

# The discovery and development of **AUY922**

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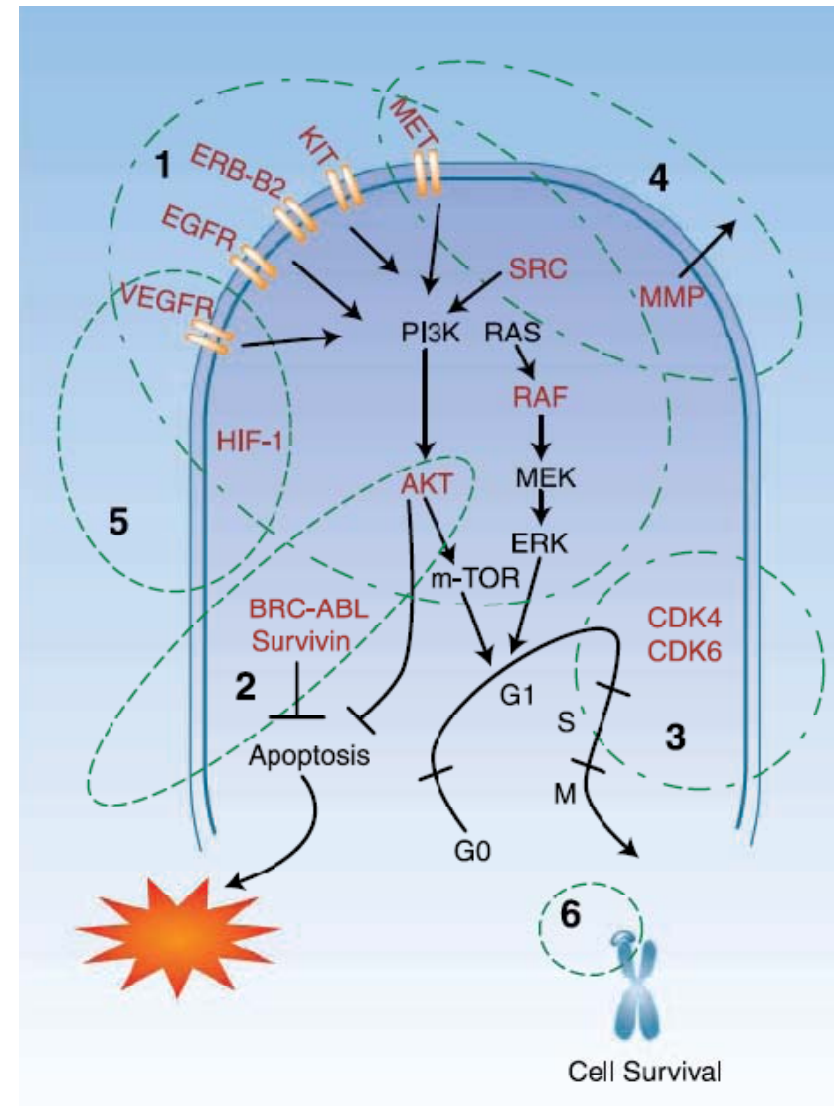
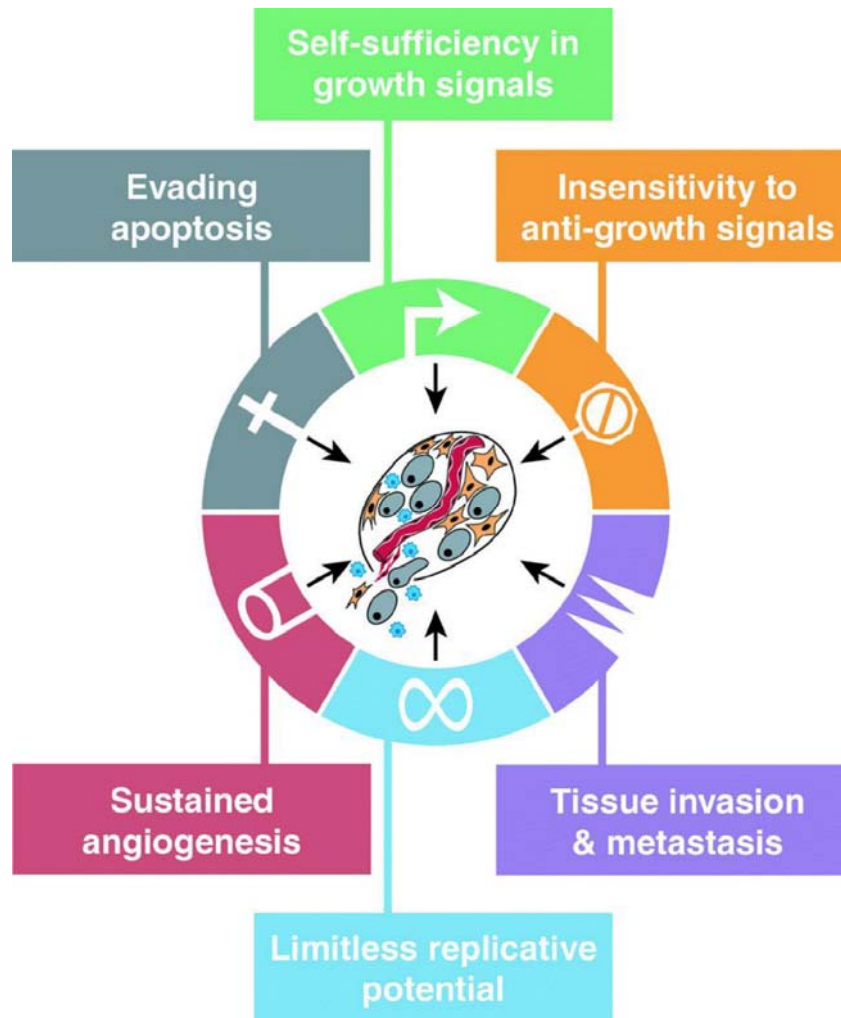
8th March 2011



# Disclosures

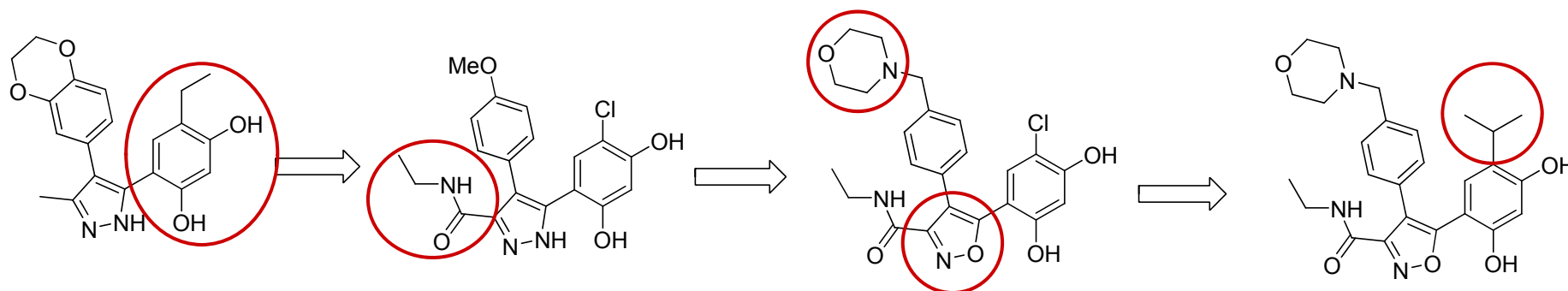
- I am an employee of The Institute of Cancer Research which along with Vernalis and Novartis was involved in the discovery and development of AUY922
- I have received research funding from Novartis
- I have been on an advisory board for Novartis

