Management of EGFR Mutant NSCLC Patients and Future Directions (excluding Resistance to EGFR TKIs)

Miami, Florida
April 29, 2023
I

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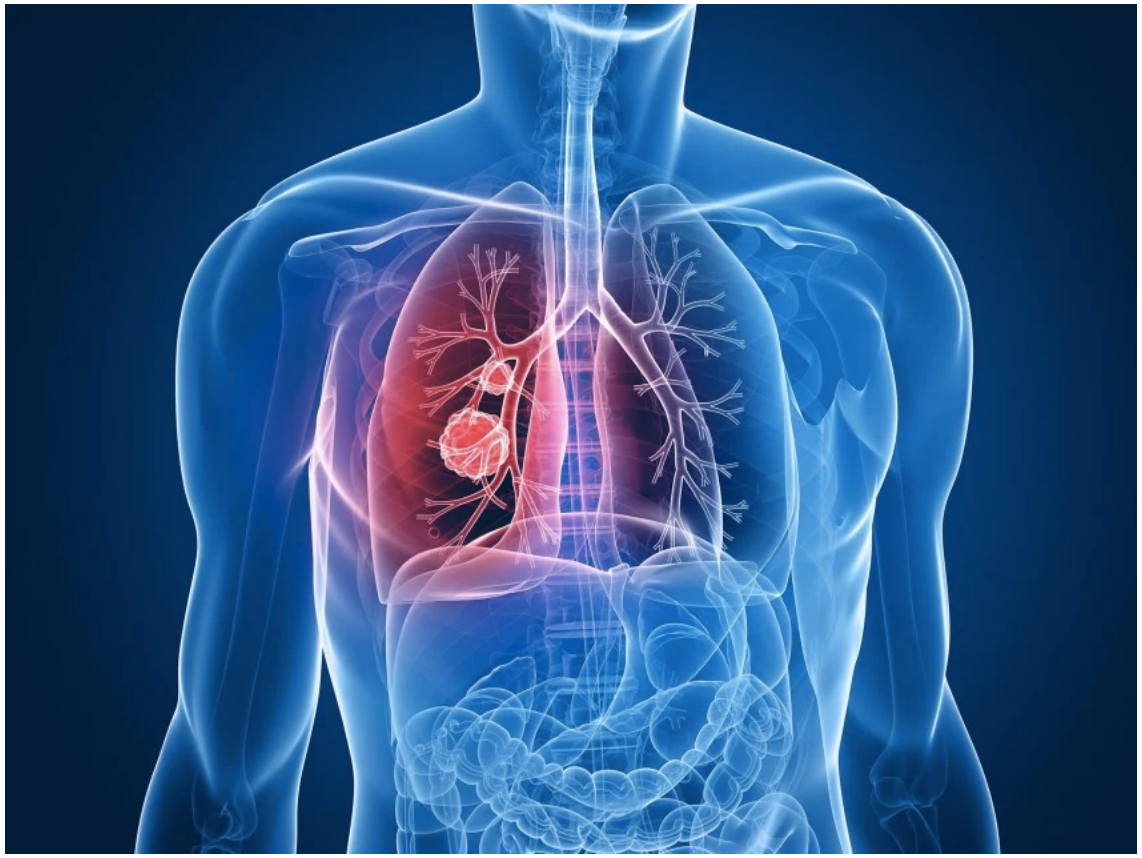
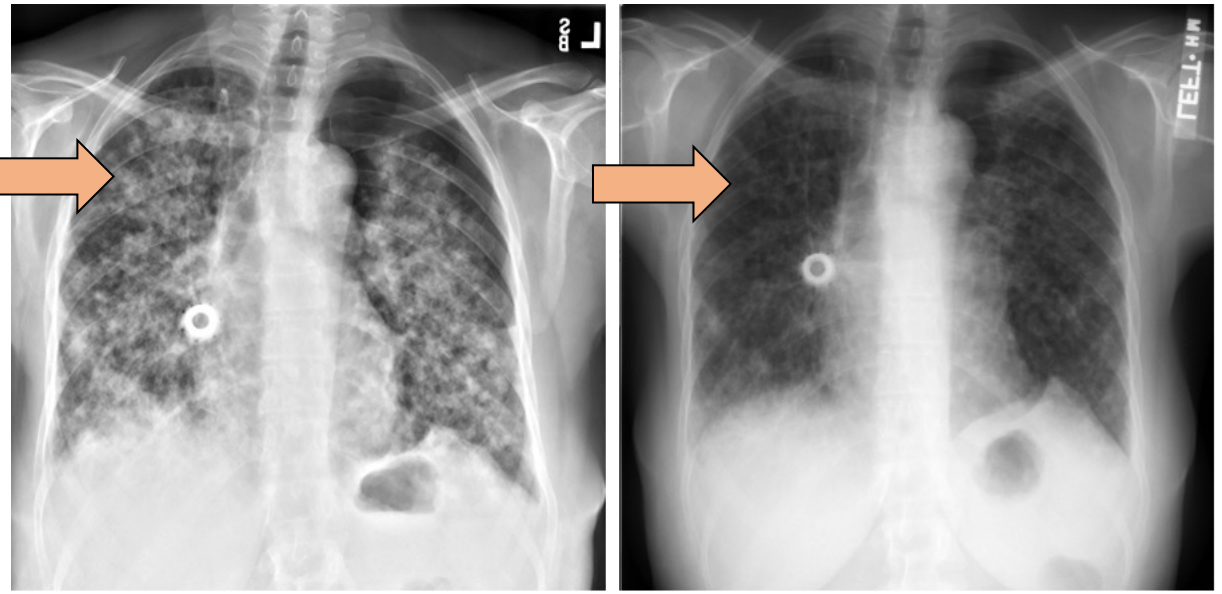
Progress in lung cancer in the last 20+ years

