Landmark Trials in Non-metastatic NSCLC

Dr. Monica Malik Irukulla
Professor & Head
Dept. of Radiation Oncology
Nizam's Institute of Medical Sciences
Hyderabad

Lung Cancer

- Highest cancer related mortality
- Second highest in incidence (GLOBOCAN 2020)

- NSCLC - 85% of all lung cancers

- >80% diagnosed in advanced stages

Screening for NSCLC

Two RCTs showed 20-26% relative mortality reduction with low dose CT –

- NLST (USA) – 3 rounds annual LDCT
- NELSON (Netherlands)- 4 rounds of LDCT at increasing intervals upto 10 yrs

- False positive rates – 8-49%
- False positive led to invasive procedures in 1.7% of screened population (NSLT)
- Overdiagnosis – upto 67%

Issues:

- Feasibility in real world settings?
- Applicability in LMICs?

Early stage NSCLC - Surgery

LCSG 821 (Ginsberg, Ann Thorac Surg 1995):

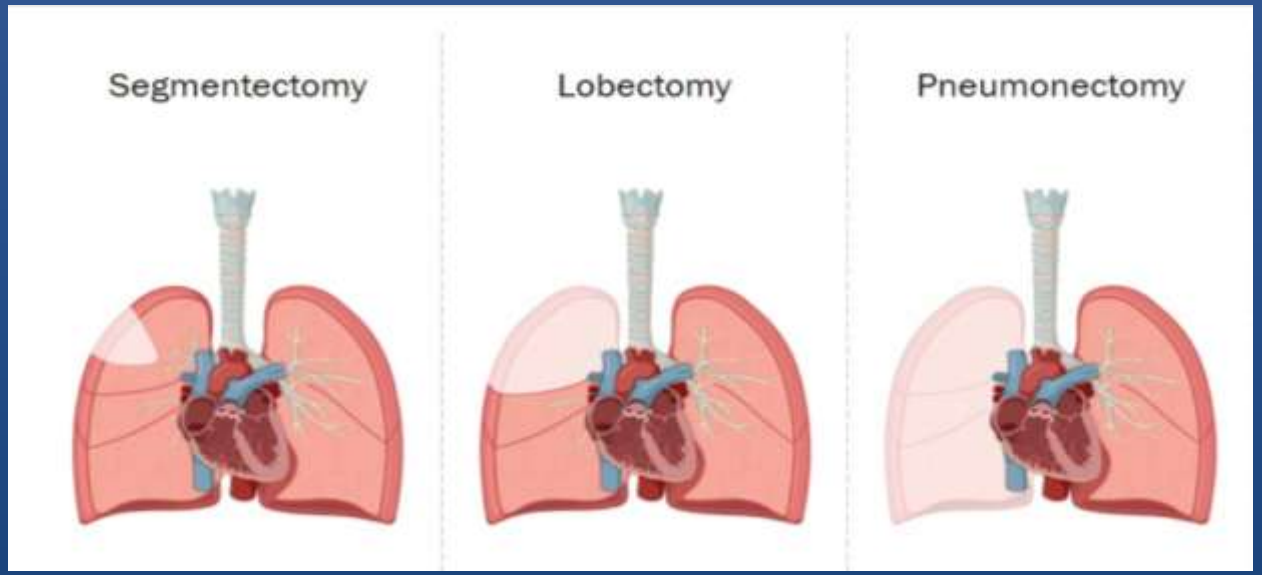
n= 247

lobectomy vs wedge resection with a 2 cm margin of normal lung

- Wedge resection tripled LRF (6 → 18%)

