The Current Status of Neo-Adjuvant Therapy in Non-Small Cell Lung Cancer

Apar Kishor Ganti, MD, MS, FACP
Professor of Internal Medicine
Division of Oncology-Hematology
VA Nebraska Western Iowa Health Care System
University of Nebraska Medical Center
Omaha, NE

University of Nebraska Medical Center

Disclosures

- Consultant
  - AstraZeneca, Jazz Pharmaceuticals, Cardinal Health, Mirati Therapeutics, Sanofi Genzyme, Zai Labs, Pfizer Inc. Regeneron Pharmaceuticals
- Research Support
  - Chimerx
- Institutional PI – Clinical Trials
  - Merck, IOVANCE Therapeutics, POSEIDA Therapeutics,

Outline

- Introduction
- Neoadjuvant IO
- Peri-operative IO
- Biomarkers to Guide Therapy Selection
- Conclusions

Introduction

- Second most common cancer in males and females (234,520 in the US)
- Main cause of cancer deaths worldwide (125,070 in the US)

Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	

Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Siegel RL. CA Cancer J Clin. 2024;74:12–49.

Management: Stage I and II

- Surgery: Standard therapy
  - Lobectomy preferred
- Mediastinal lymph node sampling
  - Significantly better 5-year OS if greater number of nodes examined.
  - Systematic sampling and mediastinal node dissection - better outcome than random sampling
    - Right - levels 4, 7, and 10
    - Left - levels 5 or 6 and 7

Peterson RP. Ann Thorac Surg. 2007;83:1245-9
Doddoli C. Ann Thorac Surg. 2005;80:2032-40
Gajra A. J Clin Oncol 2003;21:1029-34

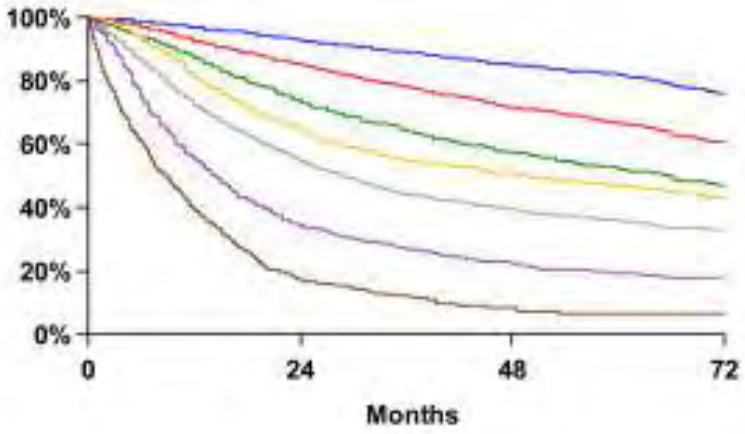
Radiation

- Stereotactic radiation
  - 18 to 75 Gy in 1 to 22 fractions
    - Most commonly used: 18-20 Gy x 3
  - Local recurrence - 15%
  - Biological equivalent dose (BED)
    - 100 Gy better <100 Gy

Onishi H. J Clin Oncol 2006; 24:375s

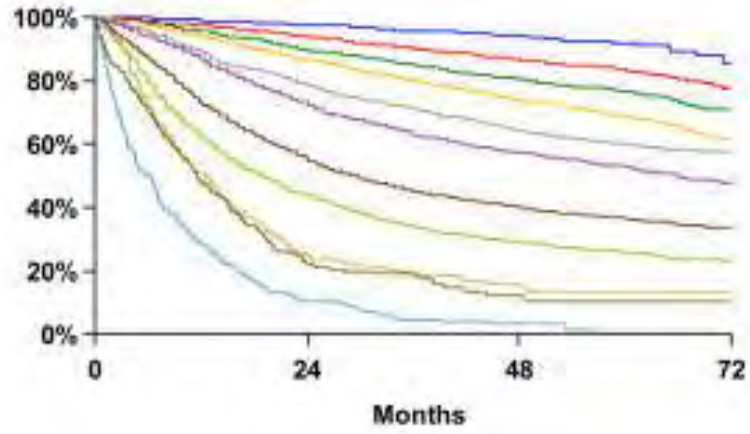
Overall survival by clinical stage

A



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

B



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

Goldstraw P. J Thoracic Oncol 2016;11:39-51

Neoadjuvant vs. adjuvant therapy

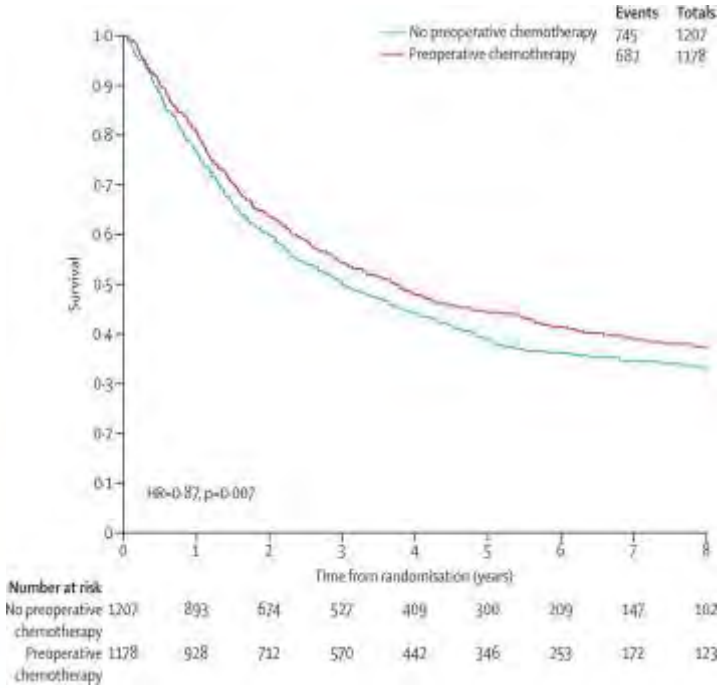
Neoadjuvant therapy

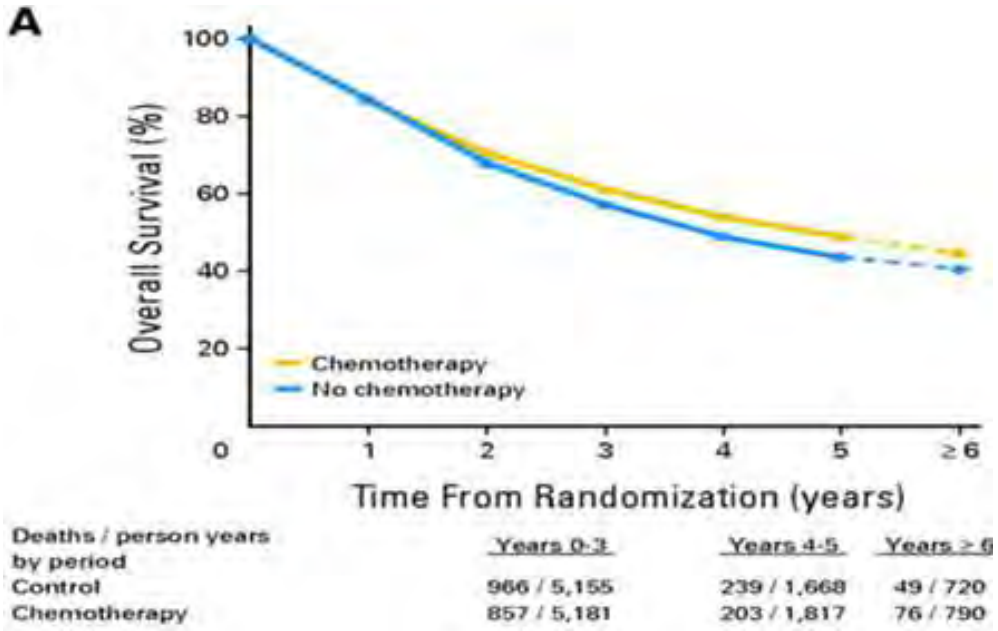
- Tumor in place – antigenicity; important for IO
- Can use response to tailor treatment
- Decrease tumor size; possible downstaging
- Some patients may not receive surgery

Adjuvant therapy

- Surgical resection complete
- Can assess tumor completely
- Surgical complications may delay therapy

Neoadjuvant vs. adjuvant chemotherapy



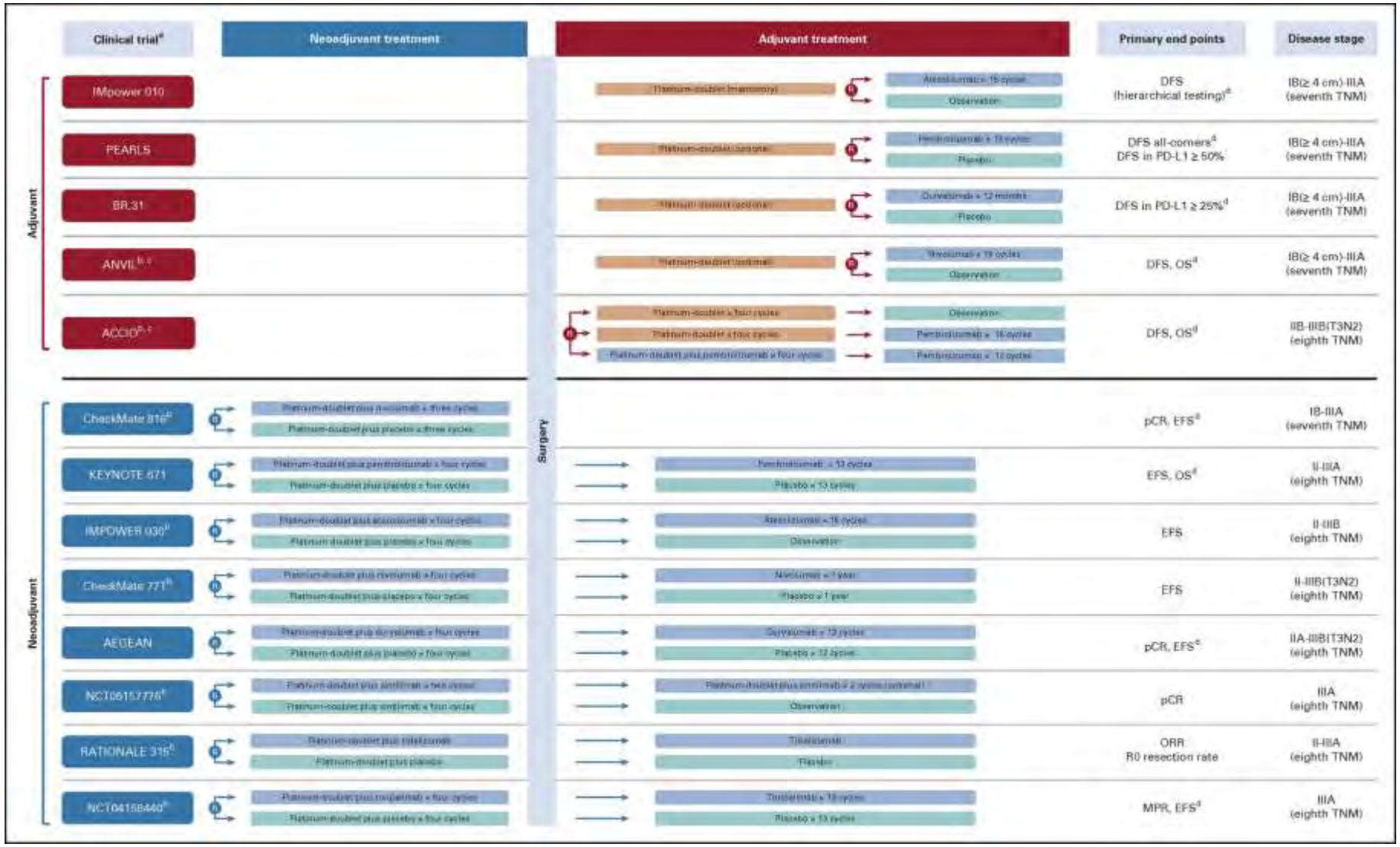


N = 2385
HR – 0.87
5% OS benefit @ 5 years

N=4584
HR – 0.89
5.4% OS benefit @ 5 years

Burdett S. Lancet 2014;383:1561-1571
Pignon J.-P. J Clin Oncol; 26:3552-3559 2008

