The Evolving Story of Fractional Dose in Lung Cancer: Hyperfractionation, Conventional Fractionation, Hypofractionation, and Ablation

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EARLY STAGE NON-SMALL CELL LUNG CANCER

Biological Effective Dose

Not all SBRT is equal

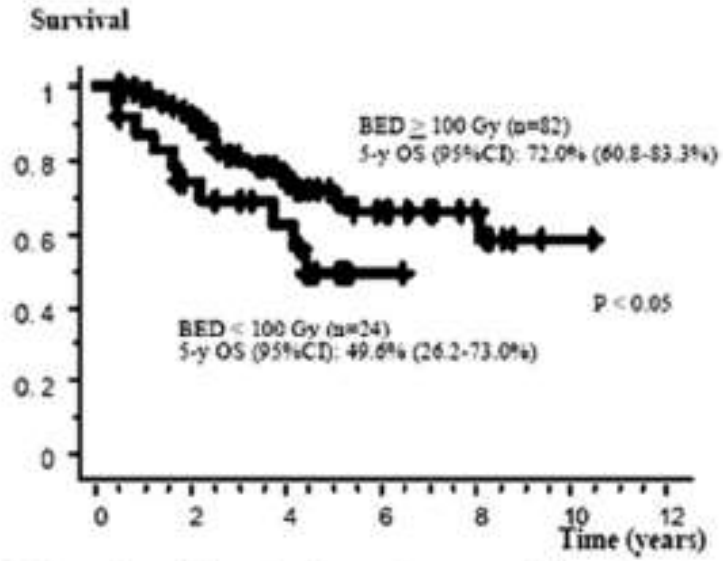


FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

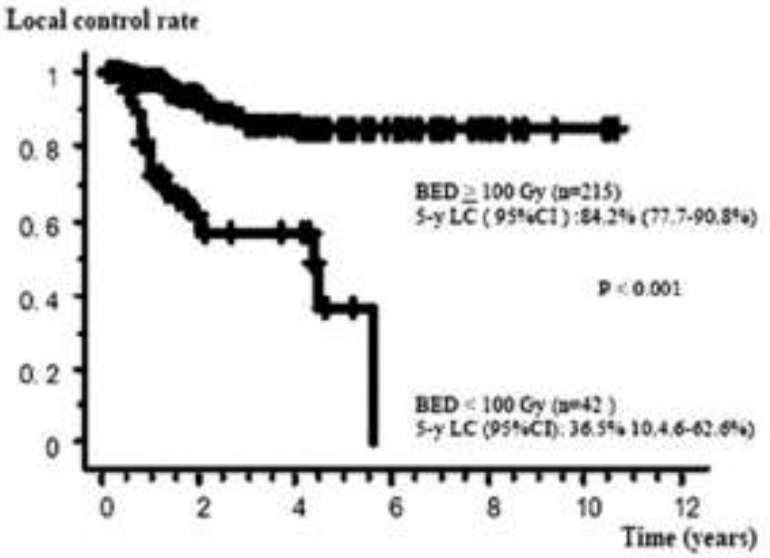
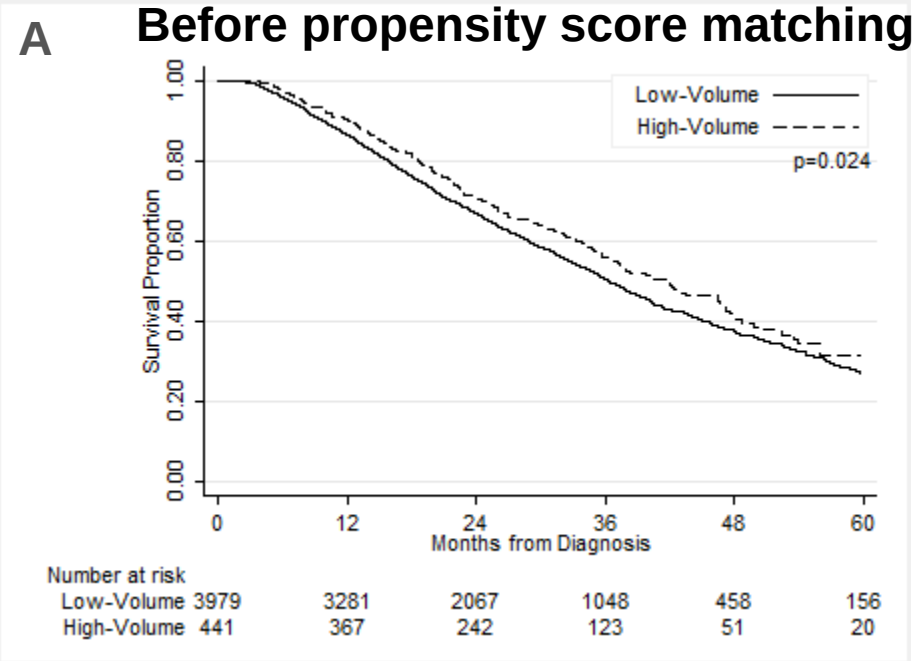


FIGURE 2. Cumulative local control rate according to the biological effective dose (BED). LC, local control rate; CI, confidence interval.

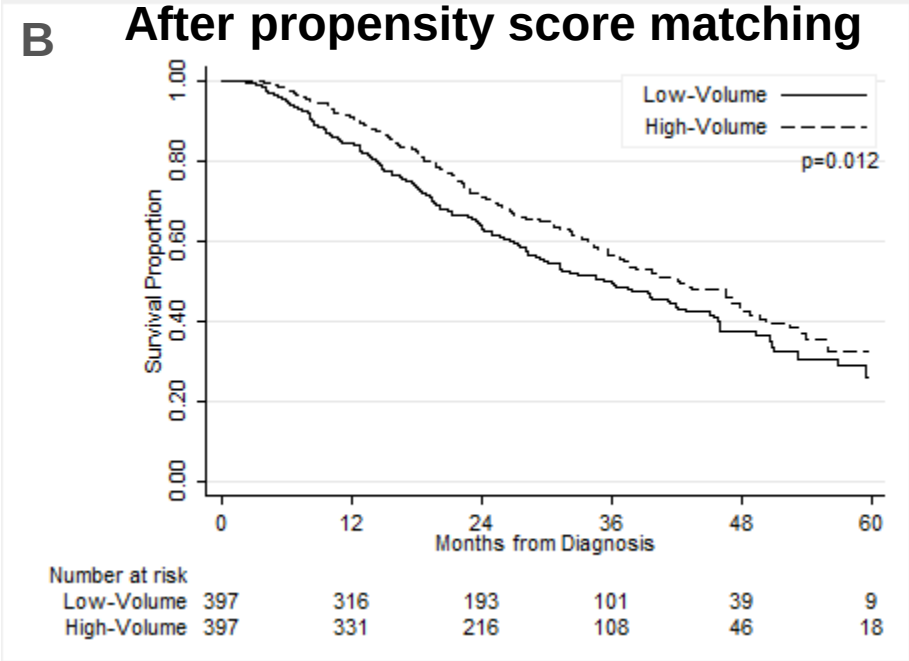
Onishi J, et al. *J Thorac Oncol*. 2007;2(7 Suppl 3):S94-100.

SBRT Results by Center Volume

- NCDB study of cT1-2aN0 NSCLC of 4,420 pts from 2007-2011
  - Variable of interest: facility volume 90th percentile (12 cases/yr)
  - Predictors of treatment at high volume facility: academic center (most associated), race, income, histologic confirmation, BED, tumor size



Median OS 41.9 months at HVF vs. 36.2 months at LVF, p=0.024



For HVF vs. LVF, propensity score-matched HR 0.77 (0.62-0.94), p=0.012

Park HS, et al. ASTRO 2015.

