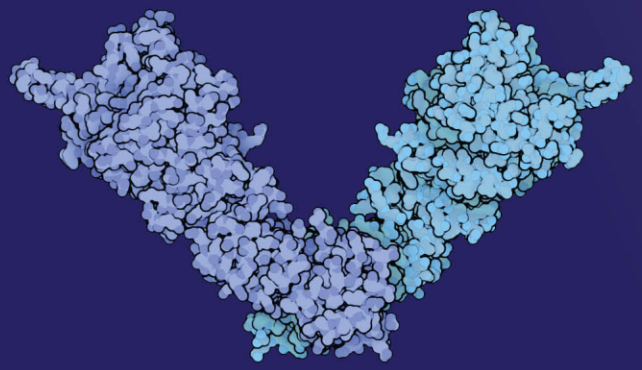
Synta Pharmaceuticals

NASDAQ: SNTA

February 2014



SYNTA PHARMACEUTICALS®

Forward-looking statements

This presentation may contain forward-looking statements. These statements reflect our current views with respect to future events and actual results could differ materially from those projected in the forward-looking statements. Factors that could cause actual results to differ are discussed in Synta's 2012 Annual Report on Form 10-K and in our reports on Form 10-Q and Form 8-K. These reports are available on our website at www.syntapharma.com in the "Investors—SEC Filings" section. Synta undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by law.

Synta

1992-2002: Academic-industry JV

Harvard, MIT founders ↔ Shionogi, Fuji Photo

High throughput screening, drug discovery

2002: Buy-out; independent

2007: IPO (Nasdaq)

120 employees; Lexington, MA

Small molecule pipeline oncology, inflammation

All compounds internally developed

All 100% owned

Highlights

Ganetespib: Phase 3 in NSCLC

- Highly selective Hsp90 chaperone inhibitor
- Durable, objective responses as single-agent
- Improves PFS and OS when added to chemotherapy in NSCLC
- Over 25 trials in multiple cancers; registration programs ongoing/planned in **breast, AML, ovarian**
- **Synta owns 100% worldwide rights**

Hsp90 inhibitor Drug Conjugate (HDC) platform

- Novel tumor-targeting small molecules, exploiting tumor retention properties of Hsp90 inhibitors
- More-targeted Alimta®, Velcade®, Taxotere®, Revlimid® …
- **Over 450 compounds generated to date**

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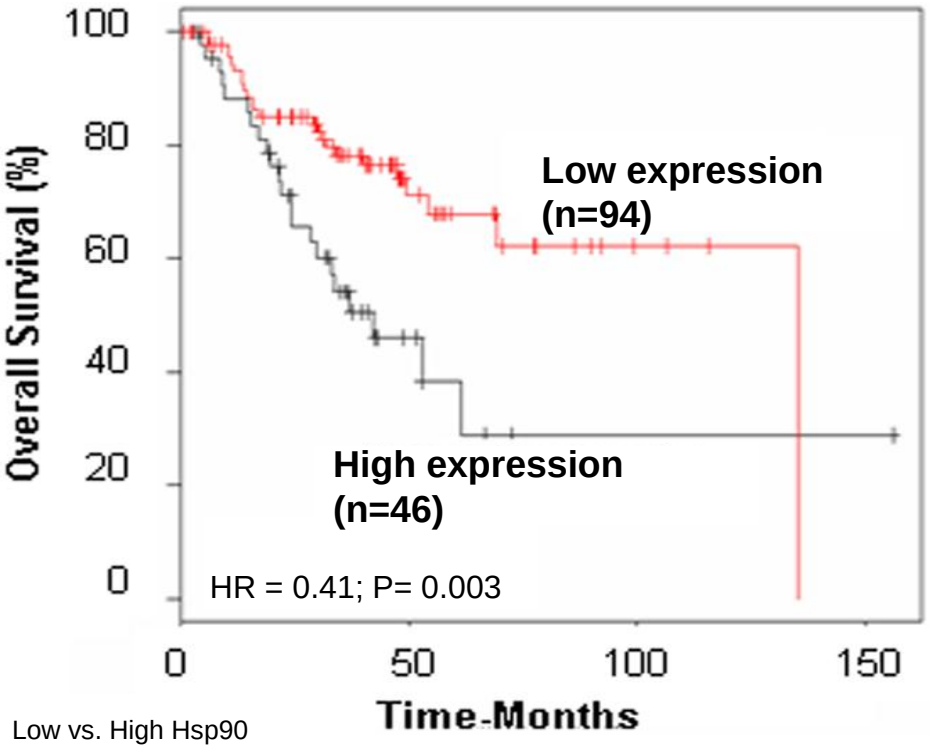
Ganetespib
Hsp90 inhibitor

Hsp90 fuels cancer growth

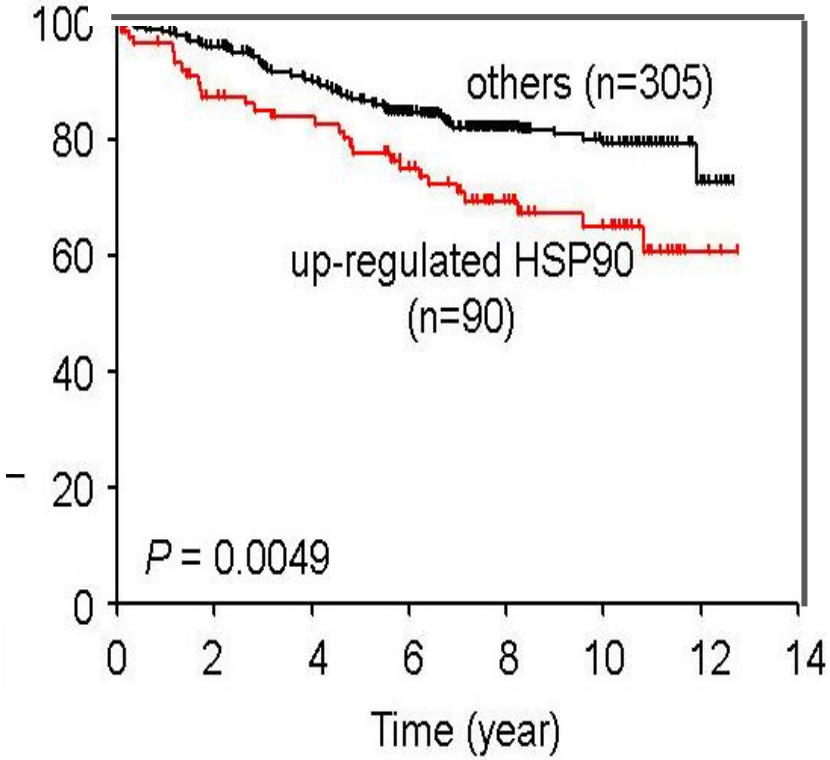
Elevated Hsp90 is associated with reduced patient survival[1-5]

NSCLC



Low vs. High Hsp90 expression: 33% cutoff

Breast Cancer



1. NSCLC Ruiz MIG et al., PLoS One. 2008; 3(3)
2. Breast Cheng Q et al Breast Ca Res. 2012; 14(2)
3. Colorectal Chen LL et al., J Biol Chem. 2010; 285(33)
4. Prostate Hance MW et al., J Biol Chem, 2012; 287(45)
5. Gastric Wang J et al., PloS One. 2013; 8(4)

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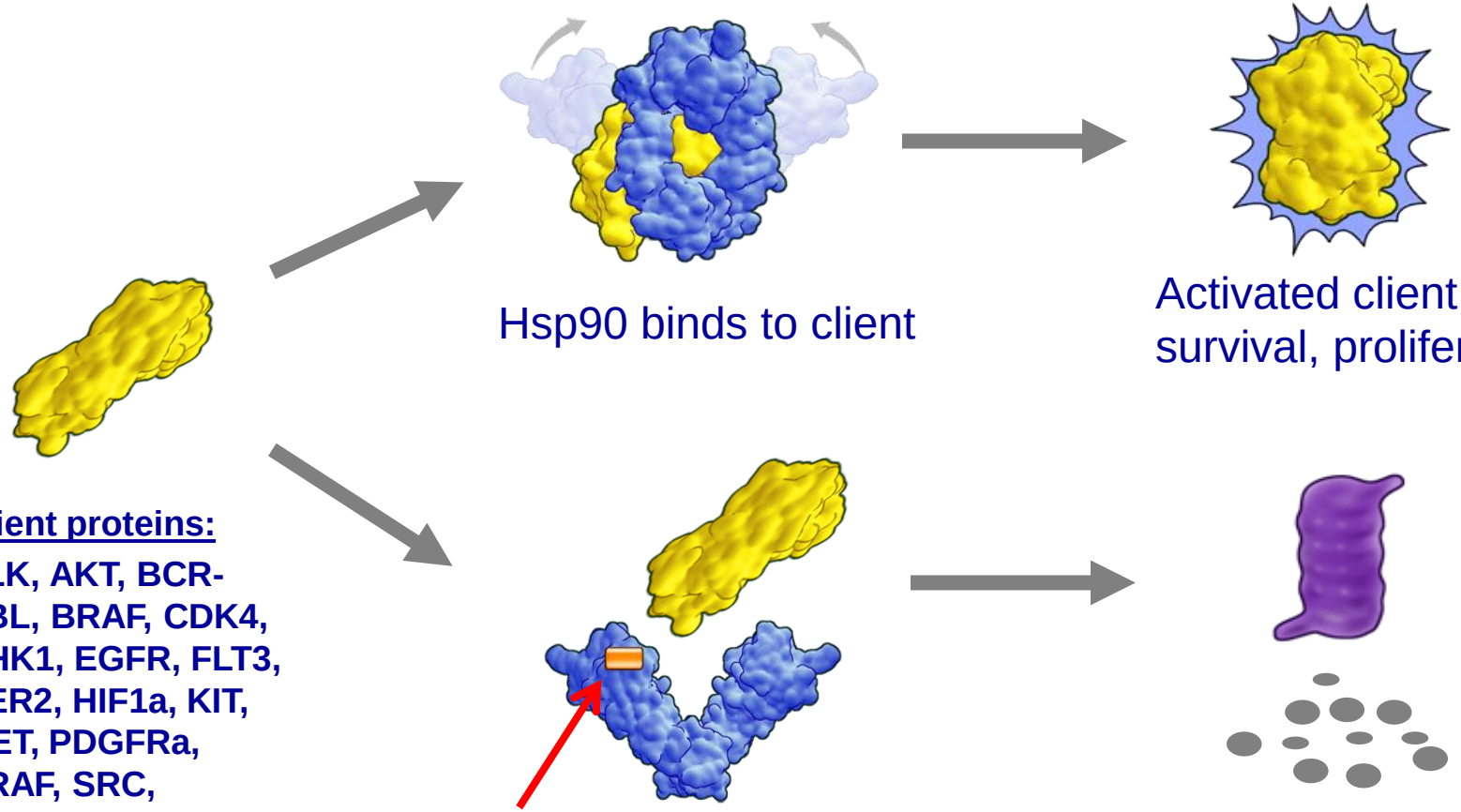
Hsp90 drives cancer growth by activating multiple cancer-promoting client proteins

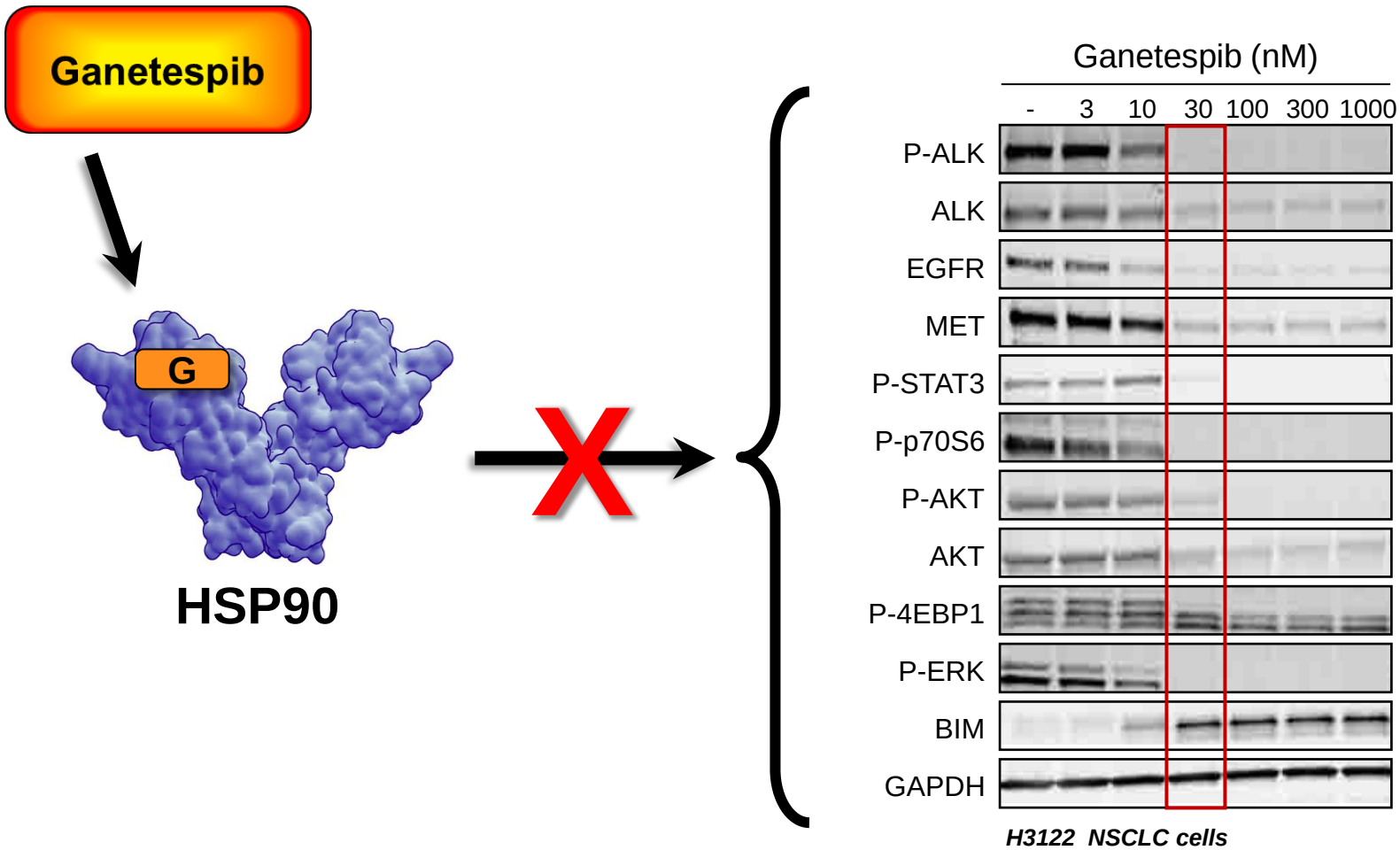


Client proteins:

ALK, AKT, BCR-ABL, BRAF, CDK4, CHK1, EGFR, FLT3, HER2, HIF1a, KIT, MET, PDGFRa, CRAF, SRC, VEGFR, AR, ER …

Inhibiting Hsp90 leads to client protein deactivation

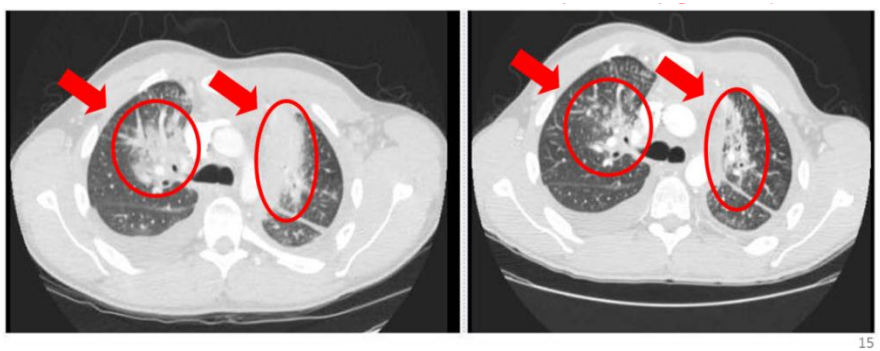
Ganetespib inhibits multiple oncogenic pathways simultaneously



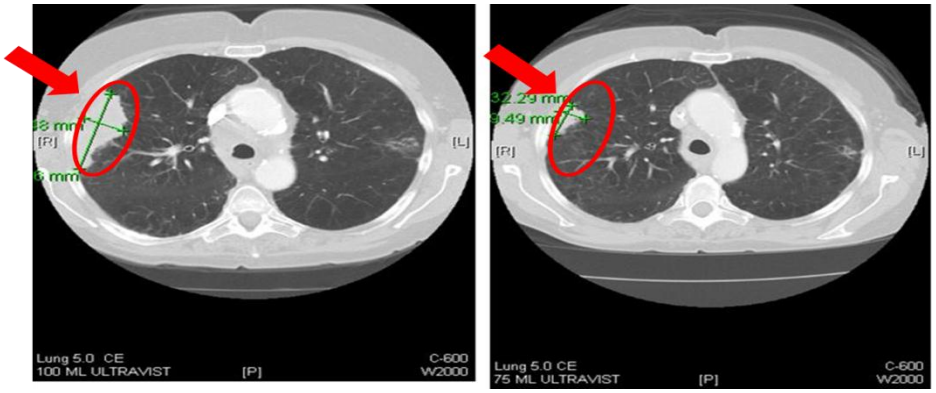
→ Targeting cancer network vs. single pathway

