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Neoadjuvant Treatment in Thoracic Surgery

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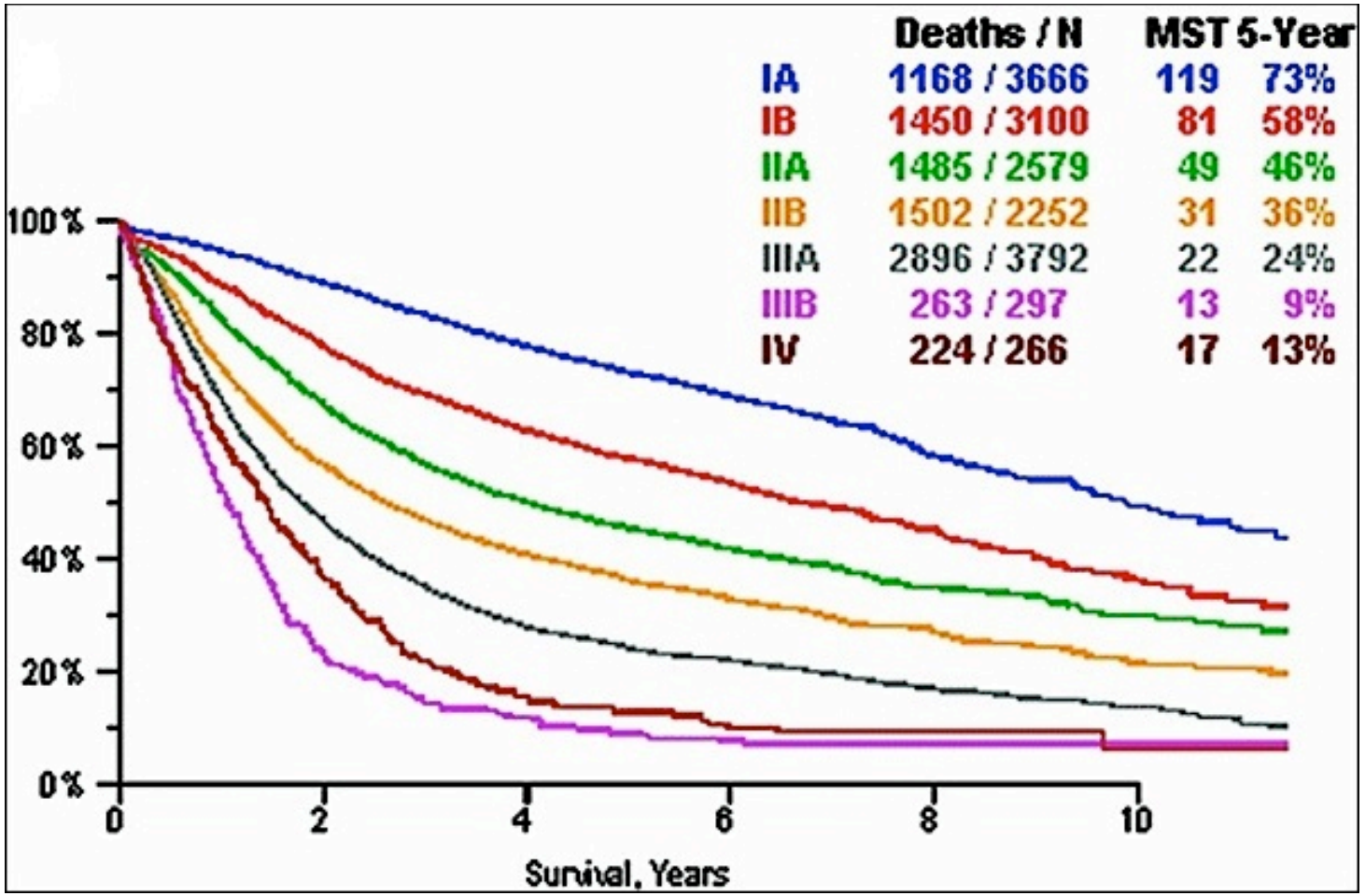
No Disclosures

Traditional Model For Early Stage Lung Cancer

- “Curable” patients should not have delay in “curative” therapy.
- Surgery alone for stage IA
- Adjuvant treatment for stage IB-IIB
- Neoadjuvant treatment for stage IIIA
- No survival benefit for targeted therapy or immunotherapy in combination with surgery.

