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Heat Shock Protein 90 Inhibition in Lung Cancer

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Abstract

The heat shock protein 90 (Hsp90) chaperone is required for the conformational maturation and stability of multiple oncogenic kinases that drive signal transduction and proliferation of lung cancer cells. The recent demonstration that mutant epidermal growth factor receptor is an Hsp90 client, irrespective of the presence of the secondary threonine-to-methionine amino acid substitution mutation at position 790 mediating anilinoquinazoline resistance, suggests Hsp90 inhibition as a novel strategy against this group of lung cancers. The rarer epidermal growth factor receptors harboring exon 20 insertions and vIII mutations are also Hsp90 clients. Lung cancers may also be driven by mutant ErbB2, mutant B-Raf, or mutant or overexpressed c-Met, all of which are also degraded on Hsp90 inhibition. Hsp90 inhibitors may be synergistic with other drugs that disrupt chaperone function, including inhibitors of histone deacetylase 6 and the proteasome and agents that inhibit Hsp70 function. Hsp90 plays a unique antiapoptotic role in small cell lung cancer cells, so that Hsp90 inhibition results in substantial cell death in both chemosensitive and chemoresistant small cell lung cancer cell lines. Clinically, the geldanamycin compounds are the most mature, with manageable toxic effects. Several new classes of Hsp90 inhibitors are emerging, including purines and pyrazoles that have entered phase 1 trials. The available data suggest that Hsp90 inhibitors should be evaluated in multiple lung cancer subsets.

Keywords

Heat shock protein 90; Epidermal growth factor receptor; Lung cancer

The heat shock protein (Hsp90) chaperone and its associated machinery mediate the conformational maturation of several families of hormone receptors, transcription factors, and kinases.[1] In normal cells, levels of Hsp90 and other heat shock proteins increase in response to stressors that cause protein denaturation to promote normal protein folding and cell survival.[2,3] Hsp90 inhibition prevents its association with client proteins; unfolded targets subsequently undergo ubiquitin-mediated proteasomal degradation.[4]

Multiple mechanisms account for the potential selectivity of Hsp90 inhibition for cancer cells over normal cells. Cancer cells may be particularly dependent on chaperone proteins to survive a hypoxic, nutrient-starved tumor microenvironment.[5,6] In addition, through the

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process of oncogene addiction,[7] cancer cells may be dependent on overexpressed or mutant kinases for viability and hence particularly sensitive to Hsp90 inhibition when the relevant kinases are Hsp90 clients.[8,9] In this regard, many Hsp90-dependent proteins, including the ErbB2, c-Met, and c-Kit receptor tyrosine kinases; the v-src family of nonreceptor tyrosine kinases; the serine-threonine kinases Raf-1, cdk4, Akt, and polo-like kinase 1; and mutant p53 and human telomerase reverse transcription, either are proto-oncogenic or contribute to deregulated signaling and proliferation in diverse human cancers. The overexpression or mutation of these proteins leads to a greater dependence on Hsp90 in cancer cells to ensure the correct folding and function of large quantities of overexpressed oncoproteins and of mutant kinases with inherent conformational instability. The chaperone dependence of mutant kinases is illustrated by activated v-src and mutated B-Raf, which are associated with an Hsp90 complex necessary for correct folding and stability, whereas c-src and wild-type B-Raf require only limited assistance from Hsp90 for maturation.[10–12] Hsp90 inhibition results in degradation of v-src or mutant B-Raf; in dependent cells, it inhibits signal transduction and cell proliferation and induces apoptosis.

In addition, Hsp90 in tumor cells is found in multichaperone complexes with increased adenosine triphosphate (ATP) activity, whereas Hsp90 from normal tissues is in a latent uncomplexed state. In vitro reconstitution experiments have demonstrated that Hsp90 complexes from tumor cells have nearly 100-fold greater binding affinity for the ansamycin Hsp90 inhibitor 17-allylamino-17-demthoxygeldanamcyin (17-AAG) compared with the uncomplexed form of Hsp90 in normal cells.[13] The nanomolar binding of 17-AAG to the ATP binding site of high-affinity tumor Hsp90 is consistent with nanomolar antitumor activity in preclinical models. The markedly higher affinity of tumor Hsp90 also explains the ability of ansamycins to accumulate at tumor sites in animals[14,15] and suggests that Hsp90 inhibition will demonstrate therapeutic selectivity for cancer cells.

The recent demonstration that mutant epidermal growth factor receptor (EGFR) is both associated with the Hsp90 chaperone and highly sensitive to degradation after Hsp90 inhibition[16] has generated great interest in the use of Hsp90 inhibitors in this lung cancer subgroup. In particular, Hsp90 inhibition may be useful for non-small cell lung cancers (NSCLCs) expressing mutant EGFRs with either primary or acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). In addition, in numerous cases, EGFR wild-type NSCLCs may also be expected to depend on kinases that are Hsp90 clients. Furthermore, Hsp90 inhibitors may be synergistic with other agents that disrupt chaperone function or inhibit Hsp70 activity. Finally, Hsp90 inhibitors may also be useful in small cell lung cancer (SCLC), in which Hsp90 plays an essential antiapoptotic role. Here, we review the evidence justifying assessment of Hsp90 inhibitors in various lung cancer subsets and discuss the current status of Hsp90 inhibitors in clinical development.

HSP90 INHIBITION IN EGFR MUTANT NSCLC

NSCLC Harboring EGFR Kinase Domain Mutation

Activating mutations in the kinase domain of EGFR, present in approximately 10% of NSCLCs in the United States, arise in four exons: G719 substitutions in the nucleotide-binding loop of exon 18, in-frame deletions within exon 19, in-frame insertions within exon

20, and substitutions for L858 and L861 in the activation loop exon 21.[17] Except for exon 20 insertions, mutation confers sensitivity to the anilinoquinazoline reversible EGFR TKIs gefitinib and erlotinib.[18–20] Responses are related to the enhanced association of mutant EGFRs with TKIs, as well as to oncogene addiction, such that EGFR inhibition suppresses an oncogenic signal on which mutant NSCLC cells are dependent. Both L858R and exon 19 deletion mutant EGFR proteins interact with the chaperone and are depleted after Hsp90 inhibition.[16] In isogenic NIH/3T3 cells that express either wild-type or mutant EGFR, and in NSCLC cell lines, mutant EGFRs were more sensitive to geldanamycin-induced degradation compared with the wild-type protein. In EGFR-mutant cells, geldanamycin caused marked depletion of phospho-Akt and cyclin D1 and induced apoptosis. Association of mutant EGFRs with Hsp90 not only confers conformational stability but also protects from Cbl-mediated ubiquitination, impairing ligand-induced receptor down-regulation by inhibiting receptor endocytosis and lysosomal degradation.[21]

Of note, wild-type EGFR is depleted slowly from cells after geldanamycin-mediated Hsp90 inhibition; therefore, it is likely that there is transient association of nascent protein with the chaperone, such that the decreased levels seen over time represent compromised appearance of newly synthesized protein. In contrast, similar to ErbB2 and other oncogenic kinases,[22] mature, membrane-bound mutant EGFR likely maintains interaction and dependence on the chaperone, such that Hsp90 inhibition leads to rapid degradation and more complete depletion. Therefore, Hsp90 function is essential to maintain high-level expression of mutant EGFR in NSCLC cells.

