IL TRATTAMENTO MEDICO DELLE NEOPLASIE POLMONARI

Dr.ssa Anna Cecilia Bettini

UO Oncologia Medica

ASST Papa Giovanni XXIII

TEAM NEOPLASIE TORACICHE AL PAPA GIOVANNI XXIII

ONCOLOGI DEDICATI

- Dr.ssa Anna Bettini
- Dr.ssa Lucia Bonomi
- Dr.ssa Laura Ghilardi
- Dr. Salvatore Intagliata

GRUPPO MULTIDISCIPLINARE

- Chirurgo toracico (dr Lucianetti)
- 2 pneumologi broncoscopisti (dr Ciaravino e dr Raimondi)
- 4 radiologi interventisti (dr Marra, dr Muglia, dr Carbone, dr Dulcetta)
- 2 radioterapisti (dr.ssa Vukcaj e dr Piccoli)
- 1 geriatra (dr.ssa Consonni)
- Oncologi

EVOLUZIONE DEL TRATTAMENTO DEL TUMORE AL POLMONE NON SMALL

PARADIGM SHIFT /TRATTAMENTI INNOVATIVI

DOVE ERAVAMO 10 ANNI FA?

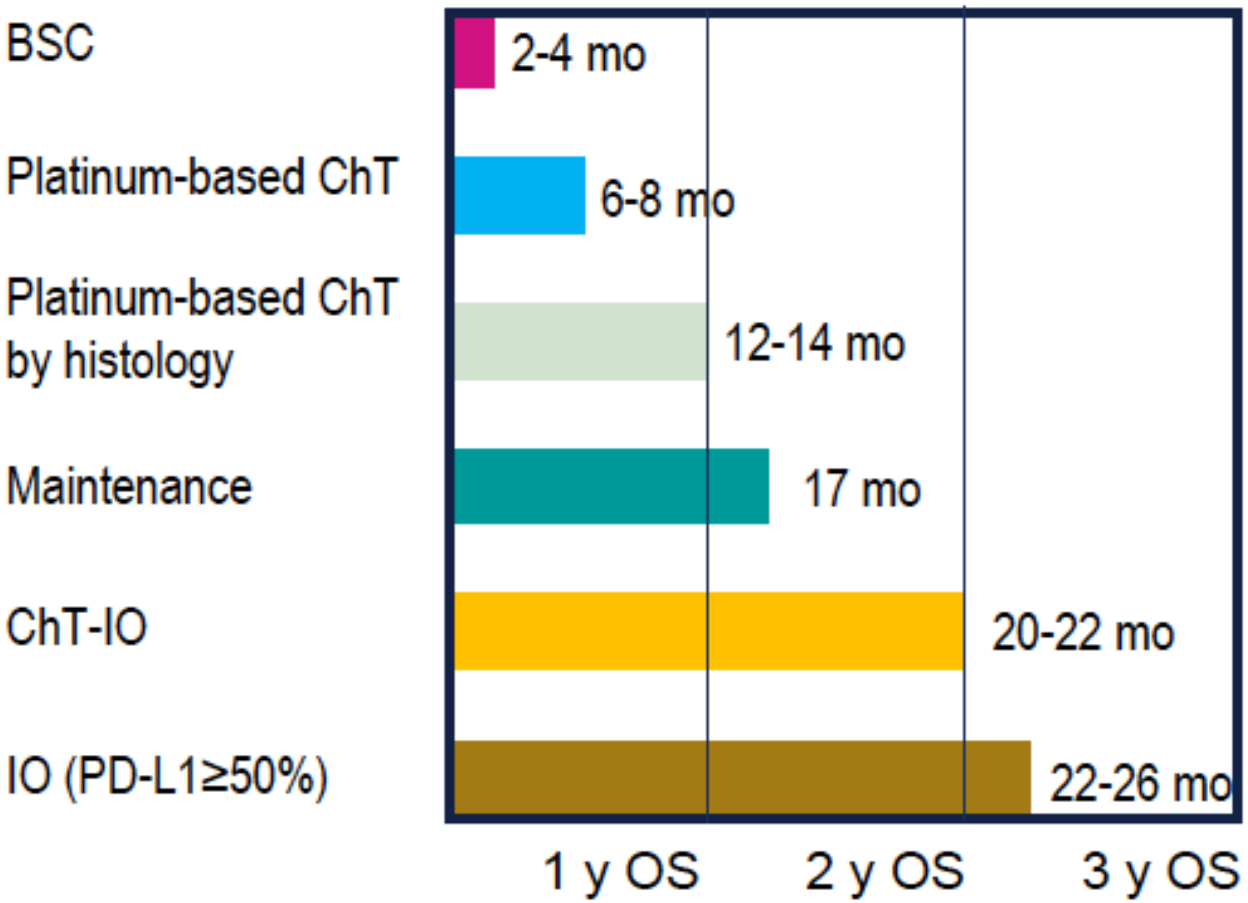
- Chemioterapia unica forma di trattamento (NON PER TUTTI!)
- Solo 1 su 3 rispondeva al trattamento, tempo medio alla progressione 4-6 mesi
- Al fallimento della prima linea poche opzioni con rischio/beneficio incerto (rischio di accanimento terapeutico)
- Aspettativa media di vita 9-12 mesi
- Probabilita' di sopravvivenza a lungo termine (5 anni) <3%

