

***PERSONALIZED / PRECISION  
MEDICINE IN ONCOLOGY***

***Development of Biomarkers and Targeted  
Therapies***

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UCSF**

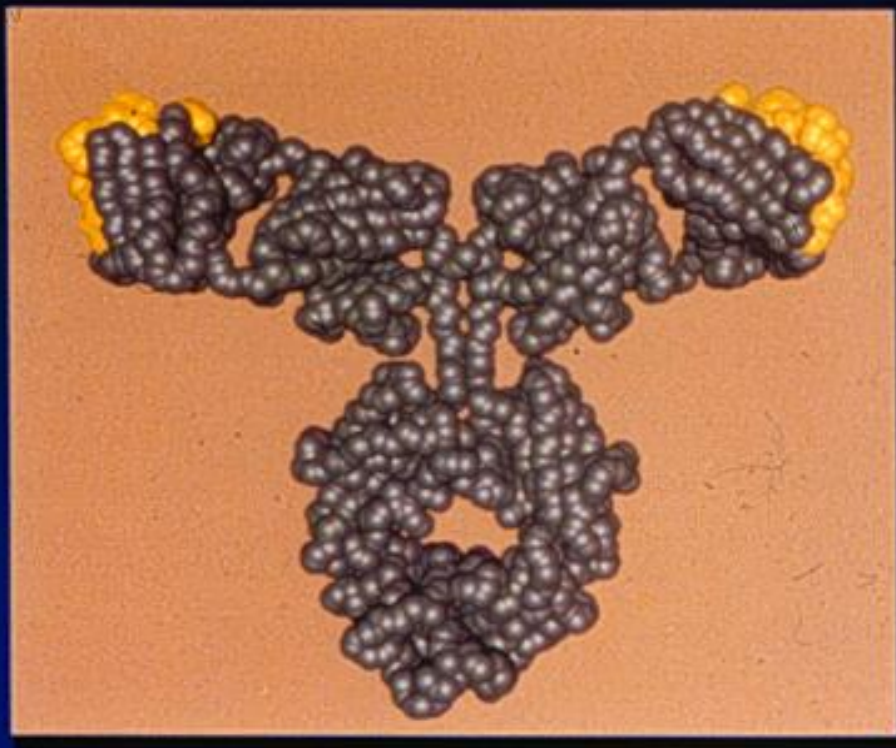
# DISCLOSURES

- Univ California: Patents
- Genentech: Speakers Bureau
- Pfizer: Speakers Bureau
- Merrimack Pharma: Equity

# Personalized / Precision Medicine *Themes*

- *Diagnosis -> Biomarker defined*
- *Therapy -> Targeted*
- *Impact -> Translational*

# Herceptin: Humanized Anti-HER2 Antibody

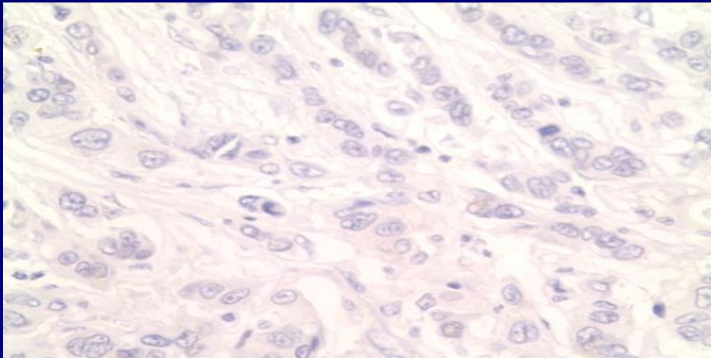


- ◆ Targets HER2 oncoprotein, which occurs in 25% to 30% of patients with breast cancer
- ◆ High affinity ( $K_d = 5\text{nM}$ ) and specificity
- ◆ 95% human, 5% murine
  - Decreased potential for immunogenicity
  - Increased potential for recruiting immune effector mechanisms

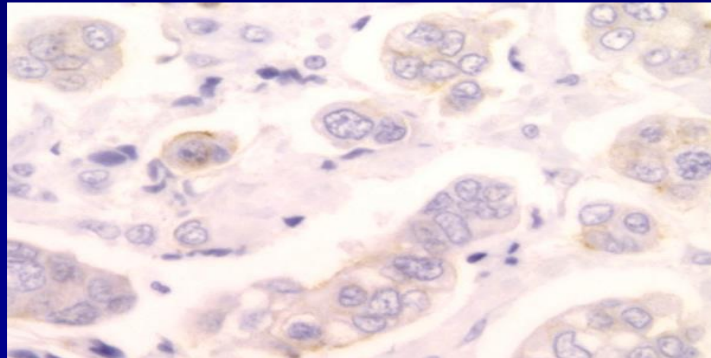
# HER2 Immunohistochemistry (IHC): (e.g. HercepTest<sup>®</sup>)

- Pre-analytical tissue processing
- Reagent variability
- Antigen retrieval
- Scoring

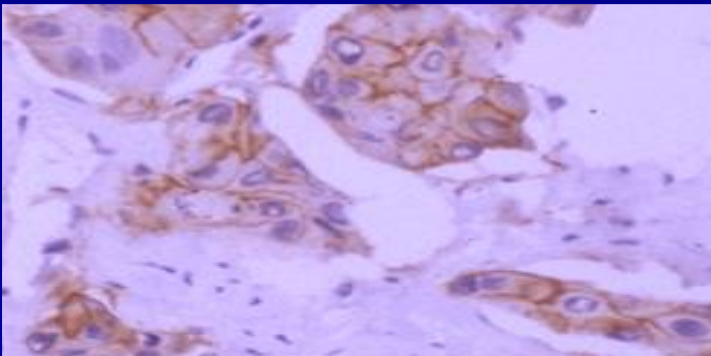
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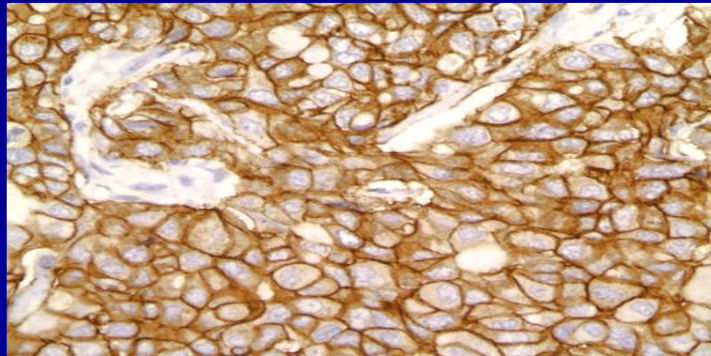
1+



