MaTOS™
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

EARLY STAGE RESECTABLE LUNG CANCER;

MRD to Decide Perioperative Management in the Era of Immuno-Oncology

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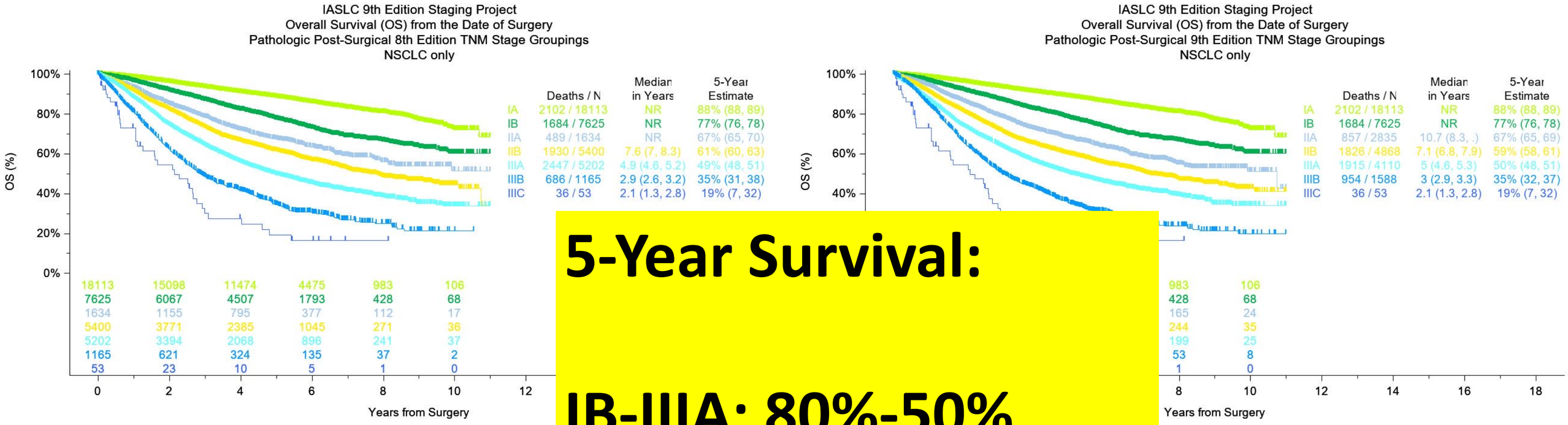
Figure 4

POST-SURGICAL PROGNOSIS



5-Year Survival:

IB-IIIA: 80%-50%

	8			logic TNM Stage Groupings		
	n=39,002; R^2=45.144			n=38,335; R^2=46.020		
Multivariable Cox Model	n/N (%)	HR (95% CI)	P-value	n/N (%)	HR (95% CI)	P-value
IB (vs IA)	7,596/39,002 (19.48%)	1.87 (1.76-2.00)	<.0001	7,596/38,335 (19.81%)	1.87 (1.75-2.00)	<.0001
IIA (vs IB)	1,623/39,002 (4.16%)	1.36 (1.23-1.51)	<.0001	2,819/38,335 (7.35%)	1.42 (1.30-1.54)	<.0001
IIB (vs IIA)	5,372/39,002 (13.77%)	1.27 (1.15-1.41)	<.0001	4,176/38,335 (10.89%)	1.27 (1.17-1.38)	<.0001
IIIA (vs IIB)	5,167/39,002 (13.25%)	1.56 (1.47-1.66)	<.0001	4,073/38,335 (10.62%)	1.45 (1.35-1.55)	<.0001
IIIB (vs IIIA)	1,155/39,002 (2.96%)	1.51 (1.39-1.65)	<.0001	1,582/38,335 (4.13%)	1.69 (1.56-1.82)	<.0001
IIIC (vs IIIB)	51/39,002 (0.13%)	1.78 (1.26-2.52)	0.0011	51/38,335 (0.13%)	1.67 (1.18-2.35)	0.0036
Age 65 or Older (vs younger than 65)	21,842/39,002 (56.00%)	1.65 (1.58-1.72)	<.0001	21,520/38,335 (56.14%)	1.67 (1.59-1.74)	<.0001
Female (vs Male)	20,188/39,002 (51.76%)	0.99 (0.95-1.03)	0.5274	19,860/38,335 (51.81%)	0.99 (0.95-1.03)	0.6735
Europe (vs Asia)	4,280/39,002 (10.97%)	1.49 (1.40-1.59)	<.0001	4,227/38,335 (11.03%)	1.48 (1.39-1.57)	<.0001
North America (vs Asia)	6,505/39,002 (16.68%)	1.51 (1.42-1.60)	<.0001	6,423/38,335 (16.75%)	1.52 (1.44-1.61)	<.0001
Rest of World (vs Asia)	1,404/39,002 (3.60%)	1.54 (1.40-1.70)	<.0001	1,393/38,335 (3.63%)	1.53 (1.39-1.69)	<.0001
Squamous (vs Non-squamous)	8,543/39,002 (21.90%)	1.43 (1.37-1.50)	<.0001	8,431/38,335 (21.99%)	1.47 (1.40-1.54)	<.0001

And then….CALGB 140503

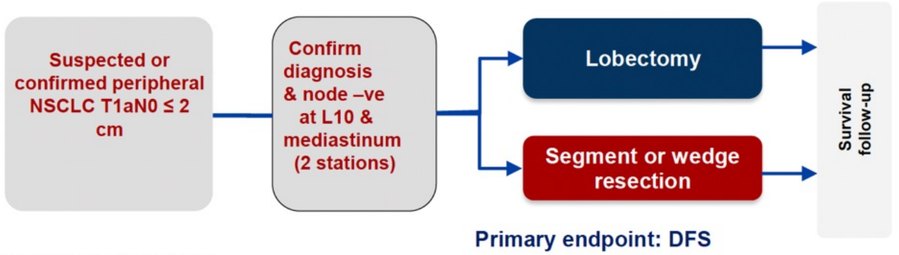
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 9, 2023 VOL. 388 NO. 6

Lobar or Sublobar Resection for Peripheral Stage IA Non–Small-Cell Lung Cancer

Nasser Altorki, M.D., Xiaofei Wang, Ph.D, David Kozono, M.D., Ph.D., Colleen Watt, B.S., Rodney Landrenau, M.D., Dennis Wigle, M.D., Ph.D., Jeffrey Port, M.D., David R. Jones, M.D., Massimo Conti, M.D., Ahmad S. Ashrafi, M.D., Moishe Liberman, M.D., Ph.D., Kazuhiro Yasufuku, M.D., Ph.D., Stephen Yang, M.D., John D. Mitchell, M.D., Harvey Pass, M.D., Robert Keenan, M.D., Thomas Bauer, M.D., Daniel Miller, M.D., Leslie J. Kohman, M.D., Thomas E. Stinchcombe, M.D., and Everett Vokes, M.D.

