Adjuvant Treatments in NSCLC

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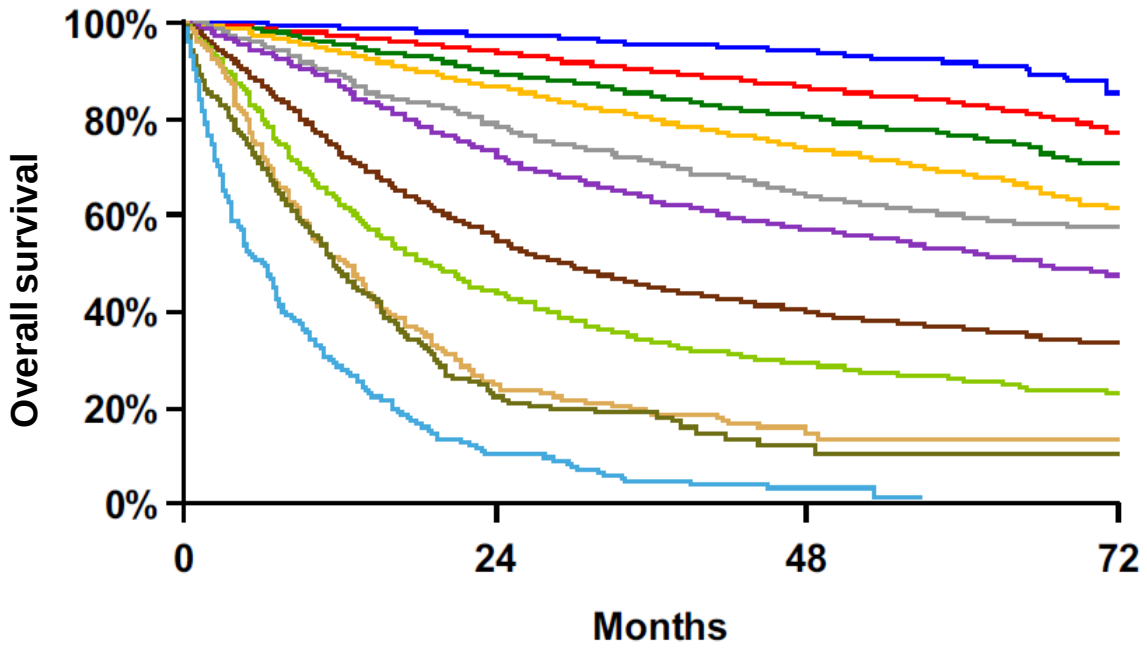
Contents

- Overview of resectable NSCLC & adjuvant treatments
- Factors influencing adjuvant chemotherapy
- Adjuvant platinum-based doublet chemotherapy
- Adjuvant Targeted therapy
- Adjuvant immune check point inhibitors

Overview of resectable NSCLC

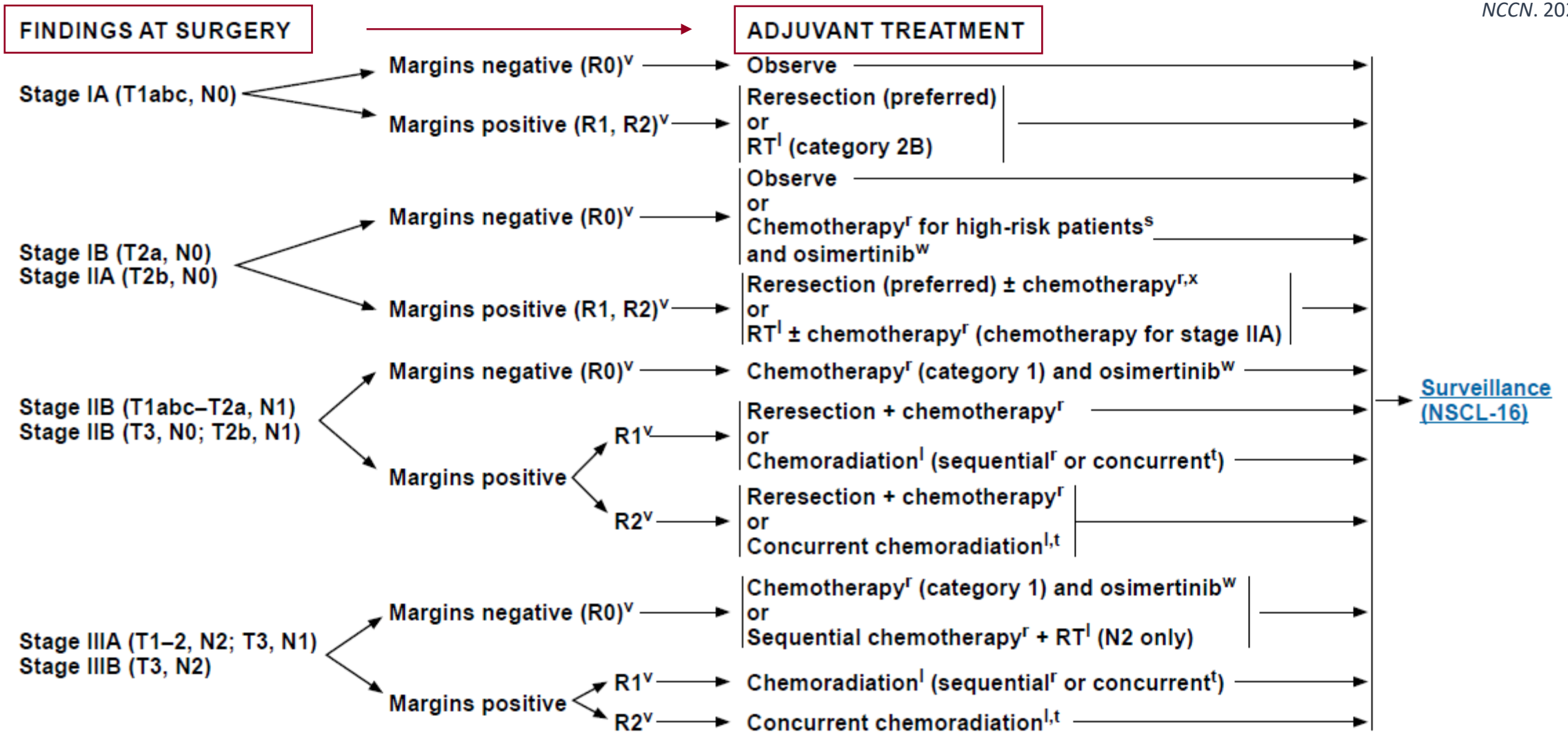
AJCC 8th Edition

5-year survival rates by stage at diagnosis



Stage	Evevts / N	MST	24 mon	60 mon
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Goldstraw et al. *JTO. 2016;11(1):39-51*



l See Principles of Radiation Therapy (NSCL-C).

r See Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).

s Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

t See Concurrent Chemoradiation Regimens (NSCL-F).

v R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

w For patients with *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.

x Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

Adjuvant treatments

- Patients with completely resected NSCLC
  - ✓May have already been cured and do not have symptoms of cancer
  - ✓Microscopically pN2 (unsuspected N2, surprise N2)

- Treatment goal
  - ✓Should be to improve long-term survival
  - ✓Disease free survival advantage may not translate to an overall survival advantage

- Detrimental effects on QOL
  - ✓The level of evidence should be higher

Gyawali et al. *JCO. 2020;39(3):175-178*

Factors influencing adjuvant chemotherapy

- For whom ?
  - ✓Stage
  - ✓Performance status
  - ✓Age
  - ✓Pathologic features
- Timing of adjuvant chemotherapy
- Chemotherapy regimen

VOLUME 35 · NUMBER 25 · SEPTEMBER 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

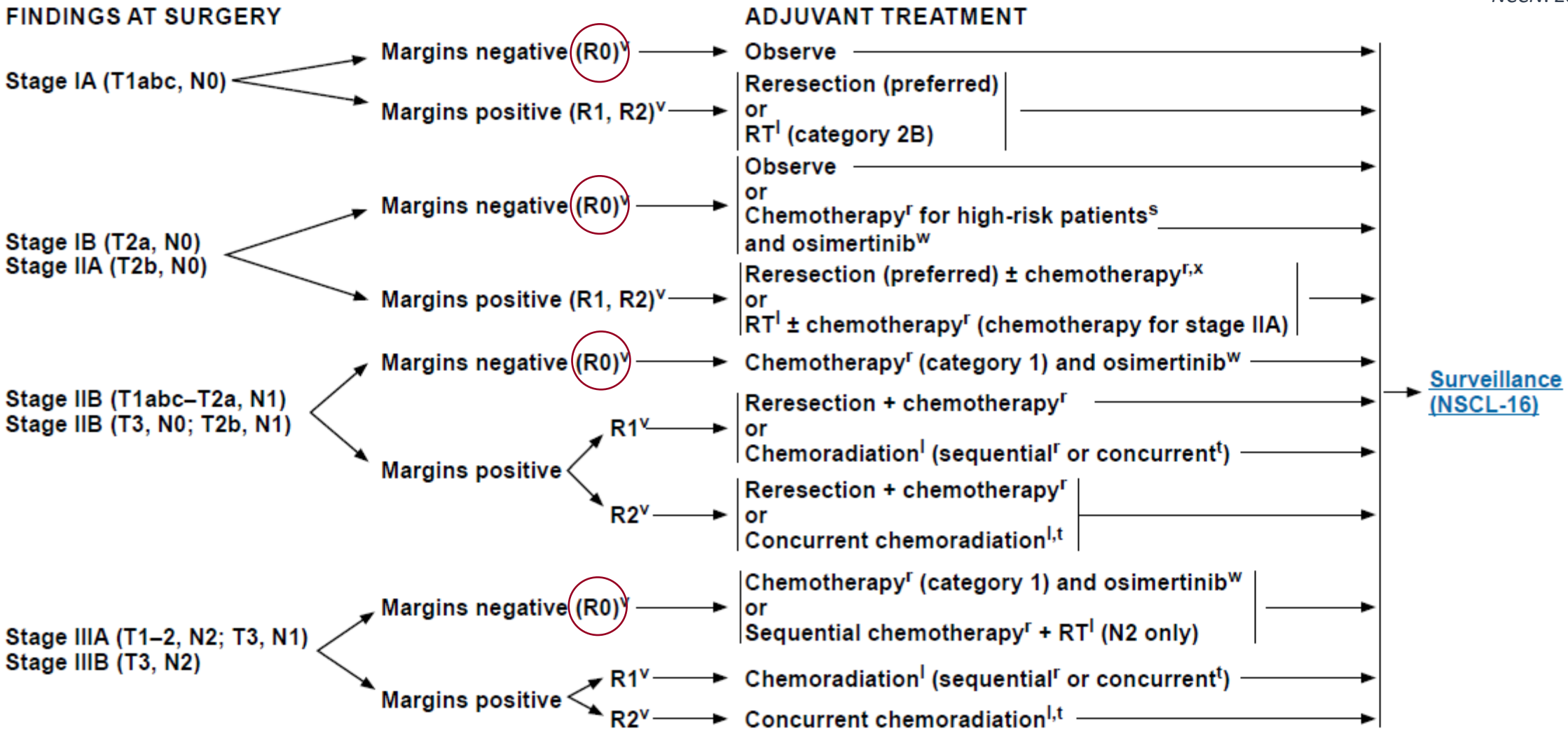
Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update

Mark G. Kris, Laurie E. Gaspar, Jamie E. Chaft, Erin B. Kennedy, Christopher G. Azzoli, Peter M. Ellis, Steven H. Lin, Harvey I. Pass, Rahul Seth, Frances A. Shepherd, David R. Spigel, John R. Strawn, Yee C. Ung, and Michael Weyant

- Recommendation 1.1. Stage IA: Adjuvant chemotherapy is not recommended. (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Intermediate; Strength of recommendation: Strong)

- Recommendation 1.2. Stage IB: Adjuvant cisplatin-based chemotherapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a medical oncologist, is recommended to assess benefits and risks of adjuvant chemotherapy for each patient. (Type: Evidence based and Panel consensus; Benefits outweigh harms, especially in patients with larger tumors; Evidence quality: Intermediate; Strength of recommendation: Moderate)

- Recommendation 1.3. Stages IIA/B and IIIA: Adjuvant cisplatin-based chemotherapy is recommended. (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong)



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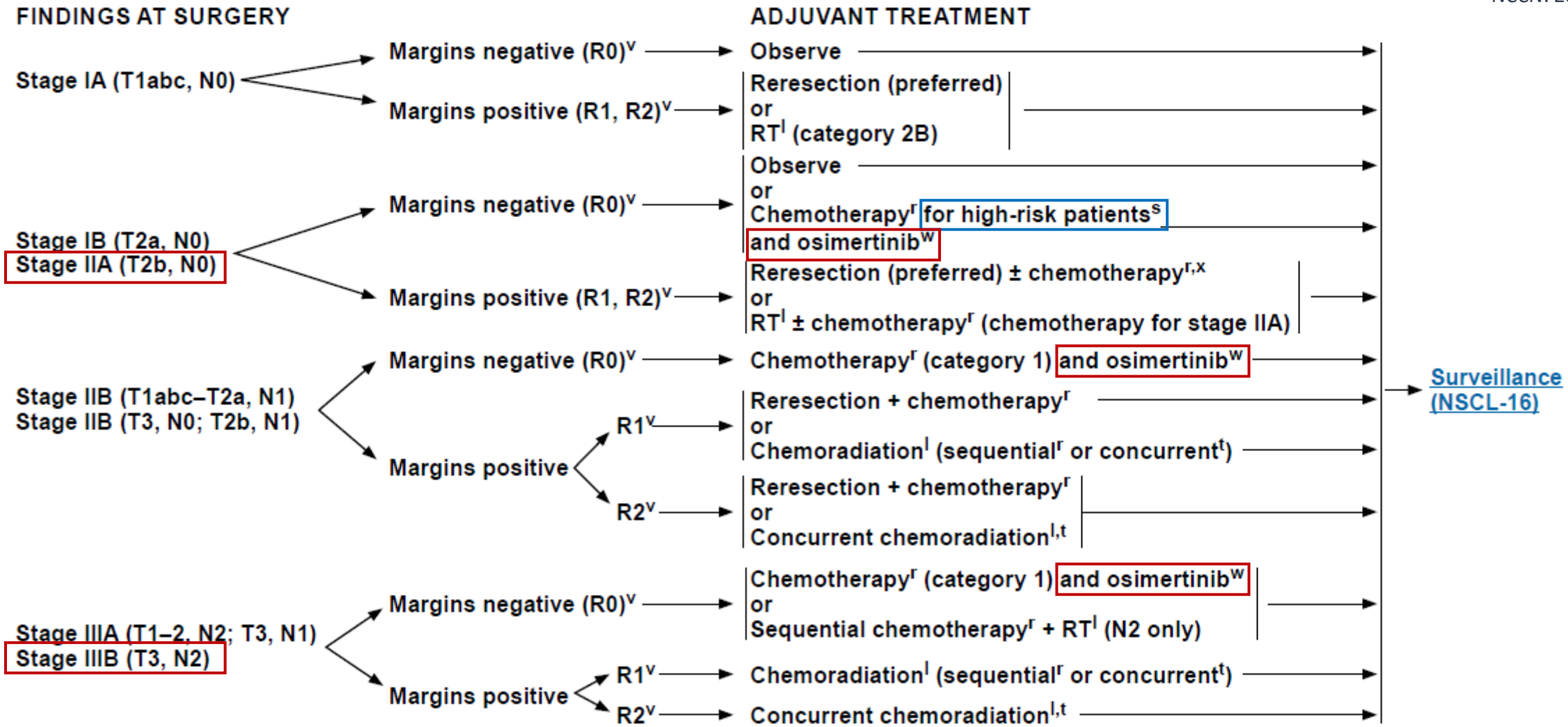

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Platinum based-doublet chemotherapy

VOLUME 26 · NUMBER 21 · JULY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

Jean-Pierre Pignon, Hélène Tribodet, Giorgio V. Scagliotti, Jean-Yves Douillard, Frances A. Shepherd, Richard J. Stephens, Ariane Dunant, Valter Torri, Rafael Rosell, Lesley Seymour, Stephen G. Spiro, Estelle Rolland, Roldano Fossati, Delphine Aubert, Keyue Ding, David. Waller, and Thierry Le Chevalier

VOLUME 26 · NUMBER 31 · NOVEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Paclitaxel Plus Carboplatin Compared With Observation in Stage IB Non–Small-Cell Lung Cancer: CALGB 9633 With the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups

LACE meta-analysis

Table 1. Trial Description

Trial Name	Inclusion Criteria	Chemotherapy (No. of cycles, dose of cisplatin by cycle, daily dose × No. of doses for other drugs)	Radiotherapy	Inclusion Period	No. of Patients Included
JBR10	pT2pN0* or pT1-2pN1	4 cycles, cisplatin (50 × 2) mg/m^2 Vinorelbine 25 mg/m^2 × 16	No radiotherapy	1994-2001	482
Adjuvant Lung Cancer Project Italy	Stage I, II, IIIA	3 cycles, cisplatin 100 mg/m^2 Mitomycin 8 mg/m^2 × 3, vindesine 3 mg/m^2 × 6	Optional After chemotherapy	1994-1999	1,088
Adjuvant Navelbine International Trialist Association 01	Stage I, II, IIIA	4 cycles, cisplatin 100 mg/m^2 Vinorelbine 30 mg/m^2 × 16	Optional for pN+ After chemotherapy	1994-2000	840
International Adjuvant Lung Trial	Stage I, II, III	3 cycles, cisplatin 100 or 120 mg/m^2 or 4 cycles, cisplatin 80 or 100 mg/m^2 Vindesine 3 mg/m^2 × 6-8, or Vinblastine 4 mg/m^2 × 6-8, or Vinorelbine 30 mg/m^2 weekly × 13, or Etoposide 100 mg/m^2 × 9-12	Optional according to pN After chemotherapy	1995-2001	1,867
Big Lung Trial	Stage I, II, III	3 cycles, cisplatin 80 mg/m^2 (biotherapies) or 50 mg/m^2 (tritherapies) Vindesine 3 mg/m^2 × 6, or Vinorelbine 30 mg/m^2 × 6, or Mitomycin 6 mg/m^2 × 3 and ifosfamide 3 g/m^2 × 3, or Mitomycin 6 mg/m^2 × 3 and vinblastine 6 mg/m^2 × 3	Optional After chemotherapy	1995-2001	307†

Abbreviation: JBR10, National Cancer Institute of Canada Clinical Trial Group trial JBR10.
*Pathologic tumor (pT) and nodal (pN) stage.
†Patients with incomplete resection (n = 61) or neoadjuvant chemotherapy (n = 13) were excluded.

