THE EVOLUTION OF COMBINED MODALITY THERAPY IN SURGICAL NSCLC OVER 40 YEARS

50th annual Toronto Thoracic Surgery Refresher Course

June 2026

Toronto, Canada



From sunrise ….

Eric Vallières MD FRCSC



Presented by the Division of Thoracic Surgery,
Department of Surgery, University of Toronto

Surgery
UNIVERSITY OF TORONTO

50th Annual

Toronto Thoracic Surgery Refresher Conference

June 12 - 13, 2026 | Windsor Arms Hotel, 18 St. Thomas Street

Declaration of Conflict of Interest:

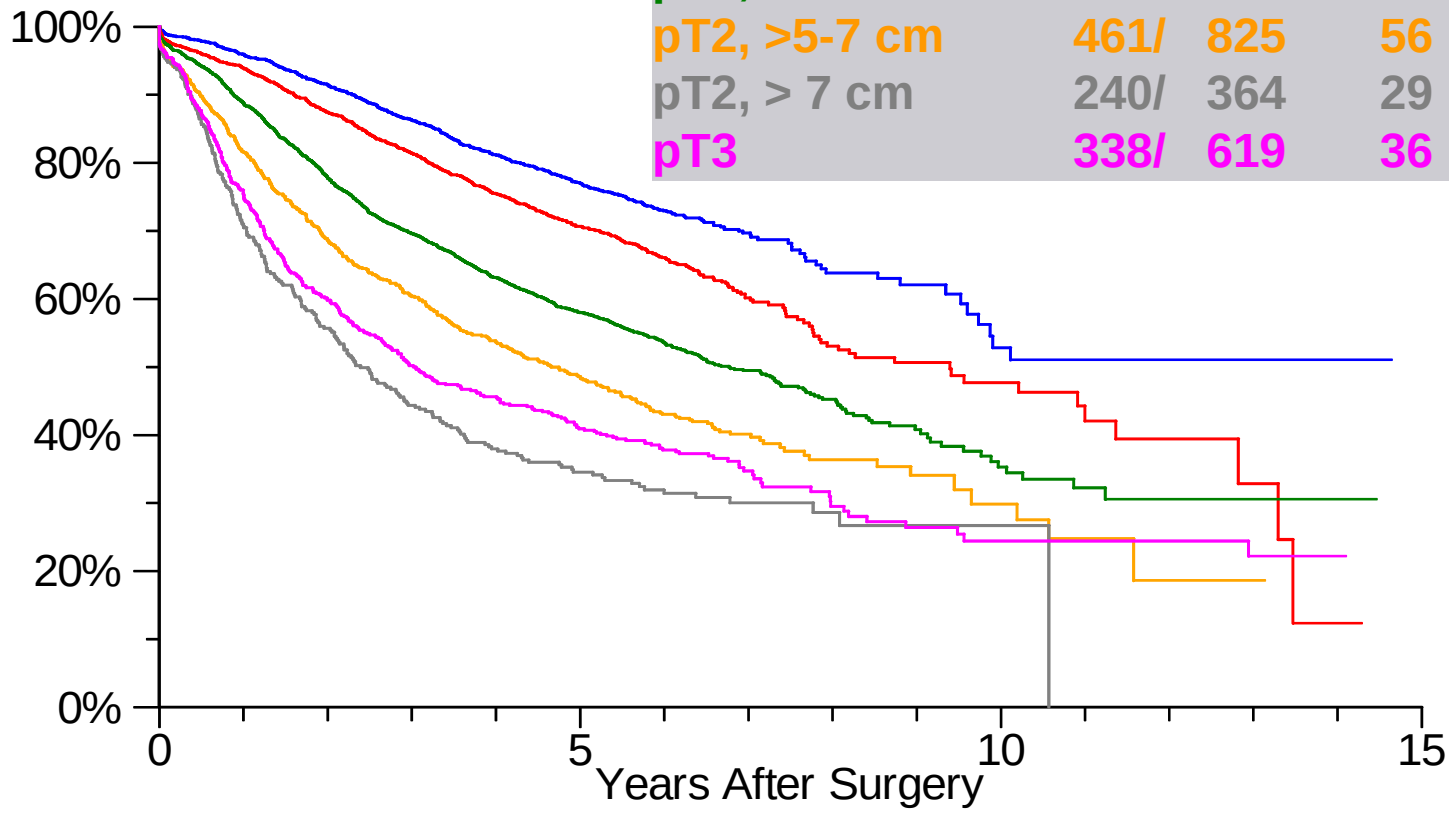
None

FACULTY/PRESENTER DISCLOSURE

- Faculty: Eric Vallières
- Relationships with financial sponsors:
  - Speakers Bureau/Honoraria: AstraZeneca, Merck.
  - Consulting Fees: Teladoc.

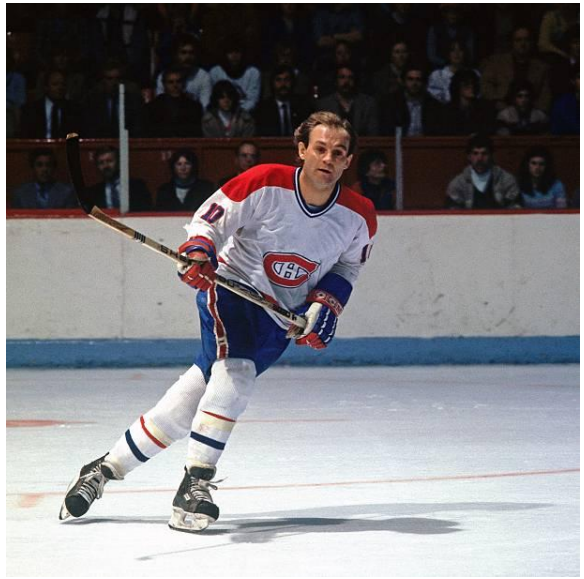
Overall survival by tumour size for patients with pT1-T3 N0 R0, UICC 6 classification

	Deaths / N	MST	5-Year
pT1, <=2cm	492/ 1816	NR	77%
pT1, >2-3 cm	582/ 1653	113	71%
pT2, <=5 cm	1311/ 2822	81	58%
pT2, >5-7 cm	461/ 825	56	49%
pT2, > 7 cm	240/ 364	29	35%
pT3	338/ 619	36	41%



Rami-Porta et al. J Thor Oncol 2007; 2(7): 593-602

The 1970s and early 1980s



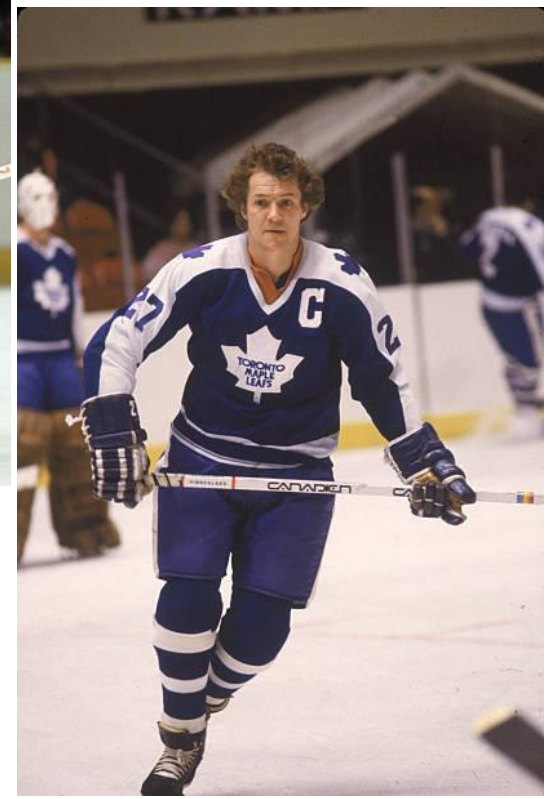
Guy Lafleur



Bobby Orr



Wayne Gretzki



Darryl Sittler

THE EVOLUTION OF COMBINED MODALITY THERAPY IN SURGICAL NSCLC OVER 40 YEARS

- **Adjuvant RT**
- Adjuvant cytotoxic C
- Induction cytotoxic C
- Clinical stage IIIA
- Induction and peri-op C-IO
- Peri-op TKI
- So many areas for research by surgeons!!!

Adjuvant Radiotherapy (PORT)



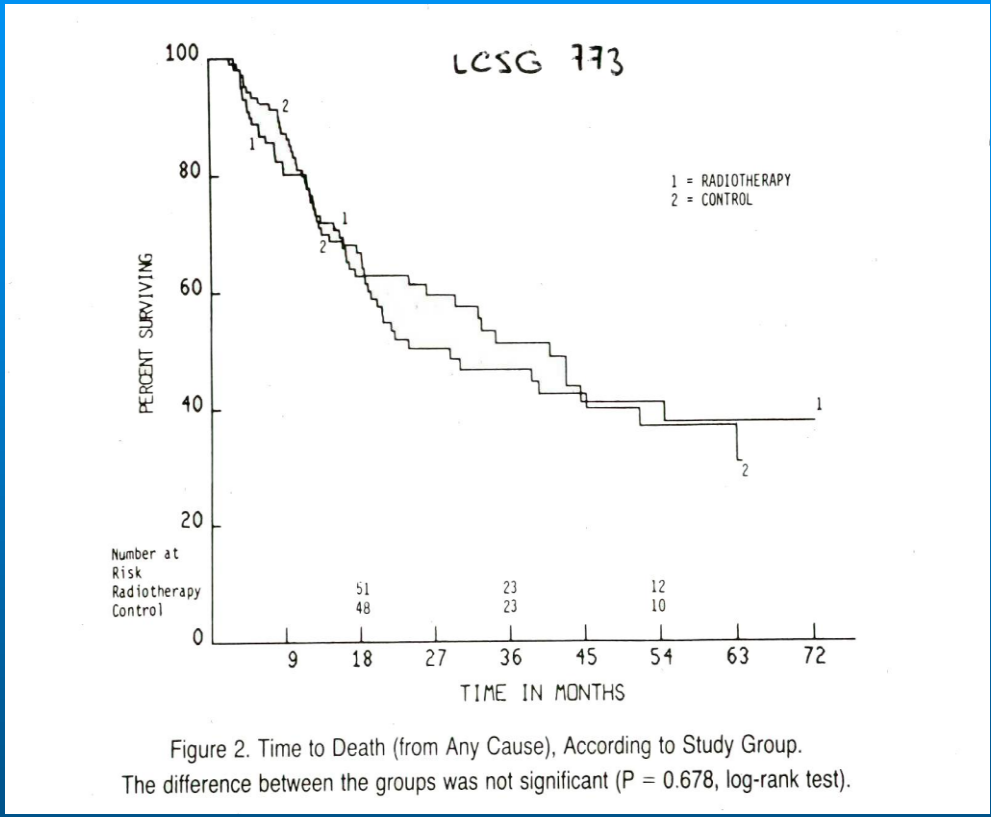


Figure 2. Time to Death (from Any Cause), According to Study Group.
The difference between the groups was not significant (P = 0.678, log-rank test).

Local recurrence went from 41% to 3% with PORT

Weisenburger et al, NEJM 1986

The 1990s and early 2000s



Mario Lemieux



Steve Yzerman



Martin St Louis

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Adjuvant Chemotherapy
Meta-analysis 1995

CDDP based adjuvant chemo, 8 trials adding up to 1394 pts

a 5% increase in 5 year survival (p = 0.08)

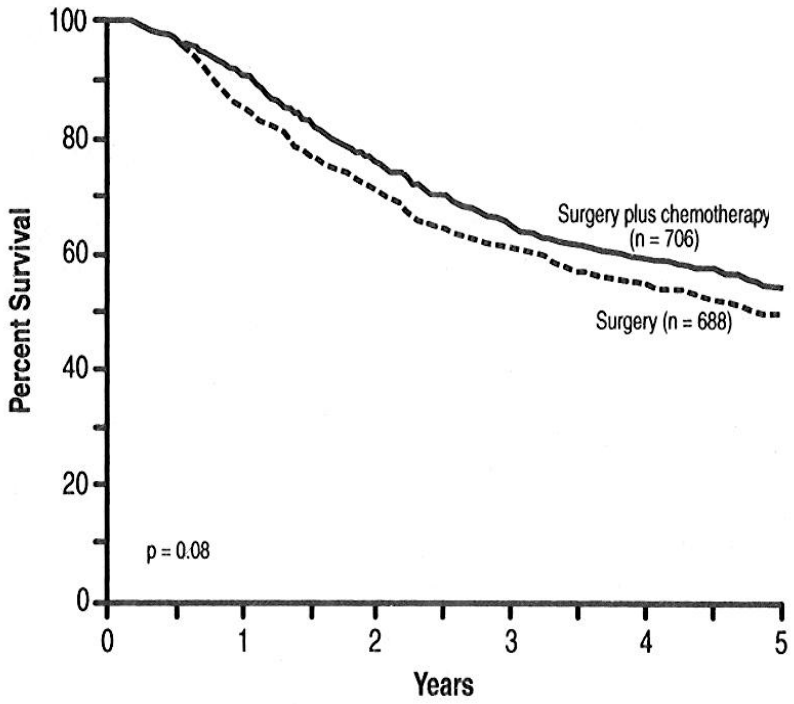


Fig. 1. Survival by meta-analysis of surgery alone versus surgery plus cisplatin-based chemotherapy in 8 trials involving 1,394 patients. The difference at 5 years was 5% (*P* = .08). (Reprinted with permission from Stewart LA, for the Non–Small Cell Lung Cancer Collaborative Group. Chemotherapy in non–small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. Br Med J 311:899-909, 1995.[1])

Stewart et al., Br Med J 311: 899, 1995

Adjuvant Therapy Guidelines 2003 (Recommendations)

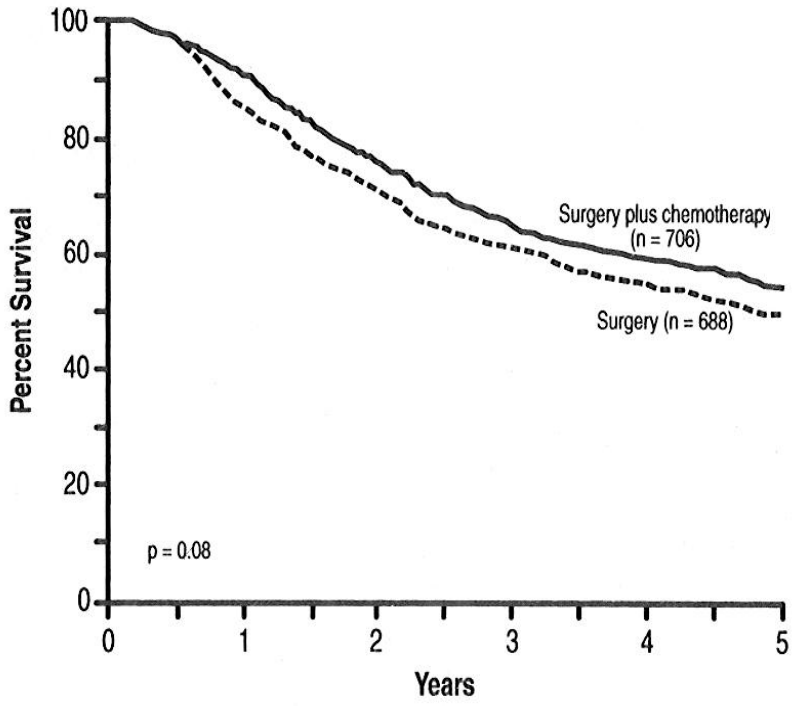
For patients with R0 resected I and II NSCLC:

The use of adjuvant chemotherapy is not recommended outside of a clinical trial.

The use of adjuvant radiation therapy should not be performed.

ACCP Guidelines, Chest Jan 2003 suppl.

