Update on Adjuvant Treatment in Resectable NSCLC

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- Backgrounds
- EGFR TKI as adjuvant treatment
- Immunotherapy as adjuvant treatment
- Radiotherapy as adjuvant treatment
- Clinical application
- Potential biomarkers

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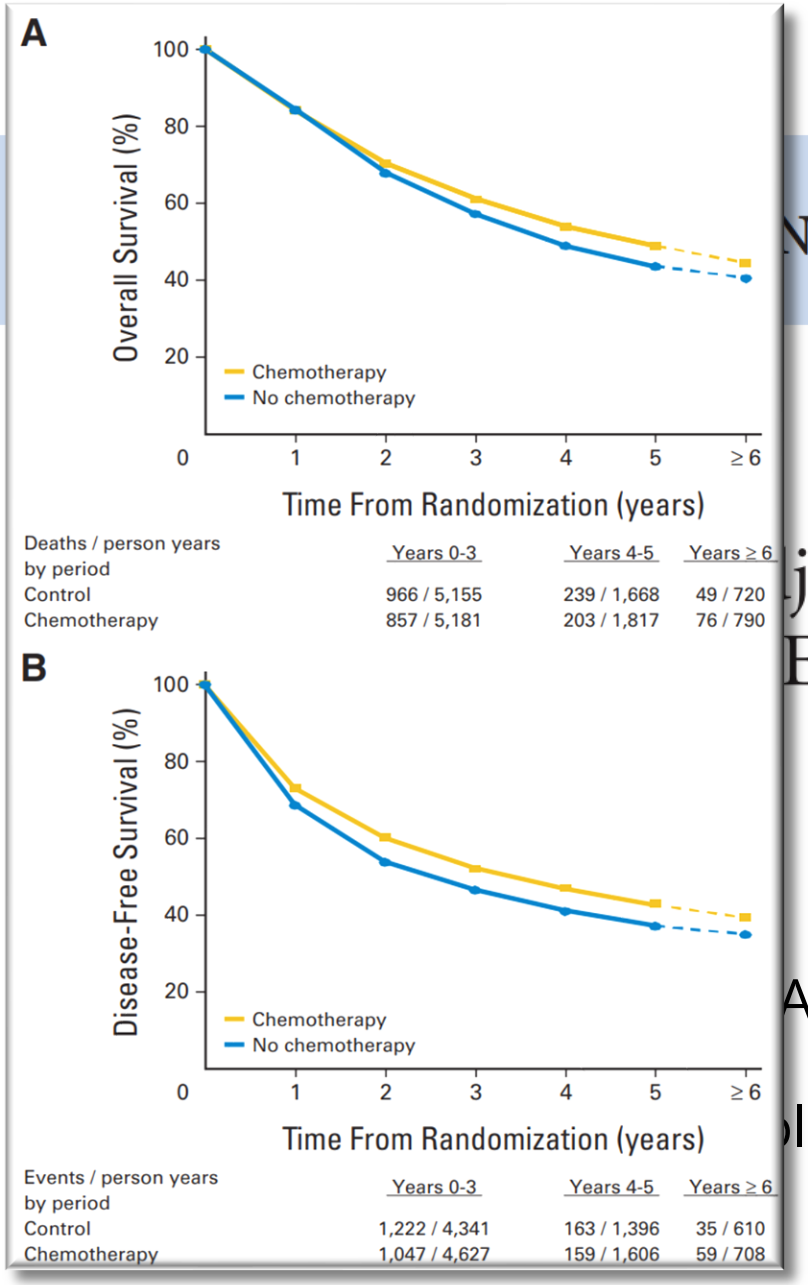
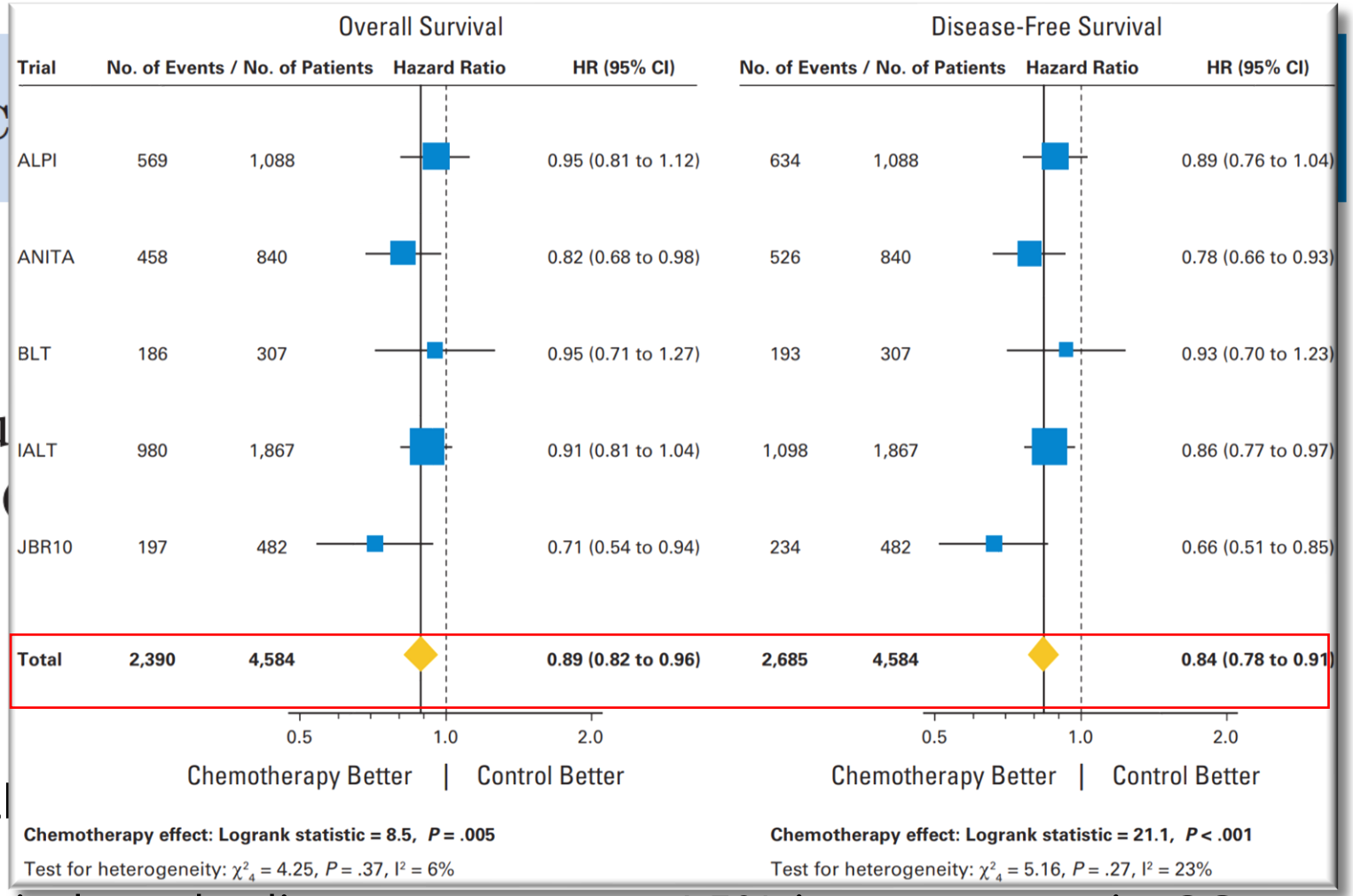
Backgrounds

- About 20% of patients diagnosed with stages I and II, and 30% with stage III in NSCLC
- Stages I–IIIA , mainstay treatment is **complete resection**, if possible.
- 5 year recurrence rate: 45% (stage Ib), 62% (stage II), 76% (stage III)

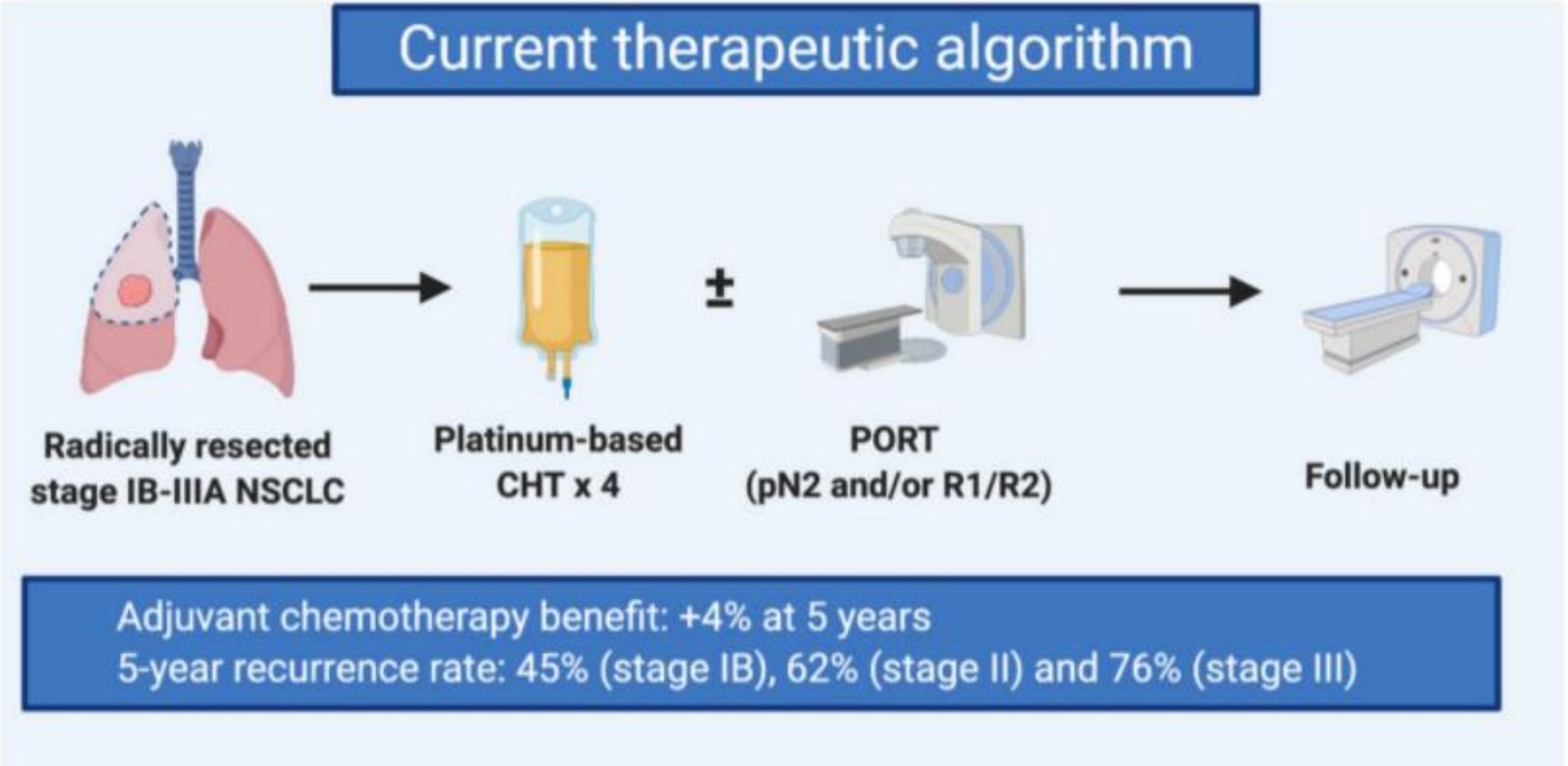
Transl Lung Cancer Res 2014;3(4):242-249





latin based adjuvant treatment 4.5% improvement in OS

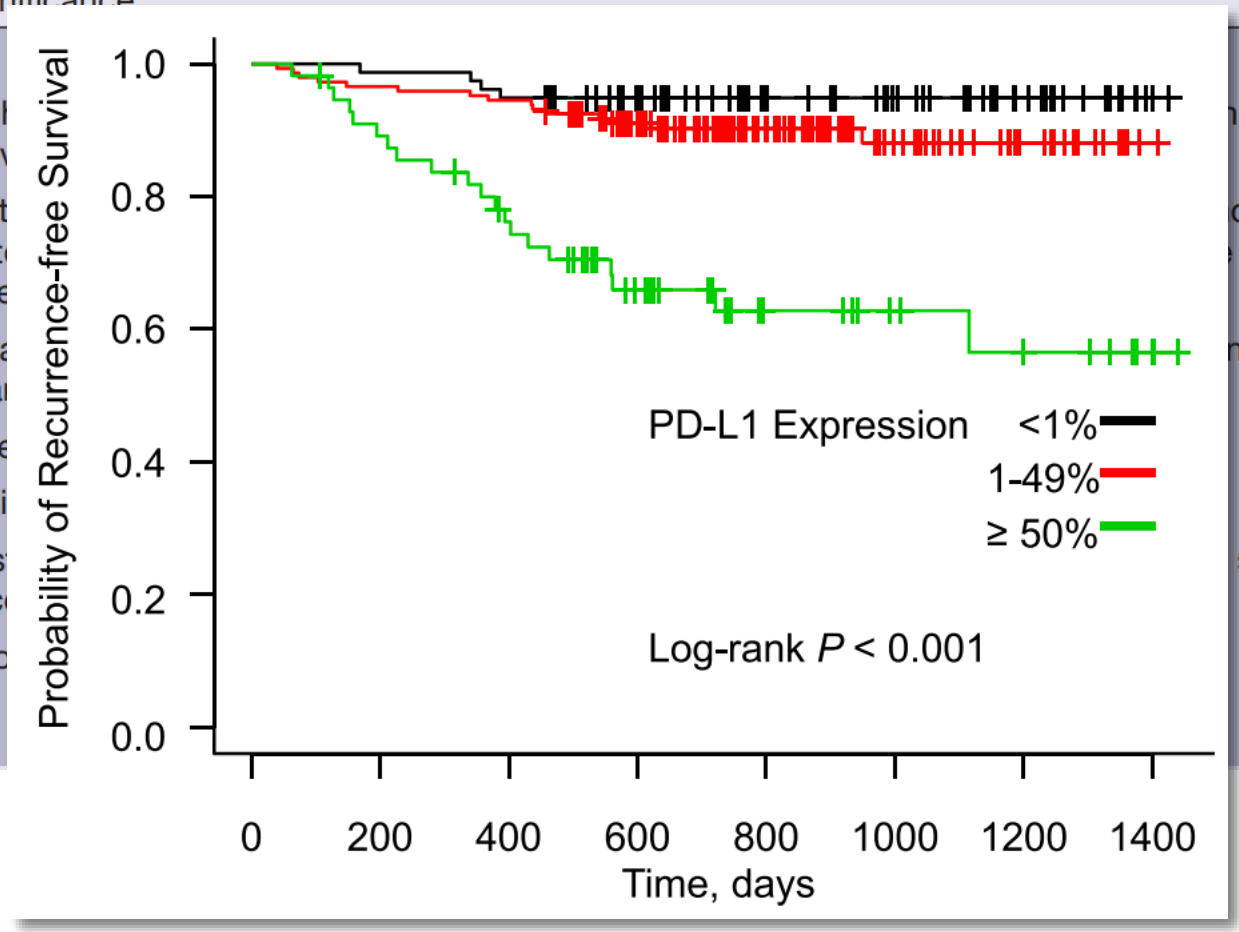
Current therapeutic algorithm



Int. J. Mol. Sci. **2020**, *21*(17), 6329
J Clin Oncol 2008 Vol. 26 Issue 21 Pages 3552-9

Backgrounds-risk factors

Parameters	Significance
Clinical parameters	
High CEA, lymphatic permeation, and pleural invasion	High prov
Histological differentiation, vessel invasion, and visceral pleural invasion	Hist hist inde
Intratumoral vascular invasion and nodal involvement	Intra yea
Intratumoral blood vessel invasion	Inde
SUV	Pati
Number of LNs	Sys in c
PS, and symptoms at recurrence, liver recurrence, stage IIB or worse, and multiple recurrences	Stro



Transl Lung Cancer Res 2014;3(4):242-249
Scientifc Reports | (2021) 11:17522

Backgrounds

- Eradication of micrometastatic disease that is not radiographically visible, prevents distant spread, and improve the cure rate
- Only **15% decrease in relapse** and **marginal increase in OS** in 5 years with **cisplatin based adjuvant chemotherapy.**
- Efficacy of EGFR TKI and immunotherapy in advanced NSCLC-> need to incorporate into adjuvant setting.

