

# Think Differently: Challenges in Immunotherapy

SITC CICT: Challenges and Solutions

April 5<sup>th</sup> 2013



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Anti-PDL1 Global Development Leader



# Presenter Disclosure Information:

## Daniel S. Chen



2

The following relationships exist related to this presentation:

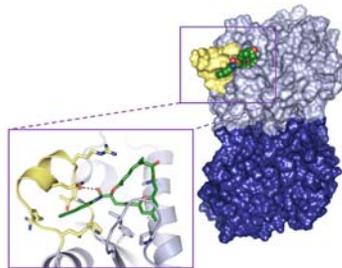
**Employee of Genentech, a member of the Roche Group**

*I will not be discussing the off-label usage of any Genentech or Roche approved drugs*



# What's Up with Immunotherapy?

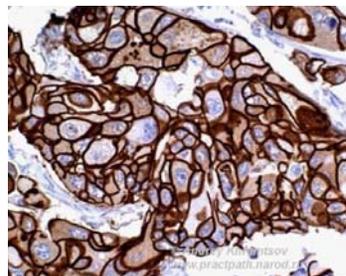
## Unlike most traditional anti-cancer therapy...



Chemotherapy  
(tubulin stabilizing agent epothilone)  
*Prota 2013*

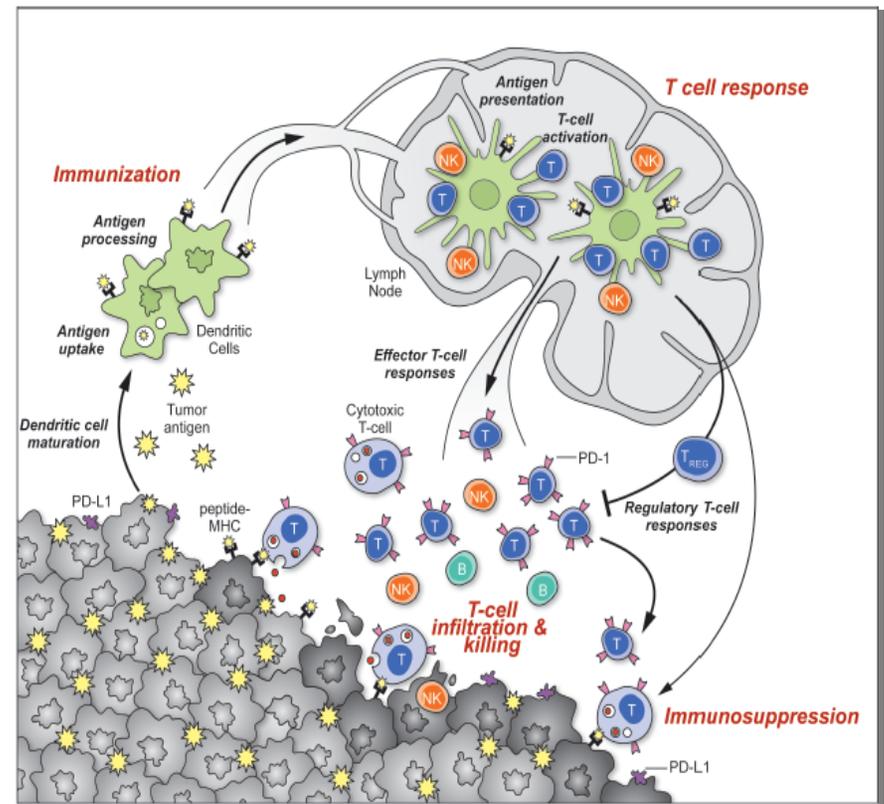


Oncogene Target  
(bRAF mutated melanoma)  
*Hsieh 2012*



Tumor Cell Target  
(Her2neu expressing breast cancer)

