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Molecular mechanisms underlying the clinical efficacy of panobinostat involve Stochasticity of epigenetic signaling, sensitization to anticancer drugs, and induction of cellular cell death related to cellular stresses

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ABSTRACT

Panobinostat, also known as Farydak®, LBH589, PNB, or panobinostat lactate, is a hydroxamic acid that has been approved by the Food and Drug Administration (FDA) for its anti-cancer properties. This orally bioavailable drug is classified as a non-selective histone deacetylase inhibitor (pan-HDACi) that inhibits class I, II, and IV HDACs at nanomolar levels due to its significant histone modifications and epigenetic mechanisms. A mismatch between histone acetyltransferases (HATs) and HDACs can negatively affect the regulation of the genes concerned, which in turn can contribute to tumorigenesis. Indeed, panobinostat inhibits HDACs, potentially leading to acetylated histone accumulation, re-establishing normal gene expression in cancer cells, and helping to drive multiple signaling pathways. These pathways include induction of histone acetylation and cytotoxicity for the majority of tested cancer cell lines, increased levels of p21 cell cycle proteins, enhanced amounts of pro-apoptotic factors (such as caspase-3/7 activity and cleaved poly (ADP-ribose) polymerase (PARP)) associated with decreased levels of anti-apoptotic factors [B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-XL)], as well as regulation of immune response [upregulated programmed death-ligand 1 (PD-L1) and interferon gamma receptor 1 (IFN-γR1) expression] and other events. The therapeutic outcome of panobinostat is therefore mediated by sub-pathways involving proteasome and/or aggresome degradation, endoplasmic reticulum, cell cycle arrest, promotion of extrinsic and intrinsic processes of apoptosis, tumor microenvironment remodeling, and angiogenesis inhibition. In this investigation, we aimed to pinpoint the precise molecular mechanism underlying panobinostat's HDAC inhibitory effect. A more thorough understanding of these mechanisms will greatly advance our knowledge of cancer cell aberrations and, as a result, provide an opportunity for the discovery of significant new therapeutic perspectives through cancer therapeutics.

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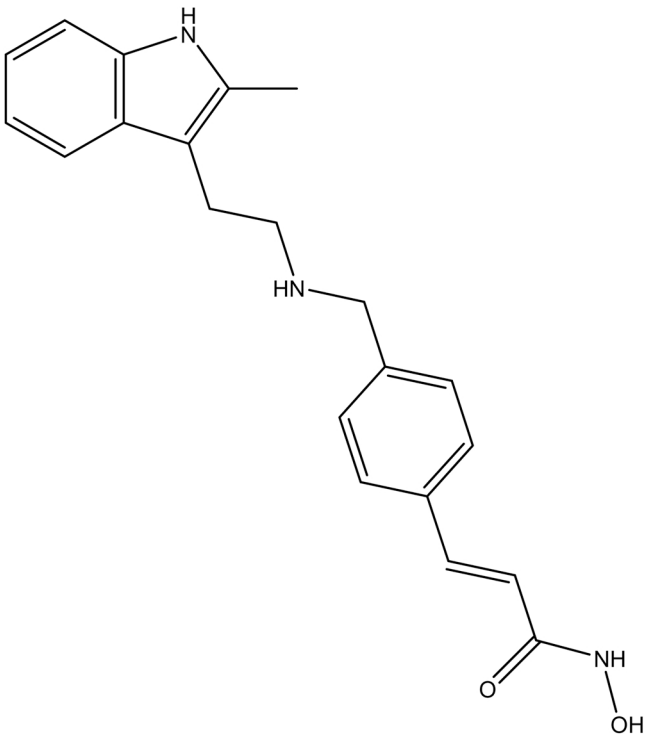

Fig. 1. Chemical structure of Panobinostat (Created with ChemDraw).

1. Introduction

Epigenetics, a term commonly used to refer to the investigation of the intricate interaction between genes and the environment, is now considered a fundamental issue in evolutionary biology [1–3]. In fact, several critical cellular processes necessary for the preservation of cellular memory integrity and cellular plasticity have been shown to be regulated by epigenetic mechanisms, particularly DNA methylation and histone modification [2–4]. These epigenetic pathways can be distorted and lead to the emergence of serious pathologies [5].

Histone deacetylases (HDACs) are a class of enzymes that target oncoproteins, histones, and tumor suppressors to regulate a wide range of cellular processes [6]. However, it should be emphasized that HDACs induce a chromatin conformation sequence that allows the expression of proteins related to tumor pathogenesis [7]. Moreover, the major biological impact of HDACis lies in their ability to inhibit HDAC activities at the molecular level. HDACs are required to maintain a well-balanced and dynamic protein acetylation pathway. They also have a significant impact on other post-translational modifications of proteins [8]. On the other side, it is well established that aberrant protein expression or HDAC gene mutation are strongly associated with several human disorders, especially cancer. This is due to the fact that a defective HDAC gene causes inconsistent and excessive amounts of oncogene expression, which can transform normal cells and increase malignant cells [4].

In order to provide a deeper understanding of the mechanism of action of HDACs and their functioning, the development of HDAC inhibitors (HDACis) has emerged as one of the most important topics concerning HDAC engineering. Due to the complexity of epigenetic transcription regulation, lysine post-translational modifications, and non-epigenetic cellular signaling pathways, many issues still need to be addressed [9]. In this respect, chemical compounds have long been used to target the HDAC inhibitory pathway, and the outcomes have indeed paved the way for anti-cancer drug discovery [2,10,11]. The borders between transcriptionally active and quiescent chromatin become unclear when these enzymes are inhibited pharmacologically, altering the acetylation state of chromatin [12]. Since few HDACis have so far received Food and Drug Administration (FDA) approval for the management of cancer, continued research is ongoing to discover potential HDACis that might be effective against cancer.

Panobinostat (Fig. 1), formerly known as Farydak®, LBH589, PNB, or panobinostat lactate, is an orally available hydroxamic acid that was approved by the FDA in February 2015 for its anti-cancer properties, specifically for the management of patients with relapsed/refractory (R/

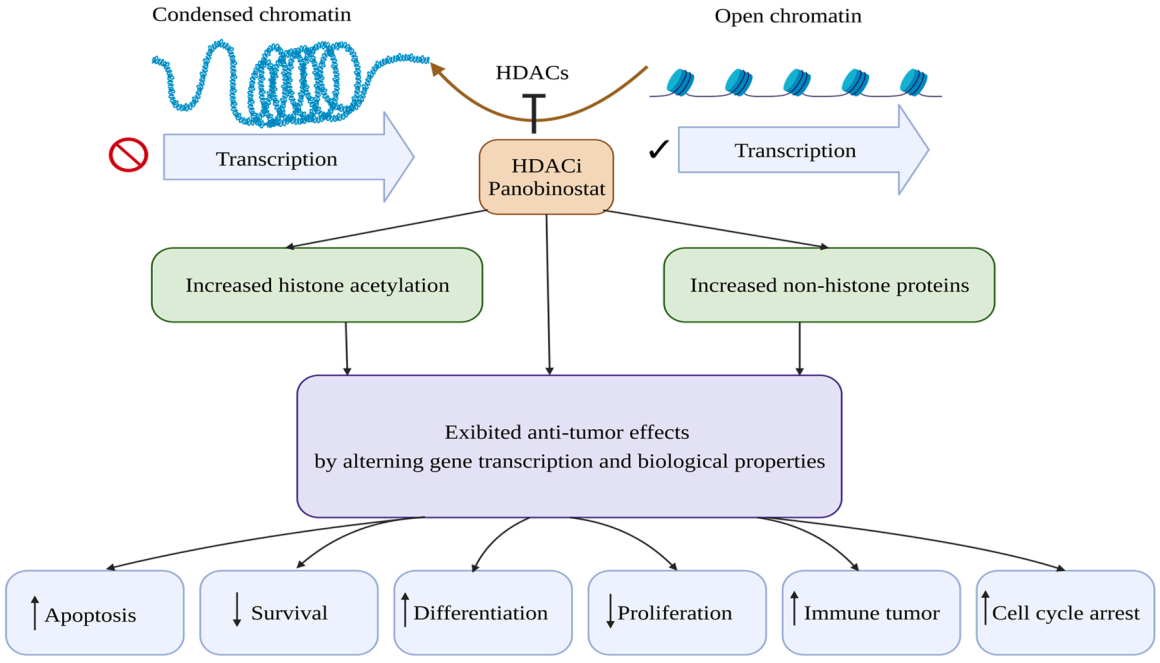

Fig. 2. Insight into biological and molecular pathways implicated in HDAC inhibition by panobinostat. *Histone acetyl transferases (HAT) and histone deacetyl transferases compete with one another to control the acetylation status of histones (HDAC). By altering gene transcription and biological properties, panobinostat inhibits HDACs and causes hyperacetylation of histone and non-histone proteins, which exhibits anticancer effects by reducing cell proliferation and survival while increasing cell cycle arrest and differentiation, inducing apoptosis, and enhancing immune response.*

R) multiple myeloma (MM) in combination with bortezomib and dexamethasone, representing the latest HDACi [13]. However, in 2021 this indication was withdrawn, as the responsible manufacturer was unable to complete the post-approval clinical investigations necessary to maintain the approval [14]. Due to its extensive histone modifications and epigenetic mechanisms, this drug is classified as a non-selective HDACi (pan-HDACi), which inhibits class I, II, and IV HDACs at nanomolar levels. Panobinostat outperforms other pan-HDACis, such as vorinostat, and is considered one of the most potent HDACis currently under investigation. Panobinostat undergoes rapid oral absorption and is largely metabolized. This medication offers a novel strategy to prevent the proliferation and survival of myeloma cells [13].

In vivo (using tumor xenograft models) and in vitro investigations using several cancer cell lines; cutaneous T-cell lymphoma (CTCL), anaplastic thyroid carcinoma (ATC) (BHT-101, CAL-62, and 8305 C), mammary carcinoma (MC) (EO771), prostate cancer (PC) (PC3, DU145, and LNCaP), human hepatocellular carcinoma (HCC), high-risk neuroblastoma (HR-NBL), pancreatic cancer (AsPC-1, BxPC-3, CFPAC-1, HPAC, MIAPaCa-2, and PANC-1), oral squamous (HN22 and HSC4 cells), triple-negative breast cancer (MDA-MB-231, BT-549), renal cancer (Caki-1, ACHN, 769-P, and 786-O), ovarian, and cervical cancers (HeLa and SiHa) were exposed to small nanomolar amounts of panobinostat, which resulted in a significant decrease in cell proliferation and an improvement in cytotoxicity. Surprisingly, normal cells showed resistance to panobinostat cytotoxicity, implying that panobinostat's effect on cell death may be limited to cancer cells [15–19]. Additionally, panobinostat, either as a single agent or in combination with other drugs, was demonstrated to affect several mechanistic pathways critical to the biological and molecular processes of major cancer types through in vivo and in vitro experiments as well as clinical studies. Indeed, this HDACi inhibited DNA methyltransferase (DNMT) activity, down-regulated DNMT protein expression, potentially caused acetylated histone accumulation, re-established normal gene expression in cancer cells, and helped drive multiple signaling pathways, including induction of histone acetylation and cytotoxicity for the majority of cancer cell lines tested, increased levels of p21 cell cycle proteins, improved the effect of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) pathway activators, induced G1 phase cell cycle arrest, reduced β-catenin stability and inhibited the wingless-int-1 (Wnt)/β-catenin pathway, enhanced amounts of pro-apoptotic factors (such as caspase-3/7 activity and cleaved poly (ADP-ribose) polymerase (PARP)) associated with decreased levels of anti-apoptotic factors (B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-XL)) as well as regulation of the immune response [up-regulated programmed death-ligand 1 (PD-L1) and interferon gamma receptor 1 (IFN-γR1) expression] and other events [15–23] (Fig. 2). At a preclinical level, panobinostat demonstrated inhibition of HDAC classes I, II, and IV. This property, which allows the inhibition of different classes of HDAC, has led to its incorporation at the clinical level. It has proven to be a valuable medicine in the management of cancer. Nonetheless, the mechanisms underlying its beneficial properties have yet to be fully explored. Accordingly, this review focuses on molecular pathways and represents a significant challenge to redefine and reconsider the molecular fundamentals of cancer chemotherapy using the powerful anti-cancer drug panobinostat.

2. Epigenetics, HDAC, and cancer

The complexity of cancer etiology arises from a combination of environmental, lifestyle, and hereditary factors. While cancer is commonly understood as a genetic disease caused by repetitive genetic aberrations, the current model has expanded to include epigenetic regulation abnormalities. Research suggests that genetic and epigenetic mechanisms interact and collaborate during tumorigenesis [2–4]. Epigenetic changes are considered the "first hits" for tumorigenesis, leading to the loss of tissue homeostasis and genetic instability that causes mutations in tumor-suppressor genes. In many cancers, tumor suppressor genes are not genetically mutated but are silenced through epigenetic means during the pre-invasive stage. Epigenetic events include histone modifications, DNA methylation, and deregulation of non-coding RNAs and their interactions with proteins or nucleic acids. Four types of epigenetic regulators dynamically regulate these events: writers, erasers, readers, and remodelers. Mutations and deregulation of genes encoding these regulators have been described in various cancers [2–4].

