

STA-9090

A Potent 2nd Generation Hsp90 Inhibitor

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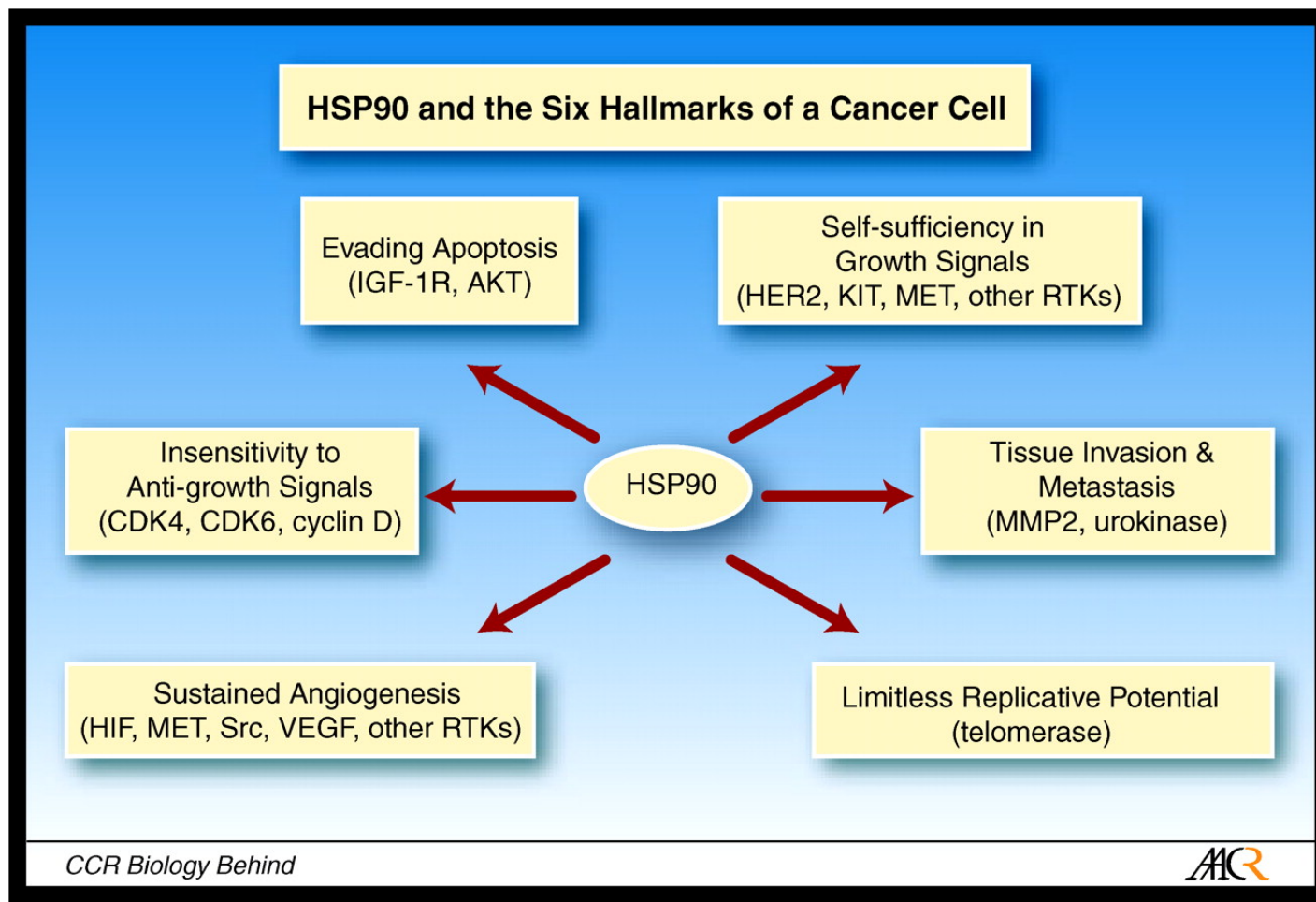
Associate Professor of Medicine, Harvard Medical School

10th Annual Targeted Therapies for the Treatment of Lung Cancer

Santa Monica, CA

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Hsp90: chaperone protein, stabilizes kinases critical to cancer cell survival, proliferation