SBRT Results by Center Volume

Sensitivity analysis varying HVF definition

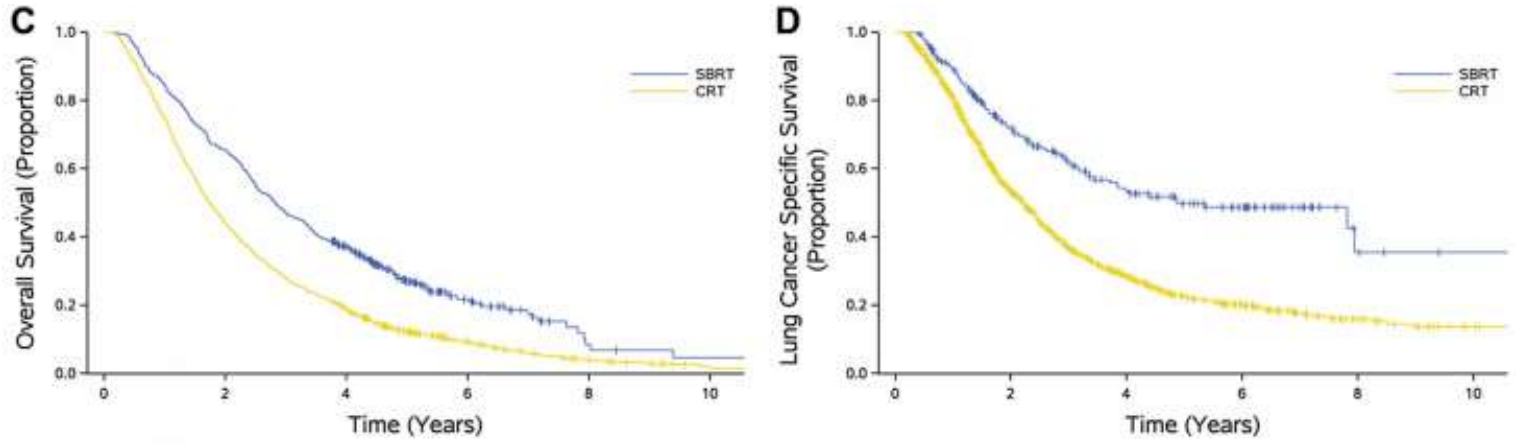
HVF Cut-Off (cases/year)	*Hazard Ratio (95% Confidence Interval)*	*P-value*
6 (59th percentile)	1.01 (0.93-1.10)	0.794
7 (66th percentile)	0.93 (0.85-1.02)	0.112
8 (73rd percentile)	0.91 (0.83-1.01)	0.069
9 (84th percentile)	**0.89 (0.79-0.99)**	**0.039**
10 (87th percentile)	**0.82 (0.72-0.93)**	**0.002**
11 (88th percentile)	**0.81 (0.71-0.92)**	**0.002**
12 (90th percentile)	**0.83 (0.71-0.96)**	**0.014**
13 (90th percentile)	**0.83 (0.71-0.96)**	**0.014**
14 (93rd percentile)	**0.82 (0.71-0.96)**	**0.014**

Conclusion: SBRT at high-volume facilities appears to be independently associated with improved overall survival among clinical stage I NSCLC patients

Park HS, et al. ASTRO 2015.

SBRT vs. Conventional Fractionation: VA Registry

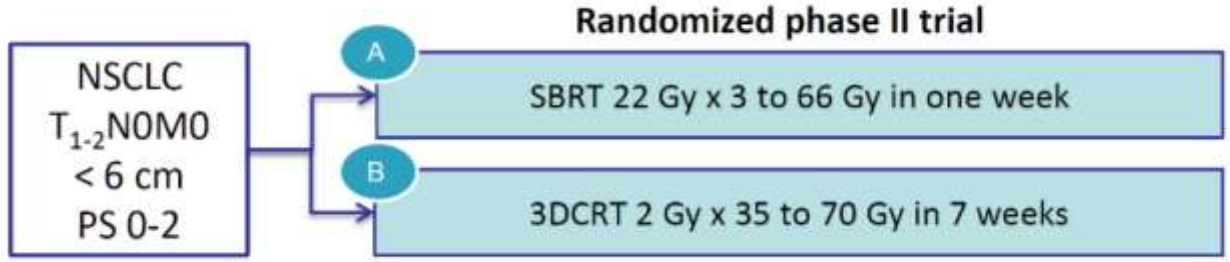
- VA Central Cancer Registry analysis of 11,997 patients with stage I NSCLC from 2001-2010
  - The 4-year OS rate increased from 38.9% to 53.2% from 2001 to 2010
  - Survival of radiated patients improved from 12.7% to 28.5%
  - SBRT significantly improved OS (HR = 0.60, 95% CI: 0.54-0.68) and lung cancer-specific survival (HR = 0.39, 95% CI: 0.32-0.46) compared with conventionally fractionated RT



Boyer MJ, et al. *J Thorac Oncol*. 2017;12(12):1814-1823.

SBRT vs. Conventional Fractionation: SPACE Trial

- Scandinavian SPACE Phase II Trial – Stereotactic Precision And Conventional radiotherapy Evaluation in stage I medically inoperable NSCLC

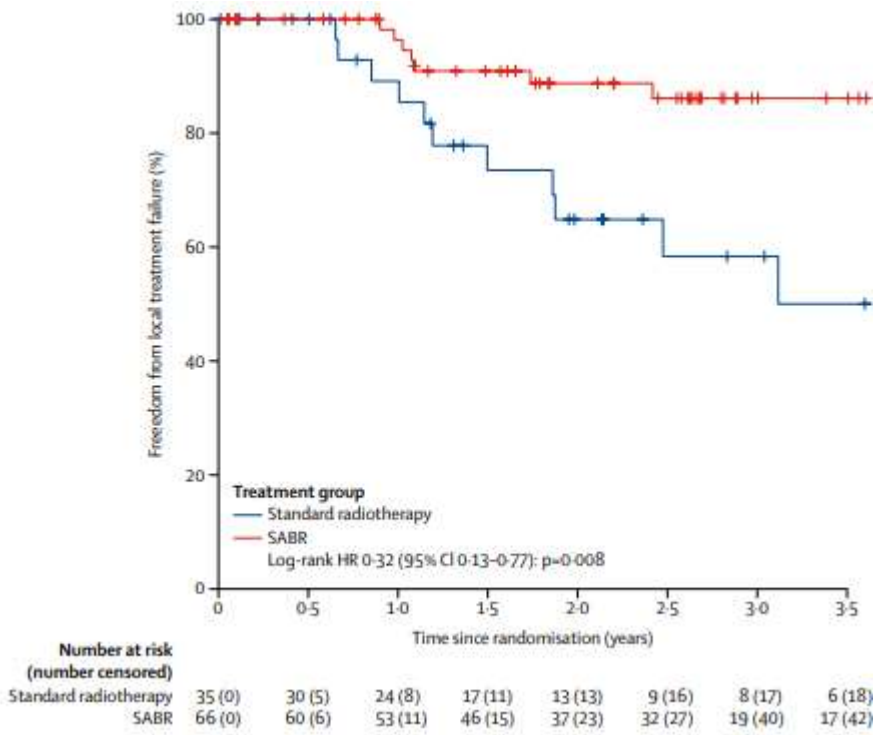


- 102 patients randomized
  - SBRT arm included more patients with T2-tumors (p=0.02), males (p=0.35)
- No difference in PFS (HR=0.85, 95% CI 0.52-1.36) or OS (HR=0.75, 95% CI 0.43-1.30)
- Pneumonitis: 19% (SBRT) vs. 34% (3DCRT), p=0.26
- Esophagitis: 8% vs. 30%, p=0.006
- HRQL using EORTC QLQ 30 and LC14:
  - 3DCRT patients had worse dyspnea (p = 0.01), chest pain (p = 0.02) and cough (>10 points difference)

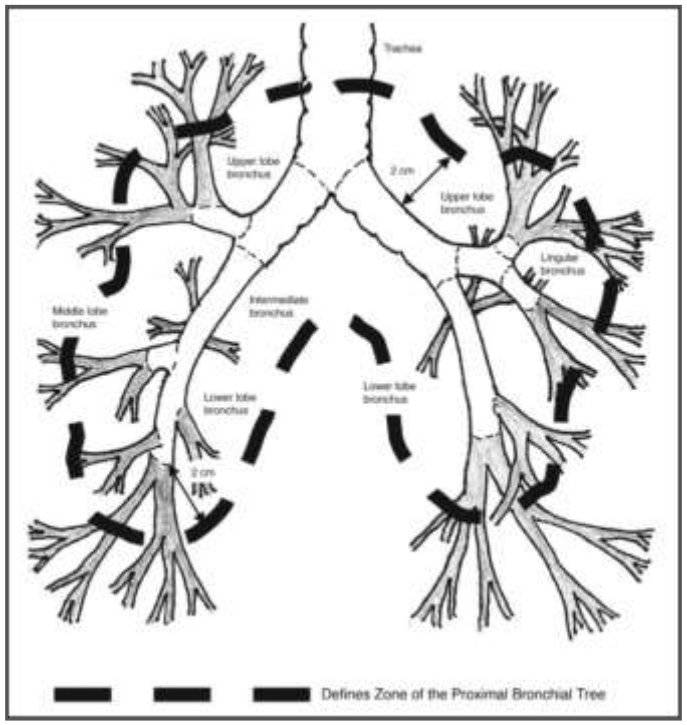
Nyman J, et al. *Radiother Oncol*. 2016;121(1):1-8.

