

# **A Phase 2 Study of the Hsp90 Inhibitor Ganetespib (STA-9090) as Monotherapy in Patients with Advanced NSCLC**

**J. R. Brahmer, M. Koczywas, J.W. Goldman,  
E.H. Paschold, L. Horn, J. Kepros, F. Teofilovici,  
G. Shapiro, M.A. Socinski**

Johns Hopkins, Baltimore, MD, Dana-Farber Cancer Institute,  
Boston, MA; City of Hope, Duarte, CA; Premiere Oncology, Santa  
Monica, CA; Piedmont Hematology-Oncology Associates, Winston-  
Salem, NC; Vanderbilt-Ingram Cancer Center, Nashville, TN; Synta  
Pharmaceuticals, Lexington, MA; University of North Carolina at  
Chapel Hill, Chapel Hill, NC

Disclosure: G. Shapiro received research funding from Synta  
prior to initiation of this clinical study

# Ganetespib (STA-9090)

- **Potent second generation Hsp90 inhibitor, structurally unrelated to first-generation ansamycin class of Hsp90 inhibitors**
  - In preclinical models, including NSCLC, ganetespib showed better activity and improved safety compared to first generation Hsp90 inhibitors
- **Ganetespib is well-tolerated in approximately 400 patients treated to date**
  - Most common AE: diarrhea; generally mild to moderate, manageable with supportive care
- **Absence of dose-limiting hepatic or ocular toxicities seen with other Hsp90 inhibitors**

# Study Design

Ganetespib 200 mg/m<sup>2</sup> q wk for 3 out of 4 weeks

- Previously treated stage IIIB/IV NSCLC
- ECOG - PS 0, 1
- Disease progression at study entry
- Genotyping\*

Stratification

A: mEGFR (n=16)

B: mK-Ras (n=17)

C: wild-type EGFR/wild-type K-Ras (n=25)  
D: Adenocarcinoma only (n=37)

