City of Hope®

Southeastern Multidisciplinary Approaches to Cancer Symposium

Current and Future Directions in Small Cell Lung Cancer

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Disclosures

- Consultant for AstraZeneca, Daiichi Sankyo & Picture Health.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

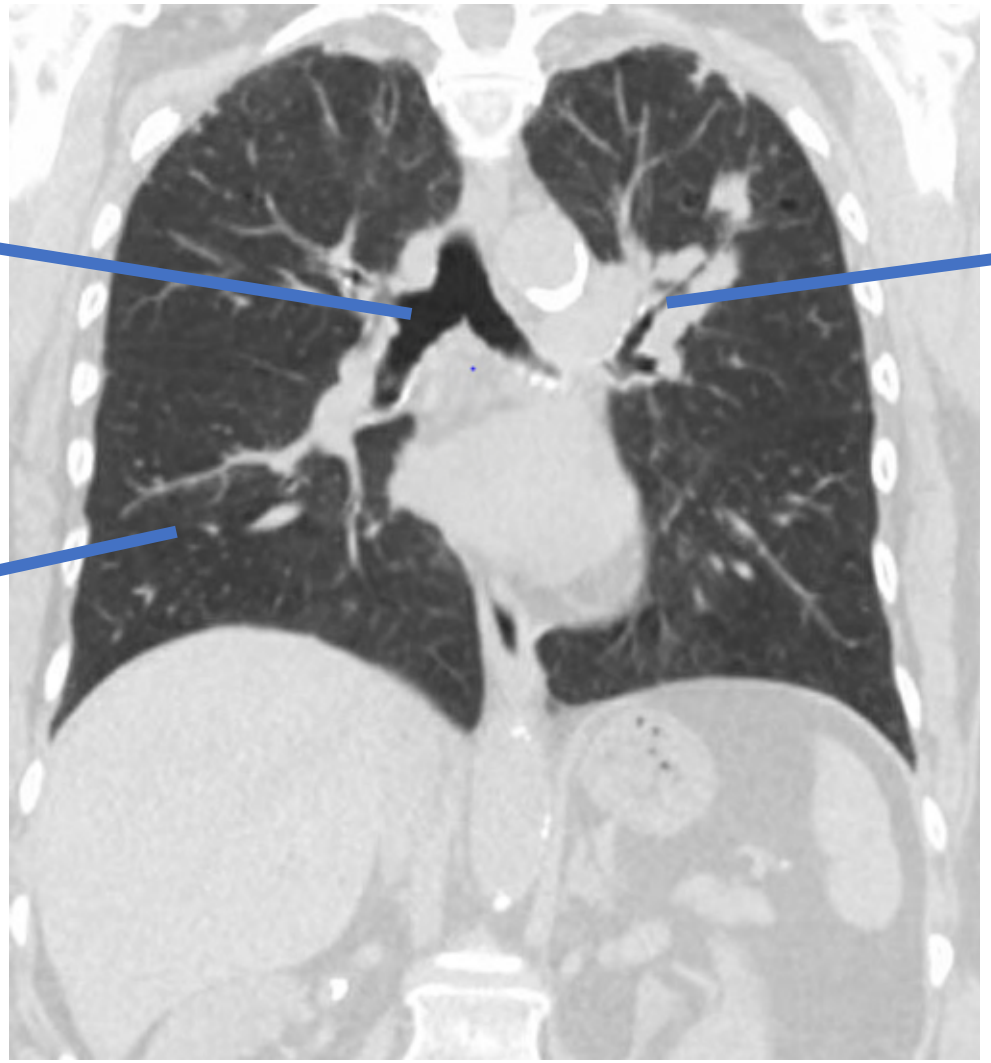
- *Discuss barriers to accessing advanced lung cancer therapies and clinical trials.*
- *Encourage self-reflection to reduce bias in clinical decision-making.*

Hallmarks of Small Cell Lung Cancer

- 13-15% percent of all lung cancers
- Strongly associated with tobacco use
- Tend to respond to therapies including chemotherapy and radiation, but develop resistance quickly
- Known to rapidly metastasize, particularly to the brain
- Scarcity of tissue specimens has limited scientific advances over the years
- Lack of therapeutic progress until recently

Small Cell Lung Cancer: Cell of Origin

Squamous epithelium lining airways cells lining bronchioles create **squamous cell** lung cancers



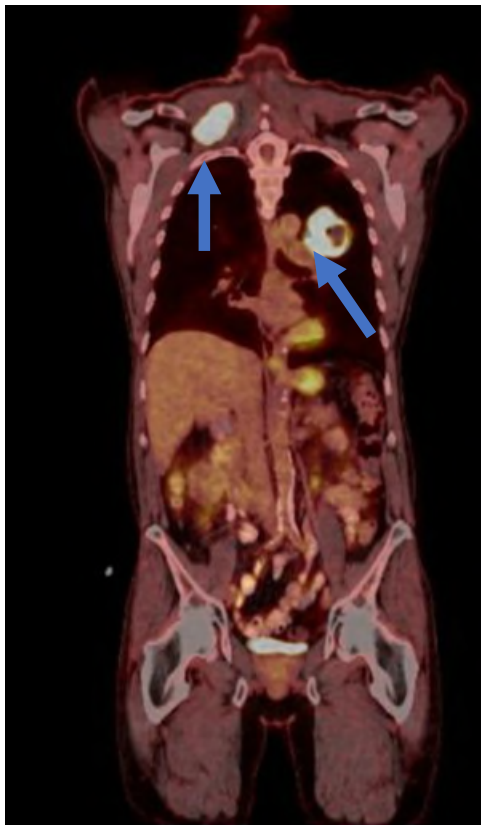
Neuroendocrine cells lining bronchioles create **small cell** lung cancers

Glands lining alveoli in the lung tissue create **adenocarcinomas**

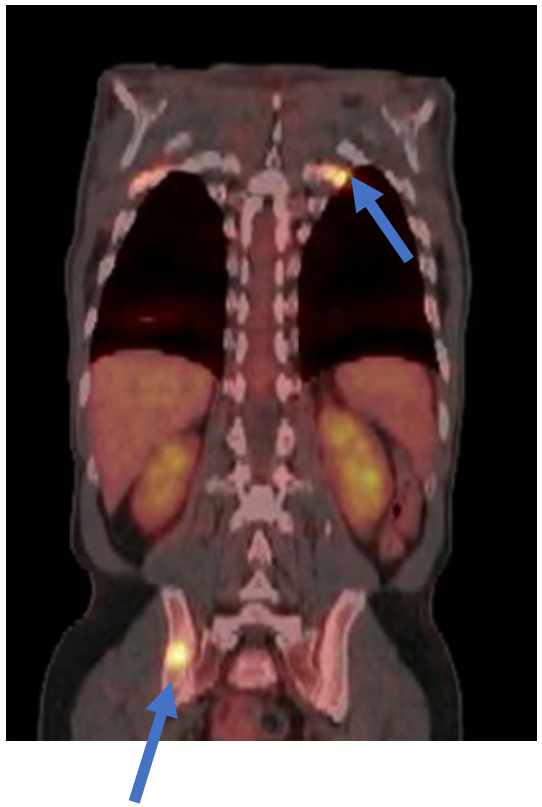
Small Cell Lung Cancer Disease Burden

- ~ 30,000 new cases per year in the U.S.
- 2/3 will have metastatic disease
    - Termed “Extensive Stage” (ES-SCLC)
- 1/3 of these patients will have disease limited to chest
    - Termed “Limited Stage” (LS-SCLC)

- Smoking cessation is meaningful
    - Studies have shown improved survival after a diagnosis of small cell lung cancer if tobacco cessation is undertaken



LS-SCLC



ES-SCLC

Small Cell Lung Cancer: A Recalcitrant Disease

- Recalcitrant Cancer Research Act of 2012

  "develop scientific frameworks that will help provide the strategic direction and guidance to make true progress against recalcitrant or deadly cancers."

- SCLC defined as recalcitrant due to 5 year survival rates of less than 7% and loss of 30,000 lives per year
- Treatment had not changed since early 1980's

- **Recent progress has been made**
  - Reason for hope for this difficult disease!

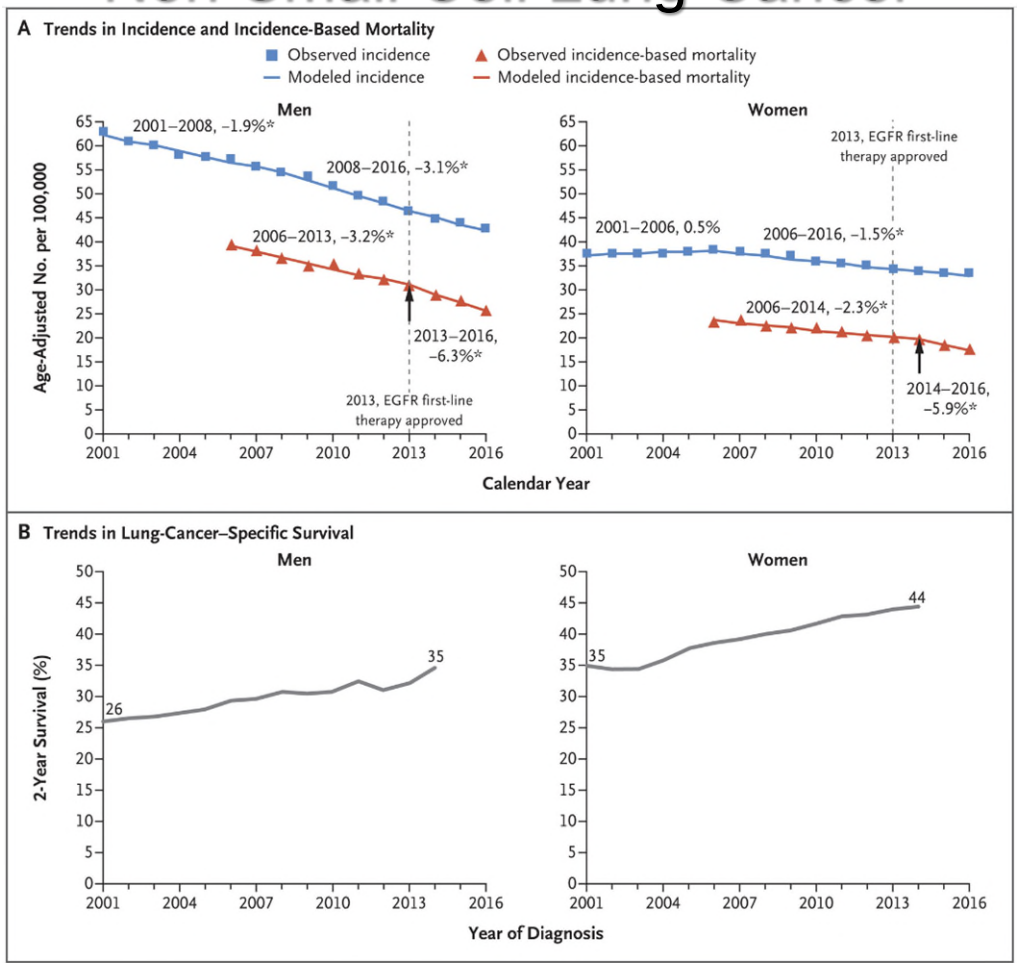
Small Cell Lung Cancer: A Recalcitrant Disease

- Why has there been lack of progress in SCLC?
  - *High risk of development of SCLC despite smoking cessation*
  - *Most SCLC are diagnosed as widely metastatic*
  - *Most SCLC quickly develop resistance to standard chemotherapy*
  - *Lack of tumor tissue for molecular studies particularly after chemo and/or radiation resistance has developed*[1]

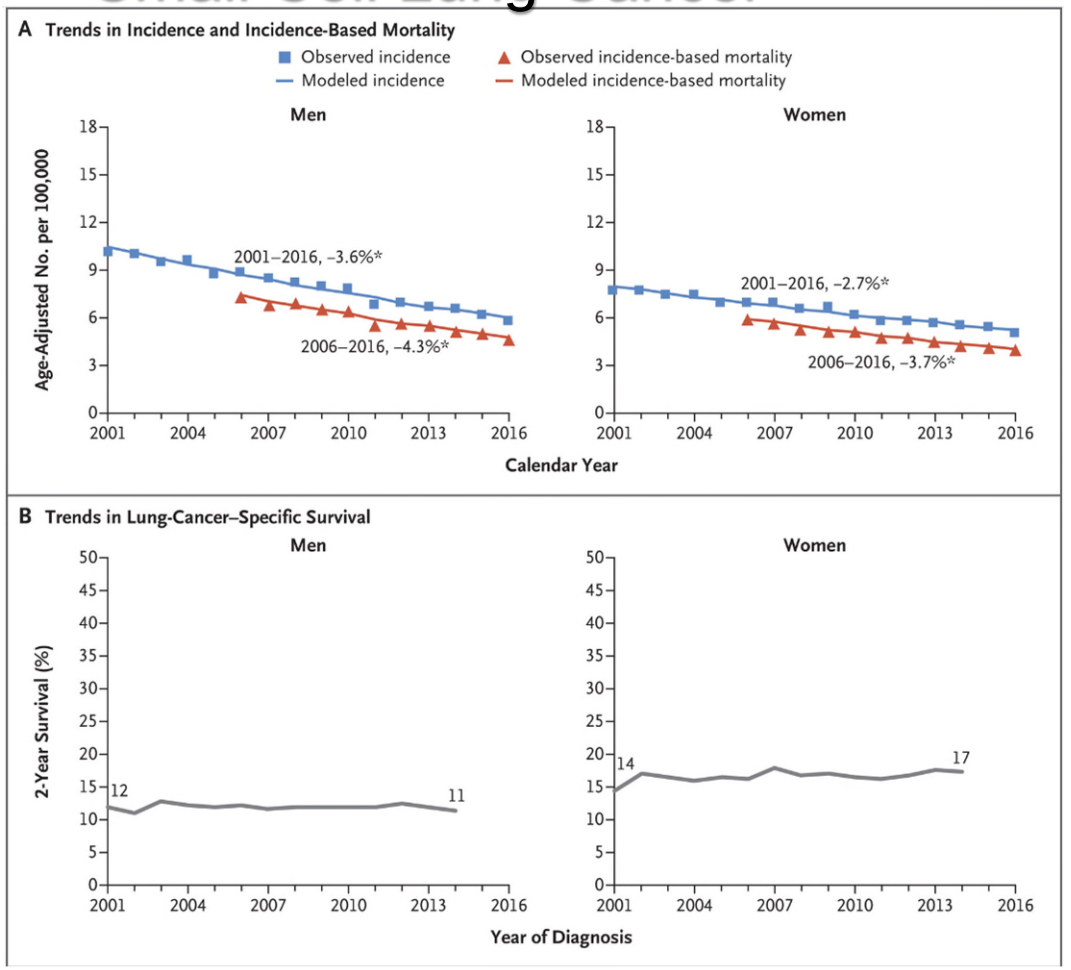
[1]NCI 2014 Scientific Framework for Small Cell Lung Cancer

Lung Cancer Mortality: NSCLC vs. SCLC

Non-Small Cell Lung Cancer



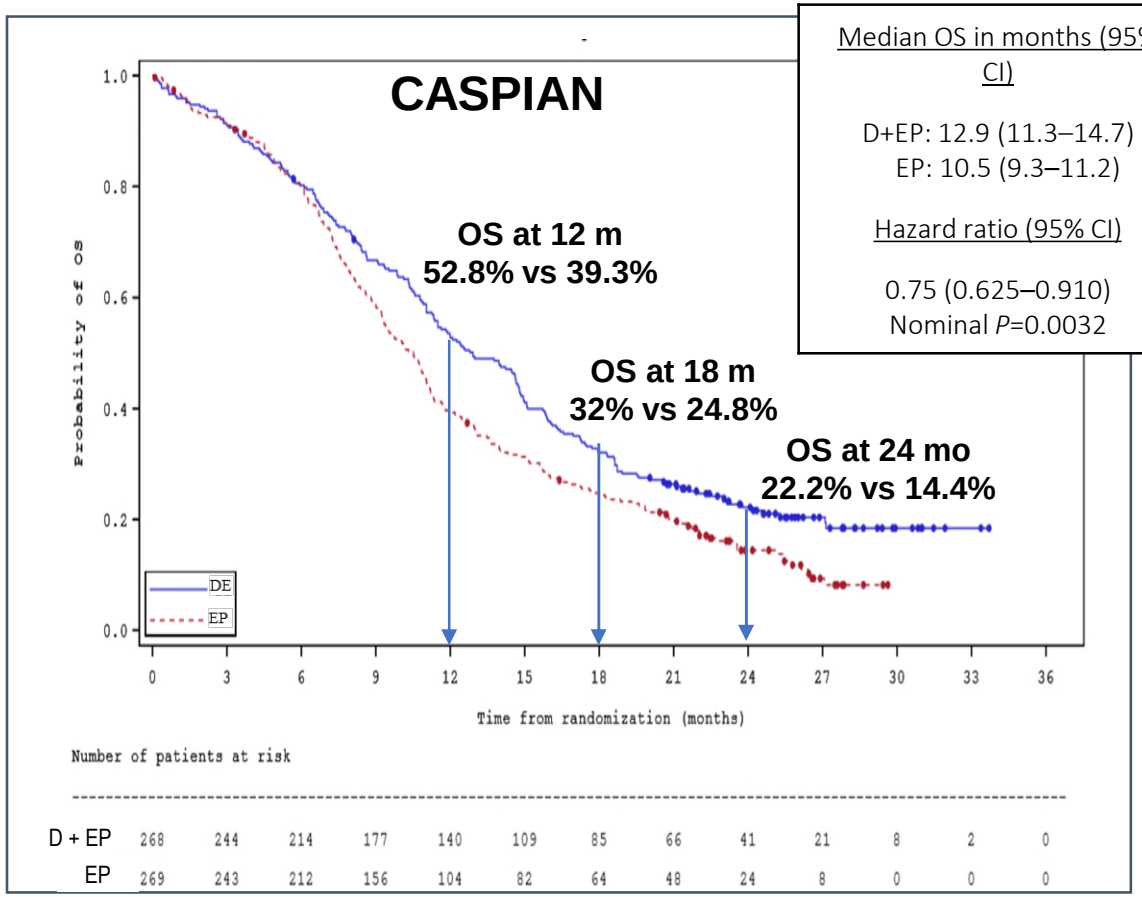
Small Cell Lung Cancer



N Engl J Med 2020; 383:640-649

CASPIAN and IMpower133

CASPIAN updated analysis (82% maturity; 25.1m mF/U)[1,a]



