Early Development of Immuno-oncology Drugs – Novel Targets, Technology Platforms, and Trial Designs

The 4th International Conference on Phase 1 and Early Phase Clinical Trials

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Oncology Early Development

Merck Sharp & Dohme Corp., NJ USA

MSD

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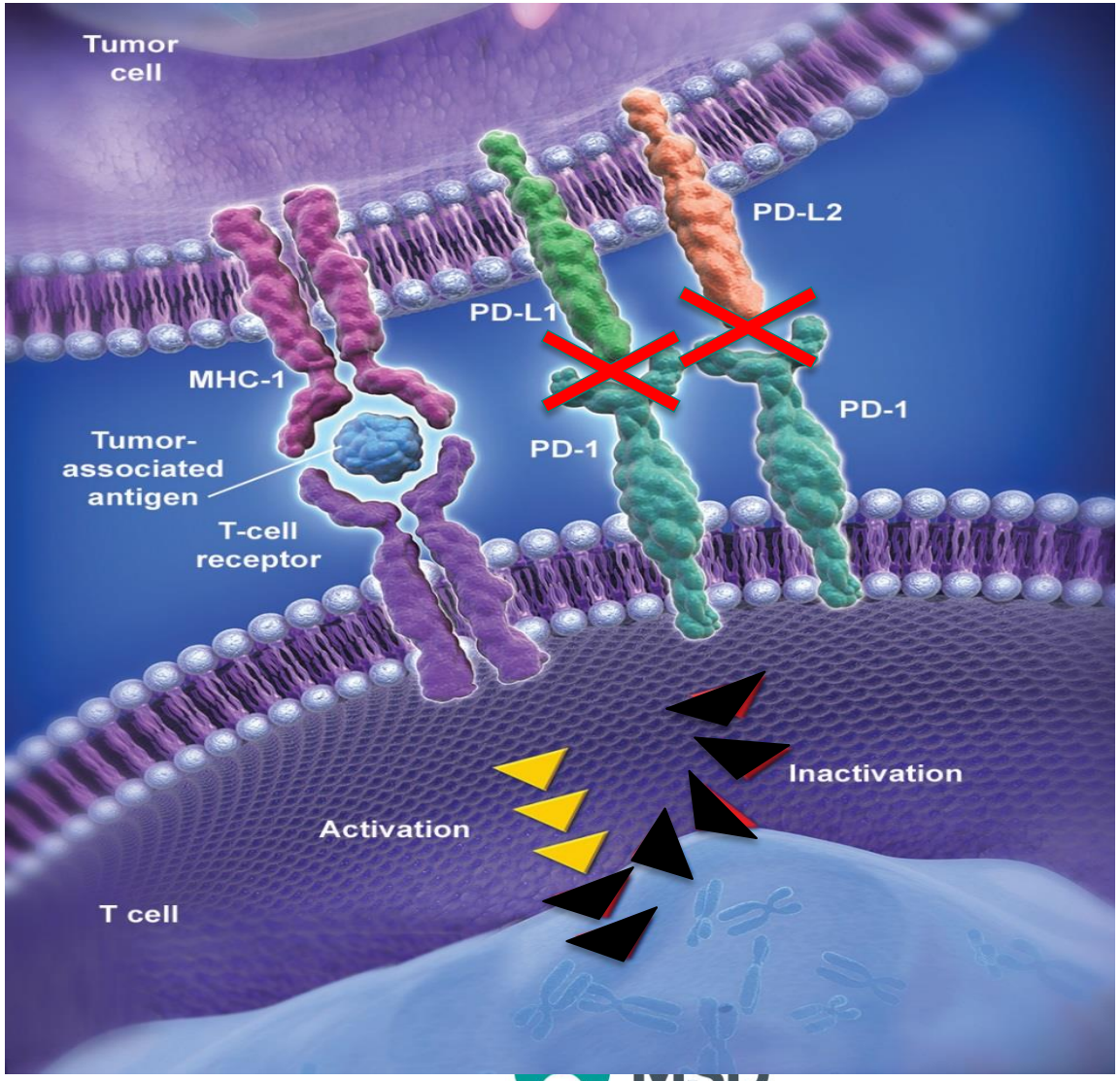
March 2 2018

Disclosure

- Full-time employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, N.J., U.S.A
- Own company stock

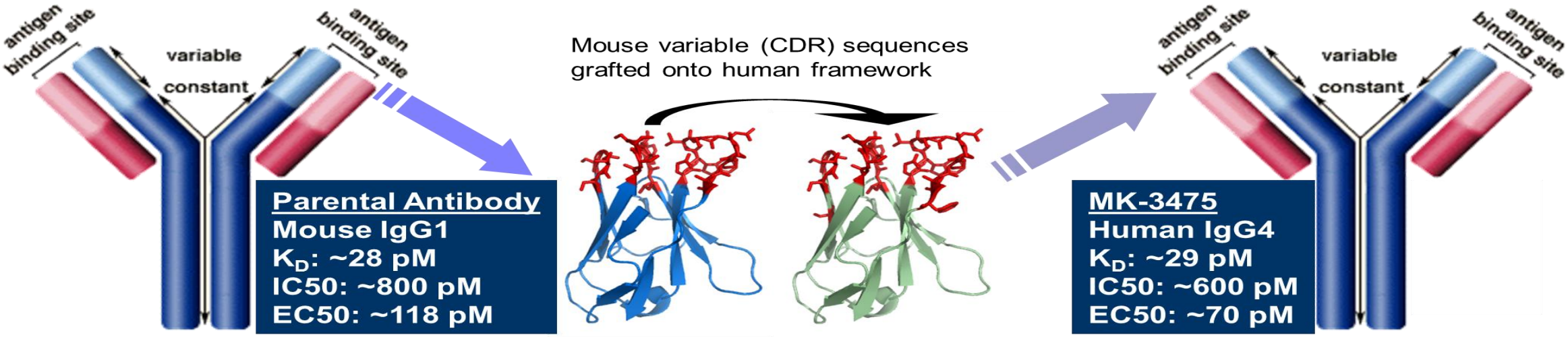
PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore and reveal effective anti-tumor immunity



Topalian et al. *N Engl J Med*. 2012.
Garon et al. *N Engl J Med*. 2015.
Robert et al. *Lancet.* 2014.

