Systemic therapy in Operable NSCLC- role for CPI in this setting?

Outline

- Why – *What is the need for systemic therapy in operable NSCLC ?*

- What –
  - *Available evidence for adjuvant and neo-adjuvant chemotherapy*
  - *Available evidence for adjuvant and neo-adjuvant CPI*
  - *Ongoing trials*

- When- *Can we choose ?*

Surgery alone does not cure most NSCLC

NSCLC SURGICAL STAGE AND PROGNOSIS

Surgical stage	*Survival (%) 5-year*	*Relapse (%) local*	*Relapse (%) distant*
IA	67	10	15
IB	57	10	30
IIA	55	12	40
IIB	39	12	40
IIIA	25	15	60

Pisters et al. JCO 23 (14): 3270-3278; 2005

surgical stage (6th ed)	5-year survival (%)	relapse (%) local	distant
IA T1N0M0	67	10	15
IB T2N0M0	57	10	30
IIA T1N1M0	55		
IIB T2N1M0 T3N0M0	39 38	12	40
IIA T3N1M0 T1-3N2M0	25 23	15	60

- distant failure more common than local relapse
- micro-dissemination at time of surgery
- >80% of relapses occur within 2 years of surgery

Mountain, Feld 84, Pairolera 84, Martini 80, Thomas 90, Scagliotti 2004

1995 BMJ meta-analysis

included 14 trials (4357 patients) of adjuvant chemotherapy

Drug category	hazard ratio	*p*	change 5-yr survival
alkylating agents	1.15 [1.04-1.27]	*0.005*	-5%
other drugs	0.89 [0.72-1.11]	*0.3*	4%
cisplatin based	0.87 [0.74-1.02]	*0.08*	5%

- alkylating agents detrimental (includes mitomycin and ifosfamide)
- cisplatin based therapy reduced risk of death by 13% (p=0.08)
- absolute benefit of 5% at 5yr - not statistically significant

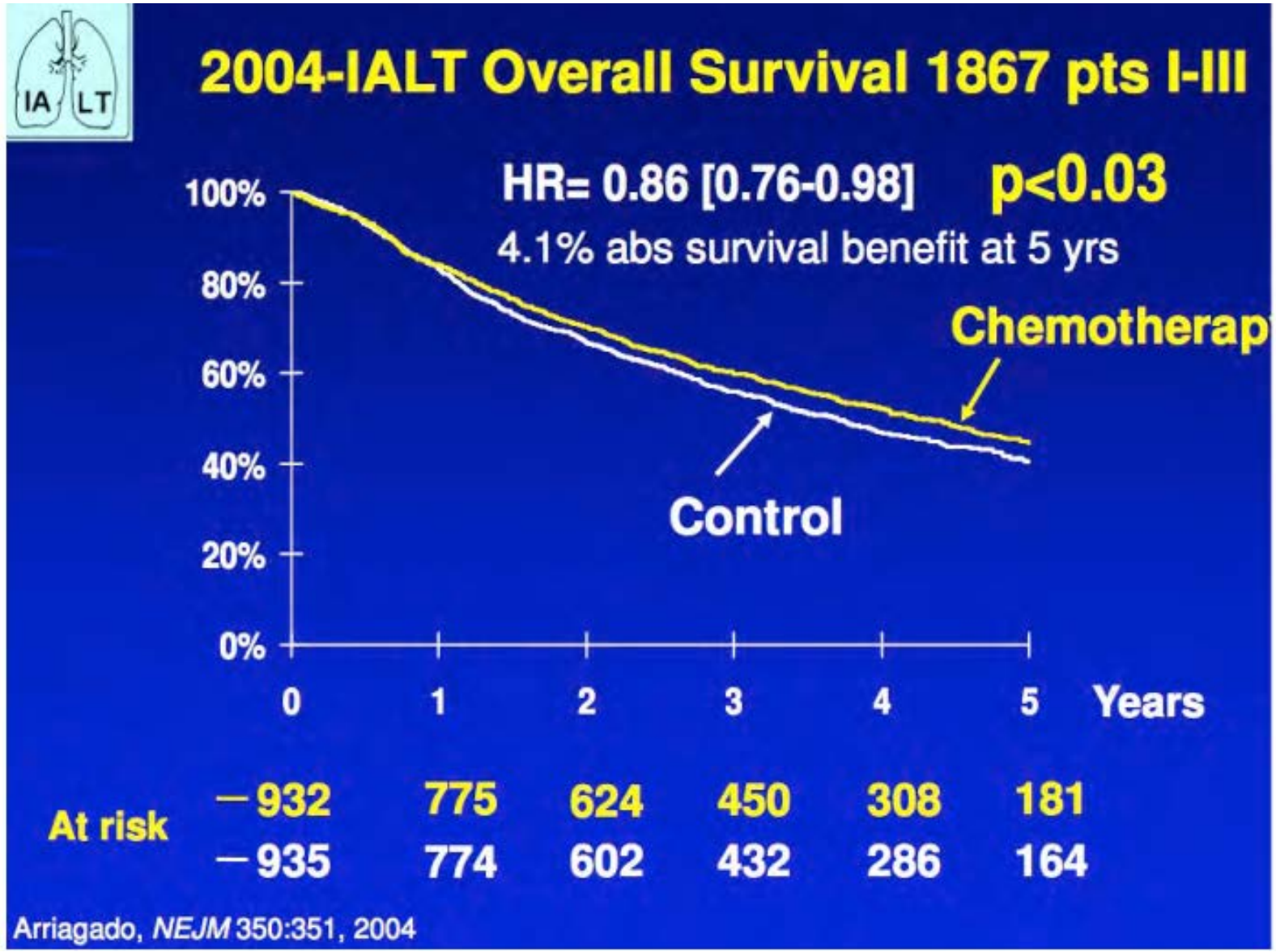
BMJ 1995;311:899-909

adjuvant studies- IALT

- large study (n=1867; planned 3300)
- stage I-III (36% were stage I)
- allowed thoracic RT at discretion of investigator
- cisplatin based (67% ≥ 300mg/m^2)
- closed early due to slow accrual
- showed survival benefit of 4.1% at 5 years
- 5yr OS 44.5% vs 40.4% (p<0.003)
- 7 patients died due to chemotherapy

Absolute survival benefit of 4.1% at 5 years

Le Chevalier N Engl J Med 2004;350:351-360

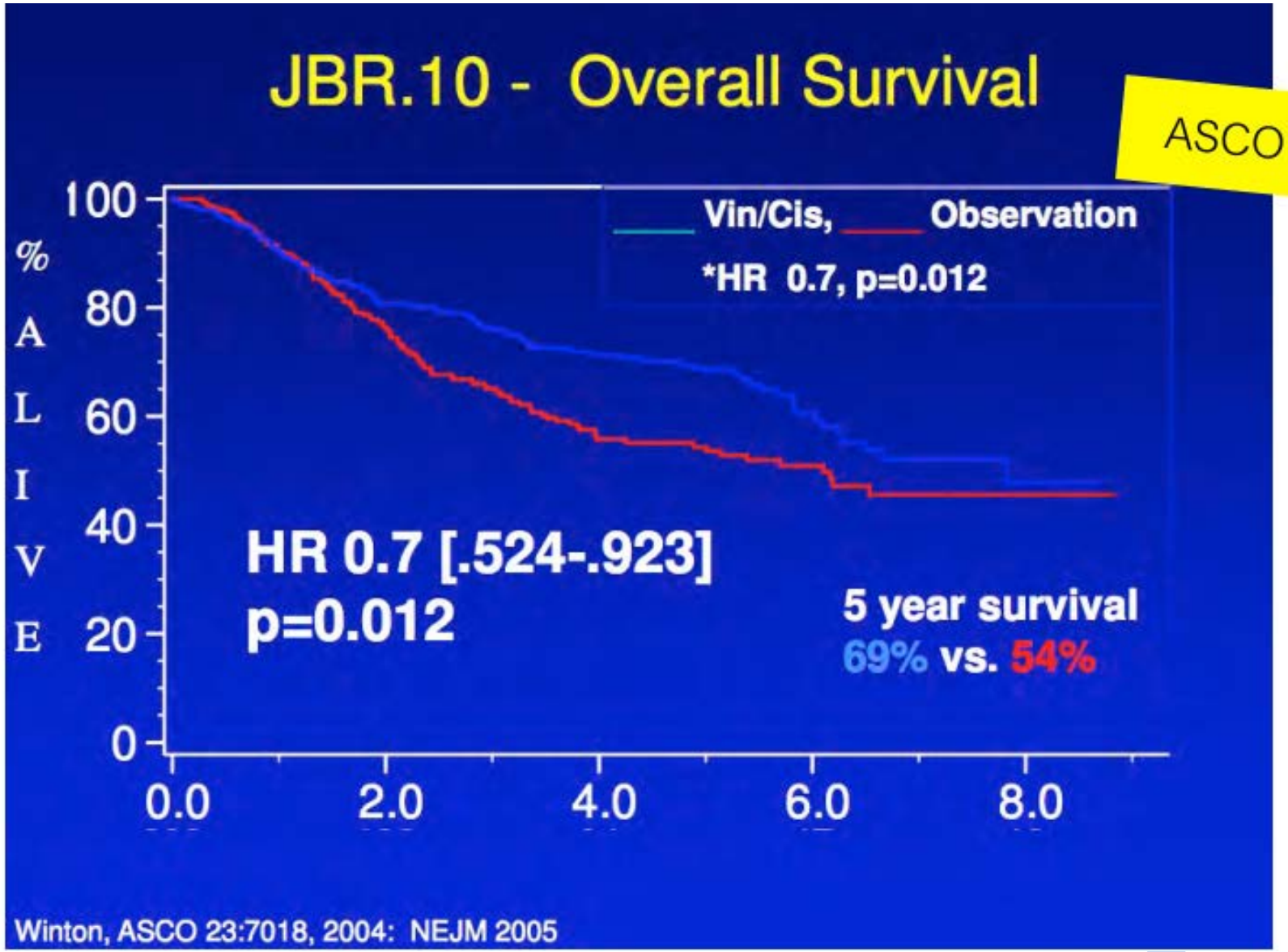

IA LT
2004-IALT Overall Survival 1867 pts I-III
HR= 0.86 [0.76-0.98]
p<0.03
4.1% abs survival benefit at 5 yrs
Chemotherap
Control
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
Years
At risk
—932 775 624 450 308 181
—935 774 602 432 286 164
Arriagado, NEJM 350:351, 2004

JBR10: establishment of adjuvant chemotherapy as a standard of care

- n = 482, stage IB/II
- cisplatin/vinorelbine versus no chemotherapy
- 7 year study (July1994 - April 2001)

Absolute survival benefit of 15% at 5 years ($p<0.011$)

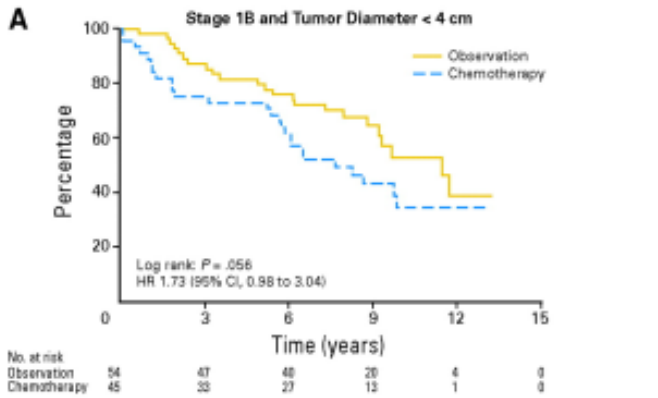
Winton N Engl J Med 2005;352:2589-97

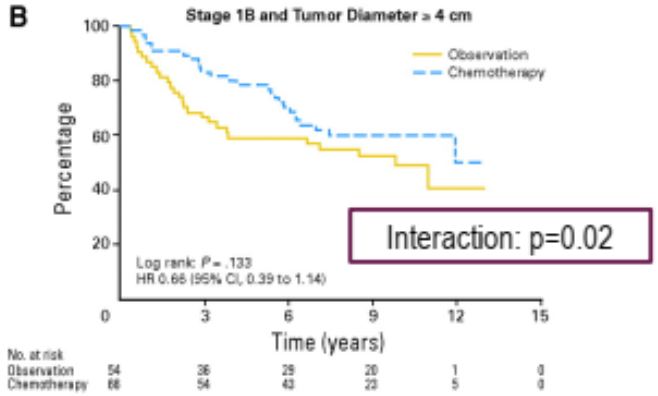

JBR.10 - Overall Survival
ASCO 2004
Vin/Cis, Observation
*HR 0.7, p=0.012
% ALIVE
100
80
60
40
20
0
HR 0.7 [.524-.923]
p=0.012
5 year survival
69% vs. 54%
0.0
2.0
4.0
6.0
8.0
Winton, ASCO 23:7018, 2004: NEJM 2005

