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State of Lung Cancer Research

Lung Cancer Research Foundation Scientific Symposium

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Cedars Sinai Cancer

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Disclosures

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Consultant

Amgen; AstraZeneca; Boehringer Ingelheim; Blueprint; Calithera; Euclises; Genentech; Guardant; Janssen; Lilly; Merck KGA; Precision Health; Seattle Genetics; Takeda; Tesaro

Research support (to prior institution)

AbbVie, Acea, Adaptimmune, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, GlaxoSmithKline, Guardant, Janssen, Loxo Oncology, Seattle Genetics, Takeda, Xcovery, Zeno

Outline

- Recent advances
  - Moving targeted therapied and IO into the curative setting
  - Lung cancer screening
  - Growing number of targeted therapies leading to improved survival
  - Immunotherapy improving long term outcomes
- Broader challenges that lung cancer research currently faces and potential changes
- How we can contribute to promote a better future and create a more collaborative scientific environment

20 years of progress on the road less traveled

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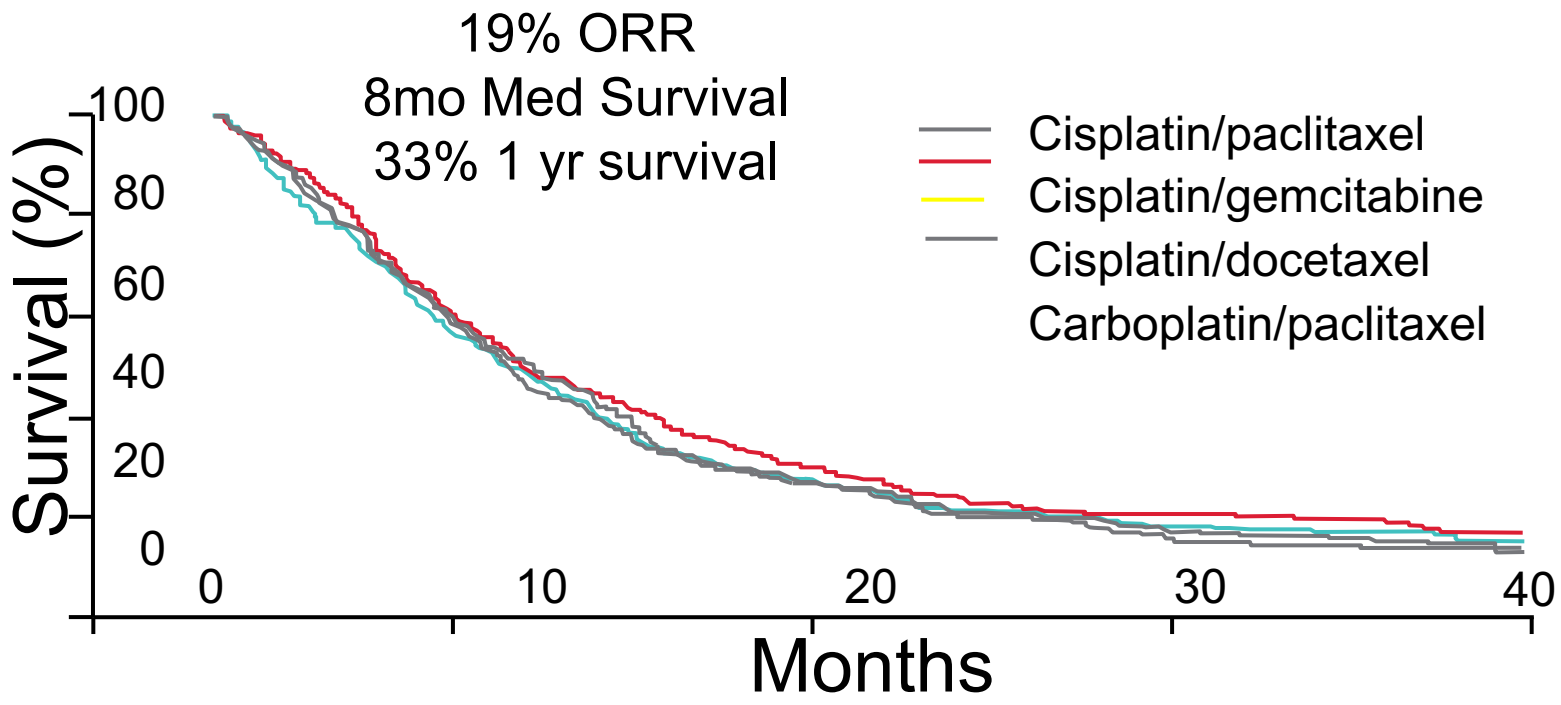
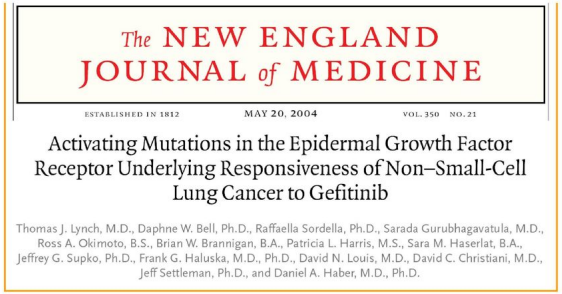
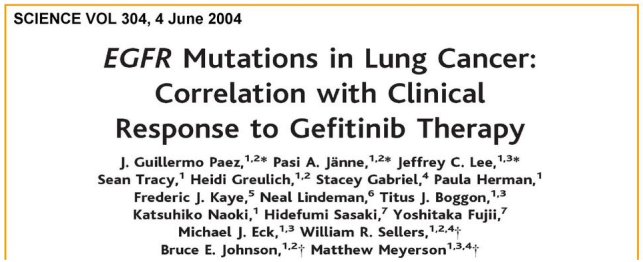
Where we started



Schiller et al. N Engl J Med. 2002;346:92.

Eternal optimism—hope





hope

noun

1a: desire accompanied by expectation of or belief in fulfillment

***also* : expectation of fulfillment or success**

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Decrease in lung cancer mortality