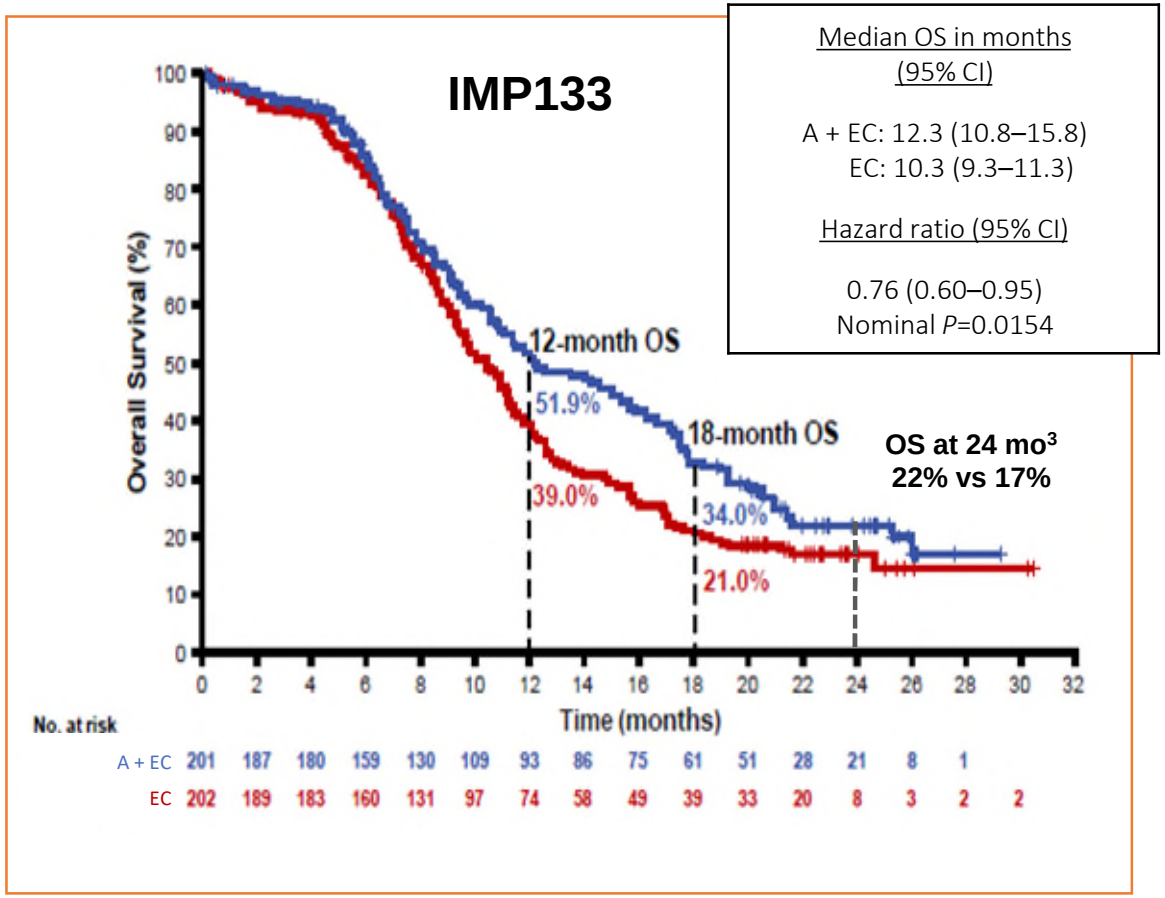
Median OS in months (95% CI)

D+EP: 12.9 (11.3–14.7)
EP: 10.5 (9.3–11.2)

Hazard ratio (95% CI)

0.75 (0.625–0.910)
Nominal *P*=0.0032

IMP133 updated analysis (~75% maturity; 22.9m mF/U)[2]



Median OS in months (95% CI)

A + EC: 12.3 (10.8–15.8)
EC: 10.3 (9.3–11.3)

Hazard ratio (95% CI)

0.76 (0.60–0.95)
Nominal *P*=0.0154

[a]Interim analysis (62.6% maturity; 14.2 m mF/U)
A, atezolizumab; CI, confidence interval; D, durvalumab; EC, etoposide–carboplatin; EP, etoposide–carboplatin/cisplatin; m, months; mF/U, median follow-up; OS, overall survival
1. AstraZeneca. Data on file; 2. Reck M, et al. Presented at European Society of Medical Oncology Congress; September 27th – October 1st, 2019; Barcelona, Spain; 3. Genentech. Available at: https://www.tecentriq-hcp.com/sclc/clinical-data-efficacy/study-efficacy.html (Accessed May 2020)

Defining a New Standard of Care

FDA approves atezolizumab for extensive-stage small cell lung cancer

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On March 18, 2019, the Food and Drug Administration approved atezolizumab (TECENTRIQ, Genentech Inc.) in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

FDA approves durvalumab for extensive-stage small cell lung cancer

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On March 27, 2020, the Food and Drug Administration approved durvalumab (IMFINZI, AstraZeneca) in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

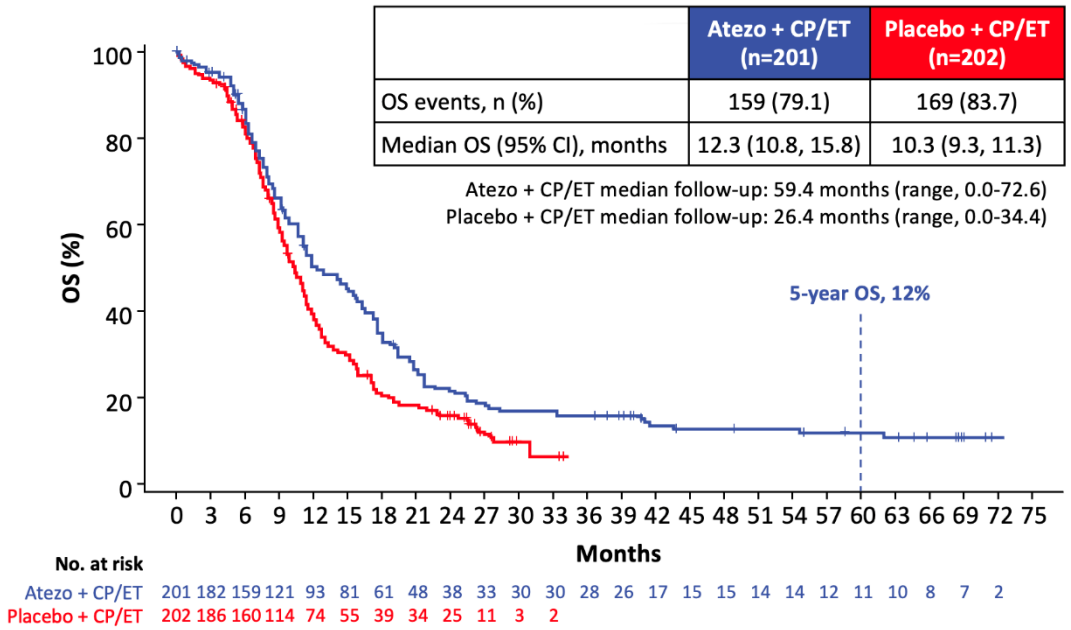
- Significance of this approval is substantial given no new agents have demonstrated survival gains in SCLC in several decades!!

- Platinum/etoposide + atezolizumab **or** platinum/etoposide + durvalumab is the new standard of care for ES-SCLC

What is the Value of IO in SCLC?

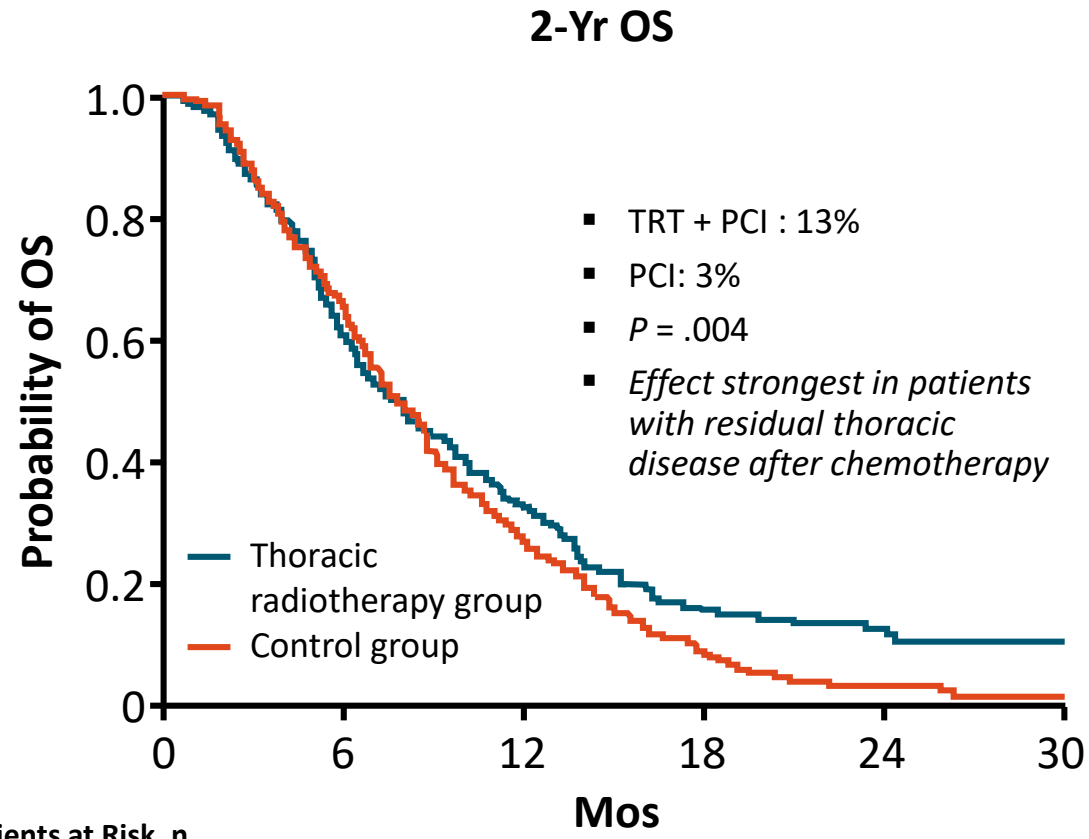
- Modest improvement in survival for all patients
- Transformative improvement in survival for a small subset of patients
- 5y OS rate 12%

OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]



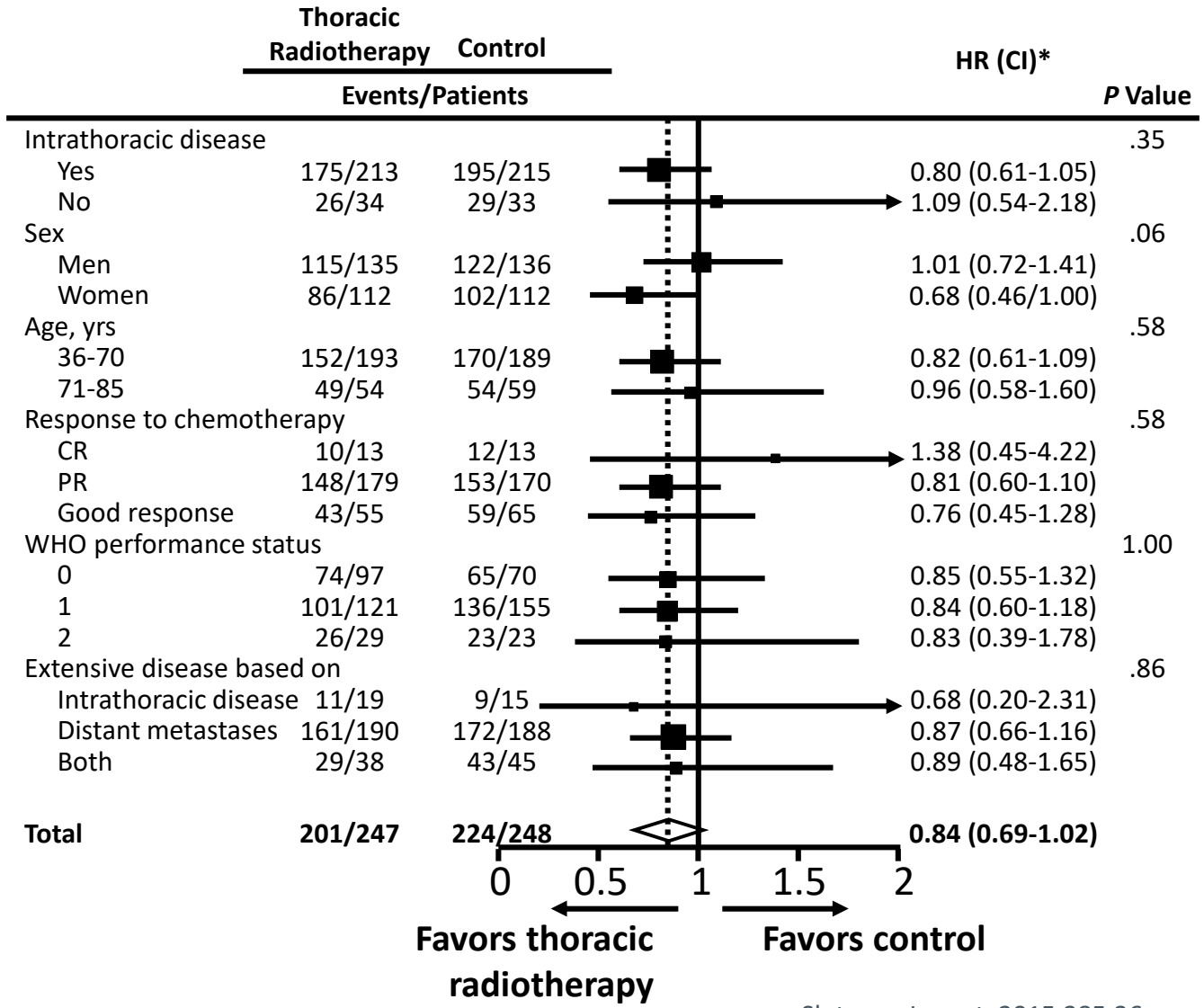
Liu, WCLC 2023

Phase III CREST: Consolidative Thoracic RT in ES-SCLC



Patients at Risk, n

Thoracic RT	247	147	67	26	14	7
Control	248	160	61	17	5	1



Slotman. Lancet. 2015;385:36.

LU007: Randomized Phase II/III Trial of Consolidation Radiation + Immunotherapy for ES-SCLC

PATIENT POPULATION:	STRATIFY	RANDOMIZE*	
Patients with extensive stage small cell lung cancer (ES-SCLC), stable disease (SD) or partial response (PR) after 4-6 cycles of etoposide/platinum (E/P) doublet plus atezolizumab	• Number of sites receiving radiation therapy (fields 1-3 vs >3) • PR vs SD • ECOG Performance Status (0/1 vs 2)		**Arm 1** Atezolizumab maintenance **Arm 2** Standard RT: (Daily up to 5 sites) Thoracic or Liver RT: 45 Gy or 30 Gy Extra-Thoracic RT: 30 Gy or 20 Gy + Atezolizumab maintenance

Randomization is 1:1.
NOTE: Since PCI is optional, co-enrollment in SWOG S1827 (*MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation (PCI): A Randomized Phase III Trial in Small-Cell Lung Cancer [MAVERICK]*) should be strongly considered.

