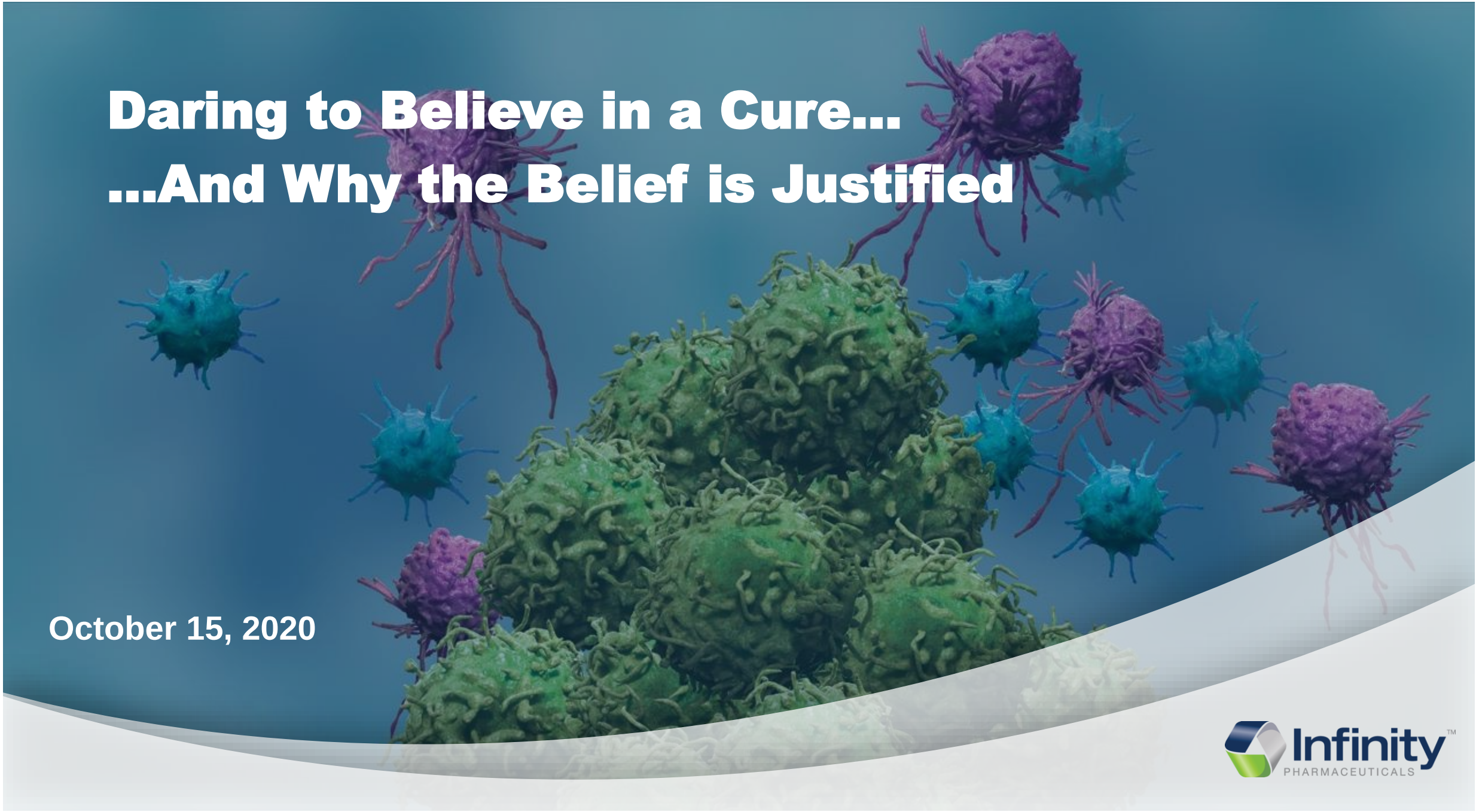
Daring to Believe in a Cure…
…And Why the Belief is Justified



October 15, 2020

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Cancer: An Insidious Disease

Worldwide

14,000,000 New Cases
8,100,000 Deaths

per year

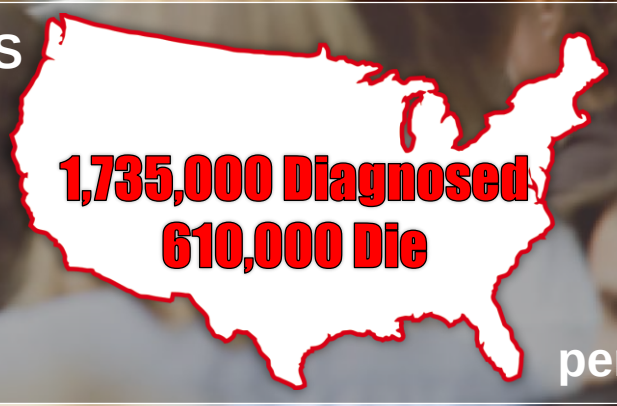
1 Out of 3

People will develop cancer in their lifetime

Worldwide

17 People Die Every Minute

In the US Alone



1,735,000 Diagnosed
610,000 Die

per year

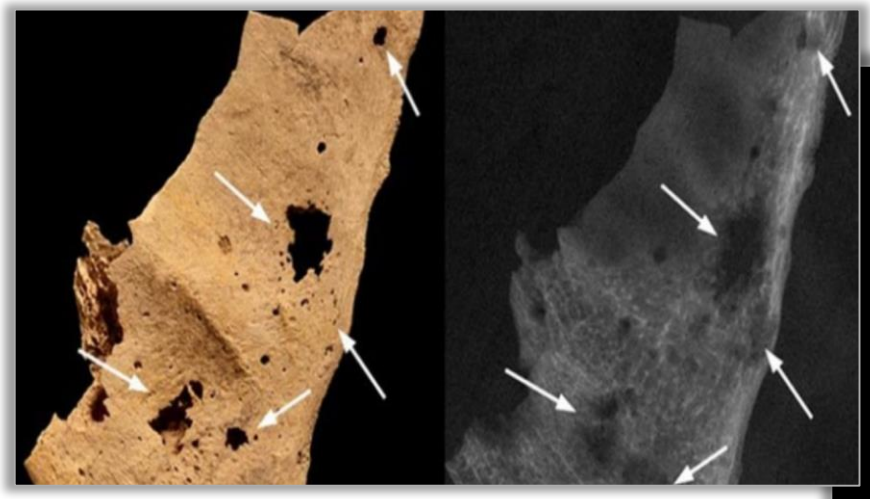
Daring to Believe in a Cure, and Why the Belief is Justified

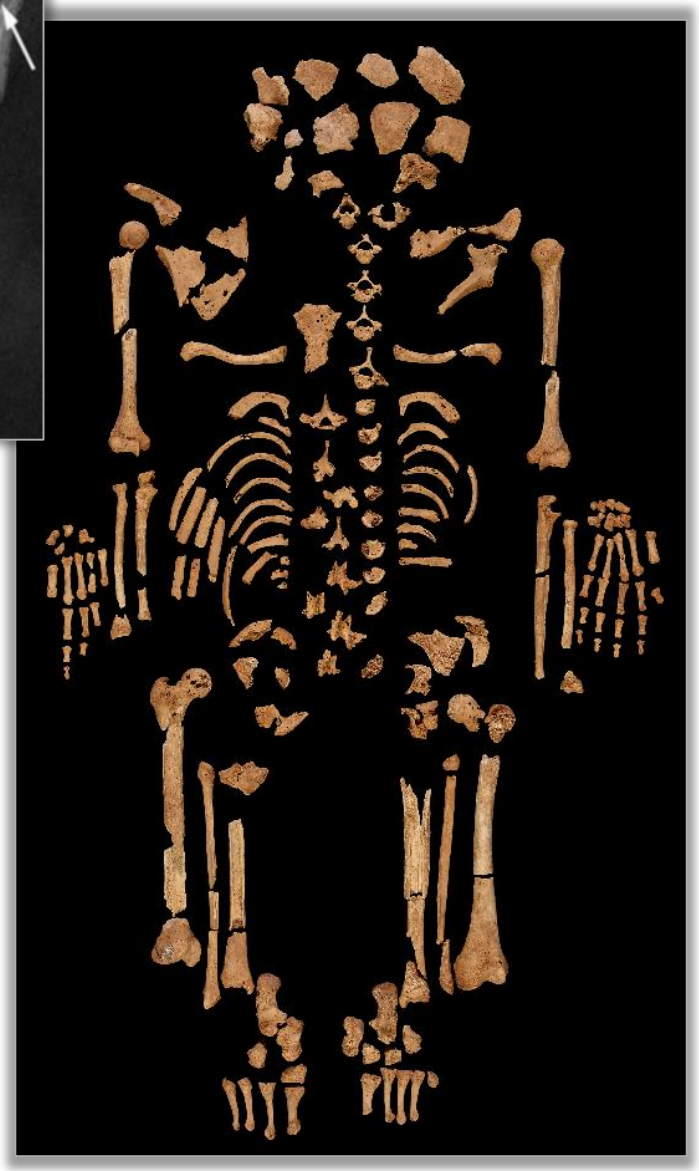
Why is cancer such a hard problem?

How are we doing in the fight against cancer?

Is a cure realistic?

3200 Year Old Diagnosis: Cancer Has Always Been with Us





Oldest case of cancer found in Sudan in 2013

Skelton of 25-35 year old male

Laid to rest in 1200 BC

Metastatic cancer throughout his body

Source:, Discover 3/18/14, John Reader, Science Source

The Potential for Cancer in Within Everyone

40%

Of women age 40-56 have microscopic cancer in their

breasts

50%

Of men age 50-60 have microscopic cancer in their

prostate

100%

Of people age 70+ have microscopic cancer in their

thyroids

Given the effectiveness of our immune systems most will never become dangerous “Cancer without Disease”

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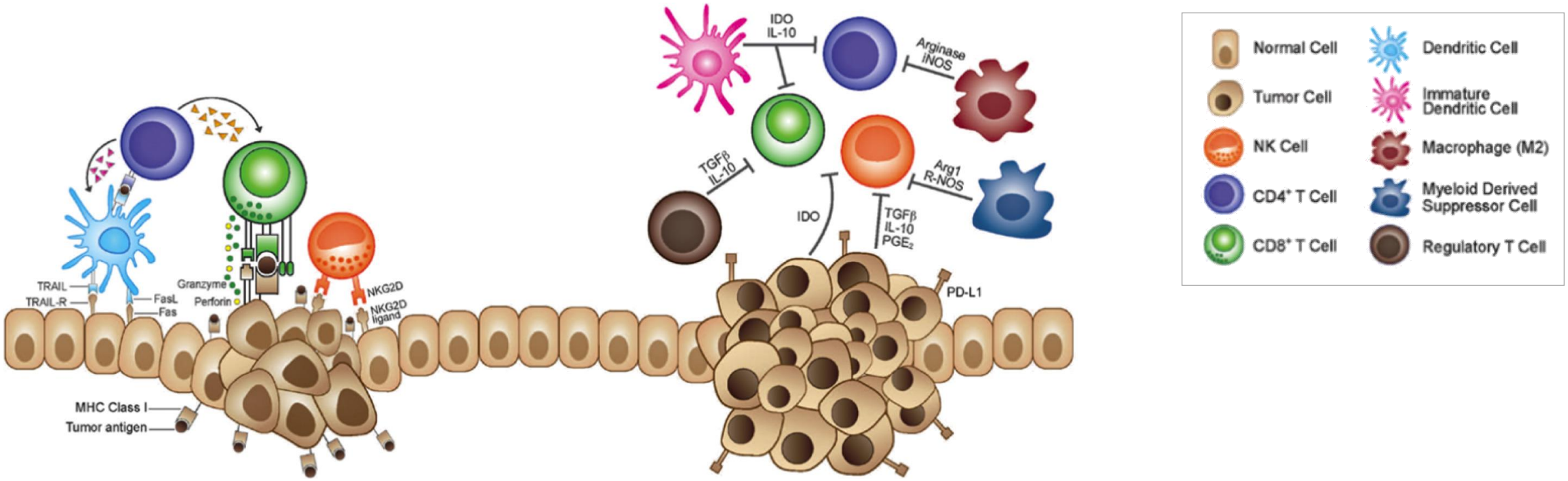
Cancer Develops When Cancer Cells Corrupts the Immune System to Escape Attack and Create its own Supportive Ecosystem



Elimination

Healthy immune systems routinely and effectively eliminating cancer cells and stop the spread of cancer

Escape

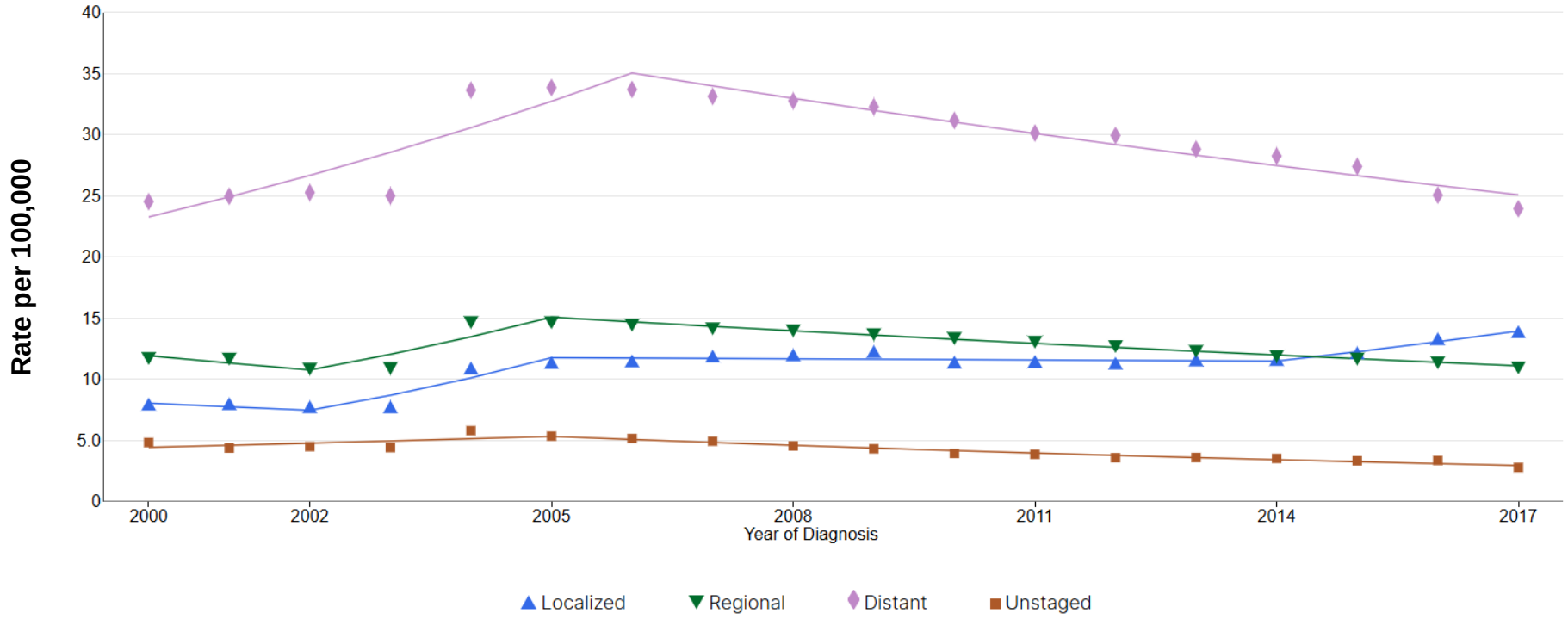
Cancer occurs when the immune system fails to do its job allowing rouge cells to establish a beach head and promote their own existence at the expense of healthy cells

Source: Being-Bioreactive.com

Cancer Develops Slowly over many Years, Is Often Asymptomatic and not Diagnosed Until very Advanced Stages Making Treatment too Late

