Radioterapia neoadiuvante e adiuvante nel NSCLC III stadio: ha ancora un ruolo?

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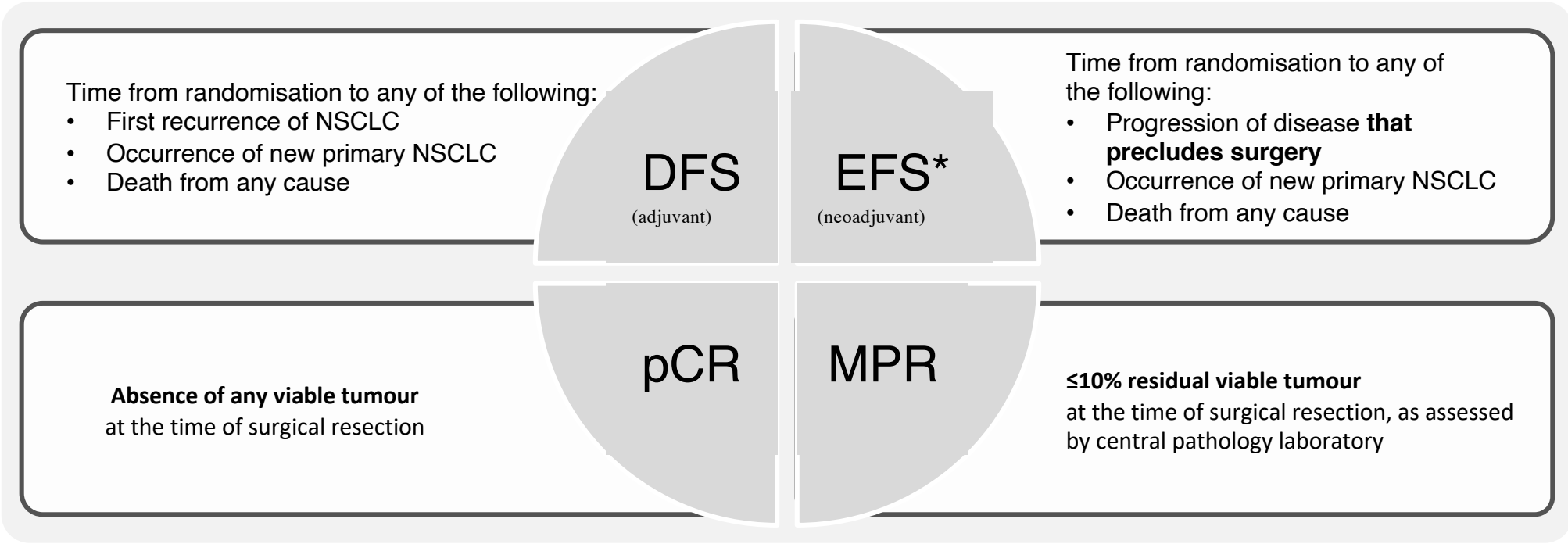
The most commonly used endpoints in phase III clinical trials for the early-stage setting



Definitions from IMpower030

*Note that EFS is functionally the same as DFS but is used instead for neoadjuvant studies because patients are technically not disease-free until they have undergone surgery

1. AEGEAN; 2. CheckMate 816; 3. IMpower030; 4. CheckMate 77T
5. KEYNOTE-671; 6. ANVIL; 7. IMpower010; 8. PEARLS; 9. BR31

DFS and EFS are accepted endpoints by the FDA and EMA*

FDA U.S. FOOD & DRUG ADMINISTRATION

DFS and EFS are listed as surrogate endpoints that were the basis of drug approvals or licensure by the FDA[1]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

DFS and EFS are also accepted endpoints by the EMA[2]

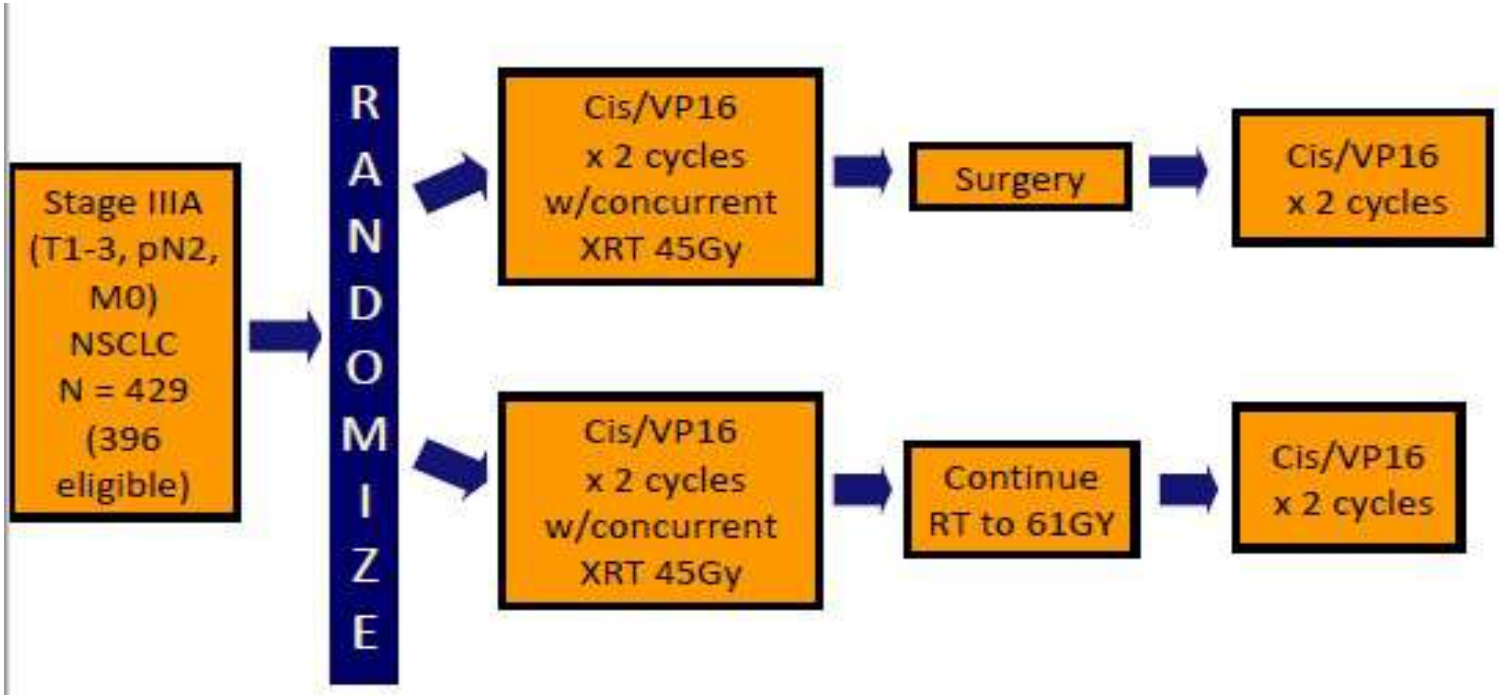
A meta-analysis found DFS to be a valid surrogate endpoint for OS with adjuvant chemotherapy and radiotherapy in resectable early-stage NSCLC[3]. **Data from phase III studies will provide further evidence on the value of DFS and EFS as surrogate endpoints for OS in CIT studies of NSCLC**

*Note that EFS is functionally the same as DFS but is used instead for neoadjuvant studies because patients are technically not disease-free until they have undergone surgery

1. FDA. Table of surrogate endpoints that were the basis of drug approval or licensure 2020
2. EMA. Guideline on the clinical evaluation of anticancer 6 medicinal products 2019
3. Mauguen, et al. Lancet Oncol 2013

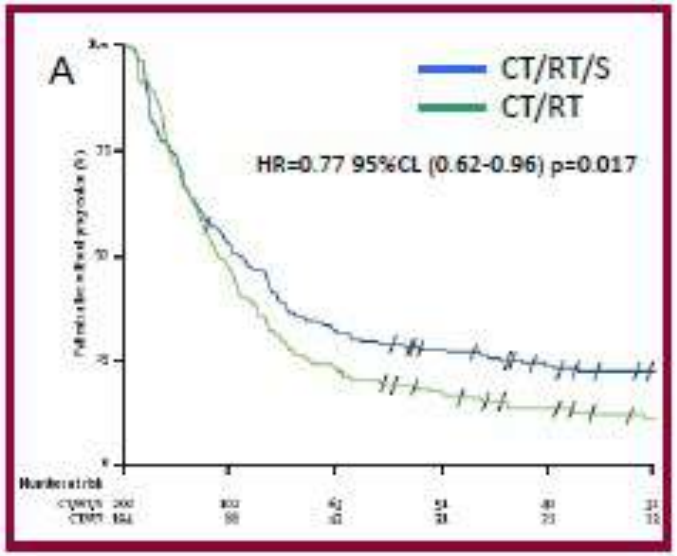
Role of neo-adjuvant radiotherapy for resectable NSCLC

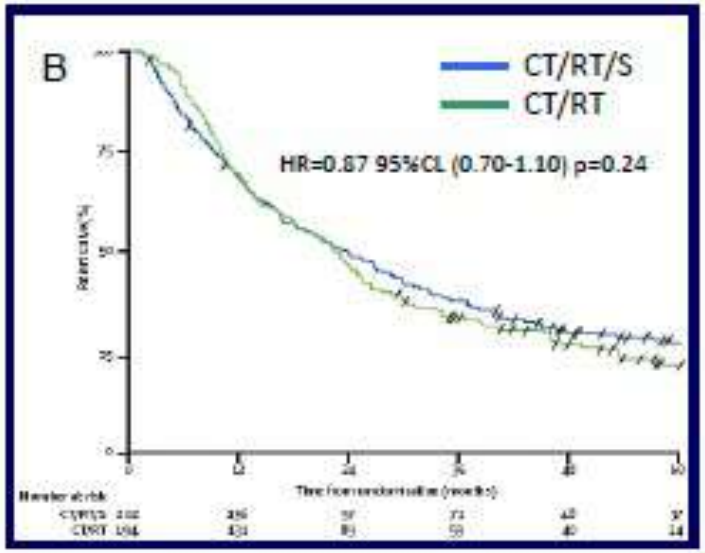
INT 0139 CHT-RT→Surgery (trimodality)