Meta-analysis 1995



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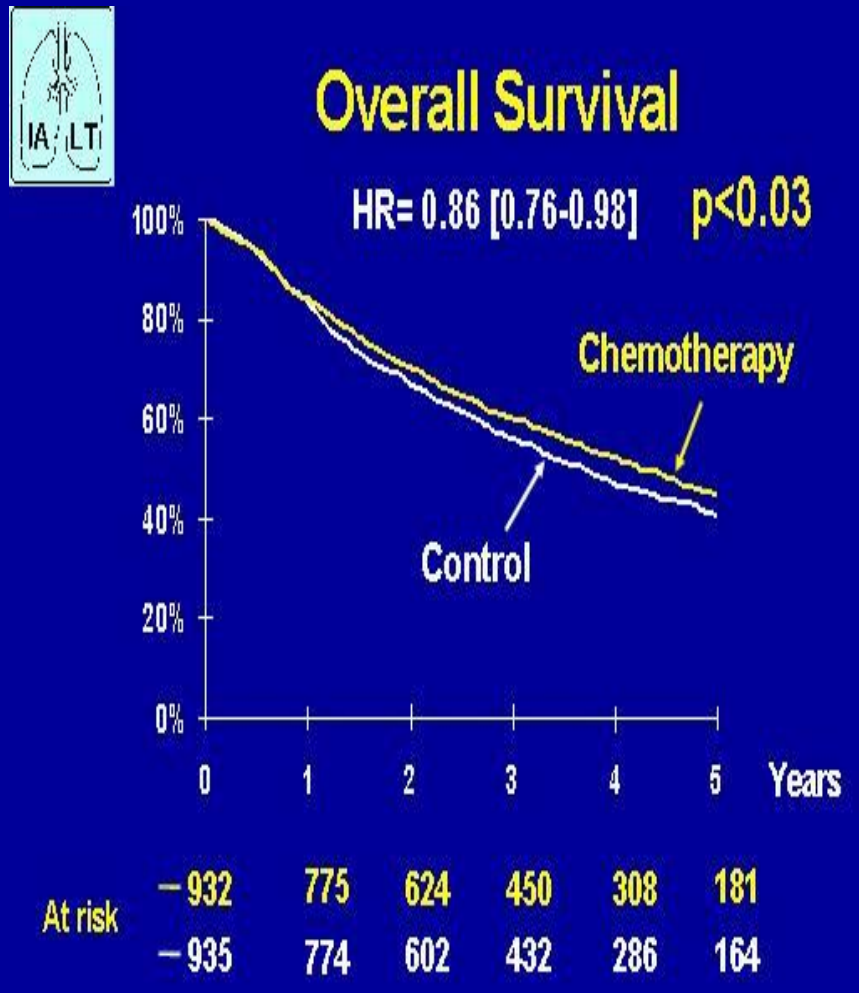
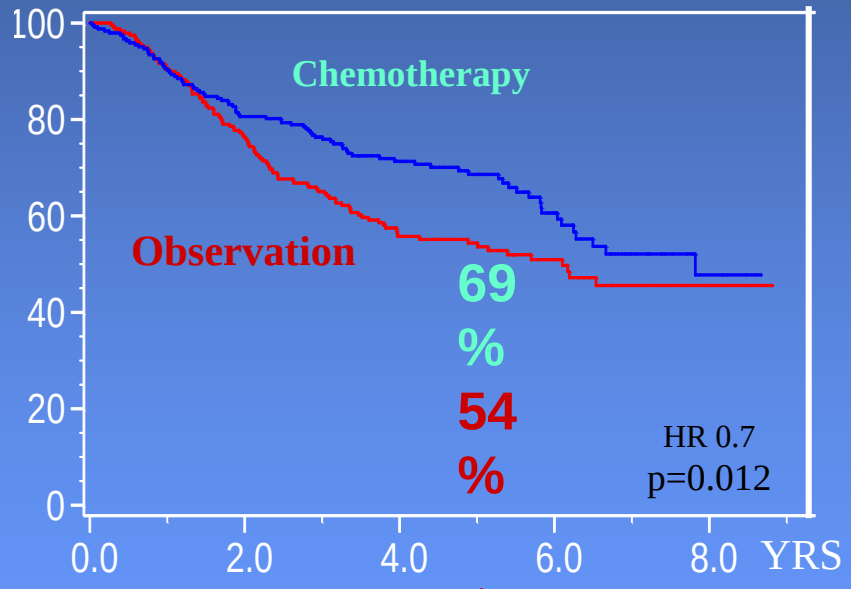
IALT ASCO 2003



IALT Group N Engl J Med 2004; 350:351-60

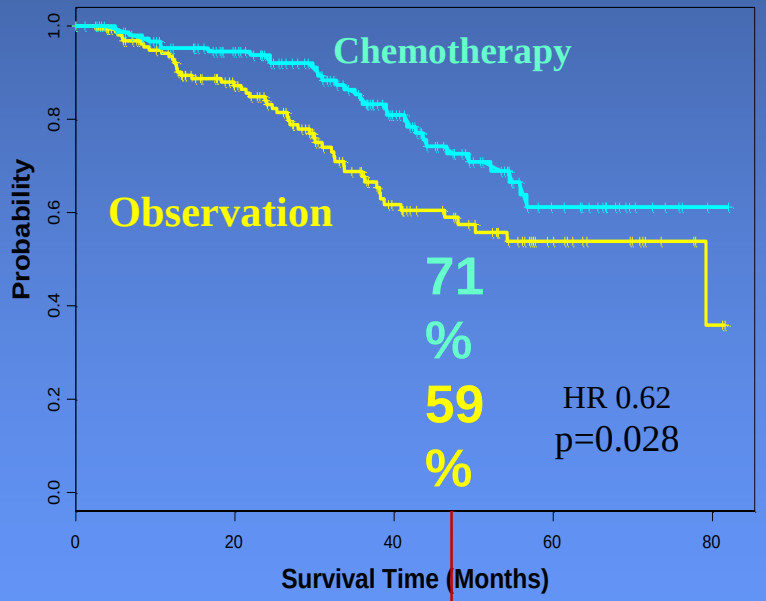
ASCO 2004

NCIC BR 10



5yrs

• CALGB 9633



4yrs

Lung adjuvant cisplatin evaluation (LACE) ASCO 2006

Individual patient data from **cisplatin** based adjuvant studies ALPI, ANITA, BLT, IALT, JBR10

5 trials including 4,584 patients

Median follow-up: 5.1 years (3.1 – 5.9)

Pignon JP et al, J Clin Oncol 2008, 26: 3552-59

Results - LACE

Overall HR (death) 0.89 (CI 0.82-0.96, p <0.005)

HR (death) by stage :

IA 1.41 (CI 0.96- 2.09)
IB 0.93 (CI 0.78-1.10)
II 0.83 (CI 0.73-0.95)
III 0.83 (CI 0.73-0.95)

Pignon JP et al, J Clin Oncol 2008, 26: 3552-59

2006

Post-operative chemotherapy is the standard of care for good PS pts after R0 anatomic resection p stages IIA-B, IIIA NSCLC, and … maybe larger IB…

The 2000s



Sydney Crosby



Vincent Lecavalier

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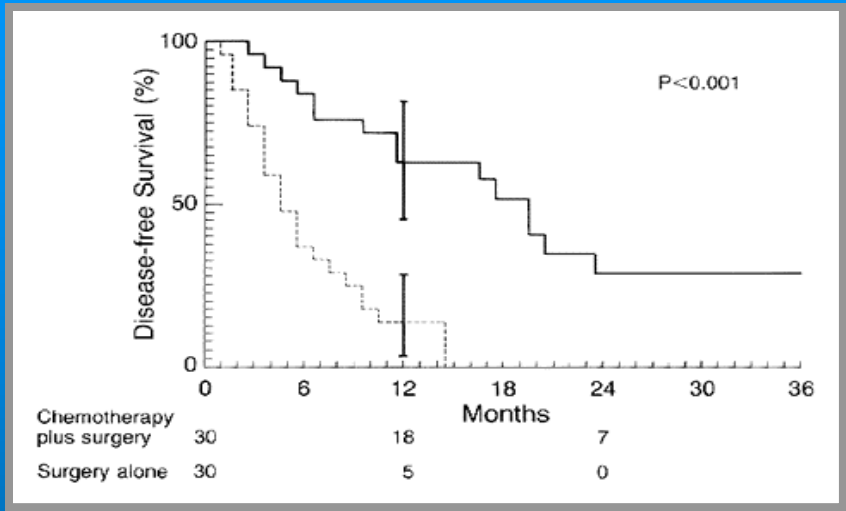
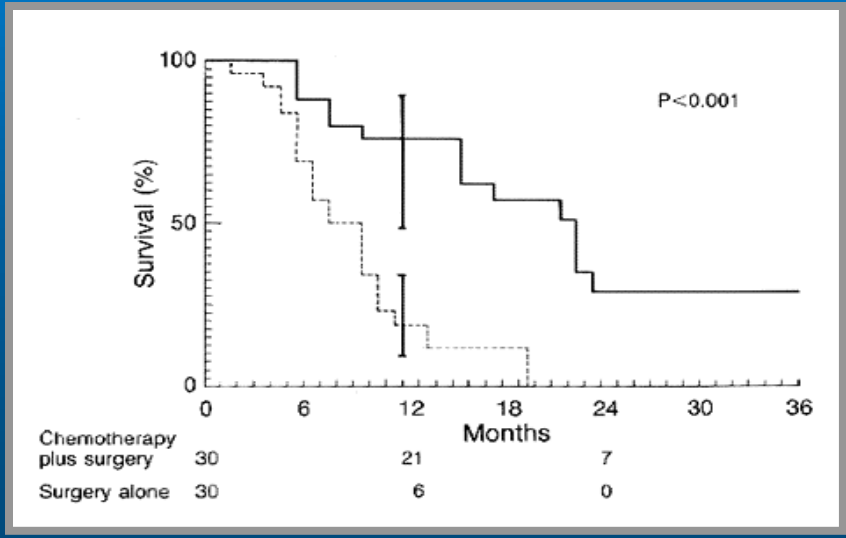
Induction Chemotherapy for Stage IIIA NSCLC

Trial, Arm	N	Med Surv	3-Year Surv.
Rosell, 1994			
Surgery	30	8 m	0%
CT → Surgery	30	26 m	23%
Roth, 1994			
Surgery	32	11 m	15%
CT → Surgery	28	64 m	56%



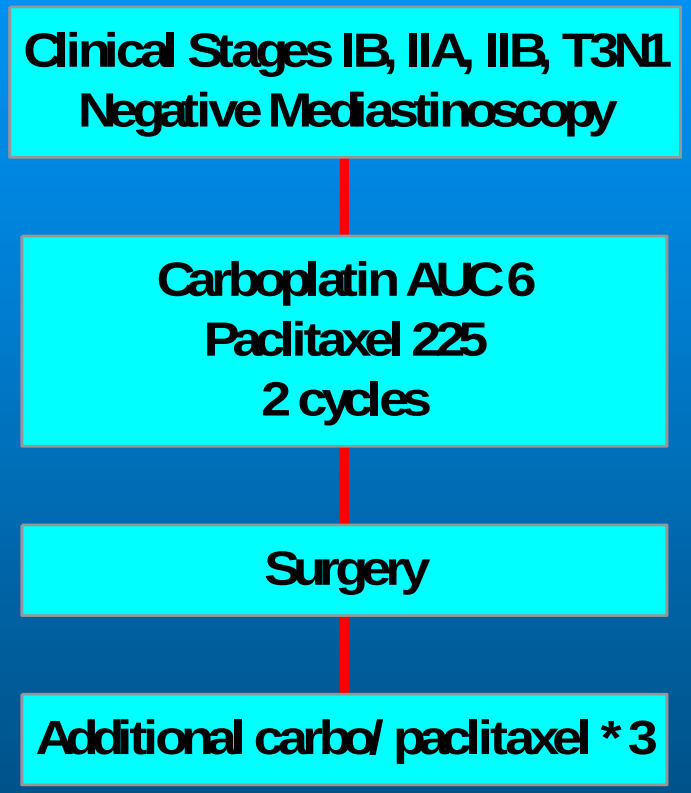


From Rosell, 1994

Rosell, NEJM 330: 153, 1994
Roth, JNCI 86: 673: 1994

Induction Chemotherapy for less than N2

The BLOT Phase II Study



Pisters K, Ginsberg RJ et al., J Thor CV Surg 2000; 119;429

The BLOT Study

94 patients

98% completed induction chemo as planned

(PHASE II STUDY!)