Mutant EGFR NSCLC with Primary Resistance to Reversible EGFR TKIs

EGFR exon 20 insertion mutations represent only a small percentage of EGFR mutations found in NSCLC (approximately 9%) and are therefore found in only 1 to 2% of NSCLCs overall. Most EGFRs harboring exon 20 insertions exhibit primary resistance to reversible EGFR TKIs.[23] Although no natural cell lines exist harboring EGFR exon 20 insertion mutations, several such mutants identified in primary patient samples have been expressed in COS7 cells.[24] In contrast to wild-type EGFR, Hsp90 was readily coimmunoprecipitated with each of the mutant EGFRs, and this association was sensitive to brief exposure of cells to 17-AAG, correlating with reduced expression of exon 20 insertion mutant EGFR and its phosphorylated forms. The expression of exon 20 insertion mutants led to up-regulation of endogenous Akt and/or Stat3 signaling proteins, and levels of phospho-Akt and phospho-Stat3 were also reduced in 17-AAG-treated cells.

EGFRs with Acquired Resistance to TKIs

Despite initial responses of EGFR-mutant tumors to small-molecule TKIs, resistance universally emerges. Acquired resistance is associated with a second somatic mutation resulting in a threonine-to-methionine amino acid substitution at position 790 (T790M) of EGFR in approximately 50% of cases.[25,26] T790M, when combined with activating kinase domain mutations, confers enhanced catalytic phosphorylating activity and cooperates to produce a more potent kinase.[27]

The primary approach under development for NSCLCs expressing mutant EGFR harboring T790M mutation is the use of irrreversible inhibitors that overcome deficient reversible inhibitor binding because they contain a reactive group that forms a covalent bond at the edge of the ATP binding cleft. Preclinical studies have shown that the irreversible EGFR inhibitor CL-387,785,[28] the irreversible dual EGFR and ErbB2 inhibitor HKI-272,[29] and the irreversible pan-ErbB inhibitor CI-1033[30] can overcome resistance to L858R-mutated EGFR harboring the T790M resistance-conferring mutation.

Recently, inducible murine lung adenocarcinoma models driven by expression of EGFR harboring L858R and T790M mutations have been described.[31,32] In contrast to murine tumors driven by EGFR-L858R, in which only peripheral tumors occurred, both peripheral and bronchial tumors developed in one of these models. Surprisingly, tumors expressing L858R/T790M responded poorly to HKI-272. These data reflect emerging clinical data with HKI-272, indicating variable durations of stable disease but no responses among NSCLC patients previously treated with gefitinib or erlotinib,[33] and suggest the predictive value of these mouse models. Further analysis indicated that mammalian target of rapamycin (mTOR) signaling was weakly suppressed by HKI-272, as measured by persistent robust phosphorylation of S6 after treatment. The limitation of HKI-272 in EGFR L858R/T790M-expressing cells was overcome by the addition of rapamycin, so that combination treatment produced cytotoxic synergy in vitro and led to regressions in vivo.[31]

The presence of the T790M mutation does not abrogate the association of mutant EGFR with Hsp90 or the dependence on Hsp90 for conformational stability.[16] In addition, Akt has been described as an Hsp90 client,[34] and mTOR-mediated signaling has been reported as diminished by Hsp90 inhibition.[35] Recent results indicate that Hsp90 inhibition overcomes limitations of irreversible EGFR inhibitors in mutant EGFR/T790M cells, causing more complete suppression of the entire EGFR-PI3K-Akt-mTOR-p70S6K signaling axis. This is accomplished by reduced expression of EGFR, with associated reduction in phospho-Akt, and by reduced mTOR signaling resulting in reduced S6 phosphorylation.[36]

Both 17-AAG and the water soluble 17-dimethylaminoethylamino-17-demethoxygaldanamcyin (17-DMAG) have been tested in murine models of lung adenocarcinoma driven by EGFR L858R-T790M. 17-AAG demonstrated activity against these tumors, manifested by EGFR degradation, in vivo radiologic responses by magnetic resonance imaging, and histologic evidence for treatment effect.[32] In the case of 17-AAG, responses were transient, attributed to its short half-life and hepatotoxicity, which affected the dosing schedule. 17-DMAG also produced antitumor activity with tumor regressions of brief duration.[36] Notably, 17-DMAG reduced S6 phosphorylation in residual tumor cells, consistent with suppression of the EGFR-mediated signaling axis. These murine models should be useful for a direct comparison of 17-AAG or 17-DMAG with other Hsp90 inhibitors, as well as for direct comparisons of Hsp90 inhibitors with irreversible EGFR inhibitors, with or without mTOR inhibitors, and may help prioritize treatments in patients with NSCLCs harboring EGFR T790M mutations.

EGFR vIII Mutation

The EGFR vIII in-frame deletion of exons 2 to 7 occurs commonly in glioblastoma, where gefitinib and erlotinib have shown only limited efficacy. EGFR vIII mutations are present in approximately 5% (3 of 56) of squamous cell lung carcinomas, and like kinase domain-mutant EGFR, tissue-specific gene expression of EGFR vIII in mice leads to the development of NSCLC.[37] EGFR vIII also interacts with the Hsp90 chaperone, suggesting Hsp90 inhibition as a strategy for this subset of NSCLCs as well.[38]

