The Next Era in Immuno-Oncology

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Declared Interests

Board of Directors	Scientific Advisory Boards	Advisory/Consultancy
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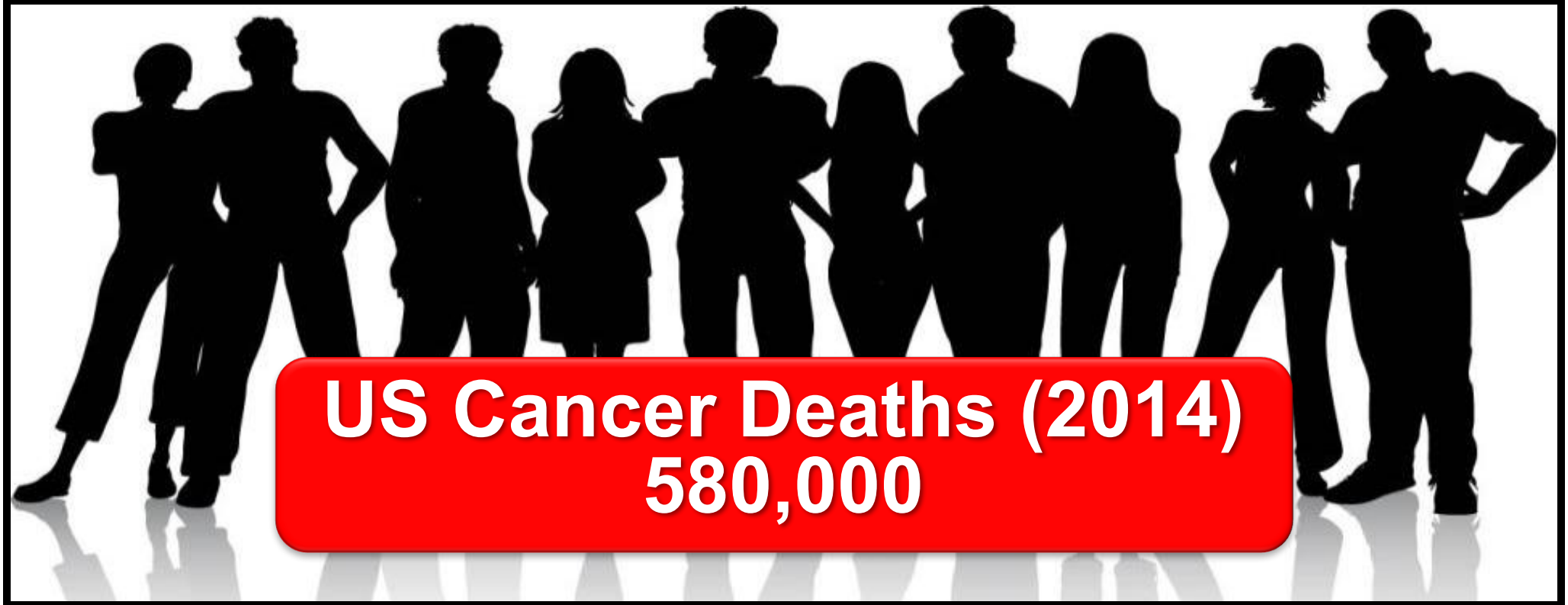
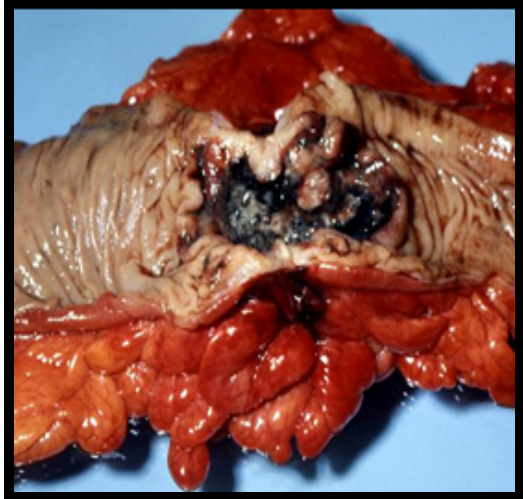
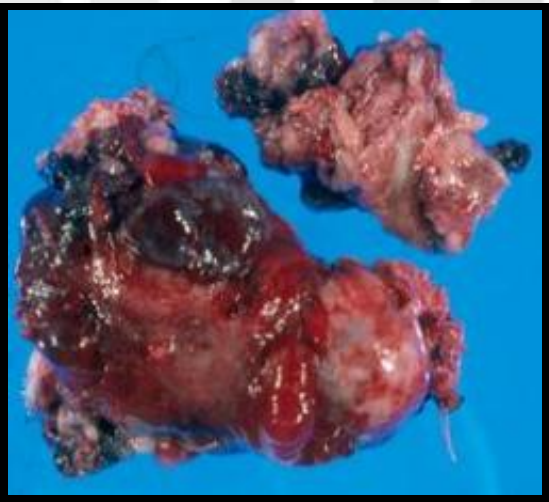
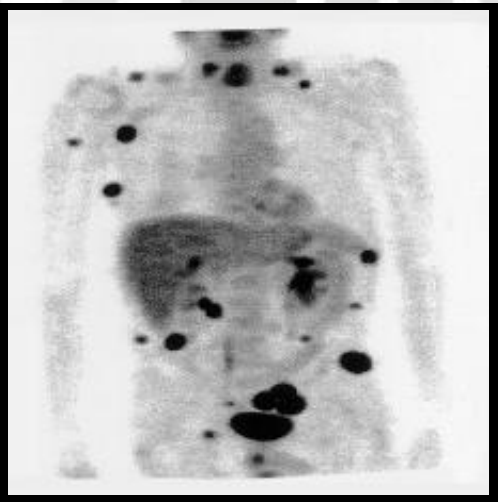
Confronting the Clinical, Economic and Human Toll of Cancer

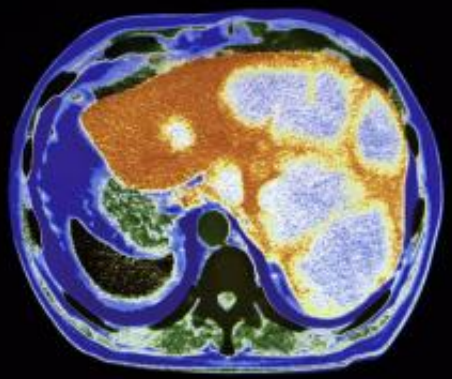


US Cancer Deaths (2014)
580,000









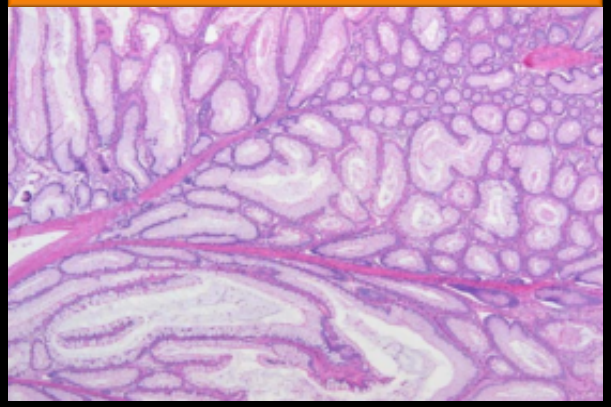
US Cancer Prevalence Estimates 2010 and 2020

Site	# People (thousands) 2010	2020	% change
Breast	3461	4538	31
Prostate	2311	3265	41
Colorectal	1216	1517	25
Melanoma	1225	1714	40
Lymphoma	639	812	27
Uterus	588	672	15
Bladder	514	629	22
Lung	374	457	22
Kidney	308	426	38
Leukemia	263	240	29
All Sites	13,772	18,071	32

From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

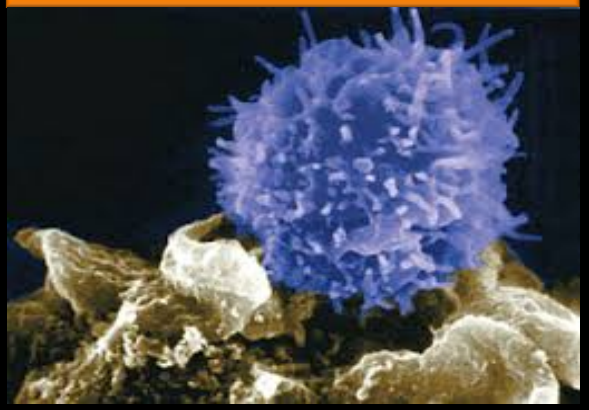
Cancer as a Complex Adaptive System: The Dynamic Interaction Between Host Immune Defenses and Relentless Emergence of Phenotypically Diverse Tumor Cell Clones

Escape From Controls for Normal Tissue Architecture



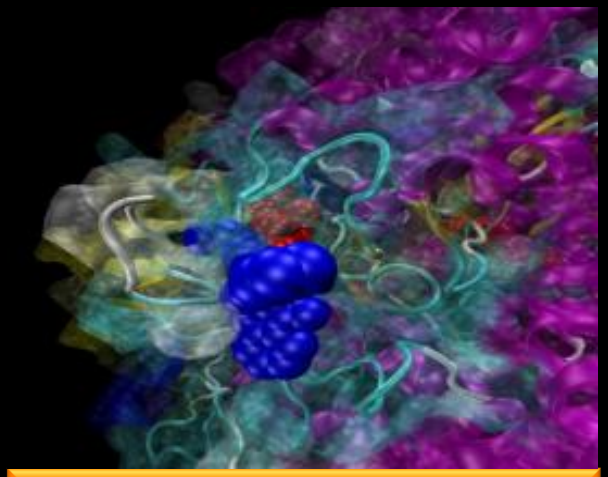
Genome Instability and Emergence of Clonal Variants

Evasion of Clonal Detection/Destruction by Host Immune System



Use of Host Systems to Promote Progression

Invasion and Metastasis



Emergence of Drug-Resistant Clones

Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
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SPECIAL ISSUE
Cancer Immunology and Immunotherapy

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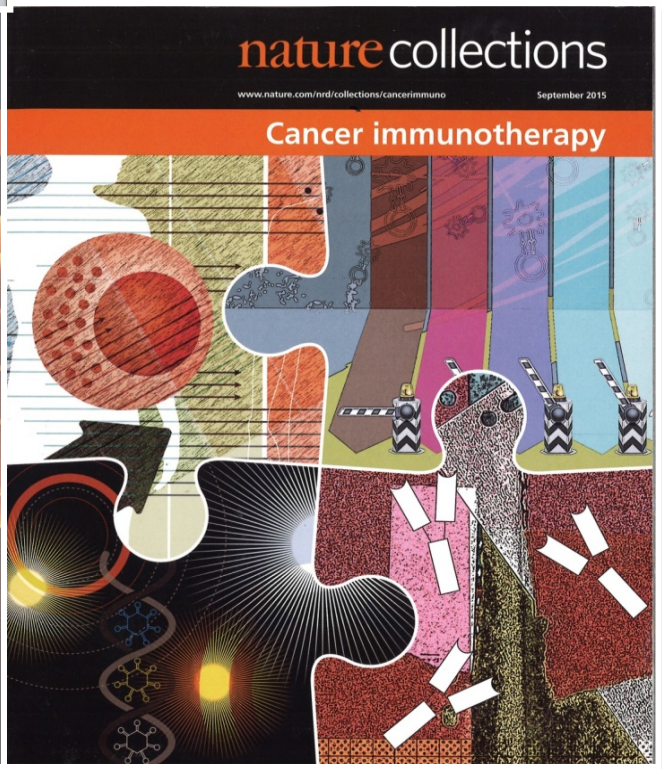
May 2015
Cancer immunotherapy
July 2015


nature collections
www.nature.com/nrd/collections/cancerimmuno
September 2015
Cancer immunotherapy

Pembrolizumab and Therapy of Metastatic Melanoma in President J. Carter

Saturation TV Advertising

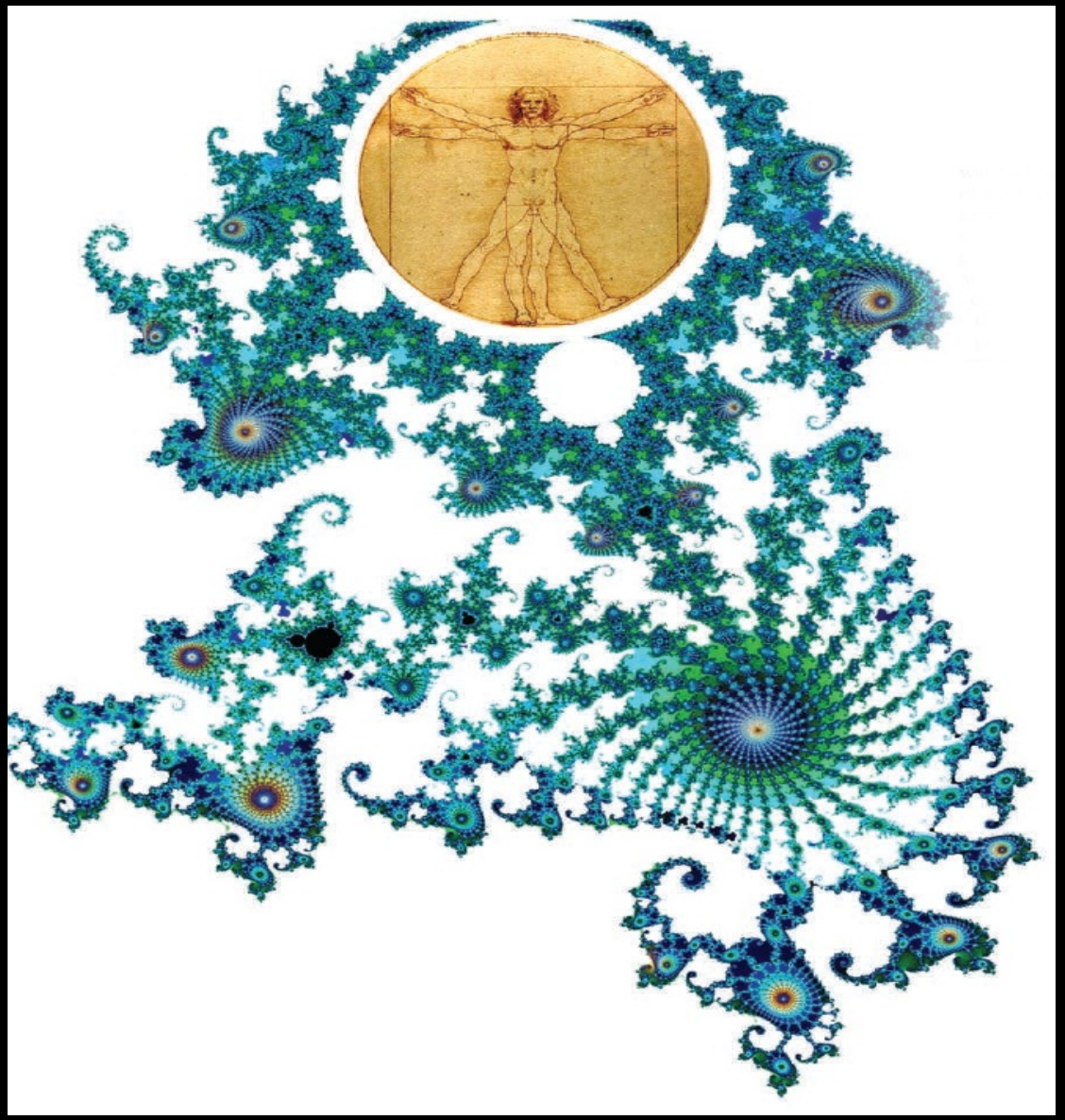
Cancer Immunotherapy Investment by Big Pharma: Big Bucks, Big Risks, Big Payoffs?