Ganetespib is active across multiple cancers

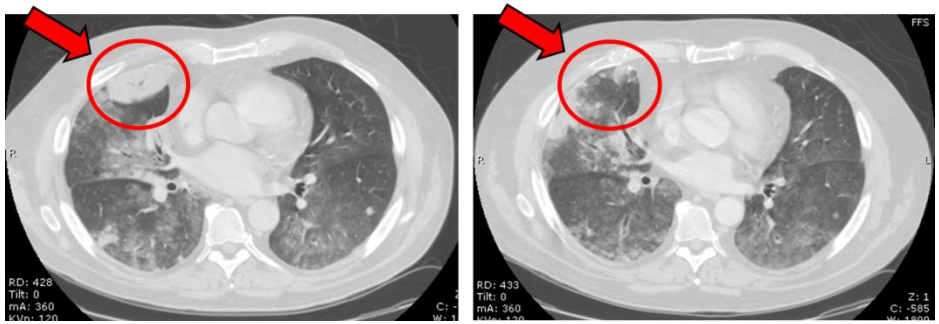
ALK+ NSCLC



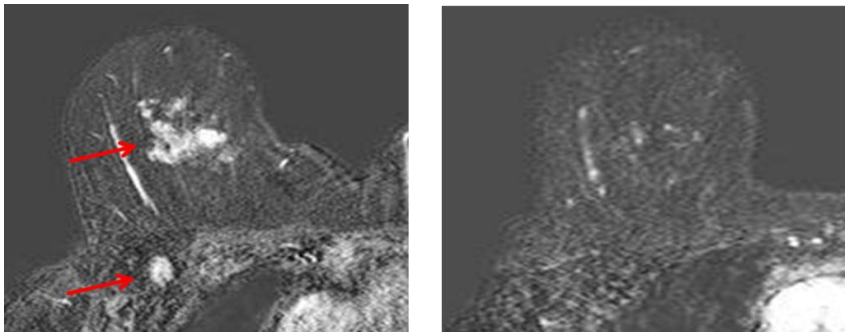
HER2+ Gastric



mut BRAF NSCLC



Triple-negative Breast Ca



Ganetespib monotherapy administration

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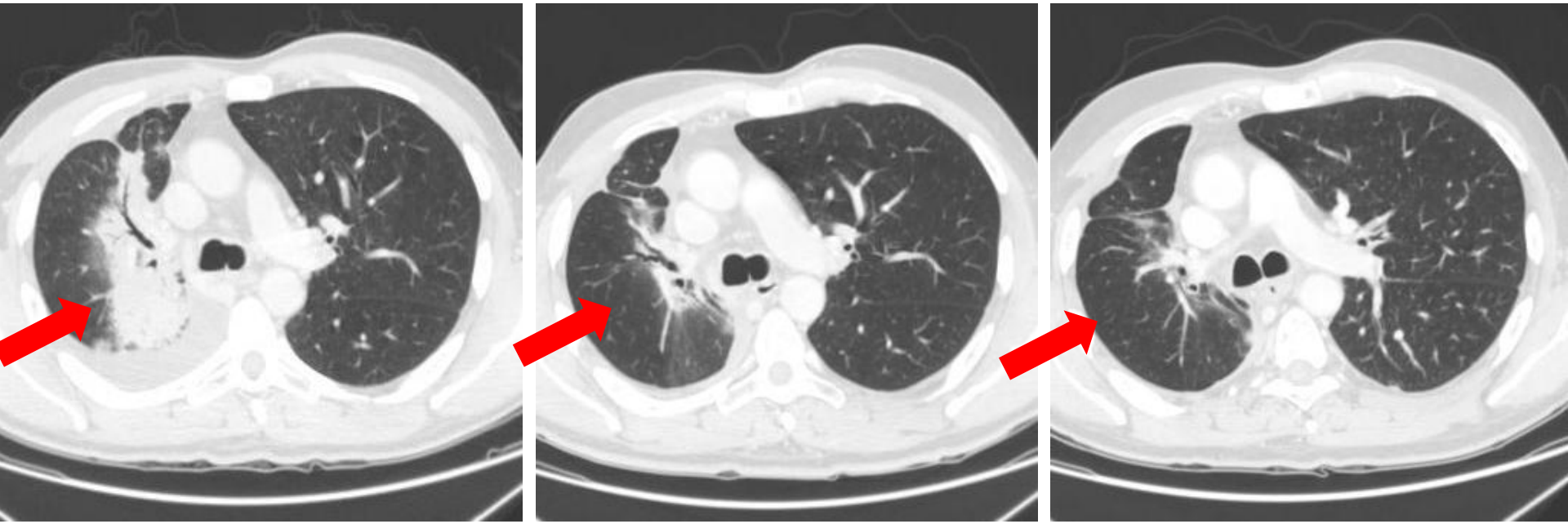
Rapid and durable responses

Baseline - Oct 15 2012 | Dec 7 2012 | Oct 4 2013



49yo M, **ALK+ NSCLC**, ganetespib monotherapy

Ongoing over 3 years: gastric (complete response), NSCLC

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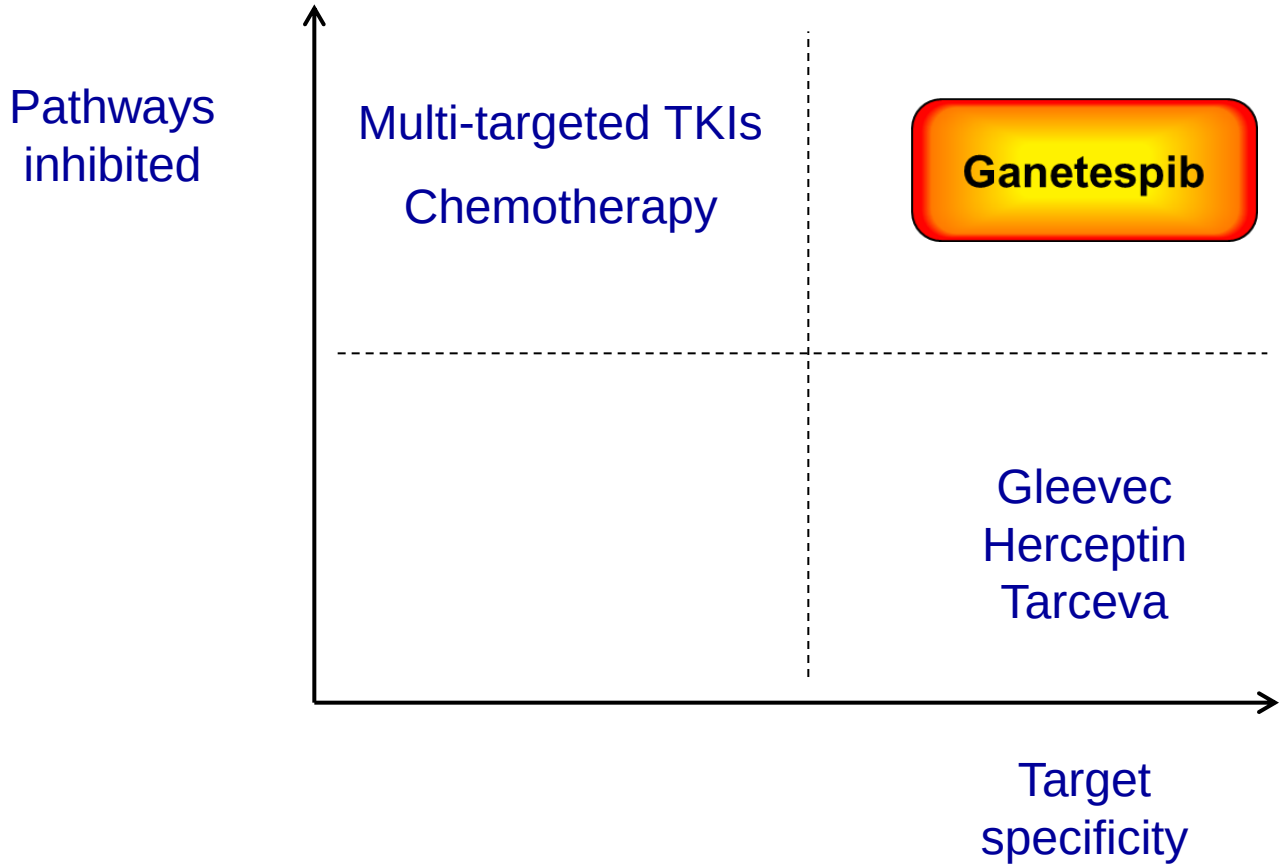
Chaperone inhibition is different

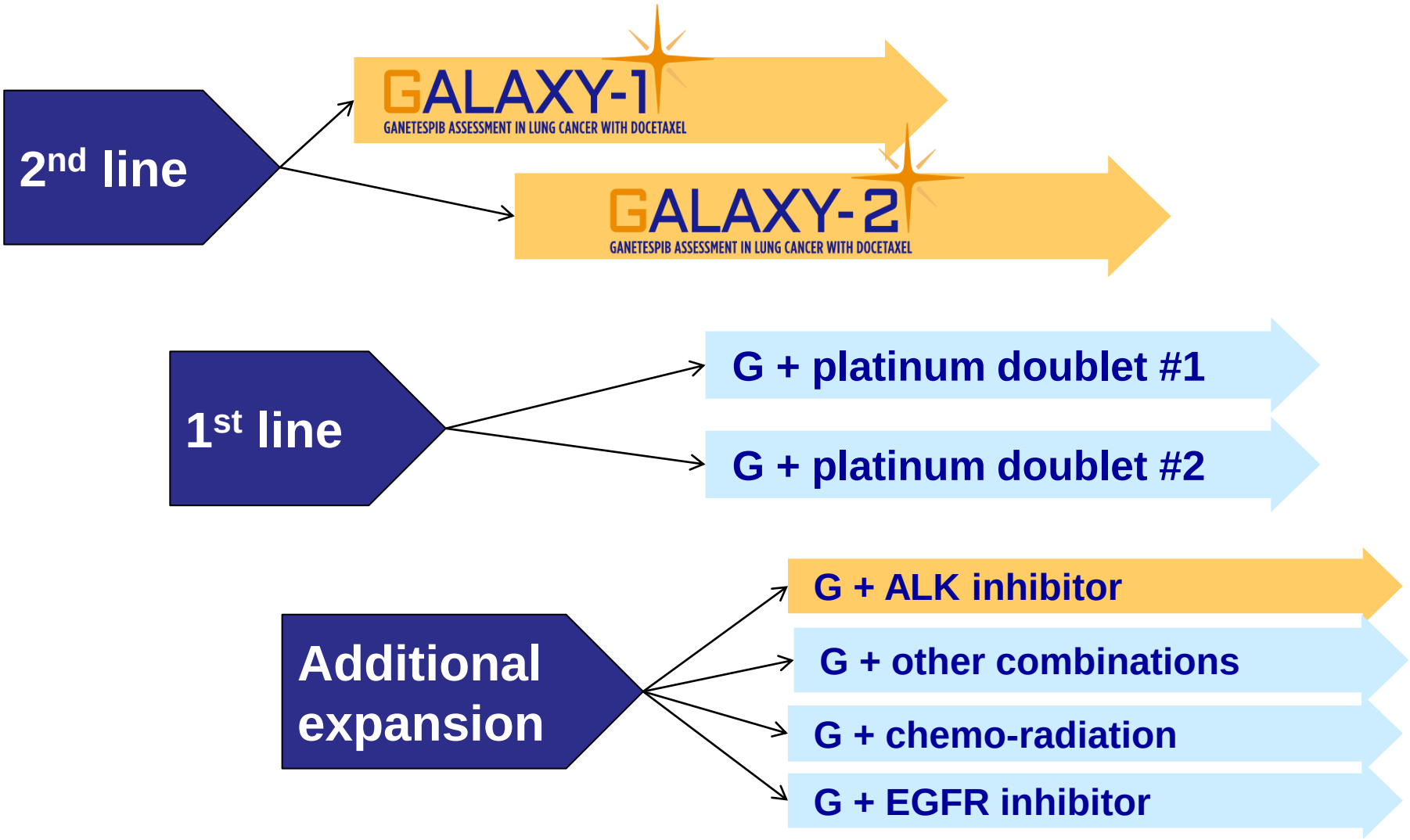


One drug,

One target,

Multiple pathways

NSCLC development



Breast cancer development

Metastatic

- **monotherapy G** — ENCHANT-1: Evaluating Ganetespib Chaperone Inhibition in Breast Cancer
- **Phase 2b/3 HER2-negative**
  Taxanes +/- G; TNBC, ER+

Neo-adjuvant

- **Phase 2b/3 TNBC**
  AC→T +/- G

Additional expansion

- **HER2+**
- **ER+**
- **Additional combinations**

ongoing
planned

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Ovarian, AML, MDS development

Ovarian

Metastatic, Pt-resistant, type II[1] → **Phase 2b mutant p53** (GANNET53 European Project)

Paclitaxel +/- G (N=200)

AML, High-risk MDS

Age > 60 yrs (low-dose chemo) → **Phase 2b/3 (AML-LI-1)**

Low dose Ara-C +/- G (up to N=400)

Age > 60yrs (high-dose chemo) → **Phase 2b/3 (AML-18)**

DA +/- G (up to N=400)

Age < 60 yrs → **Phase 2b/3 (AML-19)**

Chemo, G → G maintenance (up to N=400)

Ovarian trial funded by European Commission, conducted by GANNET53 consortium
AML trials funded by Cancer Research, Leukemia & Lymphoma Research Fund UK; sponsored by Cardiff University, UK

(1) Type-II High-grade serous, high-grade endometrioid or undifferentiated, platinum-resistant ovarian cancer

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Investigator/Cooperative Group Sponsored Studies

Indication	Ganetespib + other targeted agents/chemo
NSCLC	Anti-ALK (crizotinib)
	Anti-EGFR (erlotinib, afatinib)
	Anti PD-1
	Anti-VEGF (afilbercept)
Breast	Anti-ER (fulvestrant)
	anti-her2 (trastuzumab) + paclitaxel
Ovarian	Paclitaxel
	Carboplatin
AML	Low-dose Ara-c
	Induction/consolidation chemo (DA)
Pancreas	Anti-mTOR (everolimus)
	Nab-paclitaxel
Endometrial	paclitaxel
Melanoma	Anti-BRAF+ anti-MET (vemurafenib + cobimetinib)
Mesothelioma	Cisplatin + pemetrexed
SCLC	Anthracycline
Multiple myeloma	bortezomib
Neurofibrosarcoma	Anti-mTOR (rapamycin)

Indication	Ganetespib + Radiotherapy (RT)
NSCLC	Cisplatin/etoposide + RT
	Carboplatin/paclitaxel + RT
Rectal	Capecitabine +RT
Upper GI	Carboplatin/paclitaxel + RT
Prostate	Anti-AR + RT
Bladder	Cisplatin + RT
GBM	Temozolomide + RT

Broad interest driven by ganetespib safety profile, combinability, and preclinical/ clinical synergy results

Trials ongoing/planned for 2014

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Investigator Sponsored Studies – Participating Institutions

Cancer Research UK

Cardiff University

Cleveland Clinic

Dana Farber Cancer Inst.

Emory Univ.

EU – GANNET53 group

EU – Gyn. Onc. Study Group

Fox Chase Cancer Center

Georgetown Univ.

Innsbruck Medical Univ.

Japan – multicenter

Johns Hopkins Univ.

Leukemia & Lymphoma Research Fund UK

Multiple Myeloma Research Foundation

NCI

NYU / Sloan Kettering

RTOG

SWOG

Univ. Colorado

UC Davis

Univ Pittsburgh Medical Center

Vanderbilt Univ.

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GALAXY program: derisking Phase 3 with ~400 patient, global Phase 2b

GALAXY-1 → GALAXY-2

GANETESPIB ASSESSMENT IN LUNG CANCER WITH DOCETAXEL

1. **Optimize patient selection**

   Broad mechanism, clinical activity → broad range of potential biomarkers, patient populations

2. **Decrease operational risk**

   Identify regional differences, heterogeneous populations, distinct treatment patterns

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Summary of key findings

GALAXY-1 → GALAXY-2

GANETESPIB ASSESSMENT IN LUNG CANCER WITH DOCETAXEL

	GALAXY-1 N=253 completed Nov 2012	GALAXY-2 Enrolling
Optimizing patient selection	Responsiveness to first-line therapy predictive for G activity	Enrolling chemosensitive population only
Decreasing operational risk	13/15 countries: consistent population 2/15 countries: atypical population	Terminated enrollment in those two countries

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GALAXY-1

Goal: selection of patient population for Phase 3 (GALAXY-2)

Advanced NSCLC
1 Prior Regimen
Adenocarcinoma

→ RANDOMIZE 1:1

→ **Ganetespib + Docetaxel**
G: 150 mg/m^2 days 1,15 q3w
D: 75 mg/m^2 day 1 q3w

→ **Docetaxel**
D: 75 mg/m^2 day 1 q3w

Stratification

- ECOG PS (0 vs. 1)
- Time since diagnosis of advanced disease (≤ 6 m vs. > 6 m)
- Baseline serum LDH (< or > ULN)
- Smoking status

Endpoints

Co-primary: PFS in mKRAS, eLDH pts

Key secondary: PFS and OS all adenocarcinoma pts (sequential testing)

Other secondary: ORR, DCR, QOL

Combination arm: option to continue G monotherapy following completion of docetaxel treatment

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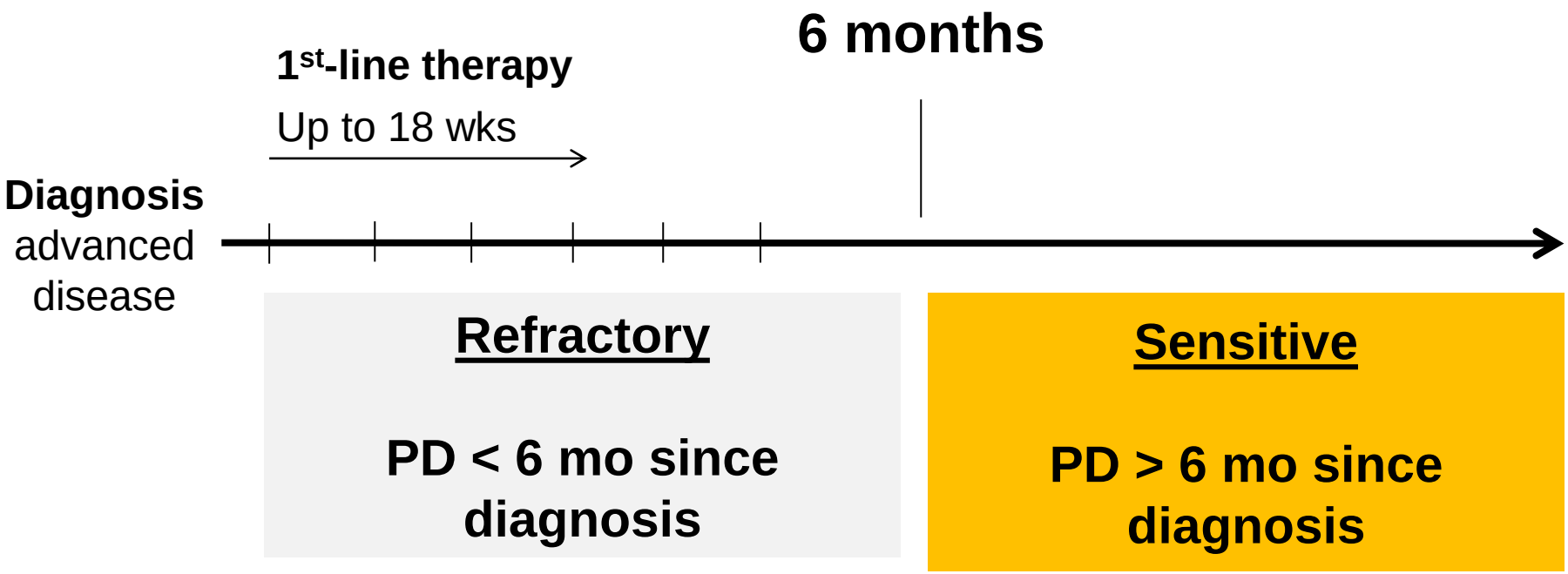
Stratification for refractory vs. chemosensitive disease



30%
of GALAXY-1 patients

70%
of GALAXY-1 patients

6 months cutoff consistent with convention in second-line NSCLC trials (time since completion of first line treatment > 3 mo)

Selection of Phase 3 patient population

OS HR G+D vs. D (90% C.I.)	**Chemosensitive** Dx>6 N=178	**Refractory** Dx<6 N=75
Rationale	**Benefit** from chemosensitizing mechanism of G	**Cross-resistant** to chemotherapy and to G*
Unadjusted	**0.75** (0.56, 1.03)	**1.32** (0.82, 2.11)
Adjusted	**0.72** (0.52, 0.98)	**1.18** (0.71, 1.94)

* “Novel Mechanisms of Sensitivity and Acquired Resistance to HSP90 inhibition by Ganetespib”, WCLC 2013 Abstract #MO12.01

