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COMMENTARY

Hsp90 inhibitors in oncology: ready for prime time?

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In the targeted oncology era, there has been a resurgence of interest in targeting members of the heat shock protein family, as evidenced by numerous ongoing trials in advanced malignancies (Table I). Heat shock protein 90 (Hsp90) is the most well-studied member of the heat shock protein family to date.

As a molecular chaperone, Hsp90 plays a critical role in maintaining protein homeostasis and in managing the conformational maturation, stability, and folding of client proteins within cells (Figure 1). These stabilizing protein interactions are ATP-mediated, and Hsp90 functions together with co-chaperone molecules including Hsp70, Hsp40, HOP, and p23. Upon exposure to proteotoxic stress in a normal cell, Hsp90 stabilizes client proteins in their natural, complex conformations, which in turn modulates key cellular signalling pathways. The list of client proteins is extensive and includes androgen receptors, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor receptor, cyclin-dependant kinase 4, anaplastic lymphoma kinase (ALK), Flt3, Abl, Akt, the mammalian target of rapamycin, and mitogen-activated protein kinase.

Compared with normal cells, neoplastic cells exhibit greater dependence on chaperone proteins, which play a critical role in signal transduction, cell cycle regulation, and apoptosis. As a result, Hsp90 represents an attractive target for cancer therapy. Indeed, Hsp90 overexpression has been associated with worsened prognosis in a number of malignancies.

Trials of early-generation Hsp90 inhibitors in oncology demonstrated limited efficacy (especially when administered as monotherapy), poor solubility, and dose-limiting toxicities (including hepatotoxicity); however, encouraging progress has been made with newer-generation inhibitors. Here, we focus on three promising Hsp90 inhibitors—retaspimycin, ganetespib, and NVP-AUY922—that are currently under evaluation either as monotherapy or in combination therapy for lung and breast cancers, and we discuss their potential relevance for future clinical practice.

HSP90 INHIBITORS

Retaspimycin

Retaspimycin (IPI-504) is a benzoquinone ansamycin antibiotic and second-generation Hsp90 inhibitor. Like other Hsp90 inhibitors, retaspimycin uses the ubiquitin–proteasome pathway to break down key client proteins important in oncogenesis. Unlike its first-generation predecessors (geldanamycin, tanespimycin, alvespimycin), which had disappointing results in clinical trials or were associated with dose-limiting toxicities (or both), retaspimycin is associated with better water solubility, greater potency, and fewer toxicities. Nonetheless, as with other second-generation Hsp90 inhibitors, retaspimycin is administered intravenously and poses a risk of hepatotoxicity.

Thus far, retaspimycin has been evaluated in malignancies such as chronic myelogenous leukemia, multiple myeloma, gastrointestinal stromal tumour, non-small-cell lung cancer (NSCLC), and breast cancer. Based on early-phase clinical trial results to date, retaspimycin has demonstrated the most promise in the NSCLC population, especially for tumours that harbour the *ALK* rearrangement. In a phase II trial in 76 patients with molecularly defined NSCLC, a greater benefit was derived in 3 patients with *ALK* rearrangement than in the NSCLC patient population as a whole, with 2 patients achieving a partial response, and 1 patient achieving stable disease for more than 3 months[1]. Those clinical findings build on preclinical data demonstrating that, compared with HER2 or EGFR, ALK is more sensitive to Hsp90 inhibition, with more tumour regression being observed in human NSCLC xenografts harboring the *ALK* rearrangement when retaspimycin was administered, and with decreased downstream signal activation with Erk and Stat3 effector proteins.

TABLE I Overview of ongoing clinical trials evaluating selected inhibitors of heat shock protein 90 (Hsp90)