CALGB 140503: Phase III randomized trial comparing lobectomy and sublobar resection for small-sized carcinoma



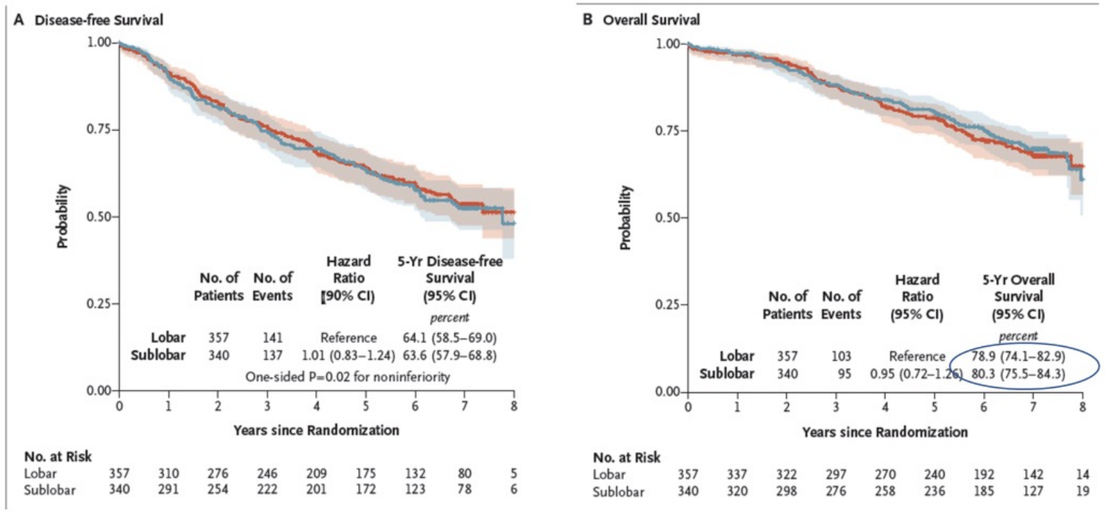
Primary endpoint: DFS

Stratification factors
- Tumor size (<1,1-15,1.6-2)
- Ever/never smokers
- Squamous/adenocarcinoma

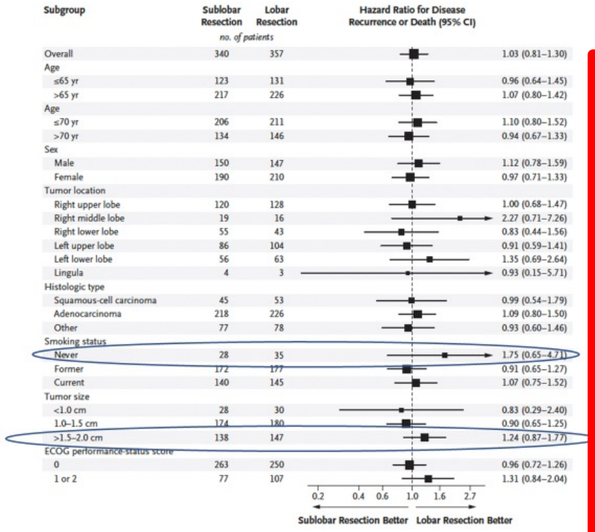
Secondary endpoints
- OS
- PFTs at 6 months
- Rates of loco-regional and systemic recurrence

CALGB 140503
Segmentectomy = 129 (42%)
Wedge = 200 (58%)

Equivalent survival



Important questions remain…



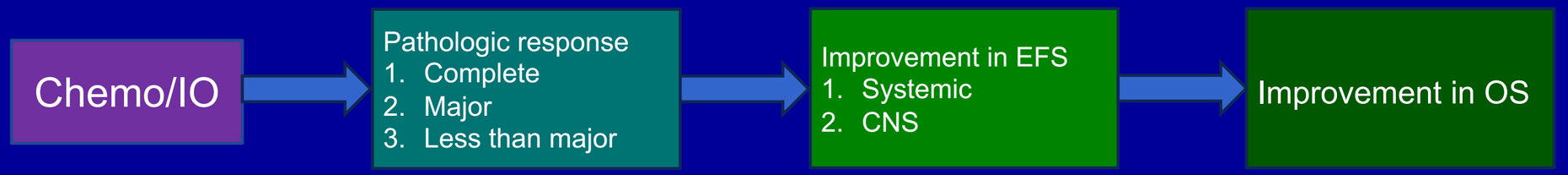
Where is wedge vs. segmentectomy?!

Disease Recurrence

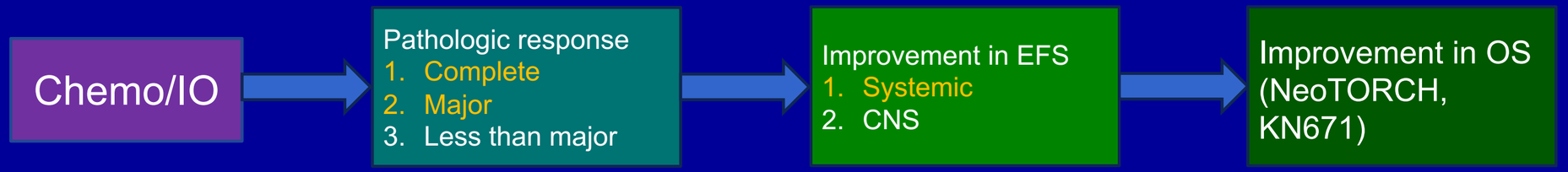
	Lobar N=351	Sublobar N=336	Total N=687	P-Value[1]
Overall	103 (29.3%)	102 (30.4%)	205 (29.8%)	0.8364
Locoregional only	35 (10%)	45 (13.4%)	80 (11.6%)	0.2011
Regional only	9 (2.6%)	6 (1.8%)	15 (2.2%)	0.6623
Any Distant	59 (16.8%)	51 (15.2%)	110 (16.0%)	0.6323

Why do "early stage" patients fail with distant disease and can we better detect those who will?!