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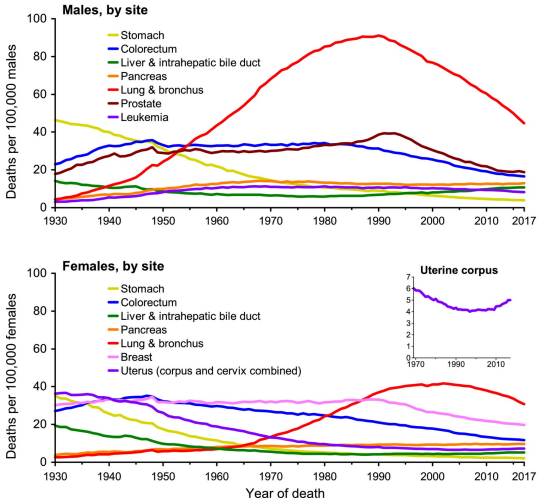
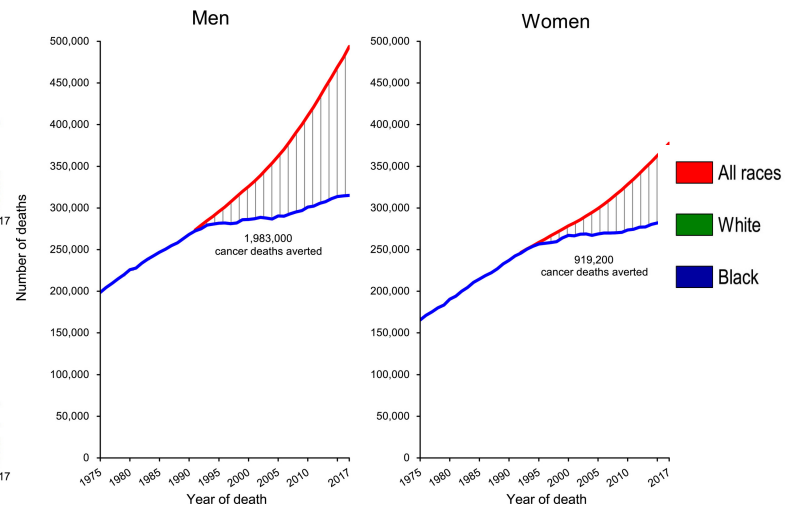
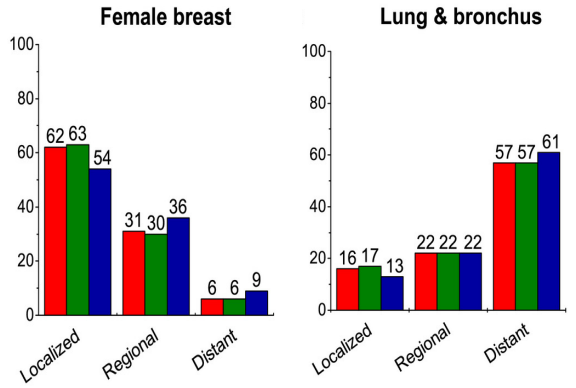
"…declines accelerated for lung cancer mortality, from 3% annually during 2008 through 2013 to 5% during 2013 through 2017 in men and from 2% to almost 4% in women, spurring the largest ever single-year drop in overall cancer mortality of 2.2% from 2016 to 2017."







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

Adjuvant and neoadjuvant chemotherapy improves 5-yr survival in early stage NSCLC

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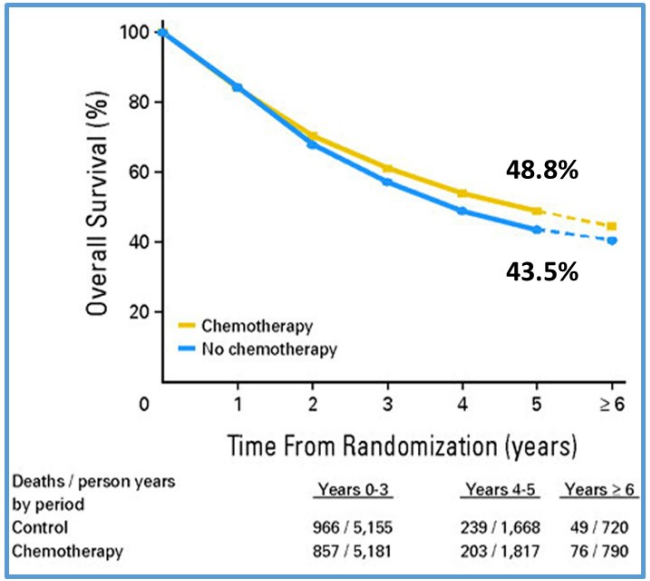
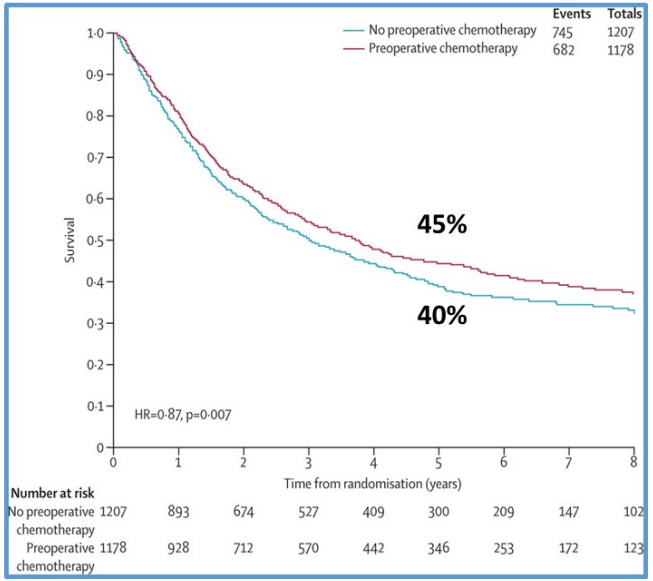
Post-Op Adjuvant CT



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Pignon J-P, et al. *J Clin Oncol* 2008;26:3552-9

Pre-Op Neoadjuvant CT



NSCLC Meta-analyses Collaborative Group. *Lancet* 2010;375:1267-77

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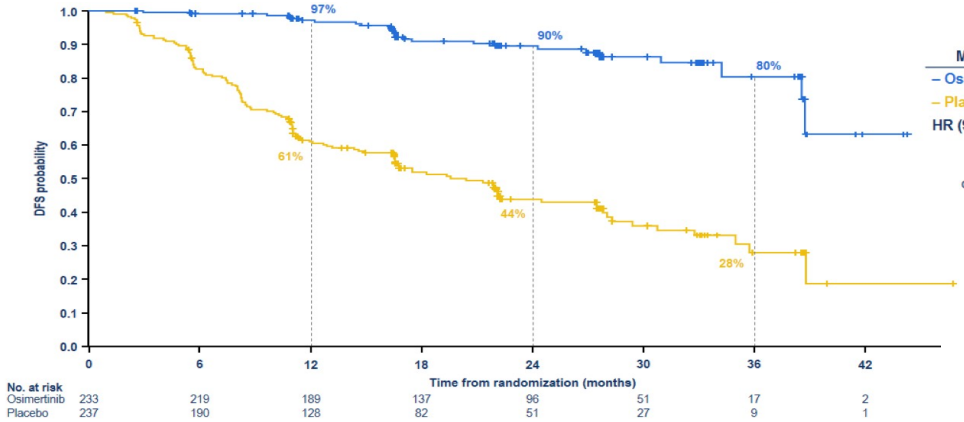
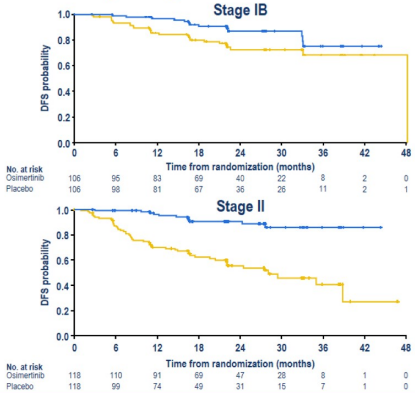
ADAURA—adjuvant osimertinib improves DFS

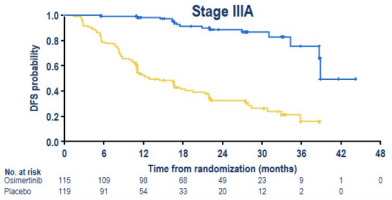


Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	0.17 (0.12, 0.23); p<0.0001

