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PERSPECTIVE AND REFLECTION ARTICLE

Combined HSP90 and kinase inhibitor therapy: Insights from The Cancer Genome Atlas

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Abstract The merging of knowledge from genomics, cellular signal transduction and molecular evolution is producing new paradigms of cancer analysis. Protein kinases have long been understood to initiate and promote malignant cell growth and targeting kinases to fight cancer has been a major strategy within the pharmaceutical industry for over two decades. Despite the initial success of kinase inhibitors (KIs), the ability of cancer to evolve resistance and reprogram oncogenic signaling networks has reduced the efficacy of kinase targeting. The molecular chaperone HSP90 physically supports global kinase function while also acting as an evolutionary capacitor. The Cancer Genome Atlas (TCGA) has compiled a trove of data indicating that a large percentage of tumors overexpress or possess mutant kinases that depend on the HSP90 molecular chaperone complex. Moreover, the overexpression or mutation of parallel activators of kinase activity (PAKA) increases the number of components that promote malignancy and indirectly associate with HSP90. Therefore, targeting HSP90 is predicted to complement kinase inhibitors by inhibiting oncogenic reprogramming and cancer evolution. Based on this hypothesis, consideration should be given by both the research and clinical communities towards combining kinase inhibitors and HSP90 inhibitors (H90Ins) in combating cancer. The purpose of this perspective is to reflect on the current understanding of HSP90 and kinase biology as well as promote the exploration of potential synergistic molecular therapy combinations through the utilization of The Cancer Genome Atlas.

Keywords Cancer · Drug resistance · HSP90 · Kinase · Evolution · TCGA

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Background

Cancer is a disease of deregulated cell growth. The presence of continuous pro-growth signals and overriding of cell cycle checkpoints allows for the initiation of neoplastic transformation and eventual cancer. Kinases, along with the phosphoinositide 3-kinase and RAS signaling pathways often perpetuate pro-growth signals that can lead to malignancy (Blume-Jensen and Hunter 2001); (Yuan and Cantley 2008); (Chang et al. 1982). The human genome encodes over 500 protein kinases, 90 of which are tyrosine kinases, and of these, 58 are receptor tyrosine kinases (Manning et al. 2002). Together, these kinases form cascading networks that signal for normal cell growth and differentiation. However, when overexpressed, mutated, or otherwise deregulated, kinases can drive a mass of cells toward malignancy (Levinson et al. 1978; Di Fiore et al. 1987); (Hudziak et al. 1987); (Davies et al. 2002); (Wong et al. 1987) (Fig. 1). Profiling these malignancy-driving alterations in distinct cancers is now possible with the establishment of The Cancer Genome Atlas (TCGA). Equally interesting is the understanding that the majority of kinases in a cancer cell associate with and depend on the HSP90 molecular chaperone complex along with CDC37 and HSP70 to bind, hold, and fold newly synthesized kinases into their proper three-dimensional arrangement—maturing them into functional signaling components (Pratt and Toft 2003); (Prince and Matts 2004); (Shao et al. 2001). Moreover, when kinases become structurally

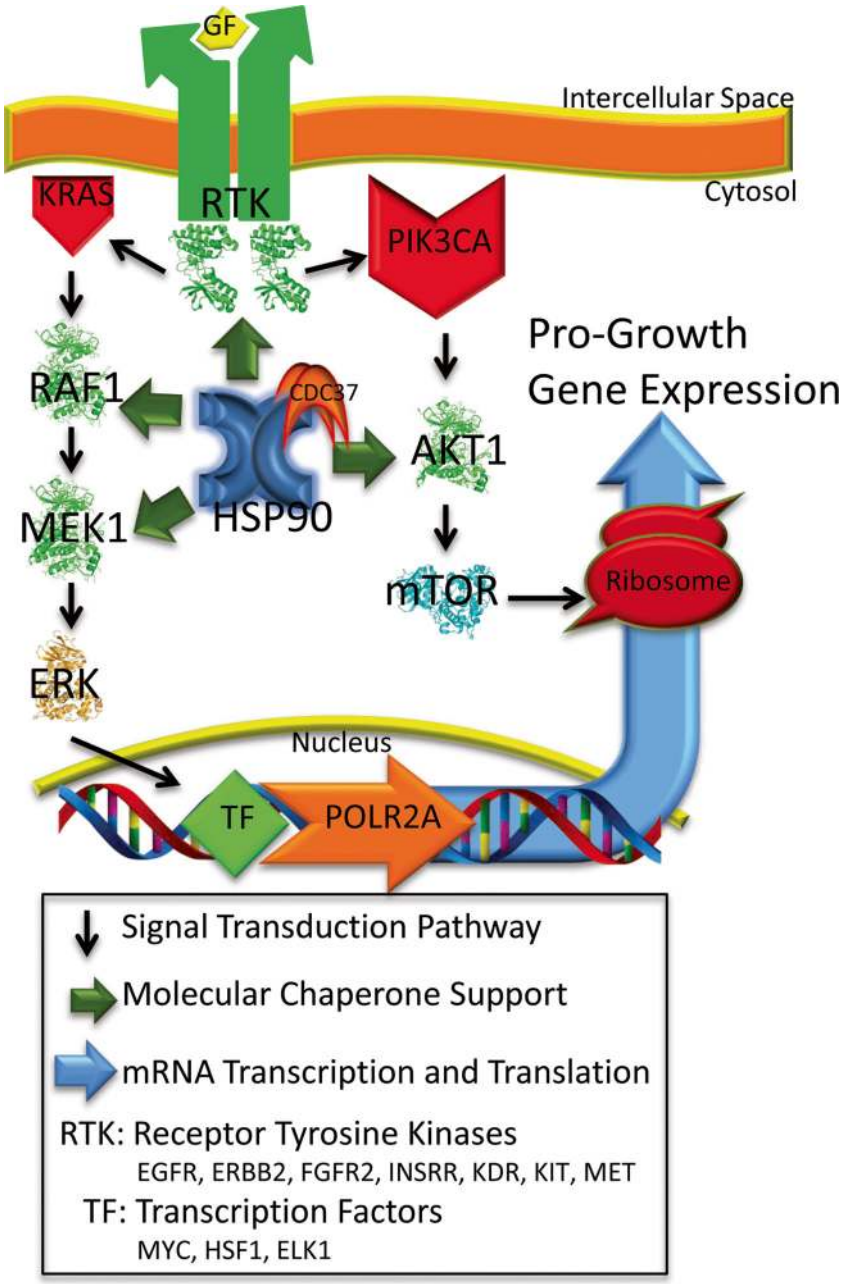

Fig. 1 Simplified model of kinase driven signaling cascades that promote pro-growth gene expression and their dependency on HSP90