2+

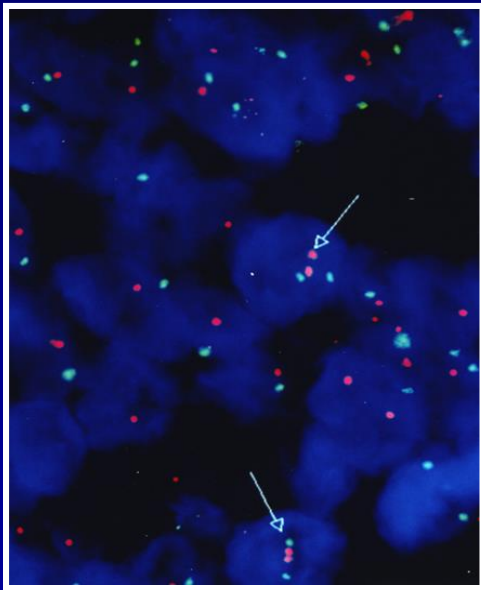


3+

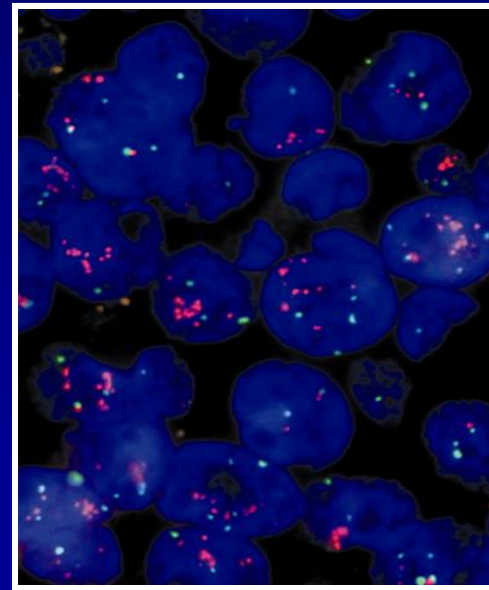


# Fluorescence In Situ Hybridization (FISH)

- Measures the level of HER2 gene amplification
- Normalization to chromosome 17 centromere

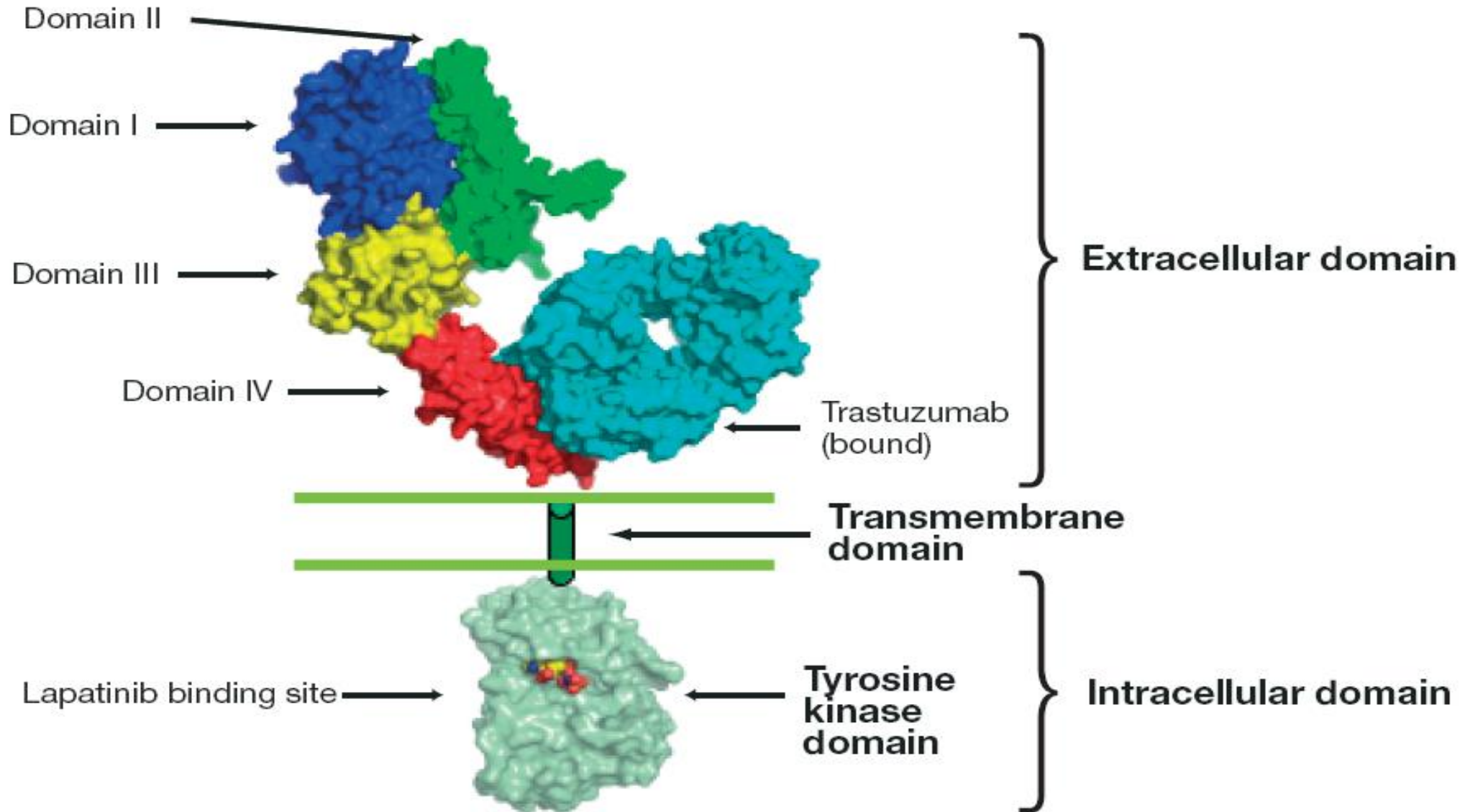


<2.0 not amplified  
(FISH-)