The Rationale for Cancer Immunotherapy

Overcoming the Tumor Cell Heterogeneity Problem?

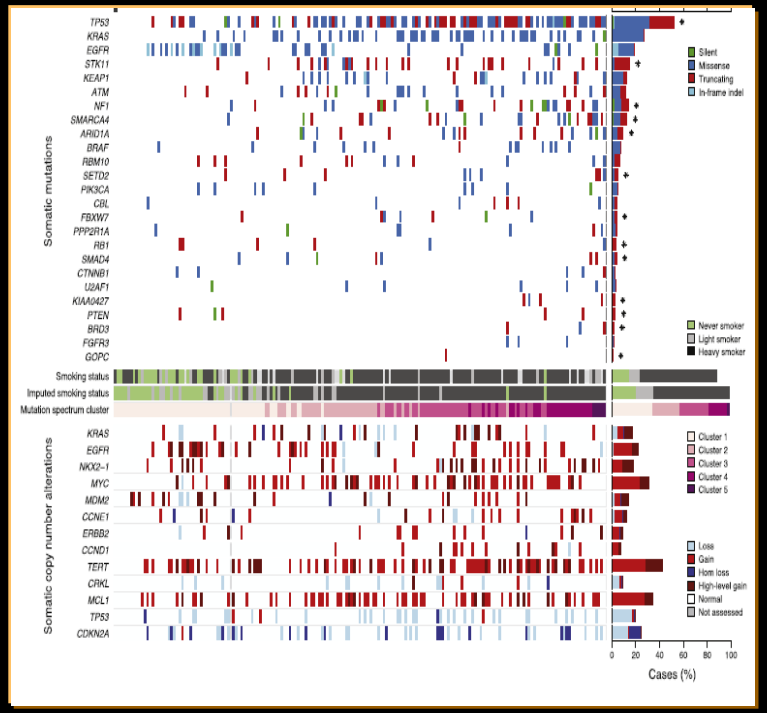
Circumventing the Omnipresent Resistance Problem in Chemotherapy and Targeted Therapies?

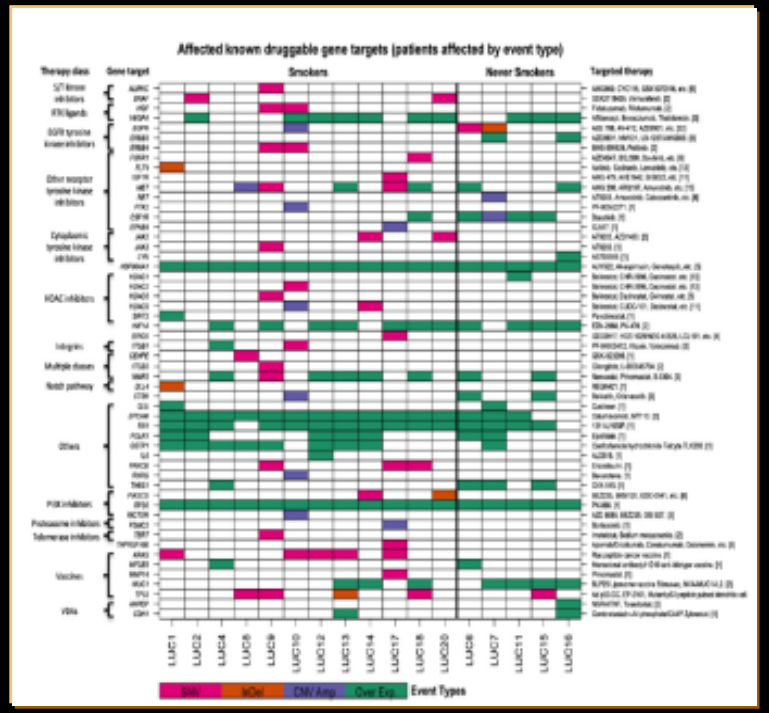
Cancer as a Complex Adaptive System
The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression



Rx Resistance
- **intrinsic**
- **acquired**

The Extravagant Landscape of Inter-individual Genomic Alterations in Cancer (Cell 2012: 150, 1107 and 1121)





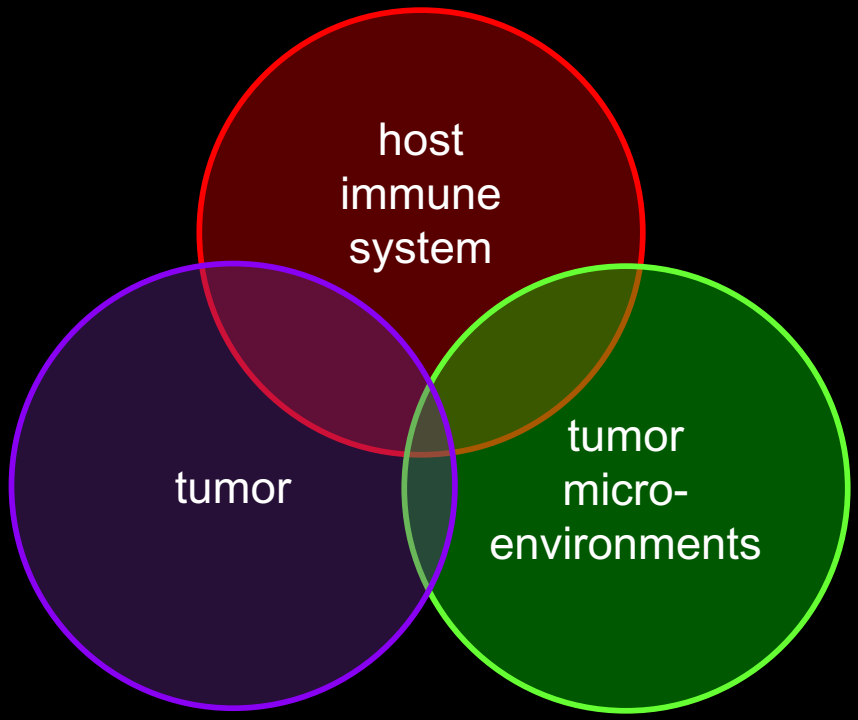
Mutations in Individual Non-small Cell Lung Cancers

Drug Targets in Individual Non-Small Cell Lung Cancers

- "malignant snowflakes": each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for therapeutic 'cure' and development of new Rx

The Multi-Dimensional Matrix for Cancer Immunotherapy

cellular and humoral multi-component system and complex regulatory networks

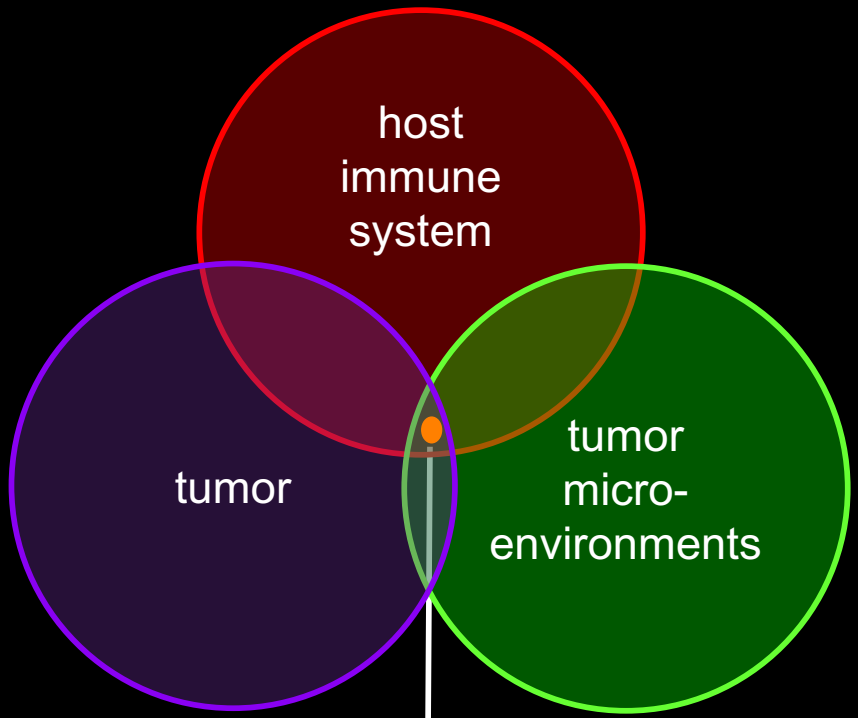


tumor cell (epi) genetic and phenotypic heterogeneity and clonal diversification

dynamic tumor-host cell interactions and complex immune activation/suppression pathways

The Multi-Dimensional Matrix for Cancer Immunotherapy

cellular and humoral multi-component system and complex regulatory networks



tumor cell (epi) genetic and phenotypic heterogeneity and clonal diversification

dynamic tumor-host cell interactions and complex immune activation/suppression pathways

impact of therapy

- **emergence of resistance**
- **immune functions**

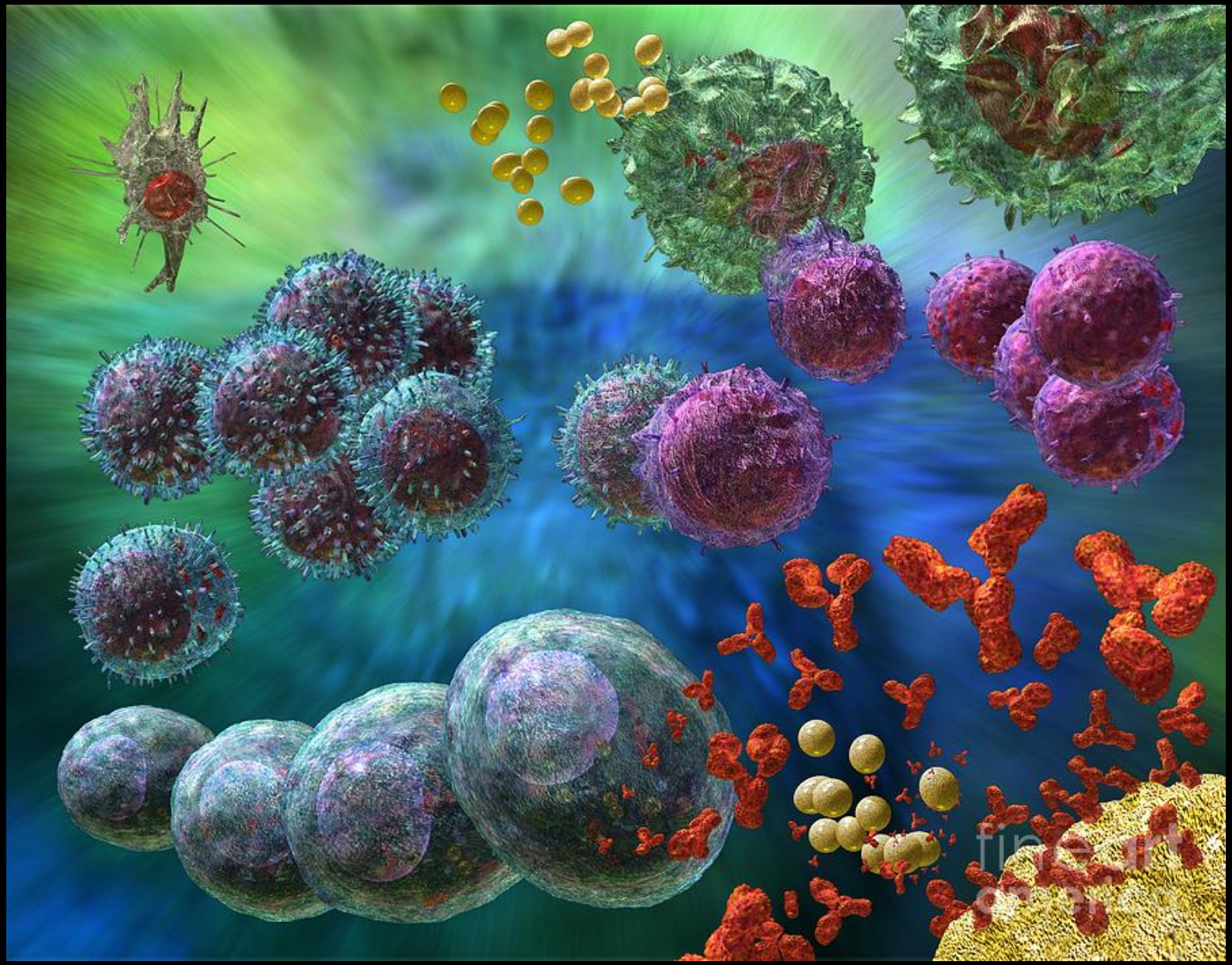
Anti-Cancer Immunotherapies

- passive therapies
- active therapies
- combination therapies

Passive Immunotherapy: Enhancement of Anti-Tumor Activities Without Direct Modification of Intrinsic Host Immune Functions

- therapeutic anti-tumor antibodies
- adoptive transfer of cytotoxic T lymphocytes (TILS, TCRs, CARs)
- oncolytic viruses

Passive Immunotherapy With Antibodies



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FDA-Approved Immunotherapy Agents

monoclonal antibodies (mabs)			
MOA	**Agent**	**Year**	**Indication**
CD52	Alemtuzumab	2001	CLL
CD20	Ofatumumab	2009	CLL
CD20	Rituximab	1997	NHL
		2010	CLL
CD38	Daratumumab	2015	Multiple Myeloma
HER2	Trastuzumab	1998	Breast cancer
		2010	Gastric cancer
EGF	Cetuximab	2004	Colorectal cancer
		2011	Head/neck cancer
CD20 ADC	Y-Ibritumomab tiutexan	2002	NHL
CD30 ADC	brentuximab vedotin	2011	Hodgkin lymphoma, ALCL

BITE antibody constructs: Bi- and Multi-Specific Antibodies			
MOA	**Agent**	**Year**	**Indication**
CD3/CD19	Blinatumomab	2014	ALL

Intrinsic Limitations of Passive Antibody Therapies

Tumor Cell Antigenic Heterogeneity and Dynamic Emergence of New Antigenically Different Clones