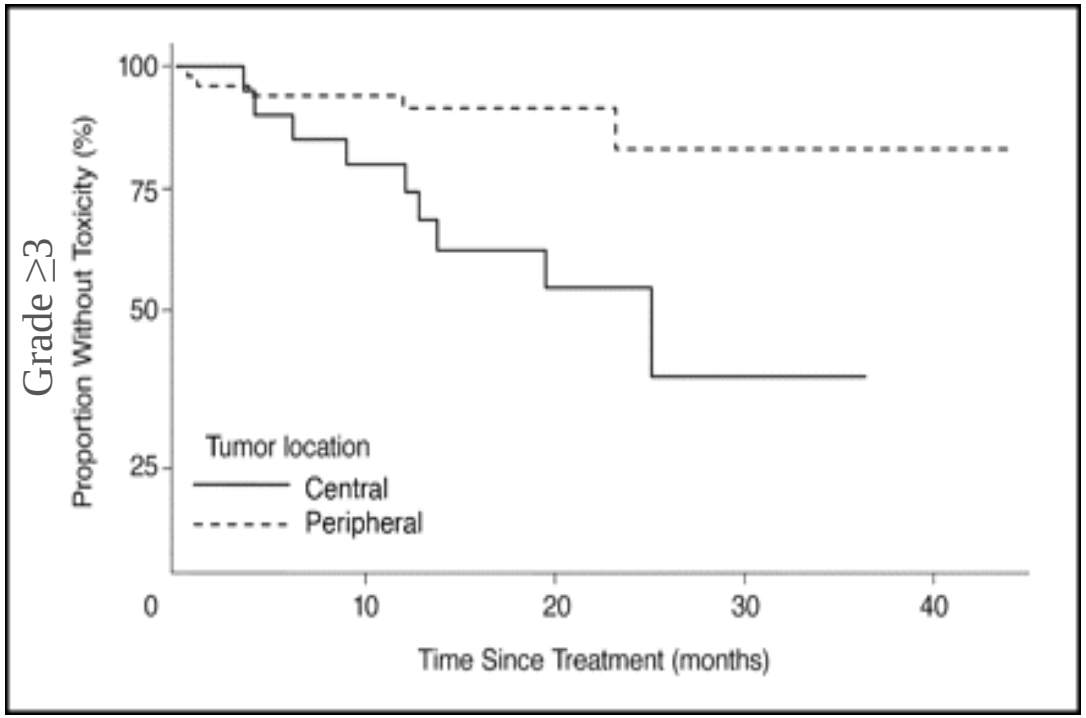
SBRT vs. Conventional Fractionation: TROG 09.02 CHISEL

- Multi-center, phase 3, randomized trial in Australia and New Zealand of 101 patients with biopsy-confirmed stage 1 (T1-T2aN0M0) peripheral NSCLC who were medically inoperable or had refused surgery randomized 2:1 to SBRT (54 Gy in 3 fx or 48 Gy in 4 fx) or standard radiotherapy (66 Gy in 33 fractions or 50 Gy in 20 fractions) from 12/2009-6/2015
- Local progression lower with SBRT (14% vs. 31%)
- Freedom from local treatment failure lower with SBRT (HR 0.32, 95% CI 0.13-0.77, p=0.0077)
- Median time to local treatment failure and OS not reached in either group
- No appreciable increase in major toxicity



Central SBRT Toxicity



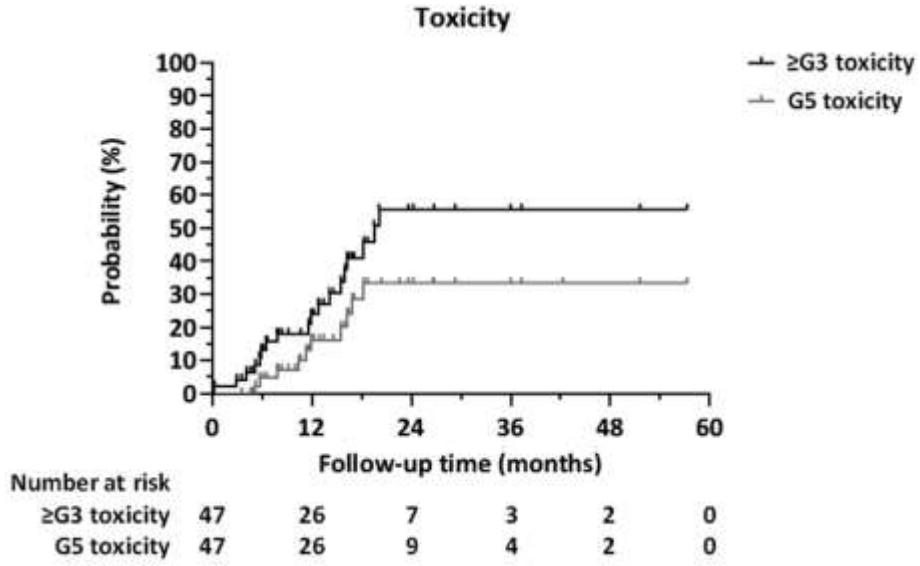


- 70 patient phase II study using 3 x 20 Gy (T1) or 22 Gy (T2)
  - 6 deaths attributable to therapy (4 in patients with perihilar/central tumors)
  - Median time to toxicity 10.5 months
- 2-year freedom from toxicity: peripheral 83% vs. central 54%, p=0.004

Timmerman R, et al. *J Clin Oncol*. 2006;24:4833-9.

ULTRA-Central SBRT Toxicity

- Hypofractionation for ULTRA-central tumors
  - 47 pts treated to 5 Gy x 12 (BED10 = 90 Gy) to ultracentral tumors (PTV overlapping the trachea or main bronchi)
  - Grade ≥3 toxicity in 38%
  - 21% with possible (n=2) or likely (n=8) treatment-related death (5.2-18.2 months after RT)
    - Fatal pulmonary hemorrhage in 15% of all pts



Tekatli H, et al. *J Thorac Oncol*. 2016;11(7):1081-9.

AUDIENCE RESPONSE: Which fractionation regimen would you administered for an ultra-central lesion immediately adjacent to esophagus and great vessels?

A. 18-20 Gy x 3 fractions

B. 12-12.5 Gy x 4 fractions

C. 10-11 Gy x 5 fractions

D. 7.5 Gy x 8 fractions

E. 7 Gy x 10 fractions

F. 4 Gy x 15 fractions

G. 3 Gy x 20 fractions

H. 2.25-3 Gy x 20-30 fractions

I. 2 Gy x 30-40 fractions

RTOG 0813: Central Tumors

- RTOG 0813 - Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients
  - 120 patients (cT1N0 in 65%) accrued from 2/2009-9/2013 with biopsy proven, PET-staged, ≤5 cm NSCLC
  - Central Location: within or touching the zone of the proximal bronchial tree or adjacent mediastinal/pericardial pleura

Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks									
Dose Level	Level 1	Level 2	Level 3	Level 4	**†Level 5**	Level 6	Level 7	Level 8	Level 9
Dose per Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	**10 Gy**	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40 Gy	42.5 Gy	45 Gy	47.5 Gy	**50 Gy**	52.5 Gy	55 Gy	57.5 Gy	60 Gy

  - DLT = any treatment-related grade ≥3 toxicity within 1 year
  - Primary Endpoint: maximal tolerated dose (SBRT dose where DLT probably was closest to but not exceeding 20%)
- At a median f/u of 37.9 months, 5 pts experienced DLTs
  - MTD was 12.0 Gy/fx, which had a probability of a DLT of 7.2% (95% CI, 2.8% to 14.5%)
  - 2-yr local control with 11.5 Gy/fx and 12.0 Gy/fx were 89.4% and 87.9%
  - 2-yr OS 67.9% and 72.7%; 2-yr PFS 52.2% and 54.5%

Bezjak A, et al. *J Clin Oncol*. 2019;37(15):1316-1325.

SBRT for Large Tumors

- 92 pts from 12 centers treated with SBRT for cN0 NSCLC ≥5.0 cm
  - Median tumor size 5.4 cm (range 5.0-7.5 cm)
  - Median dose/fractionation 50 Gy in 5 fx

	1 Year	2 Year
Local Control	95.5%	73.2%
Disease-free Survival	72.1%	53.5%
Disease-specific Survival	95.5%	78.6%
Overall Survival	76.2%	46.4%

- Multivariate analysis: pre-SBRT SUVmax associated survival
- Pattern of failure: distant (33%), local (26%), elsewhere in the lung (23%)
- Grade 3-5 toxicities: 1% grade 3 dermatitis, 4% grade 3 pneumonitis, 1% grade 5 pneumonitis
- 46 pts treated daily, 46 pts treated to other schedule (QOD, n=40)
  - QOD/other with fewer grade ≥2 toxicities (7% vs. 43%, p<0.001), pulmonary toxicities (p=0.014), any toxicities (p<0.001)
- Tumor location: 3-4 fx regimens more likely for peripheral lesions, no difference in toxicity by location
- NCBD Analysis: chemotherapy with SBRT improves survival for tumors ≥5 cm

Verma V, Simone CB 2nd, et. *Cancer*. 2017;123(4):688-698 Verma V, Simone CB 2nd, et. *IJROBP*. 2017;97(1):146-154. Verma V, Simone CB 2nd, et. *IJROBP*. 2017;97(1):146-154.

