Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Early-Stage NSCLC: A Therapeutic Revolution 20 Years in the Making



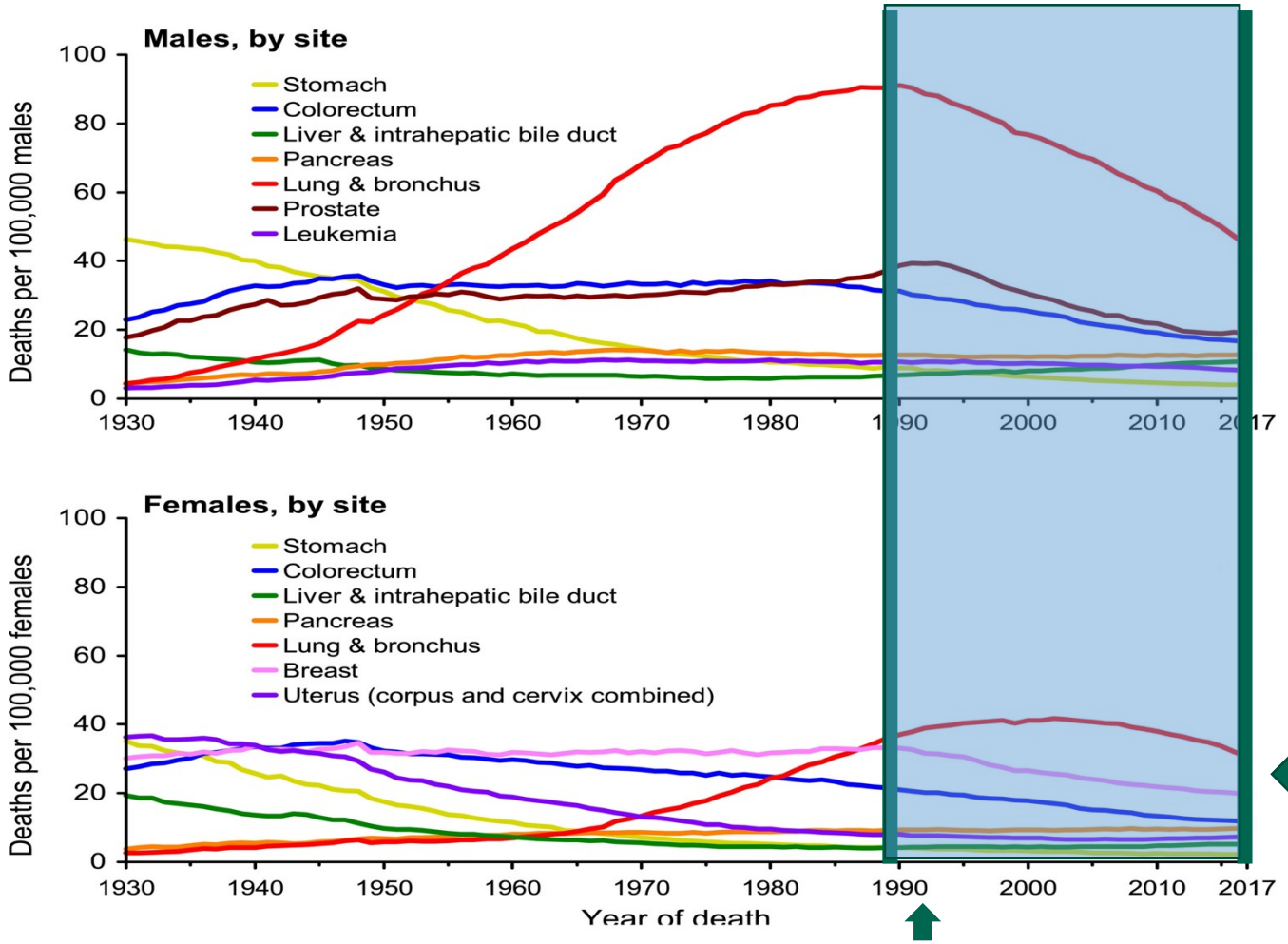
Roy S. Herbst MD, PhD
Director, Dartmouth Cancer Center
November 7, 2026

Dartmouth Health

DARTMOUTH GEISEL SCHOOL OF MEDICINE

Dartmouth Cancer Center

Lung Cancer Mortality



Mortality rates has declined by 51% since 1990 for men (26% since 2002 in women) due to reductions in smoking

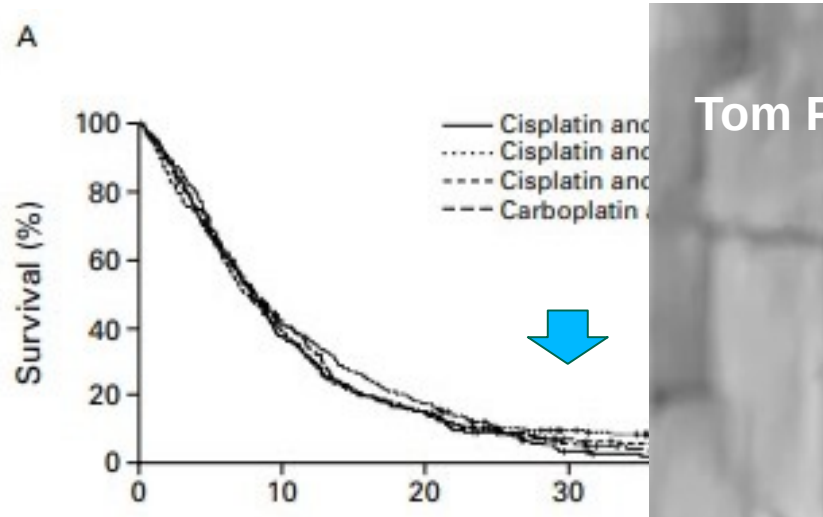
		Average annual percent change
Males	Incidence (2011-15) Mortality (2012-16)	-2.6 -4.3
Females	Incidence (2011-15) Mortality (2012-16)	-1.2 -3.1

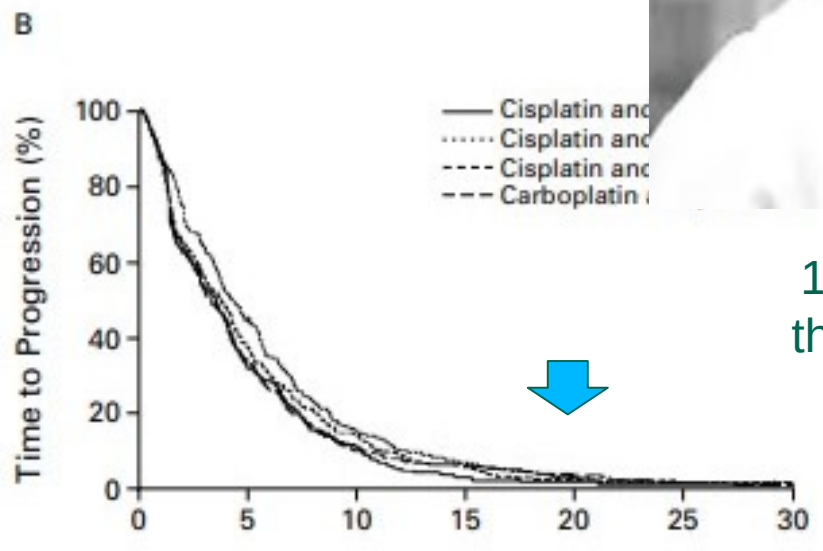
Incidence: age standardized, delay-adjusted rate
Mortality: age-standardized rate

Targeted Therapy for Lung Cancer with EGFR Inhbitors began in 1996/97

Siegel RL et al. Cancer statistics, 2020 CA CANCER J CLIN 2020;70:7–30; Annual Report to the Nation on the Status of Cancer. J Natl Cancer (2019) 111(12); Cancer Facts and Figures, American Cancer Society 2020;

Development of Modern Chemotherapy for lung cancer







Journal of Medicine

HERAPY REGIMENS FOR ADVANCED
LL LUNG CANCER

D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D.,
NMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D.,
ERATIVE ONCOLOGY GROUP

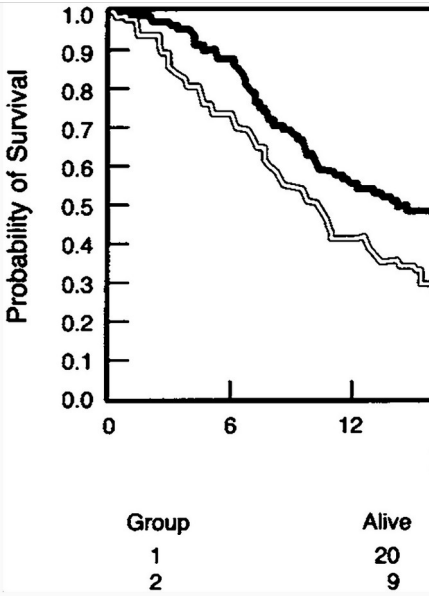
al 33%
val 7.9 months

1994- NCI Think Tank : Bring the Best Drugs to Early Stage Disease

ECOG 1594 Schiller et al, NEJM 2000

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Use of chemoradiation to treat early-stage disease



Stage III N

A RANDOMIZED TRIAL OF INDUCTION CHEMOTHERAPY PLUS HIGH-DOSE RADIATION VERSUS RADIATION ALONE IN STAGE III NON-SMALL-CELL LUNG CANCER

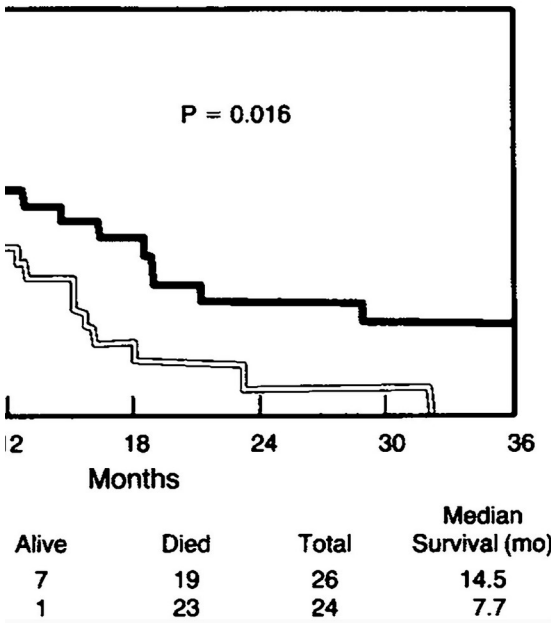
ROBERT O. DILLMAN, M.D., STEPHEN L. SEAGREN, M.D., KATHLEEN J. PROPERT, M.S., JULIO GUERRA, M.D., WALTER L. EATON, M.D., MICHAEL C. PERRY, M.D., ROBERT W. CAREY, M.D., EMIL F. FREI, III, M.D., AND MARK R. GREEN, M.D.

Abstract *Background.* For patients with locally or regionally advanced non-small-cell lung cancer radiation is the standard treatment, but survival remains poor. We therefore conducted a randomized trial to determine whether induction chemotherapy before irradiation improves survival.

Methods. All the patients had documented non-small-cell cancer of the lung with Stage III disease established by clinical or surgical staging. Eligibility requirements included excellent performance status, minimal weight loss, and visible disease on radiography. Patients randomly assigned to group 1 received cisplatin (100 mg per square meter of body-surface area given intravenously on days 1 and 29) and vinblastine (5 mg per square meter given intravenously on days 1, 8, 15, 22, and 29) and then began radiation therapy on day 50 (60 Gy over a 6-week period). Patients assigned to group 2 received the same radiation therapy but began it immediately and received no chemotherapy.

Results. The eligible patients in group 1 (n = 78) and group 2 (n = 77) were comparable in terms of age (median, 60 years), sex, performance status, histologic features, stage of disease, and completeness of radiation therapy. The median survival was greater for those in group 1 — 13.8 versus 9.7 months (P = 0.0066 by log-rank test). Rates of survival in group 1 were 55 percent after one year, 26 percent after two years, and 23 percent after three years, as compared with 40, 13, and 11 percent, respectively, in group 2. Those in group 1 had a higher incidence of serious infections requiring hospitalization (7 percent, vs. 3 percent in group 2) and severe weight loss (14 percent vs. 6 percent), but there were no treatment-related deaths.

Conclusions. In patients with Stage III non-small-cell lung cancer, induction chemotherapy with cisplatin and vinblastine before radiation significantly improves median survival (by about four months) and doubles the number of long-term survivors, as compared with radiation therapy alone. Since three quarters of the patients still die within three years, however, further improvements in systemic and local therapy are needed. (N Engl J Med 1990; 323:940-5.)



Alive	Died	Total	Median Survival (mo)
7	19	26	14.5
1	23	24	7.7

lenocarcinoma

Solid line - group 1
Open line - group 2

Adjuvant therapy for lung cancer



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non–Small-Cell Lung Cancer

The International Adjuvant Lung Cancer Trial Collaborative Group*

ABSTRACT

BACKGROUND

On the basis of a previous meta-analysis, the International Adjuvant Lung Cancer Trial was designed to evaluate the effect of cisplatin-based adjuvant chemotherapy on survival after complete resection of non–small-cell lung cancer.

METHODS

The writing committee for the International Adjuvant Lung Cancer Trial (IALT) (Rodrigo Arriagada, M.D., Instituto de Radiomedicina, Santiago, Chile; Bengt Bergman, M.D., Sahlgrenska Hospital, Göteborg, Sweden; Ariane Dunant, M.S., Thierry Le Chevalier, M.D., and Jean-Pierre Pignon, M.D., Ph.D.,

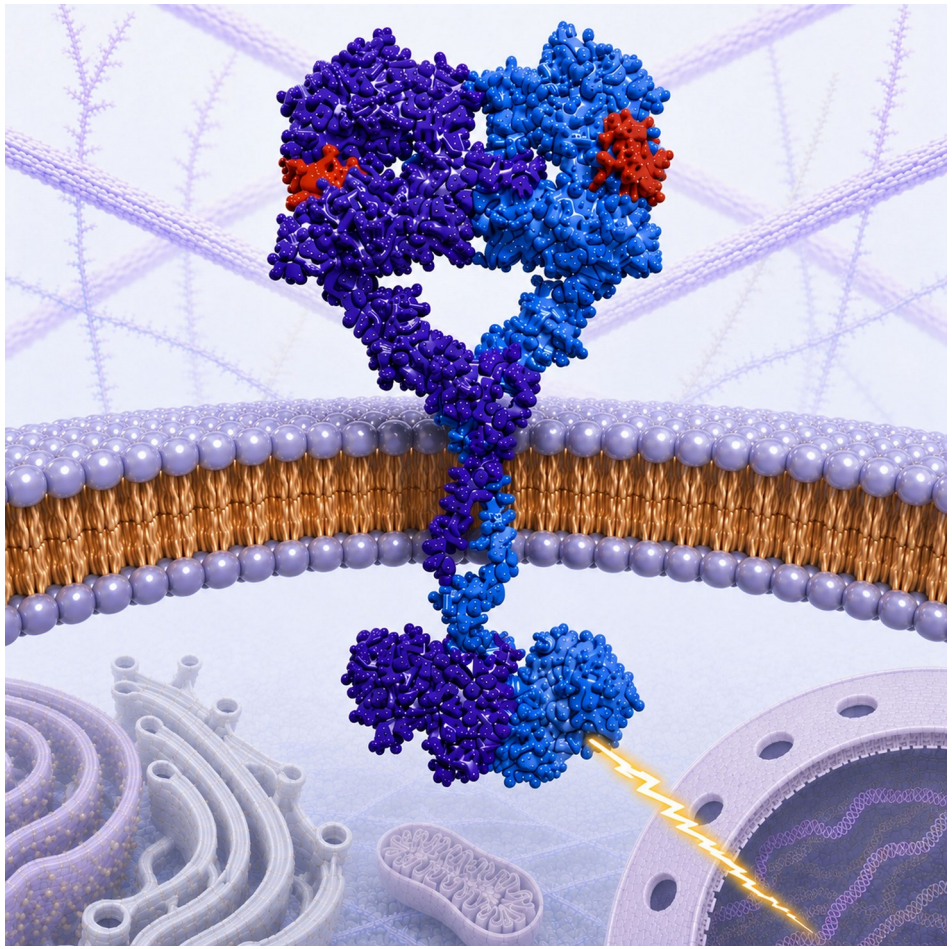
Rosenberg et al., Nature. 1965;205:698–699.
Kelland, Nat Rev Cancer. 2007 Aug;7(8):573-84

Progress in lung cancer in the last 20+ years

1. Targeted Therapy
2. Immunotherapy
3. Access



Discovery and Cloning of the EGFR Receptor : 40 plus Years ago



PHILOSOPHICAL TRANSACTIONS B

royalsocietypublishing.org/rstb

CC BY

Review

Cite this article: Schlessinger J. 2026 Molecular mechanisms governing the action of the epidermal growth factor receptor and receptor tyrosine kinases, a personal perspective. *Phil. Trans. R. Soc. B* **381**: 20240498.
https://doi.org/10.1098/rstb.2024.0498

Received: 13 March 2025
Accepted: 8 August 2025

One contribution of 14 to a discussion meeting issue 'Epidermal growth factor receptor after 40 years'.