## ...Immunotherapy relies on the function of immune cells

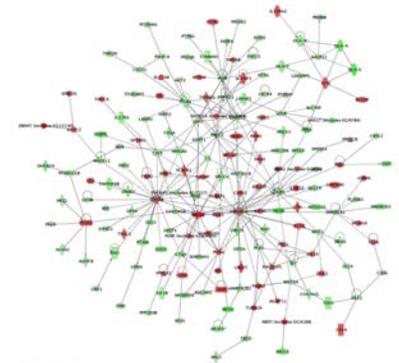


Mellman et al. 2011

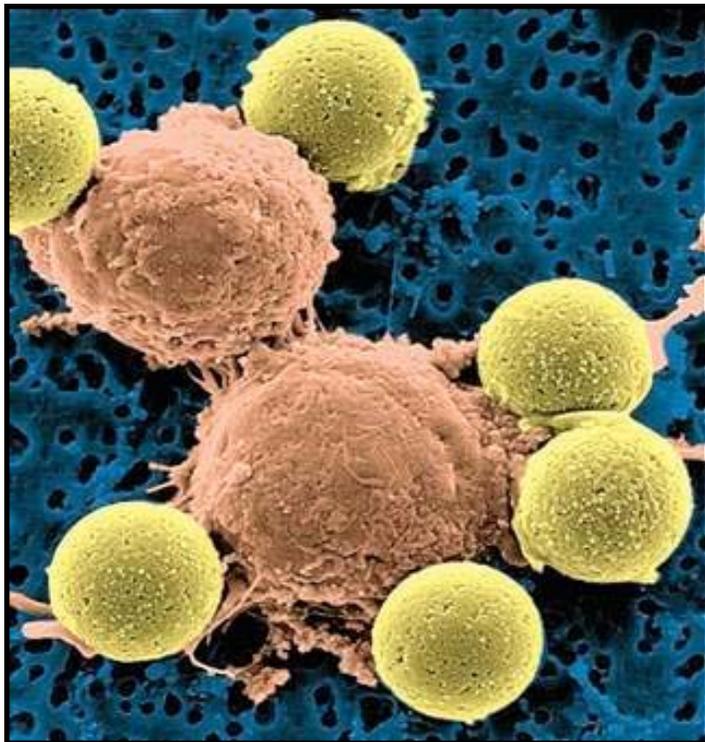


# Relying on an Intact Immune System

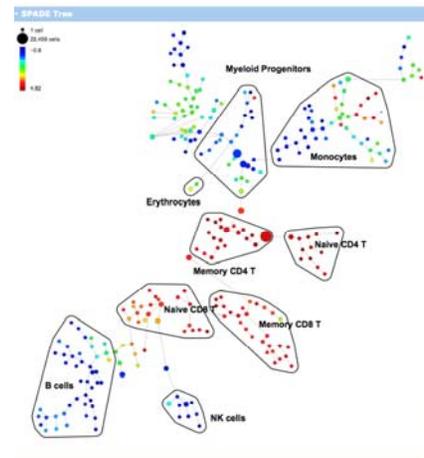
***Need to understand a complex network of cells, compartments and cytokines***



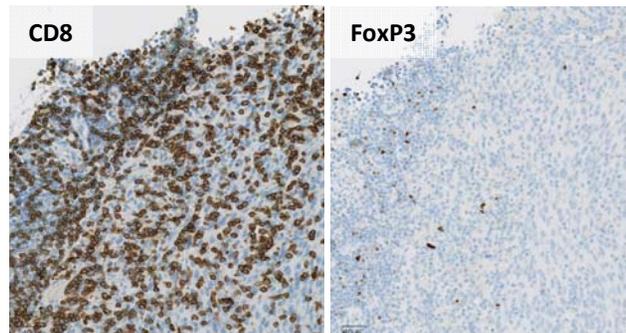
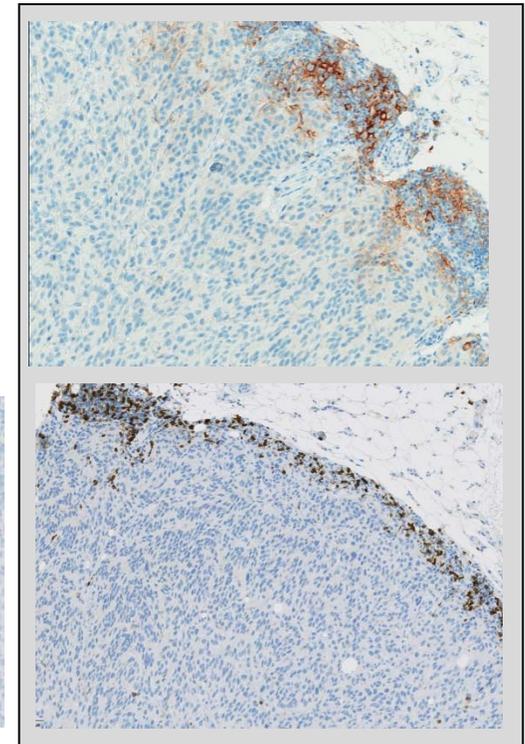
*BMC Genomics 2008*