Survival for Lung Cancer



Neoadjuvant therapy in other cancers

- Breast, esophageal, rectal
  - Decrease extent of surgery required
  - Improved survival
  - Pathologic complete response

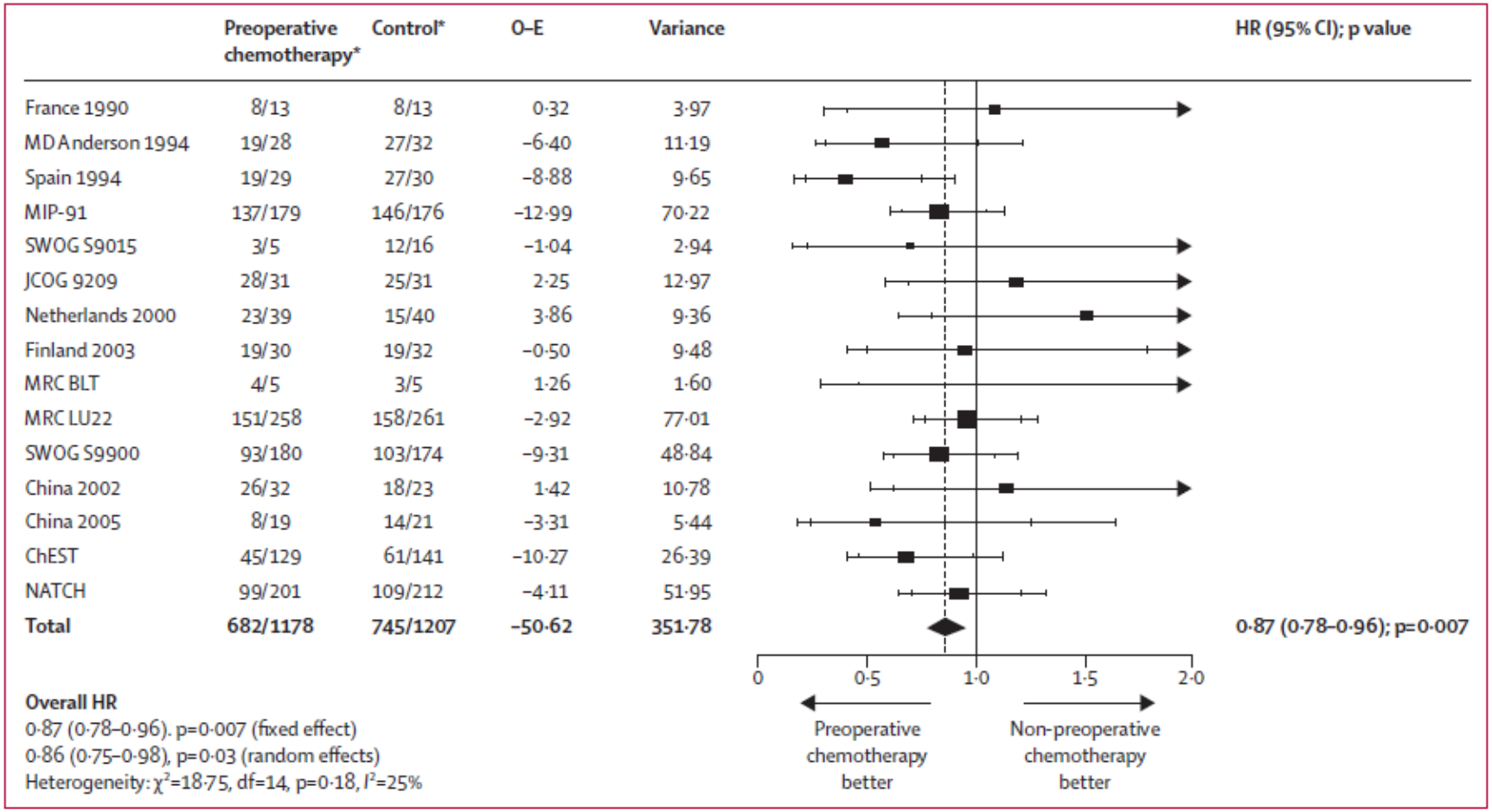
Advantages of Neoadjuvant Therapy

- Early treatment of micrometastases
- Improved adherence/tolerability of treatment
- Downstaging
- In vivo assessment of treatment
  - Pathologic response

Neoadjuvant chemotherapy

- 15 randomized trials (stage IB-IIIA)
- Most trials small (< 100 patients)
  - Poor accrual
  - Stopped due to positive data from adjuvant trials
- Meta-analyses indicate relative survival benefit of HR 0.87 (0.78-0.96) and absolute survival benefit of 5% at 5 years (similar to adjuvant trials)

