

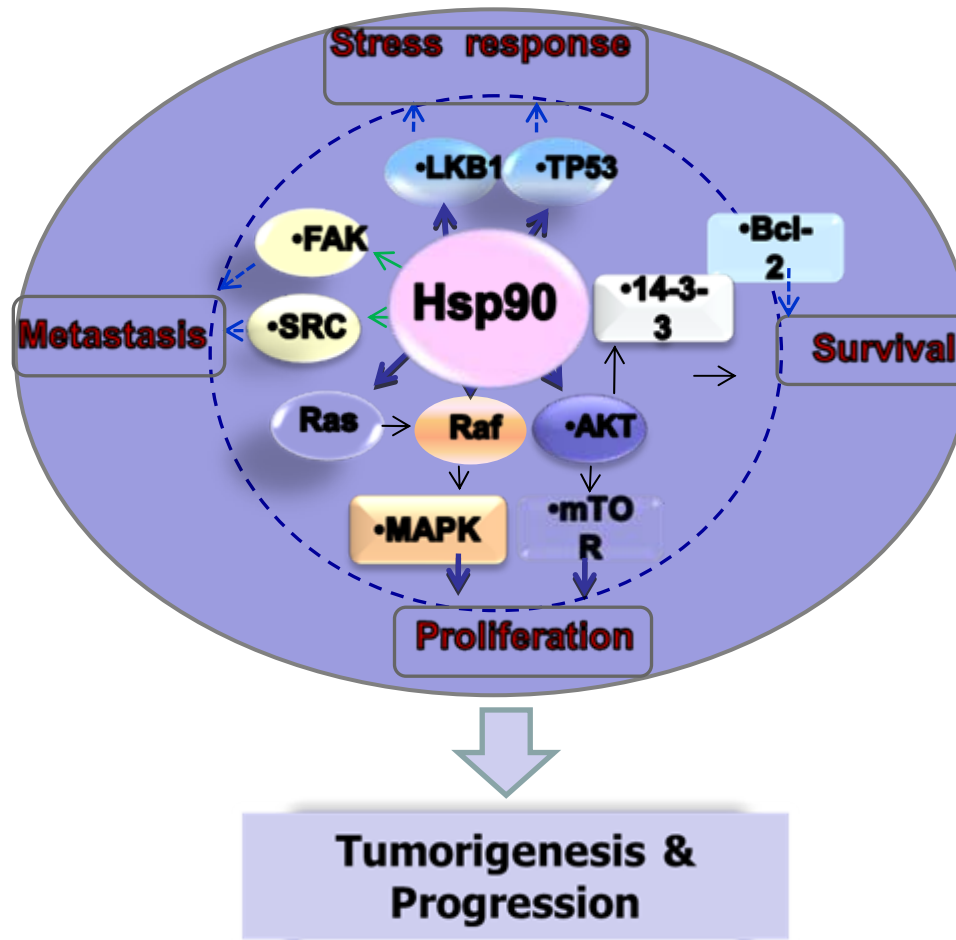
Ganetespib and Docetaxel in NSCLC

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Role of Docetaxel in Advanced NSCLC

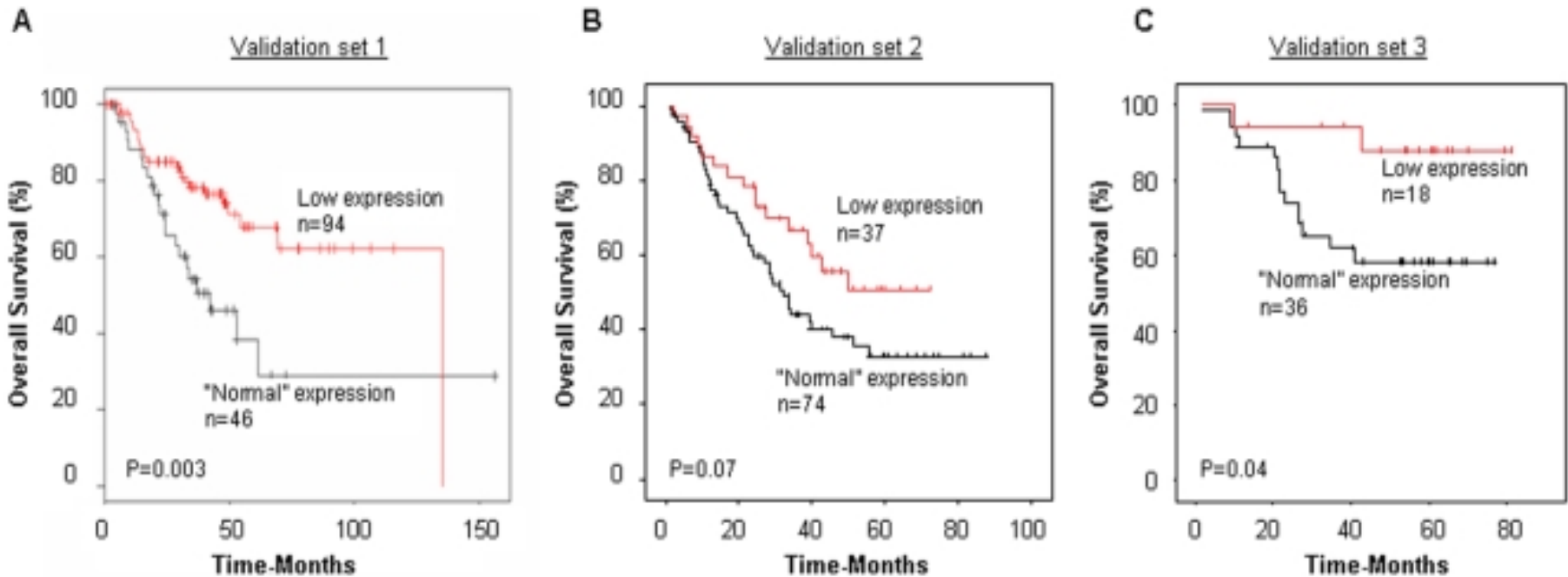
- Docetaxel has been approved by the FDA for first-line and salvage therapy of patients with advanced NSCLC
 - It is effective against all histological sub-types of NSCLC
- It has also demonstrated efficacy in the maintenance therapy setting
- In refractory NSCLC, docetaxel provides modest survival benefit
 - Response rate < 10%
 - Median PFS- 3 months
 - Median survival 6-8 months
- An efficacy plateau has been reached in salvage therapy of NSCLC with currently available agents