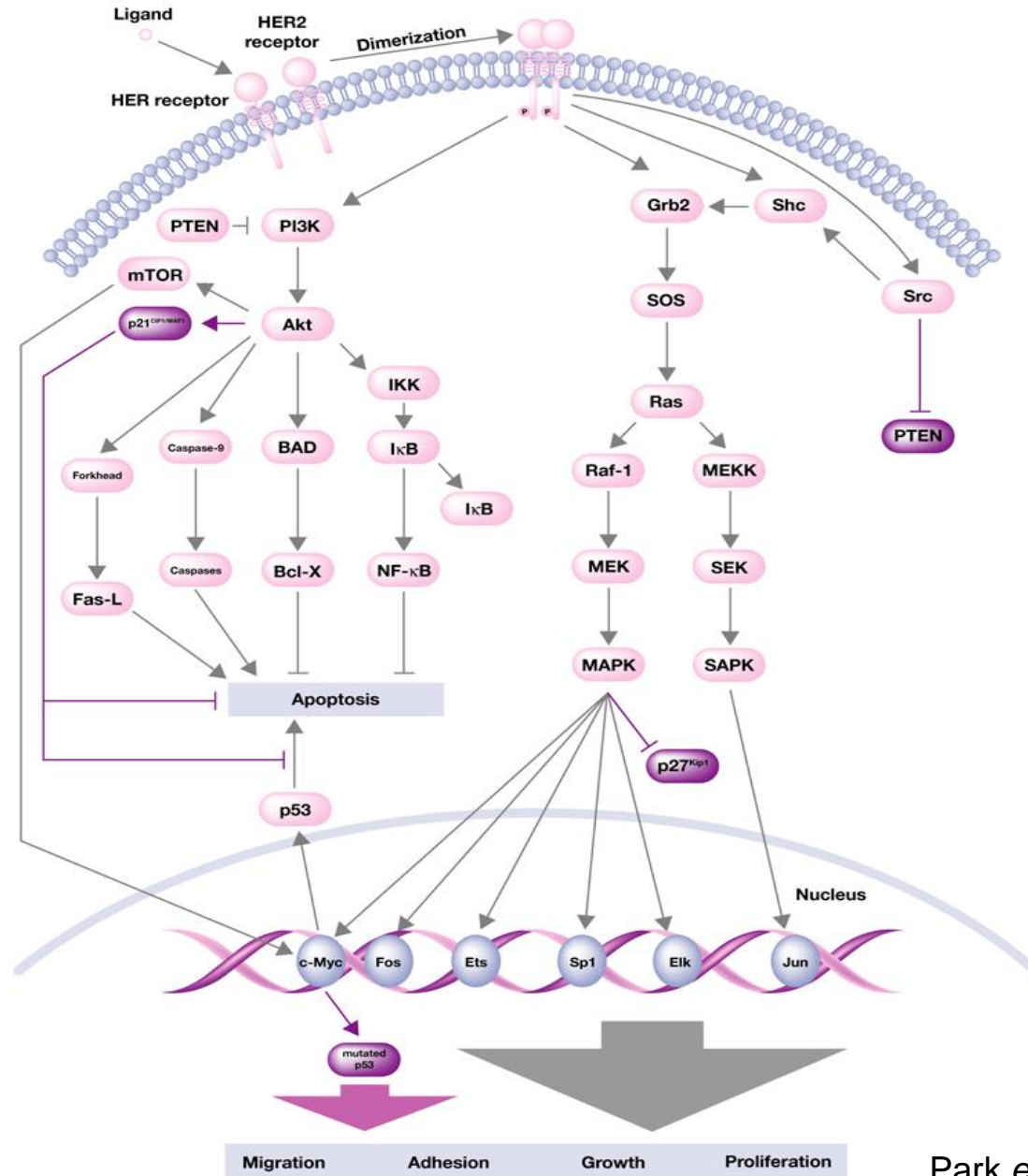


≥2.0 amplified  
(FISH+)

# HER2 Structure



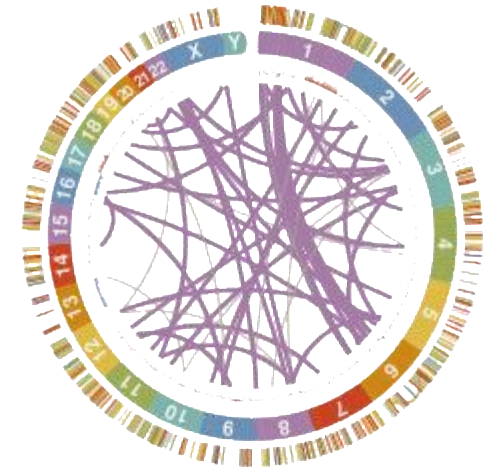
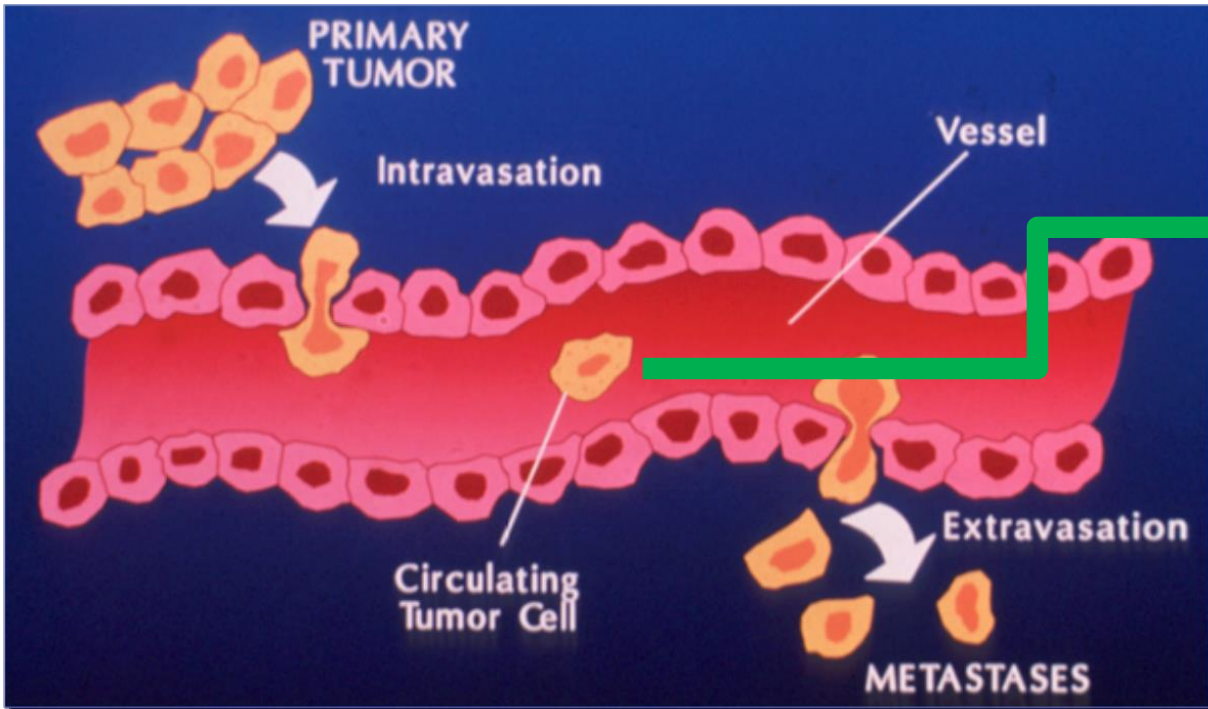
# HER2 Signaling Pathways