Maturity 33%:
osimertinib 11%, placebo 55%

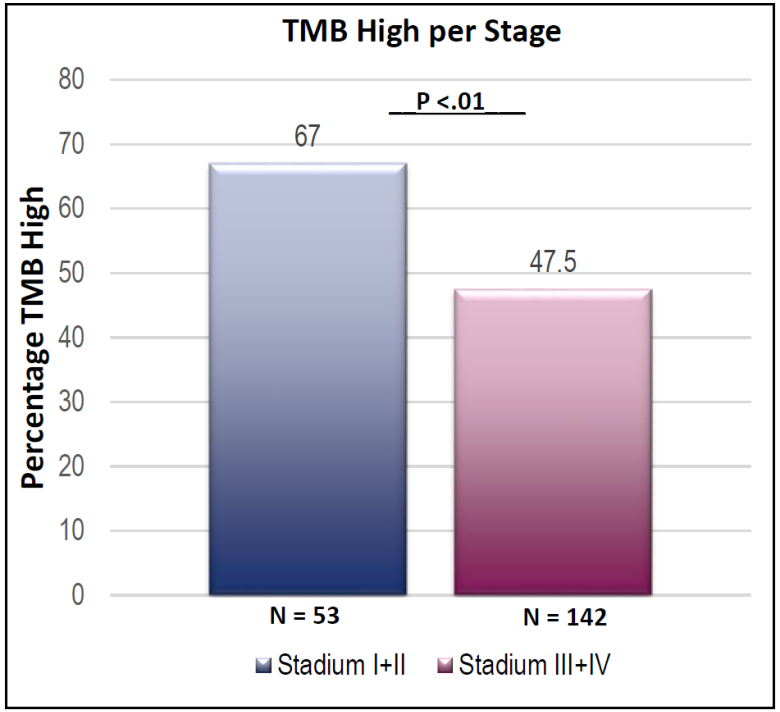


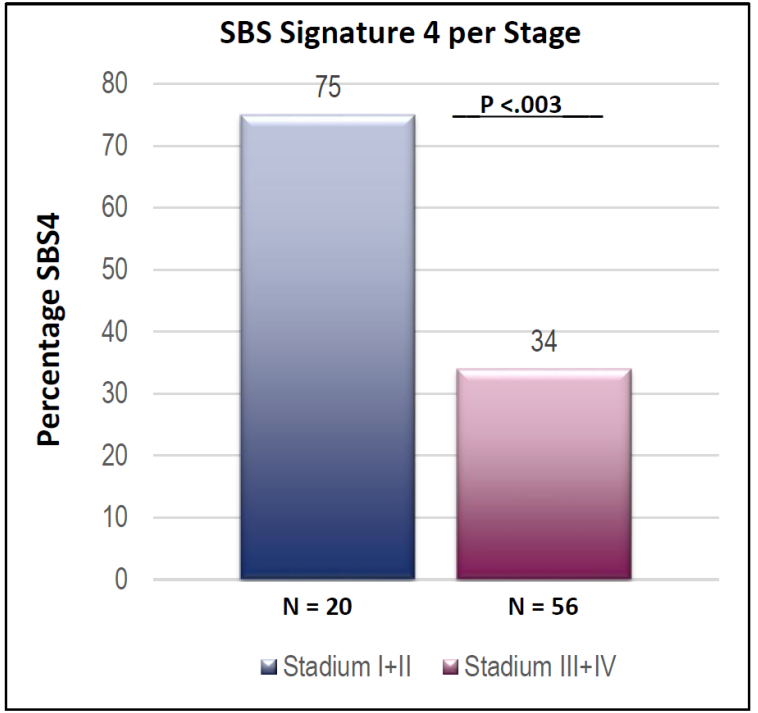
	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	0.50 (0.25, 0.96)	0.17 (0.08, 0.31)	0.12 (0.07, 0.20)



Herbst et al ASCO 2020; Wu et al NEJM 2020

TMB by stage in NSCLC





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MAP virtual congress 2020—Heuvel GVD et al. Ann Oncol 2020 31 (suppl_5): S1217-S1239.

Ongoing Phase III Clinical Trials With Adjuvant Immune Checkpoint Inhibitors

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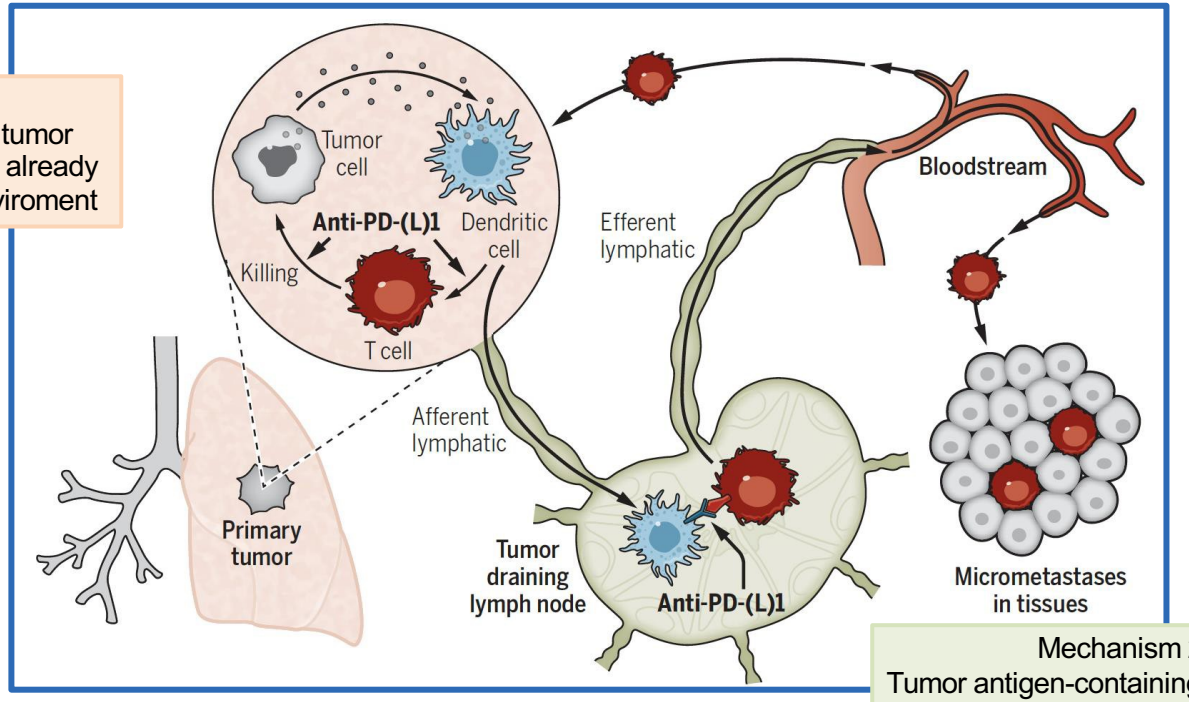
Trial	NCT	Drug	Stage	Target Accrual	Phase	End Point
PEARLS	NCT02504372	S with or without CT → pembrolizumab vs. placebo	IB–IIIA	1080	III	DFS
BR31	NCT02273375	S with or without CT → durvalumab vs placebo	IB–IIIA	1360	III	DFS, DFS in PD-L1 positive
ANVIL	NCT02595944	S with or without CT → nivolumab vs. observation	IB–IIIA	903	III	DFS, OS
ALCHEMIST CHEMO I-O	NCT04267848	S → CT > observation vs CT > pembrolizumab vs. CT + pembrolizumab > pembrolizumab	IB–IIIA	1263	III	DFS, OS
IMpower010	NCT02486718	S with CT → atezolizumab vs best supportive care	IB–IIIA	1280	III	DFS

CT, adjuvant chemotherapy; DFS, disease-free survival; NCT, National Clinical Trial; OS, overall survival; PD-L1, programmed death-ligand 1; S, surgery.

