Evaluate Vantage

September 20, 2020

Esmo 2020 – Kras cools off

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A long-awaited update from Amgen's Kras inhibitor shows waning single-agent efficacy – a situation apparently pre-empted by Mirati.

An editorial in the New England Journal of Medicine hailing the druggability at last of Kras does not alter the fact that investor expectations have likely been dashed again. The commentary relates to the latest update from Amgen's study of sotorasib, simultaneously published in the NEJM and presented at Esmo today, which offers little fresh hope to followers of this space.

It is still unclear whether Kras blockers have significant activity beyond lung cancer, and how durable any effect is. And, as if to acknowledge the limited single-agent efficacy, two other Kras players, Mirati and Boehringer Ingelheim, have moved to put their respective assets into a combo study.

The tie-up, announced on Thursday, is mechanistically intriguing. It will see Mitati's MRTX849, which like sotorasib is a Kras G12C-selective inhibitor, combined with Boehringer's BI 1701963, a SOS1/pan-Kras inhibitor said to block Kras independent of mutation type.

SOS1 is a helper protein that turns Kras from an "off" to an "on" state, but it seems questionable whether additionally blocking a specific sub-mutation can improve the efficacy of a broadly acting agent. Nevertheless, Boehringer says this is one of several combinations it is exploring with BI 1701963 to optimise its activity in broad populations.

Monotherapy

At last year's Triple (EORTC-NCI-AACR) meeting Mirati reported MRTX849 monotherapy data in 12 subjects, amounting to a 50% remission rate in NSCLC, 25% in colorectal and 0% in appendiceal tumours.

This pretty much mirrors what Amgen is seeing with sotorasib, though in a larger dataset. At a previous update at Asco, sotorasib's Codebreak-100 study comprised 55 evaluable subjects given the target 960mg once-daily dose.

At Esmo today there was little more to get enthusiastic about. Among an additional 11 NSCLC subjects given the target dose there has been just one more partial remission, so the ORR falls from 48% to 32%.

Meanwhile, in colorectal cancer the dataset has more than doubled to 25 subjects, and with two more PRs the remission rate creeps up from 8% to 12%. And additional isolated responses have now been seen in pancreatic and endometrial cancers and melanoma, adding to the appendiceal tumour PR already reported.

Amgen's latest sotorasib update (Codebreak-100 study)		
	At target dose (960mg once daily)	**All doses (180-360mg)**
NSCLC	12/34 PRs (35% ORR)	19/59 PRs (32% ORR)
Colorectal cancer	3/25 PRs (12% ORR)	3/42 PRs (7% ORR)
Other tumours	1 PR each in pancreatic, endometrial, appendiceal & melanoma, out of 28 additional subjects	
Source: NEJM & Esmo. PR=partial remission; ORR=overall response rate.		

The study authors wrote that a 35% response rate among NSCLC subjects was “particularly promising”, but some will undoubtedly note the waning of sotorasib’s efficacy as the dataset has grown.

And lack of durability in some patients, highlighted previously, remains an issue. Median response duration was 10.9 months across all responders, but some patients had disease progression shortly after an initial remission.

“Rapid progression might suggest a high degree of tumour heterogeneity…or an early adaptation to treatment, as reported in a preclinical study with a precursor inhibitor,” they wrote in the NEJM.

The editorial hails the study as very encouraging, showing the first step in “drugging the undruggable. Clinical inhibition of this previously untouchable target is now possible.” Mirati, for instance, is now valued at $7.3bn, so some might have been hoping for much more.