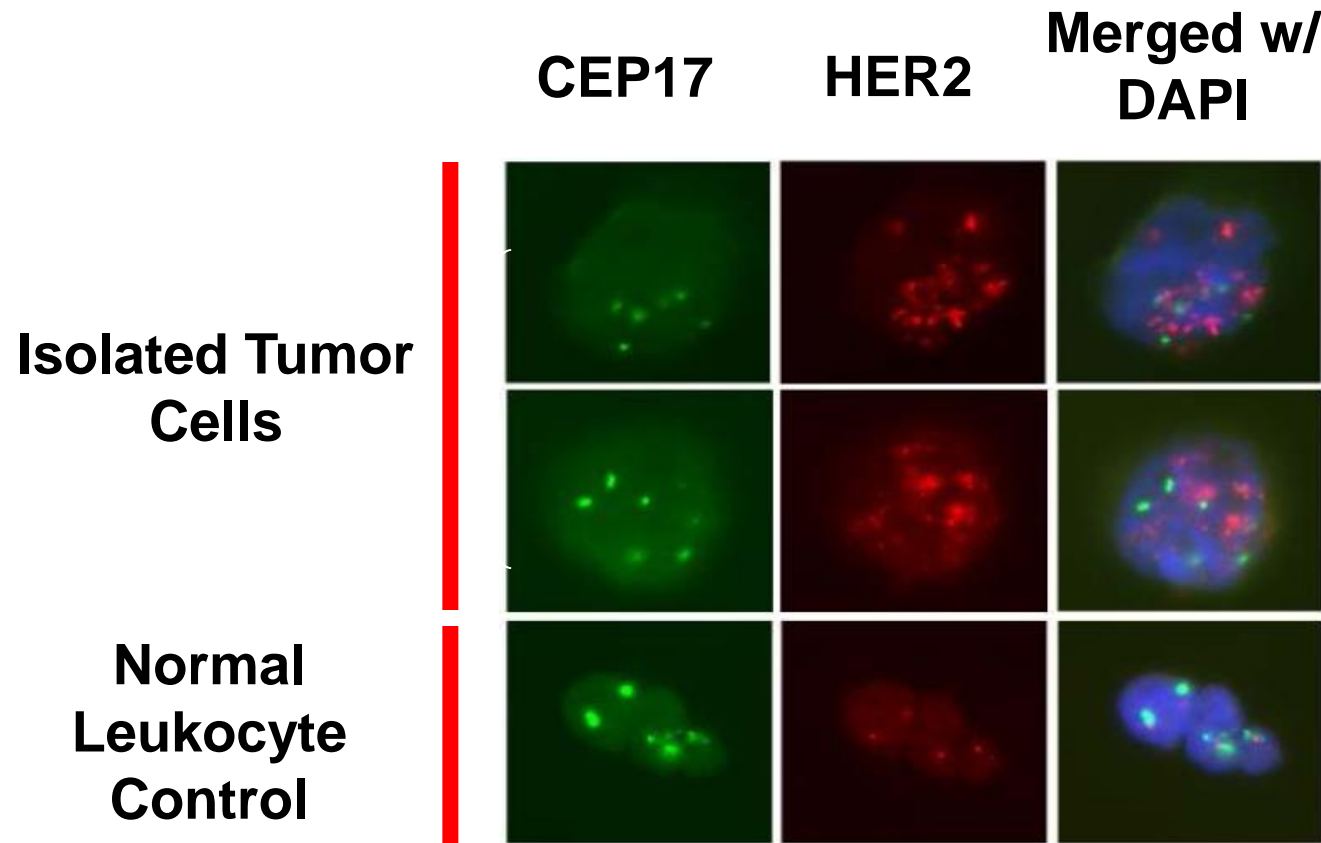
# “LIQUID BIOPSY”

## CTC Analysis



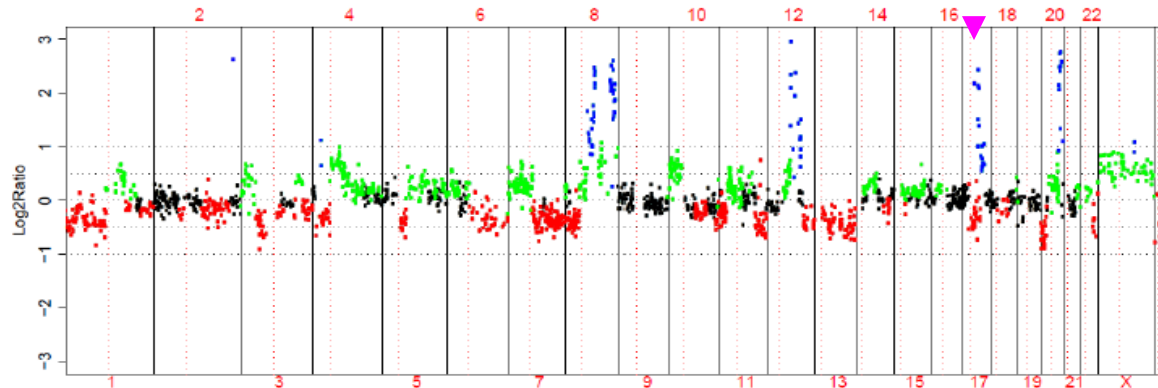
- Detection / Enumeration
- Transcriptome via expression array
- Copy number via CGH
- Mutation analysis
- Whole genome via NGS