Pembrolizumab is a Humanized IgG4, High-Affinity Anti-PD-1 Blocking Antibody

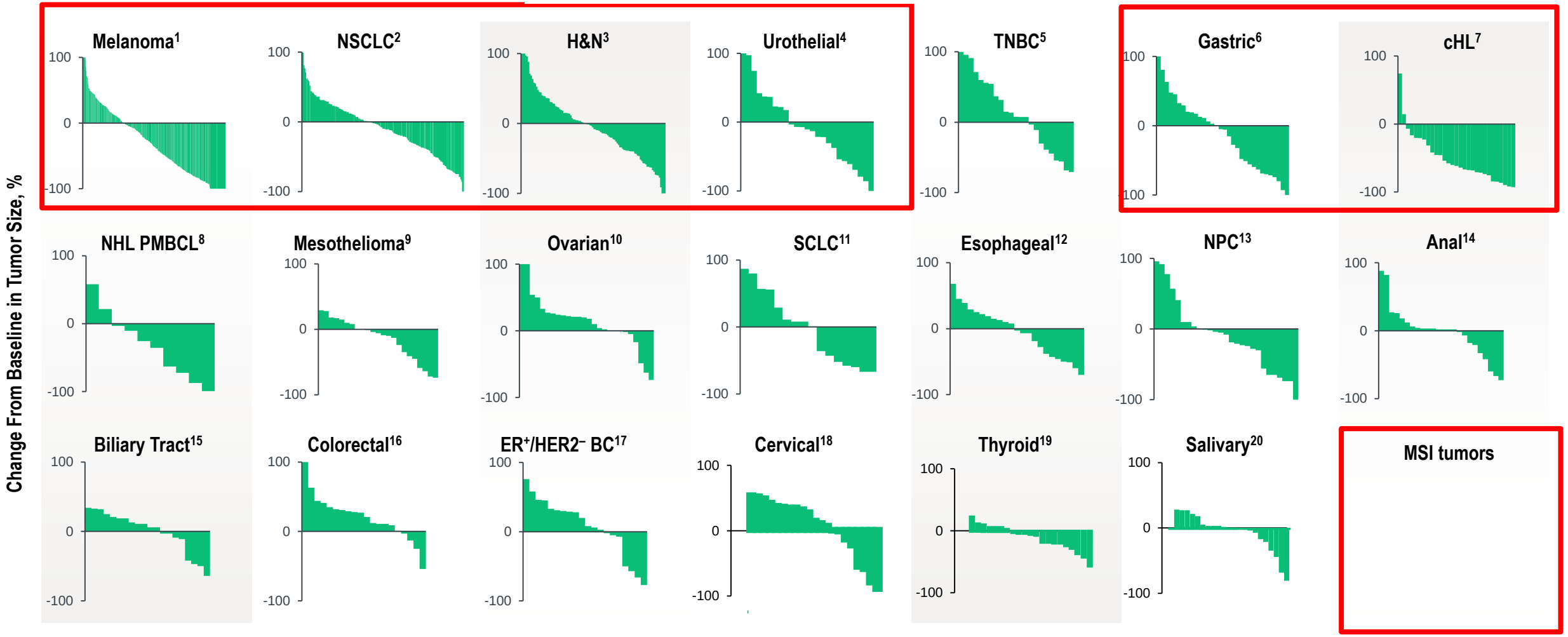


- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics supportive of dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics

Presented by: Antoni Ribas ASCO 2013

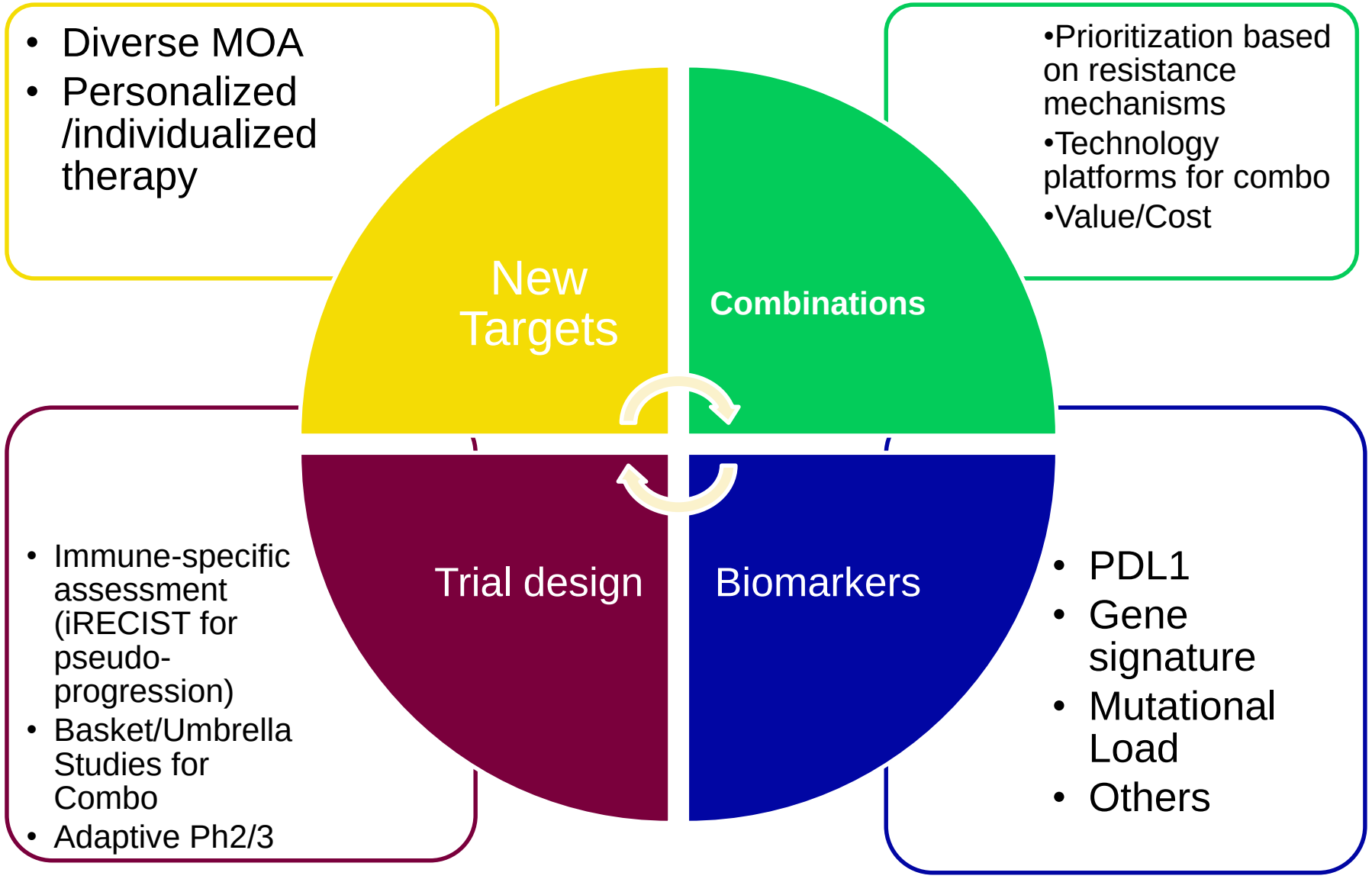
Anti-PD1 has become a Cornerstone of Cancer Treatment – KEYTRUDA monotherapy is active in multiple tumor types

Tumor types with approved indication(s)



1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. O'Neil B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015;
nel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016.

