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REVIEW

Combination therapy involving HSP90 inhibitors for combating cancer: an overview of clinical and preclinical progress

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Abstract

The molecular chaperone heat shock protein 90 (HSP90) regulates multiple crucial signalling pathways in cancer by driving the maturation of key signalling components, thereby playing a crucial role in tumorigenesis and drug resistance in cancer. Inhibition of HSP90 results in metastable conformational collapse of its client proteins and their proteasomal degradation. Considerable efforts have been devoted to the development of small-molecule inhibitors targeting HSP90, and more than 20 inhibitors have been evaluated in clinical trials for cancer therapy. However, owing to disadvantages such as organ toxicity and drug resistance, only one HSP90 inhibitor has been approved for use in clinical settings. In recent years, HSP90 inhibitors used in combination with other anti-cancer therapies have shown remarkable potential in the treatment of cancer. HSP90 inhibitors work synergistically with various anti-cancer therapies, including chemotherapy, targeted therapy, radiation therapy and immunotherapy. HSP90 inhibitors can improve the pharmacological effects of the above-mentioned therapies and reduce treatment resistance. This review provides an overview of the use of combination therapy with HSP90 inhibitors and other anti-cancer therapies in clinical and preclinical studies reported in the past decade and summarises design strategies and prospects for these combination therapies. Altogether, this review provides a theoretical basis for further research and application of these combination therapies in the treatment of cancer.

Keywords HSP90 inhibitors · Cancer therapy · Drug combination · Synergistic effect · Drug resistance

Introduction

Heat shock proteins (HSPs) are a family of evolutionarily conserved molecular chaperons. They are responsible for maintaining protein homeostasis and play an essential role in preventing misfolding and aggregation of proteins, stabilising the conformation of intracellular proteins, assisting the transmembrane transport of proteins, mediating the transport of proteins to target organelles, driving the assembly and degradation of oligomeric structures and degrading irreversibly damaged proteins in cells (Lang et al. 2021).

HSP90 is one of the most active molecular chaperones in cells. The HSP90 family has four members that are localised in different organelles. Inducible HSP90α and constitutive HSP90β are located in the cytosol, whereas GRP94 and TRAP1 are located in the endoplasmic reticulum (ER) and mitochondria, respectively. HSP90 contains three conserved regions as follows: (1) the N-terminal domain (NTD) containing an ATP-binding pocket known as the 'Bergerat fold' and a subdomain that binds co-chaperones, such as p50 and cdc37 (Smith et al. 2015); (2) the C-terminal domain (CTD)

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containing subdomains that form HSP90 dimers and sites for interaction with other co-chaperones (Donnelly and Blagg 2008); (3) the middle domain (MD), which is a stretch of highly charged amino acid sequences connecting the NTD and CTD (Ali et al. 2006).

Although HSP90 inhibitors hold great promise in the treatment of cancer, clinical trials have not demonstrated satisfactory results. Monotherapy with HSP90 inhibitors leads to complications such as organ toxicity and acquired drug resistance (Erlichman 2009). In recent years, combination therapy involving HSP90 inhibitors has emerged as an important strategy for treating cancer (Ren et al. 2022). In this review, we summarised the typical examples of the combined use of HSP90 inhibitors and other anti-cancer therapies in both clinical trials and preclinical experiments reported in the past decade. In addition, we discussed the rationale for using HSP90 inhibitors to increase the efficacy of other anti-cancer therapies and overcome drug resistance. These anti-cancer therapies include traditional chemotherapy, targeted therapy, radiotherapy and immunotherapy.

Role of HSP90 in cancer

HSP90 has received substantial attention from scholars owing to its role in the prevention of misfolding and degradation of several mutated and overexpressed oncoproteins. Consequently, it serves as a critical factor for oncogene addiction and cancer cell survival (Whitesell and Lindquist 2005; Hoter et al. 2018). HSP90 is responsible for stabilising and activating more than 400 client proteins that are involved in signal transduction, hormone response and transcriptional regulation in cells (Zhao et al. 2005; Schopf et al. 2017). The updated list of HSP90 clients is available on the Picard lab website (https://www.picard.ch/downloads/Hsp90interactors.pdf). The client proteins of HSP90 mediate tumour cell proliferation and survival as well as tumour angiogenesis, invasion and metastasis and are involved in the evolution of all hallmarks of cancer (Miyata et al. 2013). Cancer cells are vulnerable to proteotoxic stress, partly because the accumulation of mutant molecules may lead to cell death (Bagatell and Whitesell 2004). Under proteotoxic stress conditions, the transcription factor heat shock factor 1 (HSF-1) dissociates from HSP90 and initiates the transcription and expression of HSPs. Cancer cells require higher expression levels of HSP90 to govern protein homeostasis. HSP90 is upregulated in various cancers. Plasma HSP90 has been identified as a biomarker for the diagnosis of hepatocellular carcinoma and assessment of treatment efficacy (Wei et al. 2020). In addition, HSP90 has been associated with the aggressiveness or metastatic potential of cancer cells and regulates the immune response in cancer (Snigireva et al. 2014; Graner 2016).

Inhibition of HSP90 leads to the degradation of cancer-related client proteins via the ubiquitin–proteasome system, consequently disturbing multiple signalling pathways, and induces the apoptosis of cancer cells. The discovery of HSP90 inhibitors can be traced back to the identification of geldanamycin, a natural antibiotic, which competitively binds to the ATP-binding pocket in the NTD of HSP90 (Whitesell et al. 1994). When HSP90 encounters geldanamycin, the client protein dissociates from the HSP90 complex, and the chaperone cycle halts. Tanespimycin (17-AAG), a geldanamycin semi-synthetic derivative, was the first HSP90 inhibitor to enter clinical trials in 1999. In the past two decades, significant attempts have been made to identify HSP90 inhibitors with good pharmacodynamic and pharmacokinetic properties and acceptable safety profiles. To date, clinical trials have evaluated the therapeutic role of more than 20 HSP90 inhibitors in cancer. The discovery of HSP90 inhibitors has been well summarised and discussed in some excellent reviews (Li et al. 2020, 2021; Xiao and Liu 2020; Serwetnyk and Blagg 2021; Yu et al. 2022). The chemical structures of representative HSP90 inhibitors are shown in Fig. 1. HSP90 inhibitors used as monotherapy in clinical trials are summarised in Table 1. The data were retrieved from *clinicaltrials.gov*, and only trials that have been completed are presented.

Combination therapy involving HSP90 inhibitors in cancer treatment

In the past several years, numerous studies have attempted to evaluate the potential of combination therapy with HSP90 inhibitors and other anti-cancer therapies. A total of 28 clinical trials on 8 HSP90 inhibitors combined with other therapies are summarised in Table 2. Targeted small-molecule drugs represent the major class of drugs that are combined with HSP90 inhibitors. Other drugs include traditional chemotherapeutics, biological therapeutics and hormones.

HSP90 inhibitors can synergistically act with other anti-cancer drugs in different ways to enhance treatment outcomes. First, HSP90 inhibitors can degrade anti-cancer biological targets given that they are clients of HSP90. Second, HSP90 inhibitors block the cooperative signalling pathways and accelerate the apoptosis of cancer cells. Third, HSP90 inhibitors delay DNA repair, which may improve the therapeutic efficacy of DNA-targeting anti-cancer drugs. Fourth, HSP90 inhibitors can reverse immunosuppression in cancer cells and enhance immunotherapies. HSP90 inhibitors have been widely used to overcome drug resistance (Jhaveri and Modi 2012). Effective cancer therapy is often hampered by drug resistance during treatment (Vasan et al. 2019). Overexpression or mutation of biological targets is a major cause of resistance to conventional or targeted anti-cancer