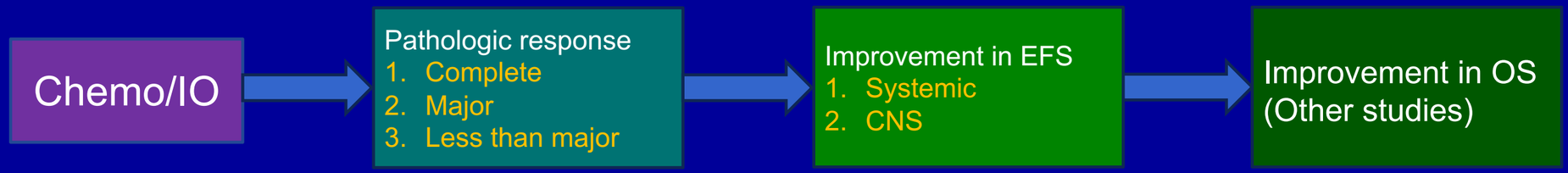
Object of neo-adjuvant IO



Current data



Future data?



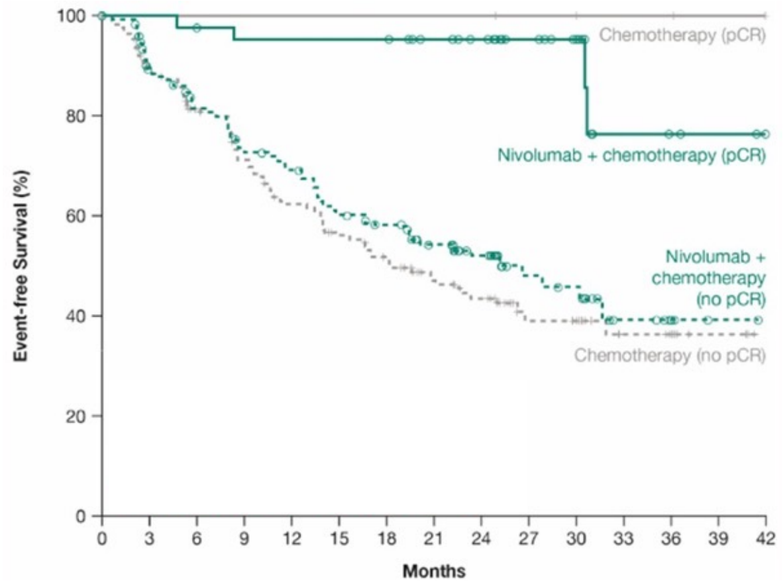
Pathologic complete response rates in randomized, phase III trials

Study	Neoadjuvant treatment	Sample Size #	% with PCR
Checkmate 816[1]	CTx + Nivolumab x 3	358	24
Keynote 671[2]	CTx + Pembrolizumab x 4	797	18
NeoTorch[3]	CTx + Toripalimab x 4	404	25
Aegean[4]	Ctx + Durvalumab x 4	740	17
Checkmate 77T[5]	Ctx + Nivolumab x 4	452	20
Mean pCR			~21

1) Forde P et. al NEJM 2022. 2) Wakelee H et al NEJM 2023. 3) Lu S et. al ASCO plenary April 2023. 4).Heymach J et. al AACR 2023. 5) Cascone T et. al ESMO 2023.

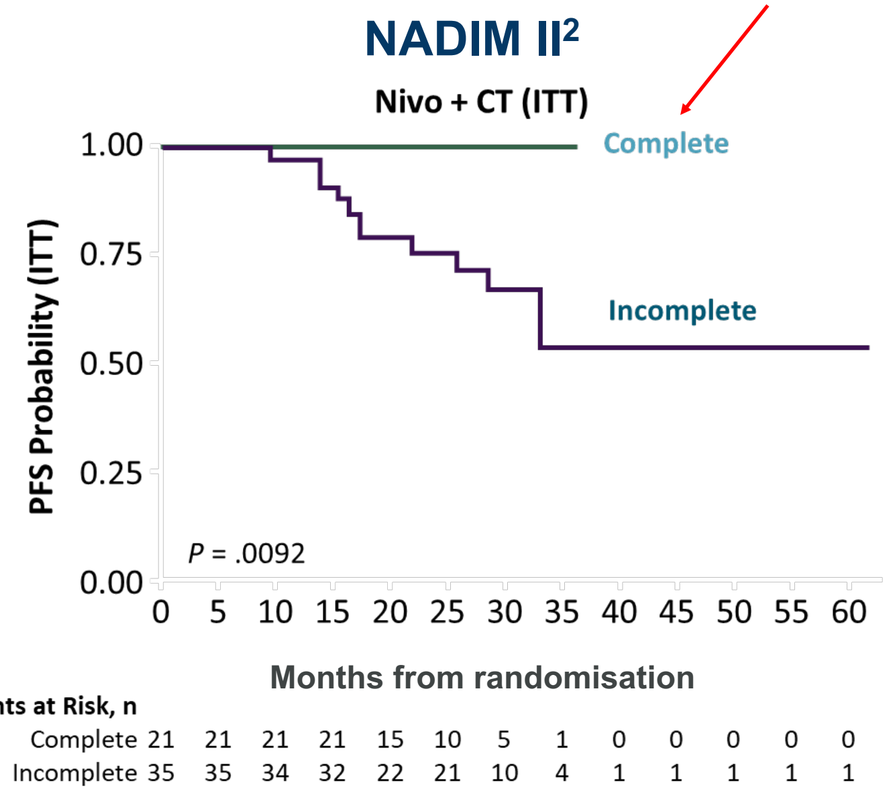
Pathologic complete response - a more promising surrogate endpoint

CheckMate 816[1]



