Next-generation immunotherapies for cancer

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MRL

The 3rd International Conference on Phase 1 and Early Phase Clinical Trials

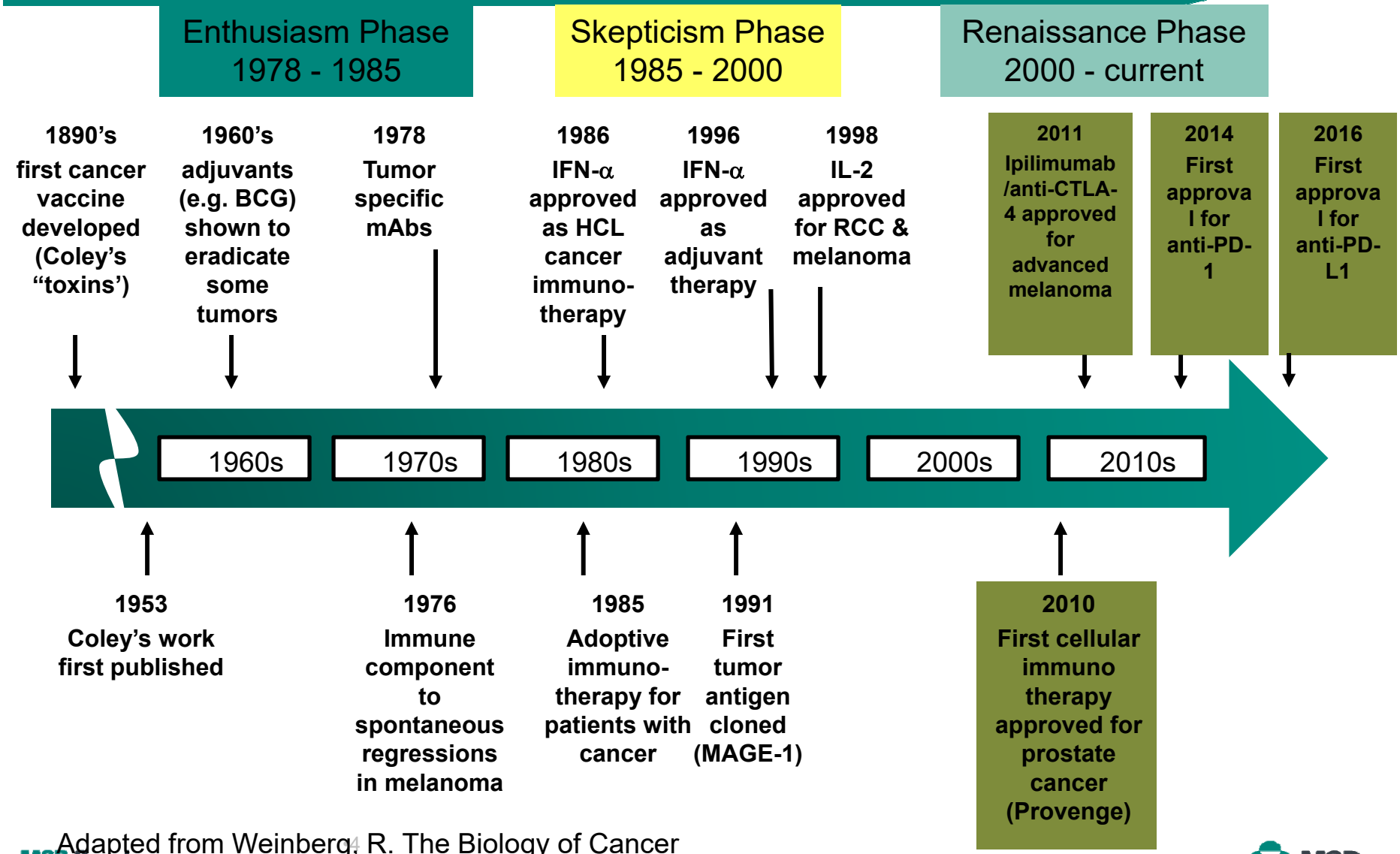
Disclosure

- Employee of MSD
- Own company stock

Case History

- May 2005 - 56 year-old Hispanic female diagnosed with Stage IV pancreatic ductal adenocarcinoma with multiple peritoneal metastases; KPS 70
- June 2005 - Palliative chemotherapy with single-agent gemcitabine
- Aug 2005 - Clinical and radiological disease progression requiring frequent paracentesis for symptomatic ascites
- Sept 2005 – Tenckhoff catheter placement for drainage of ascitic fluid
- Oct 2005 – Hospitalized for ***peritonitis*** with fever and abdominal pain; underwent removal of Tenckhoff catheter and antibiotic therapy; discharged to home-hospice
- Dec 2005 – F/U in clinic with improvement of ascites and performance status
  - ***CT scan showed shrinkage of peritoneal metastases!***
- April 2006 – Disease progression

Key Events in the History of Cancer Immunotherapy – Evolution from Anecdotes to Cornerstone



Adapted from Weinberg, R. The Biology of Cancer

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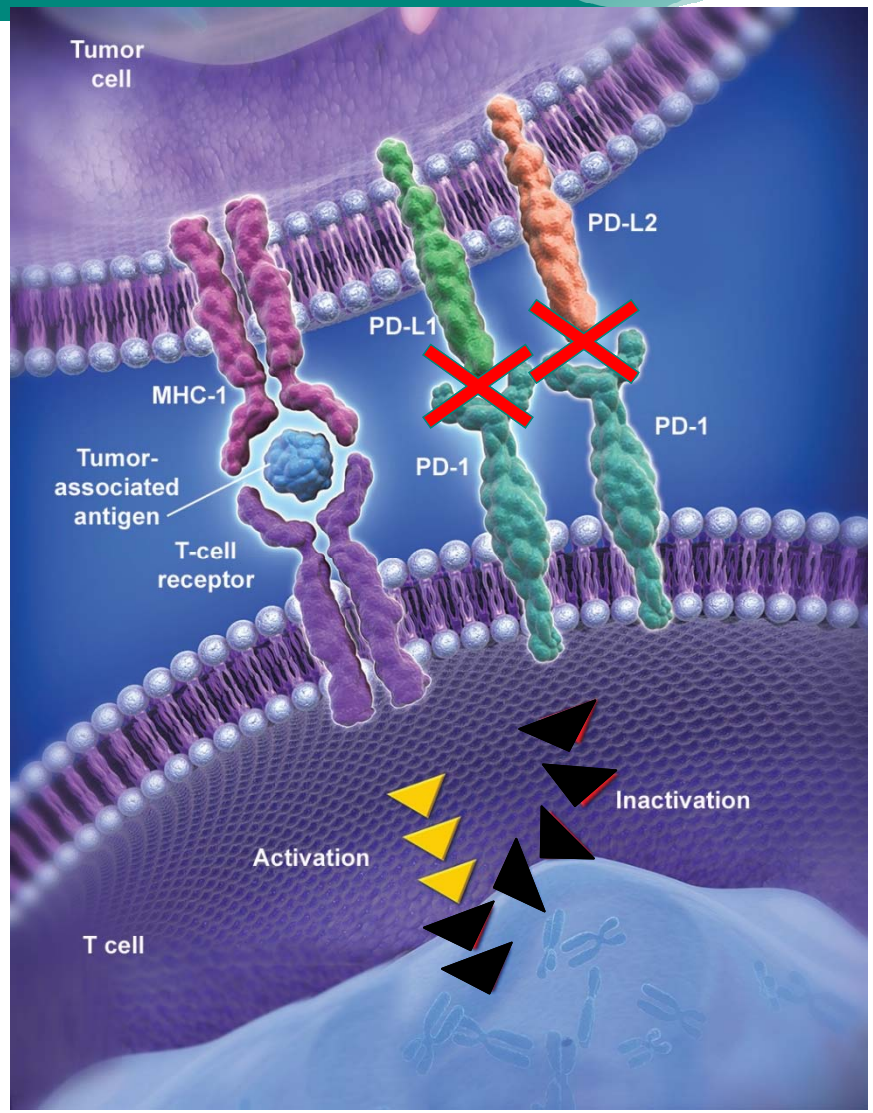
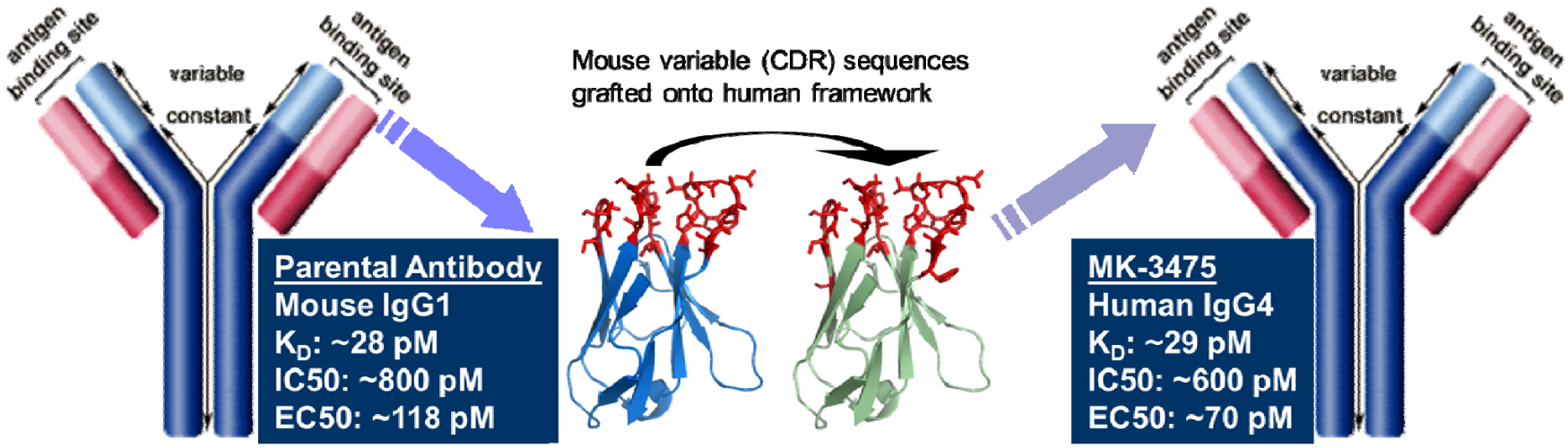
PD-1 and PD-L1/L2 Pathway

- 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.