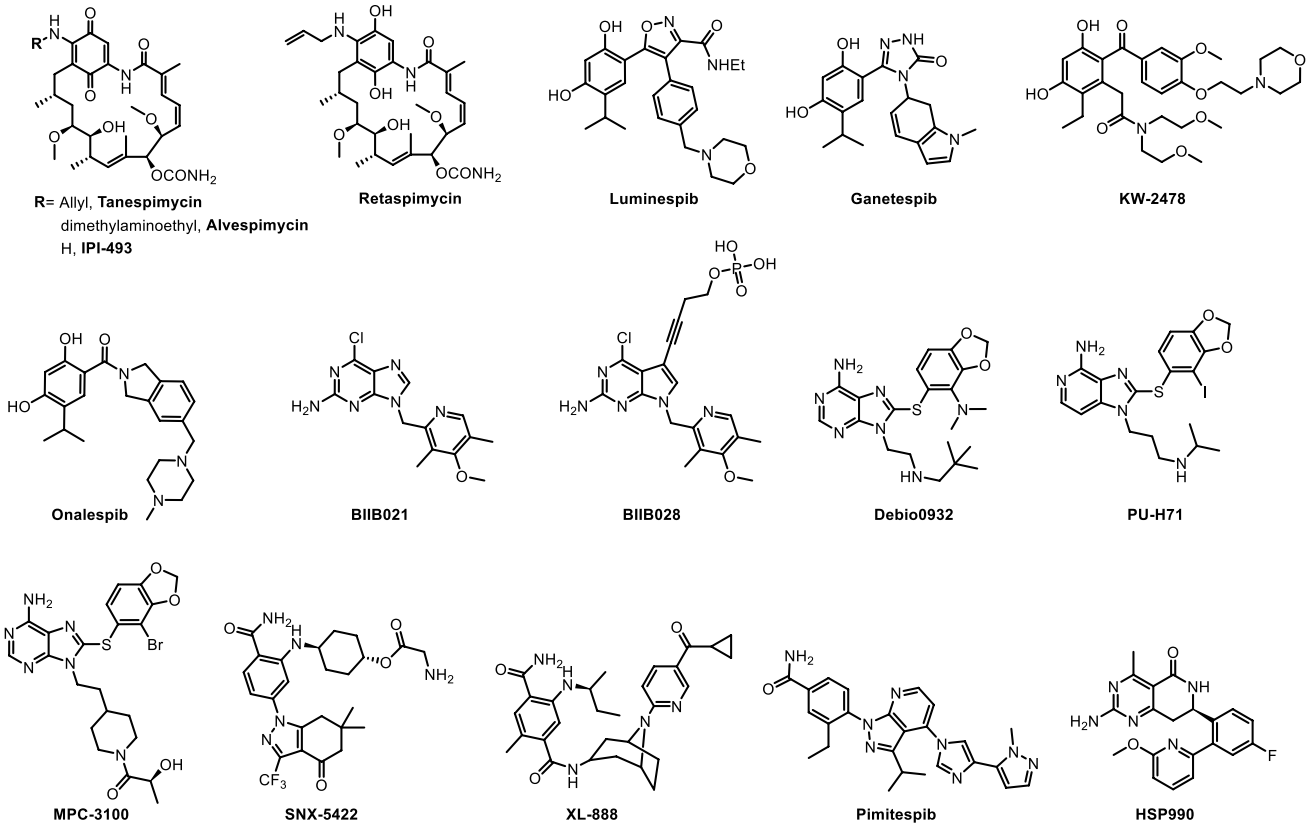

Fig. 1 Representative HSP90 inhibitors

drugs in many human cancers. Because many biological targets are clients of HSP90, inhibition of HSP90 leads to their degradation irrespective of whether they are mutated. The client proteins of HSP90 involved in drug resistance are well summarised in a review by Vergnaud-Gauduchon (Mathieu et al. 2019). Activation of bypass signalling often impairs the action of anti-cancer drugs, especially kinase inhibitors. HSP90 inhibitors can disrupt compensatory signalling pathways and restore the therapeutic potential of anti-cancer drugs. In addition, some drug resistance-related proteins in cancer cells have been identified as clients of HSP90; therefore, their depletion by HSP90 inhibitors is considered an effective strategy for overcoming the corresponding resistance.

Combination with HSP90 inhibitors in clinical trials

Pimitespib (TAS-116)

Pimitespib is an orally active HSP90 inhibitor that competitively binds to the ATP-binding site in the NTD of HSP90 (Uno et al. 2019). Pimitespib exhibits a stronger specific binding affinity for HSP90α and HSP90β than for the highly homologous HSP90 family members GRP94 and TRAP1. In 2022, pimitespib received its first approval in Japan for the treatment of gastrointestinal stromal tumour (GIST). Pimitespib exhibits strong anti-cancer activity in xenograft models without causing evident ocular toxicity in rats (Ohkubo et al. 2015). A phase I study revealed that pimitespib had an acceptable safety profile with potent anti-tumour activity in patients with advanced solid tumours, including those with heavily pre-treated GIST (Shimomura et al. 2019). In a phase II study, pimitespib exerted significant therapeutic effects against advanced GIST that was refractory to standard treatment with imatinib, sunitinib and regorafenib (Doi et al. 2019). The median progression-free survival (PFS) was 4.4 months, and the 12-week progression-free rate was 73.4%. Treatment-related adverse events were observed in all patients; however, they can be resolved via dose modification. In phase III trials of pimitespib, patients with previously treated GIST had significantly prolonged PFS when compared with patients treated with a placebo (Honma et al. 2021; Kurokawa et al. 2022; Sawaki et al. 2022).

Imatinib is an oral tyrosine receptor kinase inhibitor targeting PDGFR, c-KIT, BCR/ABL and v-ABL (Cohen et al. 2021). It has been approved for the treatment of Ph-positive

Table 1 Monotherapy with HSP90 inhibitors in the clinical trials

Entry	HSP90 inhibitors	Conditions	Phase	Registration no
1	Ganetespib	Leukemia	I	NCT00964873
2	Ganetespib	Solid tumors	I	NCT00687934
3	Ganetespib	Hematologic malignancies	I	NCT00858572
4	Ganetespib	Colon cancer Rectal cancer	I	NCT01111838
5	Ganetespib	Hepatocellular carcinoma	I	NCT01665937
6	Ganetespib	Non small cell lung cancer	II	NCT01031225
7	Ganetespib	Ocular melanoma	II	NCT01200238
8	Ganetespib	$HER2^+$ or triple negative breast cancer	II	NCT01677455
9	Ganetespib	Small cell lung cancer	II	NCT01173523
10	Ganetespib	Metastatic hormone-resistant prostate cancer	II	NCT01270880
11	Ganetespib	Advanced esophagogastric cancer	II	NCT01167114
12	Luminespib	Gastrointestinal stromal tumor	II	NCT01404650
13	Luminespib	Non small cell lung cancer	II	NCT01752400 NCT01124864
14	Luminespib	Advanced solid tumors	I	NCT01132625
15	Luminespib	Breast cancer, hematologic neoplasms	I/II	NCT00526045
16	Onalespib	Refractory solid tumors	I	NCT01246102
17	Onalespib	Metastatic solid tumors	I	NCT00878423
18	SNX-5422	Refractory solid tumor malignancies	I	NCT00506805 NCT01611623
19	SNX-5422	Hematologic neoplasms	I	NCT00595686
20	SNX-5422	Neuroendocrine tumors	I	NCT02063958
21	SNX-5422	Resistant lung adenocarcinoma	I	NCT01851096
22	SNX-5422	Solid tumor cancers and lymphomas	I	NCT00644072
23	SNX-5422		I	NCT00647764
24	SNX-5422	Refractory hematological malignancies	I	NCT01635712
25	BIIB021	Advanced solid tumors	I	NCT00345189
26	MPC-3100	Refractory or relapsed cancer	I	NCT00920205
27	Pimitespib	Advanced solid tumors	I	NCT02965885
28	HSP990	Advanced solid malignancies	I	NCT00879905
29	BIIB028	Advanced solid tumors	I	NCT00725933
30	Debio 0932(CUDC-305)	Solid tumors or lymphoma	I	NCT01168752
31	Alvespimycin	Advanced solid tumor or lymphoma	I	NCT00088868
32	PU-H71	Advanced malignancies	I	NCT01393509
33	Retaspimycin	Lung cancer	I/II	NCT00431015

chronic myeloid leukaemia (CML) and GIST. Mutations in *KIT* or *PDGFRA* block the clinical activity of imatinib against GIST. Both KIT and PDGFRA are clients of HSP90 and can be downregulated by HSP90 inhibitors. Therefore, the combination of an HSP90 inhibitor and imatinib is considered an effective strategy for overcoming imatinib resistance in GIST. Saito et al. reported that pimitespib inhibited the growth of both imatinib-resistant GIST cell lines and EGFR-mutated lung cancer cell lines (Saito et al. 2020). Recently, a phase I study has been initiated to investigate the effects of pimitespib combined with imatinib in 78 patients with advanced GIST refractory to imatinib (NCT05245968).

Nivolumab is a human monoclonal antibody that targets programmed cell death-1 ligand 1 (PD-L1) and blocks its interaction with programmed cell death-1 (PD-1) (Sharma and Allison 2015). The Food and Drug Administration (FDA) has approved nivolumab for the treatment of metastatic non-small cell carcinoma, metastatic melanoma, relapsed Hodgkin's lymphoma, metastatic head and neck cancer (HNC) and advanced renal cell carcinoma. However, nivolumab does not benefit patients with microsatellite-stable (MSS) or mismatch repair (MMR)–proficient colorectal cancer (CRC) (Hirano et al. 2021). Regulatory T cells are reported to induce resistance to anti-PD1/PD-L1 inhibitors by inhibiting effective anti-tumour immunity (Togashi et al. 2019). Pimitespib can degrade the signal transducer and activator of transcription 5 (STAT-5) and reduce the regulatory