Subject Areas:
biochemistry, biophysics, cellular biology, biotechnology, structural biology

Molecular mechanisms governing the action of the epidermal growth factor receptor and receptor tyrosine kinases, a personal perspective

Joseph Schlessinger†

Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06520, USA

JS, 0000-0002-5085-5969

I have been studying the mechanism of action of epidermal growth factor (EGF) receptor (EGFR), other receptor tyrosine kinases (RTKs) and their cellular signalling pathways for the past 45 years. A decade ago, I authored a review detailing the first two decades of research and highlighting critical milestones in this field (*Cold Spring Harb. Perspect. Biol.* 6, a008912 (2014) (doi:10.1101/cshperspect.a008912)). In the present article, I offer a personal perspective first on why and how I became interested in exploring the mechanism of action of EGF, and later about deciphering the modes of action of EGFR and other RTKs. These insights have also been pivotal in advancing the development of novel therapeutics.

This article is part of the discussion meeting issue 'Epidermal growth factor receptor after 40 years'.

The First Clinical Studies around 2000



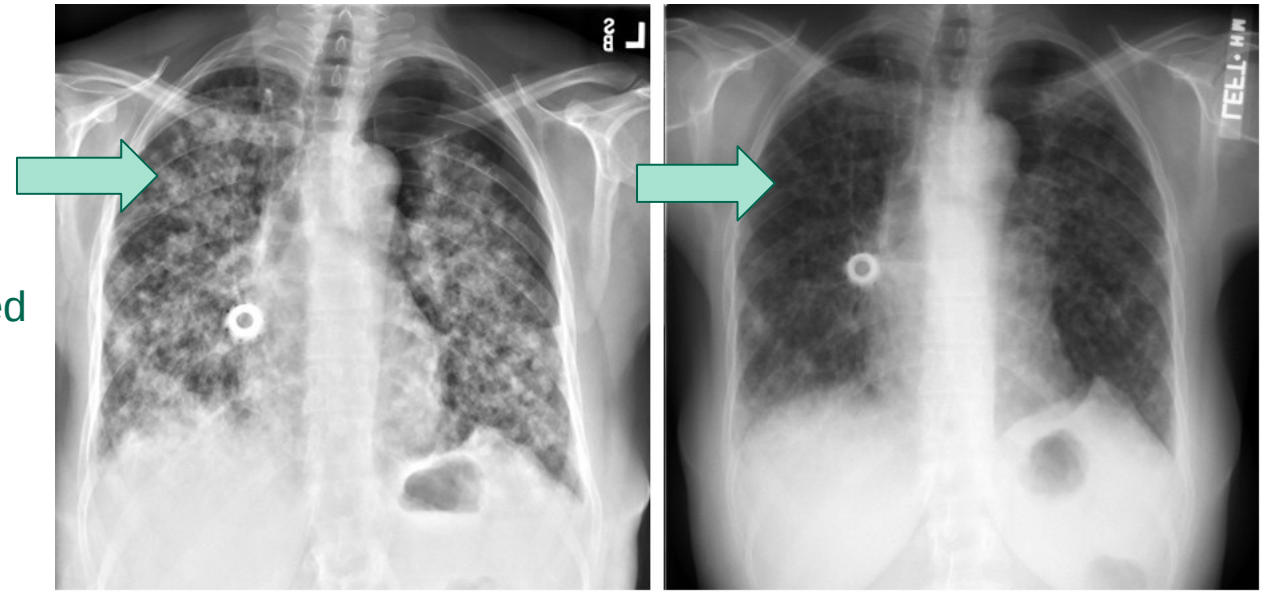
2003-4

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

EGFR inhibitors become standard of care for NSCLC

Gefitinib (known as Iressa 1996-1997) continuous phase I study (1998)

FDA Approved
May 2003



Baseline 1 Week Later

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 LoRusso

Herbst RS et al. *J Clin Oncol*. 2002;20(18):3815-3825.


You should have taken an EGFR Inhibitor!!
I miss my lung, Bob.

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Some of very first patients treated with Gefitinib (1997!)

The Boston Globe

A drug that works — for some

Researchers try to solve mystery of lung cancer medicine



GLOBE STAFF PHOTO/SUZANNE KREITER

The drug Iressa has allowed Kate Robbins to resume activities and spend precious time with her family.

By Raja Mishra
GLOBE STAFF

CONCORD — Early last year, Kate Robbins started her death journal. It was meant to guide her two children after lung cancer killed her. Robbins poured out advice: on dating, on morality, on family. The things a mother explains to her teens.

She also memorialized quiet, poignant moments. One rainy day, watching 10-year-old Hillary board the school bus, Robbins began weeping. She wrote simply, "You looked really pretty today." The kids would read the journal years later, she hoped, and feel their mother's love.

Advanced lung cancer patients rarely live one year. Robbins had months left. Then, last autumn, she began taking an experimental drug called Iressa, as did hundreds of other patients in the United States. Most continued to worsen.

But a small group, including Robbins, thrived. Doctors were stunned because lung cancer, the speediest and most widespread killer among cancers, had resisted virtually every treatment.

Now researchers are racing to unravel why Iressa — the first significant new lung cancer drug in a generation — appears to help only select patients. They are studying the DNA of patients for clues, hoping to develop a genetic screening test that would enable them to get the drug to the right people quickly. If they succeed, a small portion of lung cancer victims would get extra years of life. Given that 157,000 Americans die annually from the disease, the impact could be considerable.

The effort is part of an emerging area of medicine seeking to genetically match patients to drugs. Such personally-tailored medicating promises to be a hallmark of 21st-century health care.

Robbins's doctor, Thomas Lynch of Massachusetts General Hospital, said he has other lung cancer patients who also are doing well as many as three years after starting on Iressa.

"I've been treating this cancer since 1989, 500 patients a year, and this is the most significant development I've seen," he said.

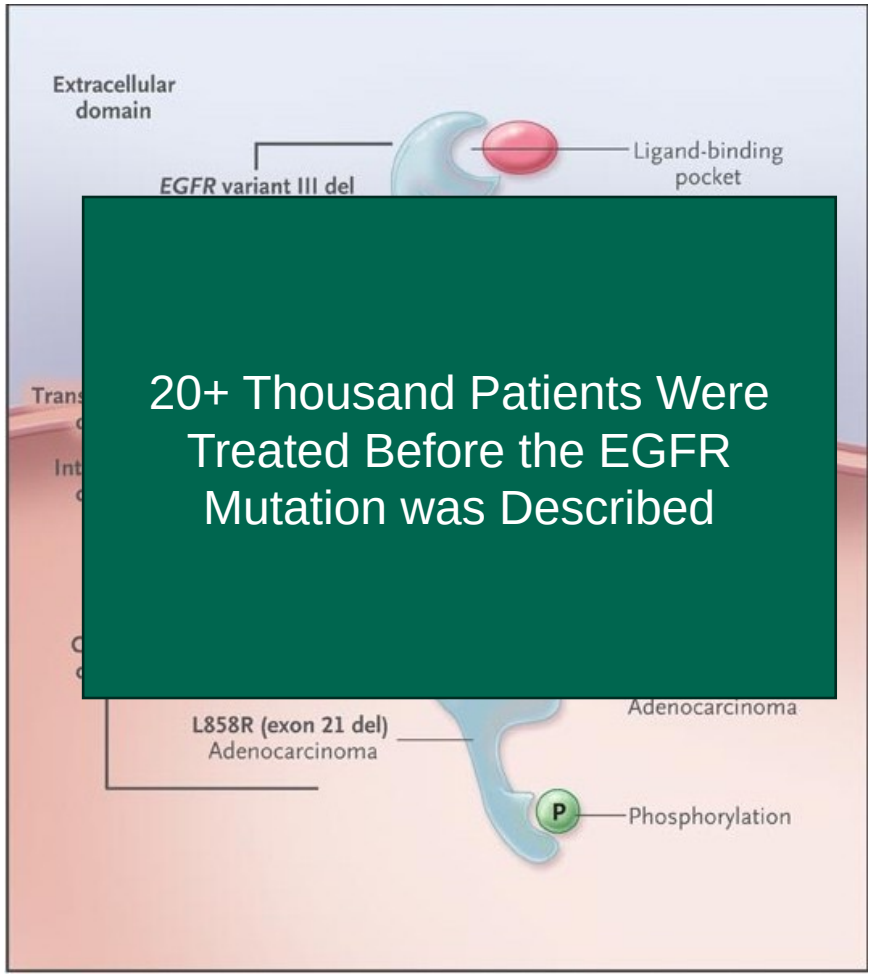
Last week, Robbins, 46, had her first checkup in five months: Out of 16 once-bulging tumors scattered throughout her organs, there appeared to be none.

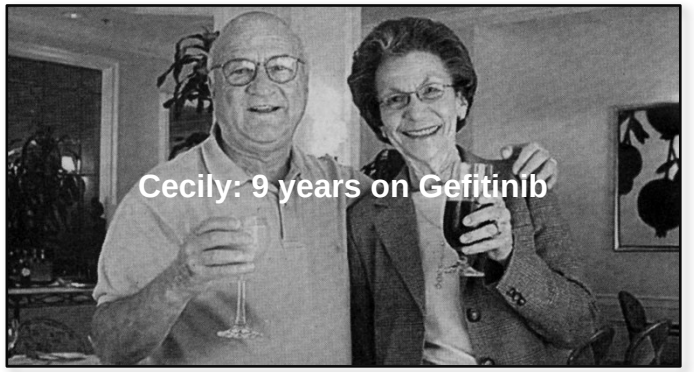
"It's the most amazing thing," she said.

Robbins has big eyes and a round, girlish face. She talks with energy and enthusiasm, her Boston accent occasionally poking through. Robbins was raised in Chelmsford and moved to Concord from rural Connecticut four months ago to be near MGH. She worked as a nurse but stopped to raise her children, Tom, now 13, and Hillary, 11. Her husband, Mark, is a cancer doctor at Emerson Hospital.

Attentive to her health, Robbins was an unlikely candidate for lung cancer in her 40s. About 85 percent of the disease's victims are current or former smokers, but Robbins has never smoked. She rarely drinks, and, moved by the suffering of animals, became a vegetarian at age 10. But one day in January 2002, she developed an intense headache. "I thought it was post-holiday stress," she said.

Effect of Deletions and Mutations in the EGFR on Disease Development and Drug Targeting: 2004






A SPECIAL REPORT PERSONAL HEALTH

PERSONAL JOURNAL.

THE WALL STREET JOURNAL

TUESDAY, FEBRUARY 11, 2003

Why *Curing* Your Cancer May Not Be the Best Idea

More doctors and patients are starting to view cancer as a chronic illness—something to be treated, not cured

By Tara Parker-Pope

IN THE UNRELENTING QUEST to cure cancer, are patients missing out on the chance to live longer?

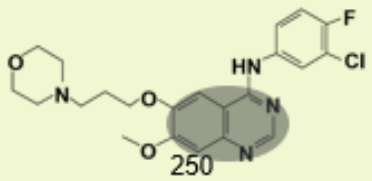
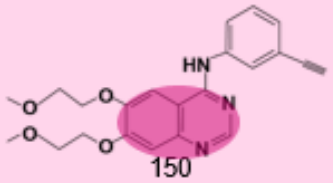
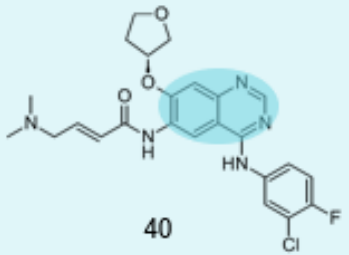
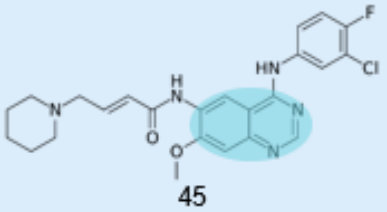
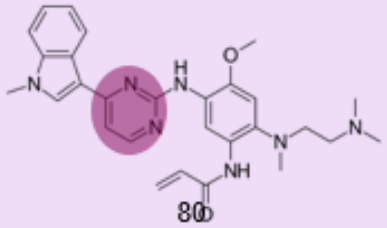
Baltimore oncologist Deborah Armstrong remembers the first time she treated patients with recurrent ovarian cancer during an early clinical trial for the drug Taxol. Some women, all of whom had a bleak prognosis to start with, weren't getting better in the trial. But they weren't getting any worse either.

Even so, many of those patients quit the study.

Tara Parker-Pope Wall Street Journal 2003

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Profiles of EGFR-TKIs

	First generation		Second generation		Third generation
Drug	**Gefitinib[1,2]**	**Erlotinib[3,4]**	**Afatinib[5–8]**	**Dacomitinib[9-11]**	**Osimertinib[12-15]**
Approved 1L	Yes	Yes	Yes	Yes	Yes
EGFR inhibition	Reversible	Reversible	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible
Primary Target	wt-EGFR, EGFR: ex19del, L858R	Wt-EGFR, EGFR: ex19del, L858R	wt-EGFR, EGFR: ex19del, L858R, wt-HER2, HER2 amp, HER4[a]	wt-EGFR, EGFR: ex19del, L858R, wt-HER2, mutant-HER2, HER2 amp, HER4[a]	EGFR: L858R, ex19del, T790M
Chemical structure (backbone highlighted)					
Recommended dose, mg/day	250	150	40	45	80
Bioavailability	59%	59%	Absolute bioavailability in humans is unknown	80%	70%

[a]Preclinical targeting of T790M. Table adapted from Sullivan & Planchard. Front Med (Lausanne) 2017;3:76.

