25 Years of the Evolution of Cancer Care:
What Have We Accomplished and Where are We Going?

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2025 Debates and Didactics in Hematology and Oncology
July 25, 2025

Office of the President | American University of Beirut

I hereby declare that I have no known conflicts of interest.

Outline

- Introduction

- Limited progress using chemotherapeutic agents

- Dawn of molecularly targeted agents

- Immunotherapy revolution

- Progress in Early-stage disease

  -Screening and early diagnosis

  -Therapeutics

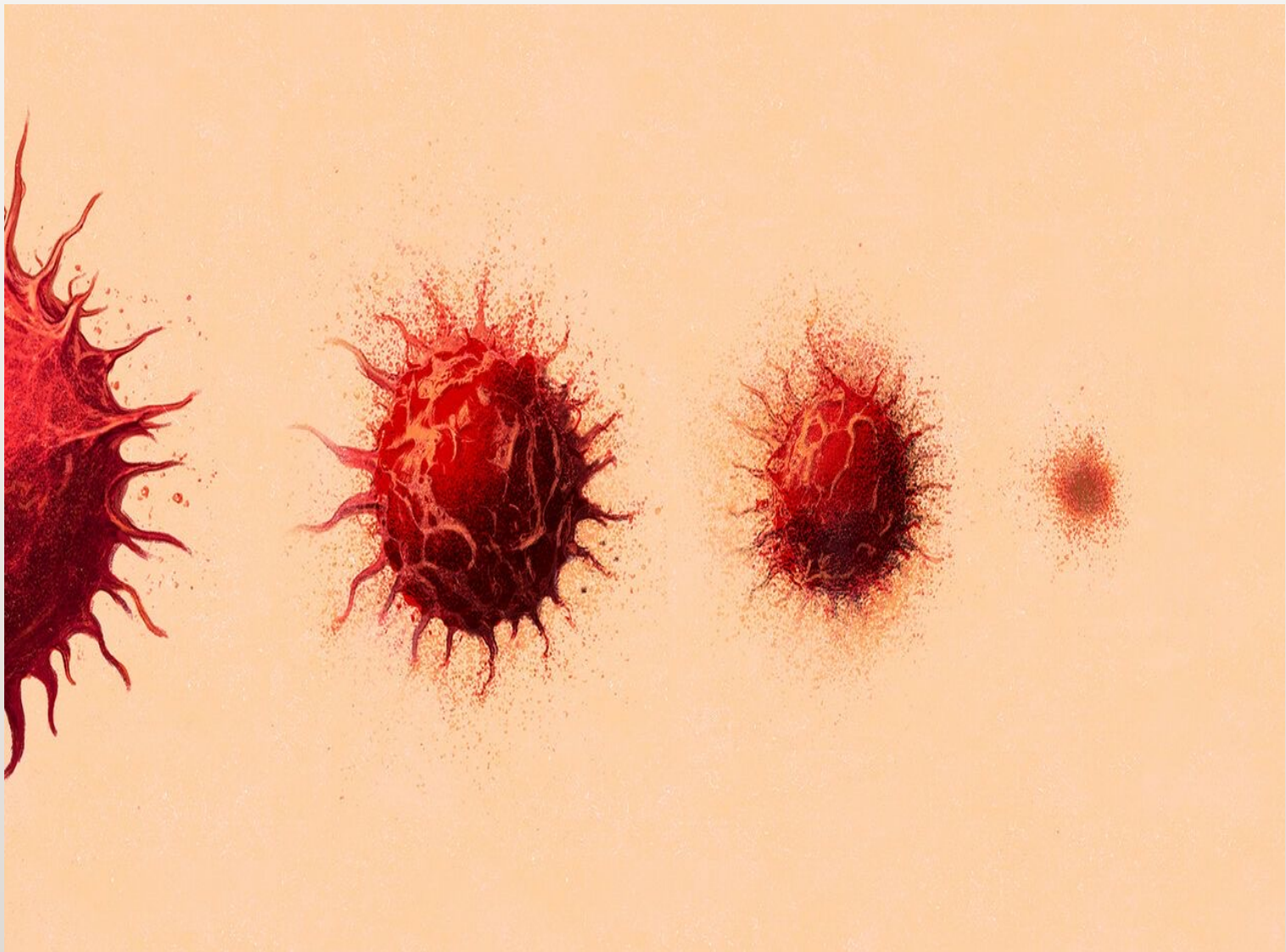- Access issues

- Future perspectives

Leaders | A slow-burn success

The world is winning the war on cancer

Progress has been remarkable. Death rates are down substantially, and are likely to fall further

The world is winning the war on cancer. *The Economist,* July 2025.

Survival Data Over 25 Years

- Overall cancer survival has improved significantly

- 5-year survival rate in the U.S. increased from ~50% to ~68%

- Notable improvements in survival, especially in lung, breast, prostate, colorectal cancers

- Some cancers (e.g., pancreatic, glioblastoma) remain particularly challenging

Figure 1. Trends in Age-adjusted Cancer Death Rates by Site, Males, US, 1930-2022
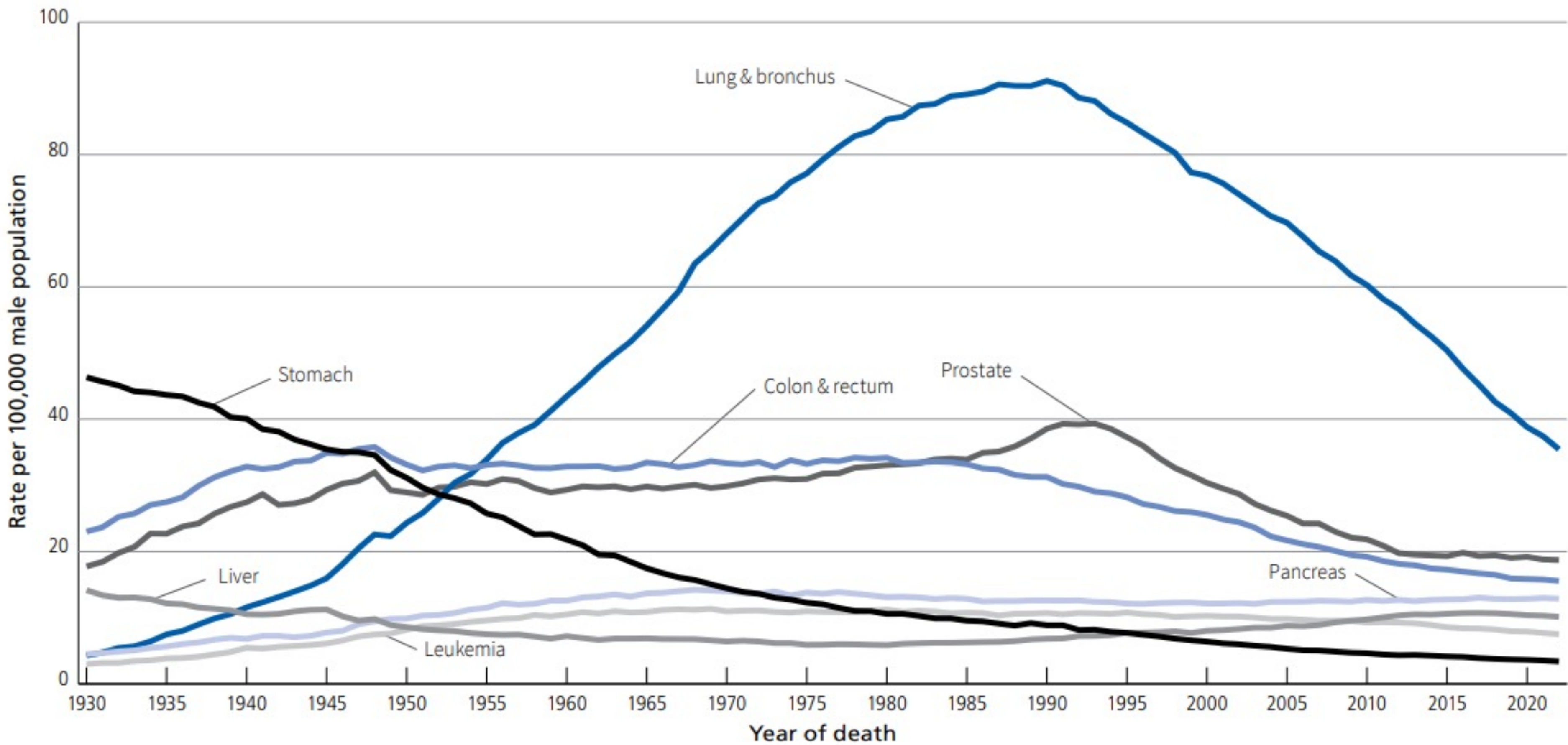
Rates are age adjusted to the 2000 US standard population and exclude deaths in Puerto Rico and other US territories. Due to improvements in classification, site-specific information differs from contemporary data for cancers of the liver, lung and bronchus, and colon and rectum.
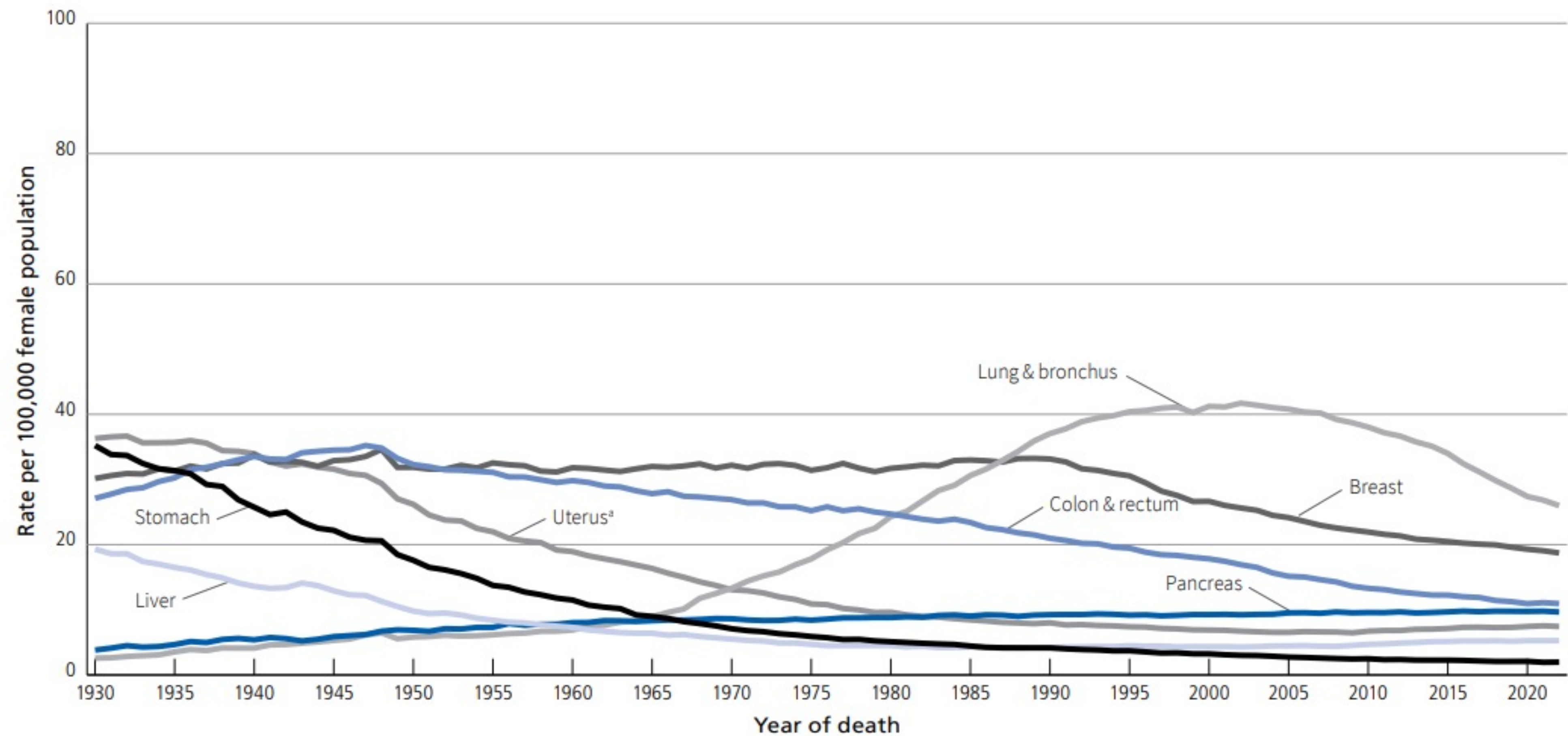
Data source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2022, National Center for Health Statistics, Centers for Disease Control and Prevention.

©2025, American Cancer Society, Inc., Surveillance and Health Equity Science

Figure 2. Trends in Age-adjusted Cancer Death Rates by Site, Females, US, 1930-2022

Rates are age adjusted to the 2000 US standard population and exclude deaths in Puerto Rico and other US territories. Due to improvements in classification, site-specific information differs from contemporary data for cancers of the liver, lung and bronchus, colon and rectum, and uterus. [a]Uterus refers to uterine cervix and uterine corpus combined.

Data source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2022, National Center for Health Statistics, Centers for Disease Control and Prevention.

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Table 8. Five-year Relative Survival Rates (%) by Stage at Diagnosis, 2014-2020

|	All stages	Local	Regional	Distant		All stages	Local	Regional	Distant
Breast (female)	91	>99	87	32	Non-Hodgkin lymphoma	74	86	78	67
Colon & rectum[a]	64	91	73	15	Oral cavity & pharynx	69	87	69	38
Colon[a]	63	91	73	13	Ovary	51	92	72	31
Rectum	67	90	74	18	Pancreas	13	44	16	3
Esophagus	22	48	28	5	Prostate	97	>99	>99	37
Kidney & renal pelvis	78	93	75	18	Stomach	36	75	36	7
Larynx	62	79	48	34	Thyroid	98	>99	98	52
Liver[b]	22	37	13	3	Urinary bladder[c]	78	72	40	9
Lung & bronchus	27	64	36	9	Uterine cervix	67	91	61	19
Melanoma of the skin	94	>99	75	35	Uterine corpus	81	95	70	19

Rates are adjusted for normal life expectancy based on cases diagnosed in the SEER 22 areas, excluding Illinois and Massachusetts, from 2014-2020, all cases followed through 2021. [a]Excludes appendix. [b]Includes intrahepatic bile duct. [c]Rate for in situ carcinoma is 97%. Stage classification based on Combined Summary Stage. **Local:** invasive cancer confined entirely to the organ of origin. **Regional:** cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** cancer has spread to body parts remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Data source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2024.

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Age-standardized rate (World) per 100 000, incidence and mortality, both sexes
All sites excl. non-melanoma skin cancer
USA*
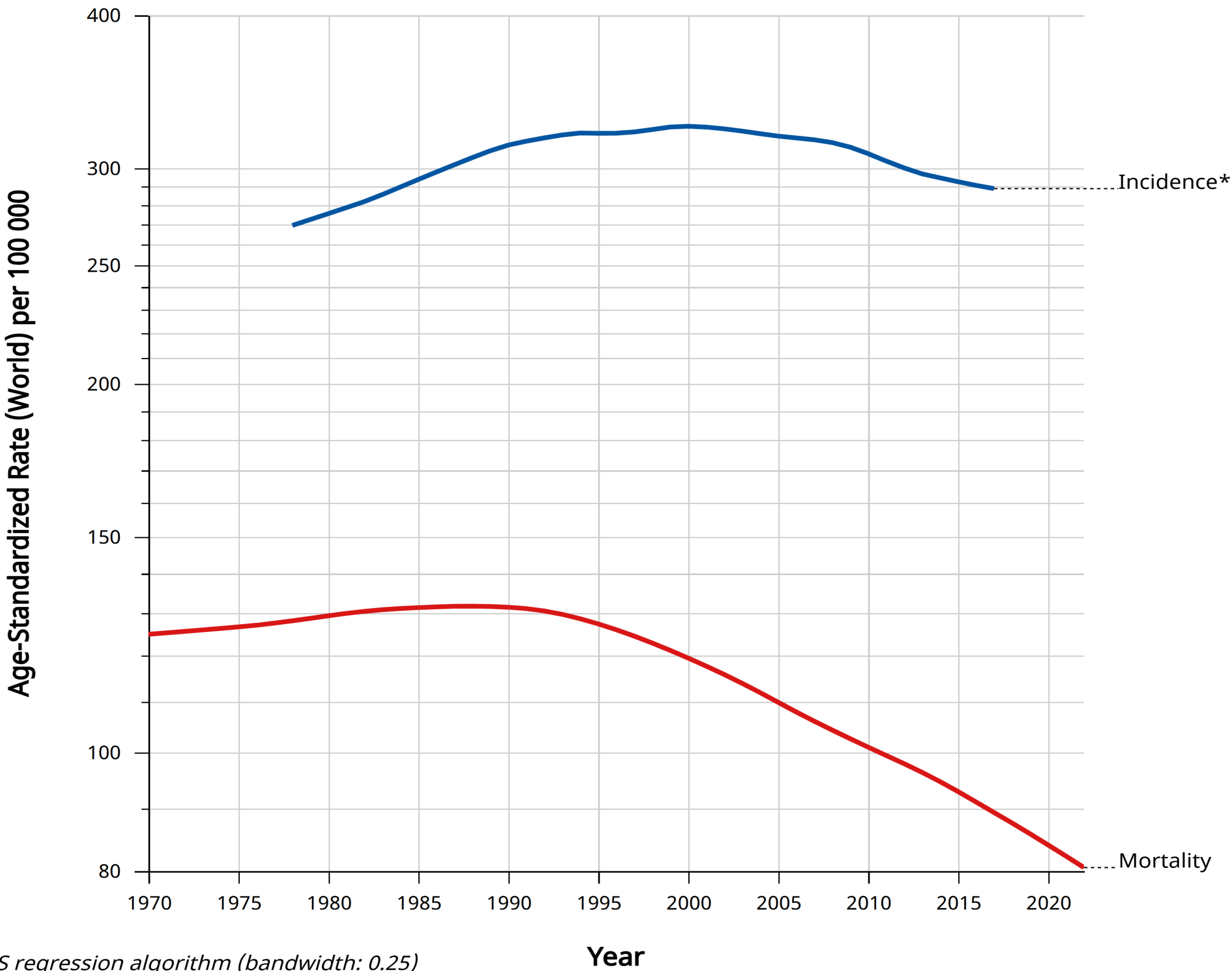
* Subnational data
Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.25)
Rates are shown on a semi-log scale
Cancer Over time | IARC - https://gco.iarc.who.int/overtime
Data version : Version 2.1
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Age-standardized rate (World) per 100 000, mortality, both sexes
All sites excl. non-melanoma skin cancer
Austria - Canada - France (metropolitan) - USA
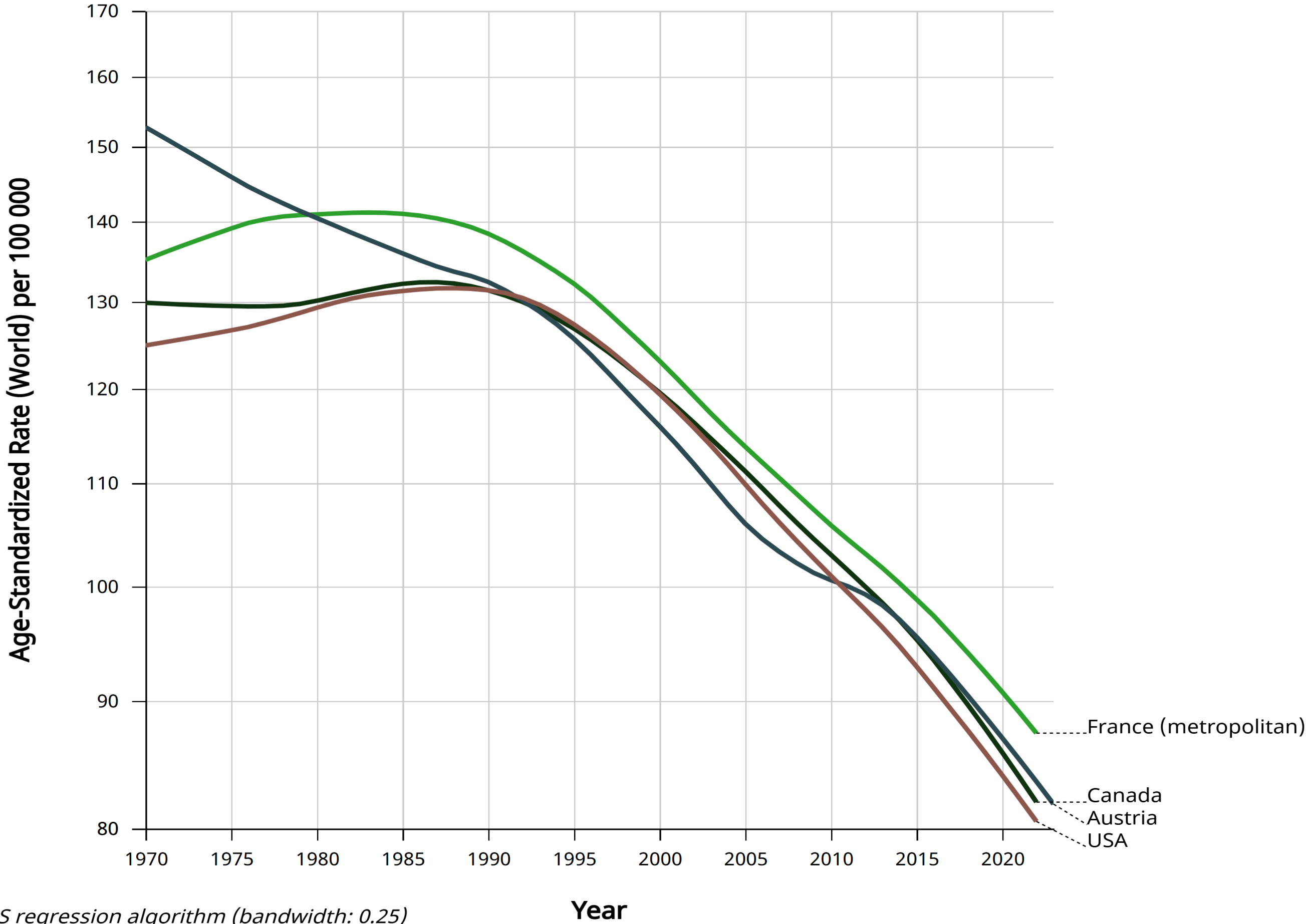
Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.25)
Rates are shown on a semi-log scale
Cancer Over time | IARC - https://gco.iarc.who.int/overtime
Data version : Version 2.1
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Reaching a Plateau with Chemotherapy