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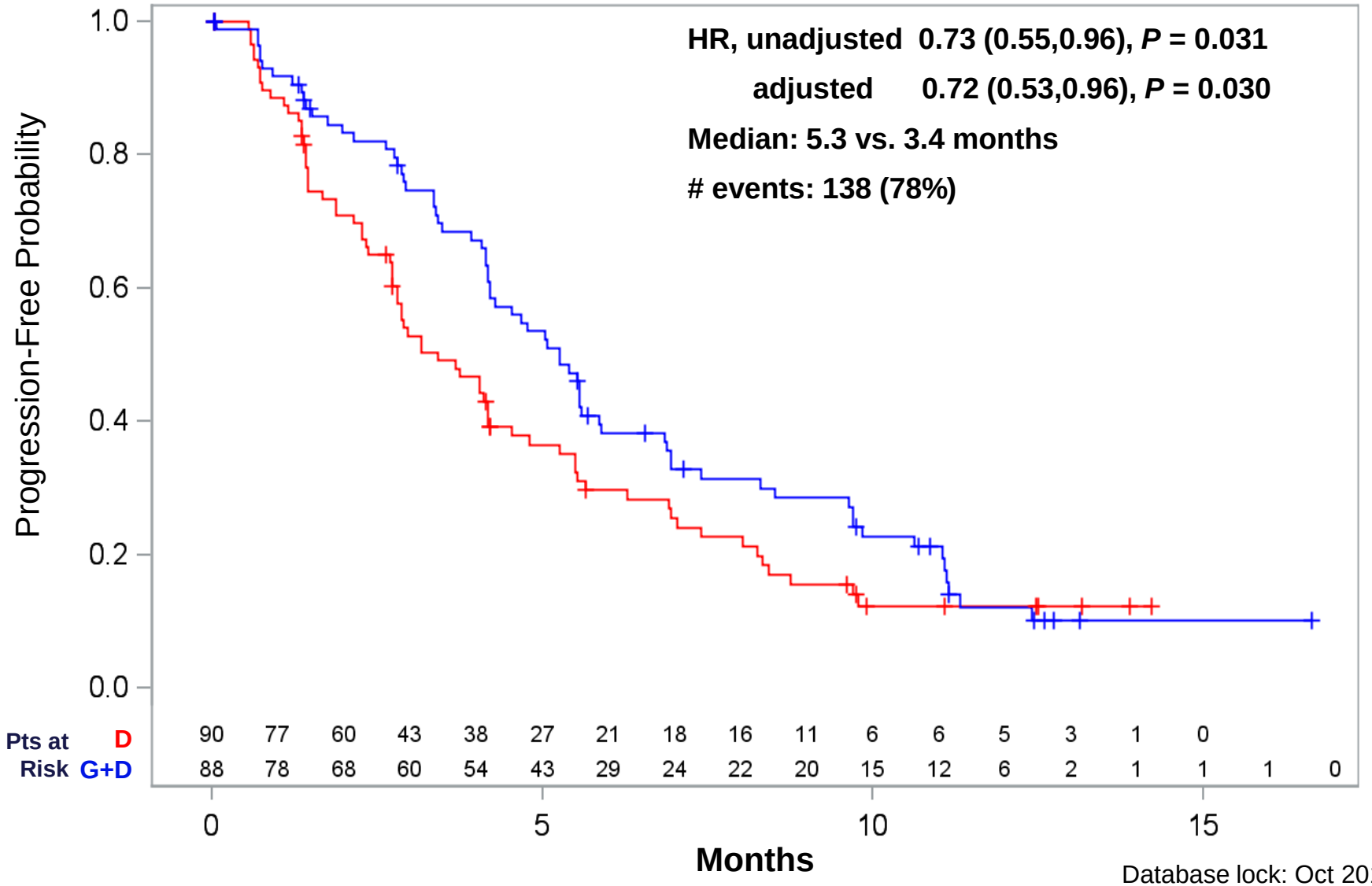
Cross-resistance to ganetespib and chemotherapy in vitro

"Novel Mechanisms of Sensitivity and Acquired Resistance to HSP90 inhibition by Ganetespib", WCLC 2013 Abstract #MO12.01

	Chemosensitive	Refractory
		
Mitochondrial apoptosis	**Functional**	**Blocked** (caspase 8)
Chemotherapy	Active	Inactive
Ganetespib	Suppresses anti-apoptotic regulators (BCL-2, MCL-1)	Inactive
	G: enhances chemo	G: no effect

PFS: Dx >6 months Population

N=178

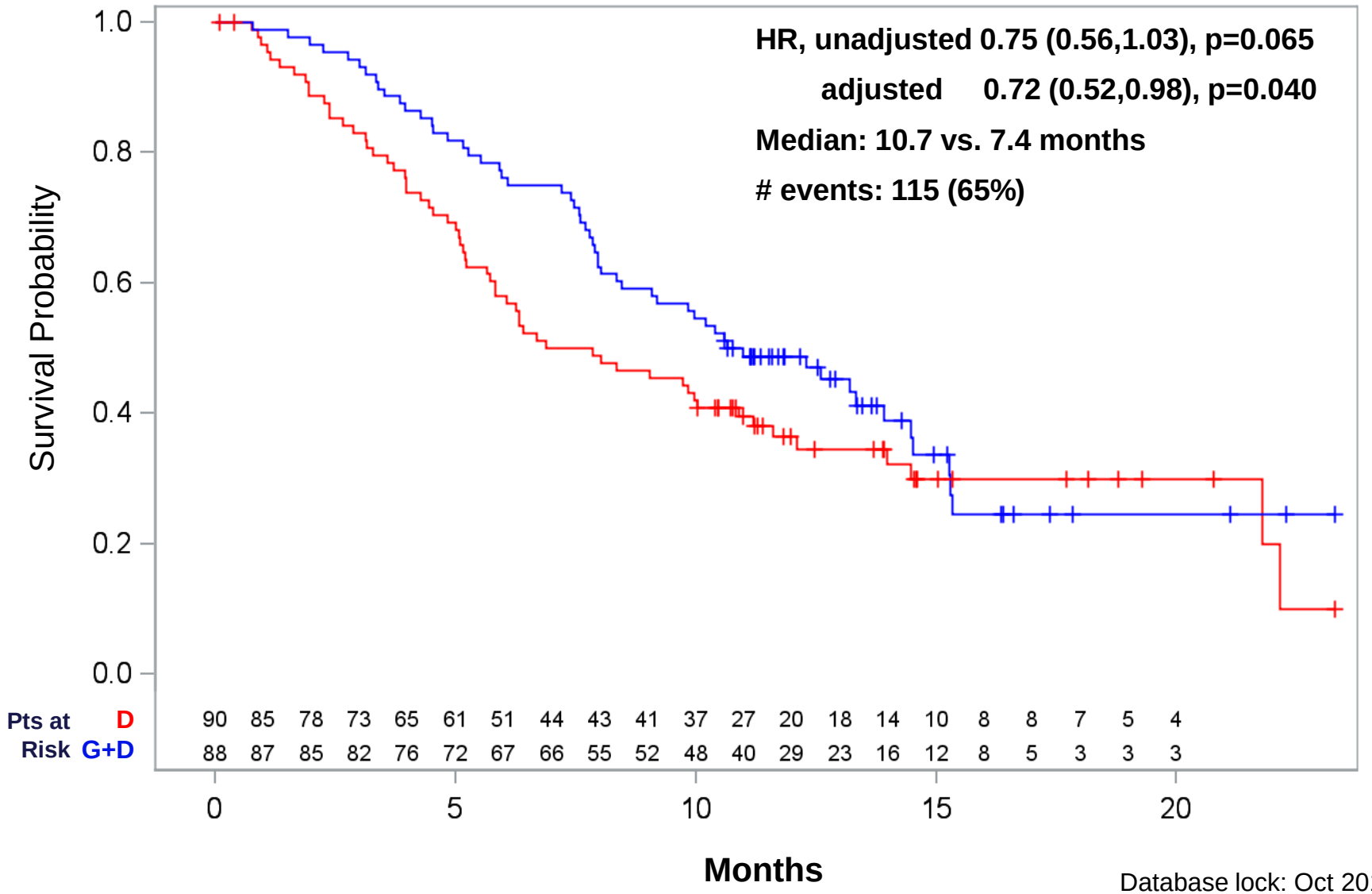


Database lock: Oct 2013

All p-values 1-sided. Hazard ratios (HR) calculated with Cox proportional hazards model. Unadjusted: univariate analysis; adjusted: prespecified multivariate analysis (adjusting for gender, smoking status, LDH, ECOG performance status, interval since diagnosis advanced disease, age, total baseline target lesion size, and geographic region).

OS: Dx >6 months Population

N=178



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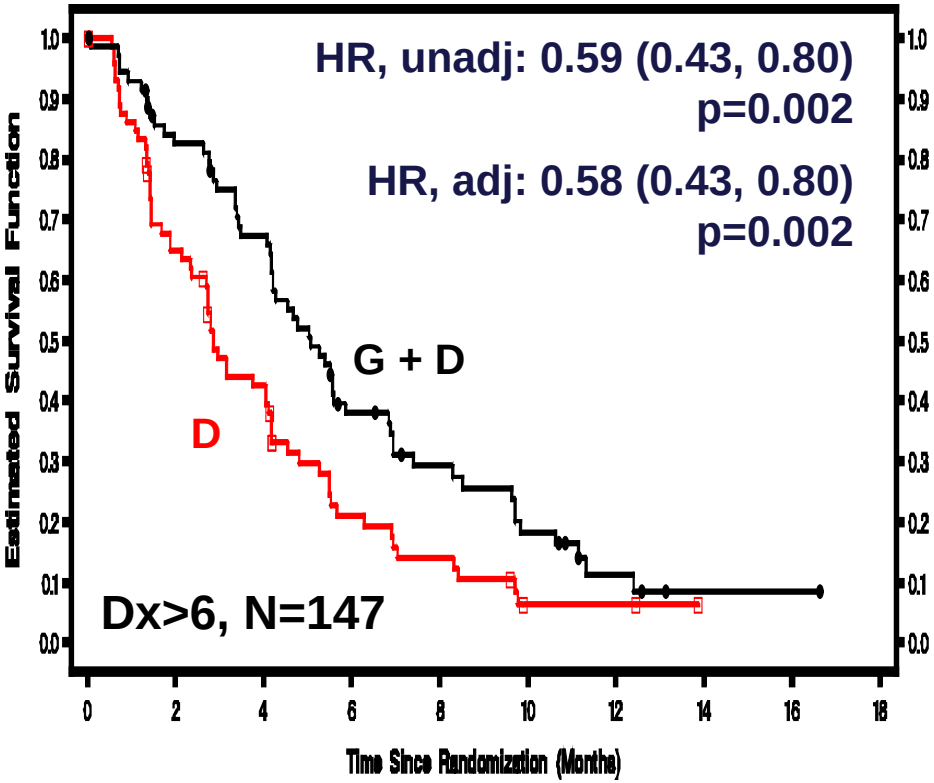
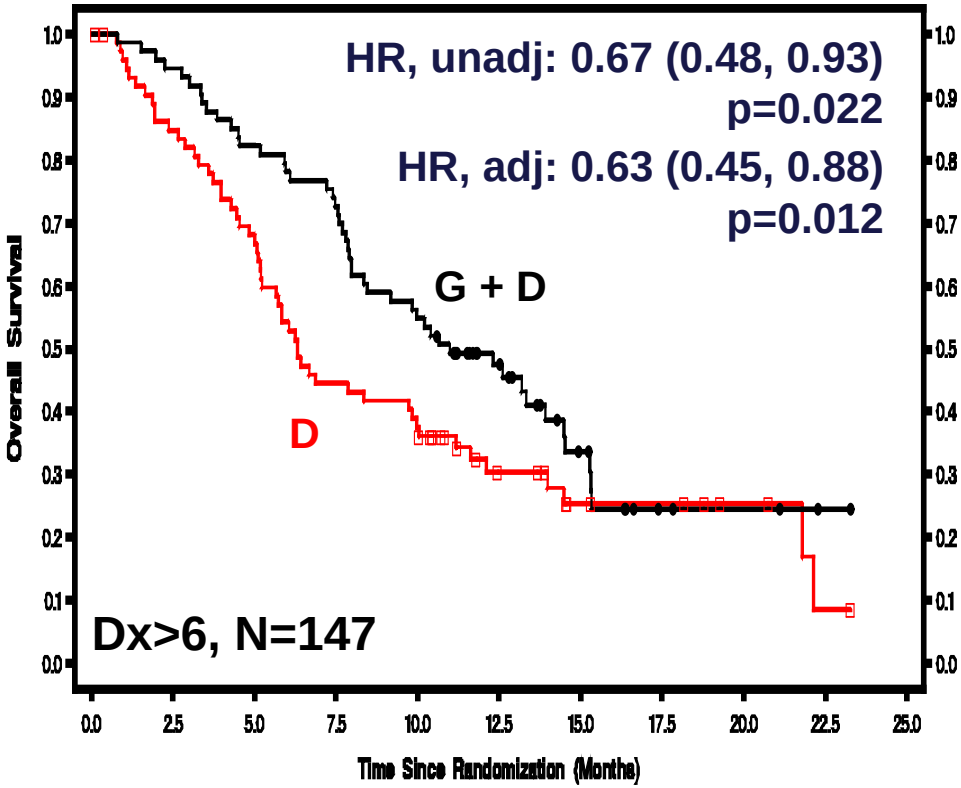
Decreasing Phase 3 operational risk: identifying regional differences

GALAXY-1 results from all regions except the two outlier E Eur countries no longer enrolling in GALAXY-2

Progression-Free Survival



Overall Survival



All p-values 1-sided. Hazard ratios (HR) calculated with Cox proportional hazards model. Unadjusted: univariate analysis; adjusted: prespecified multivariate analysis (adjusting for gender, smoking status, LDH, ECOG performance status, interval since diagnosis advanced disease, age, total baseline target lesion size, and geographic region).

Only two drugs approved for NSCLC with OS advantage against active comparators 1999-2013

Compound	Trial	OS hazard ratio
Pemetrexed	Cis-pem v gem-cis (1st line)	**0.94** (ITT) **0.84** (non-squamous subset)
	Pem vs docetaxel (2nd line)	**0.99** (ITT) **0.89** (non-squamous subset)
Bevacizumab	Carbo-paclitaxel +/- bev (1st line)	**0.80**

EGFR inhibitors, trials for mEGFR patients only: Afatanib vs. pem-cis, OS HR=0.91; erlotinib vs. platinum doublet: OS HR=0.93

Source: FDA, EMA

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Enrollment ongoing in GALAXY-2 Phase 3, data expected 2015

Advanced non-small cell lung adenocarcinoma

- **1 prior chemo regimen**
- **Diagnosis > 6 months**

RANDOMIZE 1:1

Ganetespib + Docetaxel

G: 150 mg/m^2 days 1,15 q3w
D: 75 mg/m^2 day 1 q3w

Docetaxel

D: 75 mg/m^2 day 1 q3w

Combination arm: option to continue G monotherapy following completion of docetaxel treatment

Primary endpoint: overall survival

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ENCHANT-1 trial in breast cancer

High interest in developing ganetespib for HER2+ and triple-negative breast cancer (TNBC)

- Each ~20% of breast ca
- HER2: prior results with ganetespib and other Hsp90i; strong Hsp90 client
- TNBC: encouraging Phase 1/2 results with ganetespib; role of Hsp90

Proof-of-concept trial design: single-agent, first-line advanced disease

- Up to 33 evaluable patients each cohort; interim at N=15

Results from first interim analysis achieved criteria to advance to stage 2*

- 4 evaluable HER2+ pts: 1 CR (radiological complete response), 2 PR, 1 SD
- 11 evaluable TNBC pts: 2 PR (one complete clinical response, restaging), 5 SD

* Data presented SABC Dec 2013. Objective response measured by RECIST; patients evaluable by independent review

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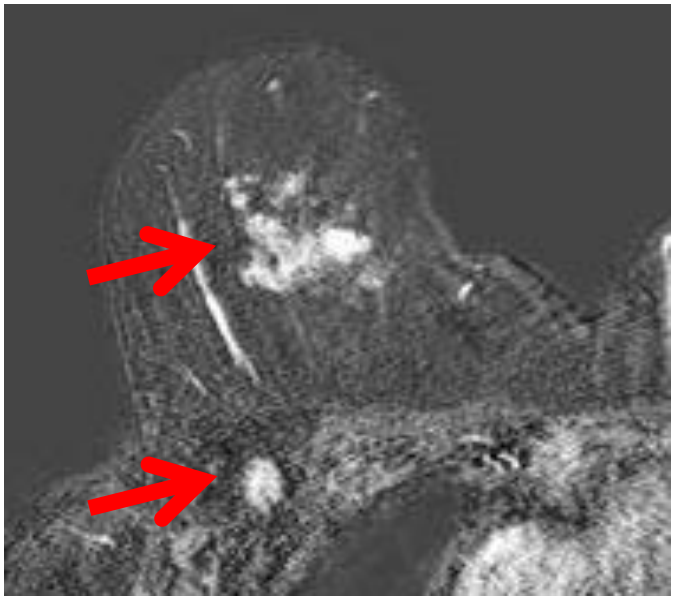
Ganetespib induced complete response in a woman with inoperable locally advanced TNBC

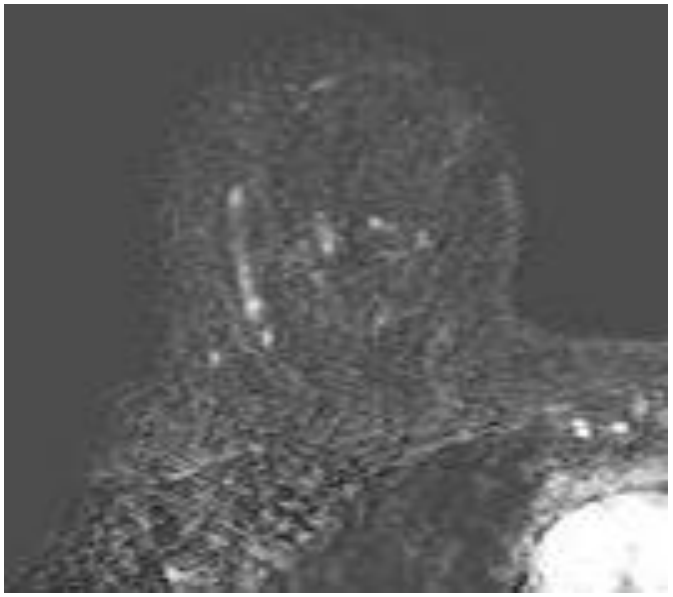
68 year old woman, TNBC, T4, N1, M0. Inoperable disease. No prior chemotherapy

Originally inoperable disease converted to an operable disease → total mastectomy with axillary clearance

Baseline



Week 12



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GANNET53 in ovarian cancer

- **Pan-European randomized trial evaluating ganetespib and paclitaxel vs. paclitaxel alone**
  - Sponsored by Innsbruck Medical University, funded by the EC
- **200 patients with metastatic, predominantly p53 mutant, platinum-resistant ovarian cancer**
  - ~70% of advanced ovarian cancers are Type II tumors, of these >95% exhibit mutations in p53 tumor suppressor gene
- **Hyperstabilized, gain-of-function mutant p53 is critical oncogenic promoter; relies on Hsp90 for stabilization**
  - Inhibition of Hsp90 destroys the complex between Hsp90 and mutant p53, leading to the degradation of the protein and cancer cell death
  - Hsp90 inhibition has also been shown to sensitize mutant p53 cancer cells to treatment with chemotherapies
- **Centers in Austria, Belgium, France, and Germany**

AML

Ganetespib inhibits apoptosis resistance mechanisms in leukemic cells, which renders them more vulnerable to treatment with chemotherapy

- **AML-LI-1 (less intensive) trial** (up to N=400)
  - Patients > 60 years old
  - G + low dose cytarabine (Ara-C) vs. low dose Ara-C
  - First stage portion (N=100) interim analysis expected in 2014

- **AML-18 trial** (up to N=400)
  - Patients > 60 years old
  - G + standard DA (daunorubicin and Ara-C) in patients over 60 years old who can tolerate intensive chemotherapy vs. treatment with standard DA alone