PARADIGM SHIFT MALATTIA NSCLC METASTATICA

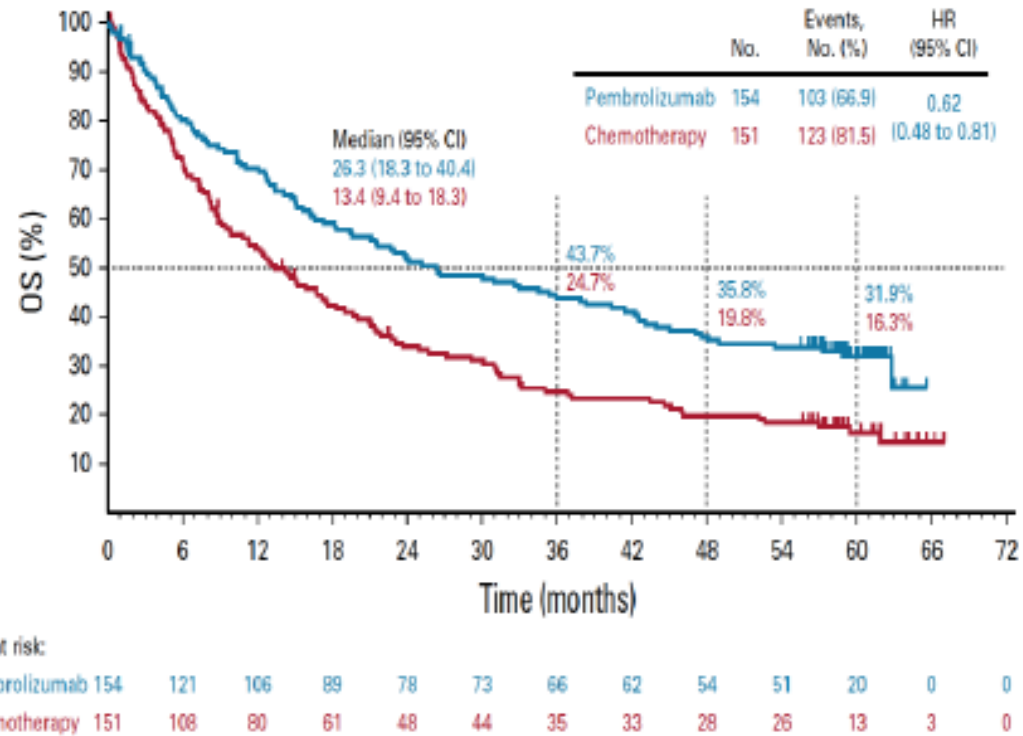
IMMUNOTERAPIA NELLA MALATTIA AVANZATA

LA TERAPIA PERSONALIZZATA IN BASE ALLA PROFILAZIONE MOLECOLARE: LA TERAPIA TARGET

Improving OS in Advanced NSCLC with Immunotherapy in 1L



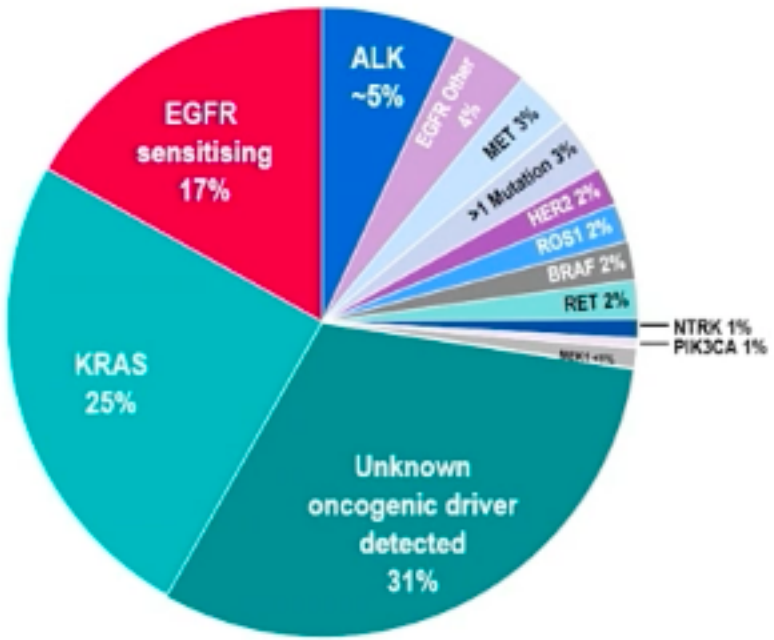
KEYNOTE 024 (PD-L1≥50%)[1]: 5 years update



1.- Brahmer J, ESMO 2020; Reck M, JCO 2021

TARGETED THERAPIES FOR PRECISION MEDICINE

Common mutations in lung cancer



Treatment is selected by genomic profiling

EGFR sensitising
- Afatinib
- Erlotinib
- Erlotinib + bevacizumab
- Gefitinib
- Necitumumab
- Osimertinib
- Amivantanab JNJ-372
- U3-1402

BRAF
- Dabrafenib
- Dabra/Trametinib
- Vemurafenib

HER2
- Afatinib
- Dacomitinib
- Emtansine
- Pertuzumab
- Trastuzumab
- TAK-778
- Poziotinib
- Trastuzumab-deruxtecan

ALK
- Alectinib
- Brigatinib
- Ceritinib
- Crizotinib
- Ensartinib
- Lorlatinib

RET
- Apatinib
- Cabozantinib
- Lenvatinib
- Selpercatinib LOXO-292
- Ponatinib
- Vandetanib
- Pralsetinib BLU-667

ROS1
- Ceritinib
- Crizotinib
- DS-6051b
- Entrectinib
- Lorlatinib
- Repotrectinib

MET
- Cabozantinib
- Crizotinib
- Capmatinib
- Savolitinib
- Reprotrectnib
- Tepotinib

NTRK
- DS-6051b
- Entrectinib
- Larotrectinib
- Selitrectinib
- Cabozantinib
- LOXO-101

PIK3CA
- LY3023414

MEK1
- Cobimetinib
- Selumetinib
- Trametinib

KRAS
- Sotorasib AMG 510
- MRTX849

WEBINAR SERIES

Adapted from Tsao AS, et al. J Thorac Oncol 2016; 11(5):613-638.