Surgery: open vs VATS –

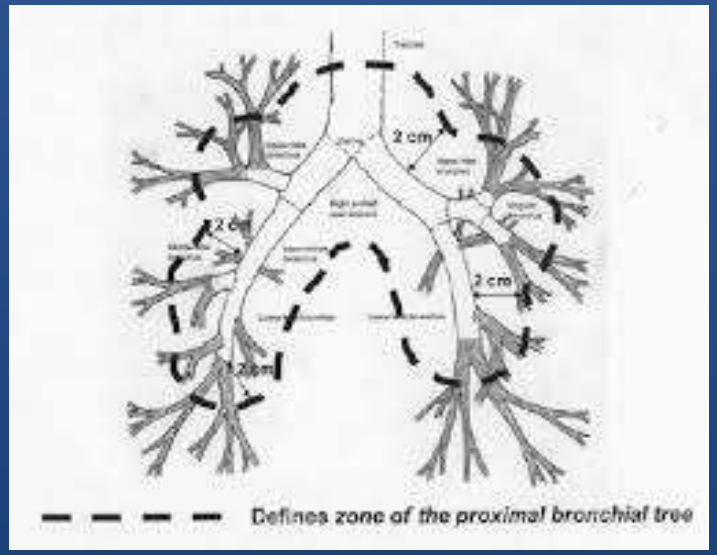
similar outcomes



Early stage - SBRT

Indiana Univ-

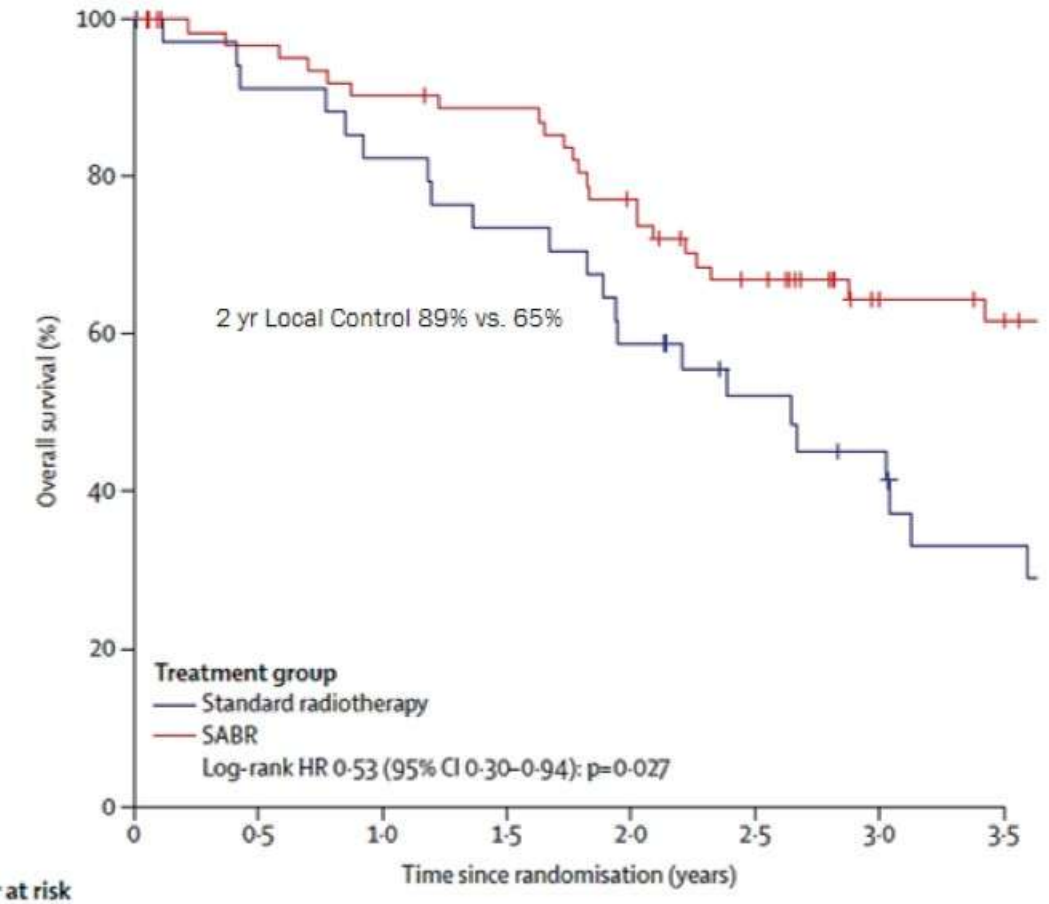
- T1-T3N0 <7 cm
- 60–66 Gy in 3 fx over 1–2 weeks
- Three-year LC 88%
- Patients with central tumors had increased risk of grade 3–5 toxicity (27% vs 10%)
- Established “no-fly-zone” of 2 cm surrounding proximal bronchial tree for 3-fraction treatment.



Timmerman JCO 2006; Fakiris, IJROBP 2009)

CHISEL Study:
SBRT vs Conventional RT

- Randomized phase III study of SBRT vs conventional RT in stage I, medically inoperable NSCLC
- Non-central tumors, PET/CT staged
- SBRT (48 Gy/4 or 54 Gy/3) vs conventional fractionation
- Primary endpoint of local control
- Significantly improved local control and survival with SBRT



Number at risk (number censored)								
Standard radiotherapy	35 (0)	31 (1)	28 (1)	25 (1)	20 (1)	15 (4)	12 (5)	8 (6)
SABR	66 (0)	60 (4)	56 (4)	54 (5)	46 (6)	37 (9)	25 (20)	22 (22)

CT, computed tomography; PET, positron emission tomography; SABR, stereotactic ablative radiotherapy.

Ball D, et al. Lancet Oncol. 2019;20:494-503.

SBRT

Japanese study:

- 245 patients with T1–2N0
- 18–75 Gy in 1–22 fx
- LF was 8% for ***BED ≥100 Gy*** vs 26% for BED

Onishi (Cancer, 2004)

Early stage – SBRT dose and efficacy

RTOG 0915 (Videtic IJROBP 2015):

Phase II randomized, ***<5 cm medically inoperable***

34 Gy in 1 fraction vs 48 Gy in 4 fractions

Single fraction arm had lower risk of serious adverse events (10.3 vs 13.3%)

RTOG 0618 (Timmerman ASCO 2013):

Medically operable T1-T3N0 (≤5 cm)

