Hsp90 inhibitor as a sensitizer of cancer cells to different therapies (Review)

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Abstract. Hsp90 is a molecular chaperone that maintains the structural and functional integrity of various client proteins involved in signaling and many other functions of cancer cells. The natural inhibitors, ansamycins influence the Hsp90 chaperone function by preventing its binding to client proteins and resulting in their proteasomal degradation. N- and C-terminal inhibitors of Hsp90 and their analogues are widely tested as potential anticancer agents *in vitro, in vivo* as well as in clinical trials. It seems that Hsp90 competitive inhibitors target different tumor types at nanomolar concentrations and might have therapeutic benefit. On the contrary, some Hsp90 inhibitors increased toxicity and resistance of cancer cells induced by heat shock response, and through the interaction of survival signals, that occured as side effects of treatments, could be very effectively limited via combination of therapies. The aim of our review was to collect the data from experimental and clinical trials where Hsp90 inhibitor was combined with other therapies in order to prevent resistance as well as to potentiate the cytotoxic and/or antiproliferative effects.

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1. Introduction

The cell responds to environmental stress by increasing synthesis of several molecular chaperons known as heat shock proteins (Hsp). These proteins are cathegorized according to their molecular weight into five classes: small Hsp, Hsp60, Hsp70, Hsp90 and Hsp100. One of the most abundant molecular chaperones is Hsp90, which is a highly conserved protein, whose association is required for the stability and function of multiple-mutated, chimeric- and overexpressed-signaling proteins that promote the growth and/or survival of cancer cells (1). Hsp90 client proteins lack specific Hsp90 binding motifs and vary in terms of intracellular localization, structure, and function. Their main common denominator is their role in promoting cell proliferation and protection from apoptosis (2). Hsp90 is involved in the maturation and stabilization of a wide range of oncogenic client proteins which are crucial for oncogenesis and malignant progression (3), such as signal transduction molecules (Src, Raf1 and cdk4) and steroid receptors and in enhancing the activity of telomerase and nitric-oxide synthase (4). For the updated list of Hsp90 client proteins see http://www.picard.ch/download. Under normal growth conditions, Hsp90 plays a major role in various aspects of the secretory pathway, cellular transport and during environmental stress. Hsp90 is required for the cell cycle, meiosis and cytokinesis (5), however, Hsp90 does not participate in general protein folding (6). Recent studies also indicate that many types of cells express Hsp90 on the cell surface and secrete Hsp90 into the extracellular space to carry out important extracellular functions (7).

2. Hsp90 inhibitors - potential therapeutic agents

There are several reasons why Hsp90 should be considered an important target for cancer therapy. One is that Hsp90 protein is involved in the maturation and stabilization of a wide range of oncogenic proteins (Bcr-Abl, HER-2, EGFR, C-Raf, B-Raf, Akt, Met, VEGFR, FLT3, AR and ER, HIF-1α) and telomerase (8), which are included in tumor formation and therefore causing certain dependence of cancer cells on Hsp90 function. Secondly, unsuitable environmental conditions in cancer cells (hypoxia, low pH, poor nutritional conditions) may result in the destabilization of proteins, and therefore the function of Hsp90 for such cells is necessary. In

addition, Hsp90 protein exists as a multi-chaperone complex with unusually high affinity for ATP and some substances in tumor cells (8), whereas in normal cells a latent form of Hsp90 protein is present. In this regard, Hsp90 protein of tumor cells has higher affinity for inhibitors (9), caused by a change in binding of ATP to Hsp90 as an effect of co-chaperones, that modulate the function of Hsp90, as well as by higher ATPase activity of Hsp90 protein, whereas in normal cells Hsp90 is found mostly in a latent or inactive form (10). Furthermore, Hsp90 is constitutively, and 2-10 times more expressed in tumor cells than in normal ones, which means, that the correct function of Hsp90 is essential for the growth and survival of tumor cells (11). Hsp90 inhibition may lead to the degradation of proteins involved in the so-called six main characteristics of cancer: i) the ability to produce growth factors, ii) resistance to anticancer agents, iii) avoidance of apoptosis, iv) unlimited replicative potential, v) uninterrupted angiogenesis and vi) invasiveness and metastasis (8,12,13).

The Hsp90 monomer is composed of four domains: a highly conserved N- and C-terminal domain, a middle domain and a charged linker region that connects to both N-terminal as well as middle domain (14). A long, highly charged linker between the N-terminal domain and the middle domain is a special characteristic of Hsp90s in eukaryotic organisms (15). N-terminal domain contains ATP-binding site, thus blocking of ATP binding can serve as a single well known mechanism of Hsp90 inhibitors. Middle domain is responsible for co-chaperone and clients binding and its function is probably discrimination between various types of client proteins during their processes of activation (16). C-terminal domain is used for dimerization of Hsp90 and it is supposed, that it contains a second nucleotide-binding site, which has been shown to bind to novobiocin, epigallocatechin (ECGC) and taxol. However, neither the apo-form crystal structure, nor any complex structure verified this prediction (17).

3. Inhibitors of the N-teminal ATP binding pocket

Hsp90 inhibitors are divided into several groups according to the form of inhibition, which includes: i) blocking the binding of ATP, ii) decoupling co-chaperon/Hsp90 and iii) antagonism of client/Hsp90 association. The benzoquinone ansamycins mimic ATP and bind to the nucleotide-binding pocket on the N-terminus of Hsp90, blocking the natural substrate ATP binding (18). Geldanamycin (GA) and its analogs specifically inhibit only Hsp90 (and its endoplasmic reticulum homolog grp94), but not other chaperones or other intracellular molecular targets (19). Hsp90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG) administration was shown to induce a pronounced downregulation of multiple Hsp90 protein clients and other downstream effectors, such as IGF-IR, Akt, IKK-α, IKK-β, FOXO1, Erk1/2 and c-Met, resulting in sequestration-mediated inactivation of NF-κB, reduced cell proliferation and decline of cell motility (20). The inhibition of Hsp90 with 17-AAG and another ansamycin derivative 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG) downregulated B-Raf, decreased cell proliferation, reduced Mek/Erk signaling activation and induced a significant inhibition of telomerase activity in melanoma cells (21,22). On the contrary, treatment with 17-AAG triggers a stress response in cells that leads to activation of the transcription factor of Hsp-1 (HSF-1), resulting in elevation of anti-apoptotic Hsp90, Hsp70, and Hsp27 chaperons (23).

Although GA exhibits very strongly *in vitro* antitumor activities, its clinical potential is unfortunately low, due to poor solubility in aqueous solutions and its hepatotoxicity (24). Therefore, GA derivatives with comparable antitumor effects and even better toxicological properties have been synthesized. Following derivatives of GA have entered into the clinical trials (per August 2014): 17-AAG (tanespimycin; CNF1010 - an oil-in-water nanoemulsion of 17-AAG; 39 trials), 17-DMAG (alvespimycin; 7 trials), IPI-504 (retaspimycin hydrochloride; 13 trials) and most recently 17-amino-17-demethoxygeldanamycin (17-AG or IPI-493; 2 trials). 17-AAG is one of the derivatives which has entered to the third phase of the clinical trials. Furthermore, there are phenol derivatives produced by Kosan and Biotica, which demonstrated cell growth inhibition comparable to 17-AAG and 17-DMAG (25). These compounds are in preclinical stages of development.

Another intensively studied N-terminal domain binder of Hsp90 is radicicol, a macrocyclic natural antibiotic isolated from the fungus *Monocillium nordinii* and from the plant-associated fungus *Chaetomium chiversii* (26). Despite the potent antitumoral activity *in vitro*, radicicol has little or no activity *in vivo* (27,28). On the contrary, newly created stable oxime derivatives of radicicol and cycloproparadicicol have shown antitumor activity with tolerable toxicity in animal models (28). Moreover, synthetic Hsp90 inhibitors with resorcinol moiety NVP-AUY922 (27 trials) and AT-13387 (6 trials) are now in phase I-II and phase I clinical trials, respectively.

