

An Overview On HSP-90 Inhibitors & Histidine Deacetylase For The Treatment Of Cancer

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Abstract: Heat shock protein 90 (HSP-90) is a molecular chaperone involved in the folding, stabilization, and function of various client proteins, many of which are key regulators of cell growth and survival. In cancer, HSP-90 is often overexpressed and plays a critical role in the stabilization of oncoproteins, making it an attractive target for cancer therapy. Histone deacetylases (HDACs), on the other hand, are enzymes that regulate gene expression by modifying the acetylation status of histone and non-histone proteins. HDAC inhibitors have emerged as a promising class of anticancer agents due to their ability to induce apoptosis, cell cycle arrest, and differentiation in cancer cells.

This review provides an overview of HSP-90 inhibitors and HDAC inhibitors as potential anticancer therapies. It discusses the molecular mechanisms of HSP-90 inhibitors and their effects on cancer cells, including the induction of apoptosis and inhibition of cell proliferation and metastasis. Similarly, the review explores the mechanisms of action of HDAC inhibitors and their ability to modulate gene expression, leading to the suppression of oncogenic pathways and the promotion of tumor cell death.

Furthermore, the review examines the preclinical and clinical studies evaluating the efficacy and safety of HSP-90 inhibitors and HDAC inhibitors in various types of cancer. It also discusses the challenges and future directions in the development of these agents, including the identification of predictive biomarkers and the exploration of combination therapies to enhance their anticancer effects. Overall, HSP-90 inhibitors and HDAC inhibitors represent promising therapeutic strategies for the treatment of cancer, and further research is warranted to optimize their clinical utility.

Keywords: Enzyme Inhibitor, HSP-90, Cancer, HSD, Histone Deacetylase, Heat Shock Protein, Anti-cancer

Introduction:

Heat shock protein 90 (Hsp90) is an atomic chaperone and as the title proposes, it ensures proteins that are included in typical cellular work. In any case, Hsp90 is moreover vital in the collapsing, steadiness, and movement of numerous proteins capable of tumor start, movement, and metastasis ^[1]. Hence, Hsp90 is recognized as a vital facilitator of oncogenic enslavement and cancer cell survival

Heat shock protein 90 (HSP90) plays a basic part in the collapsing, stabilization, and work of different client proteins including in cell signaling, multiplication, and survival.^[1] In cancer, HSP90 is frequently overexpressed and plays a key part in the stabilization of oncoproteins that drive tumorigenesis.^[2] In neurodegenerative illnesses, HSP90 is included in the collapsing and stabilization of misfolded proteins that contribute to illness pathogenesis. HSP90 inhibitors have risen as a promising course of helpful specialists that target these basic pathways.^[14] This audit examines the instruments of activity of HSP90 inhibitors, their preclinical and clinical advancement in cancer and neurodegenerative illnesses, and the challenges and openings in their helpful application^[25]

Heat Shock Proteins (HSPs), moreover known as atomic chaperones, were found to be upregulated when cells were exposed to conditions of push, counting warm stun, chemical variables, and other neurotic modifications.^[4,5] The HSP90 family, which are exceedingly moderated atoms, are included in the direction of the collapsing of recently synthesized proteins, as well as in rectifying erroneously collapsed proteins and blocking the accumulation of inaccurately collapsed proteins. The HSP90 chaperone apparatus plays a vital part in ensuring overexpressed and changed proteins from misfolding and actuating their corruption where fitting. Intuitive between HSP90 and client proteins are fundamental forms in tumor survival, multiplication and relocation. In addition up to, >400 client proteins have been recognized, with these proteins being included in a wide run of vital natural exercises, counting signaling cascades, DNA harm repair, protein transportation, and hormone receptor enactment.

HSP90 comprises of three spaces:

The N-terminal space (NTD), the C-terminal space (CTD), and the center space (MD). The NTD has an ATP authoritative location and a client protein authoritative location, the MD is imperative for hydrolysis of ATP to ADP, and the CTD contains one location for protein dimerization and another for calmodulin official; a charged linker space interfaces the NTD to MD, contributing to keeping up the work, interaction and flexibility of the HSP90 chaperone. HSP90 actuates and encourages the exercises of its client proteins through the ATPase cycle, which is completed by dimerization. The HSP90 family incorporates four isoforms that are shown in diverse areas in cells. HSP90 α and HSP90 β are shown in the cytoplasm and core, GRP94 is displayed in the endoplasmic reticulum, and TRAP-1 is basically found in the mitochondrion, but is shown in the endoplasmic reticulum. All four isoforms share a tall degree of arrangement homology in their N-termini; in this way, the ATP authoritative locales displayed in their N-termini are curiously target areas, and significant inquiries have been committed to disturbing the atomic chaperone work by focusing on this space. A add up to 18 inhibitors of HSP90 have been distinguished and have entered clinical trials.^[10,13,14]

These inhibitors can be partitioned into five categories based on chemical structure:

- i) Normal items and their subordinates;
- ii) purine-based;
- iii) benzamide;
- iv) resorcinol-containing; and
- v) different.

None of these inhibitors are as of now utilized as clinical medications, due to their dose-limited harmfulness and destitute bioavailability. CTD inhibitors and the isoform-selective inhibitors that particularly tie to HSP90 α , HSP90 β , GRP94, or TRAP-1 have moreover been created, endeavoring to make strides in their antitumor impacts. In the show audit, the show armamentarium of HSP90 inhibitors as a monotherapy in cancer administration and the potential combination treatments of HSP90 inhibitors are examined, along with other conventional clinical treatments, counting chemotherapies, focused specialists, immunotherapy, and radiotherapy. Besides, imminent candidates for HSP90-targeting anti-neoplastic treatment are proposed