- Initial treatments focused on rapidly dividing cells

- Limited specificity led to significant side effects

- First successes in leukemia and lymphomas

- High dose therapy/stem cell transplant cures several previously incurable hematologic malignancies
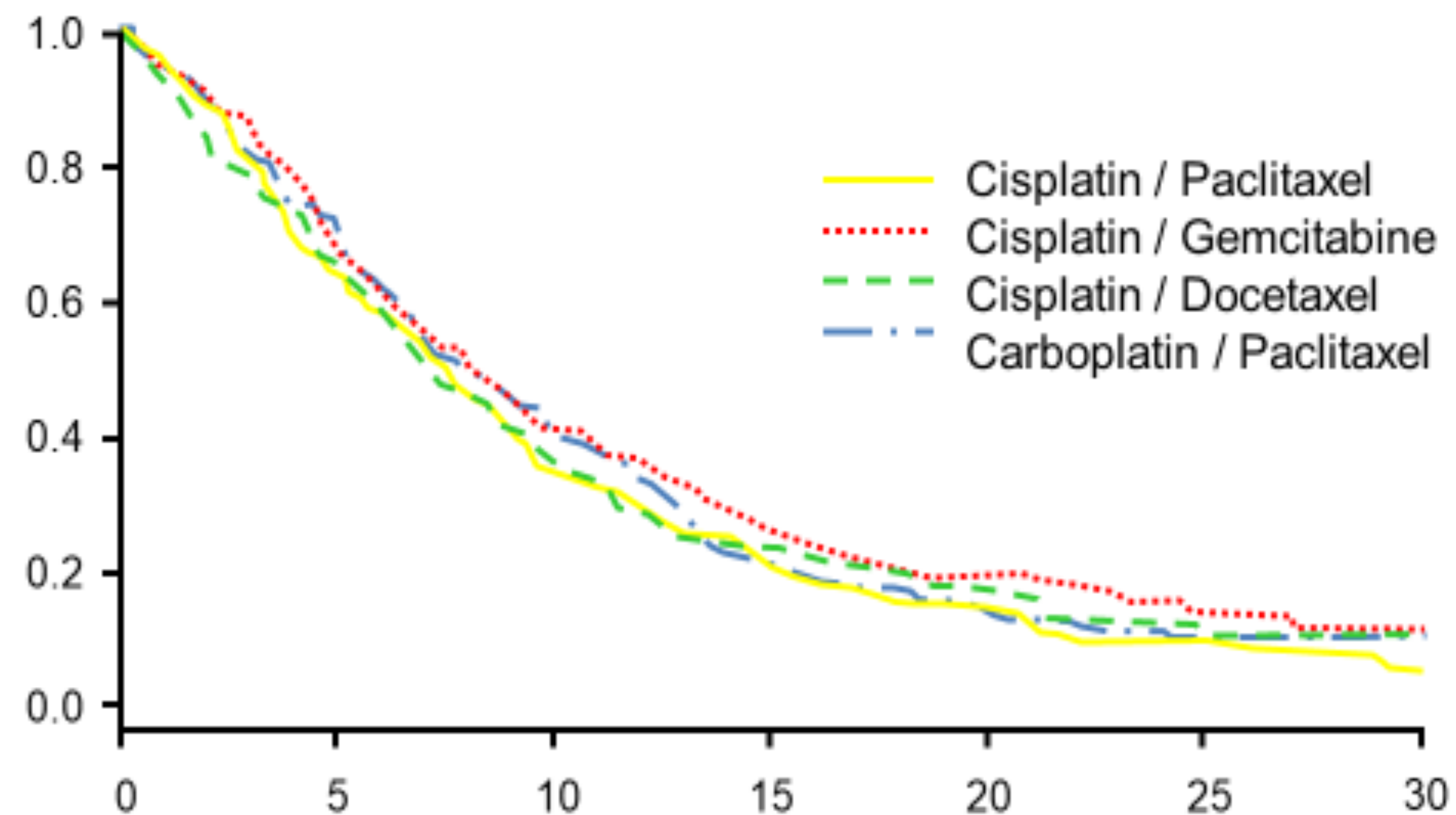
- Set foundation for modern drug development

# Modest benefit of platinum-based chemotherapy in NSCLC
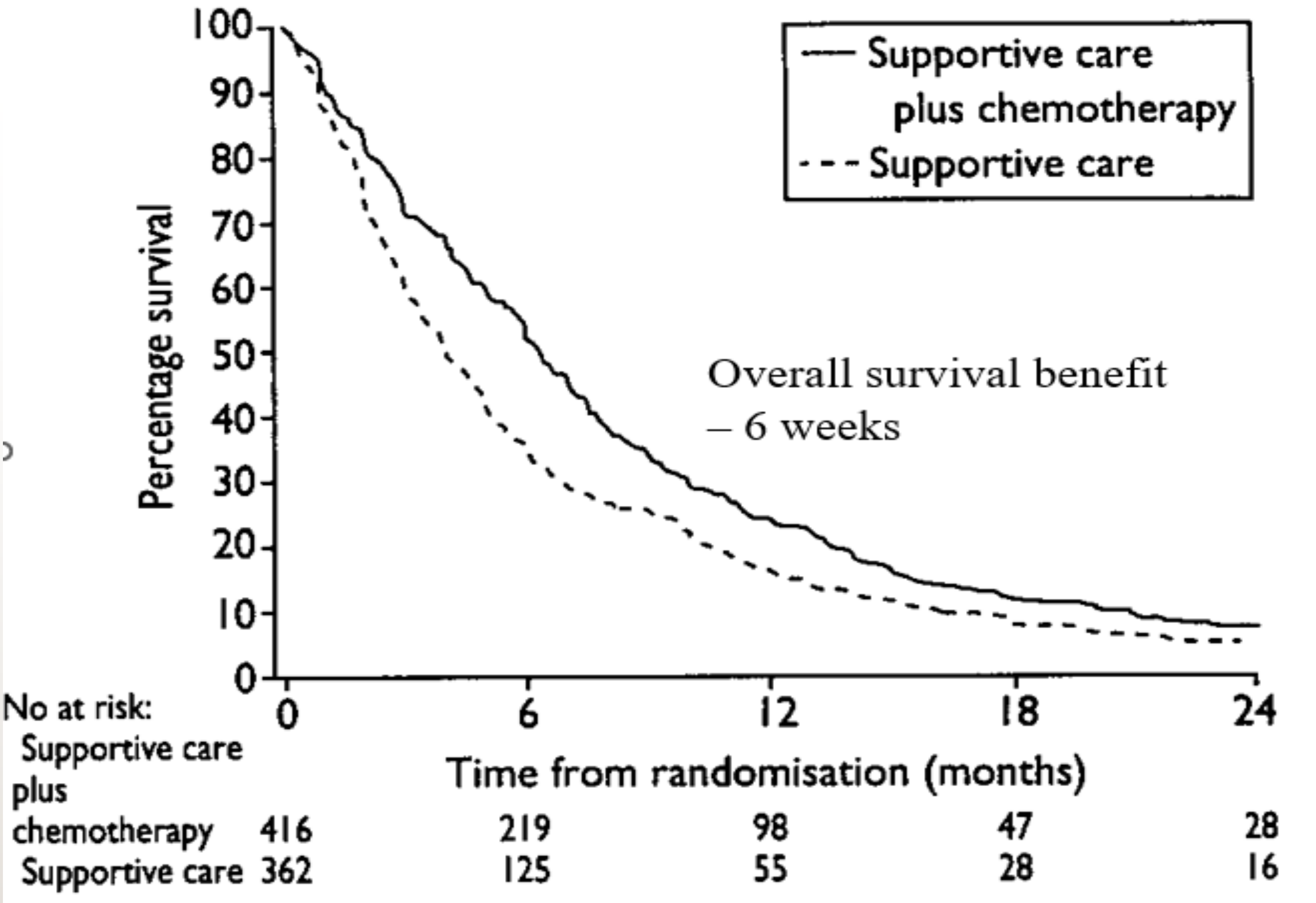
ECOG 1594: Plateau in advanced NSCLC

Schiller JH et al. *N Engl J Med*. 2002;346:92-98

Oncolytic Viruses: an Early Targeted Therapy

Gene therapy, siRNA, oncolytic viruses (eg ONYX-15)

Phase II trial combining Onyx-015 with chemotherapy

Oncolytic viruses demonstrate reversal of premalignancy

Phase III trial of Onyx-015 plus chemotherapy in nasopharynx cancer using in China showed a dramatic advantage in ORR

Khuri et al. Nature Med 2000;6:879-885.
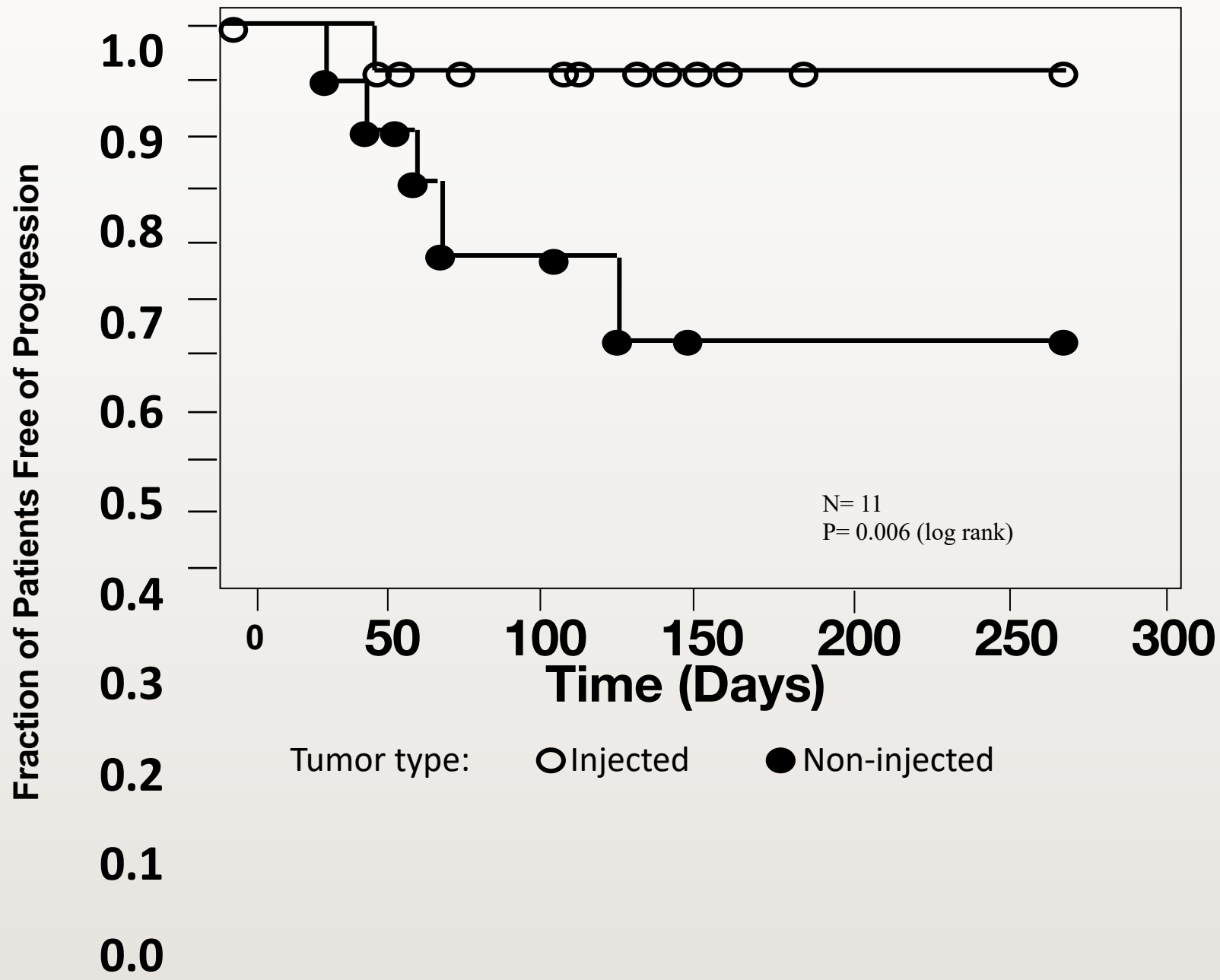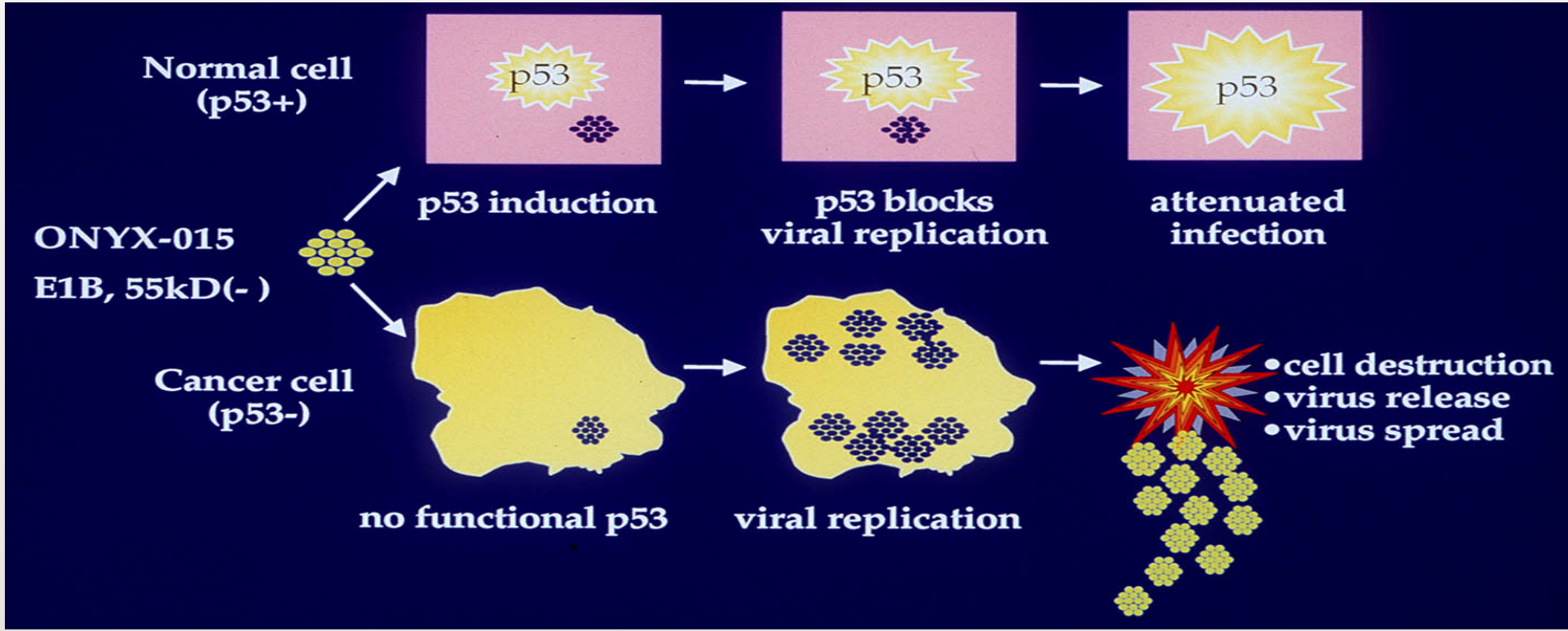
Oncogene Addiction-Guiding Hypothesis

Gene addiction and hypersensitivity in cancer cells are
exploitable targets for chemoprevention and therapy of cancers.

