

Think Differently: Challenges in Immunotherapy

SITC CICT: Challenges and Solutions

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Genentech
BIO₂NCOLOGY™

Presenter Disclosure Information:

Daniel S. Chen



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The following relationships exist related to this presentation:

Employee of Genentech, a member of the Roche Group

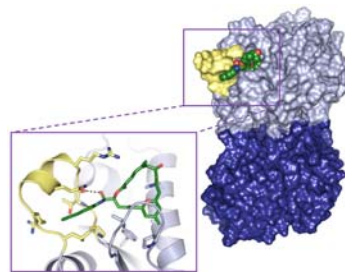
I will not be discussing the off-label usage of any Genentech or Roche approved drugs

What's Up with Immunotherapy?

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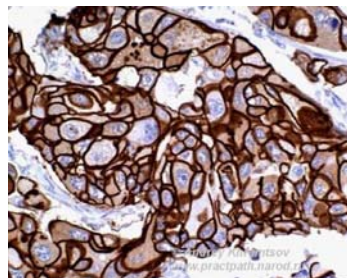
Unlike most traditional anti-cancer therapy...



Chemotherapy
(tubulin stabilizing agent epothilone)
Prota 2013

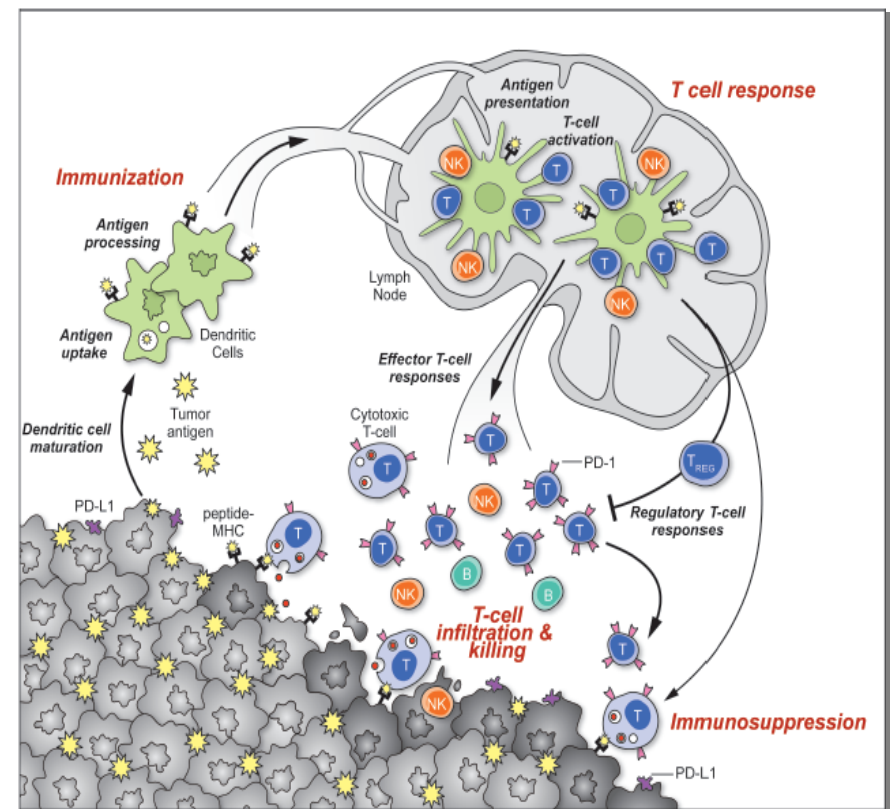


Oncogene Target
(bRAF mutated melanoma)
Hsieh 2012



Tumor Cell Target
(Her2neu expressing breast cancer)

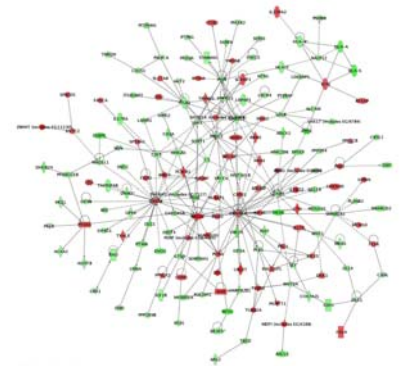
...Immunotherapy relies on the function of immune cells