# FISH analysis of IE/FACS-isolated BT474

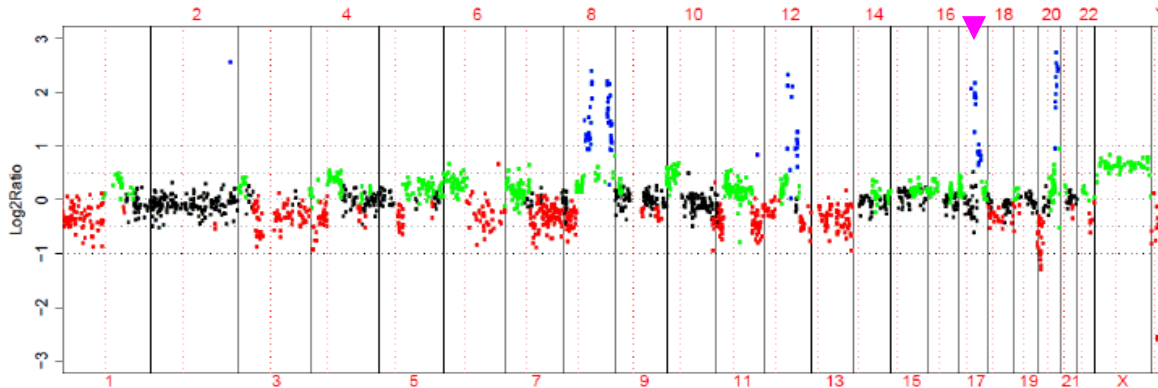


# Serial Analysis of CTCs & Matched Primary Tumor

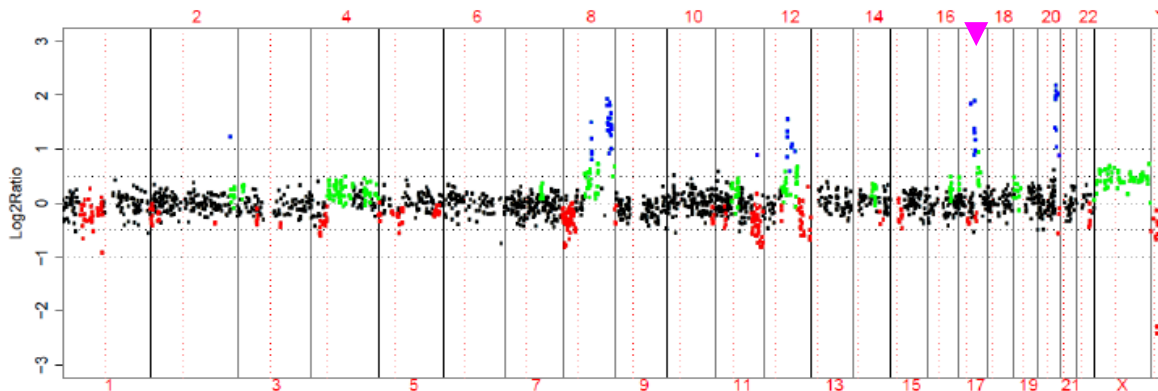
**Patient #4013**  
**50 yo F**  
**ERpos HER2pos M**



**Day 15 (20 CTCs)**  
**8.5 CTC/ml**



**Day 56 (20 CTCs)**  
**40.5 CTC/ml**



**Primary tumor**  
**6 yrs earlier**

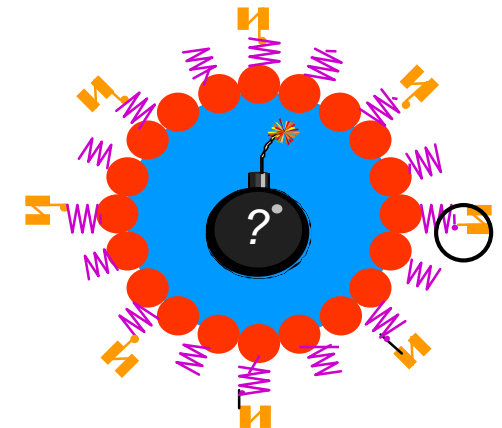
**HER2** ▼

- Amplification**
- Gain**
- Loss**

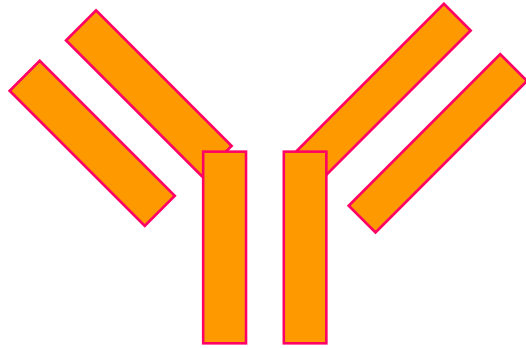
# LIPIDIC NANOPARTICLES

## *From Liposomes to Novel Multifunctional Constructs*

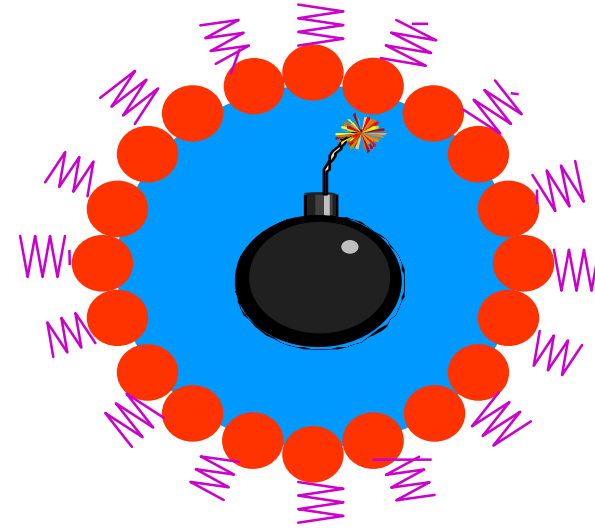
- *Liposomes as scaffold*
  - Biodegradable, safe, manufacturable
  - “Stealth” = non-immunogenic, long circulating
  - Clinically validated system with multiple agents in use
- *Limitations of previous liposomes*
  - Efficient drug loading has historically been limited (anthracyclines, amphotericin)
  - No direct tumor cell targeting
- *Next Generation Lipidic Nanoparticles*
  - Increased versatility of delivery
  - Molecular targeting (e.g. MAb)
  - Multicapability systems approach incl. imaging