destabilized as a result of over-activation, mutation and/or proteotoxic stress, HSP90 and CDC37 reassociate, refold them, and restore their kinase function (Fig. 2) (Gray et al. 2008); (Xu et al. 2005); (Citri et al. 2006); (Miyajima et al. 2013). Inhibiting HSP90 destabilizes the kinase, resulting in its subsequent degradation and in a reduction in overall pro-growth signaling (Xu et al. 2002); (Trepel et al. 2010); (Citri et al. 2002); (Lerdrup et al. 2006). Based on the premise that structure dictates function, this relationship suggests that kinase activity is at least partially dependent on HSP90. Due to this relationship and the fact that a number of clinically relevant HSP90 inhibitors (H90Ins) currently exist (Alarcon et al. 2012), the concept of targeting HSP90 as a way to broadly inhibit kinase activity in cancer deserves continued consideration (Whitesell and Lindquist 2005); (Trepel et al. 2010); (Lu et al. 2012a); (Barrott and Haystead 2013).

While the success of the small molecule kinase inhibitor (KI) imatinib, which targets the BCR-ABL fusion protein in treating chronic myelogenous leukemia (CML), and that of the ALK inhibitor crizotinib in treating certain forms of non-small-cell lung cancer (NSCLC) is certainly promising (Druker et al. 1996); (Ou et al. 2011); the clinical benefit tends to be short lived, as most cancers evolve resistance to such targeted KIs (Carroll 2006); (Vaidya et al. 2015). This evolved resistance often is a consequence of a number of cellular events that allow the reprogramming of oncogenic signals in

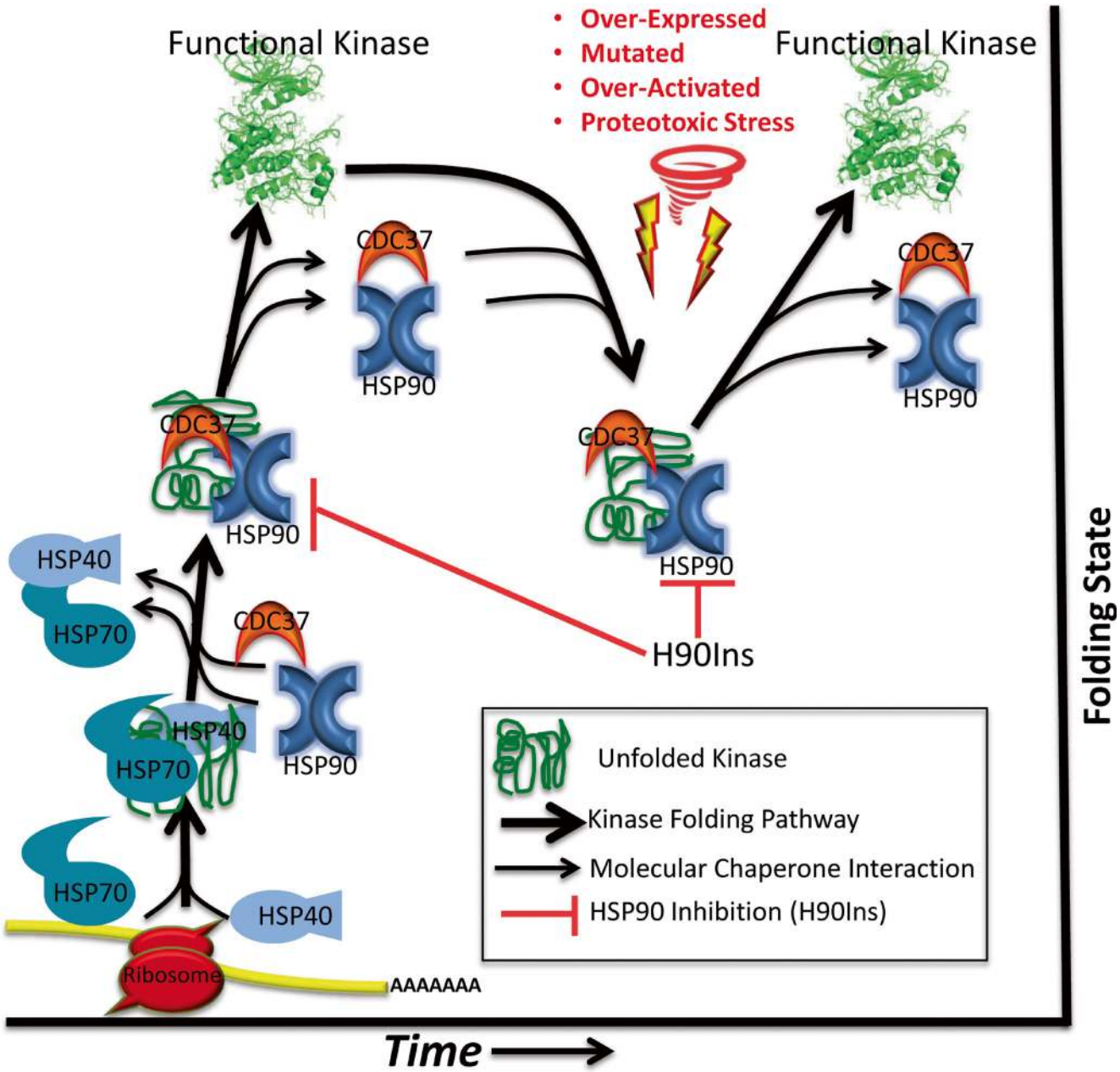

Fig. 2 Cartoon of molecular chaperone-dependent kinase folding, maturation, and maintenance along with the possible effect of H90Ins on distinct kinase populations