E: addition of qw docetaxel on PD if clinical benefit

F/U  
Until  
PD

Simon two stage design

Enrolled N=96

Evaluable N=76

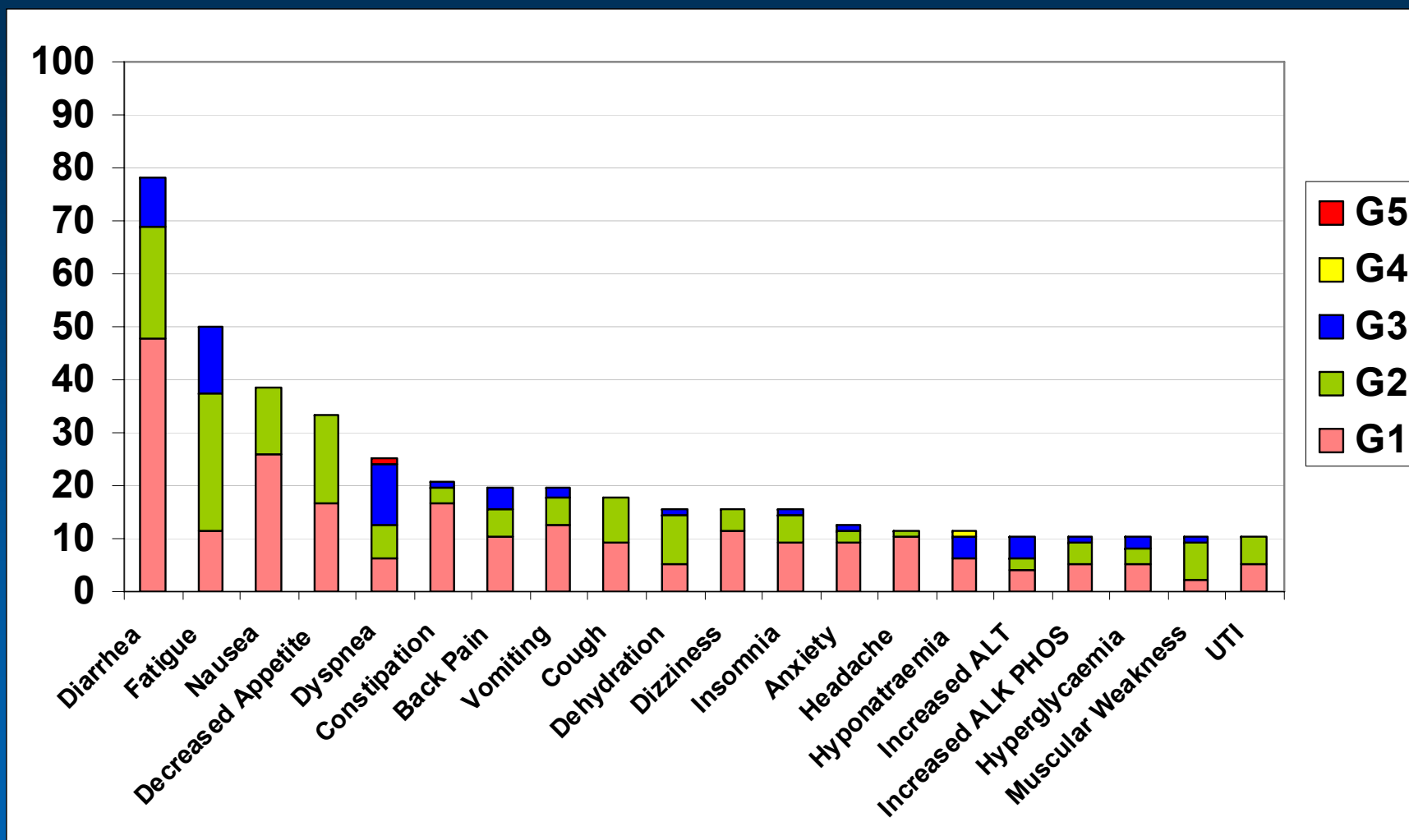
\*1 patient with unknown genotype  
First Patient First Visit, Dec, 2009;  
Last Patient first visit, May, 2011

Primary endpoint: PFS rate at 16 weeks

# Baseline Patient Characteristics

		Cohort A mEGFR n=16	Cohort B mKRAS n=17	Cohort C + D wild/wild type n=62
<b>Median Age (Range)</b>		<b>60 (49, 79)</b>	<b>64 (28, 76)</b>	<b>62 (36, 82)</b>
<b>Sex (n, %)</b>	<b>Male</b>	<b>6 (37.5)</b>	<b>4 (23.5)</b>	<b>35 (56.5)</b>
	<b>Female</b>	<b>10 (62.5)</b>	<b>13 (76.5)</b>	<b>27 (43.5)</b>
<b>ECOG Status (n, %)</b>	<b>0</b>	<b>7 (43.8)</b>	<b>4 (23.5)</b>	<b>14 (22.6)</b>
	<b>1</b>	<b>9 (56.3)</b>	<b>13 (76.5)</b>	<b>46 (74.2)</b>
<b>Stage (n, %)</b>	<b>IIIB</b>	<b>2 (12.5)</b>	<b>0</b>	<b>0</b>
	<b>IV</b>	<b>14 (87.5)</b>	<b>17 (100.0)</b>	<b>62 (100.0)</b>
<b>Histology (n, %)</b>				
<b>Adenocarcinoma</b>		<b>16 (100.0)</b>	<b>15 (88.2)</b>	<b>54 (87.1)</b>
<b>Squamous cell ca</b>		<b>0</b>	<b>2 (11.8)</b>	<b>5 (8.1)</b>
<b>Large cell</b>		<b>0</b>	<b>0</b>	<b>2 (3.2)</b>
<b>Other</b>		<b>0</b>	<b>0</b>	<b>1 (1.6)</b>
<b># Prior Treatments</b>	<b>Mean</b>	<b>3</b>	<b>2</b>	<b>3</b>
	<b>Median</b>	<b>2</b>	<b>2</b>	<b>2</b>
	<b>(Range)</b>	<b>(1, 6)</b>	<b>(1, 4)</b>	<b>(1, 10)</b>