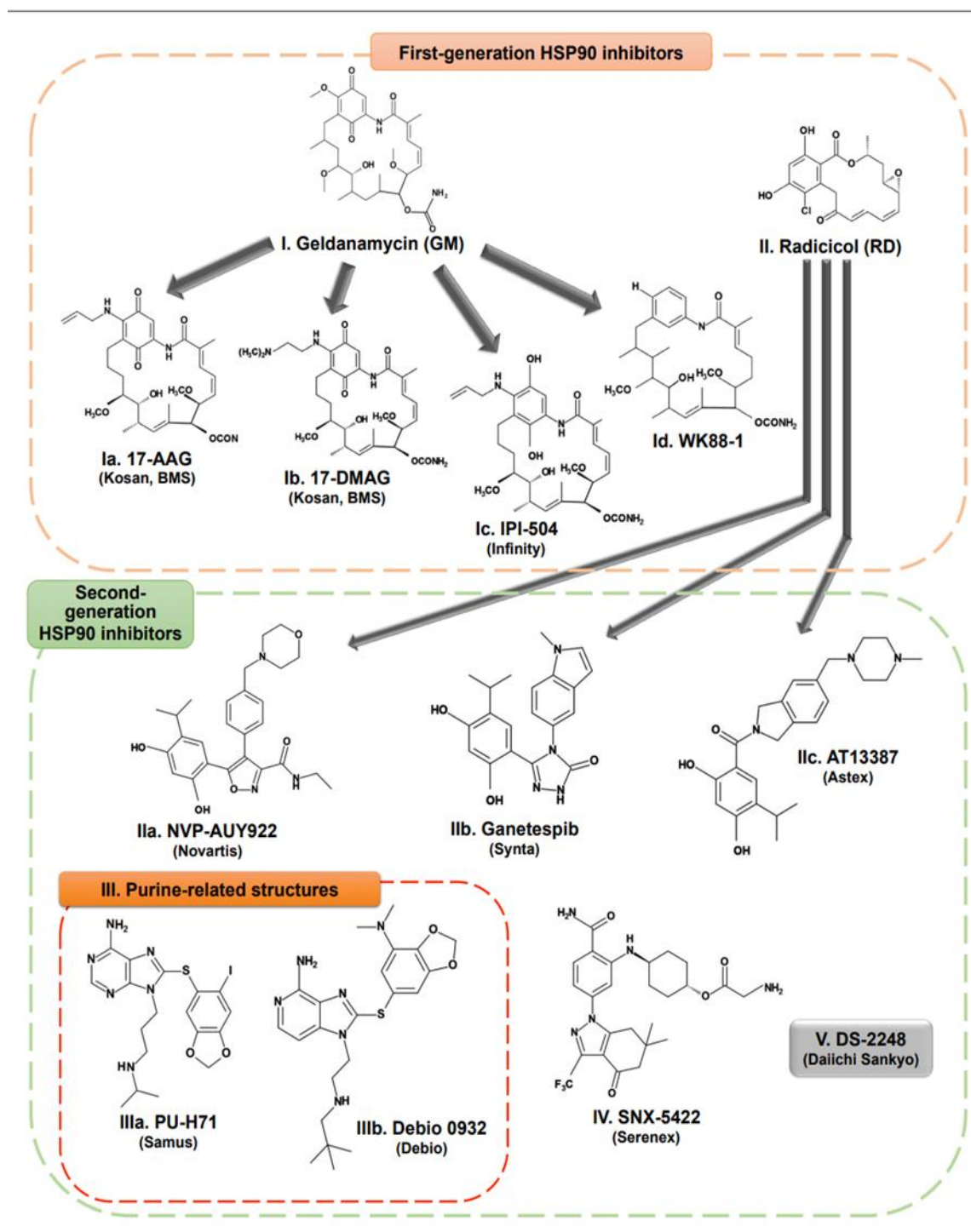


Figure 01 (First & Second Generation HSP90 Inhibitors)

Oncogene soundness and homeostasis interceded by the HSP90 chaperone is a pivotal assurance characteristic of cancer cells. Hence, HSP90 speaks to an appealing helpful target for numerous cancers, counting colorectal cancer. Although monotherapy has constrained clinical adequacy, preclinical and early-phase clinical considers demonstrate made strides in antitumor movement when HSP90 inhibitors are combined with chemotherapies or focused on specialists.^[15,16] This may be assist moved forward with a biomarker-guided approach based on oncogenic HSP90 clients, or stratification based on the agreement atomic subtypes of colorectal cancer, proposing a synergistic movement with 5-fluorouracil in preclinical models of the chemorefractory mesenchymal subtype. Besides, HSP90 restraint may enact instruments to turn non-immunogenic tumors hot and make strides their acknowledgment by the resistant framework, proposing cooperative energy with resistant checkpoint blockade.^[8]

The improvement of HSP90 inhibitors started with 2 normal items: geldanamycin, a benzoquinone ansamycin and radicicol, a resorcyclic corrosive lactone. These are commonly alluded to as first-generation HSP90 inhibitors. Geldanamycin, determined from *Streptomyces hygroscopicus*, was appeared to tie to the N-terminal nucleotide stash of HSP90, driving to hindrance of the ATPase action of HSP90. In spite of promising in vitro and in vivo viability, geldanamycin fizzled to reach any clinical trial owing to its destitute solvency, chemical and metabolic insecurity, and hepatotoxicity. On the other hand, radicicol, inferred from *Monosporium border*, was illustrated to target the center of the ATP-binding take of HSP90, coming about in powerful hindrance in vitro. Owing to profoundly responsive auxiliary challenges, be that as it may, it fizzled to create the same strength in vivo.^[11,14,23]

To overcome these issues, geldanamycin auxiliaries were made. Tanespimycin (17-N-allylamino-17-demethoxygeldanamycin [17-AAG]); was the to start with geldanamycin subordinate to be surveyed in the clinic.⁷ This was taken after by alvespimycin (17-dimethylaminoethylamino-17-demethoxygeldanamycin [17DMAG]); In show disdain toward of the truth that clinical development was observed with these compounds, advancement was ceased since of their unfavorable hurtfulness profiles.

The taking after geldanamycin backup to be made was retaspimycin hydrochloride, or IPI-504 (17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride;). A diminished shape of 17-AAG, it showed up more vital ensure than the other first-generation HSP90 inhibitors owing to its water dissolvability and lessened hepatotoxicity.^{3,4} The hydroquinone ring in IPI-504 was a more solid inhibitor of HSP90. Another geldanamycin straightforward, a nonquinone, was WK88-1 (Figure 2Id); it besides has less side impacts and made strides in HSP90 definitive properties.^[8]

To make a more secure and more particular approach to target HSP90, a course of action of essential alterations of the parent compounds were made. The second-generation inhibitors either carry the resorcinol moiety of radicicol (Figure 2II) or are purine scaffold-based (Figure 2III). They additionally require hepatotoxicity since of transfer of the benzoquinone moiety. NVP-AUY922 (as well called luminespib or VER-52269; ganetespib (STA-9090; Figure 2IIb), and AT13387 (onalespib; are basic resorcinol subordinates. NVP-AUY922 is a resorcinol backup with a structure based on the 4,5-diarylisoazole stage. Not at all like the geldanamycin analogs, it offers most essential official enjoying for the N-terminal nucleotide-binding area of HSP90. Ganetespib ([5-[2,4-dihydroxy-5-(1-methyl) phenyl]-4-(1-methyl-1H-indol-5-yl)-2,4-dihydro-[1,2,4] triazole-3-one]) is a small-molecule HSP90 inhibitor that contains a triazole, which contributes to its favorable pharmacologic and security characteristics in comparison with all the first-generation inhibitors. Ganetespib is basically smaller than the prototypical first-generation compound and most of the second-generation compounds (Figure 2). At final, AT13387 is a high-affinity and long-acting HSP90 inhibitor that ties interior the N-terminal ATPase catalytic area of HSP90 covering the ATP official site.^[32]

Several additional HSP90 inhibitors are as of presently in enhancement or in arrange 1 considers, tallying the purine system administrators PU-H71 and Debio 0932 (CUDC-305; the curiously dihydroindazolone scaffold-based small particle SNX-5422 and DS-2248, which has an undisclosed structure .

