# A phase I trial of Herceptin and paclitaxel in combination with IL-12 for HER2-overexpressing malignancies

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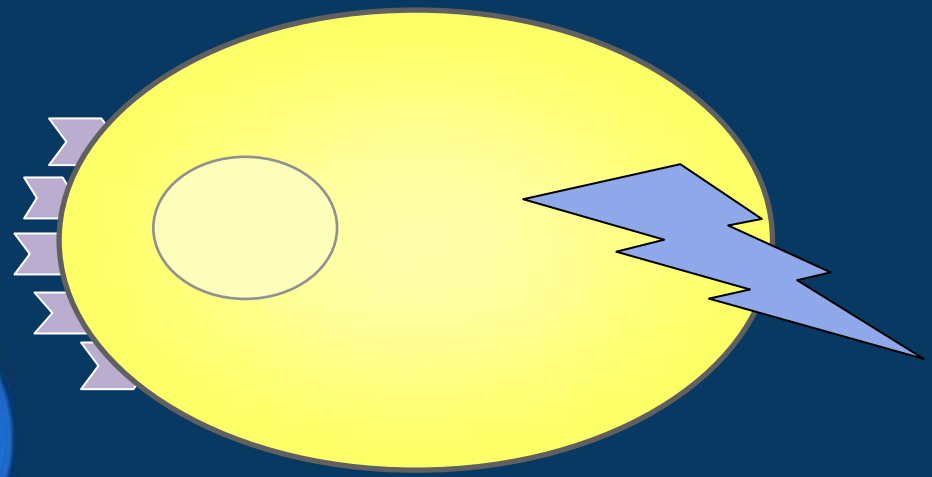
# NK cells are uniquely equipped for antibody-mediated effector functions



FcγRIIIa (CD16)

