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REVIEW

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Hsp90 Inhibitors in Cancer

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ABSTRACT

Hsp90 is a member of chaperone family responsible for maintaining cellular homeostasis by regulating proper folding of proteins into mature and functional forms. In various cancers, it is overexpressed and is responsible for chaperoning of oncogenic client proteins such as Her2, EGFR, Akt, ERK, mutant p53 etc. that are involved in cancer survival and metastasis signaling pathways. Thus, inhibition of Hsp90 has emerged as an important strategy in the treatment of cancer, where inhibition of Hsp90 function can lead to improper folding of oncogenic client proteins eventually leading to degradation of these client proteins. The proof of concept for clinical efficacy of Hsp90 inhibition is attested by advancement of numerous small molecule Hsp90 inhibitors in clinical trials for the treatment of various cancers. This mini-review discusses development of small molecule Hsp90 inhibitors and their current clinical status for the treatment of cancer.

Keywords: *Hsp90 inhibitors, Cancer, Signaling pathways, Clinical Trials*

INTRODUCTION

Heat Shock Protein 90 kDa (Hsp90) is the molecular chaperone that is responsible for proper folding and maturation of client proteins required to maintain cellular homeostasis and constitutes about 1-2 % of total protein under normal conditions. In various disease conditions where there is increased production of aberrant proteins, Hsp90 level is amplified as seen in cancer where it constitute about 4 % of total protein. Hsp90 is over expressed in many cancers where it acts as a buffer for cellular stress by chaperoning various oncoproteins into their functional three dimensional structures. Through chaperoning of clientele oncoproteins such as Her2, Raf, Akt, Erk, mutant p53, and EGFR, Hsp90 allows for constant activation of pro-survival and anti-apoptotic oncogenic pathways [1]. Clinically, expression of Hsp90 correlates with advanced stage and poor survival in a variety of cancers and is closely linked to cancer growth and metastasis. In the presence of Hsp90 inhibitors, Hsp90 is unable to chaperone the client proteins into functional mature form and this leads to ubiquitination and proteosomal degradation of the client proteins [2,3]. Therefore, inhibition of Hsp90 by small molecules enables for the simultaneous targeting of multiple cancer causing pathways. Additionally, finding of Hsp90 as molecular target for anticancer activity of geldanamycin has led to increased interest in the development of Hsp90 inhibitors for cancer treatment [4].

Hsp90 is a dimer consisting of three different domains, N-terminal nucleotide binding domain, middle domain and C-terminal dimerization domain. Hsp90 belongs to the family of GHKL proteins that are characterized by presence of Bergerat fold in the ATP binding domain. Hsp90 is ATPase protein and its catalytic cycle is driven by the binding and hydrolysis of ATP [5]. In addition to binding of nucleotide, co-chaperones (i.e. Hsp70, HOP, $p50^{cdc37}$, p23, Aha1) and other proteins (i.e. immunophilins) binding to Hsp90 is required for driving the catalytic cycle forward and thus proper folding of client proteins [6-9]. Thus, preventing binding of these ligands to Hsp90 will potentially inhibit the chaperone cycle and thereby prevents maturation of oncoproteins into active conformation. Amongst these, small molecules inhibiting the ATPase activity of Hsp90 at N-terminal nucleotide binding pocket are most promising as

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exemplified by the advancement of numerous small-molecule Hsp90 inhibitors into clinic for the treatment of various malignancies [10,11]. Structurally, these molecules can broadly be classified into natural product geldanamycin (GM) type, resorcinol type and purine scaffold type (Figure 1). This mini review will discuss advancement of N-terminal Hsp90 inhibitors into clinical trials for cancer treatment, problems associated with them and their current clinical status.

Geldanamycin and Its Derivatives

The anticancer activity of GM, a benzoquinone ansamycin, was first revealed following aphenotypic screening of compounds capable of reversing *v-src* oncogene transformed cells [12]. By competing with ATP for binding to the N-terminal domain nucleotide binding pocket, GM was shown to inhibit ATPase activity of Hsp90 and thus interfere with Hsp90-v-src heterocomplex formation [13,14]. Even though GM was the first Hsp90 inhibitor identified with significant anti-proliferative activity against various cancer cell lines, it was not assessed for its anti-cancer properties in clinical trials because of its metabolic instability, dose limiting hepatotoxicity in animals and low solubility [15].