HSP90 INHIBITION IN EGFR WILD-TYPE NSCLC

NSCLC Harboring ErbB2 Mutation

Other subsets of NSCLCs expressing wild-type EGFR may also be dependent on Hsp90 client kinases for viability.[39] Recently, in a series of 394 adenocarcinomas, 11 were found to harbor an ErbB2 mutation, targeting residues homologous to those affected by exon 20 insertions in EGFR.[40] Mutations included G776insV_G/C, which is found in the NCI-H1781 NSCLC cell line, and YVMA 776–779ins. In NCI-H1781 cells, ErbB2 is constitutively active in a ligand-independent fashion and drives EGFR phosphorylation as well. NCI-H1781 cells are resistant to erlotinib but sensitive to HKI-272, which causes dephosphorylation of both ErbB2 and EGFR in these cells.[41] Wild-type ErbB2 is a client extremely sensitive to degradation after Hsp90 inhibition.[22] Interestingly, mutant ErbB2 associates more strongly with Hsp90 than wild-type ErbB2, but this association is disrupted by brief exposure to 17-AAG, resulting in mutant ErbB2 degradation and loss of viability in addicted NSCLC cells.[24]

NSCLC Harboring Other Activated Kinases

NSCLCs may also depend on activated B-Raf or activated c-Met for viability, both documented Hsp90 client kinases.[11,12,42–44] B-Raf is activated by mutation in approximately 3% of lung adenocarcinomas,[45,46] usually non-V600E mutations that prevent Akt-mediated phosphorylation and down-regulation of B-Raf activity. The chaperone dependence of lung cancer-derived B-Raf mutants has not been determined. Similarly, c-Met may be activated by gain-of-function mutation, resulting in deletion in the juxtamembrane domain,[47,48] or by gene amplification, identified in 4% of lung cancers.[49] *c-Met* amplification defines lung and gastric cancer cell lines dependent on the c-Met kinase for growth and survival in vitro, suggesting that Hsp90 inhibitor-mediated c-Met degradation may be therapeutically useful in this group of tumors.[50,51] In addition, c-Met amplification accounts for approximately 20% of TKI resistance in NSCLCs harboring EGFR kinase domain mutation, such that there is codependence on mutant EGFR and c-Met unresponsive to the inhibition of either kinase alone.[52] Hsp90 inhibition would be expected to result in degradation of both mutant EGFR and c-Met and so again may be of benefit after the failure of gefitinib or erlotinib. Finally, cyclin-dependent kinase 4 (cdk4), another Hsp90 client, is amplified in approximately 3% of NSCLC,[49,53] potentially representing a subset prone to proliferative arrest after Hsp90 inhibition.

NSCLC Expressing Activated IGF-1R

Recently, insulin-like growth factor 1 receptor (IGF-IR) activation has been shown to confer resistance to erlotinib in NSCLC cells.[54] In the EGFR wild-type NCI-H460 and NCI-H1299 cells, erlotinib induced phosphorylation of IGF-IR, which formed a heterodimer with EGFR to activate Akt and mTOR, resulting in de novo protein synthesis of EGFR and survivin. Inhibition of IGF-IR activation, suppression of mTOR-mediated protein synthesis, or knockdown of survivin expression abolished resistance to erlotinib and induced apoptosis. Because Hsp90 inhibition can affect IGF-IR expression,[35,55] and expression of mTOR-related signaling proteins, subsets of EGFR wild-type cells may be rendered erlotinib-sensitive through Hsp90 inhibition.

POTENTIAL SYNERGISM OF HSP90 INHIBITORS WITH OTHER MOLECULAR AGENTS

Other Agents that Disrupt Chaperone Function

Histone deacetylase 6 (HDAC6) is a cytoplasmic, microtubule-associated member of the class II family of HDACs that possesses α-tubulin deacetylase activity.[56,57] HDAC6 also deacetylates Hsp90; small interfering RNA (siRNA)-mediated depletion of HDAC6 induces Hsp90 acetylation, inhibiting its binding to ATP and to client proteins, which are depleted by proteasomal degradation.[58,59] HDAC6 also plays a larger role in the management of the misfolded protein stress response by recruiting aggregates of misfolded proteins that are not efficiently degraded by the proteasome to dynein motors for transport to structures known as aggresomes.[60] Cells that lack HDAC6 do not form aggresomes properly and fail to clear misfolded protein aggregates, which themselves are toxic. Therefore, HDAC6 inhibition is expected to cause misfolding of Hsp90 clients, resulting in cell death if they are degraded in cells that depend on them for viability[61–63]; in addition, if misfolded clients aggregate, inhibition of HDAC6 prevents aggresome formation, allowing the aggregates to induce cellular toxicity. Recently, the HDAC6 inhibitor LBH589 has been shown to induce Hsp90 acetylation, with reduced association of Hsp90 with mutant EGFR, Akt, and STAT3 and depletion of these proteins. Apoptosis selectively occurred in EGFR mutant NSCLC cell lines.[64] Synergism of LBH589 with erlotinib was demonstrated, suggesting that Hsp90 inhibitors and HDAC6 inhibitors may also demonstrate cytotoxic synergism.

Proteasome inhibition may also disrupt chaperone function. The nonselective accumulation of cellular proteins may overload the capacity of Hsp90 to fold proteins in the cytosol, reducing the overall availability of Hsp90 and compromising the stability of the most chaperone-dependent cellular kinases. The accumulation of cytosolic proteins also inhibits the ability of the endoplasmic reticulum (ER) to sort, fold, and transport proteins.[65,66] Under conditions of ER stress, ER-specific chaperones are induced, including Grp78 and Grp94, which may bind and trap chaperone-dependent kinases, an event associated with the termination of translation, the release of caspase 4, and the ultimate proteasomal or lysosomal degradation of trapped proteins.[67,68] Bortezomib has demonstrated a low rate of response in NSCLC,[69] but correlation with EGFR mutation has not been investigated. Synergism with Hsp90 inhibition has been demonstrated in models of multiple myeloma, results that could extend to EGFR-mutant NSCLC.