Median f/u 5.2yrs

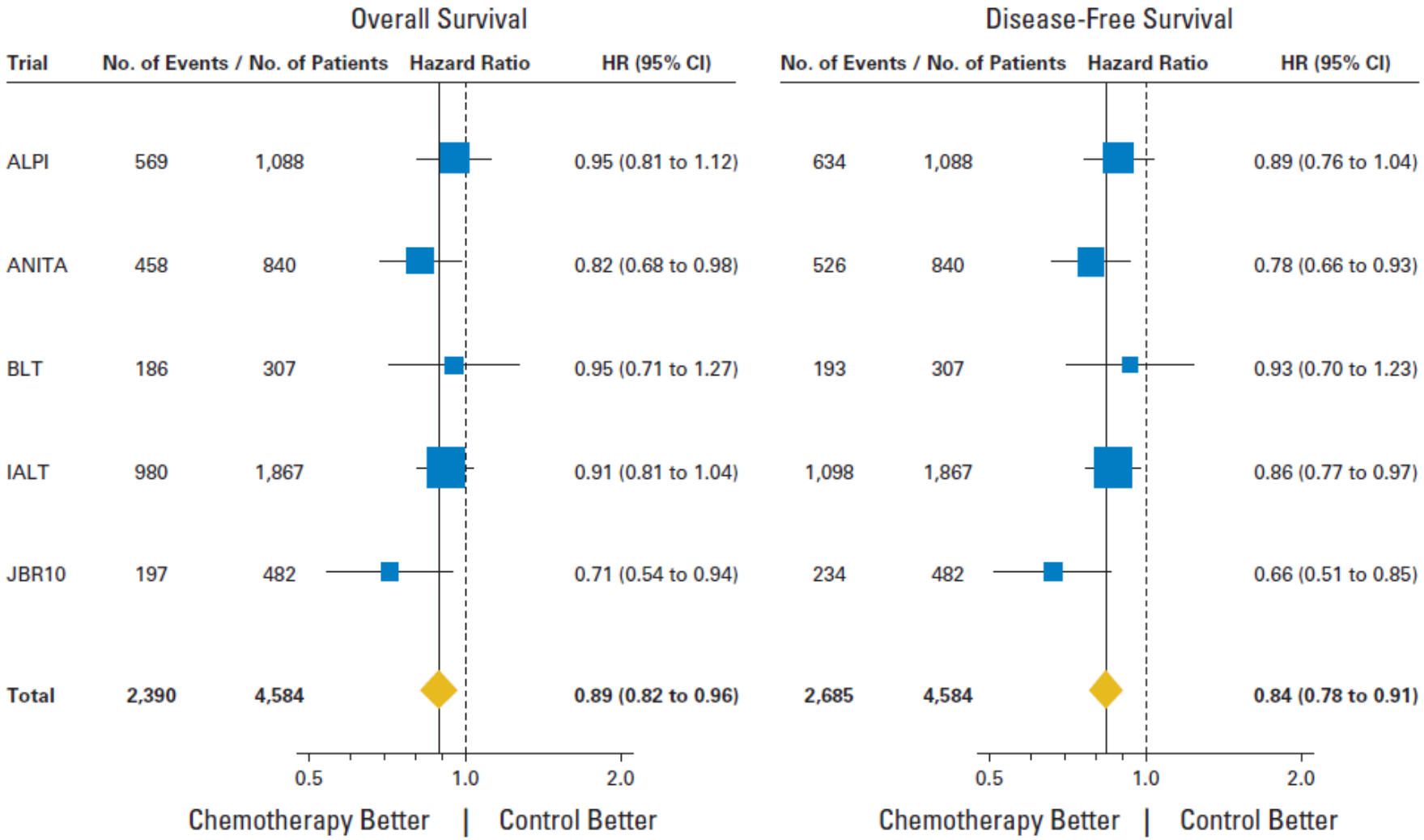
Pignon et al. *JCO*.2008; 26(21): 3552-3559

Baseline characteristics

	Chemotherapy (n=2,281)		Control (n=2,303)	
	No. of patients	%	No. of patients	%
Age, years				
Median	59		60	
5th-95th percentiles	45-72		43-71	
Sex				
Male	1,827	80	1,858	81
Female	452	20	443	19
Unknown	2	<1	2	<1
Pathologic TNM stage				
IA	185	8	162	7
IB	671	29	700	30
II	796	35	820	36
III	628	28	619	27
unknown	1	<1	2	<1

	Chemotherapy (n=2,281)		Control (n=2,303)	
	No. of patients	%	No. of patients	%
WHO performance				
0	874	39	895	39
1	756	33	777	34
2	98	4	85	3
unknown	553	24	546	24
Histologic type				
Sqcc	1,108	49	1,123	49
Adenocarcinoma	913	40	904	39
Others	260	11	276	12
Area of the world				
Europe	1,863	82	1,878	82
North America	253	11	253	11
Other	165	7	172	7

Results



Chemotherapy effect: Logrank statistic = 8.5, $P = .005$

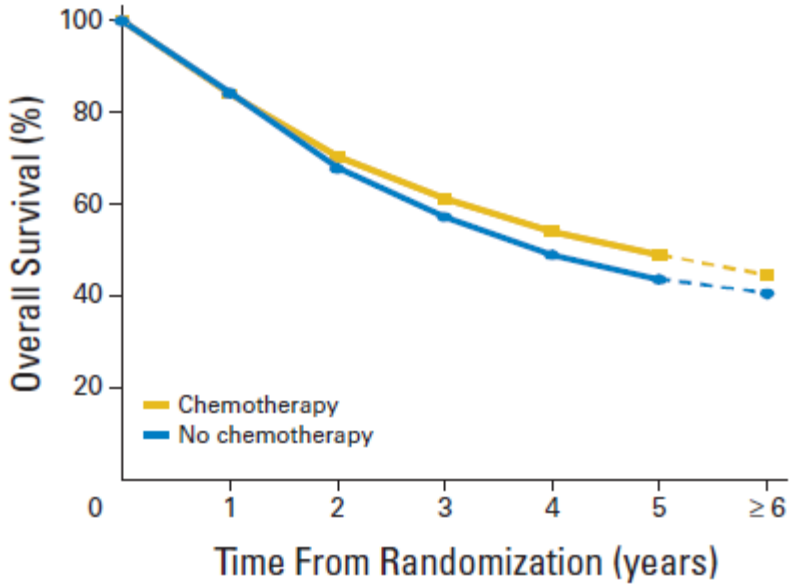
Test for heterogeneity: $\chi^2_4 = 4.25$, $P = .37$, $I^2 = 6\%$

Chemotherapy effect: Logrank statistic = 21.1, $P < .001$

Test for heterogeneity: $\chi^2_4 = 5.16$, $P = .27$, $I^2 = 23\%$

OS & DFS

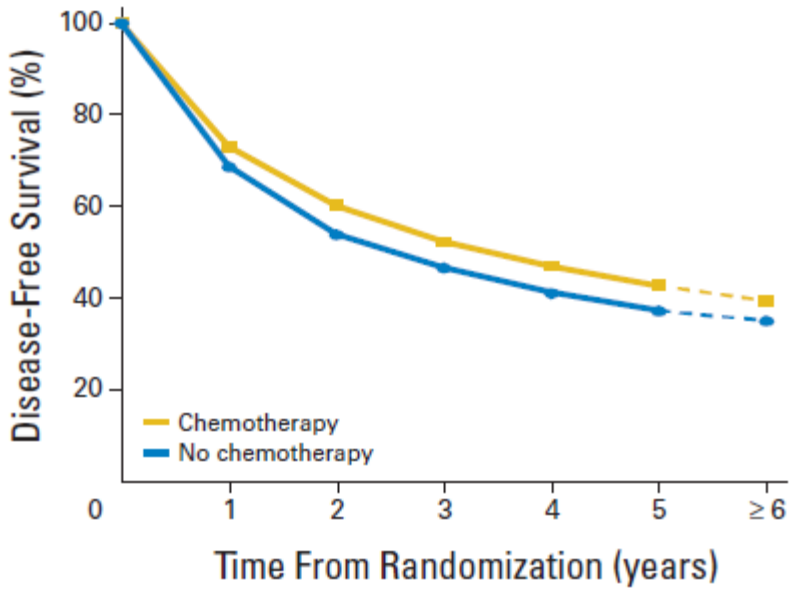
A



5.4% absolute benefits

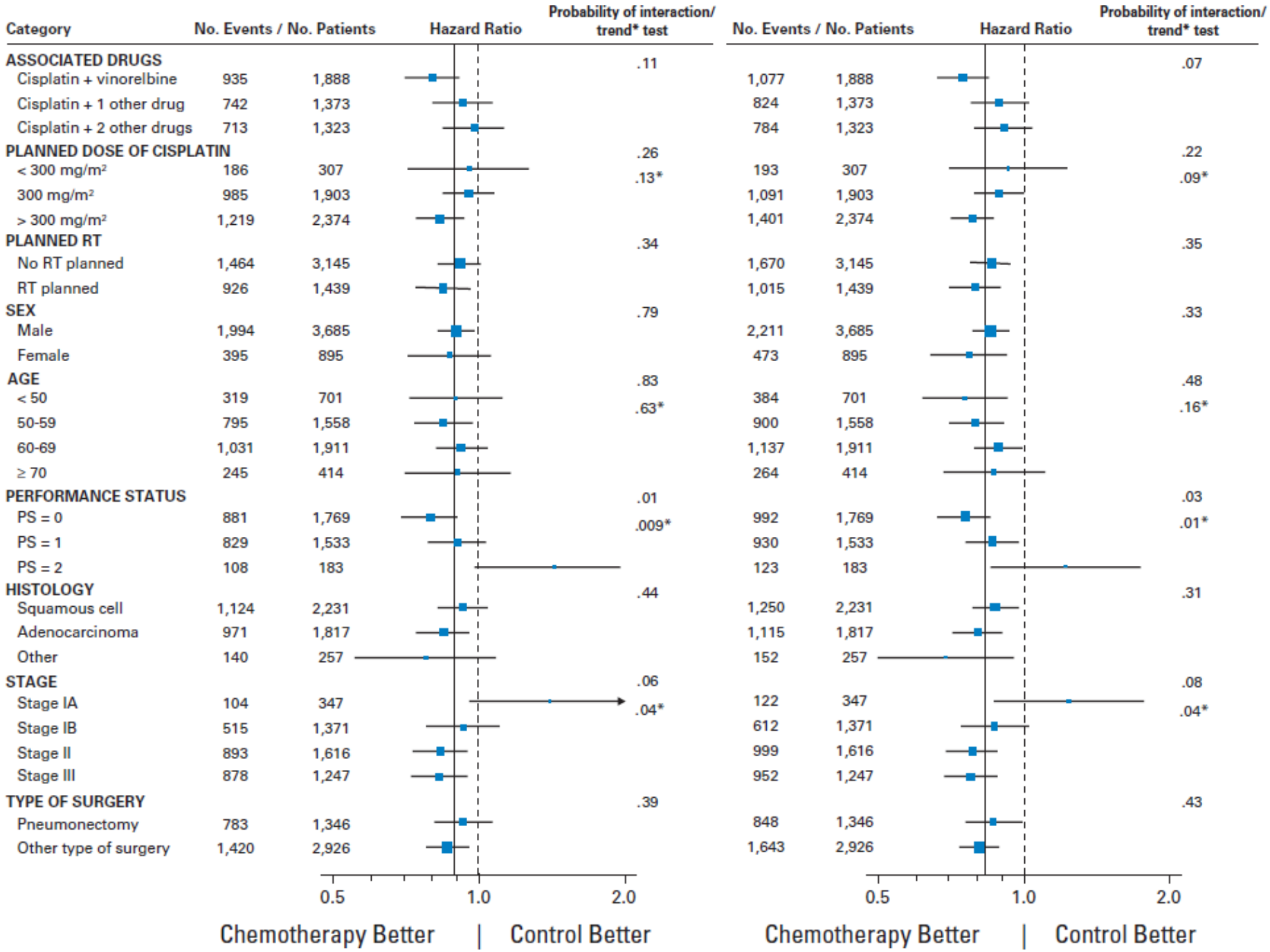
Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

B



5.8% absolute benefits

Events / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	1,222 / 4,341	163 / 1,396	35 / 610
Chemotherapy	1,047 / 4,627	159 / 1,606	59 / 708


