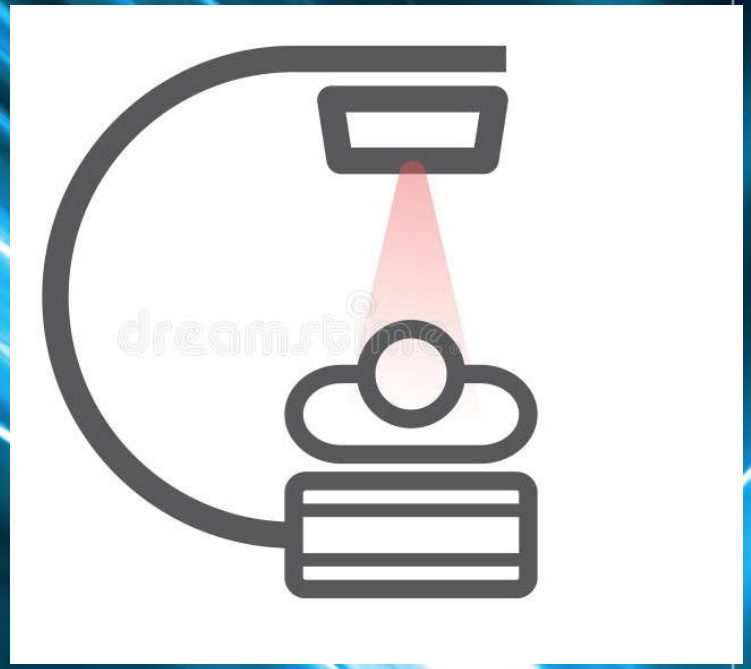
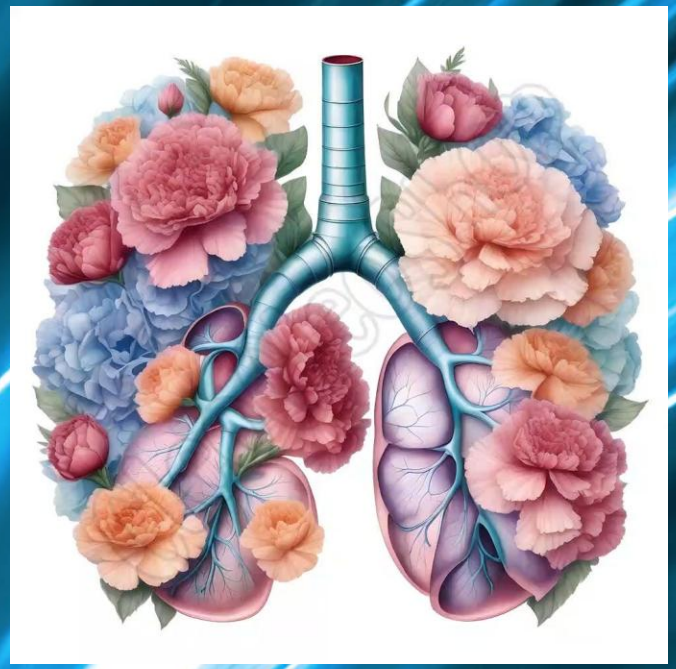
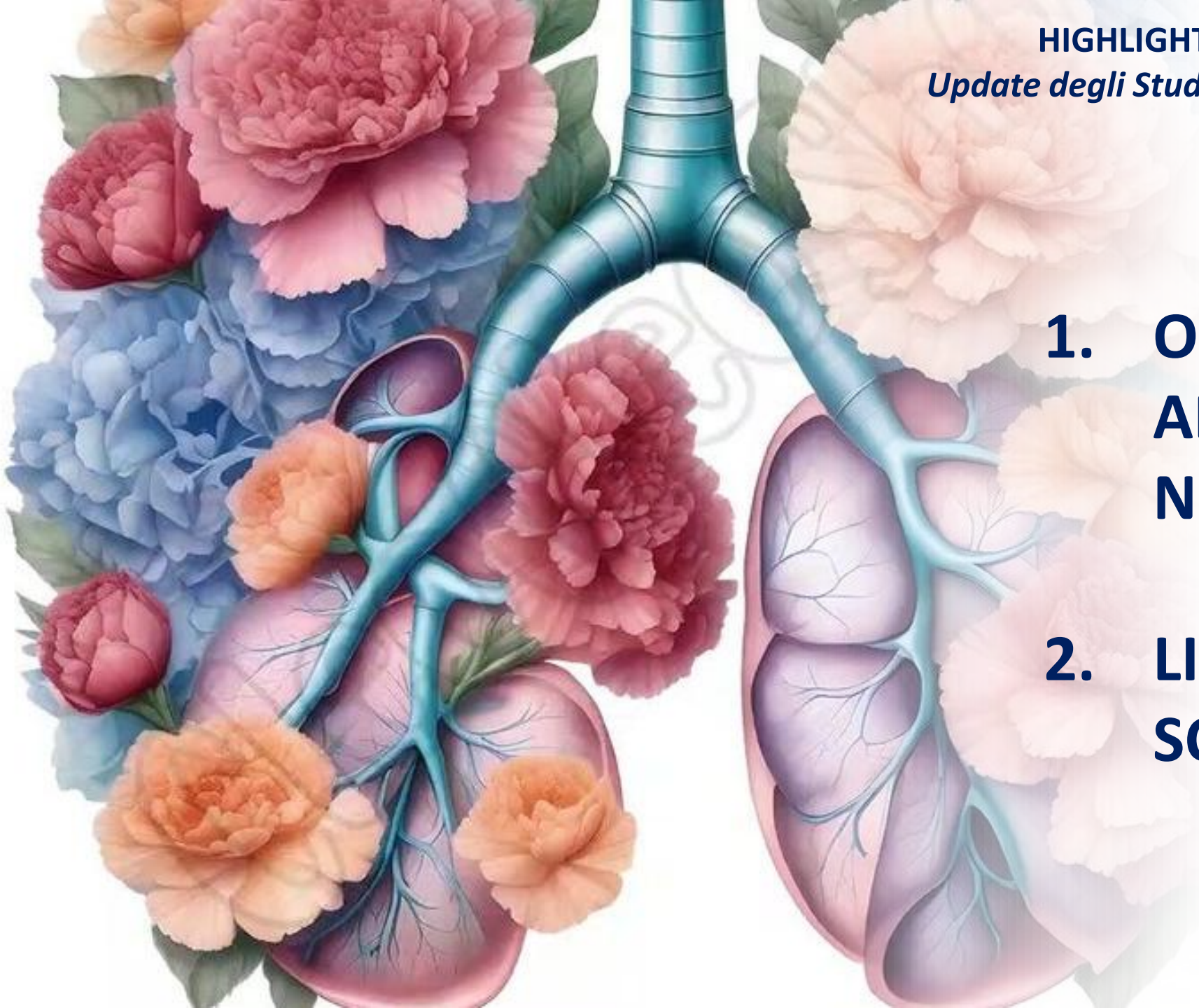
HIGHLIGHTS RADIOTERAPIA

Update degli Studi Practice Changing 2024
in Thoracic Tumors





Sara Ramella
Campus Bio-Medico University
Fondazione Policlinico Universitario Campus Bio-Medico



HIGHLIGHTS RADIOTERAPIA

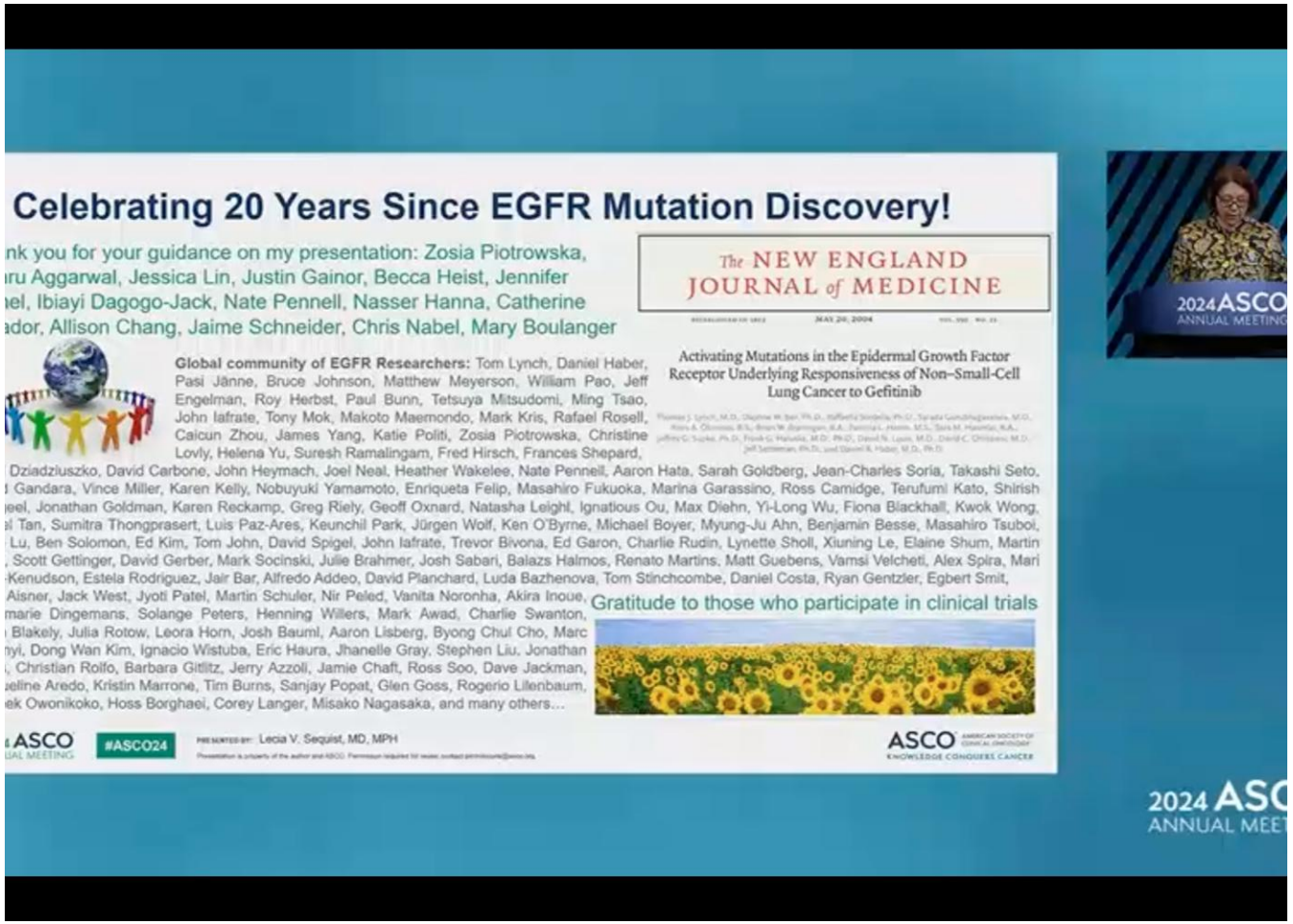
Update degli Studi Practice Changing 2024

1. **ONCOGENE-ADDICTED LA-NSCLC**
2. **LIMITED STAGE SCLC**

UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA

DECLARATION OF INTERESTS

Astra Zeneca	Advisory Board, Research Funding, Honoraria for lectures and presentations
Roche	Advisory Board, Research Funding, Honoraria for lectures and presentations
Meck (MSD)	Advisory Board, Research Funding, Honoraria for lectures and presentations
Tema Sinergie	Honoraria for lectures and presentations
Elekta	Support for attending meetings and/or travel


Celebrating 20 Years Since EGFR Mutation Discovery!
nk you for your guidance on my presentation: Zosia Piotrowska,
ıru Aggarwal, Jessica Lin, Justin Gainor, Becca Heist, Jennifer
el, Ibiayi Dagogo-Jack, Nate Pennell, Nasser Hanna, Catherine
ador, Allison Chang, Jaime Schneider, Chris Nabel, Mary Boulanger
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
Global community of EGFR Researchers: Tom Lynch, Daniel Haber, Pasi Jänne, Bruce Johnson, Matthew Meyerson, William Pao, Jeff Engelman, Roy Herbst, Paul Bunn, Tetsuya Mitsudomi, Ming Tsao, John Iafrate, Tony Mok, Makoto Maemondo, Mark Kris, Rafael Rosell, Caicun Zhou, James Yang, Katie Politi, Zosia Piotrowska, Christine Lovly, Helena Yu, Suresh Ramalingam, Fred Hirsch, Frances Shepard,
Dziadziuszko, David Carbone, John Heymach, Joel Neal, Heather Wakelee, Nate Pennell, Aaron Hata, Sarah Goldberg, Jean-Charles Soria, Takashi Seto,
Gandara, Vince Miller, Karen Kelly, Nobuyuki Yamamoto, Enriqueta Felip, Masahiro Fukuoka, Marina Garassino, Ross Camidge, Terufumi Kato, Shirish
eel, Jonathan Goldman, Karen Reckamp, Greg Riely, Geoff Oxnard, Natasha Leighl, Ignatious Ou, Max Diehn, Yi-Long Wu, Fiona Blackhall, Kwok Wong,
l Tan, Sumitra Thongprasert, Luis Paz-Ares, Keunchil Park, Jürgen Wolf, Ken O'Byrne, Michael Boyer, Myung-Ju Ahn, Benjamin Besse, Masahiro Tsuboi,
Lu, Ben Solomon, Ed Kim, Tom John, David Spigel, John Iafrate, Trevor Bivona, Ed Garon, Charlie Rudin, Lynette Sholl, Xiuning Le, Elaine Shum, Martin
, Scott Gettinger, David Gerber, Mark Socinski, Julie Brahmer, Josh Sabari, Balazs Halmos, Renato Martins, Matt Guebens, Vamsi Velcheti, Alex Spira, Mari
-Kenudson, Estela Rodriguez, Jair Bar, Alfredo Addeo, David Planchard, Luda Bazhenova, Tom Stinchcombe, Daniel Costa, Ryan Gentzler, Egbert Smit,
Aisner, Jack West, Jyoti Patel, Martin Schuler, Nir Peled, Vanita Noronha, Akira Inoue,
marie Dingemans, Solange Peters, Henning Willers, Mark Awad, Charlie Swanton,
Blakely, Julia Rotow, Leora Horn, Josh Bauml, Aaron Lisberg, Byong Chul Cho, Marc
nyi, Dong Wan Kim, Ignacio Wistuba, Eric Haura, Jhanelle Gray, Stephen Liu, Jonathan
, Christian Rolfo, Barbara Gitlitz, Jerry Azzoli, Jamie Chaft, Ross Soo, Dave Jackman,
eline Aredo, Kristin Marrone, Tim Burns, Sanjay Popat, Glen Goss, Rogerio Lilenbaum,
ek Owonikoko, Hoss Borghaei, Corey Langer, Misako Nagasaka, and many others…
Gratitude to those who participate in clinical trials
2024ASCO
ANNUAL MEETING
#ASCO24
PRESENTED BY: Lecia V. Sequist, MD, MPH
ASCO
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2024 ASC
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ORIGINAL ARTICLE

Updated estimates of eligibility for and response to genome-targeted oncology drugs among US cancer patients, 2006-2020

A. Haslam[1*], M. S. Kim[2] & V. Prasad[1]

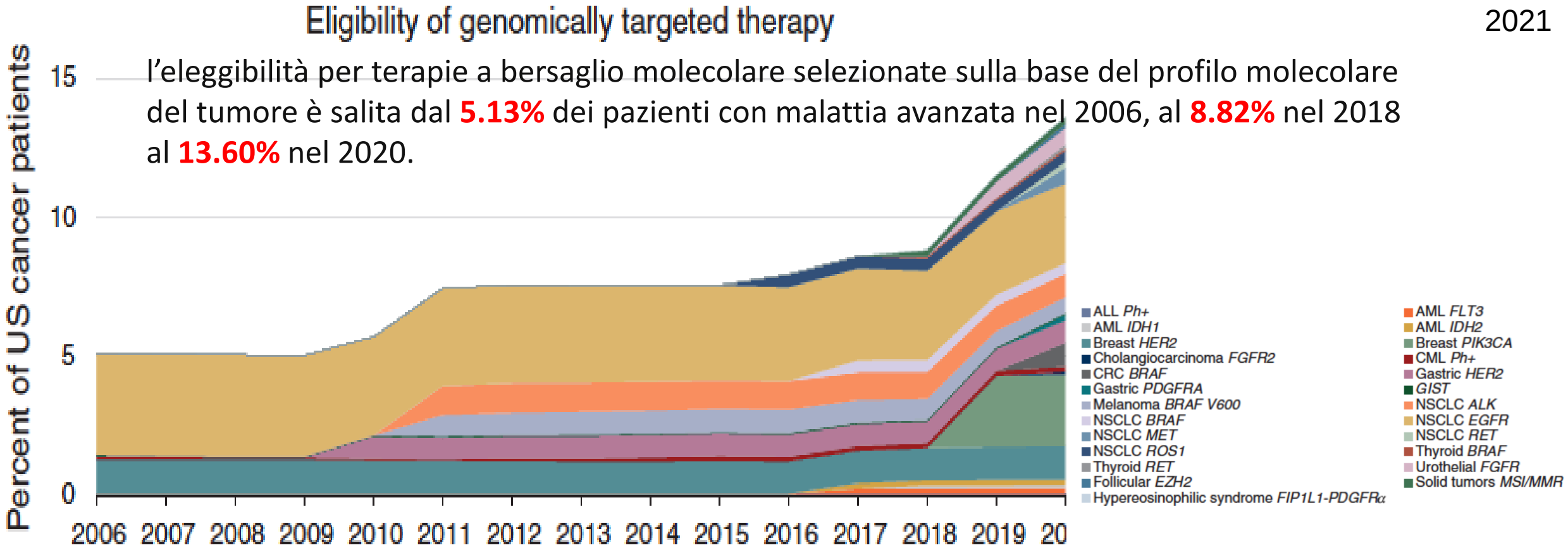
[1]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco; [2]Division of Hematology and Medical Oncology, Oregon Health and Science University, Portland, USA

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

2021

l'eleggibilità per terapie a bersaglio molecolare selezionate sulla base del profilo molecolare del tumore è salita dal **5.13%** dei pazienti con malattia avanzata nel 2006, al **8.82%** nel 2018 al **13.60%** nel 2020.