Key Research Questions for Next Steps



MSD Early Immuno-Oncology Pipeline

Immune Agonists	GITR (MK-4166)	GITR (MK-1248)
	STING (MK-1454)	
Negative Immune Regulators	IL-10 (MK-1966)	IDO (MK-7162)
	TIGIT (MK-7684)	A2a (MK-3814A)
	LAG-3 (MK-4280)	Multi-specific Nanobodies
	CTLA4 (MK-1308)	Other checkpoint inhibitors
		IDO &/ TDO
Personalized Cancer Vaccines	mRNA-4157 (V-940)	
Tumor Microenvironment	CDK 1,2,5,9 (MK-7965)	ERK (MK-8353)

Clinical Programs

Preclinical Programs

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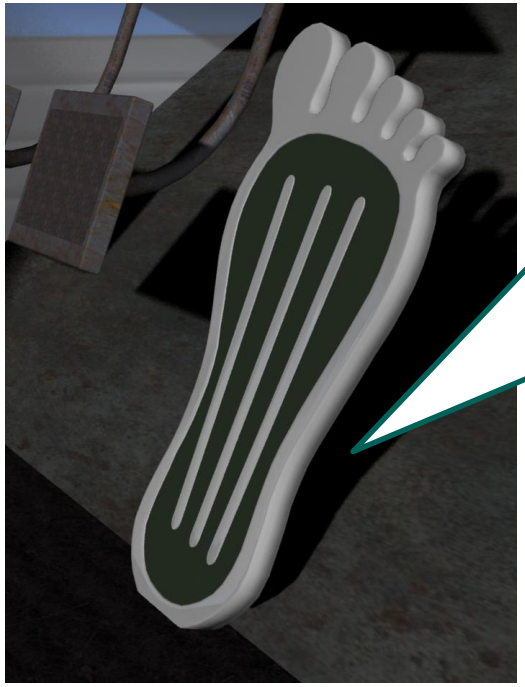
Mechanisms and Strategies Driving Cancer Immunotherapy

Negative immune regulators e.g. PD1, LAG3

Cancer vaccines

Immune agonists e.g. STING



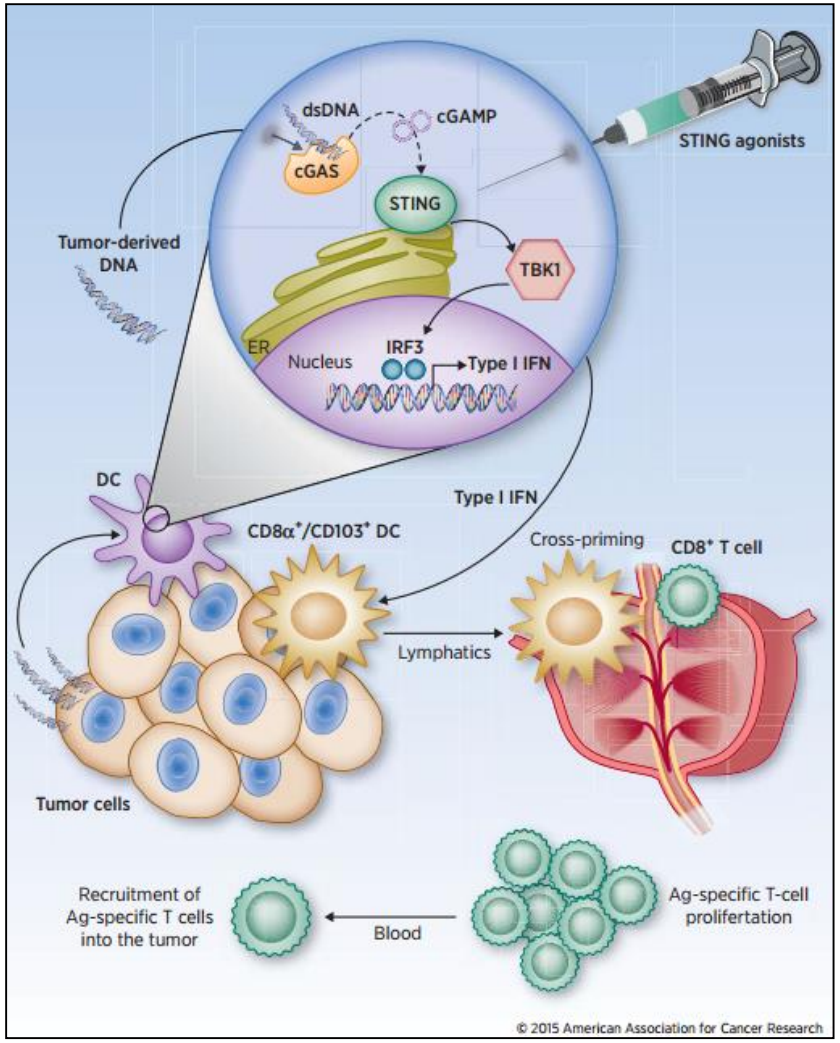
- Predictive biomarkers
- Combinations
- Personalized drug product

Personalized

In Situ Vaccination via STING (Stimulator of Interferon Genes)

Rationale For A STING Agonist In Tumor Immunotherapy

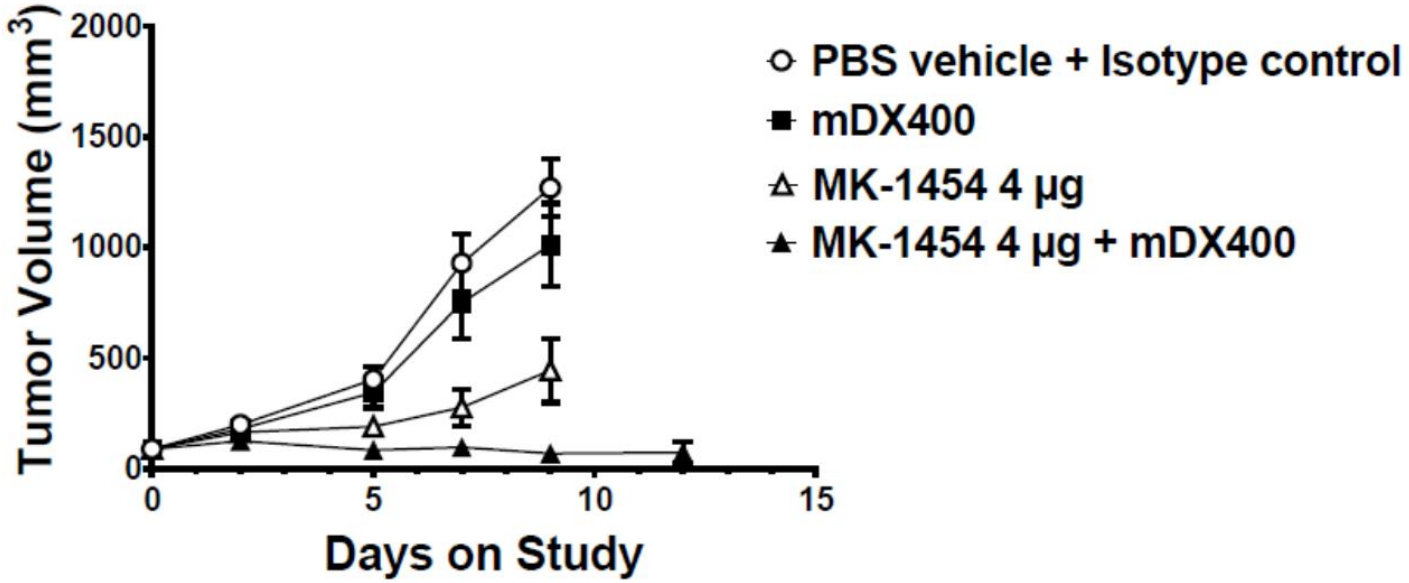
- cGAS/STING pathway is the central innate immune sensor that responds to viral or self dsDNA and bacterial cyclic dinucleotides (CDNs) in the cytosol
- STING activation leads to type-I interferons & pro-inflammatory cytokine (IFN-β, IL-6, TNF-α) release
- IFN-β induced upon intra-tumoral (IT) injections of STING agonists leads to activation of cross-presenting CD8a^{+}, CD103^{+} dendritic cells (DCs)
- CD8^{+} T cell cross-priming propagates antigen-specific T cell proliferation and recruitment of T cells into the tumor
- Efficacy in non-injected lesions is obtained in an abscopal manner



http://clincancerres.aacrjournals.org/content/early/2015/09/15/1078-0432.CCR-15-1362.full.pdf+html

