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ADISINSIGHT REPORT

Tazemetostat: First Approval

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Abstract
Tazemetostat (Tazverik™), a first-in-class, small molecule enhancer of zeste homolog 2 (EZH2) inhibitor, received accelerated approval in January 2020 in the USA for the treatment of adults and adolescents aged ≥ 16 years with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection. Developed by Epizyme, in collaboration with Eisai, it is the first therapy to be approved specifically for the treatment of epithelioid sarcoma in the USA. The recommended dosage regimen is 800 mg twice daily, administered orally with or without food, until disease progression or unacceptable toxicity. Tazemetostat is also undergoing clinical development in various countries worldwide for use in several other tumour types, including diffuse large B-cell lymphoma and mesothelioma, with the US FDA accepting a New Drug Application and granting priority review for its use in the treatment of follicular lymphoma. This article summarizes the milestones in the development of tazemetostat leading to this first approval for the treatment of adults and adolescents aged ≥ 16 years with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection.

Tazemetostat (Tazverik™): Key points

A first-in-class EZH2 inhibitor developed by Epizyme, in collaboration with Eisai, for the treatment of epithelioid sarcoma

Received its first approval on 23 January 2020 in the USA

Approved for the treatment of adults and adolescents aged ≥ 16 years with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection

1 Introduction

The modification of histone proteins (which organize DNA into nucleosomes) plays a key role in both normal cell function and tumourigenesis [1, 2]. Indeed, the mutation or overexpression of the histone methyltransferase enhancer of zeste homolog 2 (EZH2) has been identified in various tumours (e.g. gain-in-function mutations in lymphomas, loss-of-function mutations in myeloid malignancies and overexpression in epithelial malignancies), making EZH2 a potential therapeutic target [1, 3].

Tazemetostat (Tazverik™) is an oral, first-in-class inhibitor of EZH2 developed by Epizyme, in collaboration with Eisai [4, 5]. It is the first therapy to be approved (in January 2020) specifically for the treatment of epithelioid sarcoma in the USA, where it is indicated in adults and adolescents aged ≥ 16 years with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection [6–8]. This was an accelerated approval based on the results of a cohort of patients with locally advanced or metastatic epithelioid sarcoma participating in a multinational, phase II study [NCT02601950 (EZH-202)] [6] (see Sect. 2.3). The recommended dosage regimen of tazemetostat is 800 mg twice daily, administered orally with or without food, until disease progression or unacceptable toxicity [8]. Local prescribing information should be consulted for information regarding dose modifications for the management of adverse events and drug interactions [8].

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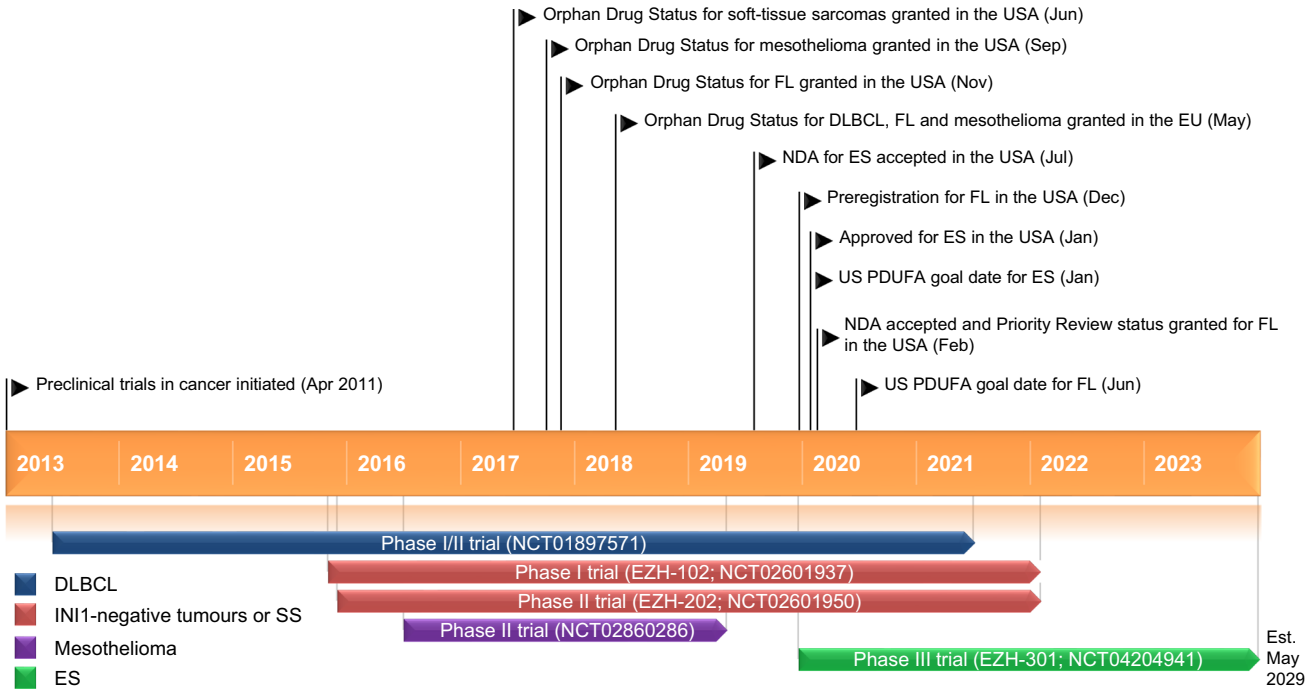