2024 ASCO ANNUAL MEETING

Osimertinib after definitive chemoradiotherapy in patients with unresectable stage III epidermal growth factor receptor-mutated (EGFRm) NSCLC: primary results of the Phase 3 LAURA study

Suresh S. Ramalingam,[1] Terufumi Kato, Xiaorong Dong, Myung-Ju Ahn, Le-Van Quang, Nopadol Soparattanapaisarn, Takako Inoue, Chih-Liang Wang, Meijuan Huang, James Chih-Hsin Yang, Manuel Cobo, Mustafa Özgüroğlu, Ignacio Casarini, Dang-Van Khiem, Virote Sriuranpong, Eduardo Cronemberger, Xiangning Huang, Toon van der Gronde, Dana Ghiorghiu, Shun Lu

[1]Emory University School of Medicine, Winship Cancer Institute, Atlanta, GA, USA

PRESENTED BY: Dr Suresh S. Ramalingam

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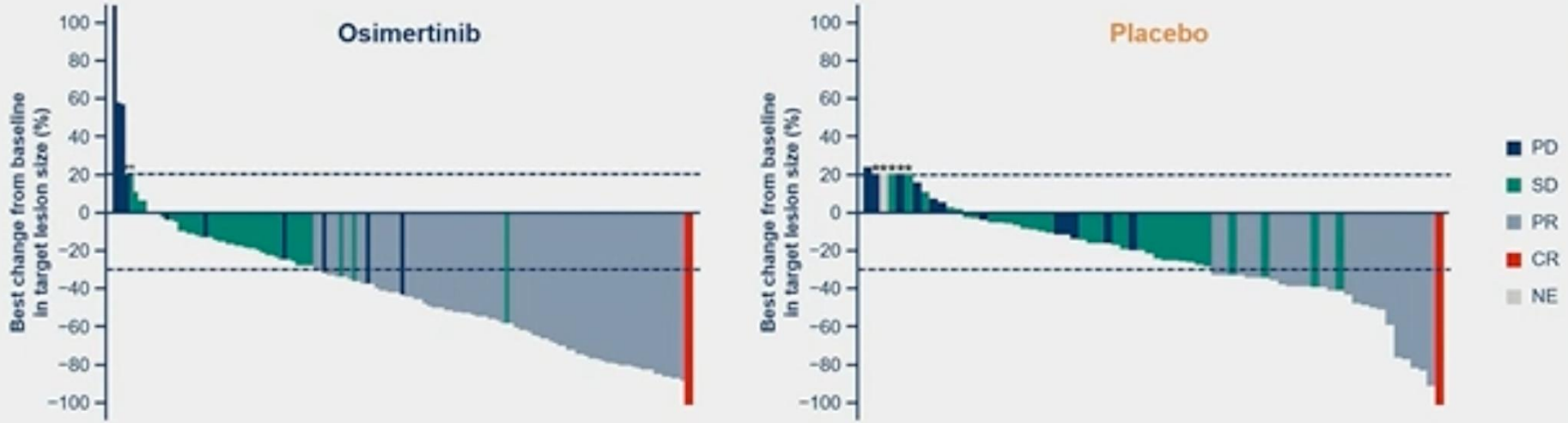
Baseline characteristics

Characteristics, %	Osimertinib (n=143)	Placebo (n=73)
Sex: male / female	37 / 63	42 / 58
Age: median (range), years	62 (36–84)	64 (37–83)
Smoking history: formerly / currently / never	26 / 3 / 71	32 / 1 / 67
Race: Asian / non-Asian	81 / 19	85 / 15
WHO PS: 0 / 1	56 / 44	42 / 58
AJCC / UICC staging (8th edition) at diagnosis: IIIA / IIIB / IIIC	36 / 47 / 17	33 / 52 / 15
Histology: adenocarcinoma / other	97 / 3	95 / 5
EGFR mutation at randomization:* Ex19del / L858R	52 / 48†	59 / 41
Type of CRT: concurrent CRT / sequential CRT	92 / 8	85 / 15
Response to prior CRT: CR / PR / SD / PD / NE	3 / 47 / 43 / 0 / 8	4 / 37 / 51 / 0 / 8
Target lesion size by BICR:‡ mean (SD), mm	33 (18)	36 (17)

Data cut-off: January 5, 2024.
*Tissue tested by central or FDA-approved local test from a CLIA-approved laboratory, or accredited local laboratory for sites outside the USA.
†One patient in the osimertinib arm had missing EGFR mutation.
‡Post-CRT.

Tumor response by BICR

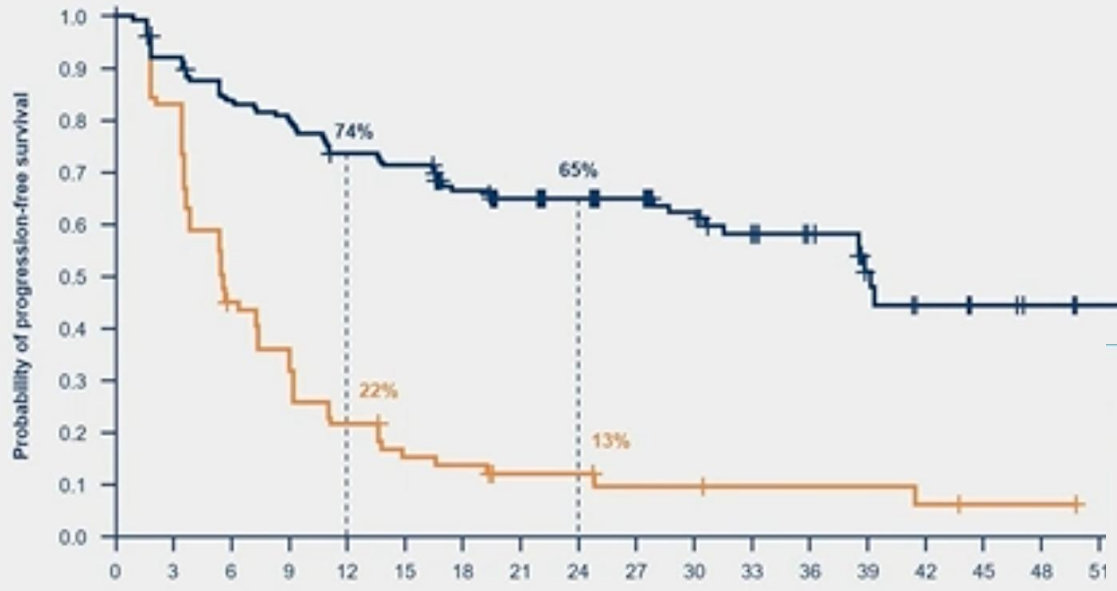


	Osimertinib (n=143)	Placebo (n=73)
Objective response rate, % (95% CI)	57 (49, 66)	33 (22, 45)
Disease control rate, % (95% CI)	89 (83, 94)	79 (68, 88)
Median duration of response, months (95% CI)	36.9 (30.1, NC)	6.5 (3.6, 8.3)

Data cut-off: January 5, 2024.
*Missing data imputed as +20% according to predefined rules.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; NC, not calculable; NE, not evaluable PD, progressive disease; PR, partial response; SD, stable disease

Progression-free survival by BICR



No. at risk																		
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0

Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.0 months, placebo 5.6 m

BICR, blinded independent central review; CI, confide

Median PFS, months (95% CI)

Osimertinib	39.1 (31.5, NC)
Placebo	5.6 (3.7, 7.4)

PFS HR (95% CI): 0.16 (0.10, 0.24), p<0.001

Maturity 56%:
osimertinib 40%, placebo 86%

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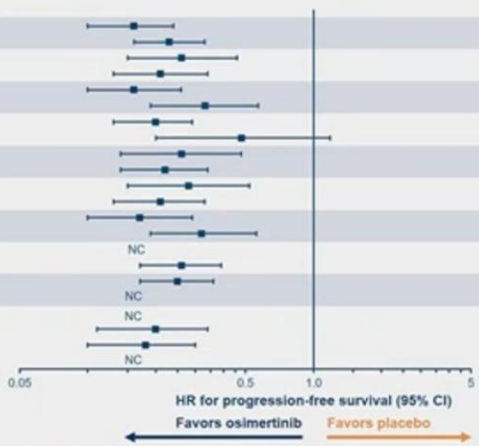
Progression-free survival by BICR across subgroups

Subgroup		No. of events / patients	HR	95% CI
Overall (N=216)	Stratified log-rank	120 / 216	0.16	0.10, 0.24
	Unadjusted Cox PH	120 / 216	0.23	0.16, 0.33
Sex	Male	50 / 84	0.26	0.15, 0.46
	Female	70 / 132	0.21	0.13, 0.34
Age	<65 years	67 / 120	0.16	0.10, 0.26
	≥65 years	53 / 96	0.33	0.19, 0.57
Race	Asian	98 / 178	0.20	0.13, 0.29
	Non-Asian	22 / 38	0.48	0.20, 1.19
Smoking history	Current / former (yes)	42 / 65	0.26	0.14, 0.48
	Never (no)	78 / 151	0.22	0.14, 0.34
Stage*	IIIA	42 / 76	0.28	0.15, 0.52
	IIIB / IIIC	78 / 140	0.21	0.13, 0.33
EGFR mutation†	Ex19del	65 / 117	0.17	0.10, 0.29
	L858R	55 / 98	0.32	0.19, 0.56
China cohort	Chinese	18 / 40	NC	NC, NC
	Non-Chinese	102 / 176	0.26	0.17, 0.39
Chemoradiotherapy	Concurrent	107 / 193	0.25	0.17, 0.36
	Sequential	13 / 23	NC	NC, NC
Response to prior CRT	Complete response	3 / 7	NC	NC, NC
	Partial response	53 / 94	0.20	0.11, 0.34
	Stable disease	58 / 98	0.18	0.10, 0.30
	Non-evaluable	6 / 17	NC	NC, NC



Note: HRs were calculated only for subgroups with >20 events across both arms to allow for meaningful analysis. Subgroup (not prespecified) of WHO PS: PS=0 HR 0.17 (95% CI 0.10, 0.28); PS=1 HR 0.34 (95% CI 0.20, 0.56)

*Stage prior to CRT by AJCC / UICC staging (8th edition)

†Central test of tumor tissue at screening, or local pre-existing test result; one patient in the osimertinib arm had missing EGFR mutation information.

Data cut-off: January 5, 2024

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CI, confidence interval; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NC, not calculable; PFS, progression-free survival; PH, proportional-hazards model; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

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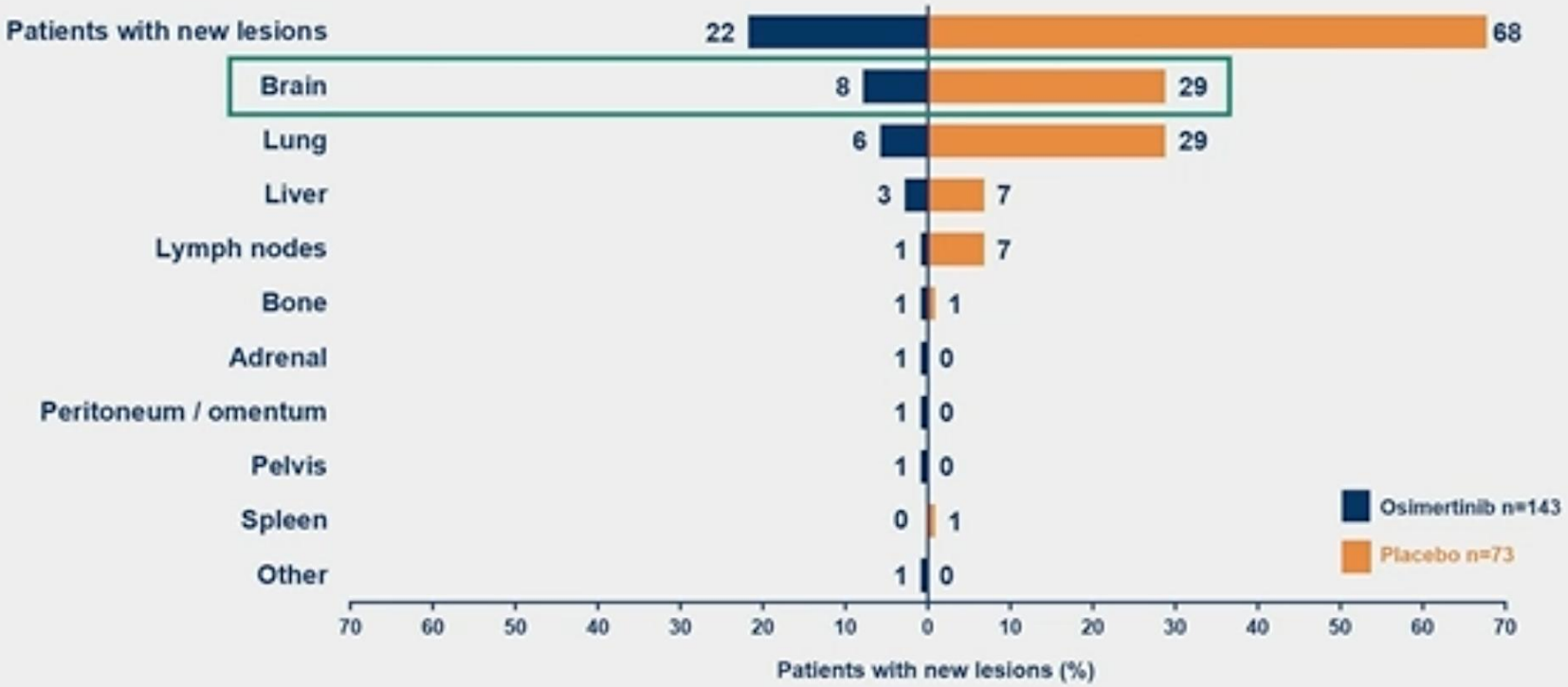
Sites of new lesions by BICR



Percentages based on number of patients in each treatment arm. Patients can have more than one new lesion site. Based on BICR assessments according to RECIST v1.1 and includes all new lesions at any time (including those whose RECIST progression event had been censored).

Data cut-off: January 5, 2024.

BICR, blinded independent central review

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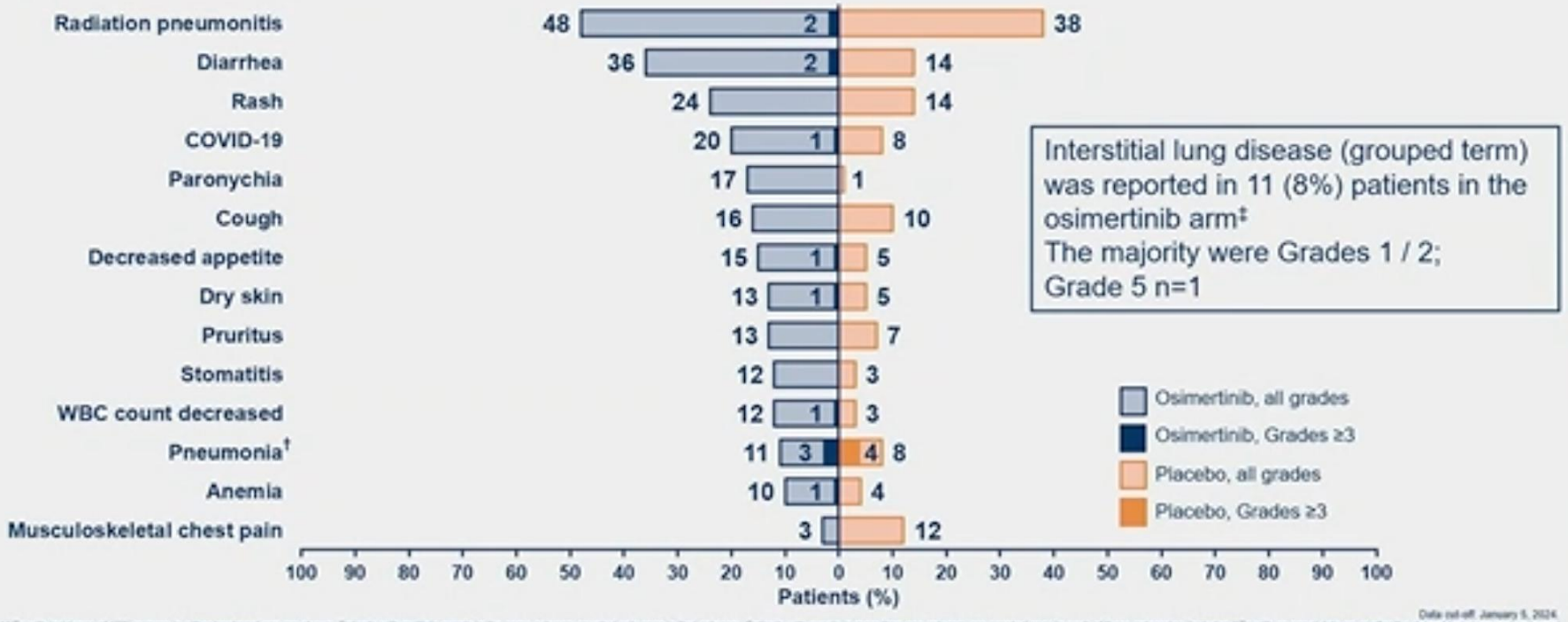
All-causality adverse events (≥10%)*

- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

Data cut-off: January 5, 2024.

*AEs with incidence of 10% or more in either treatment arm are shown. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy; †One grade 5 AE of pneumonia was reported in the osimertinib arm; ‡Interstitial lung disease (grouped term) was reported in 1 patient (1%) in placebo arm; AE was pneumonitis, Grade 1.

AE, adverse event; WBC, white blood cells

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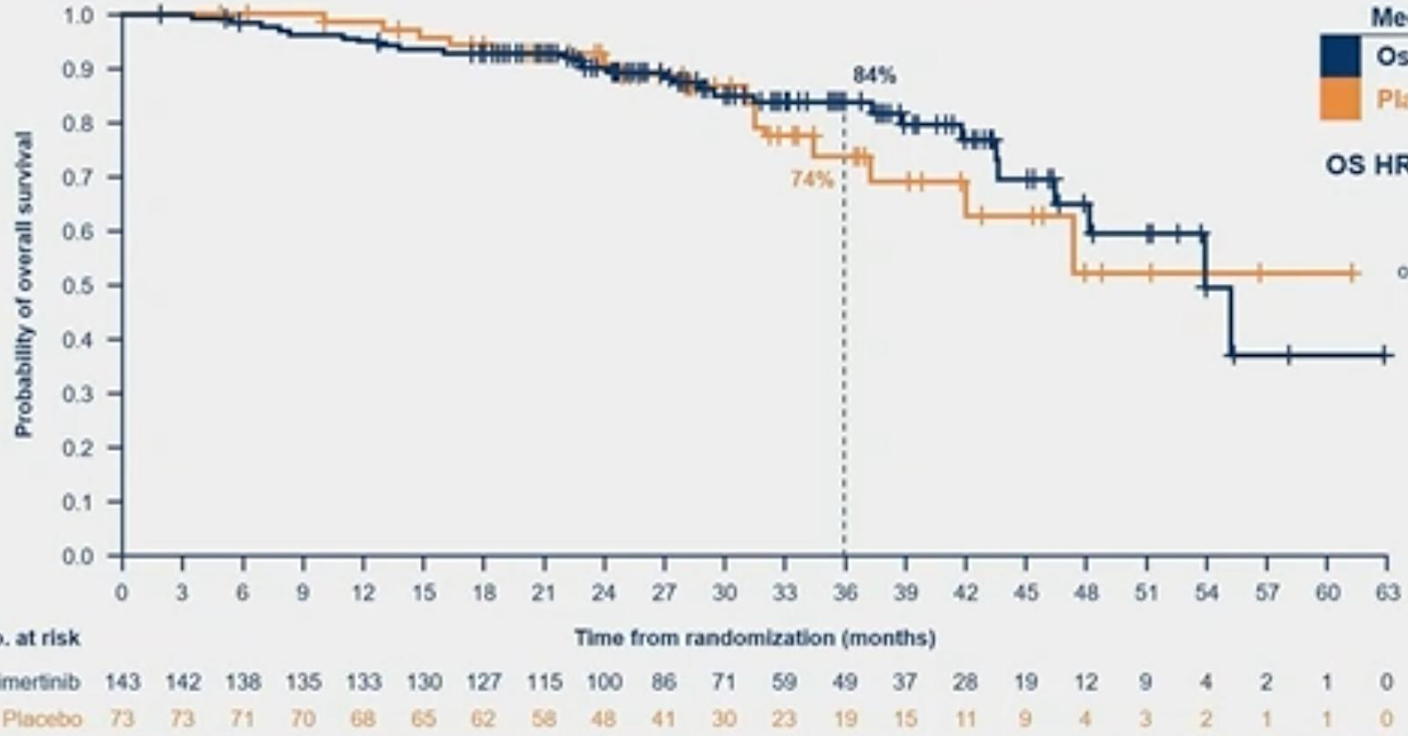
Interim analysis of overall survival

- In the placebo arm, 81% of patients with BICR-confirmed progression crossed over to osimertinib



Median OS, months (95% CI)

Osimertinib	54.0 (46.5, NC)
Placebo	NR (42.1, NC)

OS HR (95% CI): 0.81 (0.42, 1.56), p=0.530*

Maturity 20%:
osimertinib 20%, placebo 21%

No. at risk

Osimertinib	143	142	138	135	133	130	127	115	100	86	71	59	49	37	28	19	12	9	4	2	1	0
Placebo	73	73	71	70	68	65	62	58	48	41	30	23	19	15	11	9	4	3	2	1	1	0

Data cut-off: January 5, 2024.