Neoadjuvant Chemotherapy

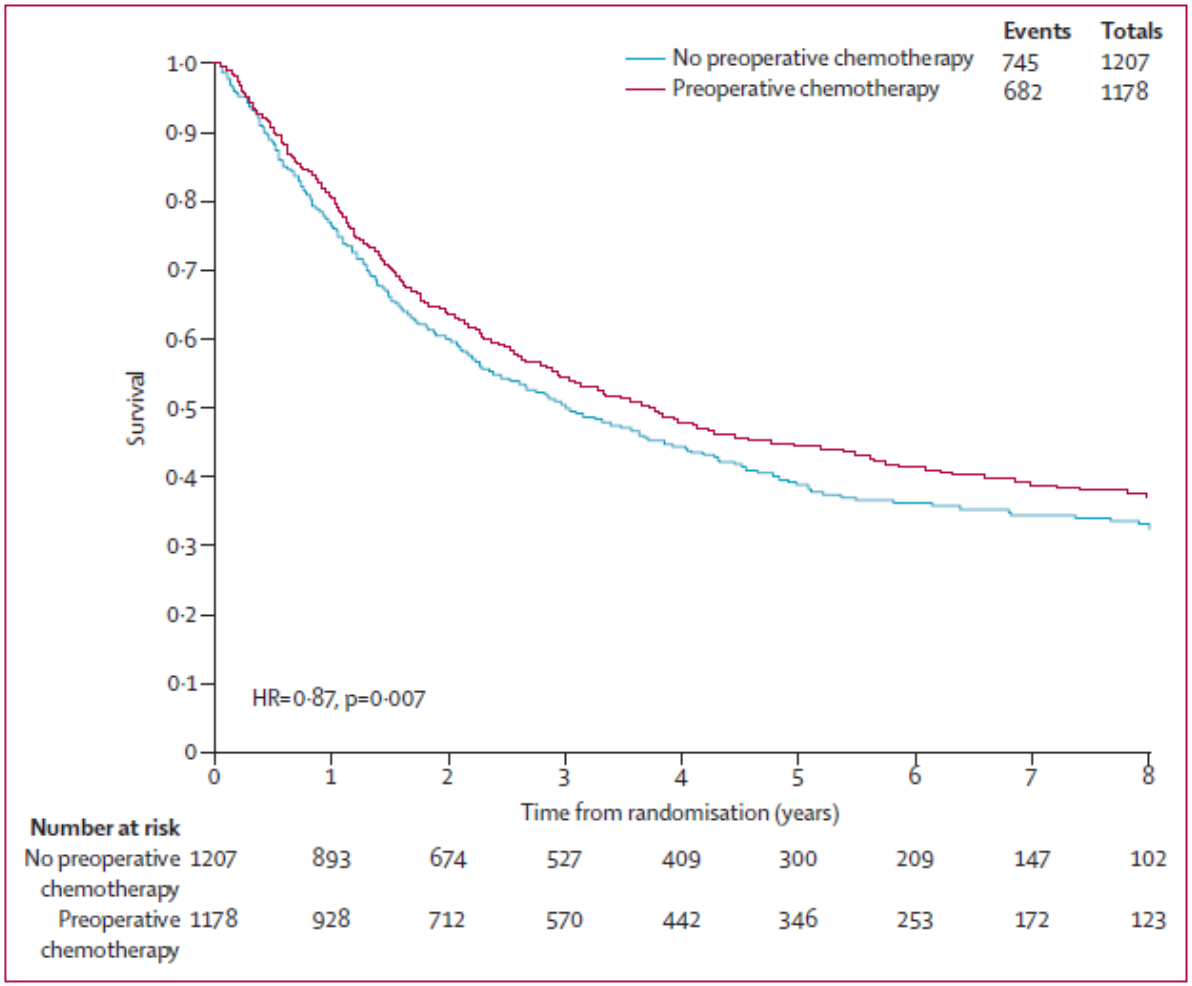


	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); p value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	−6·40	11·19	
Spain 1994	19/29	27/30	−8·88	9·65	
MIP-91	137/179	146/176	−12·99	70·22	
SWOG S9015	3/5	12/16	−1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	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 S9900	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%