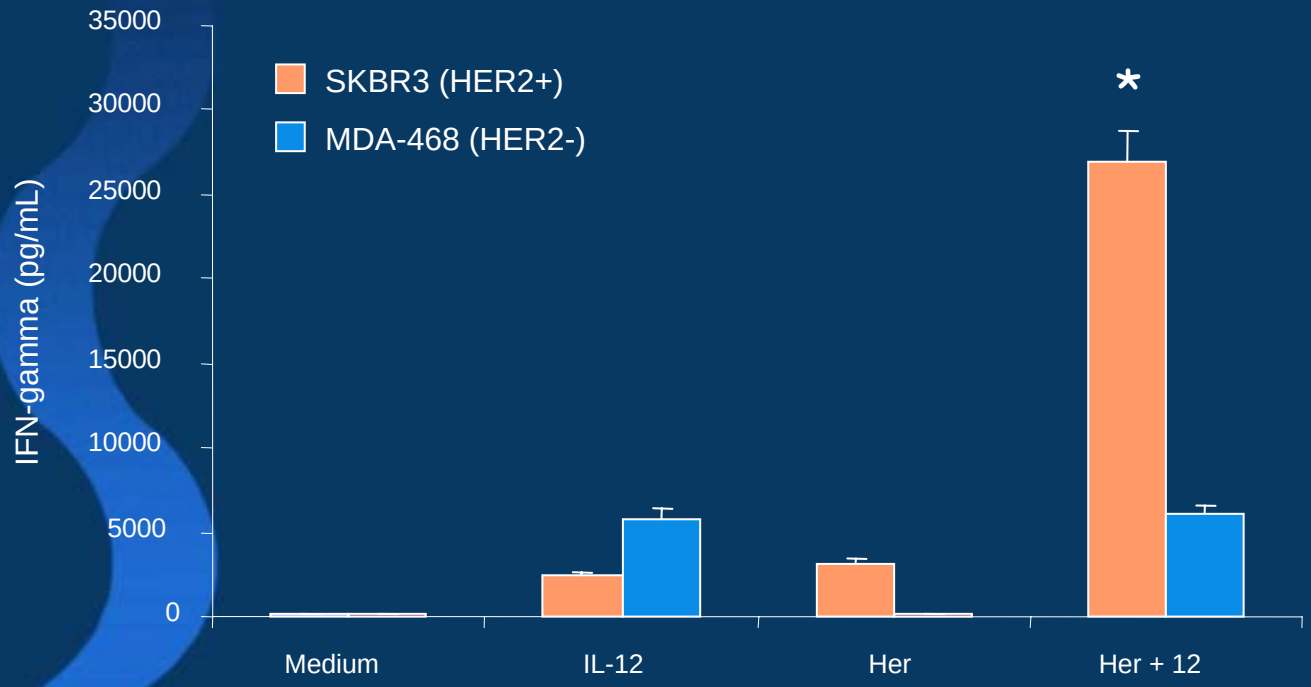
Cytokine Secretion

$CD56^+$ NK Cell

# Herceptin Therapy for Human Cancers

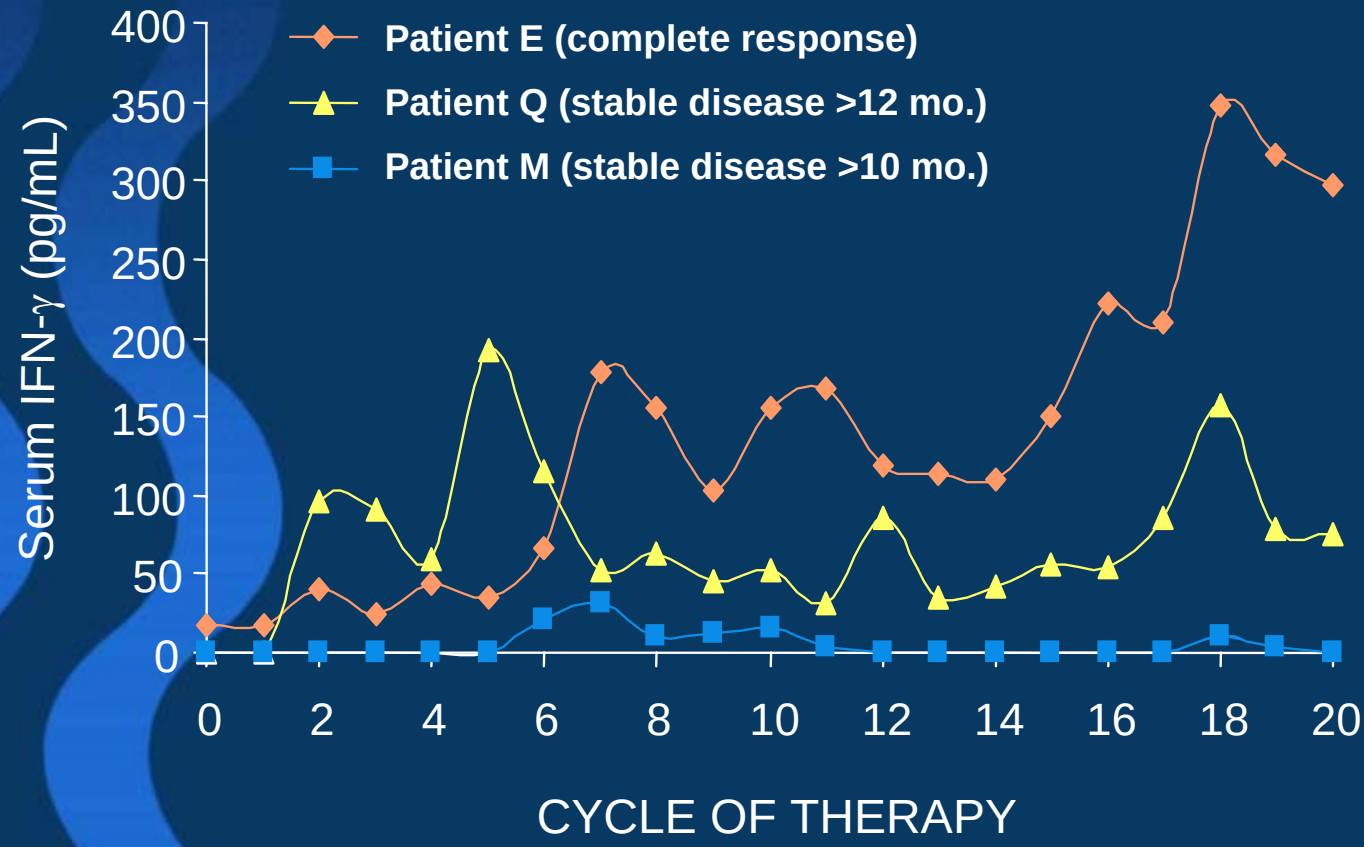
- HER2 is amplified in 30% of adenocarcinomas
- Herceptin – a humanized anti-HER2 mAb
- Herceptin stimulates immune responses from cells that express Fc receptors (inc. NK cells)

