Do Biomarkers and MRD Matter?

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COI Disclosure

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Board of Directors	AstraZeneca Ltd; HutchMed Ltd, Insigta Ltd.

Does it matter?

Does it matter?

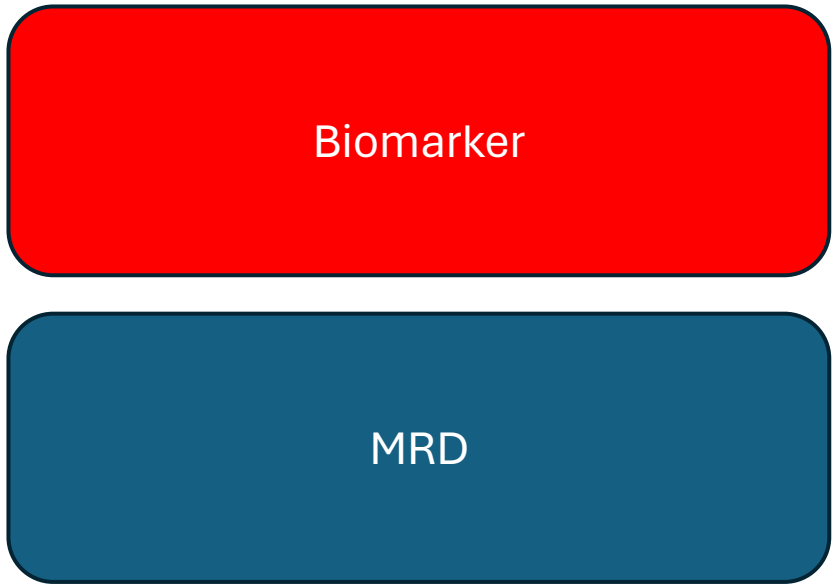
To whom?

For what?

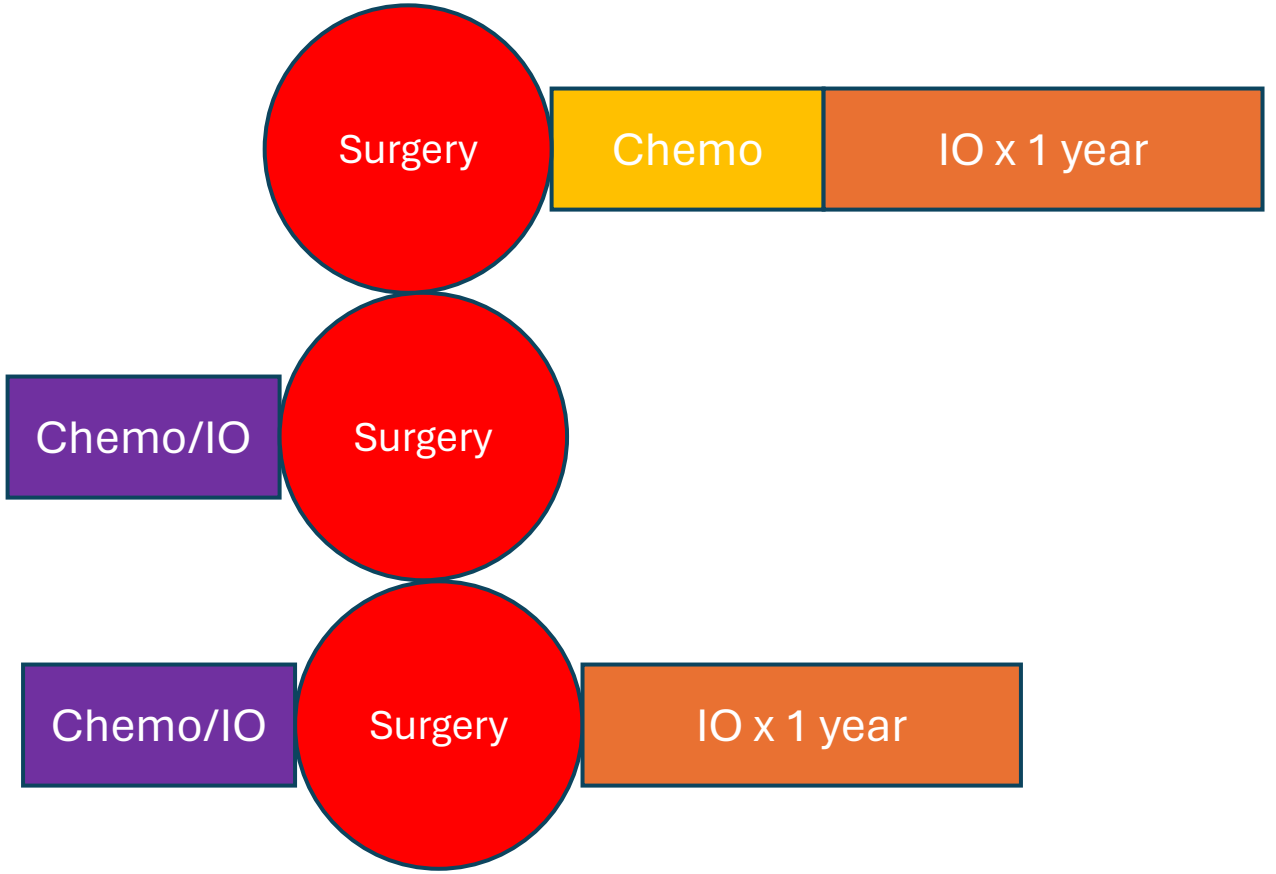
To patient
For survival

Does it matter?

Does it matter?



Immunotherapy for early stage lung cancer



IMpower150
KN090

CM816

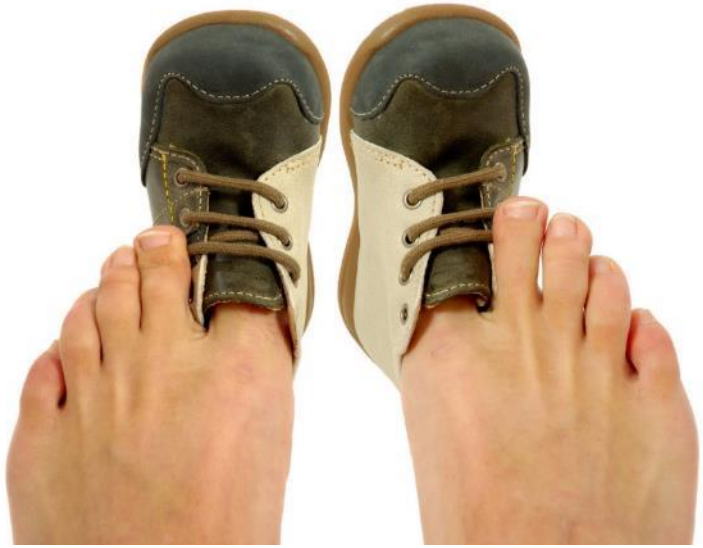
AEGEAN
KN671
NeoTORCH
CM 77T

Biomarker matters if not all patients benefit equally from pre-operative chemo-IO or post-operative IO.

You can’t walk properly in either case

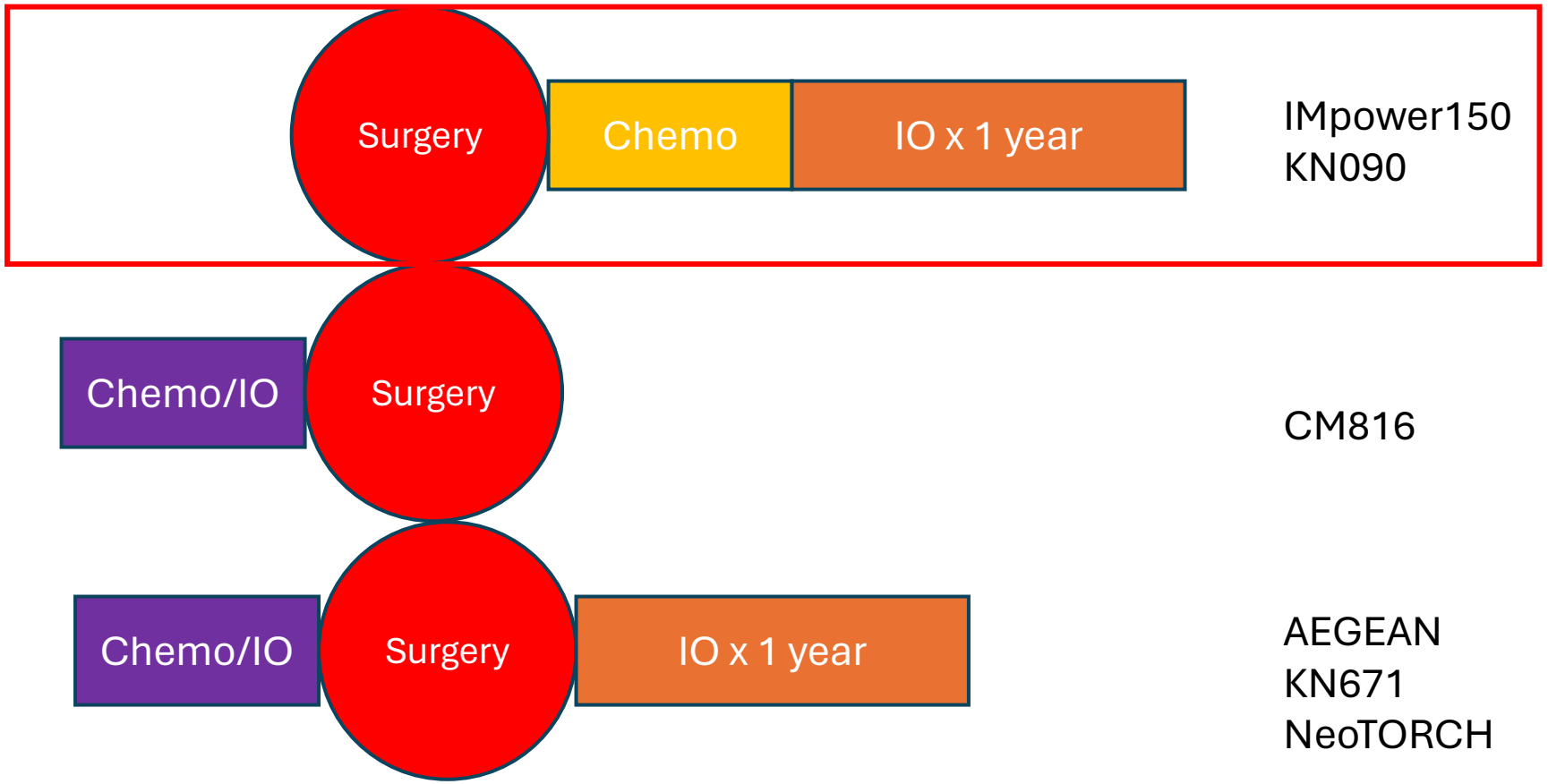
Small feet in big shoes

Big feet in small shoes

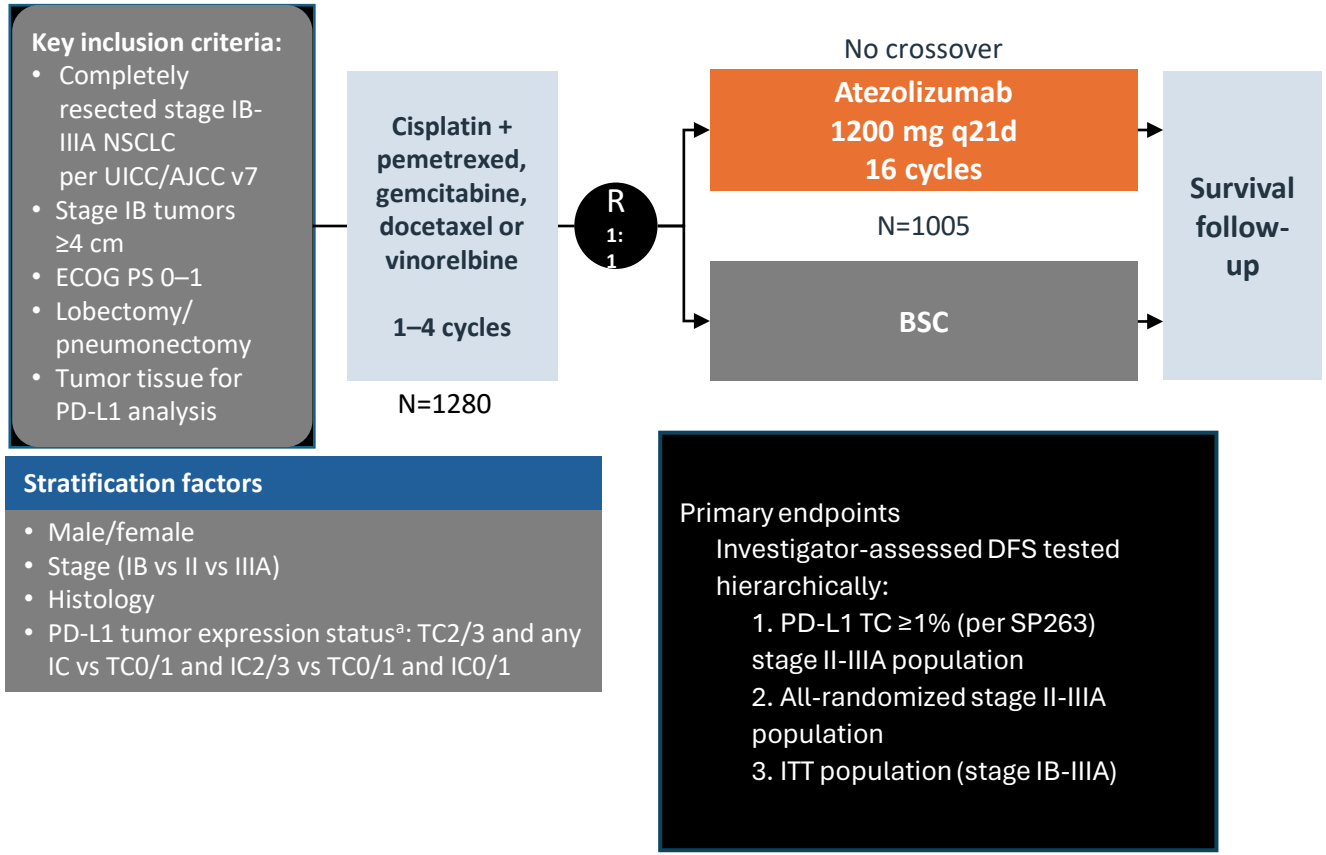


Giving too much therapy for those who don’t need it!
Giving not enough therapy for those who need more!