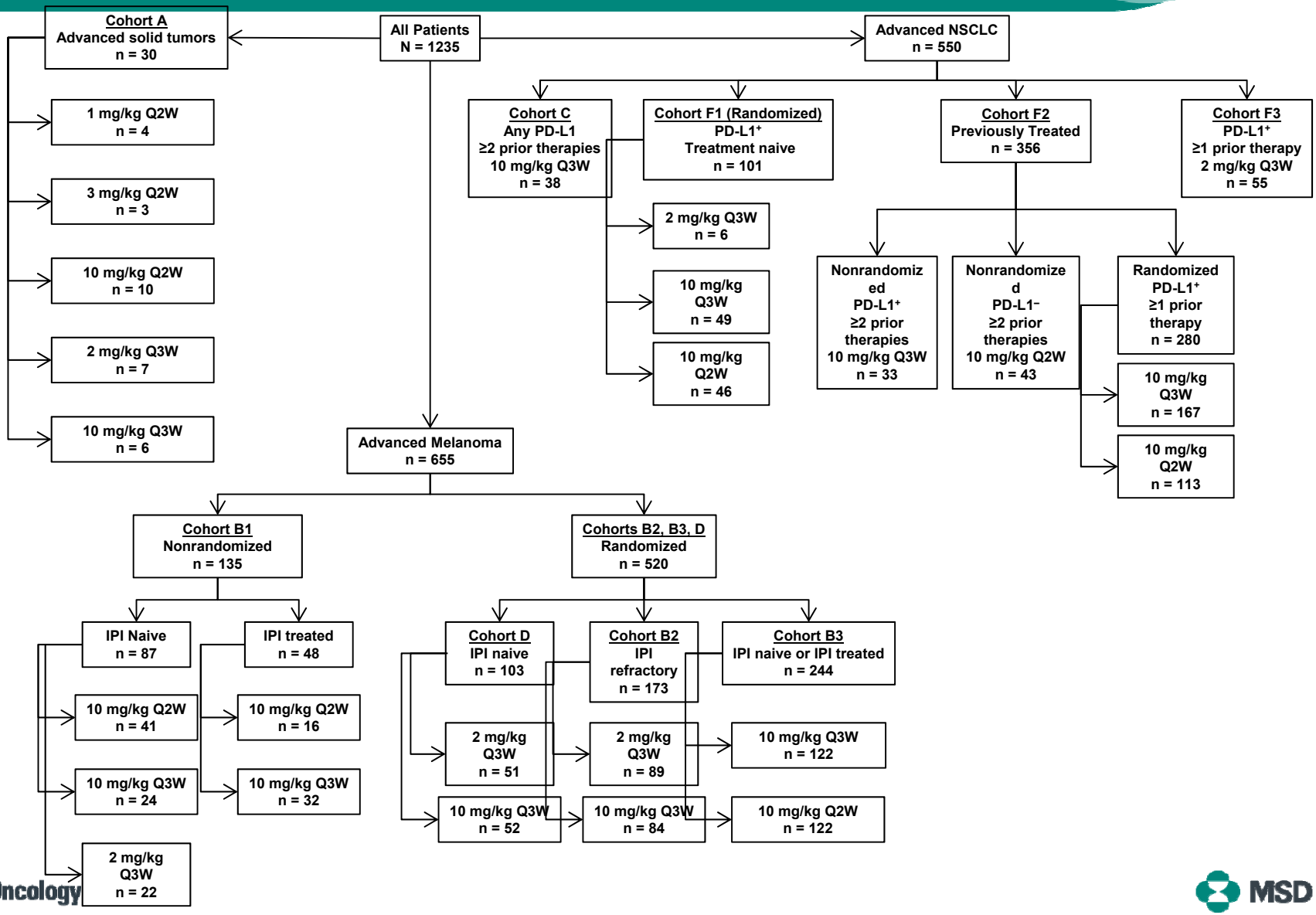
Pembrolizumab is a Humanized IgG4, High-Affinity Anti-PD-1 Blocking Antibody



- 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

Keynote 001 – Adaptive FIH Approach



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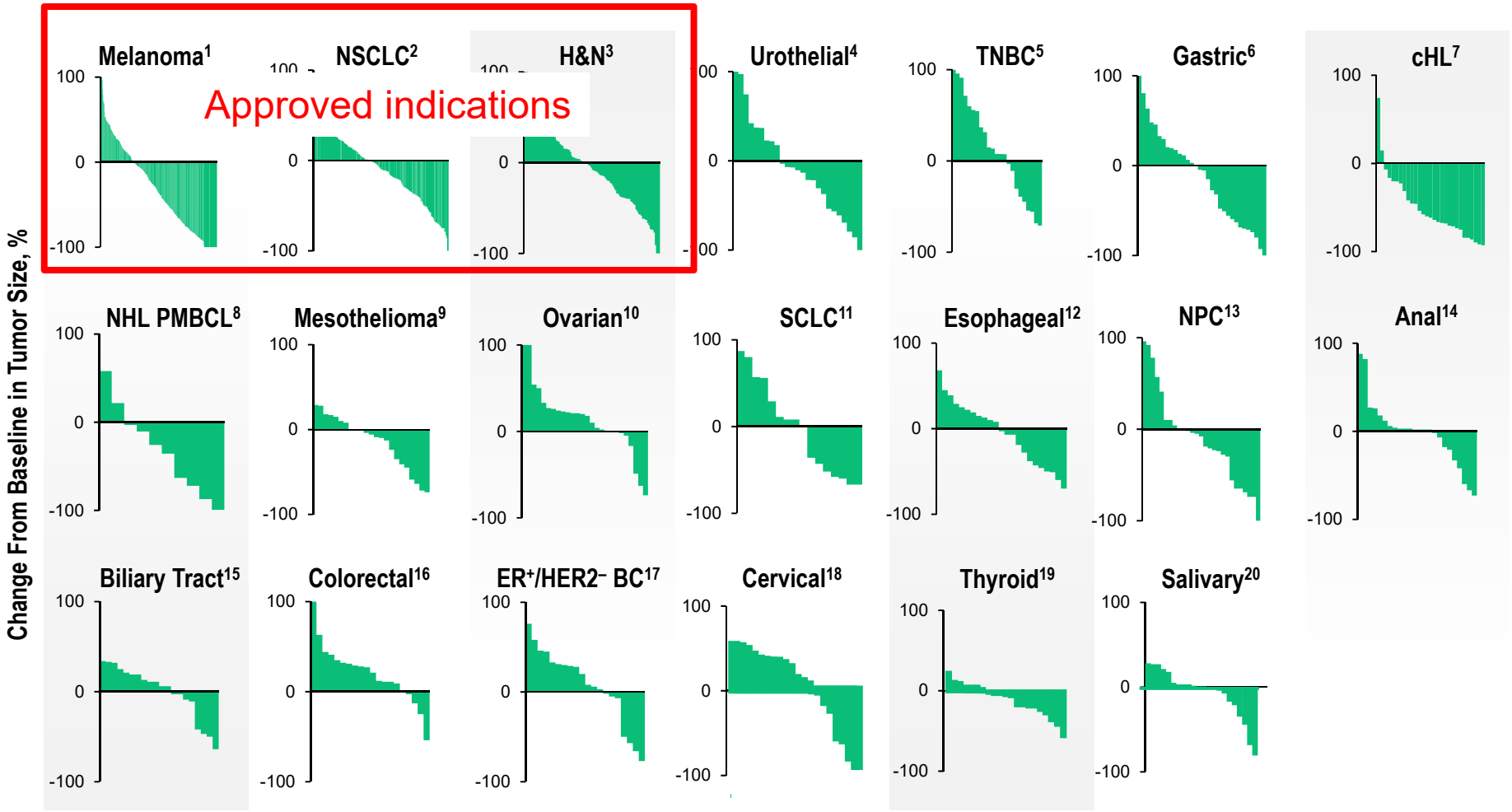
Keynote 001 Results

This adaptive “phase 1” study was the basis for 3 FDA approvals:

1. Accelerated approval for patients with ipi-refractory melanoma (first FDA approval of anti-PD-1 antibody)
2. Accelerated approval for patients with previously treated NSCLC with tumors that express PD-L1
3. Dako PD-L1 IHC 22C3 pharmDx test, the first FDA-approved test designed to detect PD-L1 expression in NSCLC

