Recent therapeutic advances and novel trial concepts for patients with locally advanced NSCLC

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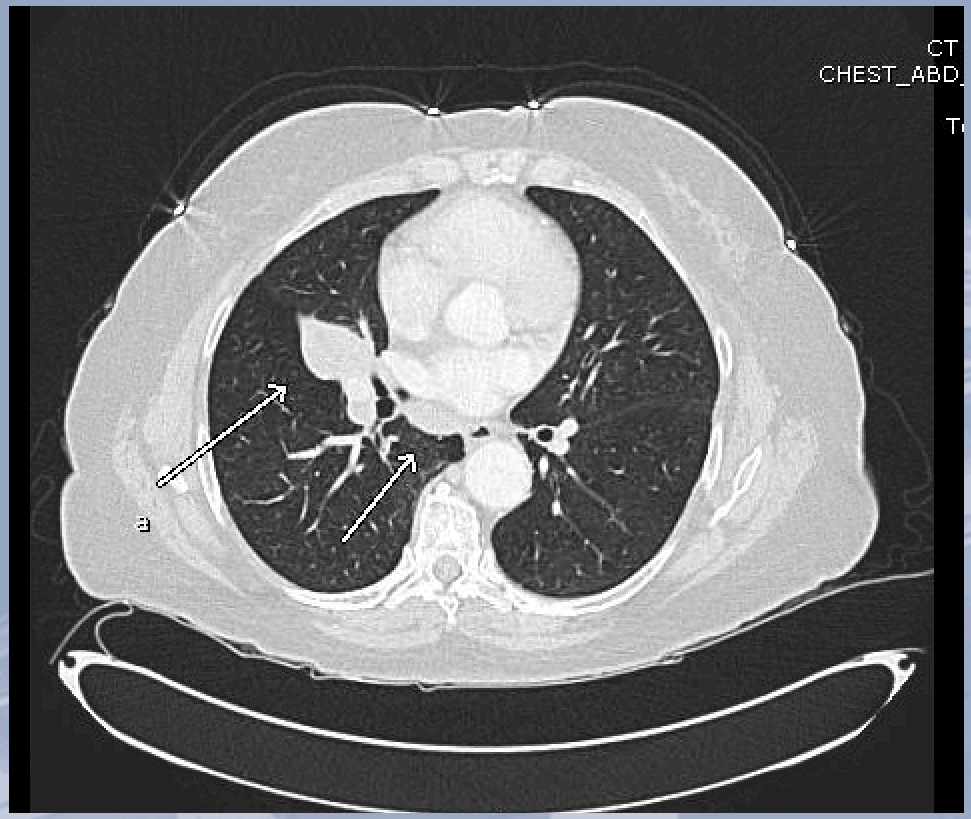
Yale CANCER CENTER

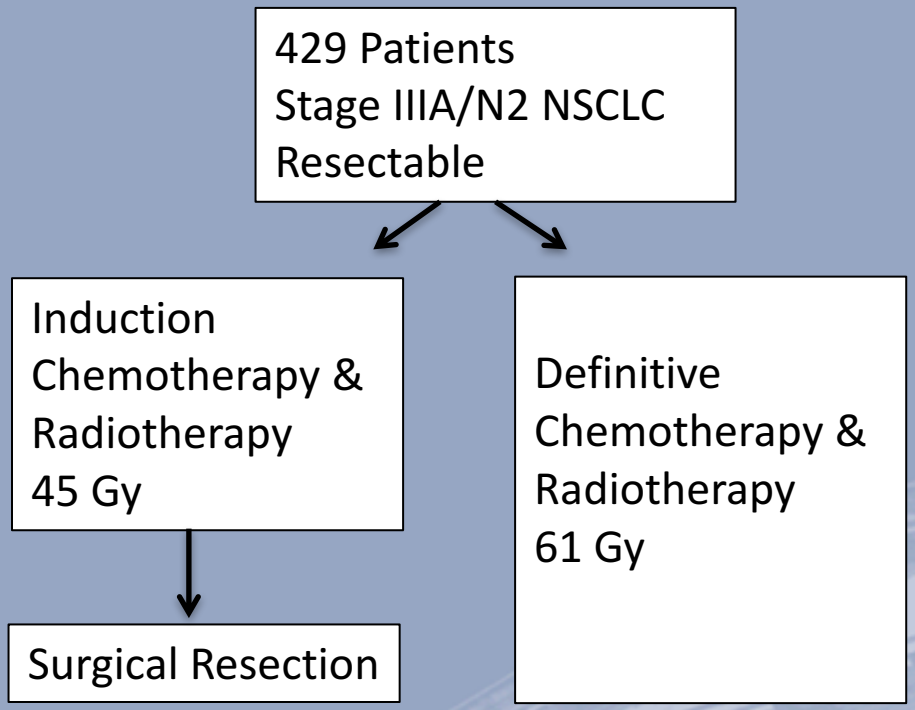
- 77-year-old presents with a worsening cough, scant hemoptysis
- Chest x-ray shows a right lung mass
- Chest CT: 3.5-cm right perihilar mass, enlarged subcarinal lymph node
- PET/CT: avid disease in right perihilar mass, subcarinal lymph node. No distant disease
- Brain MRI negative
- No weight loss. CBC, laboratory studies are WNL

- Bronchoscopy and EBUS biopsies positive in RML, subcarinal and 4R stations
  - TTF1+ adenocarcinoma
  - EGFRwt, ALK-



Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyau Chen, Robert B Livingston, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, Willliam T Sause, James D Cox