The evolving landscape (as explained by Molly)

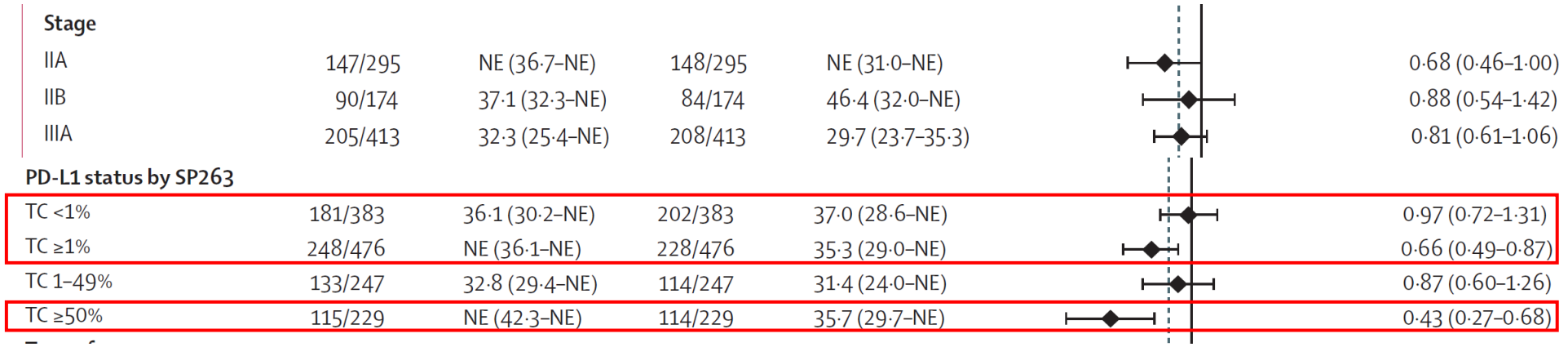


IMpower010 (primary results): Atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA NSCLC



Felip et al Lancet 2021

The impact of PDL1 status on EFS with adjuvant IO



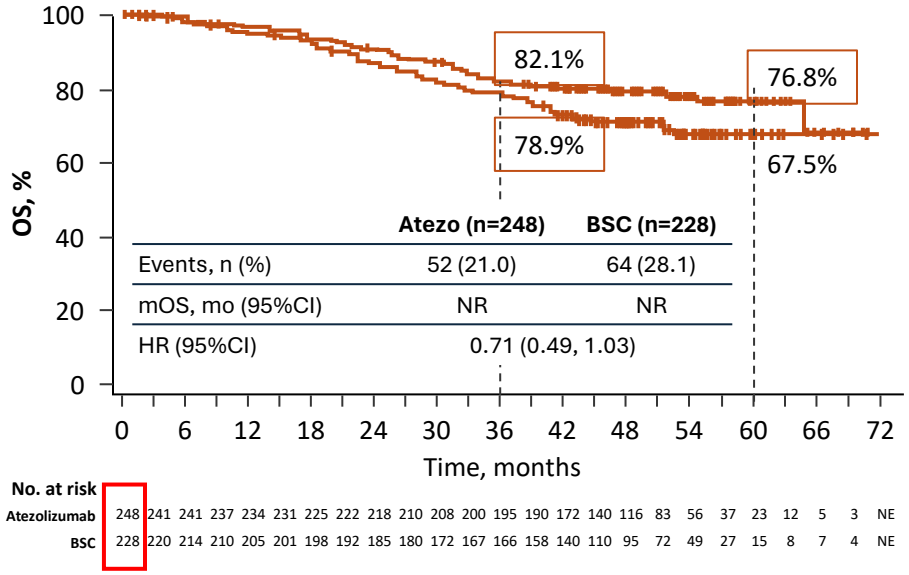
Stage					
IIA	147/295	NE (36·7–NE)	148/295	NE (31·0–NE)	0·68 (0·46–1·00)
IIB	90/174	37·1 (32·3–NE)	84/174	46·4 (32·0–NE)	0·88 (0·54–1·42)
IIIA	205/413	32·3 (25·4–NE)	208/413	29·7 (23·7–35·3)	0·81 (0·61–1·06)
PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)

The benefit associated with the PDL1>1% is driven by the PDL1>50% population

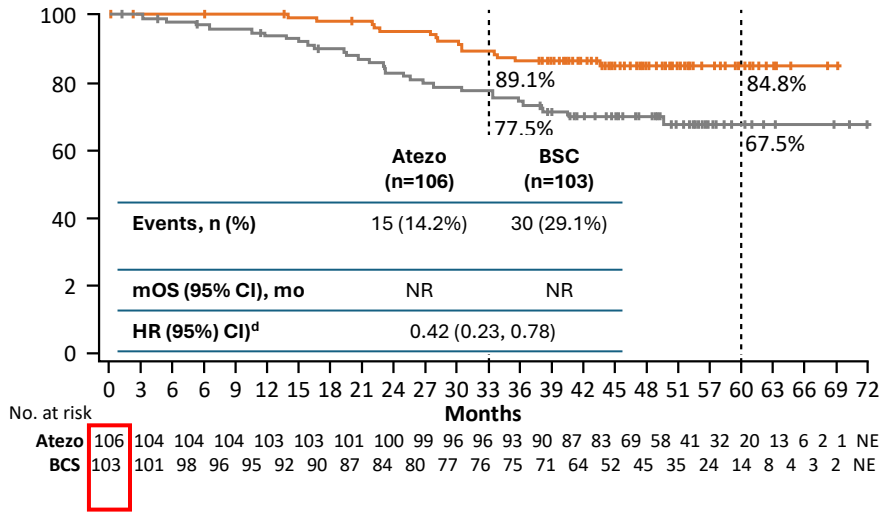
Felip et al Lancet 2021

The impact of PDL1 status on OS with adjuvant IO

OS: PD-L1 TC ≥1% (Stage II–IIIA) excluding EGFR/ALK

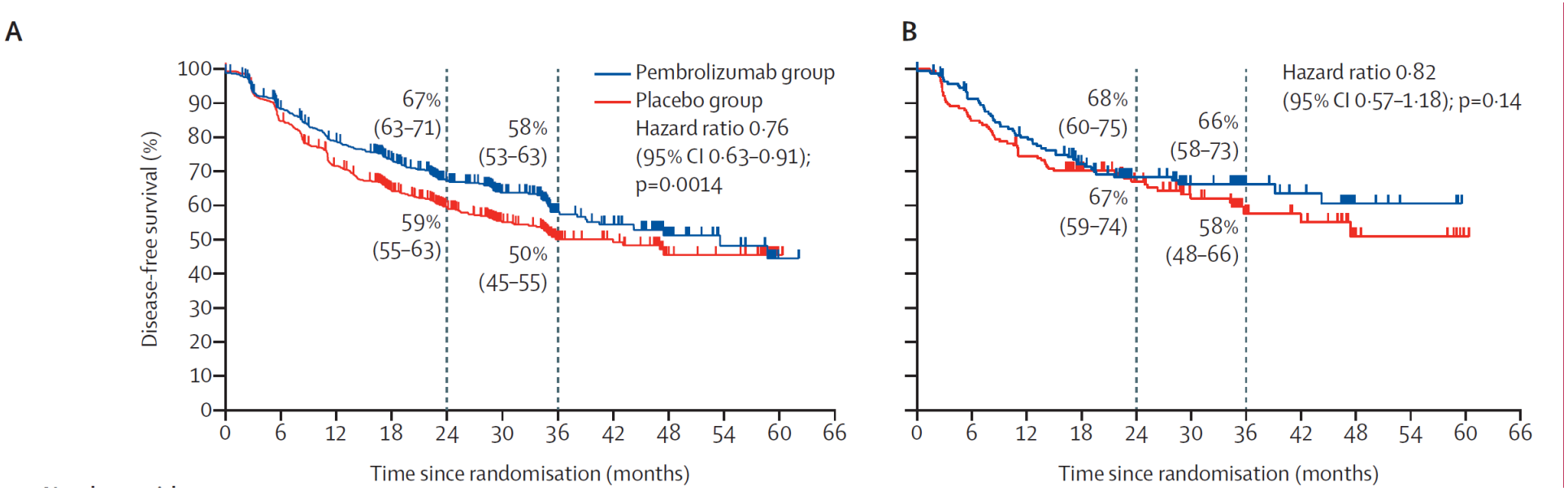


OS: PD-L1 TC ≥50% (Stage II-IIIA) excluding *EGFR/ALK+*



Felip E, et al. WCLC 2022. Abstract PL03.09

PEARL/KEYNOTE-091: DFS



Overall population

PDL1 >50% population

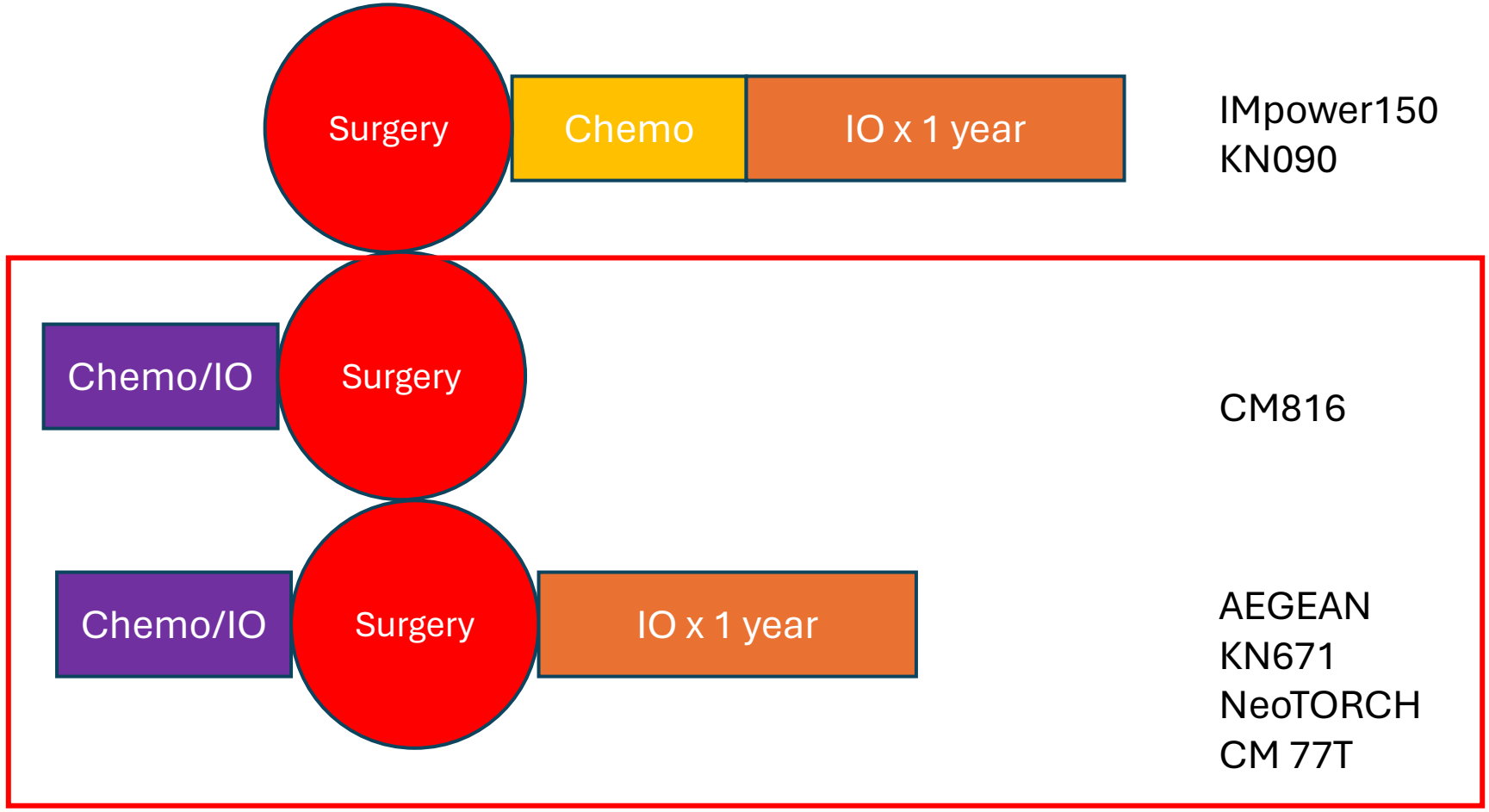
No good explanation!

O'Brien et al Lancet Oncology 2022

Does PDL1 status matter for adjuvant IO?

- Yes, it does but current data is a bit confusing
  - Minimal benefit in both PFS and OS if PDL1 <1%
  - Approved indication for PDL1>1% but most of the benefit is driven by the PDL1>50% subgroup.
  - Contradictory outcomes between IMpower 010 and KN091 on the PDL1>50% subgroup.

