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Astra’s first attempt fails, but there’s no giving up on KRAS

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After completing a phase I study Astrazeneca discontinues development of the Ionis-partnered AZD4785.

As investors’ attention turns to the Asco meeting and Amgen and Mirati’s efforts to target the oncogene KRAS, Astrazeneca today revealed that its own first attempt to hit this apparently “undruggable” target had come to nought.

AZD4785, an anti-KRAS antisense oligonucleotide licensed from Ionis back in 2012, has been discontinued, Astra said in its first-quarter earnings call. “We had better programmes to invest in, and we’re still very much committed to KRAS as a target; we’re going at it through other approaches,” it told *Vantage* today.

Mirati bulls will take some heart from this, given that it suggests that Astrazeneca’s problem was mechanistic rather than target-related. Mirati’s MRTX1257, just like Amgen’s AMG 510, is a small-molecule inhibitor that takes advantage of a hidden groove in the KRAS G12C mutated protein that might be hit with optimal potency.

Work is still early, but AMG 510 appears to be in the lead, with Amgen at Asco set to present results on a few subjects treated in phase I, having already stated that it was looking for best-in-class activity (*Asco 2019 – not a Marker of excellence, April 18, 2019*).

Target engagement

Apart from the mechanism, a key difference was that the Amgen and Mirati projects hit mutated KRAS, while Astra/Ionis’s AZD4785 targeted the protein regardless of its mutation status. AZD4785 (previously known under the code IONIS-KRAS-2.5 Rx) had just completed its first phase I trial, but came up short.

“The molecule was safe and well tolerated,” Mene Pangalos, Astra’s vice-president of biopharmaceutical R&D, said in response to a question on this morning’s press call. “It didn’t demonstrate sufficient KRAS lowering in terms of target engagement to warrant moving it forward.”

The thinking behind the approach was that an antisense oligonucleotide complementary to a sequence in KRAS mRNA could target mutant and wild-type KRAS isoforms for degradation. A 2017 paper described preclinical data showing target knockdown after subcutaneous delivery.

The Astra/Ionis tie-up dates back to a 2012 preclinical collaboration, and in 2016 resulted in a $28m payment from the UK company when IND-enabling studies were completed. Other approaches to hitting KRAS include

an engineered T-cell receptor therapeutic originated by the NCI, licensed to Kite Pharma and now in the hands of Gilead.

Selected projects against cancers harbouring KRAS mutations				
Project	**Company**	**Mechanism**	**Status**	**Trial ID**
AMG 510	Amgen/Carmot Therapeutics	KRAS G12C inhibitor	1st in human data possible at Asco	NCT03600883
TNO155	Novartis	SHP2 inhibitor	Study in KRAS, NRAS, HRAS, BRAF or PTPN11 (SHP2) mut tumours	NCT03114319
MRTX849	Mirati (ex Array)	KRAS G12C inhibitor	Trial in KRAS G12C mut cancers started Jan 2019	NCT03785249
KRAS TCR	Gilead (ex Kite/NCI)	Anti-KRAS G12D engineered T-cell receptor	NCI trial started Apr 2019	NCT03745326
AZD4785	Astrazeneca/Ionis	KRAS antisense oligonucleotide	Discontinued after phase I	NCT03101839
ARS-1620	Araxes/Johnson & Johnson	KRAS G12C inhibitor	Preclinical	None
"Compound B"	Sanofi/X-Chem Pharmaceuticals	KRAS G12C inhibitor	Preclinical	None
Unnamed	Boehringer Ingelheim	SOS1 inhibitor	Preclinical	None
Unnamed	Mirati	KRAS G12D inhibitor	Preclinical	None
MRTX1257	Mirati	KRAS G12C inhibitor	Early pipeline lead	None

Other oncology discontinuations revealed by Astra today included the PI3k beta/delta inhibitor AZD8186 – logical given the industry's recent focus on the alpha subtype – and AZD4547, an inhibitor of FGFR, which has generated interest as a targeted approach (*Esmo 2018 – Bile duct cancer doctors herald the age of targeted therapy, October 21, 2018*).

As for KRAS, Astra has not revealed what other projects it has in development, but work is presumably still very early. The immediate focus remains on Asco and the presentation by Amgen, which claims to have identified a previously unknown pocket induced near KRAS's G12 cysteine residue.

"We are applying our learnings from G12C to explore other mutations," Phuong Khanh Morrow, Amgen's therapy area head of haematology, recently told *Vantage*.