Tick marks indicate censored data. *For statistical significance at this interim analysis, a p-value of <0.00036 was required.

Median follow-up for OS (all patients): osimertinib 29.5 months, placebo 28.1 months. Median follow-up for OS (censored patients): osimertinib 30.9 months, placebo 29.1 months.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival

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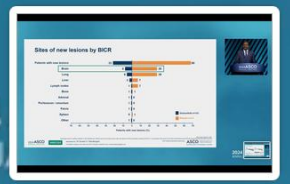

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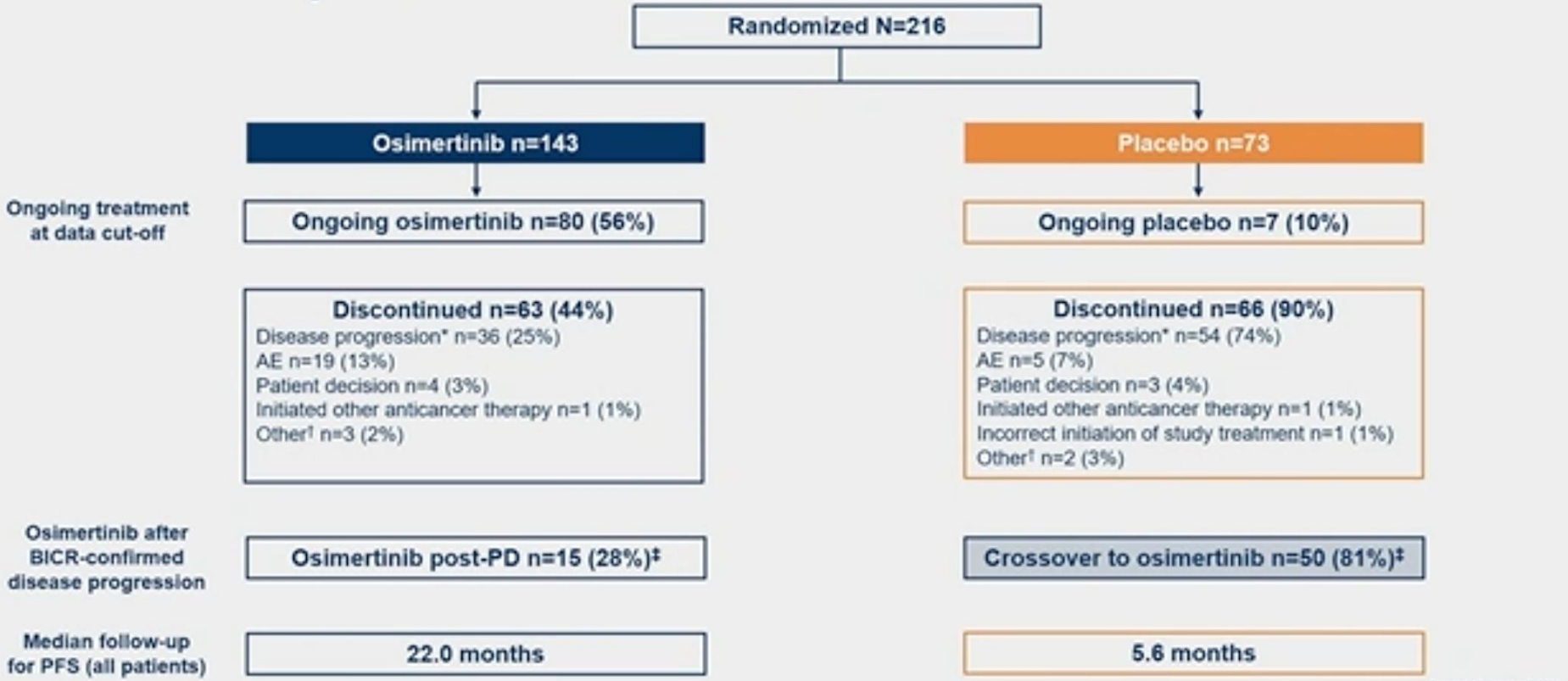
Patient disposition



Data cut-off: January 5, 2024.

*Assessed by BICR per RECIST v1.1 prior to primary PFS analysis.

†Any other reason not specifically captured in earlier categories. Osimertinib arm: death (n=2); disease progression by investigator (n=1); placebo arm: death (n=1); disease progression by investigator (n=1).

‡Percentages calculated using patients with BICR-confirmed disease progression in each treatment arm as denominator: osimertinib, n=53; placebo, n=62.

AE, adverse event; BICR, blinded independent central review; PD, progressive disease; PFS, progression-free survival

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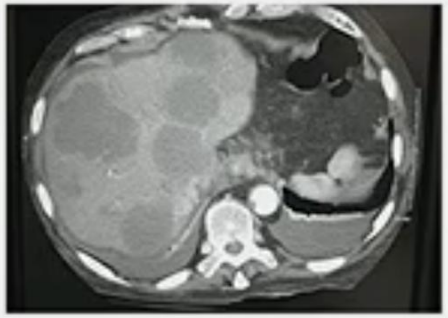
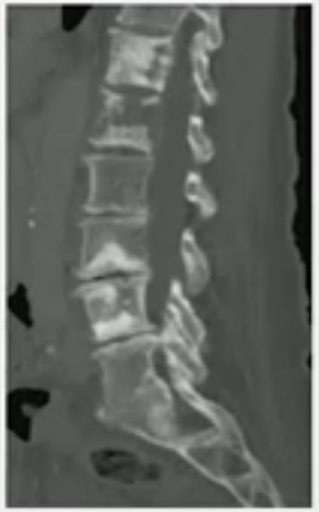
The LAURA trial had high crossover, but relying on crossover leaves some patients stranded

Symptomatic NSCLC Progression





Crossover Data: 1st line stage IV EGFR + Trialsp

Trial	1st line therapy→ 2nd line EGFR TKI	Among pts progressed on chemo, how many received 2nd line EGFR TKI (%)
NEJ002	Chemo → Gefitinib	96%
IPASS	Chemo → Gefitinib	64%
WJTOG 3405	Chemo → any EGFR TKI	91%
OPTIMAL	Chemo → any EGFR TKI	69%
Lux-Lung 3	Chemo → any EGFR TKI	75%
Lux-Lung 6	Chemo → any EGFR TKI	56%

Mitsudomi Lancet Onc 2010, Inoue Ann Onc 2013, Mok NEJM 2009, Fukuoka JCO 2011, Maemondo NEJM 2010, Yoshioka Ann Onc 2019, Zhou Ann Onc 2015, Sequist JCO 2013, Wu Lancet Oncol 2014, Yang Lancet Oncol 2015

LAURA Trial Design

Clear winning arm for PFS, but what about the length of therapy course?

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO performance status 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
cCRT vs sCRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

Endpoints
- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

Ramalingam, ASCO24

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PRESENTED BY: Lecia V. Sequist, MD, MPH

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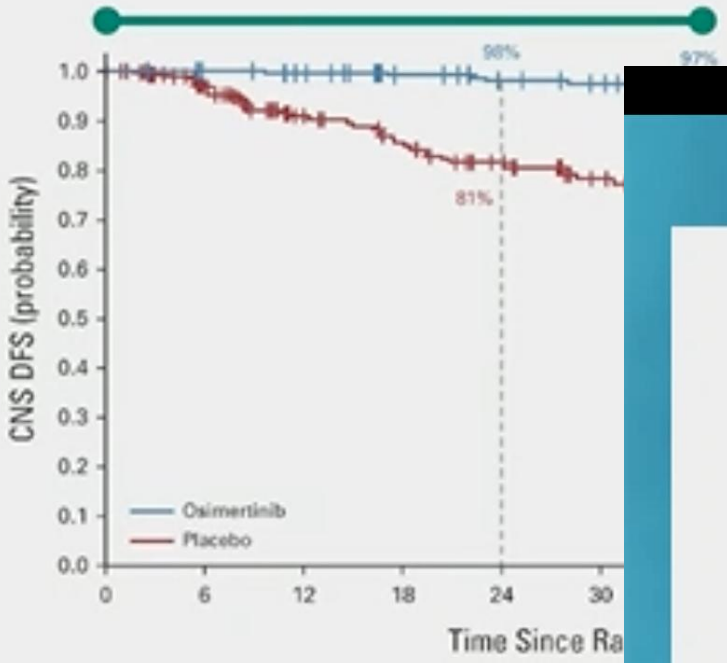
Long Term CNS Protection with Osimertinib

ADAURA study: adjuvant osimertinib or placebo after surgery ± chemo; stages IB, II, and IIIA

3-year course of adjuvant osimertinib/placebo



No. at risk:						
Osimertinib	233	222	216	202	196	192
Placebo	237	192	142	126	107	91

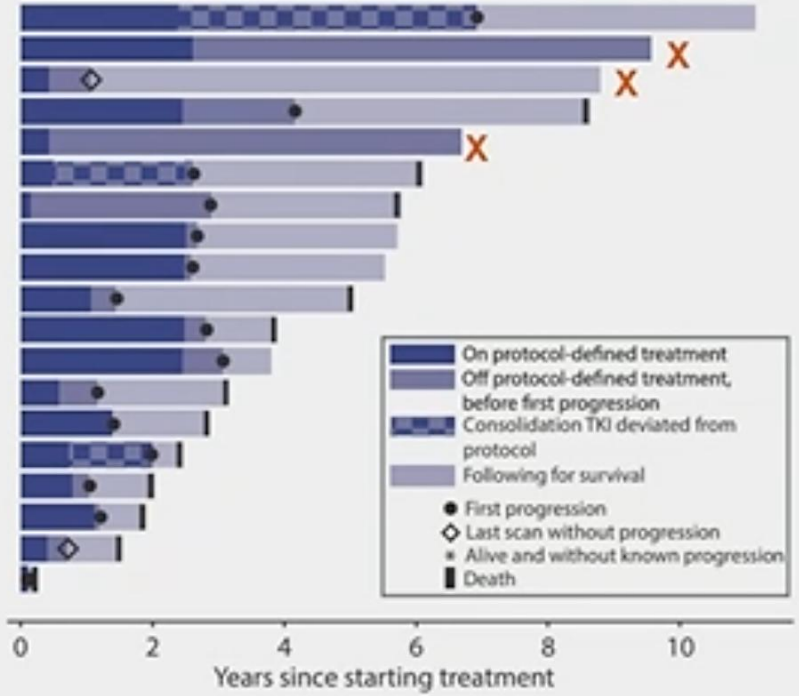
Factors to Consider with Indefinite Osimertinib

- CNS protection

- Cost
- Side effects/QoL
- Not all patients need

Is There a Subset of Patients Who Do *Not* Require Indefinite Treatment?

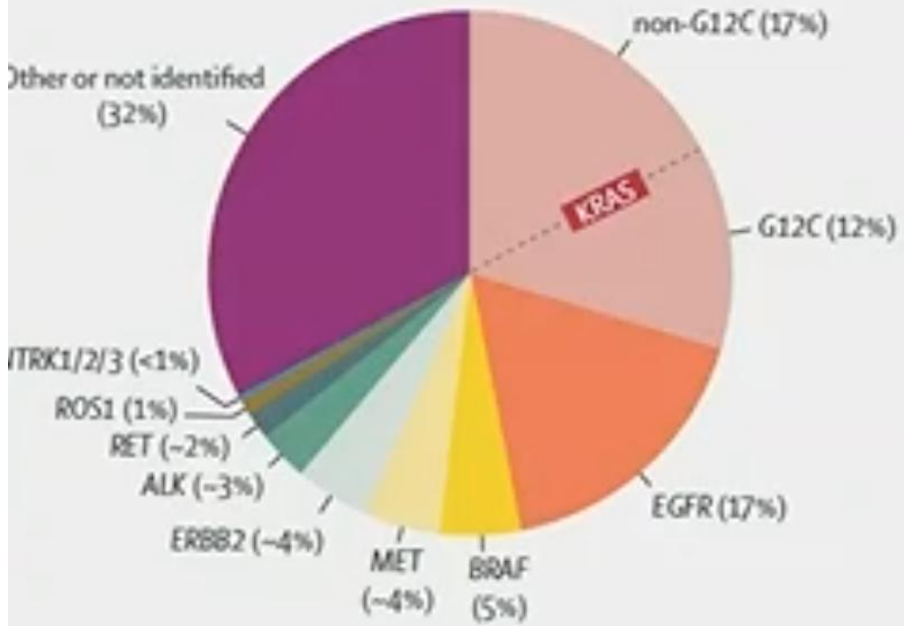
- Small phase 2 trial called ASCENT
- Stage III EGFR + NSCLC
- Afatinib x 2mo, chemoRT ± surgery, then adjuvant afatinib x 2y
- Med f/u = 5 years, range up to 11y
- **3/19 (15%) patients without recurrence after 7-10 years**



Chang, Oncologist 2024

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
- Crizotinib
- Ceritinib
- Alectinib
- Brigatinib
- Lorlatinib

EGFR (exon20ins)
- Amivantamab

KRAS (G12C)
- Sotorasib
- Adagrasib

ROS1
- Crizotinib
- Entrectinib
- Repotrectinib

MET (exon 14)
- Capmatinib
- Tepotinib

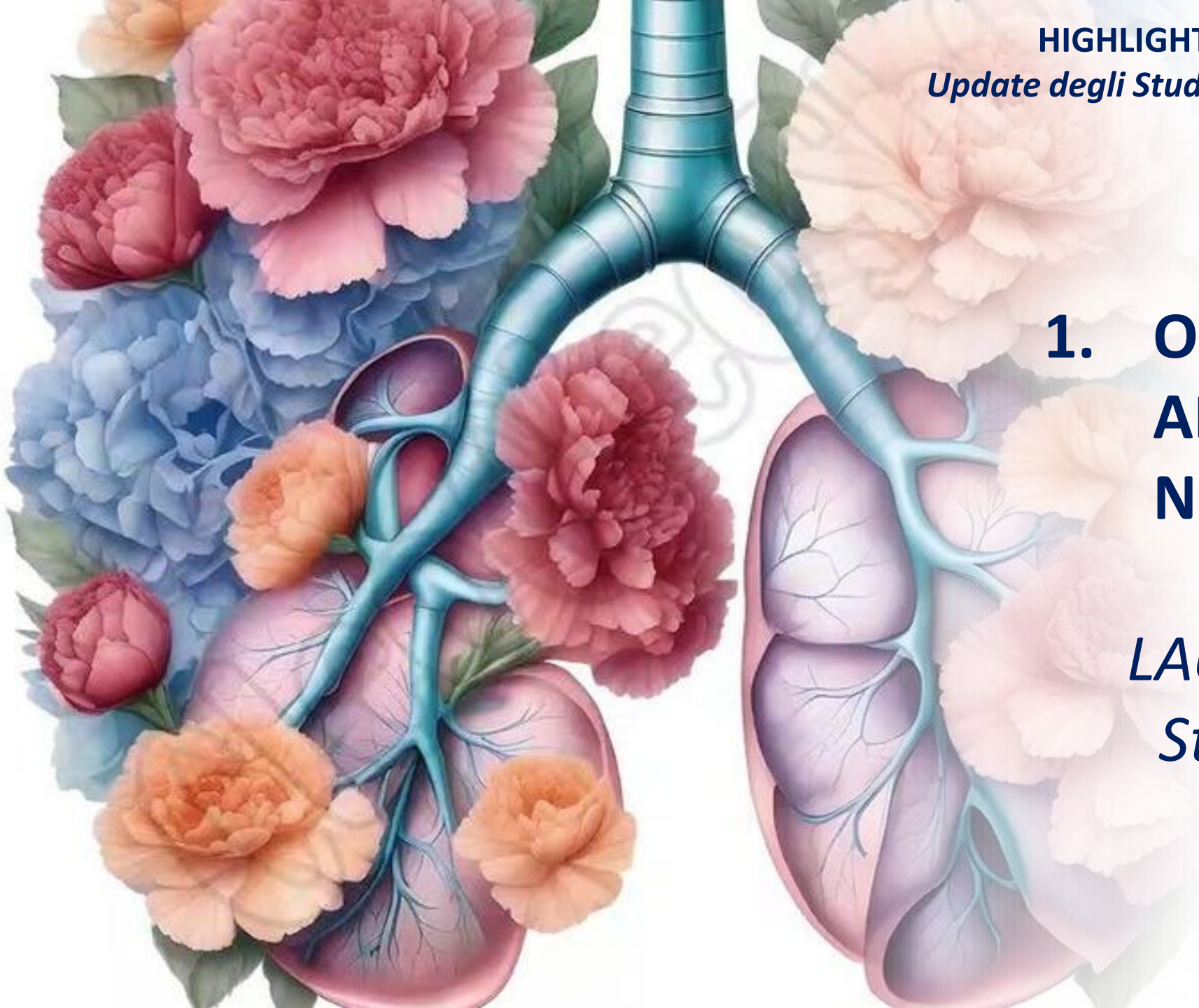
RET
- Selpercatinib
- Pralsetinib

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



HIGHLIGHTS RADIOTERAPIA

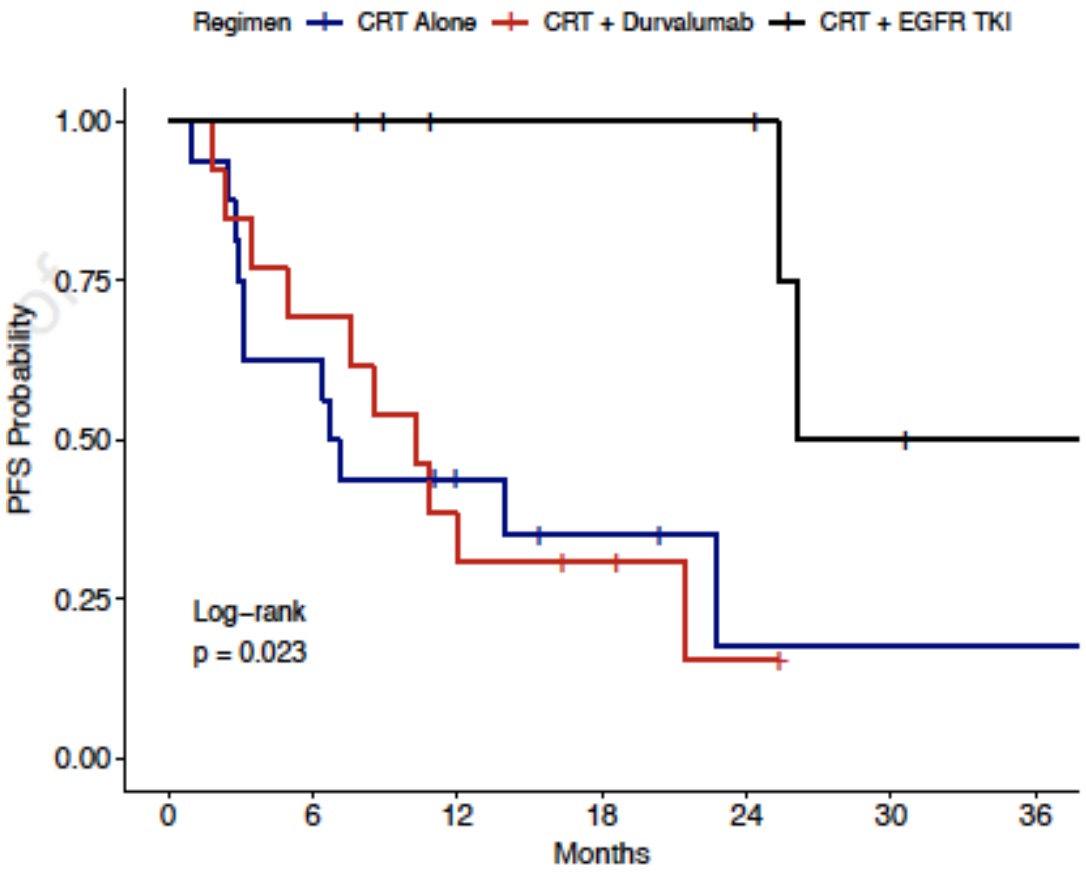
Update degli Studi Practice Changing 2024