>2 cm from proximal bronchial tree

60 Gy in 3 fractions (54 Gy with heterogeneity correction).

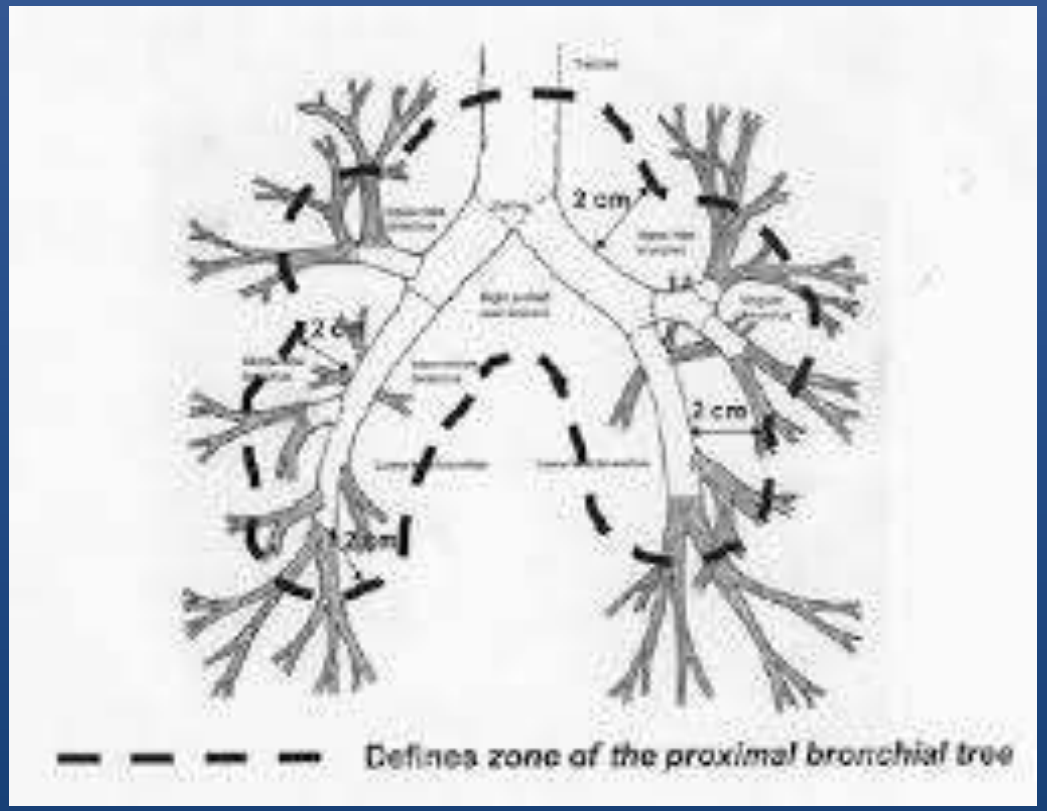
2-year primary failure rate 7.8%

16% grade 3 toxicity

SBRT for central tumors

RTOG 0813

- N=120
- <5 cm PET staged
- MTD – 12 Gy/fraction x 5 fr



SBRT for ultracentral tumors- Nordic Hilus trial

- Within 1 cm of prox bronchial tree
- 7Gy x 8 fr
- 34% gr 3-5 toxicity

Authors recommend max dose to trachea/main bronchi 70-80 Gy EQD2

Currently recommended doses for ultracentral tumors

- 5 Gy x 12
- 4 Gy x 15

(Lindberg, JTO, 2021)

Early stage SBRT vs Surgery

Two RCTs STARS and ROSEL – failed to accrue

Combined ROSEL/STARS analysis (Chang Lancet Oncol 2015):

- N=58; T1-T2 (<4 cm) N0
- SBRT (54 Gy in 3 fractions, 50 Gy in 4 fractions if central) vs lobectomy and mediastinal lymph node dissection
- 3-year OS improved for SBRT (95%) vs surgery (79%)
- Grade 3–4 toxicity 10% for SBRT vs 44% for surgery

SBRT Summary

- Indication: T1-T3, < 5 cm, node negative
- Typically 3 to 5 fractions, 12-18 Gy per fr
- Caution required in central and ultracentral tumors

Ongoing trials: SBRT + Immunotherapy

Study Name	Phase	Arm I SBRT	Arm II SBRT + IO	Placebo	Primary Endpoints
PACIFIC-4[a] N = 706	III	Standard of care 3, 4, 5 or 8 fraction regimens	SBRT followed by Durvalumab 1500 mg Q 4 w x 24 months	Yes	PFS
SWOG/NRG[b] **S1914** N = 480	III	Standard of care 3-5 fractions	Atezolizumab x Q 3 w x 2 → SBRT + Atezolizumab → Atezolizumab (8 cycles total)	No	EFS, OS
KEYNOTE-867[c] N = 530	III	Standard of care 3 – 5 fractions	SBRT followed by Pembrolizumab 200 mg Q 3 week x 12 months	Yes	OS

Early stage- Adjuvant chemotherapy

LACE Meta-analysis

- 5 largest adjuvant cisplatin based chemotherapy trials (>4000 patients)
- 5.4% absolute OS benefit at 5 years
- Benefit most pronounced in stage II/III disease

(Pignon JCO 2008):

Post op RT (PORT)

PORT meta-analysis:

- Survival detriment with PORT
- Older techniques
- Inadequate staging
- 25% node negative

Newer studies:

- Improved survival in N2 disease
- Survival detriment in N1 disease

Trial	Patients	Results
PORT ,1998	Meta-analysis 9 RCT 2128 Pt.	↓ OS N0,1 ↑ toxicity N2 unclear
SEER, 2006	Cohort 7465 Pt.	N0,1↓OS N2 ↑OS
ANITA, 2008	RCT : 840 Pt. Adj. CMT vs observe Subgr.analysis: PORT (N=232)	PORT N1 no CMT ↑OS N1 + CMT ↓OS N2 ↑ OS