The evolving landscape



CheckMate 816 study

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB–II vs IIIA),
PD-L1[b] (≥ 1% vs < 1%[c]), and sex

Primary analysis population

N = 358

R 1:1

NIVO 360 mg Q3W
+
chemo[d] Q3W (3 cycles)

Chemo[e] Q3W (3 cycles)

NIVO 3 mg/kg Q2W (3 cycles)
+ IPI 1 mg/kg (cycle 1 only)[f]

Radiologic restaging

Surgery (within 6 weeks post-treatment)

Optional adjuvant chemo ± RT[g]

Follow-up

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

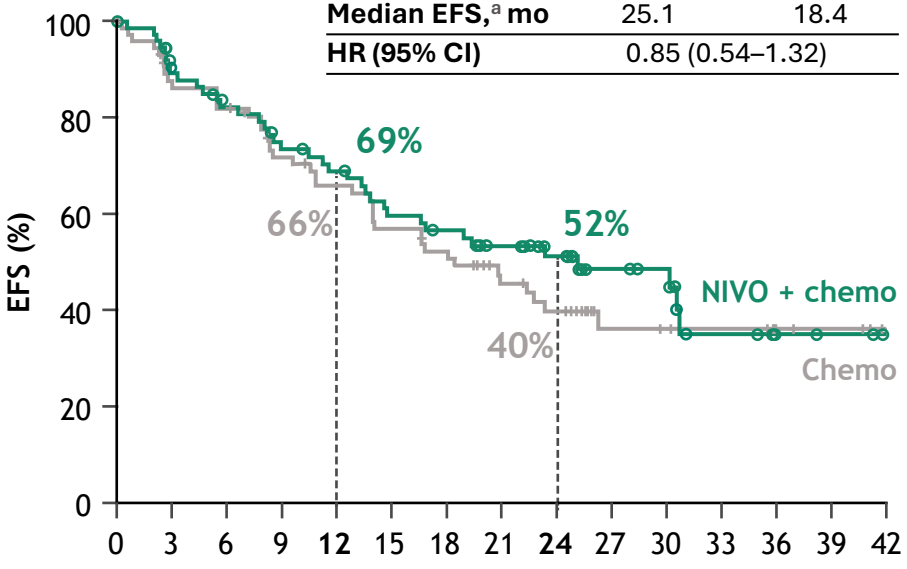
Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

Forde et al NEJM 2022

EFS by PD-L1 expression < 1% or ≥ 1%

PD-L1 < 1%

	NIVO + chemo (n = 78)	Chemo (n = 77)
Median EFS,[a] mo	25.1	18.4
HR (95% CI)	0.85 (0.54–1.32)	

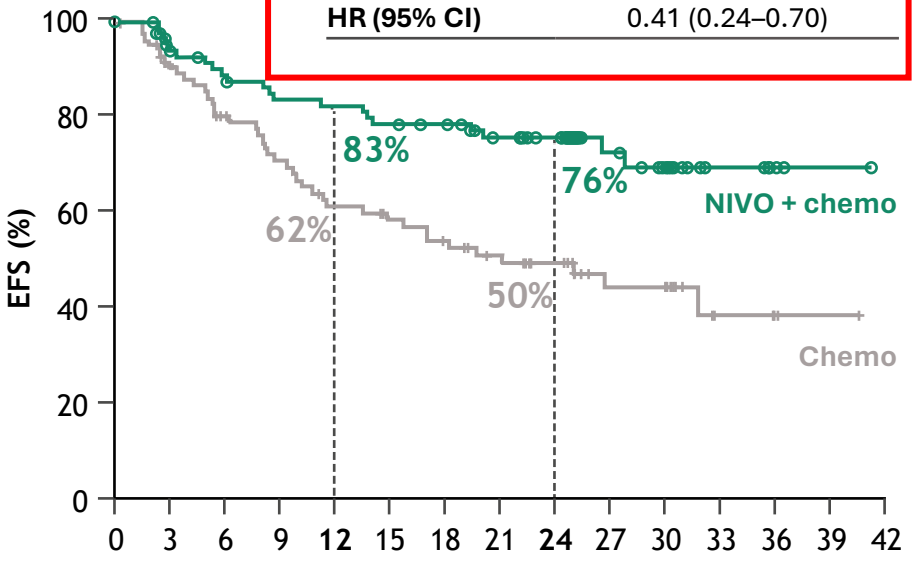


No. at risk

NIVO + chemo	78	65	57	51	46	39	36	30	24	15	13	6	3	2	0
Chemo	77	62	58	49	44	38	34	25	21	10	9	8	6	3	0

PD-L1 ≥ 1%

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median EFS,[b] mo	NR	21.1
HR (95% CI)	0.41 (0.24–0.70)	



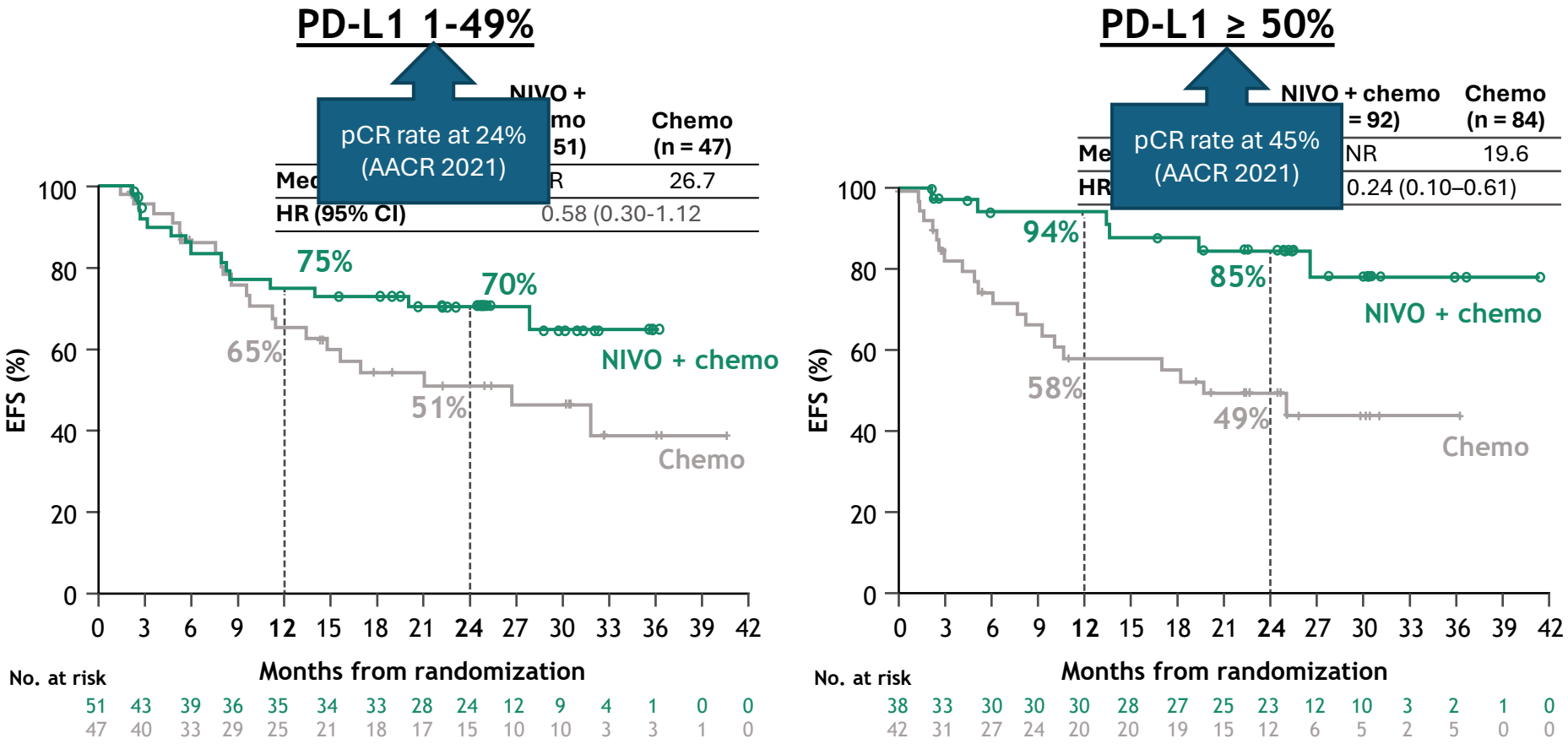
No. at risk

NIVO + chemo	89	76	69	66	65	62	60	53	47	24	19	7	3	1	0
Chemo	89	71	60	53	45	41	37	32	27	16	15	5	5	1	0

Minimum follow-up: 21 months.

[a]95% CI = 14.6–NR (NIVO + chemo) and 13.9–26.2 (chemo); [b]95% CI = NR–NR (NIVO + chemo) and 11.5–NR (chemo).

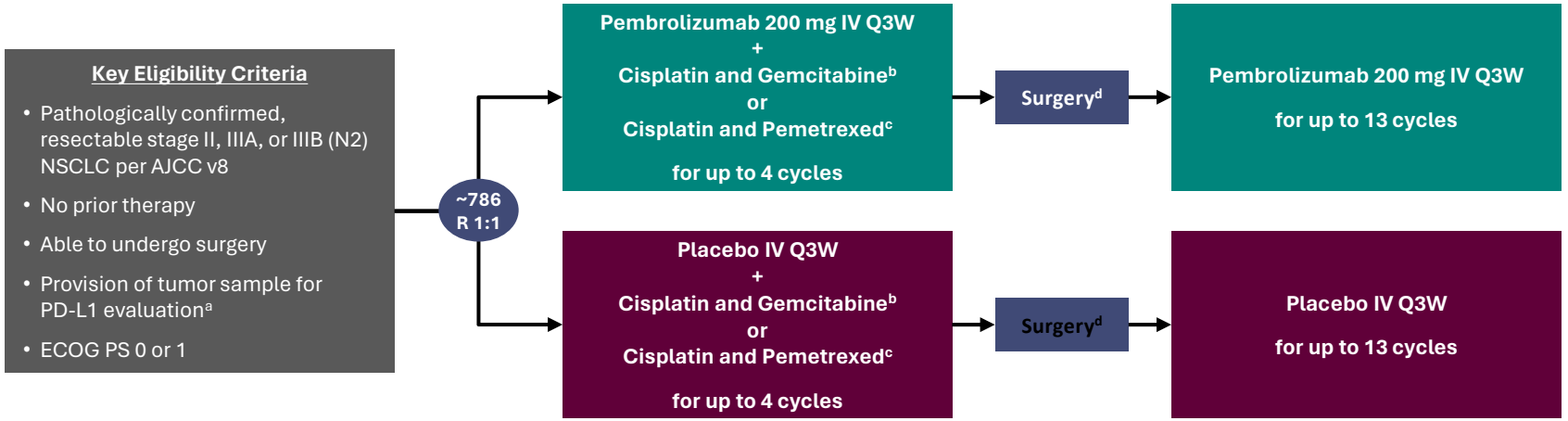
EFS by PD-L1 expression 1-49% or ≥ 50%



Minimum follow-up: 21 months.

[a]95% CI = 27.8-NR (NIVO + chemo) and 11.5-NR (chemo); [b]95% CI = NR–NR (NIVO + chemo) and 8.2–NR (chemo).

KEYNOTE-671 (Phase III): Neoadjuvant pembrolizumab + chemotherapy followed by resection and adjuvant pembrolizumab for early-stage NSCLC



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

Interim analysis 1 (IA1)

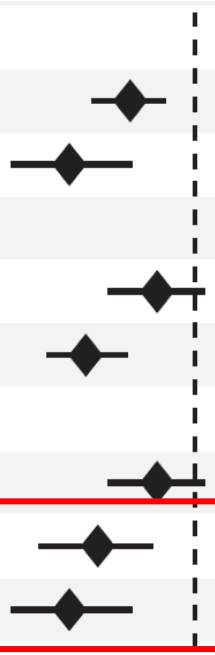
Prespecified to occur after ~326 EFS events observed and ~5 months after the last participant was randomized

Final analysis of mPR and pCR, interim analysis of EFS and OS

Felip et al Lancet 2022

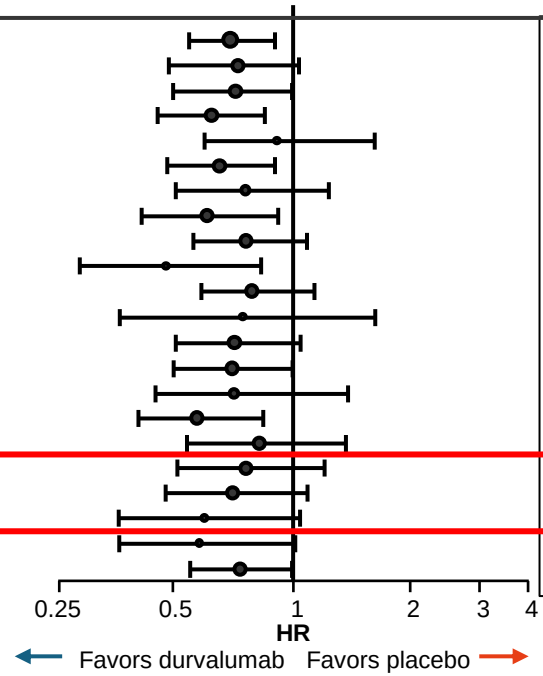
KN671: EFS as per PDL1 expression

PD-L1 TPS (50% cutoff)			
<50%	107/265	142/266	0.64 (0.49–0.82)
≥50%	32/132	63/134	0.42 (0.28–0.65)
PD-L1 TPS (1% cutoff)			
<1%	63/138	80/151	0.77 (0.55–1.07)
≥1%	76/259	125/249	0.47 (0.36–0.63)
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)



AEGEAN: EFS as per PDL1 expression

Subgroup		n	Median EFS, mo (95%CI) D arm (N=366)	Median EFS, mo (95%CI) PBO arm (N=374)	HR (95% CI)
All patients		**740**	NR (31.9, NR)	25.9 (18.9, NR)	0.68 (0.53, 0.88)
Age at randomization	<65 years	358	NR (NR, NR)	NR (18.9, NR)	0.71 (0.47, 1.04)
	≥65 years	382	NR (17.9, NR)	24.5 (13.6, 31.1)	0.69 (0.48, 0.97)
Sex	Male	530	NR (31.9, NR)	22.9 (14.3, 31.1)	0.61 (0.44, 0.82)
	Female	210	NR (17.5, NR)	NR (13.6, NR)	0.95 (0.58, 1.56)
ECOG PS	0	506	NR (31.9, NR)	25.4 (14.3, NR)	0.65 (0.47, 0.89)
	1	234	NR (21.8, NR)	25.9 (14.3, NR)	0.78 (0.49, 1.22)
Race*	Asian	307	NR (NR, NR)	25.4 (13.9, NR)	0.60 (0.40, 0.90)
	Non-Asian	433	31.9 (21.8, NR)	26.2 (14.3, NR)	0.76 (0.54, 1.06)
Smoking	Current	190	NR (NR, NR)	14.3 (8.1, NR)	0.48 (0.28, 0.80)
	Former	443	NR (31.9, NR)	25.9 (19.5, NR)	0.79 (0.57, 1.10)
	Never	107	NR (NR, NR)	24.5 (14.3, NR)	0.76 (0.35, 1.58)
Histology	Squamous	360	NR (31.9, NR)	26.2 (13.0, NR)	0.71 (0.49, 1.03)
	Nonsquamous	375	NR (NR, NR)	25.4 (14.3, NR)	0.69 (0.48, 0.99)
Disease stage (AJCC 8th ed)	II	214	NR (NR, NR)	31.1 (25.4, NR)	0.76 (0.43, 1.34)
	IIIA	338	NR (NR, NR)	19.5 (11.7, NR)	0.57 (0.39, 0.83)
	IIIB	186	31.9 (11.7, NR)	18.9 (11.8, NR)	0.83 (0.52, 1.32)
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)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR, NR)	31.1 (14.3, NR)	0.59 (0.35, 1.00)
	Carboplatin	544	NR (31.9, NR)	25.4 (14.3, NR)	0.73 (0.54, 0.98)