# Adverse Events Occurring in $\geq 10\%$ Patients



Drug-related SAEs, one patient each: asthenia, atrial fibrillation, cardiac arrest, diarrhea, lipase elevation, renal failure, vomiting

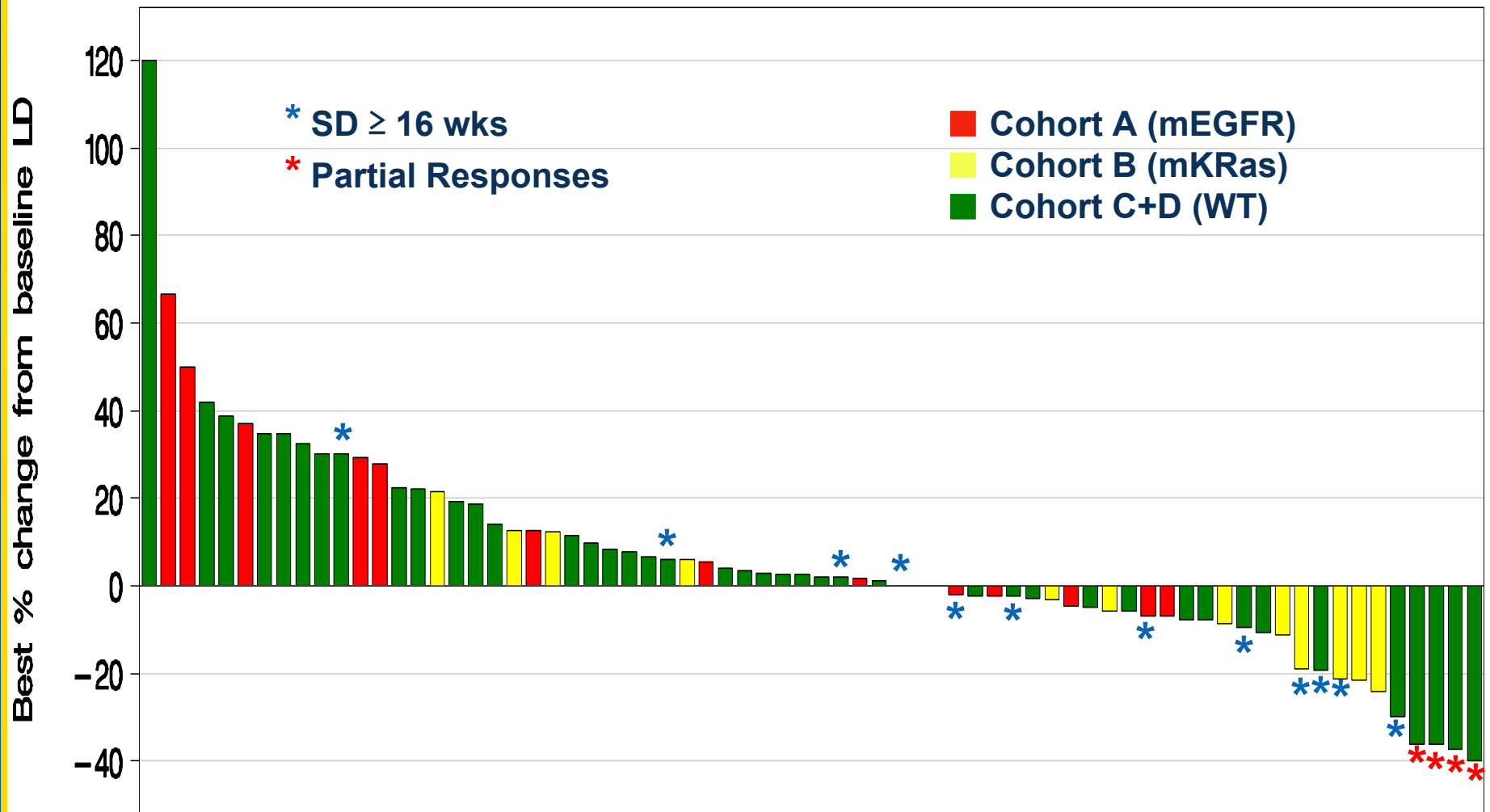
# Clinical Activity-Investigator Assessment (Evaluable Patients\*)