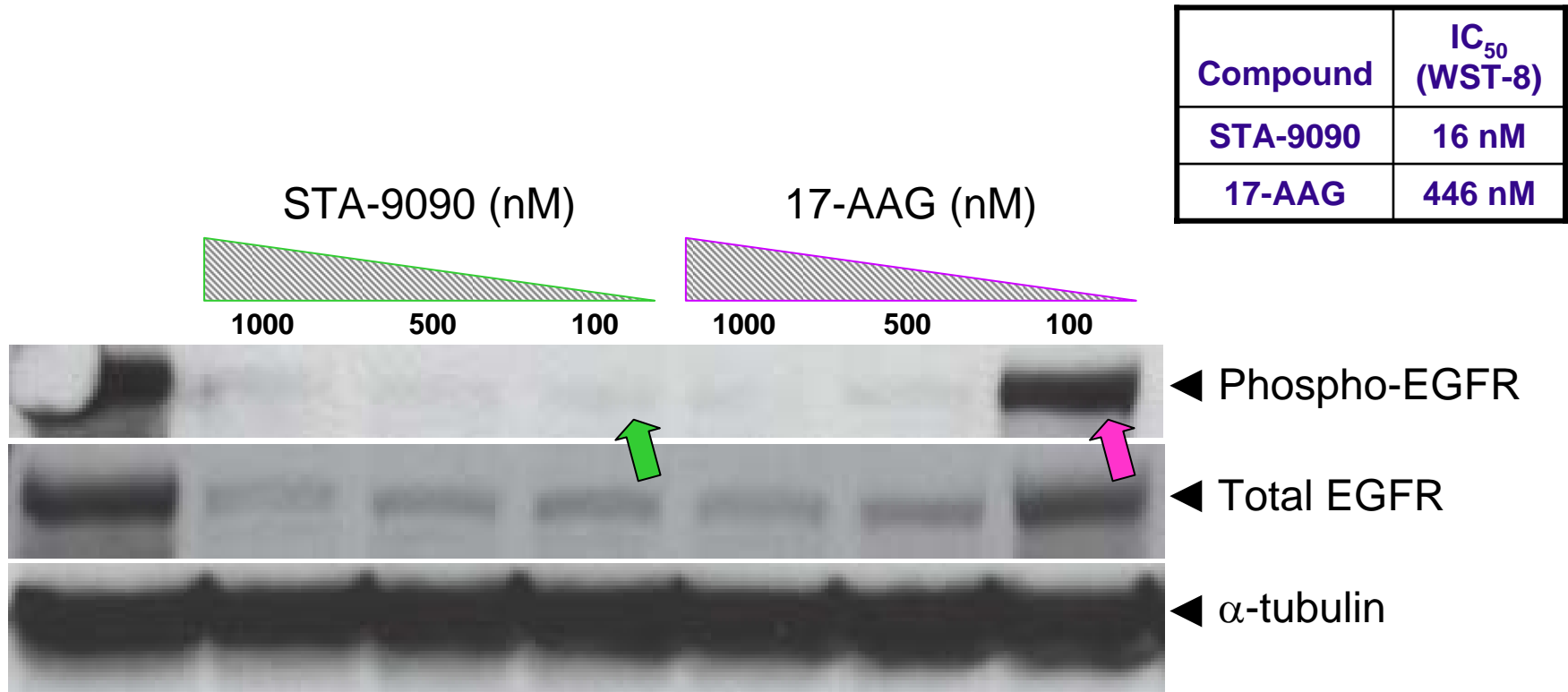


Xu, W. et al. Clin Cancer Res 2007;13:1625-1629

STA-9090: summary

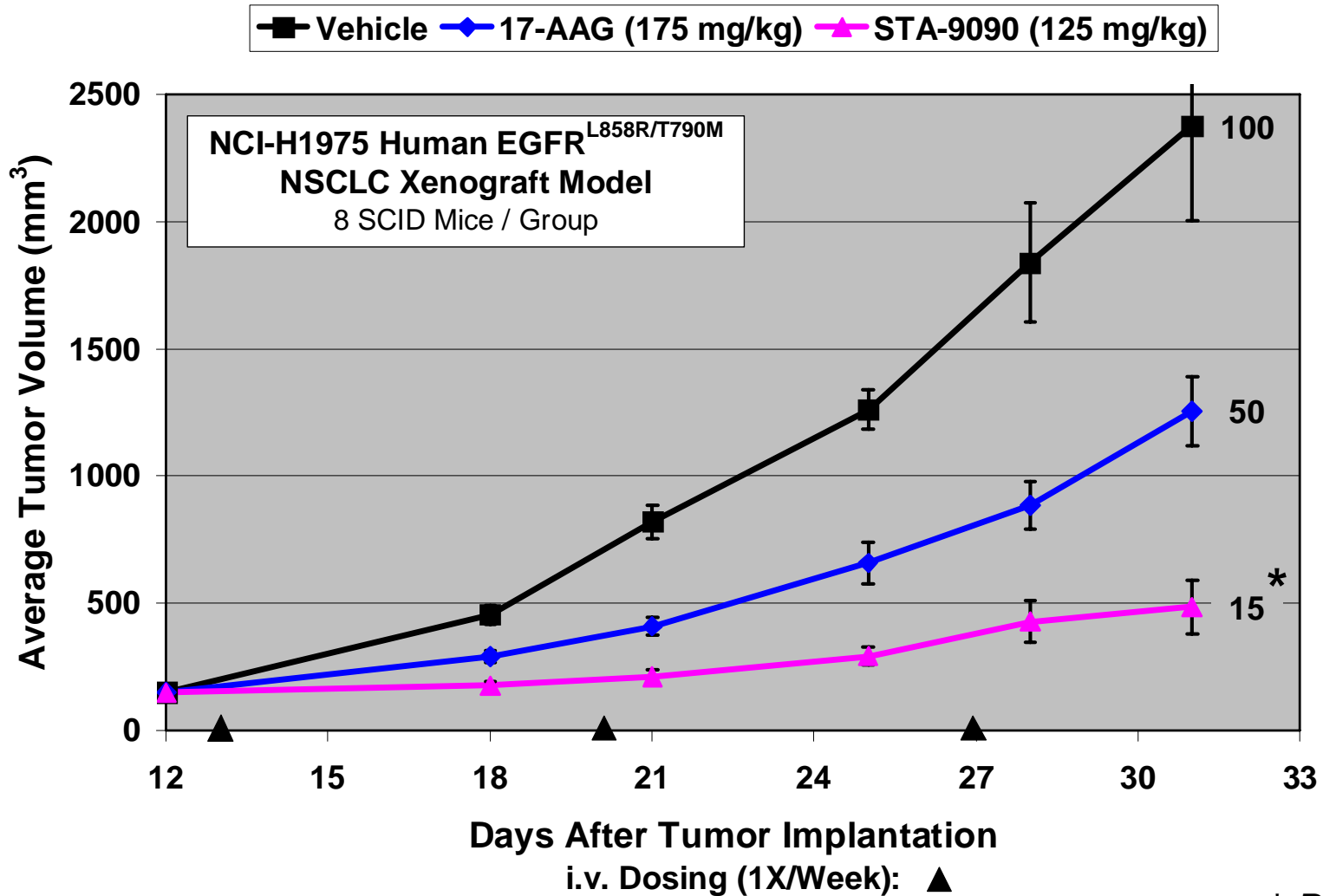
- Potent 2nd generation small molecule Hsp90 inhibitor
 - Structurally unrelated to 1st generation Hsp90 inhibitors (17-AAG, 17-DMAG & IPI-504).
 - Superiority in-vitro potency vs. 17-AAG
- Strong preclinical results and scientific rationale
 - Potently degrades multiple clinically validated oncogenic client proteins
 - Penetrates deeply into hypoxic tumors, inhibits HIF-1 α
 - Activity in 17-AAG resistant tumors
 - Single-agent activity observed in canine endogenous tumors
 - Shows synergy with other anti-cancer agents
 - Hepatotoxicity is not DLT
- Dosing: Administered 1hr IV infusion; once or twice weekly
- **Clinical Safety: Well tolerated; DLTs are fatigue and diarrhea**
- In 6 ongoing Phase 1 and Phase 2 clinical trials
 - Single-agent responses, disease control observed in multiple cancers, refractory pts

STA-9090 client protein degradation: EGFR in NSCLC



- Human NCI-H1975 erlotinib-resistant NSCLC cells (expressing EGFR^{L858R/T790M})
- STA-9090 is more potent than 17-AAG at inducing EGFR degradation

