THE NEW FRONTIER IN LIMITED-STAGE SCLC

Quynh-Nhu Nguyen, M.D., M.H.C.M
MD Anderson Cancer Center

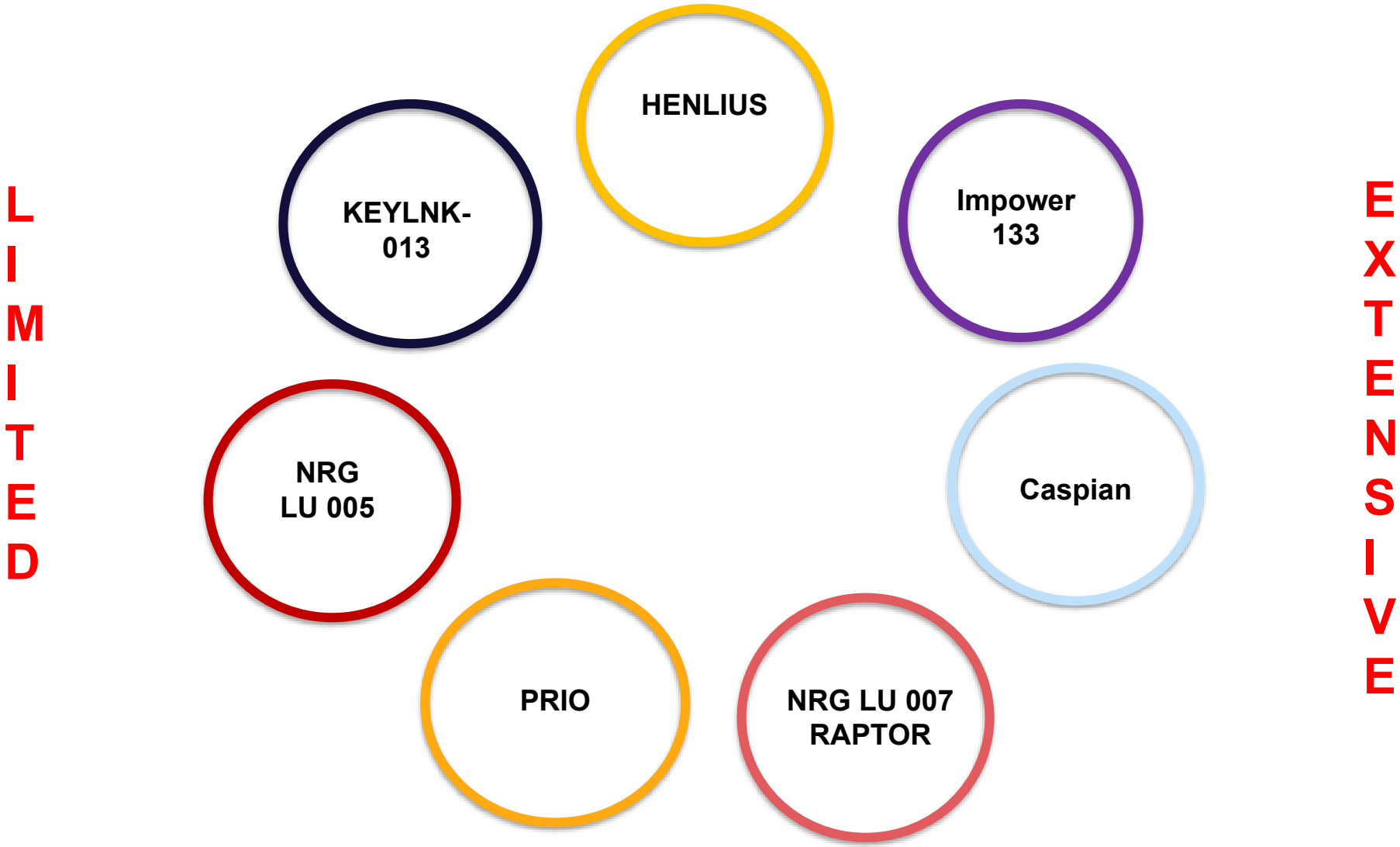
Date: April 19, 2024

Endorsed by
IASLC International Association for the Study of Lung Cancer
Conquering Thoracic Cancers Worldwide

Accredited by
PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

Presented by
IDEOlogy Health
Creating Aha! Moments In Healthcare

Small Cell Lung Cancer Trial Portfolio



TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURRISI, III, M.D., KYUNGMANN KIM, PH.D., RONALD BLUM, M.D., WILLIAM T. SAUSE, M.D., ROBERT B. LIVINGSTON, M.D., RITSUKO KOMAKI, M.D., HENRY WAGNER, M.D., SEENA AISNER, M.D., AND DAVID H. JOHNSON, M.D.

Concurrent RT + cisplatin/etoposide

Randomization

Arm 1 45 Gy at 1.5 Gy BID

Arm 2 45 Gy at 1.8 Gy Daily

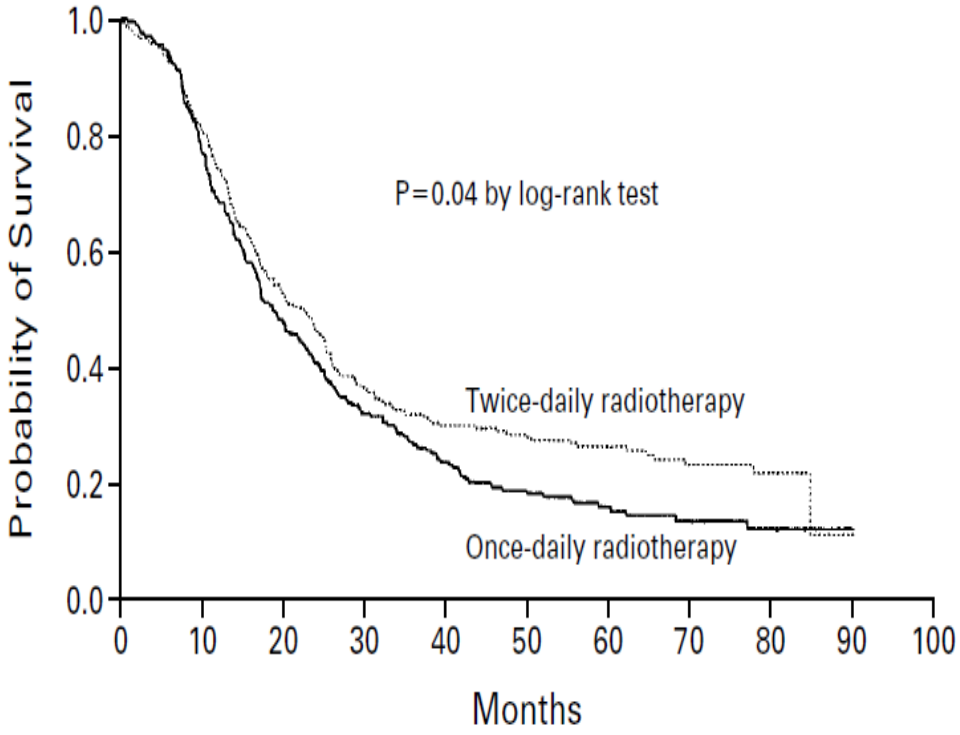
All received PCI to 25 Gy in 10 fractions