Histone modifications play a crucial role in regulating the active and inactive states of chromatin, ultimately affecting gene expression [24]. Certain histone modifications, such as acetylation, methylation, and deregulation, have been associated with epigenetic abnormalities in cancer cells [25,26]. Methylation of specific residues in core histones H3 and H4, as well as loss of acetylation, are considered markers of cancerous cells [25,26]. Histone modification is a crucial process that involves the activity of several enzymes, including HDAC, histone acetyltransferase (HAT), histone demethylase (HDM), histone methyltransferase (HMT), E3-ubiquitin, and kinases [27].

The acetylation and deacetylation of histones are known to be closely related to chromatin conformation, with acetylation promoting an active and open state and deacetylation inducing an inactive and condensed form. The dynamic regulation of histone acetylation, which is a key mechanism in modulating gene expression, is finely controlled by the activity of HDAC and HAT enzymes [28]. HATs catalyze the transfer reaction of an acetyl group from acetyl-CoA to the lysine position of histones, which has the ability to neutralize the positive lysine charge and disrupt the electrostatic interaction between DNA and histones. This process results in a more relaxed chromatin structure, significantly affecting gene assembly and modifying transcriptional activity by promoting the access of transcription factors to gene promoter sites [29]. In contrast, HDACs have the opposite effect by removing acetyl groups from histones, thereby favoring the formation of compact chromatin structure and repressing gene expression. Additionally, HDACs can interact with transcription factors or form corepressor complexes with nuclear receptors, further inhibiting gene expression [30]. An imbalance in histone acetylation has been observed in various cancers, including lung cancer, Rubinstein-Taybi syndrome, acute myeloid leukemia (AML), and glioblastomas (GBMs) [31]. HAT mutations have been implicated in different stages of tumor development, including B-cell non-Hodgkin lymphoma, leukemia, and solid cancers [32–34]. Chromosomal translocations involving HATs and their fusion proteins have also been linked to acute leukemia [35].

Dysregulation of HDAC proteins can lead to aberrant deacetylation and inhibition of tumor suppressor genes (TSGs), as well as the regulation of gene transcription by deacetylating other epigenetic factors, such as DNMTs, HATs, and other HDACs [36].

There are 18 mammalian HDACs divided into 4 families based on their homology with yeast HDACs [37,38]. Class I HDACs (1, 2, 3, and 8), homologous to yeast reduced potassium dependency 3 (RPD3), are located in the nucleus of human cells. Class II HDACs (4, 5, 6, 7, 9, and 10), homologous to yeast histone deacetylase 1 (HDA-1), exhibit tissue-specific expression and can shuttle between the nucleus and cytoplasm. Class III HDACs, or sirtuins (SIRT1–7), are homologous to yeast silent information regulator 2 (SIR2) and require the cofactor nicotinamide adenine dinucleotide (NAD+) for their activity. Finally, class IV HDACs, including the recently discovered HDAC11, exhibit characteristics of both class I and class II HDACs [37,38].

The involvement of HDACs in cancer development was first reported in hematological malignancies through inappropriate complex formation involving HDACs [38,39]. To date, very rare mutations altering the expression and/or activity of HDACs have been recorded in tumors, while dysregulation of their activity has been associated with abnormal gene expression and carcinogenesis. Many studies have reported that HDAC1 is overexpressed in prostate, colon, stomach, and breast carcinomas [40,41] [42,43], while HDAC2 is overexpressed in colorectal

[44], cervical [45], and gastric cancers [46]. Overexpression of HDAC1, HDAC2, and HDAC3 is associated with poor survival in patients with gastric and ovarian cancers (OCs), while HDAC6 has been found to be highly expressed in breast cancer specimens [47]. Overexpression of HDAC8 has been reported in neuroblastoma, while low levels of HDAC4 have been reported in gastric cancers [48,49].

The overexpression or aberrant function of HDACs is implicated in the development of several types of human cancers, particularly leukemias resulting from a differentiation defect in stem cells. The involvement of HDACs in cancer is linked to various mechanisms such as cell cycle arrest and apoptosis, differentiation, DNA damage, metastasis, angiogenesis, and autophagy [6,50].

3. Biochemical inhibition of HDAC by panobinostat

By inhibiting HDACs, panobinostat leads to increased acetylation of histones and other proteins, which can result in changes in gene expression and various cellular processes. The mechanism of HDAC inhibition by panobinostat is not fully understood, but it is thought to involve binding to the catalytic site of HDACs and blocking their activity. Specifically, panobinostat appears to bind to the zinc ion in the catalytic site of HDACs, preventing the enzyme from removing acetyl groups from histones and other proteins [13].

Panobinostat is a molecule whose mechanisms have been rigorously and chronologically studied. In 2015, its clinical use was approved for the treatment of different types of cancer. However, prior to these clinical applications, the molecular mechanisms underlying its efficacy were not clearly understood. Thus, successive investigations were conducted, starting with cellular models (in vitro) and then animal models (in vivo), in order to dissect the various involved mechanisms. Each research team has identified a series of mechanisms related to the indirect efficacy of this molecule, following a rigorous chronological progression. It is therefore important to highlight all the mechanisms identified to date, respecting the chronological order of the various studies carried out over time, to better understand the currently known mechanisms of this molecule.

4. In vitro and in vivo anticancer mechanisms of panobinostat

The mode of action of panobinostat has been progressively unraveled through a series of fundamental discoveries. Interestingly, despite being used in cancer treatment, its precise mechanism of action is not yet fully understood. In the upcoming section, we will examine the molecular mechanisms in chronological order based on various research studies that have been conducted over several years to determine the underlying actions responsible for panobinostat's therapeutic effects.

In February 2015, the FDA approved panobinostat for the treatment of patients with MM, representing the last approved HDACi [51]. Since 2008, the anticancer activity of this molecule, alone or combined, was the subject of several preclinical studies. Indeed, Wang et al. [15] evaluated in vitro and in vivo the antitumor activity of panobinostat against colon cancer. In vitro, they found that this molecule used alone has promising anti-proliferative effects against colon cancer cell lines, while its intravenous administration to an HCT116 tumor xenograft model inhibits tumor growth and induces acetylation of histones H3 and H4. In addition, 3-week intravenous treatment with the combination of panobinostat (30 mg/kg 3 × per week) with 5-FU (75 mg/kg 1 × per week) increased the median time and induced a level of tumor regression in a Colo205 tumor xenograft model.

A year later, Crisanti et al. [20] studied in vitro and in vivo the effect of panobinostat against a wide range of mesothelioma and lung cancer cells. Their results showed that this HDACi is cytotoxic for the majority of selected cancer cell lines, including small-cell lung cancer (SCLC) cell lines. Additionally, panobinostat reduced tumor growth (62%) in animal models of mesothelioma and lung cancer.

Interestingly, in SCLC xenografts, panobinostat combined with etoposide, a chemotherapeutic agent, potentiated anticancer effects, indicated by elevated amounts of p21 cell cycle proteins and increased levels of pro-apoptotic factors (caspase-3/7 activity and cleaved PARP) associated with decreased levels of anti-apoptotic factors (Bcl-2 and Bcl-XL). The anticancer effect of this HDACi is in addition to the three others previously shown to be effective against thoracic malignancies, particularly SCLC and non-SCLC (NSCLC).

Moreover, the efficacy of panobinostat was tested in vivo against human gastrointestinal stromal tumors (GIST) from patient biopsies using a mouse xenograft model [52]. After 12 days of treatment with panobinostat (10 mg/kg/day), GIST xenografts rapidly showed significant responses such as apoptosis, cell proliferation arrest, necrosis, tumor regression, fibrosis, and increased histone acetylation (H3 and H4). In addition, the majority of these parameters were improved following the combination with imatinib (150 mg/kg p.o.), an anticancer drug, administered twice daily during the same study period. To the best of our knowledge, this study is the first and only one evaluating the in vivo therapeutic activity of panobinostat on human GIST derived from patient biopsies, justifying a more advanced exploration of this HDACi in the treatment of patients with GIST.

Respecting the chronology of the preclinical investigations carried out, Hernandez-Ilizaliturri et al. [53] evaluated the impact of panobinostat on the anticancer effect of bortezomib against patient-derived primary tumor cells, rituximab-resistant cell lines (RRCL), and rituximab-sensitive cell lines (RSCL). They showed that panobinostat has a dose-dependent effect against all tumor cells tested, with a synergistic effect when combined with bortezomib. Mechanistically, in lymphoma cells, down-regulation of Bcl-XL was induced by panobinostat, whereas bortezomib down-regulated Bcl-XL and myeloid cell leukemia-1 (Mcl-1) and up-regulated Bcl-2 homologous antagonist/-killer (Bak) and phorbol-12-myristate-13-acetate-induced protein 1 (Noxa).

Furthermore, this proteasome inhibitor, bortezomib, was used in triple combination for the treatment of patients with MM who often relapse to conventional treatments [54]. The authors evaluated in vitro and in vivo the anti-MM activity of a triple therapy combining panobinostat and dexamethasone with either lenalidomide or bortezomib. The results showed that panobinostat alone had a promising effect on MM by inhibiting tumor progression, decreasing tumor burden, and preserving bone integrity. Importantly, the triple combinations suggested in this study were safe, with remarkable anti-MM activity attributed to the activation of a group of genes that differ from those triggered by the same agents in monotherapy.

Clinically, panobinostat has been shown to be very effective against advanced CTCL [55]. However, the underlying cellular and molecular mechanisms of action remain unclear. For this reason, using in vitro and in vivo models of CTCL, Shao et al. [16] showed high cellular sensitivity to the inhibitory power of panobinostat, with only half of the cells tested having a response to its cytotoxic effect. Indeed, panobinostat showed strong action in inhibiting HuT78 growth with an IC50 of 4 nM and triggering apoptosis with an LD50 of 28 nM. HuT78 cells, on the other hand, were far more resistant to vorinostat treatment, with an IC50 of 687 nM and an LD50 of 2.7 M. These results were attributed to constitutive nuclear factor kappa-B (NF-κB) activation and elevated Bcl-2 levels, whereas Bcl-2 associated X protein (Bax) inactivation decreased cellular sensitivity. Additionally, down-regulation of phosphorylated signal transducer and activator of transcription 3 (STAT3) and STAT5 proteins was noted in vorinostat-resistant CTCL cells following induced cytotoxicity. In vivo, complete tumor regression was achieved following panobinostat treatment. These data show that the anticancer activity of panobinostat is mainly related to intrinsic apoptotic signaling and that its association with the inhibition of anti-apoptotic factors can improve cellular sensitivity to treatment.

Since the acetylation of α-tubulin, a non-histonic protein, is a major process of the antitumor effect of HDACis in addition to the acetylation of histones, Catalano et al. [56] studied this cytotoxic mechanism in the

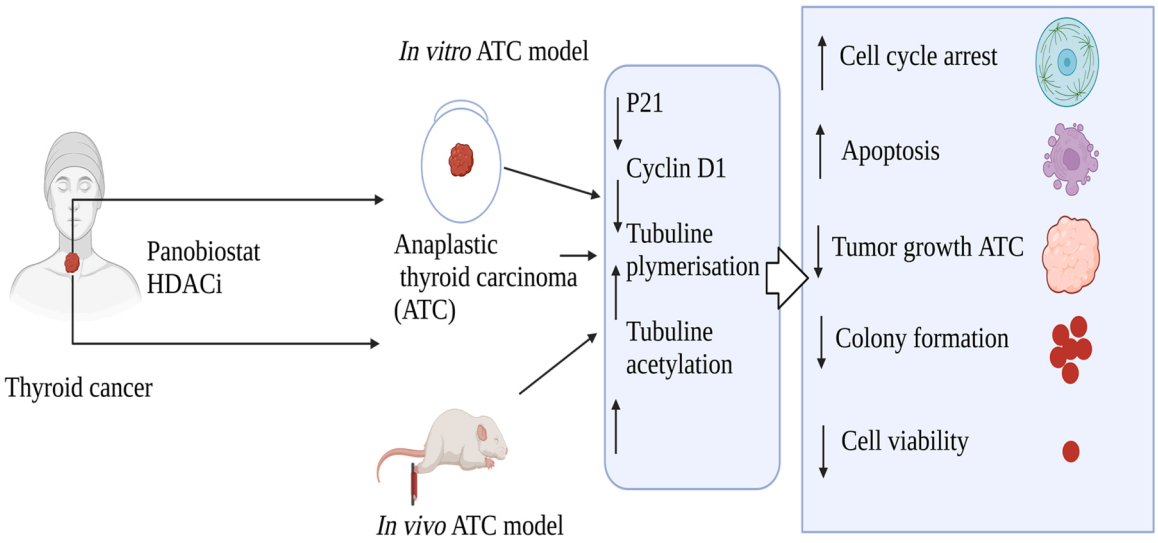

Fig. 3. Schematic illustration of the molecular pathways involved in the inhibition of anaplastic thyroid carcinoma (ATC) growth by panobinostat (LBH589). ATC is extremely resistant to conventional systemic drugs, clinically aggressive, undifferentiated tumors that are often incurable or metastatic at the time of presentation. In this regard, LBH589, as an HDACi, exhibits anticancer properties by promoting cell cycle arrest and apoptosis. In terms of mechanism, LBH589 has been shown to significantly alter microtubule stabilization, as evidenced by tubulin acetylation and enhanced tubulin polymerization, in addition to its effects on p21 and cyclin D1 expression, as demonstrated in an in vivo ATC experiment.

in vitro and in vivo treatment of anaplastic thyroid carcinoma (ATC), which responds poorly to conventional therapies. In fact, α/β tubulin heterodimers are involved in several biological processes; forming an important target in cancer treatments. In three ATC cell lines, panobinostat inhibited colony formation, impaired cell viability, induced apoptosis and cell cycle arrest. This was attributed to reduced expression of p21 and cyclin D1 and particularly to stabilization of microtubules via increased tubulin polymerization and tubulin acetylation. In an in vivo ATC model, treatment with panobinostat (20 mg/kg) suppressed tumor growth with a negative correlation of acetyl-tubulin levels without side effects. These findings indicate that the targeting of tubulin acetylation by panobinostat may play a primary role in the inhibition of ATC growth (Fig. 3).