Hsp90 Regulates Multiple Hallmarks of Cancer



Rationale For Targeting Hsp90 in NSCLC

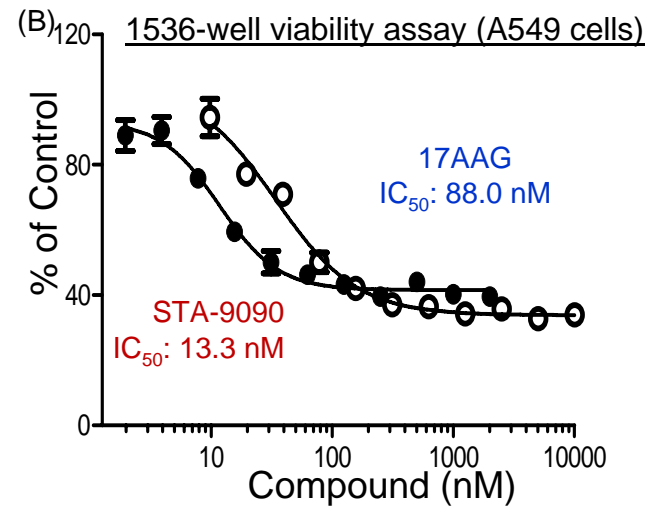
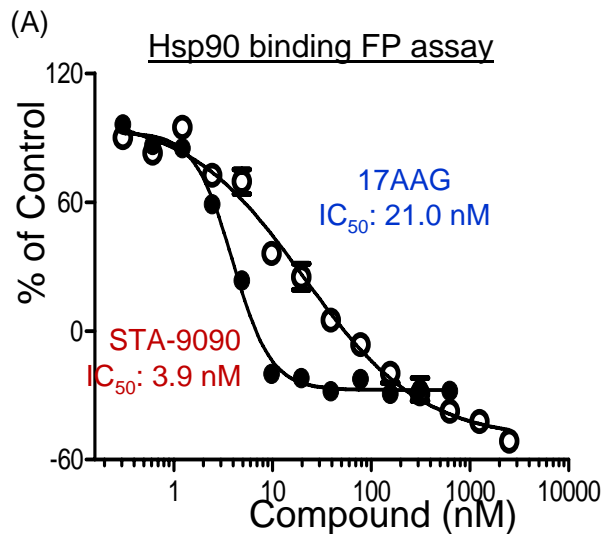
Lower gene expression of HSP90 correlates with improved Survival in NSCLC



PLoS One. 2008 Mar 5;3(3):e0001722. Integration of gene dosage and gene expression in non-small cell lung cancer, identification of HSP90 as potential target.