NSCLC Meta-analysis Collaborative Group. Lancet 2014

Neoadjuvant Chemotherapy

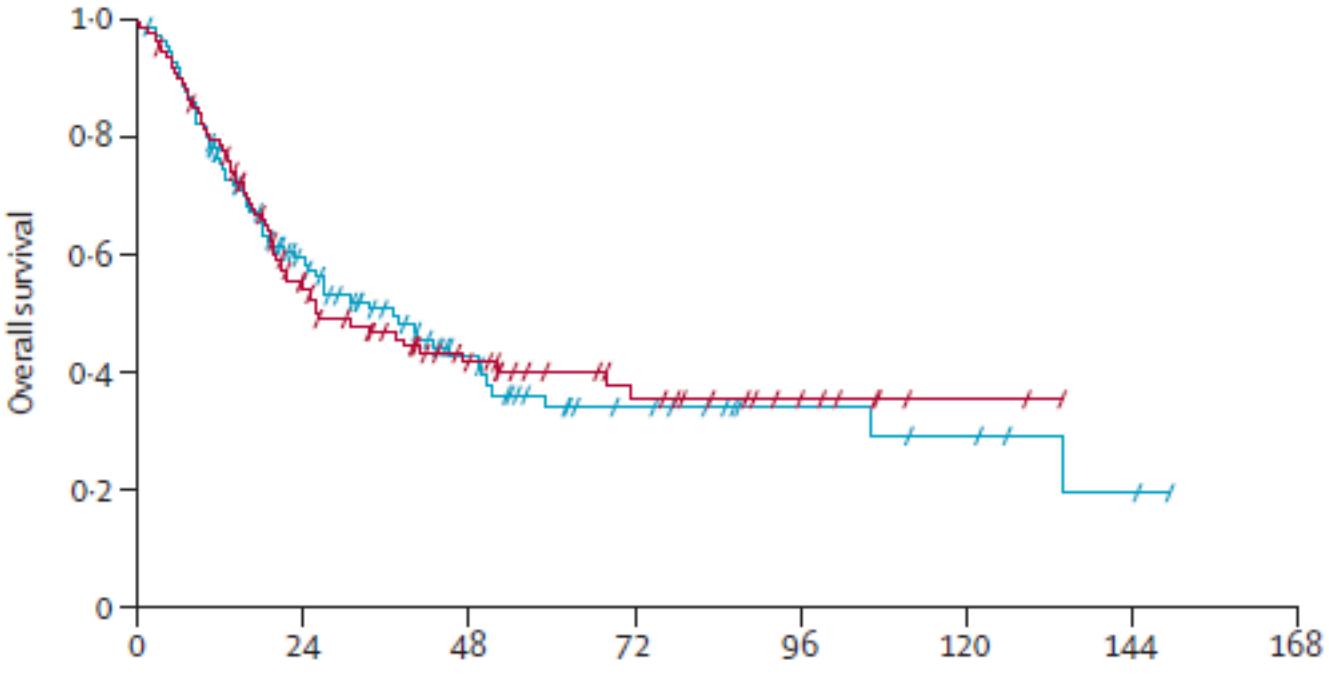


NSCLC Meta-analysis Collaborative Group. Lancet 2014

Neoadjuvant chemoradiotherapy

- Addition of radiotherapy for improved local control.
- Generally, for stage IIIA, given excellent local control with stage I-II.
- Little evidence for improved outcomes vs. neoadjuvant chemo.

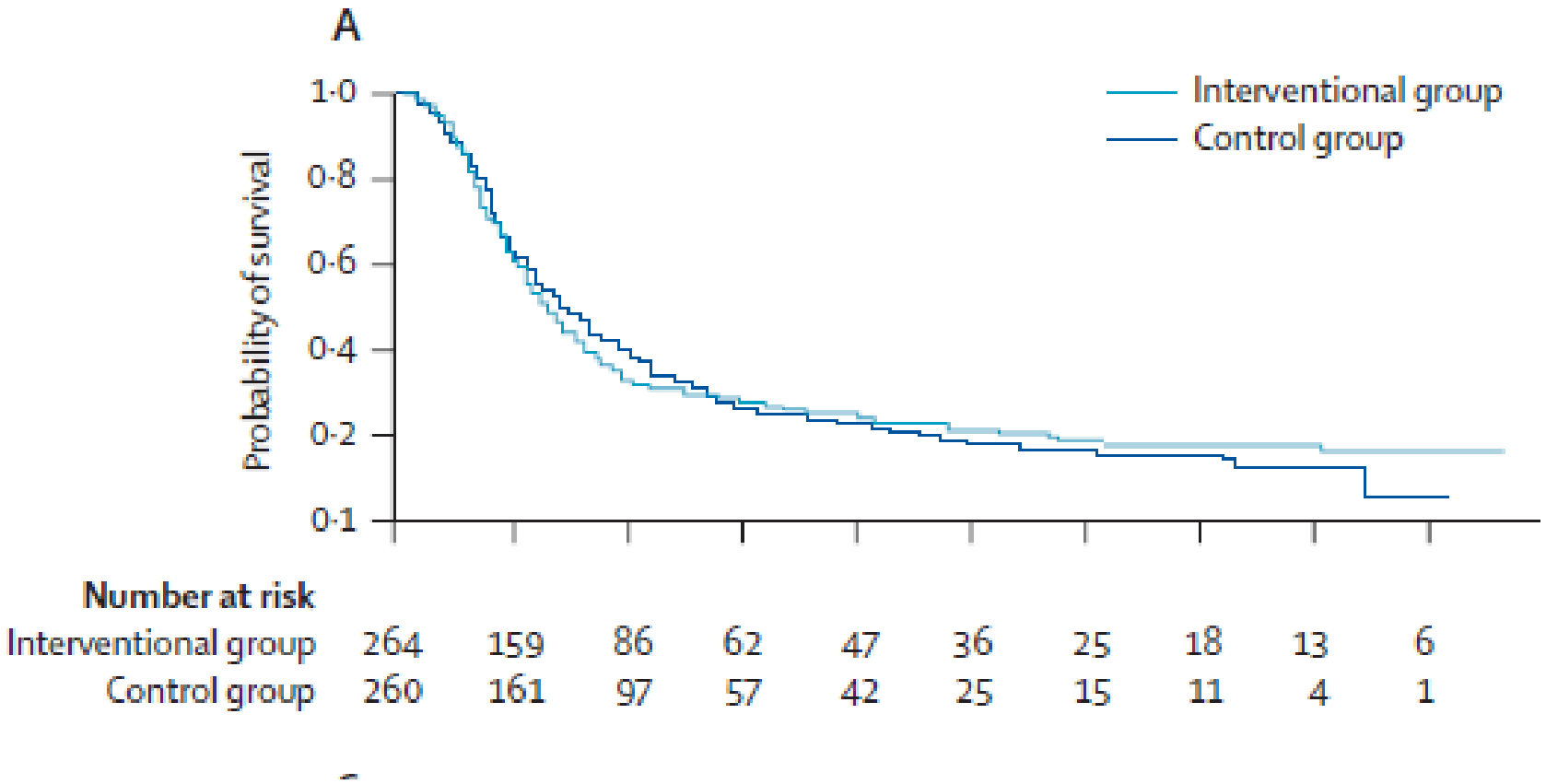
Neoadjuvant Chemoradiotherapy vs. Chemotherapy