Dearden S, et al. Ann Oncol 2013; 24:2371-2376.

PARADIGM SHIFT NELLE FASI PRECOCI DI MALATTIA

IMMUNOTERAPIA DIVENTA STANDARD DOPO CHEMIO-RADIOTERAPIA PER LA MALATTIA LOCALMENTE AVANZATA NON OPERABILE

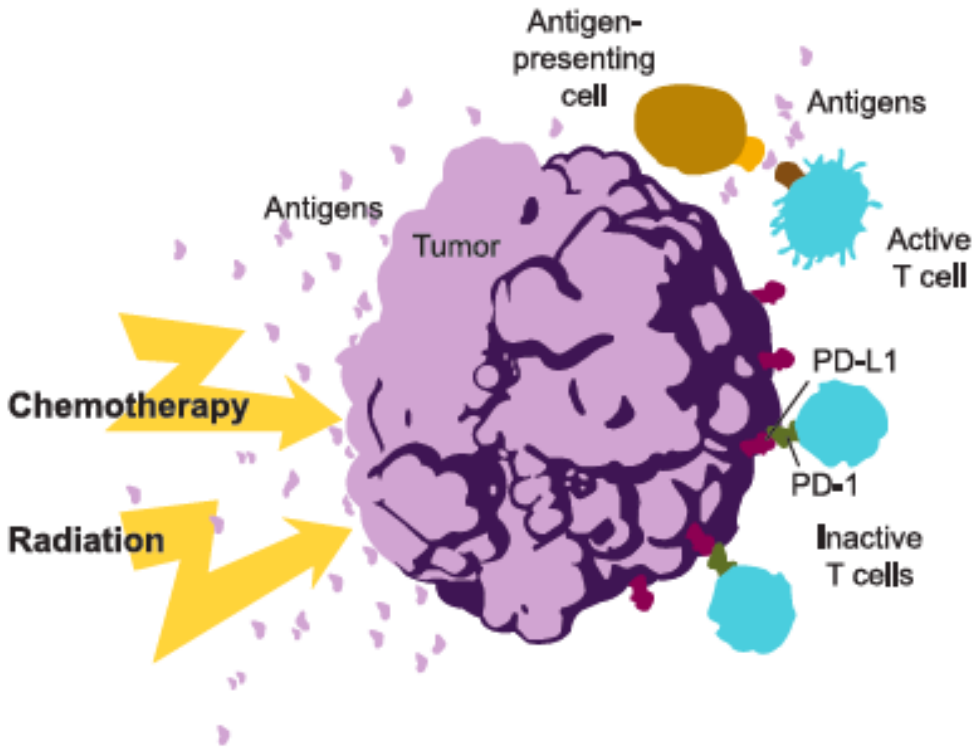
IMMUNOTERAPIA SI SPOSTA NEL TRATTAMENTO DELLE NEOPLASIE PRIMA E DOPO CHIRURGIA: FASE PREOPERATORIA E ADIUVANTE

LA TARGET THERAPY SI SPOSTA IN ADIUVANTE

Chemoradiation

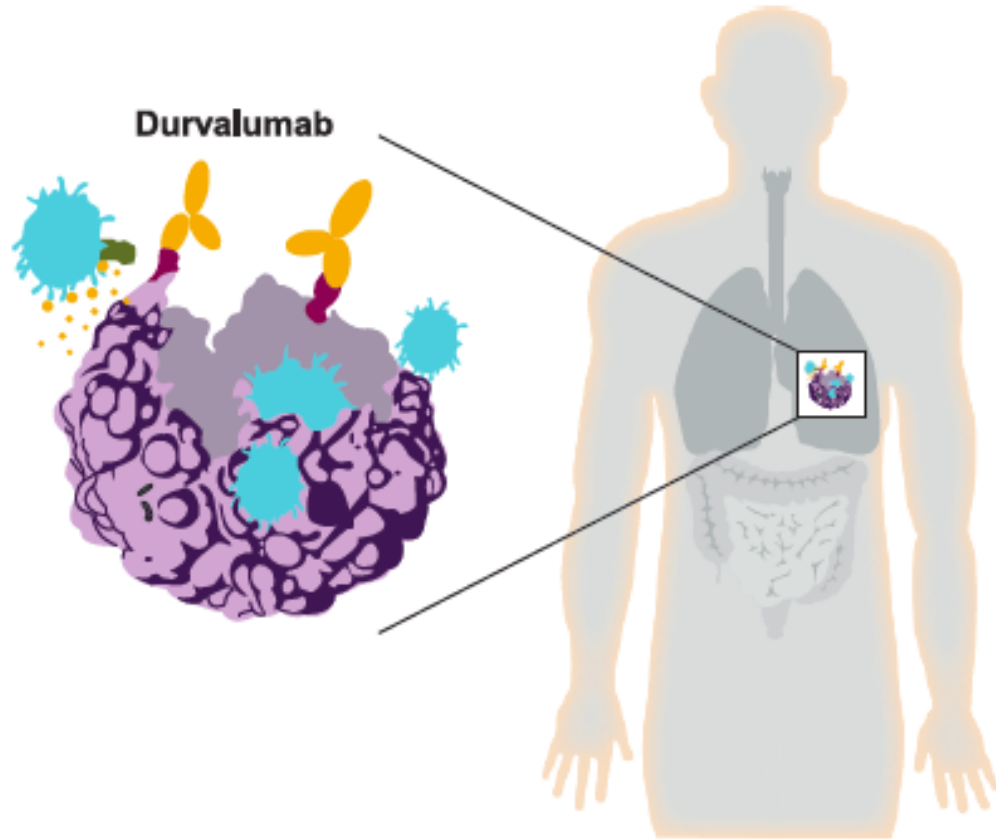
Chemoradiation induces tumor antigen release and an adaptive immune response