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Table 1. Summary of Various Prospective Studies That Have Used EGFR Inhibitors in the Adjuvant Setting in NSCLC

Study	Phase, Study Design, and Sample Size	Stage	*EGFR* Mutation Status	AdCT/ Percentage of Patients Receiving AdCT	Treatment Regimen	Primary End Points	Median Follow-Up (y)	Outcome
BR.19 Goss et al. 2013[8]	Phase 3 Randomized, double-blind, placebo-controlled (n = 503)	IB-IIIA	All comers; only 15 patients had *EGFR* mutation	Optional 17	Gefitinib (n = 251) vs. placebo (n = 252) for 2 y	OS, DFS	4.7	No difference in DFS and OS between the two arms *EGFR* mutation positivity (n = 15) not prognostic for DFS and OS
RADIANT Kelly et al. 2015[9]	Phase 3 Randomized, double-blind, placebo-controlled (n = 973)	IB-IIIA	*EGFR*-positive by IHC and/or FISH[a]; 161 patients had *EGFR* mutation	Optional 52.9	Erlotinib (n = 623) vs. placebo (n = 350) for 2 y	DFS	3.9	No difference in DFS between the two arms; OS data immature No statistical difference in DFS between the two arms in the EGFRm subset
SELECT Pennell et al. 2019[10]	Phase 2 Single-arm, open-label (n = 100)	IA-IIIA	All patients with sensitizing *EGFR* mutation	As per staging NR	Erlotinib for 2 y	2-y DFS	5.2	2-y DFS was 88%
CTONG1104 Wu et al. 2020[3]; Zhong et al. 2018[11]	Phase 3 Randomized, open-label (n = 222)	II-IIIA	All patients with sensitizing *EGFR* mutation	Offered to chemo-arm; 50	Cisplatin + vinorelbine (n = 111) for 4 cycles vs. gefitinib (n = 111) for 2 y	DFS	6.4	Median DFS was significantly longer in the gefitinib arm No significant difference in OS between the two arms
ADAURA Wu et al. 2020[14]	Phase 3 Randomized, double-blind, placebo-controlled (n = 682)	IB-IIIA	All patients with sensitizing *EGFR* mutation	Optional 60	Osimertinib (n = 339) vs. placebo (n = 343) for 3 y	DFS in patients with stage II-IIIA disease	1.84 in osimertinib arm and 1.24 in the placebo arm	2-y DFS was 90% in osimertinib arm vs. 44% in the placebo arm

Gefitinib versu
treatment for s
(ADJUVANT/CT
phase 3 study

Wen-Zhao Zhong, Qun Wang, Wei-
Xiao-Fei Li, Jian Li, Cheng Huang, Zl
Hong-Hong Yan, Xue-Ning Yang, Q
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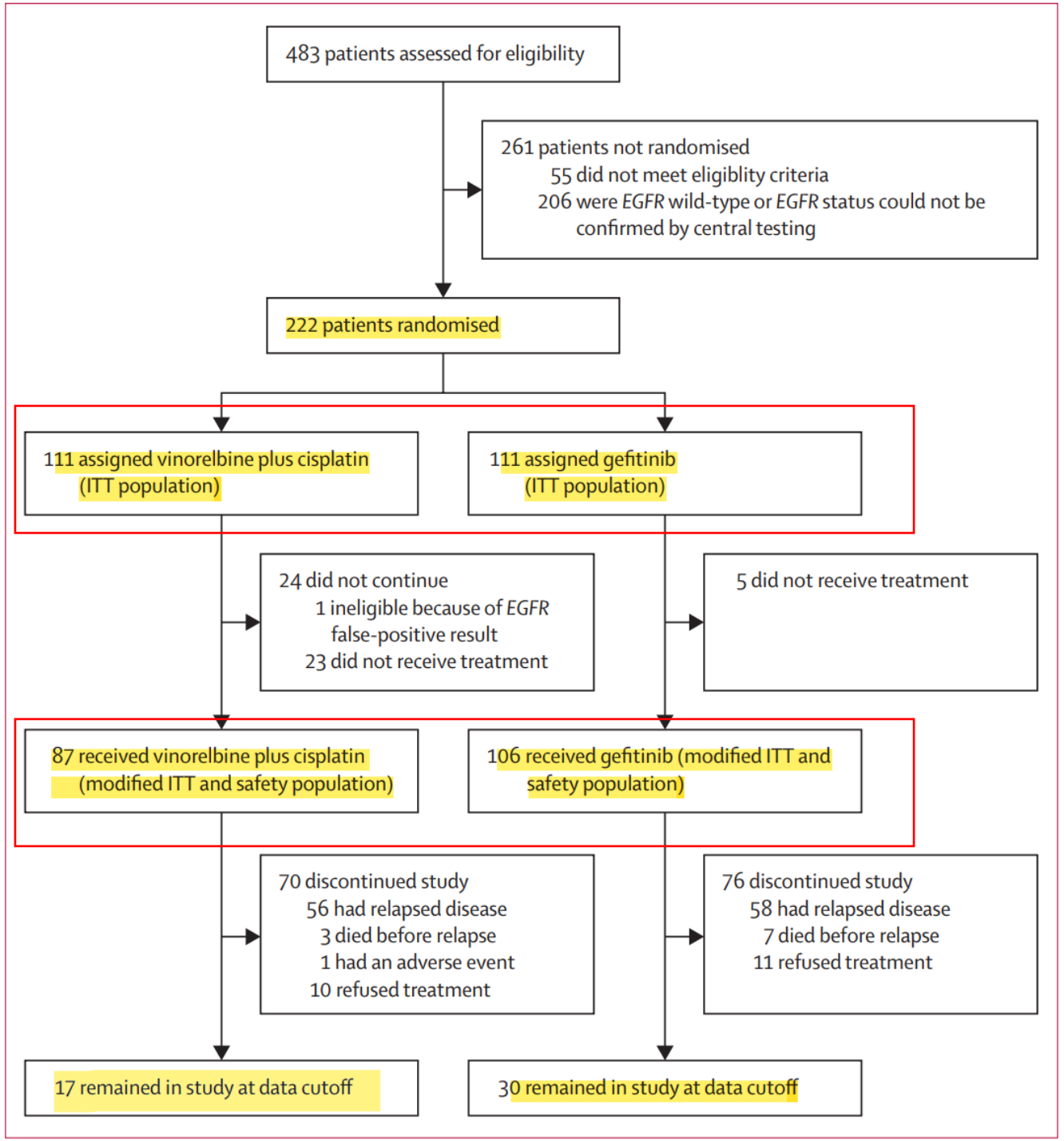
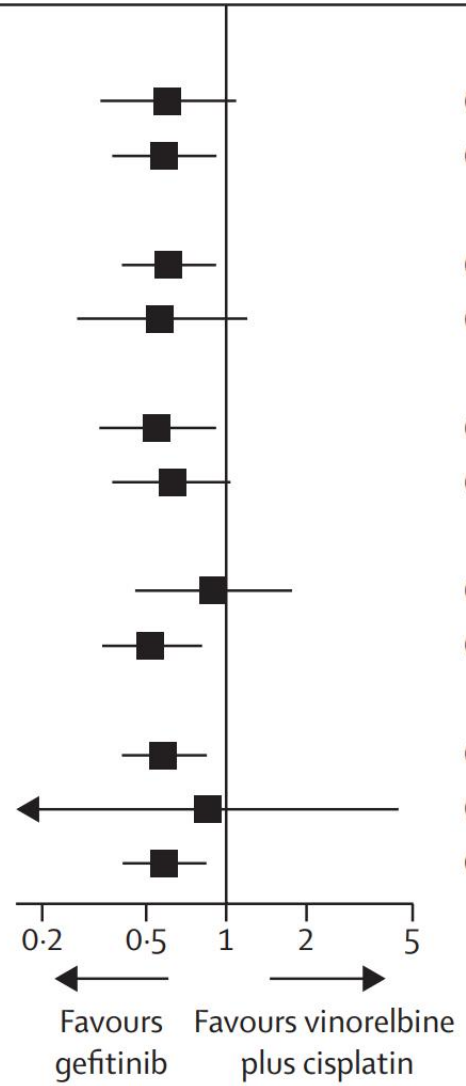
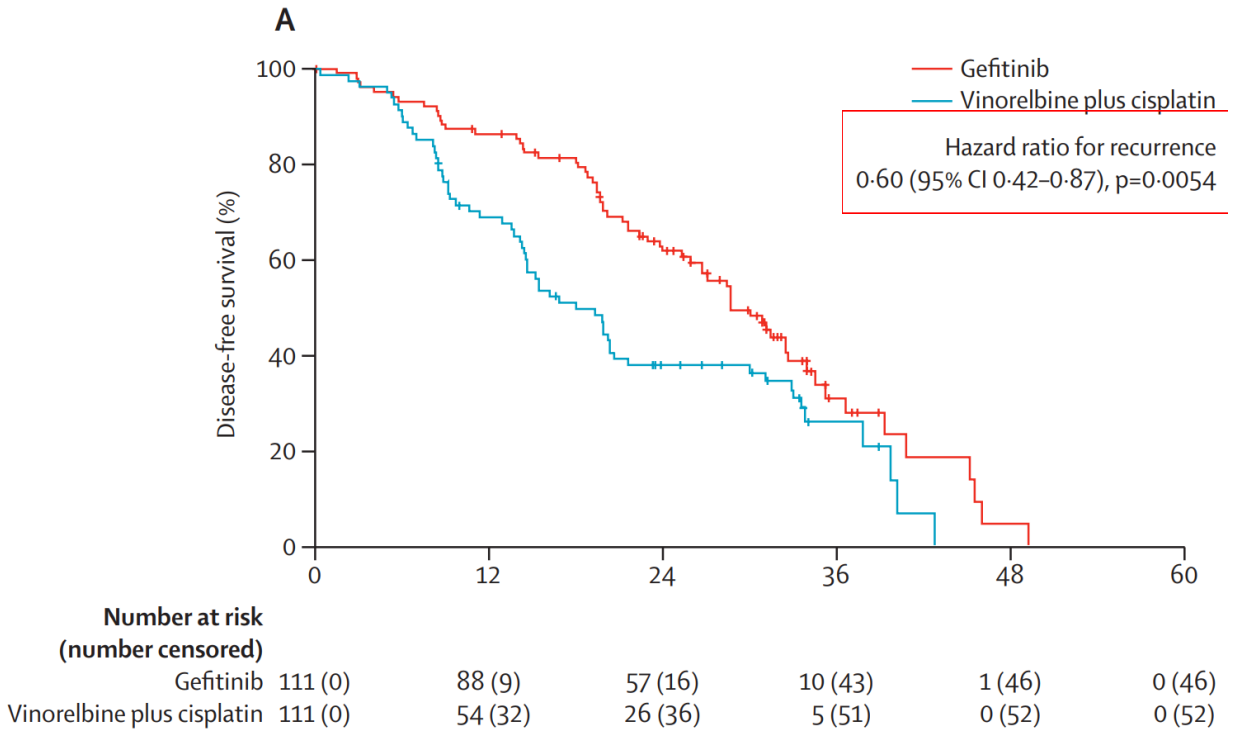
- Open label phas
- Completely resec
  n or exon 21
  Leu858Arg) NSCI