	Total n = 76 (%)
PFS at 16 wks, (95% CI)	24.1 (13.6, 36.1)
Objective response rate** CR + PR, (95% CI)	4 (5.3) (1.5, 12.9)
Disease control rate (CR+PR+SD ≥ 8 wks), (95% CI)	41 (54.0) (42.1, 65.5)
Disease control rate (CR+PR+SD ≥ 16 wks), (95% CI)	16 (21.1) (12.5, 31.9)

\* Received at least 1 cycle of Ganetespib and had at least 1 follow-up scan

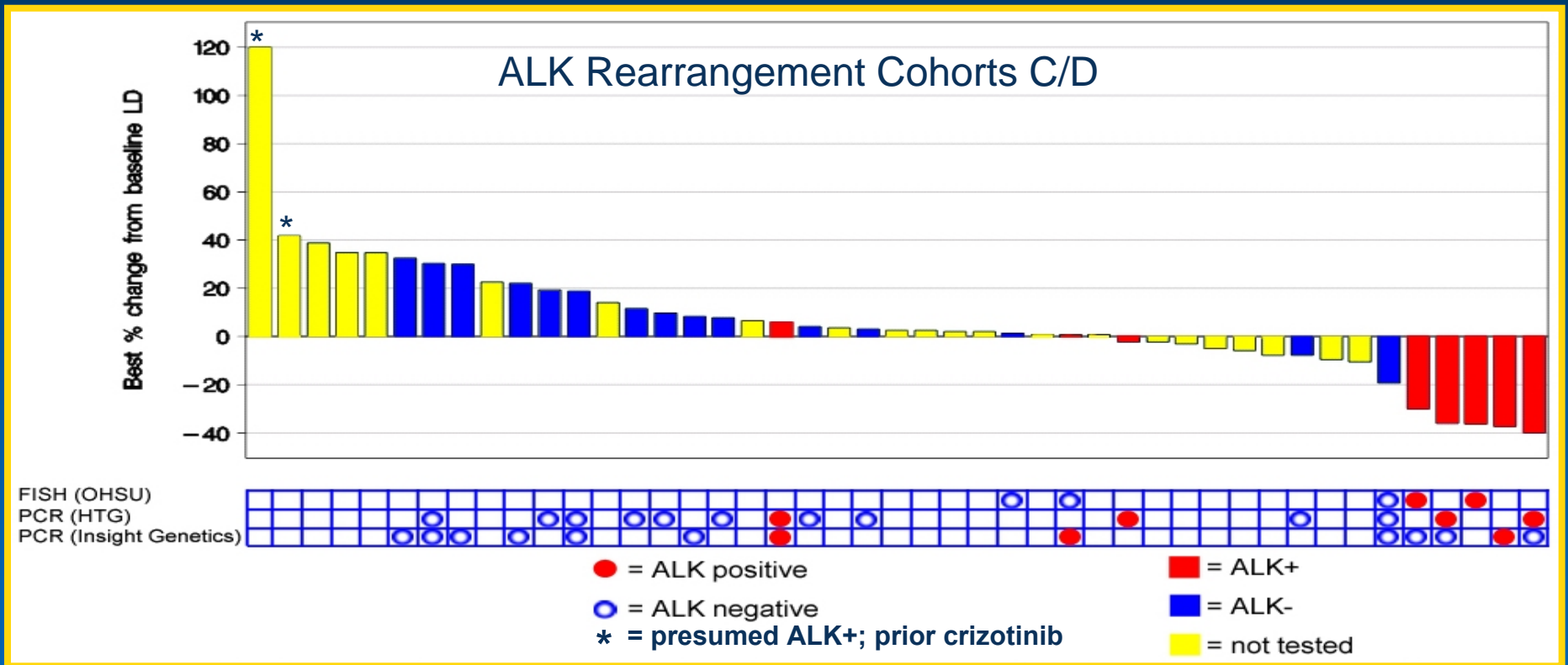
\*\* One PR yet to be confirmed

# Best Response in Target Lesions



# Genetic Profiling

- no mutations detected beyond EGFR and KRAS (Sequenom)
- 4 patients had EGFR polysomy