With the aim to improve pharmacological properties and even increase the specificity of Hsp90 inhibitors, many phamacological companies focused on the synthesis of small molecules. Chiosis *et al* (29) demonstrated the effect of the first identified purine scaffold inhibitor PU3 comparable to GA in breast cancer cells. Kasibhatla *et al* (30) modified such a purine inhibitor by rotating the C8-attached aryl ring to the N9 position. This resulted in the compound CNF2024/BIIB021 identified as a stronger inhibitor compared to 17-AAG *in vitro* and *in vivo* (31), which is currently involved in phase II clinical trials (7 trials). Interestingly, purine-scaffold inhibitors have better solubility in aqueous solutions, metabolic stability and can be administered orally compared to ansamycin Hsp90 inhibitors (32). PU-H71 derivative is now in phase I clinical trials (2 trials).

Using a chemical proteomics approach, Serenex company identified small molecules, that are distinct from GA (structures not disclosed). Water soluble and orally active compound SNX-5422, administered in xenograft models, resulted in partial tumor regression (33) and is currently involved in phase I clinical trials (10 trials).

Synta Pharmaceuticals Corporation developed another second-generation Hsp90 inhibitor ganetespib (formerly STA-9090), a unique resorcinolic triazolone (chemical structure distinct from 17-AAG), undergoing now phases II-III clinical trials (32 trials).

Couple of additional Hsp90 inhibitors have been described and entered phase I-II of clinical trials. Details as follows: KW-2478 (2 trials), Hsp990 (2 trials), MPC-3100 (1 trial),

Table I. Published phase II study results of Hsp90 inhibitors.

Hsp90 inhibitor	Responses of cancer patients	Authors (Ref.)
17-AAG	No objective response in the treatment of clear cell or papillary renal cell carcinoma	Ronnen *et al*, 2006 (163)
17-AAG	No activity with regard to prostate-specific antigen response	Heath *et al*, 2008 (164)
17-AAG	No objective antimelanoma responses	Solit *et al*, 2008 (90)
IPI-504	Activity in NSCLS patients, particularly among those with ALK rearrangements	Sequist *et al*, 2010 (165)
IPI-504	Not warranted in patients with castration-resistant prostate cancer	Oh *et al*, 2011 (166)
17-AAG + bortezomib	Significant and durable responses with acceptable toxicity (relapsed or relapsed and refractory multiple myeloma)	Richardson *et al*, 2011 (167)
17-AAG + trastuzumab	Significant anticancer activity in patients with HER-2-positive, metastatic breast cancer previously progressing on trastuzumab	Modi *et al*, 2011, (168)
17-AAG	Further study not recommended (metastatic or locally advanced, unresectable breast cancer)	Gartner *et al*, 2012 (169)
17-AAG	Study endpoints were not reached because of early termination (further study in melanoma should be considered)	Pacey *et al*, 2012 (170)
STA-9090	Activity in NSCLS patients, particularly among those with ALK rearrangements	Socinski *et al*, 2013 (171)
IPI-504 + trastuzumab	Modest clinical activity in patients with advanced or metastatic HER-2-positive breast cancer	Modi *et al*, 2013 (172)
STA-9090	Activity was observed in trastuzumab-refractory HER2-positive and TNBC cancer patients	Jhaveri *et al*, 2014 (173)

Debio 0932 (2 trials), XL888 (2 trials), BIIB028 (1 trial) and DS-2248 (1 trial). The outcome of phase I clinical trials with Hsp90 inhibitors are well summarized in reviews of Jhaveri *et al* (34,35). For detailed published results of phase II studies see Table I.

4. Inhibitors of the C-terminal ATP binding pocket

Unsatisfactory, results with N-terminal inhibitors in experimental and clinical trials arising from the increased toxicity and resistance induced by heat shock response led to development and characterization of a novel C-terminal inhibitors of Hsp90. Novobiocin (antiobiotic of coumarin group) and its analogues (clorobiocin and coumermycin A1) have been generated as agents for the treatment of bacterial infections with multi-resistant gram-positive bacteria such as *Staphylococcus aureus* and *S. epidermidis* (36,37). Coumarin antibiotics were reported to bind strongly to gyrase B (DNA topoisomerase II) (38) but also weakly to the Hsp90 C-terminal nucleotide-binding site (39) followed by induced degradation of Hsp90 client proteins such as v-Src, Raf-1, ErbB2 and mutant p53 (39). Moreover, novobiocin disrupted the interaction of both the cochaperons p23 and Hsp70 with the Hsp90 complex (40). Structural modification of this compound has led to analogues with 1,000-fold greater efficacy in antiproliferative assays against various cancer cell lines (41-43). In this regard, 3-aminocoumarin analogue with introduced tosyl substituent on C-4 position of coumarin nucleus (4TCNA) promoted apoptosis through activation of caspases 7 and 8 in MCF-7 human breast cancer cells. Furthermore, 4TCNA induced cleavage of p23 which plays an important role in activity of number of transcription factors of steroids/thyroid receptors family (40). The same group of scientists identified a new family of novobiocin analogues in which the coumarin unit was replaced by a 2-quinoleinone moiety. Compound 4-tosyl-3[(chroman-6-yl)carboxylamino]-2-quinolon (4TCCQ) was 100-fold more potent than the parental natural novobiocin and 6-fold more active than the synthetic analogue 4TCNA. Additionally, 4TCCQ induced the degradation of estrogen receptor α and strongly induced the cell death in MCF-7 cells (40). Compound A4, lacking the 4-hydroxyl of the coumarin moiety and containing an N-acetyl side chain in lieu of the benzamide, was the most active compound, which induced degradation of Hsp90-dependent client proteins at 70-fold lower concentration than novobiocin (40). 4-hydroxy moiety of the coumarin ring and the 3'-carbamate of the noviose appendage were detrimental to Hsp90 inhibitory activity. In an effort to confirm these findings, 4-deshydroxy novobiocin (DHN1) and 3'-descarbamoyl-4-deshydroxynovobiocin (DHN2) were prepared and evaluated against Hsp90. Both compounds were significantly more potent than the natural product (44).

Novel novobiocin-derived C-terminal Hsp90 inhibitor KU135 induced antiproliferative effects in Jurkat T-lymphocytes, caused the degradation of known Hsp90 client proteins and revealed more potent antiproliferative effects than the known N-terminal Hsp90 inhibitor 17-AAG. Moreover, KU135 in comparison to 17-AAG was found to be a potent inducer of mitochondria-mediated apoptosis as evidenced, in part, by the fact that cell death was inhibited to a similar extent by Bcl-2/Bcl-x_L overexpression or the depletion of apoptotic protease-activating factor-1 (Apaf-1). Intriguingly, KU135 did not induce upregulation of Hsp70 and Hsp90 in Jurkat T-lymphocytes (45). The study of Samadi *et al* (46) demonstrated similar effect of KU135 in most melanoma cells, where it reduced cell survival, proliferation, and induced apoptosis more significantly than 17-AAG. Additionally, levels of Hsp90 and Hsp70 did not increase, while the levels of phosphorylated HSF-1 levels decreased after KU135 treatment of melanoma cells. KU135 inhibited cell proliferation by regulating signaling pathways, which are different from those targeted by 17-AAG and as such represents a novel opportunity for Hsp90 inhibition. In this regard, KU135 seems to be a potential candidate for cancer therapy against melanoma. Recently developed C-terminal Hsp90 inhibitor KU174 exhibited very robust antiproliferative and cytotoxic activity together with client protein degradation and disruption of Hsp90 native complexes without induction of an HSR in prostate cancer cells. In a pilot *in vivo* proof-of-concept study KU174 demonstrated efficacy at 75 mg/kg in a PC3-MM2 rat tumor model (47).