1. Targeted Therapy



The Very First Gefitinib Continuous Phase I Study (1998)

FDA Approved
May 2003



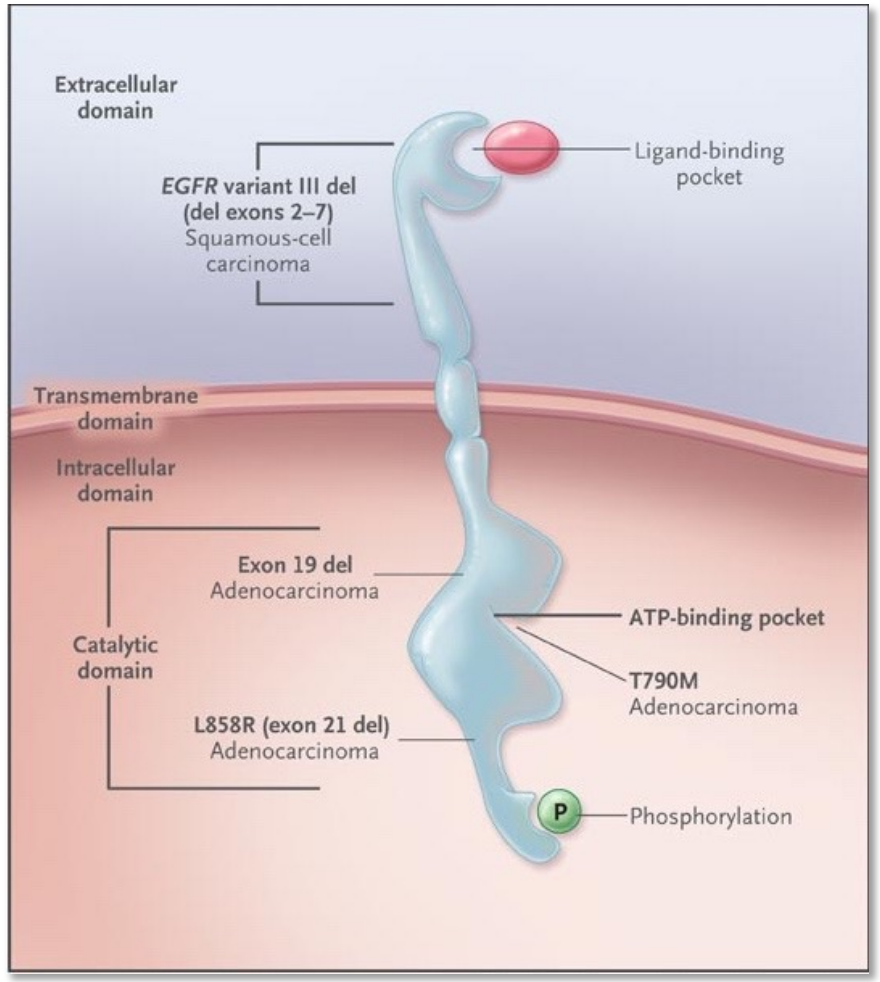
Baseline 1 Week Later

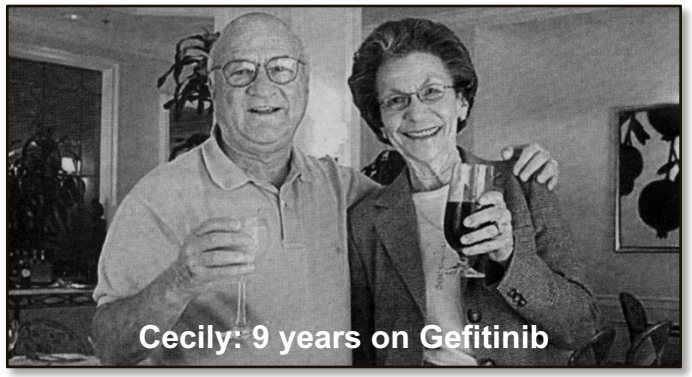
Selective Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor ZD1839 Is Generally Well-Tolerated and Has Activity in Non–Small-Cell Lung Cancer and Other Solid Tumors: Results of a Phase I Trial

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.

Effect of Deletions and Mutations in the Epidermal Growth Factor Receptor Gene (EGFR) on Disease Development and Drug Targeting