CALGB 9633

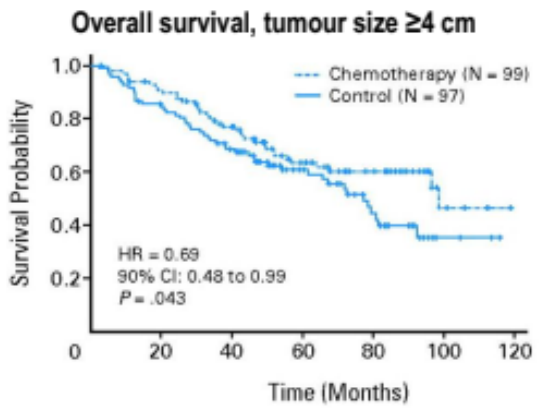
- n = 344
- stage IB (T2N0M0) completely resected
- paclitaxel 200mg/m^2 + carboplatin AUC6 for 4 cycles versus observation
- Sept. 1996 - suspended Nov 2003 after pre-planned interim analysis

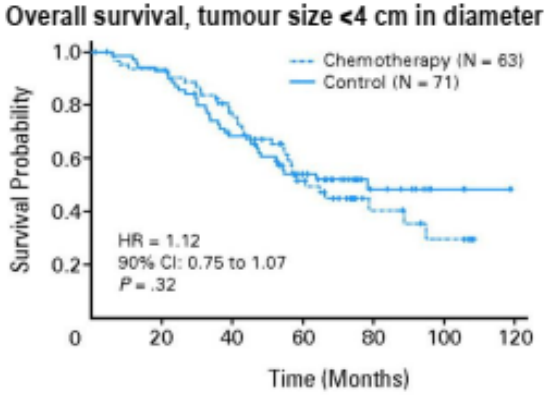
Absolute survival benefit of 12% at 4 years but no significant benefit at 5yr





Interaction: p=0.02





Subgroups within stage I and their benefit from chemotherapy

s CA, *et al.* Randomized Phase III Trial of Vinorelbine Plus Cisplatin Compared With Observation in Completely Resected Stage IB and II Non–Small-Cell Lung Cancer: Updated Survival Analysis of JB Oncol 2010;28(1):29–34. Available at: https://ascopubs.org/doi/full/10.1200/JCO.2009.24.0333; accessed July 2021. © 2010 American Society of Clinical Oncology;
uss GM, *et al.* 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 Or orth Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26(31):5043–51. Reprinted with permission. © 2008 American Society of Clinical Oncology.

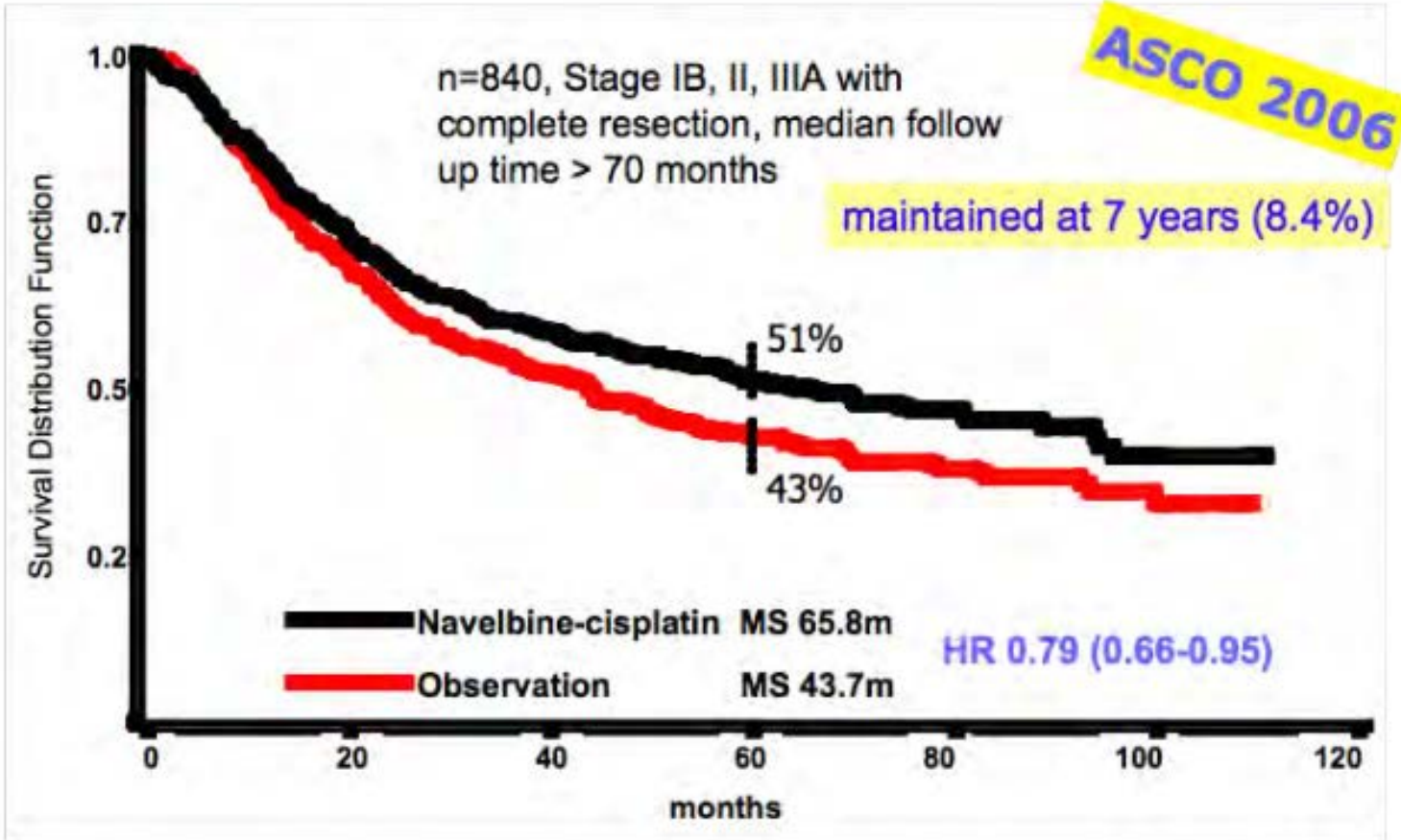
ANITA

- n = 840 patients
- stage IB (36%) to IIIA
- cisplatin/vinorelbine x 4 cycles versus observation
- allowed thoracic RT at discretion of investigator

Absolute survival benefit of 8.6% at 5 years (8.4% at 7yr)

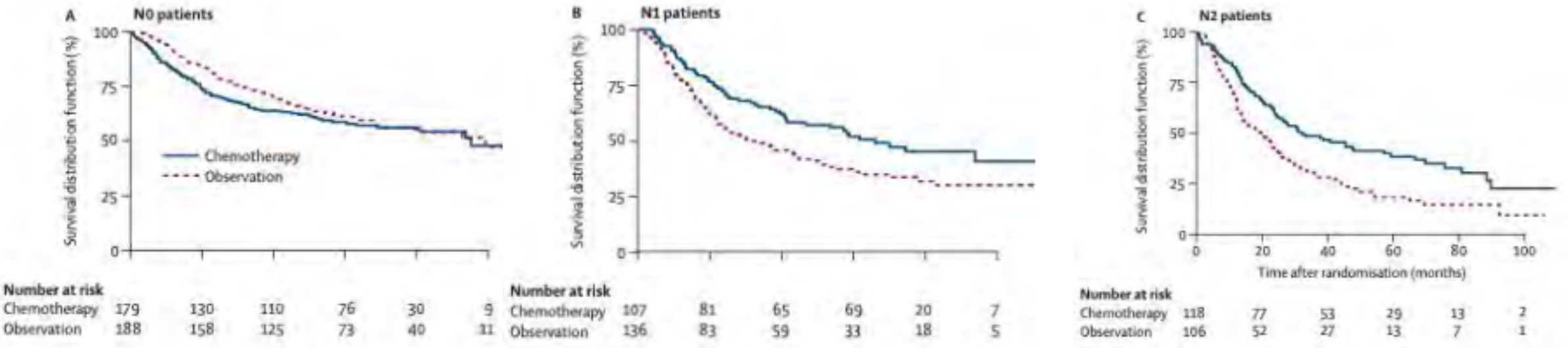
Douillard Lancet Oncology 2006 7(9):719-27

ANITA



Douillard Lancet Oncology 2006 7(9):719-27

ANITA overall survival by nodal involvement

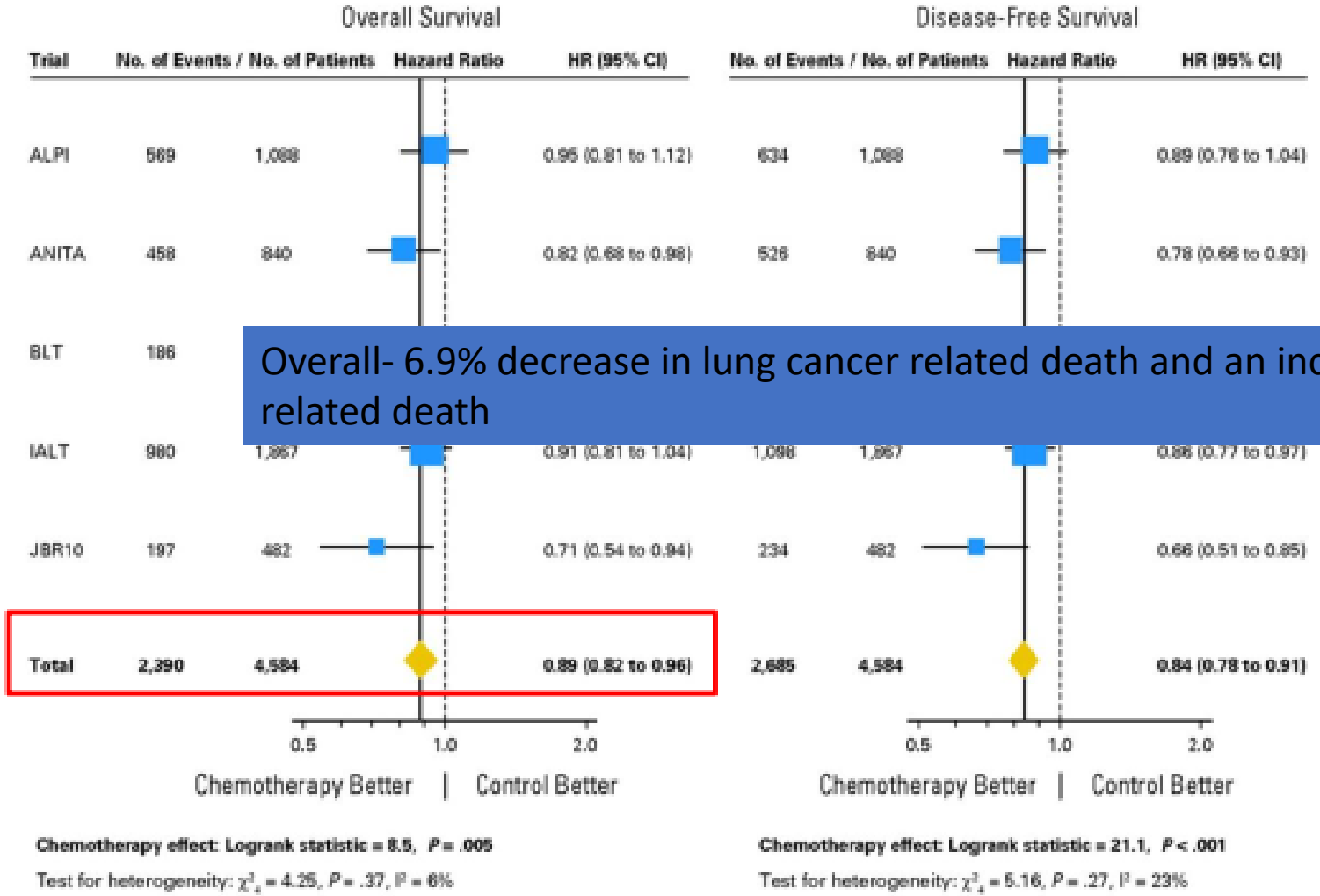


	N0	N1	N2
number: chemo/observation	179/188	107/136	118/106
5yr OS chemo/observation	58/61% HR 1.14 [0.83-1.57]	52/36% HR 0.67 [0.47-0.94]	40/19% HR 0.60 [0.44-0.82]

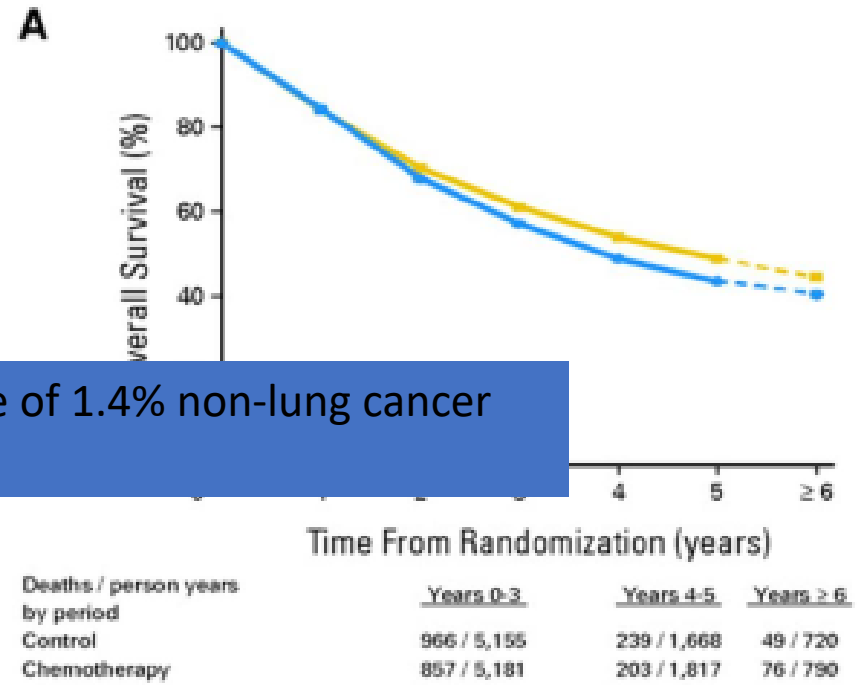
- benefit seen in N1, N2 patients not in node negative patients

Douillard Lancet Oncology 2006 7(9):719-27

THE CISPLATIN-BASED ADJUVANT CHEMOTHERAPY META-ANALYSIS



Overall- 6.9% decrease in lung cancer related death and an increase of 1.4% non-lung cancer related death



+5.4% at 5 years

Pignon JP, et al. Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group. J Clin Oncol, 26(21): 3552-9. Available at: https://ascopubs.org/doi/full/10.1200/JCO.2007.13.9030; accessed Aug 2021. © 2008 by American Society of Clinical Oncology.

