REVIEW

Profile of panobinostat and its potential for treatment in solid tumors: an update

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Abstract: The histone deacetylase (HDAC) inhibitors have emerged as novel therapies for cancer. Panobinostat (LBH 589, Novartis Pharmaceuticals) is a pan-deacetylase inhibitor that is being evaluated in both intravenous and oral formulations across multiple tumor types. Comparable to the other HDACs, panobinostat leads to hyperacetylation of histones and other intracellular proteins, allowing for the expression of otherwise repressed genes, leading to inhibition of cellular proliferation and induction of apoptosis in malignant cells. Panobinostat, analogous to other HDAC inhibitors, also induces apoptosis by directly activating cellular death receptor pathways. Preclinical data suggests that panobinostat has inhibitory activity at nanomolar concentrations and appears to be the most potent clinically available HDAC inhibitor. Here we review the current status of panobinostat and discuss its role in the treatment of solid tumors.

Keywords: panobinostat, LBH589, histone deacetylase inhibitor, solid tumors

Introduction

The important role of epigenetic changes in the development of cancer has recently been recognized.[1] The two main epigenetic modifications are DNA methylation and posttranslational histone modifications, such as acetylation, methylation, and phosphorylation.[1] The acetylation of lysine residues on histones leads to an open chromatin state that allows for gene transcription whereas deacetylation leads to a condensed chromatin state and gene silencing. Histone deacetylases (HDACs) are thought to be dysregulated in malignancy, leading to aberrant gene repression and the survival of malignant cells.[2] In this setting, the HDAC inhibitors have been developed as potentially effective cancer therapies. Currently, vorinostat and romidepsin are the only Food and Drug Administration (FDA)-approved HDAC inhibitors; they have been approved for treatment of cutaneous T-cell lymphoma.[2] Panobinostat (Figure 1) is an investigational pan-deacetylase inhibitor (pan-DACi) that has demonstrated greater inhibitory activity in vitro against all Class I, II, and IV HDAC enzymes than the current FDA-approved HDACs.[3]

Preclinical studies have shown panobinostat to have antitumor activity in several hematologic malignancies, including acute myeloid leukemia, chronic myeloid leukemia, Hodgkin lymphoma, multiple myeloma, and non-Hodgkin lymphoma (NHL), specifically cutaneous T-cell lymphoma (CTCL).[4] Given the promising preclinical activity of panobinostat in hematologic malignancies, its potential efficacy is being evaluated both as a single agent and also in combination with chemotherapeutic, biologic, and small molecule inhibitor therapies for solid tumors.

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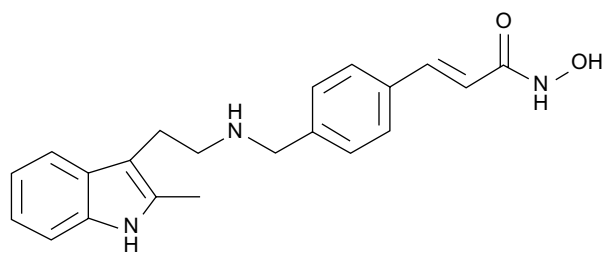Tel +1 516 524 8179
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Figure 1 Structure of panobinostat.
Note: The systematic (IUPAC) name is (2E)-N-hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino}methyl)phenyl]acrylamide.

Panobinostat: mechanism of action

HDAC enzymes regulate transcription and other cellular processes by removing acetyl groups from target proteins.[5] HDACs can be classified as either zinc-dependent HDACs (Class I, Class II, and Class IV) or the zinc-independent, nicotinamide adenine dinucleotide (NAD)-dependent Class III sirtuin enzymes (Table 1).[3] Class I HDACs, which are located within the cell nucleus, remove acetyl groups from lysine residues on histones, thus leading to a condensed chromatin state and gene silencing.[1] They play a role in cell survival and proliferation through interaction with transcription factor p53.[6] Class II HDACs shuttle between the cytoplasm and nucleus and act on nonhistone proteins. HDAC6, a member of Class IIb HDAC mainly localized to the cytoplasm, deacetylates heat shock protein 90 (Hsp90), which is a chaperone protein involved in protein stabilization.[6,7] HDAC6 plays a role in the transport of misfolded proteins to aggresomes for lysosomal degradation.[8] Inhibition of the aggresome pathway in tumor cells results in the accumulation of polyubiquinated proteins, leading to endoplasmic reticulum stress, inducing apoptosis.[8] HDAC6 also downregulates pro-apoptotic factor HR23B, which plays a role in shuttling ubiquinated proteins to proteasomes for degradation.[9] HDAC inhibitors cause apoptosis in cells with high expression of HR23B while also causing autophagy in cells with low expression of HR23B. HR23B has been identified in CTCL cells as a predictive biomarker for response to treatment with panobinostat.[10]

Table 1 Classification of HDACs

Zinc-dependent	Zinc-independent
Class I	Class III
HDAC1, HDAC2, HDAC3, HDAC8	Sirtuins 1–7
Class II	
Class IIa: HDAC4, HDAC5, HDAC7, HDAC9	
Class IIb: HDAC6, HDAC10	
Class IV	
HDAC11	

Abbreviation: HDAC, histone deacetylase.