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

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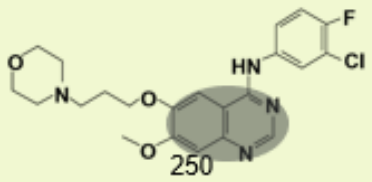
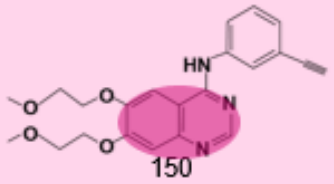
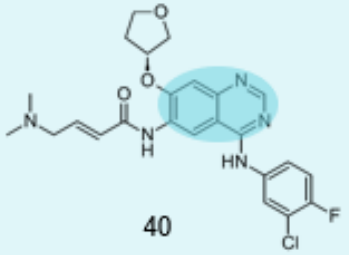
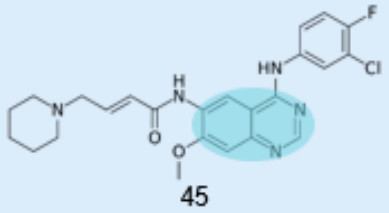
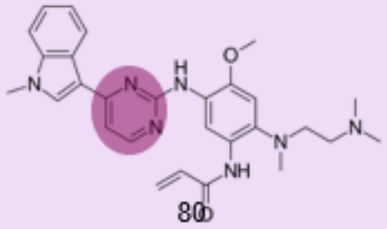
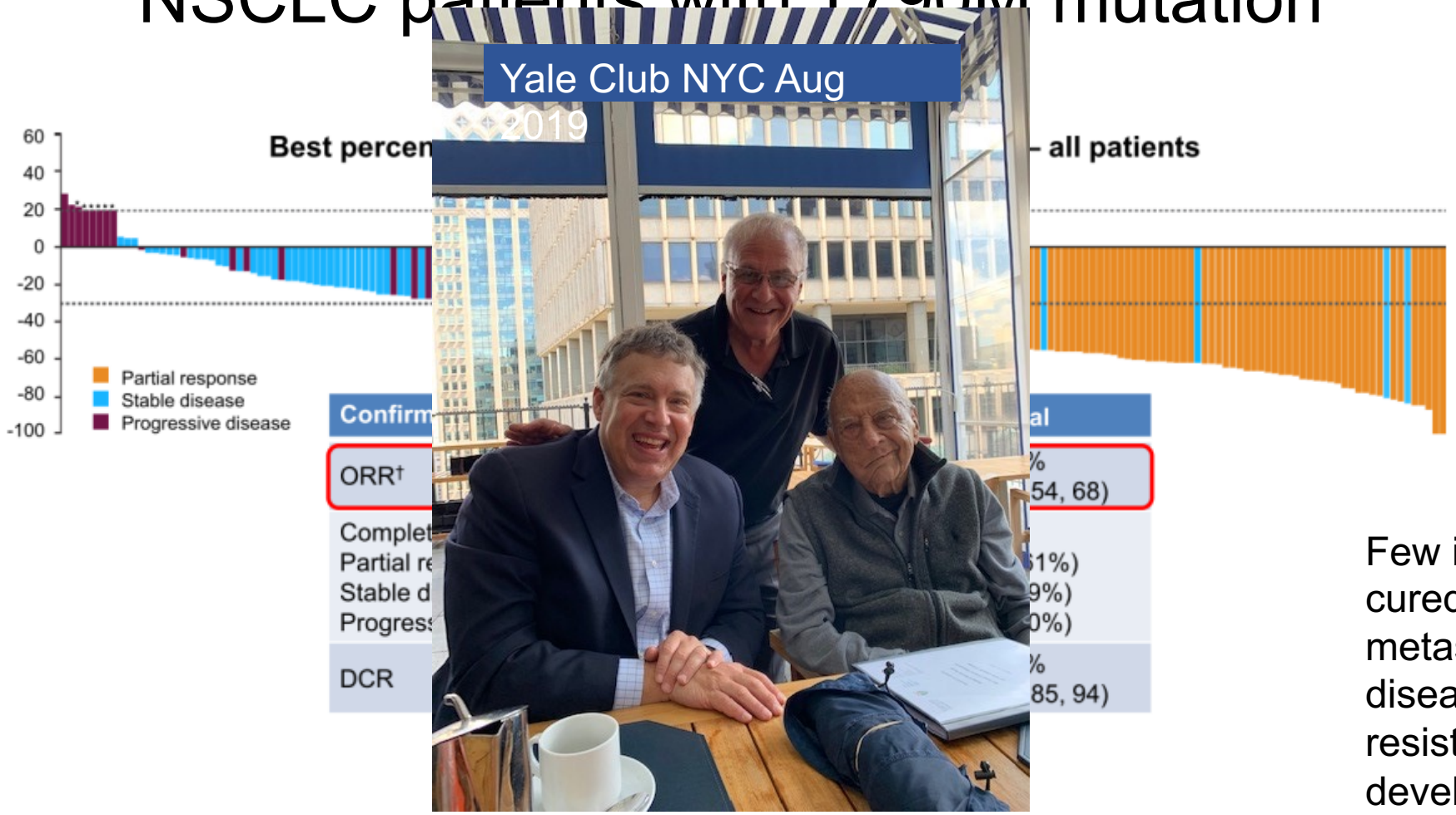
Paez JG et al. *Science.* 2004;304(5676):1497-500.
Lynch TJ et al. *N Engl J Med.* 2004;350:2129-39.
Herbst RS et al. *N Engl J Med*. 2008;359:1367-80.

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.

