Evaluate Vantage

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What next for developers seeking to emulate Zydelig?

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When Gilead’s Zydelig bombed commercially the writing was pretty much on the wall for PI3K inhibitors in haematological cancers, and yet the class continued to attract biotech dollars. So yesterday’s US adcom vote – 16 to none in favour of randomised data and against accelerated approvals based on uncontrolled trials – is another black mark against this approach, now widely recognised as being toxic. Some PI3K developers already saw this coming: Incyte discontinued parsaclisib, MEI Pharma’s zandelisib was hit by an FDA request for a phase 3 study, while TG Therapeutics’ Ukoniq was pulled from the market. What about the remaining PI3K assets in haematology? Zydelig remains marketed in its fully approved indication, as does Verastem’s Copiktra. Bayer’s Aliqopa clings on to an accelerated green light, its future resting on September's outcome of the confirmatory Chronos-4 trial. As for development-stage projects, Hutchmed’s amdizalisib, Shanghai Yingli's linperlisib and Rhizen’s tenalisib must surely now be considered no hopers, given that their ongoing lymphoma studies are uncontrolled. Some will also see in this class review another example of the FDA tightening its stance in general, though a recent *Vantage* analysis found that accelerated approvals were being converted increasingly quickly.

Selected PI3K inhibitors in haematological cancers				
Company	**Project**	**Pharmacology**	**Indication**	**Status**
Marketed				
Gilead Sciences	Zydelig	PI3K delta	2nd-line CLL (Rituxan combo)	Full approval Jul 2014, PFS benefit vs Rituxan
			3rd-line FL & SLL	Accelerated approval Jul 2014; withdrawn Jan 2022
Bayer	Aliqopa	Pan-PI3K	3rd-line FL	Accelerated approval Sep 2017; confirmatory Chronos-4 trial reads out Sep 2022
			2nd-line indolent NHL (Rituxan combo)	Filed May 2021, withdrawn Dec 2021
Verastem (ex Infinity)	Copiktra	PI3K delta & gamma	3rd-line CLL & SLL	Full approval Sep 2018, PFS benefit vs Arzerra
			3rd-line FL	Accelerated approval Sep 2018, withdrawn Dec 2021
Withdrawn/discontinued				
TG Therapeutics (ex Rhizen)	Ukoniq	PI3K delta	2nd-line MZL & 4th-line FL	Accelerated approval Feb 2021, withdrawn Apr 2022
Incyte	Parsaclisib	PI3K delta	3rd-line+ FL & others	Discontinued Jan 2022
Phase 3				
MEI Pharma/ Kyowa Kirin	Zandelisib	PI3K delta	3rd-line+ FL	FDA "discouraged" accelerated approval filing in Mar 2022; randomised Coastal trial reads out 2024
Phase 2				
Rhizen Pharmaceuticals	Tenalisib	PI3K delta & gamma	PTCL (chemo combo)	Uncontrolled study; NHL trials completed, cHL terminated
Hutchmed	Amdizalisib	PI3K delta	r/r MZL & FL	Uncontrolled study
Shanghai Yingli	Linperlisib	PI3K delta	T/NK cell lymphoma	Uncontrolled study
Phase 1				
Beigene	BGB-10188	PI3K delta	B-cell cancers	Early trial of monoRx or combos
Ionctura	IOA-244	PI3K delta	NHL	Early trial of monoRx or chemo combo
Acerta (Astrazeneca)	ACP-319	PI3K delta	NHL (Calquence combo)	Not in Astra's pipeline
Karus Therapeutics	KA2237	PI3K beta & delta	B-cell cancers	Under review by potential Chinese licensor; financial compensation "modest"

FL=follicular lymphoma; MZL=marginal zone lymphoma; SLL=small lymphocytic leukaemia. CLL=chronic lymphoblastic leukaemia; NHL=non-Hodgkin's lymphoma; PTCL=peripheral T-cell lymphoma. Source: Evaluate Pharma & company communications.

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