Albain et al, Lancet 2009

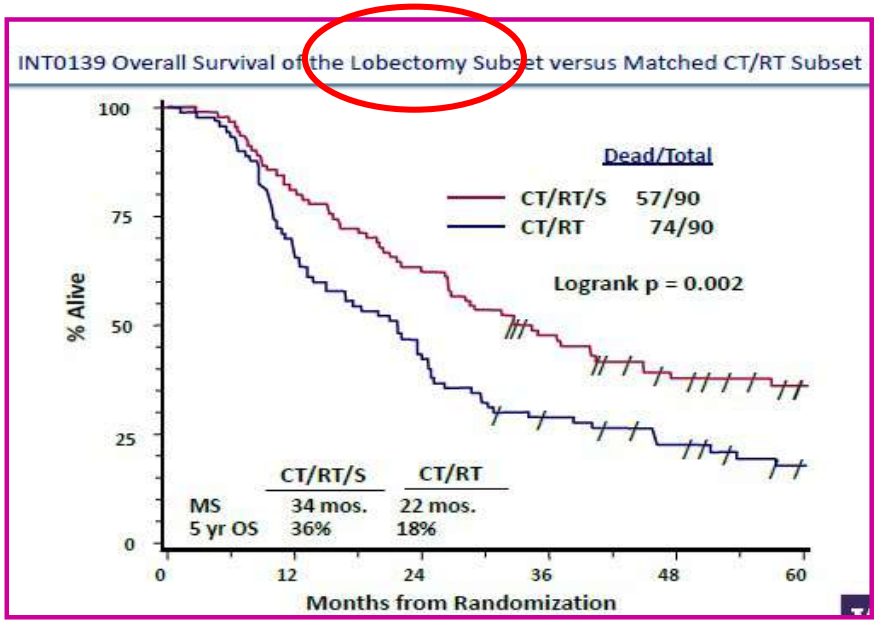
INT 0139 CHT-RT→Surgery (trimodality)





Progression-free survival (A) and overall survival (B) of intention-to-treat population
CT/RT/S=chemotherapy plus radiotherapy followed by surgery (group 1,n=202).
CT/RT=chemotherapy plus radiotherapy (group 2, n=194).
median follow-up for all patients was 22·5 months (range 0·9–125·1)

INT 0139 CHT-RT→Surgery (trimodality)



- All but 1 postoperative death followed a pneumonectomy
- hypothesized survival advantage on CT/RT/S if lobectomy performed
- Trimodality therapy should not be used to "convert" a marginally resectable patient to resectable
- Absolute contraindication if patient requires a right pneumonectomy

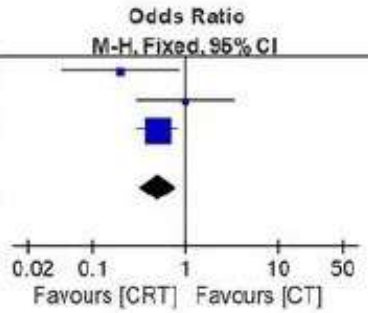
This approach only applies to resectable patients.
Lobectomy has to be planned from the start.

Metaanalysis Induction Treatment for Resectable Stage IIIa N2
Chen Y World J Surg Oncol 2018

Tumor response

Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Girard et al.	8	14	27	31	13.8%	0.20 [0.04, 0.88]
Katakami et al.	7	28	7	28	10.1%	1.00 [0.30, 3.35]
Pless et al.	50	115	71	117	76.2%	0.50 [0.30, 0.84]
Total (95% CI)		**157**		**176**	**100.0%**	**0.51 [0.32, 0.80]**
Total events	65		105			

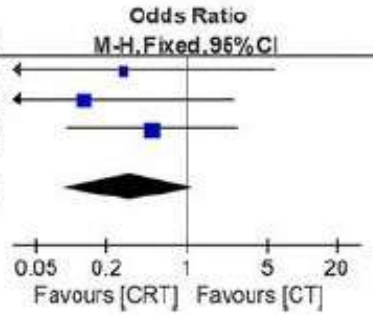
Heterogeneity: $Chi^2 = 2.75$, $df = 2$ ($P = 0.25$); $I^2 = 27\%$
Test for overall effect: $Z = 2.93$ ($P = 0.003$)



Pathological complete response

Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Girard et al.	0	14	3	31	22.7%	0.28 [0.01, 5.81]
Katakami et al.	0	28	3	28	36.2%	0.13 [0.01, 2.60]
Pless et al.	2	115	4	117	41.0%	0.50 [0.09, 2.78]
Total (95% CI)		**157**		**176**	**100.0%**	**0.32 [0.09, 1.16]**
Total events	2		10			

Heterogeneity: $Chi^2 = 0.63$, $df = 2$ ($P = 0.73$); $I^2 = 0\%$
Test for overall effect: $Z = 1.73$ ($P = 0.08$)

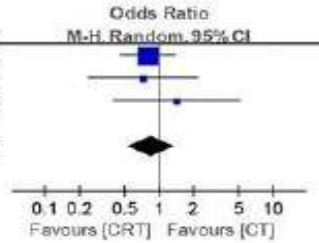


Metaanalysis Induction Treatment for Resectable Stage IIIa N2
Chen Y World J Surg Oncol 2018

PFS at 2-year

Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Random, 95% CI
Pless et al.	31	115	37	117	68.9%	0.80 [0.45, 1.41]
Katakami et al.	8	29	10	29	17.7%	0.72 [0.24, 2.21]
Girard et al.	6	14	11	32	13.4%	1.43 [0.40, 5.18]
Total (95% CI)		158		178	100.0%	0.85 [0.53, 1.36]
Total events	45		58			

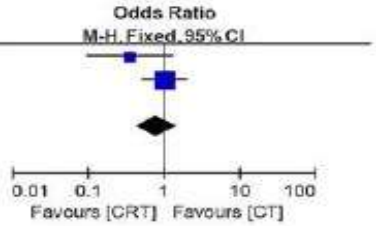
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)



PFS at 4-year

Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Katakami et al.	4	29	9	29	33.0%	0.36 [0.10, 1.33]
Pless et al.	19	115	19	117	67.0%	1.02 [0.51, 2.05]
Total (95% CI)		144		146	100.0%	0.80 [0.44, 1.47]
Total events	23		28			

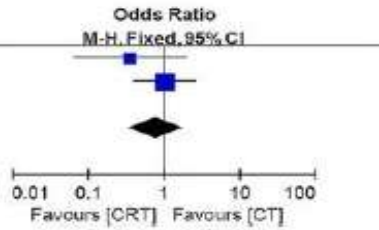
Heterogeneity: Chi² = 1.93, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 0.72 (P = 0.47)



PFS at 6-year

Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Katakami et al.	2	29	5	29	36.1%	0.36 [0.06, 2.00]
Pless et al.	9	115	9	117	63.9%	1.02 [0.39, 2.67]
Total (95% CI)		144		146	100.0%	0.78 [0.34, 1.78]
Total events	11		14			

Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%
Test for overall effect: Z = 0.59 (P = 0.55)

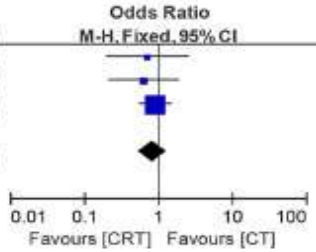


Metaanalysis Induction Treatment for Resectable Stage IIIa N2
Chen Y World J Surg Oncol 2018

OS at 2-yeat

Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Girard et al.	8	14	21	32	12.5%	0.70 [0.19, 2.53]
Katakami et al.	18	29	21	29	18.1%	0.62 [0.21, 1.89]
Pless et al.	53	115	57	117	69.4%	0.90 [0.54, 1.51]
Total (95% CI)		**158**		**178**	**100.0%**	**0.82 [0.53, 1.28]**
Total events	79		99			

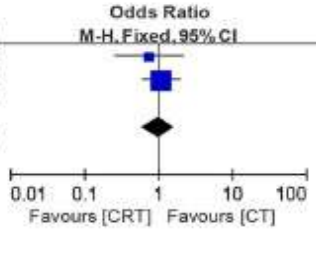
Heterogeneity: Chi² = 0.42, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)



OS at 4-year

Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Katakami et al.	9	29	11	29	27.3%	0.74 [0.25, 2.18]
Pless et al.	28	115	27	117	72.7%	1.07 [0.59, 1.97]
Total (95% CI)		**144**		**146**	**100.0%**	**0.98 [0.58, 1.66]**
Total events	37		38			

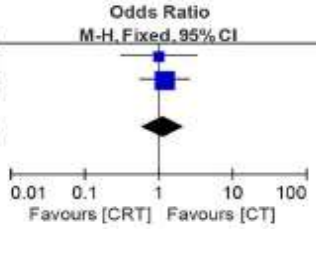
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)



OS at 6-year

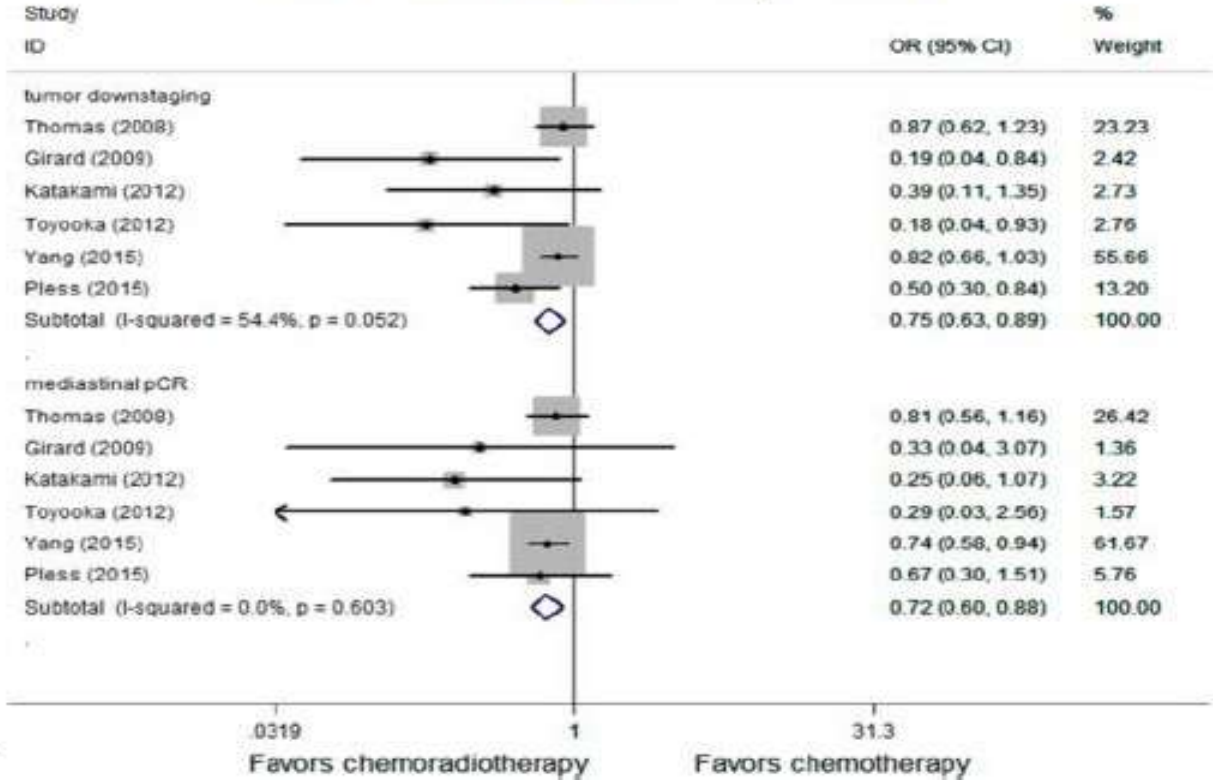
Study or Subgroup	CT Events	CT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Katakami et al.	7	29	7	29	32.2%	1.00 [0.30, 3.33]
Pless et al.	15	115	13	117	67.8%	1.20 [0.54, 2.65]
Total (95% CI)		**144**		**146**	**100.0%**	**1.14 [0.59, 2.20]**
Total events	22		20			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.71)