Overall Survival
Disease-Free Survival
Category
No. Events / No. Patients
Hazard Ratio
Probability of interaction/ trend* test
ASSOCIATED DRUGS .11 .07
Cisplatin + vinorelbine 935 1,888 1,077 1,888
Cisplatin + 1 other drug 742 1,373 824 1,373
Cisplatin + 2 other drugs 713 1,323 784 1,323
PLANNED DOSE OF CISPLATIN .26 .22
< 300 mg/m² 186 307 193 307 .13* .09*
300 mg/m² 985 1,903 1,091 1,903
> 300 mg/m² 1,219 2,374 1,401 2,374
PLANNED RT .34 .35
No RT planned 1,464 3,145 1,670 3,145
RT planned 926 1,439 1,015 1,439
SEX .79 .33
Male 1,994 3,685 2,211 3,685
Female 395 895 473 895
AGE .83 .48
< 50 319 701 384 701 .63* .16*
50-59 795 1,558 900 1,558
60-69 1,031 1,911 1,137 1,911
≥ 70 245 414 264 414
PERFORMANCE STATUS .01 .03
PS = 0 881 1,769 992 1,769 .009* .01*
PS = 1 829 1,533 930 1,533
PS = 2 108 183 123 183
HISTOLOGY .44 .31
Squamous cell 1,124 2,231 1,250 2,231
Adenocarcinoma 971 1,817 1,115 1,817
Other 140 257 152 257
STAGE .06 .08
Stage IA 104 347 122 347 .04* .04*
Stage IB 515 1,371 612 1,371
Stage II 893 1,616 999 1,616
Stage III 878 1,247 952 1,247
TYPE OF SURGERY .39 .43
Pneumonectomy 783 1,346 848 1,346
Other type of surgery 1,420 2,926 1,643 2,926
0.5
1.0
2.0
Chemotherapy Better | Control Better
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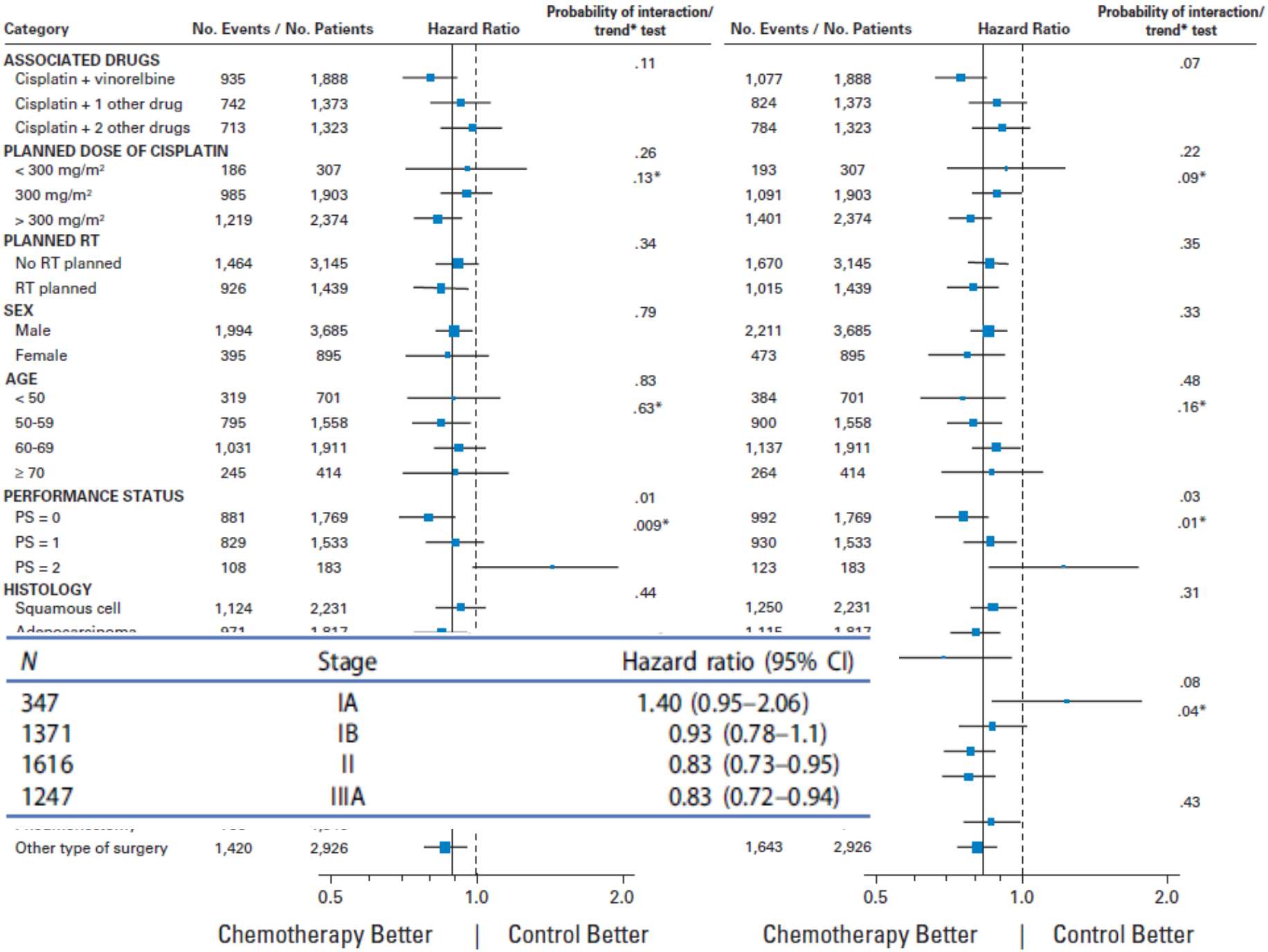
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.009* .01*
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PS = 2 108 183 123 183
HISTOLOGY .44 .31
Squamous cell 1,124 2,231 1,250 2,231
N Stage Hazard ratio (95% CI)
347 IA 1.40 (0.95–2.06)
1371 IB 0.93 (0.78–1.1)
1616 II 0.83 (0.73–0.95)
1247 IIIA 0.83 (0.72–0.94)
.08
.04*
.43
Other type of surgery 1,420 2,926 1,643 2,926
0.5
1.0
2.0
Chemotherapy Better | Control Better
Chemotherapy Better | Control Better

Compliance & Toxicity

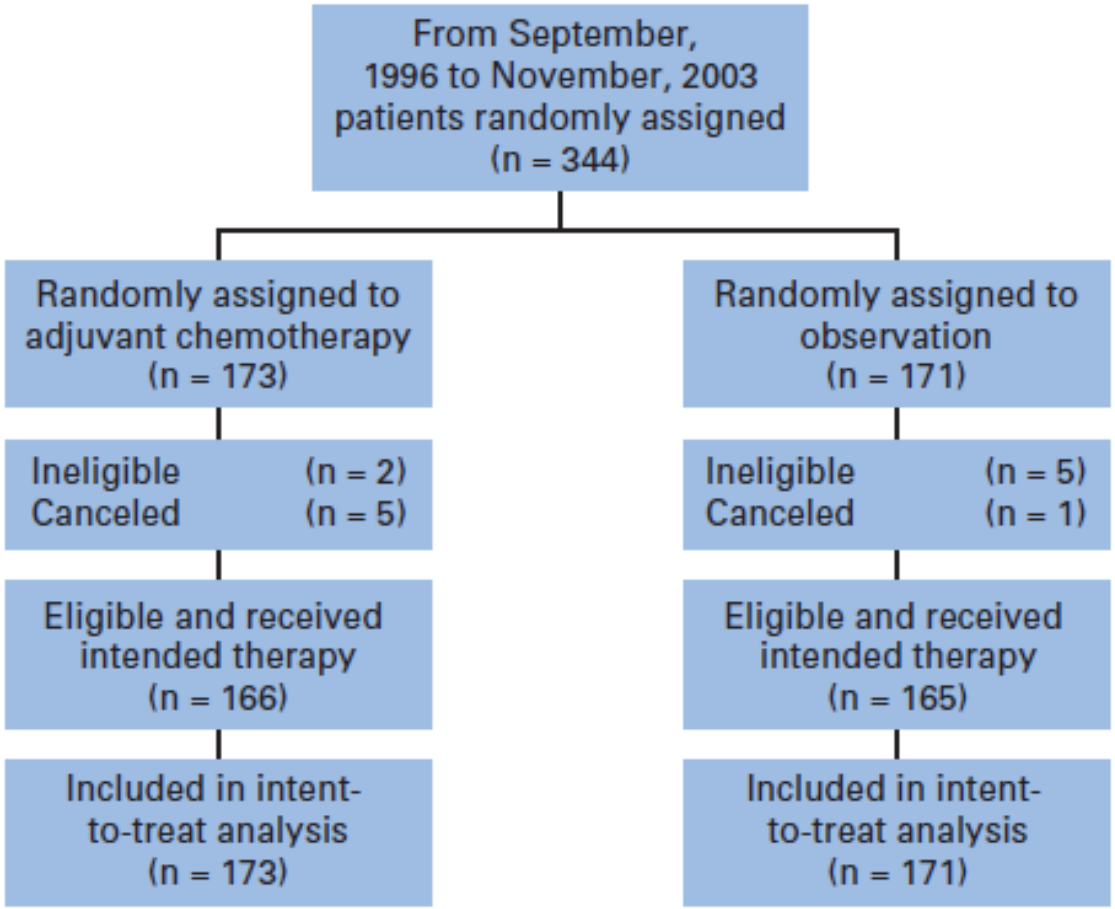
- ≤ 2 cycles : 33%
- ≥ 240mg/m2 of cisplatin : 59%
- Overall grade 3-4 toxicity : 66%
- Median delay time: 39days
- > 60days : 7%

Summary of LACE meta-analysis

- Cisplatin based adjuvant chemotherapy: 5.4% benefit
- Subgroup analysis
  - ✓stage IA: HR 1.4
  - ✓stage IB: HR 0.93 (0.78-1.1)
  - ✓PS 0 or 1
- Median delay time : 5weeks
- 1/3 to 1/2 of patients do not finish the planned chemotherapy

CALGB-9633

- Within 4 to 8 weeks
- Lobectomy or pneumonectomy
- ECOG PS 0 or 1
- T2N0 (1996-2003)
- Paclitaxel 200mg/m^2 & carboplatin AUC 6



Strauss et al. *JCO*.2008; 26(31): 5043-5051

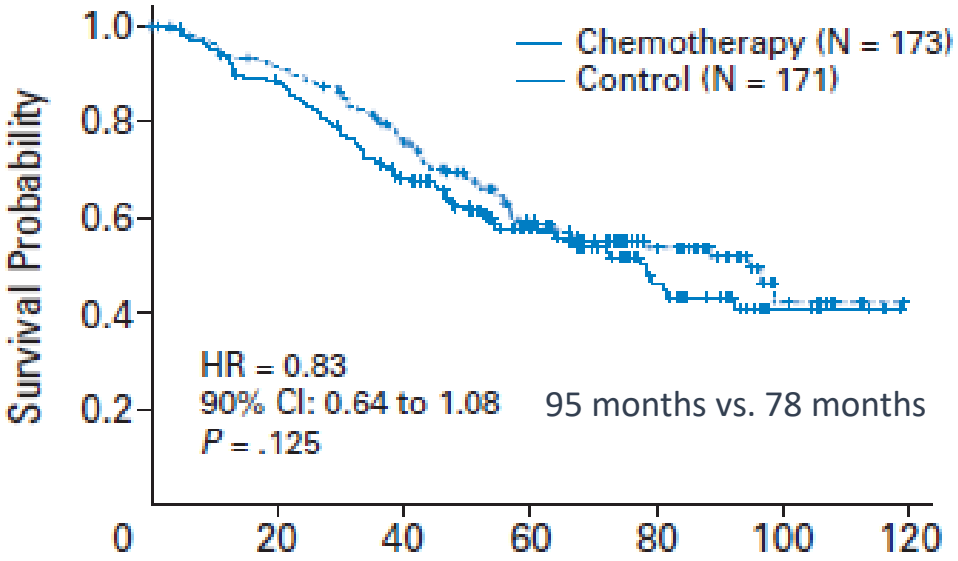
Baseline characteristics

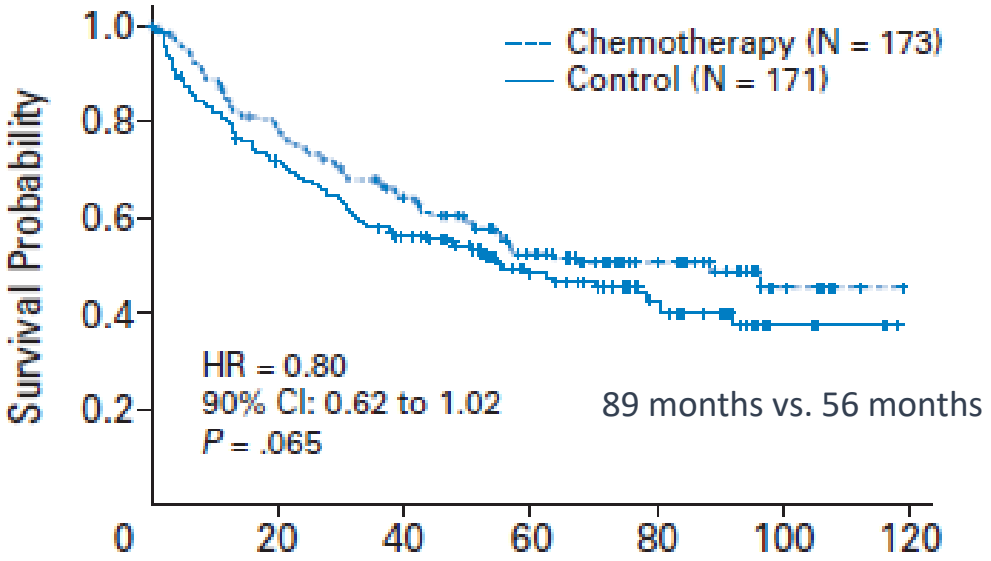
	Chemotherapy (n=173)		Control (n=171)	
	No. of patients	%	No. of patients	%
Age, years				
Median	61		62	
Range	34-78		40-81	
Sex				
Male	112	65	108	63
Female	61	35	63	37
Performance status				
0	94	56	98	58
1	74	44	70	41
2	1	1	1	1
Mediastinoscopy				
Yes	139	80	135	79
No	34	20	36	21

	Chemotherapy (n=173)		Control (n=171)	
	No. of patients	%	No. of patients	%
Extent of resection				
Lobectomy	146	88	151	89
Pneumonectomy	19	12	18	11
Tumor diameter, cm				
Mean	4.59		4.50	
Range	0-14		1-12	
Histology				
Sqcc	58	35	58	34
Adenoca	90	54	84	49
Others	20	12	28	16
Tumor differentiation				
Well or moderate	86	50	85	50
Poor	87	50	86	50

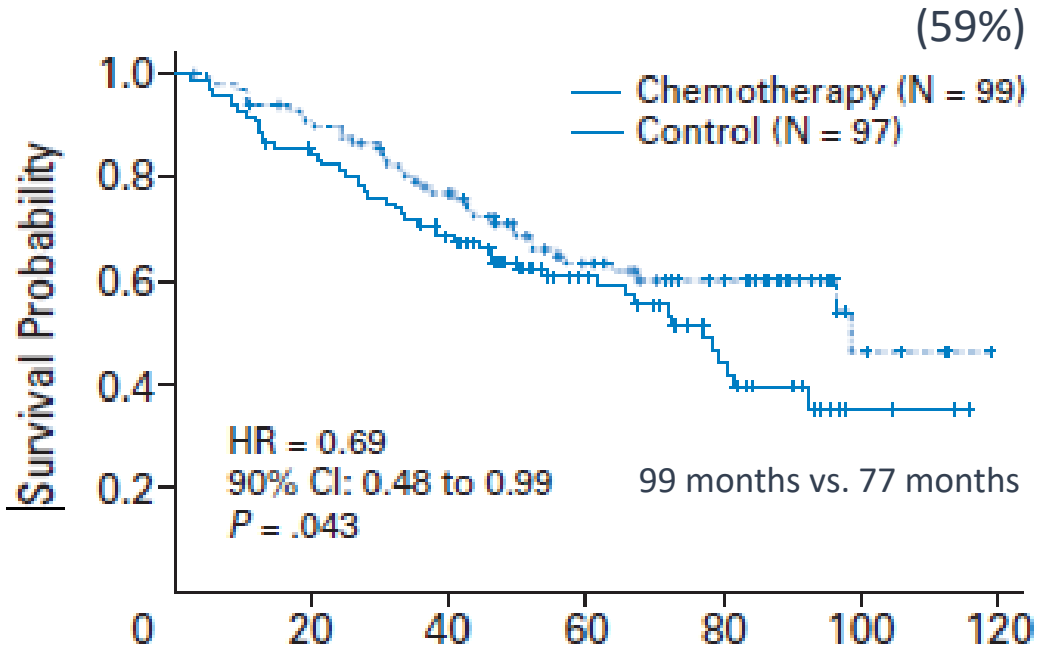
Results

Cause of Death	Treatment Group: Adjuvant Chemotherapy (n = 173) No.	%	Control (n = 171) No.	%	Analysis: P	HR	90% CI
Lung cancer	39	22.5	50	29.2	.059	0.72	0.50 to 1.02
Other	35	20.2	31	18.1	.47	1.02	.68 to 1.53
All	74	42.7	81	47.4	.125	0.83	0.64 to 1.08

