



The Role of Radiation Therapy in Small Cell Lung Cancer

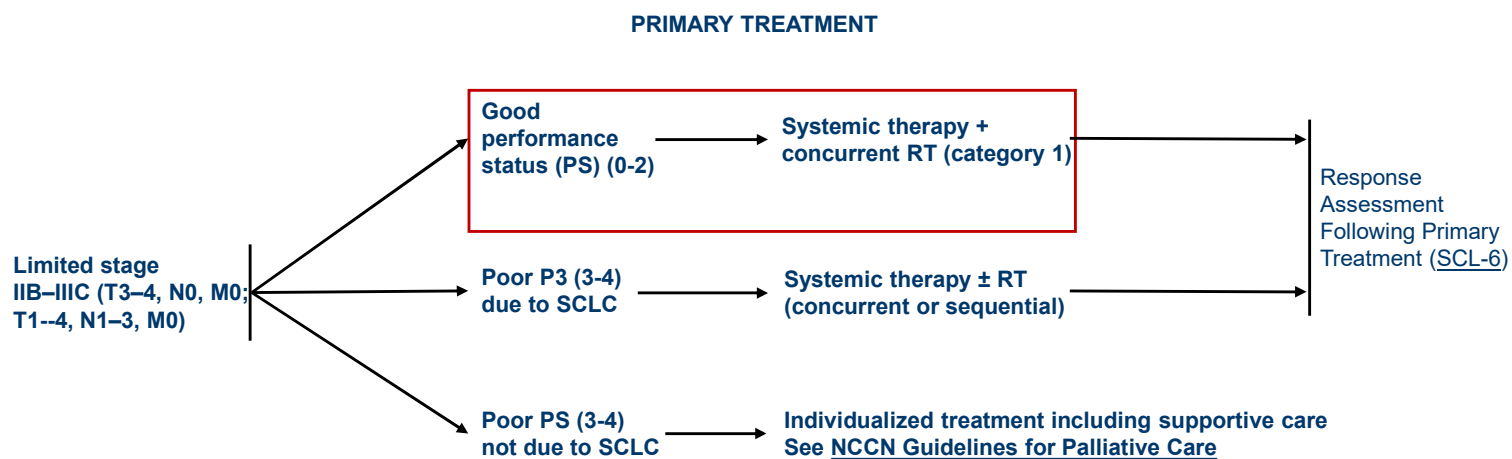
Aditya Juloori, MD

The UChicago Medicine Comprehensive Cancer Center



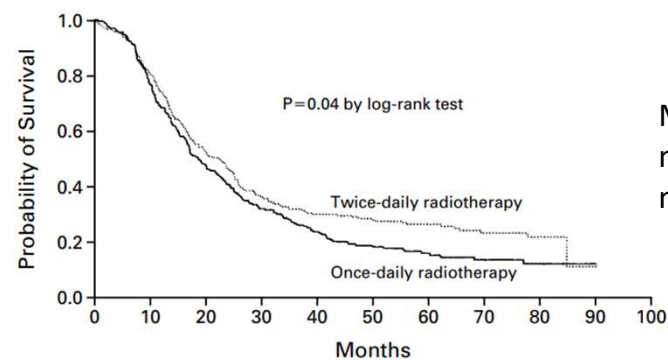
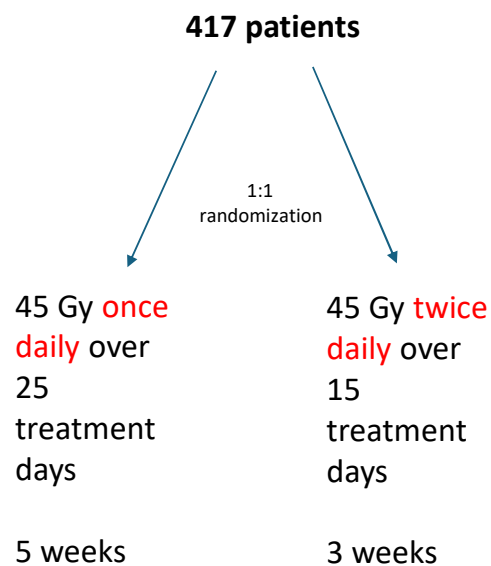
National Comprehensive
Cancer Network®

Limited Stage Small Cell Lung Cancer: Radiation Therapy



The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer (Version 2.2026). SCL-4.
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Fractionation Schedule



Median OS 23
months vs 19
months

TREATMENT GROUP	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

5-year OS 26% vs
16%

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

Turrisi et al, NEJM 1999

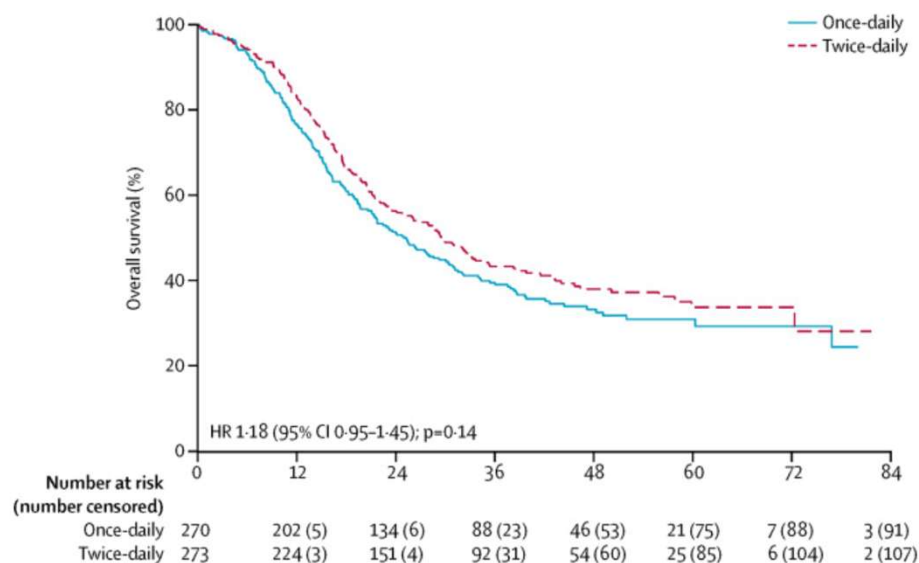


Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial



Corinne Faivre-Finn, Michael Snee, Linda Ashcroft, Wiebke Appel, Fabrice Barlesi, Adityanarayan Bhatnagar, Andrea Bezjak, Felipe Cardenal, Pierre Fournel, Susan Harden, Cecile Le Pechoux, Rhona McMenemin, Nazia Mohammed, Mary O'Brien, Jason Pantarotto, Veerle Surmont, Jan P Van Meerbeeck, Penella J Woll, Paul Lorigan, Fiona Blackhall, for the CONVERT Study Team

CONVERT Trial – Daily vs BID



- 45 Gy BID vs 66 Gy once daily
- Phase III RCT
- 547 patients
- Median OS 30 months vs 25 months (p = ns)

Faivre-Finn, C. et al. (2017) *The Lancet Oncology*

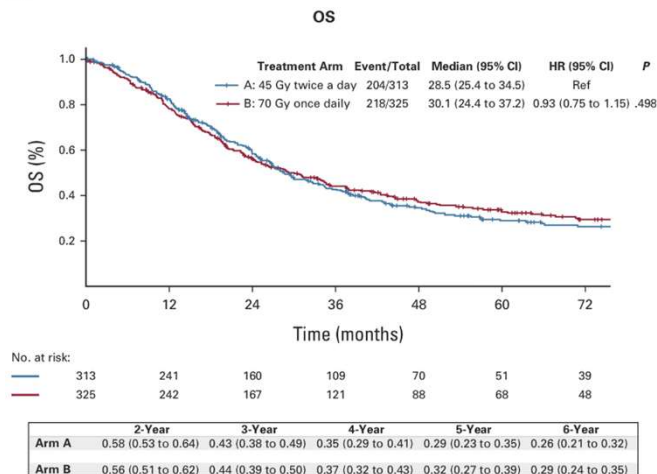
original reports

High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538

Jeffrey Bogart, MD¹; Xiaofei Wang, MD²; Gregory Masters, MD³; Junheng Gao, MD²; Ritsuko Komaki, MD⁴; Laurie E. Gaspar, MD^{5,6}; John Heymach, MD⁴; James Bonner, MD⁷; Charles Kuzma, MD⁸; Saiama Waqar, MD⁹; William Petty, MD¹⁰; Thomas E. Stinchcombe, MD¹¹; Jeffrey D. Bradley, MD¹²; and Everett Vokes, MD¹³