I. Bernard Weinstein, M.D.
Scientist, humanist, mentor
1930-2008

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Remarkable Examples of Oncogene Addiction in Human Neoplasms*

Disease	Oncogene	Therapy
Chronic Myelogenous Leukemia	bcr/abl	Imatinib
Breast Cancer	her2/neu	Traztuzumab
Lung Adenocarcinoma	EGFR	Gefitinib, Erlotinib
GastroIntestinal Stromal Tumors	KIT	Imatinib

_____

* recurrent leukemia or tumors can display additional
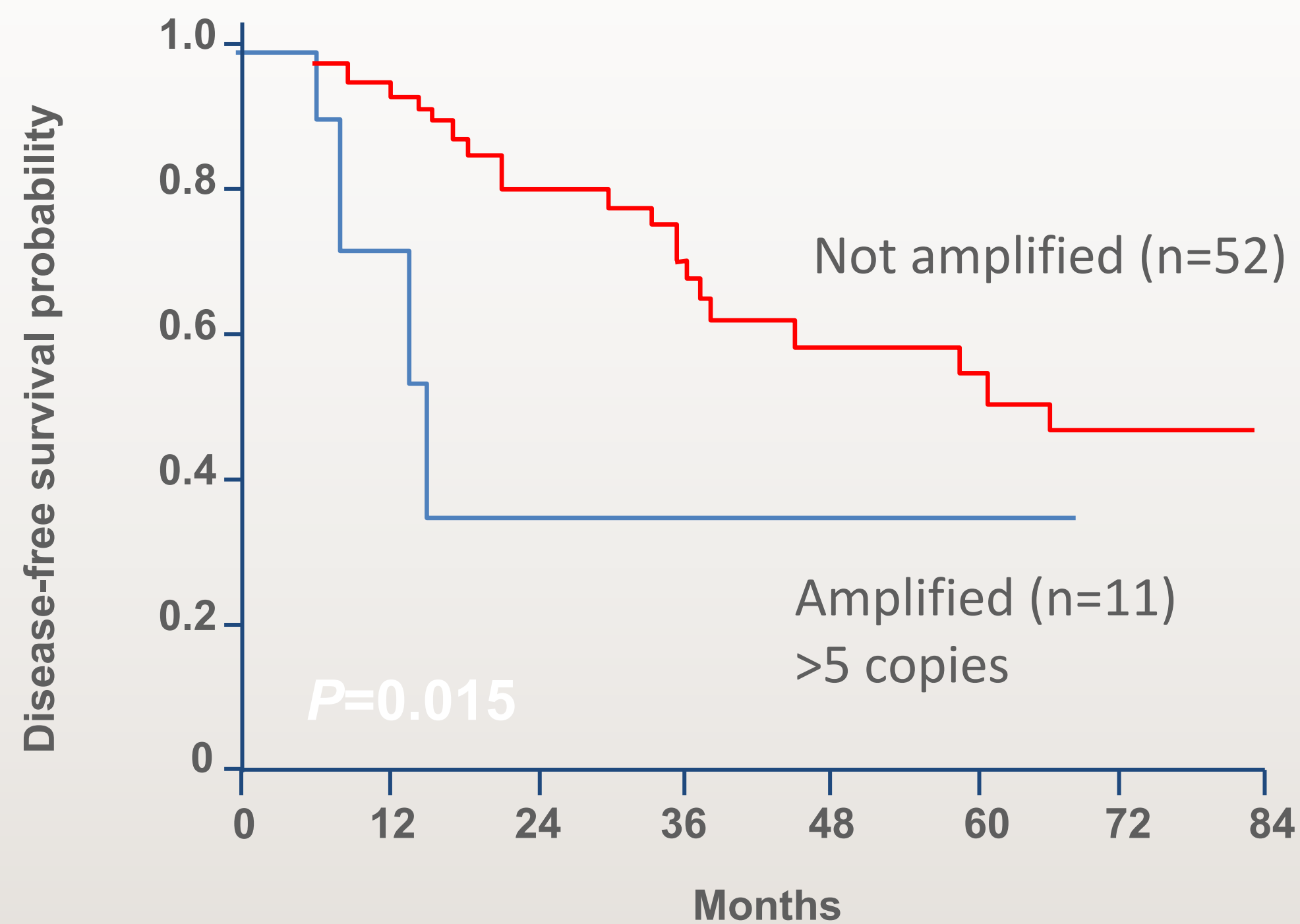 mutations in the kinase domain of the respective oncogene
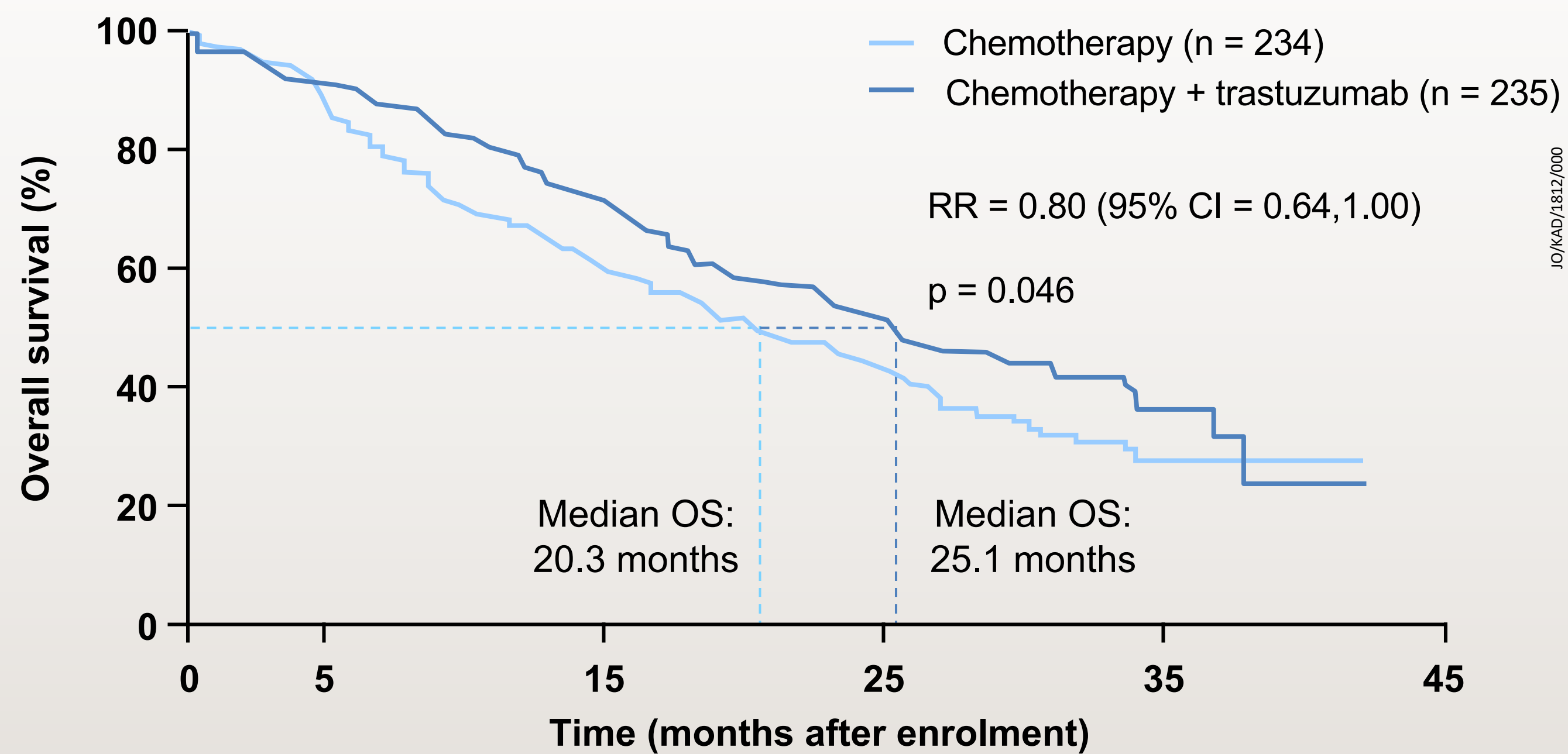
Rise of Targeted Agents

- Focus on specific molecular targets in cancer cells

- Inhibitors of BCR/abl, HER2, EGFR, BRAF reach the clinic

- Improved efficacy and reduced toxicity in "oncogene addicted" cancers

- Precision medicine approach gains traction

Her-2 in Breast Cancer

**Trastuzumab in Metastatic Breast Cancer**

Not amplified (n=52)

Amplified (n=11)
>5 copies

P=0.015

Disease-free survival probability

Months

Chemotherapy (n = 234)
Chemotherapy + trastuzumab (n = 235)

RR = 0.80 (95% CI = 0.64,1.00)

p = 0.046

Overall survival (%)

Median OS:
20.3 months

Median OS:
25.1 months

Time (months after enrolment)

OS was a secondary endpoint in the study
Chemotherapy = either doxorubicin or epirubicin + cyclophosphamide or paclitaxel
OS, overall survival; RR, relative risk of death

JO/KAD/1812/000

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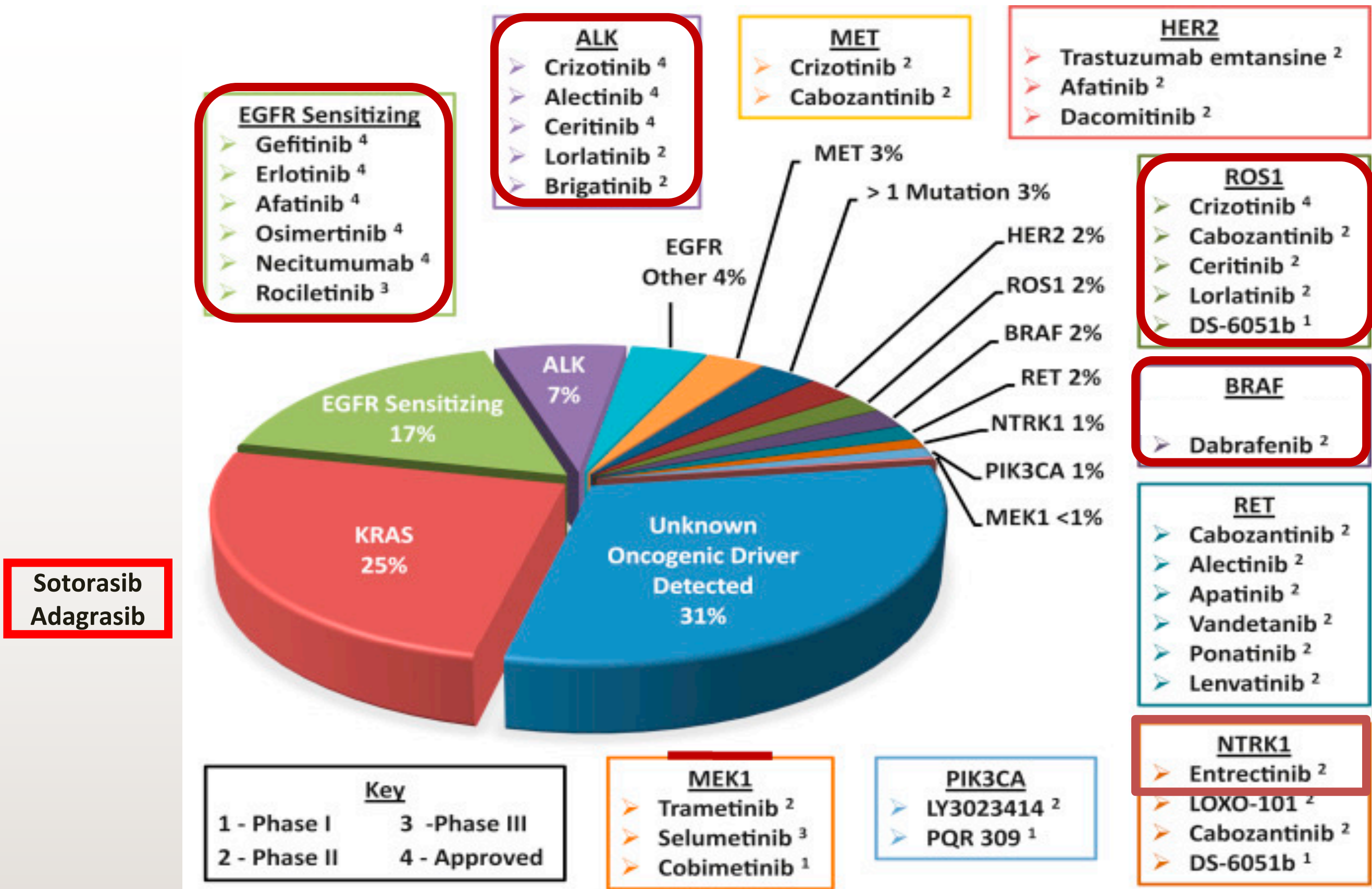Slamon DJ, *et al. N Engl J Med* 2001; 344:783–792.