Limited ampleness of HSP90 inhibitor monotherapy:-

Reliable with the require of a vital antitumor development of ganetespib in the arrange II consider of metastatic CRC (Table 1), clinical ampleness of HSP90 limitation as a single administrator has been confined. Right presently, no HSP90 inhibitors have been embraced for clinical utilize, in show disdain toward of wide clinical endeavors to illustrate their ampleness in a few cancer sorts. Various clinical trials have been finished or put off due to as it were coordinate impacts of the inspected inhibitors (clinicaltrials.gov). The best clinical reasonability with HSP90 inhibitor monotherapy has been finished in tumors decidedly subordinate to particular client oncoproteins, such as ALK in a subtype of non-small cell lung cancers and in HER2-overexpressing breast cancers. Common resistance components to HSP90 inhibitors have been portrayed and may grant clues to move forward their practicality. Warm daze calculate protein 1 (HSF1) development is broadly recognized as a key resistance calculate of HSP90 restriction. HSF1 ties

HSP90 and is released to outline energetic homotrimers after HSP90 obstacle (with N space inhibitors), along these lines activating a prosurvival warm daze response.

Furthermore, overexpression of the multidrug resistance efflux pump P-glycoprotein 1 (P-gp) bypasses the anti-cancer development of benzoquinone-based HSP90 inhibitors, whereas tall expression of UDP glucuronosyltransferase 1A (UGT1A) is related with resistance to resorcinol-based inhibitors such as ganetespib and luminespib. These proteins might control the activity of HSP90 inhibitor monotherapy, but trading to C-terminal HSP90 inhibitors or custom fitted co-inhibition strategies have been showed up to rearrange the resistance. A afterward think approximately found that chaperone combination (named epichaperome) is prescient of affectability to HSP90 obstacle, or possibly than the expression levels of individual people of the epichaperome (HSP90, HSC70, Bounce, HSP110, CDC37, AHA1), HSP90 clients, antiapoptotic proteins and genetic modifications.^[7,22]

Interestingly, this finding suggests that patients can be stratified based on the riches of the epichaperome and not solely its nearness. This favorable epichaperome for HSP90 restriction treatment was recognized in 60–70% of cell lines decided from breast-, lung-, pancreatic- and gastric cancers, as well as leukemia and lymphomas. All things considered, the epichaperome course of action has not been inspected as a potential prescient figure for HSP90 restriction in CRC

Rectal cancers are commonly treated with chemoradiation earlier to surgery, to encourage total surgical resection and decrease the hazard of neighborhood repeats. Comparative to a few chemotherapeutics, ionizing radiation presents intemperate DNA harm that comes about in cell passing. A few preclinical ponders have given compelling prove for radiosensitization movement of HSP90 inhibitors in a few cancer sorts, counting CRC. Potential modes of activity incorporate hindrance of cell cycle checkpoint enactment and DNA double-strand break repair, which along these lines lead to acceptance of cell cycle capture, apoptosis and corruption, as well as diminished cell relocation and invasiveness. Clinical potential for the combined utilize of radiation treatment and HSP90 restraint has been appeared in a stage I consider, where capecitabine and radiation treatment was combined with ganetespib as neoadjuvant treatment in arrange II and III rectal cancers, accomplishing pathologic total reaction in 25% of the patients, in expansion to lymph hub clearance in the resected example in 67%.^[7,16]

SN-38 is the active metabolite of irinotecan that inhibits topoisomerase I, the unwinding enzyme required during DNA replication, resulting in irreversible DNA damage and cell death. Irinotecan is part of the combinatorial conventional chemotherapy regimens FOLFIRI or FOLFOXIRI, commonly used as first-line treatment for patients with metastatic CRC. Inhibition of topoisomerase I by SN-38 leads to G2/M cell cycle arrest that is regulated by several proteins such as the DNA response mediators Serine/threonine-protein kinase Chk1 (CHEK1) and Wee1-like protein kinase (WEE1). Both CHEK1 and WEE1 are HSP90 clients, and their depletion with the HSP90 inhibitor tanespimycin proved to increase the cytotoxicity of SN-38 in TP53defective cells. This observed effect was then investigated in a phase I clinical study in 27 patients with different solid tumor types treated with irinotecan and tanespimycin. Six of the enrolled subjects were CRC patients, and stable disease was the best response observed. In 16 patients with known TP53 status, stable disease was measured predominantly in patients with TP53 mutated (five out of ten) compared to wild-type tumors (two out of six). Although there was no subsequent phase II trial on this combination, possibly due to the introduction of newer HSP90 inhibitors, another clinical study was initiated with the novel PEN-886 conjugate in patients with advanced solid malignancies . PEN-886 (STA-8666) is a miniature conjugate of an HSP90 targeting moiety linked to SN-38 that has shown promising preclinical activity in other cancer models.^[28]