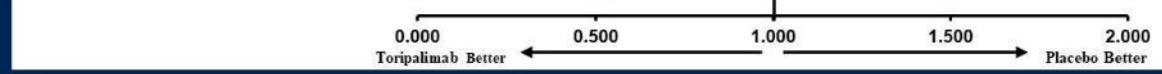
*Race was self-reported per the electronic case report form;
†determined using the Ventana SP263 IHC assay

Heymach JV, et al. AACR; 2023. Abstract nr CT005

NeoTORCH: EFS as per PDL1 expression

INV-EFS Treatment Effects in Key Subgroups

Subgroups	Toripalimab + Chemo Events/Total	Placebo + Chemo Events/Total	Hazard Ratio (95% CI)
Disease Stage			
IIIA	34/136	65/136	0.44 (0.287, 0.661)
IIIB	13/65	31/64	0.30 (0.149, 0.559)
PD-L1 Expression			
TC>=1%	28/133	65/132	0.31 (0.197, 0.481)
TC<1% or Not Evaluable	19/69	32/70	0.59 (0.327, 1.034)
Pathological Type			
Non-squamous Cell Carcinoma	12/45	21/45	0.54 (0.257, 1.079)
Squamous Cell Carcinoma	35/157	76/157	0.35 (0.234, 0.523)
Age			
<65	33/140	66/138	0.41 (0.267, 0.618)
>=65	14/62	31/64	0.34 (0.177, 0.635)
Sex			
Male	42/181	91/189	0.38 (0.259, 0.541)
Female	5/21	6/13	0.54 (0.154, 1.796)
ECOG			
0	20/70	38/73	0.44 (0.249, 0.743)
1	27/132	59/129	0.36 (0.226, 0.566)
Smoking			
Yes (Including Smoker or Former)	39/174	88/181	0.37 (0.252, 0.539)
No	8/28	9/21	0.52 (0.193, 1.358)

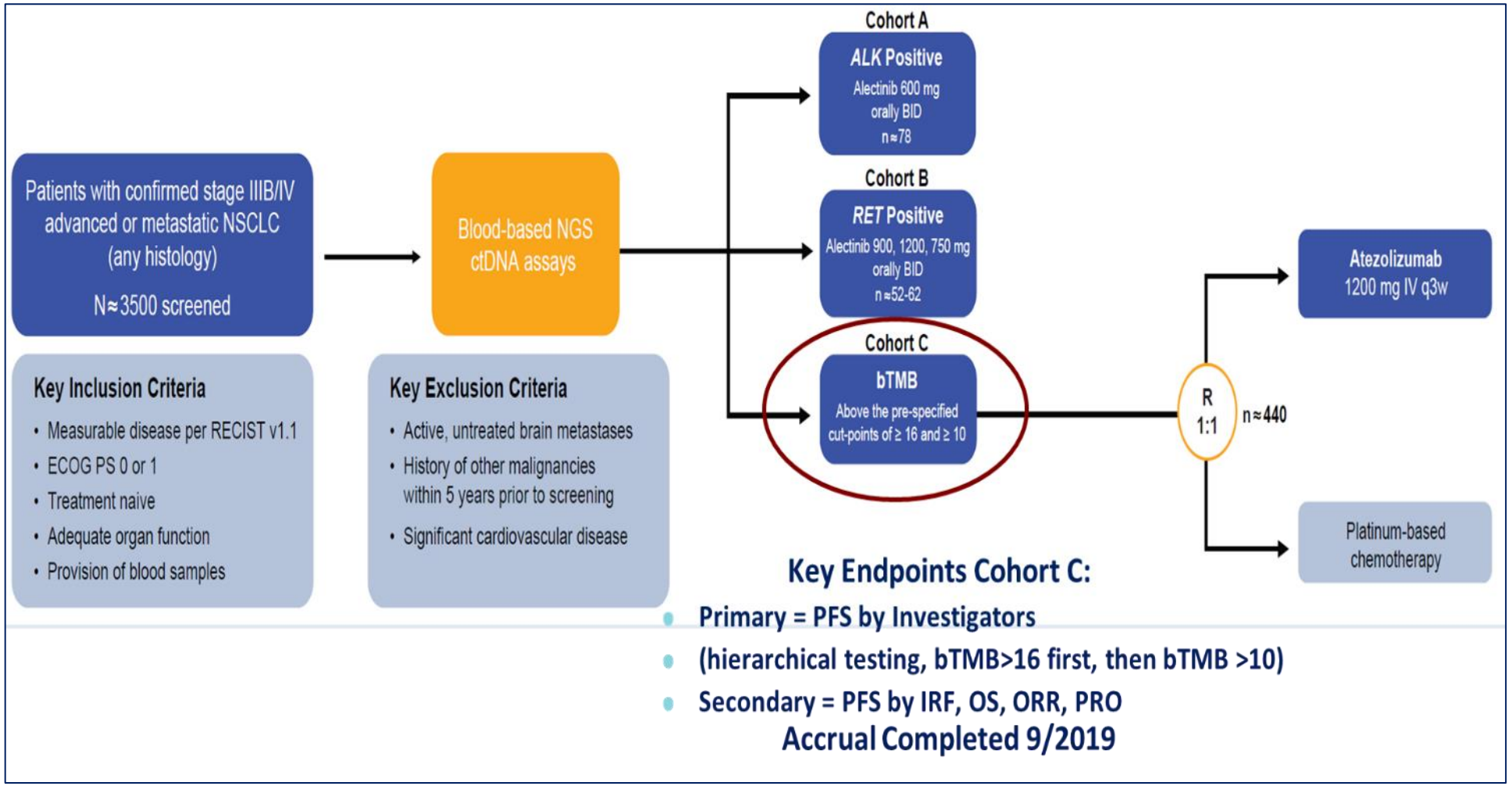


Does PDL1 status matter for neo-adjuvant chemo-IO?

- Yes, it does
- Multiple studies have shown lesser benefit for patients with PDL1 <1%
- It appears that both PDL1 1-49% and >50% subgroup may benefit from neo-adjuvant chemo-IO

Can TMB help?

BFAST (Blood First Assay Screening Trial)
Phase II/III Trial in Advanced Treatment-naïve Advanced NSCLC

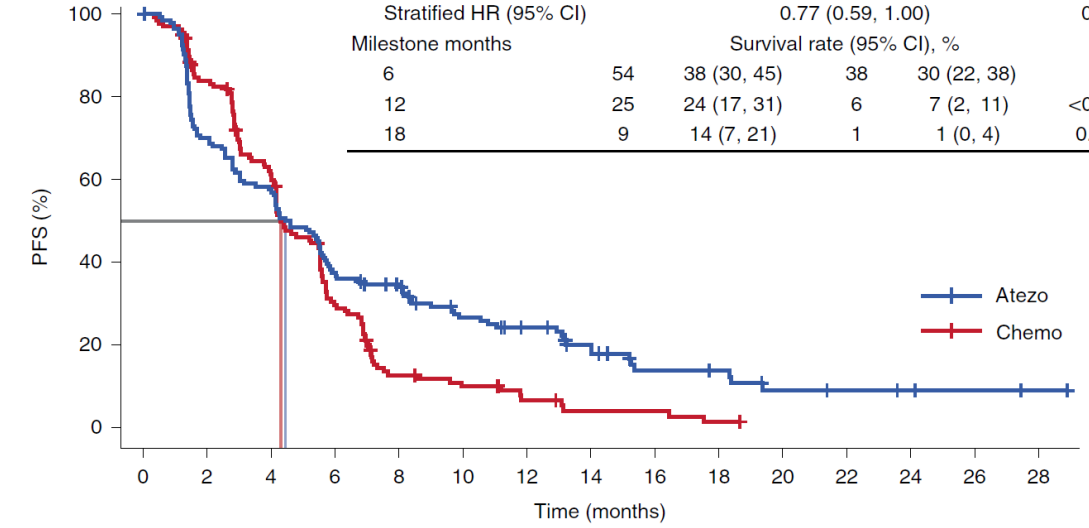


Dziadziuszko, R er al, Translational Oncology, 2021

Plasma-DNA based TMB is not a predictive biomarker for advanced stage NSCLC

a

	n	Atezo	*n*	Chemo	*P*
Median, months (95% CI)		4.5 (3.9, 5.6)		4.3 (4.2, 5.5)	
Stratified HR (95% CI)		0.77 (0.59, 1.00)			0.052
Milestone months		Survival rate (95% CI), %			
6	54	38 (30, 45)	38	30 (22, 38)	
12	25	24 (17, 31)	6	7 (2, 11)	<0.0001
18	9	14 (7, 21)	1	1 (0, 4)	0.0006

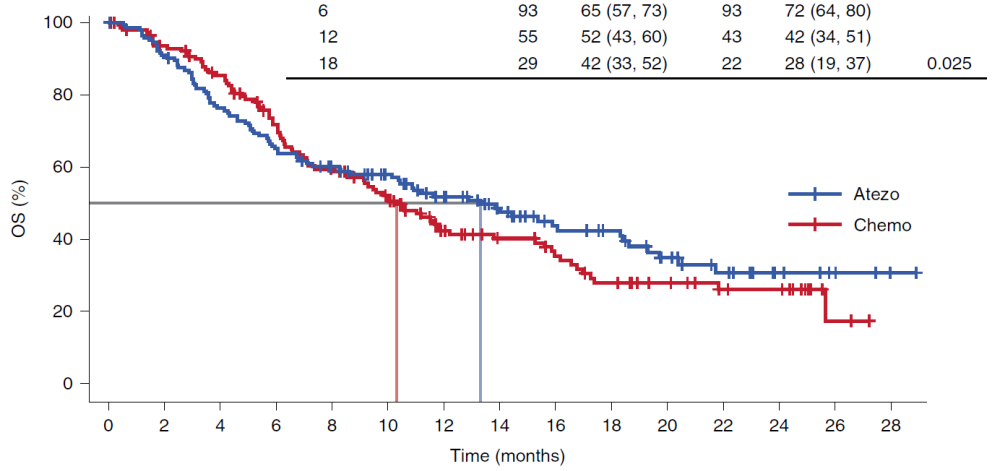


No. at risk

Atezo	145	101	83	54	46	32	25	18	10	9	5	4	3	2	1
Chemo	146	113	81	38	15	11	6	3	3	1	0	0	0	0	0

b

	n	Atezo	*n*	Chemo	*P*
Median, months (95% CI)		13.3 (8.6, 18.4)		10.3 (8.5, 13.8)	
Stratified HR (95% CI)		0.87 (0.64, 1.17)			
Milestone months		Survival rate (95% CI), %			
6	93	65 (57, 73)	93	72 (64, 80)	
12	55	52 (43, 60)	43	42 (34, 51)	
18	29	42 (33, 52)	22	28 (19, 37)	0.025

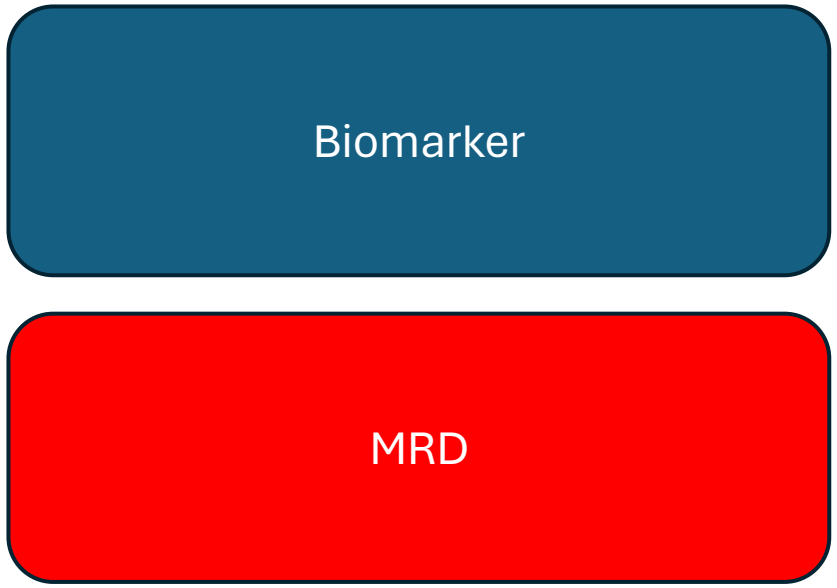


No. at risk

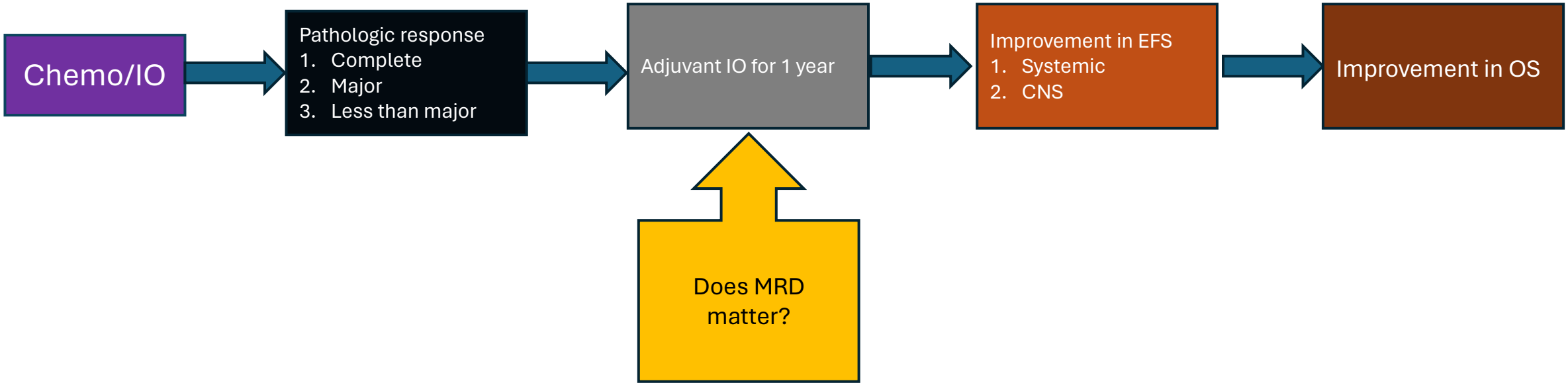
Atezo	145	131	109	93	81	67	55	44	33	29	20	14	7	4	1
Chemo	146	129	115	93	76	62	43	35	29	22	17	12	11	2	0

Peters & Mok et al Nature Medicine 2022

Does it matter?