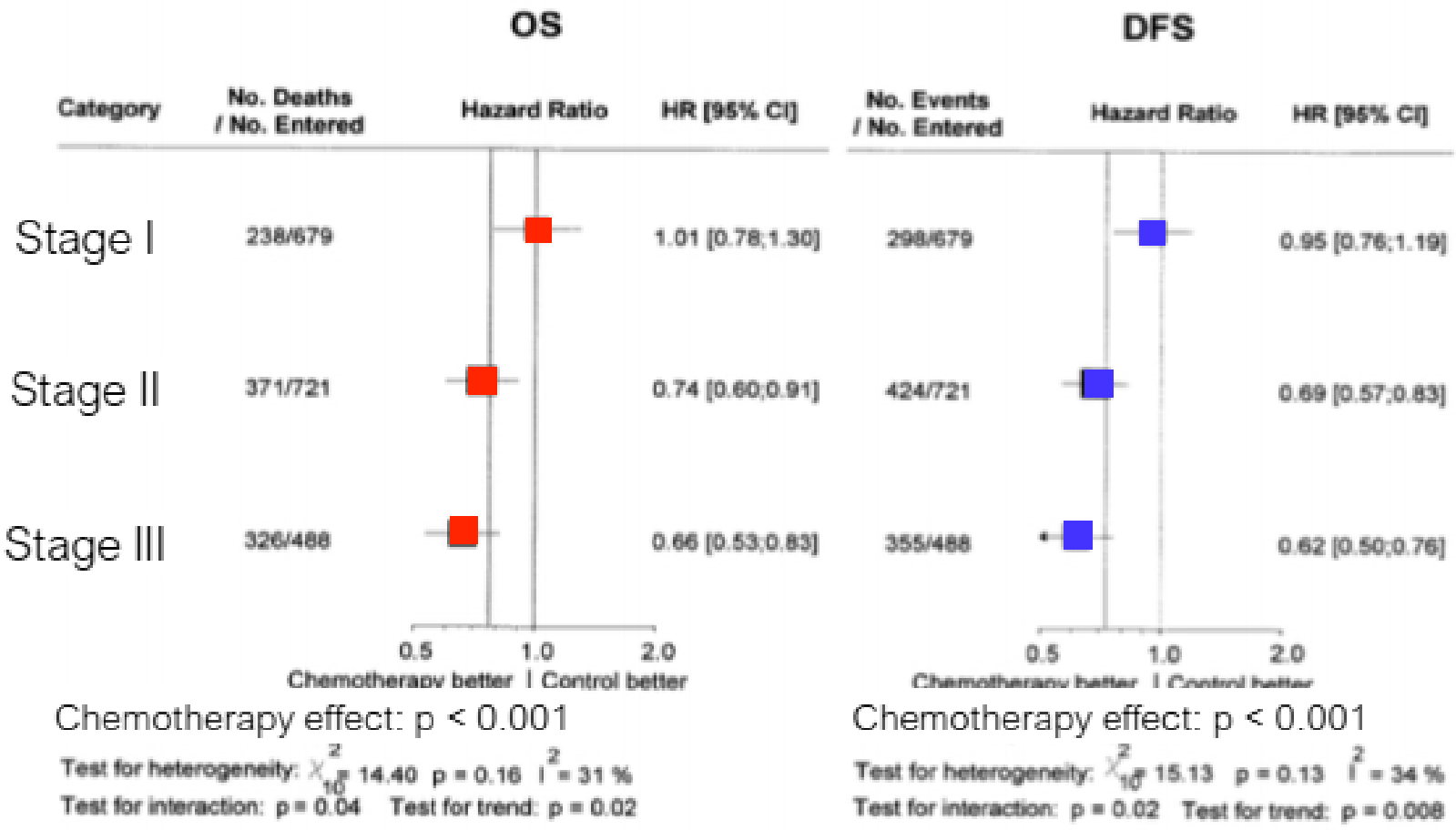
chemotherapy effect according to stage: LACE

cisplatin/vinorelbine

- 1888 pts. from 4 studies
- survival benefit at 5 years
  8.9% cf observation HR
  0.80 [95% CI 0.70-0.91]

OS

- stage I HR 5yr benefit of 1.8% HR
  1.01 [0.78 -1.30] (-1.2% at 3yr)
- stage II 5yr benefit of 11.6% HR
  0.74 [0.60 - 0.91]
- stage III 5yr benefit of 14.7% HR
  0.66 [0.53 - 0.83]



Douillard J Thorac Oncol 2010 5: 220-2

Initial NACT trials

	Accrual years	Number of patients	Clinical stage	Preoperative chemotherapy used (dose per cycle)	Postoperative chemotherapy cycles planned	Postoperative radiotherapy planned	Reached target accrual	Stopping reason	Median follow-up (years)
France 1990[28]	1985–87	26	I–III	Cyclophosphamide (600 mg/m²), vindesine (3 mg/m²), cisplatin (100 mg/m²); 2 cycles every 4 weeks	2	No	No	High progression rate with preoperative chemotherapy	3·2
MD Anderson 1994[29]	1987–93	60	IIA	Cyclophosphamide (500 mg/m²; d1), etoposide (100 mg/m²; d1–3), cisplatin (100 mg/m²; d1); 3 cycles every 4 weeks	3 to responders	Yes, if surgery incomplete or unresectable	No	Benefit of preoperative chemotherapy	6·7
Spain 1994[17]	1989–91	59	IIA	Mitomycin (6 mg/m²), ifosfamide (3 g/m²), cisplatin (50 mg/m²); 3 cycles every 3 weeks	0	Yes	No	Benefit of preoperative chemotherapy	6·3
MIP-91[20]	1991–97	355	I–IIIA	Mitomycin (6 mg/m², d1), ifosfamide (1·5 g/m², d1–3), cisplatin (30 mg/m², d1–3); 2 cycles every 3 weeks	2 to responders	Yes, if surgery incomplete or pT3 or pN2	Yes	NA	12·9
SWOG S9015[30]	1992–94	21	I–IIIA	Etoposide (80 mg/m²; d1–3), carboplatin (350 mg/m²; d1); 2 cycles every 3 weeks	3 to responders	No	No	Poor accrual	6·3
JCOG 9209[31]	1993–98	62	IIA	Vindesine (3 mg/m²; d1,8), cisplatin (80 mg/m²; d1); 3 cycles every 4 weeks	0	Yes, if surgery incomplete	No	Poor accrual	5·7
Netherlands 2000[32]	1994–99	79	IB–II	Paclitaxel (175 mg/m²; d1), carboplatin (AUC=7; d1); or teniposide (120 mg/m²; d1–3), cisplatin (80 mg/m²; d1); at least 2 cycles every 3 weeks	0	No	No	Poor accrual	2·2
Finland 2003[33]	1995–99	62	III	Docetaxel (100 mg/m²; d1); 3 cycles every 3 weeks	0	No	No	Poor accrual	3·1
MRC BL1[27]	1995–2001	10	I–III	Vindesine (3 mg/m²; d1,8), cisplatin (80 mg/m²; d1); or vinorelbine (30 mg/m²; d1,8), cisplatin (80 mg/m²; d1); or mitomycin (6 mg/m²; d1), ifosfamide (3 g/m²; d1), cisplatin (50 mg/m²; d1); or mitomycin (6 mg/m²; d1), vinblastine (6 mg/m²; d1), cisplatin (50 mg/m²; d1); number of cycles/interval unknown	0	Yes	No	Poor accrual	3·9
MRC LU22[26]	1997–2005	519	I–III	Mitomycin (8 mg/m²; first 2 cycles only), vinblastine (6 mg/m²; max 10 mg), cisplatin (50 mg/m²); or mitomycin (8 mg/m²; first 2 cycles only), ifosfamide (3 g/m²), cisplatin (50 mg/m²); or vinorelbine (30 mg/m²; d1,8; max 60 mg), cisplatin (80 mg/m²; d1); or paclitaxel (175 mg/m²), carboplatin (AUC=5); or gemcitabine (1250 mg/m²; d1,8), cisplatin (80 mg/m²; d1); or docetaxel (75 mg/m²), carboplatin (AUC=6); 3 cycles every 3 weeks	0	Yes, if surgery incomplete or progression	Yes	NA	7·6
SWOG S9900[34]	1999–2004	354	IB–IIIA	Paclitaxel (225 mg/m²), carboplatin (AUC=6); 3 cycles every 3 weeks	0	No	No	Positive results of adjuvant chemotherapy trials	5·5
China 2002[35]	1999–2004	55	IIA	Docetaxel (75 mg/m²; d1), carboplatin (AUC=5; d1); 2 cycles every 3 weeks	0	Yes, if surgery incomplete	No	Positive results of adjuvant chemotherapy trials/ poor accrual	7·8
China 2005[21]	1999–2004	40	IIA	Gemcitabine (1200–1250 mg/m²; d1,8), cisplatin (30 mg/m²; d1–3); or gemcitabine (1200–1250 mg/m²; d1,8), carboplatin (AUC=5; d1); 2 cycles every 3 weeks	2 to responders	No	No	Poor accrual	3·3
ChEST[22]	2000–04	270	IB–IIIA	Gemcitabine (1250 mg/m²; d1,8), cisplatin (75 mg/m²; d1); 3 cycles every 3 weeks	0	No	No	Positive results of adjuvant chemotherapy trials	3·10
NATCH[36]	2000–07	413	IA–IIIA	Paclitaxel (200 mg/m²), carboplatin (AUC=6); 3 cycles every 3 weeks	0	Yes, if pathological pN2	Yes	NA	4·8

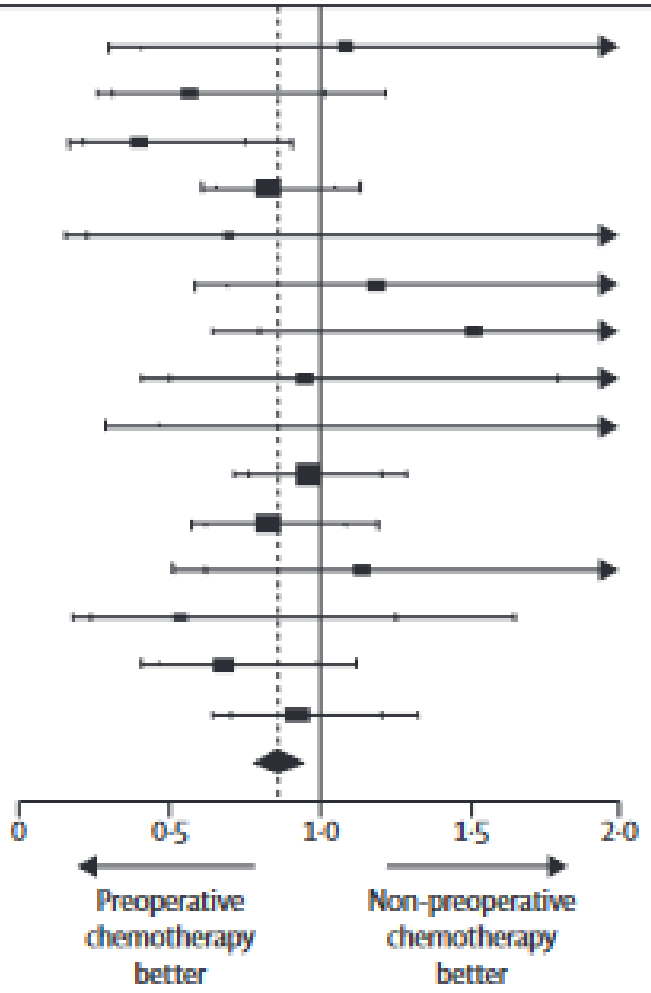
NA=not applicable. AUC=area under the curve.