**For crizotinib-naïve patients:**

7 out of 8 (88%) patients with ALK-positive tumors had disease control lasting at least 16 weeks.

6 out of 8 (75%) patients with ALK-positive tumors had tumor shrinkage in target lesions.

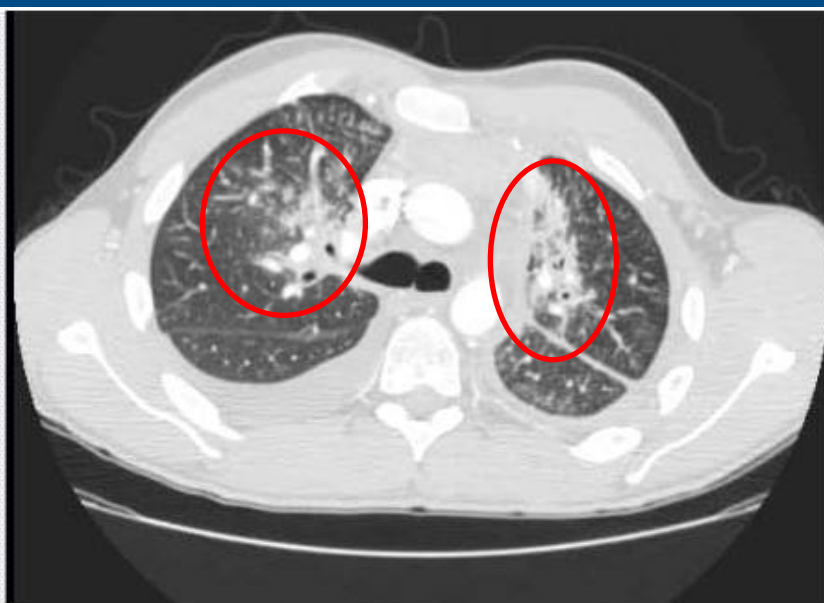
4 out of 8 (50%) patients with ALK-positive tumors had objective response.

# Ganetespiib activity in crizotinib refractory ALK positive NSCLC

- 24 y. old male with NSCLC, diagnosed Jan 2009
- pem/cis w pem maintenance until Feb 2010
- EML4-ALK positive
- crizotinib for ~ 1 year; re-biopsy shows resistance mutation