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



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

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

Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination

CANC

Home About

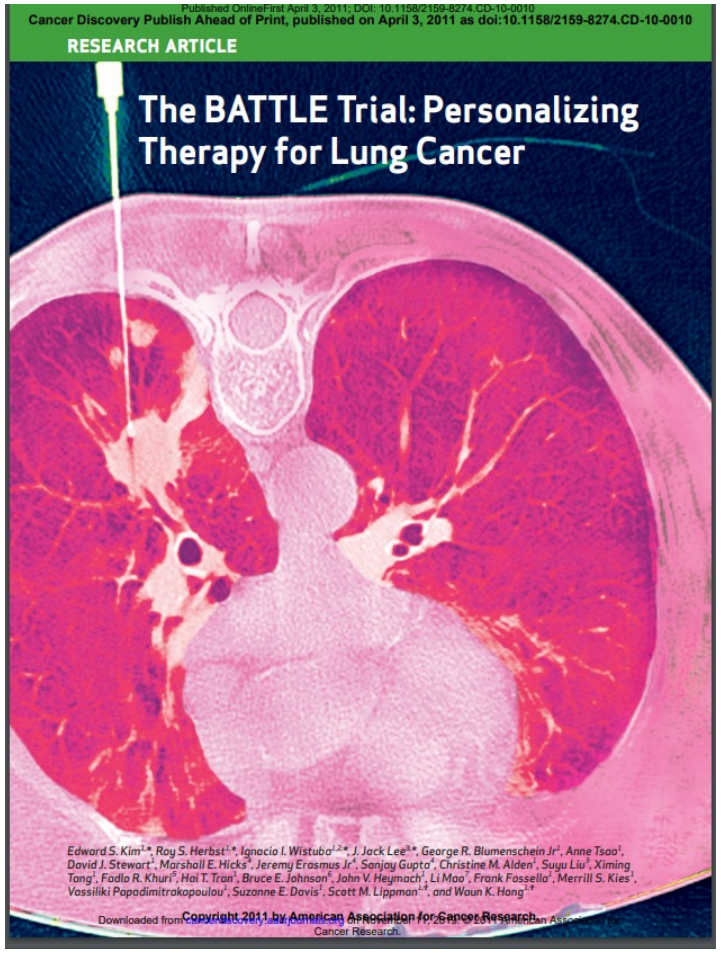
Celebrating the 10th Anniversary

A Decade of Discoveries in *Cancer Discovery*. For the Community. By the Community.

The BATTLE Trial: Personalizing Therapy for Lung Cancer

Cancer Discovery's first clinical trial research article.

The inaugural issue includes **the BATTLE Trial**, which represented a major advance in clinical trial design that established the feasibility of performing core biopsies and real-time biomarker analysis to assign therapy. Read **the author interview** describing this impactful study.



Authors

Their impactful studies. In their words.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The BATTLE Trial: Personalizing Therapy for Lung Cancer

June 2011

Q: **What unanswered questions in the field were these studies addressing?**

A: **(Edward Kim)** BATTLE was the first study to address personalizing medicine for patients with lung cancer in which biopsies were required after diagnosis and treatment. The use of real-time biomarkers and adaptive randomization to drive treatment decisions was novel not only to lung cancer, but to many solid tumors.

Remembering the late Waun Ki Hong and his extraordinary contribution to *Cancer Discovery*'s first clinical trial

Fundamental Lessons Learned From BATTLE

"Raising the bar for NSCLC"

- Core biopsies are feasible and safe
- Biomarker results can be obtained in less than 2 weeks
- Drugs can be obtained from multiple companies and used in a trial
- Adaptive randomization is a viable technique
- We could accrue from two sites (YCC/Smilow and MD Anderson)
- We did 41 biopsies at Smilow in one year!

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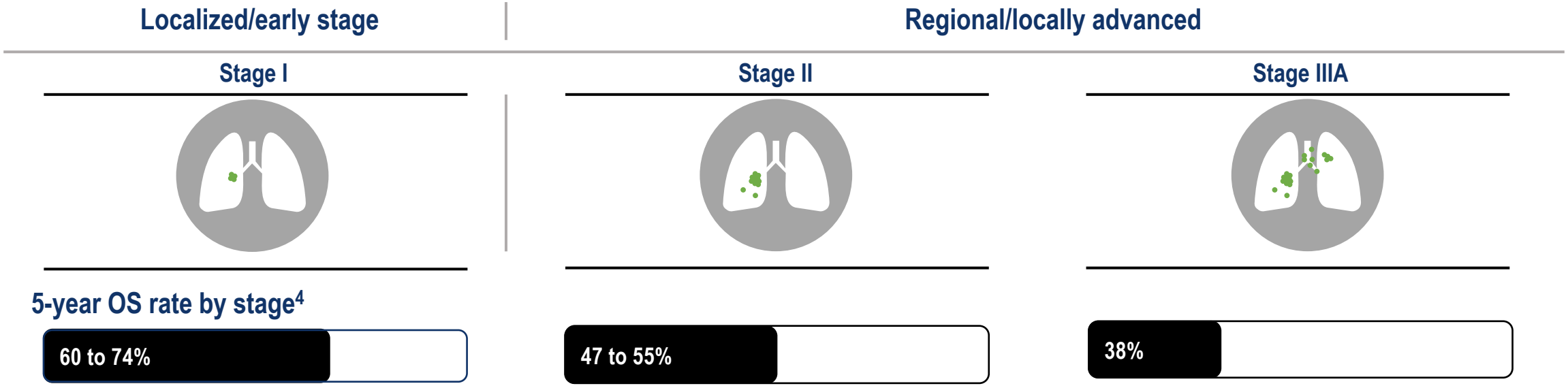
Moving Targeted Therapy to Earlier NSCLC: Outcomes in early-stage NSCLC need to be improved

- 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]



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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.

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

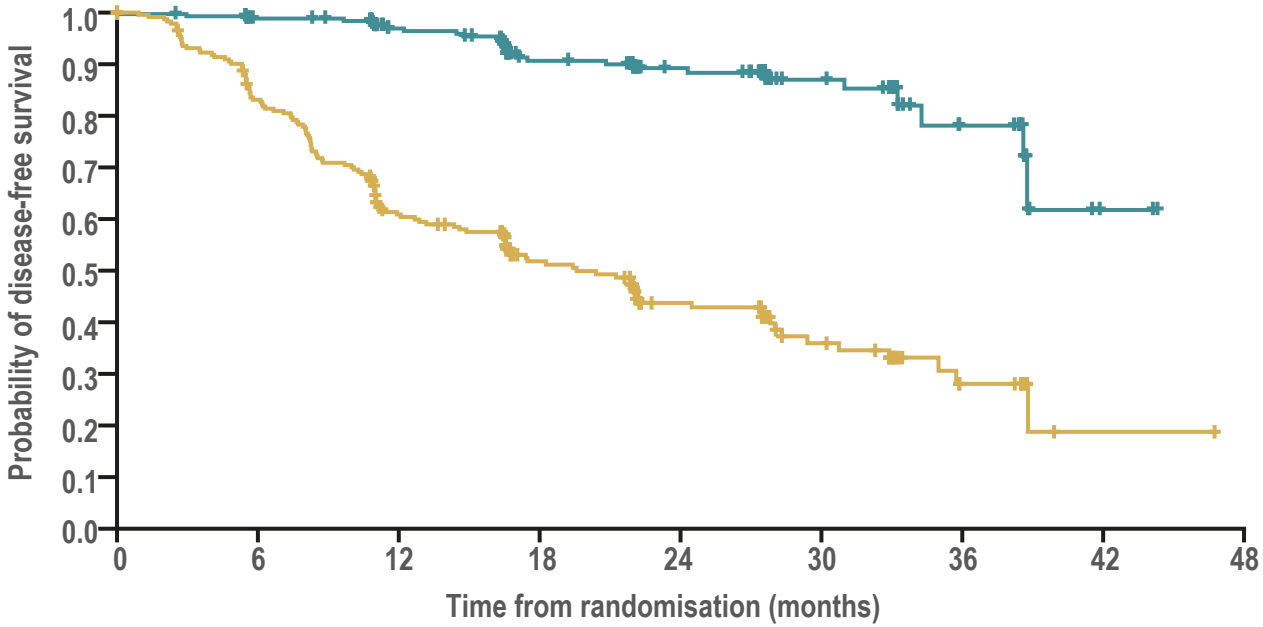
- **Primary**: DFS, by investigator, in stage II–IIIA patients (powered for a HR of 0.7)
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, overall survival, safety, quality of life, pharmacokinetics

