LUNG CANCER: YEAR IN REVIEW

THE TOP 5+ ARTICLES 2017-2018

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UNC™
LINEBERGER COMPREHENSIVE CANCER CENTER

- RISK
- SCREENING
- TREATMENT OF:
    - EARLY STAGE NSCLC
    - LOCALLY ADVANCED DISEASE
    - ADVANCED NSCLC
    - SMALL CELL LUNG CANCER
- IMMUNOTHERAPY TOXICITY

RISK

Global trends and projections for tobacco use, 1990–2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control

Ver Bilano, Stuart Gilmour, Trevor Moffiet, Edouard Tursan d'Espaignet, Gretchen A Stevens, Alison Commar, Frank Tuyl, Irene Hudson, Kenji Shibuya

If trends remain unchanged, 1.1 billion smokers world wide in 2025

The Lancet 2015:385;966-76

IJC
International Journal of Cancer

Association between long-term low-intensity cigarette smoking and incidence of smoking-related cancer in the national institutes of health-AARP cohort

Maki Inoue-Choi, Patricia Hartge, Linda M. Liao, Neil Caporaso and Neal D. Freedman

Int. J Cancer 2017; 142: 271-280

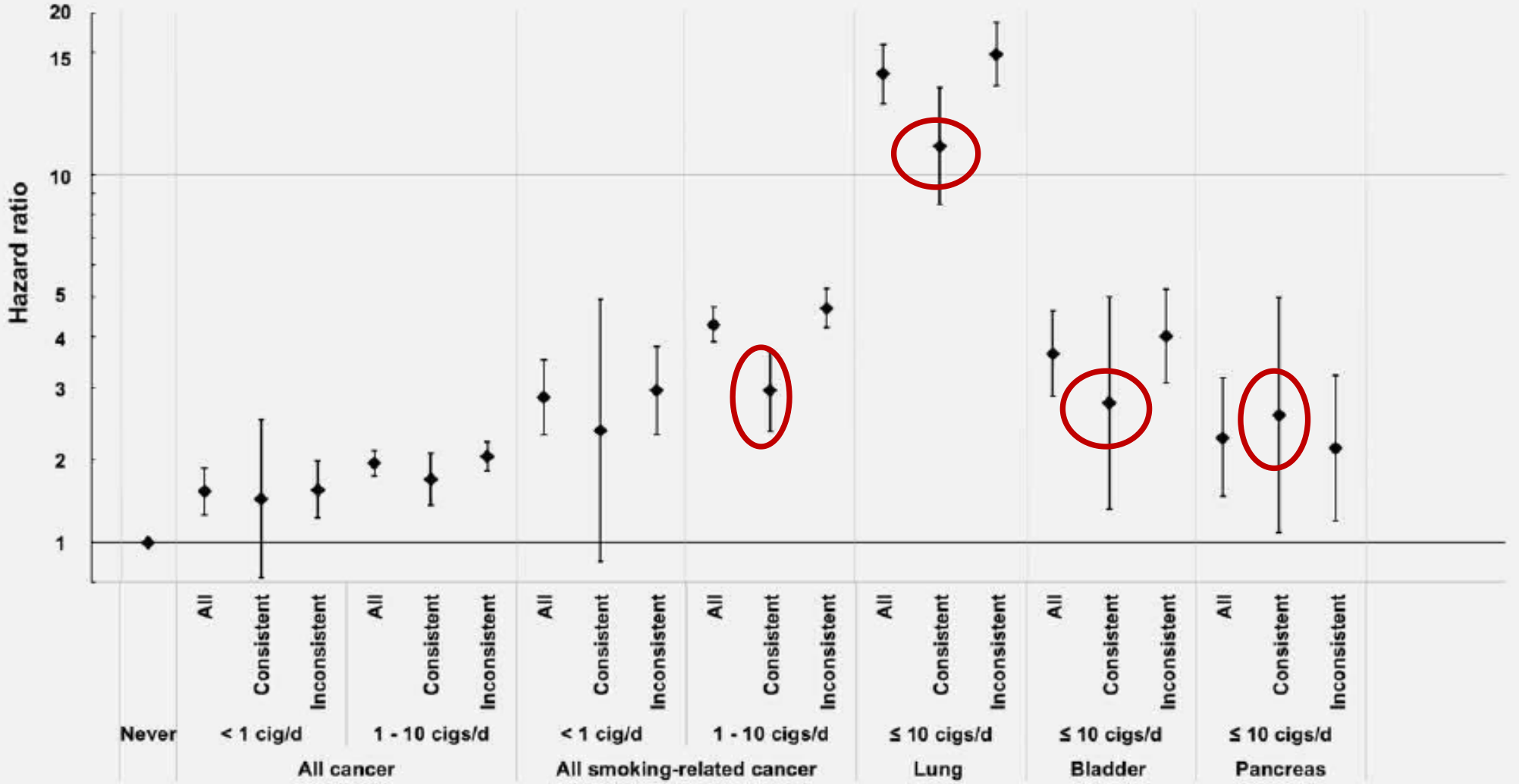
Fact: Smoking major risk for lung cancer

Unknown: The impact of "low-intensity" smoking

-Is there less harm from indulging in the occasional cigarette (1- <10 per day) when compared to heavy smoking (>10 per day)?

NIH- AARP Diet and Health Study

- Over 230,000 patients, aged 59-82
- Questionnaire assessed cigarettes per day (CPD)
- Calculated cancer risk (HR)



Stratified by consistent or varied cigarettes per day (CPD) during the lifetime:

- compared to never smokers, consistent lifelong 1-10 CPD smokers had higher risk of smoking-related cancer (HR 2.34)
- Associations for lifelong smoking ≤ 10 with:

Lung cancer (HR 9.6), bladder cancer (HR 2.22), and pancreatic cancer (HR 2.03)

Even low-levels of cigarette smoking cause cancer

SCREENING

Annals of Internal Medicine

ORIGINAL RESEARCH

Risk-Targeted Lung Cancer Screening

A Cost-Effectiveness Analysis

Vaibhav Kumar, MD; Joshua T. Cohen, PhD; David van Klaveren, PhD; Djøra I. Soeteman, PhD; John B. Wong, MD; Peter J. Neumann, ScD; and David M. Kent, MD, MS

Ann Intern Med 2018;168:161-69

- Participants at highest predicted risk for lung cancer death are most likely to benefit from screening (account for most of screening prevented lung cancer mortality) (NEJM 2013)

- Limitation, benefits of screening with LDCT measured in terms of reduced lung cancer mortality over 5-7 years per patient screened

- In this study:
  - Applied multistate regression model to calculate predicted lifetime benefits and costs of screening for each NLST participant

  - Examine value of applying an individualized risk approach to selecting participants for screening compared with the NLST inclusion criteria

Annals of Internal Medicine

ORIGINAL RESEARCH

Risk-Targeted Lung Cancer Screening

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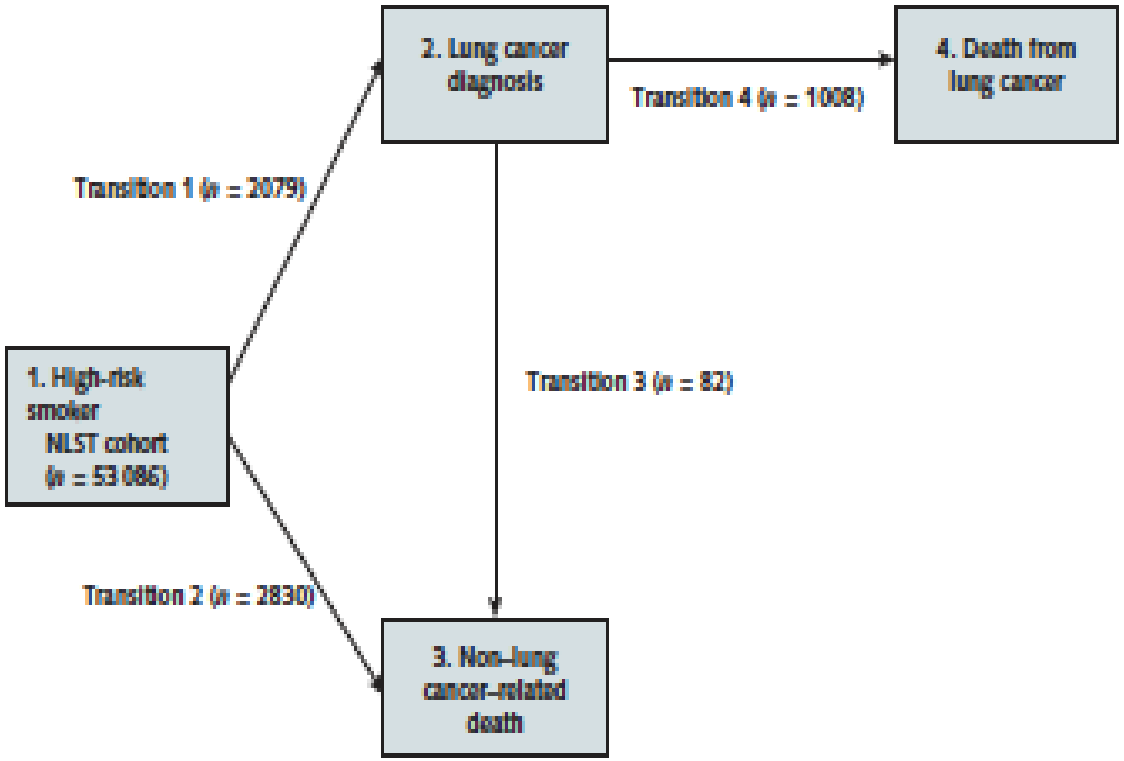
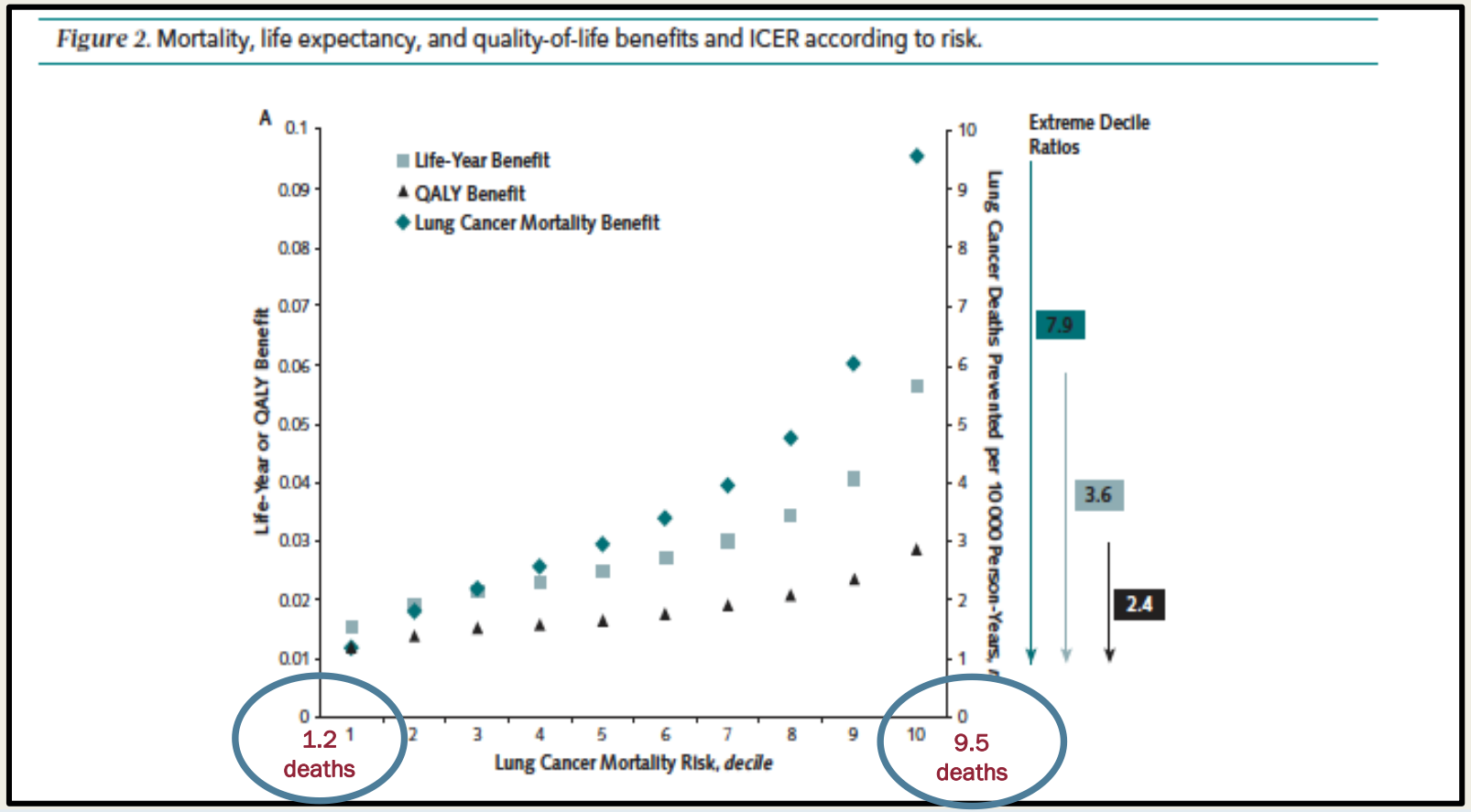
Figure 1. Structure of the multistate model.