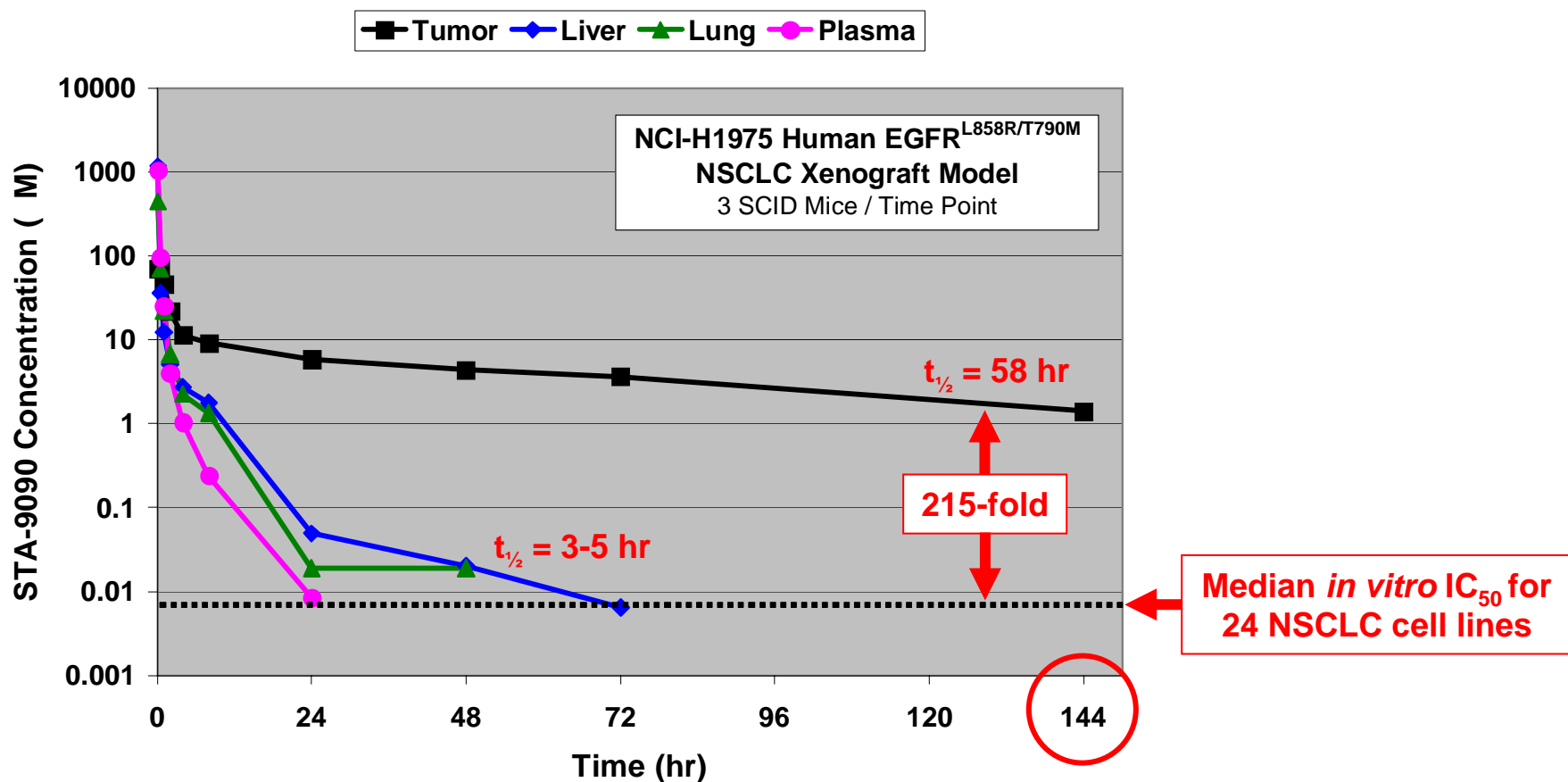
Superior tumor response in an erlotinib-resistant NSCLC (EGFR^{L858R/T790M}) mouse xenograft model