Uprety D et al J Thorac Oncol 2020

Mechanisms of enhancing a systemic immune response with neoadjuvant IC inhibitors

Mechanism 1
"in situ" expansion of tumor
Specific T cell clones already
In the tumor microenviroment



Mechanism 2
Tumor antigen-containing dendritic cells in the tumor traffic to the tumor-draining lymph nodes to enhance production of tumor-specific T cells

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Topilian SL, et al. Science Jan 2020

Summary of Results of Trials Using Neoadjuvant Immunotherapy in Patients With Resectable NSCLC

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Study	Stage	Sample Size	Neoadjuvant Immunotherapy	No. of Cycles	Failure to Surgery After Neoadjuvant, %	Primary End Point	MPR, %
Forde et al.2018	I–IIIA	22	Nivolumab	2	0	Safety and feasibility	45
Kwiatkowski et al.2019	Ib–IIIB	101	Atezolizumab	2	11	MPR	19
Cascone et al.	I–IIIA	44	Nivolumab vs. nivolumab + ipilimumab	3[a]	11	MPR	17 vs. 33 (ITT) 19 vs. 44 (evaluable)
Li et al.2019	IA–IIIB	40	Sintilimab	2	7.5	Safety	40.5
Shu et al.2018	IB–IIIA	14	Atezolizumab + carboplatin + nab-paclitaxel	4	21.4	MPR	50
Provencio et al.2019	IIIA	46[b]	Nivolumab + carboplatin + paclitaxel	3	0	PFS at 24 mo	83

ITT, intention-to-treat; MPR, major pathologic response; PFS, progression-free survival.
[a] Three cycles of nivolumab with or without one dose of ipilimumab.
[b] Preliminary data of 41 patients.

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Uprety D et al J Thorac Oncol 2020

Ongoing Clinical Trials With Neoadjuvant Immune Checkpoint Inhibitors With or Without Chemotherapy

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Trial	NCT	Drug	Stage	Target Accrual	Phase	End Point
MK3475-223	NCT02938624	Pembrolizumab different dose/regimens → S	I–II	28	I	Toxicity, MPR
TOP 1501	NCT02818920	Pembrolizumab (200 mg) × 2 cycles → S → pembrolizumab (200 mg) × 4 cycles	IB–IIIA	32	II	Surgical feasibility
PRICNEPS	NCT02994576	Atezolizumab (1200 mg) × 1 cycle → S	IB–IIIA (no N2)	60	II	Toxicity
SAKK 16/14	NCT02572843	CT × 3 → durvalumab (750 mg) × 2 cycles → S → durvalumab (750 mg) × 1 y	IIIA (N2)	68	II	EFS
IONESCO	NCT03030131	Durvalumab (750 mg) Q2W × 3 cycles → S	IB–II	81	II	R0 resection
Columbia University	NCT02716038	CT + atezolizumab (1200 mg) × 4 cycles → S	IB–IIIA	30	II	MPR
KEYNOTE 617	NCT03425643	CT + pembrolizumab (200 mg)/placebo × 4 cycles → S → pembrolizumab/placebo × 13 cycles	II–IIIB (T3-4N2)	786	III	EFS, OS
CheckMate 816[a]	NCT02998528	CT + nivolumab (360 mg) × 3 cycles → S vs. CT × 3 cycles → S	IB–IIIA	350	III	EFS, pCR
IMpower 030	NCT03456063	CT + atezolizumab (1200 mg)/placebo × 4 cycles → S → atezolizumab/placebo × 16 cycles	II–IIIB (cT3N2)	374	III	MPR, EFS
AEGEAN	NCT03800134	CT + durvalumab (1500 mg)/placebo × 3 cycles → S → durvalumab/placebo Q4W × 12 cycles	IIA–IIIB	300	III	MPR

CT, chemotherapy; EFS, event-free survival; MPR, major pathologic response; NCT, National Clinical Trial; OS, overall survival; pCR, pathologic complete response; Q4W, every 4 weeks; S, surgery.
[a]The third arm of the trial, nivolumab plus ipilimumab, was withdrawn after results from NADIM trial.

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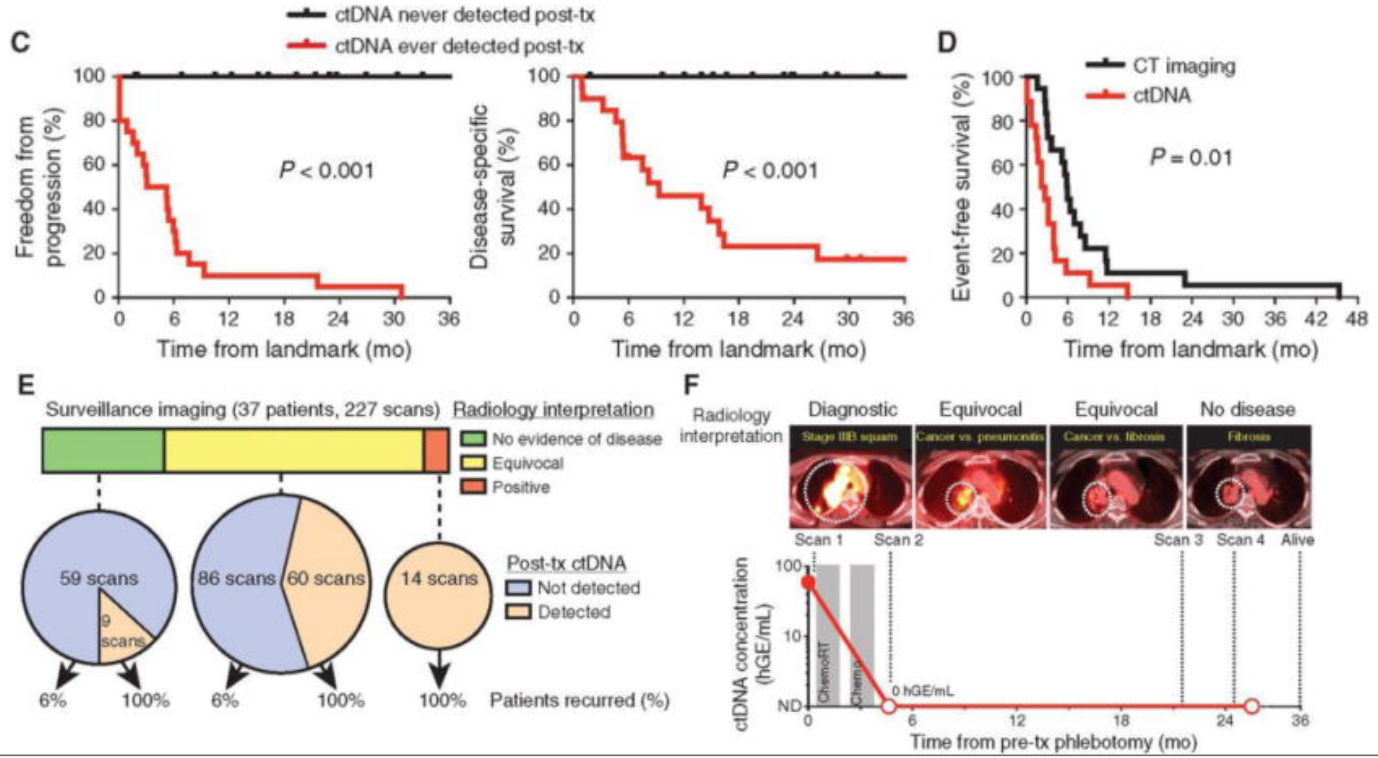
Uprety D et al J Thorac Oncol 2020