# Biology of HSP90



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# Multiparameter evolution of NVP-AUY922



Starting point

HTS hit

CCT018159

FP IC<sub>50</sub> = 280nM

GI<sub>50</sub> = 6000nM

5-amides

Potency breakthrough

VER-49009

FP IC<sub>50</sub> = 25nM

GI<sub>50</sub> = 260nM

Solubiliser, isoxazole

Cell potency

VER-51047

FP IC<sub>50</sub> = 21nM

GI<sub>50</sub> = 83nM

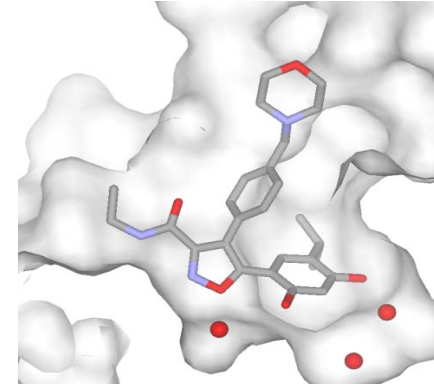
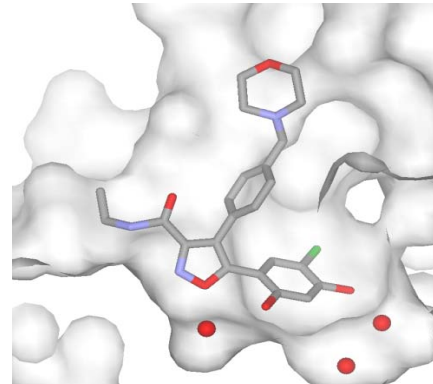
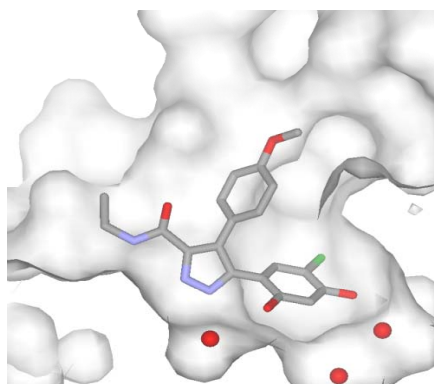
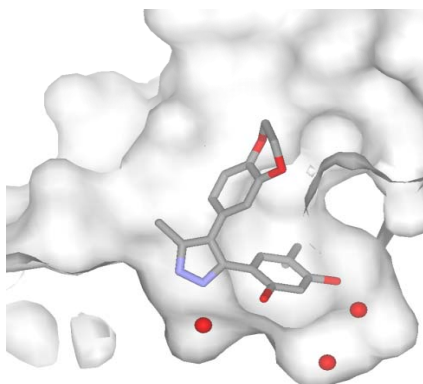
Development candidate

PK/PD, xenograft efficacy

NVP-AUY922/VER-52296

FP IC<sub>50</sub> = 9nM

GI<sub>50</sub> = 14nM



GI<sub>50</sub> in HCT116 colon cell line

Brough et al J Med Chem 51 196-218 2008

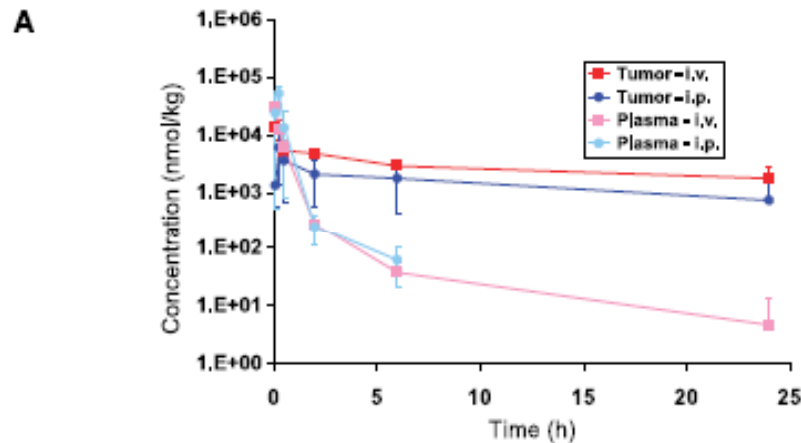
# Discovery of AUY922

## Research Article

### NVP-AUY922: A Novel Heat Shock Protein 90 Inhibitor Active against Xenograft Tumor Growth, Angiogenesis, and Metastasis

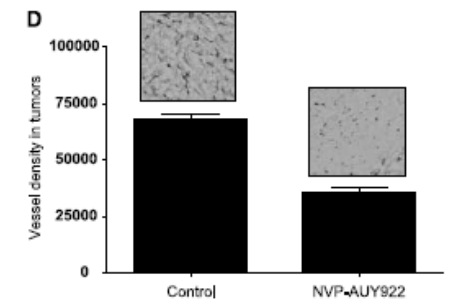
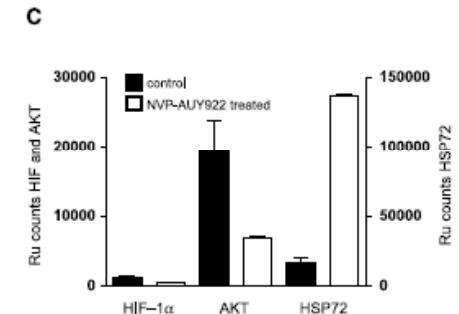
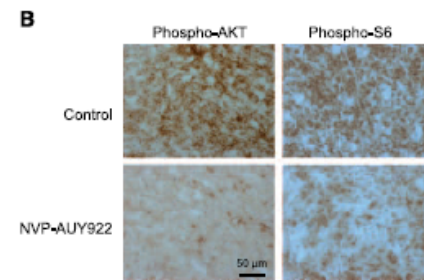
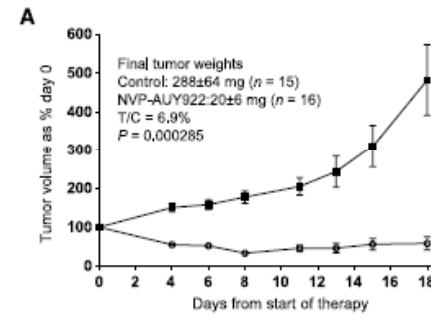
Suzanne A. Eccles,<sup>1</sup> Andy Massey,<sup>3</sup> Florence I. Raynaud,<sup>1</sup> Swee Y. Sharp,<sup>1</sup> Gary Box,<sup>1</sup> Melanie Valenti,<sup>1</sup> Lisa Patterson,<sup>1</sup> Alexis de Haven Brandon,<sup>1</sup> Sharon Gowan,<sup>1</sup> Frances Boxall,<sup>1</sup> Wynne Ahern,<sup>1</sup> Martin Rowlands,<sup>1</sup> Angela Hayes,<sup>1</sup> Vanessa Martins,<sup>1</sup> Frederique Urban,<sup>1</sup> Kathy Boxall,<sup>1</sup> Christostomos Prodromou,<sup>2</sup> Laurence Pearl,<sup>2</sup> Karen James,<sup>1</sup> Thomas P. Matthews,<sup>1</sup> Kwai-Ming Cheung,<sup>1</sup> Andrew Kalusa,<sup>1</sup> Keith Jones,<sup>1</sup> Edward McDonald,<sup>1</sup> Xavier Barril,<sup>3</sup> Paul A. Brough,<sup>3</sup> Julie E. Cansfield,<sup>3</sup> Brian Dymock,<sup>3</sup> Martin J. Drysdale,<sup>3</sup> Harry Finch,<sup>3</sup> Rob Howes,<sup>3</sup> Roderick E. Hubbard,<sup>3</sup> Alan Surgenor,<sup>3</sup> Paul Webb,<sup>3</sup> Mike Wood,<sup>3</sup> Lisa Wright,<sup>3</sup> and Paul Workman<sup>1</sup>