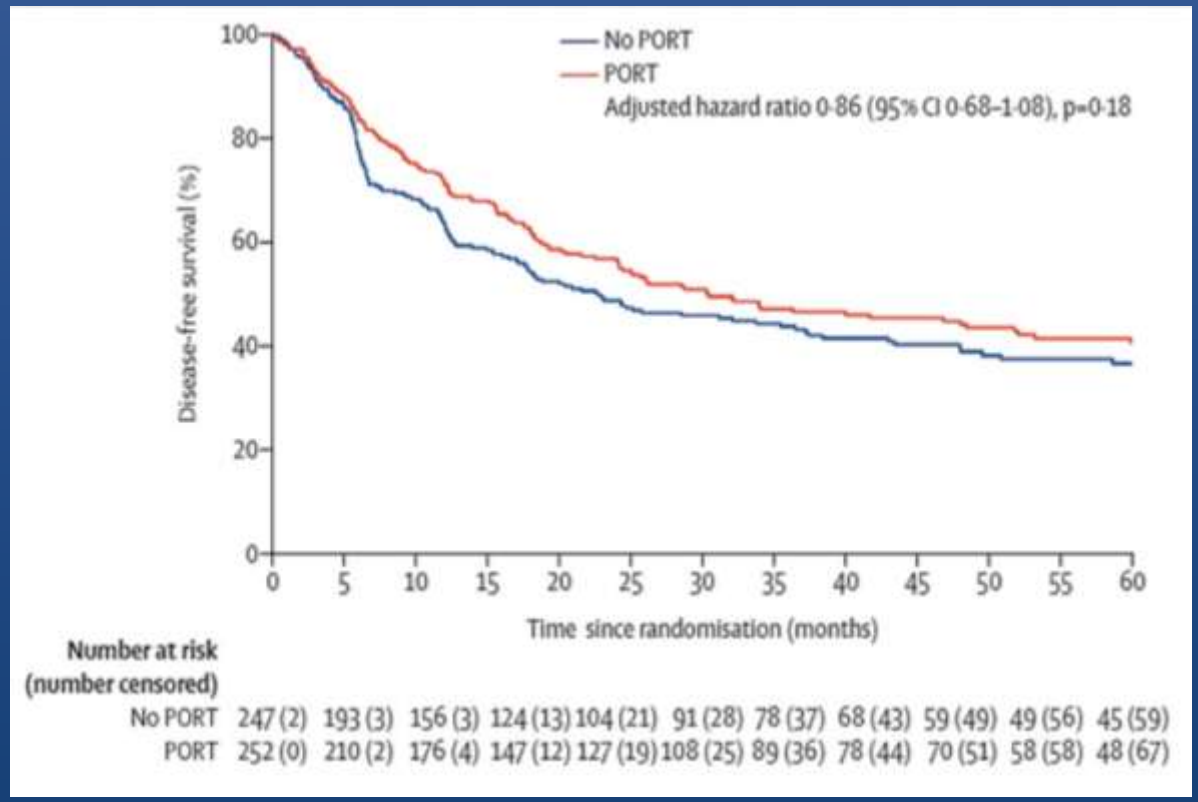
Post op RT (PORT): Conformal

Lung ART (EORTC 22055–08053):

PORT (3DCRT/IMRT) vs observation in completely resected N2 disease

No diff in DFS/OS

Conclusion: PORT not recommended in R0 resection



Le Pechoux, Lancet Oncology 2022

Early stage NSCLC: Summary

- Sublobar resection- high local recurrences
- Minimally invasive surgery (VATS/RATS) equiv to open thoractomies
- Survival benefit with adjuvant cisplatin based chemo
- PORT not indicated in R0 resection
- SBRT is an alternative to surgery in T1-2 N0 < 5cm

Stage III NSCLC

Heterogeneous group

Stage III: Pre-op chemo +/-RT

Meta-analysis (13 randomized trials) –preop chemo improved survival vs surgery alone

Song, J Thorac Oncol 2010

German trial (Thomas, Lancet Oncol 2008):

- n=524
- NACT cisplatin/etoposide × 3
- Pre-op chemo-RT → Sx vs Sx → post-op RT
- No difference in 5-year OS or PFS
- Pre-op chemo-RT increased complete resection rates (37% vs 32%)
- Increased mediastinal downstaging (46% vs 29%)
- Increased G3-4 hematologic toxicity and esophagitis
- 14% treatment-related mortality in pts undergoing pneumonectomy

Pre-op CRT→Surgery in Stage III NSCLC

Intergroup/RTOG 0139:

- CRT 45 Gy → CRT to 61 Gy vs Surgery
- Adjuvant chemo (PE) x 2c

Results:

5-yr PFS better in Sx arm (22% vs 11%)

More treatment related deaths with Pnuemonectomy

Survival advantage for pts who had lobectomy

Induction chemo → Sx (+/-PORT) vs RT

EORTC 08941 (JNCI 2007)

ESPATUE (JCO 2015)

- No diff in OS/PFS
- Pts with pneumonectomy and incomplete resections fared worse

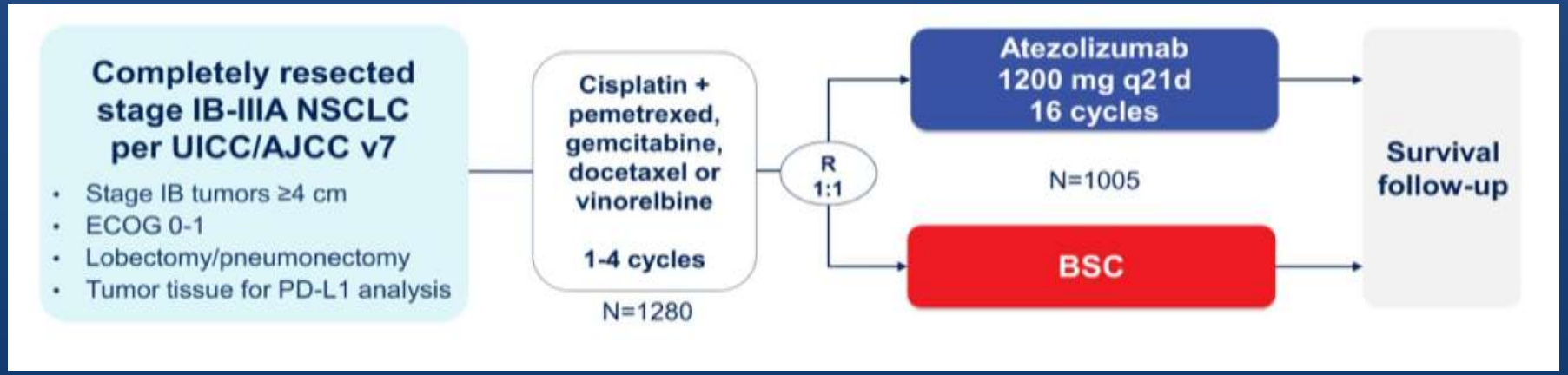
Neo-adjuvant and adjuvant Immunotherapy

Checkmate 0816

- Neo-adj Nivo+ chemo vs NACT
- Encouraging response rates pCR 24% vs 2.2%
- More lung sparing surgeries with IO