order to compensate for the loss of activity of the targeted kinase (Garraway and Janne 2012). Some of these cellular events include the following: increased rates of mutagenesis resulting in alteration of the drug-binding site (Vaidya et al. 2015); (Ma et al. 2002); (Pao et al. 2005); (Yu et al. 2014), chromosomal deletions or rearrangements creating chimeric transcripts that provide deregulated growth signals (Grammatikakis et al. 2002); (Duesberg et al. 2001); (Lee et al. 2011); (Hingorani et al. 2005); (Hashida et al. 2015), epigenetic rewiring of gene expression (Ricketts et al. 2014); (Hill et al. 2011); (Abdel-Hafiz and Horwitz 2015), hyper-activation of alternative but overlapping kinase signaling cascades (Drake et al. 2014); (Shattuck et al. 2008); (Maroun and Rowlands 2014); (Chen et al. 2012), relaxation of protein translational control to favor increased production of oncogenes (Pelletier et al. 2015); (Boussemart et al. 2014); (Konicek et al. 2008), and additional mechanisms as yet not fully appreciated such as altered non-coding RNA expression and cellular metabolic reprogramming (Klinge 2015); (Ward et al. 2014); (Ward and Thompson 2012); (DeBerardinis et al. 2008); (Linehan and Rouault 2013). The relationship of oncogenic reprogramming to evolved resistance is supported by the clonal diversity and genetic heterogeneity of most tumors along with the ability of most cancers to relapse after several

rounds of therapy (Hiley and Swanton 2014); (Calderwood 2013). Therefore, targeting this phenomenon is critical to preventing resistance to KIs. HSP90 is associated with each cellular event required for oncogenic reprogramming, consistent with its ability to act as an evolutionary capacitor, and suggesting that inhibition of HSP90 may represent a viable strategy to combat resistance (Trepel et al. 2010); (Hanahan and Weinberg 2011) (Taipale et al. 2010); (Rutherford and Lindquist 1998); (Zhao et al. 2005); (Lu et al. 2012b); (Barrott and Haystead 2013); (Methot et al. 2015); (Fig. 3).

KIs and H90Ins

Kinases and HSP90 both utilize ATP in their molecular function. Kinases employ ATP by adding the gamma phosphate group onto substrates in order to transmit a signal (Burnett and Kennedy 1954; Fischer et al. 1959), while HSP90 uses ATP hydrolysis to fuel the conformational dynamics that drive its chaperone activity (Grenert et al. 1997; Prodromou et al. 1997). Targeting the structural pocket that binds ATP in kinases has been a major focus of the pharmaceutical industry for over two decades and has yielded an arsenal of kinase inhibitors. These KIs vary as the ATP-binding pocket varies from kinase to kinase allowing for a degree of specificity and the ability to target key signaling pathways that promote malignant growth (Knight and Shokat 2005). However, in response to such inhibition, tumors often mutate the ATP-binding pocket and other structural features of the kinase domain in order to greatly reduce the affinity of the KI, and thus reinitiating pro-growth signaling (Pao et al. 2005; Miyajima et al. 2013); (Katayama et al. 2011). Importantly, many of these mutations make the kinase structurally unstable and more dependent on HSP90 to maintain function (Miyajima et al. 2013); (Shimamura et al. 2008); (Barrott and Haystead 2013); (Shimamura et al. 2005; Sang et al. 2013; Lachowiec et al. 2015). Conversely, a kinase may also evolve HSP90 independence through mutations that stabilize its structure as observed throughout evolution (Nony et al. 2003; Taipale et al. 2012). However, combined administration of KIs and H90Ins would place opposing pressures upon the kinase to alter the KI-binding site in order to regain kinase activity, while at the same time, altering its structure to attain HSP90 independence, thus making the evolutionary walk of such a kinase improbable. Indeed, in a random mutagenesis screen of BCR-ABL, while numerous KI resistance mutants were identified, no H90Ins resistance mutants were identified (Tauchi et al. 2011). Alternatively, a tumor may also compensate for the inhibition of one growth promoting kinase by activating another kinase signaling pathway (Chen et al. 2012); (Lee et al. 2013). Such phenomena demonstrate the need to simultaneously inhibit multiple kinases, which may be accomplished by targeting HSP90. Clinically evaluated H90Ins target the ATP-binding pocket of HSP90, which is distinct from kinase ATP-binding pockets (Whitesell et al. 1994; Neckers and Trepel 2014). H90Ins operate by locking HSP90 into a static structural conformation that prevents it from chaperoning its client kinases. This leads to destabilization of the kinases and their eventual degradation by the proteasome (Trepel et al. 2010); (Barrott and Haystead 2013); (Miyata et al. 2013); (Fig. 4).

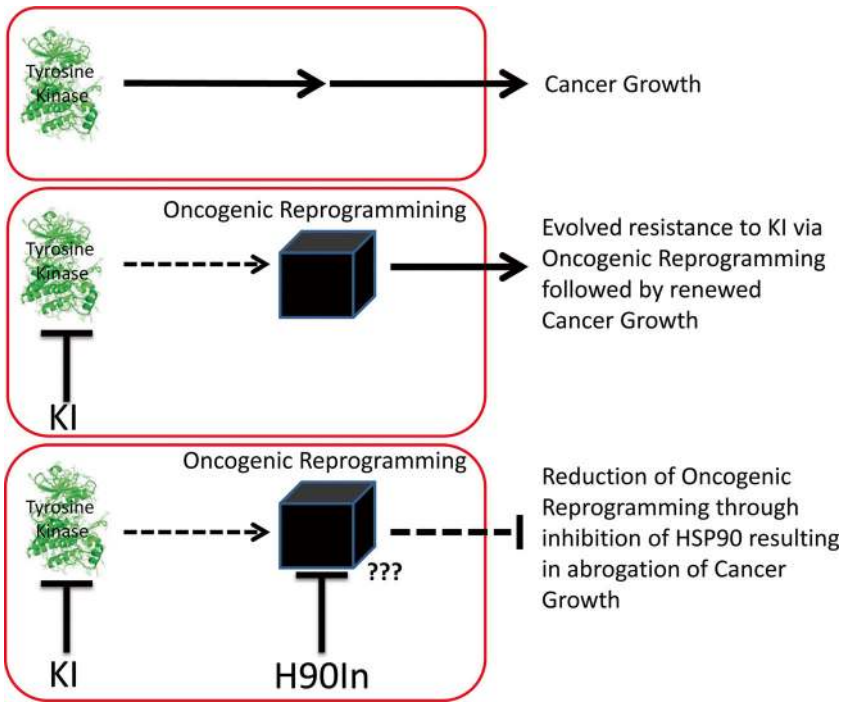

Fig. 3 Model of the oncogenic reprogramming concept that allows for evolved drug resistance in cancer