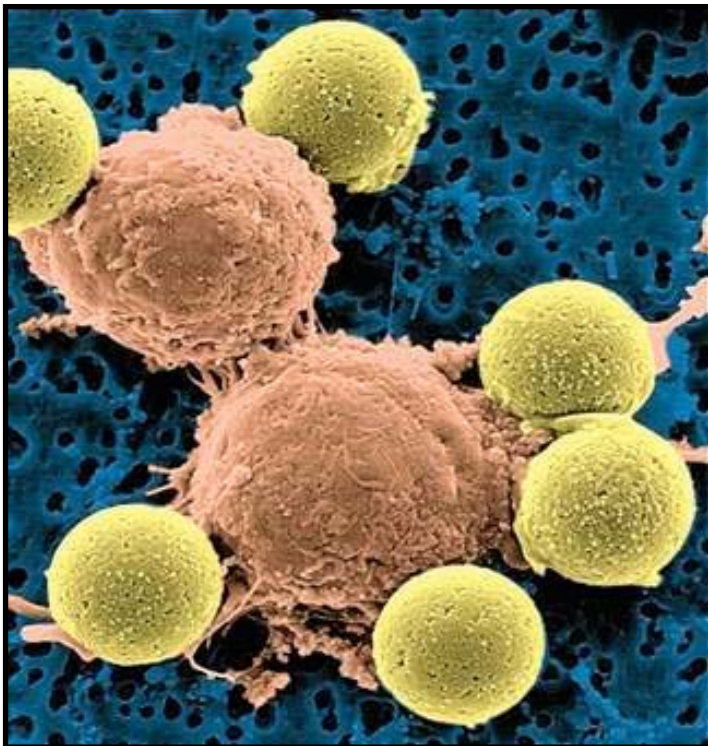
Mellman et al. 2011

Relying on an Intact Immune System

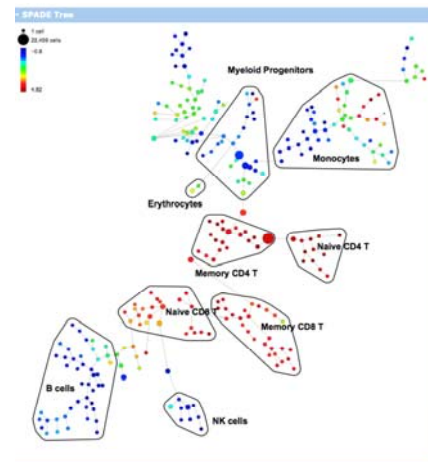
Need to understand a complex network of cells, compartments and cytokines



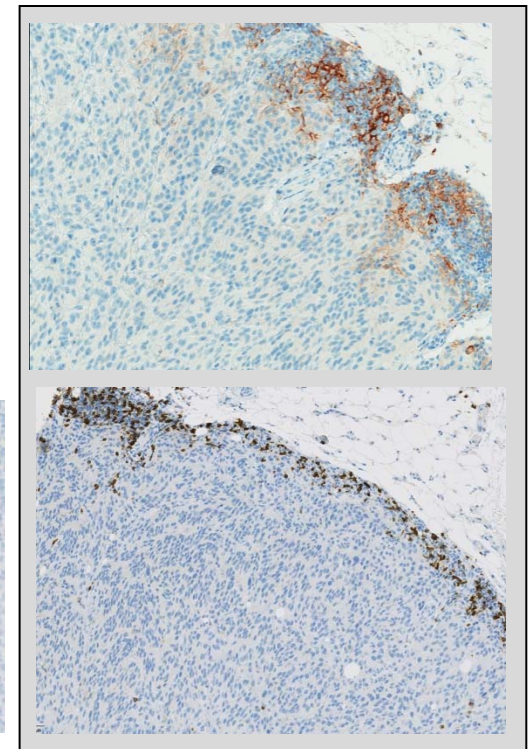
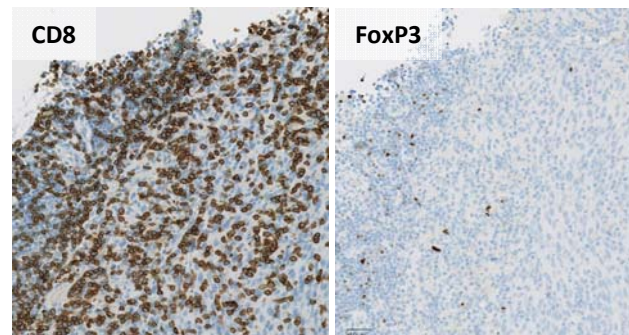
BMC Genomics 2008



