Otis W. Brawley, MD, MACP, FASCO, FACE

Chief Medical and Scientific Officer
American Cancer Society

Professor of Hematology, Medical Oncology,
Medicine, and Epidemiology
Emory University

Some perspectives on American healthcare: the past, the present and the future of cancer medicine.

What we must do to control cancer?

US Cancer Statistics, 2016

It is estimated that this year will see:

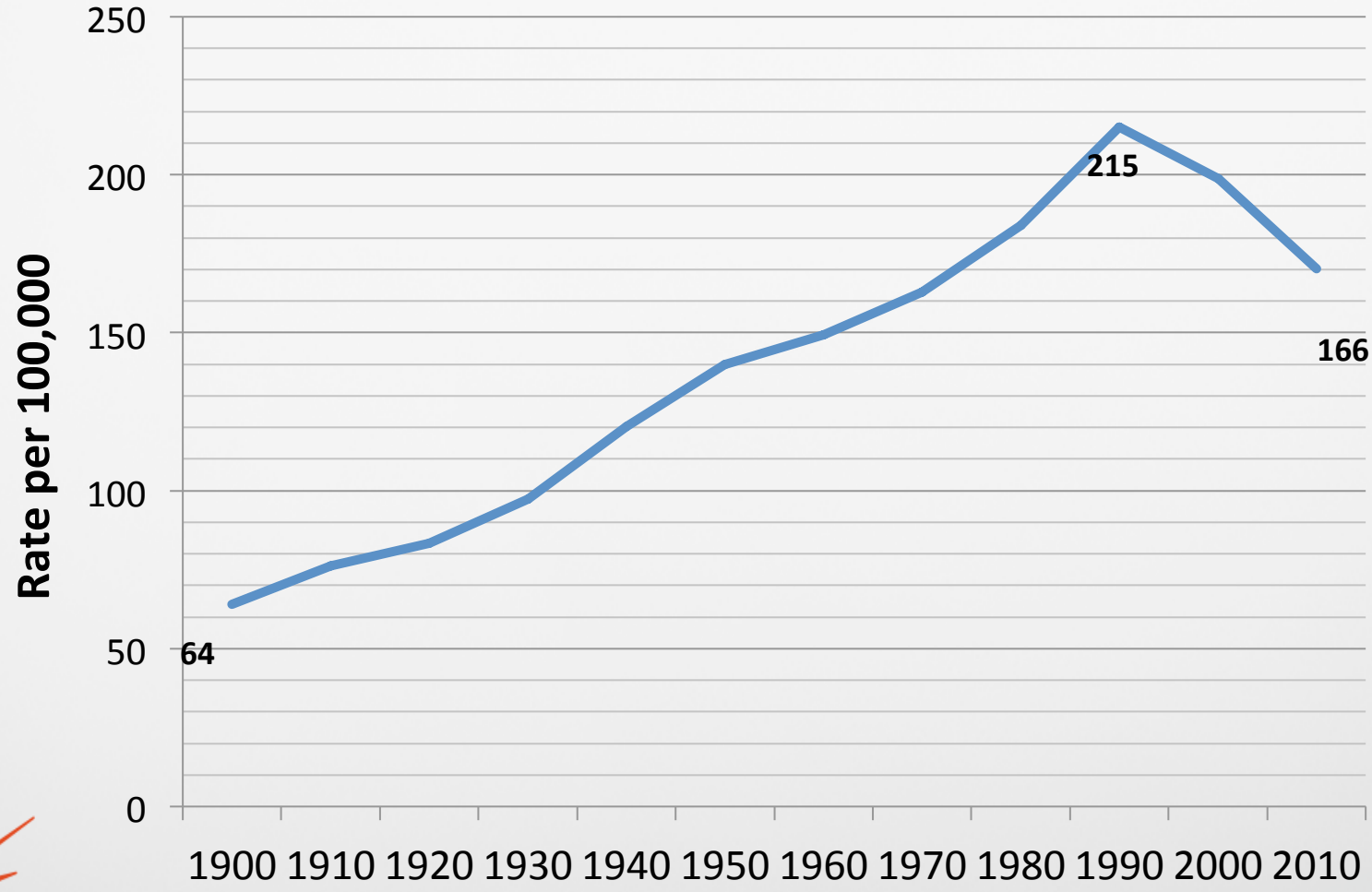
-1.69 million cancers diagnosed

-596,000 cancer deaths

-148,000 Cancer deaths preventable*

*If all known prevention and treatment disseminated

US Cancer Age-Adjusted Death Rate
1900 to 2012



1900-1970, US Public Health Service, Vital Statistics of the US, Vol. 1 and Vol 2;
1971-2012, US National Center for Health Statistics, Vital Statistics of the U.S

Cancer Statistics, 2016

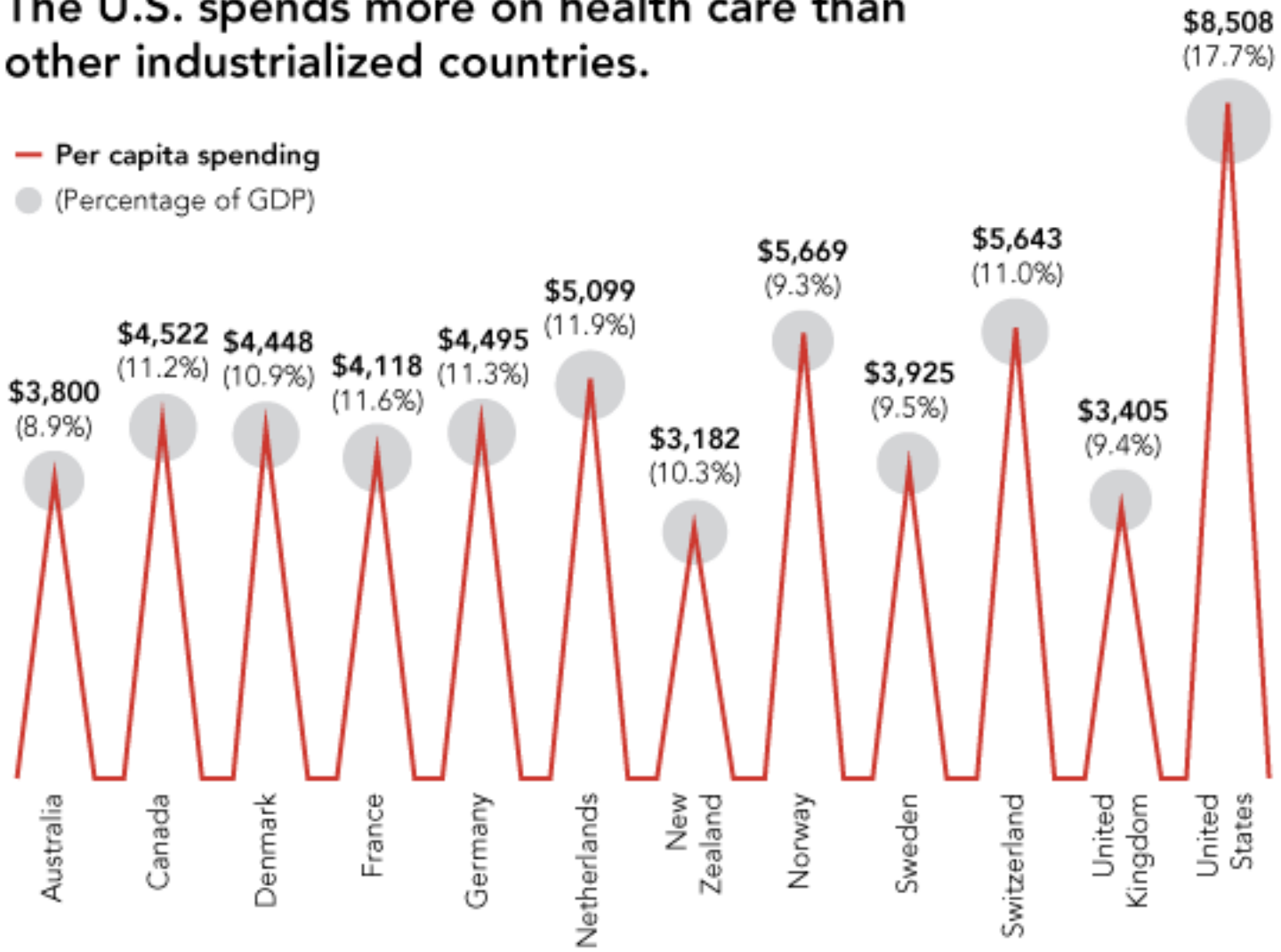
A 23% decline in age-adjusted mortality rate over 23 years.

1.7 million Americans did not die a cancer death!

Reasons for the Decline in Age-Adjusted Death Rate

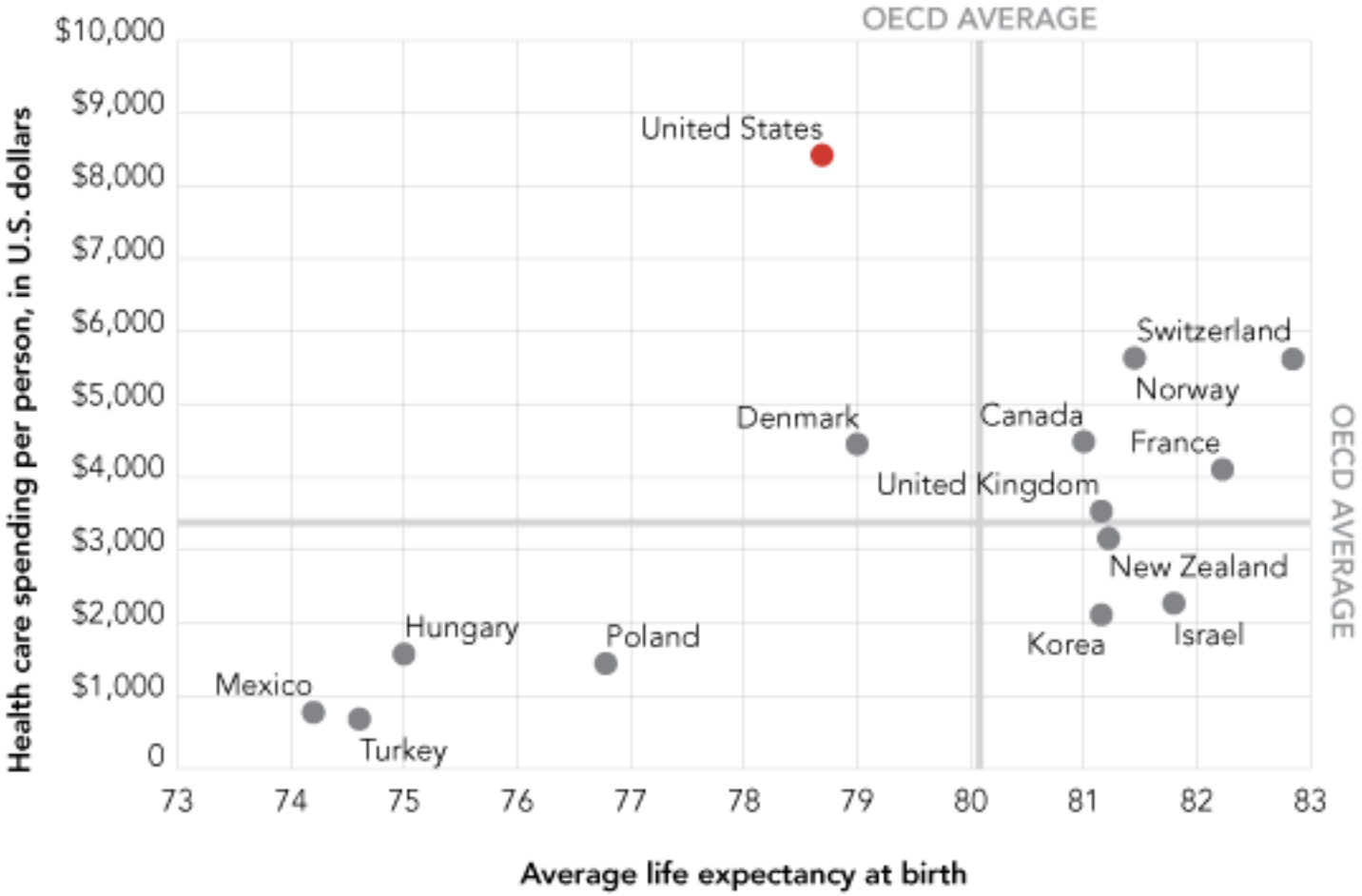
1. Prevention of Cancer
2. Improvements in Treatment
3. Increased Awareness of Cancer
4. Effective Cancer Screening

The U.S. spends more on health care than other industrialized countries.