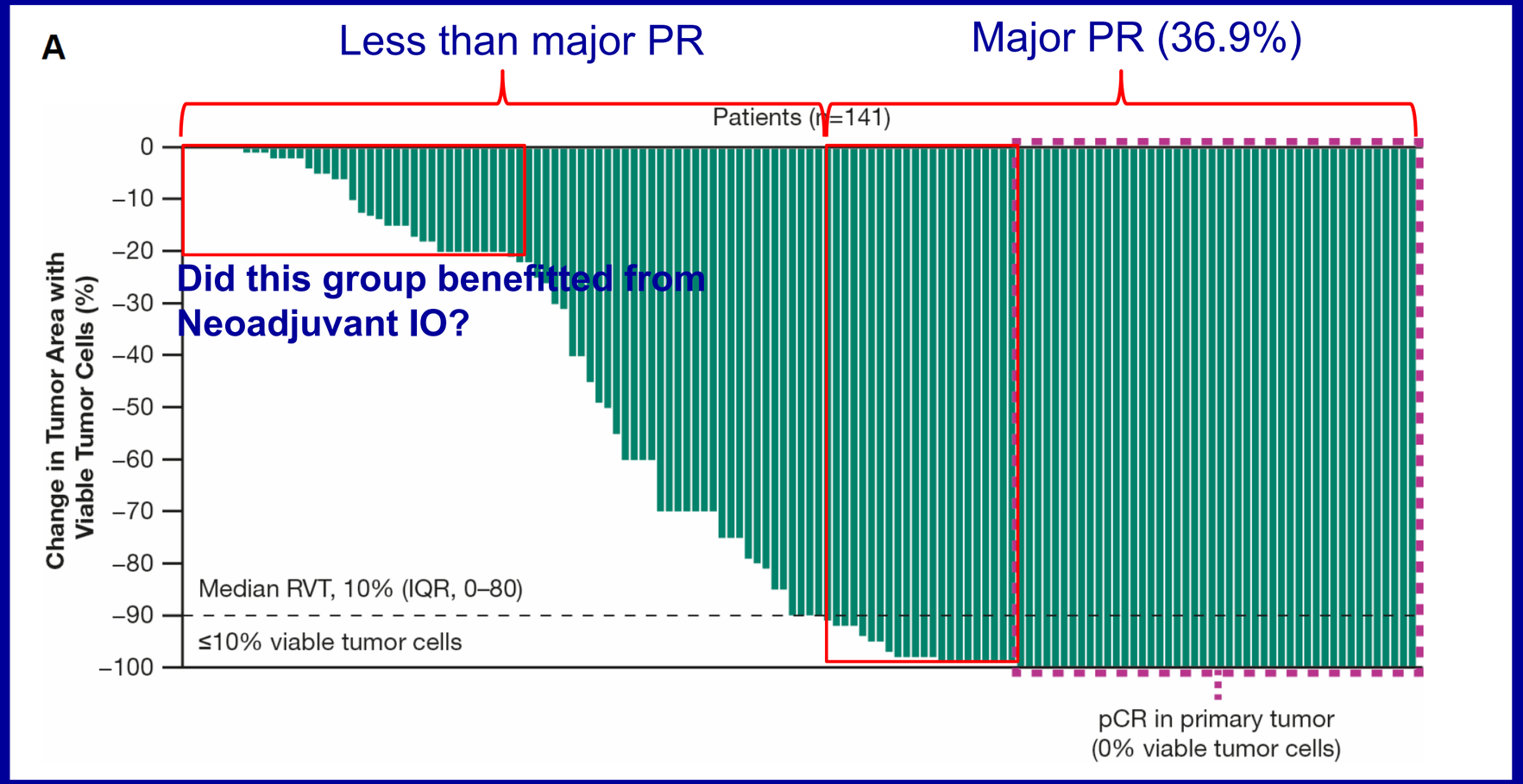
	Nivo + CT		CT	
	pCR	No pCR	pCR	No pCR
mEFS, months	NR	26.6	NR	18.4
HR (95% CI)	0.13 (0.05, 0.37)		Not computed*	

NADIM II[2]



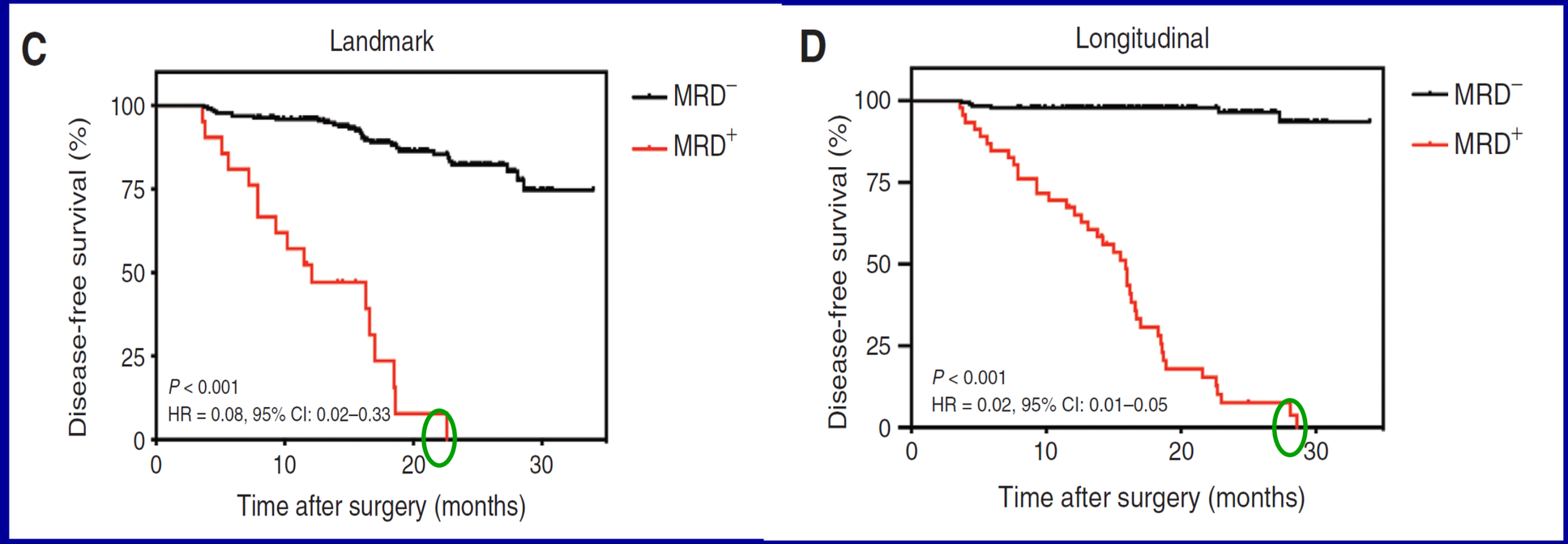
Courtesy of Dr. David Planchard and Dr. N. Leighl *1. Forde PM, et al. N Engl J Med 2022;386:1973–85; 2. Provencio M, et al. Presented at WCLC 2022 (Abstract PL03.12)