RTOG 0915: SBRT Fractionation

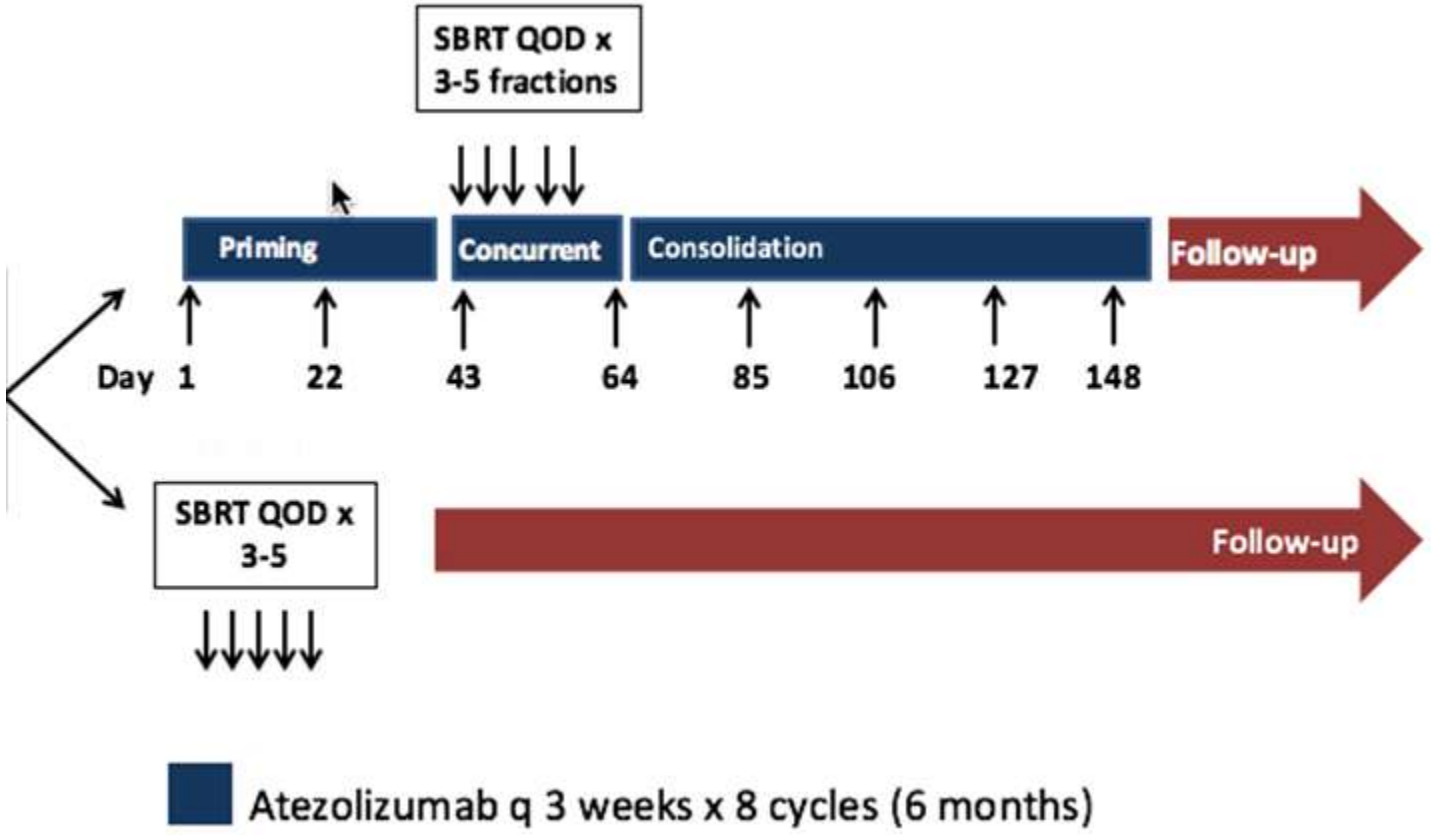
- Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer: NRG Oncology RTOG 0915 (NCCTG N0927)
  - Biopsy-proven T1-T2 N0 NSCLC
  - Primary endpoint: grade ≥3 adverse events at 1 year
  - Randomized to 34 Gy in 1 fraction or 48 Gy in 4 fractions
- 94 patients from 9/2009-3/2011 (84 analyzable), 2019 IJROBP update with median f/u 4.0 years
  - Grade ≥3 toxicity 2.6% in 1 fx and 11.1% in 4 fx
  - Median survival: 4.1 vs. 4.6 years
  - Primary tumor failure rate 10.6% vs. 6.8%
  - OS 29.6% vs. 41.1%, PFS 19.1% vs. 33.3%

Videtic GM, et al. *IJROBP*. 2015;93(4):757-64.

Videtic GM, et al. *IJROBP*. 2019; 103(5):1077-1084.

SWOG/NRG S1914: A Randomized Phase III trial of Induction/ Consolidation Atezolizumab + SBRT versus SBRT Alone in High risk, Early Stage NSCLC (PIs: Simone/Daly)

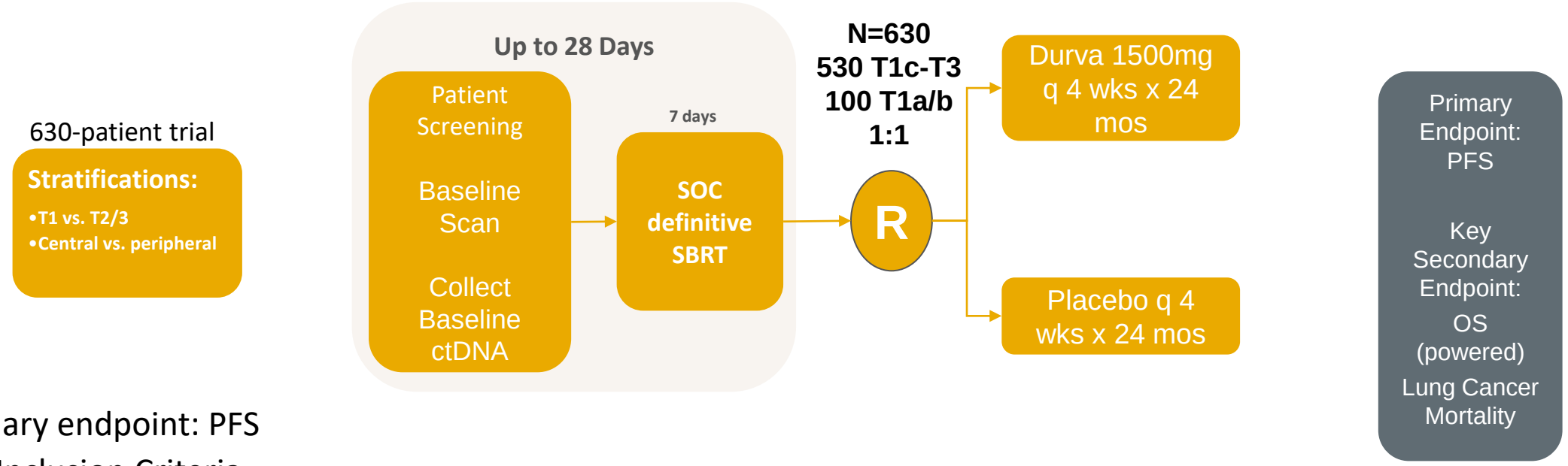
- Histologically proven stage I-IIa NSCLC ≤7 cm diameter without nodal or distant involvement
- Inoperable or refuses surgery
- ECOG PS 0-2
- One or more high-risk feature identified:
  - Tumor diameter ≥ 2 cm
  - Tumor SUV max ≥ 6.2
  - Moderately, poorly differentiated or undifferentiated histology



Stratification factors:
- Location (central vs peripheral)
- Size (<4 cm vs ≥4 cm)
- Zubrod PS (0-1 vs 2)

Primary Endpoint = Overall Survival; n=480 pts

PACIFIC-4/RTOG-3515: A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab Following Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Patients with Stage I/II Non-small Cell Lung Cancer (PI: Robinson)



- Primary endpoint: PFS
- Key Inclusion Criteria
  - Histologically or cytologically documented NSCLC
  - Clinical Stage I/II lymph node-negative (T1-T3 N0 M0) disease receiving SBRT
  - Medically inoperable or refuse surgery
  - ECOG PS 0-2
  - Central or peripheral lesions eligible, “ultra-central” excluded

Necessities of SBRT: Tumor Motion Control

- Motion encompassment
  - Account for motion from respiration (commonly 4DCT)
- Motion mitigation
  - Breath hold
  - Active breathing control/coaching/biofeedback techniques
  - Forced swallow breathing (commonly abdominal compression)
  - Respiratory gating
  - Dynamic tumor tracking

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER:

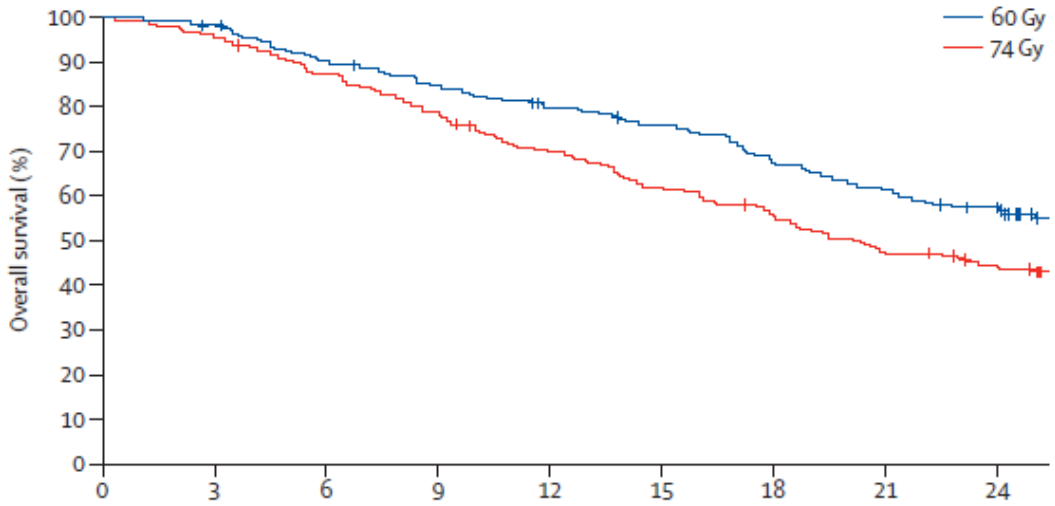
CONVENTIONAL FRACTIONATION

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0617/NCCTG N0628/CALGB 30609

A RANDOMIZED PHASE III COMPARISON OF STANDARD- DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

	60 Gy	74 Gy	P Value
Grade ≥3 Pulmonary	20%	19%	0.71
Grade ≥3 Pneumonitis	7%	4%	0.25
Grade ≥3 Esophagitis	**7%**	**21%**	**<0.0001**
Grade ≥3 Any	76%	79%	NS
Grade 5 Toxicity	**N=3**	**N=8**	**<0.05**



Median overall survival: 28.7 months (60 Gy) vs. 20.3 months (74 Gy), p=0.0042

Bradley JD, et al. *Lancet Oncol*. 2015;16(2):187-99.