Active Immunotherapies

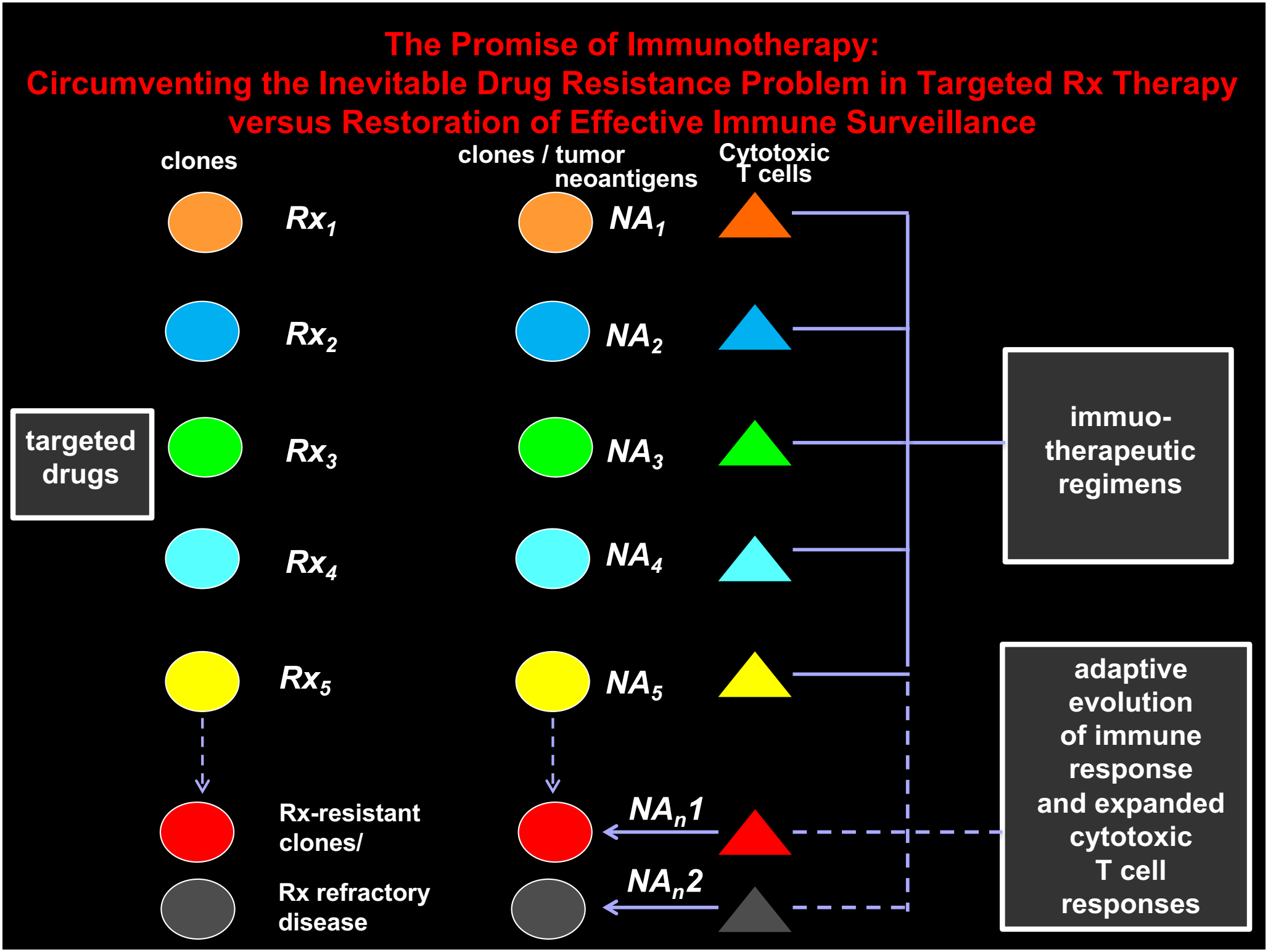
Clone Wars

Relentless Emergence of New Tumor Cell Clones During Tumor Progression and Immune Evasion

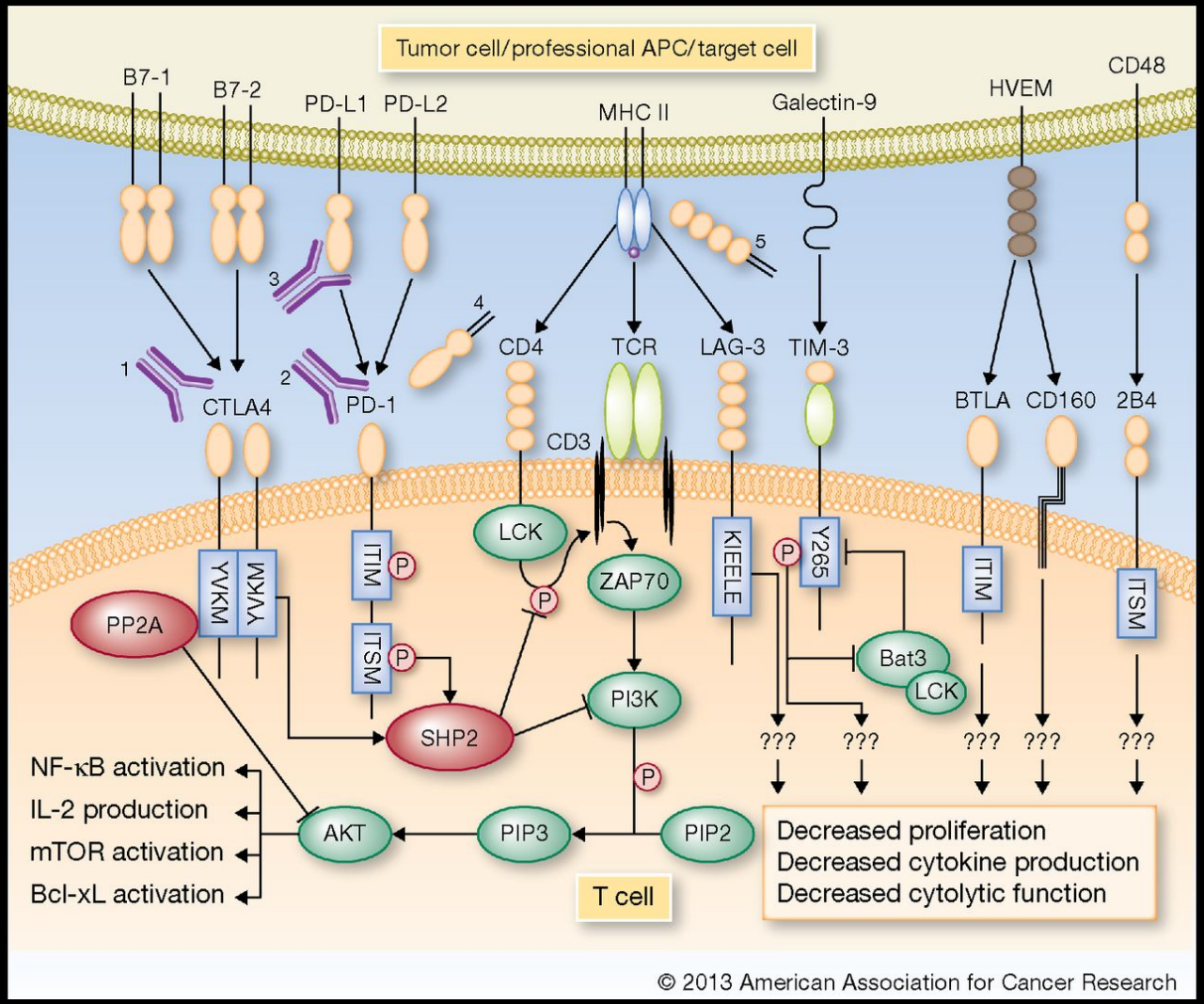
versus

Activation of Host T Lymphocyte Clones to Kill (Neo)Antigen-Specific Tumor Clones

The Promise of Immunotherapy: Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance



Mapping the Molecular Control Pathways in Immune Responses for Rational Design of New Immunotherapeutics



Immunologic Networks

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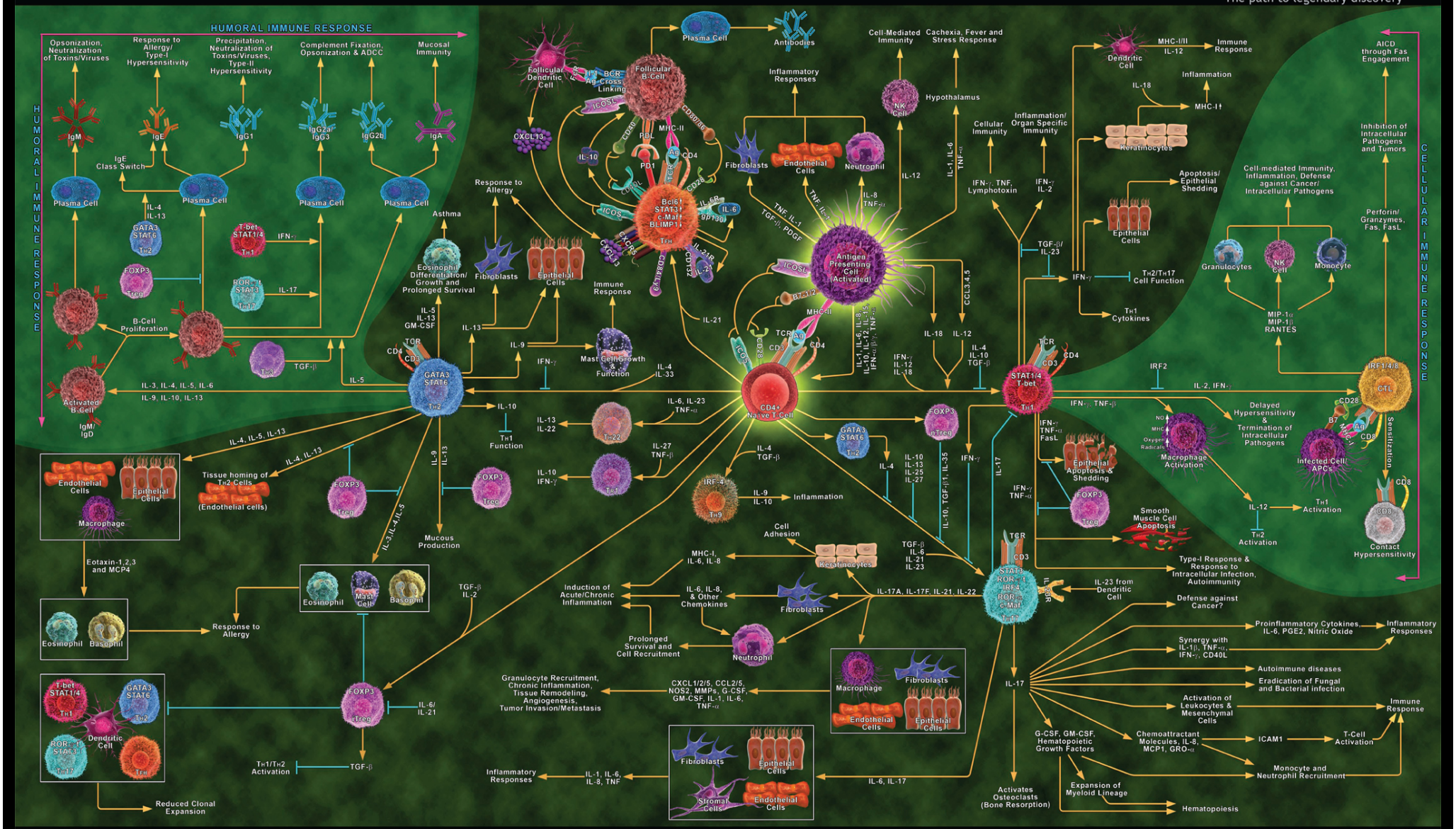

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We would like to thank *Dr. Vijay K. Kuchroo* of Harvard Medical School for his contributions to this poster.

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Understanding Molecular Signaling (Information) Systems and Feedback Control in the Immune System

The Immunostat:
The Constantly Shifting Balance Between Activation and Suppression

Active Immunotherapies

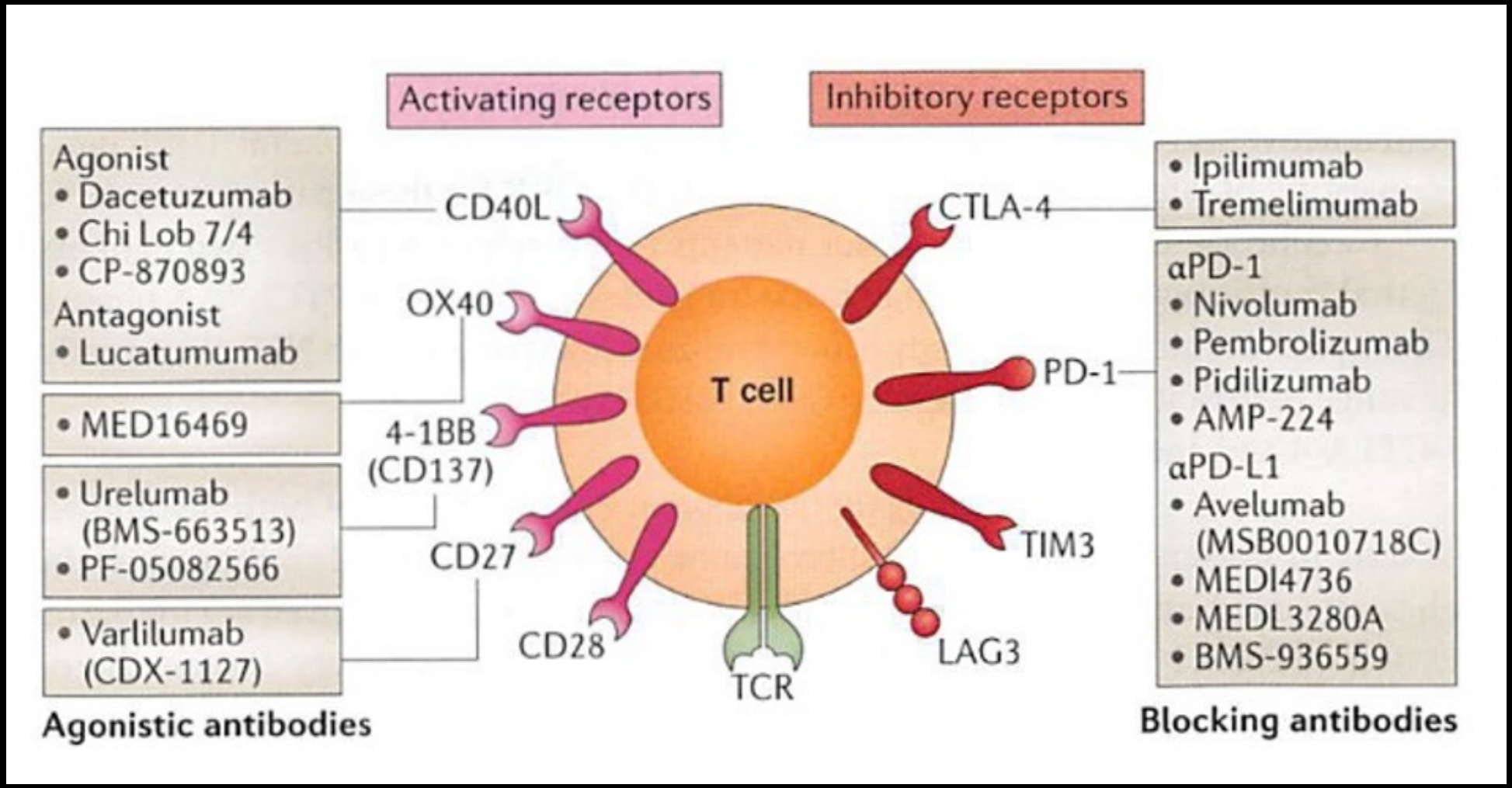
activation of cytotoxic T cells

- immunostimulatory cytokines
- vaccine-induced expansion of cytotoxic T cells to cancer neoantigens
- unanticipated immune-stimulation by targeted Rx/SOC

blockade/inhibition of immunosuppressive pathways

- immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1)
- inhibition of Tregs and myeloid-derived suppression cells
- inhibition of immunosuppressive signals from non-immune cells in the tumor microenvironment

Cancer Immunotherapy



C.L. Batlevi; et. al. (2016) Nature Reviews | Clinical Oncology 13,25

The Immune-Checkpoint Axis

- complex networks of multiple negative checkpoint regulators to limit the scale and duration of activated immune reactions
- maintain self-tolerance
- prevent autoimmunity
- limit cytokine release storms