1. ONCOGENE-ADDICTED LA-NSCLC

LAURA trial in the State of the Art

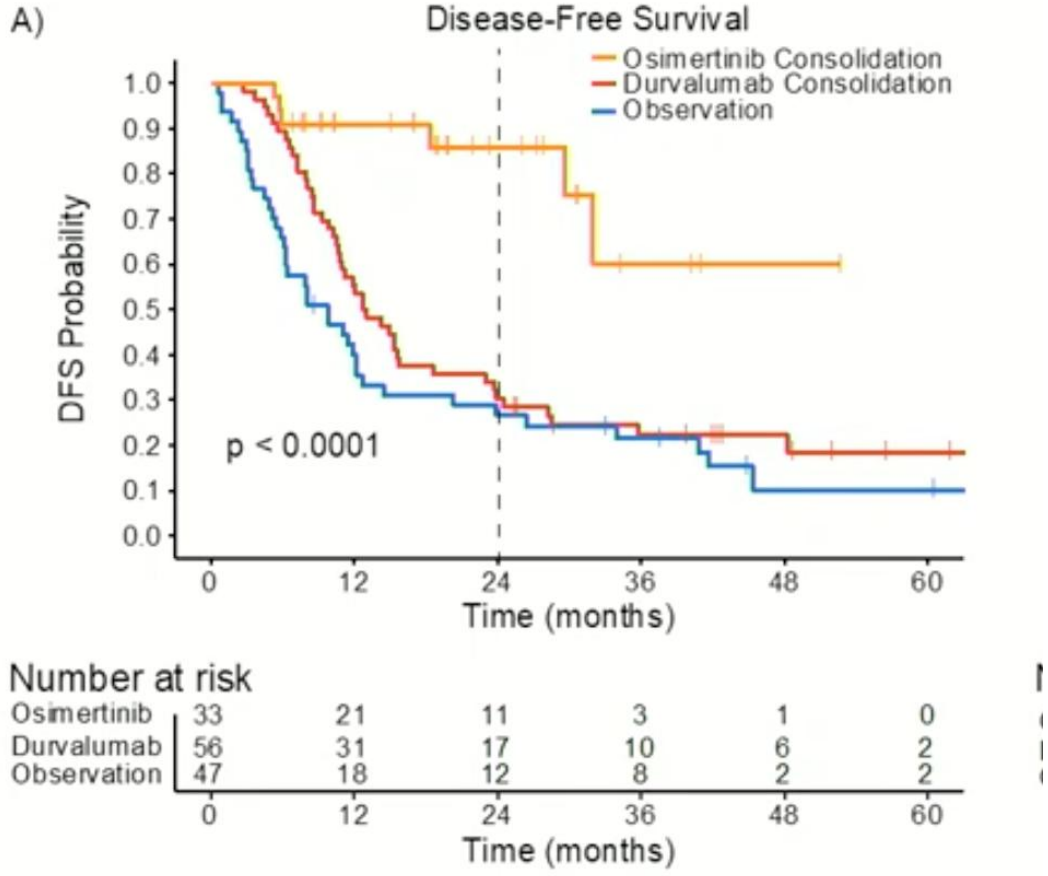
Focus on RADICAL CHEMORADIATION in EGFR Mut Pts

Aredo JTO 2021 EGFR+= N=37



RT alone=43%
RT+DURVA= 35%
RT+EGFR TKI 22%

NASSAR 2024



24-month CNS-DFS: Osimertinib: 6.7% (95% CI, 1

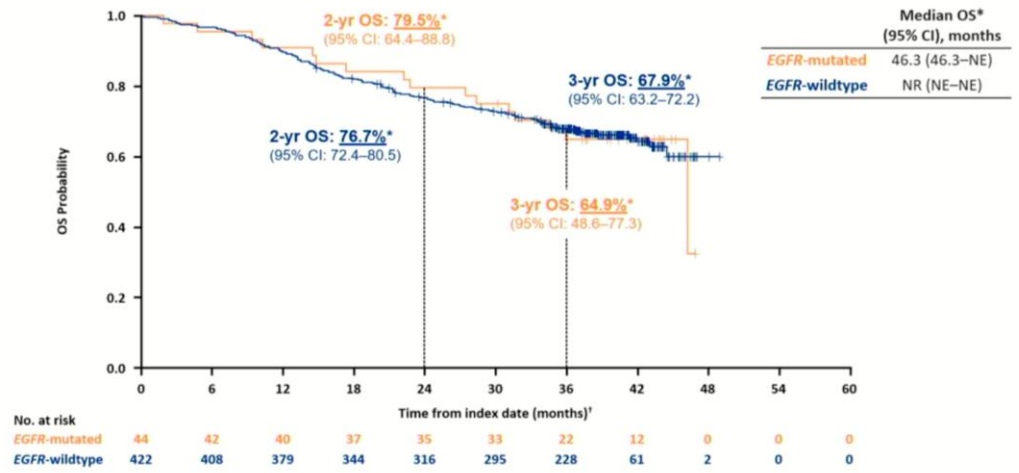
POST-HOC PACIFIC Trial
EGFR+= N=35

EGFR-Mutated	Placebo (11)	Durva (24)
Male	73%	54%
IIIA	64%	46%
preRT induction CT	36%	8%
PS0	64%	54%
PFS	**10.9**	**11.2m**
OS	**43m**	**46.8m**

Real-world outcomes with durvalumab after chemoradiotherapy in unresectable stage III *EGFR*-mutated NSCLC (PACIFIC-R)

Solange Peters,[1] Daniel C. Christoph,[2] John K. Field,[3] Rainer Fietkau,[4] Andrea R. Filippi,[5] Marina Garassino,[6] Pilar Garrido,[7] Fiona McDonald,[8] Françoise Mornex,[9] Ben Markman,[10] Benjamin J. Solomon,[11] Shawn Anand,[12] Pratibha Chander,[12] Yao Qiao,[12] Nicolas Girard[13]

Overall survival by *EGFR* status



Optimization of treatment options for EGFR-mutant, stage III, unresectable NSCLC: A systematic review and meta-analysis.

2022 ASCO ANNUAL MEETING

A total of **3291 patients** were identified in 17 studies and 5 treatment:

	PFS	OS
Concurrent chemoradiotherapy (CRT)	TKI-free vs TKI-containing HR 2.17, 95%CI 1.47-3.19 In detail, the PFS with TKI-containing measures, including TKI monotherapy (0.66, 0.50-0.87), RT+TKI (0.37, 0.28-0.50), or CRT+TKI (0.14, 0.03-0.75) were all significantly longer than CRT	The integrated analysis found that RT+TKI had the longest OS (65.7 months, 55.5-76.0 months) and PFS (21.8 months, 18.0-25.7 months) and the highest response rate (77.7%, 68.8%-86.6%).
CRT followed by durvalumab (CRT+Durva)		
TKI monotherapy		
Radiotherapy combined with TKI (RT+TKI)		
CRT combined with TKI (CRT+TKI)		

Lian Liu, ASCO 2022

RESULT- efficacy and safety profiles of the Bayesian network meta-analysis

OS

PFS

TKI	1.27 (0.73, 2.20)		0.88 (0.34, 2.26)	0.86 (0.61, 1.22)
1.78 (1.17, 2.67)	RT+TKI		0.70 (0.26, 1.89)	0.68 (0.44, 1.05)
4.80 (0.86, 26.01)	2.70 (0.49, 15.19)	CRT+TKI		
0.71 (0.38, 1.30)	**0.40 (0.21, 0.76)**	**0.15 (0.03, 0.74)**	CRT+Durva	0.97 (0.40, 2.34)
0.66 (0.50, 0.87)	**0.37 (0.28, 0.50)**	**0.14 (0.03, 0.75)**	0.93 (0.53, 1.59)	CRT

≥3AE

ORR

RT+TKI	0.74 (0.03, 24.67)	0.78 (0.16, 3.66)
0.52 (0.01, 10.01)	CRT+TKI	1.05 (0.02, 41.36)
2.48 (1.06, 6.05)	4.83 (0.22, 209.62)	CRT

- **ORR** of RT+TKI was significantly higher than CRT
- **PFS** with TKI-containing measures, including TKI , RT+TKI or CRT+TKI were all significantly longer than CRT
- **PFS** with both RT+TKI and CRT+TKI were significantly longer than CRT+Durva
- TKI alone had significantly shorter **PFS** than RT+TKI
- No significant difference observed in **OS** among the treatments
- **RT+TKI ranking first in the Bayesian ranking of OS**

Lian Liu, ASCO 2022

2024 World Conference on Lung Cancer

SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

#WCLC24
wclc2024.iaslc.org

POLESTAR

Screening Period

Key inclusion criteria:
- ≥18 years
- ECOG score 0 / 1
- Locally advanced, unresectable stage III* NSCLC
- EGFR Ex19del / L858R
- No progression during or following definitive CRT# treatment
- Interval between last dose of CRT and randomization: ≤6 weeks

Treatment Period

2:1

Arm 1: Aumolertinib 110mg QD; (N=94)

Stratification by
- Ex19del vs L858R
- Stage IIIA vs Stage IIIB/IIIC
- cCRT vs sCRT

Arm 2: Placebo 110mg QD; (N=53)

- Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria
- Tumor assessment: every 8 weeks to week 48, then every 12 weeks until progression
- Crossover§ is allowed for patients in placebo arm

- Primary endpoint: PFS assessed by BICR (sensitivity analysis: PFS assessed by investigator)
- Secondary endpoints: OS, ORR, DCR, DoR, CNS PFS, TTDM, safety

LAURA Phase 3 double-blind study design

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT# treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIA vs stage IIB/IIC
China vs non-China

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

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

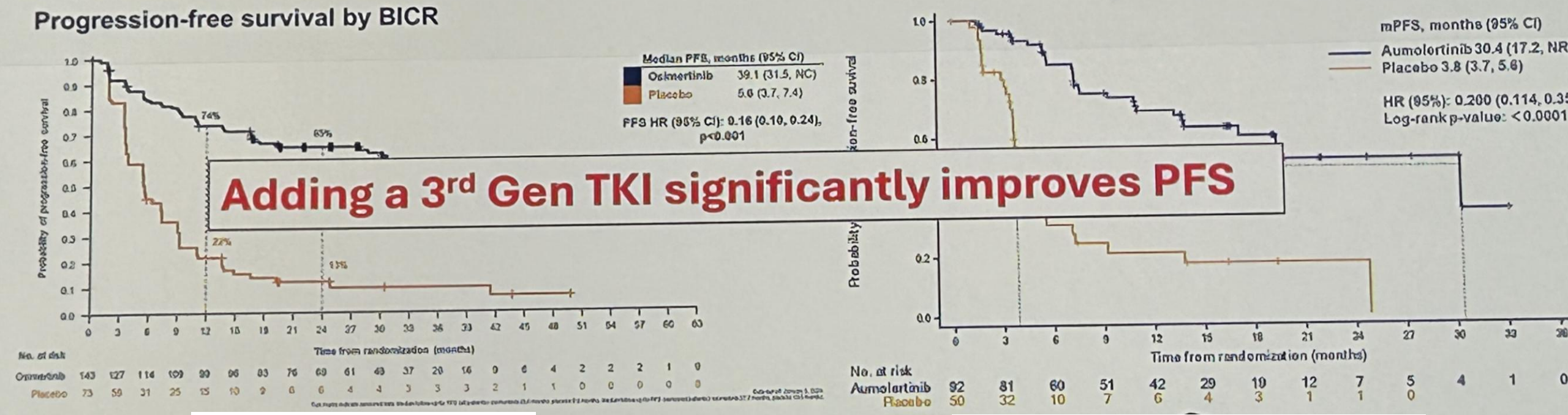
Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

- Both "Black-box" studies for chemoradiation
  - Similar design
  - Same endpoints
- Patients recruited after CRT completed
- Planned Interim analysis of POLESTAR

Lu S. N Engl J Med 2024

Fiona Hegi-Johnson | Discussant PL04.13

PFS

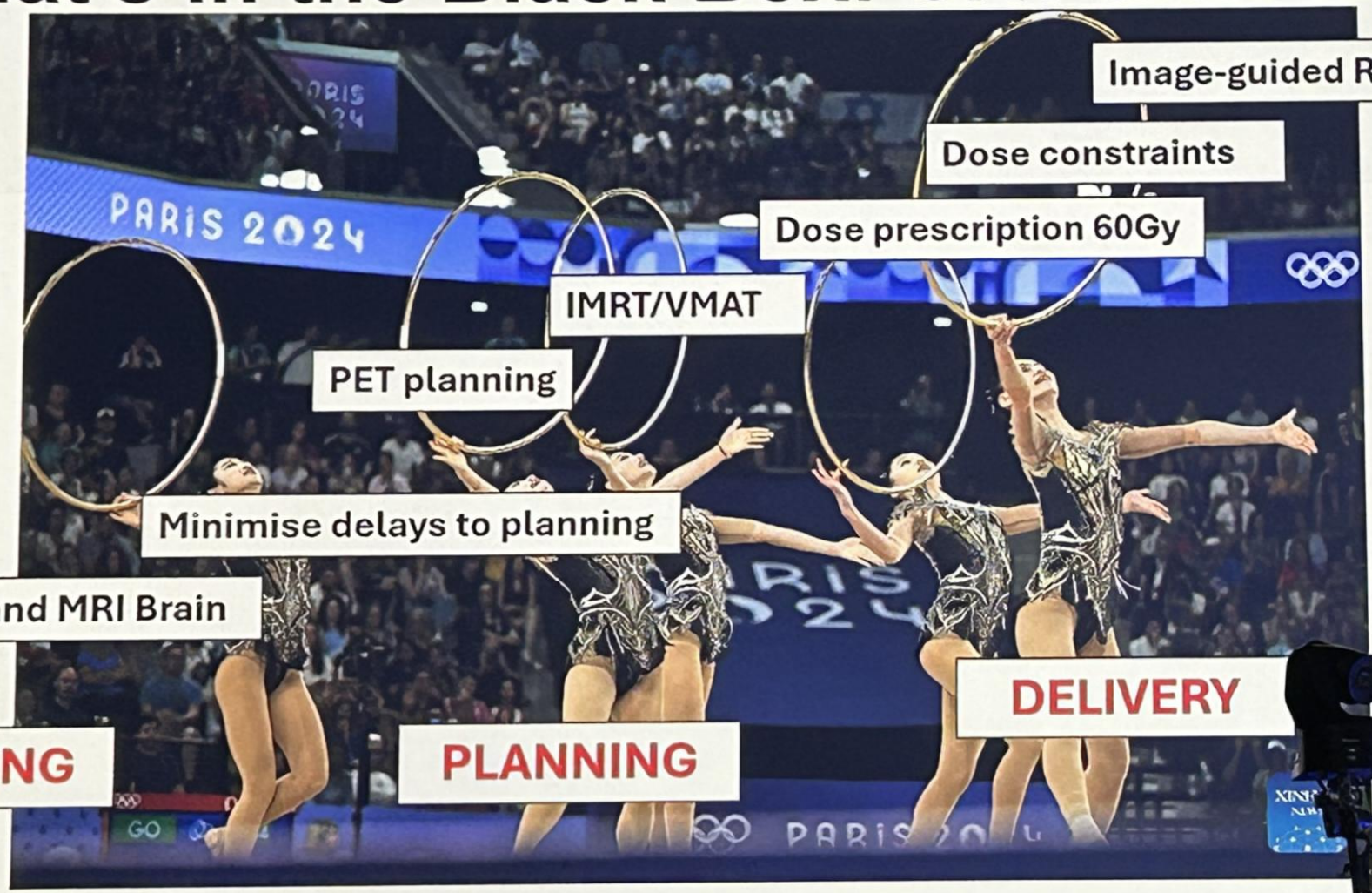


Adding a 3rd Gen TKI significantly improves PFS

LAURA TRIAL

POLESTAR TRIAL

What's in the Black Box: CRT after RTOG 0617



Each step

- Improves accuracy
- Increases survival
- Reduces toxicity.

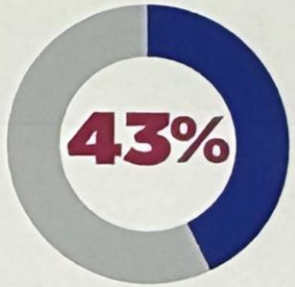
Gold-Medallist Chinese Rhythmic Gymnastics Team, Paris Olympics 2024

OA03.03: The 2024 IASLC Global Survey on Biomarker Testing

Respondents report that testing rates have improved but continued, substantial barriers exist.