Maintenance Immunotherapy: PACIFIC

- 713 patients randomized 2:1 between 1-42 days after chemoradiation to durvalumab:Placebo delivered Q2 weeks for up to 12 months
- Outcomes
  - Median OS: NR vs. 28.7 mo, HR 0.68, p=0.0025
  - 2-yr OS: 66.3% vs. 55.6%, p=0.005
  - Median PFS: 17.2 months vs. 5.6 months
  - Median time to death or distant metastasis: 28.3 vs. 16.2 mo
  - Fewer new lesions, fewer brain mets, higher response rate, longer duration of response, longer time to next therapy
- Toxicity
  - Grade 3-4 AEs: 30.5% vs. 26.1%
  - Most frequent AEs leading to the discontinuation of treatment: pneumonitis (4.8% vs. 2.6%), radiation pneumonitis (1.3% vs. 1.3%), pneumonia (1.1% vs. 1.3%)
  - Grade 5 AEs: 4.4% and 6.4%

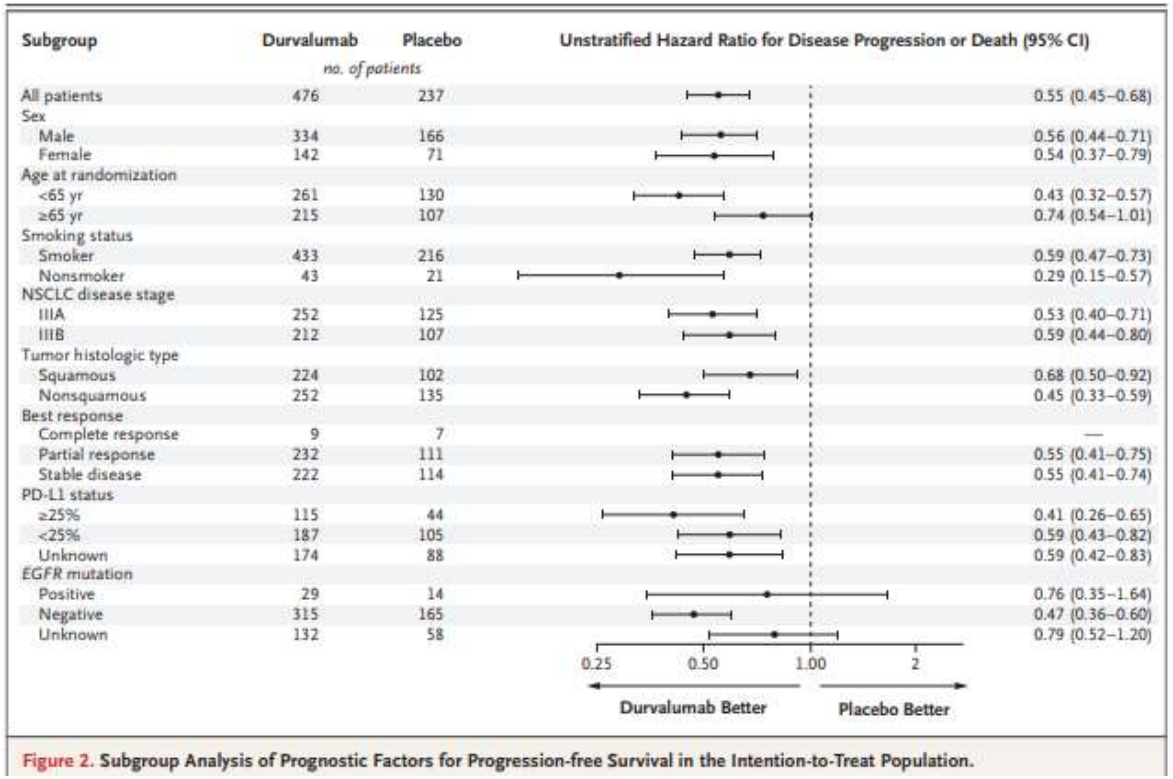


Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

Antonia SJ, et al. *N Engl J Med. 2018;379(24):2342-2350.* Antonia SJ, et al. *N Engl J Med. 2017;377(20):1919-1929.*

PORT Meta-Analysis and Toxicity

- 2,343 patients from 11 trials
  - Using outdated RT techniques, significant adverse effect of PORT on survival HR 1.18
- Benefit of improved local-regional control of PORT offset by excess toxicity and death from RT
  - Causes of death primarily cardiac and pulmonary

	NSCLC	Treatment	Other	Non-Cancer
PORT	82%	4%	14%	**18%**
No PORT	89%	2%	9%	**11%**

- PORT toxicities related to:
  - Technique (cobalt → Linac; lateral fields → conformal/IMRT)
  - Volume irradiated (whole mediastinum → involved field)
  - Total dose (50-60 Gy → 50-54 Gy) [Machtay M, et al. J Clin Oncol. 2001;19(19):3912-7. → increased risk of death from intercurrent death if ≥ 54 Gy RT]
  - Dose per fraction (1.8-3.0 Gy → 1.8-2.0 Gy) [Dautzenberg B, et al. Cancer. 1999;86(2):265-73. → increased risk of death from intercurrent death if >2 Gy per fraction]

Cochrane Database Syst Rev. 2005;(2):CD002142.

LA-NSCLC NRG Oncology Current Enrolling Study

- RTOG 1308: Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC (PI: Liao)
  - Protons vs. photons up to 70 Gy with concurrent chemotherapy (platinum-based doublet) +/- consolidation chemotherapy and/or immunotherapy
  - Primary outcomes: overall survival AND major cardiac toxicities (grade ≥2) and lymphocyte reduction (grade ≥4 lymphopenia)
  - Secondary outcomes: progression-free survival, grade ≥3 adverse events, QOL/PROs, cost-effectiveness outcomes, PFT changes
  - 330 patient targeted accrual

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER:

HYPERFRACTIONATION

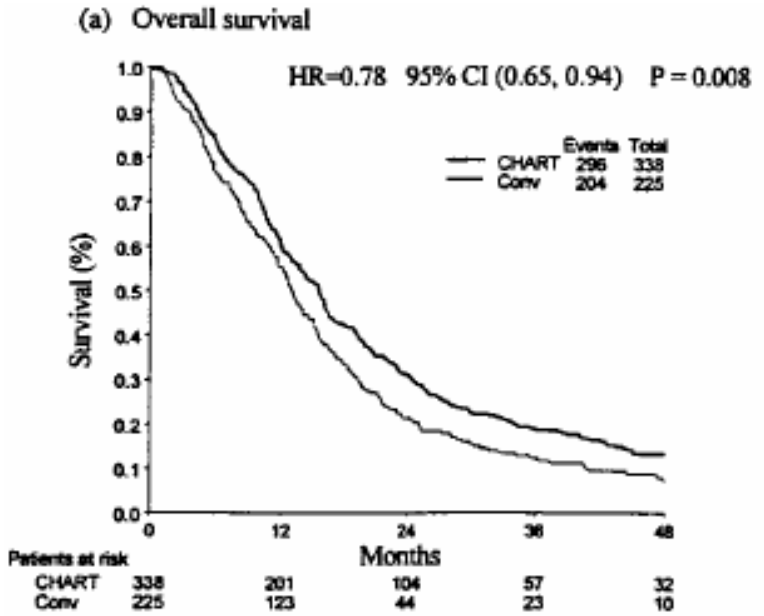
Hyperfractionation and Acceleration: Rationale in NSCLC

- Accelerated fractionation
  - Rapid doubling time of epithelial cells (esp. squamous cell > adenocarcinoma)
  - Shorter RT intervals may prevent accelerated repopulation after treatment damage
  - Clinical evidence for improvements in survival with shorter treatment times for NSCLC
    - NCDB analysis: median OS significantly worse in NSCLC patients with >2 vs. ≤2 days treatment delay (18.6 vs. 22.7 mo., p<0.0001)
      - OS worsened with each cumulative interval of delay (standard RTT vs. prolonged 1-2 days, 20.5 mo., p=0.009; prolonged 3-5 days, 17.9 mo., p<0.0001; prolonged 6-9 days, 17.7 mo., p<0.0001; prolonged >9 days, 17.1 mo., p<0.0001)
      - On MVA, prolonged RTT was independently associated with inferior OS (HR 1.21, p<0.0001)
      - Prolonged RTT as a continuous variable was also significantly associated with worse OS (p=0.0007)
- Hyperfractionation
  - Smaller fraction size may decrease late normal tissue toxicity
    - No survival benefit seen in RTOG 88-08/ECOG 4588/SWOG 8992 (sequential) or RTOG 94-10 (concurrent)