To overcome challenges associated with GM, it was structurally modified to substitute non essential groups with favorable groups that impart metabolic stability and increase water solubility. These efforts led to the discovery of less hepatotoxic 17-AAG (tanespimycin, KOS-953) [16] and more water soluble 17-DMAG (alvespimycin) [17]. 17-AAG was the first Hsp90 inhibitor to be evaluated by National Cancer Institute (NCI) in clinical trials for the treatment of solid tumors and provided proof-of-concept for Hsp90 inhibition in humans [18-22]. 17-AAG has poor solubility and therefore it was formulated in dimethyl sulfoxide and egg phospholipid vehicle for intravenous administration. This formulation was well tolerated up to 100mg/m^2 dose but at higher doses it causes significant toxicities such as bad odor, nausea and anorexia. In this study, serum concentrations achieved were higher than the minimum required for the depletion of client proteins in vitro and in xenograft animals. Though patients with solid tumors had stable disease, 17-AAG failed to reach its objective of complete or partial response in Phase-II clinical trial as determined by RECIT (Response Evaluation Criteria in Solid Tumors) [18,21]. This was attributed to its limited solubility and could be rectified by developing better formulation for administration. Indeed, Cremophor containing injectable formulation of 17-AAG showed anti-tumor activity in patients with Her2+ metastatic breast cancer. In the follow-up Phase-II clinical trials involving Her2+ breast cancer patients, 17-AAG (Cremophor formulation) in combination with trastuzumab had a response rate of 22% and clinical benefit rate of greater than 50% [23,24]. Similar to the studies for the treatment of solid tumors, combination of Cremophor formulation of 17-AAG and bortezomib showed anti-tumor activity in Phase-II study for the treatment of multiple myeloma [25]. This combination demonstrated reasonable response rate in patients suffering from multiple myeloma, which led to initiation of Phase-III study. This study was suspended in 2008 by Kosen Biosciences for non-clinical reasons [26].

Introduction of polar dimethyl amino group led to the development of water soluble derivative, 17-DMAG, which has better oral bioavailability compared to 17-AAG[17]. In the Phase-I clinical trial for the treatment of acute myelogenous leukemia, 17-DMAG showed promising results of complete response. In several other clinical trials, 17-DMAG was found to be toxic and caused renal dysfunction, cardiotoxicity, thrombocytopenia and ocular toxicity. Because of this unfavorable toxicity profile and commercial reasons, further development of 17-DMAG was suspended.

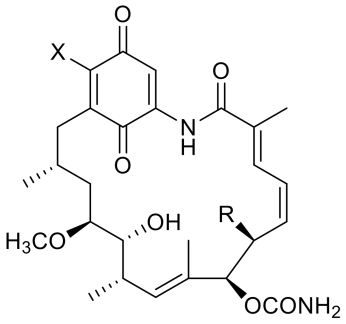
Quinone moiety of geldanamycin derivatives is primarily responsible for the drug related hepatotoxicity. To overcome this problem, Infinity Pharmaceuticals synthesized the hydroquinone derivative of 17-AAG by reducing quinone core that resulted in development of retaspimycin (IPI-504) [16]. Additionally, it was reported that Hsp90 inhibitory activity and thus anti-tumor activity of 17-AAG *in vivo* is because of its reduced hydroquinone form through the action of NADPH:quinone oxidoreductase 1 (NQO1). Thus, IPI-504 retains the potent Hsp90 inhibitory activity without toxicity associated with quinone moiety of 17-AAG. IPI-504 has been evaluated in various Phase I-III clinical trials in patients with breast cancer, non-small cell lung cancer (NSCLC), castration-resistant prostate cancer, multiple myeloma, gastrointestinal stromal tumors (GIST), and metastatic melanoma. IPI-504 at 400mg/m^2 in the Phase II clinical trial in patients with NSCLC, first clinical trial to evaluate Hsp90 inhibitor in NSCLC, achieved overall response rate of about 20% and thus for the first time showed the clinical benefits of Hsp90 inhibitors in NSCLC [27]. IPI-504 in combination with trastuzumab showed modest clinical activity in the Phase-II clinical trials in patients with HER2+ metastatic breast cancer. After promising result in Phase-I/II clinical trials in patients with GIST, IPI-504 was advanced for the large Phase-III clinical trials for the treatment of GIST. But the study was terminated in 2009 because of increased mortality rate.

Resorcinol Type Derivatives

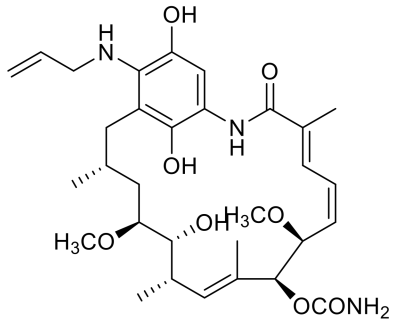
Radicicol (RD), a macrocylcic lactone antibiotic, was the first resorcinol type derivative to exhibit potent anti-Hsp90 activity [28]. Though RD was not evaluated in clinical trials because of its inherent chemical stability *in vivo*, several Hsp90 inhibitors in clinical development have maintained the resorcinol core structure of RD.