Modulation of Hsp70 Activity

Hsp90 inhibitors have been shown to universally induce expression of Hsp70. This is caused by disruption of the association of Hsp90 and heat shock factor 1 (HSF-1), allowing its nuclear localization and binding to heat shock elements (HSEs) in the *hsp70* promoter. Hsp70 itself is a powerful chaperone that helps cells to cope with increased concentrations of unfolded or denatured proteins. Hsp70 is a potent inhibitor of apoptosis at multiple levels.[70,71] At the premitochondrial level, Hsp70 inhibits stress-activated kinases, such JNK1. Hsp70 also prevents mitochondrial membrane permeabilization through the blockage of Bax translocation. At the postmitochondrial level, Hsp70 interacts with both apoptosis-inducing factor[72] and apoptosis protease activating factor (Apaf-1),[73,74] preventing the recruitment of procaspase-9 to the apoptosome, and also protects essential nuclear proteins from caspase 3-mediated cleavage. The cytoprotective effects of Hsp70 suggest that its inhibition may sensitize cells to Hsp70-inducing stimuli, such as Hsp90 inhibition. In leukemia models, abrogation of Hsp70 induction by siRNA or by the benzylidene lactam compound KNK437, which attenuates the binding of HSF-1 to HSEs in the *hsp70* promoter, leads to increased apoptosis induced by 17-AAG.[75]

The expression of *hsp70* messenger RNA in response to cellular stress has been linked to the activity of cyclin-dependent kinase 9 (cdk9), also known as positive transcription elongation factor b.[76] The C-terminal domain of RNA polymerase II, which contains tandem repeats of the heptapeptide YKSPTSPS, is phosphorylated by cdk9 at Ser2, which couples transcriptional elongation with 3 ‘-end processing. Inhibition of cdk9 reduces Ser2 phosphorylation, reduces transcriptional elongation, and impairs 3’-end processing, leading to the rapid degradation of messenger RNAs that are particularly cdk9 dependent.[77,78] Flavopiridol is the most potent known inhibitor of cdk9[79–81] and has been shown to impair *hsp70* messenger RNA accumulation in response to heat.[76] These results suggest that flavopiridol or other cdk9 inhibitors may prevent the induction of Hsp70 in response to Hsp90 inhibition and may further sensitize cells to apoptosis induced by Hsp90 inhibition.[82]

HSP90 INHIBITION IN SCLC

Unlike Hsp70, Hsp90 is not a general inhibitor of apoptosis. However, it has recently been shown that Hsp90 assumes this role in SCLC cells.[83] In SCLC cells, including those refractory to chemotherapy, Hsp90, and not Hsp70, negatively regulates Apaf-1, which is required for caspase activation. Upon Hsp90 inhibition, Apaf-1 is released from binding to the chaperone, but not degraded, leading to formation of the Apaf-1-caspase 9 apoptosome complex. This complex is activated by cytochrome *c* release, which occurs when Hsp90 inhibition causes degradation of Akt (an Hsp90 client), resulting in BAD dephosphorylation and its release from 14-3-3 proteins so that it can heterodimerize with Bcl-2 family members or activate proapoptotic Bax, leading to mitochondrial depolarization. Therefore, Hsp90 inhibition reduces Akt levels, causing cytochrome *c* release, and removes negative regulation of Apaf-1 so that it can bind to caspase 9, a complex poised for activation by cytochrome *c*. These two events conspire to induce substantial apoptosis in SCLC cells both in vitro and in vivo and suggest that this lung cancer subset should be tested in trials of Hsp90 inhibitors.

STATUS OF HSP90 INHIBITORS

Geldanamycins

Several phase 1 trials of 17-AAG have been reported using a variety of schedules.[84] Initially weekly schedules were examined.[85–87] Modulation of Hsp90 targets was demonstrated in peripheral blood leukocytes and in posttreatment tumor biopsies, including depletion of Raf-1 in four of six patients, and cdk4 depletion and Hsp70 induction in eight of nine patients.[85] However, it was not possible to reproducibly demonstrate changes in biopsy specimens taken 5 days after treatment. The lack of a sustained pharmacodynamic effect prompted evaluation of twice-weekly dosing and five times daily schedules.[88–93] Dose-limiting toxic effects have included reversible elevations of transaminase levels, hyperbilirubinemia, nausea, vomiting, diarrhea, headache, and abdominal pain. Some of the nonhepatic toxic effects may be attributable to dimethyl sulfoxide- or Cremophor-based formulations required.

The poor solubility of 17-AAG prompted chemical modification that resulted in 17-DMAG (Kosan), a water-soluble analogue with properties desirable for formulation that is also orally bioavailable.[14,94–96] In addition, the synthesis of a highly soluble hydroquinone hydrochloride derivative of 17-AAG, IPI-504 (Infinity), recently has been reported.[97,98] IPI-504 rapidly converts to 17-AAG in human plasma in a pH and oxygen-dependent manner. Moreover, in a cellular setting, there is also an enzymatic conversion of 17-AAG to IPI-504, so that not only is IPI-504 a water-soluble 17-AAG analogue, it is also an active 17-AAG metabolite. Both 17-DMAG and IPI-504 maintain high binding affinity to human Hsp90, inhibit the growth of cells overexpressing Hsp90 clients such as ErbB2, and cause induction of Hsp70, all consistent with Hsp90 inhibition. 17-DMAG and IPI-504 have entered phase 1 trials. Intravenous 17-DMAG has been tested in weekly, twice-weekly, and daily dosing schedules.[99–101] IPI-504, used in a twice-weekly schedule 3 weeks of every four, has been well tolerated.[102]

Although stable disease was documented in the early clinical experience, responses in solid tumors were not observed. This finding suggests it may be most worthwhile to test Hsp90 inhibitors in cancer types dependent on the more sensitive Hsp90 client kinases, including Her2-positive breast cancer. This population is indeed the focus of current 17-AAG and 17-DMAG studies. In combination with trastuzumab, 17-AAG has produced partial and minor responses and extended disease stabilization in patients with trastuzumab-refractory Her2-positive metastatic breast cancer.[103] In addition, 17-DMAG has demonstrated activity in 3 of 13 patients with refractory acute myelogenous leukemia, where Flt3 is a client kinase.[101] The initial development of IPI-504 in solid tumors has adopted a similar strategy and has focused on imatinib-refractory, c-kit-dependent gastrointestinal stromal tumors. Metabolic responses have been seen in fluorodeoxyglucose positron emission tomography analysis, corroborated by clinical observations such as resolution of pleural effusions, reduction in hepatomegaly, and prolonged stable disease.[102] Taken together, these data indicate that the geldanamycins are producing clinically meaningful antitumor activity in a variety of settings. To date, few patients with lung cancer have been treated with geldanamycins.

Recently, a phase 1/2 trial in advanced NSCLC has been launched, with extended stable disease noted in patients positive for EGFR mutation.[104]

Other Classes of Hsp90 Inhibitors

Limitations of the geldanamycin derivatives, including off-target toxicity and formulation challenges, have prompted the development of small molecule Hsp90 inhibitors. Other classes of Hsp90 inhibitors have recently been extensively reviewed.[105] These include purine scaffold inhibitors[106] that are orally available, including CNF-2024 (Conforma), and diarylpyrazole compounds such as the 3,4 diarylisoxazole NVP-AUY922/VER-52296, discovered through structure-based drug design.[107] Compounds in purine and pyrazole classes have high potency and have favorable properties, including activity in 17-AAG resistant cell lines and independence of P-glycoprotein, respectively. These and other small molecule inhibitors are in early phase 1 development, where pharmacodynamic end points, including client target depletion and Hsp70 induction, are being analyzed. The multiplicity of Hsp90 client kinases on which NSCLCs may depend for viability and the antiapoptotic role of Hsp90 in SCLC suggest that Hsp90 inhibitors merit evaluation in multiple lung cancer populations.