*Smith, BioTechniques 2012*



*Bodenmiller, Nature BioTech 2012*

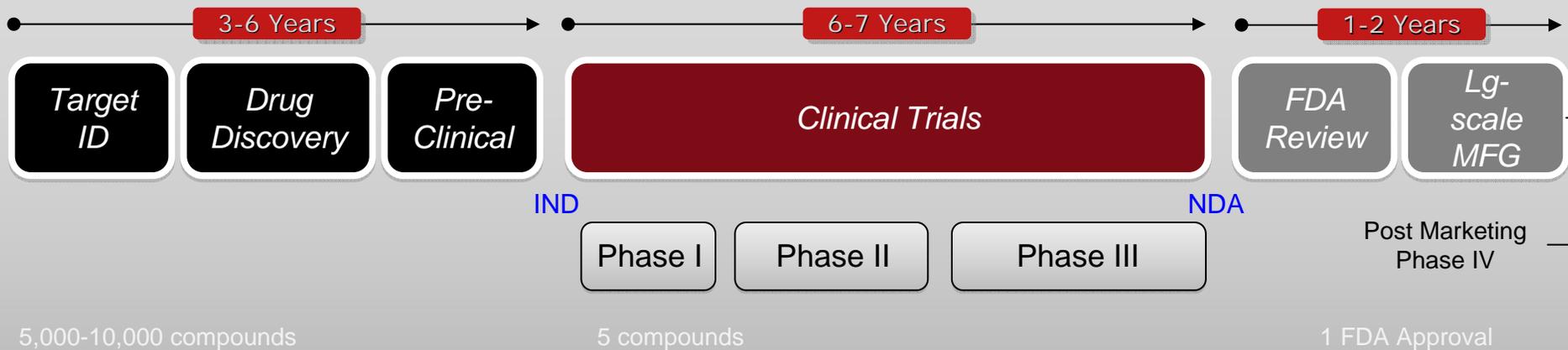




# Immunotherapy vs Targeted Therapy

	Targeted Therapy	Immunotherapy
Example:	bRAF-targeted tx	Anti-CTLA4
Biology	Block bRAF-mediated signaling	Complex (enhanced priming? Clear Tregs?)
Relevance	High prevalence of mutation in melanoma	CTLA4 expressed on many cell types; not on tumors
Pre-clinical	High throughput human tumor cell line screening	Limited number of syngeneic models; variability in vivo efficacy
Biomarker	Presence of mutation	Unknown
Dose	MTD, MTD-1	3mg/kg vs 10mg/kg? 4 doses? More?
Safety	AEs manageable with decreased dose	irAEs, delayed and persistent; may require steroids or more potent immune suppression
PD	Inhibition of MAPK signaling, ORR	Complex; immune infiltrates? Changes in T cell subsets? irAEs?
Endpoints	OS, PFS, ORR	OS? Tail of curve? ORR?

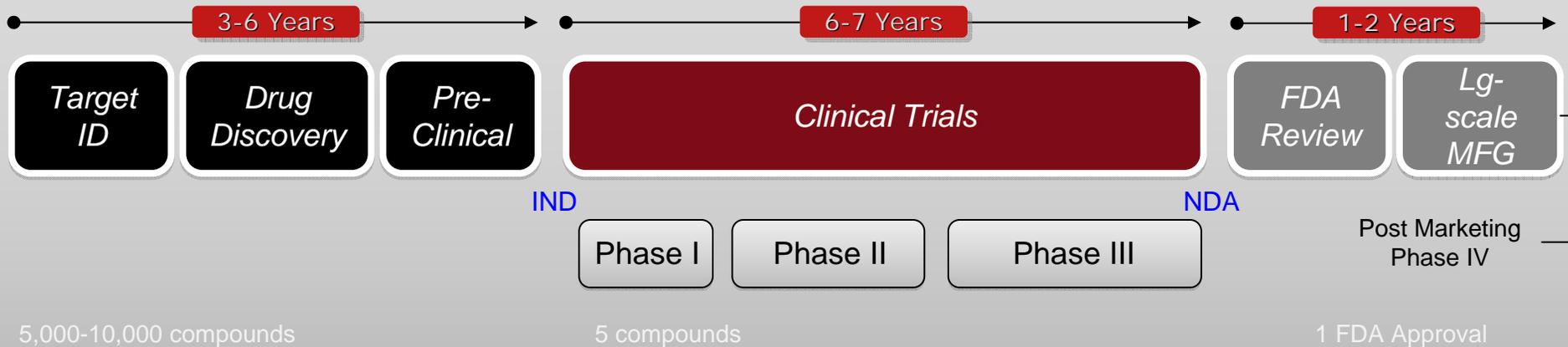
# Drug Development Cycle



Duration: 10-15 Years  
Cost: >1 billion US Dollars

- Biologic plausibility
- Pre-clinical activity
- Biomarker ID
- Acceptable tox
- Dose & schedule
- Safety
- PD biomarkers
  - Estimate efficacy
  - Evaluate predictive biomarker
    - Confirm efficacy
    - Validate predictive biomarker

# Drug Development Cycle: Pre-clinical



Duration: 10-15 Years  
Cost: >1 billion US Dollars

- Biologic plausibility
- Pre-clinical activity
- Biomarker ID
- Acceptable tox

*Complex biology/biomarkers*  
*Challenging pre-clinical models*



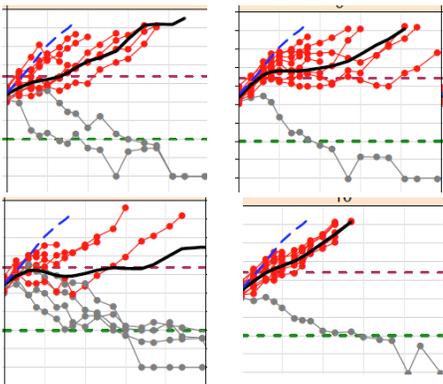
# How Well Do Pre-clinical Models Predict Human Immunobiology?