HDAC inhibitors do not inhibit Class III HDACs. Class I-specific inhibitors include mocetinostat (MGCD0103), entinostat (MS275), and romidepsin. Class I- and IIa-specific inhibitors include butyrate and valproate. Pan-DACis inhibit Classes I, II, and IV, and include panobinostat, vorinostat, and belinostat (PXD101) (Figure 2).[11] Pan-DACis have also been shown to decrease angiogenesis, induce apoptosis and cell cycle arrest, decrease tumor cell motility, and decrease oncoprotein expression through effects on nonhistone protein targets.[12] Such targets include transcription factors that regulate gene expression, including p53, NF-kB and E2F1, as well as decreased oncoprotein expression of BCR-Abl and HER2 (human epidermal growth factor receptor 2). Other targets include Ku70, which regulates DNA repair, and alpha-tubulin, which regulates the cellular cytoskeleton, as well as Hsp90 (Figure 3).[3,11] HDAC inhibitors are also thought to sensitize malignant cells to tumor necrosis factor-related apoptosis, inducing ligand-mediated apoptosis through degradation of the anti-apoptotic factor, c-FLIP.[11,13]

Panobinostat pharmacology

Panobinostat is currently under development in intravenous and oral forms for use across a range of tumor types. In vitro studies have demonstrated potent inhibitory activity against Class I, II, and IV HDAC enzymes, even at nanomolar LD_{90} (concentration needed for 90% cell death, range 14–541 nM).[3] In studies using enzymatic assays, panobinostat IC_{50} (concentration needed for 50% inhibition) values were <13.2 nM for all Class I, II, and IV HDAC enzymes, except HDAC4, HDAC7, and HDAC8, all of which had IC_{50} in the mid-nanomolar range.[3] Panobinostat IC_{50} values were lower than those for vorinostat, belinostat, and mocetinostat. Panobinostat had at least ten-fold greater potency when compared with vorinostat.[4]

Panobinostat has unique cancer type specific cytotoxicity, which has been demonstrated in vitro.[3] Solid tumor cells, such as breast and pancreas require higher LD_{90} for cytotoxicity (306–541 nM) than hematological cell lines (14–57.5 nM).[3] Toxicity to normal human cell lines occurred at much greater LD_{90} (values >5 µM) than concentrations required to achieve toxicity in malignant cells.[3]

Analysis of multiple Phase I and II studies demonstrated panobinostat pharmacokinetics to be linear.[14] The exact metabolism and clearance mechanism of panobinostat, a hydroxamic acid derivative, has not as yet been elucidated. Preclinical studies suggest that the mechanism of clearance is complex, involving reduction, hydrolysis, and carbon group shortening of the hydroxamic acid group.[15] Additional pathways including glucuronidation and mono-oxygenation of the ethyl-methyl indole moiety have been implicated.

HDACi class		HDAC specificity											
HDAC cellular distribution		Nuclear				Nuclear, cytoplasmic				Cytoplasmic		Nuclear
HDAC class		I				IIa				IIb		IV
HDAC		1	2	3	8	4	5	7	9	6	10	11
Short chain fatty acids	Butyrate	■	■	■	■	■	■	■	■			
	Valproate	■	■	■	■	■	■	■	■			
Hydroxamic acid derivative	Trichostatin A	■	■	■	■	■	■	■	■	■	■	■
	Vorinostat (suberoylanilide hydroxamic acid, SAHA)	■	■	■	■	■	■	■	■	■	■	■
	Panobinostat (LBH589)	■	■	■	■	■	■	■	■	■	■	■
	Belinostat (PXD101)	■	■	■	■	■	■	■	■	■	■	■
	Tubacin									■		
Benzamide	Entinostat (MS-275)	■	■	■								
	Mocetinostat (MGCD0103)	■	■	■								■
Cyclic tetrapeptide	Romidepsin (depsipeptide)	■	■									

Figure 2 Classes, targets and cellular distribution of HDAC inhibitors.
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Abbreviation: HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor.

A study using ^{14}C-radiolabeled panobinostat at an oral dose of 20 mg in patients with advanced solid tumors and hematologic malignancies measured total radioactivity in blood and metabolites in urine and feces on days one to eight post-administration. Elimination through the urinary and fecal routes was relatively equal, contributing to 40.6% and 54.3%, respectively, of the total dose administered. Of the 77 metabolites detected, 40 were detected in circulating plasma and 1.1%–2.4% of administered drug was detected unchanged in the urine.[15]
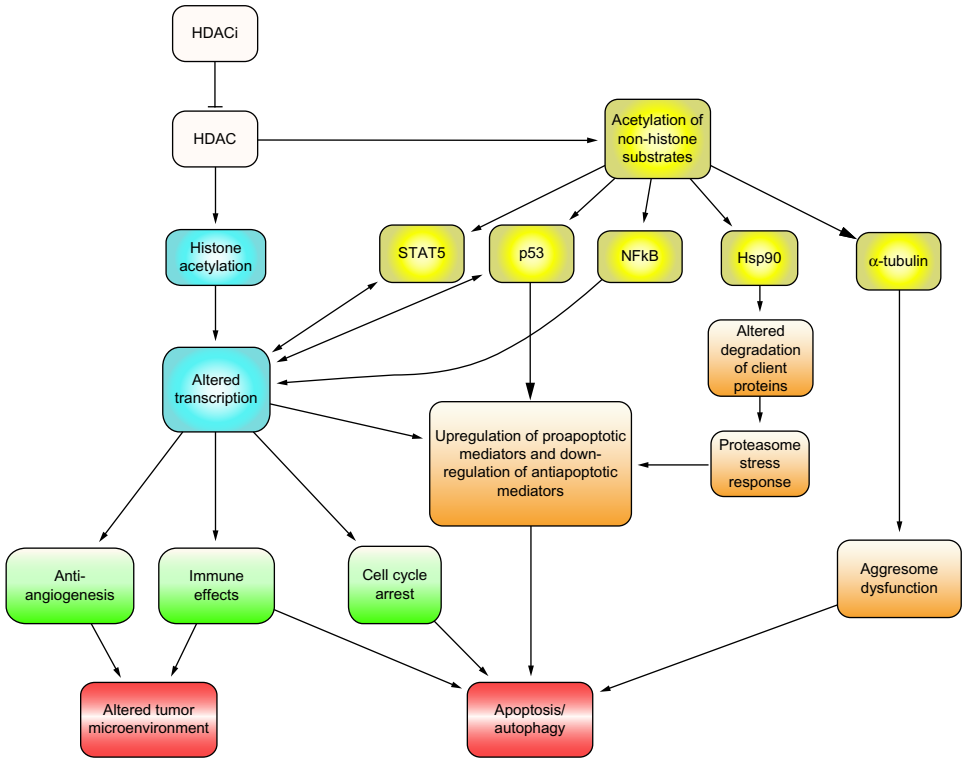