Furthermore, novel novobiocin analogue F-4 as a putative C-terminal inhibitor of Hsp90 also demonstrated improved potency and efficacy compared to novobiocin in antiproliferative assays and decreased the expression of client proteins. Prostate specific antigen (PSA) secretion was inhibited in a dose-dependent manner that paralleled a decrease in androgen expression (AR). In addition, superior efficacy was demonstrated by F-4 compared to 17-AAG in experiments measuring cytotoxicity and apoptosis (48). Recently, assisted by molecular docking studies, a scaffold containing a biphenyl moiety in lieu of the coumarin ring system found in novobiocin, was identified for development of new Hsp90 C-terminal inhibitors. A library of small molecules containing the biphenyl moiety was designed, synthetised, and evaluated against two breast cancer cell lines with good antiproliferative activity manifested (49).

The most abundant polyphenolic catechin with chemopreventive and anticancer activities is epigallocatechin-3-gallate (EGCG) (50). Palermo *et al* (51) demonstrated that EGCG can inhibit the transcriptional activity of aryl hydrocarbon receptor (AhR) through a mechanism involving direct binding to the C-terminal region of Hsp90. A novel Hsp90 inhibitor impaired the association of Hsp90/Hsc70 and Hsp90/p23, by directly binding to the C-terminal region of Hsp90, inhibited Hsp90 chaperoning function, and simultaneously degraded multiple cancer-related Hsp90 client proteins (52,53). EGCG specifically inhibited the expression of Hsp70 and Hsp90 by inhibiting the promoter activity of Hsp70 and Hsp90. Pretreatment with EGCG increased the stress sensitivity of MCF-7 cells upon heat shock (44˚C for 1 h) or oxidative stress (H_2O_2, 500 μM for 24 h). Moreover, treatment with EGCG (10 mg/kg) in a xenograft model resulted in delayed tumor incidence and reduced tumor size, as well as the inhibition of Hsp70 and Hsp90 expression (54).

5. Combination of Hsp90 inhibitor with second therapy

The interaction of survival signals that occured as side effects of treatments could be very effectively limited through combination of therapies. In this regard, Hsp90 inhibitors may be a promising strategy e.g., to sensitize cisplatin-resistant Fancony anemia pathway-proficient tumor cells to cisplatin (55), to overcome autophagy, a mechanism protecting rhabdomyosarcoma cells from drug-induced cytotoxicity (56), to sensitize human tumors to irradiation (57) or simply to enhance the effect of therapy when combined with the non-genotoxic Hsp90 inhibitor (58).

Oral, esophageal, gastrointestinal, colon and pancreatic cancer. The Hsp90 inhibitor 17-AAG enhanced significantly the radiation sensitivity and induced apoptosis in oral squamous cell carcinoma cell line SAS/neo which has a wild-type p53. On the other hand, the radiation sensitizing effect of 17-AAG was limited in the SAS/Trp248 cells which has a mutated p53 (59). 17-AAG was also shown to inhibit ATP-binding cassette sub-family G member 2 (ABCG2) upregulation, thereby reversing the ABCG2-mediated multidrug resistance (MDR) and in this regard can be used as a chemosensitizer for the treatment of esophageal cancer (60). Furthermore, 17-AAG sensitized esophageal cancer cells to γ-photon radiation, probably through its ability to affect a range of signalling components simultaneously, for example both EGF and IGF-1 (61).

Hsp90 inhibitors, IPI-493 as well as IPI-504, revealed antitumor activity and induced receptor tyrosine kinase KIT downregulation in xenograft model of gastrointestinal stromal tumor (GIST) with heterogeneous KIT mutations (62,63). IPI-493 synergized with tyrosine kinase inhibitors, that are commonly used for the treatment of advanced or imatinib-resistant GIST (63). Treatment effects of IPI-504 were also enhanced and/or more potent in combination with imatinib or sunitinib (62). Similarly a combination of imatinib and Hsp90 inhibitor AT13387 treatment in the imatinib-resistant GIST430 model significantly enhanced tumor growth inhibition over the monotherapies. These results, as well as good tolerance of AT13387, suggest this Hsp90 inhibitor as an excellent candidate for clinical testing in gastrointestinal stromal tumors in combination with imatinib (64). Moreover, by blocking Hsp90, Lang *et al* (65) disrupted rapamycin-induced activation of alternative signaling pathways in hepatocellular carcinoma and substantially improved the growth-inhibitory effects of mTOR inhibition *in vivo*.

Hsp90 inhibition may be also an attractive target for innovative treatment of gastroenteropancreatic neuroendocrine tumors alone or in combination with either IGF-1R or mTOR inhibitors (66). Unusually, Hsp90 inhibitor 17-AAG was more responsive in colon cancer cells with $BRAF^{V600E}$ mutation than selective $BRAF^{V600E}$ inhibitor PLX4720, probably due to the multiple oncogenic proteins that are Hsp90 clients (67). Indeed, the inhibition of Hsp90 with 17-DMAG abrogated the invasive properties of colon cancer cells and modulated the expression of the antimetastatic factor acti-

vating transcription factor-3 and improved the efficacy of oxaliplatin (68). Furthermore, 17-AAG interventions directed to cell cycle arrest in G1 may potentiate oxaliplatin activity in colon cancer cells with impaired p53 (69) and may be critical for its ability to reverse cisplatin resistance (70). Similarly, GA reversed topotecan induced upregulation of the anti-apoptotic protein Bcl-2 in both $p53^{+/+}$ and $p53^{-/-}$ HCT116 cells and sensitised human colon cancer cells to topoisomerase I poisons via depletion of key anti-apoptotic and cell cycle checkpoint proteins (71). On the other hand, the combination of an active metabolite of irinotecan SN-38 and 17-AAG was shown to be synergistic in p53-null, but not in parental HCT116 cells by median effect. Taken together, 17-AAG specifically inhibited the G(2)/M checkpoint in p53-defective cells by downregulation of checkpoint kinases Chk1 and Wee1 (72). Similarly, GA enhanced the effect of ionizing radiation in p53 and p21 null cells (73).

The inhibition of Hsp90 with GA destabilised Cdc25A independent of Chk1/2, whereas the standard drug for pancreas carcinoma treatment, gemcitabine caused Cdc25A degradation through the activation of Chk2. Both agents applied together additively inhibited the expression of Cdc25A and the proliferation of pancreatic carcinoma cells, as well as reduced the resistance of pancreatic carcinoma cells to treatment with gemcitabine (74). Indeed, the combined therapy of 17-DMAG and Akt inhibitor perifosine overcame tumor growth and resistance induced by bone marrow stromal cells and endothelial cells as well as the proliferative effect of exogenous interleukin-6, insulin-like growth factor-I, and vascular endothelial growth factor. The combination induced also apoptosis and growth inhibition in endothelial cells and inhibited angiogenesis (75). Moreover, short interfering RNA (siRNA) was used to knockdown ErbB3 in the resistant cell line AsPC1. Whereas individual treatments with siRNA to ErbB3 or 17DMAG had no effect on radiosensitivity, the combination, which reduced both ErbB2 and ErbB3, resulted in a significant enhancement in AsPC1 radiosensitivity (76). Interestingly, the dietary component from broccoli and broccoli sprouts sulforaphane also potentiated the efficacy of 17-AAG against pancreatic cancer through enhanced abrogation of Hsp90 function (77). For the complete list of oral, esophageal, pancreatic, gastrointestinal and colon cancer cell response to combination of Hsp90 inhibitor and other therapy (treatment) *in vitro* and/or *in vivo* see Table II.