Number at risk								
Chemoradiotherapy group	117	57	27	13	7	5	2	0
Chemotherapy group	115	53	28	15	7	2	0	0

Pless M et al. Lancet 2015

Neoadjuvant Chemoradiotherapy vs. Chemotherapy



Thomas M et al. Lancet Oncol 2008

Pathologic Response

Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint

Matthew D Hellmann, Jamie E Chaft, William N William Jr, Valerie Rusch, Katherine M W Pisters, Neda Kalhor, Apar Pataer, William D Travis, Stephen G Swisher, Mark G Kris, and The University of Texas MD Anderson Lung Cancer Collaborative Group

- Clinical trials for earlier stage patients require many patients and a long time
- mPR (<10% residual viable tumor) strongly associated with survival

Lancet Oncol 2014

Pathologic response and survival

	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

Lancet Oncol 2014

Neoadjuvant Immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

Forde et al. NEJM. May 24, 2018

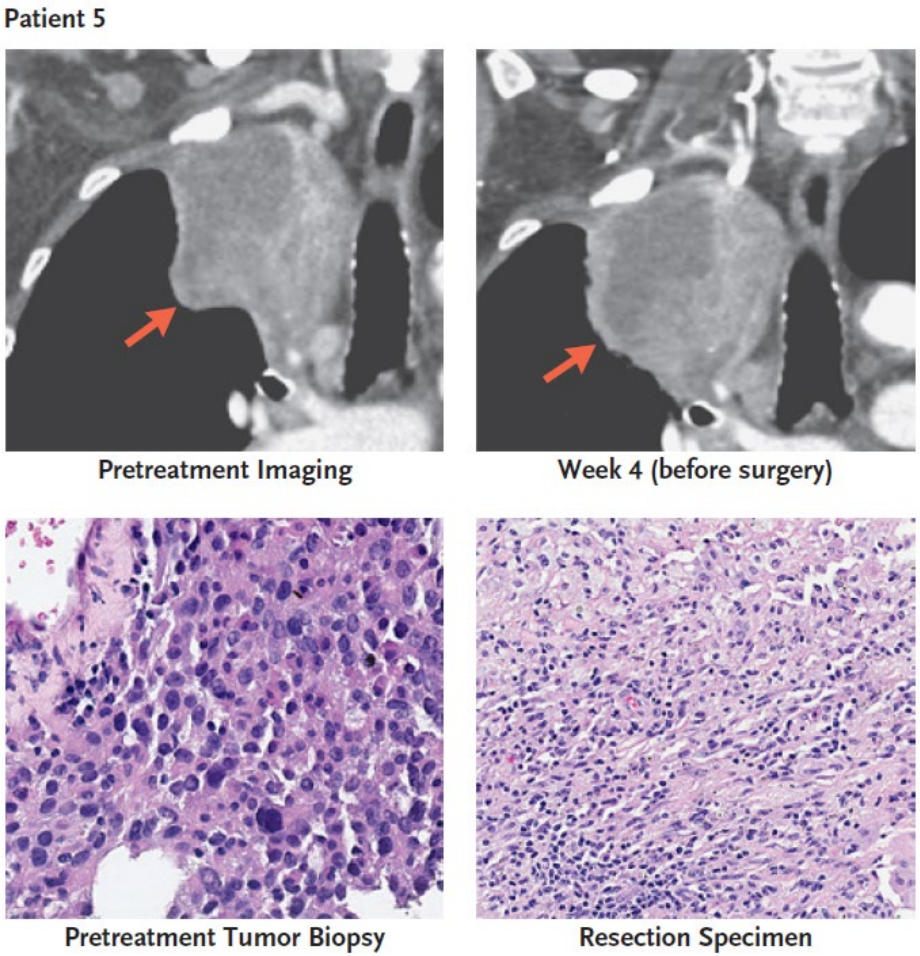
Neoadjuvant Immunotherapy