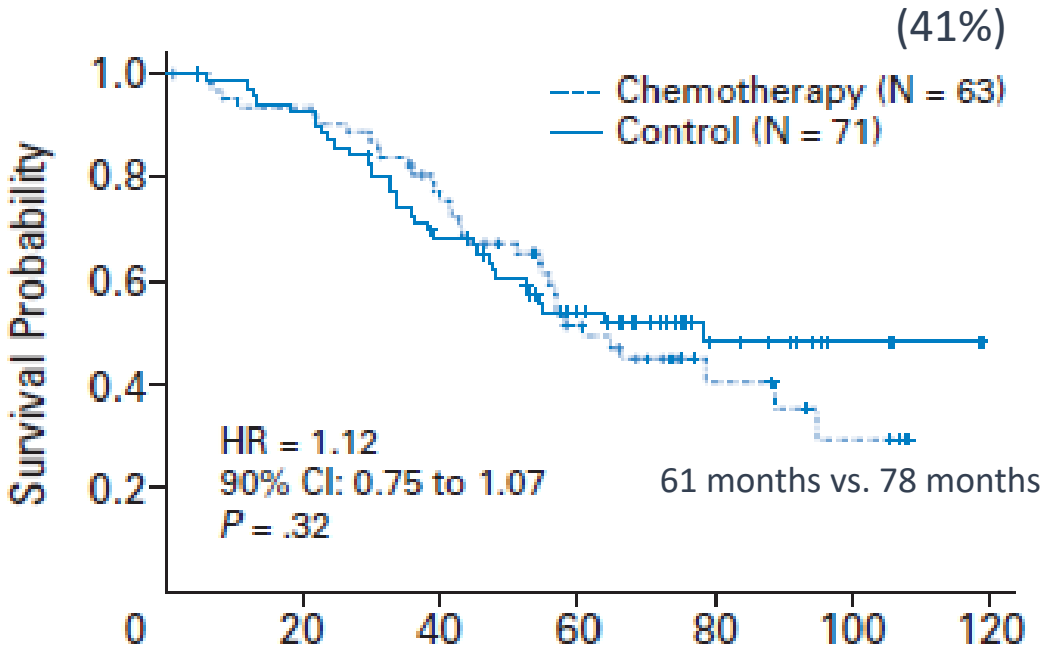




OS based on tumor size



Tumor size ≥4cm



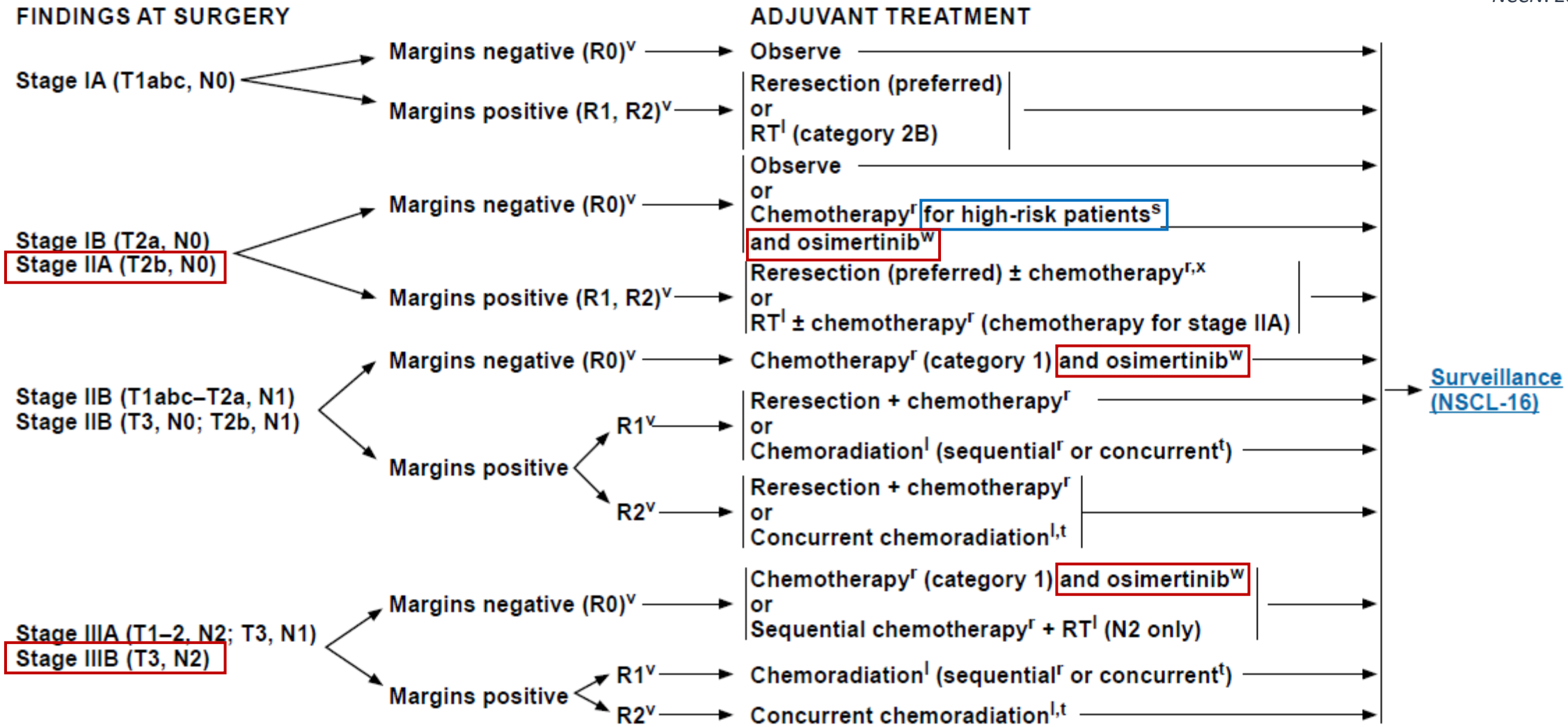
Tumor size <4cm

Compliance & Toxicity

- 4 cycles: 86%
- 4 cycles of full dose: 57%
- Gr 3-4 neutropenia: 35%
- Overall Gr 4: 28%

Summary of CALGB-9633

- Paclitaxel + Carboplatin adjuvant chemotherapy: no benefit of stag IB
- Subgroup analysis
  - ✓Tumor size ≥4cm : HR 0.69 (0.48-0.99)
- Within 4-8 weeks of resection
- 1/2 of patients do not finish the planned chemotherapy



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The difference between the 7th and 8th Edition

T	T Descriptor in 7th E	T Descriptor in 8th E	N0	N1	N2	N3
T1	T1a *≤2 cm*	T1a *≤1 cm*	IA	IIA → **IIB**	IIIA	IIIB
		T1b *>1-2 cm*				
	T1b *>2 but ≤3 cm*	T1c >2-3 cm				
T2	-	T2a *Central, Visceral Pleura*	IB	IIB	IIIA	
	T2a *>3 cm but ≤5 cm*	T2a *>3cm but ≤4 cm*	IB	IIA → **IIB**		
	T2b *>5 cm but ≤7 cm*	T2b *>4cm but ≤5 cm*	IB → **IIA**	IIB		
T3	T3 *>7 cm*	T3 *>5cm but ≤7 cm*	IIB	IIIA	IIIA → **IIIB**	IIIB → **IIIC**
	T3 *invasion*	T3 *invasion*				
	T3 *Satellite*	T3 *Satellite*				
T4	-	T4 *>7cm*	IIIA	IIIA	IIIB	
	T4 *Invasion*	T4 *Invasion*				
	T4 *Ipsilateral Nodule*	T4 *Ipsilateral Nodule*				

Pathologic features

- Worse prognosis (NCCN)
  - ✓Visceral pleural involvement
  - ✓Vascular invasion
  - ✓Poorly differentiated tumors (Neuroendocrine tumors)

- ASCO recommendations (IASLC/ATS/ERS)
  - ✓Tumor necrosis, perineural invasion, vascular/lymphatic invasion
  - ✓Adenocarcinoma subtype: Micropapillary or solid (high risk), acinar, papillary, invasive mucinous (intermediate risk), minimally invasive, lepidic (low risk)

Kudo et al. *Lung Cancer. 2012;78(2):153-160*

Schchert et al. *Ann Thorac Surg. 2011;91(4):1059-1065*

Kris et al. *JCO. 2017;35:2960-2974*

A new grading system for invasive adenocarcinoma

- A proposal from the IASLC pathology Committee

Predominant pattern-based Grading System		New proposed IASLC Grading System		
Grade (risk)	**Predominant patterns**	**Grade**	**Predominant patterns**	**High grade patterns**
High	Micropapillary, Solid	3 (PD)	Any pattern	≥ 20%
Intermediate	Acinar, Papillary	2 (MD)	Acinar, Papillary	< 20%
Low	Lepidic	1 (WD)	Lepidic	< 20%

High grade patterns: solid, micropapillary, comlex glandular

Moreira et al. *JTO*.15(10):1599-1610

JAMA Oncology | Original Investigation

Association of Survival With Adjuvant Chemotherapy Among Patients With Early-Stage Non–Small Cell Lung Cancer With vs Without High-Risk Clinicopathologic Features

Ranjan Pathak, MD, MHS; Sarah B. Goldberg, MD, MPH; Maureen Canavan, PhD, MPH; Jeph Herrin, PhD; Jessica R. Hoag, PhD, MPH; Michelle C. Salazar, MD; Marianna Papageorge, MD; Theresa Ermer, MD; Daniel J. Boffa, MD

- Retrospective cohort study (National Cancer Database; 2010-2015)
- R0 resection

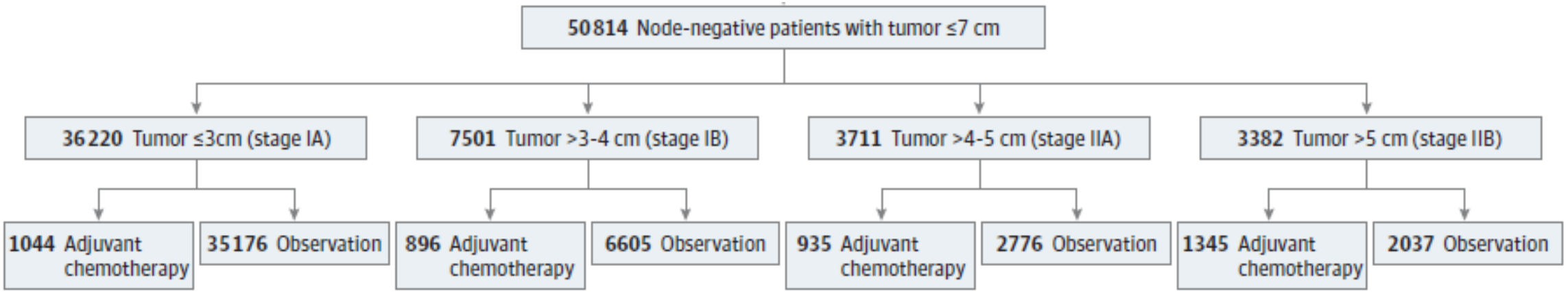


Figure 2. Association of Survival With Adjuvant Chemotherapy Based on the Presence of High-Risk Pathologic Features or Sublobar Resection in Patients Stratified by the 4 Tumor Size Categories or Stages

Tumor size (stage)	HR for death (95% CI)	*P* value
High-risk features		
≤3 cm (IA)		
Overall	1.10 (0.96-1.26)	.17
LVI	0.88 (0.66-1.16)	.35
VPI	0.90 (0.72-1.14)	.38
High grade	1.02 (0.84-1.25)	.81
≥2 Risk factors	0.92 (0.76-1.11)	.40
Sublobar surgery[a]	1.07 (0.85-1.33)	.53
>3-4 cm (IB)		
Overall	0.90 (0.78-1.03)	.21
LVI	0.82 (0.60-1.11)	.21
VPI	0.76 (0.51-1.12)	.22
High grade	1.04 (0.86-1.25)	.64
≥2 Risk factors	0.96 (0.73-1.26)	.23
Sublobar surgery[a]	0.72 (0.56-0.93)	.004
>4-5 cm (IIA)		
Overall	0.75 (0.64-0.86)	<.001
LVI	0.62 (0.42-0.91)	.005
VPI	0.50 (0.32-0.79)	<.001
High grade	0.58 (0.47-0.72)	<.001
≥1 Risk factor	0.67 (0.56-0.80)	.02
0 Risk factors[a]	1.06 (0.81-1.40)	.37
>5 cm (IIB)		
Overall	0.69 (0.62-0.78)	<.001
0 Risk factors	0.75 (0.61-0.91)	.004

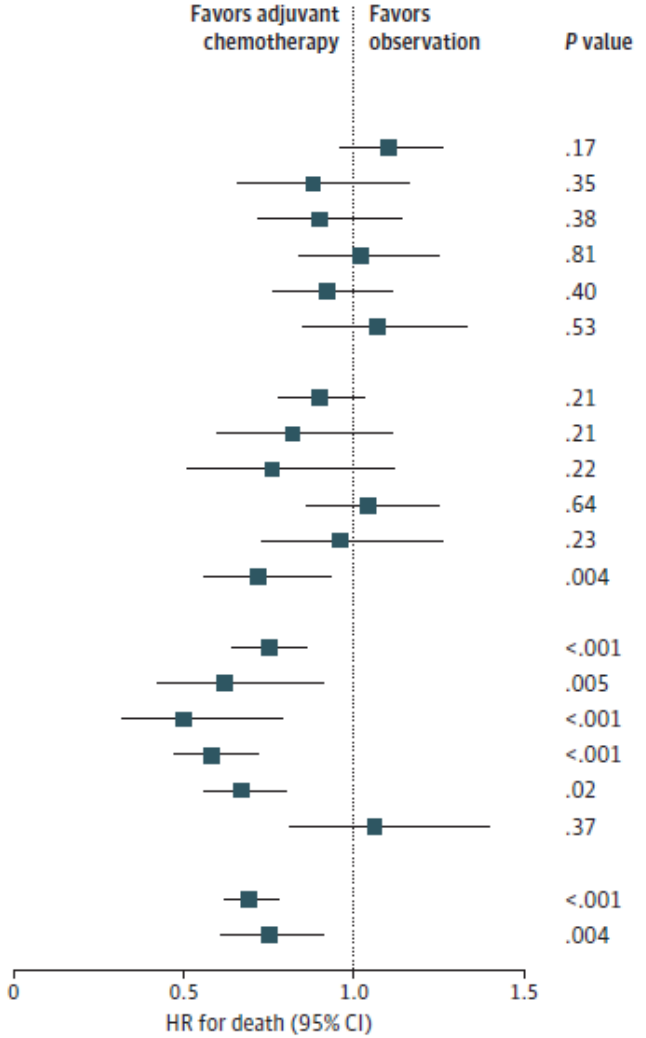
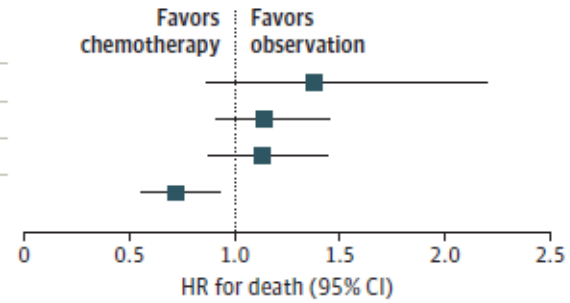


Figure 3. Association of Survival With Adjuvant Chemotherapy in Patients With Tumors 4 cm or Smaller Who Underwent Sublobar Resection

Tumor size, cm	HR for death (95% CI)	*P* value
0.1-1.0	1.38 (0.87-2.20)	.07
1.1-2.0	1.14 (0.91-1.45)	.59
2.1-3.0	1.13 (0.88-1.44)	.53
3.1-4.0	0.72 (0.56-0.93)	.004



Other considerations

- Timing of chemotherapy
  - ✓Typically offered within 8-10 weeks
  - ✓After 10 weeks: not inferior

- Toxicity
  - ✓LACE meta-analysis: Overall grade 3-4 toxicity → 66%
  - ✓CALGB 9633: grade 3 → 41%, grade 4 → 45%
  - ✓1/3 to 1/2 of patients do not finish the planned chemotherapy

Nagasaka et al. *Expert Review of Anticancer Therapy*. 2018;18(1):63-70
Chouaid C et al. *Lung Cancer*. 2018;124:310-316