Agents dosed at highest non-severely toxic doses in this model

Prolonged STA-9090 half life in tumors

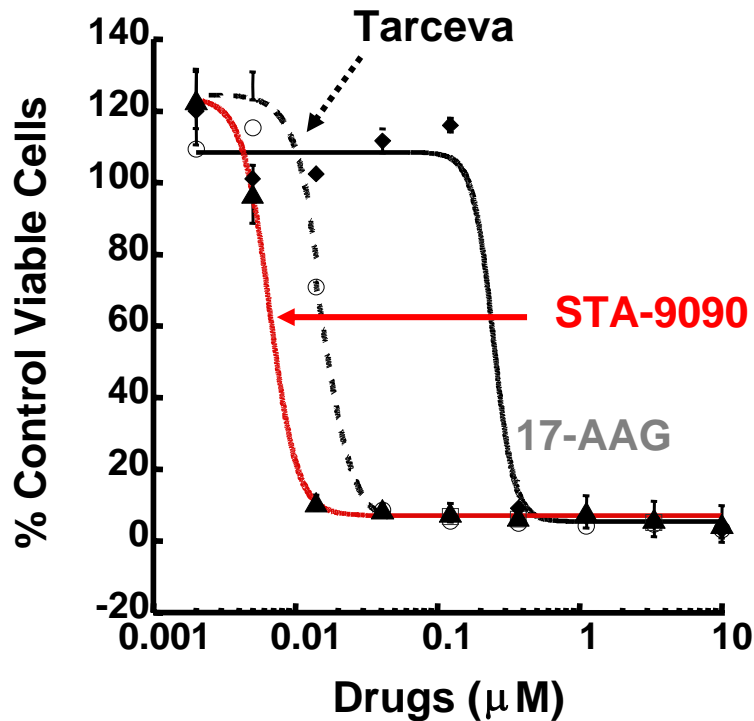
- Cancer cells have increased active Hsp90 relative to normal tissues
 - STA-9090 $t_{1/2}$: xenograft tumors \gg plasma, normal tissues



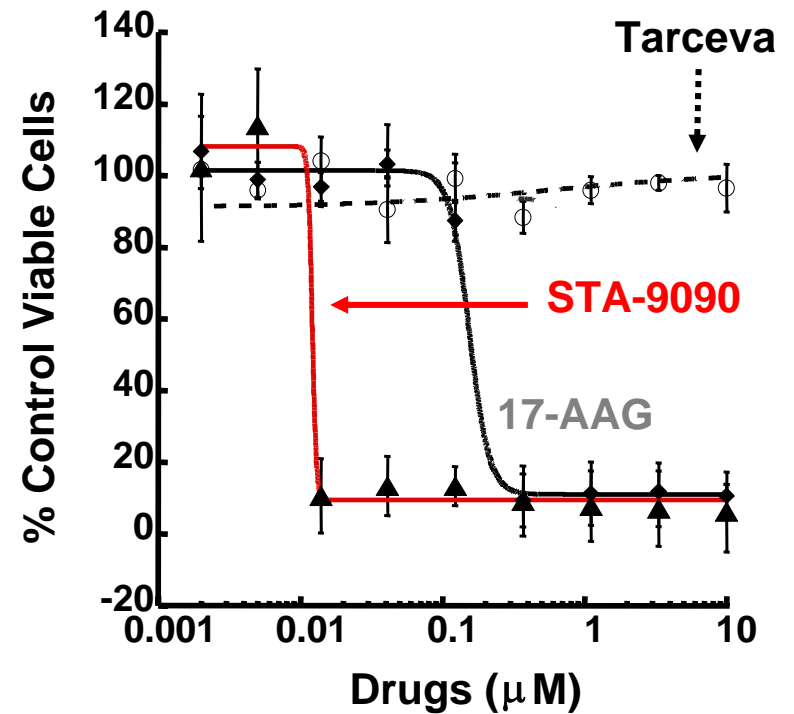
Overcoming resistance due to mutation: NSCLC

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Tarceva-sensitive EGFR



Tarceva-resistant EGFR



Data from Dr. Geoffrey Shapiro (DFCI); AACR April 2009

Overcoming resistance due to mutation: NSCLC

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Activity against Tarceva-resistant NSCLC, by mutational status – T790M