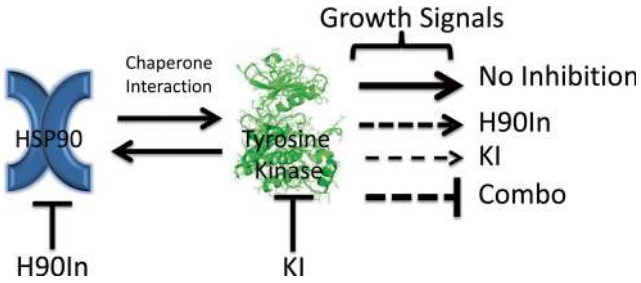

Fig. 4 Model of oncogenic growth signal output reduced by combined treatment

Despite their theoretical efficacy and initial promise (Kamal et al. 2003); (Neckers and Workman 2012), treating cancer patients with H90Ins alone has not proven to be particularly effective (Barrott and Haystead 2013). As single agents, H90Ins require higher effective dosages for inhibiting tumor growth, often resulting in increased toxicity (Barrott and Haystead 2013); (Johnson et al. 2015); (Jhaveri et al. 2012); (Sequist et al. 2010); (Sessa et al. 2013). Some of these side effects may be the result of off-target inhibition of the HSP90 homologues, which reside in the endoplasmic reticulum (GRP94) and mitochondria (TRAP1), although this has not been determined. Moreover, these side effects and the need for increased dosing may be related in part to the phenomenon that HSP90 inhibition leads to activation of a feedback loop that involves HSF1, the master stress response transcription factor (Bagatell et al. 2000); (Ciocca et al. 2013). HSF1 is responsible for initiating an adaptive, pro-survival, and anti-apoptotic gene expression program, which includes a number of molecular chaperones. Consequently, HSF1 activation likely reduces the effectiveness of HSP90 inhibition in cancer and may even enhance transcription of certain cancer-promoting genes that comprise a unique cancer-specific HSF1 transcriptional signature (Dai et al. 2007); (Santagata et al. 2013); (Mendillo et al. 2012). Thus, identifying approaches to uncouple this feedback loop are a major focus in the HSP90 research field. Combining H90Ins with specific KIs is one possible strategy since HSF1 activity is regulated by kinase cascades to some degree (Guettouche et al. 2005); (Holmberg et al. 2002); (Calderwood et al. 2010). For example, mTORC and MEK1 have been shown to phosphorylate HSF1 on S326, a post-translational modification important for inducing the heat shock response. Moreover, inhibition of these kinases reduces HSF1 overall transcriptional activity, suggesting a possible combination of inhibitors that may prove effective in treating specific tumor types (Chou et al. 2012); (Tang et al. 2015); (Acquaviva et al. 2014a, b).

TCGA

The Cancer Genome Atlas is a national initiative to characterize over 80 forms of cancer at the molecular level. Its goal is to sequence the entire genome and quantitatively characterize a representative number of cases of a defined tumor type, providing information on gene copy number, promoter methylation patterns, RNA expression levels, global mutation analysis, and eventually proteomic profiling (http://cancergenome.nih.gov/). These data are made publicly available as they are processed and published, allowing for further analysis by the cancer research community. Several sites and institutes host and distribute TCGA data including cBioPortal at Memorial Sloan-Kettering Cancer Center, which was utilized here (Gao et al. 2013); (Cerami et al. 2012).

In our analysis of the mRNA expression levels and open reading frame mutations of 31 representative kinases that associate with HSP90, we found that a large percentage of samples from each of 23 tumor types either overexpress or possess a mutated HSP90-dependent kinase or parallel activator of kinase activity (PAKA) such as PIK3CA or KRAS (Table 1, see Supplemental Tables 2 and 3 for sources). When the number of overexpressed (blue column) HSP90-dependent kinases is combined, this percentage exceeds 50 % in all tumor types compared to normal corresponding tissue. This frequency reaches 80 % or greater in seven tumor types: cervical cancer (CESC), chromophobe renal cell carcinoma (KICH), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), stomach adenocarcinoma (STAD), bladder cancer (BLCA), and uterine carcinoma (UCS). Further, when combined with PAKA overexpression, this frequency increased by an additional 12 % in lung squamous cell carcinoma (LUSC) and by 15 % in ovarian cancer (OV). When the sum total (orange row) of all overexpressed kinases and PAKAs within the table is calculated, the value exceeds 100 and is often more than twice the actual grand total (red row) provided by TCGA, indicating that more than one HSP90-dependent kinase is overexpressed in a single tumor. Indeed, this has been observed in other studies where one third of stomach cancers were found to overexpress multiple HSP90-dependent receptor tyrosine kinases (Nagatsuma et al. 2014); (Sjoblom et al. 2006); (Greenman et al. 2007). In contrast, the combined number of mutated (green column) HSP90 dependent kinases and PAKAs does not exceed a frequency of 50 % in most tumor types. However, in certain tumor types, including colon and rectal adenocarcinoma (COAD), cutaneous melanoma (SKCM), lung adenocarcinoma (LUAD), papillary thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC), mutation frequencies are above 70 %.

Based on these TCGA data, we suggest that individual KI and H90In combinations should be explored in a variety of tumor types. For example, in breast cancer (BRCA), the kinase ERBB2 is overexpressed in 13 % of 526 tumor samples while the signaling component PIK3CA is mutated in 35 % of 507 tumor samples. Combining an H90In with either an ERBB2 inhibitor or a number of PIK3CA inhibitors may

Table 1 Profile of the percentage of tumors upregulating mRNA expression by two standard deviations or possessing a mutant form of an HSP90-dependent kinase or parallel activator of kinase activity (PAKA). *Blue columns*, list of the percentage of tumors with mRNA expression; *green columns*, list of the percentage of tumors with mutants; *gold rows*, list of the TCGA totals for each tumor type; *red row*, list of the TCGA grand totals of both kinases and PAKAs; and *orange row*, list of the sum totals of kinases and PAKAs, which was calculated by adding up all the observed percentages within the column. Inhibitors are listed on the right. Data was collected from TCGA cBioPortal (Gao et al. 2013); (Cerami et al. 2012) and Blue Ridge Institute for Medical Research (Roskoski 2015)