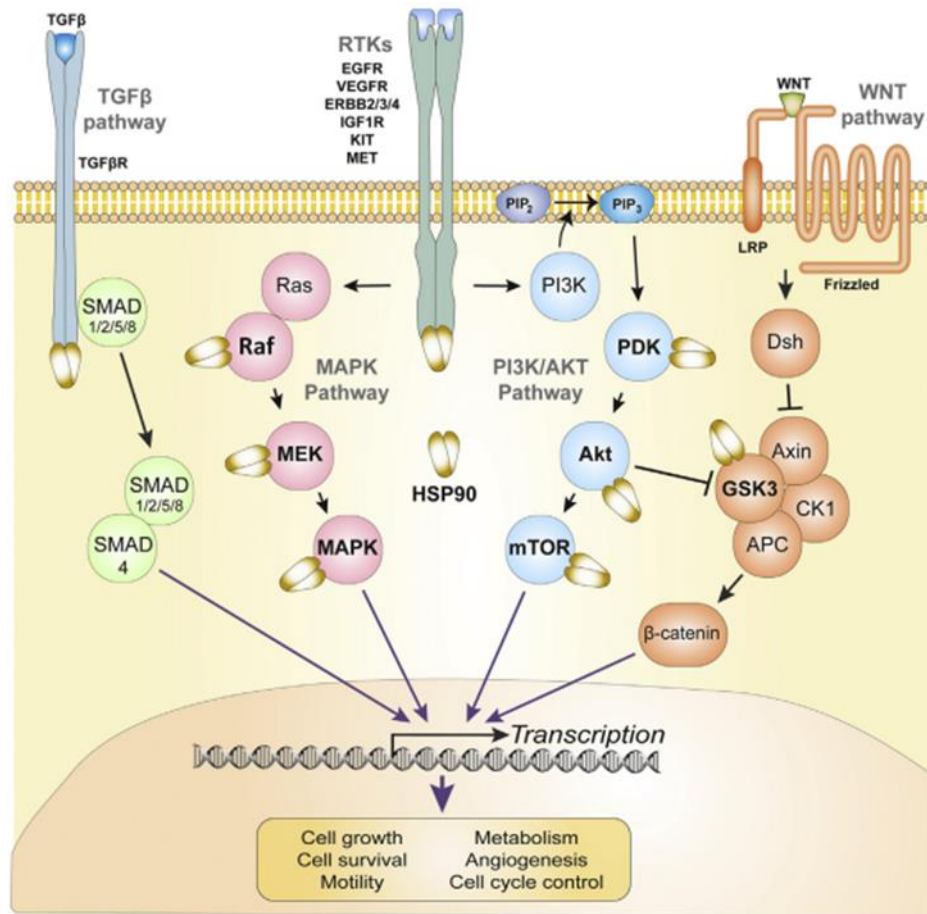


Figure 02 (Mechanism of HSP90)

Structure: -

HSP90 is a vital chaperone protein that capacities to keep up the redress collapsing of client proteins. It directs protein collapsing and corruption, a few cell signaling pathways, cell multiplication and survival, and cell apoptosis by means of collaboration with co-chaperones and client proteins. [12,18,20]

HSP90 comprises of three particular spaces:

- i) The NTD, which incorporates an ATP official location and the client protein authoritative location;
- ii) an MD that is capable for the hydrolysis of ATP to ADP; and
- iii) a CTD, which is comprised of a protein dimerization location and a calmodulin-binding location;

there is too a linker space interfacing the NTD to the MD, contributing to the support of the capacities, intelligent, and versatility of the HSP90 chaperone. The NTD, which is too alluded to as the nucleotide-binding location, is essential for the liking between client proteins and HSP90, and for the chaperone cycle, due to the nearness of the authoritative location for ATP which are pivotal for the HSP90 ATPase movement. Hence, the NTD is considered a basic target in the improvement of inhibitors. The CTD is fundamentally included in the dimerization of HSP90. There is moreover an ATP authoritative location that as it were opens when the ATP-binding location in the NTD is inaccessible, making the C-terminal an allosteric controller of the N-terminal ATPase action. There are extraordinary themes, counting MEEVD or KDEL on CTD, which vary concurring to the distinctive isoform sorts and the cellular localization. [1,2,3]

Heat Shock protein 90 (HSP90) is a exceedingly moderated atomic chaperone that is fundamental for the collapsing, development, and soundness of a wide extend of client proteins. These client proteins incorporate numerous key controllers of cell development, survival, and signaling pathways, making HSP90 a central player in cellular homeostasis. In cancer, HSP90 is frequently overexpressed and plays a vital part in the stabilization of oncoproteins

that drive tumor development and survival. In neurodegenerative infections, HSP90 is included in the collapsing and stabilization of misfolded proteins that shape poisonous totals in the brain. Given its central part in these infection forms, HSP90 has developed as an alluring restorative target.

HSP90 inhibitors are small molecules that bind to the ATP-binding pocket of HSP90, leading to the destabilization and degradation of client proteins. By targeting HSP90, these inhibitors can selectively induce the degradation of oncoproteins in cancer cells or misfolded proteins in neurodegenerative diseases. HSP90 inhibitors can also disrupt the interaction between HSP90 and its co-chaperones, leading to further destabilization of client proteins.

Preclinical and clinical development:

Preclinical data indicate that HSP90 inhibition can enhance the effects of all chemotherapies used in the standard treatment of CRC, including 5-fluorouracil (5-FU), irinotecan and oxaliplatin, but combinations have only been clinically tested with the previous two. Despite new findings in the anticancer armamentarium, the fluoropyrimidine 5-FU remains the mainstay of treatment for CRC patients, both in adjuvant and metastatic settings [5]. 5-FU is an antimetabolite that inhibits DNA and RNA synthesis and repair by binding to the nucleotide sequence and inhibiting thymidylate synthesis.

When the latter is overexpressed or amplified, it acts as a resistance factor to 5-FU. Inhibition of HSP90 leads to downregulation of thymidylate synthase and thus synergizes with fluoropyrimidine-based chemotherapy as shown in CRC cell lines and xenograft models. A phase I clinical trial testing luminespib and capecitabine (an oral 5-FU prodrug) in 19 patients with mostly advanced CRC produced a partial response or stable disease in 63% of study patients..Numerous HSP90 inhibitors have been developed and evaluated in preclinical models of cancer and neurodegenerative diseases. These studies have demonstrated potent anti-tumor activity in various cancer types, as well as neuroprotective effects in models of neurodegenerative diseases. Several HSP90 inhibitors have also advanced to clinical trials, where they have shown promising results in terms of safety and efficacy. However, challenges remain in optimizing the therapeutic window and minimizing off-target effects of these inhibitors.^[7,11,13]

Preclinical Studies on Therapeutic Targets of HSP90 Inhibitors in Lung Cancer

Preclinical studies have demonstrated that HSP90 activity significantly increases in cancer cells⁵ and that the continued activity of HSP90 is required for oncogene-driven tumorigenesis because inhibition of HSP90 leads to growth inhibition and apoptosis. In this section, we discuss the important oncogenic targets of HSP90 inhibitors. EGFR Mutant Non-Small Cell Lung Cancer EGFR mutations are found in nearly 20% of advanced lung adenocarcinomas and can be targeted by EGFR TKIs. Unfortunately, resistance to these drugs develops within 9-12 months after starting treatment. Because mutant EGFR is a client protein of HSP90, one strategy to overcome such acquired resistance is to target the mutant EGFR protein with HSP90 inhibitors. Inhibition of HSP90 in lung cancer with mutant EGFR was first demonstrated by geldanamycin and its derivatives 17-AAG, 17-DMAG and IPI-504 in both cell line and animal models. Efficacy was observed in EGFR mutant cell lines and animal models with acquired resistance to EGFR TKIs secondary to EGFR mutation T790M. In addition, resorcinol derivatives NVP-AUY922 and ganetespib were effective against EGFR mutant NSCLC. AT13387 was able to suppress EGFR signaling long-term both in vitro and in vivo. This is in contrast to ganetespib, where EGFR inhibition was not sustained in vivo.²³ The long-term pharmacodynamic effects of AT13387 make it a worthy candidate for further investigation in several ongoing phase 1 and 2 clinical trials. of.