# NK cells secrete large quantities of IFN-γ in the presence of Herceptin-coated human breast cancer cells and IL-12




* $p < 0.005$ vs. all conditions shown

# Phase I Trial of Herceptin and IL-12: Serum IFN-γ was associated with clinical benefit



# Phase I Trial of Herceptin/Paclitaxel and IL-12:

## Hypothesis

The addition of IL-12 to the standard Herceptin/paclitaxel regimen would lead to cytokine production by host NK cells, providing an additional anti-tumor effect.

# Treatment Schema (Cycle 1)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Week 1: | | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Treatment | ▲,P | | | | | | |
| Week 2: | | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Treatment | △ | | | | | | |
| Week 3: | | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Treatment | △ | | | | | | |

▲ Herceptin (4 mg/kg i.v.)

△ Herceptin (2 mg/kg i.v.)

P Paclitaxel (175 mg/m$^2$ over 3 hrs.)

# Treatment Schema (Cycles 2+)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Week 1: | | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Treatment | ▲,P | ★ | | | ★ | | |
| Week 2: | | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Treatment | ▲ | ★ | | | ★ | | |
| Week 3: | | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Treatment | ▲ | ★ | | | ★ | | |

▲ Herceptin (2 mg/kg i.v.)

★ IL-12 (100, 200, or 300 ng/kg i.v.)