-Albain et al, Lancet 2009

	CT/RT/S (group 1, n=202)	CT/RT (group 2, n=194)	Total (n=396)
Age (years)			
Median (range)	59 (31-77)	61 (32-78)	60 (31-78)
≤60	113 (56%)	95 (49%)	208 (53%)
>60	89 (44%)	99 (51%)	188 (47%)
Karnofsky performance status			
70-80	23 (11%)	25 (13%)	48 (12%)
90-100	179 (89%)	169 (87%)	348 (88%)
Estimated weight loss in past 6 months (kg)			
<5	154 (76%)	146 (75%)	299 (76%)
5-10	36 (18%)	30 (15%)	67 (17%)
>10	7 (3%)	10 (5%)	17 (4%)
Unknown	5 (2%)	8 (4%)	13 (3%)
T stage			
T1	50 (25%)	47 (24%)	97 (24%)
T2	130 (64%)	121 (62%)	251 (63%)
T3	22 (11%)	26 (13%)	48 (12%)
Number of positive nodal stations reported			
1	153 (76%)	146 (75%)	299 (76%)
2	39 (19%)	39 (20%)	78 (20%)
3	4 (2%)	4 (2%)	8 (2%)
Unknown	6 (3%)	5 (3%)	11 (3%)

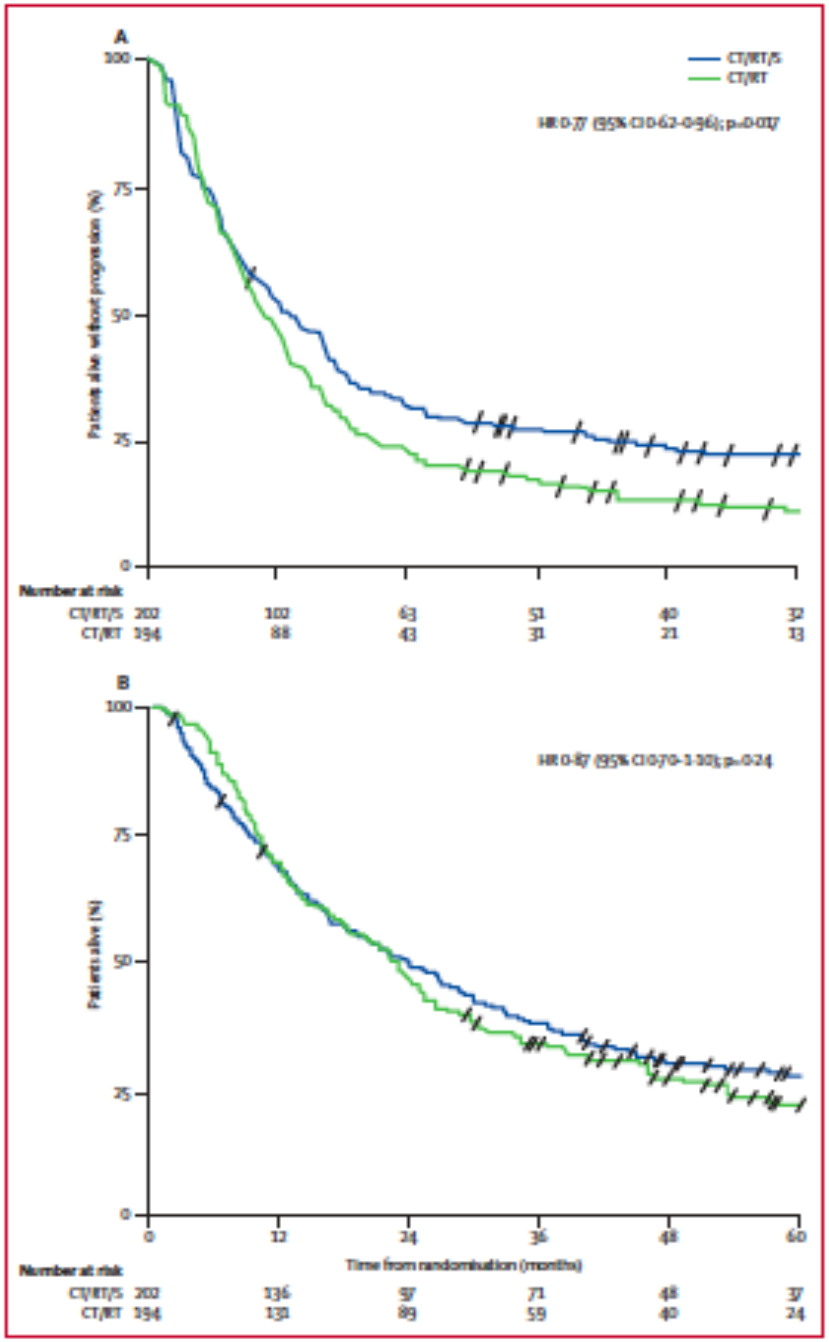
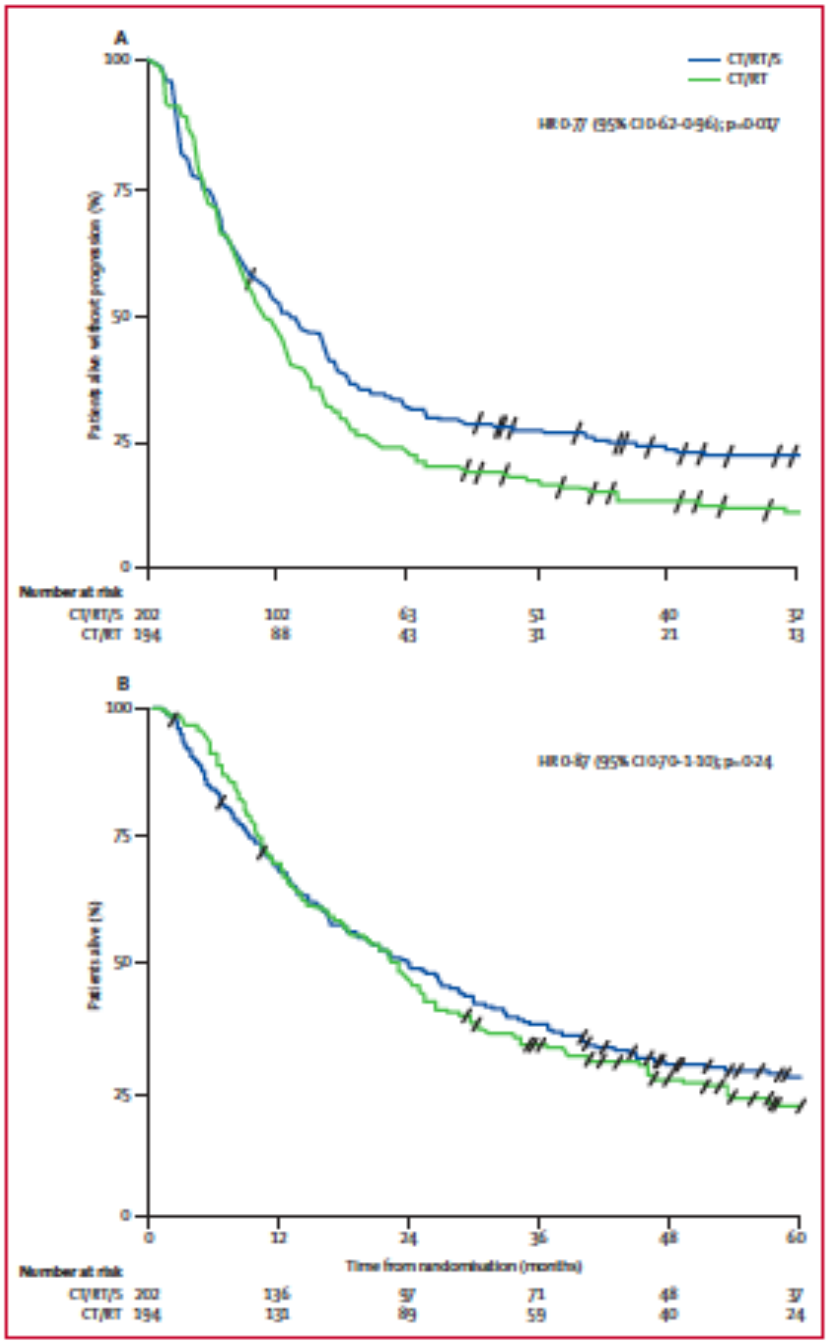