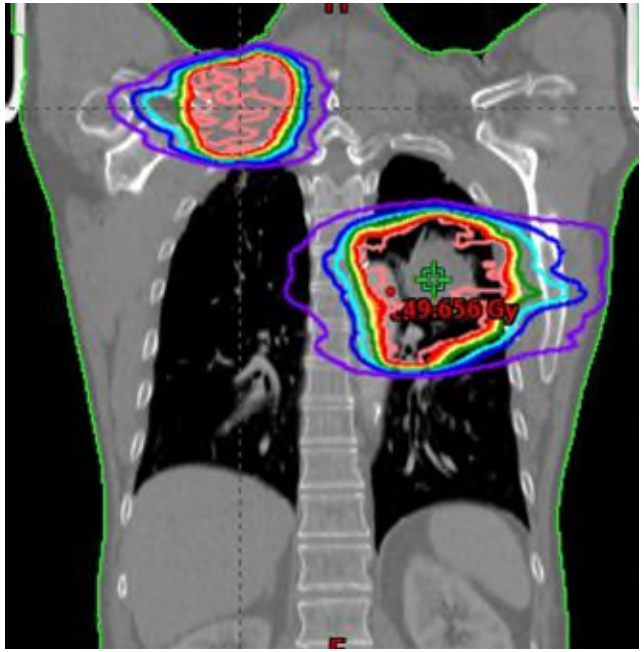
Phase II endpoint: PFS
Phase III endpoint: OS

Protocol activation: August 2020

PI: Dr. Quynh Nguyen

Moving the Needle in LS-SCLC

- Historical, pre-IO era 5 year survival was 25-30% with CRT + PCI
  - 45 Gy twice daily or 66 Gy one daily RT
- In the U.S., only 55% of patients are receiving curative therapy with chemotherapy + radiation[1]
- How can we improve outcomes for our LS-SCLC patients?
  - CRT + durvalumab now standard of care



[1]Chun SG et al, JAMA Onc 2018

CONVERT Phase III Trial: to Determine Optimal RT Dose Schedule in LS-SCLC

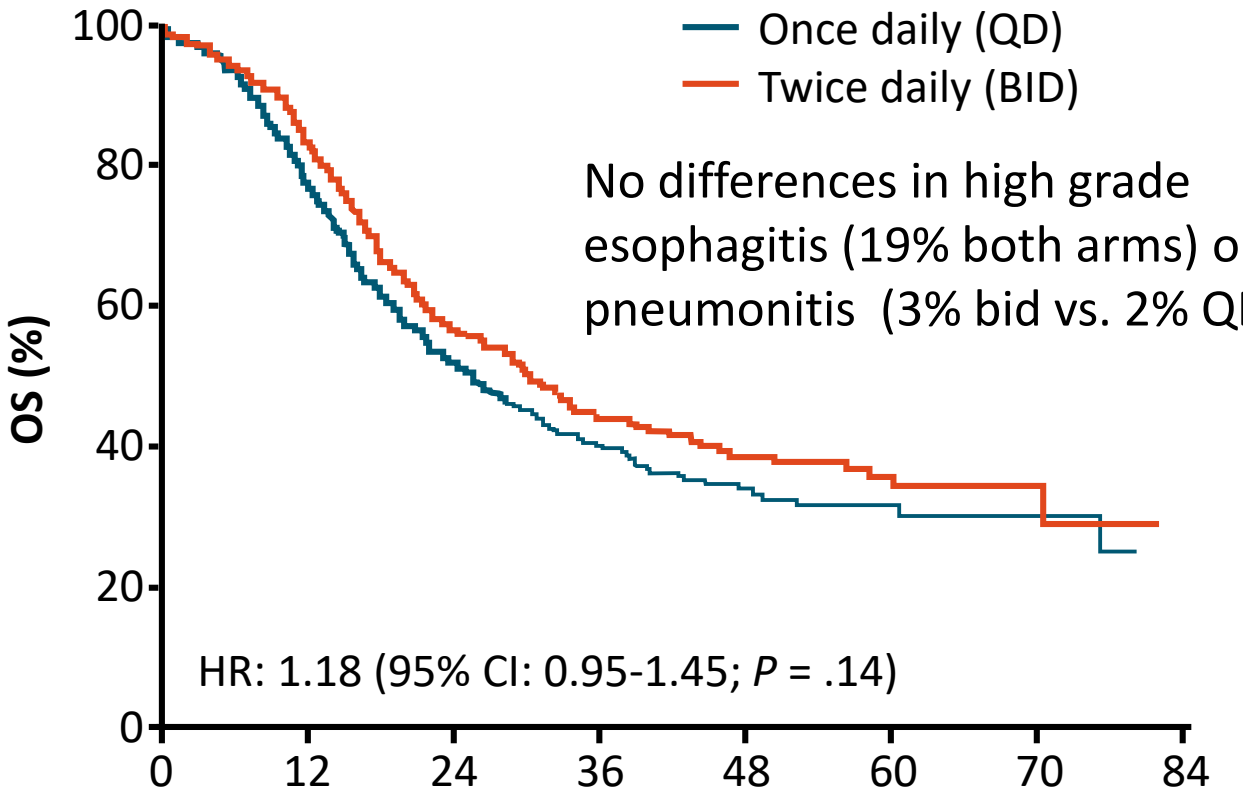
Stratified by center, chemotherapy cycles (4 vs 6), and PS (0-1 vs 2)

Pts with LS-SCLC; ECOG PS 0-1 (or PS 2 if due to disease), adequate pulmonary function (N = 547)

- **QD 2 Gy thoracic RT 66 Gy/33F/45D* + Chemotherapy†** (n = 273)
- **BID 1.5 Gy thoracic RT 45 Gy/30F/19D* + Chemotherapy†** (n = 274)

*RT started on Day 22 after starting chemotherapy.

†Cisplatin 25 mg/m^2 on Days 1-3 or cisplatin 75 mg/m^2 on Day 1 and etoposide 100 mg/m^2 on Days 1-3 for 4 or 6 cycles Q3W.



Patients at Risk, n (n censored)

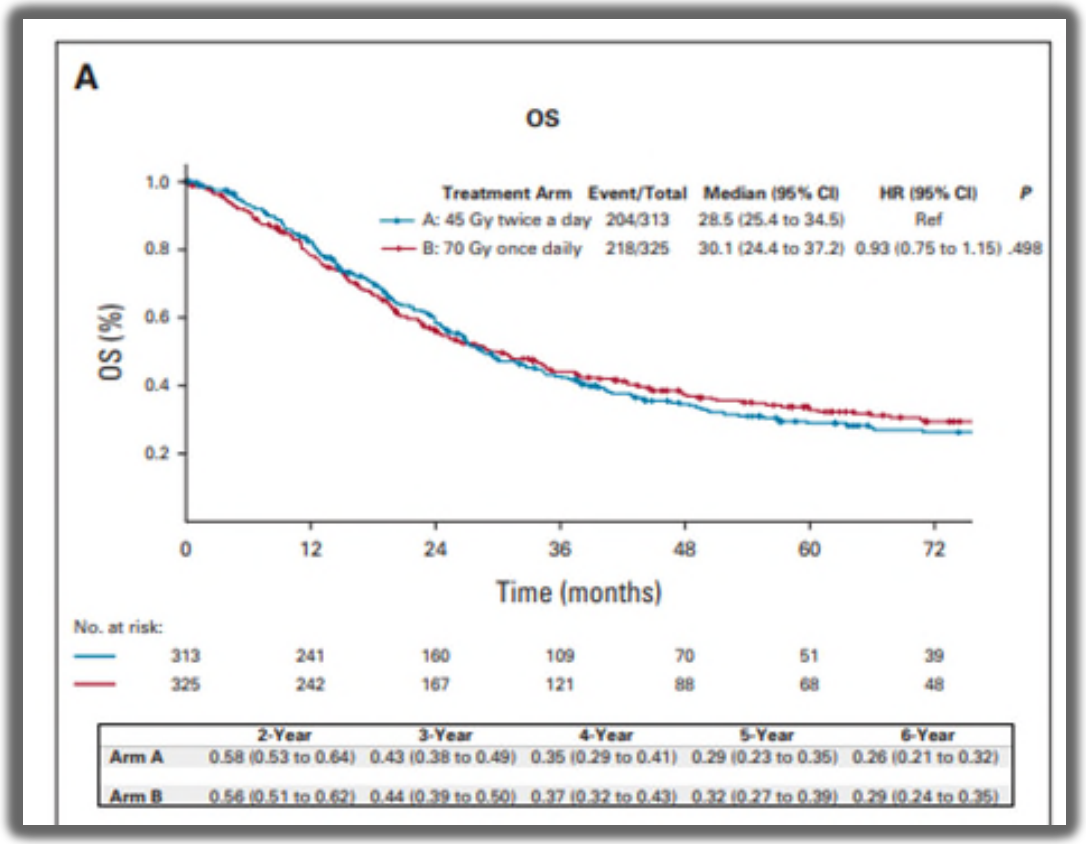
Once daily	270	202 (5)	134 (6)	88 (23)	46 (53)	21 (75)	7 (88)	3 (91)
Twice daily	273	224 (3)	151 (4)	92 (31)	54 (60)	25 (85)	6 (104)	2 (107)

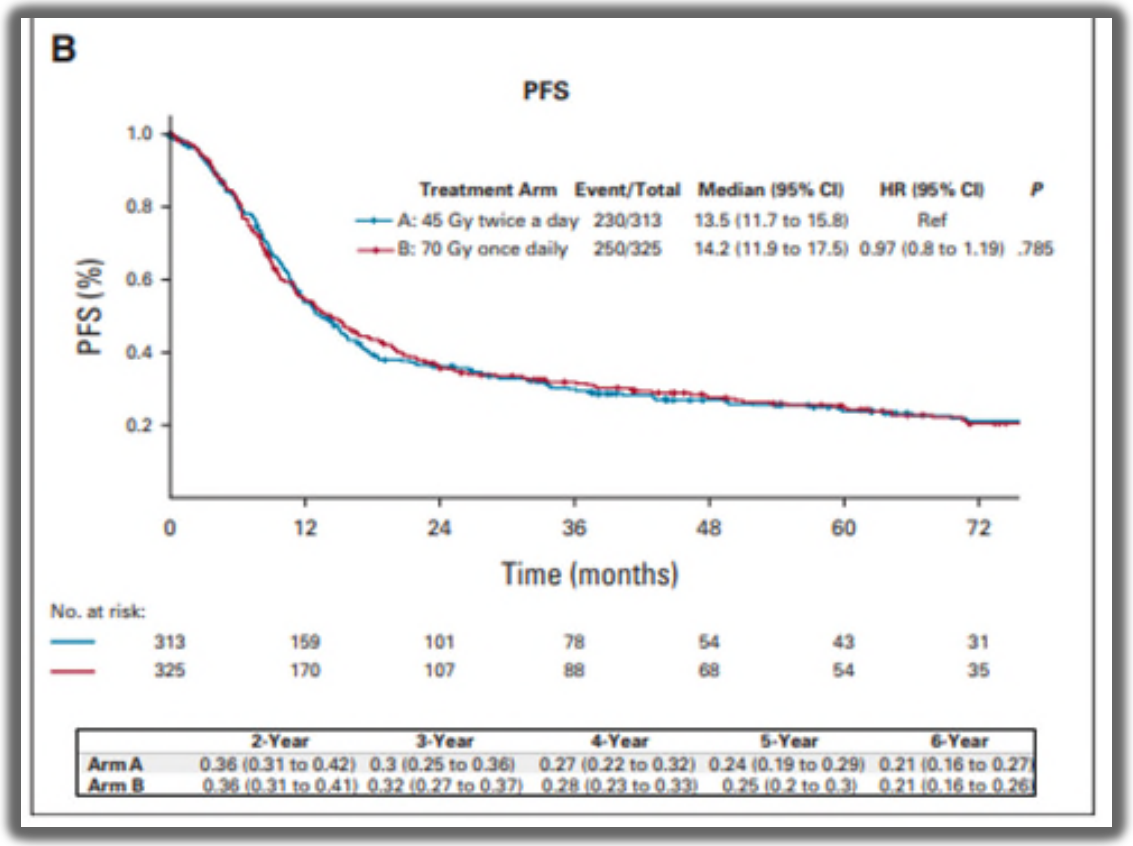
- Powered to detect a 12% OS benefit in daily RT arm

Faivre-Finn. Lancet Oncol. 2017;18:1116.

CALGB 30610/RTOG 0538

638 pts accrued from 2008-2019





- 45 Gy BID vs. 70 Gy daily RT + cisplatin or carboplatin and etoposide
- ECOG 0-2, stratified by gender, PS, TRT technique, > 5% weight loss prior 6 months
- Primary objective to determine whether 70 Gy will improve OS

Bogart et al, JCO 2023

Hyperfractionated, Accelerated Dose Escalation in LS-SCLC

- Dutch phase II study
- 176 pts enrolled with LS-SCLC enrolled, 2014-2018
- Included ECOG 0-2
- Randomized 1:1 to 45 Gy bid vs. 60 Gy bid
- RT with second cycle of chemotherapy
- Stratified variables included PS, AJCC stage, and presence of pleural effusion

	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%)
Smoking history		
Current	54 (61%)	57 (70%)
Former	33 (37%)	22 (27%)
Never	1 (1%)	2 (3%)
Data missing	1 (1%)	0
Median pack years for current or former smokers	35 (23·5–50·0)	30 (23·0–40·0)
Weight loss in 3 months before inclusion		
>5%	16 (18%)	18 (22%)
Data missing	17 (19%)	7 (9%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

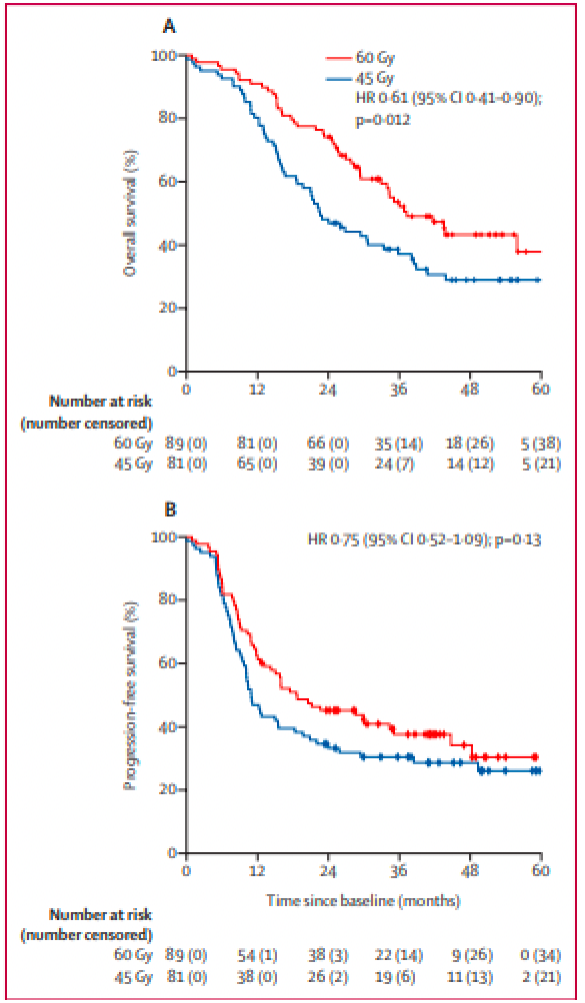
Gronberg et al, Lancet Oncol 2021 Mar;22(3):321-331

Hyperfractionated, Accelerated Dose Escalation in LS-SCLC

	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
Neutropenic infection	0	19 (21%)	5 (6%)	1 (1%)	0	24 (31%)	6 (8%)	0	0·30
Thrombocytopenic bleeding	1 (1%)	0	0	0	2 (3%)	0	0	1 (1%)	0·61
Infection	14 (16%)	2 (2%)	0	0	11 (14%)	5 (7%)	0	0	0·14
Kidney failure	10 (11%)	1 (1%)	0	0	10 (13%)	0	1 (1%)	0	0·80
Nausea	15 (17%)	5 (6%)	1 (1%)	0	19 (25%)	3 (4%)	0	0	0·62
Fatigue	11 (12%)	0	0	0	8 (10%)	1 (1%)	0	0	0·83
Erythaema	7 (8%)	0	0	0	6 (8%)	1 (1%)	0	0	0·87
Headache	13 (15%)	1 (1%)	0	0	5 (7%)	1 (1%)	0	0	0·078
Neuropathy	3 (3%)	0	0	0	1 (1%)	1 (1%)	0	0	0·89
Myelopathy	0	1 (1%)	0	0	0	0	0	0	1·0
Myocardial infarction	0	1 (1%)	0	0	0	0	0	0	1·0
Aortic dissection	0	0	0	1 (1%)	0	0	0	0	1·0
Ototoxicity	2 (2%)	1 (1%)	0	0	1 (1%)	0	0	0	1·0
Thromboembolism	0	2 (2%)	0	0	1 (1%)	1 (1%)	0	0	0·79

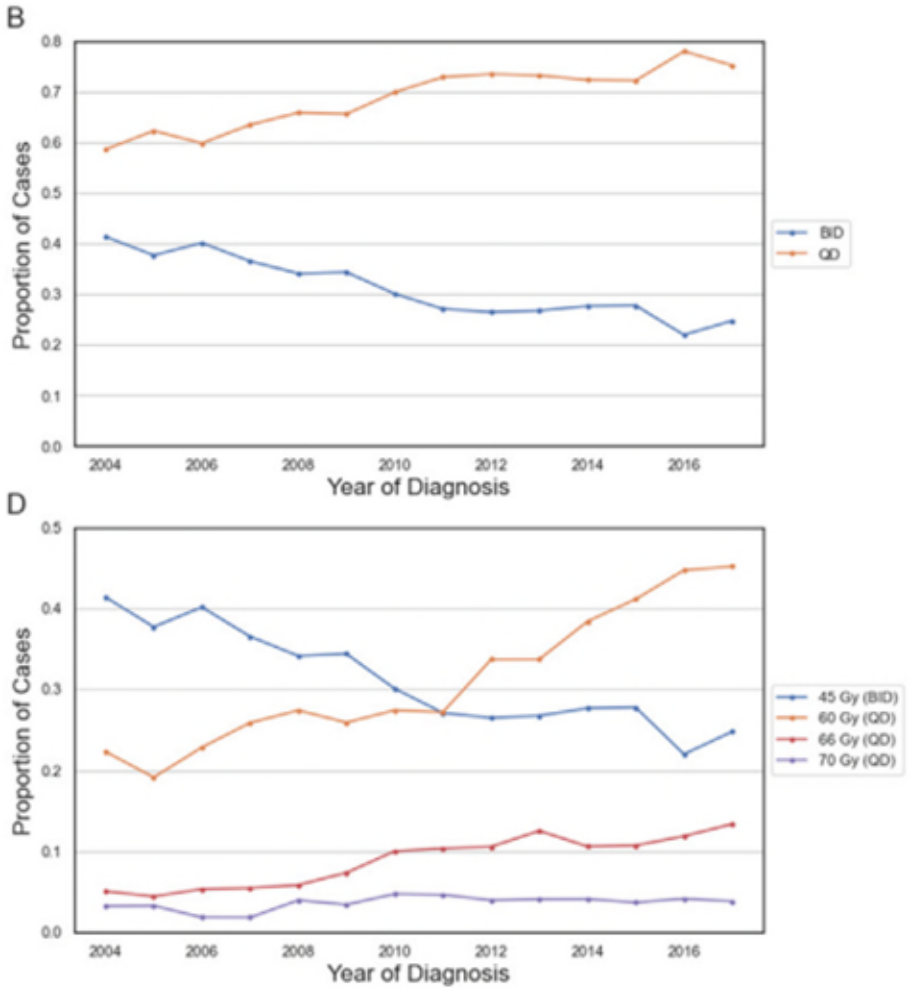
Table 4: Toxicity in patients who commenced thoracic radiotherapy