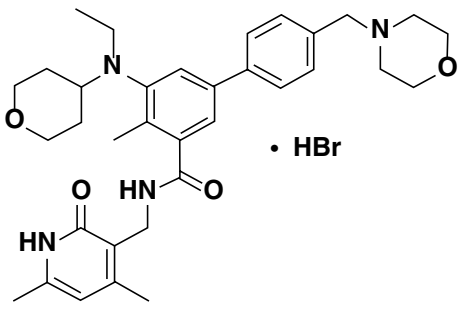
Key milestones in the development of tazemetostat, focussing on epithelioid sarcoma. *DLBCL* diffuse large B-cell lymphoma, *ES* epithelioid sarcoma, *Est* estimated, *FL* follicular lymphoma, *INI1* integrase interactor 1, *NDA* New Drug Application, *PDUFA* Prescription Drug User Fee Act, *SS* synovial sarcoma

In February 2020, the US FDA accepted the New Drug Application and granted priority review for tazemetostat in the treatment of follicular lymphoma (FL) [9]. Tazemetostat received orphan designation for the treatment of soft-tissue sarcoma in June 2017, mesothelioma in September 2017 and FL in November 2017 in the USA [10], and for the treatment of diffuse large B-cell lymphoma (DLBCL) [11], FL [12] and mesothelioma [13] in May 2018 in the EU. It is also undergoing clinical development in various countries worldwide for use in several other tumour types, including metastatic castration-resistant prostate cancer [14].

1.1 Company Agreements

In March 2011, Epizyme and Eisai entered into a worldwide partnership to discover, develop and commercialise EZH2-targeting therapeutics for the treatment of patients with lymphoma and other cancers [15]. In March 2015, Epizyme reacquired the global rights to its EZH2 programme, including tazemetostat, from Eisai [5]. Under the terms of the agreement, Epizyme is responsible for development, manufacturing and commercialisation in all countries outside Japan, with Eisai retaining the rights and funding development in Japan. Eisai also has a limited right of first negotiation for rights in Asia if Epizyme decides to license those rights to a third party [5].

In June 2016, Epizyme and Genentech entered into a collaboration agreement to evaluate the antitumour efficacy of tazemetostat in combination with atezolizumab (an anti-programmed death ligand 1 cancer immunotherapy) in patients with relapsed or refractory DLBCL [the most common form of non-Hodgkin's lymphoma (NHL)] [16]. Under the terms of the agreement, study operations for the phase Ib trial are to be managed by Genentech [16]. In June 2017, the two companies expanded this collaboration in order to assess the combination of tazemetostat and atezolizumab in patients with relapsed/refractory metastatic non-small cell lung cancer [17]. Although financial terms were not disclosed, Genentech will be sponsoring the phase Ib/II trial



Chemical structure of tazemetostat

and Epizyme will retain global development and commercialisation rights to tazemetostat [17].