MK-1454 Efficacy In Mouse Tumor Models Resistant To Anti-PD-1 Treatment ('B16F10 Model')

- MK-1454 intratumoral treatment, as a single agent, induced robust anti-tumor immunity and complete responses in multiple syngeneic mouse models (MC38, CT26, B16F10)
- Efficacy observed in bilateral tumor models (CT26 and MC38) but questionable if efficacy is due to true abscopal effect vs. drug exposure in non-injected tumors

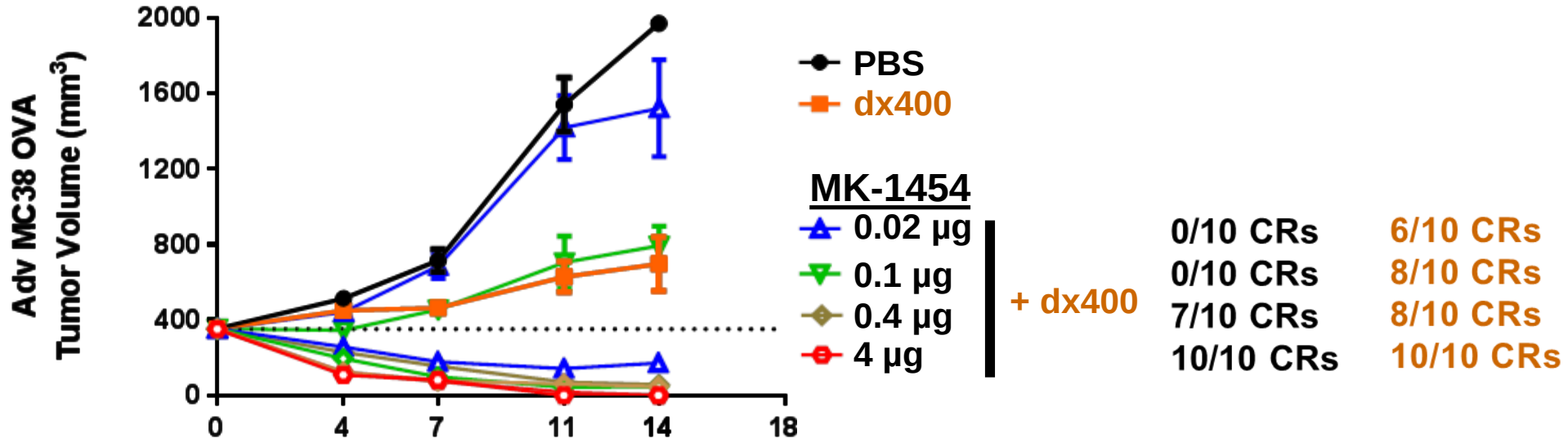


- Improved anti-tumor efficacy in the B16F10 model is achieved when combining anti-PD-1 with a sub-efficacious, intratumoral dose of MK-1454

Cemerski et al. SITC 2017

MK-1454 Efficacy In Mouse Tumor Models Resistant To Anti-PD-1 Treatment ('Large MC38 Model')

- MC38 mouse syngeneic tumor model: Benchmark tumor model that fully responds to anti-PD-1 therapy (9-10/10 CRs) if treatment starts when tumors are ~100 mm^3
- If treatment is delayed to when tumors are > 350 mm^3, anti-PD-1 is only partially efficacious (rare CRs)

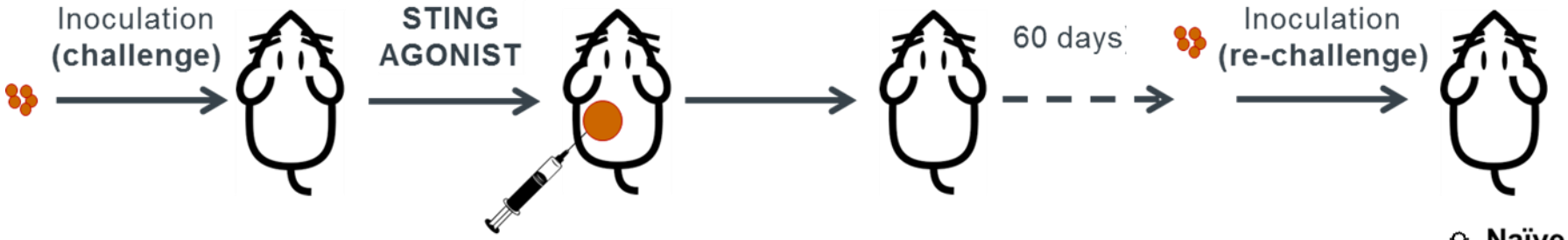


- PD-1 blockade does not induce complete tumor regression in mice with advanced syngeneic tumors
- MK-1454 induces complete tumor eradication of the advanced MC38 mouse syngeneic tumor
- STING agonism in combo with PD-1 blockade provides a 20-fold increase in anti-tumor responses

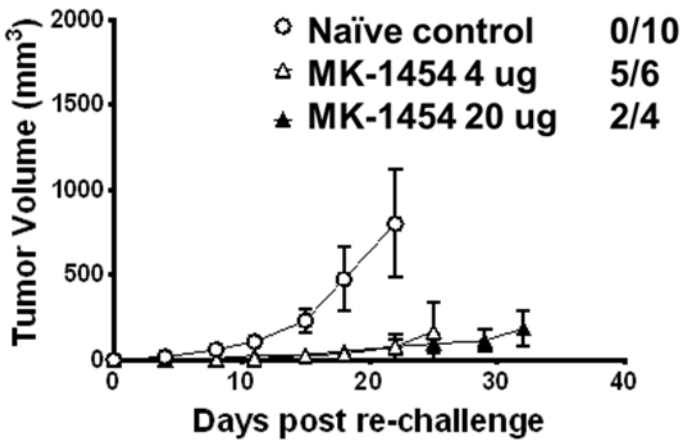
Cemerski et al. SITC 2017

MK-1454 Treatment Induces Long-Lasting Anti-tumor Immune Memory

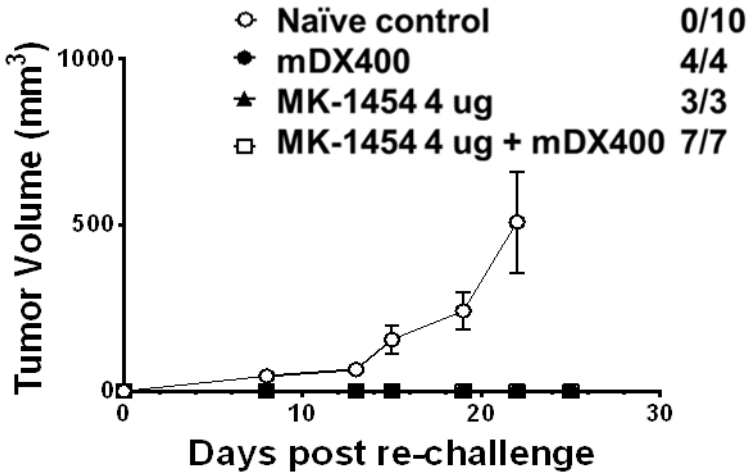
- 'Re-challenge' studies were performed to asses the ability of **MK-1454**, alone or in combination with anti-PD-1, to induce durable anti-tumor responses



