LIMITED STAGE SMALL CELL LUNG CANCER

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March 31, 2023

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IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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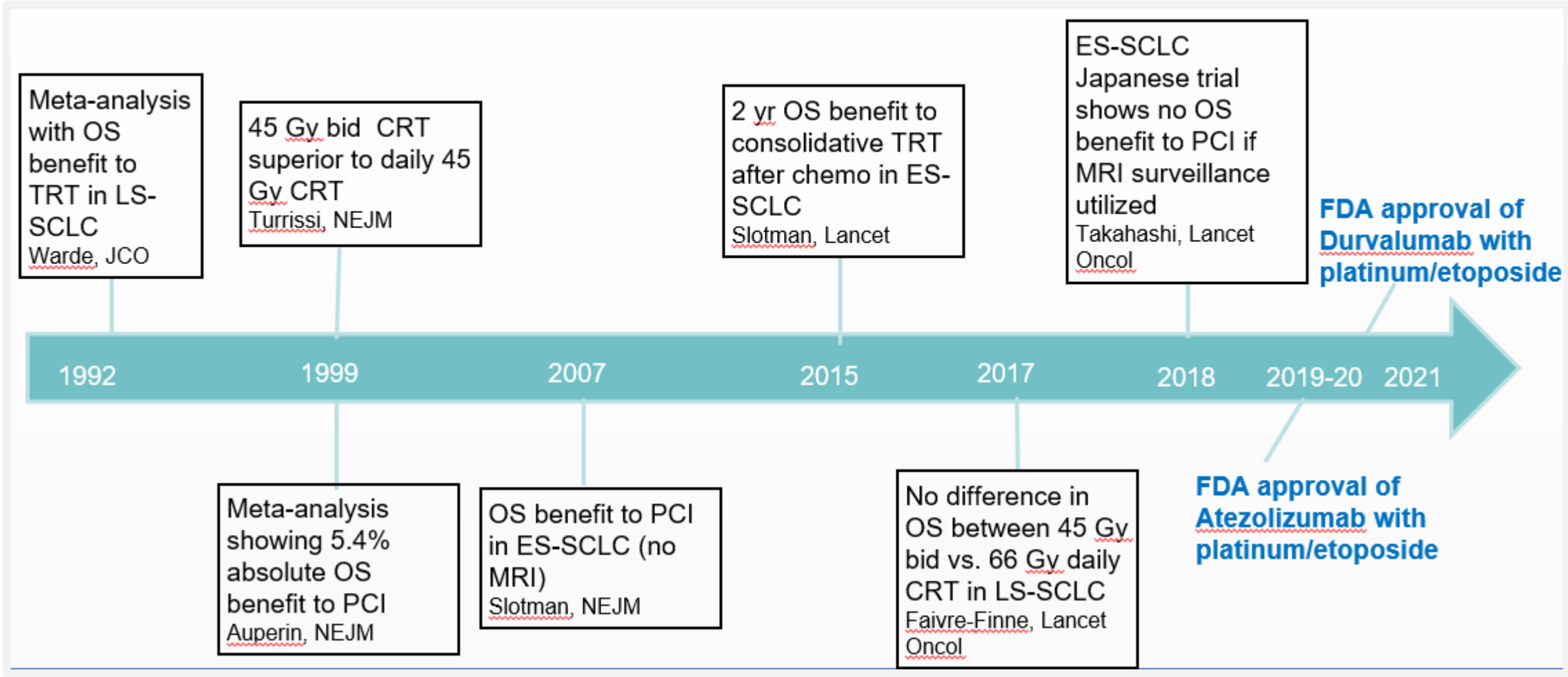
Historical Context of Radiation in SCLC



Limited Stage Small Cell Lung Cancer: Current State

Standard of care is currently platinum/etoposide + thoracic radiation followed by prophylactic cranial irradiation

