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Seeking alpha in PI3K inhibition

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Novartis hails the most advanced alpha-directed PI3K inhibitor after success in breast cancer, but it's not the only one.

It seems like the PI3K mechanism has received the last rites several times now, but nevertheless it refuses to die. And Novartis's success last week with alpelisib in the pivotal Solar-1 trial renewed hope that the approach could have promise against breast cancer.

Of course, it is all about specificity now, and it is thought that in certain uses it is the alpha subtype of the kinase that needs to be targeted. The Swiss firm says alpelisib is "the only alpha-specific PI3K inhibitor" – a claim that an analysis of the competitor pipeline reveals to be incorrect.

In fact, alpelisib is one of four alpha-specific PI3Ks in clinical trials. These are TAK-117, a phase II agent from Takeda, and two phase I assets: Shanghai Haihe Pharmaceutical's HH-CYH33, which is in a Chinese trial listed on Clinicaltrials.gov, and RG6114 from Roche.

The industry pipeline also includes a further two agents specific for the alpha as well as the beta isoform: Bayer's BAY1082439 recently completed phase I for unspecified advanced cancers, while Onconova's preclinical ON 146040 is up for licensing out as the company focuses on rigosertib.

Selected PI3K inhibitors with activity on the alpha isoform				
Project	**Pharmacology target(s)**	**Company**	**Primary focus**	**Trial ID**
Phase III				
BYL719/alpelisib	PI3K alpha inhibitor	Novartis	Breast cancer	NCT02437318
Phase II				
TAK-117	PI3K alpha inhibitor	Takeda	Breast cancer	NCT03193853
Phase I				
GDC-0077/ RG6114	PI3K alpha inhibitor	Roche	Solid cancers incl breast	NCT03006172
HH-CYH33	PI3K alpha inhibitor	Shanghai Haihe Pharmaceutical	Oesophageal	NCT03544905
BAY1082439	PI3K alpha & beta inhibitor	Bayer	"Advanced cancer"	NCT01728311
Preclinical				
ON 146040	PI3K alpha & beta inhibitor	Onconova Therapeutics	Not specified	NA

While the Novartis claim is thus wrong, the company is correct in stating that alpelisib is the first alpha-specific PI3K inhibitor to show a potential benefit with acceptable tolerability.

Roche's taselisib illustrated why lack of specificity is problematic. The asset initially showed promise in the phase II Lorelei trial in ER-positive/Her2-negative breast cancer; though the effect was borderline it was driven by subjects carrying PIK3CA mutant cancer cells, supporting the mechanistic rationale for hitting the alpha isoform (*Esmo 2017 – Roche's Lorelei gives PI3K agents another second chance, September 8, 2017*).

However, it all went wrong at Asco, when taselisib's Sandpiper trial showed very modest efficacy. Roche blamed an unacceptable level of toxicity on the fact that the compound also hit delta and gamma subtypes. Taselisib was subsequently abandoned in favour of the more targeted RG6114.

Setbacks

Novartis too has had its setbacks, studying numerous PI3K inhibitors over the years. For instance, buparlisib, a pan-PI3K inhibitor, flunked breast cancer trials but is still in the clinic in haematology.

Its most advanced asset, however, is alpelisib, and the design of Solar-1 shows that lessons from Roche are being learned. The trial specifically recruited HR-positive/Her2-negative breast cancer patients who had PIK3CA mutations, which Novartis says drive some 30% of HR-positive breast cancers.

The full Solar-1 data have not been revealed, and all Novartis disclosed last week was that the trial met its primary endpoint of progression-free survival, with side effects "generally consistent" with previous studies. The group says the data are strong enough for it to begin regulatory filing discussions.

In the meantime, others focused on this mechanism will have to wait a little longer: TAK-117 is being studied in triple-negative breast cancer in combination with sapanisertib, a Torc1/2 inhibitor, but this trial will not read out for a couple of years, a similar timeframe to phase I studies of HH-CYH33 and RG6114.

It has been quite a journey from the disappointing launch of Gilead's idelalisib, a delta-specific agent with effects on B-cell signalling, through Infinity's sale of develisib to Verastem, to the current interest in the alpha isoform.

Novartis says mutations in beta, delta and gamma PI3K subtypes are not normally associated with breast cancer. It will be hoping that with alpelisib a therapeutic window has been found at last.

Other clinical-stage PI3K inhibitors			
Project	**Pharmacology target(s)**	**Company**	**Primary focus**
Marketed			
Zydelig/idelalisib	PI3K delta inhibitor	Gilead Sciences	CLL
Aliqopa/copanlisib	Pan-PI3K inhibitor	Bayer	NHL
Filed			
Duvelisib	PI3K delta & gamma inhibitor	Verastem (ex Infinity)	CLL & NHL
Phase III			
TGR-1202/umbralisib	PI3K delta inhibitor	TG Therapeutics	CLL
CDZ173/leniolisib	PI3K delta inhibitor	Novartis	Non-oncology uses
Phase II			
INCB050465	PI3K delta inhibitor	Incyte	NHL
ACP-319	PI3K delta inhibitor	Acerta Pharma	NHL
Nemiralisib	PI3K delta inhibitor	Glaxosmithkline	COPD
Buparlisib	Pan-PI3K inhibitor	Novartis	CLL (disc for breast cancer)
GDC-0084	Pan-PI3K inhibitor	Kazia Therapeutics (ex Roche)	Glioblastoma multiforme
Phase I			
GSK2636771	PI3K beta inhibitor	Glaxosmithkline	Prostate cancer
KA2237	PI3K beta & delta inhibitor	Karus Therapeutics	B-cell cancers
GSK2292767	PI3K delta inhibitor	Glaxosmithkline	Not specified
HMPL-689	PI3K delta inhibitor	Hutchison China Meditech	B-cell cancers
Tenalisib	PI3K delta & gamma inhibitor	Rhizen Pharmaceuticals	NHL
IPI-549	PI3K gamma inhibitor	Infinity/Takeda	Solid tumours
PA799	Pan-PI3K inhibitor	Menarini (ex Chugai)	Solid tumours
Source: EvaluatePharma.			

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