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REFERENCES

1. Pratt WB. The hsp90-based chaperone system: involvement in signal transduction from a variety of hormone and growth factor receptors. Proc Soc Exp Biol Med. 1998; 217:420–434. [PubMed: 9521088]
2. Whitesell L, Lindquist SL. HSP90 and the chaperoning of cancer. Nat Rev Cancer. 2005; 5:761–772. [PubMed: 16175177]
3. Leppa S, Sistonen L. Heat shock response: pathophysiological implications. Ann Med. 1997; 29:73–78. [PubMed: 9073326]
4. Sepp-Lorenzino L, Ma Z, Lebwohl DE, Vintsky A, Rosen N. Herbimycin A induces the 20 S proteasome- and ubiquitin-dependent degradation of receptor tyrosine kinases. J Biol Chem. 1995; 270:16580–16587. [PubMed: 7622464]
5. Workman P. Altered states: selectively drugging the Hsp90 cancer chaperone. Trends Mol Med. 2004; 10:47–51. [PubMed: 15106614]
6. Jolly C, Morimoto RI. Role of the heat shock response and molecular chaperones in oncogenesis and cell death. J Natl Cancer Inst. 2000; 92:1564–1572. [PubMed: 11018092]
7. Weinstein IB. Addiction to oncogenes-the Achilles heal of cancer. Science. 2002; 297:63–64. [PubMed: 12098689]
8. Xu W, Neckers L. Targeting the molecular chaperone heat shock protein 90 provides a multifaceted effect on diverse cell signaling pathways of cancer cells. Clin Cancer Res. 2007; 13:1625–1629. [PubMed: 17363512]
9. Bishop SC, Burlison JA, Blagg BS. Hsp90: a novel target for the disruption of multiple signaling cascades. Curr Cancer Drug Targets. 2007; 7:369–388. [PubMed: 17979631]
10. Xu Y, Singer MA, Lindquist S. Maturation of the tyrosine kinase c-src as a kinase and as a substrate depends on the molecular chaperone Hsp90. Proc Natl Acad Sci USA. 1999; 96:109–114. [PubMed: 9874780]

11. da Rocha Dias S, Friedlos F, Light Y, Springer C, Workman P, Marais R. Activated B-RAF is an Hsp90 client protein that is targeted by the anticancer drug 17-allylamino-17-demethoxygeldanamycin. Cancer Res. 2005; 65:10686–10691. [PubMed: 16322212]
12. Grbovic OM, Basso AD, Sawai A, et al. V600E B-Raf requires the Hsp90 chaperone for stability and is degraded in response to Hsp90 inhibitors. Proc Natl Acad Sci USA. 2006; 103:57–62. [PubMed: 16371460]
13. Kamal A, Thao L, Sensintaffar J, et al. A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. Nature. 2003; 425:407–410. [PubMed: 14508491]
14. Egorin MJ, Lagattuta TF, Hamburger DR, et al. Pharmacokinetics, tissue distribution, and metabolism of 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (NSC 707545) in CD2F1 mice and Fischer 344 rats. Cancer Chemother Pharmacol. 2002; 49:7–19. [PubMed: 11855755]
15. Xu L, Eiseman JL, Egorin MJ, D'Argenio DZ. Physiologically-based pharmacokinetics and molecular pharmacodynamics of 17-(allylamino)-17-demethoxygeldanamycin and its active metabolite in tumor-bearing mice. J Pharmacokinet Pharmacodyn. 2003; 30:185–219. [PubMed: 14571691]
16. Shimamura T, Lowell AM, Engelman JA, Shapiro GI. Epidermal growth factor receptors harboring kinase domain mutations associate with the heat shock protein 90 chaperone and are destabilized following exposure to geldanamycins. Cancer Res. 2005; 65:6401–6408. [PubMed: 16024644]
17. Janne PA, Engelman JA, Johnson BE. Epidermal growth factor receptor mutations in non-small-cell lung cancer: implications for treatment and tumor biology. J Clin Oncol. 2005; 23:3227–3234. [PubMed: 15886310]
18. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to Gefitinib therapy. Science. 2004; 304:1497–1500. [PubMed: 15118125]
19. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004; 350:2129–2139. [PubMed: 15118073]
20. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA. 2004; 101:13306–13311. [PubMed: 15329413]
21. Yang S, Qu S, Perez-Tores M, et al. Association with HSP90 inhibits Cbl-mediated down-regulation of mutant epidermal growth factor receptors. Cancer Res. 2006; 66:6990–6997. [PubMed: 16849543]
22. Xu W, Mimnaugh E, Rosser MF, et al. Sensitivity of mature Erbb2 to geldanamycin is conferred by its kinase domain and is mediated by the chaperone protein Hsp90. J Biol Chem. 2001; 276:3702–3708. [PubMed: 11071886]
23. Greulich H, Chen TH, Feng W, et al. Oncogenic transformation by inhibitor-sensitive and -resistant EGFR mutants. PLoS Med. 2005; 2:e313. [PubMed: 16187797]
24. Xu W, Soga S, Beebe K, et al. Sensitivity of epidermal growth factor receptor and ErbB2 exon 20 insertion mutants to Hsp90 inhibition. Br J Cancer. 2007; 97:741–744. [PubMed: 17712310]
25. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med. 2005; 352:786–792. [PubMed: 15728811]
26. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med. 2005; 2:1–11.
27. Mulloy R, Ferrand A, Kim Y, et al. Epidermal growth factor receptor mutants from human lung cancers exhibit enhanced catalytic activity and increased sensitivity to gefitinib. Cancer Res. 2007; 67:2325–2330. [PubMed: 17332364]
28. Kobayashi S, Ji H, Yuza Y, et al. An alternative inhibitor overcomes resistance caused by a mutation of the epidermal growth factor receptor. Cancer Res. 2005; 65:7096–7101. [PubMed: 16103058]