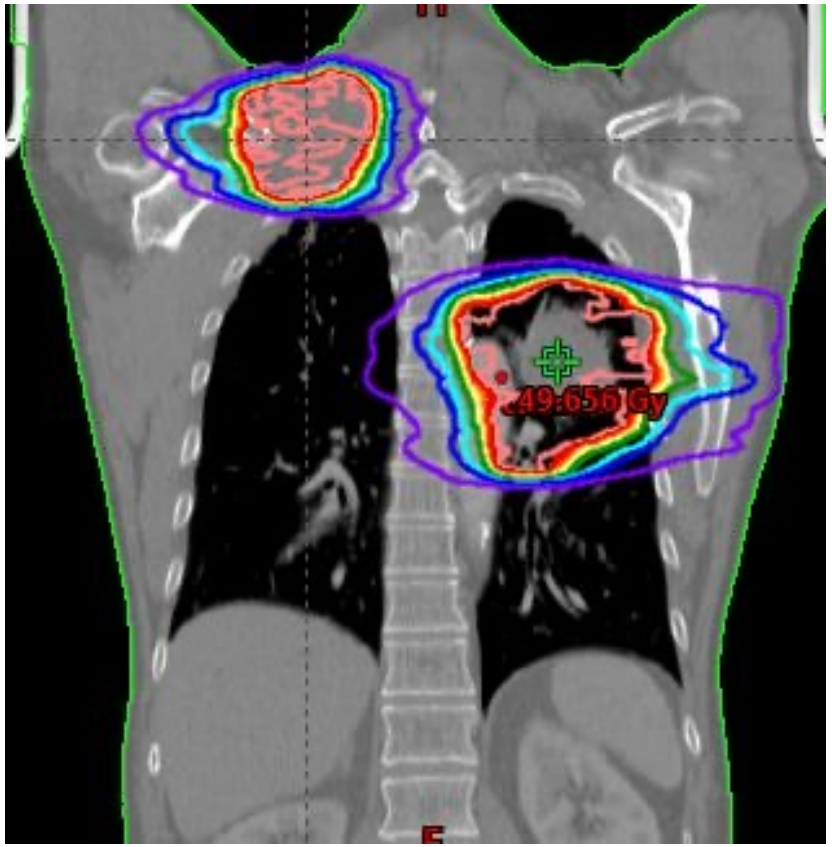
45 Gy bid or 66-70 Gy daily RT + 4 cycles platinum/etoposide

5 year survival is 25-30% with this approach

In the U.S., only 55% of LS-SCLC patients are receiving curative therapy with chemotherapy + radiation[1]

How can we improve outcomes for our LS-SCLC patients?

RT + IO combinations



[1]Chun SG et al, JAMA Onc 2018

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

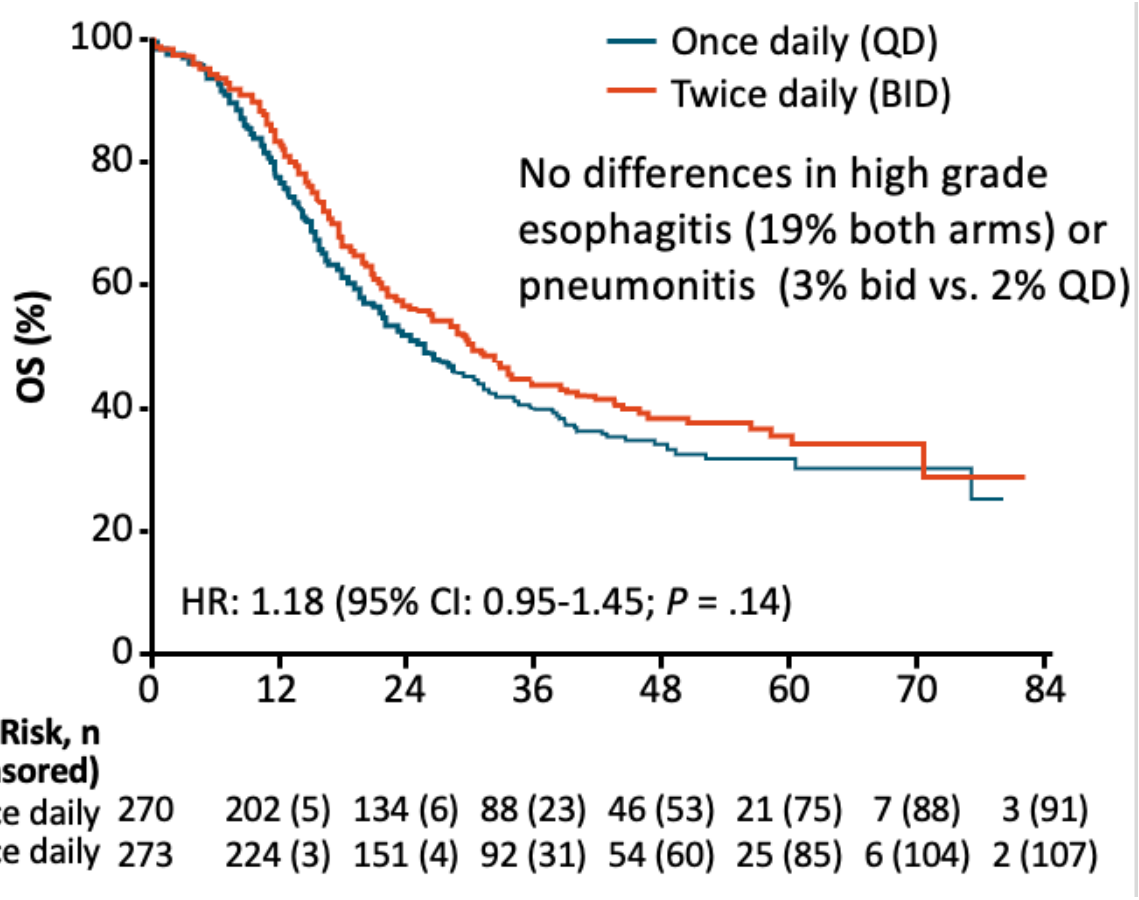
Stratified by center, chemotherapy cycles (4 vs 6), and PS (0-1 vs 2)