A Golden Age for Cancer Drug Development

Fig. 1: Overview of oncology therapeutic products
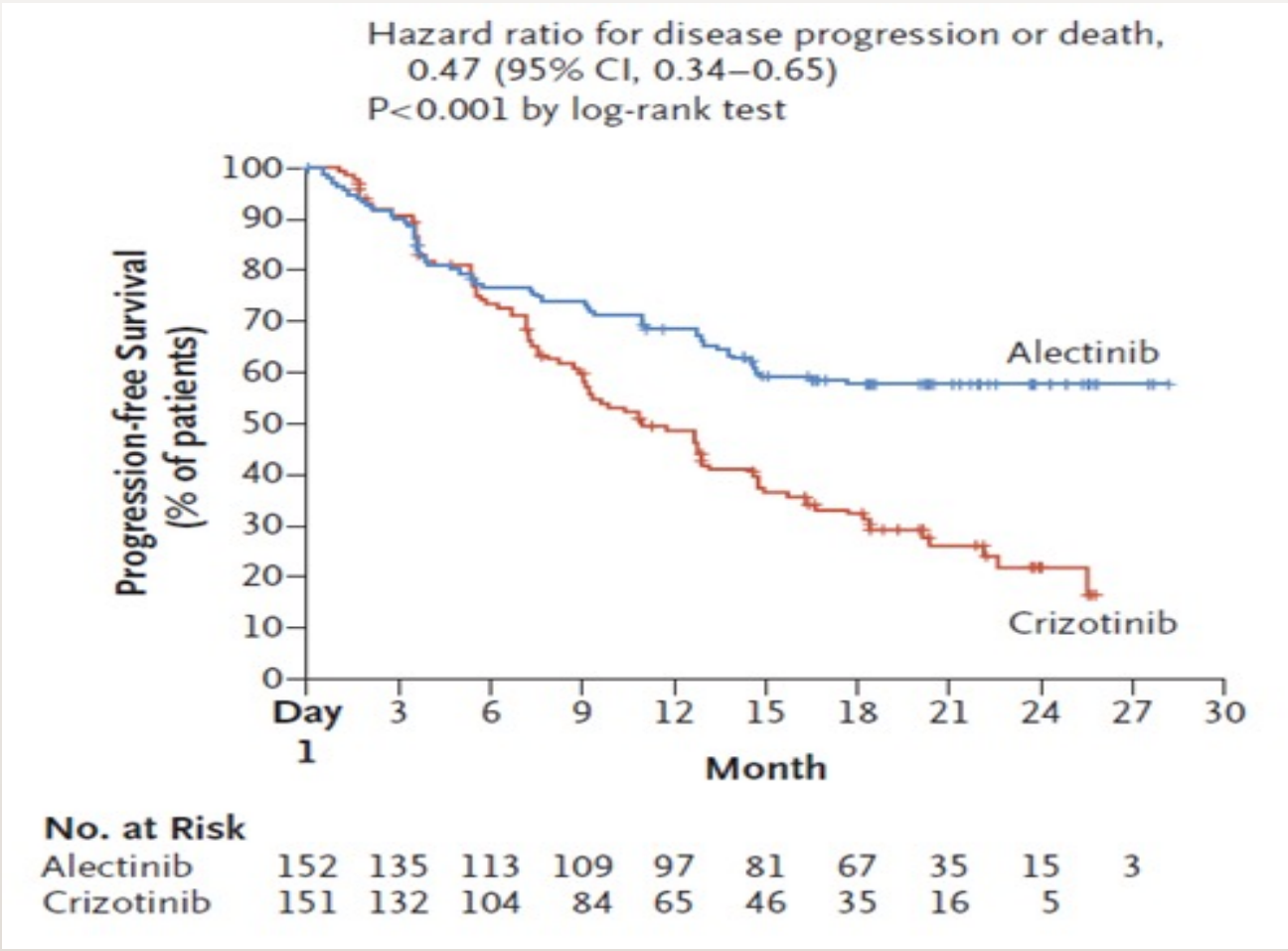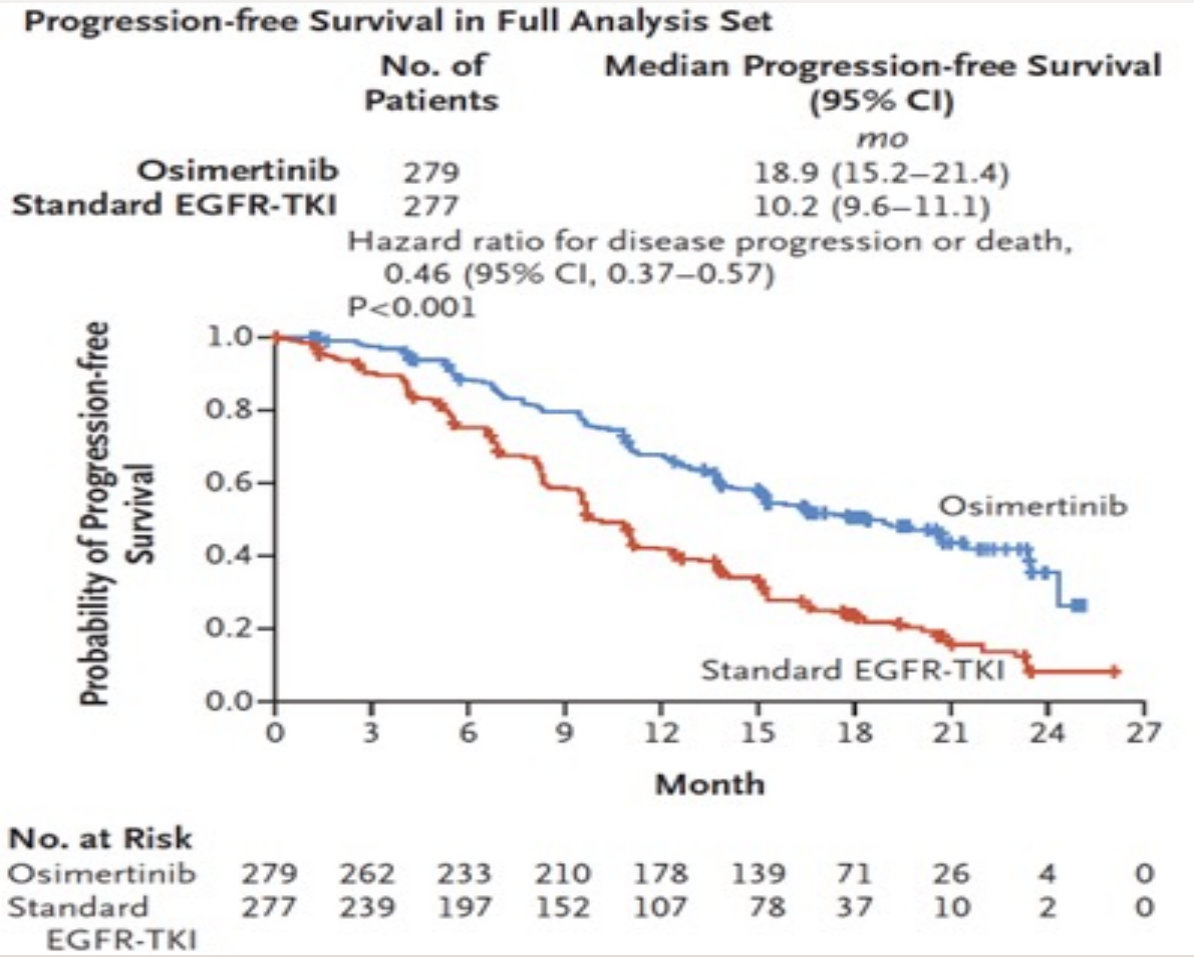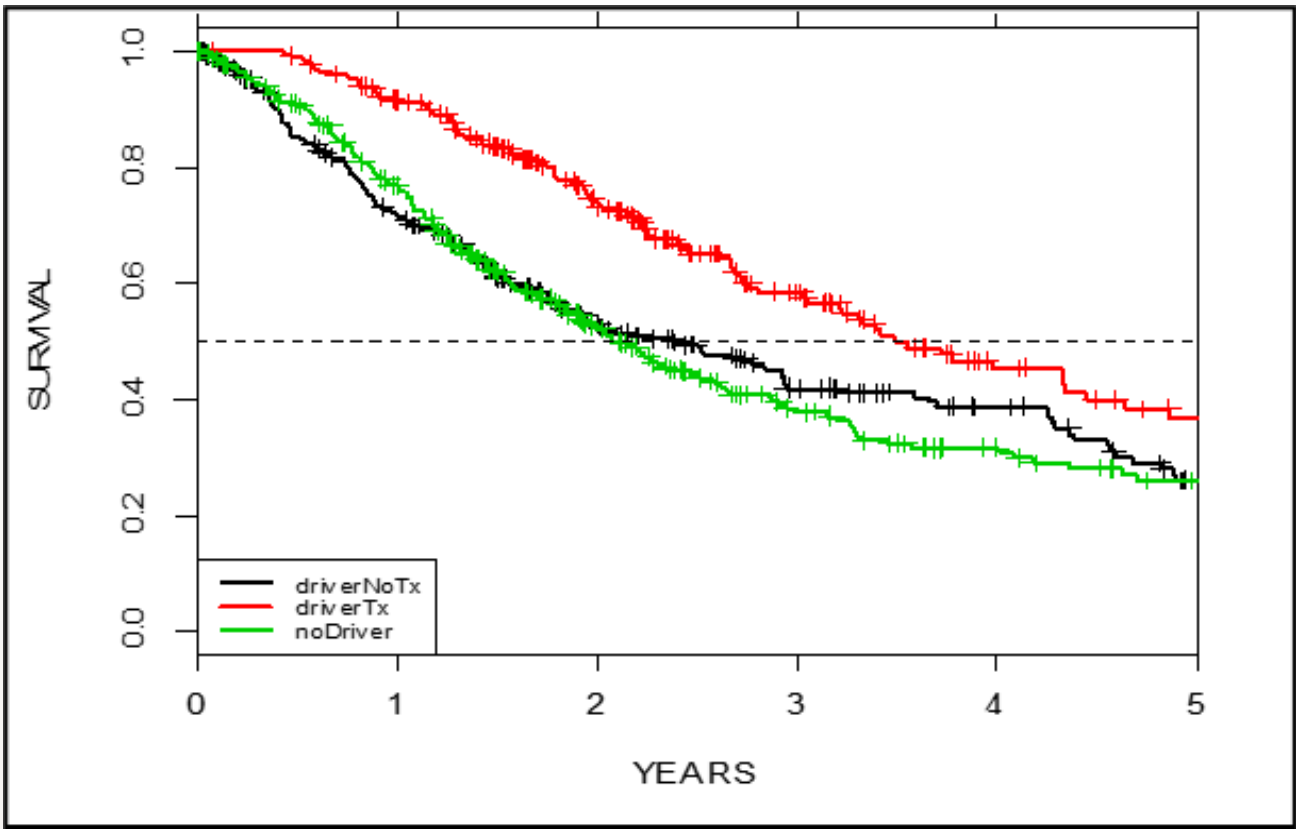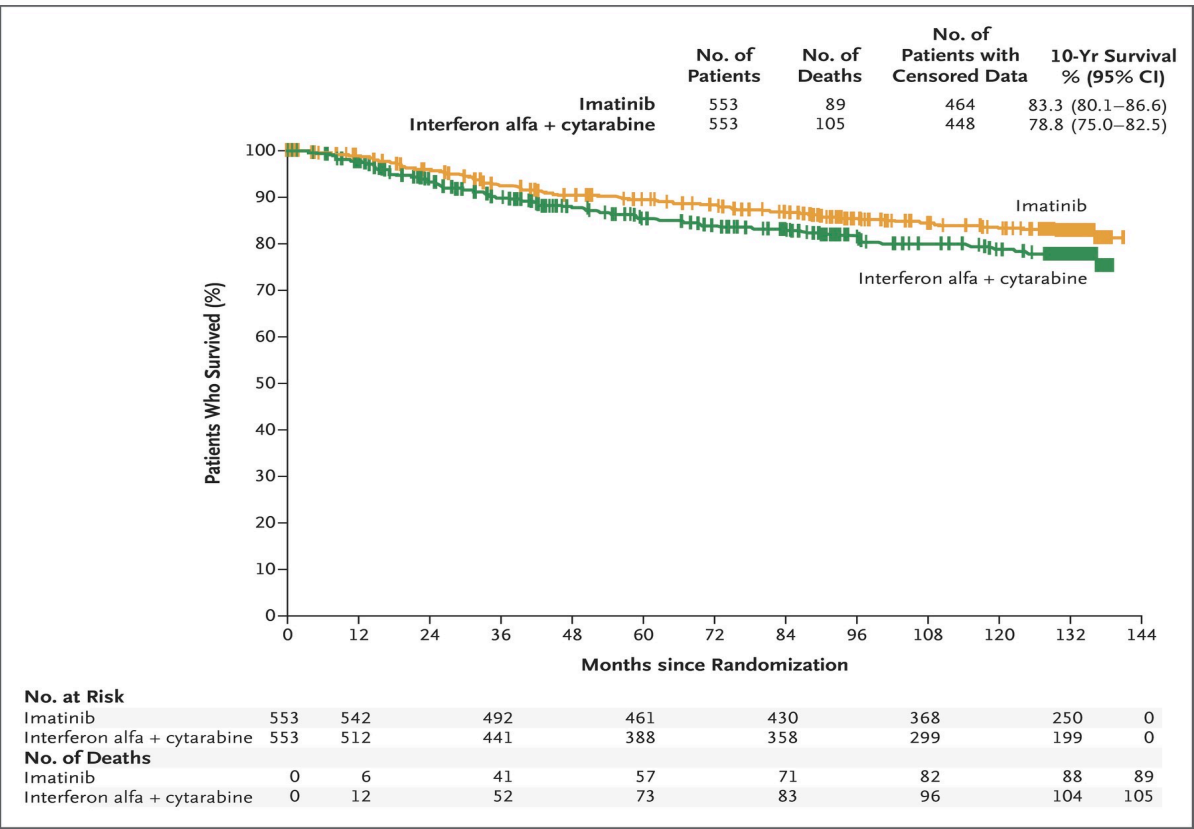approved by the FDA since 2000 by mechanism of action

https://doi.org/10.1038/s41573-023-00723-4
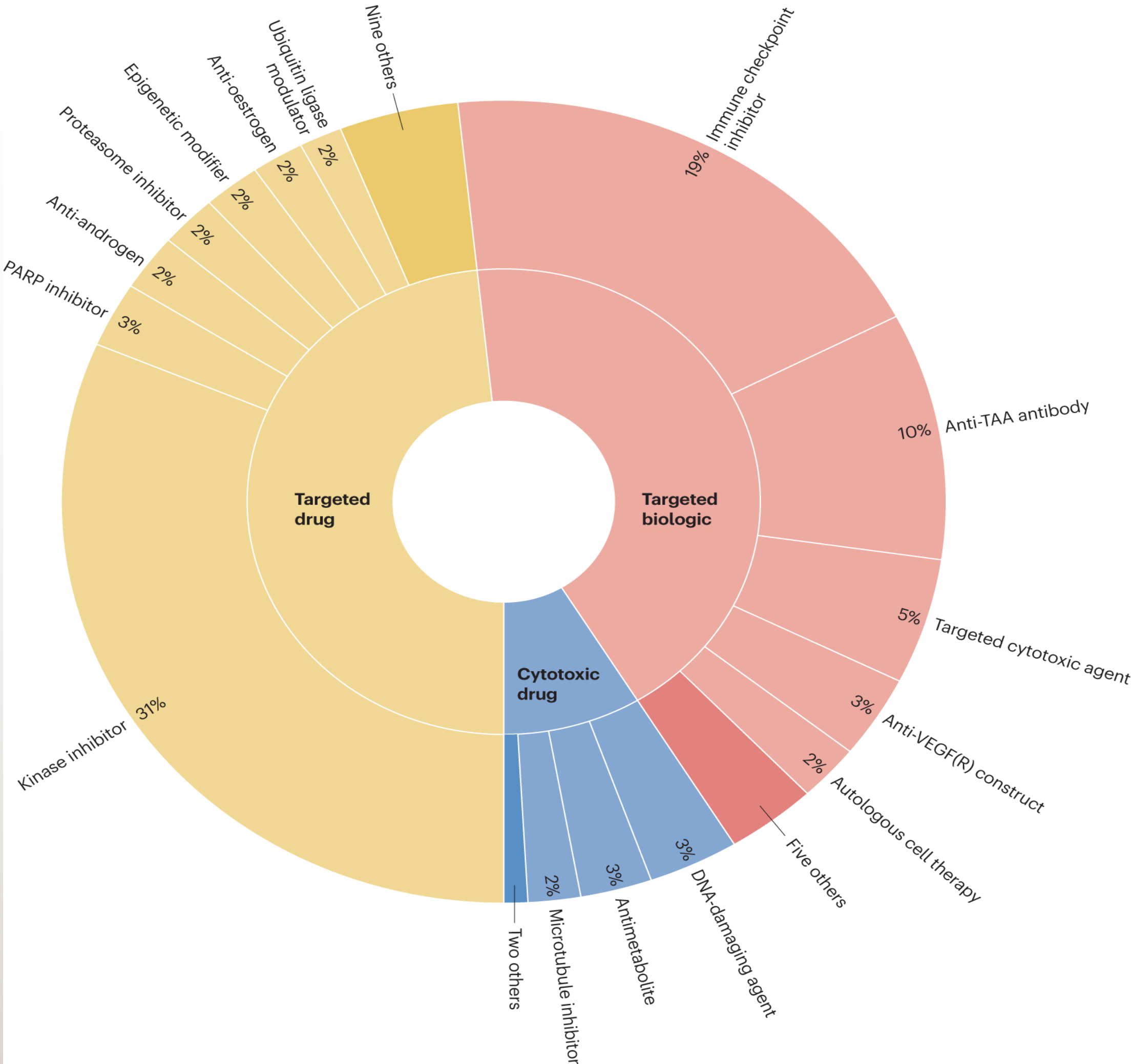
Selected Targeted Agents for Lung Adenocarcinoma

Continued Survival Impact of Targeted Agents

Hochhaus. N Engl J Med 2017; 376:917-927. Kris, M, et al, JAMA, 2014. Soria . N Engl J Med. 2018;378:113-125 Peters NEJM 2017
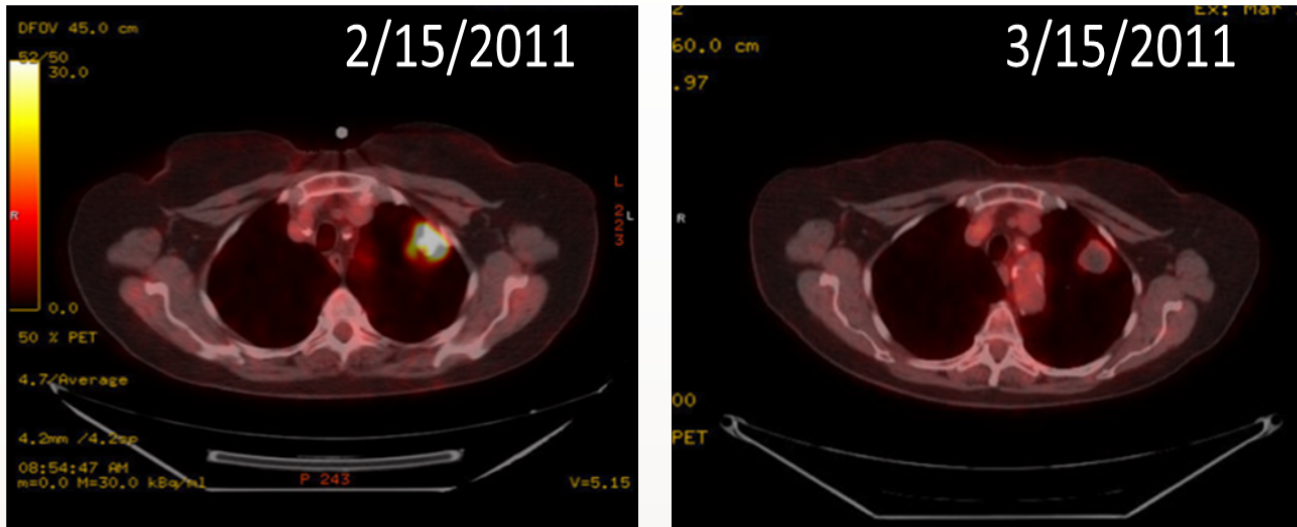
Targeting Cell Survival Pathways in the Lab and Clinic

Linking basic findings to clinical trials with molecular imaging

Energy stress

LKB

Akt — TSC2 — AMPK

Rheb

Rap — mTOR

p70S6K

S6

Akt

Protein synthesis
(Cyclin D, c-Myc, etc)
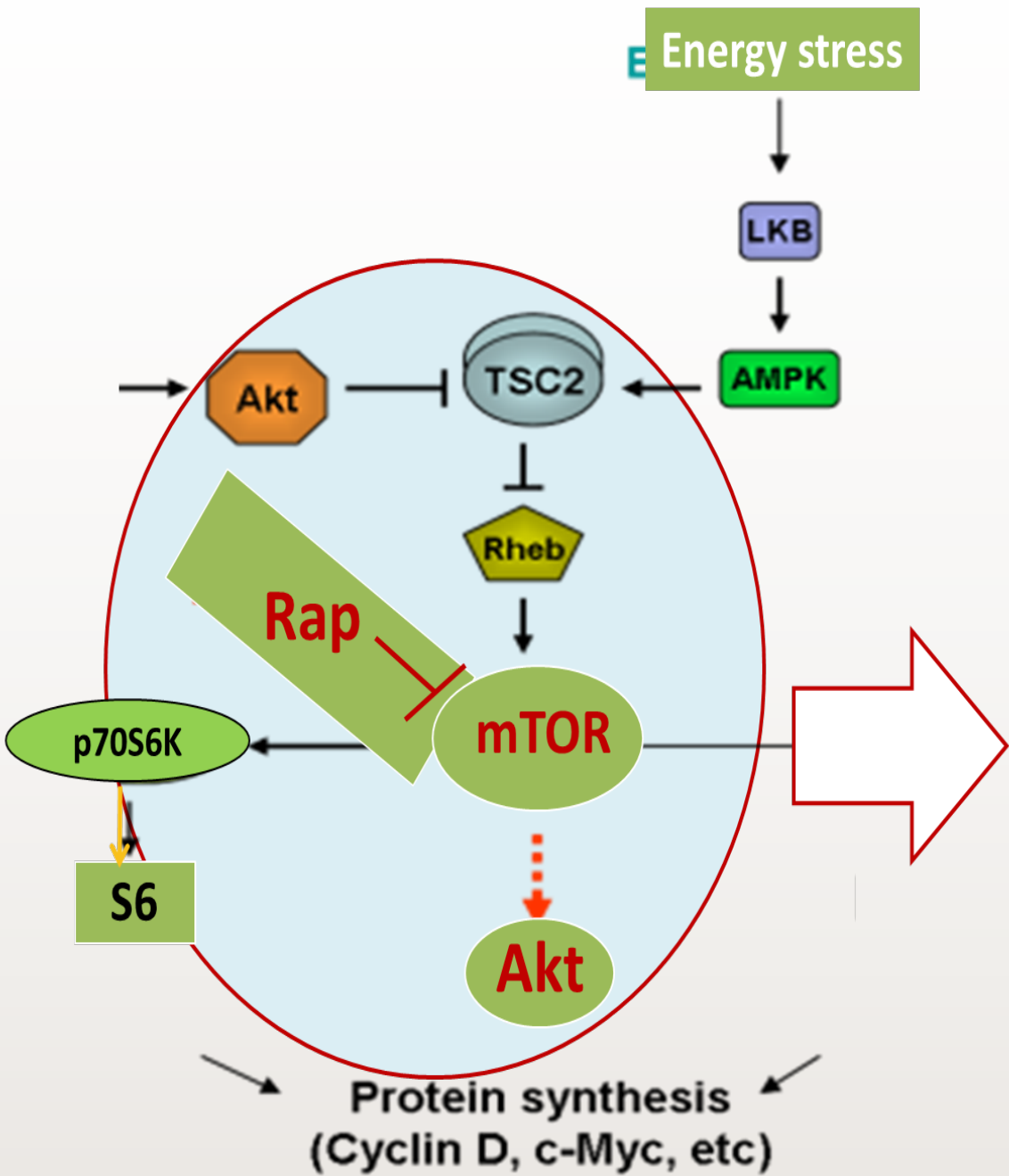
Sun et al. Cancer Res 2005
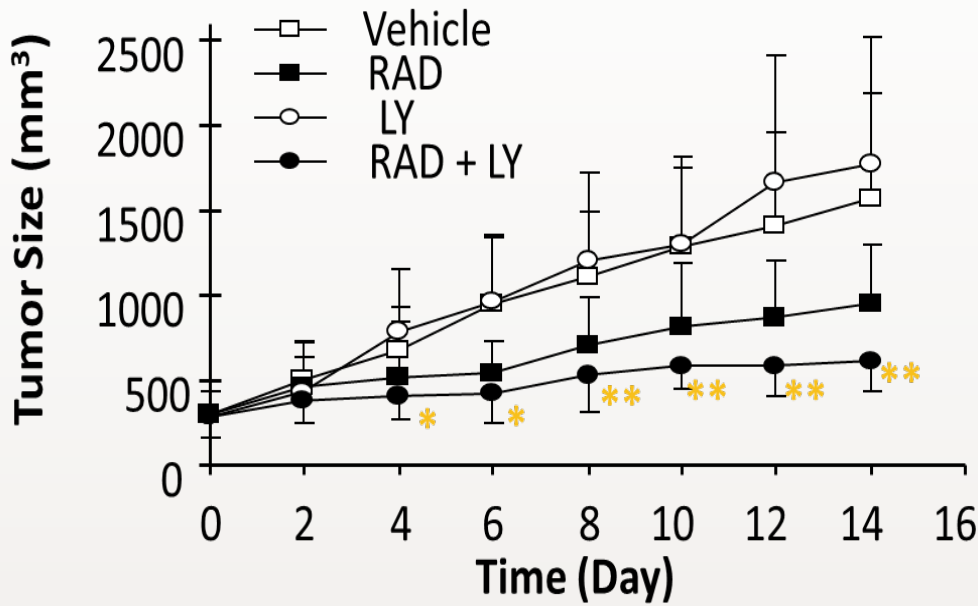
2/15/2011   3/15/2011