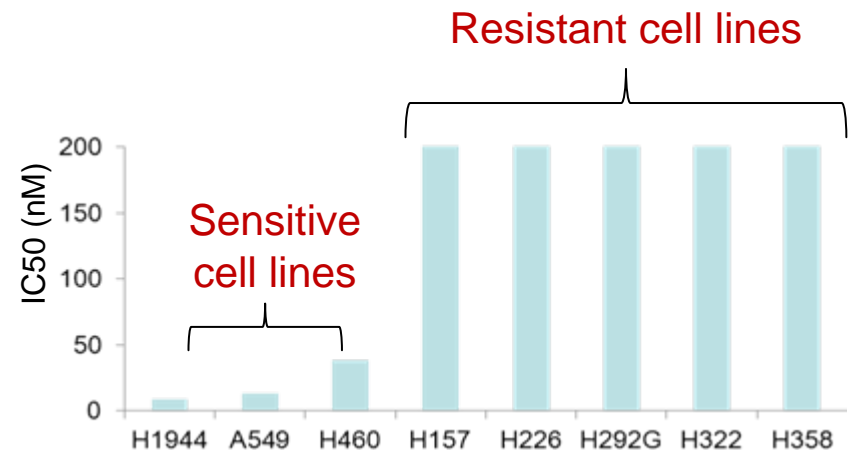
Comparison of Ganetespib with 17-AAG

STA-9090 has better potency compared to 17AAG in Hsp90 binding and lung cancer cell growth inhibition.



STA-9090 selectively inhibits the growth of a subgroup of NSCLC cells.

Du et al, Unpublished data



Ganetespib is broadly active in NSCLC with EGFR mutations

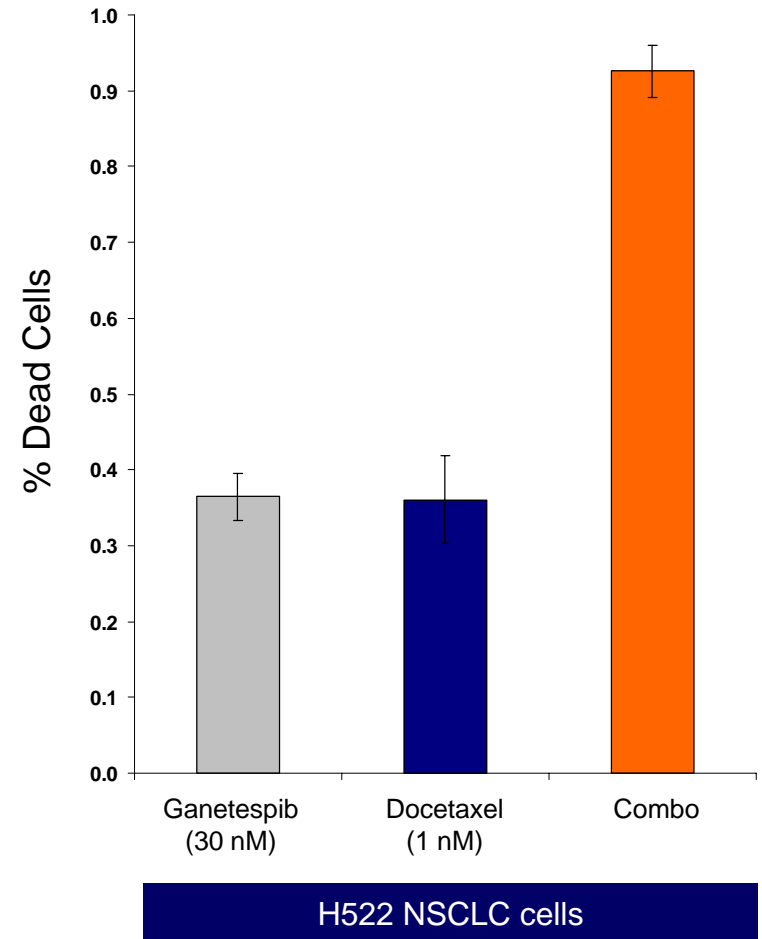
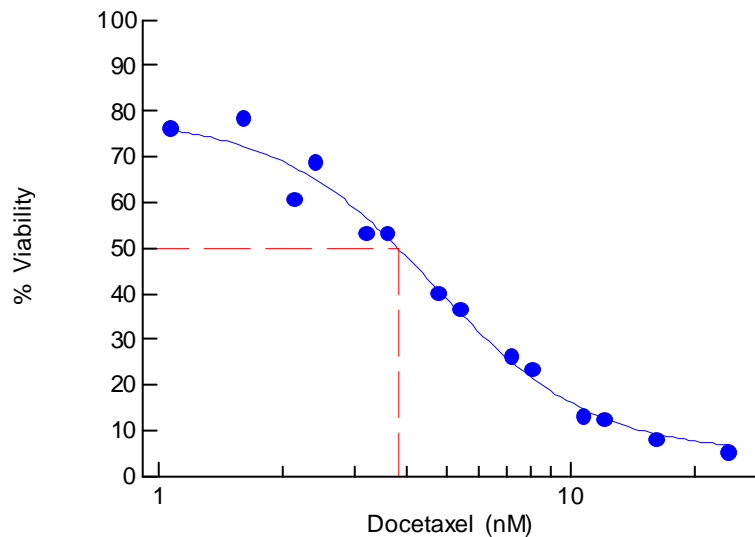
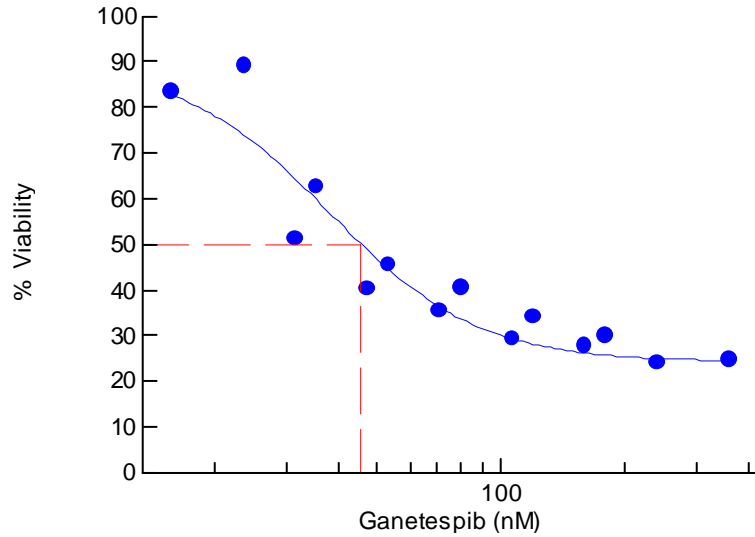
Cell Line	EGFR Status	ERBB2 Status	KRAS Status	Other	Erlotinib	17-AAG	Ganetespib
<i>H3255</i>	L858R	Wild-type	Wild-type		Sensitive	28	22
<i>HCC827</i>	Del E746_A750	Wild-type	Wild-type		Sensitive	18	7
<i>PC9</i>	Del E746_A750	Wild-type	Wild-type		Sensitive	7	2
<i>NCI-H1975</i>	L858R/T790M	Wild-type	Wild-type		Resistant	75	<1
<i>NCI-H820</i>	Del747_L751, Ins S/T790M	Wild-type	Wild-type		Resistant	34	3
<i>DFCI-LU011</i>	Del L747_E749, A750P	Wild-type	Wild-type		Resistant	111	2