- Improvement in 2 yr OS
- Trend towards improvements in PFS
- No difference in local control
- No differences in high grade esophagitis or pneumonitis



RT Fractionation: Real World Data

- NCDB retrospective study, 2004-2017
- Pts getting thoracic RT for LS-SCLC in U.S.
- Examined trends in fractionation
- 17,543 patients
- 60 QD most common
- 28% of patients received BID treatment, overall decreasing over time

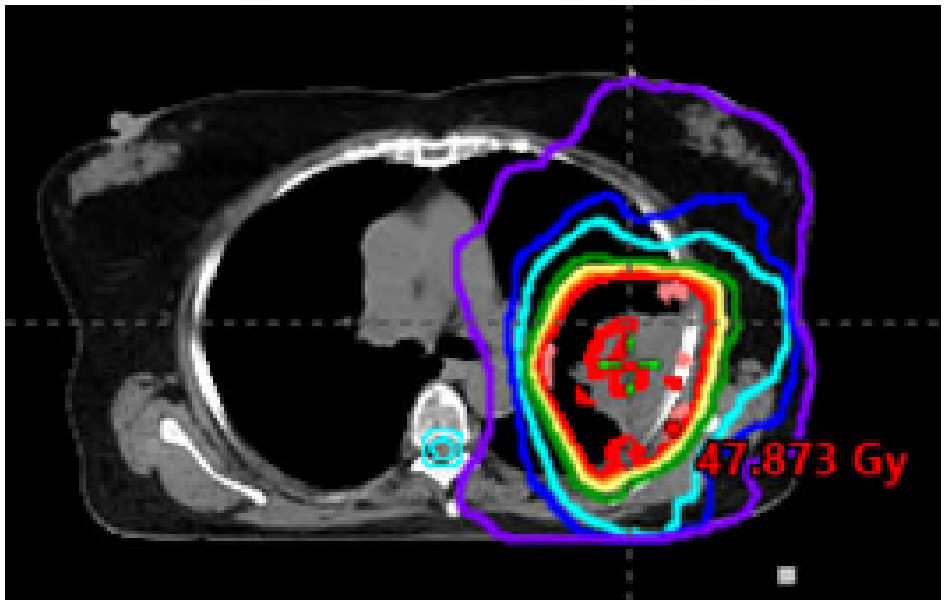


Kazemi et al, Clin Lung Cancer. 2023 Jun;24(4):322-328

LS-SCLC Guideline Supported TRT Dose Recommendations

NCCN guidelines

- 45 Gy bid recommended
- 66-70 Gy daily is acceptable
- hyperfractionated, accelerated RT to 54-60 Gy has shown a survival benefit in several trials



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.

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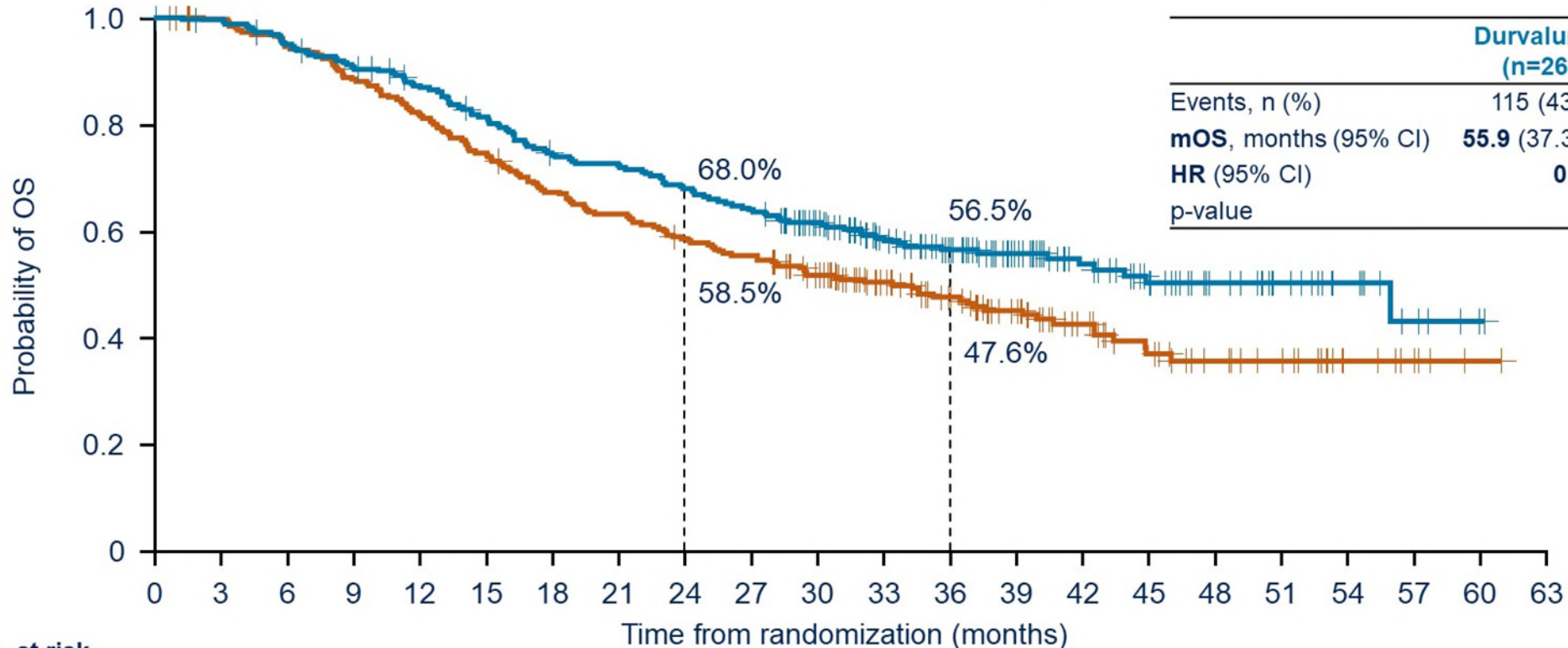
Overall survival (dual primary endpoint)

- 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	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

PRESENTED BY: Dr David R. Spigel

CI, confidence interval; mOS, median OS; NE, not estimable.

Conclusions

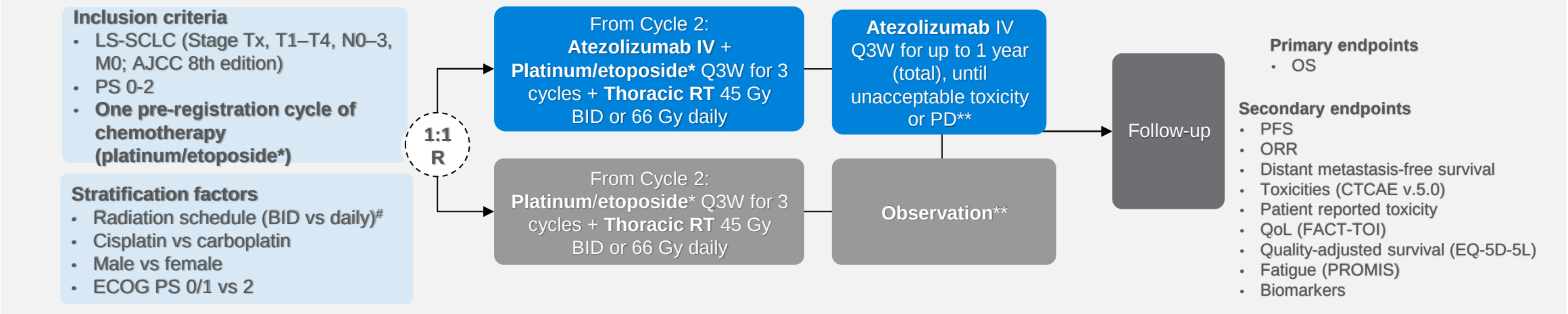
- **Durvalumab as consolidation treatment after cCRT demonstrated statistically significant and clinically meaningful improvement in OS and PFS compared with placebo in patients with LS-SCLC**
  - **OS HR 0.73** (95% CI 0.57–0.93), p=0.0104; mOS 55.9 (95% CI 37.3–NE) vs 33.4 (95% CI 25.5–39.9) months
  - **PFS HR 0.76** (95% CI 0.61–0.95), p=0.0161; mPFS 16.6 (95% CI 10.2–28.2) vs 9.2 (95% CI 7.4–12.9) months
  - Treatment benefit was generally consistent across predefined patient subgroups for both OS and PFS
- **Durvalumab consolidation treatment for up to 2 years was well tolerated, and safety findings were consistent with the known safety profile of durvalumab monotherapy in the post-cCRT setting**

Consolidation durvalumab will become the new standard of care for patients with LS-SCLC who have not progressed after cCRT

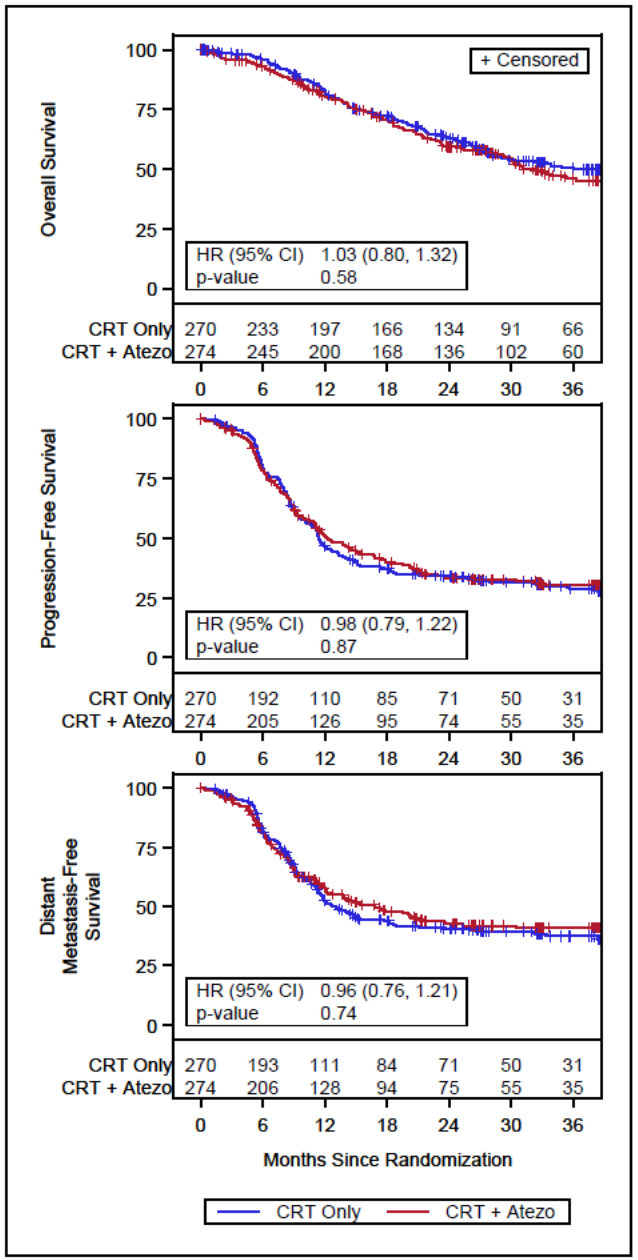
PRESENTED BY: Dr David R. Spigel

NRG LU005 Schema

Phase III (N = 544; US & Japanese sites**)** NCT03811002



#Thoracic RT 45 Gy BID (1.5 Gy x 30 fractions ->3 weeks) or 66 Gy daily (2 Gy x 33 fractions ->6.5 weeks) beginning with cycle 2 of chemotherapy; *cisplatin (preferred) or carboplatin; first cycle of chemotherapy given prior to study entry, 3 given on study (for a total of 4 cycles); **All patients with a CR or near CR are strongly recommended to receive prophylactic cranial irradiation (PCI; 25 Gy)



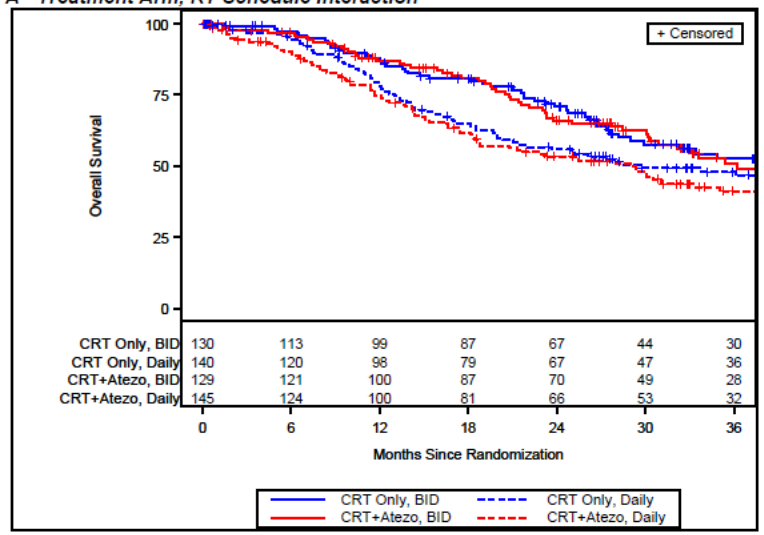
Higgins et al, JCO in press

NRG LU005 Results

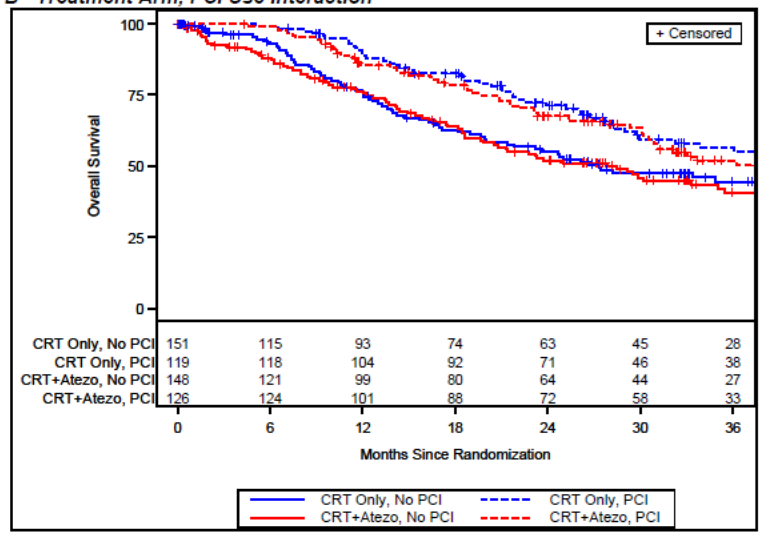
- No differences in OS, PFS or DMFS
- Control arm median OS of 36 months

NRG LU005 Results

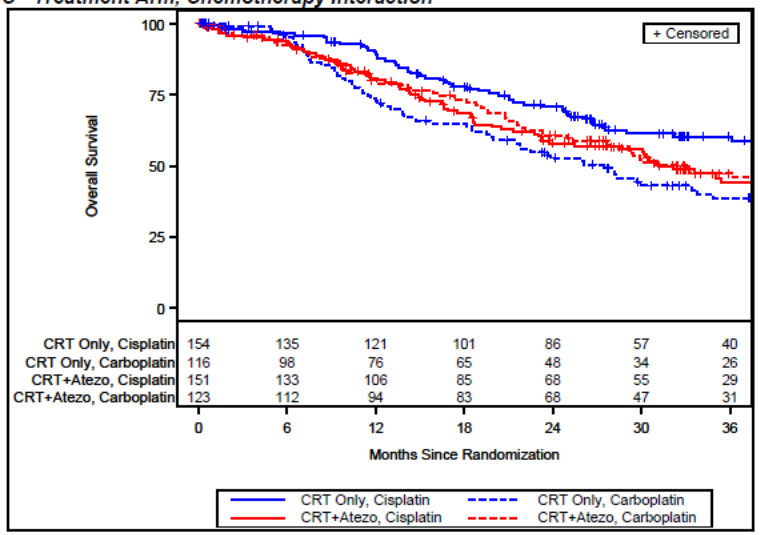
A - Treatment Arm, RT Schedule Interaction