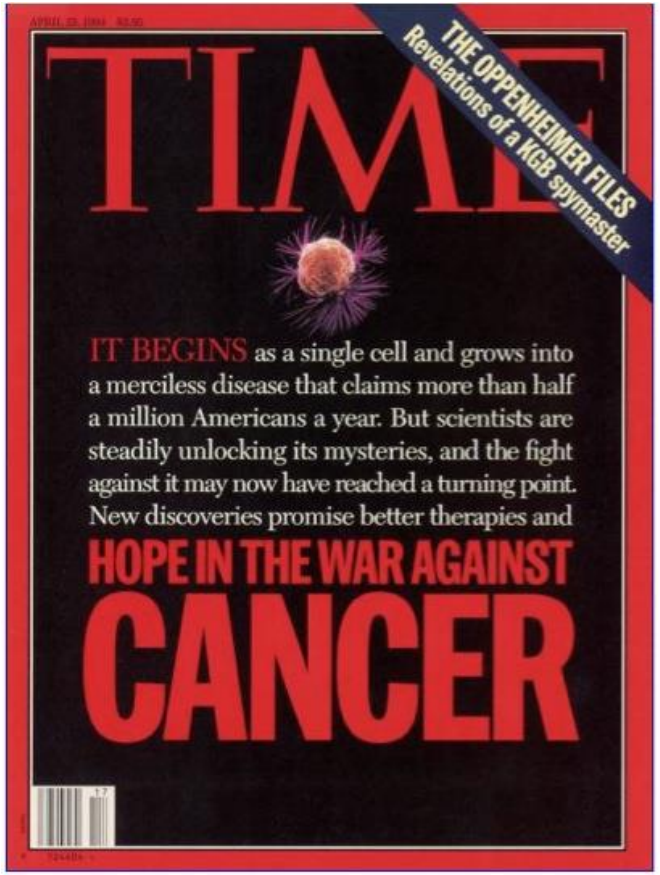
Distribution of Lung Cancer Diagnoses by Stage at Diagnosis, 2000-2017

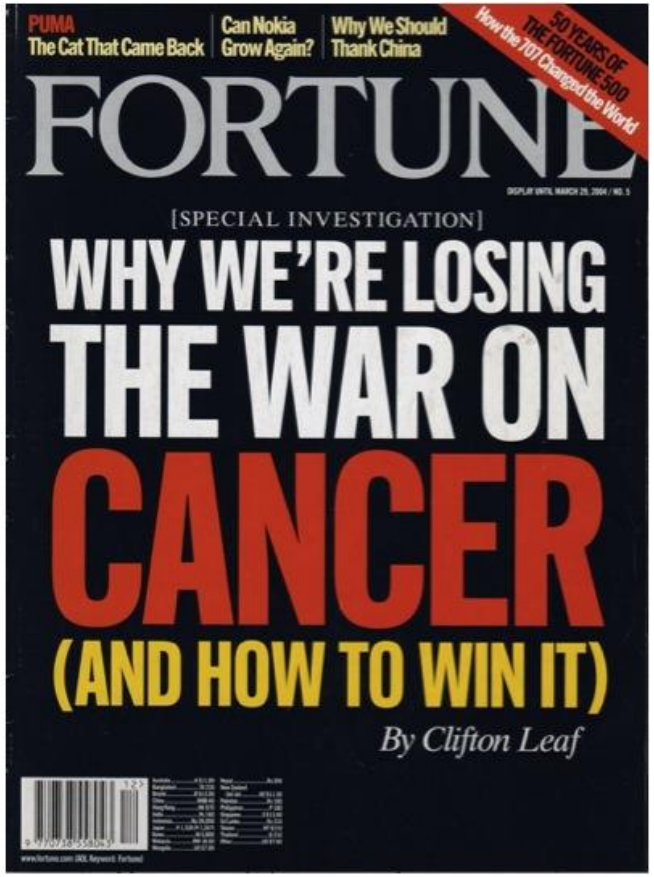
~Half of Patients are Diagnosed with Metastatic Stage III/IV Disease



SEER National Cancer Institute.

How Are We Doing in the 50 Year War on Cancer?





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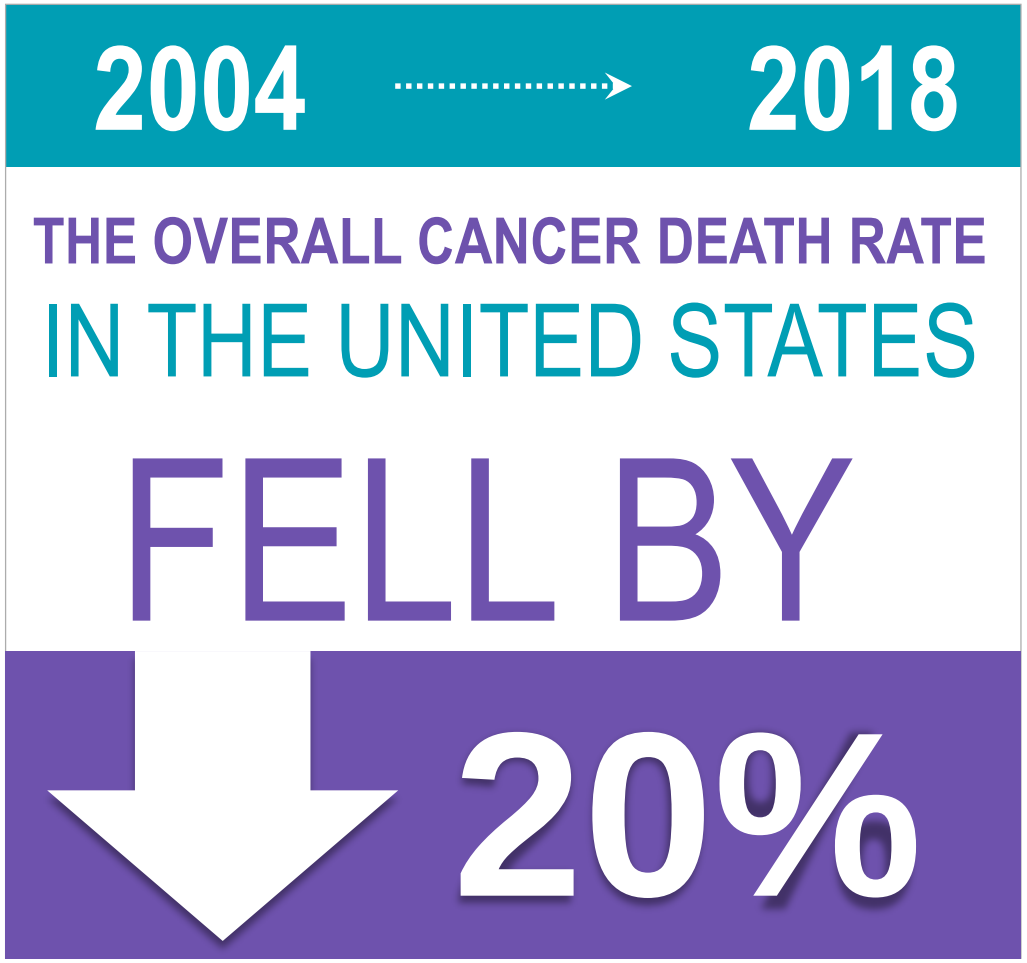
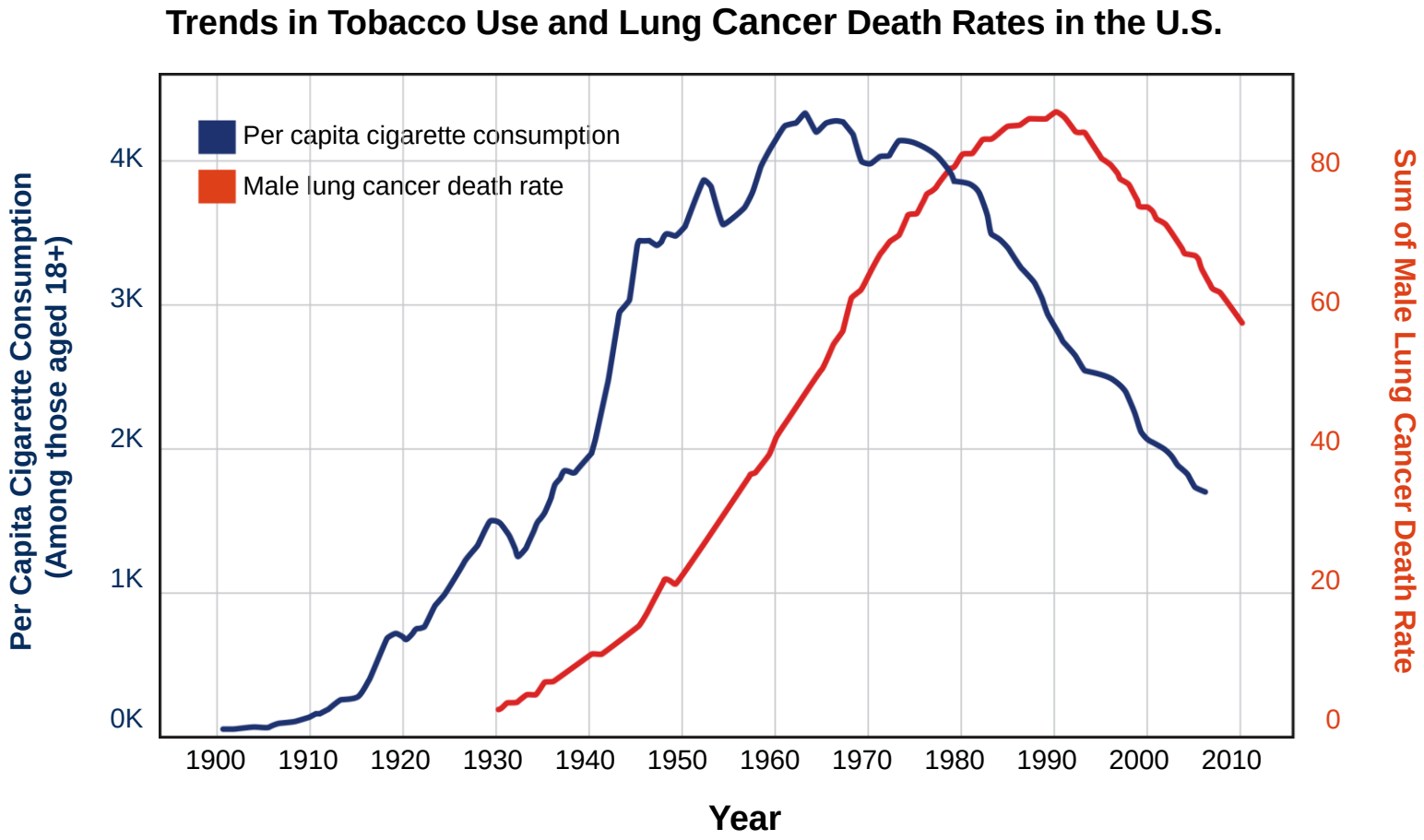
Unequivocal Progress!!



Source: SEER Cancer Statistics Review 1975-2018

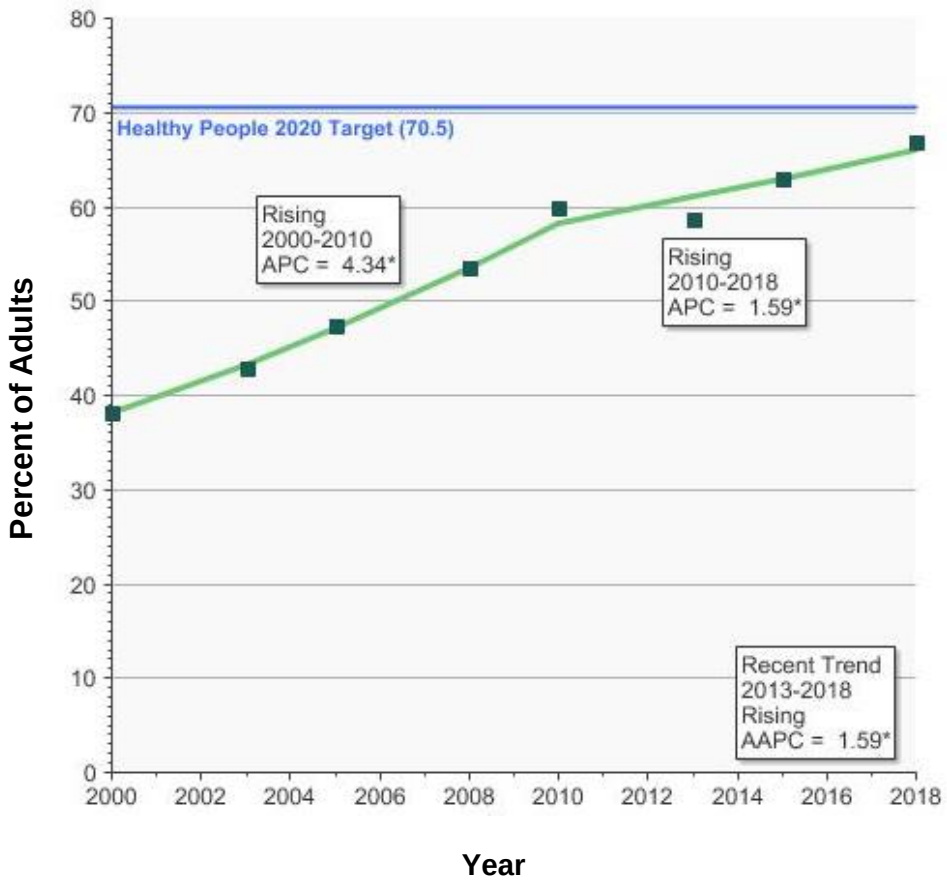
Prevention! Lung Cancer



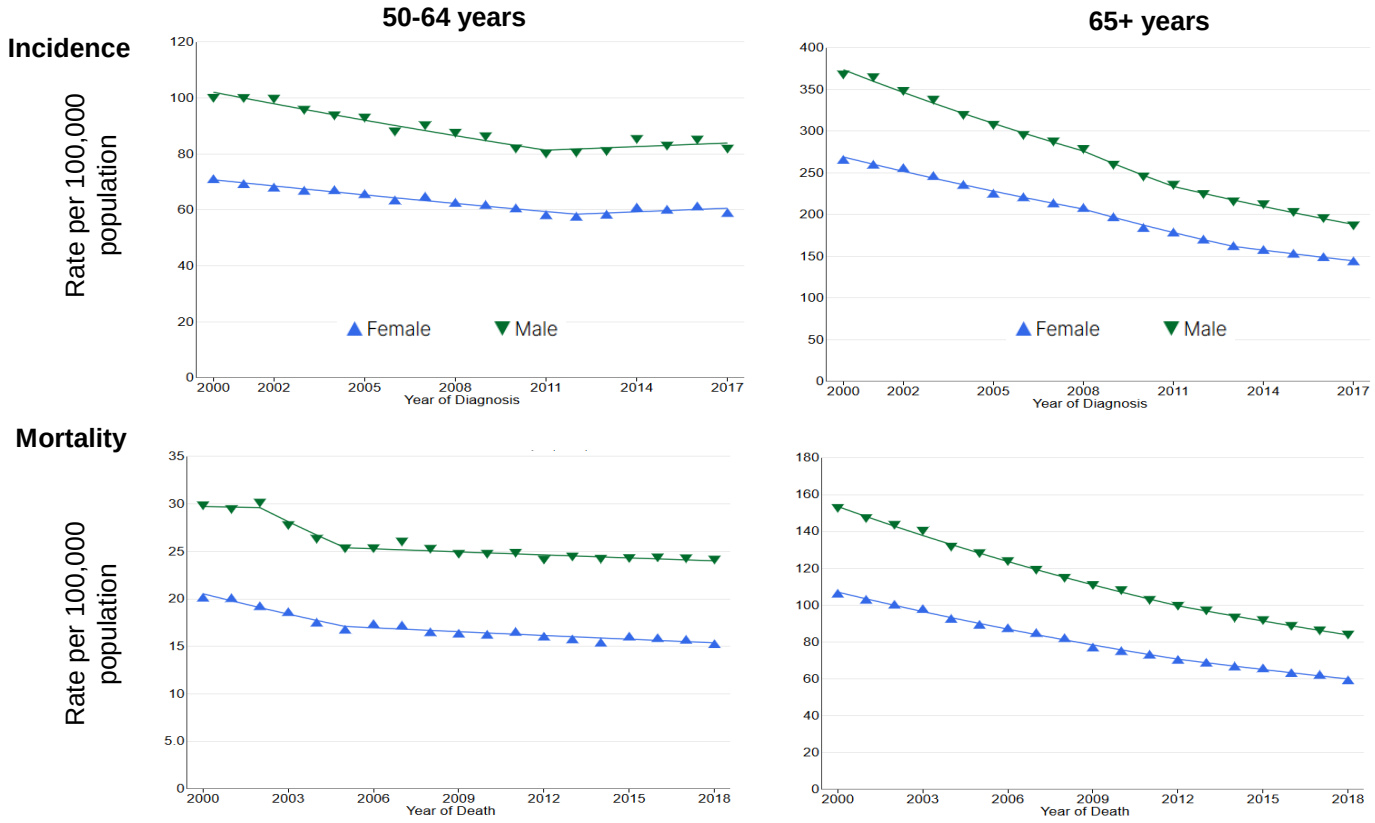
Death rates source: US Mortality Data, 1960-2010, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention.
Cigarette consumption source: US Department of Agriculture, 1900-2007.