- **AML-19 trial** (up to N=400)
  - Patients < 60 years old
  - Standard induction chemotherapy plus ganetespib followed by ganetespib maintenance vs. induction chemotherapy alone

Supported by the Leukemia & Lymphoma Research Fund and Cancer Research UK

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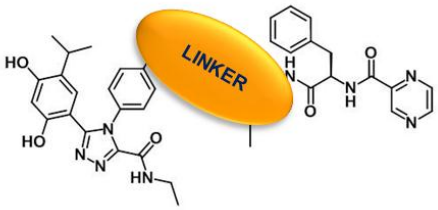
Hsp90 Inhibitor Drug Conjugate Platform (HDC)

Novel Anti-cancer Category

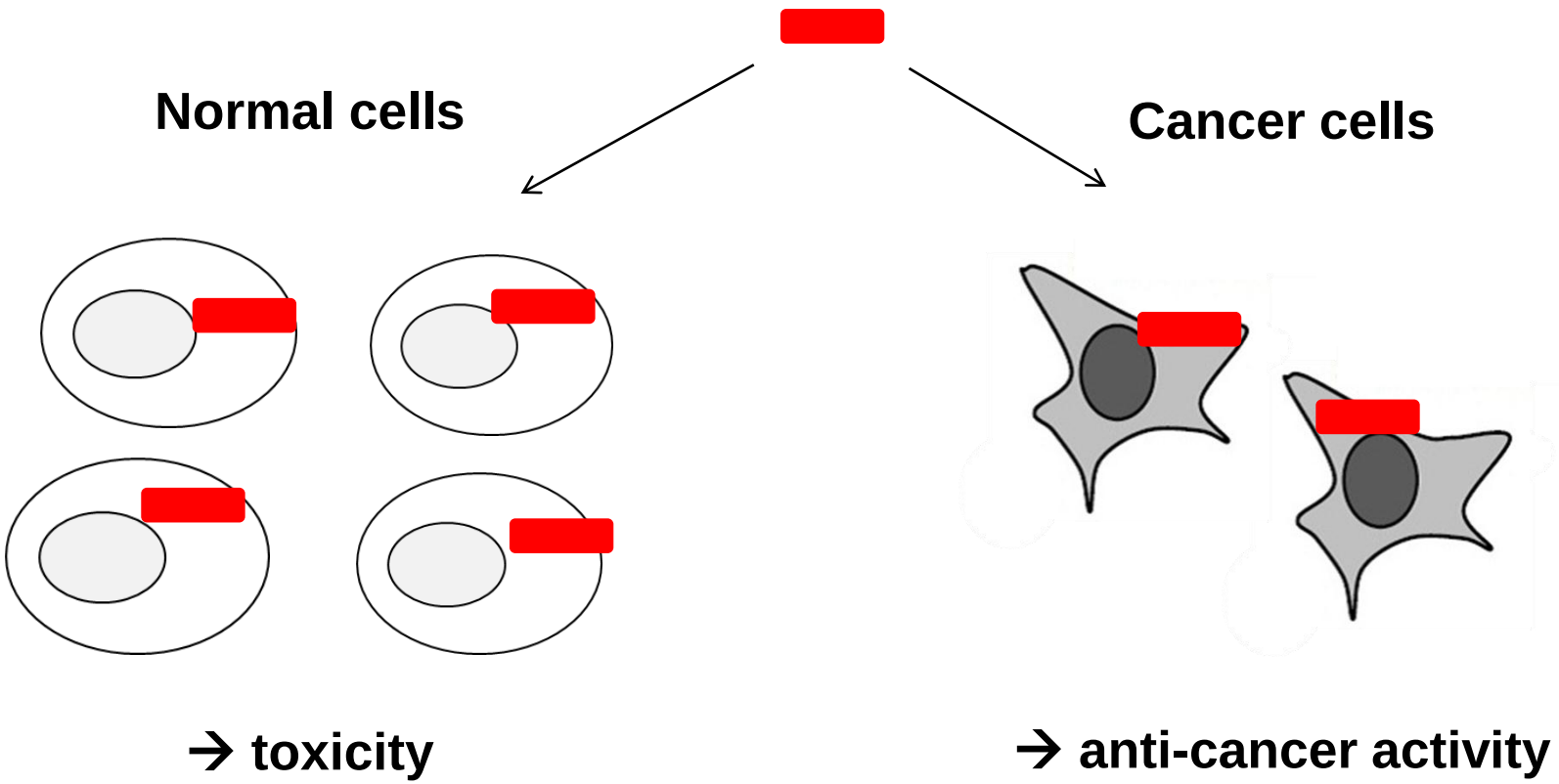
HDC-pemetrexed
(Alimta®)

HDC-bortezomib
(Velcade®)



HDC-carboplatin
(Paraplatin®)

Efficacy of many chemotherapies and targeted agents limited by toxicity to normal tissues



Can increase drug delivery to cancer cells, reduce drug delivery to normal cells?

Delivery categories to date

Antibody Drug Conjugates (ADCs)

+ Clear protein target, delivery rationale
+ Clinical validation (HER2 breast, CD30 NHL)

Requires unique cell surface antigen

Requires endocytosis

Low achieved payload concentration (pM)

Limited choice of payloads (pM-active toxins)

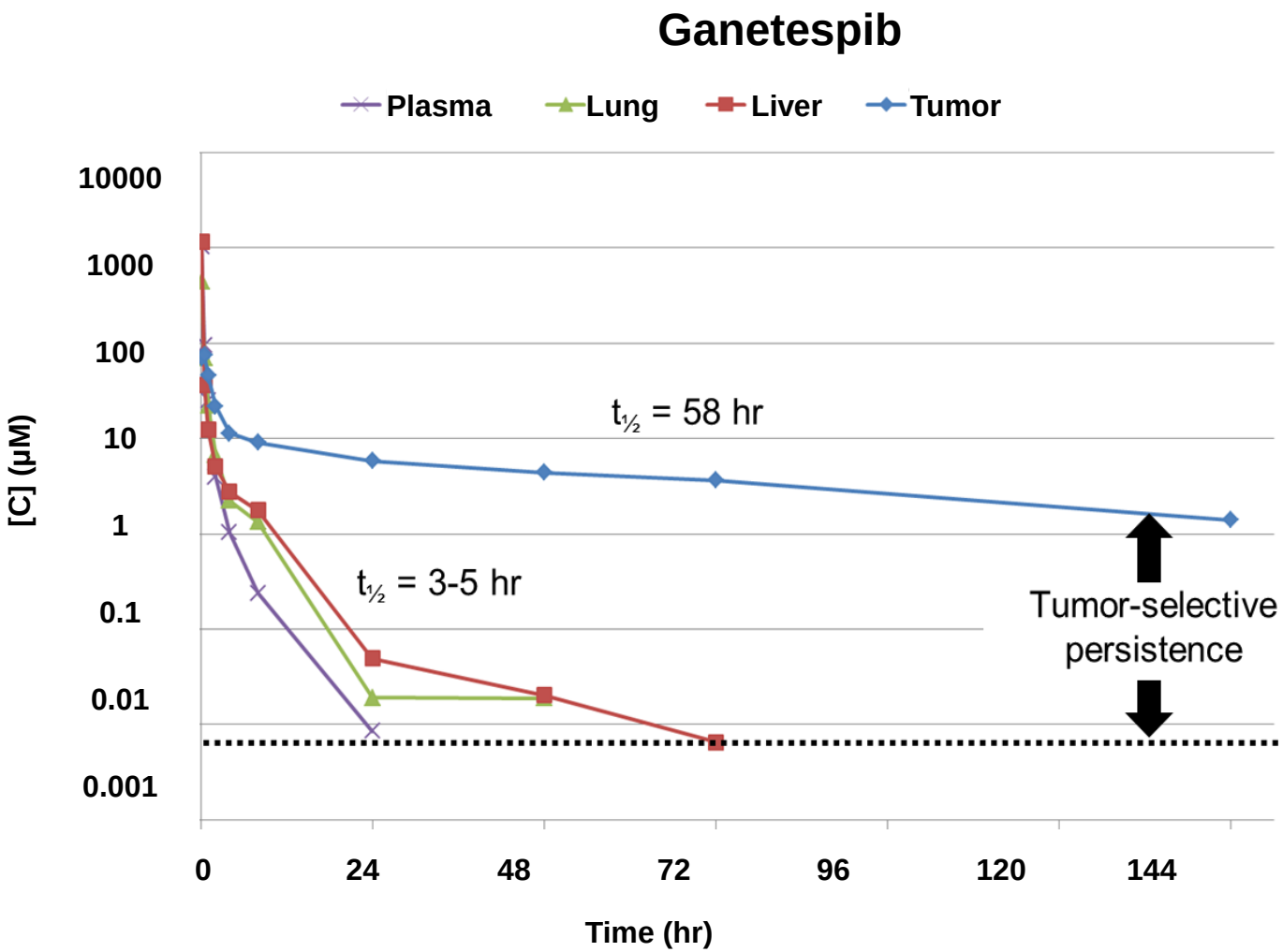
Nanoparticles, Polymer Conjugates and Other

+ Broader choice of payload

Limited examples of clinical validation

Often rely on EPR – Enhanced Permeability and Retention

Hsp90 inhibitors are retained in tumors for days, cleared rapidly from rest of body



i.v. administration in mouse H1975 mEGFR NSCLC xenograft models

Hsp90i retention in tumors is a class effect – published PK results

Compound	Findings(1)		
	Plasma [C]@24hrs	Tumor [C]@24hrs	Other measures
17AAG, 17DMAG(2,3)			Tumor $AUC^{0\text{-}24hrs}$ > 25X Plasma $AUC^{0\text{-}24hrs}$
IPI-504(4)	~ 0	~ 3 μM	Tumor [C]@48hrs ~ Plasma $[C]^{0\text{-}2hrs}$
AUY922(5)	10 pM		Tumor $AUC^{0\text{-}8hrs}$ ~ 5-10X Plasma $AUC^{0\text{-}8hrs}$
PU-H71(6)	0	~ 1 μM	
PU24FCI(7)	~ 0	~ 10μM (~IC90) – maintained to 30 hrs	Normal tissue [C]@24hrs ~ 0
AT13387(8)	~ 0.3 μM	~ 10 μM	Detectable in tumors 10 days after dosing
Purine(9)	~ 0	> IC90	

(1) Time measured post compound administration; all data from xenografts except PU-H71 from clinical studies
(2) Banerji U. *et al.* Clin. Cancer Res. 11 p. 7023; (3) Cancer Chemother Pharmacol. 2005 Jan;55(1):21-32.; (4) Sydor J.R. *et al.* Clin. PNAS vo. 103, no. 46 p.17409; (5) Breast Cancer Research Vol 10 No 2 Jensen et al.; (6) Gerecitano et al., ASCO 2013, Abstr. 11076; (7) M. Vilenchik *et al.* Chem. and Biol. vol. 11, p. 787; (8) Cancer Sci. vol 103, no. 3, p. 525; (9) H. He. *Et al.* J. Med. Chem, 49, 1 381-390;

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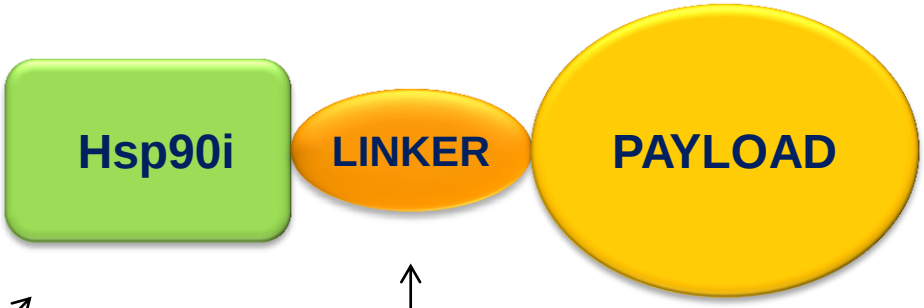
Hsp90-inhibitor Drug Conjugate (HDC)

Exploit preferential accumulation of Hsp90 inhibitors in tumors to selectively deliver anti-cancer payloads



Tumor targeting arm

Cleavable linker

Optimized for controlled release of payload in cancer cells

Anti-cancer payload

Chemotherapies, targeted agents

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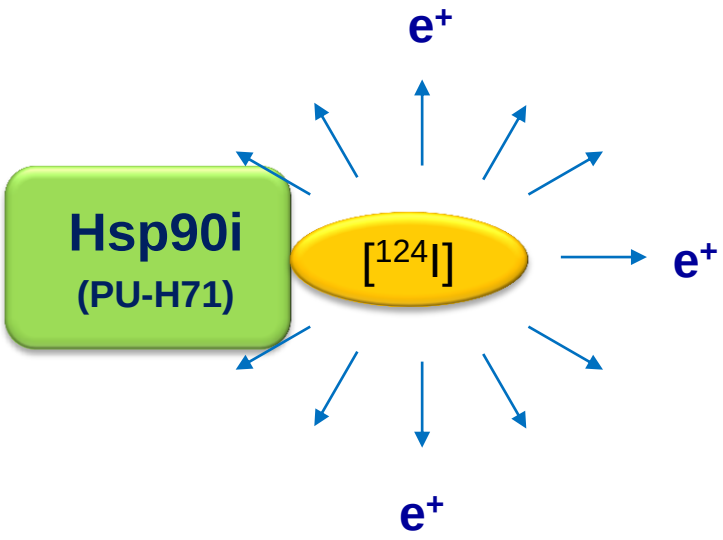
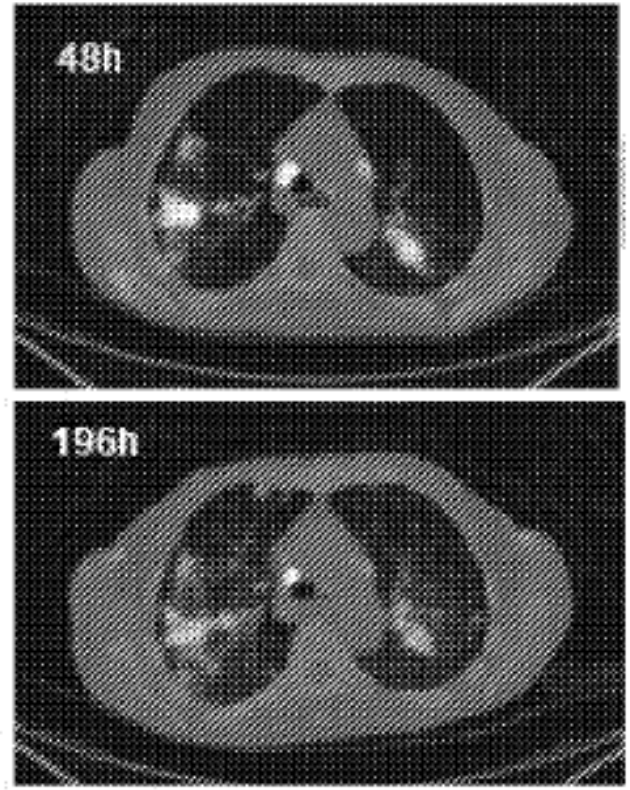
PET scans on radiolabeled Hsp90 inhibitors show selective, persistent retention in patient tumors up to 8 days



Pancreatic cancer patient



Day 2

Day 8

^{124}I-PUH71
PET-CT

Gerecitano et al., ASCO 2013, Abstr. 11076 "Using ^{124}I-PU-H71 PET imaging to predict intratumoral concentration in patients on a Phase 1 trial of PU-H71"

Chiosis et al., Patent application WO 2013009657

HDC differentiators

HDC: small molecules, intracellular target

ADC: large proteins, extracellular target

HDCs

→ Do not require unique cell surface antigen

→ Enter cells generally through passive diffusion (vs. endocytosis for ADCs)