Everolimus Ph1 clinical trial PET scan
Phase I: N = 29 (RAD001)
Phase I/II: N= 52 (RAD001+docetaxel)

↑ **p-AKT** in all 17 patients

↓ **pS6** only inhibited in **1 patient**

Limited clinical activity of RAD001:
Limited target effect

Inhibitors of PI3K + mTOR Synergistically inhibit tumor growth in xenograft

Vehicle
RAD
LY
RAD + LY

Tumor Size (mm^3) vs Time (Day)

Phase I trial:
BKM120 + RAD001
to achieve complete target blockade (Proj 1, P01)

Ramalingam et al. Cancer, 2010,
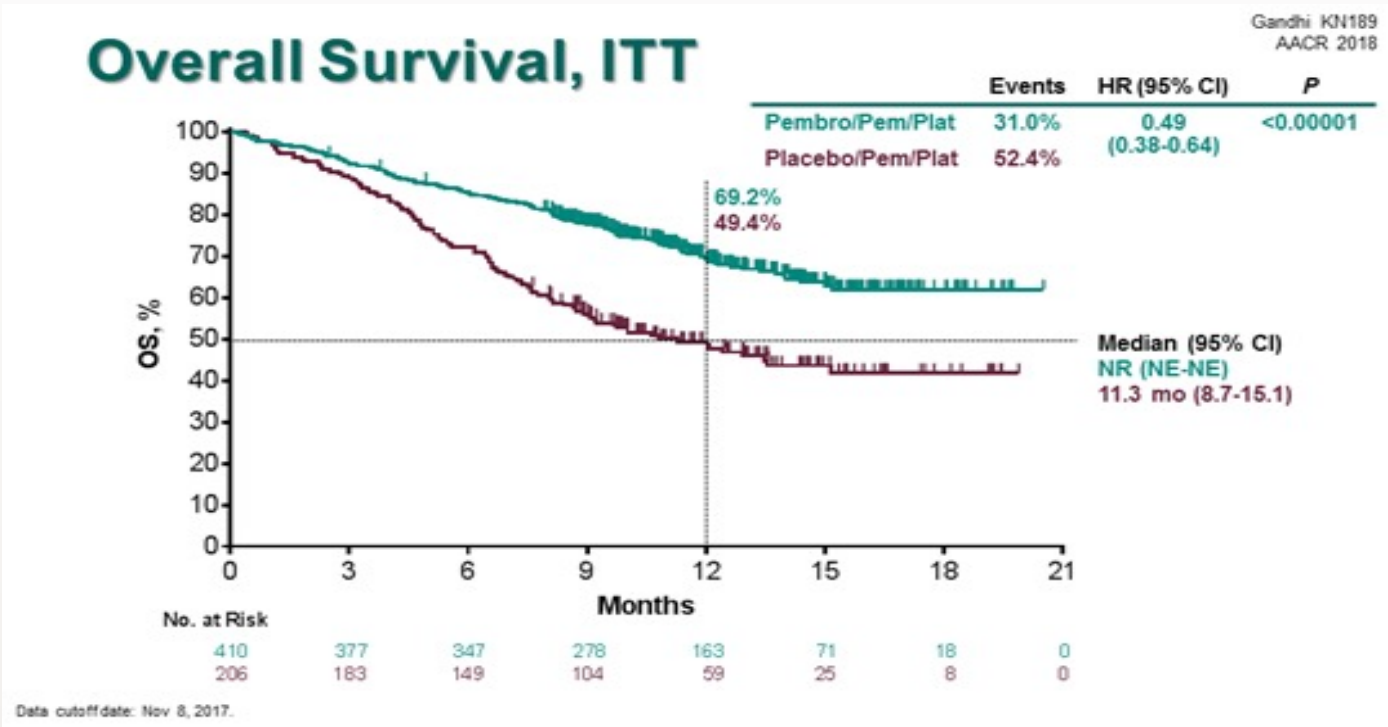Owonikoko et al. Clinical Cancer Research, 2015;

Breakthroughs in Immunotherapy

- Checkpoint inhibitors revolutionized treatment

- CAR-T therapy shows promise in hematologic cancers

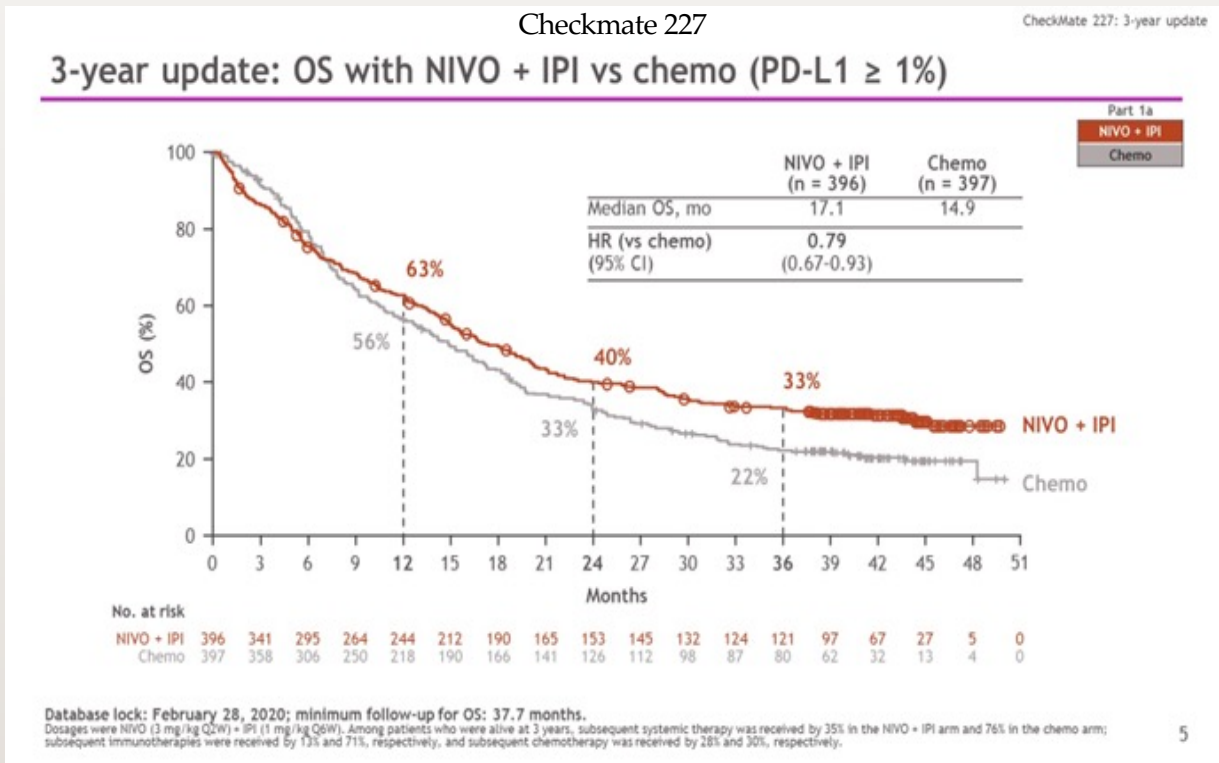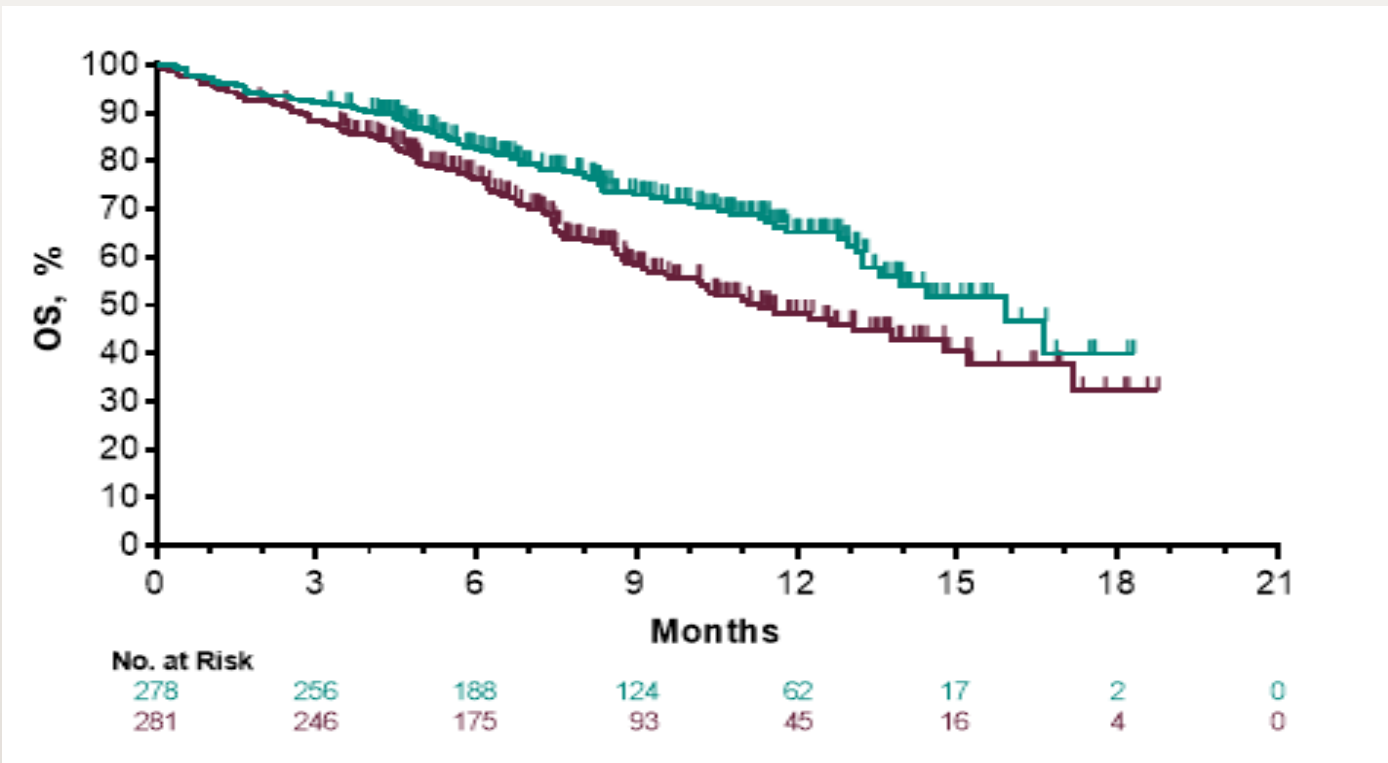- Durable responses in some metastatic cancers
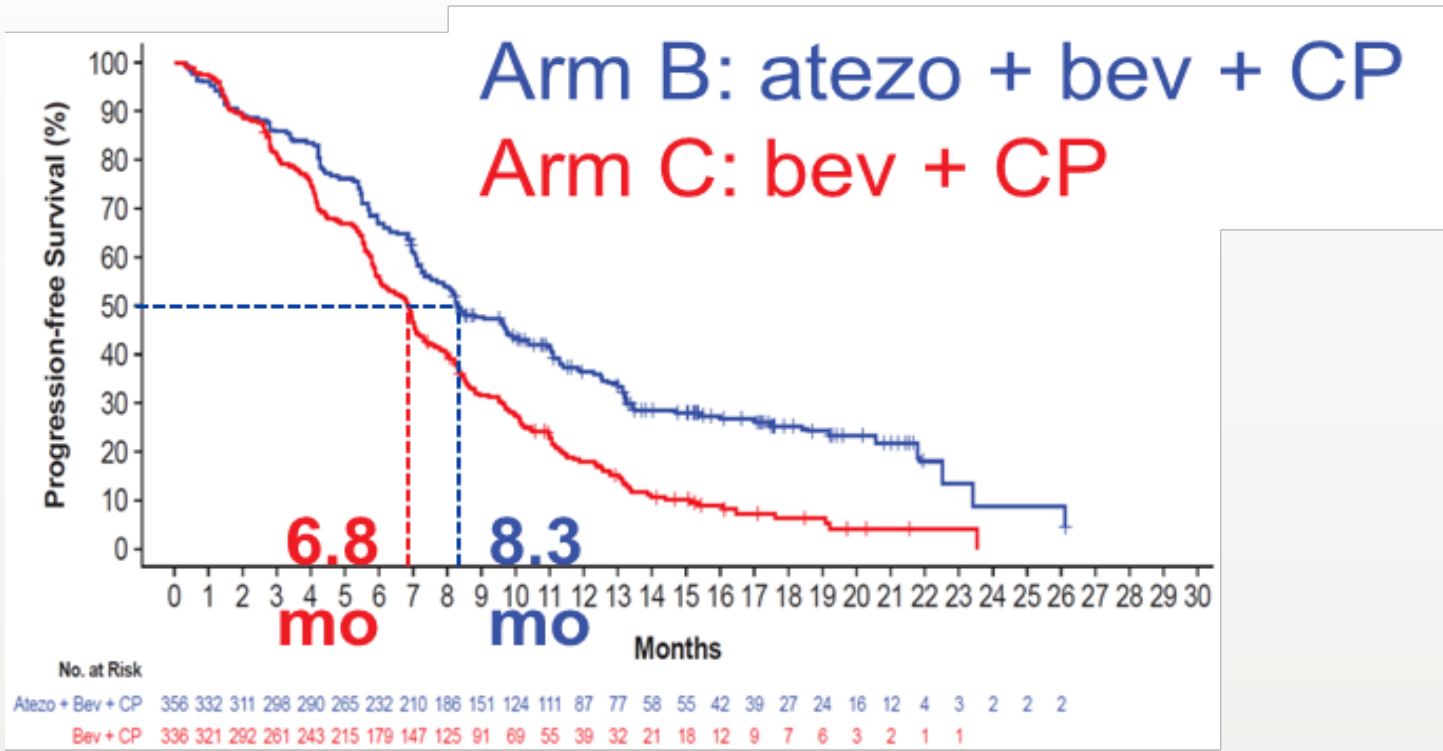
Growing Survival Impact of Immunotherapy

KEYNOTE-189

IMpower 150

Checkmate 227

Gandhi L et al. *N Engl J Med.* 2018. Paz-Ares L et al. *N Engl J Med.* 2018. Reck, NEJM 2016. Hellmann MD, et al. *N Engl J Med* 2019;381:2020–2031
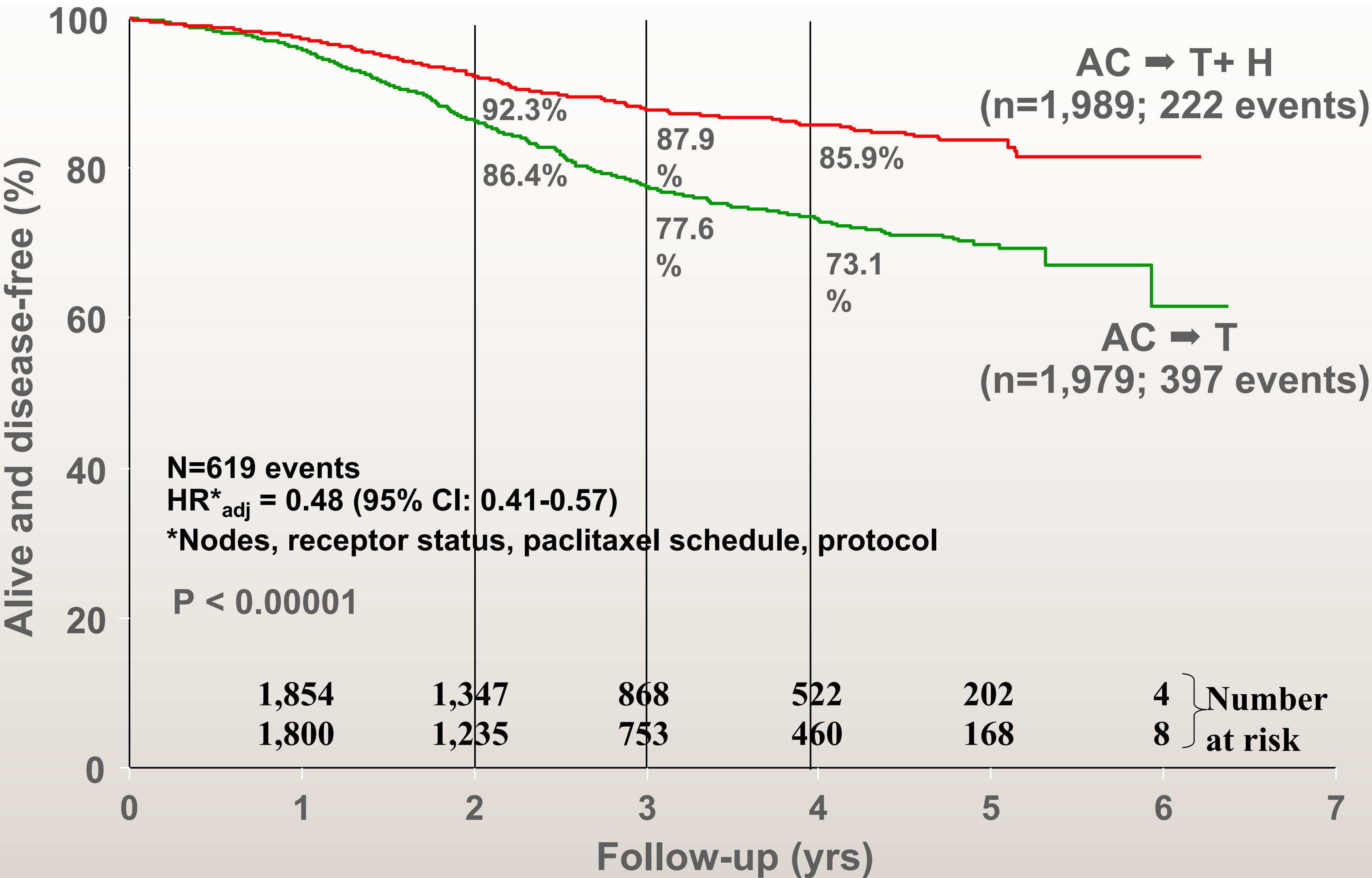
Effect on Early-stage Disease