On the other hand, targeting the TRAIL pathway has garnered significant interest in the development of anti-cancer treatments [57]. This is due to the ability of this pathway to selectively induce tumor cell apoptosis [58]. However, TRAIL receptor agonists have demonstrated some limitations. To enhance the effect of TRAIL pathway activators in oncology, they were combined with panobinostat in the treatment of human solid cancers in vitro and in vivo [59]. Indeed, a co-treatment of this HDACi with MD5–1 (anti-DR5 antibody) in mice induced synergistic apoptosis and a therapeutic effect in vivo, with an increase in the sensitivity of cancer cells to apoptosis mediated by MD5–1. In vivo, however, MD5–1 caused fatal gastrointestinal toxicities following high

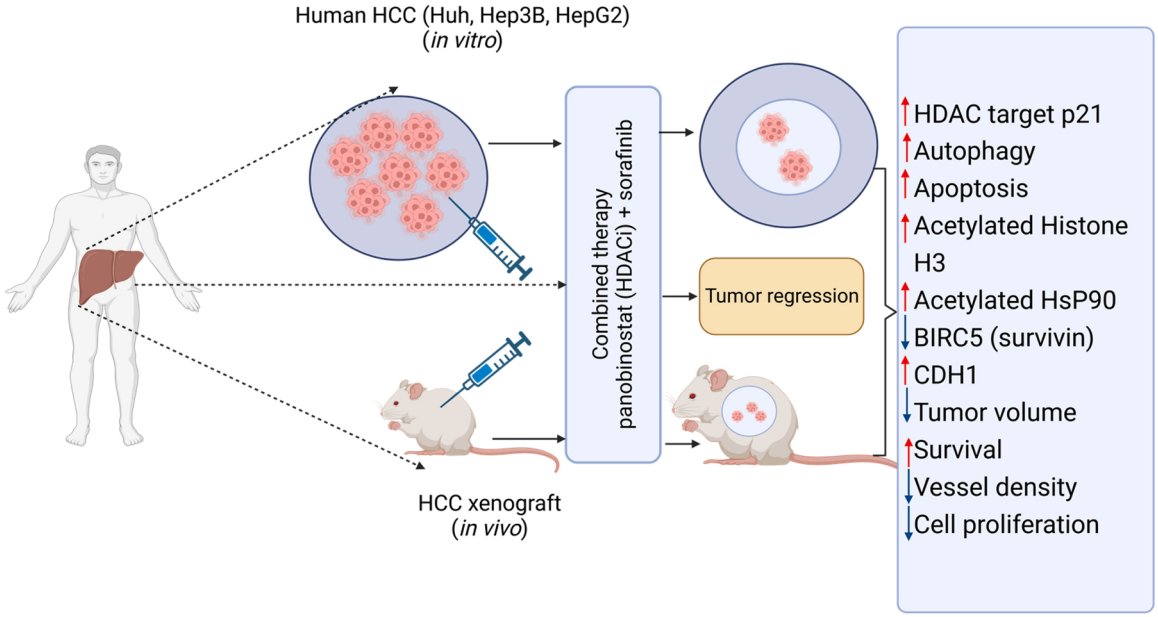

Fig. 4. Schematic representation of the synergistic effect of the HDACi panobinostat with sorafenib as combined therapy against hepatocellular carcinoma in in vitro and in vivo experiments. The apoptosis inhibitor BIRC5 (survivin), the tumor suppressor gene and Wnt pathway regulator CDH1, and the cyclin-dependent kinase inhibitor CDKN1A (p21), which are known to be associated with growth arrest, senescence, and apoptosis, are effectively controlled by the combination therapy. The latter notably improved histone H3 and HSP90 hyperacetylation, reduced tumor volume, and significantly increased the survival of HCC xenografts.

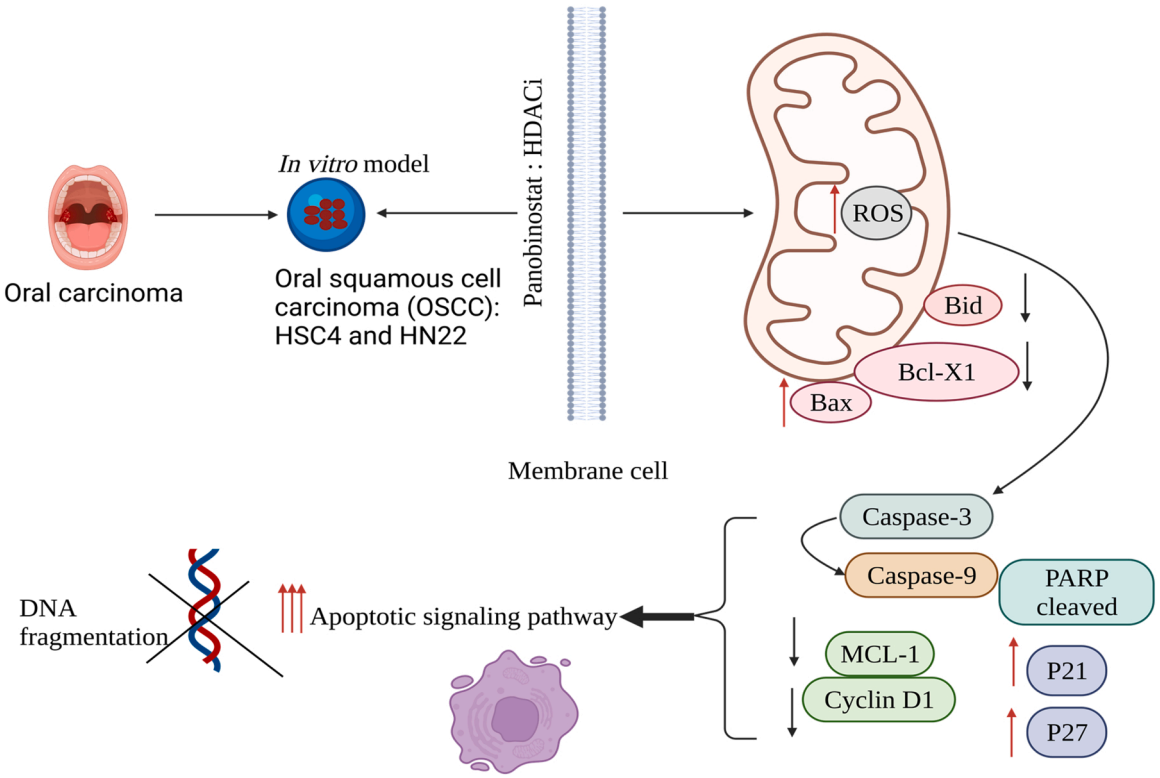

Fig. 5. Anticancer effects of panobinostat in OSCC involving different molecular mechanisms leading to apoptotic signaling pathway activation. *Panobinostat treatment of two OSCC cell lines (HSC4 and HN22) causes cleavage of PARP and caspase-3, and downregulation of Mcl-1 and cyclin D1 expression. This treatment also decreases Bcl-X_L and Bid expression and increases Bax expression in HSC4 and HN22 cells, which increases p21, p27, and ROS production. Such events have triggered the apoptotic signaling pathway.* **Abbreviations:** OSCC, oral squamous cell carcinoma; ROS, reactive oxygen species; Bcl-X_L, B-cell lymphoma-extra-large; Bax, Bcl-2 associated X, apoptosis regulator; Bid, Bcl-2 interacting domain; PARP, poly (ADP-ribose) polymerase; Mcl-1, myeloid cell leukemia-1.

doses of co-administered panobinostat. These data highlight the deleterious effects of clinical treatment regimens combining HDACi and TRAIL pathway activators that may limit the use of this regimen.

A remarkable antitumor effect was observed against AML by combining vorinostat with an fms-like tyrosine kinase 3 (FLT3) inhibitor through the induction of apoptosis via Mcl-1 down-regulation [60]. In this context, a study with the same objective was carried out by combining panobinostat with bortezomib and by evaluating cell sensitivity to Adriamycin, an anticancer drug [61].

On chemoresistant AML cells, this combined therapy showed synergistic cytotoxicity, whereas on HL60/ADR cells, an increased sensitivity to Adriamycin was noted compared to monotherapy. This synergistic interaction was mediated by increasing intracellular Adriamycin accumulation and expression of apoptotic molecules via inhibition of the protein kinase B (PKB, also known as AKT)/NF-κB pathway.

Another regimen of combination therapies was adopted in the in vitro treatment of PC cells by combining panobinostat with the lipid peroxidation end product, 4-hydroxynonenal (HNE) [17]. Consequently, HNE significantly potentiated the anticancer activity of the HDACi, and their combination synergistically inhibited cell proliferation, induced G2/M phase cell cycle arrest, cell death, and DNA damage. Moreover, this combination led to mitosis mediated by cell division cycle 2 (Cdc2) dephosphorylation.

Furthermore, using PCa cell lines and an in vivo model of PC, Bruzzese et al. [62] showed that a combination of panobinostat and zoledronic acid induces a synergistic anti-proliferative effect by increasing reactive oxygen species (ROS) production and modulating p38 mitogen-activated protein kinase (p38-MAPK) and mevalonate pathways. In fact, panobinostat inhibited colony formation in DU145 by approximately 37% and 45% at IC25 and IC50 at 96 h, respectively. In contrast, Toffanin et al. [18] combined panobinostat with sorafenib for the treatment of HCC (in vitro and in vivo). In fact, sorafenib is the cancer drug of first choice for advanced HCC. In vitro results of this combination showed apoptosis and inhibition of cell proliferation and viability at 72 h. After 20 days of in vivo treatment, both agents combined significantly inhibited tumor growth and increased animal survival compared to their effects alone. Additionally, this combination increased autophagy, p21 protein levels, and histone 3 acetylation, with up-regulation of cadherin-1 (CDH1) and down-regulation of baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5), also known as "Survivin" (Fig. 4). Moreover, compared to sorafenib alone, panobinostat at 50 and 100 nM significantly reduced cell viability by 15.7–41.8% three days after treatment in all HCC cell lines examined ($p = 0.004$). These results fully corroborate those obtained by Lachenmayer et al. [63], who tested the same combination (panobinostat/sorafenib) following the same experimental protocol in the treatment of HCC. Interestingly, panobinostat alone at a dose of 0.1 μM inhibited DNMT activity and down-regulated the expression of DNMT proteins and mRNAs associated with reduced methylation of adenomatous polyposis coli (APC) and ras association domain family member 1 isoform A (RASSF1A) target genes in prostate cell lines (in vitro and in vivo) [64].

On the other hand, HR-NBL is another fatal pathology with a low survival rate (<40%) due to its high resistance to conventional chemotherapy. Therefore, the development of new and more effective antitumor agents is necessary, particularly through the combination of several chemotherapeutic drugs. To this end, Wang et al. [65] treated four HR-NBL cell lines with panobinostat alone and in combination with other drugs, namely cisplatin, etoposide, or doxorubicin. This HDACi in monotherapy dose-dependently induced apoptosis and inhibited cell growth, while its combination with the other drugs demonstrated highly synergistic anticancer interactions associated with cooperative induction of apoptosis.

Mechanistically, panobinostat alone abrogated the G2/M cell cycle checkpoint and suppressed the checkpoint kinase 1 (CHK1) signaling pathway, which promotes DNA repair and induces cell cycle progression. These findings indicate that inhibition of this pathway is largely involved in the observed synergistic anticancer interactions between panobinostat and DNA-damaging drugs in HR-NBL cells, making the CHK1 protein an important target for the development of new antitumor approaches. Two years later, this was the aim of the same research team in the development of new therapy against pancreatic cancer, which today constitutes a significant clinical challenge [19]. In fact, based on the results of the previous study showing the down-regulation of CHK1 in HR-NBL cells following treatment with panobinostat, these researchers reassessed the same impact of this HDACi in combination with a selective inhibitor of Wee1, MK-1775, against preclinical models of pancreatic cancer. The Wee1 protein is strongly involved in the control of the G2/M cell cycle checkpoint and in cell cycle arrest via the regulation of Cdc2 phosphorylation; therefore, inhibition of this protein may lead to abrogation of the G2/M checkpoint, leading to cell death. The combination of MK-1775 with DNA damaging agents, particularly CHK1 inhibitors, has demonstrated interesting results against various malignancies. Wang et al. [19] found that the combination between panobinostat and MK-1775 led to a promising synergistic anticancer effect against pancreatic cancer in vitro and in vivo. This synergy was attributed to the ameliorating effect of panobinostat on the efficacy of MK-1775 through the activation of cyclin-dependent kinases (CDKs) (CDK1 and CDK2) and the inactivation of the CHK1 pathway, leading to the accumulation of DNA damage caused by MK-1775 and hence the induction of apoptosis. All these data justify the development of a new clinical therapeutic strategy combining panobinostat and Wee1 inhibitors against pancreatic cancer.