All patients enter the multistate model as high-risk smokers defined by the NLST entry criteria. The model consists of 4 health states with 4 possible

Risk targeted lung cancer screening
Cost effectiveness

- Individualized predictions of the probability of being in each of the 4 states at any given time point
- These predictions used to estimate individualized lung cancer mortality benefits of screening at 7 years
- Cost estimated using NLST data and linear regression prediction models combined with assumptions to estimate lifetime medical costs
- Calculated incremental net monetary benefit for each participant based on NLST inclusion criteria vs risk stratification screening strategy



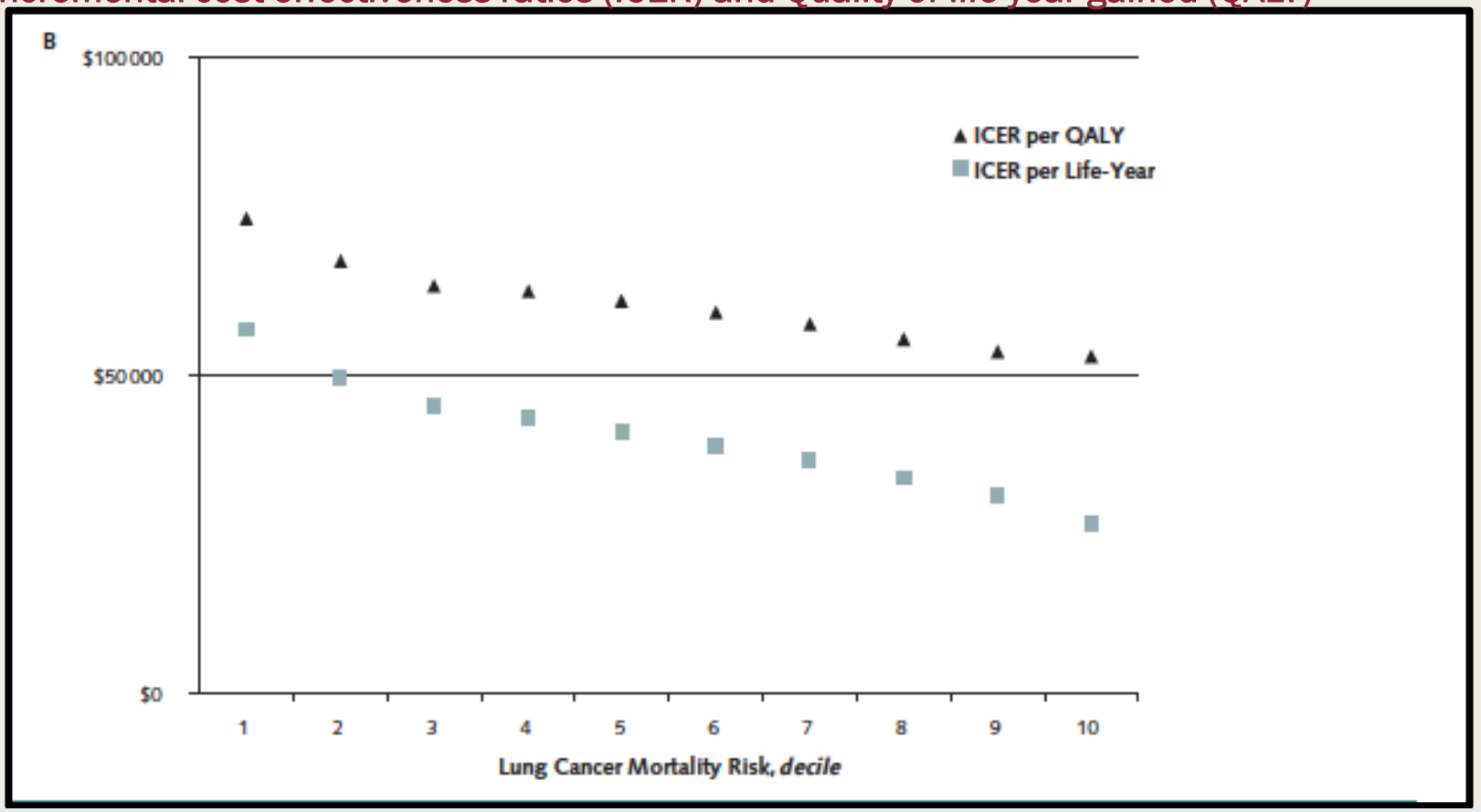
Health benefits:

- Lung cancer mortality benefit increased with increasing baseline risk for lung cancer death: 1.2 Vs 9.2 per 10,000 person-years

Benefit gradient across risk groups:

- Lung cancer mortality benefit greater ratio: 7.9
- But attenuated when comparing life-years gained ratio: 3.6
- Further attenuation when comparing QALYs gained ratio: 2.4

Incremental cost effectiveness ratios (ICER) and Quality of life year gained (QALY)



Screening with LDCT increased lifetime cost by 1089 compared to CXR, yielding and ICER of 37 000 per life year gained or 60 000 per QALY

Cost of screening increased based on risk of lung cancer mortality

- In high risk group: not only increased cost of lung cancer treatment but also had more invasive testing after positive results
- Among higher risk patients, the greater incremental costs offset the incremental benefits

Risk targeted lung cancer screening
Cost effectiveness

- Individuals at high baseline risk for lung cancer death:
  - *Achieve greatest benefit in terms of LDCT-prevented lung cancer deaths in the first 7 years*
  - *But, are older, have greater smoking history and more likely to have coexisting illness such as COPD*
  - *Had increased cost not only due to treatment of screen- detected cancer but had more procedures to evaluate screen-detected abnormalities*
  - *Benefit of screening was greatly attenuated when expressed as life years and QALYs over a lifetime*

- Conclusion:
  - *Each older higher risk person with more comorbid conditions who survives lung cancer because of screening accrues fewer additional life years than younger healthier participants*
  - *While individualized risk-targeted approach to selection for screening may be better at selecting high risk patients, it proved no more cost effective that the broader NLST inclusion criteria.*

Lung Cancer Screening With Low-Dose Computed Tomography in the United States—2010 to 2015

JAMA Oncology 2017;3:1278-80

- Survey 2347 individuals who met NLST and USPSTF criteria for screening
- 2167 available for analyses
- **Eligible smokers who reported LDCT screening:**
  - *2010 3.3%*
  - *2015 3.9%*
- No significant increase in screening in the five years for any of the socioeconomic groups
- Over 50% of smokers meeting recommendations for screening were uninsured or Medicaid insured
- **Resons for low uptake of LCS:**
  - *Lack of knowledge about screening among smokers*
  - *Lack of access to care*
  - *Physician knowledge about recommendations*
  - *Reimbursement*

Lung Cancer Screening (LCS) Implementation: Challenges

- LCS took the stage at a time when traditional approaches to mass screening are being challenged

- Moving away from:
  - Paternalistic model, screening is considered mandatory to a patient-centered model, individualizing decisions that are informed by discussion of potential benefits and harms
  - The one-size-fits-all model of screening is simple to implement, unable to acknowledge diverse values and patient preferences

- The decision to screen or not to screen for lung cancer places additional demands on patients, providers, and health care systems

  - *Ann Am Thorac Soc 2017;8:1261–1265*

Multilevel barriers to effective lung cancer screening

Patient-level barriers	Provider-level barriers	System-level barriers
1. Competing needs and demands for health care 2. Cost 3. Fear (e.g., procedures, diagnosis, treatment) 4. Lack of awareness 5. Lack of interest due to stigma associated with smoking 6. Limited access to care due to financial or social factors 7. Limited information and misinformation 8. Logistical issues (e.g., inconvenience, time) 9. Mistrust of the health care system and/or health care 10. Nihilism	1. Competing demands for time 2. Evolving attitudes about the effectiveness of screening 3. Lack of awareness 4. Limited information and misinformation 5. Limited training in shared decision-making 6. Nihilism related to treatment of lung cancer 7. Requirement for behavior change (adaptive challenge)	1. Lack of support from health system leaders 2. Limited resources including equipment, personnel, and information technology resources 3. Competing demands for limited resources (e.g., other screening programs or preventive health interventions) 4. Uncertain return on investment 5. Complexity of implementation (requires multidisciplinary collaboration) 6. Conflicting upper age range recommendations for screening 7. Identification of screening-eligible patients (gaps in smoking status data)

Ann Am Thorac Soc 2017;8:1261–1265

TREATMENT OF NSCLC: TIMING OF SURGERY

Impact of Timing of Lobectomy on Survival for Clinical Stage IA Lung Squamous Cell Carcinoma

CHEST 2017; 152(6):1239-1250

Chi-Fu Jeffrey Yang, MD; Hanghang Wang, MD, PhD; Arvind Kumar, BS; Xiaofei Wang, PhD; Matthew G. Hartwig, MD, MHS; Thomas A. D'Amico, MD; and Mark F. Berry, MD, MHS

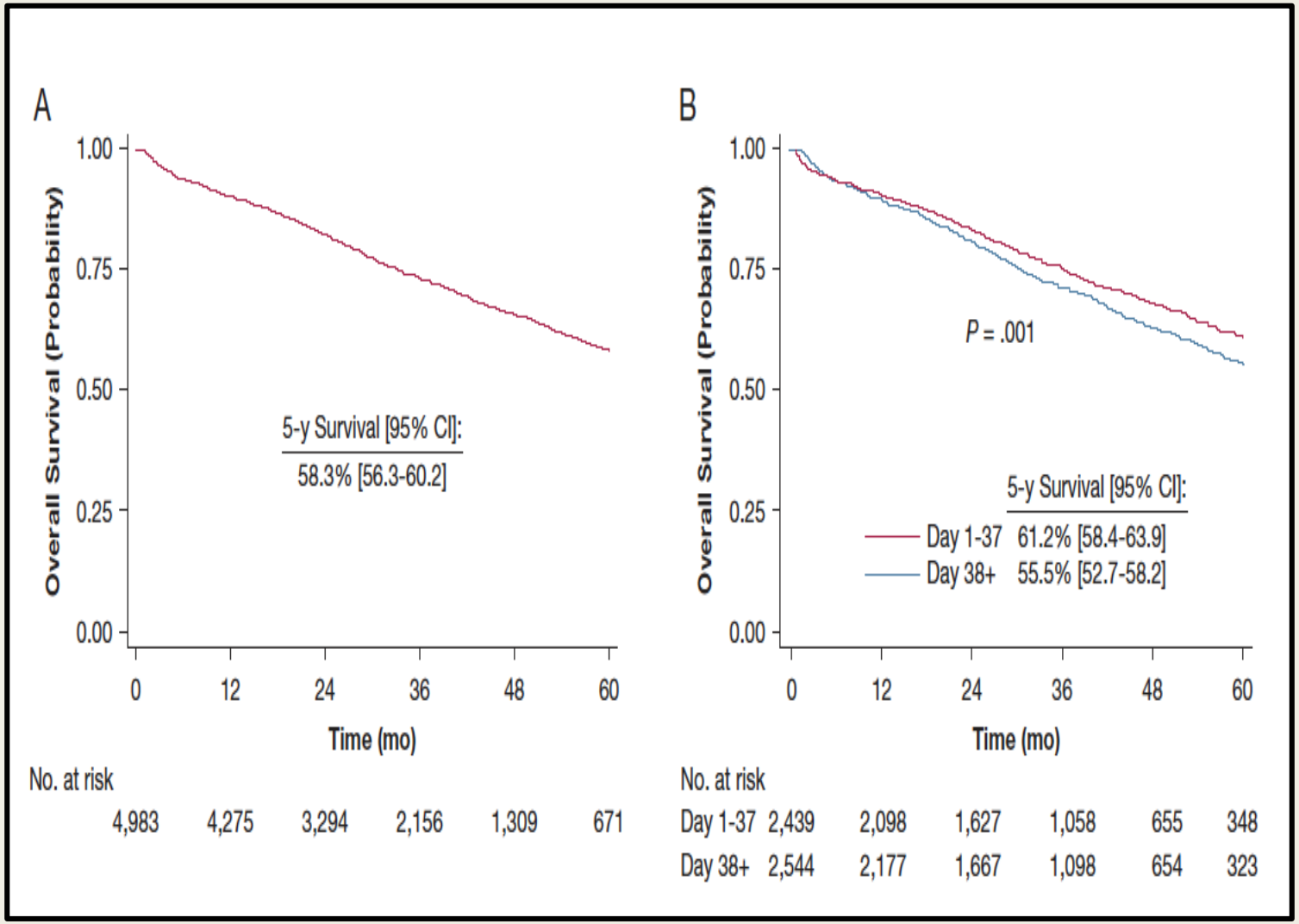
The relationship between the timing of surgery following diagnosis of lung cancer and survival has not been precisely described.

This study tested the hypothesis that increasing the time between diagnosis and lobectomy for stage IA squamous cell carcinoma (SCC) would be associated with worse survival.

Choice of timing, 30 days, felt to be clinically reasonable as 30 days -1 mo has been previously used threshold in the literature and BTS guidelines

National Cancer Data Base (2006-2011). Multivariable Cox proportional hazard analysis

Impact of Timing of Lobectomy in Squamous Cell Carcinoma



Results:

A. The 5-year overall survival of 4,984 patients who met study inclusion criteria was 58.3% (95% CI, 56.3-60.2).

Surgery was performed within 30 days of diagnosis in 36% patients. Median time to surgery was 38 days (interquartile range, 23, 58).

B. Patients who had surgery 38 days or more after diagnosis had significantly worse 5-year survival than patients who had surgery earlier (HR, 1.13 [95% CI, 1.02-1.25]; P . .022).

HR associated with time to surgery increased steadily the longer resection was delayed; the threshold time associated with statistically significant worse survival was 90 days or greater.