Depth of pathologic response: CM816



Forde et al NEJM 2022 Supplementary data

Presence of MRD is indicative of recurrence

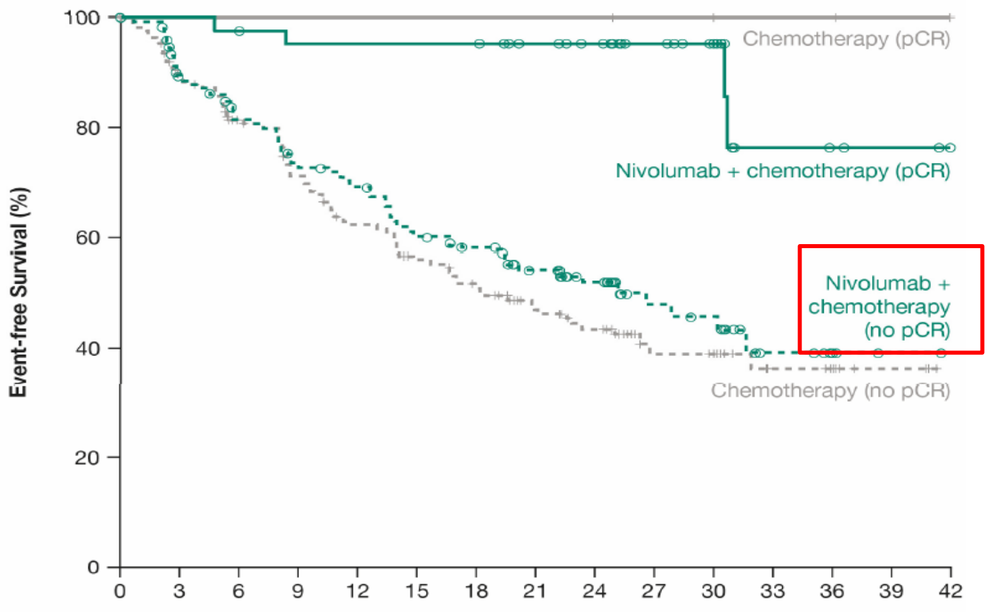


Zhang JT, et al. Cancer Discov 2022;12(7):1690–1701

EFS of patients with no CPR from CM816 (Major + Less Than Major pathologic response)

Was there a difference in EFS between the major and less than major responder?

	Nivolumab + chemotherapy		Chemotherapy	
	pCR (n=43)	No pCR (n=136)	pCR (n=4)	No pCR (n=175)
Median EFS, mo (95% CI)	NR (30.6–NR)	26.6 (16.6–NR)	NR (NR–NR)	18.4 (13.9–26.2)
HR (95% CI)*	0.13 (0.05–0.37)		Not computed†	