Screening, Prevention, Early Detection and Treatment Decreased Colorectal Cancer Incidence and Mortality Rates

Colorectal test use rates' for adults aged 50-75 years, Both Sexes, 2000-2018[1]



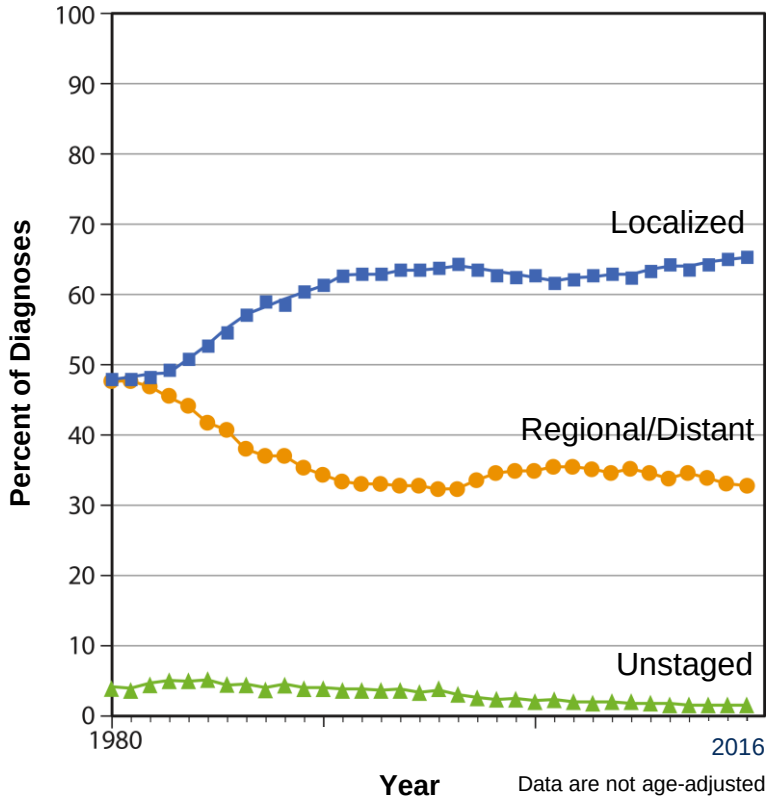
Colorectal Incidence and Mortality[2]



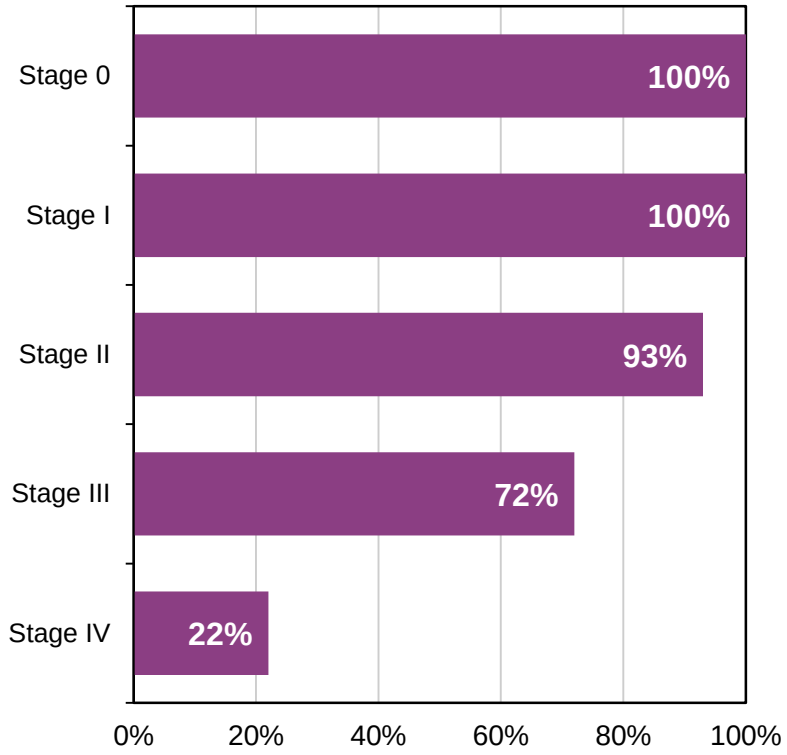
[1]Centers for Disease Control and Prevention, National Center for Health Statistics. National health Interview Survey.
[2]https://seer.cancer.gov

Screening, Prevention, Early Detection and Treatment in Breast Cancer Decreased Mortality Rate in the US

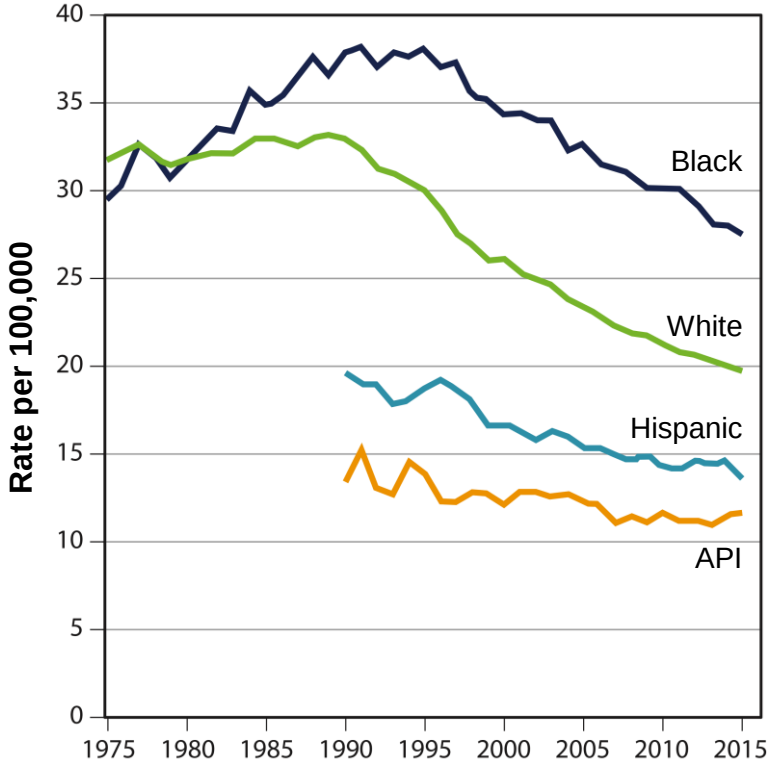
Breast Cancer Diagnoses by Stage, Women, US*



Five Year Survival Rate, Women, US†



Trend in Breast Cancer Death Rate, Women, US ‡



*SEER Program, National Cancer Institute. Incidence data are from the SEER 9 areas seer.cancer.gov/registries/terms.html

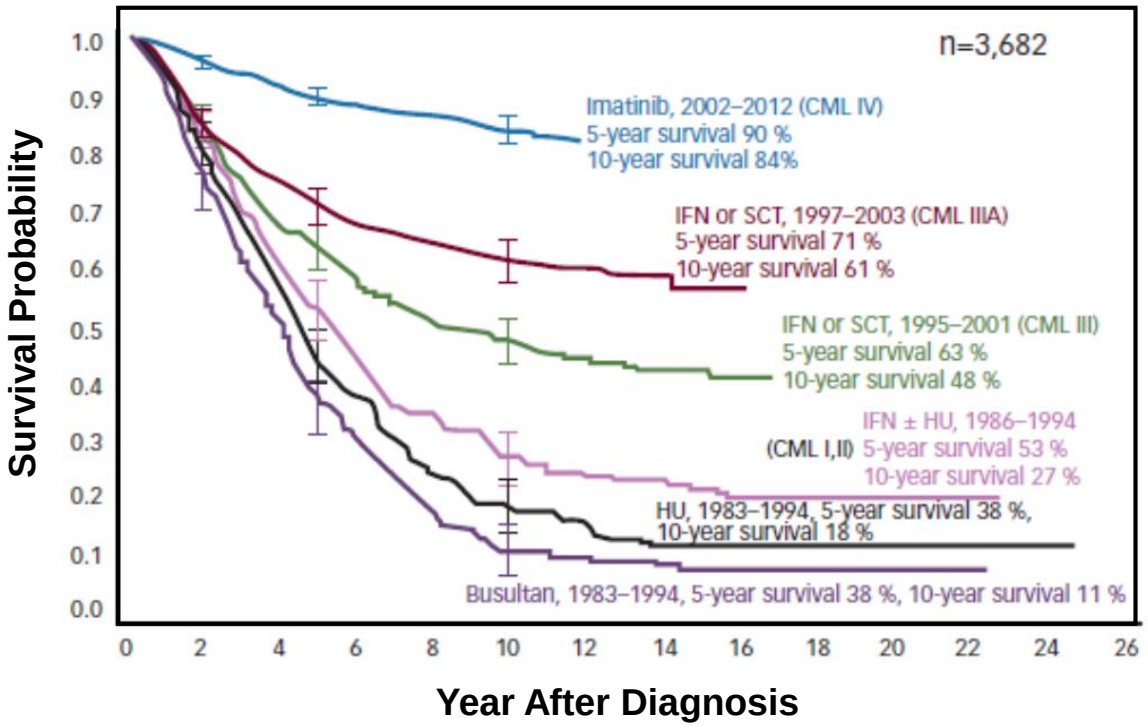
† BreastCancer.Org/symptoms/diagnosis/prognosis

‡ Volume 67, Issue 6, pages 439-448, 3 OCT 2017 DOI: 10.3322/caac.21412 onlinelibrary.wiley.com/doi/10.3322/caac.21412/full#caac21412-fig-0008

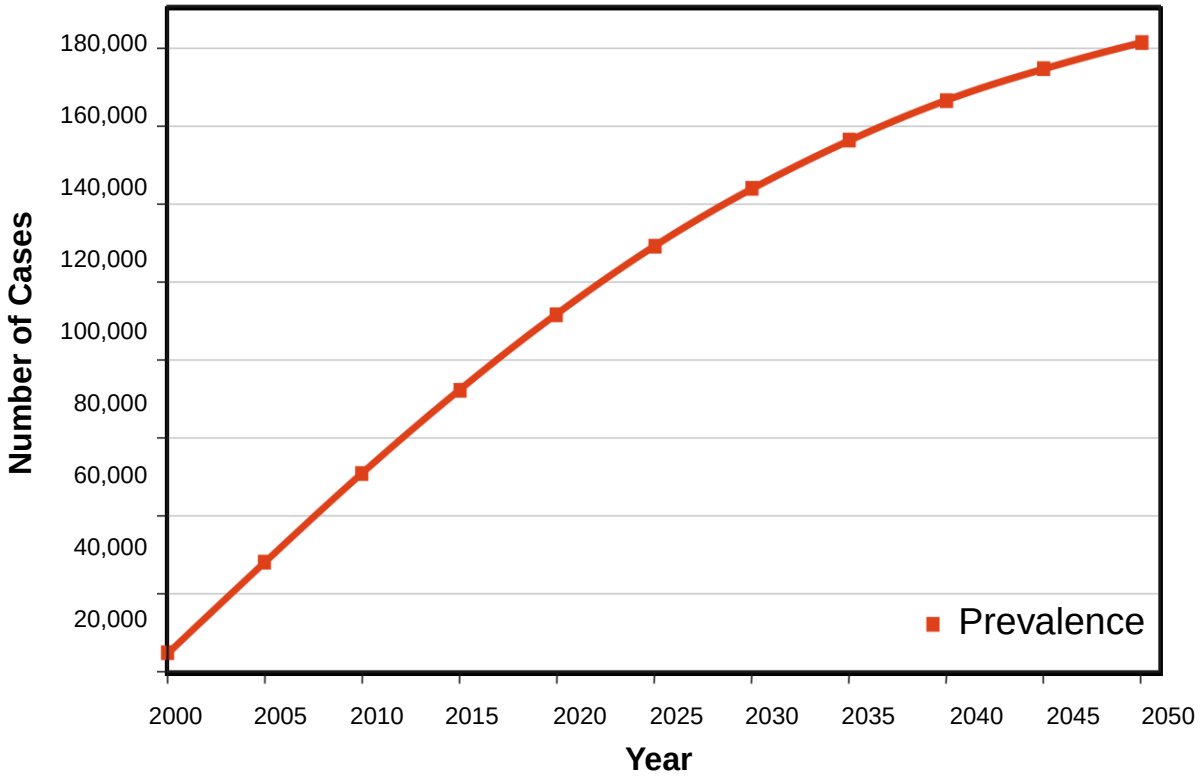
CA: A Cancer Journal for Clinicians

Treatment!
CML: Cancer as a Chronic Condition with Potential Cures

Survival with CML Over Time –
The German CML-Study Group Experience 9/2014*



Projected Growth in Prevalence of CML†



Nov 2019 Analysis of Nilotinib vs Imatinib showed over 40% improvement in molecular response at 10 years**
Newer Therapies Ibrutinib and Venetoclax expected to further change treatment paradigms in CLL

HU = hydroxyurea; IFN = interferon; SCT = stem cell transplantation. Survival with chronic myeloid leukaemea (CML) as observed in five consecutive randomised treatment options studies of the German CML Study Group 1983-2014. Kindly authorized by R Hehlmann.