In October 2016, Epizyme and the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) entered into a Cooperative Research and Development Agreement to evaluate the efficacy and safety of tazemetostat in patients with haematological malignancies and solid tumours [18]. Under the terms of the agreement, the NCI will predominantly fund the studies and manage the study operations [18].

In November 2019, Epizyme established several funding agreements with Royalty Pharma for up to US$270 million in order to support the commercialisation and pipeline advancement of tazemetostat [19]. In January 2020, it exercised its prespecified option to sell US$50 million of its common stock to Royalty Pharma [4].

2 Scientific Summary

2.1 Pharmacodynamics

EZH2 is the catalytic subunit of polycomb repressive complex 2 (PRC2); it mediates the mono-, di-, and trimethylation of histone H3 lysine 27 (H3K27) by PRC2, with trimethylation repressing target gene transcription [8, 20]. Aberrations in EZH2 itself or components [e.g. integrase interactor 1 (INI1), with the loss of INI1 expression seen in various tumour types, including epithelioid sarcomas and those with rhabdoid morphology [21]] of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex (which antagonises PRC2 function) can result in abnormal EZH2 expression or activity and subsequently an oncogenic dependence on EZH2 [3, 8], while inhibiting PRC2 has been shown to decrease cell survival and tumour growth in various cancers [20].

Tazemetostat is an EZH2 inhibitor (inhibitory constant against wild-type EZH2 of 2.5 nmol/L) [8, 22]. It has also shown inhibitory activity against EZH1, albeit at a half-maximal inhibitory concentration (of 392 nmol/L) approximately 36-fold higher than that for EZH2 [8]. In vitro, tazemetostat inhibited the trimethylation of H3K27 (in a concentration-dependent manner) [22, 23] and exhibited antitumour activity [22–25]. Antitumour activity has also been displayed in various murine xenograft models, including SMARCB1-mutant malignant rhabdoid tumour (MRT) [22], mutated EZH2 NHL [23] and SMARCA2- and SMARCA4-deficient small cell carcinoma of the ovary hypercalcaemic type (SCCOHT) [24]. The benefit of combining tazemetostat with other agents has been assessed in preclinical studies, with tazemetostat demonstrating synergistic effects in combination with B-cell receptor pathway modulators, glucocorticoid receptor agonists, immunomodulatory agents or venetoclax in mantle cell lymphoma cell lines [26], abiraterone or enzalutamide in prostate cancer cell lines and a murine xenograft model of prostate cancer [25], and mitogen-activated protein kinase inhibitors in $BRAF^{V600E}$-mutant papillary thyroid cancer cell lines [27].

In a skin punch biopsy analysis of 32 adults with relapsed or refractory B-cell NHL or advanced solid tumours participating in the phase I part of a phase I/II study (NCT01897571) [see Sect. 2.3], tazemetostat demonstrated dose-dependent reductions in trimethylated H3K27 over the 100–800 mg twice daily dosage range [28]. Reductions in trimethylated H3K27 were predicted to be > 80% of the maximum effect at the observed mean area under the concentration–time curve (AUC) from time 0–12 h (AUC_{12}) value on day 15 in the 800 mg twice daily dosage cohort, suggesting that target inhibition of the skin was near maximum at this dosage. Doubling the dosage (to 1600 mg twice daily) resulted in only a small incremental increase in the inhibition of H3K27 trimethylation and was associated with a dose-limiting toxicity (grade 4 thrombocytopenia) in one patient. Following a composite evaluation of pharmacodynamics, pharmacokinetics, efficacy and adverse events, the recommended dosage of tazemetostat was determined to be 800 mg twice daily. In this part of the study, a paired tumour biopsy analysis found that 75% of four patients with solid tumours experienced target inhibition of EZH2-mediated histone methylation in tumour tissue at week 4 compared with baseline. Moreover, in a molecular analysis of one patient with an INI1-negative solid tumour who experienced disease progression, RNA sequencing indicated a fourfold reduction from baseline in *EZH2* expression and the differential expression of several known SWI/SNF complex and *EZH2* target genes following treatment with tazemetostat. A specific resistant *EZH2* mutation was not found on exome sequencing [28].