Adjuvant Targeted therapy

Adjuvant clinical trials of EGFR-TKIs

Agent	Stage	Phase	Sample Size	Primary End Point	Secondary End Points	DFS in *EGFR*-Mutant	OS in *EGFR*-Mutant	Reference
Gefitinib for 2 years *v* VP for 4 cycles (ADJUVANT-CTONG1104)	II-IIIA	Phase III	222	DFS	OS, 3 year and 5 year DFS, 5 year OS, AE, QOL	3 year and 5 year DFS 39.6% and 22.6% with gefitinib and 32.5% and 23.2% with VP, median DFS 30.8 months with gefitinib and 19.8 months with VP	5 year OS 53.2% and 51.2% for gefitinib and VP, median OS 75.5 months for gefitinib *v* 62.8 months for VP	Zhong et al[15]
Erlotinib for 2 years (SELECT)	IA-IIIA	Phase II	100	2 year DFS	Safety, tolerability and OS	88% at 2 years (96% for stage I, 78% for stage II, 91% for stage III), median DFS NR	5 year OS 86%, median OS NR	Pennell et al[13]
Erlotinib *v* placebo for 2 years (RADIANT)	IB-IIIA	Phase III	2,500 screened, 973 randomly assigned, including 161 in *EGFR*-mutant subset	2 year DFS	OS, DFS and OS in *EGFR*-mutant subgroup, and safety	Median DFS 46.4 months for erlotinib *v* 28.5 months for placebo; 2 year DFS 75% for erlotinib and 54% for placebo	Median OS NR for both groups	Kelly et al[12]
Erlotinib *v* VP for 4 cycles (EVAN)	IIIA	Phase II	102	2 year DFS	Median DFS, OS, safety	2 year DFS 81.4% with erlotinib versus 44.6% with VP, Median DFS 42.4 months with erlotinib *v* 21 months with VP	Median OS NR for both groups	Yue et al[16]
Osimertinib *v* placebo for 3 years (ADAURA)	IB-IIIA	Phase III	682	DFS in stage II and IIIA	DFS in stage IB-IIIA, OS, QOL and safety	2 year DFS for stage II/IIIA 90% with osimertinib *v* 44% with placebo, 2 year DFS for stage I-IIIA 89% for osimertinib versus 52% for placebo	OS data immature, 2 year OS in stage II/IIIA 100% for osimertinib and 93% for placebo	Wu et al[14]

Waqar, Govindan. *JCO*. 2021;39(7):697--701

Adjuvant clinical trials of EGFR-TKIs

Agent	Stage	Phase	Sample Size	Primary End Point	Secondary End Points	DFS in *EGFR*-Mutant	OS in *EGFR*-Mutant	Reference
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Erlotinib for 2 years (SELECT)	IA-IIIA	Phase II	100	2 year DFS	Safety, tolerability and OS	88% at 2 years (96% for stage I, 78% for stage II, 91% for stage III), median DFS NR	5 year OS 86%, median OS NR	Pennell et al[13]
Erlotinib *v* placebo for 2 years (RADIANT)	IB-IIIA	Phase III	EGFR-amplification EGFR IHC +		OS, DFS and OS in *EGFR*-mutant subgroup, and safety	Median DFS 46.4 months for erlotinib *v* 28.5 months for placebo; 2 year DFS 75% for erlotinib and 54% for placebo	Median OS NR for both groups	Kelly et al[12]
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Osimertinib *v* placebo for 3 years (ADAURA)	IB-IIIA	Phase III	682	DFS in stage II and IIIA	DFS in stage IB-IIIA, OS, QOL and safety	2 year DFS for stage II/IIIA 90% with osimertinib *v* 44% with placebo, 2 year DFS for stage I-IIIA 89% for osimertinib versus 52% for placebo	OS data immature, 2 year OS in stage II/IIIA 100% for osimertinib and 93% for placebo	Wu et al[14]

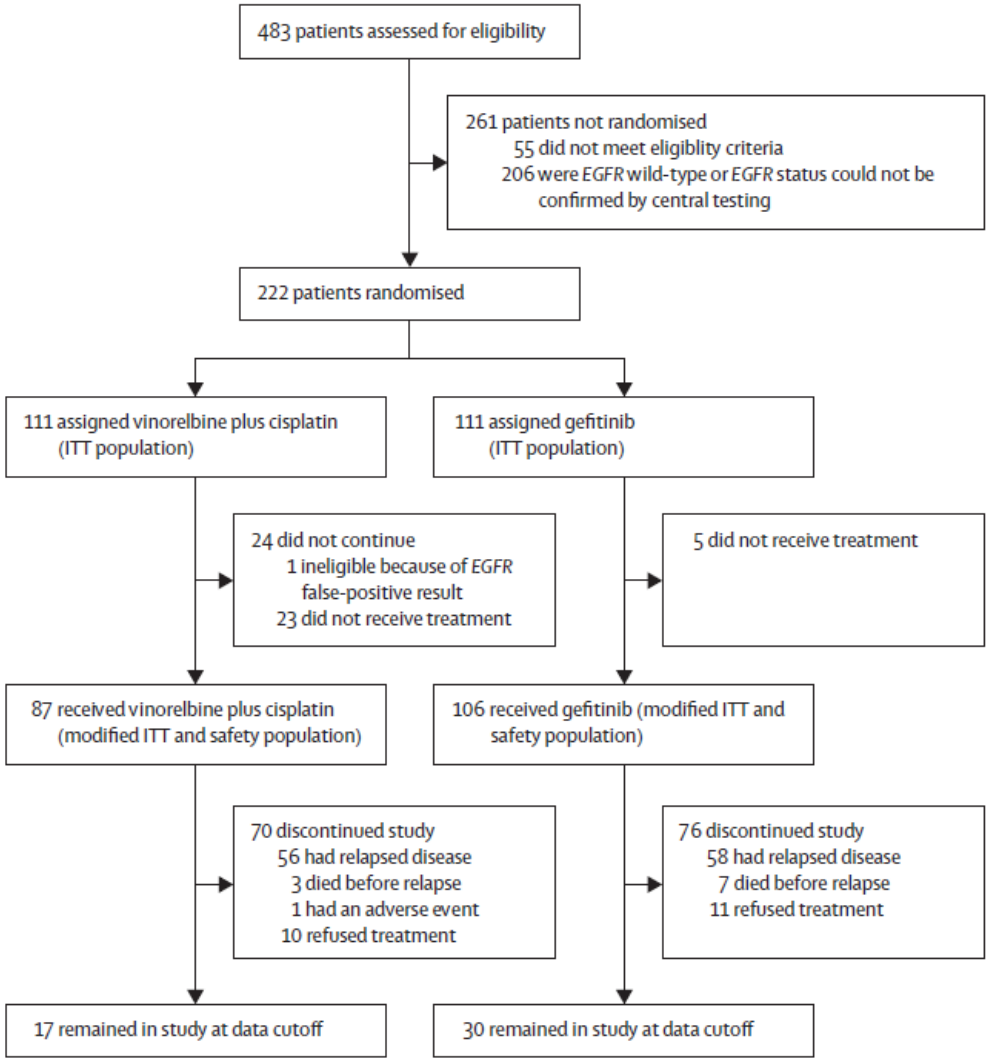
Waqar, Govindan. *JCO*. 2021;39(7):697--701

Adjuvant CTONG-1104

- Stage II-IIIA (N1-N2)
- Lobectomy or Pneumonectomy: R0 resection
- Age: 18-75
- ECOG PS 0 or 1
- EGFR exon 19del or exon 21 Leu858Arg
- 21-42 days after surgery
- Gefitinib (2 years) vs Vinorelvine + Cisplatin (4 cycle)
- Primary Endpoint: disease free survival

Adjuvant CTONG-1104

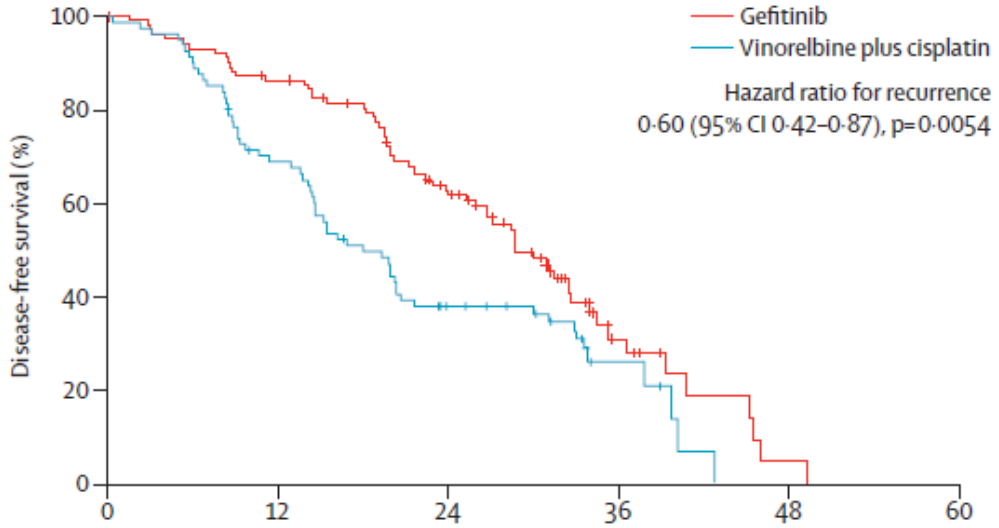
Zhong et al. *Lancet Oncol*. 2018;19:139-48
Zhong et al. *JCO*. 2021;39(7):713-722



	ITT Population		PP Population	
Parameter	**Gefitinib (n = 111)**	**VP (n = 111)**	**Gefitinib (n = 106)**	**VP (n = 87)**
Age, y, (median: min-max)	58 (32-74)	60 (26-76)	58.6 (32-74)	59.0 (26-73)
Female sex, n (%)[a]	65 (58.6)	65 (58.6)	63 (59.4)	50 (57.5)
Never smoked, n (%)	82 (73.9)	85 (76.6)	79 (74.5)	67 (77.0)
Baseline ECOG PS, n (%)				
0	35 (31.5)	22 (19.8)	35 (33.0)	16 (18.4)
1	72 (64.9)	85 (76.6)	69 (65.1)	71 (81.6)
Not available	4 (3.6)	4 (3.6)	2 (1.9)	0 (0)
Pathology stage, n (%)				
IIA (N1)	33 (29.7)	33 (29.7)	31 (29.2)	26 (29.9)
IIB	4 (3.6)	4 (3.6)	4 (3.8)	2 (2.3)
IIIA	72 (64.9)	71 (64.0)	71 (67.0)	58 (66.7)
Not available	2 (1.8)	3 (2.7)	0 (0.0)	1 (1.1)
Pathology, n (%)				
Adenocarcinoma	102 (91.9)	105 (94.6)	99 (93.4)	84 (96.6)
Squamous carcinoma	5 (4.5)	1 (0.9)	5 (4.7)	1 (1.1)
Adenosquamous carcinoma	2 (1.8)	3 (2.7)	2 (1.9)	2 (2.3)
Not available	2 (1.8)	2 (1.8)	0 (0)	0 (0)
EGFR mutation status, n (%)				
Exon 19 deletions	58 (52.3)	57 (51.4)	57 (53.8)	48 (55.2)
Exon 21 L858R	53 (47.7)	53 (47.7)	49 (46.2)	39 (44.8)
EGFR false-positive	0 (0)	1 (0.9)	0 (0)	0 (0)
Lymph node status, n (%)				
N1	40 (36.0)	37 (33.3)	36 (34.0)	28 (32.2)
N2	71 (64.0)	72 (64.9)	70 (66.0)	58 (66.7)
Not available	0 (0)	2 (1.8)	0 (0)	1 (1.1)
Type of resection, n (%)				
Lobectomy	106 (95.5)	105 (94.6)	103 (97.2)	83 (95.4)
Pneumonectomy	3 (2.7)	3 (2.7)	3 (2.8)	3 (3.4)
Other	2 (1.8)	3 (2.7)	0 (0)	1 (1.1)

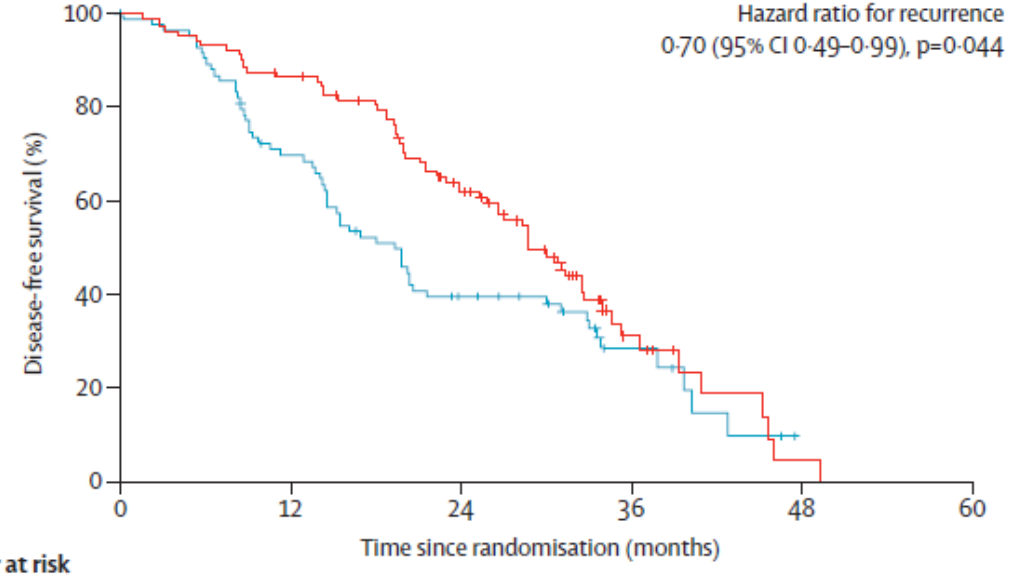
Disease free survival

Median follow up: 36.5 months



Number at risk (number censored)						
Gefitinib	111 (0)	88 (9)	57 (16)	10 (43)	1 (46)	0 (46)
Vinorelbine plus cisplatin	111 (0)	54 (32)	26 (36)	5 (51)	0 (52)	0 (52)

ITT

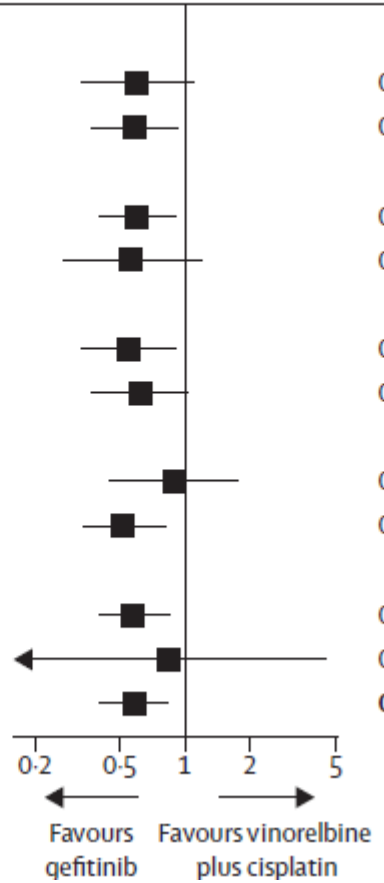


Number at risk (number censored)						
Gefitinib	106 (0)	88 (4)	57 (11)	10 (38)	1 (41)	0 (41)
Vinorelbine plus cisplatin	87 (0)	56 (6)	28 (10)	7 (25)	0 (28)	0 (28)