KEYTRUDA Monotherapy Active In Many Tumor Types



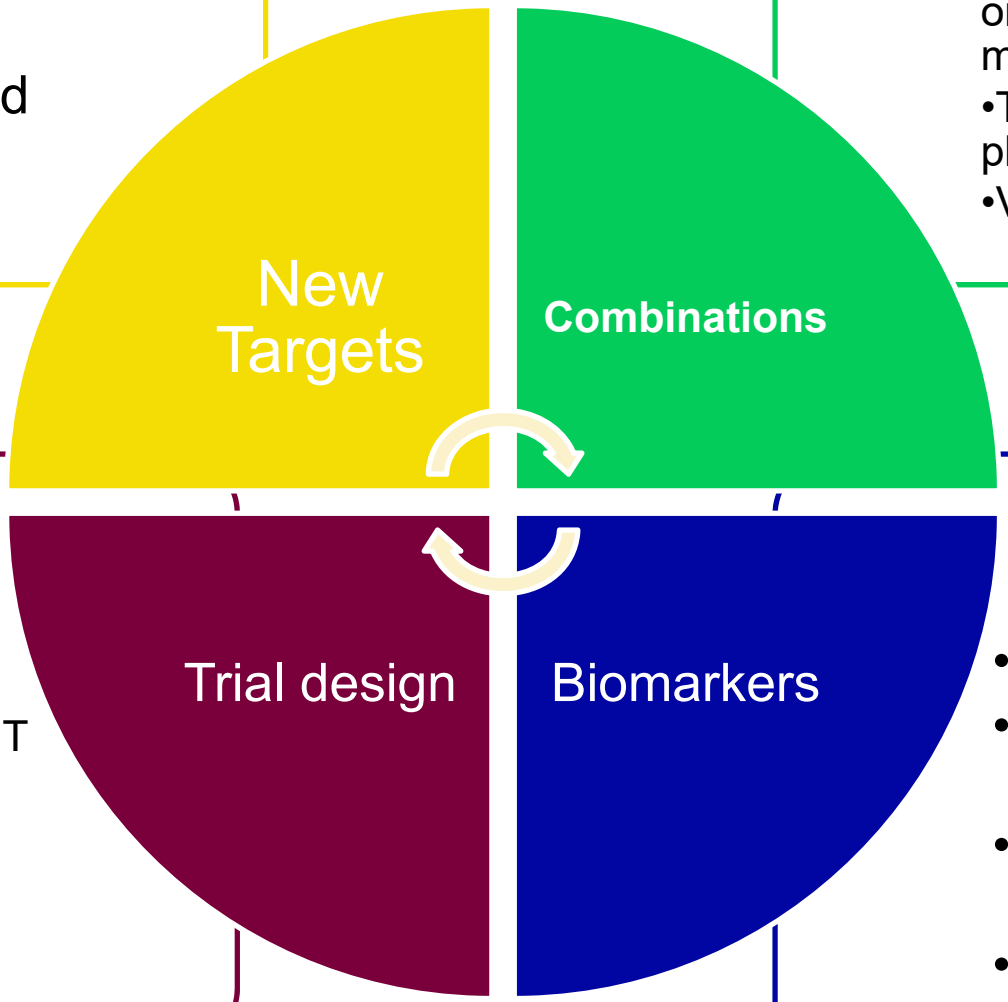
•1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 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; •18. Frenel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016.

Immunotherapy has Transformed Oncology - Myths that have been Debunked

- Immunotherapy only works for “immune-sensitive” cancers such as melanoma
- Immunotherapy works in a small percentage of patients but with accompanying severe toxicity
- Unlike chemotherapy, immunotherapy does not result in rapid and robust tumor shrinkage
- The tumor immune microenvironment is not important in determining the effectiveness of chemotherapy

Key Research Questions for Next Steps

- Diverse MOA
- Personalized /individualized therapy



- Prioritization based on resistance mechanisms
- Technology platforms for combo
- Value/Cost

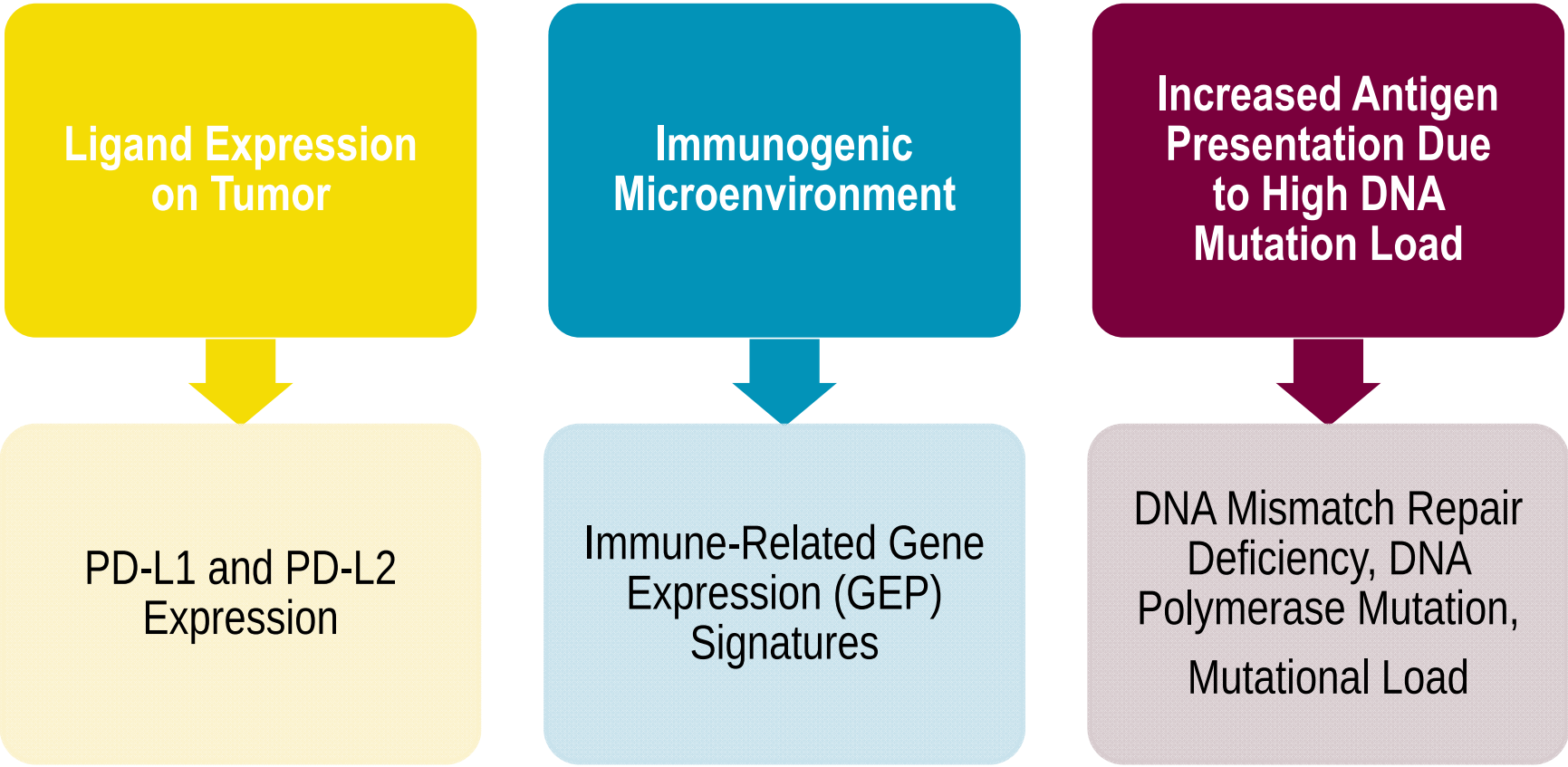
- Immune-specific assessment (modified RECIST for pseudo-progression)
- Novel combo design
- Disproportional hazard

- PDL1
- Gene signature
- Mutational Load
- Others

Using Predictive Biomarkers (Companion Diagnostics) to Select Patients for Treatment

- "No test is perfect, but some tests are useful"
  - Histology is an imperfect biomarker that is used to select cancer patients for treatment
  - Imperfect HER2 IHC test allowed rapid development of an effective treatment for breast cancer patients
  - Companion diagnostics may be used to select among treatment options, vs excluding patients from an immunotherapy treatment