PD-L1 overexpression leads to immune cell evasion

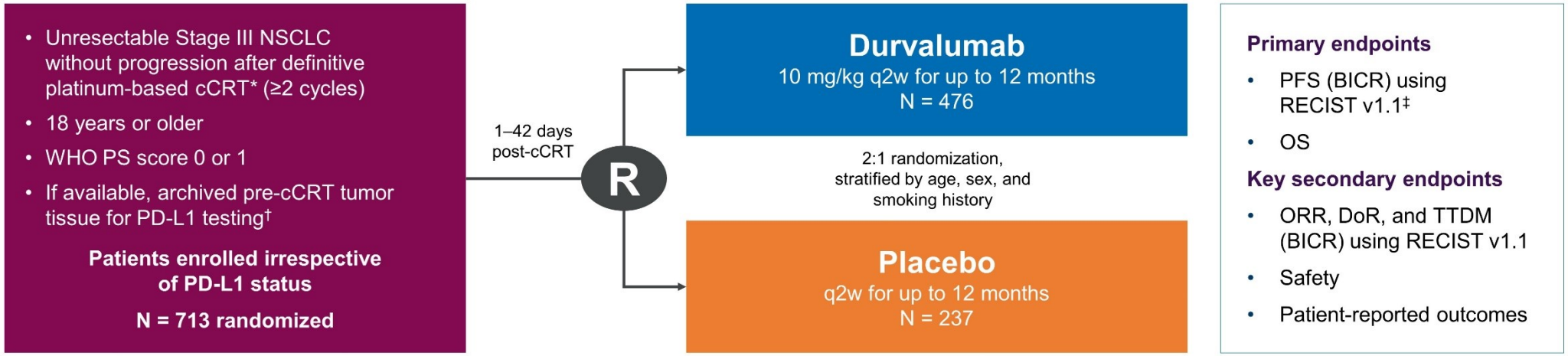


Durvalumab

Durvalumab reverses immune suppression and leads to a systemic antitumor response



PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Trial

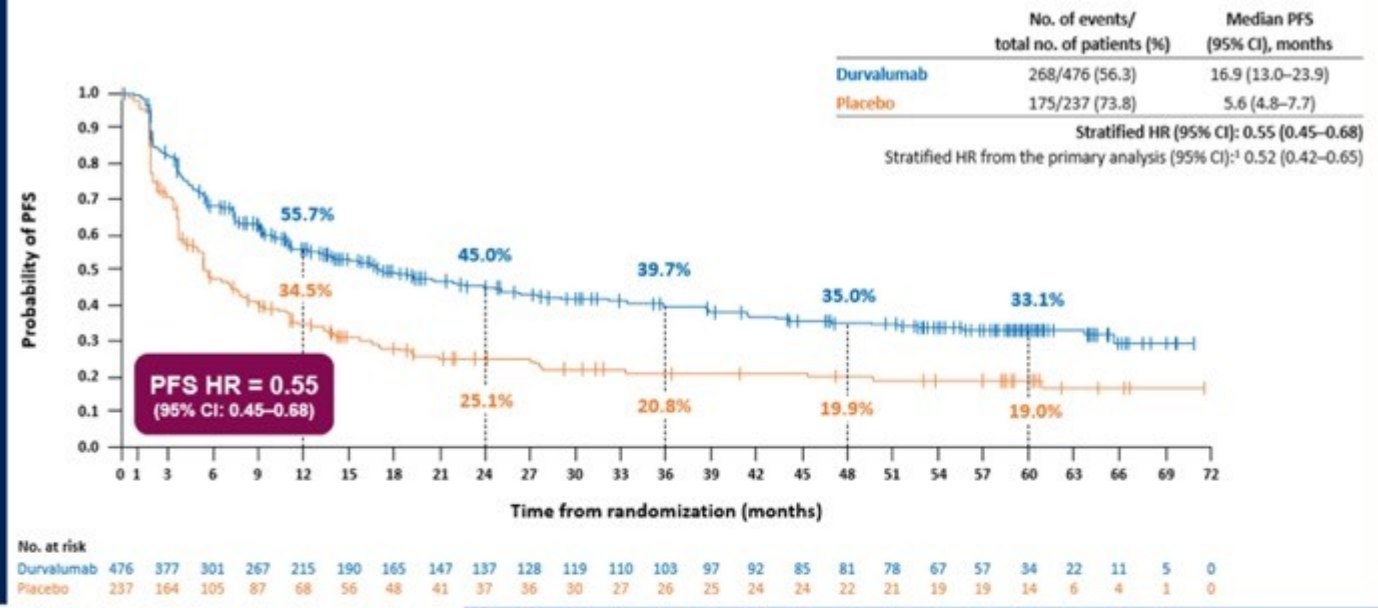


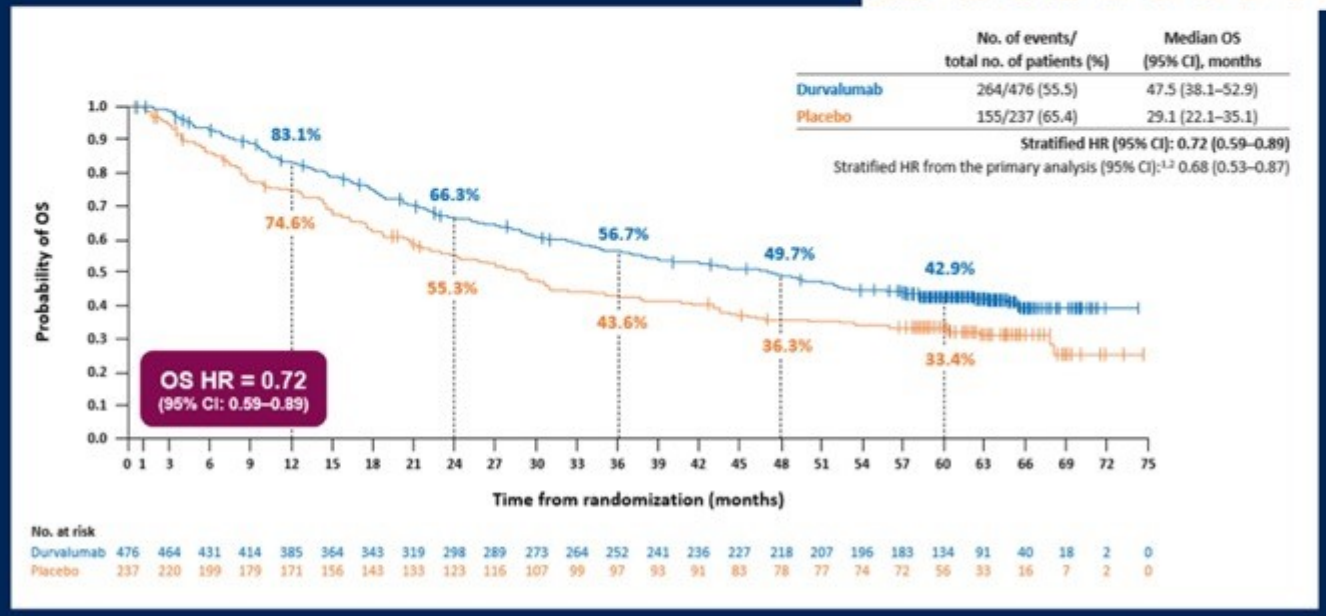
- **Updated analyses of OS and PFS, assessed ~5 years after the last patient was randomized (data cutoff: 11 January 2021; exploratory, post-hoc analysis)**
  - **Treatment effects were estimated using stratified log-rank tests in the ITT population**
  - **Medians and yearly landmark rates were estimated using the Kaplan–Meier method**

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; ITT, intent-to-treat; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

NCT02125461. *Radiation dosage typically 60–66 units of gray in 30–33 fractions. †Using the Ventana SP263 immunohistochemistry assay. ‡Defined as the time from randomization to the date of objective disease progression or death by any cause in the absence of progression

PACIFIC: 5 year survival outcomes with durvalumab after chemoradiotherapy





Presented By: Bradford Perez

2021 ASCO ANNUAL MEETING

There are no "Good Prognosis" Lung Cancers

8th Edition			5 Year Survival	5 Year Survival
T Stage (all N0M0)	Primary Size (cm)	N (%)	Clinical Stage	Pathological Stage
T1a	0.1-1	785 (8)	92%	92%
T1b	1.1-2	3157 (31)	83%	86%
T1c	2.1-3	2469 (24)	76%	81%
T2a	3.1-4	1944 (19)	67%	74%
T2b	4.1-5	612 (6)	60%	65%
T3	5.1-7	814 (8)	52%	57%
T4	>7	403 (4)	38%	47%

Rami-Porta J Thorac Oncol 2015

Adjuvant chemotherapy of completely resected NSCLC

	N	Stage	Chemo	5-year survival (%)		HR (95% CI)	P
				Chemo	Control		
ALPI-EORTC	1,088	I-IIIA	MVP	49.0	48.0	0.96 (0.81-1.13)	NS
IALT	1,867	I-III	Cis/Vinca	44.5	40.4	0.86 (0.76-0.98)	<0.03
JBR.10	482	IB-II	Cis/Vino	69.0	54.0	0.69 (0.52-0.91)	0.04
ANITA	840	IB-IIIA	Cis/Vino	51.2	42.6	0.80 (0.66-0.96)	0.02
CALGB	344	IB	Carbo/Pacl	57.0	59.0	0.80 (0.60-1.07)	0.1
BLT	381	I-III	Cis-based	NR	NR	1.0	NS
LACE meta-analysis	4,584	I-IIIA	Cis-based	48.8	43.5	0.89 (0.82-0.96)	0.004

NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer.

Lots of room for improvement!

Pirker, TLCR. 2014

Fast Forward — Neoadjuvant Cancer Immunotherapy

Thomas F. Gajewski, M.D., Ph.D.

temic antitumor T-cell response.[7] Induction of a systemic immune response before surgery could lead to immunologic memory that may protect against tumor recurrence over a long term.