Result

Local failure – 52% → 36%

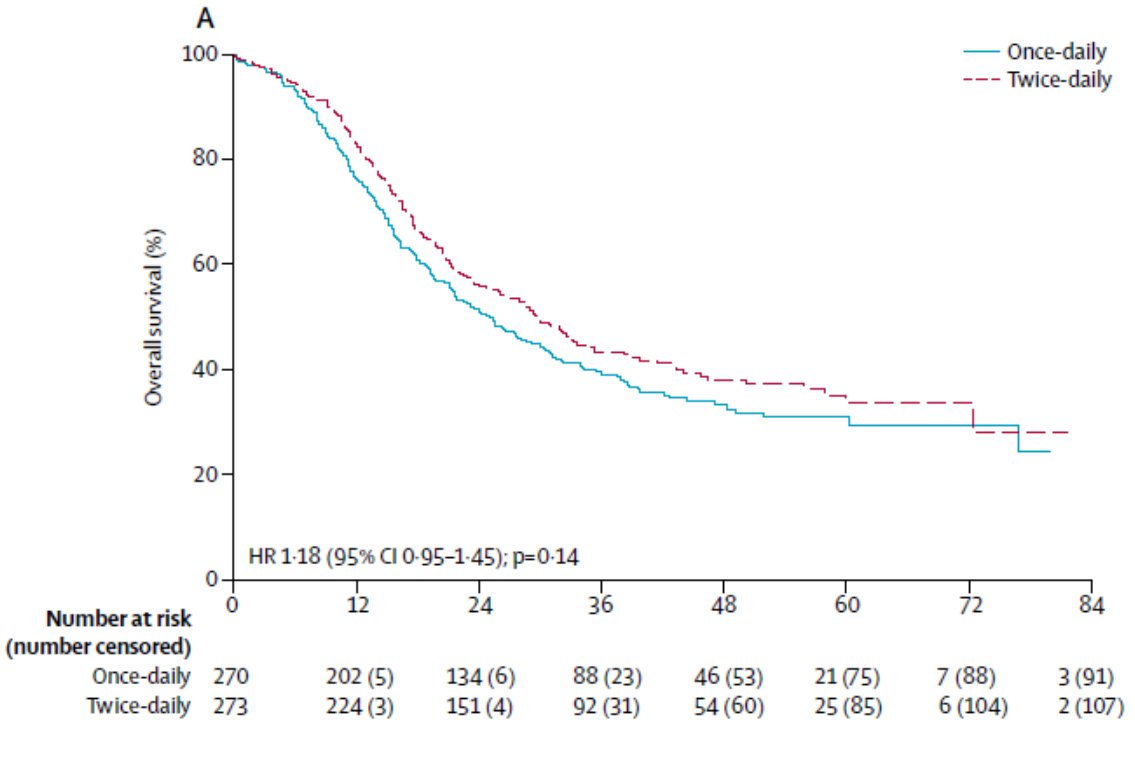
Overall survival 16 → 26% with acceleration

Criticism – daily doses not biologically equivalent to BID doses

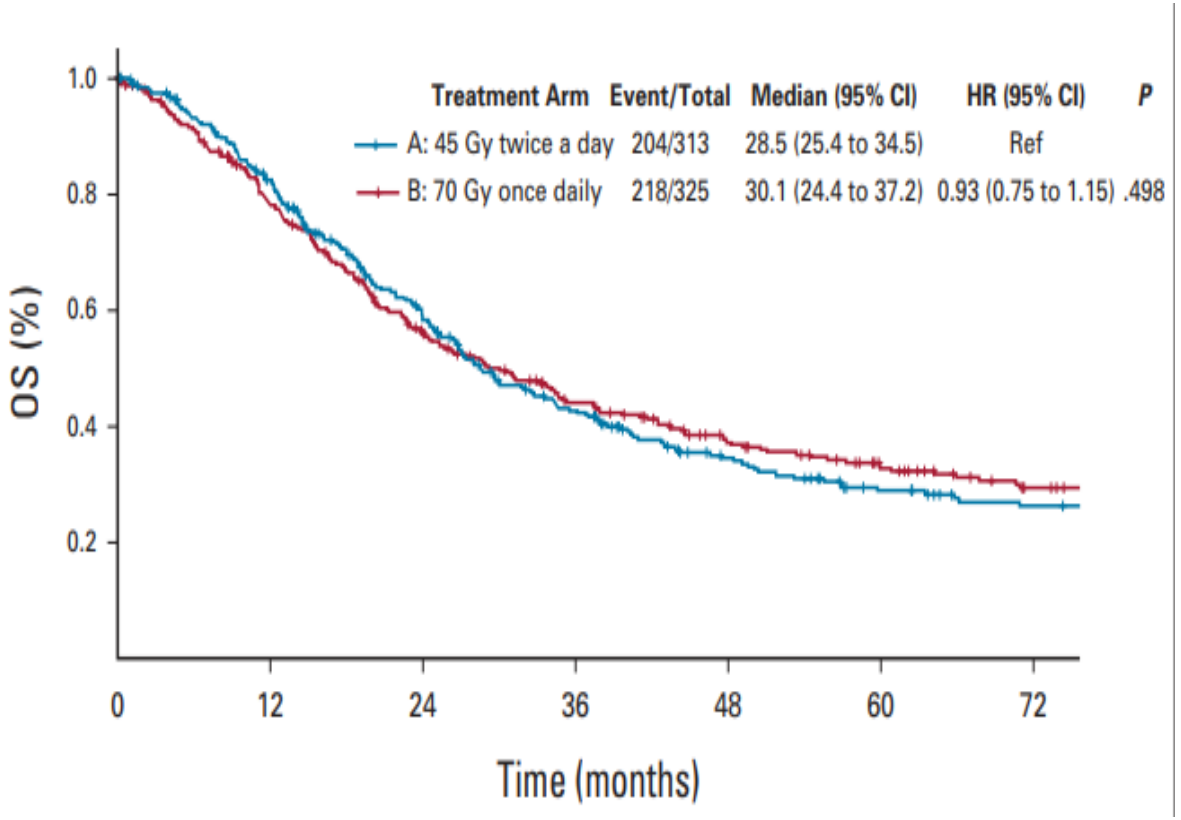


The NEW ENGLAND JOURNAL of MEDICINE

Challenging hyperfractionation with daily radiotherapy?