Impact of Timing of Lobectomy in Squamous Cell Carcinoma

TABLE 3] Independent Predictors of Mortality Following Cox Proportional Hazards Adjustment for Patients Who Underwent Lobectomy for cT1, N0, M0 NSCLC

Variable	HR	95% CI	*P* Value
Day of surgery (day 38+ vs days 1-37)	1.13	1.02-1.25	.022
Age, y	1.04	1.03-1.04	< .001
Female vs male sex	0.72	0.65-0.80	< .001
Race (reference = white)			
Black	1.14	0.94-1.38	.18
Other	1.09	0.70-1.88	.76
CDCC score (reference = 0)			
1	1.16	1.03-1.31	.015
2+	1.42	1.24-1.62	< .001
Insurance status (reference = uninsured)			
Private	0.46	0.28-0.74	.001
Medicare	0.84	0.50-1.42	.52
Medicaid	0.55	0.34-0.88	.014
Other government	0.35	0.16-0.76	.008
Unknown	0.71	0.36-1.40	.32
Tumor size, mm	1.00	1.00-1.00	.002
Facility type (reference = community)			
Comprehensive	0.81	0.68-0.97	.023
Academic	0.80	0.65-0.99	.036
Other	0.38	0.05-2.76	.34
Distance to facility, miles	1.00	1.00-1.00	.78
Hospital volume, No. of cases	1.00	1.00-1.00	.44
Median income (reference = first quartile)			
Second quartile	0.95	0.82-1.10	.49
Third quartile	0.87	0.75-1.01	.077
Fourth quartile	0.75	0.64-0.88	< .001
Tumor location (reference = RUL)			
RML	0.98	0.77-1.25	.88
RLL	1.03	0.89-1.20	.66
LUL	1.00	0.88-1.14	.97
LLL	1.04	0.88-1.22	.65
Primary site biopsy (reference = no biopsy)			
Biopsy before lobectomy	0.98	0.88-1.09	.72
Other/unknown	1.49	1.06-2.09	.023

Predictors of Survival

Age

Sex

Comorbidities

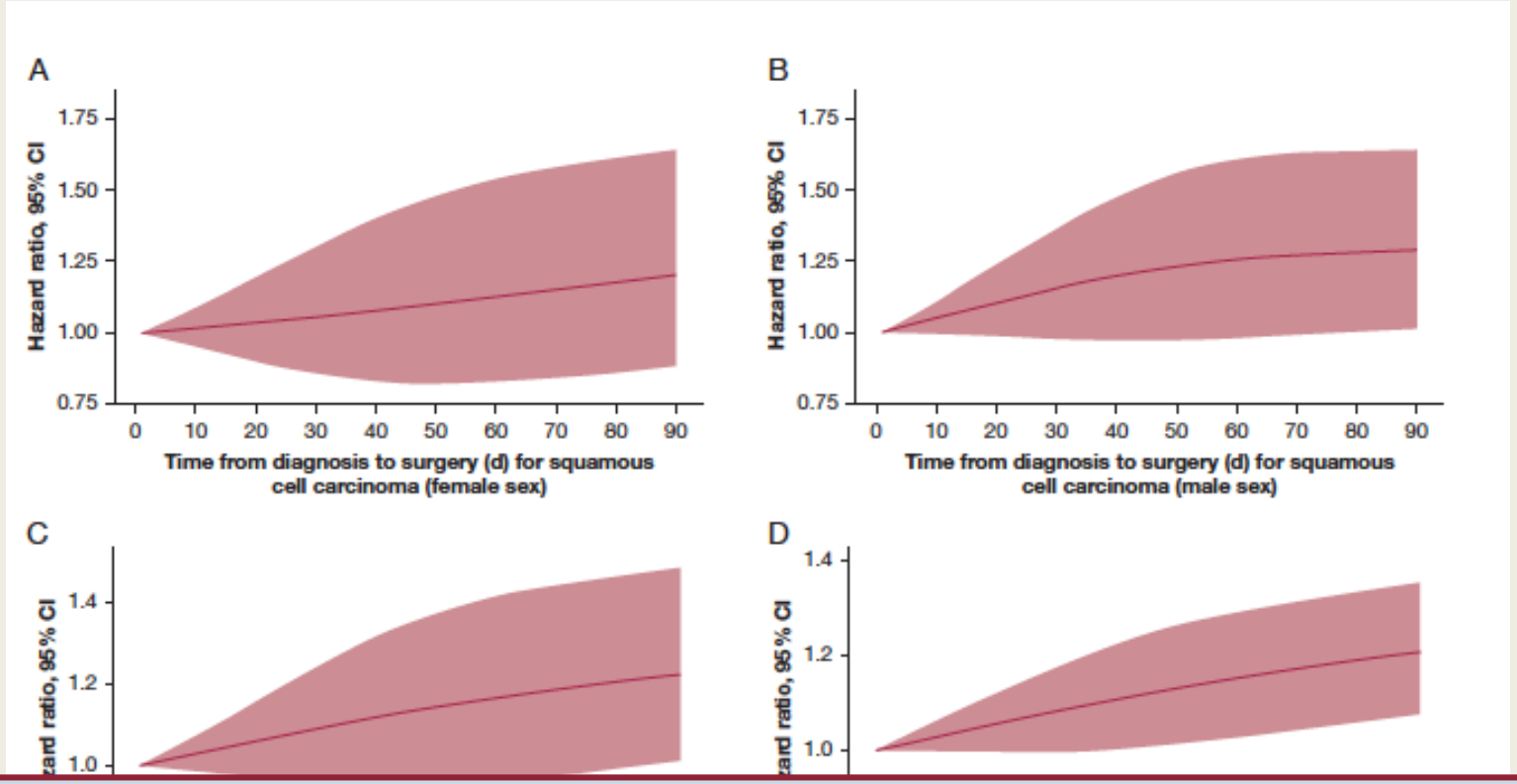
Tumor size

Type of insurance

Facility type

Median income level

Impact of Timing of Lobectomy in Squamous Cell Carcinoma



Restricted multivariate cubic plots show relationship between delayed surgery and HR stratified by sex (A and B) And for entire cohort (C, D)

HR immediately begins to increase with increasing time to surgery from

Conclusion: Longer intervals between diagnosis of early-stage lung SCC and surgery are associated with worse survival.

Although factors other than the timing of treatment may contribute to this finding, these results suggest that efforts to minimize delays beyond those needed to perform a complete preoperative evaluation may improve survival

TREATMENT OF EARLY STAGE NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NEJM 2018; 1-11

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

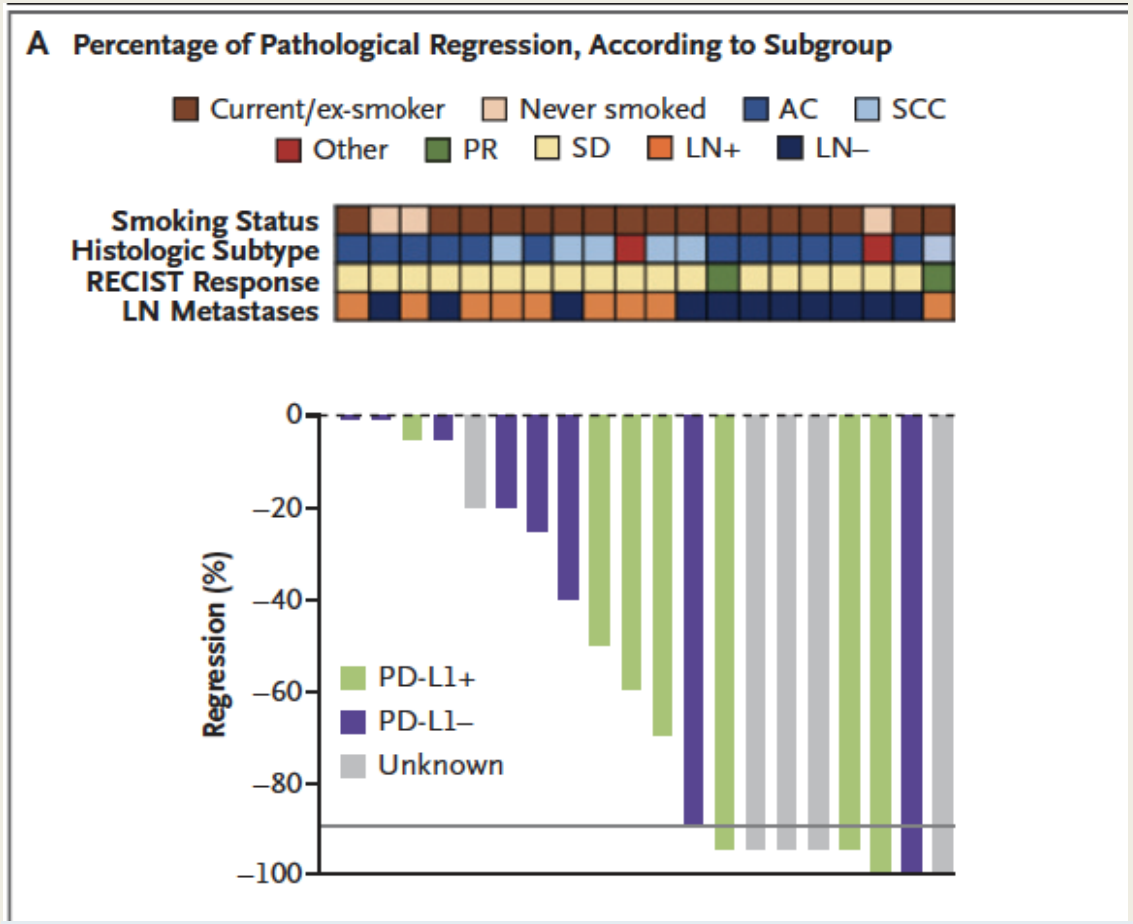
P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

Standard of care in early stage NSCLC: surgery followed by adjuvant chemotherapy

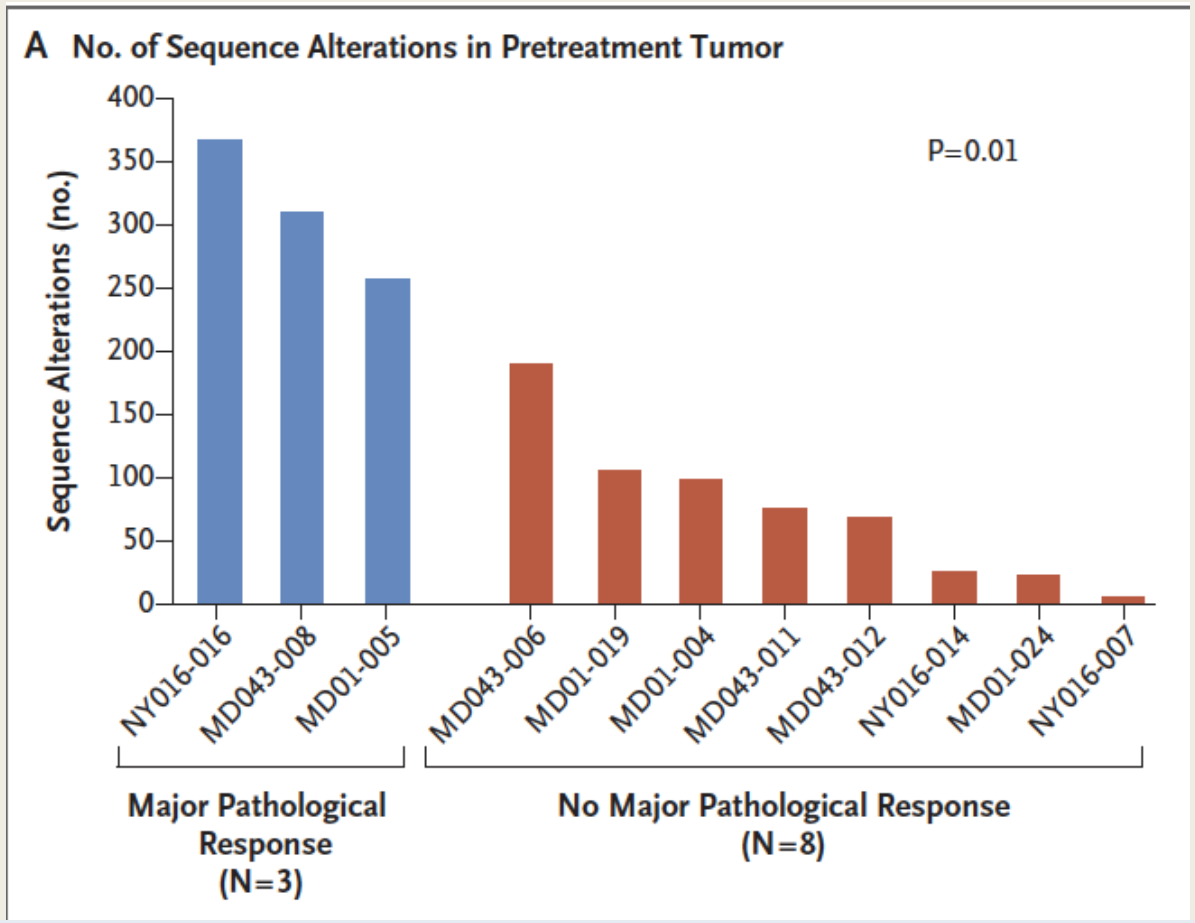
Study evaluated the efficacy of neoadjuvant immunotherapy

- 21 patients with Stage I, II or IIIa deemed resectable
- Two doses of nivolumab every two weeks with surgery planned about 4 weeks after first dose
- Primary endpoints were safety and feasibility
- Also evaluated tumor pathologic response, PDL-1 expression and mutational burden
  -

Pathological regression in the resected primary tumor after neoadjuvant administration of nivolumab



Sequence alterations in pretreatment tumor samples from 11 patients who underwent surgery



Neoadjuvant nivolumab:

- Induced a major pathological response in 45% of resected specimens
- Was associated with few side effects
- Did not delay surgery
- Induced expansion of mutation-associated neoantigen-specific T-cell cones