Table 2 Combination therapies with HSP90 inhibitors in clinical trials

Entry	Combination therapy	Conditions	Phase	Registration no
1	**Luminespib/**alpelisib	Advanced or metastatic gastric cancer	I	NCT01613950
2	**Luminespib/**capecitabine	Metastatic or unresectable solid tumor malignancy	I	NCT01226732
3	**Luminespib/**pemetrexed disodium	Recurrent NSCLC; squamous cell lung cancer; Stage IV non-small cell lung cancer	I	NCT01784640
4	**Luminespib/**cetuximab	KRAS wild-type metastatic colorectal cancer	I	NCT01294826
5	**Luminespib/**erlotinib hydrochloride	Adenocarcinoma of the lung; non-small cell lung cancer	I/II	NCT01259089
6	**Luminespib/**bortezomib/dexamethasone	Relapsed or refractory multiple myeloma	I/II	NCT00708292
7	**Luminespib/**trastuzumab	Advanced HER2-positive breast cancer	I/II	NCT01271920
8	**Luminespib/**bortezomib/dexamethasone	Relapsed or refractory multiple myeloma	I/II	NCT00708292
9	**Ganetespib/**carboplatin/paclitaxel/radiation	Esophageal cancer	I	NCT02389751
10	**Ganetespib/**docetaxel	Solid tumor malignancies	I	NCT01183364
11	**Ganetespib/**paclitaxel/trastuzumab/pertuzumab	Metastatic HER2 positive breast cancer	I	NCT02060253
12	**Ganetespib/**pemetrexed/cisplatin (carboplatin)	Pleural mesothelioma	I	NCT01590160
13	**Ganetespib/**plerixafor/quizartinib	Acute myeloid leukaemia; high risk myelodysplastic syndrome	I/II	NCT01236144
14	**Ganetespib/**paclitaxel	Platinum-resistant epithelial ovarian cancer	I/II	NCT02012192
15	**Ganetespib/**paclitaxel	Refractory sarcomas and MPNSTs	I/II	NCT02008877
16	**Ganetespib/**standard chemotherapy	Breast cancer	II	NCT01042379
17	**Ganetespib/**docetaxel	Non-small cell lung cancer	II/III	NCT01348126
18	**Onalespib/**olaparib	Advanced solid tumor	I	NCT02898207
19	**Onalespib/**abiraterone acetate/prednisone (prednisolone)	Castration-resistant prostate cancer	I/II	NCT01685268
20	**Onalespib/**imatinib	Gastrointestinal stromal tumor	II	NCT01294202
21	**Onalespib/**crizotinib	Non-small cell lung cancer	I/II	NCT01712217
22	**Onalespib/**AT7519	Advanced solid tumor	I	NCT02503709
23	**Pimitespib/**imatinib/sunitinib	Gastrointestinal stromal tumor	I	NCT05245968
24	**Pimitespib/**nivolumab	Colorectal cancer; solid tumor	II	EPOC1704
25	**XL888/**vemurafenib	Advanced $BRAF^{V600E}$-mutant melanoma	I	NCT01657591
26	**SNX-5422/**carboplatin/paclitaxel	Advanced non-small cell lung cancer and small cell lung cancer	I	NCT01892046
27	**KW-2478/**bortezomib	Relapsed/refractory multiple myeloma	I/II	NCT01063907
28	**Tanespimycin/**bortezomib	Multiple myeloma in first relapse (BMS TIME-1)	III	NCT00546780

T cells to enhance the anti-tumour activity of anti-PD1/PD-L1 inhibitors. Therefore, the combination of pimitespib and anti-PD1/PD-L1 inhibitors is considered an effective strategy for the treatment of cancer. The maximum tolerated dose and recommended phase II dose of the combination of pimitespib and nivolumab were evaluated in a dose-discovery and -expansion phase Ib trial (Kawazoe et al. 2021). A total of 44 patients with CRC and other solid tumours were enrolled in this trial. Dose-limiting toxicity was not observed at any dose level. The trial revealed that the combination of 160 mg pimitespib plus nivolumab had a manageable safety profile and antitumour activity, especially in MSS CRC, with an objective response rate (ORR) of 16%.

Onalespib (AT13387)

Onalespib, a resorcinol-derived HSP90 inhibitor, has a strong affinity for HSP90α (Woodhead et al. 2010). A first-in-human phase I dose-escalation study revealed that onalespib had an acceptable safety profile and exhibited linear pharmacokinetic properties and preliminary antitumour activity (Shapiro et al. 2015). HSP70 induction was observed as proof of target engagement. Notably, the unfavourable hepatotoxicity of the first-generation ansamycin class of HSP90 inhibitors that hampered their clinical development has not been observed in studies on onalespib. Moreover, dose-limiting toxicity has not been observed with a once-weekly regimen. In another phase I clinical

trial, no responses were observed in 31 patients with various advanced solid tumours (Do et al. 2015). However, 8 patients had stable disease for > 2 cycles, and 1 patient with hepatocellular carcinoma remained under observation for six cycles.

AT7519, a pan-inhibitor of cyclin-dependent kinases (CDKs), exhibits anti-tumour activity in patients with advanced solid tumours, chronic lymphocytic leukaemia and mantle cell lymphoma (Wyatt et al. 2008). Do et al. reported that AT7519 inhibited the compensatory expression of HSP70 induced by onalespib (Do et al. 2020). They conducted a phase I clinical trial of onalespib combined with AT7519 in patients with advanced solid tumours. Plasma analysis revealed an increase in HSP70 expression after treatment with onalespib alone and a decrease in HSP70 expression after treatment with the combination of onalespib and AT7519. Therefore, AT7519 may overcome the acquired drug resistance to HSP90 inhibitors caused by heat shock response, providing a rationale for combining AT7519 with HSP90 inhibitors. Partial responses were observed in a palate adenocarcinoma and Sertoli–Leydig tumor; a colorectal and an endometrial cancer patient remained on study for 10 cycles with stable disease as the best response. Most adverse effects accounted for grades 1 and 2 (92.3%), followed by grade 3 (7%) and grade 4 (0.7%). In addition, no clinically relevant pharmacokinetic interactions were observed for either drug. In a later work, the El-Deiry group discovered that co-inhibition of CDK and HSP90 resulted in the destabilisation of hypoxia-inducible factor-1α (HIF-1α) and showed a synergistic effect on reducing the viability of cancer cells (Zhao et al. 2021).

Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that has been approved for the treatment of patients with advanced ovarian cancer and human epidermal growth factor receptor 2 (HER2)-negative breast cancer with deleterious germline BRCA mutation (gBRCAm), who have been previously treated with chemotherapy (Paik 2021). Olaparib has shown remarkable anti-tumour activity in homologous recombination (HR)-deficient cancers but not in HR-proficient cancers (Parsels et al. 2021). Choi et al. (2014) identified the HSP90 inhibitor tanespimycin as a suppressor of HR based on a connectivity map. They found that it enhanced sensitivity to olaparib and carboplatin in HR-proficient ovarian cancer cells, suggesting a rational combination of HSP90 inhibitors and olaparib. Konstantinopoulos et al. conducted a phase I clinical trial of onalespib combined with olaparib in patients with advanced solid tumours (Konstantinopoulos et al. 2022) Although no objective responses were observed, disease stabilisation for ≥ 24 weeks was observed in 7/22 (32%) patients, including those with BRCA-mutated ovarian cancer and acquired resistance to PARP inhibitors and those with tumours harbouring alterations in the retinoblastoma pathway. Dose-limiting toxicity was not observed in patients treated with 300 mg olaparib/40 mg onalespib and 200 mg olaparib/80 mg onalespib. Pharmacokinetic analysis revealed that co-administration of olaparib and onalespib did not affect the steady-state pharmacokinetic behaviour of either agent.

Abiraterone is an inhibitor of 17α-hydroxylase/C17, 20-lyase (CYP17) that has been approved for the treatment of castration-resistant prostate cancer (CRPC) in combination with prednisone. Resistance to abiraterone is attributed to the increased expression of androgen receptor (AR), the expression of alternatively spliced AR and somatic point mutations (Rice et al. 2019). Therefore, alternative strategies that can effectively target both persistent full-length AR (AR-FL) and AR splice variants should be developed for the treatment of CRPC. Onalespib can effectively deplete both AR-FL and AR-V7 protein, thereby inhibiting the growth of 22Rv1 (CRPC) cells expressing AR-V7 and VCaP cells overexpressing AR-FL (Ferraldeschi et al. 2016). These results indicate that the depletion of AR-FL and AR-V7 by HSP90 inhibitors can benefit CRPC. Therefore, future studies should investigate the efficacy of the combination of HSP90 inhibitors and abiraterone in the clinical treatment of advanced CRPC. However, in the phase I/II clinical trial, the combination of onalespib and abiraterone with either prednisone or prednisolone was not found to benefit patients with CRPC (Slovin et al. 2019). No patient showed an objective or prostate-specific antigen response in either regimen. Moreover, circulating tumour cell counts declined transiently and increased rapidly after treatment, suggesting that HSP90 inhibition was not effective in blocking the AR signalling pathway and inducing the apoptosis of cancer cells.

Like other HSP90 inhibitors, onalespib has been demonstrated to be effective in overcoming imatinib resistance in GIST. In a dose-escalation phase I study, the combination of onalespib and imatinib was well tolerated in patients with TKI-resistant metastatic GIST (Wagner et al. 2016). In particular, 9 (35%) patients, including 2 patients with KIT mutations, had stable disease, which was considered the best response. Disease control was achieved at 4 months in 5 patients (19%), and the median PFS period was 112 days. In addition, 1 patient with PDGFRA-mutant GIST had a partial response for more than 376 days. The highest dose of onalespib in combination with imatinib in patients with normal baseline renal function was 220 mg/m^2 once weekly for 3 weeks of every 4-week cycle. Approximately 81% of patients reported > 1 onalespib-related gastrointestinal disorder.

Small-molecule BRAF inhibitors, such as vemurafenib and dabrafenib, lead to rapid and effective responses in patients with metastatic melanoma; however, resistance resulting in therapeutic escape is common (Savoia et al. 2020). Relapse is often caused by the recovery of signalling in the MAPK and/or PI3K/AKT pathway (Shi et al.