European CONVERT Trial (45 Gy BID vs 66 Gy daily)



CALGB 30610/RTOG 0538

Role for addition Immunotherapy for Limited Stage Small Cell Lung Ca?

- Preliminary data supporting this concept include interaction of radiation with the host immune system both at the T-cell level and at the tumor cell through radiation induced release of tumor neoantigens.
- Phase I studies have shown an acceptable safety profile with concurrent immunotherapy + chemoradiation in both small cell and non-small cell lung cancer.
- A recent randomized phase III trial showed improved survival with atezolizumab + chemotherapy for the first line treatment of extensive stage small cell lung cancer.
- Studying Immunotherapy for Limited Stage Lung cancer…

Limited Stage Small Cell Lung Cancer (LS-SCLC): A Phase II/III Randomized Study of Chemoradiation Versus Chemoradiation Plus Atezolizumab

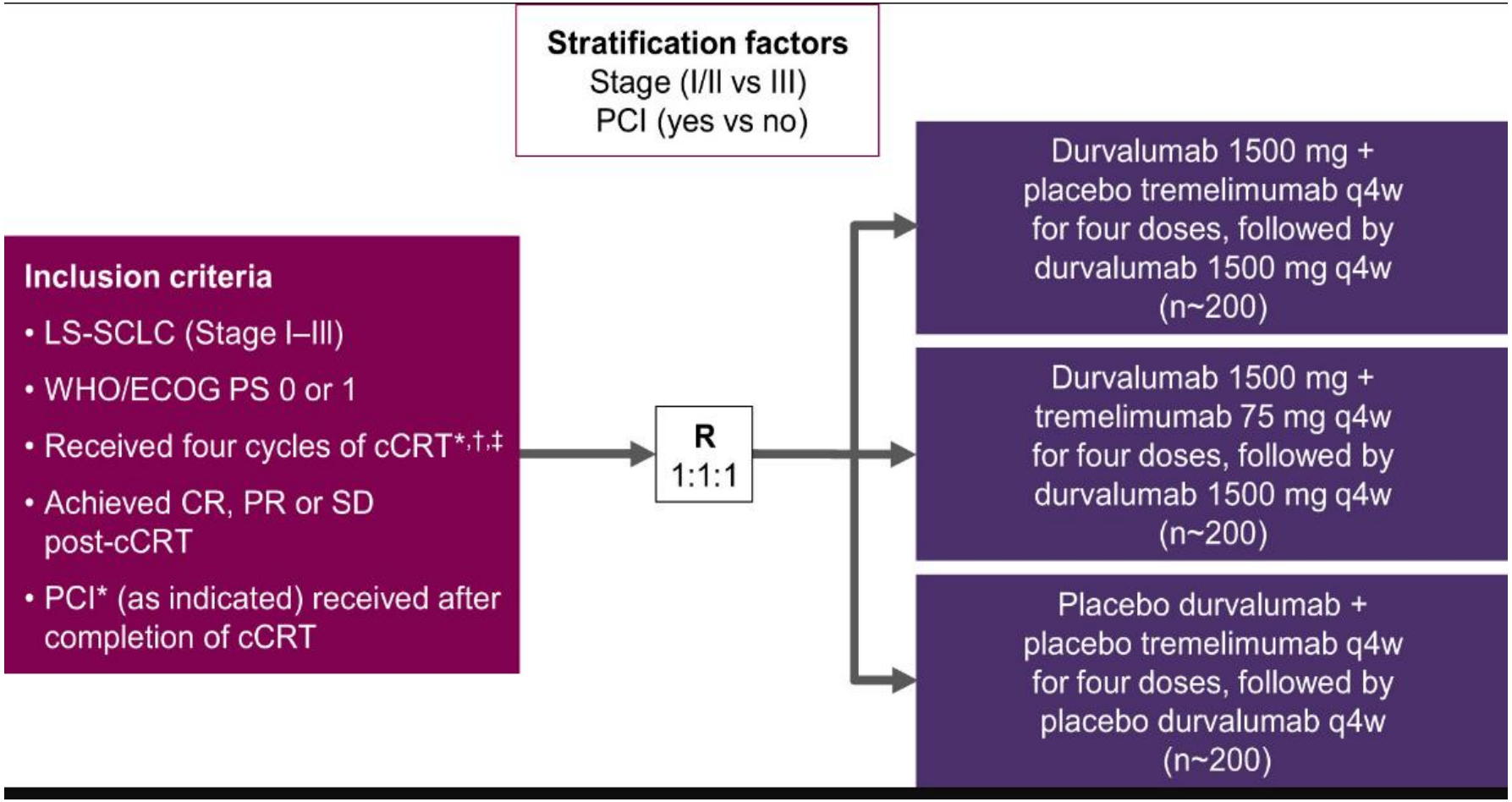
PATIENT POPULATION Limited stage (Tx, T1- T4, N0-3, M0) small cell lung cancer (LS-SCLC)	**STRATIFY**	•Radiation schedule, BID (3 weeks) vs daily (6.5 weeks) •Chemotherapy (cisplatin vs carboplatin) •Sex (male vs female) •ECOG Performance Status (0/1 vs 2)	**RANDOMIZE***	**<u>Arm 1</u>** Platinum**/etoposide q3 weeks x 4 cycles + Thoracic RT 45 Gy bid or 66 Gy daily beginning with cycle 2 of chemotherapy*** **<u>Arm 2</u>** Platinum**/etoposide q3 weeks x 4 cycles + Thoracic RT 45 Gy bid or 66 Gy daily beginning with cycle 2 of chemotherapy*** + Atezolizumab q3 weeks x 1 year, beginning with cycle 2 of chemotherapy