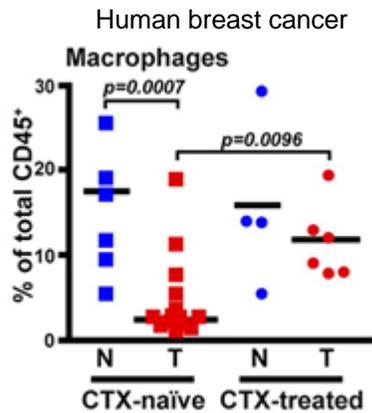
- Intact immune system required
- Limited syngeneic models
- Immunogenicity of antigens
- Tumor immune microenvironment differences?
- Intrinsic vs adaptive immune suppression
- Variability in models
- Genetic diversity vs human tumors



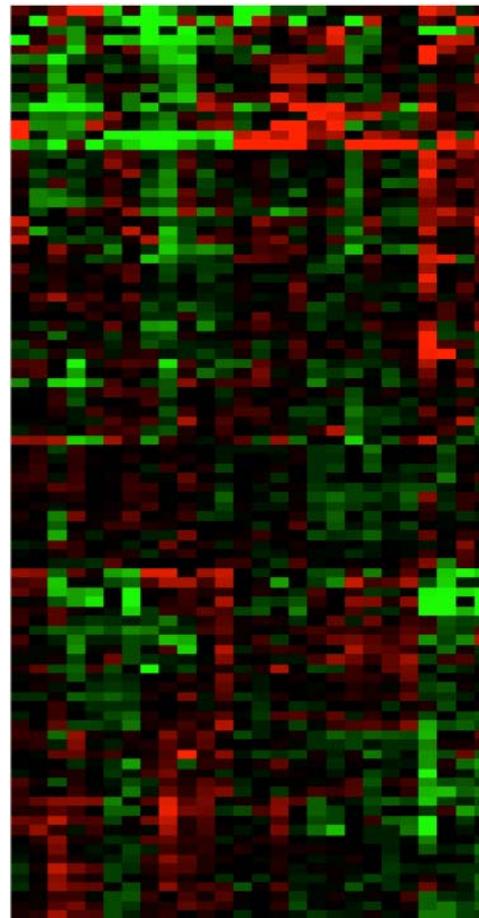
Dillow 2010



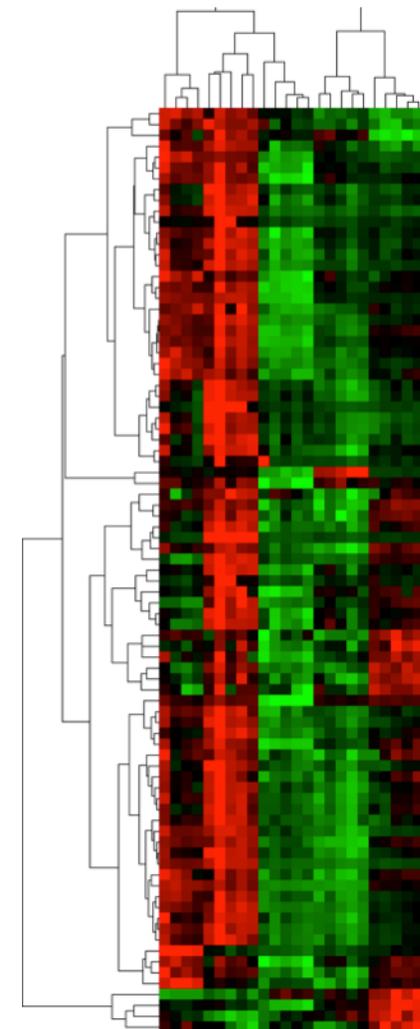
Irving et al (Genentech)



Ruffell et al 2012



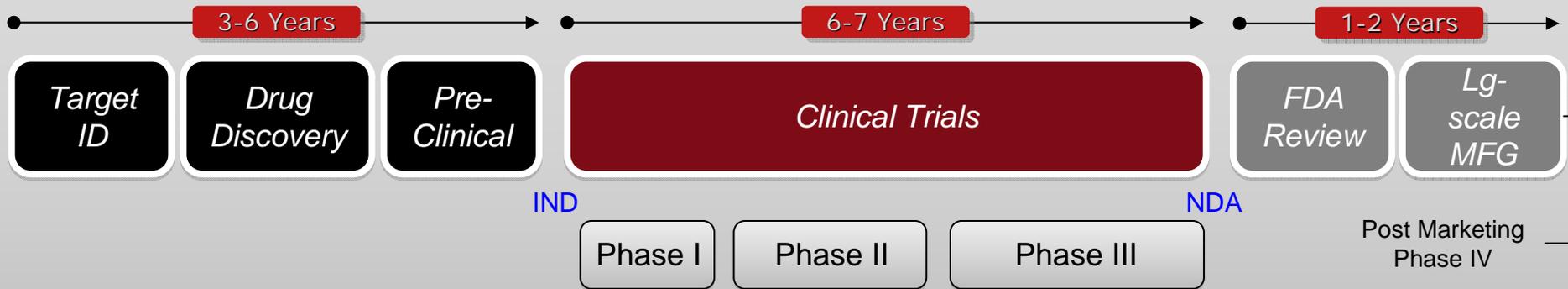
Kowanetz et al (Genentech)