2014). Since many key drivers in both signalling pathways are known as the clients of HSP90, inhibition of HSP90 is considered a promising strategy for overcoming resistance to BRAF inhibitors. Both N-terminal and C-terminal inhibitors of HSP90 have been shown in preclinical investigations to reverse the resistance to BRAF and BRAF-MEK inhibitors and delay the onset of BRAF inhibitor resistance (Paraiso et al. 2012; Smyth et al. 2014; Sanchez et al. 2021; Sasame et al. 2022). The safety and efficacy of onalespib, in combination with dabrafenib and trametinib (a MEK inhibitor), were examined in a recent Phase I study by the Mooradian group in $BRAF^{V600E/K}$-mutant solid tumors (Mooradian et al. 2023). In this study, twenty-two patients with metastatic, $BRAF^{V600E}$-mutant solid tumors were enrolled. With an overall response rate of 9.5%, a disease control rate of 47.6%, and a median overall survival of 5.1 months, two patients had a partial response and eight had stable disease. Dose-limiting toxicities were myelosuppression and fatigue that occurred in two patients at high dose levels, respectively.

Ganetespib (STA-9090)

Ganetespib is an injectable second-generation small-molecule inhibitor of HSP90. It exhibits a favourable safety profile and does not cause ocular and liver toxicities associated with the use of first-generation ansamycin-type HSP90 inhibitors and some second-generation HSP90 inhibitors (Proia and Bates 2014). In a Phase II study, ganetespib administered once weekly was well tolerated in patients with heavily pre-treated advanced GIST, with no evidence of severe liver, ocular, cardiac or renal toxicity (Demetri et al. 2011). In other phase II clinical trials, ganetespib showed controllable toxicity in previously treated patients with advanced oesophageal gastric cancer and patients with refractory metastatic CRC (Kwak et al. 2013; Cercek et al. 2014).

Pemetrexed, an antifolate drug, inhibits several key enzymes, including dihydrofolate reductase (DHFR), thymidylate synthetase (TS) and glycinamide ribonucleotide formyltransferase (GARFT) in the folate metabolic pathway (Rossi et al. 2018). It significantly affects DNA synthesis in cancer cells and inhibits cancer growth. Combination chemotherapy with pemetrexed and cisplatin is a standard treatment strategy for pleural mesothelioma (PM); however, the median overall survival (OS) is only approximately 12 months. Oncogenic kinases such as AXL and MET, which are involved in the progression of PM, are clients of HSP90. In addition, TS is also a client of HSP90 and has been associated with pemetrexed activity and antifolate resistance (Abu Lila et al. 2016). Therefore, the combined use of pemetrexed and HSP90 inhibitors may lead to synergistic anti-tumour effects and help to overcome drug resistance. In phase I clinical trial, combination therapy with ganetespib, pemetrexed and cisplatin/carboplatin was well-tolerated in patients with PM, with evident anti-tumour activity, particularly at the recommended dose of 200 mg/m^2 (Fennell et al. 2018). The partial tumour response rate was 61%. Among 27 patients, 7 patients had tumour burden reduction of > 50%, and 1 patient remained progression-free even after 37 months.

Taxanes, such as paclitaxel (Taxol) and its derivative docetaxel, are widely used chemotherapeutic drugs. They inhibit tubulin depolymerisation and are widely used in the treatment of various solid tumours, including breast, prostate, gastric, head and neck, ovarian and pancreatic cancers and non-small cell lung cancer (NSCLC) (Mosca et al. 2021). Nguyen et al. reported that tanespimycin led to a 5–22-fold increase in the cytotoxicity of paclitaxel in the lung cancer cell line H358 (Nguyen et al. 2001). The combination of tanespimycin and paclitaxel effectively suppressed tumour growth in vivo and significantly prolonged the survival of mice bearing H358 xenografts. Tanespimycin downregulated the expression of mutant EGFR and p53, and reduced microvasculature, thus increasing the sensitivity of tumours to taxanes. Ray-Coquard et al. completed the first clinical trial potentially targeting stabilized mutant gain-of-function p53 protein via the mechanism of depletion by HSP90 inhibition (Ray-Coquard et al. 2019). In the phase I/II trial in women with high-grade platinum-resistant epithelial ovarian cancer, administration of ganetespib combined with paclitaxel was found to be safe. Of the 10 enrolled patients, 2 patients achieved a partial response with an ORR of 20% and 4 patients had stable disease (disease control rate of 60%). In addition, no ocular or liver toxicity was observed in the 10 patients. Lang et al. evaluated ganetespib in combination with standard chemotherapy in patients with high-risk early-stage breast cancer (Lang et al. 2022). A total of 93 patients with HER2-negative breast cancer were administered ganetespib every 3 weeks with weekly paclitaxel over 12 weeks, followed by doxorubicin. In the overall study population, ganetespib exhibited limited clinical efficacy in hormone receptor-positive early-stage breast cancer. The final estimated pathological complete response rates were 26% versus 18% in patients with HER2-negative cancer, 38% versus 22% in patients with HR-negative/HER2-negative cancer and 15% versus 14% in HR-positive/HER2-negative cancer in the ganetespib versus the control group, respectively. None of the 18 tested biomarkers (including HSP90, GR/efflux, proliferation, DNA repair and immune biomarkers) was significantly associated with pathological complete response in HER2-negative breast cancer. This suggests HSP90 inhibitors may serve as potential anti-cancer agents in other clinical settings such as HER2-positive disease or in combination with anti-PD1 neoadjuvant chemotherapy in triple-negative breast cancer. In a phase II clinical study, Ramalingam et al. evaluated the combination of ganetespib

and docetaxel for the second-line treatment of 381 patients with advanced NSCLC (Ramalingam et al. 2015). Although no efficacy was observed in non-adenocarcinoma patients, PFS (4.5 months) and OS (10.2 months) were significantly prolonged in advanced lung adenocarcinoma patients after > 6 months of diagnosis of advanced disease. In addition, the combination therapy exhibited an acceptable safety profile, as ganetespib did not increase adverse events compared with docetaxel alone. The subsequent phase III trial included 677 patients with stage IIIB or IV adenocarcinoma; 335 were randomly assigned to ganetespib and docetaxel, while 337 received docetaxel alone (Pillai et al. 2020). However, this combination regimen did not improve the survival for salvage therapy of patients. The most common grade 3 or 4 adverse event in both arms was neutropenia.

Sirolimus (Rapamune), a macrocyclic antibiotic with immunosuppressive activity, was approved in 1999 for use in patients undergoing organ transplantation. Recently, it has received substantial attention owing to its potential as an anti-cancer drug. As an inhibitor of the mammalian target of rapamycin (mTOR), sirolimus prevents the propagation of IL-2-mediated cell proliferation signalling through the PI3K/AKT/mTOR pathway (Namba et al. 2006). De Raedt et al. (2011) reported that malignant peripheral nerve sheath tumours (MPNST) are hypersensitive to ER stress-inducing agents (De Raedt et al. 2011). Considering that HSP90 inhibitors can enhance ER stress in cancer cells, they tested the combination of IPI-504, an HSP90 inhibitor, and sirolimus in aggressive mouse models. The two drugs exerted synergistic effects by promoting unresolvable ER stress, resulting in catastrophic damage to ER and mitochondria. Based on this result, a phase I/II clinical trial was conducted to examine the efficacy of ganetespib combined with sirolimus in 20 patients with refractory sarcoma and MPNST (Kim et al. 2020a, b). Ganetespib was intravenously administered, and sirolimus was orally taken. The most common adverse reactions were diarrhoea, elevated liver transaminase levels and fatigue, which were not attributed to dose-limiting toxicity. Although the combination was well tolerated and toxicity was manageable, no responses were observed.

XL888

XL888, an oral HSP90 inhibitor with a good kinase selectivity profile, can significantly inhibit the activity of HSP90 and exert minimal inhibitory effects against 29 other diverse kinases (Bussenius et al. 2012). Preclinical studies have revealed that XL888 is a good candidate for the treatment of melanoma, advanced pancreatic cancer/CRC and liver cancer (Haarberg et al. 2013). A phase I study evaluating the safety and pharmacokinetic properties of XL888 in adult patients with solid tumours was initiated in 2015 but terminated 3 years later. At present, several clinical trials are actively investigating the combination of XL888 and other anti-cancer drugs.

Eroglu et al. initiated a clinical study to evaluate the combination of vemurafenib and XL888 in 21 patients with advanced $BRAF^{V600E}$-mutant melanoma (Eroglu et al. 2018). Objective responses were observed in 15 of 20 evaluated patients, with 3 patients demonstrating a complete response and 12 patients demonstrating a partial response. The median PFS and OS were 9.2 months and 34.6 months, respectively. The side effects were tolerated, and the most common grade-3/4 toxicity was skin toxicity.

SNX-5422

SNX-5422 is an oral prodrug of SNX-2112, a highly selective inhibitor targeting HSP90 (Huang et al. 2009). SNX-5422 has been investigated in clinical trials in patients with various cancers, including those with HER2-positive breast cancer, neuroendocrine tumour, resistant lung adenocarcinoma and refractory haematological malignancies. In phase I clinical trials, the preliminary clinical activity of SNX-5422 has been validated in patients with prostate cancer, HER2-positive breast cancer, transformed lymphoma and multiple myeloma (Rajan et al. 2011; Reddy et al. 2013; Infante et al. 2014). However, ocular toxicity has been observed in patients and animal models treated with SNX-5422, preventing further investigation of SNX-5422 as a monotherapy for cancer.