- Novel targeted and immunotherapeutic agents increasingly incorporated to great effect in patients in early-stage disease.
- Improved complete response rates will likely lead to higher cure rates.
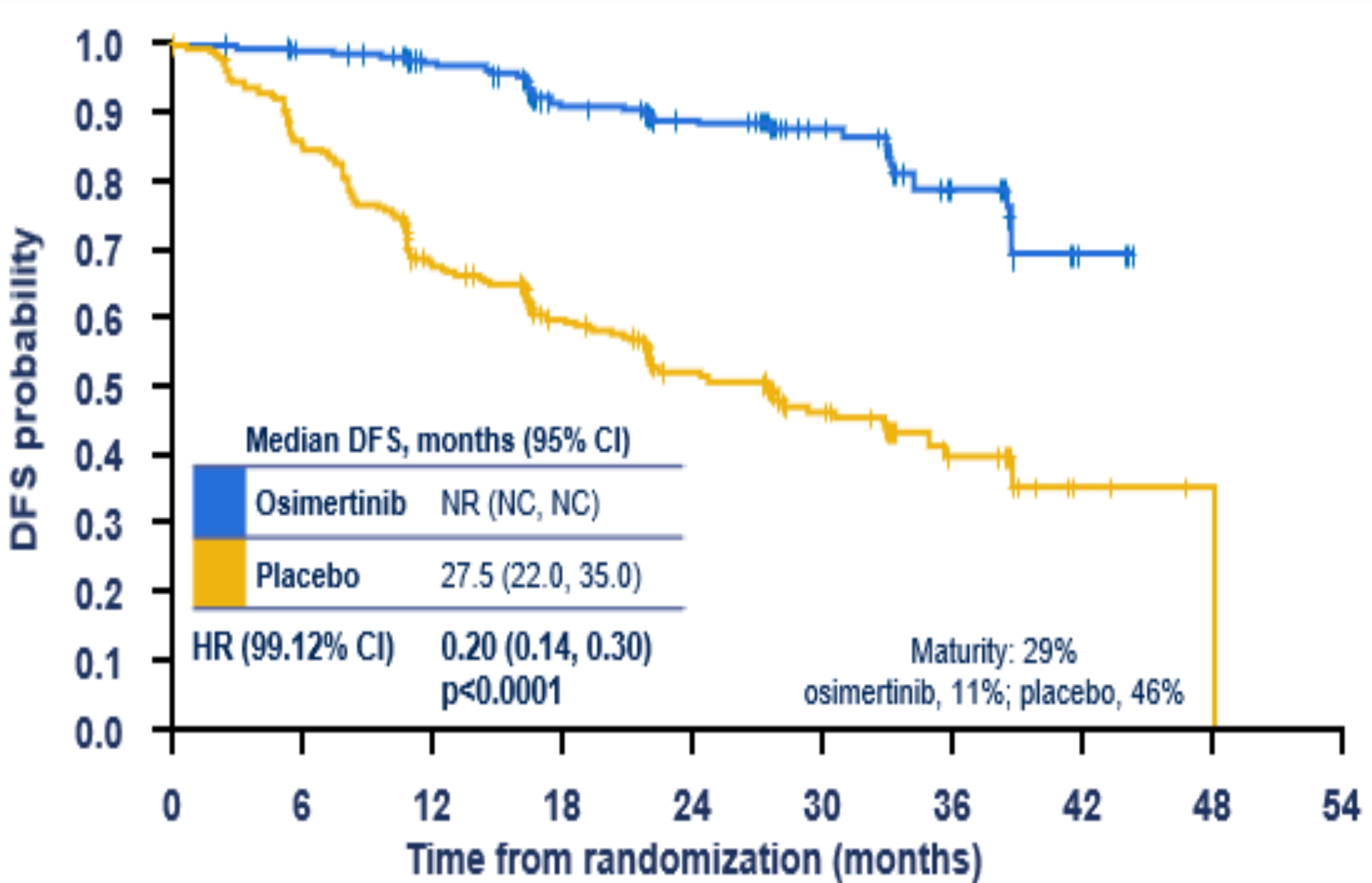- Limited duration of therapy with higher impact on outcome.

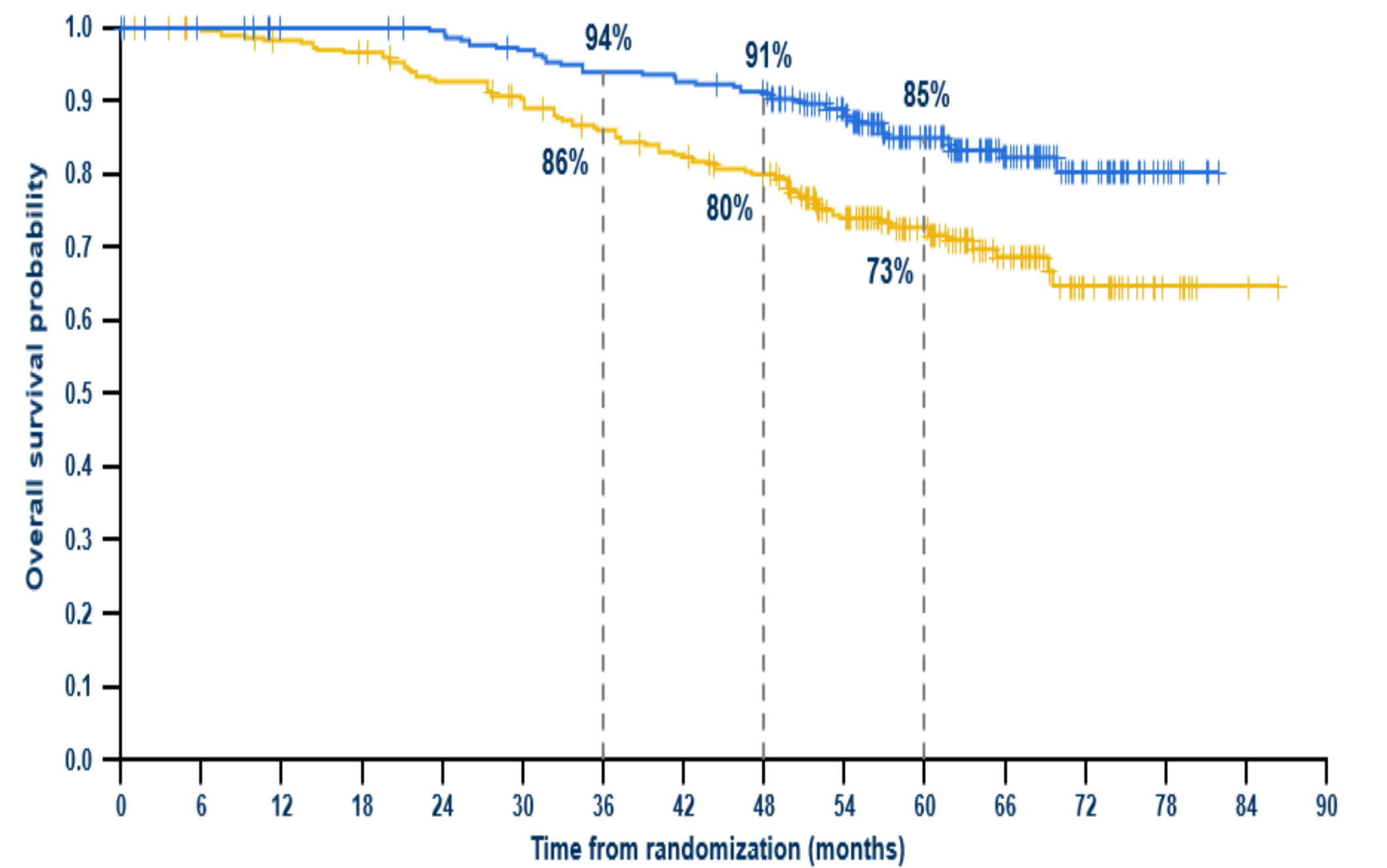**AMERICAN UNIVERSITY OF BEIRUT**

Updated N9831/B-31 Joint Analysis
Disease-Free Survival

ADAURA Trial

DFS

OS

ALINA trial
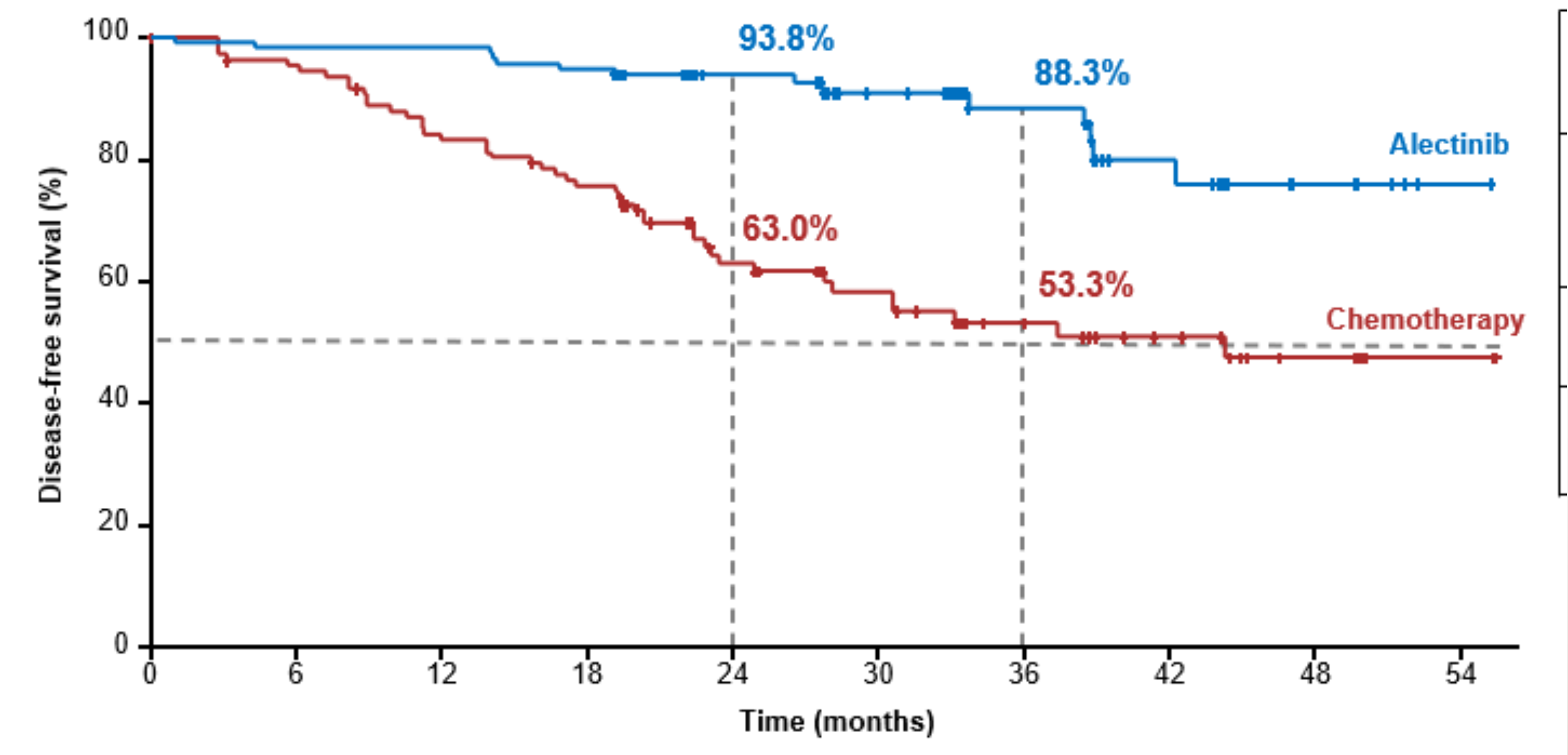
CK 816
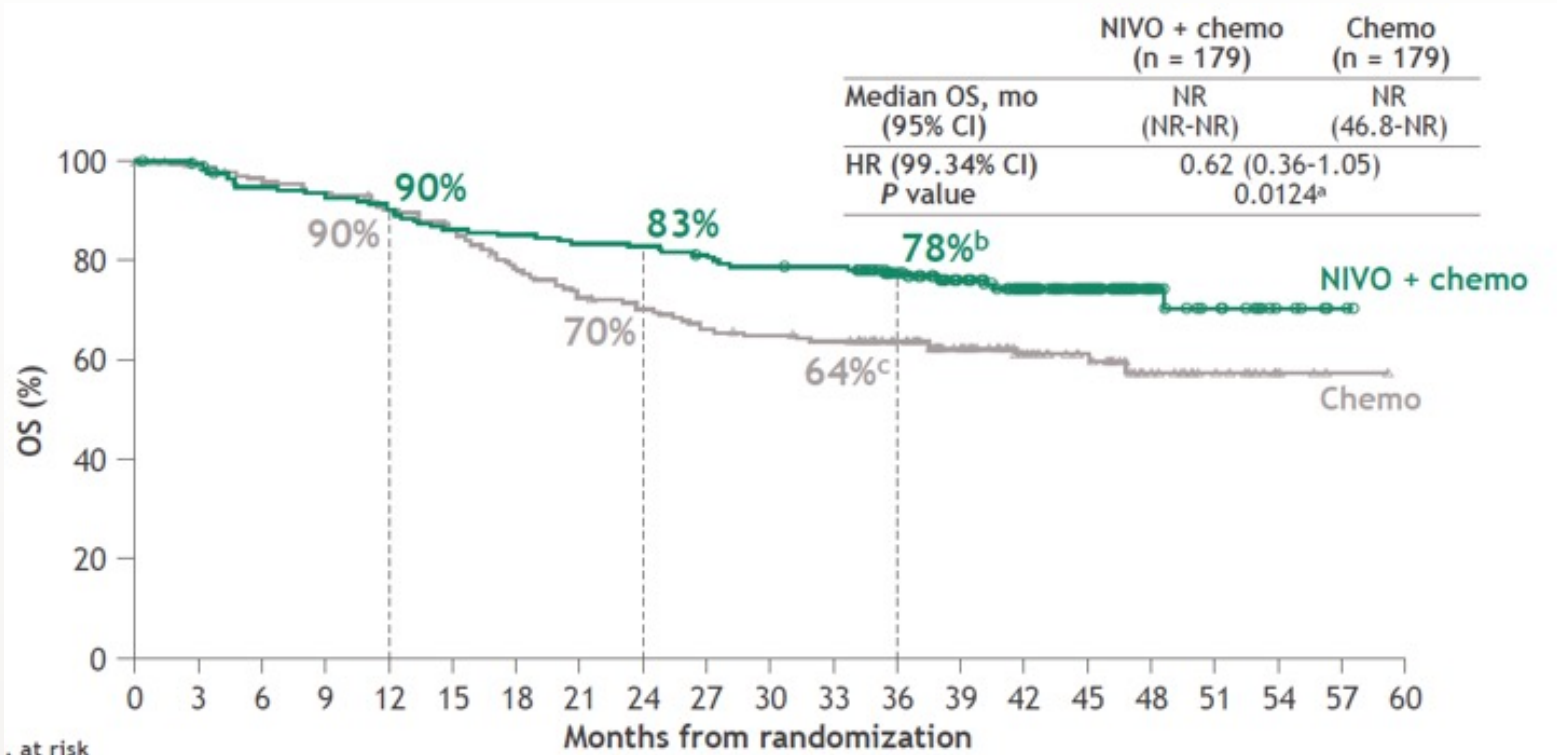
Impower 010

KN 671

CK 77T

Aegean

Forde et al, N Engl J Med 2022;386:1973-1985. Felip et al, Lancet 398, 2021. Wakelee et al. NEJM 389 (6) .Cascone et al. N Engl J Med 2024;390:1756-1769. Heymach et al. N Engl J Med 2023;389:1672-84.

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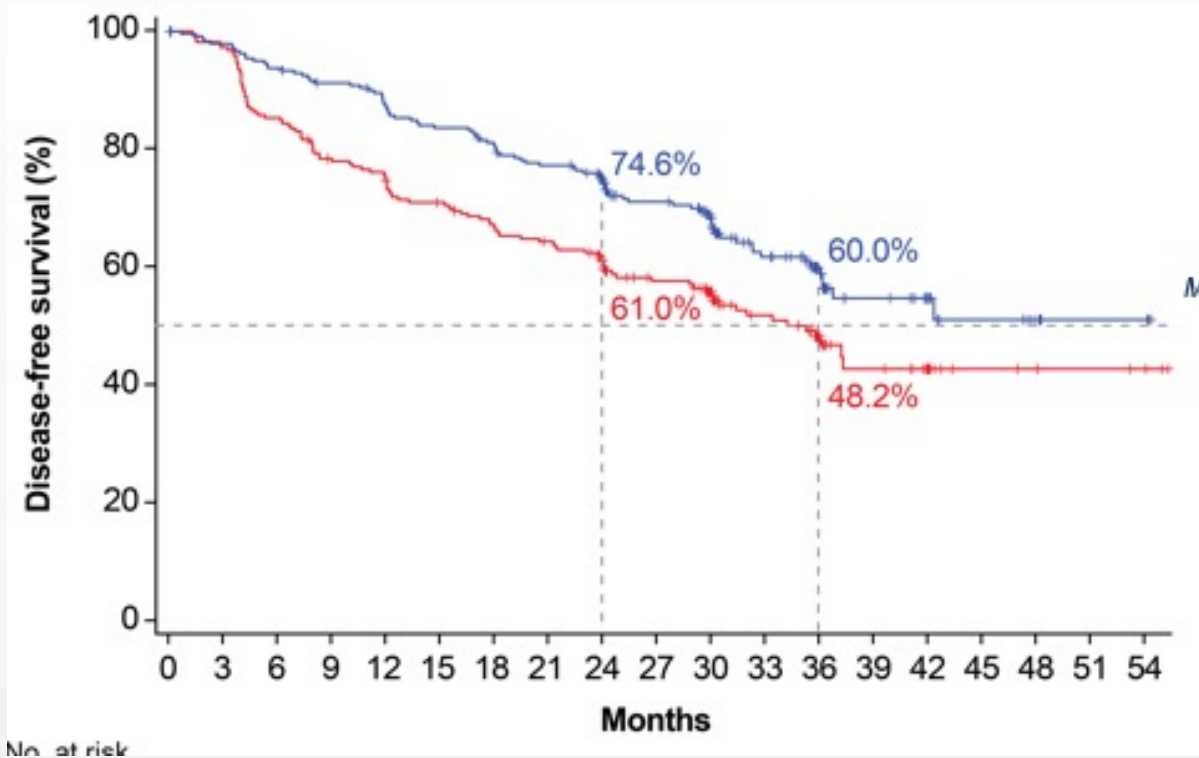
Advances in Screening Technologies