Kinase table	AML		ACC		BRCA		CESC		KICH		KIRC		COAD		SKCM		
12/29/2014	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	
Sample size:	173	200	79	91	526	507	207	39	66	65	469	424	244	224	384	345	Clinically approved inhibitors
ABL1	5	2	9	0	4	1	6	3	5	0	3	1	3	1	2	4	Imatinib, Nilotinib, Ponatinib, Regorafenib (BCR-Abl), Dasaitinib, Bosutinib
AKT1	3	0	9	0	4	2	9	0	24	0	4	0	4	1	5	1	
ALK	5	0	3	2	4	1	5	3	9	0	3	1	1	5	3	10	Crizotinib, Ceritinib
AXL	4	0	4	2	2	0	6	0	3	0	6	0	5	2	4	4	Cabozantinib
BRAF	2	0	14	1	5	1	4	3	3	0	6	0	5	9	9	51	Vemurafenib (V600E)
CSF1R	5	0	8	1	2	0	3	3	6	2	2	1	5	1	3	3	Sunitinib
DDR2	2	1	5	0	1	1	9	0	11	2	3	0	5	2	7	2	
EGFR	5	1	6	3	6	1	8	3	2	0	5	2	9	4	4	6	Afatinib, Erlotinib, Gefitinib, Lapatinib, Vandetanib
EPHB1	3	1	4	1	7	1	2	3	5	2	1	0	3	4	5	8	
EPHB6	4	0	5	1	6	0	5	5	8	0	5	1	2	2	4	8	
ERBB2	5	0	6	0	13	1	10	3	2	0	7	1	8	5	6	3	Lapatinib
ERBB4	2	0	4	3	0	1	5	3	2	2	4	1	3	8	3	16	
FGFR1	6	0	14	0	7	0	8	0	2	0	5	1	3	1	4	3	Pazopanib, Regorafenib, Lenvatinib, Nintedanib
FGFR2	5	0	5	2	3	1	3	0	20	0	4	0	6	1	4	8	Regorafenib, Levantinib
FGFR3	8	0	3	0	3	0	2	0	14	0	3	1	4	1	6	3	Lenvatinib, Pazopanib
FLT3	5	27	4	1	1	1	6	0	2	0	4	0	5	2	2	8	Sorafenib, Sunitinib, Cabozantinib, Ponatinib
IGF1R	5	0	4	1	3	0	5	0	2	0	4	0	4	4	10	4	Ceritinib
INSRR	2	0	1	1	2	1	2	0	33	0	6	1	5	3	1	9	
JAK2	5	1	5	1	4	1	7	3	2	0	3	1	4	2	2	2	Ruxolitinib
KDR	4	1	5	1	2	0	2	0	2	0	4	1	1	4	2	13	Axitinib, Cabozantinib, Pazopanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib, Levantinib, Nintedanib
KIT	5	4	6	0	3	1	3	0	3	0	4	1	2	3	7	4	Sorafenib, Sunitinib, Cabozantinib, Dasatinib, Imatinib, Pazopanib, Ponatinib, Regorafenib, Levantinib
MET	6	0	9	0	3	1	6	0	3	0	9	1	4	2	6	8	Cabozantinib, Crizotinib
MST1R	5	1	9	0	0	0	4	8	3	0	4	1	4	0	4	3	
NEK2	4	0	5	1	6	0	7	0	17	0	7	0	7	1	11	2	
NTRK3	2	1	6	2	5	1	5	0	3	3	6	0	1	4	6	8	
PDGFRA	3	1	1	1	1	1	3	0	12	0	6	1	2	5	2	10	Regorafenib, Sorafenib, Sunitinib, Pazopanib, Imatinib, Levantinib, Nilotinib, Nintedanib, Ponatinib
RAF1	3	0	6	0	6	0	5	0	5	0	3	0	5	2	6	3	Sorafenib, Vemurafenib
RET	1	0	1	2	0	1	4	0	5	0	1	0	5	4	4	6	Cabozantinib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib, Levantinib
STYK1	7	0	1	2	0	0	3	3	9	0	7	0	7	0	4	5	
TEK	3	1	5	0	1	0	6	3	5	0	3	0	4	4	3	6	
TNK2	2	0	4	0	3	0	27	0	6	0	4	0	7	0	4	3	
Total	62	37	68	19	61	16	84	28	86	8	60	19	67	34	71	85	
ERBB3	4	0	1	1	1	2	5	5	11	2	5	1	5	6	4	2	
HRAS	4	0	5	0	3	0	5	0	8	0	5	0	5	0	5	1	
KRAS	2	4	8	0	3	1	7	3	3	0	4	0	7	42	7	1	
NRAS	5	8	5	1	3	0	3	0	0	2	3	0	5	9	7	28	
PIK3CA	3	0	14	1	8	35	33	23	2	0	4	3	4	20	3	3	Apitolisib, Buparlisib, Copanlisib, Dactolisib, BYL719, GDC-0941, PF-04691502, PKI-587
Total	15	12	27	3	16	36	46	31	23	3	18	4	21	56	22	33	
Grand total	64	45	75	20	65	48	92	46	86	9	65	22	71	72	75	90	
Sum total	144	54	204	32	125	57	233	77	252	15	157	21	159	164	169	259	
2/27/15																	Not clinically approved
HSPAA1	5	0	4	1	5	0	7	2	5	0	5	0	4	1	2	1	Paralog Unspecific: STA-9090, SNX-2112, NVP-AUY922, PU-H71, AT13387, 17-AAG, XL888, TAS-116, DS-2248
HSPAB1	2	0	3	1	6	0	6	0	8	2	6	0	9	0	17	2	
CDC37	5	0	28	1	3	0	11	0	6	0	4	0	7	0	8	0	
Total	10	0	32	3	11	1	21	2	14	2	13	2	17	1	25	4	

Table 1 (continued)