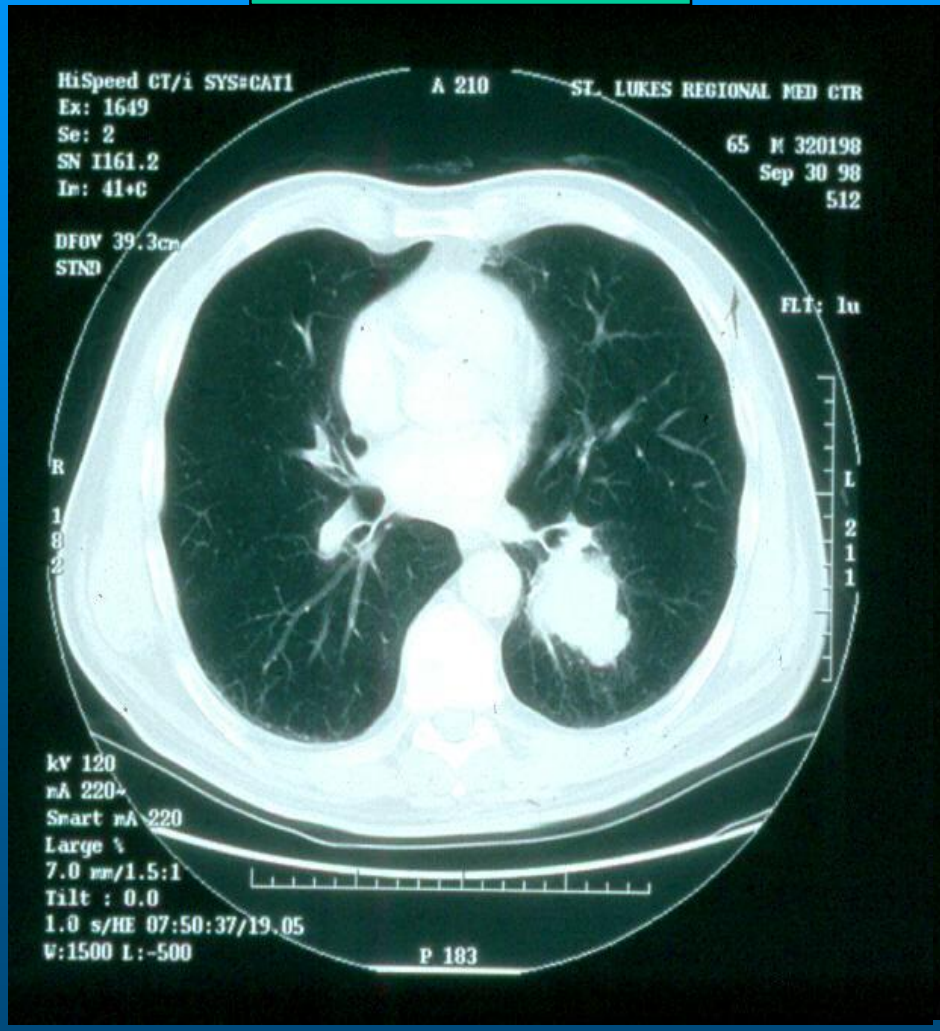
Clinical major RR: 58.9%

Progression during induction: 3%

Pisters K et al., J Thor CV Surg 2000; 119;429

INDUCTION CARBO/ PACLITAXEL * 3

PRE



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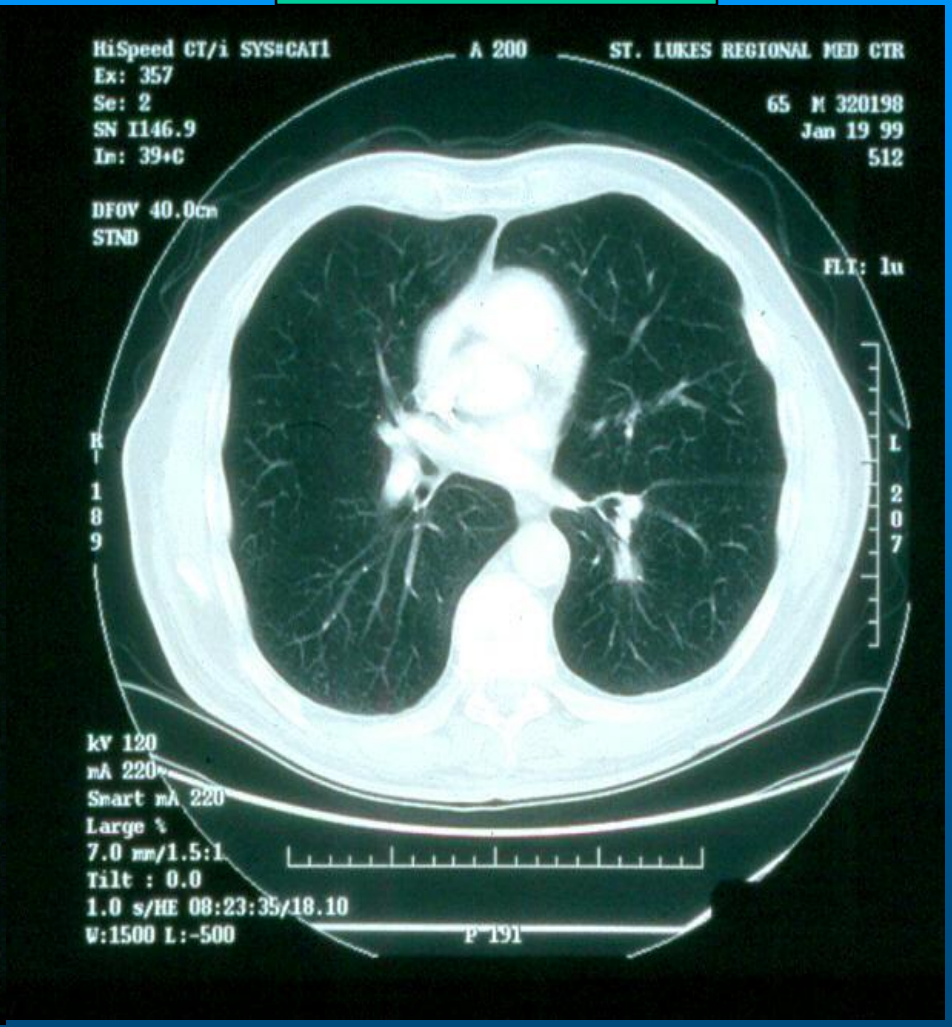
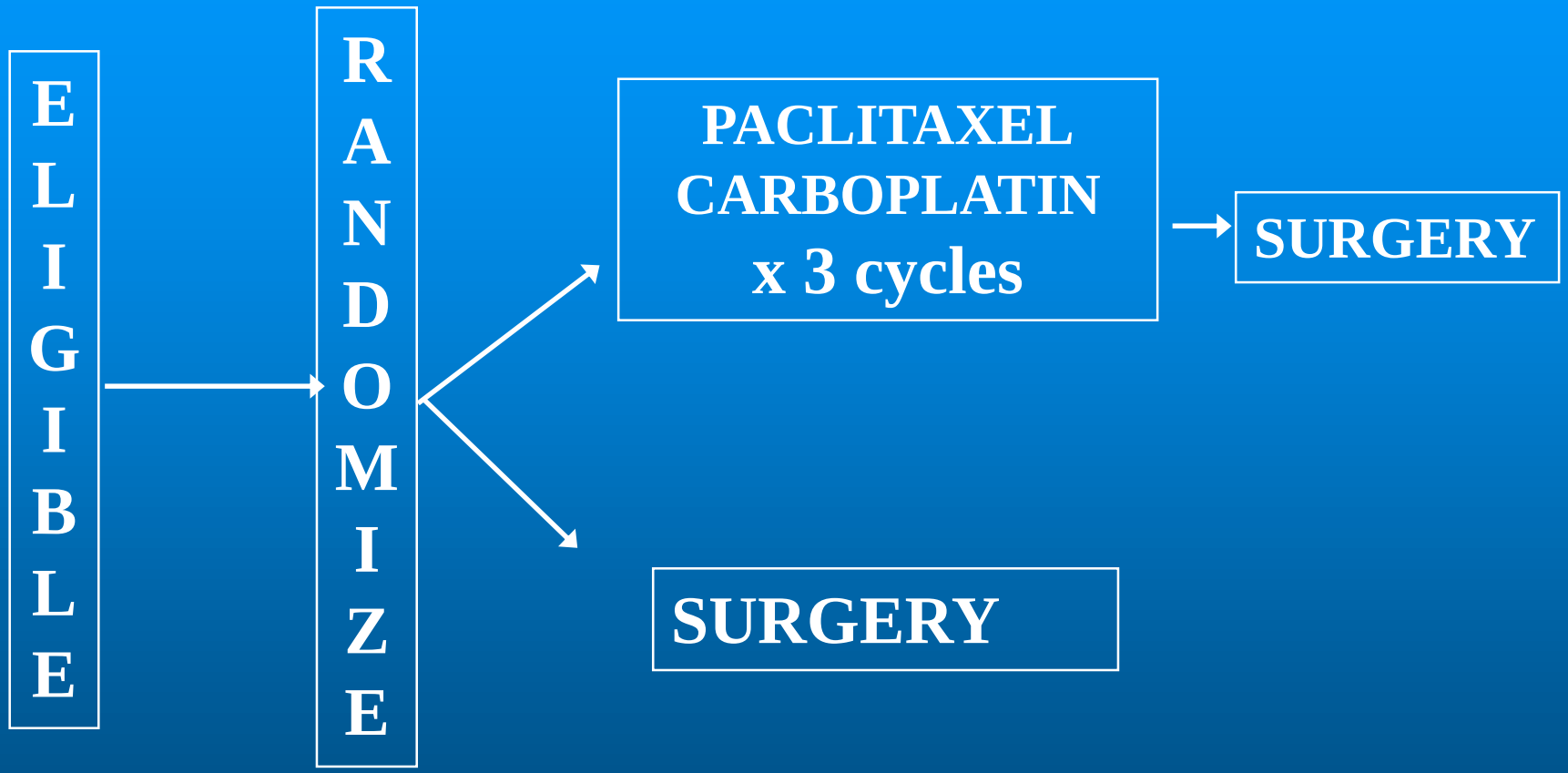


S9900 Study Design



- Clinical stage T2N0, T1-2N1, T3N0-1
- Mediastinoscopy if LN > 1 cm on CT
- Stratification: IB/IIA vs IIB/IIIA

S9900 Study

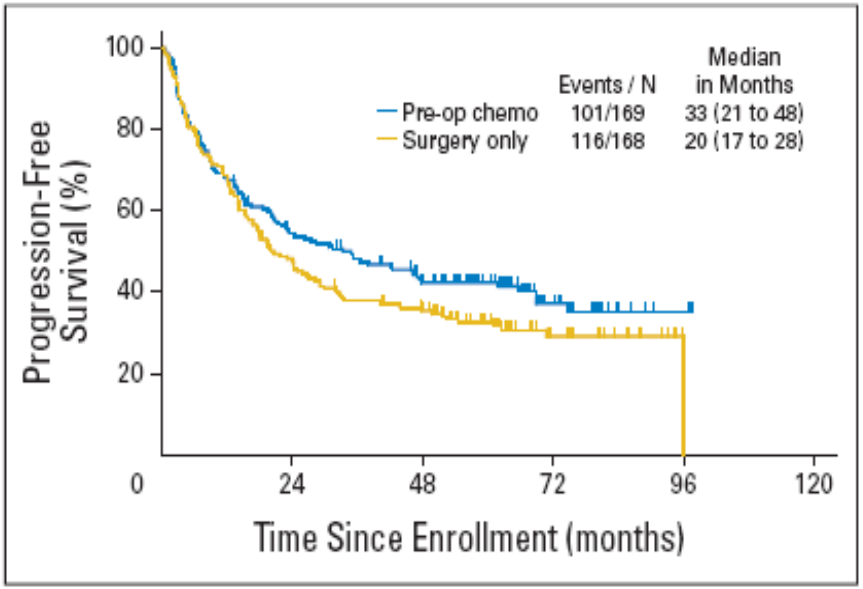


Fig 2. Progression-free survival by treatment arm (median follow-up, 64 months). Pre-op, preoperative; chemo, chemotherapy; N, number.

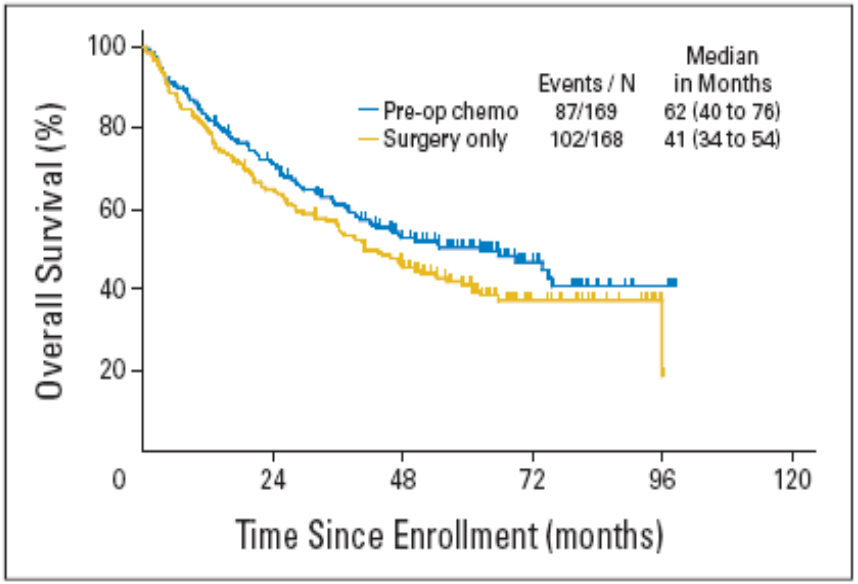


Fig 3. Overall survival by treatment arm (median follow-up, 64 months). Pre-op, preoperative; chemo, chemotherapy; N, number.

HR 0.80 (0.61-1.04), P= 0.10

HR 0.79 (0.60-1.06), P=0.11

Pisters K et al., J Clin Oncol 2010; 28; 1843-49

pCR only 3%

Conclusions S9900

- Closed too early (re: The Positive Adjuvant studies) and underpowered
- The PFS and OS trend (N.S.) in favor of preoperative chemotherapy.

Pisters K et al., J Clin Oncol 2010; 28; 1843-49

Types of resection

- CS (n=169)

• Explored	151
• Lobect/Bilob	114
• **Pneumonectomy**	**24 (16%)**
• < lobe	8
• O/C	5

- S only (n=167)

• Explored	160
• Lobect/Bilob	112
• **Pneumonectomy**	**25 (16%)**
• < lobe	17
• O/C	6

Pre op vs. Post op meta-analysis

	Pre op(1)	Post op(2)
Hazard Ratio	.87	.86
Absolute survival	5%	4%

(1) Burdett S et al., Lancet epub Feb 2014

(2) Burdett/ Pignon et al., Lancet 2010; 375:1267-77

2014

Post-operative chemotherapy is the standard of care for good PS pts after R0 anatomic resection p stages IIA-B, IIIA NSCLC, and … maybe larger IB…

Also in 2000s!



Patrick Roy



Joe Thornton

Roy



Jarome Iginla

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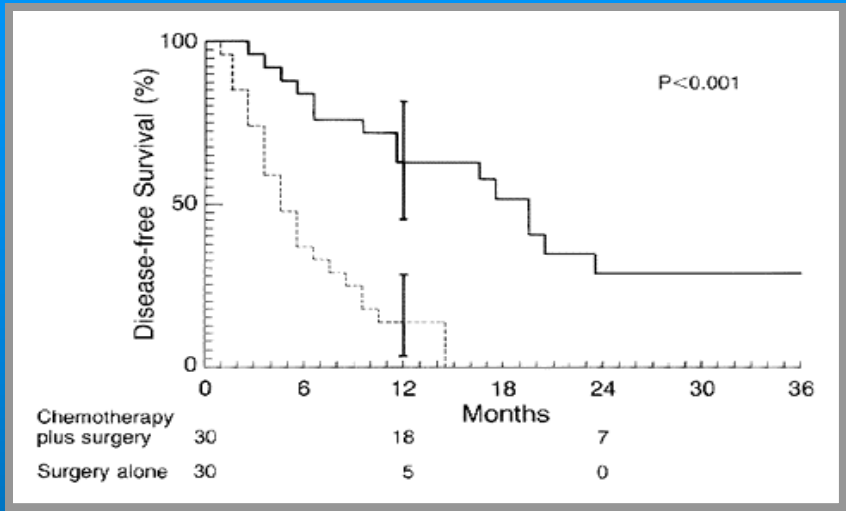
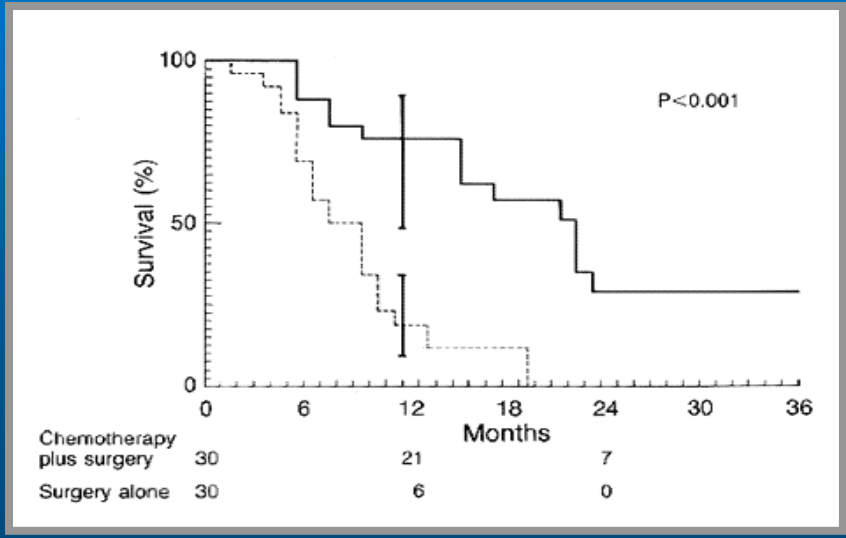




From Rosell, 1994

SURGERY FOR IIIA N2 DISEASE

- **If N2 found at mediastinoscopy but attempt at resection**

IIIA

9% / 5y survival

- **If mediastinoscopy negative but N2 found at thoracotomy**

IIIA

24% / 5y survival

Pearson, J Thorac CV Surg 1982

Surgical N2 disease

Heterogeneity of population

↓

Xray N2 ≠ mediastinoscopy N2 ≠ resection N2

↓

Difficult to compare reported series and trial results

SWOG 8805

Induction Chemoradiotherapy Stages IIIA & IIIB

Phase II

Induction CDDP/ VP-16 *2

w/ concurrent RTx to 45 Gy

T 1-4 N 2-3 diseases, pathologically documented

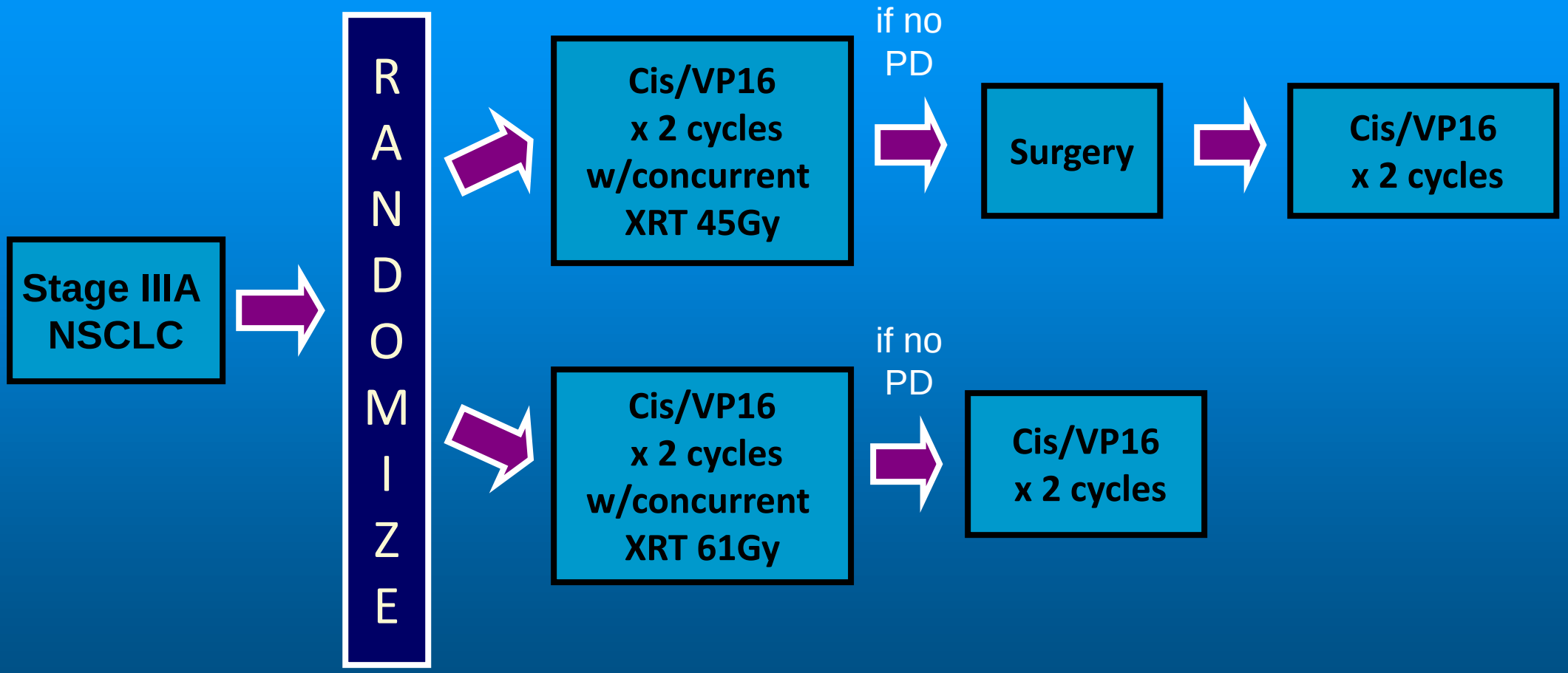
SWOG 8805

Induction Chemoradiotherapy Stages IIIA & IIIB

WHAT HAVE WE LEARNED ?