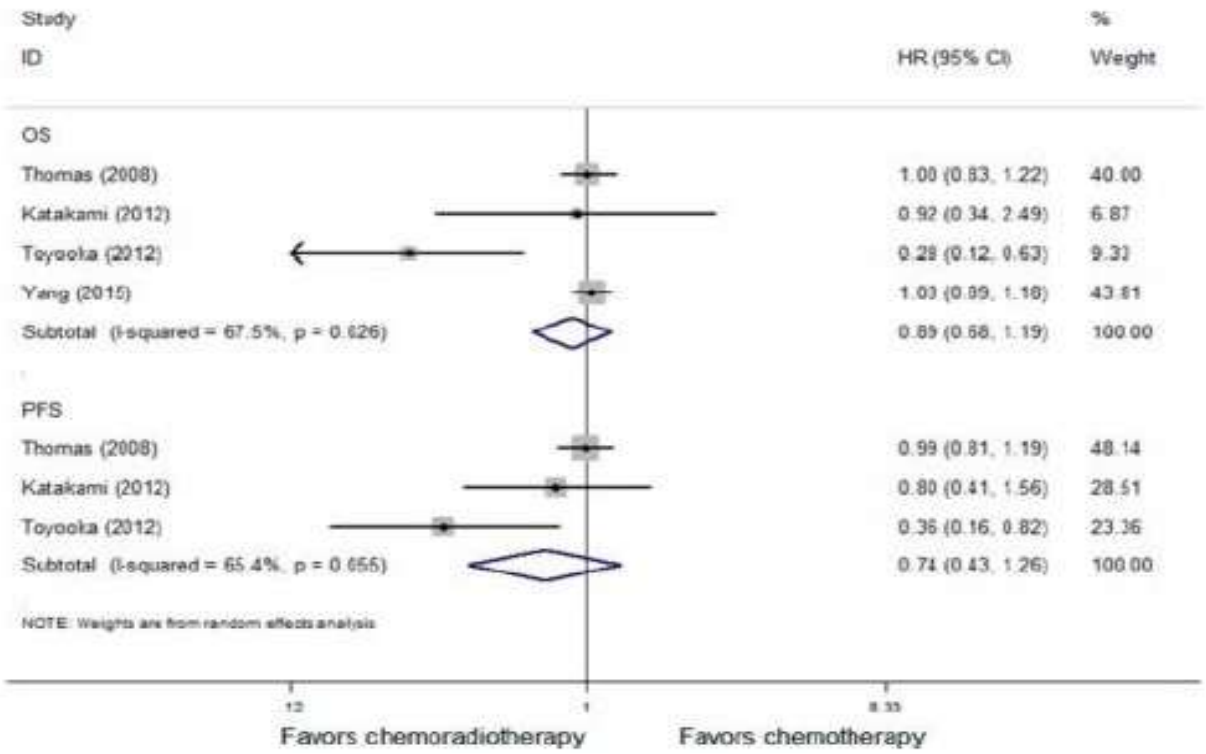
A metaanalysis of induction chemoRT or chemo for stage III NSCLC : Tumor response

Guo SX et al Sci Rep 2016



A metaanalysis of induction chemoRT or chemo for stage III NSCLC : Survival, PFS (5 Year data)

Guo SX et al Sci Rep 2016



Role of neo-adjuvant immunotherapy for resectable NSCLC

Clinical trials using neoadjuvant ICI-mono or dual therapy

Registration #	Trial & Stage	Neoadjuvant Therapy	N (Plan)	N (Reported)	Delay of Surgery (%)	Failure to Surgery (%)	R0 Resection (%)	TRAE (≥G3) (%)	MPR (%)	pCR (%)	Survival	Status	Ref.
NCT02259621	Johns Hopkins Univ. (p2) IB (>4 cm) to IIIA	nivolumab (twice)	30	22	0	0	95	Preope: 4.5	45	15	Median RFS: NR 18 m RFS: 73%	On going	[31]
NCT02927301	LCMC3 (p2) IB to IIIA, IIIB (T3N2, T4 (size))	atezolizumab (twice)	180	181	12	12	92	Preope: 6 Postope: 14	21	7	1 y DFS: 85% 1 y OS: 95%	On going	[32]
NCT02994576	PRINCEPS (p2) IA (≥2 cm) to IIIA(non-N2)	atezolizumab (once)	60	30	0	0	97	0	0	No data	No data	On going	[29]
NCT03030131	IONESCO (p2) IB to IIIA	durvalumab (3 times)	81	46	No data	0	90	ICI-related: 0 (Death:9)	No data	No data	Median OS/DFS: NR/NR 18 m OS/DFS: 89%/70%	Terminated (mortality *)	[33]
NCT03158129	NEOSTAR (p2) I to IIIA	nivolumab (3 times) or nivolumab (3 times) + ipilimumab	44	44	22	Nivo: 4 N + I: 19	100	Nivo: 13 N + I: 10	Nivo: 22 N + I: 38	Nivo: 9 N + I: 29	Median OS/RFS: NR/NR	On going	[30]

#, number; p2, phase 2; Nivo, nivolumab; R0 resection, complete resection; TRAE, treatment-related adverse event; MPR, major pathologic response; pCR, pathological complete response; RFS, recurrence-free survival; OS, overall survival; DFS, disease-free survival; NR, not reached; N + I, nivolumab + ipilimumab; *, an excess in 90-day postoperative mortality (4 deaths, 9%).

Completed trials

TABLE 1 | The results of completed clinical trials of neoadjuvant therapy with ICIs for resectable NSCLC.

Clinical trial	Phase	Stage	Intervention used	Sample size	Primary endpoint	Primary outcomes
CheckMate 159	I	I–IIA	Nivolumab	22	Safety and feasibility	MPR: 45%, pCR: 10%
LCMC3	II	IB–IIA	Atezolizumab	101	MPR	MPR: 18%, pCR: 5%
Li et al. (13)	II	IA–IIB	Sintilimab	40	Safety	MPR: 40.5%, pCR: 16.2%
Li et al. ChiCTR-OIC-17013726	IB	IA–IIA	Sintilimab	22	Drug-related adverse event; surgery complications; no-delay surgery rate	MPR: 45.5%, pCR: 18.2%
NADIM	II	IIIA	Nivolumab + chemotherapy	46	PFS at 24 months	MPR: 83%, pCR: 71%
NEOSTAR	II	I–IIIA	Nivolumab vs. nivolumab + ipilimumab	44	MPR	MPR: 24%, pCR: 18%

NSCLC, non-small cell lung cancer; MPR, major pathologic response; pCR, pathologic complete response; ICIs, immune checkpoint inhibitors; PFS, progression-free survival.

Phase I-II , single arm, small simple size

Safety was good (Neostar: surgey related mortality 3%, postoperative complications rate 21% and overall resection rate comparable to neoadjuvant chemotherapy)

MPR was low and unconfirmed

Bai, Front Oncol, 2020

Role of adjuvant radiotherapy for resectable NSCLC

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

Postoperative radiotherapy for non-small cell lung cancer

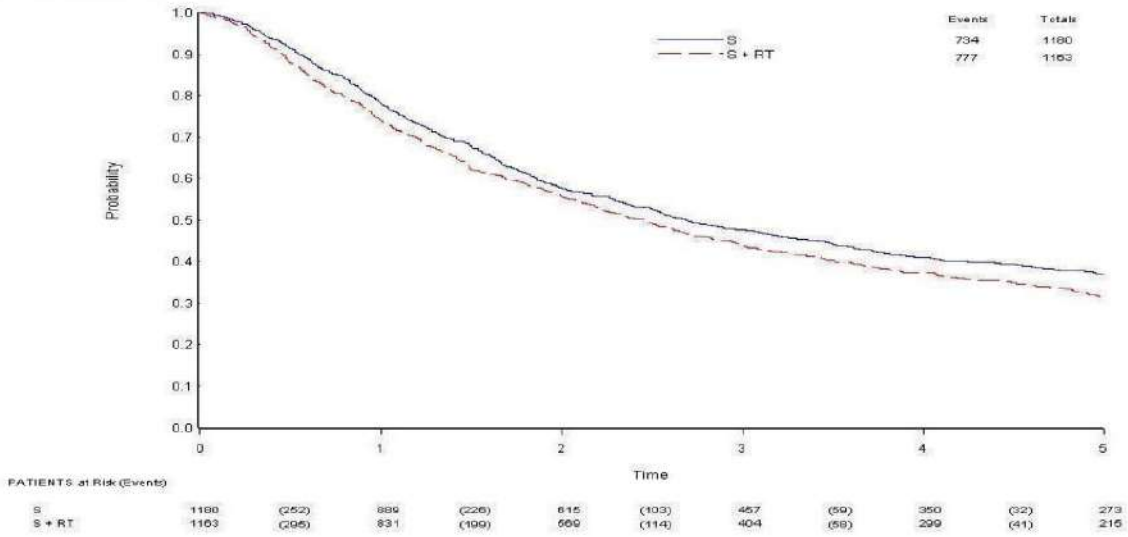
Sarah Burdett[1], Larysa Rydzewska[1], Jayne Tierney[1], David Fisher[2], Mahesh KB Parmar[2], Rodrigo Arriagada[3], Jean Pierre Pignon[4], Cecile Le Pechoux[5], on behalf of the PORT Meta-analysis Trialists Group[1]

[1]Meta-analysis Group, MRC Clinical Trials Unit at UCL, London, UK. [2]MRC Clinical Trials Unit at UCL, London, UK. [3]Karolinska Institutet, Stockholm, Sweden. [4]Plateforme LNCC de Méta-analyse en Oncologie et Service de Biostatistique et d'Epidémiologie, Gustave Roussy Cancer Campus, Villejuif, France. [5]Département de Radiothérapie, Gustave Roussy Cancer Campus, Villejuif, France

In 1998, a meta-analysis concluded that PORT was deleterious with regards to survival patients with pN0 and pN1 NSCLC.

