not split out sales since 2017. Source: US prescribing information & Evaluate Pharma sellside consensus.*

First-generation Raf inhibitors are approved in melanoma and several other cancers, all of which must carry a class 1 (also known as V600) Braf mutation. Novartis's Tafinlar is the best-seller, but the market also includes

Pfizer's Braftovi and Roche's Zelboraf.

Kinnate, however, says KIN-2787 additionally targets class 2 and 3 Braf mutations, and wants to position it as a first-line targeted therapy. It designed its phase 1 monotherapy trial in two parts, first a dose escalation in class 1, 2 or 3 tumours or Nras-positive melanoma, and then dose-expansion cohorts in class 2 and 3 cancers only.

However, the dose-escalation phase, the subject of the delays, allowed pretreated patients. This brings up the first possible problem, namely that this has resulted in too heterogeneous a population.

In a statement after market close yesterday Kinnate said KIN-2787 had achieved "meaningful exposures" with the 300mg twice-daily dose that preclinical models suggested would be efficacious. "Encouraging initial clinical responses" have been seen, it claimed, but crucially it did not say whether these included clinical remissions.

Thus it seems that actual response rates so far have been low – worrying given that target dosing has been achieved, though Stifel analysts caution that preclinical models might have been misleading. A 400mg dose is now being tested, and going up to 500mg is possible.

Kinnate also blames Covid on the trial delay, but Stifel does not buy this, citing the fact that enrolment has been sufficient to reach dose level five. Perhaps too many subjects with difficult tumours (ie, not melanoma) have been recruited, but surely Kinnate has had enough time to rectify this and enrol more of the right patients.

So maybe KIN-2787 just does not work very well. As well as claiming activity beyond class 1 Braf mutations Kinnate has argued that KIN-2787 is more selective than two other second-generation projects, Novartis's naporafenib and Hanmi/Roche's belvarafenib, claims that are now in doubt.

Developmental Raf inhibitors with possible activity beyond class 1 Braf mutations

Porject	Company	Activity	Clinical trial
Tovorafenib (DAY101)	Day One (ex Sunesis/ Biogen/ Takeda)	Pan-Raf	Ph3 1st-line Raf+ve glioma
FORE-8394	Fore (ex Daiichi Sankyo)*	Class 1 & 2	Ph2 in Braf-altered cancers
Naporafenib (LXH-254)	Novartis	Pan-Raf	Ph2 in 2nd-line melanoma
Belvarafenib (HM95573)	Hanmi/ Roche	Pan-Raf	Ph2 in class 2 mutant or fusion +ve tumours
LUT014	Lutris Pharma	Unclear	Ph2 in colorectal cancer
Avutometinib (VS-6766)	Verastem (ex Roche)	Dual Raf/Mek inhibitor	Ph2 in low-grade serous ovarian cancer
XP-102	Xynomic (ex Boehringer Ingelheim)	Pan-Raf	Ph1/2 is in V600 only
BGB-3245	Beigene/ Springworks**	Unclear	Ph1, incl class 2 & 3
KIN-2787	Kinnate	Class 1, 2 & 3	Ph1 in various cancers
PF-07284890	Pfizer	Unclear	Ph1 includes substudy in class 2 Braf

*Note: *Fore was earlier known as Novellusdx, and Daiichi rights stem from acquisition of Plexxikon; **via the Mapkure JV. Source: company information.*

Kinnate is not the only Raf player to trip up recently. Verastem is active in a slightly different sphere, with the Roche-derived dual Raf/Mek inhibitor avutometinib, but earlier this month discontinued a study in Kras G12V-mutant NSCLC.

Avutometinib had shown promise in a separate setting, Kras-mutated low-grade serous ovarian cancer. However, that trial also tests wild-type disease, and lack of clarity on whether this too might be addressable, combined with Verastem's decision not to release further data, seemed to upset investors.

One notable win has come courtesy of Day One Pharmaceuticals with tovorafenib, another molecule with a convoluted ownership history, said to have pan-Raf activity. The success came this year in the Firefly-1 study

in paediatric glioma, and the project is now in phase 3.

Interestingly, tovorafenib's previous owner, Takeda, had studied and discontinued the molecule in melanoma. Day One has a phase 1/2 trial that includes melanoma, but this use has clearly taken a back seat.

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