VIRTUAL 2020 ESMO congress

Ongoing prospective phase III neoadjuvant trials

Sponsor	NCT#	stage	Treatment	Primary end point	N	Estimated completion
CM 816	02998528	IB-IIA	Nivo/Ipi vs. Nivo/Chemo vs. Chemo	EFS pCR	350	May 2023
IMPOWER 030	03456063	II-IIIB	Atezolizumab + chemo vs chemo+Placebo	MPR EFS	450	Nov 2024
KN 671	03425643	IIB-IIIA	Pembro/chemo vs chemo	EFS, OS	786	Jan 2024
Agean	03800134	IIA-IIIB	Durva/Chemo vs. Chemo	MPR EFS	800	Jan 2024

The NEW ENGLAND JOURNAL of MEDICINE

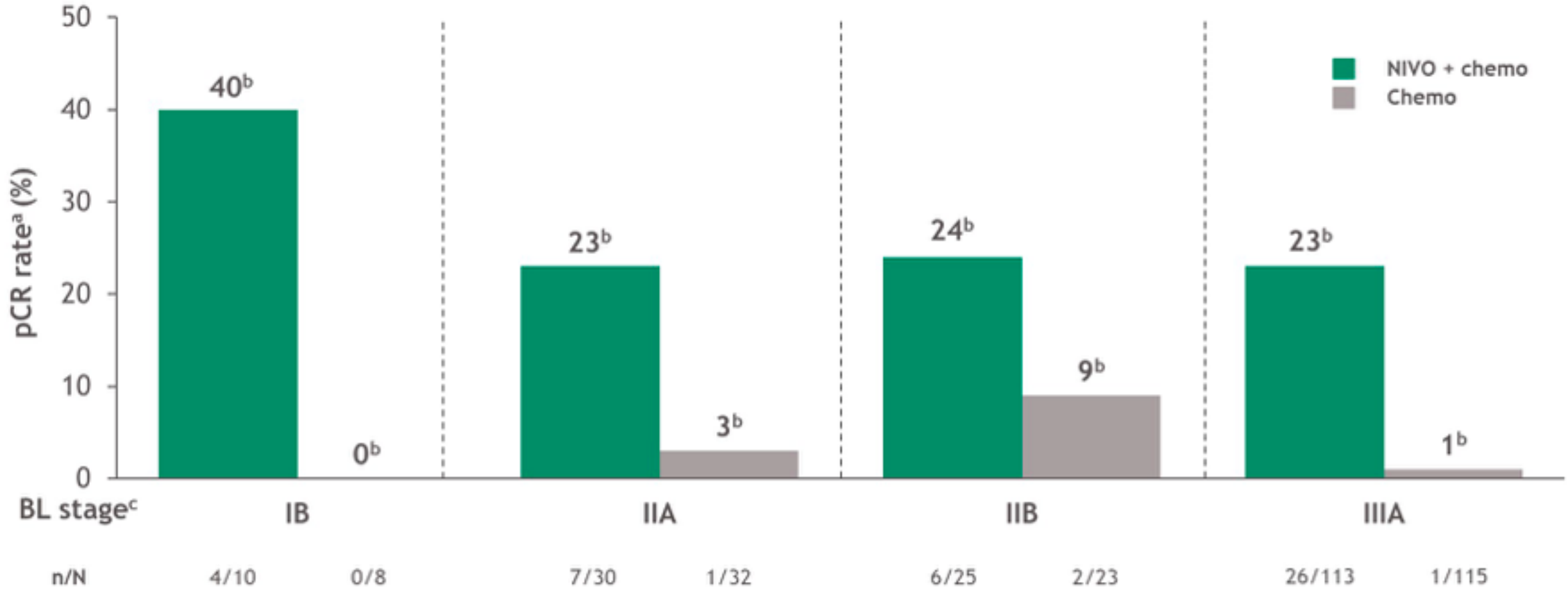
ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

Patrick M. Forde, M.B., B.Ch., Jonathan Spicer, M.D., Ph.D., Shun Lu, M.D., Ph.D., Mariano Provencio, M.D., Ph.D., Tetsuya Mitsudomi, M.D., Ph.D., Mark M. Awad, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Stephen R. Broderick, M.D., M.P.H.S., Julie R. Brahmer, M.D., Scott J. Swanson, M.D., Keith Kerr, M.B., Ch.B., Changli Wang, M.D., Ph.D., et al., for the CheckMate 816 Investigators*

April 11, 2022

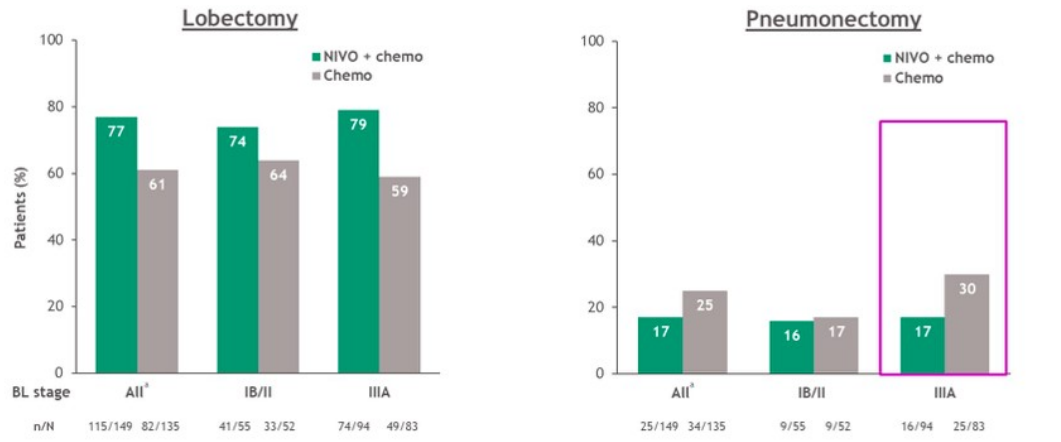
pCR by baseline stage of disease



- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging[d]