Multiple Biomarkers Predict Response to Pembrolizumab

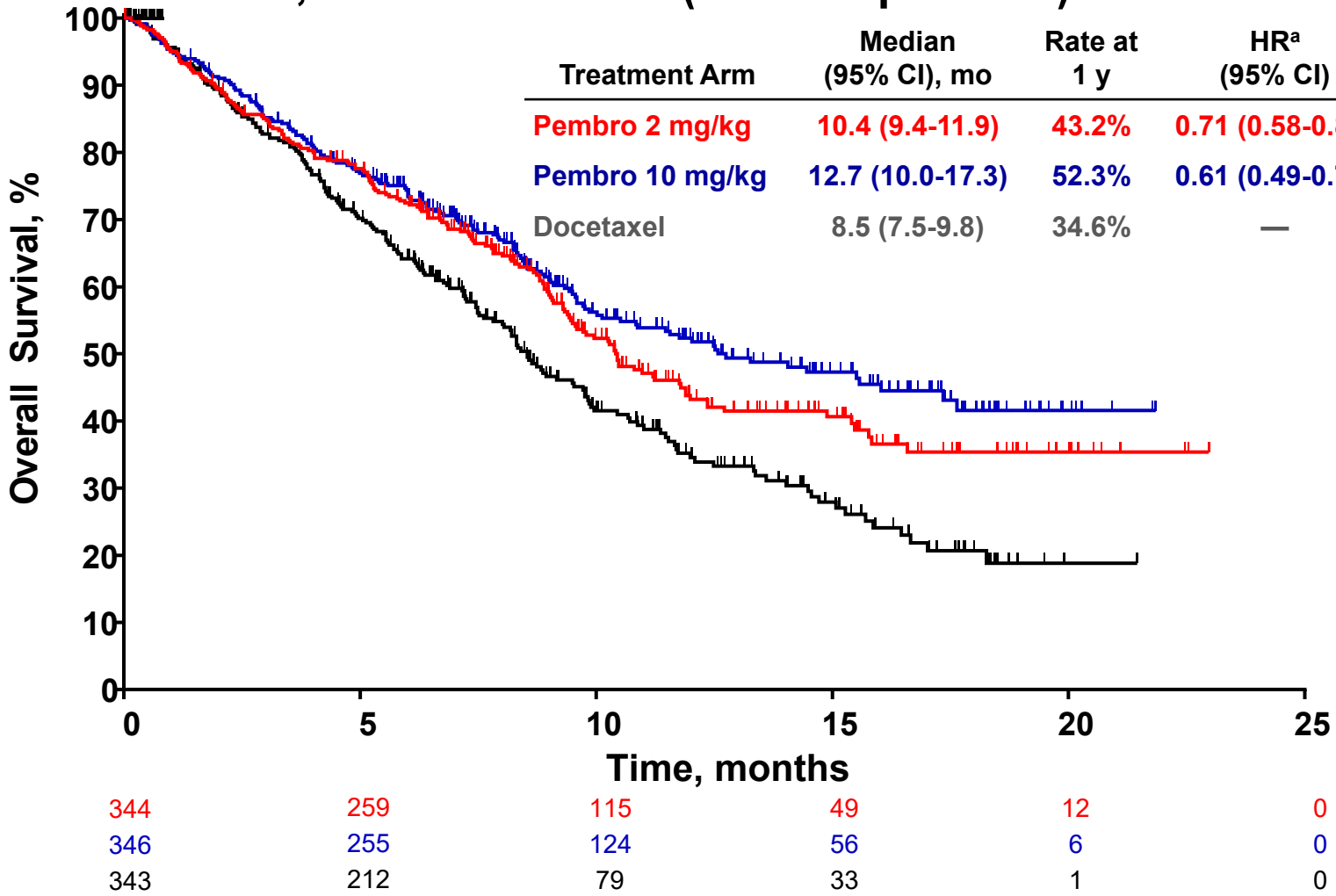


Clinical Utility of PD-L1 Expression in Lung Cancer

- PD-L1 expression among the earliest biomarkers evaluated as potentially predictive for response to PD-1 pathway inhibitors
- Current data indicate that PD-L1 expression predicts survival outcome in lung cancer patients treated with PD-1 antibodies
  - In a randomized study of pembrolizumab in 2L NSCLC, a survival benefit vs docetaxel was observed in patients with ≥1% PD-L1 tumor staining (Herbst, et al, Lancet 2015)
  - In a randomized study of pembrolizumab in 1L NSCLC, a survival benefit vs platinum-based chemotherapy was observed in patients with ≥50% PD-L1 tumor staining (Reck et al., NEJM 2016)
  - In a randomized study in 2L non-squamous NSCLC, survival was similar in patients with PD-L1-negative tumors treated with nivolumab vs docetaxel (Borghaei, et al, NEJM 2015)

Pembrolizumab vs Docetaxel in Previously Treated NSCLC Patients

•OS, PD-L1 TPS ≥1% (Total Population)



Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

[a]Comparison of pembrolizumab vs docetaxel.
Analysis cut-off date: September 30, 2015.

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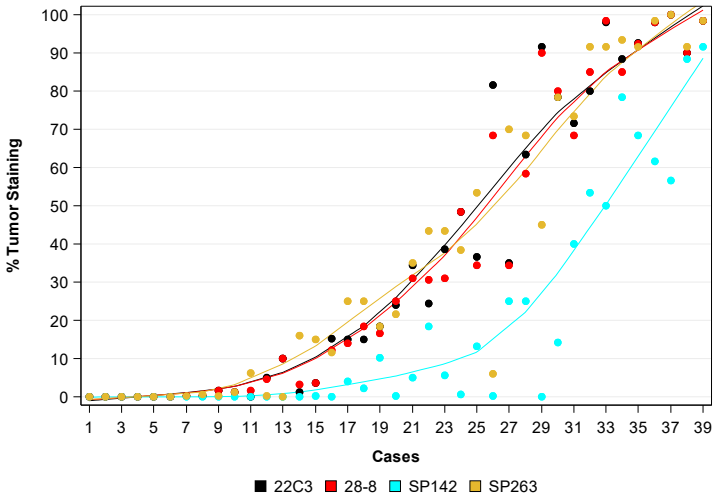
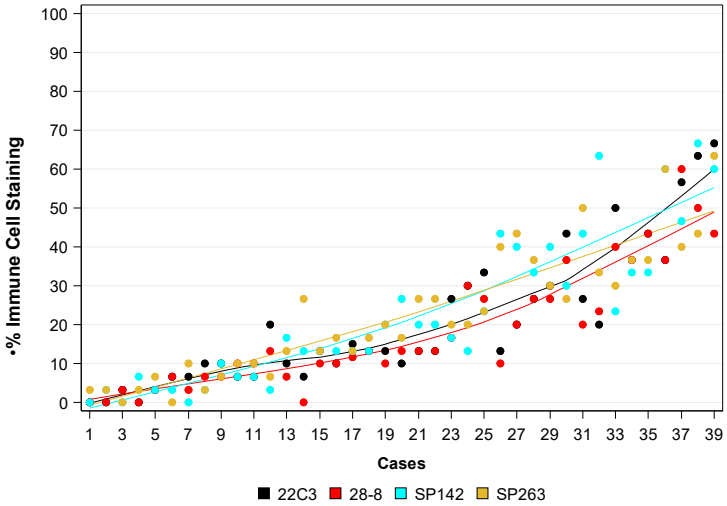
Multiple PD-L1 IHC Assays and Cutoffs

Agent	Pembrolizumab	Nivolumab	Durvalumab	Atezolizumab
Diagnostic Platform	Dako		Ventana	
Antibody	22-C3	28-8	SP 263	SP 142
Cut-off(s) being tested	TC[1] ≥1%, 50%	1%, 5% or 10% (TC[1])	TC[1] ≥ 25%	TC[1] or IC[2] 1%, 5%,10%

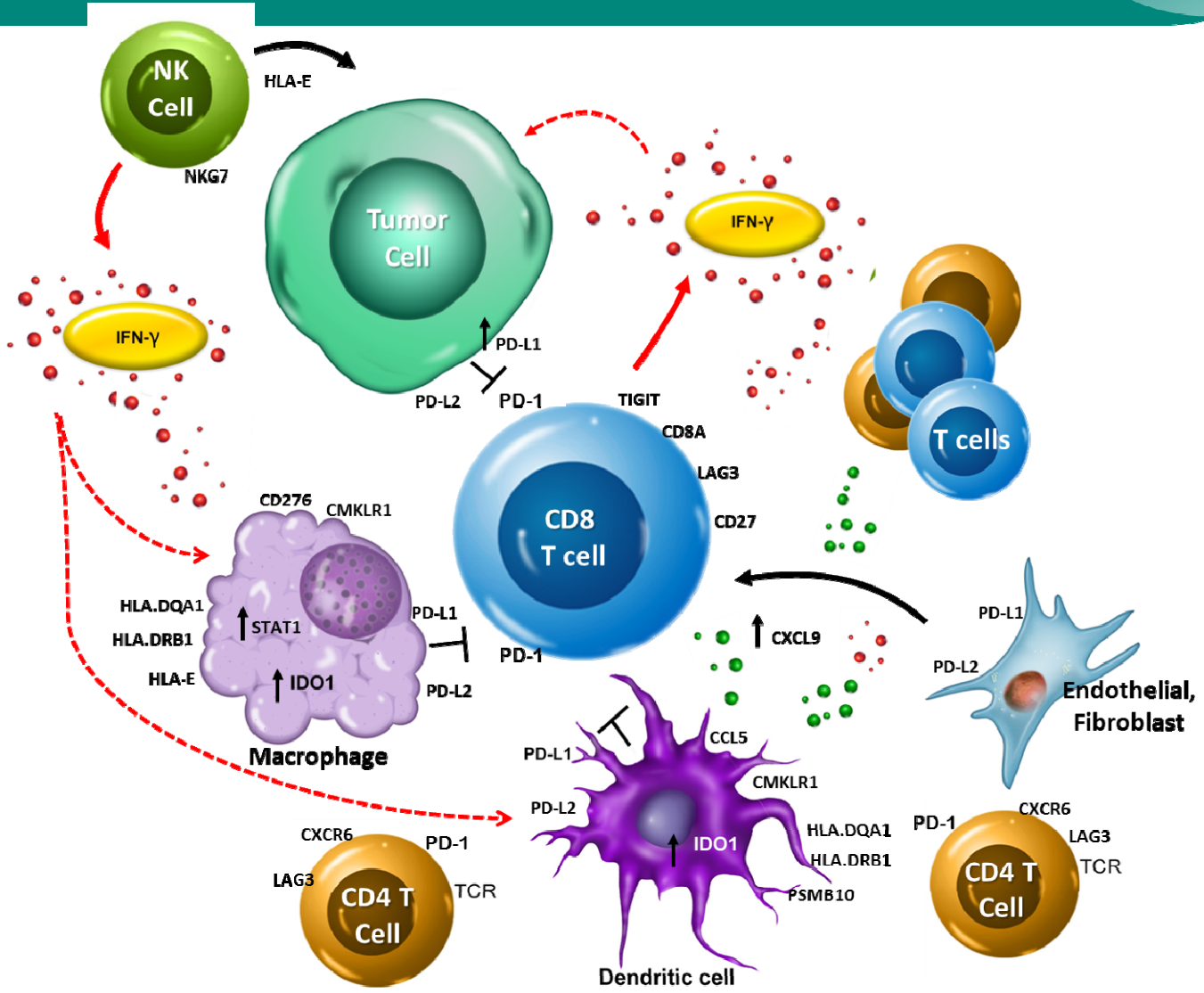
1) TC = tumor cell staining.
2) IC = infiltrating immune cell staining