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.

Learnings from CONVERT: Secondary Analyses

- Secondary analysis of pts ≥ 70 years showed similar esophagitis and pneumonitis rates, hematologic toxicity slightly increased in elderly patients

  Fewer elderly pts completed prescribed RT (73% vs. 85%). No differences in chemotherapy compliance[1]

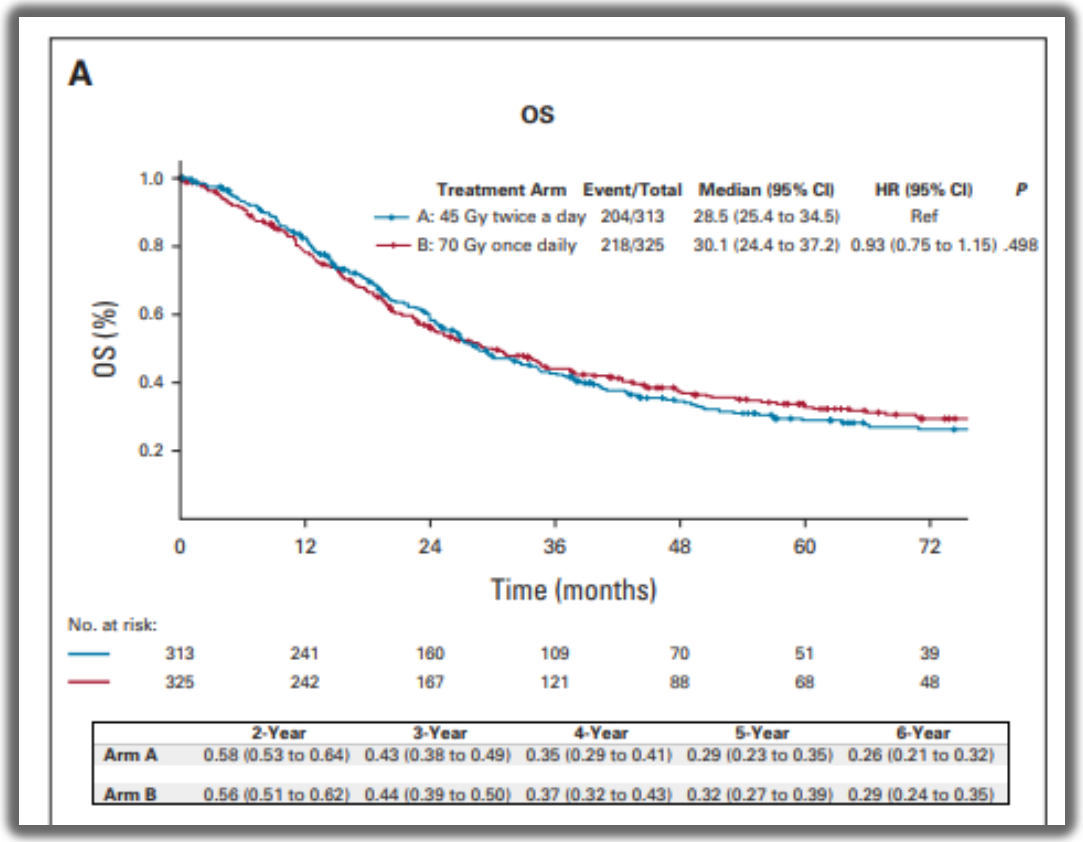
- TNM classification applied to CONVERT pts, with OS of stage I-II compared with III, median OS of 50 vs. 25 months[2]