# IMMUNOLIPOSOMES (ILs): *Targeted Drug Delivery*



+



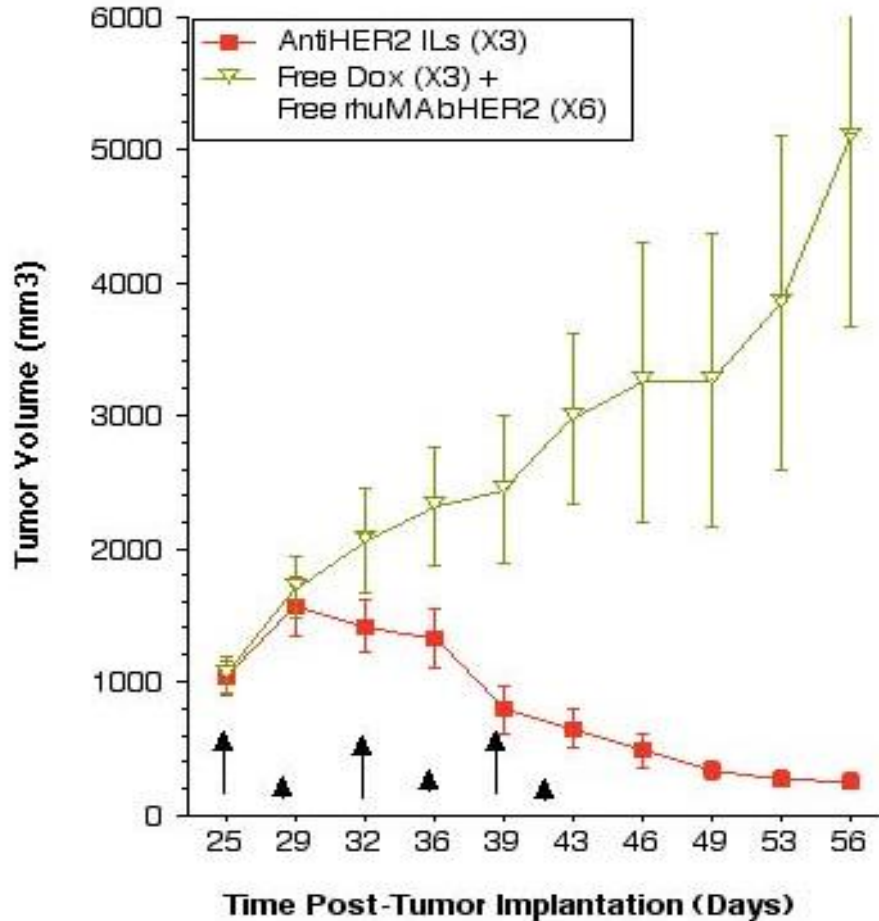
## ***Tumor Cell Targeting***

- Binding
- Internalization

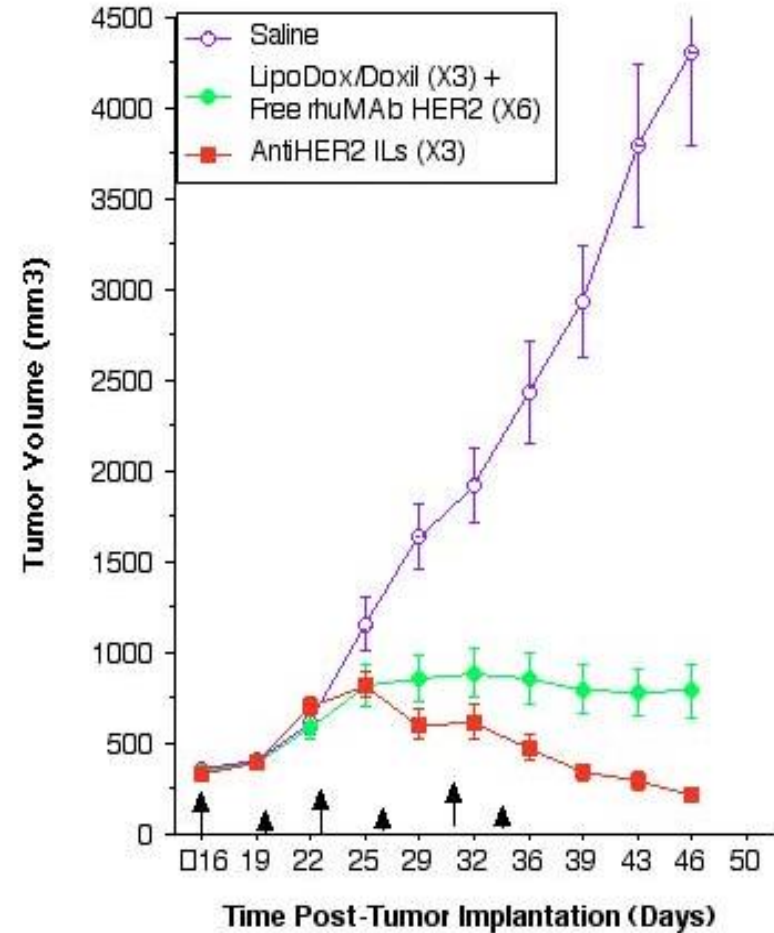
## ***Drug Delivery***

- High capacity carrier
- Repertoire of drugs
  - Approved chemoRx
  - Novel compounds
- Long circulation as stable construct
- Non-immunogenic
- Bystander killing