EGFR Activating Mutations					EGFR Activating Mutations in <i>cis</i> with T790M				
EGFR Mutation	Erlotinib IC ₅₀	CL-387,785 IC ₅₀	17-AAG IC ₅₀	STA-9090 IC ₅₀	EGFR Mutation	Erlotinib IC ₅₀	CL-387,785 IC ₅₀	17-AAG IC ₅₀	STA-9090 IC ₅₀
Del E746_A750	4	1	92	4	Del E746_A750/T790M	>10000	294	73	10
Del S752_I759	37	<1	180	12	Del S752_I759/T790M	>10000	537	88	7
Del L747_A750InsP	5	21	67	4	Del L747_A750InsP/T790M	>10000	445	38	4
Del L747_A753InsS	1	<1	136	3	Del L747_A753InsS/T790M	>10000	258	119	4
Del E746_S752InsV	25	274	58	5	Del E746_S752InsV/T790M	>10000	756	40	2
L858R	16	5	246	7	L858R/T790M	>10000	950	155	12
A767_V769dupASV	>3000	427	2262	34					
H773_V774insH	>3000	229	110	40					
D770_N771insNPG	>3000	7	12	1					

*Units: nmol/L

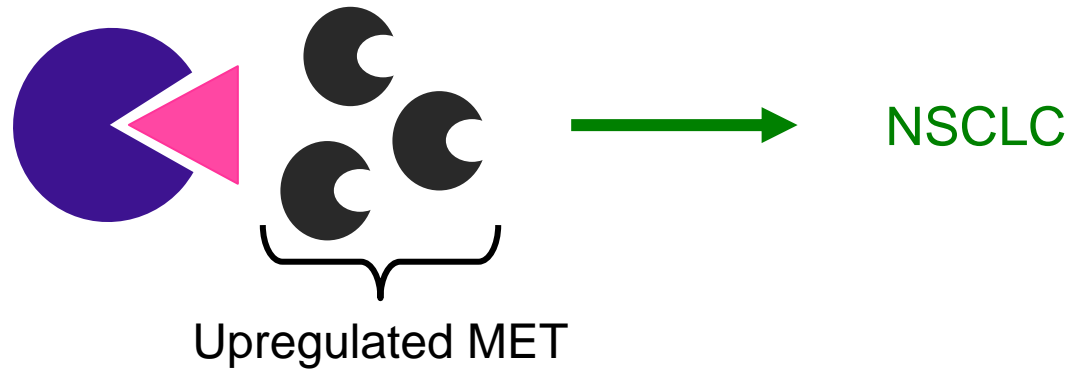
Ba/F3 cells transformed with activated forms of EGFR and treated with drugs for 72 hrs

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

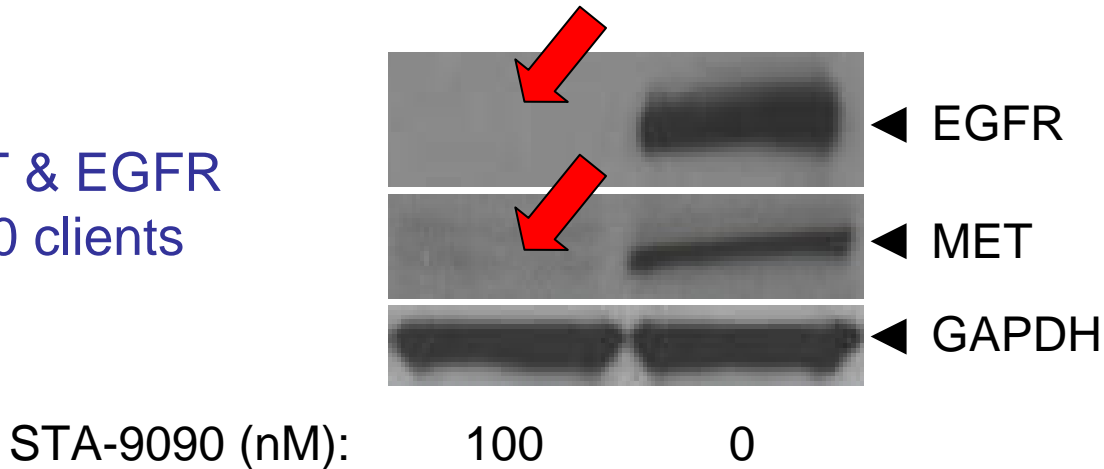
Overcoming resistance due to compensation: MET upregulation in NSCLC

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Increased MET compensates for inhibition of EGFR by Tarceva*



Both MET & EGFR are Hsp90 clients



* Engleman et al., Science 2007