Neither tazemetostat nor its metabolite EPZ-6930 (see Sect. 2.2) were associated with mean increases of > 20 ms in the corrected QT (QTc) interval in patients with advanced malignancies receiving oral tazemetostat 800 mg twice daily (i.e. the recommended dosage; see Sect. 1) for 15 days [8]. The largest mean increases in the QTc interval at therapeutic and supratherapeutic (1600 mg twice daily) dosages were 6.1 and 9.3 ms [8].

2.2 Pharmacokinetics

Tazemetostat displays time-dependent pharmacokinetics and has a mean absolute oral bioavailability of approximately 33% [8]. Twice-daily oral tazemetostat exhibited approximately dose proportional increases in AUC_{12} and maximum concentration (C_{max}) values over a 200–1600 mg dose range (0.25- to 2-fold the recommended dosage; see Sect. 1) in the phase I part of the phase I/II study (NCT01897571) [see

Sect. 2.3] in 38 adults with relapsed or refractory B-cell NHL or advanced solid tumours [8, 28]. Food has no substantial effect on tazemetostat exposure (see Sect. 1), with the C_{max} of tazemetostat reached in a median of 1–2 h [8]. Steady state was reached by day 15 with oral tazemetostat 800 mg twice daily therapy, and the mean accumulation ratio was 0.58. In vitro, tazemetostat is 88% bound to human plasma proteins [8].

In vitro, tazemetostat is metabolized by cytochrome P450 (CYP) 3A to form the inactive major metabolites M5 (EPZ-6930) and M3 (EPZ006931), with M5 undergoing further metabolism via CYP3A [8]. The major route of elimination is via the faeces, with approximately 79% and 15% of a single oral dose of radiolabelled tazemetostat excreted in the faeces and urine over 12 days. The estimated mean terminal elimination half-life of tazemetostat at steady-state is 3.1 h [8].

The pharmacokinetics of tazemetostat were not affected to a clinically relevant extent by age (16–91 years), bodyweight (37.3–173 kg), mild hepatic impairment [total bilirubin level of > 1 to 1.5 × the upper limit of normal (ULN) or AST level > ULN], race, renal impairment (including end-stage renal disease) or sex [8]. The effect of moderate to severe hepatic impairment is not yet known [8].

Coadministration of tazemetostat and moderate or strong CYP3A inhibitors (resulting in elevated tazemetostat AUC and C_{max} values at steady-state) should be avoided; if the concomitant use of tazemetostat with moderate CYP3A inhibitors is unavoidable, the tazemetostat dose should be reduced [8]. Coadministration of tazemetostat with moderate or strong CYP3A inducers should also be avoided [8]. Local prescribing information should be consulted for detailed information regarding these and other potential drug interactions.

2.3 Therapeutic Trials

2.3.1 INI1-Negative Tumors and Synovial Sarcoma

The efficacy of oral tazemetostat (800 mg twice daily) as monotherapy in adults with INI1-negative tumours, or relapsed or refractory synovial sarcoma is currently being evaluated in an open-label, multinational, phase II study [NCT02601950 (EZH-202)] [29]. EZH-202 is a basket study, with patients enrolled into one of several cohorts based on tumour type, including epithelioid sarcoma, MRT and synovial sarcoma. Treatment with tazemetostat is to continue until disease progression, unacceptable toxicity, withdrawal of consent or study termination [29].

Preliminary antitumour activity with tazemetostat was demonstrated in a futility analysis of data (available as an abstract) from 32 patients ($n = 16$, 13 and 3 with a non-mesenchymal solid tumour, sarcoma or a gain-in-function mutated EZH2 solid tumour, respectively) participating in EZH-202 [30]. Overall, three patients (two with spindle cell sarcoma and one with sinonasal carcinoma) achieved a partial response (PR), which persisted for ≥ 16 weeks. Stable disease as the best response occurred in 41% of patients. Stage 1 of the futility analysis was performed after the first 15 patients had completed the 24-week assessment or final study visit, or had prematurely withdrawn from the study, and required 1 patient to achieve a confirmed complete response (CR) or PR. Stage 2 required the achievement of a CR or PR in ≥ 5 of 30 patients [30].