Modified ITT

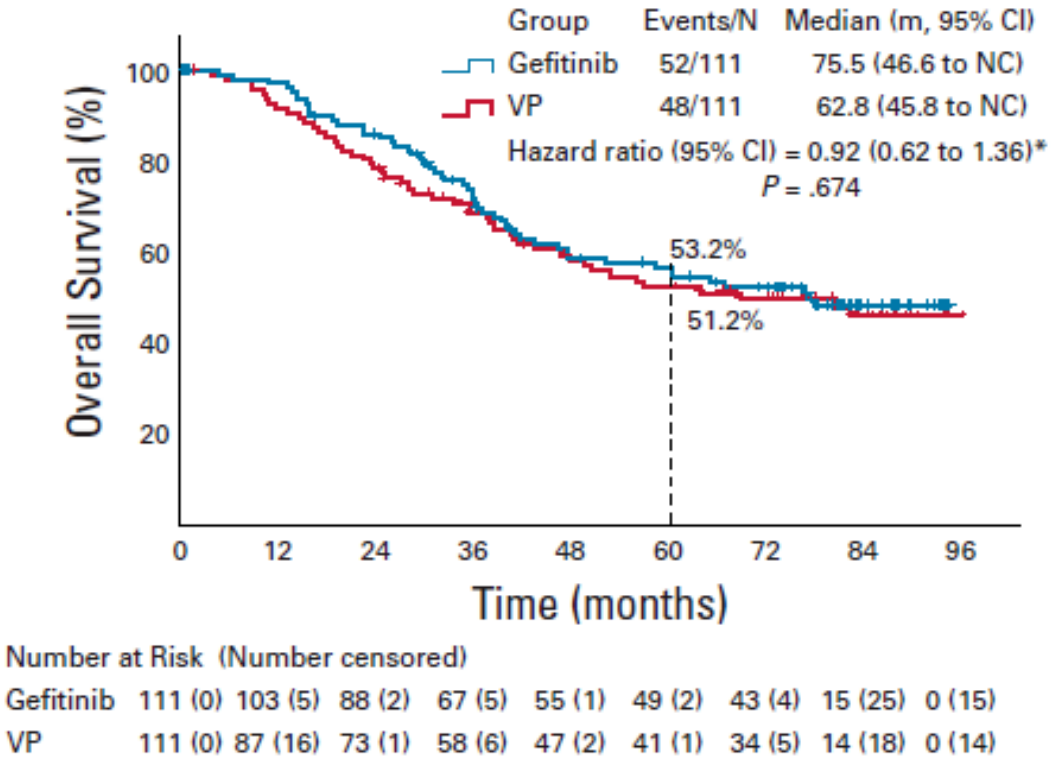
Disease free survival

	Total number of patients/events (n/N)	Gefitinib (n/N)	Vinorelbine plus cisplatin (n/N)	HR (95% CI)	p value	$p_{interaction}$
Sex						0·754
Male	89/46	44/23	45/23	0·60 (0·33–1·09)	0·094	
Female	130/78	65/42	65/36	0·58 (0·37–0·92)	0·020	
Smoker						0·896
No	167/95	82/49	85/46	0·61 (0·40–0·92)	0·018	
Yes	52/29	27/16	25/13	0·56 (0·27–1·19)	0·132	
EGFR mutation status						0·701
EGFR exon 19 deletion	115/63	58/33	57/30	0·55 (0·33–0·92)	0·024	
EGFR exon 21 Leu858Arg	106/61	53/32	53/29	0·62 (0·37–1·04)	0·071	
Lymph nodes						0·232
N1	77/36	40/18	37/18	0·89 (0·45–1·76)	0·743	
N2	143/87	71/47	72/40	0·52 (0·34–0·80)	0·0032	
Pathology						0·506
Adenocarcinoma	207/115	102/58	105/57	0·58 (0·40–0·84)	0·0039	
Non-adenocarcinoma	11/9	7/7	4/2	0·85 (0·16–4·46)	0·852	
Overall	**222/124**	**111/65**	**111/59**	**0·58 (0·40–0·83)**	**0·0033**	



Overall survival

Median follow up: 80.0 months



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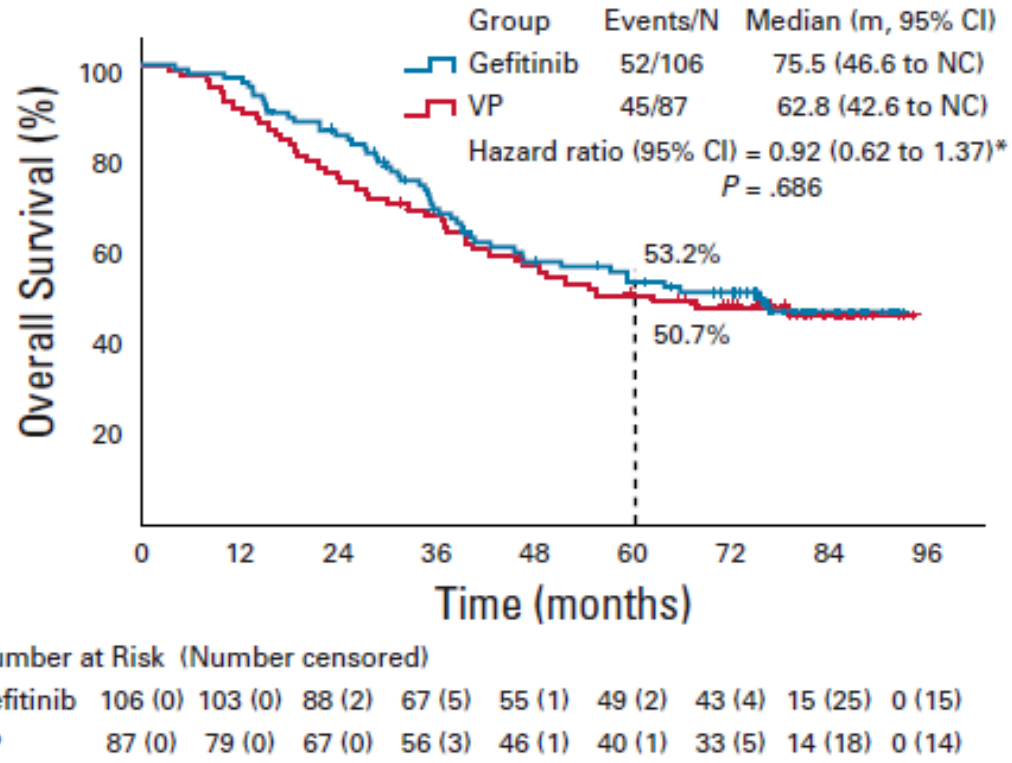
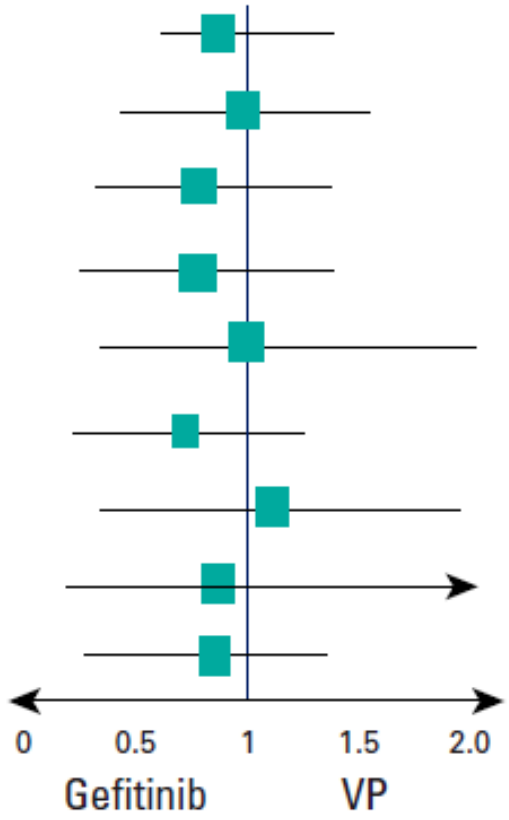


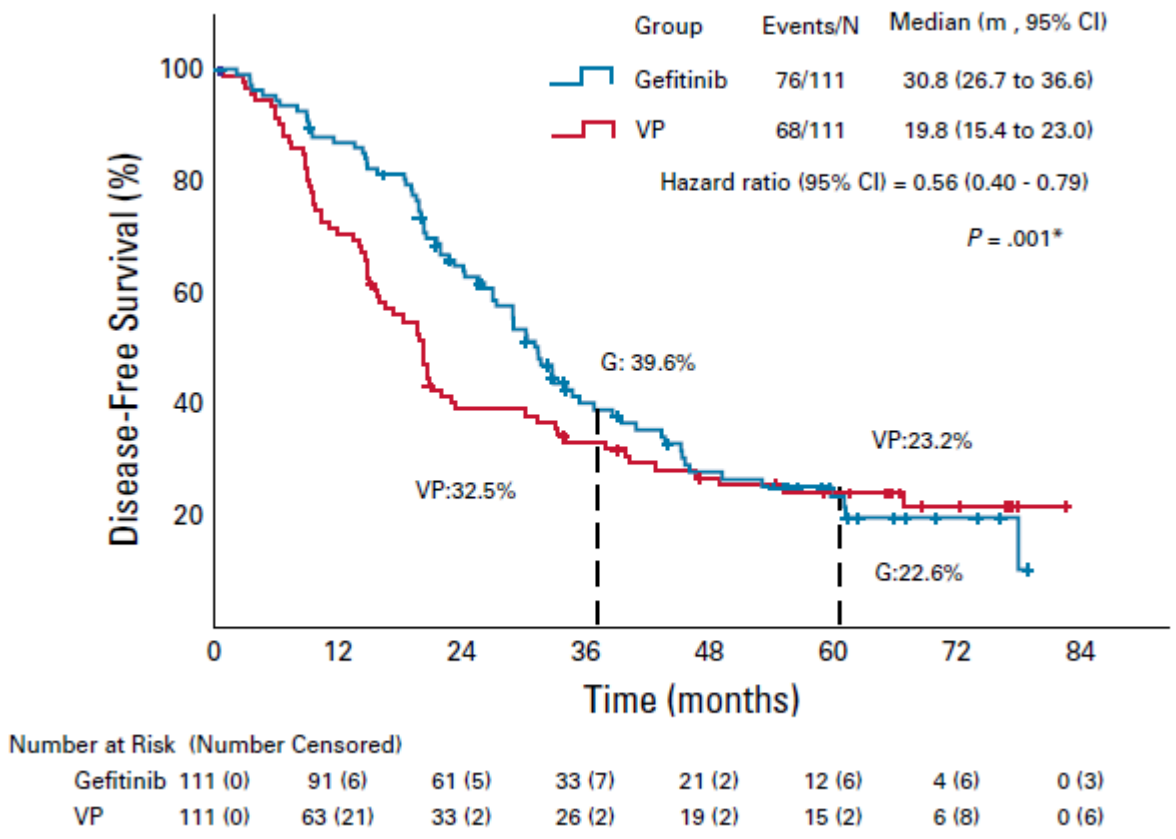
PP

Overall survival

Variables	Subgroup	N (%)	OS	HR (95% CI)†	*P* value	*P* for Interaction
Overall HR model		222 100.0)		0.92 (0.62 to 1.36)	.674	
Age (Years)	≤ 60	126 (56.8)		0.99 (0.58 to 1.70)	.977	.683
	> 60	96 (32.3)		0.85 (0.48 to 1.50)	.572	
Gender	male	89 (40.1)		0.81 (0.44 to 1.49)	.501	.604
	female	130 (58.6)		1.00 (0.60 to 1.98)	.977	
EGFR Mutation	Exon 19 del	115 (51.8)		0.76 (0.44 to 1.32)	.328	.323
	Exon 21 L858R	106 (47.7)		1.13 (0.64 to 1.98)	.683	
Lymph Nodes	N1	77 (34.7)		0.97 (0.45 to 2.11)	.945	.864
	N2	143 (64.4)		0.92 (0.58 to 1.45)	.705	



Disease free survival



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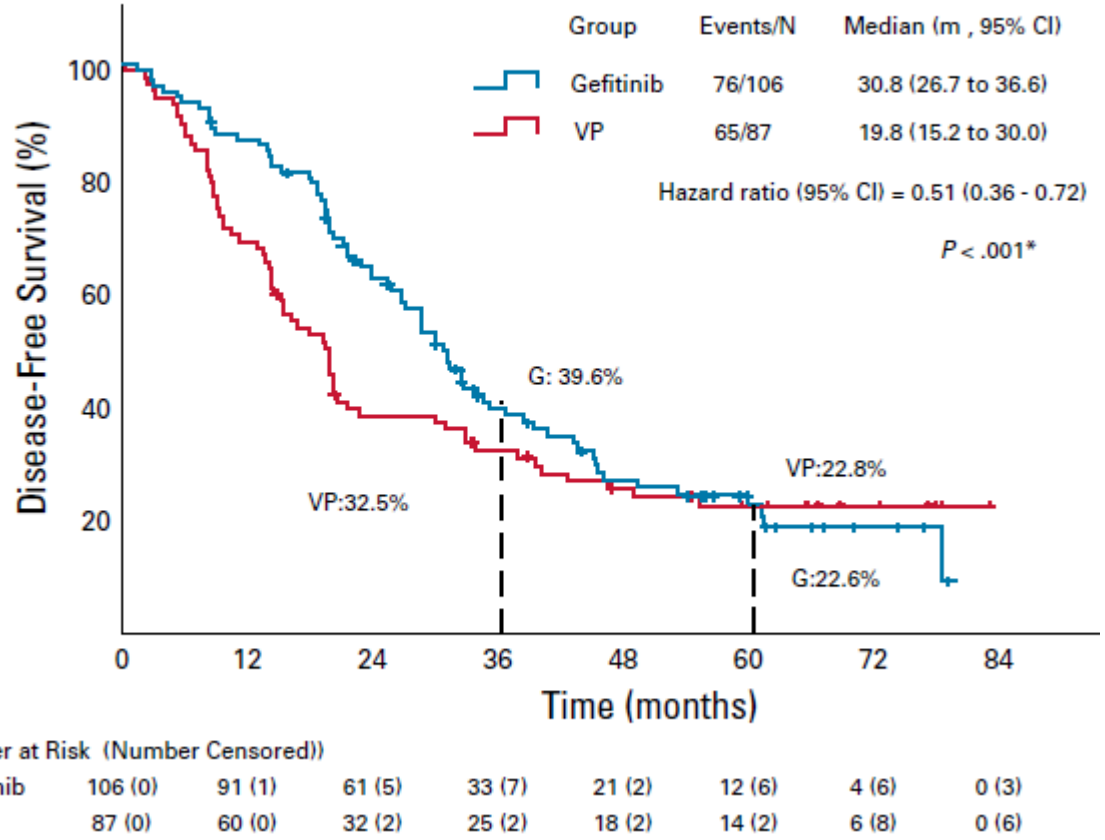
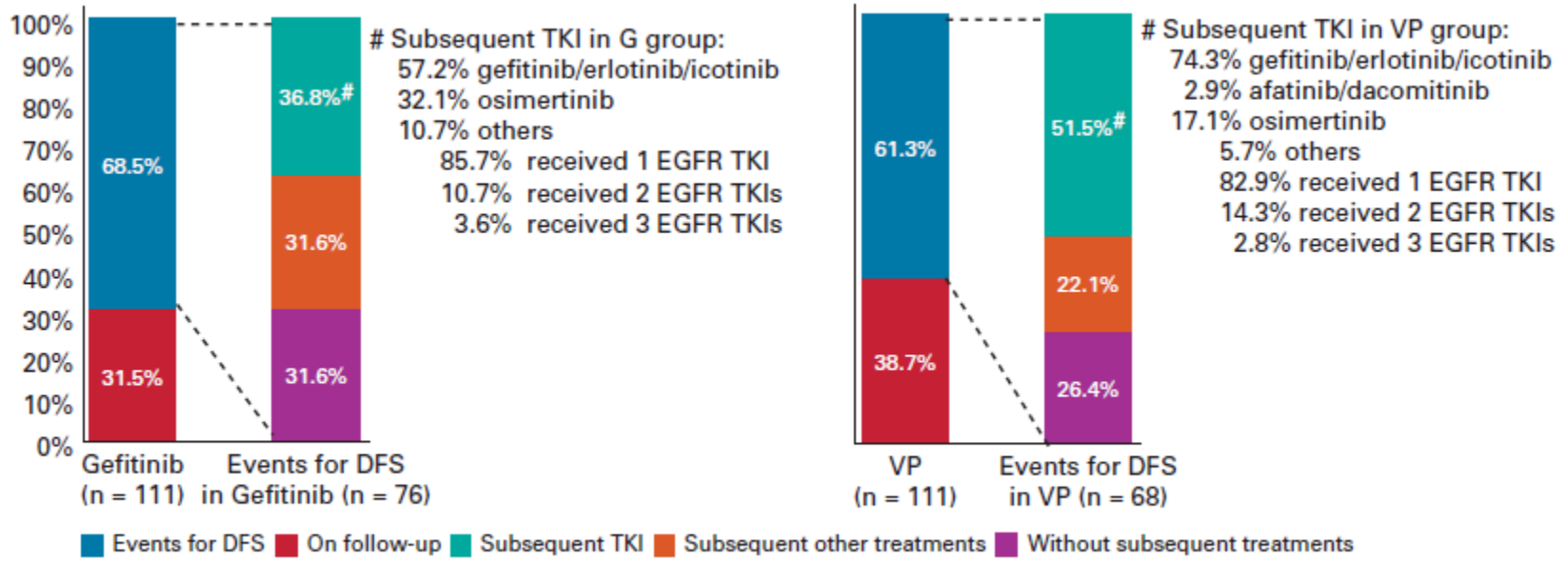
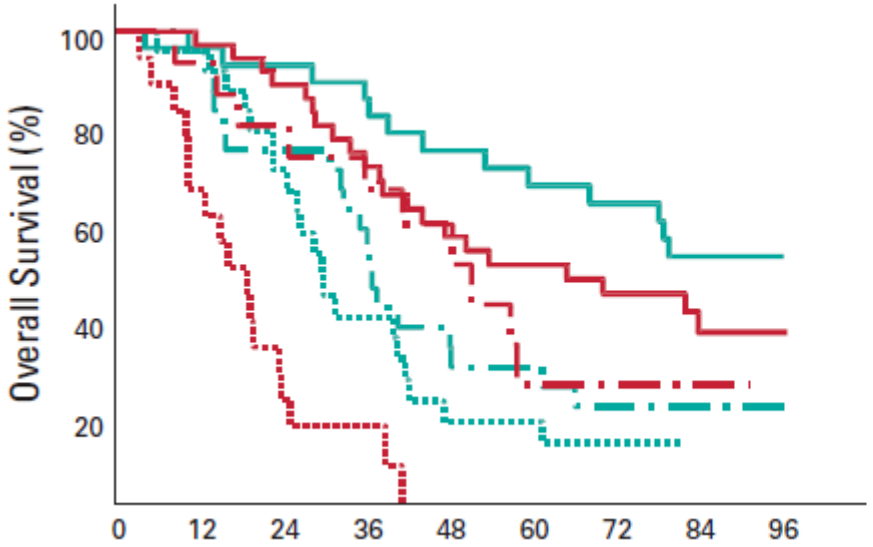