Figure 3 Targets and downstream effects of HDAC inhibitors.
Note: Reprinted with permission from Springer, and Dickinson M, Johnstone RW, Prince HM. Histone deacetylase inhibitors: potential targets responsible for their anti-cancer effect. *Invest New Drugs.* 2010;28(Suppl 1):S3–S20.[11] With kind permission from Springer Science and Business Media.
Abbreviations: HDACi, histone deacetylase inhibitor; HDAC, histone deacetylase; Hsp90, heat shock protein 90; STAT5, signal transducer and activator of transcription 5; p53, tumor suppressor protein 53; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells.

In a Phase I study of 36 patients with solid tumors, the effect of food on the half-life and bioavailability of panobinostat was studied.[16] Three different prandial states were evaluated, including: (1) fasting (10 hours prior to and four hours post-administration of panobinostat); (2) after high-fat breakfast (administration within 30 minutes after consumption of meal); and (3) after regular breakfast (administration within 60 minutes after consumption of meal). No significant association with food intake was found when pharmacokinetic parameters were measured during these states, with unchanged oral bioavailability (similar area under the curve [AUC] when interpatient variability was accounted for) in fasting as well as in different prandial states.[16]

Panobinostat is metabolized primarily by cytochrome P450, CYP3A4, along with CYP2D6, and CYP2C19.[17] The strong CYP3A4 inhibitor, ketoconazole, was coadministered with panobinostat and demonstrated an increase in C_{max} (maximum concentration achieved after administration) and AUC of panobinostat of 1.6- and 1.8-fold respectively, without significant change in T_{max} (time to reach maximum concentration after administration) or half-life.[17] Monitoring for potential toxicities is needed if panobinostat is coadministered with a CYP3A4 inhibitor. A Phase I trial is underway to evaluate the effect of various degrees of hepatic dysfunction on the pharmacokinetics of panobinostat.

The effect of renal dysfunction on the pharmacokinetics of panobinostat is also being evaluated in a Phase I study, and preliminary results have been reported.[18] Panobinostat was administered at a dose of 30 mg orally three times weekly with varying degrees of renal dysfunction (mild, moderate or severe according to 24-hour creatinine clearance). Plasma and urine concentrations of panobinostat assessed by liquid chromatography tandem mass spectrometry following administration did not suggest higher drug exposures (C_{max}, AUC, half-life) with increasing severity of renal dysfunction.[18] A formal algorithm for dosing in patients with significant renal dysfunction has not yet been developed.

Safety and tolerability of panobinostat in the clinical setting

Several Phase I and Phase II studies have been performed to evaluate the pharmacokinetics, maximum tolerated dose (MTD), and the safety and tolerability of panobinostat in hematologic malignancies and solid tumors. Panobinostat appears to be well tolerated, with the most common side effects being fatigue, nausea, vomiting, and diarrhea. Early Phase I studies of intravenous panobinostat administered daily found dose-limiting toxicity (DLT) of electrocardiographic

QTc prolongation; hence, subsequent studies have utilized an intermittent dosing schedule.[19] Oral dosing of panobinostat has also been studied in various schedules. In an analysis performed on pooled data from eight completed or ongoing Phase I or Phase II trials using panobinostat, thrombocytopenia was the most common laboratory abnormality of any grade, as well as the most common DLT.[20] Of note, the MTD in hematologic malignancies appears to be two- to three-fold higher than that in solid tumors. Table 2 summarizes the pharmacokinetic data along with DLTs and the most common CTCAE (Common Terminology Criteria for Adverse Events) from Phase I studies performed in advanced solid tumors and advanced NHL.

A Phase I pharmacokinetic and pharmacodynamic study evaluated intravenous administration of panobinostat at three dose levels weekly in advanced solid tumors and NHL (Table 2).[21] The MTD in this intravenous weekly schedule was 20 mg/m². One DLT of grade 4 thrombocytopenia was found at this dose. In addition, QTcF (QT interval corrected for heart rate using Fridericia's formula) prolongation occurred at 20 mg/m². Common adverse events (AE) included transient thrombocytopenia (9.1%), anemia (9.1%), and fatigue (4.5%).[21]

In a Phase Ia/II dose escalation study in patients with advanced hematologic malignancies, the most common AEs included diarrhea (58%), nausea (53.4%), and fatigue (52.8%) (Table 2).[22] Grade 3 QTcF prolongation was observed at 80 mg. Thrombocytopenia was the most common DLT. MTD differed by malignancy; the recommended dose was 60 mg in patients with leukemia and myeloid disorders, whereas for lymphoma and myeloma the recommended dose was 40 mg weekly and 60 mg biweekly.[22]

A Phase I dose escalation study of oral panobinostat in patients with advanced solid tumors and non-Hodgkin lymphoma showed a MTD of 20 mg (Table 2).[23] In this study, the DLT was grade 3 and 4 diarrhea and thrombocytopenia, respectively, at 30 mg, and grade 3 fatigue at 20 mg. The most common AEs were anorexia, nausea, fatigue, diarrhea and transient thrombocytopenia.