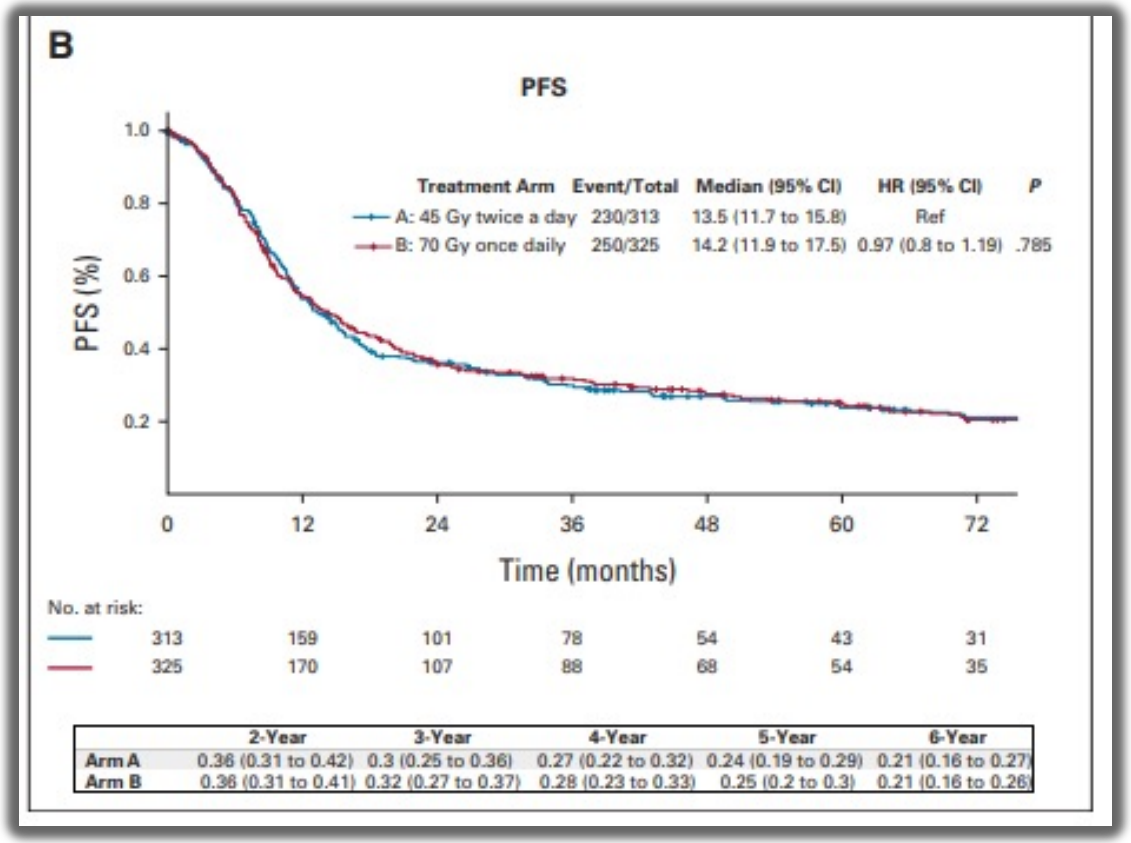
- Impact of PET/CT staging – no differences in OS and PFS in pts staged with or without PET/CT[3]