→ Achieve sustained µM payload drug concentration

→ Allow much broader choice of payload, range therapeutic applications than ADCs

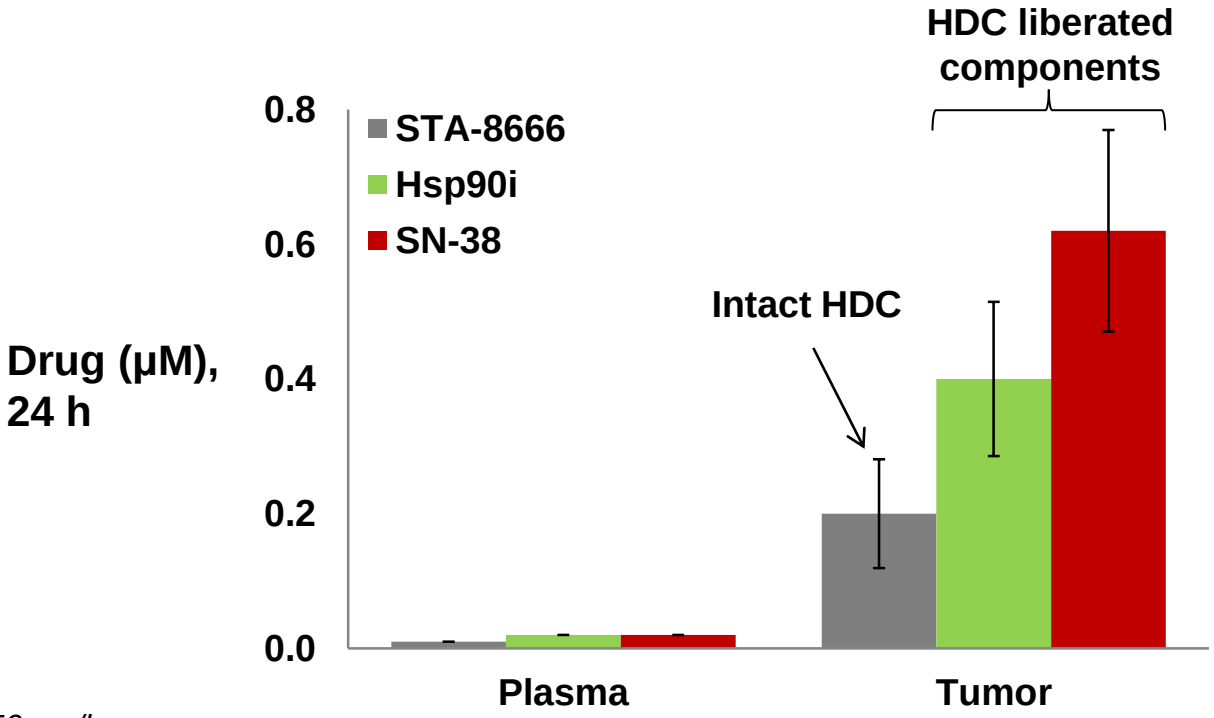
SYNTA

STA-12-8666 achieves >30x preferential tumor accumulation of payload

STA-12-8666

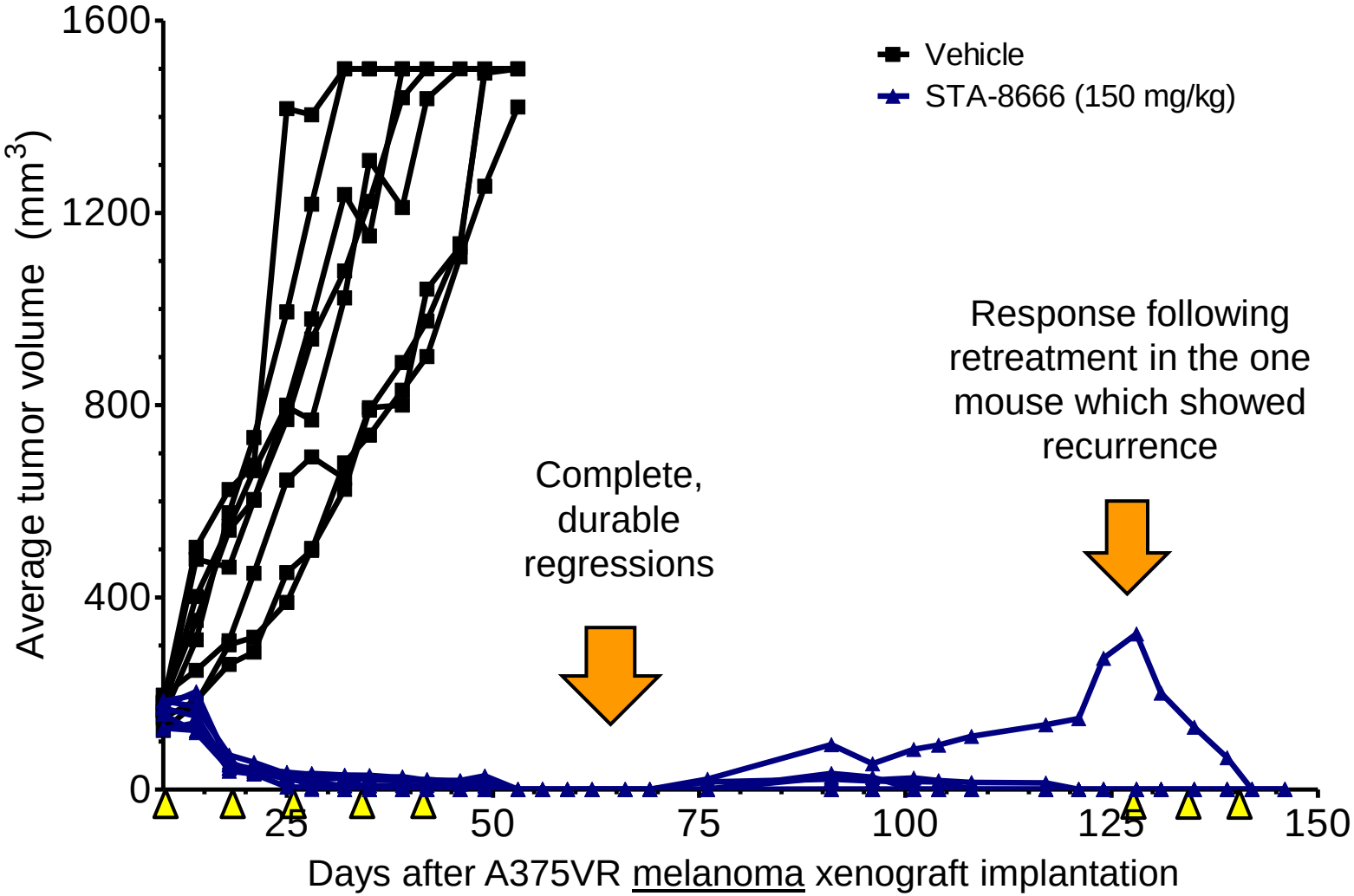
HDC achieves >30x greater SN-38 in tumor vs. plasma

HDC achieves >10x greater SN-38 in tumor vs. irinotecan at MTD



STA-12-8666, 50 mg/kg

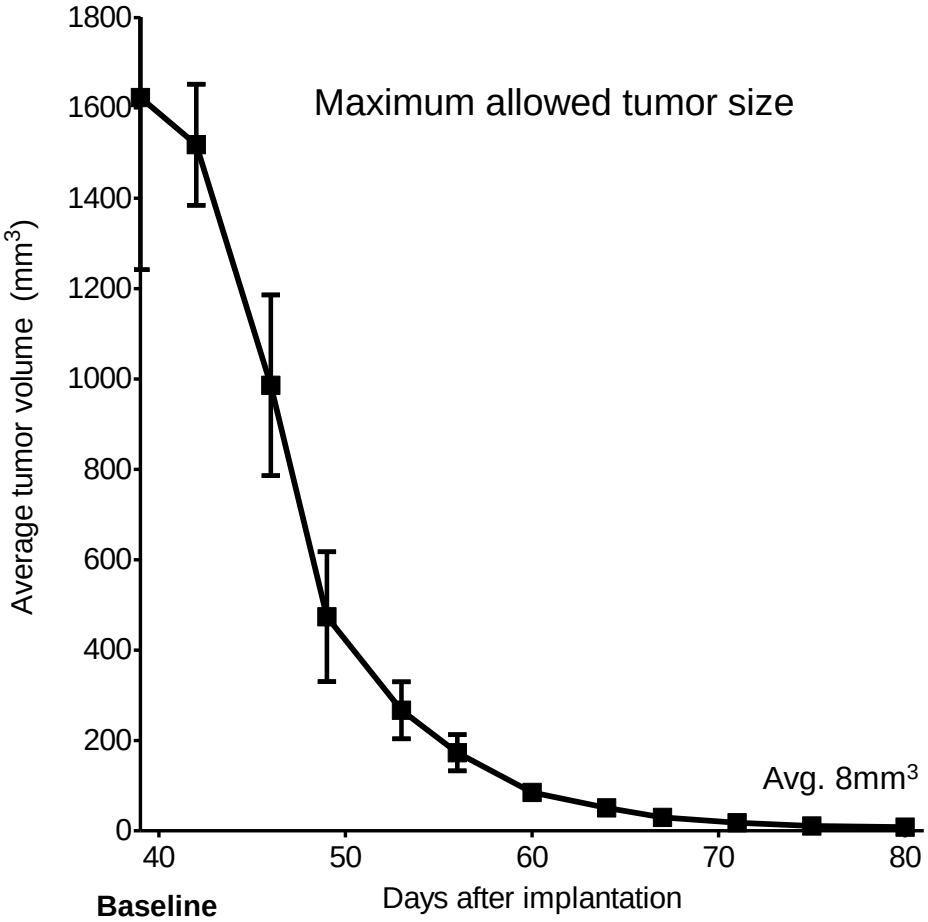
Complete, durable regressions after five doses

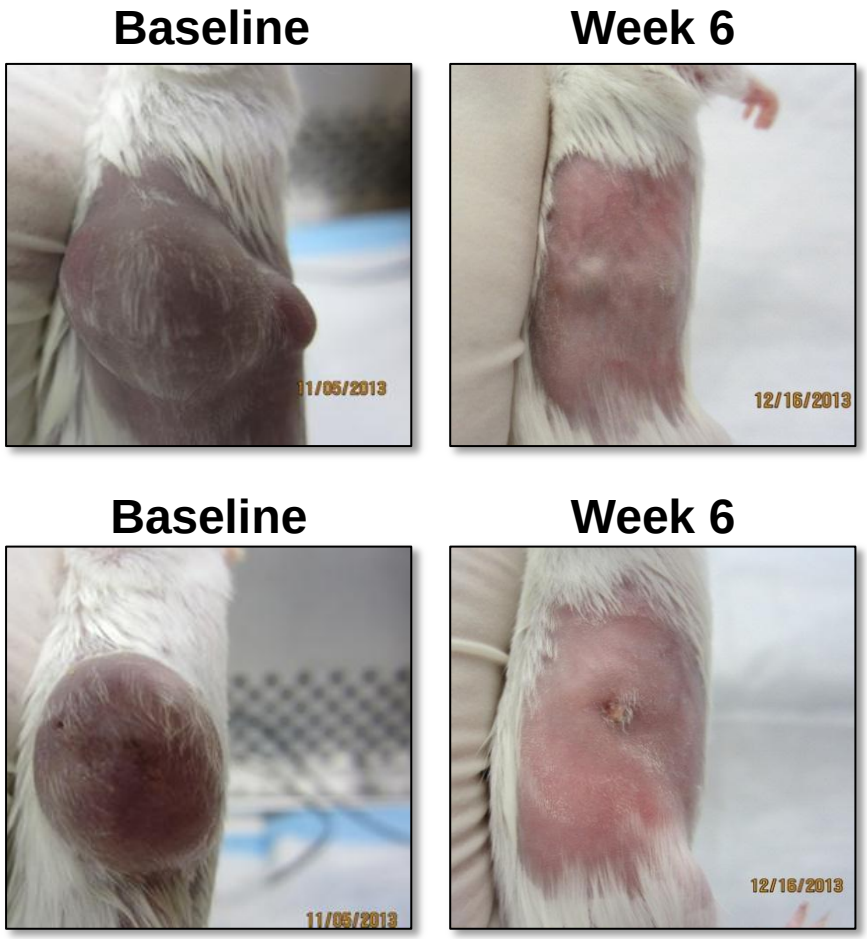


STA-12-8666 shows complete regressions in large NSCLC xenografts

H1975 NSCLC xenografts (N=4)

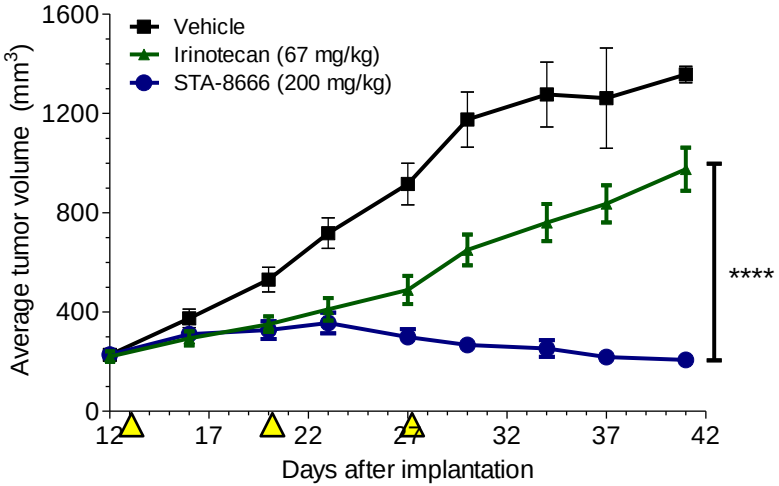
STA-12-8666 - 2x wk. *i.v.* 125 mg/kg



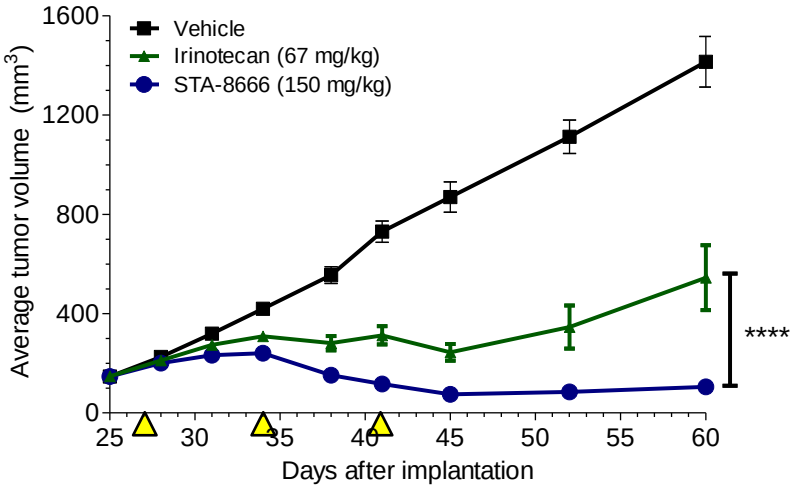


STA-12-8666 is efficacious in multiple tumor types

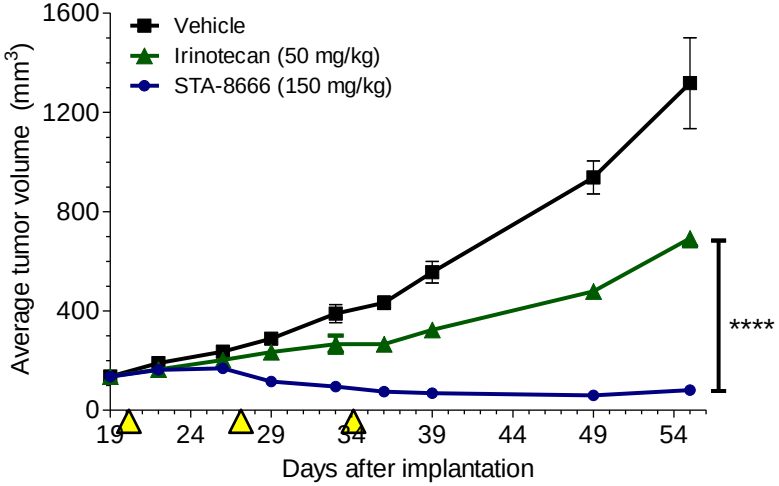
HCT 116 xenograft (CRC)



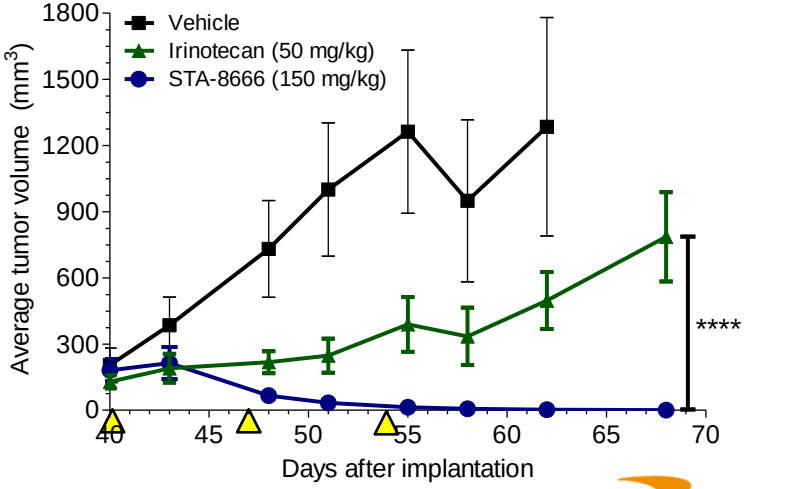
SCLC-1 xenograft (SCLC)



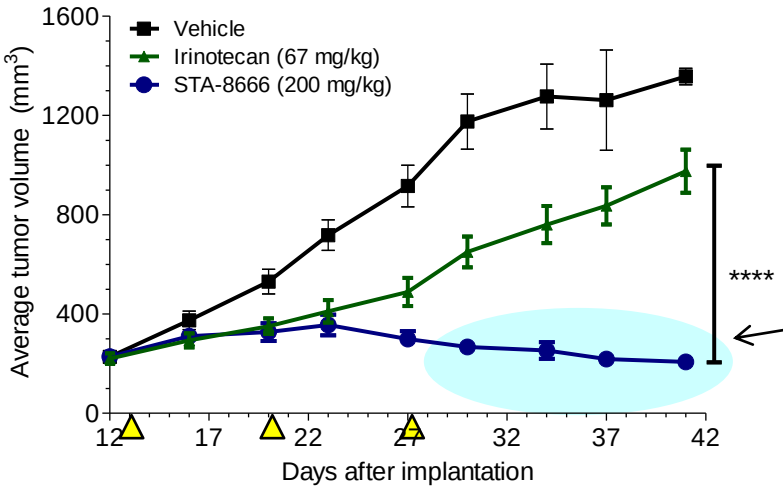
MCD-231 xenograft (TNBC)



Patient derived xenograft (pancreatic)



HCT 116 xenograft (CRC)



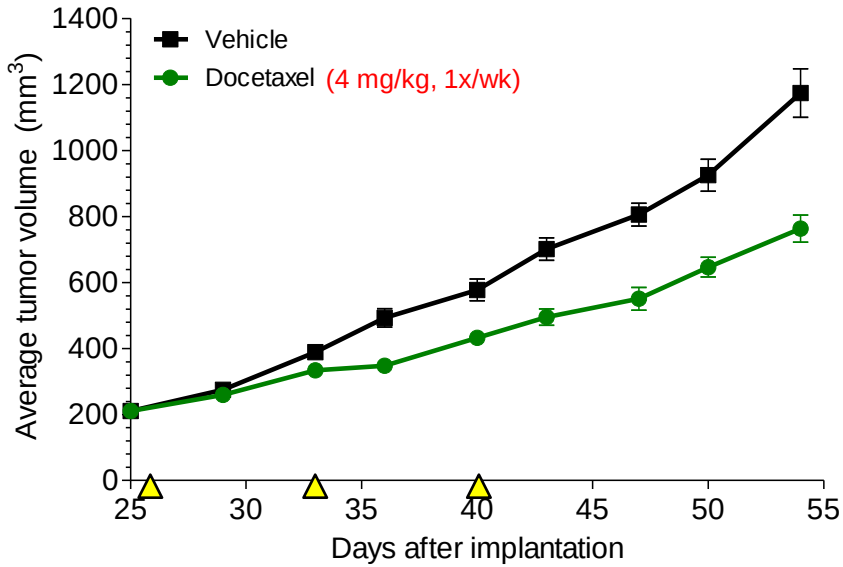
Tumors continue to shrink after last dose:

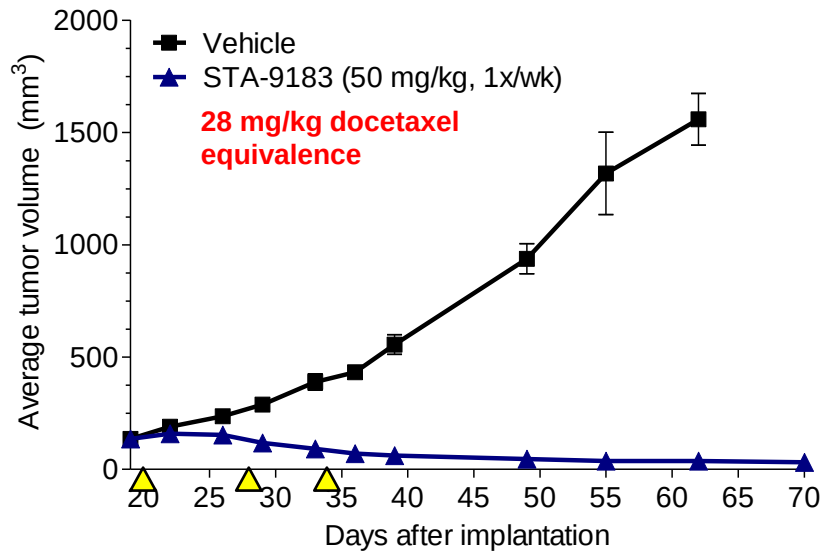
HDC retained in tumor, slow-releases toxin

5-7x greater docetaxel delivered with HDC docetaxel vs. unconjugated docetaxel

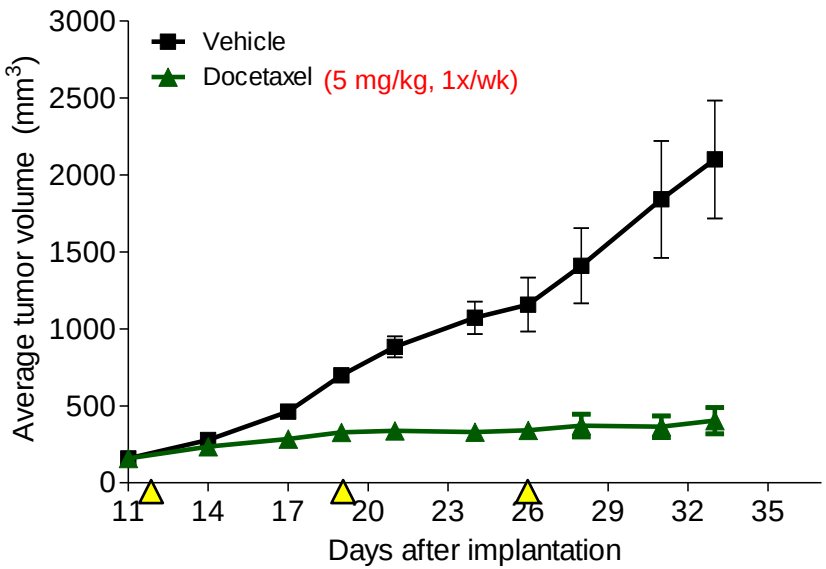
Docetaxel | **HDC docetaxel (STA-9183)**