However, there was still potential for its use in patients with mediastinal nodal involvement (pN2).

Figure 3. Overall survival.



Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial

Jean-Yves Douillard, Rafael Rosell, Mario De Lena, Francesco Carpagnano, Rodryg Ramlau, Jose Luis Gonzáles-Larriba, Tomasz Grodzki, Jose Rodrigues Pereira, Alain Le Groumellec, Vito Larusso, Claude Clary, Antonio J Torres, Jabrail Dahabreh, Pierre-Jean Souquet, Julio Astudillo, Pierre Fournel, Angel Artal-Cortes, Jacek Jassem, Leona Koubkova, Patricia His, Marcello Riggi, Patrick Hurteloup

Lancet Oncol 2006; 7: 719–27

	Chemotherapy		Control	
	Radiotherapy (n=73)	No radiotherapy (n=152)	Radiotherapy (n=128)	No radiotherapy (n=114)
N1 (n=243)				
1-year survival	92%	85%	83%	73%
2-year survival	76%	70%	61%	52%
5-year survival	40%	56%*	43%	31%
N2 (n=224)				
1-year survival	98%	71%	74%	57%
2-year survival	77%	49%	48%	35%
5-year survival	47%	34%	21%	17%
All (n=467)				
1-year survival	96%	79%	78%	68%
2-year survival	76%	61%	54%	46%
5-year survival	45%	46%*	32%	27%

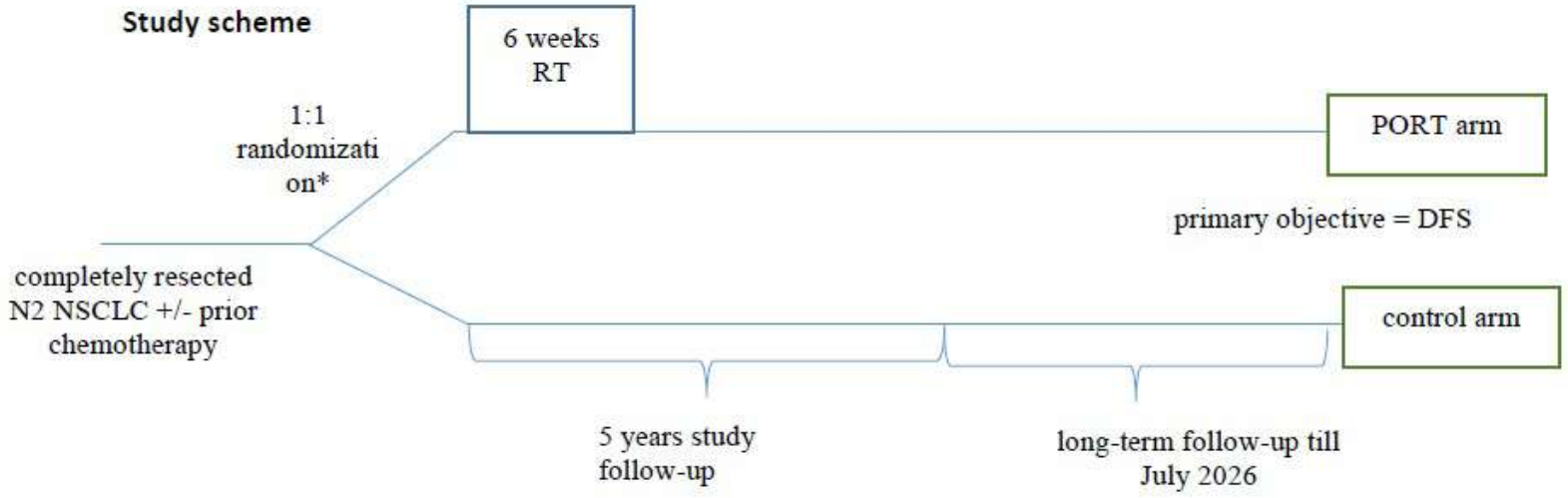
*42% of patients censored at 5 years.

Table 6: Overall survival estimates according to radiotherapy and lymph node status

Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial

Cecile Le Pechoux, Nicolas Pourel, Fabrice Barlesi, Delphine Lerouge, Delphine Antoni, Bruno Lamezec, Ursula Nestle, Pierre Boisselier, Eric Dansin, Amaury Paumier, Karine Peignaux, François Thillays, Gerard Zalcman, Jeannick Madelaine, Eric Pichon, Anne Larrouy, Armelle Lavole, Delphine Argo-Leignel, Marc Derollez, Corinne Faivre-Finn, Matthew Q Hatton, Oliver Riesterer, Emilie Bouvier-Morel, Ariane Dunant, John G Edwards, Pascal Alexandre Thomas, Olaf Mercier, Aurelie Bardet

Lancet Oncol 2022; 23: 104–14



54 Gy in 27 fractions of 2·0 Gy or 30 fractions of 1·8 Gy, on five consecutive days a week for 5·5 weeks.

Considering a 3-year DFS rate of 30% in the control group,[5] 430 events were required to be able to detect a 10% absolute improvement in DFS in the PORT group (ie, 40% at 3 years) in comparison by a log-rank test with a power of 80% and a bilateral 5% level of significance. 700 patients were therefore needed.

On Dec 12, 2016, because of the slow recruitment caused by competitive trials, the protocol was amended to lower the targeted accrual to 500 patients (292 events), corresponding to a hypothesised 12% difference in 3-year DFS

Baseline characteristics

	PORT group (n=252)	Control group (n=249)
Sex		
Men	167 (66%)	165 (66%)
Women	85 (34%)	84 (34%)
Age, median	61 (55–67)	61 (55–67)
Smoking status		
Current	26/251 (10%)	28/247 (11%)
Former	205/251 (82%)	193/247 (78%)
Never	20/251 (8%)	26/247 (11%)
Missing information	1	2
Performance status (WHO)		
0	121 (48%)	123 (49%)
1	129 (51%)	122 (49%)
2	2 (1%)	4 (2%)
N2 status before any treatment		
N0 nodal involvement (N2 unforeseen)	59/240 (25%)	70/239 (29%)
N1 (N2 unforeseen)	43/240 (18%)	29/239 (12%)
Single station N2	83/240 (35%)	80/239 (34%)
Multiple station N2	55/240 (23%)	60/239 (25%)
Missing information	12	10
Histology		
Squamous cell carcinoma	57 (23%)	51 (21%)
Adenocarcinoma	177 (70%)	189 (76%)
Large cell carcinoma	7 (3%)	5 (2%)
Mixed	8 (3%)	2 (1%)
Other*	3 (1%)	2 (1%)
Methods of adjuvant chemotherapy treatment		
No chemotherapy	10 (4%)	11 (4%)
Preoperative chemotherapy	36 (14%)	31 (12%)
Postoperative chemotherapy	189 (75%)	195 (78%)
Preoperative and postoperative chemotherapy	17 (7%)	12 (5%)
Pretreatment PET scan	232 (92%)	224 (90%)

Data are shown as median (IQR) or n (%). Percentages are calculated using non-missing values. PORT=postoperative radiotherapy. *Specific information on type was not collected.

Table 1: **Baseline characteristics**

Surgery and radiotherapy characteristics

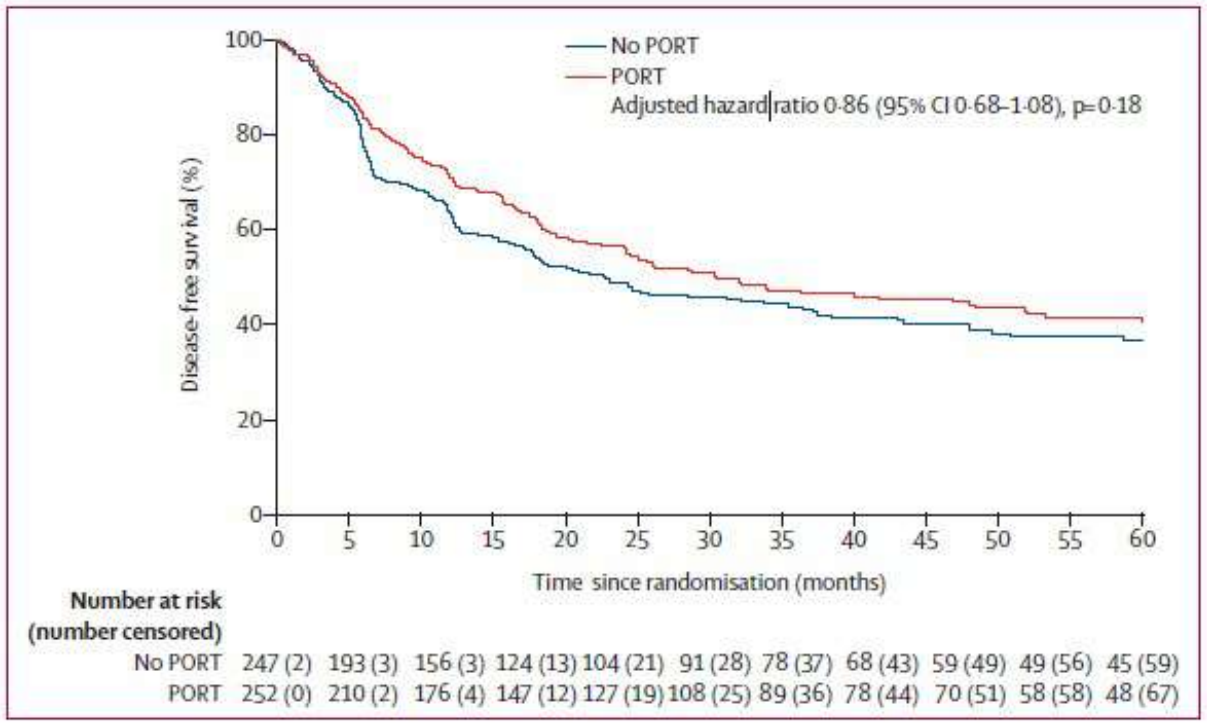
	PORT group (n=252)	Control group (n=249)	
Number of mediastinal node stations involved			
None	9 (4%)	6 (2%)	
One station involved	169 (67%)	160 (64%)	
Two or more stations involved	74 (29%)	83 (33%)	
Nodal extracapsular extension			
Yes	59 (23%)	63 (25%)	
No	98 (39%)	113 (45%)	
Unspecified	95 (38%)	73 (29%)	
Type of surgery			
Bilobectomy	19 (8%)	17/247 (7%)	
Lobectomy	197 (78%)	201/247 (81%)	
Pneumonectomy	31 (12%)	24/247 (10%)	
Sublobar resection	5 (2%)	5/247 (2%)	
Missing information	0	2	
Quality of resection before surgical committee review intervention*			
R0	249/250	242/243	
R2	1/250 (<1%)	1/243 (<1%)	
Quality of resection according to surgical committee review*			
R (uncertain)	101/250 (40%)	102/243 (42%)	
R0	74/250 (30%)	65/243 (27%)	
R1 (nodal extracapsular extension)	74/250 (30%)	75/243 (31%)	
R2	1/250	1/243	
Missing information	2	6	
Thoracic irradiation	241 (96%)	--	
Total received dose (in Gy)†			
≤50	7/241 (3%)	--	
51–57	231/241 (96%)	--	
>57	3 (1%)	--	
Main radiotherapy variables†			
Lung V20	23% (17–27)	--	
Mean lung dose (Gy)	13 (10–15)	--	
Mean heart dose (Gy)	13 (8–19)	--	
Heart V35	15% (8–24)	--	
PORT technique†			
Three-dimensional conformal radiotherapy	201/226 (89%)	--	
Intensity-modulated radiotherapy	25/226 (11%)	--	
Missing information	15	--	

Data are median (IQR) or n (%). Percentages are calculated using non-missing values. Heart V35=percentage of the normal heart receiving at least 35 Gy. Lung V20=percentage of the normal lung receiving at least 20 Gy. PORT=postoperative radiotherapy. *Two patients in the PORT group and six patients in the control group did not have a surgical report or anatomopathological files, or both, available in the included centres and were thus not reviewed by the surgical committee. †11 patients did not receive radiotherapy.