Immune Checkpoint Inhibitors
Timelines of FDA Approvals

March 2011

- ipilimumab: melanoma

September 2014

- pembrolizumab : melanoma

October 2014

- pembrolizumab: NSCLC

December 2014

- nivolumab: melanoma

March 2015

- nivolumab: NSCLC

October 2015

- nivolumab: renal cancer

Combination Immunotherapies

Combination Immunotherapy

- ipilimumab + nivolumab
  - melanoma 60% response versus single agent responses 44% (nivo), 19% (ipi)
  - 12% CR
  - 80% two year survival

Combination Immunotherapies

Combination Therapy	Mechanisms of Action	Phase	Indication
Nivolumab + ipilimumab	Anti-PD1 + anti-CTLA-4	I/II	Gastric, TNBC, PA, SCLC, Bladder, Ovarian
		II/III	Melanoma, RCC
		II	SCLC, GBM, NSCLC
Nivolumab + BMS-986016	Anti-PD1 + anti-LAG3	I	Solid tumors
Nivolumab + Viagenpumatucel-L	Anti-PD1 + vaccine	I	NSCLC
Nivolumab + urelumab	Anti-PD1 + anti-4-1ββ	I/II	Solid Tumors, B-Cell NHL
Atezolizumab + MOXR0916	Anti-PDL1 + anti-OX40	I	Solid Tumors
Atezolizumab + varlilumab	Anti-PDL1 + anti-CD27	II	RCC
Atezolizumab + GDC-0919	Anti-PDL1 + IDO inhibitor	I	Solid Tumors
Epacadostat + atezolizumab, durvalumab, or pembrolizumab	IDO inhibitor + anti-PDL1 or anti-PD1	I/II	Solid Tumors
Pembrolizumab + T-Vec	Anti-PD1 + vaccine	III	Melanoma
Durvalumab + tremelimumab	Anti-PDL1 + anti-CTLA-4	I/II	Melanoma
		I/II/III	SCCHN
		II	Mesothelioma, UBC, TNBC, PA
		III	NSCLC, Bladder
Pidilizumab + dendritic cell/RCC fusion cell vaccine	Anti-PD1 + vaccine	II	RCC

Immunotherapy Plus Chemotherapy

Combination Therapy	Mechanisms of Action	Phase	Indication
Nivolumab + platinum doublet chemo	Anti-PD1 + chemotherapy	III	NSCLC
Pembrolizumab + cisplatin	Anti-PD1 + chemotherapy	III	Gastric
Pidilizumab + lenalidomide	Anti-PD1 + chemotherapy	I/II	Multiple Myeloma
Pidilizumab +sipuleucel-T + cyclophosphamide	Anti-PD1 + vaccine + chemotherapy	II	Prostate
Atezolizumab + carboplatin/paclitaxel +/- bevacizumab	anti-PDL1 + chemotherapy +/- anti-VEGF	III	NSCLC

Immunotherapy Plus Targeted Therapy

Combination Therapy	Mechanisms of Action	Phase	Indication
Atezolizumab + bevacizumab	Anti-PDL1 + anti-VEGF	II/III	RCC
Atezolizumab + cobimetinib	Anti-PDL1 + MEK inhibitor	I	Solid Tumors
Atezolizumab + vemurafenib	Anti-PDL1 + BRAF inhibitor	I	Melanoma
Atezolizumab + erlotinib or alectinib	Anti-PDL1 =EGFR or ALK inhibitor	I	NSCLC
Nivolumab + bevacizumab	Anti-PD1 + anti-VEGF	II	RCC
Pembrolizumab + pazopanib	Anti-PD1 + tyrosine kinase inhibitor	I	RCC
Pembrolizumab + dabrafenib + trametinib	Anti-PD1 + BRAF inhibitor + MEK inhibitor	I/II	Melanoma
Durvalumab + dabrafenib + trametinib	Anti-PDL1 + BRAF inhibitor + MEK inhibitor	I/II	Melanoma
Nivolumab + sunitinib, pazopanib or ipilimumab	Anti-PD1 + RTK inhibitor, RTK inhibitor	I	RCC

Combination of PD-1, PDL-1 and CTLA-4 Blockade

- higher clinical response rates than single agent
  - melanoma, NSCLC, head and neck
- lower tolerability and higher discontinuation rates
- management of toxicity in broad patient populations in community settings
- cost
- dosing and sequence
- competition and cutting corners in dose optimization

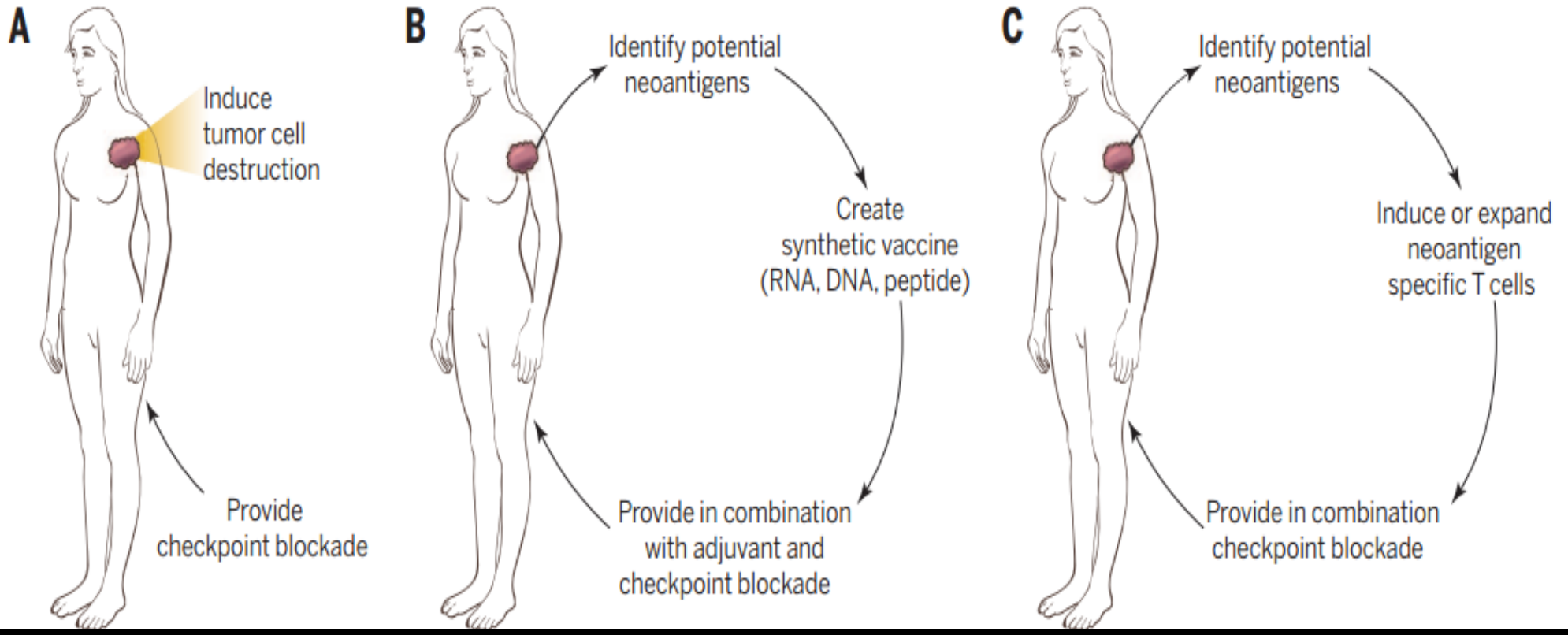
Cell-Based Therapies

Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

Immune Checkpoint Modulation

Cancer Neoantigen Vaccines

Adoptive Cell Therapy TILs, TCRs, CARs



Adapted From: T. N. Schumacher and R. D. Schreiber (2015) Science 348, 69

Adoptive T Cell Transfer in Cancer Immunotherapy

- collect patient's T cells
- expand T cells ex vivo
- +/- lymphodepletion/conditioning prior to reinfusion of expanded cells

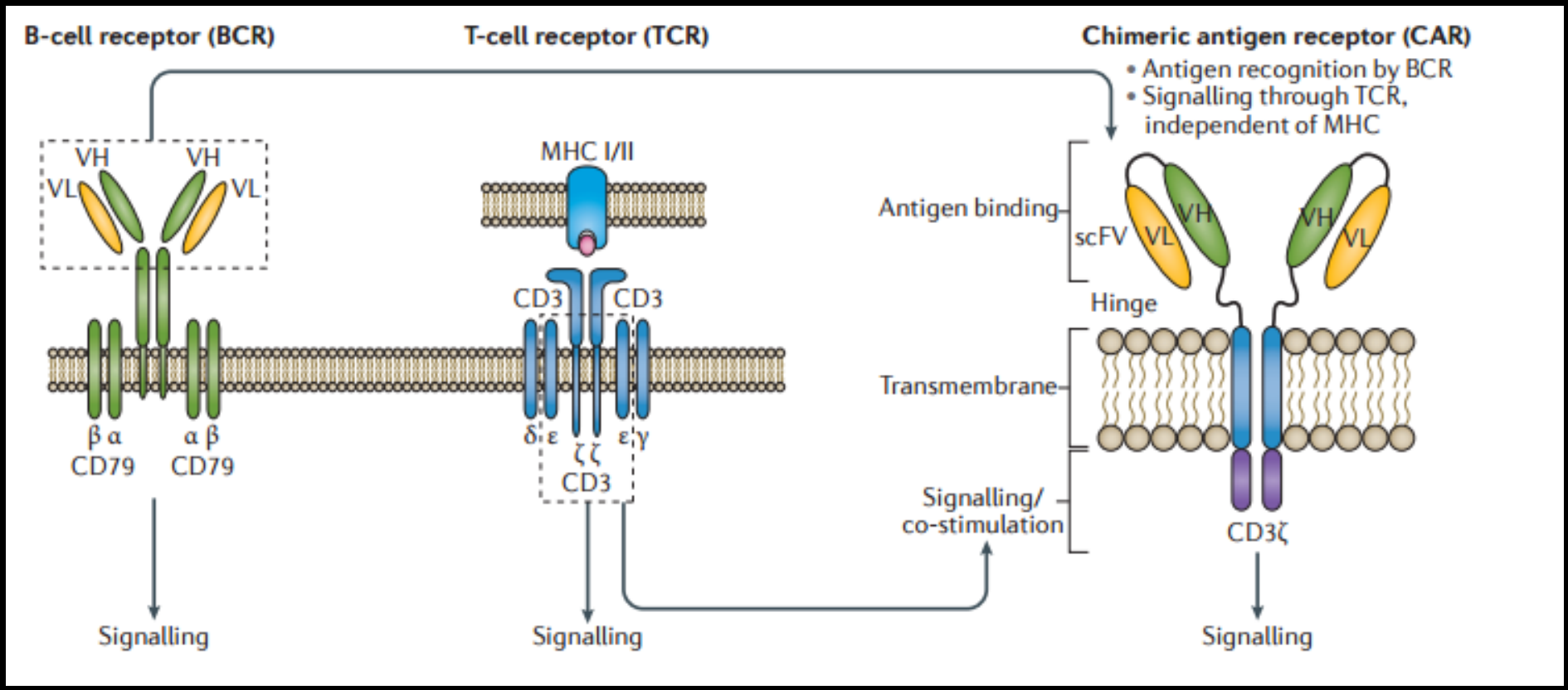
TILs

- no modification only expansion

TCRs and CARs

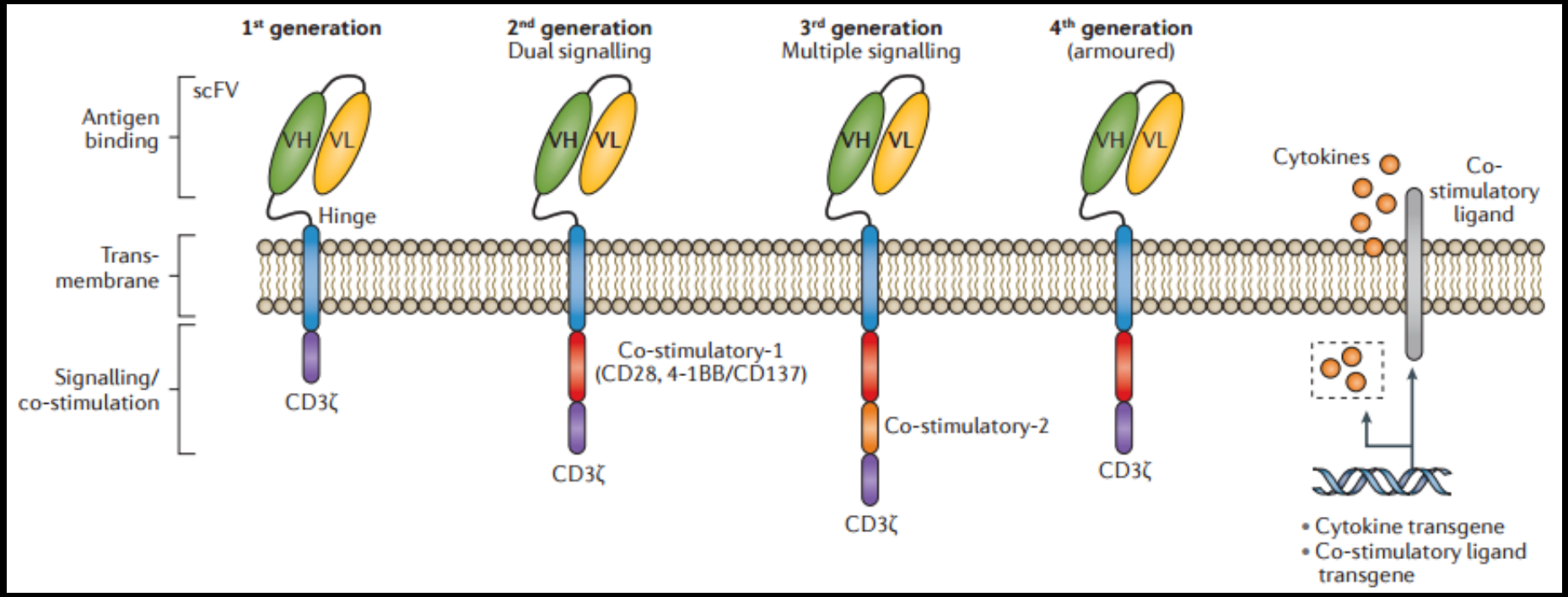
- transfection with genes for T cell receptors (TCRs) or chimeric antigen receptors (CARs) against specific tumor neoantigens

Design of Chimeric Antigen Receptors for Cancer Immunotherapy: Engineered Combination of Elements of Antibody Structure and T Cell Receptors



C.L. Batlevi et al. (2016) Nature Reviews Clinical Oncology 13,25

Design of Chimeric Antigen Receptors for Cancer Immunotherapy



C.L. Batlevi et al. (2016) Nature Reviews Clinical Oncology 13,25

Design of Chimeric Antigen Receptors

‘armored CARs’

- incorporation of additional T cell activation mechanisms into CAR-T cells to counter immunosuppression in the tumor microenvironment

‘switchable CARs’

- integration of ‘kill switches’ (reversible/irreversible) to shut down CAR-T cells for better control of toxicities

Future Needs in the Evolution CAR Therapy

- need to establish efficacy in solid tumors
- lymphodepletion by preconditioning appears necessary for successful treatment and CAR-cell persistence
- reduction of AEs and CRS
  - CRS is observed more frequently in patients with high tumor burden
  - merits of prior Rx tumor-debulking in improving safety profile?
- dose selection is difficult since transferred cell expansion in vivo appears highly variable
- reduce cost and complexity of ex vivo scale up of cells for reinfusion
- ‘off-the-shelf’ use of allogeneic cells HLA matched to recipients

NK Cells: The Next Target for Selective Activation of Anti-Tumor Cell Responses?