- **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

ADAURA: Osimertinib improves DFS versus placebo in resected EGFRm NSCLC

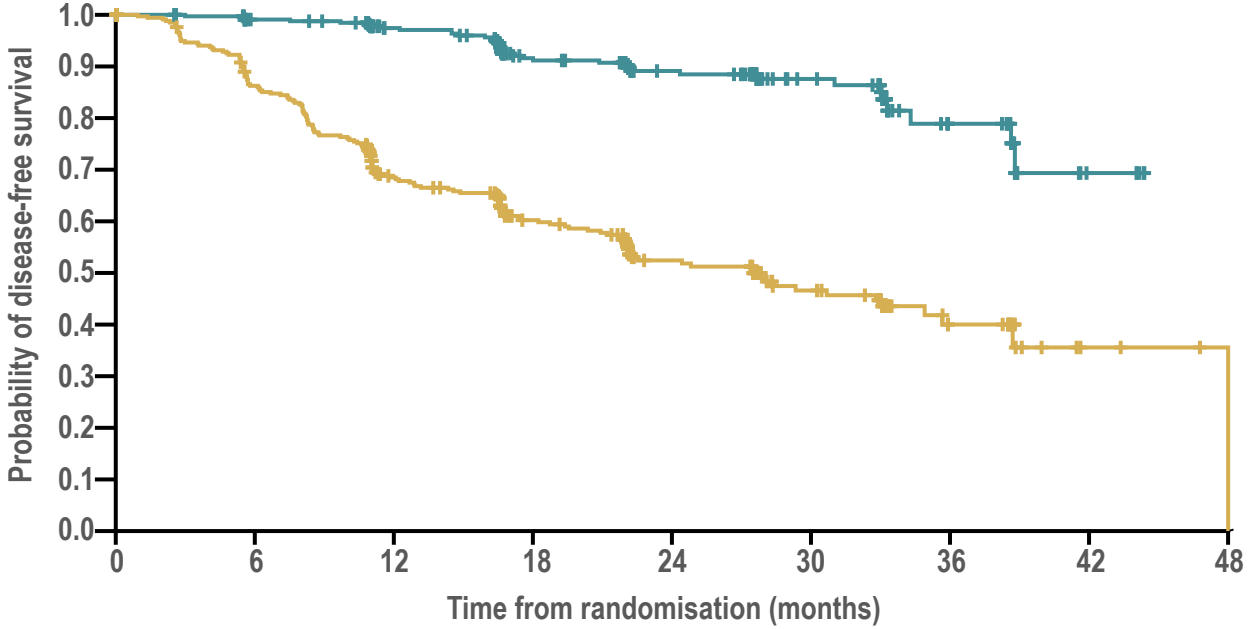
Primary population: Stage II/IIIA



No. at risk									
Osimertinib	233	219	189	137	97	52	18	2	0
Placebo	237	190	127	82	51	27	9	1	0

	Median DFS, months (95% CI)	HR (99.06% CI)
– Osimertinib	NR (38.8, NC)	0.17 (0.11, 0.26) P<0.0001
– Placebo	19.6 (16.6, 24.5)	

Overall population: Stage IB/II/IIIA



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

	Median DFS, months (95% CI)	HR (99.12% CI)
– Osimertinib	NR (NC, NC)	0.20 (0.14, 0.30) P<0.0001
– Placebo	27.5 (22.0, 35.0)	