Analysis of ctDNA for posttreatment surveillance



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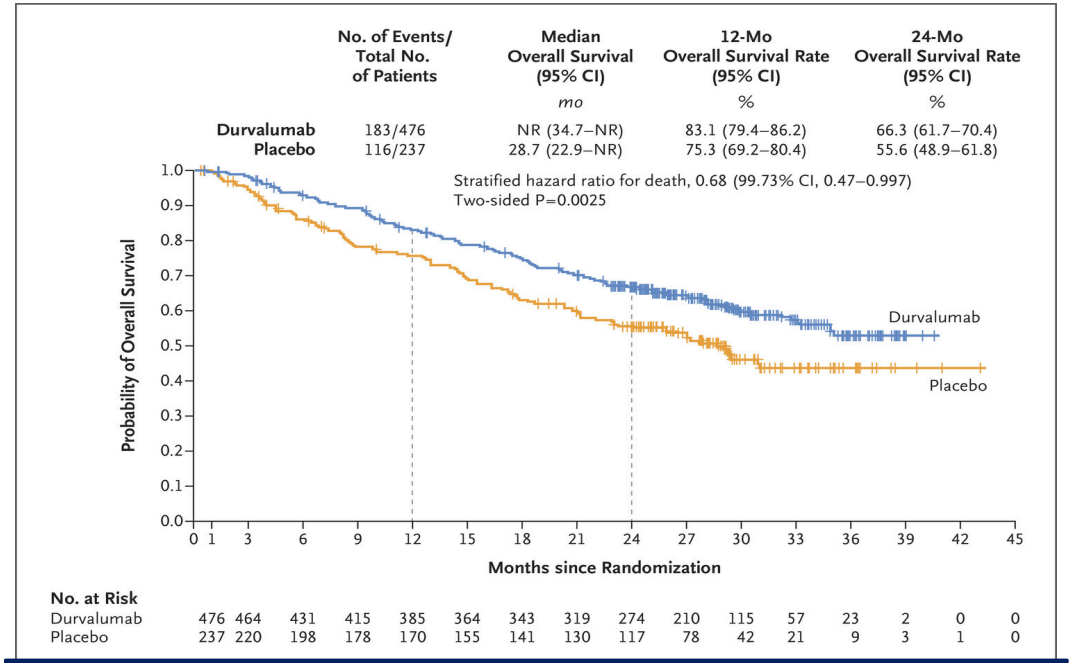
Chaudhuri AA et al Cancer Discov 2018

Pacific trial—durvalumab consolidation following chemoradiation



4 yr OS update ESMO September 2020
49.6% vs. 36.5%, favoring durvalumab

SJ Antonia et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1809697

NLST and NELSON Lung Cancer Incidence and Mortality

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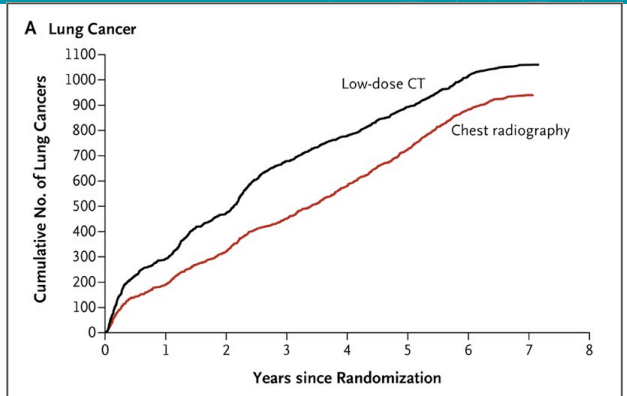
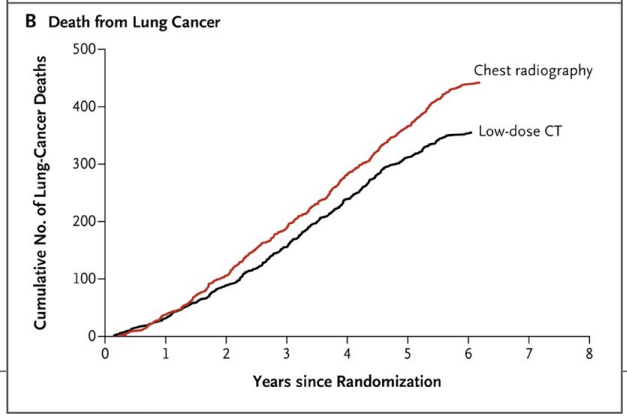
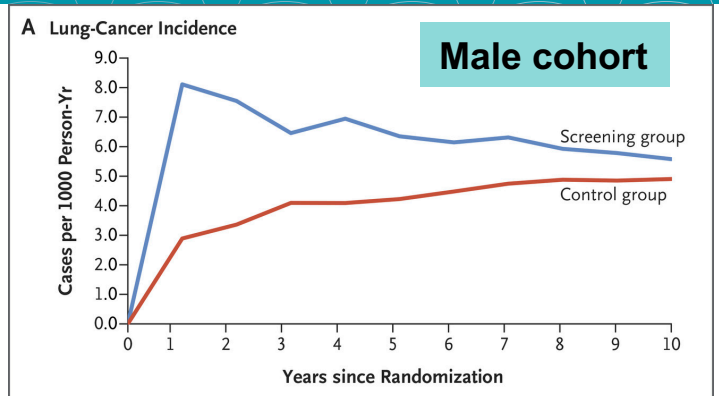
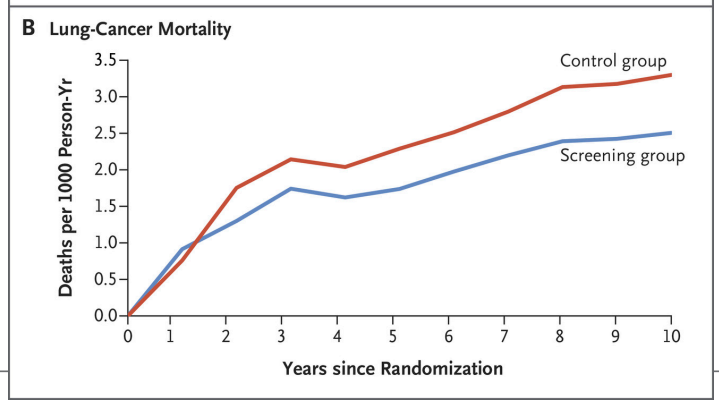
NLST