The Next Generation of Immuno-Oncology Therapeutics

Beyond CTLA-4 and PD-1/PD-L1 as Targets for Cancer Immunotherapeutics

Next Generation Immunotherapies

- better response rates
- extended durable clinical benefits
- better tolerability
- improved knowledge of how to best use I/O combinations or I/O plus SOC
- predictive biomarkers for reliable stratification of responder and non-responder patients and monitoring treatment efficacy

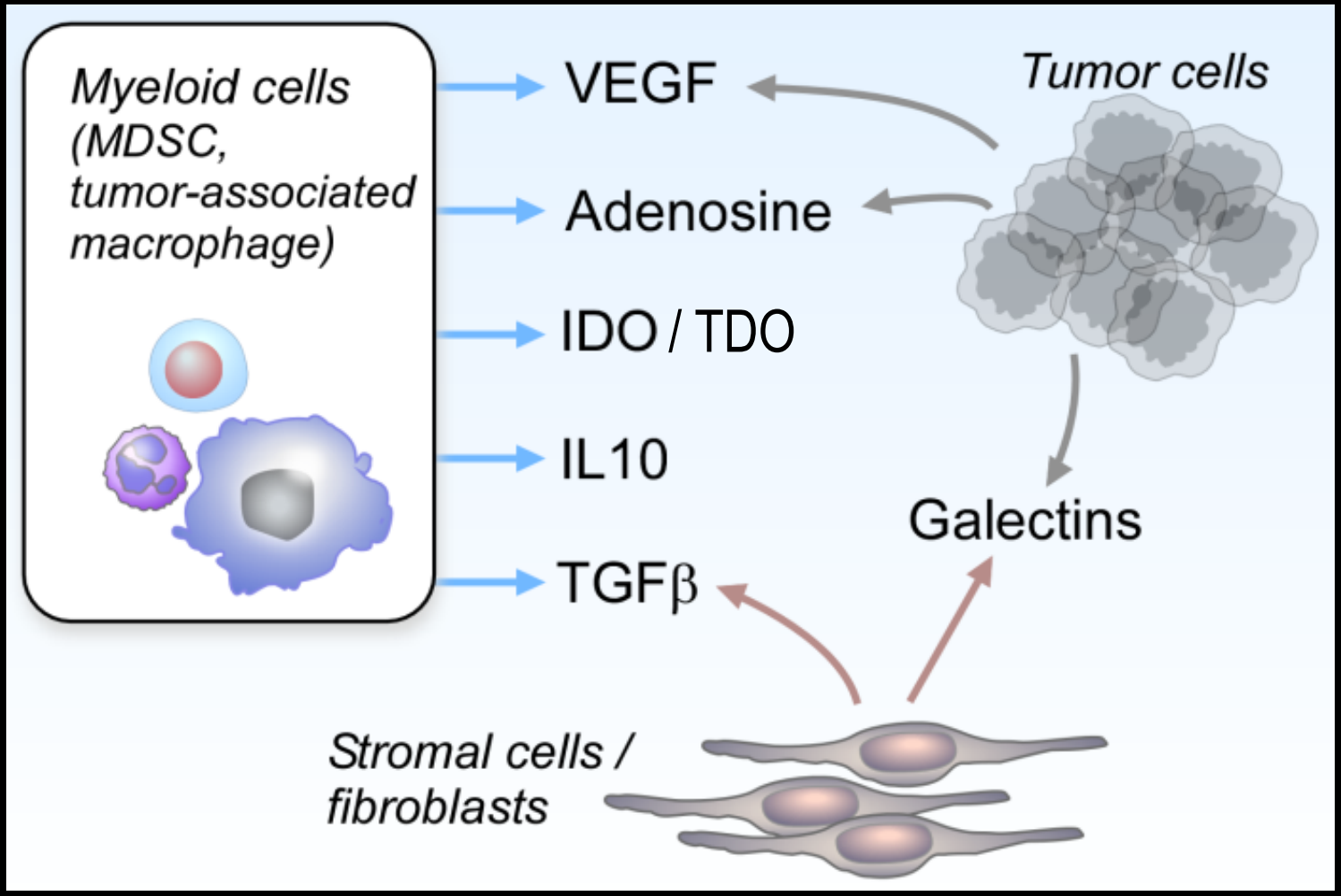
The Complex Dynamics of the Host Immune System-Tumor Ecosystem

- corrupted tumor microenvironment
  - protumor inflammatory responses and immunosuppressive signals
- intrinsic immune checkpoint regulators (suppression)
  - CD28-CTLA-4, PD1-PD-L1, TIM-3, LAG
- blockade of T cell infiltration
- extrinsic checkpoint regulators (suppression)
  - regulatory T cells (Tregs), myeloid suppressor cells (MDSC)
- T cell energy and exhaustion (suppression)
- immune evasion (escape)
  - antigen-deletion clones, neoantigens with low affinity

Negative Immune Checkpoint Regulators (NCRs) as New Targets for Next-Generation Immunotherapeutics

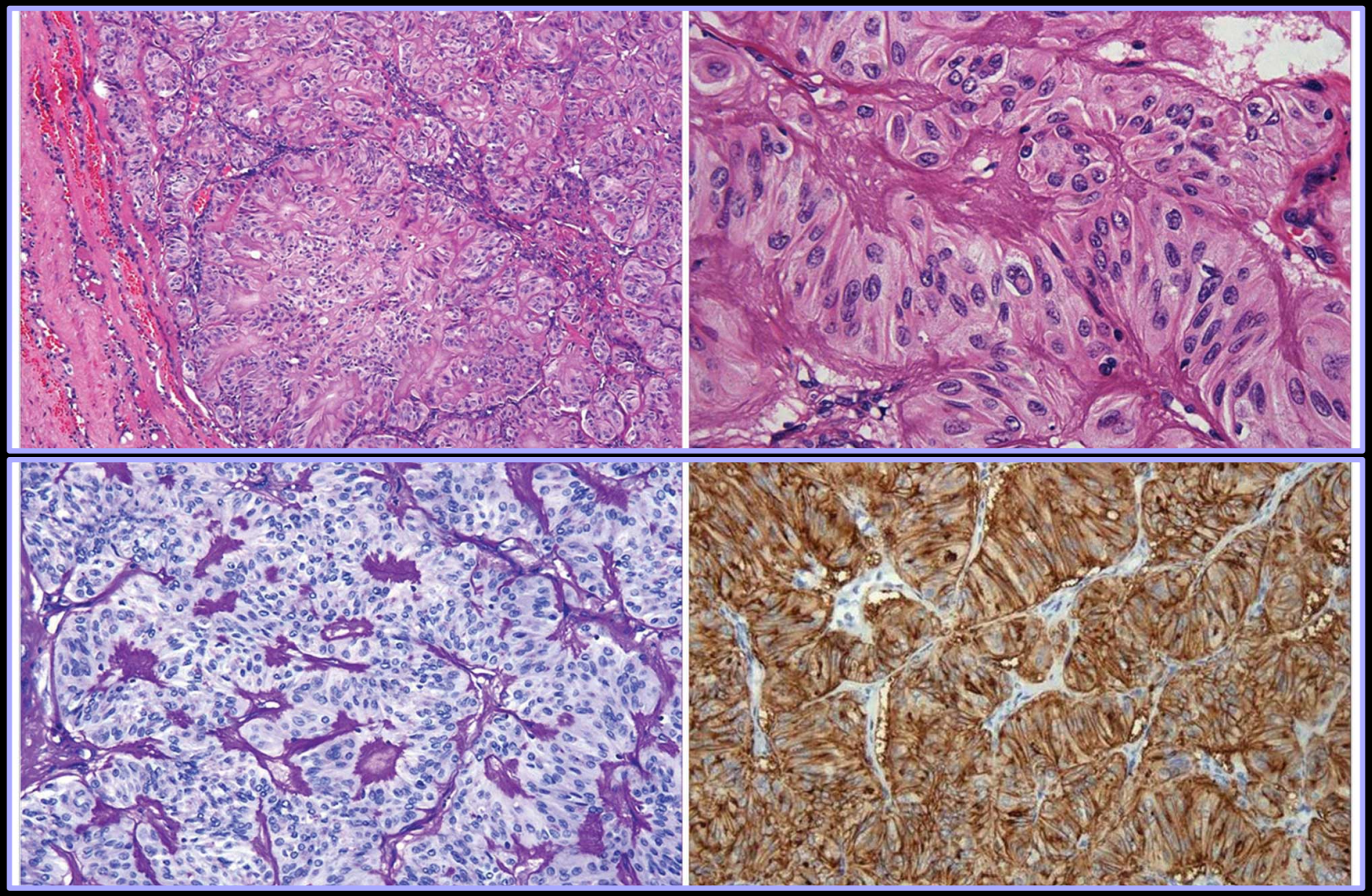
- TIM-3
  - T-cell immunoglobulin and mucin-containing protein 3
- LAG-3
  - lymphocyte-activated gene-3 (CD223)
- TIGIT
  - T-cell immunoreceptor with Ig and ITIM domains
- BTLA
  - B- and T-lymphocyte attenuator
- VISTA
  - V-domain Ig suppressor or T cell activatin

The Immunosuppressive Tumor Microenvironment
The New Frontier, A Wealth Of Targets



From: K.M. Mahoney et al. (2015) Clinical Therapeutics 34, 764

The Tumor Microenvironment and the "Stromagenic Switch"



The Stromagenic Switch

- role of stroma surveillance mechanisms in preventing tumorigenesis or imposition of dormant states
- transition of cancer-associated stromal cells (CASC) to protumorigenic drivers
  - inflammation
  - ECM remodeling
  - immunosuppressive signaling
  - M1 to M2 macrophage conversion
  - angiogenesis
  - invasion, EMT and metastasis
- altered stromal elements as new Rx Targets

Predictive Identification of Responder and Non-Responder Patients

Why Are Some Cancer Types More Responsive to Immunotherapy?

More Responsive

- melanoma
- NSCLC
- bladder
- renal
- head and neck

Less Responsive

- pancreatic
- colorectal
- ovarian

Immunogenic Versus Non-Immunogenic Tumor Microenvironments?

Immunogenic

- ‘hot’
- ‘inflamed’
- ‘stimulatory’

Non-Immunogenic

- ‘cold’
- ‘non-inflamed’
- ‘silent’

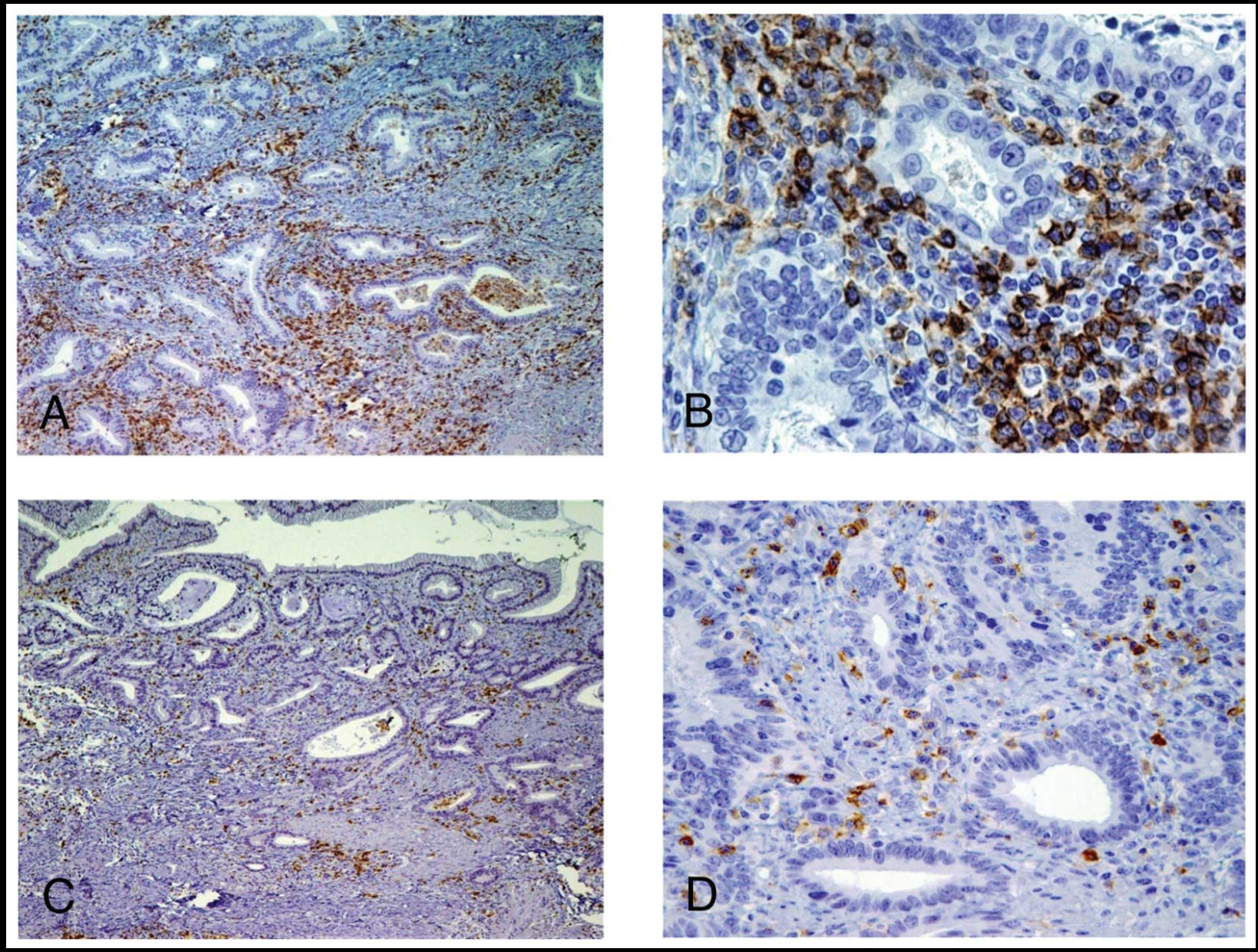
Immunogenic Versus Non-Immunogenic Tumor Microenvironments

Immunogenic	Non-Immunogenic
‘hot’	‘cold’
‘inflamed’	‘non-inflamed’
‘stimulatory’	‘silent’
high mutagenic burden	low mutagenic burden
high tumor neoantigen expression	low tumor neoantigen expression

Cancer Immunotherapy

- in situ infiltration of activated T cells is critical for therapeutic response and tumor regression
- not all immune infiltrates are equal
- therapeutic success depends on the dynamics balance of immune activation/suppression factors in the tumor microenvironment

T-Cell Tumor Infiltration



From: K. Wkatsuki et al. (2013) Spandidos Publications (DOI: 10.3892/or.2013.2302

Profiling Intratumoral Immune Cell Populations

positive prognosis: immune activation dominant

- cytotoxic T cells and memory-T cells
- antigen-presenting cells

negative prognosis: immune suppression dominant

- T regulatory cells (Treg)
- Th2 helper T cells
- myeloid-derived suppressor cells
- M2 phenotype macrophages