Smith, BioTechniques 2012



Bodenmiller, Nature BioTech 2012

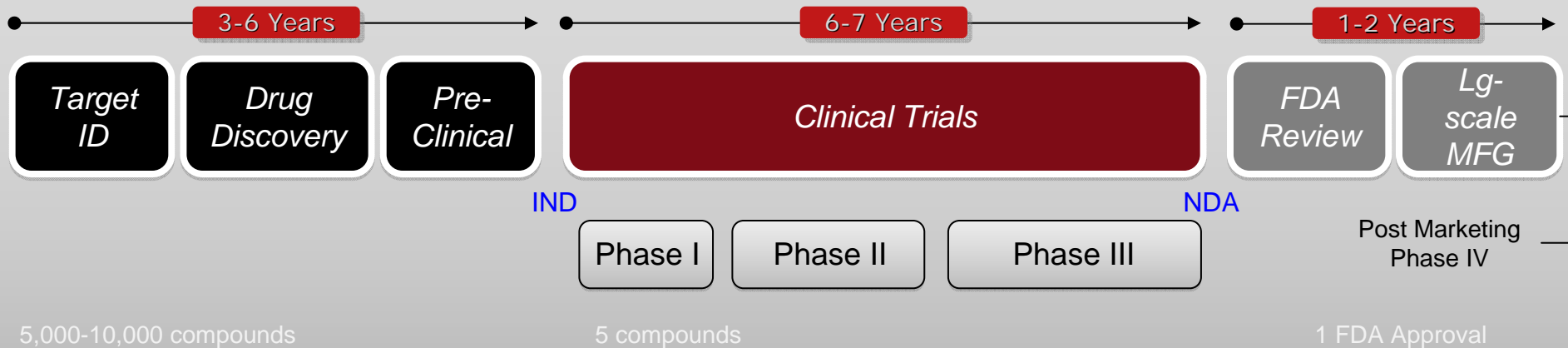




Immunotherapy vs Targeted Therapy

	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?

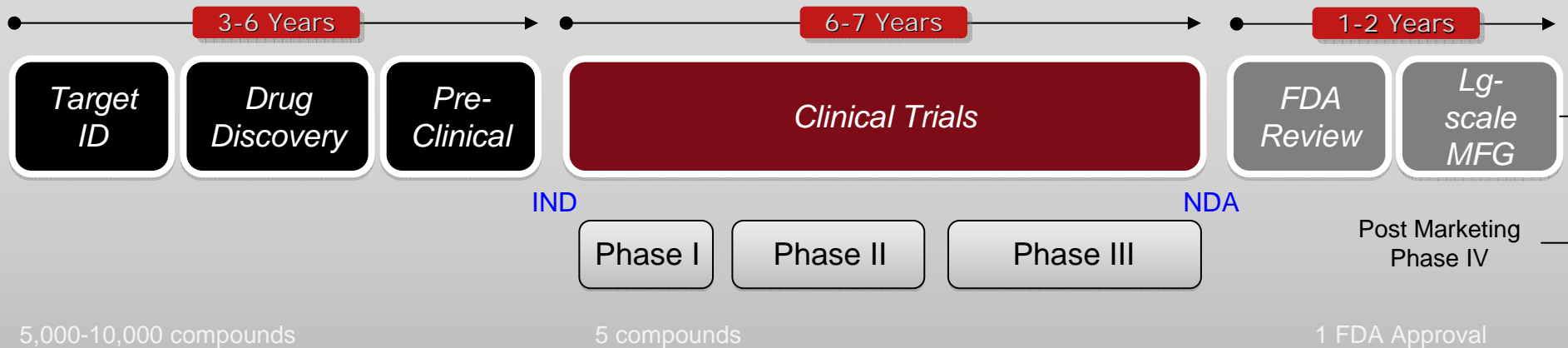
Drug Development Cycle



- 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?

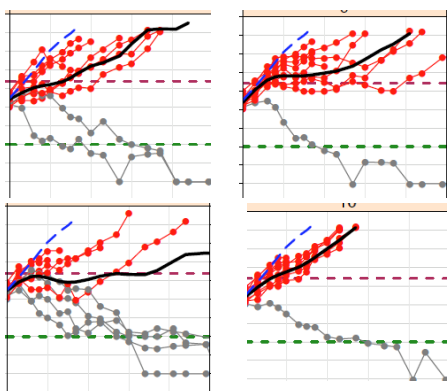
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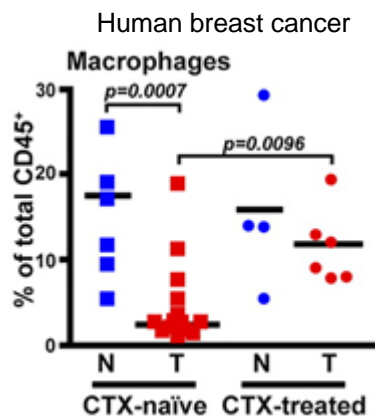
- Intact immune system required
- Limited syngeneic models
- Immunogenicity of antigens
- Tumor immune microenvironment differences?
- Intrinsic vs adaptive immune suppression
- Variability in models
- Genetic diversity vs human tumors