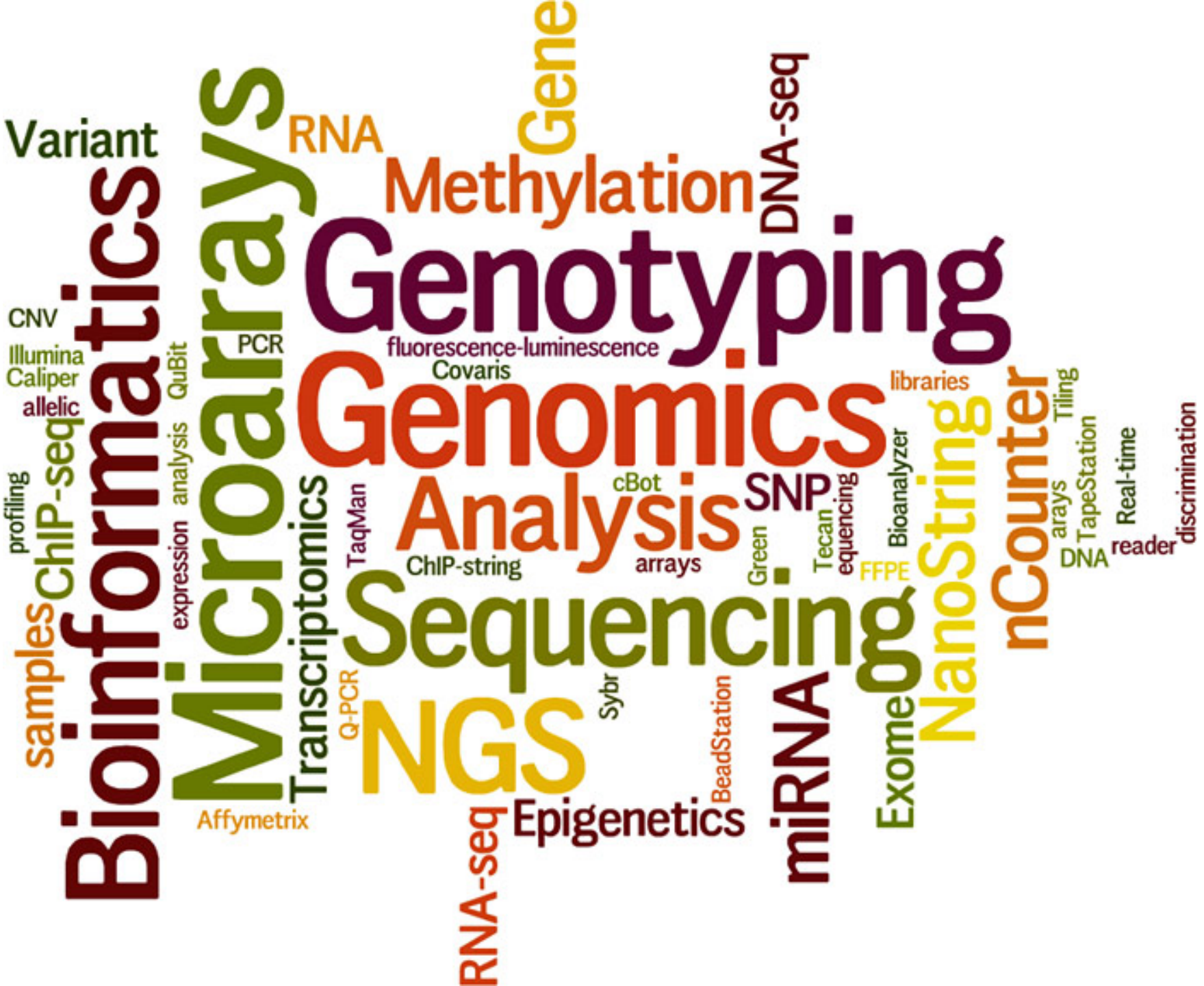
Notes: Data is from 2011 or nearest year. Netherlands spending measured as current expenditure. New Zealand numbers exclude investments.
Source: OECD Health Data 2013

Americans don't live longer than people in countries that spend much less on health care.



Notes: Data is from 2011 or nearest year. New Zealand numbers exclude investments. Not all OECD countires are inlcuded.
Source: OECD Health Data 2013

The National Cancer Act, December 23, 1971


Variant
RNA
Gene
Methylation
DNA-seq
Genotyping
Bioinformatics
Microarrays
CNV
PCR
fluorescence-luminescence
Illumina
Caliper
QuBit
Covaris
Genomics
libraries
allelic
Tiling
profiling
analysis
TaqMan
cBot
SNP
Bioanalyzer
TapeStation
Real-time
ChIP-seq
expression
Transcriptomics
Analysis
Tecan
arays
DNA
reader
discrimination
samples
ChIP-string
arrays
Green
equencing
FFPE
nCounter
Sequencing
Q-PCR
Sybr
NanoString
NGS
BeadStation
Exome
miRNA
Affymetrix
Epigenetics
RNA-seq

Redefining Cancer
Moving from a mid 19th Century Definition to a 21th Century Definition

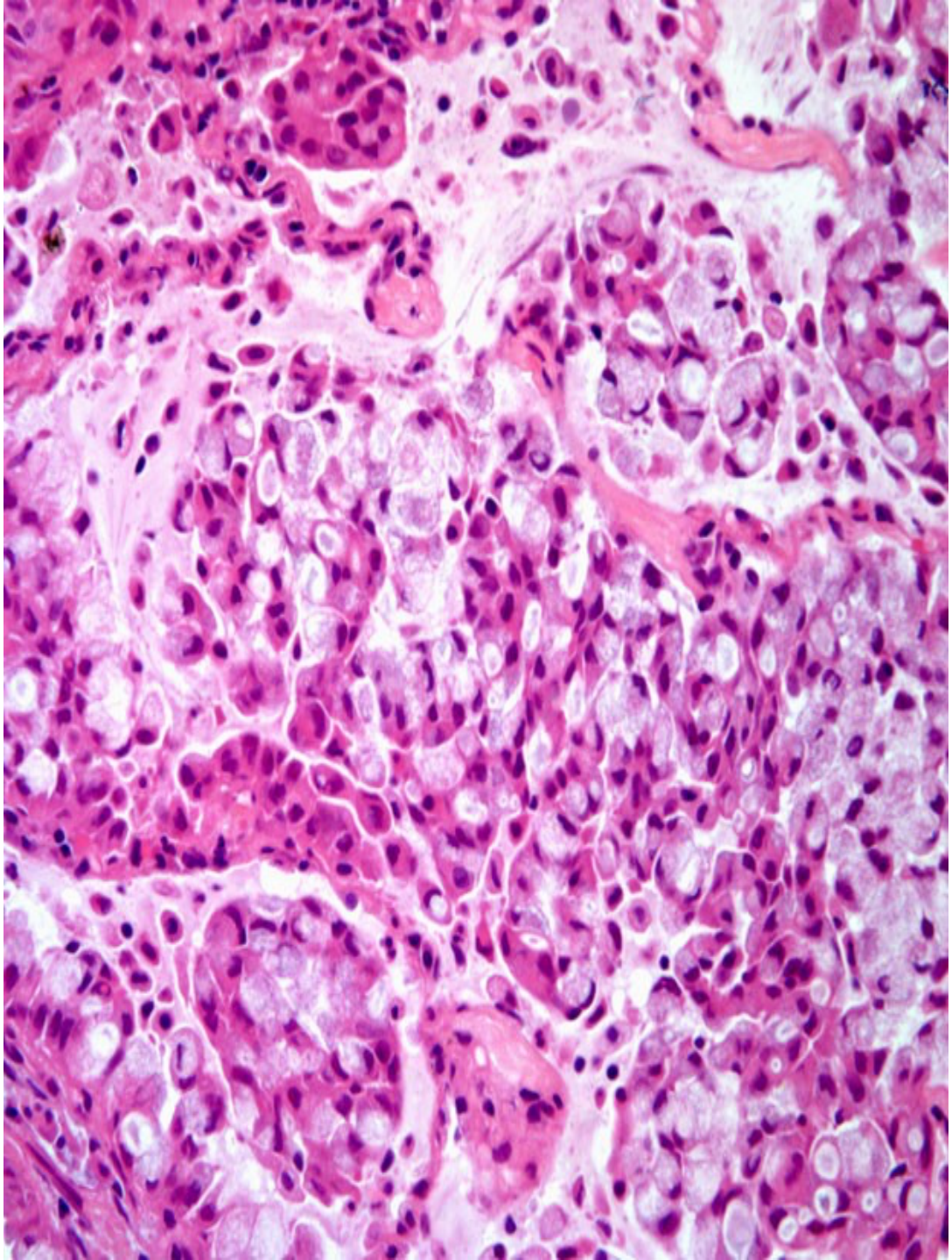
Rudolph Ludwig Karl Virchow

1821- 1902

Virchow's Accomplishments

The histologic definition of cancer used in 2015 is largely that of Virchow and colleagues with minor modifications

More than 160 years later, we still use their definitions using a light microscope.



Adenocarcinoma of the Lung with Signet Ring Features

H and E staining

A 21st Century Definition of Cancer

Involves Pathology and Genetic/Genomic analysis

- What genes are present
- What genes are activated
- What genes are over expressed

A 21st Century Definition of Cancer

An understanding of the varying biologic behaviors of cancer based on histology and genomics. There are "cancers of no threat" that do not need treatment.

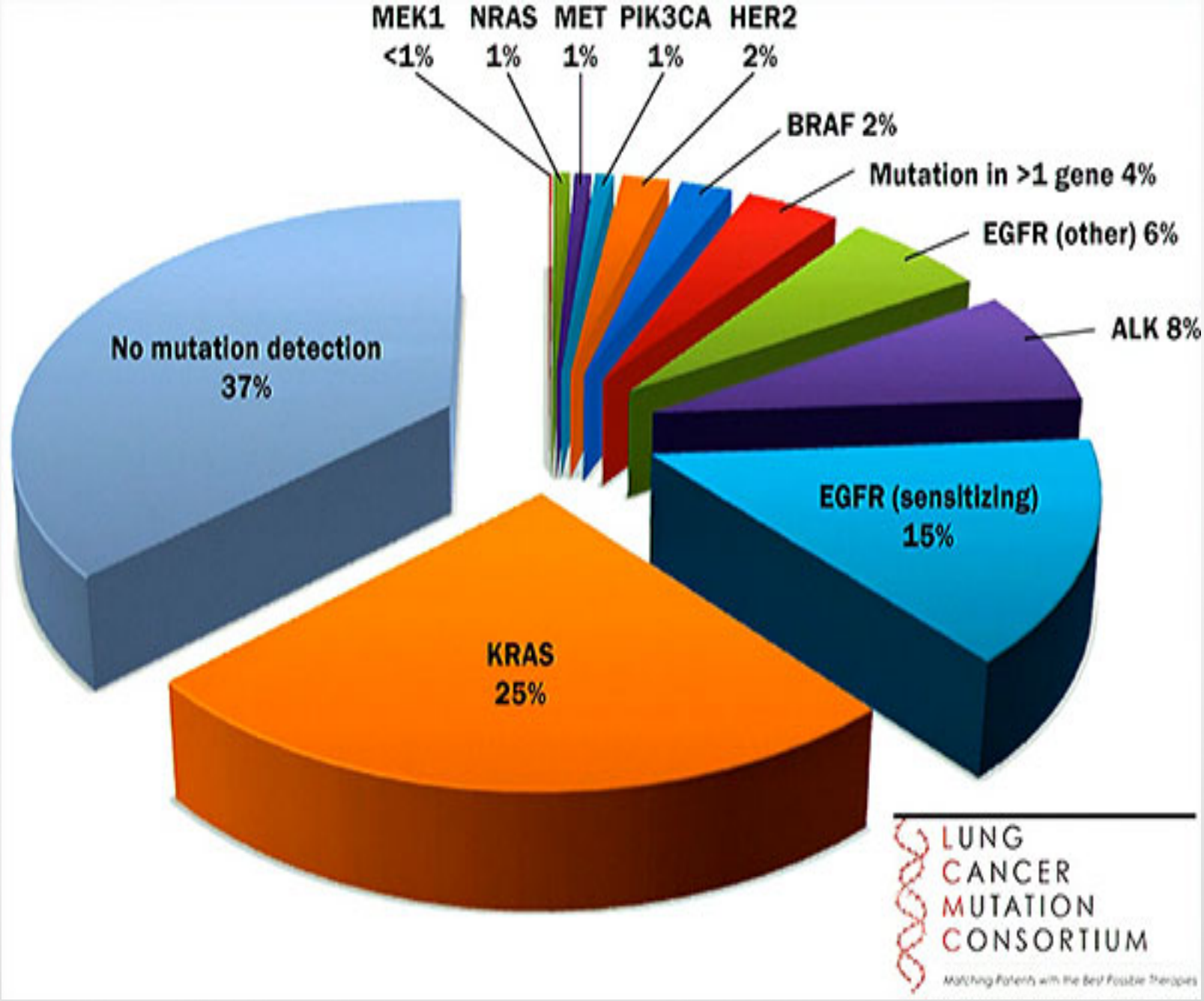
An understanding of the varying vulnerabilities of cancers to medical interventions.

Numerous molecular targets have and are being defined. Many are drugable targets!

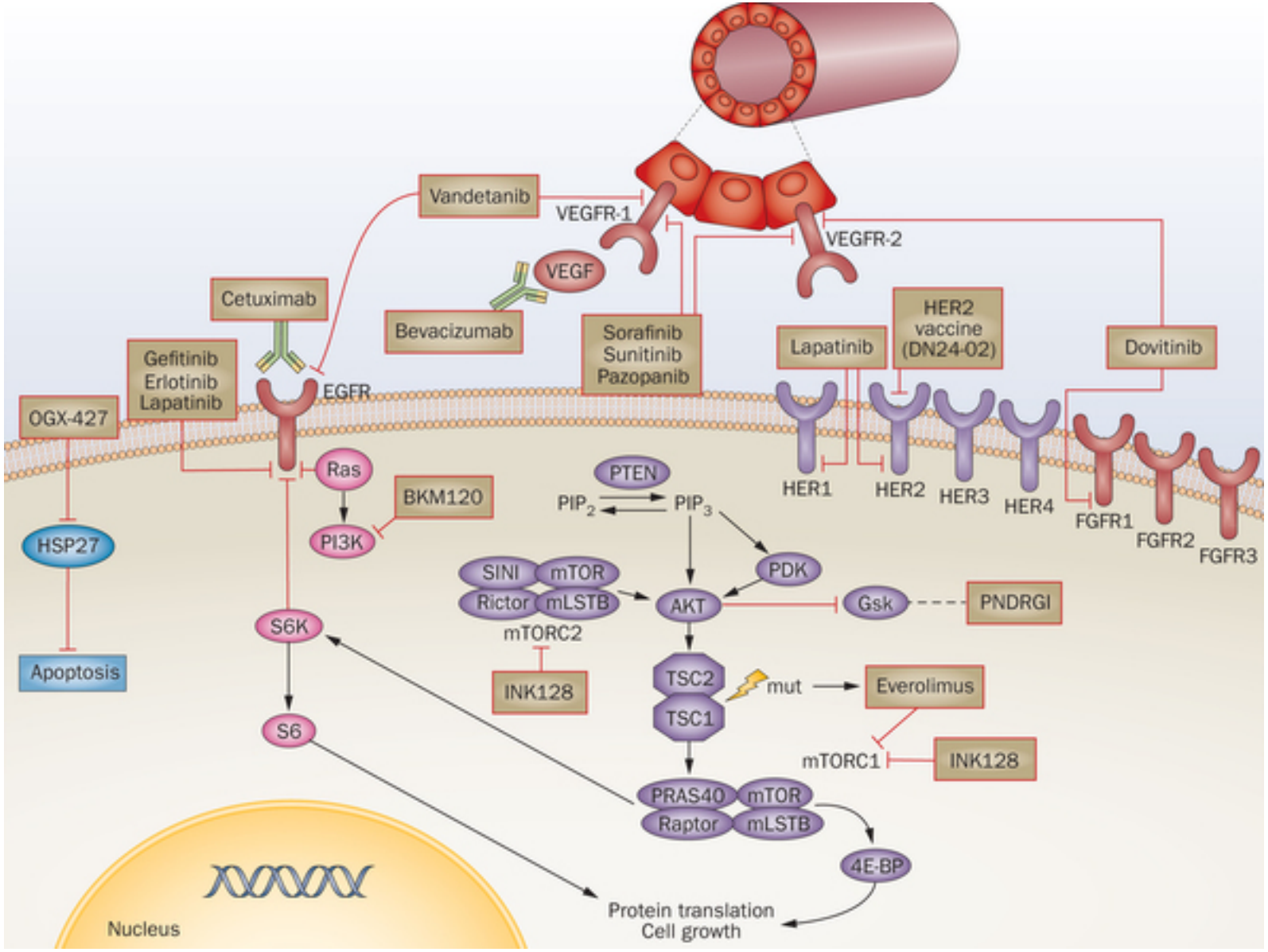
The Perfect Target

- Somatically altered in cancer cell and not in normal cells
- Driver of cancer initiation, maintenance and/or drug resistance
- Shared by most tumors within a histological subtype or across tumor types