McMillian MT, Simone CB 2nd, et al. *IJROBP. 2017;98(5):1142-1152.*

EORTC - CHART

- 563 pt w/ inoperable NSCLC (81% squamous cell) not receiving chemotherapy randomized:
  - CHART: 54 Gy in 1.5 Gy TID fractions (12 consecutive days)
  - Conventional: 60 Gy/2.0 Gy (6 weeks)
- Toxicity
  - Acute: severe dysphagia 19% vs. 3% ($p<0.05$), radiation pneumonitis (NS)
  - Intermediate: Lhermittes in 8 vs. 0 pts (occurred 3+/-16 mo after RT)
  - Late: trend towards increased RT pneumonitis requiring treatment/ hospitalization in CHART (NS)
- Results: all pts
  - MST: 16.5 mo vs. 13.0 mo
  - 3-yr OS: 20% vs. 13%, p=0.008
  - 21% reduction in RR of local progression (p=0.033)
- Results: squamous cell
  - MST: 18.0 mo vs. 12.5 mo
  - 3-yr OS: 21% vs. 11%, p=0.0007
  - 27% reduction in RR of local progression (p=0.012)
  - 24% reduction in RR of metastasis (P = 0.043)
    - Reduced risk of metastasis likely due to improved local tumor control

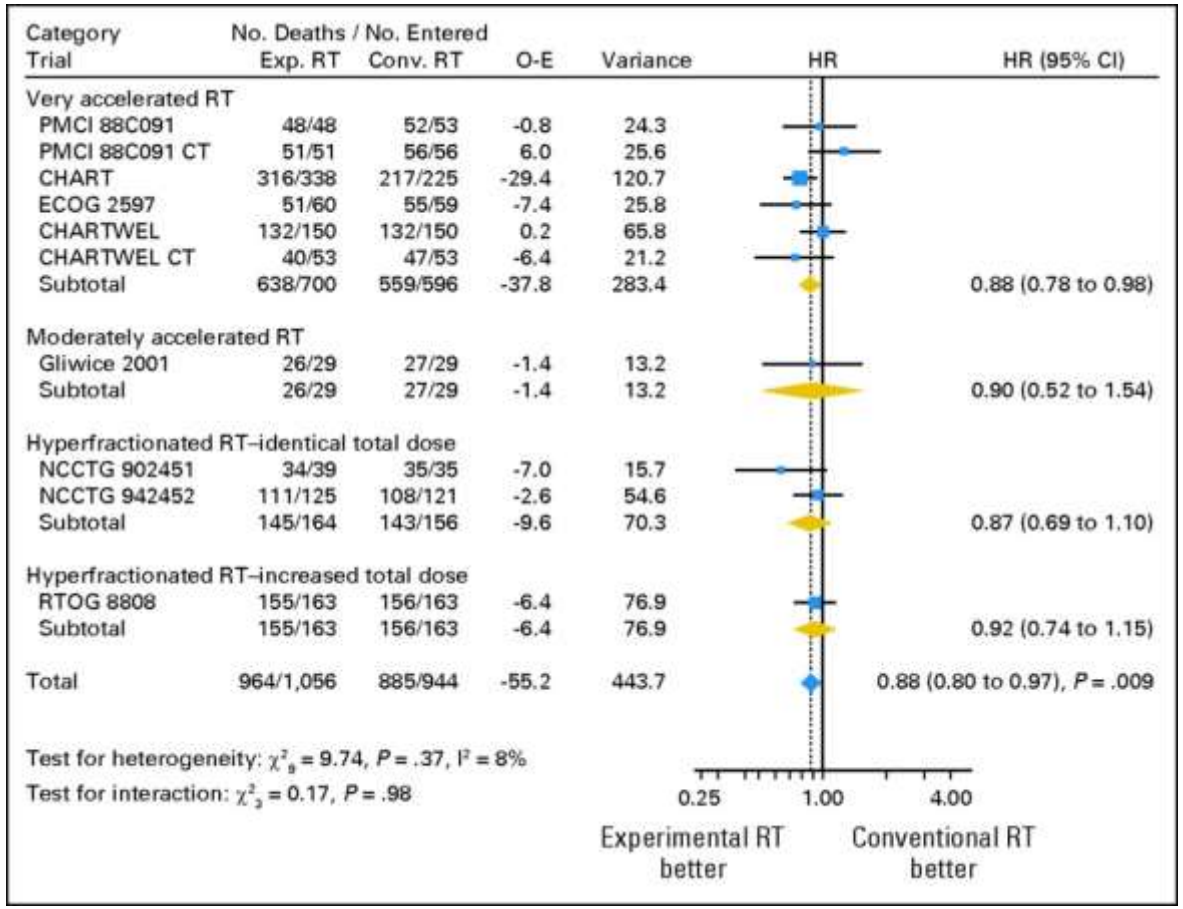


Saunders M, et al. *Lancet*. 1997;350(9072):161-5.

Saunders M, et al. *Radiother Oncol*. 1999;52(2):137-48.

Future of HyperFractionation for NSCLC

- Meta-analysis of 10 trials (2,000 pts) using modified fractionation for NSCLC
  - Improved OS (HR 0.88, p=0.009)
  - 5-yr survival increased by 2.5% (from 8.3% to 10.8%)
  - No difference in PFS (p=0.19)
  - Increased esophageal toxicity
- No major trials pending, more interest in hypofractionation



Mauguen A, et al. *J Clin Oncol*. 2012;30(22):2788-97.

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER:

HYPOFRACTIONATION

RTOG 93-11: Mild Hypofractionation

- 177 pts w/ stage I-III inoperable NSCLC in phase I-II 3DCRT dose-escalation trial
  - Concurrent chemotherapy not allowed, 14% received induction chemo
  - Stratified at escalating RT doses by V20
- Treatment groups
  - V20 <25% (Group 1): 70.9 Gy, 77.4 Gy, 83.8 Gy, 90.3 Gy (2.15 Gy fx)
  - V20 25-36% (Group 2): 70.9 Gy, 77.4 Gy
  - V20 ≥37% (Group 3): did not accrue (n=2)
- Results
  - 24-month locoregional control: no difference (50-78%)
  - 24-month OS: no difference (20-50%)
  - Regional nodal failure: no difference (18%)

Group	RT Dose (Gy)	Acute Grade ≥3 Lung Toxicity (n)	Acute Grade ≥3 Esoph-ageal Toxicity (n)	Late Grade ≥3 Lung Toxicity – 18 months	Late Grade ≥3 Esophageal Toxicity – 18 months
1	70.9	0	0	7%	8%
	77.4	0	0	16%	0%
	83.8	0	0	0%	4%
	90.3	3	0	13% (1 fatal)	6% (1 fatal)
2	70.9	0	0	15%	0%
	77.4	2	0	15%	5%

Bradley J, et al. *Int J Radiat Oncol Biol Phys*. 2005;61(2):318-28.

NRG LU004: Phase I Trial of Accelerated or Conventionally Fractionated Radiotherapy Combined With MEDI4736 (durvalumab) in PD-L1 High Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (ARCHON-1) (PI: S. Lin)

Registration: Institution-determined PD-L1 expression ≥ 50%

INITIAL SAFETY SCHEDULES

First 6 patients are registered to Cohort 1, then the next 6 to Cohort 2.

Cohort 1 (n=6)	Cohort 2 (n=6)
Durvalumab[†] **q4 weeks** x 13 doses + ACRT 60 Gy in 15 fractions x 3 weeks (weeks 1-3)	Durvalumab[†] **q4 weeks** x 13 doses + standard RT 60 Gy in 30 fractions x 6 weeks (weeks 1-6)

EXPANSION COHORTS

If Cohort 1 only is deemed safe, all patients will be registered to Cohort 3. If Cohort 2 only is deemed safe, all patients will be registered to Cohort 4. Otherwise, patients will be randomized 1:1 to Cohorts 3 and 4.