High throughput screening of 56,000 compounds identified resorcinol containing pyrazole CCT018159 [29] which was further optimized by structure based drug design to isoxazole derivative NVP-AUY922/VER52296[30]. This isoxazole derivative has better cellular activity compared to the corresponding pyrazole derivative because of its improved cellular uptake and retention in cancer cells [31]. VER-52296/

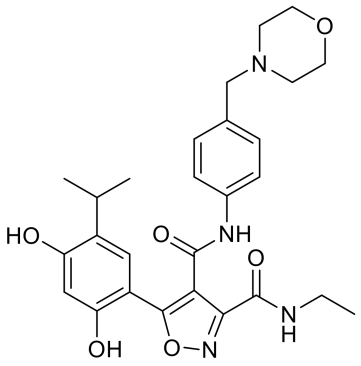
Figure 1: Hsp90 inhibitors undergoing clinical trials.



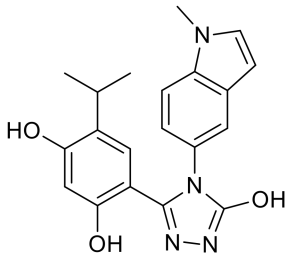
Tanespimycin (17-AAG, KOS-953) R = -OCH_3 X = -$NHCH_2CH{=}CH_2$
Alvespimycin (17-DMAG) R = -OCH_3 X = -$NHCH_2CH_2N(CH_3)$



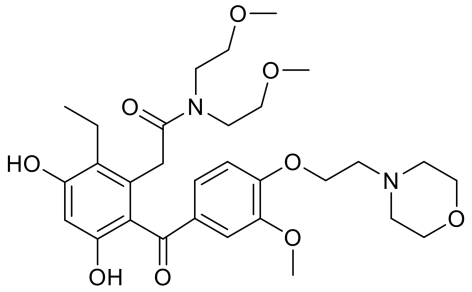
Retaspimycin (IPI-504)