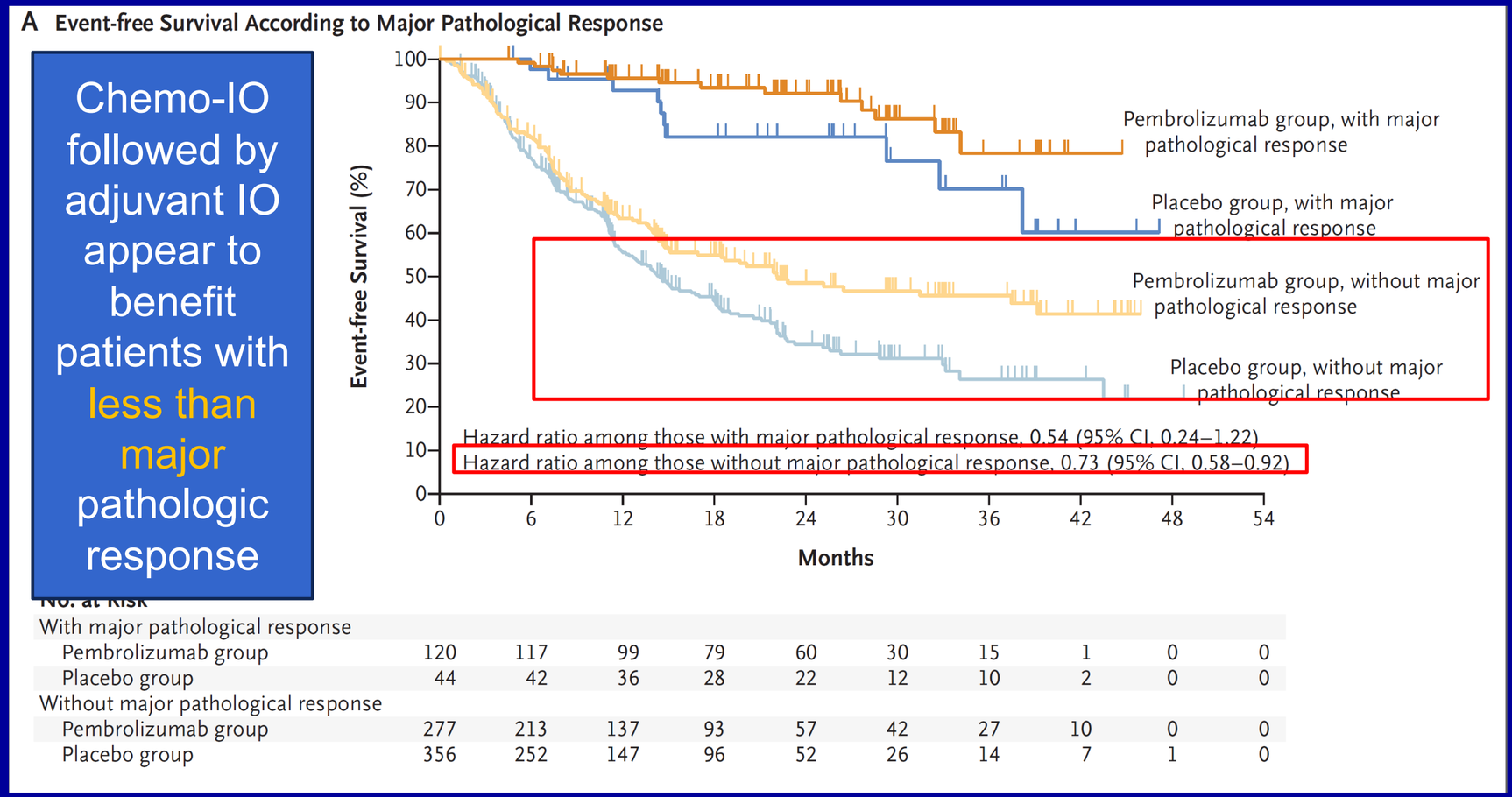


No. at Risk															
Nivolumab + chemotherapy (pCR)	43	43	41	40	40	40	40	35	32	19	14	6	3	2	0
Chemotherapy (pCR)	4	4	4	4	4	4	4	4	4	3	2	2	2	1	0
Nivolumab + chemotherapy (no pCR)	136	108	95	84	78	67	62	52	42	22	20	7	3	1	0
Chemotherapy (no pCR)	175	140	122	105	90	79	71	57	48	23	22	11	9	3	0

Forde et al NEJM 2022

Insights from KN671

Chemo-IO followed by adjuvant IO appear to benefit patients with less than major pathologic response



No. at Risk

With major pathological response										
Pembrolizumab group	120	117	99	79	60	30	15	1	0	0
Placebo group	44	42	36	28	22	12	10	2	0	0
Without major pathological response										
Pembrolizumab group	277	213	137	93	57	42	27	10	0	0
Placebo group	356	252	147	96	52	26	14	7	1	0

Wakelee et al NEJM 2023

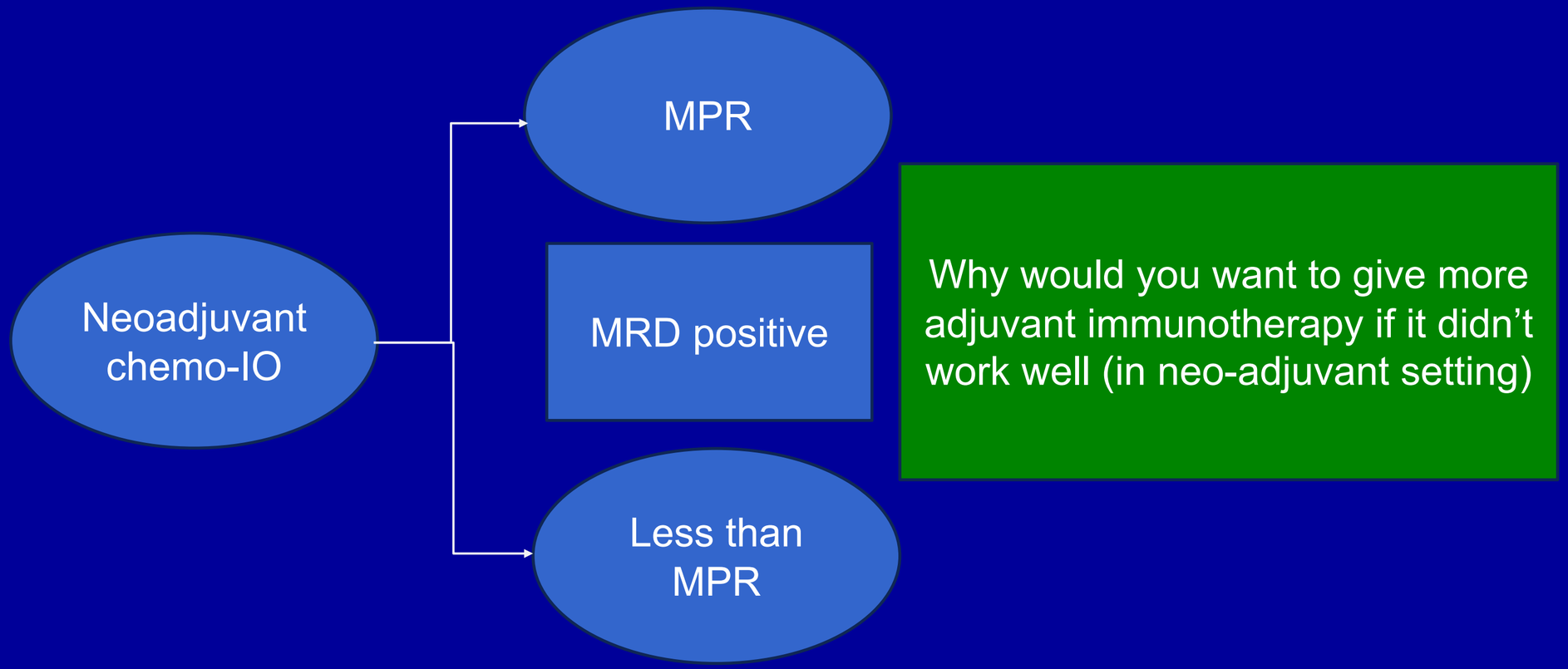
To rephase the question on the role of adjuvant therapy

Should we give adjuvant therapy to patients with major pathologic response after neo-adjuvant chemo-IO?