Kristin Higgins, MD

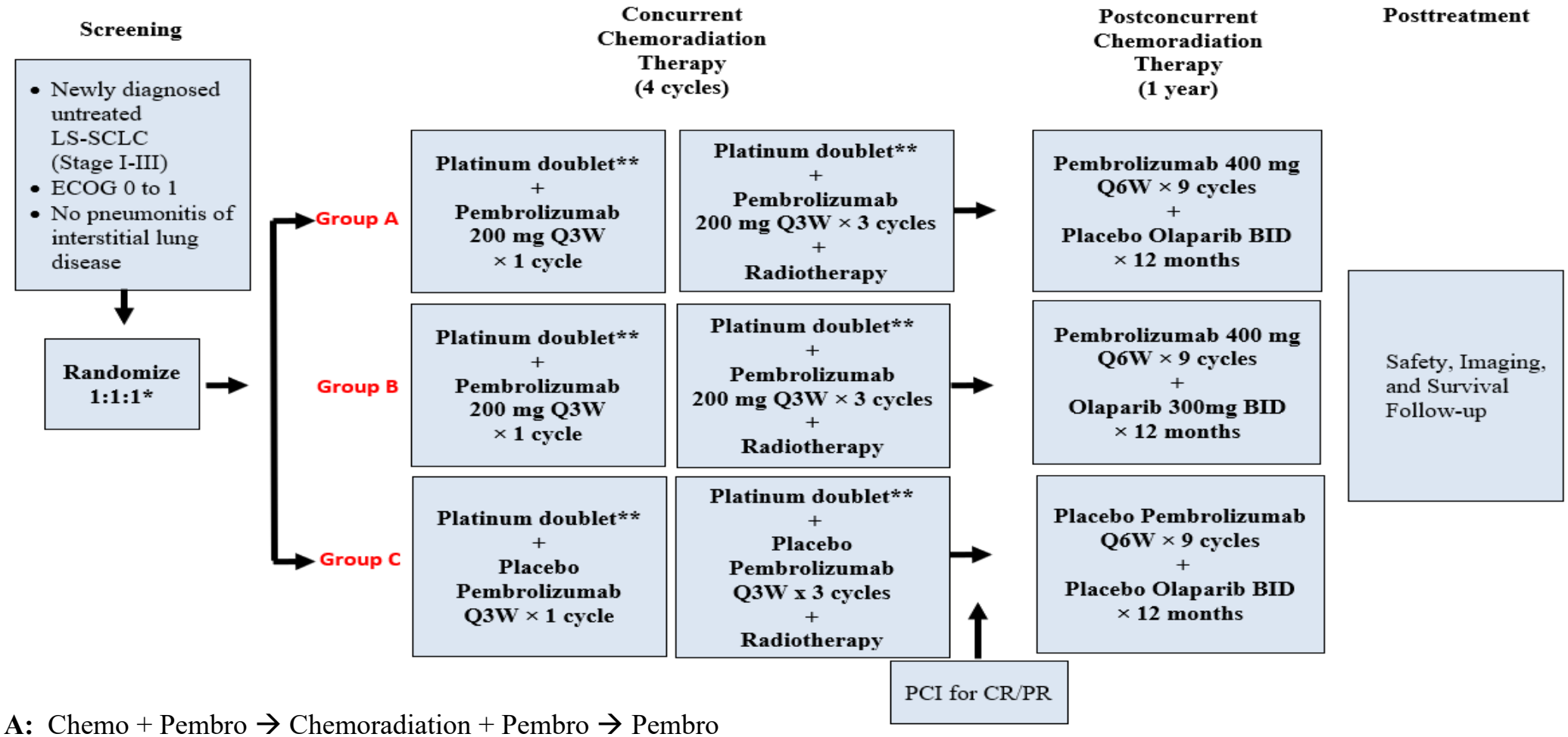
NRG LU 005

- **Target Accrual**
  - Phase II : PFS endpoint (280 patients)
    - Accrual may be suspended if 280 patients are accrued and either 140 PFS events or 79 deaths have not been observed.
  - Phase III: OS endpoint (226 patients)
  - Total 506 patients accrued

ADRIATIC: Phase III RCT Multicenter Trial



KEYLINK



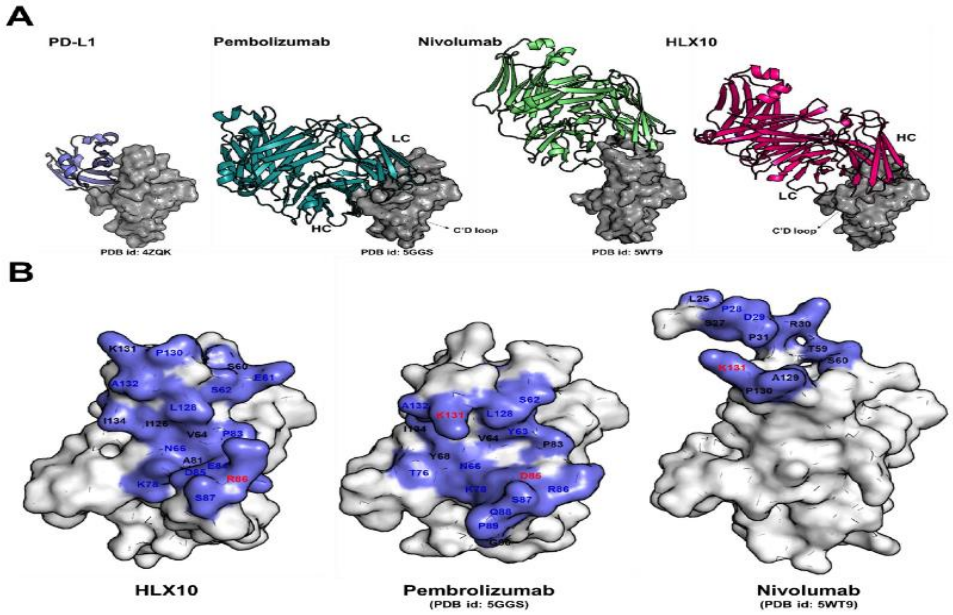
Group A: Chemo + Pembro → Chemoradiation + Pembro → Pembro
Group B: Chemo + Pembro → Chemoradiation + Pembro → Pembro+Olaparib
Group C: Chemo → Chemoradiation

HLX10 PD-1 antibodies

- Unique mode of recognition: Mechanistically, structural analysis of PD-1-HLX10-Fab complex suggests that HLX10 competes with PD-L1 binding in similar fashion to nivolumab and pembrolizumab. Detailed epitope analysis showed that HLX10 has a unique mode of recognition compared to pembrolizumab and nivolumab. Notably, the epitope of HLX10 is more similar to that of pembrolizumab than nivolumab. However, HLX10 and pembrolizumab showed an opposite heavy chain (HC) and light chain (LC) usage, which recognizes several overlapping amino acid residues on PD-1.