ALK-Positive Non-Small Cell Lung Cancer

A total of 2-5% of NSCLC patients have anaplastic lymphoma kinase (ALK) rearrangements, often with echinoderm microtubule-associated protein-like 4 (EML4). Sudo and colleagues first identified the EML4-ALK rearrangement as an oncogene and showed that the EML4-ALK fusion protein has potent transforming activity. Several ALK inhibitors (eg, crizotinib, cetinib, and alectinib [Alecensa, Genentech]) have shown significant efficacy in both preclinical and clinical studies, but acquired resistance is inevitable.²⁷ Because ALK fusion proteins are clients of HSP90, inhibition of HSP90 is acceptable . . . treatment, especially in patients with acquired resistance to ALK-TKIs. In addition to potent growth inhibitory effects on EML4ALK expression in NSCLC, 17-AAG was able to reduce the expression of EML4-ALK and downstream effectors, including phosphoAKT, phospho-ERK1/2, and phospho-S6, and inhibit cell growth. in crizotinib-resistant NSCLC.

In vivo treatment of EML4-ALK driven xenografts with 17-DMAG or IPI-504 resulted in significant tumor regression. In addition, IPI-504 induced degradation of EML4-ALK, which triggered a rapid depletion of phospho-ERK, phosphoSTAT3 and phospho-AKT, followed by growth arrest and apoptosis. Second-generation HSP90 inhibitors have also shown activity against ALK-positive cancers. Ganetespib alone or in combination with an ALK inhibitor in addition to crizotinib was active in the treatment of ALK-positive NSCLC cells that were naïve to crizotinib or had acquired resistance to crizotinib, including cells with secondary ALK mutations. NVP-AUY922 also showed potential against ALK-driven NSCLC. AT13387 has demonstrated significant success in treating ALK-positive disease both in

Drug formulation	Phase/ recruitment status	Condition		Outcome measure/response	Secondary outcome measures	Clinical trials. govtrial annotation and study
Ganetespib	Phase I Completed	Advanced malignancies CRC	solid incl.	42/53 evaluable patients 23 – stable disease	HSP70	NCT0068793 4 Goldman, J.W. et al. (2013)
	Phase I Completed	Refractory mCRC		17 evaluable patients No overall response 2 – stable disease (KRAS mut)	pERK, pAKT, CyclinD1, HIF-1 α , VEGFR2, p70S6, HSP70. KRAS, BRAF, PIKC3A	NCT0111838 Cercek, A. et al. (2014)
Ganetespib + Capecitabine and Radiation	Phase I Completed	Stage II/III rectal cancer		15/16 evaluable patients 3/12 – pathologic complete response 2 – residual tumor 6/9 – clearing of lymph node disease	Half-life of ganetespib and capecitabine	NCT0155496 9 El-Rayes, B.F. et al. (2015)
Ganetespib + Ziv-aflibercept	Phase I Terminated	Progressive malignancies incl. mCRC		4/5 evaluable patients 3 stable disease 1 progressive disease	HIF-1 α , EGFR	NCT0219254 1 Meehan, R.S. et al. (2018)
Luminespib + Capecitabine	Phase I Completed	Advanced malignancies CRC	solid incl.	19/23 evaluable patients 4 partial response 8 stable disease 7 progressive disease	Drug related toxicities	NCT0122673 2 Bendell, J.C. et al. (2015)
Luminespib + Cetuximab	Phase IB Completed	KRAS wt mCRC		15/16 evaluable patients 1 – partial response 4 – stable disease	Half-life of luminespib	NCT0129482 6 Subramaniam, S. et al. (2015)
Tanespimycin + Irinotecan	Phase I Completed	Advanced malignancies CRC	solid incl.	22/27 evaluable patients no complete or partial responses 11 – stable disease	HSP70, pH2AX, pChk1, p- histone H3, cl. caspase 3, p53	NCT00119236 Tse, A.N. et al. (2008)
Tanespimycin + Sorafenib	Phase I Completed	Advanced malignancies CRC	solid incl.	23/28 evaluable patients 2 – partial response 14 – stable disease stable disease in 1/4 CRC patients	Half-life of tanespimycin and sorafenib. HSP90, HSP70, CDK4, pAKT, pERK, RAF1, β -actin	NCT0012126 4 Vaishampayan U.N. et al. (2010)
PEN-866 (HSP90 targeting ligand linked to SN-38)	Phase I/IIA Recruiting	Advanced malignancies CRC	solid incl.	Phase I – determine the dose and toxicity. Phase II – determine ORR	Half-life of PEN-866 and its metabolites. Radiographic PFS. OS.	NCT0322140 0

XL888 + Pembrolizumab

Phase IB
RecruitingAdvanced
malignancies
CRCGI Determine the dose and
incl. toxicity of the combinationImmune profile in the serum
and in tumor biopsiesNCT0309578
1

vitro and in vivo, and is currently being evaluated for clinical trials.^[14]

Here is some information on the clinical and preclinical trials of HSP90 inhibitors:

Table:02

Agent(s)	Phase	Number of Patients	Setting	Study Results	Reference
IPI-504	2	76	Advanced NSCLC with prior therapy	- Median PFS, 2.86 mo - ORR, 7% - 2 PRs among patients with <i>ALK</i> rearrangement	70
IPI-504 and docetaxel	1	23	Advanced NSCLC with prior systemic therapy	- Higher response among patients with squamous histology (43%) and among former smokers (33%)	71
AUY922	2	112	Advanced NSCLC with prior systemic therapy	- ORR of 25% in patients with <i>ALK</i> gene rearrangement - ORR of 50% in patients with crizotinib-naive <i>ALK</i> positive disease - 18% ORR in patients with <i>EGFR</i> mutation	74
AUY922 and erlotinib	½	37	Advanced NSCLC that had progressed while patient on TKIs	- <i>EGFR</i> T790M identified by second tumor biopsy in 10 of 25 patients (40%) - ORR in 4 of 25 patients (16%; 95% CI, 6%-35%) - <i>EGFR</i> T790M in 3 of 4 patients with PR	75
AUY922 and erlotinib	1	10	Advanced NSCLC and <i>EGFR</i> exon 20 insertion	- 1 PR - 3 patients with disease stabilization lasting more than 3 mo and PFS lasting more than 6.1 mo	76
Ganetespib	2	99	Advanced NSCLC with prior systemic therapy	- PFS at 16 wk: 13.3% among patients with <i>EGFR</i> mutation, 5.9% among patients with <i>KRAS</i> mutation, 19.7% among patients with wild-type <i>KRAS/EGFR</i> - <i>ALK</i> gene rearrangement in 4 patients with PR	79
Ganetespib and docetaxel	2	381	Advanced disease with prior systemic therapy	- Increased hemoptysis and decreased efficacy in non-adenocarcinoma after first 71 patients enrolled, so study limited to adenocarcinoma - Median survival of 3.9 mo in combination group vs 3.0 mo in control group - OS of 7.6 mo in combination group vs 6.4 mo in control group; HR, 1.23	80