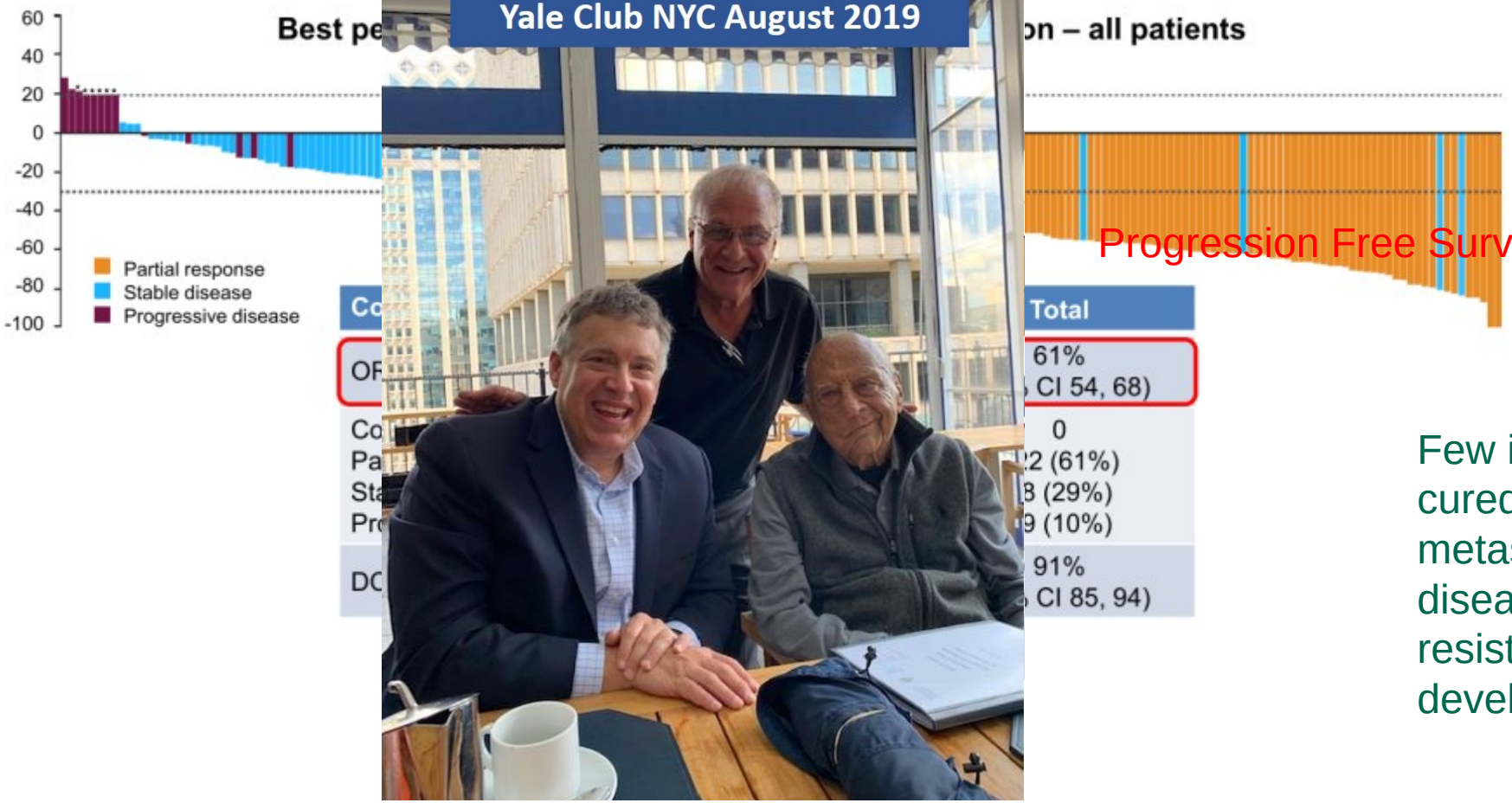
References in slide notes.

Dartmouth Health

DARTMOUTH GEISEL SCHOOL OF MEDICINE

Dartmouth Cancer Center

Osimertinib response in pre-treated EGFR+ NSCLC patients with T790M mutation



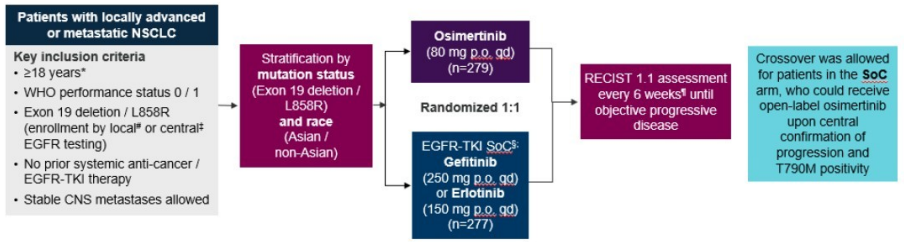
Few if any are cured with metastatic disease -- resistance develops

Yang JC, et al. Presented at WCLC 2015. Abstract 943.

Dartmouth | DARTMOUTH GEISEL SCHOOL OF | Dartmouth Cancer Center

FLAURA: Study Design

Phase III, Double-Blind, Randomized Trial of Osimertinib as First-Line Therapy



- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

FLAURA data cut-off: 12 June 2017; NCT02296125.

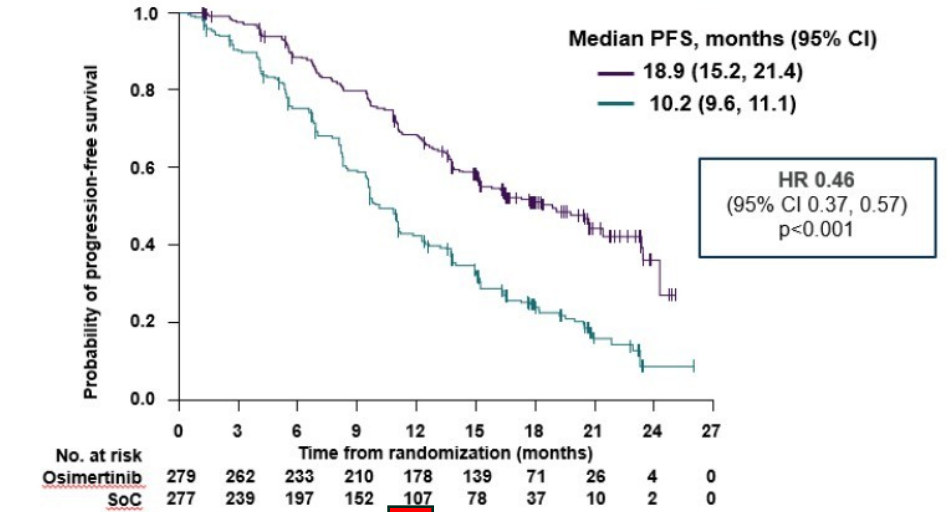
*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months

CNS = central nervous system; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PFS = progression-free survival; p.o. = orally; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; qd = once daily; SoC = standard-of-care; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.

Soria J-C et al. *N Engl J Med*. 2018;378:113-125.

Progression Free Survival

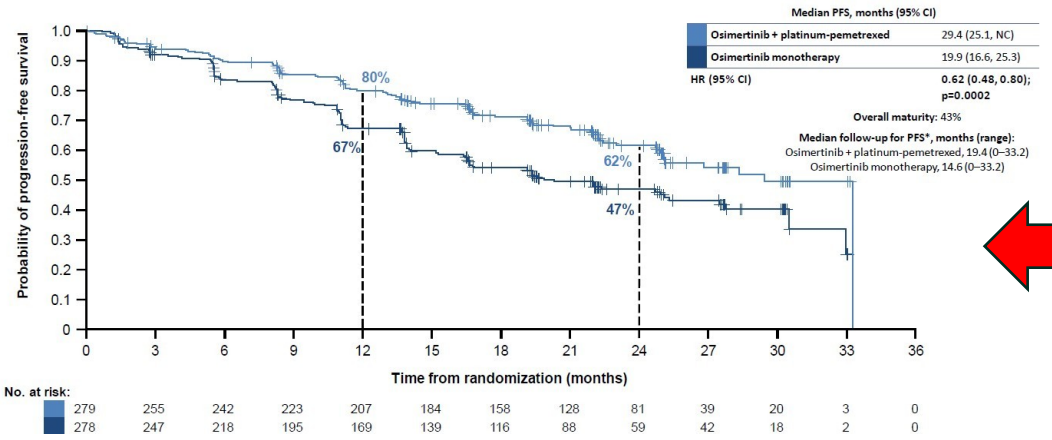
342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)

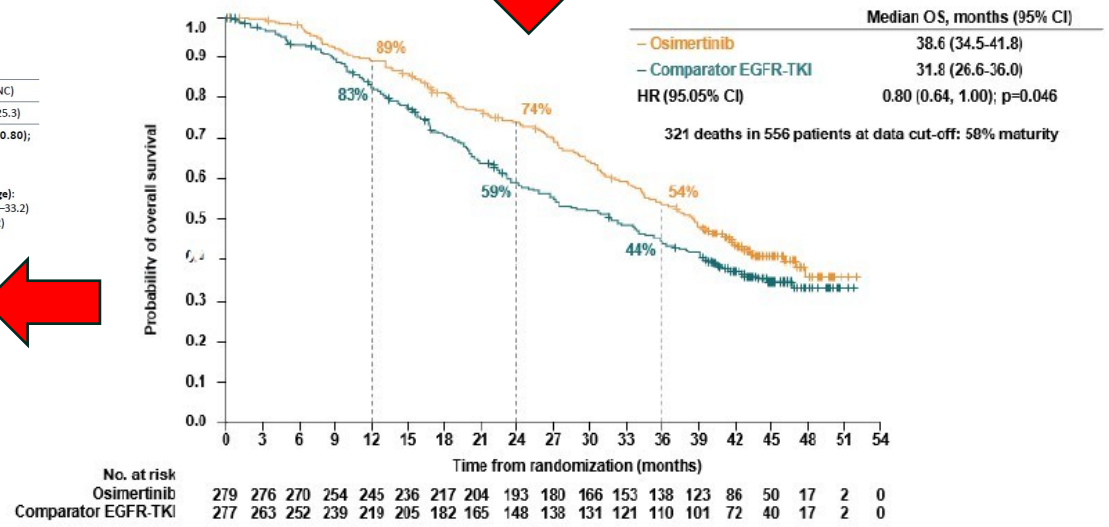


Addition of Chemotherapy: FLAURA 2

Progression-free survival per BICR

- Median PFS was improved by ~9.5 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



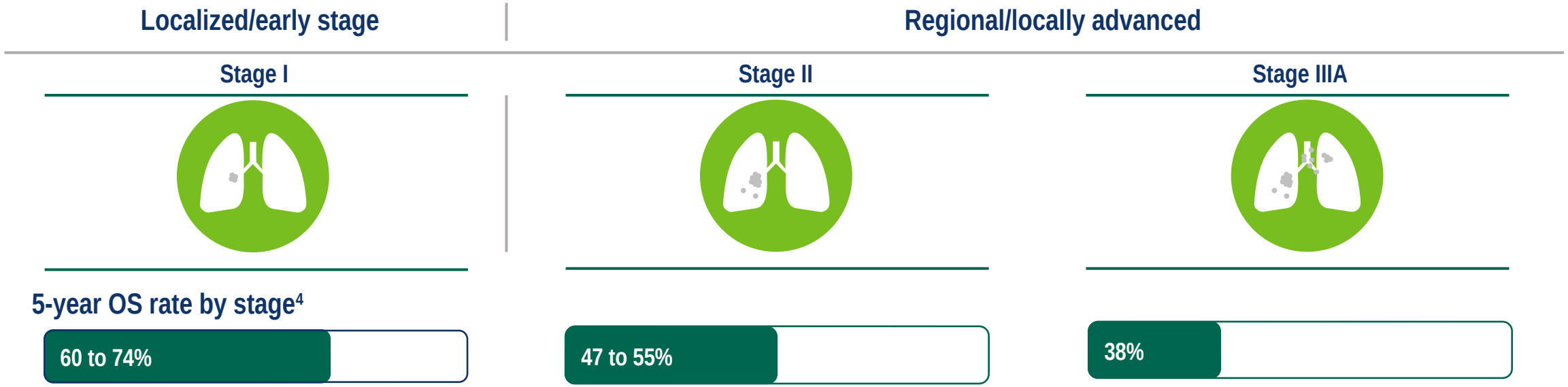


Overall Survival

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

ADAURA: bringing targeted therapy to early-stage disease

- Surgery is the primary treatment for patients with early stage NSCLC[1]
- Adjuvant cisplatin-based chemotherapy is recommended for patients with resected stage II⊣IIIA NSCLC and select patients with stage IB disease[2]
  - This recommendation was based on results from large randomized trials and meta analyses, showing a 5-year OS benefit with adjuvant chemotherapy in patients with early stage NSCLC[3]
- Overall, disease recurrence or death following surgery and adjuvant chemotherapy remains high across disease stages[4]



1. Chansky et al. J Thorac Oncol 2017;12:1109-21; 2. Kris et al. J Clin Oncol 2017;35:2960-74; 3. Chansky et al. J Thorac Oncol 2017; 4. Pignon et al. J Clin Oncol 2008;26:3552-9. Detterbeck, Boffa, Kim, Tanoue Chest. 2017 Jan;151(1):193-203.