Table 1: Kinetics and binding affinities of anti-PD-1 antibody to human PD-1 determined by BLI.

Sample	Human PD-1		
	k_a [1/(M s)]	k_d [1/s]	K_D [M]
HLX10	1.57×10^{5}	3.29×10^{-4}	2.42×10^{-9}
Nivo	1.28×10^{5}	1.50×10^{-3}	11.9×10^{-9}
Pembro	3.18×10^{5}	2.56×10^{-3}	8.04×10^{-9}



Study Design of HLX10-020-302

A Randomized, Double-Blind, International Multicenter, Phase III Study (NCT05353257)

Main eligibility criteria :

1. Age≥18 years
2. Histologically confirmed SCLC
3. Diagnosed with LS-SCLC (stage I-III of the AJCC 8th edition of the cancer staging), which can be safely treated with curative radiation doses.
4. Subjects unsuitable for surgery.

(N=482)

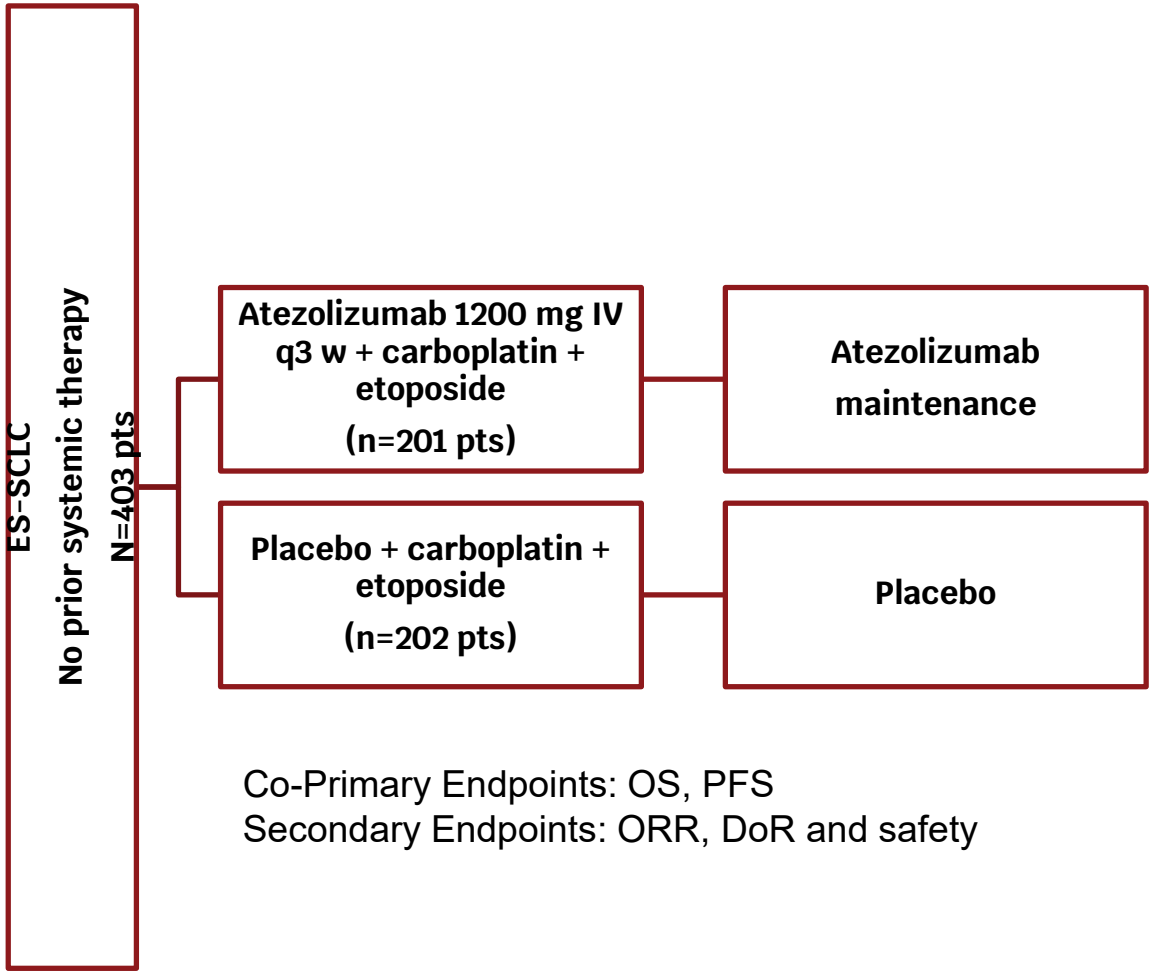
R 1:1

IV, Q3W, C1	IV, Q3W, C2-C4		IV, Q3W, C5-C22
HLX10 (300mg, D1) + Carboplatin (Max750mg/Cisplatin75mg /m^2 D1) + Etoposide (100mg/m^2, D1–3)	HLX10 300mg D1 +Carboplatin (Max750mg/Cisplatin 75mg/m^2 D1) +Etoposide (100mg/m^2 D1-3) +Chest radiotherapy*	**Evaluate whether PCI** highly recommended for CR/PR SD at the discretion of PI recommended to start within 3-4 weeks after the fourth cycle recommended dose: 25Gy/10times If PCI is not available, head MRI is recommended.	HLX10 (300mg D1) until PD or up to 1 year after cCRT
Placebo D1 +Carboplatin (Max750mg/Cisplatin75mg /m^2, D1) +Etoposide (100mg/m^2 D1-3)	Placebo D1 +Carboplatin (Max750mg/Cisplatin 75mg/m^2 D1) +Etoposide (100mg/m^2 D1-3)		Placebo (D1)

- **Primary endpoint:** OS
- **Secondary endpoints:** PFS(INV), ORR, DOR, Safety, PK(HLX10), ADA/ NAb (HLX10)

Stratification factors: ECOG PS (0 or 1), staging (I/II/III), radiation fraction (QD or BID), region (Asia or non-Asia)