CALGB 30610 – Daily vs BID

A

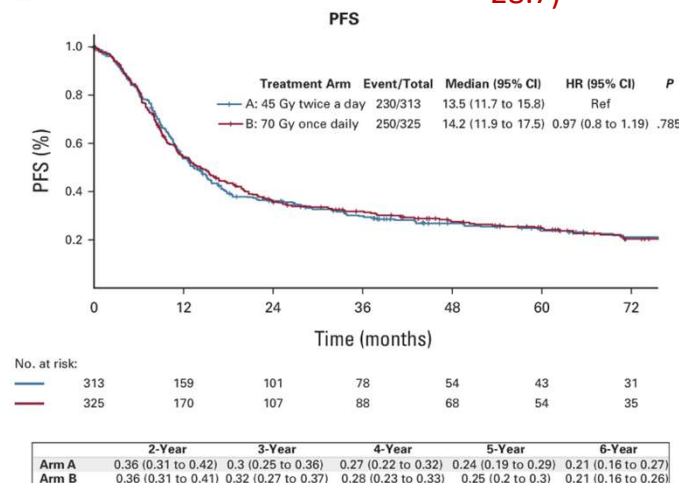


638 patients

45 Gy BID (standard arm) vs **70 Gy** once daily

No difference in OS (median 30.5 mo vs 28.7)

B



JCO 2023, Bogart et al. – CALGB 30610/ RTOG 0538 Trial

High Dose BID?

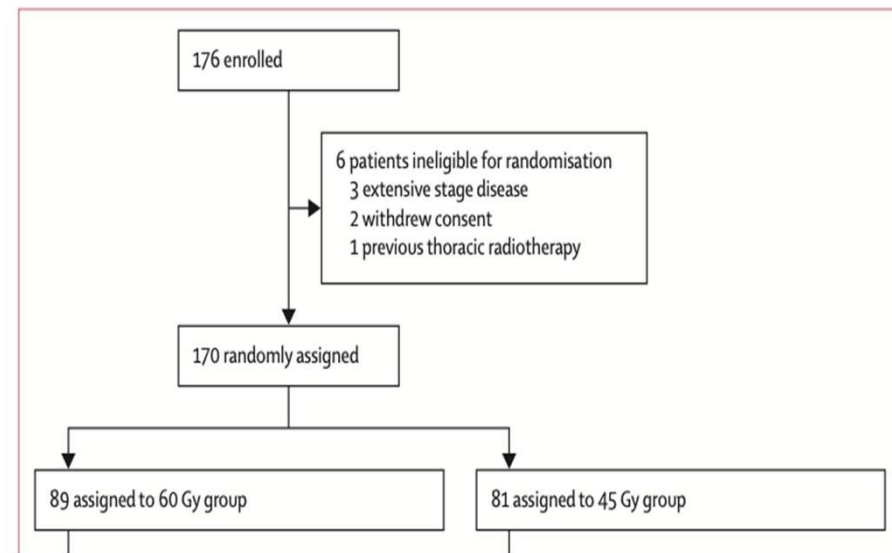
High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

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

Grønberg et al, Lancet Oncology

High Dose BID?

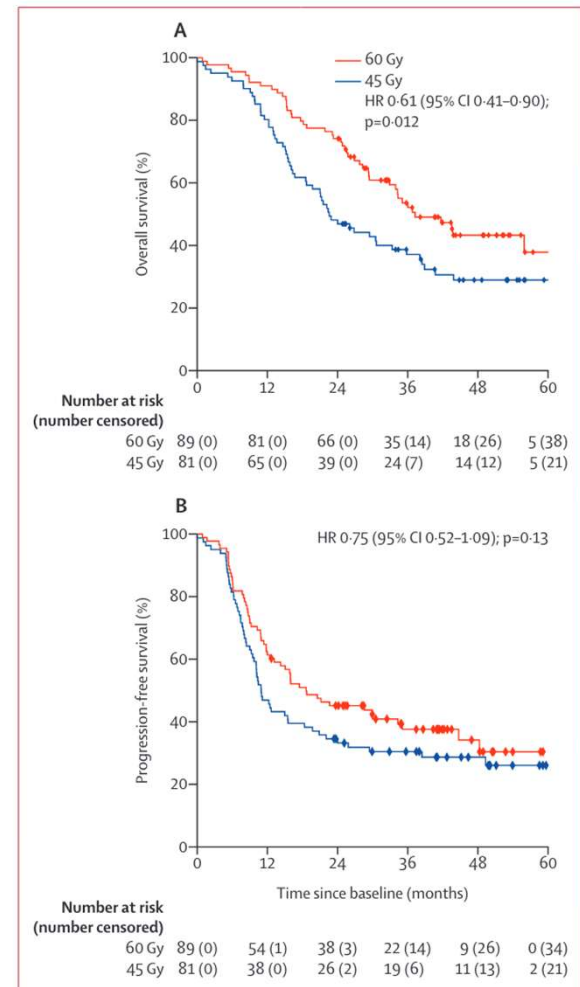
- 45 Gy BID vs 60 Gy BID
- 170 patients in randomized phase II study
- Primary endpoint: 2-year OS



Grønberg et al, Lancet Oncology

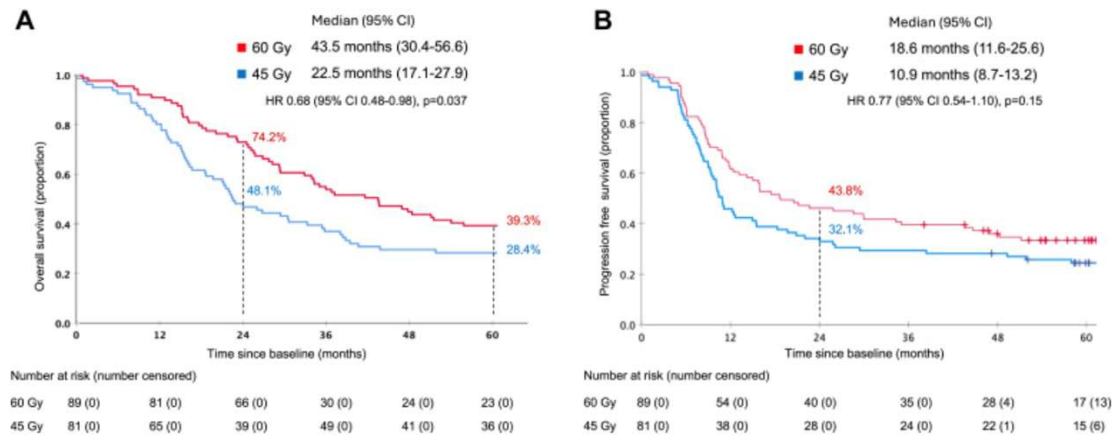
High Dose BID?

- 2-year OS improved: 74% vs 48%
- Similar acute toxicity profiles
- No statistically significant difference in PFS



Grønberg et al, Lancet Oncology

High Dose BID?