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

ADAURA phase III double-blind study design

Patients with completely resected stage IB, II, IIIA* NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
18 years (Japan / Taiwan: ≥20)
WHO PS 0 / 1
Confirmed primary non-squamous NSCLC
Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins
Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration:
3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: W12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years , then yearly

Endpoints

- **Primary**: DFS, by investigator, in stage II⊣IIIA patients (powered for a HR of 0.7)
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, overall survival, safety, quality of life, pharmacokinetics

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
  - **The study completed enrollment and all patients were followed up for at least 1 year**

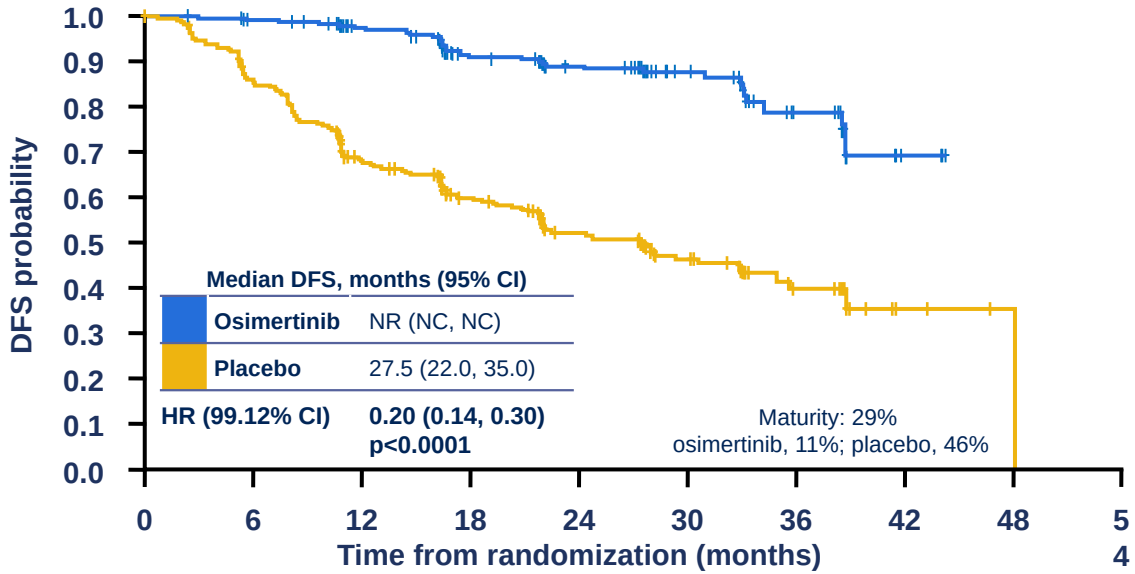
Wu, et al (Herbst). NEJM Sept 2020 DOI: 10.1056/NEJMoa2027071

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

- Adjuvant osimertinib has demonstrated a highly statistically significant[1,2] and clinically meaningful improvement in DFS in completely resected, EGFRm NSCLC vs placebo in both the primary (stage II–IIIA) and overall (IB–IIIA) populations, along with a tolerable safety profile[1–4]

ADAURA primary DFS analysis[1,2] (stage IB–IIIA)*

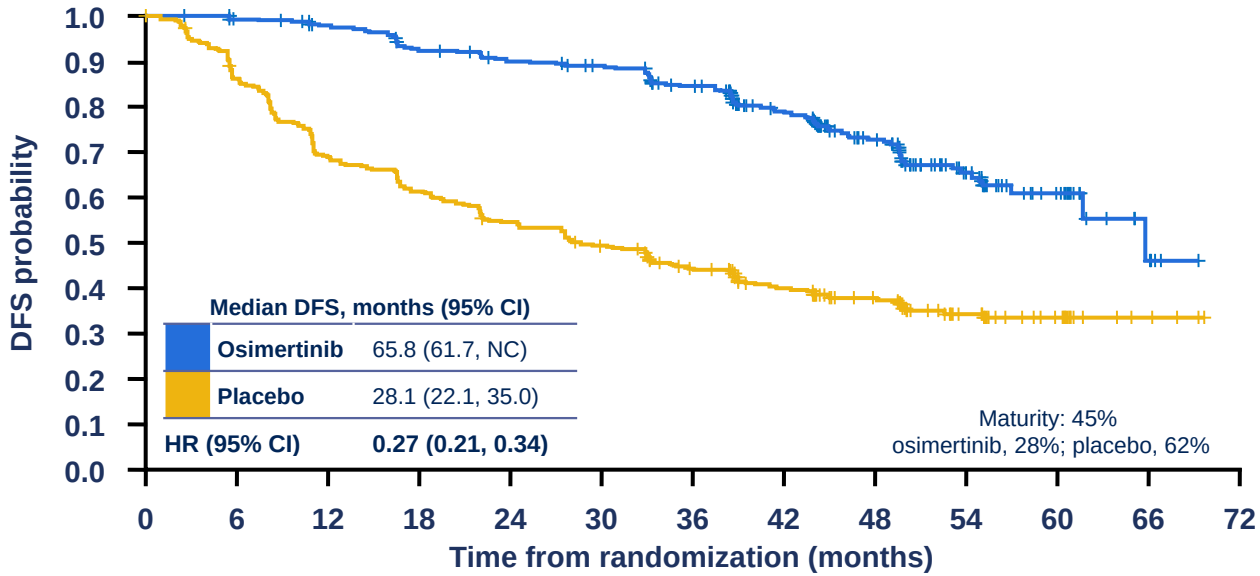
Published in NEJM October 2020



No. at risk										
Osimertinib	339	313	272	208	138	74	27	5	0	-
Placebo	343	287	207	148	88	53	20	3	1	0

ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†

Published in JCO January 2023



No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

*Data cut-off: January 17, 2020. †Data cut-off: April 11, 2022.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5; 3. Herbst et al. J Clin Oncol 2023;41:1830–1840; 4. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47.

CI, confidence interval; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; *JCO*, Journal of Clinical Oncology; *NEJM*, New England Journal of Medicine; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

Adjuvant Osimertinib has significantly improved CNS DFS

- CNS metastases are a poor prognostic factor among patients with NSCLC, associated with deterioration in quality of life[1]

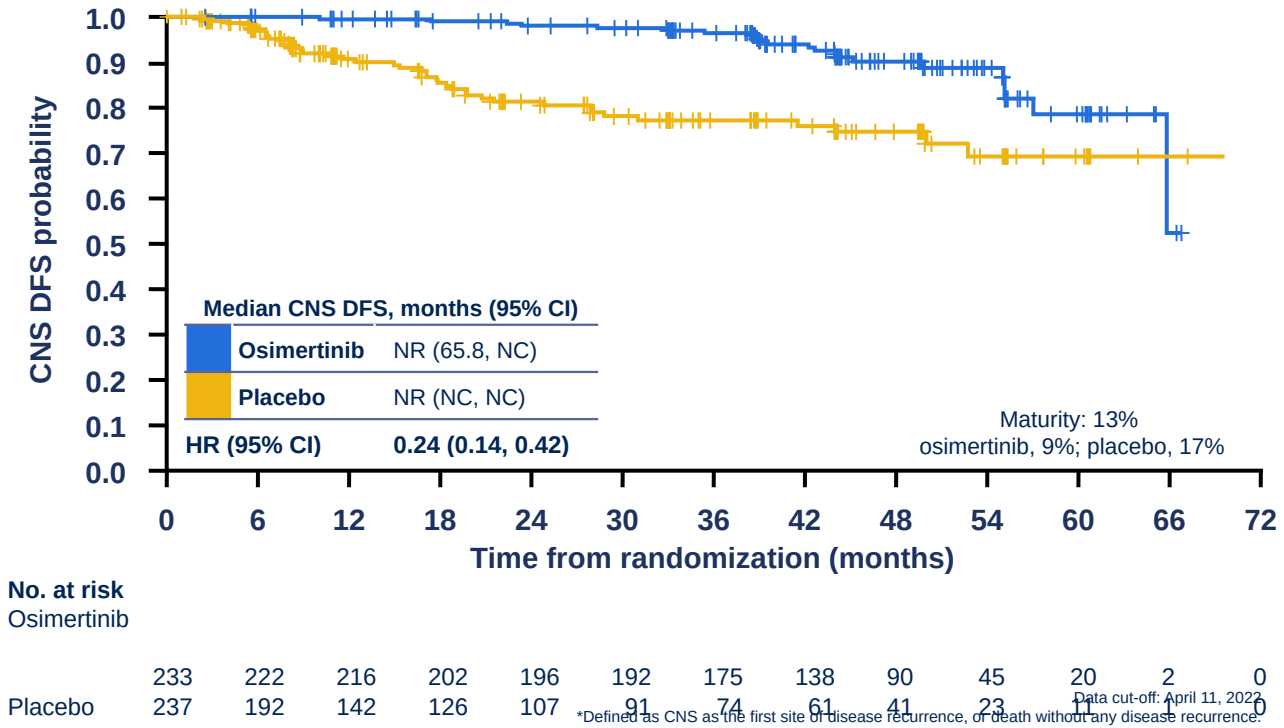
Improved CNS efficacy with Osimertinib treatment



- Osimertinib has shown greater penetration of the blood-brain barrier and higher exposure in the brain, compared with other EGFR-TKIs[2–4]
- Adjuvant Osimertinib demonstrated CNS DFS benefit vs placebo in both the stage II⊣IIIA and IB⊣IIIA populations; in the updated CNS DFS analysis, 63 patients (Osimertinib n=22, placebo n=41) had CNS DFS events[5,6]*

ADAURA updated CNS DFS analysis[5,6] (stage II⊣IIIA)

Published in JCO January 2023



Data cut-off: April 11, 2022

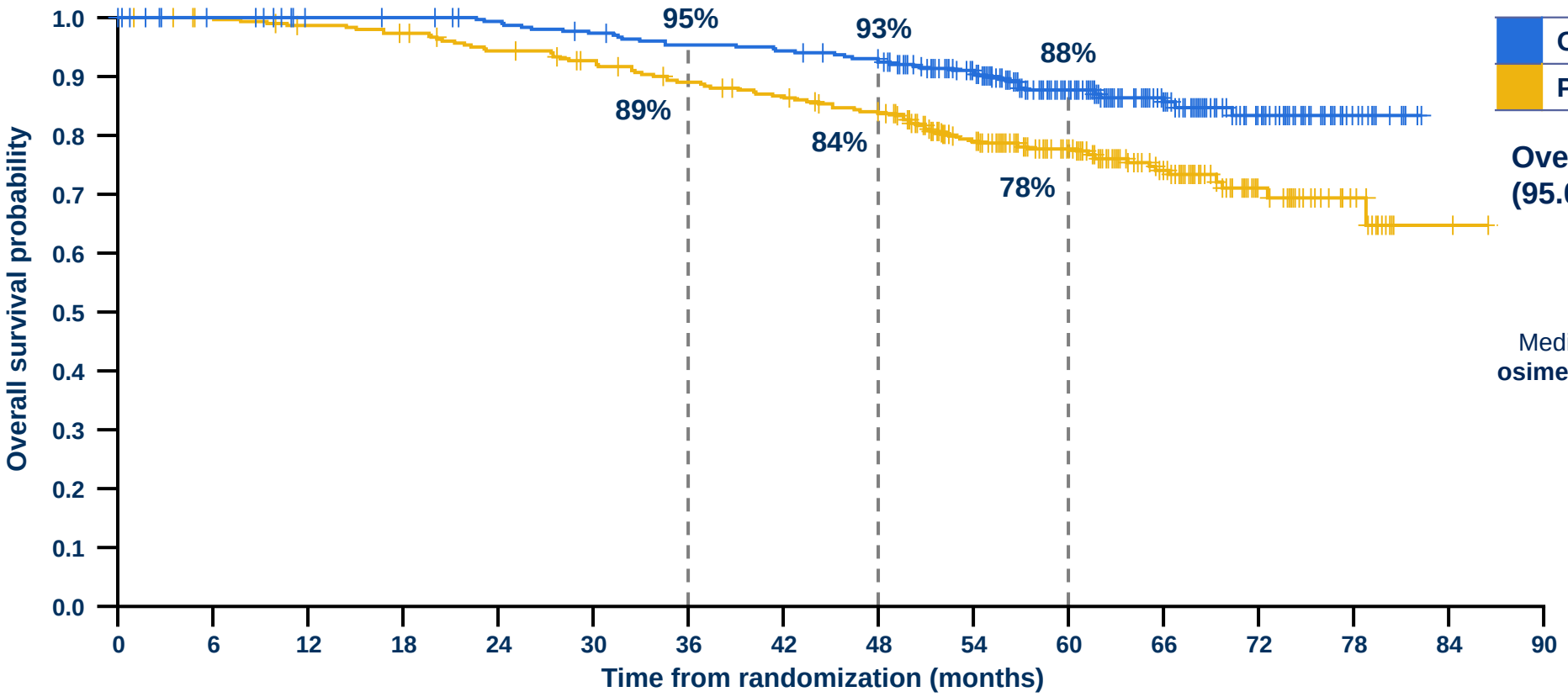
*Defined as CNS as the first site of disease recurrence, or death without any disease recurrence.

1. Peters et al. Cancer Treat Rev 2016;45:139–162; 2. Colclough et al. Eur J Cancer 2016;69:S28; 3. Ballard et al. Clin Cancer Res 2016;22:5130–5140; 4. Vishwanathan et al. Cancer Res 2018; 78:CT013; 5. Herbst et al. J Clin Oncol 2023;41:1830–1840; 6. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47.

CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; HR, hazard ratio; *JCO*, Journal of Clinical Oncology; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Overall survival: overall population (stage IB / II / IIIA)



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

No. at risk

Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

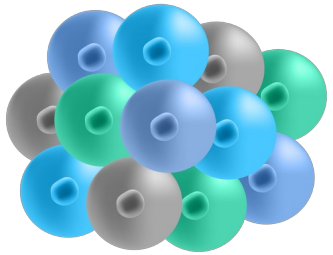
Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

CI, confidence interval; HR, hazard ratio; OS, overall survival

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

ADAURA translational analyses

- Rare tumor cells can persist during treatment and lead to relapse, often after treatment completion[1,2]
- Understanding tumor biology and its response to treatment may help to further personalize treatment in this setting
- Tumor and ctDNA molecular profiling for analyses of MRD in ADAURA may provide more information on persistence and resistance mechanisms, facilitating future research



Ongoing osimertinib studies in resectable EGFRm NSCLC

Phase III NeoADAURA study (NCT04351555)
Neoadjuvant osimertinib with or without CT vs CT alone in resectable EGFRm stage II–IIIB N2 NSCLC

Phase III ADAURA2 study (NCT05120349)
Adjuvant osimertinib vs placebo in resected EGFRm stage IA NSCLC

Phase II TARGET study (NCT05526755)
5-year adjuvant osimertinib in resected EGFRm stage II–IIIB NSCLC

1. Shen et al. Cell 2020; 183:860–874; 2. Oren et al. Nature 2021;596:576–582.

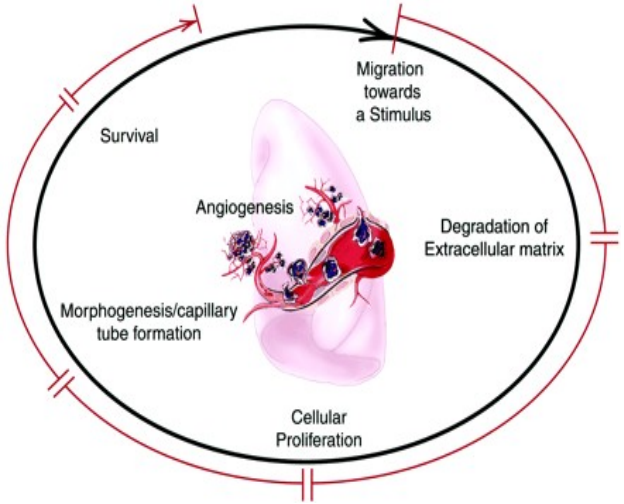
CT, chemotherapy; ctDNA, circulating tumor deoxyribonucleic acid; EGFRm, epidermal growth factor receptor-mutated; MRD, minimal residual disease; NSCLC, non-small cell lung cancer; OS, overall survival

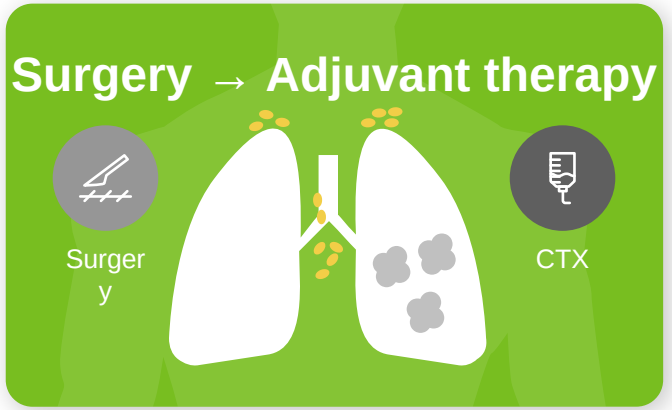
Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