A similar Phase I dose escalation trial in Japanese patients with advanced CTCL, as well as in solid tumor patients, showed that a dose of 20 mg daily was well tolerated (Table 2).[24] In this study, anemia (n = 1) and thrombocytopenia (n = 2) were the most common grade 4 AEs. The most common AE were diarrhea and nausea (both, 76.9%) and transient thrombocytopenia (92.3%). Absolute QT prolongation (>480 ms) was not observed though prolongation >60 ms from baseline was observed in two patients without symptoms.

Table 2 Summary of pharmacokinetics, adverse events and dose limiting toxicities

Study and indication	Dose	Route	Schedule	T_{max}	$t_{1/2}$	Other AEs	DLT
Sharma et al[21] Phase I Dose escalation Advanced solid tumors or NHL	10–20 mg/m²	IV	Weekly, day 1, 8, 15 out of 28 day cycle	0.5 hours	16 hours	Thrombocytopenia, anemia, fatigue, neutropenia, nausea, pruritus, hypokalemia, hypophosphatemia	Grade 4 thrombocytopenia at 20 mg/m²
Deangelo et al[22] Phase Ia/II Dose escalation Hematologic malignancies	Arm 1: 20–80 mg Arm 2: 30–80 mg	Oral	Arm 1: TIW weekly, 28 day cycle Arm 2: TIW weekly every other week, 28 day cycle	2 hours	16 hours	Nausea, diarrhea, fatigue, anorexia, thrombocytopenia	Arm 1: Grade 3 fatigue at 40–80 mg, Grade 3 QTcF prolongation at 80 mg, Grade 3, 4 thrombocytopenia at 40–60 mg; Arm 2: Grade 4 thrombocytopenia at 60 mg, grade 3 QTcF prolongation at 80 mg, grade 3 cardiac toxicity over 60 mg (including congestive heart failure, atrial fibrillation, rising troponin), grade 3 fatigue at 80 mg, grade 3 increase bilirubin at 80 mg
Prince et al[23] Phase I Dose escalation Advanced solid tumors and NHL	15–30 mg	Oral	TIW weekly of 28 day cycle	1.5 hours	16 hours		Grade 3 diarrhea at 30 mg, Grade 4 thrombocytopenia at 30 mg, Grade 3 fatigue at 20 mg
Fukutomi et al[24] Phase I Dose escalation Advanced solid tumors and NHL	10–20 mg	Oral	TIW weekly of 28 day cycle	1–2 hours	9–14 hours	Nausea, diarrhea, thrombocytopenia, anorexia, fatigue	Grade 4 anemia and thrombocytopenia but not DLT
Rathkopf et al[25] Phase I Metastatic prostate cancer	Arm 1: 20 mg Arm 2: 15 mg in combination with docetaxel 75 mg/m² and prednisone 5 mg twice daily	Oral	Arm 1: TIW weekly 2 out of 3 weeks Arm 2: TIW weekly 2 out of 3 weeks + docetaxel once every 3 weeks	0.5–3 hours	14.6 hours	Arm 1: Nausea, diarrhea, thrombocytopenia Arm 2: Fatigue, febrile neutropenia, anemia, hyperglycemia, nausea	Arm 1: Grade 3 dyspnea Arm 2: Grade 3 neutropenia

Abbreviations: AEs, adverse events; DLT, dose-limiting toxicity; TIW, three times weekly schedule; T_{max}, time to reach maximum concentration after administration; $t_{1/2}$, elimination half-life; NHL, non-Hodgkin lymphoma; QTcF, QT interval corrected for heart rate using Fridericia's formula.

Another Phase I trial in patients with castration-resistant metastatic prostate cancer evaluated panobinostat alone as compared with the combination with docetaxel 75 mg/m^2 (Table 2).[25] In this study, the DLT was dyspnea in one patient in the single agent arm (arm 1) and neutropenia in the combination arm (arm 2) with docetaxel. The most common AEs were nausea (75%), diarrhea (50%), and thrombocytopenia (50%) for arm 1, and neutropenia (87.5%), fatigue (62.5%), anemia (62.5%), and nausea (62.5%) for arm 2.

Panobinostat in solid tumors

In what follows, we review preclinical (summarized in Table 3) and clinical (summarized in Table 4) studies of panobinostat in specific tumor types.

Breast cancer

In vitro studies by Tate et al[26] have shown that triple negative breast cancer cell lines incubated with panobinostat have increased histone acetylation as well as drug dose-dependent decrease in cell proliferation. Additionally, in vivo studies of panobinostat in triple negative breast cancer mice models, at a concentration of 10 mg/kg/day for 5 days per week, resulted in significant decreases in tumor volume (Table 3).[26] Other preclinical studies in triple negative breast cancer have found similar results, as seen with a study of co-treatment of panobinostat and chloroquine, an autophagy inhibitor,

which demonstrated that this drug combination reduced tumor burden and increased survival in triple negative breast cancer xenografts.[27]

Panobinostat was found to have synergistic effects with docetaxel, doxorubicin, and gemcitabine in both hormone receptor rich and poor cell lines.[28] Bortezomib has also been shown to enhance synergism of panobinostat and gemcitabine. Triplet combinations with panobinostat and doxorubicin/carboplatin or gemcitabine/carboplatin have been shown to be extremely potent in cell lines.[28]

In a Phase I study, patients who had progressed on treatment with trastuzumab were treated with either intravenous panobinostat, or oral panobinostat in combination with trastuzumab.[29] Preliminary analysis of 25 patients revealed that eight patients had stable disease, with two of these patients having 29% tumor reduction (Table 4).