- **AACR-sponsored "Blueprint" project designed to compare the 4 assays**

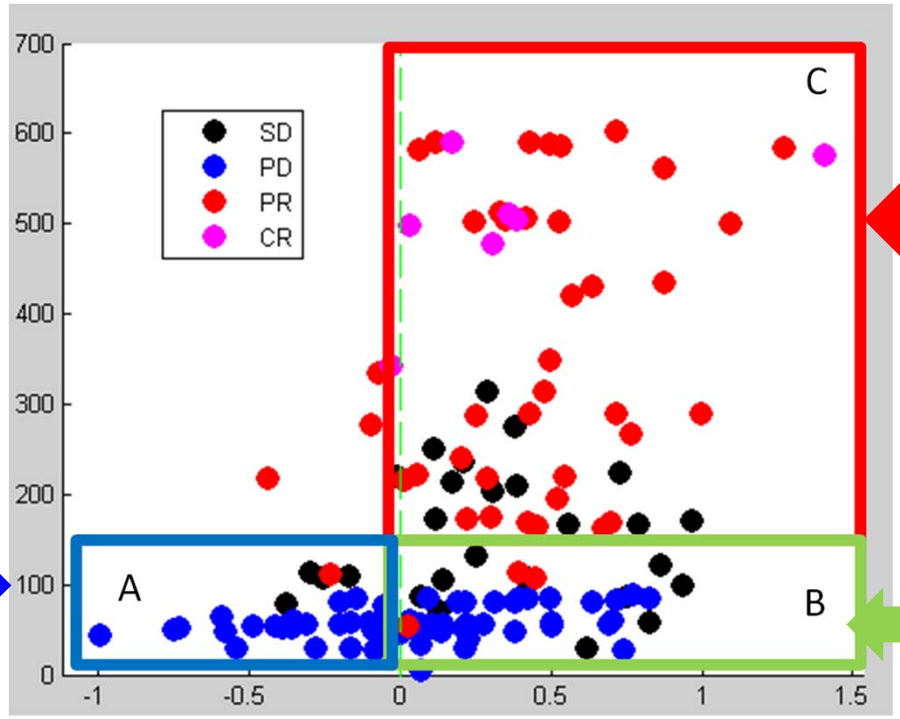




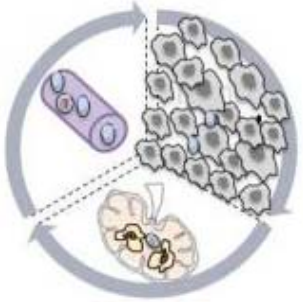
GEP Defines Biology of the T-Cell Inflamed Tumor



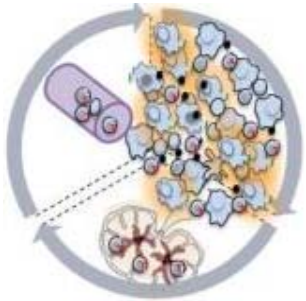
GEP Delineates Categories of Non-Responders



Group A: T-cell non-inflamed tumors rarely respond to pembrolizumab



Group C: almost all responders have baseline T-cell inflammation

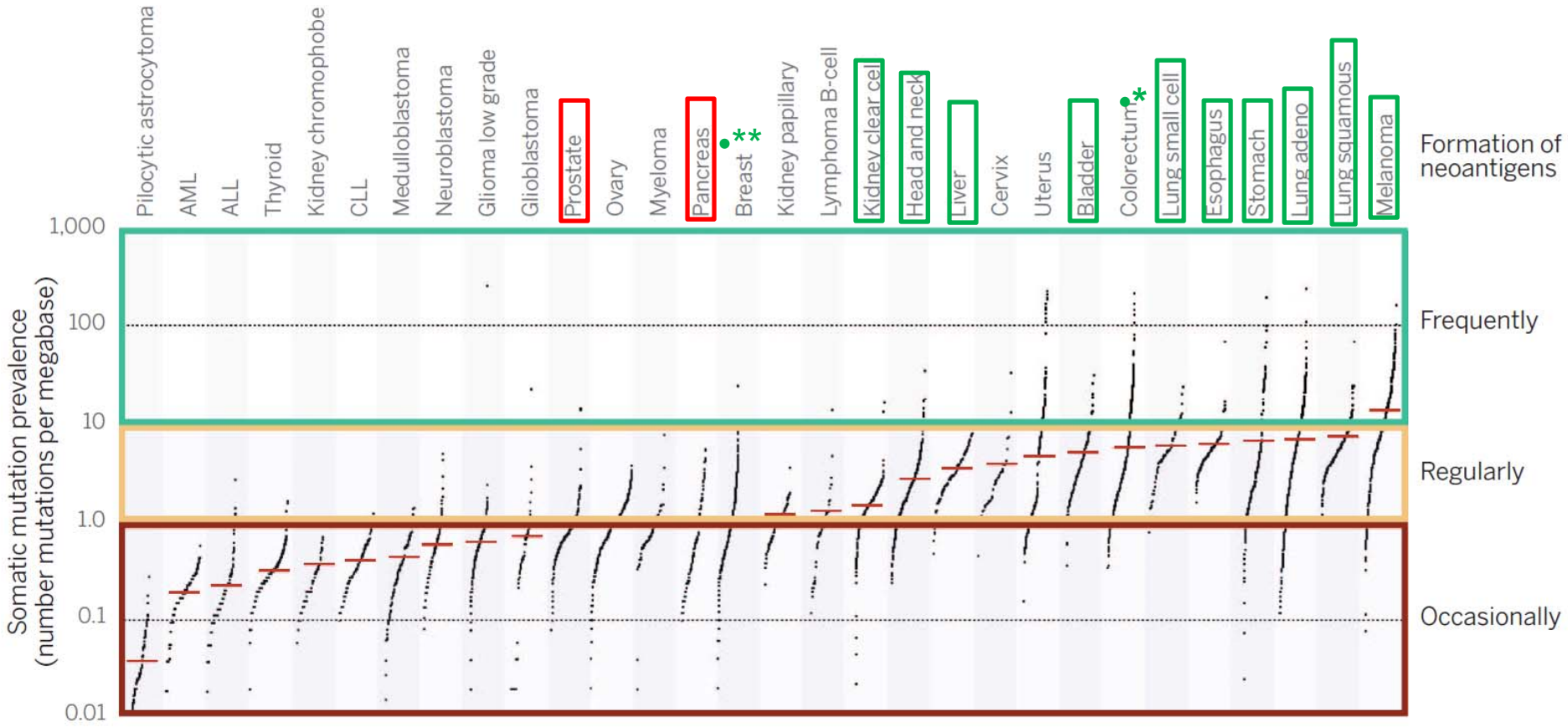


Group B: some non-responders have T-cell inflamed tumors

Predict Keytruda monotherapy response
New target identification/validation
Inform drug combinations

Combined data from KEYNOTE 001 melanoma and KEYNOTE 012 (SCCHN, bladder and gastric) cohorts