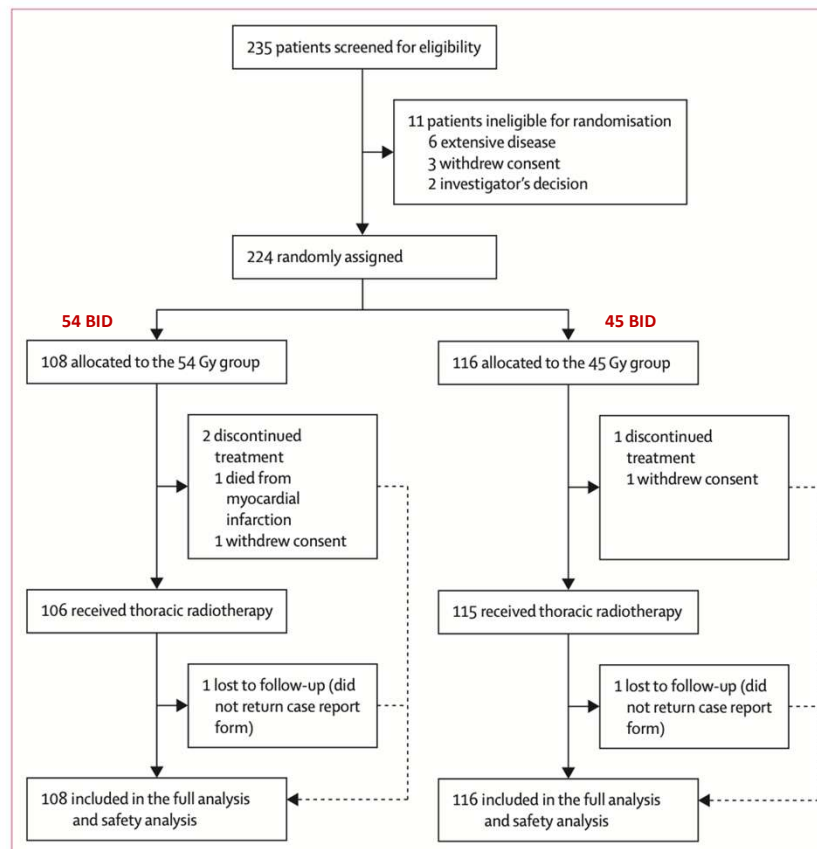
Grønberg et al, Lancet Oncology

High Dose BID?

High-dose hyperfractionated simultaneous integrated boost radiotherapy versus standard-dose radiotherapy for limited-stage small-cell lung cancer in China: a multicentre, open-label, randomised, phase 3 trial

Jiayi Yu, Leilei Jiang*, Lina Zhao*, Xue Yang*, Xiaomin Wang*, Dan Yang, Minglei Zhuo, Hanxiao Chen, Wei Huang, Zhengfei Zhu, Min Zhang, Yipeng Song, Quanfu Li, Zhanshu Ma, Qifeng Wang, Yanli Qu, Rong Yu, Huiming Yu, Jun Zhao‡, Anhui Shi‡, for the Trial Management Group§*

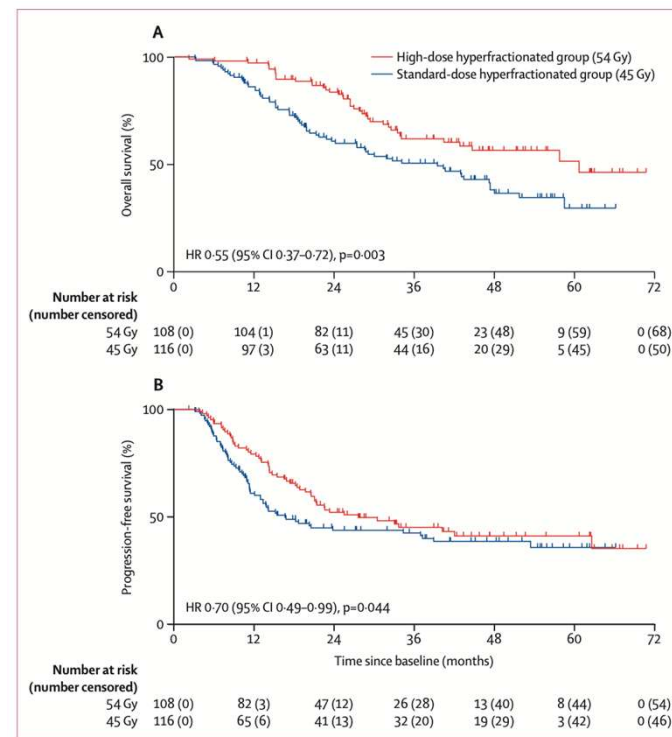
High Dose BID?



Yu et al, Lancet Respir Medicine 2024

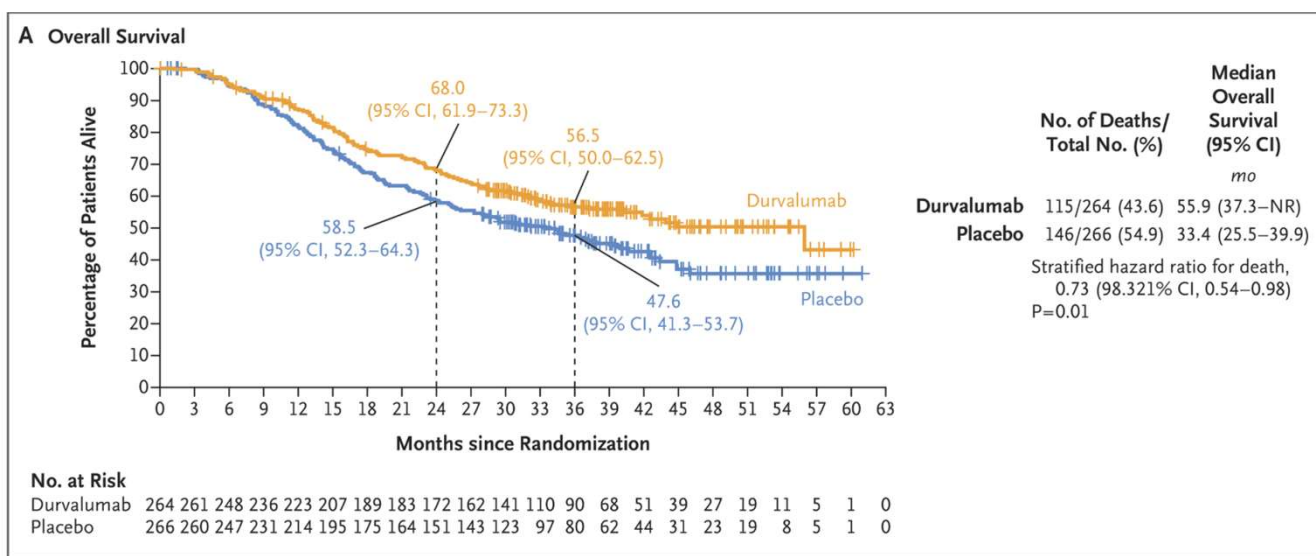
High Dose BID?

- Median OS 60.7 months vs 39.5 months HR 0.55, $p=0.003$
- Grade 3+ esophagitis (13% vs 12%) and pneumonitis (5% vs 6%) similar between arms
- Recruitment planned for 326 patients, study stopped early based on interim efficacy analysis