The Immunophenotype

Biomarker Development for Immuno-Oncology

Developing An Immunoscore for Individual Patients

The Paucity of Biomarkers to Identify Responder and Non-Responder Patients

- major problem in patient selection and cost of futile Rx
- conflicting data on relationship of PD-L1 expression and responsiveness to anti-PD1 therapy
  - KEYNOTE – 001: 45.2% of patients below predetermined PD-L1 cutoff still responded to pembrolizumab
- use of different antibody assay platforms and PD-L1 cutoff levels in different clinical trials

PD-L1 Expression and Response Rate (RR) for Immune Checkpoint Modulation in Melanoma

Agent	Response Rate		Median PFS Months	
	PD-L1 none/low	PD-L1 high	PD-L1 none/low	PD-L1 high
iplimumab	18	21	3	4
nivolumab	41	57	5	14
iplimumab plus nivolumab	54	72	11	14

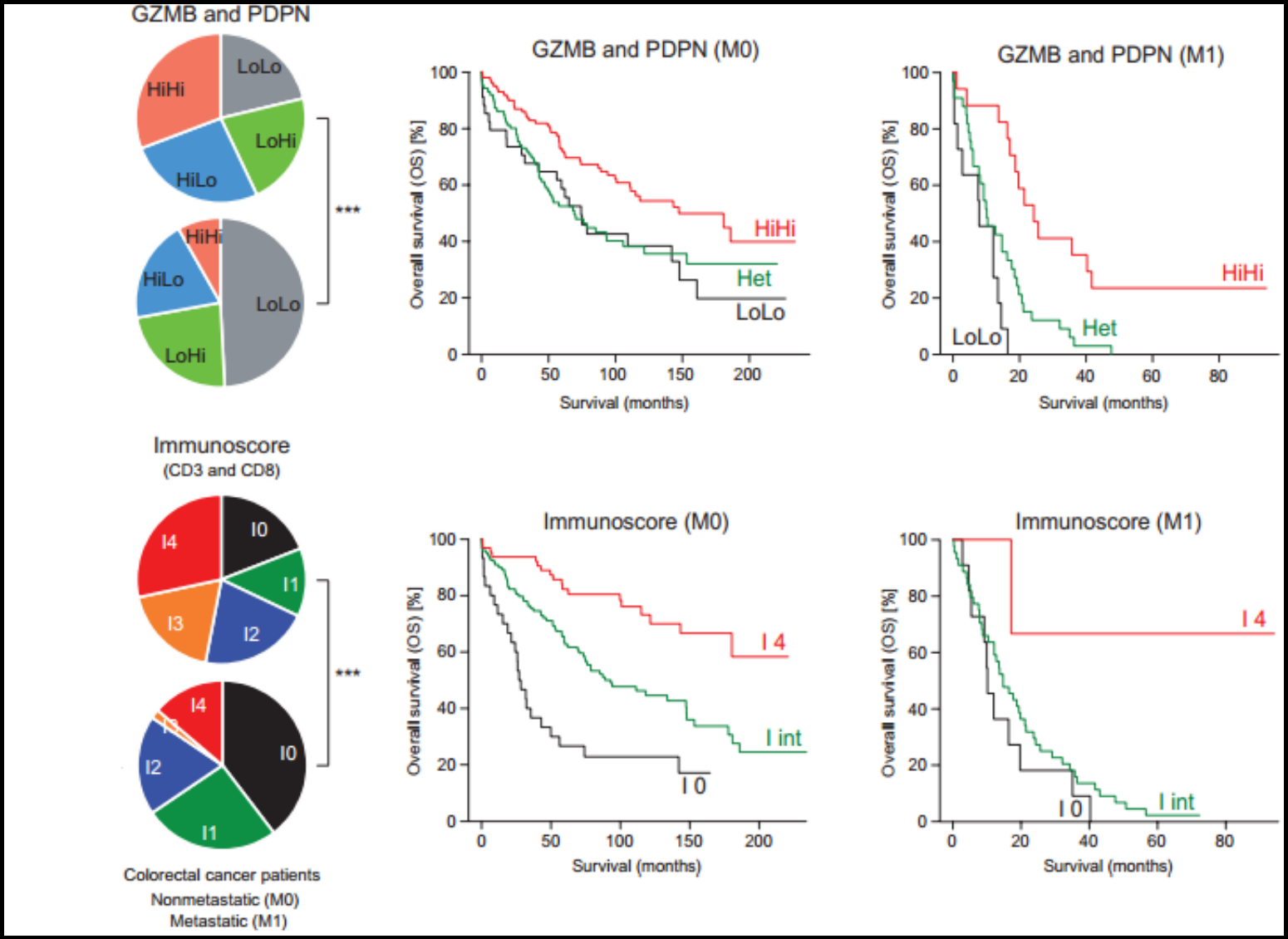
From: E.I. Buchbinder and F.S. Hodi (2016) Nature Rev. Oncol 13, 47

Immunophenotyping:
Biomarkers for Evaluation of Immune System 'States' and Prediction of Responder: Non-Responder Cohorts for Immunotherapy

- characterization of immune functions in three anatomic compartments
  - lymphoid organs/nodes, systemic circulation and neoplastic lesions

- formation of international consortium to establish a classification metric designated TNM-I (TNM-Immune)

Profiling of Intratumoral Core (GZMB) Cytotoxic T Cells and Lymphatic Vessel Density at the Invasive Margin (PDPN) in 838 CRC Patients and Relationship to Overall Survival

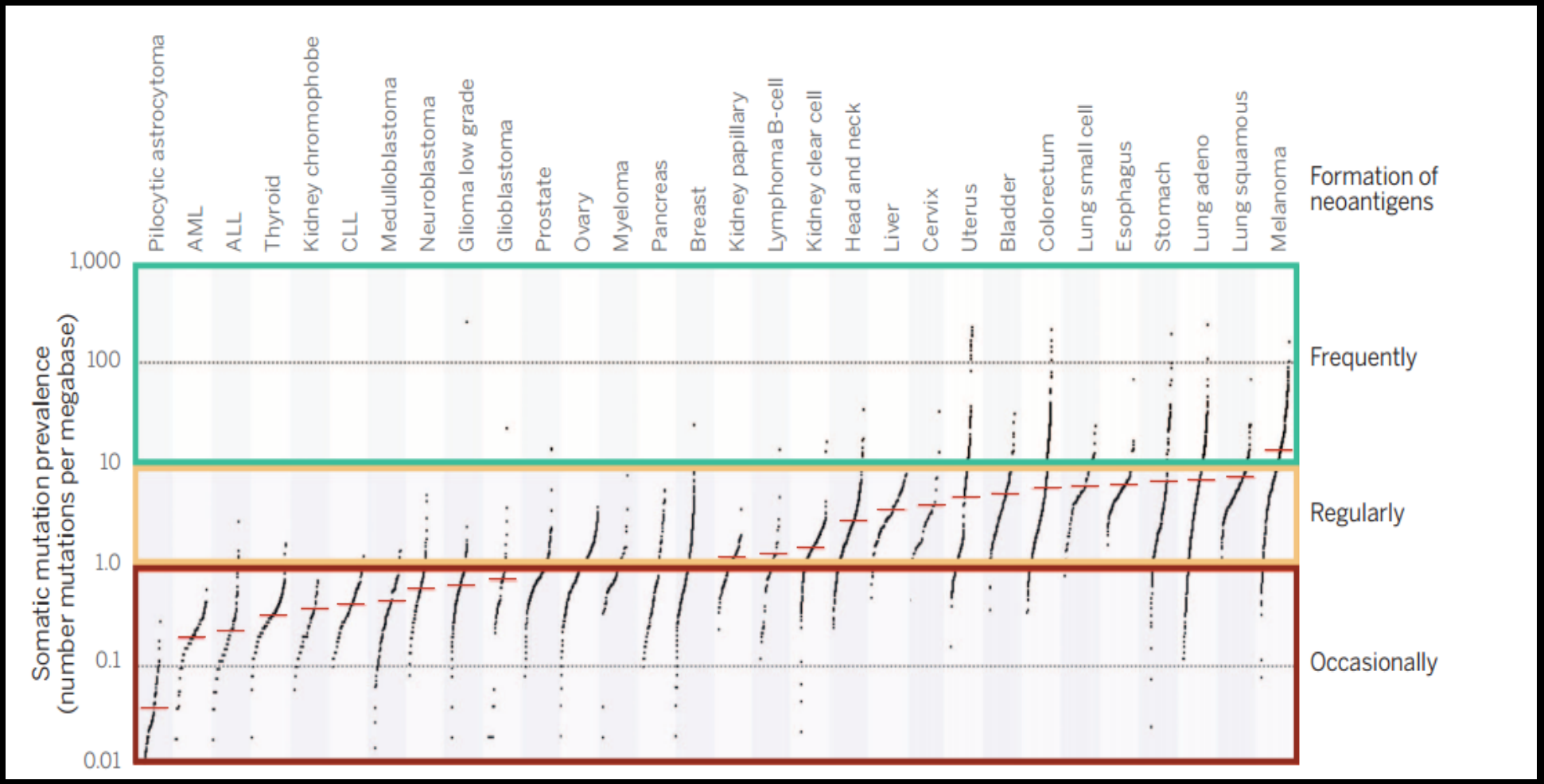


From: B. Mlecnik et al. (2016) Science Translational Medicine 8, 327ra26

The Tumor Mutational Landscape and Responses to Immunotherapy Agents

- hypothesis that high(er) non-synonymous mutation burden generates neoantigens recognized by the immune system
- patients with higher neoantigen burden exhibit higher durable clinical benefit (DCB)
- 'mutanome' profiling
  - ID mutant nonamer peptides with <500nM binding affinity for patient-specific class I HLA alleles
- combination with targeted anti-cancer agents
  - increase neoantigen release?

Estimates of Likelihood of Neoantigen Expression Based on Somatic Mutation Prevalence in Different Tumor Types

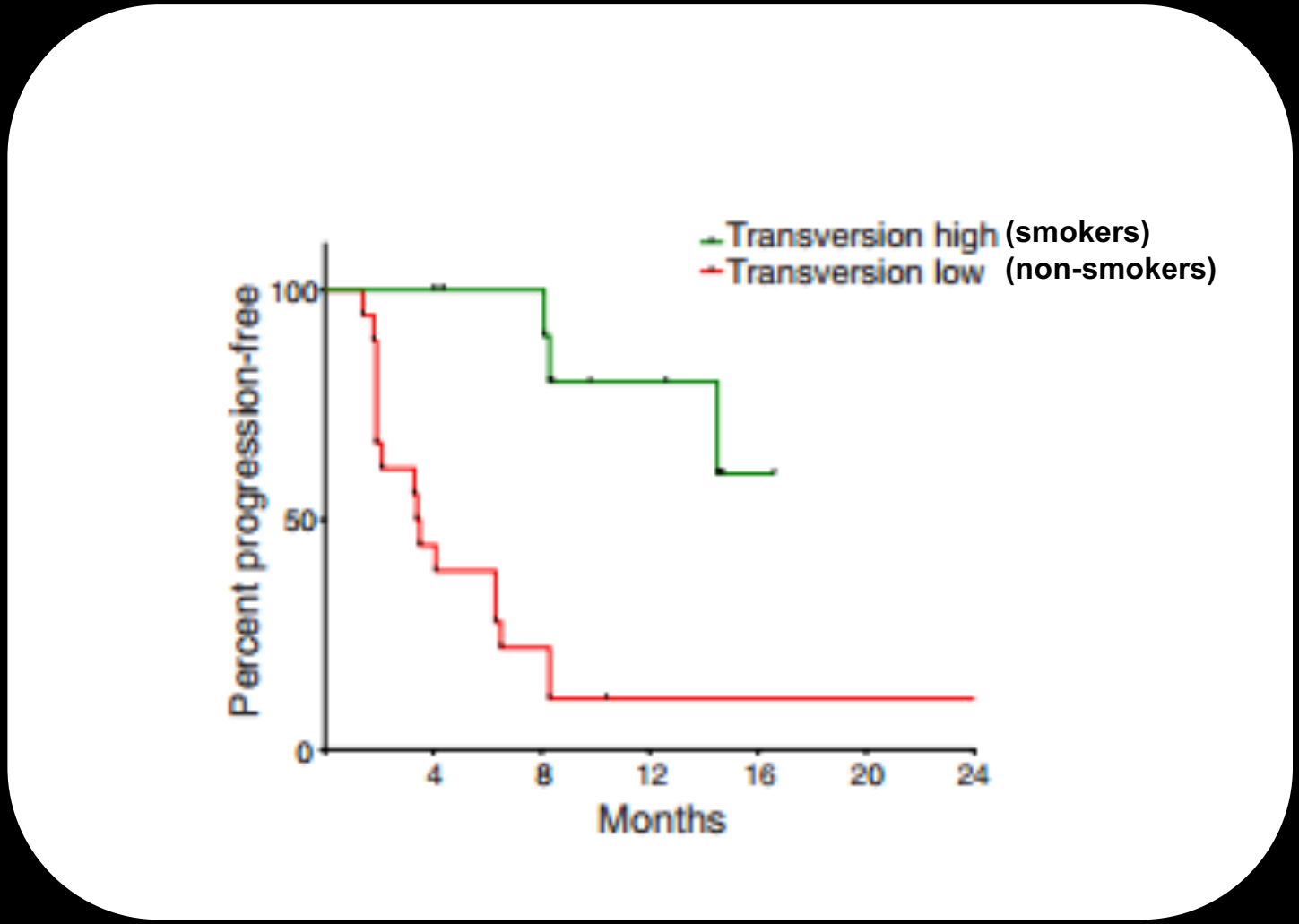


Adapted from: T. N. Schumacher and R. D. Schreiber (2015) Science 348, 69
and L. B. Alexandrov et al. (2013) Nature 500, 415