April 30, 2011



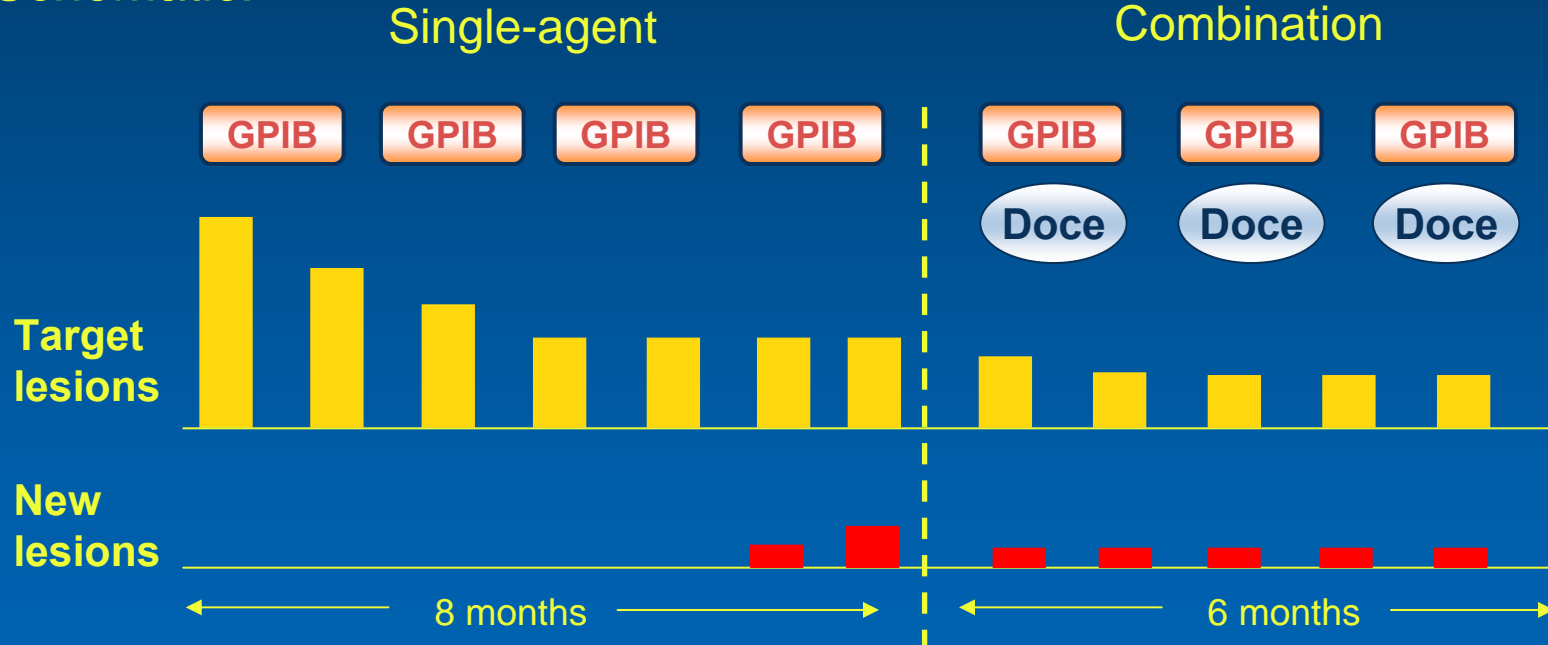
Start Ganetespiib May 9, 2011

May 31, 2011

# Improved disease control with combination ganetespib+docetaxel: case study

Patient 0059-6003, TL shrinkage 16% , rolled over to Cohort E upon PD

Schematic:



**PD at month 8:** mixed response – TL shrinkage; appearance of new lesions

Combination controls both TL and new lesions

# Conclusions

- **Ganetespib once weekly is well-tolerated in advanced pre-treated NSCLC patients**
  - **Most common AE: diarrhea; generally Grade 1 and 2, manageable with supportive care**
- **Ganetespib has shown promising clinical activity as single agent in NSCLC patients with actively progressing disease**
- **All patients with durable objective responses had tumors harboring ALK rearrangement**
  - **Sign of clinical activity in crizotinib refractory disease**
- **Further biomarker analysis is in progress to identify additional genetic profiles sensitive to ganetespib single agent treatment**
- **A phase 2b/3 trial of ganetespib and docetaxel in 2<sup>nd</sup> line advanced NSCLC patients has been initiated**

# Acknowledgments

## The Patients and their Families

### Investigators

- M. Socinski
- G. Shapiro
- M. Koczywas
- J. Goldman
- L. Horn
- E. Paschold
- H. West
- J. Brahmer
- R. Salgia
- C. Belani
- P. Bonomi
- L. Chen
- T. Webb
- H. Harper
- S. Ramalingam
- A. Sandler

### Molecular Labs

- OHSU
- Insight Genetics/Clariant R&D
- HTG
- Alexei Protopopov, DFCI

### Synta Pharmaceuticals

- Wei Guo
- Vojo Vukovic
- Iman El-Hariry

### Mouse Models

- Kwok-Kin Wong

### Preclinical

- Weiwen Ying
- David Proia
- Takeshi Shimamura