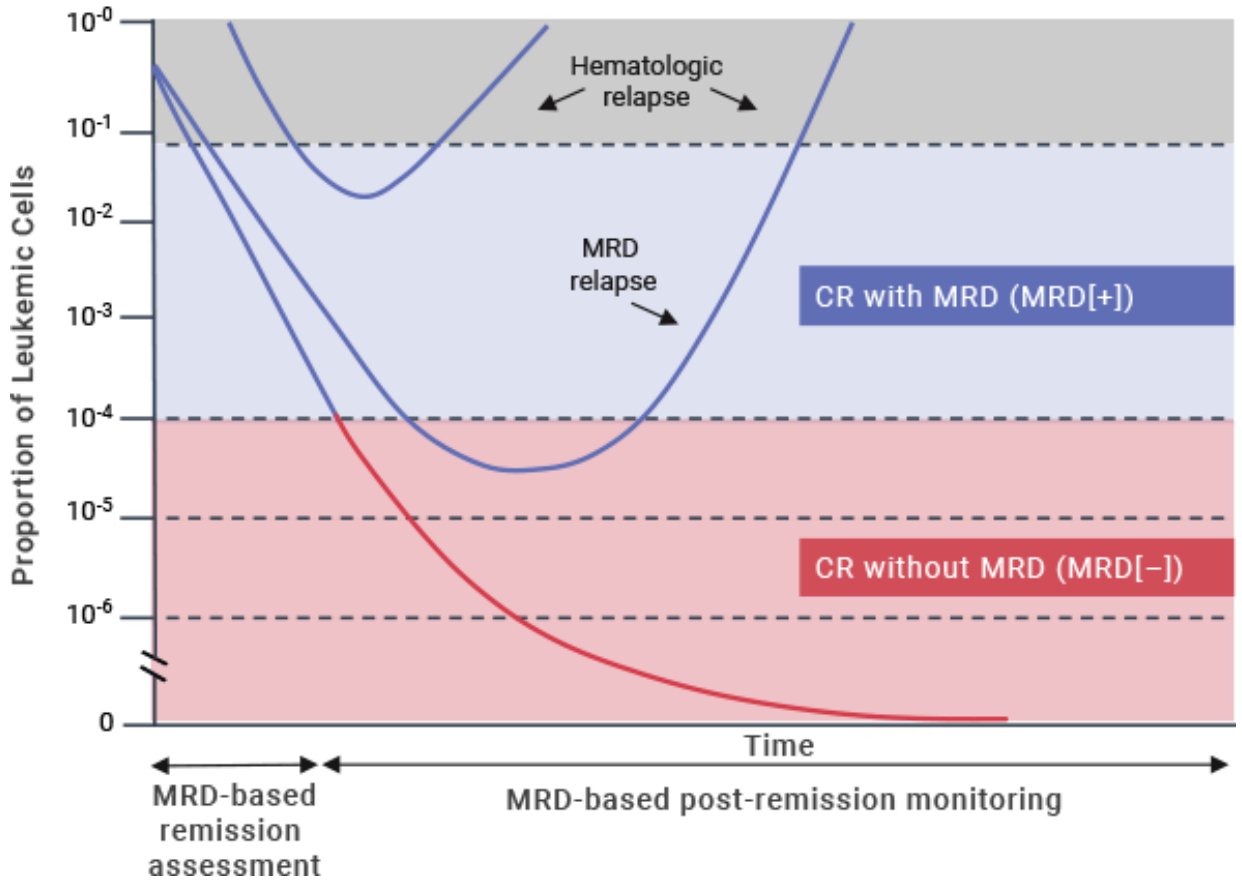
Lack of biomarker for subsequent adjuvant IO



Minimal residual disease (MRD) is a small number of cancer cells left in the body after treatment. These cells have the potential to come back and cause relapse in our patients.

Ghayas Issa, MD Anderson

MRD was first coined by hematologists referring to residual leukemic cell

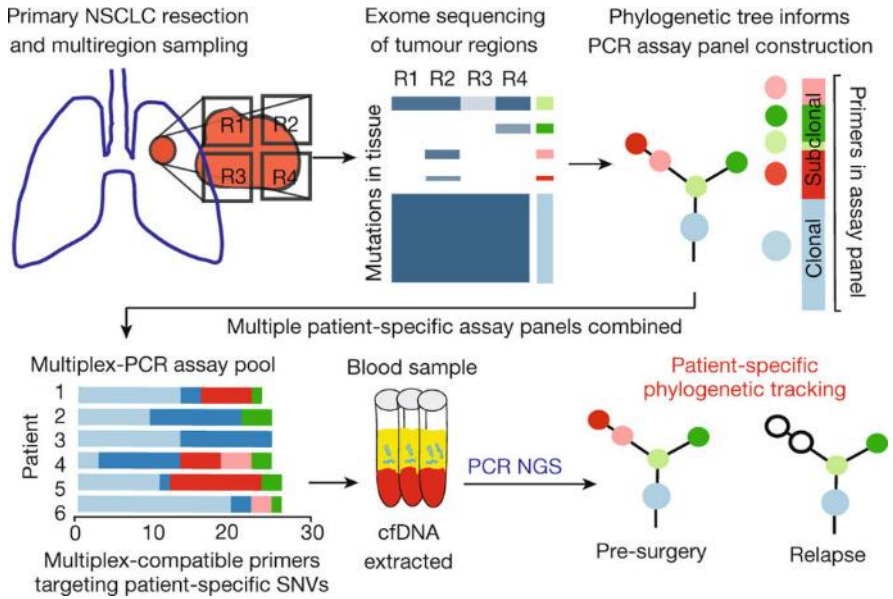


Berry DA, et al. *JAMA Oncol*. 2017;3:e170580

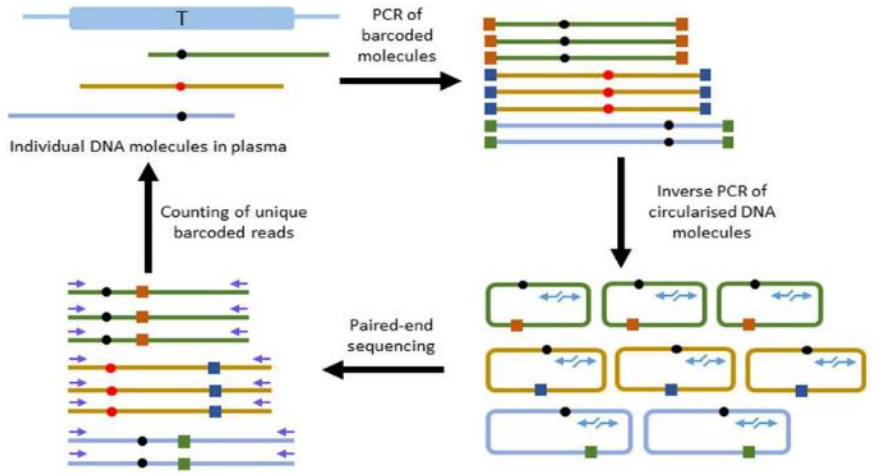
MRD for lung cancer refers to detection of ctDNA that is associated with residual cancer cell after curative surgery