[1]Christodoulou et al, JTO 2019, [2]Salem et al, JAMA Oncol 2019, [3]Manoharan et al, JTO 2019

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

NRG/Alliance LU005

- This is the first NCI funded trial to test the utility of immunotherapy in LS-SCLC

- Atezolizumab is the first new drug to become FDA approved for the treatment of ES-SCLC in the last several decades

- We are hopeful that using immunotherapy in the treatment of earlier stages of small cell will cure more patients

  LU005 launched in 6/2019 and met accrual in 6/2022

NRG-LU005: Phase II/III randomized study of chemoradiation vs. chemoradiation plus atezolizumab

PATIENT POPULATION:
Limited stage SCLC

STRATIFICATION
- Radiation schedule (BID vs daily)
- Chemotherapy (cisplatin vs carboplatin)
- Sex
- ECOG Performance Status (0/1 vs 2)

N = 506

R

Platinum/etoposide x 4 cycles
+
Thoracic RT 45 Gy bid or 66 Gy daily

Platinum/etoposide x 4 cycles
+
Thoracic RT 45 Gy bid or 66 Gy daily
+
Atezolizumab q3 weeks beginning with cycle 2

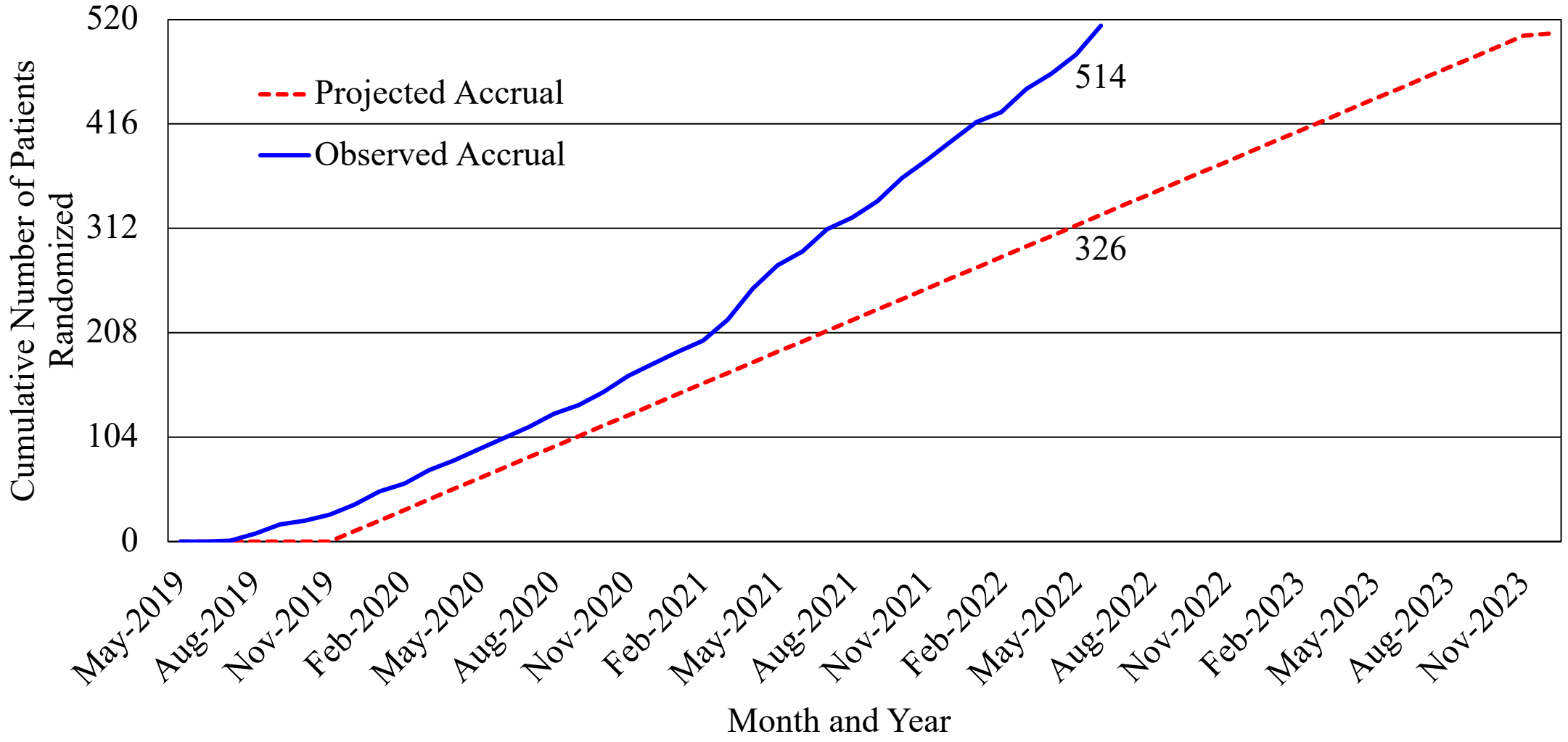
Atezolizumab q3 weeks for 1 year

Primary Endpoints and Statistics

- **Phase II primary endpoint is PFS**
  - –HR of .62 is hypothesized for PFS (improving median PFS from 13 to 21 months)