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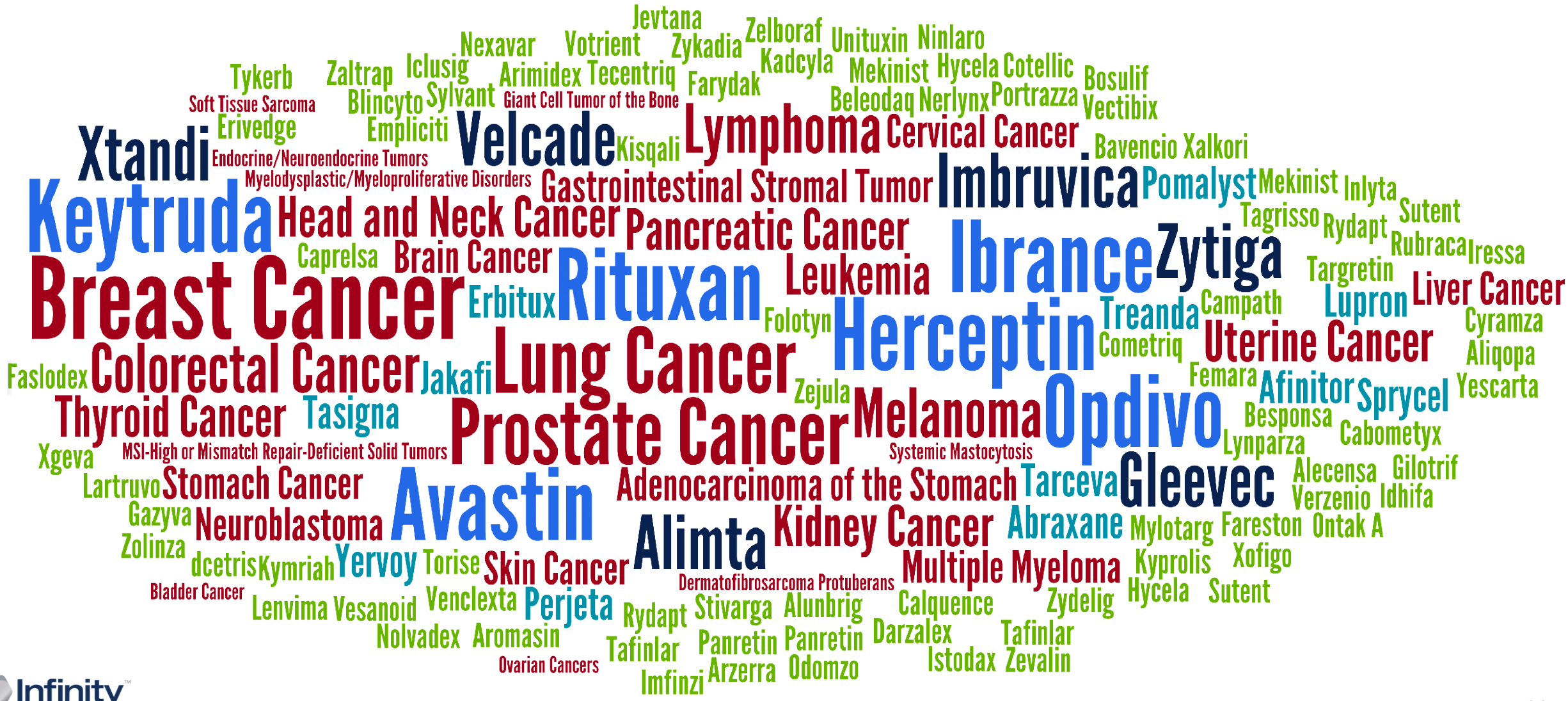
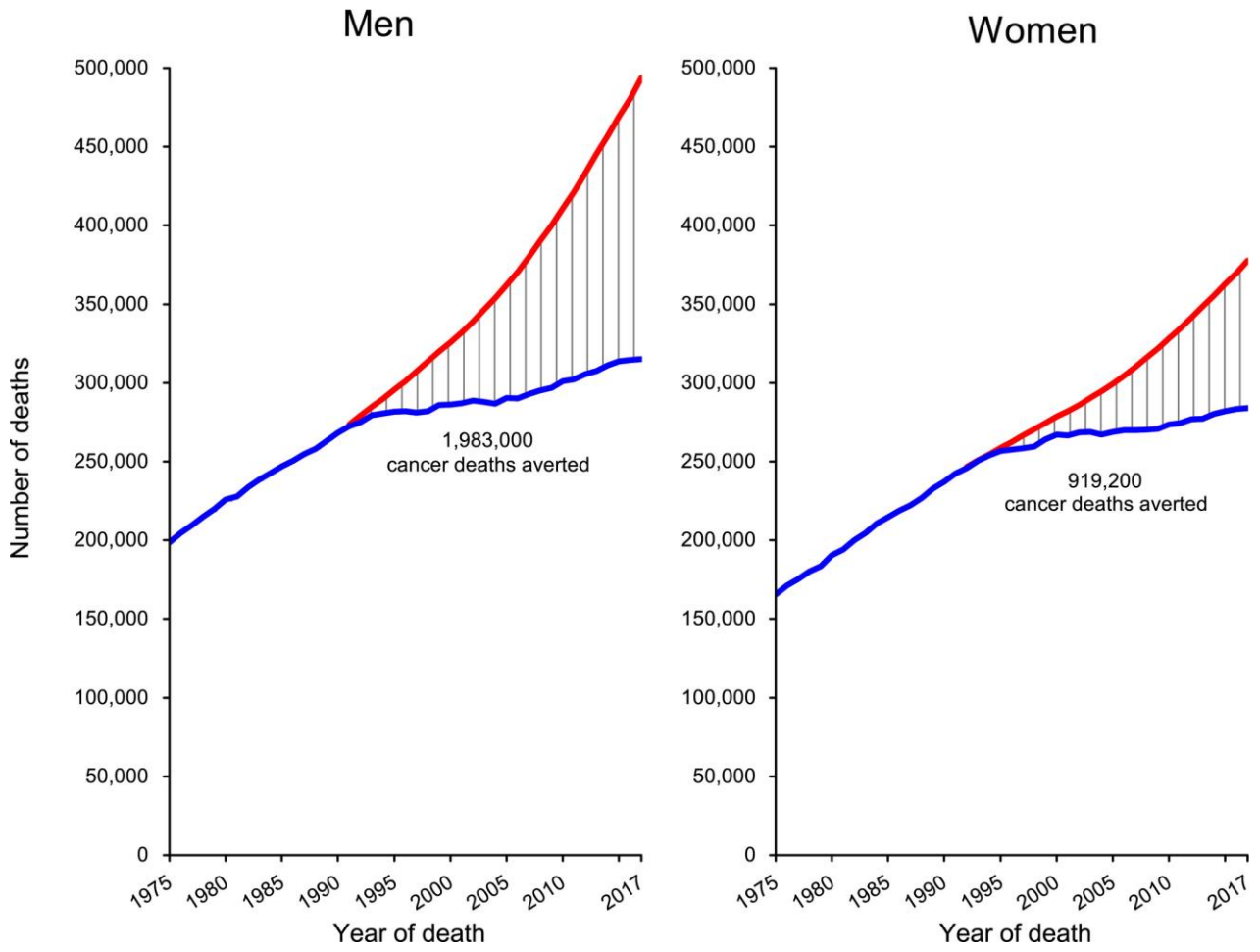
* touchonocology.com, † Cancer 2012 June 15 118(12): 31223-3127, ***Blood* (2019) 134 (Supplement_1): 2924.

Treatment Advances Leverage Successes in Prevention and Detection

In Last 20 Years, Over 80 Targeted Therapies Approved for Over 30 Cancers



Unequivocal Progress
Over 2.9 M Cancer Deaths Averted in US in 25 Years From 1990 to 2017



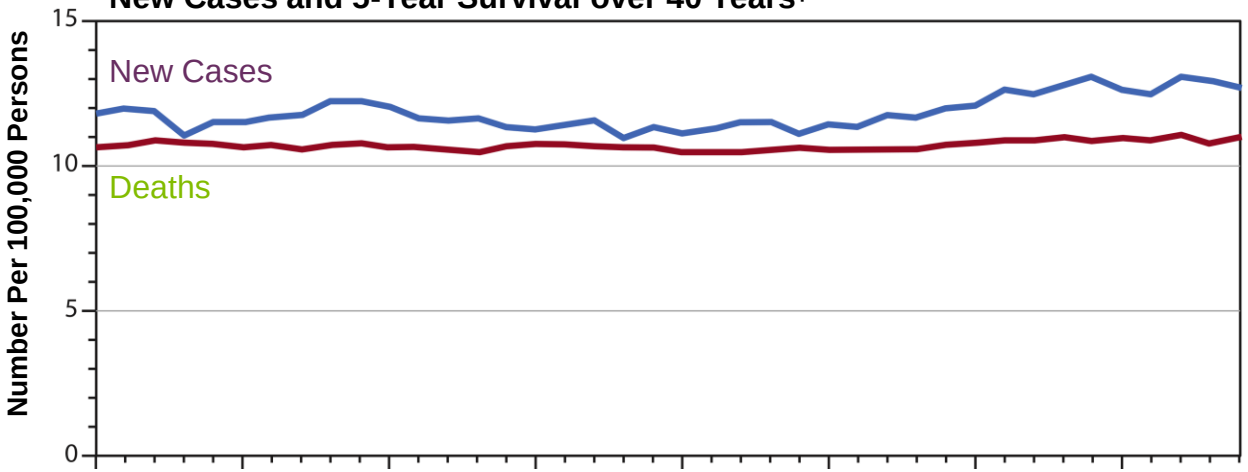
CA: A Cancer Journal for Clinicians, Volume: 70, Issue: 1, Pages: 7-30, First published: 08 January 2020, DOI: (10.3322/caac.21590)

Despite Successes, We Have a Very Long Way to Go
Minimal Progress Against Many Cancers

Pancreas Cancer 5 Year Survival in 2016*

Percent Surviving 5 Years
10.0%

New Cases and 5-Year Survival over 40 Years†



Year	1975	1980	1985	1990	1995	2000	2005	2010	2014
5-Year Relative Survival	3.0%	3.3%	3.2%	3.7%	3.6%	5.1%	6.2%	8.5%	

* Based on data from SEER 18 2010-2016. Gray figures represent those who have died from pancreatic cancer. Green figures represent those who have survived 5 years or more.
† SEER 9 Incidence & U.S. Mortality 1975-2014, All Races, Both Sees, Rates are Age Adjusted.

AND, Global Cancer Outlook Is Grim

2012 ⇢ 2030*

WORLDWIDE CANCER CASES
ARE PROJECTED TO INCREASE BY

50%

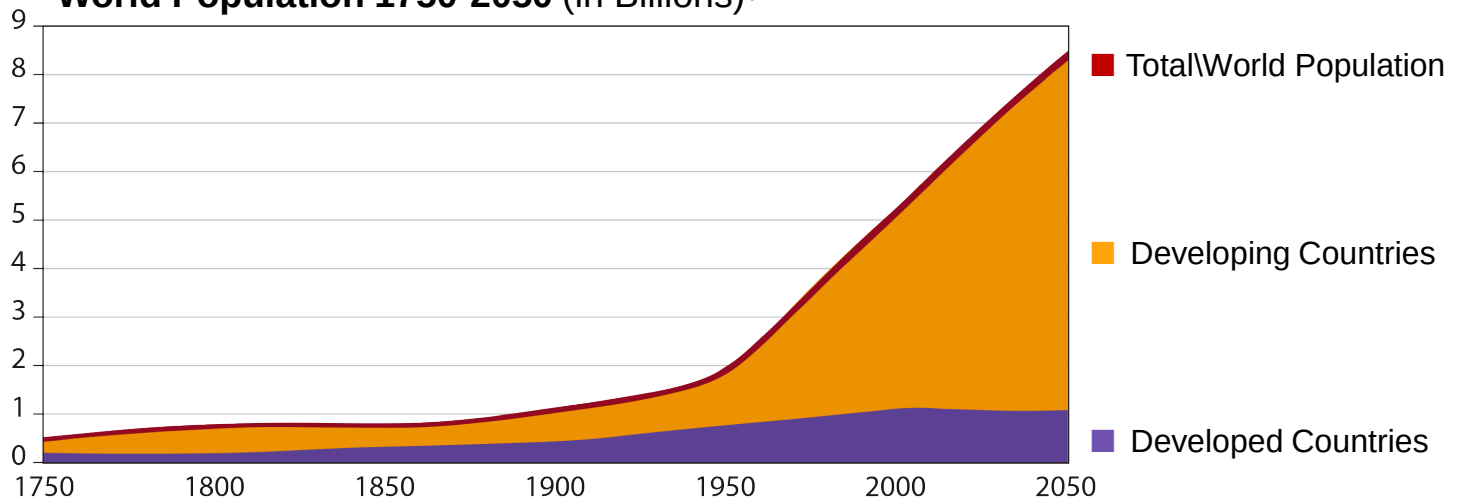
FROM **14 million** TO **21 million**

WORLDWIDE CANCER DEATHS
ARE PROJECTED TO INCREASE BY

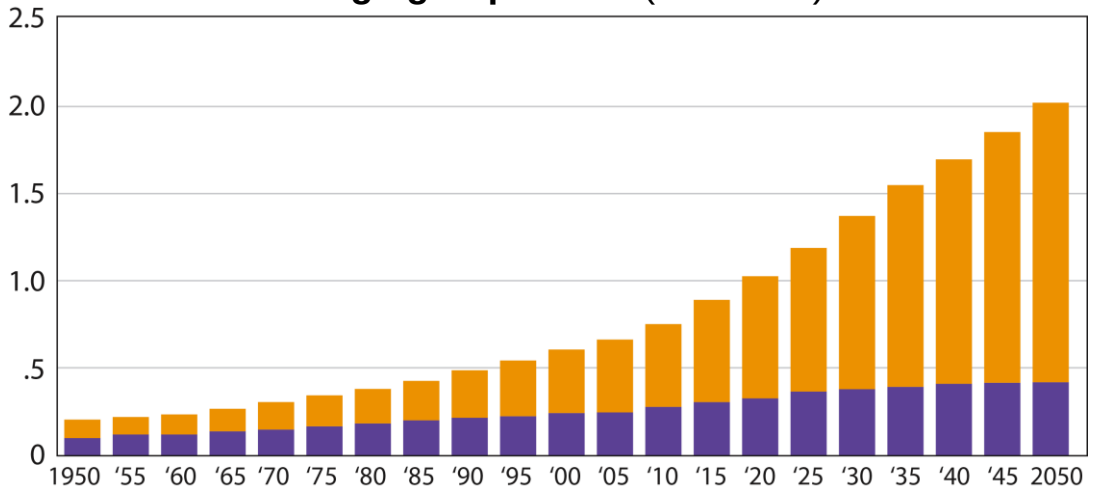
60%

FROM **8 million** TO **13 million**

World Population 1750-2050 (in Billions)†



Global Rise in Aging Population (in Billions)‡

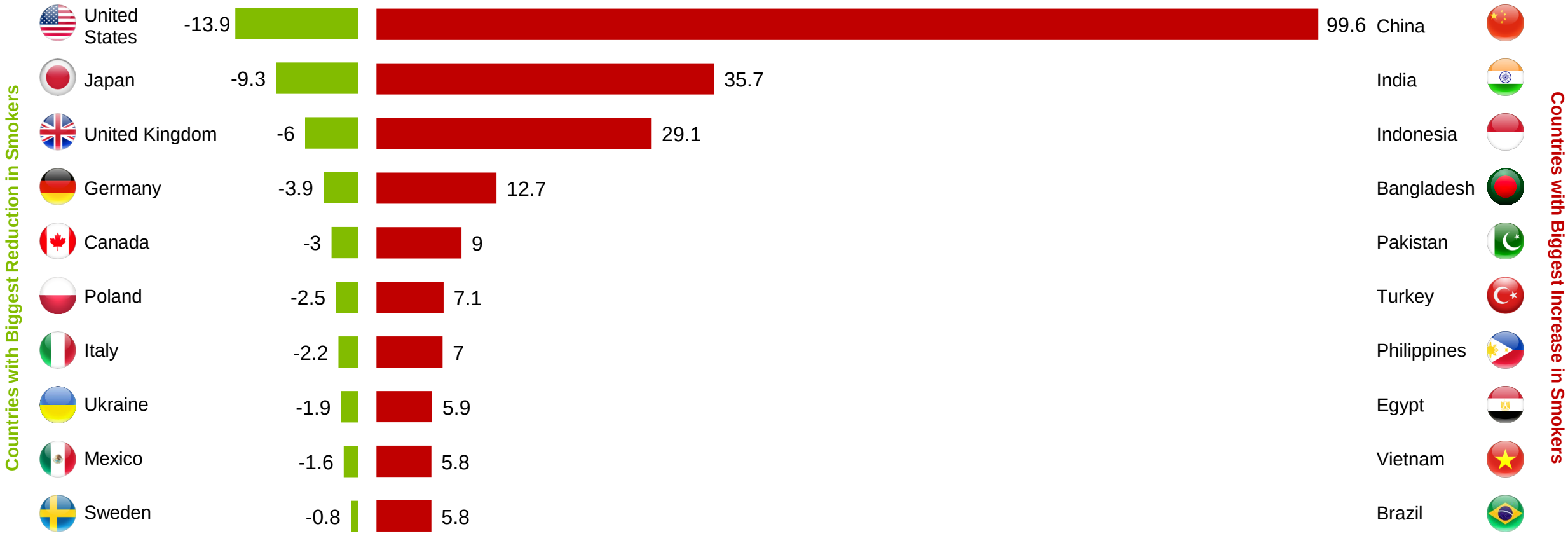


The number of people in the world aged 60 and older is expected to grow past 2 billion by the year 2050.