# HER2-Targeted ILs-Dox: Superior to Combinations



**vs. Free Dox + Trastuzumab**



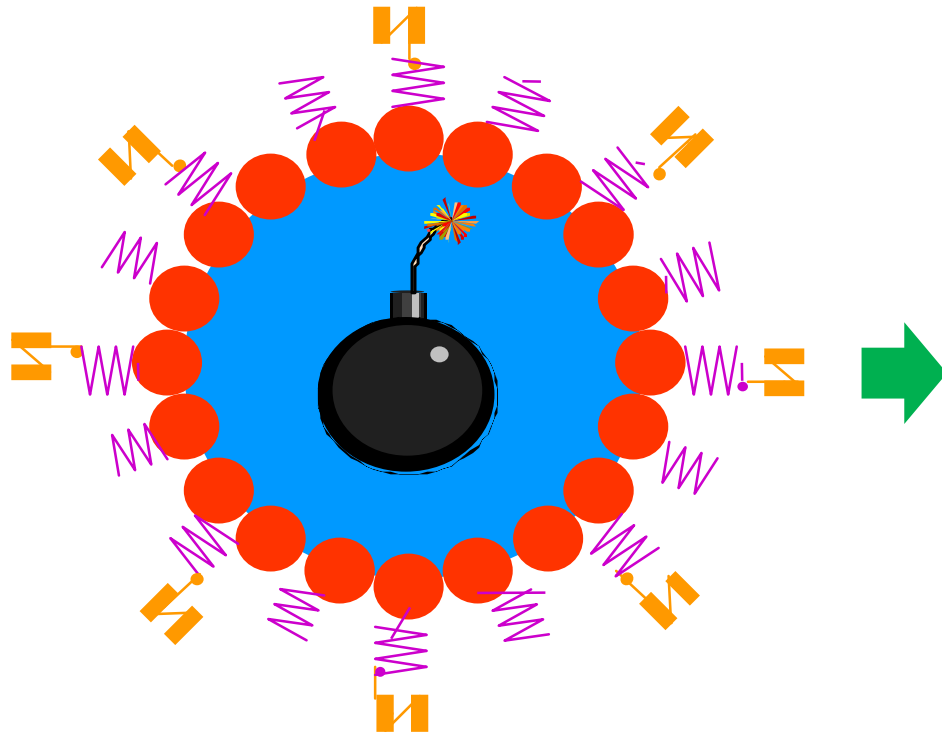
**vs. Doxil + Trastuzumab**

# HER2-Targeted ILs-Dox

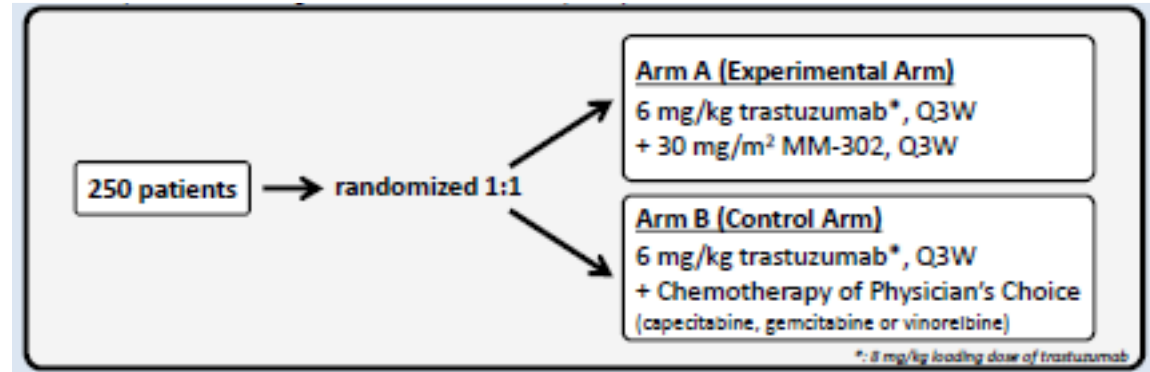
## *Translation to the Clinic*

- **NSC 701315**
  - GMP scale up and manufacturing by NCI DTP (DDG/RAID)
- **AP49**
  - Licensed to ALZA/Johnson&Johnson
  - Primate tox completed:
    - Cardiotoxicity: ILs = PLD/Doxil << Free Doxorubicin
    - HER2 undetectable in primate myocardium at necropsy
  - GMP manufacturing at ALZA/Centocor
  - ALZA closed by Johnson&Johnson
- **MM302**
  - Licensed to Merrimack Pharmaceuticals
  - PreIND meeting completed
  - GMP manufacturing at Merrimack
  - IND filing Jan 2011