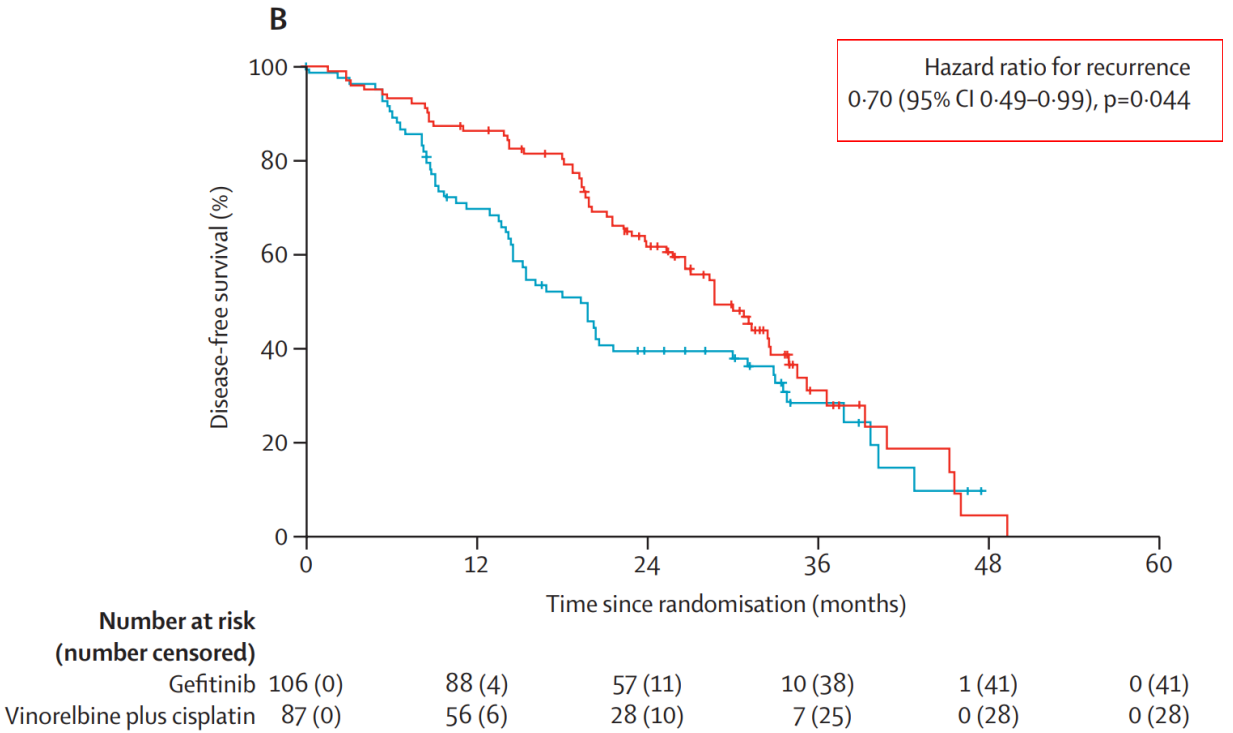


	Total number of patients/events (n/N)	Gefitinib (n/N)	Vinorelbine plus cisplatin (n/N)	HR (95% CI)	p value	$p_{interaction}$
Sex						0·754
Male	89/46	44/23	45/23	0·60 (0·33–1·09)	0·094	
Female	130/78	65/42	65/36	0·58 (0·37–0·92)	0·020	
Smoker						0·896
No	167/95	82/49	85/46	0·61 (0·40–0·92)	0·018	
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**	



DFS in ITT and mITT





- DFS did not translate to **OS** and **recurrence in the CNS was common**.
- **Did not** translate to **changes in clinical practice**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

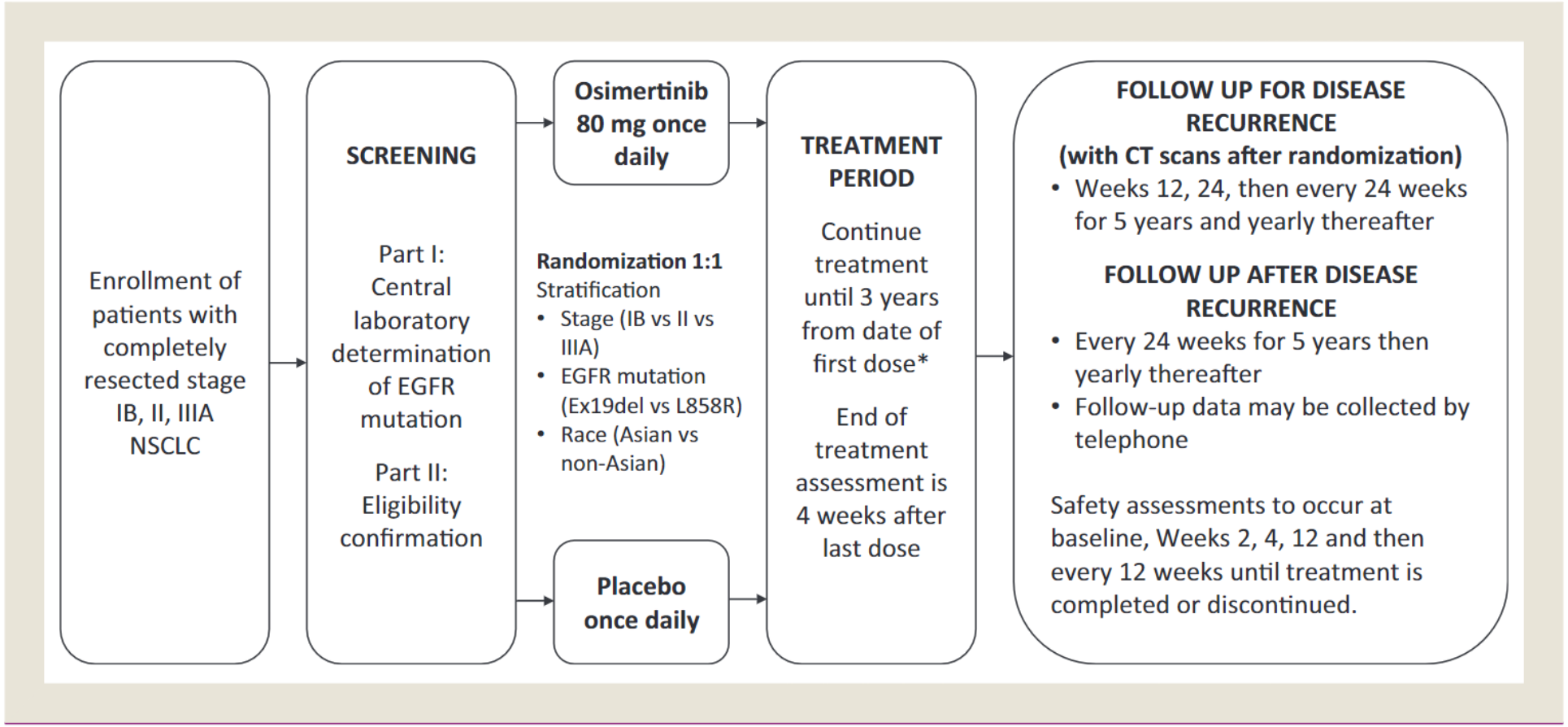
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

ADAURA study

- Phase 3 randomized double blind placebo study
- 682 EGFR mutation positive patients
- 80% reduction in the risk of disease recurrence of death with osimertinib

N Engl J Med 383;18 nejm.org October 29, 2020

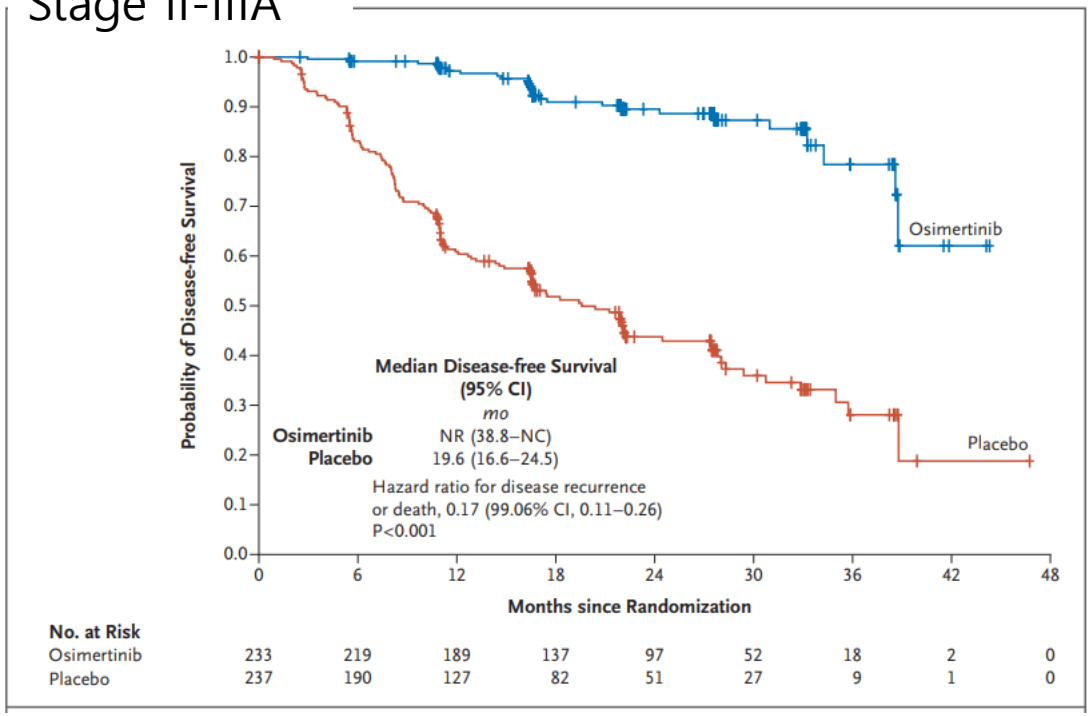
ADAURA study



Clinical Lung Cancer July 2018

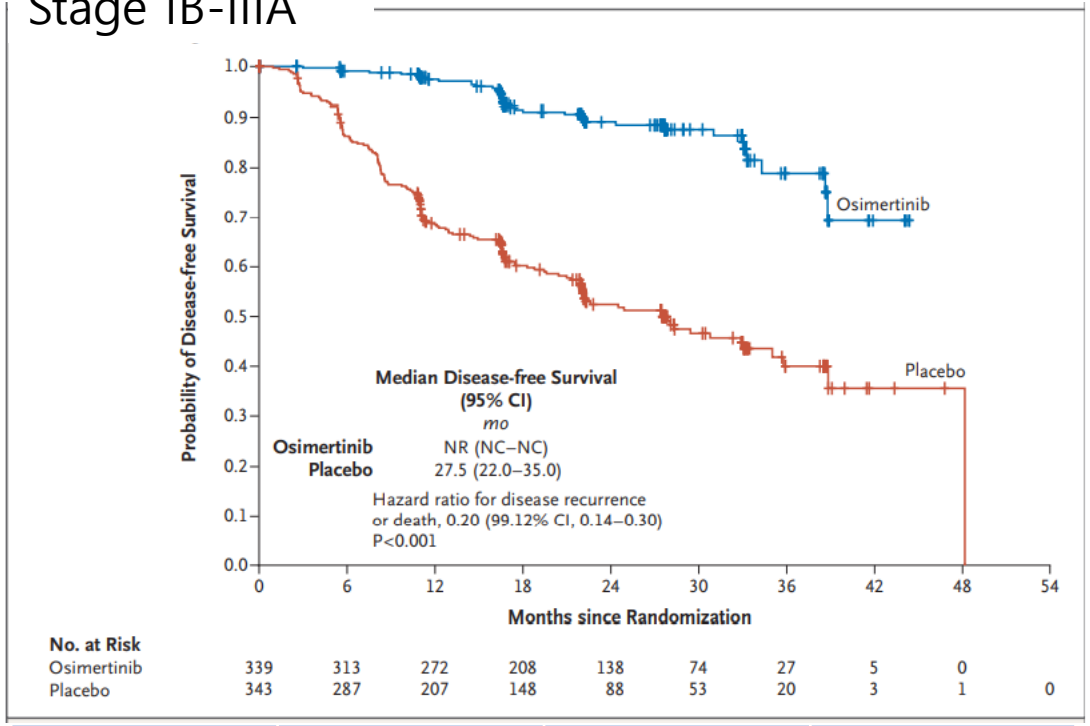
ADAURA study

Stage II-IIIA



Stage II-IIIA disease (470)	Median follow up for DFS	DFS, 2 years	Median DFS
Osimertinib (233)	22.1 mo	**90%**	not reached
Placebo (237)	14.9 mo	**44%**	19.6 months

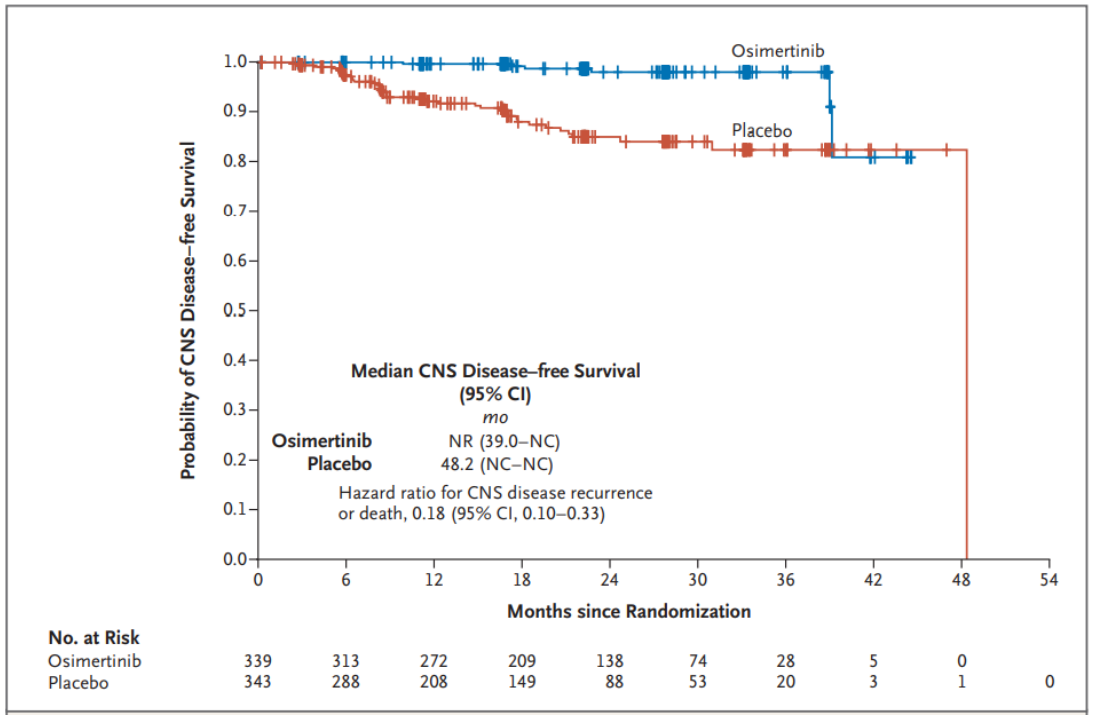
Stage IB-IIIA



Stage IB-IIIA disease (682)	Median follow up	DFS, 2 years	Median DFS
Osimertinib (339)	22.5 mo	**89%**	not reached
Placebo (343)	18.7 mo	**52%**	27.5 months