  - –Sample size of 280, projected that final PFS analysis to occur 38 months after study initiation
  - – Interim Futility Analysis with both objectives below required to be met to move to phase III:
  - •When 140 PFS events available, the HR for PFS needs to be less than 0.84
  - •When at least 79 deaths available, HR for OS < 1.46

- **Phase III primary endpoint is OS**
  - –HR of 0.71 hypothesized for OS, median OS will improve from 27 to 38 months
  - –Total sample size of 506

Actual vs Projected Accrual : NRG LU005



ADRIATIC STUDY: Phase III trial of consolidation Durvalumab, Durvalumab + Tremelimumab or Placebo in limited-stage SCLC after chemo-radiotherapy

Key Eligibility Criteria

- Histologically confirmed SCLC
- Untreated limited-stage disease (I-IIIB)
- ECOG PS ≤1

4 Cycles Chemo + Thoracic RT + PCI

R 1:1:1

- **Durvalumab + Placebo**
- **Durvalumab + Tremelimumab**
- **Placebo + Placebo**

Stratification

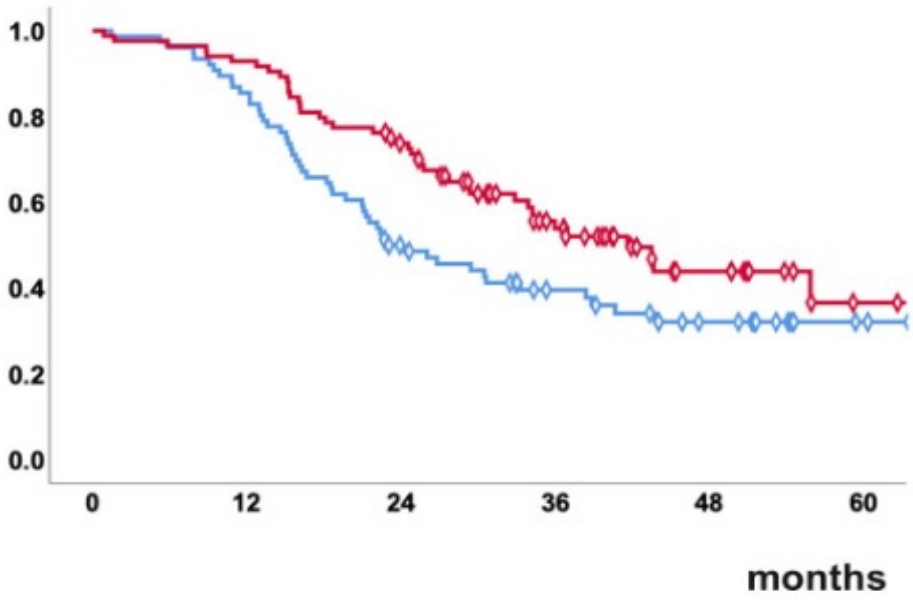
- Stage I/II vs. III
- PCI Y vs. No

Dose Escalation in LS-SCLC: Dutch Study

Phase II RCT of 45 Gy bid vs. 60 Gy bid (PCI for responders)

Primary endpoint 2 yr OS

176 pts enrolled from 2014-18



	2-year survival		
	%	95% CI	*p*
- 60 Gy	70.2%	59.3 - 79.7	
- 45 Gy	46.1%	34.5 - 57.9	*0.002*