Table 2: **Surgery and radiotherapy characteristics**

R uncertain:
- incomplete nodal staging
- involved N2 nodes removed in the fragments
- the highest N2 station being positive

R1:
- nodal extracapsular extension



- Median follow-up was 4·8 years
- 3-year DFS 47% (95% CI 40–54) with PORT vs 44% (37–51) without PORT
- Median DFS was 30·5 months (95% CI 24–49) in the PORT group and 22·8 months (17–37) in the control group

	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.

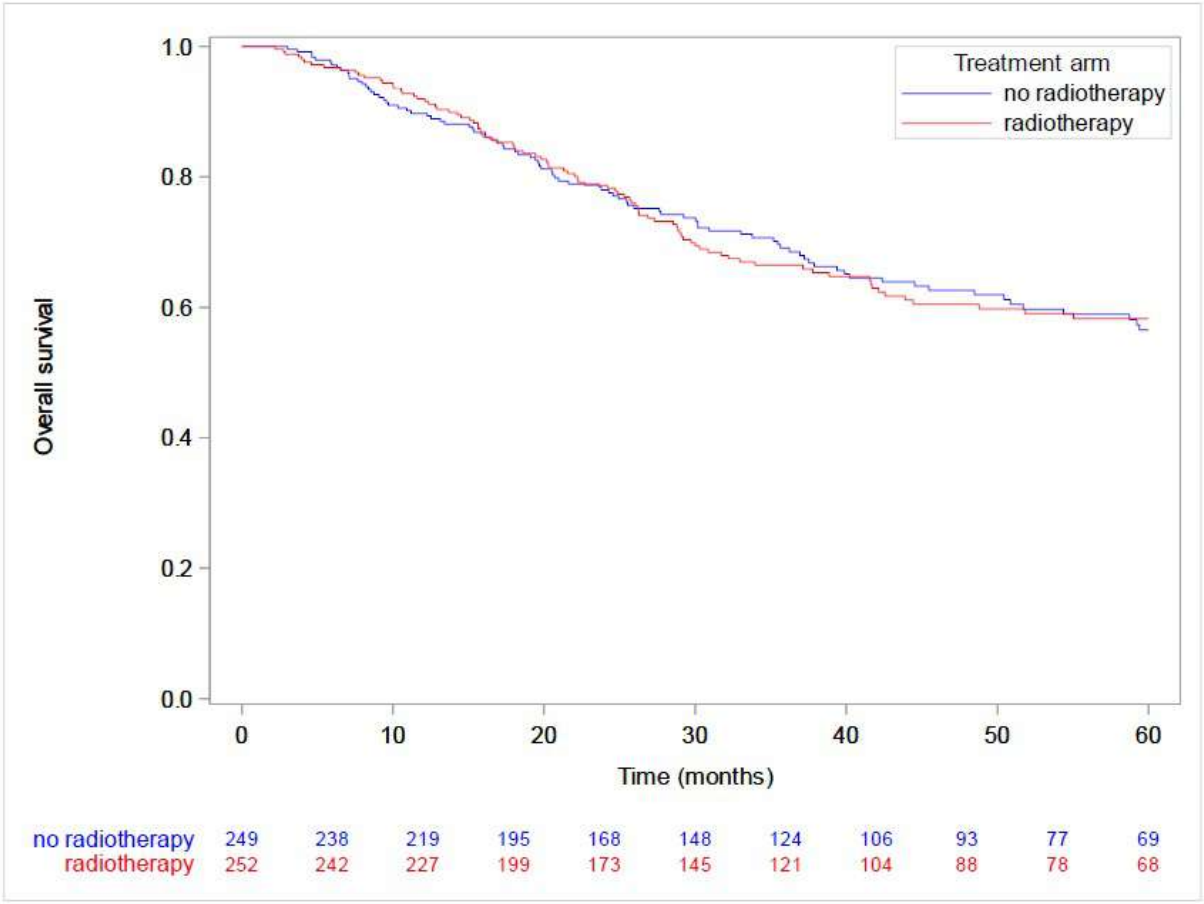
Table 3: **Disease-free survival events**

Appendix 10: Prognostic model of DFS

Variable	n	HR	95% CI	p-value
Treatment arm				0.33
- Control	249	1		
- PORT	252	0·89	[0·7;1·2]	
Gender				0·02
- Male	332	1		
- Female	169	0·73	[0·5;1·0]	
Histology				0·03
- Other	393	1		
- Squamous cell carcinoma	108	0·71	[0·5;1·0]	
N2				<·01
- without N1 involvement	188	1		
- with N1 involvement (left or right)	313	1·50	[1·1;2·0]	
Number of mediastinal nodes stations involved				0·01
- None	15	0·99	[0·4 ;2·2]	
- One	328	1		
- ≥ 2	158	1·46	[1·1 ;1·9]	
Quality of resection*				<·0001
- R0	139	1		
- R(uncertain)	206	1·29	[0·9;1·8]	
- R1(ECE)	149	1·31	[0·9;1·9]	
- R2	2	1·95	[0·5;8·1]	

	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%)	..

Appendix 7: Kaplan-Meier survival estimates for OS



Conclusions

- 3-year DFS was higher than initially hypothesised in both groups
- Excess of deaths related to cardiopulmonary diseases.
- Mediastinal relapse was lower in the PORT group. This finding is clinically relevant.
- IMRT has become more widely available for thoracic cancers such as lung cancer and It is able to reduce the cardiac and pulmonary toxicity risk
- In resected NSCLC with N2 disease, the role of extracapsular extension has been poorly studied.
- Lung ART provides robust evidence that 3D conformal PORT cannot generally be recommended as the standard of care in patients with resected stage IIIAN2 NSCLC. We hope that ongoing analyses will allow for refining the profile of optimal candidates for PORT.

JAMA Oncology | Original Investigation

Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non–Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy
The Phase 3 PORT-C Randomized Clinical Trial

Zhouguang Hui, MD; Yu Men, MD; Chen Hu, PhD; Jingjing Kang, MD; Xin Sun, MD; Nan Bi, MD, PhD; Zongmei Zhou, MD; Jun Liang, MD; Jima Lv, MD; Qinfu Feng, MD; Zefen Xiao, MD; Dongfu Chen, MD; Yan Wang, MD; Junling Li, MD; Jie Wang, MD; Shugeng Gao, MD; Luhua Wang, MD; Jie He, MD

Jama Oncology 2021

OBJECTIVE To evaluate the effect of PORT using modern techniques on survival and safety in patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy.

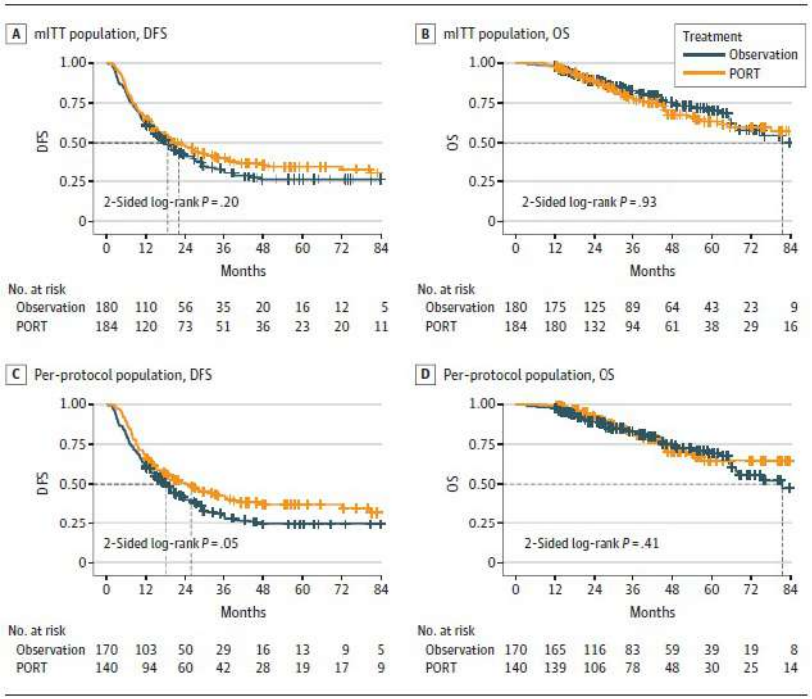
DESIGN, SETTING, AND PARTICIPANTS 394 patients with pIIIA-N2 NSCLC treated with complete resection and 4 cycles of platinum-based chemotherapy. Pneumonectomy was not permitted.

INTERVENTIONS Patients were randomized equally into the PORT arm (n = 202) or the observation arm (n = 192). The total dose of PORT was 50 Gy.

MAIN OUTCOMES AND MEASURES The primary endpoint was 3-years DFS. Secondary end points included OS, LRFS, DMFS, and toxic effects.