N Engl J Med 383;18 nejm.org October 29, 2020

ADAURA study-CNS disease free survival

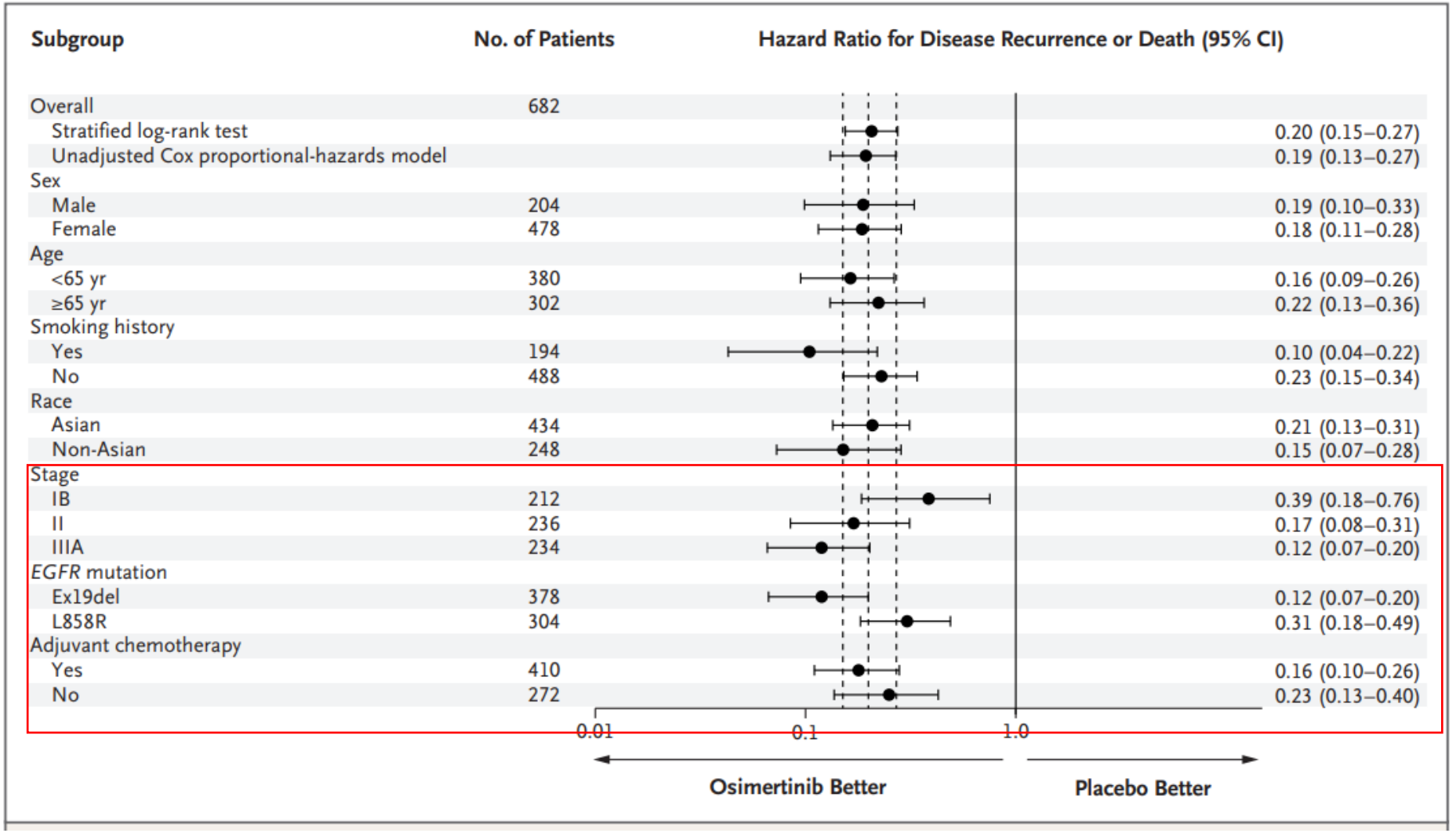


Stage IB-IIIA disease (682)	Locoregional recurrence	Distant recurrence	Recurrence of CNS-related disease
Osimertinib (339)	7%	4%	2%
Placebo (343)	18%	28%	11%

Stage IB-IIIA disease (682)	% without CNS Disease (2 years)	Median CNS DFS	Deaths
Osimertinib (339)	98%	Not reached	9
Placebo (343)	85%	48.2 mo	20

N Engl J Med 383;18 nejm.org October 29, 2020

ADAURA study-Subgroup analysis



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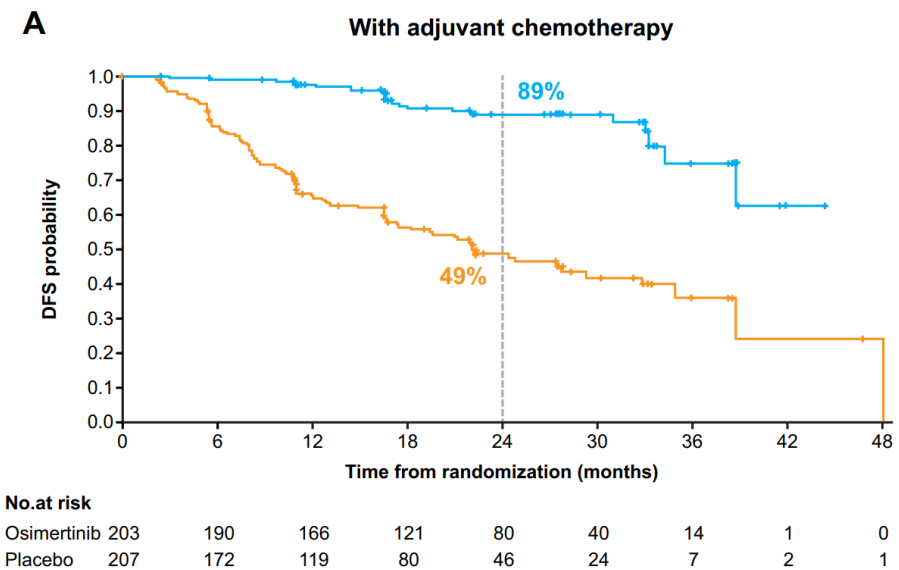
ADAURA study- Safety

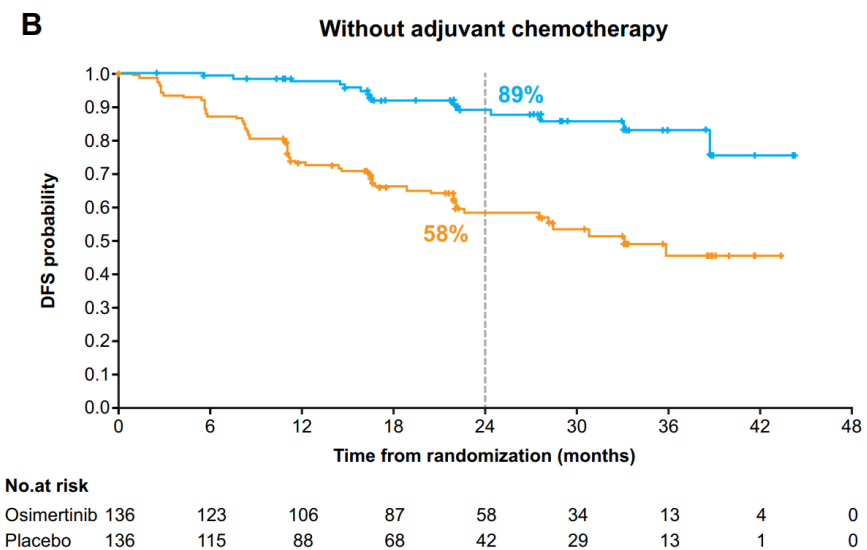
Table 2. Adverse Events.*

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

N Engl J Med 383;18 nejm.org October 29, 2020

Postoperative Chemotherapy Use and Outcomes From ADAURA: Osimertinib as Adjuvant Therapy for Resected EGFR-Mutated NSCLC





FDA Approves First Adjuvant Therapy for Most Common Type of Lung Cancer

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For Immediate Release: December 18, 2020

- The U.S. Food and Drug Administration approved Tagrisso (osimertinib) as the first adjuvant treatment for patients with non-small cell lung cancer whose tumors have a specific type of genetic mutation.

US Food and Drug Administration. FDA approves osimertinib for first-line treatment of metastatic NSCLC with most common EGFR mutations. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-first-line-treatment-metastatic-nsclc-most-common-egfr-mutations.

AZ 타그리소, EGFR TKI 최초 수술 후 보조요법 적응증 승인

의약뉴스 송재훈 기자 | 승인 2021.02.25 17:03 | 댓글 0

◇한국아스트라제네카 타그리소, EGFR TKI 최초 수술 후 보조요법 적응증 승인

한국아스트라제네카(대표: 김상표)의 타그리소(성분명 오시머티닙)가 EGFR변이 비소세포폐암 환자의 수술 후 보조요법으로 이달 23일 식품의약품안전처(이하 식약처) 허가를 받았다.

식약처는 23일 EGFR 엑손 19 결손 또는 엑손 21(L858R) 치환 변이된 비소세포폐암 환자의 완전 종양 절제술 후 보조 치료로 타그리소의 사용을 허가했다.

▲ 한국아스트라제네카의 타그리소가 EGFR변이 비소세포폐암 환자의 수술 후 보조요법으로 이달 23일 식품의약품안전처(이하 식약처) 허가를 받았다.

http://www.newsmp.com/news/articleView.html?idxno=212691

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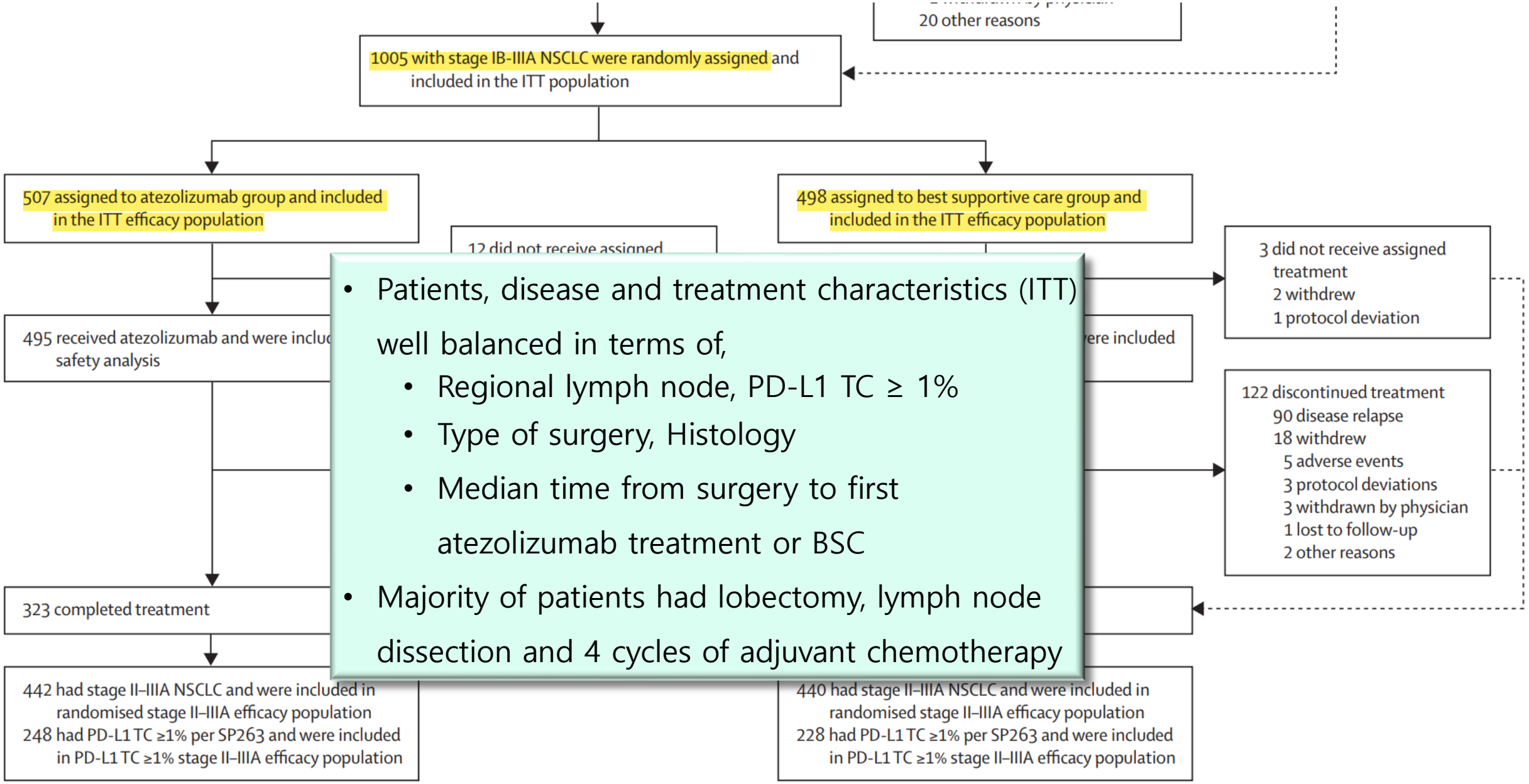
IMpower010: adjuvant atezolizumab

- Randomised, multicentre, **open-label**, phase 3 study
- **Completely resected stage IB (tumours ≥4 cm) to IIIA NSCLC (AJCC 7th edition)**
- **Atezolizumab (1200 mg every 21 days; for 16 cycles or 1 year)** or best supportive care after adjuvant platinum-based chemotherapy
- **DFS benefit with atezolizumab** versus best supportive care after adjuvant chemotherapy in patients with resected stage **II–IIIA NSCLC**