A Phase I study is currently underway evaluating panobinostat in combination with letrozole.[30] Letrozole was administered at a dose of 2.5 mg daily along with panobinostat at a dose of either 20 mg or 30 mg orally three times weekly. To date, results from 12 enrolled patients have been reported. One patient at 30 mg has a confirmed partial response. No DLTs were observed at a dose of 20 mg, but the DLT of thrombocytopenia was observed at the dose of 30 mg. Another Phase I study is underway evaluating panobinostat in combination with capecitabine with or without lapatinib.

Table 3 Preclinical studies of panobinostat

Cancer	Study	Results
TNBCA xenografts[26]	Panobinostat 10 mg/kg IP injections daily × 5 days/week versus placebo	3–4 fold reduction in tumor volume compared to control at 41 days
CRC xenografts[40]	Panobinostat 2.5 mg/kg IP injections daily × 5 days/week versus lapatinib 30 mg/kg oral twice daily versus the combination	Panobinostat monotherapy: 23.8% reduction TV Lapatinib monotherapy: 4.1% reduction TV Combination: 49.8% reduction TV
HCC xenografts[46]	Panobinostat 15 mg/kg IP injections daily × 5 Sorafenib 30 mg/kg daily × 7 Combination panobinostat 7.5 mg/kg daily × 5 + sorafenib 30 mg/kg daily × 7	Delay in tumor growth observed in 58.3% in combination group, 42.9% in panobinostat monotherapy and 10% in sorafenib monotherapy, and 8.3% in control group
GIST xenografts[47]	Control versus panobinostat 10 mg/kg IP daily, versus imatinib 150 mg/kg po bid versus combination	Control group tumors increased 2 fold; panobinostat alone 25% reduction tumor, imatinib alone 62% reduction tumor, combination 73% reduction tumor
ATC xenografts[52]	Panobinostat at 10 mg/kg, 20 mg/kg, 30 mg/kg IP injections 5 days/week × 21 days	At 20 mg/kg: significant reduction tumor growth, Ki67
SCCHN xenografts[56]	Panobinostat 30 mg/kg IP injection daily versus BGT226 10 mg/kg po daily versus BEZ235 30 mg/kg po daily versus BKM120 7.5 mg/kg po daily versus panobinostat + each of above 3 drugs	Treatment with BCT226, BEZ235, BKM120 each more effective than combination with panobinostat or with panobinostat monotherapy

Abbreviations: TNBCA, triple negative breast cancer; CRC, colorectal cancer; HCC hepatocellular cancer; ATC, anaplastic thyroid cancer; SCCHN, squamous cell cancer of head and neck; GIST, gastrointestinal stromal tumors; IP, intraperitoneal; TV, tumor volume, po, per oral; bid, twice daily.

Table 4 Summary of panobinostat studies in solid tumors

Disease	Study	Dosage	N	Efficacy	Grade 3–4 AE	Ref
HER + metastatic breast cancer	Phase I	Arm 1: Panobinostat 10–20 mg/m^2 IV day 1, 8 every 21 days + trastuzumab IV weekly (4 mg/kg load then 2 mg/kg/week) or Arm 2: Panobinostat 15–40 mg po TIW + trastuzumab IV weekly (4 mg/kg load then 2 mg/kg/week)	25	8 SD (2 with liver metastases had 29% tumor reduction)	Thrombocytopenia, neutropenia, diarrhea, pyrexia, hyperkalemia, dyspnea, leucopenia, tachycardia	29
Small cell lung cancer	Phase II	Panobinostat 20 mg/m^2 IV day 1, 8 every 21 days	21	3 SD and 2 patients with response: 30% decrease in tumor	Hypertension (n = 1)	35
High grade gliomas	Phase I	Arm 1: Panobinostat 20 mg po weekly, TIW for 4 weeks + bevacizumab 10 mg/kg IV every other week × 2 (day 1, day 15) Arm 2: Panobinostat 20 mg po every other week, TIW, 3 weeks on, 1 week off + bevacizumab 10 mg/kg IV every other week × 2 (day 1, day 15) Arm 3: Panobinostat 30 mg po every other week, TIW, 3 weeks on, 1 week off + bevacizumab 10 mg/kg IV every other week × 2 (day 1, day 15)	3 3 6	3 PR (1 in arm 2, 2 in arm 3), 2 PD (1 in arm 1, 1 in arm 3), 7 SD; median OS 8.2 months	(n = 1 each): thrombocytopenia, hypophosphatemia, esophageal hemorrhage, deep venous thrombosis, QTc prolongation, lymphopenia	36
Castrate resistant prostate cancer	Phase I	Arm 1: Panobinostat 20 mg po three times weekly, for 2 weeks, 1 week off, every 21 days Arm 2: Panobinostat 15 mg po three times weekly for 2 weeks, 1 week off, every 21 days + docetaxel 75 mg/m^2 IV every 21 days + prednisone po 10 mg/day	8 8	Arm 1: 1 SD Arm 2: 2 PR (1 with prior taxane exposure) and 4 SD	Arm 1: (n = 1 each) dyspnea, nausea, diarrhea Arm 2: Fatigue (n = 2), anemia (n = 1), leucopenia (n = 2), neutropenia (n = 7), hyperglycemia (n = 2)	25
Castrate resistant prostate cancer	Phase Ib	Cohort 1: Panobinostat 10 mg/m^2 IV day 1, 8, 15 (out of 21 days) + docetaxel 75 mg/m^2 IV every 21 days, + prednisone 10 mg/day Cohort 2: Panobinostat 15 mg/m^2 IV day 1, 8, 15 (out of 21 days) + docetaxel 75 mg/m^2 IV every 21 days, + prednisone 10 mg/day Cohort 3: Panobinostat 20 mg/m^2 IV day 1, 8, 15 (out of 21 days) + docetaxel 75 mg/m^2 IV every 21 days, + prednisone 10 mg/day	22	5 patients with >30% decline in PSA; 4 patients with >50% decline in PSA	Neutropenia (n = 12), febrile neutropenia (n = 3), bradycardia (n = 1), dizziness (n = 2), DVT (n = 1)	37
Refractory metastatic CRC	Phase II	Panobinostat 30 mg po TIW until disease progression	29	3 SD, no objective responses, TTP 7.7 weeks, median OS 5.1 months	Thrombocytopenia (n = 6)	41
Metastatic HCC	Case report	Sorafenib 800 mg po daily + panobinostat 20 mg po day 1, 4 (2 out of 3 weeks)	1	Regression of liver and skeletal metastases	N/A	45
Refractory GIST	Phase I	Imatinib 400 mg po daily + panobinostat 20 mg–30 mg po TIW (3 out of 4 weeks)	12	1 PR, 7 SD, 3 PD	Thrombocytopenia (n = 2)	48
Advanced pancreatic cancer	Phase II	Panobinostat 20 mg TIW × 2 weeks every 21 days + Bortezomib 1.3 mg/m^2 twice weekly × 2 weeks every 21 days	7	Terminated early due to lack of treatment responses and unacceptable toxicity Median PFS 2.1 months	Grade 3 thrombocytopenia (57%) Grade 4 diarrhea (29%)	51
Medullary thyroid cancer and iodine refractory thyroid cancer	Phase II	Panobinostat 20 mg po TIW	13	7 SD, 6 PD, no objective responses, median OS 18.4 months	Thrombocytopenia (n = 3)	54
Refractory metastatic RCC	Phase II	Panobinostat 45 mg po twice weekly	12	No objective responses, all patients with PD or discontinued therapy	Reportedly well tolerated	60