Huseni et al (Genentech)

*Complex biology/biomarkers*  
*Challenging pre-clinical models*

# Drug Development Cycle: Early Clinical Development



5,000-10,000 compounds

5 compounds

1 FDA Approval

Duration: 10-15 Years  
Cost: >1 billion US Dollars

- Dose & schedule
- Safety
- PD biomarkers

*Starting dose*  
*Dose and schedule*

# Immunotherapy Dose and Schedule Can Be Challenging



## Starting Dose:

- MABEL vs NOAEL
- Minimal efficacious dose
- Maximum tolerated dose

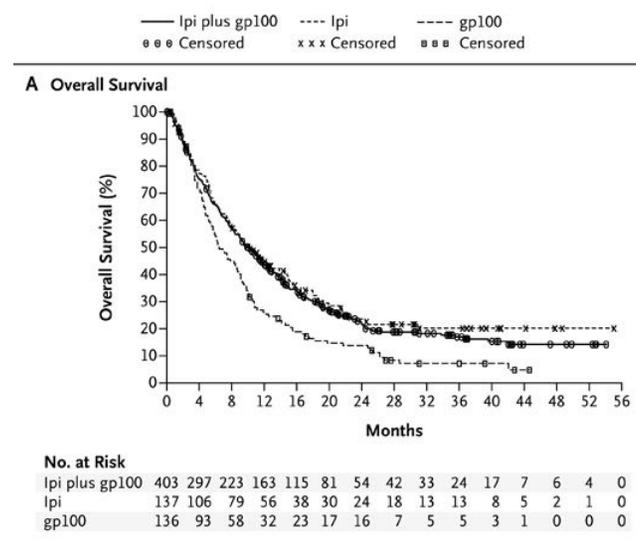
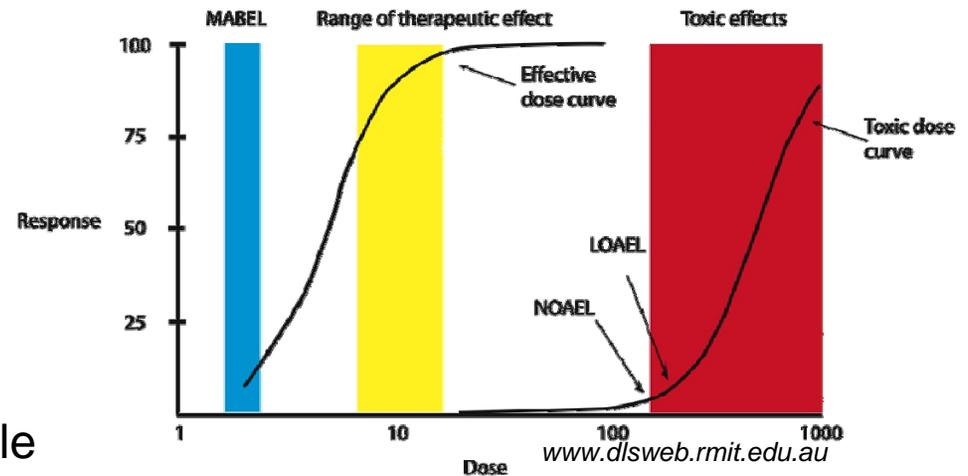
## Schedule:

Persistent immune activation may complicate identification of a schedule

- Single dose?
- 4 doses
- Dose for 1 year?
- Dose until PD or CR?
- Tx duration confounded by pseudoprogression