NELSON





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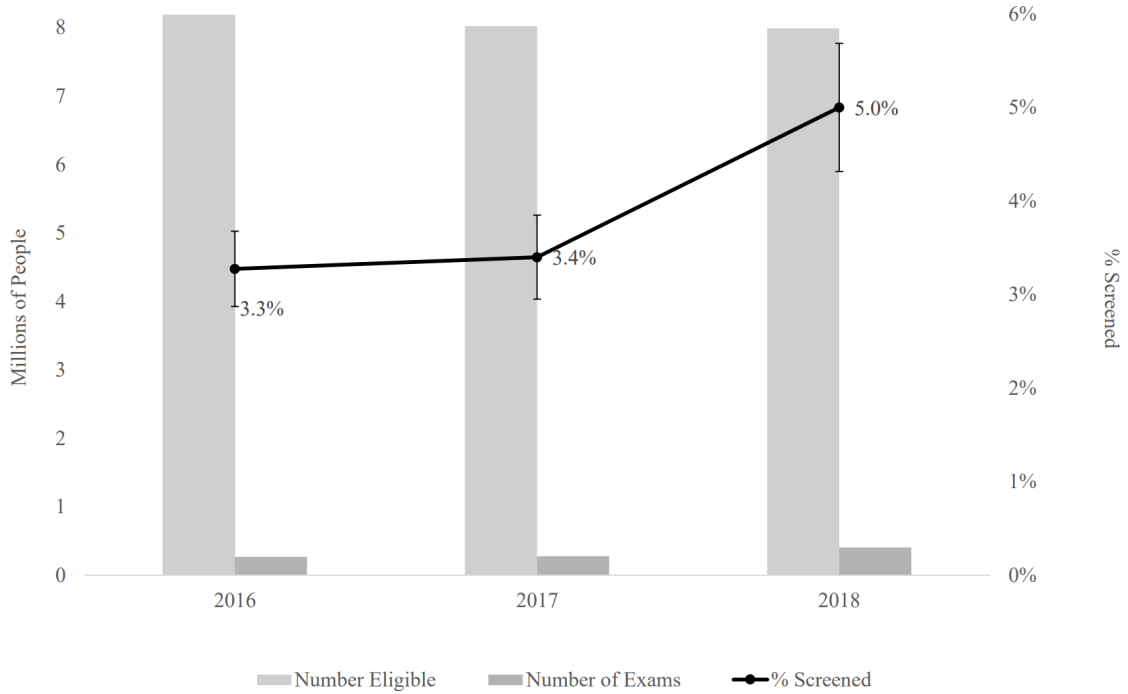
The National Lung Screening Trial Research Team. N Engl J Med 2011;365:395-409

HJ de Koning et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa1911793

Lung cancer screening misses the mark



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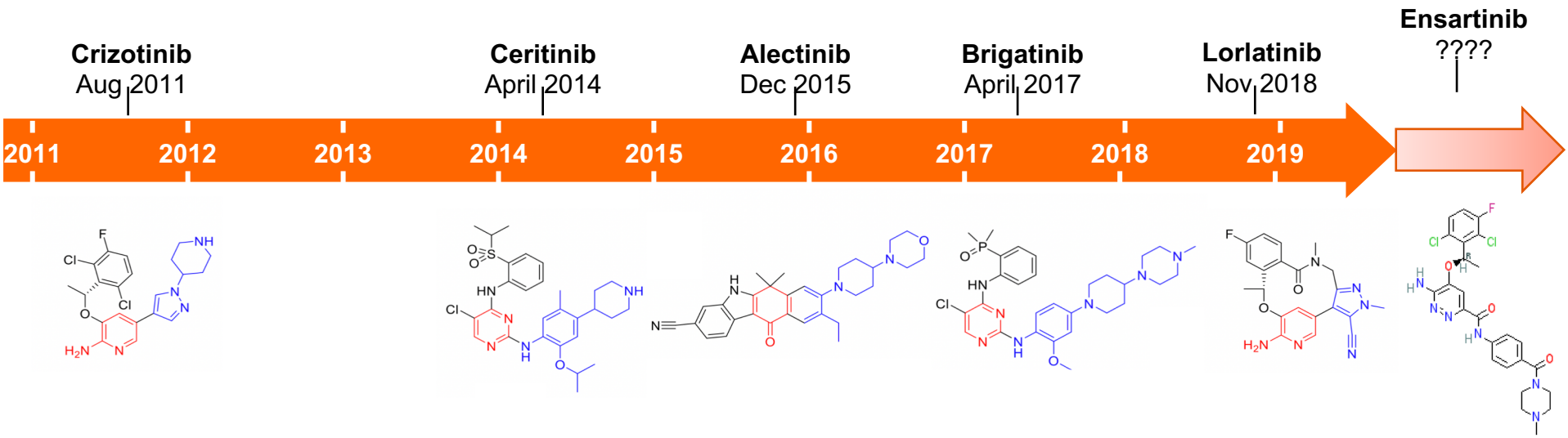
Fedewa SA et al. JNCI 2020

Oncogene	Mutation prevalence	Therapy	Predicted response rate
EGFR	Asians 30-40%/ Caucasian 10-20%	EGFR TKIs (most mutations)/pan-HER inhibitors	**Erlotinib 60-80%** **Gefitinib 70%** **Afatinib 60%** **Dacomitinib 75%** **O tinib 80%/ 50-60% (T790M)**
ALK	1-7%	ALK inhibitors/HSP90 inhibitors	**50-60%** **0%** **%** **%** **%**
ROS1	1.7%, higher in A		**otinib 60-70%; Ceritinib 60%** **Lorlatinib 62%; Entrectinib 77%**
NTRK	<	rs	**Larotrectinib 76%** **Entrectinib 70%**
RET	1.7% EGFR	RET inhibitors/ multitargeted TKI	**Selpercatinib 60-80%** **Pralsetinib 60-70%** Cabozantinib 40%;Vandetinib 20%
BRAF	2%	BRAF/MEK inhibitors	Dabrafenib 30% **Dabraf/trametinib 60%**
MET	4%	MET inhibitors/ multitargeted TKI	**Capmatinib 60%** Tepotinib/Savolitinib ~50%; Crizotinib 25%
HER2	2%	Trastuzumab; pan-HER inhibitors	Trastuzumab Deruxtecan 60% Dacomitinib 12% Ado-trastuzumab 20%; TDM-1 44%
KRAS G12C	9%	KRAS G12C inhibitors SHP inhibitors	AMG 510 35%; MRTX 849 45%, LY3499446; JNJ-74699157, others

Timeline of FDA Accelerated Approvals of Small Molecule Tyrosine Kinase Inhibitors Targeting ALK