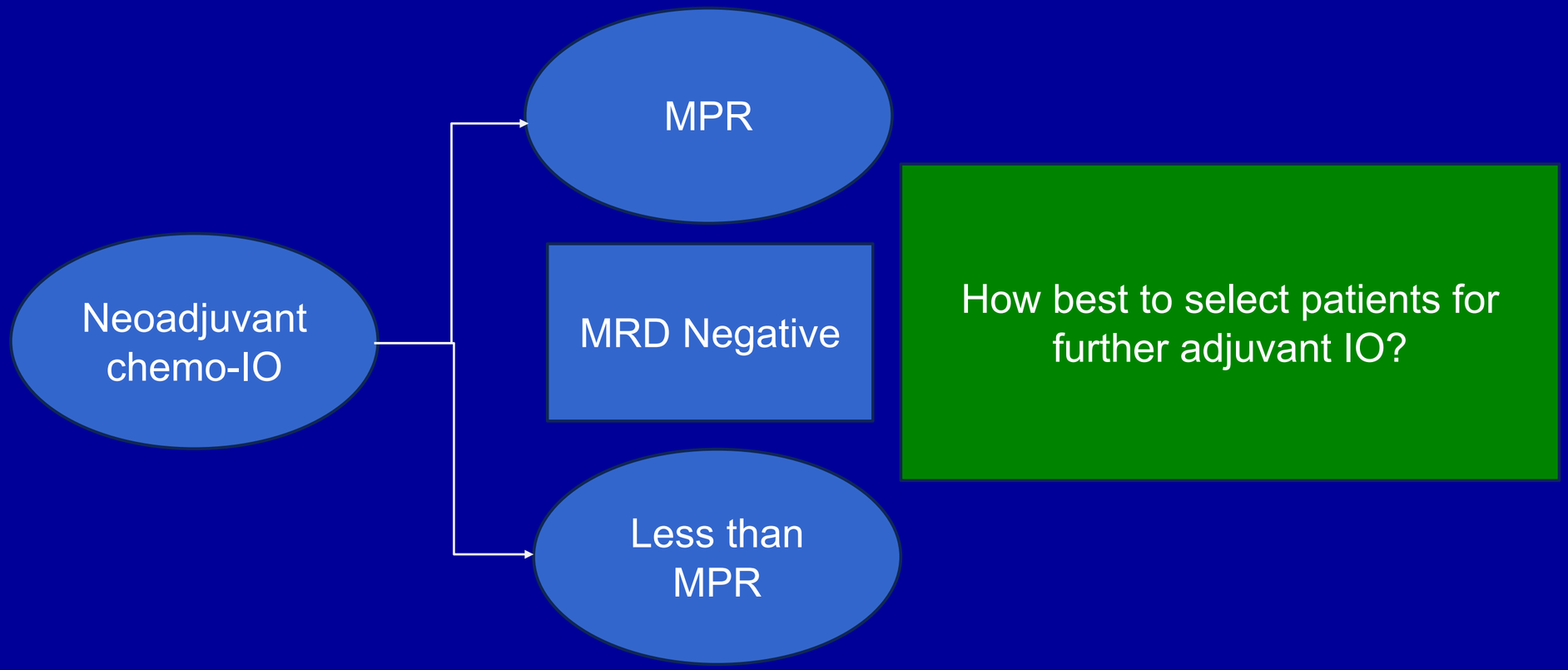
Should we give adjuvant therapy to patients with less than major pathologic response after neo-adjuvant chemo-IO?

Can we use MRD to personalize adjuvant IO for patients with major or less than major pathologic response?

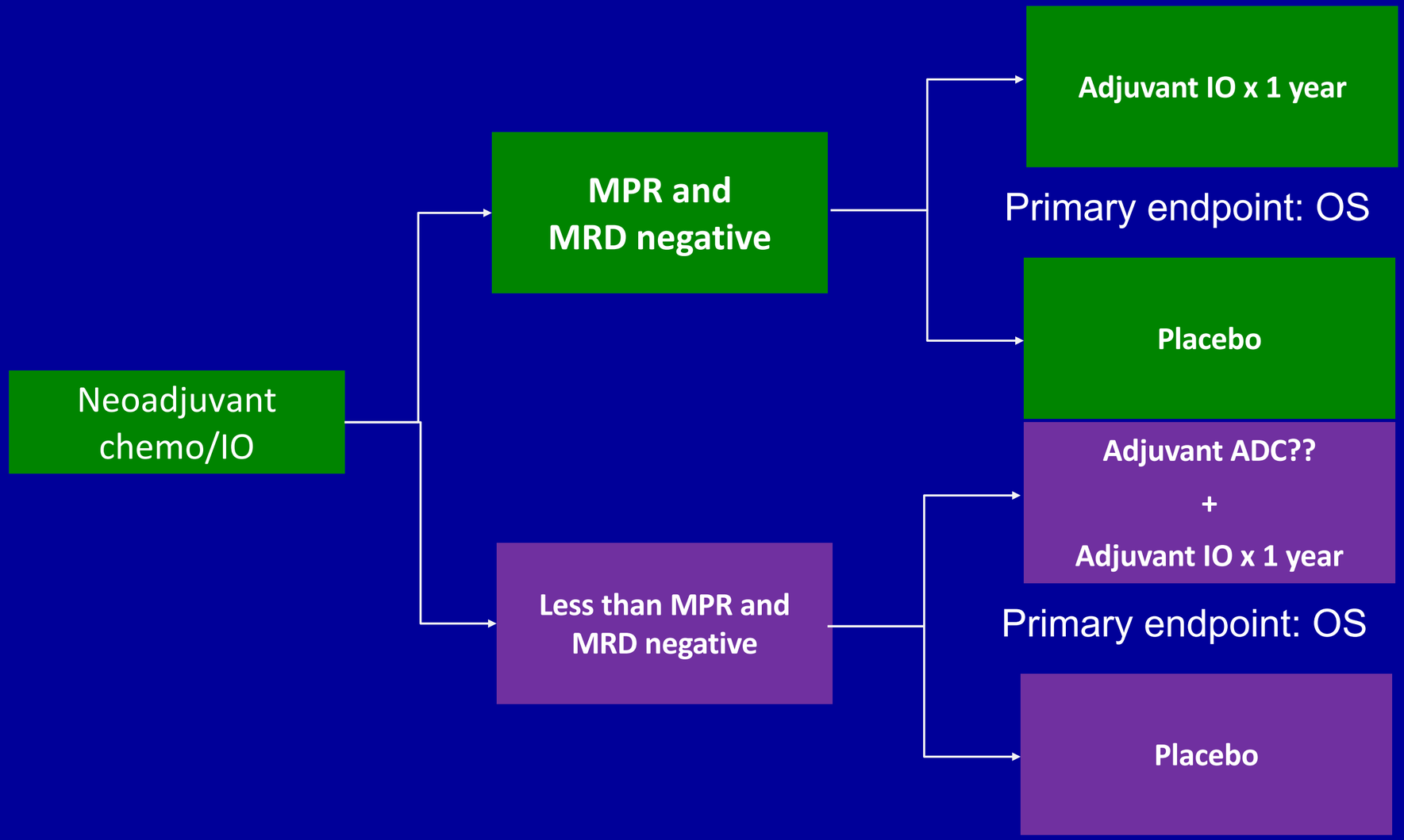
More adjuvant IO for MRD positive??