Table 1: Trial characteristics

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

NSCLC Meta-analysis Collaborative Group*

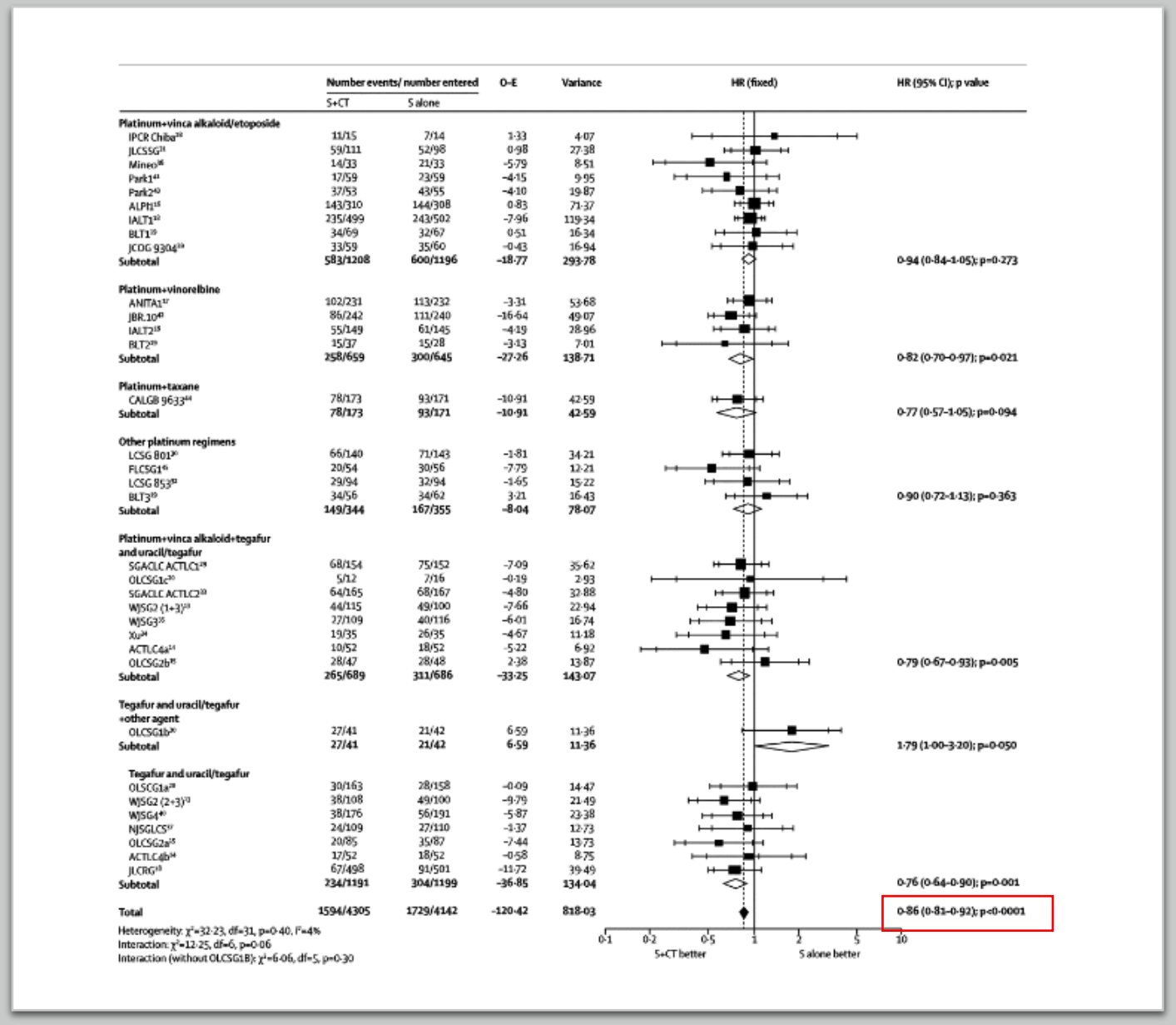
	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); p value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	−6·40	11·19	
Spain 1994	19/29	27/30	−8·88	9·65	
MIP-91	137/179	146/176	−12·99	70·22	
SWOG 59015	3/5	12/16	−1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	23/39	15/40	3·86	9·36	
Finland 2003	19/30	19/32	−0·50	9·48	
MRC BLT	4/5	3/5	1·26	1·60	
MRC LU22	151/258	158/261	−2·92	77·01	
SWOG 59900	93/180	103/174	−9·31	48·84	
China 2002	26/32	18/23	1·42	10·78	
China 2005	8/19	14/21	−3·31	5·44	
ChEST	45/129	61/141	−10·27	26·39	
NATCH	99/201	109/212	−4·11	51·95	
Total	**682/1178**	**745/1207**	**−50·62**	**351·78**	**0·87 (0·78–0·96); p=0·007**



Overall HR
0·87 (0·78–0·96), p=0·007 (fixed effect)
0·86 (0·75–0·98), p=0·03 (random effects)
Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

NSCLC Meta-analyses Collaborative Group ‡



	Number events/ number entered		O-E	Variance	HR (fixed)	HR (95% CI); p value
	S+CT	S alone				
Platinum+vinca alkaloid/etoposide						
IPCR Chiba[22]	11/15	7/14	1·33	4·07		
JLCSSG[21]	59/111	52/98	0·98	27·38		
Mineo[36]	14/33	21/33	−5·79	8·51		
Park1[41]	17/59	23/59	−4·15	9·95		
Park2[40]	37/53	43/55	−4·10	19·87		
ALPI[15]	143/310	144/308	0·83	71·37		
IALT1[12]	235/499	243/502	−7·96	119·34		
BLT1[19]	34/69	32/67	0·51	16·34		
JCOG 9304[39]	33/59	35/60	−0·43	16·94		
Subtotal	**583/1208**	**600/1196**	**−18·77**	**293·78**		**0·94 (0·84–1·05); p=0·273**
Platinum+vinorelbine						
ANITA1[17]	102/231	113/232	−3·31	53·68		
JBR.10[42]	86/242	111/240	−16·64	49·07		
IALT2[13]	55/149	61/145	−4·19	28·96		
BLT2[20]	15/37	15/28	−3·13	7·01		
Subtotal	**258/659**	**300/645**	**−27·26**	**138·71**		**0·82 (0·70–0·97); p=0·021**
Platinum+taxane						
CALGB 9633[44]	78/173	93/171	−10·91	42·59		
Subtotal	**78/173**	**93/171**	**−10·91**	**42·59**		**0·77 (0·57–1·05); p=0·094**
Other platinum regimens						
LCSG 801[30]	66/140	71/143	−1·81	34·21		
FLCSG1[16]	20/54	30/56	−7·79	12·21		
LCSG 853[32]	29/94	32/94	−1·65	15·22		
BLT3[29]	34/56	34/62	3·21	16·43		
Subtotal	**149/344**	**167/355**	**−8·04**	**78·07**		**0·90 (0·72–1·13); p=0·363**
Platinum+vinca alkaloid+tegafur and uracil/tegafur						
SGACLC ACTLC1[28]	68/154	75/152	−7·09	35·62		
OLCSG1c[35]	5/12	7/16	−0·19	2·93		
SGACLC ACTLC2[33]	64/165	68/167	−4·80	32·88		
WJSG2 (1+3)[23]	44/115	49/100	−7·66	22·94		
WJSG3[25]	27/109	40/116	−6·01	16·74		
Xu[24]	19/35	26/35	−4·67	11·18		
ACTLC4a[14]	10/52	18/52	−5·22	6·92		
OLCSG2b[31]	28/47	28/48	2·38	13·87		
Subtotal	**265/689**	**311/686**	**−33·25**	**143·07**		**0·79 (0·67–0·93); p=0·005**
Tegafur and uracil/tegafur +other agent						
OLCSG1b[26]	27/41	21/42	6·59	11·36		
Subtotal	**27/41**	**21/42**	**6·59**	**11·36**		**1·79 (1·00–3·20); p=0·050**
Tegafur and uracil/tegafur						
OLSCG1a[27]	30/163	28/158	−0·09	14·47		
WJSG2 (2+3)[23]	38/108	49/100	−9·79	21·49		
WJSG4[45]	38/176	56/191	−5·87	23·38		
NJSGLCS[37]	24/109	27/110	−1·37	12·73		
OLCSG2a[35]	20/85	35/87	−7·44	13·73		
ACTLC4b[34]	17/52	18/52	−0·58	8·75		
JLCRG[43]	67/498	91/501	−11·72	39·49		
Subtotal	**234/1191**	**304/1199**	**−36·85**	**134·04**		**0·76 (0·64–0·90); p=0·001**
Total	**1594/4305**	**1729/4142**	**−120·42**	**818·03**		**0·86 (0·81–0·92); p<0·0001**

Heterogeneity: χ^2=32·23, df=31, p=0·40, I^2=4%
Interaction: χ^2=12·25, df=6, p=0·06
Interaction (without OLCSG1B): χ^2=6·06, df=5, p=0·30

0·1 0·2 0·5 1 2 5 10
S+CT better S alone better

Preoperative versus Postoperative Chemotherapy in Patients with Resectable Non-small Cell Lung Cancer

Systematic Review and Indirect Comparison Meta-Analysis of Randomized Trials

Eric Lim, MB, ChB, MD, MSc, FRCS, Grace Harris, MBBS,* Amit Patel, MB, ChB, MRCS,* Iki Adachi, MD,* Lyn Edmonds, MCLIP,† and Fujian Song, BMed, MMed, PhD‡*

TABLE 3. Estimated 5-yr Survival Probability, Impact on Survival and Limits of the Difference Between Postoperative and Preoperative Administration

Stage	5-yr Survival Reported	Postoperative Chemotherapy			Preoperative Chemotherapy			Difference (Postoperative versus Preoperative)		
		Expected	Lower 95% CI	Upper 95% CI	Expected	Lower 95% CI	Upper 95% CI	Expected	Upper 95% CI	Lower 95% CI
IA	73	78.4	76.4	80.3	78.1	73.7	81.8	−0.30	−4.23	4.51
IB	54	63.2	59.8	66.4	62.7	55.2	69.0	−0.51	−7.20	7.68
IIA	**48**	**58.5**	**54.6**	**62.0**	**57.9**	**49.4**	**64.9**	**−0.58**	**−8.14**	**8.68**
IIB	**38**	**50.5**	**45.9**	**54.7**	**49.8**	**39.7**	**58.2**	**−0.69**	**−9.71**	**10.35**
IIIA	**25**	**40.1**	**34.5**	**45.3**	**39.3**	**27.0**	**49.4**	**−0.84**	**−11.75**	**12.52**
IIIB	19	35.3	29.3	40.9	34.4	21.2	45.3	−0.91	−12.68	13.53
IV	21	36.9	31.0	42.3	36.0	23.1	46.7	−0.88	−12.37	13.19

All numbers are given as a percentage. Bold font indicates the tumour stage for which the data is most applicable.

Summary

Surgery does not cure (in most NSCLC)

Chemotherapy is beneficial

- Improved DFS and OS

Timing of chemotherapy does not make a difference (NACT vs Adjuvant)

- Absolute 5-year OS benefit 5%

Platinum containing regimens form the backbone

Pros and cons of pre-operative systemic therapy

Pros

- Increased patient compliance
  - 97% (90% all 3 cycles) v 66.2% (61% all 3 cycles) (Felip et al. JCO 2010)
- Potential nodal clearance of tumor with down-staging
- *in vivo* chemosensitivity testing of the chemotherapy regimen;
- Leverage on reservoir of tissue resident effector immune cells
- Opportunity to adapt adjuvant strategies based on *in vivo* response
- Decreasing tumor size to allow more ready resection
- Decreased surgical seeding

Cons

- Delay in primary tumor control (resection)
  - **Patients do not proceed to surgery**
  - e.g. tumor progresses while on systemic therapy
- Increased surgical morbidity and mortality
  - **Technical challenges due to treatment effect (chemoRT, chemo, targeted, ICI)**

Does response or pathology CR rate mean anything in NSCLC?

Pathological response predicts for survival

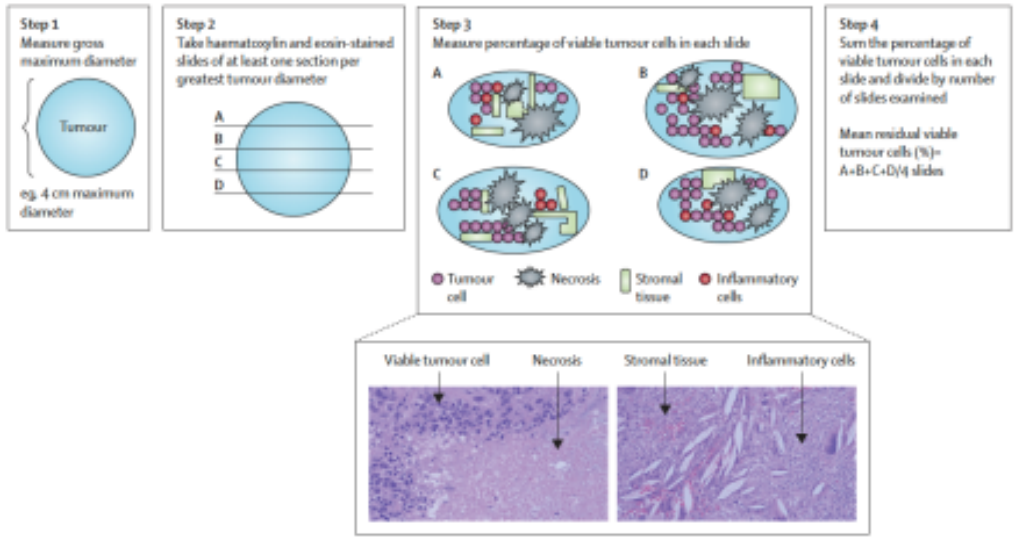
Tumor

- Complete pathological response:
  - 5% viable tumor left
- Major pathological response:
  - 10% viable tumor

	Hazard ratio for death
1–10%	1·00
11–30%	2·51 (95% CI 0·91–6·96)
31–50%	3·39 (95% CI 1·40–8·22)
51–70%	4·57 (95% CI 1·98–10·52)
71–100%	4·78 (95% CI 2·06–11·11)

Table 2: Percentage of residual viable tumour after neoadjuvant chemotherapy relative to the risk of death

Methodology



8-11% path CR rate
5-year survival significantly improved
(80% vs 56% without path CR p<0.01).