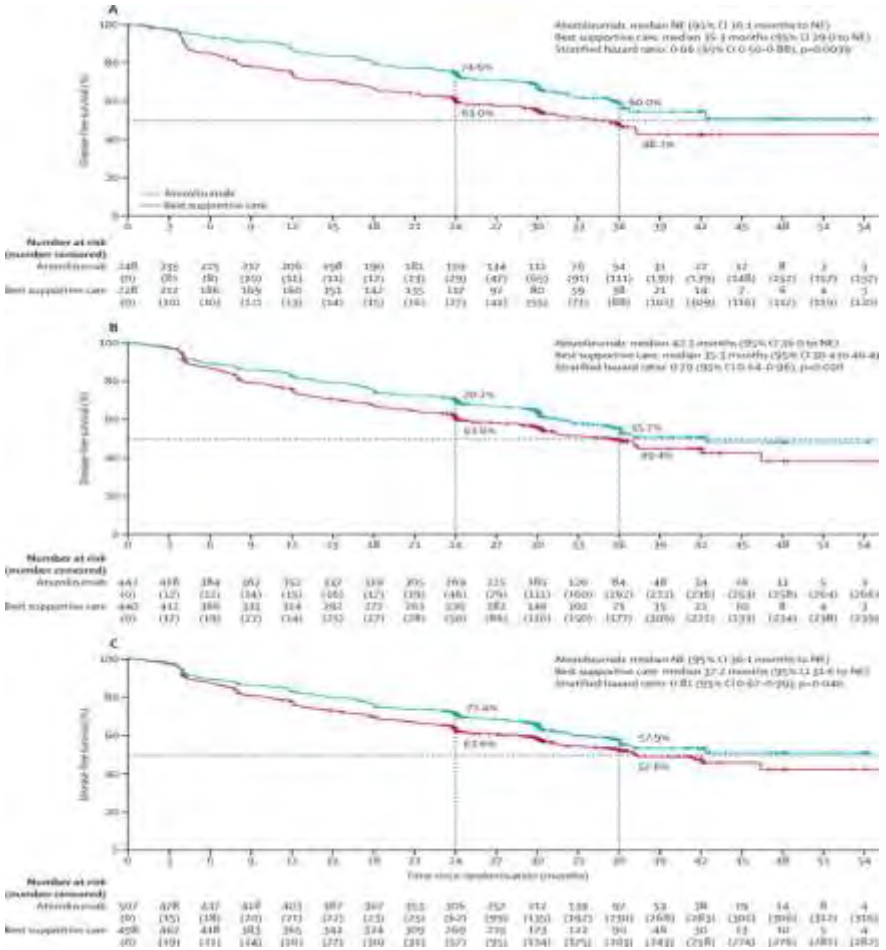
Perioperative Immunotherapy Trials



Passaro A. J Clin Oncol 2022;40:2871-77

Adjuvant Immunotherapy

- IMPower 010
  - Randomized, multicenter, open-label, phase 3 study
  - Completely resected IB (tumors ≥4 cm) - IIIA NSCLC
  - Adjuvant atezolizumab (16 cycles or 1 year) or BSC after adjuvant chemotherapy
  - Primary endpoint: DFS



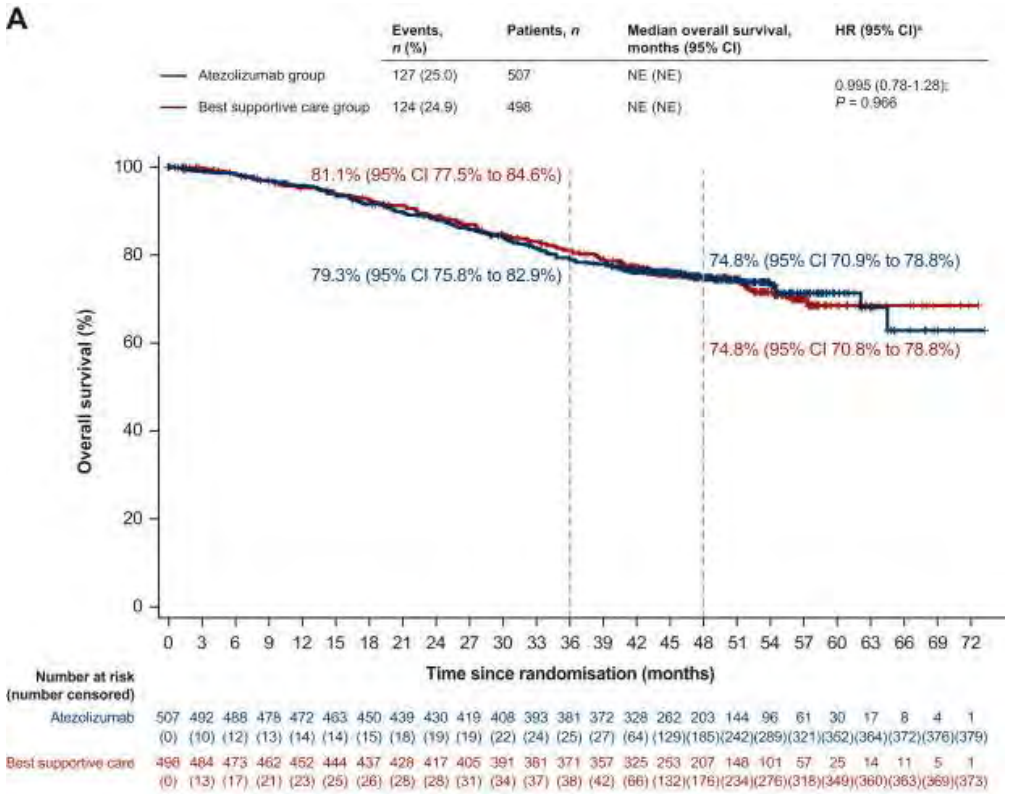
Stage II-IIIA PD-L1 Positive

All Stage II-IIIA

ITT: Stage IB-IIIA

Felip E. Lancet 2021;398:1344-57

Adjuvant Immunotherapy



Felip E. Ann Oncol 2023. https://doi.org/10.1016/j.annonc.2023.07.001

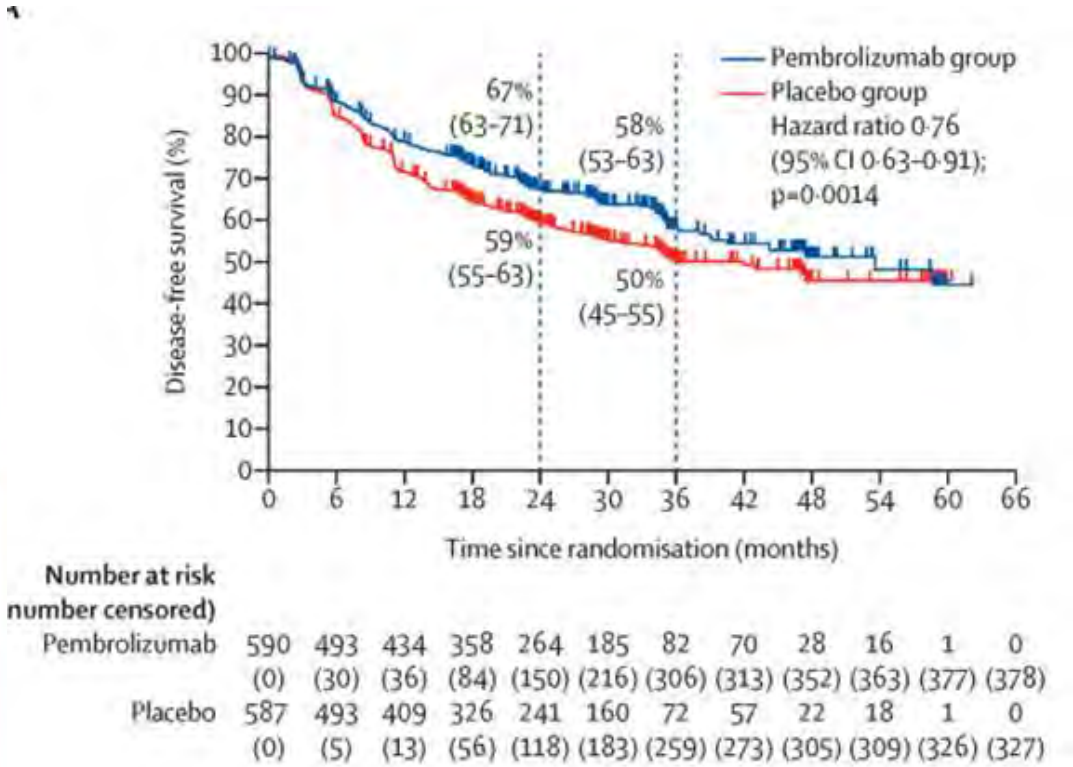
Adjuvant Immunotherapy

- PEARLS/KEYNOTE-091
  - Randomized, multicenter, open-label, phase 3 study
  - Completely resected stage IB (tumors ≥4 cm) to IIIA NSCLC
  - Adjuvant chemotherapy - considered for stage IB; strongly recommended for stage II and IIIA
  - Adjuvant pembrolizumab (up to 18 cycles) or placebo
  - Primary endpoint: DFS

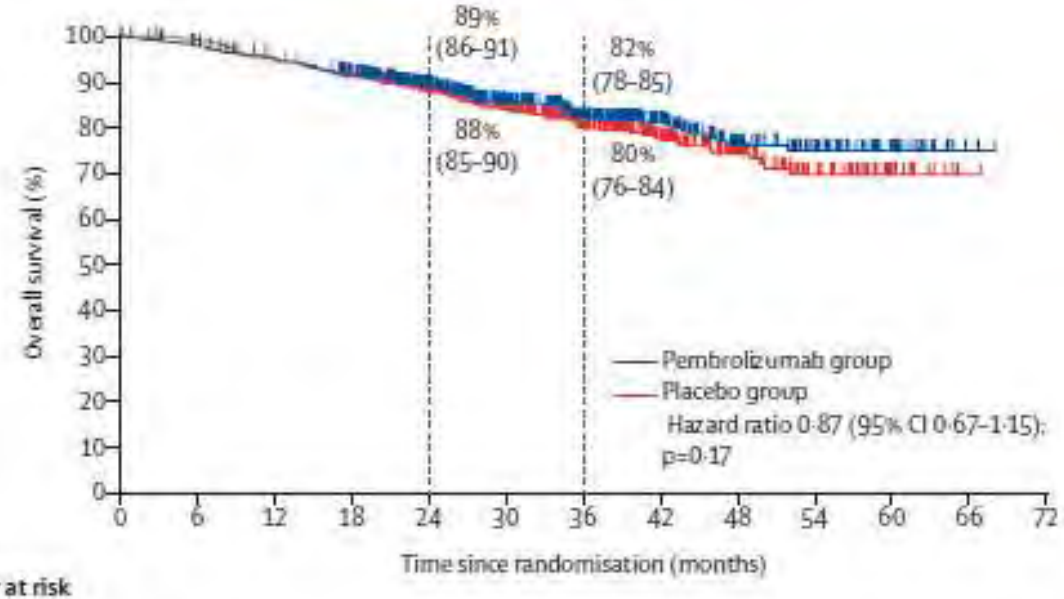
O'Brien M. Lancet Oncol 2022;23:1274-86

Adjuvant Immunotherapy

PEARLS/KEYNOTE-091



Number at risk number censored)												
Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