Small MC38-model
Complete regression induced by MK-1454



Large MC38-model
Complete regression induced by MK-1454 +/- anti-PD-1



- Re-challenge protection is observed in mice that developed complete responses upon either **MK-1454** single agent treatment or **MK-1454** combo with anti-PD-1

Public Oncology

Cemerski et al. SITC 2017

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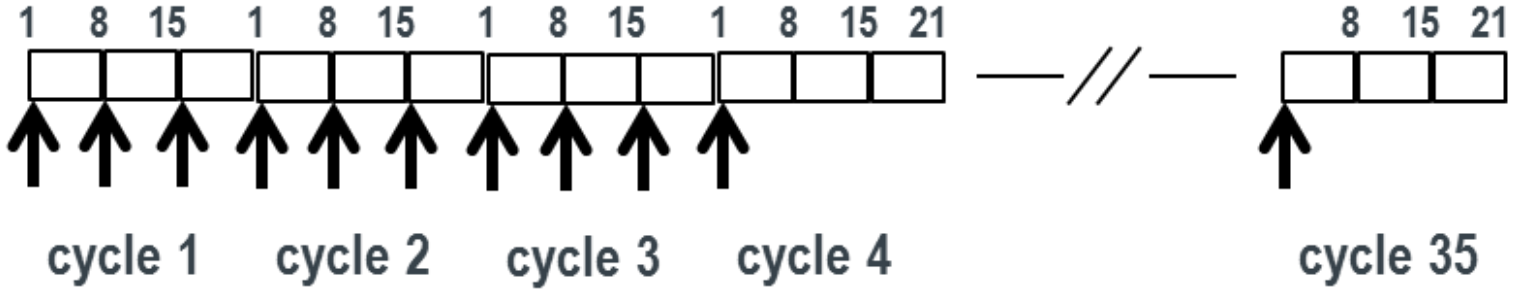
MK-1454-001 (NCT03010176 FIH Study)

Phase 1 Open Label, Multicenter Study of MK-1454 Administered by Intratumoral Injection as Monotherapy and in Combination with Pembrolizumab for Patients with Advanced/Metastatic Solid Tumors or Lymphomas

- At least one measurable lesion which is amenable to injection via visual inspection for a cutaneous lesion or via ultrasound guidance for a subcutaneous lesion
- Has ≥1 injectable lesion which is amenable to injection and biopsy and is measurable
- Has ≥1 distant, discrete non-injected lesion which is amenable to biopsy and is measurable

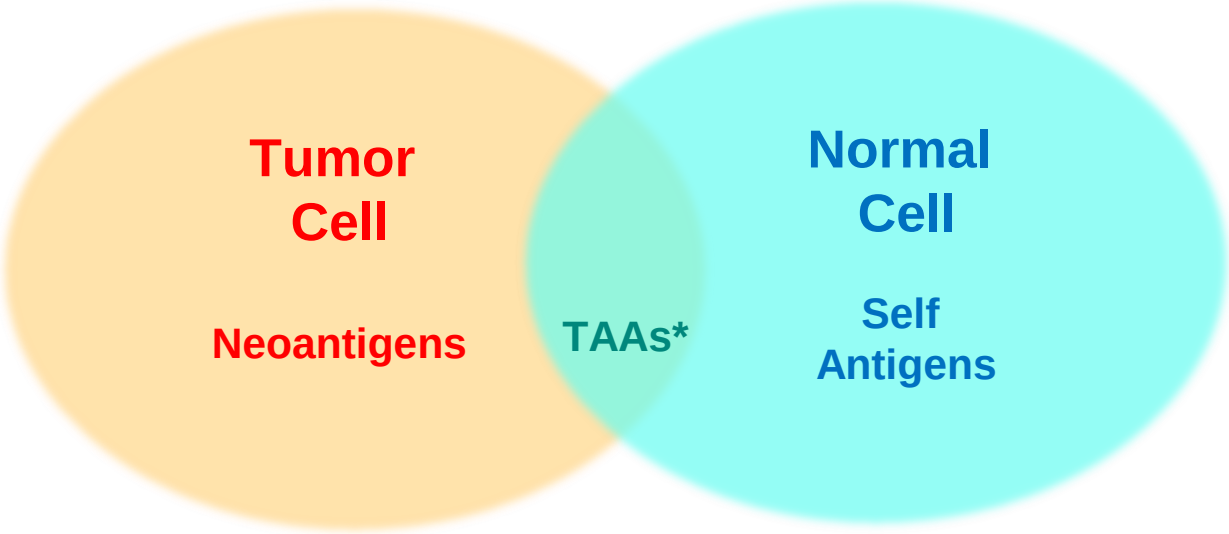


Personalized Cancer Vaccine (mRNA-4157/V-940)