MRD is NOT a single entity

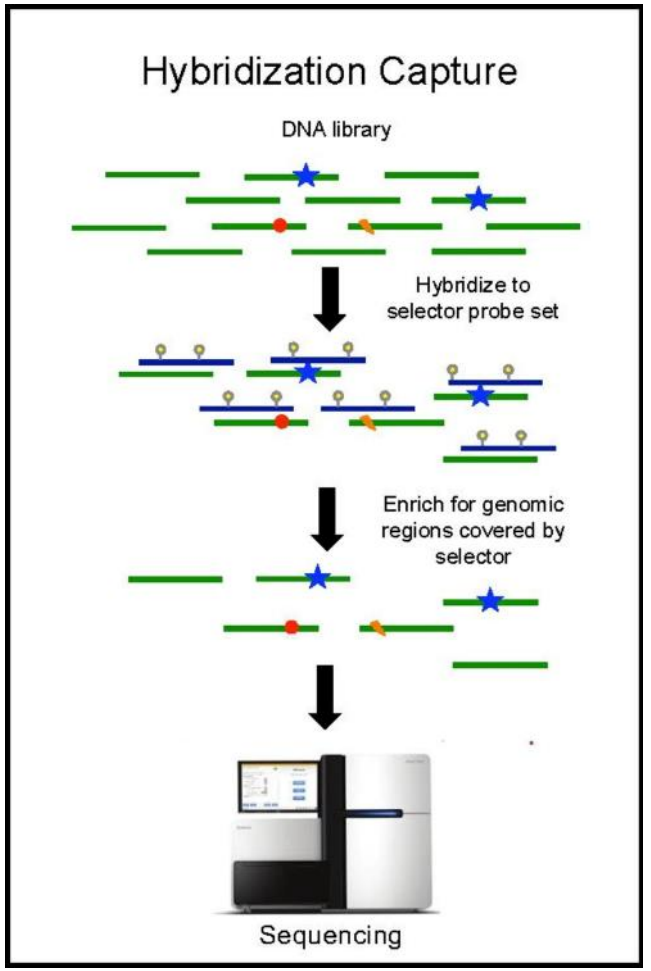
Signatera



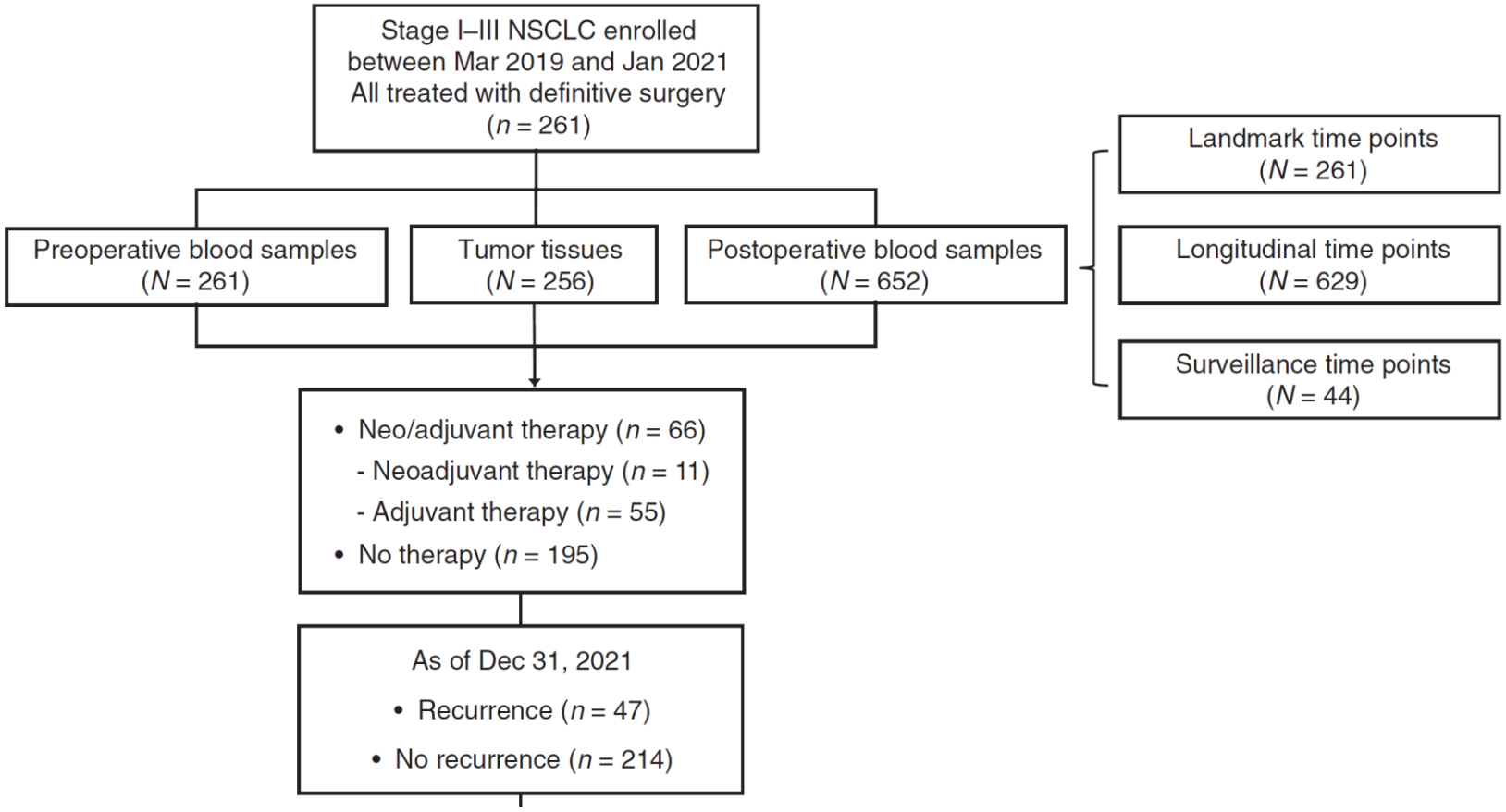
cSMART



CAPP-seq

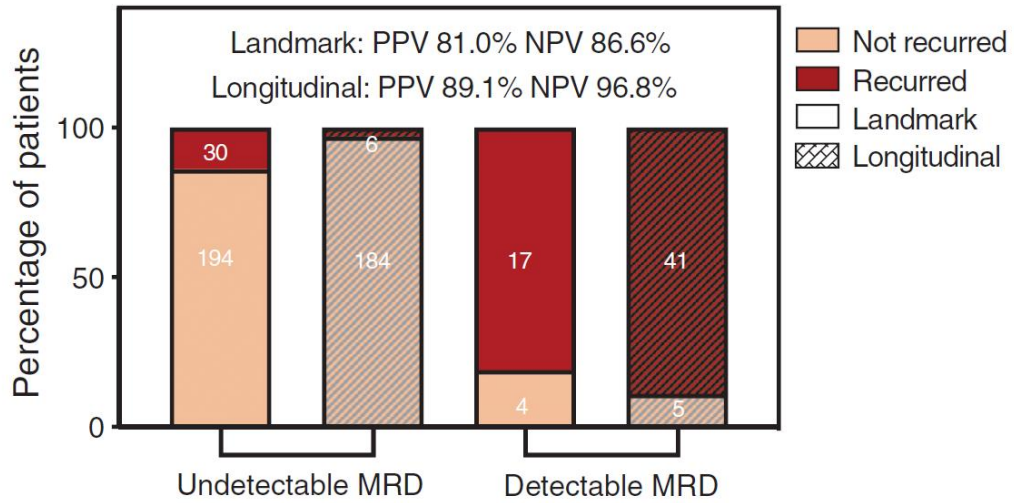


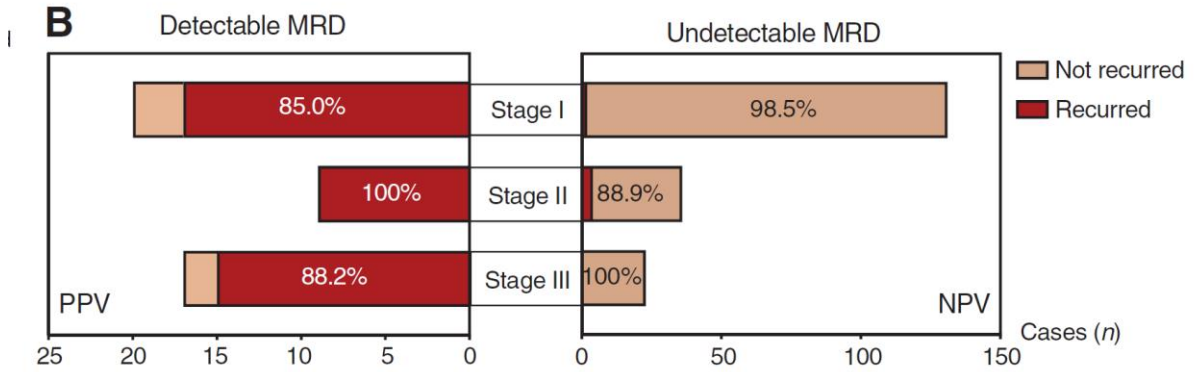
Retrospective cohort from China



Zhang et al Cancer Discovery 2022

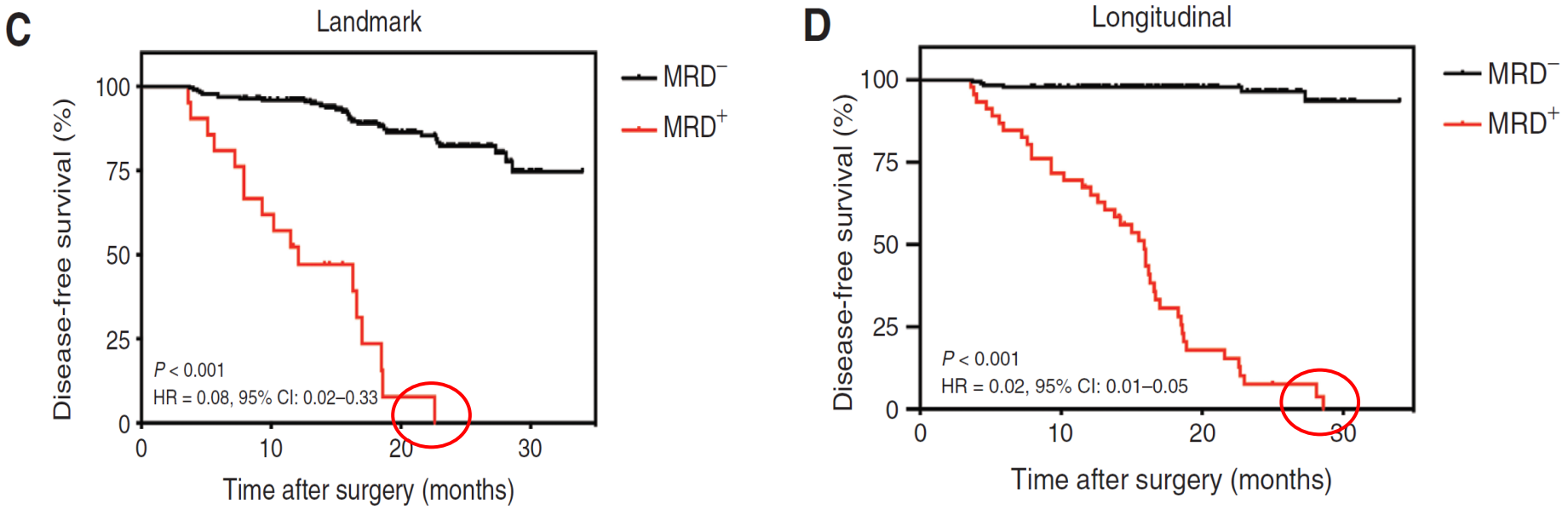
Both landmark and longitudinal MRD is predictive of recurrence





Zhang et al Cancer Discovery 2022

Both landmark and longitudinal MRD is predictive of recurrence

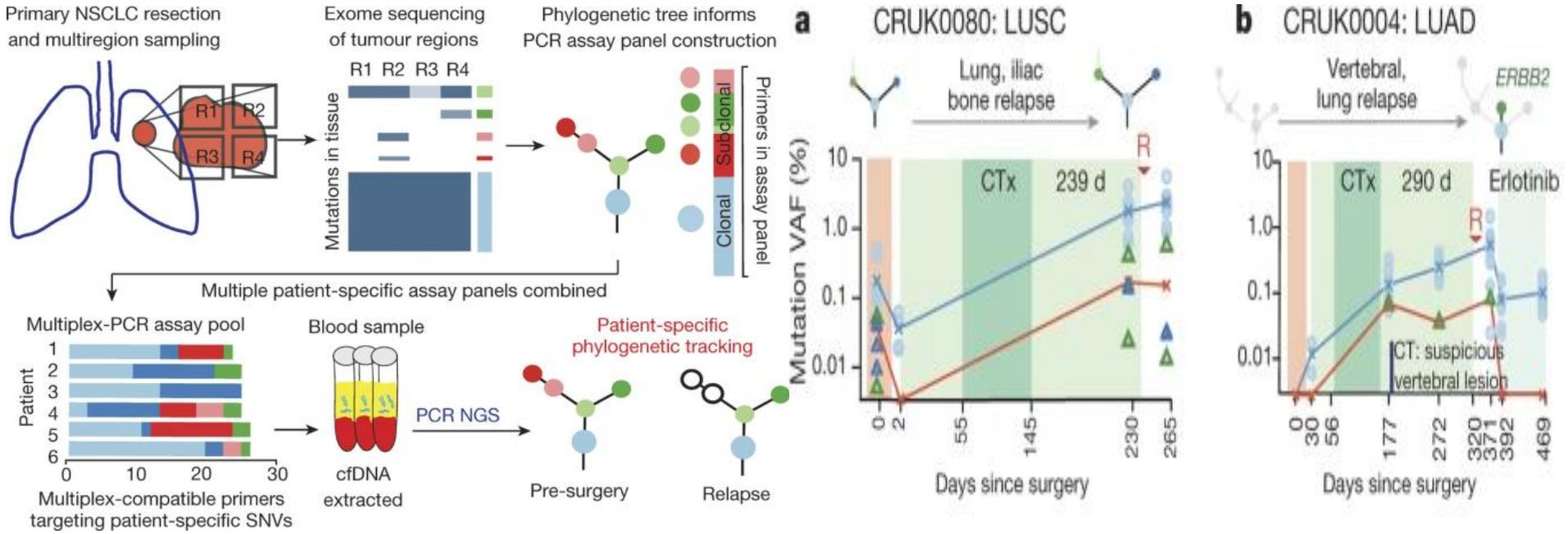


Zhang et al Cancer Discovery 2022

TRACERx

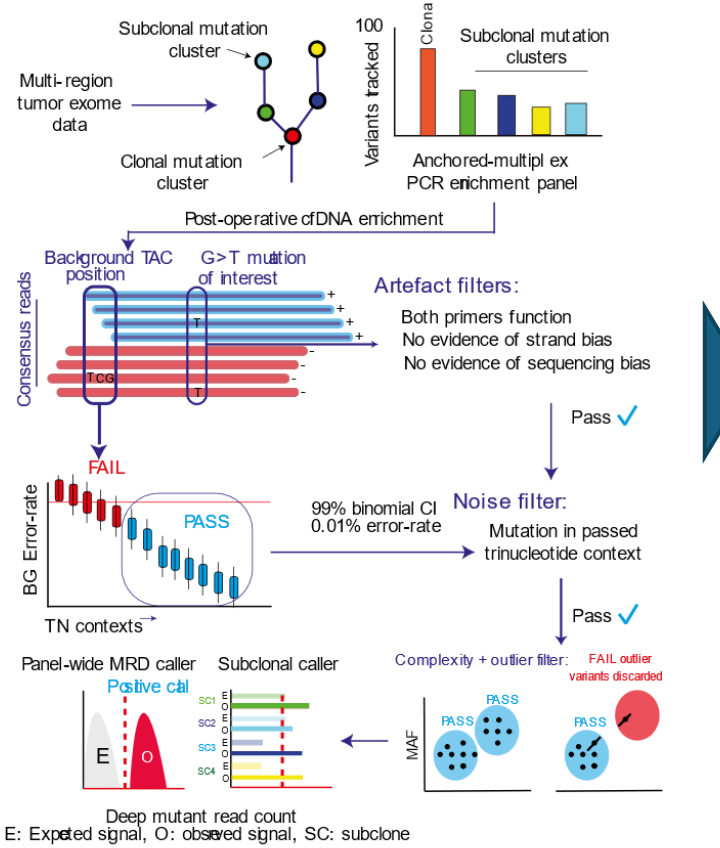
2017: Tumor-informed personalized ctDNA detection identified disease relapse before routine clinical surveillance and detected subclones present at relapse:

~100 postoperative plasma samples analysed from 24 patients



Abbosh et al., Nature 2017 –"Prototype" Assay became Signatera

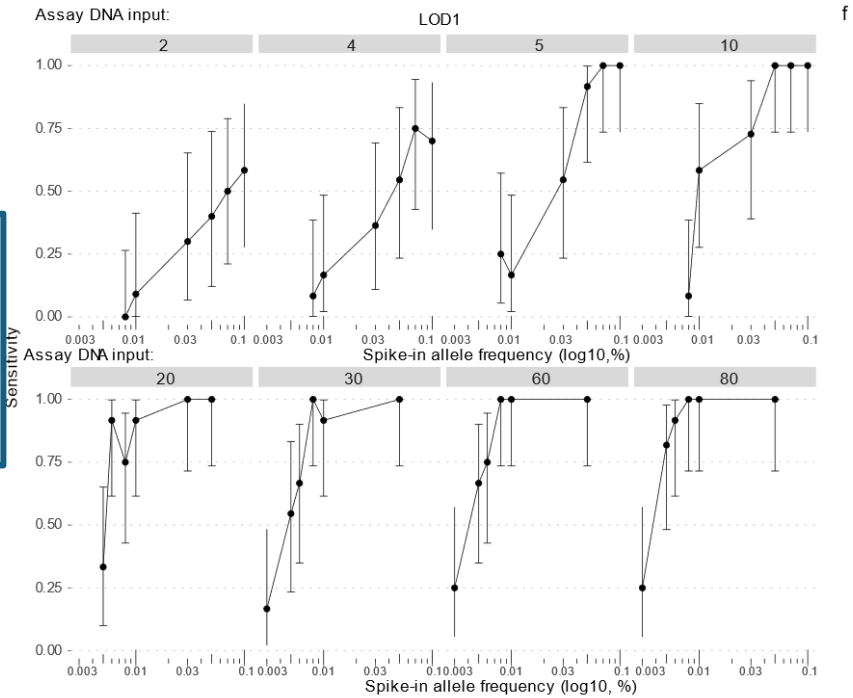
2023: Development of an Anchored-Multiplex PCR approach targeting up to 200 mutations; Sensitive and specific detection of ctDNA at AFs of 80ppm



Dr Chris Abbosh

Locked version of the ctDNA detection algorithm analyzed in n=659 spike-in samples

SENSITIVITY (50-variant panel)