Table 1. Characteristics of Patients for Modified Intent-to-Treat Analysis

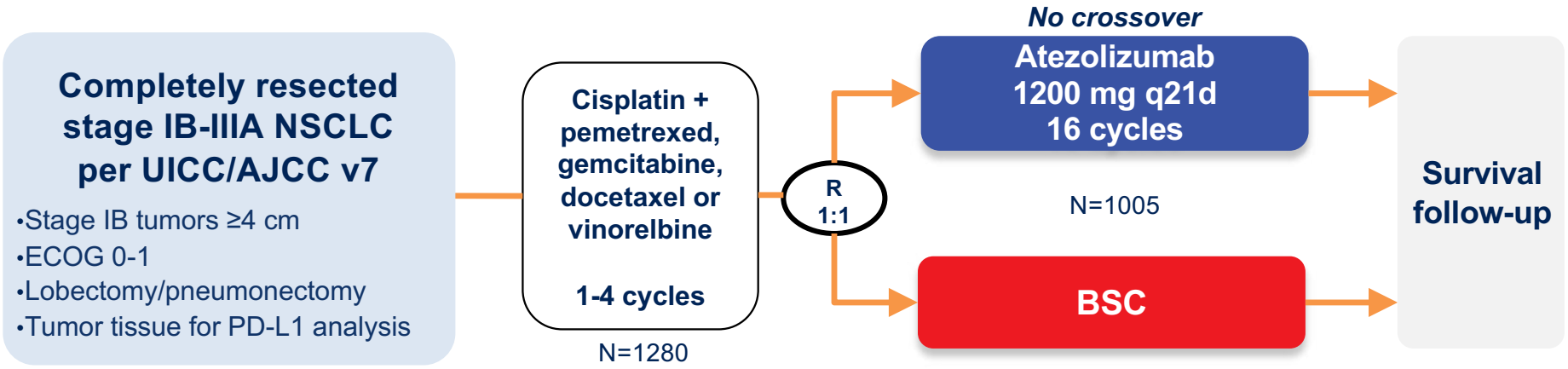
Characteristics	No. (%) Total (n = 364)	PORT (n = 184)	Observation (n = 180)
Gender			
Male	202 (55.5)	108 (58.7)	94 (52.2)
Female	162 (44.5)	76 (41.3)	86 (47.8)
Age, y			
≤60	271 (74.5)	141 (76.6)	130 (72.2)
>60	93 (25.5)	43 (23.4)	50 (27.8)
Median (range)	55 (25-70)	55 (25-70)	55 (32-70)
ECOG PS			
0	177 (48.6)	88 (47.8)	89 (49.4)
1	187 (51.4)	96 (52.2)	91 (50.6)
Smoking history			
Absence	202 (55.5)	94 (51.1)	108 (60.0)
Presence	162 (44.5)	90 (48.9)	72 (40.0)
Tumor location			
Right lung	220 (60.4)	114 (62.0)	106 (58.9)
Left lung	144 (39.6)	70 (38.0)	74 (41.1)
cN2			
No	211 (58.0)	101 (54.9)	110 (61.1)
Yes	144 (39.4)	80 (43.5)	64 (35.6)
Unknown	9 (2.5)	3 (1.6)	6 (3.3)
Pathology			
Non-SCC	305 (83.8)	155 (86.1)	150 (81.5)
SCC	59 (16.2)	25 (13.9)	34 (18.5)
Tumor size			
≤3 cm	190 (52.2)	92 (50.0)	98 (54.4)
>3 cm	174 (47.8)	92 (50.0)	82 (45.6)
Visceral pleura			
Positive	241 (66.2)	123 (66.8)	118 (65.6)
Negative	123 (33.8)	61 (33.2)	62 (34.4)
pT			
T1	81 (22.3)	40 (21.7)	41 (22.8)
T2-3	283 (77.7)	144 (78.3)	139 (77.2)
DLNs			
≤20	172 (47.3)	96 (52.2)	76 (42.2)
>20	192 (52.7)	88 (47.8)	104 (57.8)
PLNs			
1-3	153 (42.0)	82 (45.6)	71 (38.6)
≥4	211 (58.0)	113 (61.4)	98 (54.4)
Positive N2 nodes, median	2 (1-20)	2 (1-17)	2 (1-20)



Grade 2 or higher radiation pneumonitis rate was 6%
Grade 3 or lower radiation esophagitis rate was 36.6%
No radiotherapy-related grade 4 or 5 adverse event was observed
Both were lower than expected, this may be mainly due to the majority of patients in the present study receiving IMRT(n = 134, 89.3%) rather than 3D-CRT.

Role of adjuvant immunotherapy/target therapy for resectable NSCLC

IMpower010: study design



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

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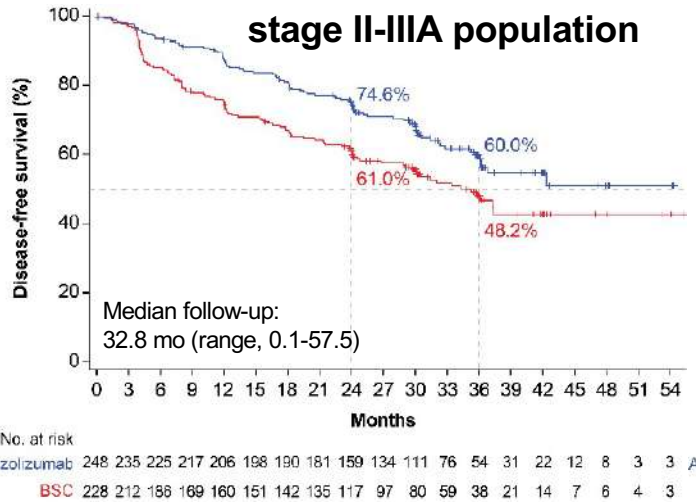
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

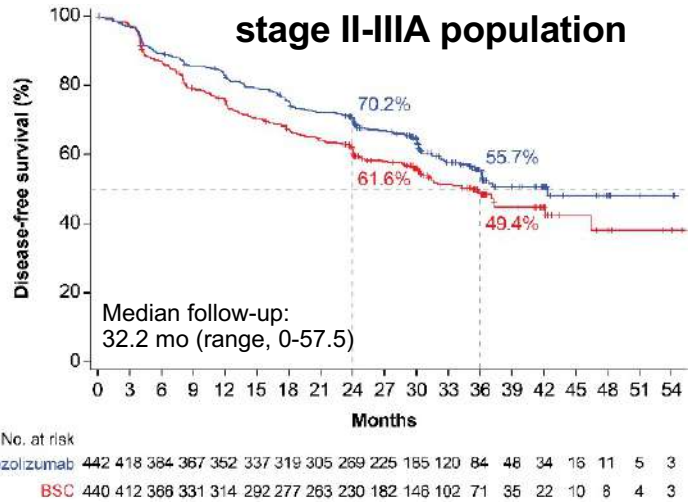
DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomised stage II-IIIA and ITT populations (primary endpoint)

PD-L1 TC ≥1% stage II-IIIA population



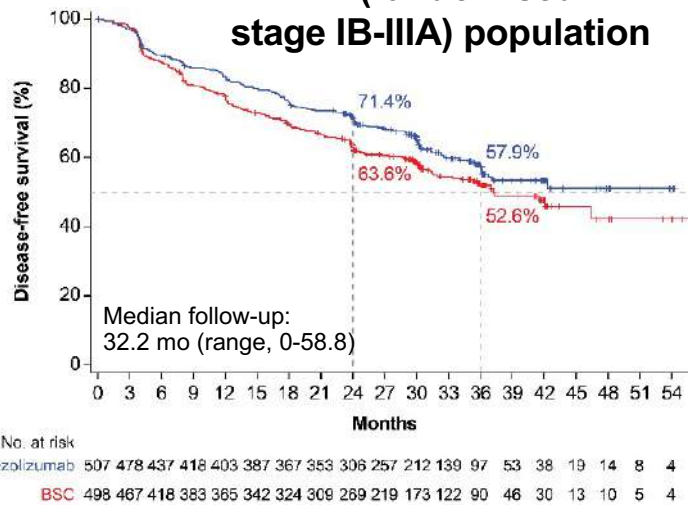
	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

All-randomised stage II-IIIA population



	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 (randomised stage IB-IIIA) population



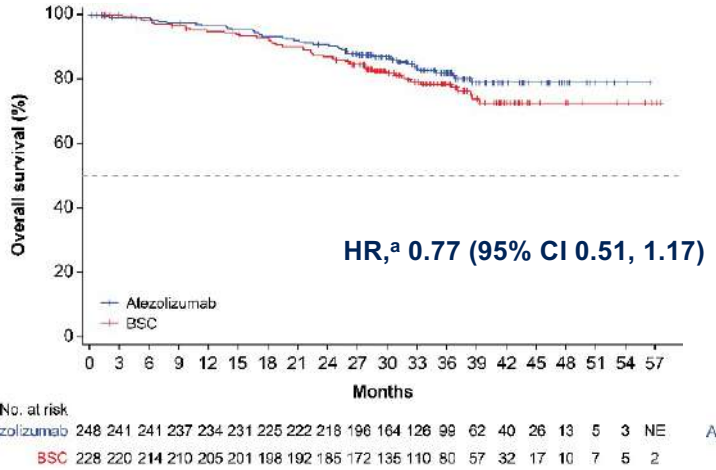
	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

Clinical cutoff: 21 January 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.
[d] The statistical significance boundary for DFS was not crossed. 1. Wakelee H, et al. J Clin Oncol. 2021;39(suppl 15):8500.

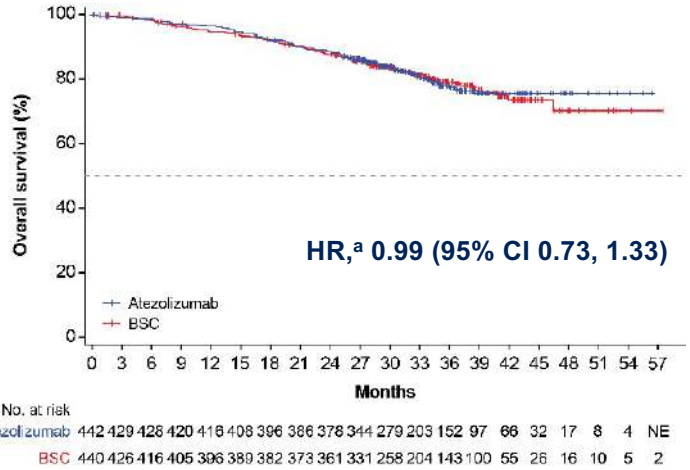
Felip et al. IMpower010 Relapse Patterns - ESMO 2021

IMpower010: early OS data at interim

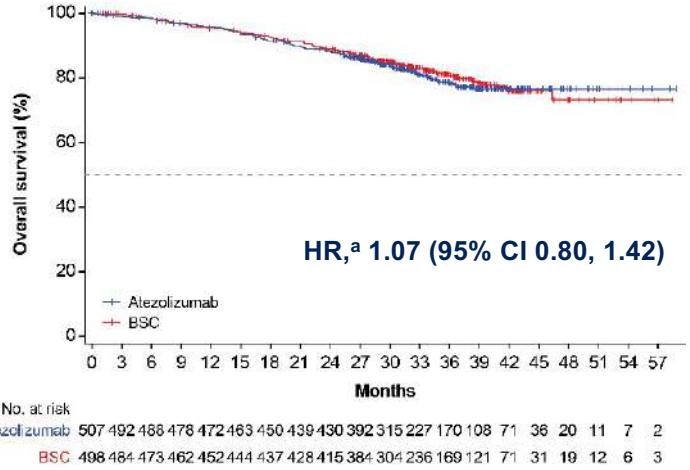
PD-L1 TC ≥ 1% stage II-IIIA



All-randomized stage II-IIIA



ITT



- OS data were immature at this pre-planned DFS interim analysis
- OS in the ITT population was not formally tested
- A trend toward OS improvement with atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population