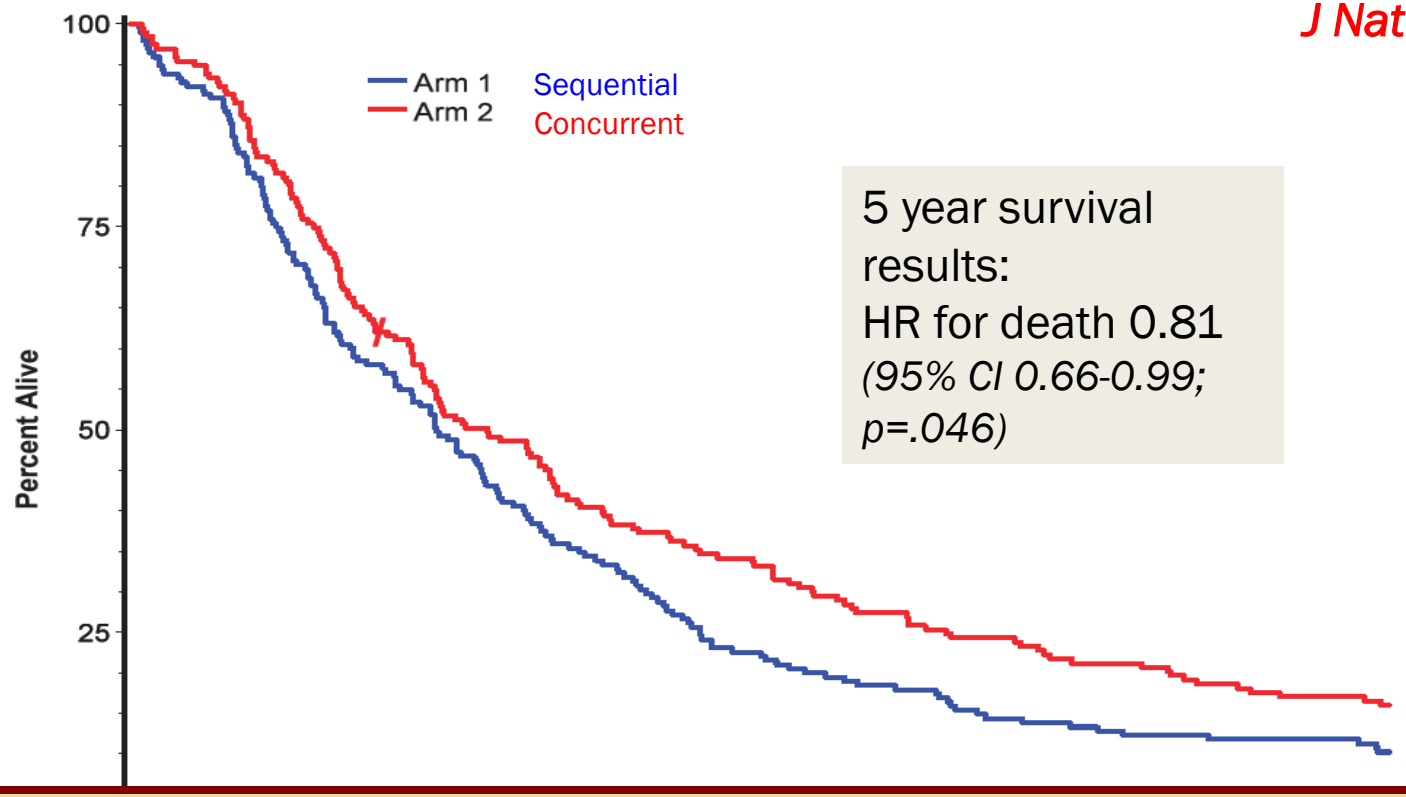
Tumor mutational burden was predictive of pathologic response

TREATMENT OF LOCALLY ADVANCED (STAGE III) UNRESECTABLE NSCLC

Sequential vs Concurrent Chemoradiation for Stage III Non–Small Cell Lung Cancer: Randomized Phase III Trial RTOG 9410

Walter J. Curran Jr, Rebecca Paulus, Corey J. Langer, Ritsuko Komaki, Jin S. Lee, Stephen Hauser, Benjamin Movsas, Todd Wasserman, Seth A. Rosenthal, Elizabeth Gore, Mitchell Machtay, William Sause, James D. Cox

J Natl Cancer Inst 2011;1452-1460



5 year survival results:
HR for death 0.81
(95% CI 0.66-0.99; p=.046)

Confirms improved local control and survival with concurrent chemo-RT in unresectable Stage III NSCLC

5 year survival 15-20%

Concurrent chemotherapy and radiation has been the standard of care for Stage III unresectable NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

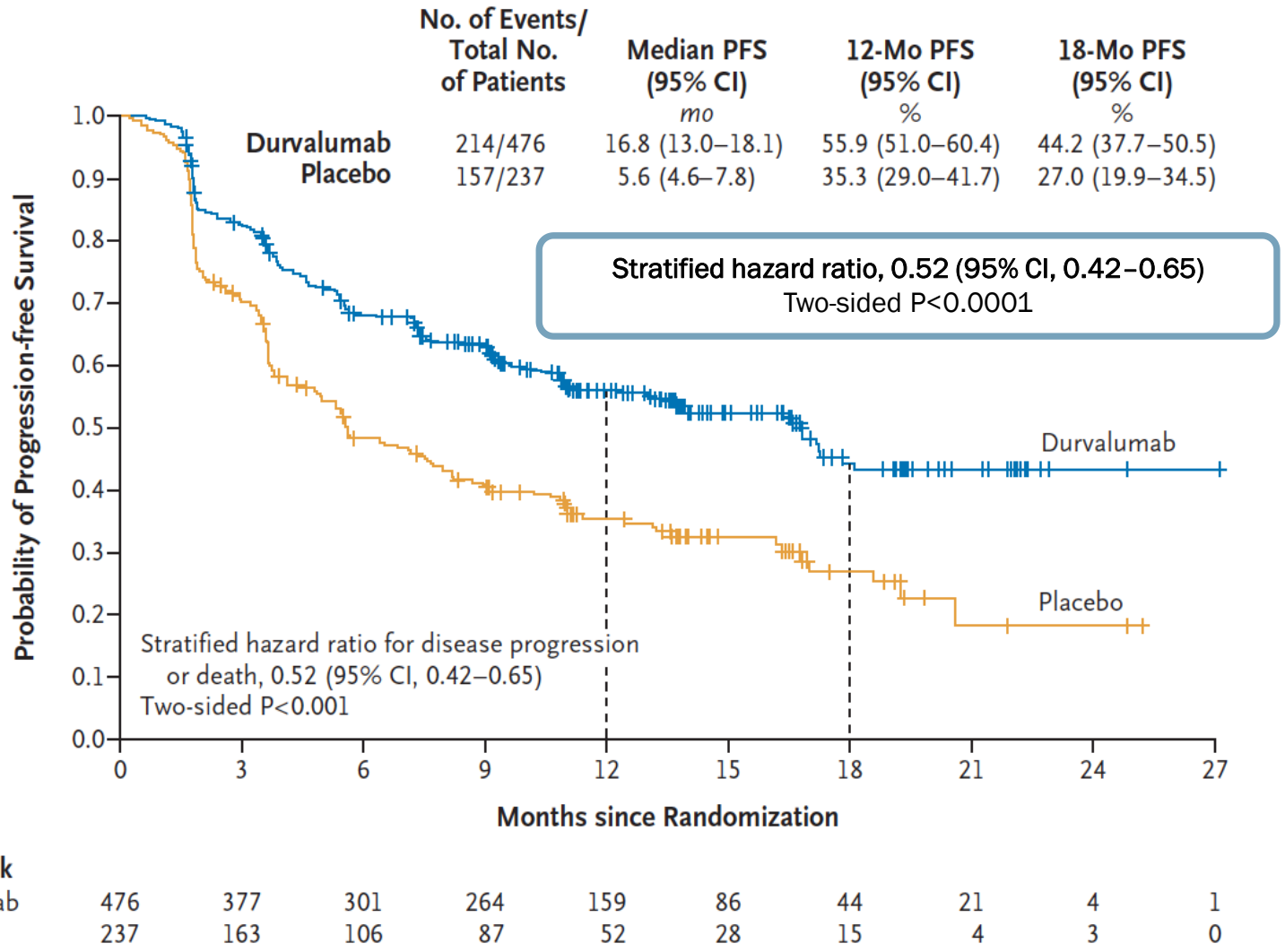
ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

New Engl J Med 2017; 8:1-11

- Therapeutic plateau reached with concurrent chemotherapy and radiation therapy
  - *Median PFS approximately 8–10 months*
  - *15-20% are alive at 5 years*
- There was a significant unmet need for novel therapeutic approaches to boost survival beyond cCRT
  - *After completion of cCRT, patients without disease progression were randomized to adjuvant durvalumab (anti PD-L1) Vs placebo*



New Engl J Med 2017; 8:1-11

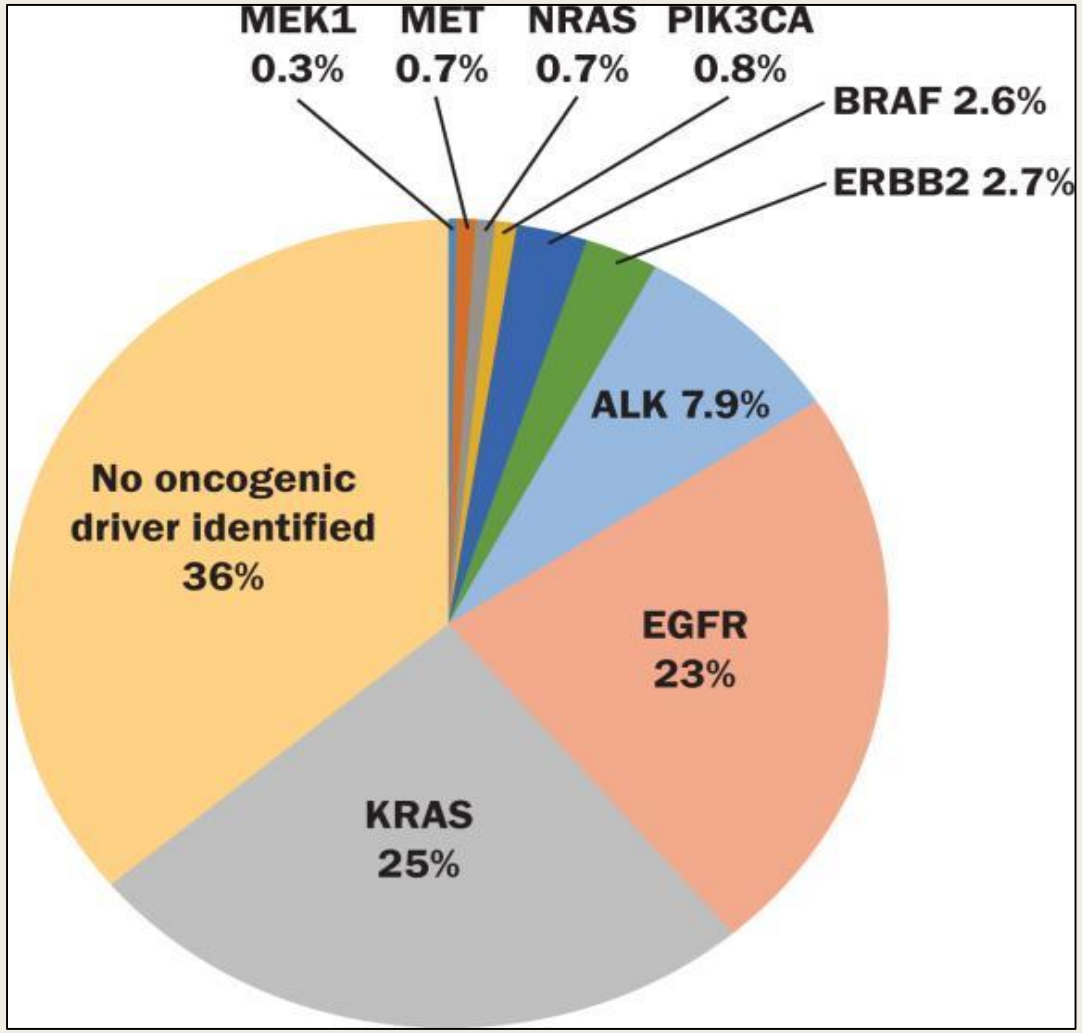
Durvalumab:

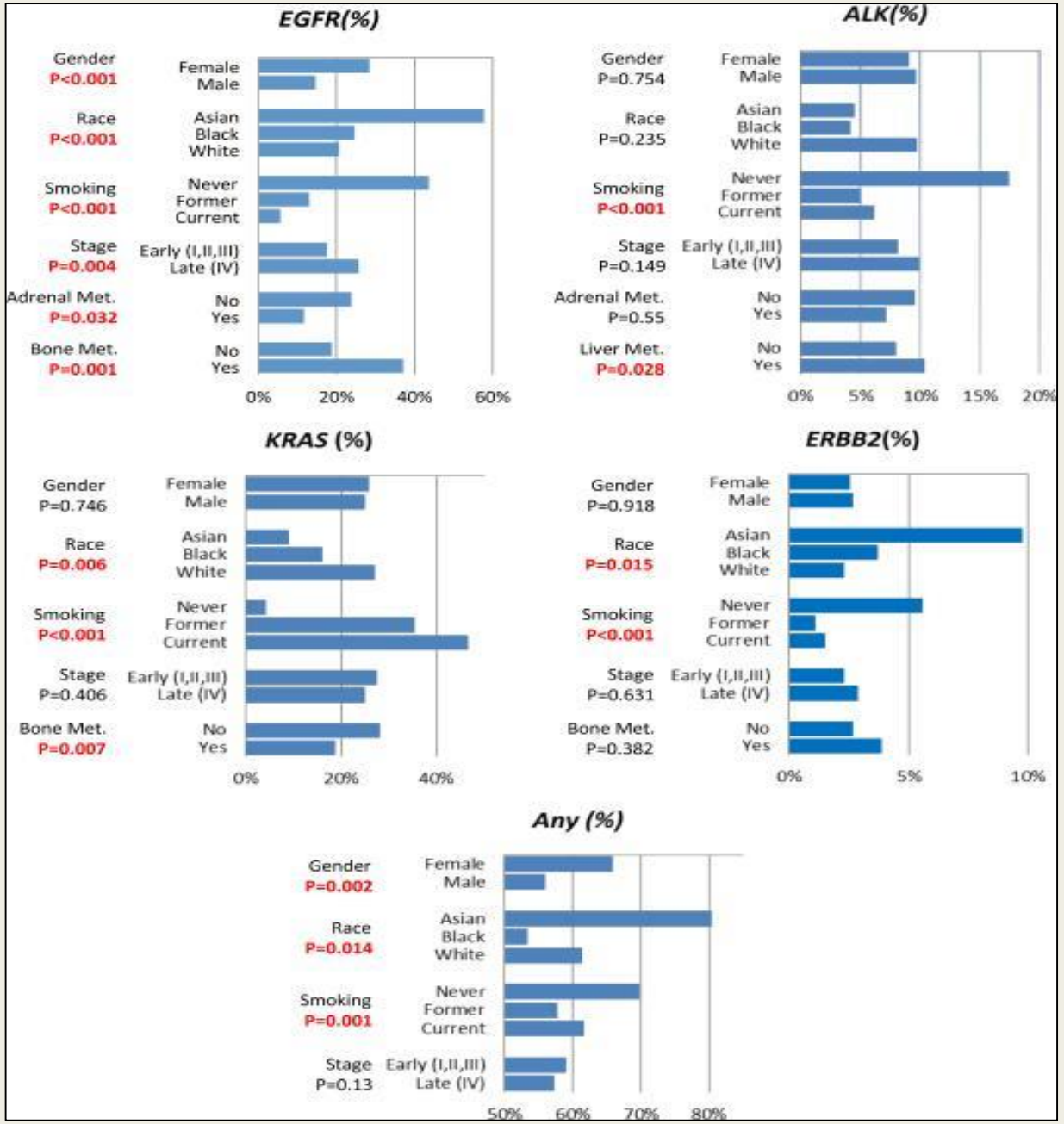
- statistically significant improvement in PFS versus placebo (HR 0.52; P<0.0001; median improvement of >11 months) at a planned interim analysis
- observed across all pre-specified subgroups
- clinically meaningful benefit in ORR (28.4% vs 16.0%; P<0.001), with durable responses versus placebo (median DoR not reached vs 13.8 months)
- lower incidence of new lesions, including new brain metastases, compared with