Figure 2: Progression-free survival (A) and overall survival (B) of intention-to-treat population
Slash marks represent censored results. CT/RT/S=chemotherapy plus radiotherapy followed by surgery (group 1, n=202). CT/RT=chemotherapy plus radiotherapy (group 2, n=194). HR=hazard ratio.

- PFS superior with C/RT/S
- No difference is OS



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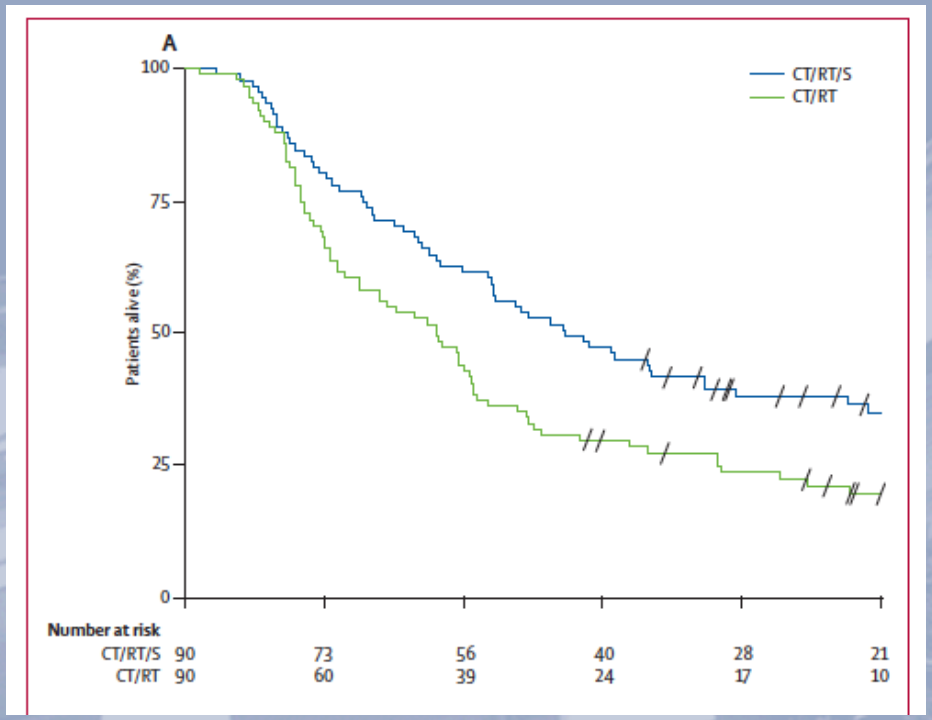
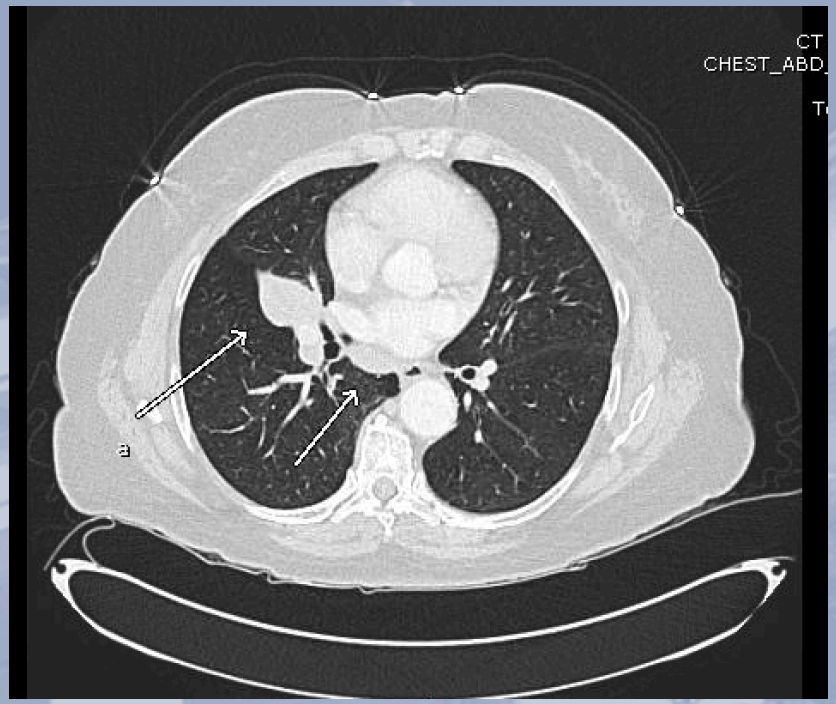
- PFS superior with C/RT/S
- No difference is OS