In a cohort of 62 patients with locally advanced or metastatic epithelioid sarcoma from EZH-202, tazemetostat was associated with promising and durable clinical activity (data from an abstract) [31]. At a data cut-off date of 17 September 2018 (median follow-up duration of 14 months), the overall response rate (assessed by blinded independent central review using

Features and properties of tazemetostat

Alternative names	E-7438; EPZ-6438; EZ-438; tazemetostat hydrobromide; Tazverik
Class	Amides; amines; antineoplastics; biphenyl compounds; dihydropyridines; morpholines; small molecules
Mechanism of action	Enhancer of zeste homolog 2 protein inhibitors
Route of administration	Oral
Pharmacodynamics	Inhibitor of the histone methyltransferase enhancer of zeste homolog 2; exhibited antitumour activity in vitro and in various murine xenograft models of cancer
Pharmacokinetics	Exhibited approximately dose proportional systemic exposure across the 200–1600 mg twice daily dosage range; median time to peak plasma concentration of 1–2 h; may be administered with or without food
Most frequent adverse events	Pain, fatigue, nausea, decreased appetite, vomiting and constipation
ATC codes	
WHO ATC code	L01X-X (other antineoplastic agents)
EphMRA ATC code	L1X (all other antineoplastics); L1X9 (all other antineoplastics)
Chemical name	N-[(4,6-dimethyl-2-oxo-1H-pyridin-3-yl)methyl]-3-[ethyl(oxan-4-yl)amino]-2-methyl-5-[4-(morpholin-4-ylmethyl)phenyl]benzamide; hydrobromide

RECIST 1.1) was 15% and the time to this response ranged from 2.4 to 18.4 months [8, 31]. At this timepoint, the CR rate was 1.6%, the PR rate was 13%, the disease control rate (defined as a CR or PR of any duration, or stable disease for ≥ 32 weeks) was 26%, the median duration of response had not been reached (with the duration of response ranging from 7.1 to 103 weeks) and median overall survival was 82.4 weeks (95% CI 47.4, not estimable) [8, 31]. Patients in this cohort were INI1-negative and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 [8]. At baseline, 77% and 61% of patients had previously undergone surgery or received systemic chemotherapy, and 44% had proximal disease [8].

Tazemetostat displayed its potential in a cohort of 31 patients from EZH-202 with difficult-to-treat MRTs (e.g. SCCOHT and thoracic sarcoma), achieving success in a stage 1, but not stage 2, futility analysis of data (available as an abstract) [32]. A PR was achieved in two patients (one with SCCOHT and one with thoracic sarcoma), with stable disease as a best response occurring in seven patients. Stage 1 of the futility analysis was performed after the first 15 patients had completed the 24-week assessment or final study visit, or had prematurely withdrawn from the study, and required 1 patient to achieve a CR or PR; stage 2 required the achievement of a confirmed CR or PR in ≥ 5 patients [32].

Tazemetostat showed promise as a treatment for synovial sarcoma in patients from EZH-202 who had received a median of two prior systemic therapies [33]. A best response of stable disease was achieved by 11 (33%) of 33 patients; stable disease persisted for ≥ 16 weeks in 5 patients. No patient achieved a CR or PR. Stage 2 success was defined as ≥ 9 of 30 patients achieving the primary endpoint of a CR, a PR or stable disease at 16 weeks [33].