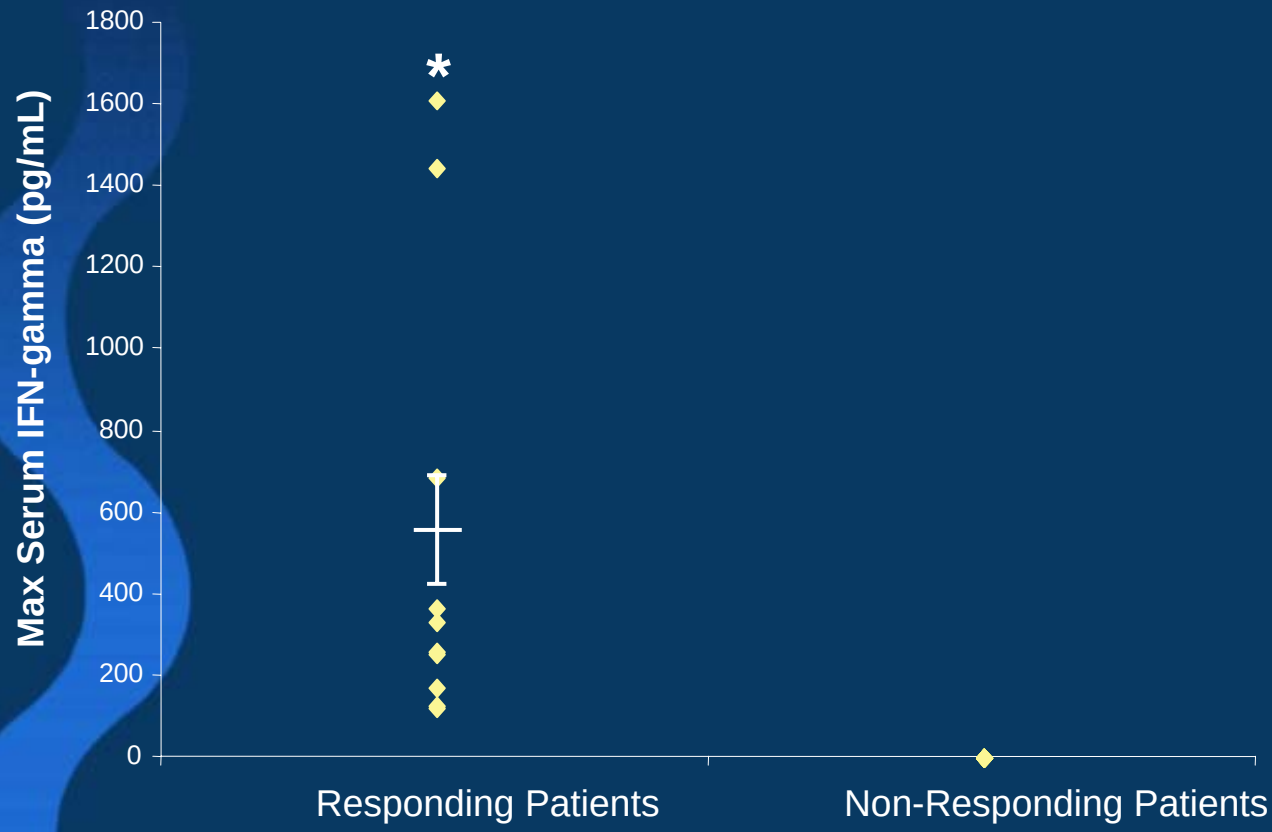
P Paclitaxel (175 mg/m$^2$ over 3 hrs.)

# Patient Profiles for NCI No. 84

| Patient | Tumor Type | IL-12 Dose (ng/kg) | Clinical Outcome | No. Cycles Received |
|---|---|---|---|---|
| A | Breast | 100 | SD | 18 |
| B | Breast | 100 | PR | 15 |
| C | Breast | 100 | PR | 6 |
| D | Colon | 300 | SD | 4 |
| E | Breast | 300 | - | < 2 |
| F | Colon | 300 | PD | 3 |
| G | Breast | 300 | PR | 3 |
| H | Breast | 300 | SD | 6 |
| I | Esoph. | 300 | PR | 6 |
| J | Colon | 200 | PD | 3 |
| K | Colon | 200 | - | < 2 |
| L | Colon | 200 | PD | 3 |
| M | Gastric | 200 | SD | 18 |
| N | Thyroid | 200 | PD | 2 |
| O | Pancr. | 200 | PD | 3 |
| P | Breast | 200 | PD | 2 |
| Q | Gastric | 200 | SD | 10 |
| R | Esoph. | 200 | PD | 3 |
| S | Esoph. | 200 | PD | 3 |
| T | Esoph. | 200 | PR | 5 |
| U | Colon | 200 | PD | 3 |