Friedman et al. reported that SNX-5422/-2112 exhibited synergistic activity with carboplatin and paclitaxel in HSP90-overexpressing head and neck squamous cancer cell lines (Friedman et al. 2013). Gutierrez et al. conducted a phase I clinical trial to evaluate the therapeutic efficacy of the combination of SNX-5422, carboplatin and paclitaxel followed by SNX-5422 maintenance therapy in 23 patients with advanced NSCLC (n = 20) and SCLC (n = 3) (Gutierrez et al. 2021). The combination therapy was well tolerated and exerted synergistic effects. A total of 6 patients with NSCLC had a partial response (33%), 10 patients had stable disease (56%) and 2 patients had primary progressive disease (11%). The most common treatment-related grade-3/4 adverse events were gastrointestinal reactions including diarrhoea and nausea. More importantly, ocular toxicity was not observed.

KW-2478

KW-2478 is an HSP90 inhibitor with high binding affinity and potent anti-tumour activity. In a phase I clinical trial on patients with B-cell malignancies, 24 of the 25 (96%) evaluated patients had stable disease, with 5 patients being free of disease progression for ≥ 6 months (Yong et al. 2016). In

addition, KW-2478 was well tolerated, with no evidence of DLT or unexpected toxicity.

Bortezomib is an FDA-approved proteasome inhibitor used for the treatment of multiple myeloma and mantle cell lymphoma (Tan et al. 2019). Inhibition of the proteasome with bortezomib leads to the accumulation of immunoglobulin-derived defective ribosomal products, known as misfolded/unfolded protein response (UPR), which causes apoptosis owing to extensive ER stress (Meister et al. 2007). Because HSP90 inhibitors can induce the accumulation of misfolded/unfolded proteins, they are supposed to enhance the anti-myeloma activity of bortezomib. Several preclinical studies have reported the synergistic anti-cancer activity of HSP90 inhibitors and bortezomib in multiple myeloma (Wright 2010). In a phase I/II clinical trial, the combination of KW-2478 and bortezomib was well tolerated in patients with relapsed/refractory multiple myeloma, with no evidence of overlapping toxicity (Cavenagh et al. 2017). The overall response rate was 39.2% and the clinical benefit rate was 51.9% in the evaluated population (n = 79). The median PFS and duration of response were 6.8 months and 5.6 months, respectively. The anti-myeloma activity of the combination therapy appeared relatively modest; however, the good tolerability of this combination may support further exploration of dosing schedules and other combinations.

Combination of HSP90 inhibitors in preclinical studies

Chemotherapeutics

Chemotherapeutic drugs usually kill cancer cells by targeting their DNA synthesis and replication, representing an essential strategy for the treatment of cancer. However, chemotherapy response is often limited by new or acquired drug resistance. Because many DNA repair-related proteins serve as HSP90 clients, HSP90 inhibitors can disrupt double-strand break repair and sensitise tumours to chemotherapeutic drugs (Pennisi et al. 2016).

Cisplatin

Platinum-based anti-cancer agents induce both intra- and inter-strand crosslinks in DNA through covalent interaction with the nucleophilic N-7 atom of the purine base (Sikov 2015). These crosslinks inhibit DNA synthesis by preventing RNA polymerase II from passing the site of the DNA adduct. The combination with HSP90 inhibitors has been demonstrated as an effective strategy for enhancing the therapeutic potential of cisplatin. Preclinical studies have demonstrated that the combination of cisplatin and HSP90 inhibitors induces DNA damage response and decreases cell viability in diffuse large B-cell lymphoma (DLBCL), ovarian cancer and HNC.

Although many patients with DLBCL achieve long-term remission after first-line treatment with platinum-based drugs, nearly 40% of these patients develop refractory disease or relapse after the initial remission (Vaidya and Witzig 2014). Tanespimycin, a first-generation HSP90 inhibitor, has been reported to enhance the anti-neoplastic effects of cisplatin in seven DLBCL cell lines (Schmidt et al. 2022). These synergistic effects were mediated by induced DNA damage, leading to increased levels of apoptosis. Cell lines with the lowest sensitivity to cisplatin treatment (e.g. RIVA, OCI-Ly7 and DB) exhibited the strongest response to the drug combination, suggesting that patients with cisplatin-resistant tumours can benefit from inhibition of HSP90.

Zhang et al. reported that exposure to three HSP90 inhibitors, including geldanamycin, tanespimycin and alvespimycin, in combination with cisplatin resulted in synergistic cytotoxic and pro-apoptotic effects on the human ovarian cancer cell line SKOV3 (Zhang et al. 2015). This combination led to a > 2-fold decrease in the resistance of SKOV3 cells to cisplatin. The mRNA and protein expression levels of various drug resistance-related genes were more dramatically altered by combination therapy than by monotherapy with HSP90 inhibitors or cisplatin. Moita et al. found that HSP90 inhibitors luminespib and HSP990 considerably improved the cisplatin potency in ovarian cancer cell lines (A2780, CaOV3, OVCAR3 and cisplatin-resistant subclones) via apoptosis induction (Rodrigues Moita et al. 2020). Triple combinations of histone deacetylase (HDAC) inhibitor, HSP90 inhibitor and cisplatin, however, did not outperform dual combinations.

The Spiegelberg group demonstrated that the HSP90 inhibitor onalespib enhanced the efficacy of cisplatin and reversed cisplatin resistance in ovarian and head and neck cancer cells (Mortensen et al. 2020). This combination delayed DNA repair as evidenced by an increase in the number of double-strand breaks in cells co-treated with cisplatin and onalespib. In addition, the Dobbelstein group reported the synergistic effects of cisplatin and onalespib in both in vitro and in vivo models of cisplatin-resistant pancreatic ductal adenocarcinoma (Ewers et al. 2021). These synergistic effects were attributed to the HSP90 inhibitor-induced degradation of factors involved in the Fanconi anaemia pathway, the increased DNA damage and chromosome fragmentation and the enhanced accumulation of DNA-bound platinum.

Mouse double minute X (MDMX) binds to the N-terminal region of p53 or heterodimerises with its homologue MDM2 by interacting with its C-terminal domain to augment p53 degradation (Marine et al. 2006). Tanespimycin can destabilise MDMX and inhibit the interaction between MDMX and p53, resulting in the activation of the p53

signalling pathway and inhibition of cancer cell survival pathways, such as PI3K/AKT (Vaseva et al. 2011). Roh et al. demonstrated that tanespimycin and cisplatin exerted synergistic anti-tumour effects on HNC cells (Roh et al. 2013). Tanespimycin effectively activated and stabilised p53, inhibited the interaction between p53 and MDMX and induced the apoptosis of HNC cells.

5-Fluorouracil

5-FU, a nucleotide analogue, inhibits TS and blocks the synthesis of 2′-deoxythymidine-5′-monophosphate (dTMP) (Chon et al. 2017). Although 5-FU is widely used in the treatment of various cancers, its clinical application is limited owing to drug resistance. The El-Rayes group hypothesised that HSP90 inhibition can sensitise CRC cells to 5-FU through downregulation of TS and disruption of proliferation-related signalling pathways (Nagaraju et al. 2014). Ganetespib decreased the RNA and protein expression levels of cyclin D1 and pRb and induced p21 expression, leading to G_0/G_1 cell cycle arrest in the CRC cell lines HCT-116 and HT-29. This effect was associated with the downregulation of the transcription factor E2F1 and its target gene TS. In addition, ganetespib inhibited the PI3K/AKT and ERK signalling pathways in CRC cells, and the combination of ganetespib, oxaliplatin and 5-FU exhibited synergistic antitumour activity in both CRC cells and animal models.

Trabectedin

Trabectedin, a minor groove DNA double helix inhibitor, is used as second line therapy for myxoid liposarcoma (MLS). According to the Aman group's work, HSP90 inhibitors 17-DMAG, luminespib and STA-9090 showed synergistic effect with trabectedin in vitro (Vannas et al. 2022). In an MLS patient-derived xenograft model, 17-DMAG inhibited the tumor growth, but surprisingly, luminespib caused an increase in tumor growth.

Methotrexate

Numerous diseases, including cancer, autoimmune diseases, and rheumatoid arthritis have been successfully treated with methotrexate. The Hussain and Lila group discovered that ganetespib acted synergistically with methotrexate against A549 cells (Subaiea et al. 2023). They demonstrated that the combination of ganetespib and methotrexate inhibited the migration and invasion of A549 cells via obstruction of the NF-kB signalling pathway. Additionally, their work showed this combination synergistically augmented the ROS production, and induced caspase activation and nuclear condensation and fragmentation in A549 cells.