Spicer J, JCO 2021

IMpower010



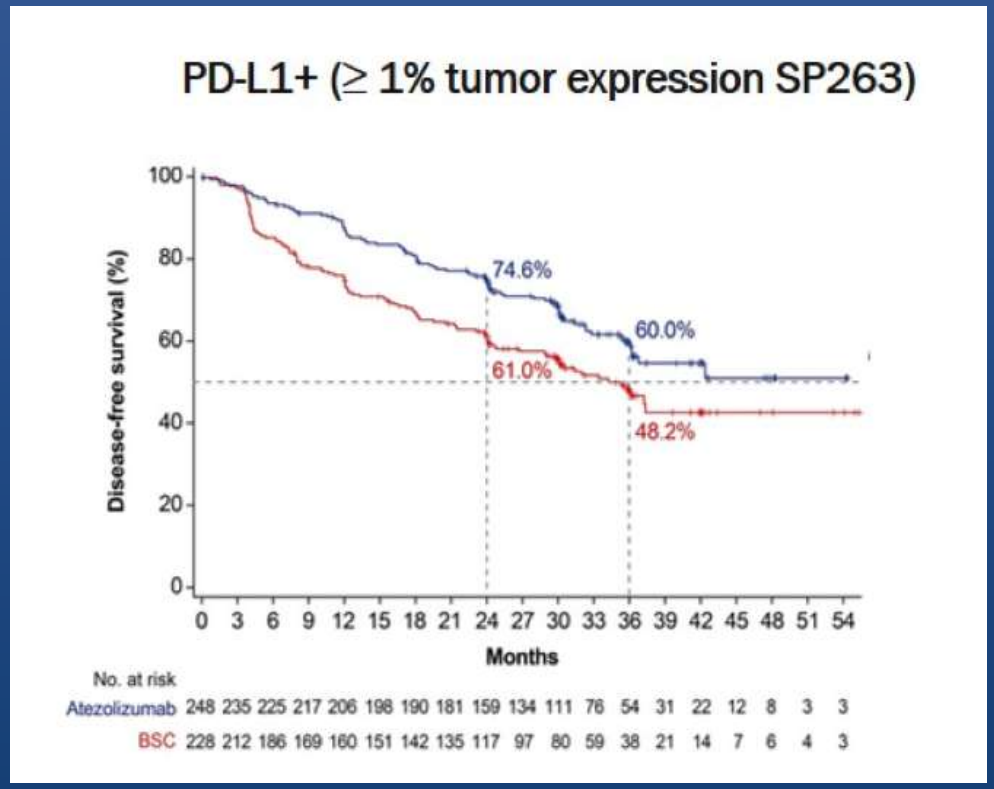
Wakelee JCO 2021

Adjuvant Atezolizumab - IMpower010

Adjuvant Atezolizumab – new standard of care for resected PD-L1 high tumors

No obvious benefit in

- Never smokers
- PD-L1 (1-49%)
- EGFR/ALK positive tumors



Wakelee JCO 2021

Adjuvant EGFR targeted therapies

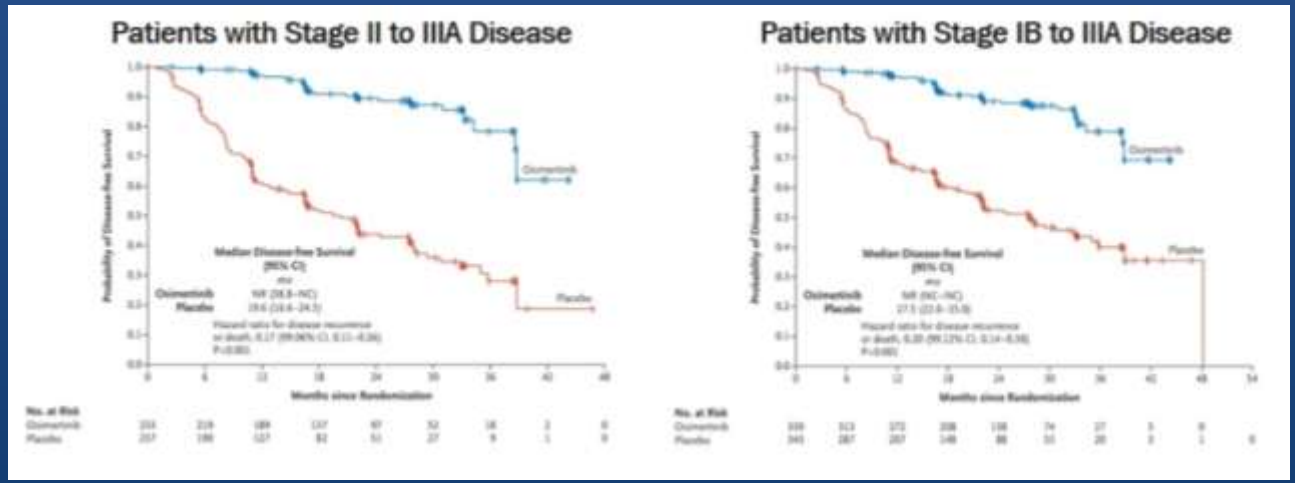
IMPACT

- Adjuvant Geftinib vs chemo (cis+vino x4)
- No diff in DFS/OS

Tada JCO 2021

ADAURA

- Sx+/-adj chemo → Osimertinib vs Placebo
- 3y DFS 84% vs 34%



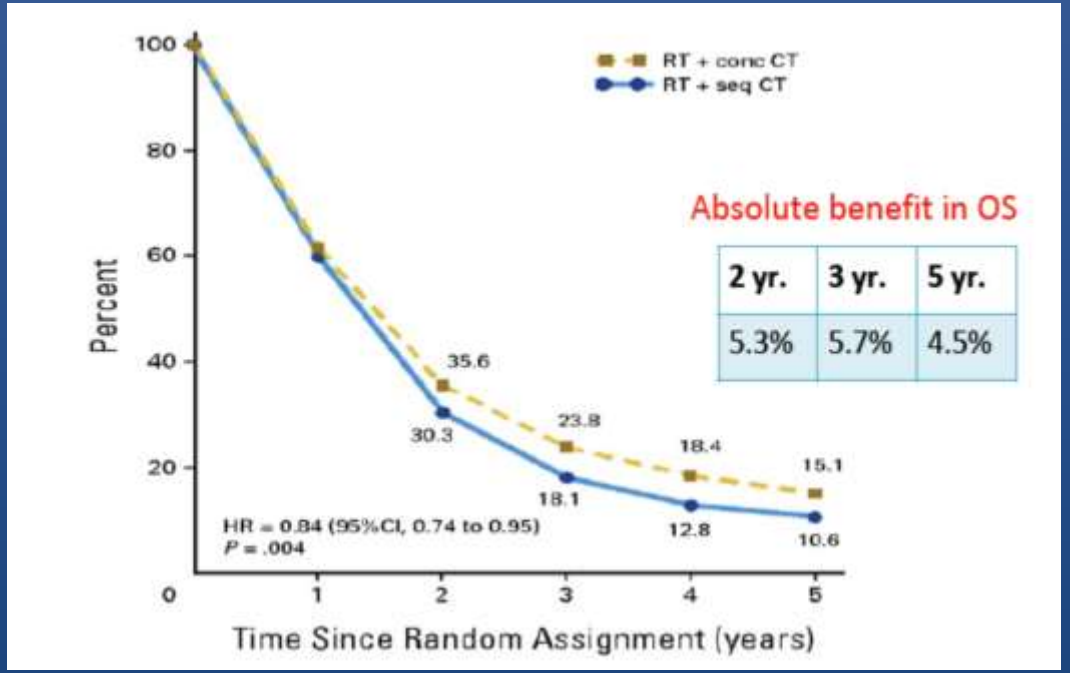
Wu NEJM 2020

Surgery in Stage III

- Selected subgroup
- R0 resction
- Candidates for lobectomy
- Single station N2
- Higher mortality with pnemonectomy