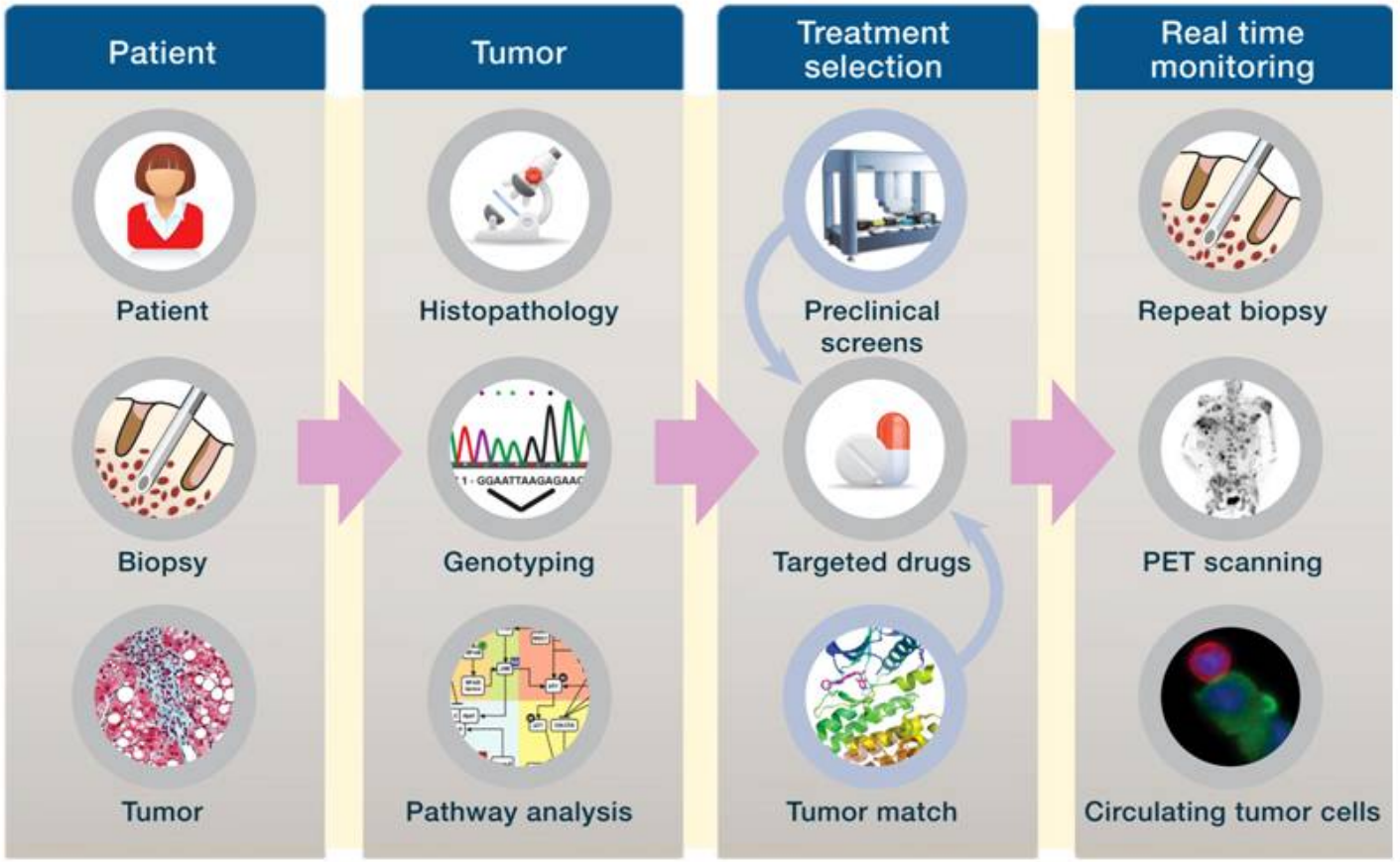
NYU Langone MEDICAL CENTER


MEK1 <1%
NRAS 1%
MET 1%
PIK3CA 1%
HER2 2%
BRAF 2%
Mutation in >1 gene 4%
EGFR (other) 6%
ALK 8%
EGFR (sensitizing) 15%
KRAS 25%
No mutation detection 37%
LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies

The Era of Precision Medicine (Tailored/Targeted Therapy)

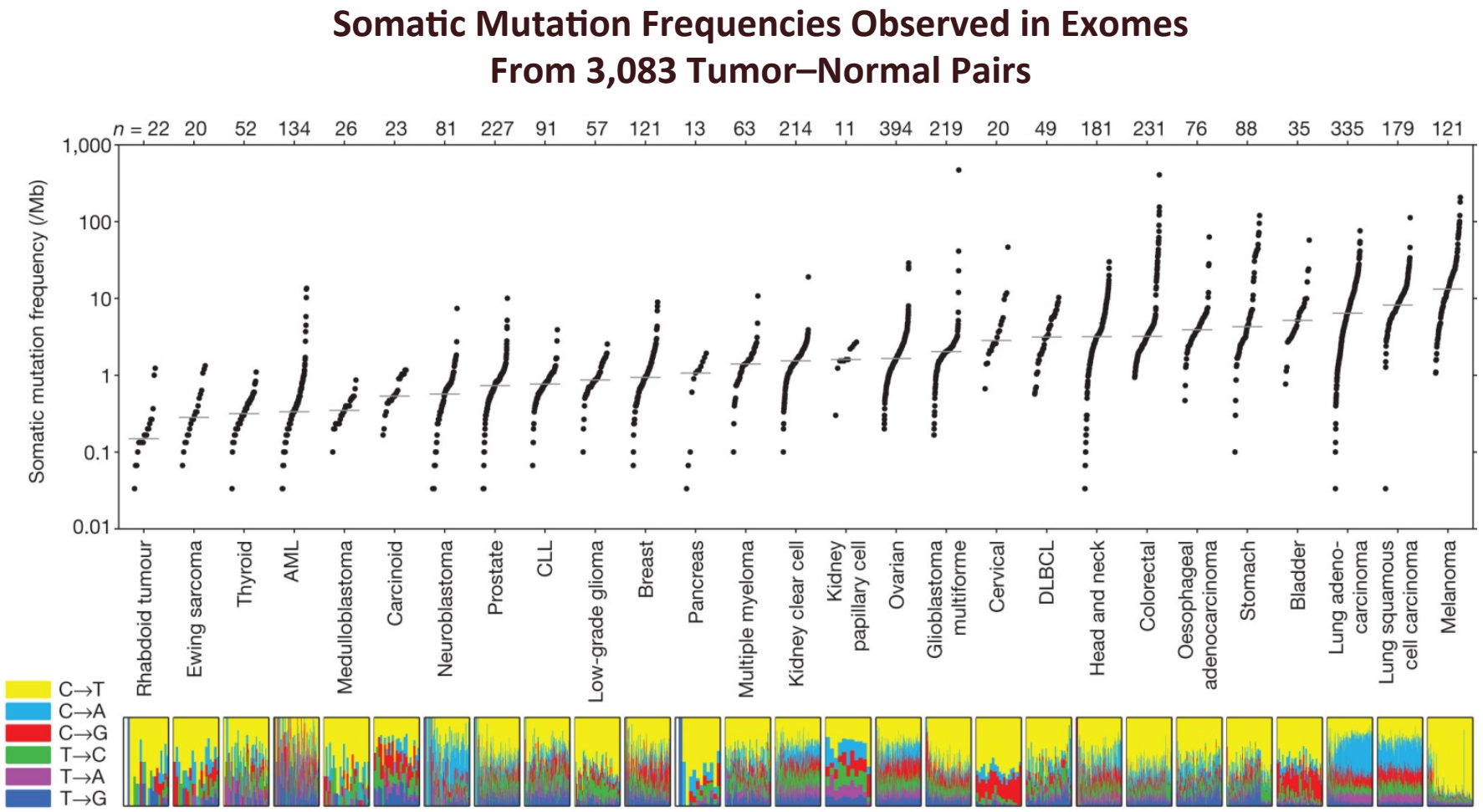

Vandetanib
VEGFR-1
VEGFR-2
VEGF
Bevacizumab
Cetuximab
Sorafinib
Sunitinib
Pazopanib
Lapatinib
HER2
vaccine
(DN24-02)
Dovitinib
Gefitinib
Erlotinib
Lapatinib
EGFR
OGX-427
HER1
HER2
HER3
HER4
FGFR1
FGFR2
FGFR3
Ras
PTEN
BKM120
PIP2
PIP3
HSP27
PI3K
SINI
mTOR
PDK
Rictor
mLSTB
AKT
Gsk
PNDRGI
S6K
mTORC2
Apoptosis
INK128
TSC2
mut
Everolimus
TSC1
S6
mTORC1
INK128
PRAS40
mTOR
Raptor
mLSTB
4E-BP
Nucleus
Protein translation
Cell growth

Vision for Precision Oncology



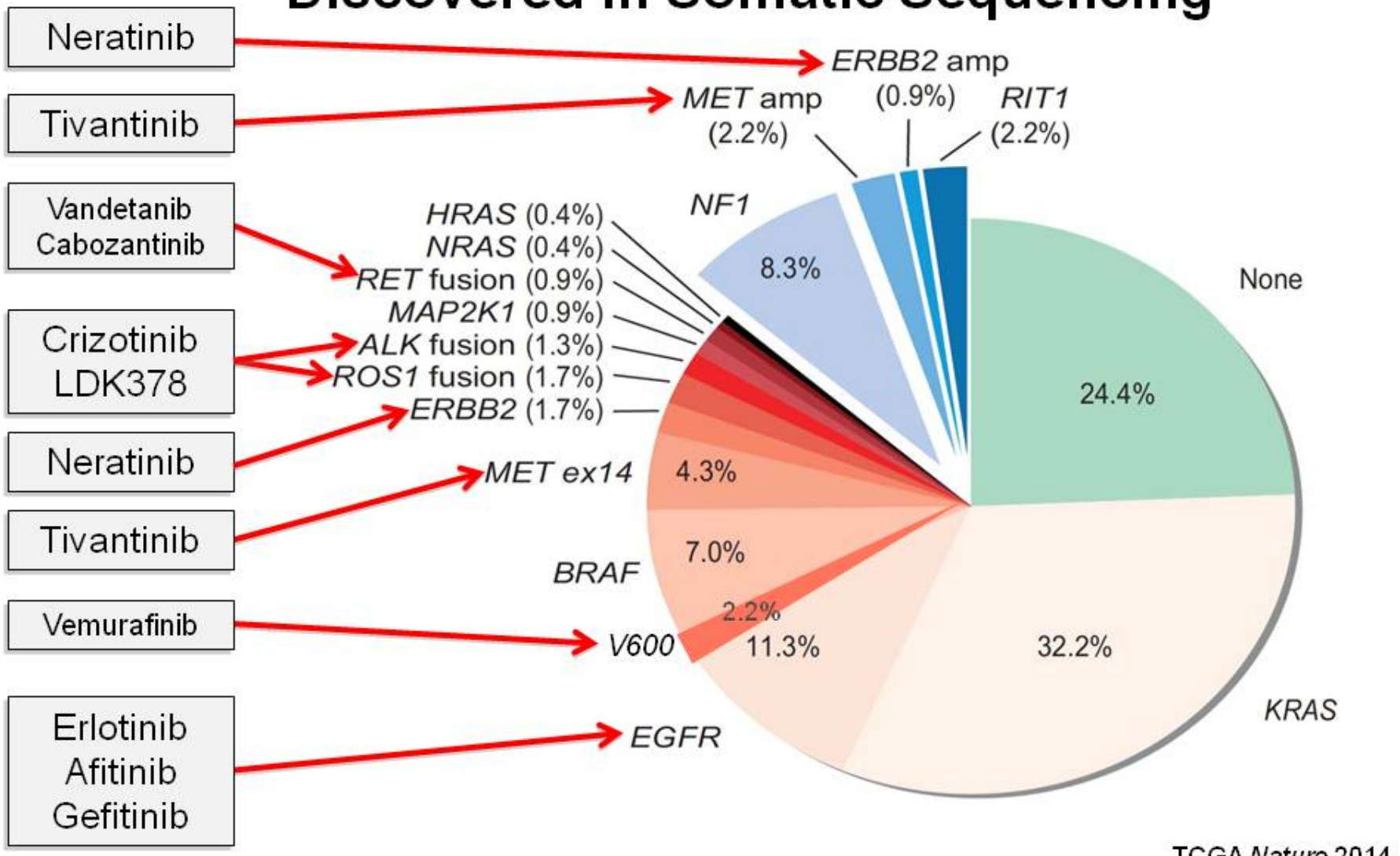
Haber, Gray, Baselga, *Cell*, 2011

Mutation Burden as predictor for response[1]