- OS improved with surgery in lobectomy patients



- Notes on patients on the Intergroup Trial
  - Excluded T4 and N3
  - Young: median < 60, and 90% had KPS 90-100
  - 75% had 1 nodal station pos., 98% had 1 or 2
  - All were technically resectable at diagnosis
  - FEV1 > 2L (or PO pred FEV1 > 800cc)

- Our patient:
  - 77 years old
  - Requires bilobectomy+
  - Multistation positive



- The standard radiation dose for stage III NSCLC was established in 1982, with the publication of the RTOG 7301 trial
  - 60 Gy continuous treatment superior to 40 or 50 Gy or split course
  - Radiation dose escalation beyond 60 Gy appears beneficial

Reference	Trial	Number of Patients	Chemotherapy	Radiation dose	Outcomes
Perez et al. (1982)	RTOG 73-01	378	–	40, 50, 60 Gy	Improvement in local control with higher dose.
Cox et al. (1990)	RTOG 8311	848	–	<69.6 Gy, >69.6 Gy, up to 79.2 Gy	Improvement in median survival (13 months) for >69.6 Gy.
Bradley et al. (2005)	RTOG 93-11	176	–	70.9–90.3 Gy	90.3 Gy maximum tolerated dose. Established safety of dose escalation based on lung V20.
Kong et al. (2005)	–	106	–	63–103 Gy	OS improved with increasing dose. MTD not reached.
Rosenman et al. (2002)	–	62	Induction and concurrent CaT	60–74 Gy	74 Gy was safe in setting of concurrent chemotherapy.
Socinski et al. (2004)	–	29	Induction CaIT. Concurrent CaT	78–90 Gy	MTD not reached.
Schild et al. (2006)	–	15	Concurrent CaT	70–78 Gy	MTD 74 Gy.
Bradley et al. (2010a)	RTOG 0117, Phase I	17	Concurrent CaT	Started at 75.25 Gy	Significant grade 3 toxicity at 75.25 Gy. MTD determined to be 74 Gy.
Socinski et al. (2008)	CALGB 30105	69	Induction and concurrent CaT v. induction CaGem with concurrent Gem.	74 Gy	Closed early due to high toxicity with Gem. Median survival 24.3 months (CaT) vs. 12.5 months (CaGem).

-Terakedis et al, Front Oncol 2011

RTOG 0617

IIIA/B NSCLC

<u>Stratified by</u>
- 3D v IMRT
- PS 0 v 1
- PET staging or not
- Squamous v non-