Durvalumab is a promising new therapeutic option in patients with stage III unresectable NSCLC who have completed cCRT

TREATMENT OF STAGE IV NSCLC

Lung Cancer Mutation Consortium
Incidence of Driver Mutations





J Thorac Oncol 2015;10:768-77

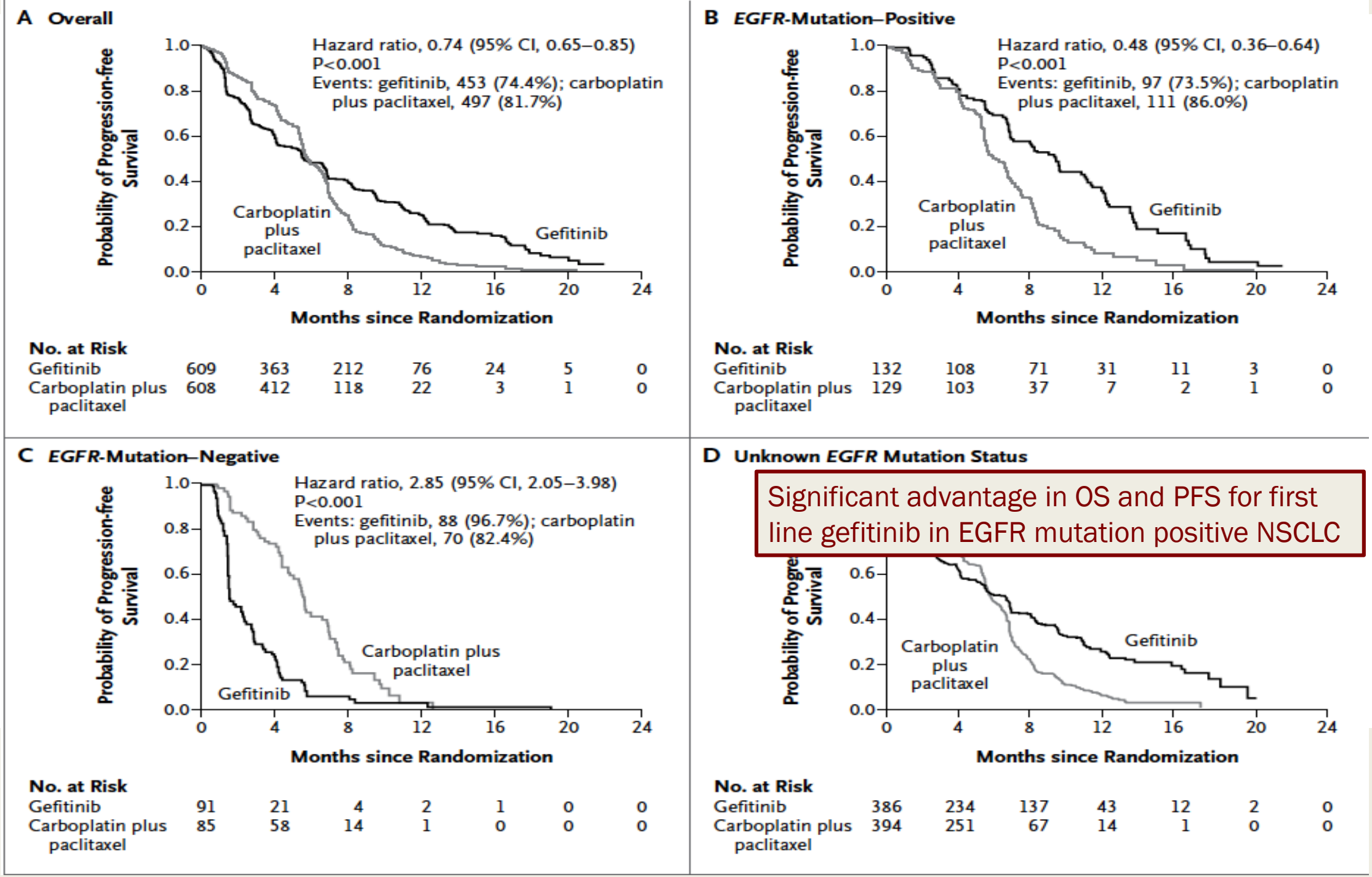
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

N Engl J Med 2004; 350:2129-39



Significant advantage in OS and PFS for first line gefitinib in EGFR mutation positive NSCLC

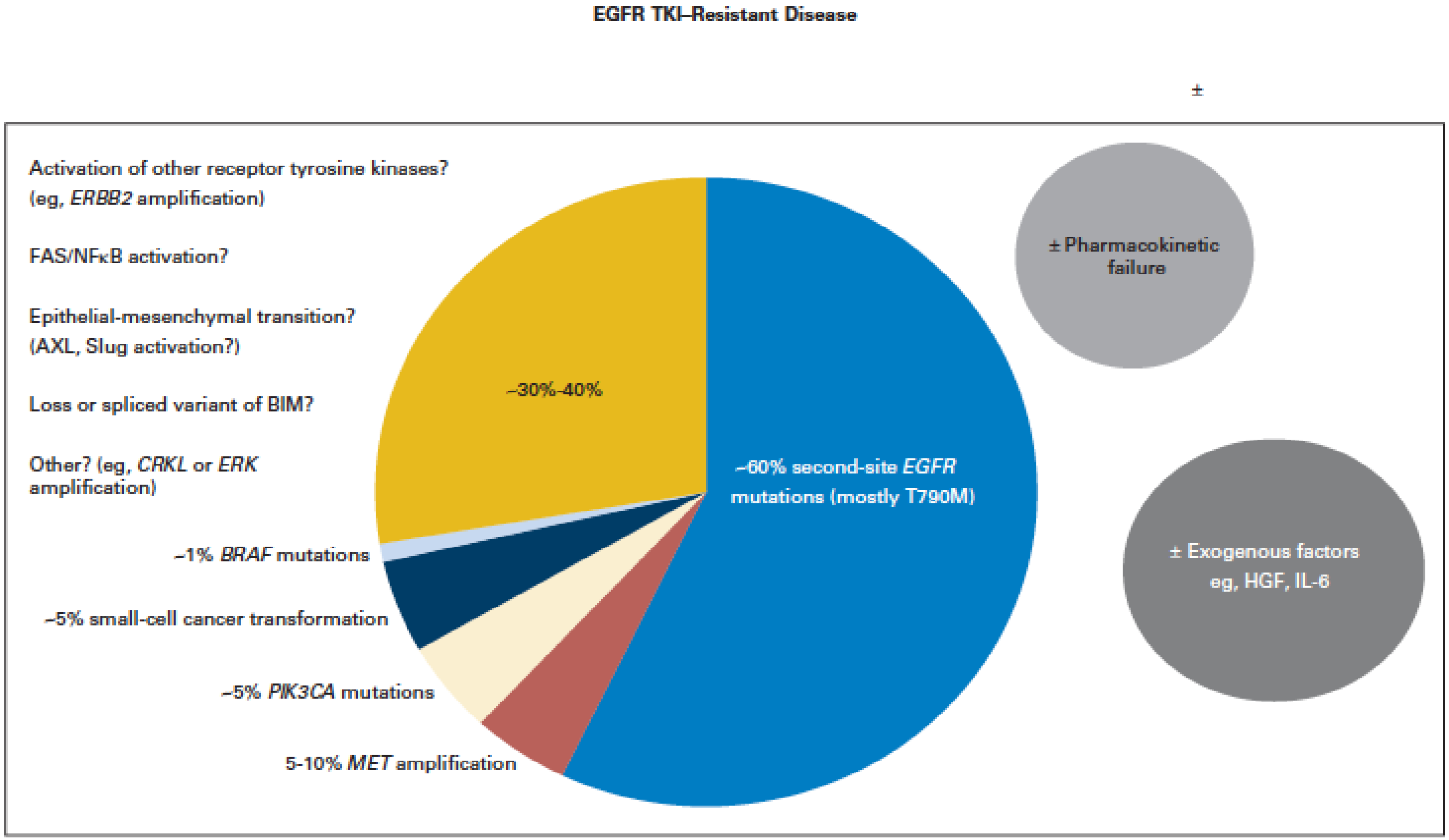


Fig 4. Mechanisms of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Multiple mechanisms have been elucidated in human samples and preclinical models. Some factors may overlap. HGF, hepatocyte growth factor; IL-6, interleukin-6.

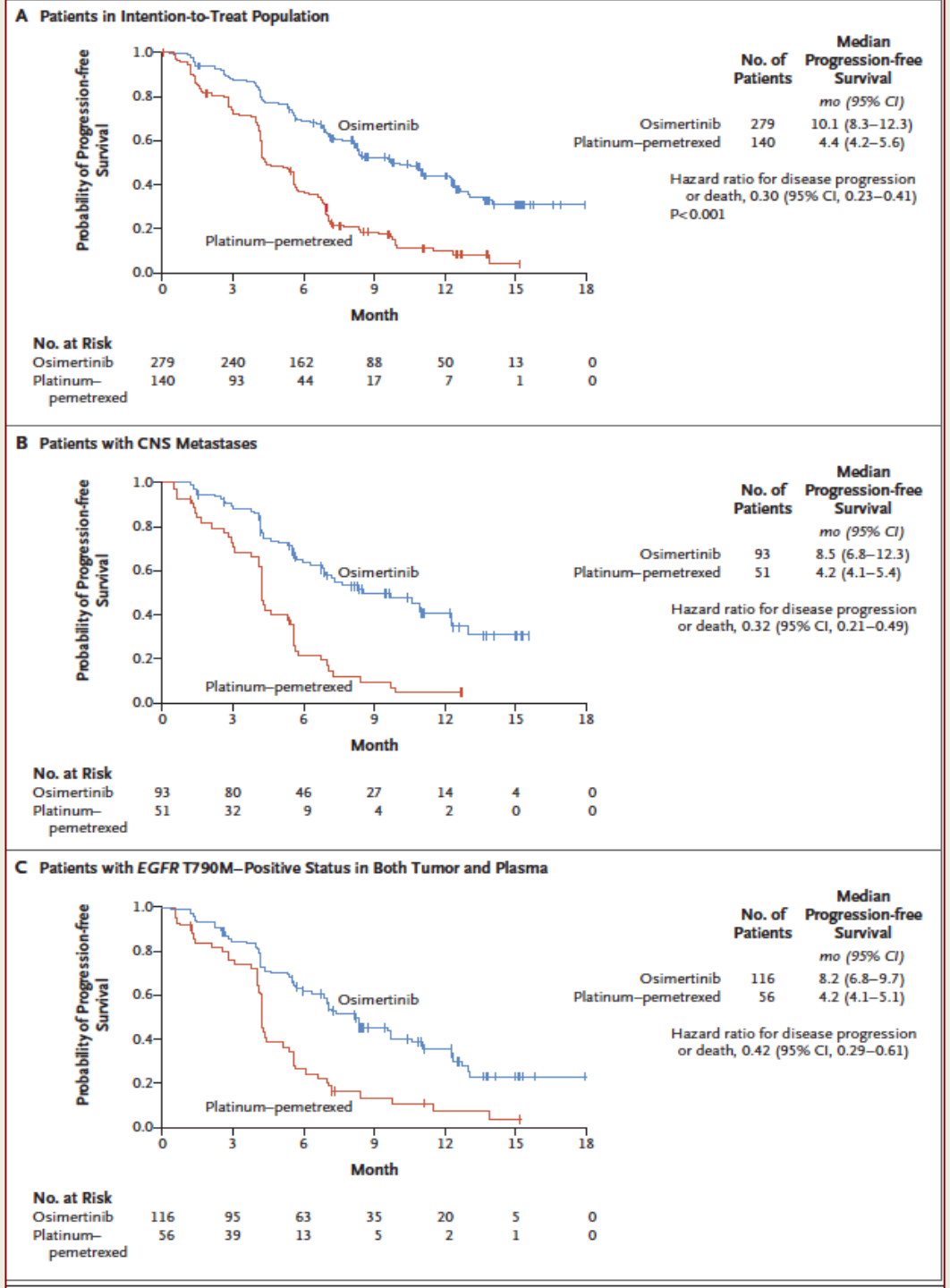
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*

N Engl J Med 2017; 376:629-40



Osimertinib:

Significantly greater efficacy than pemetrexed-platinum in patients with T790M-positive advanced NSCLC