- Widespread use of mammograms reduced breast cancer mortality

- Low-dose CT improves early lung cancer detection

- Colonoscopy detects and removes precancerous polyps

- Emerging blood-based tests aim for multi-cancer detection

A Cautionary Tale: Large-Scale Aerodigestive Cancer Chemoprevention Trials Fail
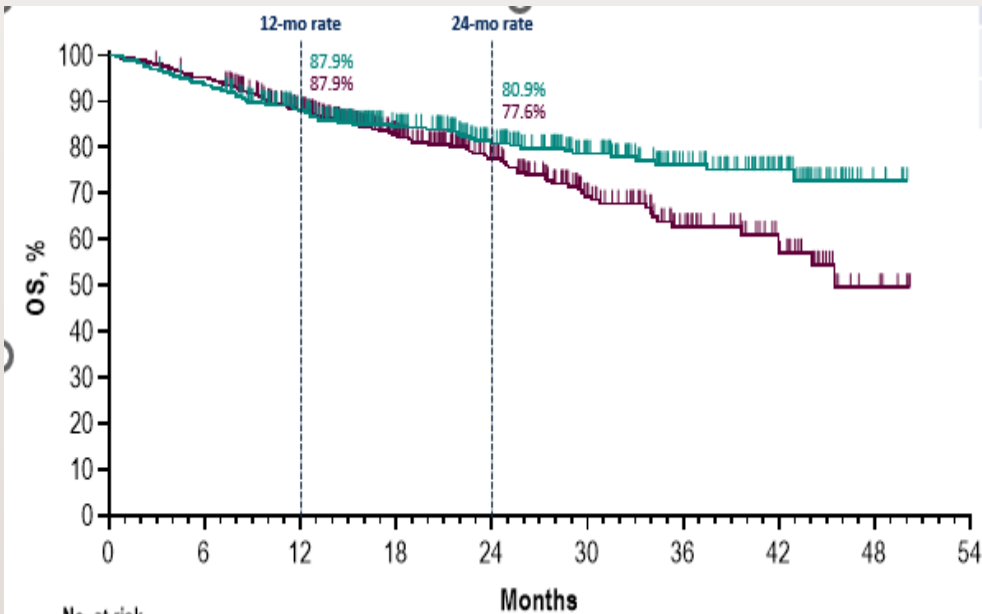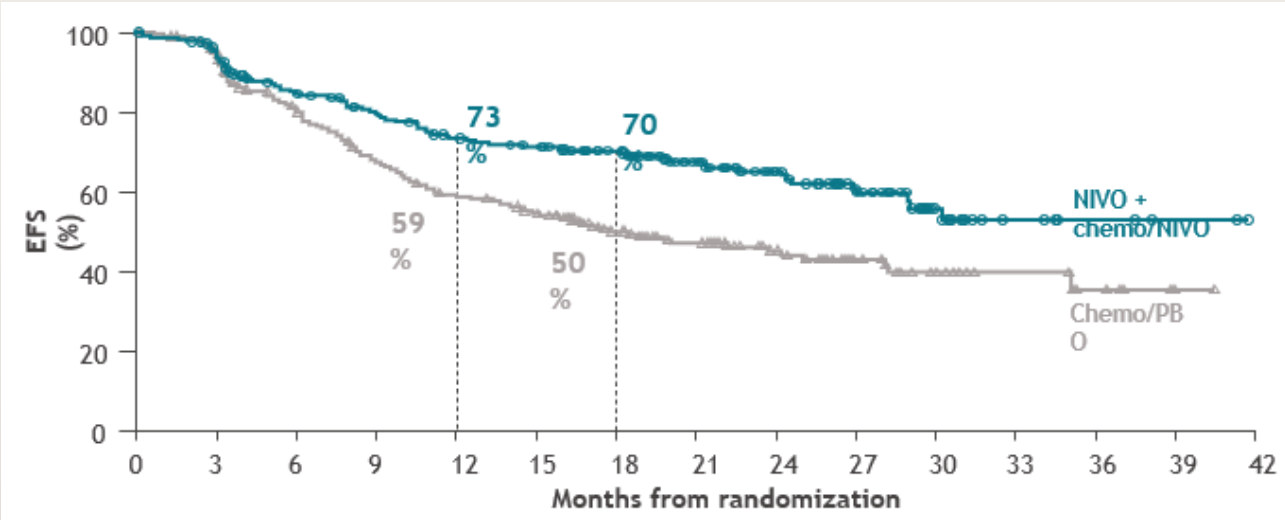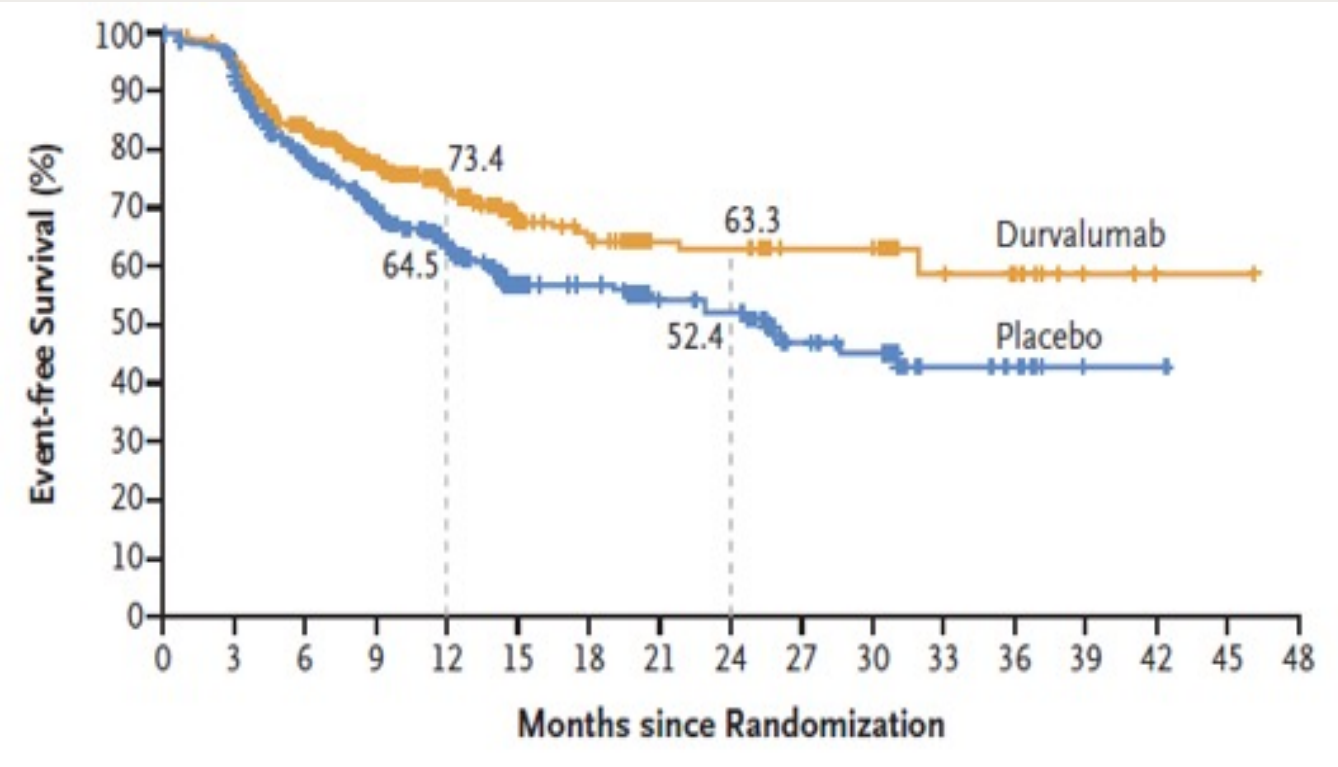
- CARET (β-Carotene and Retinol)
- ATBC (α-Tocopherol and β-Carotene)
- Euroscan (Retinyl Palmitate and NAC)
- NCI Intergroup (13cRA)-Lung and Head & Neck trials
- Selenium

MAJOR FINDINGS

- β-carotene increases lung cancer incidence in current smokers, but not in former smokers
- 13cRA has no impact on reduction of incidence of second primary tumors in patients of any smoking status.
- Data suggest that 13cRA is beneficial in non-smokers and possibly beneficial in former smokers for reduction of locoregional recurrence and improving survival, but harmful in current smokers.
- Greatest benefit in aerodigestive cancer prevention is tobacco control.
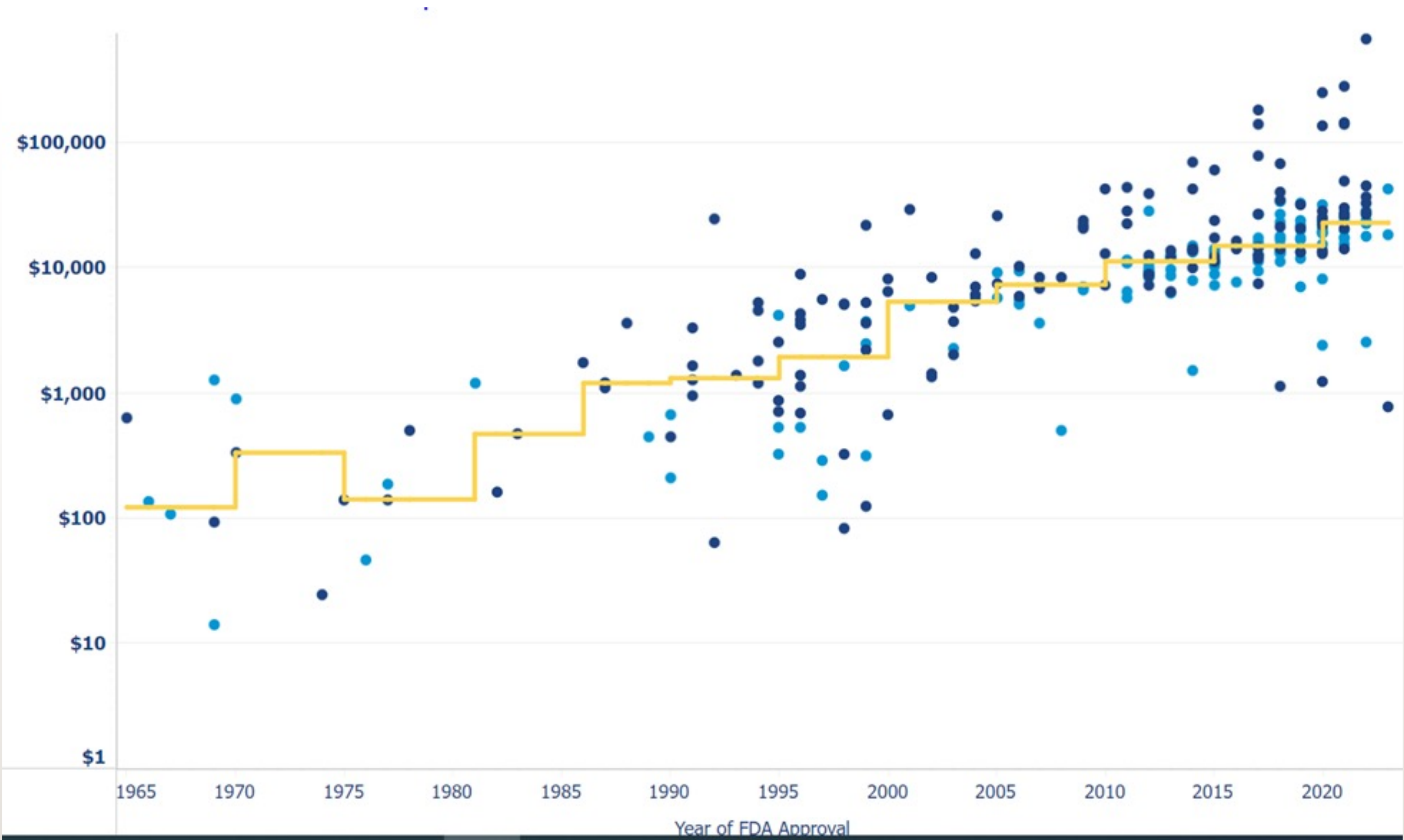
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Growing Disparities in Cancer Care

- Persistent gaps in outcomes across race and socioeconomic status

- Under-representation in clinical trials

- Access to screening and treatment remains unequal

- Need for equitable care models and community engagement

Sale Price Change over Time

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Ethical Dilemmas in Resource Allocation and Global Impact

- Is it ethical for the world's wealthiest economies to utilize the vast majority of cancer therapeutics with relatively stable cancer incidence?

- At the peak of the COVID-19 pandemic, 10 countries utilized 90% of the world supply of COVID-19 vaccine.

- Disease control and outcomes improved in those 10 countries but the infections kept spreading.

- LMICs are expected to face an epidemic of cancer cases in the next few decades.

Countries in the developing world bear the greatest burden of new cancer cases as well as deaths
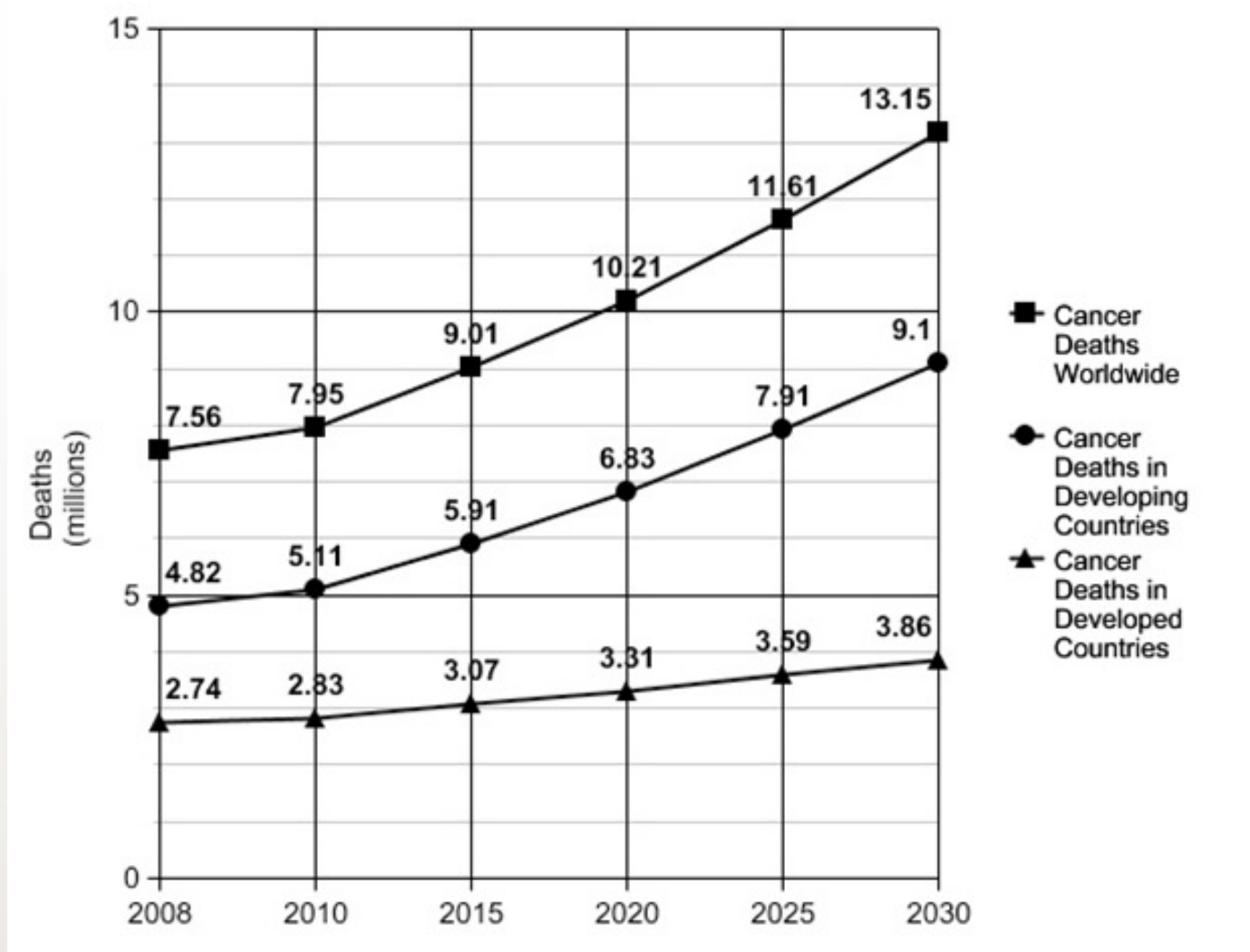
By 2030, the developing world is expected to account for 70% of newly reported cancer cases

Moten et al. J Global Health 2014;4:010304.American Cancer Society. Global cancer facts & figures

Cancer Incidence to Mortality Ratio

Lopes et al. Global Health Equity: Cancer Care Outcomes Disparities in High, Middle and Low Income Countries. J Clin Oncol 2017. Based on Data from GLOBOCAN
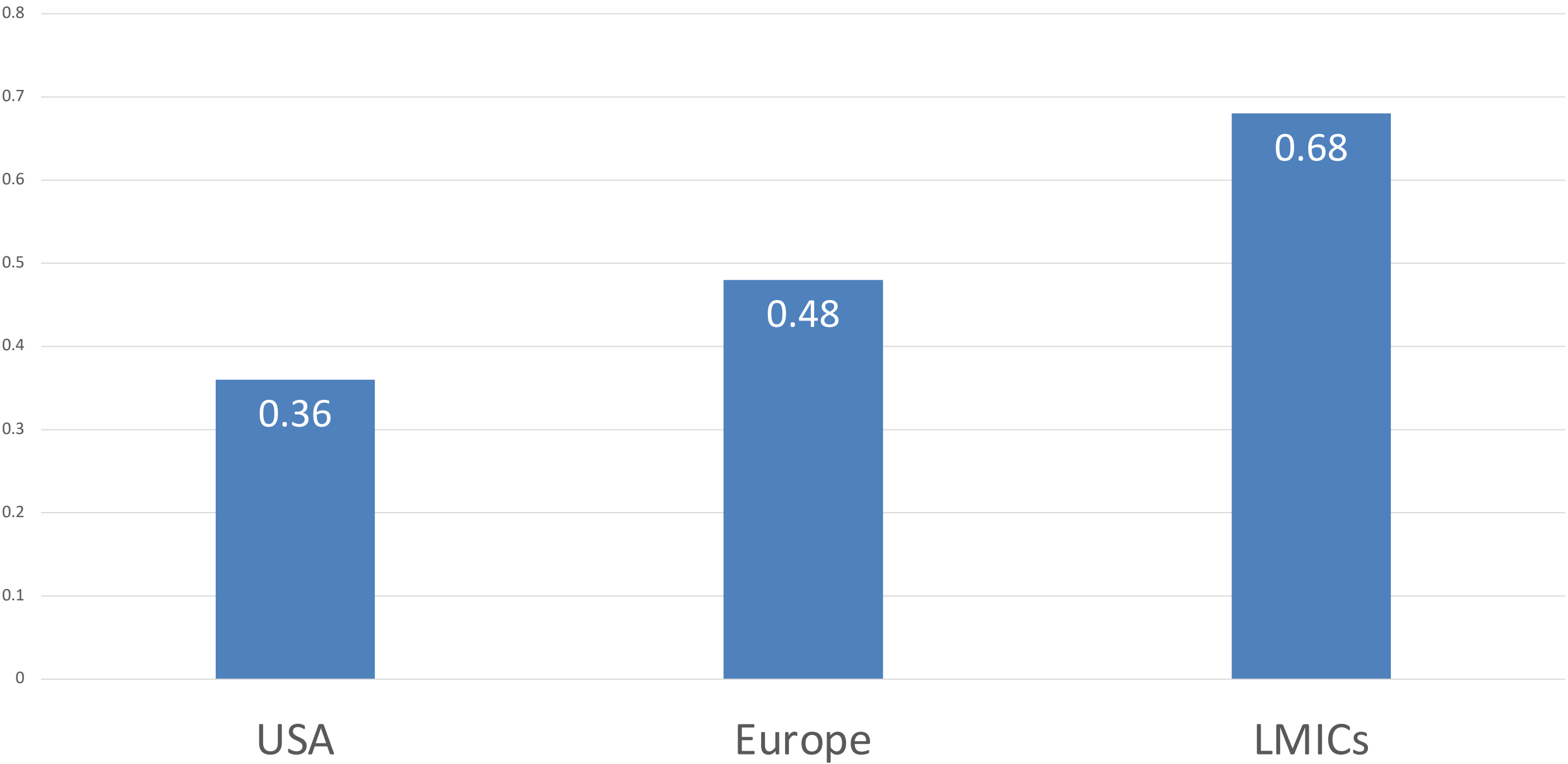
Looking to the Future