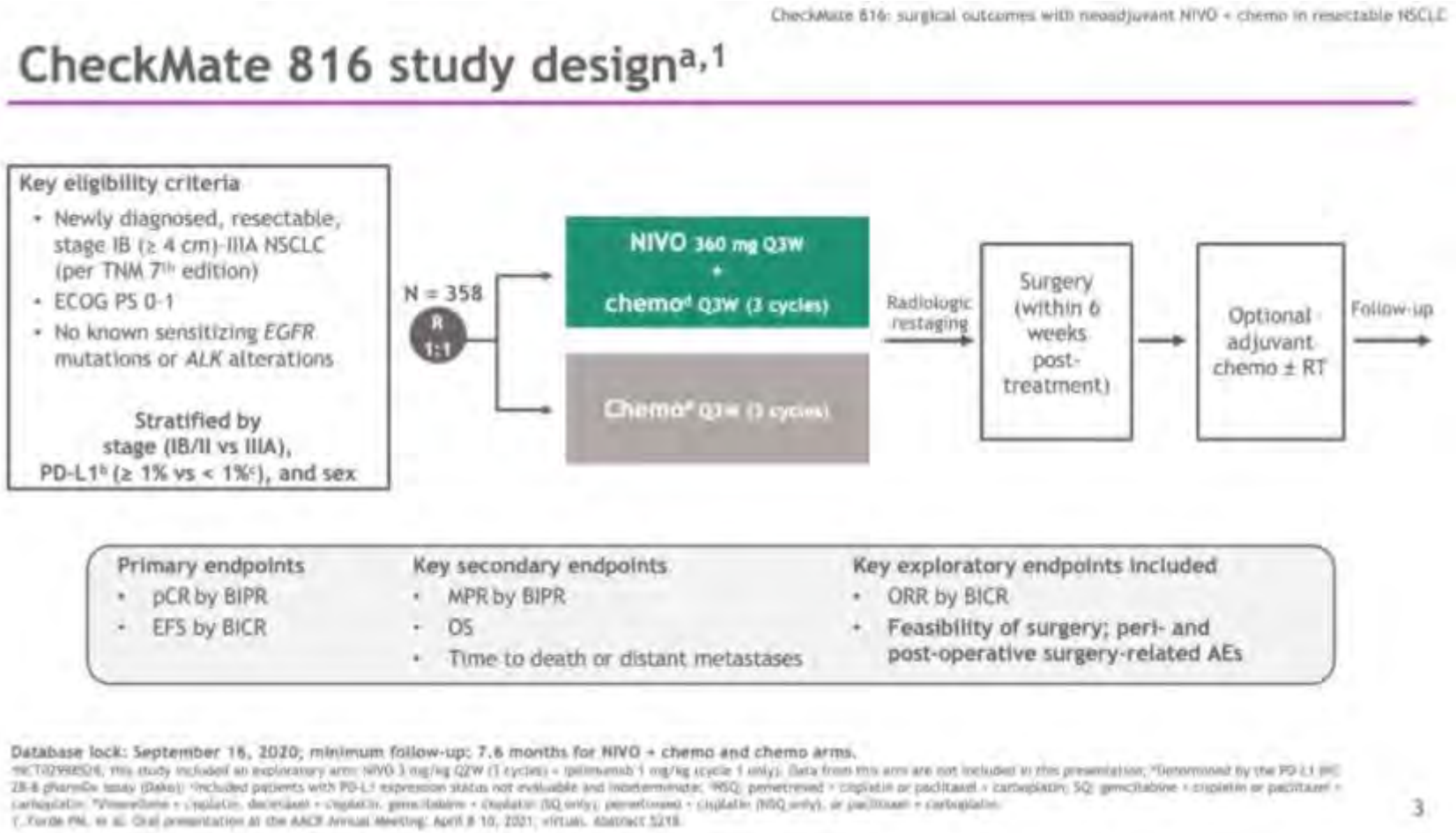


Number at risk (number censored)													
Pembrolizumab	590	572	548	520	419	318	226	143	83	52	23	2	0
	(0)	(7)	(14)	(22)	(109)	(194)	(276)	(357)	(410)	(440)	(469)	(490)	(492)
Placebo	587	582	556	524	420	309	213	135	78	44	16	1	0
	(0)	(2)	(3)	(12)	(99)	(193)	(277)	(350)	(402)	(432)	(460)	(475)	(476)

O'Brien M. Lancet Oncol 2022;23:1274-86

Neoadjuvant Immunotherapy

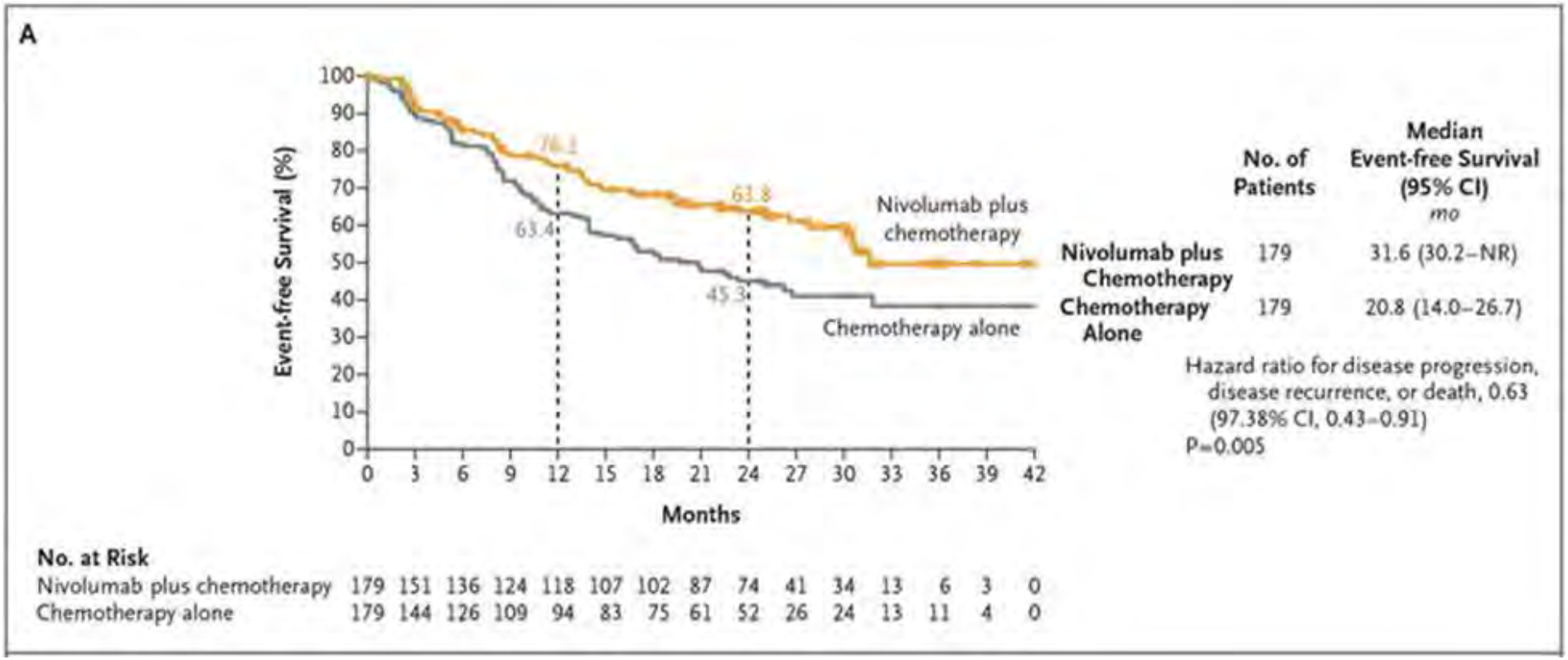
- CHECKMATE 816



Forde PM.

Neoadjuvant Immunotherapy

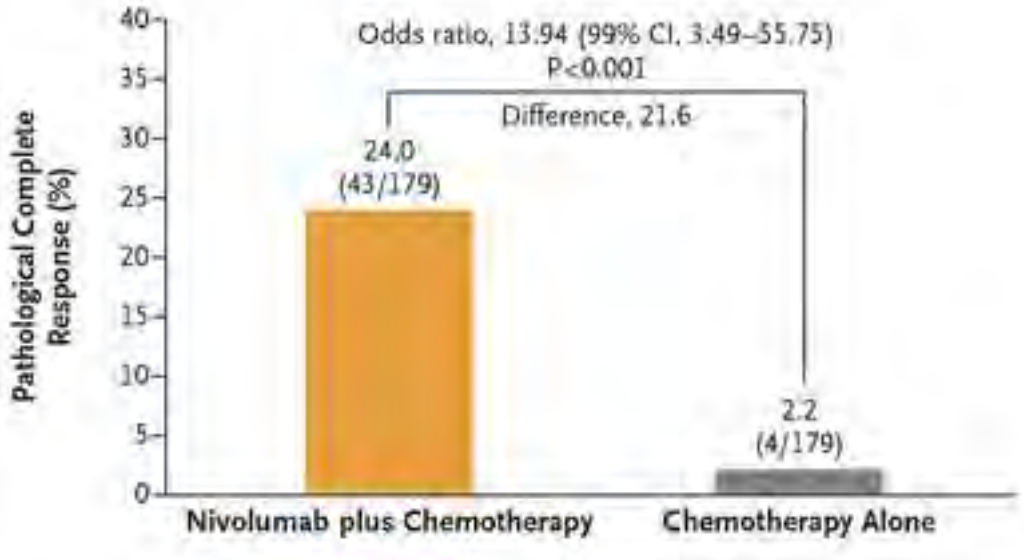
- CHECKMATE 816

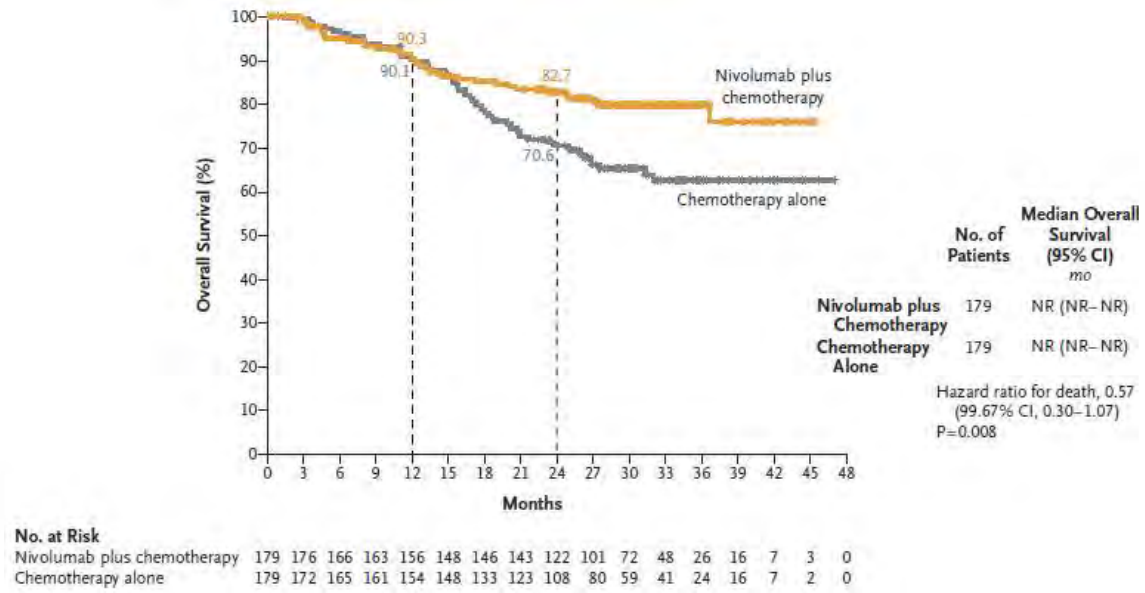


Forde PM. N Engl J Med. 2022;386:1973–85.

Neoadjuvant Immunotherapy

- CHECKMATE 816

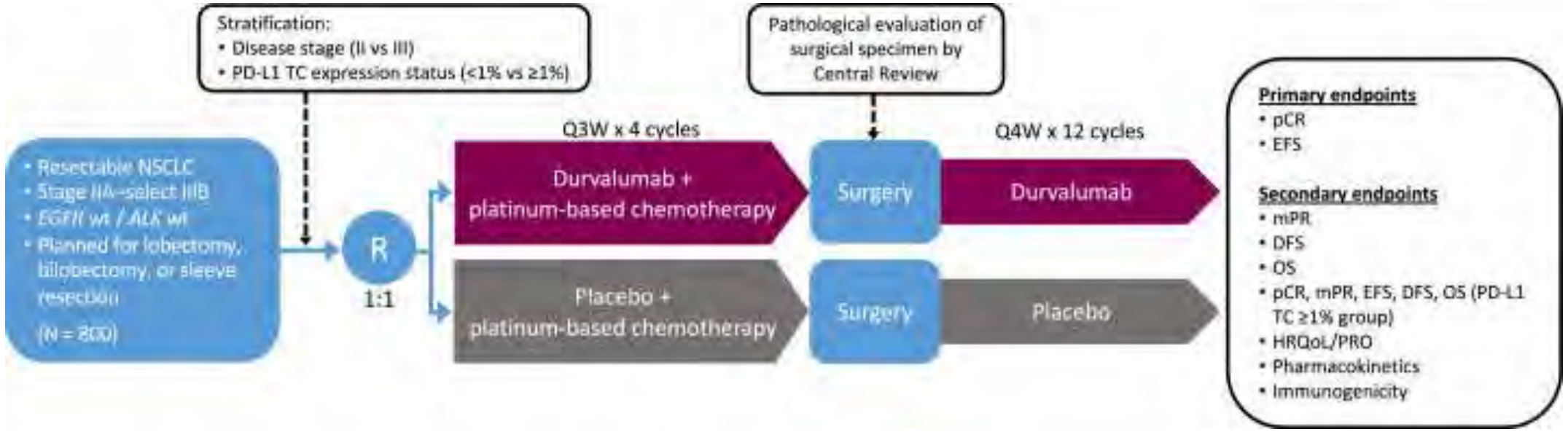




Forde PM. N Engl J Med. 2022;386:1973–85.