1. Acceptable morbidity and op mortality
2. Best survival if CR at resection
3. If persistence of N2 disease, prognosis < 9%/5y
4. X-rays often under estimate the response to therapy

INT 0139: Definitive CT/RT vs. Induction CT/RT → Surgery for Stage IIIA NSCLC

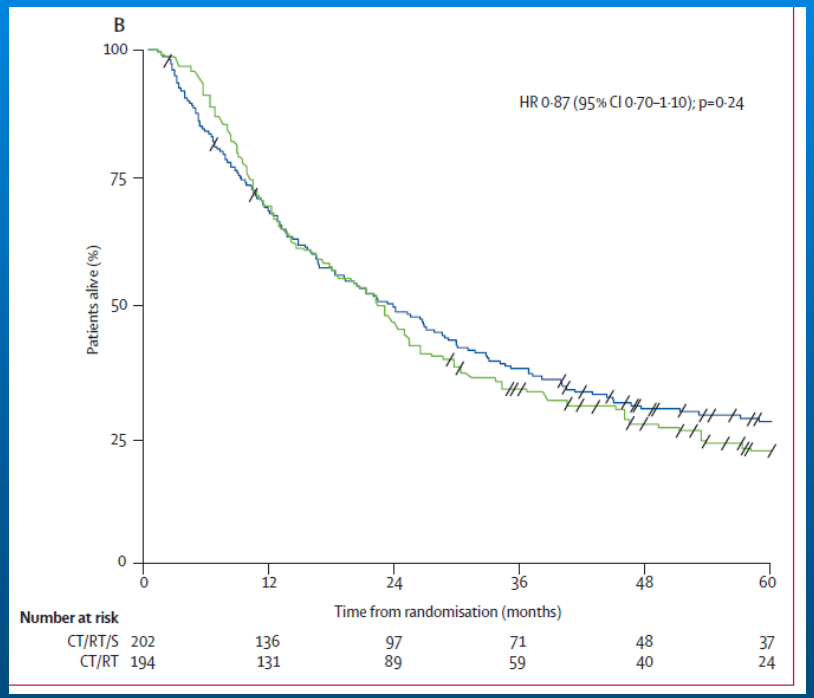


Albain: ASCO, 2003

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

INT 0139



5 y survival C/RT/S 27% vs 20% C/RT

Op mortality of lobectomy was 1%

R pneumonectomies (29%)
or complex pneumonectomies did not do so well !

Relapse at T site 3% vs 19% (6.3 X) favoring surgery arm

Albain KS, Lancet Oncol 2009; 374: 379-86

Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non–Small-Cell Lung Cancer

Jan P. van Meerbeeck, Gijs W. P. M. Kramer, Paul E. Y. Van Schil, Catherine Legrand, Egbert F. Smit, Franz Schramel, Vivianne C. Tjan-Heijnen, Bonne Biesma, Channa Debruyne, Nico van Zandwijk, Ted A. W. Splinter, Giuseppe Giaccone

On behalf of the European Organisation for Research and Treatment of Cancer-Lung Cancer Group

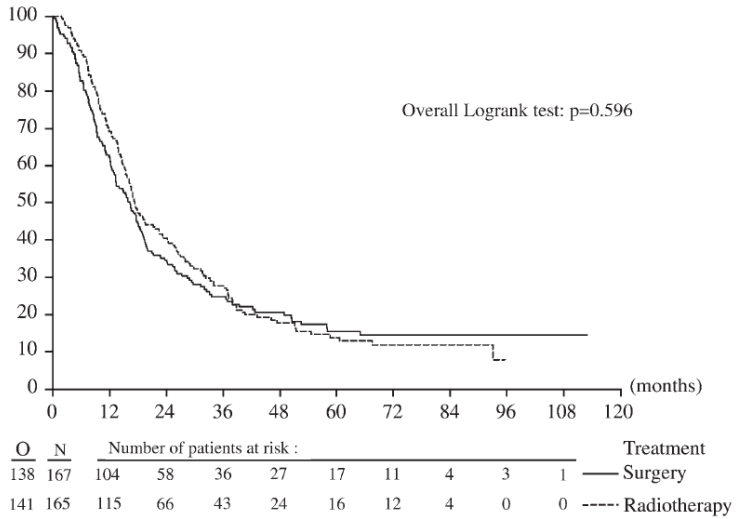


Fig. 2. Overall survival rates estimated from time of randomization using Kaplan–Meier analyses. *P* value (two-sided) was calculated using the log-rank test. O = number of deaths; N = number of patients. Hazard ratio = 1.06, 95% confidence interval = 0.84 to 1.35; *P* = .596.

EORTC

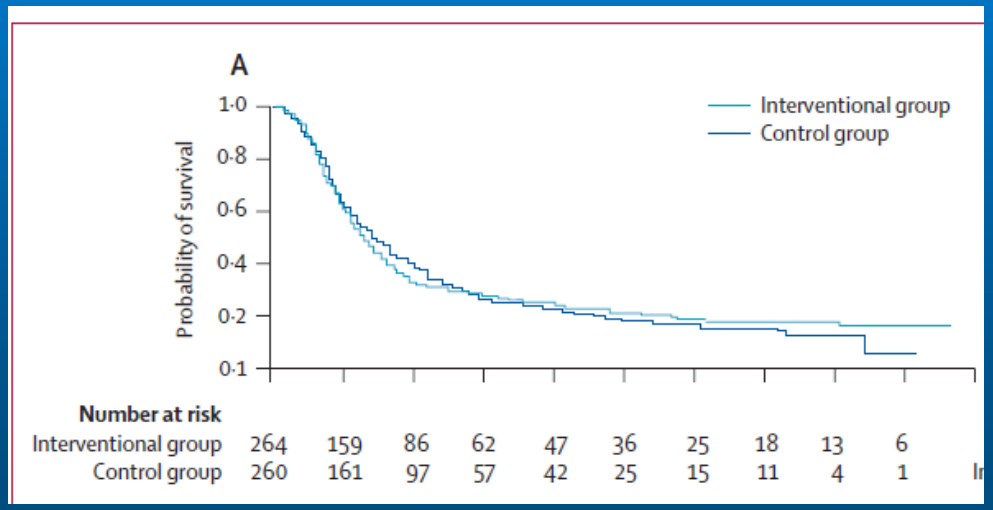
Op mortality of 72 pneumonectomies was 6.9%

5 y survival C/S 15.7% vs 14% C/RT

Van Meerbeck, J Natl Cancer Inst 2007; 99: 442-50

Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer

Michael Thomas, Christian Rübe, Petra Hoffknecht, Hans N Macha, Lutz Freitag, Albert Linder, Norman Willich, Michael Hamm, Gerhard W Sybrecht, Dieter Ukena, Karl-Matthias Deppermann, Cornelia Dröge, Dorothea Riesenbeck, Achim Heinecke, Cristina Sauerland, Klaus Junker, Wolfgang E Berdel, Michael Semik*, for the German Lung Cancer Cooperative Group***



GLCGG

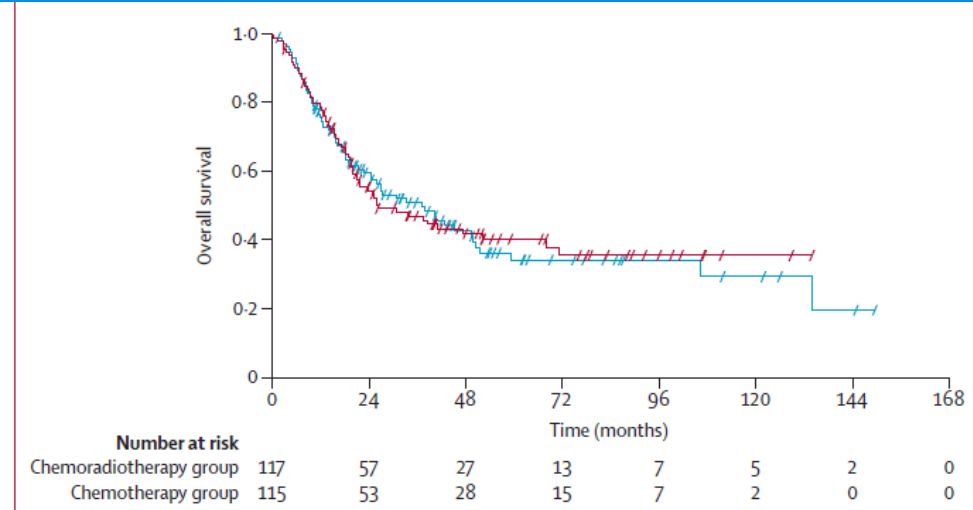
5 y survival C/S 21% vs 18% C/RT/S

Thomas M et al Lancet Onc 2008; 9: 636-48

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

SAKK16/00

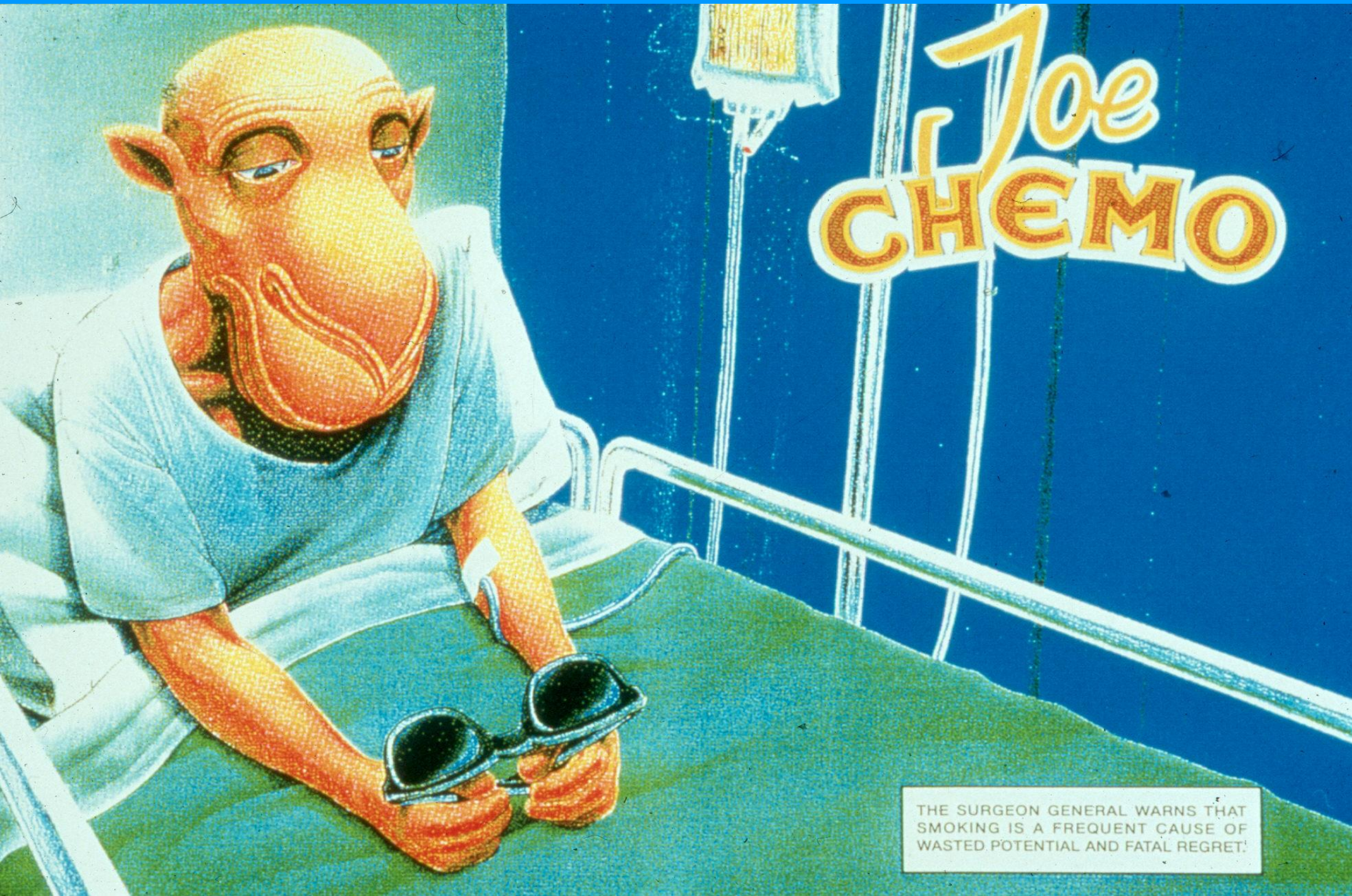
Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group



"We suggest that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 non-small-cell lung cancer."

Pless M et al (SAKK), Lancet Oncol 2015

A 20 year gap without significant progress

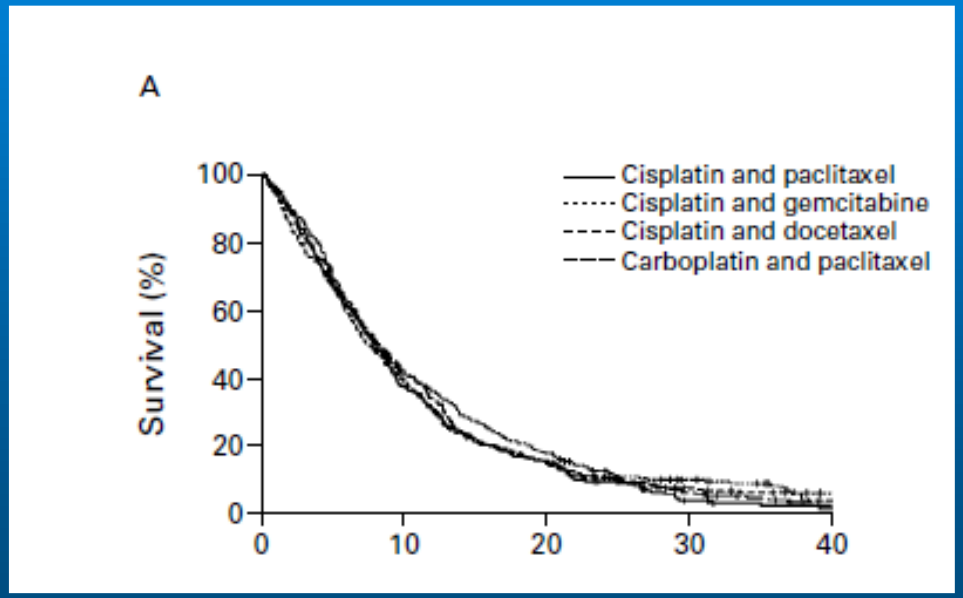

Joe
CHEMO
THE SURGEON GENERAL WARNS THAT SMOKING IS A FREQUENT CAUSE OF WASTED POTENTIAL AND FATAL REGRET.