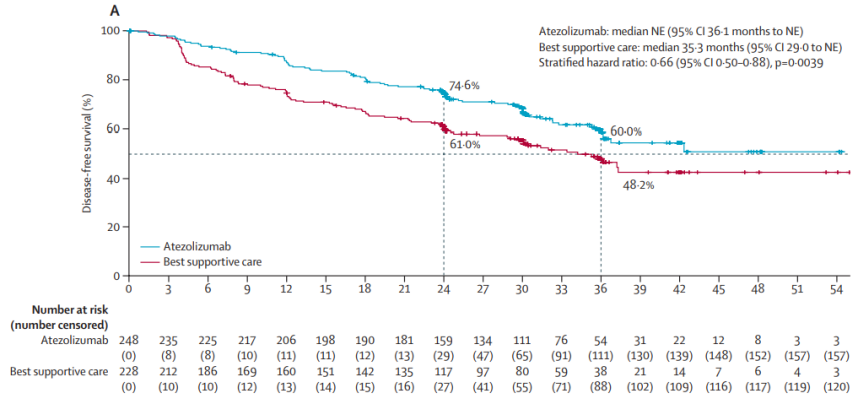
Lancet 2021; 398: 1344–57

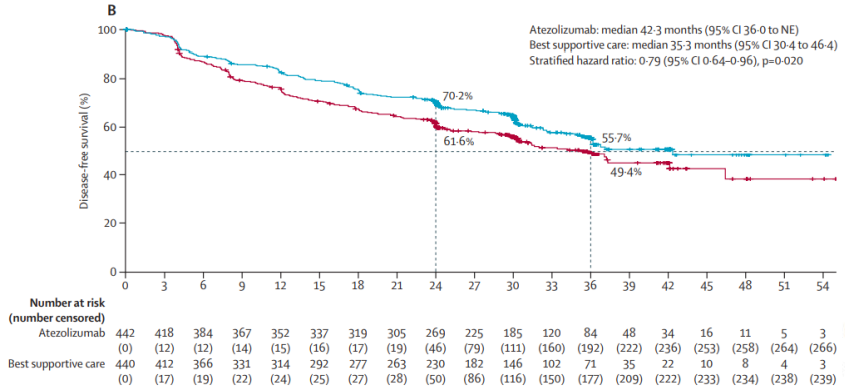


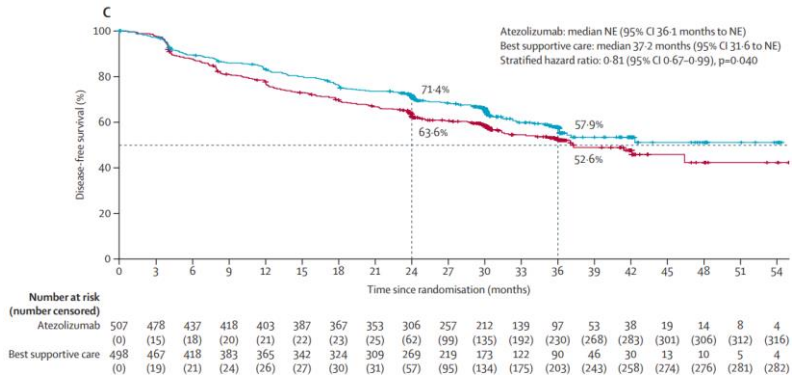
- Patients, disease and treatment characteristics (ITT) well balanced in terms of,
  - Regional lymph node, PD-L1 TC ≥ 1%
  - Type of surgery, Histology
  - Median time from surgery to first atezolizumab treatment or BSC
- Majority of patients had lobectomy, lymph node dissection and 4 cycles of adjuvant chemotherapy

Lancet 2021; 398: 1344–57

IMpower010: DFS PD≥1% & all patients







PD-L1 TC≥1% stage II-IIIA (SP263)

	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

All randomized stage II-IIIA

	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

ITT (randomized stage IB-IIIA)

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

Lancet 2021; 398: 1344–57
Altorki et al. IMpower010 Prior Therapies
https://bit.ly/36gV0j

IMpower010: Subgroup Analysis

PD-L1 ≥ 1% (n=476)	Favor Atezolizumab
Stage IIA	0.73 (0.43-1.24)
Stage IIB	0.77 (0.35-1.69)
Stage IIIA	**0.62 (0.42-0.90)**
N1 (Regional LN, pN)	**0.59 (0.36-0.97)**
N2 (Regional LN, pN)	**0.66 (0.44-0.99)**
Squamous	0.78 (0.47-1.29)
Non-squamous	**0.60 (0.42-0.84)**
All patients	**0.66 (0.50-0.88)**

All patients (n=882)	Favor Atezolizumab
Stage IIA	0.68 (0.46-1.00)
Stage IIB	0.88 (0.54-1.42)
Stage IIIA	0.81 (0.61-1.06)
N1 (Regional LN, pN)	**0.67 (0.47-0.95)**
N2 (Regional LN, pN)	0.83 (0.61-1.13)
Squamous	0.80 (0.54-1.18)
Non-squamous	**0.78 (0.61-0.99)**
All patients	**0.79 (0.64-0.96)**

Lancet 2021; 398: 1344–57

IMpower010: Safety & Summary

	Atezolizumab group (n=495)	Best supportive care group (n=495)
Adverse event		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
Immune-mediated adverse events		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

	Atezolizumab group (n=495)			Best supportive care group (n=495)		
	All grades	Grade 3–4	Grade 5	All grades	Grade 3–4	Grade 5
Any cause	459 (93%)	108 (22%)	8 (2%)†	350 (71%)	57 (12%)	3 (1%)‡
Cough	66 (13%)	0	0	46 (9%)	0	0
Pyrexia	65 (13%)	4 (1%)	0	11 (2%)	1 (<1%)	0
Hypothyroidism	55 (11%)	0	0	3 (1%)	0	0
Alanine aminotransferase increased	53 (11%)	8 (2%)	0	16 (3%)	1 (<1%)	0
Aspartate aminotransferase increased	53 (11%)	7 (1%)	0	16 (3%)	0	0
Arthralgia	52 (11%)	2 (<1%)	0	26 (5%)	0	0
Pruritus	51 (10%)	0	0	3 (1%)	0	0
Nasopharyngitis	33 (7%)	0	0	50 (10%)	0	0

- Atezolizumab showed **statistically significant DFS benefit** in the **PD-L1 TC ≥1% stage II-IIIA and all-randomized stage II-IIIA**
- Improved DFS was observed in the PD-L1 ≥ 1% stage and all II-IIIA populations **across most disease stages, in patients with nodal involvement, and most surgery types and chemotherapy regimens.**

Lancet 2021; 398: 1344–57

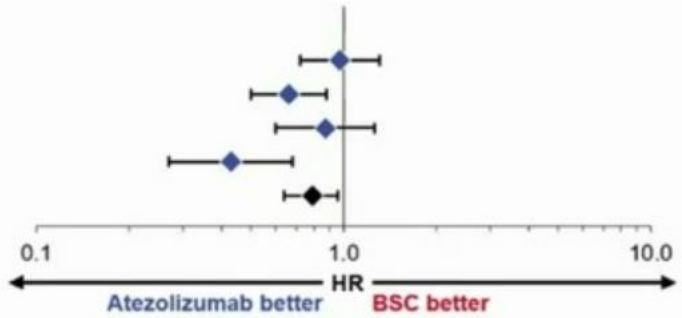
ESMO 2021

DFS by PD-L1 status[a]

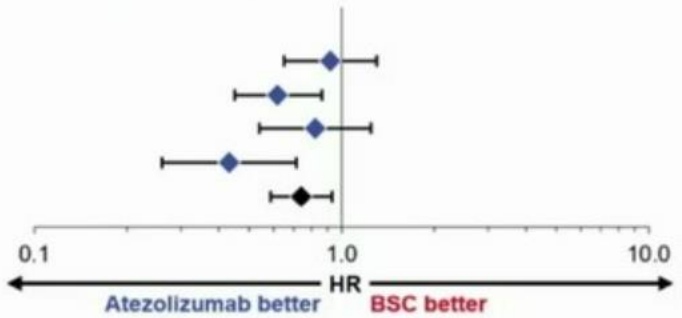
All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

2021 ESMO congress

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)



Subgroup *(excluding EGFR/ALK+)*[e]	n	HR (95% CI)[f,g]
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1-49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)



Clinical cutoff: 21 January 2021. [a] Per SP263 assay.
[b] Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. [d] 23 patients had unknown PD-L1 status as assessed by SP263. [e] Excluding patients with known *EGFR/ALK+* NSCLC. [f] Unstratified for all subgroups. [g] EGFR/ALK+ exclusion analyses were post hoc. [h] 21 patients had unknown PD-L1 status as assessed by SP263.

Felip et al. IMpower010 Relapse Patterns. https://bit.ly/3mNMSAi

Enriqueta Felip

IMpower010: sites of relapse and subsequent therapy from a Phase 3 study of atezolizumab vs best supportive care after adjuvant chemotherapy in stage IB-IIIA NSCLC

FDA approves atezolizumab as adjuvant treatment for non-small cell lung cancer

On October 15, 2021, the Food and Drug Administration approved atezolizumab (Tecentriq, Genentech, Inc.) for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.

Today, the FDA also approved the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.) as a companion diagnostic device to select patients with NSCLC for adjuvant treatment with Tecentriq.

Other immunotherapy trials

Trial names	Phase	Stage	Compound	Primary endpoint
PEARLS III NCT02504372	III	IB-IIIA	**Pembrolizumab for 1-year vs placebo** after resection and completion of standard adjuvant therapy if necessary	DFS and OS (overall and PDL1 ≥ 50%)
ANVIL NCT02595944	III	IB-IIIA	**Nivolumab for 1-year vs observation** after resection and completion of standard adjuvant therapy if necessary	DFS, OS
BR31 NCT02273375	III	IB-IIIA	**Durvalumab for 1-year vs placebo** after resection and completion of standard adjuvant therapy if necessary	DFS
NCT03130764	II	IB-IIIA	**Durvalumab for 1 year and tremelimumab for 4 doses** after surgery and after completed standard adjuvant therapy if necessary	Percentage of induced T-cell response
NCT03053856	II	IIIA (N2)	**Pembrolizumab for up to 24 months** after neoadjuvant CCRT followed by curative resection	DFS

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- Potential biomarkers

Study name	Study type	Published years	Number of patients	Disease stage	Main findings
PORT meta-analysis[1]	Meta-analysis	1998	2128	I–III	• PORT increase risk of death in stage I/II disease • The value of PORT in stage III/N2 was not clear
SEER[2,3]	Retrospective	2006	7465	II–III	• PORT was associated with better survival in patients with N2 nodal disease but not in patients with N0-1 nodal disease
Wang[4]	Retrospective	2011	221	pIIIA-N2	• PORT significantly prolonged OS and DFS • PORT prolonged locoregional recurrence-free survival and distant metastasis-free survival.
NCDB[5]	Retrospective	2015	4483	pN2	• PORT was associated with better 5 year-OS
Fu[6]	Retrospective	2021	1401	pIIIA-N2	• PORT significantly reduced the risk of LRR and improved OS in high-risk population (Heavy cigarette smoking history, clinical N2 status, and the number of positive lymph nodes >4)
PORT-C[7]	RCT	2021	394	pIIIA-N2	• PORT did not increase 3-year DFS and OS • PORT increased 3-year DFS and but no OS in per-protocol population
Lung ART[8]	RCT	2021	501	pN2	• PORT did not increase 3-year DFS • OS data was not mature

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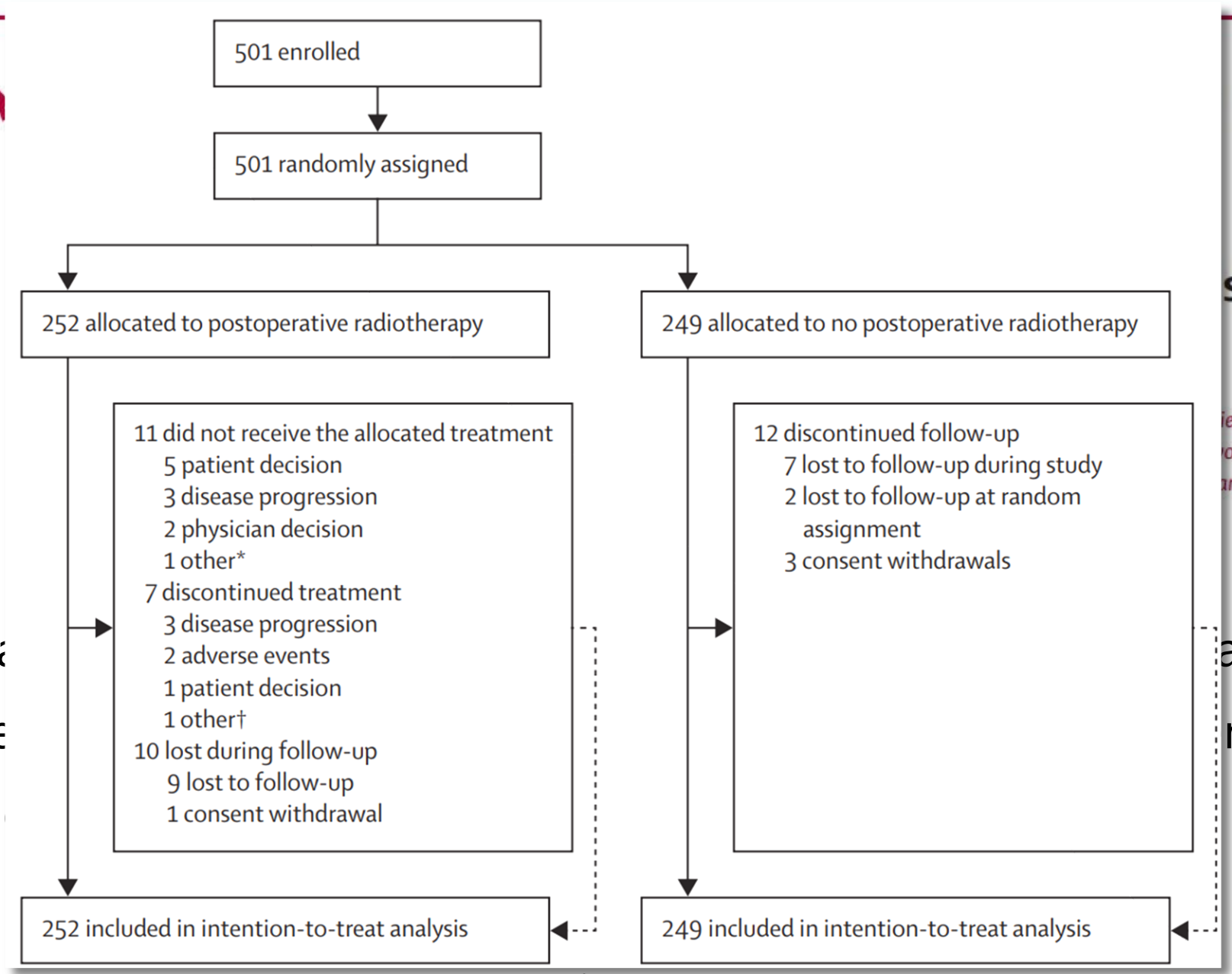
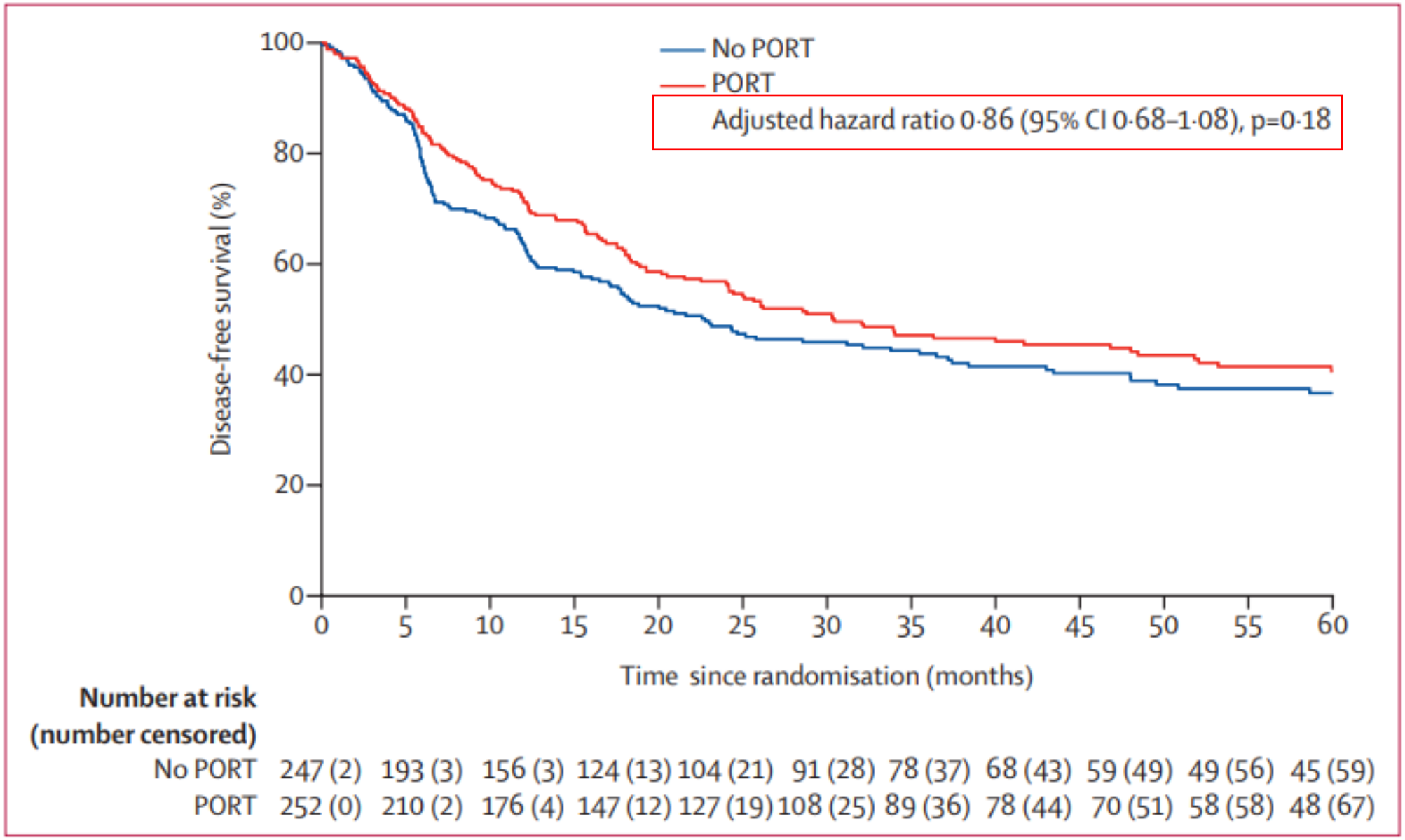