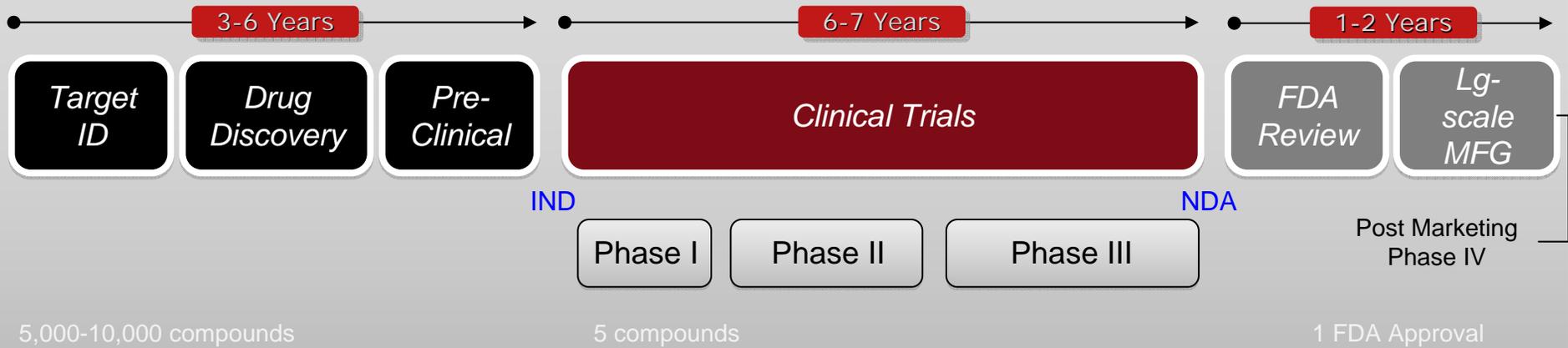
## Endpoint: Long term OS

- Long time to endpoint
- May require large studies to evaluate the tail on the curve



Hodi et al 2010

# Drug Development Cycle: Clinical Development

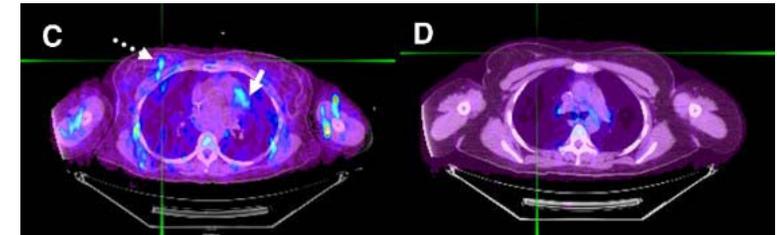
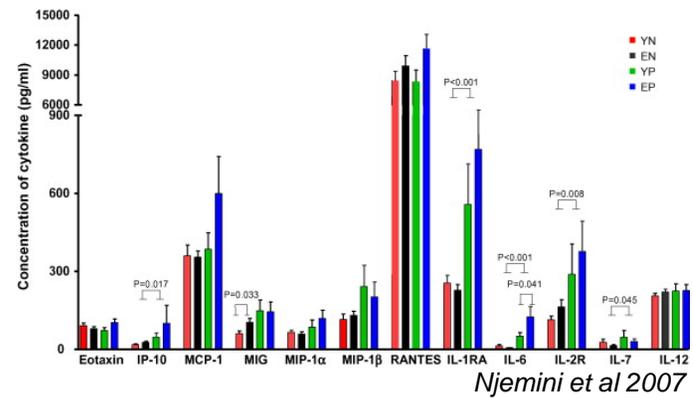
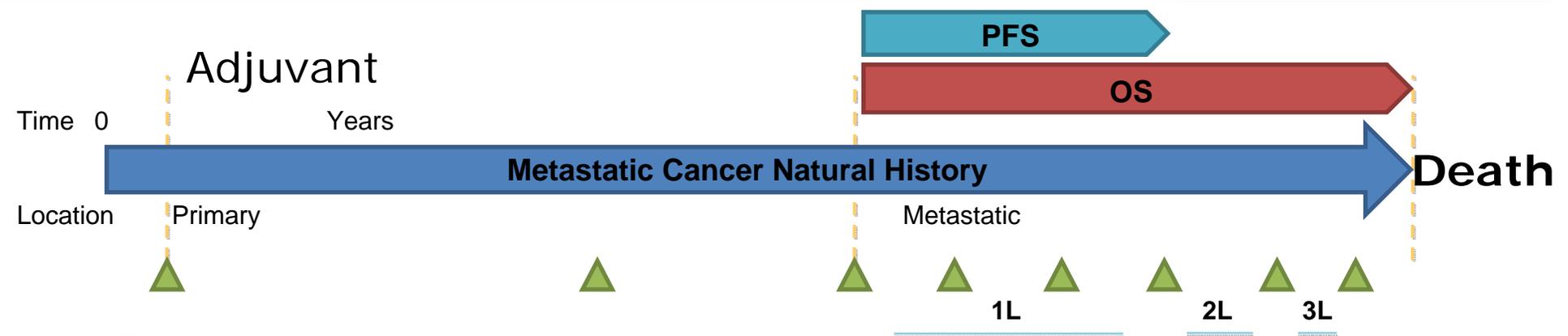


Duration: 10-15 Years  
Cost: >1 billion US Dollars

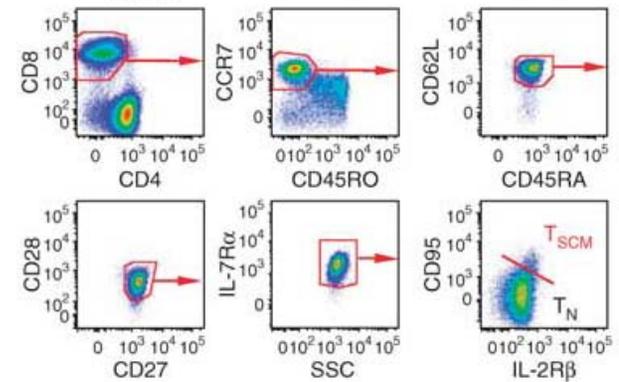
- Estimate efficacy
- Evaluate predictive biomarker