<i>NCI-H1650</i>	Del E746_A750	Wild-type	Wild-type		Resistant	7	7
<i>NCI-H1781</i>	Wild-type	G776insV_G/C	Wild-type		Resistant	22	2
<i>NCI-H1734</i>	Wild-type	Wild-type	G13C		Resistant	96	12
<i>A549</i>	Wild-type	Wild-type	G12S		Resistant	75	22
<i>NCI-H460</i>	Wild-type	Wild-type	Q61H		Resistant	77	14
<i>NCI-H358</i>	Wild-type	Wild-type	G12C		Resistant	3	1
<i>A427</i>	Wild-type	Wild-type	G12D		Resistant	4	<1
<i>NCI-H441</i>	Wild-type	Wild-type	G12V		Resistant	111	26
<i>NCI-H1299</i>	Wild-type	Wild-type	Wild-type	NRAS(Q61K)	Resistant	36	6
<i>NCI-H1666</i>	Wild-type	Wild-type	Wild-type	BRAF(G466V)	Medium	27	6
<i>NCI-H1819</i>	Wild-type	Wild-type (Amp)	Wild-type		Sensitive	749	7
<i>NCI-H1703</i>	Wild-type	Wild-type	Wild-type		Resistant	3	3
<i>NCI-H596</i>	Wild-type	Wild-type	Wild-type	RB Null	Resistant	3,500	7
<i>NCI-H522</i>	Wild-type	Wild-type	Wild-type		Resistant	7	6
<i>HCC1833</i>	Wild-type	Wild-type	Wild-type		Resistant	4	<1
<i>Calu-3</i>	Wild-type	Wild-type (Amp)	Wild-type		Resistant	16	9