Mutational Burden, Neoantigens, and Response to Checkpoint Blockade



•* MSI subset

•**Triple-negative subset

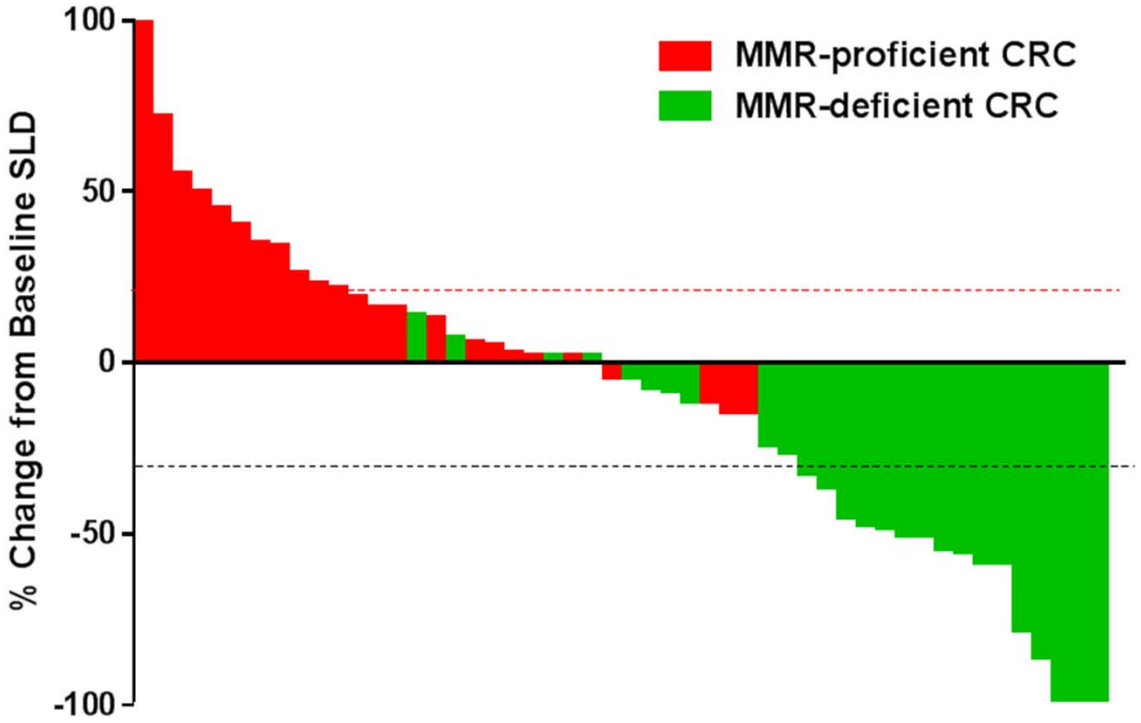
•*Schumacher and Screiber, Science 2015*

Pembrolizumab Efficacy in MSI-H Colorectal Cancer

Best Radiographic Response

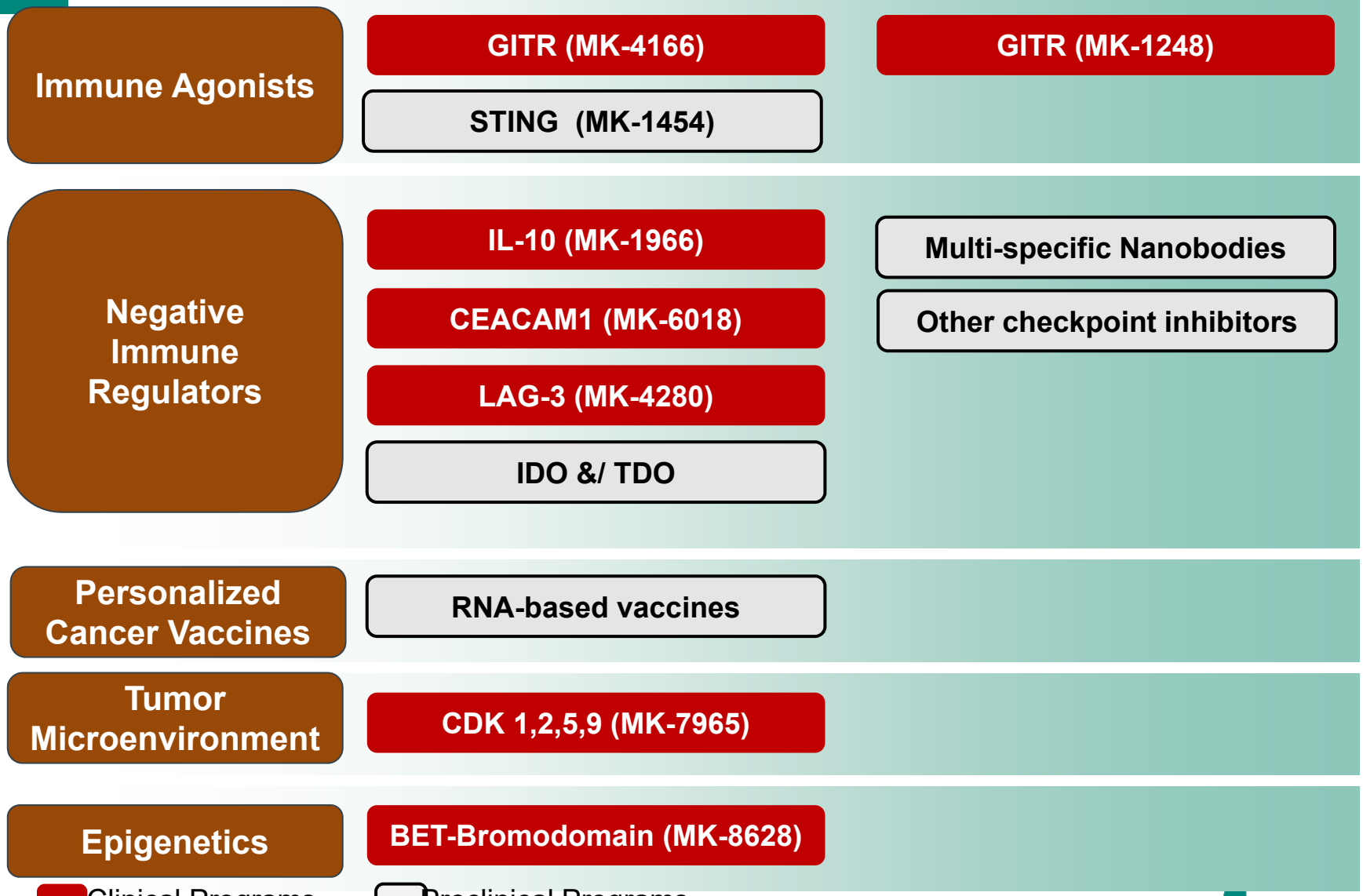
•MMR-deficient CRC – 11% complete response, 46% partial response

•MMR-proficient CRC - no complete or partial responses



D Le, ASCO 2016

Merck Early Immuno-Oncology Pipeline



Clinical Programs Preclinical Programs

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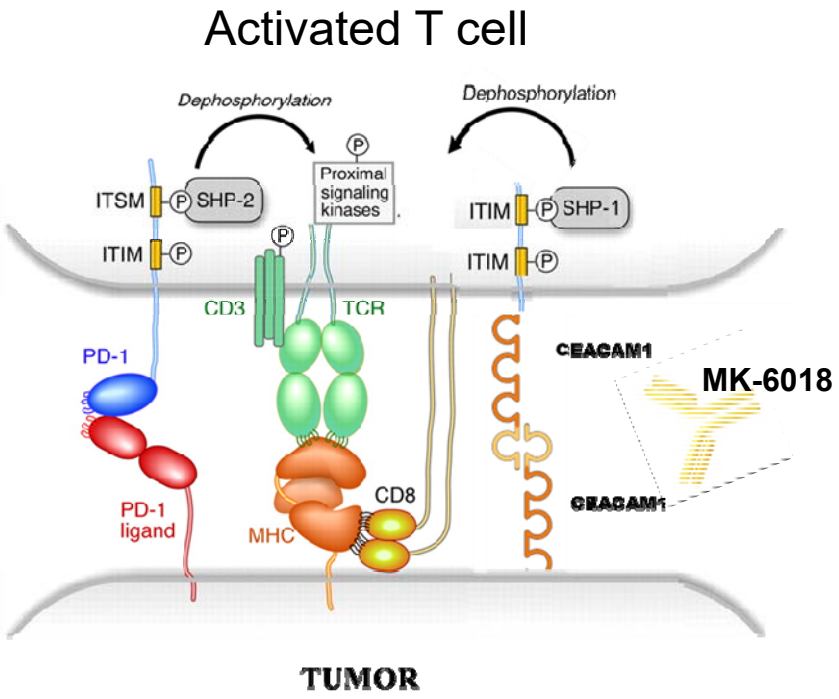
MK-6018 (anti-CEACAM1 mAB)

MK-6018 (CM-24) is a Potent and Selective Inhibitor of CEACAM1-Dependent Interactions

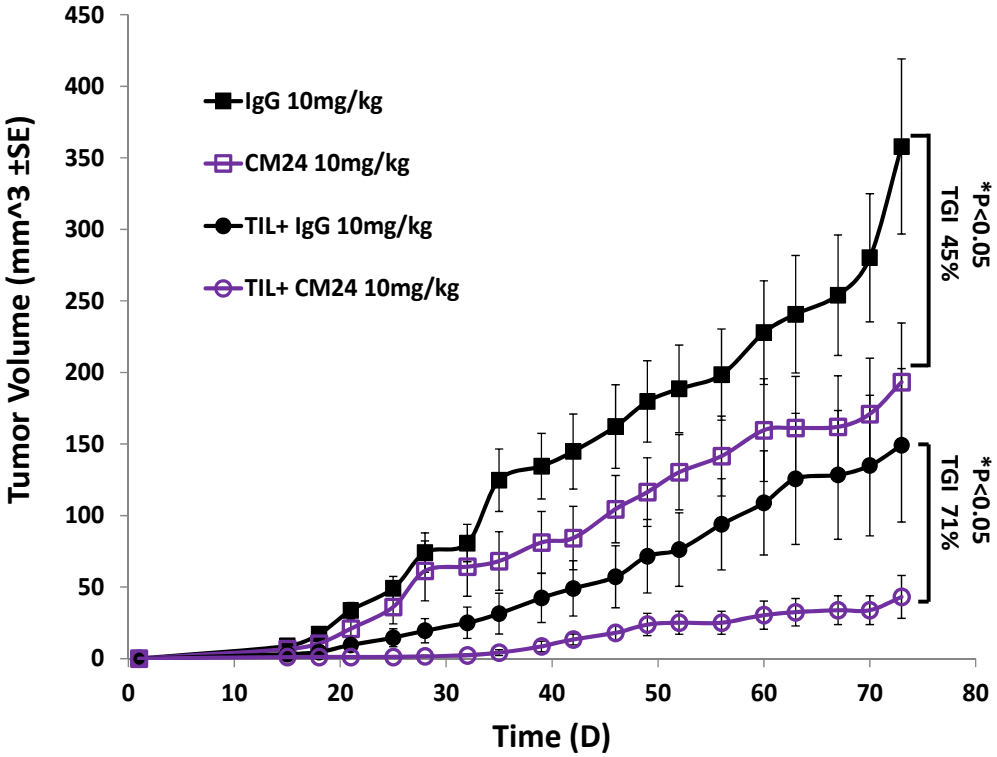
- Carcinoembryonic antigen related cell adhesion molecule 1 (CEACAM1; CD66a) is a cell adhesion molecule of the immunoglobulin family
- CEACAM1 is expressed on certain epithelial, endothelial, lymphoid, and myeloid cells
- CEACAM1 expression up-regulated on
  - Activated T and NK cells
  - Various cancer cells
- CEACAM1(tumor) and CEACAM1 (T-cell) interaction prevents killing of tumor cell
- CEACAM1 is induced by IFNγ
- MK-6018 is a humanized IgG4 monocloncal antibody against N-terminus of CEACAM1