Continuing to expand the use of panobinostat against malignant tumors with poor prognosis, Jeon et al. [21] examined the effect of this drug on two oral squamous cell carcinoma (OSCC) cell lines (HSC4 and HN22). After panobinostat treatment, the authors revealed a reduction in the sub-G1 cell population, cell growth, and specificity protein 1 (Sp1) expression in a dose-dependent manner. This treatment also induced cleavage of PARP and caspase-3, down-regulated the expression of Mcl-1, cyclin D1, and survivin, and up-regulated the expression of p21 and p27, leading to the apoptotic signaling pathway activation by decreasing the expression of Bcl-XL and Bcl-2 interacting domain (Bid) and increasing that of Bax in the HSC4 and HN22 cells (Fig. 5). These results are in line with those obtained previously against SCLC [20] and patient-derived primary tumor [53] cell lines. This study associated the induced apoptosis in panobinostat-treated OSCC cells with suppression of Sp1 expression through the involvement of multiple signaling pathways. Panobinostat was shown to be cytotoxic in nearly all of the 37 cancer cell lines investigated. The IC50 and LD50 values ranged from 4 to 470 nmol/L, with a median of 20 nmol/L. SCLC cell lines were among the most sensitive, with LD50 values of 25 nmol/L consistently. Panobinostat dramatically reduced tumor growth in lung cancer and mesothelioma animal models by an average of 62% when compared to a vehicle control [20].

In conclusion, the preclinical studies discussed here highlight the potential of panobinostat as a promising anticancer agent, either as monotherapy or in combination with other drugs. The HDACi has demonstrated significant anticancer activity in various cancer types, including SCLC, pancreatic cancer, and OSCC. Its effects are primarily attributed to the modulation of key signaling pathways involved in cell cycle regulation, apoptosis, and DNA damage repair. The combination of panobinostat with other chemotherapeutic agents, such as DNA-damaging drugs or kinase inhibitors, has shown synergistic effects that enhance its anticancer properties.

These promising preclinical findings support further investigation into the clinical applications of panobinostat, either alone or in combination with other targeted therapies. The development of new therapeutic strategies combining panobinostat with other agents, such as Wee1 inhibitors, offers hope for improved treatment outcomes in pancreatic cancer and other malignancies with poor prognosis. Continued research is needed to optimize treatment regimens, identify potential biomarkers to predict patient response, and better understand the underlying molecular mechanisms of panobinostat's anticancer activity.

In a different context, panobinostat has been studied for its anti-melanoma effect in vitro using melanoma cell lines and in vivo in a mouse melanoma model [66]. The growth of all treated melanocytes was inhibited with IC50 values ranging from 25 nM to 100 nM, and was characterized by G1-phase cell cycle arrest and increased apoptosis. In addition, melanoma differentiation antigen expression was greatly increased. The survival of animals with melanoma was increased following this treatment. Taken together, this HDACi not only affected melanoma growth and improved animal survival, but also increased its immunogenicity. These effects support the results shown in the treatment of melanoma with vorinostat [67,68]. Furthermore, vorinostat has been shown to sensitize two triple-negative breast cancer (TNBC) cell lines (MDA-MB-231 and Hs578T) to cancer treatment [69]. One of these cell lines was the subject of another study investigating the anti-tumor potential of panobinostat by targeting epithelial-mesenchymal transition (EMT), a major contributor to the metastatic process [70]. In fact, treatment of three TNBC cell lines with this HDACi altered their morphology and gene expression and strongly inhibited EMT. Additionally, an inhibition of MDA-MB-231 cell metastasis was noted in vivo. This potential was attributed to the inhibition of zinc finger E-box binding homeobox (ZEB) 1 and 2, two molecules related to signaling pathways responsible for tumor cell survival, in particular the improvement of cell proliferation, by promoting cell invasion and migration, and inducing resistance to anticancer agents.

Despite the remarkable effects obtained from HDACis alone in the treatment of solid tumors, their efficacy remains limited, hence the interest in discovering other combinations that could improve this epigenetic therapy. In this sense, Sato et al. [71] hypothesized that an HDACi, panobinostat, combined with a protease inhibitor, ritonavir, might more effectively treat advanced kidney cancer. So far, no cure for this type of cancer is available. Study results showed that in vitro treatment with panobinostat alone increases histone acetylation, which is further enhanced by co-treatment with ritonavir, testifying to the potentiating effect of ritonavir on that of panobinostat. In addition, panobinostat with ritonavir synergistically inhibited HDAC expression, which is involved in enhancing histone acetylation. Furthermore, this combination induced apoptosis of renal cancer cells in a caspase-dependent manner and inhibited colony formation of these cells as well as their growth. Also, treatment for 10 days with this co-therapy inhibited tumor growth in vivo. Currently, this is the only study determining the combinatorial effect of panobinostat and ritonavir in advanced renal cancer therapy.

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Continuing in the treatment of kidney cancer, but focusing on the embryonic type "Wilms tumor (WT)", Yan-Fang et al. [72] assessed the anticancer activity of panobinostat alone in vitro on two WT cell lines, SK-NEP-1 and G401, and in vivo on SK-NEP-1 tumor-carrying mice. In a dose-dependent manner, panobinostat treatment inhibited tumor cell proliferation (in vitro and in vivo) and induced apoptosis. More interestingly, new networks and targets were identified in response to this treatment in SK-NEP-1 cells, while determining myelocytomatosis oncogene (MYC), heat shock protein 70 (HSP70), and Reprimo, Escaping G2 and M checkpoints (RPRM) as major regulators; providing more data on the pro-apoptotic mechanism of this substance.

We previously observed in the study conducted by Ocio et al. [54] a promising anti-MM activity of panobinostat in monotherapy as well as in tritherapy. This activity was subsequently re-verified in bitherapy (in vitro and in vivo) combining panobinostat with a selective inhibitor of nuclear export (SINE), KPT-8602 [73]. Indeed, co-treatment with KPT-8602 inhibited MM cell viability with a synergistic anti-tumor effect (in vitro and in vivo). At sub-cytotoxic doses, panobinostat enhanced the cytotoxic activity of KPT-8602 (IC50 = 23 nM) and inhibited tumor growth in mice (69.4%) after 22 days of administration. In turn, KPT-8602 enhanced panobinostat's inhibitory potential on deacetylation. Remarkably, the combination of both drugs completely treated some tumors (3 out of 8 tumors) with 95% tumor regression. Moreover, this drug combination induced the cleavage of PARP-1 and caspase-3 and induced DNA damage, all confirming cell death. The same bitherapy was reassessed by Elloul et al. [74] by combining panobinostat with another SINE, selinexor, against MM both in vitro and in vivo. In MM 0.1 S and NCI-H929 cell lines, this combination synergistically inhibited cell proliferation, increased levels of pro-apoptotic factors (cleaved caspase-3 and Bax), and reduced levels of anti-apoptotic factors (NF-κB and p21) as well as those of c-MYC mRNA and proteins. Whereas in xenografted mice with MM 0.1 S cells, the panobinostat/selinexor combination increased tumor growth inhibition to 93%. From these two studies [73,74], it can be seen that the combination of panobinostat with a SINE provides an amplified anti-MM activity, allowing it to be investigated in clinical trials. This activity was confirmed in vitro the following year by adopting the same therapeutic approach as that already demonstrated by Ocio et al. [54], combining panobinostat and the proteasome inhibitor, bortezomib, to treat patients with MM [75]. At increasing concentrations of panobinostat alone or in combination with bortezomib, proliferation inhibition of MM cell lines, U266 and RRMM-BMMNC, was obtained in a dose and time-dependent manner. In RRMM-BMMNC cells, the proteasome/bortezomib combination additively induced apoptosis and G0/G1 phase cell cycle arrest. On key markers of apoptosis, progressive up-regulation of mRNA level of apoptotic protease activating factor 1 (APAF1) and caspase-3 and down-regulation of TOSO gene expression were noted following this combination in myeloma cells. Similarly, this HDACi alone decreased Bcl-X level, increased PARP level, and induced histone H4 hyperacetylation.

In contrast, in an effort to innovate in OC therapy, Garrett et al. [76] evaluated in vitro and in vivo the anticancer effect of panobinostat using OC cells (OCCs). As a single agent, this HDACi inhibited the viability of taxol-sensitive/resistant OCCs as well as the tumor growth of patient-derived xenograft (PDX) models in vivo after 21 days of treatment. The combination of this agent with conventional chemotherapy, paclitaxel/carboplatin, showed an important additive effect, as evidenced by increased tumor regression. In the same year, other researchers showed that this HDACi improves the response of overexpressing cyclin E, homologous recombination (HR)-proficient OCCs to a PARP inhibitor (PARPi), olaparib [77]. Indeed, several positive effects were recorded following a co-treatment combining panobinostat with olaparib, such as down-regulation of gene expression of HR and cyclin E repair pathways, induction of apoptosis and DNA damage, and inhibition of clonogenicity and cell growth (in vitro and in vivo). These results suggest the involvement of panobinostat in the treatment of PARPis-resistant HR-proficient OCs and in cases of cyclin E overexpression, as an effective strategy to enhance the activity of these inhibitors.

In another context, Wasim and Chopra, two Indian researchers carried out two in vitro studies evaluating the effect of panobinostat, as a single agent or in combination with topoisomerase inhibitors, on two cervical cancer cell lines, SiHa and HeLa, and the associated mechanisms [78,79]. In the first study, they showed that panobinostat alone induces apoptosis and inhibits the viability of HeLa and SiHa cells with cell cycle arrest at G0/G1 and G2/M phases, respectively [78]. The underlying cellular mechanisms were the disruption of mitochondrial membrane potential and excessive production of ROS, while the molecular mechanisms involved were reduced expression of the anti-apoptotic gene Bcl-XL and increased levels of caspase-9 and CDK inhibitor p21 as well as histone H3 acetylation. Simultaneously, this treatment increased levels of pro-apoptotic factors (caspase-3/7 activity), which were excessively increased by co-treatment with topoisomerase inhibitors, etoposide and topotecan. Similarly, the therapeutic potential of this synergy was observed in the second study via an intrinsic apoptotic pathway by activating the ERK pathway and inhibiting the NF-κB and phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathways [79].

In another study, panobinostat treatment was proposed as a new approach against gefitinib-resistant Kirsten rat sarcoma viral oncogene homolog (KRAS)-mutant/epidermal growth factor receptor (EGFR)-wild-type NSCLC [80]. Although KRAS is the most common oncogene in this type of cancer, no direct anti-KRAS therapy is available. This makes KRAS downstream signaling an important target for optimal therapy against NSCLC. Therefore, Lee et al. [80] demonstrated that panobinostat alone sensitizes NSCLC cell lines to gefitinib in vitro and that the combination of these two molecules synergistically reduces tumor growth (in vitro and in vivo). The study of the underlying molecular mechanisms showed that panobinostat monotherapy inhibits the expression of the transcriptional co-activator with the PDZ binding motif (TAZ) related to tumor progression. Additively, the panobinostat/gefitinib combination reduced TAZ and its downstream targets. This consequently reduces EGFR compensatory signaling and increases the sensitivity of tumor cells to gefitinib.

These anticancer effects can be attributed to the ability of this HDACi to involve host immunity. This concept was applied to enhance the antitumor efficacy of a monoclonal antibody, trastuzumab, against HER2 + breast tumors [81]. Indeed, panobinostat combined with trastuzumab induced tumor regression and blocked AKT signaling in animals lacking adaptive and/or innate immune effector cells. Interestingly, panobinostat alone enhanced the anti-human epidermal growth factor receptor 2 (HER2) activity of trastuzumab (in vivo) by allowing it to induce natural killer (NK) cell-mediated responses responsible for eradicating these tumors. Currently, this is the only report highlighting this anti-HER2 association strategy, strongly justifying the continuation of its clinical development.

In 2018, a Chinese research team investigated for the first time the anti-cancer potential of this emerging HDACi against esophageal squamous cell carcinoma (ESCC), which has no effective treatment [82]. Their investigation was based on the hypothesis that ESCC cells are sensitive to panobinostat, given the high expression of HDAC genes in these cells. Indeed, their results revealed significant suppression of cell proliferation, inhibition of tumor protein 53 (TP53) mRNA and protein expression, a decrease in cyclin D1 expression, and an increase in p21 expression.