Inhibitor	*Tumour type*	*Trial phase*	*Sample size (n)*	*Treatment arms*	*Trial registration*[a]
Retaspimycin (IPI-504)	Advanced NSCLC	II	226	Retaspimycin–docetaxel	NCT01362400
	KRAS-mutant advanced NSCLC	IB/II	70	Retaspimycin–everolimus	NCT01427946
Ganetespib	Advanced NSCLC	III	500	Ganetespib–docetaxel vs. docetaxel	NCT01798485 (GALAXY-2)
	Advanced NSCLC	II/III	240	Ganetespib–docetaxel vs. docetaxel	NCT01348126 (GALAXY-1)
	Advanced NSCLC	II	88	Ganetespib	NCT01031225
	ALK-positive NSCLC	II	100	Ganetespib	NCT01562015 (CHIARA)
	ALK-positive NSCLC	I/II	55	Ganetespib–crizotinib	NCT01579994
	Metastatic breast cancer	II	105	Ganetespib	NCT01677455 (ENCHANT-1)
	Advanced breast cancer	II	71	Fulvestrant–ganetespib vs. fulvestrant	NCT01560416
	Advanced or metastatic HER2-positive breast cancer	I	18	Ganetespib–paclitaxel–trastuzumab	NCT02060253
	Recurrent ovarian, fallopian tube, or primary peritoneal cancer	II	74	Ganetespib plus weekly paclitaxel	NCT01962948
	Malignant pleural mesothelioma	I/II	24	Cisplatin–pemetrexed–ganetespib vs cisplatin–pemetrexed–placebo	NCT01590160 (MESO-02)
	Metastatic ocular melanoma	II	30	Ganetespib	NCT01200238
	AML and high-risk MDS	I/II	90	Chemotherapy (daunorubicin–cytarabine–etoposide) plus AC220 or plerixaforor and ganetespib	NCT01236144
NVP-AUY922	Advanced NSCLC	II	153	NVP-AUY922	NCT01124864
	Advanced *EGFR*-mutation–positive NSCLC	II	108	NVP-AUY922 vs. docetaxel or pemetrexed	NCT01646125
	Advanced NSCLC with exon 20 insertion mutations in *EGFR*	II	29	NVP-AUY922	NCT01854034
	ALK-positive NSCLC	II	20	NVP-AUY922	NCT01752400
	Advanced HER2-positive breast cancer	IB/II	45	NVP-AUY922–trastuzumab	NCT01271920
	Metastatic pancreatic adenocarcinoma	II	37	NVP-AUY922	NCT01484860
	Refractory GIST	II	34	NVP-AUY922	NCT01404650
	Advanced GIST	II	25	NVP-AUY922	NCT01389583
	Relapsed and refractory lymphoma	II	42	NVP-AUY922	NCT01485536
	Myeloproliferative neoplasms	II	25	NVP-AUY922	NCT01668173

[a] Can be searched at http://clinicaltrials.gov/.

NSCLC = non-small-cell lung cancer; ALK = anaplastic lymphoma kinase; HER2 = human epidermal growth factor receptor 2; AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; GIST = gastrointestinal stromal tumour.

Other studies have reported the use of retaspimycin in combination with other chemotherapeutics. In a phase IB trial in 23 patients with metastatic NSCLC who had received 1–2 prior chemotherapy regimens without prior docetaxel, the combination of retaspimycin plus docetaxel resulted in a partial response in 6 patients (overall response rate: 26%), with higher rates observed in patients with squamous cell histology and in heavy smokers[2]. Because of those encouraging results, a phase II randomized trial of retaspimycin plus docetaxel in previously treated advanced NSCLC patients with at least a 15 pack–year smoking history was recently completed, and results are currently pending (search for NCT01362400 at http://clinicaltrials.gov/).

Evidence of retaspimycin activity in breast cancer has also been demonstrated, particularly in the HER2-positive population. Preclinically, antitumour