The Tumor Mutational Landscape and Response to Immunotherapy Agents

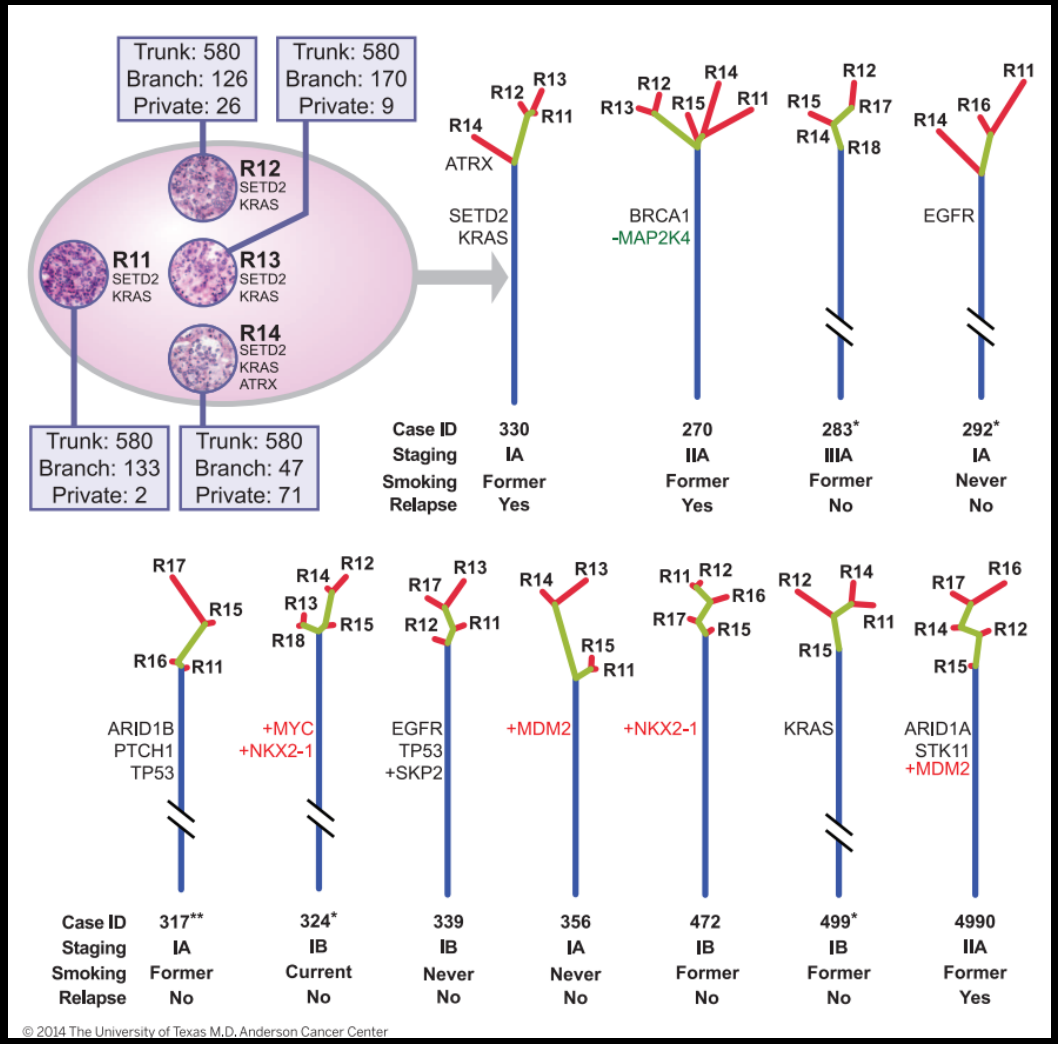
- higher non-synonymous mutation burden correlates with improved objective response, PFS and durable clinical benefit
- highest response rates in melanoma and NSCLC
  - chronic mutagen burden (UV, tobacco carcinogens)
- high inter-patient variation in NSCLC
  - smokers vs non-smokers
  - paradoxical greater DCB in smokers to PD-1 blockade

Molecular 'Smoking Signature' in NSCLC and PFS in Patients Treated with Pembrolizumab



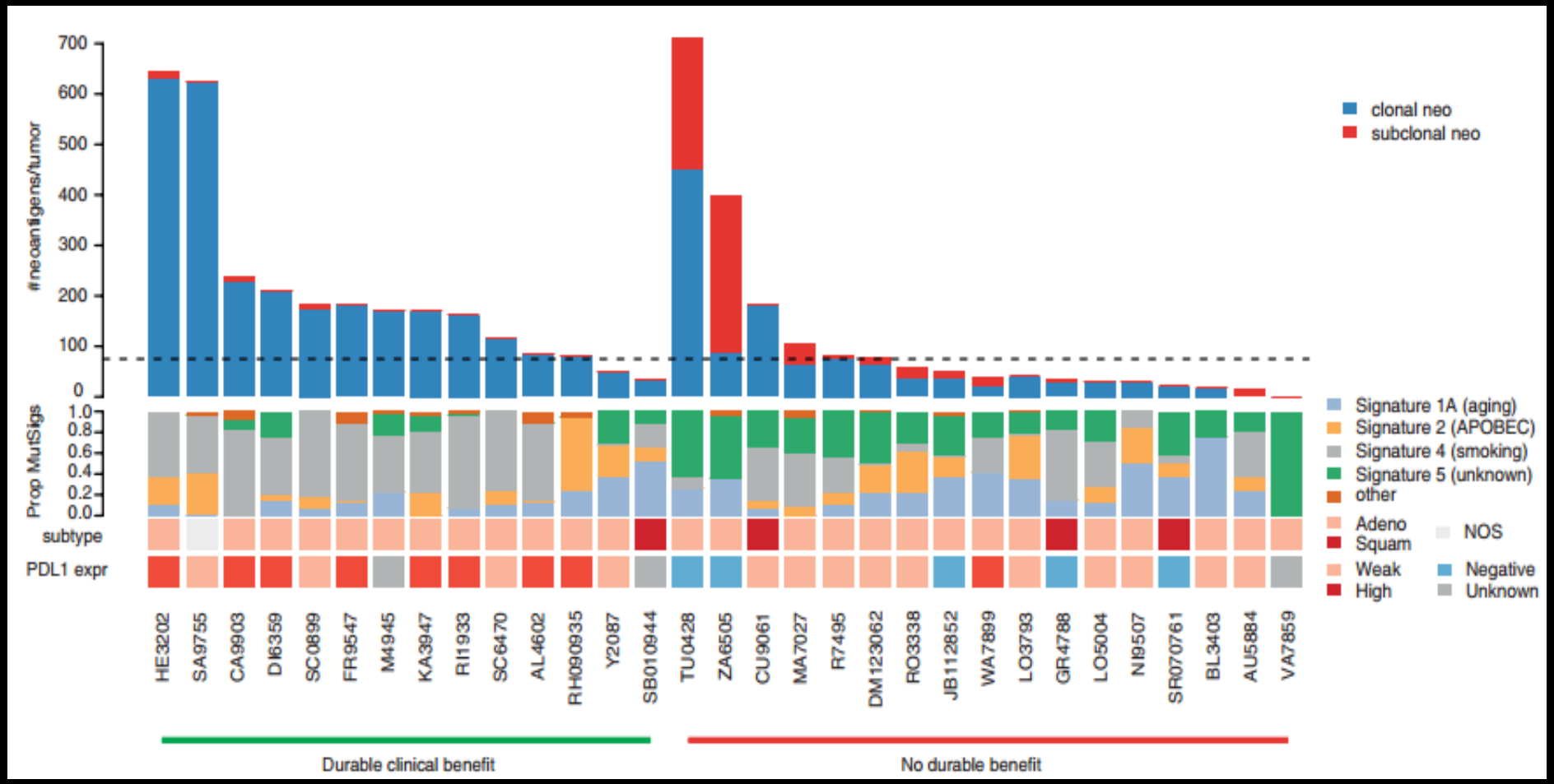
From: N.A. Rizvi et al. (2016) Science 348, 124

Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches



From: J. Zhang et al. (2014) Science 346, 256

Neoantigen Clonal Architecture and Clinical Benefit of Immune Checkpoint Blockade (anti-PD1 pembrolizumab)



From: N. McGranahan et al. (2016) Science DOI.10.1126/aaf490

Use of Combination Therapies to Increase Neoantigen Expression and Release

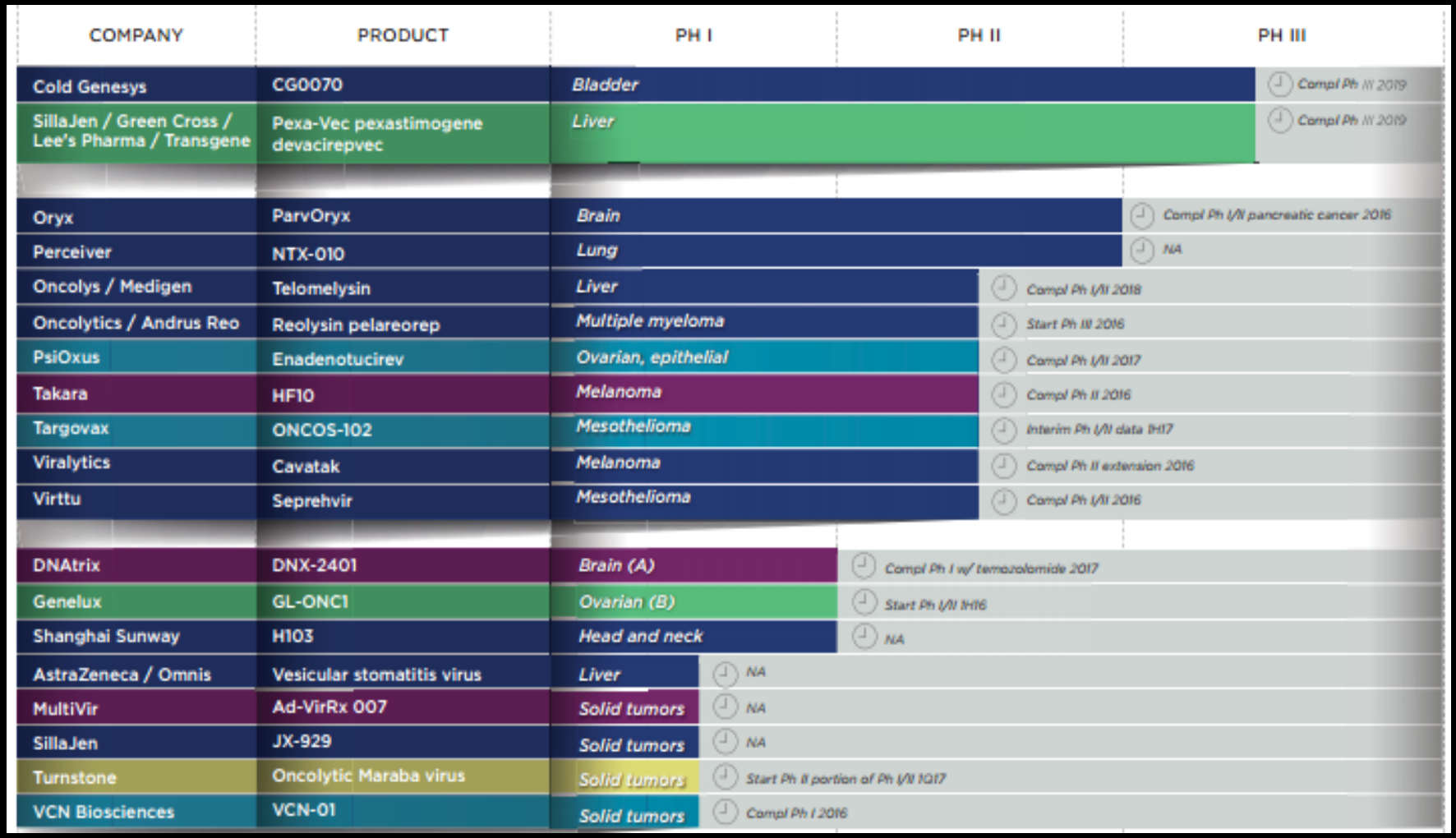
Lessons from Breast Cancer Trials of HER-2 Kinase Inhibitors

- trastuzumab as a singular success story for HER-2 positive breast cancer
- exploration of value of small molecular TKIs
  - lapatinib (EGFR + HER2) afatinib (EGFR, HER2, HER4) neratinib (HER1, HER2, HER4)
  - inferior outcomes and higher toxicity
- is consistent superiority of trastuzumab over other TKIs due to additional effects on immune responses?
  - tumors enriched for immune signatures benefit from trastuzumab
  - level of tumor-infiltrating lymphocytes predicts trastuzumab benefit
  - not all studies concordant

Potential Previously Unrecognized Immunostimulatory Effects of Conventional Chemotherapeutics?

- low dose, metronomic administration schedule with immune checkpoint agents and enhanced responses?
- off-target effects in activation of immune system directly?
  - 5-fluorouracil killing of tumor-associated myeloid suppressor cells
- value in increasing mutagen burden and neoantigen expression as activation trigger for immune response?

Oncolytic Pipeline

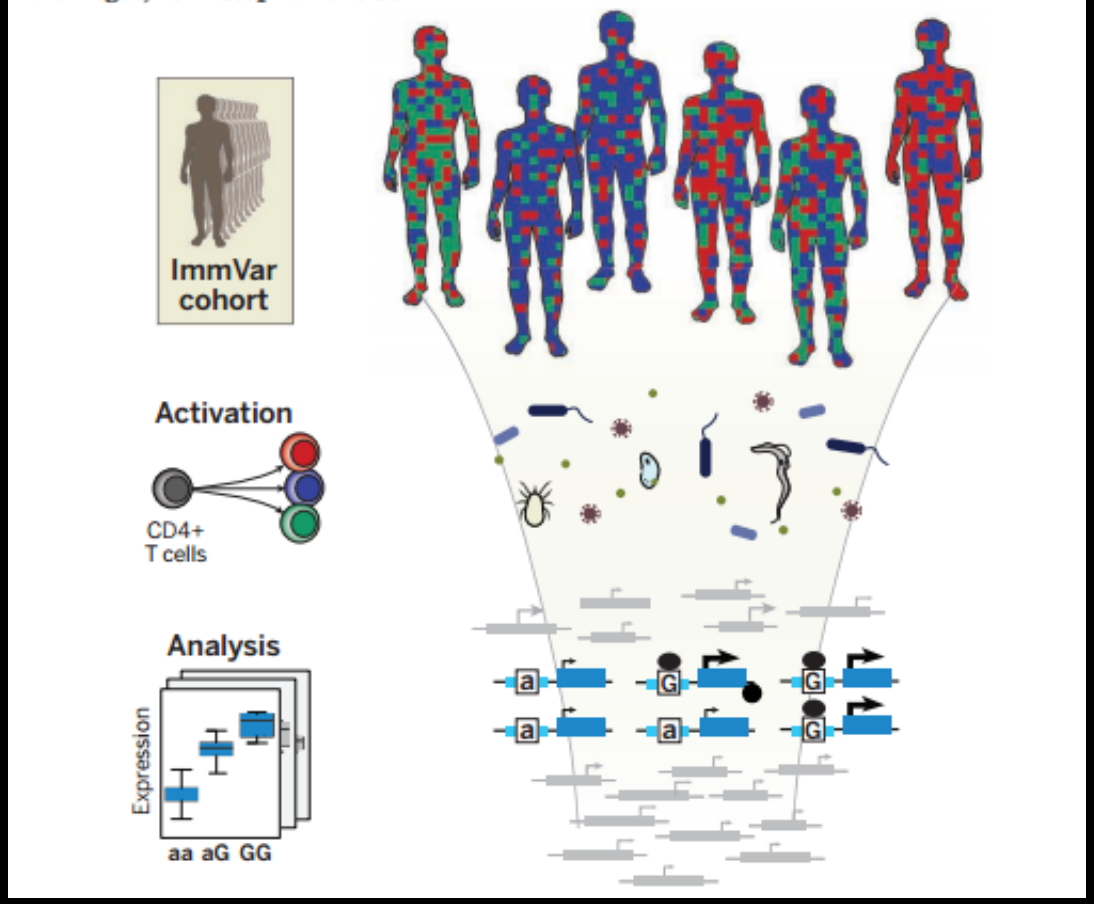


Biocentury 02/29/16

Science (2014) 345, 1254, 665

Intersection of population variation and autoimmunity genetics in human T cell activation