B - Treatment Arm, PCI Use Interaction



C - Treatment Arm, Chemotherapy Interaction



Panel	Subset	Comparison	HR (95% CI)	Interaction p-value
A	BID RT	CRT Alone (Ref) vs CRT+Atezo	1.13 (0.77, 1.68)	0.63
	Daily RT	CRT Alone (Ref) vs CRT+Atezo	1.00 (0.73, 1.38)	
	CRT Alone	BID RT (Ref) vs Daily RT	1.51 (1.05, 2.18)	
	CRT+Atezo	BID RT (Ref) vs Daily RT	1.37 (0.97, 1.94)	
B*	No PCI by landmark	CRT Alone (Ref) vs CRT+Atezo	0.95 (0.66, 1.35)	0.89
	PCI by landmark	CRT Alone (Ref) vs CRT+Atezo	1.07 (0.73, 1.58)	
	CRT Alone	No PCI by landmark (Ref) vs PCI by landmark	0.68 (0.46, 0.99)	
	CRT+Atezo	No PCI by landmark (Ref) vs PCI by landmark	0.77 (0.53, 1.11)	
C	Cisplatin	CRT Alone (Ref) vs CRT+Atezo	1.31 (0.93, 1.87)	0.06
	Carboplatin	CRT Alone (Ref) vs CRT+Atezo	0.83 (0.58, 1.17)	
	CRT Alone	Cisplatin (Ref) vs Carboplatin	1.65 (1.15, 2.36)	
	CRT+Atezo	Cisplatin (Ref) vs Carboplatin	1.03 (0.73, 1.45)	

Higgins et al, JCO in press

NRG LU005 Results

Supplemental Table 4
Overall Survival Multivariable Analysis

Parameter	Comparison	Fail/Total RL	Fail/Total Comparison	HR (95% CI)	p-value*
Treatment Arm	No Atezolizumab (RL) vs Atezolizumab	120/270	132/274	1.05 (0.82, 1.34)	0.72
Sex	Male (RL) vs Female	119/267	133/277	1.10 (0.85, 1.41)	0.47
RT Schedule	BID (RL) vs Once daily	95/257	157/287	1.69 (1.30, 2.18)	<0.0001
Platinum agent	Cisplatin (RL) vs Carboplatin	133/322	119/222	1.42 (1.10, 1.82)	0.0061

HR=Hazard ratio, CI=Confidence interval, RL=Referent level

Supplemental Table 5
Landmark Analysis: Landmark = 180 Days Post Randomization
Overall Survival Multivariable Analysis

Parameter	Comparison	Fail/Total RL	Fail/Total Comparison	HR (95% CI)	p-value*
Treatment Arm	No Atezolizumab (RL) vs Atezolizumab	110/233	114/246	0.99 (0.76, 1.28)	0.91
Sex	Male (RL) vs Female	107/241	117/238	1.09 (0.83, 1.42)	0.54
RT Schedule	BID (RL) vs Once daily	90/233	134/246	1.50 (1.14, 1.97)	0.0035
Platinum agent	Cisplatin (RL) vs Carboplatin	118/284	106/195	1.40 (1.08, 1.83)	0.012
PCI Prior to Landmark	No PCI prior (RL) vs PCI prior	123/241	101/238	0.77 (0.59, 1.01)	0.055

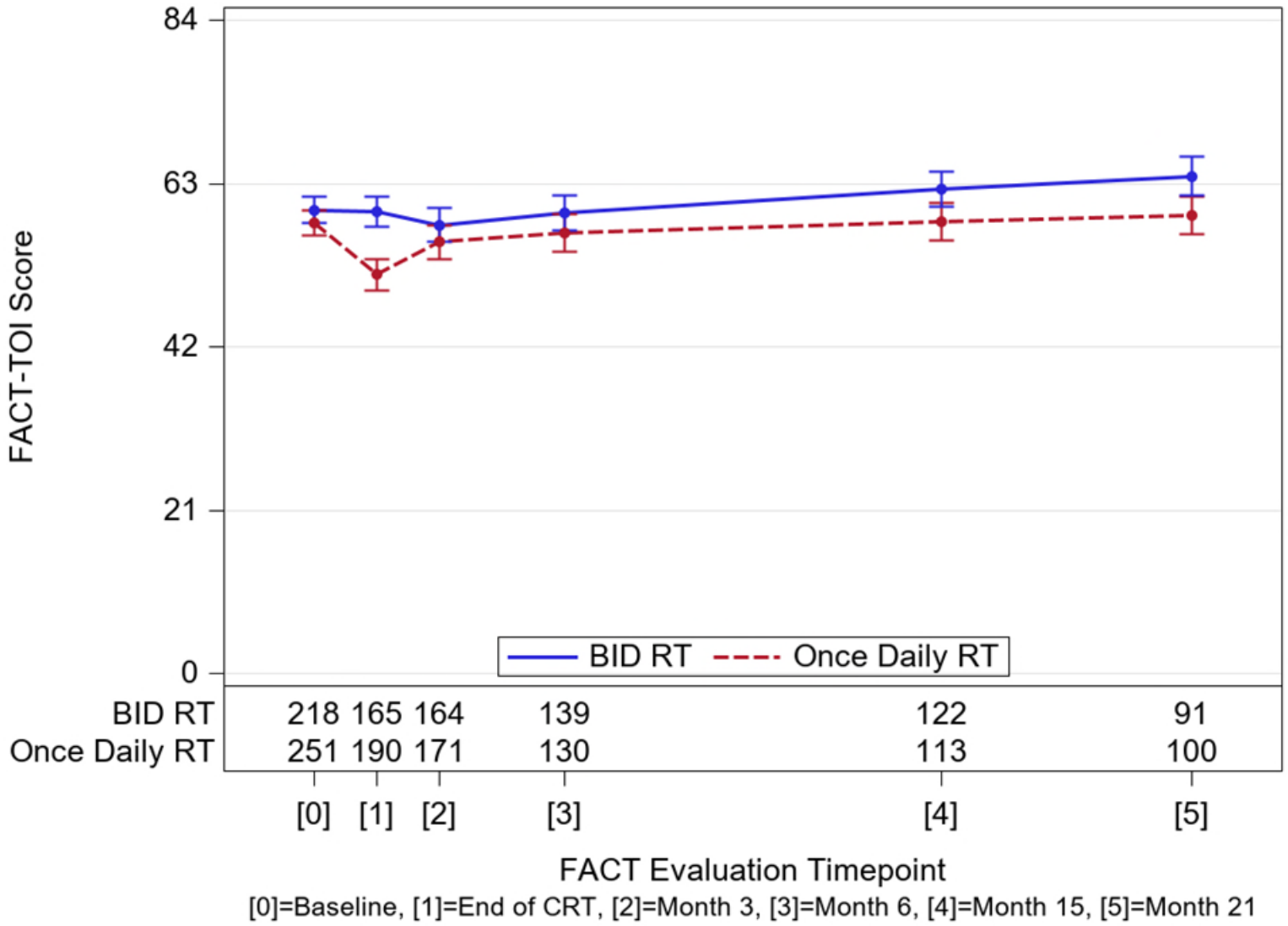
HR=Hazard ratio, CI=Confidence interval, RL=Referent level

Higgins et al, JCO in press

QOL: FACT-TOI Scores by RT Schedule

52.8% of all pts received BID RT, which was associated with better QOL than qday RT across all timepoints

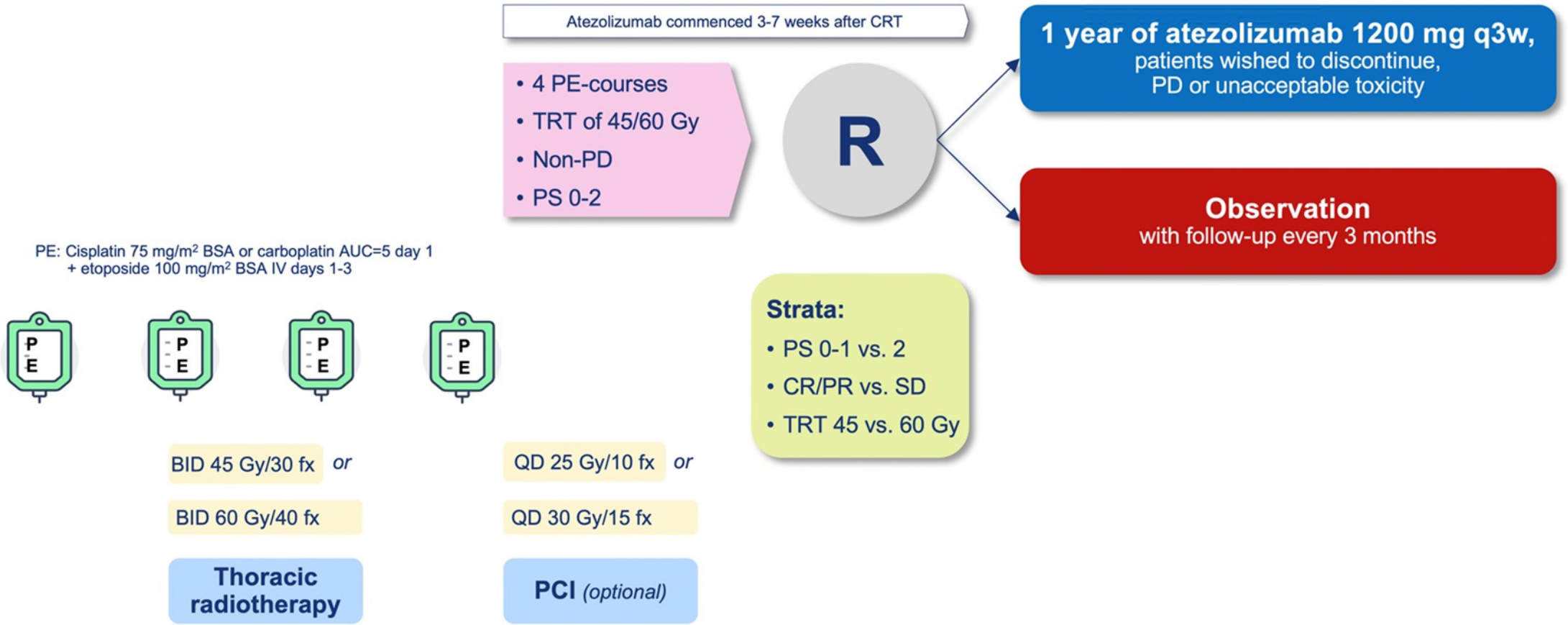
***Stratification factor; non-randomized comparison**



Movsas et al, ASTRO 2025

Study design

Randomized phase II trial investigating whether atezolizumab after chemoradiotherapy (CRT) prolongs survival in limited stage (LS) small cell lung cancer (SCLC)



Gronberg BH, et al. *J Clin Oncol.* 2025;43(17_suppl):LBA8005.

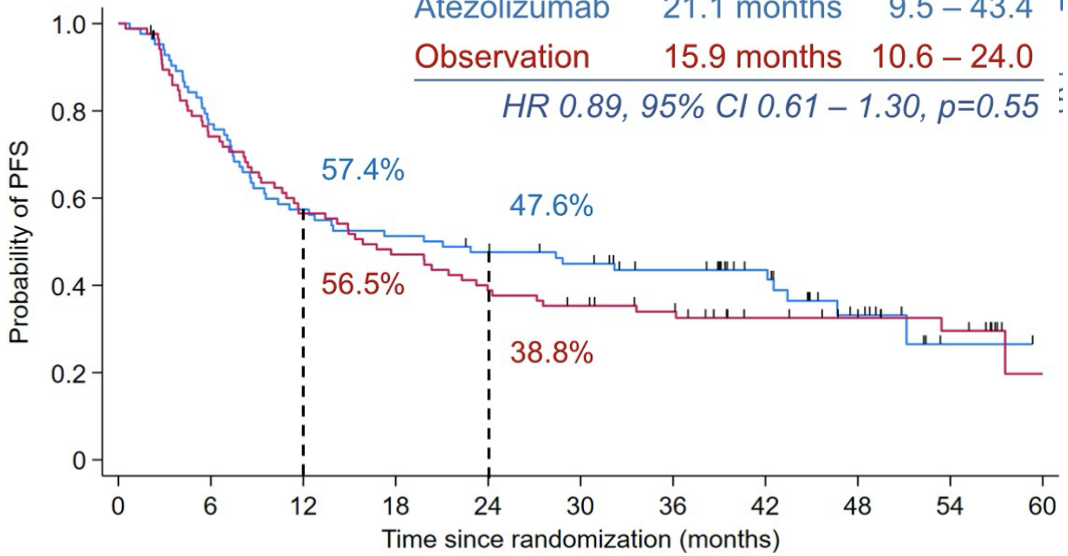
Randomized phase II trial investigating whether atezolizumab after chemoradiotherapy (CRT) prolongs survival in limited stage (LS) small cell lung cancer (SCLC)

ACHILES PHASE 2

Progression free survival

	Median	95% CI
Atezolizumab	21.1 months	9.5 – 43.4
Observation	15.9 months	10.6 – 24.0

HR 0.89, 95% CI 0.61 – 1.30, p=0.55



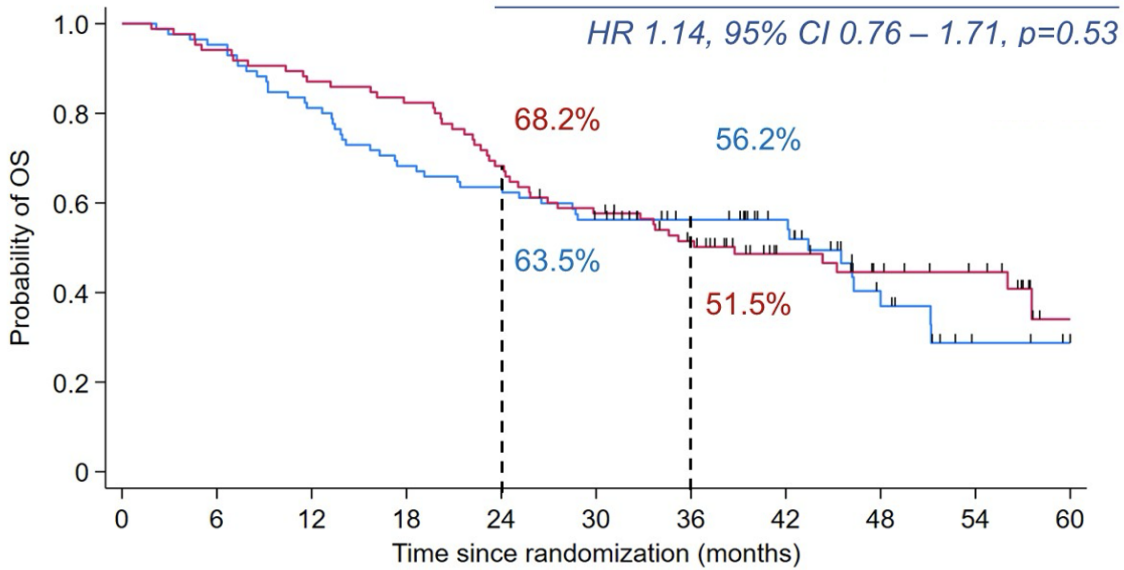
Number at risk

Atezolizumab	85	63	47	42	37	34	28	20	9	1	0
Observation	85	63	48	40	33	29	25	17	13	10	2

Overall survival

	Median	95% CI
Atezolizumab	43.4 months	25.1 – 51.2
Observation	38.8 months	25.8 – 57.6

HR 1.14, 95% CI 0.76 – 1.71, p=0.53



Number at risk

Atezolizumab	85	81	69	58	54	45	36	26	12	3	1
Observation	85	80	74	70	58	49	40	25	18	14	3

Gronberg BH, et al. *J Clin Oncol.* 2025;43(17_suppl):LBA8005.

Summary of Completed CRT/IO Trials

Study	cCRT	Treatment after cCRT	Key results
ADRIATIC[1] Phase 3	4 cycles ± PCI	• Durva → Durva maintenance • Durvalumab + tremelimumab → Durva maintenance	*Durva vs PBO* • **PFS:** 16.6 vs 9.2 mo • **OS:** 55.9 vs 33.4
ETOP/IFCT 4-12 STIMULI[2] Phase 2	4 cycles PCI	• Nivo + Ipi → Nivo maintenance	*Nivo + Ipi vs observation* • **PFS:** 10.7 mo vs 14.5 mo • **OS:** NR vs 32.1 mo
ACHILES[3] Phase 2	4 cycles ± PCI	• Atezo → Atezo maintenance	*Atezo vs observation* • **PFS:** 21.1 vs 15.9 mo • **OS:** 43.4 vs 38.8 mo
NRG LU005[4] Phase 3	cCRT ± Atezo ± PCI → Atezo maintenance		*Atezo + cCRT vs cCRT* • **PFS:** 12.0 vs 11.5 mo • **OS:** 33.1 vs 39.5 mo

Reference(s): 1. Cheng Y et al. *N Engl J Med* 2024;391:1313-1327; 2. Peters S et al. *Ann Oncol*. 2022;33:67-79; 3. Grønberg BH et al. ASCO 2025. Presentation LBA8005; 4. Higgins KA et al. ASTRO 2024. Presentation LBA02.