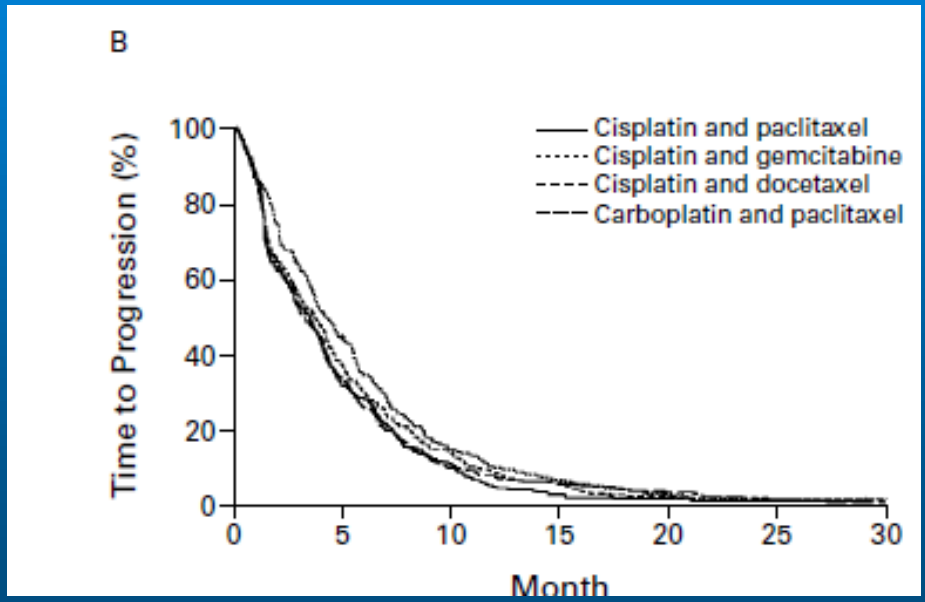
A 20 year gap without significant progress

The New England Journal of Medicine

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP





SchillerJH al NEJM 346(2):92-98, 2002

The 2020s



Connor McDavid

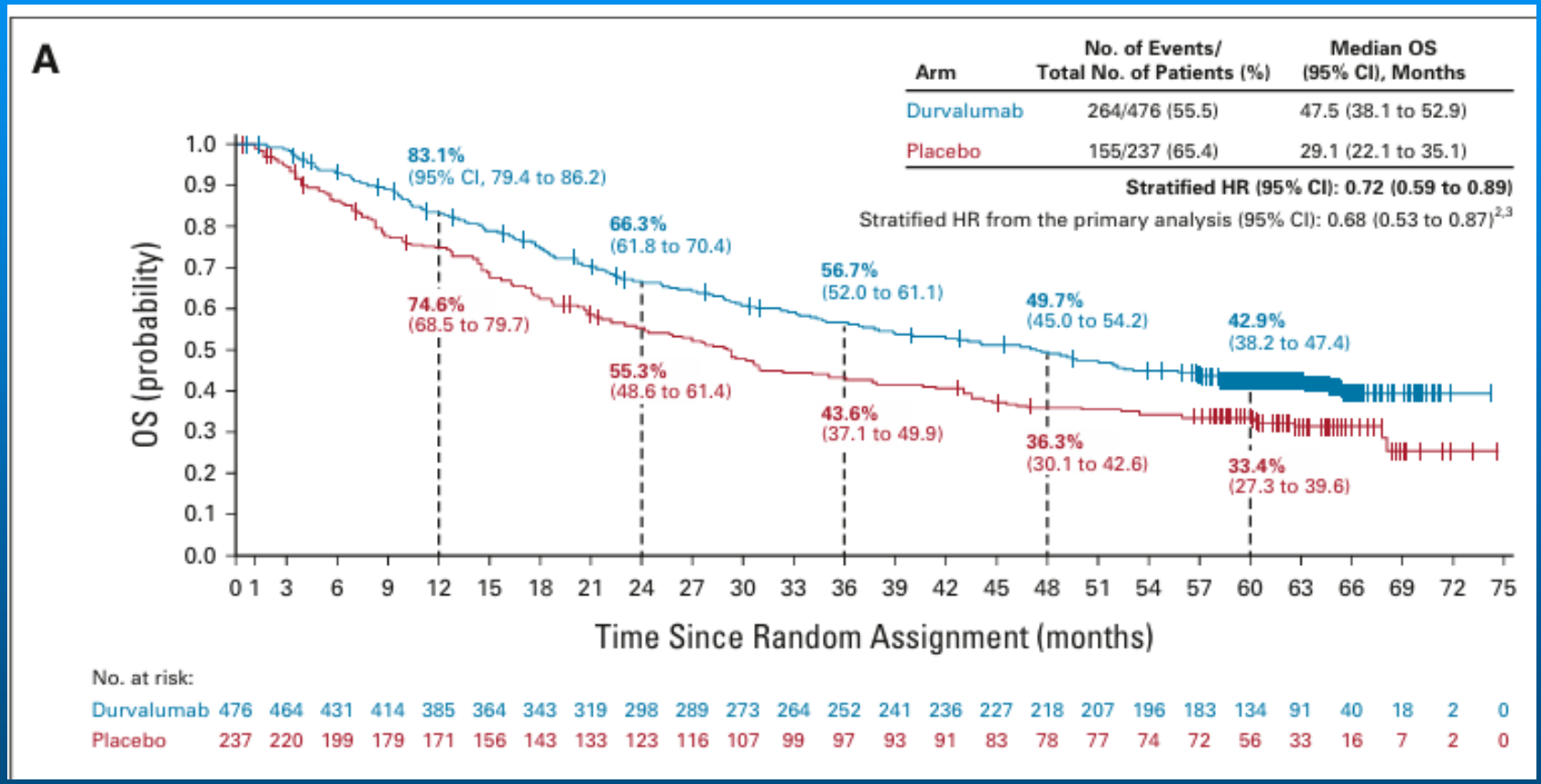


Cale Makar



Nathan MacKinnon

PACIFIC Trial: Durvalumab After Chemoradiotherapy in unresectable Stage III Non–Small-Cell Lung Cancer



Spigel DR et al J Clin Oncol 40:1301-11, 2022

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- So many areas for research by surgeons!!!

The current neoadjuvant and perioperative ICI-based treatment landscape in NSCLC

Completed and Ongoing Select Phase 3 Trials

Resectable NSCLC

Neoadjuvant

Trial	Regimen
CheckMate 816[1]	Nivolumab + Chemotherapy

Adjuvant

Trial	Regimen
KEYNOTE-091/PEARLS[2]	Pembrolizumab
IMpower010[3]	Atezolizumab
CCTC BR31[4]	Durvalumab
ANVIL[5]	Nivolumab
NADIM-ADJUVANT[6]	Nivolumab + Chemotherapy

Perioperative

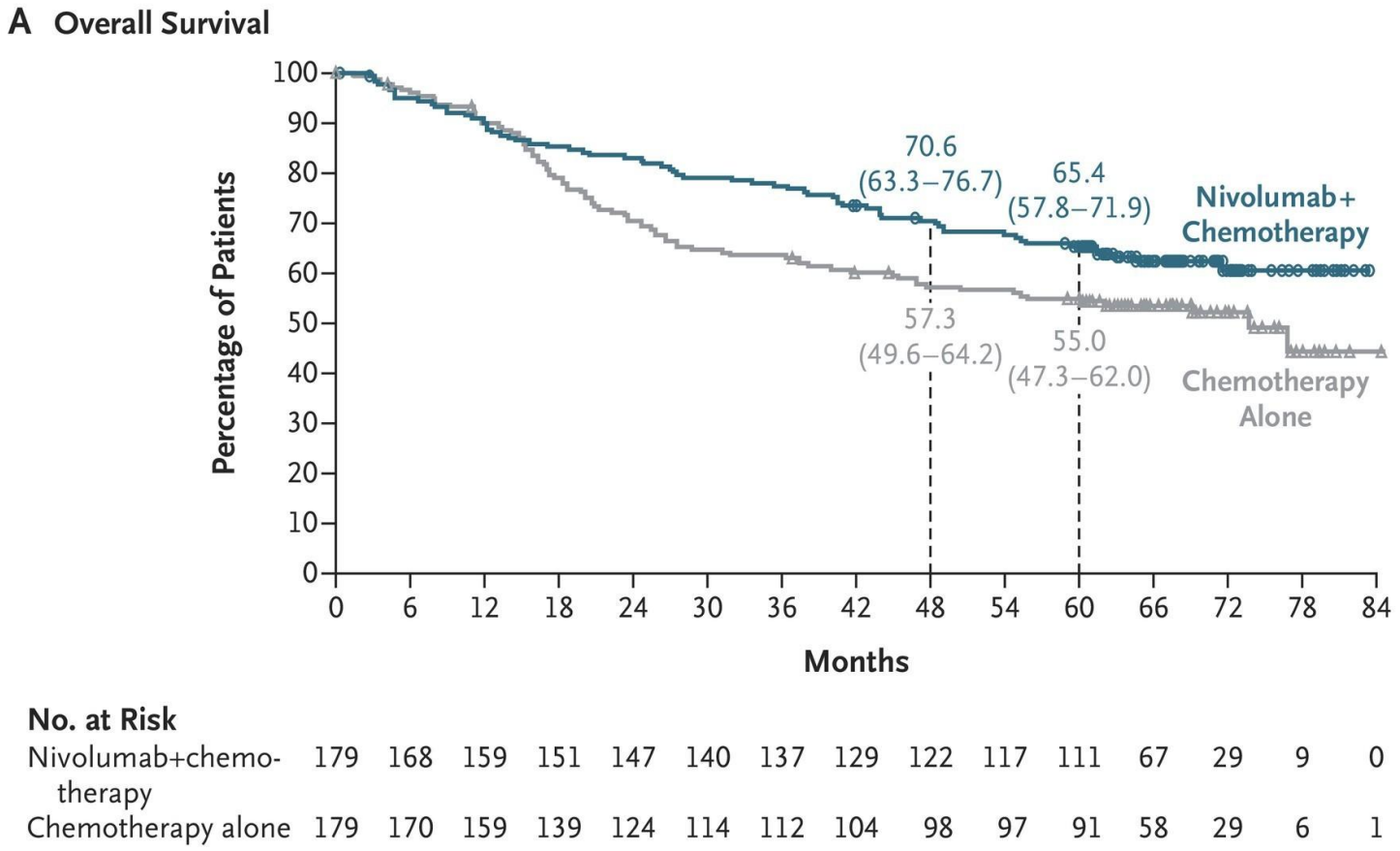
Trial	Regimen
CheckMate 77T[7]	Nivolumab + Chemotherapy → Nivolumab
IMpower030[8]	Atezolizumab + Chemotherapy → Atezolizumab
AEGEAN[9]	Durvalumab + Chemotherapy → Durvalumab
KEYNOTE-671[10]	Pembrolizumab + Chemotherapy → Pembrolizumab
Neotorch[11]	Toripalimab + Chemotherapy → Toripalimab + Chemotherapy → Toripalimab

- **Higher rates of pCR with chemo-immunotherapy vs chemotherapy alone**
- **Patients with pCR have superior EFS compared to those without pCR**
- **OS data are premature**

Forde PM et al, N Engl J Med 2022; 386:1973-1985
Wakelee H et al, N Engl J Med 2023; 389:491-503

Overall Survival with Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer

Checkmate 816



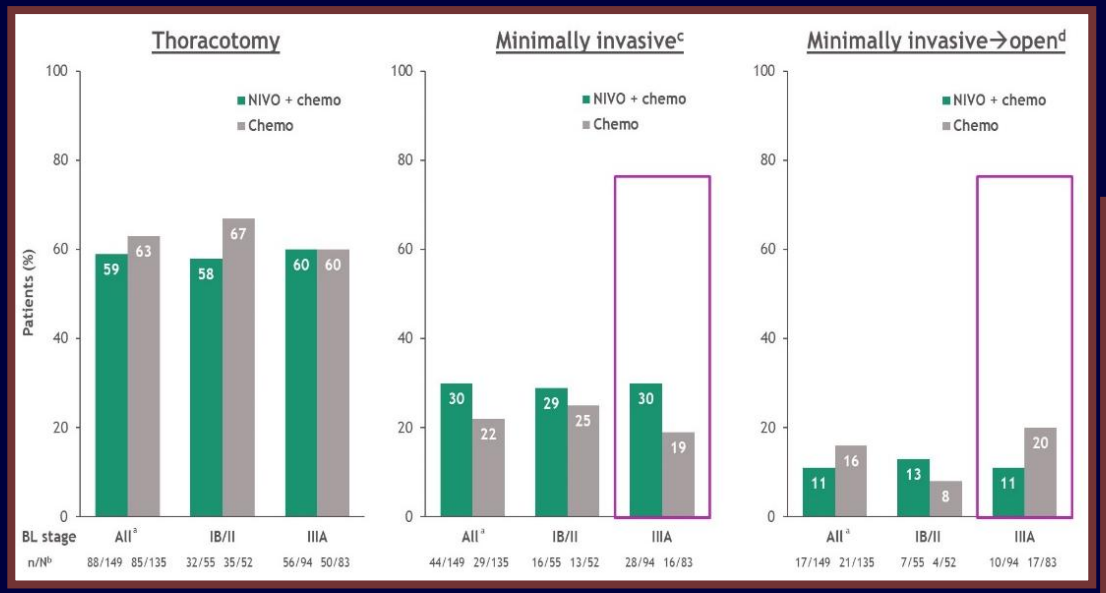
pCR: 24% vs. 2.2%

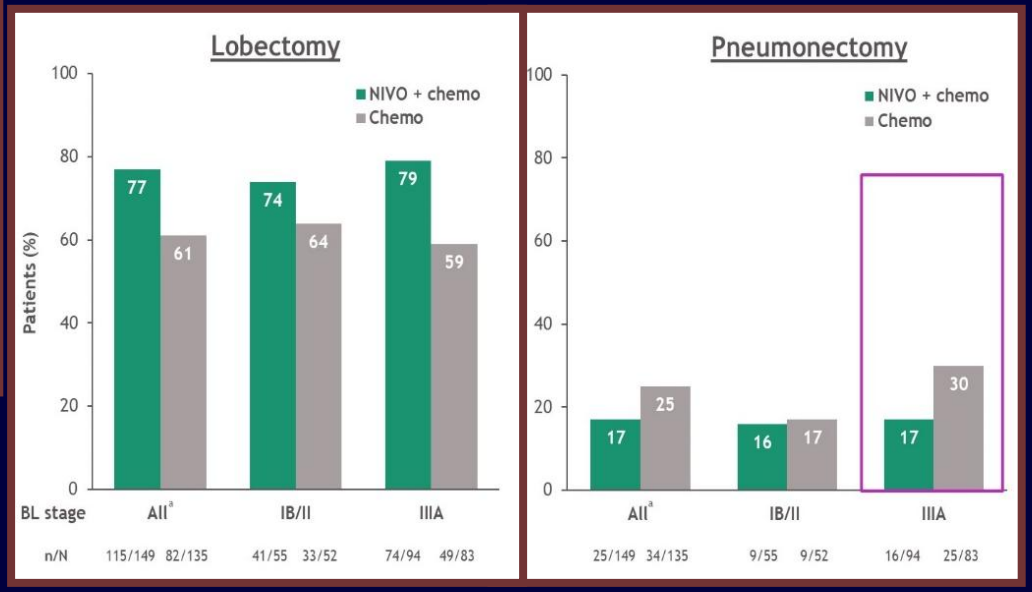
	Median Overall Survival (95% CI)
	mo
Nivolumab+Chemotherapy (N=179)	NR (NR–NR)
Chemotherapy Alone (N=179)	73.7 (47.3–NR)