Table 1. Characteristics of the Patients at Baseline, According to Pathological Response.*

Characteristic	All Patients (N=21)	Patients with Major Pathological Response (N=9)	Patients without Major Pathological Response (N=11)†
Age at enrollment — yr			
Mean ±SD	66.9±8.3	67.7±8.3	65.8±8.5
Median (range)	67 (55–84)	66 (57–79)	67 (55–84)
Sex — no. (%)			
Female	11 (52)	6 (67)	4 (36)
Male	10 (48)	3 (33)	7 (64)
Histologic diagnosis — no. (%)			
Adenocarcinoma	13 (62)	6 (67)	6 (55)
Squamous-cell carcinoma	6 (29)	2 (22)	4 (36)
Other‡	2 (10)	1 (11)	1 (9)
Clinical disease stage — no. (%)§			
I	4 (19)	2 (22)	2 (18)
II	10 (48)	5 (56)	5 (45)
IIIA	7 (33)	2 (22)	4 (36)
Smoking status — no. (%)			
Never	3 (14)	1 (11)	2 (18)
Former or current	18 (86)	8 (89)	9 (82)

Forde et al. NEJM. May 24, 2018

Neoadjuvant Immunotherapy



Forde et al. NEJM. May 24, 2018

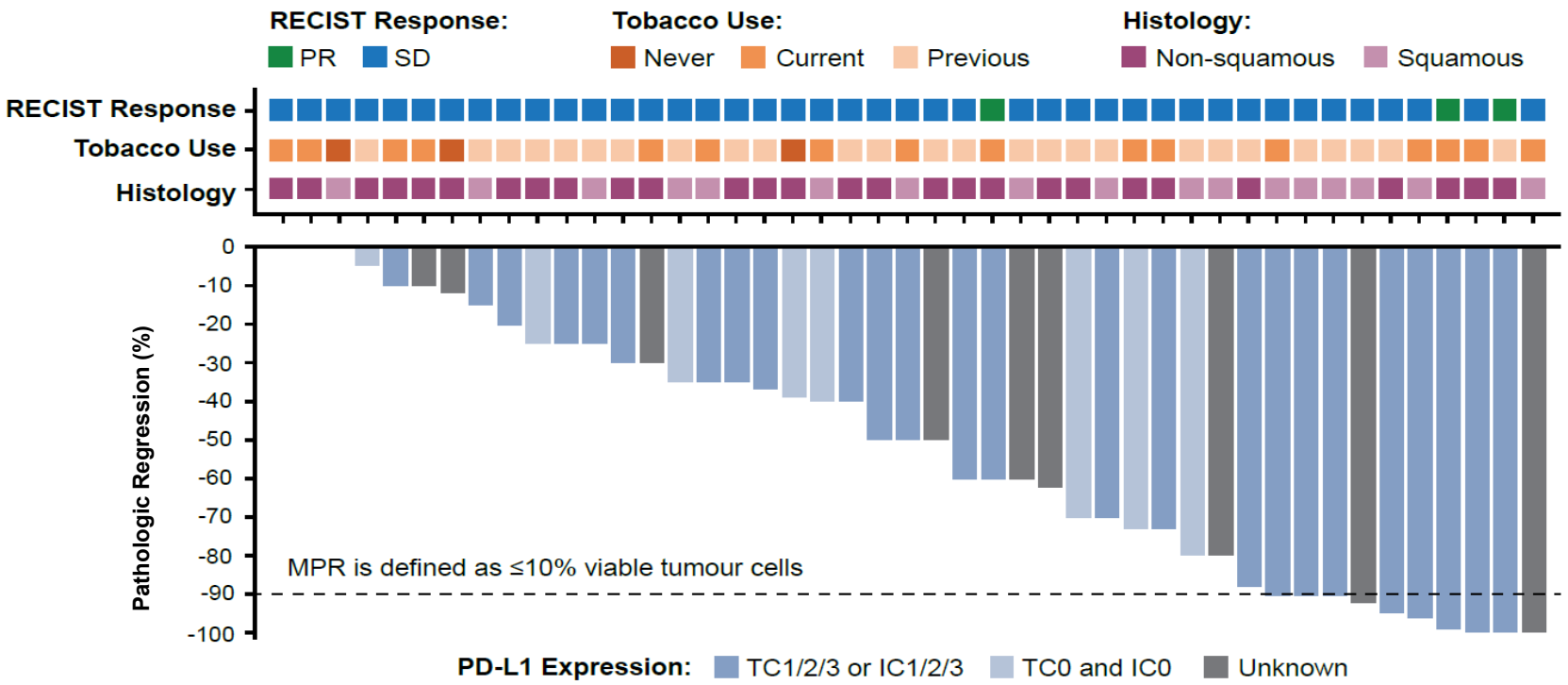
IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Updated results from a multicenter study (LCMC3)