Phase III trials with novel approaches

ID	Study phase	Intervention	Standard	Exp. Completion
NCT04691063	Induction	CRT + Adebrelimab (ICI)	CRT	2025-05-15
NCT05353257	Induction	CRT + Serplulimab (ICI)	CRT	2026-12-30
NCT04624204 (KEYLYNK 013)	Induction + maintenance	CCRT + Pembro followed by Pembro + Olaparib CCRT + Pembro followed by Pembro	CRT	2027-10-28
NCT06469879	Maintenance	TQB2450 (ICI)+Anlotinib	Placebo	2026-09-30
NCT06526624	Maintenance	HS20093 (B7-H3 ADC)	OBS	2029-01-31
NCT06095583	Maintenance	Tifcemalimab + toripalimab (ICI) Toripalimab (ICI)	Placebo	2029-07-31
NCT06117774 (DELPHI 306)	Maintenance	Tarlatamab (BiTE)	Placebo	2029-10-31
NCT05496166	Maintenance	CRT + SHR1316 (ICI) followed by surgery	CRT + SHR1316 (ICI) followed by RT	2030-08-01

Slide courtesy of Dr. Luis Paz Ares

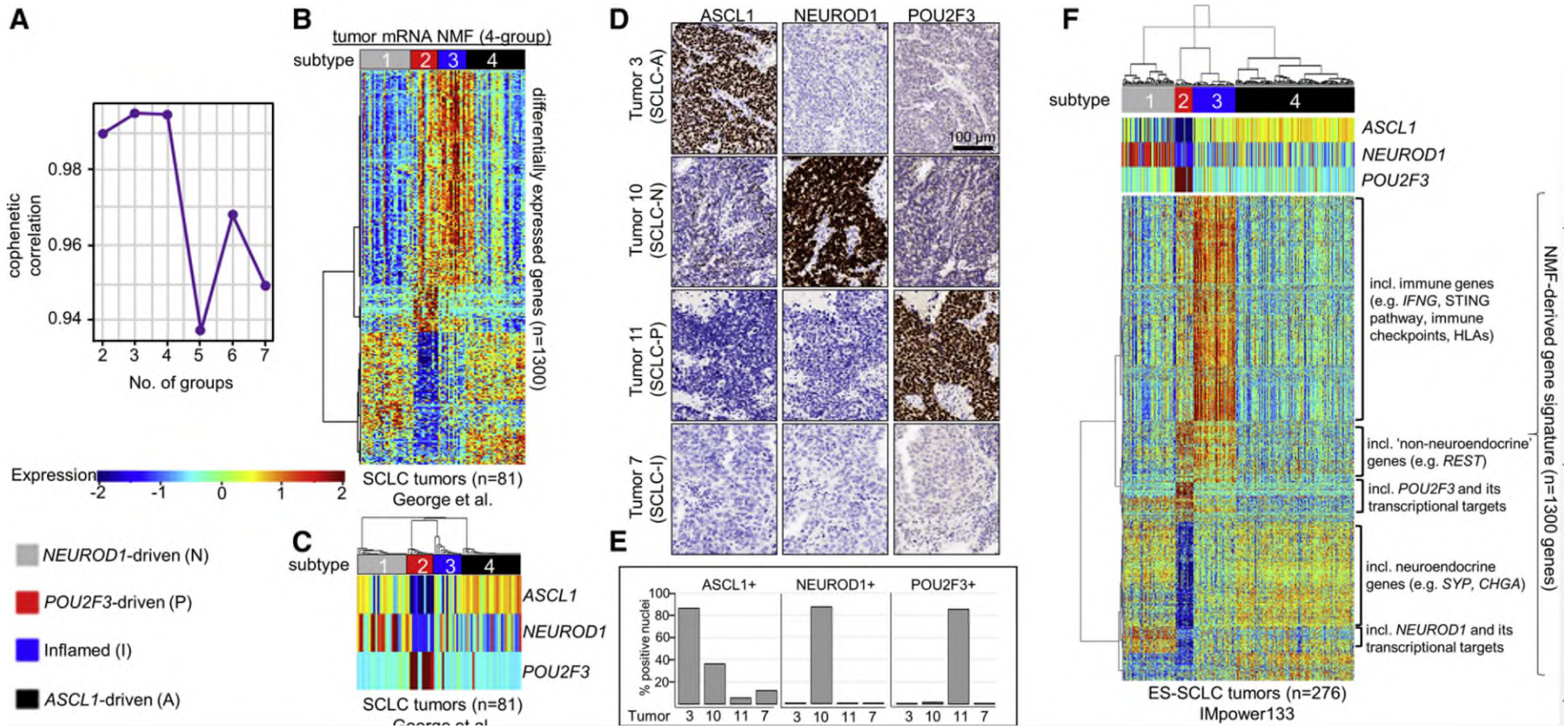
BID vs. Daily RT in LS-SCLC

- Data from Stimuli, LU005 and Adriatic suggesting twice daily may be better
- Randomized trials prior to IO era testing 45 Gy bid vs. 66-70 Gy daily showed no difference, with 45 Gy bid remaining standard
- BID approaches poorly utilized for unclear reasons
- Fractionation should be re-examined in the IO era → optimal RT dose in the context of consolidative durvalumab remains undefined
- Shorter and or BID approaches could be less immune depleting, less toxicity?

Future Directions in Small Cell Lung Cancer

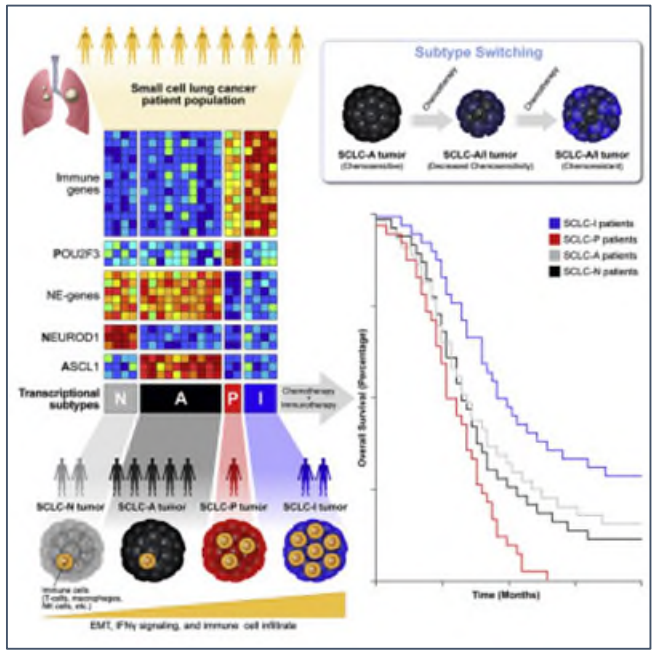
Transcriptional Subtypes of SCLC

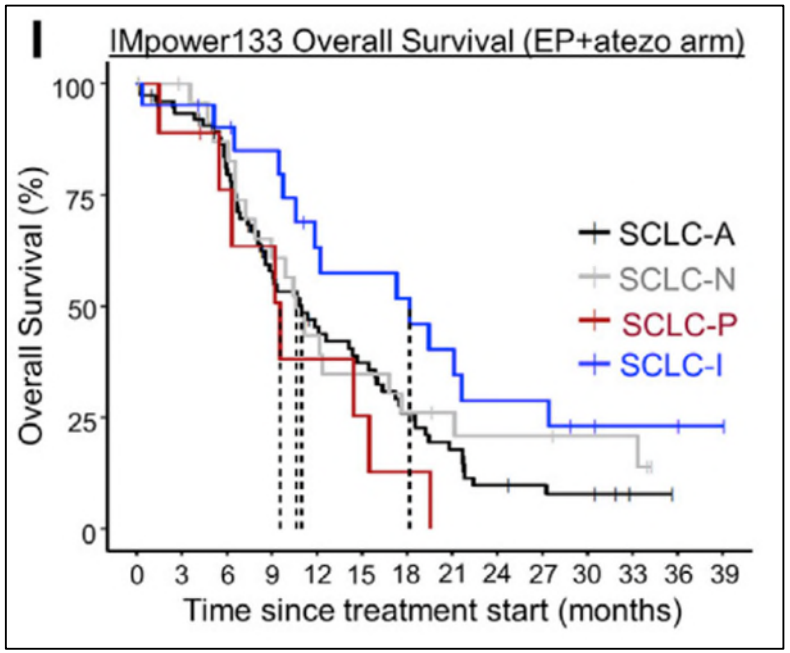
- Differential Expression of ASCL1, NEUROD1, POU2F3
- Inflamed SCLC has low expression of ASCL1, NEUROD1 and POU2F3

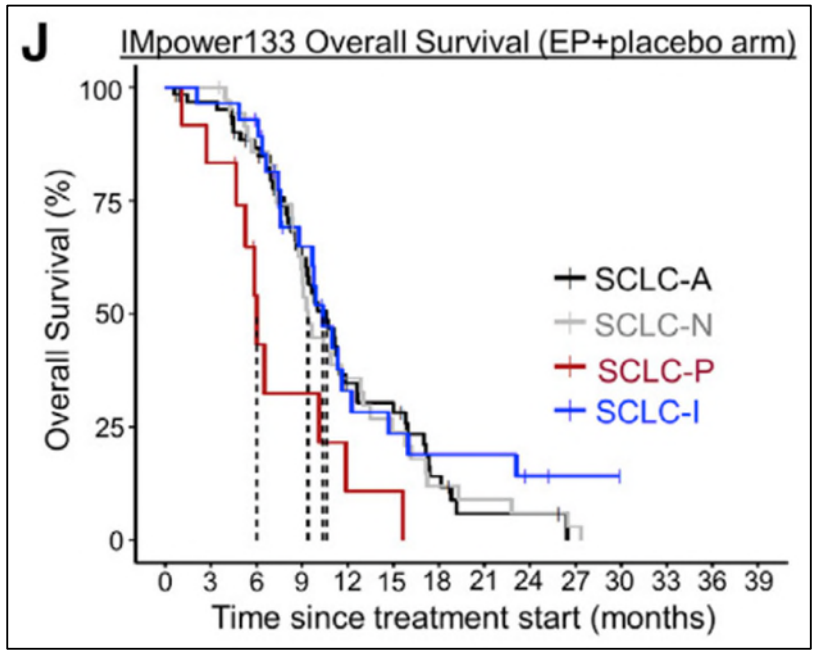


Gay CM et al., 2021, Cancer Cell 39, 1–15 March 8, 2021

SCLC transcriptional subtyping as a predictive biomarker of anti-PD-L1 therapy in Impower133 trial







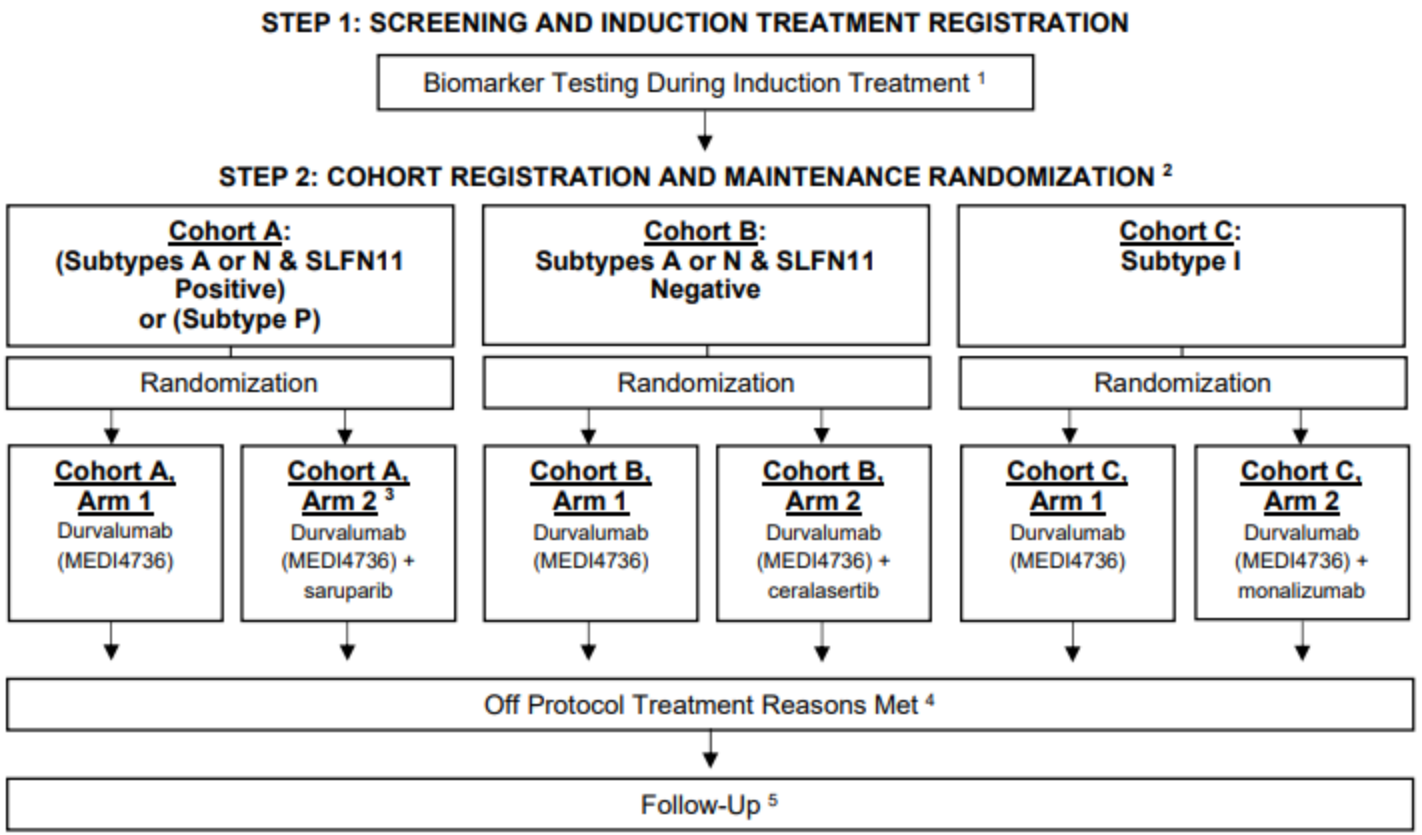
SCLC-I showed most benefit from IO in this exploratory analysis

Gay CM et al., 2021, Cancer Cell 39, 1–15 March 8, 2021

Phase II PRISM Study: S2409

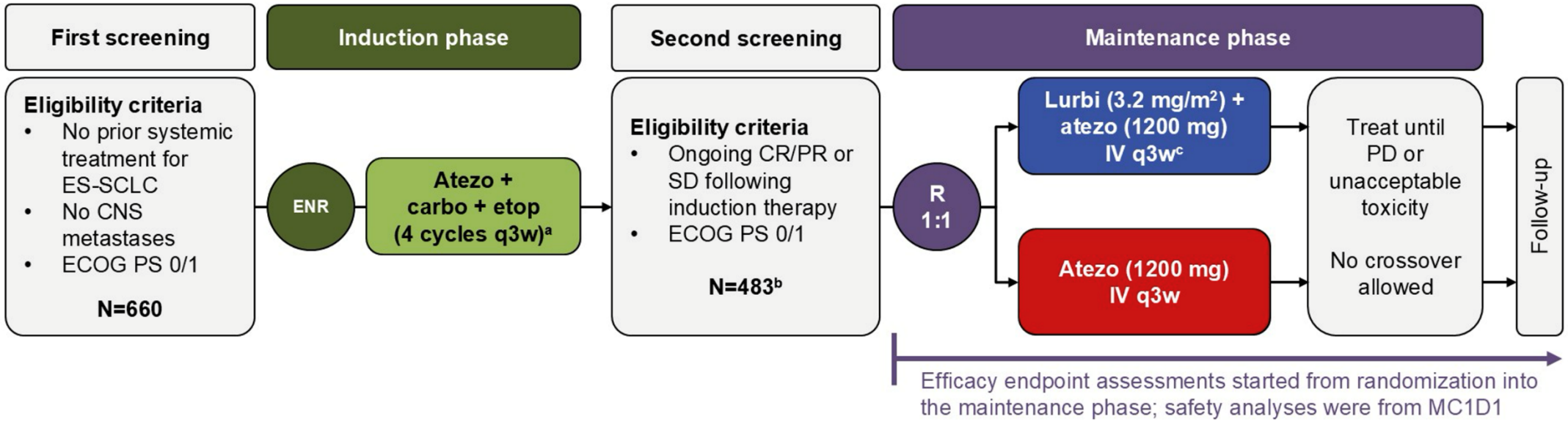
PRecIsion in SCLC Via a Multicohort Study: Randomized Phase II Studies Evaluating Maintenance Durvalumab with or Without Biomarker-Directed Therapy for Extensive Stage Small Cell Lung Cancer (ES-SCLC)

SCHEMA



Enhancing Maintenance Therapy in SCLC

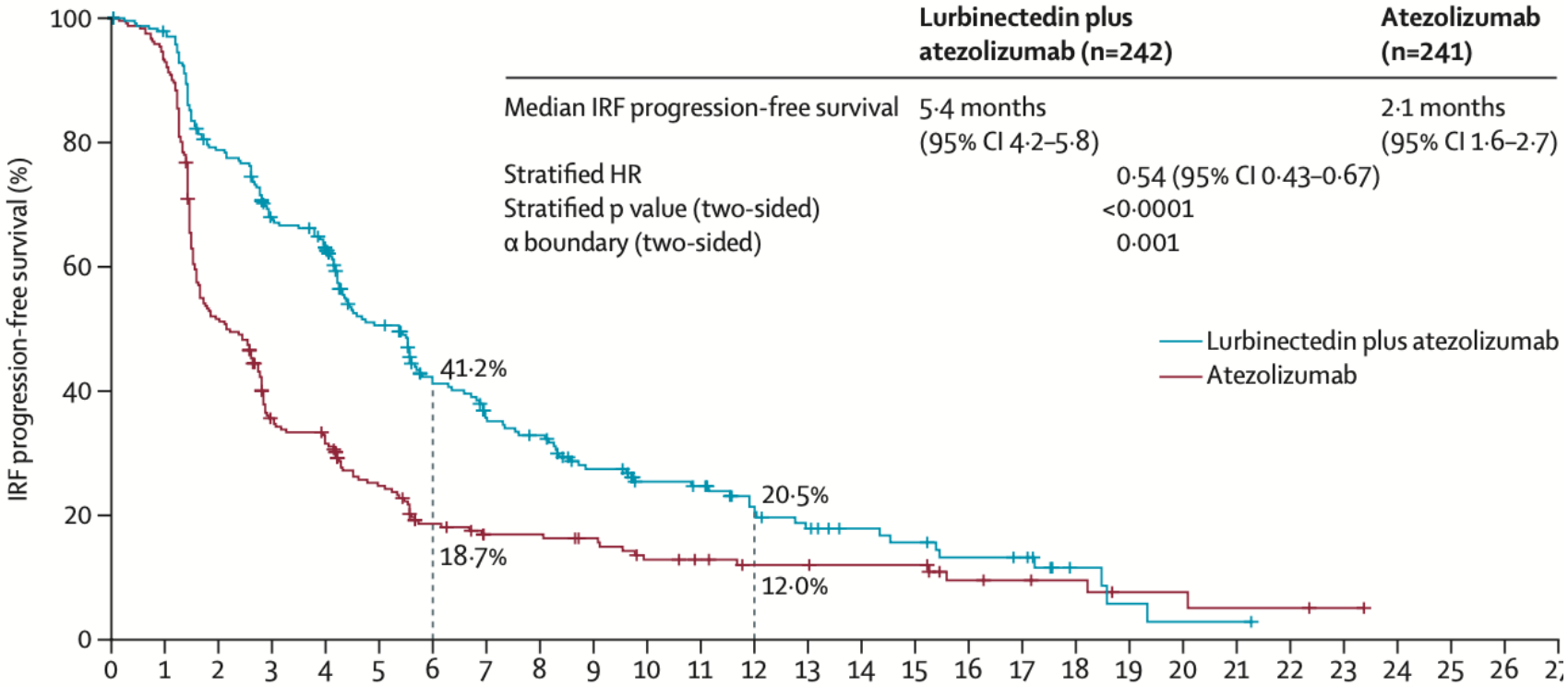
- Most patients will still progress on immunotherapy
- Less than 50% of patients receive any second line therapy
- Will delivering novel therapy before progression improve outcomes?