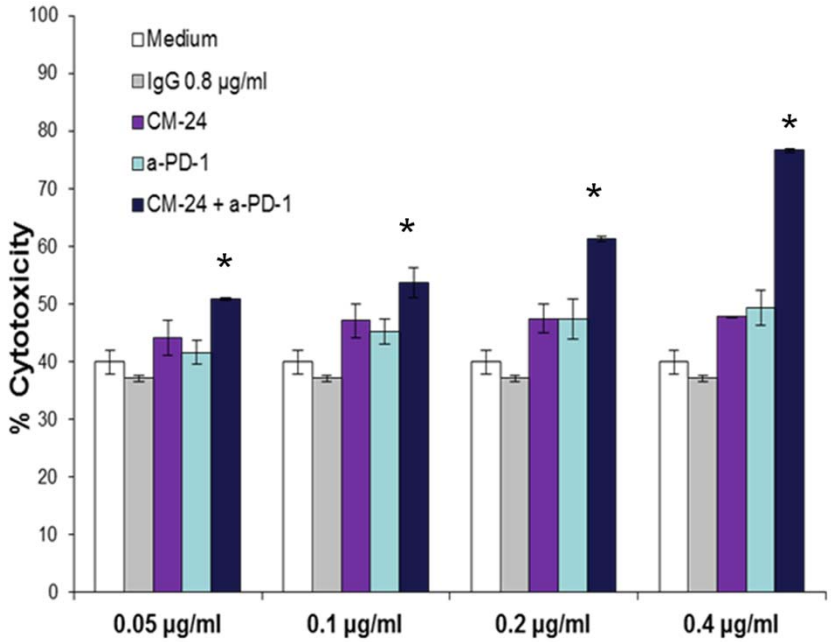
•Adapted and modified from Freeman G J PNAS 2008

MK-6018 (CM-24) enhances anti-tumor activity of lymphocytes as monotherapy or in combination with anti-PD1

MK-6018 enhances tumor infiltration lymphocytes activity *in vivo* against CEACAM1+ SKMel 5 melanoma cells



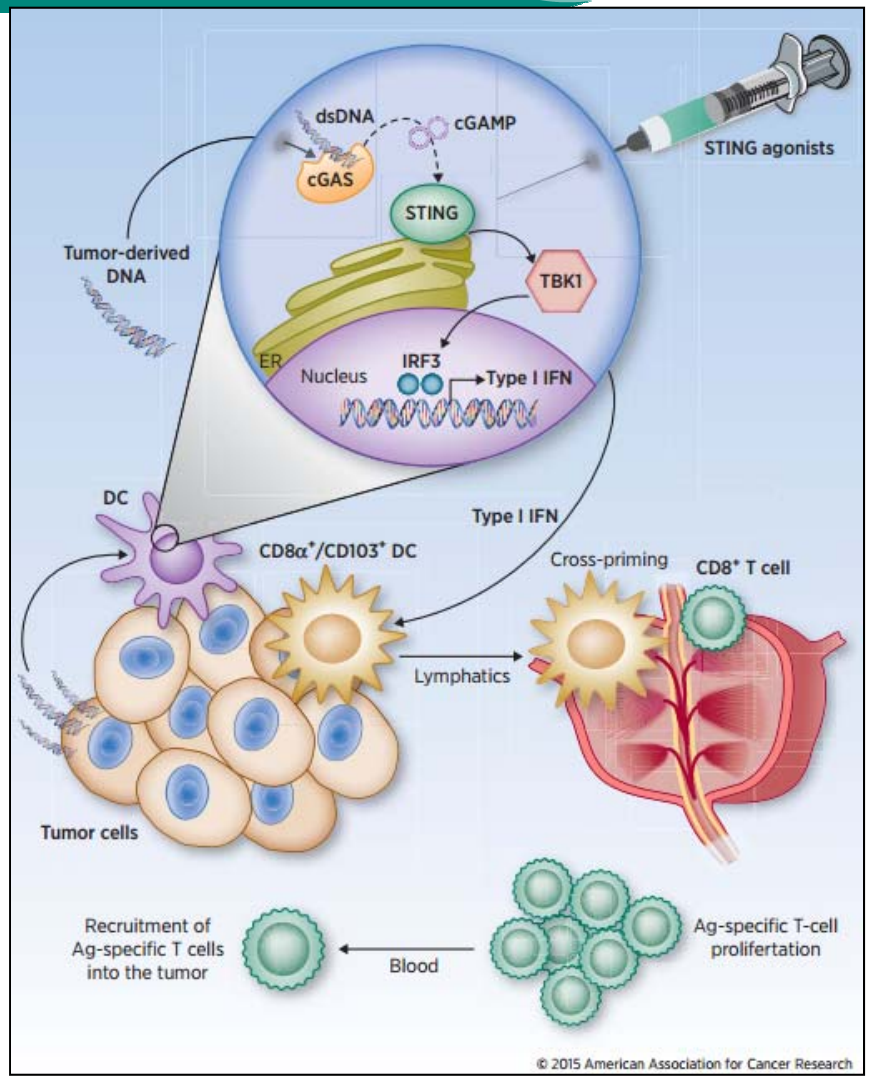
Combination of MK-6018 with αPD-1 antibody resulted in synergistic killing of CEACAM1+ MALME-3M melanoma cells by TIL *in vitro*



MK-1454 STING (Stimulator of Interferon Genes) Agonist

Rationale for targeting STING in cancer

- Intra-tumoral (IT) injections of cyclic dinucleotide (CDN) STING agonists leads to NFκB & IRF3 activation in innate immune cells in the TME and to the production of type-I IFNs and proinflammatory cytokines
- IFN-β strongly enhances cross-presentation of tumor antigens by $CD8\alpha^+$ $CD103^+$ cross-presenting DCs either in the tumor or tumor-draining lymph node
- Activated tumor-specific $CD8^+$ T cells proliferate and mediate tumor killing
- Non-injected lesions could respond via an abscopal effect: Primed tumor-specific T cells recirculate to other sites in the body to mediate anti-tumor effects similar to the ones in the injected tumor



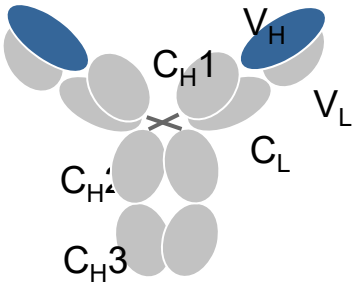
•http://clincancerres.aacrjournals.org/content/early/2015/09/15/1078-0432.CCR-15-1362.full.pdf+html

Ablynx Multi-specific Nanobody Platform

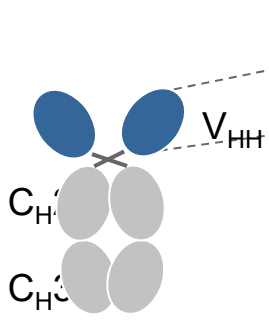
Ablynx - Nanobodies as Building blocks for Multi-specific Immuno-Oncology Therapeutics

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

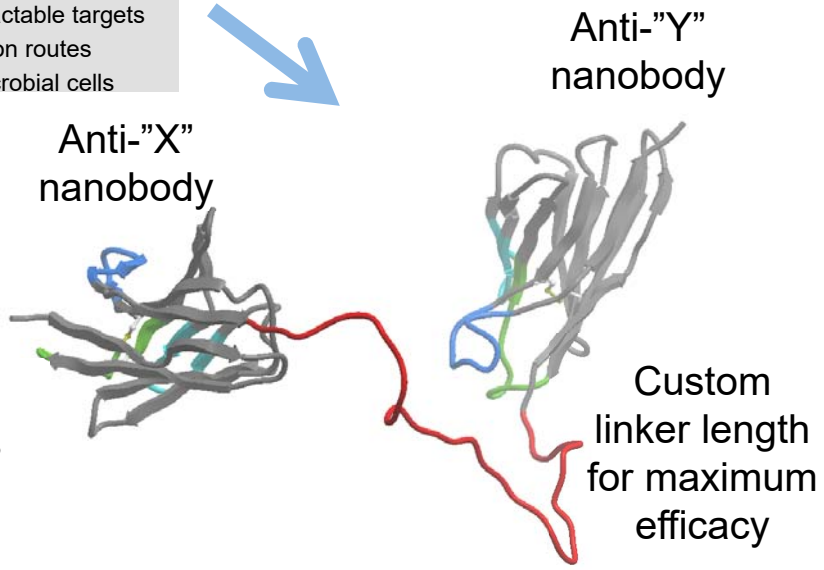


Heavy chain only antibodies

V_{HH} 12-15kD

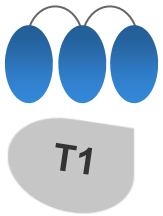
Ablynx's Nanobody[a]