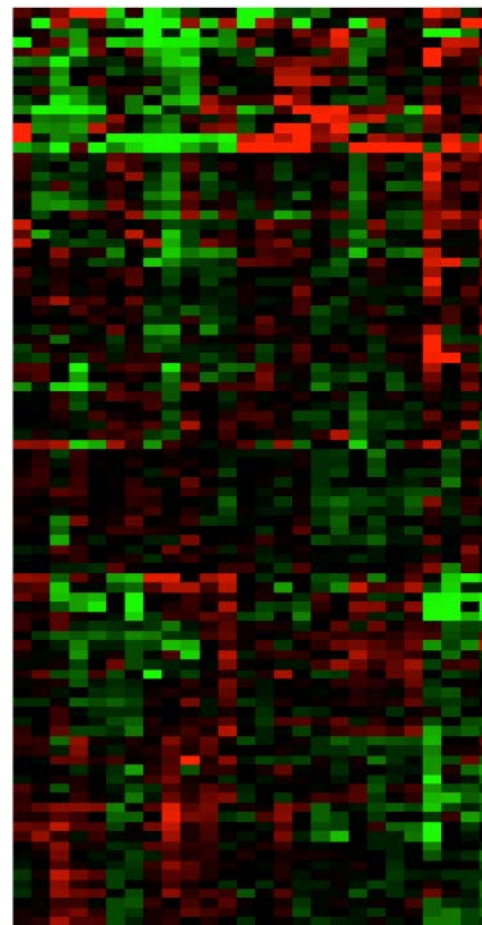
Dillow 2010



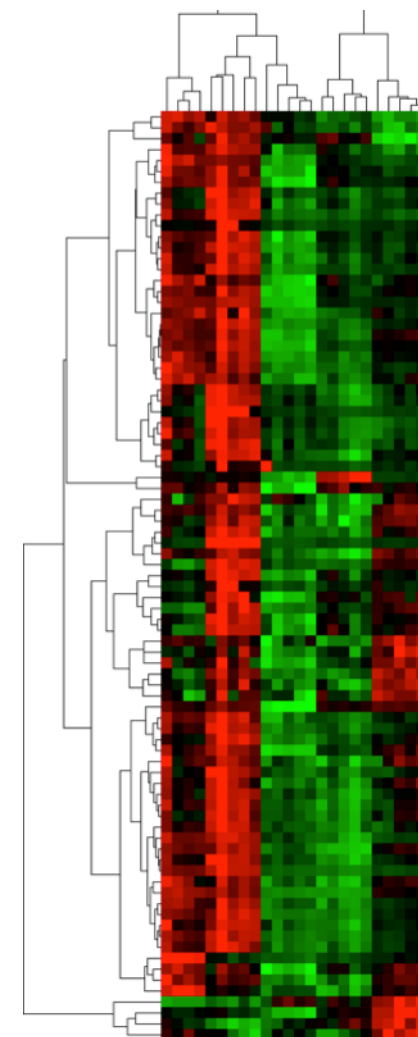
Irving et al (Genentech)



Ruffell et al 2012



Kowanetz et al (Genentech)



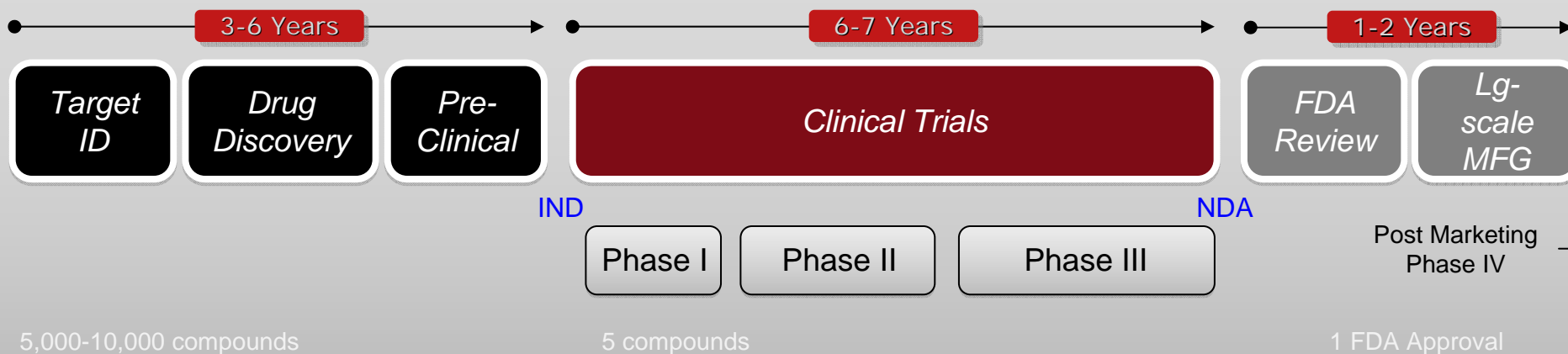
Huseni et al (Genentech)