Targeted anti-cancer agents

Kinase inhibitors

Epidermal growth factor receptor (EGFR), a member of the HER family, is a transmembrane receptor tyrosine kinase. EGFR alternations, including amplification of the EGFR gene and point mutations within the kinase-coding domain of EGFR, have been detected in many cancers, including lung, colorectal, ovarian and breast cancers and glioblastoma (Sabbah et al. 2020). The first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) gefitinib, lapatinib erlotinib, icotinib, afatinib and dacomitinib have advantages over various platinum-based chemotherapeutic drugs for the treatment of patients with advanced NSCLC with EGFR mutation. However, most patients treated with EGFR TKIs inevitably develop acquired resistance through multiple mechanisms after a median period of 10–14 months (Sequist et al. 2011). EGFR mutation in exon 20 (T790M) and c-MET amplification are responsible for acquired resistance to EGFR TKIs (Chong and Jänne 2013; He et al. 2021). The T790M mutation accounts for approximately 50% of these resistance cases. In addition, c-MET amplification can transactivate ERBB3 (HER3), resulting in PI3K activation independent of EGFR kinase activity. Combining HSP90 inhibitors with EGFR inhibitors is a promising therapeutic strategy for EGFR inhibitor-resistant NSCLC because HSP90 inhibitors can deplete various receptor tyrosine kinases, including EGFR, and inhibit the entire EGFR–PI3K–AKT–mTOR–p70S6K–S6 signalling axis irrespective of the presence of the T790M mutation (Shimamura et al. 2008). Codony-Servat et al. demonstrated that osimertinib and HSP90 inhibitors, ganetespib and luminespib, synergistically inhibited the growth of NSCLC cell lines and osimertinib-resistant cell lines, indicating that combination therapy is a promising strategy for overcoming osimertinib resistance (Codony-Servat et al. 2019). Luminespib decreased the protein expression of membrane receptors, such as EGFR, STAT3, MET, YAP and AKT, and reduced the phosphorylation of several membrane receptors activated by osimertinib. The Ye and Xu group found that ganetespib was able to reverse the development of lapatinib resistance in HER2-positive breast cancer cells (Ye et al. 2021). Ganetespib and lapatinib synergistically decreased the expression of HER2/3, EGFR, AKT and ERK, and enhanced the induction of apoptosis and G1 arrest. Additionally, this combination led to the depletion of STAT3, which is probably involved in the lapatinib resistance of HER2-positive breast cancer cells. In both SKBR3 and SKBR3-L xenografts, ganetespib augmented the inhibition of tumor growth. The Park group reported that HSP90 was involved in the lapatinib resistance mechanisms, and the combination of 17-DMAG and lapatinib showed synergistical antitumour

effect in the ER-positive, HER2-overexpressing breast cancer cell line LR-BT474, and the xenograft model as well (Lee et al. 2020).

Sorafenib is a multikinase inhibitor that is considered the standard first-line option for treating advanced hepatocellular carcinoma. However, prolonged treatment with sorafenib leads to the resistance, which are featured by the reduction of microvessel density and intratumoral hypoxia (Tang et al. 2020). This hypoxia is mediated by a client of HSP90, hypoxia-inducible factors (HIFs). The Saber group reported that ganetespib augmented sorafenib efficacy via necroptosis induction in hepatocellular carcinoma (Saber et al. 2023a, b). It is interesting that the treatment with sorafenib, ganetespib, or their combination did not result in a significant change in the levels of HSP90 in HepG2 cells subjected to hypoxia. Ganetespib reduced the expression of LAMP2 and increased the expression of MLKL, suggesting that ganetespib treatment enhanced the process of necroptosis when combined with sorafenib. They further found that ganetespib and STAT3 inhibitor nifuroxazid exerted a synergistic effect in hepatocellular carcinoma (Saber et al. 2023a, b). Ganetespib decreased the levels of the HSP90 client proteins HIF-1α and pSTAT3, resulting in the suppression of the STAT3/HIF-1α complex transcriptional activity. This combination therapy exhibited promising survival prolongation in mice models.

Burkitt lymphoma (BL) is a germinal centre B cell-derived malignancy with a survival rate of < 20% in patients with recurrent disease. Giulino-Roth et al. used PU-H71 as a probe and identified multiple proteins in the PI3K/AKT/mTOR signalling pathway as HSP90 clients in BL (Giulino-Roth et al. 2017). PU-H71 and the PI3K/mTOR inhibitor dactolisib (BEZ235) exerted synergistic effects in both in vitro and in vivo models of lymphoma. In another work, the Choi group reported a strong synergistic effect between 17-DMAG and dactolisib in cisplatin-resistant human bladder cancer cells (Kim et al. 2020a, b).

To identify effective pancreatic ductal adenocarcinoma (PDAC) therapies, the Leach group performed a large-scale, unbiased screen of 16 single-agent and 41 two-drug targeted therapy combinations, and found the synergy between HSP90 inhibition and MEK inhibition in an orthotopic mouse model (Grbovic-Huezo et al. 2020). The MEK1/2 inhibitor trametinib and the broad-spectrum receptor tyrosine kinase (RTK) inhibitor sunitinib significantly increased the effectiveness of PU-H71 without significant body weight loss over the 2-week treatment period. The combination of PU-H71 and trametinib led to an 80% increase in the survival of PDAC-bearing mice. Mechanistic study revealed HSP90 inhibition by PU-H71 can overcome the compensatory activation of resistance pathways, including components of the PI3K/AKT/mTOR signalling axis, which was induced by single-agent MEK inhibition. Later research in Wiener's group revealed that this combination also acted synergistically in colorectal cancer organoid (Soós et al. 2023). The Takahashi group recently reported that the combination of HSP90 inhibitor pimitespib and sunitinib exerted synergistic effect on imatinib-resistant gastrointestinal stromal tumors (Teranishi et al. 2023). This combination effective downregulated KIT signalling and angiogenic signalling pathways in GIST cells, and decreased the tumour microvessel density in the xenograft models.

Ibrutinib, the first small-molecule drug targeting Bruton's tyrosine kinase (BTK), has been approved for the treatment of various blood cancers and chronic graft-versus-host disease (cGVHD). Although it has demonstrated excellent activity in the clinical treatment of patients with chronic lymphocytic leukaemia (CLL), it does not eliminate the disease or induce durable responses without continuous therapy (Byrd et al. 2013). The TC481S mutation in BKT has been identified as the primary mechanism underlying resistance to ibrutinib in patients with CLL. In addition, survival-related signalling pathways such as the PI3K–AKT, classical and alternative NF-κB and receptor tyrosine kinase-like orphan receptor 1 (ROR1)-mediated pathways may contribute to primary resistance to ibrutinib (Yu et al. 2017). Given that inhibition of HSP90 affects multiple signalling pathways involved in the development of ibrutinib resistance, the Yu group performed iTRAQ-based quantitative proteomic analysis and identified 130 potential client proteins of HSP90 (Liu et al. 2020). Specifically, ROR1 was identified as a novel client protein of HSP90. Inhibition of HSP90 induced ROR1 degradation and hence attenuated the tumour escape ability of ibrutinib. In addition, ibrutinib inhibited HSP90 inhibitor-induced degradation of ibrutinib-binding proteins including BTK, BLK, LCK and LYN but not that of proteins that do not bind to ibrutinib, such as ROR1. The HSP90 inhibitor alvespimycin induced ROR1 degradation and worked synergistically with ibrutinib in vitro and in vivo. Further analysis revealed that inhibition of HSP90 by alvespimycin suppressed the BCR signalling pathway in CLL cells. Furthermore, the Hertlein group demonstrated that the HSP90 inhibitor SNX-5422 was effective in depleting both wild-type BTK and BTK-C481S (Chen et al. 2021). Compared with vehicle treatment or monotherapy, the combination of SNX-5422 and ibrutinib resulted in a significant survival benefit in the Eμ-TCL1 mouse model of CLL. Later work in the Tu and Liu group reported that the HSP90 inhibitor ganetespib improved the sensitivity of mantle cell lymphoma to brutinib (Lu et al. 2022). Ganetespib enhanced the cell cycle arrest and apoptosis in vitro, and significantly increased inhibition of tumor growth mediated by ibrutinib in the mouse models.

Proteostasis inhibitors

Cancer cells are particularly reliant on the proteostasis network, however targeting single component in this network might result in compensation. The Gestwicki group investigated the binary combinations of four proteostasis inhibitors, including 17-DMAG, JG-98 (HSP70 inhibitor), bortezomib (proteasome inhibitor) and CB-5083 (p97 inhibitor) in prostate cancer cell line 22Rv1 cells (Shkedi et al. 2021). The combinations of Hsp90-p97 and Hsp90-Hsp70 were modestly synergistic, while the combination of p97 and proteasome inhibitor was the most strongly synergistic. The synergistic effects of the combinations with Hsp90 and Hsp70 inhibitors may be partly attributable to the induced degradation of both AR-FL and AR splice variants, interrupting the AR signalling required for growth of 22Rv1 cells.

Anti-androgen drugs

Anti-androgens are a class of drugs that bind to AR and block the effects of androgen to inhibit the growth of cancer cells (Student et al. 2020). They are commonly used to treat metastatic castration-sensitive prostate cancer (mCSPC) and mCRPC. Because AR is a client protein of HSP90, HSP90 inhibitors may enhance the therapeutic efficacy of anti-androgen drugs in prostate cancer. Recently, the Stoyanova group tested 22 chalcones for their inhibitory effects on tumour growth across the National Cancer Institute's 60 human cancer cell lines and found that SU086 was highly effective in inhibiting the growth of two prostate cancer cell lines, DU145 and PC3, and its activity was independent of the AR status (Rice et al. 2022). HSP90 was identified as the target of SU086 based on cellular thermal shift assay. SU086 can bind to HSP90α and HSP90β isoforms and, unlike classical HSP90 inhibitors, reduce HSP90 protein levels in prostate cancer cells. Further evaluation revealed that SU086 exerted excellent inhibitory effects on tumour growth in vivo both as a single drug and in combination with anti-androgen therapy. SU086 worked synergistically with the second-generation anti-androgen drugs enzalutamide and abiraterone in C4-2 CRPC cells. In C4-2 xenografts, SU086 combined with enzalutamide or abiraterone halted tumour growth without causing measurable toxicity during 21 days of treatment.