T.Shimamura & G.Shapiro, Dana-Farber Cancer Institute; AACR-NCI-EORTC Nov 2009

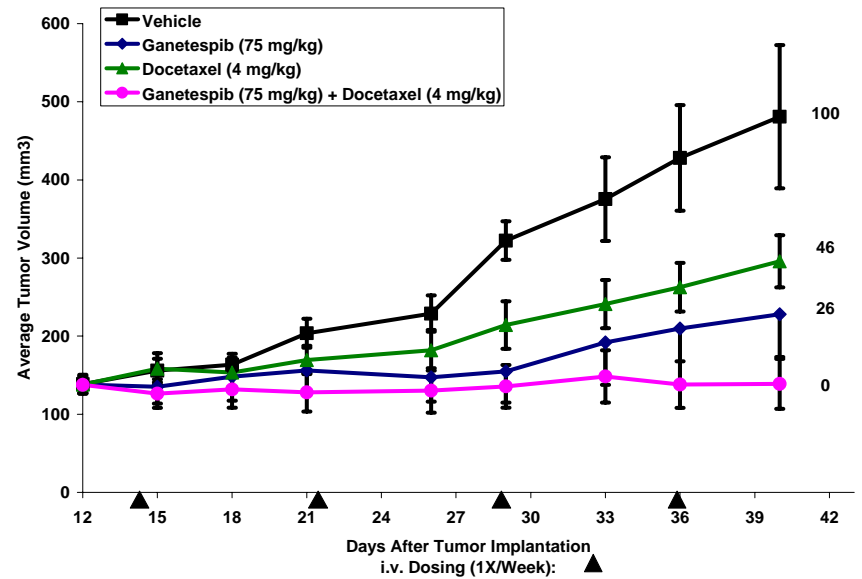
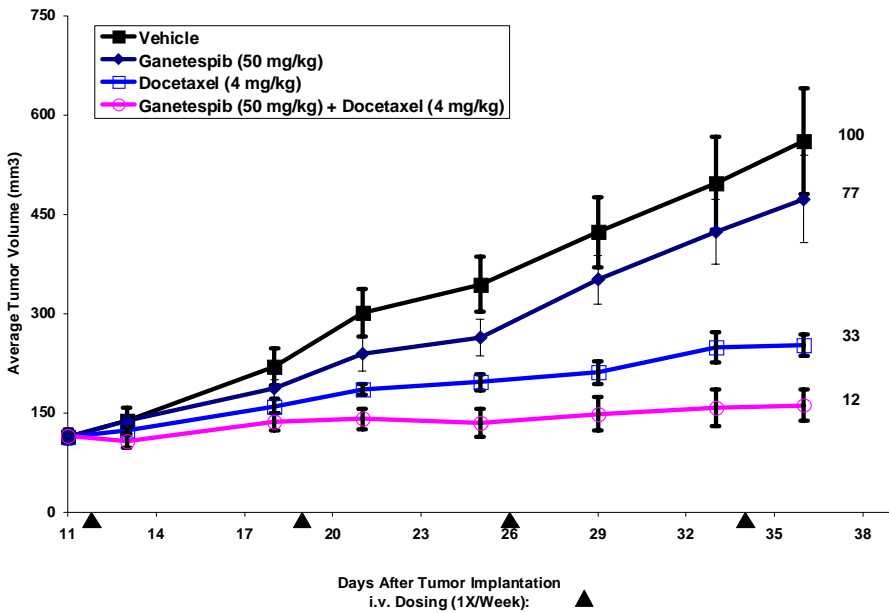
Rationale for Combining Hsp90 inhibitors and Taxanes

- Both drugs have single agent activity in NSCLC
- Ganetespib and docetaxel have synergistic MOAs
 - Cell cycle
 - Both drugs affect microtubule assembly
 - Hsp90 inhibitors interfere with taxane resistance mechanisms (eg, AKT expression, anti-apoptotic signaling through VEGF)
 - Effects of Hsp 90 inhibition on microenvironment sensitize tumors to docetaxel (vasculature, blood flow, metabolic state)
- Non-overlapping toxicity profile
 - Docetaxel DLT is bone marrow toxicity
 - Ganetespib DLT is diarrhea