Lung cancer. Hsp90 inhibitor IPI-504, induced tumor regression in aggressive *Nf1*-deficient malignancies and *KRas*/*p53*-mutant lung cancer mouse models, but only when combined with rapamycin (78). Combinations of low-dose of non-ansamycin inhibitor of Hsp90, ganetespib (STA-9090 a unique resorcinolic triazolone) with MEK or PI3K/mTOR inhibitors, resulted in superior cytotoxic activity than single agents alone in a subset of mutant KRAS cells, and the antitumor efficacy of STA-9090 was potentiated by cotreatment with the PI3K/mTOR inhibitor BEZ235 in A549 xenografts *in vivo* (79). Similar combination of STA-9090 with paclitaxel, docetaxel or vincristine resulted in synergistic antiproliferative effects in the H1975 cells *in vitro* as wells as enhanced tumor growth inhibition observed in combination with paclitaxel and tumor regressions seen with docetaxel (80). Furthermore, Hsp90 inhibitors have overcame the resistance to EGFR tyrosine kinase inhibitors in subcutaneous xenograft models of H1975 and A549 (81) and enhanced the antitumor activity of paclitaxel and camptothecin, respectively, in breast and colorectal tumor models (82). Hsp90 inhibition overcame the hepatocyte growth factor-triggered resitance to EGFR tyrosine kinase inhibitors and resulted in more successful treatment of patients with EGFR-mutant lung cancers (83). The effectiveness of combined therapy of EGFR tyrosine kinase inhibitors and Hsp90 inhibitors was also confirmed in the treatment of lung cancers co-driven by mutant EGFR containing T790M and MET (84,85). Moreover, 17-AAG decreased the etoposide-induced p38 MAPK-mediated ERCC1 expression (DNA repair capacity) (86) and downregulated the cisplatin-induced thymidine phosphorylase (a key enzyme in pyrimidine nucleoside salvage pathway) expression and Erk1/2 and Akt activation (87) what sensitized lung cancer cells to etoposide and cisplatin, respectively.

Hsp90 inhibitors were also effective in treating crizotinib-resistant tumors harboring secondary gatekeeper mutations within the ALK TK domain (88). Furthermore, Normant *et al* (89) observed partial responses to administration of IPI-504 as a single agent in a phase II clinical trial in patients with NSCLC, specifically in patients that carry an ALK rearrangement. The experimental data of Solit *et al* (90) suggested that Hsp90 inhibition in combination with chemotherapy may represent an effective treatment strategy for patients, whose tumors express EGFR kinase domain mutations, including those with *de novo* and acquired resistance to EGFR tyrosine kinase inhibitors. Acquired resistance limits the efficacy of ALK inhibitors, such as crizotinib and TAE684, however, combining inhibitors of ALK and Hsp90 resulted in synergistic cytotoxicity (91,92).

Hsp90 inhibitor 17-DMAG, as well as purine-scaffold inhibitor PU-H71, were shown to be the most effective as radiosensitizer of lung cancer cells, when administered before radiation, because of its suppression of DNA repair at multiple levels, including BER and ATM-regulated pathways (93,94). Recent results of Kim and Pyo (95) show that combined treatment of 17-AAG and celecoxib at clinically relevant concentrations may significantly enhance the therapeutic efficacy of ionizing radiation therapy. Moreover, very recent combination of 17-DMAG and histone deacetylase inhibitor belinostat synergistically inhibited *in vitro* proliferation of selected panel of 12 NSCLC cell lines. Importantly, both agents and their combination almost completely prevented TKI-resistant tumor formation (EGFR T790M mutation) in a xenograft model (96). For the above, and even further studies with the response of lung cancer cells to combination of Hsp90 inhibitor and another therapy see Table III.

Breast, ovary and prostate cancer. Hsp90 inhibitor IPI-504 resulted in a marked decrease in the levels of HER-2, Akt, p-Akt, and p-MAPK in trastuzumab-resistant xenografts as early as 12 h after a single dose of IPI-504 inhibitor. IPI-504-mediated Hsp90 inhibition may represent, together with other Hsp90 inhibitors, a novel therapeutic approach in HER-2 overexpressing and/or trastuzumab refractory HER-2-positive cancer (97-100), and provide a promising strategy to overcome the development of resistance against trastuzumab.

Table II. The response of oral, esophageal, pancreatic, gastrointestinal and colon cancer cells to combination of Hsp90 inhibitor with another therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
Oral squamous	17-AAG	Ionizing radiation	*In vitro*	↑ p53-dependent	(59)
Esophageal	17-AAG	Ionizing radiation	*In vitro*	↑	(61)
Esophageal	17-AAG	Cisplatin	*In vitro*	↑	(174)
Esophageal	Radicicol	Heat	*In vitro*	↑	(175)
Pancreatic	GA	5-Fluorouracil	*In vitro*	↑ in presence of serum	(176)
Pancreatic	GA	Gemcitabine	*In vitro*	↑	(74)
Pancreatic	GA, 17-AAG	3-Bromopyruvate	*In vitro, in vivo*	↑	(177,178)
Pancreatic	17-AAG	U0126	*In vitro*	↑	(179)
Pancreatic	17-AAG	Sulforaphane	*In vitro, in vivo*	↑	(77)
Pancreatic and other	17-DMAG	Ionizing radiation	*In vitro*	↑ predicted by ErbB3 expression	(76)
Hepatocellular	17-DMAG	Rapamycin	*In vitro, in vivo*	↑ + ECs, and VSMCs	(65)
Pancreatic, glioblastoma	NVP-HSP990	Ionizing radiation, hyperthermia	*In vitro*	↑	(180)
Gastrointestinal stromal	IPI-504	Imatinib, sunitinib	*In vivo*	↑	(62)
Gastroentero-pancreatic	IP-504	IGF1R and mTOR inhibitors	*In vitro, in vivo*	↑	(66)
Gastrointestinal stromal	IP-493	Imatinib, sunitinib	*In vivo*	↑	(63)
Gastrointestinal stromal	AT13387	Imatinib	*In vitro, in vivo*	↑	(64)
Colon	GA	Ionizing radiation	*In vitro*	↑ in p53 compromised cells	(73)
Colon	GA	Topotecan	*In vitro*	↑ p53-independent	(71)
Colon and other	GA	Ionizing radiation	*In vitro*	↑ more in SQ-5 than in DLD-1 cells	(181)
Colon	17-AAG	TRAIL	*In vitro*	↑ greater in TRAIL-resistant cells	(182)
Colon	17-AAG	AHA1 siRNA	*In vitro*	↑	(183)
Colon	17-AAG	Cisplatin	*In vitro*	↑ in cells with sustained JNK	(70)
Colon	17-AAG	Oxaliplatin	*In vitro*	↑ in p53 deficient cells	(69)
Colon	17-AAG	Irinotecan SN-38	*In vitro*	↑ in p53 defective cells	(72)
Colon	17-AAG	TRAIL	*In vitro*	↑ in BRAF (V600E) mutant cells	(67,184)
Colon and other	17-AAG	Nutlin	*In vitro, in vivo*	↑	(58)
Colon	17-DMAG	Oxaliplatin	*In vitro, in vivo*	↑ in p53 deficient cells	(68)
Colon	STA-9090	Ionizing radiation, 5-fluorouracil	*In vitro, in vivo*	↑	(185)

The symbol ↑ means at least the additive effect of the combination compared to single therapies.

Table III. The response of lung cancer cells to combination of Hsp90 inhibitor with another therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
NSCLC	17-AAG	Paclitaxel	*In vitro*	↑ in cells with high levels of p185	(186)
NSCLC	17-AAG	Cisplatin	*In vitro*	↑	(87)
NSCLC	17-AAG	Etoposide	*In vitro*	↑	(86)
NSCLC	17-AAG	VER-155008	*In vitro*	↑	(187)
NSCLC	17-DMAG	Ionizing radiation	*In vitro*	↑	(93)
NSCLC	17-DMAG	PTACH, belinostat	*In vitro*, *in vivo*	↑	(96,188)
NSCLC	17-DMAG	WZ4002	*in vivo*	↑ in EGFR (T790M) mutant cells	(84)
NSCLC	17-DMAG	Velcade	*In vitro*	↑	(189)
NSCLC	STA-9090	Paclitaxel, docetaxel, vincristine	*In vitro*, *in vivo*	↑	(80)
NSCLC	STA-9090	BEZ235	*In vitro*, *in vivo*	↑ in KRAS mutant cells	(79)
NSCLC	STA-9090	Crizotinib	*In vitro*, *in vivo*	↑ in ALK- and MET-driven cells	(92,190,191)
NSCLC	SNX-2112 STA-9090	Erlotinib	*In vitro*, *in vivo*	↑ in wild-type or mutant EGFR (L858R, T790M) cells	(85,192)
NSCLC	CH5164840	Erlotinib	*In vitro*, *in vivo*	↑ in EGFR overexpressed and mutant cells	(193)
NSCLC	CUDC-305	Paclitaxel	*In vitro*, *in vivo*	↑ in EGFR (T790M) or KRAS mutant cells	(81)
NSCLC	WK88-1	Gefitinib	*In vitro*, *in vivo*	↑ in MET-driven cells	(194)
Lung	GA	TRAIL	*In vitro*	↑ in TRAIL-resistant cells; adverse effects of high-dose GA	(195)
Lung and other	GA, 17-AAG	Ionizing radiation, celecoxib	*In vitro*, *in vivo*	↑ in transformed cells only	(95,196-198)
Lung	17-AAG	Paclitaxel	*In vitro*, *in vivo*	↑ in EGFR mutant cells	(199)
Lung and other	17-AAG	Smac mimetic compound 3	*In vitro*	↑	(200)
Lung	17-DMAG	Crizotinib	*In vitro*	↑ EML4-ALK-expressing cells	(91)
Lung	IP-504	Rapamycin	*In vitro*, *in vivo*	↑ in RAS- driven cells	(78)
Lung	PU-H71	Ionizing radiation	*In vitro*	↑	(194)