Abbreviations: TIW, three times weekly; po, per oral; IV, intravenous; SD, stable disease; PD, progressive disease; PR, partial response; OS, overall survival; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; GIST, gastrointestinal stromal tumor; RCC, renal cell carcinoma; HER, human epidermal growth factor receptor; DVT, deep venous thrombosis; TTP, time to progression; PFS, progression free survival; AE, adverse event; Ref, reference; N/A, not available.

Lung cancer

There has been considerable interest in studying panobinostat for the treatment of both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In vivo studies using human NSCLC xenografts in a nude mouse model demonstrated that when panobinostat was combined with radiation, there was a growth delay of 20 days compared with 4 days with radiation alone or 2 days with panobinostat alone.[31] This data suggests that panobinostat may be a useful adjunct as a radiation sensitizer in the treatment of NSCLC.[32] Panobinostat has also been shown to be synergistic in combination with EGFR (epidermal growth factor receptor) inhibitors such as erlotinib in lung cancer cell lines that are dependent upon EGFR.[33] Panobinostat allows acetylation of Hsp90, reducing its association with chaperone proteins, including EGFR, thereby triggering apoptosis in EGFR-mutated cells. In this sense, future studies of panobinostat and NSCLC may focus on targeting tumors dependent on EGFR mutations. Trials of panobinostat in combination with standard cytotoxic therapy are also underway in patients with NSCLC.

Small cell lung cancer cell lines have also been shown to be highly sensitive to panobinostat. In vivo and in vitro models of 37 cell lines of all thoracic malignancies treated with panobinostat displayed the most potent antiproliferative activity and cytotoxicity in the SCLC cell lines. The SCLC cell lines displayed the most sensitivity to the drug, with the majority of cell lines showing $IC_{50} < 10$ nmol/L.[34] In a Phase II study of intravenous panobinostat in patients with progressive or relapsed small cell lung cancer, among 21 enrolled patients, two had tumor response of greater than 30%, and three cases had stable disease (Table 4).[35] Further studies with panobinostat in combination with chemotherapy are underway.

CNS malignancy

Responses with current chemotherapeutic and biologic therapies such as bevacizumab for high grade gliomas have not been shown to be durable. In this setting, the addition of panobinostat to bevacizumab has been studied. A Phase I study of twelve patients with recurrent high grade glioma were treated with panobinostat in two different schedules, in combination with bevacizumab.[36] In this small sample study, three of the twelve patients achieved a radiographic partial response, two had progressive disease, and seven patients had stable disease, with an 8.2 month median overall survival from the date of registration (Table 3).[36] Given the possibility of drug activity in high grade gliomas, and

overall tolerability seen in the Phase I trial, there is now a Phase II study to further investigate this drug combination's efficacy and tolerability in patients with recurrent high grade gliomas.

Prostate cancer

A Phase I study of 16 patients with castration-resistant prostate cancer comparing oral panobinostat alone or in combination with docetaxel demonstrated that none of the patients in the panobinostat alone arm had a clinically significant disease response (Table 4).[25] In the panobinostat plus docetaxel arm, two of the seven evaluable patients had a partial response, and an additional four patients had stable disease on imaging. In another Phase I study in 21 castration-resistant prostate cancer, intravenous panobinostat along with docetaxel in chemotherapy naïve patients demonstrated greater than 30% decline in prostate specific antigen (PSA) in five patients and greater than 50% decline in PSA in four patients (Table 4).[37] These results indicate that there may be a role for panobinostat in future therapy for prostate cancer treatments, although likely in combination with other drugs, given that disease activity with monotherapy was negligible. A Phase II trial of panobinostat in combination with bicalutamide is currently underway.