- Improved ORR and PFS with pre-op chemo/pre-op CRT/preop immunotherapy/adj immunotherapy - ongoing trials

Definitive CRT in locally advanced NSCLC

- Meta-analysis of sequential vs concurrent CRT
- OS and PFS better with concurrent CRT
- No proven role for induction or consolidation chemo

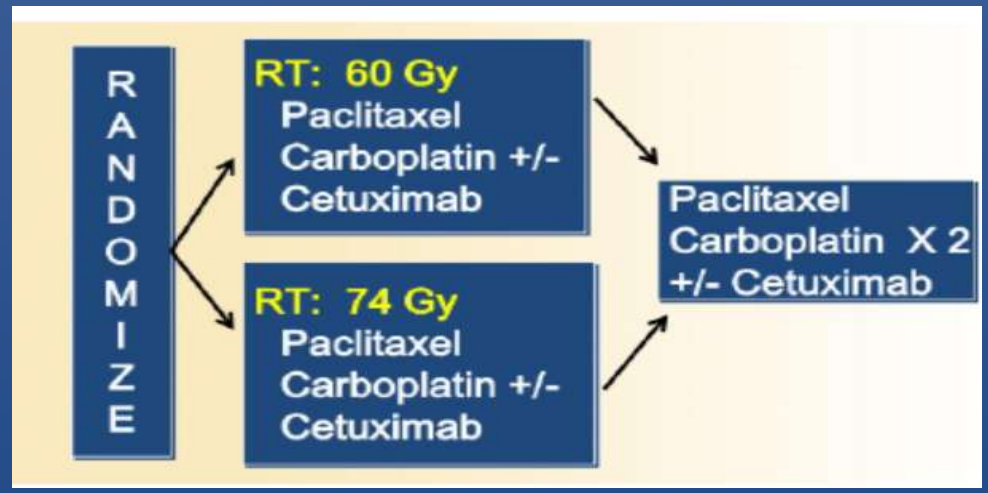


Auperin JCO 2010

RT Dose escalation in advanced NSCLC

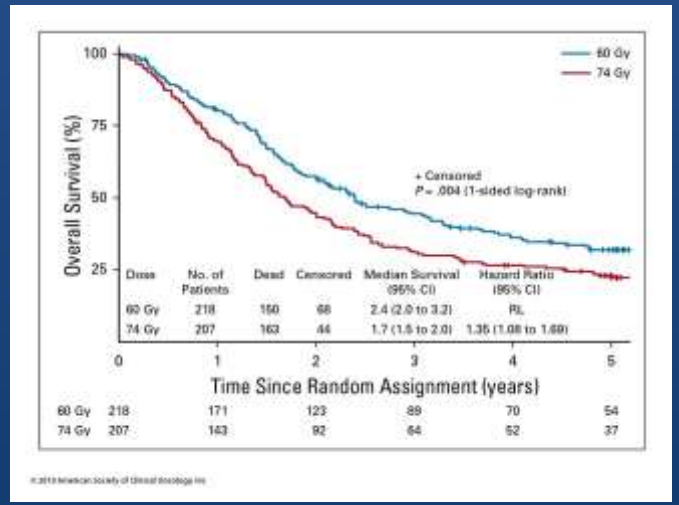
RTOG 0617

- Stage III
- 2x2 randomization
- 60 vs 74 Gy +/- cetuximab



Results:

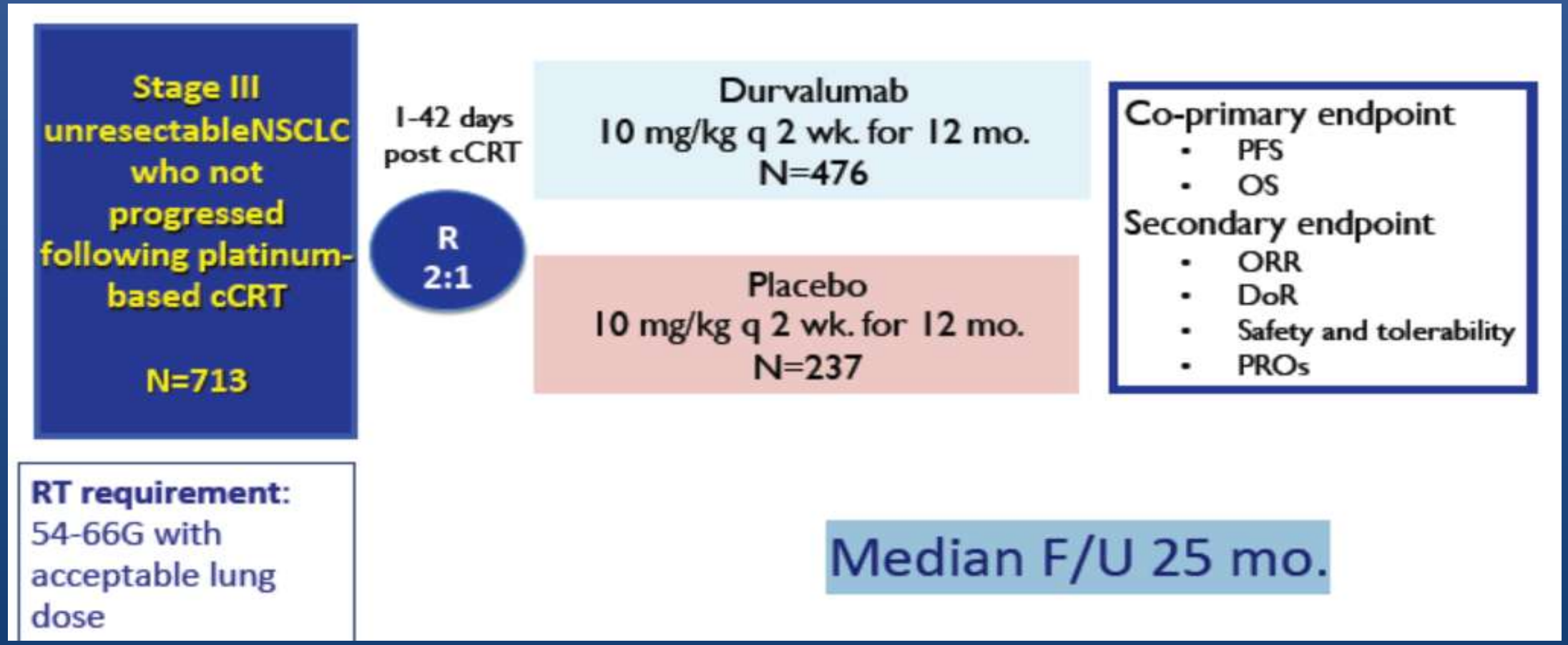
- Worse survival with 74 Gy
- Higher toxicity with cetuximab
- Less pneumonitis and heart dose with IMRT
- ?higher toxicity and inadequate coverage in 74 Gy arm