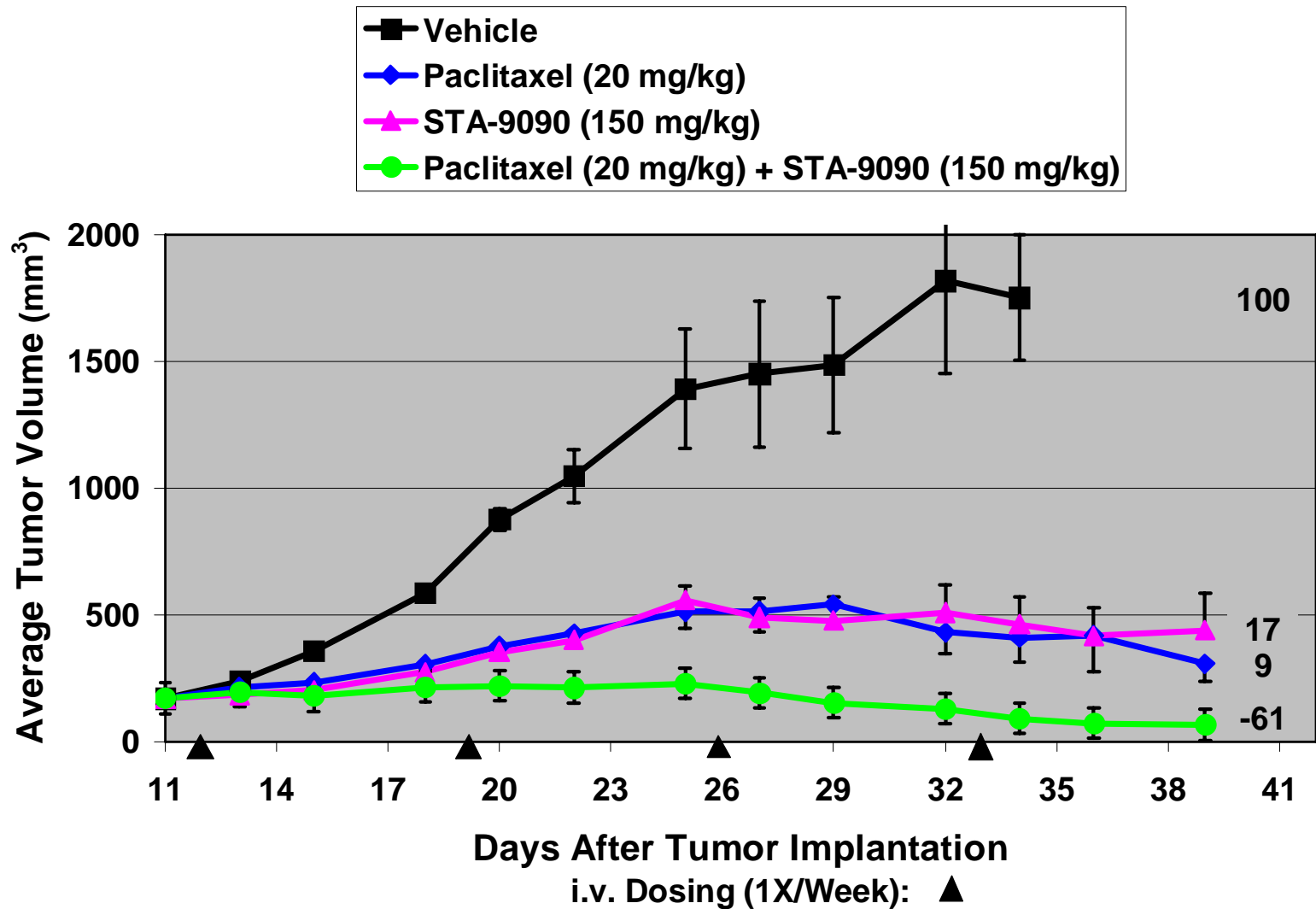
In vitro Synergy between Ganetespib and Docetaxel in H522 NSCLC cells



In vivo Synergy Between Ganetespib + Docetaxel



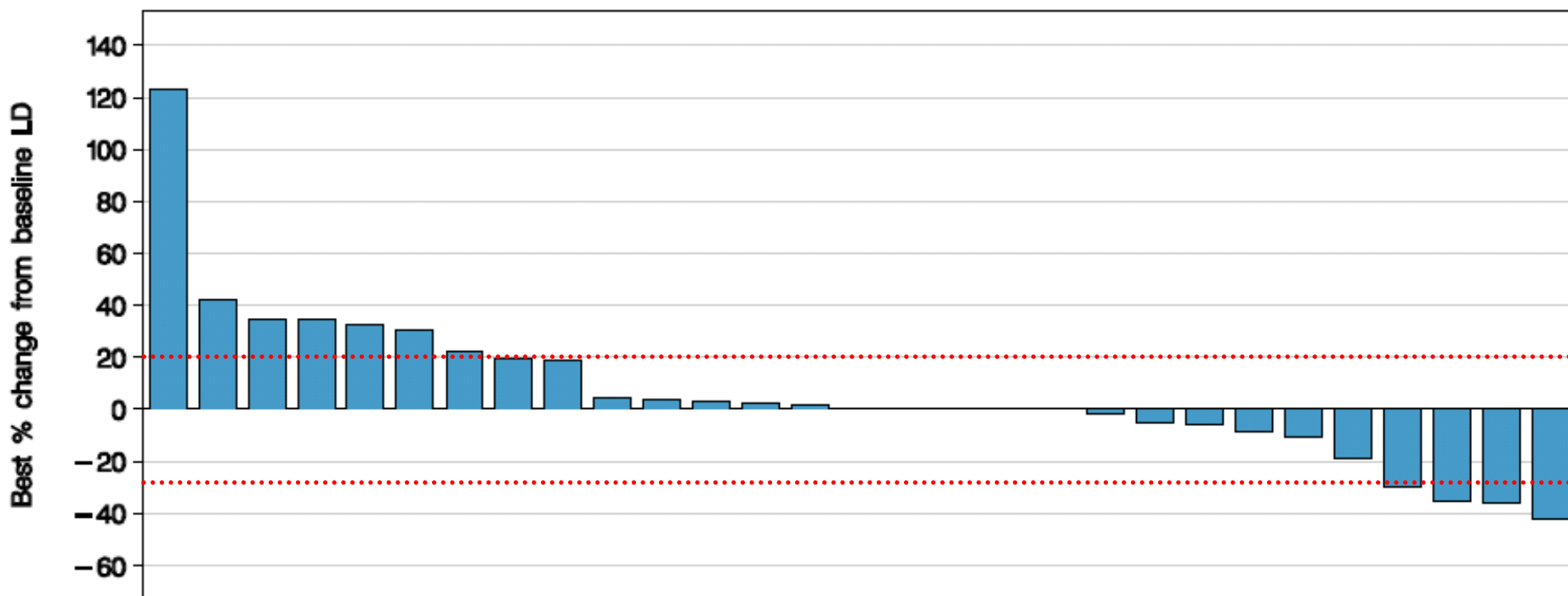
In vivo Synergy Between Ganetespib + Paclitaxel