1. Lawrence MS et al. *Nature.* 2013;doi:10.1038/nature12213.

'Driver Genes' in Adult Lung Adenocarcinoma Discovered in Somatic Sequencing



TCGA *Nature* 2014

Precision Medicine Studies Opened in the Past Year

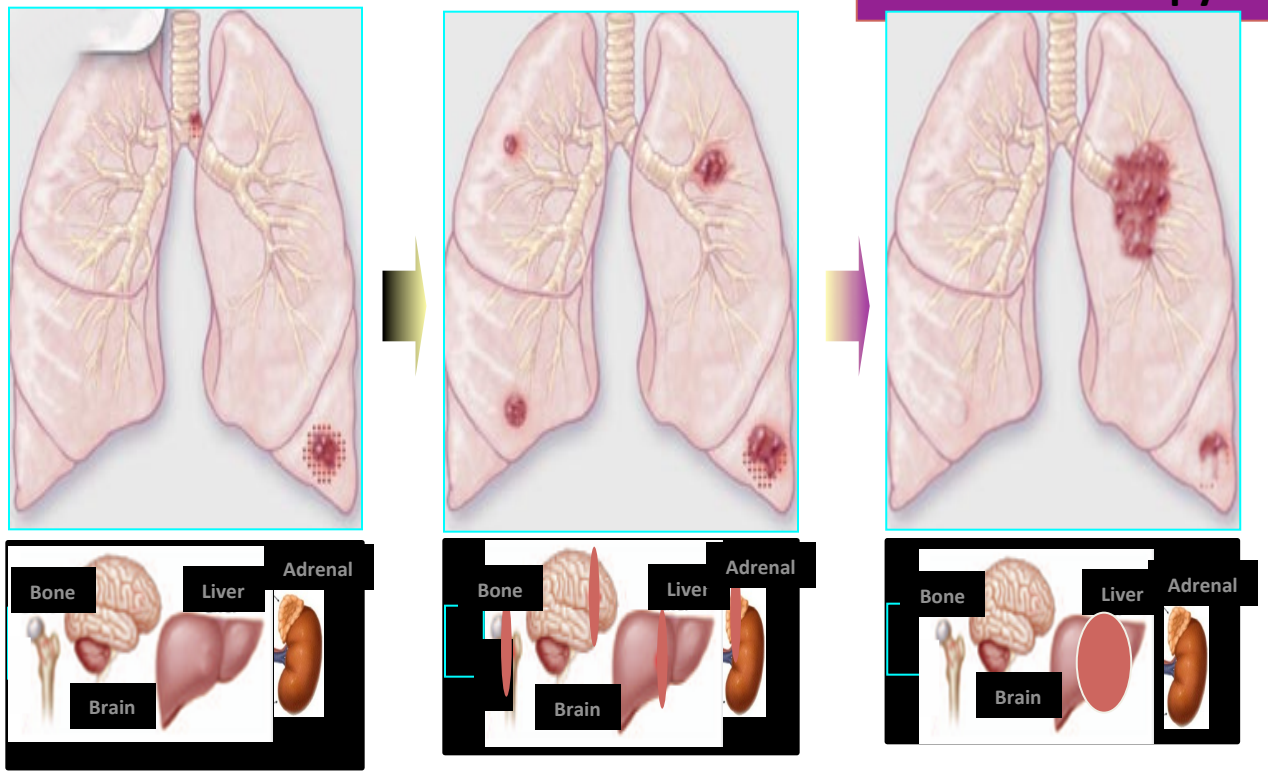
- Lung-MAP (Lung Cancer Master Protocol)
- ALCHEMIST (Adjuvant Lung Cancer Enrichment and Sequencing Trials)
- MPACT (Molecular Profile based Assignment of Cancer Therapeutics
- Exceptional Responders: excellent intake of patients from entire cancer community--sequencing efforts underway

Natural History of Lung Cancer

Stages I-III Surgically

Advanced – Stage IV Untreated

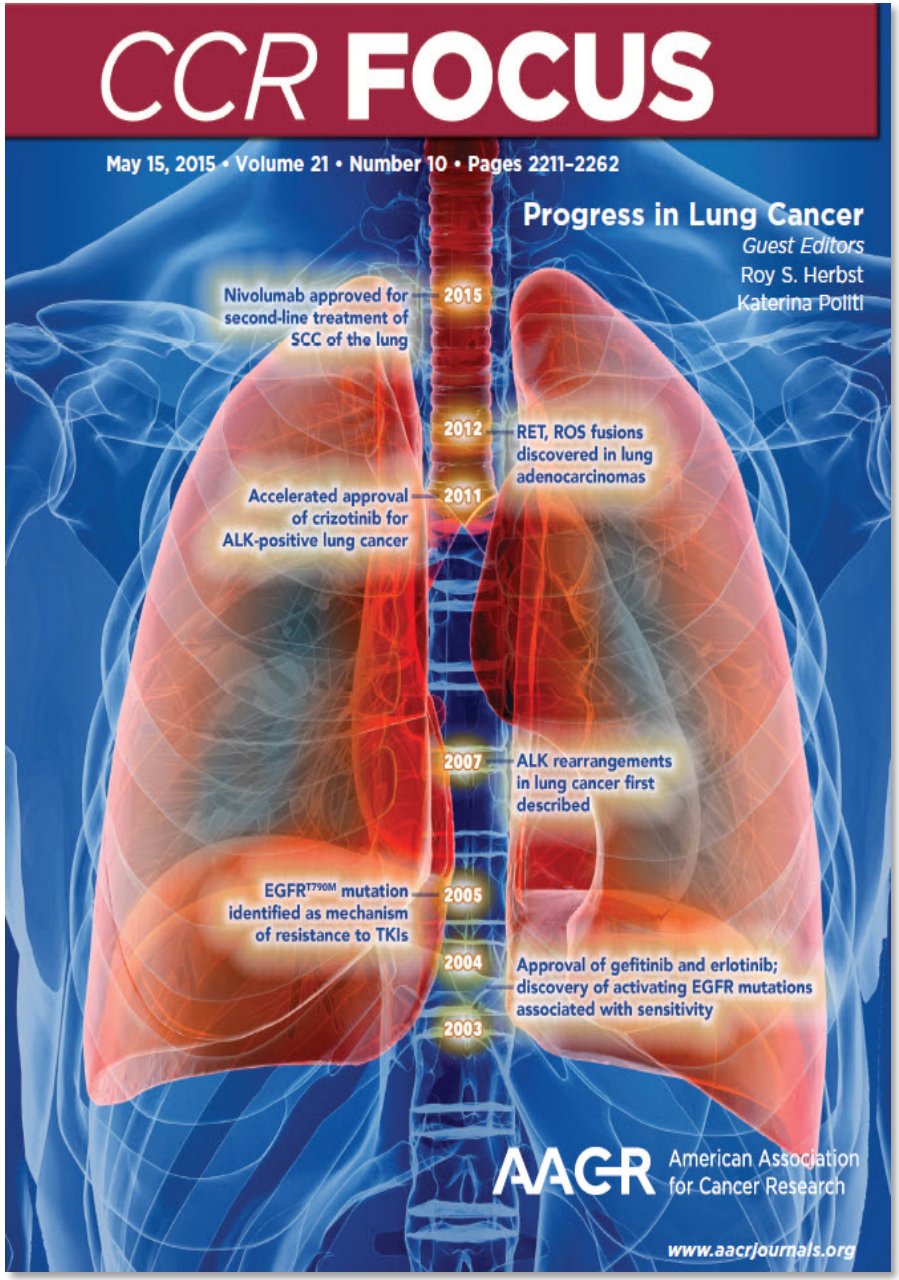
Advanced - Stage IV Refractory to Chemotherapy



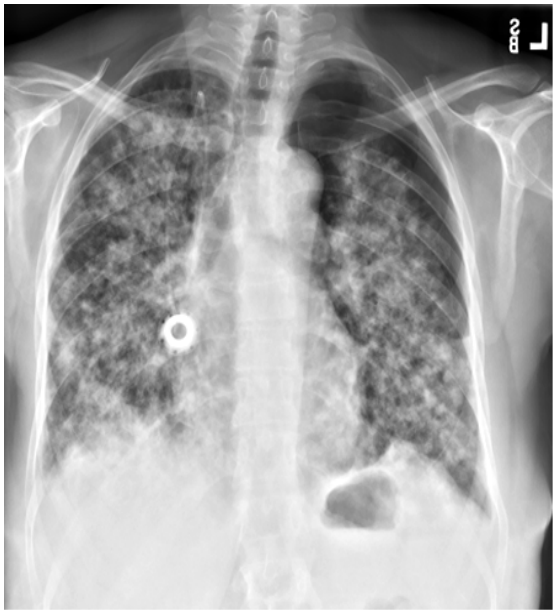
Tissues Available **Frequent** **Infrequent** **Rare**

Adapted from Herbst, Heymach and Lippman; N Engl J Med 359:1367, 2008

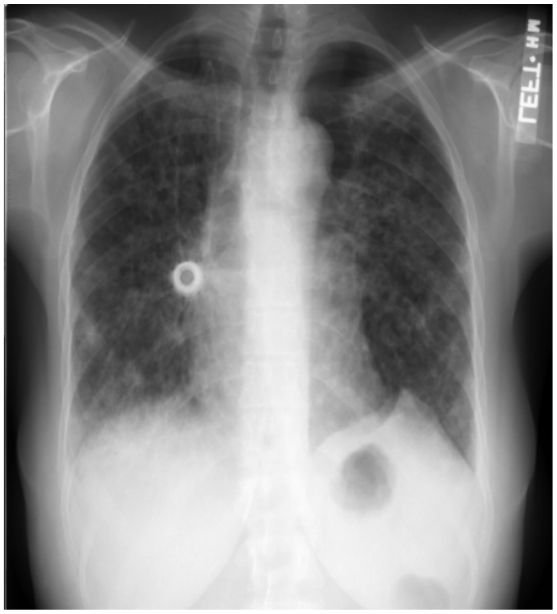
Which Ushered in New Era for NSCLC Treatment!



First Gefitinib Continuous Phase I Study at MDACC



February 6, 2002



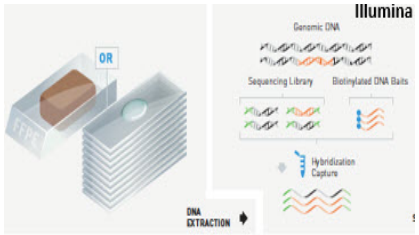
February 11, 2002

Selective Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor ZD1839 Is Generally Well-Tolerated and Has Activity in Non–Small-Cell Lung Cancer and Other Solid Tumors: Results of a Phase I Trial

By Roy S. Herbst, Anne-Marie Maddox, Mace L. Rothenberg, Eric J. Small, Eric H. Rubin, Jose Baselga, Federico Rojo, Waun Ki Hong, Helen Swaisland, Steven D. Averbuch, Judith Ochs, and Patricia Mucci LaRusso

Steering Committee Chair, PI: R. Herbst (YALE, SWOG)
PI: V. Papadimitrakopoulou (MDACC,SWOG)
Lung Committee Chair: D. Gandara
Translational Chair: F. Hirsch
Statistical Chair: M. Redman

Gene	Event Type	Frequency
FGFR1	Amplification	20-25%
FGFR2	Mutation	5%
PIK3CA	Mutation	9%
PTEN	Mutation/Deletion	18%
CCND1	Amplification	8%
CDKN2A	Deletion/Mutation	45%
PDGFRA	Amplification/Mutation	9%
EGFR	Amplification	10%
MCL1	Amplification	10%
BRAF	Mutation	3%
DDR2	Mutation	4%
ERBB2	Amplification	2%



LUNG-MAP

Drug	Company	Target
AZD4547	AstraZeneca	Fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor
GDC-0032	Genentech	PI3K pathway inhibitor
MEDI4736	MedImmune	Anti-PD-L1 monoclonal antibody
Palbociclib	Pfizer	CDK 4/6 inhibitor
Rilotumumab	Amgen	Hepatocyte growth factor receptor/c-met inhibitor

- 500 Patients/year screened
- Biomarker selected trials
- >100 $million of industry support
- FDA collaboration- seeks to get drugs approved and to patients!
- Genomic profiling delivered to the community
- A new paradigm for drug development and scientific discovery

Lung-MAP: Major Goals and Hypothesis

Ultimate goal is to identify and quickly lead to approval safe and effective regimens (monotherapy or combinations) based on matched predictive biomarker-targeted drug pairs.