<sup>1</sup>Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research, Sutton, Surrey United Kingdom; <sup>2</sup>Section of Structural Biology, The Institute of Cancer Research, Chester Beatty Laboratories, London, United Kingdom; and <sup>3</sup>Vernalis Ltd., Cambridge, United Kingdom



**B**

|        | Route | Tmax (h) | Cmax (nmol/L) | AUClast (h*nmol/L) | HL_Lambda_z (h) | Vss_obs (L) | Cl_obs (L/h) | AUCINF_obs (h*nmol/L) | Vz_obs (L) |
|--------|-------|----------|---------------|--------------------|-----------------|-------------|--------------|-----------------------|------------|
| Plasma | i.v.  | -        | 48936         | 15009              | 4.243           | 0.090       | 0.143        | 15038                 | 0.875      |
|        | i.p.  | 0.25     | 52506         | 26254              | 0.655           | -           | 0.082        | 26311                 | 0.077      |
| Tumor  | i.v.  | 0.08     | 13907         | 70027              | 15.462          | -           | 0.020        | 109114                | 0.440      |
|        | i.p.  | 0.25     | 6078          | 36126              | 14.746          | -           | 0.041        | 51834                 | 0.883      |



- Causes xenograft growth inhibition
- Achieves levels in tumour > plasma
- Achieves modulation of Proof of Mechanism PD biomarkers

Cancer Research 2008, 68:2850-60

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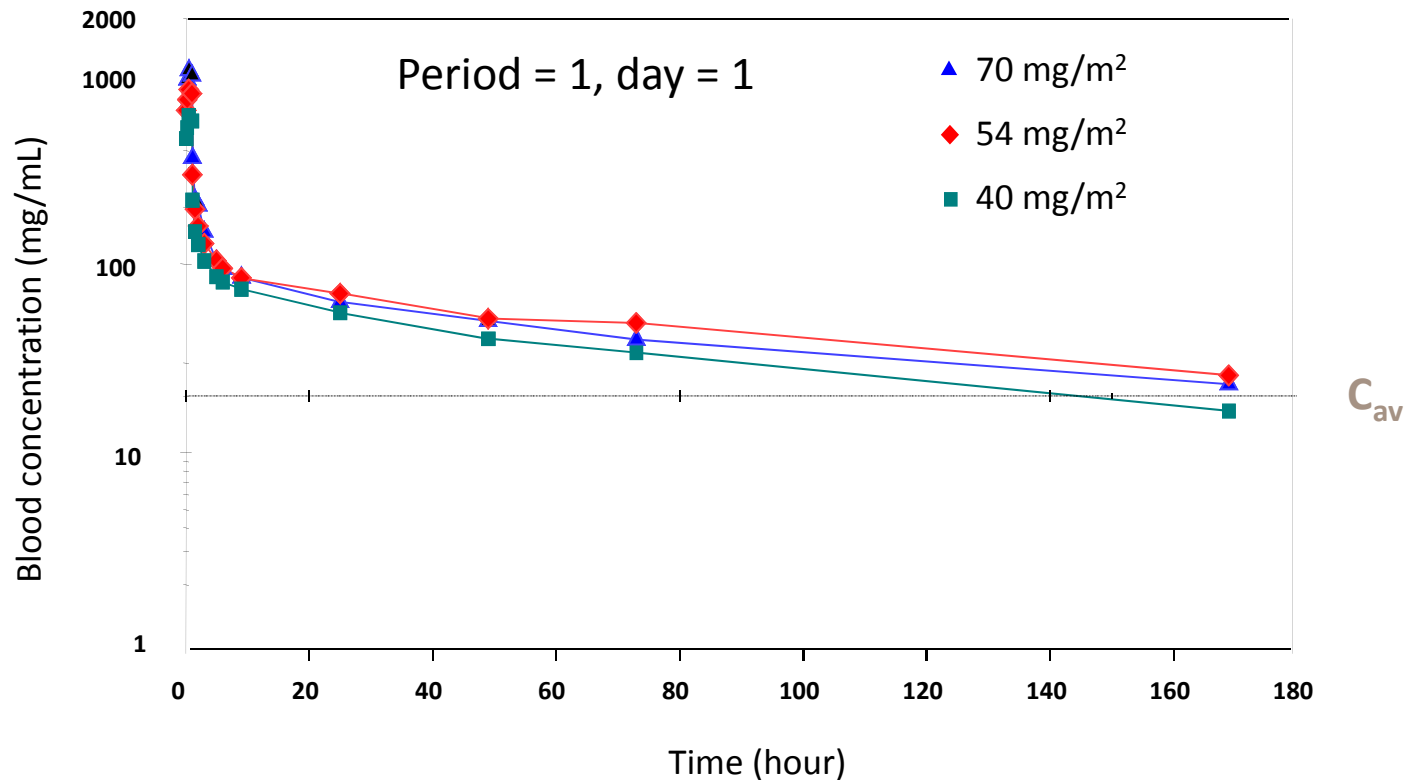
# Safety- DLTs in phase I study AUY922