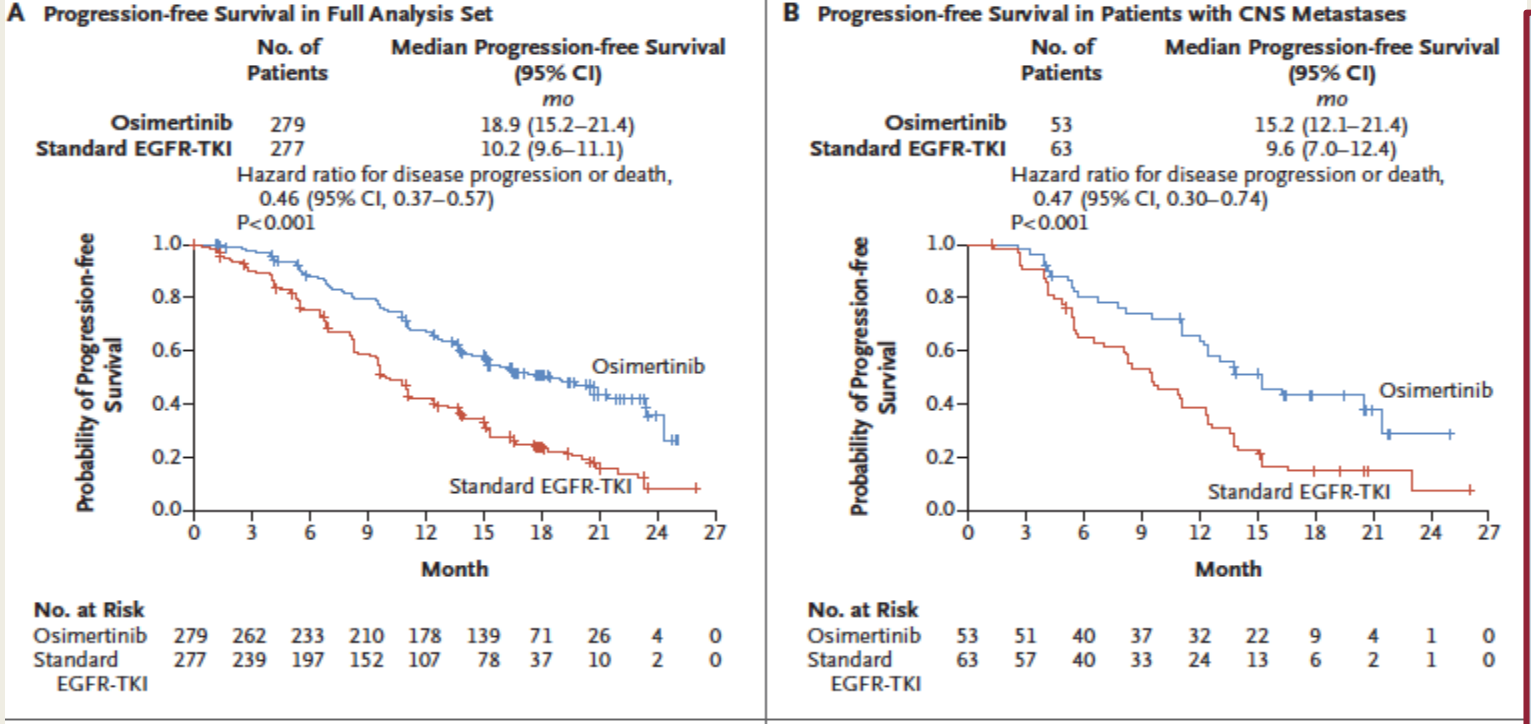
Including those with CNS metastases in whom disease had progressed during first-line EGFR-TKI therapy

ORIGINAL ARTICLE

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

Jean-Charles Soria, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Thanyanan Reungwetwattana, M.D., Busyamas Chewaskulyong, M.D., Ki Hyeong Lee, M.D., Ph.D., Arunee Dechaphunkul, M.D., Fumio Imamura, M.D., Ph.D., Naoyuki Nogami, M.D., Takayasu Kurata, M.D., Ph.D., Isamu Okamoto, M.D., Ph.D., Caicun Zhou, M.D., Ph.D., Byoung Chul Cho, M.D., Ph.D., Ying Cheng, M.D., Eun Kyung Cho, M.D., Ph.D., Pei Jye Voon, M.D., David Planchard, M.D., Ph.D., Wu Chou Su, M.D., Jhanelle E. Gray, M.D., Siow-Ming Lee, M.D., Ph.D., Rachel Hodge, M.Sc., Marcelo Marotti, M.D., Ph.D., Yuri Rukazenkov, M.D., Ph.D., and Suresh S. Ramalingam, M.D. et al., for the FLAURA Investigators*

N Engl J Med 2018; 378:113-125



Median PFS:

- Osimertinib, 18.9 months
- EGFR-TKIs 10.2 months

(HR for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001))

Median duration of response:

- Osimertinib, 17.2 months
- EGFR-TKIs, 8.5 months

Survival rate at 18 months was 83% with osimertinib and 71% with EGFR-TKIs.

Adverse events less frequent with osimertinib than with EGFR-TKIs (34% vs. 45%).

Conclusion: Osimertinib showed efficacy superior to that of standard EGFR-TKIs in first-line treatment of EGFR mutation–positive advanced NSCLC, with lower rates of serious adverse events.

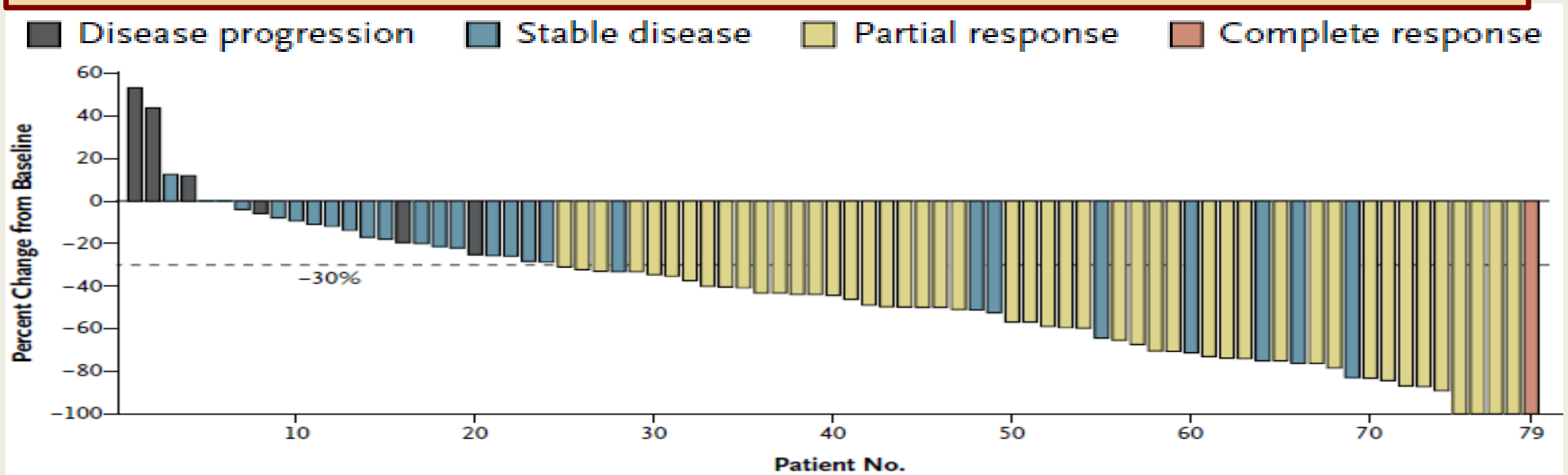
The NEW ENGLAND JOURNAL of MEDICINE

New Engl J Med 2010:363;1693-703 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D.,

Led to accelerated FDA approval of crizotinib for treatment of advanced ALK positive adenocarcinoma



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2017;377:829-38.

ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

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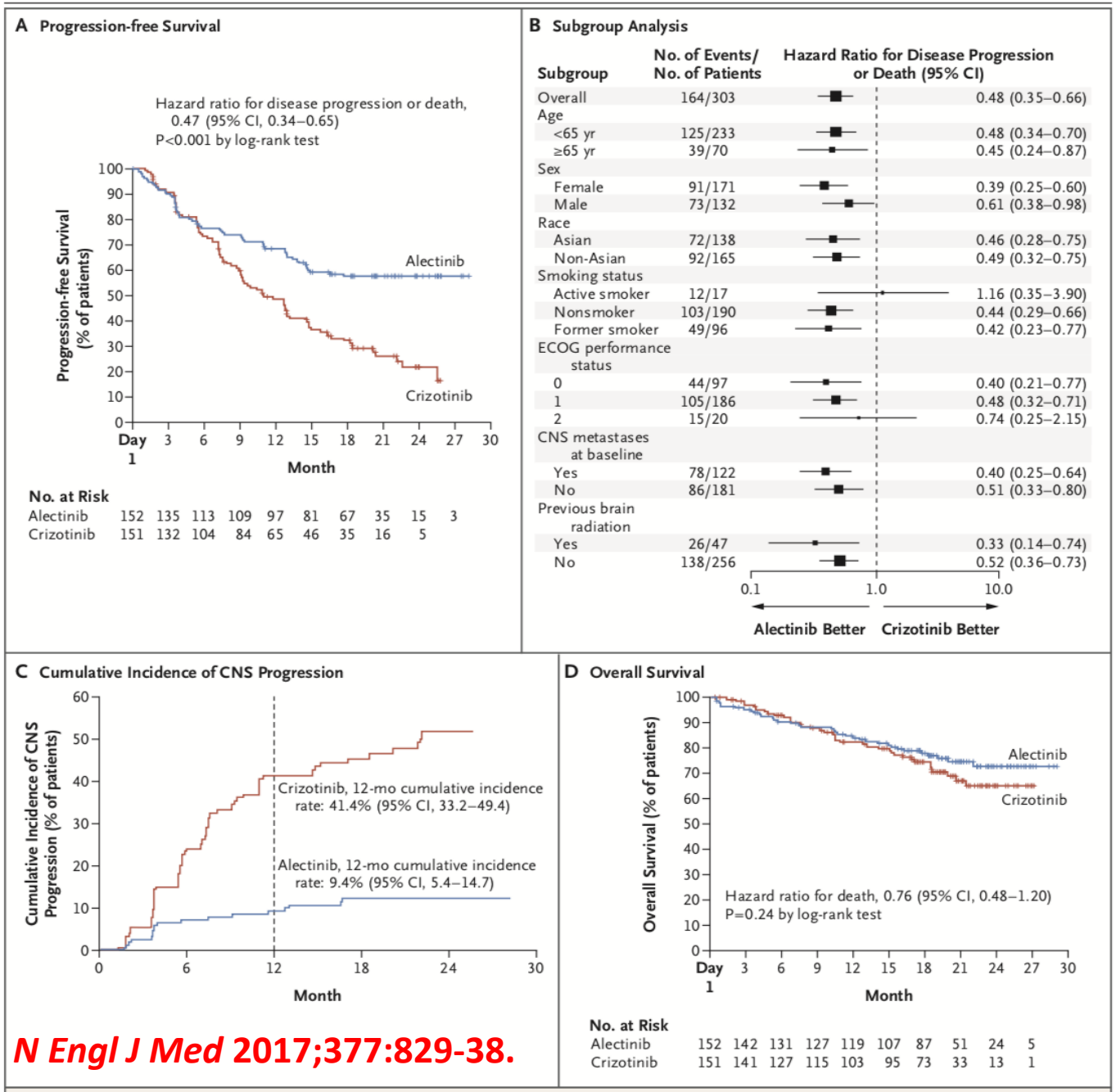
BACKGROUND

- Standard of care in ALK positive metastatic has been crizotinib

- Alectinib, a highly selective inhibitor of ALK, has shown systemic and central nervous system (CNS) efficacy in the treatment of *ALK*-positive NSCLC

- Study investigated alectinib compared with crizotinib in patients with previously untreated, advanced *ALK*-positive NSCLC, including those with asymptomatic CNS disease.

Alectanib vs Crizotinib in Alk positive advanced NSCLC



N Engl J Med 2017;377:829-38.

Progression-free survival at 12 months was significantly higher with alectinib vs. crizotinib

Alectanib: 68.4% [95% CI,61.0 to 75.9]
Crizotinib: 48.7% [95% CI, 40.4 to 56.9]

- HR for disease progression or death, 0.47 [95% CI, 0.34 to 0.65]; P<0.001)
- Median progression-free survival with alectinib was not reached
- 18 patients (12%) on alectinib had an event of CNS progression, compared with 68 patients (45%) on crizotinib
- Adverse events were less frequent with alectinib (41% vs. 50%with crizotinib).

TREATMENT OF SMALL CELL LUNG CANCER

Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study

Charles M Rudin, M Catherine Pietanza, Todd M Bauer, Neal Ready, Daniel Morgensztern, Bonnie S Glisson, Lauren A Byers, Melissa L Johnson, Howard A Burris III, Francisco Robert, Tae H Han, Sheila Bheddah, Noah Theiss, Sky Watson, Deepan Mathur, Bharathi Vennapusa, Hany Zayed, Satwant Lally, Donald K Strickland, Ramaswamy Govindan, Scott J Dylla, Stanford L Peng, David R Spigel, for the SCRX16-001 investigators*

The Lancet Oncology 2017;18:43-51

Patients with recurrent or refractory small-cell lung cancer have very poor survival outcomes with no approved drugs beyond Topotecan for second-line therapy, and until now, no identified molecular biomarkers to guide targeted therapy.

The novel therapeutic target DDL3 is a potential predictive biomarker for small-cell lung cancer.