# HER2-Targeted ILs-Dox: Current Registration Trial



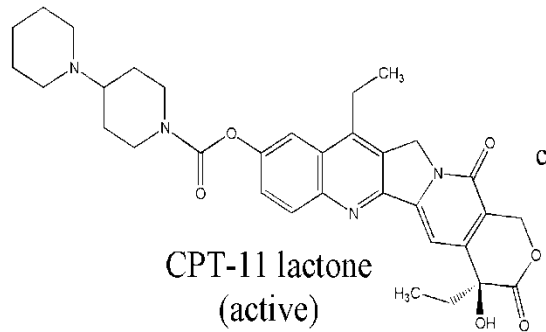
**NSC701315 / MM-302**



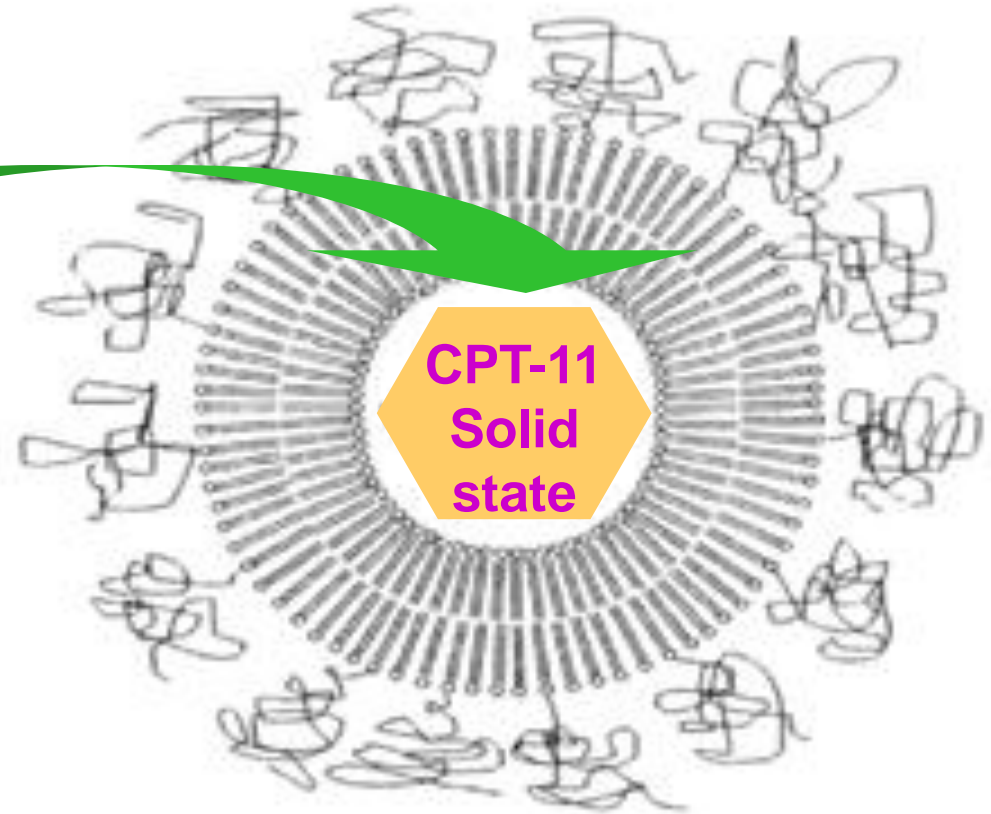
**HERMIONE Trial**



# NanoLiposomal Irinotecan/CPT-11



Nano-X



- “Nano-X” encapsulation
  - ~100% efficiency
  - 10e5 drugs/particle
- Drug stability
  - >90% drug retention in circulation (released drug undetectable)
- PK
  - Long circulating

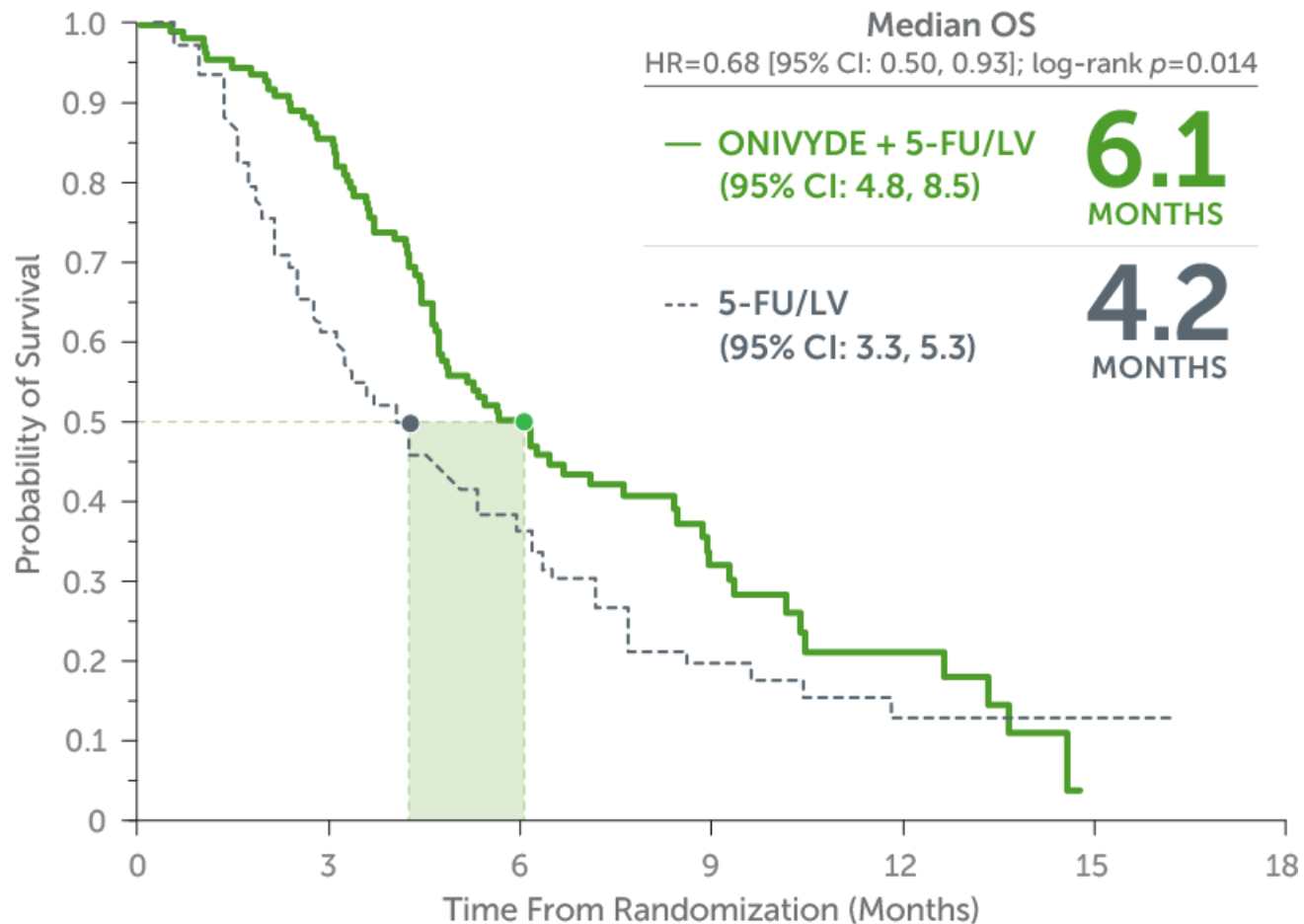
*Drummond et al., Cancer Res. 2006*

*Noble et al., Cancer Res. 2006*

# NanoLiposomal CPT-11

## *Clinical Development*

- “PEP02”
  - Partnership with PharmaEngine (Taiwan)
  - GMP manufacturing, toxicology -> clinic
- *FIH Phase I Trial*
  - Taipei: CGMH, NHRI, NTUH
  - Responses observed
- *Phase II Trials*
  - Phase II in Pancreas (UCSF, A Ko): increased OS vs. historic
  - Other tumor types
- *Phase III in Pancreas (NAPOLI-1, Merrimack Pharma)*
  - NanoLiposomal CPT-11 + 5FU/LV vs. 5FU/LV showed superior OS
- “Onivyde™” (*Irinotecan Liposome Injection*)
  - US FDA approval 2015
  - NCCN Guideline listed



# at risk:

ONIVYDE + 5-FU/LV:	117	99	51	20	8	0	0
5-FU/LV:	119	73	37	12	7	1	12

**1-year** probability of survival was  
**24%** with ONIVYDE + 5-FU/LV and **17%** with 5-FU/LV alone<sup>3</sup>

# SUMMARY

- *Diagnosis -> Biomarker defined*
  - Recent example: HER2+ Breast Cancer
  - Current example: Liquid biopsy
- *Therapy -> Targeted*
  - Recent example: Trastuzumab (Herceptin™)
  - Current example: Nanoparticle drugs
- *Impact -> Translational*
  - Bench to Bedside / Clinic

# ACKNOWLEDGEMENTS

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