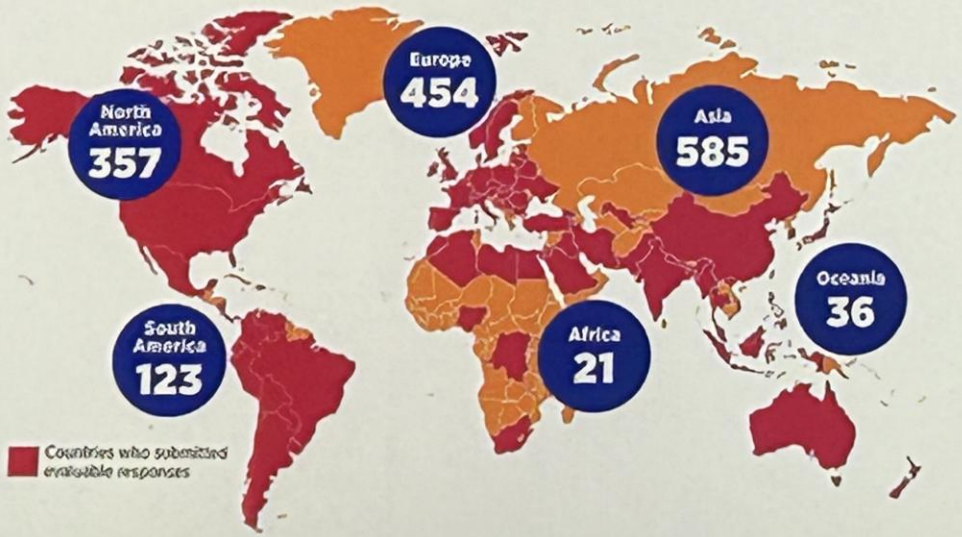
67% estimate more than half of individuals with lung cancer are biomarker tested in their country, up from

39% in the 2018 survey (p-value<0.0001)

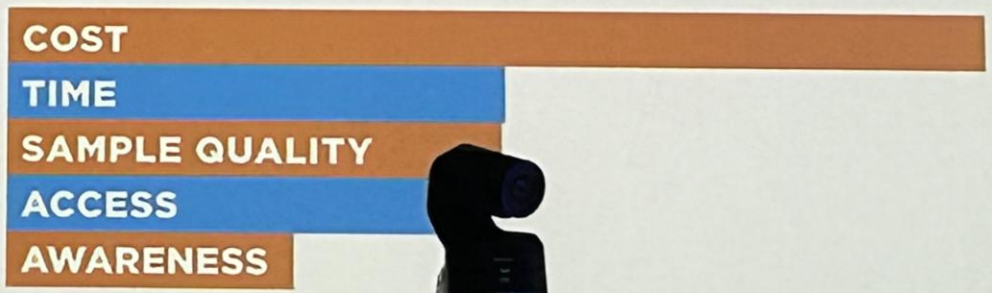


Sometimes or often treat patients prior to receiving biomarker results

1,677 responses across **90** countries and **14** disciplines.



The Highest Ranked Barriers



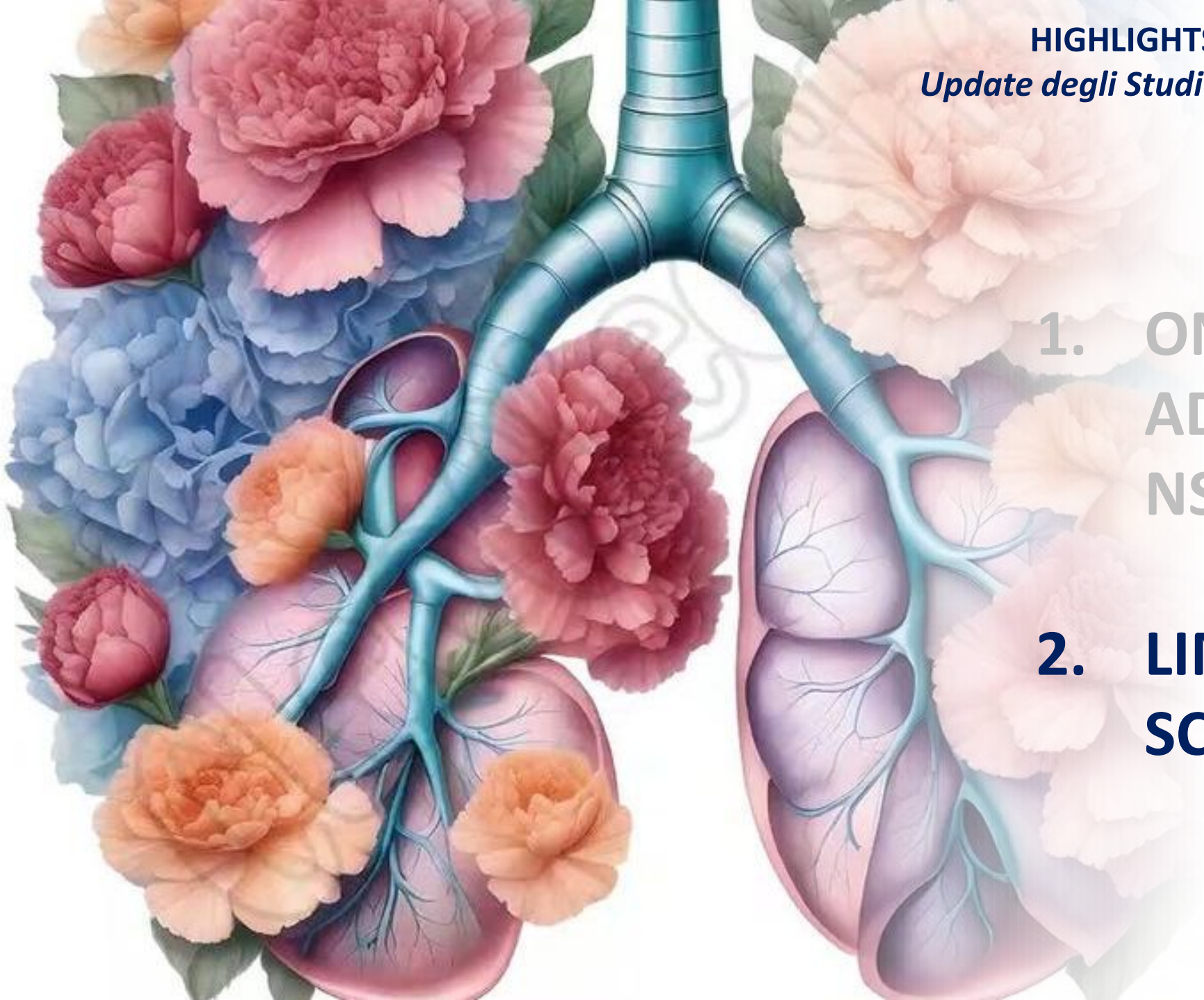
HIGHLIGHTS RADIOTERAPIA

Update degli Studi Practice Changing 2024

KEYPOINTS for ONCOGENE-ADDICTED LA-NSCLC

- Adjuvant osimertinib after RTCT in EGFRm+ is the new standard of care
- Look into the Black Box

UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA



HIGHLIGHTS RADIOTERAPIA

Update degli Studi Practice Changing 2024

1. ONCOGENE-ADDICTED LA-NSCLC

2. **LIMITED STAGE SCLC**

2024 ASCO ANNUAL MEETING

ADRIATIC: durvalumab as consolidation treatment for patients with limited-stage small-cell lung cancer (LS-SCLC)

David R. Spigel, Ying Cheng, Byoung Chul Cho, Konstantin Laktionov, Jian Fang, Yuanbin Chen, Yoshitaka Zenke, Ki Hyeong Lee, Qiming Wang, Alejandro Navarro, Reyes Bernabe, Eva Buchmeier, John Wen-Cheng Chang, Isamu Okamoto, Sema Sezgin Goksu, Andrzej Badzio, Bethany Gill, Hema Gowda, Haiyi Jiang, Suresh Senan

PRESENTED BY: Dr David R. Spigel, Sarah Cannon Research Institute, Nashville, TN, USA

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

cCRT components
- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:
- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:
- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:
- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization.

Baseline characteristics

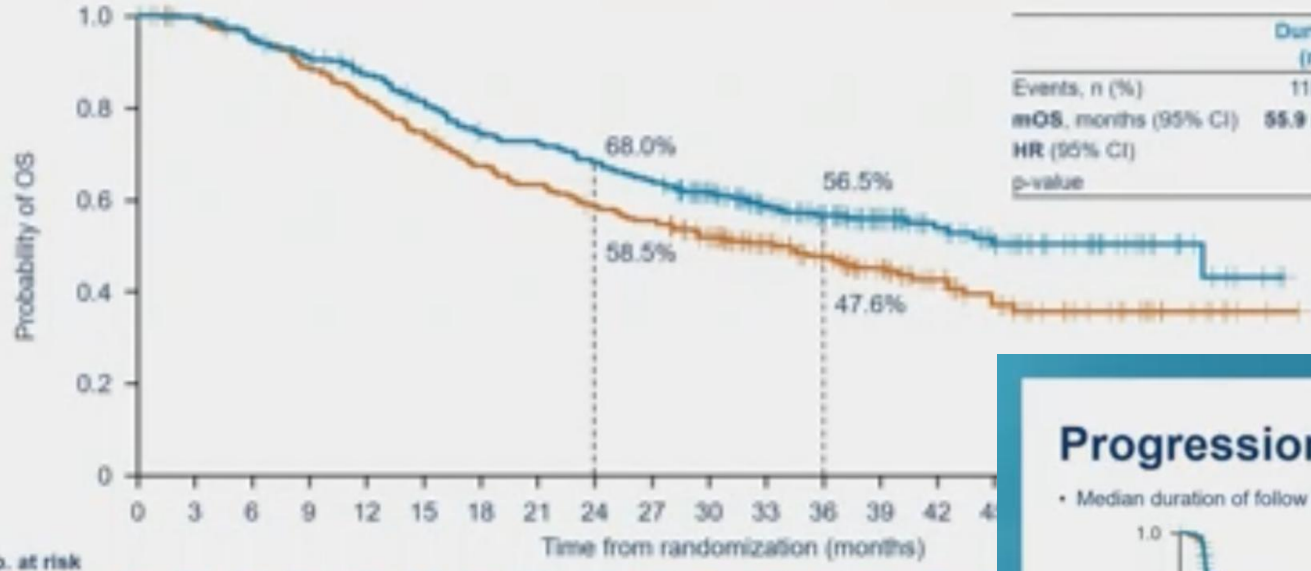
		Durvalumab (n=264)	Placebo (n=266)
Age, years	Median (range)	62.0 (28–84)	62.0 (28–79)
Sex, %	Male / Female	67.4 / 32.6	70.7 / 29.3
Race, %	White / Asian / Other	49.2 / 49.6 / 1.1	51.5 / 45.5 / 3.0
WHO performance status, %	0 / 1	50.0 / 50.0	47.4 / 52.6
Smoking status, %	Current / Former / Never	23.9 / 67.4 / 8.7	20.7 / 69.5 / 9.8
AJCC disease stage at diagnosis, %	I / II / III	3.0 / 9.5 / 87.5	4.1 / 8.6 / 87.2
Prior chemotherapy regimen, %*	Cisplatin-etoposide / Carboplatin-etoposide	65.5 / 34.5	66.9 / 33.1
Prior radiation schedule, %	Once daily / Twice daily	73.9 / 26.1	70.3 / 29.7
Best response to prior cCRT, %	CR / PR / SD	11.7 / 72.3 / 15.9	12.8 / 75.2 / 12.0
Prior PCI, %	Yes / No	53.8 / 46.2	53.8 / 46.2

*Based on the first cycle of chemotherapy.

AJCC, American Joint Committee on Cancer; CR, complete response; PR, partial response; SD, stable disease

Overall survival (dual primary endpoint)

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

No. at risk																
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	3
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	3

OS was analyzed using a stratified log-rank test adj
analysis was 0.01579 (2-sided) at the overall 4

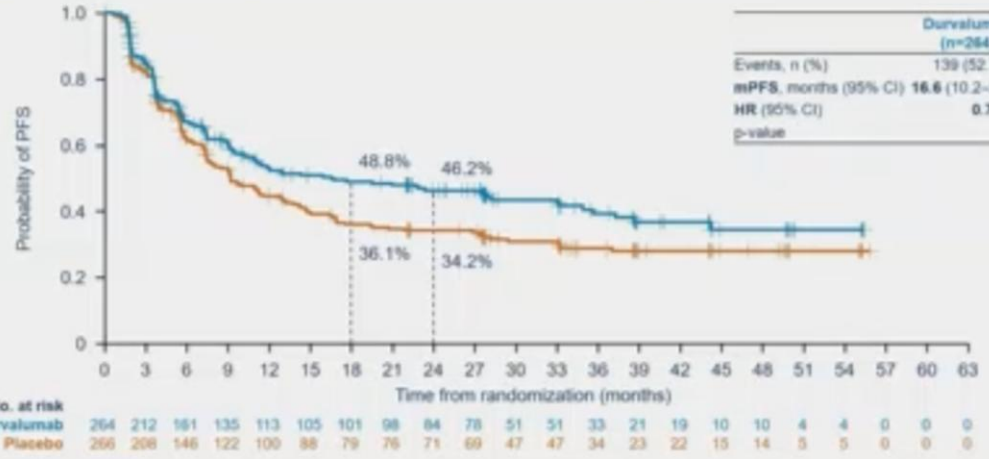
2024 ASCO ANNUAL MEETING #ASCO24

Presentation by: Dr David R. Spigel

DURVA-ARM:
mOS 55.9 m.
mPFS 16.6 m.

Progression-free survival* (dual primary endpoint)

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																						
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*By BICR per RECIST v1.1.

PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).

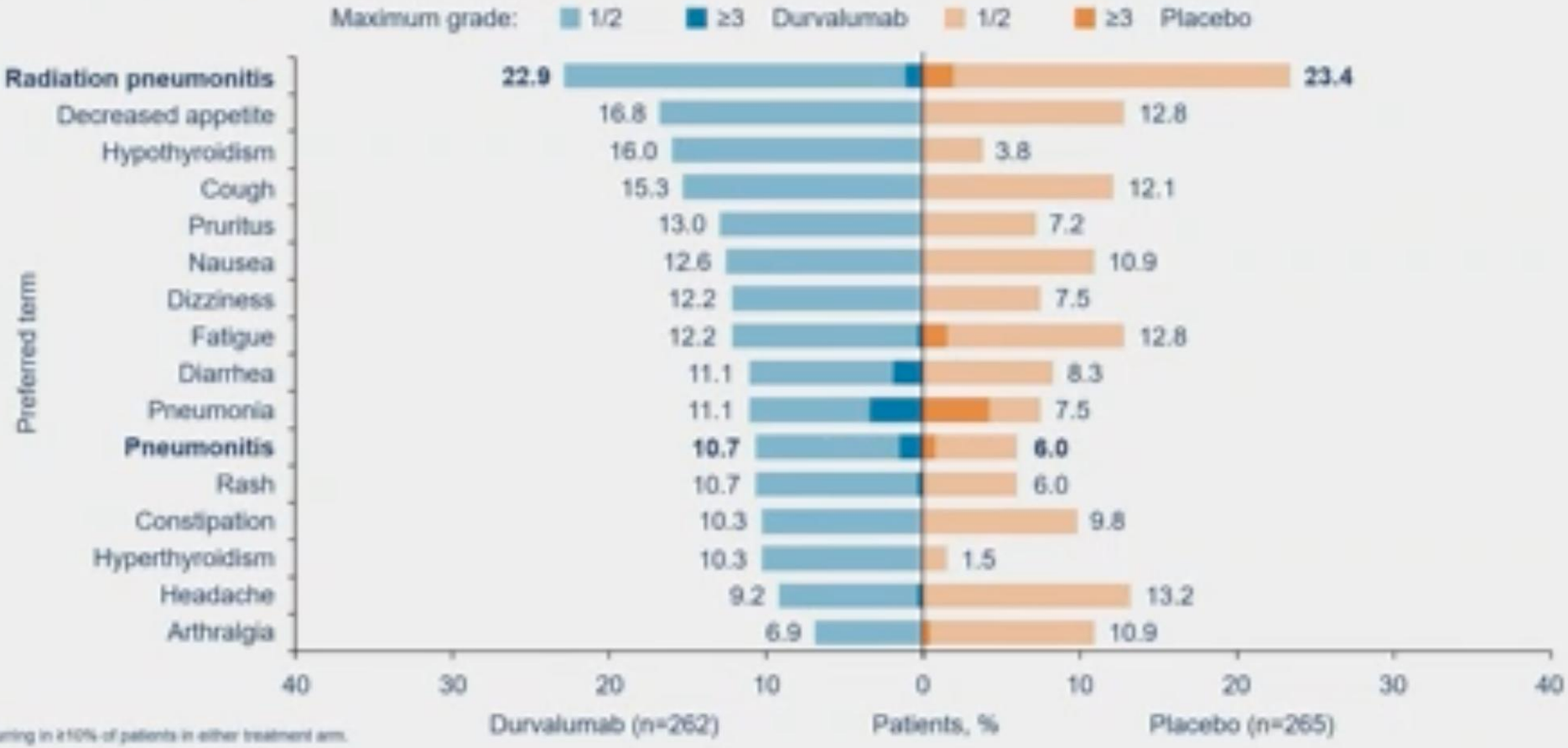
2024 ASCO ANNUAL MEETING #ASCO24

Presentation by: Dr David R. Spigel

mPFS, median PFS

ASCO KNOWLEDGE CONQUERS CANCER

Most frequent AEs*



*Occurring in ≥10% of patients in either treatment arm.

Presenter: Dr David R. Spigel

BARCELONA 2024 ESMO congress

Durvalumab as consolidation therapy in limited-stage SCLC (LS-SCLC): Outcomes by prior concurrent chemoradiotherapy (cCRT) regimen and prophylactic cranial irradiation (PCI) use in the ADRIATIC trial

Suresh Senan,[1] David Spigel,[2] Byoung Chul Cho,[3] Konstantin K. Laktionov,[4] Yoshitaka Zenke,[5] Ki Hyeong Lee,[6] Qiming Wang,[7] Alejandro Navarro,[8] Eva Lotte Buchmeier,[9] Sema Sezgin Goksu,[10] Andrzej Badzio,[11] Anhui Shi,[12] Davey B. Daniel,[13] Milada Zemanova,[14] Puneeth Iyengar,[15] Luis Paz-Ares,[16] Leah Szadkowski,[17] Priti Chugh,[18] W. Victoria Lai,[19] Ying Cheng[20]

[1]Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [4]Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Chungbuk National University Hospital, Cheongju, South Korea; [7]The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, 450008, China; [8]Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [9]Hospitals of the City of Cologne gGmbH, Cologne, Germany; [10]Akdeniz University Medical Faculty, Antalya, Türkiye; [11]Medical University of Gdansk, Gdansk, Poland; [12]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Department of Radiation Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [13]Tennessee Oncology PLLC, Nashville, TN, USA; [14]First Faculty of Medicine, Charles University, and General University Hospital, Prague, Czech Republic; [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [16]Hospital Universitario 12 de Octubre, CNIO-H120 Lung Cancer Unit, Ciberonc and Universidad Complutense, Madrid, Spain; [17]AstraZeneca, Mississauga, ON, Canada; [18]AstraZeneca, Waltham, MA, USA; [19]AstraZeneca, New York, NY, USA; [20]Jilin Cancer Hospital, Changchun, China.