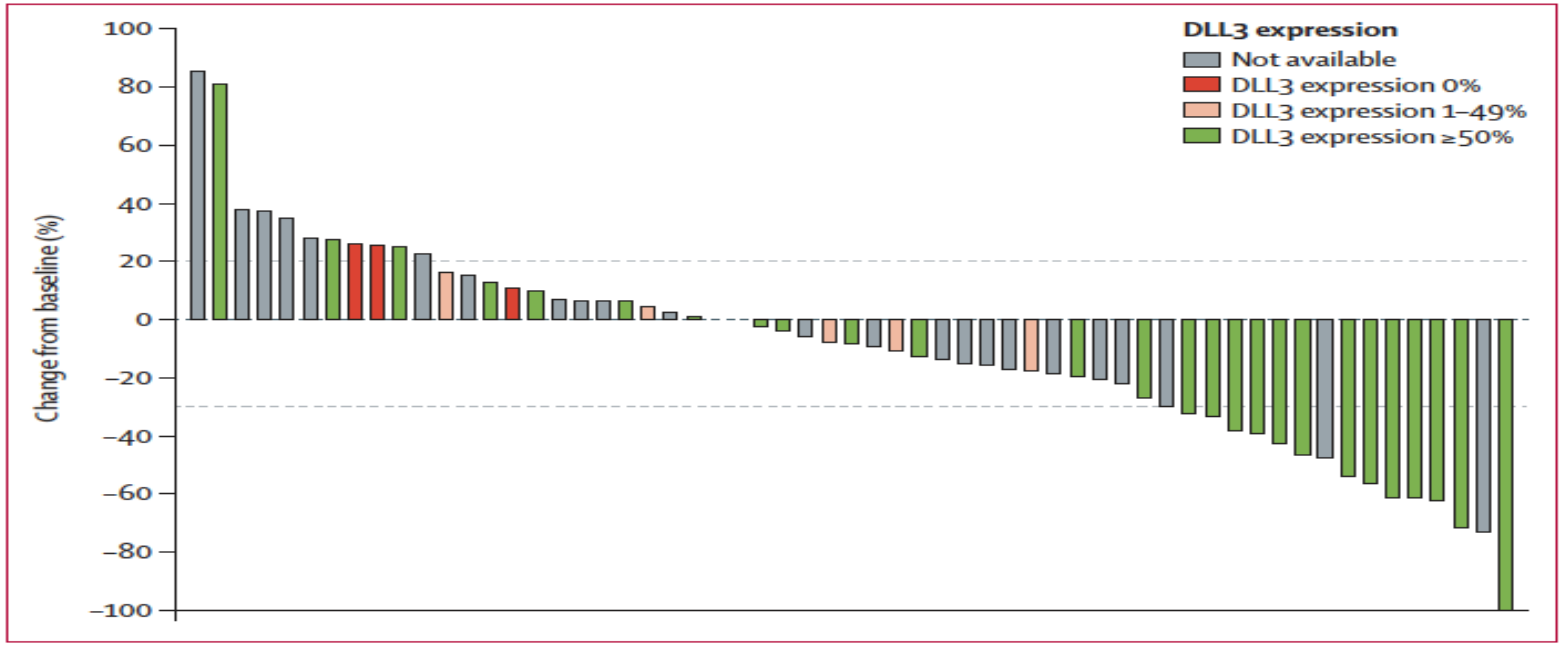


Figure 1: **Waterfall plot showing best change in tumour burden from baseline at active treatment doses (n=60)**
Investigator-assessed best change from baseline was the change in the sum of longest diameters of target lesions for patients treated with rovalpituzumab tesirine 0·2 mg/kg or 0·4 mg/kg every 3 weeks or 0·3 mg/kg or 0·4 mg/kg every 6 weeks. Grey dotted line at 20% indicates the threshold for progressive disease and the line at −30% the threshold for partial response. One patient did not have a measurable target lesion.

	Investigator-assessed			Central review		
	All patients (n=60)	DLL3 expression 0–49% (n=8)	DLL3 expression ≥50% (n=26)	All patients (n=56)	DLL3 expression 0–49% (n=6)	DLL3 expression ≥50% (n=26)
Confirmed objective response (complete response and partial response)	11 (18%)	0 (0%)	10 (38%)	9 (16%)	0 (0%)	8 (31%)
Confirmed disease control (complete response, partial response, and stable disease)	41 (68%)	4 (50%)	23 (88%)	36 (64%)	2 (33%)	22 (85%)
Duration of response (months)	5·6 (2·5–8·3)	0	4·3 (2·2–15)	4·4 (2·2–6·5)	0	4·6 (2·2–6·9)
Progression-free survival (months)	2·8 (2·5–4·0)	2·2 (1·3–2·5)	4·3 (2·8–5·6)	4·0 (2·6–4·8)	2·2 (1·1–3·7)	4·6 (4·0–5·7)

Data are number of patients (%) or median (95% CI). Responses reflect confirmed responses according to RECIST version 1.1, based on two consecutive assessments at least 4 weeks apart, in patients treated with 0·2 mg/kg or 0·4 mg/kg every 3 weeks or 0·3 mg/kg or 0·4 mg/kg every 6 weeks. RECIST=Response Evaluation Criteria in Solid Tumors.

Table 3: **Activity outcomes in response-assessable patients treated at active doses, assessed by the investigator and by central review**

DDL3 is a clinically relevant novel target in small-cell lung cancer.

Rovalpituzumab teresine is a novel antibody-drug conjugate agent for DDL3-positive small-cell lung cancer

IMMUNOTHERAPY INDUCED PNEUMONITIS

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy

Jarushka Naidoo, Xuan Wang, Kaitlin M. Woo, Tunc Iyriboz, Darragh Halpenny, Jane Cunningham, Jamie E. Chaft, Neil H. Segal, Margaret K. Callahan, Alexander M. Lesokhin, Jonathan Rosenberg, Martin H. Voss, Charles M. Rudin, Hira Rizvi, Xue Hou, Katherine Rodriguez, Melanie Albano, Ruth-Ann Gordon, Charles Leduc, Natasha Rekhtman, Bianca Harris, Alexander M. Menzies, Alexander D. Guminski, Matteo S. Carlino, Benjamin Y. Kong, Jedd D. Wolchok, Michael A. Postow, Georgina V. Long, and Matthew D. Hellmann

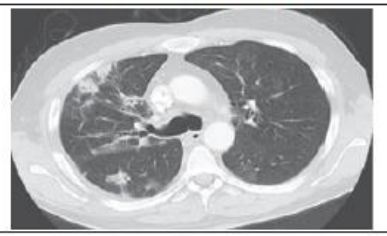
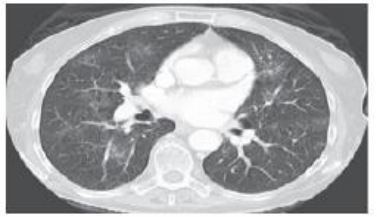
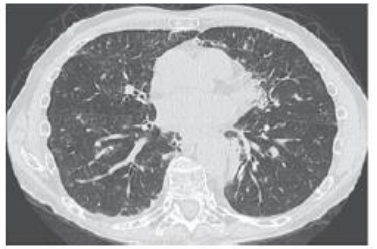
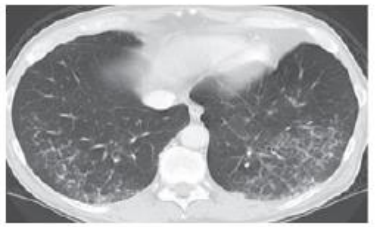
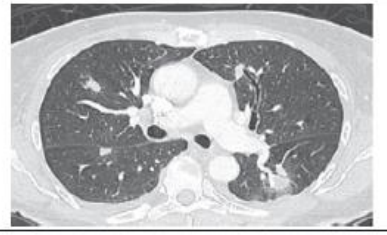
J Clin Oncol 35:709-717.

- Study of 915 patients with advanced solid tumors who received PD-1/PD-L1 monotherapy or in combination with CTL-4 maybe inhibitors :
  - 43 (5%) developed any grade pneumonitis (95% CI 3% to 6%).
  - 1% grade 3 or higher
  - Incidence higher for combination immunotherapy (10%) Vs. monotherapy (3%)

Clinical findings:

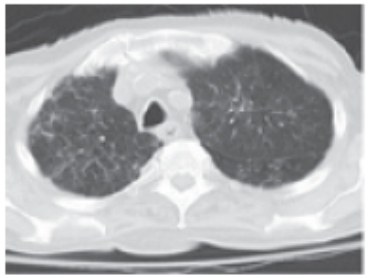
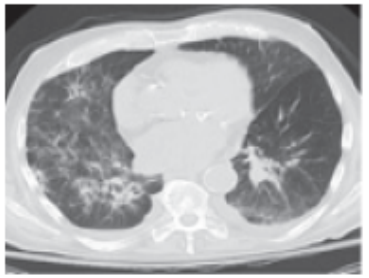
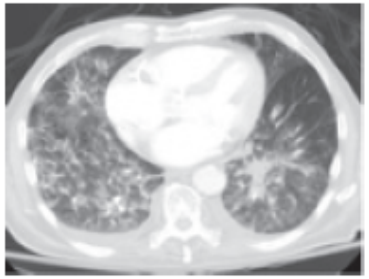
- Median time 2.8 months (9 days to 19 months)
- Dyspnea and dry cough, fever is rare
- 1/3 asymptomatic
- More than 50% experienced additional immune-related toxicity
  - Colitis, hepatitis, hyperthyroidism, myositis

Radiographic findings:

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Pneumonitis in Patients Treated with PD-1/PDL-1 Therapy. JCO 2017; 35: 709-717

Severity of Radiographic Findings

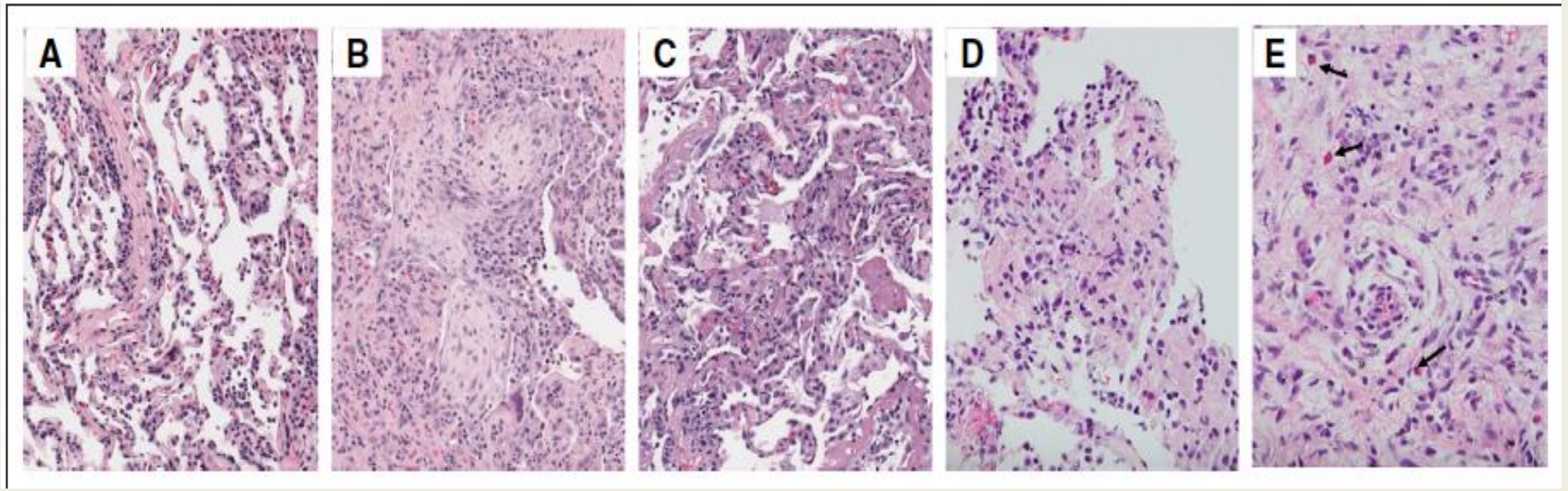
Severity	Mild 56%	Moderate 22%	Severe 22%
CT Image			
Description	Confined to one lobe of the lung or Confined to < 25% of lung parenchyma	Involves more than one lobe of the lung or Involves 25%-50% of lung parenchyma	Involves all lobes of the lung or Involves > 50% of lung parenchyma

Journal Clinical Oncology 2016;35:709-717

- Will help guide steroid therapy
- Rapid changes (pattern/extent) common on sequential CT

Bronchoscopic Findings:

- **BAL: lymphocyte-predominant**
- **Pathology: 11/27 patients at MSKCC**
  - ***A. Cellular interstitial pneumonia (NSIP): 4***
  - ***B. Cryptogenic organizing pneumonia (COP): 3***
  - ***C. Diffuse alveolar damage (DAD): 1***
  - ***D. Poorly formed granulomas: 3***
  - ***E. Eosinophilic infiltrate: 2***



Journal Clinical Oncology 2016;35:709-717

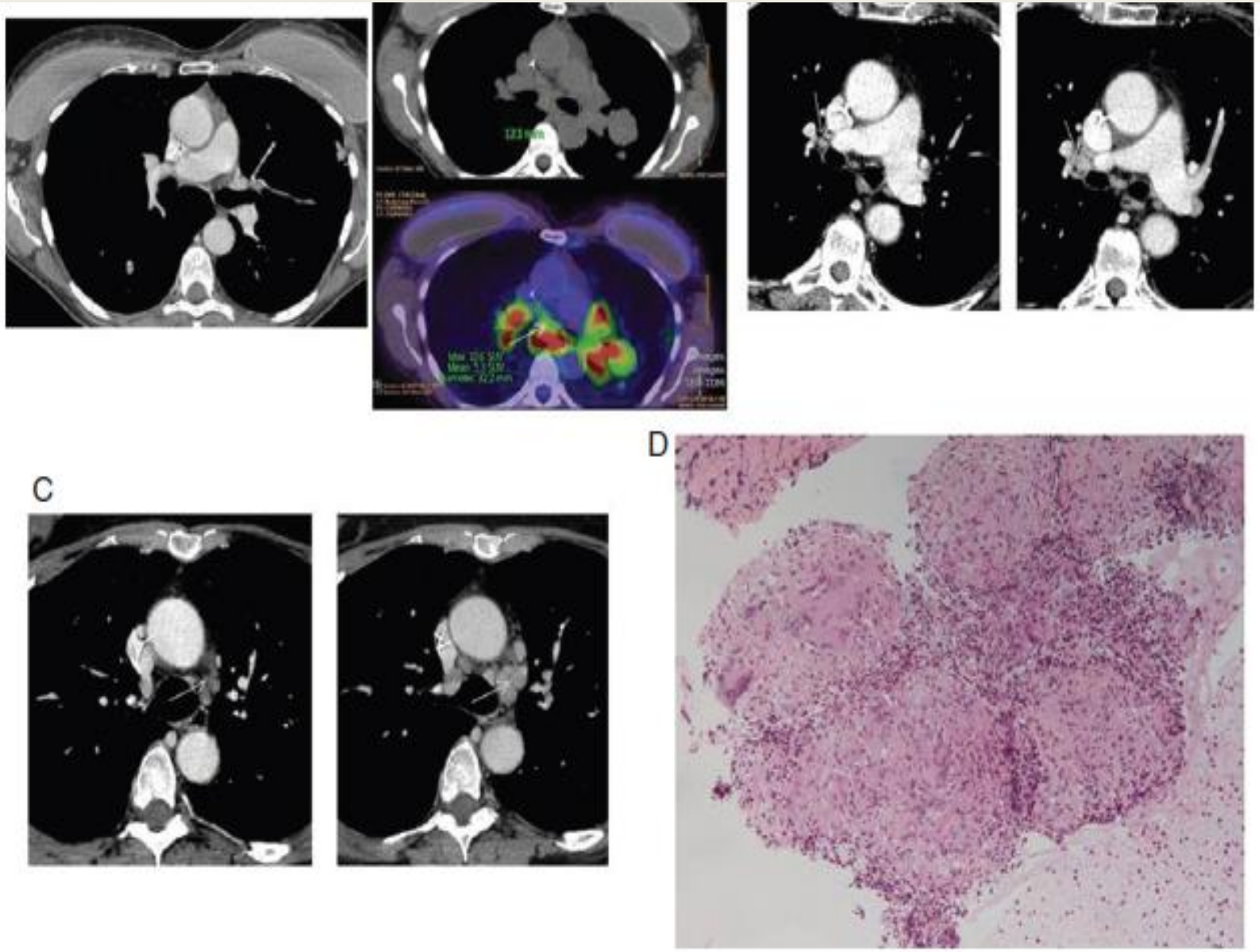


Figure 1. (A) CT scan and FDG–PET scan before and after 2 months of pembrolizumab treatment of the case report patient showing hypermetabolic mediastinal and hilar lymph nodes appearance. (B and C) CT scans of the second and third patients before and after 2 months of pembrolizumab treatment showing mediastinal lymph nodes appearance. (D) Lymph node biopsy showing well-formed giant cell granulomas.