Gastrointestinal cancers
Colon cancer

In vitro studies have shown that panobinostat treatment of colon cancer cell lines inhibits proliferation and survival at nanomolar concentrations. Panobinostat has been shown to activate the tumor suppressor death-associated protein kinase (DAPK), which plays a role in induction of autophagy and apoptosis.[38] Analysis of gene expression profiles of colorectal cancer (CRC) cell lines treated with panobinostat revealed that only 5%–7% of genes were altered. These selective genes regulate cellular processes such as angiogenesis, mitosis, DNA replication, and apoptosis.[39]

In preclinical studies by LaBonte et al,[40] after treatment with panobinostat, all CRC cell lines tested showed concentration-dependent growth inhibitory activity with IC50 values from 5.5–25.9 μmol/L. Furthermore, simultaneous treatment with lapatinib, an EGFR/HER2 kinase inhibitor, resulted in a synergistic inhibition in growth (Table 3). This drug combination was found to decrease protein expression of EGFR and HER2.[40] These results may warrant further clinical investigation with panobinostat, alone and in combination with drugs such as lapatinib, for treatment in colorectal carcinoma.

A Phase II study of panobinostat in patients with refractory metastatic CRC (median of three prior therapies) was performed (Table 4). Results from 29 patients showed three patients with stable disease, without any objective responses. The time to progression was 7.7 weeks, with a median overall survival time of 5.1 months.[41]

Hepatocellular carcinoma

A novel mechanism of apoptosis involving the endoplasmic reticulum stress pathway has been described in hepatocellular cancer (HCC) cell lines treated with panobinostat.[42] Panobinostat has been demonstrated to induce cellular unfolded protein response and upregulate pro-apoptotic factors, which ultimately leads to activation of caspases and to apoptosis.[43]

Inactivation of tumor suppressor genes like the Ras-associated domain family 1 isoform A (RASSF1A) and adenomatous polyposis coli (APC), and overexpression of DNA methyltransferases (DNMT), have previously been shown to be common in HCC and have been linked to malignant potential and poor prognosis.[44] Cell lines treated with panobinostat have demonstrated inhibition of DNMT as well as diminished methylation of RASSF1 A and decreased expression of APC.[44] Other studies in HCC cell lines and a xenograft model have shown that panobinostat can inhibit proliferation pathways via upregulation of p21, an endogenous cell cycle inhibitor.[45]

Furthermore, panobinostat has shown to inhibit mitogen-activated protein kinase (MAPK) activity. MAPK is the final downstream target of receptor tyrosine kinases and the Ras-Raf signaling pathway, which is the main target of sorafenib.[45] Such information provides rationale for combination therapy and a basis for possible additive effects between these two drug classes.

Lachenmayer et al[46] have shown that use of panobinostat in several liver cancer cell lines leads to in vitro and in vivo antitumor effects, which were found to be enhanced with the addition of sorafenib. In several human HCC cell lines cultured with panobinostat, cell viability and proliferation declined in a time- and dose-dependent manner, and apoptosis, as well as autophagy, increased.[46] Cell lines cultured with panobinostat experienced reduced tumor volumes as compared with controls. When sorafenib was added to the regimen, researchers found decreased vessel density and further decreased tumor volume, as well as increased survival (Table 4).[46]

One case report of a patient with metastatic HCC demonstrates response to treatment with sorafenib and panobinostat.[45] The report describes a 68-year-old male with metastatic multilocular HCC initially treated with sorafenib at 800 mg daily, who showed a mixed radiographic response on MRI 6 weeks after treatment. The patient was subsequently started on panobinostat at a dose of 20 mg in addition to daily sorafenib. After eight cycles, there was evidence of regression of liver and skeletal metastases lesions (Table 4).[45]

Gastrointestinal stromal tumors

In an experimental study by Floris et al,[47] 36 mice, each bearing two gastrointestinal stromal tumor (GIST) xenografts, were assigned to four treatment groups: no-treatment, panobinostat, imatinib, and a panobinostat–imatinib combination. While the tumors in the no-treatment group continued to grow from baseline, the tumors in the panobinostat group shrunk by 25%, and tumors in the combination therapy group shrunk by 73% at 12 days (Table 3). Notably, responses were seen even in xenografts with the kit-exon 9 mutation, which is known for resistance to imatinib. This early study suggests the potential therapeutic activity of panobinostat in human GIST. Results from a Phase I dose-escalating trial of 12 patients with refractory GIST (median five prior therapies) treated with a combination of imatinib and panobinostat are summarized in Table 4.[48]

Gastric carcinoma

Preclinical data suggests that further study of panobinostat as therapy in gastric cancer may be useful as adjunct to other chemotherapies, such as anthracyclines.[49] Microarray analysis of mRNA (messenger RNA) isolates from gastric cancer cell lines found that several genes indicative of doxorubicin resistance were down regulated after treatment with panobinostat. It was also shown that panobinostat down-regulated expression of genes that mediate anthracycline resistance via activation of *CITED2* (*Cbp/p300-interacting transactivator 2*), a gene that mediates cell sensitivity to chemotherapeutics such as anthracyclines.[49] Future study in this area may therefore focus on the use of panobinostat as a chemosensitizing agent for use along with anthracyclines, which constitute the backbone of many of the chemotherapy regimens for gastric cancer.