Lancet Oncol 2022; 23: 104–14



Lancet Oncol 2022; 23: 104–14

	PORT group (n=252)	Control group (n=249)
All disease-free survival events	144	152
Relapses and metastases	123 (85%)	144 (95%)
Mediastinal relapse	36 (25%)	70 (46%)
Brain metastasis	34 (24%)	27 (18%)
Extracranial metastasis	71 (49%)	71 (47%)
Death	21 (15%)	8 (5%)
Causes of death		
Cardiopulmonary	11 (8%)	0
Non-cancer related	0	1 (1%)
PORT toxicity	2 (1%)	0
Progression	1 (1%)	0
Second primary cancer	4 (3%)	2 (1%)
Vascular	0	1 (1%)
Unknown	3 (2%)	4 (3%)

Data are n (%), regarding the number of patients with event. Patients can have several different events at the same time. PORT=postoperative radiotherapy.

Table 3: **Disease-free survival events**

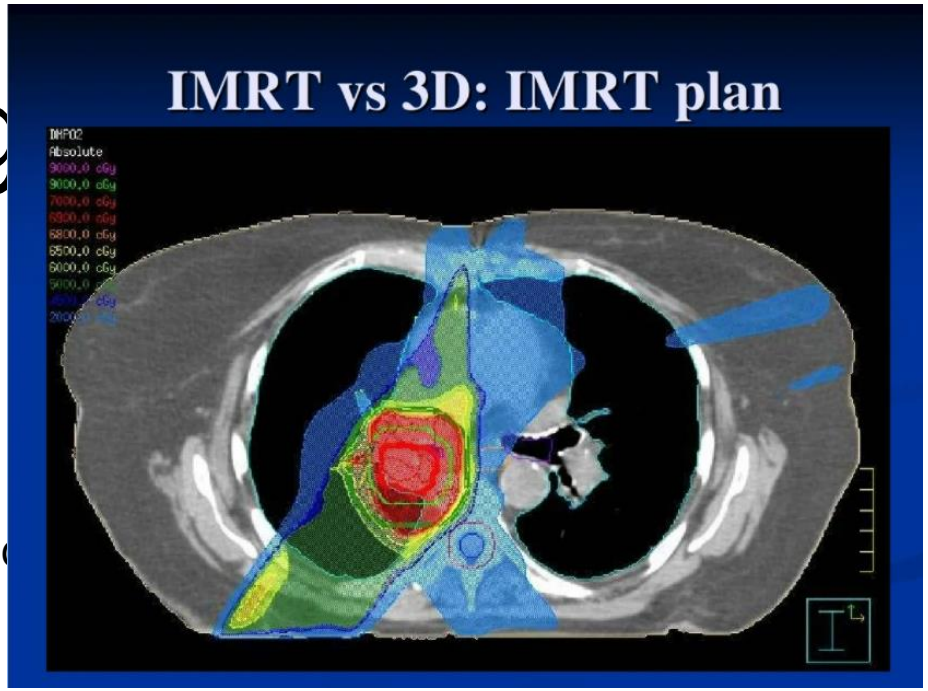
	PORT group (n=241)	Control group (n=246)
Deaths*	99 (41%)	102 (42%)
Progression of recurrence	68 (69%)	87 (85%)
Chemotherapy toxicity	1 (1%)	..
Radiotherapy toxicity	2 (2%)	..
Cardiopulmonary disease	16 (16%)	2 (2%)
Second primary cancer	5 (5%)	1 (1%)
Pulmonary infection	1 (1%)	..
Vascular	1 (1%)	1 (1%)
Other†	..	3 (3%)
Unknown	5 (5%)	8 (8%)
Adverse event, any grade‡	222 (92%)	200 (81%)
Early adverse events	215 (89%)	183 (74%)
Late adverse events	188 (78%)	153 (62%)
Adverse events, grade 3–5	60 (25%)	37 (15%)
Adverse events, grade 3 or 4	57 (24%)	37 (15%)
Early adverse events	28 (12%)	19 (8%)
Late adverse events§	36 (15%)	22 (9%)
Total late cardiac events	10 (4%)	5 (2%)
Cardiac ischaemia or infarction	3 (1%)	..
Total late thoracic events	28 (12%)	9 (4%)
Dyspnoea (thoracic)	7 (3%)	5 (2%)
Pneumonitis (thoracic)	9 (4%)	..

Data are n (%). Presented numbers are the numbers of patients with at least one event. *Percentages calculated from the total number of deaths. †The other causes of death here were one suicide, one myeloma chemotherapy toxicity, and one chronic endstage renal disease. ‡Percentages calculated from the total number of patients. §The most reported adverse events categories (more than 3%) and terms (more than two events) are shown.

Table 4: **Safety profile**

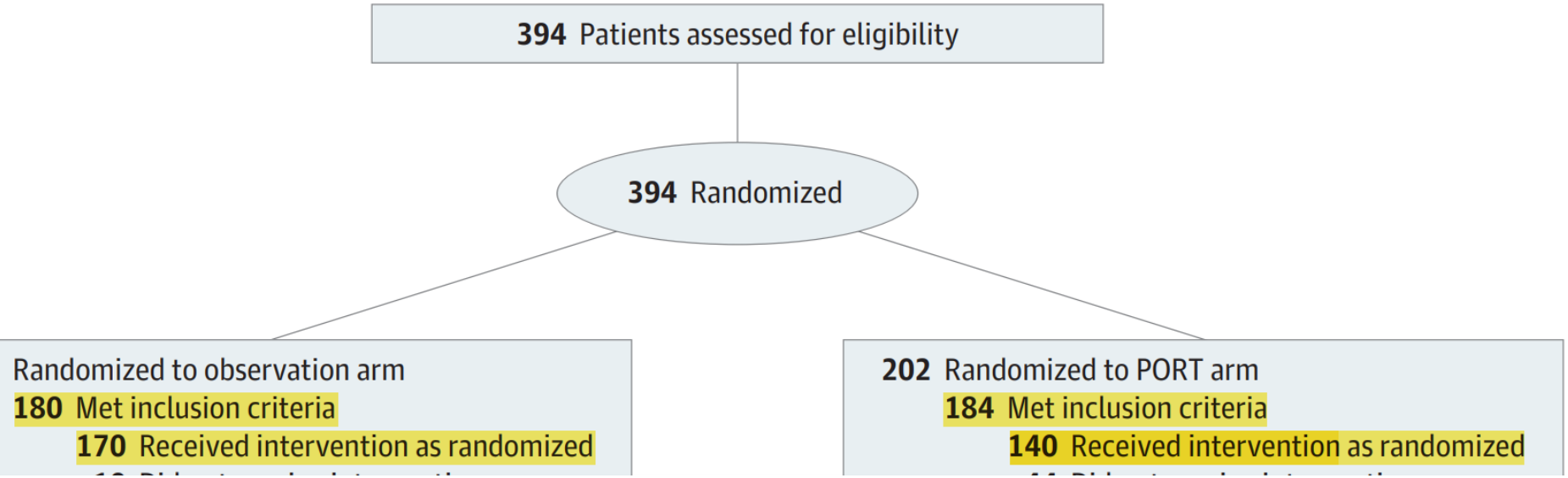
Lancet Oncol 2022; 23: 104–14

Clinical significance (Lung



- Most patients treated with 3D-conformal radiotherapy,
- Only 11% received intensity-modulated radiotherapy.
- A significant **reduction in mediastinal relapse** was reporte
  PORT)
- Does not translate into a significant difference in **DFS** (hazard ratio =0.85 [95% confidence interval: 0.67–1.07]; p = 0.16).
- Similarly, no significant difference was reported in **OS** (3-year OS 66.5% with PORT versus 68.5% with no PORT).
- Significant increase in **early and late grades 3 to 5 cardiopulmonary toxicity** with the delivery of PORT (7% and 20% in PORT versus 3.2% and 7.7% with no PORT, respectively

Lancet Oncol 2022; 23: 104–14
Journal of Thoracic Oncology Vol. 17 No. 2: 197–199



-
- **vival**

Outcome	mITT analysis HR (95% CI)	*P* value	PP analysis HR (95% CI)	*P* value	AT analysis HR (95% CI)	*P* value
DFS	0.84 (0.65-1.09)	.20	0.75 (0.57-1.00)	.05	0.73 (0.56-0.96)	.02
OS	1.02 (0.68-1.52)	.93	0.83 (0.53-1.30)	.41	0.72 (0.48-1.09)	.12
LRFS	0.71 (0.51-0.97)	.03	0.56 (0.39-0.80)	.002	0.52 (0.37-0.74)	<.001
DMFS	0.94 (0.72-1.22)	.62	0.85 (0.63-1.14)	.28	0.82 (0.62-1.08)	.15

- Similar number of deaths owing to progression as patients who did not receive PORT.

JAMA Oncol 2021 Vol. 7 Issue 8 Pages 1178-1185

Completetly Resected Stage III-N2

Table 1. Summary of Evidence to Support Whether PORT Should Be Considered in Completely Resected Stage III-N2 NSCLC

Clinical Feature	PORT?	Evidence
Persistent N2 disease after chemotherapy	Strongly consider	SAKK—Worse OS in patients with persistent N2 disease compared with patients with nodal downstaging to N0-1 after induction chemotherapy, suggesting a role for further consolidative therapies, such as PORT.[8]
Extensive mediastinal involvement	Consider	PORT-C—Improved DFS with PORT in patients with ≥4 lymph nodes compared with patients with 1-3 lymph nodes.[4] Matsuguma et al.[5]—Improved DFS with PORT in patients with multistation N2 disease compared with patients with single-station N2 disease.
Extracapsular extension	Unclear	Vanderbilt—ECE is associated with worse LRFS. Counterintuitively, PORT was associated with improved OS in patients with negative ECE but not in patients with positive ECE. This warrants further study.[10]
Presence of actionable mutations	Do not offer	ADAURA—Improved DFS with targeted therapies, such as osimertinib after surgery in EGFR-mutated mutated disease. The relative benefit of PORT may be lower and likely should not be offered.[9]