Phase 3 ADRIATIC trial subgroup analyses

Post-hoc analyses of durvalumab versus placebo in prespecified subgroups defined by PCI use and prior cCRT-related variables

PCI/cCRT components (in line with standards of care)*

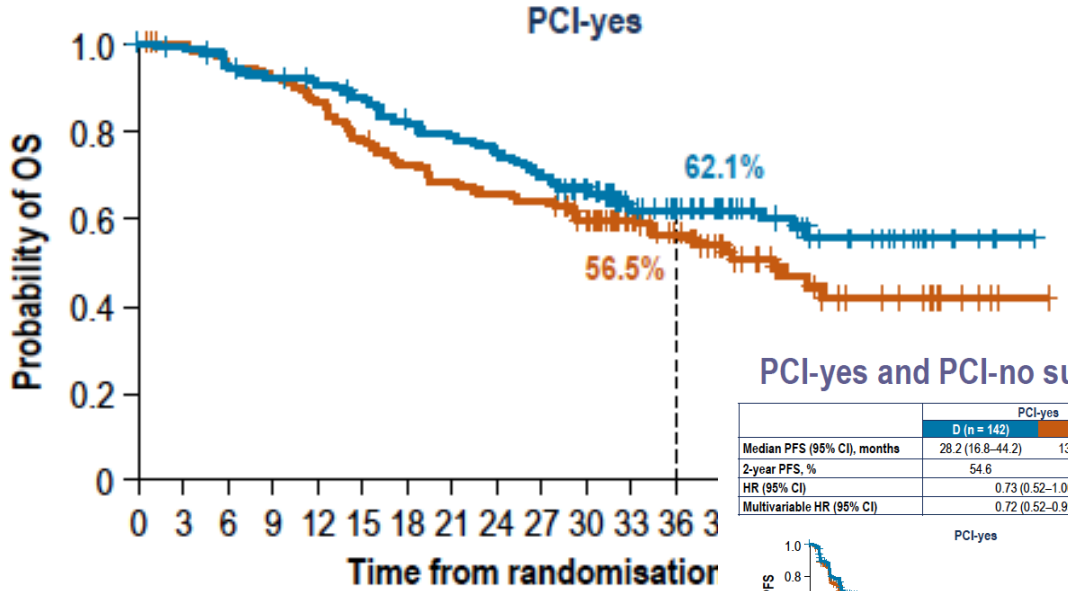
- PCI delivered before randomisation, as clinically indicated
- Four cycles of platinum (cisplatin or carboplatin) and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks‡

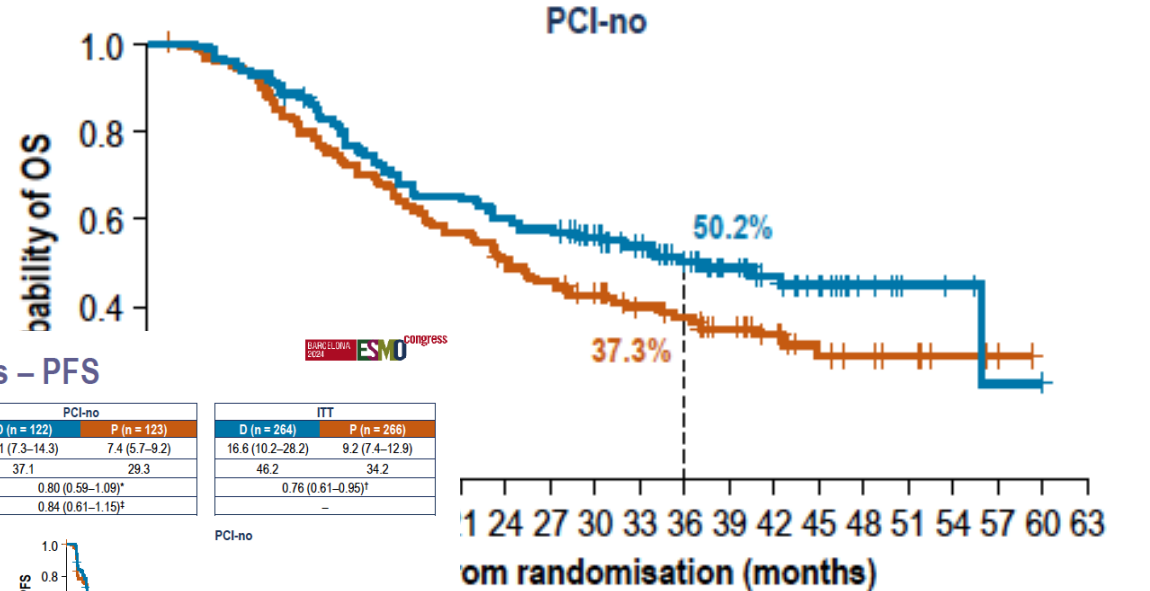
ITT population	Durvalumab (n = 264)	Placebo (n = 266)
Received PCI, %	54	54
Carboplatin / cisplatin CT,§ %	34 / 66	33 / 67
BID / QD thoracic RT, %	26 / 74	30 / 70

- Analyses of OS, PFS, and safety with durvalumab vs placebo in subgroups of patients who received:
  - PCI or no PCI
  - Carboplatin- or cisplatin-based CT
  - BID or QD RT
- Multivariable analyses: for each subgroup, HRs for durvalumab vs placebo were calculated from an unstratified multivariable Cox proportional hazards model with a treatment-by-subgroup (PCI, CT, or RT) interaction term that was adjusted for PCI, CT, RT, time from cCRT to randomisation, response to cCRT, age, sex, WHO PS, and disease stage

PCI-yes and PCI-no subgroups – OS

	PCI-yes		PCI-no		ITT	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (43.9–NE)	42.5 (33.4–NE)	37.3 (24.3–NE)	24.1 (18.8–31.1)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	62.1	56.5	50.2	37.3	56.5	47.6
HR (95% CI)	0.75 (0.52–1.07)*		0.71 (0.51–0.99)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.72 (0.50–1.03)‡		0.73 (0.52–1.02)‡		–	

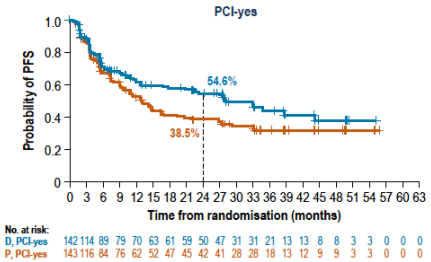


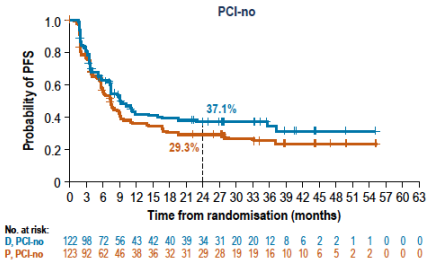


CI, confidence interval; NE, not estimable; NR, not reached; yr, year.

PCI-yes and PCI-no subgroups – PFS

	PCI-yes		PCI-no		ITT	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)
Median PFS (95% CI), months	28.2 (16.8–44.2)	13.0 (9.2–17.0)	9.1 (7.3–14.3)	7.4 (5.7–9.2)	16.6 (10.2–28.2)	9.2 (7.4–12.9)
2-year PFS, %	54.6	38.5	37.1	29.3	46.2	34.2
HR (95% CI)	0.73 (0.52–1.00)*		0.80 (0.59–1.09)*		0.76 (0.61–0.95)†	
Multivariable HR (95% CI)	0.72 (0.52–0.99)‡		0.84 (0.61–1.15)‡		–	





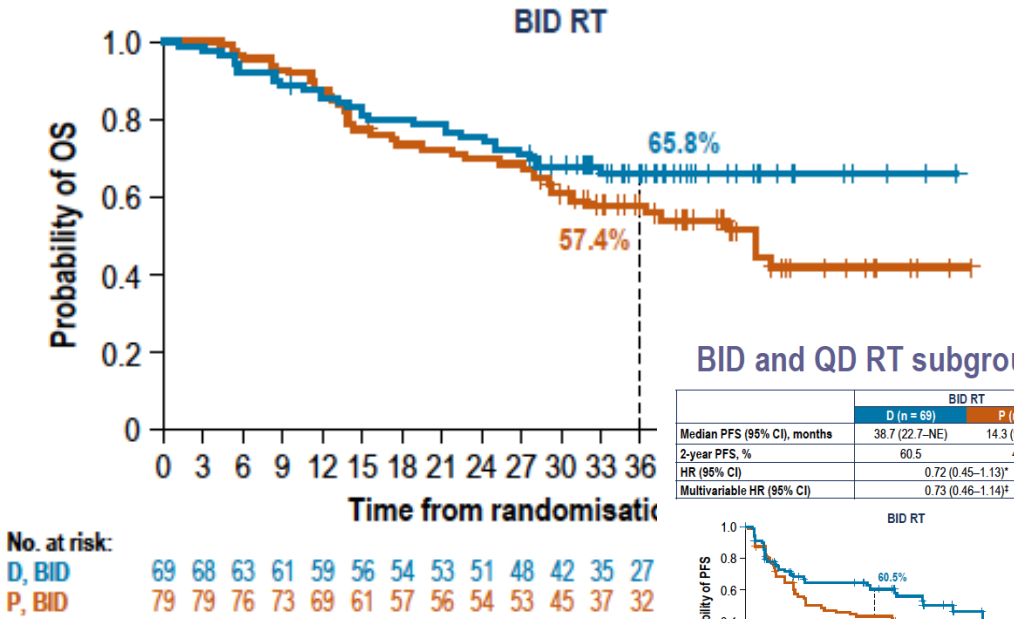
TNM, Tumour-Node-Metastasis.

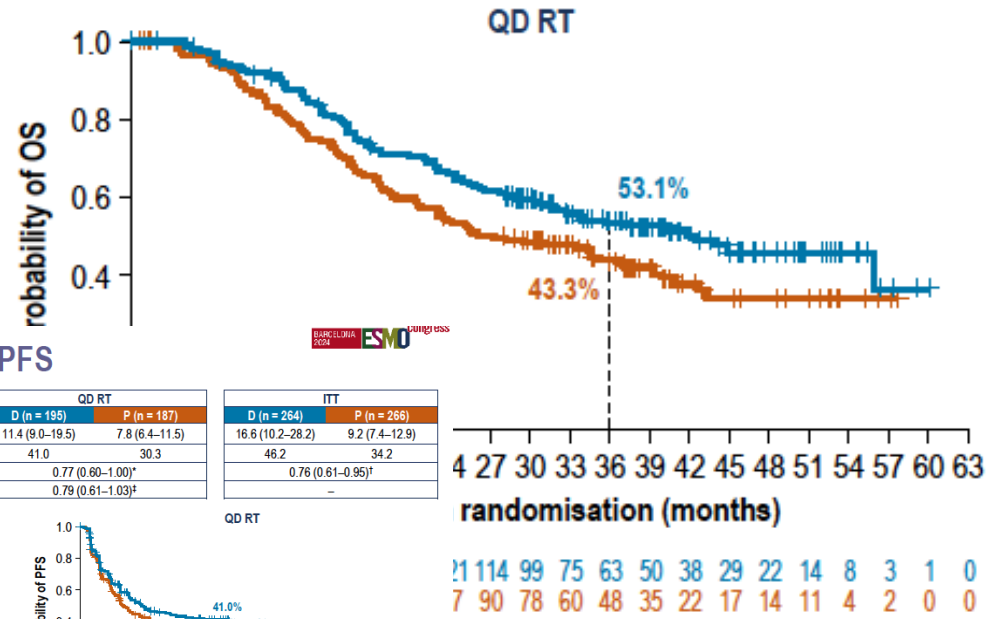
*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.
†ITT HR and CIs calculated using a Cox proportional hazards model stratified by TNM stage and receipt of PCI.
‡Multivariable analysis interaction p-value 0.50.

ls calculated using an unstratified Cox proportional hazards model.
using a Cox proportional hazards model stratified by receipt of PCI.
‡Multivariable analysis interaction p-value 0.96.

BID and QD RT subgroups – OS

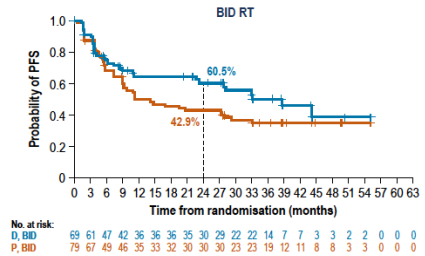
	BID RT		QD RT		ITT	
	D (n = 69)	P (n = 79)	D (n = 195)	P (n = 187)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (NE–NE)	44.8 (29.4–NE)	41.9 (32.0–NE)	26.1 (21.7–36.8)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	65.8	57.4	53.1	43.3	56.5	47.6
HR (95% CI)	0.68 (0.40–1.14)*		0.72 (0.55–0.96)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.71 (0.42–1.18)‡		0.73 (0.55–0.96)‡		–	

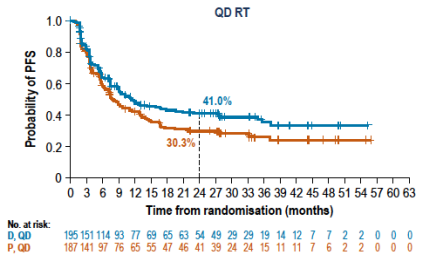




BID and QD RT subgroups – PFS

	BID RT		QD RT		ITT	
	D (n = 69)	P (n = 79)	D (n = 195)	P (n = 187)	D (n = 264)	P (n = 266)
Median PFS (95% CI), months	38.7 (22.7–NE)	14.3 (9.1–28.1)	11.4 (9.0–19.5)	7.8 (6.4–11.5)	16.6 (10.2–28.2)	9.2 (7.4–12.9)
2-year PFS, %	60.5	42.9	41.0	30.3	46.2	34.2
HR (95% CI)	0.72 (0.45–1.13)*		0.77 (0.60–1.00)*		0.76 (0.61–0.95)†	
Multivariable HR (95% CI)	0.73 (0.46–1.14)‡		0.79 (0.61–1.03)‡		–	





lculated using an unstratified Cox proportional hazards model.
a Cox proportional hazards model stratified by receipt of PCI.
‡Multivariable analysis interaction p-value 0.95.

*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.
†ITT HR and CIs calculated using a Cox proportional hazards model stratified by TNM stage and receipt of PCI.
‡Multivariable analysis interaction p-value 0.75.

ASTRO 2024
Targeting Provider Wellness
FOR EXCEPTIONAL PATIENT CARE

NRG ONCOLOGY
Advancing Research. Improving Lives.℠

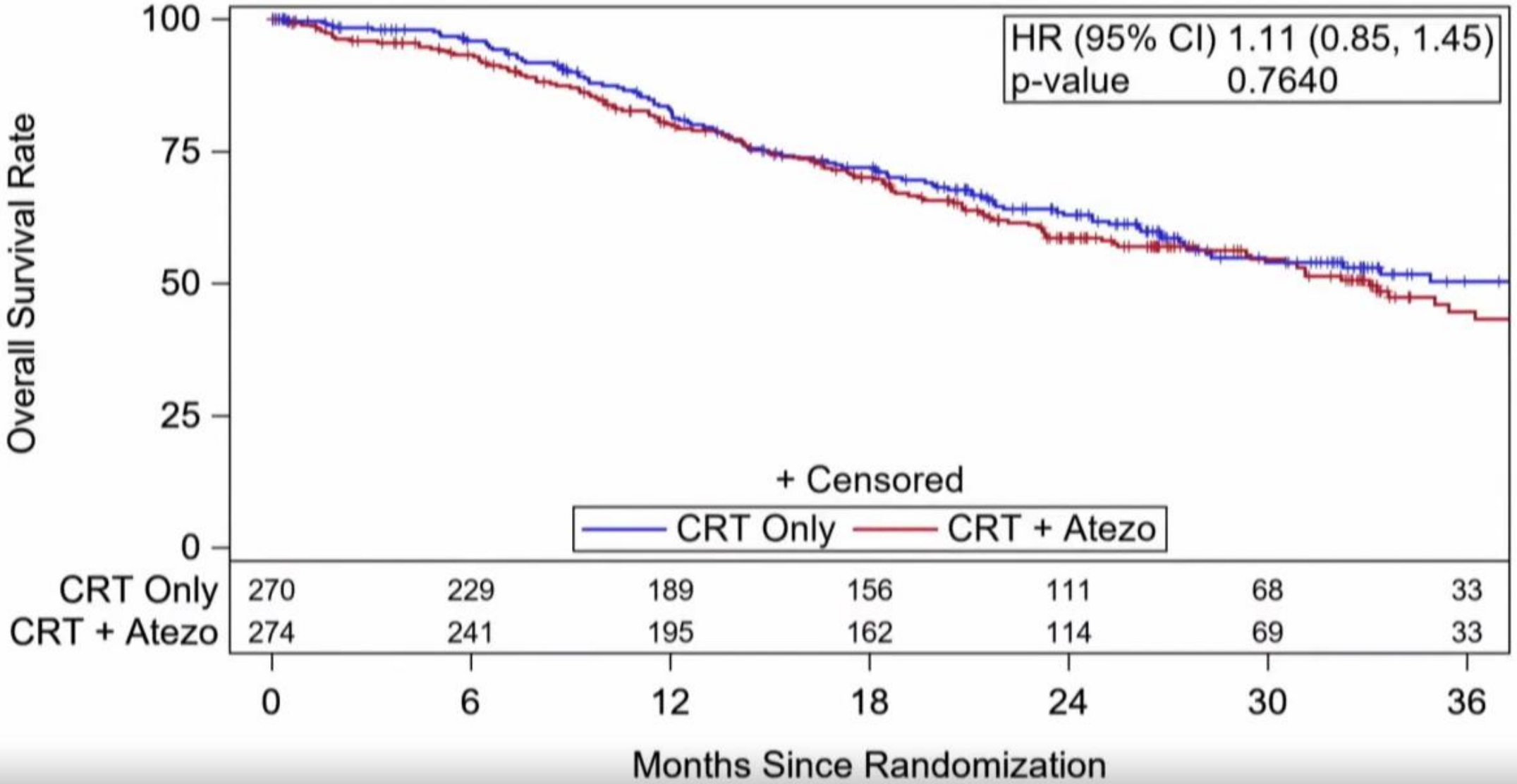
ASTRO 2024
Targeting Provider Wellness
FOR EXCEPTIONAL PATIENT CARE

Concurrent Chemoradiation +/- Atezolizumab (atezo) in limited-stage small cell lung cancer (LS-SCLC): Results of NRG Oncology/Alliance LU005

Kristin A. Higgins, Chen Hu, Helen J. Ross, Salma K. Jabbour, David E. Kozono, Taofeek K. Owonikoko, Kyoichi Kaira, Amit K. Gupta, Pranshu Mohindra, Elie G. Dib, Jeremy Brownstein, Stephen Chun, Charles S. Kuzma, Rupesh R. Kotecha, Adedayo A. Onitilo, Yuhchyau Chen, Tom Stinchcombe, Xiaofei F. Wang, Rebecca Paulus, Jeffrey D. Bradley