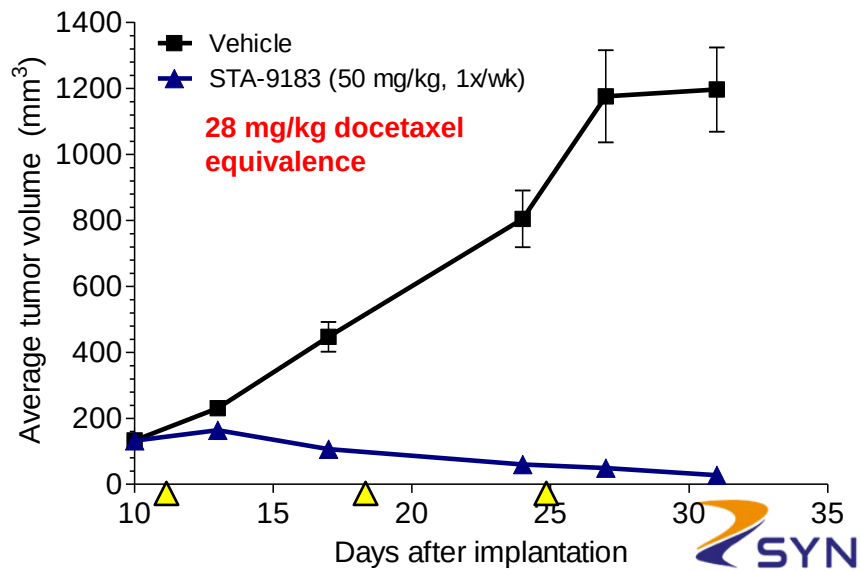
MDA-MB-231 TNBC xenografts





H1975 NSCLC xenografts





Over 450 HDC compounds created to date

Category	Example synthesized HDCs
Alkylating agents	HD-Conjugated bendamustine (Treanda®) HD-Conjugated temozolomide (Temodar®)
Anthracyclines	HD-Conjugated doxorubicin (Adriamycin®)
Antimetabolites	HD-Conjugated 5-FU (Xeloda®) HD-Conjugated pemetrexed (Alimta®)
Camptothecins	HD-Conjugated SN-38 (Camptosar®) HD-Conjugated topotecan (Hycamtin®)
Epigenetic modifiers	HD-Conjugated vorinostat / SAHA (Zolinza®) HD-Conjugated panobinostat (Faridak®)
Hormonal therapy	HD-Conjugated fulvestrant (Faslodex®) HD-Conjugated abiraterone (Zytiga®)
IMIDs	HD-Conjugated lenalidomide (Revlimid®) HD-Conjugated pomalidomide (Pomalyst®)
Microtubule stabilizers	HD-Conjugated docetaxel (Taxotere®)
Platinums	HD-Conjugated carboplatin (Paraplatin®)
Proteasome inhibitors	HD-Conjugated bortezomib (Velcade®)
Tyrosine Kinase Inhibitors	HD-Conjugated sunitinib (Sutent™) HD-Conjugated sorafenib (Nexavar®)

Additional details: see www.syntapharma.com

Plans for Synta HDC Platform

Opportunity to improve activity, safety profile of wide range of small molecule anti-cancer therapies

Partner selectively for certain opportunity categories

Retain other HDC compounds for Synta

Upcoming milestones

ENCHANT-1: metastatic breast cancer		
	SABCS: Presentation of preliminary results	Dec 2013
GALAXY-1: non-small cell lung cancer		
	Final data	1H 2014
GALAXY-2: non-small cell lung cancer		
	interim and final results	2014 and 2015
ENCHANT-2: HER2 neg metastatic breast cancer		
	Trial initiation	contingent on partnership

Financials

	9 months ended September 30, 2013 (in thousands)	9 months ended September 30, 2012 (in thousands)
Total revenues	$ 0	$ 147
Operating expenses		
R&D	$ 51,879	$ 35,061
G&A	$ 12,236	$ 8,324

	September 30, 2013	December 31, 2012
Cash, cash equiv., marketable securities	$ 53,384	$ 100,599

Nov 18 2013: completed 16.1 million share equity offering, $60.4 M

85.2 M shares outstanding post-offering

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Opportunity

Ganetespib: GALAXY program

# new cases adeno NSCLC patients, second-line+ (US, EU5, Japan)	~ 160,000 / year
Penetration	~ 20-40%
Pricing	Recent oncology approvals
	$2B+ / year

Ganetespib: NSCLC and breast ca expansion

- Front-line NSCLC
- Triple-negative breast cancer
- HER2-negative breast cancer

2-4 x second-line NSCLC opportunity

HDC Program

- Chemotherapeutic / targeted small-molecules market

EU5: UK, Germany, France, Spain, Italy
Sources: Decision resources, Synta estimates

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Highlights

Ganetespib: Phase 3 in NSCLC

- Highly selective Hsp90 chaperone inhibitor
- Durable, objective responses as single-agent
- Improves PFS and OS when added to chemotherapy in NSCLC
- Over 25 trials in multiple cancers; registration programs ongoing/planned in **breast, AML, ovarian**
- **Synta owns 100% worldwide rights**

Hsp90 inhibitor Drug Conjugate (HDC) platform

- Novel tumor-targeting small molecules, exploiting tumor retention properties of Hsp90 inhibitors
- More-targeted Alimta®, Velcade®, Taxotere®, Revlimid® …
- **Over 450 compounds generated to date**

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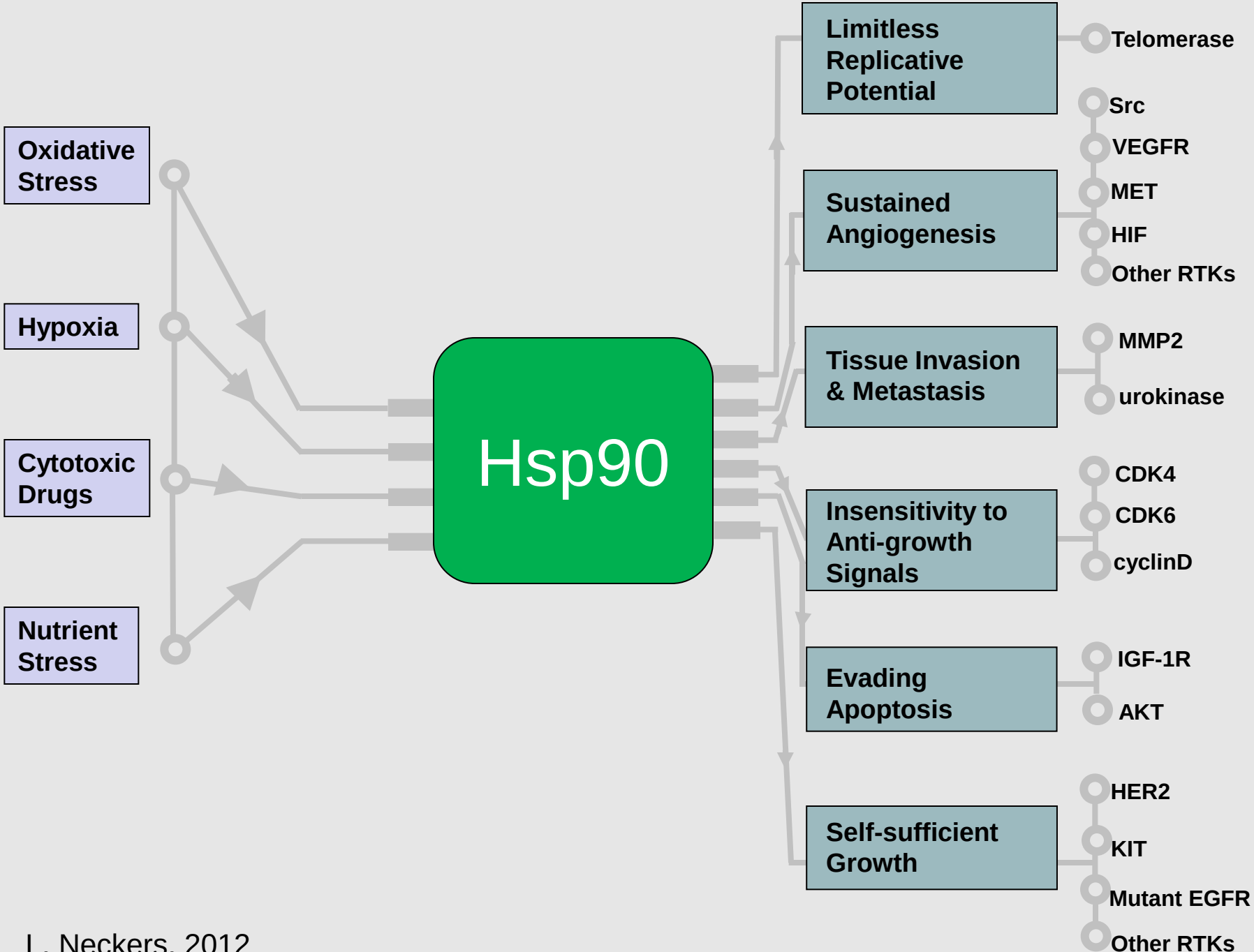
Additional slides

- Hsp90 and ganetespib background
- GALAXY-1 trial
- HDC platform

Hsp90 senses environmental stress & coordinates cellular responses to promote survival

L. Neckers, 2012



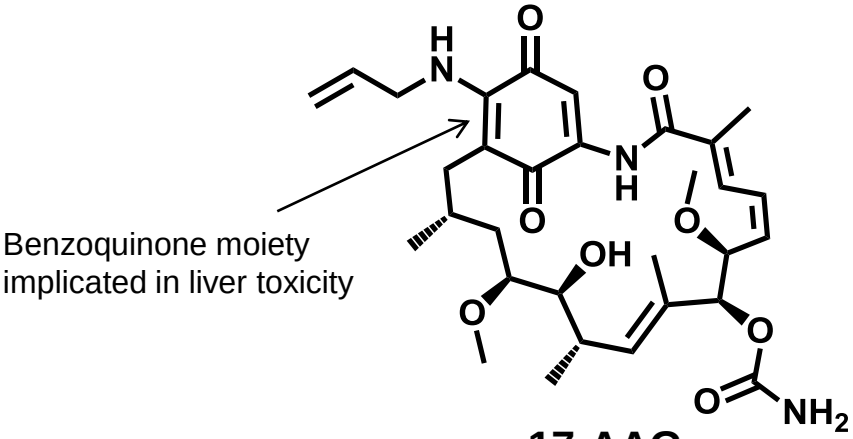
L. Neckers, 2012

Ganetespib: next-generation Hsp90 inhibitor

1st-gen Hsp90 inhibitors

17-AAG, 17-DMAG, IPI-504

- Liver toxicities, weak binding



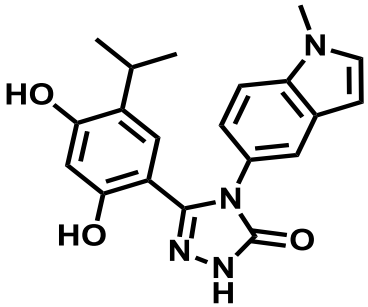
17-AAG

2nd-gen synthetics

- High incidence of visual impairment

Ganetespib

- No serious liver toxicities or common visual impairment
- Up to 100x more potent than 17-AAG



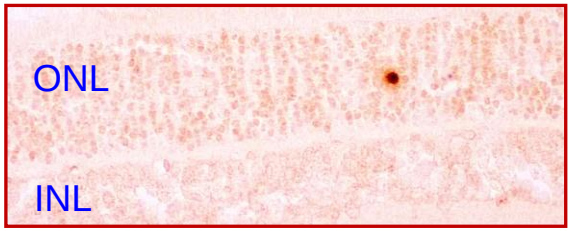
Frequent visual impairment with certain 2nd-gen Hsp90i, <u>not</u> seen with ganetespib

Correlation with Hsp90i accumulation in retina

Rodent *In Vivo* study: TUNEL assay

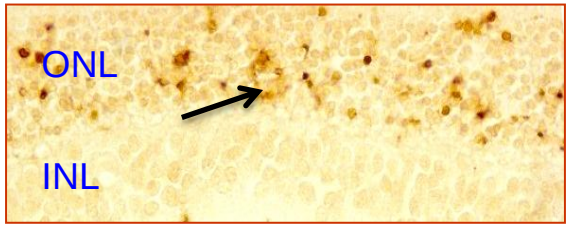
<u>Hydrophobic Hsp90 inhibitors</u>
No accumulation in retina

Ganetespib

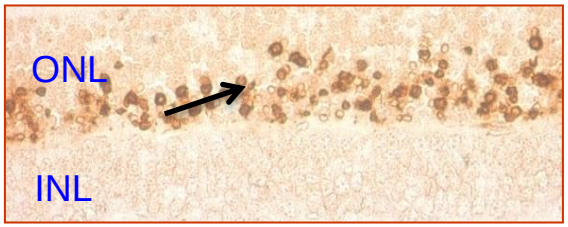


ONL: outer nuclear layerr; elevated Hsp90

<u>Hydrophilic Hsp90 inhibitors</u>
Accumulation in retina



AUY-922



17-DMAG

Visual impairment in clinical trials: <3% with ganetespib vs. >50% other 2nd-gen Hsp90i

Zhou et al, ASCO June 2012 Abst. #3086

Ganetespib blocks HIF-1 activity and inhibits tumor growth, vascularization, stem cell maintenance, invasion, and metastasis in orthotopic mouse models of triple-negative breast cancer

L Xiang, DM Gilkes, P Chaturvedi, W Luo, H Hu, N Takano, H Liang and GL Semenza
J Mol Med 2013

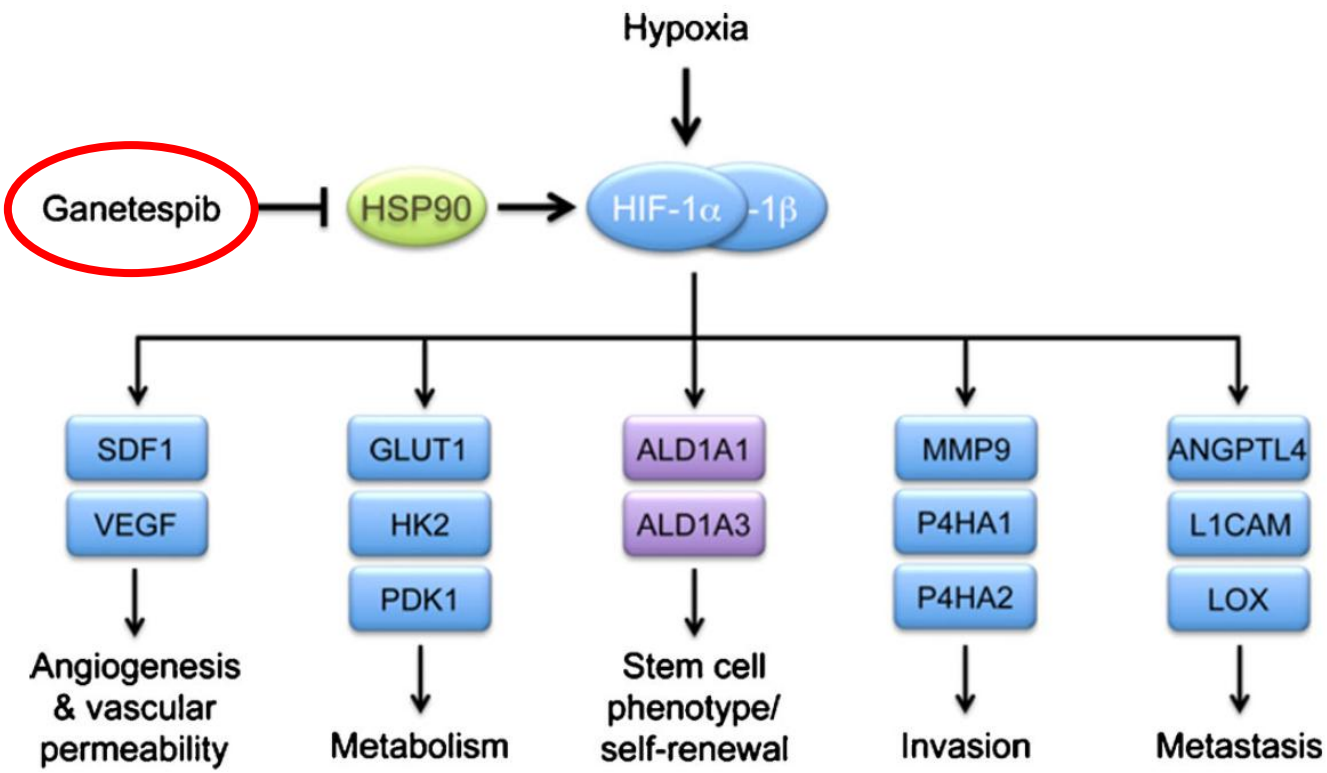


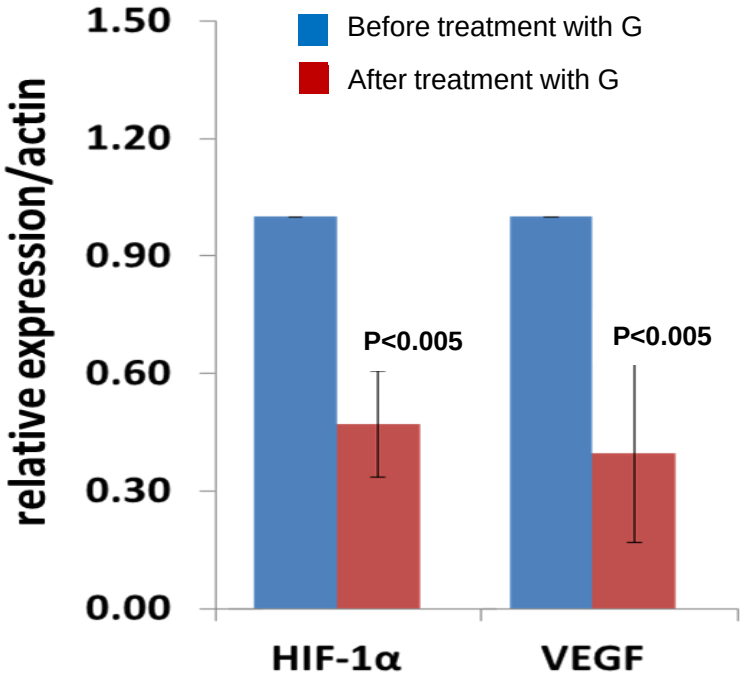
Fig. 8 Consequences of HIF-1α inhibition by ganetespib in triple-negative breast cancer cells. Ganetespib inhibits HSP90-dependent stabilization of HIF-1α and transcription of HIF-1 target genes (*blue rectangles*) whose protein products mediate angiogenesis and vascular permeability (*SDF1*, *VEGF*), glycolytic metabolism (*GLUT1*, *HK2*, *PDK1*), invasion (*MMP9*, *P4HA1*, *P4HA2*), and metastasis (*ANGPTL4*, *L1CAM*, *LOX*). Ganetespib also reduced the number of Aldefluor^{+} cancer stem cells and decreased ALDH1A1 and ALDH1A3 mRNA levels, although the latter genes (*purple rectangles*) are not directly regulated by HIF-1 in breast cancer cells