PP

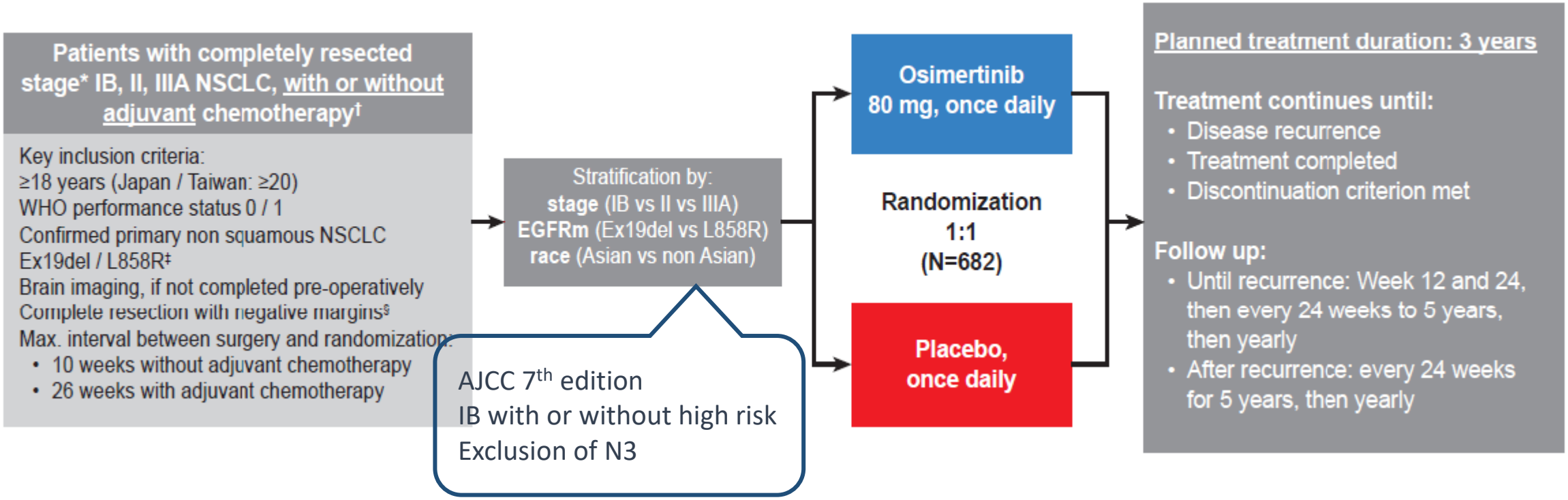
Subsequent treatment & OS





Group	Events / N	Median (m,95% CI)
Subsequent TKI in G (A)	13 / 28	NR (65.9 to NC)
Other subsequent treatments in G (B)	19 / 24	35.3 (31.7 to 59.4)
Without subsequent treatment in G (C)	20 / 24	28.7 (23.8 to 40.8)
Subsequent TKI in VP (D)	21 / 35	62.8 (40.5 to NC)
Other subsequent treatments in VP (E)	10 / 15	49.5 (34.7 to NC)
Without subsequent treatments in VP (F)	17 / 18	15.6 (10.0 to 24.2)

Osimertinib in Resected EGFR-Mutated NSCLC



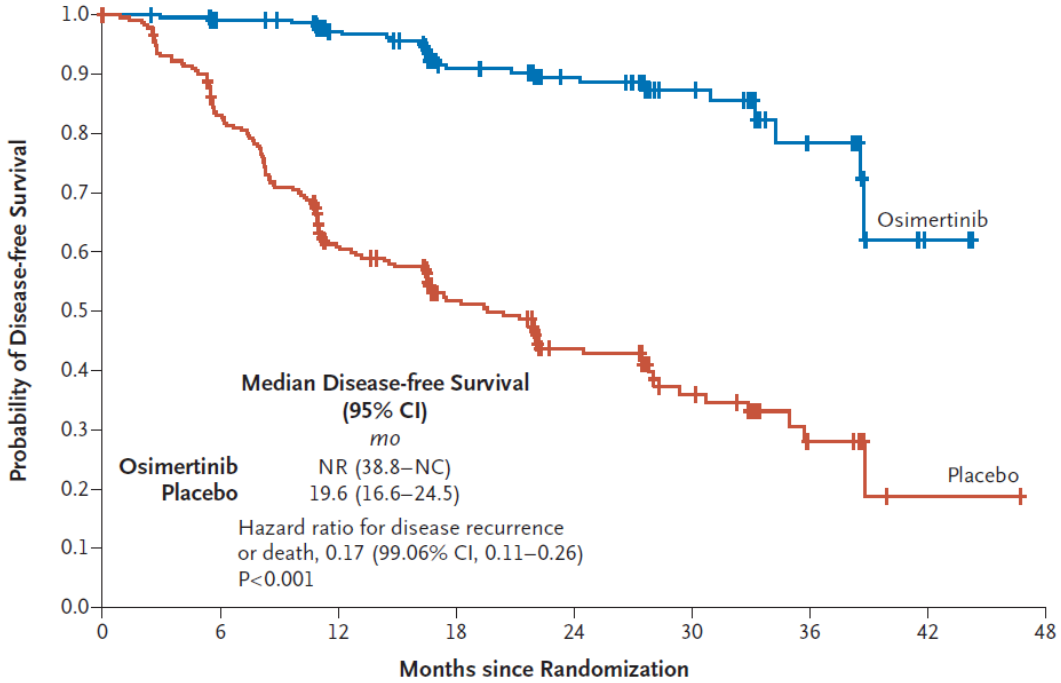
Comparison between CTONG 1104 and ADAURA

	CTONG 1104	ADAURA
Primary endpoint	DFS	DFS
mDFS	30.8 months	
Stage IB	Not included	Included
N2	65%	35%
Prior Adj CTx	Not permitted	Permitted (60%)
Control	Vino, Cis	Placebo
Duration of EGFR TKI	2yrs	3yrs

Baseline characteristics

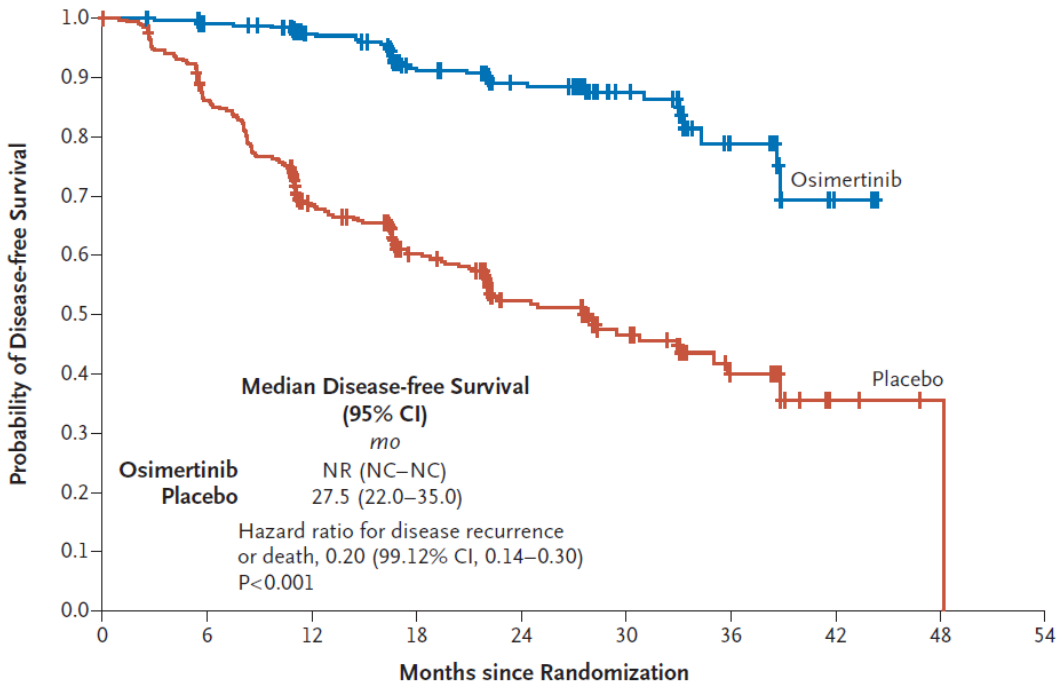
Characteristic	Osimertinib n=339	Placebo n=343
Sex: male / female, %	32 / 68	28 / 72
Age, median (range), years	64 (30–86)	62 (31–82)
Race*: Asian / non-Asian, %	64 / 36	64 / 36
Smoking status: never / current or former, %	68 / 32	75 / 25
WHO performance status: 0 / 1, %	64 / 36	64 / 36
Histology: adenocarcinoma / other, %	96 / 4	97 / 3
EGFR mutation at randomisation: Ex19del / L858R, %	55 / 45	55 / 45
Adjuvant chemotherapy: yes / no, %	60 / 40	60 / 40

Results - DFS



No. at Risk									
Osimertinib	233	219	189	137	97	52	18	2	0
Placebo	237	190	127	82	51	27	9	1	0

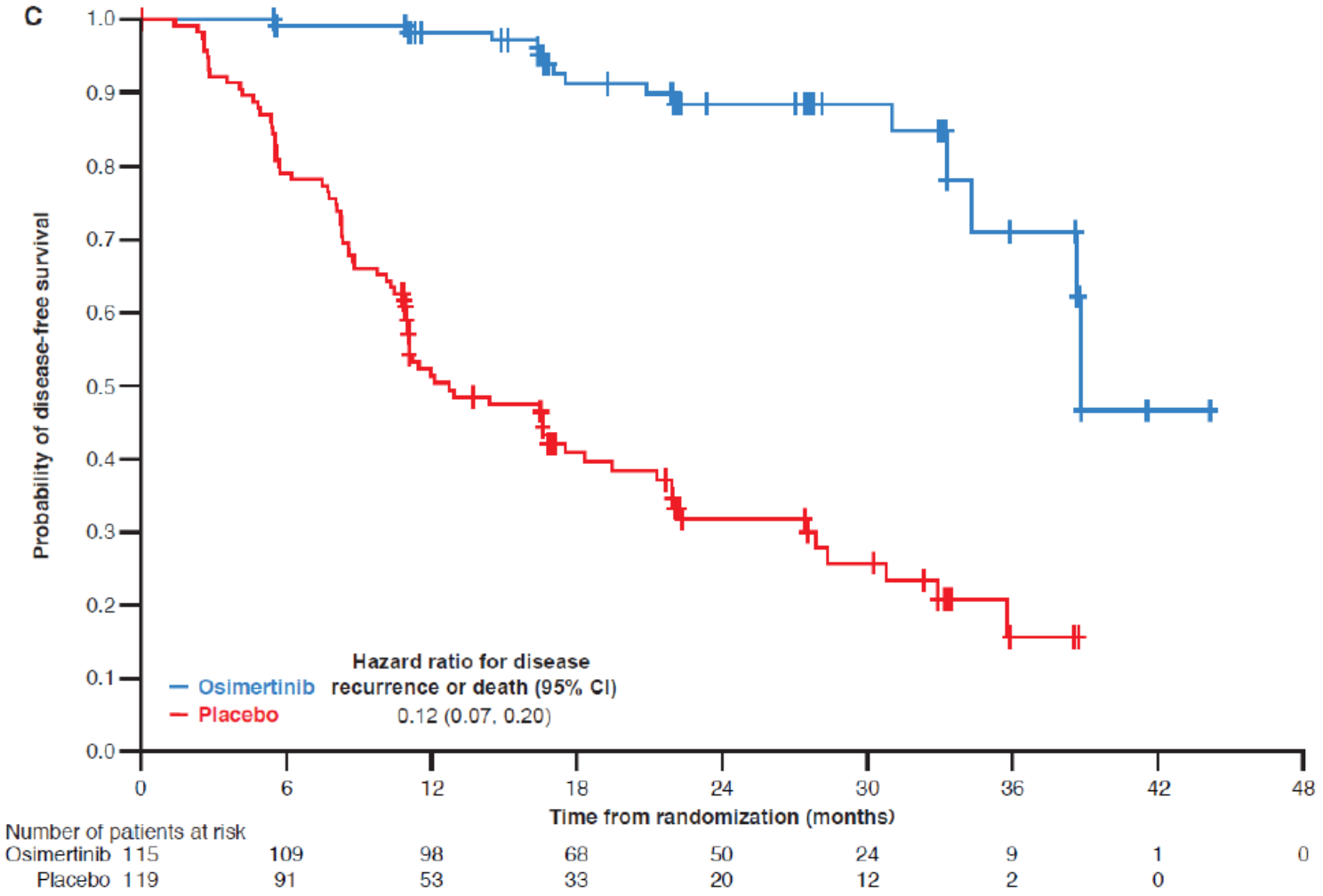
Stage II to IIIA



No. at Risk										
Osimertinib	339	313	272	208	138	74	27	5	0	
Placebo	343	287	207	148	88	53	20	3	1	0

Stage IB to IIIA

DFS of stage IIIA

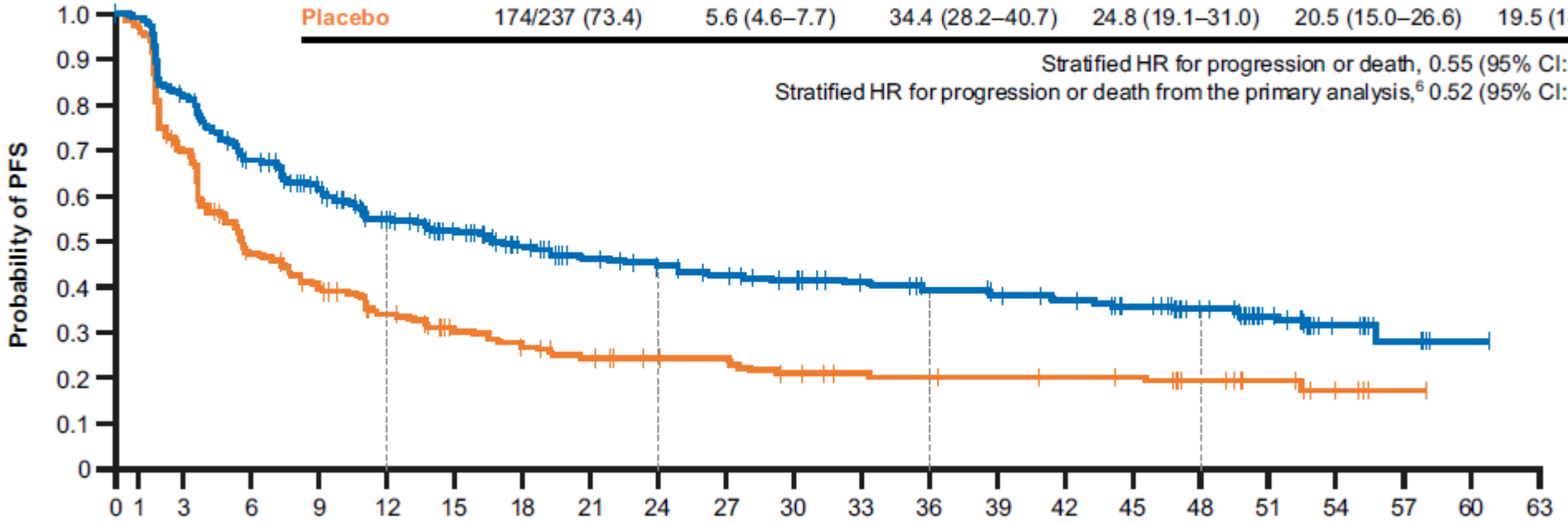


4-year PFS data with Durvalumab

B

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months	12-month PFS rate (95% CI) %	24-month PFS rate (95% CI) %	36-month PFS rate (95% CI) %	48-month PFS rate (95% CI) %
Durvalumab	266/476 (55.9)	17.2 (12.3–23.8)	55.3 (50.5–59.8)	44.8 (39.8–49.6)	39.8 (34.8–44.8)	35.3 (30.3–40.4)
Placebo	174/237 (73.4)	5.6 (4.6–7.7)	34.4 (28.2–40.7)	24.8 (19.1–31.0)	20.5 (15.0–26.6)	19.5 (14.1–25.7)