Despite current therapeutic advances against non-Hodgkin's lymphoma (NHL), mortality rates remain high due to the lack of valid clinical models. For this, Dias et al. [83] used canine lymphoma, having similar characteristics to its human counterpart, to evaluate the anticancer activity of panobinostat in comparison to other HDACis, on canine diffuse large B-cell lymphoma (DLBCL) cell lines, CLBL-1, as well as on mice xenografted with these cells. The most promising results were recorded with panobinostat, which inhibited cell proliferation by

promoting the acetylation of α-tubulin and histones H3. Moreover, it strongly inhibited tumor growth and induced apoptosis and histone H3 acetylation in vivo. This investigation validates the natural model of this type of lymphoma for the translational evaluation of panobinostat.

On the other hand, human adipose tissue-derived mesenchymal stem cells expressing the secreted form of TRAIL (hAT-MSC.sTRAIL) were used in the treatment of several types of cancers. In this sense, Choi et al. [22] used panobinostat to potentiate the therapeutic effect of hAT-MSC. sTRAIL against malignant glioma (in vitro and in vivo). In GBM cells, treatment combining panobinostat and hAT-MSC.sTRAIL improved apoptosis and inhibited cell viability, with IC50 values ranging from 0.03 to 0.23 μM. Whereas in a murine model of diffuse intrinsic pontine glioma, this combination prolonged survival and decreased tumor volume.

Considering all the research work conducted in this review to assess the anti-MM activity of panobinostat and its ability to modify antitumor immune responses, Iwasa et al. [84] investigated the effect of this HDACi on regulating the expression of immune checkpoint molecules in MM cells. Among these molecules is PD-L1, which impairs beneficial anti-cancer immune responses. Therefore, the combination of panobinostat with IFN-γ, an essential cytokine in immune responses, enhanced in a ligand-dependent manner the expression of PD-L1 by promoting the IFN-γ/STAT1 apoptotic signaling pathway.

On the other hand, given the already demonstrated antitumor activity of panobinostat targeting EMT in breast cancer [70], the search for new targets was the major objective of more recent studies [23,85]. Indeed, Qin et al. [23] showed that panobinostat exerts a cytotoxic effect in TNBC cells and inhibits metastasis and tumor growth in a mouse model by down-regulating the expression of β-catenin and up-regulating that of adenomatous polyposis coli-like protein (APCL), a regulator of the Wnt/β-catenin pathway promoting the degradation and ubiquitylation of β-catenin. This suggests that panobinostat's anticancer activity in breast cancer is associated with Wnt/β-catenin signaling pathway inhibition by targeting APCL. Another target was determined in the other study [85], recording the same anticancer potential in vitro and in vivo on TNBC cells. Indeed, this potential was increased via the decrease in HER3-EGFR signaling, making targeting of HER3 as well as EGFR a new therapeutic strategy for TNBC patients. Regarding the study conducted by Wu et al. [86], the combination of this HDACi with a mammalian target of rapamycin (mTOR) inhibitor, rapamycin, resulted in several beneficial effects against TNBC, such as inhibition of TNBC cell growth (in vitro and in vivo) and induction of cell apoptosis that have been attributed to overproduction of ROS responsible for the activation of the endoplasmic reticulum stress.

In contrast, the anti-leukemic properties of this HDACi were investigated on acute lymphoblastic leukemia (ALL) cells [87]. As monotherapy, panobinostat prolonged ALL cell transition from the G1 phase and induced cell apoptosis, which may be increased via inactivation of the NF-κB pathway. More remarkably, panobinostat enhanced the cytotoxic effect of a chemotherapeutic agent, vincristine, in pre-B ALL-derived cells. This anti-leukemic activity was confirmed very recently in vivo in an animal model of ALL with t(4;11) by increasing overall survival and promoting antagonistic effects in vitro in association with two antimetabolites (6-mercaptopurine and methotrexate) in the ALL cell line (RS4;11) [88].

In this review, we previously found in the study conducted by Wilson et al. [77] that panobinostat combined with olaparib exerts several antitumor effects on OCCs. Furthermore, they recently carried out two experiments combining the same inhibitors (HDACi/PARPi) in order to identify novel mechanisms in OC therapy using the same experimental OCC models (in vitro and in vivo) [89,90]. In the first experiment [89], panobinostat/olaparib treatment reduced the expression of several genes implicated in apoptosis, cell proliferation, and DNA damage, and enriched cytokine secretion, immune cell engagement [chemokine (CXC motif) ligand (CXCL) 3, interleukin (IL)− 8, etc.], and T cell activation (TNFSF9, CD274/PD-L1, etc.). In vivo, this treatment attenuated tumor growth and burden. Additionally, an important antitumor immunity was noted following this combination through the increase in CD8 + T cell infiltration. In the second experiment [90], the same outcomes were obtained by this combination in addition to attenuation of 20/37 HR pathway gene expression as well as M2 macrophage marker expression. From the data of the three studies carried out by Wilson and collaborators, it can be concluded that the HDACi/PARPi combinations exert increased anti-tumorigenic effects against ovarian tumors through various mechanisms, namely indirect immune-modulatory and direct cytotoxic effects. Moreover, to shed more light on the anti-OC mechanisms of panobinostat, it was combined with an autophagy inhibitor, chloroquine [91]. This combination synergistically induced apoptosis and inhibited OCC proliferation. In fact, chloroquine alone increased the production of ROS, inducing DNA damage, whereas panobinostat blocked their repair. This explains the strong synergy noted by these two combined drugs.

Given the anticancer potential previously investigated in the study performed by Wang et al. [19] following the panobinostat/MK-1775 combination against pancreatic cancer, Ali et al. [92] tested the effect of this HDACi on the anticancer effect of chimeric antigen receptor (CAR) T cells in the treatment of pancreatic cancer using two in vitro and in vivo models. Indeed, this combination suppressed HER2 + pancreatic cancers, which eradicated the majority of cancers. Interestingly, panobinostat alone induced apoptosis and improved CAR T cell gene accessibility, and eradicated cancer xenografts in vivo. These studies suggest that administering a scheme containing panobinostat and CAR T cells to patients with pancreatic cancer may show promising results.

Regarding PC therapy, we have previously cited several studies highlighting the anticancer properties of the combined therapy between panobinostat and other chemotherapeutic agents [17,64,62]. Recently, an HDACi/DNMTi (hydralazine) combination synergistically attenuated the malignant characteristics of PC cells by inducing apoptosis and DNA damage, reducing colony formation, proliferation, and cell viability, and increasing tumor cell migration and invasion [93].

Regarding the anti-neuroblastoma activity, we found above in the study performed by Wang et al. [65] interesting results in monotherapy as well as in combination therapy. In this sense, Xiao et al. [94] studied in vitro and in vivo the effect of the panobinostat-curaxin CBL0137 combination against HR-NBL by targeting chromatin stability. In neuroblasts, this treatment improved nucleosome destabilization and inhibited cell growth and DNA damage repair. While in animal models of neuroblastoma, it delayed tumor progression and induced an immune response and type I IFN. These data make this combination an optimal anti-neuroblastoma strategy for addition to immunotherapies.

In contrast, the last part of this work was devoted to discussing the most recent investigations about the anticancer activity of panobinostat and the underlying mechanisms of action [95–99]. Indeed, in a Mexican research laboratory, this activity was examined for the treatment of GBM multiforme, known for its poor prognosis, frequent tumor recurrences, and high resistance to chemotherapeutics [95]. This can be ameliorated via immunogenic cell death (ICD) inducers capable of stimulating the antitumor immune response. However, the low permeability of the blood-brain barrier in patients with this brain tumor constitutes a limit for all ICD inducers. Panobinostat has been shown to cross this barrier [100] and exert antitumor effects via various mechanisms. Therefore, on a C6 glioma cell line, Franco-Molina et al. [95] showed that this HDACi induces apoptosis in a time- and dose-dependent manner, whereas in an animal glioma model, a decrease in tumor volume without ICD induction was observed, suggesting an antitumor mechanism independent of immunogenic cell death. This explains the tumor recurrences recorded after conventional treatments in these patients.

In another study, the effect of this molecule was verified in vitro and in vivo against epithelioid sarcoma and rhabdoid tumor, two malignant tumors with poor prognosis and characterized by deregulation of growth factor receptors [97]. The authors observed an anti-proliferative effect

of panobinostat in VAESBJ/GRU1 epithelioid sarcoma and A204 rhabdoid tumor cell lines, with induced apoptosis and tumor growth inhibition in vivo. Moreover, in rhabdoid tumor, this HDACi up-regulated EGFR, whereas in epithelioid sarcoma, it induced mesenchymal-epithelial transition and down-regulated EGFR. Interestingly, the apoptosis observed was improved by further sensitizing cell lines following a treatment combining panobinostat with an EGFR inhibitor, erlotinib. It can be inferred that the anticancer activity of panobinostat against these malignancies is strongly attributed to the modulation of the growth factor receptor.

Regarding the therapeutic effect of this HDACi on gastric cancer, few reports have been made. This effect and the associated mechanism were investigated by Lee et al. [98]; in vitro on gastric cancer cells and in vivo on mice carrying these cells. Results showed that this substance induces apoptosis (cleavage of PARP-1 and caspase-3), reduces colony formation, and inhibits tumor cell proliferation and viability. In addition, it induced G_2/M phase cell cycle arrest, inhibited cell metastasis by regulating E-cadherin and matrix metalloproteinase (MMP)− 9 expression, reduced p-Akt and forkhead box protein M1 (FOXM1) levels, and suppressed tumor growth in vivo. Taken together, the efficacy of panobinostat against gastric cancer cell proliferation and metastasis was related to inactivation of the Akt/FOXM1 signaling pathway.

In the same year, Afolabi et al. [96] tested the anticancer effect of this HDACi alone or combined with immune cell therapy against a varied panel of tumor cells. They revealed anti-proliferative and anticancer effects on all tumor cells tested following treatment with panobinostat alone, whereas its combination with NK cells synergistically induced tumor cell cytolysis. Although NK cells have a high cytotoxic potential in anti-tumor immune responses, their combined effect with that of panobinostat is not fully explored. Mechanistically, the authors attributed tumor cytolysis to the establishment of conjugation between tumor cells and NK cells and to the increased expression of genes related to tight junctions. This data show that NK cell-based immunotherapy can be enhanced by panobinostat anti-tumor potential.

This was exactly the aim of a very recent study evaluating the effect of panobinostat on NK cell cytotoxicity in the therapy of soft tissue sarcoma (STS) [99]. The results showed that NK cell-mediated cytotoxicity was enhanced by panobinostat treatment alone. Evaluation of the mechanism of action involved showed that this treatment activates the Wnt/β-catenin pathway, which contradicts the results previously demonstrated in the study conducted by Qin et al. [23]. Importantly, inhibition of this pathway reduced the cytotoxic effect of NK cells stimulated by this molecule against STS.

5. Clinical investigations of anticancer use of panobinostat

Given the promising results observed with panobinostat in the treatment of several cancers in preclinical studies, the evaluation of its anticancer activity in the clinic has become a crucial topic in oncology. However, in order to determine its effectiveness and safety in this clinical setting, it is necessary to conduct rigorous clinical trials. The results of these studies will help determine the role of this HDACi in cancer treatment and identify the patient populations that can benefit the most.

Before receiving FDA approval in February 2015 for the treatment of multiple myeloma, panobinostat's potential as an anti-cancer drug was already being studied in clinical trials for various types of cancers.

From the preclinical data cited above, it was revealed that the cancer-fighting properties of panobinostat are largely due to intrinsic signaling that triggers apoptosis, and its combination with the inhibition of anti-apoptotic factors may enhance the cells' responsiveness to treatment [16]. A clinical study conducted in 2008 by Ellis and collaborators assessed the efficacy and safety of this molecule in CTCL patients receiving this drug orally [55]. Results indicated varying responses from complete and partial response to stable and progressive disease. The study found a common regulation of genes related to angiogenesis, immune regulation, and apoptosis, which may serve as biomarkers for the activity of panobinostat. Overall, this study determined that panobinostat is well-tolerated and produced noteworthy clinical responses in CTCL patients.

Many preclinical studies have demonstrated the therapeutic efficacy of panobinostat in treating prostate cancer (PC), either as a single agent or in combination with other chemotherapeutic agents, through various mechanisms of action. This was also clinically verified in the phase I study by Rathkopf et al. [101], which determined the most appropriate oral dose of this HDACi that was examined alone and in combination with a chemotherapy drug against castration-resistant PC (CRPC). The panobinostat/docetaxel combination was feasible, whereas the pharmacokinetics of panobinostat alone was not impacted by docetaxel. In addition, some patients experienced a worsening of their condition even though there was an increase in acetylated histones. While 63% of patients experienced a 50% or greater decrease in the amount of prostate-specific antigen (PSA), a substance produced by PC cells, the decrease in its level in the blood may indicate a reduction in tumor size or a response to treatment.