Personalized Cancer Vaccines: Biology Background and Early Clinical Success

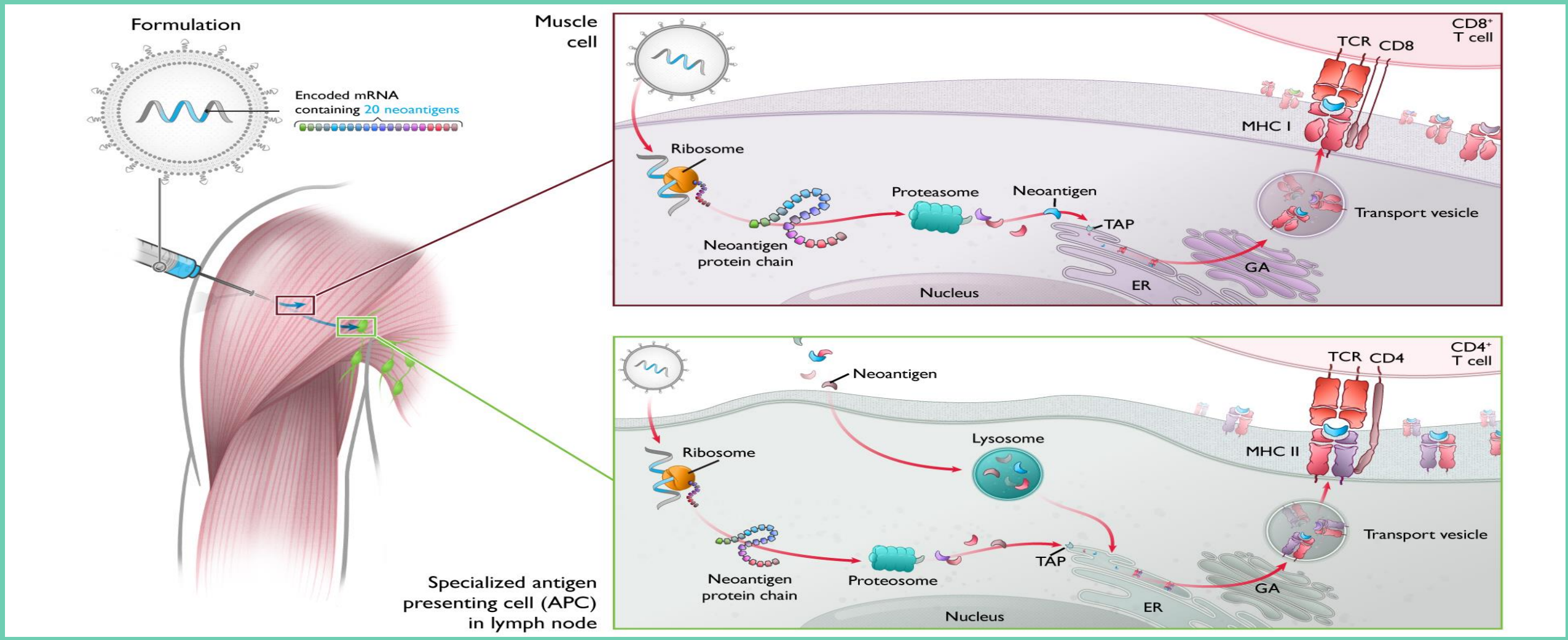
- **Whole Exome Sequencing (WES) has allowed for the identification of neoantigens/tumor specific antigens (TSA) which are mutated proteins expressed due to somatic mutations, posttranslational modifications, or oncogenic viral proteins.**
- **Tumor infiltrating lymphocytes (TIL) expanded *ex vivo* contain neoepitope-reactive CD8+ and CD4+ T-cells** *Rosenberg SA et al. Nat Med 2013; Wick DA Clin Can Res 2014; C Wu et al. Blood 2014; Schumacher TN Nat Med 2014; Rosenberg SA et al. Science 2014; Cohen et al, 2015;* Friedman KM et al *J. Immunol.* 2012; Quezada SA *et al. J. Exp. Med.* 2010; Dudley ME, *et al. Clin. Cancer Res* 2010.
- **High neoepitope burden is associated with response to PD-1 checkpoint blockade** *Rizvi et al. Science, 2015*
- **mRNA and peptide-based PCVs encoding multiple neoantigens (10-20) have been tested in the clinic and appear to be safe and well-tolerated** *Sahin et al, Nature, 2017, Ott et al, Nature 2017*

- **PCVs have been demonstrated to generate T cell responses against ~60% of neoantigens encoded in their vaccines and the responses discriminated between the mutant and the wild-type (self) sequences** *Sahin et al, Nature, 2017, Ott et al, Nature 2017*
- **PCVs have demonstrated early signs of clinical activity in melanoma** *Sahin et al, Nature, 2017, Ott et al, Nature 2017*



*TAAs= tumor associated antigens

Mechanism of Action of an mRNA-Based PCV



Courtesy of Moderna

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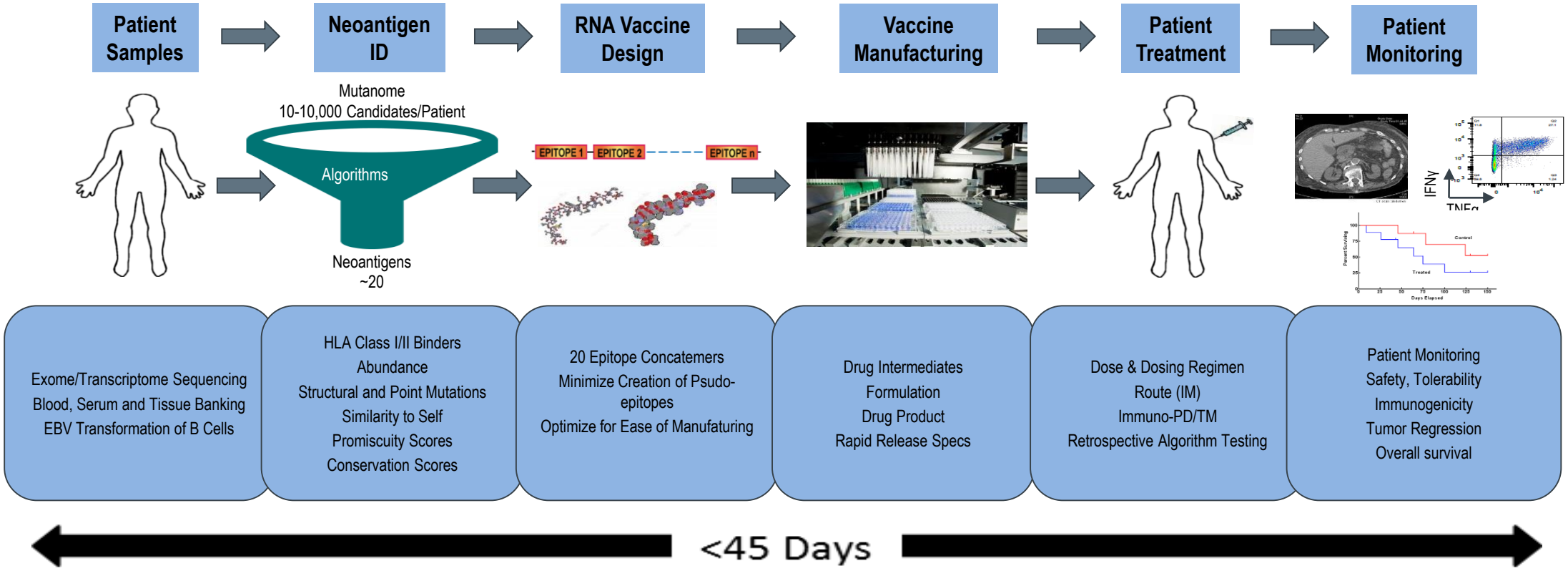
Moderna's Personalized Cancer Vaccine Work Flow



Courtesy of Moderna

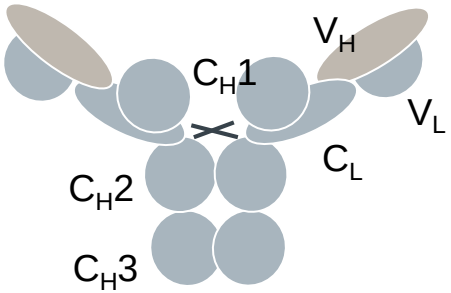
Ablynx Multi-specific Nanobody Platform

Ablynx - Nanobodies as Building blocks for Multi-specific Immuno-Oncology Therapeutics