| Drug-related AE<br>n (%) | Grades | Dose, mg/m <sup>2</sup> (n) |            |            |             |              |             |              |              |              | Total<br>(N=101) |
|--------------------------|--------|-----------------------------|------------|------------|-------------|--------------|-------------|--------------|--------------|--------------|------------------|
|                          |        | 2<br>(n=3)                  | 4<br>(n=4) | 8<br>(n=4) | 16<br>(n=7) | 22<br>(n=12) | 28<br>(n=8) | 40<br>(n=16) | 54<br>(n=19) | 70<br>(n=28) |                  |
| Diarrhoea                | All    | 1 (33)                      | 0          | 0          | 1 (14)      | 2 (17)       | 5 (63)      | 13 (81)      | 14 (74)      | 23 (82)      | 59 (58)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 2 (25)      | 1 (6)        | 1 (5)        | 1 (4)        | 5 (5)            |
| Nausea                   | All    | 0                           | 0          | 1 (25)     | 3 (43)      | 1 (8)        | 5 (63)      | 9 (56)       | 8 (42)       | 11 (39)      | 38 (38)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 0           | 0            | 0            | 0            | 0                |
| Fatigue                  | All    | 0                           | 0          | 2 (50)     | 3 (43)      | 2 (17)       | 4 (50)      | 5 (31)       | 7 (37)       | 8 (29)       | 31 (31)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 0           | 1 (6)        | 0            | 0            | 1 (1)            |
| Vomiting                 | All    | 1 (33)                      | 0          | 1 (25)     | 2 (29)      | 0            | 2 (25)      | 5 (31)       | 5 (26)       | 5 (18)       | 21 (21)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 1 (13)      | 0            | 0            | 1 (4)        | 2 (2)            |
| Asthenia                 | All    | 0                           | 0          | 1 (25)     | 0           | 1 (8)        | 2 (25)      | 3 (19)       | 3 (16)       | 2 (7)        | 12 (12)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 1 (13)      | 0            | 1 (5)        | 0            | 2 (2)            |
| Anorexia                 | All    | 0                           | 0          | 0          | 0           | 1 (8)        | 2 (25)      | 3 (19)       | 4 (21)       | 1 (4)        | 11 (11)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 1 (13)      | 1 (8)        | 0            | 0            | 2 (2)            |
| Anemia                   | All    | 0                           | 0          | 0          | 1 (14)      | 0            | 1 (13)      | 3 (19)       | 3 (16)       | 3 (11)       | 11 (11)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 0           | 0            | 0            | 0            | 0                |
| Visual symptoms          | All    | 0                           | 0          | 0          | 0           | 0            | 0           | 4 (25)       | 15 (79)      | 25 (89)      | 44 (44)          |
|                          | 3-4    | 0                           | 0          | 0          | 0           | 0            | 0           | 0            | 0            | 2 (7)        | 2 (2)            |

# Safety- DLTs in phase I study AUY922

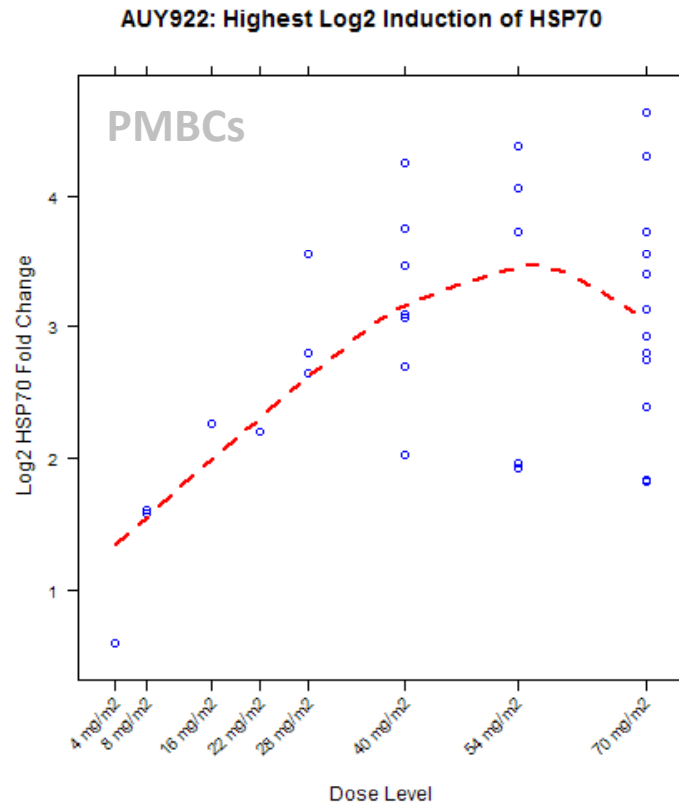
| Patients | Dose received<br>No. of infusions<br>(study day) | Original patient<br>diagnosis | Specific event                        |
|----------|--------------------------------------------------|-------------------------------|---------------------------------------|
| 1        | 22 mg/m <sup>2</sup><br>3 infusions (day 15)     | Liposarcoma                   | Atrial flutter/fibrillation (grade 3) |
| 2        | 40 mg/m <sup>2</sup><br>2 infusions (day 14)     | Colon cancer                  | Anorexia and fatigue (both grade 3)*  |
| 3        | 40 mg/m <sup>2</sup><br>1 infusion (day 2)       | Breast cancer                 | Diarrhea (grade 3)                    |
| 4        | 54 mg/m <sup>2</sup><br>3 infusions (day 16)     | Colon cancer                  | Asthenia (grade 3) <sup>†</sup>       |
| 5        | 54 mg/m <sup>2</sup><br>1 infusion (day 2)       | Ovarian cancer                | Diarrhea (grade 3)                    |
| 6        | 70 mg/m <sup>2</sup><br>3 infusions (day 16)     | Esophageal cancer             | Visual symptoms (grade 3)             |
| 7        | 70 mg/m <sup>2</sup><br>3 infusions (day 19)     | Esophageal cancer             | Visual symptoms (grade 3)             |
| 8        | 70 mg/m <sup>2</sup><br>3 infusions (day 16)     | Colon cancer                  | Diarrhea (grade 3)                    |

# Pharmacokinetics- AUY922



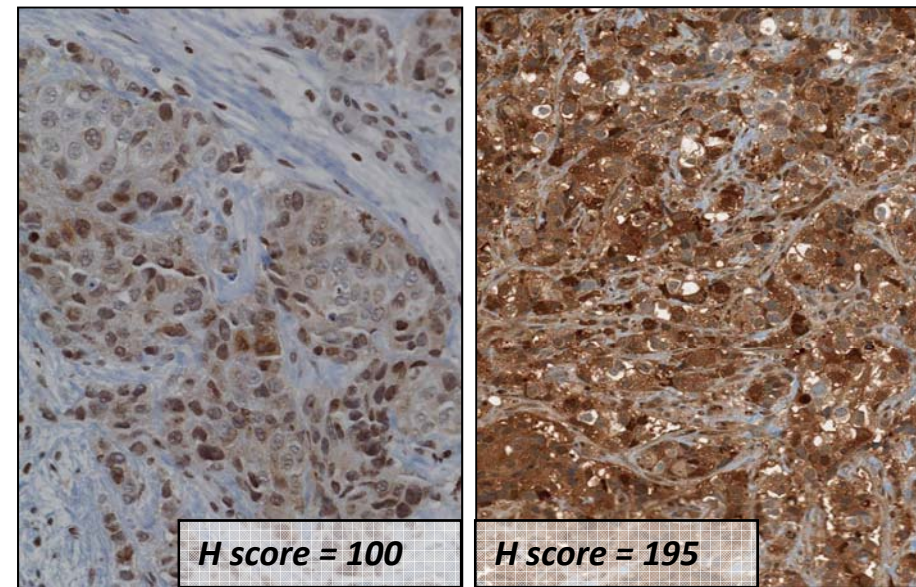
- Trough plasma concentration at 54 and 70 mg/m<sup>2</sup> greater than efficacious average concentration ( $C_{av}$ ) in mouse model
- Terminal half-life = 120 h at 70 mg/m<sup>2</sup>