† World Bank, Development Education Program
‡ Source: United Nations Population Fund
* American Cancer Society Global Cancer Facts & Figures, Second Edition Cancer.gov

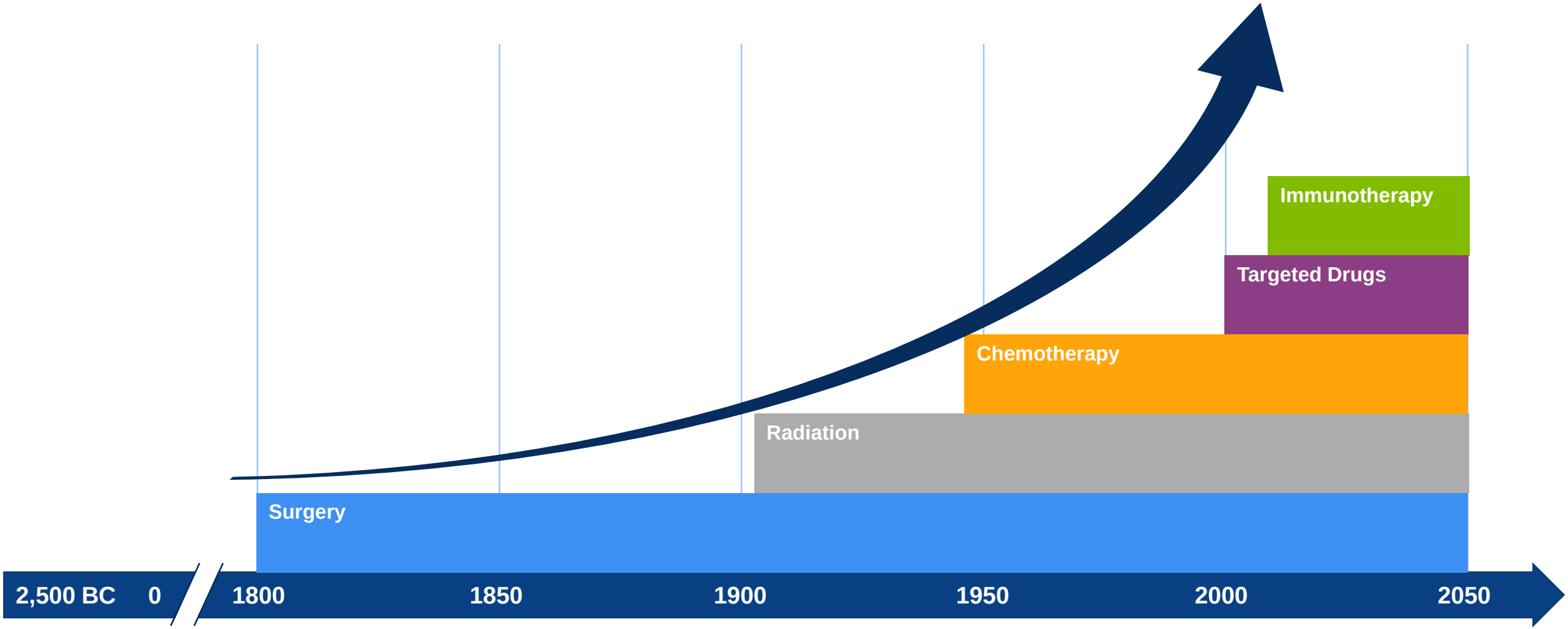
Unhealthy Lifestyle Changes in Developing Countries
Significant Increase in Smokers

Change in millions of smokers, 1980-2012



University of Washington, Institute for Health Metrics and Evaluation. JAMA. January 2014;311(2):183-192

The Path Ahead: Challenges Ahead



Immunotherapy Has Transformed the Treatment of Many Cancers, Advances From 2010+ Will Drive Progress for the next 25+ Years

New drug 'doubles survival rates for lung cancer patients' by helping the body detect and attack tumour cells

- New study shows immunotherapy could be better than chemotherapy
- Early results show it could double survival rates for common lung cancer
- Drug works by interfering with a protein that is found on tumour cells
- It reactivates the ability of the immune system to detect and kill disease

By LIZZIE PARRY FOR MAILONLINE
PUBLISHED: 06:59 EST, 29 May 2015 | **UPDATED:** 10:48 EST, 29 May 2015

2018 Nobel Prize in Medicine
1500 Trials now underway
Annual revenue >$7B

To Your Health

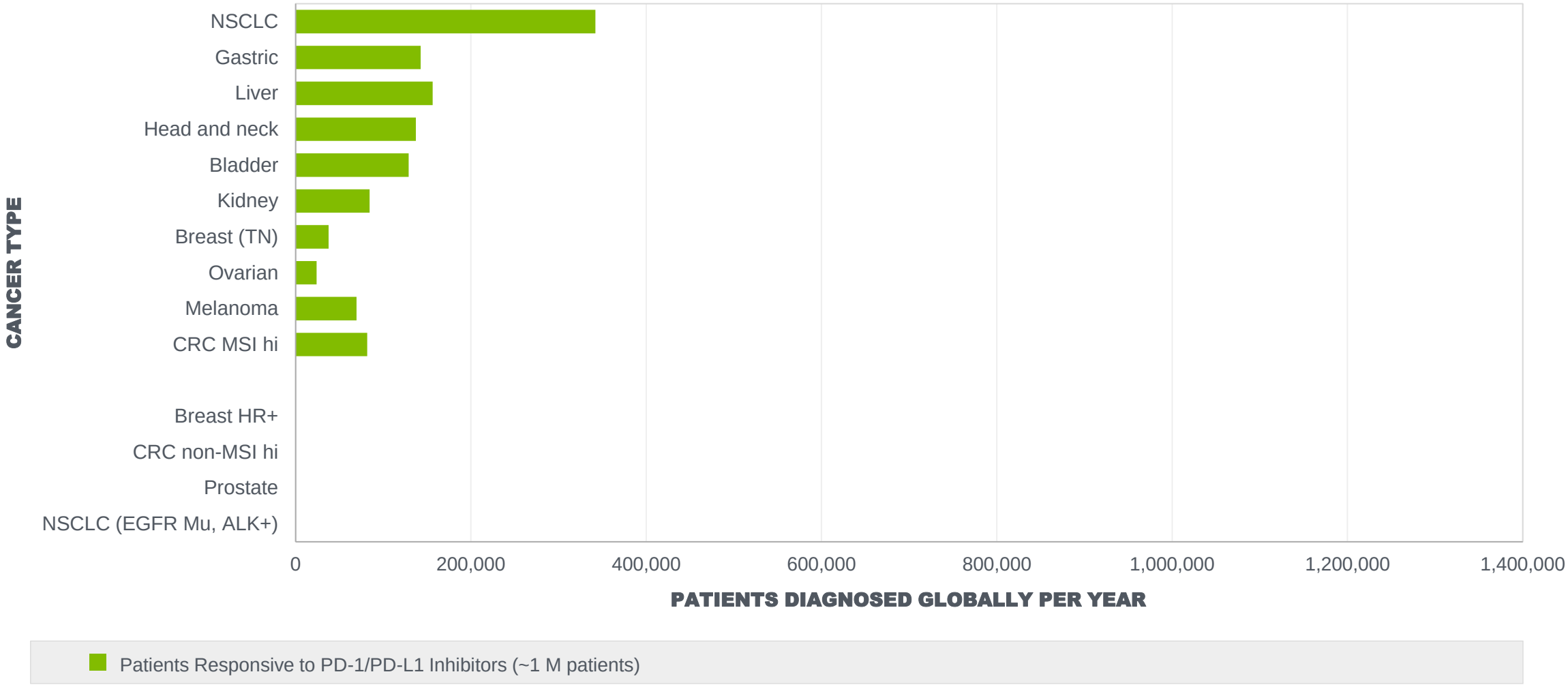
Long-term survival rates double for melanoma patients getting immunotherapy

By Laurie McGinley April 17, 2016 Email the author

UNIVERSITY OF CAMBRIDGE

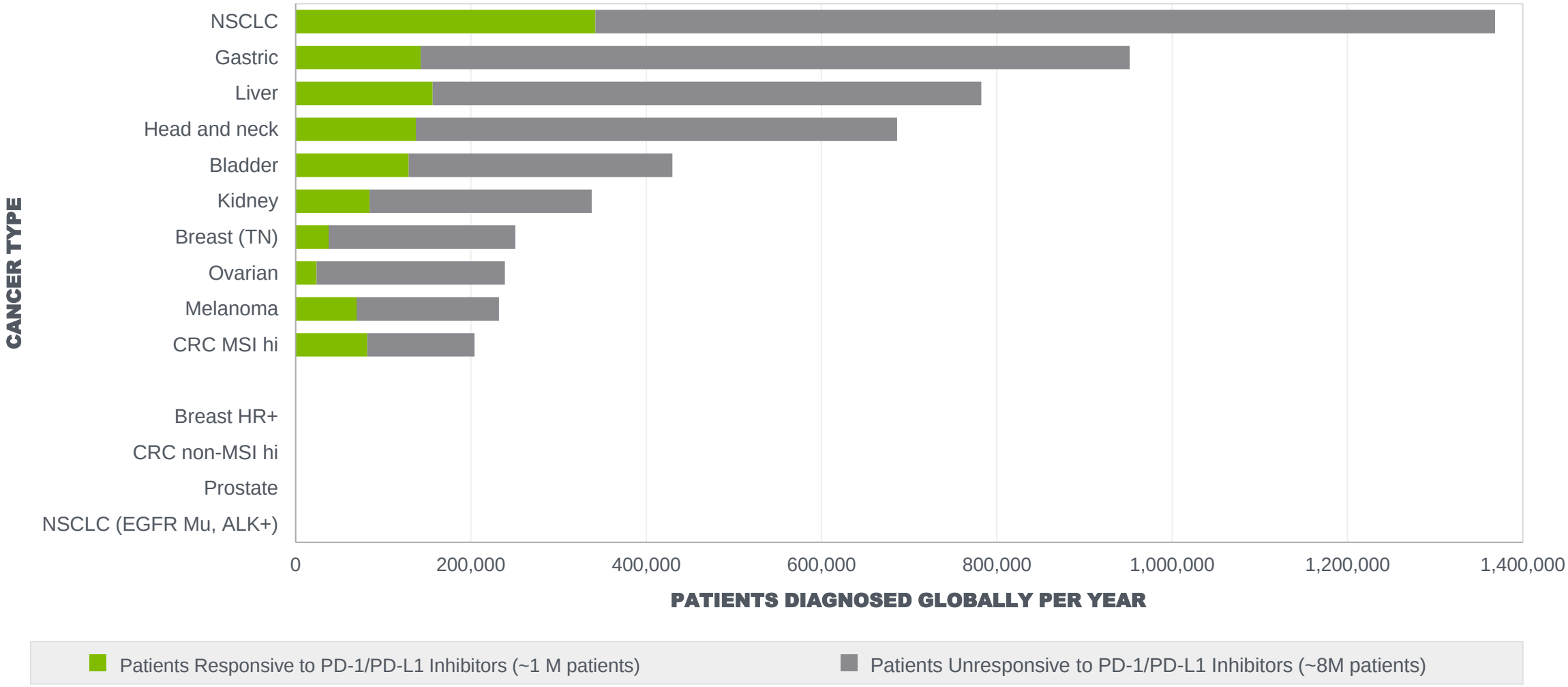
The Power of Harnessing the Immune System!

Checkpoint Inhibitors Can Generate an Effective Anti-Tumor Immune Response in Some Patients Across a Broad Range of Cancers



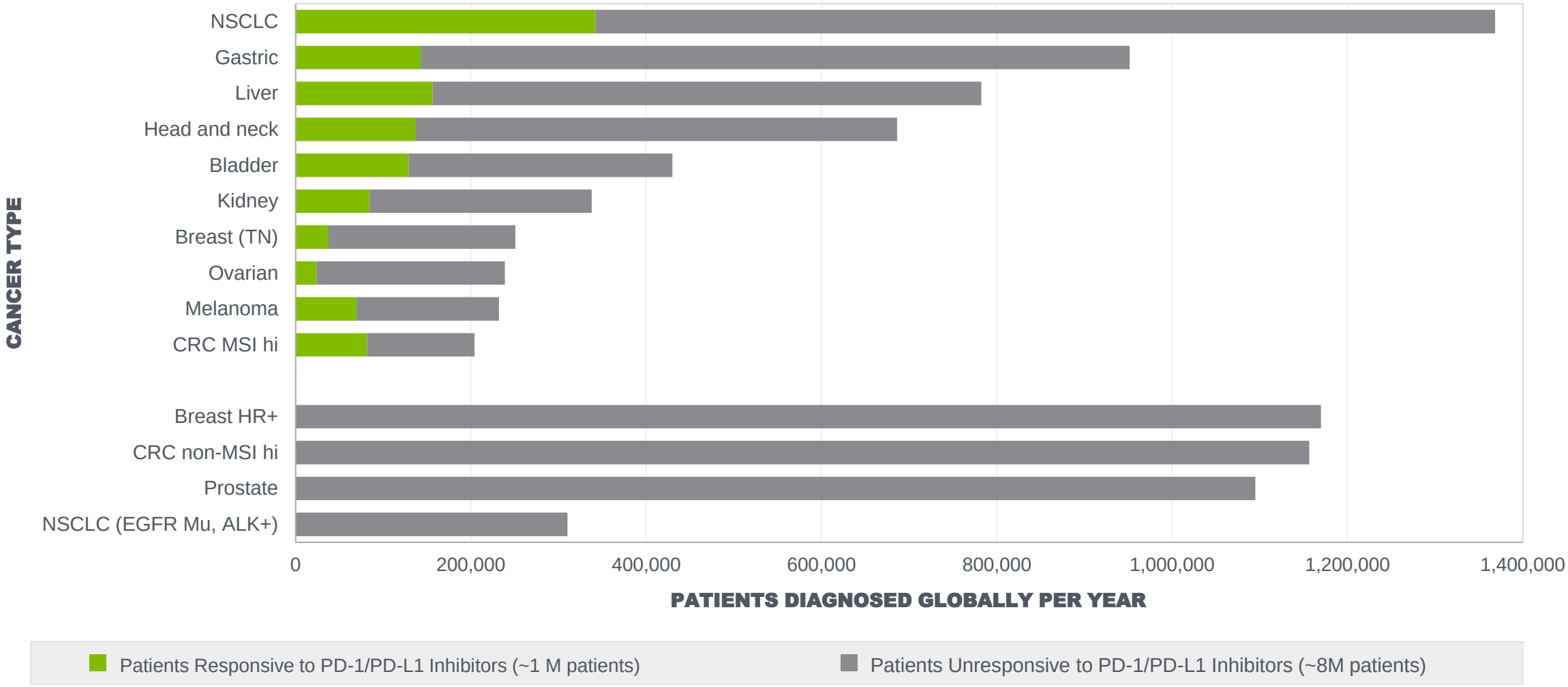
GLOBOCAN 2018. Estimated cancer incidence in 2018.

But an Effective Immune Response is Not Generated in Most Patients



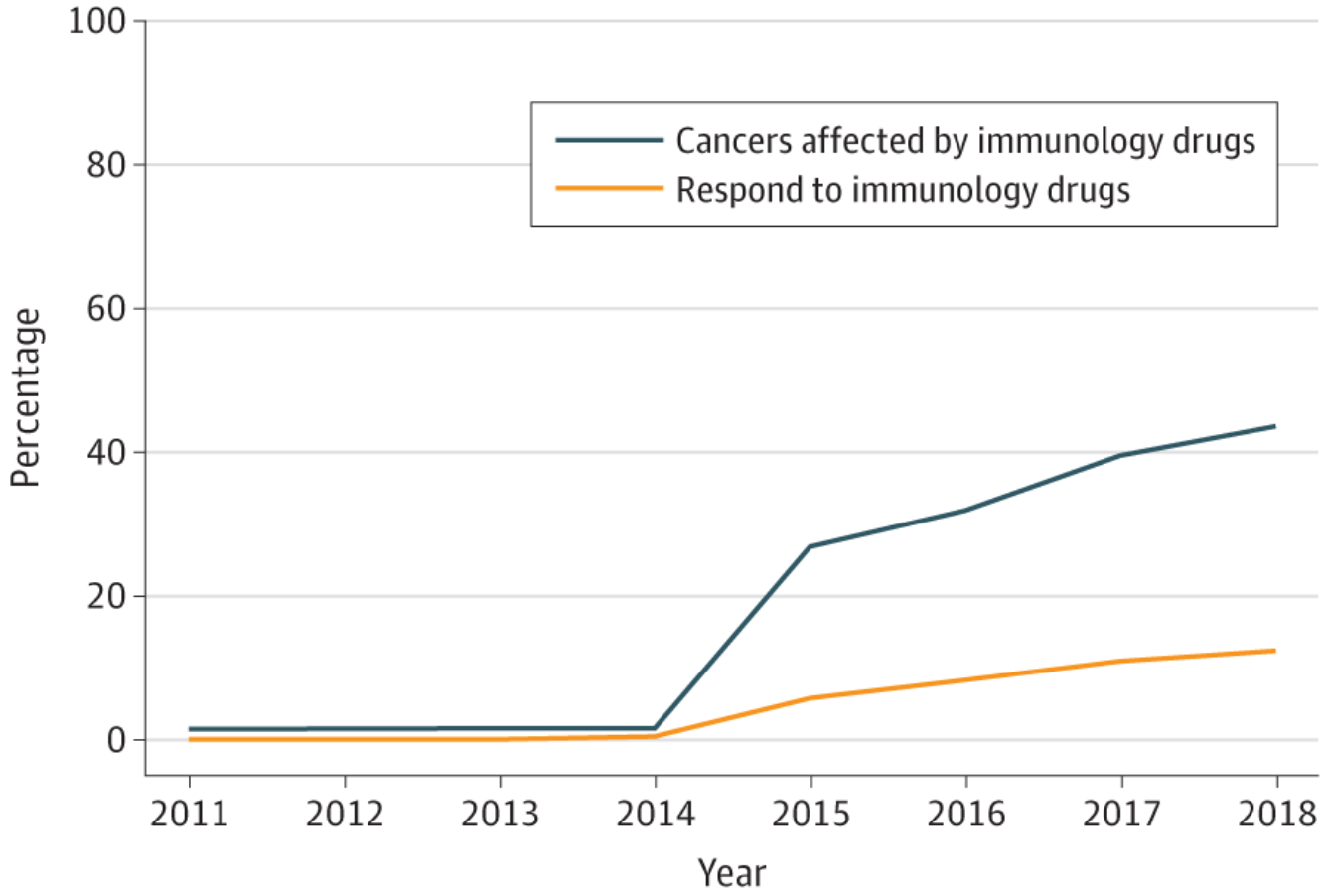
GLOBOCAN 2018. Estimated cancer incidence in 2018.

