Table 1 | Selected EZH2 inhibitors in clinical development

Company	Small-molecule agent	Indications	Stage
Epizyme	Tazverik (tazemetostat)	Epithelioid sarcoma	FDA approved (January 2020)
		Follicular lymphoma	FDA approved (June 2020)
		Mesothelioma	Phase 2
		Diffuse large B-cell lymphoma	Phase 2
		Pediatric rhabdoid tumors	Phase 1
Daiichi Sankyo (Tokyo)	Valemetostat (dual EZH1/EZH2 inhibitor)	Adult T-cell leukemia or lymphoma	Pivotal phase 2
		Prostate cancer (with ipilimumab)	Phase 1
Constellation Pharmaceuticals	CPI-1205	Prostate cancer	Phase 1b/2 complete
	CPI-0209	Solid tumors	Phase 1
Jiangsu Hengrui (Lianyungang, China)	SHR2554	Prostate cancer	Phase 1/2
		Blood cancers	Phase 1
Pfizer	PF-06821497	Follicular lymphoma, diffuse large B-cell lymphoma, prostate cancer, small-cell lung cancer	Phase 1

EZH2 drug resistance in lymphoma is also a puzzle. Later-stage tumors, under the pressure of therapy, may develop clones that can tolerate the loss of EZH2, says Melnick. As a result, Epizyme is now supporting an investigator-sponsored clinical trial to test Tazverik together with chemotherapy as frontline treatment for lymphoma.

How to best combine EZH2 inhibitors with other drugs, however, is unknown. Several companies are combining with standard androgen signaling inhibitors in prostate cancer, in part based on the ability of EZH2 inhibitors to reverse resistance to antiandrogen drugs in cells. A series of recent papers have also implicated EZH2 mutation and overexpression in immune dysfunction, including impaired antigen presentation and skewing of the T cell response. That's part of the rationale for a new trial at MD Anderson Cancer Center, combining the Daiichi Sankyo dual EZH1/EZH2 inhibitor valemetostat with the immune checkpoint blocker Yervoy (ipilimumab) in bladder, renal and prostate cancer.

There is also room for improvement in the drugs themselves. Constellation Pharmaceuticals began EZH2 drug discovery back around 2009. "This was by far not a trivial undertaking, not for us and not for anyone in the field," says CSO Patrick Trojer. Like other methyltransferases, EZH2 obtains the methyl group from the compound *S*-adenosylmethionine (SAM), and most EZH2 inhibitors block EZH2 by out-competing SAM for binding, thus preventing transfer of the methyl group to the histone substrate. These EZH2 inhibitors all contain the same core motif, which binds the SAM pocket and is critical for drug potency. But the core also impairs drug solubility. GlaxoSmithKline dropped its EZH2 inhibitor in 2017 after phase 1 due to short plasma half-life. Companies including Epizyme optimized their compounds with good results, but many continue to fashion new ones with better properties. Constellation recently scrapped phase 3 plans for its EZH2 inhibitor, instead prioritizing a second-generation compound with "best in class potential," says Trojer, because it stays bound to its target for much longer time.

The upshot of Tazverik's lymphoma approval is that it should boost company and investor interest in epigenetics. But there are pitfalls. BET bromodomain inhibitors, which target 'reader' proteins that recognize histone marks, are a good example. There are specificity issues when targeting histone readers. "My impression of these compounds is that they are somewhat unselective and toxic to cells," says Melnick. Single-agent clinical trial results overall have been disappointing. Overinterpretation of preclinical experiments using high drug concentrations may be one reason, says Trojer.

Constellation's BET bromodomain inhibitor program is moving forward because the company eventually found a tumor type, myelofibrosis, highly sensitive to the drug. But Constellation has now decided to advance only those agents

Intercept's NASH hopes dashed

The FDA has rejected Intercept Pharmaceuticals' obeticholic acid for nonalcoholic steatohepatitis (NASH), another disappointment for a crowded field littered with failures.

Obeticholic acid, a farnesoid X receptor agonist, was aiming to become the first drug for NASH, a potentially fatal disease characterized by fat accumulation, inflammation and fibrosis in the liver. A 1,968-patient phase 3 trial of obeticholic acid reported encouraging, if modest, results: 18–23% of treated patients experienced an improvement in fibrosis, as measured histologically on biopsy, compared with 12% of patients on placebo. On another primary endpoint, NASH resolution, there was no statistically significant difference. A 2018 FDA draft guidance on NASH recommended that sponsors consider improvement in fibrosis as one of three suggested efficacy endpoints for pivotal trials in this setting. The guidance also noted that, of the histologic features of NASH, "fibrosis is the strongest predictor of adverse clinical outcomes."

The FDA has now rejected obeticholic acid, reportedly deciding that the drug's predicted benefit, based on the surrogate histopathologic fibrosis endpoint, remains uncertain and does not sufficiently outweigh its risks. "On behalf of the hepatology community, we are very concerned that the agency's apparently still evolving expectations will make it exceedingly challenging to bring innovative therapies to NASH patients with high unmet medical need," says Intercept CEO Mark Pruzanski. Intercept will meet with the FDA to discuss next steps.

Separately, a phase 2a trial of Akero Therapeutics' efruxifermin is offering hope. The company announced in March that its FGF21 (fibroblast growth factor 21) mimetic met its primary endpoint in this trial, reducing hepatic fat as measured by MRI. On 30 June, an exploratory efficacy analysis of end-of-treatment histological results in a subset of 40 patients whose disease responded is now bolstering enthusiasm. 48% of these patients experienced NASH resolution without worsening of fibrosis, and 48% experienced fibrosis improvement without worsening of NASH. Akero plans to start a phase 2b/3 trial of efruxifermin in 2021.

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