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Boehringer’s big cancer reveal draws near

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The company might finally become an oncology player.

Boehringer Ingelheim has been trying to become a big gun in cancer for years. So far, it has fallen short of its ambition, but it hopes that things might begin to change in 2021.

A big focus for Boehringer is its Kras portfolio, with the company’s global head of innovation, Michel Pairet, telling *Evaluate Vantage* that its strategy here will be unveiled at the upcoming AACR meeting. But Boehringer is also investing in antibody-drug conjugates, via its recent acquisition of NBE-Therapeutics, T-cell engagers and cancer vaccines.

Kras is coming

Boehringer’s most advanced Kras-targeting project is BI 1701963, a SOS1 inhibitor in phase 1. 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 enzyme itself.

SOS1 inhibitors could also work synergistically with selective Kras mutant inhibitors, Mr Pairet believes, and Boehringer plans to test a combination approach for BI 1701963 – initially with Mirati’s Kras G12C-selective inhibitor MRTX849, under a tie-up signed last year, and later with its own other Kras-targeting compounds.

AACR should shed more light on the identity of these additional Boehringer projects; for now, Mr Pairet will only say: “We have a broad portfolio to address all the most relevant components of the Kras cycle.”

The identity of one of these, the preclinical-stage G12C inhibitor BI 1823911, was revealed recently with the publication of this year’s AACR abstract titles (*AACR 2021 preview – the early themes emerge, March 22, 2021*).

Boehringer is also working on a G12D inhibitor, but this is at an earlier stage and the project has no code as yet.

As well as combining its Kras projects, Boehringer also plans to test its SOS1 inhibitor alongside LNP3794, a Mek inhibitor licensed from Lupin.

Indeed, the SOS1 project is already being combined another Mek inhibitor, Novartis’s Mekinist, in a phase I trial in solid tumours with Kras mutations, with initial data expected this year.

As a benchmark of sorts, the most advanced Kras inhibitors, Amgen’s sotorasib and Mirati’s MRTX849, have

shown ORRs of 37% and 45% respectively in non-small cell lung cancer. The only other tumour in which Kras inhibitors have worked so far is colorectal, so a signal in any other cancer types would be a bonus for Boehringer.

ADCs back in vogue

Beyond Kras, antibody-drug conjugates are back in vogue at the company, as demonstrated by the recent acquisition of NBE-Therapeutics (*Ror1 delivers its second takeout in five weeks, December 10, 2020*).

The deal, which could be worth up to €1.2bn ($1.5bn), gives Boehringer access to NBE's lead project, the anti-Ror1 ADC NBE-002. But, perhaps just as importantly, it also means that the German group now has its own ADC technology.

Boehringer had previously deprioritised ADCs to focus on T-cell engagers, where it has a DLL3xCD3 bispecific in phase 1. But in the background the company continued to explore ADCs "because we didn't want to miss the next-generation ADCs with significantly higher specificity than the first ones", Mr Pairet says.

After making an early investment in NBE, he adds that Boehringer came to the conclusion that the smaller group's technology could be "best in class with respect to specificity". However, this bet was based on preclinical data, so it has some way to go to prove this.

The other area that Mr Pairet highlights is cancer vaccines, where Boehringer has also struck a couple of deals in the past few years: the takeout of the oncolytic virus company Viratherapeutics in 2018, followed by the acquisition of Amal Therapeutics in 2019.

A phase 1/2 trial testing the Amal-originated ATP128, with or without Boehringer's PD-1 inhibitor BI 754091, is due to complete this year, so there could be clues soon as to whether the German company has invested wisely.

Meanwhile, projects originating at Viratherapeutics have yet to reach the clinic, but should do so this year.

However, there is no longer room for mRNA cancer vaccines. Boehringer had been evaluating this route via a 2014 deal with Curevac, but Mr Pairet says this has now been deprioritised.

Notable oncology projects in Boehringer Ingelheim's pipeline

Project	Description	Status, trial details
BI 1701963	SOS1 inhibitor	Ph1 in solid tumours +/- Mekinist, NCT04111458; ph1 in bowel cancer + irinotecan (China only, NCT04627142)
NBE-002*	Anti-Ror1 ADC	Ph1/2 in TNBC & other solid tumours, NCT04441099
ATP128**	Cancer vaccine	Ph1/2, +/- BI 754091, in colorectal cancer, NCT04046445
BI 754091	Anti-PD-1 MAb	Ph1/2, +ATP128, in colorectal cancer, NCT04046445
BI 764532	DLL3/CD3 bispecific MAb	Ph1 in SCLC & neuroendocrine tumours, NCT04429087
BI 754111	Anti-Lag3 MAb	Ph1, +/- BI 754091, in solid tumours inc NSCLC, NCT03156114
BI 1823911	Kras G12C-selective inhibitor	Preclinical

**Via acquisition of NBE-Therapeutics; **via acquisition of Amal Therapeutics. Source: Evaluate Pharma & clinicaltrials.gov.*

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