Carboplatin & Paclitaxel → Consolidation C&P
60 Gy in 6 weeks

Carboplatin & Paclitaxel → Consolidation C&P
74 Gy in 7.5 weeks

Carboplatin & Paclitaxel & Cetuximab → Consolidation C&P & Cetuximab
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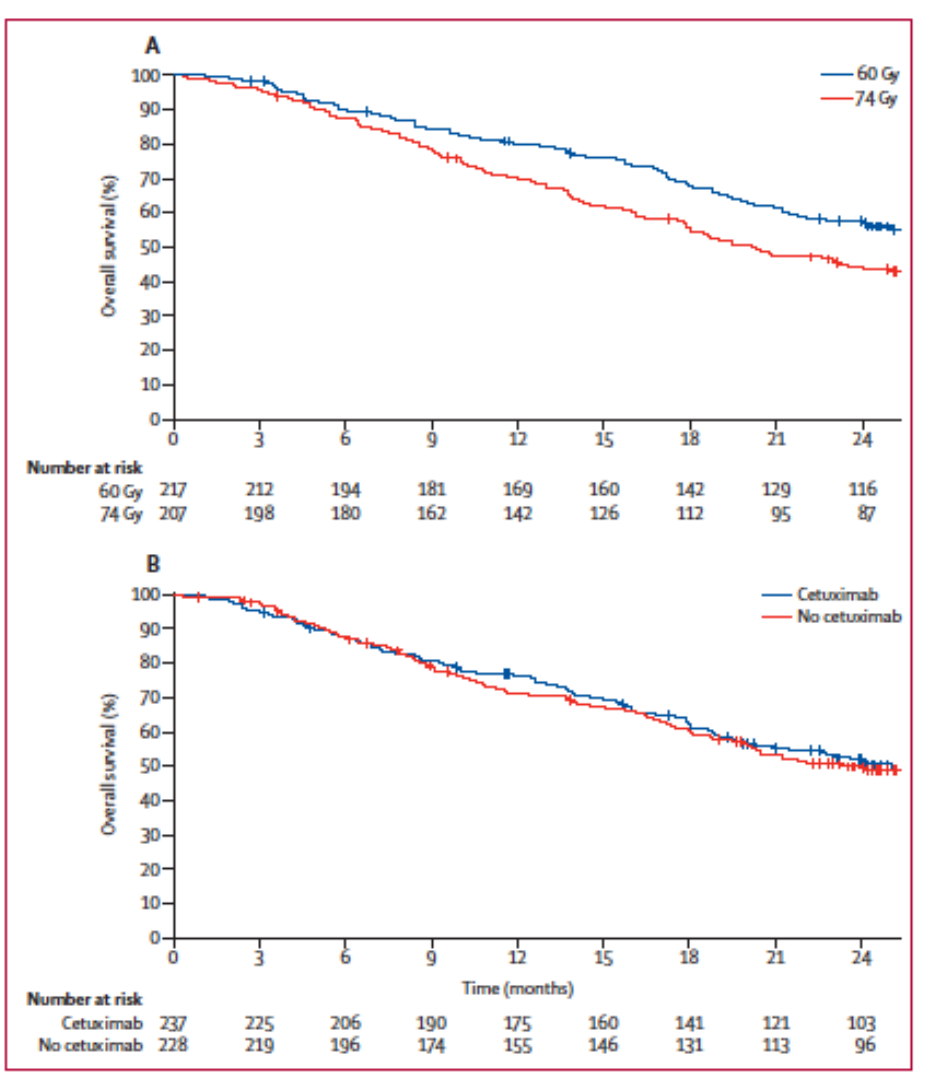
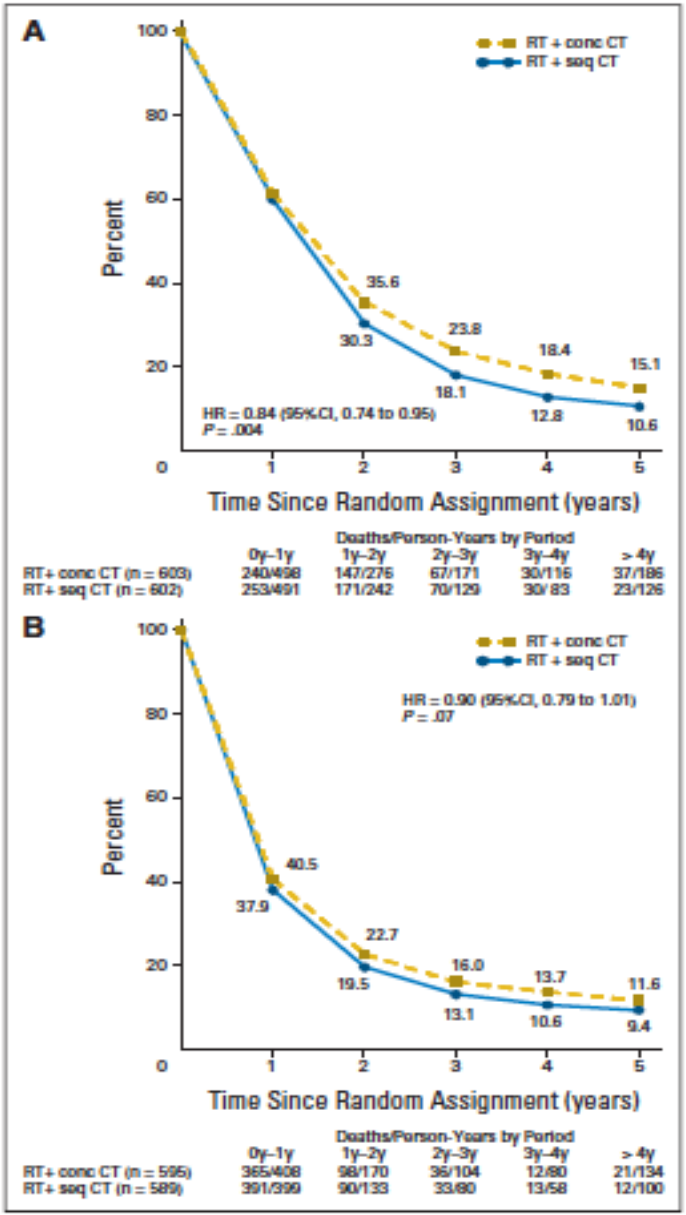
RTOG 0617



- High-dose arms closed early for futility
- OS significantly worse in high-dose arms, 20.3 vs 28.7 months
- More treatment-related deaths in high-dose arms (8 vs 3)
- No difference in tumor volume, radiation coverage
- Heart dose was a significant predictor of worse OS