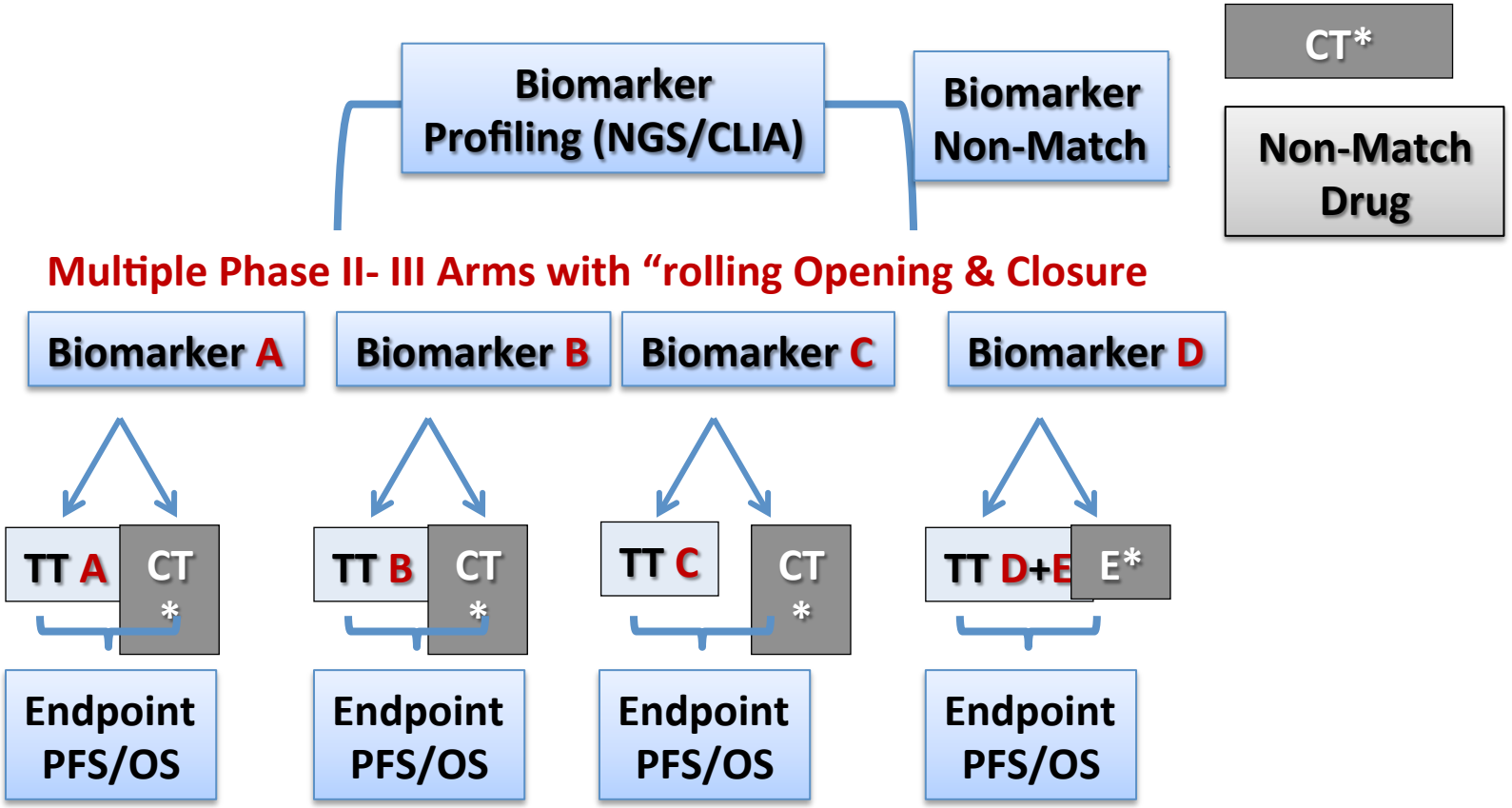
Drug Selection Committee Nominations

A selection committee, which includes experts in Lung Cancer, has nominated several molecules for inclusion in the Lung-MAP master protocol initiative, these include:

Drug	Company	Target
AZD4547	AstraZeneca	Fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor
GDC-0032	Genentech	PI3K pathway inhibitor
MEDI4736	MedImmune	Anti-PD-L1 monoclonal antibody
Palbociclib	Pfizer	CDK 4/6 inhibitor
Rilotumumab	Amgen	Hepatocyte growth factor receptor/c-met inhibitor

LUNG-MAP

S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy



TT=Targeted therapy, CT=chemotherapy (docetaxel), E=erlotinib

PI: V. Papadimitrakopoulou (SWOG)
Steering Committee PI, Co-Chair: R. Herbst (YALE, SWOG)
Lung Committee Chair: D. Gandara
Translational Chair: F. Hirsch
Statistical Chair: M. Redman

The Era of Immunotherapy (after a century of trying)

Immunotherapy Is in the News …

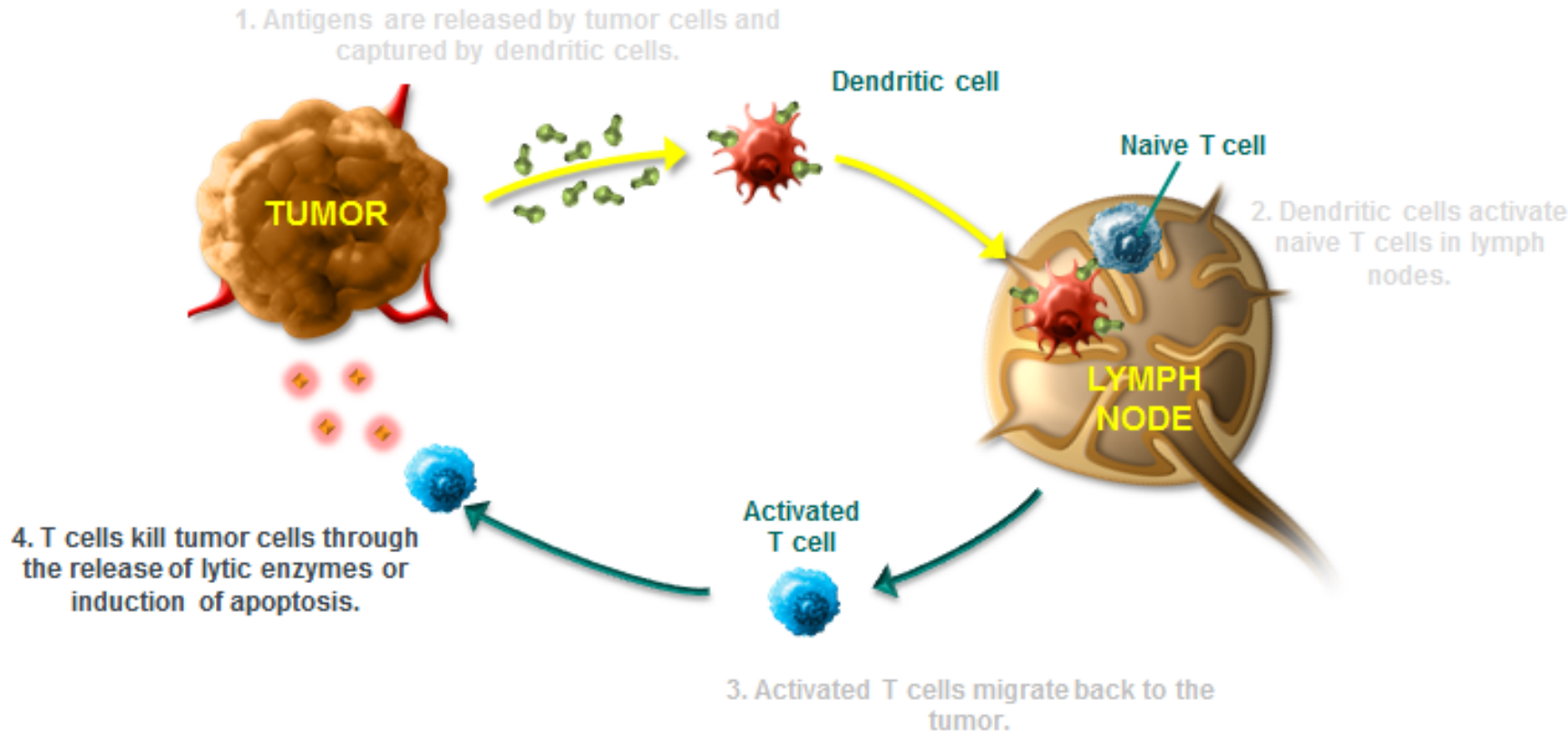
The New York Times

SCIENCE

Arming the Immune System Against Cancer

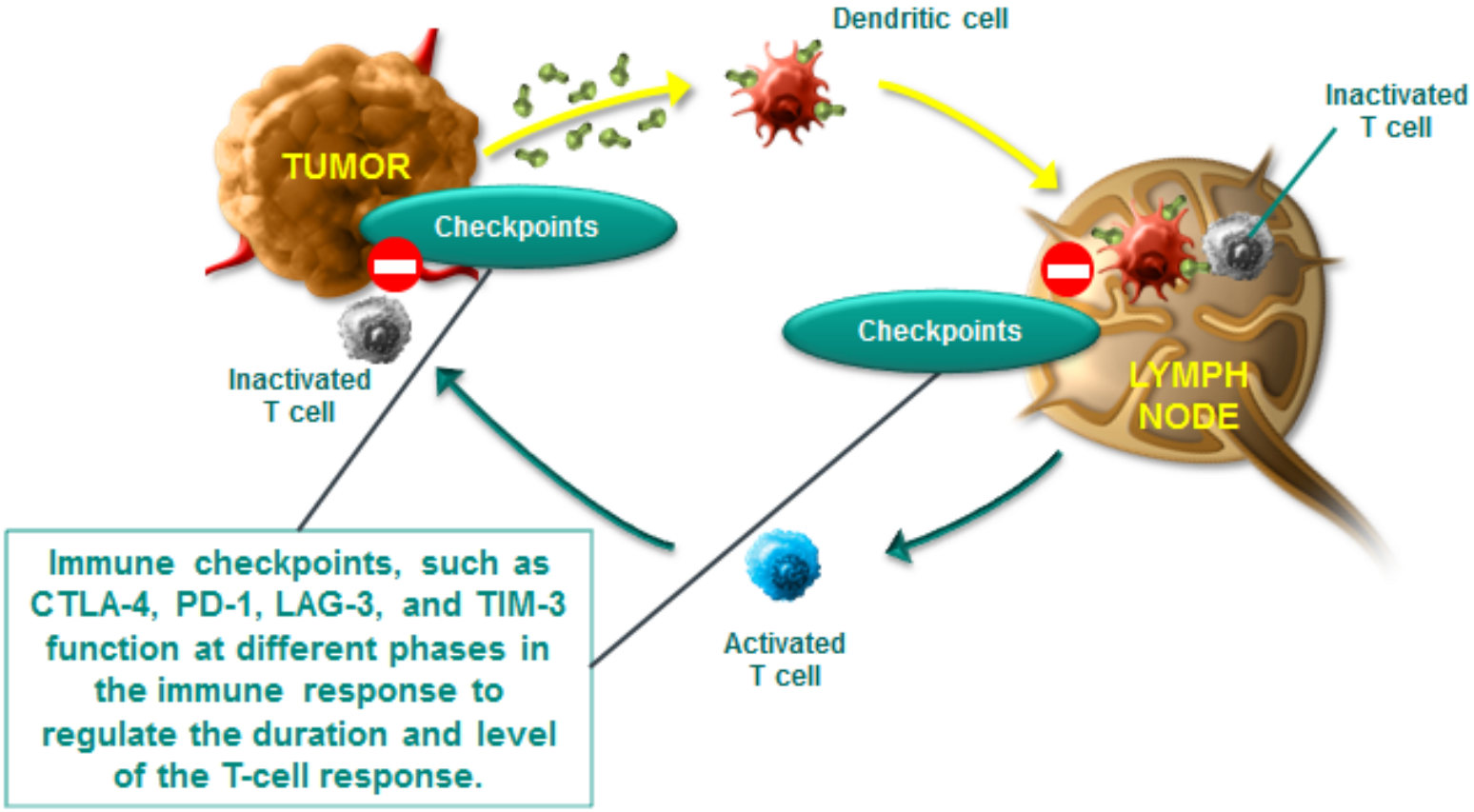
Recall, the immune system failed in the first place allowing for cancer growth…

T cells Are Important in the Ability of the Immune System to Detect and Destroy Tumor Cells[1]



1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity[1]



CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1; LAG-3 = lymphocyte activation gene 3; TIM-3 = T-cell immunoglobulin and mucin protein 3.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Unique Kinetics of Response in Patients Treated With Ipilimumab

Screening

Week 12: swelling and progression

Week 12: improved

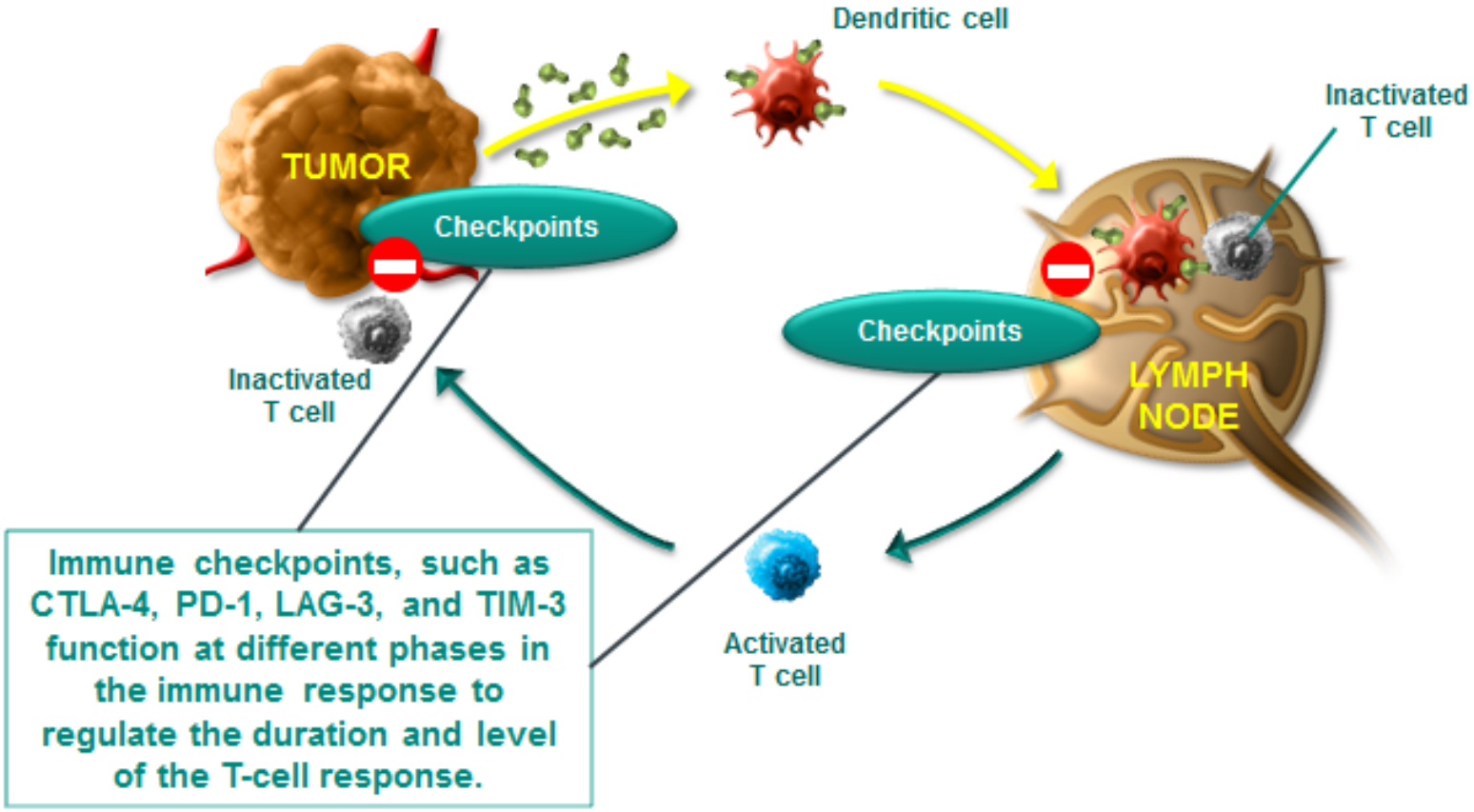
Week 16: continued improvement

Week 72: complete remission

Week 108: complete remission

Images courtesy of Jedd D. Wolchok, MD.