29. Kwak EL, Sordella R, Bell DW, et al. Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. Proc Natl Acad Sci USA. 2005; 102:7665–7670. [PubMed: 15897464]
30. Carter TA, Wodicka LM, Shah NP, et al. Inhibition of drug-resistant mutants of ABL, KIT, and EGF receptor kinases. Proc Natl Acad Sci USA. 2005; 102:11011–11016. [PubMed: 16046538]
31. Li D, Shimamura T, Ji H, et al. Bronchial and peripheral murine lung carcinomas induced by T790M-L858R mutant EGFR respond to HKI-272 and rapamycin combination therapy. Cancer Cell. 2007; 12:81–93. [PubMed: 17613438]
32. Regales L, Balak MN, Gong Y, et al. Development of new mouse lung tumor models expressing EGFR T790M mutants associated with clinical resistance to kinase inhibitors. PLoS ONE. 2007; 2:e810. [PubMed: 17726540]
33. Wong KK, Fracasso PM, Bukowski RM, et al. HKI-272, an irreversible pan erbB receptor tyrosine kinase inhibitor: preliminary phase I results in patients with solid tumors (abstract). Proc Am Soc Clin Oncol. 2006; 24:A3018.
34. Basso AD, Solit DB, Chiosis G, Giri B, Tsichlis P, Rosen N. Akt forms an intracellular complex with heat shock protein 90 (Hsp90) and Cdc37 and is destabilized by inhibitors of Hsp90 function. J Biol Chem. 2002; 277:39858–39866. [PubMed: 12176997]
35. Ohji G, Hidayat S, Nakashima A, et al. Suppression of the mTOR-raptor signaling pathway by the inhibitor of heat shock protein 90 geldanamycin. J Biochem (Tokyo). 2006; 139:129–135. [PubMed: 16428328]
36. Shimamura T, Li D, Ji H, et al. Hsp90 inhibition suppresses mutant EGFR-T790M signaling and overcomes kinase inhibitor release. Cancer Res. 2008 in press.
37. Ji H, Zhao X, Yuza Y, et al. Epidermal growth factor receptor variant III mutations in lung tumorigenesis and sensitivity to tyrosine kinase inhibitors. Proc Natl Acad Sci USA. 2006; 103:7817–7822. [PubMed: 16672372]
38. Lavictoire SJ, Parolin DA, Klimowicz AC, Kelly JF, Lorimer IA. Interaction of Hsp90 with the nascent form of the mutant epidermal growth factor receptor EGFRvIII. J Biol Chem. 2003; 278:5292–5299. [PubMed: 12471035]
39. Stephens P, Hunter C, Bignell G, et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature. 2004; 431:525–526. [PubMed: 15457249]
40. Shigematsu H, Takahashi T, Nomura M, et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res. 2005; 65:1642–1646. [PubMed: 15753357]
41. Shimamura T, Ji H, Minami Y, et al. Non-small-cell lung cancer and Ba/F3 transformed cells harboring the ERBB2 G776insV_G/C mutation are sensitive to the dual-specific epidermal growth factor receptor and ERBB2 inhibitor HKI-272. Cancer Res. 2006; 66:6487–6491. [PubMed: 16818618]
42. Webb CP, Hose CD, Koochekpour S, et al. The geldanamycins are potent inhibitors of the hepatocyte growth factor/scatter factor-meturokinase plasminogen activator-plasmin proteolytic network. Cancer Res. 2000; 60:342–349. [PubMed: 10667586]
43. Shen Y, Xie Q, Norberg M, Sausville E, Woude GV, Wenkert D. Geldanamycin derivative inhibition of HGF/SF-mediated Met tyrosine kinase receptor-dependent urokinase-plasminogen activation. Bioorg Med Chem. 2005; 13:4960–4971. [PubMed: 15978816]
44. Maulik G, Kijima T, Ma PC, et al. Modulation of the c-Met/Hepatocyte growth factor pathway in small cell lung cancer. Clin Cancer Res. 2002; 8:620–627. [PubMed: 11839685]
45. Brose MS, Volpe P, Feldman M, et al. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res. 2002; 62:6997–7000. [PubMed: 12460918]
46. Naoki K, Chen TH, Richards WG, Sugarbaker DJ, Meyerson M. Missense mutations of the BRAF gene in human lung adenocarcinoma. Cancer Res. 2002; 62:7001–7003. [PubMed: 12460919]
47. Ma PC, Jagadeeswaran R, Jagadeesh S, et al. Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. Cancer Res. 2005; 65:1479–1488. [PubMed: 15735036]
48. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res. 2006; 66:283–289. [PubMed: 16397241]