Yu et al, Lancet Respir Medicine 2024

ADRIATIC

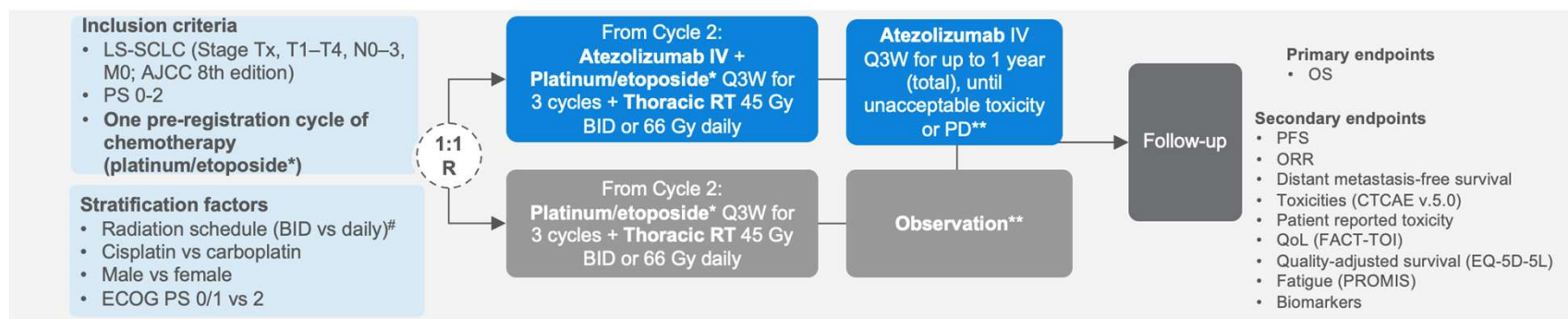


Cheng et al, NEJM, 2024

NRG LU-005

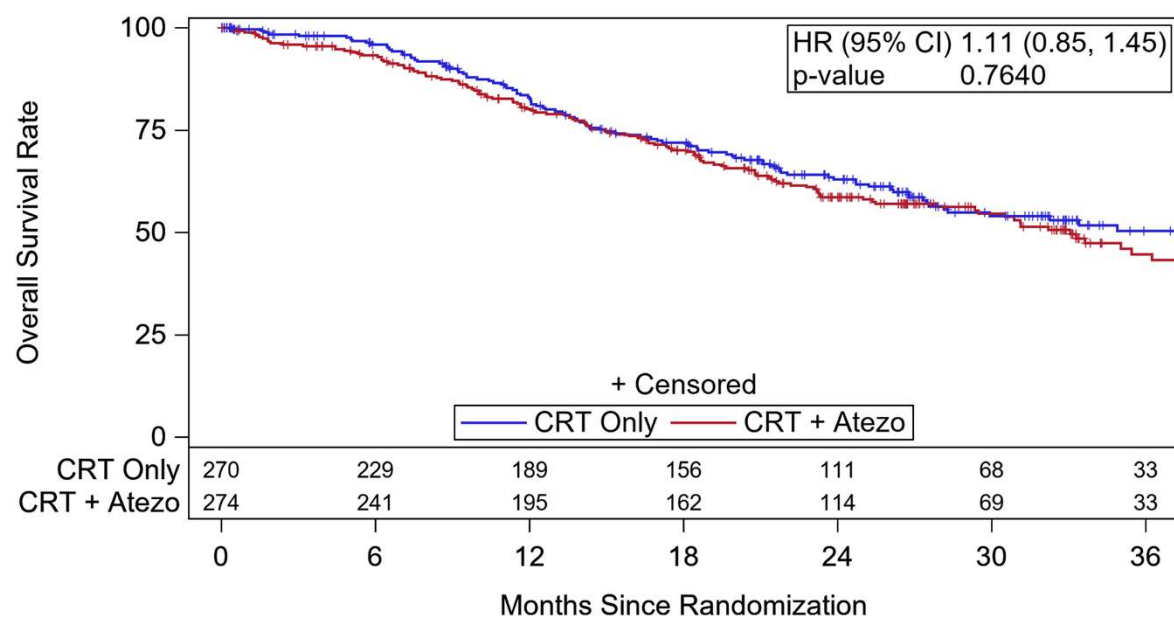
Phase III (N = 544; US & Japanese sites)

NCT03811002



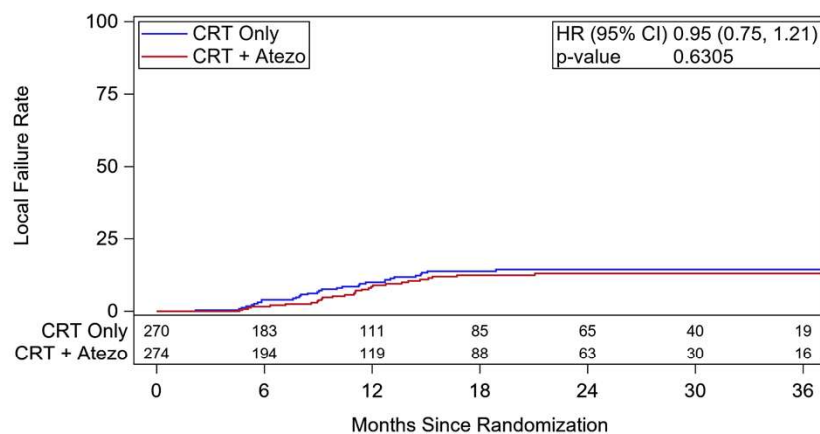
NRG Oncology

Overall Survival

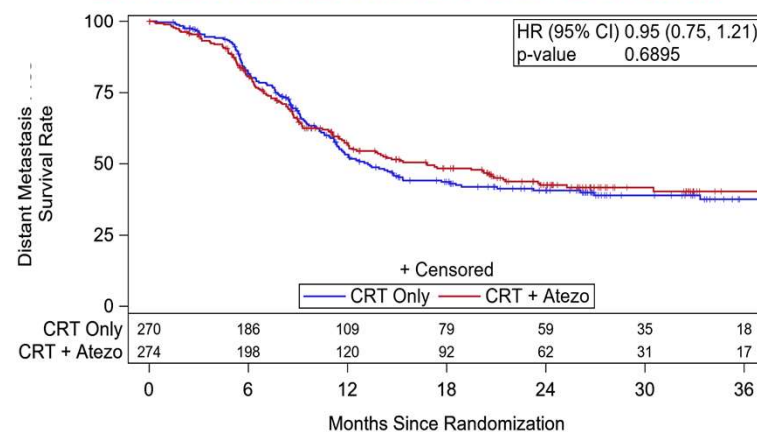


Slide courtesy of Kristen Higgins, ASTRO 2024d

Time to Local Failure



Distant Metastasis Free Survival



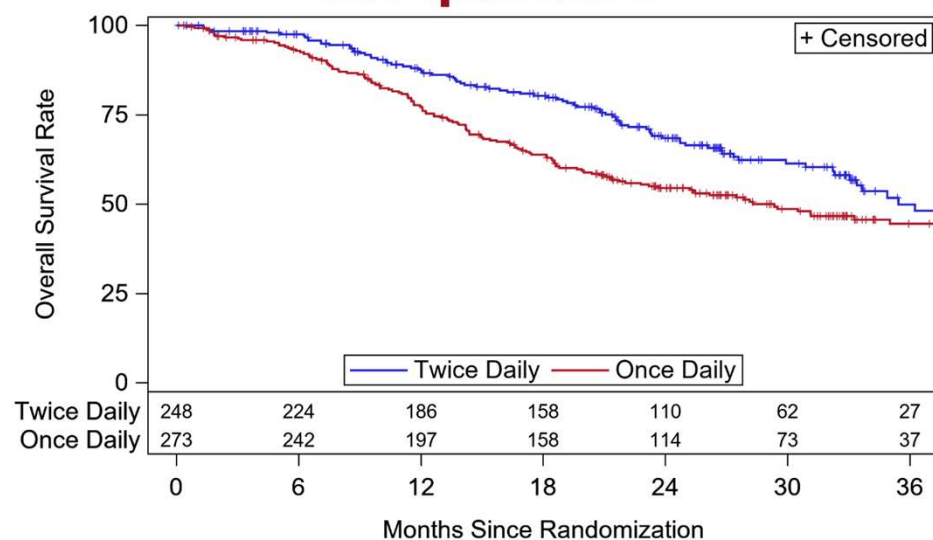
Slide courtesy of Kristen Higgins, ASTRO 2024d

Pneumonitis

	CRT Only (n = 254)	CRT + Atezo (n = 267)
Any grade	30 (11.8)	70 (26.2)
Grade 3/4	8 (3.2)	13 (4.9)
Grade 5	0 (0)	2 (0.7)

Slide courtesy of Kristen Higgins, ASTRO 2024d

Overall Survival: Unadjusted RT Schedule Comparison



Slide courtesy of Kristen Higgins, ASTRO 2024d

Radiotherapy in Advanced SCLC

- Radiotherapy has multiple potential uses in extensive-stage and/or systemic treatment refractory small cell lung cancer
 - Palliation of symptoms (bone metastasis, airway obstruction/bleeding, etc)
 - Intracranial control for brain metastasis (SRS versus whole brain)
 - Consolidation of disease in ES-SCLC patients with initial response to first-line therapy

Standard Treatment Schemes in Small Cell Lung Cancer

- Definitive treatment (with chemotherapy): 45 Gy BID or 66 Gy in 33 daily fractions
- Palliative doses: 8 Gy in 1 fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions

Management of CNS Disease

- Open Questions:

- HA-WBRT vs Stereotactic Radiosurgery
- PCI versus observation/surveillance MRI

Prophylactic Cranial Irradiation (PCI)?