Growing Evidence that BOTH ‘Enabling’ Effectors and ‘Suppressing’ Suppressors Are Necessary to Generate Clinically Meaningful Immune Responses



GLOBOCAN 2018. Estimated cancer incidence in 2018.

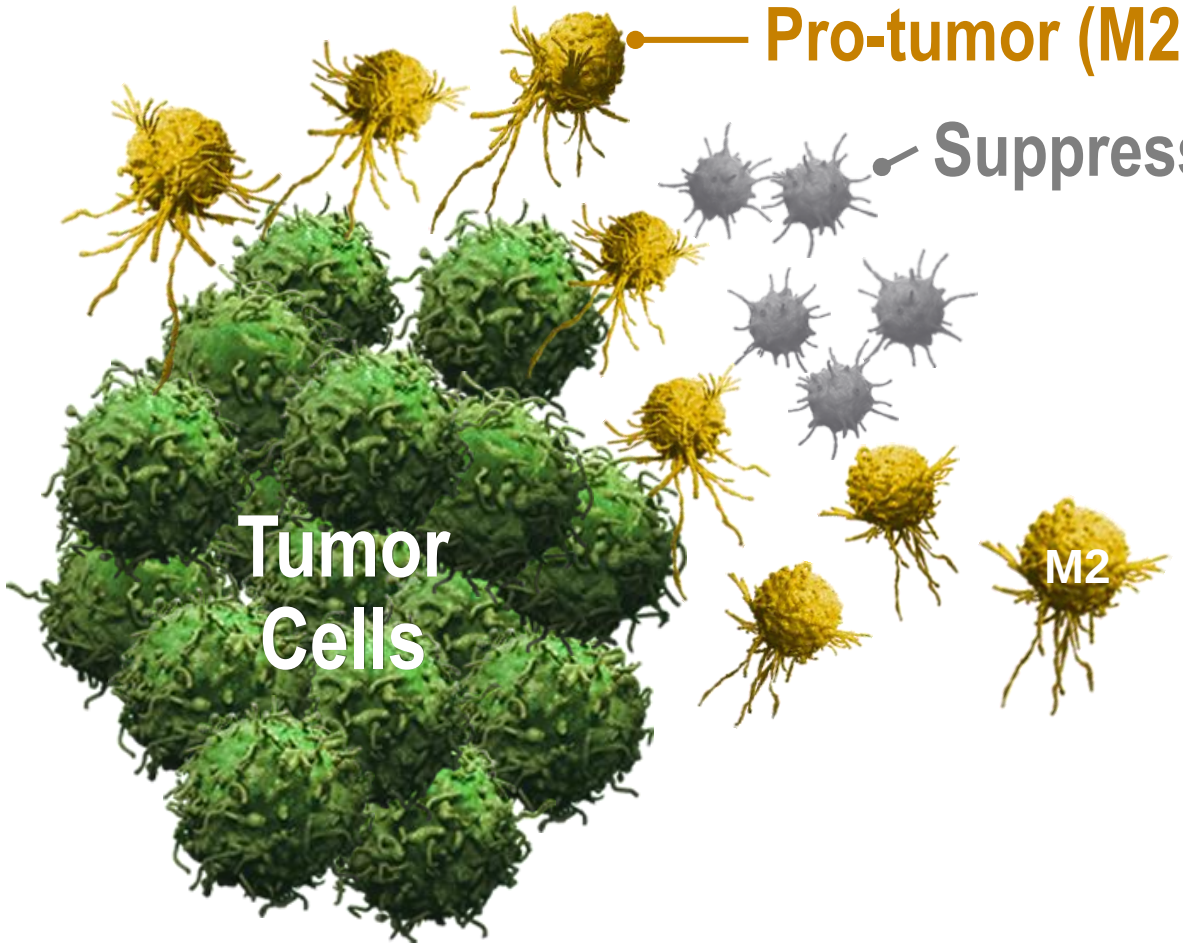
Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs (2011-2018)



- As of 2019, only 13% of US cancer patients are eligible to receive and are likely to respond to Checkpoint inhibitor therapy (CPI)
- Characteristics of responders vs non-responders MUST be identified to develop better treatment options for the 87% not currently benefitting from CPI

JAMA Netw Open. 2019;2(5):e192535. doi:10.1001/jamanetworkopen.2019.2535
Analysis based on 6 approved checkpoint inhibitors in 14 approved indications between 2011 and 2018

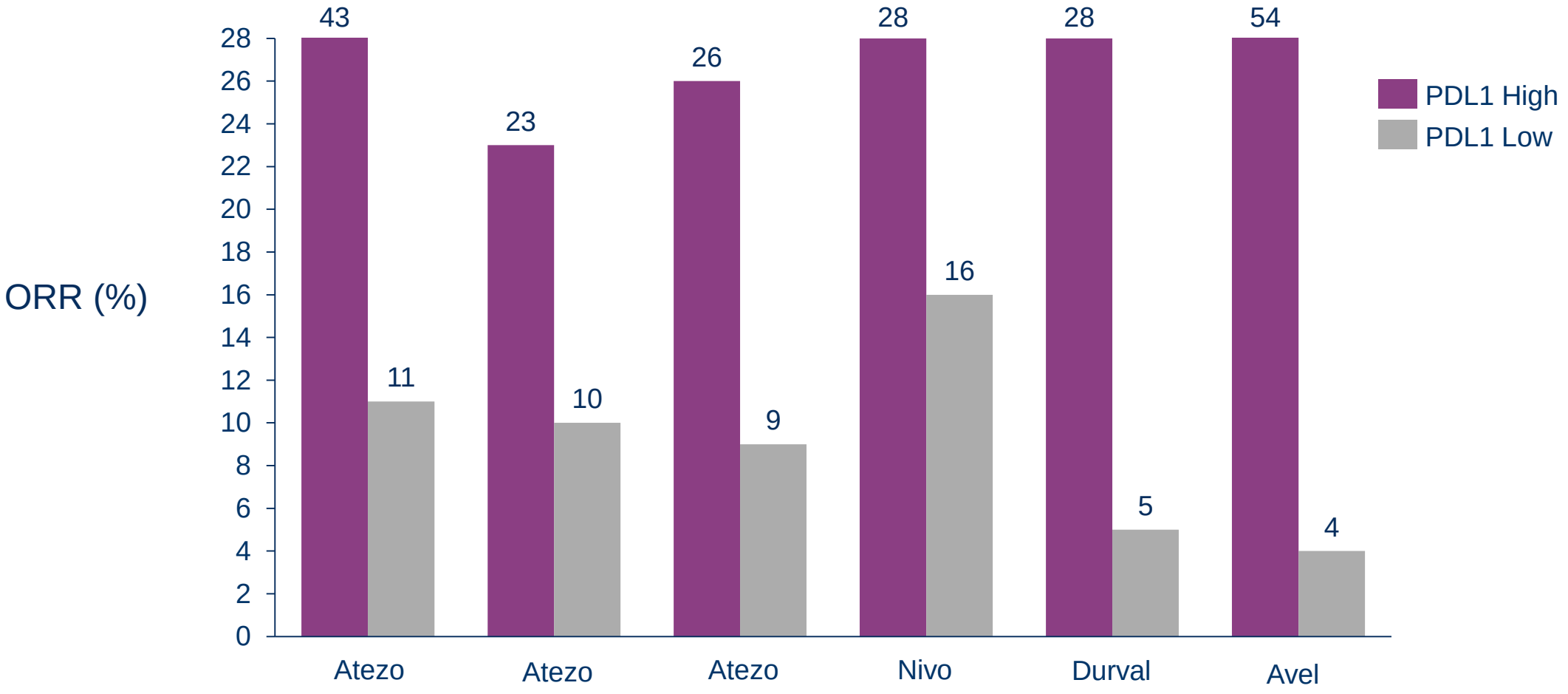
Why Aren't Checkpoint Inhibitors Effective in More Patients?
Tumor Associated Macrophages/MDSCs Suppress Anti-Tumor T Cell Immune Responses



- Macrophage mediated suppression of T Cells reduces expansion and activated of T Cells and dampens γ-IFN Mediated Immune Response
- Results in "Cold" Tumor Microenvironment characterized by low levels of tumor PDL1 expression and less responsiveness to checkpoint inhibitor therapy

[1]Kaneda et al. *Nature*. 2016.

Post Platinum Metastatic Bladder Cancer Patients with Low PDL1 Expression Levels Do Not Respond As Well to Checkpoint Inhibitors



Notes:
From Biomarkers of Immunotherapy in urothelial and renal cell carcinoma: PD-L1, tumor mutational burden, and beyond
Assays used for Atezo: SP142 (Ventana); assay used for Nivo: 28-8 (Dako); assay used for Durval: SP263 (Ventana) and assay used for Avel: 73-10 (Dako)

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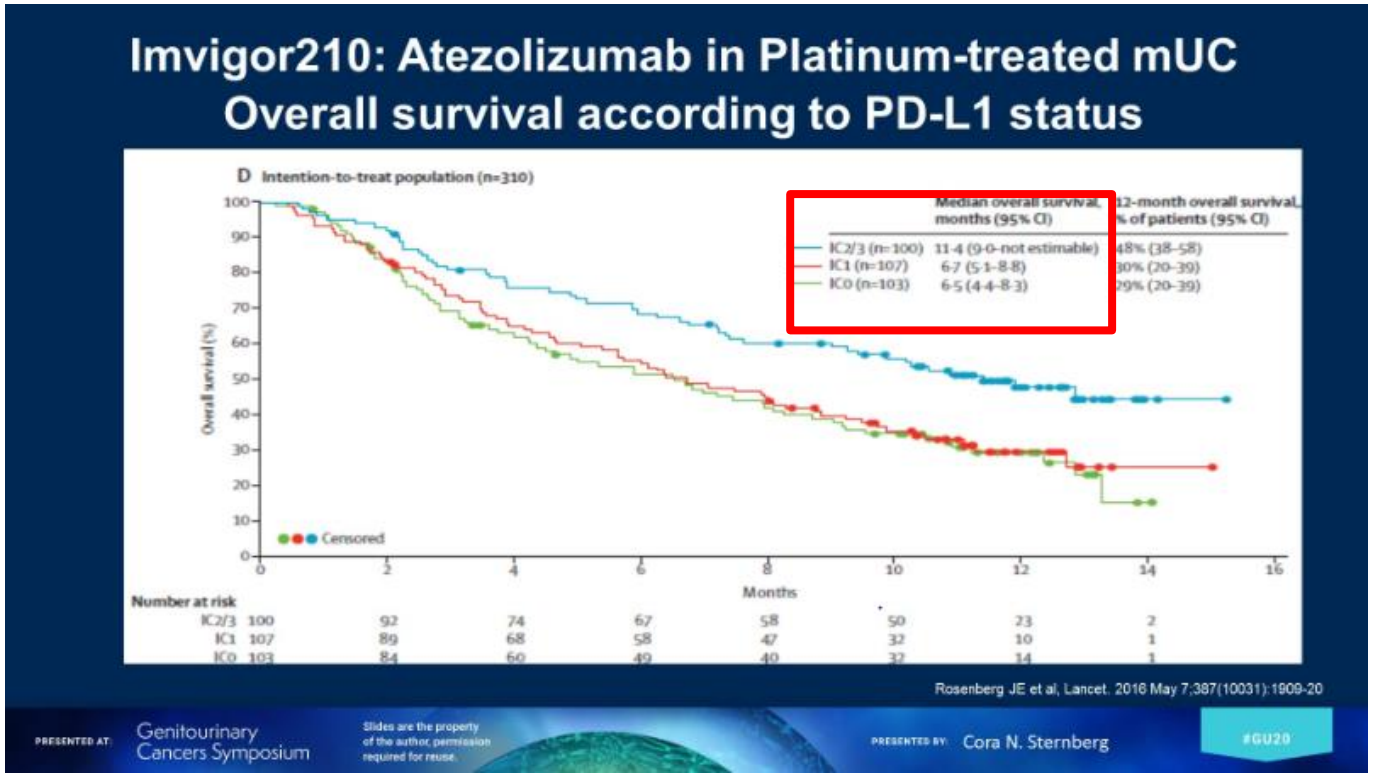
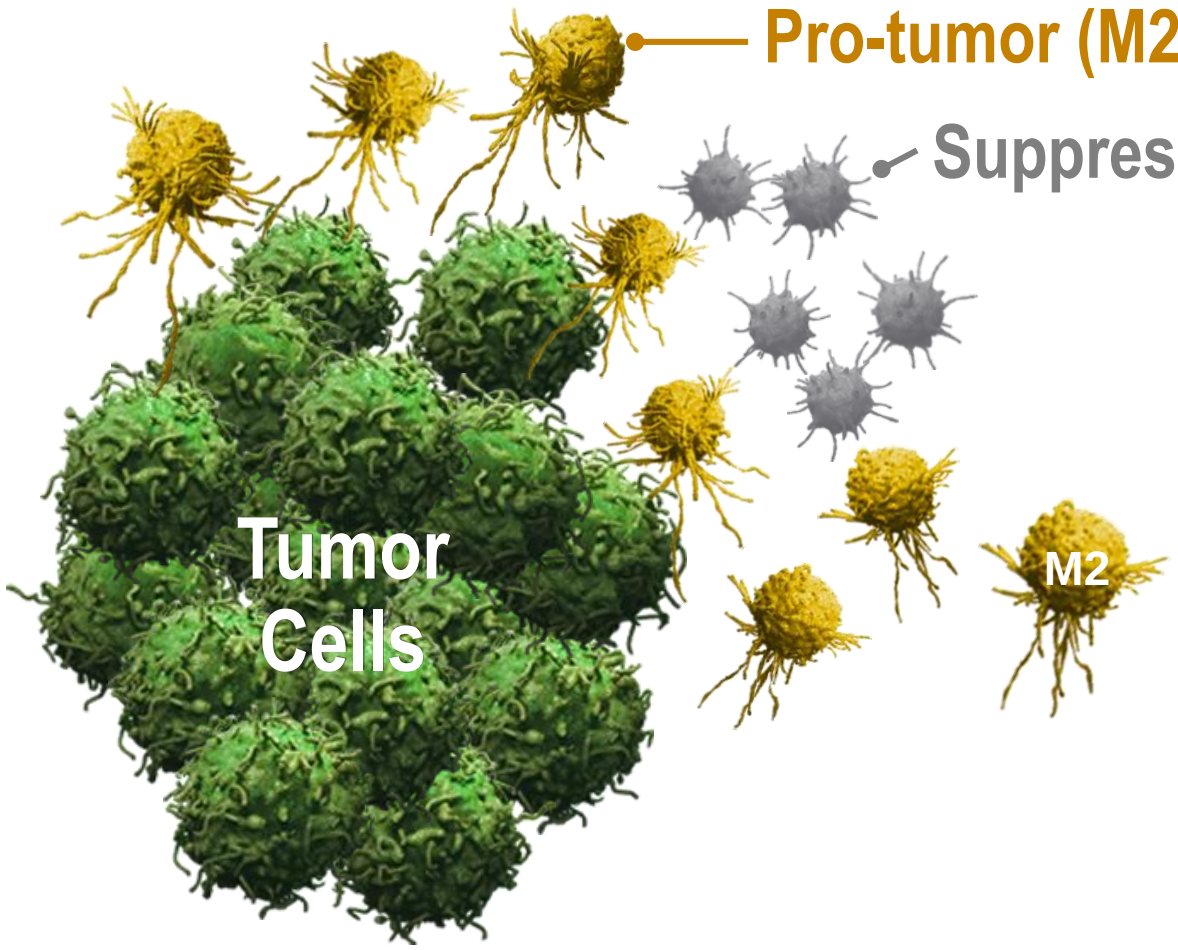
~Doubling of Overall Survival in Bladder Cancer Patients with Higher PDL1 Expression Levels, Better Treatments Needed for PDL1 Low Patients

CheckMate 275: Opdivo Patient Benefit According to PDL1 Status in 2L Platinum-Treated mUC Patients

	ORR	DCR	Median OS (mo.)	Median PFS (mo.)
All (n=270)	21% (16-26)	41% (36-48)	8.6 (6.1–11.3)	1.94 [1.87, 2.33]
PDL1 ≥1%	26% (18-34)	52% (42-61%)	11.9 (9.1–19.1)	3.45 [1.91, 3.71]
PDL1 <1%	16% (11-23%)	33% (25-41%)	6.0 (4.4–8.1)	1.87 [1.74, 2.00]



How to Address the Problem Pro-Tumor Macrophages Suppressing Immune Responses and Limiting the Effectiveness of Checkpoint Inhibitors



- Macrophage mediated suppression of T Cells reduces expansion and activated of T Cells and dampens γ-IFN Mediated Immune Response
- PI3K-γ signaling plays a key role in programming macrophages to the pro-tumor M2 phenotype driving the immunosuppressive function of these cells[1]
- Targeting PI3K-γ in myeloid cells shown to re-program macrophages; relieving suppression, activating T cells, generating an immune response that can then be enhanced by checkpoint inhibitors[1]

[1]Kaneda et al. *Nature*. 2016.