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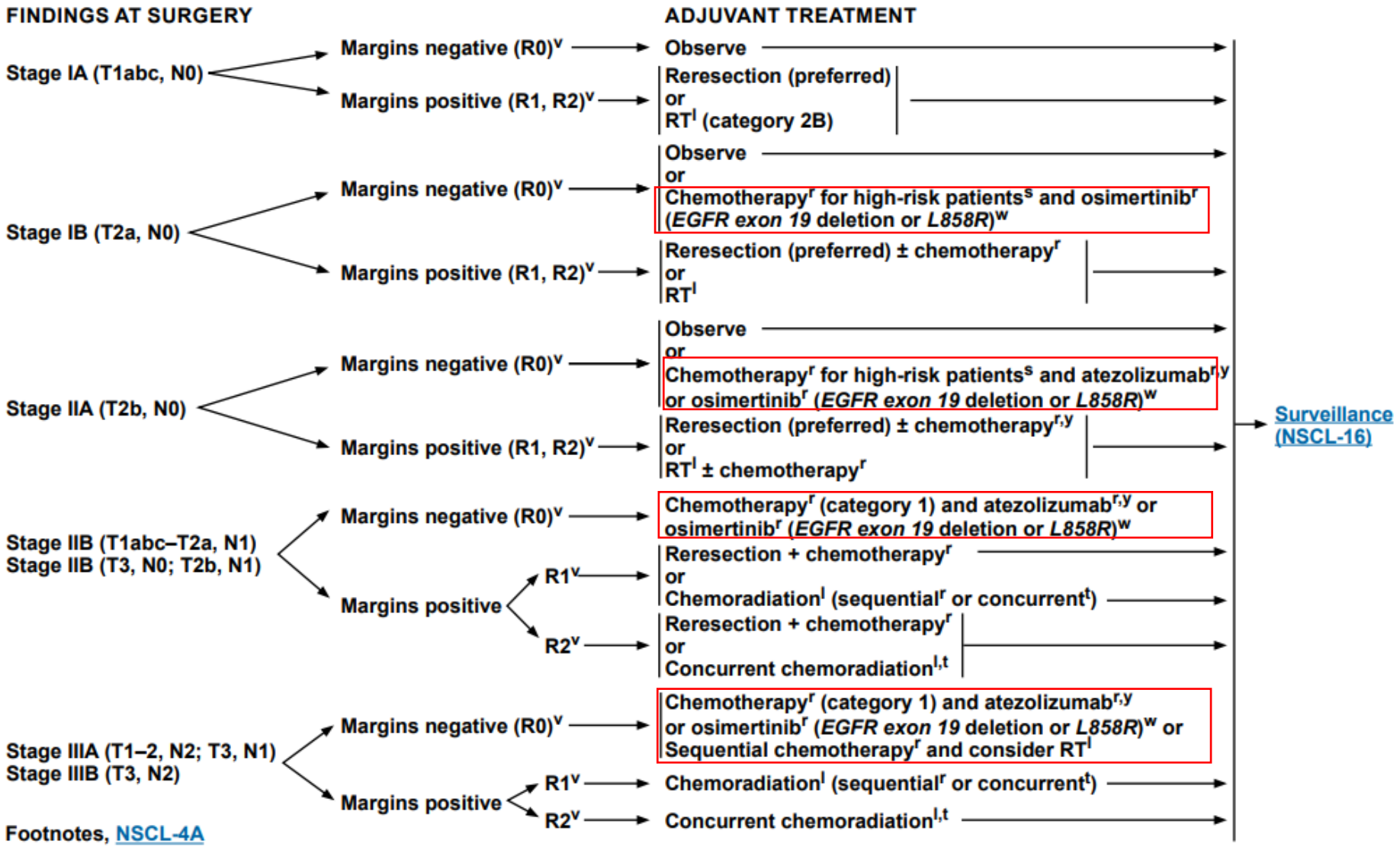
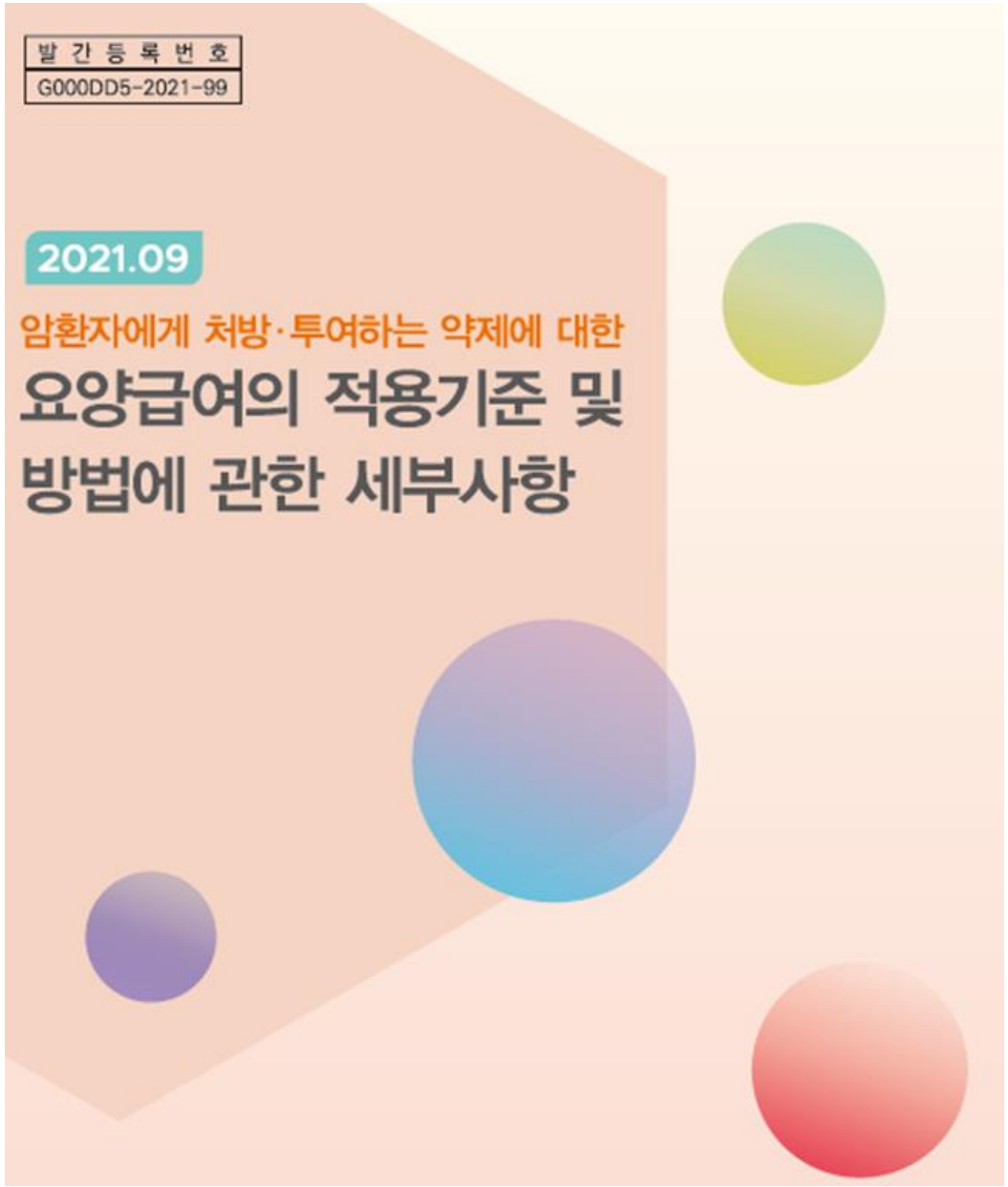
Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I-IIIA Completely

Treatment	Stage IB (3 < T ≤ 4 cm, N0M0)	Stage IIA-IIIA
Cisplatin chemotherapy	Not recommended for routine use	Recommended for all patients
Osimertinib	Strong recommendation, **EGFR (Ex19del or L858R)** mutations	Recommended, **EGFR (Ex19del or L858R)** mutations:
Atezolizumab	Not recommended for routine use	For all patients **PD-L1 ≥1%, EGFR (-),** after cisplatin-based chemotherapy

J Clin Oncol 2022 Pages JCO2200051



Footnotes, NSCL-4A



1. 선행화학요법(neoadjuvant)

- platinum은 cisplatin 또는 carboplatin을 의미함
- 선행화학요법(neoadjuvant)에 효과가 있는 요법의 경우 2.수술후보조요법(adjuvant)으로 연장투여 가능함. (선행화학요법과 수술후보조요법을 포함하여 4주기까지 인정)

(제2006-3호: 2006.4.1, 개정 제2006-6호: 2006.8.1, 개정 제2021-129호: 2021.5.1)

연번	항암요법	투여대상
1	paclitaxel + platinum	stage III
2	docetaxel + platinum	
3	gemcitabine + platinum	
4	irinotecan + platinum	
5	pemetrexed + platinum (개정 제2021-129호: 2021.5.1)	stage III(비편평상피세포)

2. 수술후보조요법(adjuvant)

- platinum은 cisplatin 또는 carboplatin을 의미함

연번	항암요법	투여대상
1	paclitaxel + platinum (개정 제2021-129호: 2021.5.1)	stage II~IIIB
2	vinorelbine + platinum (개정 제2021-129호: 2021.5.1)	
3	pemetrexed + platinum (개정 제2021-129호: 2021.5.1)	stage II~IIIB(비편평상피세포)

Considerations-Osimertinib

- ADAURA study showed evident clinical benefit in DFS
- But, three years of treatment, should it be longer?

-Patients **cost burden,** not reimbursed in Korea

-Despite low incidence of high grade AE, **AE can still occur**

- **OS advantage** to be confirmed

-Delaying disease progression without impacting OS?

- If recur, can osimertinib be **retreated**?

Journal of Thoracic Oncology Vol. 16 No. 3: 368-370

Considerations-immunotherapy

- In **EGFR wild type, stage IIIA, high PD-L1 expression patients**, adjuvant atezolizumab can be effective.
- **Impact on OS** should be confirmed.
- **Neo-adjuvant or adjuvant use of ICI?**

Strengths:

-profuse neoantigen presentenation->increased immunogenicity

-reduce tumor bulk before surgery

Limitations:

-possibe delay of resection due to AEs,

-frequent open thoracic operation due to tumor inflammation

Or maybe both?

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Molecular biomarkers

- Postoperative tumor recurrence after complete resection is focused on **finding macroscopic relapse by radiological examination** such as computed tomography(CT).
- Tumor recurrence hard to distinguish from **postoperative changes of normal tissues**
- Poor differentiation, lymphovascular invasion, and large tumor burden, etc. are associated with poor outcomes in completely resected NSCLC patients
- Due to advents of new anticancer modalities (**targeted therapy and ICI**), new biomarkers are necessary.

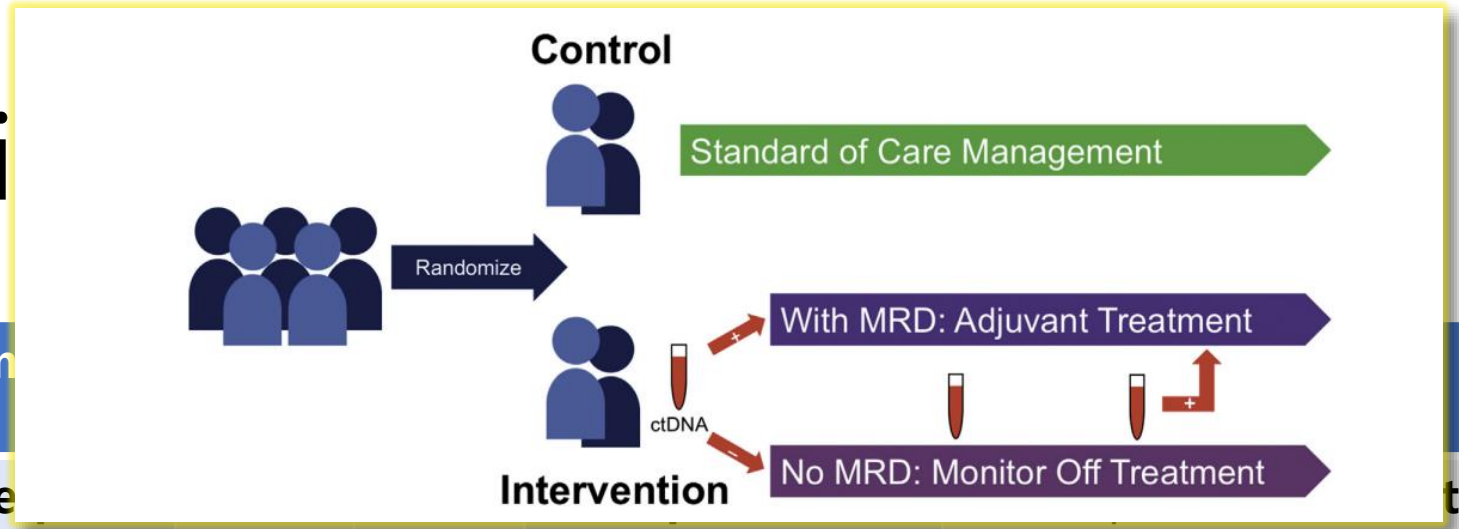
Lim JU, Yeo CD. Update onadjuvant therapy in completely resected NSCLCpatients. Thorac Cancer. 2022;13:277–83.

CtDNA

- Short DNA sequences shed by tumor cells, distinguished on the presence of **novel mutations** not found in normal tissue
- EGFR, KRAS, BRAF, TP53, V600E, etc.
- Focused on **detecting minimal residual disease**
- TheCAncer personalized profiling by deep sequencing **(CAPP-seq)** technique utilized complementary oligonucleotides to target 139 cancer-associated mutations
- Personalized, tumor-informed assay such as **Signatera**, and **whole exome sequencing** (WES) method are also used

Journal of Thoracic Oncology Vol. 14 No. 1: 16-24

Cli of ctDNA



Platform	
CAPP-Se	tDNA negative after **definitive therapy** and did not have recurrence 21–
CAPP-Se	ecurrence, with a (-) had
Single nucleotid variation	nt had of 70 days currence

Strengths	• **Non-invasive**, also can be measured serially • Can detect disease relapse **ahead of radiologic diagnosis** • Can distinguish **types of mutation**
Limitations	• High cost • Not standardized (cutoff for **allele frequency not set**) • **False positives** (some mutations detectable in benign diseases) • Should be complemented by **tissue biopsy**

nature COMMUNICATIONS

ARTICLE

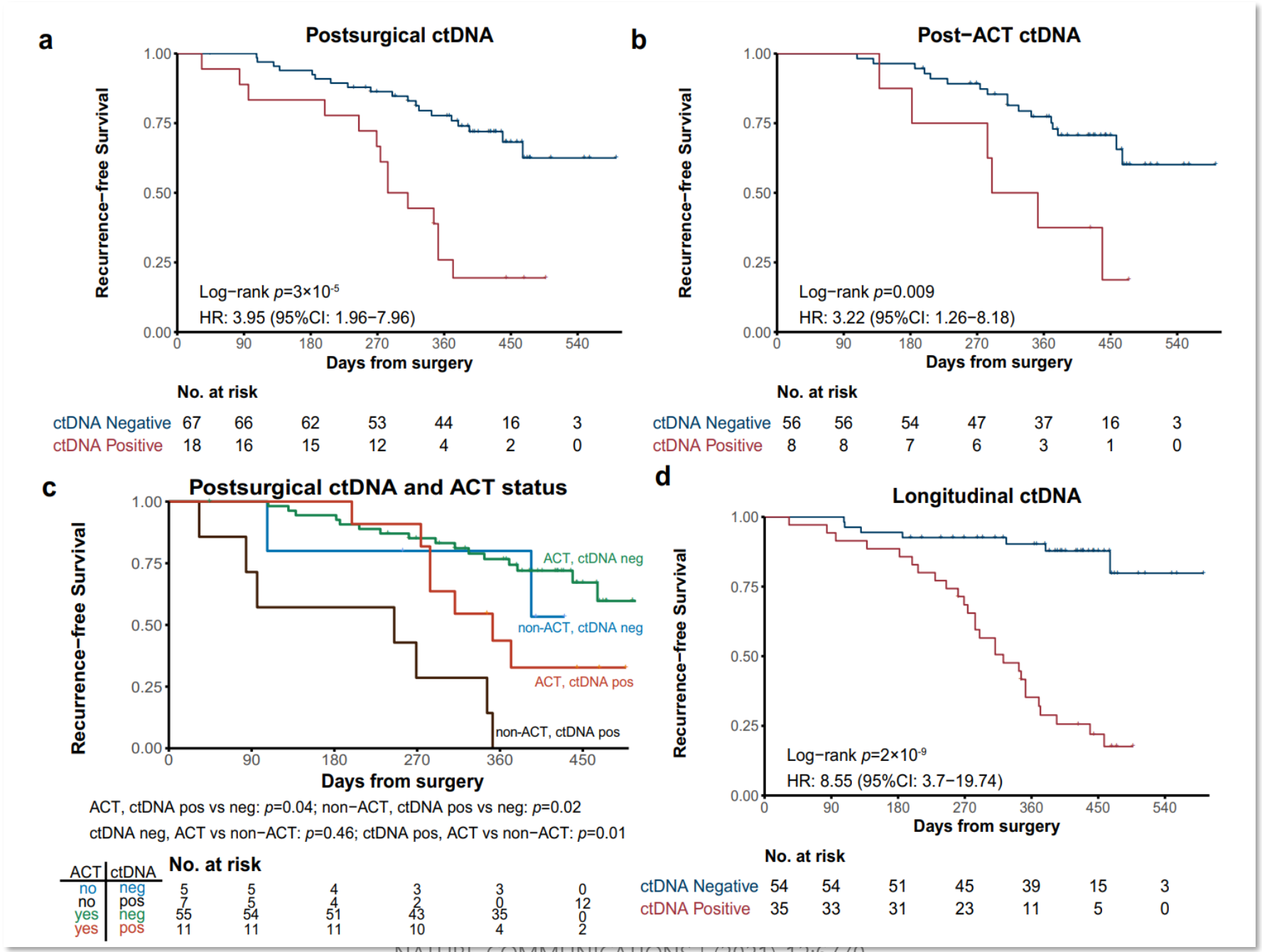
https://doi.org/10.1038/s41467-021-27022-z OPEN