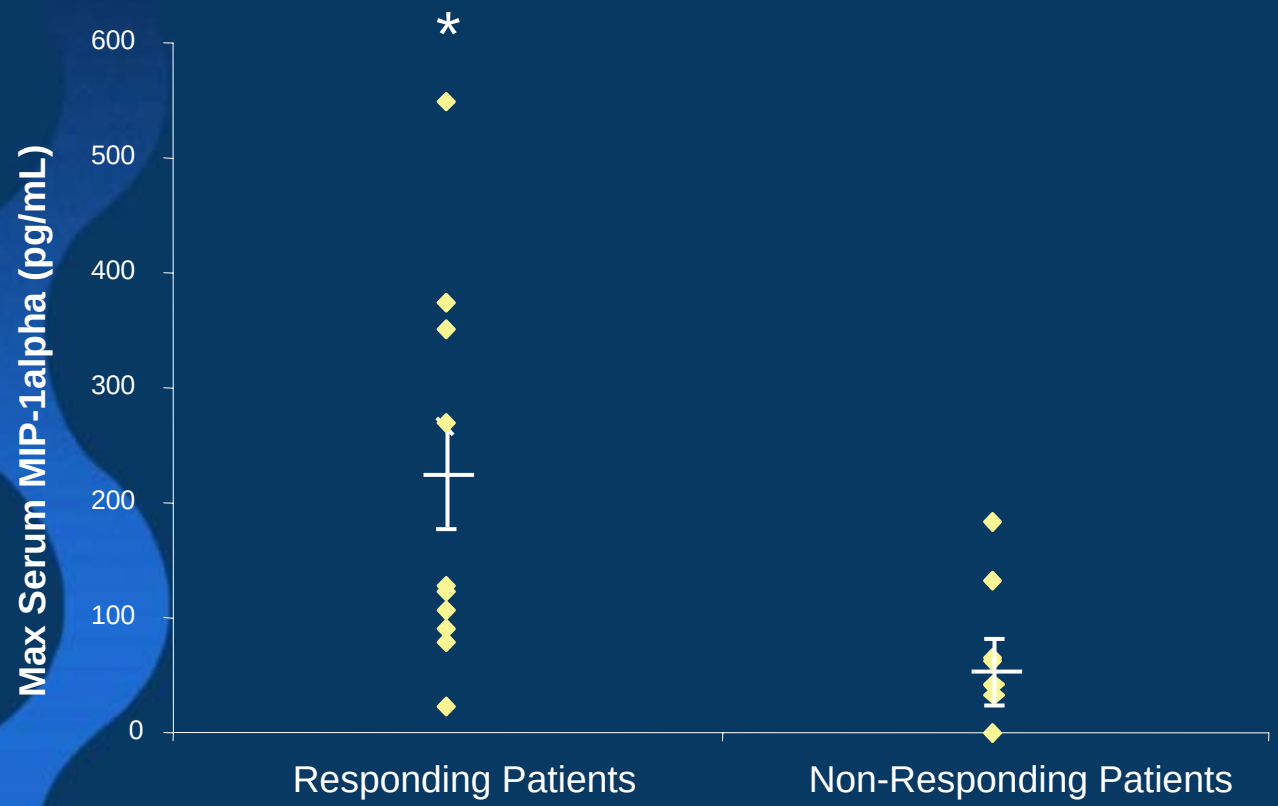
PD, progressive disease; PR, partial response; SD, stable disease

# Serum IFN-γ Correlates with Clinical Outcome




* $p < 0.001$

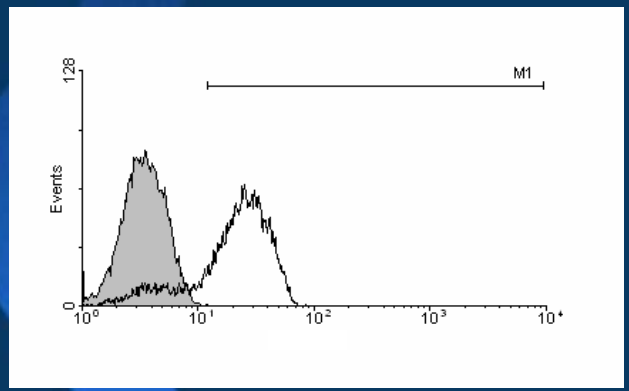
# Serum MIP-1α Correlates with Clinical Outcome