New Discoveries on The Role of PI3K-γ in Programming Macrophages

LETTER

nature

doi:10.1038/nature19834

PI3Kγ is a molecular switch that controls immune suppression

Megan M. Kaneda[1], Karen S. Messer[1,2], Natacha Ralainirina[1], Hongying Li[1,2], Gyunghwi Woo[1], Abraham V. Nguyen[1], Camila C. Figueiredo[1,3], Philippe Fou David G. Winkler[4], Matthew Rausch[4], Vito J. Palombella[4], Jeffery Kutok[4], Ka Michael Karin[7], Roman Sasik[8], Ezra E. W. Cohen[1,9] & Judith A. Varner[1,9,10]

Macrophages play critical, but opposite, roles in acute and chronic inflammation and cancer[1–5]. In response to pathogens or injury, inflammatory macrophages express cytokines that stimulate cytotoxic T cells, whereas macrophages in neoplastic and parasitic diseases express anti-inflammatory cytokines that induce immune suppression and may promote resistance to T cell checkpoint inhibitors[1–7]. Here we show that macrophage PI 3-kinase γ controls a critical switch between immune stimulation and suppression during inflammation and cancer. PI3Kγ signalling through Akt and mTOR inhibits NFκB activation while stimulating C/EBPβ activation, thereby inducing a transcriptional program that promotes immune suppression during inflammation and tumour growth. By contrast, selective inactivation of macrophage PI3Kγ stimulates and prolongs

upon expo
Fig. 1i–k),
responses
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nists (TG1
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growth of
and HPV–
carcinoma
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growth or s
(Extended
growth an

LETTER

nature

doi:10.1038/nature20554

Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells

Olivier De Henau[1], Matthew Rausch[2], David Winkler[2], Luis Felipe Campesato[1], Cailian Liu[1], Daniel Hirschhorn-Cymerman[1], Sadna Budhu[1], Arnab Ghosh[1], Melissa Pink[2], Jeremy Tchaicha[2], Mark Douglas[2], Thomas Tibbitts[2], Sujata Sharma[2], Jennifer Proctor[2], Nicole Kosmider[2], Kerry White[2], Howard Stern[2], John Soglia[2], Julian Adams[2], Vito J. Palombella[2], Karen McGovern[2], Jeffery L. Kutok[2], Jedd D. Wolchok[1,3]§ & Taha Merghoub[1]§

Recent clinical trials using immunotherapy have demonstrated its potential to control cancer by disinhibiting the immune system. Immune checkpoint blocking (ICB) antibodies against cytotoxic-T-lymphocyte-associated protein 4 or programmed cell death protein 1/programmed death-ligand 1 have displayed durable clinical responses in various cancers[1]. Although these new immunotherapies have had a notable effect on cancer treatment, multiple mechanisms of immune resistance exist in tumours. Among the key mechanisms, myeloid cells have a major role in limiting effective tumour immunity[2–4]. Growing evidence suggests that high infiltration of immune-suppressive myeloid cells correlates with poor prognosis and ICB resistance[5,6]. These observations

but contain more activated $CD8^+$ T cells (Fig. 1b, c). Additionally, $CD8^+$ T cells express more granzyme B in the B16-F10 model. They also express higher levels of PD-1 and CTLA4 (Fig. 1c, data not shown), which might explain their sensitivity to ICB. Furthermore, myeloid cells from 4T1 tumours or spleens suppress proliferation of T cells to a greater extent compared to myeloid cells from B16-F10 models (Fig. 1d and Extended Data Fig. 1b). These data suggest that TAMCs have varying phenotypes and are more suppressive in ICB-resistant tumours. Tumour-derived soluble factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) help shape the tumour microenvironment by promoting myelopoiesis and recruitment of suppressive myeloid cells[12,13]. To directly assess the ability

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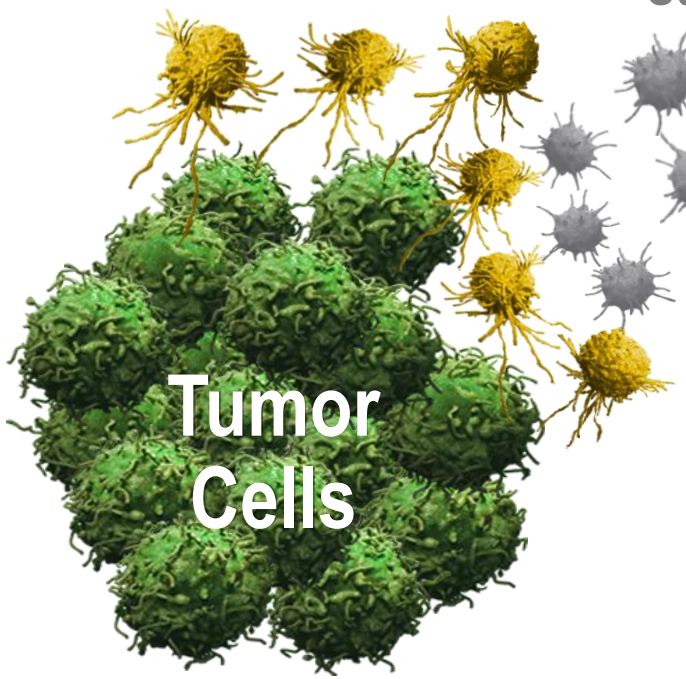
PI3K-γ Inhibition Reprograms Macrophages, Turning Tumor MicroEnvironment (TME) from "Cold" To "Hot"

TME "COLD" Tumors

Suppressed T cells
(low tumor PDL1)



M2

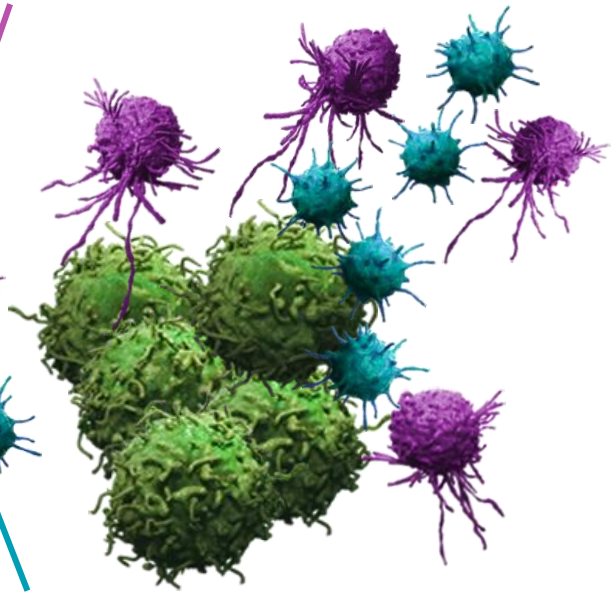
PI3Kγ i
Eganelisib

1. Eganelisib Inhibition of PI3K γ Re-programs Pro-tumor (M2) Macrophages/MDSCs to Anti-Tumor (M1) Function

TME "HOT" Tumors

Anti-tumor (M1) Macrophages/Activated Myeloid Cells

M1



2. Relieves Macrophage Suppression, Expands Activated T Cells and Generates γ-IFN Mediated Immune Response

3. Up-Regulates PDL1 to Blunt T Cell Response → 4. Enhances Response to CPI, Overcomes CPI Resistance

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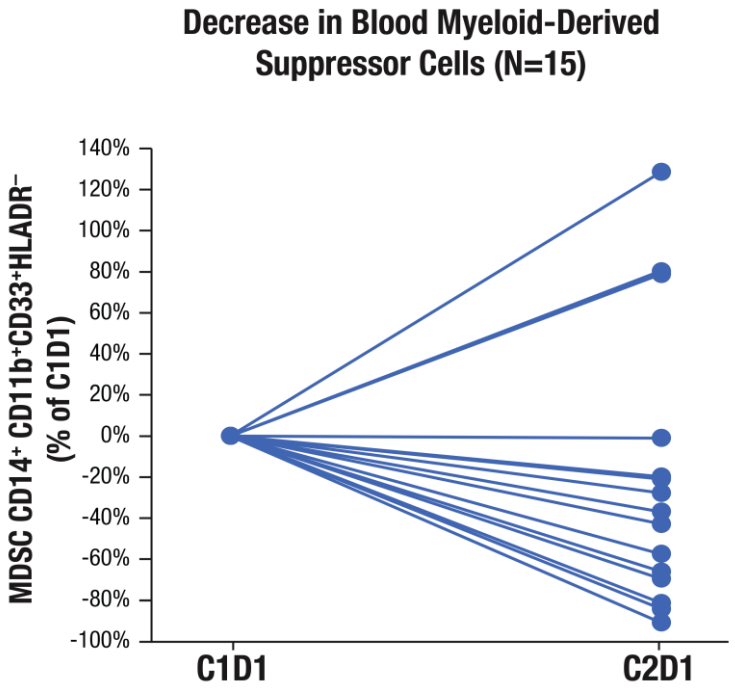
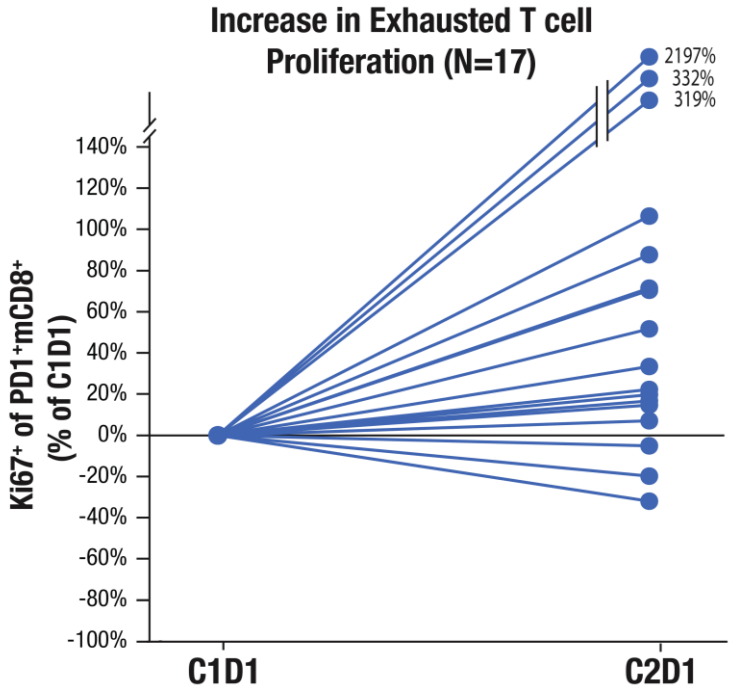
1. Eganelisib Inhibition of PI3K-γ Re-programs Pro-tumor (M2) Macrophages/MDSCs to Anti-Tumor (M1) Function Which:

2. Relieves Macrophage Suppression of T Cells



2. Expands Activated T Cells and Generates γ-IFN Mediated Immune Response



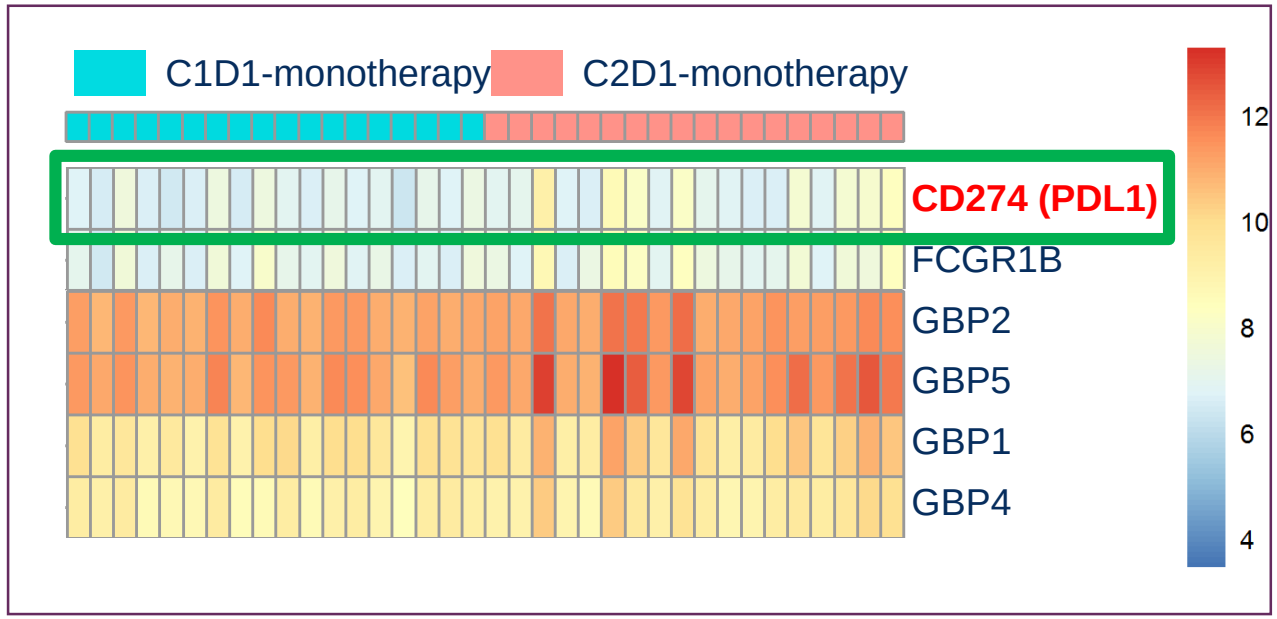
C=cycle (28 days), D=days; Sullivan et al., ASCO 2018.

2. Eganelisib Reduces Macrophage Suppression, Expands Activated T Cells and Generates γ-IFN Mediated Immune Response Which:

3. Upregulates PDL1 Expression, Increasing Importance of Check Point Inhibitors to Enhance Responses

IFN-γ - responsive genes	Fold increase at C2D1	P value
CD274 (PDL1)	2.4	3.5×10^{-5}
FCGR1B	1.8	1.5×10^{-3}
GBP2	1.5	5.6×10^{-4}
GBP5	2.3	1.3×10^{-4}
GBP1	2.0	1.9×10^{-4}
GBP4	1.7	9.4×10^{-4}

RNA Seq peripheral blood across all dose levels

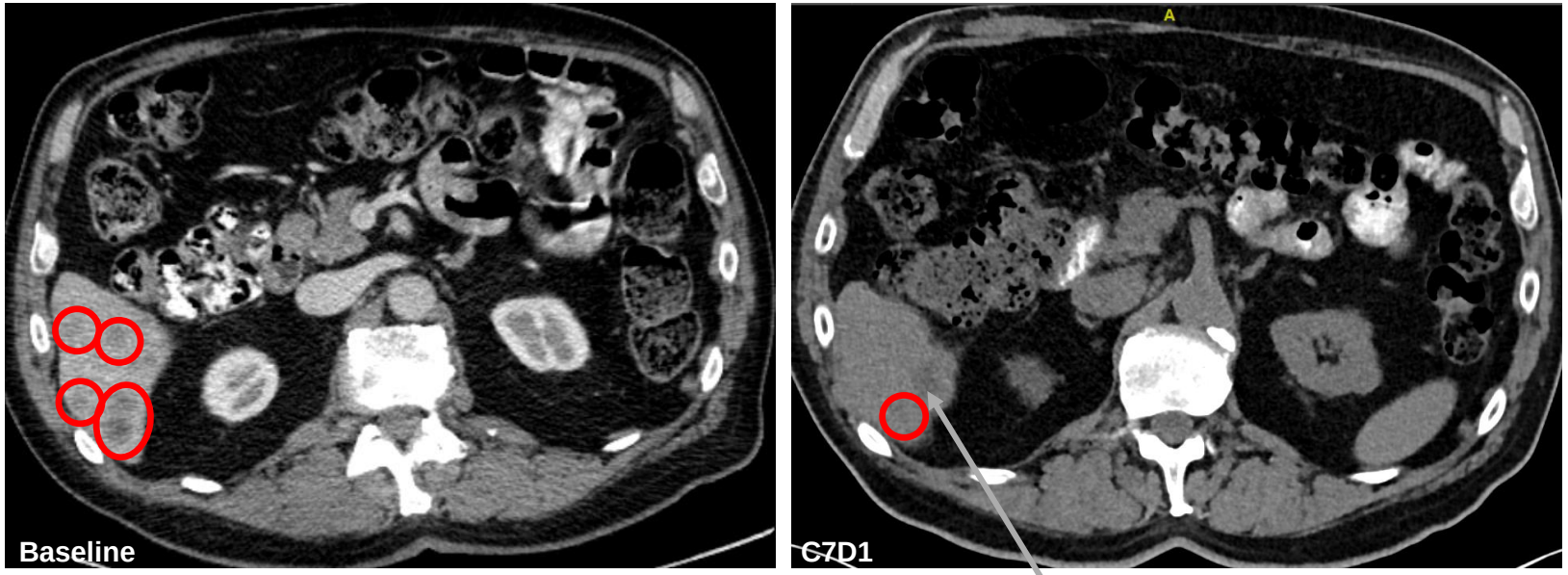


The above interferon-γ-responsive genes were among the top 30 most significantly differentially expressed genes

Hong et al., SITC 2017.