TABLE 1. CHARACTERISTICS OF THE SEVEN TRIALS INCLUDED IN THE META-ANALYSIS.*

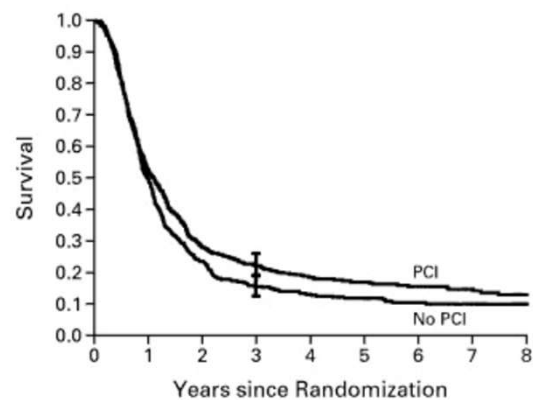
TRIAL	ENROLLMENT PERIOD	MEDIAN FOLLOW-UP	INDUCTION THERAPY	TOTAL DOSE/ NO. OF FRACTIONS (DOSE/FRACTION)	MEDIAN TIME BETWEEN START OF INDUCTION THERAPY AND ENROLLMENT	NO. OF PATIENTS	NO. OF PATIENTS SURVIVING
		yr			mo		
UMCC ²⁹	1977–1980	18.5	CT	30 Gy/10 (3 Gy)	3.6	29	2
Okayama ³⁰	1981–1986	11.7	CT or CT plus RT	40 Gy/20 (2 Gy)	2.5	46	4
PCI-85 ⁵	1985–1993	8.4	CT or CT plus RT	24 Gy/8 (3 Gy)	5.3	300	32
Danish–NCI (unpublished)	1985–1991	8.8	CT	24 Gy/8 (3 Gy)	4.4	55	7
UKCCCR–EORTC ¹⁵	1987–1995	3.5	CT or CT plus RT	8–36 Gy/1–18†	NA	314	54
PCI-88 ³¹	1988–1994	5.1	CT or CT plus RT	24 Gy/8 (3 Gy)	5.1	211	37
ECOG–RTOG ³²	1991–1994	3.9	CT or CT plus RT	25 Gy/10 (2.5 Gy)	NA	32	5

*UMCC denotes University of Maryland Cancer Center, CT chemotherapy, RT thoracic radiotherapy, PCI-85 the Prophylactic Cranial Irradiation trial started in 1985, NCI National Cancer Institute, UKCCCR–EORTC United Kingdom Coordinating Committee for Cancer Research–European Organisation for Research and Treatment of Cancer, NA not available, PCI-88 the Prophylactic Cranial Irradiation trial started in 1988, and ECOG–RTOG Eastern Cooperative Oncology Group–Radiation Therapy Oncology Group.

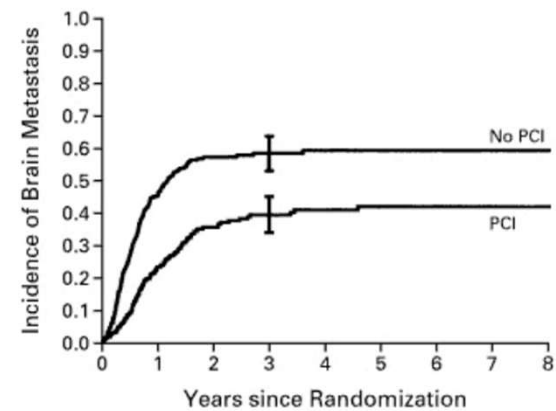
†During the first period of the trial, there were three treatment groups: no prophylactic cranial irradiation, prophylactic cranial irradiation at a total dose of 24 Gy in 12 fractions, and prophylactic cranial irradiation at a total dose of 36 Gy in 18 fractions. During the second period of the trial, there were only two treatment groups: no prophylactic cranial irradiation and prophylactic cranial irradiation at various doses.

Auperin et al, NEJM 1999

PCI?



No. AT RISK									
No PCI	461	224	103	61	44	34	23	19	15
PCI	526	276	139	101	66	52	40	29	17



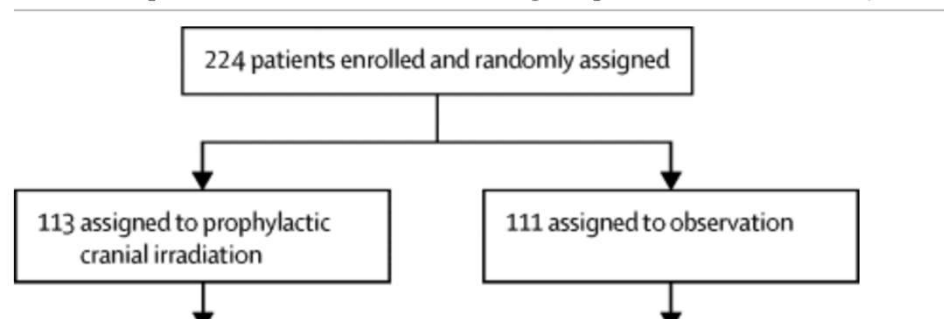
No. AT RISK									
No PCI	457	171	88	57	41	32	21	18	14
PCI	524	248	133	96	66	52	40	29	17

5.4% overall survival benefit at 3 years with use of PCI

Auperin et al, NEJM 1999

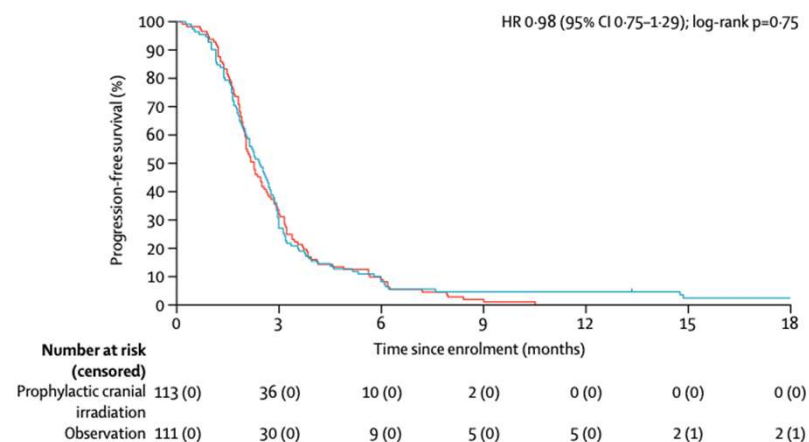
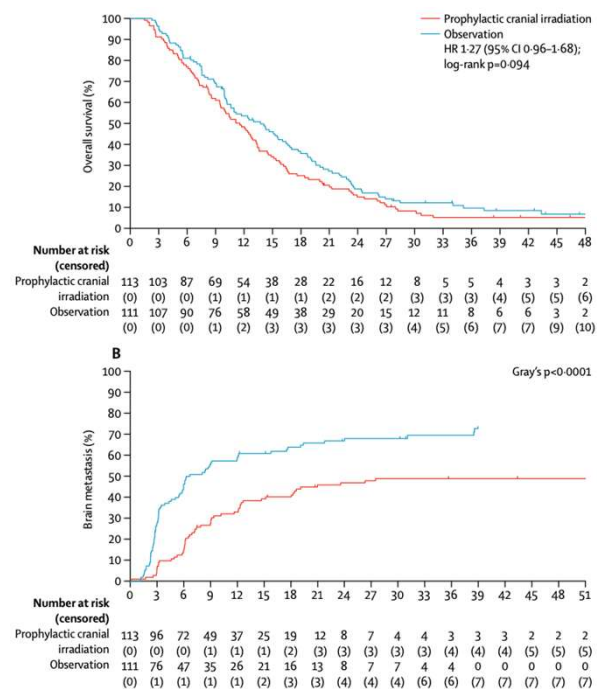
PCI in Extensive Stage?

Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial



Takahashi et al, Lancet Oncology 2017

PCI in Extensive Stage?