Moreover, the management of this type of cancer was evaluated in a recent study by combining panobinostat with bicalutamide [102], a non-steroidal anti-androgen drug often used in combination with other treatments against PC [103]. This combination showed synergistic anticancer effects and inhibition of androgen receptor (AR) activity in CRPC patients. Additionally, patients treated with this combination at a dose of 40 mg experienced higher radiographic progression-free survival than those treated with bicalutamide alone, while side effects were tolerable and required dose reduction for an extended duration of treatment. The general insight that can be drawn from these studies is that epigenetic therapy with panobinostat can improve the efficacy of treatment with bicalutamide or docetaxel for patients with CRPC. This suggests that this therapy may be a useful strategy to address treatment resistance in these patients and potentially improve their response to treatment.

In contrast, Hamberg et al. [104] assessed the impact of ketoconazole, a potent inhibitor of Cytochrome P450 3 A (CYP3A), on the safety and pharmacokinetics of panobinostat. The study showed that when panobinostat and ketoconazole were administered concurrently, the area under the curve (AUC) and the maximum concentration (Cmax) of panobinostat increased by 1.6 and 1.8 times, respectively. The most commonly reported side effects were related to the gastrointestinal system. The authors concluded that it is possible to administer panobinostat alongside CYP3A inhibitors, but careful monitoring of side effects is required due to variability in exposure, and because chronic dosing of this HDACi with CYP3A inhibitors has not been investigated.

Due to the promising preclinical results of the combination of panobinostat with bortezomib against various types of cancer, it is important to investigate this combination in the clinic. In 2012, a phase II clinical trial was conducted to evaluate the safety and efficacy of this combination in patients with advanced pancreatic cancer who had progressed on standard treatment with gemcitabine [105]. However, the study had to be abandoned due to ineffective treatment and a lack of positive results. The results showed a median progression-free survival (PFS) of 2.1 months, with thrombocytopenia and diarrhea being the most common adverse events. Based on these findings, the authors concluded that the combination of panobinostat and bortezomib is not an effective treatment option for advanced pancreatic cancer.

On the other hand, the tolerability and safety of using panobinostat alone was evaluated in 14 Japanese patients with advanced solid tumors (ASTs) [106]. The results indicated that intravenous administration of panobinostat at three dose levels (10, 15, and 20 mg/m2) may be effective and relatively safe for these patients.

In the same year, a phase II study was conducted to evaluate the efficacy and safety of panobinostat monotherapy in the treatment of relapsed or refractory (R/R) Hodgkin's lymphoma (HL) [107]. The study recorded some common side effects related to panobinostat treatment (fatigue, vomiting, nausea, diarrhea, anemia, thrombocytopenia), but

demonstrated promising antitumor activity with durable responses in patients with R/R HL. Given its ability to alter several cellular mechanisms, as evidenced by preclinical studies, panobinostat may enhance the activity of other agents used in combination. Hence, there is a need for carefully designed clinical trials to explore the use of this HDACi in combination with monoclonal antibodies, chemotherapy, and other molecule inhibitors. The following year, a study was conducted by Oki et al. [108] to evaluate the combination of panobinostat and everolimus in the treatment of relapsed HL and NHL. Everolimus is an immunosuppressive drug used to treat various diseases, particularly cancer, and acts by inhibiting the mTOR signaling pathway, which stimulates cell growth and proliferation. The combination showed good clinical activity in 33% of patients with objective responses associated with decreased IL-5 levels. However, the study also observed thrombocytopenia as the most common toxicity (64%), requiring treatment discontinuation. Further trials are recommended to explore different combinations of HDACi panobinostat with mTOR inhibitors, including correlative analysis of cytokine concentrations to assess their clinical relevance.

We demonstrated in the Mechanism section of our work that panobinostat can act alone or in synergy with other bioactive compounds against SCLC and NSCLC (in vitro and in vivo). In this context, a Phase II clinical study was conducted to test the safety and efficacy of 20 mg/mq (i.v.) of this substance in SCLC patients for 8 days every 3 weeks [109]. Although the study was stopped early due to inactivity, a positive safety profile and modest antitumor activity were observed, suggesting that panobinostat could be further explored in future trials. Moreover, the same parameters (efficacy/safety) were examined in another study in patients with NSCLC, but this time to verify the synergistic potential of the combination of panobinostat with erlotinib [110], an oral drug used to treat specific types of cancer, particularly NSCLC, by inhibiting EGFR, a protein involved in the progression of cancer cells [111]. Consequently, the panobinostat/erlotinib combination exhibited adverse effects such as rash, nausea, and fatigue, with a disease control rate of 54% and higher PFS in patients with mutations in EGFR than in those without. Better response and PFS have been shown to correlate with low levels of CHK1 expression. Importantly, the pharmacodynamic effect of panobinostat was confirmed while the pharmacokinetics of erlotinib were unaffected. These outcomes establish the basis for biomarker-driven trials to verify these results and validate the ability of CHK1 to predict the response to treatments involving panobinostat.

Based on the results obtained in the study by Morita et al. [106] in the treatment of patients with AST, another subsequent study (Phase I) with the same objectives was carried out following two administration schedules: daily and weekly, which provided a maximum tolerated dose (MTD) of 7.2 g/m2 and 20.0 mg/m2, respectively [112]. Additionally, cardiac arrhythmias and fatigue were common side effects of the drug, with myelosuppression being the dose-limiting toxicity (DLT). Analysis of pharmacodynamic and pharmacokinetic phenomena revealed that the bioavailability and maximum concentrations of panobinostat increase in proportion to the dose.

These findings constituted the perspective for a further investigation into the effect of panobinostat on Cytochrome P450 2D6 (CYP2D6) substrate in patients with AST [113]. Previous preclinical research showed that panobinostat can inhibit CYP2D6 [114]. It is, therefore, crucial to determine the potential impact of inhibiting its activity in the clinic on drugs that are dependent on CYP2D6. This study investigated the impact of panobinostat on dextromethorphan (DM), which is a CYP2D6 substrate, in patients with AST who have functional CYP2D6 genes. On day 1, patients received treatment with DM alone, on days 3 and 5 with panobinostat alone, and on day 8 with both drugs. Therefore, exposure to DM and its metabolite (dextrorphan) increased under the effect of panobinostat by 64% and 29%, respectively. This means that panobinostat weakly reduced CYP2D6 activity in patients with AST by augmenting DM exposure approximately less than two-fold.

Regarding AML therapy, it has previously been indicated that a combination of panobinostat and bortezomib exhibits synergistic cytotoxicity caused by an increase in the amount of adriamycin accumulated inside tumor cells and an increase in the expression of molecules involved in apoptosis by inhibiting the Akt/NF-κB pathway [61]. These data have encouraged other researchers to clinically examine new combinations in the treatment of this type of cancer. Indeed, Govindaraj et al. [115] combined panobinostat with azacitidine (a DNMTi) to target Tregs (regulatory T cells) in AML patients. Azacitidine is a chemotherapy drug often used in AML treatment by inhibiting RNA and DNA production, thereby interfering with tumor cell replication and growth. The study enrolled 14 AML patients and 30 healthy donors and treated the patients with panobinostat and azacitidine for 4-week cycles. The findings indicated that there was a rise in the number of TNF receptor-2 (TNFR2 +) Tregs in AML with a strong capability to move to the bone marrow. This combined treatment lowered the concentration of TNFR2 + Tregs in patients' bone marrow and peripheral blood, leading to increased production of IL-2 and IFN-γ by effector T cells, which was related to positive clinical outcomes. This study provides a promising avenue for the development of a more effective treatment for AML by targeting Tregs. Indeed, this combination was re-examined in the treatment of AML and myelodysplastic syndrome (MDS) in a phase Ib/II clinical study to assess the efficacy of HDACi/DNMTi therapy and determine the MTD [116]. The study enrolled 39 patients with AML or MDS who received panobinostat orally for seven doses followed by azacitidine subcutaneously for five days in 4-week cycles. In addition, the study showed that an increase in acetylation of histones H3 and H4 is a reliable early biomarker of clinical activity. Overall, the administration of panobinostat in combination with azacitidine on a semi-sequential basis was a practical and encouraging treatment option for patients with AML and MDS.

Given the promising anti-melanoma activity of panobinostat alone demonstrated in preclinical studies [66], a phase I clinical trial tested the tolerability and safety of a triple therapy, combining two epigenetic agents (panobinostat and decitabine) with temozolomide in the treatment of patients with resistant metastatic melanoma [117]. Temozolomide is an antineoplastic agent used in the treatment of various cancers, predominantly melanoma and brain tumors, by disrupting tumor cell DNA, inhibiting their ability to divide and proliferate [118]. None of the patients exhibited any DLTs when treated with the three drugs under a combined schedule. Generally, patients tolerated this combination well, with some side effects attributed to the treatment. Disease progression was the primary reason for stopping the study. The authors concluded that the combination of the three drugs tested is sufficiently safe to continue in a phase II study.

However, it was established in a subsequent phase I clinical trial that the single use of panobinostat has no efficacy against metastatic melanoma [119]. Indeed, the patients in this study were divided into two groups and received different doses of panobinostat, which showed a high rate of toxicity, a disease control rate of 27%, and an overall response rate of 0%. These studies reinforce the approach of combinatorial treatments in the management of melanoma.

In contrast, Tan et al. [120] reassessed the panobinostat/bortezomib combination previously studied in the treatment of advanced pancreatic cancer [105] but in the treatment of patients with R/R peripheral T-cell lymphoma (PTCL). The results of this study demonstrated for the first time that the combination of HDAC and proteasome inhibitors is feasible and safe, constituting a promising approach for PTCL treatment. These findings validate preclinical studies that have shown synergistic activities with this combination.

The significant results obtained from these various combination therapies have encouraged other researchers to investigate the potential of this HDACi when combined with other therapeutic agents. In fact, an American research team combined panobinostat with a monoclonal antibody, bevacizumab, which neutralizes a protein called vascular endothelial growth factor (VEGF) involved in the formation of new blood vessels in certain types of tumors, to treat recurrent high-grade

glioma (HGG) in 39 patients, 15 of whom had recurrent anaplastic glioma (AG) and 24 had recurrent GBM [121]. AG and GBM are recurrent forms of HGG and are considered the most aggressive and complex brain tumors to treat. In this phase II clinical trial, the primary endpoint of the panobinostat/bevacizumab combination was the 6-month PFS rate, which was low compared to bevacizumab monotherapy (historical controls). Despite reasonable tolerability, this combination in patients with recurrent GBM or AG did not provide a significant improvement in 6-month PFS compared to historical data. Therefore, continuing this treatment in combination is not recommended.

Due to the considerable anticancer efficacy of panobinostat confirmed by several clinical trials, determining the pharmacokinetics of its population has become imperative. This was the aim of a Swiss-American collaboration in patients with solid and hematological tumors, using a nonlinear mixed-effect model to fit plasma concentration data obtained from 14 phase I and II trials of panobinostat [122]. The results indicated that panobinostat is more accurately characterized when using a three-compartment model that incorporates first-order absorption and elimination. While the analysis of the impact of clinical and demographic factors on the pharmacokinetics of this substance showed that race, age, and body size may have a slight effect, but this is overshadowed by the greater inter-individual variability. More interestingly, body surface area was found to decrease panobinostat AUC, and increasing age and being of Caucasian race were found to decrease this AUC. No significant effect on the pharmacokinetics of panobinostat was identified in relation to factors such as liver markers, kidney function, tumor type, sex, or concurrent medications. These findings indicate that clinical and demographic factors have a limited impact on panobinostat pharmacokinetics, highlighting the need for further specialized studies.

On the other hand, Zaja et al. [123] performed a phase II trial to evaluate the effectiveness of panobinostat in patients with R/R DLBCL. This study, which included 35 adult patients, was conducted due to the good clinical outcomes and durable responses observed with this HDACi in patients with R/R HL and NHL, as previously demonstrated [107, 108]. In fact, R/R DLBCL is a type of NHL representing a group of cancers that originate in the lymphatic system. The results of this study showed moderate efficacy of panobinostat in the treatment of R/R DLBCL, but it may provide a durable and effective response for a small proportion of patients. However, hematologic side effects, particularly grade 3 and 4 thrombocytopenia, can make treatment difficult, which supports previous studies that have recorded this condition as the major toxicity. It is therefore important to determine the biomarkers associated with panobinostat response in order to better target patients who could benefit from a single treatment based on this drug.

Recently, the efficacy and safety of the panobinostat/everolimus (HDACi/mTORi) combination was re-investigated in 3-week cycles in the treatment of 21 patients with advanced clear cell renal cell carcinoma (ccRCC) [124]. The study examined the presence of microRNA 605 (miR-605) in serum samples and found that patients with progressive disease (PD) had higher levels of miR-605 compared to those with stable disease (SD). Patients with PD had low levels of miR-605 after the first cycle of treatment, while patients with SD experienced increased levels. This study determined a tolerable and safe dose-schedule for panobinostat/everolimus combination. However, this therapy did not significantly ameliorate clinical outcomes in advanced ccRCC patients. Additionally, differential miR-605 expression was found in relation to treatment response. It is therefore recommended to undertake further study on the role of miR-605 as a prognostic and predictive factor in this group of patients.

6. Concluding remarks and perspectives

According to the findings from this study review, it can be concluded that HDAC inhibitor panobinostat possesses considerable strength in the regulation of signaling pathways that are indirectly involved in the

Table 1
In vitro anticancer mechanisms related to HDAC inhibition by Panobinostat.