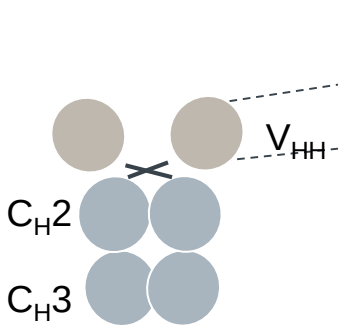
Nanobodies -- Derived from heavy-chain only antibodies

Camelid heavy-chain only antibodies are stable and fully functional

Nanobodies represent the next generation of antibody-derived biologics



Conventional antibodies



Heavy chain only antibodies

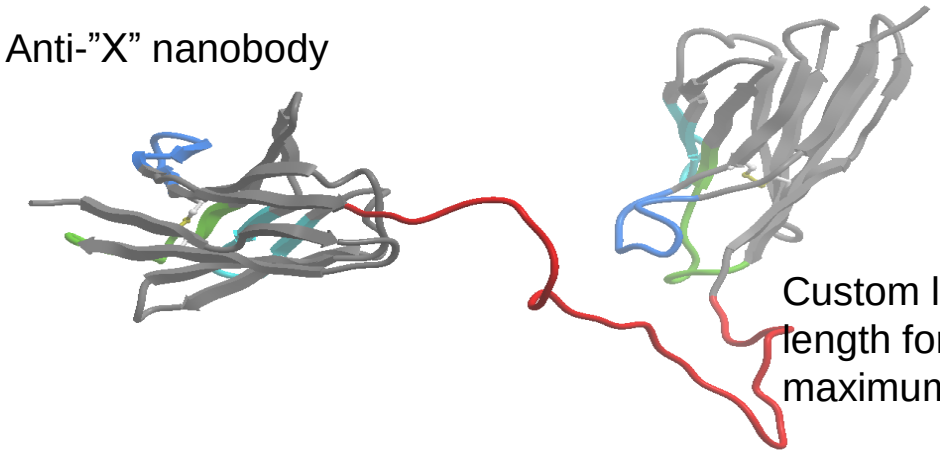
V_{HH} 12-15kDa

Ablynx's Nanobody

- small and robust
- easily linked together
- sequence homology comparable to humanised/human mAbs
- nano- to picomolar affinities
- challenging and intractable targets
- multiple administration routes
- manufacturing in microbial cells

Anti-"Y" nanobody

Anti-"X" nanobody



Individual binding arms with tailored affinity

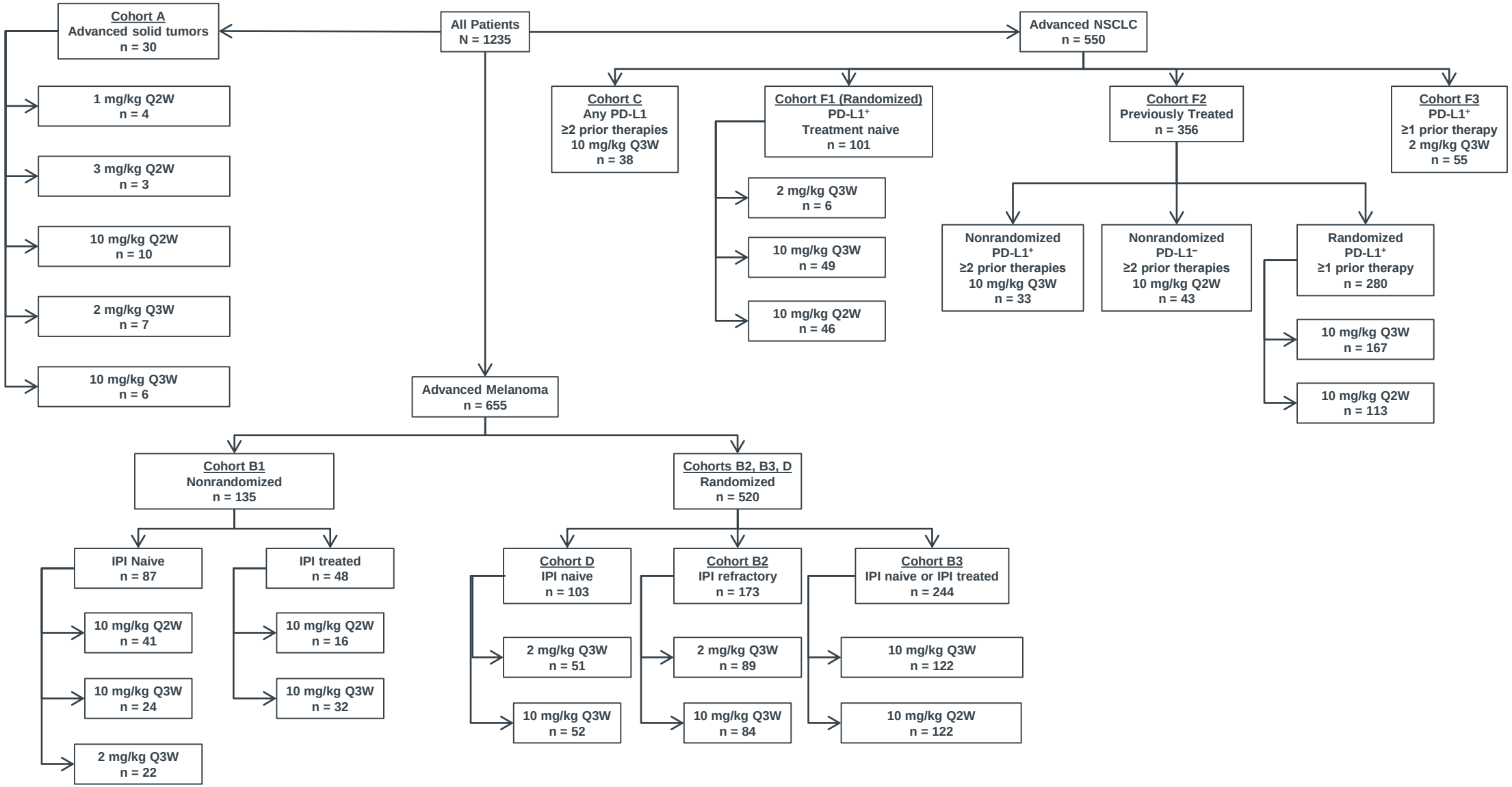
Custom linker length for maximum efficacy

Trial Design

I/O Early Development Challenges – Some Examples

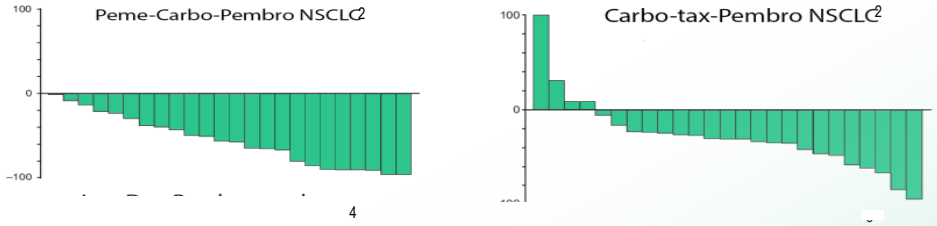
- Ph2 are routinely skipped nowadays
- Dose-finding vs speedy signal-finding in early development
- Platform Design
  - Basket
  - Umbrella