1. AUY922 (Luminespib):

Clinical Trials: AUY922 has been evaluated in multiple clinical trials for various cancers, including breast cancer, lung cancer, and leukemia. These trials have assessed its safety, efficacy, and tolerability both as a single agent and in combination with other therapies. Overall, AUY922 has shown promising antitumor activity in certain patient populations.

Preclinical Trials: Preclinical studies have demonstrated the efficacy of AUY922 in inhibiting the growth of cancer cells, both in vitro and in vivo. It has shown synergistic effects when combined with other anticancer agents, such as chemotherapy and targeted therapies.

2. 17-AAG (Tanespimycin):

Clinical Trials: 17-AAG has been studied in clinical trials for various cancers, including breast cancer, lung cancer, and melanoma. These trials have shown mixed results, with some indicating modest antitumor activity and others showing limited efficacy. 17-AAG has also been studied in combination with other agents, such as trastuzumab and bortezomib.

Preclinical Trials: Preclinical studies have demonstrated the potential of 17-AAG as an anticancer agent, particularly in cancers that are dependent on HSP90 client proteins. It has shown synergistic effects when combined with other anticancer agents, such as proteasome inhibitors and PI3K inhibitors.

3. Ganetespib:

Clinical Trials: Ganetespib has been evaluated in clinical trials for various cancers, including lung cancer, breast cancer, and gastric cancer. These trials have shown promising antitumor activity, particularly in patients with certain molecular subtypes of cancer. Ganetespib has also been studied in combination with other agents, such as docetaxel and trastuzumab.

Preclinical Trials:

Preclinical studies have demonstrated the efficacy of ganetespib in inhibiting the growth of cancer cells, both in vitro and in vivo. It has shown synergistic effects when combined with other anticancer agents, such as mTOR inhibitors and PARP inhibitors.

These examples highlight the potential of HSP90 inhibitors as a therapeutic strategy for cancer. However, further research is needed to fully understand their mechanisms of action and optimize their clinical utility.

17-AAG and 17-DMAG

Although 17-AAG was the first HSP90 inhibitor introduced into the clinic in a phase 1 trial, it was never examined in lung cancer. In the early phase 1 trials in patients with solid organ malignancies, hepatotoxicity and diarrhea were the dose-limiting toxicities. Similar toxicities and ocular toxicity were seen with the second HSP90 inhibitor, 17-DMAG. Owing to the lack of objective responses and the presence of severe side effects, these drugs were abandoned, and new, second-generation HSP90 inhibitors were developed.⁶⁸

IPI-504

After a small phase 1 trial in patients with gastrointestinal stromal tumor or soft-tissue sarcoma,⁶⁹ IPI-504 was tested in patients with molecularly defined (*EGFR* mutation and *ALK*)

Histone Deacetylase

Histone deacetylase inhibitors (HDACIs) are a class of drugs that affect histone deacetylases, enzymes that remove acetyl groups from histones, causing changes in gene expression. The potential of these drugs in cancer therapy has been investigated due to their ability to regulate gene expression, cell cycle arrest, apoptosis, and differentiation in cancer cells. HDACIs can affect both cancer cells and the tumor microenvironment and affect several pathways involved in cancer progression and metastasis.

They have shown promise in preclinical studies and in certain types of cancer in clinical trials, both as a stand-alone therapy and in combination with other therapies such as chemotherapy, radiation and targeted therapy. Chromatin, the higher order structure of DNA and protein, forms a barrier to gene transcription. The basic unit of chromatin is the nucleosome, which consists of 147 base pairs of DNA wrapped around a histone core containing two copies of histones H2A, H2B, H3 and H4. This core is important for interactions between nucleosomes and within the nucleosome itself (Khorasanizadeh, 2004).^[31]

Chromatin can adopt different structural forms depending on epigenetic modifications that occur on DNA and histone tails protruding from nucleosomes. Changes in the chromatin state of certain genes can lead to their repression or activation. Several post-translational histone modifications have been described, including acetylation, methylation, phosphorylation, and sumoylation (Bannister and Kouzarides, 2011). Histone post-translational modifications form the so-called histone code, which is read and recognized by other proteins to regulate gene expression (Strahl and Allis, 2000).

HISTORY:

About fifty years ago, Vincent Allfrey and colleagues discovered lysine acetylation of histones, indicating that acetylation of the ε-amino group of histone lysine residues can play a role in gene expression (Allfrey et al., 1964; Gershey et al., 1968). . Acetylation neutralizes the positive charge of histone lysine residues, relaxes chromatin

conformation and allows better access to the transcriptional machinery (Haberland et al., 2009). Therefore, protein acetylation is usually associated with gene activation. In contrast, removal of acetyl groups from histones induces chromatin condensation and repression of gene transcription (Haberland et al., 2009). It is known that lysine acetylation also occurs in many non-histone proteins, such as transcription factors and cytoplasmic proteins, and affects gene transcription and other cellular processes (Peng and Seto, 2011). Lysine acetylation is a reversible modification driven by the antagonistic actions of two types of enzymes, histone acetylases (HATs) and histone deacetylases (HDACs) (Bannister and Kouzarides, 2011). HATS catalyze the transfer of acetyl groups from acetyl-CoA to the ϵ -amino group of a lysine residue.^[33]

In contrast, HDACs promote the removal of the acetyl group from the acetylated residue, releasing an acetate molecule (For recent reviews on HDAC targets, see (Bosch-Presegue and Vaquero, 2011; Peng and Seto, 2011; Reichert et al.) al., 2012)).In recent decades it has become clear that epigenetic abnormalities can be one of the hallmarks of cancer. For example, post-translational modifications of histones can play an important role in cancer development and progression by modulating gene transcription, chromatin remodeling and nuclear architecture. Histone acetylation, a well-studied posttranslational histone modification, is regulated by the opposing functions of histone acetyltransferases (HATs) and histone deacetylases (HDACs).