T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity[1]



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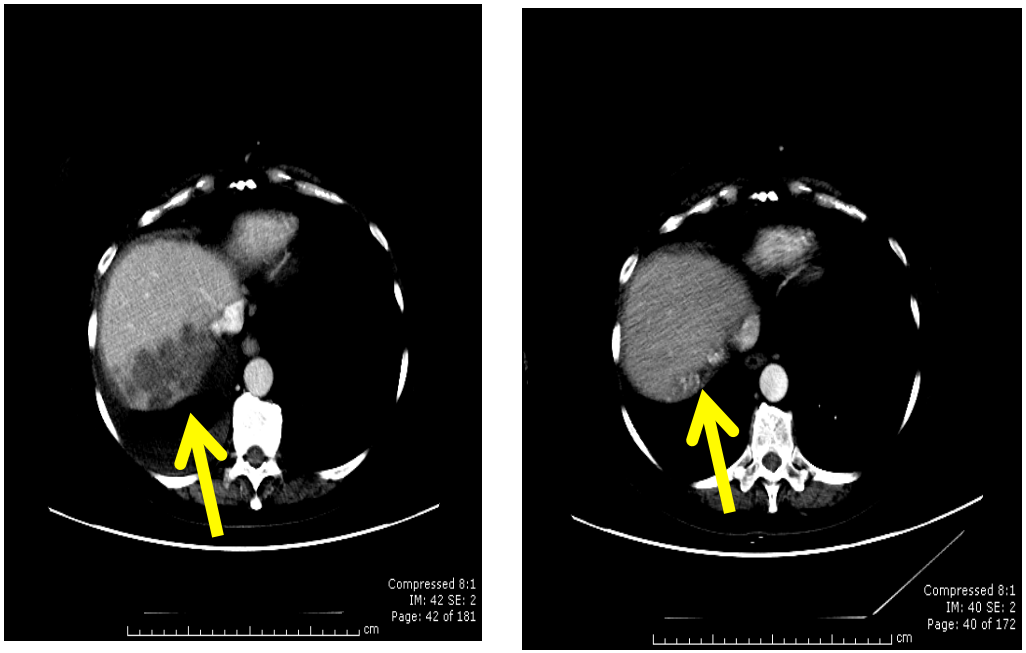
1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Anti-PD-1 Therapy Nivolumab

Pre/Post MDX 1106 (Dec / Feb ’10)

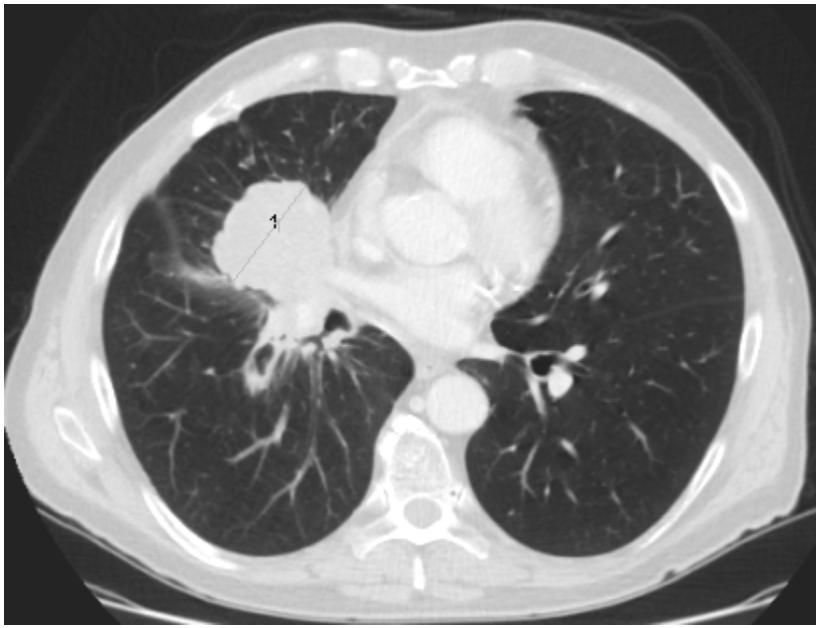


- 66 y/o ex smoker with KRAS mutant adenocarcinoma of the lung
- 5 prior treatments for Stage IV disease
- RUQ abdominal pain, anorexia and fatigue resolved within 2 months
- Duration of response: 10 months

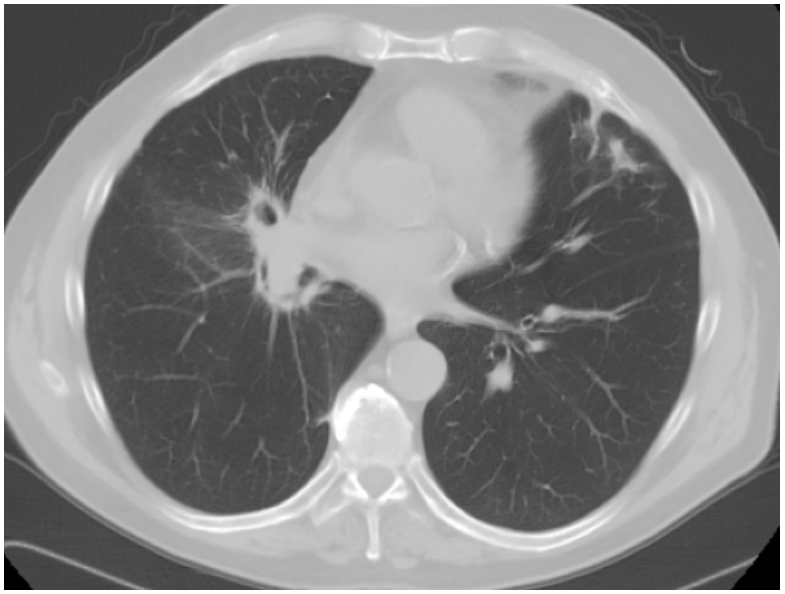
Courtesy of S. Gettinger

PD-1 Inhibition in NSCLC Patient

single dose of nivolumab on May 3, 2013.



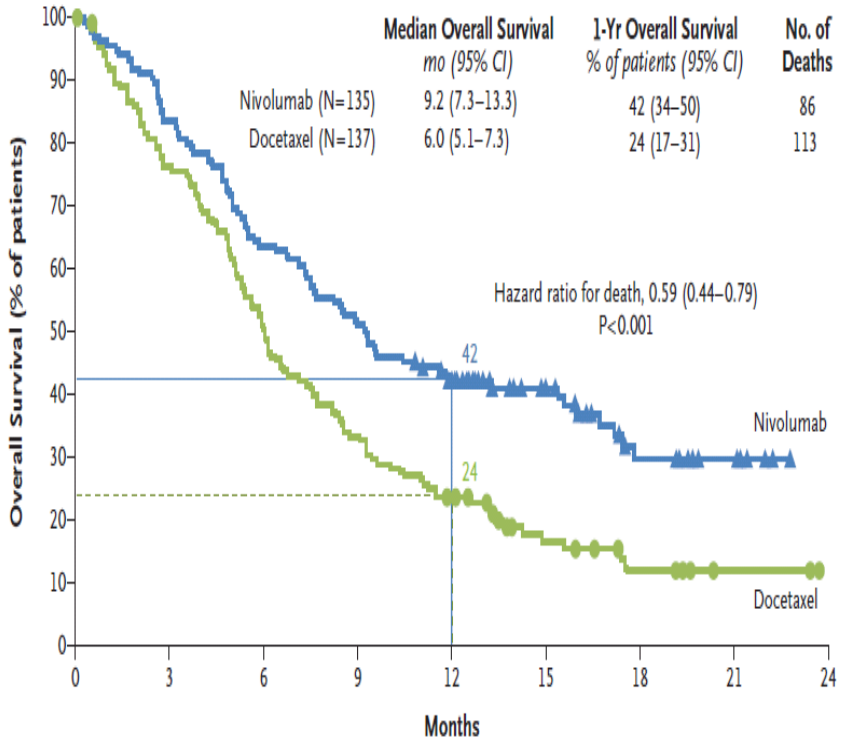
April 24, 2013



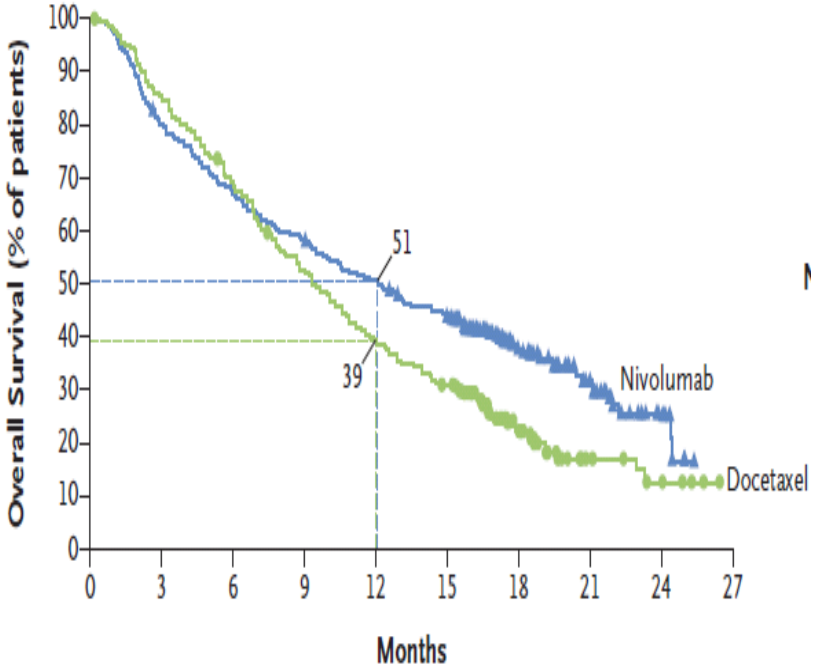
April 17, 2014

Nivolumab Superior to Docetaxel in NSCLC

Squamous NSCLC



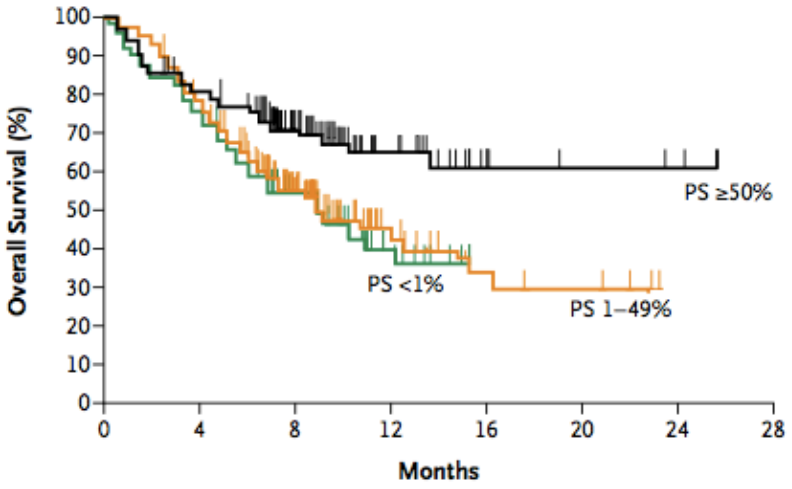
Non-Squamous NSCLC



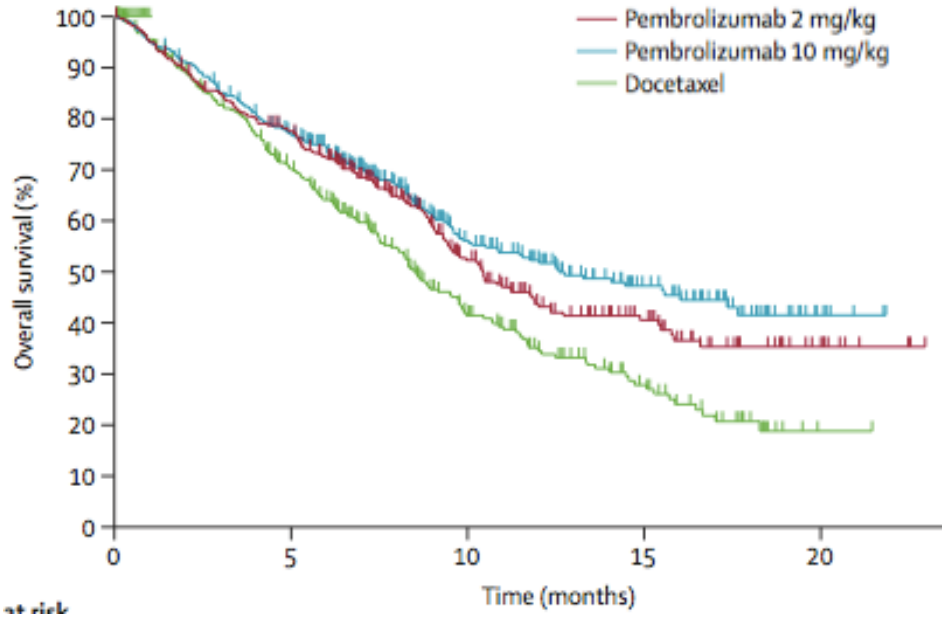
Brahmer JR, et al. N Engl J Med 2015.
Borghaei H, et al. N Engl J Med 2015.