Hellmann et al. TLO 2014

IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy

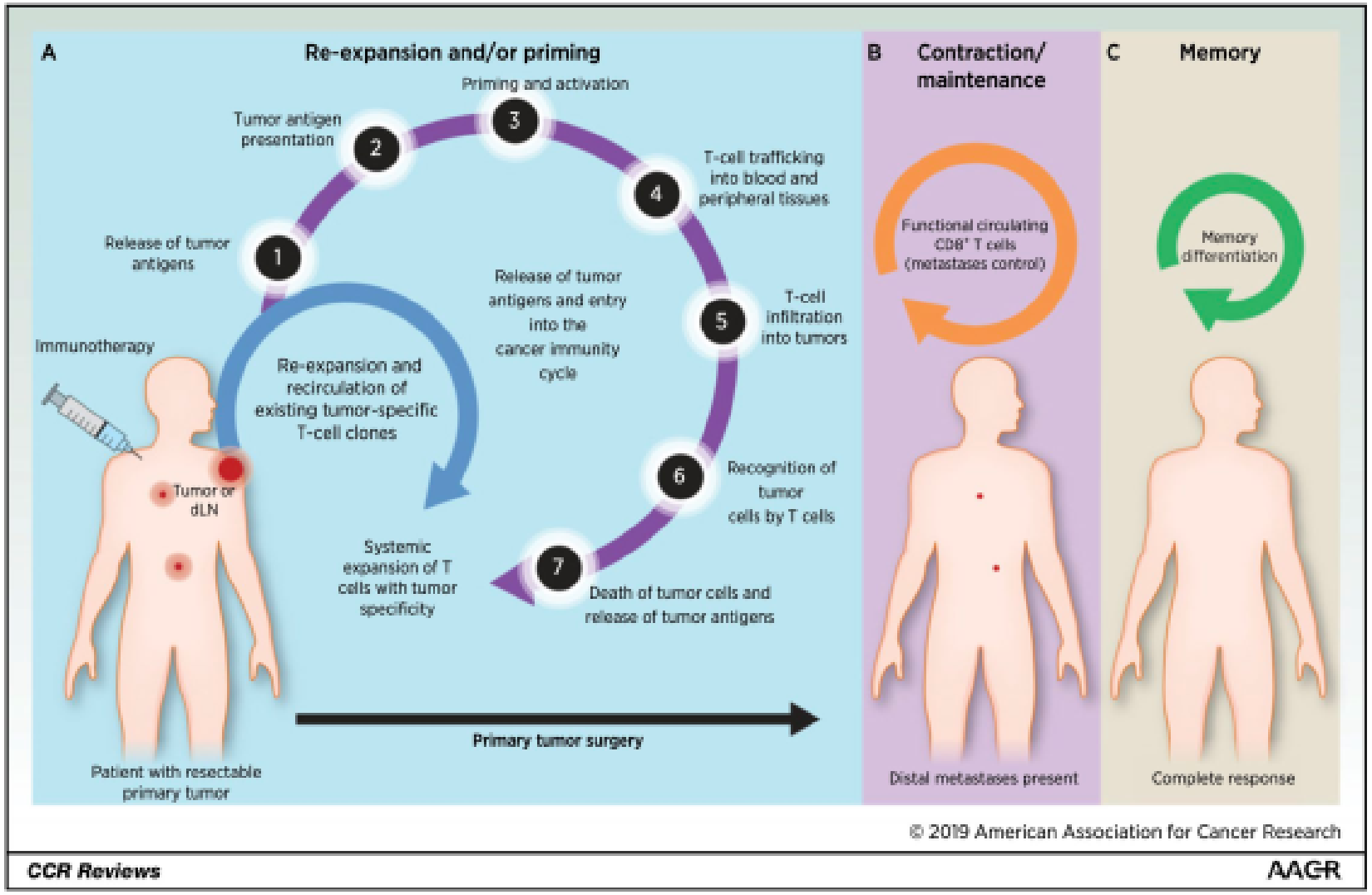
Definition of Major Pathologic Response (MPR) and Complete Pathologic Response (CPR)

Recommendation 6.

Definition of MPR.MPR is defined as the reduction of viable tumor to the amount beneath an established clinically significant cutoff based on prior evidence according to the individual histologic type of lung cancer and a specific therapy (Fig. 2*A–D*).

The historical Definition of MPR for all histologic types of lung cancer is less than or equal to 10% of viable tumor, with no viable tumor required for CPR. MPR is calculated as the estimated size of viable tumor divided by the size of the tumor bed. For the

Rationale for neoadjuvant immunotherapy



- Immunotherapy is generally well tolerated compared to chemotherapy
- Preclinical mouse studies with long-term survivors observed in those with expanded tumour-specific CD8+ T cells
- Primary tumour can be leveraged as antigen source for expansion and activation of tumour-specific T-cells and systemic surveillance of micrometastases

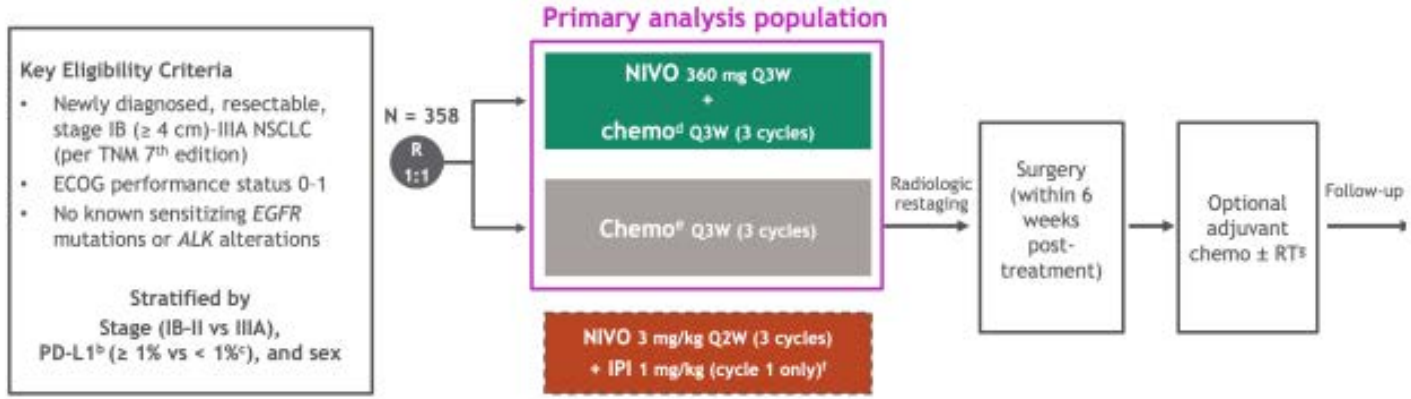
Studies of CPI in operable NSCLC

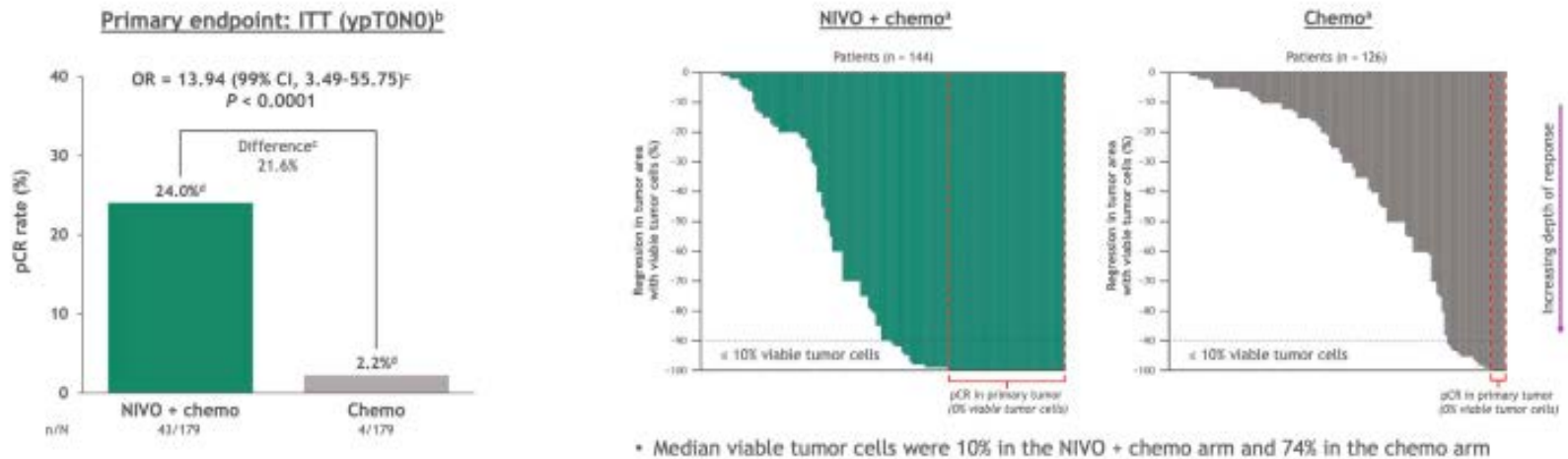
- Single arm CPI alone
- Single arm CPI + Chemo
- RCT of chemo+ CPI OR Dual CPI

Checkmate 816

Chemo-IO as a neoadjuvant strategy

Primary endpoint
- **Path CR**
- **EFS**





• Median viable tumor cells were 10% in the NIVO + chemo arm and 74% in the chemo arm