Tumoral cavitation

A and C:

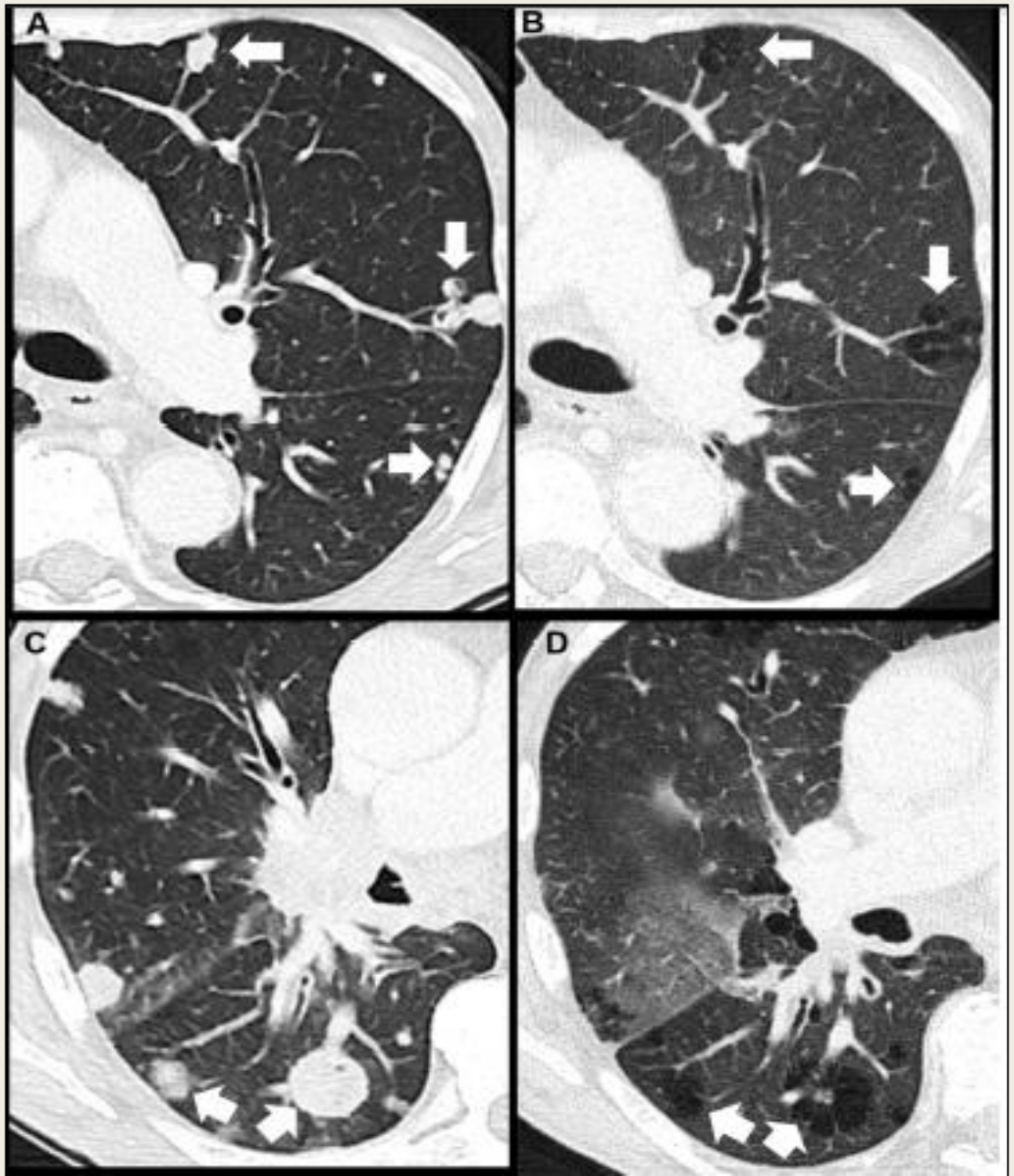
Multiple lung metastases

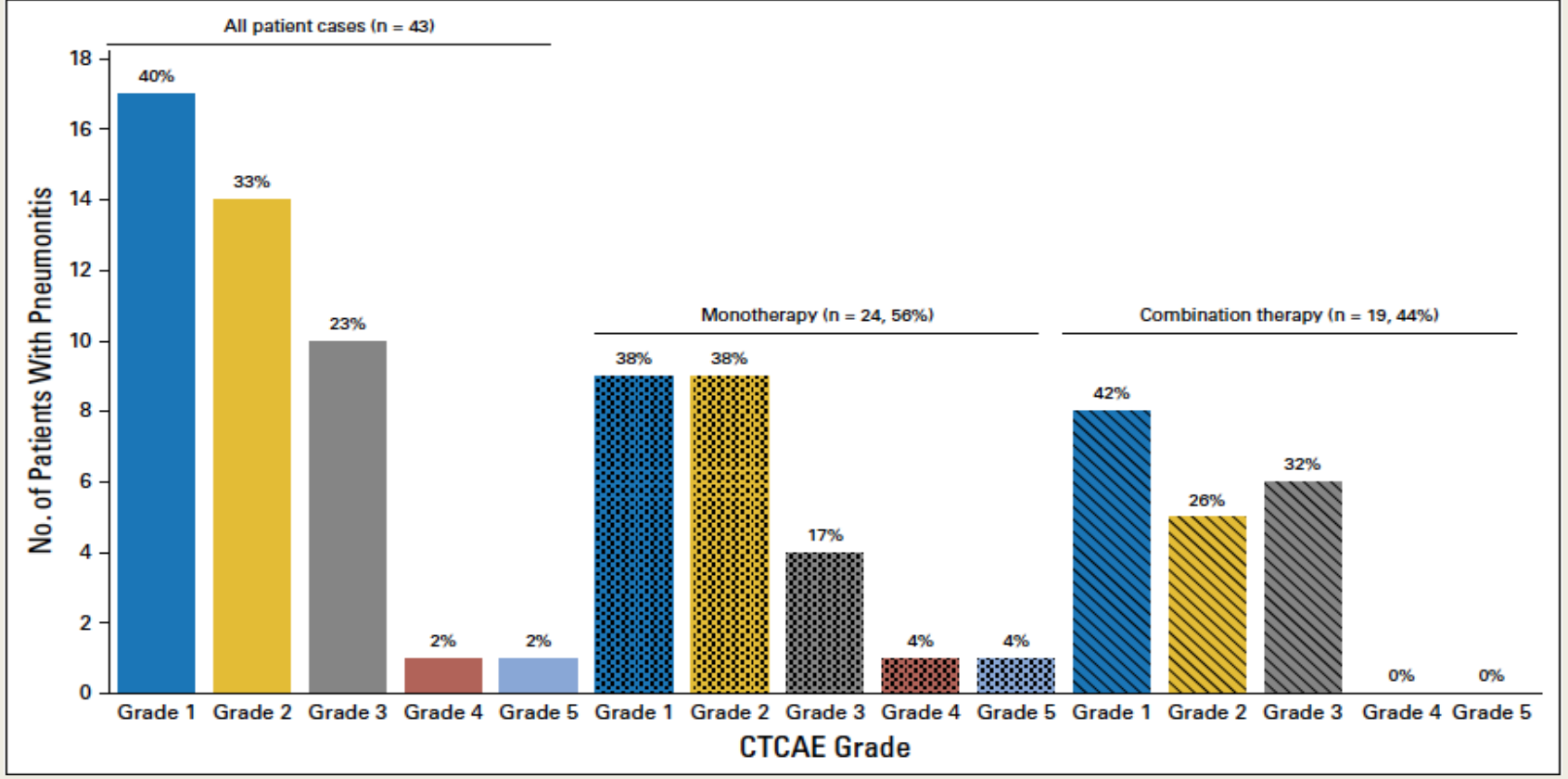
B and D:

Following 12 cycles of nivolumab.

Arrows show disappearance of nodules replaced by cystic lesions

AJRCCM 2017;196:1349-





- **Clinical outcomes:**
  - *72% were grade 1 or 2 and 86% responded to steroid therapy*
  - *5 patients died (progression of pneumonitis and infection related to immunosuppression)*
  - *Worsening outcomes associated with:*
    - Current smoking hx
    - Underlying lung disease (fibrosis)

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

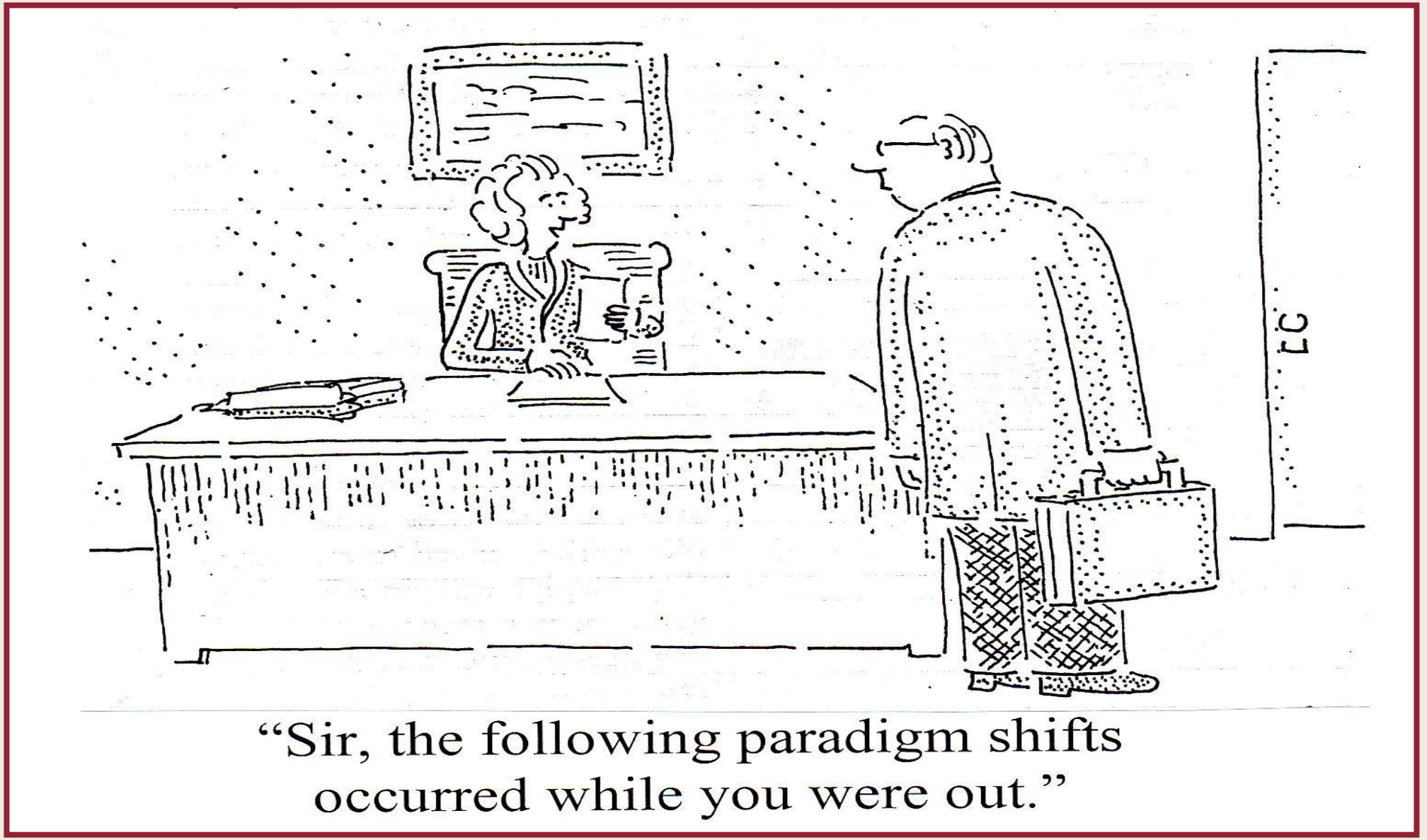
J Clin Oncology 2018; 1-55

Table 3. Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities	
3.1 Pneumonitis	
Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging) No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis	
Diagnostic work-up Should include the following: CXR, CT, pulse oximetry For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management
Additional considerations GI and *Pneumocystis* prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines[34-37] Consider calcium and vitamin D supplementation with prolonged corticosteroid use The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines[33] Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; PPI, proton pump inhibitor.

The Impact of Advances in Lung Cancer



"Sir, the following paradigm shifts occurred while you were out."

Thank you