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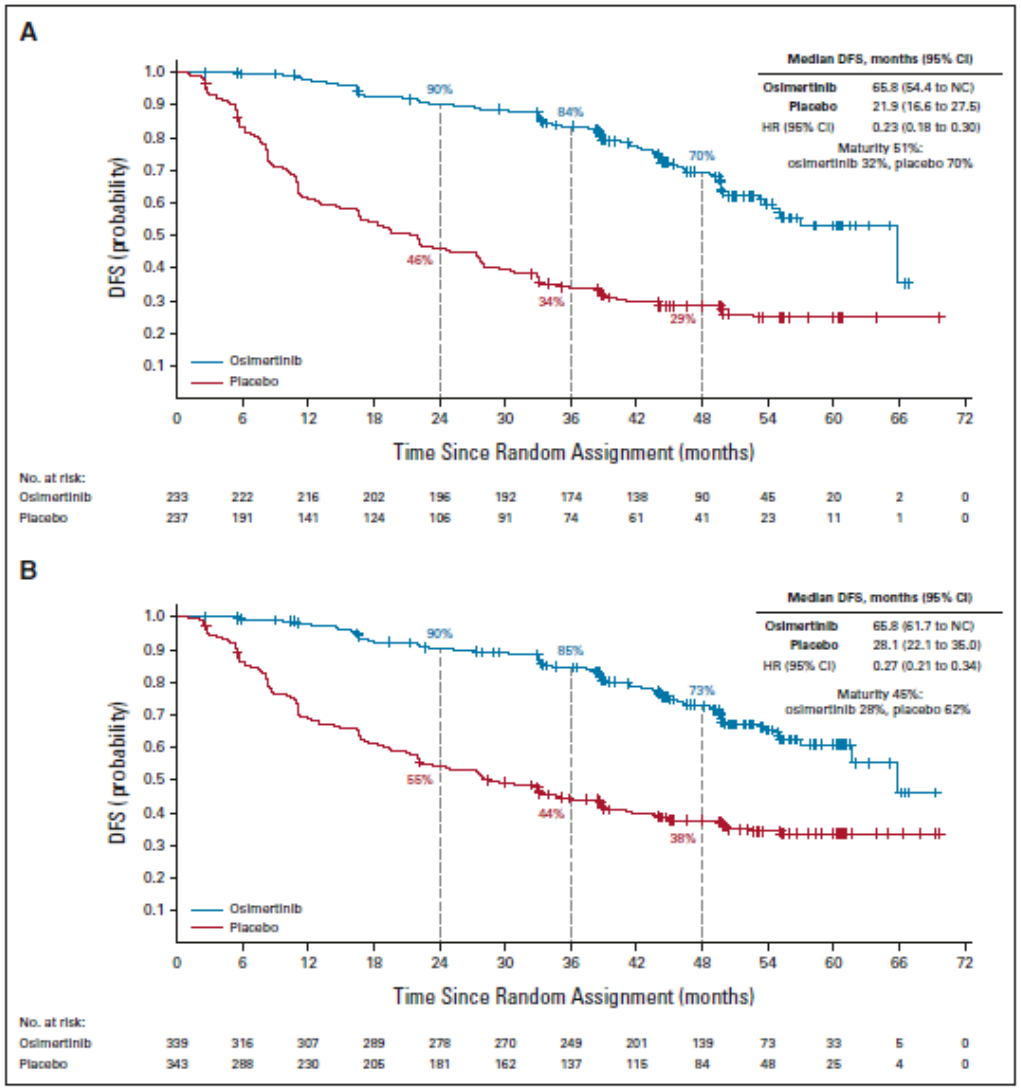
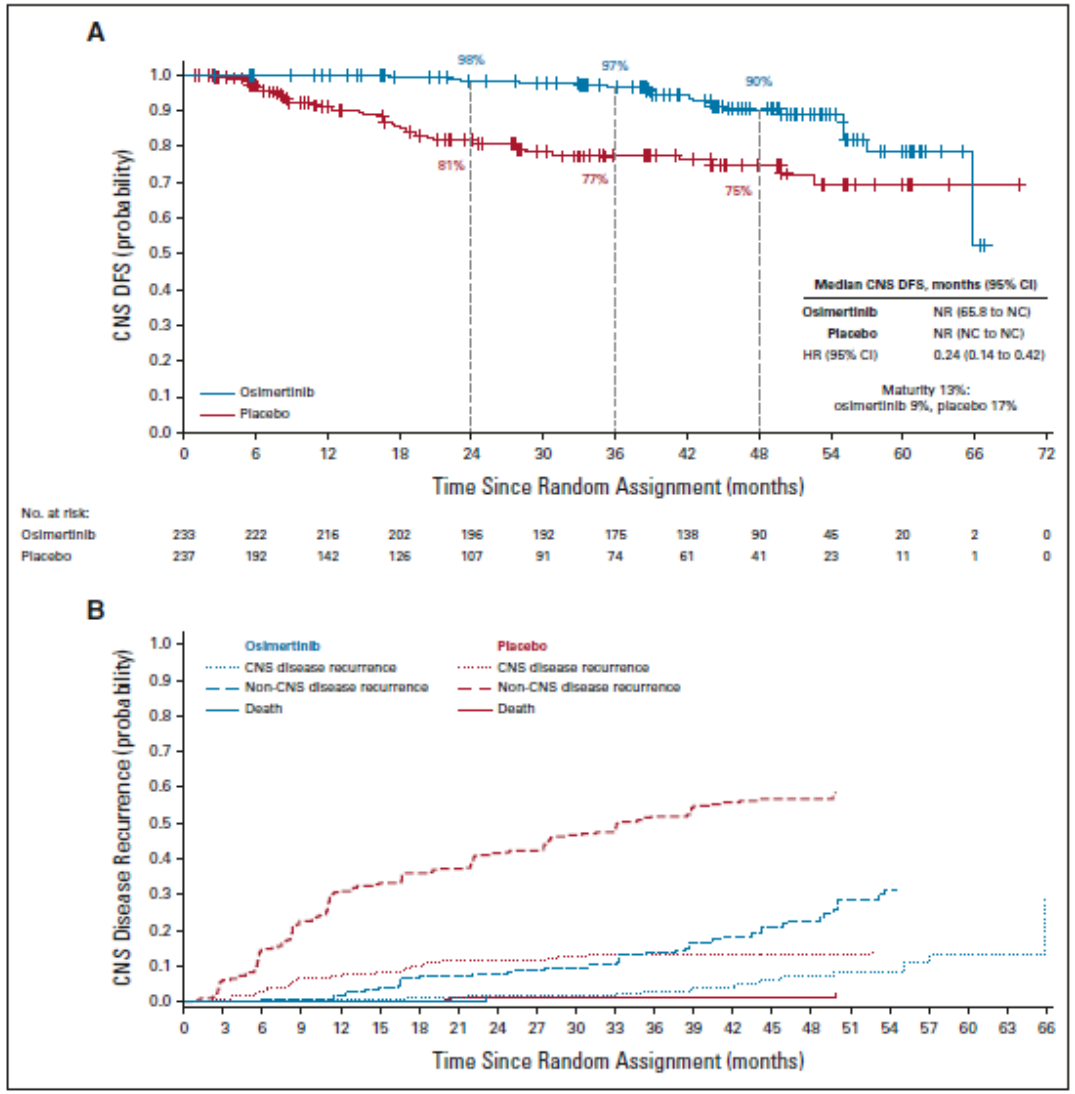
Wu, et al (Herbst). NEJM Sept 2020 DOI: 10.1056/NEJMoa2027071