Key clinical trials of tazemetostat

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Tazemetostat, atezolizumab, obinutuzumab	Relapsed/refractory FL and DLBCL	I	Completed	Multinational	NCT02220842	Hoffmann-La Roche
Tazemetostat	Relapsed or refractory INI1-negative tumours or SS	I	Recruiting	Multinational	NCT02601937 (EZH-102)	Epizyme Inc.
Tazemetostat, abiraterone/prednisone, enzalutamide	mCRPC	I	Recruiting	USA	NCT04179864 (EZH-1101)	Epizyme Inc.
Tazemetostat	Advanced solid tumours, BCL, DLBCL	I/II	Active, not recruiting	Multinational	NCT01897571	Epizyme Inc.
Tazemetostat, pembrolizumab	Locally advanced or metastatic urothelial carcinoma	I/II	Recruiting	USA	NCT03854474	NCI
Tazemetostat	Relapsed or refractory malignant mesothelioma	II	Completed	Multinational	NCT02860286 (EZH-203)	Epizyme Inc.
Tazemetostat	INI1-negative tumours, relapsed/refractory SS	II	Recruiting	Multinational	NCT02601950 (EZH-202)	Epizyme Inc.
Tazemetostat	ATRT, DLBCL, ES, FL, mesothelioma advanced solid tumours, MRT, RTK, SS	II	Recruiting	Multinational	NCT02875548 (TRuST)	Epizyme Inc.
Tazemetostat	Relapsed or refractory advanced solid tumours, NHL or histiocytic disorders	II	Recruiting	Puerto Rico, USA	NCT03213665	NCI
Tazemetostat, doxorubicin, placebo	Advanced soft-tissue sarcoma or ES	III	Recruiting	USA	NCT04204941 (EZH-301)	Epizyme Inc.
Tazemetostat, lenalidomide, placebo, rituximab	Relapsed/refractory FL	III	Not yet recruiting	USA	NCT04224493 (EZH-302)	Epizyme Inc.
Tazemetostat	ES	Expanded access	Available	USA	NCT04225429 (EZH-801)	Epizyme Inc.

ATRT atypical teratoid rhabdoid tumours, *BCL* B-cell lymphoma, *DLBCL* diffuse large B-cell lymphoma, *ES* epithelioid sarcoma, *FL* follicular lymphoma, *INI1* integrase interactor 1, *mCRPC* metastatic castration-resistant prostate cancer, *MRT* malignant rhabdoid tumours, *NCI* National Care Institute, *NHL* Non-Hodgkin's lymphoma, *RTK* rhabdoid tumours of the kidney, *SS* synovial sarcoma

2.3.2 Solid Tumours and B-Cell NHL

A first-in-human, open-label, multinational, phase I/II basket study (NCT01897571) is currently investigating the efficacy of oral tazemetostat in adults with relapsed or refractory B-cell NHL or advanced solid tumours (phase I, dose escalation part) [28] and in those with relapsed or refractory DLBCL or FL (phase II part) [34, 35].

Monotherapy with tazemetostat was associated with promising outcomes in the phase I part of the phase I/II study [28]. At a data cut-off date of 11 November 2016 (median duration of exposure to tazemetostat of 8.1 weeks), the objective response rate (assessed using IWG 2007) in 21 patients with relapsed or refractory B-cell NHL was 38% [28]. The median time to first (partial) response in these patients was 3.5 months and the median duration of response (defined as the time from the earliest onset of CR or PR to progressive disease or death) was 12.4 months. At the same timepoint, 5% of 43 patients with locally advanced or metastatic solid tumours achieved an overall response (as assessed using RECIST 1.1). Both of these patients had INI1- or SMARCA4-negative tumours; indeed, 38% of the 13 patients with INI1- or SMARCA4-negative tumours in the advanced solid tumour cohort achieved a best response of stable disease. The four patients who achieved a CR (three patients with relapsed or refractory B-cell NHL and one with an advanced solid tumour) continued to receive therapy with tazemetostat, with ongoing responses observed 2.3–2.8 years after the start of treatment. In this part of the study, patients received oral tazemetostat 100–1600 mg twice daily, with treatment continuing until disease progression, unacceptable toxicity or withdrawal of consent. Patients had an ECOG performance status score of 0–1 and had undergone a median of three previous lines of anticancer therapy, with almost all (98%) having documented disease progression a median of 1 month prior to study entry [28].