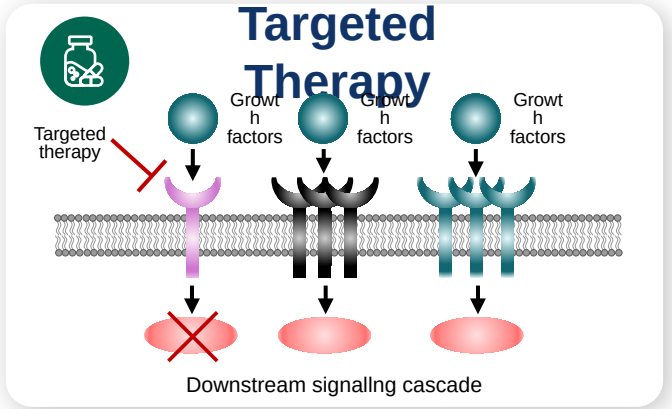
Biology has spoken: bringing targeted therapy to early disease

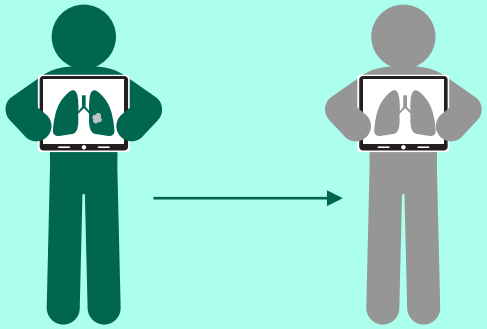


Isaiah J. Fidler, DVM, PhD, FAACR









Best therapies earlier in disease course for the most enhanced patient benefit

Prevent metastasis



Herbst R, Fidler M. CCR 2000.

nature medicine

Article

https://doi.org/10.1038/s41591-025-03577-y

Molecular residual disease analysis of adjuvant osimertinib in resected *EGFR*-mutated stage IB–IIIA non-small-cell lung cancer

Received: 9 September 2024

Accepted: 7 February 2025

Published online: 17 March 2025

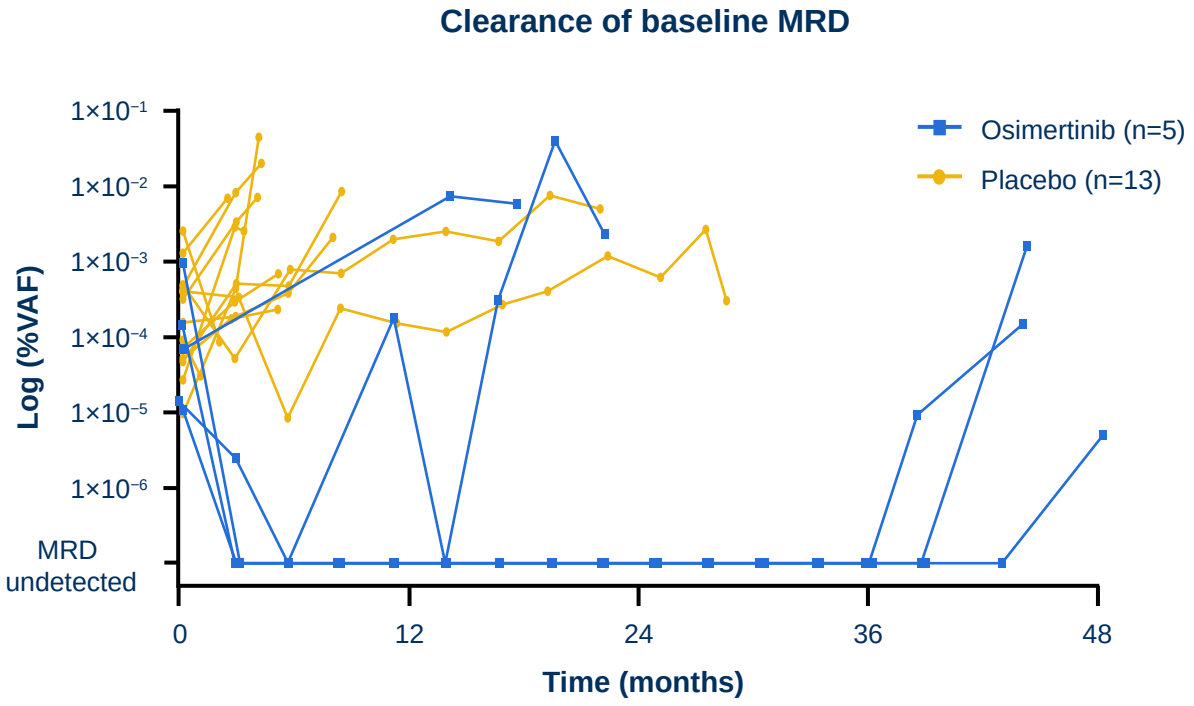
Check for updates

A list of authors and their affiliations appears at the end of the paper

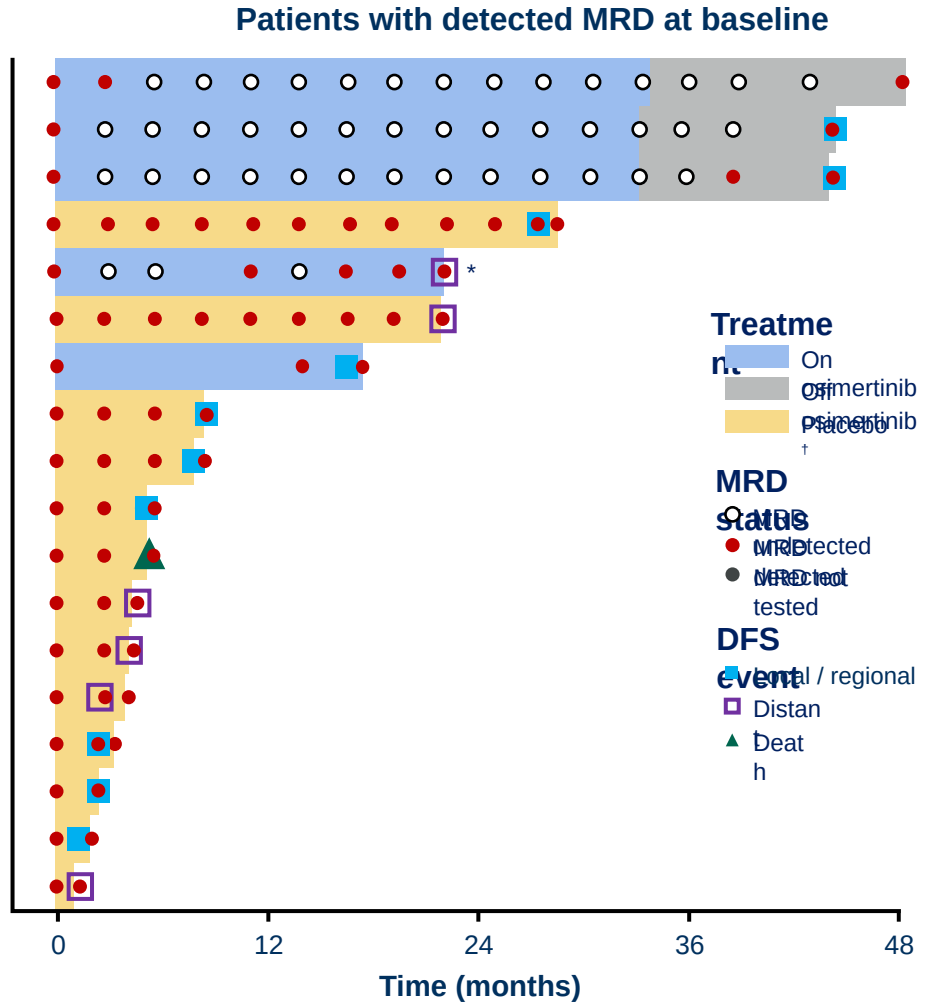
Osimertinib—a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor—is recommended as adjuvant therapy for resected stage IB–IIIA epidermal growth factor receptor-mutated non-small-cell lung cancer, based on significant disease-free survival (DFS) and overall survival

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Detected MRD at baseline was associated with poor outcomes



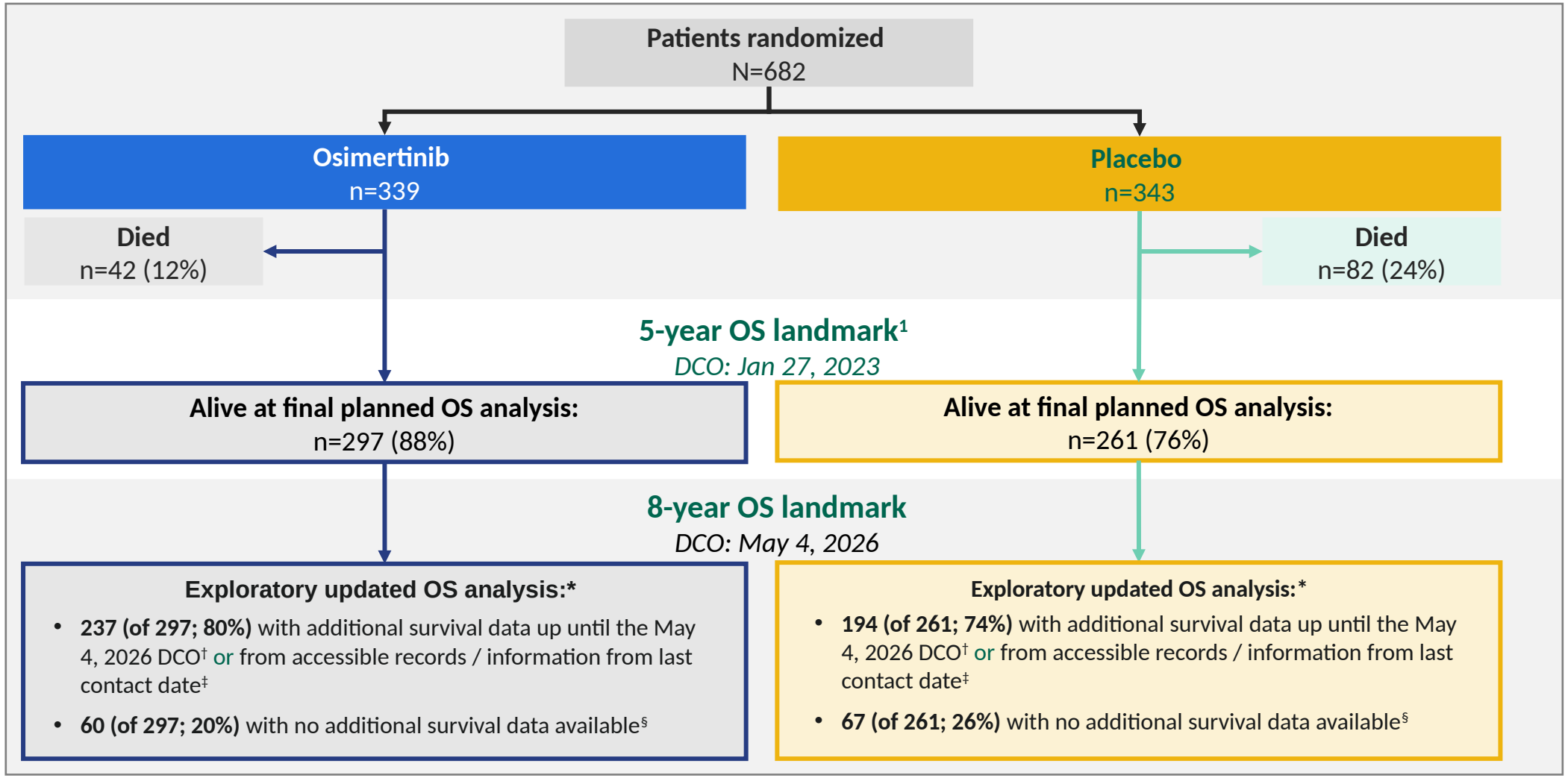
- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD



*CNS only DFS event. †Patients received placebo for up to 36 months.

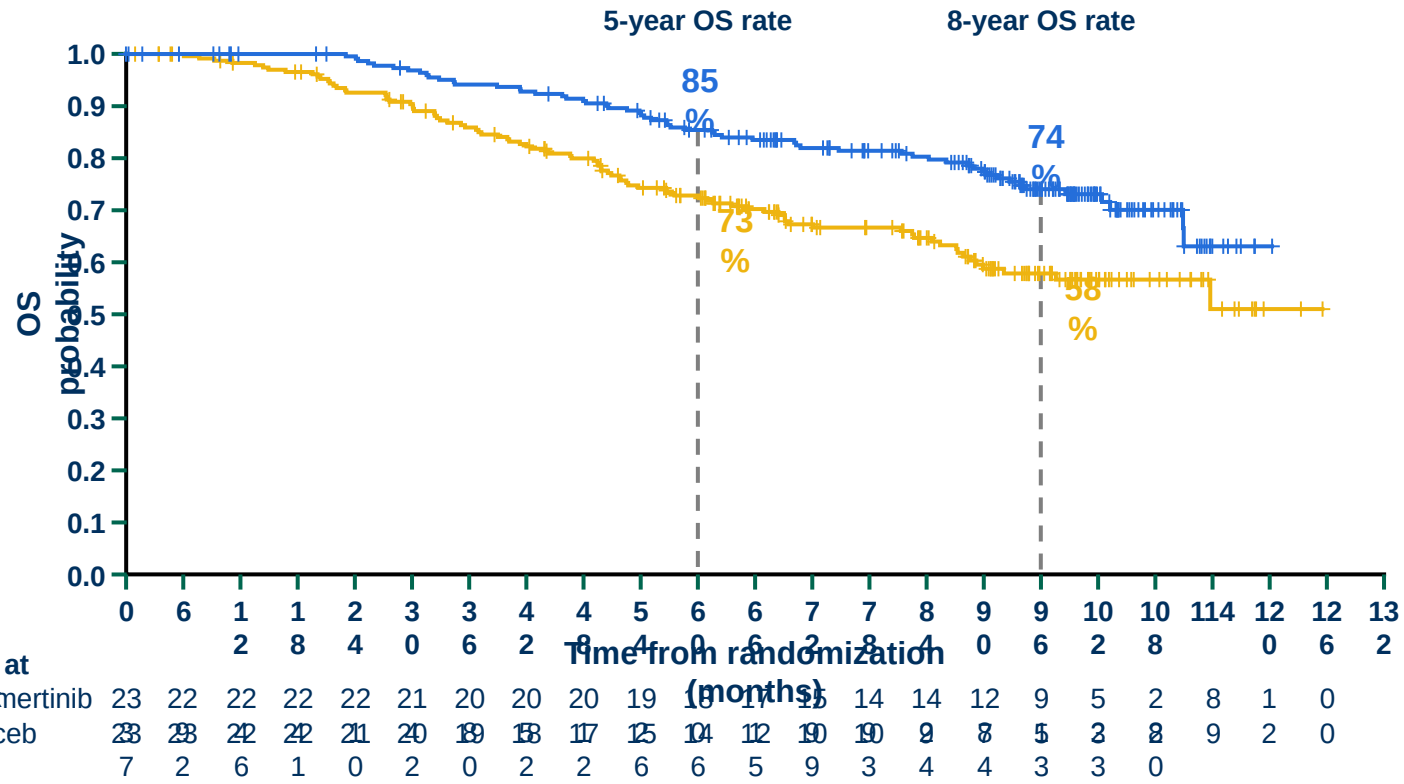
CNS, central nervous system; DFS, disease-free survival; MRD, molecular residual disease; VAF, variant allele frequency

Adaura Patient disposition



Disease progression data were not collected after Apr 11, 2022; at this date, among patients with additional survival data, 302/431 (70%) were disease free (osimertinib, 193/237 [81%]; placebo, 109/194 [56%]). Among those without additional survival data, 64/127 (50%) were disease free (osimertinib, 46/60 [77%]; placebo, 18/67 [27%]). *Following a protocol amendment (Aug 2023), additional consent was requested from patients for yearly follow-up after the final planned OS analysis until the current DCO (May 4, 2026). †Patients who provided additional consent were followed yearly for survival after the final planned OS analysis. ‡If no known date of death was available, patients were censored at the last date they were known to be alive after the final planned OS DCO. §Patients remained censored at their last known alive date, survival time unchanged from the final planned OS analysis DCO (Jan 27, 2023). 1. Tsuboi et al. N Engl J Med 2023;38:137–147. DCO, data cut-off; OS, overall survival.