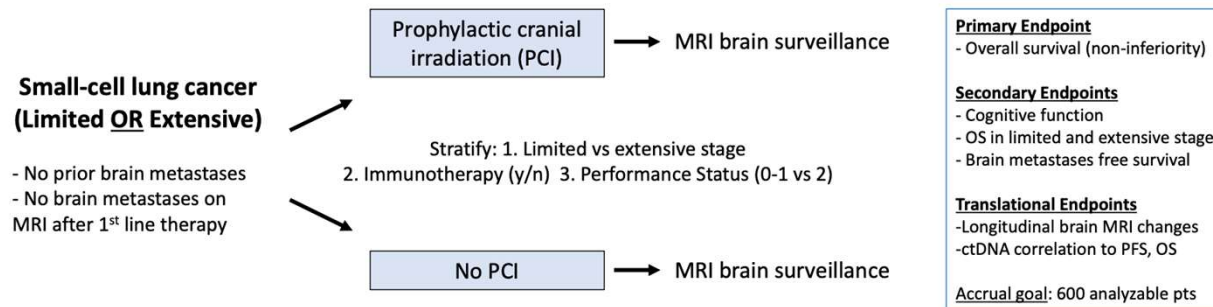


Takahashi et al, Lancet Oncology 2017

Radiation Therapy

MAVERICK (SWOG 1827)

MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation: A Randomized Phase III Trial in Small-Cell Lung Cancer



- MRI brain surveillance scheduled at 3, 6, 9, 12, 18, 24 months
- Hippocampal-avoidance PCI and WBRT are allowed
- Radiation therapy is recommended at the time of brain metastases (WBRT and SRS allowed)
- Patients managed with any/all NCCN-acknowledged first-line treatment strategies are eligible

Takahashi et al, Lancet Oncology 2017; Pls Dr. Chad Rusthoven and Paul Brown

PCI in ADRIATIC?

Time to brain/central nervous system progression or death (95% CI)	Durvalumab (n = 264)	Placebo (n = 266)
Median, months (95% CI)	Not reached (not reached, not reached)	Not reached (not reached, not reached)
Brain/central nervous system progression-free survival at 24 months, % (95% CI)	84.0 (77.2, 89.0)	72.9 (64.5, 79.6)
Hazard ratio	0.64 (0.40, 1.01)	

Senan et al, ESMO 2024

PCI in ADRIATIC?

			Median OS	3-year OS
PCI-yes	D	142	NR	62.1
	P	143	42.5	56.5
PCI-no	D	122	37.3	50.2
	P	123	24.1	37.3

Senan et al, ESMO 2024

Radiation Therapy

RESPONSE ASSESSMENT FOLLOWING PRIMARY TREATMENT

- C/A/P CT with contrast
- Brain MRI (preferred) or CT with contrast
- CBC
- Electrolytes, LFTs, BN, creatinine

Complete
response
or partial
response

Stable
disease

Primary
progressive
disease

Limited
stage

Extensive
stage

Limited
stage

Extensive
stage

ADJUVANT THERAPY

- Durvalumab (category 1)
- Prophylactic cranial irradiation (PCI) or Consider MRI brain surveillance

- MRI brain surveillance ±
- Consider PCI
- Consider thoracic RT

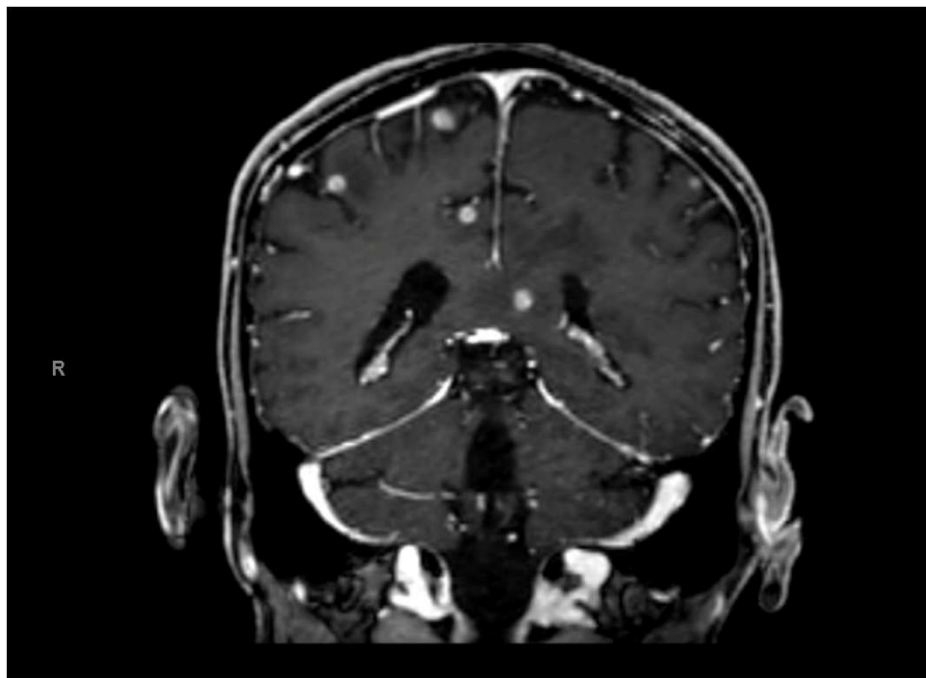
Durvalumab (category 1)

See
Surveillance
(SCL-7)

Subsequent Therapy/Palliative Therapy (SCL-8)

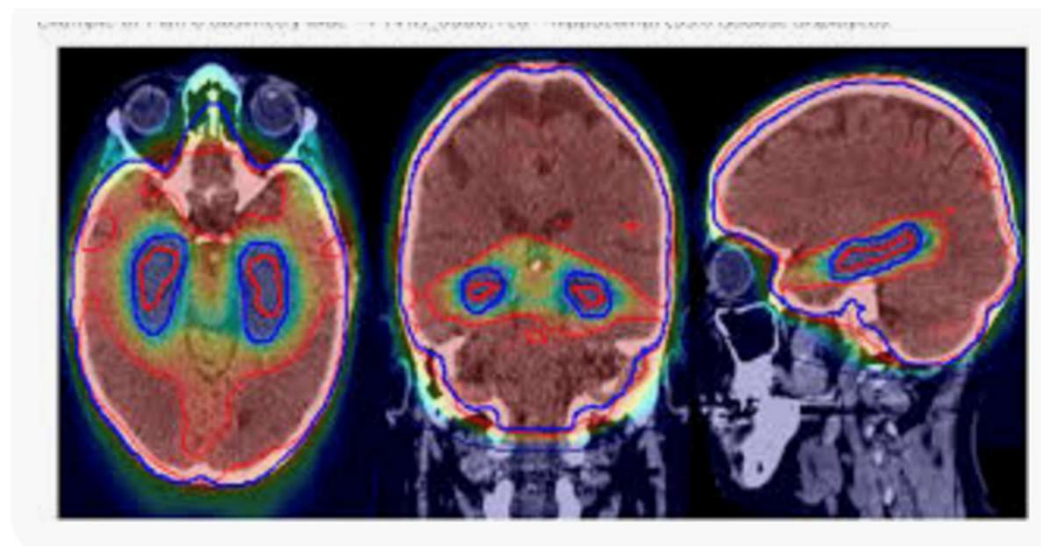
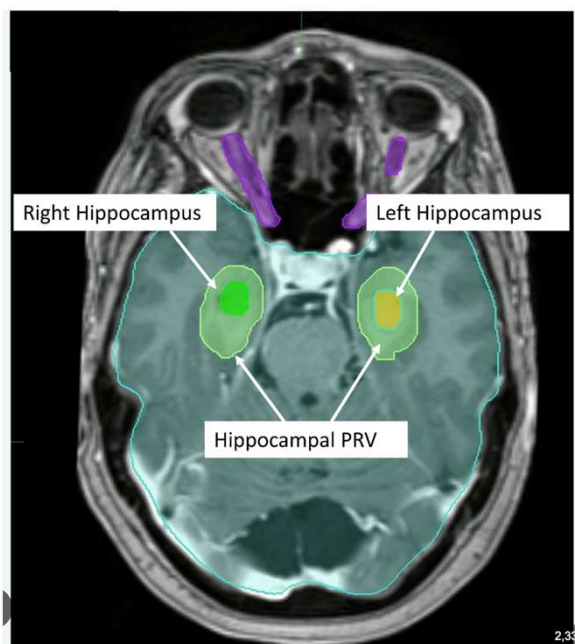
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer (Version 2.2026). SCL-4.
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Diffuse CNS Metastatic Disease