Combination of Taxanes with Hsp90 Inhibitors

- Phase I study of 17-AAG in combination with weekly paclitaxel
- N=25 patients with advanced solid tumors
- Regimen was tolerated well
- No overlapping toxicity
- No evidence of drug-drug interactions
- Modest anti-cancer activity

Ganetespib single agent activity in patients with NSCLC



Clinical Experience of Ganetespib + Docetaxel Combination

5 patients (4 evaluable) treated with ganetespib+docetaxel combination

Patient 0059-6003

Ganetespib single agent 8 cycles 16% TL shrinkage, PD new lesions	Combo 6 cycles Shrinkage both TL and new lesions
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Patient 0656-6006

Ganetespib single agent 8 cycles 3% TL shrinkage, PD new lesions	Combo 3 cycles Shrinkage both TL and new lesions
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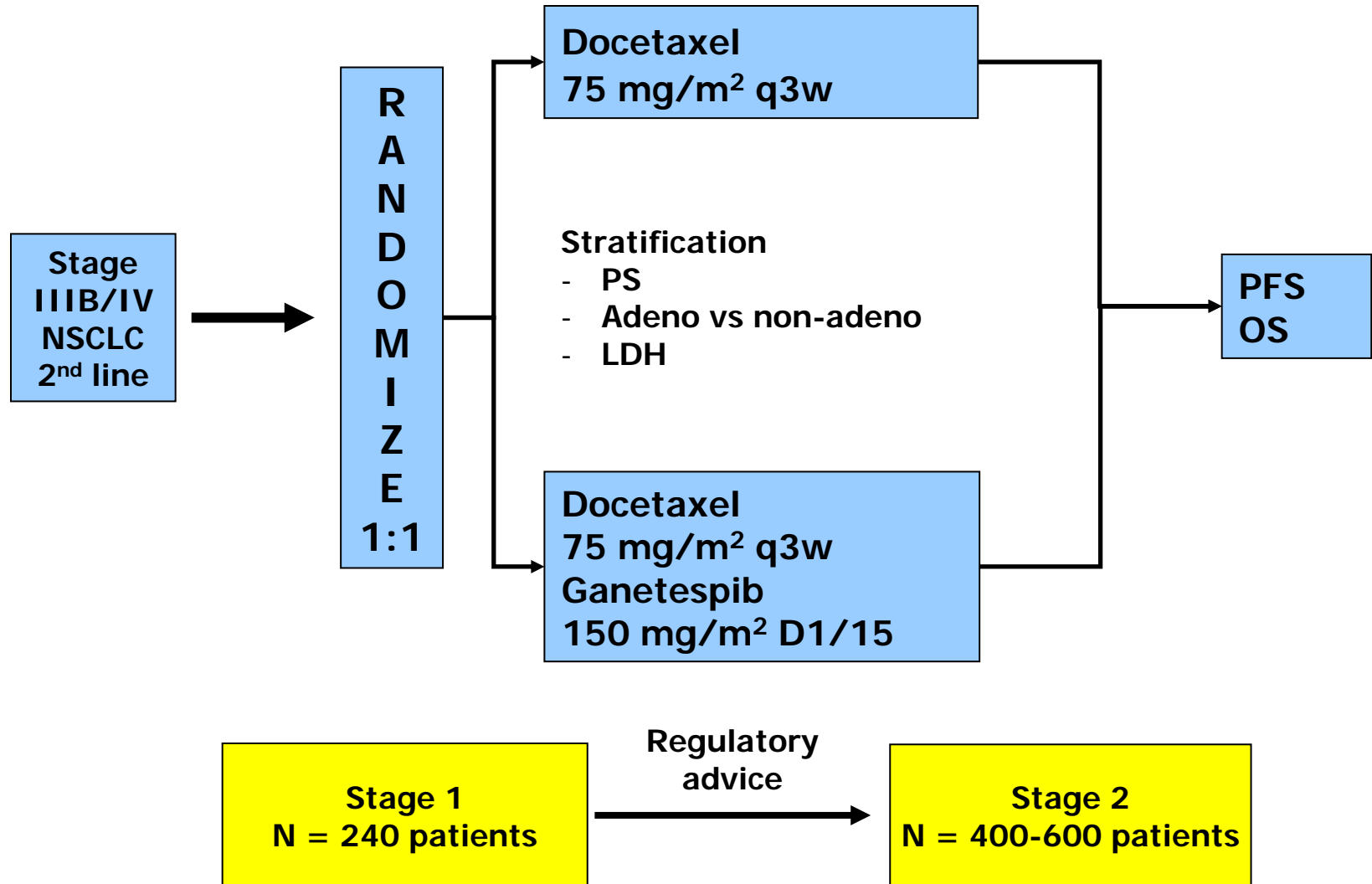
Phase 1 Docetaxel + Ganetespib Combination