Kinase table	DLBC		GBM		HNSC		LIHC		LGG		LUAD		LUSC		OV		
12/29/2014	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	
Sample size:	28	N/A	154	291	279	279	212	202	527	289	230	230	178	178	489	316	Clinically approved inhibitors
ABL1	7	N/A	6	0	7	0	7	0	3	0	3	1	6	1	1	0	Imatinib, Nilotinib, Ponatinib, Regorafenib (BCR-Abl), Dasaitinib, Bosutinib
AKT1	0	N/A	4	0	15	1	5	1	3	0	6	1	7	1	5	0	
ALK	4	N/A	5	0	3	3	3	4	4	0	3	8	8	3	7	1	Crizotinib, Ceritinib
AXL	4	N/A	4	1	4	1	6	4	3	0	4	2	4	2	3	0	Cabozantinib
BRAF	14	N/A	10	2	8	1	8	1	5	1	10	10	8	4	9	1	Vemurafenib (V600E)
CSF1R	4	N/A	4	0	2	0	4	1	6	0	3	2	2	1	3	0	Sunitinib
DDR2	4	N/A	5	0	5	2	6	2	5	0	3	3	6	1	4	0	
EGFR	11	N/A	44	21	17	5	8	3	12	6	13	14	16	3	4	2	Afatinib, Erlotinib, Gefitinib, Lapatinib, Vandetanib
EPHB1	7	N/A	9	0	11	3	3	3	4	0	4	7	7	9	7	1	
EPHB6	4	N/A	8	1	5	1	3	0	5	1	3	9	5	1	10	0	
ERBB2	4	N/A	4	0	5	2	7	2	6	0	15	3	2	2	3	1	Lapatinib
ERBB4	4	N/A	5	0	3	5	2	4	3	0	2	8	4	5	0	0	
FGFR1	11	N/A	5	0	5	0	5	1	4	0	6	1	12	2	7	0	Pazopanib, Regorafenib, Lenvatinib, Nintedanib
FGFR2	4	N/A	1	0	8	1	6	4	3	0	3	2	7	3	3	0	Regorafenib, Levantinib
FGFR3	4	N/A	8	1	2	2	6	3	5	0	8	0	5	0	4	0	Lenvatinib, Pazopanib
FLT3	7	N/A	3	1	2	1	3	5	3	0	4	5	4	2	5	1	Sorafenib, Sunitinib, Cabozantinib, Ponatinib
IGF1R	7	N/A	4	1	9	2	5	5	5	1	6	1	7	1	2	0	Ceritinib
INSRR	4	N/A	9	0	3	0	9	4	3	0	3	7	5	4	3	2	
JAK2	0	N/A	2	0	8	1	3	4	3	0	4	3	5	2	5	1	Ruxolitinib
KDR	11	N/A	4	2	3	1	3	6	4	1	8	8	3	7	3	0	Axitinib, Cabozantinib, Pazopanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib, Levantinib, Nintedanib
KIT	4	N/A	10	1	1	1	1	4	3	1	4	2	1	4	7	2	Sorafenib, Sunitinib, Cabozantinib, Dasatinib, Imatinib, Pazopanib, Ponatinib, Regorafenib, Levantinib
MET	7	N/A	19	0	6	1	7	0	6	1	16	8	3	1	6	1	Cabozantinib, Crizotinib
MST1R	4	N/A	1	1	4	2	6	2	3	0	2	0	3	2	3	1	
NEK2	4	N/A	5	0	6	0	16	1	6	0	8	0	7	0	3	0	
NTRK3	4	N/A	4	0	5	3	2	3	3	0	4	8	1	3	6	1	
PDGFRA	7	N/A	19	3	5	2	5	5	4	2	4	6	7	4	3	1	Regorafenib, Sorafenib, Sunitinib, Pazopanib, Imatinib, Levantinib, Nilotinib, Nintedanib, Ponatinib
RAF1	4	N/A	3	0	1	1	6	1	3	0	6	1	3	1	5	0	Sorafenib, Vemurafenib
RET	11	N/A	1	0	5	3	2	2	4	1	6	4	2	1	3	0	Cabozantinib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib, Levantinib
STYK1	4	N/A	3	0	8	0	2	1	5	0	3	0	13	1	3	1	
TEK	11	N/A	5	1	3	1	4	6	3	1	2	2	2	2	3	1	
TNK2	7	N/A	5	1	21	1	5	2	4	0	4	2	31	1	9	0	
Total	71	N/A	86	34	81	37	67	49	62	16	77	69	77	39	69	17	
ERBB3	7	N/A	5	0	3	3	4	4	3	0	5	0	8	2	2	1	
HRAS	4	N/A	2	0	3	4	7	0	3	0	5	0	2	2	2	0	
KRAS	7	N/A	3	1	12	0	5	2	6	0	11	33	12	1	18	1	
NRAS	4	N/A	5	0	3	0	8	0	3	0	7	0	3	0	6	1	
PIK3CA	11	N/A	5	9	39	21	7	4	5	9	9	7	58	10	33	1	Apitolisib, Buparlisib, Copanlisib, Dactolisib, BYL719, GDC-0941, PF-04691502, PKI-587
Total	29	N/A	16	10	47	26	25	11	18	9	29	39	66	14	51	3	
Grand total	71	N/A	87	42	89	51	71	53	66	23	82	84	89	44	84	20	
Sum total	215	0	239	47	250	75	189	94	153	25	207	168	279	89	200	22	
2/27/15																	Not clinically approved
HSPAA1	4	N/A	0	0	11	1	3	0	3	0	9	2	8	0	3	0	Paralog Unspecific: STA-9090, SNX-2112, NVP-AUY922, PU-H71, AT13387, 17-AAG, XL888, TAS-116, DS-2248
HSPAB1	4	N/A	4	0	10	2	14	0	5	0	13	1	8	1	4	0	
CDC37	4	N/A	6	0	5	0	6	0	5	0	2	0	6	1	10	0	
Total	11	N/A	10	0	20	4	20	1	12	0	21	4	18	3	16	0	

Table 1 (continued)