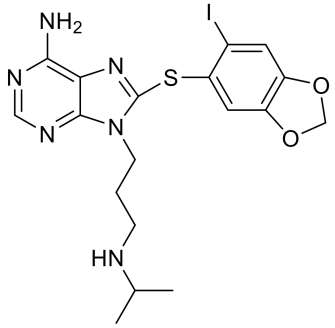
VER-52269/NVP-AUY922



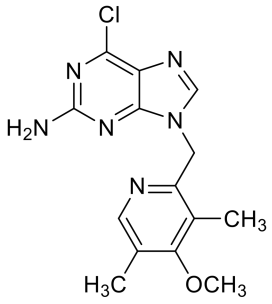
STA-9090



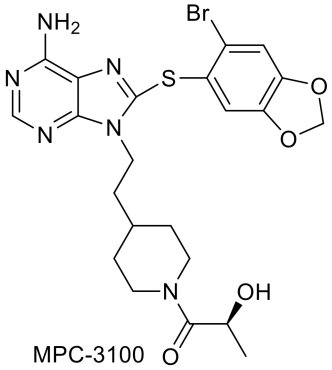
KW-2478



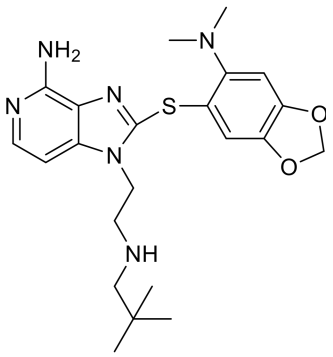
PU-H71



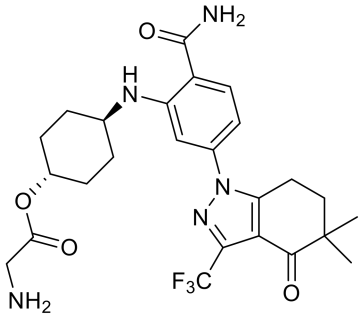
CNF2024/BIIB021



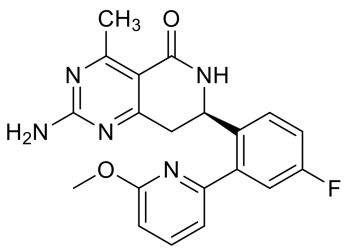
MPC-3100



CUDC-305/Debio 0932



SNX5422



HSP990

NVP-AUY922 has been evaluated in clinical trials as a single agent or in combination in patients with various cancers such as breast cancer, multiple myeloma, non small cell lung cancer, gastric tumor. In 2012, NVP-AUY922 completed Phase I/II clinical trials in patients with advanced HER2+ and ER+ metastatic breast cancer to determine the maximum tolerated dose (MTD) [32]. From this study, MTD was found to be 70mg/m^2 and adverse effects associated with the drug were diarrhea, fatigue, atrial flutter, darkening of vision and anorexia. Currently, a combination of NVP-AUY922 with trastuzumab is being evaluated in phase II expansion studies in patients with HER2+ and ER+ metastatic breast cancer [33]. NVP-AUY922 is also undergoing Phase-I/II clinical evaluation in combination with erlotinib in patients with NSCLC to determine the dose and side effects associated with this combination [34].

STA-9090 (Ganetespib) is a triazole containing resorcinol derivative developed by Synta Pharmaceuticals. It has been evaluated in multiple clinical trials in both advanced solid tumors and hematological malignancies. In a Phase-I trial in patients with advanced solid tumors MTD of STA-9090 was found to be 216 mg/m^2 and disease was stabilized in several patients with GIST, NSCLC and renal cell carcinoma. Common adverse events associated with drug as determined in this study included fatigue, diarrhea and elevated amylase [35].

A Phase-II trial of STA-9090 was conducted in patients with non-small cell lung cancer caused by mutation in EGFR and KRAS. Drug related common adverse events included fatigue, diarrhea, nausea, anorexia and dyspnea. STA-9090 showed promising clinical efficacy in this study where 7 patients having mutated EGFR and wild type KRAS had stable disease for more than 16 weeks [36]. Also, 75% of crizotinib naïve patients and 62% patients with KRAS mutation had tumor shrinkage in the target lesions. This has led to starting of Phase IIb/III trial of STA-9090 in combination with docetaxel in advanced non-small cell lung cancer patients [37]. In September 2013, it has been granted fast track designation to improve survival when administered in combination with docetaxel for the treatment of metastatic lung cancer. In addition to clinical trial in NSCLC, STA-9090 is also currently being evaluated in Phase-II trial in patients with unselected metastatic breast cancer to determine overall response rate using RECIST 1.1 [38].

In Phase-I safety, PK and PD study of novel resorcinol analog KW-2478 in patients with relapsed/refractory multiple myeloma, chronic lymphocytic leukemia or B-cell nonhodgkins lymphoma there were no toxicities up to dose of 99mg/m^2 when given intravenously [39]. Currently, Phase-I/II clinical trial is ongoing, which is evaluating the combination of KW2478 with bortezomib in patients with relapsed and refractory multiple myeloma [40]. Another resorcinol derivative AT13387, discovered by a fragment-based drug discovery approach [41,42], is currently being evaluated at different dosing schedules in Phase-I trials in patients with advanced solid tumors [43]. In another study, it is being evaluated with or without imatinib in Phase-II study in patients with advanced gastrointestinal stromal tumor, in whom tumors were not stabilized with tyrosine kinase inhibitors. The goal of this study is to evaluate the ability of AT-13387 with or without imatinib to reduce or stabilize tumor at 4 months of treatment using RECIST 1.1 criteria [44].

Purine and Purine-like Derivatives

As mentioned earlier, Hsp90 has distinctive Bergerat fold in the N-terminal of nucleotide binding site. By resolving the X-ray crystal structure of GM and RD, it was determined that GM and RD bind to Hsp90 in unique C-shape conformation. This enabled for the design and synthesis of purine derivative PU3, first small molecule Hsp90 inhibitor, through structure based drug design [45]. Extensive medicinal chemistry effort and several optimization step of PU3 led to development of PU-H71 which has more drug-like characteristics. This purine-scaffold class has also been optimized by numerous groups to result in potent and selective inhibitors such as CNF2024/BIIB021, MPC-3100, and purine-like Debio 0932 (CUDC-305) that have advanced to clinical trials.

Purine derivative PU-H71 was developed by Chiosis group at Memorial Sloan-Kettering [46-48][88–90], and is currently undergoing Phase-I clinical trial in patients with advanced solid tumors, lymphoma and myeloproliferative to assess safety, tolerability, MTD, and PK of PU-H71 [49]. This study will also help in assessing secondary objectives of anti-tumor activity and evaluation of ^{124}I-PU-H71 as a non-invasive means to determine tumor PK and intratumor concentration. PU-H71 is also being evaluated at different doses in Phase-I clinical trials at NCI in patients with advanced solid tumors and low-grade non-hodgkins lymphoma.