By removing acetyl groups, HDACs reverse chromatin acetylation and alter the transcription of oncogenes and tumor suppressor genes. In addition, HDACs deacetylate many non-histone cellular substrates that control many biological processes, including cancer initiation and progression. This review discusses the role of HDACs in cancer and the therapeutic potential of HDAC inhibitors (HDACi) as emerging drugs in cancer therapy.

The classification and function of HDACs

2.1. Classification of HDACs^[31,32,33,34,35]

According to cofactors and primary homologous structures, the 18 HDAC members are phylogenetically divided into Zn-dependent HDACs and NAD-dependent HDACs. Zn²⁺-dependent HDACs are also known as classical HDACs (mostly include class I, II, IV) and catalyze the zinc cation-based deacetylation of histones. On the other hand, NAD-dependent enzymes belong to class III (Sirt 1e7), which use NAD⁺ as a cofactor.

In particular, Sirt 1e7 is structurally and developmentally unrelated to classical HDACs, and the term "HDAC" generally refers to classical HDACs. In general, class I HDACs share many similarities in structure and function, and their excellent reactivity gives them the most important intracellular deacetylation functions. Namely, class I HDACs are ubiquitously expressed by various cells, are mostly located in the nucleus, and participate in several biological events through their enzymatic functions or the formation of multiprotein corepressor complexes.

In addition, many studies have shown that overexpression of class I HDACs is common in various malignancies, and class I HDACs are closely related to cancer progression. Class IIa HDACs and class IIb HDACs share high sequence homology, but the additional catalytic domain of HDAC6 generally results in low homology between class II HDACs. Although class IIa HDACs share 57% homology with class I HDACs in their catalytic domains, their reactivity is significantly lower than that of class I HDACs.

In addition, class II HDACs are located in the cytoplasm and nucleus, where they can deacetylate histone proteins and non-histone proteins. As the only member of class IV HDACs, HDAC11 is the smallest histone deacetylase, with its catalytic domain accounting for more than 80% of its sequence. HDAC11 was first characterized in 2002 and is somewhat more distantly related to other members of the HDAC family. Interestingly, HDAC11 removes the acetyl group from lysine with lower efficiency, but is the most efficient fatty acid deacetylase of the HDAC family..

Why are cancer cells sensitive to HDIs?

The basis for the selective toxicity of HDI to cancer cells is unclear. If altered gene expression were the main mechanism of HDI-induced apoptosis, then normal cells and tumor cells would be expected to be equally sensitive. Indeed, given that disruption of apoptotic pathways is an important event in tumorigenesis (Johnstone et al., 2002), normal cells can be expected to be more sensitive to HDI-induced death than tumor cells. However, if HDI-induced

apoptosis is associated with abnormal mitosis, the fact that cancer cells typically lose cell cycle checkpoints may make these cells inherently more sensitive to the agents.

In support of this, leukemic cell lines treated with HDI initially accumulate 4n DNA and then undergo apoptosis. However, when these cells are manipulated in G1 to arrest overexpression of p16INK4a, Bid is no longer activated and the cells remain viable, although global histone hyperacetylation continues to occur (RW J., unpublished data). Therefore, loss of the G1 checkpoint due to impairment of p16INK4a or other RB function, which is an almost common occurrence in tumors, may explain the increased sensitivity of cancer cells to HDI. Another unresolved question is which factors determine whether a cancer cell undergoes cell cycle arrest, differentiation, or death in response to HDI. Drug level is one factor, as most HDIs are toxic at higher doses and cause G1 arrest at lower doses. It is not known whether this is due solely to the effects of HDI on chromatin remodeling and gene transcription. Another factor is the type of tissue. At the same drug dose, one cell type may undergo G1 arrest and differentiation, while the other cell type immediately undergoes apoptosis.

Why this happens is not entirely clear, but it may be related to the intracellular metabolism of the drug or to a subset of certain genetic defects that affect cell cycle regulation or apoptosis in a particular cancer cell. In support of the latter idea, the cell's existing apoptotic set point may alter the balance between HDI-induced growth arrest and cell death. For example, cells engineered to overexpress Bcl2 are resistant to HDI-mediated apoptosis, but the effect on the cell cycle is unchanged (Johnstone, 2002). In addition, as noted, cell fate can determine the cell's decision to arrest in G1 or progress through the cell cycle and experience the effects of HDIs on mitosis. In support of this idea is the inverse correlation between p21WAF1/CIP1 induction and cell cycle arrest and apoptosis (Burgess et al., 2001). If HDI-treated cells fail to induce p21WAF1/CIP1 due to epigenetic changes involving the CDKN1 locus or have functional defects in the G1 checkpoint, the cells may undergo apoptosis. We propose that the possible interplay of direct effects of HDI on transcription and indirect effects caused by aberrant mitosis determines the final biological outcome.^[41,43,45]

HDACs and cancer

The expression of HDACs in different tumors

A significant number of studies have shown that HDAC overexpression is closely related to tumor progression and 13 out of 15 tumors (breast cancer, colon cancer, stomach cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, lymphoma, pancreatic cancer, prostate). cancer, medulloblastoma, neuroblastoma and chronic lymphocytic leukemia) overexpress HDACs. Accumulating evidence has shown that HDACs are required for tumor-related functions such as cell growth/proliferation, cell differentiation, cell cycle, cell motility/migration, drug resistance, prognosis, angiogenesis, autophagy, and apoptosis.

Due to their overexpression and tumorigenic functions, HDACs have emerged as promising anticancer targets. HDACs in Cancer Pathogenesis HDACs have several roles in tumor progression. In tumorigenesis, overexpressed HDACs transcriptionally silence tumor suppressor genes and promote tumorigenesis. In tumorigenesis, overexpressed HDACs (1) induce angiogenesis via hypoxia-inducible factor 1 (HIF-1) and provide nutrients for tumor growth and metabolism; (2) interrupt the cell cycle and promote the proliferation of tumor cells; (3) increases cellular infiltration and enhances metastasis and tumor cell invasion; (4) reduce the sensitivity of tumor cells to apoptotic signals or chemical drugs, leading to apoptosis escape or drug resistance. HDACs in angiogenesis Hypoxia is a prominent feature of the tumor microenvironment (TME), and tumor cells can induce angiogenesis in the TME via HIF1 α . In malignant cells, HDACs regulate HIF-1 α activity in several ways.

Functionally, acetylation of Lys-532 leads to ubiquitin-dependent degradation of HIF-1 α , while HDAC1 and HDAC4 can induce deacetylation of HIF-1 α and inhibit ubiquitination and degradation processes. In addition, HDAC5 and HDAC6 promote the maturation and stabilization of HIF-1 α by regulating the deacetylation of the chaperones HSP70 and HSP90, rather than directly regulating HIF-1 α acetylation. After inhibition of HDAC5 and HDAC6, hyperacetylation of HSP70 and HSP90 leads to.