# Pharmacodynamics- AUY922



In surrogate tissue PMBCs, HSP70 is induced in a dose-dependent manner from dose levels 4–40 mg/m<sup>2</sup>, followed by saturation

## AUY922 70mg/m<sup>2</sup> ER+ breast cancer



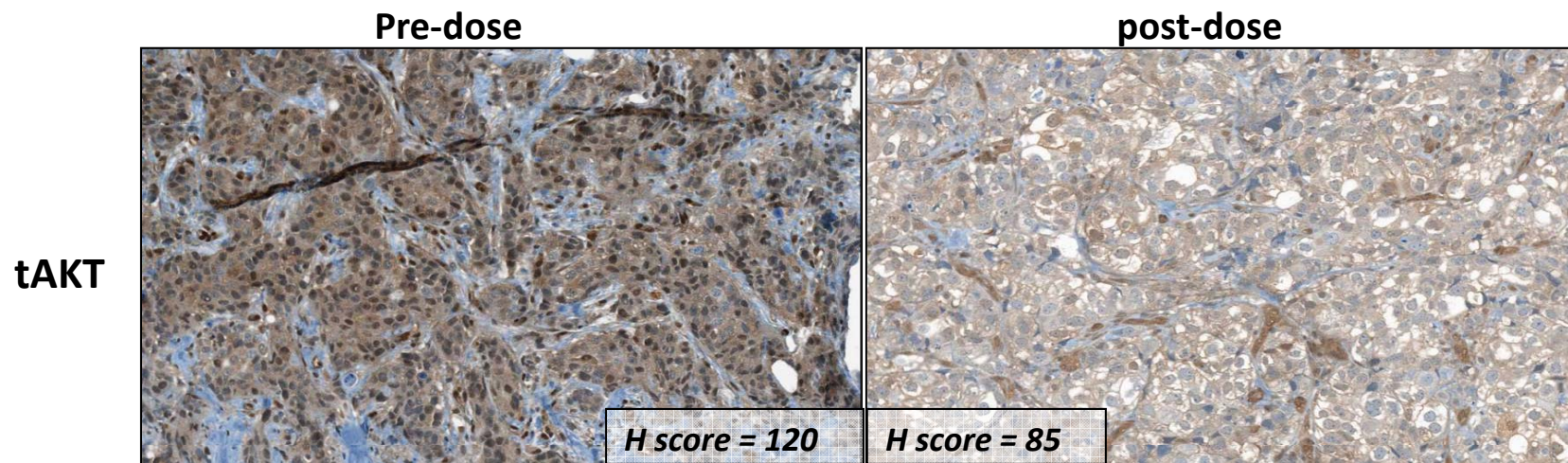
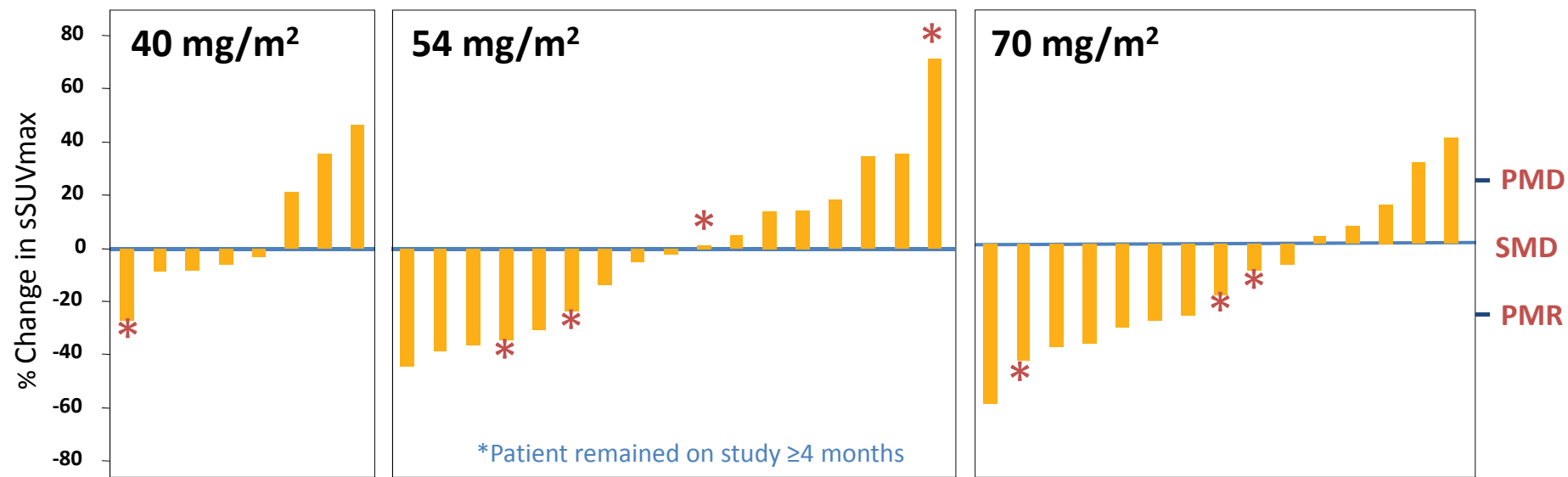
archival

post-dose

HSP70 is induced post-treatment in a tumor biopsy from an ER+ breast cancer patient

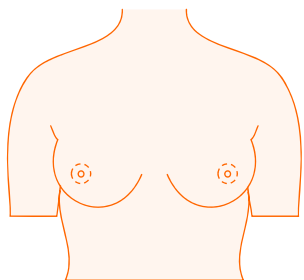
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# Pharmacodynamic Changes AUY922