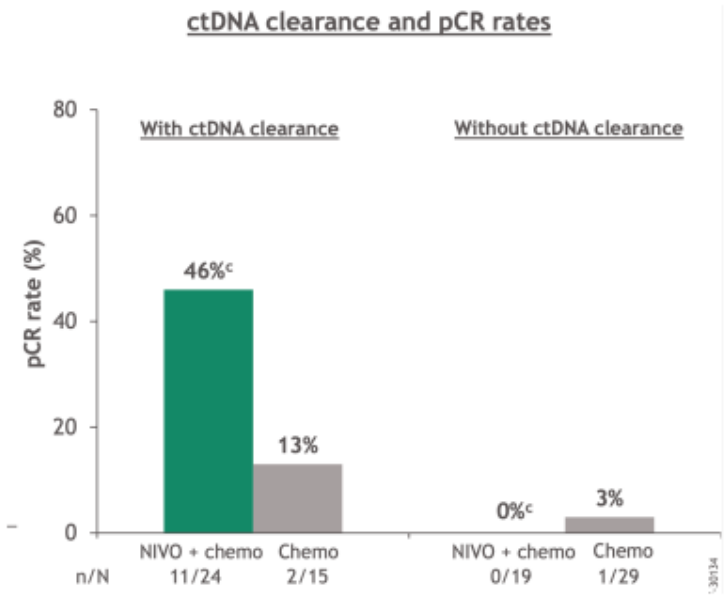
ORR: 54% vs 37%

Forde et al. AACR 2021

Subgroup analysis

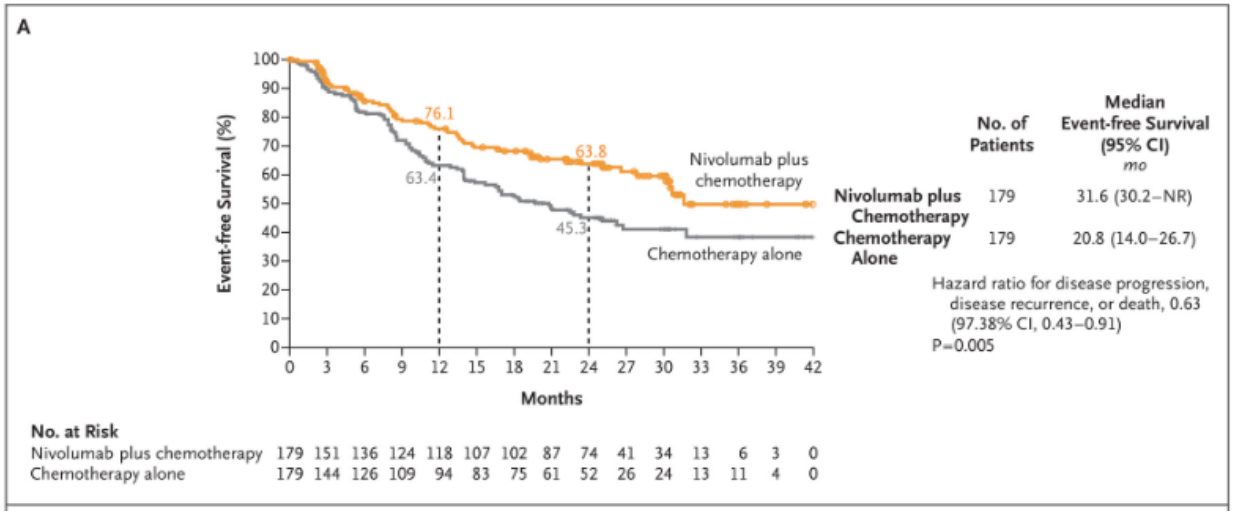
	pCR[a] rate, %		Unweighted pCR difference, % (95% CI)	Unweighted pCR difference, %
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	24	2		22
< 65 years (n = 176)	27	0		27
≥ 65 years (n = 182)	21	4		17
Male (n = 255)	23	2		20
Female (n = 103)	28	2		26
North America (n = 91)	22	2		20
Europe (n = 66)	24	0		24
Asia (n = 177)	28	3		25
Stage IB-II (n = 128)	**26**	**5**		**21**
Stage IIIA (n = 228)	**23**	**1**		**22**
Squamous (n = 182)	**25**	**4**		**21**
Non-squamous (n = 176)	**23**	**0**		**23**
Current/former smoker (n = 318)	26	2		23
Never smoker (n = 39)	10	0		10
PD-L1 < 1% (n = 155)	**17**	**3**		**14**
PD-L1 ≥ 1% (n = 178)	**33**	**2**		**30**
PD-L1 1-49% (n = 98)	24	0		24
PD-L1 ≥ 50% (n = 80)	45	5		40
TMB < 12.3 mut/Mb (n = 102)	22	2		21
TMB ≥ 12.3 mut/Mb (n = 76)	31	3		28
Cisplatin (n = 258)	22	2		20
Carboplatin (n = 72)	31	0		31

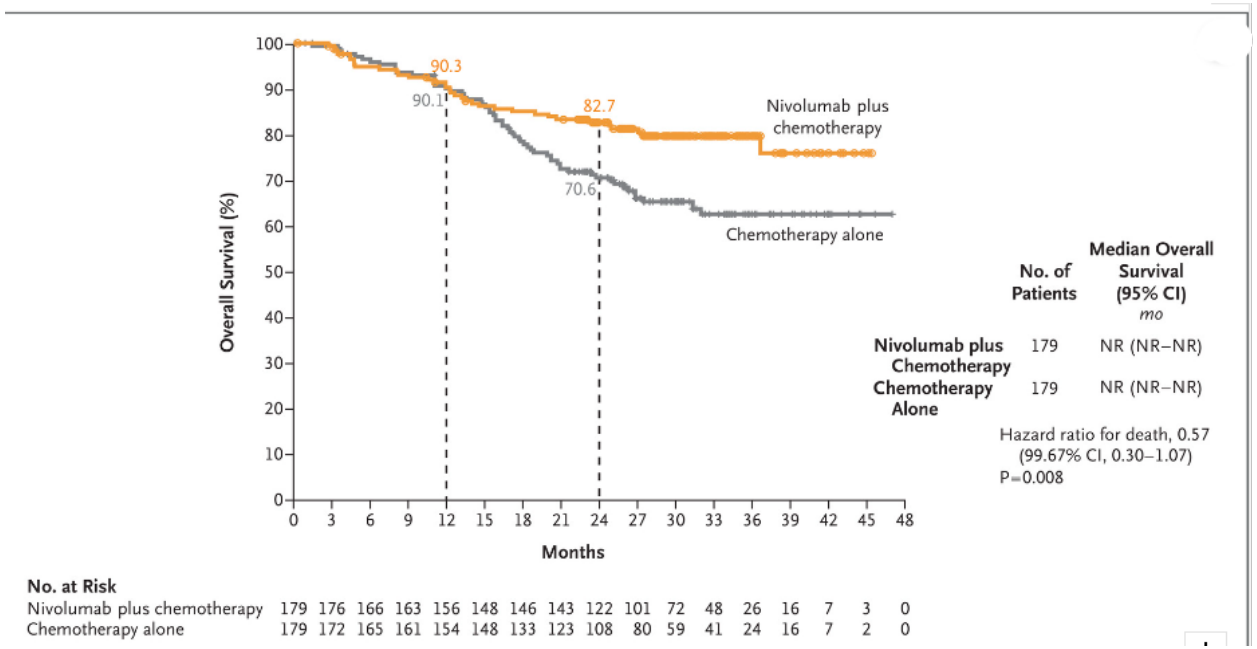
[a]Per BIPR in ITT.



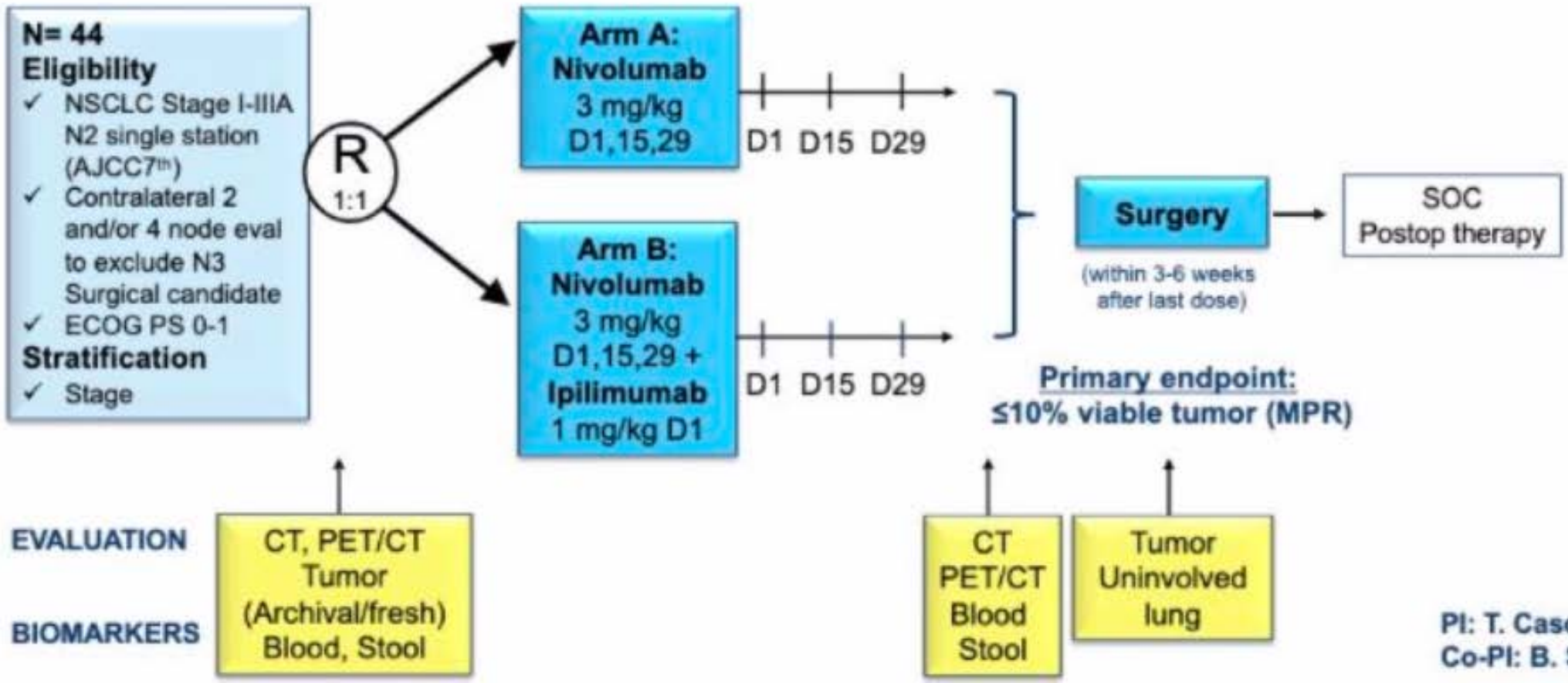
Forde et al. AACR 2021

EFS and OS


A
Event-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
76.1
63.8
63.4
45.3
Nivolumab plus chemotherapy
Chemotherapy alone
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42
Months
No. at Risk
Nivolumab plus chemotherapy 179 151 136 124 118 107 102 87 74 41 34 13 6 3 0
Chemotherapy alone 179 144 126 109 94 83 75 61 52 26 24 13 11 4 0
No. of Patients
Median Event-free Survival (95% CI) mo
Nivolumab plus Chemotherapy 179 31.6 (30.2–NR)
Chemotherapy Alone 179 20.8 (14.0–26.7)
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005


Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
90.3
90.1
82.7
70.6
Nivolumab plus chemotherapy
Chemotherapy alone
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months
No. at Risk
Nivolumab plus chemotherapy 179 176 166 163 156 148 146 143 122 101 72 48 26 16 7 3 0
Chemotherapy alone 179 172 165 161 154 148 133 123 108 80 59 41 24 16 7 2 0
No. of Patients
Median Overall Survival (95% CI) mo
Nivolumab plus Chemotherapy 179 NR (NR–NR)
Chemotherapy Alone 179 NR (NR–NR)
Hazard ratio for death, 0.57 (99.67% CI, 0.30–1.07)
P=0.008

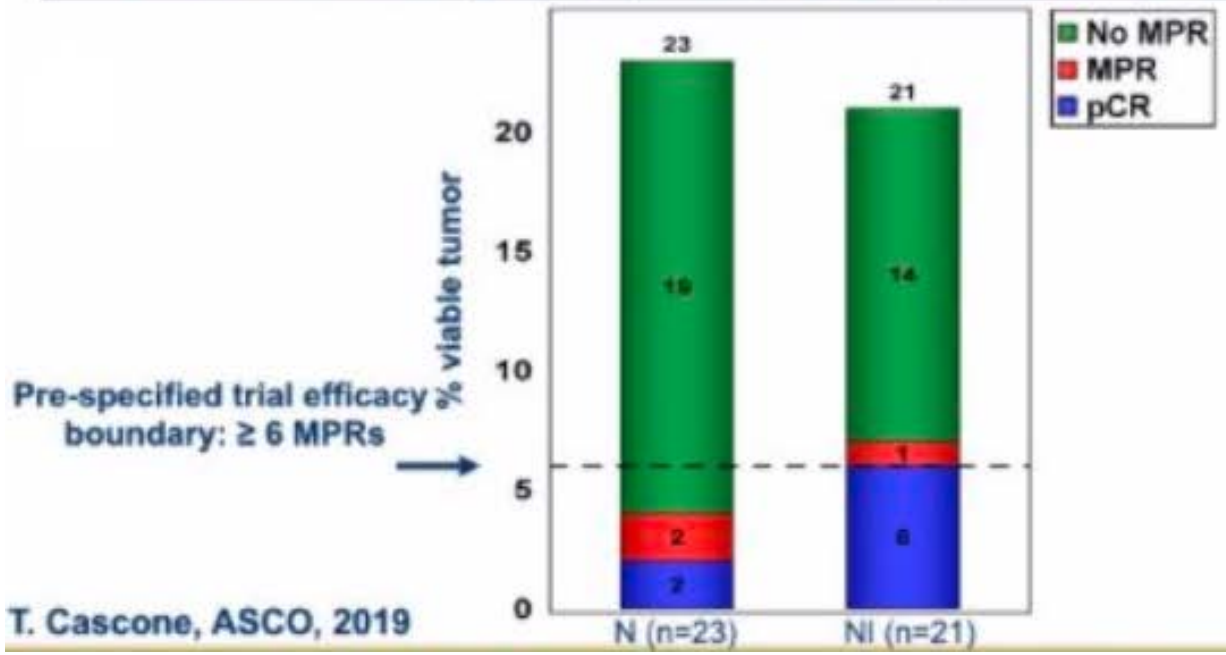
NEOSTAR: phase II study of induction checkpoint blockade for untreated stage I-IIIA NSCLC amenable for surgical resection