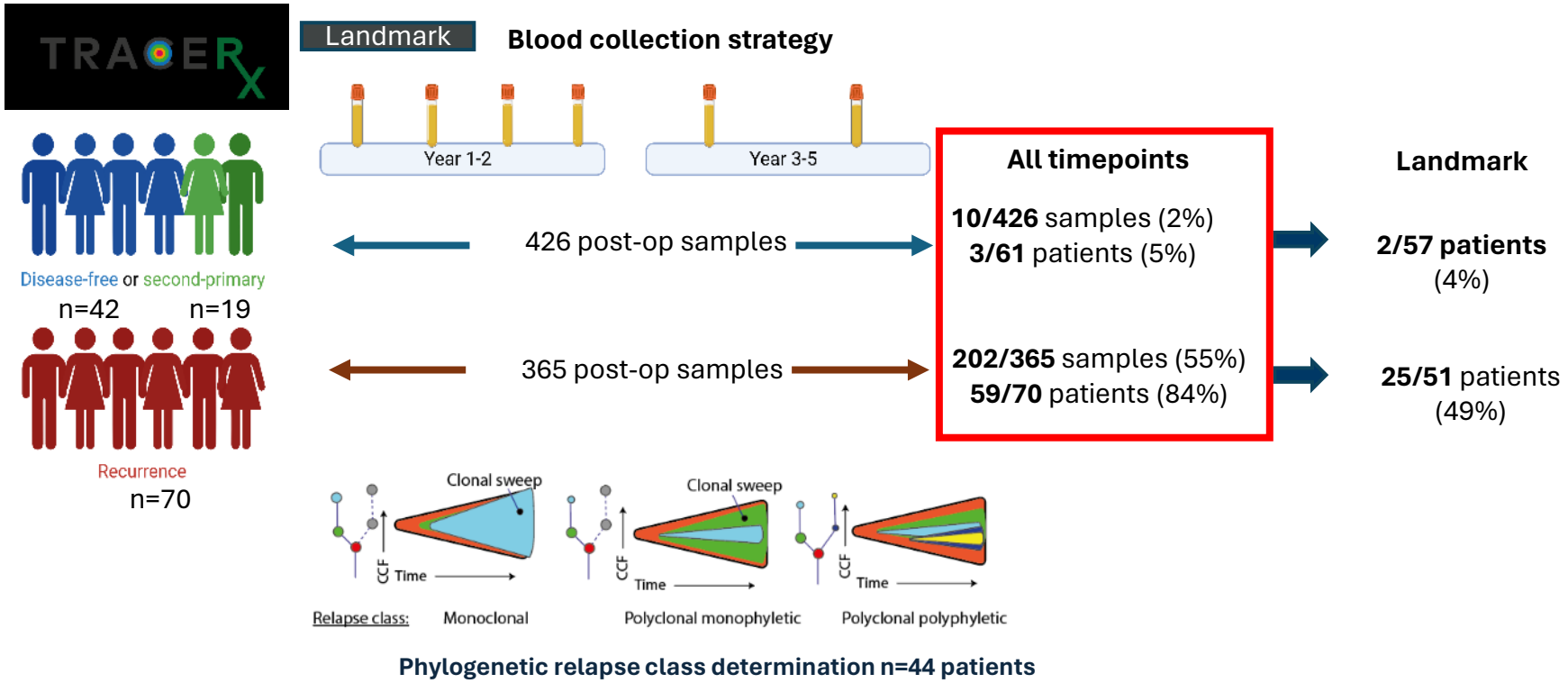


SPECIFICITY

- 100% (95% CI: 93 to 100%, n=48 negative controls, 50-var panel)
- 99.3% in simulation (n=3157 simulated negatives with 200-var panel)

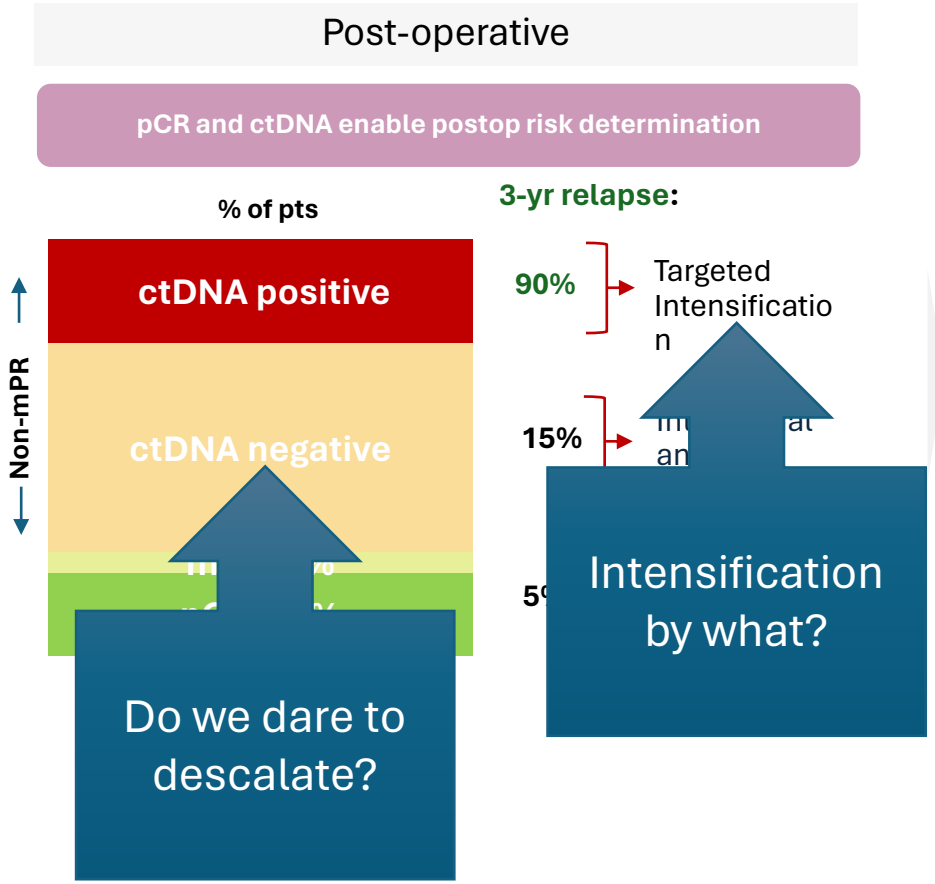
Abbosh et al., Nature 2023 –"Prototype" Assay became PCM

2023: High incidence of MRD positive in the recurrent population from 791 Postoperative plasma samples (from 131 patients)



Abbosh et al., Nature 2023

Suggested by authors: will be risk-stratified based on a combination of ctDNA status and pCR status:



Consequences:

Unmet need highest in ctDNA+ patients; rationale for treatment intensification, enables MRD driven adjuvant studies.

Limit use of long adjuvant regimens in ctDNA negative.

Treatment of ctDNA negative patients declines.

Chris Abbosh

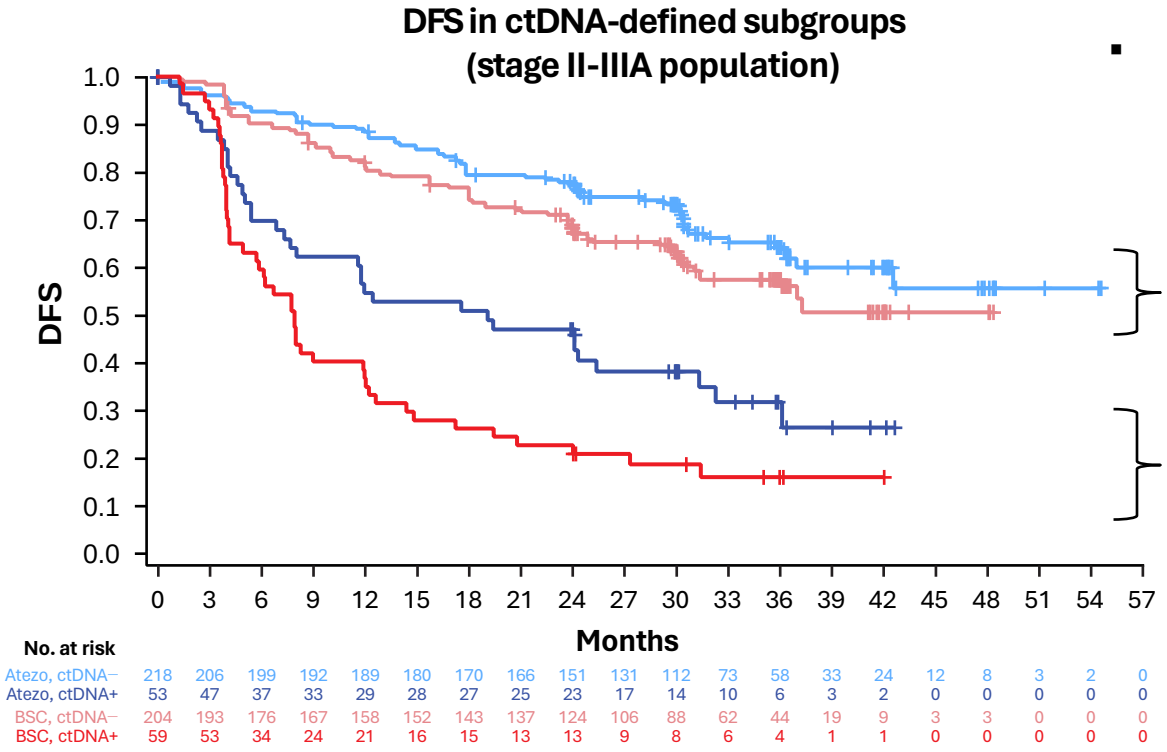
ctDNA from IMpower 010

- 600 patients in the ITT population (60%) were ctDNA evaluable, 534 of whom had stage II-IIIA NSCLC
- Treatment arms were balanced in the ctDNA-evaluable population (ctDNA+ and ctDNA– patients) and comparable to the ITT population (data not shown)

Characteristic		ctDNA+ patients, % (n/N)
Disease stage	II-IIIA	**21%** (112/534)
	IB-IIIA	**20%** (118/600)
	IB	**9%** (6/66)
	II	**14%** (37/273)
	IIIA	**29%** (75/261)
Nodal status	N0	**7%** (14/193)
	N1	**20%** (43/218)
	N2	**32%** (61/189)
Smoking history	Never	**20%** (25/123)
	Current/previous	**19%** (93/477)
Sex	Male	**21%** (86/412)
	Female	**17%** (32/188)
ECOG PS	0	**19%** (69/356)
	1	**20%** (48/243)
***EGFR* mutation**	Detected	**30%** (23/76)
	Not detected	**16%** (54/337)
	Unknown	**22%** (41/187)
Region	Asia-Pacific	**17%** (24/143)
	Europe and Middle East	**22%** (85/382)
	North America	**12%** (9/73)

Zhou et al ESMO IO 2021

ctDNA positivity was strongly prognostic



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

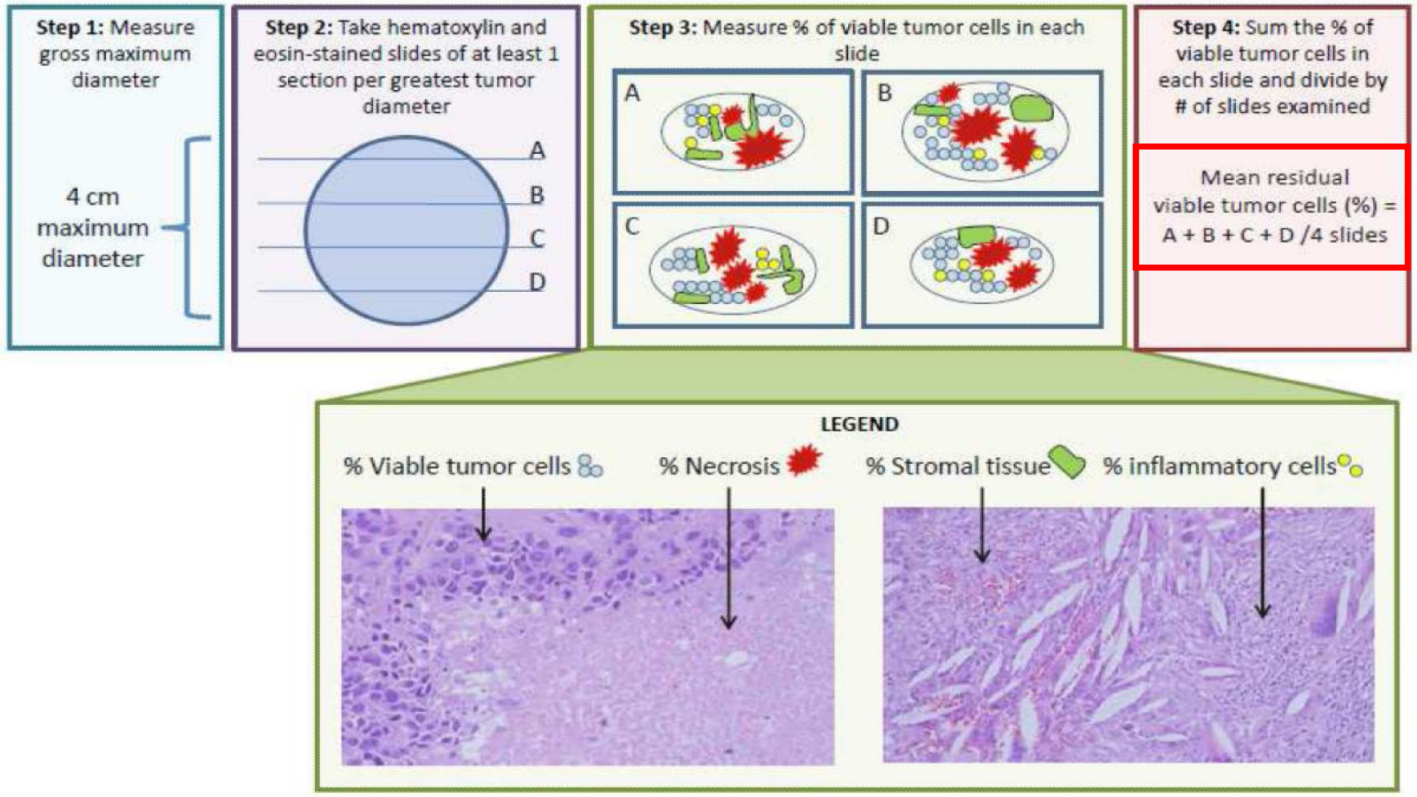
ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Clinical cutoff: 21 January 2021. Unstratified HRs are shown.

Factors that may contribute to the decision for adjuvant therapy?