Perioperative Immunotherapy

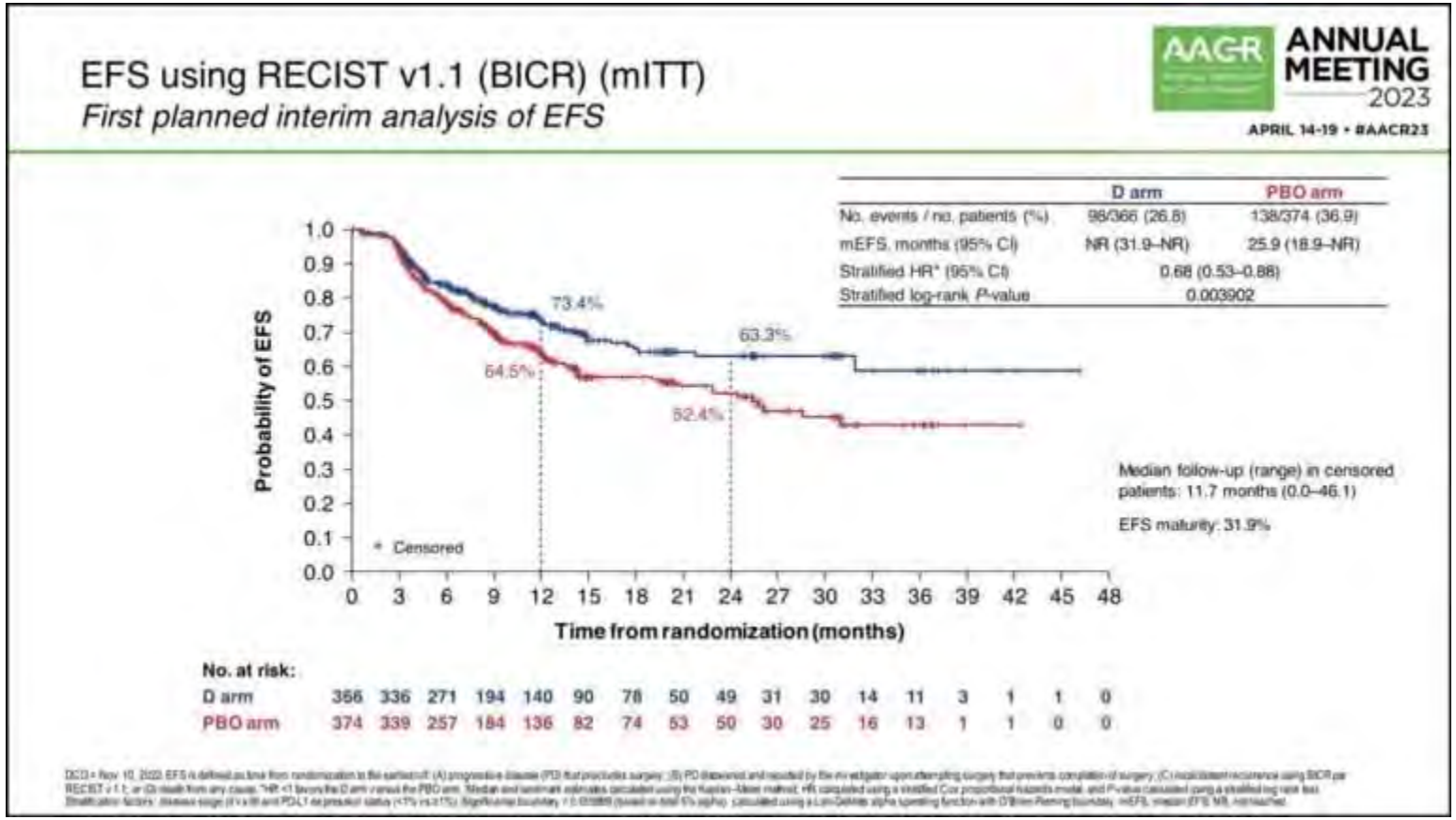
- AEGEAN



Heymach JV. Clin Lung Cancer. 2022 May;23(3):e247-e251.

Perioperative Immunotherapy

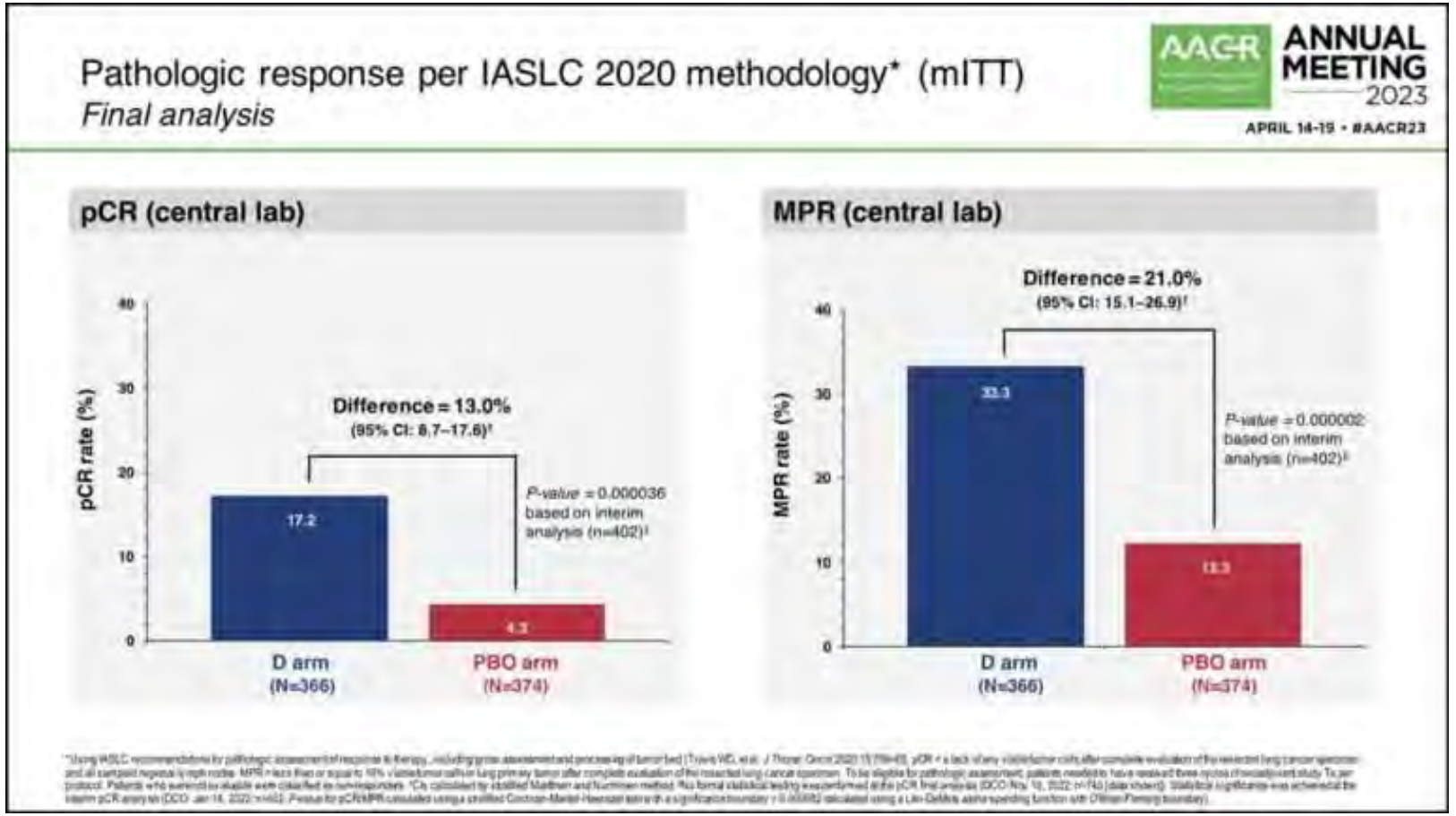
- AEGEAN



Heymach JV. AACR. 2023.

Perioperative Immunotherapy

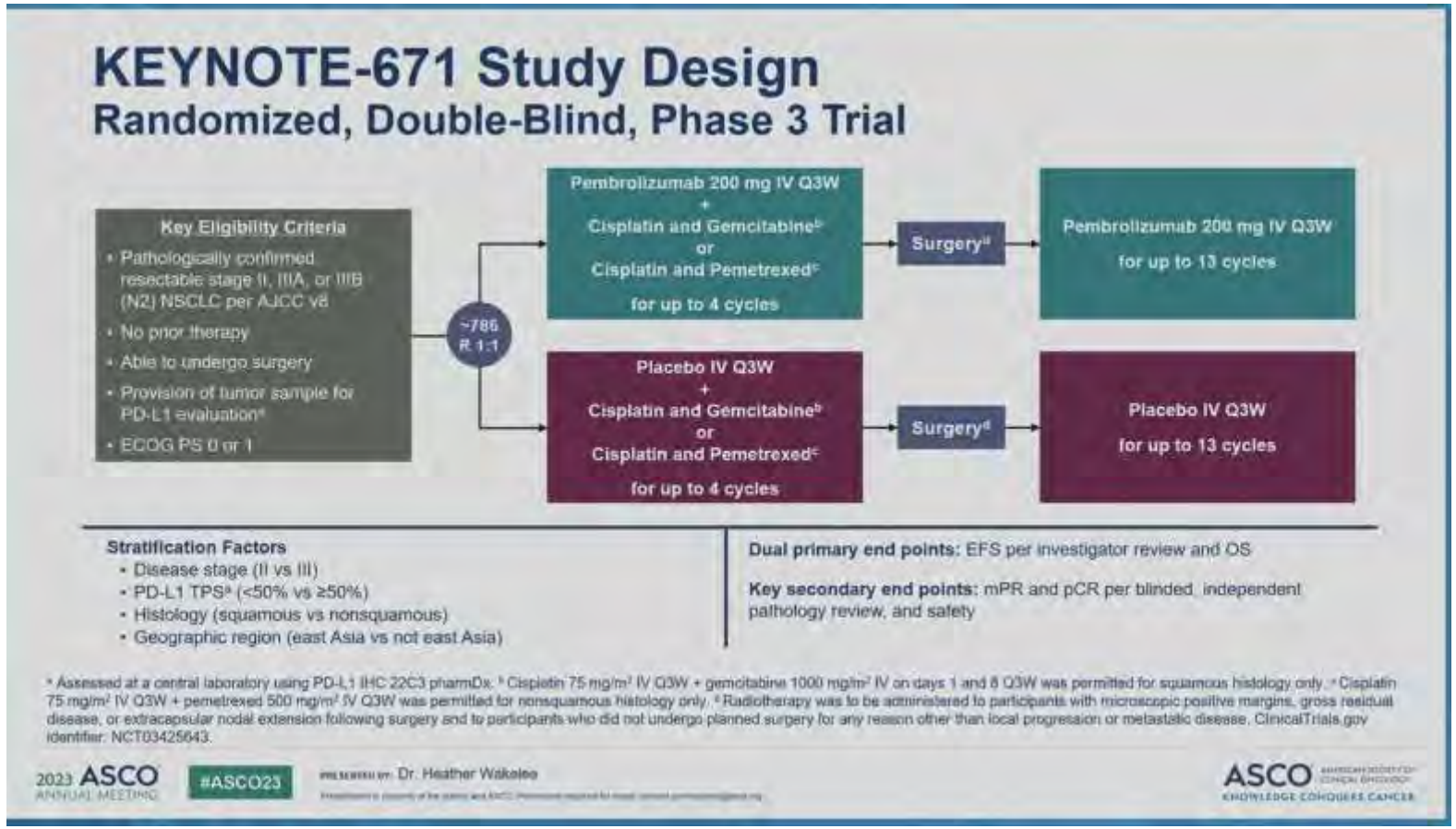
- AEGEAN



Heymach JV. AACR. 2023.