CI, confidence interval; NC, not calculable; HR, hazard ratio; NR, not reached

ADAURA data cut-off: 17 January, 2020

Updated ADAURA Data- With 2 Years More Maturity





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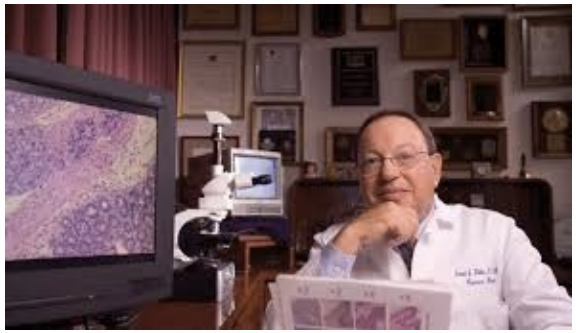
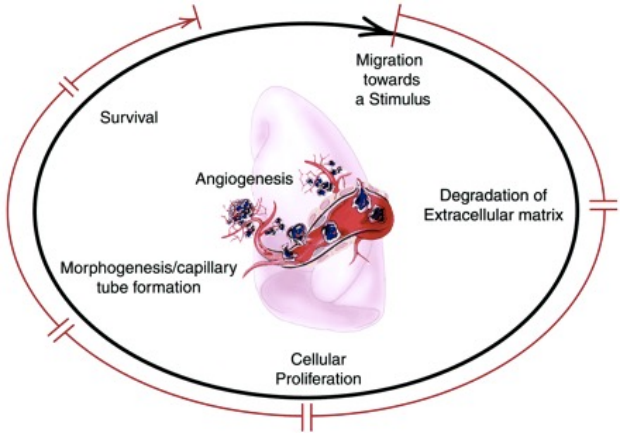
JCO January 21, 2023

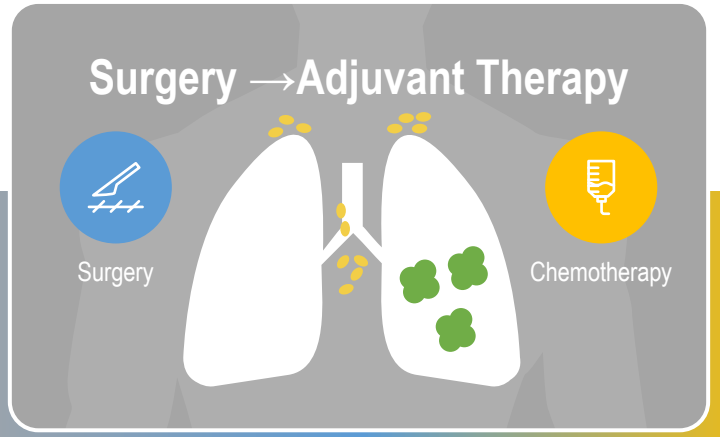
Biology has spoken

Drug Approval December 2020 for Adjuvant Therapy



Isaiah J. Fidler, DVM, PhD, FAACR





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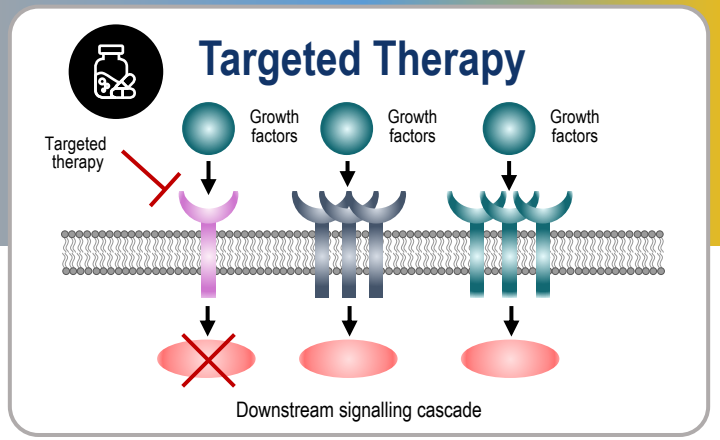