Tumour models	Anticancer	Ref.
35 colon cancer cell lines	Induced potent anti-proliferative effects	[15]
Small-cell lung cancer (SCLC) cell lines	IC_{50} and LD_{50}: ranged from 4 to 470 nmol/L Elevated amounts of cell cycle regulators and proapoptosis factors Decreased levels of antiapoptotic factors Reduced tumor growth (62%)	[20]
Rituximab-[chemotherapy]-sensitive cell lines (RSCL), rituximab-[chemotherapy]-resistant cell lines (RRCL), and primary lymphoma cells	Exhibited dose-dependent antitumor activity Induced down-regulation of B-cell lymphoma-extra-large ($Bcl\text{-}X_L$) in lymphoma cells	[53]
MM1S cell line	Reduced tumor burden, inhibited disease progression, and preserved bone integrity Panobinostat + Dexamethasone + either Bortezomib or Lenalidomide showed promising anti-myeloma efficacy	[54]
Cutaneous T-cell lymphoma (CTCL): HUT78, HuT102, MJ, and HH cells	HUT78: $IC_{50} = 4$ nM HUT78: LD_{50} of 28 nM Inhibited cell growth Induced cell death Down-regulated the activated Signal Transducers and Activators of Transcription (STAT) proteins in CTCL cells resistant to vorinostat	[16]
Anaplastic thyroid cancer cell lines (BHT-101, CAL-62, and 8305 C)	Altered cell viability Inhibited colony formation Induced cell cycle arrest Induced apoptosis	[56]
4T1.2, 4T1.2/MSCV, 4T1.2/Bcl-2, 4T1.2/CrmA and EO771 mammary carcinoma cells (MCCs)	Panobinostat + MD5–1 induced apoptosis	[59]
HL60/ADR cells Refractory acute myeloid leukemia (AML) primary cells	Panobinostat + Bortezomib induced synergistic cytotoxicity Panobinostat + Bortezomib increased adriamycin accumulation in HL60/ADM cells (64.81 ± 3.69%) Attenuated phosphorylated form of protein kinase B (PKB, also known as AKT)	[61]
PC3, DU145, and LNCaP cells	Panobinostat + Lipid peroxidation end product 4-hydroxynonenal (HNE) inhibited proliferation of PC3 cells Panobinostat + HNE induced G_2/M arrest and cell death Panobinostat + HNE induced significant DNA damage	[17]
Human hepatocellular carcinoma (HCC) cells	Panobinostat + Sorafenib inhibited cell viability (26.3–73.4%) and proliferation (0.1–14.2%) and induced apoptosis (23% Huh7 sub-G_1 phase)	[18]
HCC cells	Panobinostat + Sorafenib induced potent antitumor effects Decreased cell viability and proliferation Increased apoptosis and autophagy Increased histone H3 and HSP90 acetylation	[63]
Human HCC cell lines HepG2 and Hep3B	Inhibited DNMT activity and expression Decreased methylation of the target genes ras association domain family member 1 isoform A (*RASSF1A*) and adenomatous polyposis coli (APC)	[64]
4 high-risk neuroblastoma (HR-NBL) cell lines	Induced dose-dependent growth arrest and apoptosis Panobinostat + Cisplatin, doxorubicin, or etoposide induced	[65]

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Table 1 (*continued*)

Tumour models	Anticancer	Ref.
	highly synergistic antitumor interactions	
Pancreatic cancer cell lines (AsPC-1, BxPC-3, CFPAC-1, HPAC, MIAPaCa-2, and PANC-1)	Panobinostat + MK-1775 induced synergistic antitumor activity	[19]
3 prostate cancer (PC) and 3 MM cell lines	Panobinostat + zoledronic acid induced a potent synergistic antiproliferative effect	[62]
Human oral squamous cancer cell (OSCC) lines (HN22 and HSC4 cells)	Inhibited cell viability and induced cell apoptosis Induced G_1 phase cell cycle arrest and apoptosis in OSCC cells Suppressed Sp1 expression in OSCC cells	[21]
B16 melanoma cells	IC_{50}: 25–100 nM Inhibited the growth of all melanoma cell lines Increased apoptosis and G_1 cell cycle arrest Increased expression of melanoma differentiation antigens	[66]
Human triple negative breast cancer (TNBC) (MDA-MB-231, BT-549) cell lines	Reduced the migratory and invasive potential of TNBC cells Altered the expression of epithelial-mesenchymal transition (EMT)-associated gene	[70]
Renal cancer cell lines (Caki-1, ACHN, 769-P, and 786-O)	Panobinostat + Ritonavir synergistically inhibited renal cancer cell growth Panobinostat + Ritonavir induced apoptosis	[71]
SK-NEP-1 and G401 human kidney cell line	Inhibited cell proliferation of SK-NEP-1 and G401 cells in a dose-dependent manner	[72]
Multiple myeloma (MM) 1 S cells	IC_{50} = 23 nM Panobinostat + KPT-8602 induced synergistic anti-cancer effect	[73]
MM 0.1 S and NCI-H929 cell lines	Panobinostat + Selinexor synergistically inhibited cell proliferation Panobinostat + Selinexor synergistically reduced c-MYC mRNA and protein levels Reduced expression of anti-apoptotic signaling molecules Increased expression of pro-apoptotic molecules	[74]
Ovarian cancer cells (OCCs)	Reduced the viability of both taxol-sensitive and taxol-resistant OCCs	[76]
Epithelial OCCs	Down-regulated cyclin E, E2F1, and HR gene expression Panobinostat + Olaparib reduced cell growth and clonogenicity Panobinostat + Olaparib induced DNA damage and apoptosis	[77]
Human cervical cancer cell lines, HeLa and SiHa	Reduced the viability of cervical cancer cells Arrested HeLa cells in G_0/G_1 and SiHa cells in G_2/M phase of the cell cycle Induced apoptosis through increased reactive oxygen species (ROS) production and the disruption of mitochondrial membrane potential	[78]
Human cervical cancer cell lines, HeLa and SiHa	Panobinostat + topoisomerase inhibitors: Enhanced the induction of cell apoptosis Increased ROS production and induction of the mitochondrial apoptotic pathway Inhibited phosphatidylinositol 3-kinase (PI3K)/AKT and nuclear factor kappa-B (NF-κB) pro-survival pathways	[79]
Human Non-SCLC (NSCLC) cell lines (A549, H441, and H460)	Overcome gefitinib resistance in kirsten rat sarcoma viral oncogene homolog (KRAS)-mutant/epidermal growth factor receptor (EGFR)-wild-type NSCLC Panobinostat + Gefitinib reduced tumor growth Inhibited TAZ transcription Panobinostat + Gefitinib down-regulated TAZ and TAZ downstream targets	[80]
MM cell line U266 and RRMM-BMMNC	Inhibited cell proliferation Induced G_0/G_1 phase arrest and apoptosis Induced hyperacetylation of histone H4 Increased protein level of PARP Decreased the level of Bcl-X	[75]
AU565 and BT474 cell lines	Panobinostat + Trastuzumab eradicated established trastuzumab-sensitive $HER2^+$ breast tumors Panobinostat + Trastuzumab induced curative response correlated with increased frequency of natural killer (NK) cells associated with $AU565^{pv}$ tumors	[81]
Esophageal squamous cell carcinoma (ESCC) cell lines (KYSE150, KYSE180, and KYSE510)	Suppressed cell proliferation of ESCC cell lines Exhibited greater potency and dose-dependent cytostatic activity on ESCC cells Decreased ESCC cell colony formation Arrested the cell cycling	[82]
CLBL-1 canine B-cell lymphoma cell line	Exhibited dose-dependent inhibitory effects on cell proliferation Induced apoptosis	[83]
Primary cultured glioblastoma (GBM) cells	IC_{50} = 0.03–0.23 μM Inhibited all malignant glioma cells Panobinostat + hAT-MSC.sTRAIL suppressed cell viability and enhanced apoptosis	[22]
Human MM cell lines (RPMI8226, U266-B1, and KMS-11)	Up-regulated PD-L1 expression Enhanced IFN-γR1 expression Enhanced the IFN-γ-mediated durable STAT1 activation	[84]
TNBC and non-TNBC cells	Inhibited breast cancer cell proliferation Induced apoptosis in breast cancer cells Suppressed cell mobility and invasion Reduced β-catenin stability and inhibited the wingless-int-1 (Wnt)/β-catenin pathway	[23]
Nalm-6, REH (human pre-B ALL cells) and NB4 (human promyelocytic leukemia (APL) cells)	Induced inhibitory effects on viability and metabolic activity of leukemic cells Induced G_1 cell cycle arrest Induced apoptotic cell death Enhanced the cytotoxic effects of vincristine on Nalm-6 cells	[87]
HR-proficient SKOV-3 OCCs	Panobinostat + Olaparib enriched genes involved in cell proliferation, apoptosis and DNA damage, and repair	[89]
C6 murine brain glial cell line	Induced cellular death in a time- and concentration-dependent manner Induced apoptosis	[95]
A375, HeLa, HepG2, Huh7, B16F10, and CT26 cell lines	Induced anti-tumor and anti-proliferative activities Increased the expression of cell adhesion and tight junction-related genes	[96]
Rhabdoid tumor cell line A204	Exhibited potent anti-proliferative activity Induced apoptosis	[97]
Gastric cancer (GC) cell lines, SNU484 and SNU638	Inhibited cell growth and proliferation Induced apoptosis	[98]

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Table 1 (*continued*)

Tumour models	Anticancer	Ref.
	Arrested SNU484 and SNU638 cells in the G_2/M phase	
Human epithelial PC cell lines (DU145, LNCaP, 22Rv1, and PC-3)	Panobinostat + Hydralazine reduced cell viability, cell proliferation, and colony formation Panobinostat + Hydralazine increased total apoptosis, DNA damage, as well as invasion and migration	[93]
Neuroblastoma cell lines (SK-N-BE (2)-C, KELLY, SH-SY5Y, and NH02A)	Panobinostat + CBL0137 enhanced nucleosome destabilization, inhibited DNA damage repair, and suppressed cancer cell growth	[94]
OCCs: IGROV-1, OVCAR-8, SK-OV-3, and A2780	Inhibited proliferation and induced G_2/M cell cycle arrest, apoptosis, and autophagy Panobinostat + Chloroquine synergistically induced cell death Panobinostat + Bafilomycin A1 synergistically induced cell death	[91]
Murine pancreatic cancer models	Enhanced chimeric antigen receptor T-cell antitumor effect	[92]
Soft tissue sarcoma (STS) cell lines: HT1080, SK-LMS-1, SW872, U2197, and NK cell line NK92	Inhibited the proliferation and colony formation of STS cells Augmented the NK cell-mediated cytotoxicity Increased the expression of NKG2D ligands MICA/MICB	[99]
HR-proficient SKOV-3 OCCs	Panobinostat + Olaparib reduced expression of 20/37 HR pathway genes Panobinostat + Olaparib enriched immune and inflammatory-related pathways Panobinostat + Olaparib decreased cell viability, HR repair, and enhanced DNA damage	[90]
TNBC, MDA-MB-231, cells	Inhibited the growth of all TNBC cells Induced apoptosis Panobinostat + Gefitinib inhibited cell growth and promoted apoptosis in TNBC cells	[85]
TNBC cells	Panobinostat + Rapamycin exerted a stronger role in repressing growth, invasion, and inducing apoptosis compared to monotherapy	[86]
Acute lymphoblastic leukemia (ALL) cell line (RS4;11)	Panobinostat + MTX or 6MP did not promote synergistic effects in RS4;11 cell line	[88]

immunomodulatory effect and cell cycle regulation, leading to cell death, and affecting the expression of tumor suppressors and oncogenic proteins as well as transcription factors. The evaluation of panobinostat's anticancer capabilities in the clinic has been a crucial area of interest in the field of oncology due to the good findings acquired with its use in the therapy of some tumors in preclinical testing. However, in order to prove its efficacy and safety in the clinical setting, extensive clinical trials are now required. To this end, recommendations have been made. Initially, when investigating potential synergistic effects, panobinostat may be used in conjunction with other medications as a component of targeted therapy. Subsequently, a deeper understanding of the underlying molecular machinery that controls tumor transformation would be made possible by a mechanistic understanding of the anti-cancer abilities of these compounds, whether panobinostat or other substances. Finally, further investigation into the benefits of HDACs like panobinostat on patients' immune responses may reveal possible synergies between panobinostat and immunotherapy. Since the blockage of a certain molecular process is the result of a series of sequential changes occurring between normal and tumor cells, the use of anti-cancer drugs has allowed researchers to discover and comprehend the biological patterns of cell activity to slow down the progression and

Table 2
In vivo anticancer mechanisms related to HDAC inhibition by Panobinostat.