Cohort 3 (n=6)	Cohort 4 (n=6)
Durvalumab[†] **q4 weeks** x 13 doses + ACRT 60 Gy in 15 fractions x 3 weeks (weeks 1-3)	Durvalumab[†] **q4 weeks** x 13 doses + standard RT 60 Gy in 30 fractions x 6 weeks (weeks 1-6)

[†] Durvalumab begins 2 weeks (Day -14) before RT (+/- 48 hours)

- All patients receive Durvalumab, chemotherapy not allowed
- Primary Objective:

Determine if the addition of Durvalumab to two schedules of RT (**60 Gy in 30 fractions vs. 60 Gy in 15 fractions**) is safe

- Secondary Objectives:

Determine if the addition of MEDI4736 (durvalumab) to RT is feasible

Assess toxicities associated with adding MEDI4736 (durvalumab) to RT

Assess the impact the addition of MEDI4736 (durvalumab) has on PFS

- Exploratory Objectives:

Circulating tumor cells and immune parameters

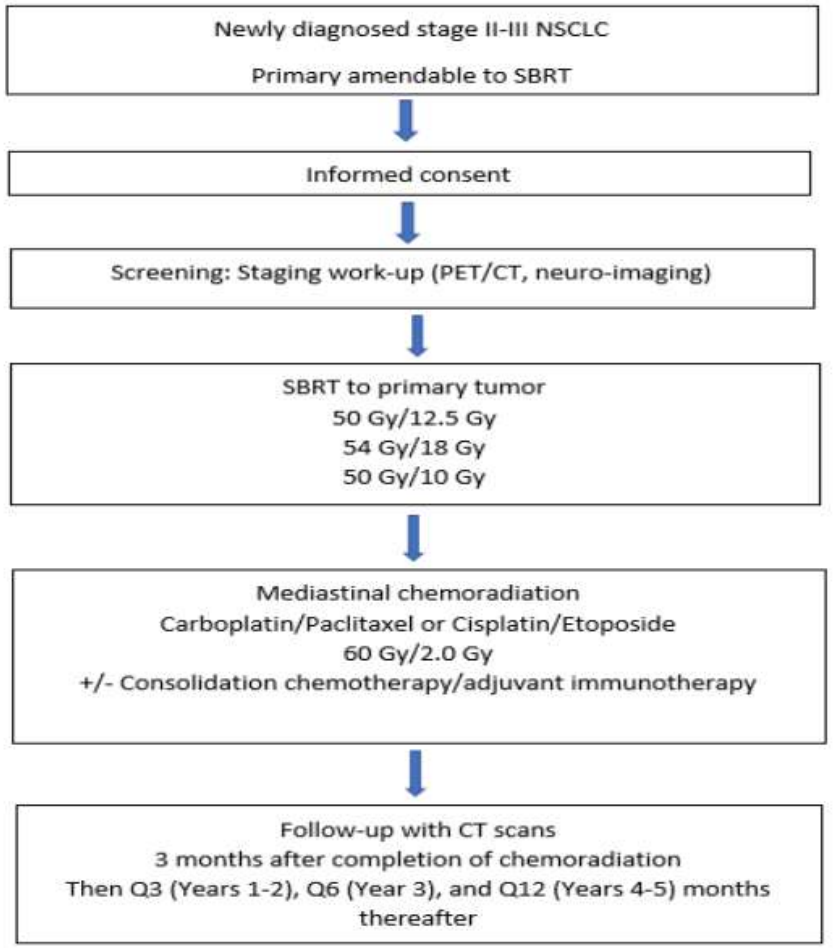
- Expected Accrual: 12-24
- Status: enrolling!

Hypofractionation with Proton Therapy

- Proton Collaborative Group LUN005: Multi-center Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III NSCLC
  - Phase I: Proton RT with concurrent chemotherapy to 60 CGE in 24 (2.5 CGE) → 20 (3.0 CGE) → 17 (3.53 CGE) → 15 (4 CGE) fractions [find maximum tolerated dose]
  - Phase II: 61 patients treated with MTD [primary endpoint: 1-yr OS]
- 18 patients enrolled to phase I, 2 SAEs (both in the 3.53 CGE arm and both from chemo unrelated to RT)
- 28 patients analyzed for phase II (22 patient stage III)
  - 1- and 2-year OS rates were 89% and 66%
  - 1- and 2-year PFS rates were 70% and 60%

Hoppe BS, Simone CB 2nd, et al. *IJROBP*. 2005;61(2):318-28.

Phase II Prospective Trial of Primary Lung Tumor Stereotactic Body Radiation Therapy Followed By Concurrent Mediastinal Chemoradiation for Locally-Advanced NSCLC

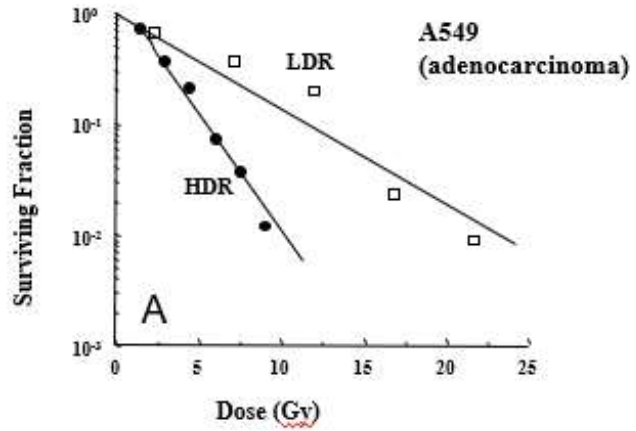


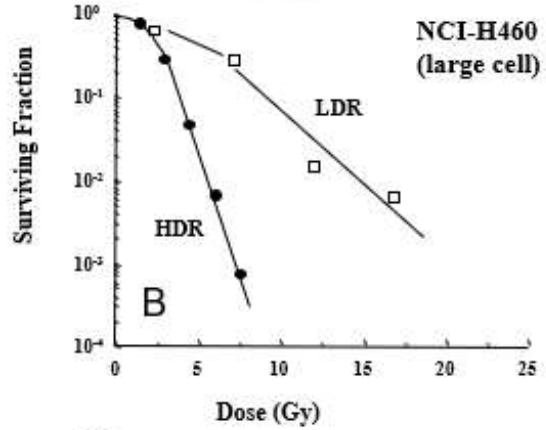
- Eligibility: LA-NSCLC primary tumor size ≤ 7 cm and located ≥2 cm from the proximal bronchial tree and involved nodal disease
- Treatment: SBRT to primary tumor → chemordiation to involved nodes → consolidative systemic therapy
- Early Results (first 31 subjects enrolled [20 pts with >1 yr f/u)]
  - Enrollment to date: 31 subjects
  - No local failures, 4 distant failures, 1 distant and regional failure
  - 1-year PFS in pts receiving durvalumab: 77%
- Radiation related toxicities:
  - Grade 3 esophagitis: 1 pt (4%) [grade 2 in 37%]
  - Grade 2 pneumonitis: 4 pts (15%)
  - No grade ≥3 pulmonary or cardiac events related to RT

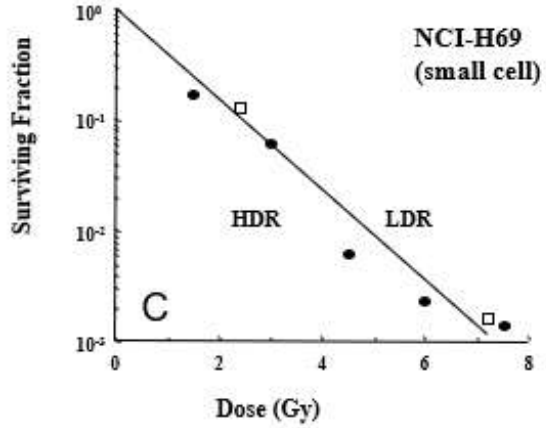
SMALL CELL LUNG CANCER

Rationale for Hyperfractionation

- SCLC cell lines among the most radiosensitive *in vitro*
  - More rapid doubling time, higher growth fraction, earlier development of widespread metastasis than NSCLC
  - Minimal shoulder on cell survival curves
  - Tumor death exponentially even at low doses
- Accelerated RT attacks rapidly proliferating population
  - Multiple small fractions of RT may provide enhanced therapeutic ratio
  - Standard total dose of RT delivered in BID regimen can shorten overall treatment interval and reduce repopulation of malignant clonogens







SCLC cell lines showed exponential cell killing without a radiation survival curve shoulder

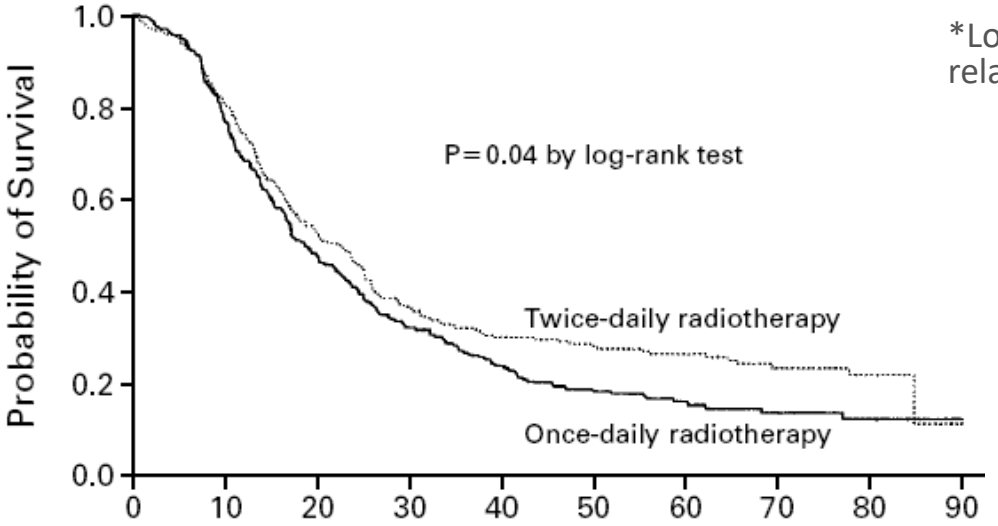
Accelerated Hyperfractionation: Intergroup

- Intergroup 0096 trial of 417 pts w/ limited-stage SCLC randomized from 5/1989-7/1992 to 45 Gy concurrent thoracic RT BID (1.5 Gy/fx/3 wks) vs. QDay (1.8 Gy/fx/5 wks)
  - Chemo: cisplatin 60 mg/m^2 D1 + etoposide 120 mg/m^2 D1-3 Q21 days x 4 cycles
  - Radiation: concurrent w/ chemo C1
    - Spinal Cord Constraint: 35-36 Gy (BID), 45 Gy (QDay)
    - BID Regimen: AP-PA week 1, AP-PA QAM and off-cord obliques QPM week 2-3
    - **RT doses not radiobiologically equivalent
  - PCI (25 Gy/2.5 Gy) to all pts w/ CR

Turrisi AT 3rd, et al. *N Engl J Med*. 1999;340(4):265-71.