Hazard ratio for death, 0.72 (95% CI, 0.523–0.998)
P=0.048

Forde PM, Spicer J et al N Engl J Med 393:741-52, 2025

CheckMate 816: Surgery Approach and Type of Surgery by Stage



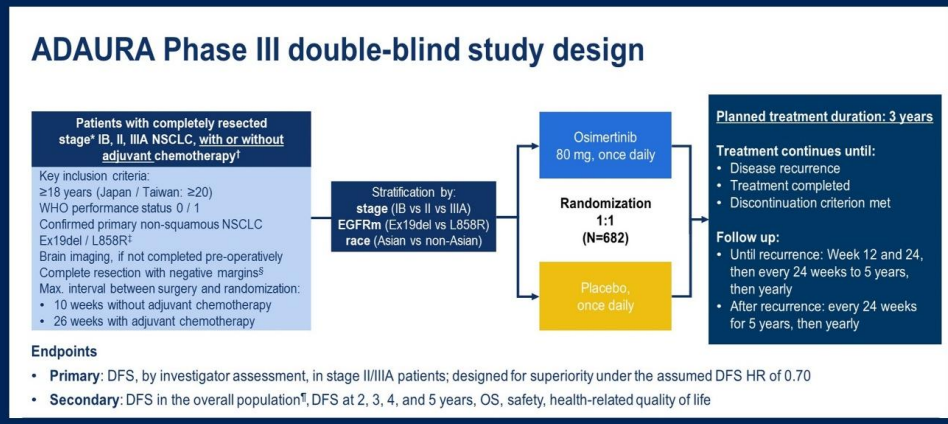


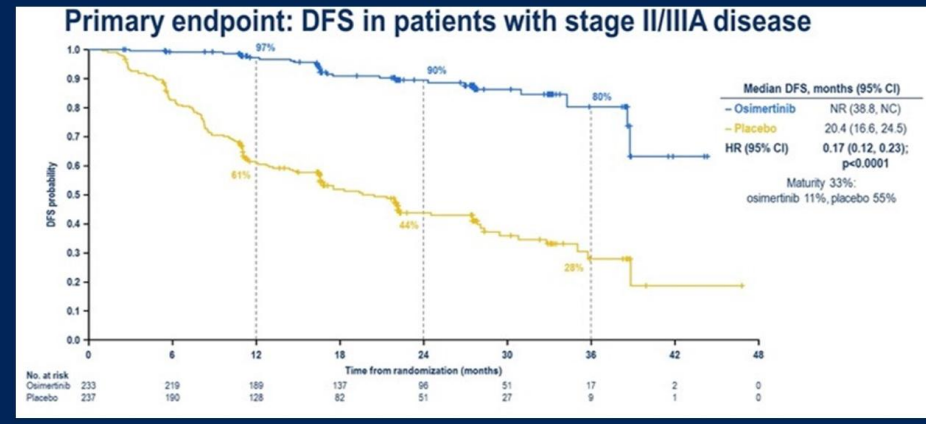
Spicer, ASCO 2021: A#8503

THE EVOLUTION OF COMBINED MODALITY THERAPY IN SURGICAL NSCLC OVER 40 YEARS

- Adjuvant RT
- Adjuvant cytotoxic C
- Induction cytotoxic C
- Clinical stage IIIA
- Induction and peri-op C-IO
- **Peri-op TKI**
- So many areas for research by surgeons!!!

… adjuvant osimertinib for EGFR driven cancers





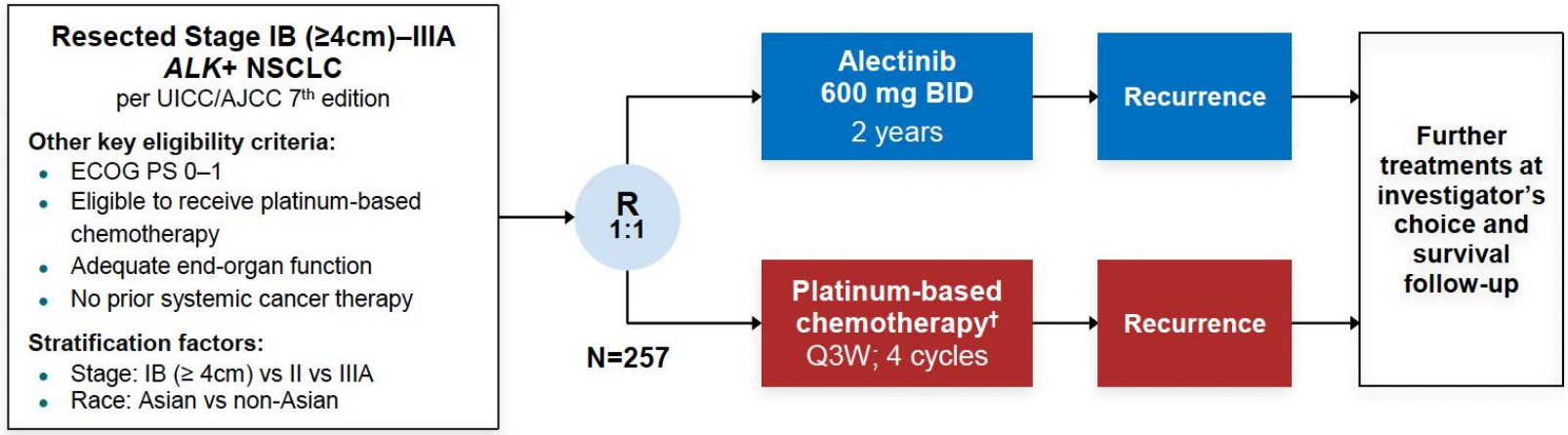
On December 18, 2020, the Food and Drug Administration approved osimertinib (TAGRISSO, AstraZeneca Pharmaceuticals LP) for adjuvant therapy after tumor resection in patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

Herbst R, ASCO 2020

Slide Courtesy – Zosia Piotrowska, MD, MHS, ASCO 2021

… adjuvant Alectinib for ALK harboring tumors

ALINA study design*



Primary endpoint

- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints

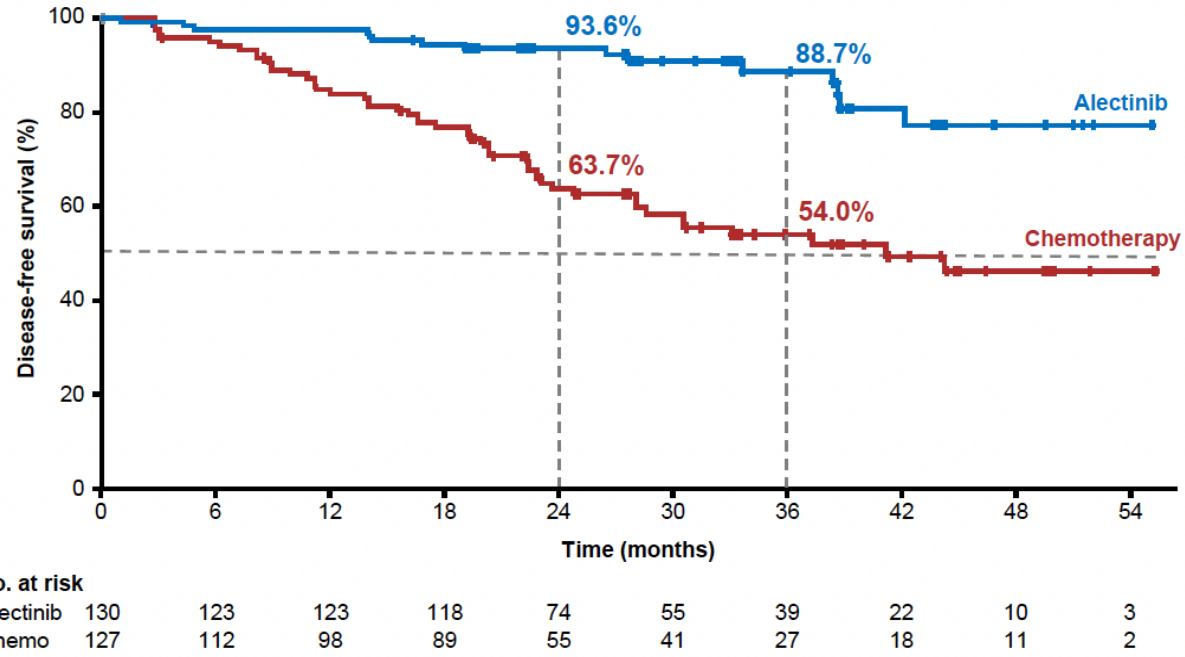
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Disease-free survival: ITT (stage IB–IIIA)*



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

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Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months
*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

2026 ASCO® ANNUAL MEETING

Neoadjuvant Lorlatinib in Stage III NSCLC Harboring ALK Fusion: Clinical and Dynamic Spatial Multi-omics Analysis of LORIN Phase II Trial

Key Takeaways

- Neoadjuvant lorlatinib demonstrated remarkable pathological response **(pCR 47%, MPR 81%)** in patients with stage III ALK-positive NSCLC, and a high surgical conversion rate **(75%)** in those with unresectable disease.

The 2020 s and beyond



Mitch Marner



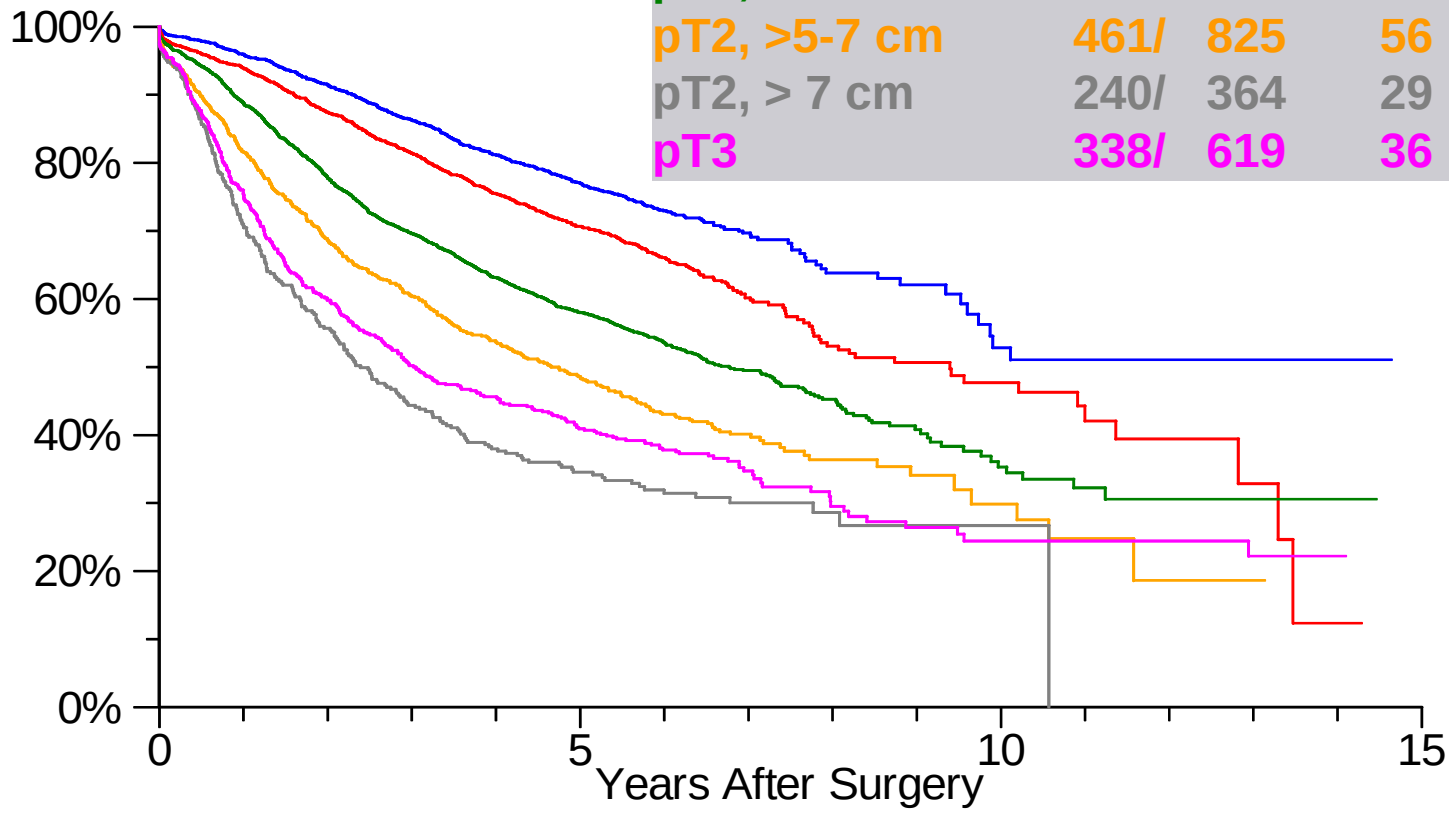
Connor Bedard

THE EVOLUTION OF COMBINED MODALITY THERAPY IN SURGICAL NSCLC OVER 40 YEARS

- Adjuvant RT
- Adjuvant cytotoxic C
- Induction cytotoxic C
- Clinical stage IIIA
- Induction and peri-op C-IO
- Peri-op EGFR TKI
- **So many areas for research by surgeons!!!**

Overall survival by tumour size for patients with pT1-T3 N0 R0, UICC 6 classification

	Deaths / N	MST	5-Year
pT1, <=2cm	492/ 1816	NR	77%
pT1, >2-3 cm	582/ 1653	113	71%
pT2, <=5 cm	1311/ 2822	81	58%
pT2, >5-7 cm	461/ 825	56	49%
pT2, > 7 cm	240/ 364	29	35%
pT3	338/ 619	36	41%



Rami-Porta et al. J Thor Oncol 2007; 2(7): 593-602

Using other tools than TNM for decision making?

- Could a gene signature of the tumor trump TNM in predicting risk of recurrence?