Check for updates

Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC

Bin Qiu[1,2,4], Wei Guo[1,2,4], Fan Zhang[1], Fang Lv[1], Ying Ji[1], Yue Peng[1], Xiaoxi Chen[3], Hua Bao[3], Yang Xu[3], Yang Shao[3], Fengwei Tan[1,2], Qi Xue[1,2], Shugeng Gao[1,2]✉ & Jie He[1]

- In stage II-III patients, the **postsurgical ctDNA positive group benefit from adjuvant chemotherapy**, while ctDNA negative patients have a low risk of relapse regardless of whether or not ACT is administered.


a
Postsurgical ctDNA
Recurrence−free Survival
1.00
0.75
0.50
0.25
0.00
0
90
180
270
360
450
540
Days from surgery
Log−rank p=3×10-5
HR: 3.95 (95%CI: 1.96−7.96)
No. at risk
ctDNA Negative 67 66 62 53 44 16 3
ctDNA Positive 18 16 15 12 4 2 0
b
Post−ACT ctDNA
Recurrence−free Survival
Log−rank p=0.009
HR: 3.22 (95%CI: 1.26−8.18)
Days from surgery
No. at risk
ctDNA Negative 56 56 54 47 37 16 3
ctDNA Positive 8 8 7 6 3 1 0
c
Postsurgical ctDNA and ACT status
Recurrence−free Survival
ACT, ctDNA neg
non-ACT, ctDNA neg
ACT, ctDNA pos
non-ACT, ctDNA pos
Days from surgery
ACT, ctDNA pos vs neg: p=0.04; non−ACT, ctDNA pos vs neg: p=0.02
ctDNA neg, ACT vs non−ACT: p=0.46; ctDNA pos, ACT vs non−ACT: p=0.01
No. at risk
ACT ctDNA
no neg 5 5 4 3 3 0
no pos 7 5 4 2 0 12
yes neg 55 54 51 43 35 0
yes pos 11 11 11 10 4 2
d
Longitudinal ctDNA
Recurrence−free Survival
Log−rank p=2×10-9
HR: 8.55 (95%CI: 3.7−19.74)
Days from surgery
No. at risk
ctDNA Negative 54 54 51 45 39 15 3
ctDNA Positive 35 33 31 23 11 5 0

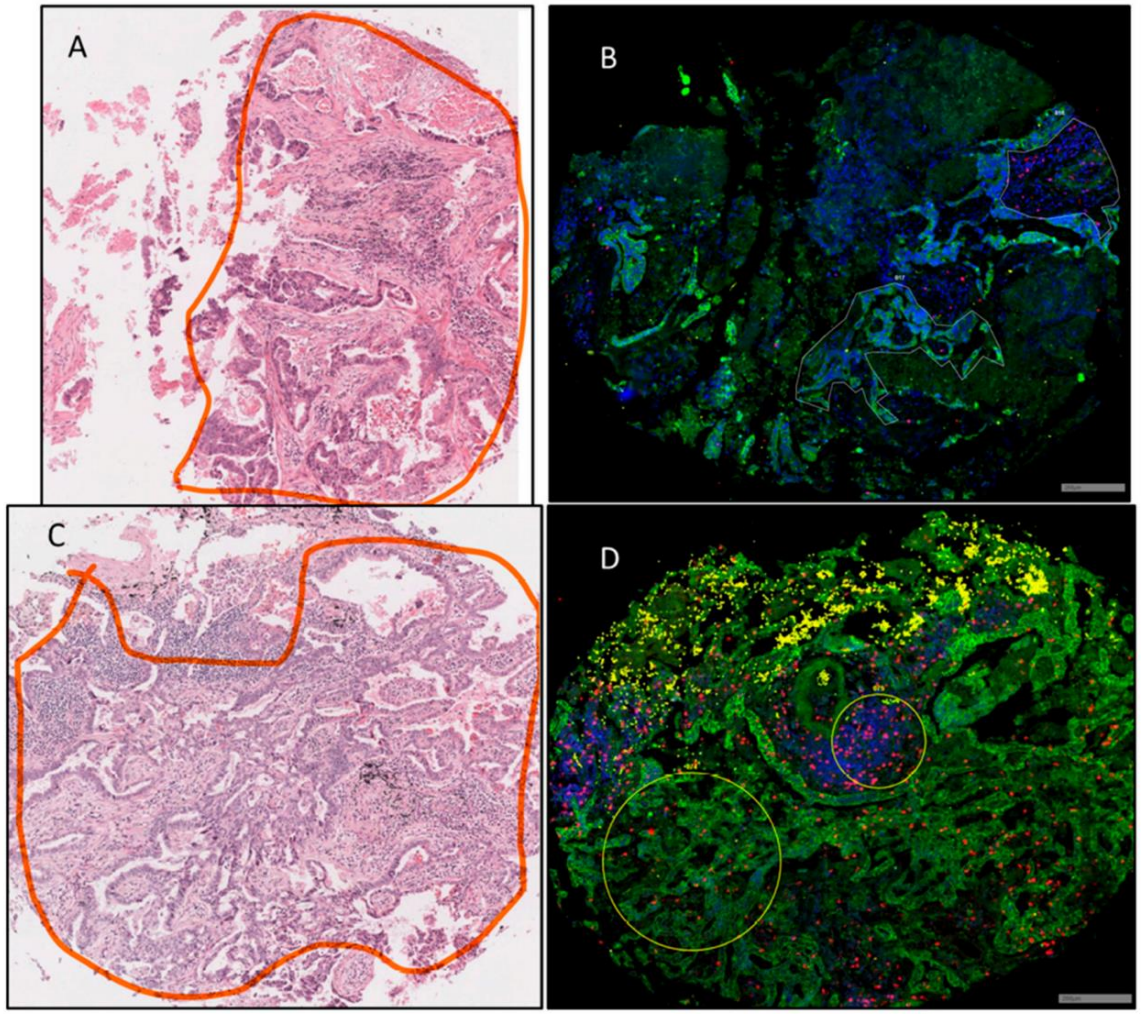
Potential biomarkers	Patients	Outcomes
CtDNA	77 NSCLC patients who underwent complete resection. Furthermore,.	pre-operative ctDNA-positivity was predictive of recurrence-free survival (RFS) and OS **postoperative detection of ctDNA** is likely to be associated with early relapse
Postoperative circulating tumor cells as well as tissue AXL overexpression		Considered as potential prognostic biomarkers in patients who undergo lung adenocarcinoma resection.
PD-L1 expression	A meta-analysis including 15 studies	PD-L1 expression was predictive of shorter PFS and OS in an early stage resected NSCLC population, of which a significant proportion of **stage III cancer** patients were present
Tumoral PD-L1 expression in combination with (NLR)	83 patients who underwent complete resection of stage I Sqcc	independently associated with RFS in a retrospective analysis
Cytokeratin 19 fragment (CYFRA21-1) and human epididymis protein 4 (HE4)		Serial measurements have shown modest sensitivity in detecting relapse after complete resection; however, the specificity was low.

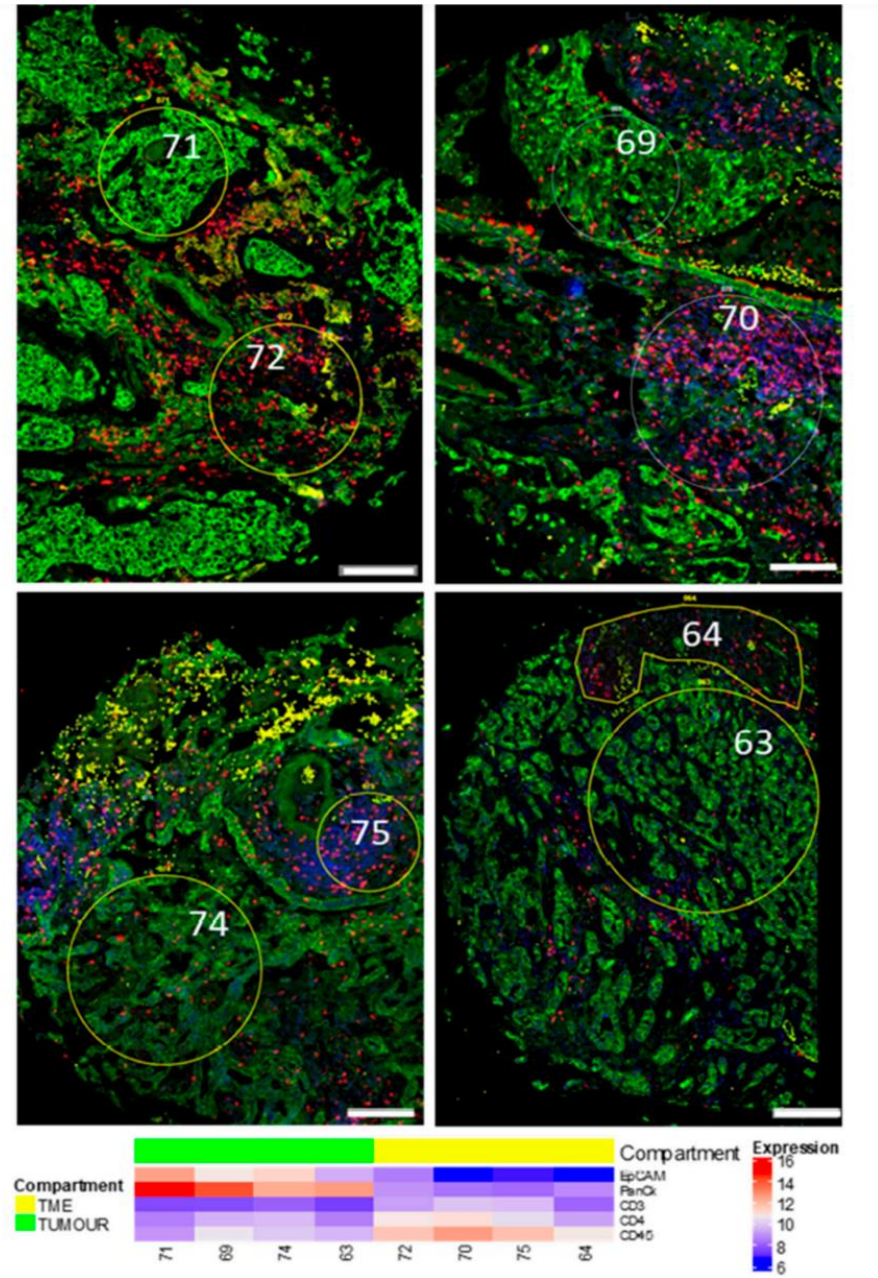
Lim JU, Yeo CD. Update onadjuvant therapy in completely resected NSCLCpatients. Thorac Cancer. 2022;13:277–83.

Potential biomarkers	Patients	Outcomes
Anaplastic lymphoma kinase(ALK) rearrangement	Patients with completely resected IA adenocarcinoma	associated with **poor DFS** and frequent **regional lymph node metastasis**
C-MET protein overexpression from tissue samples	patients undergoing adjuvant treatment.	showing **correlations with OS** and potential values as a biomarker
Next-generation sequencing (NGS)	230 patients with resected stage I–II lung adenocarcinoma	After median follow-up time of 49 months, **recurrence was observed in 64 patients (27.8%).** CTNNB1 mutation and fusion genes (ALK, ROS1, RET) detected from targeted NGS were negative prognostic factors for recurrence.
Neo-antigen load	91 paired resected stage II/III NSCLC along with matching normal tissues	An analysis of revealed that **higher neoantigen load** (>2 neoantigens/Mb) was associated with better DFS in squamous cell carcinoma patients (p = 0.021)
A 14-gene expression assay using quantitative PCR	performed on paraffin-embedded tissue samples	assisted in identifying subjects with localized nonsquamous NSCLC at higher risk of poor outcome after resection
Immune cell signatures	specimens obtained from 384 NSCLC patients who underwent complete re-section	Immune signatures were evaluated for predictive value

Lim JU, Yeo CD. Update onadjuvant therapy in completely resected NSCLCpatients. Thorac Cancer. 2022;13:277–83.

Digital Spatial Profiling





Cancers 2020, 12, 3551; doi:10.3390/cancers12123551

Summary

- Unmet needs in resectable NSCLC
- **Osimertinib** is associated with improved DFS in resectable NSCLC with **EGFR mutation**
- **Atezolizumab** in combination with platinum chemotherapy can improve outcomes in resectable NSCLC **(PD-L1 ≥1%) without EGFR mutations**
- **PORT** should not be routine, can be considered in certain postoperative findings
- Potential biomarkers, including ctDNA can be significant

Thank you for your attention!