Fatty acid oxidation inhibitors

The Butler group conducted a proteomic analysis of 30 clinical prostate tumors and found that HSP90 inhibitor luminespib significantly increased the abundance of proteins involved in oxidative phosphorylation and fatty acid metabolism (Nassar et al. 2020). Therefore, the inhibition of fatty acid oxidation would sensitize prostate cancer cells to HSP90 inhibition. The combination of luminespib and perhexiline significantly reduced the cell viability of prostate cancer cells by inducing cell arrest and apoptosis. It is notable that perhexiline attenuated the heat shock response of luminespib.

Glucose-6-phosphate dehydrogenase (G6PD) inhibitor

Dehydroepiandrosterone (DHEA) is endogenously secreted as a precursor for the synthesis of various hormones. DHEA is a non-competitive inhibitor of G6PD. The Saeed group found that PU-H71 and DHEA exerted a synergistic effect on promoting apoptosis in triple-negative breast cancer cell line MDA-MB-231 (Soudan et al. 2020). The cells treated with PU-H71 and DHEA combination showed a highly significant increase in ROS levels in comparison to either drug alone. It is interesting that the combination of PU-H71 and DHEA resulted in a significant reduction in HSP90 expression, suggesting a better therapeutic outcome in comparison to the single drug, PU-H71.

Monoclonal antibodies

Trastuzumab, a humanized monoclonal antibody targeting HER2, has been approved for the treatment of early and advanced HER2-positive breast cancer and advanced HER2-positive gastric cancer (Swain et al. 2023). Mechanisms underlying the development of resistance to trastuzumab include the activation of PI3K signalling, presence of a truncated form of HER2 lacking an antibody-binding epitope and enhancement of signal through HER3 or other receptor tyrosine kinases such as IGF-IR (Bai et al. 2018; Derakhshani et al. 2020). Because many signalling proteins involved in the development of resistance are known client proteins of HSP90 (Huang et al. 2010), the combined use of HSP90 inhibitors and trastuzumab is a rational strategy for overcoming resistance to trastuzumab. Wainberg et al. examined the synergistic effects of the HSP90 inhibitor luminespib and trastuzumab in both breast and gastric cancers. This combination therapy induced more potent HER2 degradation and G_2-phase cell cycle arrest and increased cell apoptosis (Wainberg et al. 2013). In addition, it exhibited stronger anti-tumour efficacy than either drug alone in a xenograft model of trastuzumab-resistant gastric cancer. Recent studies also revealed that the combination of trastuzumab and HSP90 inhibitors such as geldanamycin and 17-AAG significantly increased the cytotoxicity compared to trastuzumab alone in HER2 overexpressing cancer cell lines (Skeie et al. 2020; McCombs et al. 2021).

Glembatumumab vedotin is an antibody drug conjugate targeting transmembrane glycoprotein NMB (GPNMB) (Rose et al. 2017). Glembatumumab vedotin exhibits variable efficacy against GPNMB-positive metastatic TNBC as

a single agent. Biondini et al. reported that suppression of HSP90 increases GPNMB expression and cell-surface localization, sensitizing breast cancer cells to glembatumumab vedotin (Biondini et al. 2022). HSP90 inhibition resulted in lysosomal dispersion towards the cell periphery and fusion with the plasma membrane, which delivered GPNMB to the surface of breast cancer cells.

Radiation therapy

Radiation therapy is an essential cancer treatment strategy that involves the use of radiation to kill cancer cells through DNA damage. However, patients with cancer often develop resistance to radiation therapy (Kabakov et al. 2010; Kim et al. 2015). Although the resistance mechanisms are multifaceted, numerous studies have revealed that multiple HSP90 clients are involved in these mechanisms.

HIF-1α is responsible for inducing radiation resistance through the hypoxia signalling pathway (Albadari et al. 2019). Given that HIF-1α is a client protein of HSP90, the Multhoff group investigated the effects of HSP90 inhibitors on radiation therapy (Schilling et al. 2012). The HSP90 inhibitors luminespib and tanespimycin significantly enhanced the radiosensitivity of H1339 lung cancer cells under normoxic and hypoxic conditions. These synergistic effects were found to be independent of HIF-1α, as HSP90 inhibitors surprisingly increased HIF-1α levels in H1339 cells. On the contrary, the El-Rayes group demonstrated that ganetespib significantly reduced HIF-1α levels in PDAC cells (Nagaraju et al. 2019). Compared with either ganetespib or radiation plus 5-FU treatment, the combination of ganetespib, radiotherapy and 5-FU resulted in more potent inhibition of tumour growth in HPAC tumour xenograft models. The combination treatment was well tolerated, with no measurable toxicity or significant reduction in the body weight of animals.

The Krawczyk group found that ganetespib potentiated cytotoxicity as well as radio- and chemosensitizing effects in cervix cancer cell lines (Vriend et al. 2017). HSP90 inhibition enhanced the induction of DNA damage by hyperthermia, and reduced thermotolerance. Later, this group demonstrated that this combination treatment was effective in 10 different cell lines (Scutigliani et al. 2022). Ganetespib can reduce the thermal dose and temperature required for sensitisation. In a subcutaneous murine model of cervix cancer, ganetespib enhanced the effects of radio-thermotherapy in four out of six mice. The Chen group demonstrated that the synergistic effect between ganetespib and hyperthermia therapy was attributable to the HSP90 inhibition-induced degradation of DNA-PKcs protein and suppression of *PRKDC* transcription (Liu et al. 2021).

The Harrington group revealed that luminespib induced radiosensitivity in athymic mice bearing tumour xenografts established using human HNC cells (Zaidi et al. 2012). The combination of radiotherapy and luminespib significantly delayed tumour growth and increased surrogate end-point survival. Luminespib depleted HSP90 clients, including AKT, ErbB2 and cRAF, in HeLa and HN3 cells and delayed Rad51 foci formation and subsequent resolution of radiation-induced double-strand DNA break repair.

In 2020, the Spiegelberg group reported that onalespib and radiotherapy exerted synergistic antitumour effect in radiosensitive HCT116 and radioresistant A431 cells (Spiegelberg et al. 2020). The Nyati group revealed that onalespib sensitised radiotherapy even at a subcytotoxic concentration (Mehta et al. 2020). A low-dose onalepib reduced the expression of DNA repair proteins, without affecting the majority of HSP90 clients. They showed that a combination of onalepib and radiotherapy produced significant tumor growth inhibition in HNSCC and pancreatic xenografts. In a recent study, the Mitchell group reported that onalespib increased radiosensitivity in both in vitro and in vivo models of HNC (Naz et al. 2021). The combined use of onalespib and ionising radiation (IR) resulted in G_2/M-phase cell cycle arrest; inhibited DNA repair and altered tumour metabolism, including nucleotide metabolism, glycolysis and tricarboxylic acid cycle. Compared with IR alone, the combination therapy synergistically delayed tumour growth in HNC xenograft models. HSP70 expression was elevated and CDK4 expression was reduced in onalespib-treated tumours, suggesting the target engagement of HSP90. Onalespib significantly reduced the expression of HIF-1 and other IR-induced marker proteins involved in vasculogenesis, such as SDF-1, $CD11b^+$ and CD45, indicating that the combination of onalespib and radiotherapy can reduce tumour recurrence after radiation therapy.

The Tran group reported that ganetespib induced radiosensitivity in liver cancer cells (Chettiar et al. 2016). The combination of ganetespib and radiotherapy induced supra-additive radiosensitivity in all tested liver cancer cell lines, including Hep3B, HepG2 and HUH7, at low nanomolar concentrations with enhancement ratios of 1.33–1.78. In addition, the combination therapy delayed tumour growth in HepG2 tumour xenografts. Furthermore, the Lin group reported that ganetespib inhibited DNA damage repair induced by radiation and intensified G_2–M-phase arrest in four types of NSCLC cells (Wang et al. 2016). Ganetespib significantly enhanced the therapeutic efficacy of radiation in H460 xenografts; however, synergistic effects were not observed in A549 xenografts. These findings suggest that radiosensitivity mediated by HSP90 inhibitors is tumour-specific.

In 2021, the Zhao and Lu group reported that HSP90 inhibitor XL888 enhanced cell apoptosis via downregulating STAT3 after insufficient radiofrequency ablation in hepatocellular carcinoma (Sun et al. 2021). XL888 increased the

heat-induced cell apoptosis of hepatocellular carcinoma cells by increasing the levels of cleaved caspase 3 and PARP. Further investigation revealed that combination of XL888 and heat treatment significantly reduced the expression level of STAT3 and its phosphorylated level, leading to the reduced expression levels of AKT, phosphorylated AKT, Bcl-xL, Bcl-2 as well as Mcl-1, and the increased expression level of BAX.

The Xue group and the Lauber group demonstrated that HSP90 inhibitors NW457, NXD30001 and onalespib, showed synergistic effects with radiotherapy in glioblastoma cells (Chen et al. 2020; Orth et al. 2021; Xu et al. 2022). HSP90 inhibitors reduced the expression of DNA damage repair regulators induced by radiotherapy. These combinations inhibited the tumor growth and prolonged the survival in animal models. Notably, Xu et al. claimed that onalespib sensitized glioblastoma cells to the combination of radiation and temozolomide by depleting the homologous recombination pathway. A recent work in the Lauber group revealed that NW457 augmented the efficacy of ionizing irradiation in CRC cells (Ernst et al. 2020). It is interesting that the combination of NW457 and radiotherapy induced the release of damage-associated molecular patterns, which enforced the differentiation of a monocyte-derived antigen presenting cell phenotype and triggered the priming of allogeneic T cell responses.