- Comparative genomics

- Integration of AI into oncology

- Targeting human metabolism

- Development of less invasive diagnostic tools

- Global efforts to reduce disparities and improve access

Relative Cancer Risk Among Mammals

Cancer risk across mammals

Orsolya Vincze ✉, Fernando Colchero, Jean-Francois Lemaître, Dalia A. Conde, Samuel Pavard, Margaux Bieuville, Araxi O. Urrutia, Beata Ujvari, Amy M. Boddy, Carlo C. Maley, Frédéric Thomas & Mathieu Giraudeau

Figure 1: Distribution of cancer mortality risk across the mammalian phylogeny.
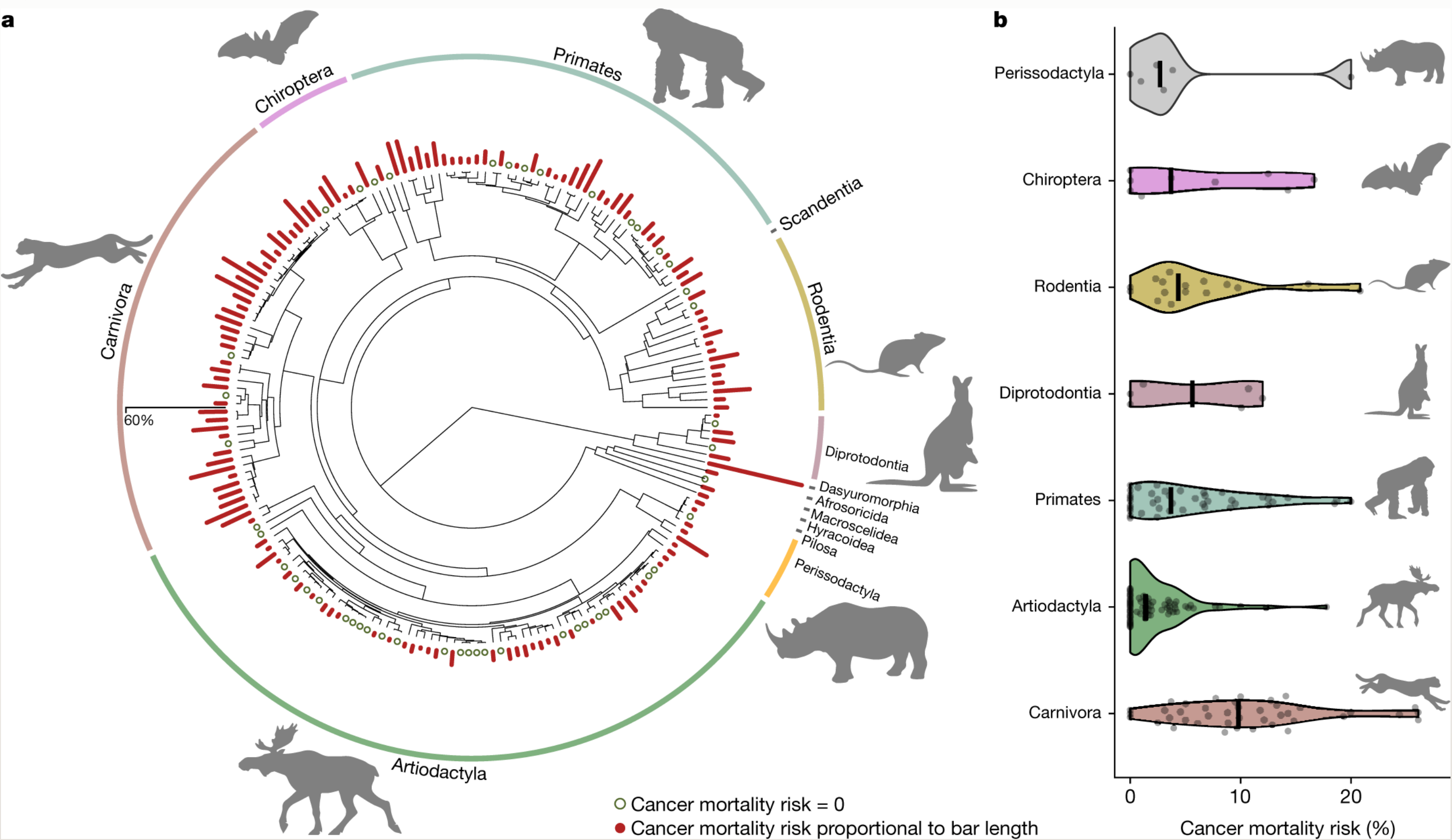
a, CMR in various mammals (scale to bar plots is provided on the left of the graph). **b**, Violin plots indicating order differences in CMR in orders with a minimum of two species represented. Solid black lines represent order medians.

Artificial Intelligence in Medicine

- Diagnostic radiologic and pathologic procedures

- AI-powered decision systems and machine learning based guidance of screening, prevention, therapy

- Fusion of AI and genotype analysis holds great promise (disease surveillance and emerging disease threats)
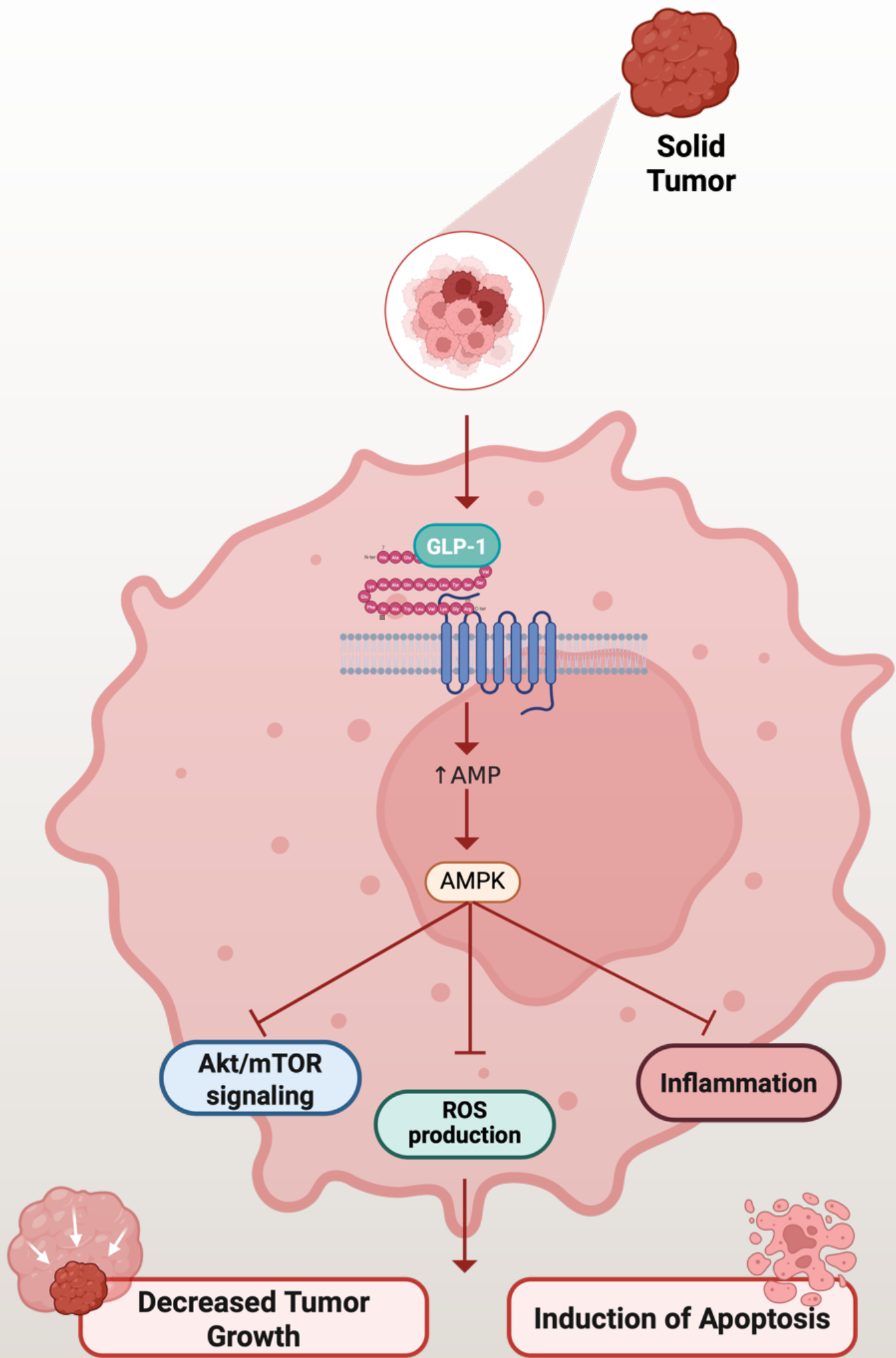
- Novel drug discovery, and more precise therapies

MECHANISTIC INSIGHTS AND SUMMARY OF GLP-1 RECEPTOR AGONISTS IN CANCER

MECHANISTIC INSIGHTS AND SUMMARY OF GLP-1 RECEPTOR AGONISTS IN CANCER

Type of Tumor	Results in Animal Studies	Results in Human Studies	Mechanism of Action	References
Obesity-associated cancers	Mixed results across tumor types, including increased or decreased tumor growth	Mixed epidemiological findings, with some showing reduced risk and improved prognosis	Anti-inflammatory, anti-proliferative, metabolic regulation via GLP-1R pathways; modulates chronic inflammation and oxidative stress	• Ungvari, Z. et al., *GeroScience*, 2025. • Ibrahim, S. et al., *Cancer and Metabolites Reviews, 2024*. • Lin A. et al., *Biomarker Research*, 2025.
General solid tumors	Demonstrates modulation of immune response and tumor metabolism in animal models	Human data show complex interactions and no consistent cancer promotion signal	GLP-1R-mediated signaling affects metabolic, immune, and cell survival pathways; influences glucose metabolism, immune cell recruitment, and cell survival	• Iqbal, A. et al., *Acta Scientific Cancer Biology*, 2018. • Benjamin D.J. et al., *Cancer Drug Resistance*, 2024.
Thyroid (C-cell tumors)	GLP-1RA promotes C-cell proliferation in rodents GLP-1RAs induce hyperplasia and tumor formation in rodent C-cells	Observed increased risk in pharmacovigilance data. Increased calcitonin levels observed; cancer risk inconclusive	Activation of GLP-1R in C-cells stimulate calcitonin release and proliferation	• Yang, Z. et al., *Frontiers in Pharmacology*, 2022. • Silverii, G.A. et al., *Diabetes, Obesity and Metabolism*, 2024.
Breast and colon cancer	Animal models show suppression of tumor growth	Some clinical correlations with reduced incidence in GLP-1RA-treated diabetic patients;	Anti-proliferative and pro-apoptotic effects; modulation of insulin/IGF pathways	• Vangoitsenhoven, R. et al., *Endocrine-related cancer*, 2012.

MECHANISTIC INSIGHTS AND SUMMARY OF GLP-1 RECEPTOR AGONISTS IN CANCER

Type of Tumor	Results in Animal Studies	Results in Human Studies	Mechanism of Action	References
Colorectal cancer	GLP-1RA blocks tumor progression via pathway modulation	Under investigation; preclinical promise	Inhibition of PI3K/Akt/mTOR pathway leading to decreased proliferation and enhanced apoptosis; blocks PI3K/Akt/mTOR pathway	• Tong, G. et al., *Frontiers in Pharmacology*, 2022.
Prostate cancer	GLP-1RAs reduce tumor volume in diabetic models	Reduced mortality in diabetic patients treated with GLP-1RAs	Modulates androgen-independent growth; anti-inflammatory and metabolic regulation	• Alhajahjeh, A. et al., *Cancers*, 2024.
Lung Cancer	Liraglutide suppresses EMT and oxidative damage in lung cancer models	Lower incidence observed in treated diabetic cohorts	Inhibits epithelial-mesenchymal transition (EMT), reduces oxidative stress and cellular senescence, regulates lung bronchial tone	• Sun, T. et al., *Redox Biology*, 2025.
Pancreatic cancer	Conflicting findings; some preclinical models show promotion of dysplasia	No definitive increase in risk shown in large human studies	Involves pancreatic enzyme stimulation and changes in ductal cell proliferation	• Nauck, M.A. et al., *Diabetes Care*, 2013.

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Association of Semaglutide With Tobacco Use Disorder in Patients With Type 2 Diabetes

Target Trial Emulation Using Real-World Data

William Wang; Nora D. Volkow, MD; Nathan A. Berger, MD; Pamela B. Davis, MD, PhD; David C. Kaelber, MD, PhD, MPH; and Rong Xu, PhD

Cumulative incidences of medical encounters for TUD diagnosis for the 7 target trial emulations of users of semaglutide compared with antidiabetes medications during a 12-month follow-up.

Each eligible patient in the matched groups was followed from the index event until the occurrence of the health care measure, death, loss to follow-up, or 12 months after the index event, whichever occurred first. DPP-4i = dipeptidyl-peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

Figure 3.

Wang W et al. *Annals of Internal Medicine*, 2024;177(8):1016–1027
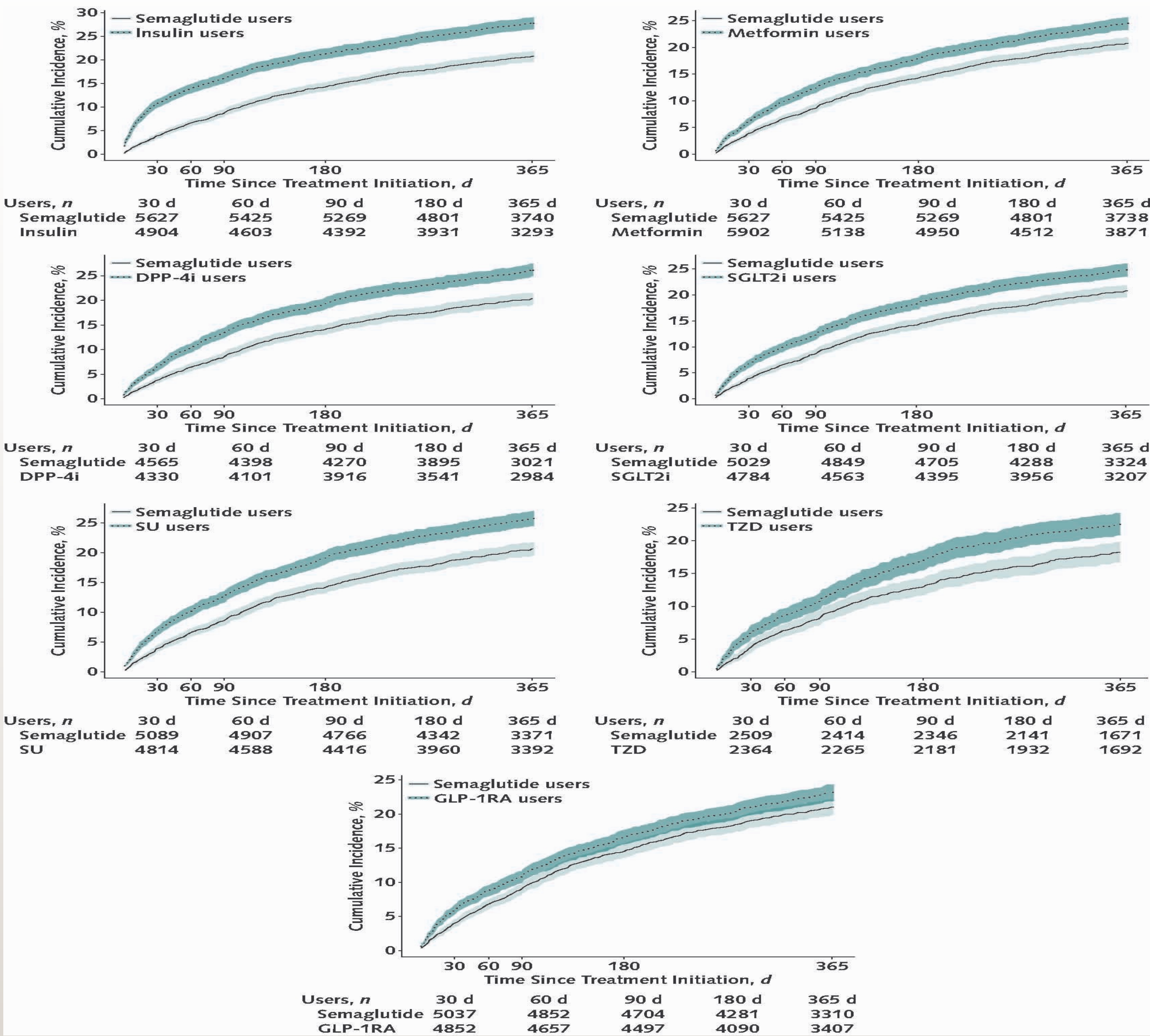
Less Invasive Diagnostic Tools

- Detection of ctDNA to determine the need for adjuvant therapy (colon cancer, aerodigestive cancers, breast cancer, bladder cancer)

- Testing for various genetic mutations in the tumor

- Potential use as early marker of therapy response and detection of relapse

- Detection of resistance mutation

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Increasing Access to Cancer Care

Most Important and Effective Options:

→ Quality generics and biosimilars

→ Price Discrimination, aka, Affordable Pricing or Price Tiering

Adequate Healthcare Funding:

Universal Coverage

Value-Based Insurance Design

→ Private Public Partnerships

Lopes. et al. Nature Rev Clin Oncol 2013

Here's to 25 more great DDHO meetings

Suresh Ramalingam named to

TIME100 Health2025

Sagar Lonial receives

Robert Kyle Lifetime Achievement Award

THANK YOU!

American University of Beirut