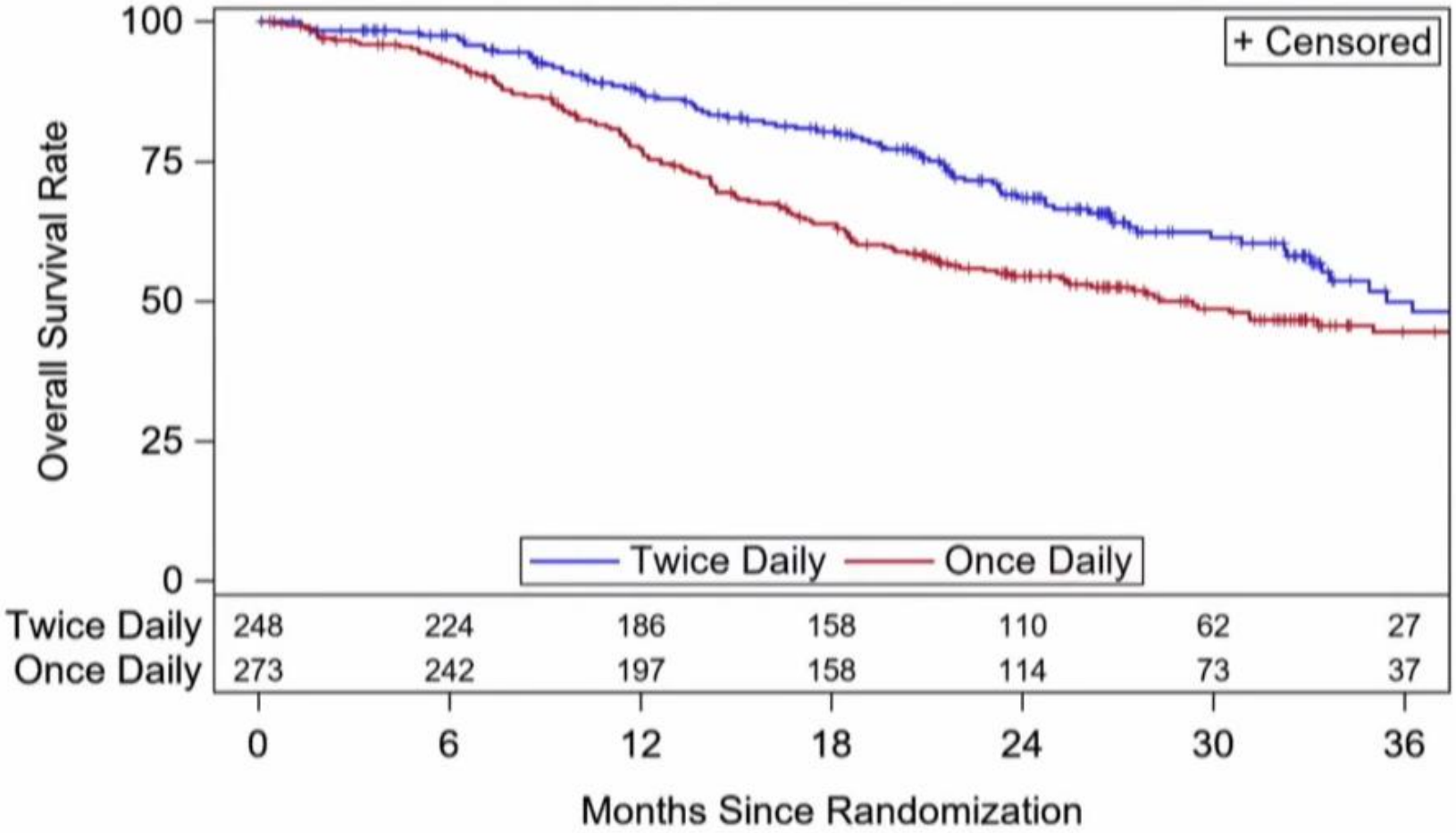
ASTRO 2024

Overall Survival

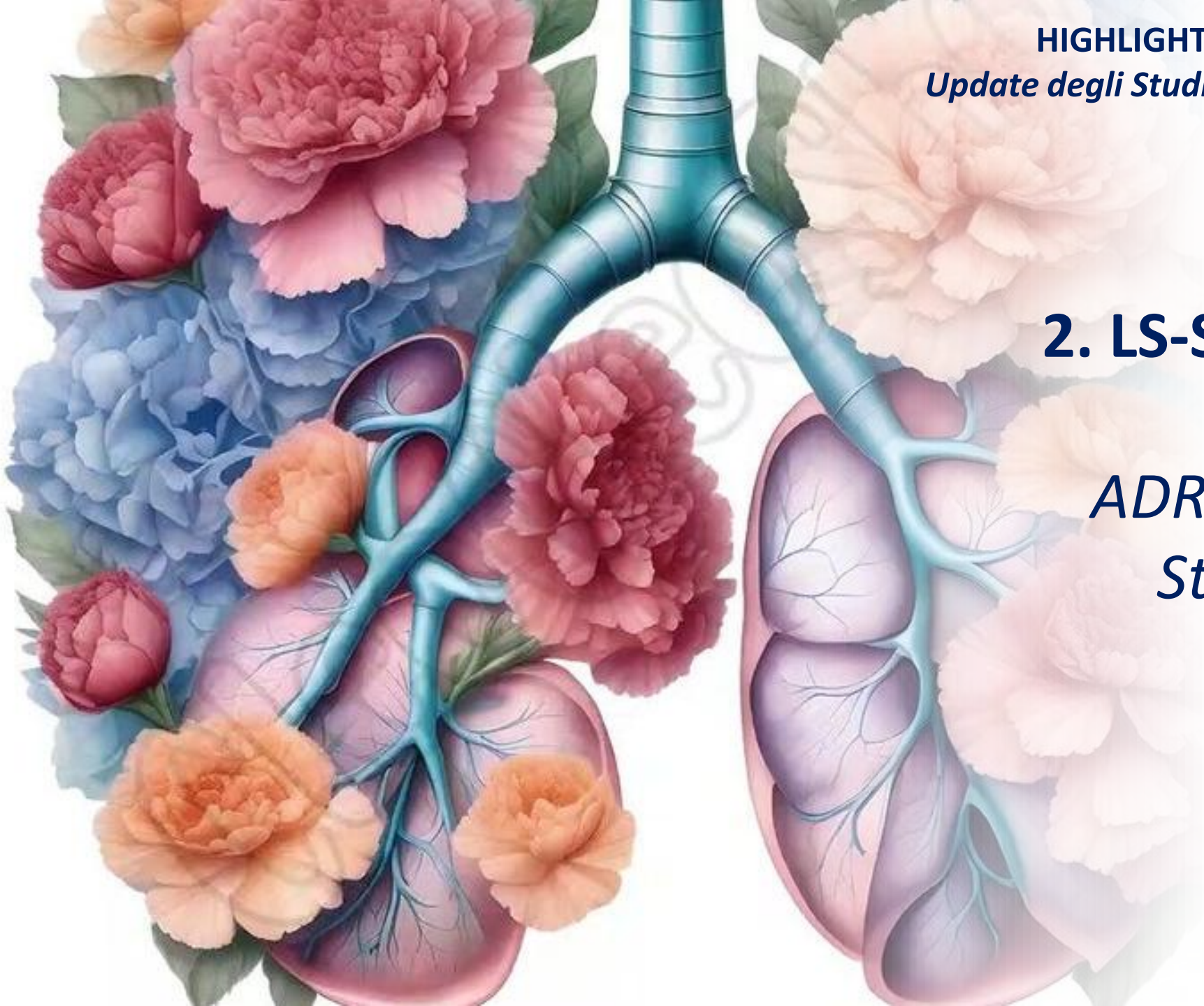


Pause

Overall Survival: Unadjusted RT Schedule Comparison



Note: Preliminary findings. Patients may have received twice daily RT over once daily for a number of reasons, including better performance status. Excludes patients who received no RT.



HIGHLIGHTS RADIOTERAPIA

Update degli Studi Practice Changing 2024

2. LS-SCLC

ADRIATIC trial in the State of the Art

UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA

SURVIVAL DATA OF LD-SCLC IN RANDOMIZED TRIALS

	TURRISI 1999 ***Once Daily 45Gy/*** ***Twice Daily 45Gy***	*CONVERT 2017* ***Once Daily 66Gy/*** ***Twice Daily 45Gy***	*CALGB 30610 (Alliance)/RTOG 0538* ***Once Daily 66Gy/*** ***Twice Daily 45Gy***
Median OS	19/23m	25/30m	30.1/28.5m
2-year OS	41/47%	51/56%	-
5-year OS	***16%***	***31/34%***	32/29%

Clinical Practice Guideline

Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline

Charles B. Simone II, MD,[a] Jeffrey A. Bogart, MD,[b] Alvin R. Cabrera, MD,[c] Megan E. Daly, MD,[d] Nicholas J. DeNunzio, MD, PhD,[e] Frank Detterbeck, MD,[f] Corinne Faivre-Finn, MD, PhD,[g] Nancy Gatschet, BA,[h] Elizabeth Gore, MD,[i] Salma K. Jabbour, MD,[j] Tim J. Kruser, MD,[k] Bryan J. Schneider, MD,[l] Ben Slotman, MD, PhD,[m] Andrew Turrisi, MD,[n] Abraham J. Wu, MD,[o] Jing Zeng, MD,[p] and Kenneth E. Rosenzweig, MD[q,*]

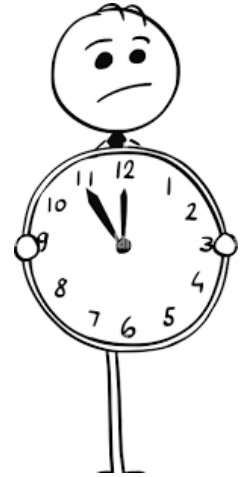
	Strength of Recommendation	0verall QoE Grade
For patients with LS-SCLC, twice-daily RT in 150 cGy fractions to 4500 cGy is recommended.	Strong	High 5,12,30-34
For patients with LS-SCLC, daily RT in 200 cGy fractions to 6000-7000 cGy is conditionally recommended as an acceptable alternative to twice-daily RT.	Conditional	Moderate 12,35-37

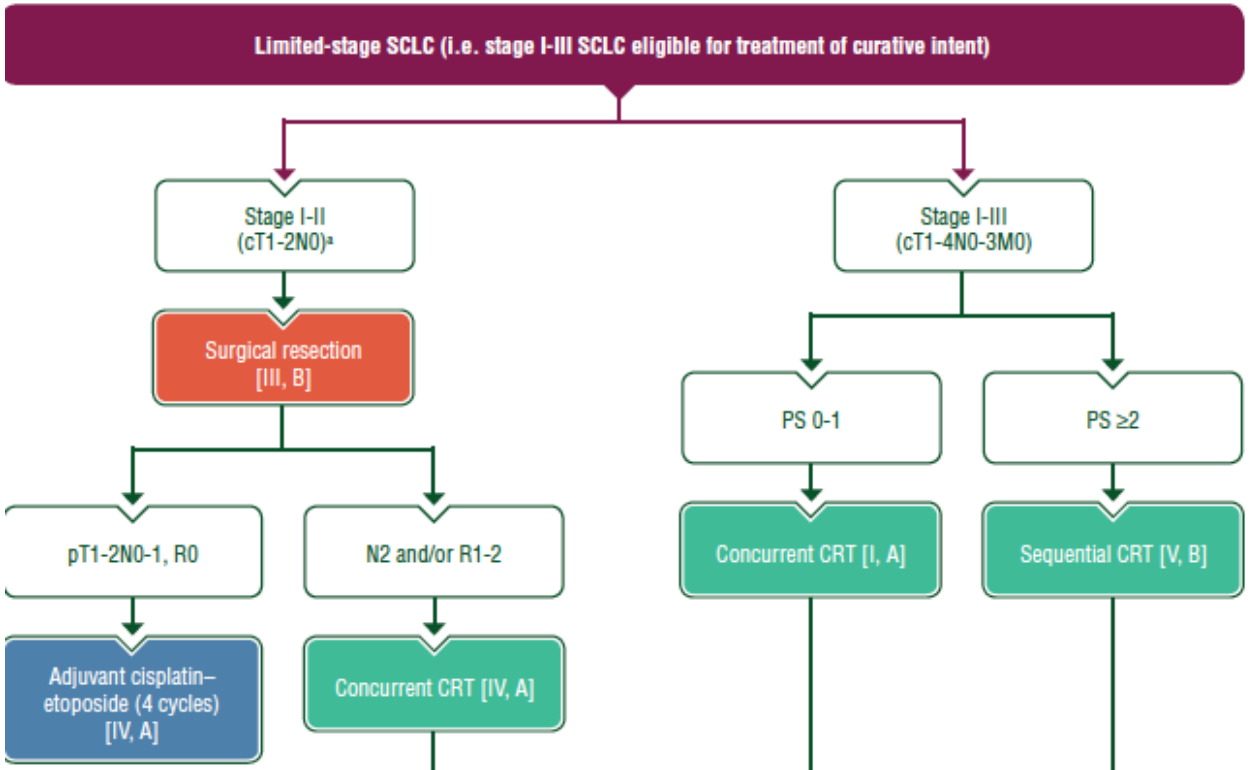
Practical Radiation Oncology® (2020) **10**, 158-173

SPECIAL ARTICLE

Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

A.-M. C. Dingemans[1,2], M. Früh[3,4], A. Ardizzoni[5], B. Besse[6,7], C. Faivre-Finn[8], L. E. Hendriks[2], S. Lantuejoul[9], S. Peters[10], N. Reguart[11], C. M. Rudin[12], D. De Ruysscher[13], P. E. Van Schil[14], J. Vansteenkiste[15] & M. Reck[16], on behalf of the ESMO Guidelines Committee*





RT SCHEDULE

RT and was not powered to show equivalence, the implication is that b.i.d. RT (45 Gy/30 fractions over 3 weeks) should remain as the standard of care in this group of patients [I, A]. When b.i.d. RT is not possible due to logistical reasons, o.d. RT (66 Gy/33 fractions over 6 weeks) is an alternative option. It should, however, be noted that the role of concurrent CRT is not as well defined in patients >70 years of age or in those who are frail.

Dingemans, Ann Oncol 2021, 32(7): 839-

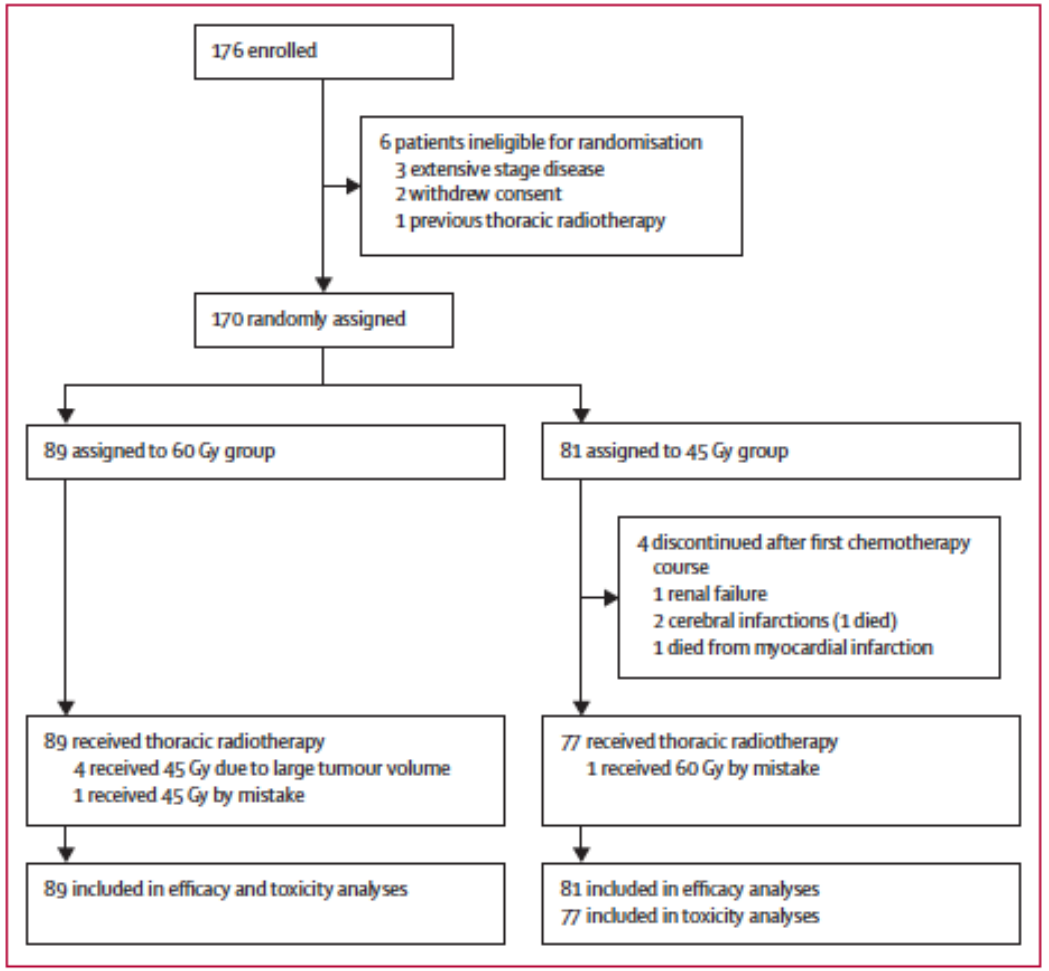
High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

Bjørn Henning Grønberg, Kristin Toftaker Killingberg, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaye Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, Tarje Onsøien Halvorsen

Norway, Denmark, and Sweden.

TOTAL DOSE OF 45Gy in 30 FX
(twice daily in 150cGy fractions)

TOTAL DOSE OF 60Gy in 40 FX
(twice daily in 150cGy fractions)



Lancet Oncol 2021; 22: 321–31

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

Bjørn Henning Grønberg, Kristin Toftaker Killingberg, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaye Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, Tarje Onsøien Halvorsen

Lancet Oncol 2021; 22: 321–31

1.5x2/die until a total dose of 45Gy (15 fx)

1.5x2/die until a total dose of 60Gy (20 fx)

	60 Gy group (n=89)	45 Gy group (n=81)
Age, years		
Median	65 (58·0–70·5)	65 (60·0–72·0)
≥70	25 (28%)	28 (35%)
Sex		
Female	50 (56%)	47 (58%)
Male	39 (44%)	34 (42%)
ECOG performance status		
0	44 (51%)	34 (42%)
1	36 (41%)	38 (47%)
2	7 (8%)	8 (10%)
Data missing	2 (2%)	1 (1%)
Disease stage		
IA	0	4 (5%)
IIA	9 (10%)	6 (7%)
IIB	5 (6%)	4 (5%)
IIIA	38 (43%)	31 (36%)
IIIB	37 (42%)	36 (44%)
Pleural fluid present	8 (9%)	5 (6%)

	60 Gy group (n=89)	45 Gy group (n=81)
Number of chemotherapy courses		
1	1 (1%)	4 (5%)
2	3 (3%)	4 (5%)
3	3 (3%)	2 (3%)
4	82 (88%)	71 (88%)
Mean	3·87 (0·50)	3·73 (0·78)
Any dose reduction	58 (65%)	66 (82%)
Received carboplatin for one or more courses	31 (35%)	34 (42%)
Completed thoracic radiotherapy as planned	86 (97%)	74 (91%)
Received prophylactic cranial irradiation	72 (85%)	68 (85%)
Received second line chemotherapy	41 (46%)	39 (48%)
Response to chemoradiotherapy		
Overall response	69 (77·5%; 67·4–85·7)	62 (76·5%; 65·8–85·2)
Complete response	16 (18·0%; 10·6–25·5)	17 (21·0%; 12·7–31·5)
Partial response	53 (59·6%; 48·6–69·8)	45 (55·6%; 44·1–66·6)
Stable disease	4 (4·5%; 1·2–11·1)	6 (7·4%; 2·8–15·4)
Progressive disease	5 (5·6%; 1·8–12·6)	5 (6·2%; 2·0–13·8)
Unknown	11 (12·4%; 6·3–21·0)	8 (9·9%; 4·4–18·5)

Data n (%), mean (SD), or n (%; 95% CI).