The symbol ↑ means at least the additive effect of the combination compared to single therapies. NSCLC, non-small cell lung cancer.

Very promising strategy to overcome the development of trastuzumab resistance in breast cancer patients seems to be a combination of the Hsp90 inhibitor and histone deacetylase 6 inhibitor carbamazepine (101). GA synergized with carbamazepine to promote HER-2 degradation and inhibited breast cancer cell proliferation. Solit *et al* (102) found that

the inhibition of Hsp90 function sensitized breast cancer xenografts to Taxol through downregulation of Akt kinase. Hsp90 inhibitors may be an effective therapy also to treat aromatase inhibitor-resistant breast cancers and improved efficacy can be achieved by combined use of an Hsp90 inhibitor and an Akt inhibitor (103,104). Moreover, Pashtan *et al* (105) demonstrated that Hsp90 inhibitor 17-AAG inhibiting multiple signaling activators including ErbB and Src kinases, it does not permit oncogene switching and resulted in a more prolonged and robust inhibition of downstream signaling pathways in breast cancer cells, than the individual tyrosine kinase inhibitors. In this way, Hsp90 inhibitors can prevent breast cancer cells from tyrosine kinase inhibition (105). Another way, to sensitize cancer cells is elimination of RIP1 protein, which can support cell survival due to activation of NF-κB. In this regard, 17-DMAG markedly reduced RIP1 expression and sensitized breast tumor cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis (eliminate the resistance to TRAIL) (106). A recent study of Stecklein *et al* (107) demonstrated the role of BRCA1, which is associated with the resistance to platinum-based chemotherapeutics and poly(ADP ribose) polymerase (PARP) inhibitors in regulating damage-associated checkpoint and repair responses to Hsp90 inhibitors. The above study pointed out BRCA1 as a clinically relevant target for enhancing sensitivity in refractory and/or resistant malignancies. Furthermore, complete regression of aggressive breast tumors in mice was observed after the combination of anti-angiogenic stress imposed by loss of Id protein and the inactivation of the HIF-1α chaperone Hsp90 (108).

Interestingly, ovarian cancer cells overexpressing HER2 showed 5-fold increased sensitivity to the Hsp90 molecular chaperone inhibitor GA. In contrast, HER2-overexpressing cells showed statistically significant resistance to cisplatin, PI3K inhibitor LY294002 and tyrosine kinase inhibitor emodin (109). On the other hand, GA and 17-AAG may sensitize ovarian cancer cells to cisplatin (110) and paclitaxel (111), respectively, particularly those tumors in which resistance is driven by HER-2 and/or p-Akt.

Pharmacological inhibition of the cell cycle-dependent kinase (essential for G2-M checkpoint) Wee1 and its molecular silencing with siRNA uniformly increased apoptotic activity of the Hsp90 inhibitor 17-AAG *in vitro* (112). Moreover, Wee1 inhibition synergized with any one of the clinically evaluated Hsp90 inhibitors to inhibit an androgen-independent and invasive human prostate carcinoma cell line PC3 *in vitro* and *in vivo* (113). Hsp90 inhibitors trigger a heat shock response associated with increased expression of Hsp90, Hsp70, Hsp27, and clusterin that attenuates drug effectiveness in the treatment of castrate-resistant prostate cancer. However, clusterin inhibitor OGX-011 revealed markedly potentiated antitumor efficacy in xenograft models of human castrate-resistant prostate cancer, leading to an 80% inhibition of tumor growth with prolonged survival compared with Hsp90 inhibitor monotherapy (114). Furthermore, administration of 17-AAG maintained androgen-sensitivity, prevented nuclear localization of endogenous androgen receptor and delayed the progression of LuCaP35 xenograft tumors to castration resistance. Thus, it appears that targeting Hsp90 may lead to new approaches to prevent and/or treat castration-resistant prostate cancer (115). Alternatively, co-administration of hyperthermia and 17-AAG released from plasmonic matrices was a powerful approach for the ablation of malignant cells and can be used in the form of similar combinations of nanoparticles and chemotherapeutic drugs for a variety of malignancies (116). For the complete list of breast, ovarian and prostate cancer cell response to combination of Hsp90 inhibitor and another therapy (treatment) *in vitro* and/or *in vivo* see Table IV.

Multiple myeloma, lymphocytic and myelogenous leukemia. Lamottke *et al* (117) demonstrated that inhibition of Hsp90 by small molecular mass inhibitors induced cell death in multiple myeloma. They analyzed the effects of the novel, orally bioavailable Hsp90 inhibitor NVP-Hsp990 on multiple myeloma cell proliferation and survival. NVP-Hsp990 inhibitor led to a significant reduction in myeloma cell viability and induced G2 cell cycle arrest, degradation of caspase-8 and caspase-3, and induction of apoptosis. Inhibition of the Hsp90 ATPase activity was accompanied by the degradation of multiple myeloma phospho-Akt and phospho-Erk1/2 and upregulation of Hsp70. In this regard, PI3K/mTOR inhibitor in combination with NVP-Hsp990 mentioned above, rendered the Hsp90 blockade-mediated stress response ineffective and considerably increased the anti-multiple myeloma toxicity (118). Similarly, Chatterjee *et al* (119) demonstrated that the knockdown of Hsp72 and/or Hsp73 or treatment with VER-155008, decreased protein levels of Hsp90-chaperone clients affecting multiple oncogenic signaling pathways, and acted synergistically with the novel Hsp90 inhibitor NVP-AUY922 in myeloma cell death induction. Inhibition of the PI3K/Akt/GSK3β pathway with siRNA or PI103 decreased expression of the heat shock transcription factor 1 and downregulated constitutive and inducible Hsp70 expression (119). Moreover, NVP-AUY922 in combination with histone deacetylase inhibitors SAHA, NVP-LBH589, melphalan or doxorubicin resulted in synergistic inhibition of viability, with strong synergy (combination index <0.3) in the case of melphalan. Importantly, resistance of the RPMI-8226 cell line and relative resistance of some primary myeloma cells against NVP-AUY922 could be overcome by combination treatment (120). In this manner, the p38 MAPK inhibitor BIRB 796, inhibited protein expression and phosphorylation of Hsp27 induced by Hsp90 inhibitor 17-AAG and enhanced its cytotoxicity (121). Transcription induction of Hsps in response to 17-AAG was also inhibited by the transcription inhibitor actinomycin D. Thus, the combination strategy of 17-AAG and actinomycin D represents a potential approach for the treatment of hematological malignancies (23).

Furthermore, Hsp90 is a promising therapeutic target also in JAK-2 driven cancer, e.g., myeloproliferative neoplasms, B cell acute lymphoblastoid leukemia, including those with genetic resistance to JAK enzymatic inhibitors (122,123). Intriguingly, Hsp90 inhibitor-based antileukemia therapy may override *de novo* or acquired resistance of acute myelogenous leukemia cells to pan-histone deacetylase inhibitors (124). On the contrary, clinically tolerable doses of tanespimycin (17-AAG) had little effect on resistance-mediating client proteins in relapsed leukemia and exhibits limited activity in combination with cytarabine (Clinicaltrials.gov identifier: NCT00098423) (125).