Tumour models	Anticancer	Ref.
HCT116 human colon cancer cells in a xenograft mouse model	Inhibited tumor growth and induced tumor regression	[15]
Colo205 tumor xenograft model	Induced durable acetylation of histones H3 and H4 Panobinostat + 5-FU led to a significant level of tumor regression	
Mesothelioma animal models	Elevated amounts of cell cycle regulators and proapoptosis factors Decreased levels of antiapoptotic factors	[20]
Human gastrointestinal stromal tumors in a xenograft mouse model	Induced necrosis, tumor regression, apoptosis, hemorrhage, and decline in cell proliferation Increased H3 and H4 acetylation	[52]
MM1S cells in a xenograft mouse model	Panobinostat + Dexamethasone + either Bortezomib or Lenalidomide showed promising anti-myeloma efficacy	[54]
CTCL cancer cells in a xenograft mouse model	Induced tumor regression in an HH CTCL	[16]
CAL-62 cells in a xenograft mouse model	Impaired tumor growth	[56]
Immunocompetent, BALB/c and C57BL/6, mice	Panobinostat + MD5–1 eradicated tumors grown subcutaneously and orthotopically Induced (at high doses) MD5–1-mediated gastrointestinal toxicities	[59]
Huh7 cells in a xenograft mouse model	Panobinostat + Sorafenib significantly inhibited tumor growth at day 20 (227.3 mm^3)	[18]
HCC cells in a xenograft animal model	Panobinostat + Sorafenib induced potent antitumor effects	[63]
HepG2 cells in a xenograft mouse model	Influenced methylation and gene expression pattern	[64]
BxPC-3 cells in a xenograft mouse model	Panobinostat + MK-1775 induced promising cooperative antitumor activity	[19]
DU145 cells in a xenograft mouse model	$IC_{25=}$37% at 96 h IC_{50} = 45% at 96 h Panobinostat + zoledronic acid induced a potent synergistic antiproliferative effect	[62]
B16 melanoma cells in a xenograft mouse model	Increased animal survival	[66]
MDA-MB-231 cells in a xenograft mouse model	Reduced metastasis of MDA-MB-231 cells to the lung and brain	[70]
Caki-1 cells in a xenograft mouse model	Panobinostat + Ritonavir significantly suppressed renal cancer cell growth	[71]
SK-NEP-1 cells in a xenograft mouse model	Inhibited the growth of SK-NEP-1 xenograft tumors	[72]
MM 0.1 S cells in a xenograft mouse model	Panobinostat + KPT-8602 induced synergistic anti-cancer effect Induced tumor growth inhibition (69.4%) within 22 days Well tolerated treatment (alone or combined)	[73]
MM 0.1 S cells in a xenograft mouse model	Tumor growth inhibition was 52% (monotherapy) and 93% (bitherapy)	[74]
Ovarian adenocarcinoma tissue in a xenograft mouse model	Reduced tumor growth Enhanced tumor regression	[76]
SKOV-3 tumor cells in a xenograft mouse model	Panobinostat + Olaparib shows enhanced robust inhibitory effects	[77]
A549 cells in a xenograft mouse model	Panobinostat + Gefitinib reduced tumor growth Inhibited TAZ transcription	[80]
BT474 or $AU565^{pv}$ tumor cells in a xenograft mouse model	Panobinostat + Trastuzumab eradicated established trastuzumab-resistant $HER2^+$ xenografts	[81]
CLBL-1 cells in a xenograft mouse model	Inhibited CLBL-1 xenograft tumor growth, and strongly induced acetylation of H3 histone and apoptosis	[83]

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Table 2 (*continued*)

Tumour models	Anticancer	Ref.
Diffuse intrinsic pontine glioma (DIPG) mouse model	Panobinostat + hAT-MSC.sTRAIL decreased in tumor volume and prolonged survival	[22]
MDA-MB-231-LUC cells in a xenograft mouse model	Inhibited the growth and metastasis of breast cancer	[23]
C57BL/6 mice with intraperitoneal ID8-luc tumors	Panobinostat + Olaparib enriched functional pathways Panobinostat + Olaparib increased apoptosis and DNA damage	[89]
C6 cells in a xenograft rat model	Decreased tumor volume	[95]
BALB/c and C57BL/6 mice	Panobinostat therapy provided better tumor control and was synergized with anti-PD-L1 therapy	[96]
VAESBJ and A204 xenografts in female mice	Inhibited tumor growth	[97]
GC cells in a xenograft mouse model	Down-regulated Akt/forkhead box protein M1 (FOXM1) signaling Inhibited tumor growth	[98]
Animal models of MYCN-amplified neuroblastoma	Panobinostat + CBL0137 delayed cancer progression in xenograft models of poor outcome HR-NBL	[94]
Murine pancreatic cancer models Human pancreatic cancer xenograft model	Enhanced chimeric antigen receptor T-cell antitumor effect	[92]
STS cells in a xenograft mouse model	Activated the Wnt/β-catenin pathway Increased the cytotoxicity of NK cells	[99]
C57BL/6 mice with intraperitoneal ID8-luc tumors	Panobinostat + Olaparib reduced expression of 20/37 HR pathway genes Panobinostat + Olaparib enriched immune and inflammatory-related pathways	[90]
MDA-MB-231 cells in a xenograft mouse model	Panobinostat + Gefitinib inhibited tumor growth and induced apoptosis	[85]
Tumor growth was assessed in nude mice	Panobinostat + Rapamycin presented a more effective anti-cancer efficacy than a single treatment	[86]
Xenotransplanted NOD-scid IL2R gamma null mice	Increased overall survival and reduced blasts in mice Induced promising antineoplastic effects	[88]

survival of tumor cells.Table. 1.

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Table 3
Clinical investigations panobinostat.

Methods	Key results	Ref.
A phase I, multicenter, clinical trial Patients with cutaneous T-cell lymphoma (CTCL) 3 days of each week on a 28-day cycle	Panobinostat was well tolerated Panobinostat induced clinical responses in CTCL patients Panobinostat induced rapid changes in gene expression, and more genes are repressed than are activated Panobinostat regulated the expression of certain genes involved in several biological processes Maximum tolerated dose (MTD) = 20 mg	[55]
A phase I clinical trial Patients with castration-resistant prostate cancer (CRPC) Arm I: Oral administration of panobinostat (20 mg) on days 1, 3, and 5 for 2 consecutive weeks Arm II: Oral administration of panobinostat (15 mg) on the same schedule combined with docetaxel (75 mg/m^2) every 3 weeks	Arm I: Grade 3 dyspnea All patients developed progressive disease Arm II: Grade 3 neutropenia Some patients (63%) presented a drop (50%) in prostate specific antigen (PSA)	[101]
A phase I clinical trial Oral administration of single doses of: Panobinostat on day 1 Ketoconazole on day 5 Panobinostat + ketoconazole on day 8 From day 15: panobinostat administered 3 times per week	The observed increase in panobinostat pharmacokinetic parameters was not clinically relevant	[104]
A phase II clinical trial Patients with advanced pancreatic cancer Treatment cycles consisted of 3 weeks: Administration of panobinostat (20 mg) three times a week Administration of bortezomib (1.3 mg/m^2) twice a week	Complete lack of response to treatment Early treatment-related toxicity Median progression-free survival (PFS) = 2.1 months Thrombocytopenia (57%) and diarrhea (29%)	[105]
Phase I and II clinical trials 14 Japanese patients with advanced solid tumors (ASTs) Cohort 1: 10 mg/m^2 (three patients) Cohort 2: 15 mg/m^2 (three patients) Cohort 3: 20 mg/m^2 (eight patients)	Panobinostat was relatively safe and potentially effective when administered once daily on days 1 and 8 of a 21-day cycle MTD = 20 mg/m^2	[106]
A Phase II clinical trial Patients with relapsed/refractory (R/R) hodgkin's lymphoma after autologous stem-cell transplantation Oral administration of panobinostat (40 mg) 3 times per week	Panobinostat exhibited antitumor activity with durable responses Objective response rate (ORR) = 27% Median PFS = 6.1 months	[107]
A phase I study Patients with R/R Hodgkin and non-Hodgkin's lymphoma (NHL) Oral administration of panobinostat 3 times per week (Monday/Wednesday/Friday) and everolimus daily	MTD = 20 mg (panobinostat) MTD = 10 mg (everolimus) ORR = 43% Active combination therapy	[108]
Multicenter, nonrandomized phase II trial Patients with previously treated small-cell lung cancer (SCLC) Administered intravenously at a dose of 20 mg/mq (days 1–8) every 21 days	Panobinostat was well tolerated Panobinostat exhibited modest antitumor activity	[109]

(*continued on next page*)

Table 3 (*continued*)

Methods	Key results	Ref.
A phase I clinical trial Patients with ASTs or lymphoma Administration of daily doses: Days 1–3 and 8–10 of a 21-day cycle Days 1–3 and 15–17 of a 28-day cycle Administration of weekly doses: Days 1, 8, and 15 of a 28-day cycle Days 1 and 8 of a 21 day cycle	MTD = 7.2 g/m^2 (daily administration) MTD = 20.0 g/m^2 (weekly administration) Panobinostat induced fatigue and cardiac arrhythmias	[112]
A phase II clinical trial Patients with AST 60 mg of dextromethorphan alone on day 1 20 mg of panobinostat alone on days 3 and 5 Both agents on day 8	Panobinostat increased dextromethorphan exposure (64%) Panobinostat increased dextrorphan exposure (29%)	[113]
A phase I clinical trial Patients with advanced Non-SCLC (NSCLC) and head and neck cancer Determined the MTD of panobinostat twice weekly plus daily erlotinib at four planned dose levels (DL)	MTD = 30 mg (panobinostat) MTD = 100 mg (erlotinib) Panobinostat had no significant effect on erlotinib pharmacokinetics	[110]
A phase Ib/II clinical trial 30 healthy donors and 14 patients with acute myeloid leukemia (AML) Treatment with panobinostat and azacitidine for 28-day cycles 7 oral doses of panobinostat (10–30 mg), for 3 times a week	Panobinostat + azacitidine increased TNF receptor-2 (TNFR2$^+$) regulatory T cells (Tregs) in AML	[115]
A Phase I clinical trial Patients with stage III or IV melanoma Oral administration of panobinostat (10, 20 or 30 mg) every 96 h + subcutaneous administration of decitabine (0.1 or 0.2 mg/kg) 3 times per week for 2 weeks + oral administration of temozolomide (150 mg/m^2/day) on days 9–13	Panobinostat was generally well tolerated No dosing-limiting toxicities (DLTs) MTD was not reached	[117]
A phase Ib/II study 39 patients with AML Azacitidine subcutaneously for 5 days + oral panobinostat for 7 doses 4-week cycles	ORR = 31% for patients with AML ORR = 50% for patients with myelodysplastic syndrome (MDS) Median overall survival (OS) = 8 months for patients with AML Median OS = 16 months for patients with MDS	[116]
An open-label, multicentre phase 2 trial Patients with R/R peripheral T-cell lymphoma (PTCL) Oral administration of panobinostat (20 mg) 3 times per week Intravenous administration of bortezomib (1.3 mg/m^2) twice a week	The combined treatment (panobinostat + bortezomib) was safe and feasible The combination of the two compounds showed a synergistic effect	[120]
A multicenter phase II clinical trial Patients with recurrent high-grade glioma (HGG) Oral panobinostat (30 mg) 3 times per week, every other week, in combination with bevacizumab (10 mg/kg) every other week	Panobinostat was well tolerated Panobinostat + Bevacizumab did not significantly improve 6-month PFS rate 6-month PFS = 30.4% for patients with GBM 6-month PFS = 46.7% for patients with AG Median OS = 9 months for patients with GBM Median OS = 17 months for patients with AG	[125]
14 phase I and phase II trials Patients with hematologic and solid tumors	Administration of panobinostat showed clinically irrelevant effects Bioavailability = 21.4%	[122]
Oral or intravenous administration	Clearance = 33.1 L/h High inter-individual variability = 74%	
An open label, phase I trial Patients with unresectable stage III or IV melanoma An oral dose of 30 mg/day (mondays, wednesdays and fridays) (Arm A) One oral dose of 30 mg three times a week every other week (Arm B)	High rate of toxicity Panobinostat has shown no activity as a single agent against melanoma	[119]
A Phase II clinical trial 35 adult patients with R/R diffuse large B-cell lymphoma (DLBCL) Administration of panobinostat (40 mg) 3 times a week	Modest activity in R/R DLBCL patients Thrombocytopenia limited the use of panobinostat ORR = 17.1% Median PFS = 2.4 months Median OS = 7.6 months	[123]
A parallel phase I/II clinical trial CRPC patients resistant to second-line antiandrogen therapy (2ndLAARx) 40 mg (A arm) or 20 mg (B arm) triweekly	Panobinostat + bicalutamide demonstrated a synergistic antitumor effect Dose-limiting toxicity was not achieved	[102]
A non-randomized, open-label, dose-escalation phase I trial Patients with advanced clear cell renal cell carcinoma An panobinostat/everolimus combination treatment with myelosuppression	3 DLTs: grade 3 and 4 thrombocytopenia, and grade 3 neutropenia 6-month PFS = 31% Median PFS = 4.1 months MTD = 10 mg for panobinostat (orally 3 times a week) MTD = 5 mg for everolimus (orally daily) Safe and tolerable treatment	[126]

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Declaration of Competing Interest

Please declare any financial or personal interests that might be potentially viewed to influence the work presented. Interests could include consultancies, honoraria, patent ownership or other. If there are none state 'there are none'.

Data availability

Data will be made available on request.

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Further reading

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