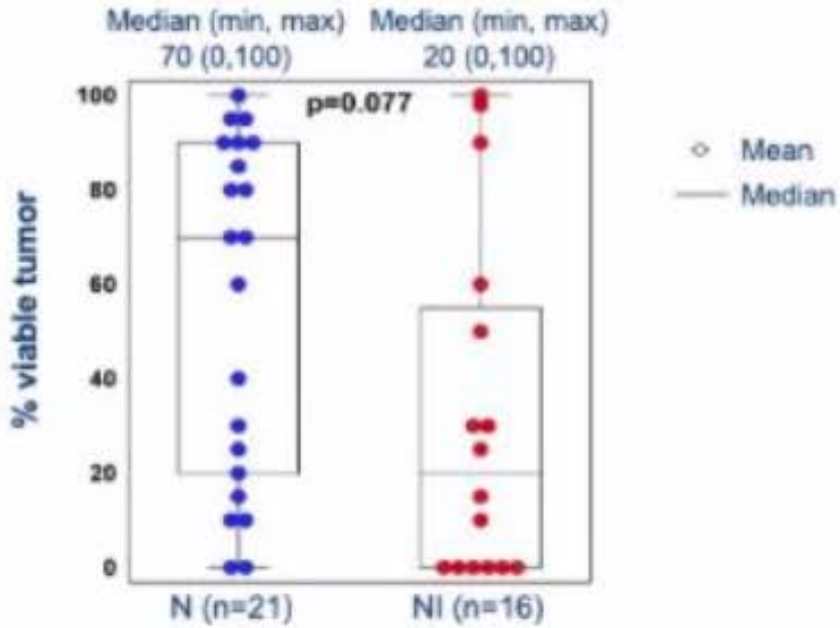


NEOSTAR Trial Primary Endpoint: MPR rate

Overall ITT Resected + not resected*	Total n = 44	N n = 23	NI n = 21
MPR + pCR	11 (25%)	4 (17%) (95% CI:5%,39%)	7 (33%) (95% CI:15%,57%)
0% viable tumor (pCR)	8 (18%)	2 (9%)	6 (29%)
1-10% viable tumor	3 (7%)	2 (9%)	1 (5%)

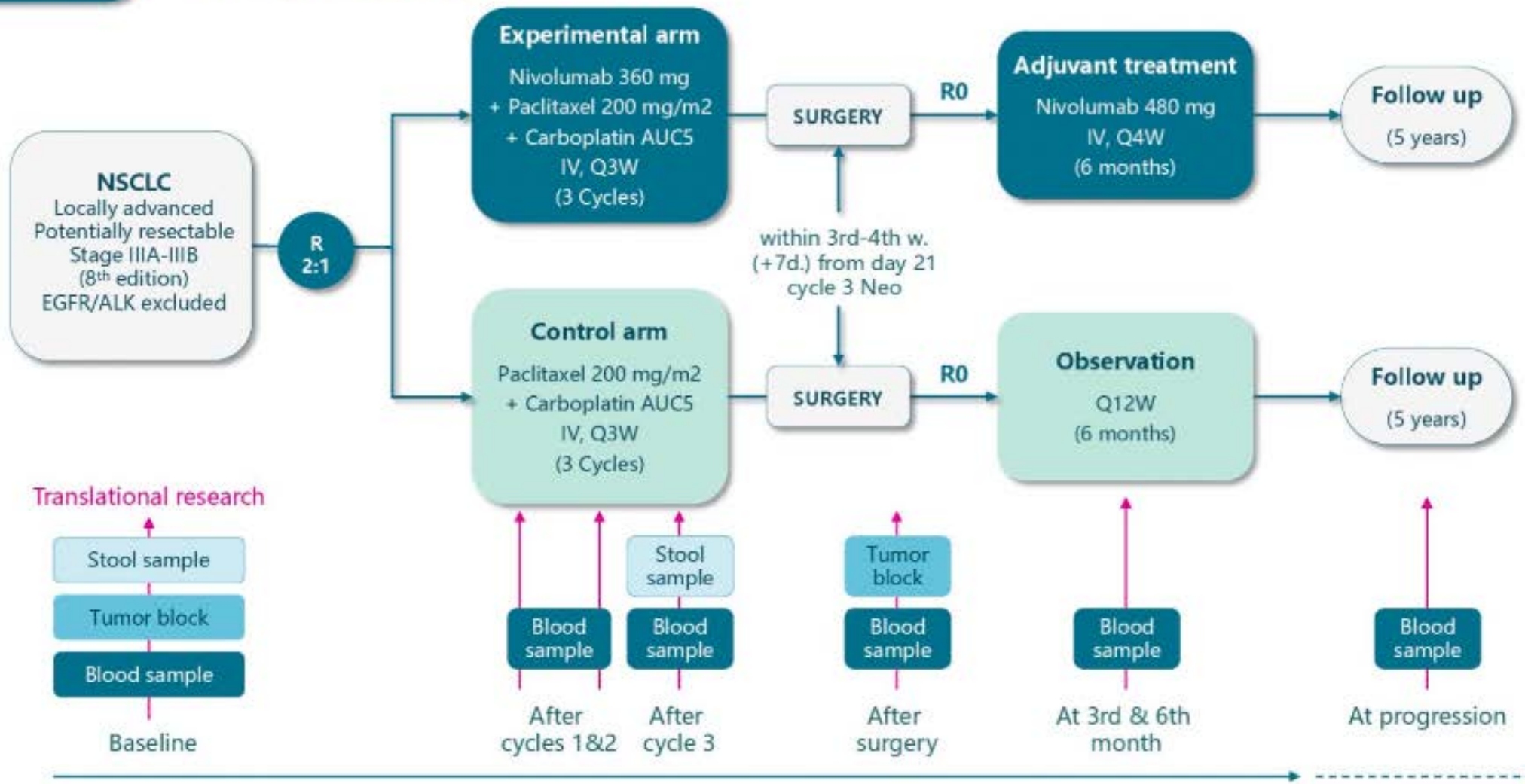
Evaluable* Resected on trial	Total n = 37	N n = 21	NI n = 16
MPR + pCR	11 (30%)	4 (19%)	7 (44%)
0% viable tumor (pCR)	8 (22%)	2 (10%)	6 (38%)
1-10% viable tumor	3 (8%)	2 (10%)	1 (6%)





T. Cascone, ASCO, 2019

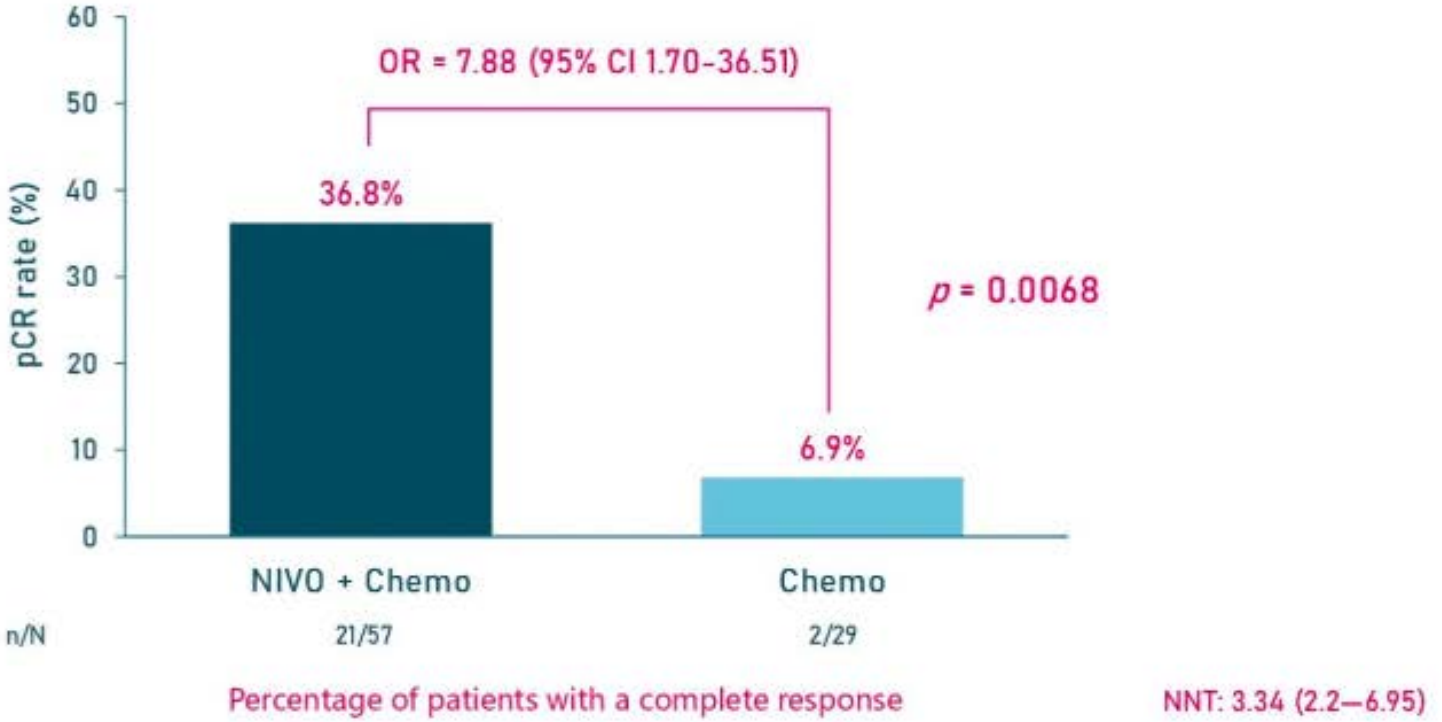
NADIM II Study design



NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

NADIM II Primary endpoint - pCR

pCR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population[b]



[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders

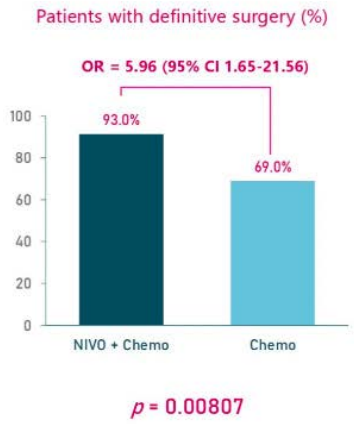
Chemo, chemotherapy; ITT, intention-to-treat; Nivo, nivolumab; pCR, pathological complete response; RR, risk ratio

Higher proportion underwent surgery

Direct correlation between PDL1 expression and pCR

NADIM II Surgery summary

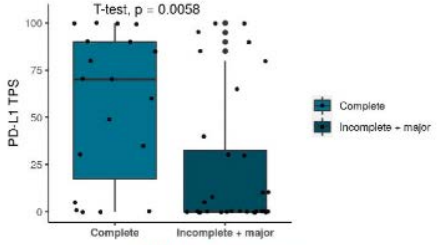
Surgery summary			
Patients, No. (%)	**NIVO + chemo (n = 57)**	**Chemo (n = 29)**	**Total**
Patients with definitive surgery	53 (93.0)	20 (69.0)	73
tients with cancelled definitive surgery	4 (7.0)	9 (31.0)	13
Due to adverse events	1 (1.7)	0 (0.0)	1
Due to disease progression	0 (0.0)	4 (13.7)	4
Not suitable for surgery	3 (5.2)	5 (17.2)	8



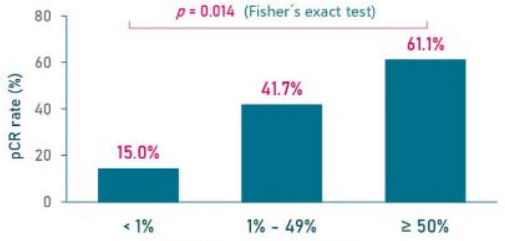
Nivo, nivolumab; Chemo, chemotherapy

Predictive biomarkers of response (pCR)[a] to neoadjuvant NIVO + CT (ITT population)[b]

- Patients who achieved pCR had higher PD-L1 expression than patients who did not
- pCR rate raised across increasing categories of PD-L1 TPS
- Predictive value of PD-L1 TPS for pCR was AUC 0.728 (95% CI 0.58-0.87; $p = 0.001$)
- **OR** for pCR in the PD-L1 positive group (**≥1%**): **16.0** (95% CI 1.86-137.61; $p = 0.007$)



Pathological response



PD-L1 Tumor Proportion Score

IMpower010 study design

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumors ≥4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

1-4 cycles cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

N=1280

R 1:1

No crossover

Atezolizumab
1200 mg q21d
16 cycles

N=1005

BSC

Survival follow-up

Hierarchical statistical testing

DFS in PD-L1 TC ≥1% stage II-IIIA population[b]

If positive:

DFS in all-randomized stage II-IIIA population[b]

If positive:

DFS in ITT population[b] (all-randomized stage IB-IIIA)

If positive:

OS in ITT population[b] (all-randomized stage IB-IIIA)