Keynote 001 – Adaptive FIH Approach

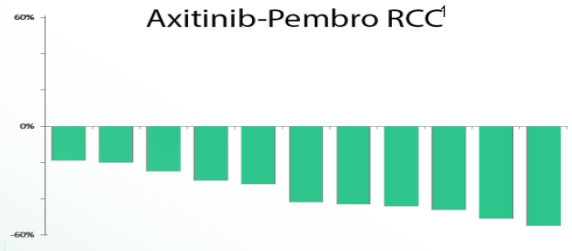


KEYTRUDA-Based Combinations Show Potential for Enhanced Activity In Many Tumor Types

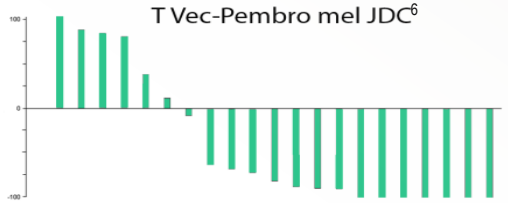
Standard Therapies



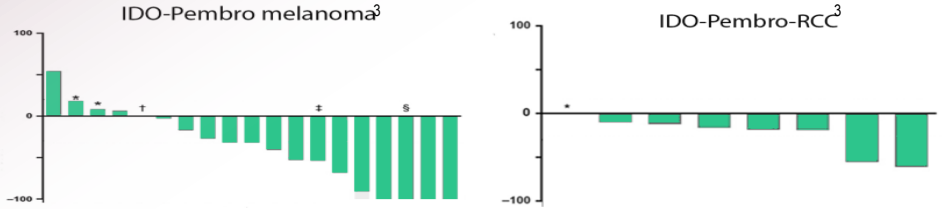
Targeted Therapies



Combination Strategy



Novel Vaccines



Immuno-modulators

1. Data on file; 2. Papadimitrakopoulou V et al. ASCO 2015; 3. Gangadhar T et al. SITC 2015; 4. San Miguel L et al. ASH 2015.
5. Badros A et al. ASH 2015; 6. Long GV et al. SMR 2015.

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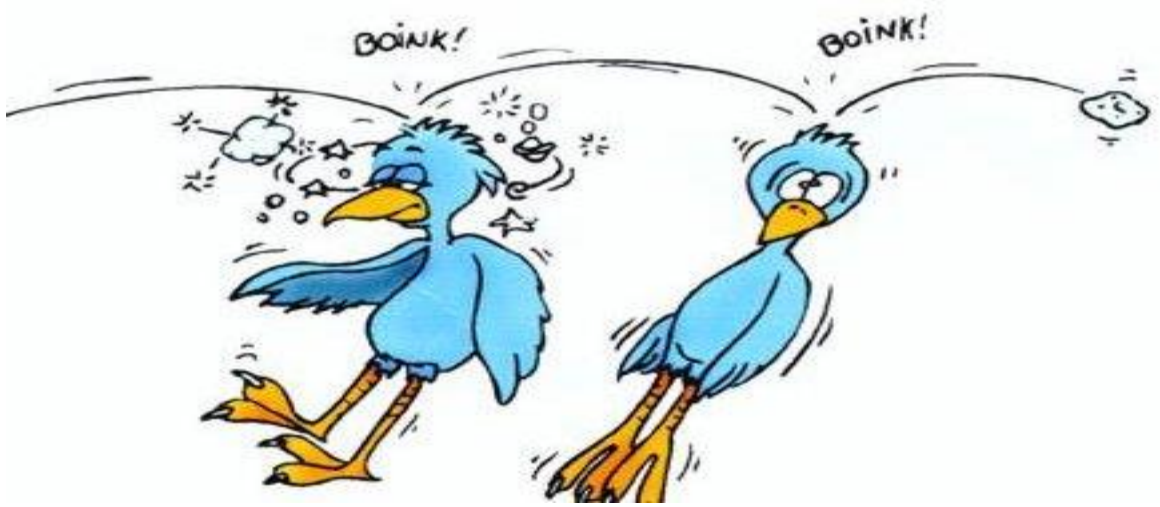
Two Birds, One Stone

A 2-in-1 adaptive phase 2/3 design for expedited oncology drug development☆

Cong Chen[a,*], Keaven Anderson[a], Devan V. Mehrotra[a], Eric H. Rubin[b], Archie Tse[b]

Contemporary Clinical Trials 2017



Two Phase 2/3 Design Strategies

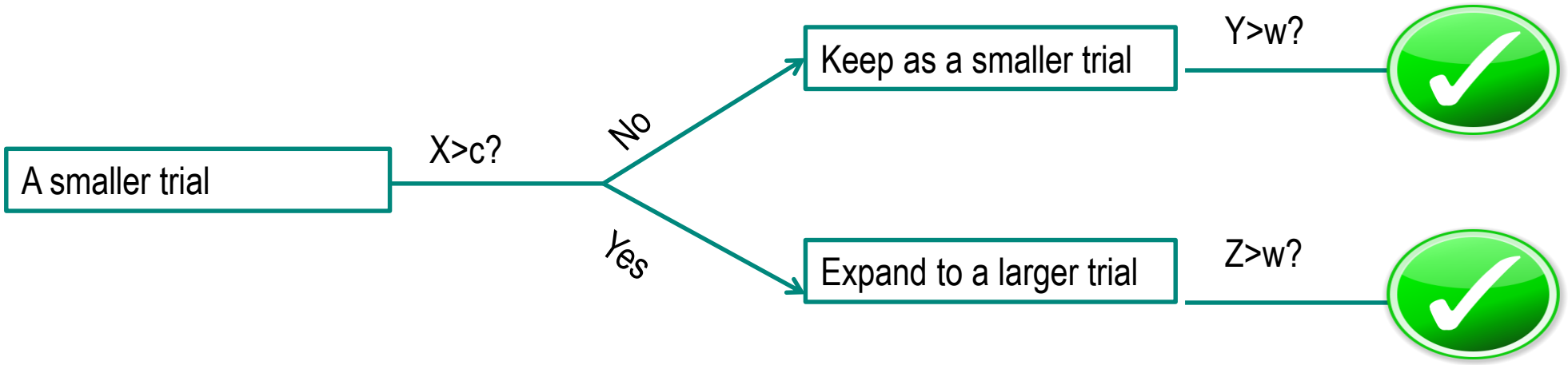
Phase 1 **Phase 2 PoC** Phase 3

Classical

Adaptive/Seamless

Population for final analysis

A General “2-in-1” Design



The three endpoints that the standardized test statistics are based upon can be different from each other

No penalty needs to be paid for multiplicity control as long as the correlations for the 3 test statistics satisfy $\rho_{XY} \geq \rho_{XZ}$

- i.e., w=1.96 to keep overall Type I error at 0.025 (1-sided)

Chen C, Anderson K, Mehrotra DV, Tse A, and Rubin EH. A 2-in-1 adaptive Phase 2/3 design for expedited drug development. Under review for publication.

THANK YOU!