Pembrolizumab in NSCLC

1



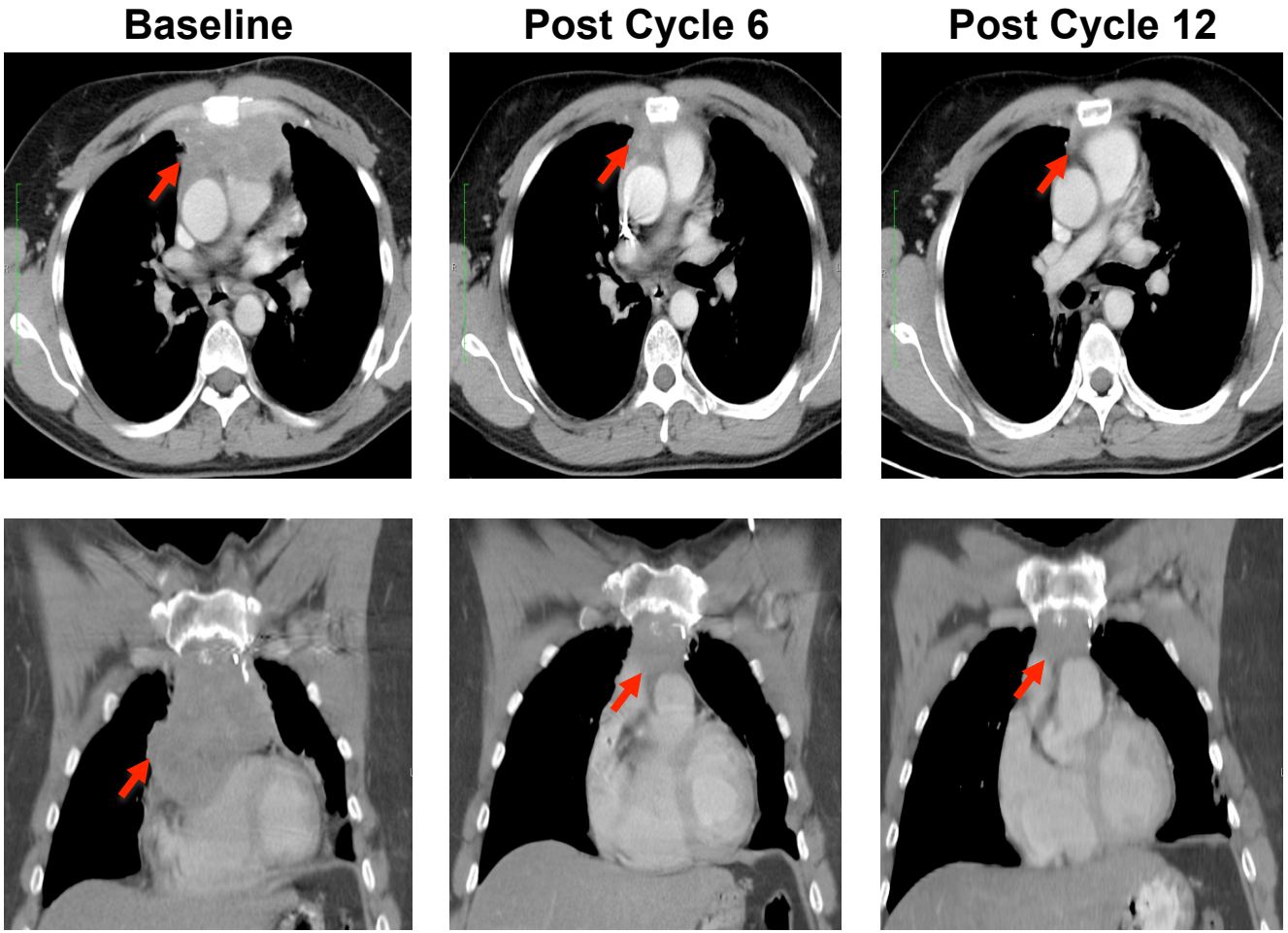
2



- NSCLC with higher PD-L1 expression (≥50%) have increased benefit from pembrolizumab.
- Pembrolizumab improves survival compared to docetaxel in previously treated NSCLC.

1 Garon E, et al. NEJM 2015. 2 Herbst RS, et al. Lancet 2015.

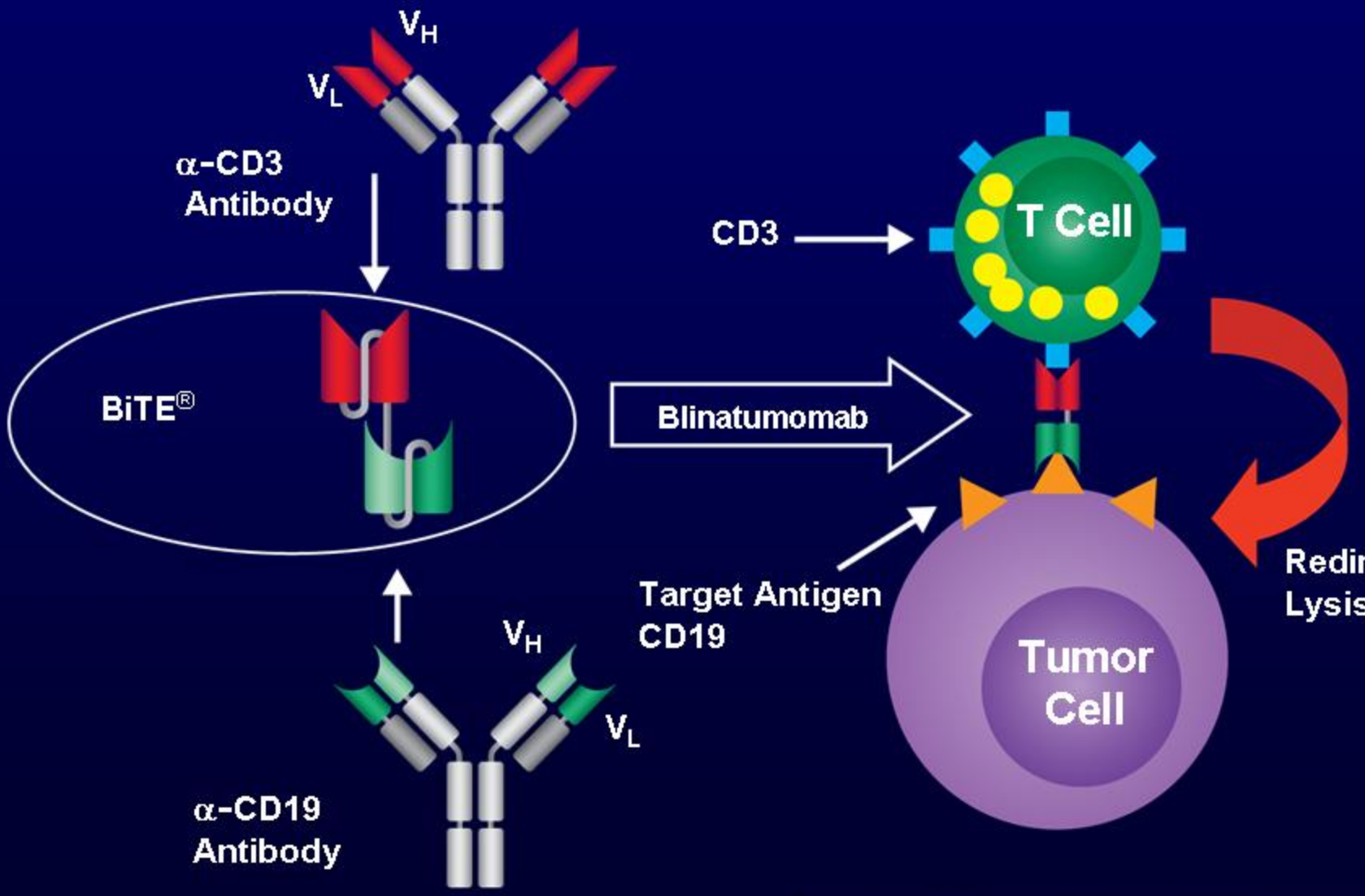
Clinical Activity of MPDL3280A (Atezolizumab) in an NSCLC Patient (anti PDL1)



- 44-year-old male with adenocarcinoma NSCLC
- S/p radiotherapy, gemcitabine + cisplatin, temozolomide + docetaxel, pemetrexed, bevacizumab, CDX-1401
- PD-L1 negative

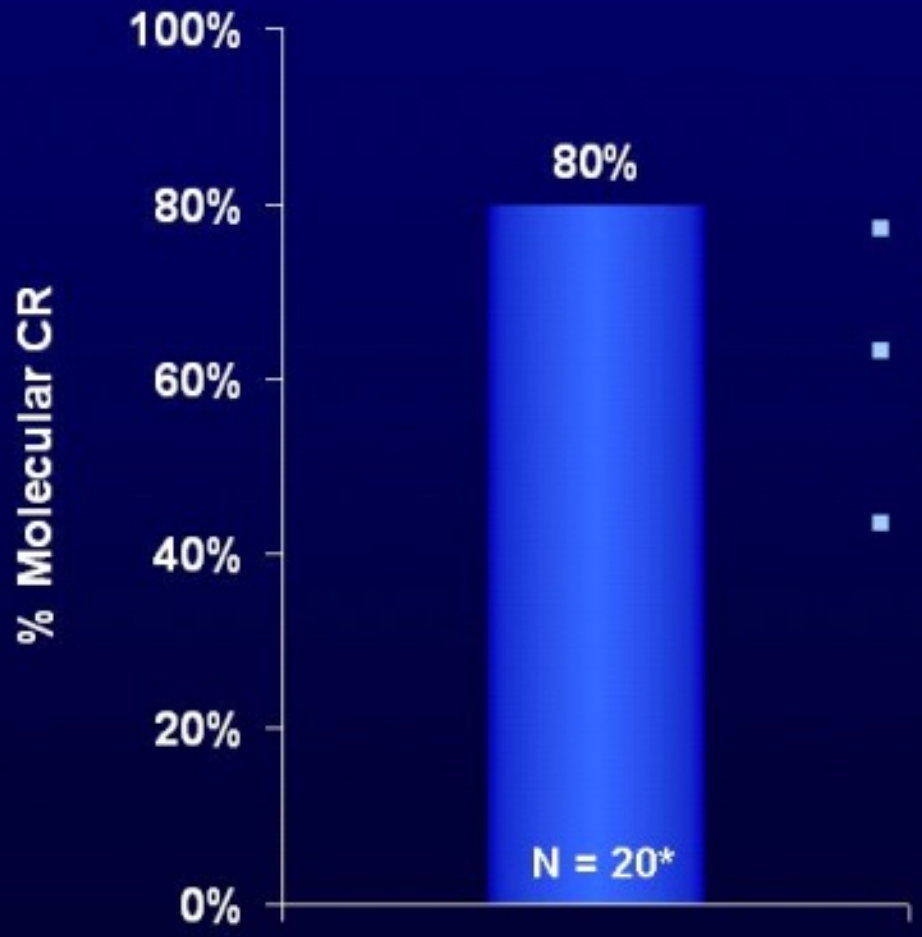
The Convergence of Immunotherapy and Precision Medicine

Blinatumomab (MT103), a Bispecific T Cell Engaging BiTE® Antibody



Topp MS, et al. *Blood*. 2010;116(21):79-80 [abstract 174].

Blinatumomab
Molecular Complete Response (CR)



- 80% of patients achieved molecular CR on blinatumomab
- Responses were rapid, all occurring within the first cycle of treatment
- Responders include
  - 3/5 patients with Ph+ ALL (one T315I mutation)
  - 1/2 patients with t(4;11)

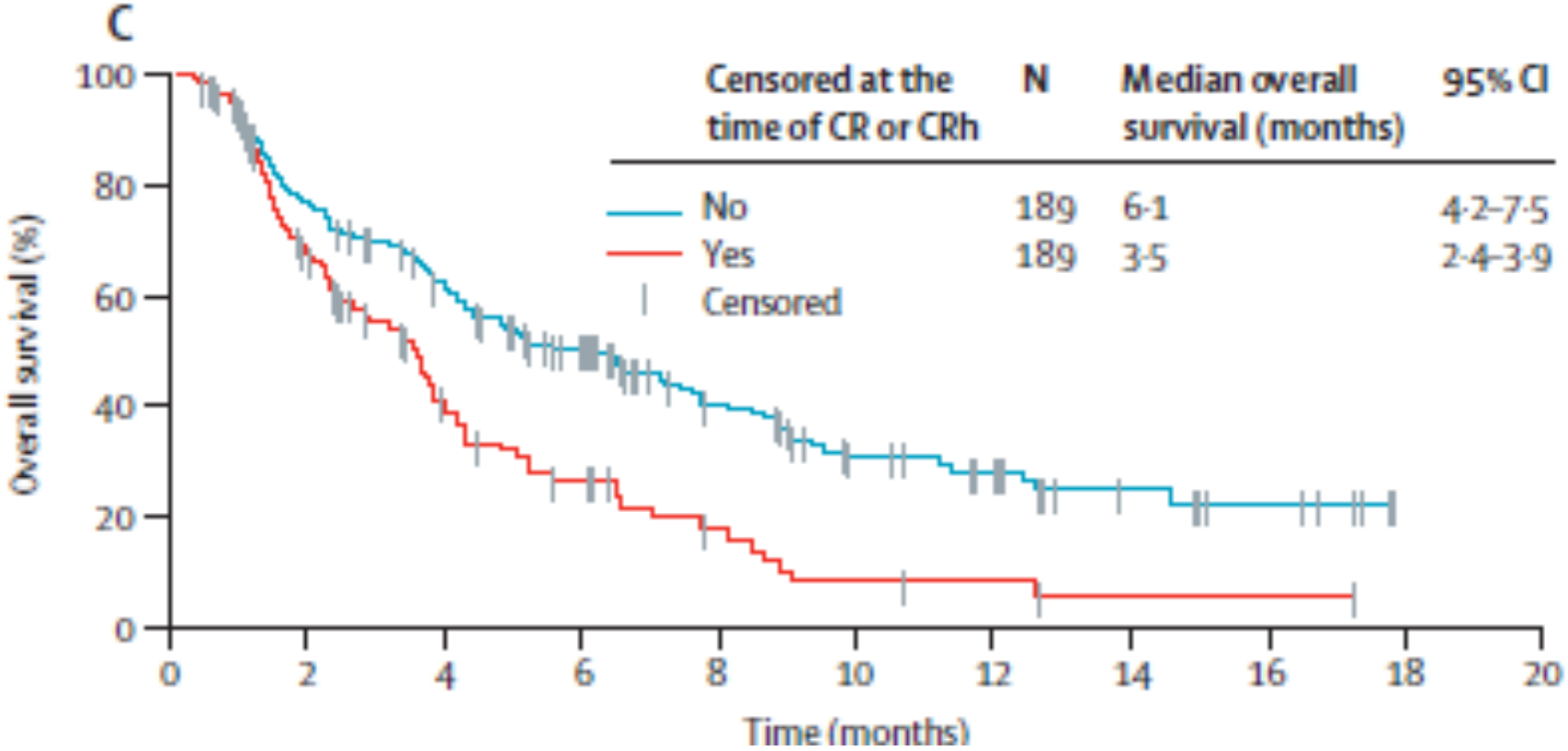
*One patient not evaluable: < 1 treatment cycle and lack of response assessment

Topp MS, et al. *Blood*. 2010;116(21):79-80 [abstract 174].