Osimertinib continued to show an OS benefit versus placebo in the primary population (stage II–IIIA disease)



8-year OS rate, % (95% CI)	
Osimertinib (n=233)	74 (67, 80)
Placebo (n=237)	58 (50, 65)

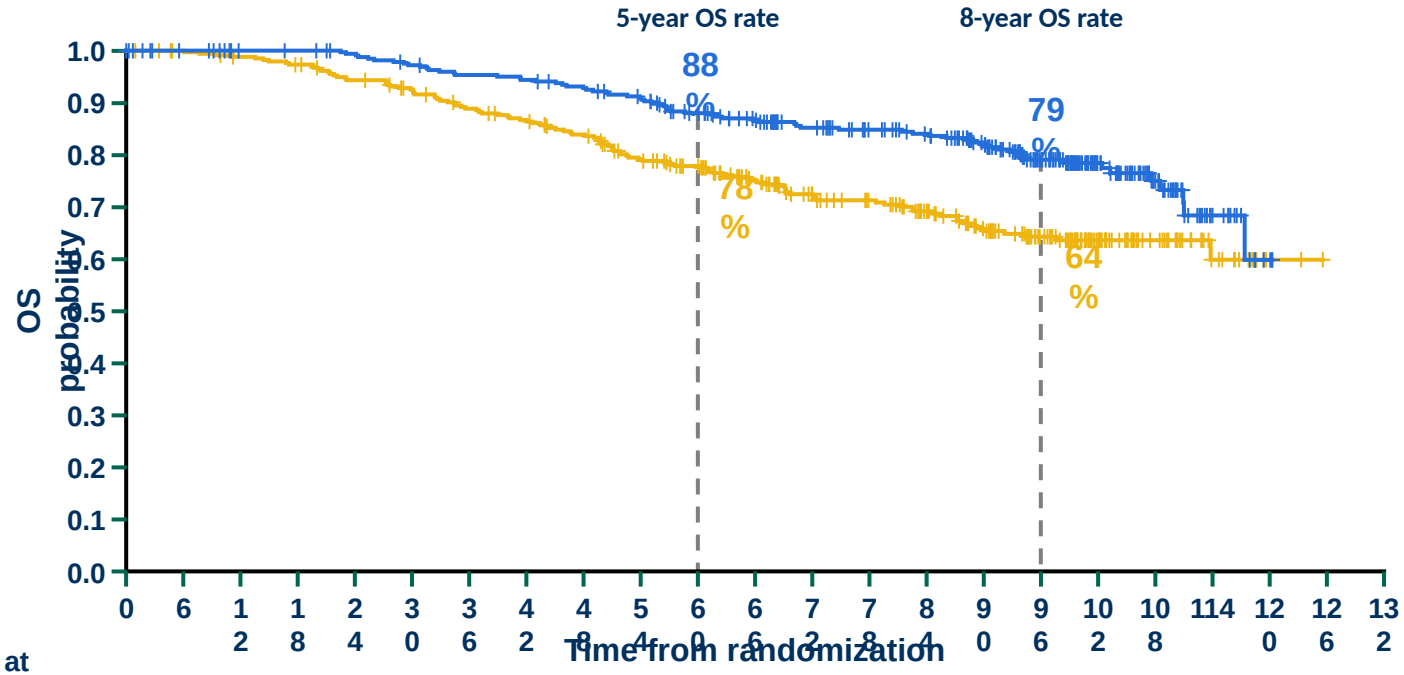
OS HR (95% CI) **0.53 (0.38, 0.75)**

Maturity: 30%
osimertinib 24%; placebo 36%

Median follow-up for OS (all patients):
osimertinib 92.0 months; placebo 68.5 months

DCO: May 4, 2026. Tick marks indicate censored data. *Among patients who were alive at the planned final OS analysis (DCO: Jan 27, 2023), updated survival data were collected through yearly follow-up until the current DCO (May 4, 2026; additional consent provided) and from accessible records / information from last contact date after the final planned OS DCO. Patients for whom no additional long-term OS data were available remained censored at their last known alive date, survival time unchanged from the final planned OS analysis DCO (Jan 27, 2023). CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival.

Osimertinib continued to show an OS benefit versus placebo in the overall population (stage IB–IIIA disease)



8-year OS rate, % (95% CI)	
Osimertinib (n=339)	79 (74, 83)
Placebo (n=343)	64 (58, 70)

OS HR (95% CI)	**0.52 (0.39, 0.71)**

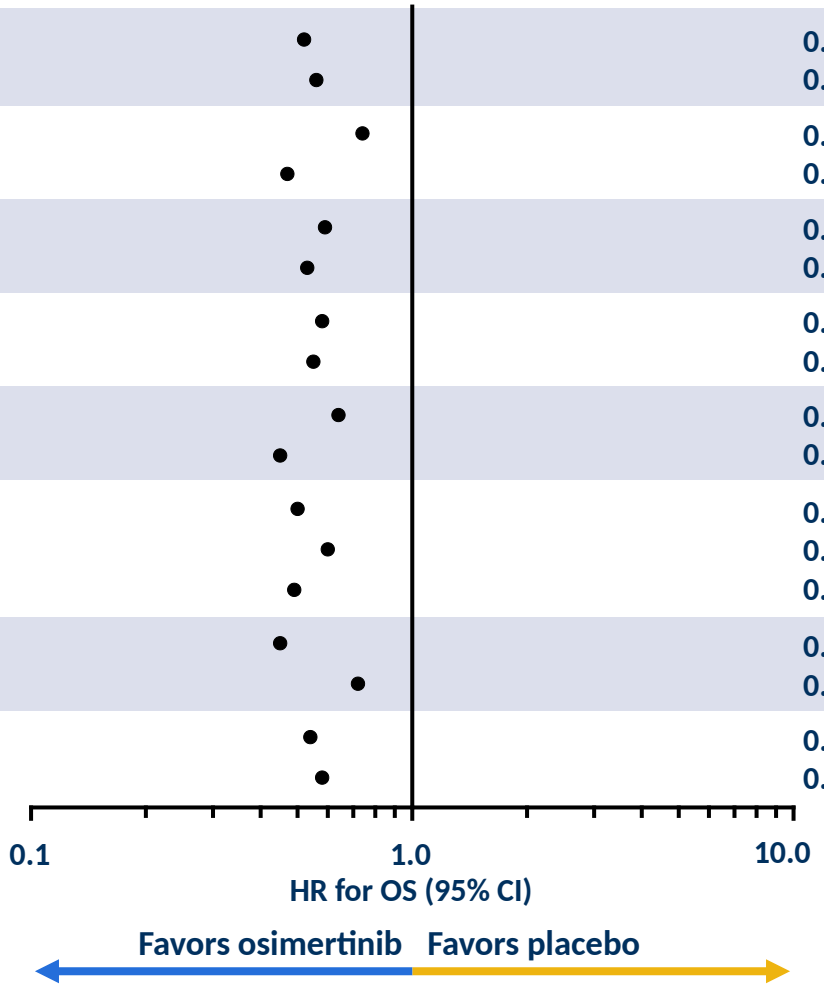
Maturity: 26%
osimertinib 20%; placebo 31%

Median follow-up for OS (all patients):
osimertinib 93.3 months; placebo 79.6 months

DCO: May 4, 2026. Tick marks indicate censored data. *Among patients who were alive at the planned final OS analysis (DCO: Jan 27, 2023), updated survival data were collected through yearly follow-up until the current DCO (May 4, 2026; additional consent provided) and from accessible records / information from last contact date after the final planned OS DCO. Patients for whom no additional long-term OS data were available remained censored at their last known alive date, survival time unchanged from the final planned OS analysis DCO (Jan 27, 2023). CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival.

OS benefit was observed across predefined subgroups in the overall population (stage IB–IIIA disease)

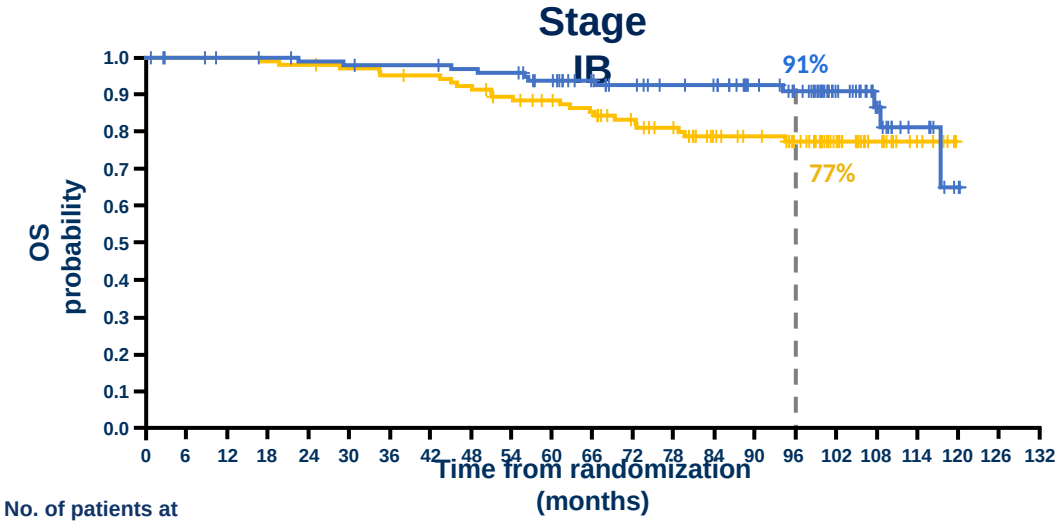
Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	175 / 682	0.52	0.39, 0.71
	Unadjusted Cox PH	175 / 682	0.56	0.41, 0.75
Sex	Male	60 / 204	0.74	0.44, 1.22
	Female	115 / 478	0.47	0.32, 0.69
Age	<65 years	83 / 380	0.59	0.38, 0.91
	≥65 years	92 / 302	0.53	0.34, 0.80
Smoking history	Yes	46 / 194	0.58	0.32, 1.04
	No	129 / 488	0.55	0.38, 0.79
Race	Asian	106 / 434	0.64	0.43, 0.93
	Non-Asian	69 / 248	0.45	0.27, 0.74
Stage*	IB	33 / 212	0.50	0.23, 1.01
	II	66 / 236	0.60	0.36, 0.97
	IIIA	76 / 234	0.49	0.31, 0.77
EGFR mutation	Ex19del	93 / 378	0.45	0.29, 0.68
	L858R	82 / 304	0.72	0.46, 1.11
Adjuvant chemotherapy	Yes	105 / 410	0.54	0.36, 0.80
	No	70 / 272	0.58	0.36, 0.94



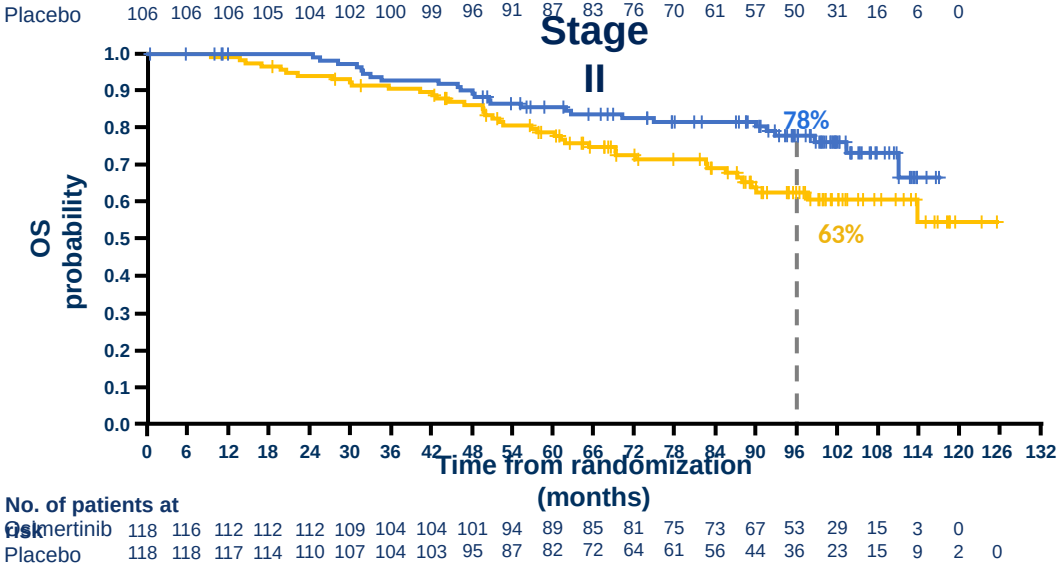
DCO: May 4, 2026. *AJCC / UICC 7th edition.

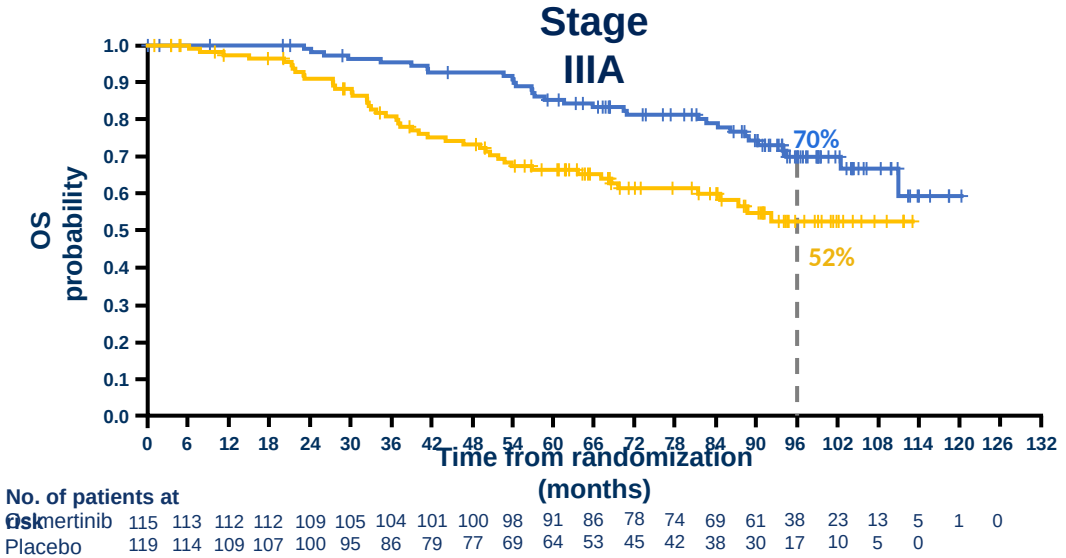
AJCC, American Joint Committee on Cancer; CI, confidence interval; DCO, data cut-off; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; OS, overall survival; UICC, Union for International Cancer Control.