- Phase I study in patients with advanced solid organ malignancies (ongoing)
- Docetaxel – day 1
- Ganetespib- days 1 & 15
- N=13 patients to date
- Recommended phase II dose: Docetaxel 75 mg/m²; Ganetespib 150 mg/m²
- DLTs- myelosuppression and diarrhea (with 200 mg/m²)
- 7 patients are still on study

Conclusions

- There is strong rationale for the combination of ganetespib and docetaxel
- The combination is tolerated well in patients with advanced solid organ malignancies
- Preliminary evidence of anti-cancer activity has been observed
- A randomized study will soon be initiated with the combination of docatexel and ganetespib

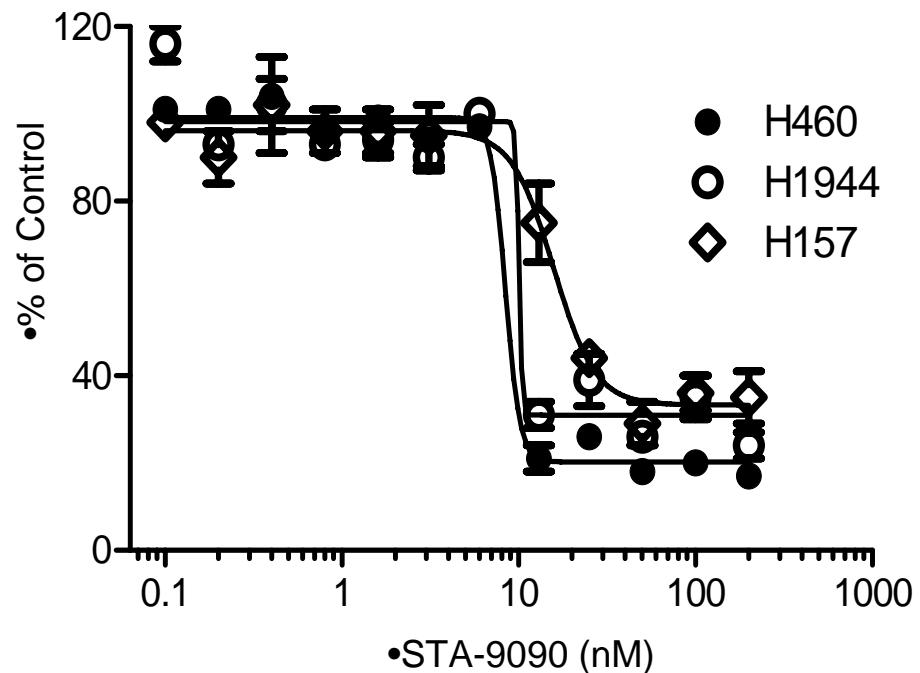
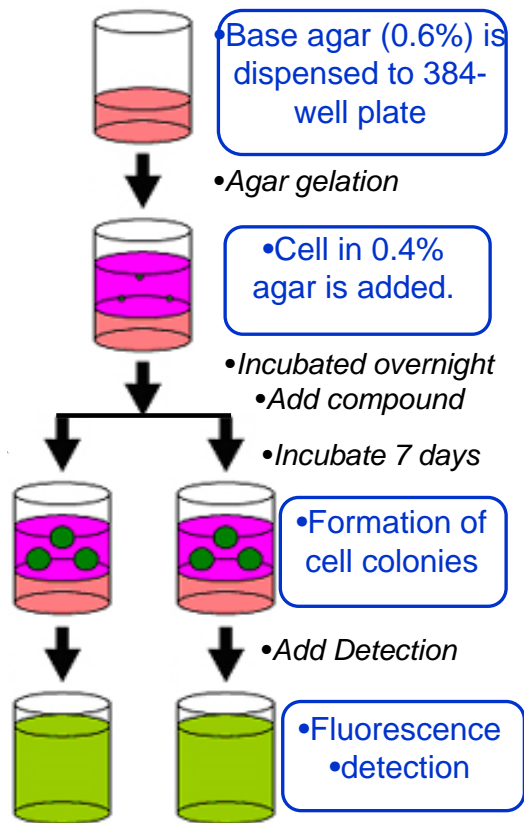
Ganetespib + Docetaxel Phase 2b/3 NSCLC Study



BACKUP / OMIT

Ganetespib in NSCLC

We have optimized and developed a HTS soft agar assay to measure the effect of compounds on anchorage-independent cell growth.



An automated soft agar anchorage-independent cell growth assay in 384-well HTS format. (A) Assay flow. (B) STA-9090 treatment inhibited A549 and H157 cell growth in soft agar. (C) The STA-9090 selectively inhibited cell growth.