Table 2: **Treatment completion and response to chemoradiotherapy**

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

Bjørn Henning Grønberg, Kristin Toftaker Killingberg, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaye Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, Tarje Onsøien Halvorsen

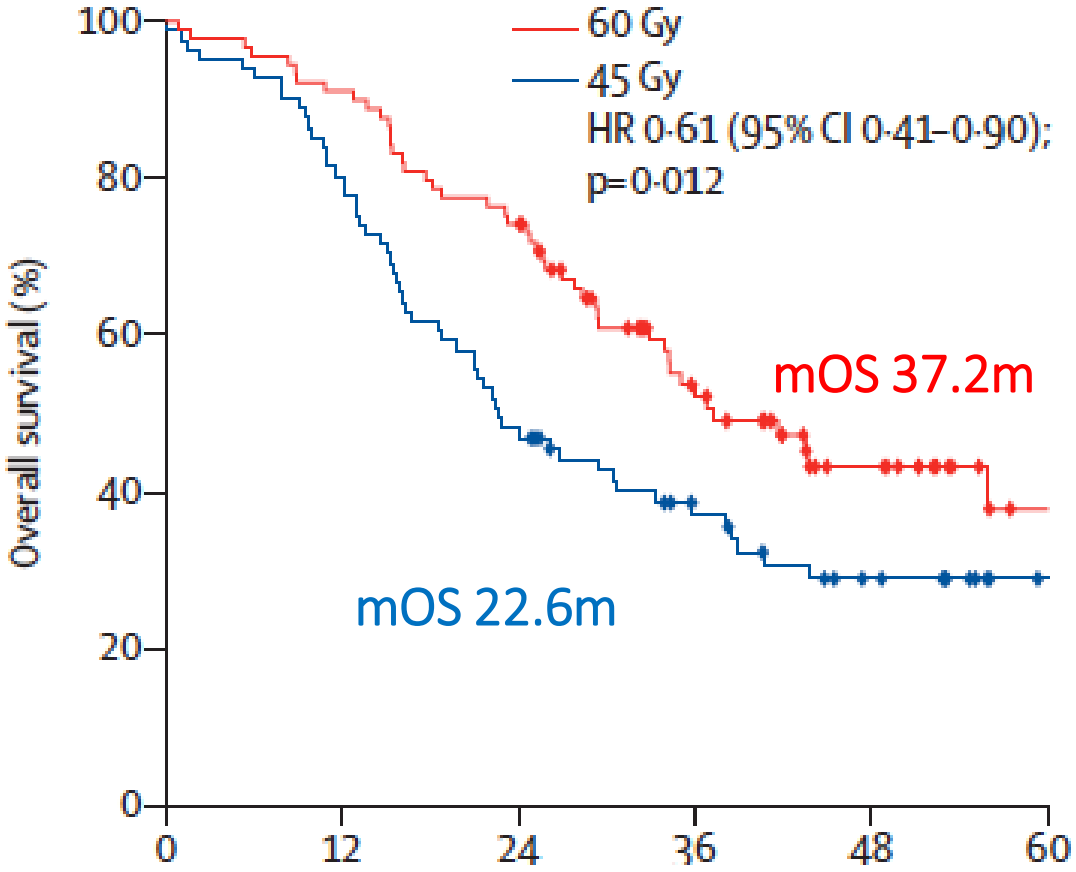
	60 Gy group (n=89)				45 Gy group (n=77)				p value
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	
Oesophagitis	33 (37%)	19 (21%)	0	0	34 (44%)	14 (18%)	0	0	0·83
Pneumonitis	8 (9%)	3 (3%)	0	1 (1%)	4 (5%)	0	0	0	0·39
Anaemia	70 (79%)	14 (16%)	0	0	59 (77%)	15 (20%)	0	0	0·85
Thrombocytopenia	47 (54%)	13 (15%)	8 (9%)	0	44 (57%)	10 (13%)	9 (12%)	0	0·96
Neutropenia	13 (15%)	14 (16%)	58 (66%)	0	8 (10%)	17 (22%)	45 (58%)	0	0·25

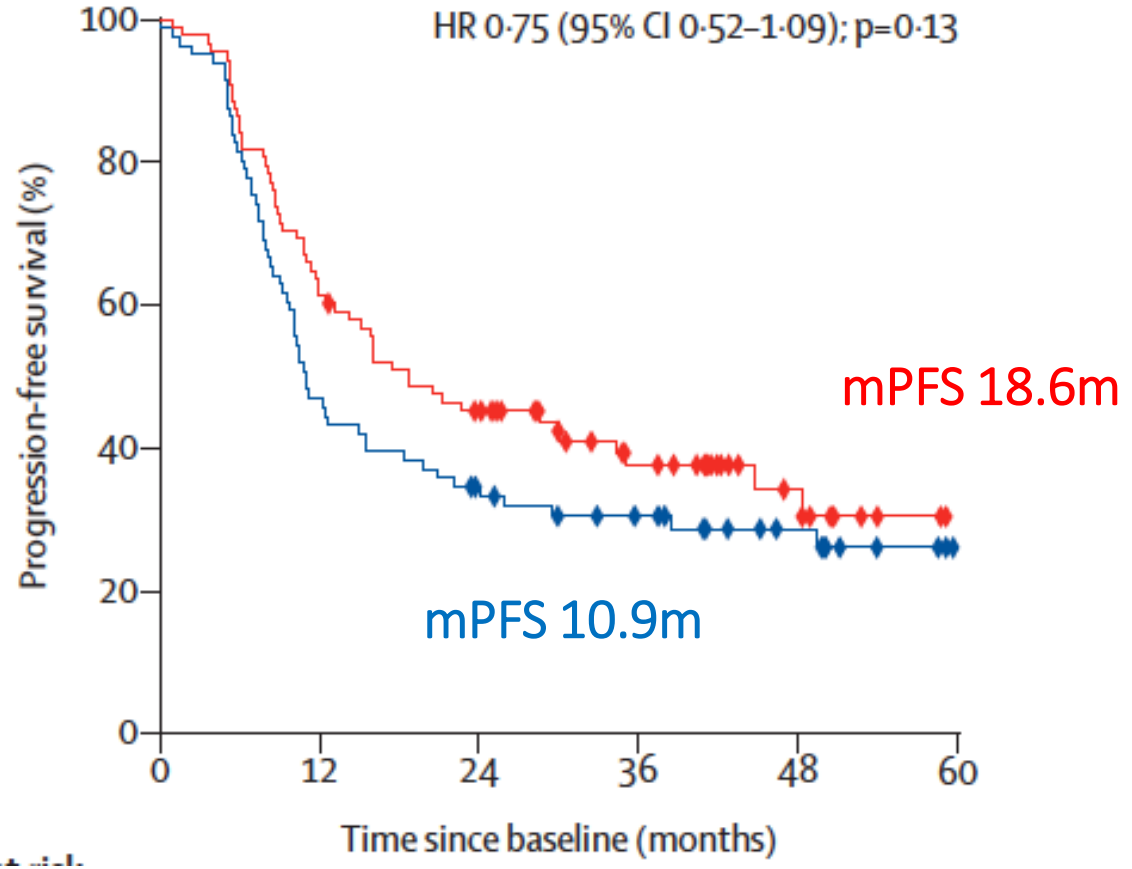
Low increase of G3 toxicity (3%)
No differences in G4-5

Lancet Oncol 2021; 22: 321–31

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

Bjørn Henning Grønberg, Kristin Toftaker Killingberg, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaye Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, Tarje Onsøien Halvorsen





Median follow-up 49 months

Lancet Oncol 2021; 22: 321–31

SURVIVAL DATA OF LD-SCLC IN RANDOMIZED TRIALS

	TURRISI 1999 *Once Daily 45Gy/ Twice Daily 45Gy*	*CONVERT 2017* *Once Daily 66Gy/ Twice Daily 45Gy*	*CALGB 30610 Alliance/RTOG 0538* *Once Daily 66Gy/ Twice Daily 45Gy*	*NORWEGIAN 2021* *Twice Daily 60Gy/ Twice Daily 45Gy*
Median OS	19/23m	25/30m	30.1/28.5m	37.2 / 22.6m
2-year OS	41/47%	51/56%	-	74% / 48%
5-year OS	16/26%	31/34%	32/29%	-
Median PFS	-	14.3/15.4m	14.2/13.5m	18.6 / 10.9m

Summary of Guidelines.

	Guideline (version), online year
1	**North America** CCO (2018), 2018[1]
2	ASTRO (2020), 2020[2]
3	ARS (2020), 2020[3,4]
4	NCCN (2.2021), 2021[5] **Europe** ESMO (2021), 2021[6]
5	NICE (2019), 2019[7]
6	FMS (2019), 2019[8-10]
7	SEOM (2019), 2020[11]
8	**China** CSCO (2020), 2020[12]
9	CSTRO (2020), 2020[13] CMA (2019), 2019[14]

Journal of the National Cancer Center 2 (2022) 113–125

Contents lists available at ScienceDirect

Journal of the National Cancer Center

journal homepage: www.elsevier.com/locate/jncc

Review

Radiotherapy for small cell lung cancer in current clinical practice guidelines☆

Haiyan Zeng[1], Dirk K.M. De Ruysscher[1], Xiao Hu[2], Danyang Zheng[3,4], Li Yang[3], Umberto Ricardi[5], Feng-Ming Spring Kong[3,4], Lizza E.L. Hendriks[6,*]

Conclusion

The major radiotherapy principles are consistent across guidelines. This reveals that experts worldwide might be duplicating unnecessary work. We suggest better international collaboration to save energy and resources. More efforts should be devoted to solving the controversial or unknown problems.

SURVIVAL DATA OF LD-SCLC IN RANDOMIZED TRIALS

	TURRISI 1999 *Once D 45Gy/ Twice D 45Gy*	*CONVERT 2017* *Once D 66Gy/ Twice D 45Gy*	*CALGB 30610/ RTOG 0538* *Once D 66Gy/ Twice D 45Gy*	*NORWEGIAN 2021* *Twice D 60Gy/ Twice D 45Gy*	*YU ASTRO 2023* *Twice D 54Gy30fx/ Twice D 4530fxGy*
Median OS	19/23m	25/30m	30.1/28.5m	37.2/22.6m	62.4/43.1
2-year OS	41/47%	51/56%	-	72/48%	77.7/53.5%

Twice daily HIGHER DOSES IMPROVE RESULTS

ASCO 2024 NEWS CHANGES THE SCENARIO AGAIN……

PUBLISHED
5 April 2024

LS-SCLC

DURVALUMAB *significantly improved overall survival and progression-free survival for patients with limited-stage small cell lung cancer in ADRIATIC Phase III trial*

OPEN QUESTION:

- **High Dose twice daily RT?**

Study Start (Actual)

2018-09-27

Primary Completion (Estimated)

2024-09-05

Study Completion (Estimated)

2024-09-05

PYRAMID OF CLINICAL EVIDENCE

NORVEGIAN TRIAL

ADRIATIC

But the relevance is not according to the study but to the clinical need

ACCORDING TO THE PYRAMID OF CLINICAL EVIDENCE ADRIATIC RESULTS ARE MORE RELEVANT THAN THOSE FROM NORVEGIAN TRIAL

OVERALL SURVIVAL-NORVEGEAN TRIAL, Lancet Oncology 2021

Certainty assessment							Summary of findings				
							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)	Certainty
Overal survival (follow-up: median 49 months)											
1	randomised trials	not serious [a,b,c]	not serious [d]	not serious	serious [e]	none	89 participants -	81 participants 72.0%	**HR 0.61** (0.41 to 0.90) [Overal survival]	- **18 fewer per 100** (from 31 fewer to 4 fewer)	⨁⨁⨁◯ Moderate

GRADEpro

TWICE DAILY HIGH DOSE RT: HIGH CLINICAL BENEFIT WITH MODERATE CERTAINTY

Explanations | References

- ☐ no detection for OS
- ☐ no performance for OS
- ☐ no attrition, 100% evaluable
- ☐ not applicable
- ☑ NNT 5 (from 3 to 25)

The NEW ENGLAND JOURNAL of MEDICINE

LETTER

TO THE EDITOR: Results of the phase 3 ADRIATIC trial (Oct. 10 issue)[1] marked a breakthrough in the treatment of limited-stage small-cell lung cancer, but some questions remain unanswered. According to the protocol, the radiotherapy dose was 60 to 66 Gy once daily or 45 Gy twice daily. Are these doses the best options for limited-stage small-cell lung cancer?

In a randomized phase 2 trial, Gronberg et al.[2] found that high-dose thoracic radiotherapy of 60 Gy twice daily improved survival as compared with the standard dose of 45 Gy twice daily (hazard ratio for death from any cause, 0.61; 95% confidence interval, 0.41 to 0.90). The authors also observed that the high-dose regimen led to the longest median overall survival duration (43.5 months)[3] that has been reported in trials of chemoradiotherapy for limited-stage small-cell lung cancer.[4-6] Although this trial is a phase 2 trial with a limited sample size, it has remarkable clinical relevance, with an absolute effect of 18 fewer deaths per 100 patients treated (number needed to treat to avoid one death, 5; range, 3 to 25).

Notwithstanding the impressive results of the ADRIATIC trial, will we be compelled to use a less effective radiation schedule such as that in the trial? The scientific world is called to answer this question, and efforts should be made to add evidence in this area.

RESPONSE

Ramella et al. suggest that a twice-daily thoracic radiotherapy dose of 60 Gy, as investigated in a randomized phase 2 trial in Scandinavia, could be a preferred radiation schedule.[2] The radiation doses and schedules used in our trial were guideline-recommended worldwide standards in 2018, when we initiated the trial. Some limitations of the findings from the Scandinavian trial, as well as promising results of other randomized trials of different radiotherapy schedules, have recently been highlighted.[3] A phase 3 trial investigating these different doses and schedules is warranted. Ongoing translational research in our trial may provide insights into the role of radiotherapy when combined with immunotherapy in patients with limited-stage small-cell lung cancer

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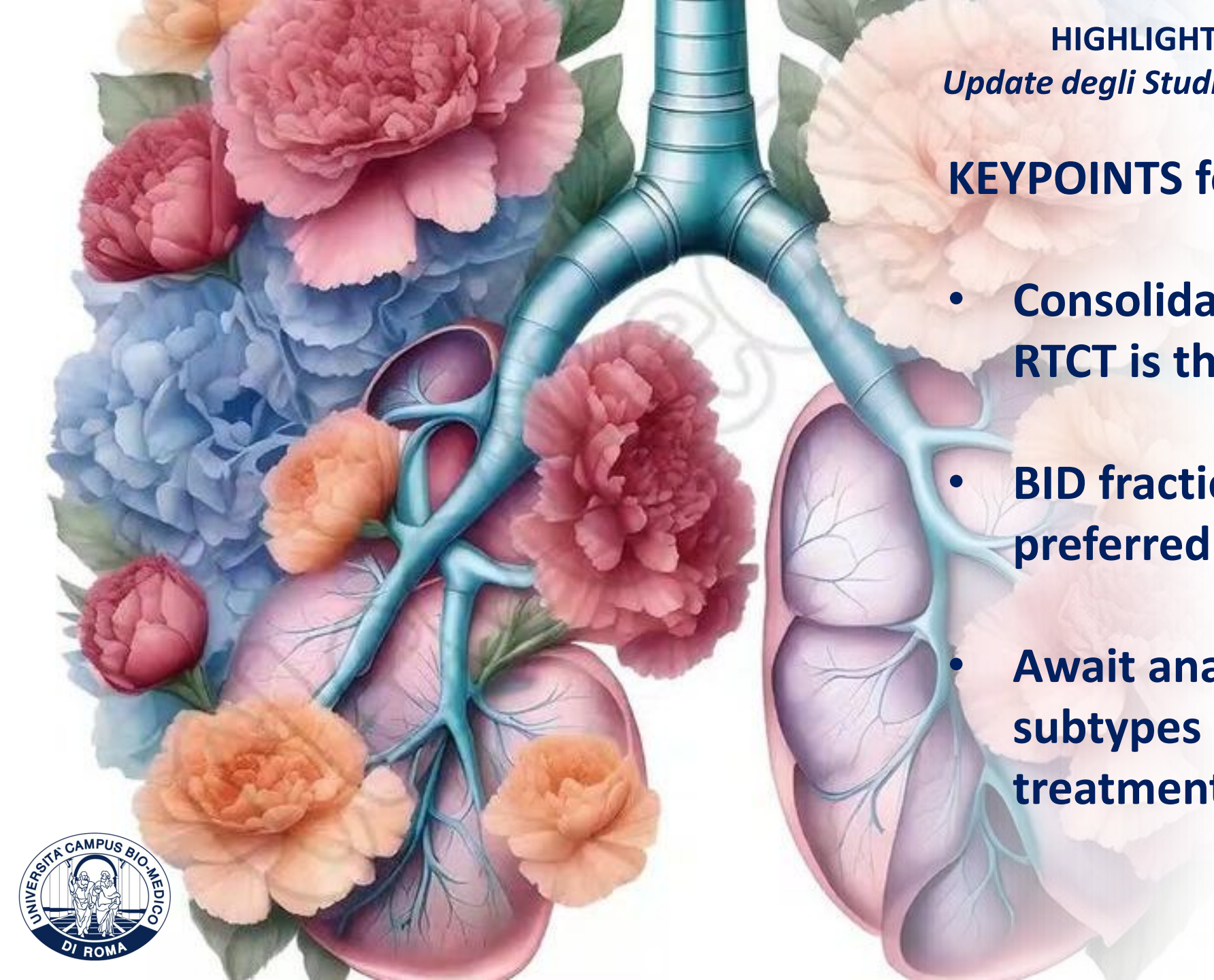
Ramella S, Ippolito E, D'Angelillo RM- 2025



HIGHLIGHTS RADIOTERAPIA

Update degli Studi Practice Changing 2024

KEYPOINTS for LS-SCLC:

- **Consolidative durvalumab after RTCT is the new standard of care**
- **BID fractionation should be the preferred regimen**
- **Await analysis of molecular subtypes but also data from RT treatment plans**

HIGHLIGHTS RADIOTERAPIA

Update degli Studi Practice Changing 2024
in Thoracic Tumors

United Nations

ESTRO

Radiation Oncology.
Optimal Health Together. **FOR ALL,**

- ESTRO VISION 2030 -

s.ramella@unicampus.it

HIGHLIGHTS RADIOTERAPIA

Update degli Studi Practice Changing 2024
in Thoracic Tumors

AS PHYSICIANS, IN WHICH WAY WE CAN CONTRIBUTE TO SUSTAINABILITY?

1. Reducing the Environmental Impact of Healthcare Facilities
2. Optimizing Therapies
3. Education and Awareness
4. Interprofessional Collaboration
5. Promotion of Cancer Prevention
6. Patient Health and Well-being

DOING OUR JOB WELL ;)))

s.ramella@unicampus.it


Thank You...
GIUBILEO 2025
PELLEGRINI DI SPERANZA
UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA
«Le cose vere nella vita non si studiano né si imparano, ma si incontrano»