Table IV. The response of breast, ovarian and prostate cancer cells to combination of Hsp90 inhibitor with another therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
Breast	GA	Carbamazepine	*In vitro*	↑	(101)
Breast	GA	Bortezomib	*In vitro*	↑	(201)
Breast	17-AAG	Trastuzumab	*In vitro*	↑ in high ErbB2	(202,203)
Breast	17-AAG	Rapamycin	*In vitro*	↑	(204)
Breast	17-AAG	Taxol, doxorubicin	*In vitro, in vivo*	↑ Rb-dependent	(102,205)
Breast	17-AAG	Gefitinib	*In vitro*	↑	(105)
Breast	17-AAG	Loss of Id protein	*In vivo*	Complete regression	(108)
Breast	17-AAG	PDT-Photofrin, PDT-NPe6	*In vitro*	↑	(206)
Breast and other	17-AAG	Paclitaxel + rapamycin	*In vitro, in vivo*	↑	(207)
Breast	17-DMAG	TRAIL	*In vitro*	↑	(106)
Breast	17-DMAG	Triciribine	*In vitro*	↑	(103)
Breast	17-DMAG	PDT-hypericin	*In vitro*	↑	(208)
Breast	IP-504	Trastuzumab	*In vitro, in vivo*	↑	(99)
Breast	SNX-2112	Trastuzumab	*In vitro, in vivo*	↑	(100)
Breast and other	CUDC-305	Paclitaxel, camptothecin	*In vitro, in vivo*	↑	(82)
Breast and other	CH5164840 NVP-AUY922	Trastuzumab, lapatinib	*In vitro, in vivo*	↑	(97,98)
Breast	NVP-AUY922	AZD8055	*In vitro*	↑	(209)
Ovarian	GA	Cisplatin	*In vitro*	↑	(110)
Ovarian	17-AAG	Carboplatin	*In vitro, in vivo*	↑ beneficial *in vivo*	(210)
Ovarian	17-AAG	Paclitaxel	*In vitro*	↑ ErbB2, p-Akt-dependent	(111)
Prostate	GA	TRAIL	*In vitro*	↑	(195)
Prostate	17-AAG	Cdc37 siRNA	*In vitro*	↑	(211)
Prostate	17-AAG	Survivin siRNA	*In vitro*	↑	(212)
Prostate	17-AAG	Wee1 siRNA	*In vitro*	↑	(112)
Prostate	17-AAG, SNX-2112, STA-9090	Wee1 inhibitor	*In vitro, in vivo*	↑	(113)
Prostate	17-AAG	Hyperthermia	*In vitro*	↑	(116)
Prostate	17-AAG PF04928473 PF04929113	Clusterin siRNA, OGX-011, OGX-427	*In vitro, in vivo*	↑	(114,159)
Prostate	17-AAG	Castration	*In vivo*	↑	(115)
Prostate	NVP-AUY922	Ionizing radiation	*In vitro, in vivo*	↑	(213)
Prostate	NVP-AUY922	Docetaxel	*In vivo*	↑	(214)

The symbol ↑ means at least the additive effect of the combination compared to single therapies.

Table V. The response of multiple myeloma, lymphocytic and myelogenous leukemia cells to combination of Hsp90 inhibitor with another therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
Myeloma	GA	Apigenin	*In vitro*	↑	(215)
Myeloma	17-AAG	GRN163L	*In vitro, in vivo*	↑	(216)
Myeloma	17-AAG	Bortezomib	*In vitro*	↑	(217)
Myeloma	17-AAG	Rapamycin	*In vitro*	↑	(218)
Myeloma	17-AAG	8-chloro-adenosine	*In vitro*	↑	(219)
Myeloma	17-AAG	Actinomycin D	*In vitro*	↑	(23)
Myeloma	17-AAG	BIRB 796	*In vitro*	↑	(121)
Myeloma	17-DMAG	Perifosine	*In vitro*	↑ + BM microenvir.	(75)
Myeloma	IPI-504	Bortezomib	*In vitro, in vivo*	↑	(220)
Myeloma	NVP-AUY922	NVP-LBH589 and SAHA, melphalan, doxorubicin	*In vitro*	↑	(120)
Myeloma	NVP-AUY922	Hsp72/73 siRNA, PI103	*In vitro*	↑	(119)
Myeloma	NVP-AUY922	Triptolide	*In vitro*	↑	(221)
Myeloma	NVP-AUY922	TG101209	*In vitro*	↑	(123)
Myeloma	NVP-AUY922	NVP_BVB808	*In vitro, in vivo*	↑	(122)
Myeloma	NVP-HSP990	Melphalan	*In vitro*	↑	(117)
Myeloma	NVP-HSP990	PI3K/mTOR inhibitor	*In vitro*	↑	(118)
Leukemia	GA	Doxorubicin	*In vitro*	↑ Bcr-Abl-dependent	(130,222)
Leukemia	GA	Flavopiridol	*In vitro*	↑	(133)
Leukemia	GA	Herbimycin A, chlorambucil, fludarabine	*In vitro*	↑	(127)
Leukemia	GA	Nutlin-3	*In vitro*	↑ p53 wild-type	(223)
Leukemia	17-AAG	SAHA, SB	*In vitro*	↑	(224)
Leukemia	17-AAG	UCN-01	*In vitro*	↑	(225)
Leukemia	17-AAG	GTP14564	*In vitro*	↑	(226)
Leukemia	17-AAG	Cytarabine	*In vitro*	↑	(227)
Leukemia	17-AAG	PKC412, LBH589	*In vitro*	↑	(228,229)
Leukemia	17-AAG	Imatinib	*In vitro*	↑	(230)
Leukemia	17-AAG	KNK437, Hsp70 siRNA	*In vitro*	↑	(160)
Leukemia	17-AAG	Histone deacetylase 6 siRNA, tubacin	*In vitro*	↑	(231)
Leukemia	17-AAG	Rituximab	*In vitro*	↑	(129)
Leukemia	17-DMAG	Dasatinib	*In vitro*	↑	(232)
Leukemia	IP-504	Imatinib	*In vivo*	↑ + leukemia stem cells	(131)
Leukemia	NVP-AUY922	Cytarabine, fludarabine	*In vitro, in vivo*	↑	(128,233)
Leukemia	NVP-AUY922	Nilotinib	*In vitro, in vivo*	↑	(132)
Leukemia	NVP-AUY922 SNX-7081	Fludarabine	*In vitro*	↑	(126,234)
Lymphoma	17-DMAG	Doxorubicin	*In vitro*	↑ when 17-DMAG after doxorubicin	(235)
Lymphoma	17-DMAG	Vorinostat	*In vitro*	↑	(236)
Lymphoma	IPI-504	Akt/PI3K inhibitor, doxorubicin	*In vitro*	↑	(237)
Lymphoma	IPI-504	Bortezomib	*In vitro*	↑	(134)

The symbol ↑ means at least the additive effect of the combination compared to single therapies.

The Hsp90 inhibitor SNX-7081, which is significantly more potent than 17-AAG synergized and restored sensitivity to fludarabine in seven lymphocytic leukemia cell lines and 23 patient samples, including TP53 mutated cell lines and TP53 or ATM disfunctional patient cells (126). Similar sensitizing effect of Hsp90 inhibitor on chronic lymphocytic leukemia cells was demonstrated by Jones *et al* (127) as well as Walsby *et al* (128) who combined GA and NVP-AUY922, respectively, in combination with fludarabine. In this regard, Hsp90 inhibitors represent a potential treatment strategy for fludarabine refractory diseases. A novel strategy to enhance therapeutic response in chronic lymphocytic leukemia may also represent the combination of Hsp90 inhibitor and therapeutic antibody rituximab (129).