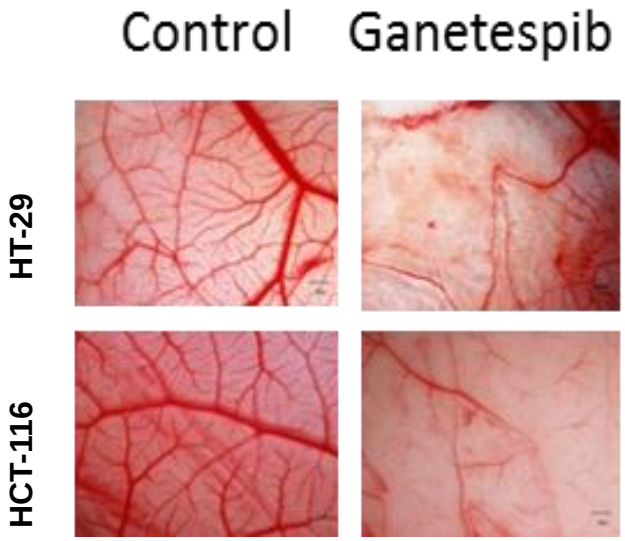
Angiogenesis
DOI 10.1007/s10456-013-9364-7

ORIGINAL PAPER

Antiangiogenic effects of ganetespib in colorectal cancer mediated through inhibition of HIF-1α and STAT-3

Purnachandra Nagaraju Ganji · Wungki Park · Jing Wen · Hemchandra Mahaseth · Jerome Landry · Alton B. Farris · Field Willingham · Patrick S. Sullivan · David A. Proia · Iman El-Hariry · LaTonia Taliaferro-Smith · Roberto Diaz · Bassel F. El-Rayes



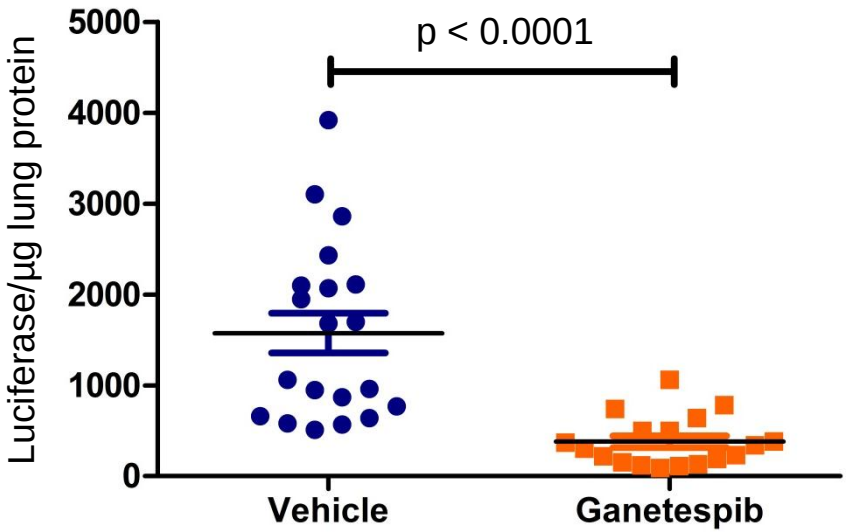


Egg cam assay

*RT-PCR, tumor samples from first 3 pts, rectal ca

Ganetespib inhibits metastasis
Preclinical models of lung metastasis

Spontaneous metastasis model



4T1-LUC mouse breast cancer cells injected into mouse mammary fat pad; treated w/ G or vehicle 1x/wk for 3 wk

- G inhibits key oncogene drivers of metastasis including HIF-1α and regulators of cell adhesion
- In vitro, G reduces cancer cell migration and invasion
- In vivo, G suppresses metastases in both experimental and spontaneous metastases models

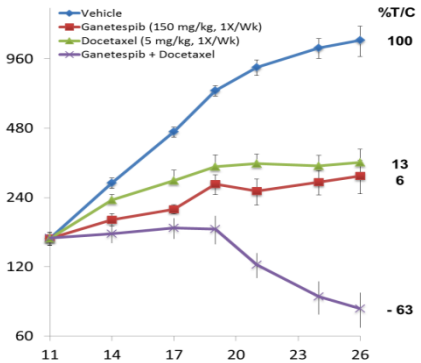
D. Proia et al, "Antimetastatic activity of ganetespib: preclinical studies and assessment of progressions due to new lesions in GALAXY-1" (ESMO 2013, #P426)

For review of chaperone biology and cancer metastasis see Tsutsumi et al., Impact of Hsp90 on cancer metastasis, Future Oncol. 2009 5(5)

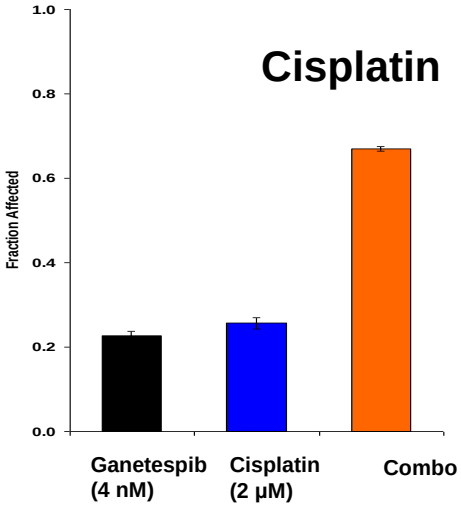
Ganetespib has shown synergy with broad range of other cancer treatments

Chemotherapy

Docetaxel

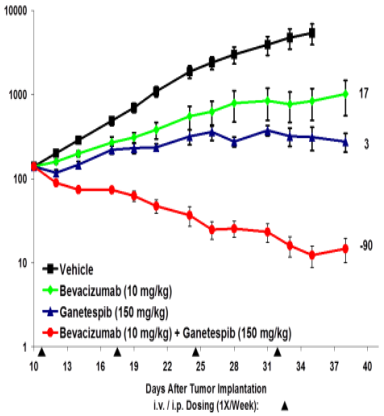


Cisplatin

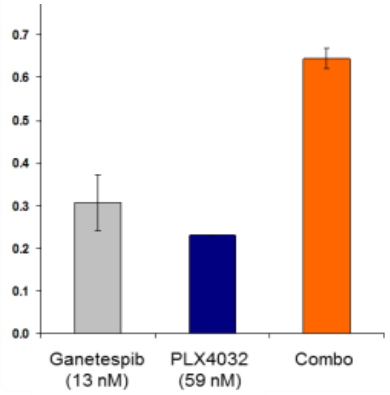


Targeted Agents

Bevacizumab

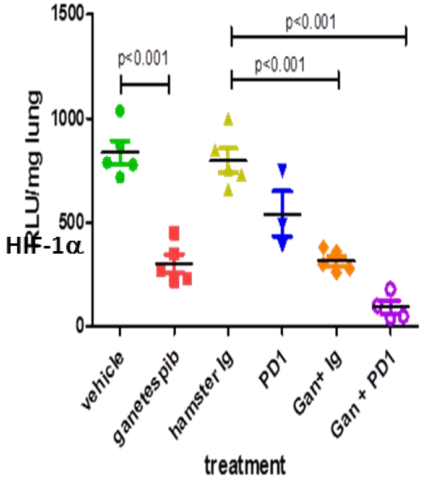


BRAFi



Immunotherapy

PD-1 inhibitor

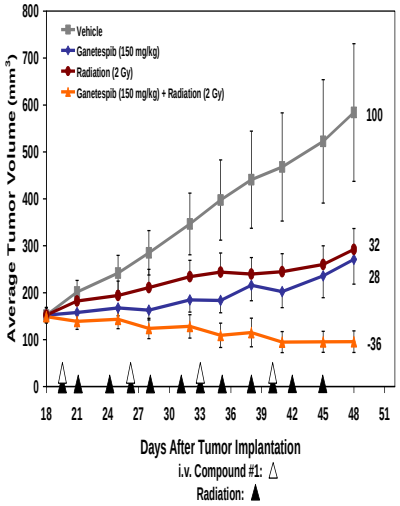


Fluorescence detected in lung from breast cancer cells metastasizing from fat pad

Hypoxia → HIF-1α → recruitment of T-regs to tumor, inhibition of immune response

G inhibits HIF- 1α

Radiation Therapy



Targeting cancer network → silencing of multiple resistance mechanisms

Hsp90 senses stress in response to anti-cancer agents and promotes survival

Inhibiting Hsp90 reduces cancer cell defense in face of this stress

→ broad combination synergy

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Additional slides

- Hsp90 and ganetespib background
- GALAXY-1 trial
- HDC platform

GALAXY-1 patient enrollment

Primary Enrollment Phase
Completed Nov 2012

Patients screened
N=539

↓

Patients randomized
N=324

↓

Adenocarcinoma
N=253

Biomarker Extension Phase
Completed May 2013

- Protocol specified target cumulative total N=120 eLDH, N=80 mKRAS
- Enrolled N=76 eLDH, N=63 mKRAS in primary enrollment phase
- Screened N=146
- Enrolled N=61 additional eLDH, mKRAS

Non-adenocarcinoma (N=71): Enrollment stopped **May 2012** due to safety signal and lack of efficacy

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Planned interim analyses for primary adenocarcinoma population

		# OS events
80% enrollment	ESMO 2012	45
6-months min. follow-up	ASCO 2013	134
1 year min. follow-up	WCLC 2013	166

Final analysis, targeting >70% >177 events

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Key GALAXY-1 patient populations

Population	Elevated LDH	KRAS mutations	Chemosensitive (Diagnosis advanced disease > 6 months)	ITT
Rationale	• **LDH-A is a marker** of HIF-1α activity • HIF-1α is Hsp90 client, drives invasiveness, metastasis	• **RAS** signaling kinases are Hsp90 clients • Medical need	• Key **cell cycle checkpoint/ DNA repair** kinases are Hsp90 clients • Potential cross-resistance to G in refractory patients	All

- eLDH and mKRAS: co-primary endpoints
- Dx>6m: stratification factor

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Summary: PFS, OS key populations

G+D vs. D		Elevated LDH N=76	mKRAS N=63	Chemosensitive (Dx >6m) N=178	ITT N=253
PFS	Median (months)	3.4 vs. 1.9	4.1 vs. 3.0	5.3 vs. 3.4	4.3 vs. 3.2
	Events	63 (83%)	50 (79%)	138 (78%)	199 (79%)
OS	Median (months)	5.2 vs. 4.3	9.8 vs. 6.3	10.7 vs. 7.4	10.4 vs. 8.4
	(90% CI)	(3.9, 9.8) vs (4.3, 5.1)	(4.3, 12.3) vs (4.9, 14.0)	(8.5, 13.9) vs (5.8, 10.0)	(8.0, 12.6) vs (6.3, 10.9)
	Events	64 (84%)	41 (65%)	115 (65%)	166 (66%)

Database lock: Oct 2013

SYNTA

Summary: PFS, OS key populations

	Hazard Ratio G+D vs. D (90% CI)	Elevated LDH N=76	mKRAS N=63	Chemosensitive (Dx >6m) N=178 (Population selected for Phase 3)	ITT N=253
PFS	Unadjusted	**0.94** (0.57, 1.36) p=0.409	**0.83** (0.52, 1.33) p=0.256	**0.73** (0.55, 0.96) p=0.031	**0.84** (0.67, 1.06) p=0.114
	Adjusted	**0.69** (0.43, 1.08) p=0.088	**0.95** (0.58, 1.54) p=0.427	**0.72** (0.53, 0.96) p=0.030	**0.84** (0.66, 1.06) p=0.110
OS	Unadjusted	**0.69** (0.45, 1.05) p=0.073	**1.12** (0.67, 1.88) p=0.641	**0.75** (0.56, 1.03) p=0.065	**0.90** (0.70, 1.17) p=0.217
	Adjusted	**0.52** (0.33, 0.81) p=0.009	**1.22** (0.71, 2.07) p=0.727	**0.72** (0.52, 0.98) p=0.040	**0.86** (0.66, 1.12) p=0.175

Database lock: Oct 2013

All p-values 1-sided. Hazard ratios (HR) calculated with Cox proportional hazards model. Unadjusted: univariate analysis; adjusted: prespecified multivariate analysis (adjusting for gender, smoking status, LDH, ECOG performance status, interval since diagnosis advanced disease, age, total baseline target lesion size, and geographic region).

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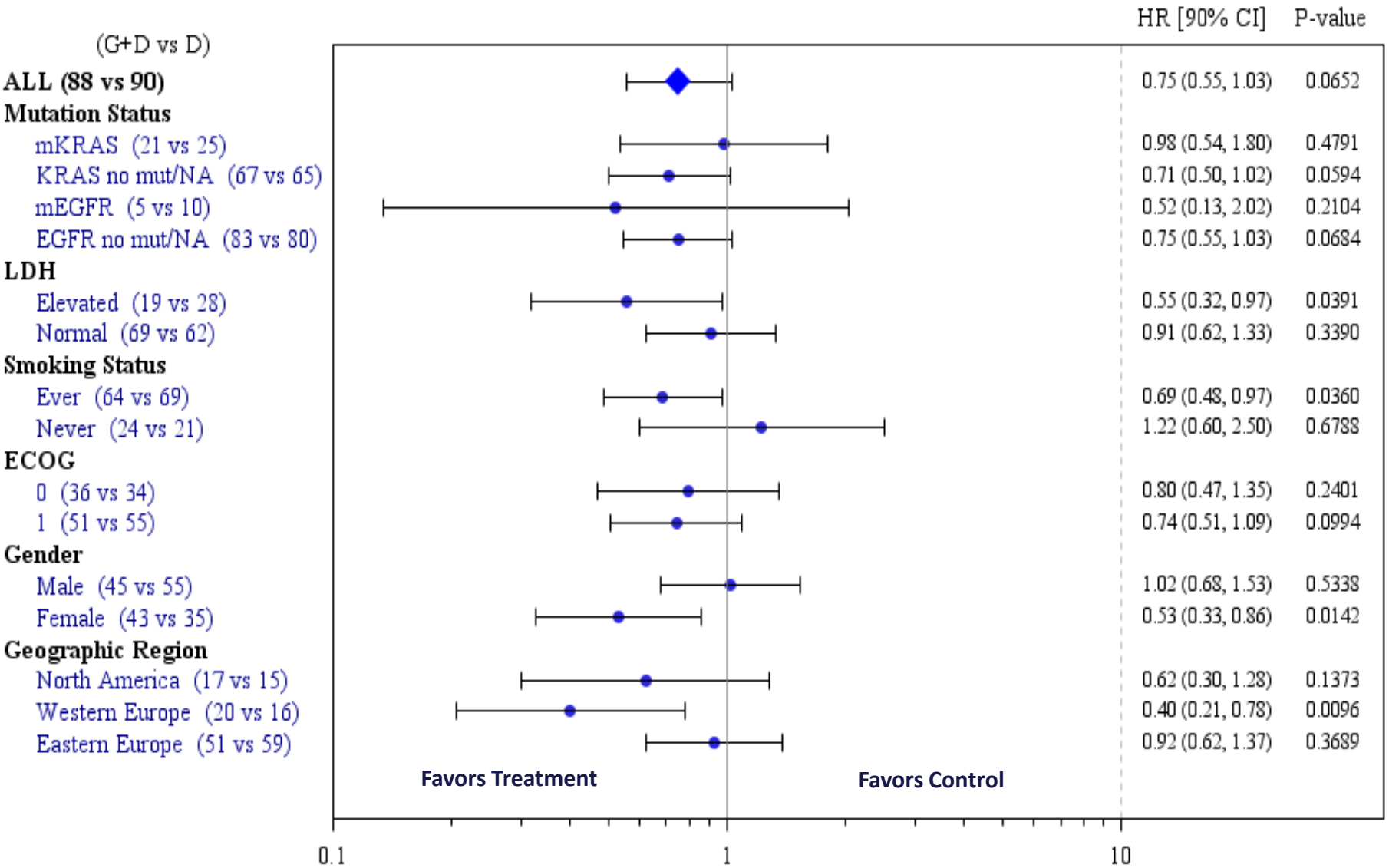
OS Forest Plot: Dx >6 months Population



All p-values 1-sided.

Decreasing Phase 3 operational risk: identifying regional differences

	Two E Eur countries	Rest of study	Other trials
Pts presenting with early stage disease (Stage I/II) on initial diagnosis	24%	4%	8-10%[1]
Pts with prior surgery	51%	19%	17-24%[2]
BAC histology	34%	8%	1-3%[3]
Median treatment duration on docetaxel arm (months)	8.3	2.8	2.5 – 3.2

Is this population truly representative of 2nd-line advanced NSCLC disease?

Reduce risk: enrollment was capped in GALAXY-2; no longer enrolling
→ Increase trial population homogeneity; decrease heterogeneity

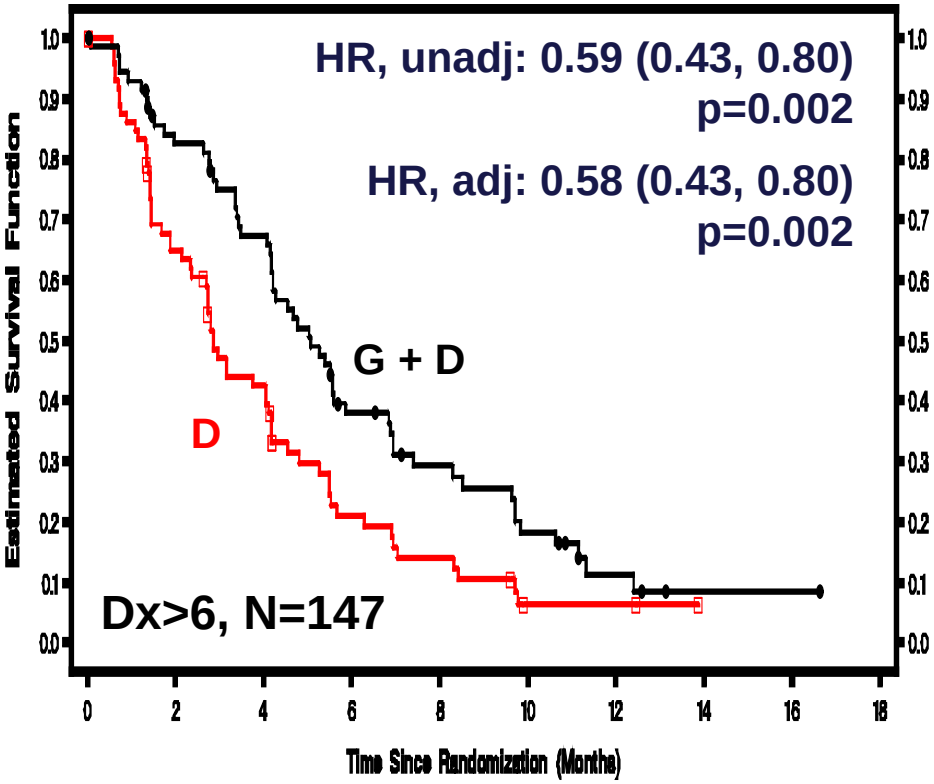
1. Kim et al., Lancet 2008; Ramlau et al., JCO 2012; Thatcher et al., Lancet Oncol 2005
2. Ramlau et al., JCO 2012; Murayama et al., JCO 2007; Hanna et al., JCO 2004
3. Kim et al., Lancet 2008; Hanna et al., JCO 2004; Thatcher et al., Lancet Oncol 2005