* $p < 0.05$

# IFN-γ Production By Patient NK Cells

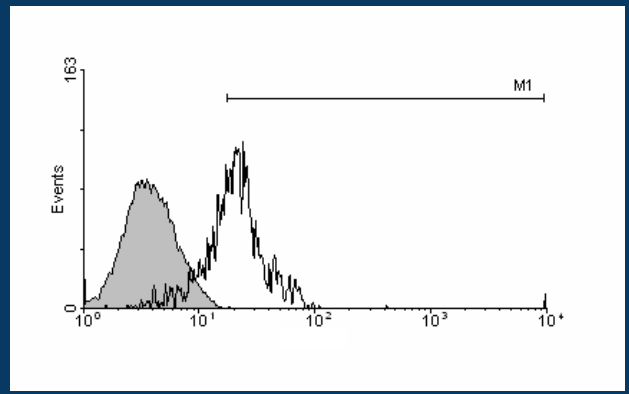
## Patient I




**IFN-γ-FITC**

% Pos: 73.8%
MFI: 28.4

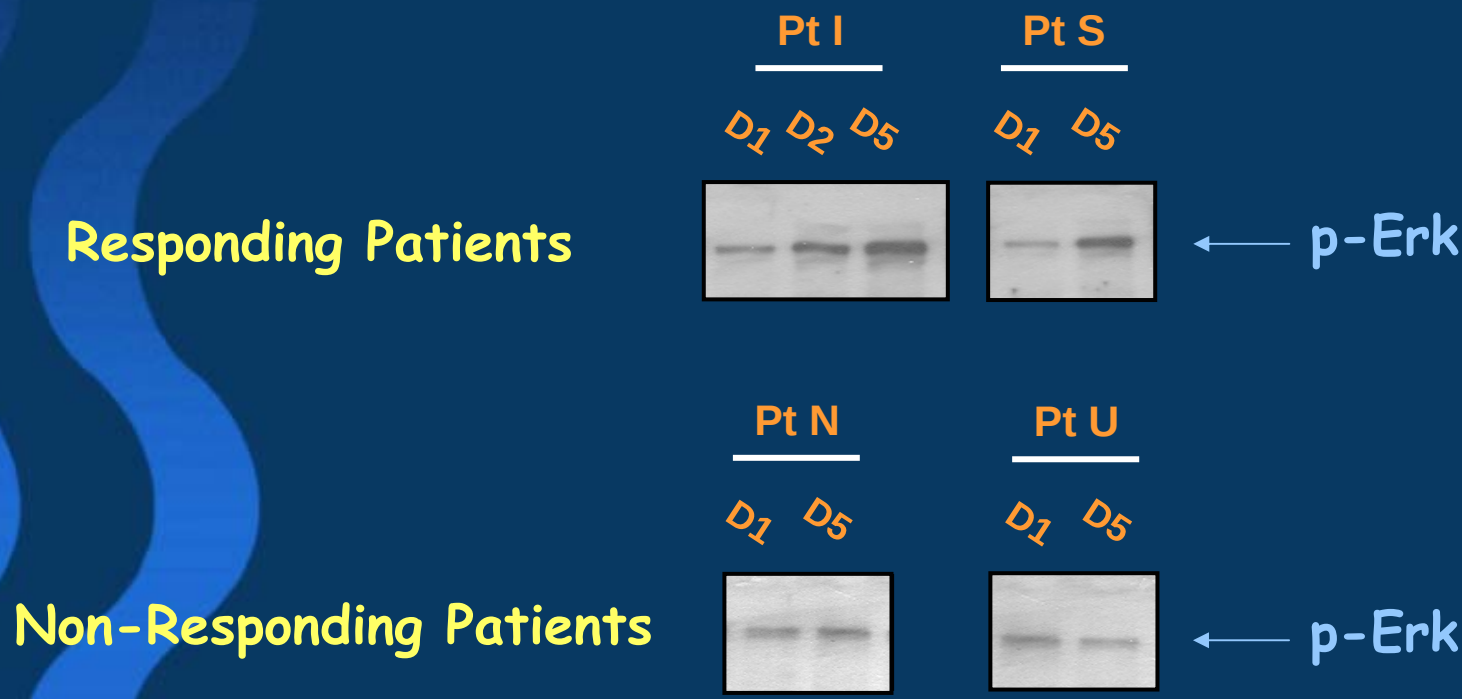
## Patient M




**IFN-γ-FITC**

% Pos: 53.3%
MFI: 32.8

# Activation of the transcription factor Erk in patient PBMCs



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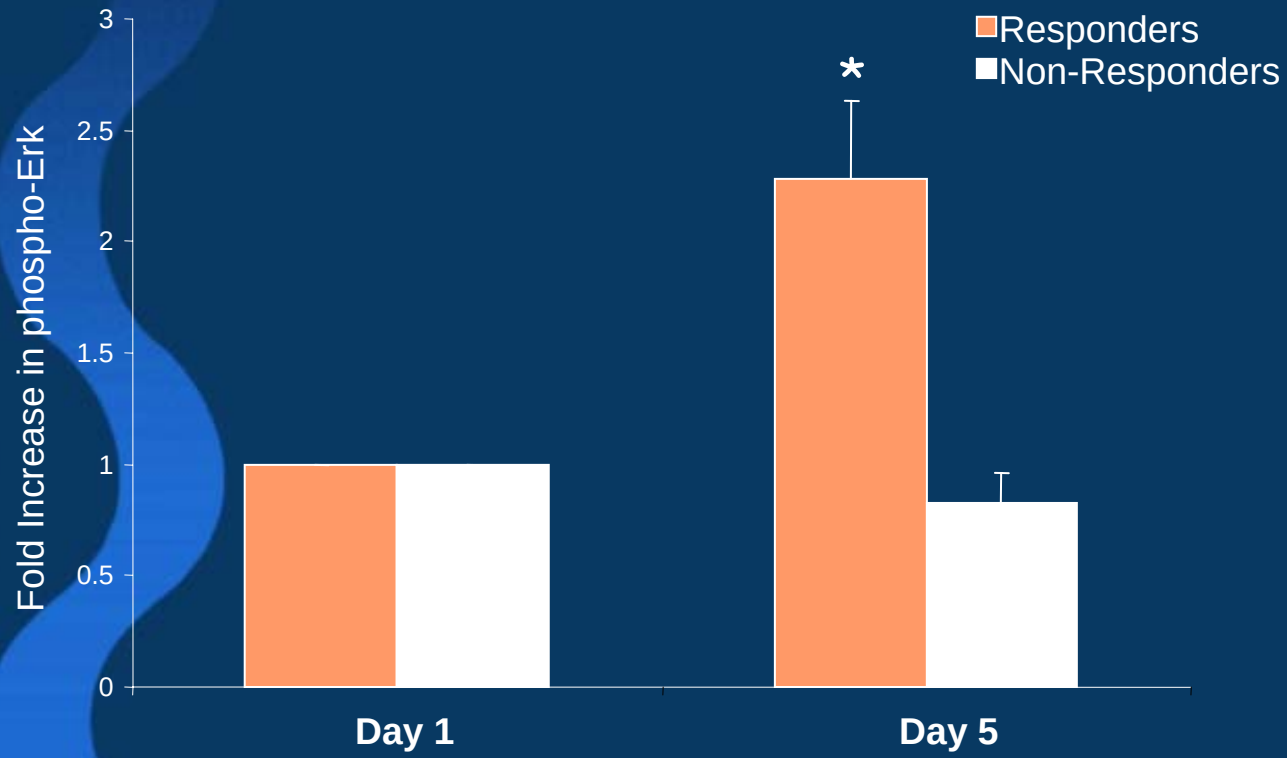


* p < 0.006 vs. all conditions shown

# Summary

- IL-12 can be safely administered in combination with Herceptin and paclitaxel
- There were 5 patients with partial responses and 5 with stabilized disease out of 19 evaluable patients
- Activity was observed in patients with upper GI as well as breast primary tumors

# Summary

- Serum levels of IFN-$\gamma$ and MIP-1$\alpha$ were elevated specifically in those patients that exhibited a clinical benefit
- NK cells were determined to be the cellular source of the IFN- $\gamma$
- Enhanced levels of phosphorylated Erk were observed within PBMCs of clinical benefit patients

# Conclusions

Addition of IL-12

to the paclitaxel/Herceptin regimen

may lead to enhanced efficacy

through the induction of anti-tumor immunity.

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