Adjuvant chemotherapy for stage IA–IIA non-squamous, non-small-cell lung cancer identified as molecular high-risk by a 14-gene expression profile (AIM-HIGH): an international, randomised, phase 3 trial

*David R Spigel, Virginie Westeel, Ian C Anderson, Laurent Greillier, Florian Guisier, Olivier Bylicki, Firas B Badin, Gaelle Rousseau-Bussac, Clotilde Deldycke, Frank Griesinger, Adam Bograd, Wangjian Zhong, Jacques Le Treut, Sylvie Van Hulst, David R Gandara, Martin Reck, Petra Hoffknecht, Matthew A Gubens, John Crowley, Heiko von der Leyen, Gavitt A Woodard, David M Jablons, Johannes R Kratz, Michael J Mann, for the AIM-HIGH investigators**

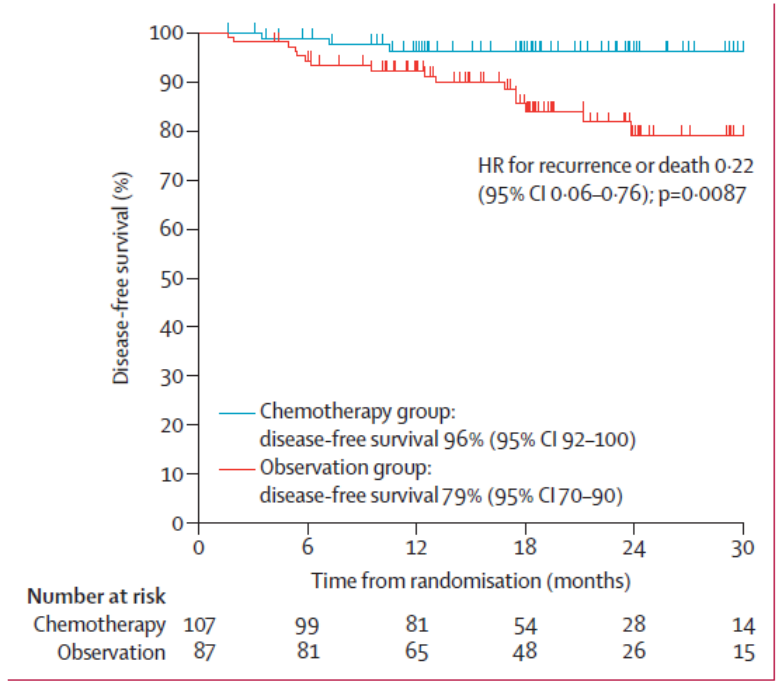


Figure 2: **Kaplan–Meier survival analysis of disease-free survival in the evaluable mITT population**
HR=hazard ratio. mITT=modified intention to treat

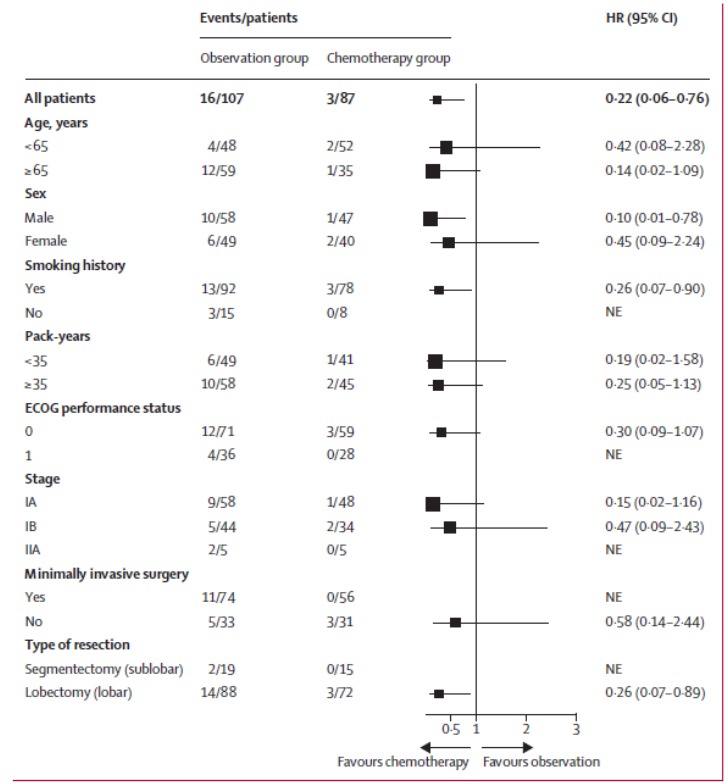
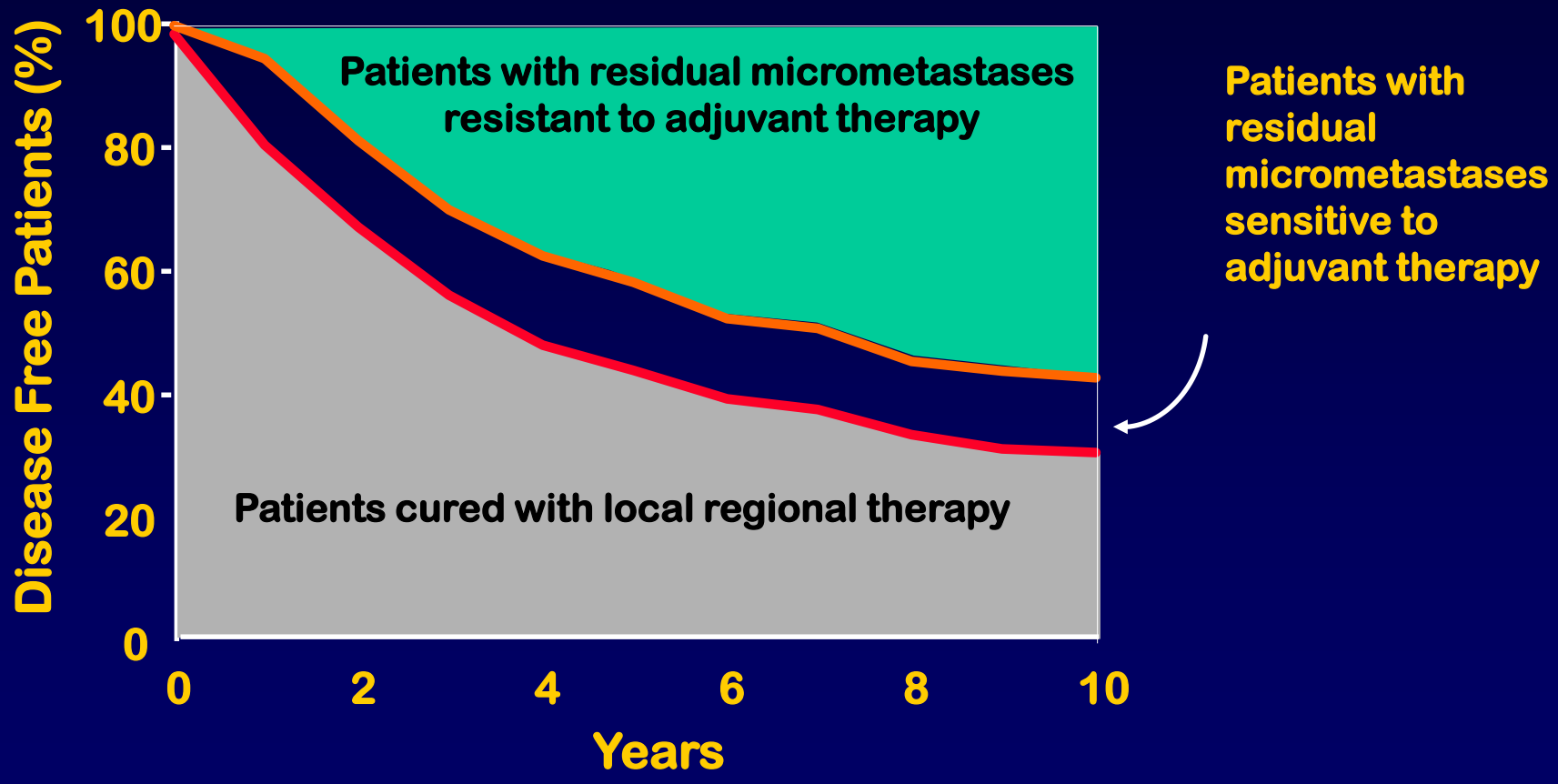


Figure 3: **Forest plot of the subgroup analysis in the mITT population**
Box size is proportional to the SE of the HR estimate, with a smaller box denoting a more precise estimate. For subgroups with no data displayed (NE), events (recurrence or death) were only observed in the observation group; no events were observed in the chemotherapy group. HR=hazard ratio. mITT=modified intention to treat. NE=not estimable.

Lancet Respir Med 2025
Published Online
June 24, 2025

RiskReveal™ (Razor Genomics)

Potential Benefit from Adjuvant Cytotoxic Therapy



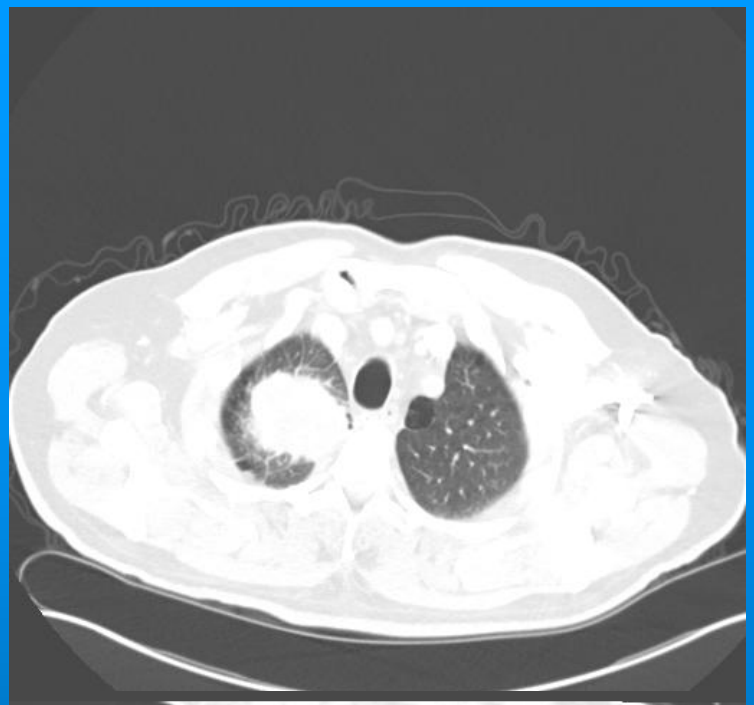
Courtesy Dr. Giorgio Scagliotti

Who are the patients who don't need additional help after preop IO then surgery?

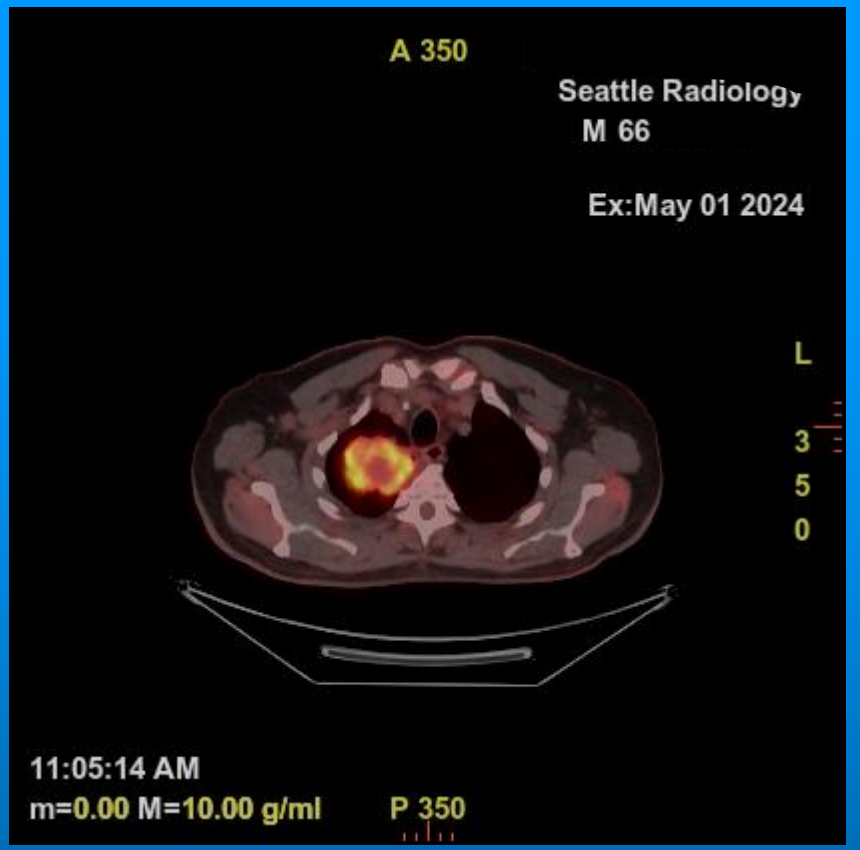
In whom should we deescalate?

pCR?

Circulating Tumor DNA ? (Mermaid Trial)





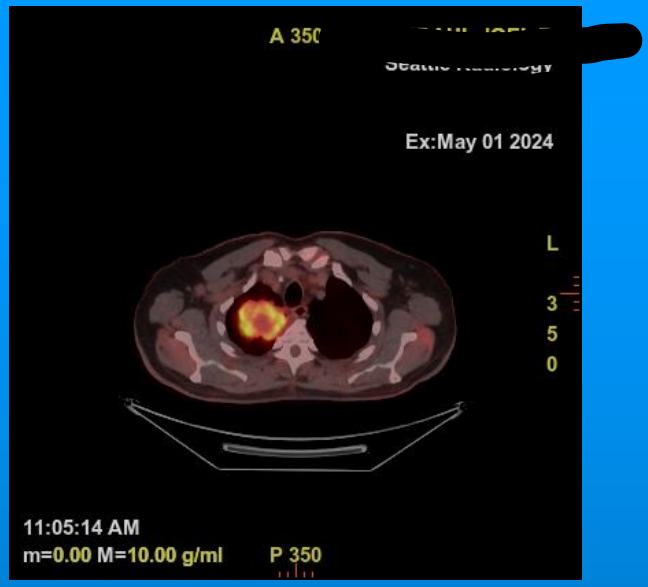


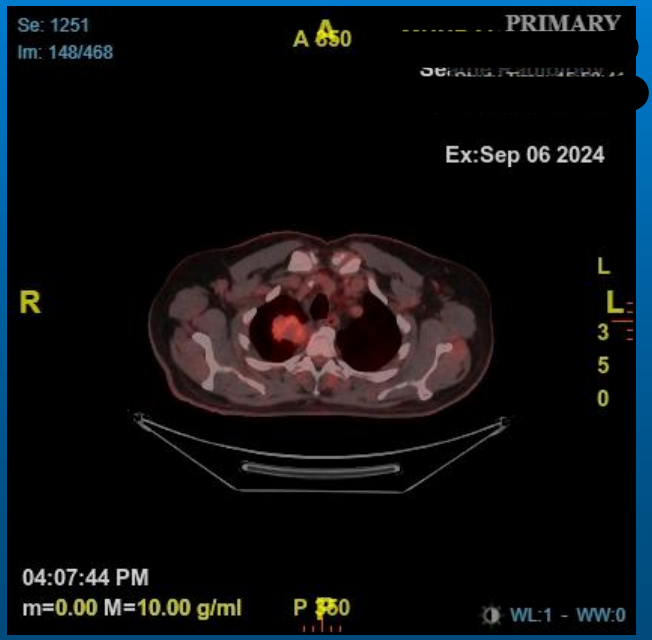
66 M FS w cough, no pain
CT = 64 mm RUL mass
PET T @18.2, 2R @4, 4R @ 4.8, M0
Brain negative
B : adeno
EBUS 4R and 10R negative

No actionable mutation
PDL1 negative

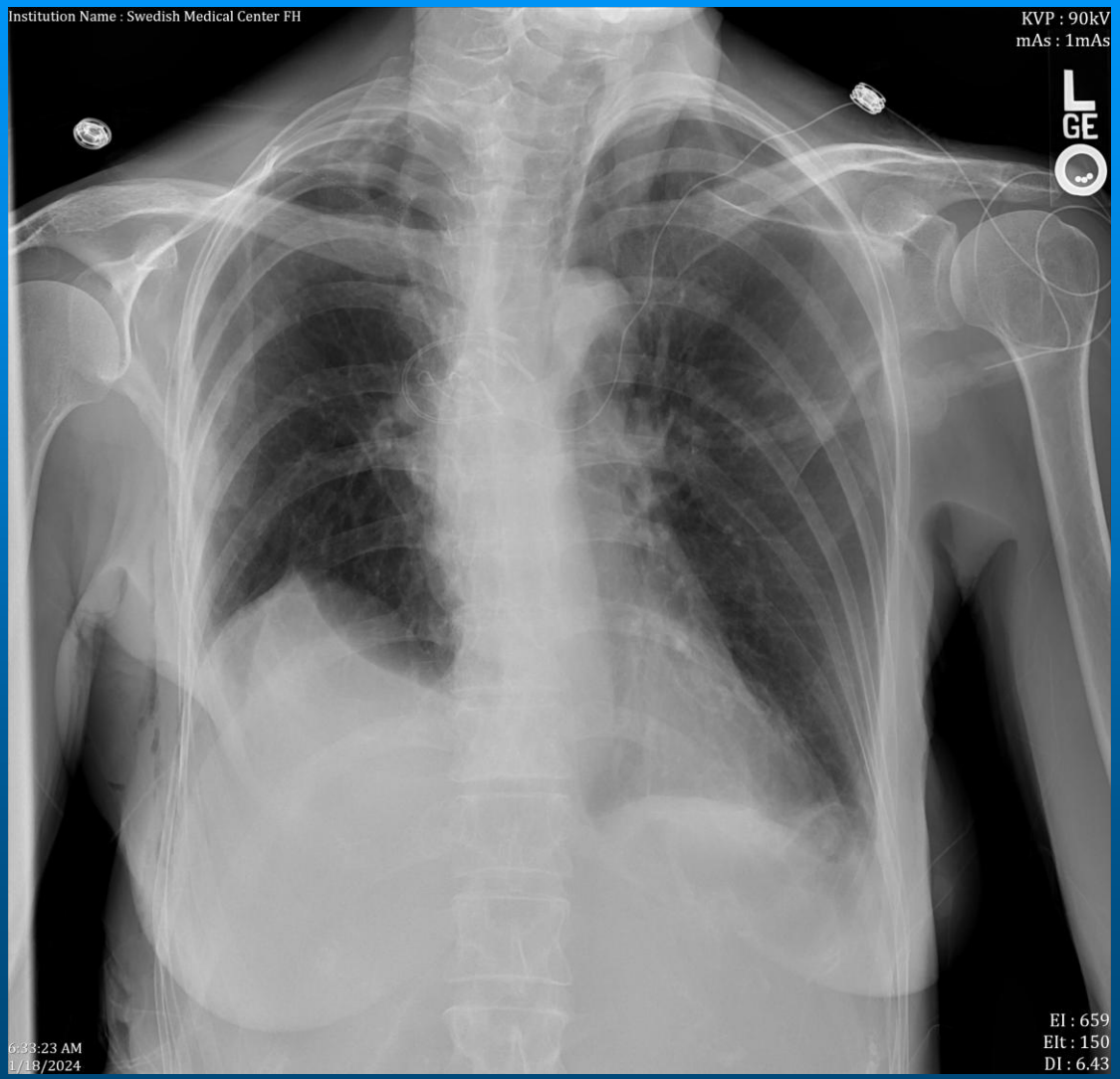
Received 4 cycles pemetrexed/carbo/ pembro
(Keynote 671)

Repeat PET
T smaller now @5.7, 4R same size, now @ 4, rest of mediastinum quiet, M0





Do pCR patients need additional therapy after induction C-IO?