Wakelee et Al. ASCO 2021
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

IMpower010: immune-mediated AEs[a]

imAEs occuring in ≥1% of patients

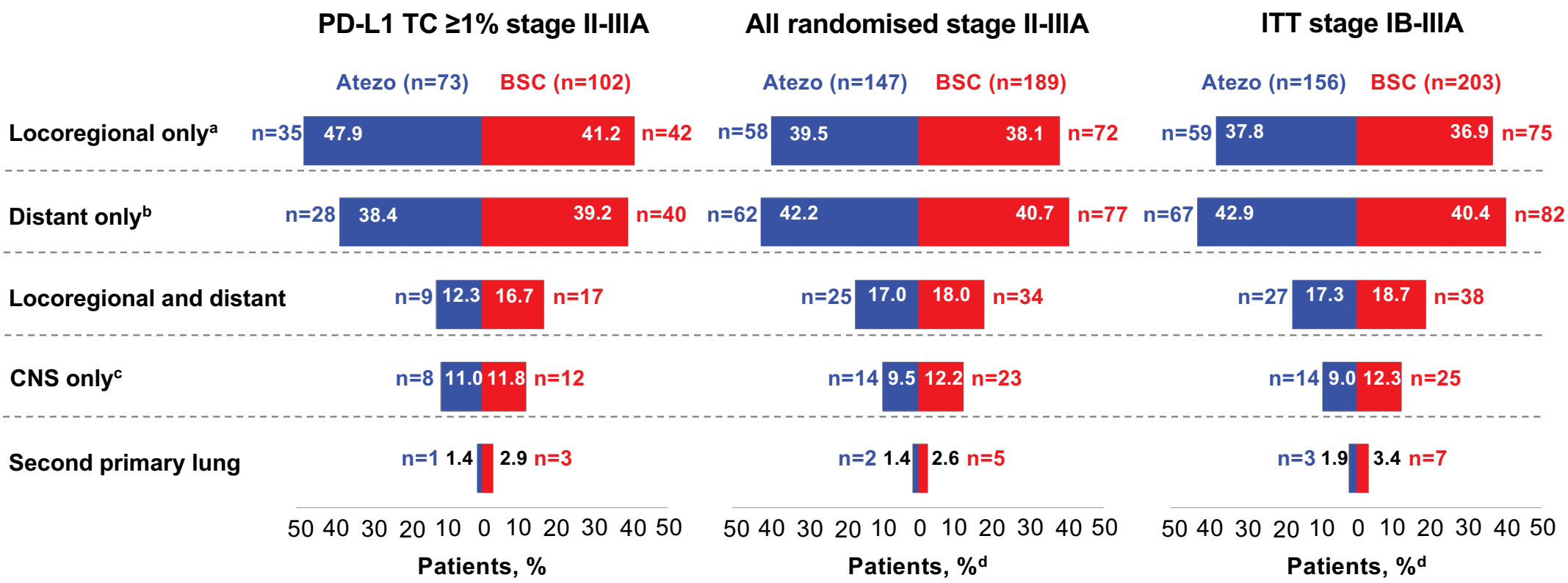
	Atezolizumab (n=495)		BSC (n=495)	
n (%)	Any grade	Grade 3-4	Any grade	Grade 3-4
Any immune-mediated AEs	256 (51.7)[b]	39 (7.9%)	47 (9.5)	5 (0.6)
Rash	91 (18.4)	7 (1.4)	11 (2.2)	0
Hepatitis (diagnosis and laboratory abnormalities)	86 (17.4)	20 (4.0)	22 (4.4)	1 (0.2)
Hepatitis (laboratory abnormalities)	81 (16.4)	16 (3.2)	21 (4.2)	1 (0.2)
Hepatitis (diagnosis)	7 (1.4)	4 (0.8)	1 (0.2)	0
Hypothyroidism	86 (17.4)	0	3 (0.6)	0
Hyperthyroidism	32 (6.5)	2 (0.4)	4 (0.8)	0
Pneumonitis	19 (3.8)[c]	4 (0.8)	3 (0.6)	0
Infusion-related reaction	7 (1.4)	1 (0.2)	0	0
Adrenal insufficiency	6 (1.2)	2 (0.4)	0	0

imAEs occuring in <1% of patients

	Atezolizumab (n=495)		BSC (n=495)	
n (%)	Any Grade	Grade 3-4	Any grade	Grade 3-4
Meningoencephalitis	4 (0.8)	3 (0.6)	0	0
Colitis	4 (0.8)	2 (0.4)	1 (0.2)	0
Diabetes mellitus	4 (0.8)	0	1 (0.2)	0
Myositis (myositis and rhabdomyolysis)	4 (0.8)	0	1 (0.2)	0
Pancreatitis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Encephalitis	2 (0.4)	2 (0.4)	0	0
Severe cutaneous adverse reaction	2 (0.4)	0	0	0
Autoimmune hemolytic anemia	2 (0.4)	0	0	0
Myocarditis	2 (0.4)[c]	0	0	0
Meningitis	2 (0.4)	1 (0.2)	0	0
Guillain-Barre syndrome	1 (0.2)	1 (0.2)	0	0
Ocular inflammatory toxicity	1 (0.2)	0	1 (0.2)	1 (0.2)
Hypophysitis	1 (0.2)	0	0	0
Nephritis	1 (0.2)	0	0	0
Vasculitis	0	0	1 (0.2)	1 (0.2)

Wakelee et Al. ASCO 2021 IMpower010 Interim Analysis

Patterns of relapse



Clinical cutoff: 21 January 2021. [a] Includes patients with 'local' and/or 'regional' recurrence only. [b] Includes patients with distant sites only; patients could have >1 distant site. [c] Subset of the Distant only category; includes patients with only distant CNS site. Patients with recurrence in CNS and other sites are not included. [d] One patient in the BSC arm had distant + second primary non-lung sites.

Felip et al. IMpower010 Relapse Patterns - ESMO 2021
https://bit.ly/3mNMSAi

ADAURA Phase III double-blind study design

Patients with completely resected stage IB, II, IIIA* NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization
1:1
(N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: W12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

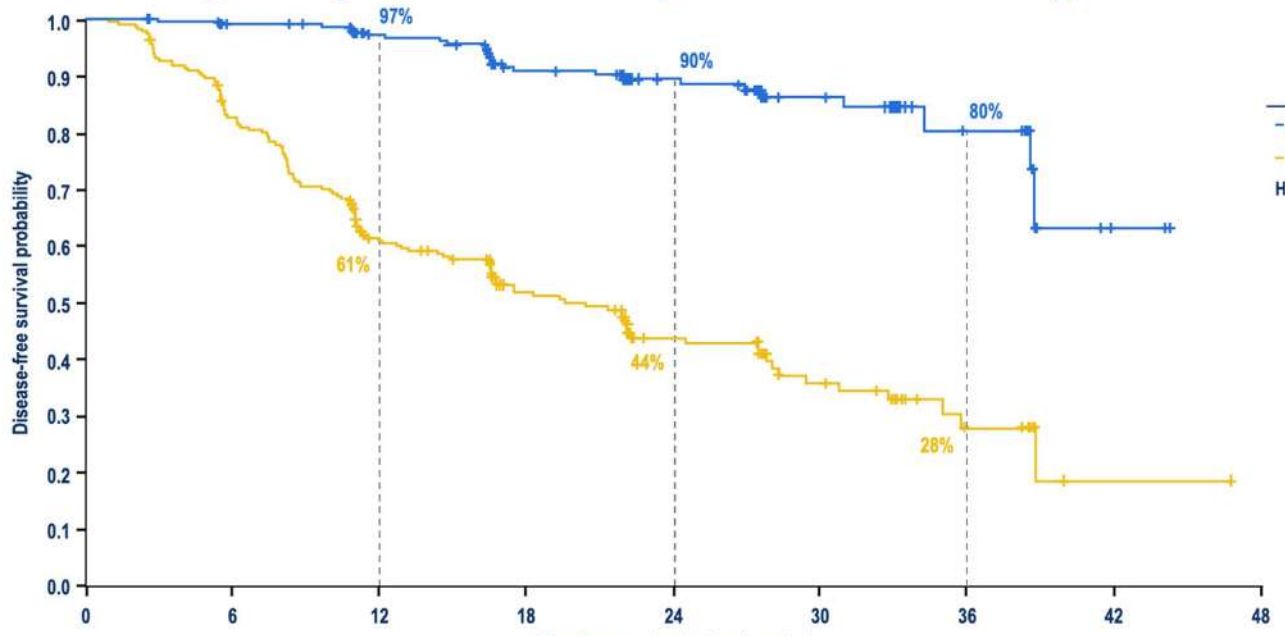
Endpoints

- **Primary**: DFS, by investigator, in stage II–IIIA patients
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