# Biomarkers: Non-invasive



*Kurdziel et al 2007*

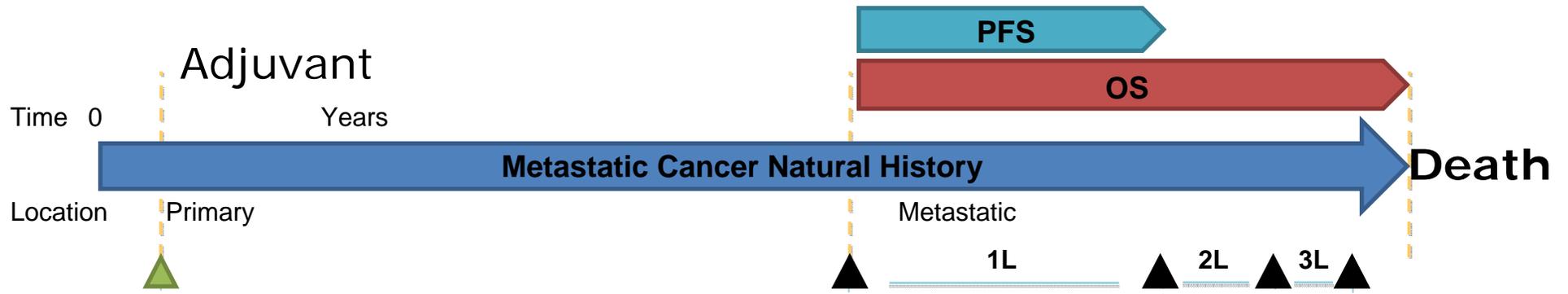


*Gattinoni et al 2011*

- Obvious advantages to being able to easily assess a dynamic immune related biology
- Challenge related to whether tumor biology is adequately reflected in blood
- Use of imaging as a biomarker for immunotherapy will likely require additional technology development

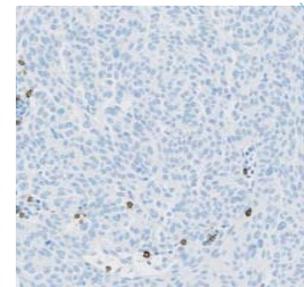
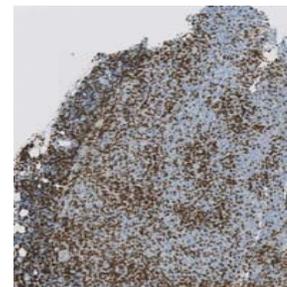
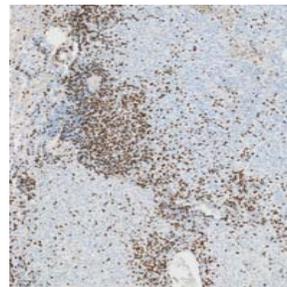
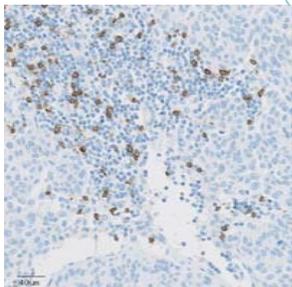


# Biomarkers: Tumor Tissue



Dynamic immune environment  
Differences between archival and met

Changes in immunogenicity  
Changes following SOC therapy  
Changes following immunotherapy