Accelerated Hyperfractionation: Intergroup

	QDay	BID	p Value
CR	49%	56%	p=0.23
2-yr FFS	24%	29%	p=0.10
LF	52%	36%	p=0.06
Simultaneous LF+DF	23%	6%	p=0.01
MS	19 mo	23 mo	p=0.04 (HR 1.2)
2-yr OS	41%	47%	
5-yr OS	16%	26%	
Grade 3 Esophagitis	11%	27%	p<0.001



*Local failure defined as lack of CR or intrathoracic relapse after CR (PR = local failure)

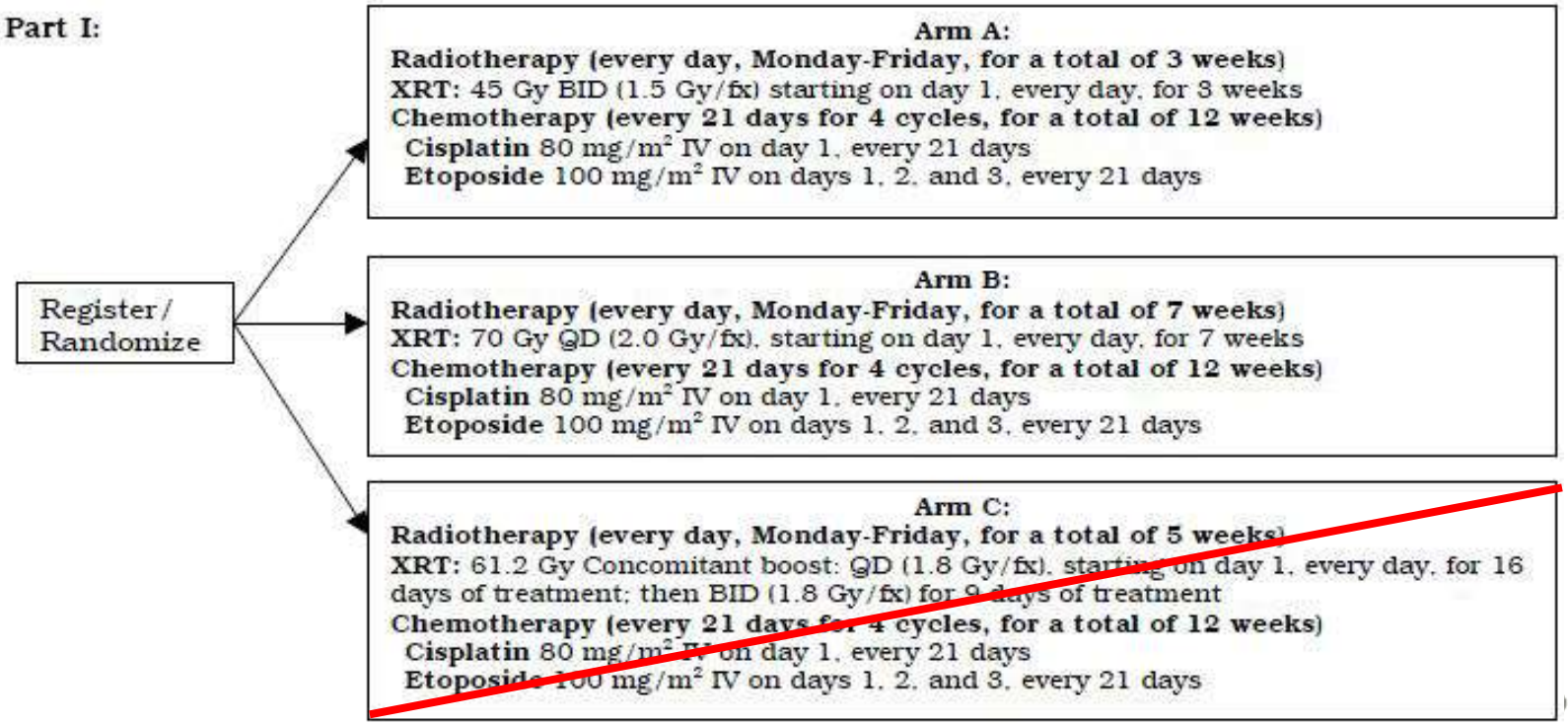
Turrisi AT 3rd, et al. *N Engl J Med*. 1999;340(4):265-71.

Twice Daily vs. Once Daily RT for LS-SCLC: CONVERT

- Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT) phase III trial
  - 547 patients randomized from 4/2008-11/2013 to 66 Gy/2 Gy QDay vs. 45 Gy/150 cGy BID
  - RT starts with C2 of 4 cycles of Q21 days cisplatin 60 mg + etoposide 120 mg, no immunotherapy allowed
    - Treats involved field only
    - RT normal tissue constraints: spinal cord 42 Gy (BID) and 48 Gy (QDay), lung V20 35%
- Median OS: 30 months BID vs. 25 months QD (HR 1.18 [95% CI 0.95–1.45]; p=0.14)
  - **Survival outcomes did not differ between twice-daily and once-daily concurrent chemoradiotherapy**
- Toxicities
  - Toxicities similar except more grade 4 neutropenia with BID (49% vs. 38%, p=0.05)
  - No difference in grade 3-4 esophagitis (19% vs. 19%, p=0.85) or pneumonitis (3% vs. 2%, p=0.70)
- Author's conclusions: survival outcomes did not differ, toxicity was similar, since the trial was designed to show superiority of QD and was not powered to show equivalence, the implication is that BID should continue to be considered the standard of care

Twice Daily vs. Once Daily RT for LS-SCLC: CALGB 30610

- Intergroup (CALGB 30610/RTOG 0538, opened 3/2008, enrolling): Phase III Randomized Study of Three Different Thoracic Radiotherapy Regimens in Patients With Limited-Stage Small Cell Lung Cancer Receiving Cisplatin and Etoposide
  - 729 pts accrued, completed 11/2019
  - PCI for all CR or near CR pts



NRG LU005: Limited Stage Small Cell Lung Cancer (LS-SCLC): A Phase II/III Randomized Study of Chemoradiation Versus Chemoradiation Plus Atezolizumab (PI: Higgins)

PATIENT POPULATION:

Limited stage (Tx, T1-T4, N1-3, M0) small cell lung cancer (LS-SCLC)

STRATIFICATION

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

RANDOMIZE*

Arm 1

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

Arm 2

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

*Randomization is 1:1.

** Chemotherapy doublets delivered concurrently, cisplatin/etoposide or carboplatin/etoposide, is required. The site/investigator must declare the chemotherapy regimen that the patient will receive prior to the patient's randomization. Patients who develop a contraindication to cisplatin after beginning therapy may receive carboplatin in subsequent cycles.

*** All patients with a complete or near complete response are recommended to receive prophylactic cranial irradiation (PCI), planned within 4-6 weeks from completion of chemoradiotherapy. Patients on Arm 2 who receive PCI will receive it concurrent with atezolizumab.

- Allows QD and BID RT with C2 of chemo
- Phase II primary endpoint = PFS
  - HR of 0.62 hypothesized (improving median PFS from 13 to 21 months)
  - Sample size of 280
  - 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 <0.84
  - When at least 79 deaths available, HR for OS <1.46
- Phase III primary endpoint = OS
  - HR of 0.71 hypothesized
  - Total sample size 506

Conclusions

Conclusions

- Early Stage NSCLC
  - SBRT improves local control and survival compared with conventionally fractionated RT
  - SBRT is most optimally delivered to a BED ≥100 Gy, in high volume centers, and with motion management
  - Central SBRT is feasible when delivered in 5 fractions
  - Dose escalation and/or immunotherapy may improve outcomes for larger node-negative patients
- Locally Advanced NSCLC
  - Conventional fractionation dose escalation results in decreased survival in unselected patients
  - Maintenance immunotherapy improves survival
  - Hyperfractionation can improve survival (especially for squamous cell) in patients not receiving chemotherapy
  - Hypofractionation can increased BED and may be feasible to deliver with concurrent immunotherapy without chemotherapy or with chemotherapy using proton therapy
- Small Cell Lung Cancer
  - Accelerated hyperfractionation exploits SCLC's rapid doubling time and limited repair of sublethal damage
  - Treatment should be to 45/1.5 Gy BID (potentially preferred) or 66-70 Gy QD, potentially with a benefit with maintenance immunotherapy

Questions?