OS benefit was observed across disease stages (IB / II / IIIA)



	Stage IB	Stage II	Stage IIIA
8-year OS rate, % (95% CI)			
Osimertinib	91 (82, 95)	78 (68, 85)	70 (59, 78)
Placebo	77 (68, 85)	63 (52, 71)	52 (41, 63)
OS HR (95% CI)	**0.50 (0.23, 1.01)**	**0.60 (0.36, 0.97)**	**0.49 (0.31, 0.77)**

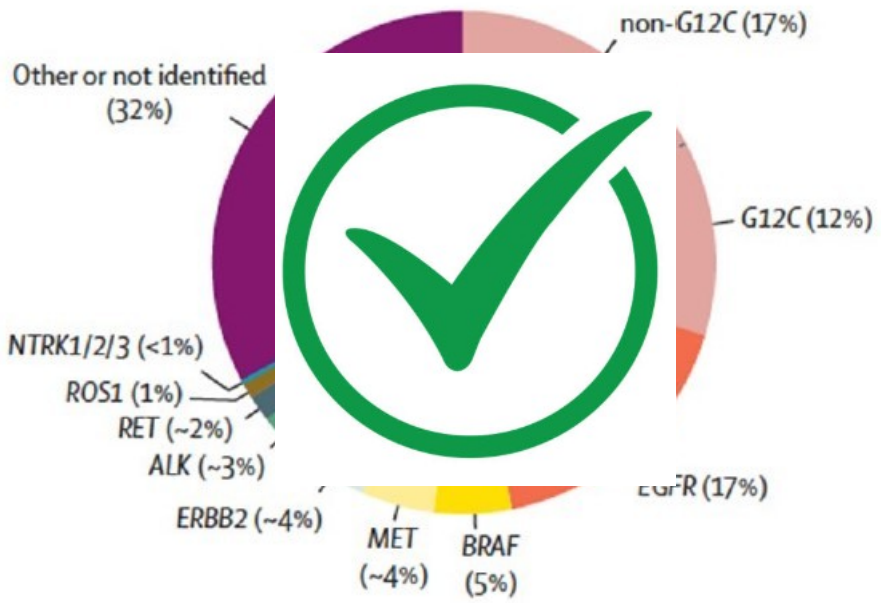




DCO: May 4, 2026. *AJCC / UICC 7th edition. AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; OS, overall survival; UICC, Union for International Cancer Control.

What about other oncogene-addicted NSCLCs?

Oncogenic Drivers in NSCLC



Genotype-Directed Therapies FDA-Approved in NSCLC*

EGFR (canonical)
- Gefitinib
- Erlotinib
- Afatinib
- Dacomitinib
- Osimertinib

ALK
- C[illegible]
- [illegible]
- Lorlatinib

EGFR (exon20ins)
- Amivantamab

KRAS (G12C)
- Sotorasib
- Adagrasib

ROS1
- Crizotinib
- Entrectinib
- Repotrectinib

MET (exon 14)
- Capmatinib
- Tepotinib

RET
- S[illegible]ib
- P[illegible]

HER2
- Traztuzumab deruxtecan

NTRK1-3
- Larotrectinib
- Entrectinib

BRAF (V600E)
- Dabrafenib + trametinib
- Encorafenib + binimetinib

*Therapies as of 5/2024, constantly evolving. Not show in boxes: erlotinib plus ramicirumab, amivantamab plus chemotherapy, and osimertinib plus chemotherapy. Slide courtesy of Jessica Lin, adapted from Thai, Lancet 2021

Presentation is property of the author and ASCO. Permission required for reuse: contact permissions@asco.org.

Progress in lung cancer in the last 20+ years with a focus on work from Yale

2. Immunotherapy

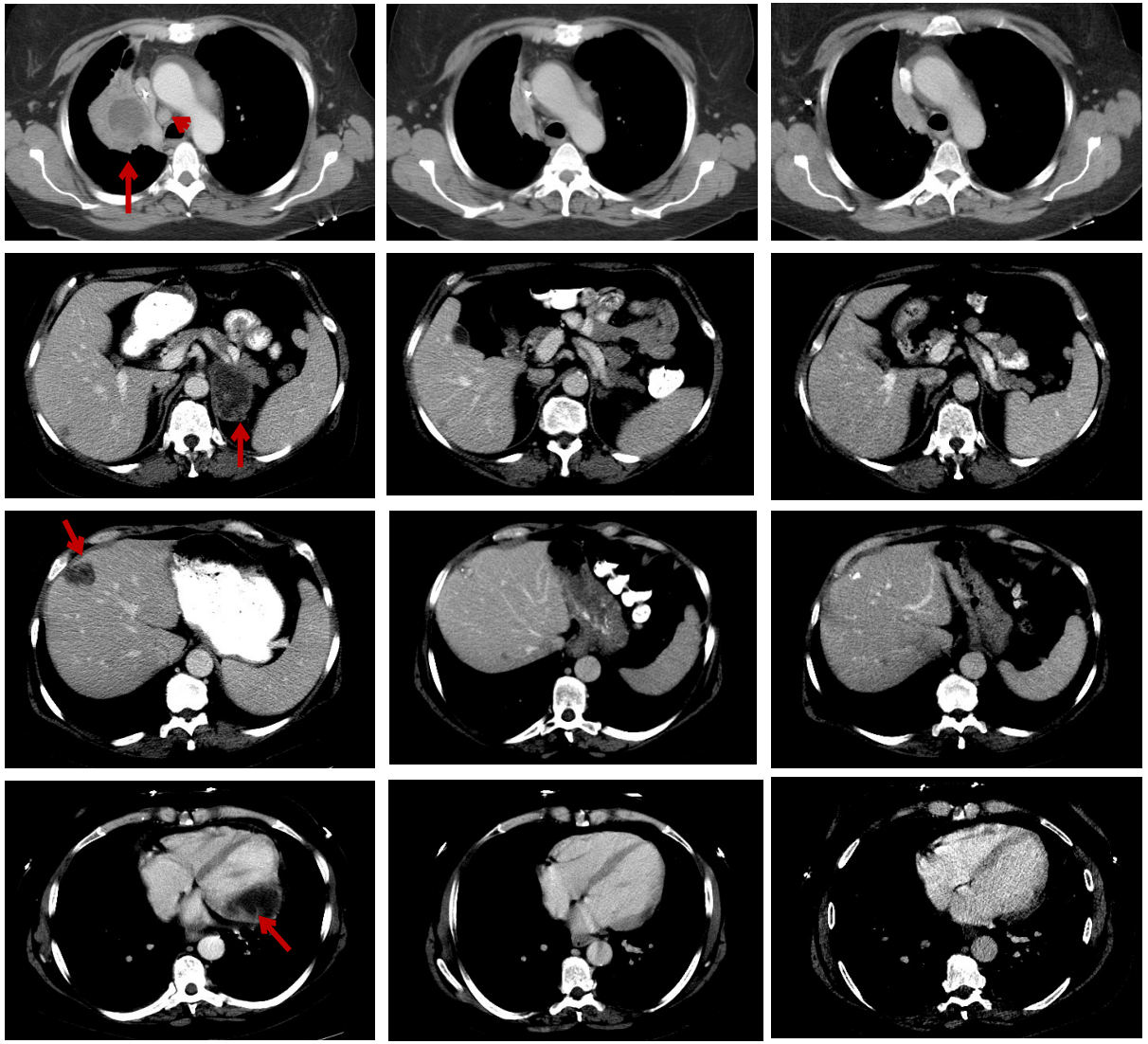


Dartmouth Health

DARTMOUTH GEISEL SCHOOL OF MEDICINE

Dartmouth Cancer Center

Immunotherapy for NSCLC



Pre- Nivolumab

2 Years on Nivolumab

year 8: > 6 Years off Nivolumab



One of the very first lung patients
on MDX-1106 (Nivolumab)
3X Chemo-Refractory
Squamous Cell NSCLC
2011

But this only happens for 15%

Courtesy of Scott Gettinger, Yale Centerpoint

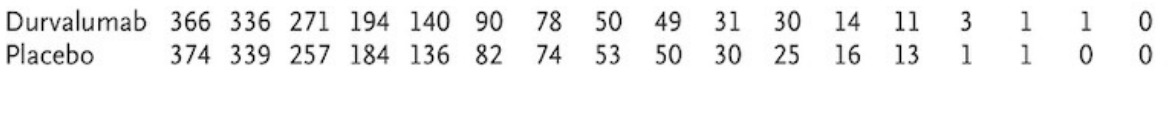
Cancer Cell

Spotlight

When immunotherapy meets surgery in non-small cell lung cancer

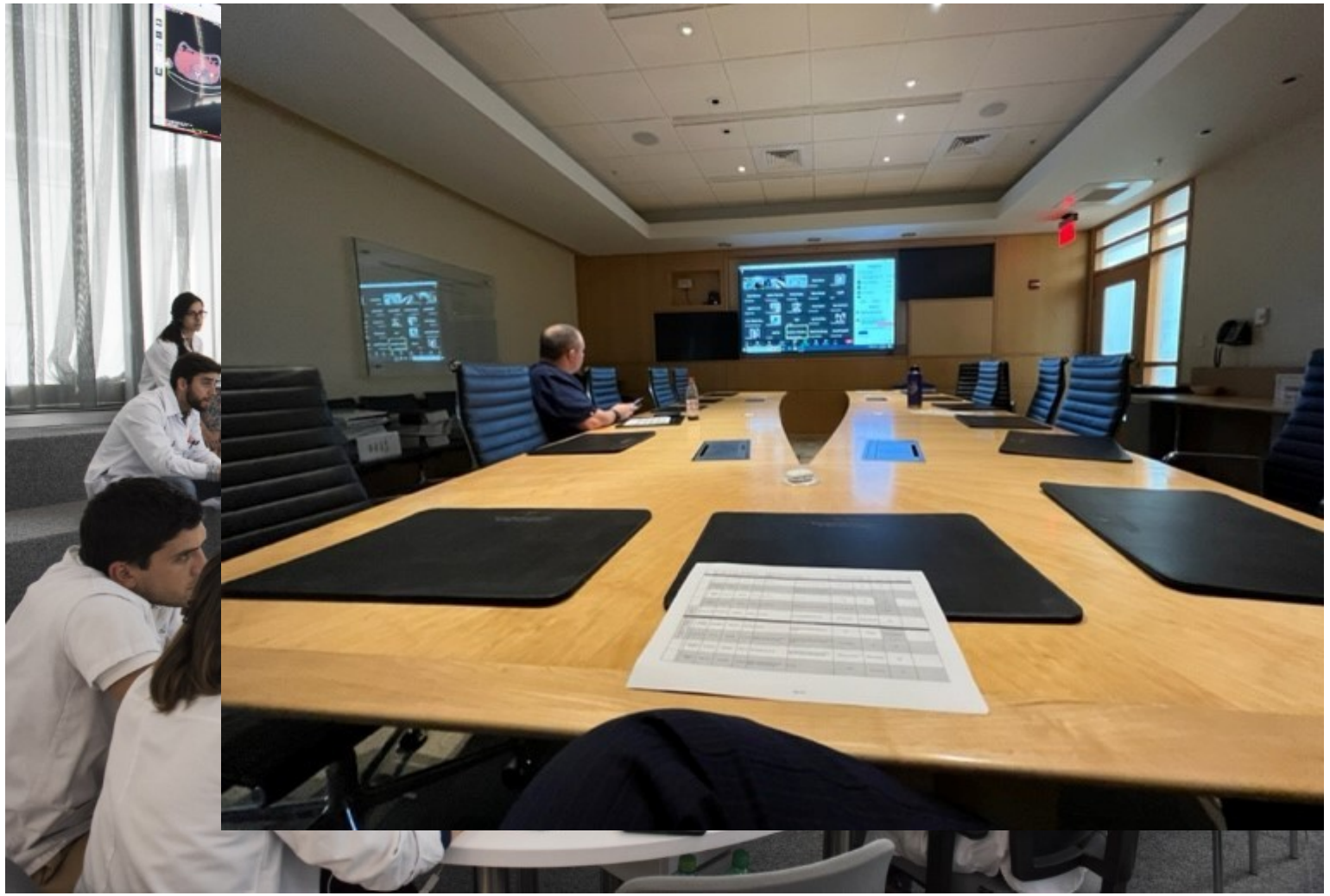
Roy S. Herbst,[1,*] Meina Wang,[1] and Lieping Chen[1,2]
[1]Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, CT 06520-8028, USA
[2]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520, USA
*Correspondence: roy.herbst@yale.edu
https://doi.org/10.1016/j.ccell.2022.05.010





Antonia et al, NEJM, 2017
Heymach et al, NEJM, 2023

So what are we going to recommend at our next tumor board?



- Multimodality review and discussion are Critical for this approach

- Which Approach?
  - Surgery
  - Chemoradiation
  - Adjuvant
  - Neoadjuvant
  - Which Agents
  - How long to treat