Perioperative Immunotherapy

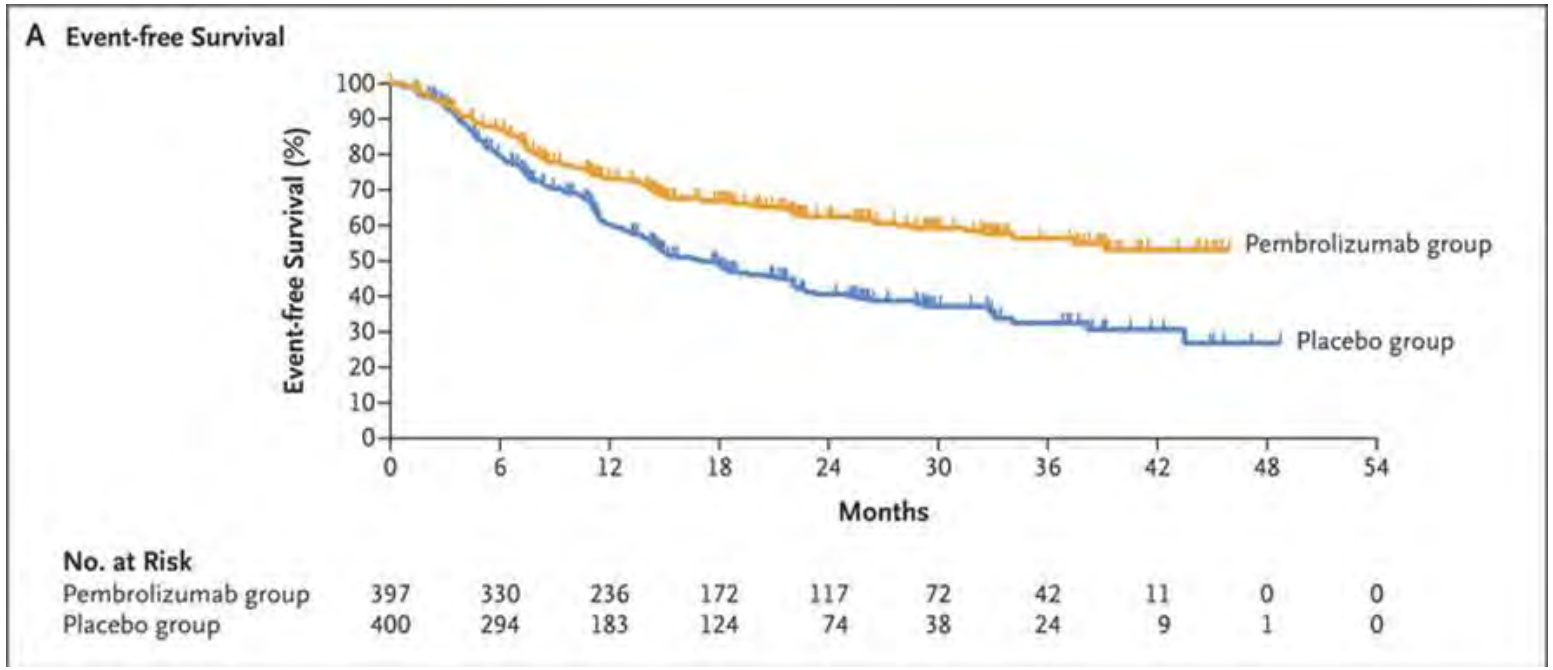
- KEYNOTE-671



Wakelee H. ASCO 2023

Perioperative Immunotherapy

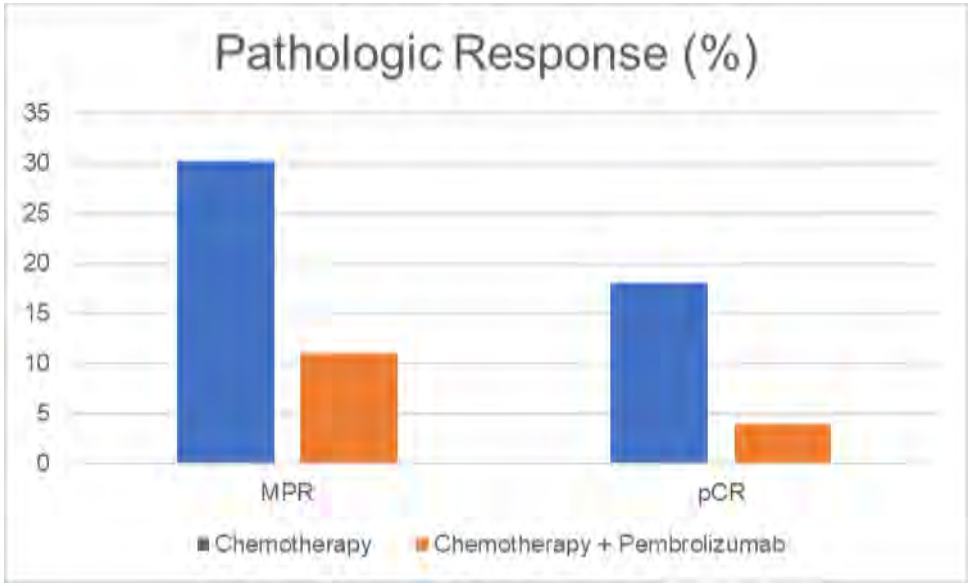
- KEYNOTE-671

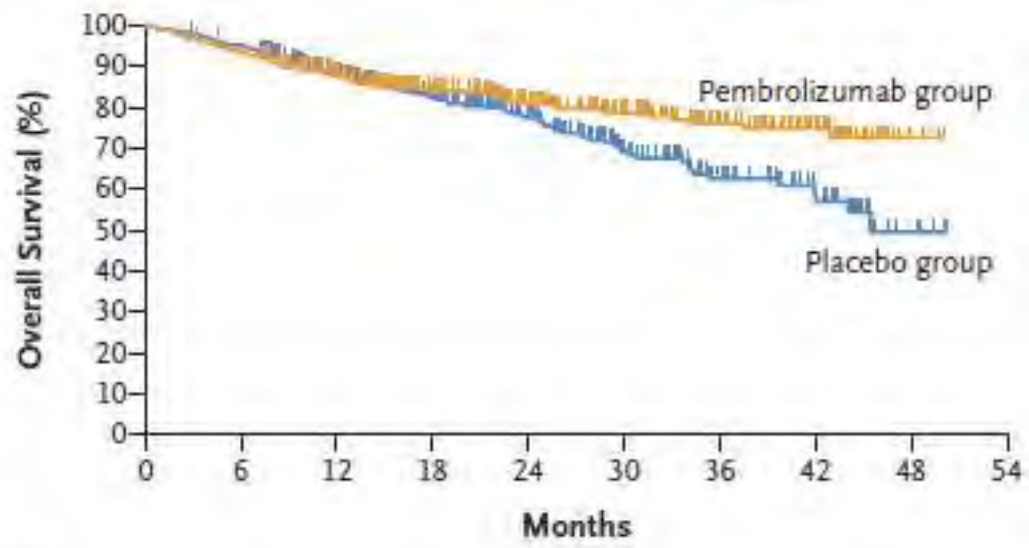


Wakelee H. N Engl J Med 2023:389:491-503

Perioperative Immunotherapy

- KEYNOTE-671



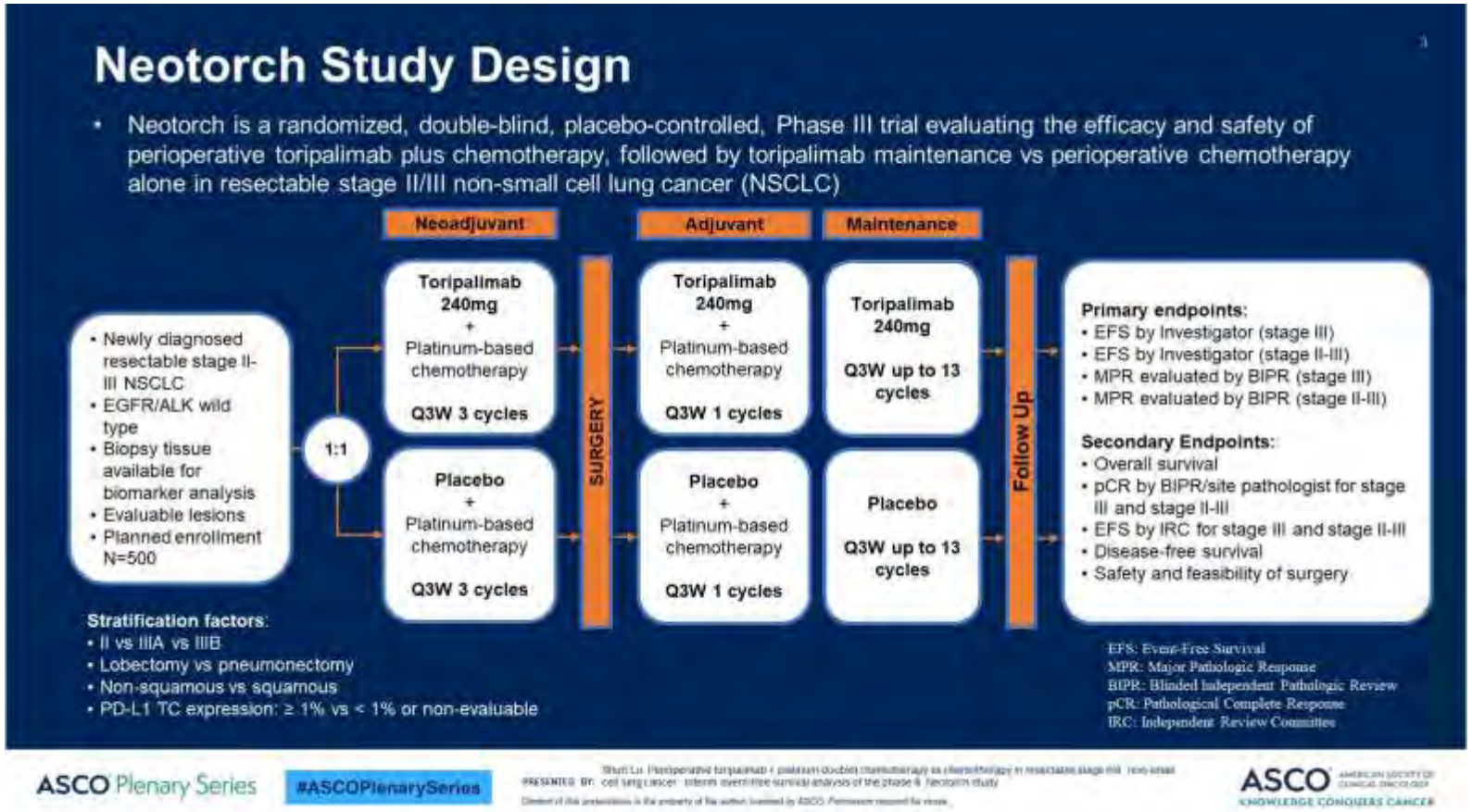


No. at Risk										
Pembrolizumab group	397	370	313	232	170	118	76	41	5	0
Placebo group	400	379	316	225	153	91	54	30	6	0