Bradley, Lancet Oncol 2015

PACIFIC : Durvalumab after CRT

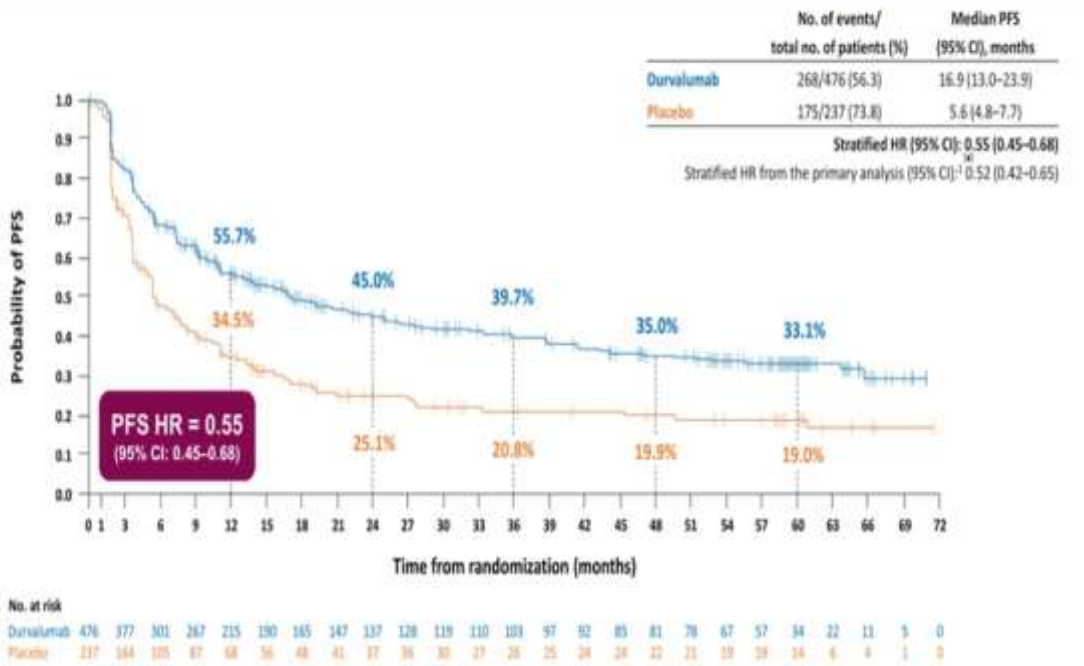
Phase III, randomized, double-blind, placebo-controlled, Multicenter study



Antonia NEJM 2018

PACIFIC 5 yr update

PACIFIC 5-Year ITT PFS



PACIFIC 5-Year ITT OS

Locally advanced NSCLC - Outcomes

	Median Survival	5-yr OS
RT alone	10 mo.	5 %
Sequential ChemoRT (CALGB 8433, RTOG 8808)	14 mo.	10 %
Concurrent ChemoRT (RTOG 9410, EORTC 08972)	17 mo.	15 %
Concurrent ChemoRT (RTOG 0617)	28 mo.	32% (2y-OS 58%)
Concurrent ChemoRT → Durvalumab (PACIFIC)	47.5 mo	43 %