Complex biology/biomarkers
Challenging pre-clinical models

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Drug Development Cycle: Early Clinical Development

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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

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Starting Dose:

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

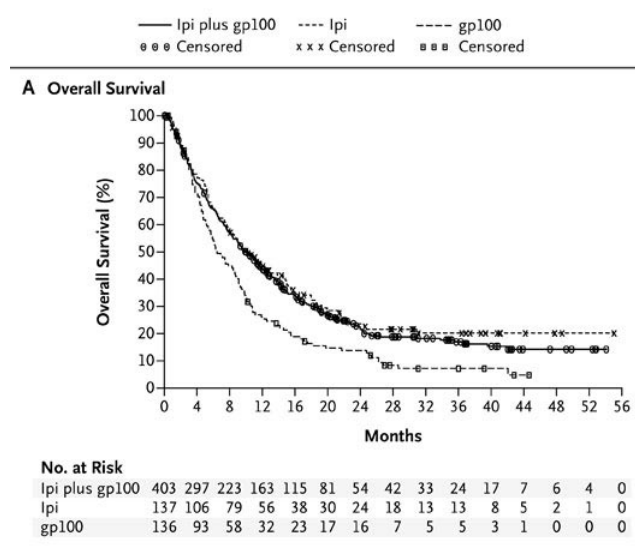
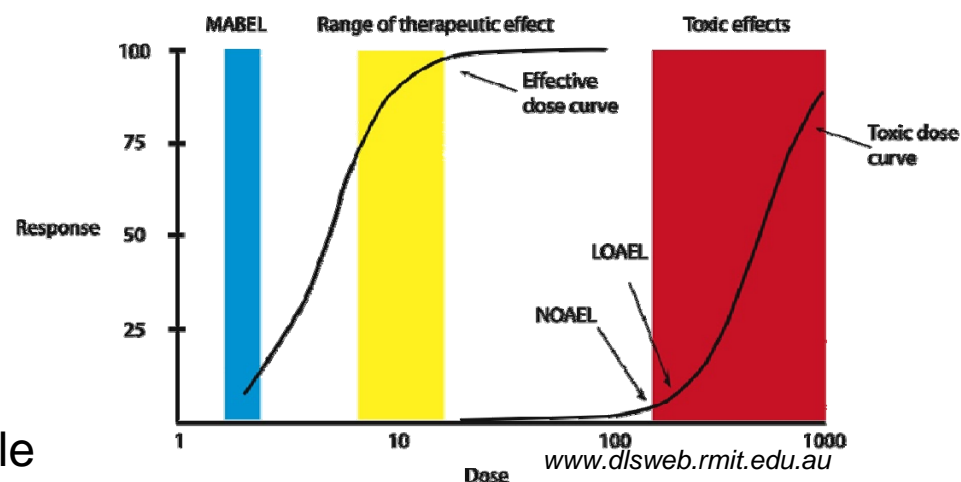
Schedule:

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

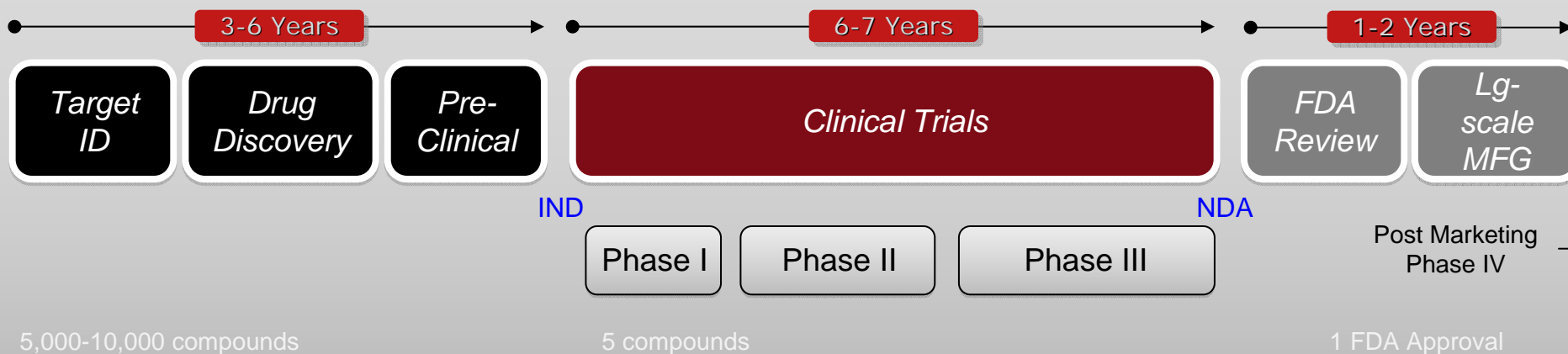
- Long time to endpoint
- May require large studies to evaluate the tail on the curve