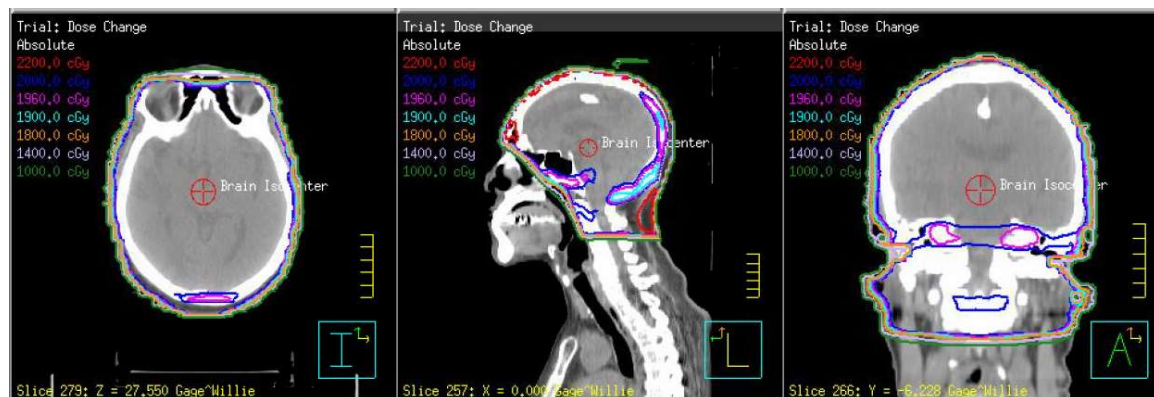


52-year-old patient with extensive-stage small cell lung cancer, progressed on 2nd line therapy, with ~50 brain metastases on MRI

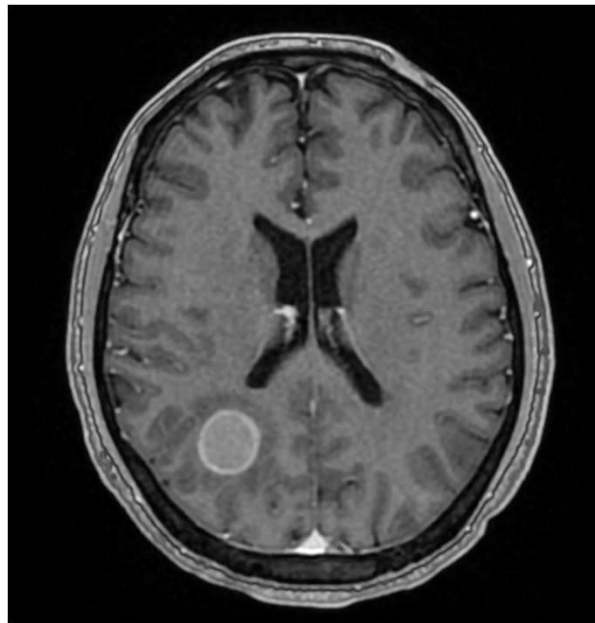
WBRT vs Hippocampal Avoidant WBRT



WBRT vs Hippocampal Avoidant WBRT



Limited CNS Metastatic Disease

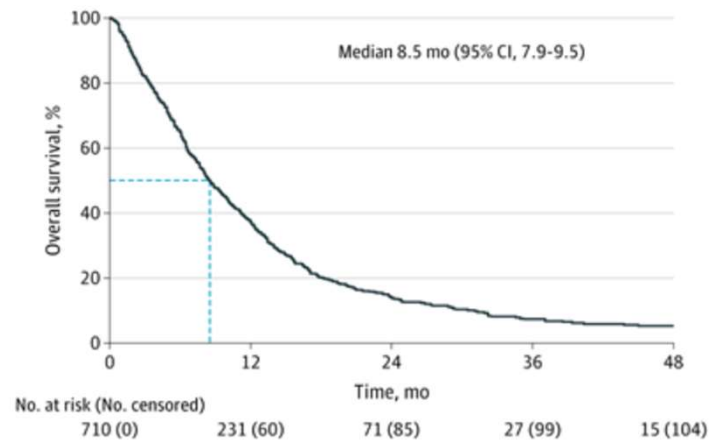


75-year-old woman with extensive-stage small cell lung cancer, presents with headache

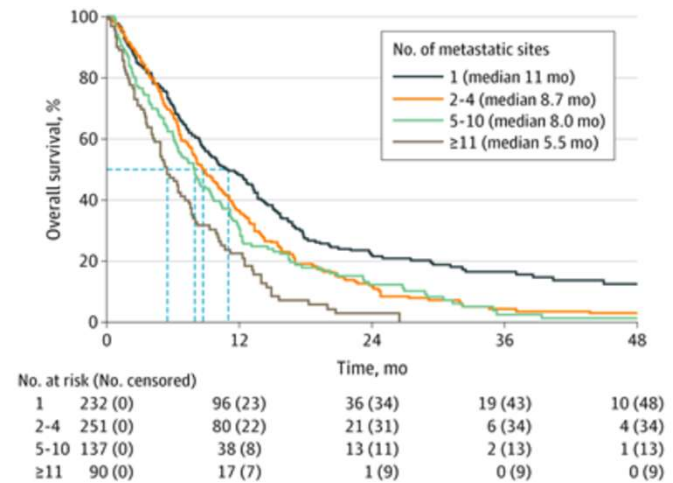
MRI demonstrates a single 1.5 cm R parietal brain metastasis

FIRE-SCLC

A OS for all patients

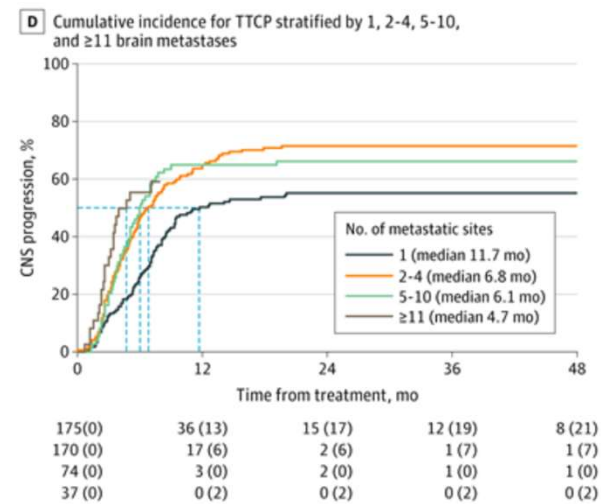
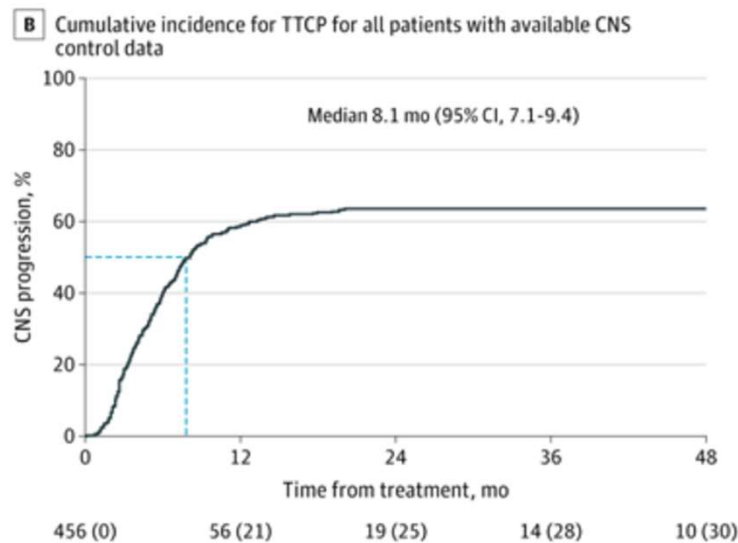