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# AUY922 and Breast Cancer



Client proteins



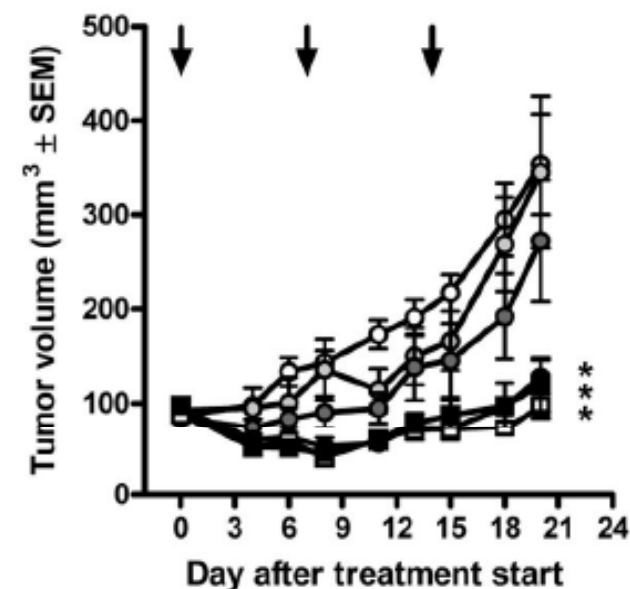
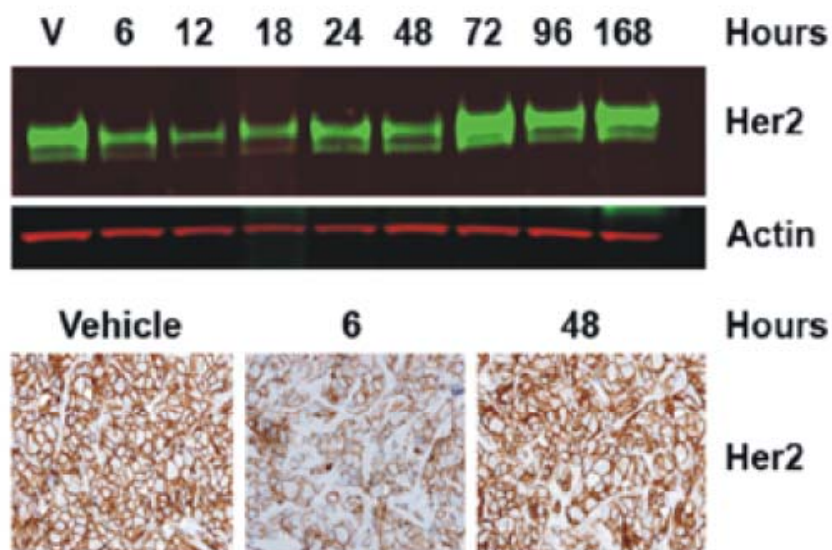
HER-2  
ER  
AKT

Research article

Open Access

## **NVP-AUY922: a small molecule HSP90 inhibitor with potent antitumor activity in preclinical breast cancer models**

Michael Rugaard Jensen<sup>1</sup>, Joseph Schoepfer<sup>1</sup>, Thomas Radimerski<sup>1</sup>, Andrew Massey<sup>2</sup>, Chantale T Guy<sup>3</sup>, Josef Brueggen<sup>1</sup>, Cornelia Quadt<sup>4</sup>, Alan Buckler<sup>3</sup>, Robert Cozens<sup>1</sup>, Martin J Drysdale<sup>2</sup>, Carlos Garcia-Echeverria<sup>1</sup> and Patrick Chène<sup>1</sup>

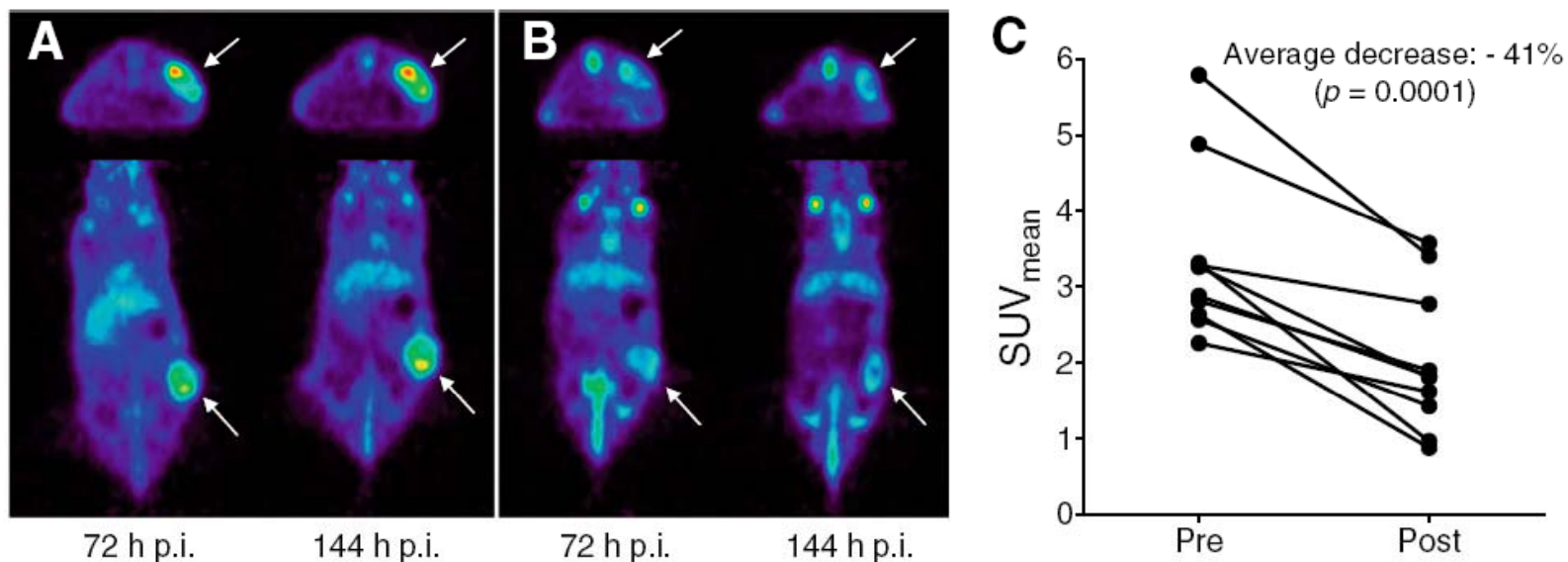


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# AUY922 and Breast Cancer

**$^{89}\text{Zr}$ -trastuzumab PET visualises HER2 downregulation by the HSP90 inhibitor NVP-AUY922 in a human tumour xenograft**

Thijs H. Oude Munnink <sup>a,g</sup>, Maarten A. de Korte <sup>a,g</sup>, Wouter B. Nagengast <sup>a</sup>,  
Hetty Timmer-Bosscha <sup>a</sup>, Carolina P. Schröder <sup>a</sup>, Johan R. de Jong <sup>b</sup>,  
Guus A.M.S. van Dongen <sup>c</sup>, Michael Rugaard Jensen <sup>d</sup>, Cornelia Quadt <sup>e</sup>,  
Marjolijn N. Lub-de Hooge <sup>b,f</sup>, Elisabeth G.E. de Vries <sup>a,\*</sup>