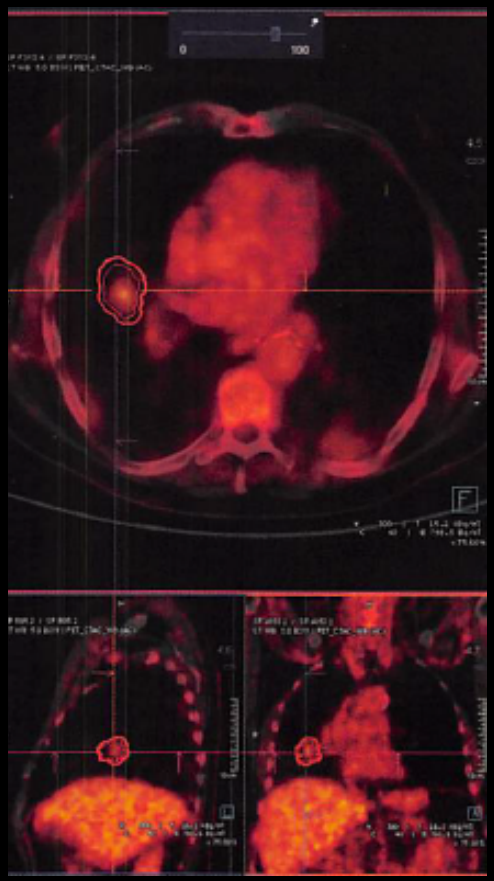
Chun Jimmie Ye, Ting Feng, Ho-Keun Kwon, Towfique Raj, Michael Wilson, Natasha Asinovski, Cristin McCabe, Michelle H. Lee, Irene Frohlich, Hyun-il Paik, Noah Zaitlen, Nir Hacohen, Barbara Stranger, Philip De Jager, Diane Mathis, Aviv Regev,* Christophe Benoist*



Immunogenetics: Individual Genetic Variation in Immune Responses

- how does individual genetic variation affect the nature and intensity of T cell responses?
- identification of single nucleotide polymorphisms that influence susceptibility/relative resistance to autoimmune diseases and responses to pathogens
- wide individual variation and eQTLs polymorphisms for activation-induced cytokine levels
- no information on how these parameters may link to individual variation in immunotherapy-induced anti-tumor responses

Imaging Endpoints for Immunotherapy Response Evaluation



- limitations of traditional RECIST criteria due to ‘pseudo-progression’ caused by T cell infiltration/inflammation edema
  - tumor size and density
- nivolumab CheckMate 057 trial
  - reported short PFS but significant prolongation of OS
  - superiority versus docetaxal at 9 months
- development of irRECIST criteria

Need for New Minimally-Invasive Assays for Monitoring Patient Responses to Immunotherapy

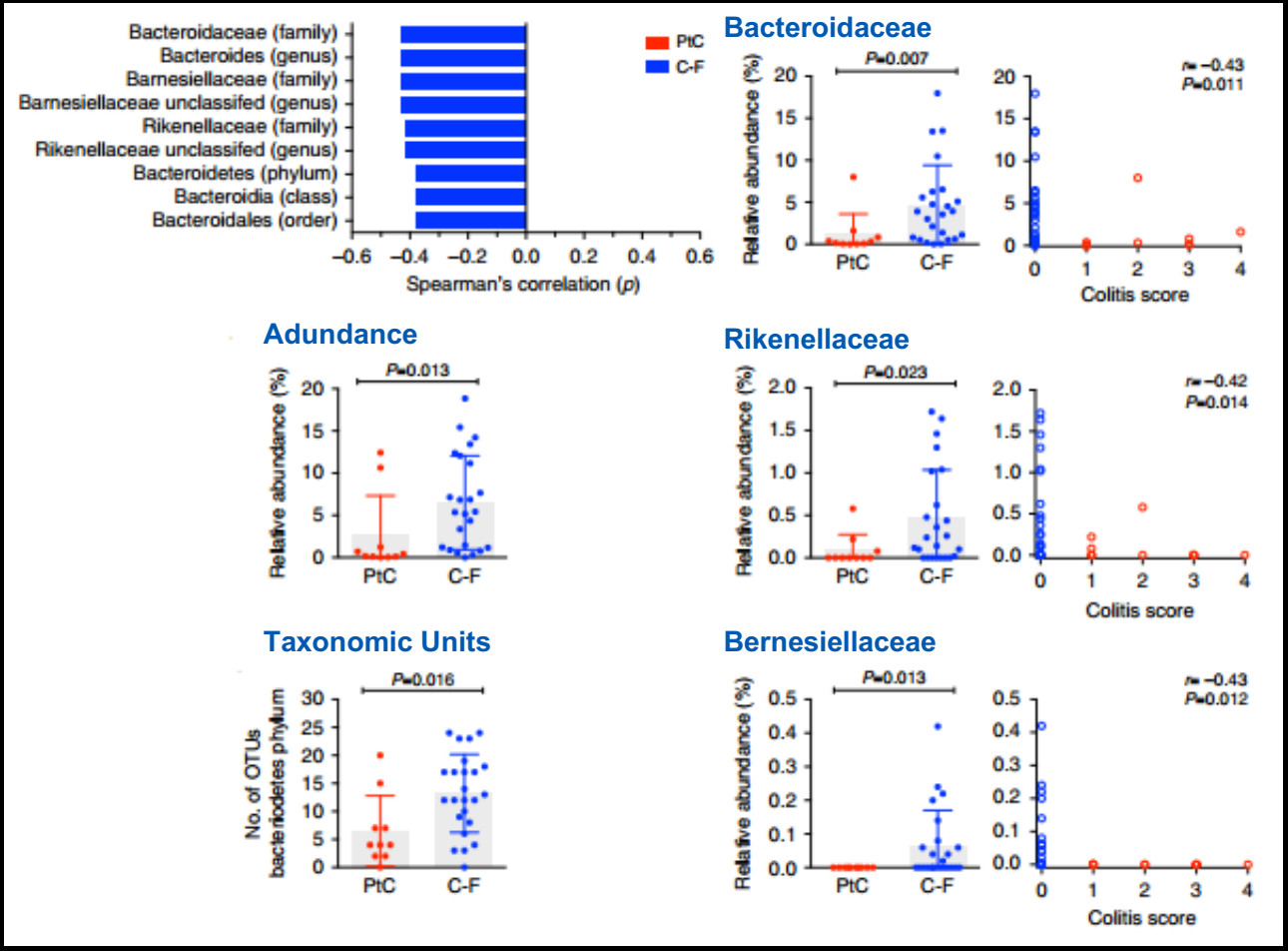
- ‘static’ snapshot of immune profile in resected lesions/biopsies versus longitudinal monitoring of dynamic changes with tumor progression /Rx responses
- how far does the immune profile assayed in blood (liquid biopsy) mirror intratumoral events in anatomically dispersed metastases?
  - immune cell subsets?
  - cytokines?
  - ctDNA?
  - exosomes?

Does the Gastrointestinal Microbiome Affect Immunotherapy Efficacy?

A Role for the Microbiome in Regulating Systemic Cancer Risk, Immune Responses and Responses to Therapy?

- gut microbiota dramatically impacted by many anti-neoplastic drugs
- translocation of gut microbiota across intestinal epithelium and activation of DCs in lympho-depleting irradiation and improved responses to ACT
- *Bifidobacterium* prevalence influences efficacy of anti-PD-1 and anti-CTLA-4 mAb therapy and efficacy reduced by antibiotic therapy

Immune-Medicated Colitis in Melanoma Patients Treated with CTLA-4 Blockade Correlates with Lower Levels of Bacteroides Phylum Families in the Gut Microbiome



Adapted from: K. Dubin et al. (2016) Nature Communications 10391

Could Selective Manipulation of Gut Microbiota Impact Cancer Risks and/or Improve Efficacy of Some Anti-Cancer Therapies?*

- adverse impact of antibodies in eliminating 'beneficial' species?
- use of antibiotics to reduce untoward bacterial species?
- use of probiotics to optimize 'beneficial' species?
- postbiotics: metabolic products from 'beneficial' species that exert therapeutically valuable effects?

*L. Zitvogel et al. (2015) Sci. Trans. Med 7, 2741psl
Cancer and the gut microbioata. an unexpected link

Price and Affordability!!!

The Cost of Complex Cancer Care

Evan Johnson sits on a terrace at the Mayo Clinic Hospital, Methodist Campus in Rochester, Minn. during the summer of 2014.

- **AML**
- **An 18 month journey to remission**
- **3 approved drugs, 2 investigational drugs**
- **2 stem cell transplants**
- **$4 million dollars**

From: Winslow, R. (2016) Cancer Treatment's New Direction. WSJ

Is Widespread Adoption of Immunotherapy Economically Feasible?

April 2016

- direct Rx cost
- indirect care cost
- escalating cost of combination regimens (> $200K)
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- complex clinical management challenges and compatibility with community oncology services

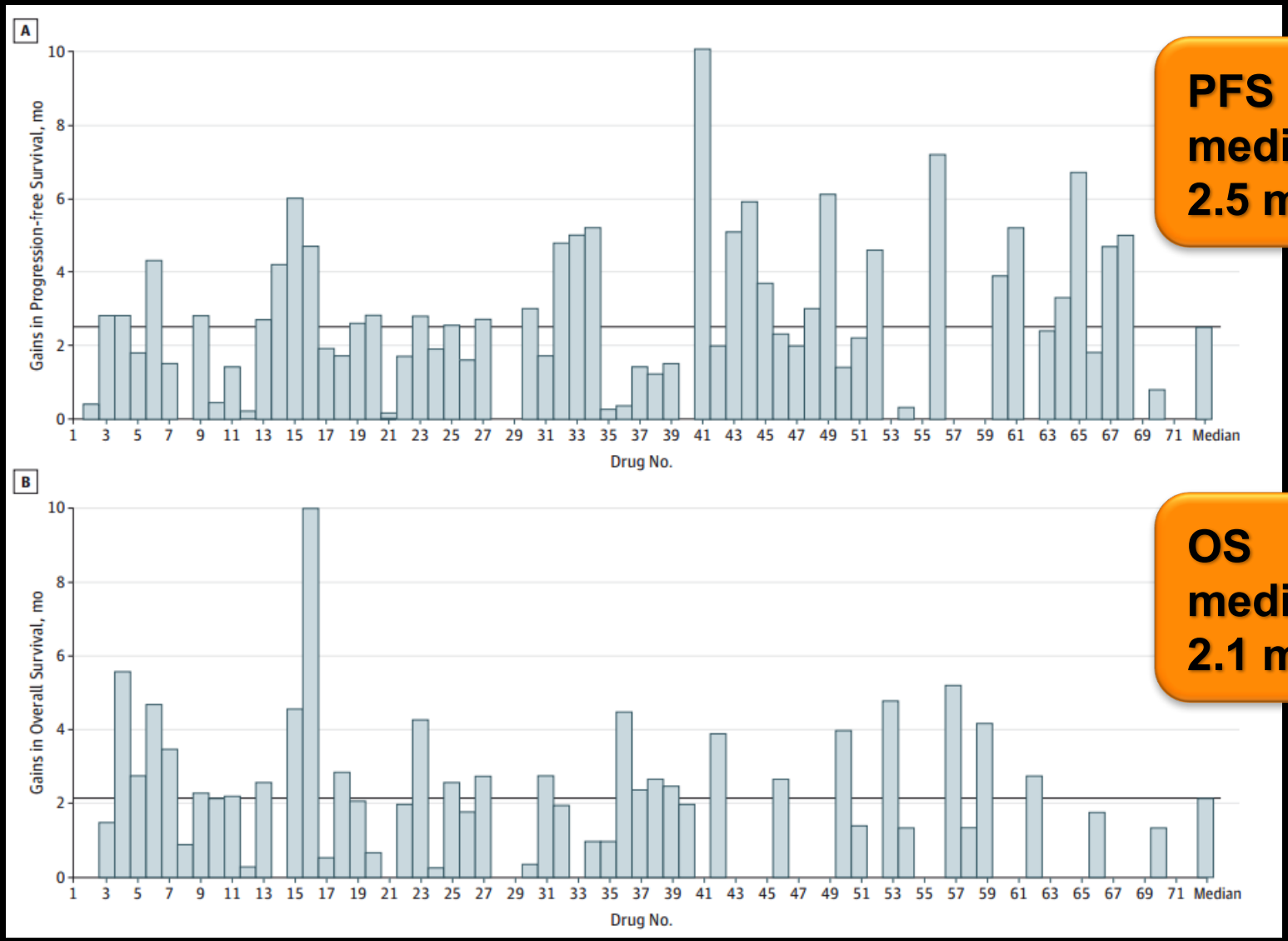
What Are We Willing to Pay for Added Months of Survival in Cancer?

Lifetime cost above standard care	If cancer is on par with other diseases ($150,000 per life year gained), months of added overall survival benefit needed	Treating cancer as worthy of much higher reimbursement ($250,000 per life year gained), months of added overall survival benefit needed
$50,000	4 months	2.4 months
$100,000	8 months	4.8 months
$150,000	12 months	7.2 months
$200,000	16 months	9.6 months
$250,000	20 months	12 months
$300,000	24 months	14.4 months
$350,000	28 months	16.8 months
$400,000	32 months	19.2 months
$450,000	36 months	21.6 months
$500,000	40 months	24 months

Source: Pink Sheet 13 Sept. 2010. Adapted from S. Ramsey FHCRC, ASCO 2010

Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors



PFS median 2.5 months

OS median 2.1 months

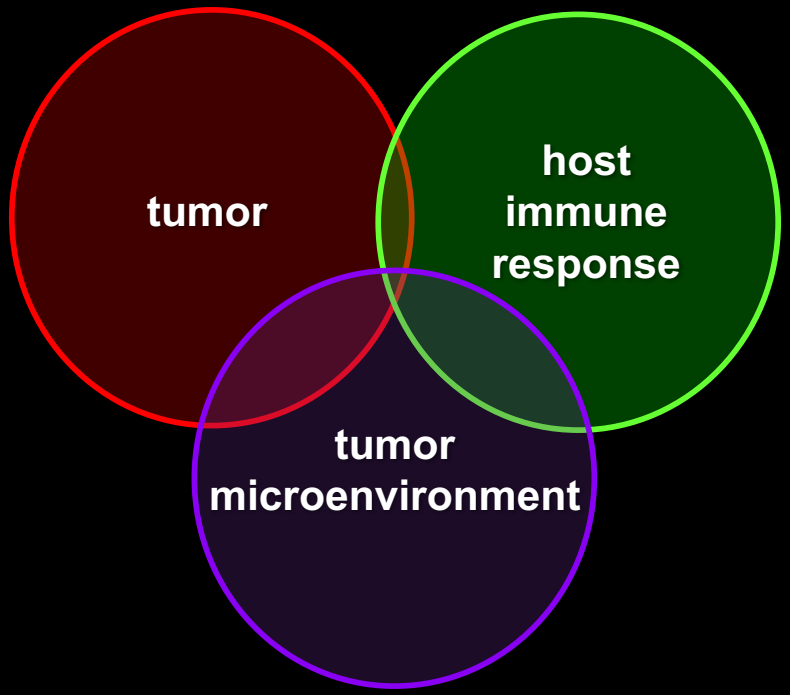
From: T. Fojo et al. (2014) JAMA Otolaryngology–Head & Neck Surgery 140, 1225

Value-Based Rx Pricing of Oncology Therapeutics

- outcomes-based payments
- indication-specific pricing
- reference pricing (maximum price for all drugs in a therapeutic class)

Deconvolution of the Multi-Dimensional Matrix of Immuno-Oncology Therapeutics

- clonal
- heterogeneity
- mutagen burden
- neoantigen profile



balance of stimulatory and suppressive factors

- complex non-immune cell contributions to suppressive environment
- localization of immune cells/ soluble mediators and impact of Rx

The Evolution of Cancer Immunotherapeutics

- likely to become SOC in increasing number of indications
- need for better informed rationale for combination regimens
- identification of new I/O intervention points
  - Tregs, MDSC, NK cells, TME resistance mechanisms
- risk of MDR and recurrence in long DOR patients?
- improved immunophenotyping (immunoscore) of individual patients for predictive ID of responders and non-responders
- intense competitive corporate landscape and massive financial investments
- price and new pharmaco-economic-realities for approval and reimbursement

KEEP
CALM
AND
boost your
immune system