Wakelee H. N Engl J Med 2023:389:491-503

Perioperative Immunotherapy

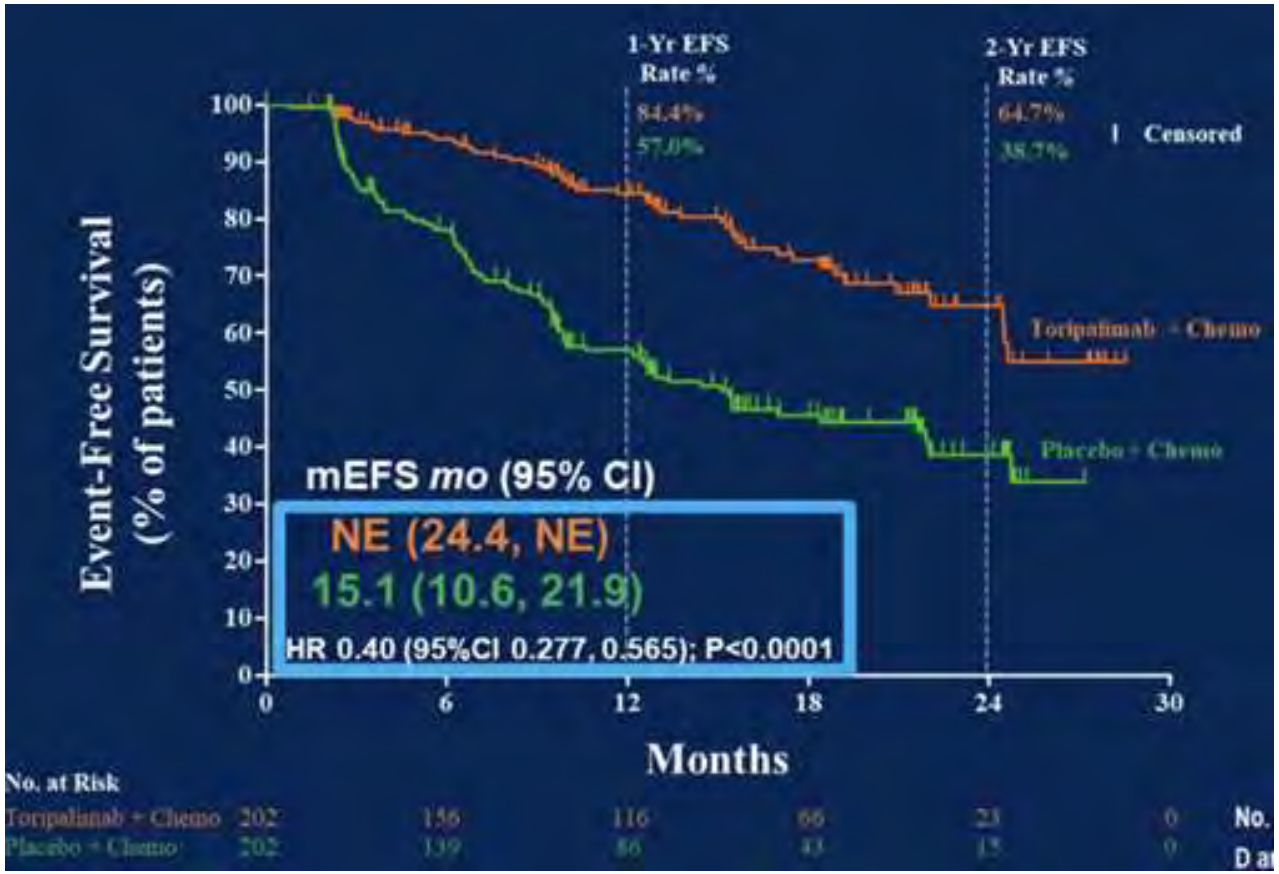
- Neotorch



Lu S. ASCO Plenary Series 2023.

Perioperative Immunotherapy

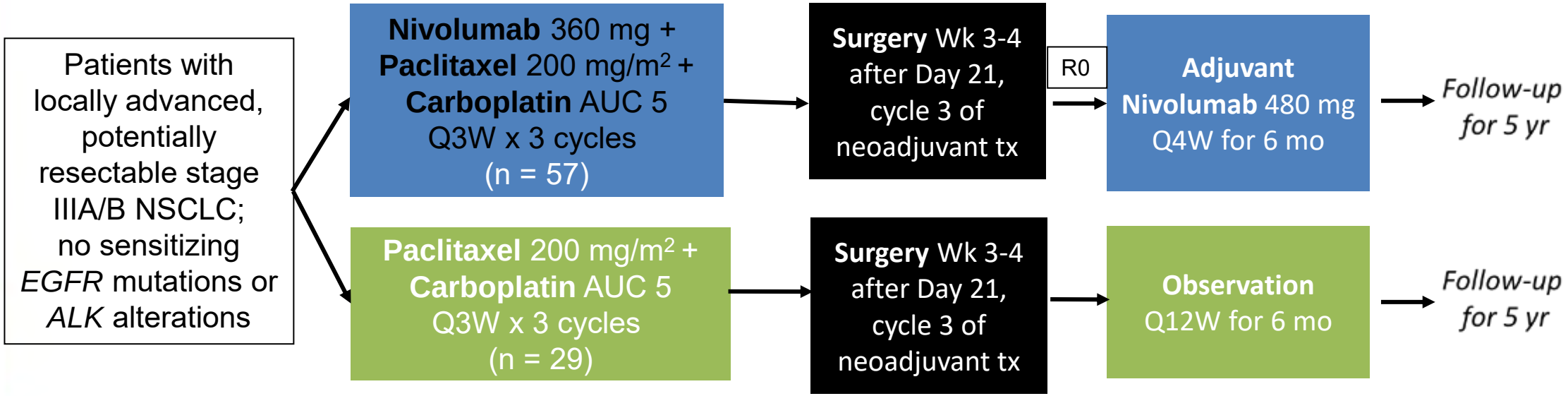
- Neotorch



Lu S. ASCO Plenary Series 2023.

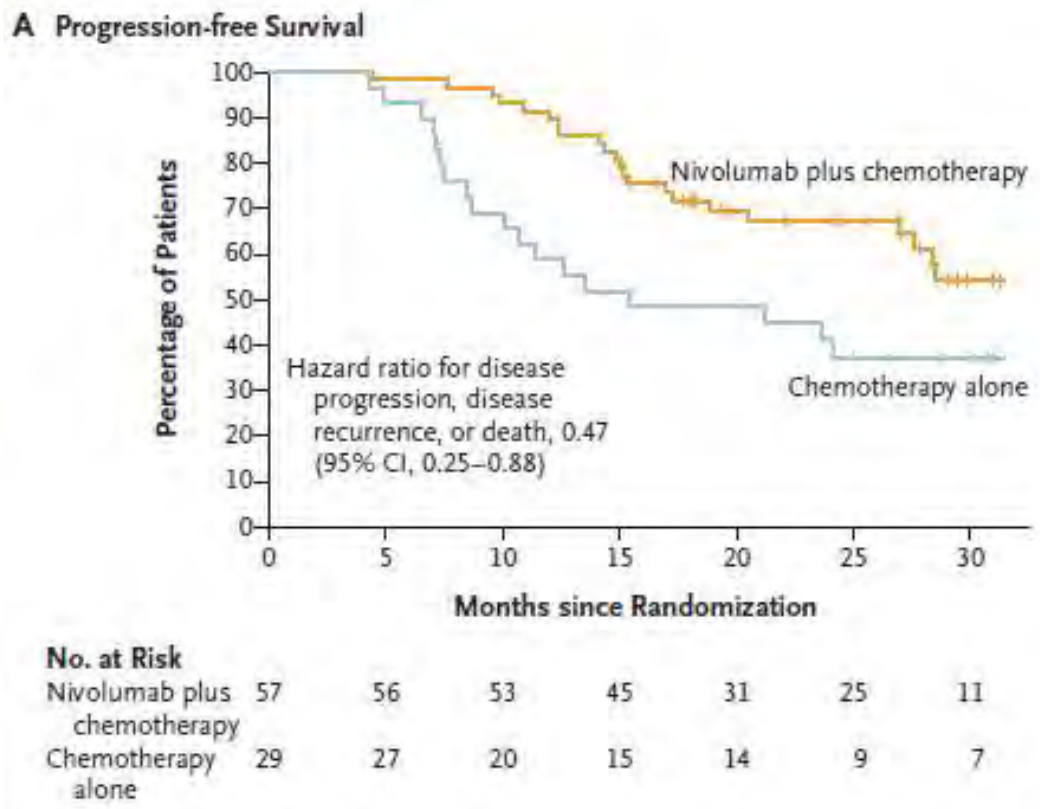
Perioperative Immunotherapy

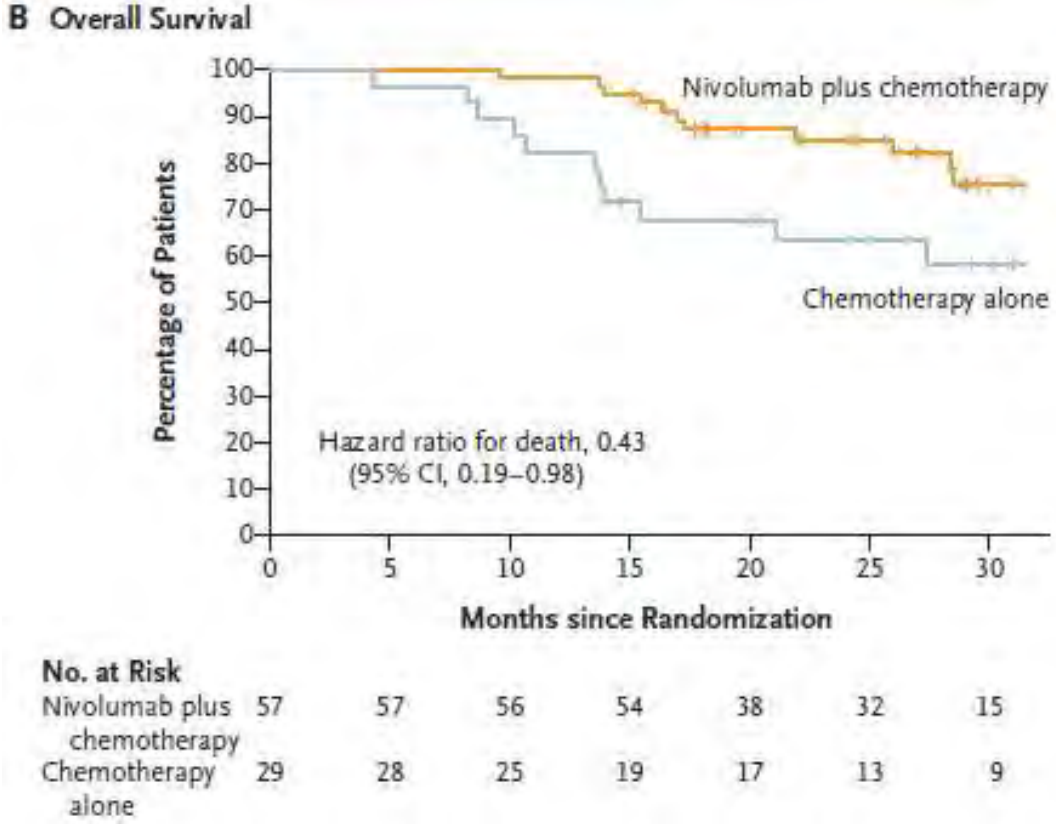
- NADIM II



Provencio M. WCLC 2022. Abstr PL03.12.