Hodi et al 2010

Drug Development Cycle: Clinical Development

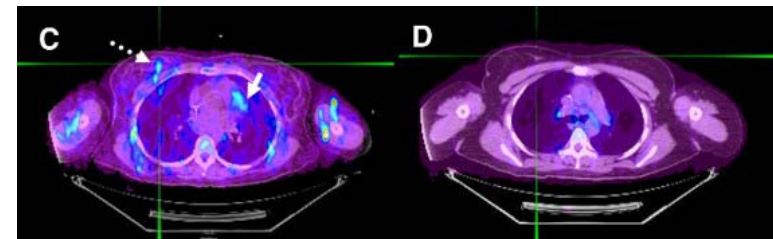
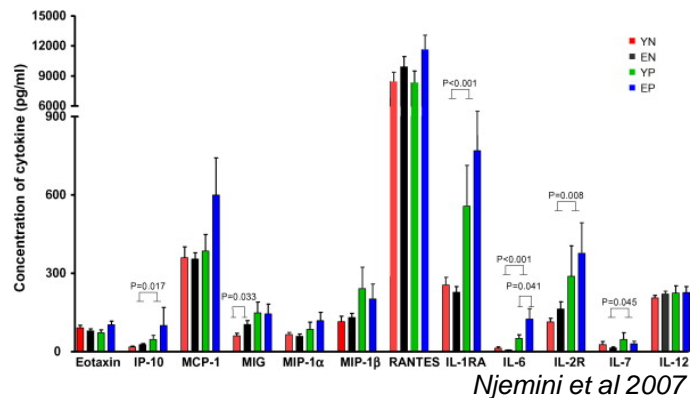
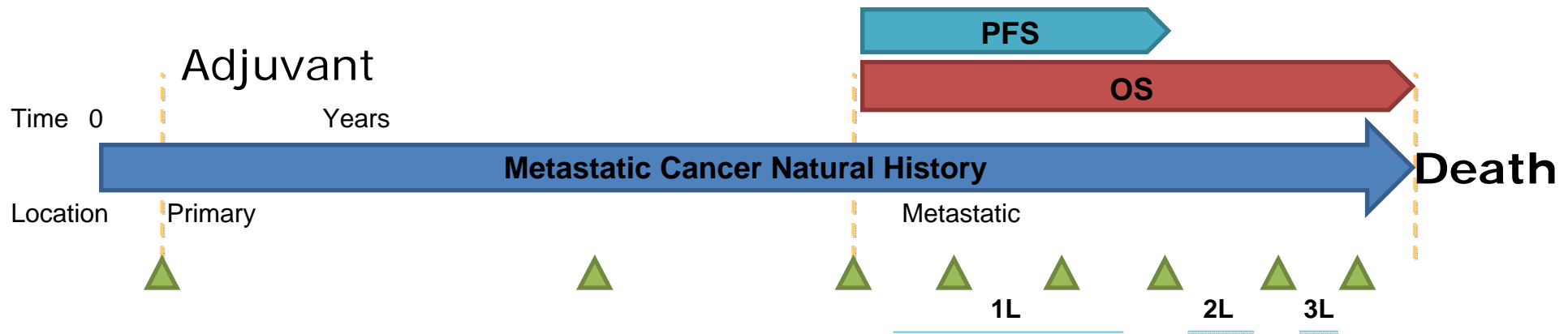
11



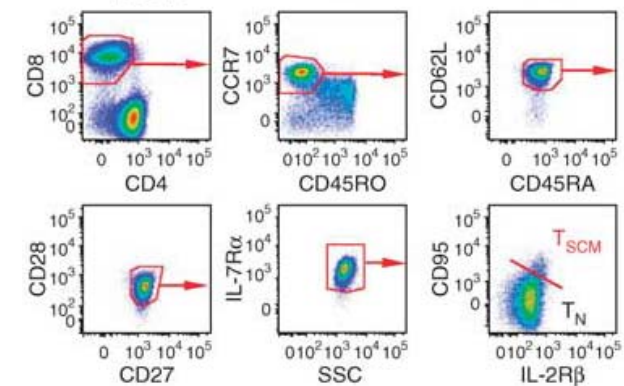
Duration: 10-15 Years
Cost: >1 billion US Dollars