-Bradley et al, Lancet Oncology 2015

Advances in Chemotherapy for Stage III…

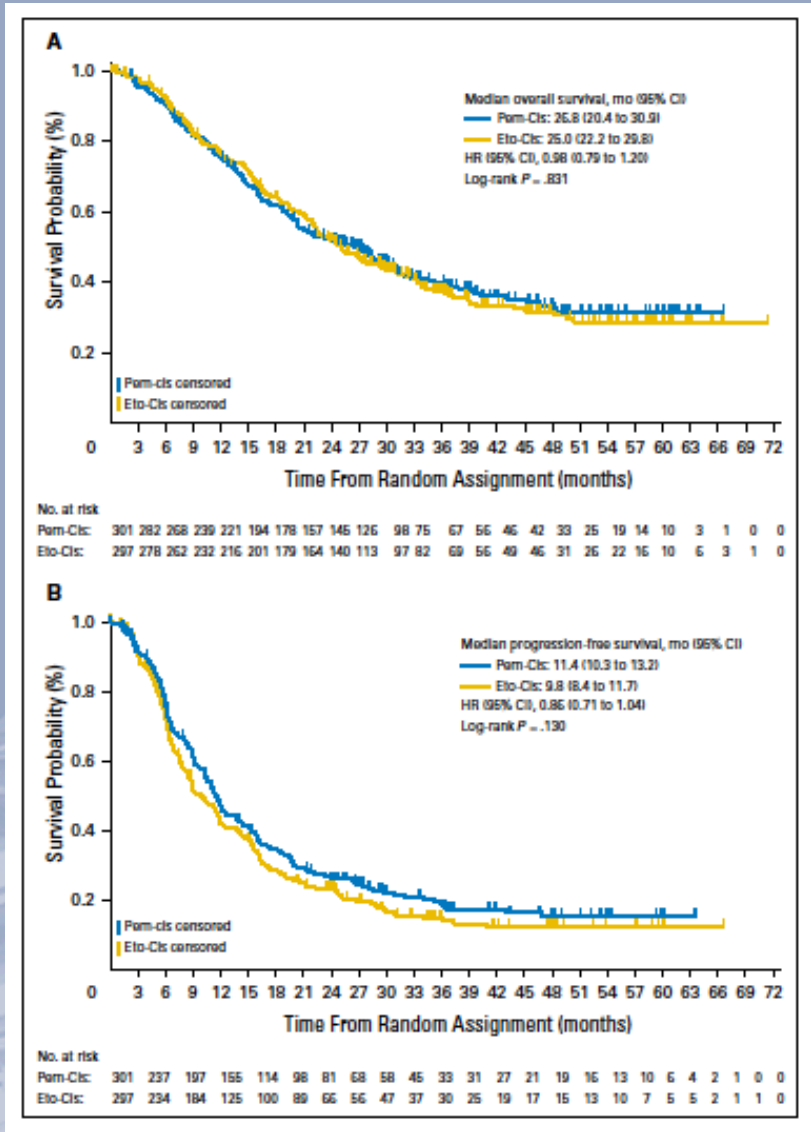


- Meta-analysis of 6 randomized trials of concomitant vs sequential chemoradiation
  - Cisplatin based, mostly doublet
  - RT 36 to 66 Gy
- Demonstrated a significant overall survival: 4.5% at 5 years
- Improved LRC
- Increased grade 3-4 esophagitis, 4% vs 18%

Auperin JCO 2010

PROCLAIM

- **<u>Non-squamous</u>**, unresectable IIIA/B NSCLC, treated with chemoradiation
- 66 Gy thoracic RT
- Randomized to
  - Cisplatin/pemetrexed q 3 weeks followed by cis/pem consolidation
  - Cisplatin/etoposide q 4 weeks followed by cis/etoposide consolidation
- Stopped for futility after 598 patients
- No significant difference in OS
- Lower grade 3-4 toxicity in cis/pem arm 64% vs 76.8%



-Senan et al, JCO 2016

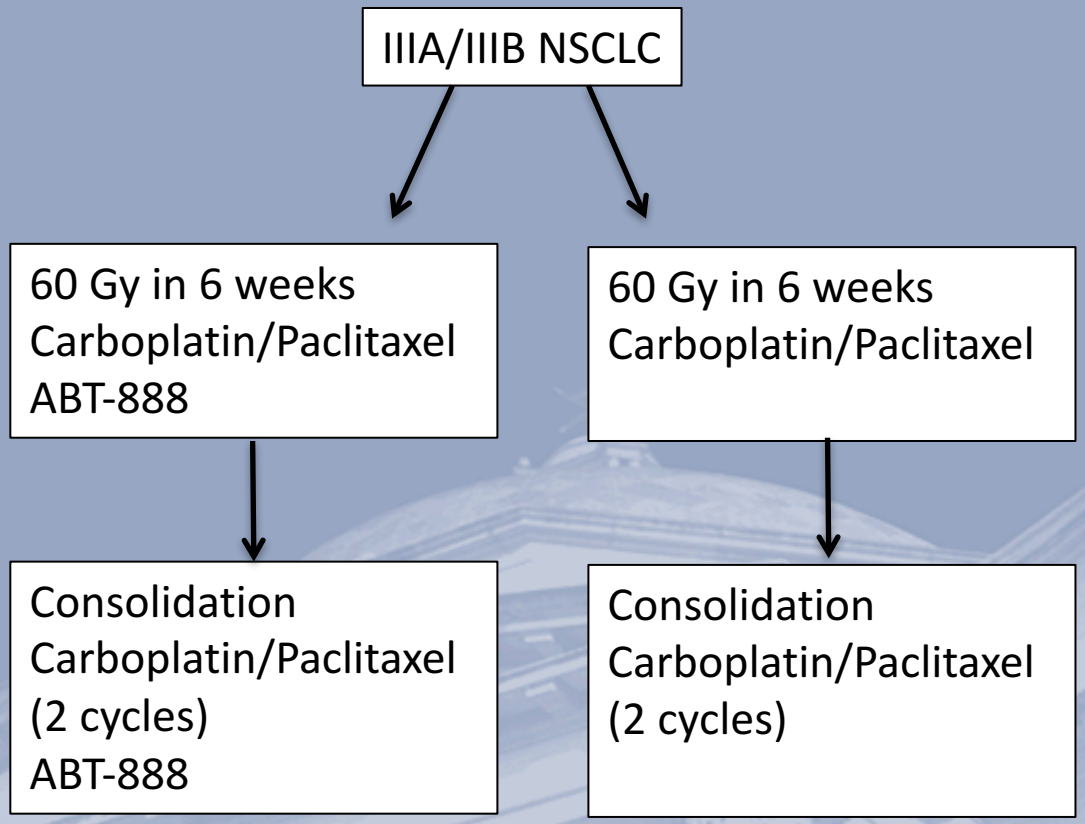
- For patients with LA-NSCLC receiving concurrent chemoradiotherapy, the standard radiation dose is 60-70 Gy