The Erin group demonstrated that PU-H71 enhanced the radiosensitivity of metastasized breast cancer cells 4T1 (Kale et al. 2020). PU-H71 decreased a variety of client proteins and increased the cytotoxicity of radiotherapy. However, the treatment of PU-H71 induced the expression of angiogenic and inflammatory factors such as MIP-2, SDF-1, and VEGF, suggesting an inflammatory response. In another work by Nowosielska's group, the combination of HSP90 inhibitor NVP-AUY922 and the whole-body low dose radiotherapy suppressed clonogenic potential in Lewis lung cancer cells and reduced tumorigenesis in mice (Nowosielska et al. 2021). However, this combination was inferior to these of radiotherapy and blockade of the immune checkpoints such as CTLA-4 and PD-1.

Immunotherapy

In addition to chemotherapy, radiotherapy and surgery, immunotherapy is an effective treatment strategy for cancer. Immunotherapy can be divided into five categories as follows: vaccine-based, cytokine-based, checkpoint blockade-based, adoptive cell transfer-based and small-molecule-based immunotherapies (Zhou et al. 2021). HSP90 is involved in immune modulation in cancer and plays an essential role in antigen presentation, effector immune cell function and regulation of inflammatory processes (Ziningaet al. 2018). Therefore, the combination of HSP90 inhibitors and immunotherapy represents a promising strategy for the treatment of cancer (Graner 2021).

The Storkus group demonstrated that the HSP90 inhibitor alvespimycin functioned as an adjuvant to erythropoietin-producing hepatoma (EPH) receptor A2 (EphA2)-specific active vaccination or adoptive transfer of EphA2-specific CD_8^+ T cells (Rao et al. 2012). Alvespimycin reconditioned the tumour microenvironment and improved the recruitment of therapeutic T cells. Treatment with alvespimycin led to degradation of the HSP90 client protein EphA2 and subsequently increased recognition of tumour cells by type-1 anti-EphA2 CD_8^+ T cells.

Given that intrinsic signalling pathways related to tumours interfere with processes essential for an effective anti-tumour immune response, the Hwu group identified small molecules with the potential to improve responses to immunotherapy by assessing their effects on autologous-T-cell-driven elimination of primary melanoma cells (Mbofung et al. 2017). The HSP90 inhibitor ganetespib was identified from 850 bioactive compounds. It enhanced the elimination of patient-derived human melanoma cells by their autologous T cells in vitro and potentiated responses to anti-CTLA4 and anti-PD1 therapies in vivo. Mechanistically, inhibition of HSP90 by ganetespib upregulated the interferon response genes IFIT1, IFIT2 and IFIT3 in tumours. Considering the intrinsic toxicities of pan-HSP90 inhibitors, the Lu group investigated the efficacy of an HSP90β-selective inhibitor NDNB1182 in affecting the immune checkpoint blockade immunotherapy (Rahmy et al. 2022). NDNB1182 effectively downregulated CDK4 and increased the expression of endogenous retroviral elements and interferon-stimulated genes. Moreover, NDNB1182 enhances immune checkpoint blockade therapy with superior tolerability to ganetespib in murine tumors.

A recent study by the Lairson group revealed that HSP90 inhibitors reduced the mRNA and protein expression levels of immune checkpoint molecules, namely, PD-L1 and PD-L2, in target cells and potentially improved the efficacy of immunotherapy (Zavareh et al. 2021). Phenotype-based high-throughput screening revealed that HSP90 inhibitors affected the expression of PD-L1 and PD-L2 at clinically relevant concentrations in vitro and in vivo. Compared with monotherapy, combination therapy with anti-PD-L1 antibody and ganetespib exhibited better anti-tumour activity in syngeneic C57BL/6 mouse models of colon adenocarcinoma established using MC-38 cells.

Peptide receptor radionuclide therapy is a highly targeted and effective form of radiotherapy with minimal side effects for treating neuroendocrine tumors with an abundance of somatostatin receptors. ^{177}Lu-DOTATATE was approved for therapy of gastroenteropancreatic neuroendocrine cancer in Europe. The Nestor group found that onalespib was a radiosensitiser to potentiate the therapeutic outcomes of ^{177}Lu-DOTATATE in neuroendocrine tumor xenografts (Lundsten

et al. 2020). Later, they further developed an anti-carcinoembryonic antigen humanized antibody ^{177}Lu-DOTA-M5A and investigated the therapeutic effect of ^{177}Lu-DOTA-M5A and/or onalespib in CRC (Mohajershojai et al. 2022). Onalespib synergistically enhanced the therapeutic effects of ^{177}Lu-DOTA-M5A in three-dimensional colorectal spheroid models. This combination exerted cooperative effects on the cellular tumor suppressive pathways RTK and MAPK and therefore increased apoptosis.

Cytokine-induced killer (CIK) cell is a novel approach for adoptive cell-based immunotherapy of cancer. The Schmidt-Wolf group demonstrated that HSP90 inhibitors showed synergistic effect with CIK cells in Burkitt's lymphoma (BL) cells (Ge et al. 2023). HSP90 inhibitors, 17-DMAG and ganetespib, worked synergistically with CIK cells against BL cell lines, BL-41 and Raji. This combination significantly increased the expression of Fas and induced the caspase 3/7-dependent apoptosis in BL cells.

Conclusion

Recent clinical and preclinical studies have revealed that the combination of HSP90 inhibitors and other anti-cancer drugs is a viable method to re-introduce HSP90 inhibitors to anti-cancer therapy. Because many oncoproteins and drug resistance-related proteins are clients of HSP90, HSP90 inhibitors can cooperate well with various clinical anti-cancer therapies, including chemotherapy, targeted therapy, radiation therapy and immunotherapy, to improve the treatment efficacy and overcome drug resistance. Pioneering examples discussed in this review have broadened the prospects for the rational and effective use of HSP90 inhibitors in cancer treatment.

Since the initial discovery of HSP90 as a promising therapeutic target for anti-cancer therapy, tremendous progress has been made in the identification of numerous HSP90 inhibitors. Because HSP90 is required for stabilising many oncoproteins, HSP90 inhibitors often have strong and broad-spectrum anti-cancer activities. Although HSP90 inhibitors have demonstrated effectiveness in both in vitro and in vivo models, clinical trials investigating their use as monotherapy have reported unsatisfactory results, which may be attributed to organ toxicity and heat shock response induced by the inhibitors. Therefore, developing robust strategies for the successful application of HSP90 inhibitors in anti-cancer therapy is necessary.

Combination therapy represents an important therapeutic strategy for improving treatment efficacy and safety. It involves the combined use of two or more therapies with different but synergistic pharmacological mechanisms of action. Theoretically, HSP90 inhibitors can act synergistically with any anti-cancer therapy given that the mechanism of action relies on the inhibition of the client proteins of HSP90. Inhibition of HSP90 results in the degradation of many drug resistance-related proteins; therefore, combination therapy involving HSP90 inhibitors may represent an effective strategy for overcoming drug resistance in advanced and refractory cancers. Unlike monotherapy, combination therapy allows the use of lower doses of each drug, which can help to reduce the intrinsic toxicity of HSP90 inhibitors. Based on the above-mentioned reasons, the combined use of HSP90 inhibitors and other anti-cancer therapies is considered an alternative to monotherapy for cancer treatment. In the past decade, many clinical and preclinical studies have evaluated different combinations of HSP90 inhibitors and other anti-cancer therapies. Some combinations exhibited positive therapeutic effects in patients with cancer, demonstrating their promising therapeutic potential, whereas some combinations demonstrated no therapeutic benefit in clinical trials. Therefore, the rational design of combination therapies involving HSP90 inhibitors should be improved, and the efficacy, toxicity, dosage and administration of these combination regimens should be continuously investigated in clinical trials.

Given that numerous proteins have been identified as clients of HSP90, inhibition of HSP90 may lead to complicated changes in signalling in cancer cells. The biological function of HSP90 warrants further investigation. Establishing a comprehensive map of HSP90 client proteins is important for rationalising combination strategies involving HSP90 inhibitors. Given that many drugs targeting HSP90 clients have not yet been evaluated in combination with HSP90 inhibitors, expanding combination therapies to clinical trials with different therapeutic targets and indications may help to realise the complete potential of HSP90 inhibitors in combination therapy.

In combination therapies reported to date, HSP90 inhibitors have been used as 'adjuvant' supporting other anti-cancer therapies to achieve the goals of enhancing efficacy or overcoming resistance. On the contrary, other anti-cancer therapies have been rarely used to improve the efficacy and safety of HSP90 inhibitors. Therefore, drugs that can negate the side effects of HSP90 inhibitors, such as organ toxicity and heat shock response, should be developed for promoting the use of HSP90 inhibitors as a 'striker' in cancer treatment. For example, the CDK inhibitor AT7519 can inhibit the compensatory expression of HSP70 induced by onalespib, suggesting a novel method to overcome the heat shock response.

HSP90 inhibitors used in existing combination therapies predominantly target the N-terminus of HSP90. Over the past several years, substantial progress has been made in the development of C-terminal and isoform-specific inhibitors of HSP90, which have a better safety profile and (or) do not induce heat shock response. These novel HSP90 inhibitors

may open broader avenues for the development of effective anti-cancer therapies. More combination therapies involving HSP90 inhibitors should be developed and investigated in clinical and preclinical trials to improve cancer treatment in the future.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

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