Paz-Ares, ASCO 2025

IMforte: Maintenance Lurbinectedin and SCLC

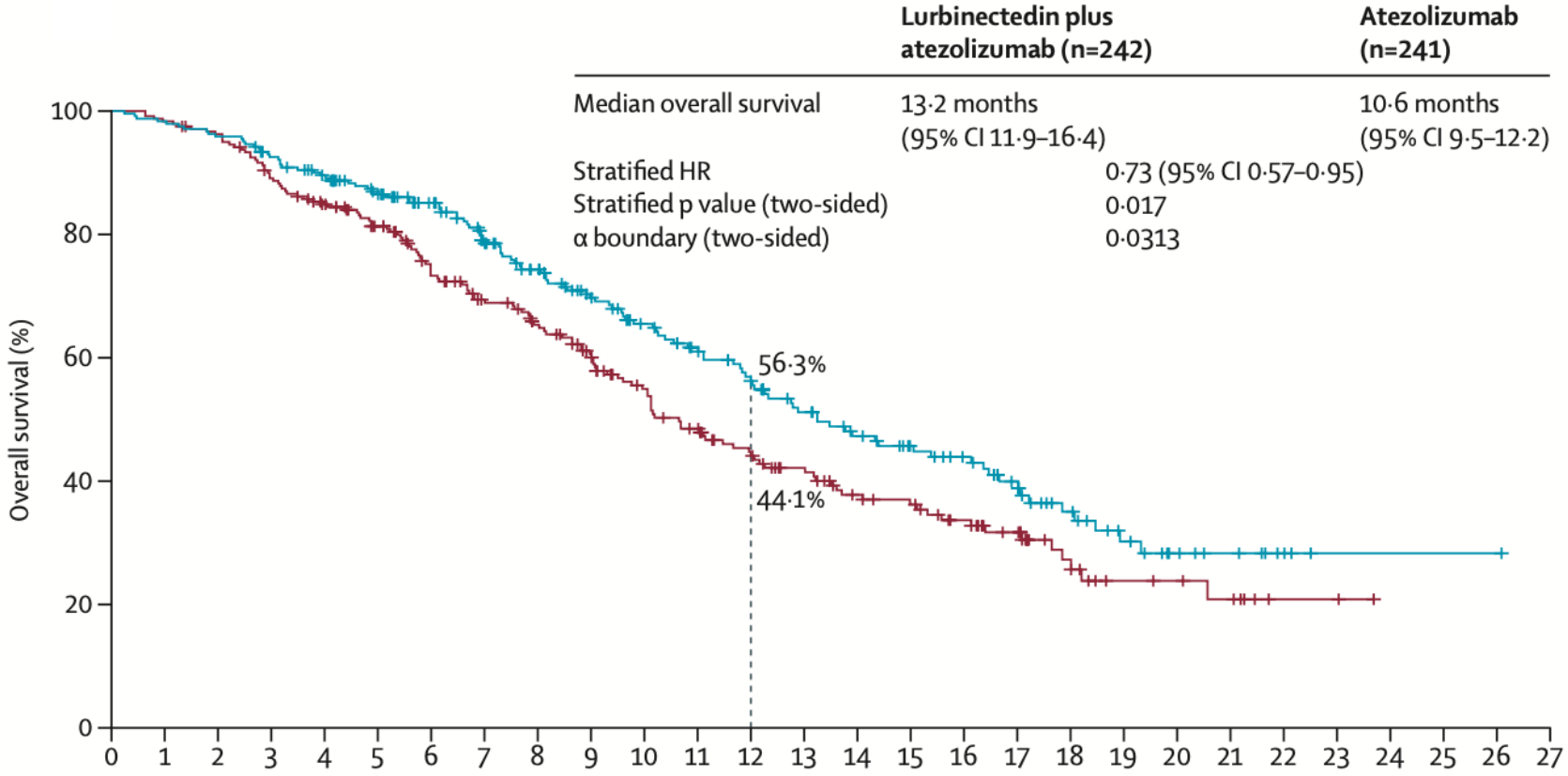
- Adding lurbinectedin to maintenance atezolizumab improves PFS
  - PFS HR 0.54
    - 5.4m vs 2.1m



Paz-Ares, Lancet 2025

IMforte: Maintenance Lurbinectedin and SCLC

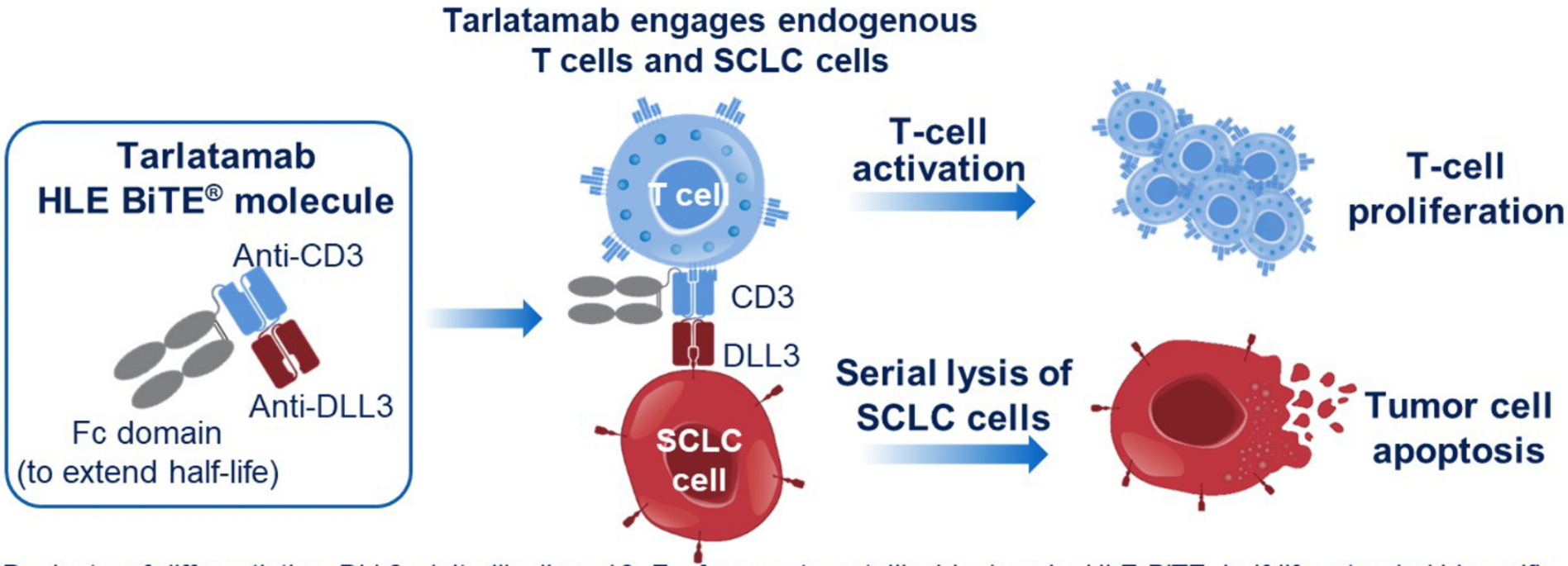
- Adding lurbinectedin to maintenance atezolizumab improves OS
  - PFS HR 0.54
    - 5.4m vs 2.1m
  - OS HR 0.73
    - 13.2m vs 10.6m



Paz-Ares, Lancet 2025

T-Cell Engagers

- Tarlatamab – Bispecific T-cell Engager (BiTE) targeting DLL3 and CD3



CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

Owonikoko, ASCO 2021

The NEW ENGLAND JOURNAL of MEDICINE

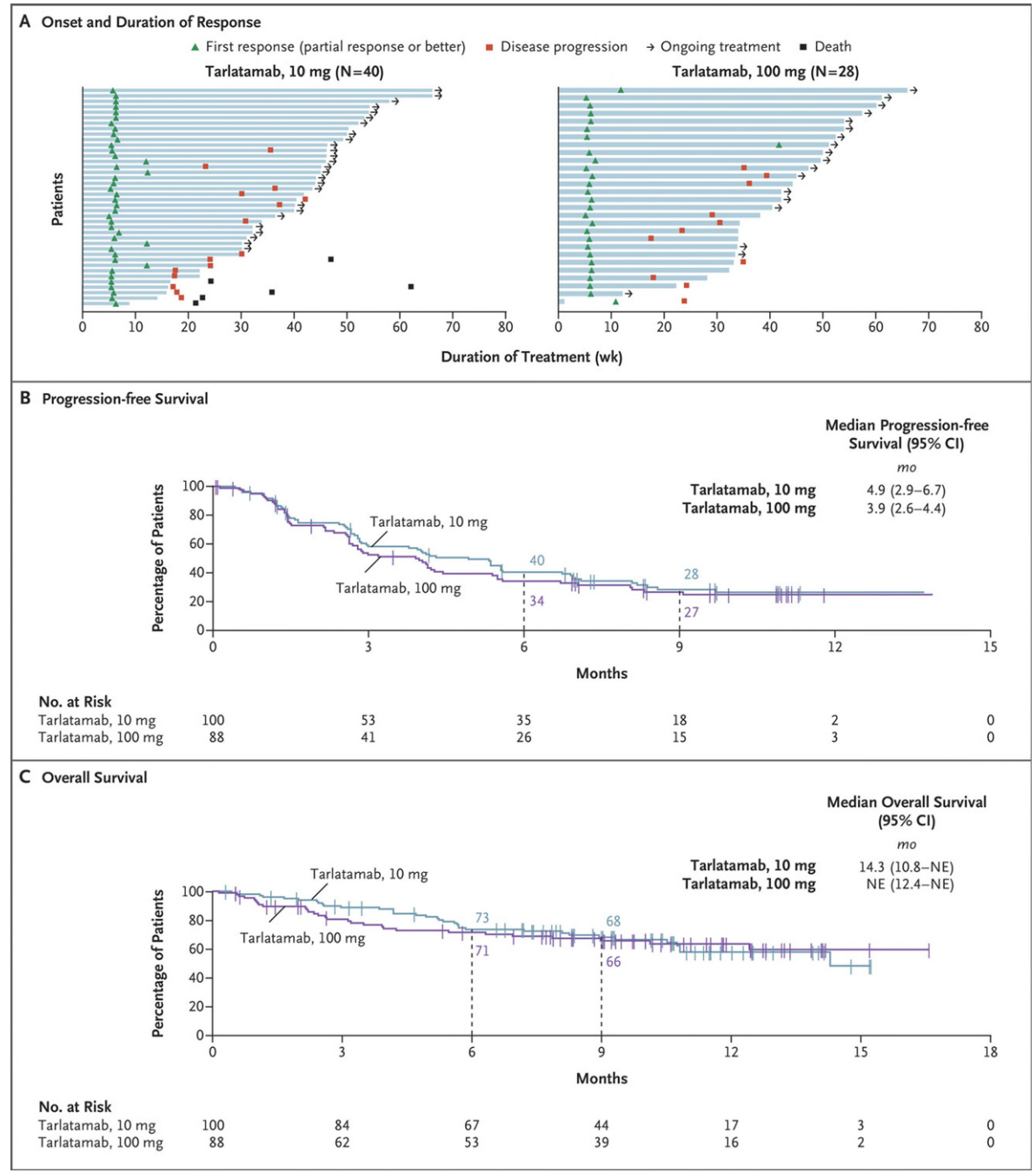
ORIGINAL ARTICLE

Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

M.-J. Ahn, B.C. Cho, E. Felip, I. Korantzis, K. Ohashi, M. Majem, O. Juan-Vidal, S. Handzhiev, H. Izumi, J.-S. Lee, R. Dziadziuszko, J. Wolf, F. Blackhall, M. Reck, J. Bustamante Alvarez, H.-D. Hummel, A.-M.C. Dingemans, J. Sands, H. Akamatsu, T.K. Owonikoko, S.S. Ramalingam, H. Borghaei, M.L. Johnson, S. Huang, S. Mukherjee, M. Minocha, T. Jiang, P. Martinez, E.S. Anderson, and L. Paz-Ares, for the DeLLphi-301 Investigators*

FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer

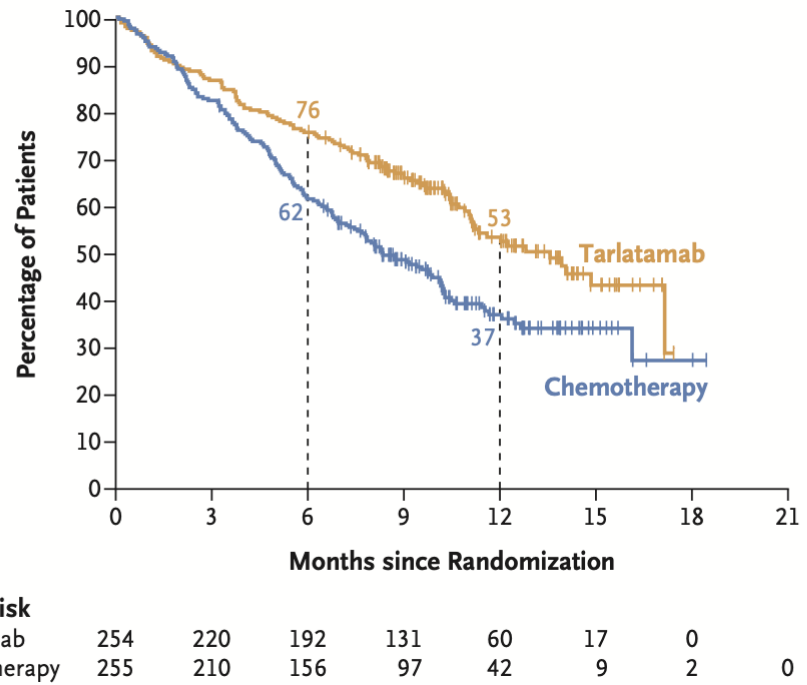
On May 16, 2024, the Food and Drug Administration granted accelerated approval to tarlatamab-dlle (Imdelltra, Amgen, Inc.) for extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.