- 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



Formatting flexibility

Multi-paratopic and multi-specific molecules



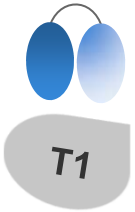
Multi-valent:

binding the same epitope on the same target

Increased potency

Example:

tri-valent anti-RSV



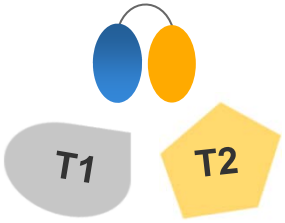
Bi-paratopic:

binding different epitopes on the same target

Increased specificity / potency

Example:

bi-paratopic anti-CXCR2



Multi-specific:

binding 2 or more different targets

Additonal mode of action

Examples:

anti-IL17A/IL17F

anti-CXCR4/CD4

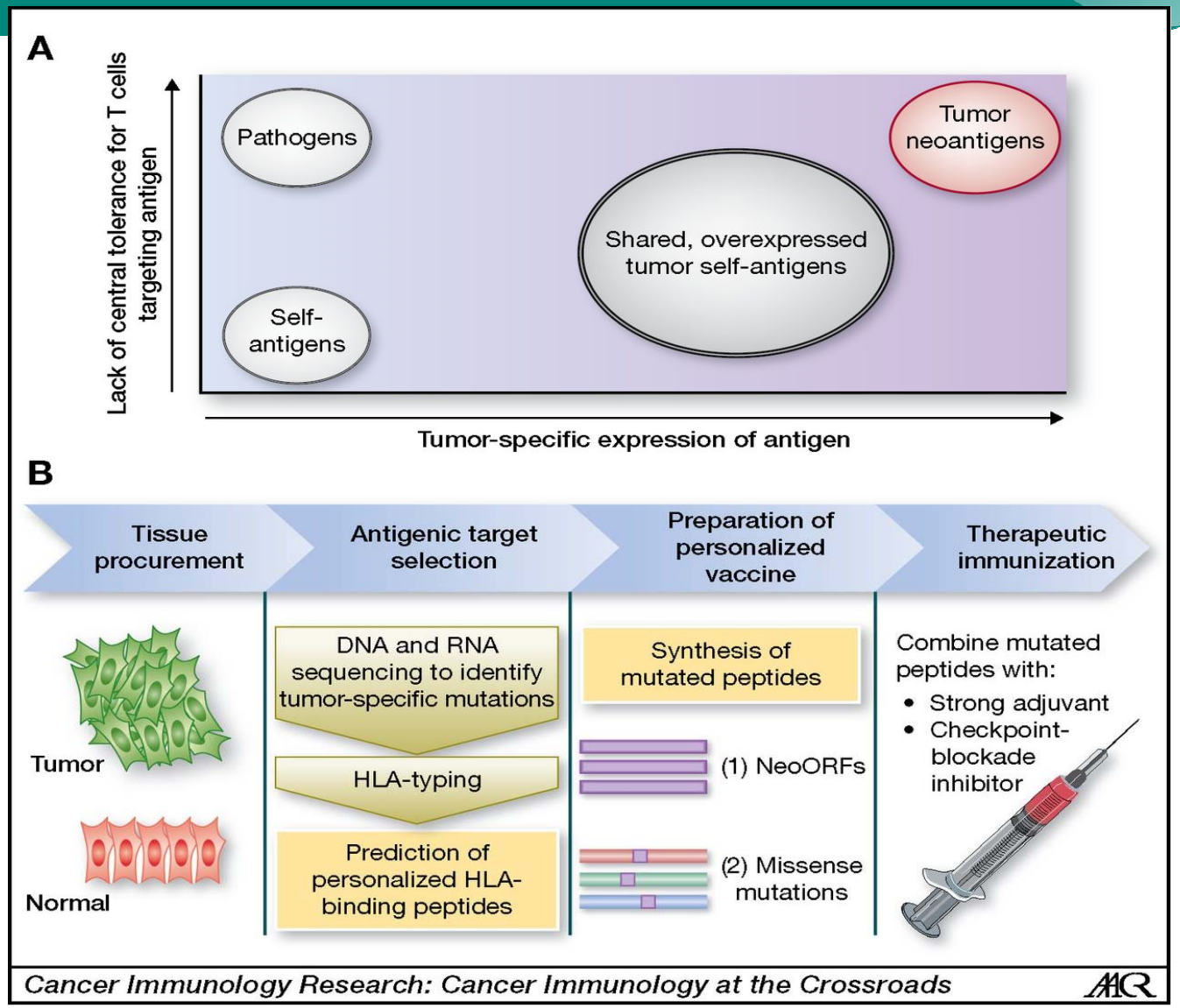
Increased specificity

Examples:

anti-IL12Rβ2/CD4

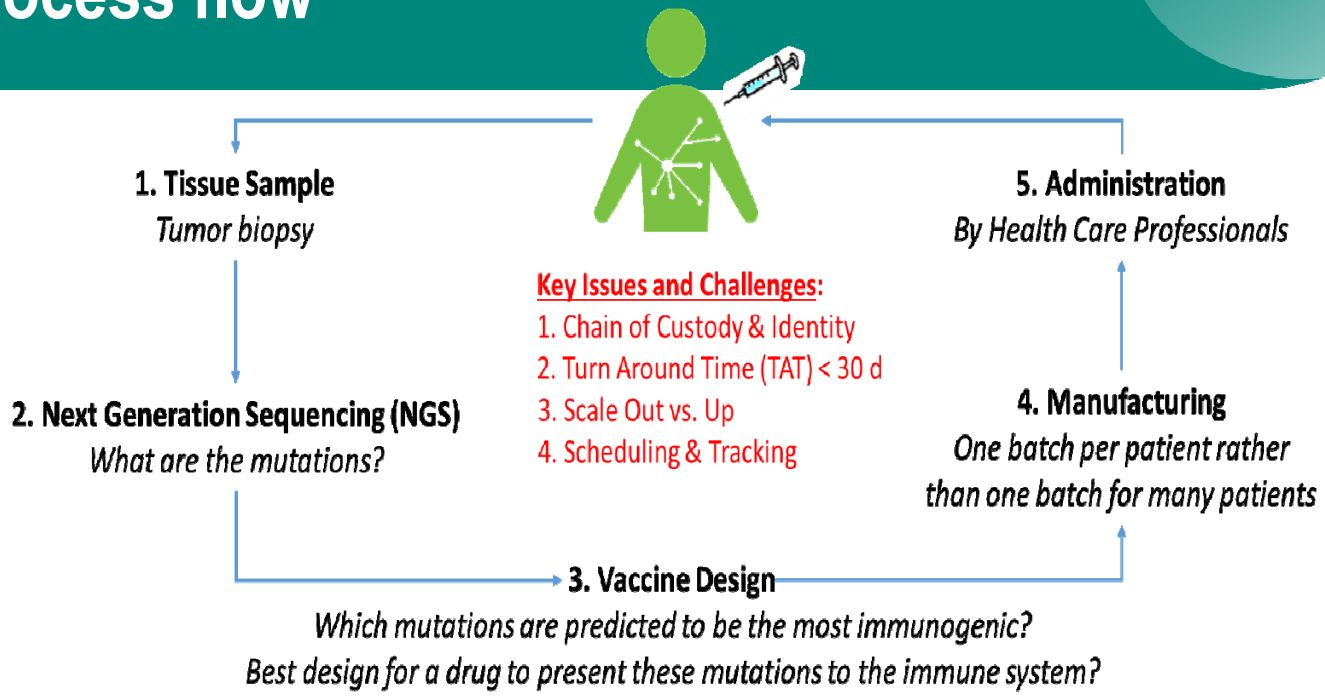
Caperna Personalized Cancer Vaccines

Tumor neoantigens may be ideal targets for a therapeutic vaccine



Nir Hacohen et al. Cancer Immunol Res 2013;1:11-15

Caperna's "needle to needle" personalized cancer vaccine (PCV) process flow



•An integrated manufacturing process involving five distinct steps will be required for create each individual patient's PCV: (1) obtaining tumor biopsy samples, (2) next generation sequencing (NGS), (3) vaccine design based on the neoantigen(s) that is/are predicted to be the most immunogenic, (4) cGMP manufacturing and (5) administration of the PCV to the right patient. Key factors for success include: (1) maintaining strict chain of identity and chain of identity, (2) minimizing turnaround times, (3) scaling up manufacturing capacity to the right level at the right time and (4) maintaining a flexible, dynamic and transparent scheduling and tracking system.

MSD has Broad Strategic Partnership to Exploring the Potential of Combinations

Immuno-oncology at ESMO 2016

Back-up

MERCK
Be well