Tazemetostat 800 mg twice daily monotherapy also showed promise as a treatment for relapsed or refractory DLBCL [34] and FL [35] in adults participating in the phase II part of the phase I/II study. In this part of the study, all patients had measurable disease and had undergone ≥ 2 prior treatment regimens [34, 35]. At an interim analysis (data cut-off date of 1 May 2018), the objective response rate (primary endpoint; assessed using IWG 2007) was 17% in 36 patients with mutated EZH2 DLBCL and 17% in 121 patients with wild-type EZH2 DLBCL [34]. In the respective cohorts, a CR occurred in 3% and 9% of patients, stable disease in 39% and 19% and progressive disease in 39% and 60%. Neither median progression-free survival (PFS) nor the median duration of response had been reached in either cohort at the time of the interim analysis [34]. At an interim analysis (data cut-off date of 7 June 2019), 77% and 34% of patients with mutated or wild-type EZH2 FL ($n = 43$ and 53; median duration of follow-up of 15.9 and 24.9 months) achieved an objective response (primary endpoint) [35]. An objective response at ≥ 6, ≥ 12 and ≥ 16 months, respectively, occurred in 45%, 21% and 12% of 33 patients in the mutated EZH2 FL cohort and in 83%, 50% and 33% of 18 patients in the wild-type EZH2 FL cohort. CR, stable disease and progressive disease rates were 7%, 23% and 0%, respectively, in the mutated EZH2 FL cohort ($n = 43$) and 6%, 30% and 36%, respectively, in the wild-type EZH2 FL cohort ($n = 53$). In the respective cohorts, PFS was 11.1 and 5.7 months, and the median duration of response was 8.3 and 13.0 months. Of note, data from the mutated EZH2 FL cohort are continuing to mature. Monotherapy with tazemetostat also demonstrated antitumour activity regardless of the prognostic category of patients with relapsed or refractory FL, with those with disease progress within 24 months of diagnosis (POD24; $n = 17$ and 30 with mutated or wild-type EZH2 FL) achieving an objective response rate of 65% and 30%. CR, stable disease and progressive disease rates were 6%, 35% and 0%, respectively, in the POD24 subgroup of the mutated EZH2 FL cohort and 0%, 27% and 30%, respectively, in the POD24 subgroup of the wild-type EZH2 FL cohort. Moreover, in the respective subgroups, PFS was 13.8 and 5.6 months and the median duration of response was 8.2 and 7.3 months [35].

Tazemetostat (administered orally at a dosage of 800 mg twice daily) has also shown promise in 61 adults with relapsed or refractory malignant mesothelioma and an inactive BRCA1-associated protein (BAP1) who had received ≥ 1 prior systemic therapy and were participating in an open-label, multinational, phase II study [NCT02860286 (EZH-203)] [36]. The disease control rate (defined as CR or PR plus stable disease) at 12 weeks of 51% surpassed the stage 2 criterion of ≥ 35%; 15 (25%) patients had sustained disease control at 24 weeks, 5 of whom were ongoing. A confirmed PR occurred in two patients [36].

Combining tazemetostat (800 mg twice daily on days 1–28 of a 28-day cycle) with prednisone (40 mg/m^2 on days 1–5 and 15–19 of a 28-day cycle) did not result in improved activity compared with tazemetostat alone in 69 adults with relapsed or refractory wild-type EZH2 DLBCL participating in the phase II part of the phase I/II study (NCT01897571) [34]. Specifically, an objective response, a CR, stable disease and progressive disease were achieved in 9%, 1%, 25% and 57% of patients, respectively. Median PFS and median duration of response had not yet been reached [34]. In addition, favourable clinical activity was not demonstrated with the combination of oral tazemetostat (800 mg twice daily on days 1–21 of each 21-day cycle) and intravenous atezolizumab (1200 mg on day 1 of each 21-day cycle) in patients with relapsed or refractory DLBCL participating in a phase Ib study (NCT02220842) [37].

2.4 Adverse Events

Oral tazemetostat had a favourable safety profile when used as monotherapy in adults with epithelioid sarcoma and other tumour types in the clinical studies discussed in Sect. 2.3. However, the risk of developing secondary malignancies is increased following the use of tazemetostat, with secondary myelodysplastic syndrome, acute myeloid leukaemia or T-cell lymphoblastic lymphoma reported in 0.8% of 725 adult and paediatric patients with solid tumours or haematological malignancies (pooled safety population) [38]. One paediatric patient developed T-cell lymphoblastic lymphoma [8].