[a]Per BIPR in the ITT population; neither of the 2 patients with stage IV disease (1 in each arm) achieved pCR; [b]95% CI: NIVO + chemo, chemo (stage): 12.2-73.8, 0.0-36.9 (IB); 9.9-42.3, 0.1-16.2 (IIA); 9.4-45.1, 1.1-28.0 (IIB); 15.6-31.9, 0.0-4.7 (IIIA); [c]Baseline stage of disease by CRF, TNM 7th edition used for classification; [d]pCR rate in patients with radiographic down-staging: 31% with NIVO + chemo vs 7% with chemo; pCR rate in patients without radiographic down-staging: 22% with NIVO + chemo vs 1% with chemo.

Type of surgery by baseline stage of disease



Patients may have had > 1 surgery type. Patient numbers (n/N) for stage IB/II and stage IIIA, respectively, for bilobectomy (NIVO + chemo: 1/55, 2/94; chemo: 2/52, 2/83), sleeve lobectomy (NIVO + chemo: 2/55, 0/94; chemo: 5/52, 5/83), and other (NIVO + chemo: 13/55, 11/94; chemo: 12/52, 9/83). [a]Patients with all baseline stages of disease with surgery.

CM816 EFS + US FDA approval

EFS HR 0.63 (97.38% CI: 0.43, 0.91; p=0.0052)

Median EFS:
31.6 mo (95% CI: 30.2, NR) nivo + chemo
20.8 mo (95% CI: 14.0, 26.7) chemo alone

CheckMate-816 trial (NCT02998528)

US FDA Approval March 4, 2022

IMpower010 study design

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumors ≥4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

1-4 cycles cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

N=1280

R 1:1

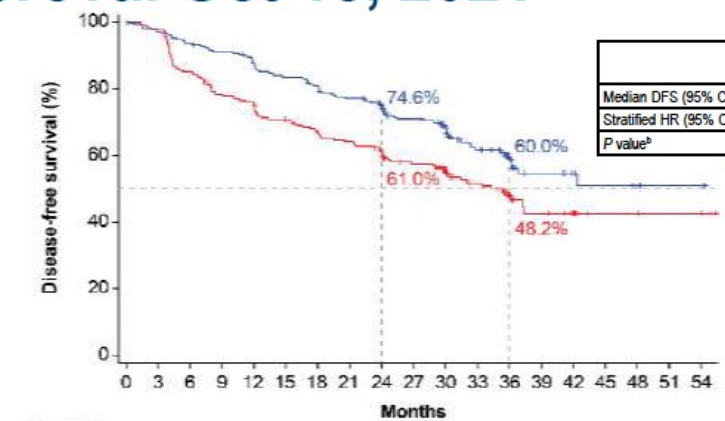
Atezolizumab *1200 mg q21d 16 cycles*

N=1005

BSC

Survival follow-up

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint) US FDA approval Oct 15, 2021



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

Wakelee ASCO 2021, abstr 8500/ Felip Lancet 2021

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

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

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

Celebrating a decade since the initial discovery of *EGFR* mutations in EGFR TKI-responsive NSCLCs (2004-2014)


Pasi Jänne


Matthew Meyerson


Bruce Johnson


Kwok-Kin Wong


Michael Eck


Nathanael Gray


Geoffrey Oxnard


David Jackman

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

Paez JG, Janne PA, et al. Science 304:1497 (2004)


Susumu Kobayashi


Balazs Halmos


Thomas Lynch Jr.


Daniel Haber


Jeffrey Engelman


Lecia Sequist


Jeffrey Settleman

The NEW ENGLAND JOURNAL *of* MEDICINE

MAY 20, 2004

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

Lynch TJ, et al. New Engl J Med 350:2129 (2004)


Tony Mok


Rafael Rosell


Tetsuya Mitsudomi


Daniel Tenen


Daniel Costa


William Pao


Harold Varmus


Mark Kriss


Vincent Miller


Mark Ladanyi


Gregory Riely


Katerina Politi

EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib

Pao W, et al. Proc Natl Acad Sci 101:13306. (2004)