Survival in Relapsed/Refractory Adult Ph-neg B-cell Acute Lymphoblastic Leukemia Treated with Single Agent Blinatumomab

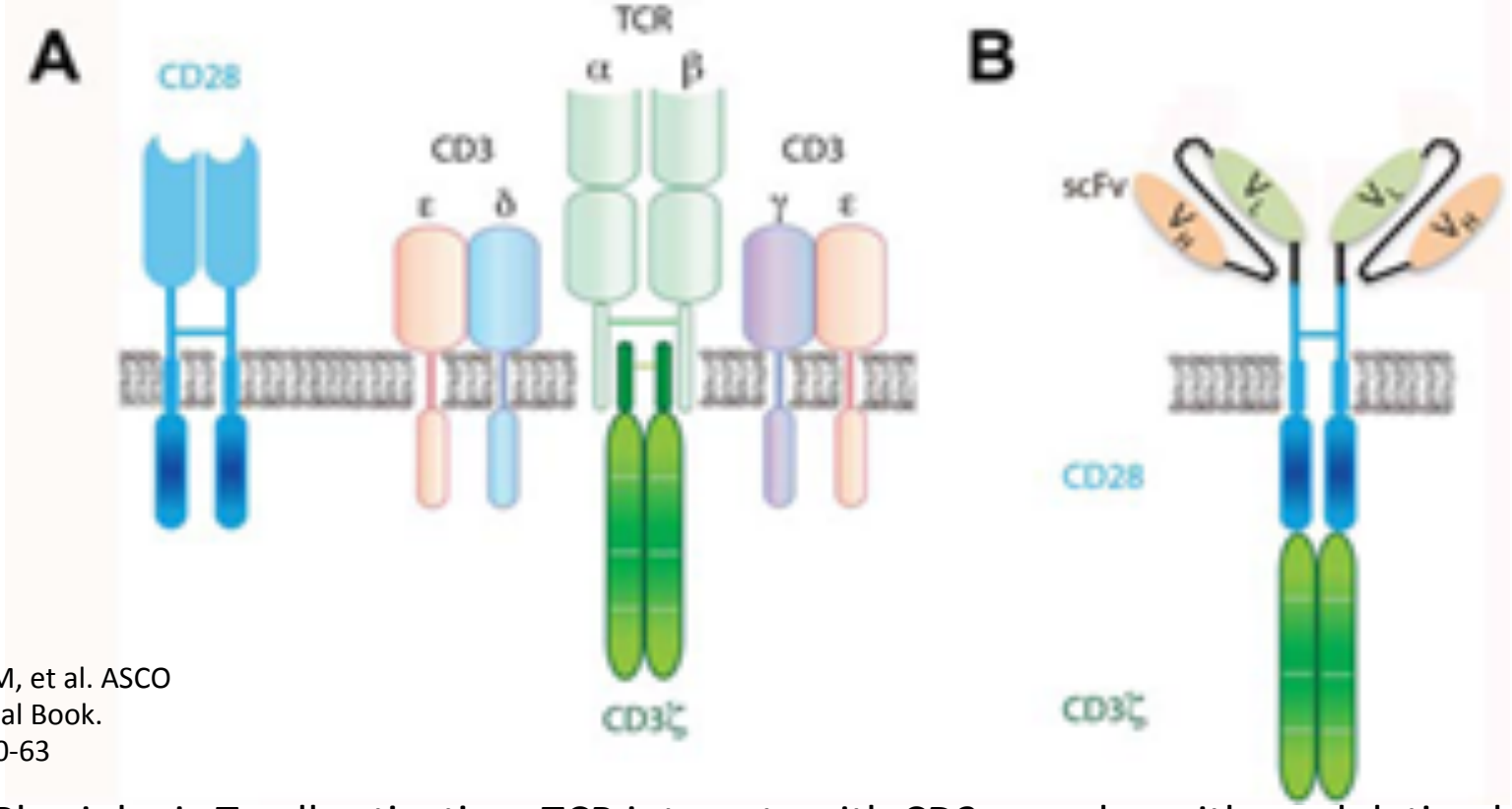
CR = 43%

CR = 73% if BM blasts <50%



Topp M, et al Lancet Oncology. 2015;16:57-66

TCR and CAR Structure



Sadelain M, et al. ASCO Educational Book. 2015:e360-63

A. Physiologic T-cell activation: TCR interacts with CD3 complex with modulation by costimulatory receptors such as CD28
B. CAR possesses in 1 molecule ability to trigger Ag-specific T-cell function by 3 domains:
   1. single chain variable fragment modulated antigen recognition
   2. CD3 zeta chain initiates T-cell activation
   3. costimulatory doamin (CD28) results in a pharmacologic boost (2nd generation CAR)

Outcomes of Patients with ALL Treated with CD19 CAR Therapy

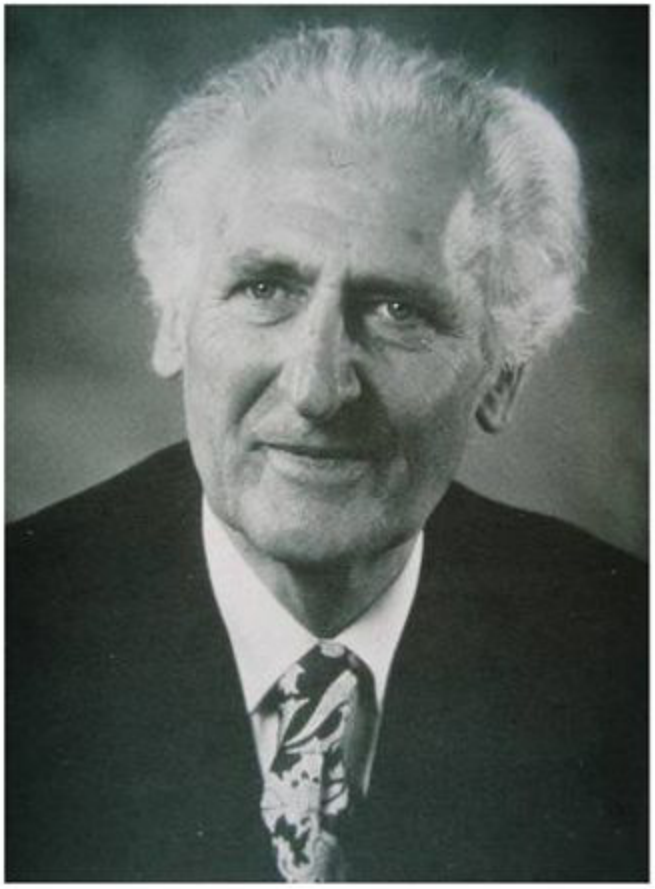
Publication/Meeting Date	Number/Age of Subjects	Complete Remission Rate
Brentjens, *Sci Transl Med*[17]	5 (adults)	100%
March 21, 2013		
Grupp, *N Engl J Med*[18]	2 (children)	100%
April 18, 2013		
Davila, *Sci Transl Med*[19]	16 adults	88%
February 19, 2014		
Lee, *Lancet*[20]	21 (children)	67%
October 13, 2014		
Maude, *N Engl J Med*[21]	30 (25 children, 5 adults)	90%
October 16, 2014		
Park, ASCO-2015	33 adults	91%
May 30, 2015		

Sadelain M, et al. ASCO Educational Book. 2015:e360-63

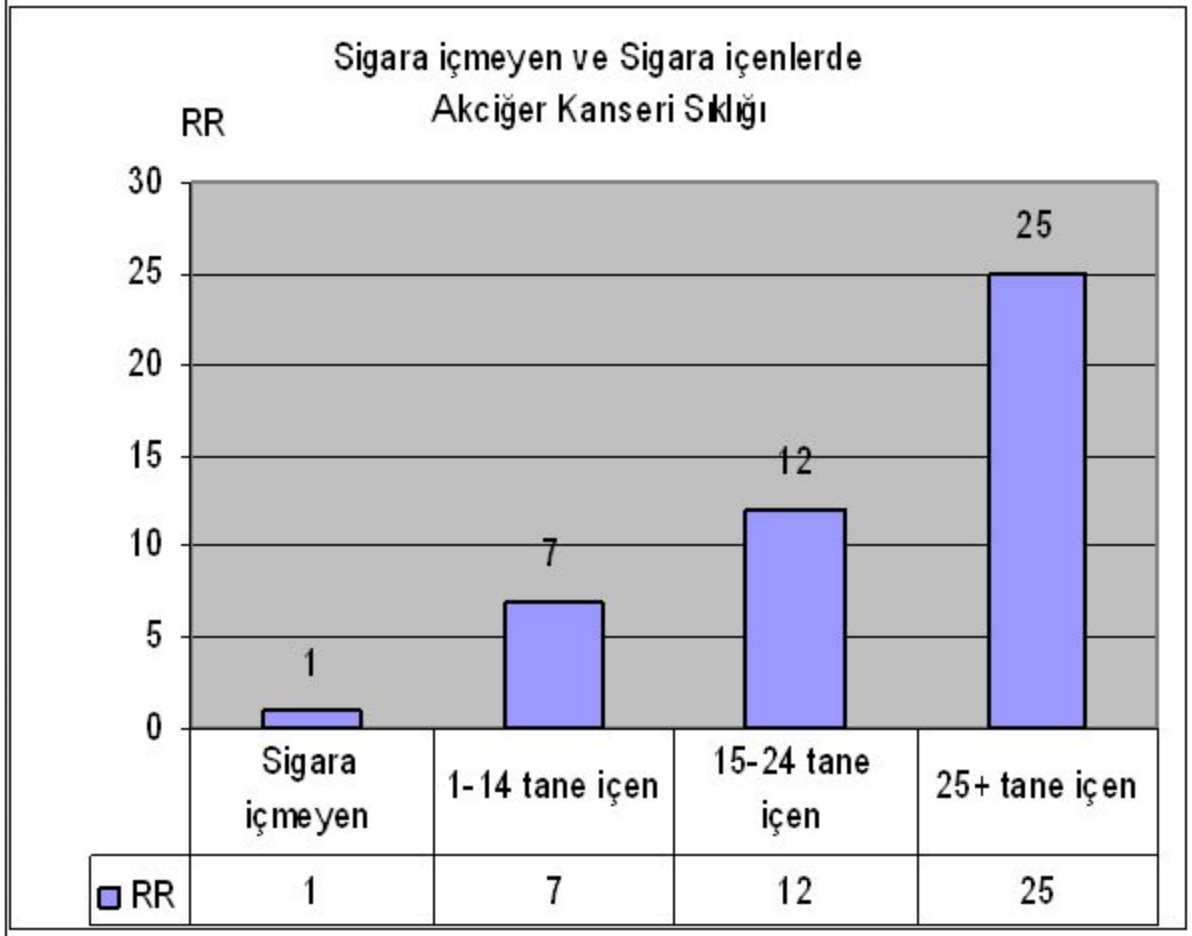
The Future: Precision Medicine and Cancer Prevention

The Hammond-Horn Study - 1955

Doll R & Hill AB. Smoking and carcinoma of lung, Preliminary Report, BMJ, 1950
Doll R, Peto R, .. Mortality in relation to smoking: 40 years' observation on male British doctors, BMJ, 1994



Sir Richard Doll



The Epidemiology Research Program's Prospective Studies

	Hammond-Horn	CPS-I	CPS-II	CPS-3
Years	1952-1955	1959-1972	1982-current	2006-current
Participants	188,000	1,000,000	1,200,000	304,000
Sex	Men	Men & Women	Men & Women	Men & Women
Volunteers	22,000	68,000	77,000	30,000
States	9	25	50	35+ PR
Cancer endpoints	Mortality	Mortality	Mortality (& incidence*)	Mortality and incidence
Exposure emphasis	Smoking	Smoking/ obesity	Multiple	Multiple
***in a subcohort of approximately 184,000**				

Use of >28000 DNA Samples CPS-II Nutrition Cohort for Inhereted Genetic Studies

	Cases	Control	Total
Breast	3422	3422	6844
Prostate in whites	5972	5972	11944
Prostate in African Americans	76	152	228
Bladder, lung, kidney, glioma, pancreas	2395	730	3125
Hematopoietic	1060	764	1464
Colorectal	716	716	1432
Male Breast	29	58	87
Nicotine dependence	1500	1500	3000
TOTAL			28142

The Cohort Studies

- Cigarettes with reduced yield of tar and nicotine do not reduce the risk of lung cancer.
- Obesity is associated with increased death rates from at least ten cancer sites, including colon and post-menopausal breast cancer.
- Discovery of the link between aspirin use and lower risk of colon cancer opened the door to research on chronic inflammation and cancer.
- Relationships of other potentially modifiable factors such as physical inactivity, prolonged hormone use and certain dietary factors with cancer risk.
- Air pollution, especially small particulates and ozone, increase death rates from heart and lung conditions.

The Potential of the Cohort Studies and Precision Medicine

- Correlate Genomics and Disease
- Identify those at risk of disease
- Create Risk Predictors
- Chemoprevention of Disease

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