Adapted from A Shaw WCLC 2019

Liquid biopsy can facilitate treatment with targeted therapy

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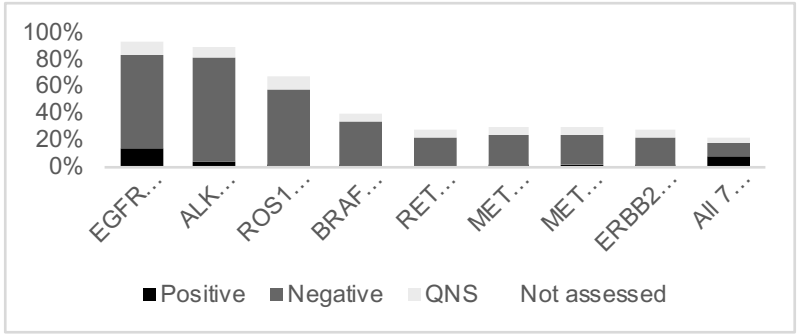
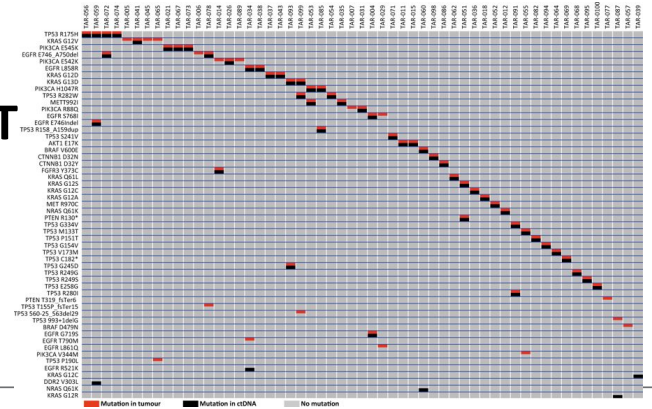
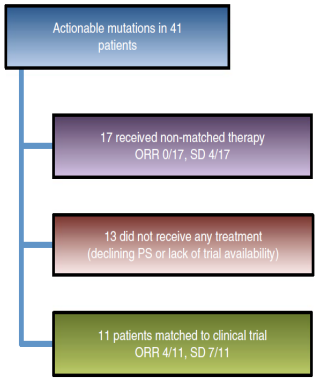
NILE



Use of cfDNA testing increased detection by 48%

TARGET





41% actionable mutations

11 received treatment

All had PR/SD

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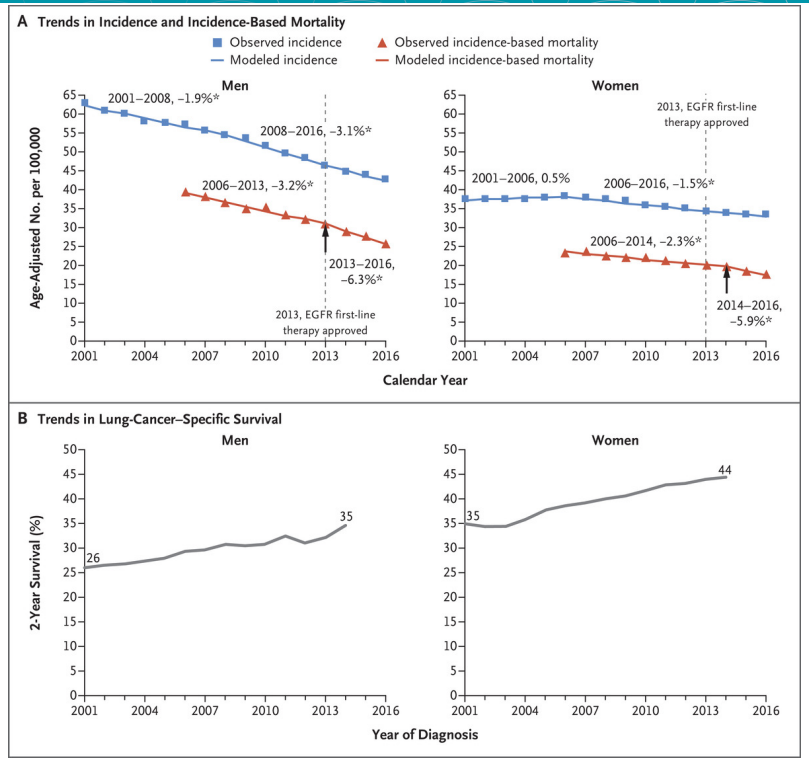
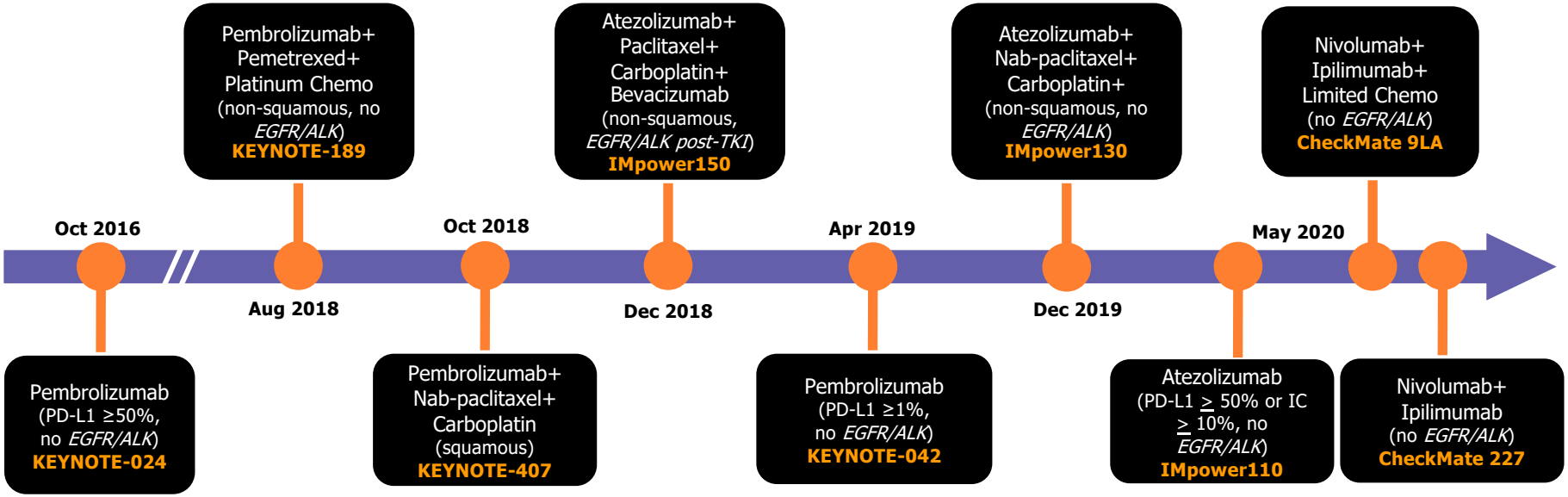
Leighl NB et al Clin Cancer Res 2019;
Rothwell DG et al Nat Med 2019

Decrease in incidence-based NSCLC mortality—due to targeted therapy



N Howlader et al. N Engl J Med 2020;383:640-649.

FDA First-line Approvals for Immunotherapy in Stage IV NSCLC



8 randomized trials have demonstrated efficacy with ICI + concurrent chemotherapy in the first-line setting in patients without an EGFR- or ALK-positive tumor (KEYNOTE-021G, -189, -407, IMpower130, -131, -132, Checkmate-9LA; IMpower150 allowed EGFR/ALK post-TKI).

3 randomized trials have demonstrated that ICI are appropriate as first-line treatment for selected patients based on tumor PD-L1 expression level and no EGFR- or ALK-driven alteration (KEYNOTE-024, -042 and IMpower110).