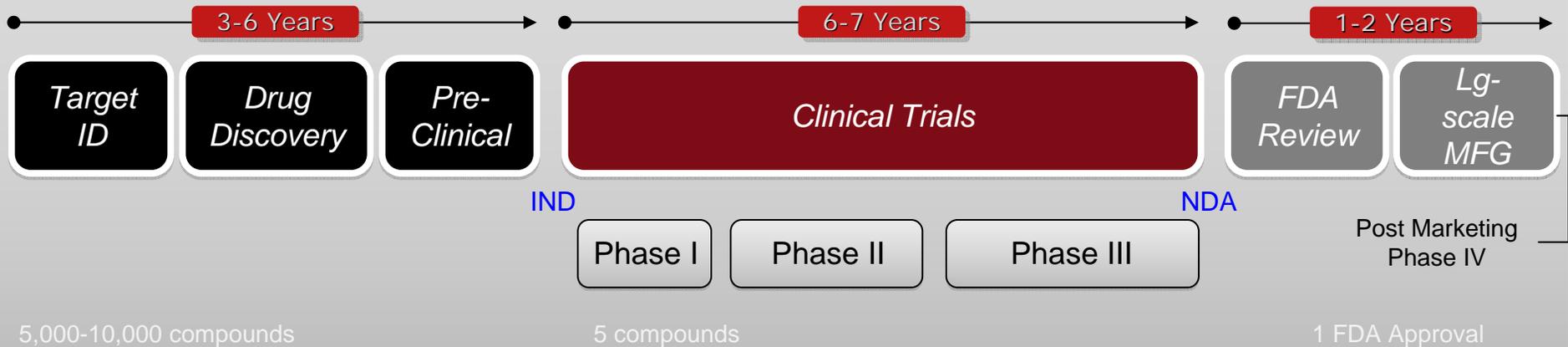


Representative IHC images

 Primary samples likely to be large resection sample

 Metastatic samples likely to be limited to a small core bx

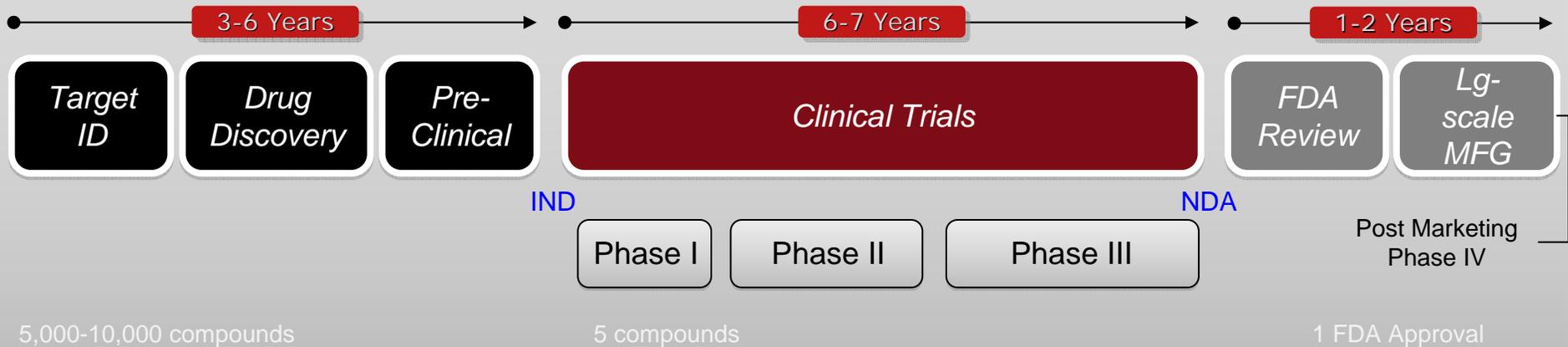
# 1NME Drug Development



Duration: 10-15 Years  
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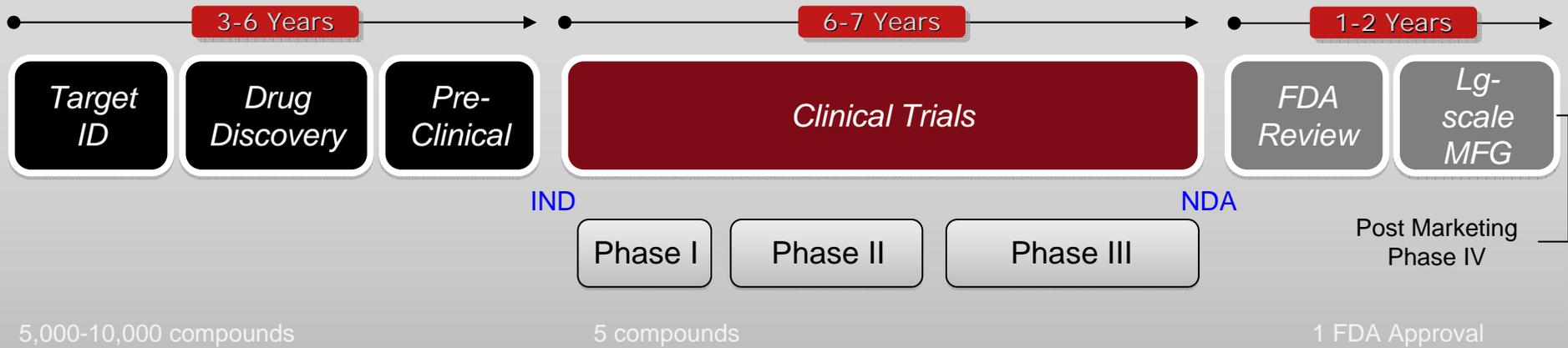
# 2NME Drug Development



Duration: 10-15 Years  
Cost: >1 billion US Dollars

- Strong combo rationale
- Pre-clinical combo activity @ tolerable doses
- Non-overlapping organ tox
- Biomarkers for combo activity
- Both drugs available
- Dose & schedule of the combo: multiple potential MTDs
- Safety: distinguish from monotox?
- PD biomarkers for combo
  - Estimate efficacy in multiarm study
  - Evaluate predictive biomarker for 1 or both
    - Confirm efficacy- contribution?
    - Validate predictive biomarker

# 2NME Drug Development



Duration: 10-15 Years  
Cost: >1 billion US Dollars

*Combinations that show high activity with good safety in early testing should be accelerated in their development*