SYNTA

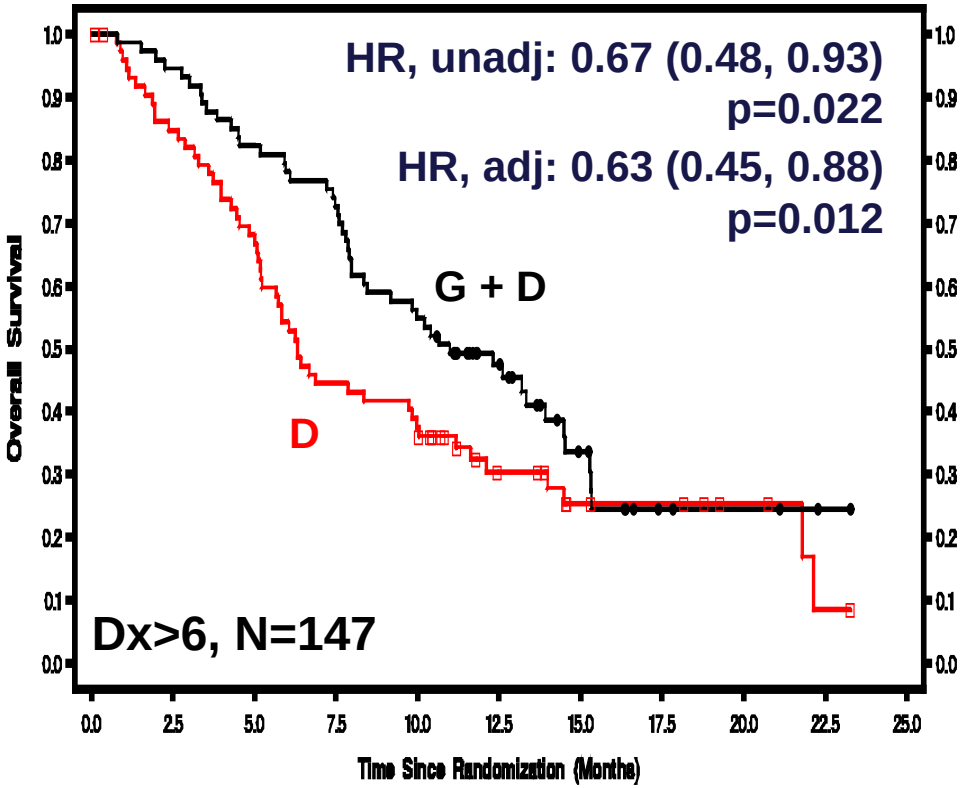
Decreasing Phase 3 operational risk: identifying regional differences

GALAXY-1 results from all regions except the two outlier E Eur countries no longer enrolling in GALAXY-2

Progression-Free Survival



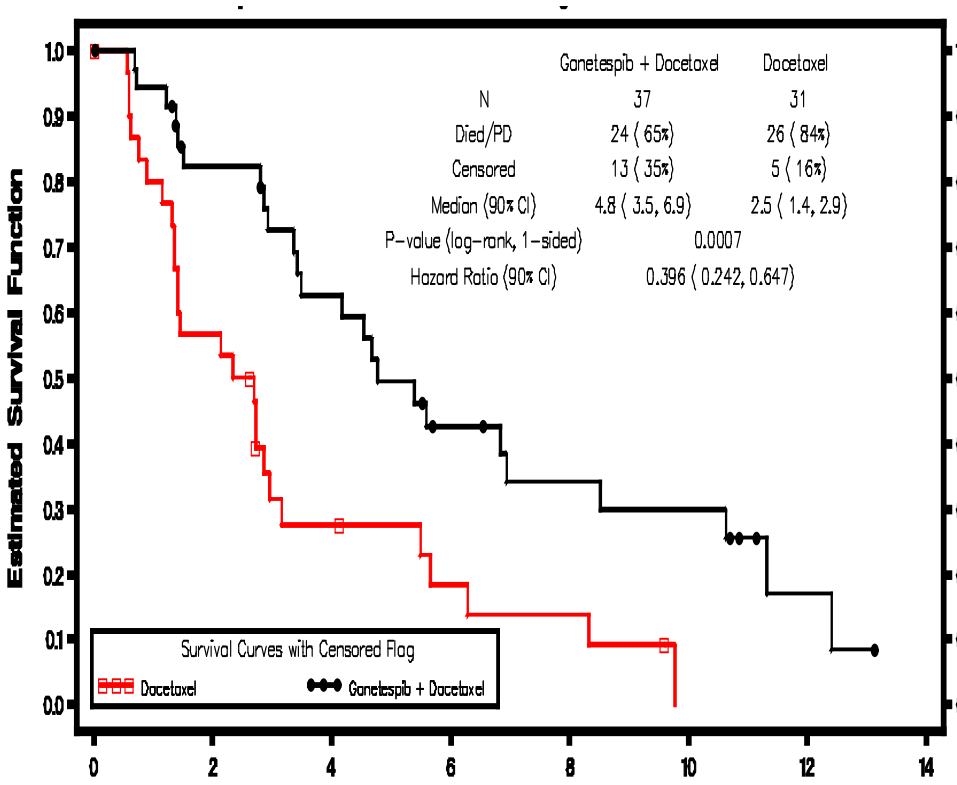
Overall Survival



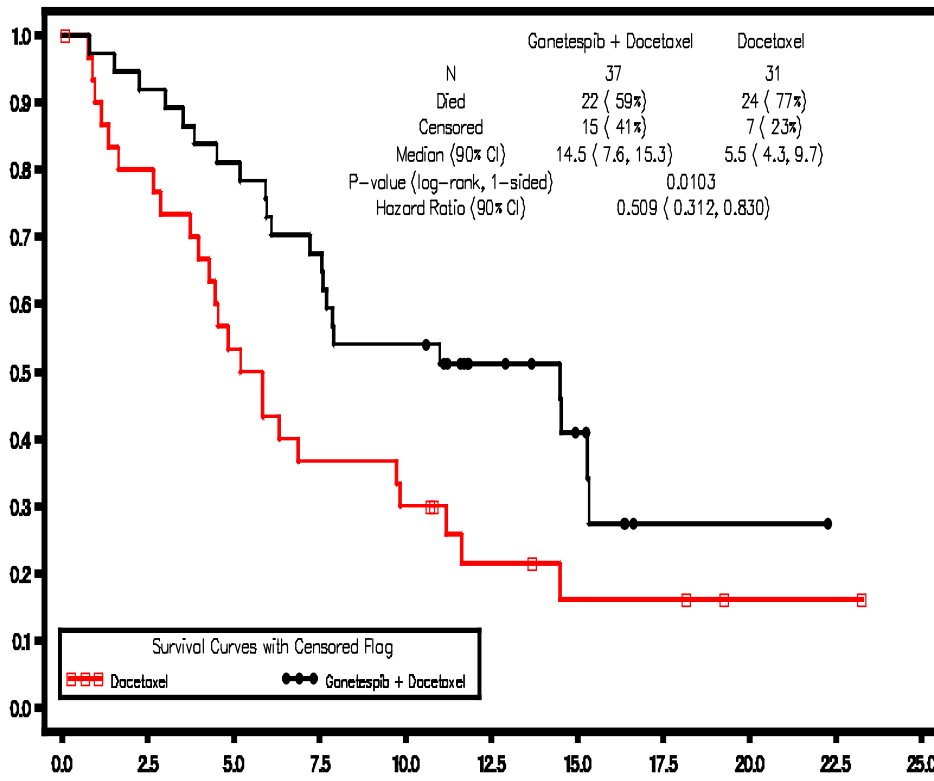
All p-values 1-sided. Hazard ratios (HR) calculated with Cox proportional hazards model. Unadjusted: univariate analysis; adjusted: prespecified multivariate analysis (adjusting for gender, smoking status, LDH, ECOG performance status, interval since diagnosis advanced disease, age, total baseline target lesion size, and geographic region).

GALAXY-1 results in West: North America + Western Europe

PFS - West



OS - West



Chemosensitive Dx>6 month population selected for Phase 3

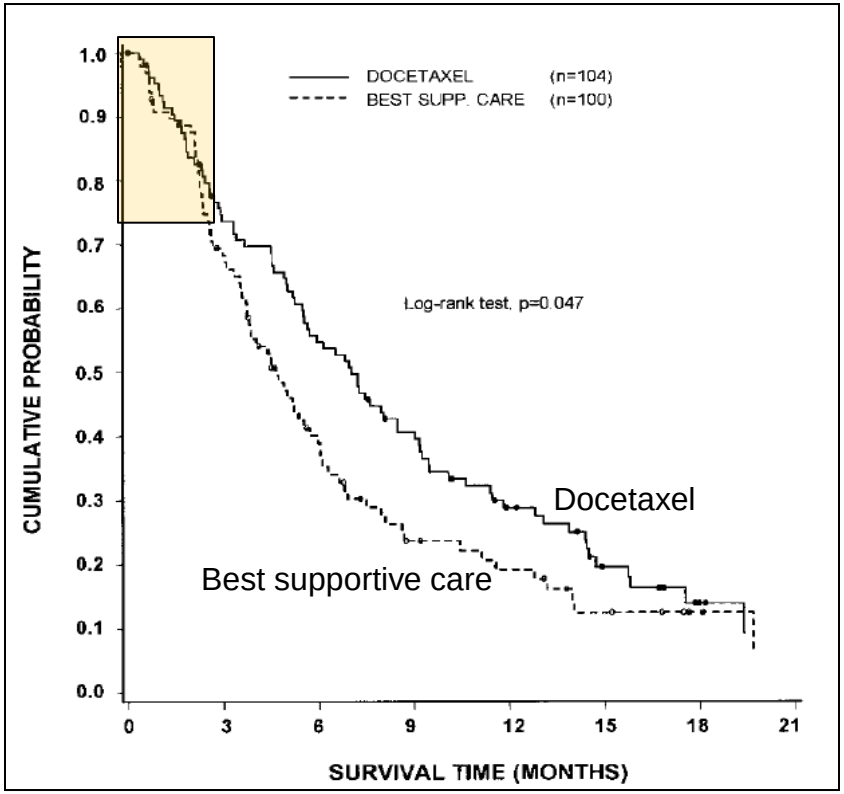
Examples: recurrence-free intervals, approved products

Brand	Drug	Indication	Indication or Clinical Studies section language
Perjeta	pertuzumab	Metastatic breast cancer	prior adjuvant or neoadjuvant therapy with a disease free interval of **>12 months**
Gemzar	gemcitabine	Ovarian cancer	relapsed **at least 6 months** after completion of platinum-based therapy
Hycamtin	topotecan	Small-cell lung cancer	disease responding to chemo but subsequently progressing **at least 60 days** after chemotherapy
Eloxatin	Oxaliplatin	Colorectal cancer	Required absence of recurrence **within 12 months** of completion of adjuvant therapy for resected disease.
Marquibo	lip-vincristine	ALL	CR to at least one prior chemotherapy; leukemia-free interval of **>=90 days**
Mylotarg	gemtuzumab ozogamicin	AML	first remission duration of **at least 6 months**

Source; FDA, US Product Inserts

Patients with refractory disease commonly show no treatment benefit in 2nd-line / salvage setting

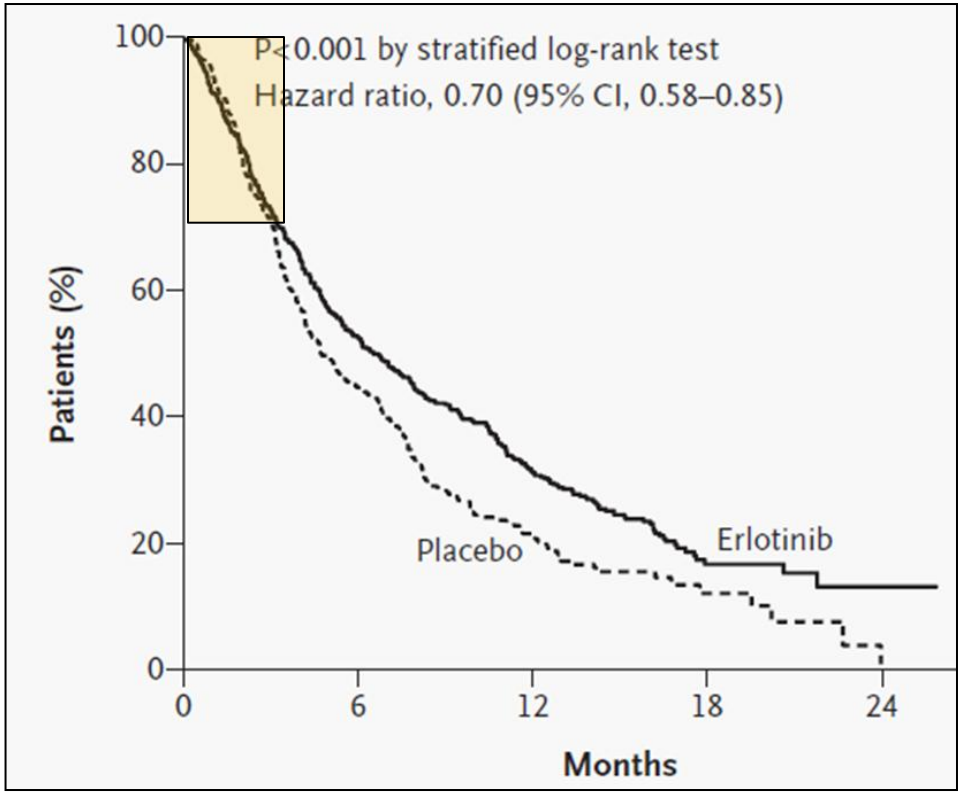
OS– Docetaxel (TAX317 registration trial)



N=204 >= 1 prior chemo No prior taxane
Med OS: 4.6m vs. 7.0m p=0.047

Shepherd, et al. J. Clin. Oncol., 18:2095 (2000)

OS – Erlotinib (BR21 registration trial)



N=731 1-2 prior chemo
Med OS: 4.7m vs. 6.7m; HR 0.70, p<0.001

Shepherd, et al. New Engl J Med., 353:123 (2005)

Example of clinical biomarker, NSCLC

Pemetrexed registration trial, 1st-line advanced NSCLC[1]

Overall survival	**cisplatin-pemetrexed vs. cisplatin-gemcitabine**		
HR (95% CI)	Non-Squamous N=1252	Squamous N=473	ITT N=1725
Unadjusted	**0.84** (0.74, 0.96)	**1.22** (0.99, 1.50)	N/A
Adjusted	**0.84** (0.74, 0.96)	**1.23** (1.00, 1.51)	**0.94** (0.84, 1.05)

1. Scagliotti et al., JCO 26:3543-3551 (2008)

Additional slides

- Hsp90 and ganetespib background
- GALAXY-1 trial
- HDC platform

Preferential retention of Hsp90 inhibitors in tumor may be due to greater presence of active conformation

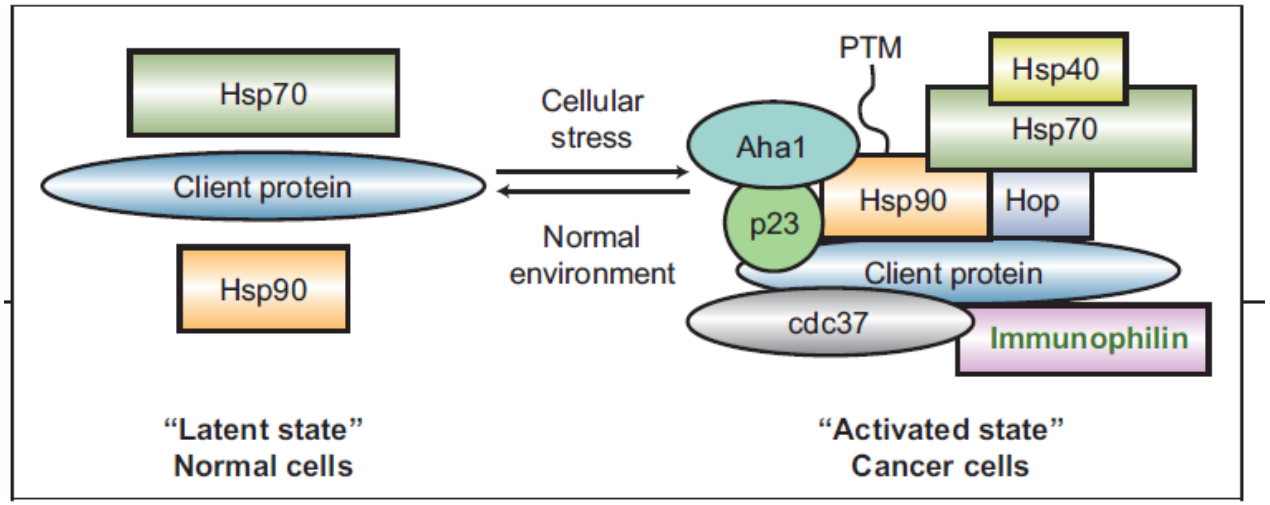


Figure 2. Hsp90 may exist in an equilibrium between an "activated" state prevalent in cancer cells and a "latent" state predominant in normal cells. The activation state of the chaperone may be regulated by co-chaperones and perhaps PTMs. This is a schematic representation of Hsp90 states and does not represent actual individual complexes.

G Chiosis and L Neckers, ACS Chem Biol. 2006 Jun 20;1(5):279-84.

Selective, persistent tumor retention in patients seen across tumor types

PU-H71 Concentrations in Patient Tumors
24hrs Post Dose [μM]
(from CNB samples)

Her-2+ Breast Cancer

Plasma	Tumor
0	**0.61**

TNBC

Plasma	Tumor
0	**0.93**

Mantle Cell Lymphoma

Plasma	Tumor
0	**0.35**

Marginal Zone Lymphoma

Plasma	Tumor
0	**0.58**

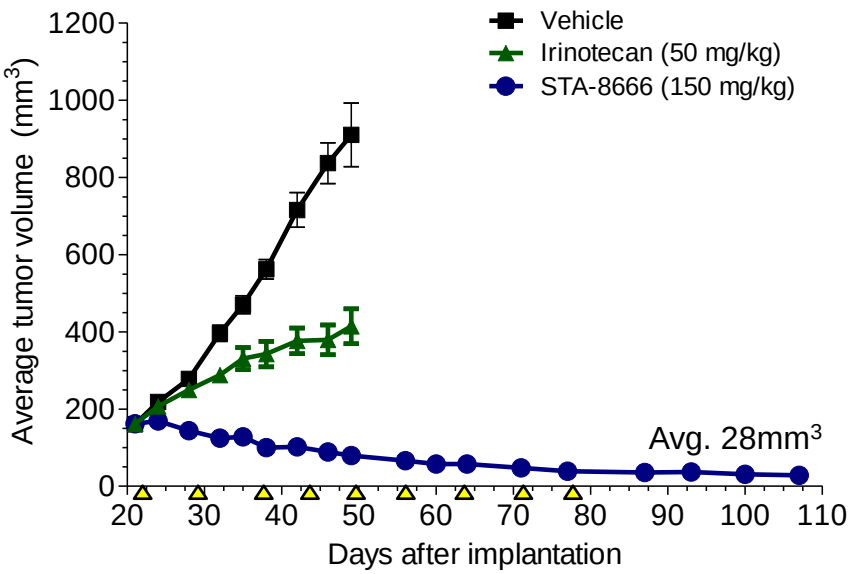
High concentrations (~1 μM) achieved in patient tumors at 24hrs vs. little/no concentration in plasma, across multiple tumor types

From Gerecitano et al., ASCO 2013, Abstr. 11076
"Using ^{124}I-PU-H71 PET imaging to predict intratumoral concentration in patients on a Phase 1 trial of PU-H71"

SYNTA

STA-8666 provides durable tumor regression without adverse impact on animal weights

Activity >30 days post-last dose



H441 mKRAS NSCLC xenograft

Weight gain on study