49. Zhao X, Weir BA, LaFramboise T, et al. Homozygous deletions and chromosome amplifications in human lung carcinomas revealed by single nucleotide polymorphism array analysis. Cancer Res. 2005; 65:5561–5570. [PubMed: 15994928]
50. Lutterbach B, Zeng Q, Davis LJ, et al. Lung cancer cell lines harboring MET gene amplification are dependent on Met for growth and survival. Cancer Res. 2007; 67:2081–2088. [PubMed: 17332337]
51. Smolen GA, Sordella R, Muir B, et al. Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752. Proc Natl Acad Sci USA. 2006; 103:2316–2321. [PubMed: 16461907]
52. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science. 2007; 316:1039–1043. [PubMed: 17463250]
53. Wikman H, Nymark P, Vayrynen A, et al. CDK4 is a probable target gene in a novel amplicon at 12q13. 3-q14. 1 in lung cancer. Genes Chromosomes Cancer. 2005; 42:193–199. [PubMed: 15543620]
54. Morgillo F, Woo JK, Kim ES, Hong WK, Lee HY. Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib. Cancer Res. 2006; 66:10100–10111. [PubMed: 17047074]
55. Mitsiades CS, Mitsiades NS, McMullan CJ, et al. Antimyeloma activity of heat shock protein-90 inhibition. Blood. 2006; 107:1092–1100. [PubMed: 16234364]
56. Verdin E, Dequiedt F, Kasler HG. Class II histone deacetylases: versatile regulators. Trends Genet. 2003; 19:286–293. [PubMed: 12711221]
57. Hubbert C, Guardiola A, Shao R, et al. HDAC6 is a microtubule-associated deacetylase. Nature. 2002; 417:455–458. [PubMed: 12024216]
58. Bali P, Pranpat M, Bradner J, et al. Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: a novel basis for antileukemia activity of histone deacetylase inhibitors. J Biol Chem. 2005; 280:26729–26734. [PubMed: 15937340]
59. Boyault C, Sadoul K, Pabion M, Khochbin S. HDAC6, at the crossroads between cytoskeleton and cell signaling by acetylation and ubiquitination. Oncogene. 2007; 26:5468–5476. [PubMed: 17694087]
60. Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A, Yao TP. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell. 2003; 115:727–738. [PubMed: 14675537]
61. Nimmanapalli R, Fuino L, Bali P, et al. Histone deacetylase inhibitor LAQ824 both lowers expression and promotes proteasomal degradation of Bcr-Abl and induces apoptosis of imatinib mesylate-sensitive or -refractory chronic myelogenous leukemia-blast crisis cells. Cancer Res. 2003; 63:5126–5135. [PubMed: 12941844]
62. Fuino L, Bali P, Wittmann S, et al. Histone deacetylase inhibitor LAQ824 down-regulates Her-2 and sensitizes human breast cancer cells to trastuzumab, taxotere, gemcitabine, and epothilone B. Mol Cancer Ther. 2003; 2:971–984. [PubMed: 14578462]
63. George P, Bali P, Annavarapu S, et al. Combination of the histone deacetylase inhibitor LBH589 and the hsp90 inhibitor 17-AAG is highly active against human CML-BC cells and AML cells with activating mutation of FLT-3. Blood. 2005; 105:1768–1776. [PubMed: 15514006]
64. Edwards A, Li J, Atadja P, Bhalla K, Haura EB. Effect of the histone deacetylase inhibitor LBH589 against epidermal growth factor receptor-dependent human lung cancer cells. Mol Cancer Ther. 2007; 6:2515–2524. [PubMed: 17876048]
65. Fribley A, Wang CY. Proteasome inhibitor induces apoptosis through induction of endoplasmic reticulum stress. Cancer Biol Ther. 2006; 5:745–748. [PubMed: 16861900]
66. Nawrocki ST, Carew JS, Pino MS, et al. Bortezomib sensitizes pancreatic cancer cells to endoplasmic reticulum stress-mediated apoptosis. Cancer Res. 2005; 65:11658–11666. [PubMed: 16357177]
67. Obeng EA, Carlson LM, Gutman DM, Harrington WJ Jr. Lee KP, Boise LH. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. Blood. 2006; 107:4907–4916. [PubMed: 16507771]

68. Boelens J, Lust S, Offner F, Bracke ME, Vanhoecke BW. Review. The endoplasmic reticulum: a target for new anticancer drugs. In Vivo. 2007; 21:215–226. [PubMed: 17436569]
69. Fanucchi MP, Fossella FV, Belt R, et al. Randomized phase II study of bortezomib alone and bortezomib in combination with docetaxel in previously treated advanced non-small-cell lung cancer. J Clin Oncol. 2006; 24:5025–5033. [PubMed: 17075122]
70. Garrido C, Schmitt E, Cande C, Vahsen N, Parcellier A, Kroemer G. HSP27 and HSP70: potentially oncogenic apoptosis inhibitors. Cell Cycle. 2003; 2:579–584. [PubMed: 14512773]
71. Garrido C, Brunet M, Didelot C, Zermati Y, Schmitt E, Kroemer G. Heat shock proteins 27 and 70: anti-apoptotic proteins with tumorigenic properties. Cell Cycle. 2006; 5:2592–2601. [PubMed: 17106261]
72. Ravagnan L, Gurbuxani S, Susin SA, et al. Heat-shock protein 70 antagonizes apoptosis-inducing factor. Nat Cell Biol. 2001; 3:839–843. [PubMed: 11533664]
73. Saleh A, Srinivasula SM, Balkir L, Robbins PD, Alnemri ES. Negative regulation of the Apaf-1 apoptosome by Hsp70. Nat Cell Biol. 2000; 2:476–483. [PubMed: 10934467]
74. Beere HM, Wolf BB, Cain K, et al. Heat-shock protein 70 inhibits apoptosis by preventing recruitment of procaspase-9 to the Apaf-1 apoptosome. Nat Cell Biol. 2000; 2:469–475. [PubMed: 10934466]
75. Guo F, Rocha K, Bali P, et al. Abrogation of heat shock protein 70 induction as a strategy to increase antileukemia activity of heat shock protein 90 inhibitor 17-allylamino-demethoxy geldanamycin. Cancer Res. 2005; 65:10536–10544. [PubMed: 16288046]
76. Ni Z, Schwartz BE, Werner J, Suarez JR, Lis JT. Coordination of transcription, RNA processing, and surveillance by P-TEFb kinase on heat shock genes. Mol Cell. 2004; 13:55–65. [PubMed: 14731394]
77. Garriga J, Grana X. Cellular control of gene expression by T-type cyclin/CDK9 complexes. Gene. 2004; 337:15–23. [PubMed: 15276198]
78. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. J Clin Oncol. 2006; 24:1770–1783. [PubMed: 16603719]
79. Chao SH, Fujinaga K, Marion JE, et al. Flavopiridol inhibits P-TEFb and blocks HIV-1 replication. J Biol Chem. 2000; 275:28345–28348. [PubMed: 10906320]
80. Chao SH, Price DH. Flavopiridol inactivates p-TEFb and blocks most RNA polymerase II transcription in vivo. J Biol Chem. 2001; 276:31793–31799. [PubMed: 11431468]
81. Lam LT, Pickeral OK, Peng AC, et al. Genomic-scale measurement of mRNA turnover and the mechanisms of action of the anti-cancer drug flavopiridol. Genome Biol. 2001; 2 RESEARCH0041.
82. Demidenko ZN, Vivo C, Halicka HD, et al. Pharmacological induction of Hsp70 protects apoptosis-prone cells from doxorubicin: comparison with caspase-inhibitor- and cycle-arrest-mediated cytoprotection. Cell Death Differ. 2006; 13:1434–1441. [PubMed: 16311509]
83. Rodina A, Vilenchik M, Moulick K, et al. Selective compounds define Hsp90 as a major inhibitor of apoptosis in small-cell lung cancer. Nat Chem Biol. 2007; 3:498–507. [PubMed: 17603540]
84. Sausville EA, Tomaszewski JE, Ivy P. Clinical development of 17-allylamino, 17-demethoxygeldanamycin. Curr Cancer Drug Targets. 2003; 3:377–383. [PubMed: 14529389]
85. Banerji U, O'Donnell A, Scurr M, et al. Phase I pharmacokinetic and pharmacodynamic study of 17-allylamino, 17-demethoxygeldanamycin in patients with advanced malignancies. J Clin Oncol. 2005; 23:4152–4161. [PubMed: 15961763]
86. Goetz MP, Toft D, Reid J, et al. Phase I trial of 17-allylamino-17-demethoxygeldanamycin in patients with advanced cancer. J Clin Oncol. 2005; 23:1078–1087. [PubMed: 15718306]
87. Ramanathan RK, Trump DL, Eiseman JL, et al. Phase I pharmacokinetic-pharmacodynamic study of 17-(allylamino)-17-demethoxy-geldanamycin (17AAG, NSC 330507), a novel inhibitor of heat shock protein 90, in patients with refractory advanced cancers. Clin Cancer Res. 2005; 11:3385–3391. [PubMed: 15867239]
88. Grem JL, Morrison G, Guo XD, et al. Phase I and pharmacologic study of 17-(allylamino)-17-demethoxygeldanamycin in adult patients with solid tumors. J Clin Oncol. 2005; 23:1885–1893. [PubMed: 15774780]