More adjuvant IO for MRD positive/negative??



My humble proposal

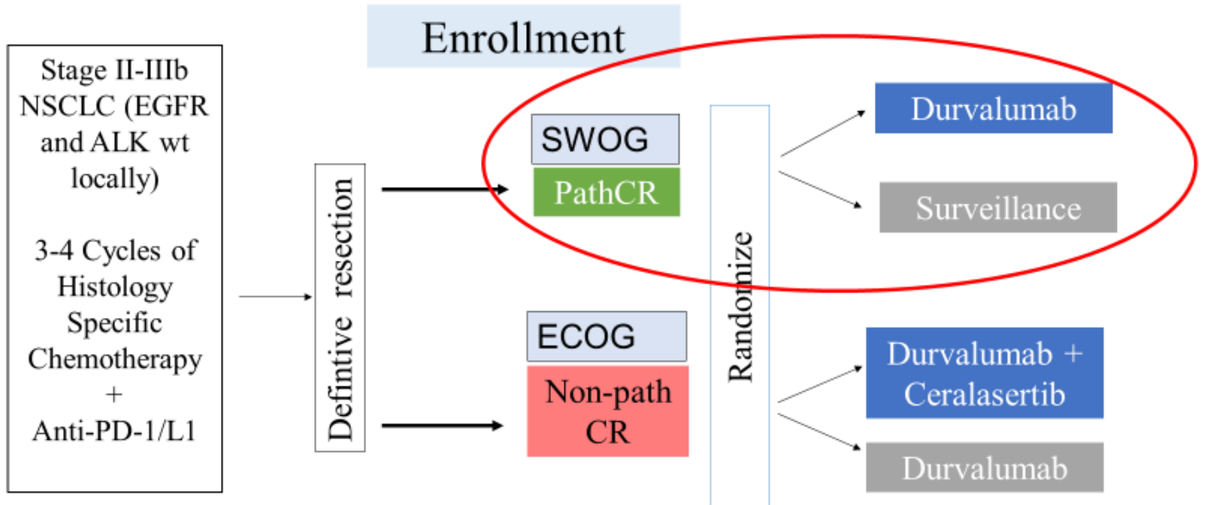


PROPOSAL:

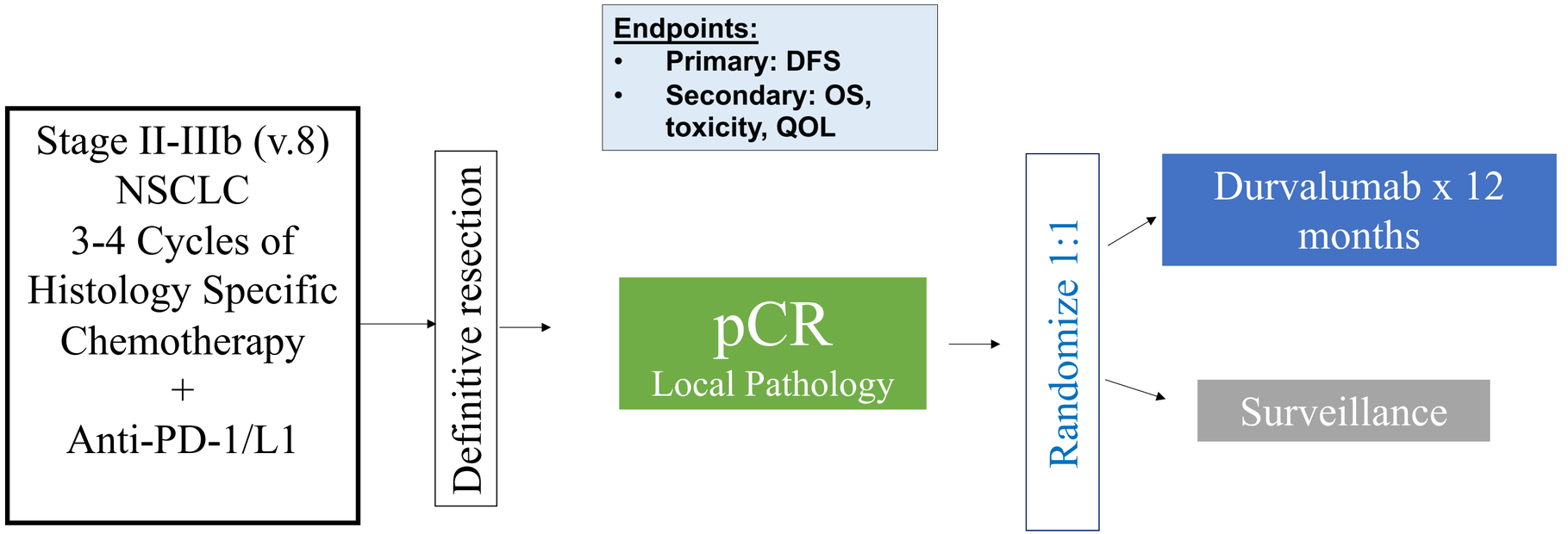
INcorporating pathologic responSe in patIents with early staGe lung cancer to optimize immunotHerapy in the adjuvanT setting (INSIGHT) – S2414

PI: Jeremy Cetnar
Co-PI: Ray Osarogiagbon
Statistician: Yingqi Zhao, Michael LeBlanc
Lung Committee Chair: Jhanelle Gray
Patient advocate: Judy Johnson
Pathology committee: TBD
QOL PI: TBD

Combined ECOG/SWOG CLEAR-INSIGHT SCHEMA



INSIGHT Schema – SWOG



Inclusion:
- ECOG 0/1
- R0 resection
- No known EGFR/ALK
- Confirmed PD-L1 status

Stratification factors:
- Stage (II v III)
- PD-L1 (<1% v ≥1%)
- Histology (Sq v NSq)

Exploratory Objectives
- AI based assessment
- ctDNA
- Central review

Follow-up evaluations:
- CT scan Q3 month yr 1
- QOL questionnaires

[1] Pts can enroll on optional pre-screening study

THANKS, See you in NYC!