Kinase table	KIRP		THCA		STAD		PRAD		BLCA		UCS		UCEC		
12/29/2014	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	mRNA	Mutation	
Sample size:	213	168	489	401	265	289	374	261	129	130	57	57	333	248	Clinically approved inhibitors
ABL1	4	2	4	0	6	2	4	1	4	3	2	2	4	3	Imatinib, Nilotinib, Ponatinib, Regorafenib (BCR-Abl), Dasaitinib, Bosutinib
AKT1	4	1	4	1	4	1	4	0	7	0	9	0	6	2	
ALK	4	2	0	1	1	4	3	0	1	1	12	4	5	6	Crizotinib, Ceritinib
AXL	5	2	3	0	2	6	2	1	7	2	16	2	5	4	Cabozantinib
BRAF	5	1	3	61	7	6	2	2	12	1	4	2	6	3	Vemurafenib (V600E)
CSF1R	6	1	5	0	3	4	4	1	2	5	4	0	2	2	Sunitinib
DDR2	2	1	2	0	5	3	4	0	5	2	7	2	5	5	
EGFR	7	1	5	0	11	5	5	1	19	2	7	0	7	3	Afatinib, Erlotinib, Gefitinib, Lapatinib, Vandetanib
EPHB1	2	3	4	0	9	7	5	1	6	3	4	4	4	7	
EPHB6	2	1	5	0	2	4	5	0	6	3	7	0	4	4	
ERBB2	5	2	4	0	16	5	3	0	10	9	25	2	12	3	Lapatinib
ERBB4	2	2	6	0	1	14	4	0	8	4	4	2	5	6	
FGFR1	6	4	5	0	6	4	3	0	8	3	21	0	6	3	Pazopanib, Regorafenib, Lenvatinib, Nintedanib
FGFR2	5	1	4	0	8	4	4	1	12	2	7	2	7	13	Regorafenib, Levantinib
FGFR3	2	3	5	0	5	2	6	0	4	15	9	0	6	2	Lenvatinib, Pazopanib
FLT3	5	0	3	0	5	3	4	0	3	2	18	2	4	4	Sorafenib, Sunitinib, Cabozantinib, Ponatinib
IGF1R	4	2	4	0	6	5	4	0	5	4	5	0	6	5	Ceritinib
INSRR	1	3	0	0	1	3	4	0	3	2	16	4	4	7	
JAK2	5	2	4	0	5	4	3	0	6	2	2	2	4	5	Ruxolitinib
KDR	2	2	6	0	5	4	5	1	3	6	5	4	4	6	Axitinib, Cabozantinib, Pazopanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib, Levantinib, Nintedanib
KIT	1	1	5	0	6	3	5	0	3	2	11	2	4	7	Sorafenib, Sunitinib, Cabozantinib, Dasatinib, Imatinib, Pazopanib, Ponatinib, Regorafenib, Levantinib
MET	20	9	3	0	9	2	4	0	7	3	2	4	4	5	Cabozantinib, Crizotinib
MST1R	3	1	4	0	2	4	4	1	2	4	2	0	5	4	
NEK2	11	2	5	0	11	1	6	0	5	1	2	2	8	2	
NTRK3	3	3	4	1	3	4	5	1	2	2	11	2	2	4	
PDGFRA	5	1	6	0	6	4	1	1	7	5	4	0	5	5	Regorafenib, Sorafenib, Sunitinib, Pazopanib, Imatinib, Levantinib, Nilotinib, Nintedanib, Ponatinib
RAF1	17	1	4	0	4	3	6	0	27	1	9	0	8	3	Sorafenib, Vemurafenib
RET	3	2	6	6	5	4	3	0	1	4	7	0	4	4	Cabozantinib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib, Levantinib
STYK1	6	1	4	0	9	3	3	0	10	1	9	0	5	2	
TEK	3	1	4	0	3	4	5	0	4	2	4	2	4	6	
TNK2	2	1	4	0	8	4	5	0	4	3	21	0	11	1	
Total	74	35	62	70	80	49	59	13	85	61	93	19	64	41	
ERBB3	9	1	2	0	8	11	5	1	11	11	16	7	6	7	
HRAS	4	1	4	3	6	0	6	1	1	5	9	0	5	0	
KRAS	10	1	4	1	13	10	5	0	9	0	25	12	4	21	
NRAS	4	1	4	8	5	1	3	0	5	2	9	2	4	4	
PIK3CA	4	1	3	0	8	20	2	3	11	20	21	35	12	53	Apitolisib, Buparlisib, Copanlisib, Dactolisib, BYL719, GDC-0941, PF-04691502, PKI-587
Total	26	5	14	14	31	33	18	5	30	29	54	47	25	61	
Grand total	79	38	65	83	83	60	64	17	89	71	95	56	68	76	
Sum total	183	64	142	82	214	168	146	17	240	137	346	102	197	221	
2/27/15															Not clinically approved
HSPAA1	4	0	3	0	4	3	4	0	9	6	4	0	4	2	Paralog Unspecific: STA-9090, SNX-2112, NVP-AUY922, PU-H71, AT13387, 17-AAG, XL888, TAS-116, DS-2248
HSPAB1	7	0	3	0	12	2	4	0	9	4	9	0	7	6	
CDC37	3	0	3	0	5	2	4	0	4	0	9	0	7	1	
Total	12	1	8	0	19	6	11	1	19	10	19	0	16	7	

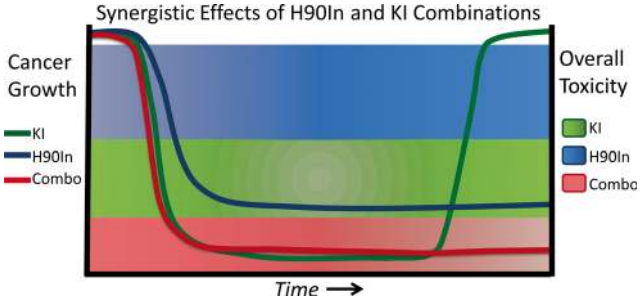

Fig. 5 Hypothesized timeline for cancer growth inhibition and overall toxicity comparing single agent KI therapy vs. combined H90In therapy

prove effective in treating certain populations of BRCA. Indeed, combination of the monoclonal antibody herceptin and H90In has shown clinical benefit (O'Connell et al. 2014). In bladder cancer (BLCA), the most cost intensive cancer to treat (Kaplan et al. 2014) RAF1 is overexpressed in 27 % while EGFR is overexpressed in 19 % of the sampled tumors. In specific cases, a combination of the RAF1 inhibitors sorafenib or vemurafenib, or a number of EGFR inhibitors, along with an H90In may prove to be effective (Acquaviva et al. 2014a, b; Huang et al. 2015). Glioblastoma multiforme (GBM) overexpresses one or more HSP90-dependent kinases in 86 % of tumors sampled. Consequently, a combination of at least 11 different KIs with an H90In is a treatment option worth exploring (Fu et al. 2013) (Wachsberger et al. 2014). Lung adenocarcinoma (LUAD), which is responsible for the largest number of cancer deaths, overexpresses EGFR in 13 %, ERBB2 in 15 %, and MET in 16 % of tumor samples. Combining a number of kinase inhibitors with an H90In may be beneficial in treating up to 77 % of patients with lung adenocarcinoma (Chen et al. 2014); (Ohkubo et al. 2015). A similar approach may be taken for uterine carcinosarcomas (UCS), which overexpress HSP90-dependent kinases in 93 % of tumors sampled.