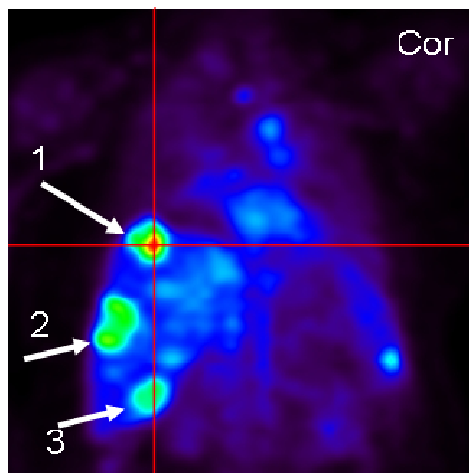
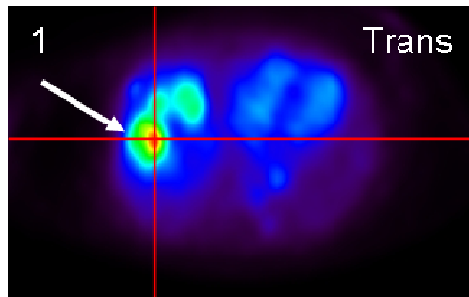


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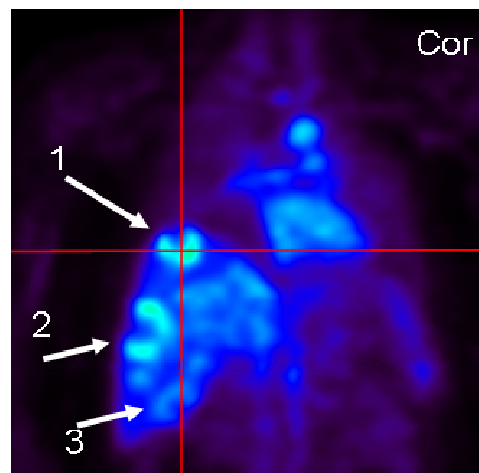
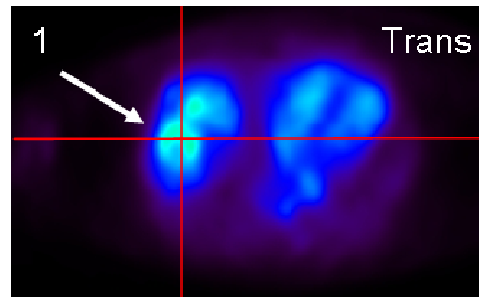
EJC 2010, 46:678-684

# AUY922 and Breast Cancer Zr89-Trastuzumab PER imaging

**Baseline HER2 PET**



**2nd HER2 PET**

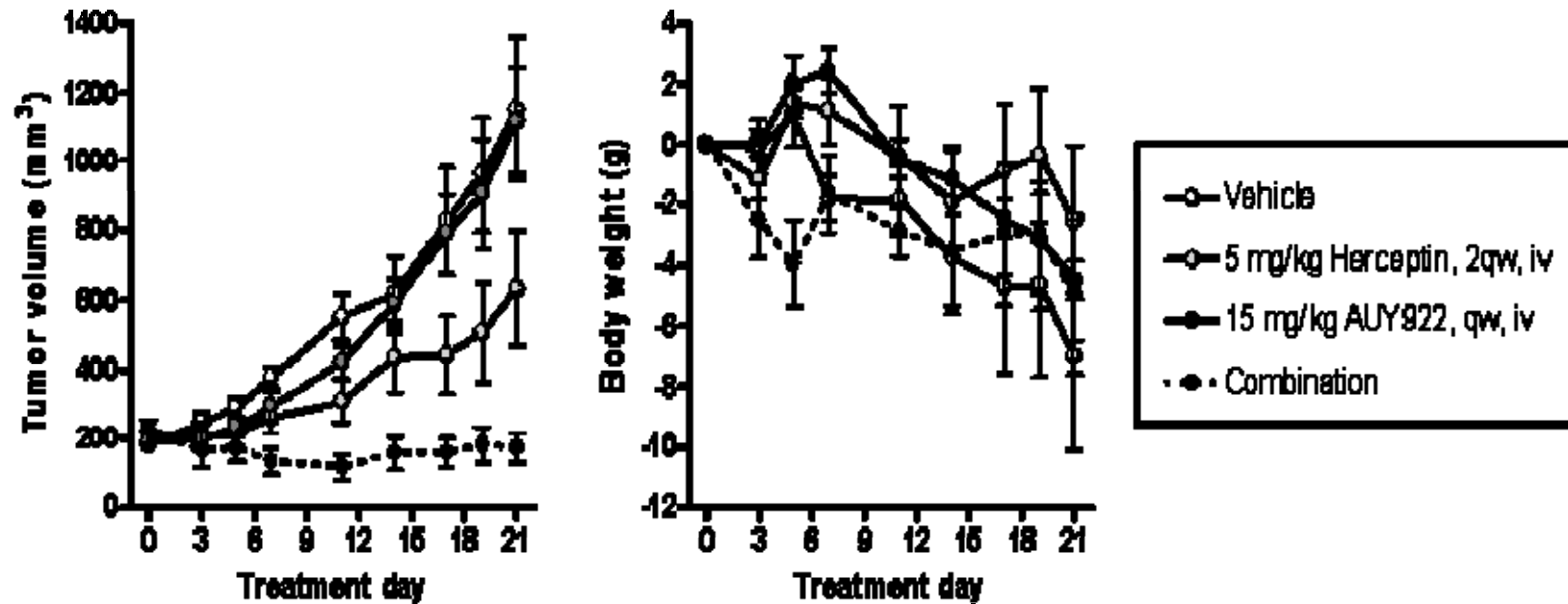


|              |          |
|--------------|----------|
|              | Lesion 1 |
| SUV pre      | 5.84     |
| SUV post     | 3.44     |
| $\Delta$ SUV | - 41%    |

Courtesy Dr Schroder and Prof DeVries

# AUY922 and Breast Cancer

BT-474 breast cancer xenografts (HER2+, ER+)



# AUY922 and Breast Cancer

Phase Ib/II study, AUY922 in combination with trastuzumab in 2nd- and 3rd-line HER2+ breast cancer



Phase Ib part: primary endpoint MTD and/or RPTD  
: Secondary Endpoint PK/PD

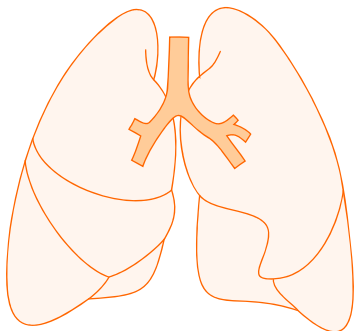
Phase II part : primary endpoint ORR  
:Secondary endpoints: OS; PFS; safety

# AUY922 and Lung Cancer

Research Article

## Epidermal Growth Factor Receptors Harboring Kinase Domain Mutations Associate with the Heat Shock Protein 90 Chaperone and Are Destabilized following Exposure to Geldanamycins