Ahn, NEJM 2023

Tarlatamab

- Phase III DeLLphi-304
- Tarlatamab superior to 2L chemotherapy
- PFS HR 0.71
  - Median PFS 5.3 vs 4.3m
- OS HR 0.60
  - Median OS 13.6m vs 8.3m
- FDA approved 5/16/24



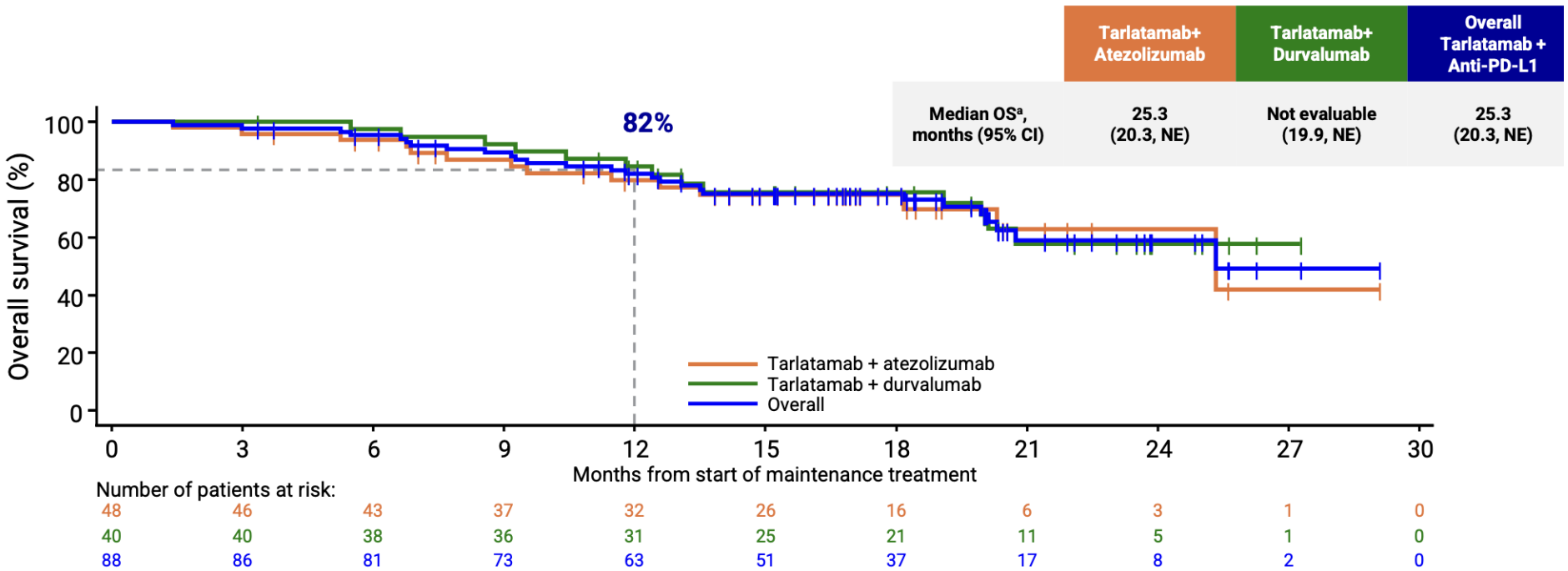
	Median Overall Survival (95% CI)
	mo
Tarlatamab (N=254)	13.6 (11.1–NR)
Chemotherapy (N=255)	8.3 (7.0–10.2)

Stratified hazard ratio for death, 0.60 (95% CI, 0.47–0.77)
P<0.001

Mountzios, NEJM 2025

Tarlatamab

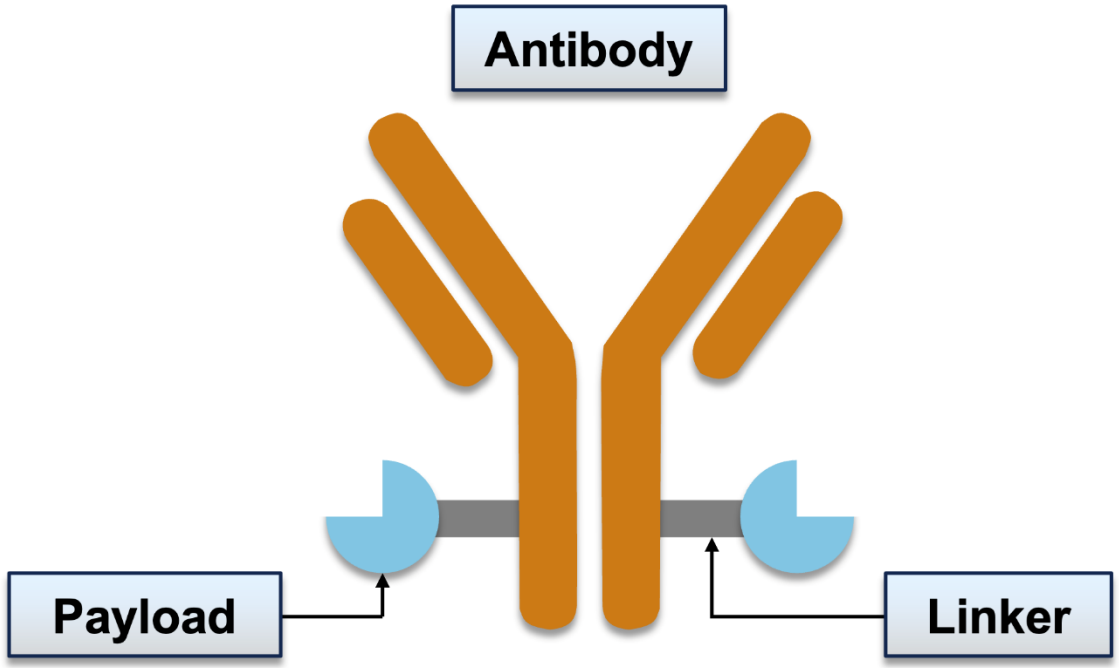
- Phase Ib DeLLphi-303
  - Maintenance tarlatamab + atezolizumab/durvalumab after chemo-immunotherapy
  - PFS 5.6m, OS 25.3m, RR 24%, ongoing randomized trials



Paulson, WCLC 2025

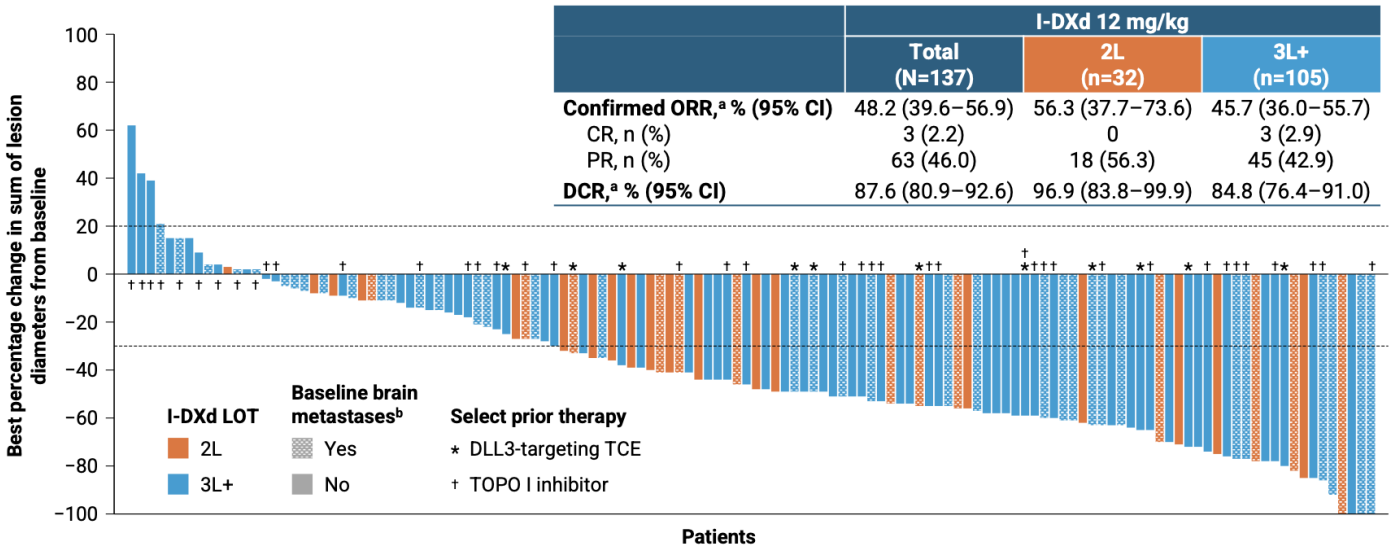
Antibody Drug Conjugates (ADCs)

- Targeted delivery of cytotoxic payload
- Many appealing targets in SCLC

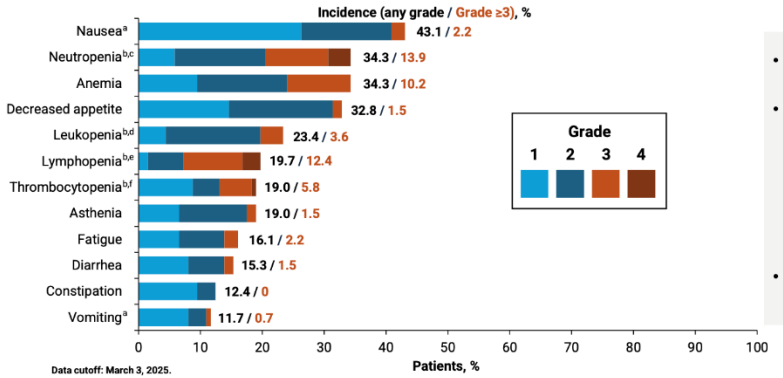


ADCs in SCLC: B7-H3

- Ifinatamab deruxtecan (I-DXd): B7-H3 IgG1 + topoisomerase I inhibitor
  - IDeate-Lung01: I-DXd at 12mg/kg q3w dosing
  - RR 48.2%, DCR 87.6%, TTR 1.4m, DOR 5.3m, mPFS 4.9m, mOS 10.3m
  - Adjudicated ILD rate 12.4% (8% G1-2, 3% G3, 1.5% G5)



	I-DXd 12 mg/kg		
	Total (N=137)	2L (n=32)	3L+ (n=105)
Confirmed ORR,[a] % (95% CI)	48.2 (39.6–56.9)	56.3 (37.7–73.6)	45.7 (36.0–55.7)
CR, n (%)	3 (2.2)	0	3 (2.9)
PR, n (%)	63 (46.0)	18 (56.3)	45 (42.9)
DCR,[a] % (95% CI)	87.6 (80.9–92.6)	96.9 (83.8–99.9)	84.8 (76.4–91.0)



- Among the most common TRAEs, the majority were Grade 1 or 2
- Adjudicated treatment-related ILD/pneumonitis was reported in 17 (12.4%) patients:
  - Grade 1 or 2, n=11 (8.0%)
  - Grade 3, n=4 (2.9%)
  - Grade 5, n=2 (1.5%)[g]
- No ILD events were pending adjudication at data cutoff

Ahn, WCLC 2025

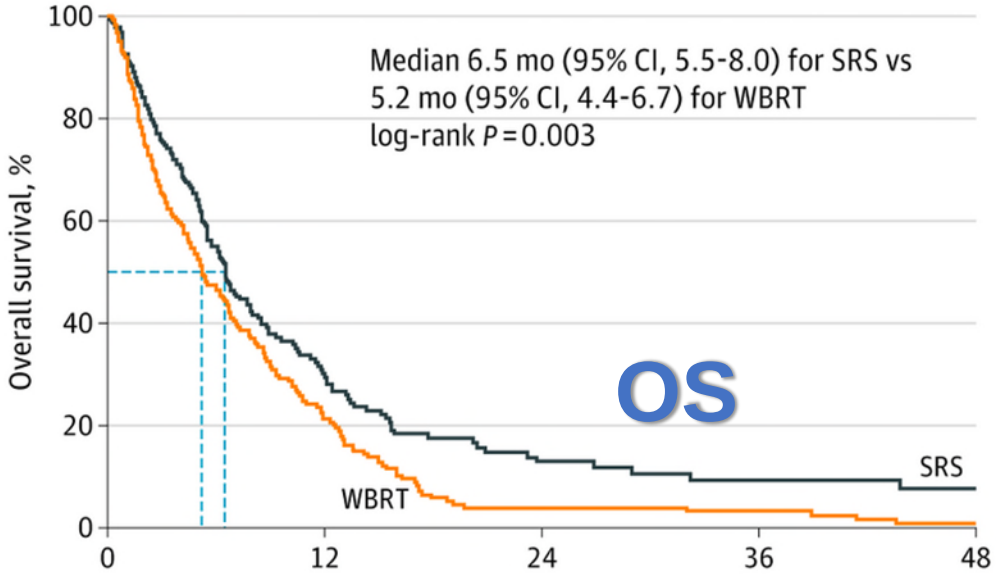
Treatment of Small Cell Lung Cancer Brain Metastases

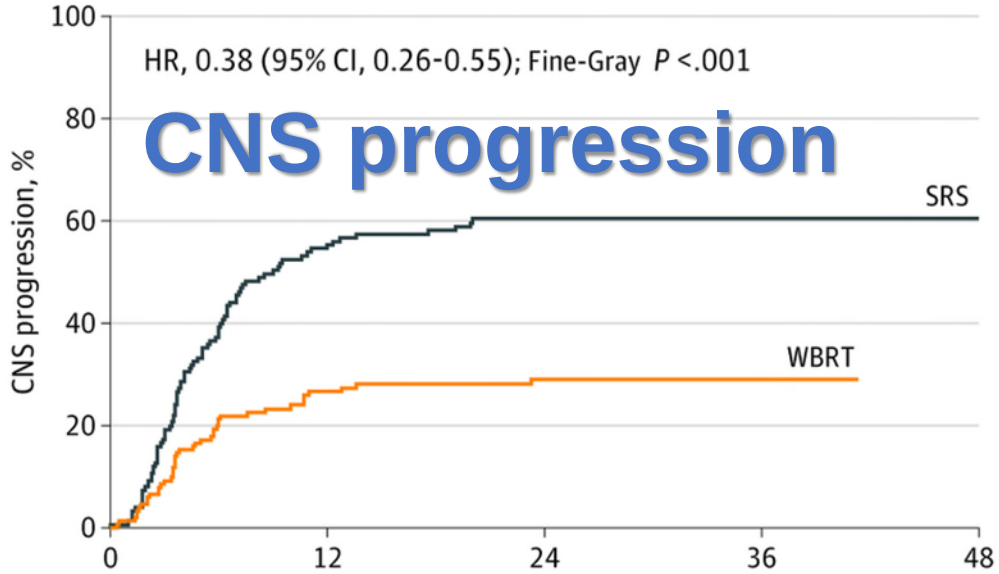
Optimal Treatment of SCLC Brain Metastases?

- Whole-brain radiotherapy is standard of care for small-cell lung cancer brain metastases
  - Prior brain metastasis trials of SRS vs WBRT or HA-WBRT did not include patients with small-cell lung cancer

- Cognitive toxicity from WBRT
  - Mitigated with SRS alone, memantine, and hippocampal avoidance
  - Historic objections to SRS in small-cell are related to concerns for short interval CNS progression impacting OS

First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The *FIRE-SCLC* Cohort Study





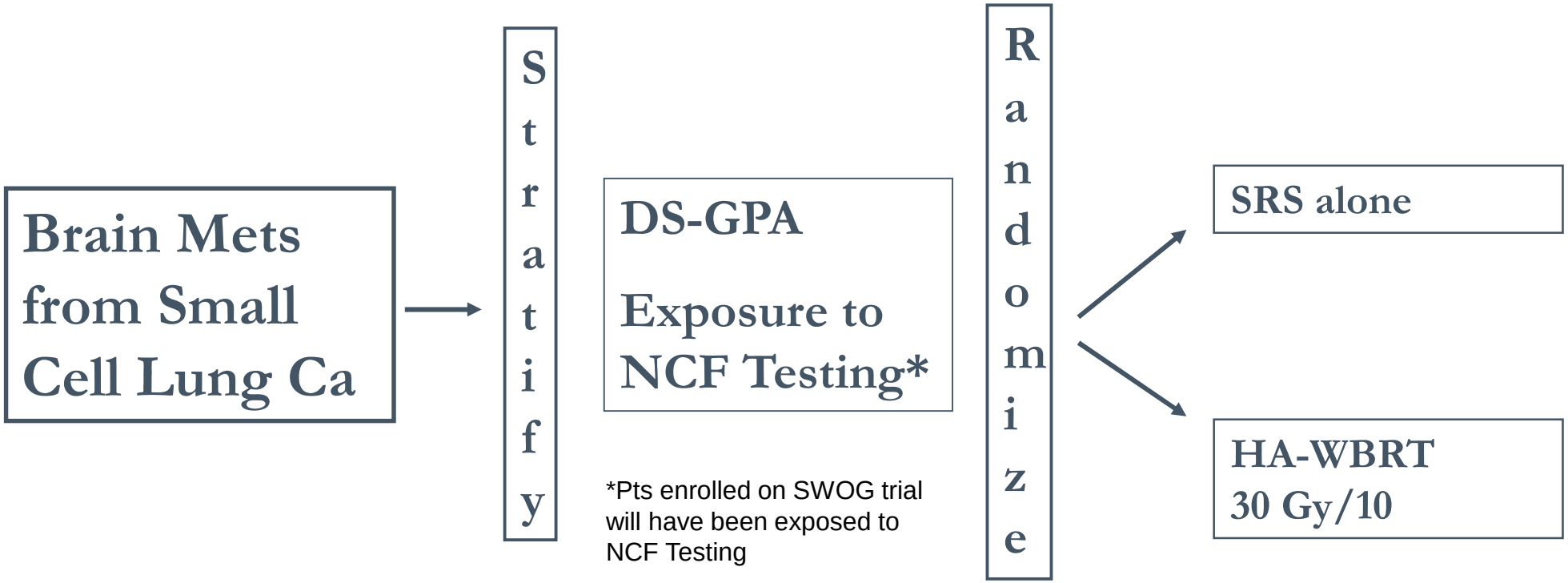
- Retrospective (28 centers in Asia, North America, Europe)
- 710 patients treated with first-line SRS without prior PCI or WBRT
- Propensity score matched analyses demonstrated superior time to CNS progression with WBRT, but no OS advantage
- After SRS, 34% underwent salvage SRS vs 16% salvage WBRT
- Leptomeningeal progression (10.8%), neurological mortality (12.4%)

Rusthoven et al., *JAMA Oncology*. 2020 Jun 4

NRG CC009: Phase III Trial Stereotactic Radiosurgery versus Hippocampal-Avoidant Whole-Brain Radiotherapy for 10 or Fewer Brain Metastases from Small Cell Lung Cancer

PIs: Vinai Gondi (Northwestern) + Chad Rusthoven (Univ of Colorado)

Basic Eligibility: Small cell lung cancer; ≤10 brain mets≤3cm; total vol 30cc; KPS≥70



Sample Size: 200 patients

Primary endpt: Time to cognitive failure--HVLT-R, COWA, and TMT A and B

Basic Statistical Design:
Cognitive fxn failure 58.8% at 6 mos with HA-WBRT+mem vs. 41.8% at 6 mos with SRS.
150 analyzable pts

NRG ONCOLOGY™

Conclusions

- New therapeutic options are finally here for small cell lung cancer
  - Systemic therapy and RT approaches continue to evolve
- Lots of opportunities for young investigators with new ideas in the small cell lung cancer space
- Clinical trials will continue to advance therapies for SCLC
  - Please offer these pts trials whenever possible!

@KHigginsMD