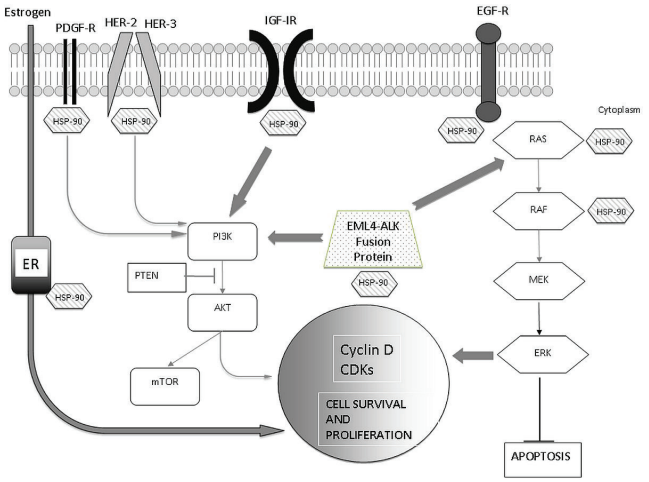

FIGURE 1 Heat shock protein 90 (Hsp90) client proteins in key cellular signalling pathways. PDGF-R = platelet-derived growth factor receptor; HER = human epidermal growth factor receptor; IGF-1R = insulin-like growth factor 1 receptor; EGF-R = epidermal growth factor receptor; ER = estrogen receptor; PI3K = phosphoinositide 3-kinase; PTEN = phosphatase and tensin homolog; AKT = protein kinase B; mTOR = mammalian target of rapamycin; CDKS = cyclin-dependent kinases; MEK = mitogen-activated protein kinase kinase; ERK = extracellular signal-regulated kinase.

effects were observed for retaspimycin both as a single agent and in combination with trastuzumab or lapatinib in HER2-positive disease resistant to standard therapies. In a phase II trial in 26 patients with HER2-positive advanced or metastatic breast cancer who had previously received trastuzumab, modest clinical benefit was observed in 20 evaluable patients (1 partial response, 14 stable disease) with retaspimycin plus trastuzumab[3].

With the advent of novel agents such as pertuzumab and T-DM1 in HER2-positive metastatic breast cancer, it would, however, be of interest to determine whether retaspimycin or other Hsp90 inhibitors retain activity upon progression after multiple lines of anti-HER2 therapies.

Ganetespib

Ganetespib (STA-9090) is another second-generation Hsp90inhibitor and a resorcinol derivative. This triazole compound inhibits Hsp90 by attaching to its ATP binding site on the N-terminus. Compared with other first- and second-generation Hsp90 inhibitors, ganetespib is smaller in molecular weight, more lipophilic, and more potent. Those characteristics result in a longer duration of Hsp90 inhibition, with fewer potential cardiac, hepatic, and ocular toxicities. Ganetespib is also reasonably well tolerated, with the most common dose-limiting toxicities being fatigue, diarrhea, and elevated serum transaminases or amylase.

Thus far, ganetespib has been evaluated in a number of malignancies, including melanoma, chronic myelogenous leukemia, gastrointestinal stromal tumour, and colorectal, lung, and breast cancers. Antitumour activity has been observed with ganetespib both as monotherapy and in combination with other agents, including synergistic effects in combination with taxanes and etoposide.

Like retaspimycin, ganetespib has shown the most encouraging clinical activity in NSCLC. Results of the phase IIB GALAXY-1 trial, which randomized 252 patients with advanced stage IIIB or IV non-small-cell lung adenocarcinoma in the second-line setting to docetaxel monotherapy or to docetaxel plus ganetespib, were presented at 2013 annual meeting of the American Society for Clinical Oncology and were updated at the World Conference on Lung Cancer in the fall of 2013[4]. The combination arm demonstrated an improvement in median progression-free survival (hazard ratio: 0.72; 90% confidence interval: 0.53 to 0.96; $p = 0.03$) and overall survival (hazard ratio: 0.72; 90% confidence interval: 0.52 to 0.98; $p = 0.04$) in the pre-specified chemosensitive patient population (n =178), defined as a diagnosis of advanced disease for more than 6 months. Grades 3–4 adverse events were comparable in the combination and monotherapy arms (respectively: neutropenia, 38% vs. 41%; fatigue, 6% vs. 4%; anemia, 8% vs. 2%; diarrhea, 4% vs. 0%), with the exception of febrile neutropenia (11% vs. 2%). Because of the promising GALAXY-1 data, an international phase III randomized controlled trial of docetaxel plus ganetespib (GALAXY-2) is currently underway to verify those results (search for NCT01798485 at http://clinicaltrials.gov/).

In NSCLC, evidence of activity has also been reported with ganetespib monotherapy in the ALK-positive subpopulation. In a phase II study, 99 patients with a median of 2 prior systemic therapies were treated with ganetespib until disease progression. A partial response was achieved in 4 patients, all of whom had the *ALK* gene rearrangement[5]. Currently, two early-phase clinical trials are evaluating ganetespib monotherapy or ganetespib plus crizotinib in patients with ALK-positive, crizotinib-naïve NSCLC (search for NCT01579994 and NCT01562015 at http://clinicaltrials.gov/).