Both HL-60 cells transfected with Bcr-Abl and naturally Ph1-positive K562 leukemia cells are resistant to most cytotoxic drugs, but were found to be sensitive to GA. In this regard, GA sensitized Bcr-Abl-expressing cells to doxorubicin and paclitaxel. However, in parental HL-60 cells, GA antagonized the cytotoxic and cell death effects of doxorubicin included inhibition of PARP cleavage and nuclear fragmentation (130). Elimination of mutant BCR-ABL (T315I) kinase seems to be more effective therapeutic strategy for treating BCR-ABL-induced leukemia than the inhibition of BCR-ABL (T315I) kinase activity. Indeed, combination treatment with Hsp90 inhibitor IPI-504 and imatinib was more effective than either treatment alone in prolonging survival of mice simultaneously bearing both wild-type and T315I leukemic cells (131). Simultaneous exposure of BaF3 cells expressing BCR-ABL mutants including T315I to AUY922 and nilotinib was more effective at reducing the outgrowth of resistant cell clones as well as at survival prolongation of mice transplanted with mixture of BaF3 cells expressing wild-type BCR-ABL and mutant forms (132). Similarly, flavopiridol (semisynthetic flavone and selective inhibitor of CDKs) sensitized imatinib-resistant HL/Bcr-Abl cells to GA and it seems that a cocktail of flavopiridol, 17-AAG (or its analogs) and imatinib may be an attractive approach for further investigations (133).

Despite the promising introduction of the proteasome inhibitor bortezomib in the treatment of mantle cell lymphoma (MCL), not all patients respond, and resistance often appears after initial treatment. In bortezomib-resistant cells, cell pretreatment with Hsp90 inhibitor IPI-504, led to synergistic induction of apoptotic cell death when combined with bortezomib (134). For the above, and further studies with a response of multiple myeloma, lymphocytic and myelogenous leukemia cells to combination of Hsp90 inhibitor and another therapy see Table V.

Glioblastoma multiforme. 17-AAG and PARP inhibitor olaparib had modest, replication-dependent radiosensitizing effects on T98G glioma cells. Additive radiosensitization was observed through the combination treatment, mirrored by increases in gammaH2AX foci in G(2)-phase cells. Unlike olaparib, 17-AAG did not increase radiation sensitivity of Chinese hamster ovary cells, indicating tumor specificity (135). In addition, 17-AAG sensitized xenografted U87MG cells to cisplatin in nude mice. Indeed, Hsp90-targeted therapy seems to be an effective strategy for potentiating chemotherapy using DNA-crosslinking agents for temozolomide-refractory gliomas (136). Moreover, treatment with subtoxic doses of 17-AAG in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced rapid apoptosis in TRAIL-resistant glioma cells, suggesting an attractive strategy for treating gliomas (137). Interestingly, 17-AAG inhibited the growth of intracranial tumors and synergized with radiation both in tissue culture and in intracranial tumors. On the contrary, 17-AAG did not synergize with temozolomide in any of glioma models (138). The response of glioblastoma cells to combination of Hsp90 inhibitor with other therapy is summarized in Table VI.

Melanoma. 17-AAG induced in uveal melanoma cells compared to cutaneous melanoma cells (with low tyrosine kinase activity of ^{WT}B-Raf) downregulation of ^{WT}B-Raf protein, followed by Mek/Erk inactivation and a decrease in cyclin D1. In this regard, the combination of 17-DMAG and imatinib mesylate was more efficient, than individual treatments of c-Kit positive uveal melanoma cells (21). The Hsp90 inhibitor XL888 increased Bcl-2 interacting mediator of cell death expression, decreased Mcl-1 expression, and induced apoptosis more effectively than dual mitogen-activated protein-extracellular signal-regulated in most resistant melanoma models. The reversal of the resistance phenotype was associated with the degradation of PDGFRβ, COT, IGFR1, CRAF, ARAF, S6, cyclin D1 and Akt (139). Inhibition of Hsp90 by GA sensitized melanoma cells also to thermosensitive ferromagnetic particle-mediated by hyperthermia with temperature 43˚C (140). The Hsp90 inhibitor ganetespib was reported to exhibit robust antitumor efficacy in preclinical model of BRAF^{V600E} melanoma and could thus readily overcome mechanisms of intrinsic and acquired resistance to selective BRAF inhibitors. The data mentioned above suggest that ganetespib may offer an alternative, and potentially complementary, strategy for therapeutic intervention in mutant BRAF-driven disease (141). The above studies are summarized in Table VII.

Bladder and renal cancer. Although up to 70% of advanced bladder cancer patients initially show good tumor response to systemic cisplatin-based combination chemotherapy, >90% of good responders relapse and eventually die of the disease. This is attributable to the re-growth of bladder cancer-initiating cells, that have survived chemotherapy. These cancer-initiating cells were more resistant to cisplatin and exhibited more activity in the Akt and Erk oncogenic signaling pathways when compared with their CD44$^-$ counterparts. On the other hand, 17-DMAG simultaneously inactivated both Akt and Erk signaling and synergistically potentiated the cytotoxicity of cisplatin against bladder cancer-initiating cells by enhancing cisplatin-induced apoptosis *in vitro* and *in vivo* (142). Similarly, low doses of 17-DMAG potentiated antitumor activity of chemoradiotherapy (cisplatin + ionizing radiation) and supported clinical trial of Hsp90 inhibitors to overcome chemoradiotherapy resistance in patients with muscle-invasive bladder cancer (143). The combination of 17-AAG and HIV protease inhibitor ritonavir inhibited renal cancer growth through the inhibition of HSF-1 expression and downregulation of Hsp27, Hsp70 and Hsp90 induced by 17-AAG (144). Recently, Ma *et al* (145) demonstrated dual targeting of two chaperones Hsp90 and Hsp70 and their combination with conventional anticancer

Table VI. The response of glioblastoma cells to combination of Hsp90 inhibitor with another therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
Glioblastoma	17-AAG	ZD1839, LY294002	*In vitro*	↑	(238,239)
Glioblastoma	17-AAG	Enzastaurin	*In vitro*	↑	(240)
Glioblastoma	17-AAG	TRAIL	*In vitro*	↑	(137)
Glioblastoma	17-AAG	Cisplatin, 1,3-bis(2-chloroethyl)-1-nitrosourea	*In vitro, in vivo*	↑	(136)
Glioblastoma	17-AAG 17-DMAG	Ionizing radiation, temozolomide	*In vitro, in vivo*	↑ to ionizing radiation, but not to temozolomide ↑ in glioma stem cells	(136,138,241)
Glioblastoma	17-AAG	Ionizing radiation, olaparib	*In vitro*	↑	(135)
Glioblastoma and other	17-DMAG	Ionizing radiation	*In vitro, in vivo*	↑	(242)
Glioblastoma	NVP-AUY922	PI3K/mTOR inhibitor, Mek inhibitor	*In vitro*	↑	(155)
Glioblastoma	HSP990	BKM120	*In vitro*	↑ independent on PTEN/p53	(243)

The symbol ↑ means at least the additive effect of the combination compared to single therapies.

Table VII. The response of melanoma cells to combination of Hsp90 inhibitor with other therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
Melanoma	GA	Hyperthermia	*In vitro, in vivo*	↑	(140)
Melanoma	17-DMAG	Imatinib mesylate	*In vitro*	↑ in WT B-Raf uveal melanoma cells	(21)
Melanoma	STA-9090	TAK-733	*In vitro, in vivo*	↑ in melanoma cells with BRAF(V600E) mutation	(141)
Melanoma and other	PU-H71	Cisplatin, melphalan	*In vitro*	↑	(244)
Melanoma	XL888	Vemurafenib, doxycycline	*In vitro*, 3D spheroids	↑	(139)

The symbol ↑ means at least the additive effect of the combination compared to single therapies.

drugs as promising therapeutic option for patients with advanced bladder cancer. The response of bladder and renal cancer cells to combination of Hsp90 inhibitor with another therapy is summarized in Table VIII.