Conclusion

Cancer is resilient. Its only function is to proliferate, and to this end, it utilizes every biological mechanism available to it to gain a proliferative advantage (Wachsberger et al. 2014); (Holmberg et al. 2002). Consequently, efforts must be focused on anticipating the routes available to cancer cells for this purpose and to implement therapies able to counter them. Indeed, evidence from preclinical models suggests that early simultaneous targeting of the HSP90 chaperone complex and specific tumor-driving kinases prolongs efficacy while possibly reducing toxicity by lowering effective drug dose (Fiskus et al. 2011); (Lu et al. 2012a, b), (Barrott and Haystead 2013); (Tonini 2015); (Miyajima et al. 2013); (Solarova et al. 2015); (Xiao et al. 2007); (Fig. 5). As with all novel treatments, determining the optimal dose combination and schedule for each tumor type will require further study.

The synergy provided by combining H90Ins with KIs is predicted to reduce the evolutionary space available to cancer by simultaneously targeting cellular proteostasis and multiple pro-growth and metastatic signaling pathways (Rutherford and Lindquist 1998); (Workman et al. 2007a; Gerlinger et al. 2014); (Whitesell et al. 2014). This hypothesis is further supported by recent observations that HSP90 influences the function of a number of other signaling components that are overexpressed, or otherwise deregulated in cancer, including transcription factors, E3-ligases, metabolic enzymes, and protein translational machinery (Taipale et al. 2014); (Liu et al. 2015); (Solier et al. 2012); (Supplemental Table 2). While development of specific inhibitors of these various signaling components lags behind the development of KIs, preliminary findings provide evidence of synergy (Brady et al. 2015).

Equally there is always the possibility that administration of H90Ins along with KIs or any other molecular therapy may result in unintended outcomes. H90Ins have the possibility of being weapons that cut both ways, and therefore, their use will require great forethought and care in wielding them. In both mouse and drosophila model systems, HSP90 inhibition has been shown to increase transposon activity in germ line cells (Specchia et al. 2010); (Ichiyanagi et al. 2014). This is understood to be related to the ability of HSP90 to maintain Piwi protein function and piRNA loading (Gangaraju et al. 2011; Izumi et al. 2013), which together function to repress transposon mobility. Uncontrolled transposon activity has been shown to result in sterility and alteration of the germ line (Fu and Wang 2014; Hadziselimovic et al. 2015). Therefore, administration of H90Ins to only the non-breeding population may be warranted, as is careful monitoring of metabolized and unmetabolized H90Ins in the water table and environment.

There is also the concern that H90Ins could impact the effectiveness of tumor suppressor pathways (Fierro-Monti et al. 2013); (Manjarrez et al. 2014). HSP90 interacts with a large portion of the proteome and is involved in maintaining tumor promoting as well as tumor suppressing cellular components (Taipale et al. 2014); (Nony et al. 2003). The tumor suppressor TP53 is mutated in a vast number of tumors, and HSP90 has been shown to associate with both mutant and WT versions of TP53 (Blagosklonny et al. 1996); (Nagata et al. 1999); (Walerych et al. 2004). However, if TP53 mutants do not function as tumor suppressors, and may even serve as tumor promoters (Walerych et al. 2012); (Shetzer et al. 2014), then compromising their stabilization by HSP90 inhibition is likely to promote anti-tumor activity (Powell et al. 2014).

HSP90 dependence of the tumor suppressor kinase STK11 (or LKB1) may be more significant, as this kinase plays a major role in regulating cellular metabolism (Nony et al. 2003); (Taipale et al. 2012); (Zhao and Xu 2014). HSP90 also participates in regulation of gene expression and genome

maintenance (Fang et al. 2014); (Sollars et al. 2003; Lu et al. 2012a, b). Despite these uncertainties, the observation that H90Ins as a class concentrate in tumor cells to a greater degree than in normal tissue is of importance and a point of hope (Kamal et al. 2003); (Moulick et al. 2011); (Taldone et al. 2014); (Suzuki et al. 2015); (Moses et al. 2015). The notion that rapidly proliferating malignant cells in a toxic microenvironment have a larger population of targetable molecular chaperones such as HSP90, and depend more on these proteostasis components for survival, fits well with the concept of chaperone addiction put forth by many others in the field (Miyata et al. 2013); (Prodromou 2009); (Workman et al. 2007a); (Calderwood et al. 2006); (Xiao et al. 2007); (Barrott and Haystead 2013).

The pioneers of combinational drug therapy, Emil Freireich, James Holland, and Emil Frei, laid the groundwork for synergistic drug combinations with their development of successful treatments for children suffering from acute lymphoblastic leukemia (Frei et al. 1958). A more recent example of this concept is the development of multi-drug cocktails for controlling HIV (Fauci et al. 2013). Unfortunately, for individuals with cancer, development of KI resistance is all too common. As a consequence, there are currently 69 clinical trials focused on targeting HSP90 (Supplemental Table 4), with 8 trials testing combinations of KIs and H90Ins (NCT01613950, NCT02192541, NCT02008877, NCT01712217, NCT02097225, NCT01657591, and NCT01236144) (Clinicaltrials.gov 2015) (Supplemental Table 5). Early reporting of the NCT01259089 phase I/II trial that combined erlotinib with the HSP90In, AUY922, for treating erlotinib-resistant non-small-cell lung cancer (NSCLC), however demonstrated only partial efficacy with an elevated toxicity profile (Johnson et al. 2015). These unfortunate findings indicate the need for improved understanding of HSP90 biology and inhibitor development but should not discourage further clinical evaluation of HS90Ins (Ohkubo et al. 2015); (Besse et al. 2014); (Hubbard 2014). Early, simultaneous administration of combined molecular therapies based on insights gathered from TCGA data should improve upon current outcomes that rely solely on single agents. Indeed, this strategy aligns with the Precision Medicine Initiative to provide quality healthcare based on individual variations in genes, environment, and lifestyle (Collins and Varmus 2015); (Zhao et al. 2015).

Cancer and its evolving genome is a complex operation given only the simple task to proliferate. An immense amount of information remains to be discovered and understood concerning the origins and driving forces of cancer. The results of ongoing clinical trials along with increased utilization of TCGA data will help not only in testing the hypothesis put forth here, but also in designing future clinical trials that incorporate HSP90 inhibition as a mechanism to combat cancer robustness and prevent oncogenic reprogramming.

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Supplemental Tables 2 and 3 provide the sources for making Table 1 and Supplemental Table 1. Supplemental Tables 4 and 5 list the current information on clinical trials using H90Ins.

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