•Valerie W. Rusch,[1] Jamie E. Chaft,[1] Bruce E. Johnson,[2] Ignacio Wistuba,[3] Mark G. Kris,[1] Jay M. Lee,[4] Paul Bunn,[5] David J. Kwiatkowski,[2] Karen L. Reckamp,[6] David Finley,[7] Eric B. Haura,[8] Saiama N. Waqar,[9] Robert Doebele,[5] Edward B. Garon,[4] Justin D. Blasberg,[10] Alan Nicholas,[11] Katja Schulze,[11] See Phan,[11] Ann Johnson,[11] David P. Carbone[12]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [5]University of Colorado School of Medicine, Denver, CO, USA; [6]City of Hope, Duarte, CA, USA; [7]Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; [8]Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [9]Washington University School of Medicine, St Louis, MO, USA; [10]Yale School of Medicine, New Haven, CT, USA; [11]Genentech, Inc., South San Francisco, CA, USA; [12]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

Neoadjuvant Immunotherapy



pCR 3/45 (6%)
MPR 10/45 (22%)

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NEO-ADJUVANT CHEMO-IMMUNOTHERAPY FOR THE TREATMENT OF STAGE IIIA RESECTABLE NON-SMALL-CELL LUNG CANCER (NSCLC): A PHASE II MULTICENTER EXPLORATORY STUDY

NADIM: Neo-Adjuvant Immunotherapy

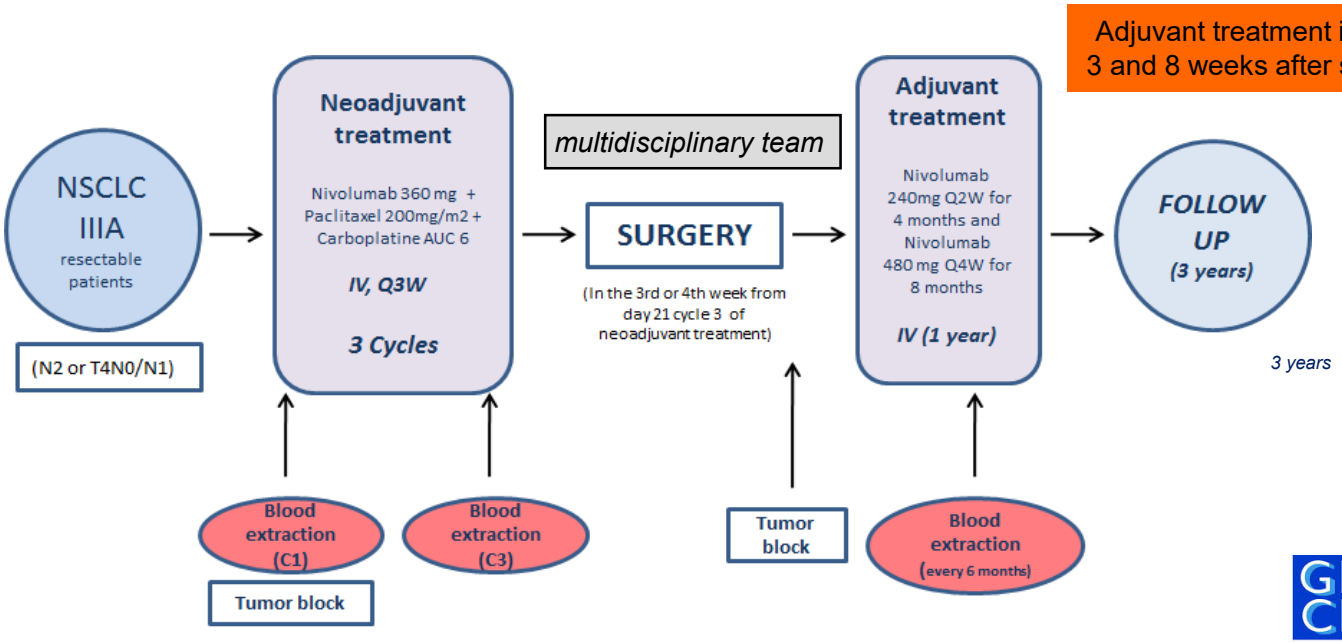
GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