C OS stratified by 1, 2-4, 5-10, and ≥ 11 brain metastases



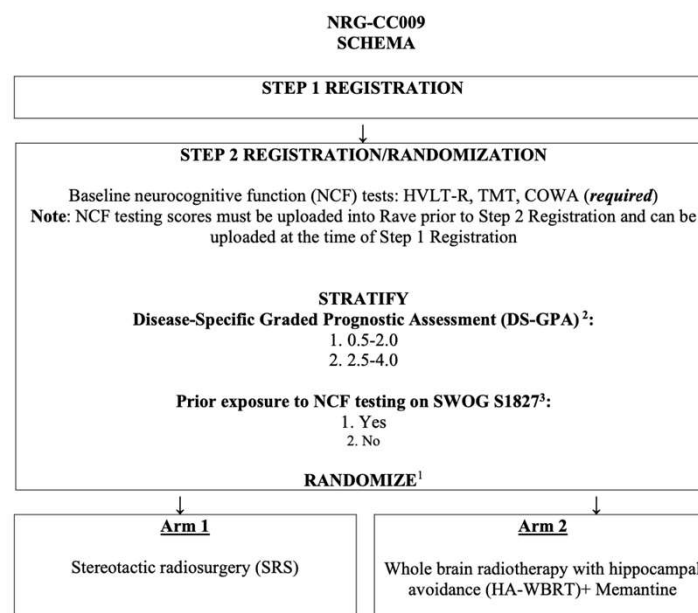
Rusthoven et al, JAMA Oncol, 2020

FIRE-SCLC



Rusthoven et al, JAMA Oncol, 2020

HA-WBRT vs SRS



¹Randomization is 1:1

Primary Endpoint:
Neurocognition

Secondary Endpoints:

- Intracranial disease control
- Overall survival
- Neurologic death

NRG CC009 Protocol

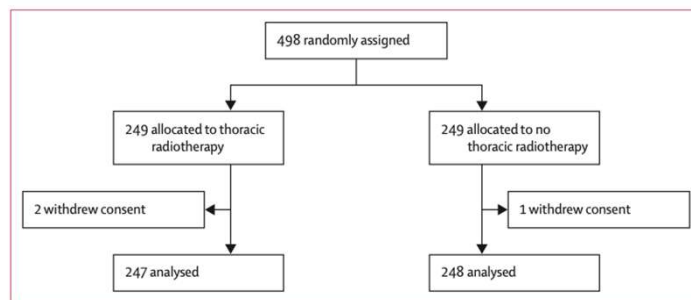
Thoracic Consolidation

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn, Suresh Senan**

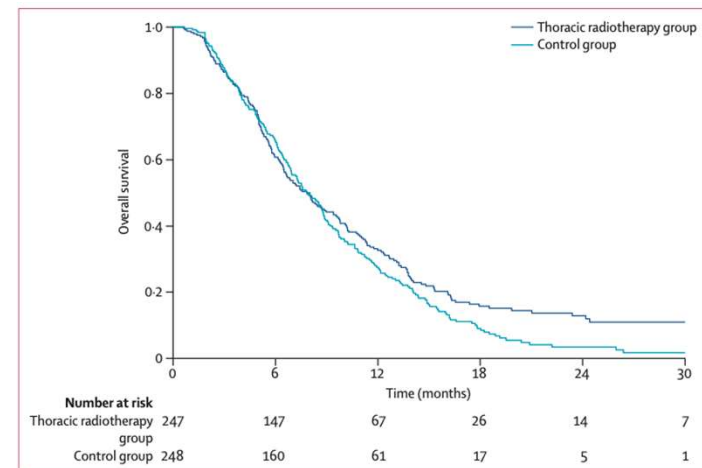
Slotman et al, Lancet 2015

Thoracic Consolidation



30 Gy in 10 fractions to thoracic disease in patients who had a response to chemotherapy

Primary endpoint: 1 year OS



Primary Endpoint: Negative

Overall: 2 year OS 13% vs 3%

When looking only at patients with residual disease in chest (excluding complete responders), improvement in median OS (HR = 0.8) and PFS (HR = 0.7)

Slotman et al, Lancet 2015

What About in the IO Era?

NRG-LU007 SCHEMA

PATIENT POPULATION:
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

STRATIFICATION

- Number of sites receiving radiation therapy (fields 1-3 vs >3)
- Partial Response (PR) vs Stable Disease (SD)
- ECOG Performance Status (0/1 vs 2)

RANDOMIZE



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

Primary endpoints

PFS (phase II) and OS (phase III)

NRG LU007 Protocol

Conclusions

- Daily or BID treatments are considered SOC. Dose escalation in the BID setting has promising data and should be considered for further investigation in the setting of consolidation IO
- Await RCTs on modern PCI use
- Evolving from WBRT as the only option for brain metastases
- Role for radiation in extensive-stage disease is evolving



National Comprehensive
Cancer Network®

Who We Are

An alliance of leading cancer centers devoted to patient care, research, and education

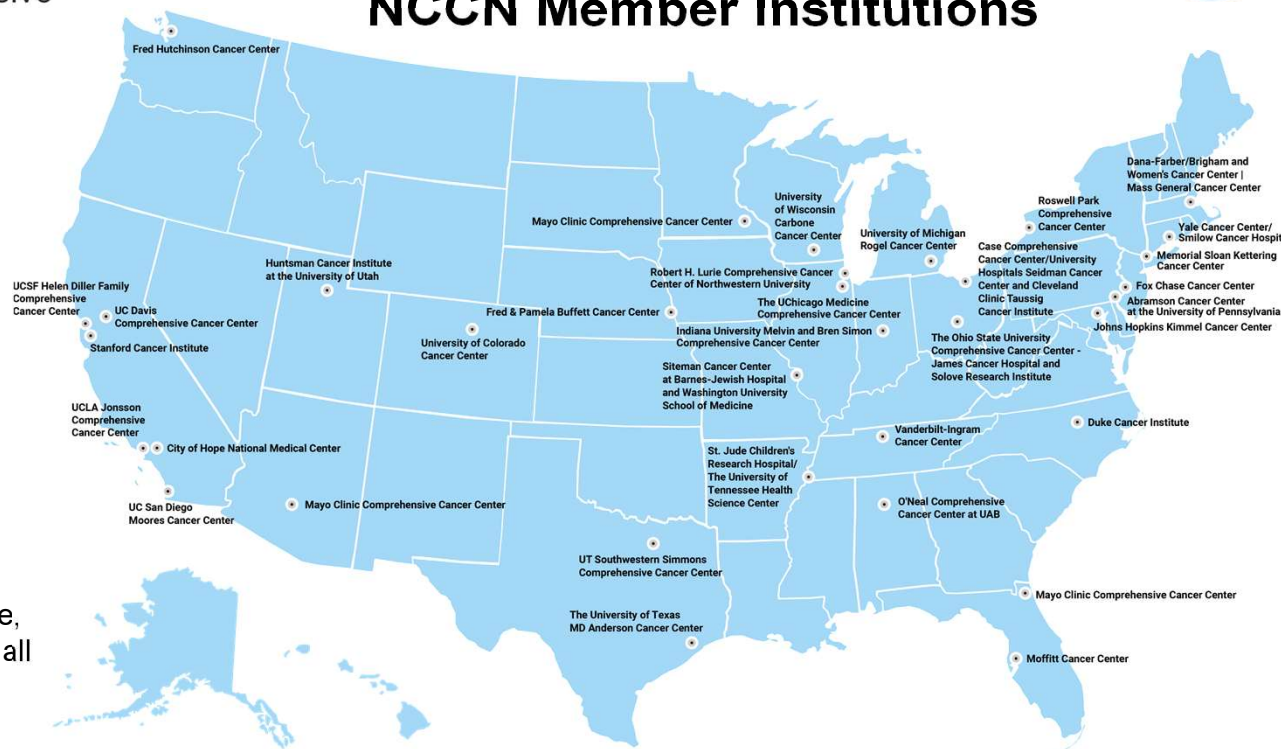
Our Mission

To define and advance quality, effective, equitable, and accessible cancer care and prevention so all people can live better lives

Our Vision

Access to high-quality, high-value, patient-centered cancer care for all people globally

NCCN Member Institutions



[NCCN.org](https://www.nccn.org) – For Clinicians | [NCCN.org/patients](https://www.nccn.org/patients) – For Patients | [Education.nccn.org](https://www.education.nccn.org) – CE Portal