Head and neck cancer. The synthetic Hsp90 inhibitor BIIB021 revealed a strong antitumor effect in head and neck squamous cell carcinoma cells *in vitro* and *in vivo*. Its antitumor effect was higher than the effect of ansamycin-based Hsp90 inhibitor 17-AAG and when combined with radiation sensitized the efficacy of radiation therapy (146). The activation of multi-chaperone complex could be a resistance mechanism to the antiproliferative and apoptotic effects induced by tipifarnib (farnesyl transferase inhibitor) and that the combination of

Table VIII. The response of bladder and renal cancer cells to combination of Hsp90 inhibitor with another therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
Bladder	GA	DNA vaccine against p185 and Met	*In vivo*	↑	(245)
Bladder	17-AAG	Pifithrin + chemotherapy	*In vitro*	↑	(145)
Renal	17-AAG	Ritonavir	*In vitro, in vivo*	↑	(144)
Bladder	17-AAG, 17-DMAG	Cisplatin	*In vitro, in vivo*	↑	(142)
Bladder	17-DMAG	Chemoradiotherapy	*In vitro, in vivo*	↑	(143)

The symbol ↑ means at least the additive effect of the combination compared to single therapies.

Table IX. The response of head and neck, neuroblastoma, osteosarcoma and other transformed cells to combination of Hsp90 inhibitor with another therapy *in vitro* and/or *in vivo*.

Cancer	Hsp90 inhibitor	Second therapy	Conditions	Tumor response	(Ref.)
Head and neck squamous cells overexpressing Hsp90	GA	Tipifarnib, docetaxel	*In vitro*	↑ after GA + tipifarnib, not after GA + docetaxel	(147)
Head and neck squamous cells	17-AAG	Cisplatin, nutlin-3a	*In vitro, in vivo*	↑ depended on p53 and MDMX	(246)
Head and neck squamous cells	BIIB021	Ionizing radiation	*In vitro, in vivo*	↑	(146)
Neuroblastoma, osteosarcoma	GA	Cisplatin	*In vitro*	↑	(247)
Osteosarcoma	NVP-AUY922	CDK inhibitor	*In vitro*	↑	(248)
SV40-transformed COS-7 cells	GA	Velcade	*In vitro*	↑	(249)
Ewing's sarcoma	17-AAG	IGF1R inhibitor	*In vitro, in vivo*	↑ in IGF1R-positive cells	(250)
HeLa, B16, MCA205 cells	17-DMAG	Quinacrine, 9-aminoacridine	*In vitro, in vivo*	↑	(251)
HeLa cells	17-AAG	Ionizing radiation	*In vitro*	↑	(252)
Rhabdomyosarcoma	17-DMAG	Bortezomib	*In vitro*	↑	(56)
Pediatric	SNX-2112	Cisplatin	*In vitro*	↑	(253)

The symbol ↑ means at least the additive effect of the combination compared to single therapies.

tipifarnib with GA is possibly a suitable therapeutic strategy in the treatment of Hsp90-overexpressing head and neck squamous cell cancers (147). Interestingly, the combination of GA with docetaxel was not able to induce any synergistic effects on cell growth inhibition of head and neck squamous cell cancers independently of Hsp90 expression and activation status. On the other hand, the combination of GA with tipifarnib was potentially able to give synergistic effects on the growth arrest of head and neck squamous cell cancers especially when Hsp90 was overexpressed and even more when it was over-activated (147). Sensitizing effect of Hsp90 inhibitor was demonstrated in many other transformed cells, the results of which are shown together with head and neck cancer cells in Table IX.

Stem cells. Recent studies of Lee *et al* (148) showed that the combination of GA with quercetin or KNK437 sensitized breast cancer stem-like cells characterized by high intracellular aldehyde dehydrogenase activity and higher expression of Hsp90α toward antiproliferation and anti-migration effects of GA. Lee *et al* (148) also found that knockdown of Hsp27 could mimic the effect of Hsp inhibitors to potentiate the breast cancer stem-like cell targeting effect of GA. Newman *et al* (149) also supported the use of Hsp90 inhibitor as a cancer stem cell targeting agent and showed, that HSF-1 is an important target for elimination of both cancer and non cancer stem cells in cancer. They found, that low concentrations of the Hsp90 inhibitor 17-AAG eliminate lymphoma cancer stem

cells *in vitro* and *in vivo* by disrupting the transcriptional function of HIF-1α (149).

6. Resistance to Hsp90 inhibitors

Kelland *et al* (150) observed a positive relationship between NAD(P)H:quinone oxidoreductase (NQO1, DT-diaphorase) expression level and growth inhibition by 17-AAG. Stable, high-level expression of the NQO1 gene transfected into the DT-diaphorase-deficient (by NQO1 mutation) BE human colon carcinoma cell line resulted in a 32-fold increase in 17-AAG growth-inhibition activity. Increased sensitivity to 17-AAG in the transfected cell line was also confirmed in xenografts (150). Low NQO1 activity could be a likely mechanism of acquired resistance to 17-AAG in glioblastoma and melanoma. Indeed, Hsp90 inhibitors which avoid the liability of NQO1 metabolism are able to avoid the resistance due to decreased NQO1 activity and provide additional support for the clinical development of such structurally novel Hsp90 inhibitors (151). In this regard, the synthetic purine-scaffold Hsp90 inhibitor BIIB021, resorcinylic diaryl pyrazole CCT018159 as well as resorcinylic diaryl pyrazole/isoxazole amides VER-49009, VER-50589 or VER-52296 (NVP-AUY922 and AUY922) are promising Hsp90 inhibitors with several advantages compared to 17-AAG, including better solubility and independence from the effects of P-glycoprotein and NQO1 (151-153). Alongside depletion of client proteins, however, the BIIB021, VER-50589, VER-49009 and NVP-AUY922 all caused induction of Hsp72 and Hsp27 (31,154,155). On the other hand, the upregulation of Hsp27 has a significant role in 17-AAG resistance, which may be mediated in part through GSH regulation. The modulation of GSH was able to enhance the efficacy of Hsp90-directed therapy in clinic (156). Sharp *et al* (157) demonstrated that thiadiazole inhibitors display a more limited core set of interactions relative to the clinical trial candidate NVP-AUY922 and consequently may be less susceptible to resistance derived through mutations in Hsp90, but these inhibitors also caused induction of the heat shock response with the upregulation of Hsp72 and Hsp27 protein expression.

7. Combination of Hsp inhibitors

The key, how to solve the problem of induced expression of heat shock proteins especially Hsp27 and Hsp70, after the treatment with Hsp90 inhibitors could be combined therapy of Hsp90 inhibitor and other Hsp inhibitors. Targeting multiple Hsps could likely shut down the heat shock response and associated rescue mechanisms, leading to low chemotherapeutic resistance (158). Dual therapy of combined Hsp inhibitors showed that Hsp27 inhibitors potentiate the effects of Hsp90 inhibitors and delay castrate-resistant prostate cancer (114,159) as well as sensitize breast cancer stem-like cells (148). Moreover, KNK437 a benzylidine lactam inhibitor of Hsp70, attenuated 17-AAG-mediated Hsp70 induction and increased 17-AAG-induced apoptosis and loss of clonogenic survival of HL-60 cells (160). The overexpression of Hsp70 induced by 17-AAG or NVP-AUY922 inhibitors in cancer cells was counteracted considerably when Hsp90 inhibitors are combined with the new type of chaperone inhibitor 1,6-dimethyl-3-propylpyrimido[5,4-e][1,2,4]triazine-5,7-dione (C9), which prevents Hsp90 from interacting with the cochaperone HOP (161). Very promising therapeutic option for cancer patients was reported by Ma *et al* (145), who targeted two chaperones Hsp90 and Hsp70 together with conventional anticancer drugs. Very similar combination of Hsp90 and Hsp70 inhibition with hyperthermia represented by ferromagnetic particles increased very effectively their antitumor effects *in vitro* as well as *in vivo* (162). For the future, it seems that the combinations of Hsp inhibitors applied with other therapies could serve as a potential solution to prevent the drug resistance and avoid the toxicity of high dose of Hsp90 inhibitors in clinical application.

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