- Estimate efficacy
- Evaluate predictive biomarker

Biomarkers: Non-invasive



Kurdziel et al 2007

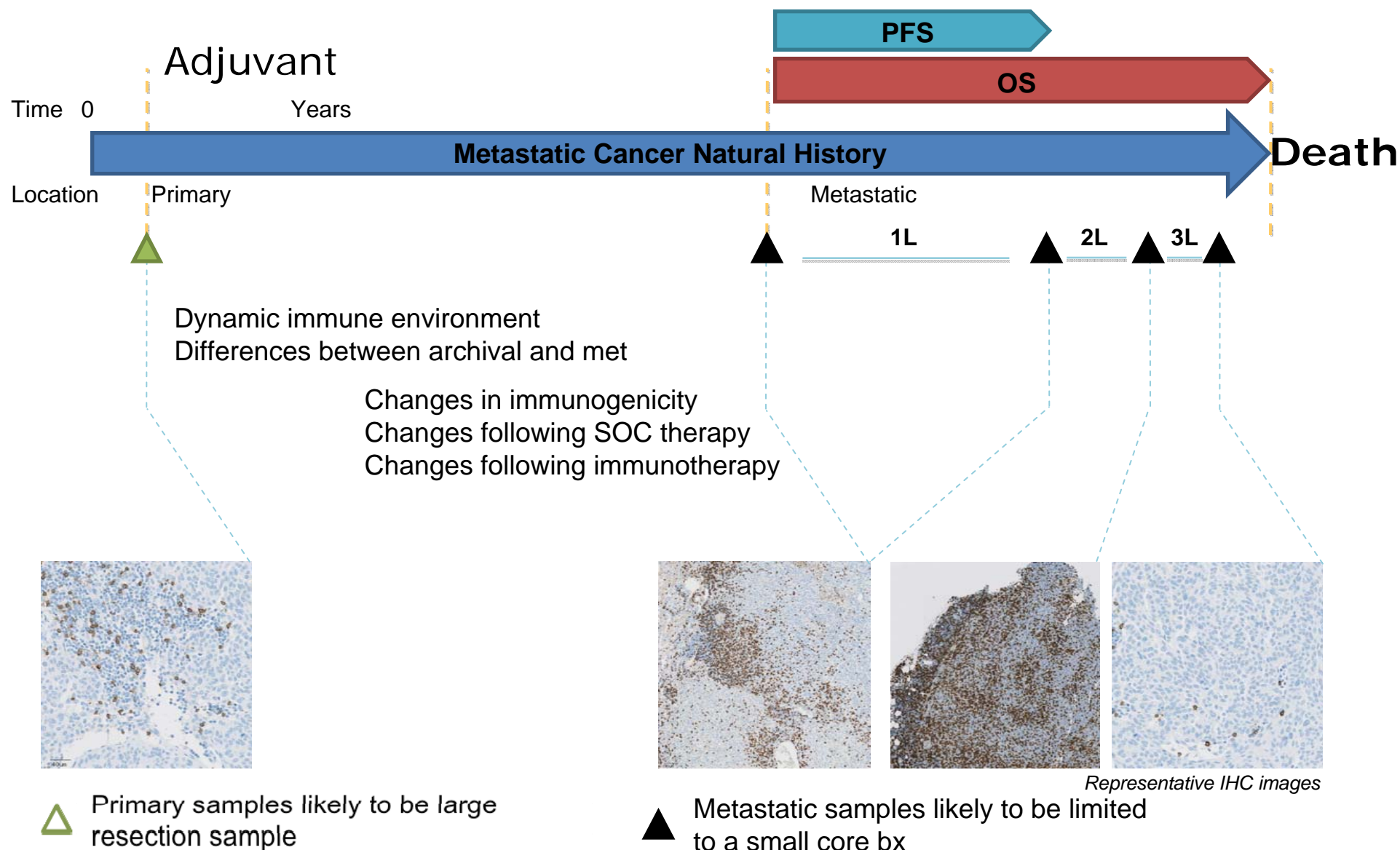


Gattinoni et al 2011

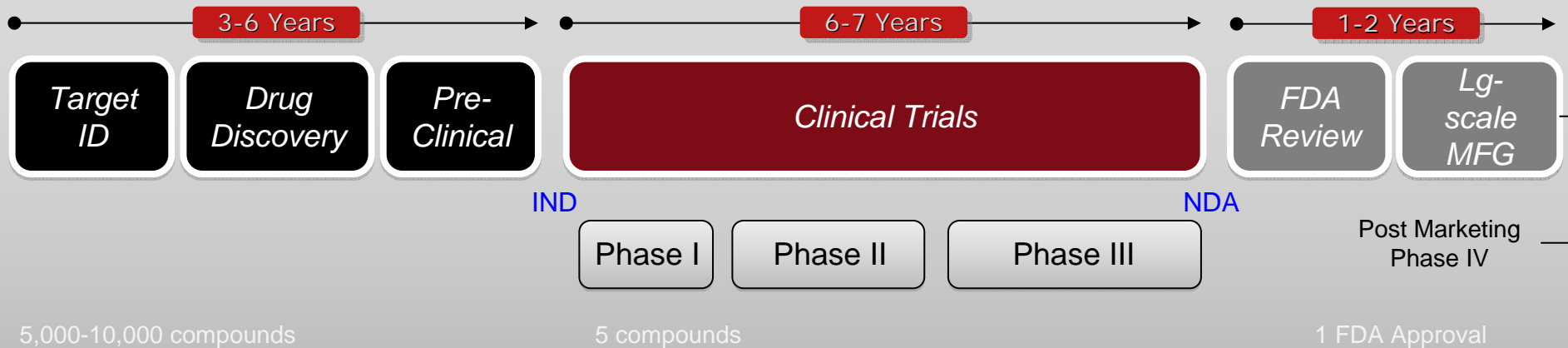
- Obvious advantages to being able to easily assess a dynamic immune related biology
- Challenge related to whether tumor biology is adequately reflected in blood
- Use of imaging as a biomarker for immunotherapy will likely require additional technology development