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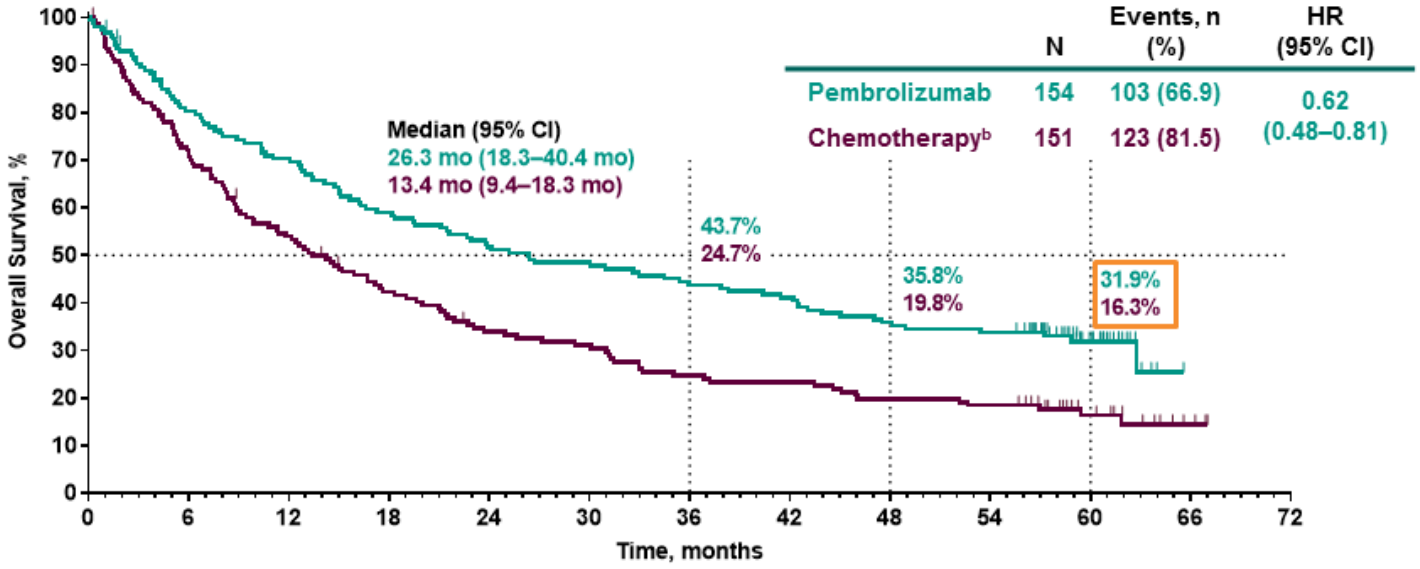
Slide courtesy of Mark Socinski, MD.

Keynote-024—Pembrolizumab frontline overall survival

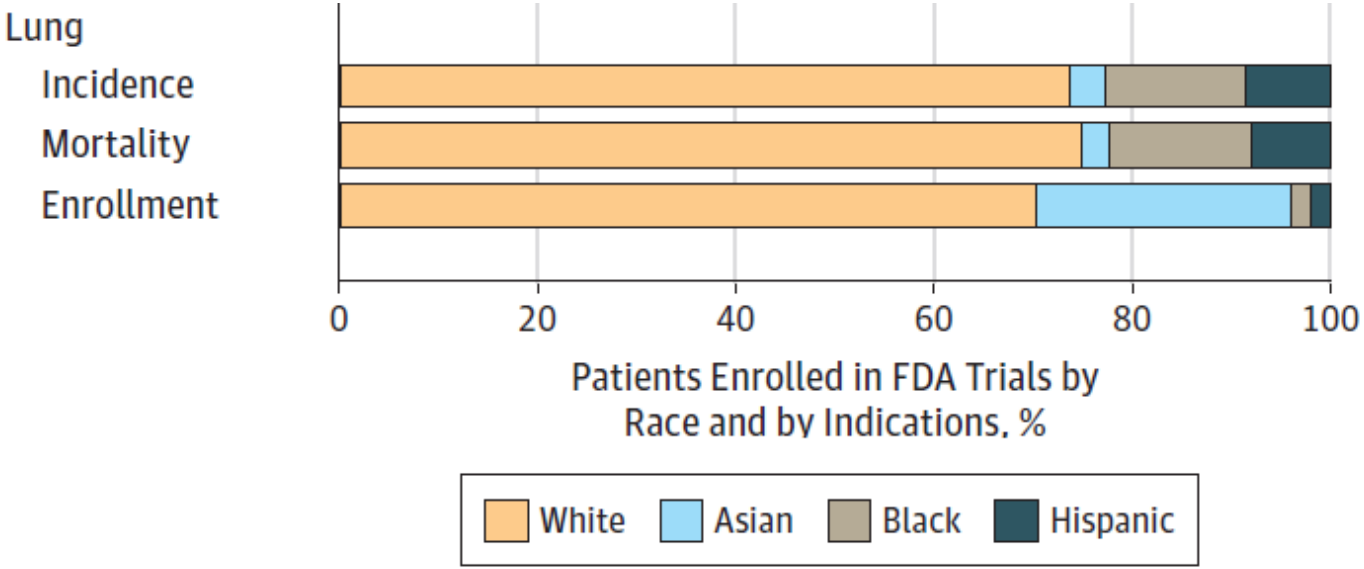


[a]ITT population.

[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

Brahmer J et al ESMO 2020

Lung cancer trial enrollment



Ethnic disparities in lung cancer clinical trials leading to FDA oncology drug approvals (vs USA LC population)

Courtesy of Janet Freeman-Daily, The ROS1ders, USA, @JFreemanDaily

Loree et al, JAMA Oncol. 2019 Aug 15;5(10):e191870. doi: 10.1001/jamaoncol.2019.1870

Continuing on the road less traveled

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The Road Not Taken—Robert Frost

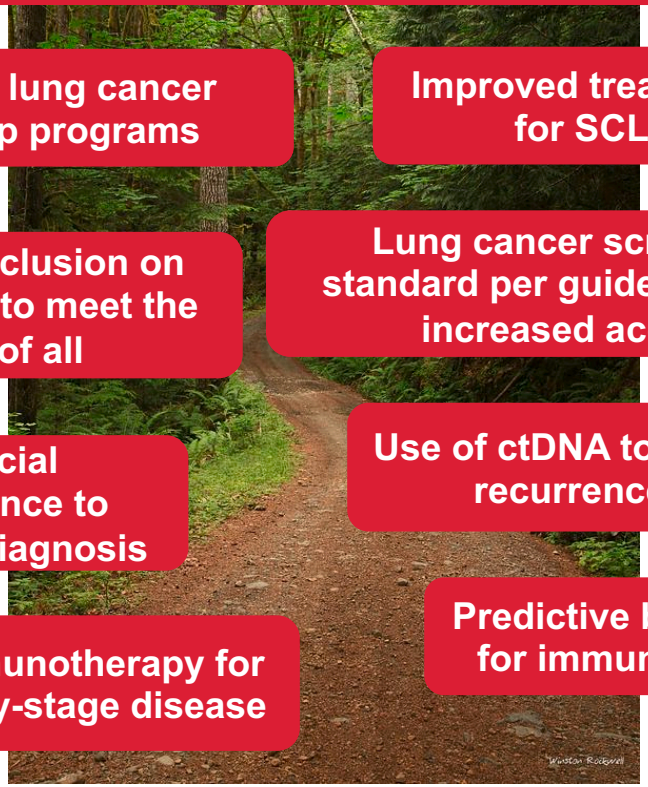
Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same,

And both that morning equally lay
In leaves, no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

Increased lung cancer cures



- Established lung cancer survivorship programs
- Improved treatments for SCLC
- Enhanced inclusion on clinical trials to meet the needs of all
- Lung cancer screening standard per guidelines, and increased access
- Artificial intelligence to improve diagnosis
- Use of ctDNA to determine recurrence risk
- Immunotherapy for early-stage disease
- Predictive biomarkers for immunotherapy

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Thank you!

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