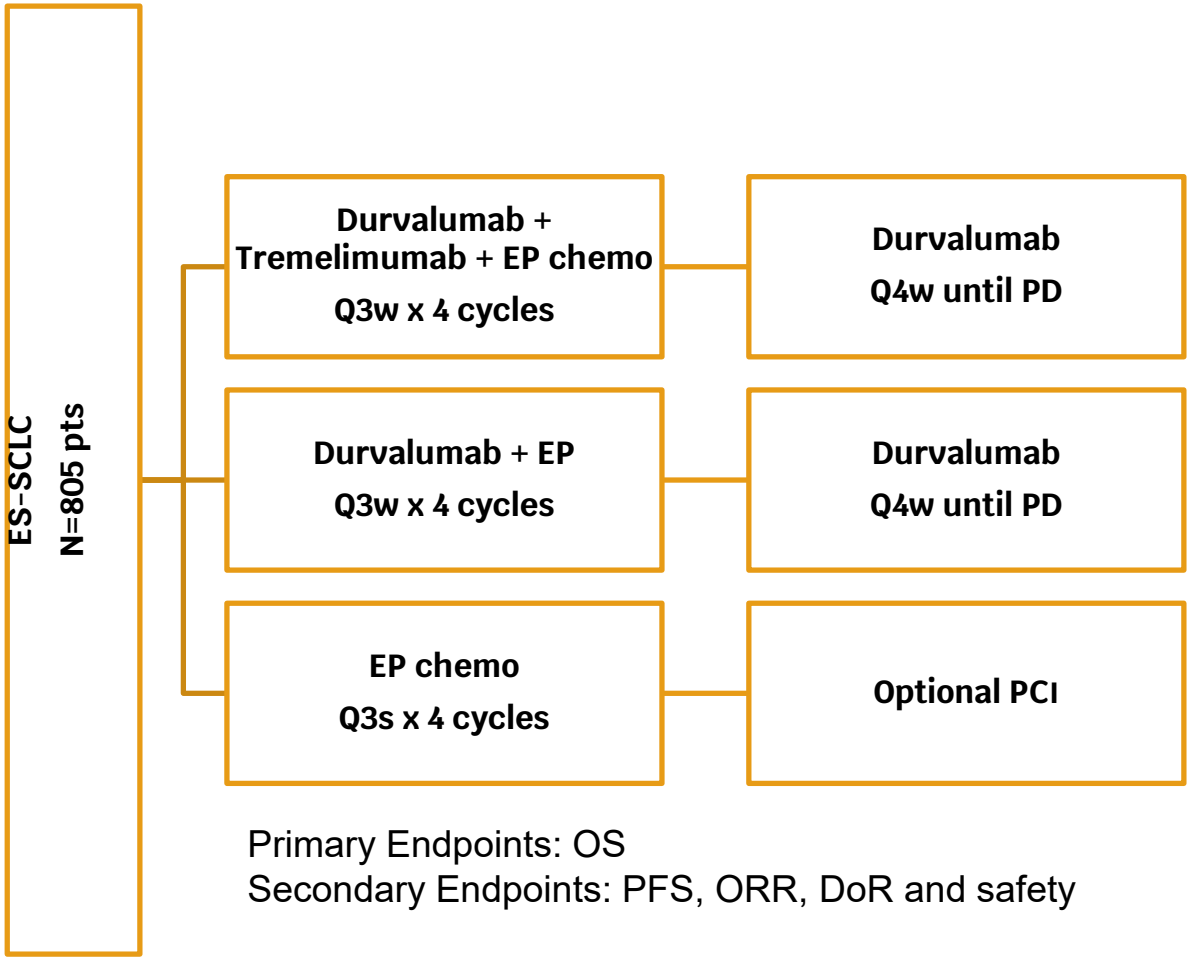
IMPOWER 133



Co-Primary Endpoints: OS, PFS
Secondary Endpoints: ORR, DoR and safety

Horn et al; NEJM, 2018:

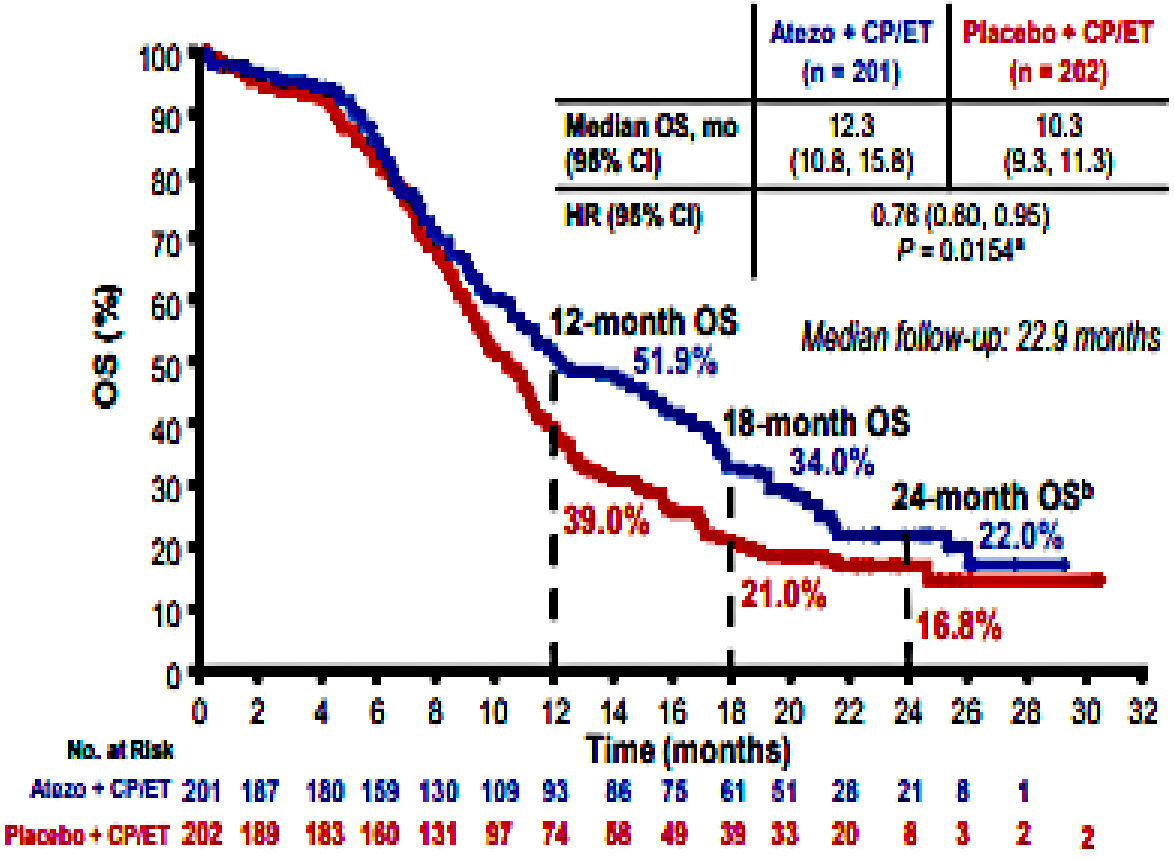
Caspian



Primary Endpoints: OS
Secondary Endpoints: PFS, ORR, DoR and safety

Paz-Ayres, Dvokin et al. Lancet 2019

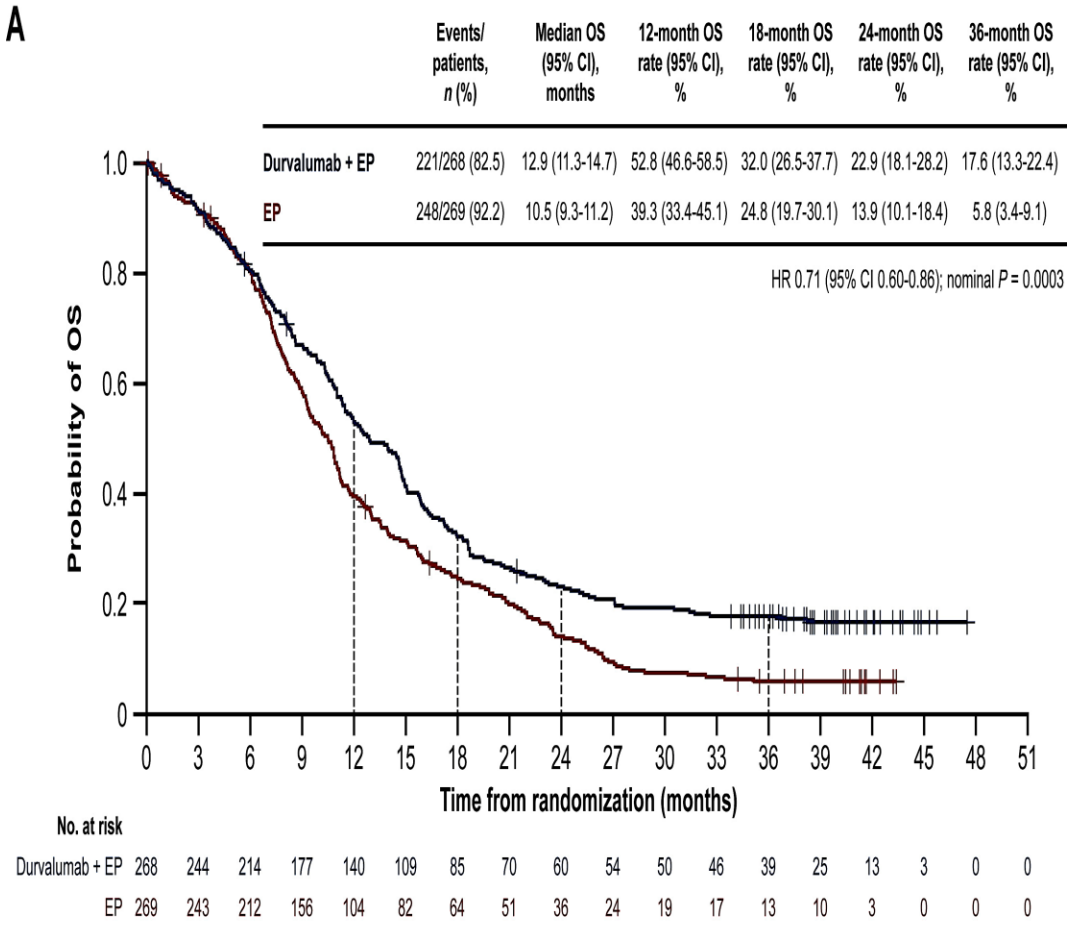
ImPower 133: 2 yr



2 yr OS: Atezo + EP 22% vs EP 16.8%
P=0.015

Paz-Ayres, Dvokin et al. Lancet 2019
Paz-Ayres, ASCO 2020

Caspian: 3 yr



3 yr OS: D + EP 18% vs EP 6%
P=0.003

First-line Atezo + EP and durvalumab + EP demonstrated ongoing improvement of OS vs EP in patients with extensive-stage SCLC

OS benefit preserved across prespecified subgroups

Safety outcomes consistent with known safety profiles of each agent

Immunotherapy plus EP chemo should be considered a new standard of care for first-line therapy in patients with extensive-stage SCLC

NRG-LU007: RAndomized Phase II/III Trial Of Consolidation Radiation + Immunotherapy for ES-SCLC (RAPTOR)

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	**STRATIFY**	• Number of sites receiving radiation therapy (fields 1-3 vs >3) • PR vs 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

Quynh Nguyen M.D., MHCM
Professor, Dept. of Radiation Oncology

NRG LU 007

PRIMARY OBJECTVE:

Phase II

Compare progression free survival (PFS) between atezolizumab + RT vs atezolizumab

Phase III

Compare overall survival (OS) between atezolizumab + RT vs atezolizumab

SECONDARY OBJECTIVES:

Assess toxicity atezolizumab + RT and atezolizumab arm

Assess impact of adding radiotherapy on PFS and OS in patients with 1-3 visible tumors and >3 visible tumors