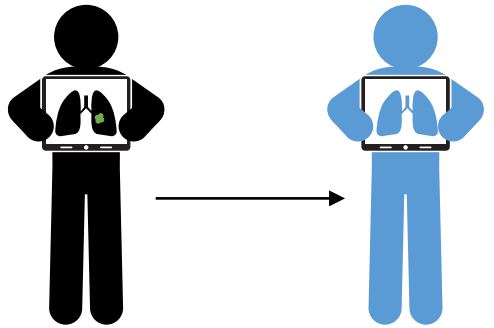

Best therapies earlier in disease course, for the most enhanced patient benefit

Prevent metastasis

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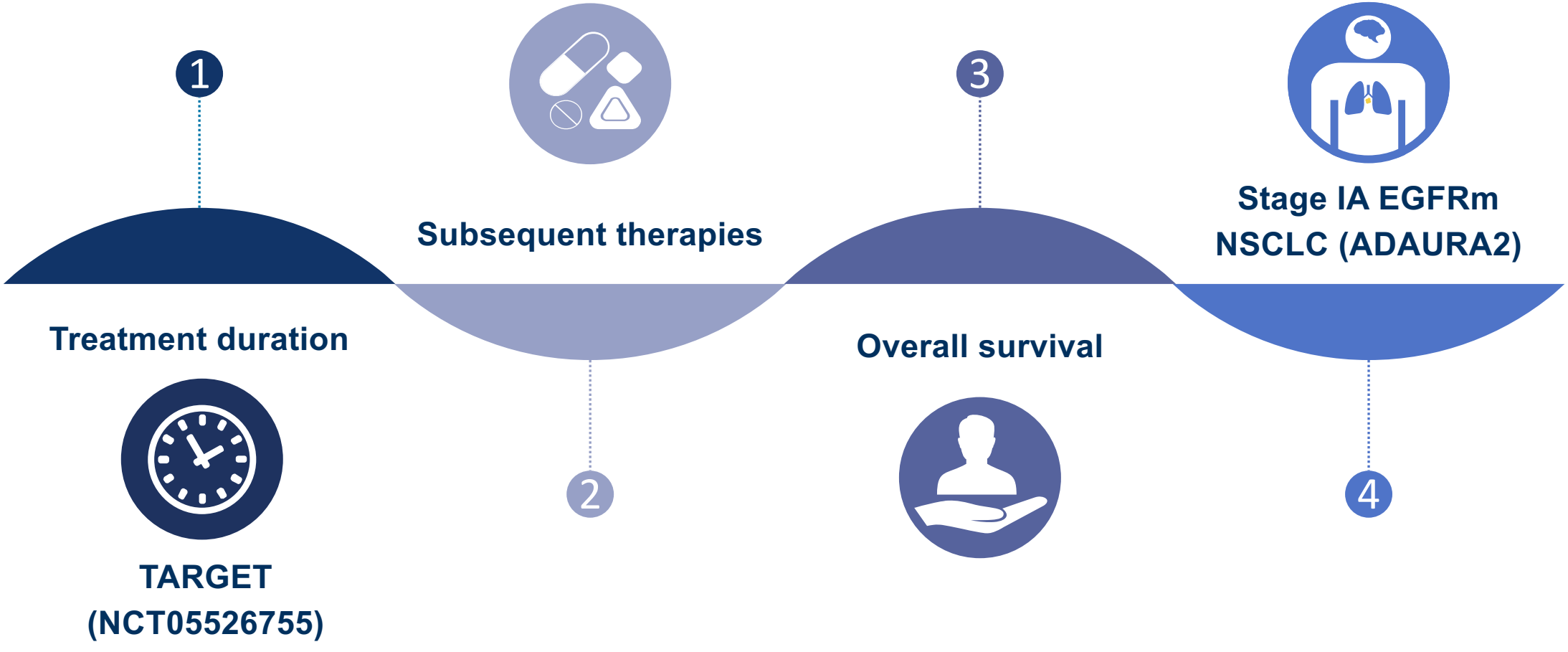
Herbst & Fidler CCR 2000

FUTURE CONSIDERATIONS



EGFRm, epidermal growth factor receptor-mutated; NSCLC, non-small cell lung cancer.

UNDERSTANDING BIOLOGY

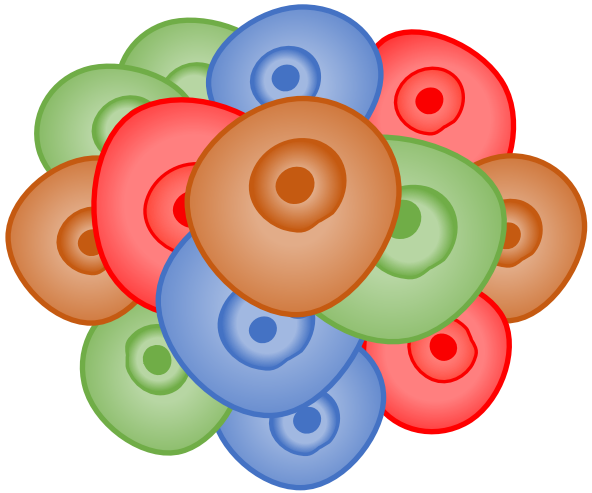
- Understanding tumor biology and its response to treatment will help to further personalize treatment in this setting
- Rare tumor cells can persist during treatment and lead to relapse, often after the completion of treatment[1,2]

Cell metabolism adaptations:

- **Ribosome dependency**
- **Mitochondria respiration**
- **Oxidative trade off**

Slowed proliferation

- **Epigenetic alteration**
- **Adaptive mutability**



PERSISTANT CANCER CELLS

Microenvironment changes:

- **Microenvironment alteration**
- **Immune suppression**
- **Tumor cell symbiosis**

Cell identity changes:

- **Transdifferentiation**
- **Epithelial-mesenchymal transition**

- Tumor and ctDNA molecular profiling for analyses of minimal residual disease and acquired resistance in ADAURA may provide important information on persistence and resistance mechanisms that can be used to optimize treatment strategies in this setting

Image reprinted from Cell, 183, Shen, et al., Persistent Cancer Cells: The Deadly Survivors, 860–874, 2020, with permission from Elsevier.

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

Next Steps

- NeoAdaura (Neoadjuvant)
- Laura (Stage III)
- Combo studies
- Other Agents

1. Herbst et al. J Clin Oncol.2020;38:18_suppl.LBA5.
ADAURA data cut-off: 17 January, 2020

Thank You

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