Biomarkers: Tumor Tissue

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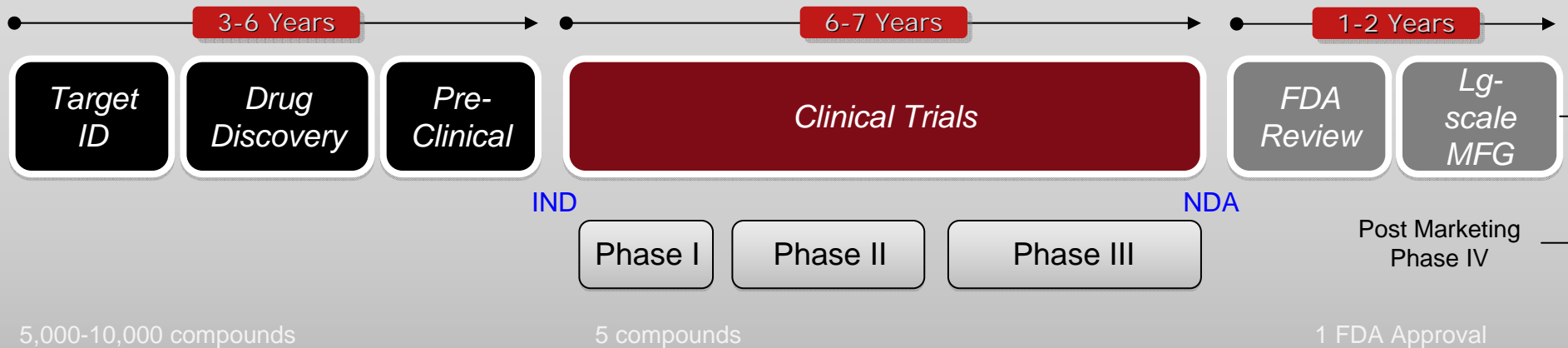
1NME Drug Development



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

- Biologic plausibility
- Pre-clinical activity
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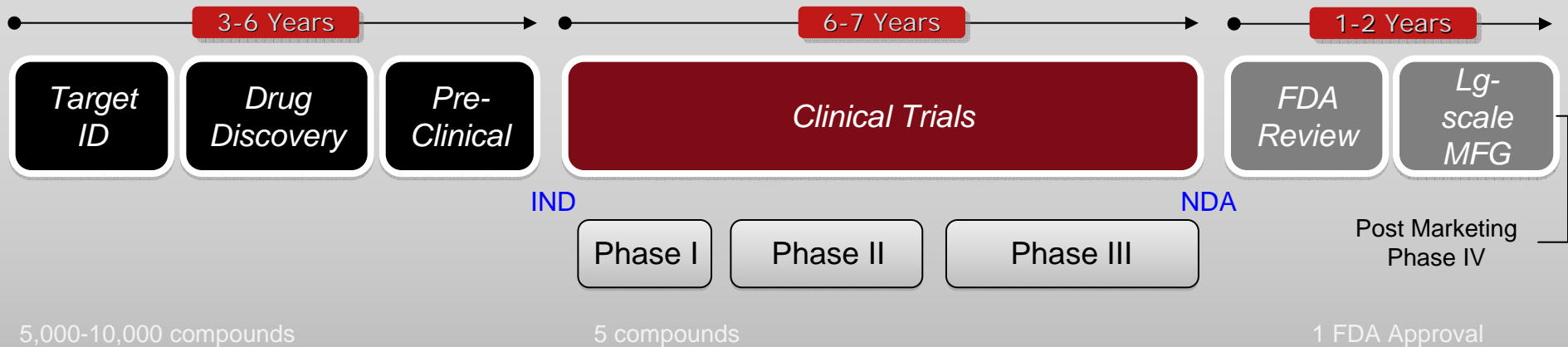
2NME Drug Development



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