Evaluate Vantage

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Why ipatasertib is not the Akt Astra wants to follow

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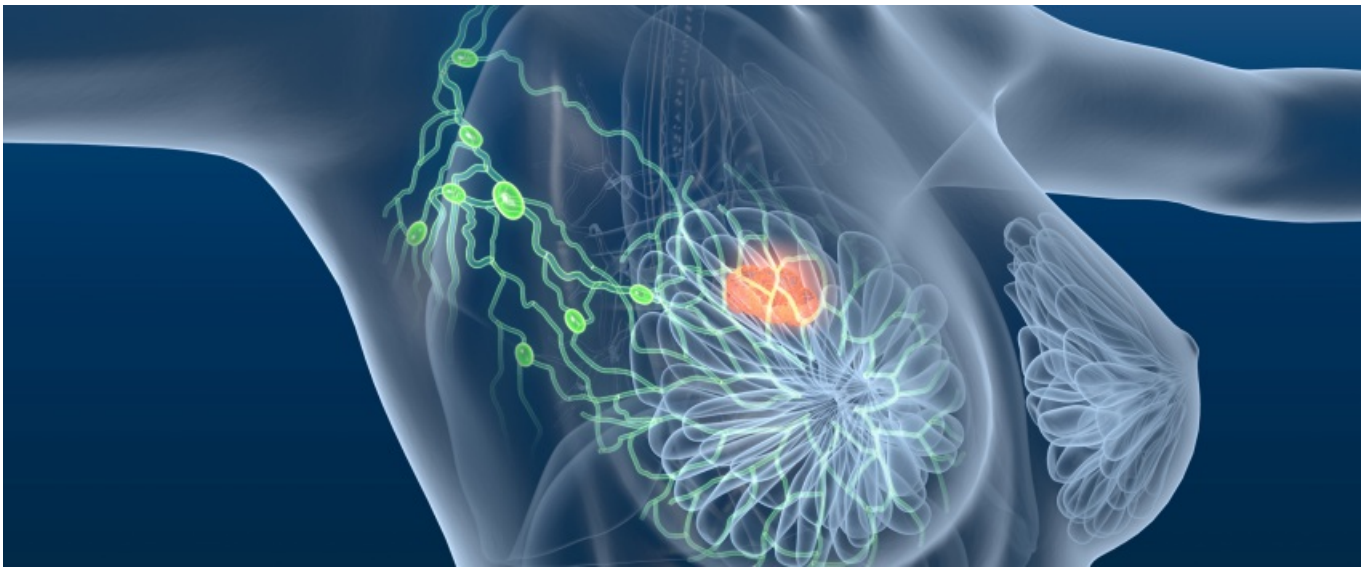

The repeated failure of Roche's ipatasertib increases the risk for Astrazeneca's rival Akt inhibitor capivasertib.

Buried deep within Roche's fourth-quarter slide deck today is news of another failure for the Akt inhibitor ipatasertib, this time in the triple-negative breast cancer trial Ipatunity-170. Until recently the Swiss group had touted the asset, licensed from Array, as a hot pipeline prospect.

Ipatunity-170's failure comes shortly after the disastrous result of Ipatunity-130 in a slightly different breast cancer setting last year (*Esmo 2020 – ipatasertib Akts up, September 18, 2020*). If Astrazeneca is now eyeing these developments nervously you can hardly blame it: it has an Akt inhibitor of its own, capivasertib, whose three pivotal studies start reading out next year.

Roche is not giving up on ipatasertib, but 2026 sellside consensus revenues of $716m, compiled by *EvaluatePharma*, are surely now in doubt. The project scored a technical success in front-line prostate cancer, but this was only in patients with PTEN-altered tumours; with no prospect of widespread screening for this gene the result appears irrelevant.

Meanwhile, breast cancer appears to be a dead end, both in the PTEN-altered setting of Ipatunity-130, and in all-comers in combination with Tecentriq and chemo, as tested in Ipatunity-170. Thus ipatasertib's one remaining pivotal trial, Ipatunity-150, in front-line hormone receptor-positive breast cancer, looks a long shot, even though Roche still expects it to yield a 2023 filing.

Duel of the Roche and Astra Akt inhibitors				
Trial	**Setting**	**Design**	**Primary**	**Result**
Ipatasertib				
Ipatential-150	1L castration-resistant prostate cancer	+Zytiga vs Zytiga	PFS in PTEN-altered & all-comers	Success in PTEN-altered, fail in all-comers
Ipatunity-130	1L TNBC & HR+/Her2- breast cancer	+paclitaxel vs paclitaxel	PFS in PTEN-altered	Fail in both cohorts
Ipatunity-170	1L TNBC	+paclitaxel+/-Tecentriq vs paclitaxel+/-Tecentriq	PFS & OS in PD-L1+ & PD-L1-	Fail
Ipatunity-150	1L HR+/Her2- breast cancer	+fulvestrant+Ibrance vs fulvestrant+Ibrance	PFS in PTEN-altered & all-comers	Ends 2023
Capivasertib				
CAPItello-290	1L TNBC	+paclitaxel vs paclitaxel	PFS & OS (all-comers)	Ends 2022
CAPItello-291	2L HR+/Her2- breast cancer	+fulvestrant vs fulvestrant	PFS (all-comers)	Ends 2022
CAPItello-281	Hormone-sensitive prostate cancer	+Zytiga vs Zytiga	rPFS in PTEN-altered	Ends 2024
Source: company presentations & clinicaltrials.gov.				

So where does this leave Astrazeneca? Its capivasertib is the industry's next most advanced Akt inhibitor, and its three pivotal trials are also in breast and prostate cancers.

But there are some differences versus the Roche programme. Astra's TNBC trial has no PD-(L)1 blockade, while hormone-sensitive breast cancer subjects are second line or later, and neither study preselects for PTEN alteration, the mutation that preclinically has been shown to confer sensitivity to Akt inhibition.

There is preselection for PTEN in Capitello-281, a trial in prostate cancer, but this is in the hormone-sensitive setting, whereas Roche's Ipatential-150 looked at castration-resistant disease. Preclinical work had revealed some differences between the Roche and Astra projects.

More disappointment

Coincidentally, a separate oncology mechanism in which Roche and Astra had been active moved closer to the scrapheap yesterday, namely Ox40 inhibition.

This had once been a highly touted immune checkpoint, but yesterday Glaxosmithkline discontinued its contender, GSK3174998, citing lack of efficacy.

This is somewhat embarrassing for Glaxo, which had committed to this asset in July 2017, just one day after Roche had dropped the similarly acting RG7888.

A sign of the promise that once lay in Ox40 blockade is that at one point Astra's pipeline had boasted not one but three such molecules. But one by one these bit the dust; the last, the humanised antibody MEDI0562, remains in two academic-sponsored studies, but no longer appears in Astra's pipeline list.

Selected Ox40 inhibitors			
Project	**Company**	**Type**	**Status**
MEDI6469	Astrazeneca	Murine MAb	Discontinued pre 2017
MEDI6383	Astrazeneca	Fusion protein	Discontinued pre 2017
RG7888	Roche	Humanised MAb	Discontinued 2017
MEDI0562	Astrazeneca	Humanised MAb	Last Astra trial ended 2019; no longer in pipeline
GSK3174998	Glaxosmithkline	Humanised MAb	Discontinued 2021
Source: company information.			