	Median	95% CI
- 60 Gy	41.6 months	32.1 - 51.2
- 45 Gy	22.9 months	14.9 - 30.9

HR 0.63, 95% CI 0.41 – 0.95

p=0.027

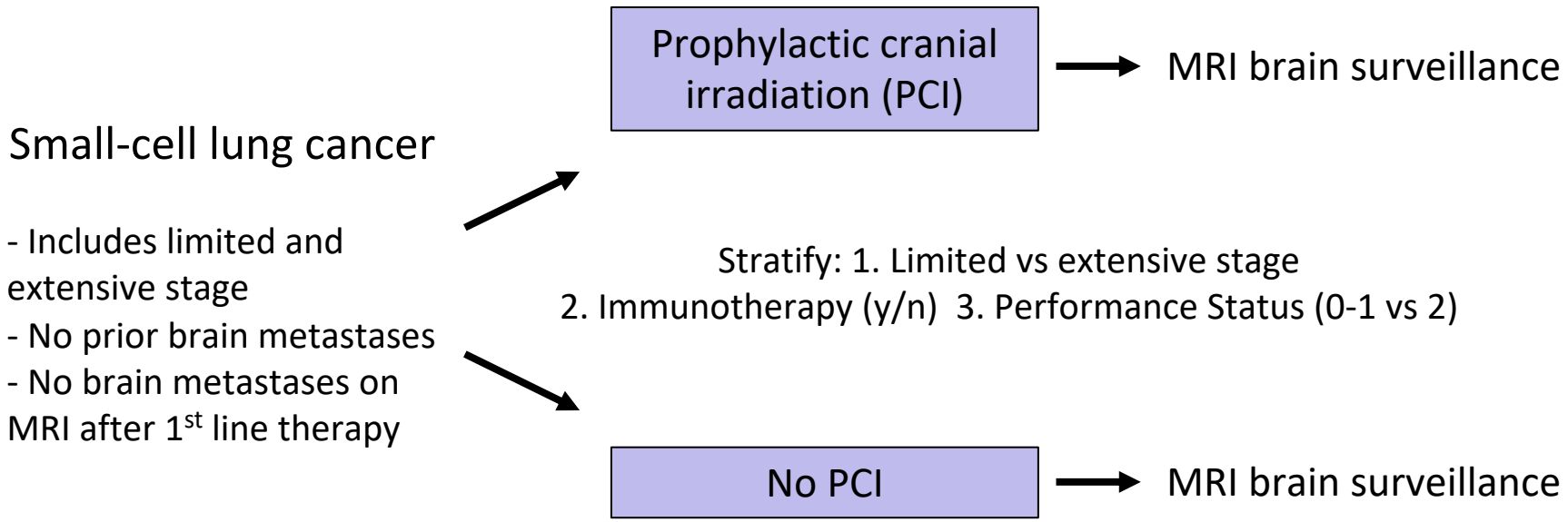
No differences in grade ≥ 3 esophagitis or pneumonitis

No difference in response rates or median PFS

2 yr OS significantly improved in 60 Gy arm

Gronberg et al, ASCO 2020

MAVERICK (SWOG 1827): MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation: A Randomized Phase III Trial in Small-Cell Lung Cancer



Primary Endpoint
- Overall survival (non-inferiority)

Secondary Endpoints
- Cognitive function
- QOL
- OS in limited and extensive stage
- Brain metastases free survival
- Toxicity

Translational Endpoints
-Longitudinal brain MRI changes
-ctDNA correlation to PFS, OS

Accrual goal: 668 patients

- MRI brain surveillance scheduled at 3, 6, 9, 12, 18, 24 months
- Radiation therapy is recommended at the time of brain metastases (WBRT and SRS allowed)
- Hippocampal-avoidance PCI and WBRT are allowed

PI: Drs. Chad Rusthoven and Paul Brown

Conclusions

- We are finally seeing progress in this recalcitrant disease
- We await RT + IO combo trials
  - NRG LU005 and Adriatic
- There is still much work to do → many patients not offered curative therapy
- Need deployment of biomarkers in next generation of LS-SCLC trials