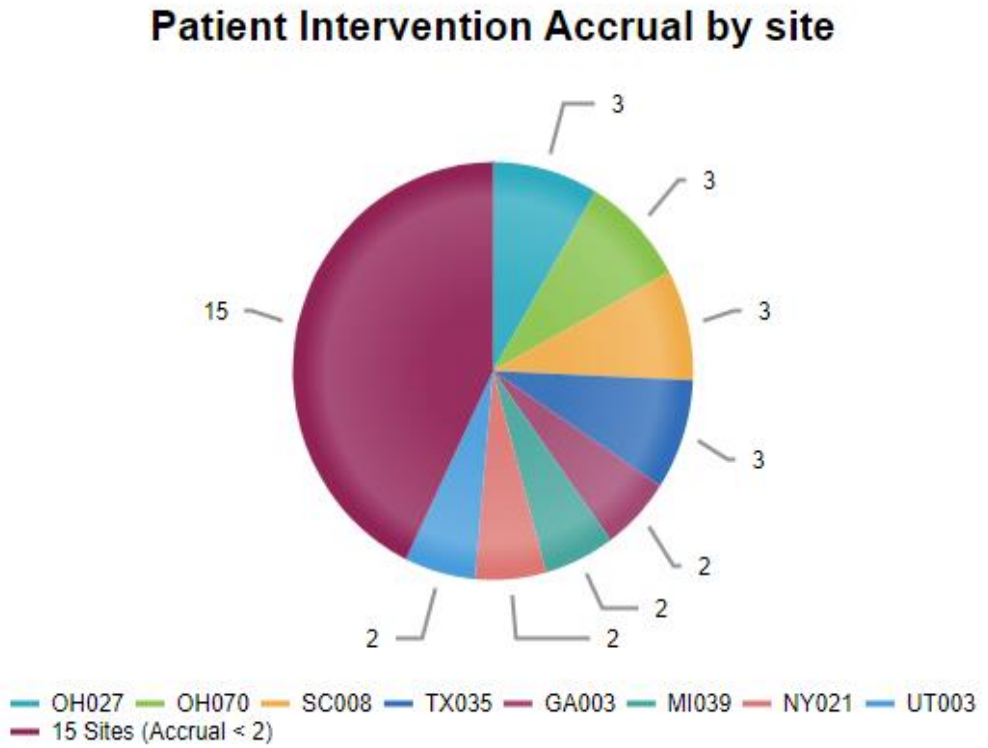
Assess impact of adding radiotherapy on PFS and OS in patients receiving consolidation radiotherapy to all visible disease “complete consolidation” vs “incomplete consolidation”

Target Accrual

Phase II = 138 eligible patients

Phase III = 186 patients

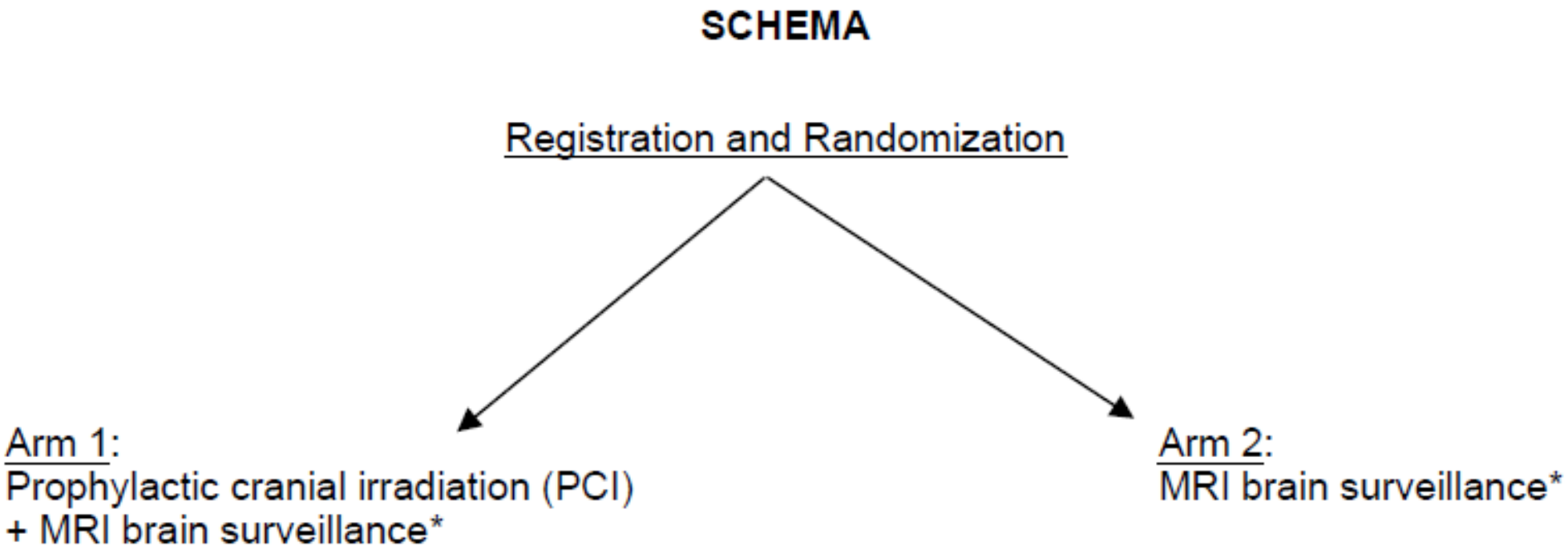
Overall sample size of Phase II/III = 324



Site Identifier	Anatomic Site	Total Dose and Fractionation Options		
		45 Gy in 15 fractions	30 Gy in 10 fractions	20 Gy in 5 fractions
1	Lung (primary)	x	x	
2	Liver	x	x	x
3	Bone		x	x
4	Spine		x	x
5	Abdomen/Pelvis		x	x
6	Soft Tissue		x	x

SWOG S1827 (Maverick)

- **Purpose: establish non-inferiority of MRI surveillance**
- Both limited-stage SCLC and extensive-stage SCLC
- Stratified by receipt of PD-L1 immune therapy
- Hippocampal avoidance allowed



Summary – Prophylactic Cranial Irradiation

Highly controversial despite randomized evidence

Most randomized trials before MRIs

PCI may improve CNS control at cost to QoL

Brain metastases remain common even with PD-L1 immune therapy

Hippocampal avoidance as standard

Supported by NCCN guidelines

European trials – Spanish PREMER and Dutch/Belgian

NRG-CCOO3 – several positive secondary endpoints (though primary endpoint negative)

Do we need PCI at all?

MRI surveillance (SWOG S1827 Maverick)

CONCLUSIONS

First Line therapy PDL1 Inhibitors combined with Platinum/Etoposide established standard of care with modest outcomes

Combination strategies appealing to further improve long term survival for SCLC patients

Future trials with PARP Inhibitor combined with immunotherapy + chemotherapy + radiotherapy?

Acknowledgements

James Welsh, MD

John Heymach, MD., PhD

Lauren Byers, MD., PhD

Marcelo Negrao, M.D.

Carl Gay, M.D., PhD

JianJun Zhang, M.D.

ZhongXing Liao, M.D.

Jeff Bradley, M.D.

NRG Headquarters

Thoracic Radiation Oncology

Thoracic Medical Oncology

Thoracic Surgery

Texas Lung Cancer Committee