- For squamous cell carcinoma, a cisplatin doublet is appropriate, most commonly cisplatin/etoposide or carboplatin/paclitaxel

- For non-squamous cancer, the combination of cisplatin/pemetrexed is equally effective as cisplatin/etoposide, but with lower incidence of serious adverse events

SWOG 1206

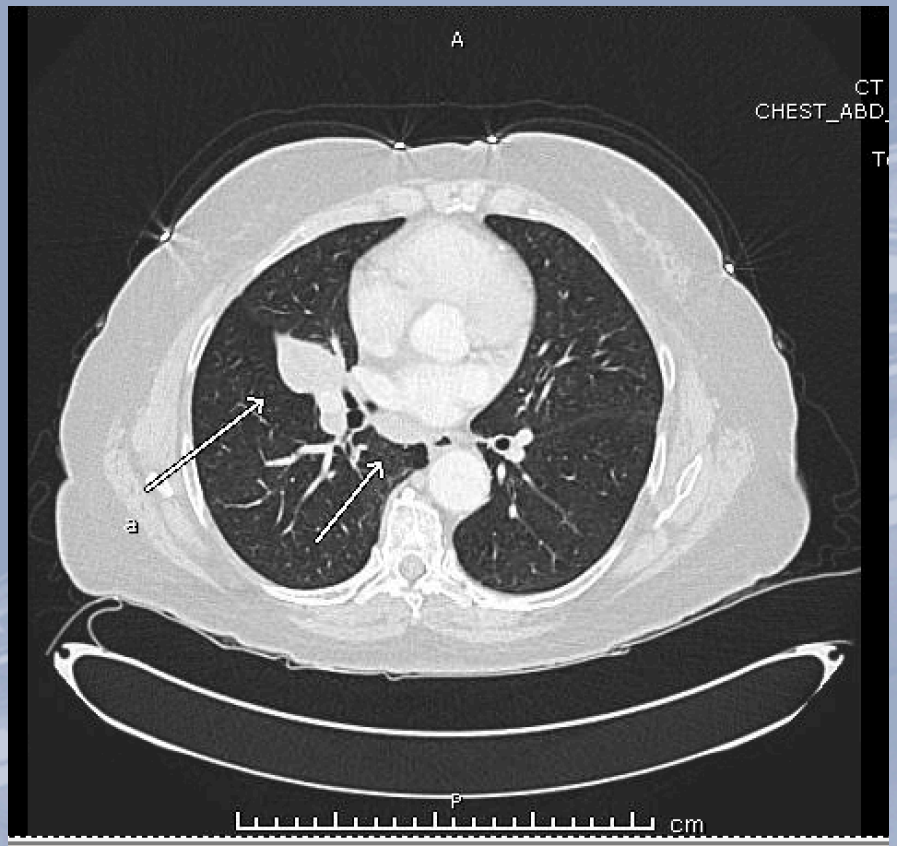
- Phase I/II trial adding veliparib to standard carboplatin/paclitaxel and thoracic radiotherapy
- Phase I dose escalation of veliparib (completed)
- Randomized placebo-controlled phase 2 (accruing)