Adi Gazdar

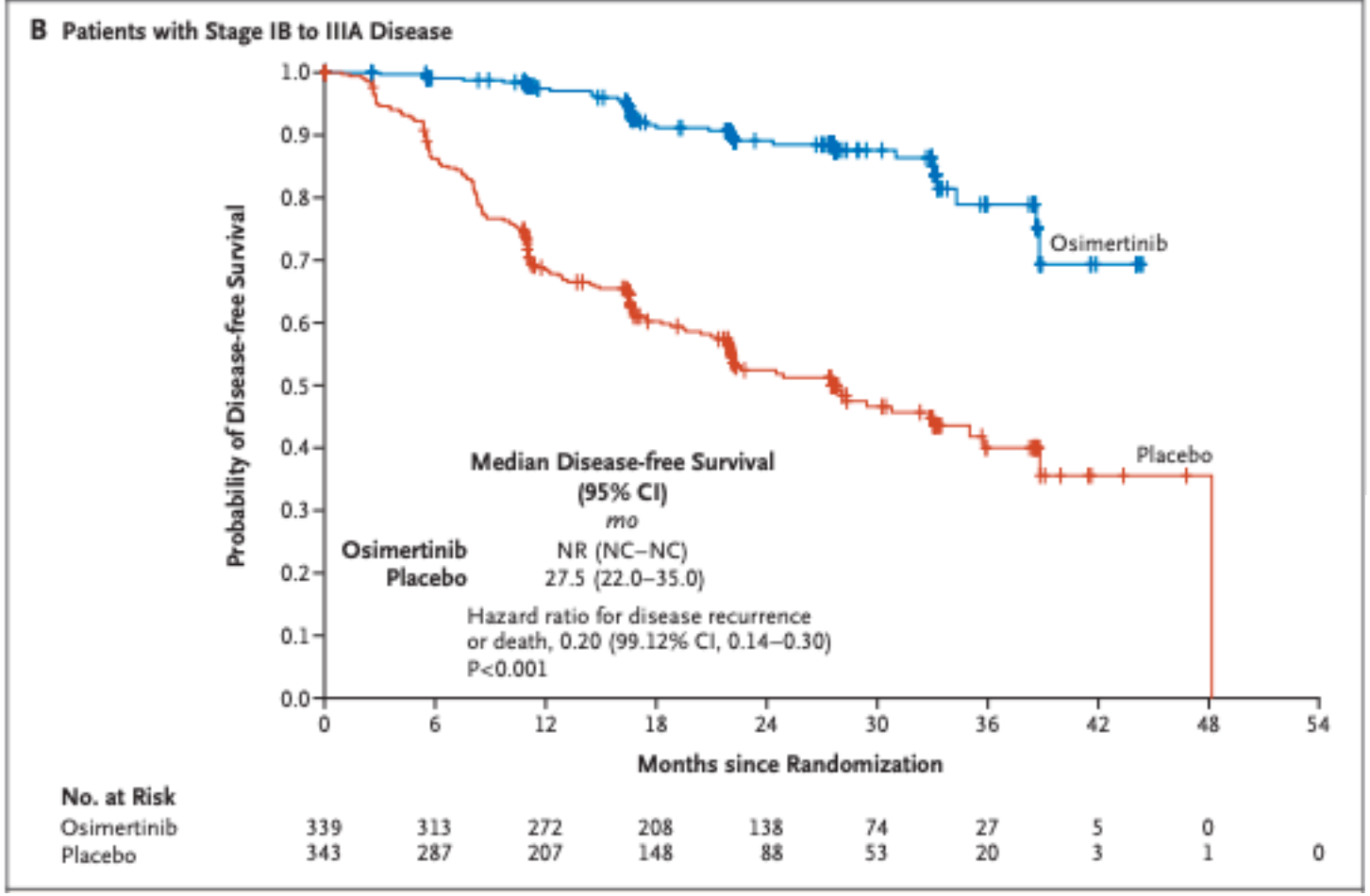

John Minna

The presenter would like to apologize to those who were instrumental in the first decade of EGFR mutation research but not included as a result of space constraints

Beth Israel Deaconess Medical Center

PRESENTED AT:

ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY



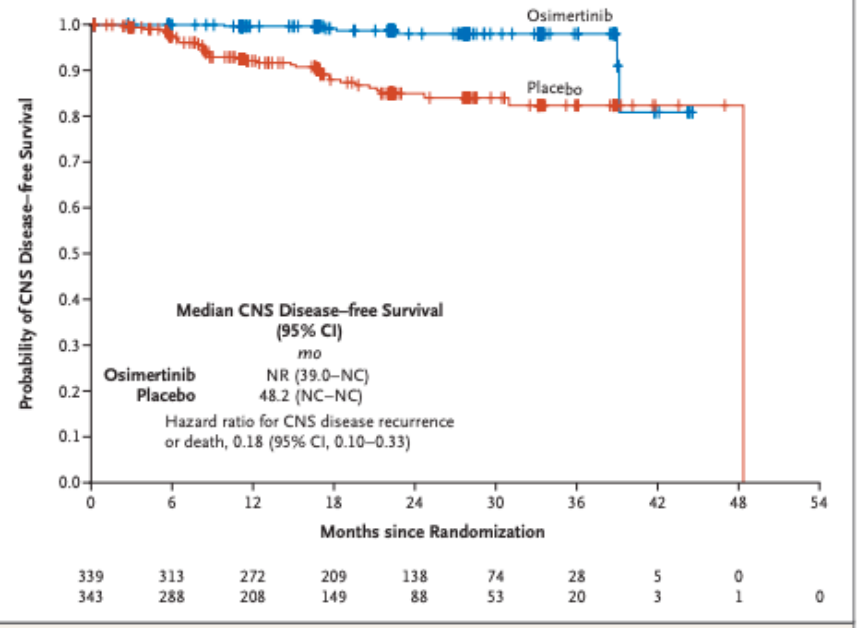


Figure 3. Central Nervous System (CNS) Disease–free Survival, According to Investigator Assessment in the Overall Population.

Shown is the Kaplan–Meier estimate of the duration of CNS disease–free survival in the overall population of patients with stage IB to IIIA disease. Tick marks indicate censored data.

CONCLUSIONI

NSCLC NON E' UN'UNICA MALATTIA

INSIEME DI MALATTIE CHE RICHIEDONO TRATTAMENTI PERSONALIZZATI CON RISULTATI TERAPEUTICI SIGNIFICATIVAMENTE MIGLIORI

EFFICCACIA CHE STA CAMBIANDO ANCHE STANDARD DELLA MALATTIA OPERABILE CON IMPATTO SU APPROCCIO CHIRURGICO

Grazie!