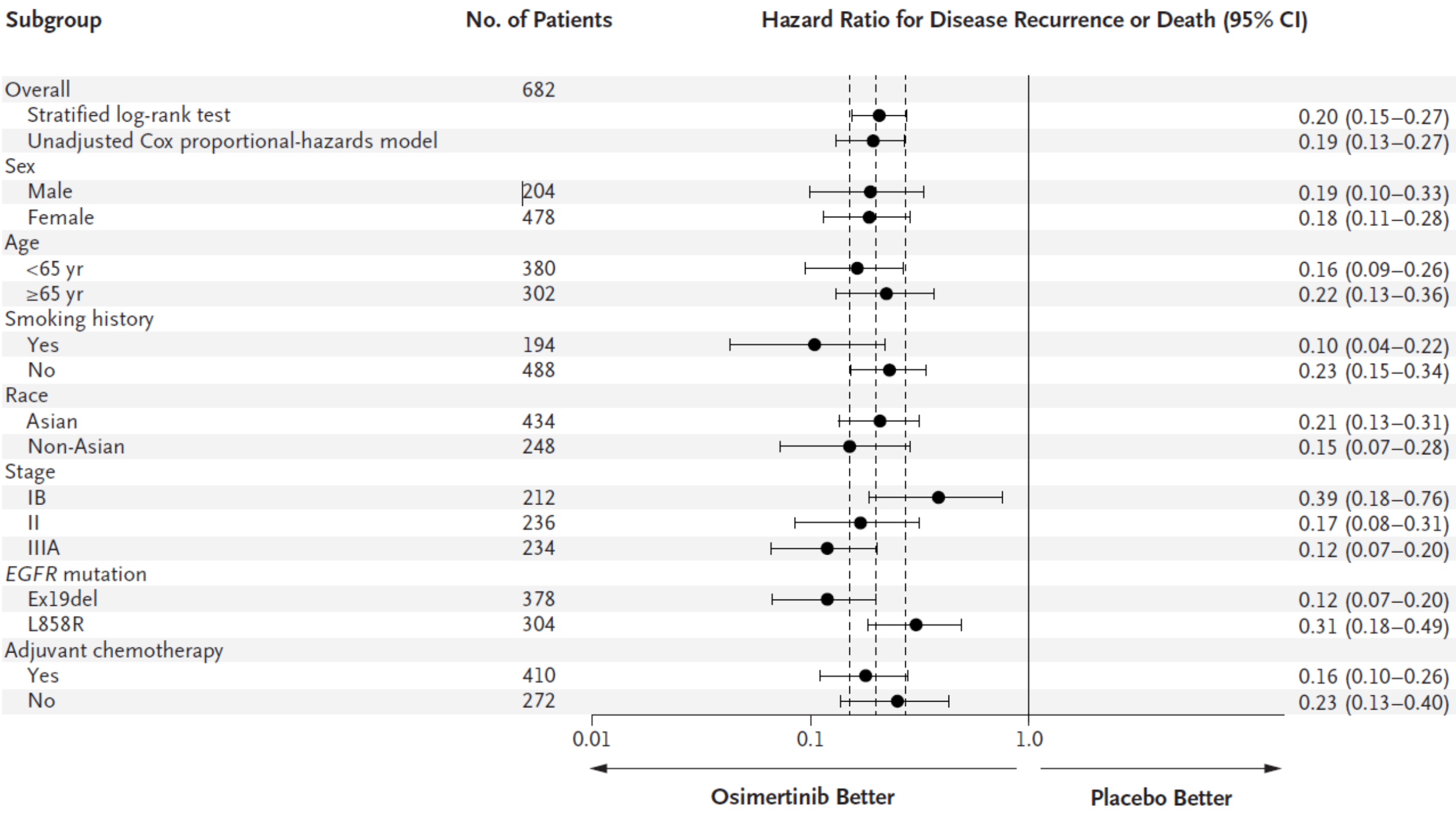
Stratified HR for progression or death, 0.55 (95% CI: 0.44–0.67)
Stratified HR for progression or death from the primary analysis,[6] 0.52 (95% CI: 0.42–0.65)



No. at risk

Durvalumab	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8	1	0
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1	0	0

Corinne Faivre-Finn et al. *JTO*. 2021. online ahead of print

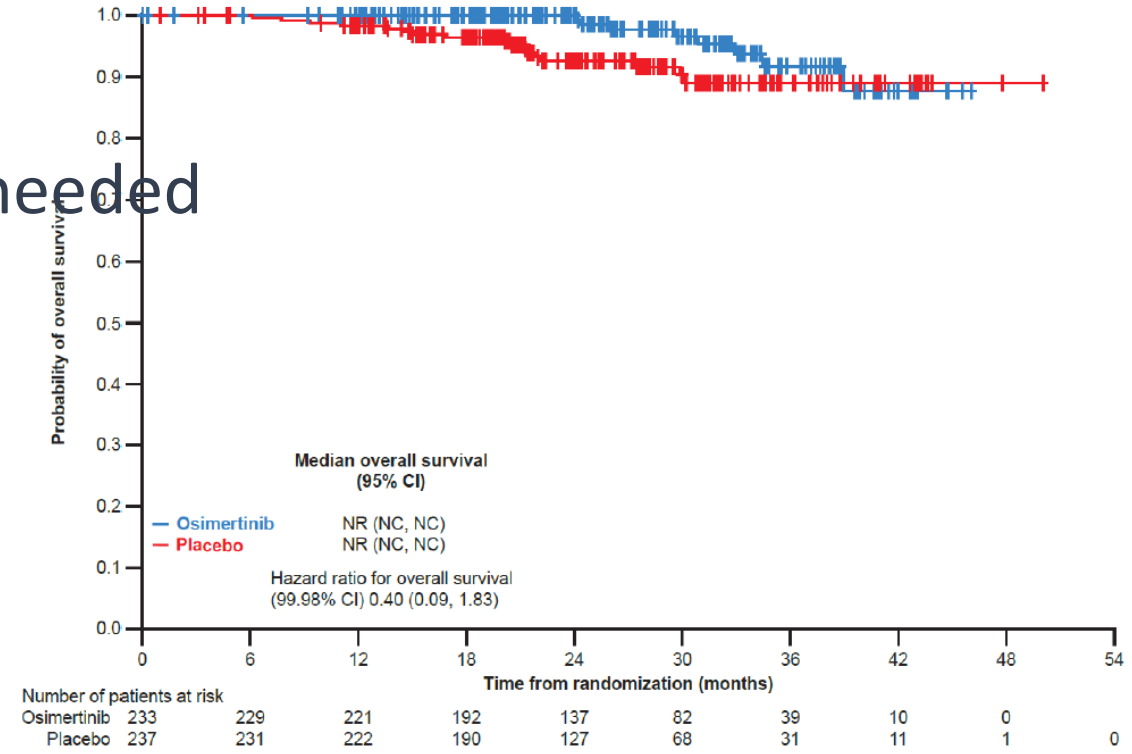

Subgroup
No. of Patients
Hazard Ratio for Disease Recurrence or Death (95% CI)
Overall 682
Stratified log-rank test 0.20 (0.15–0.27)
Unadjusted Cox proportional-hazards model 0.19 (0.13–0.27)
Sex
Male 204 0.19 (0.10–0.33)
Female 478 0.18 (0.11–0.28)
Age
<65 yr 380 0.16 (0.09–0.26)
≥65 yr 302 0.22 (0.13–0.36)
Smoking history
Yes 194 0.10 (0.04–0.22)
No 488 0.23 (0.15–0.34)
Race
Asian 434 0.21 (0.13–0.31)
Non-Asian 248 0.15 (0.07–0.28)
Stage
IB 212 0.39 (0.18–0.76)
II 236 0.17 (0.08–0.31)
IIIA 234 0.12 (0.07–0.20)
EGFR mutation
Ex19del 378 0.12 (0.07–0.20)
L858R 304 0.31 (0.18–0.49)
Adjuvant chemotherapy
Yes 410 0.16 (0.10–0.26)
No 272 0.23 (0.13–0.40)
0.01
0.1
1.0
Osimertinib Better
Placebo Better

Adverse Events

Adverse Event	Osimertinib (N=337)				Placebo (N=343)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	156 (46)	116 (34)	32 (9)	8 (2)	68 (20)	54 (16)	13 (4)	1 (<1)
Paronychia	85 (25)	31 (9)	50 (15)	3 (1)	5 (1)	3 (1)	2 (1)	0
Dry skin	79 (23)	75 (22)	3 (1)	1 (<1)	22 (6)	18 (5)	4 (1)	0
Pruritus	65 (19)	49 (15)	16 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	62 (18)	43 (13)	19 (6)	0	57 (17)	42 (12)	15 (4)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	14 (4)	10 (3)	4 (1)	0
Nasopharyngitis	47 (14)	30 (9)	17 (5)	0	35 (10)	25 (7)	10 (3)	0
Upper respiratory tract infection	45 (13)	24 (7)	19 (6)	2 (1)	35 (10)	19 (6)	16 (5)	0
Decreased appetite	44 (13)	29 (9)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	8 (2)	6 (2)	2 (1)	0
Dermatitis acneiform	37 (11)	29 (9)	8 (2)	0	16 (5)	12 (3)	4 (1)	0

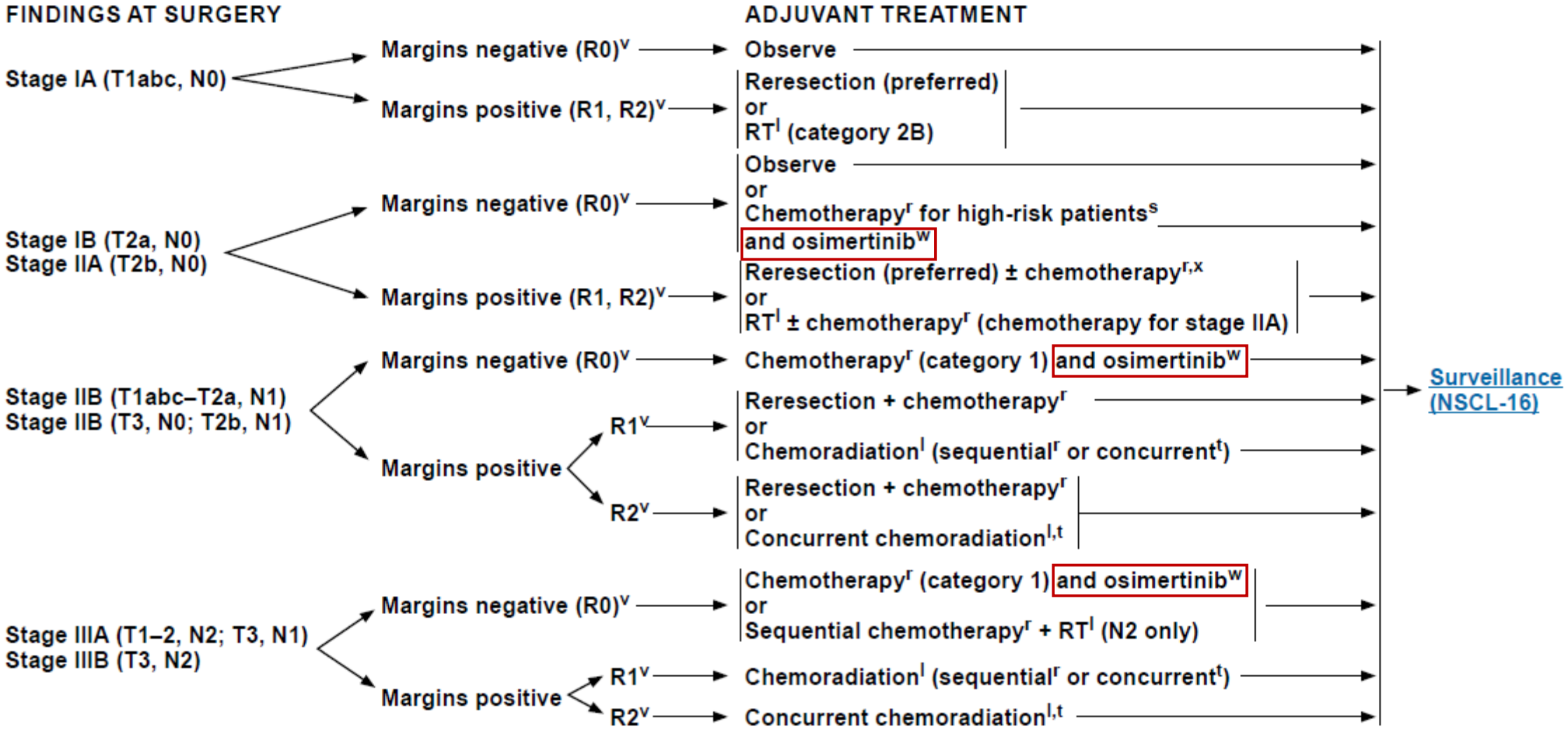
Limitations

- DFS rate on the control arm of ADAURA (44%) at 2 years vs. chemotherapy in the LACE meta-analysis (60%) for the same time point
- Disease free survival advantage may not translate to an overall survival advantage
- Treatment for up to 3 years
- Adjuvant chemotherapy may be still needed



Summary of ADAURA

- Adjuvant osimertinib showed a statistically significant improvement in DFS in patients with stage IB/II/IIA EGFRm NSCLC.
- In ADAURA, patents with stage IB not at high risk were enrolled.
- Overall, there was a 79% risk reduction of disease recurrence or death with osimertinib. (HR 0.21)
- A consistent improvement in DFS was seen regardless of whether patients received prior adjuvant chemotherapy.



l See Principles of Radiation Therapy (NSCL-C).

r See Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).

s Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

t See Concurrent Chemoradiation Regimens (NSCL-F).

v R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

w For patients with *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.

x Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

Adjuvant immunotherapy

Ongoing clinical trials

Clinical trial	Phase	Stage	Intervention used	Estimated sample size	Primary endpoints
ANVIL (NCT02595944)	III	IB–IIIA	Nivolumab vs. observation with or without adjuvant chemotherapy	903	OS, DFS
PEARLS/Keynote-091 (NCT02504372)	III	IB–IIIA	Pembrolizumab vs. placebo with or without adjuvant chemotherapy	1,380	DFS
IMpower010 (NCT02486718)	III	IB–IIIA	Atezolizumab + chemotherapy vs. best supportive care + chemotherapy	1,280	DFS
BR31 (NCT02273375)	III	IB–IIIB	Durvalumab vs. placebo with or without adjuvant chemotherapy	1,100	DFS in PD-L1-positive patients and in all randomized patients

NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; OS, overall survival; DFS, disease-free survival; PD-L1, programmed cell death-ligand 1.

Expected to completed during 2024-2027

Rilan Bai et al. *Front Oncol.* 2020. Oct 9;10:575472

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→ DFS benefit with II-IIIA in PD-L1+

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Conclusion

- The treatment goal of adjuvant chemotherapy is OS
- Adjuvant chemotherapy is not recommended in stage IA.
- The benefit of adjuvant chemotherapy in stage IB remains unknown. It is recommended to assess benefits and risks for each patient.
- Platinum-based doublet chemotherapy might increase 5% of survival ratio in stage II-IIIA.
- In ADAURA, adjuvant osimertinib demonstrated a highly significant improvement DFS in stage IB-IIIA EGFRm NSCLC. But it is still unknown about OS data.
- In NCCN guideline, prior adjuvant chemotherapy is required when using osimertinib.