- Bronchoscopy and EBUS biopsies positive in RML, subcarinal and 4R stations

  TTF1+ adenocarcinoma

  EGFRwt



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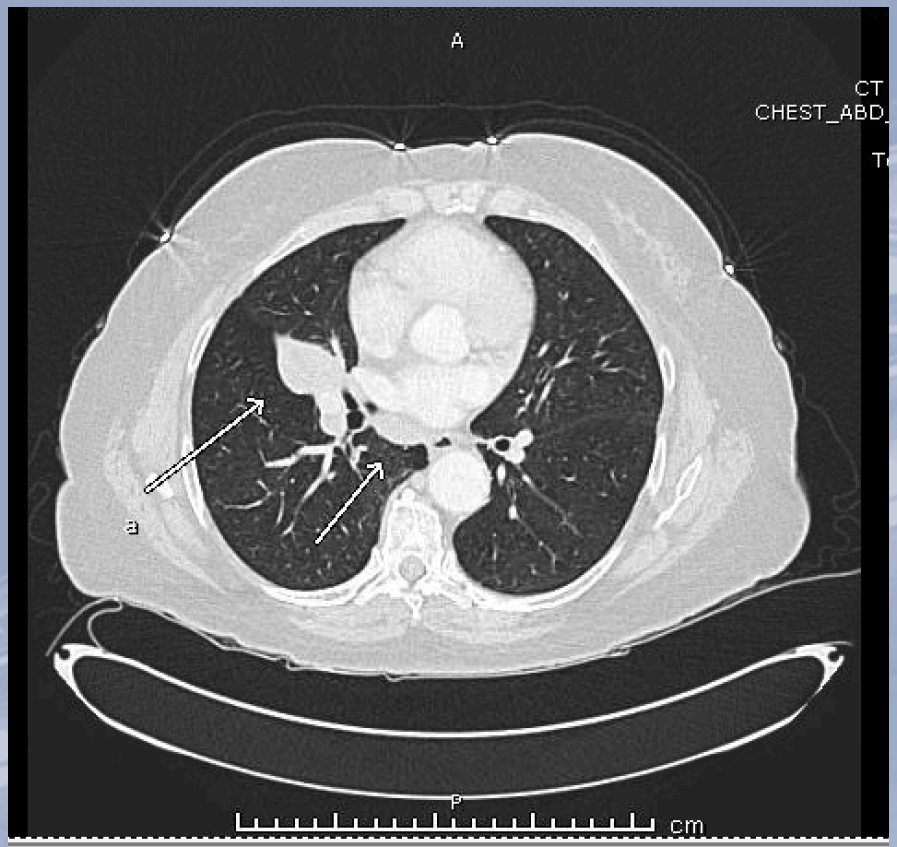
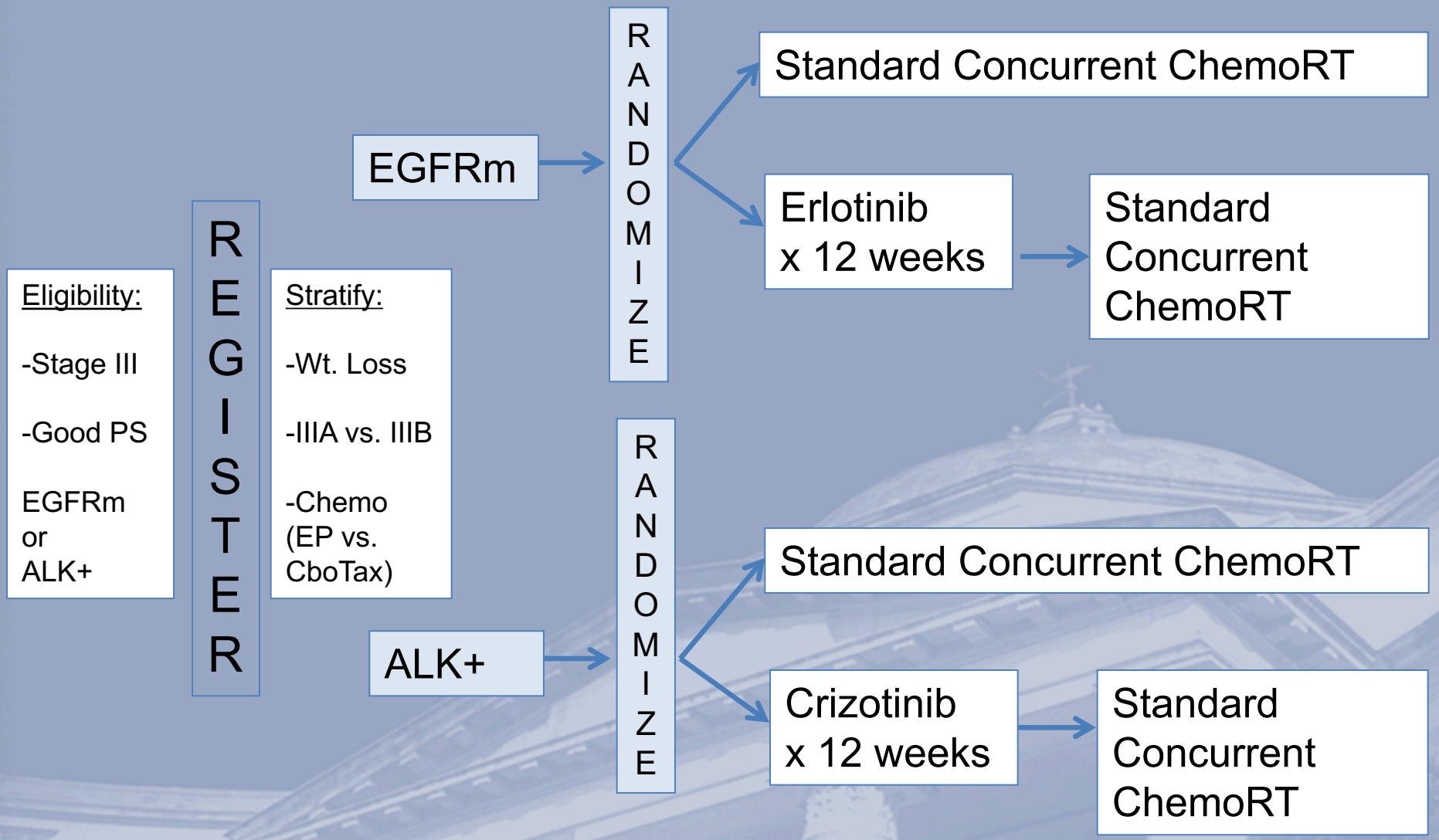
  EGFR exon 19 del



NRG/Alliance 1306



- For patients with LA-NSCLC receiving concurrent chemoradiotherapy, the standard radiation dose is 60-70 Gy
- For squamous cell carcinoma, a cisplatin doublet is appropriate, most commonly cisplatin/etoposide or carboplatin/paclitaxel
- For non-squamous cancer, the combination of cisplatin/pemetrexed is equally effective as cisplatin/etoposide, but with lower incidence of serious adverse events
- Efforts are under way to incorporate targeted agents into the standard backbone of chemoradiation