- NADIM II

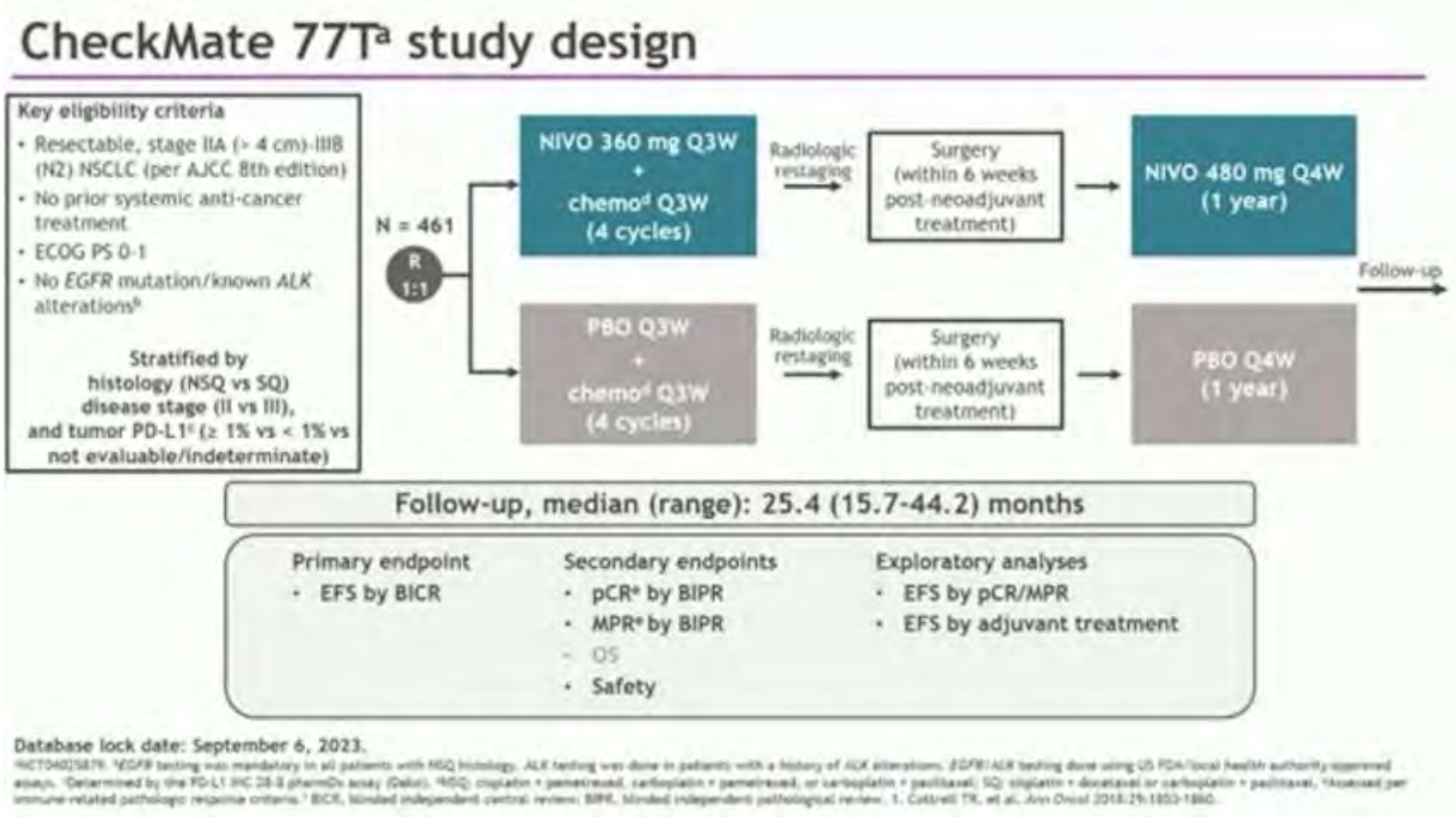




Provencio M. N Engl J Med 2023;389:504-13

Perioperative Immunotherapy

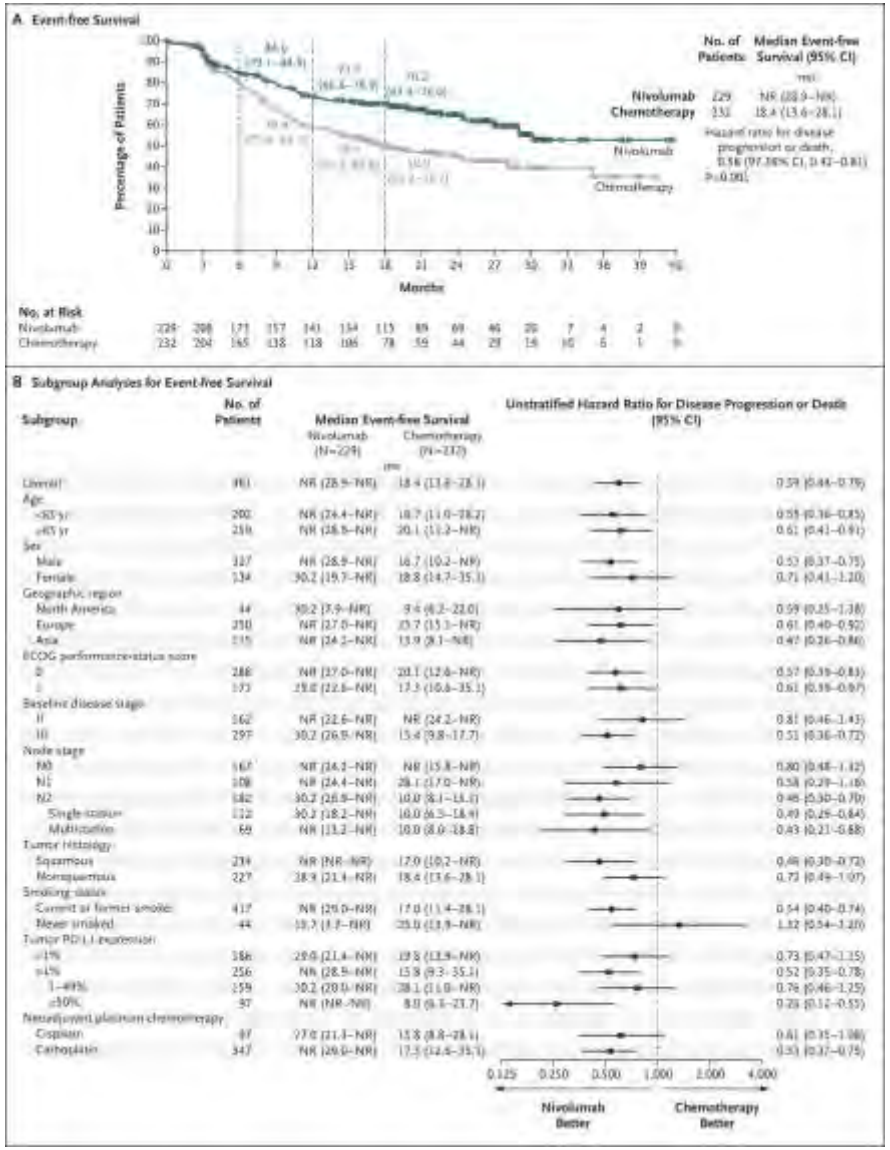
- CHCEKMATE 77T



Cascone T. ESMO 2023.

Perioperative Immunotherapy

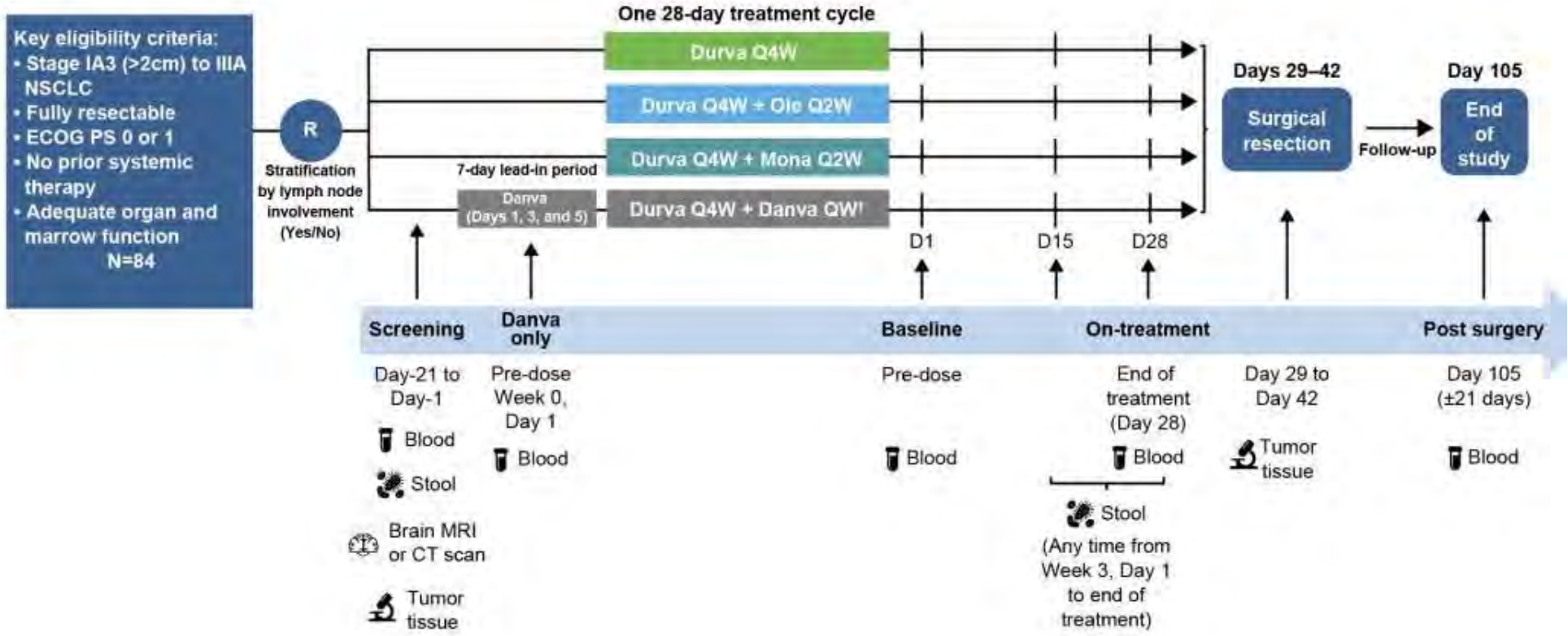
- CHCEKMATE 77T



Cascone T. N Engl J Med 2024;390:1756-1769

Perioperative Immunotherapy

- NeoCOAST



Cascone T. Cancer Discov 2023, https://doi.org/10.1158/2159-8290.CD-23-0436

Predictive markers for immunotherapy

– CheckMate 816

PD-L1 expression level				
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)

– AEGEAN

PD-L1 expression at baseline†					
	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)

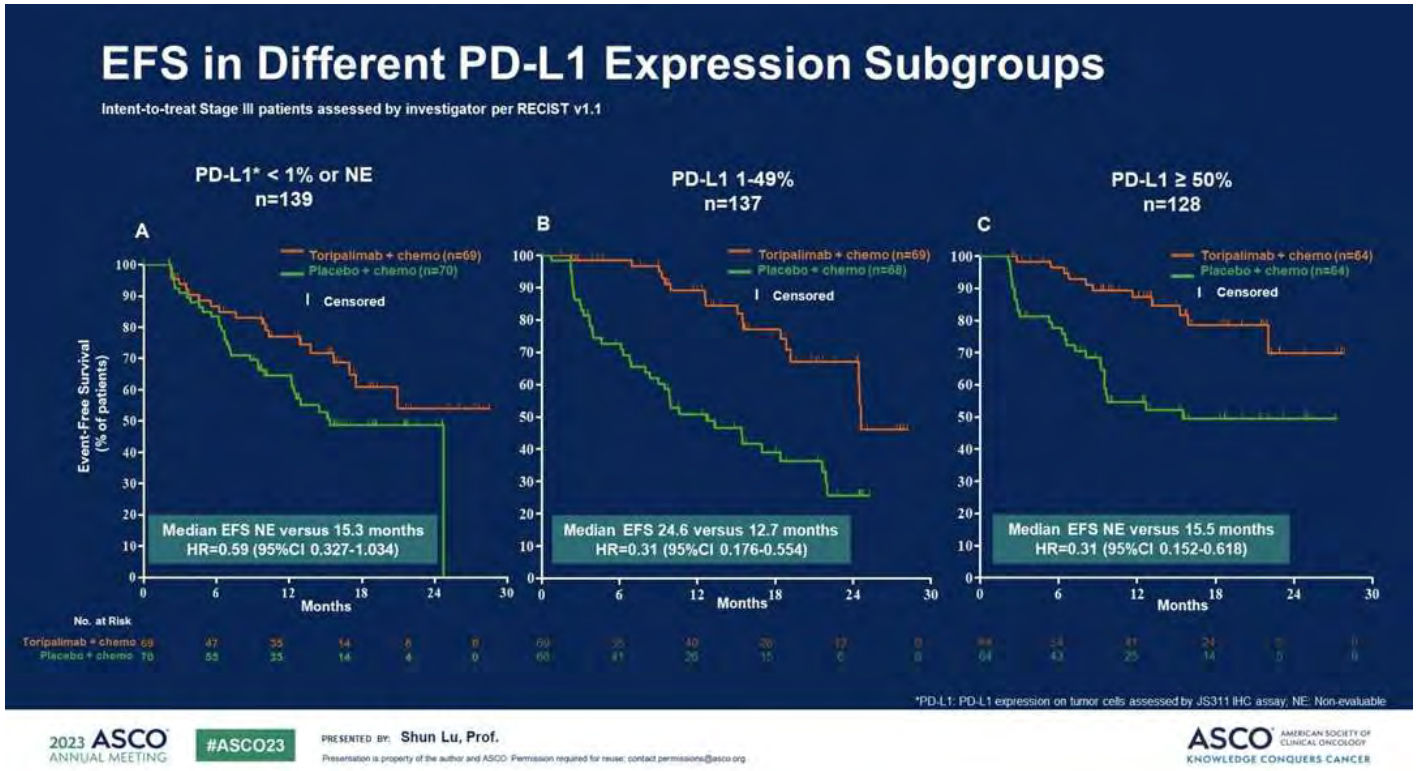
– KEYNOTE-671

PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55–1.07)
1–49%	44/127	62/115	0.51 (0.34–0.75)
≥50%	32/132	63/134	0.42 (0.28–0.65)

Forde PM. N Engl J Med. 2022;386:1973–85
Heymach JV. AACR 2023
Wakelee H. N Engl J Med 2023:389:491-503

Predictive markers for immunotherapy

– Neotorch



Lu S. ASCO Plenary Series 2023.