In the cohort of 62 patients (44% and 24% of whom were exposed to tazemetostat for ≥ 6 and ≥ 12 months) with locally advanced or metastatic epithelioid sarcoma participating in EZH-202, the most frequently reported (incidence of ≥ 20%) adverse reactions were pain (including arthralgia, back pain, bone pain, cancer pain, flank pain, non-cardiac chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity and tumour pain) [in 52% of patients], fatigue (47%), nausea (36%), decreased appetite (26%), vomiting (24%) and constipation (21%) [8]. Anaemia (in 13% of patients), pain (7%) and decreased weight (7%) were the most common (incidence of > 5%) grade 3–4 adverse reactions observed. Adverse reactions resulting in dosage interruptions were reported in 34% of tazemetostat recipients, with haemorrhage, increased alanine aminotransferase levels and increased aspartate aminotransferase levels the most commonly (incidence of ≥ 3%) reported. Adverse reactions leading to dose reductions occurred in one patient (who experienced decreased appetite). Serious adverse reactions occurred in 37% of tazemetostat recipients, with haemorrhage, pleural effusion, skin infection, dyspnoea, pain, and respiratory distress the most frequently (incidence of ≥ 3%) reported. One patient permanently discontinued therapy due to an adverse reaction of altered mood. The most frequently (incidence of ≥ 30%) reported laboratory abnormalities were a reduction in haemoglobin (in 49% of patients), a reduction in lymphocytes (36%), increased triglyceride levels (36%), increased glucose levels (33%) and decreased sodium levels (30%). A reduction in haemoglobin (in 15% of patients) and a reduction in lymphocytes (13%) were the most commonly (incidence of ≥ 10%) observed grade 3 or higher laboratory abnormalities [8].

Tazemetostat as monotherapy or in combination with prednisolone was generally well tolerated in adults with relapsed or refractory DLBCL participating in the phase II part of a phase I/II study (NCT01897571) [34]. The most frequent (incidence of ≥ 15%) treatment-emergent adverse events (AEs) [all grades] were thrombocytopenia (in 20% of patients), nausea (17%), anaemia (15%), neutropenia (15%) and vomiting (15%); 12% of patients discontinued treatment with tazemetostat or withdrew from the study because of treatment-emergent AEs. Grade 3 or higher treatment-related AEs occurred in 27% of patients [34].

Monotherapy with tazemetostat was also generally well tolerated in adults with FL participating in the phase II part of the phase I/II study (NCT01897571) [35]. The most frequently reported AEs were thrombocytopenia (3% of patients), anaemia (2%), asthenia (2%), vomiting (1%), and fatigue (1%). Grade 3 or higher treatment-related AEs, dose reductions and treatment discontinuation occurred in 17%, 9% and 5% of patients, respectively. No grade 5 treatment-related AEs or deaths were reported. In the POD24 subgroup, the nature of the most commonly reported AEs were similar to those seen in the total population; 15% of patients in the POD24 subgroup experienced grade 3 or higher treatment-related AEs [35].

Monotherapy with tazemetostat was generally well tolerated in the cohorts of adults with difficult-to-treat MRTs [32] and synovial sarcoma [33] participating in EZH-202; in adults with relapsed or refractory malignant mesothelioma and BAP1 participating in EZH-203 [36]; and in adults with relapsed or refractory B-cell NHL, or locally advanced or metastatic solid tumours participating in the phase I, dose-escalation part of a phase I/II study (NCT01897571) [28]. Most adverse events were mild or moderate in severity [28, 32, 33, 36].

2.5 Ongoing Clinical Trials

There are several ongoing phase I [NCT02601937 (EZH-102); NCT04179864 (EZH-1101)], I/II (NCT01897571; NCT03854474) and II [NCT02601950 (EZH-202); NCT02875548 (TRuST); NCT03213665] studies of tazemetostat for the treatment of various haematological malignancies and genetically defined solid tumours. In addition, two Phase III studies are assessing tazemetostat for the treatment of advanced soft-tissue sarcoma or epithelioid sarcoma [NCT04204941 (EZH-301)] and relapsed/refractory FL [NCT04224493 (EZH-302)]. EZH-301 has been initiated to support the full approval of tazemetostat for epithelioid sarcoma [39].

3 Current Status

Tazemetostat received its first approval on 23 January 2020 for the treatment of adults and adolescents aged ≥ 16 years with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection in the USA [7, 8].

Compliance with Ethical Standards

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