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested

Stratification factors

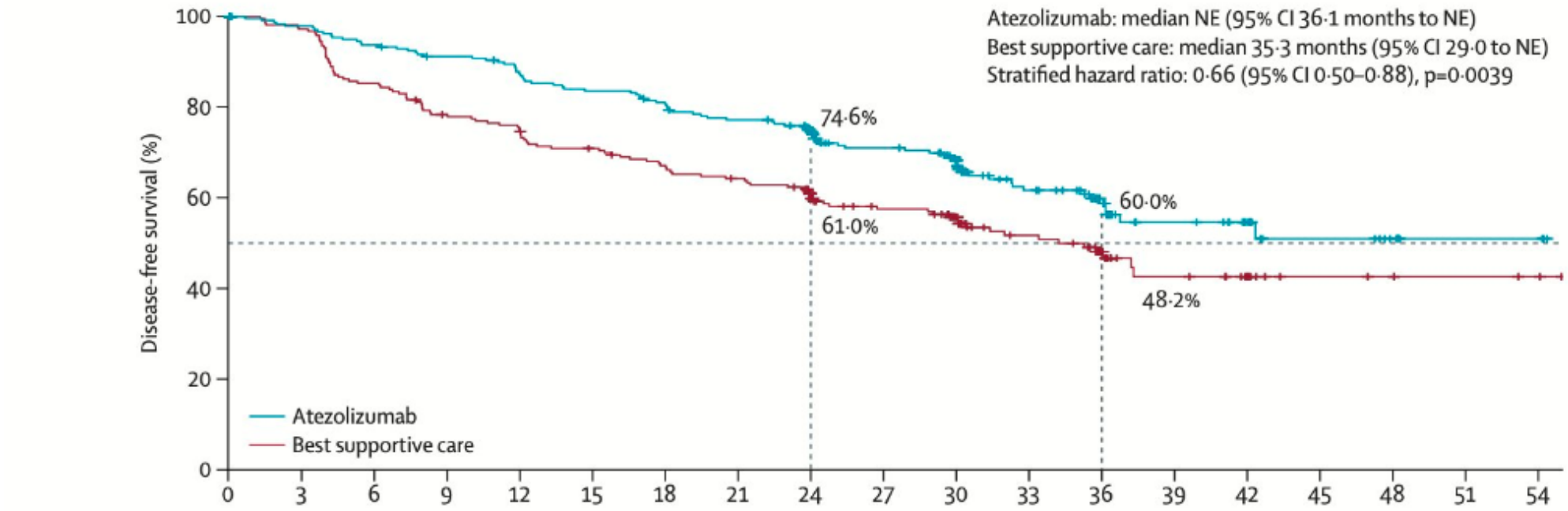
- Male vs female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomized stage II-IIIA population
  3. ITT (all-randomized stage IB-IIIA) population

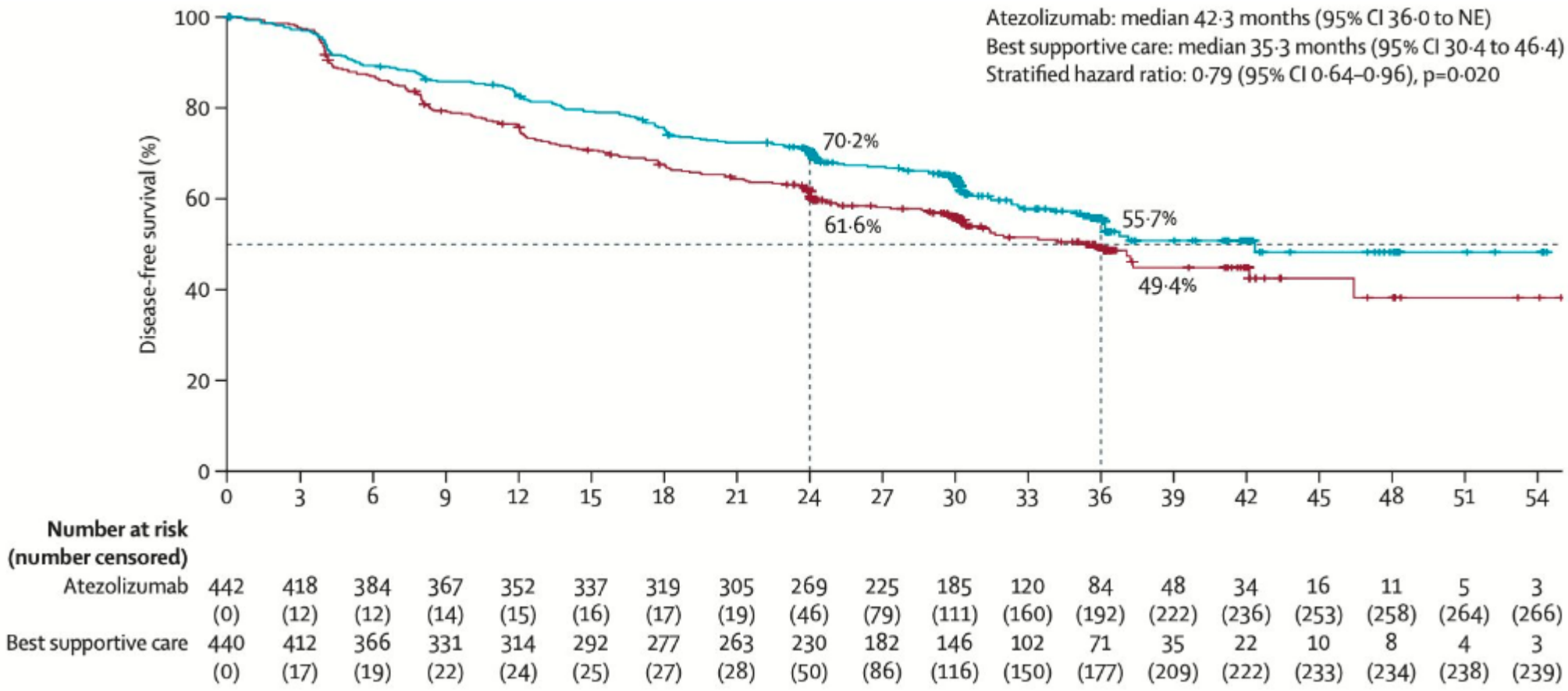
Both arms included observation and regular scans for disease recurrence on the same schedule.
IC, tumor-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

DFS in PDL-1 + Stage II-IIIA

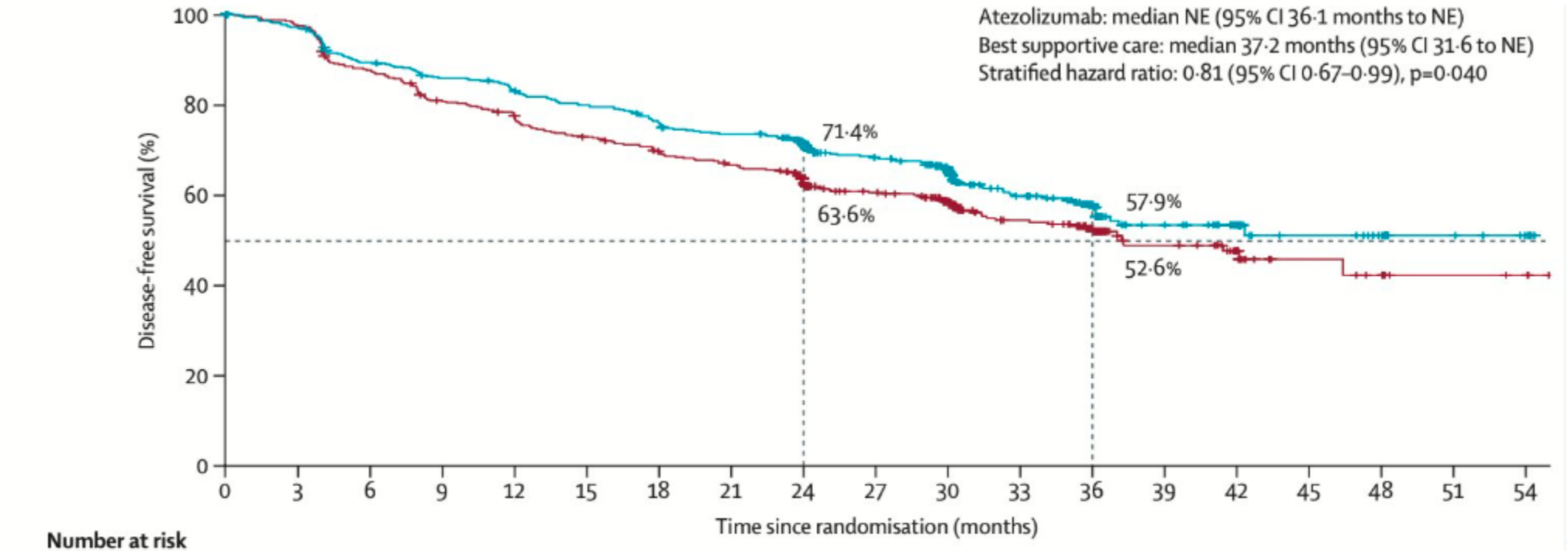


Number at risk (number censored)																			
Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
	(0)	(8)	(8)	(10)	(11)	(11)	(12)	(13)	(29)	(47)	(65)	(91)	(111)	(130)	(139)	(148)	(152)	(157)	(157)
Best supportive care	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3
	(0)	(10)	(10)	(12)	(13)	(14)	(15)	(16)	(27)	(41)	(55)	(71)	(88)	(102)	(109)	(116)	(117)	(119)	(120)

DFS for all Stage II- IIIA



DFS in the ITT population (Stage I-IIIA)



Number at risk (number censored)																			
Atezolizumab	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
	(0)	(15)	(18)	(20)	(21)	(22)	(23)	(25)	(62)	(99)	(135)	(192)	(230)	(268)	(283)	(301)	(306)	(312)	(316)
Best supportive care	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4
	(0)	(19)	(21)	(24)	(26)	(27)	(30)	(31)	(57)	(95)	(134)	(175)	(203)	(243)	(258)	(274)	(276)	(281)	(282)

d
& future

If NACT +/- IO is equivalent to adjuvant CT +/- IO with no compromise in surgical outcomes – Can we do NACT+ IO in all Stage II-IIIA NSCLC?

Is the one year of IO really needed?

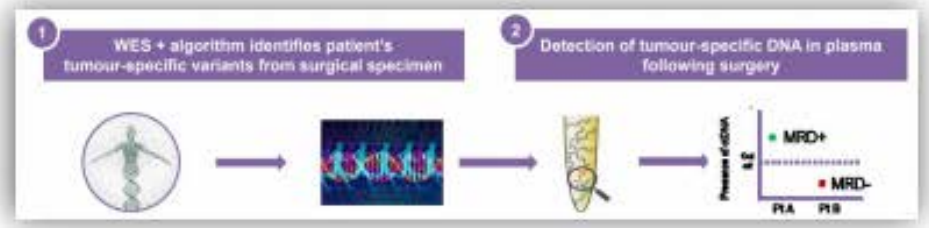
Checkmate 816 vs NADIM II vs IM power 010

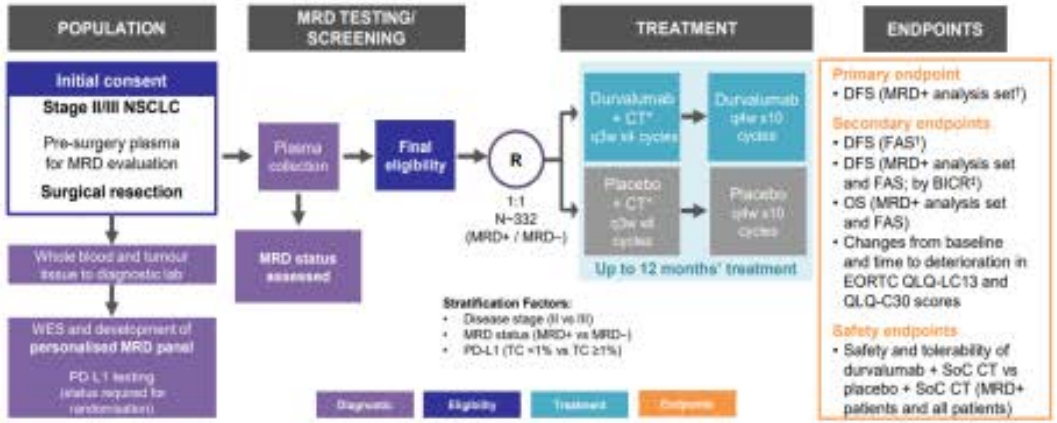
Lessons from PACIFIC and further trials of Durvalumab

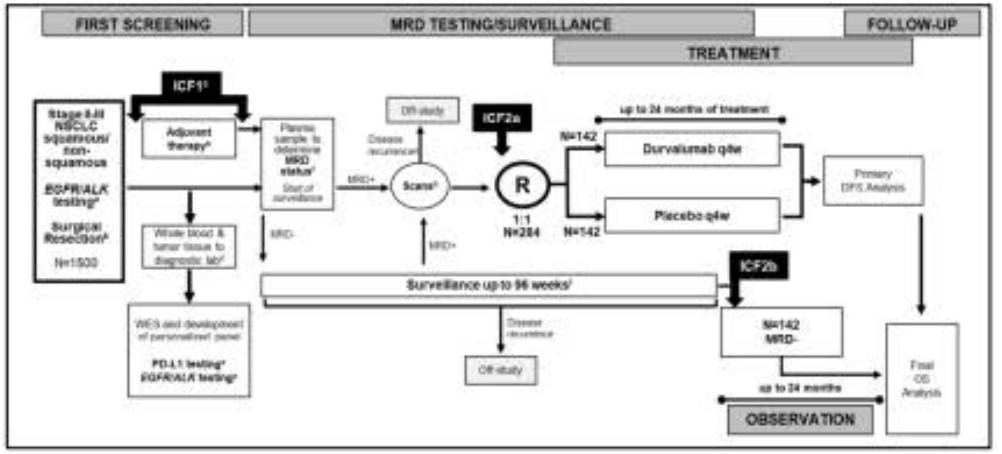
Low dose IO in this space...

MRD status as a stratification and surveillance tool

Stage II/III







MERMAID-1: *post-Sx MRD status,*
tailoring treatment depending on MRD+ status
randomized to durvalumab/placebo + chemo

MERMAID-2 *after surgery + adj chemo:*
During surveillance MRD+ with negative imaging
randomized to Durvalumab/placebo


Thank you