M. Provencio[1], E. Nadal[2], A. Insa[3], R. García-Campelo[4], G. Huidobro[5], M. Dómine[6], M. Majem[7], D. Rodríguez-Abreu[8], V. Calvo[1], A. Martínez-Martí[9], J. de Castro[10], M. Cobo[11], G. López-Vivanco[12], E. del Barco[13], R. Bernabé[14], N. Viñolas[15], I. Barneto[16], B. Massuti[17]

[1]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, [2]Institut Catalá de Oncología-Hospitalet, Barcelona, [3]Hospital Clínico Universitario, Valencia, [4]Hospital Universitario de la Coruña, La Coruña, [5]Hospital Universitario de Vigo, Pontevedra, [6]Fundación Jiménez Díaz, Madrid,[7]Hospital de la Santa Creu i Sant Pau, Barcelona, [8]Hospital Insular de Gran Canaria, Las Palmas, [9]Hospital Universitario Vall Hebrón, Barcelona, [10]Hospital Universitario la Paz, Madrid, [11]Hospital Provincial de Málaga, Málaga, [12]Hospital de Cruces, Bilbao, [13]Hospital Universitario de Salamanca, Salamanca, [14]Hospital Universitario Virgen del Rocío, Sevilla, [15]Hospital Clínic de Barcelona, Barcelona, [16]Hospital Universitario Reina Sofía, Córdoba, [17]Hospital General de Alicante, Alicante

WCLC 2018

NADIM: Study design & Flow-chart



- Phase II
- Single-arm
- Open-label
- Multicenter
- Resectable IIIA NSCLC
- 46 patients

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

WCLC 2018

Pathological response

	N	%
Overall Major Response	24	80.0
PCR	18	60.0
MPR	6	20.0
Total	30	100.0

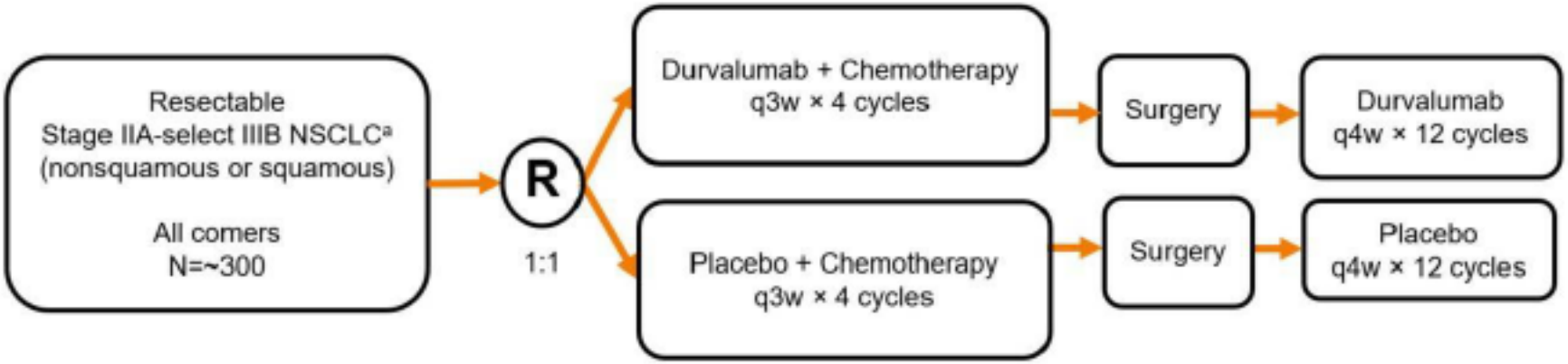
[1]**Major pathological response defined as <10% viable tumor cells in the resected specimen.**

- ***Median patient follow-up = 4.1 months, range 0.2-14.6 months.***
- ***None of the patients have suffered recurrence.***

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Neoadjuvant chemo + immunotherapy

- AEGEAN: Phase III, Double-blind, Placebo-controlled, Multi-Center, International Study of Neoadjuvant/Adjuvant Durvalumab (anti-PDL-1) for the Treatment of Patients with Resectable Stages II and III NSCLC: opening soon.



Summary

- Survival benefit for neoadjuvant chemo for NSCLC
- No clear superiority for any treatment combination for stage IIIA
- Potential for major pathologic response as surrogate endpoint
- Exciting preliminary results from neoadjuvant immunotherapy trials

The last part of surgery, namely, operations, is a reflection on the healing art;

it is a tacit acknowledgement of the insufficiency of surgery.

It is like an armed savage who attempts to get that by force which a civilized man would get by strategem.

John Hunter (1728-1793)