There is also encouraging evidence for the use of ganetespib in metastatic breast cancer. In a phase II trial that evaluated 22 patients with metastatic breast cancer who had previously received up to 3 lines of chemotherapy in the metastatic setting, ganetespib monotherapy was associated with a modest overall response rate of 9% (partial responses) in 2 of 13 patients who had trastuzumab-refractory HER2-positive disease[6]. Based on those results, the open-label multicentre phase II ENCHANT-1 trial is currently ongoing. This window-of-opportunity study is evaluating ganetespib monotherapy in metastatic breast cancer patients with visceral disease who have not received any systemic treatment in the metastatic setting, stratified

into 3 arms: HER2-positive, triple-negative, and hormone-refractory. The primary endpoint in the study is objective response rate, with secondary endpoints of progression-free survival and duration of response (search for NCT01677455 at http://clinicaltrials.gov/).

NVP-AUY922

NVP-AUY922 is another resorcinol derivative and second-generation Hsp90 inhibitor currently under clinical investigation. As an isoxazole amide, it is considered one of the most potent Hsp90 inhibitors developed to date. In a phase I trial in 96 patients with advanced solid tumours, disease stabilization was observed in 16 patients, and a partial metabolic response based on fluorodeoxyglucose positron-emission tomography was reported in 9 patients[7]. The drug was reasonably well tolerated, with the main adverse effects being diarrhea, nausea and vomiting, fatigue, and ocular toxicities (night blindness, blurred vision, flashing).

Like other Hsp90 inhibitors in development, NVP-AUY922 appears to hold the greatest promise in NSCLC. In a phase II trial in 112 treatment-refractory patients with advanced NSCLC, promising clinical activity was observed, with partial responses observed in 13 of 101 patients (13%), including 2 of 8 who were ALK-positive, 6 of 33 with *EGFR* mutation, and 4 of 30 with wild-type *EGFR, KRAS,* and *ALK*[8].

In breast cancer, the focus has been in the HER2-positive population. In a phase IB/II trial in 22 evaluable patients with HER2-positive metastatic breast cancer and disease progression after at least 1 anti-HER2 agent, 5 partial responses was reported with the combination of NVP-AUY922 and trastuzumab[9]. That study is currently ongoing, but is closed to recruitment.

SUMMARY

Since the early 2000s, there has been renewed interest in the development of Hsp90 inhibitors in oncology, with more than 15 compounds currently under evaluation in clinical trials. Because of Hsp90's important role as a key molecular chaperone and its extensive list of oncogenic client proteins, there is sound biologic rationale in targeting it in anticancer therapy.

The early-generation Hsp90 inhibitors (geldanamycin, tanespimycin, alvespimycin) were unsuccessful because of limited efficacy, poor solubility, and dose-limiting toxicities including hepatotoxicity, but the second-generation agents—including retaspimycin, ganetespib, and NVP-AUY922—have shown some promising clinical activity that merits further clinical investigation. Although Hsp90 inhibitors are not currently ready for prime time, their role in targeting molecular subsets in solid tumours appears to hold the greatest promise, either as monotherapy or combination therapy for EGFR- or ALK-positive NSCLC, chemosensitive NSCLC adenocarcinoma, and possibly other yet-to-be-unidentified subtypes. The clinical relevance of Hsp90 inhibition in HER2-positive metastatic breast cancer is, however, less clear, given the advent of novel agents such as pertuzumab and T-DM1, which have demonstrated robust activity in the trastuzumab-refractory population. It would certainly be of value to determine whether Hsp90 inhibitors retain activity after progression on multiple lines of anti-HER2 therapies. Nonetheless, the triple-negative arm of the phase II ENCHANT-1 breast cancer trial evaluating ganetespib monotherapy has completed enrollment, and results are awaited with interest.

Moving forward, the question of whether off-target toxicities can be successfully minimized while clinical efficacy is achieved remains open, and the answer will ultimately determine the fate and success of Hsp90 inhibitors in clinic.

CONFLICT OF INTEREST DISCLOSURES

The authors have no relevant financial conflicts of interest.

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