Herbst, ASCO 2020

Primary endpoint: DFS in patients with stage II–IIIA disease

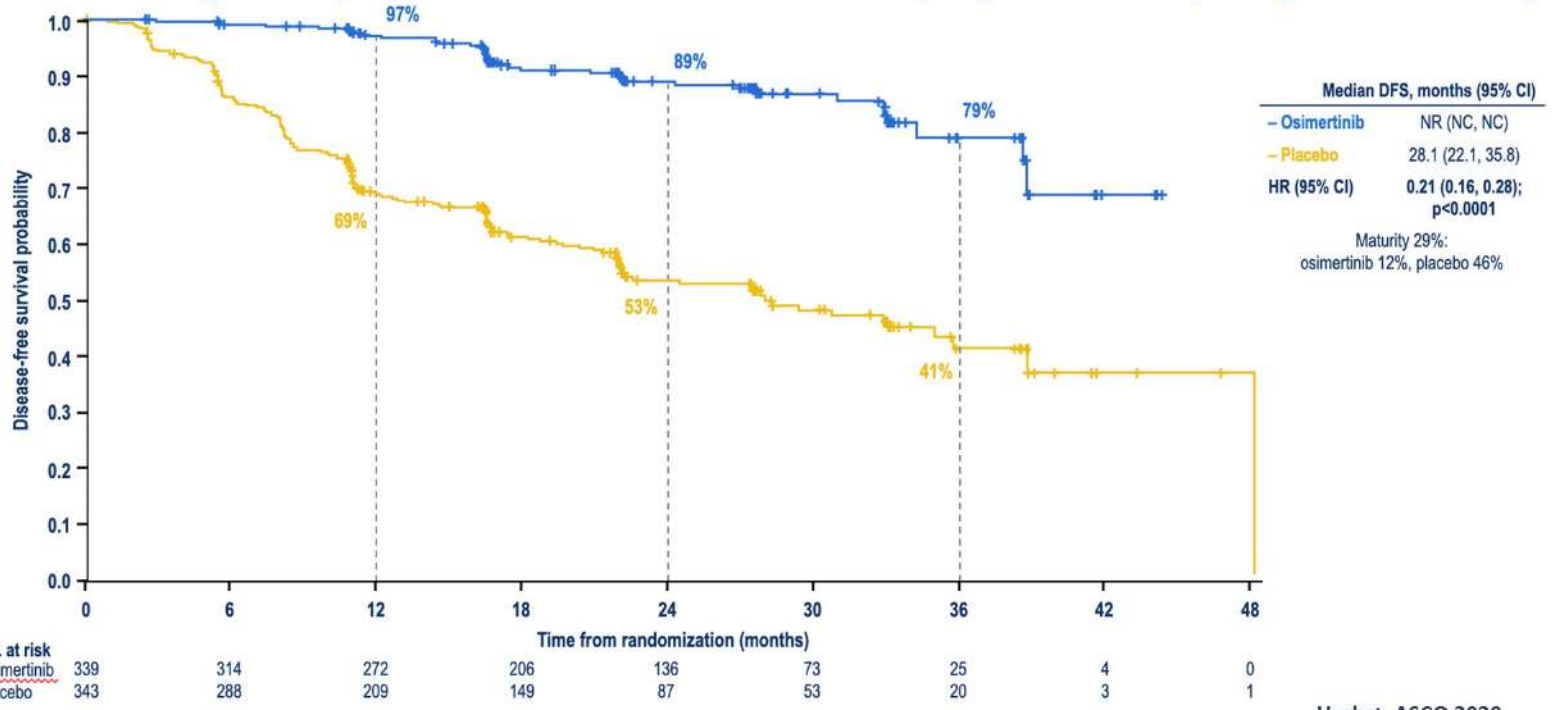


Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	0.17 (0.12, 0.23); p<0.0001

Maturity 33%:
osimertinib 11%, placebo 55%

Herbst, ASCO 2020

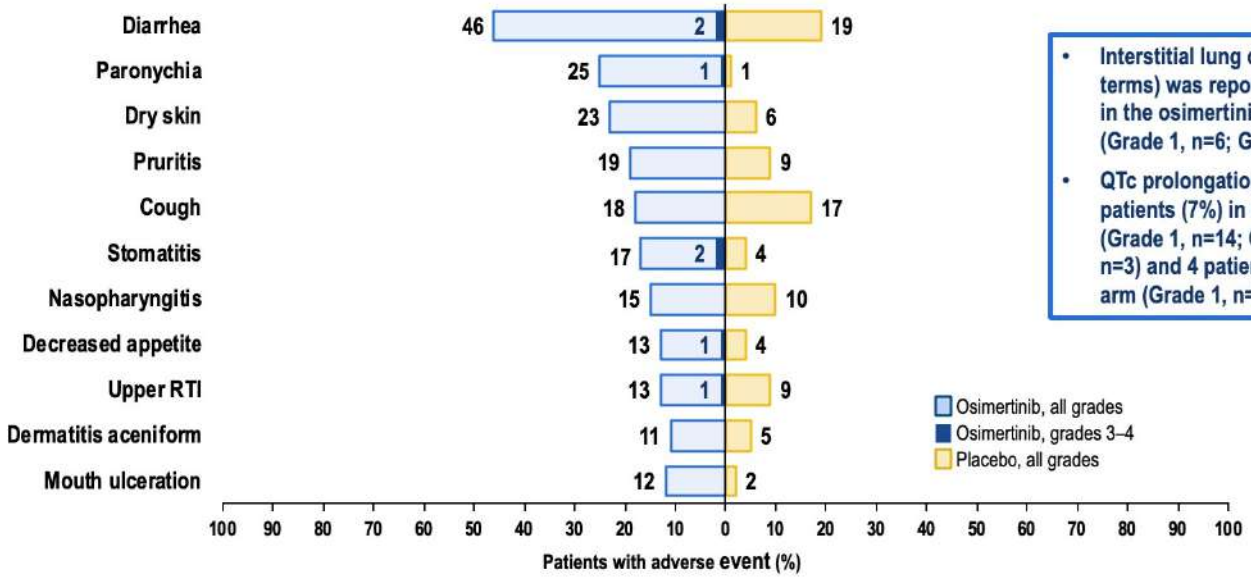
Secondary endpoint: DFS in the overall population (stage IB/II/IIIA)



Herbst, ASCO 2020

All causality adverse events (≥10% of patients)

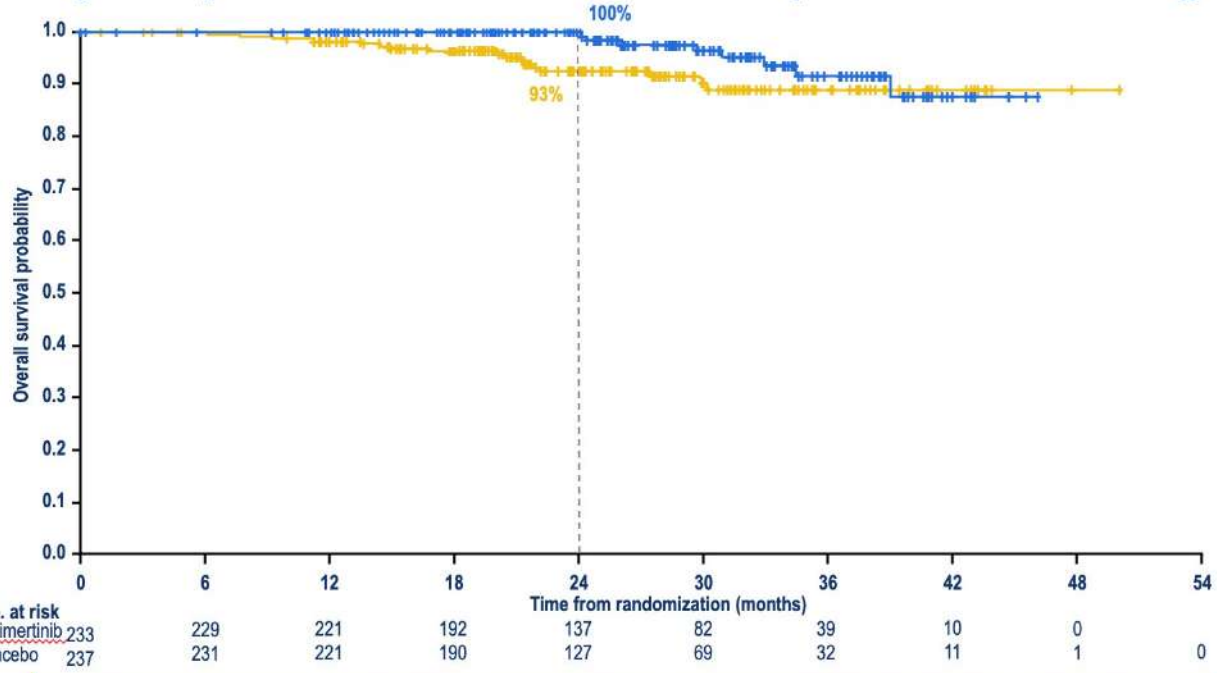
Median duration of exposure: osimertinib: 22.3 months (range 0 to 43), placebo: 18.4 months (range 0 to 48)



- Interstitial lung disease (grouped terms) was reported in 10 (3%) patients in the osimertinib arm (Grade 1, n=6; Grade 2, n=4)
- QTc prolongation was reported in 22 patients (7%) in the osimertinib arm (Grade 1, n=14; Grade 2, n=5; Grade 3, n=3) and 4 patients (1%) in the placebo arm (Grade 1, n=3; Grade 3, n=1)

Herbst, ASCO 2020

Early snapshot: overall survival in patients with stage II–IIIA disease



Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	0.40 (0.18, 0.90)

Maturity 5%:
osimertinib 3%, placebo 7%

There were a small number of deaths in stage IB patients: osimertinib: 1 death, placebo: 3 deaths

Herbst, ASCO 2020

Conclusions

Lessons from ADAURA on adjuvant cancer drug trials: Evidence, Ethics, and Economics

Gyawali, JCO, 2020

DFS benefit

ADAURA demonstrated a **striking DFS benefit** for adjuvant osimertinib in EGFRm1 resectable NSCLC that led the independent data monitoring committee (IDMC) **to unblind treatment assignments**.

DFS is a good endpoint in adjuvant setting?

The level of evidence required to justify an adjuvant cancer treatment should be higher than that for an advanced or metastatic disease. The goal of an adjuvant therapy should be to improve long-term survival, as patients may have already been cured and do not have symptoms of cancer.

Absence of tumor burden

Moreover, treatment in the metastatic setting is for known disease that can be followed for response and progression over time; by contrast, **adjuvant treatment by necessity is blind to a patient's disease status, with no tumor burden to allow us to assess treatment response or to detect who is being effectively treated versus overtreated**.

Resistence

Without further follow-up, we also cannot know whether early introduction of osimertinib preceding evidence of disease provides a treatment disproportionately more effective in treating micrometastatic disease that will translate to an OS benefit, or perhaps whether **proactive administration of osimertinib will do nothing more than lead to the early development of acquired resistance even before patients become aware of their disease**.

Crossover

Since osimertinib is the standard of care first-line therapy for advanced disease on the basis of improvement in OS, it is an important ethical mandate that the control arm patients in ADAURA receive osimertinib at the time of relapse.

Social and economic costs

Despite the tolerability of adjuvant targeted therapy, **the impact on patients and society is considerable**. While the current standard of care adjuvant therapy for NSCLC is a fixed course of four cycles of chemotherapy after which the patient can remain off of any further treatment in the absence of relapse, **daily treatment for up to 3 years** represents a substantial longitudinal therapeutic burden particularly as some of these patients would have already been rendered cured without osimertinib.

Toxicities

Although osimertinib is considered to be a generally well-tolerated drug, in ADAURA, **osimertinib was associated with diarrhea in 46% of patients (2% with grade 3 or higher), paronychia in 25% of patients, and stomatitis in 18% of patients.** Such adverse effects, even if low grade, can be quite debilitating when a therapy is given over several years. In contrast to metastatic setting, where a therapy can improve quality of life by reducing tumor burden, adjuvant therapy can only incur detrimental effects on quality of life. That loss in quality of life for years can be ethically justified only if there is compelling evidence of benefit over starting the same therapy at the time of relapse among those with demonstrated need.

Grazie per l'attenzione