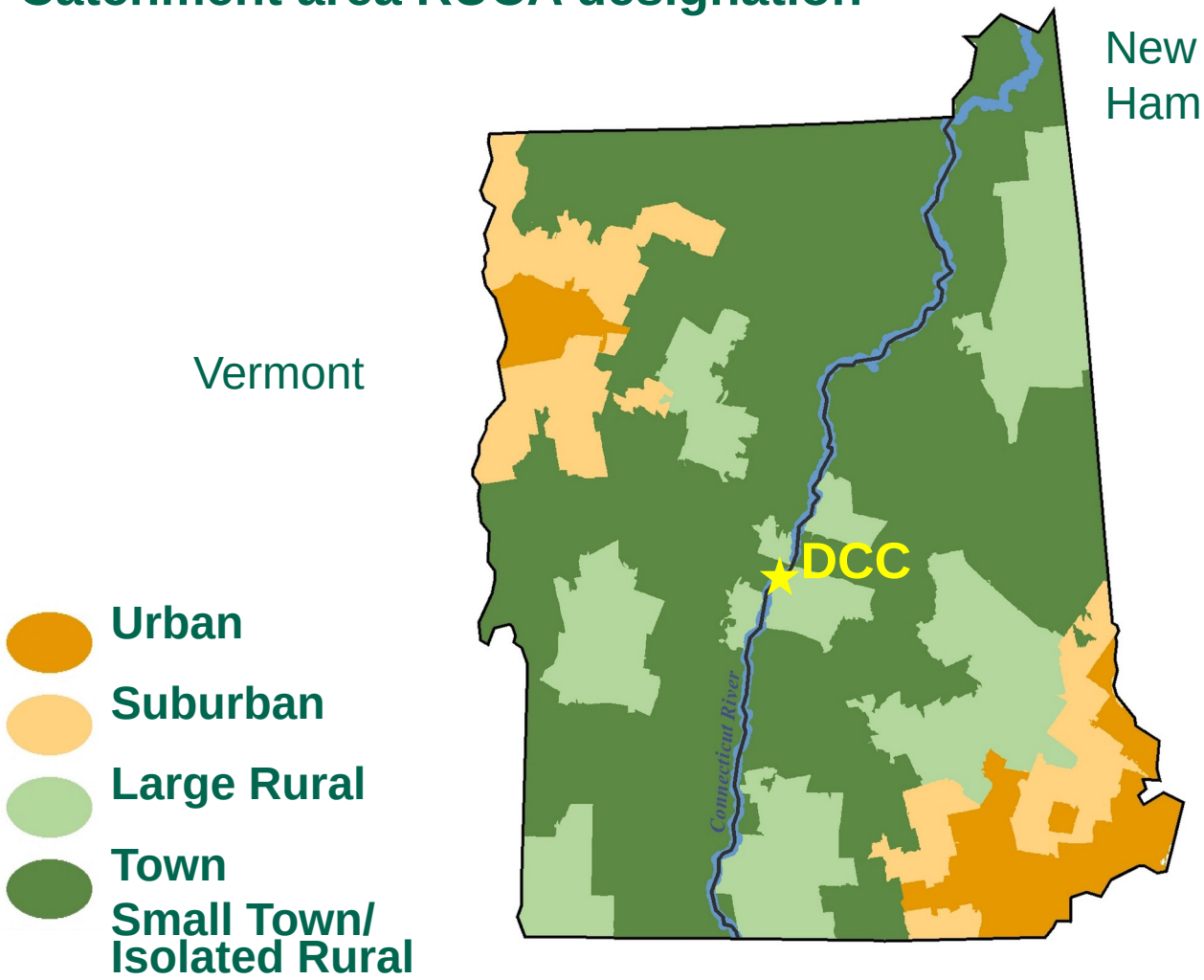
3. Access

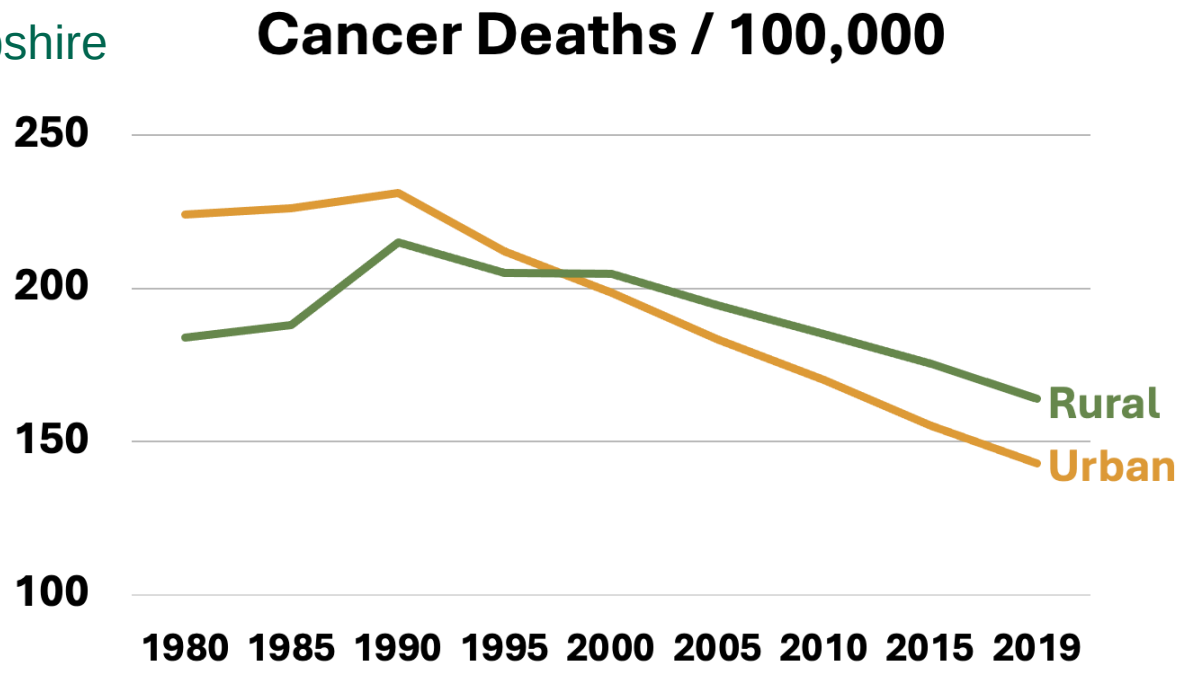


Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Our Catchment Area is Predominantly Rural

Catchment area RUCA designation





Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Design of a Disease-Specific Master Protocol

2012 Friends of Cancer Research / Brookings Institution Conference on Clinical Cancer Research





ISSUE BRIEF

Conference on Clinical Cancer Research

November 2012

Design of a Disease-Specific Master Protocol

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center
Eric Rubin, Vice President, Clinical Research Oncology, Merck
Lisa LaVange, Director, Office of Biostatistics, CDER, FDA
Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, NCI
David Wholley, Director, The Biomarkers Consortium, FNIH
Karen Arscott, Patient Advocate, Lung Cancer Alliance
Shakuntala Malik, Medical Officer, FDA

Introduction

Despite several impressive therapeutic advances in recent years, cancer remains the second-leading cause of death in the United States, and effective new therapies are still desperately needed. Developing a potential therapy from the initial discovery stage through clinical testing and regulatory review is a complicated, expensive, and often inefficient process that can take up to 15 years. Included among the many challenges of drug development are the difficulties in recruiting cancer patients to clinical trials, the extensive bureaucratic processes required to initiate any clinical trial, and lengthy regulatory review. Modernizing this process with innovative approaches and new clinical trial designs is of high importance.



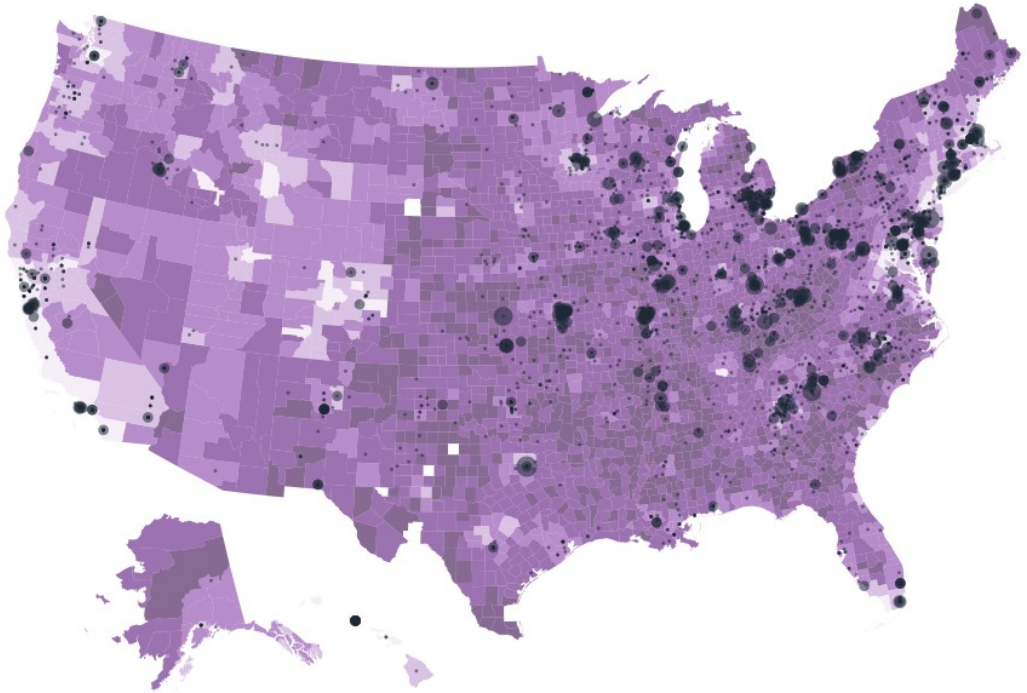


FRIENDS of CANCER RESEARCH

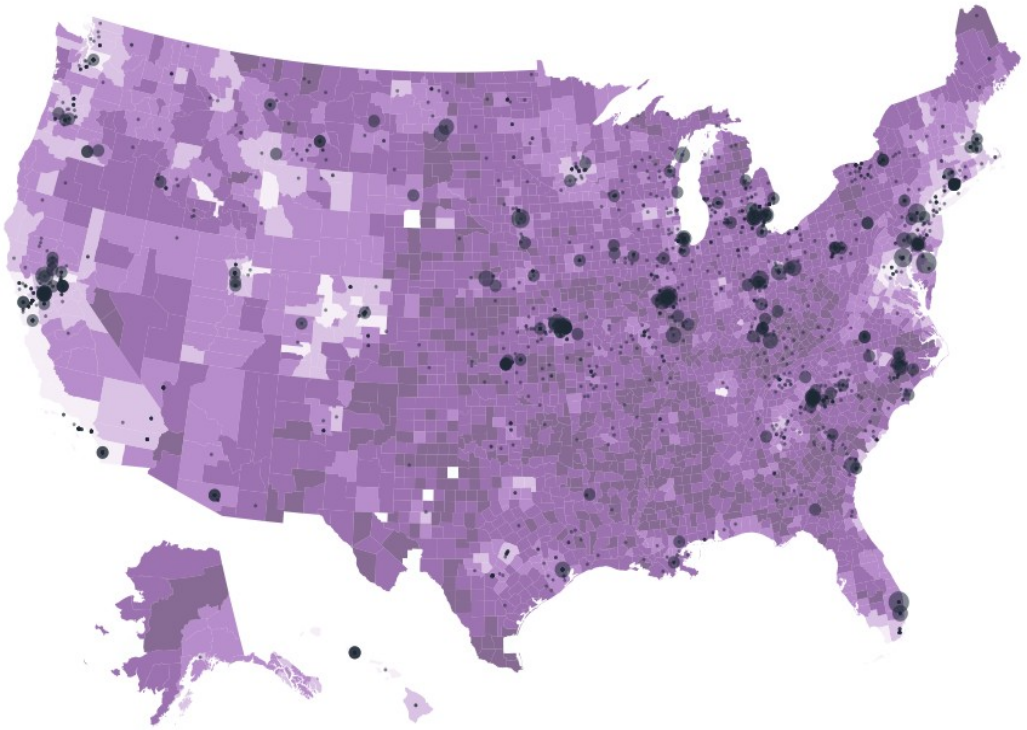
http://www.focr.org/events/design-lung-cancer-master-protocol

Enrollment by Area Deprivation (Rural)

LUNGMAP Accruals 1/1/2014 - 12/31/2020



NSCLC Studies Accruals 1/1/2001 - 12/31/2020



Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Pragmatic Design
Data capture

PRAGMATIC

- Minimize the data collection burden
  - Reduced time points for data submitted
  - Reduced number of forms
  - Reduced number of data elements
- No protocol required disease assessment (CT, imaging)
- No protocol required lab tests
- No specimen collection
- No Patient-Reported Outcome instruments
- Grade 5 and unexpected, related Grade 3-4 AE (~90% fewer AEs reported)
- No conmed collection
- Reduced data to monitor and audit

STANDARD

- Extensive, complex electronic data capture
- Collection of labs
- Collection of RECIST and associated queries
- Conmed collection and dates
- Extensive study monitoring and auditing

Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center

Team Building

Lung Map Meeting 2019 Friends of Cancer Research, Washington DC





Dartmouth Health | DARTMOUTH GEISEL SCHOOL OF MEDICINE | Dartmouth Cancer Center



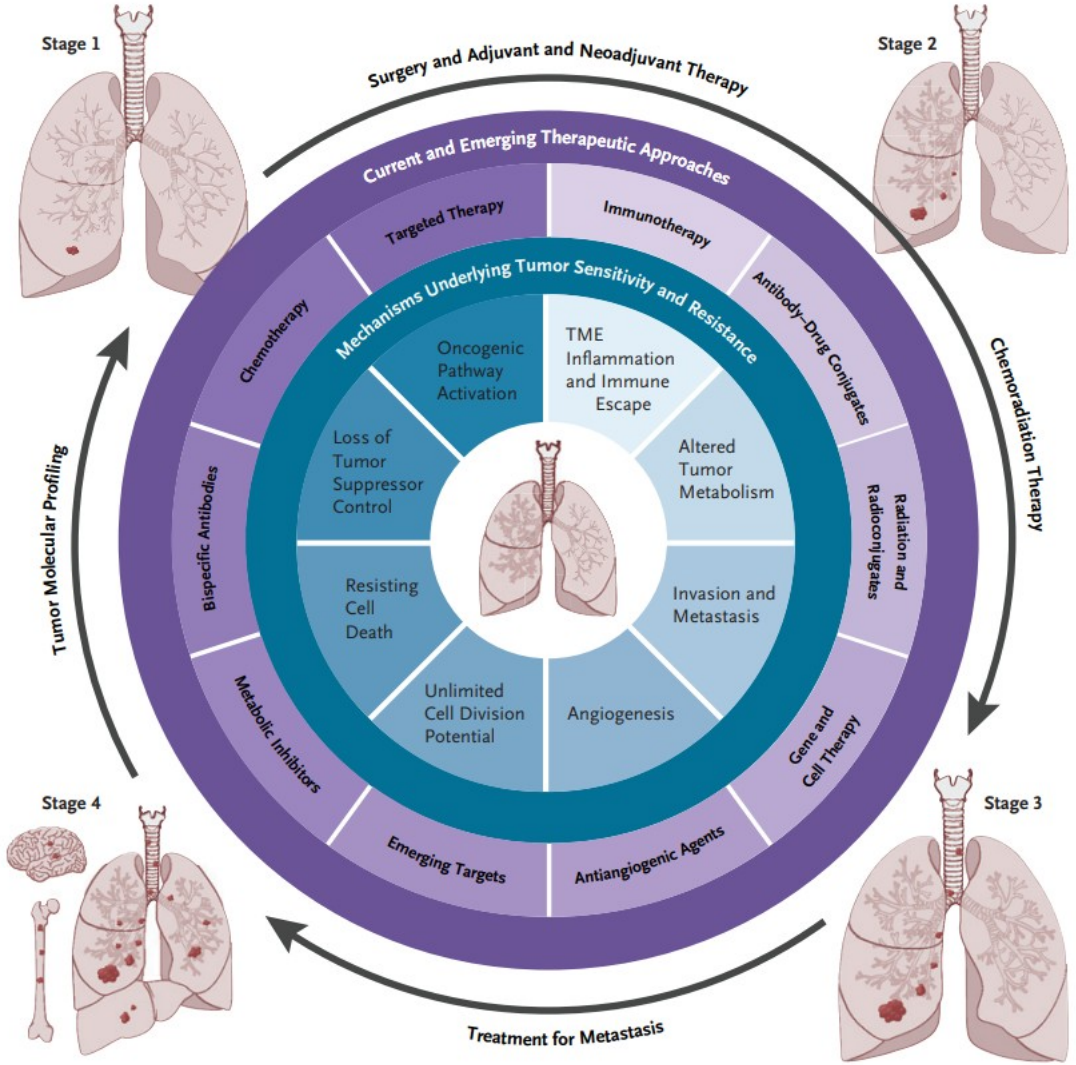
The Paradigm Has Shifted!!!

Over the last 20+ years, we have taken the best chemotherapy, radiation, targeted therapy and immune therapy for lung cancer and brought them to the earliest stages of disease - where they can have the maximal benefit and, in some cases, cure this disease.

Dartmouth Health

DARTMOUTH GEISEL SCHOOL OF MEDICINE

Dartmouth Cancer Center



The Hallmarks of Lung Cancer

Herbst NEJM January 1, 2026



Thank You

The Annual Prouty

Questions?
Roy Herbst
Roy.S.Herbst@Dartmouth.EDU