89. Nowakowski GS, McCollum AK, Ames MM, et al. A phase I trial of twice-weekly 17-allylamino-demethoxy-geldanamycin in patients with advanced cancer. Clin Cancer Res. 2006; 12:6087–6093. [PubMed: 17062684]

90. Ramanathan RK, Egorin MJ, Eiseman JL, et al. Phase I and pharma-codynamic study of 17-(allylamino)-17-demethoxygeldanamycin in adult patients with refractory advanced cancers. Clin Cancer Res. 2007; 13:1769–1774. [PubMed: 17363531]

91. Solit DB, Ivy SP, Kopil C, et al. Phase I trial of 17-allylamino-17-demethoxygeldanamycin in patients with advanced cancer. Clin Cancer Res. 2007; 13:1775–1782. [PubMed: 17363532]

92. Bagatell R, Gore L, Egorin MJ, et al. Phase I pharmacokinetic and pharmacodynamic study of 17-N-allylamino-17-demethoxygeldanamycin in pediatric patients with recurrent or refractory solid tumors: a pediatric oncology experimental therapeutics investigators consortium study. Clin Cancer Res. 2007; 13:1783–1788. [PubMed: 17363533]

93. Weigel BJ, Blaney SM, Reid JM, et al. A phase I study of 17-allylaminogeldanamycin in relapsed/refractory pediatric patients with solid tumors: a Children's Oncology Group study. Clin Cancer Res. 2007; 13:1789–1793. [PubMed: 17363534]

94. Tian ZQ, Liu Y, Zhang D, et al. Synthesis and biological activities of novel 17-aminogeldanamycin derivatives. Bioorg Med Chem. 2004; 12:5317–5329. [PubMed: 15388159]

95. Eiseman JL, Lan J, Lagattuta TF, et al. Pharmacokinetics and pharmacodynamics of 17-demethoxy 17-[[(2-dimethylamino)ethyl]amino]-geldanamycin (17DMAG, NSC 707545) in C.B-17 SCID mice bearing MDA-MB-231 human breast cancer xenografts. Cancer Chemother Pharmacol. 2005; 55:21–32. [PubMed: 15338192]

96. Smith V, Sausville EA, Camalier RF, Fiebig HH, Burger AM. Comparison of 17-dimethylaminoethylamino-17-demethoxy-geldanamycin (17DMAG) and 17-allylamino-17-demethoxygeldanamycin (17AAG) in vitro: effects on Hsp90 and client proteins in melanoma models. Cancer Chemother Pharmacol. 2005; 56:126–137. [PubMed: 15841378]

97. Ge J, Normant E, Porter JR, et al. Design, synthesis, and biological evaluation of hydroquinone derivatives of 17-amino-17-demethoxygeldanamycin as potent, water-soluble inhibitors of Hsp90. J Med Chem. 2006; 49:4606–4615. [PubMed: 16854066]

98. Sydor JR, Normant E, Pien CS, et al. Development of 17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride (IPI-504), an anti-cancer agent directed against Hsp90. Proc Natl Acad Sci USA. 2006; 103:17408–17413. [PubMed: 17090671]

99. Shadad FN, Ramanathan RK. 17-dimethylaminoethylamino-17-demethoxygeldanamycin in patients with advanced-stage solid tumors and lymphoma: a phase I study. Clin Lymphoma Myeloma. 2006; 6:500–501. [PubMed: 16796784]

100. Cartwright EP, Kummar S, Muir CA, et al. Interim analysis of phase I trial of 17-DMAG (abstract). Proc Am Soc Clin Oncol. 2006; 24:A13148.

101. Lancet J, Gojo I, Baer M, et al. Phase 1, pharmacokinetic (PK) and pharmacodynamic (PD) study of the Hsp90 inhibitor KOS-1022 (17-DMAG) in patients with refractory hemtological malignancies (abstract). Proc Am Soc Clin Oncol. 2006; 24:A2081.

102. Demetri GD, George S, Morgan JA, et al. Overcoming resistance to tyrosine kinase inhibitors (TKIs) through inhibition of Heat Shock Protein (Hsp90) chaperone function in patients with metastatic GIST: results of a Phase I Trial of IPI-504, a water-soluble Hsp90 inhibitor (abstract). Eur J Cancer. 2006; 4:A570.

103. Modi S, Stopeck AT, Gordon MS, et al. Combination of trastuzumab and tanespimycin (17-AAG, KOS-953) is safe and active in trastuzumab-refractory HER-2 overexpressing breast cancer: a phase I dose-escalation study. J Clin Oncol. 2007; 25:5410–5417. [PubMed: 18048823]

104. Sequist L, Janne PA, Walker J, Sweeney J, Grayzel D, Lynch TJ. Phase I/II trial of the novel Hsp90 inhibitor, IPI-504, inpatients with relapsed and/or refractory stage IIIB or stage IV non-small cell lung cancer stratified by EGFR mutation status (abstract). Proc AACR-NCI-EORTC. 2007:B29.

105. Sharp S, Workman P. Inhibitors of the HSP90 molecular chaperone: current status. Adv Cancer Res. 2006; 95:323–348. [PubMed: 16860662]

106. Chiosis G, Lucas B, Shtil A, Huezo H, Rosen N. Development of a purine-scaffold novel class of Hsp90 binders that inhibit the proliferation of cancer cells and induce the degradation of Her2 tyrosine kinase. Bioorg Med Chem. 2002; 10:3555–3564. [PubMed: 12213470]

107. Brough PA, Aherne W, Barril X, et al. 4,5-Diarylisoxazole Hsp90 chaperone inhibitors: potential therapeutic agents for the treatment of cancer. J Med Chem. 2008; 51:196–218. [PubMed: 18020435]