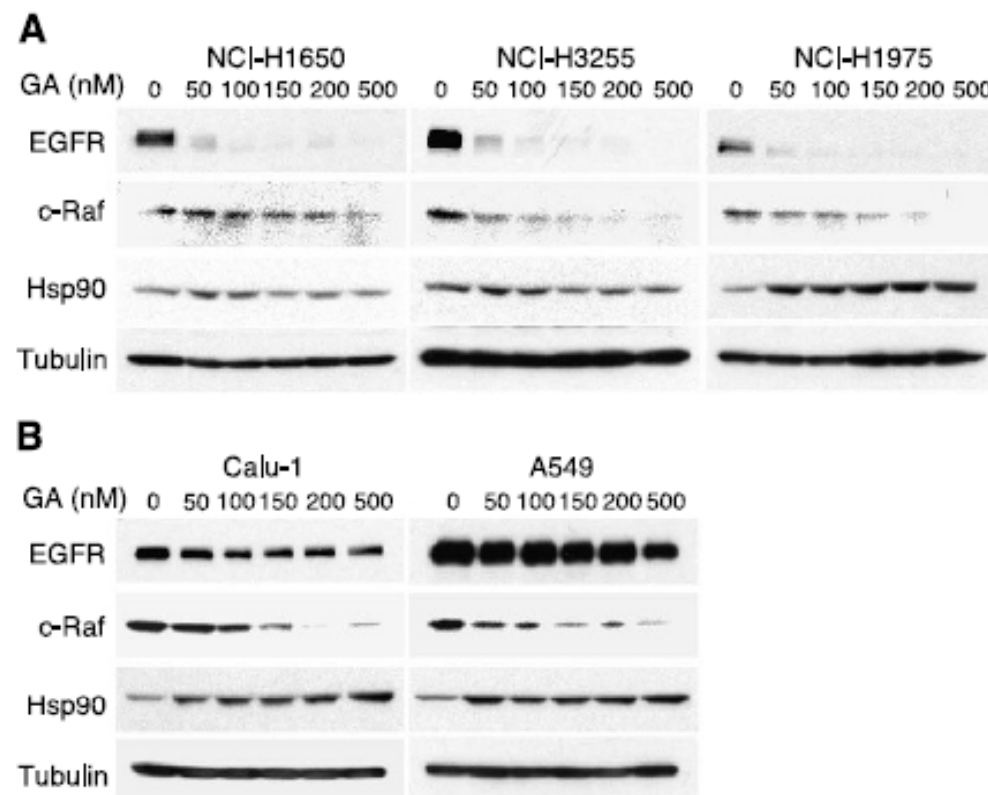
Takeshi Shimamura,<sup>1,3</sup> April M. Lowell,<sup>1</sup> Jeffrey A. Engelman,<sup>1,2,3</sup> and Geoffrey I. Shapiro<sup>1,3</sup>



Client proteins



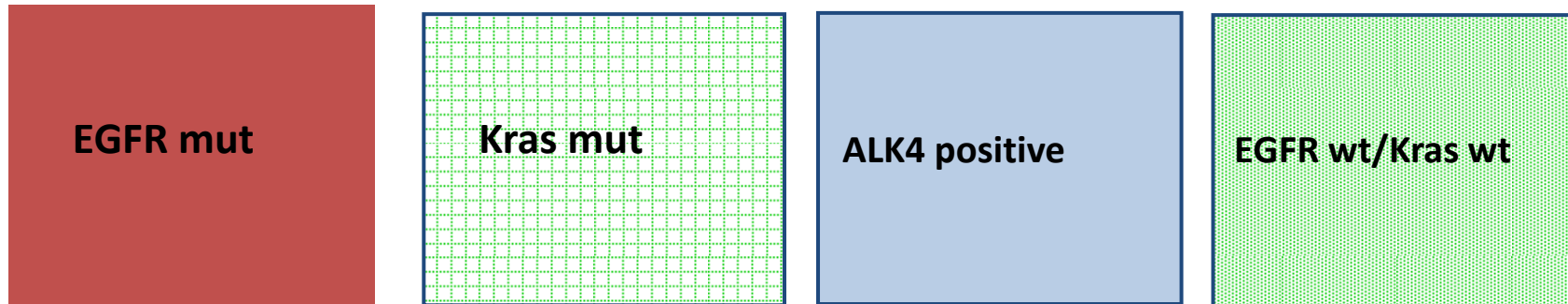
Mutant EGFR  
AKT  
CRAF  
?ALK



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Cancer Res 2005,65:6401-8

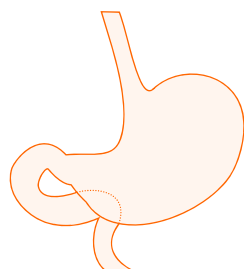
# AUY922 and Lung Cancer



- Primary Objective:
  - To estimate efficacy for each study strata at 18 weeks as assessed by RECIST
- Key Secondary Objectives:
  - Overall survival (OS); Progression free survival (PFS); Safety and tolerability of AUY922 in NSCLC patients
- All patients receive AUY922: 70 mg/m<sup>2</sup> as i.v. infusion, once per week

# AUY922 and Gastric Cancer

The Prognostic Significance of Amplification and Overexpression of *c-met* and *c-erb B-2* in Human Gastric Carcinomas



Client protein



**HER-2  
c-MET**

PD after 1st-line treatment for metastatic/recurrent gastric cancer. Approximately 120 patients

**AUY922 70 mg/m<sup>2</sup>  
i.v. infusion, once per week**

**Docetaxel 75 mg/m<sup>2</sup>, i.v., once every 3 weeks  
OR  
Irinotecan 350 mg/m<sup>2</sup>, i.v., once every 3 weeks**

Multivariate Analysis of Predictive Prognostic Factors

| Prognostic factor                                      | P value           |                       |                                   |
|--------------------------------------------------------|-------------------|-----------------------|-----------------------------------|
|                                                        | <i>c-met</i> only | <i>c-erb B-2</i> only | <i>c-met</i> and <i>c-erb B-2</i> |
| Overexpression of <i>c-met</i>                         | 0.0006            | —                     | —                                 |
| Overexpression of <i>c-erb B-2</i>                     | —                 | 0.2400                | —                                 |
| Coexpression of both <i>c-met</i> and <i>c-erb B-2</i> | —                 | —                     | 0.0021                            |
| Depth of invasion                                      | 0.5124            | 0.6818                | 0.9076                            |
| Histologic type                                        | 0.7460            | 0.1875                | 0.1577                            |
| Stromal type                                           | 0.3450            | 0.4733                | 0.3176                            |
| Lymph node metastasis                                  | 0.0047            | 0.0038                | 0.0013                            |
| Lymphatic invasion                                     | 0.0871            | 0.2382                | 0.1886                            |
| Vascular invasion                                      | 0.8203            | 0.8060                | 0.3337                            |

Nakajima et al Cancer 1999,85:1894-902

# Conclusions

- AUY922 is a resorcinyl isoxazole second generation HSP90 inhibitor
- The recommended phase II dose is 70mg/m<sup>2</sup>/week IV
- It has shown manageable toxicity and has achieved plasma levels that have been shown to be efficacious in pre-clinical models
- It has shown proof of mechanism biomarker modulation in normal tissue and tumour
- Early clinical efficacy as a single agent demonstrated
- Phase I combination trials ongoing
- An exciting time for the HSP90 inhibitors as more results of trials of HSP90 inhibitors are announced

# Acknowledgements