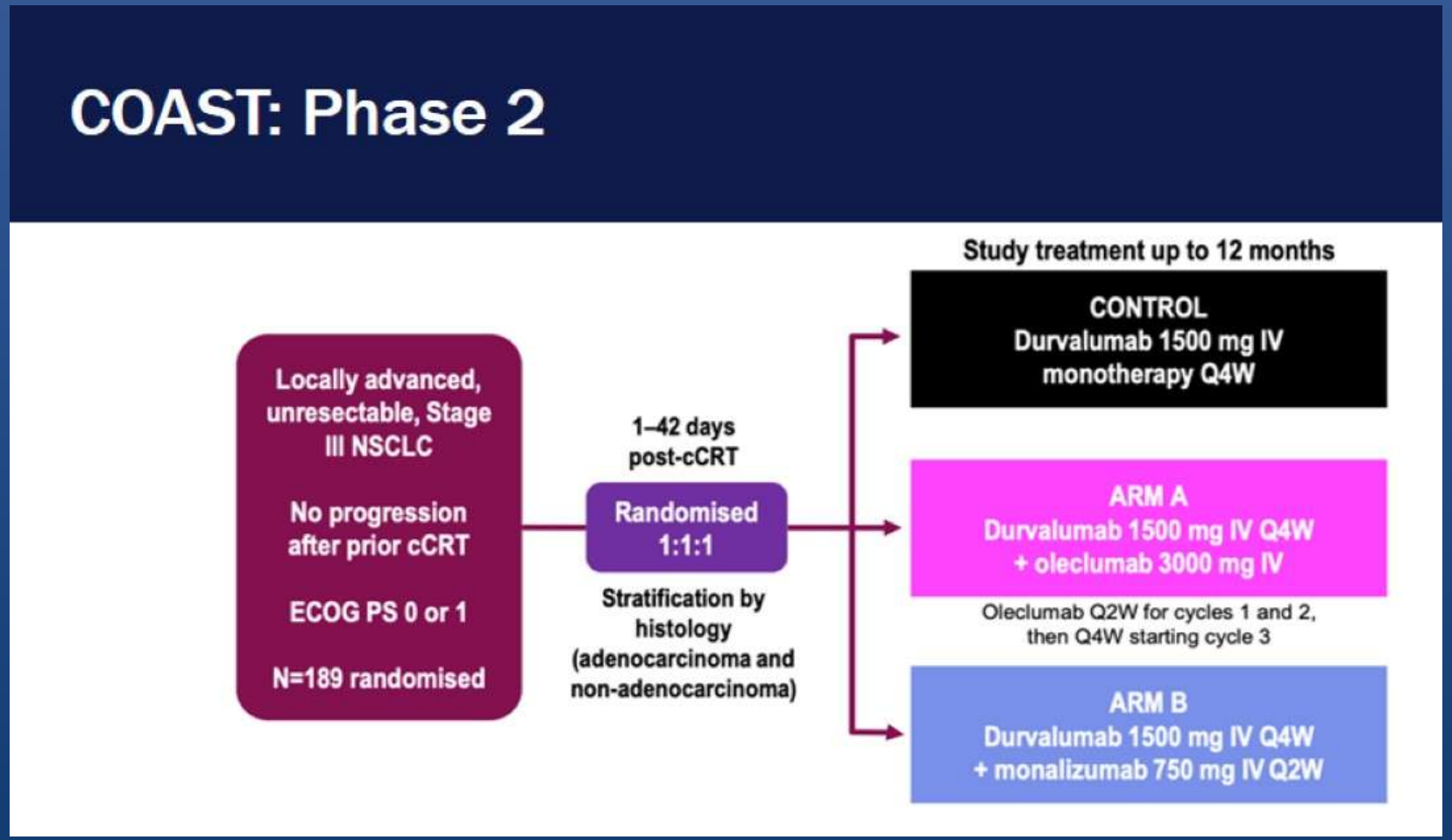
Immunotherapy after CRT single vs multiple agent

Durvalumab alone or with

- Anti-CD73 mAB Oleclumab

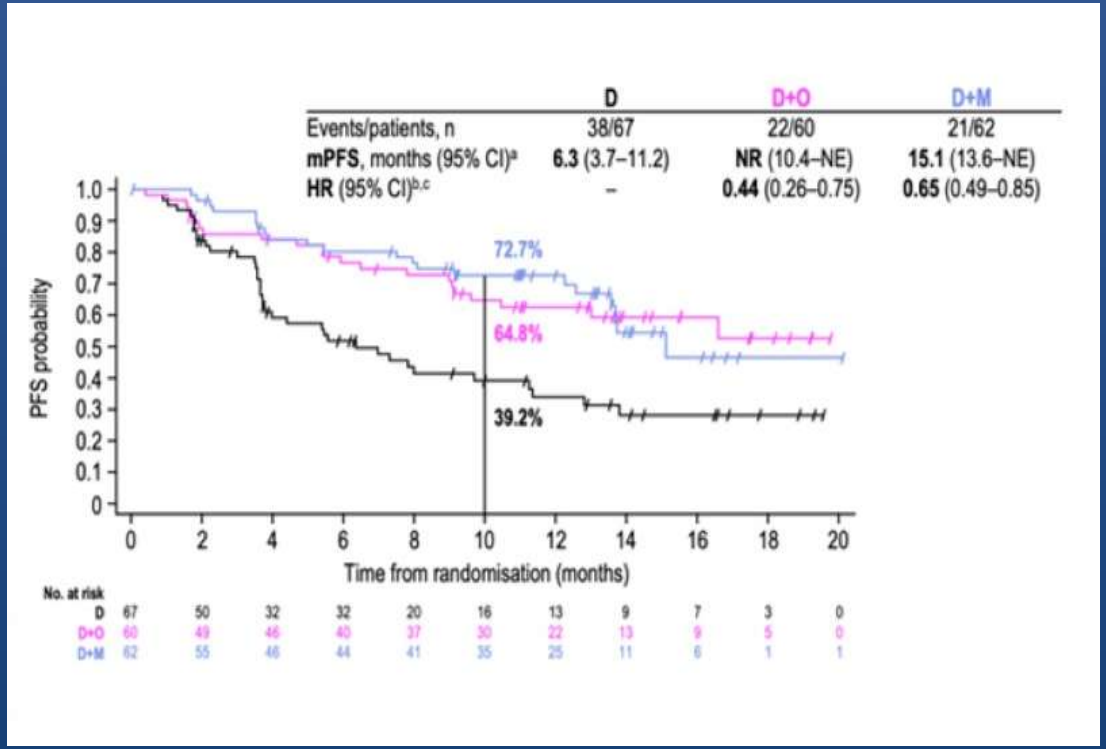
  or

- Anti-NKG2A mAB Monalizumab



COAST Trial: Single vs combination immunotherpy

- Improved ORR and PFS with Durvalumab combined with Oleclumab or Monalizumab
- Combination immunotherapies may further improve survival rates



Summary: Locally advanced NSCLC

- Concurrent CRT is the treatment of choice
- Sx limited to resectable pts who are candidates for lobectomy with limited N2 disease (single station < 3cm)
- Improved PFS and OS with Durvalumab following CRT (PACIFIC)
- Combination immunotherapy and optimal sequencing under investigation