Med/ VATS > OPEN
extrapleural RUL and LND
Home POD 3

Path : 42 mm residual mass, 17 LN
ypT0N0M0R0

What now?

2026 ASCO ANNUAL MEETING

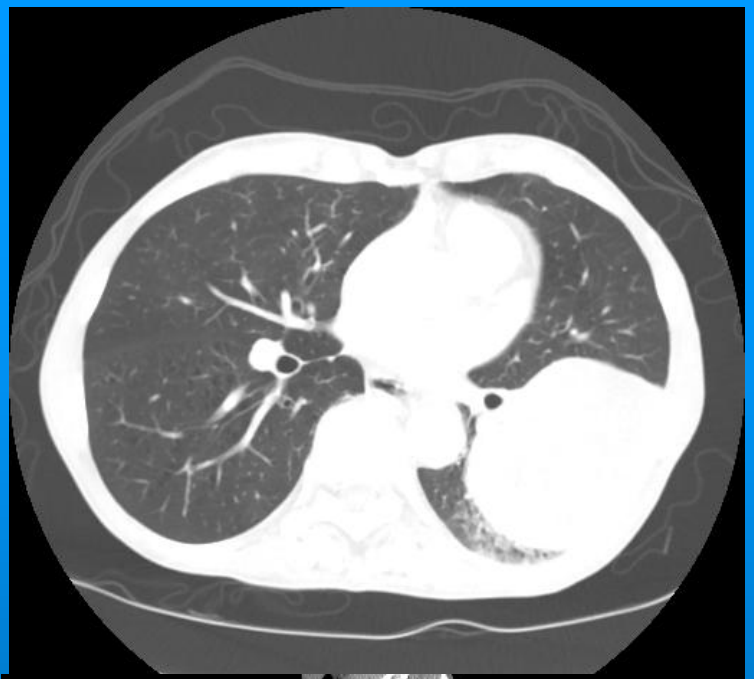
Clinical validity of ultrasensitive single-digit parts per million ctDNA detection in non–small cell lung cancer

James R.M. Black[1,2], **Jonathan C. M. Wan**[1,2], Charles W. Abbott[3], Bailiang Li[3], Takahiro Karasaki[1,2], Alexander A. Azizi[1,2], Lydia Y. Liu[2], Olivia Lucas[1], Charlotte Grieco[1,2], Aino-Maija Leppä[1,2], Maise Al Bakir[1,2], Wing Kin Liu[1], David A. Moore[1], Oliver Shutkever[1], Cian Murphy[1,2], Mariam Jamal-Haniani[1,2], Rachel Marty Pyke[3], Sean M. Boyle[3], Richard O. Chen[3], Charles Swanton[1,2]

Key Conclusions

1. Current assays frequently miss ultra-low signal that precedes recurrence in early-stage NSCLC: particularly in the <10 PPM range
2. Postoperative ctDNA <10 PPM independently predicts relapse, identifying high-risk patients otherwise classified as "low-risk"
3. <10 PPM sensitivity further improves molecular lead time for 25% of recurring patients, enabling earlier clinical intervention

We need better test(s) to predict C-IO response!

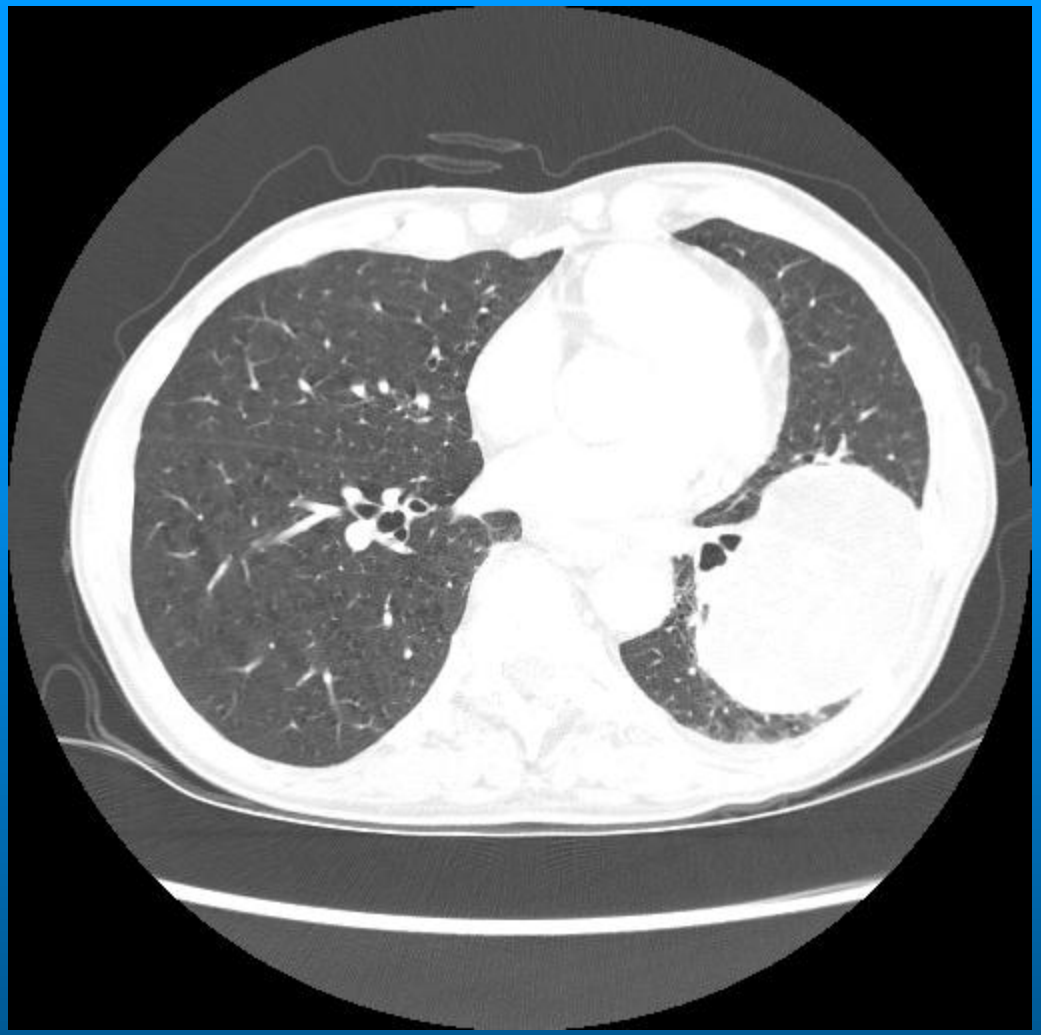


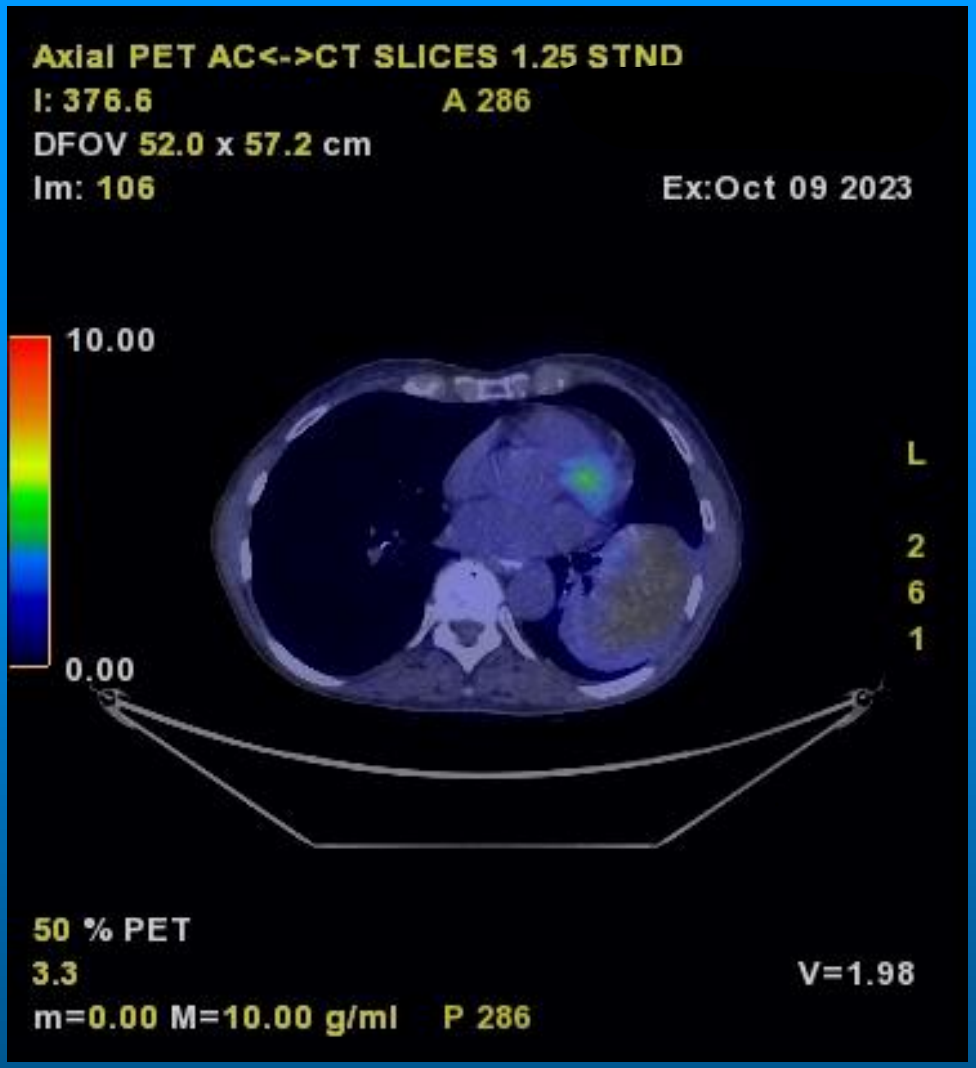




68 F FS
Large mass 11 cm LLL
LCNE,
PD-L1 < 1%, no mutation
cIIIa N0

> C-IO * 4





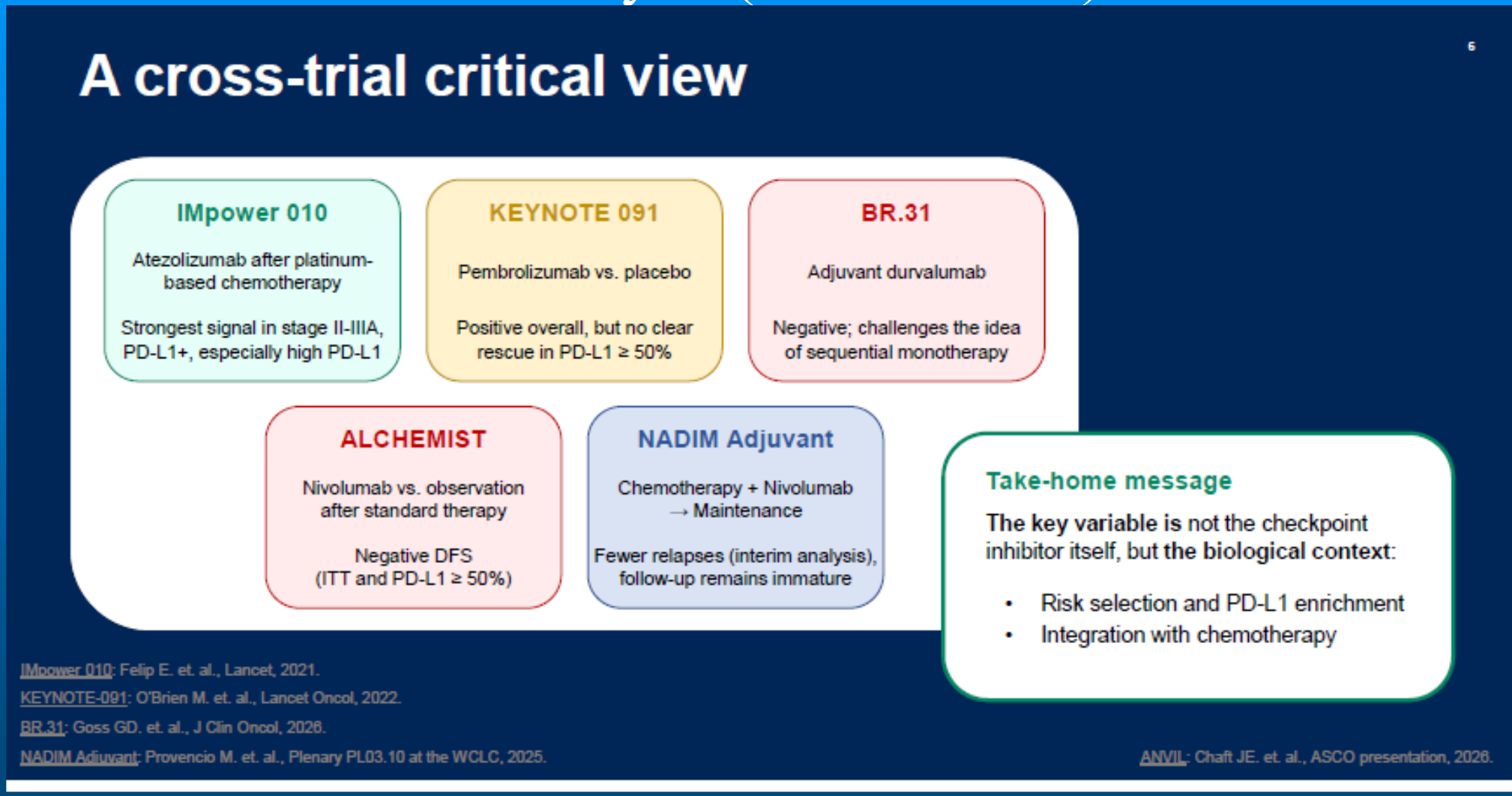
Brain is quiet

Large residual LLL mass but FDG went from 15.6 to 2, N0

Underwent LL lobectomy: 98 mm mass, 3% viable LCNE, 0/14 LN (yp T1aN0M0R0)

Is induction IO superior to adjuvant IO?

Potentially… (ASCO 2026)



Can we alter the host to improve C-indction IO response?

Radiation to the primary bed?

Being looked at, a strategy that has failed in other cancers…

Patient's diet?

Patient's microbiome?

Can we potentiate the IO effect

Using dual IOs may be too toxic…

By combining with antibody drug conjugates ?
(NeoCoast2)

By combining w vaccines as we have seen in melanoma?

Conclusions

- **The landscape of surgical NSCLC has become more complex and interesting…**

  and it keeps evolving very rapidly

- **As systemic therapies improve, it creates opportunities to re-evaluate peri-operative strategies**

It is very exciting to be a thoracic oncologist in 2026 and should remain so for years to come…

Congratulations to the Toronto Thoracic Surgery Division for this 50th annual refresher course!
Thank you

… to moonrise !