Some HDACIs have been approved for the treatment of certain types of cancer, such as:

1. Vorinostat (Zolinza): Approved for the treatment of cutaneous T-cell lymphoma (CTCL).

2. Romidepsin (Istodax): Approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL).
3. Belinostat (Beleodaq): Approved for the treatment of PTCL.
4. Panobinostat (Farydak): Approved for the treatment of multiple myeloma.

Research is ongoing to explore the potential of HDACIs in other types of cancer and to improve their effectiveness and reduce side effects.

Histone deacetylase inhibitors (HDACIs) work by blocking the activity of histone deacetylases (HDACs), which are enzymes that remove acetyl groups from histone proteins. Histone proteins are involved in the packaging of DNA into chromatin, and their acetylation state plays a role in gene expression.

The mechanism of action of HDACIs can be summarized as follows:

1. Histone acetylation: Histone proteins can be acetylated (acetyl groups added) or deacetylated (acetyl groups removed). Acetylation is generally associated with gene activation, as it loosens the chromatin structure, making the DNA more accessible to transcription factors and RNA polymerase. HDACIs inhibit the removal of acetyl groups, leading to an accumulation of acetylated histones and a more open chromatin structure, which can promote gene expression.
2. non-histone protein acetylation: HDACs also target non-histone proteins, such as transcription factors and signaling molecules, affecting their function. By inhibiting HDAC activity, HDACIs can alter the acetylation status of these proteins, leading to changes in their activity and downstream signaling pathways.
3. Cell cycle arrest: HDACIs can induce cell cycle arrest at various stages, depending on the specific inhibitor and cell type. This effect is mediated by changes in the expression of genes involved in cell cycle regulation, such as cyclins and cyclin-dependent kinases (CDKs).
4. Apoptosis: HDACIs can induce programmed cell death (apoptosis) in cancer cells. This effect is mediated by the upregulation of pro-apoptotic genes and downregulation of anti-apoptotic genes, leading to activation of the apoptotic pathway.
5. Differentiation: HDACIs can promote the differentiation of cancer cells, leading to a more mature and less aggressive phenotype. This effect is mediated by changes in gene expression that promote differentiation pathways.

Overall, the mechanism of action of HDACIs involves a complex interplay of effects on gene expression, chromatin structure, and protein function, ultimately leading to anti-cancer effects such as cell cycle arrest, apoptosis, and differentiation.

Group	Compound	HDAC target ¹	Current state
Hydroxamic acid	Vorinostat (SAHA, Zolinza)	class I, II, IV	FDA approved
	Panobinostat (LBH589)	class I, II, IV	phase III CT
	Belinostat (PXD101)	class I, II, IV	phase II CT
	Abexinostat (PCI24781)	class I, II	phase II CT
	Resminostat (RAS2410)	class I, II	phase II CT
	Givinostat (ITF2357)	class I, II	phase II CT
	Dacinostat (LAQ824, NVP-LAQ824)	class I, II	phase I CT
	Pracinostat (SB939)	class I, II	phase II CT
Cyclic tetrapeptide	Romidepsin (Depsipeptide, FK228)	HDAC1, 2	FDA approved
	Apicidin	HDAC2, 3	Phase II CT
	Trapoxin A	HDAC1, 4, 11	ND ²
Benzamide	Mocetinostat (MGCD0103)	HDAC1, 2, 11	phase II CT
	Entinostat (MS-275, SNDX-275)	HDAC1, 9, 11	phase II CT
	Rocilinostat (ACY-1215)	HDAC6	phase II CT
Aliphatic acid	Valproic acid (VPA)	class I	phase III CT
	Pivanex (AN-9)	ND	phase II CT
	Butyrate	class I, IIa	Phase II CT
Electrophilic ketone	Trifluoromethylketone	ND	ND

Table 03

CLINICAL TRIALS

Clinical trials of HDAC inhibitors (HDACIs) have been conducted to evaluate their efficacy and safety in various cancers and other diseases. These studies can be broadly classified into clinical and non-clinical (pre-clinical) studies: Clinical studies

1.: These are studies involving human subjects to evaluate the safety and efficacy of HDACI. Clinical trials are conducted in several phases:-

Phase I: These trials evaluate the safety, dosage and side effects of HDACI in a small group of people.-

Phase II: These trials evaluate the effectiveness of HDACI in a larger group of people with certain types of cancer or disease and further evaluate their safety.-

Phase III: These studies compare the effectiveness of HDACI with standard treatments in larger groups of people to further evaluate their safety and effectiveness.-

Phase IV: These trials are conducted after a drug is approved to learn more about its risks, benefits and optimal use.

2. Non-clinical studies (pre-clinical studies): These are laboratory studies using cell cultures or animal models to understand the biological effects, mechanisms of action and possible uses of HDACIs.

Preclinical studies are necessary to obtain preliminary data before starting clinical studies.-

In Vitro Studies: These studies use cell lines to evaluate the effects of HDACI on cell growth, gene expression and cell signaling pathways.-

In vivo studies: These studies use animal models to evaluate the efficacy and safety of HDACI in a more complex biological system.

Animal studies can provide valuable information about dosage, toxicity, and potential side effects. Both clinical and nonclinical studies play an important role in advancing our understanding of HDACIs and their potential as therapeutic agents. Clinical studies provide direct evidence of efficacy and safety in humans, while nonclinical studies provide valuable information about underlying mechanisms and guide the design of clinical trials..

Conclusion:

In conclusion, HSP-90 inhibitors and histone deacetylase (HDAC) inhibitors have shown promising potential as targeted therapies for the treatment of cancer. HSP-90 inhibitors, by targeting the molecular chaperone function of HSP-90, can destabilize and degrade key oncoproteins, leading to inhibition of tumor cell growth and survival. HDAC inhibitors, on the other hand, modulate gene expression by altering the acetylation status of histone and non-histone proteins, resulting in the suppression of oncogenic pathways and induction of tumor cell death.

Both classes of inhibitors have demonstrated efficacy in preclinical studies and have shown promise in early-phase clinical trials. However, challenges such as drug resistance, toxicity, and limited efficacy in certain cancer types remain to be addressed. Future research should focus on developing more potent and selective inhibitors, identifying predictive biomarkers to guide patient selection, and exploring combination therapies to enhance therapeutic efficacy.

Overall, HSP-90 inhibitors and HDAC inhibitors represent valuable additions to the armamentarium of cancer therapeutics, and continued research in this field holds great promise for improving outcomes in cancer patients.

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