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Accelerated filing delay could be the least of Epizyme's problems

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Until yesterday Epizyme's lead project, tazemetostat, had a chance to become one of next year's biggest drug launches. US clinical hold, prompted by a secondary lymphoma seen in a paediatric trial subject, takes this off the table given that the 2018 accelerated filing Epizyme had been gunning for is now highly unlikely.

Still, this is not the company's biggest problem, as judging by the FDA's recent track record a best-case scenario has a three-month delay before enrolment can resume. The bigger question is what the US hold implies about the rest of Epizyme's strategy – especially as this is not the first time this problem has been encountered (see tables below).

This broader fear was reflected in Epizyme's share price, which this morning fell 14%. Of course, the company tried to put a brave face on things, stressing that secondary lymphomas are known to be associated with many therapies, that this was the first case seen in over 750 tazemetostat-treated subjects, and that the dose tested was higher than that used in other phase II trials.

However, a 2016 filing with the US SEC states that an earlier preclinical safety study had revealed the development of lymphoma in Sprague Dawley rats in which tazemetostat was being tested. This prevented Epizyme from starting a US phase II trial in lymphoma until early 2017 – over a year after an IND had been submitted.

Investigation

The precise nature of the secondary T-cell lymphoma incident will now have to be investigated in depth. Such lymphomas are the result of a primary malignancy spreading from its original site into the lymphatic system.

The clinical subject in question had been enrolled into Epizyme's phase I childhood sarcoma study, and had an advanced, poorly differentiated chordoma, a rare type of cancer. Existing patients can continue to receive tazemetostat, but no new subjects can be enrolled into any US study – and that affects nine trials.

Actively recruiting US tazemetostat clinical trials			
Indication	**Details**	**Trial ID**	**Note**
INI1-ve tumours or synovial sarcoma	Monotherapy, adults	NCT02601950	US, Europe & others
INI1-ve tumours or synovial sarcoma	Monotherapy, paediatric*	NCT02601937	US, Europe & others
Molecularly targeted tumours incl NHL	Paediatric Match monotherapy trial	NCT03213665	US (NCI) study
Molecularly targeted tumours incl NHL	Paediatric Match screening trial	NCT03155620	US (NCI) study
Lymphomas & solid tumors	Adults, monotherapy in solid tumours/B-cell lymphomas, prednisone combo in DLBCL	NCT01897571	US, Europe & others
NSCLC	NSCLC, Tecentriq + tazemetostat	NCT03337698	US, Europe & others
Ovarian, peritoneal or endometrial cancers	Monotherapy, adults	NCT03348631	US (NCI) study
Various	Trust rollover trial, monotherapy, adults	NCT02875548	US & Europe study
Various	CYP3A inhibitor interaction trial	NCT03028103	US
**Study in which secondary lymphoma was seen. Source: Clinicaltrials.gov.*			

Tazemetostat is designed to inhibit the methyltransferase EZH2 and thus affect gene expression via the process known as epigenetics. Before yesterday's clinical hold sellside consensus for 2022 sales stood at $895m, according to *EvaluatePharma*.

So far Epizyme was to have used an adult phase II trial as the basis for a fourth-quarter accelerated US filing for epithelioid sarcoma, leading to launch in 2019. The bigger indication was to come later: a filing in follicular lymphoma, based on a phase II monotherapy trial, was to be made next year, though separately there had been doubts about tazemetostat's standalone efficacy.

It might be too soon to suggest that the adverse event was related to tazemetostat's mechanism, though a link between EZH2 and lymphoma has separately been made preclinically. Competing companies looking at EZH2 inhibition should pay very close attention to the findings of any investigation; these include the private group Constellation Pharmaceuticals, which has a deal with Roche.

And Epizyme should consider any link with other epigenetic mechanisms, purely as a precaution. The company's pipeline includes the DOT1L inhibitor pinometostat and a protein arginine methyltransferase 5 inhibitor project in partnership with Glaxosmithkline.

As ever, the sellside remains bullish: Leerink analysts today called the US hold a "minor setback", said they expected studies to resume "in a matter of weeks", and stressed that EU enrolment remained unaffected. The markets, for now, seem unconvinced.

EZH inhibitor pipeline				
Project	**Company**	**Mechanism**	**Indication(s)**	**Trial ID**
Phase II				
Tazemetostat	Epizyme/Eisai	EZH 2 chromatin inhibitor	See above	See above
CPI-1205	Constellation/Roche	EZH 2 chromatin inhibitor	Prostate cancer, B-cell lymphomas	NCT03480646, NCT02395601
Phase I				
DS-3201	Daiichi Sankyo	EZH 1 & 2 inhibitor	Lymphomas, AML, ALL	NCT02732275, NCT03110354
Preclinical				
EZH2-EED inhibitor project	Oncofusion Therapeutics	EZH 2 & EED inhibitor	Solid tumours	NA
KM301	Kainos Medicine	EZH 2 inhibitor	Non-Hodgkin's lymphoma	NA
KMT EZH2 Target	Domainex	MLL2 enhancer of EZH2 inhibitor	General cancers	NA
Source: EvaluatePharma.				

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