Evaluate Vantage

October 17, 2019

Triple meeting – clinical data, and competition, loom for Mirati

Jacob Plieth

Mirati pulls a rabbit out of its hat, but the conference will serve up three new competitors too.

Mirati investors fretting over the first disclosure of clinical data for the $3bn company's KRAS inhibitor MRTX849 were left unsatisfied by yesterday's unveiling of abstracts from the Triple meeting. The long-awaited Mirati presentation outlined nothing beyond pharmacokinetics and activity in cell lines.

It was thus left to the company itself to issue a statement this morning stressing that the Triple meeting would, after all, be the venue for its big clinical reveal, with October 28 being the big day. But the conference abstracts also describe at least three new projects that would be expected to compete against MRTX849 in KRAS-mutant cancers.

These include duelling SOS1 approaches from Bayer and Boehringer Ingelheim; until now the former was not known to be active in pursuing elusive KRAS-positive cancers, but it has now revealed early work on an asset coded BAY-293. The latter had hinted that it was looking to target KRAS mutations via SOS1, but beyond starting a clinical trial of BI 1701963 little is known about its work.

The third approach comes from the Bridgebio subsidiary Navire Pharma, in the form of the SHP2 inhibitor IACS-13909. This will also be of relevance to Novartis, whose own SHP2-targeting asset, TNO155, is in phase I; Bridgebio is separately working preclinically on a pan-KRAS inhibitor, BBP-454.

For now the abstracts relating to Bayer, Boehringer and Navire are, like Mirati's, accounts of preclinical work, something that does not preclude hints of clinical activity being presented on the day. All will be revealed at the Triple meeting (the EORTC-NCI-AACR Molecular Targets and Cancer Therapies symposium), which takes place in Boston, US, on October 26-30.

KRAS-relevant presentations at 2019 Triple meeting			
Project	**Mechanism**	**Company**	**Abstract**
MRTX849	KRAS G12C inhibitor	Mirati	C069
BI-3406	KRAS-SOS1 interaction inhibitor	Boehringer Ingelheim	C133
BAY-293	KRAS-SOS1 interaction inhibitor	Bayer	CN05-03
IACS-13909	SHP2 inhibitor	Navire (Bridgebio)	C036
Source: EORTC-NCI-AACR Molecular Targets and Cancer Therapies symposium.			

While Boehringer's poster mentions BI 1701963 its main focus is actually a separate SOS1 inhibitor, BI-3406. This is described as a first-in-class, orally bioavailable SOS1:KRAS inhibitor.

SOS1 is a helper protein that turns KRAS from an "off" to an "on" state, so blocking it could be an easier way of inhibiting KRAS than trying to hit the kinase itself. The researchers claim that BI-3406 elicits activity against many KRAS variants, including all major G12 and G13 oncoproteins, and suggest combining with Mek inhibition.

Bayer, too, seems to be angling for a combinatorial approach, stating that BAY-293, a small molecule, might synergise with covalent inhibitors like ARS-853 or ARS-1620 that target mutant KRAS G12C. ARS-1620 is the result of a collaboration between Araxes and Johnson & Johnson, and is thought to have informed the design of Amgen's AMG 510.

Expectations

So far AMG 510 has carried Mirati investors' hopes of KRAS inhibition, despite Amgen's latest data disappointing (*Esmo 2019 – Kras springs a leak, September 28, 2019*). A central question, therefore is what Mirati needs to show at the Triple meeting for its $3bn valuation to remain intact.

Presumably AMG 510's 54% remission rate in NSCLC subjects given the target dose, and an underwhelming 8% in colorectal cancer – all responses being partial – represents a baseline of sorts for MRTX849. More important, for Mirati and Amgen alike, will be the durability of any remissions.

Other KRAS approaches that might be sailing beneath the radar of Mirati bulls include SBT-100, a bispecific antibody targeting KRAS and Stat3 in development by the private group Singh Biotechnology. A phase I trial in triple-negative breast cancer is in preparation, the company tells *Vantage*.

Meanwhile, Navire's approach is also based on the idea that SHP2 is required for RAS activation, though its Triple meeting abstract on IACS-13909 does not specifically mention KRAS mutations. Recently Mirati agreed to collaborate with Novartis to combine MRTX849 with TNO155, while other groups working on SHP2 include Revolution/Sanofi (RMC-4630/SAR442720) and Redx.

It seems that KRAS, once thought to be undruggable, is suddenly the subject of much work.