3. Eganelisib Mediated Relief of Immune Suppression Activates an Immune Response Which:

4. Enhances Responses to Checkpoint inhibitors, Overcomes CPI Resistance



Courtesy of Bartosz Chmielowski, MD, PhD, University of California Los Angeles.

- Patient A: 71 yo male with stage I BRAF WT Melanoma
- Single lung metastasis after 3 doses of Opdivo, continued on nivolumab therapy
  - Subsequent progression with new lung and liver lesions
- Extensive disease in lungs and liver at study start
- Normalization of LDH 528 ➞ 211 (ULN 256) and PR (-40% tumor reduction of target lesions) observed at C7D1
- Remains on study after > 8 months with confirmed PR as best response

Data Snapshot October 14th, 2018
Chmielowski, et al. SITC 2018

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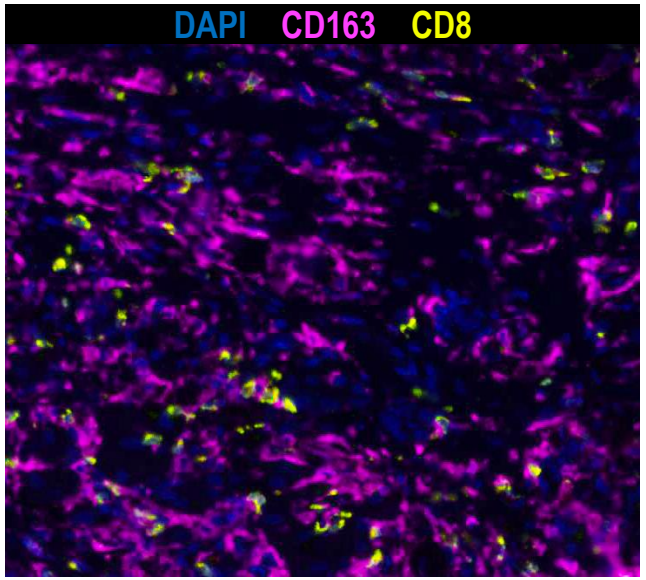
4. Eganelisib Overcomes Resistance to Checkpoint Inhibitors, On-Mechanism Activity

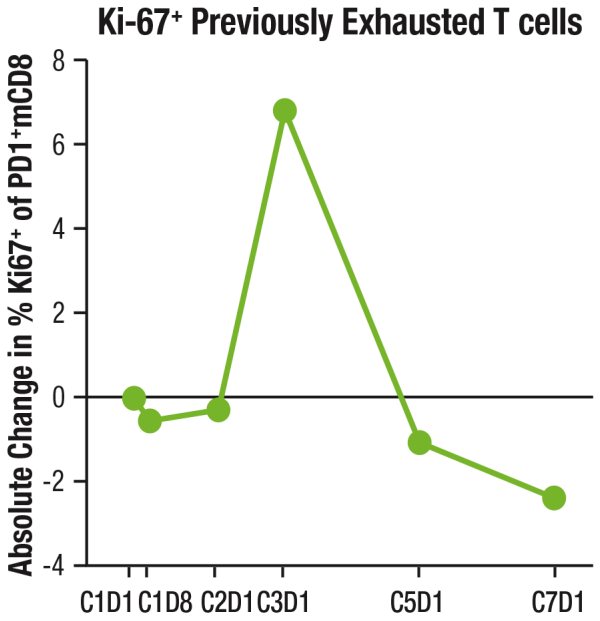
Melanoma Patient A progressing with new liver and lung lesions after 3 Opdivo cycles

Eganelisib Macrophage Re-programming Relieves Macrophage Suppression of T Cells

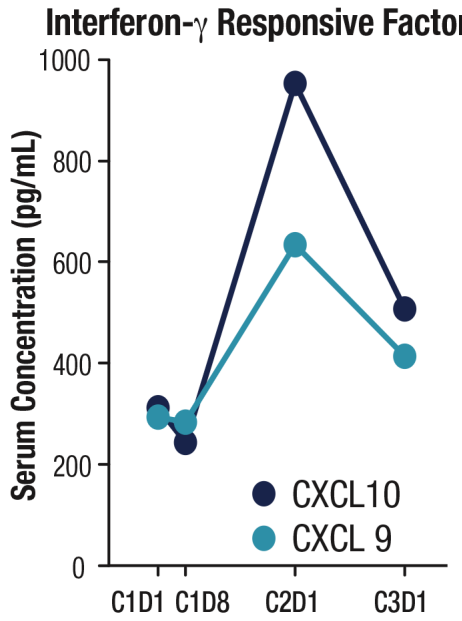


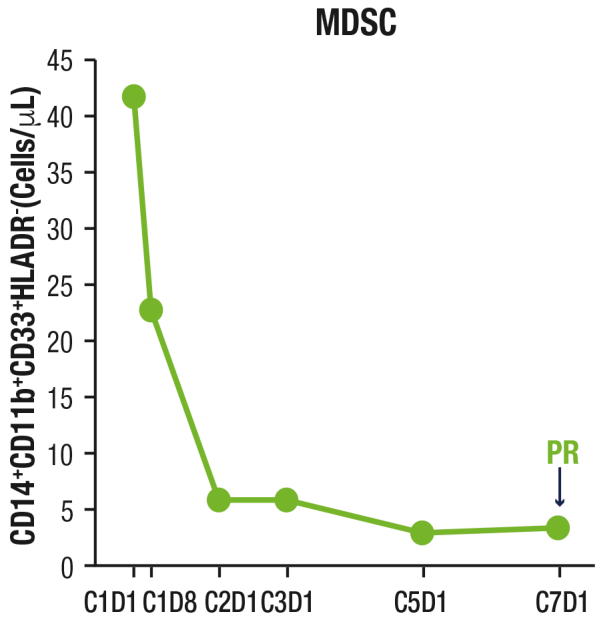
High levels of immunosuppressive M2 macrophages ($CD163^+$ in purple) and adjacent cytotoxic T cells ($CD8^+$ in yellow) in tumor observed at baseline.

Expands Activated T Cells



Generates γ-IFN Mediated Immune Response





Data Snapshot
October 14th, 2018
Chmielowski, et al.
SITC 2018

MARIO-275: Global, Randomized, Blinded Trial of Eganelisib in mUC

Designed to Show Benefit of Adding Eganelisib to Improve Outcomes for Patients Currently Underserved by Standard of Care

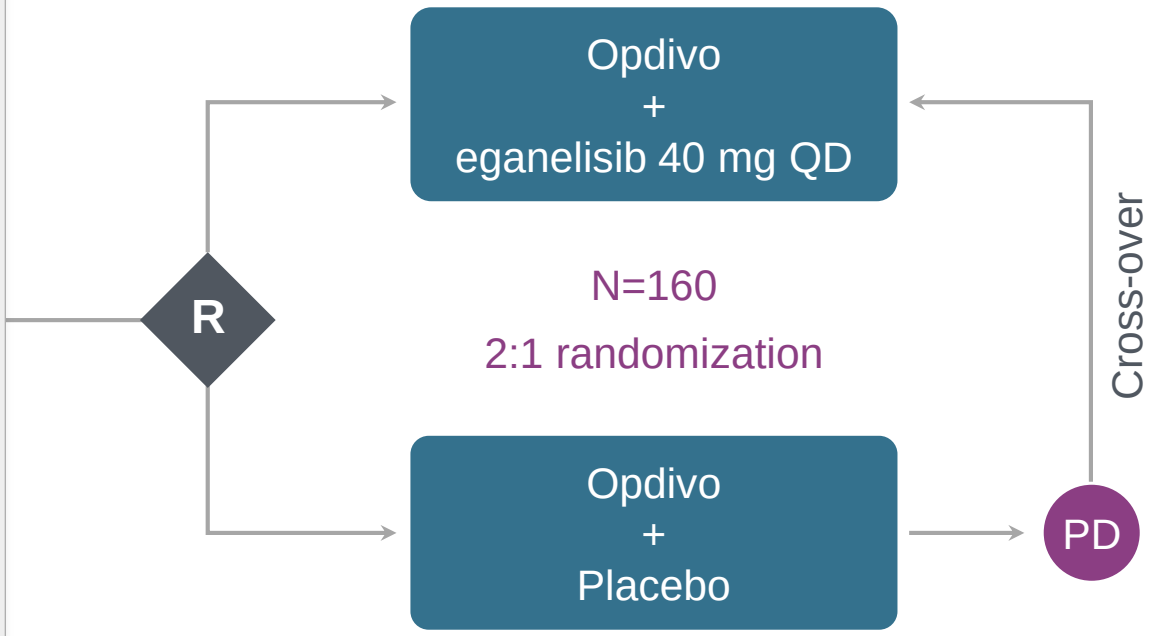
Advanced Platinum Refractory 2nd Line Urothelial Cancer Patients

- Incl/excl criteria per CheckMate-275
- MDSC all comers (stratified)
- PDL1 status all comers (non-stratified)

Primary objective: ORR in MDSC High

Secondary objectives: DOR, PFS, OS, ORR in Total population + MDSC subset

CheckMate-275: ORR 20.7%, mPFS 1.9 months mOS (8.6 months)



MARIO 275
MACROPHAGE REPROGRAMMING IN IMMUNO-ONCOLOGY

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https://pubmed.ncbi.nlm.nih.gov/32532789/

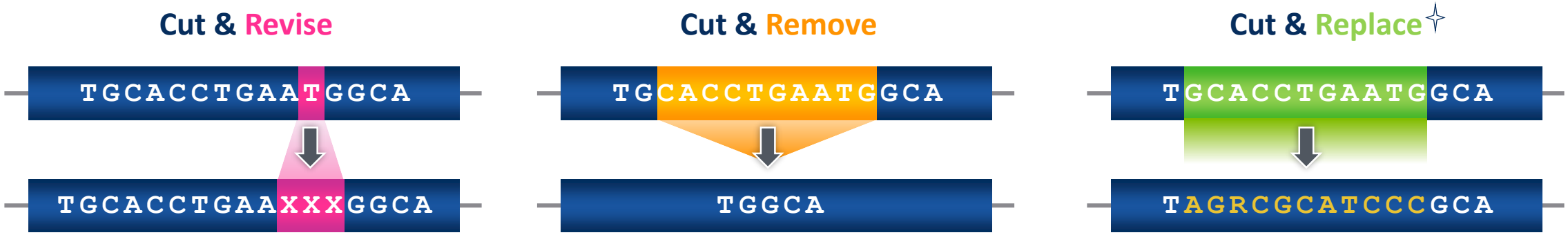
Tremendous Opportunity to Take Immuno-Oncology Therapy to the Next Level

- Studies Must Identify Those Patients Most/Less Likely to Benefit, and to Experience Side Effects, From Specific Therapies
  - Tumor Biopsies and Translational Medicine Are Essential
- The Evolutionary Nature of Cancer and the Heterogeneity of Tumors Increases this Challenge
- There is a Significant Effort Across Academia and Industry to Identify Accurate, Predictive Biomarkers to Meet This Challenge
- Outputs from Genomics, Transcriptomics, Proteomics, Metabolomics, as well as Exploring Discreet Blood Niches and Circulating Tumor Cells, Will Be Extremely In Realizing the Full Value of Immuno-Oncology and Increasing the Effectiveness of Drug Development

Dramatic Scientific and Medical Advances Are Further Leveraging the Bodies Immune System to Win the Evolutionary Battle Against Cancer

- Vaccines
  - Two vaccines approved Provenge (prostate) and Imlygic (melanoma) and many more in development

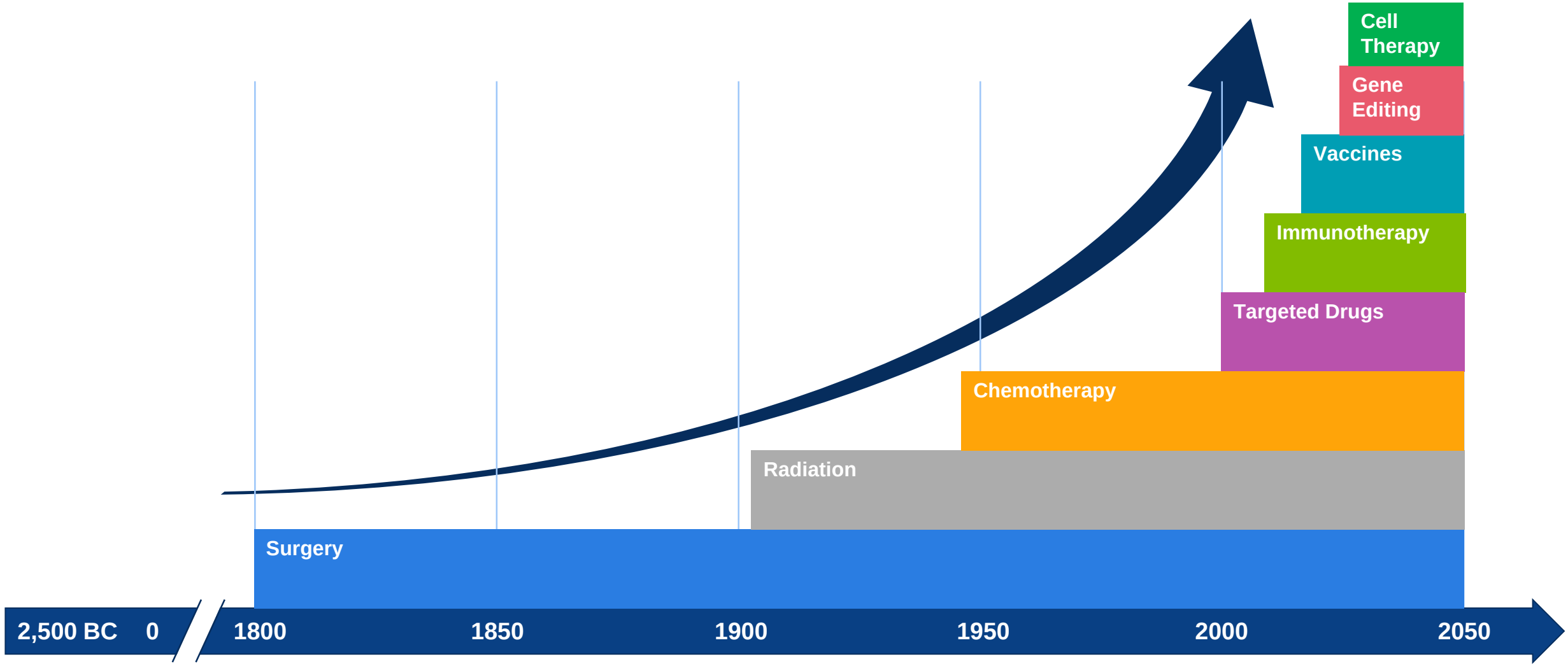
- Gene Editing: Addressing the Root Cause of Diseases Caused by Mutations in Our DNA and Repairing Broken Genes: Multiple Gene Editing Programs in Clinical Studies



- Cell Therapy
  - CAR-T (Chimeric Antigen Receptor T-cells): Using Your own Cells to Identify Cancer and Activate a T Cell Response
  - First Induced Pluripotent Stem Cells Derived Therapies for 'Off the Shelf' Delivery of T Cell and NK Therapies to Large Number of Patients Now in Clinical Studies

Source: Editas Medicine Website

Incredible Acceleration in Advances Over Just Last 20 Years! Pace of Ongoing Innovation is Critical to Tackling the Global Challenges Ahead



Daring to Believe in a Cure, and Why the Belief is Justified

Why is cancer such a hard problem?

Very complex, evolutionary problem

How are we doing in the fight against cancer?

Unequivocal progress…. with a long way to go!

Is a cure realistic?

Absolutely!

Enabled by unprecedented technological advances


Daring to Believe and Committed
to Finding a Cure for all!