Pancreatic cancer

One study investigating panobinostat and BEZ235, a PI3K (phosphatidylinositide 3-kinase) and mTOR (mammalian target of rapamycin) inhibitor, suggests that there may be activity with these drugs alone, and also in combination, against pancreatic cancer.[50] Treatment with BEZ235 or

panobinostat inhibited cell cycle progression via induction of the cell cycle inhibitory proteins p21 and p27. BEZ235 and panobinostat were also found to dose-dependently induce the loss of cell viability in cultured pancreatic ductal adenocarcinoma cells. Co-treatment with both drugs also displayed a significant reduction in growth of cells in xenograft models of pancreatic ductal adenocarcinoma in nude mice.[50]

A Phase II study in advanced pancreatic cancer patients who had progressed on gemcitabine-based therapy was performed using a combination of panobinostat along with bortezomib.[51] The study was suspended because of lack of treatment responses and unacceptable early toxicity (Table 4).

Head and neck cancer
Thyroid cancer
In preclinical studies of anaplastic thyroid cancer cell lines, panobinostat has been found to induce G1 cell cycle arrest at low concentrations.[52] In vivo, mice models of anaplastic thyroid cancer treated with 20 mg/kg of panobinostat displayed higher levels of apoptotic nuclei and decreased levels of Ki67 as compared with controls (Table 3).[52] Other studies have examined anaplastic thyroid cancer cells and E-cadherin levels.[53] E-cadherin is a protein that typically functions in the role of epithelial cell–cell adhesion and has been shown to prevent tumor invasion. This protein is found in high levels in normal thyroid tissue and at reduced or absent levels in anaplastic thyroid cancer. After culture of three anaplastic thyroid cancer cell lines with panobinostat, E-cadherin expression was found to be induced, leading to impaired cancer cell migration and invasion.[53] These results suggest that further studies with panobinostat in anaplastic thyroid cancer are warranted.

Panobinostat is also being studied in differentiated thyroid cancers. Results from a Phase II trial of panobinostat in medullary thyroid cancer and iodine refractory differentiated thyroid cancer are summarized in Table 4.[54]

Squamous cell cancer
Panobinostat has also been studied in squamous cell cancer of the head and neck (SCCHN) and has been found to cause up regulation of p21, G2/M cell cycle arrest and cell death of cell lines.[55] When gene expression profiles of 41 SCCHN samples were examined, many of the genes required for DNA replication, repair, and growth arrest that have increased expression in SCCHN were down regulated by panobinostat, suggesting that this malignancy may respond to treatment with panobinostat.[55]

Panobinostat was tested either alone or in combination with dual PI3K-mTOR inhibitors, BEZ235, BGT226, and the PI3K inhibitor BKM120 in SCCHN cell lines.[56] AKT (also known as protein kinase B) activation has been shown to be an early event in SCCHN progression and panobinostat has been shown to induce a persistent inhibition of AKT. Additionally, the combination of panobinostat to any of the above drugs caused additional inhibition of AKT as compared with drug monotherapy.[56]

Reduced tumor growth rates have been demonstrated in xenograft models treated with the above drugs (BEZ235, BGT226, BKM120) alone or in combination with panobinostat. However, treatment with BEZ235, BGT226, or BKM120 proved to be more effective than treatment with panobinostat alone. Furthermore, addition of panobinostat to any of the above drug therapies did not lead to greater tumor response as compared to treatment with drug monotherapy (Table 3).[56] These varying results suggest that further investigation of the use of panobinostat as adjunct therapy for SCCHN is needed.

Ovarian cancer
Observations in preclinical studies using several human ovarian cancer cell lines have identified panobinostat to have synergistic effects with drugs commonly used to treat ovarian cancer, such as gemcitabine, paclitaxel, docetaxel, and 5′-DFUR (metabolite of capecitabine).[57,58] Additionally, the treatment of panobinostat in combination with cisplatin of ovarian cancer previously resistant to cisplatin may be a viable treatment option based upon preclinical data showing that the presence of panobinostat lowered the inhibitory concentration for cisplatin in previously cisplatin resistant ovarian cancer cell lines.[59]

Renal cell carcinoma
Panobinostat has not been shown to be promising in renal cell carcinoma (RCC). There was one patient with metastatic RCC treated as part of a Phase I study, who experienced a confirmed partial response, and remained on the drug for more than 2 years.[16] However, a Phase II trial of panobinostat in 20 refractory RCC patients previously treated with an angiogenesis inhibitor and an mTOR inhibitor showed no activity, with all patients either progressing or stopping treatment prior to the 16-week evaluation period (Table 4).[60] Phase I trials are underway studying panobinostat in combination with sorafenib or everolimus in advanced RCC.

Conclusion
The biology of epigenetics has emerged as important in development of malignancies. While the histone protein is

one major substrate in which HDAC enzymes act, HDAC proteins have also been shown to modulate cancer cell growth via non histone protein targets, including transcription factors, growth factors, and molecular chaperones. HDAC inhibitors have been studied for the treatment of hematologic malignancies as well as solid tumors. In addition to single agent activity, HDAC inhibitors have been shown to be synergistic with cytotoxic therapy by means of their inhibition of DNA repair and synthesis. Panobinostat is a novel pan-HDAC inhibitor which has shown greater inhibitory potential than the currently FDA approved HDAC inhibitors. Data from Phase I and Phase II studies have demonstrated that it is well tolerated with minimal toxicity. Studies are underway to evaluate its efficacy in specific solid tumor types as well as to identify appropriate synergistic cytotoxic, biologic and small molecule inhibitor combinations.

Disclosure

The authors report no conflicts of interest in this work.

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