Predictive markers for immunotherapy

- Tumor Mutational Burden
  - CheckMate 816

TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)

Forde PM. N Engl J Med. 2022;386:1973–85

Predictive markers for immunotherapy

- EGFR and ALK mutation
  - IMpower 010

***EGFR* mutation status**					
Yes	23/43	29·7 (18·0–NE)	20/43	16·6 (6·7–31·4)	0·57 (0·26–1·24)
No	123/248	NE (35·5–NE)	125/248	36·0 (26·7–NE)	0·67 (0·45–1·00)
Unknown	102/185	NE (36·1–NE)	83/185	35·3 (23·9–NE)	0·61 (0·38–0·98)
***ALK* rearrangement status**					
Yes	12/23	30·5 (17·1–NE)	11/23	37·2 (21·3–NE)	1·05 (0·32–3·45)
No	133/254	42·3 (35·5–NE)	121/254	30·4 (23·9–NE)	0·64 (0·44–0·93)
Unknown	103/199	NE (36·7–NE)	96/199	37·3 (30·1–NE)	0·62 (0·39–1·00)

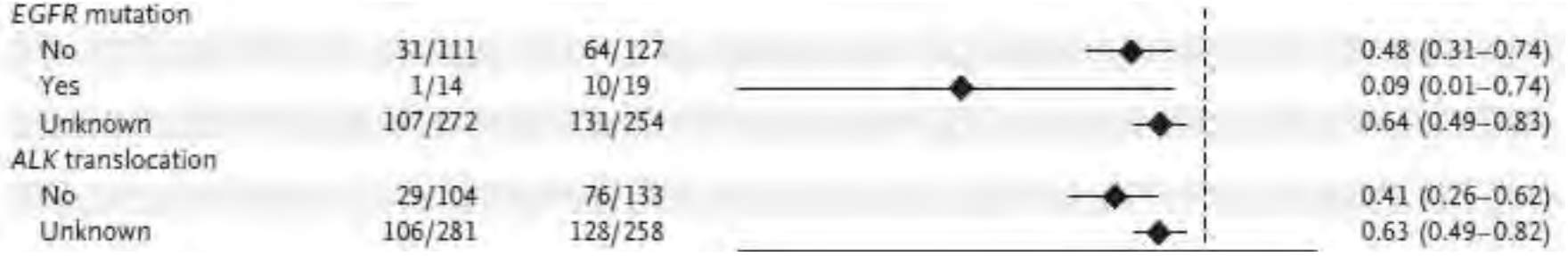
  - PEARLS

***EGFR* mutation**				
No	84/218	102/216		0·78 (0·59–1·05)
Yes	18/39	22/34		0·44 (0·23–0·84)
Unknown	110/333	136/337		0·82 (0·63–1·05)

Felip E. Lancet 2021;398:1344-57
O'Brien M. Lancet Oncol 2022;23:1274-86

Predictive markers for immunotherapy

- CheckMate 816
  - Excluded patients with EGFR mutations and ALK translocations
- AEGEAN
  - Initially patients with EGFR and ALK aberrations were enrolled, but a subsequent amendment excluded these patients
  - Data not reported
- KEYNOTE-671



Forde PM. N Engl J Med. 2022;386:1973–85
Heymach JV. AACR 2023
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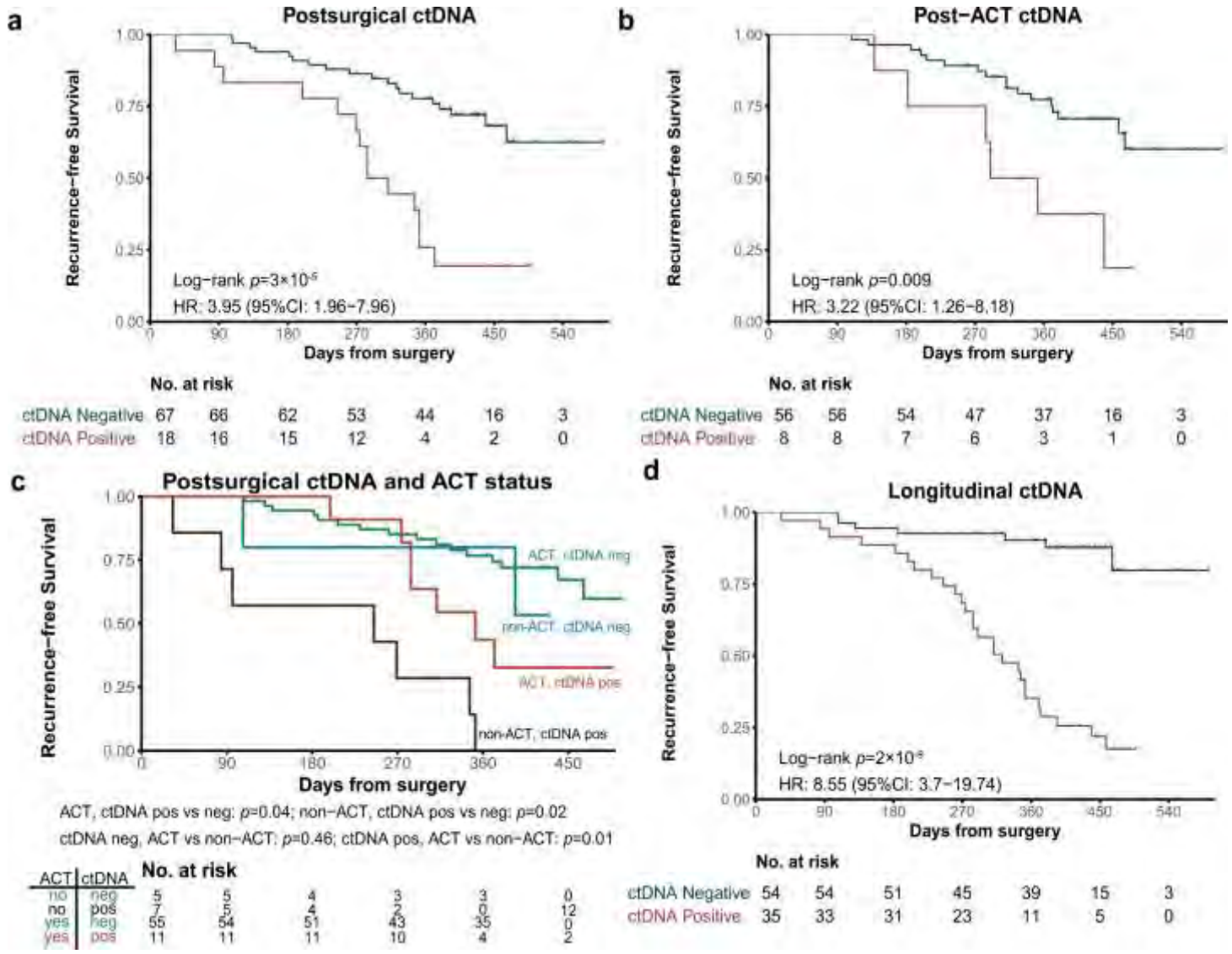
Role of ctDNA



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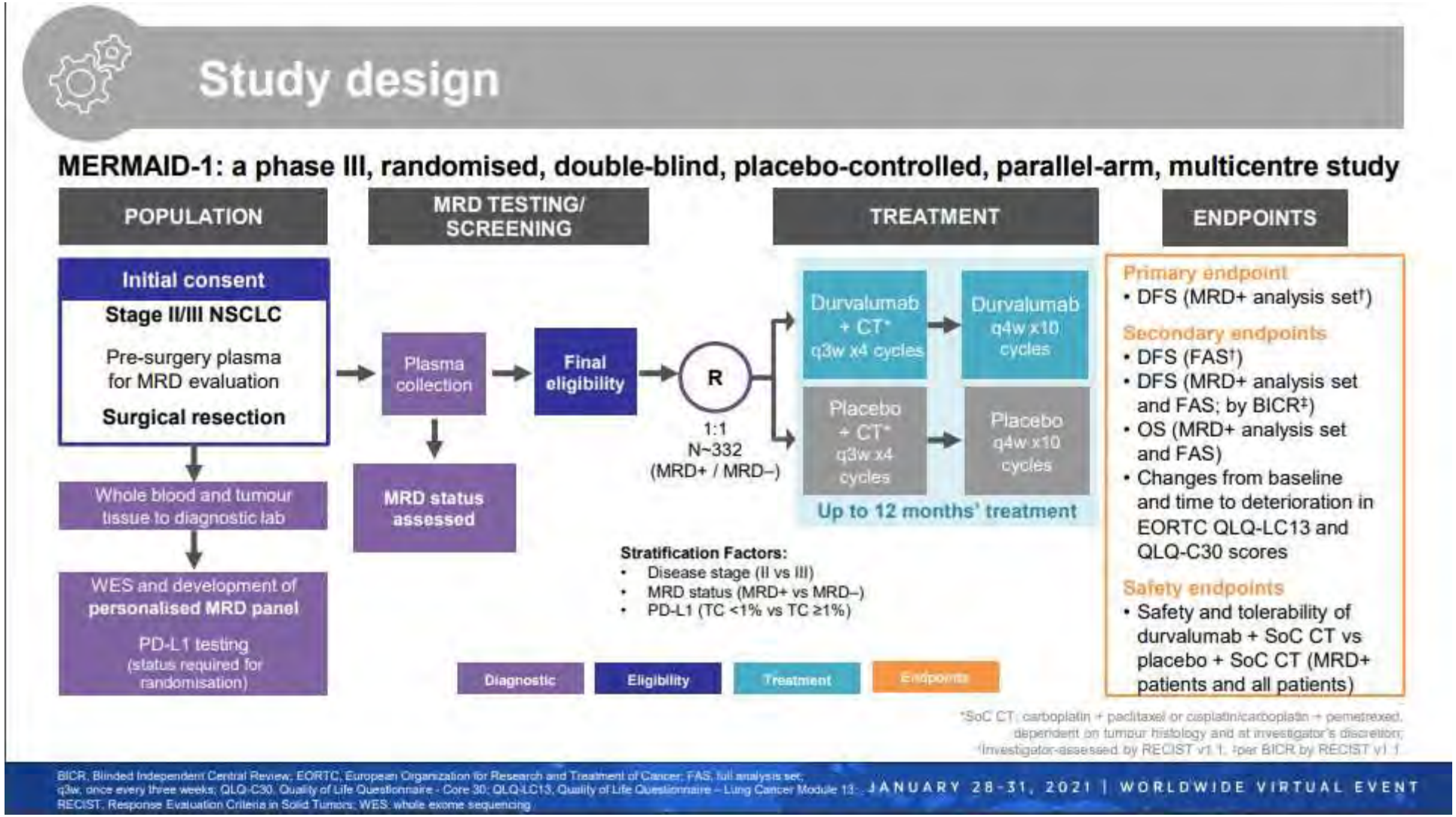
MERMAID trial



Peters S. WCLC 2021.

Neoadjuvant vs. Adjuvant Approach

- No survival advantage of one vs. other in the chemotherapy era
- If EGFR activating mutation (or ALK translocation) – surgery followed by adjuvant chemotherapy and targeted therapy
- In the absence of driver mutations, addition of ICI
  - Improved PFS in both settings
  - OS data not mature yet
- Clinical stage I – Surgery followed by adjuvant therapy
- Clinical stage IIIA – Neoadjuvant chemo-IO followed by surgery
- Clinical stage II - ???
  - Tailor to individual patient, based on local expertise, patient choices
  - Multidisciplinary discussion

Unanswered questions

- Neoadjuvant vs. adjuvant vs. neoadjuvant + adjuvant
  - Does a patient who has achieved a pCR following neoadjuvant chemo-IO need further adjuvant IO?
- Duration of immunotherapy
- Predictive biomarkers – immune side effects are a real thing!

Summary

- Immunotherapy – emerging as an important part of management of early-stage NSCLC
- Neoadjuvant, adjuvant and perioperative immunotherapy – improvement in DFS
- Overall survival data – premature
- Multidisciplinary discussion to determine optimal strategy

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