CNF 2024/BIIB021 is unique amongst the purine type Hsp90 inhibitors in that the aryl moiety is attached to the 9-position of the purine. In Phase-I clinical trial, intravenously administered BIIB021 was evaluated in patients with chronic lymphocytic leukemia and in patients with advanced solid tumors. From this study, MTD was determined at 800 mg twice weekly in patients with advanced solid tumors. Additionally, clinical efficacy assessment revealed that 11 of 16 evaluable patients with solid tumors had stable disease [50]. BIIB021 was also evaluated in combination with trastuzumab in Phase I dose-escalation trial in patients with HER2+ metastatic breast cancer to evaluate the safety and tolerability of BIIB021 when administered in combination with trastuzumab. MTD was determined at 600 mg twice weekly. In terms of clinical efficacy assessment, 10 out of 30 patients had stable disease as determined by RECIST and 16 had stable disease on FDG-PET imaging [51]. Though these data are promising, BIIB021 is no longer being developed as the company is shifting focus away from oncology, and plan to outlicense its further development [52].

Another purine derivative MPC-3100 was evaluated in Phase-I dose-escalation trial in patients with refractory or relapsed cancer. Drug limiting toxicity included prerenal azotemia in one patient, supraventricular tachycardia and respiratory failure in

two patients after day 21 dose [53]. MPC-3100 has poor solubility and bioavailability and to overcome this limitation pro-drug MPC-0767 was developed.

Replacement of N3 nitrogen of the purine with a carbon led to the development of a purine-like derivative, Debio 0932 (CUDC-305) [54]. It is being evaluated in Phase-I trial to evaluate the MTD and safety in patients with advanced solid tumors or lymphoma. Phase-Ia is an open-label, dose-escalation study and Phase-Ib portion will further assess the safety, PK and PD and will make a preliminary assessment of anti-tumor activity. The trial is currently ongoing and results are awaited[55]. In 2012, a clinical trial was initiated to evaluate the efficacy of Debio 0392 in combination with standard care of chemotherapy in patients with advanced NSCLC.

Dihydroindazolone Derivatives

SNX-5422 is a dihydroindazolone-containing Hsp90 inhibitor that was discovered following optimization of a hit identified through chemoproteomics-based drug design approach [56]. In this novel approach, an ATP-affinity column was first loaded with ATP-binding proteins, which was challenged with a library of structurally diverse compounds capable of displacing unspecified proteins from the column. Mass spectrum analysis of the protein eluted by initial hit compound identified it as Hsp90. Further optimization of the hit compound led to the development of SNX-5422, which is actually the glycine prodrug of SNX-2112. SNX-5422 was evaluated for MTD and PK in Phase-I clinical trial in patients with solid tumor and lymphoma. Later, clinical trial of SNX-5422 in the treatment of refractory hematological malignancies was discontinued based on reports of ocular toxicity [57,58].

Dihydropyridopyrimindine Derivatives

HSP990, an oral Hsp90 inhibitor, is a follow-up compound of NVP-AUY922 and has advanced into clinical trial in patients with advanced solid tumors. It was evaluated in Phase-I trial in patient with advanced solid tumors to assess MTD, DLT, efficacy, PK and PD [59]. Recently, another Phase-I trial assessing the dose escalation studies of HSP990 in Japanese and Korean patients with solid tumors was terminated [60].

Conclusion

Cancer is a complex disease, in which a cluster of oncogenic mechanisms contribute to cellular proliferation, survival and metastasis. Because of such heterogeneity and complexity, drug therapies that only target a single activating oncoprotein are not able overcome the multitude of aberrant cellular processes and are of limited therapeutic benefit. Therapies which are able to simultaneously target multiple dysregulatory pathways, therefore, offer the opportunity to overcome these limitations. As outlined in this mini-review, targeting Hsp90 in cancer with small molecule inhibitors led to degradation of multiple oncogenic proteins and thus caused inhibition of cancer causing dysregulatory pathways. This targeted inhibition of Hsp90 is a promising anti cancer strategy as attested by numerous Hsp90 inhibitors of distinct chemical scaffolds currently being evaluated in clinical trials for the treatment of various cancers. Hsp90 inhibitors cause not only degradation of oncogenic proteins but also sensitize cancer cell to toxic effects of chemotherapeutic agents. Thus, most of these Hsp90 inhibitors show clinical efficacy either alone or in combination with other chemotherapeutic agents such as tyrosine kinase inhibitors and anticancer antibodies.

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