- Pathologic response
  - CPR
  - MPR
  - Less than MPR
- MRD
  - Presence
  - Absence

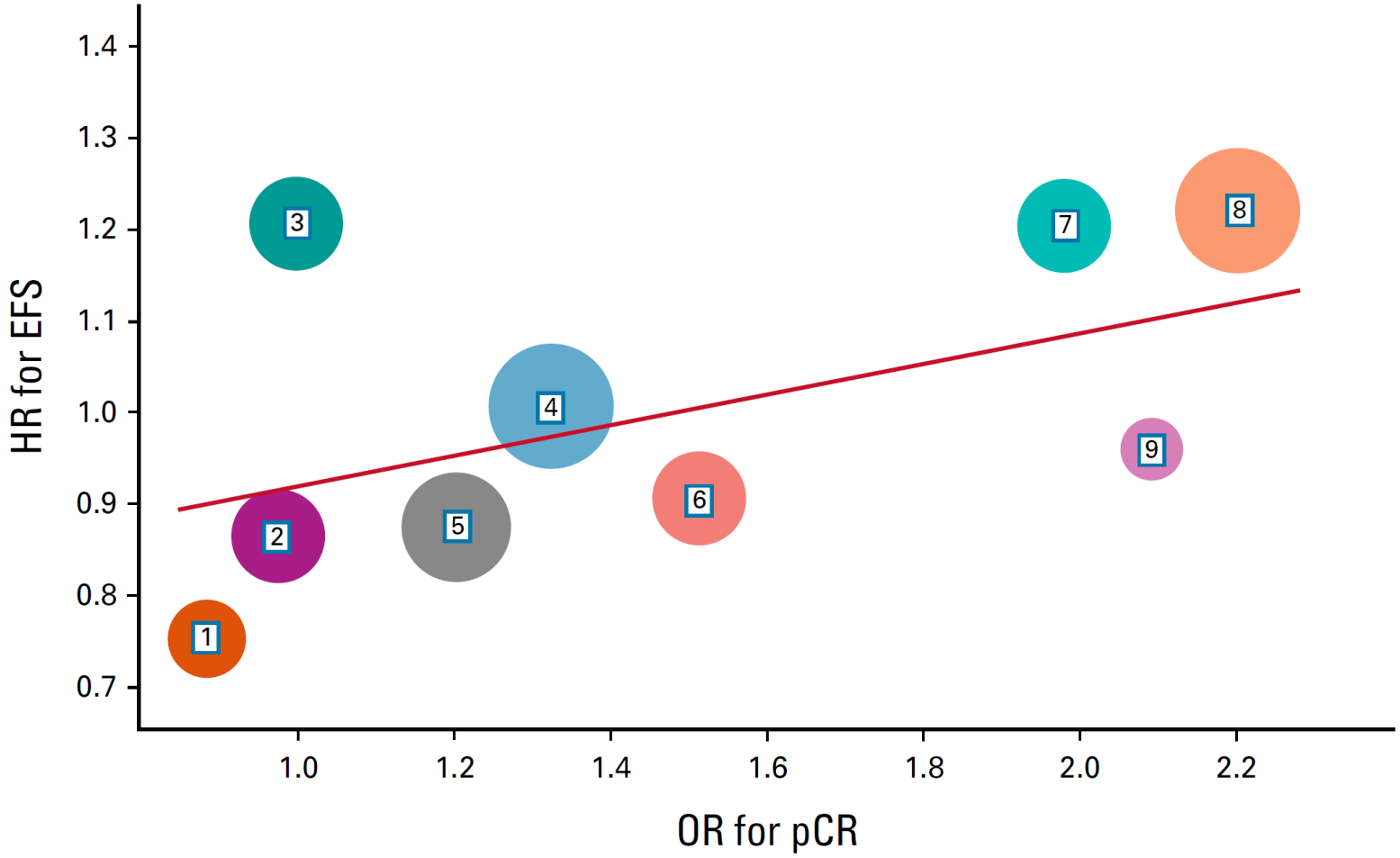
MPR and CPR



"Major pathologic response" (MPR), defined as =10% residual tumor following neoadjuvant therapy, should be adopted as an outcome measurement in NSCLCs.

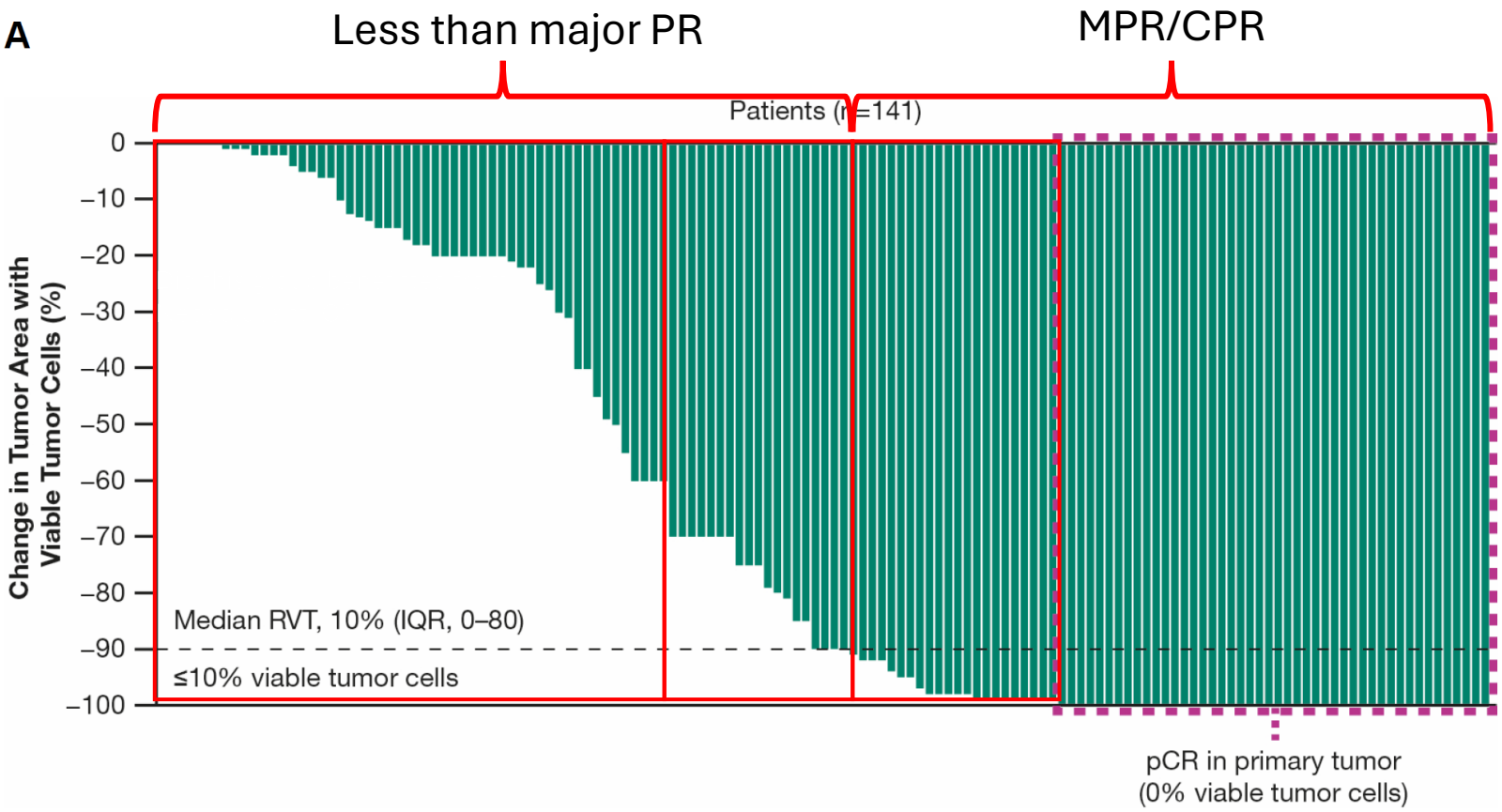
Hellman et al Lancet Oncol 2014

Correlation between pCR and EFS



Chaft et al JCO 2022

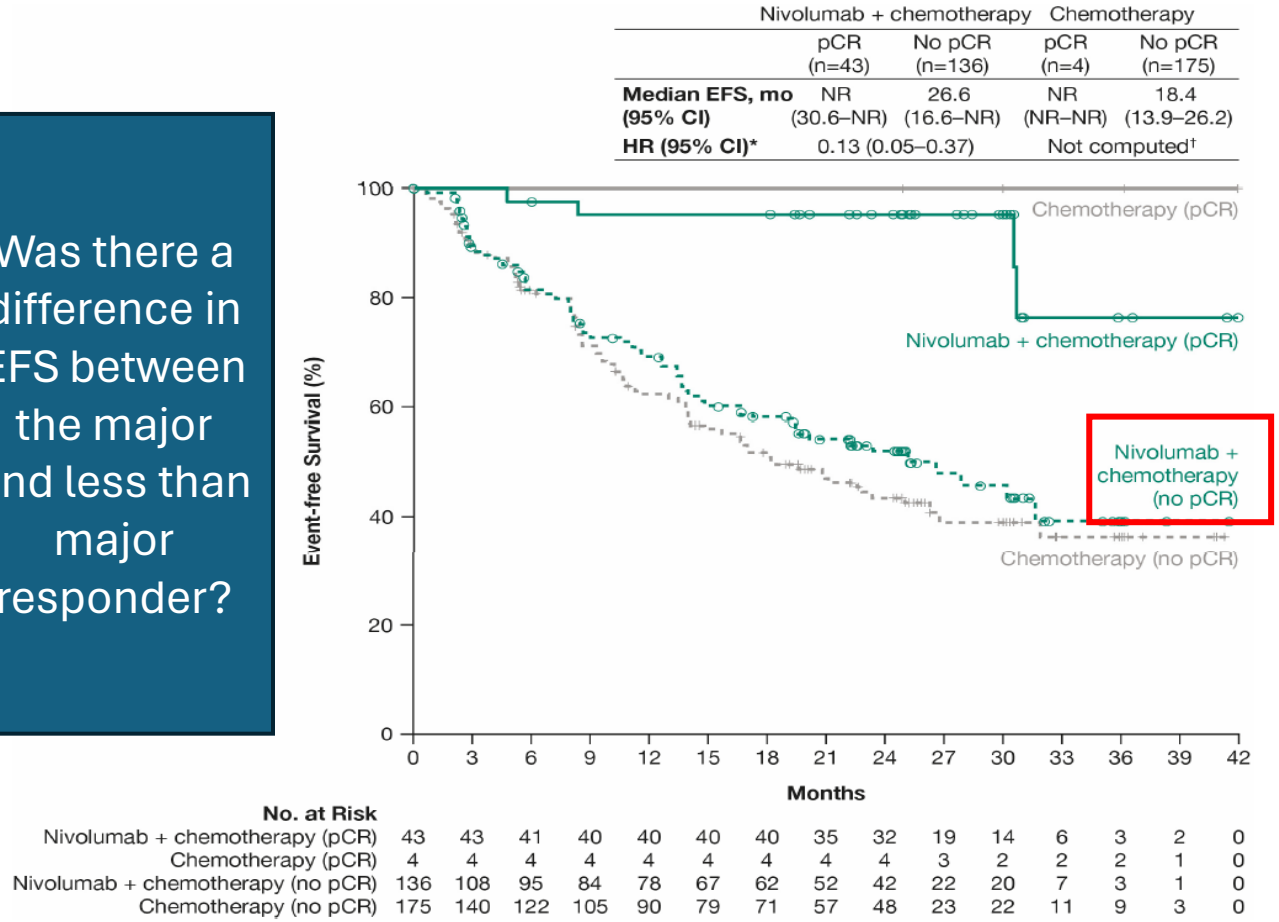
Depth of pathologic response: CM816



Forde et al NEJM 2022 Supplementary data

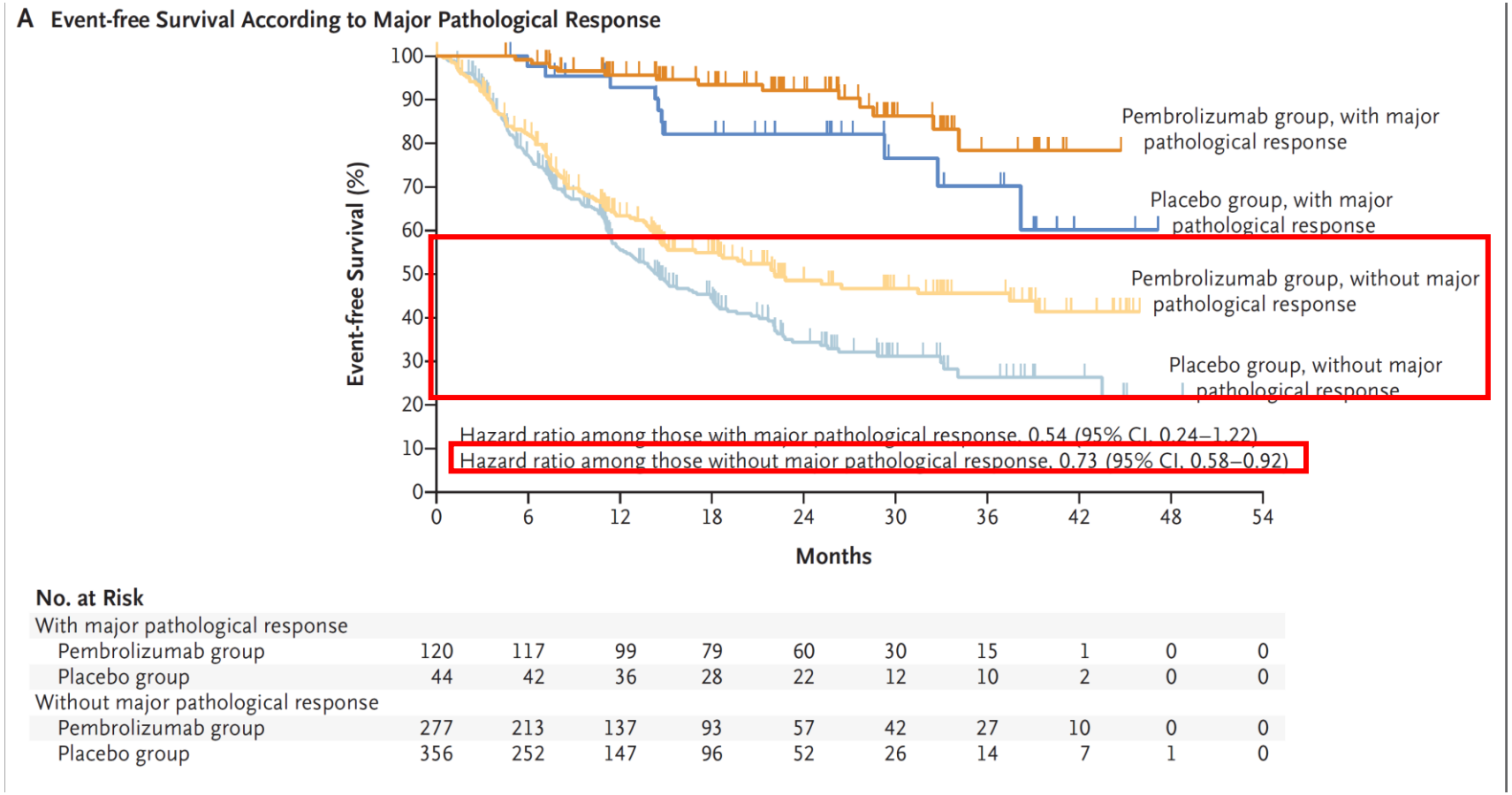
EFS of patients with no CPR from CM816 (Major + Less Than Major pathologic response)

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



Forde et al NEJM 2022

Insights from KN671



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

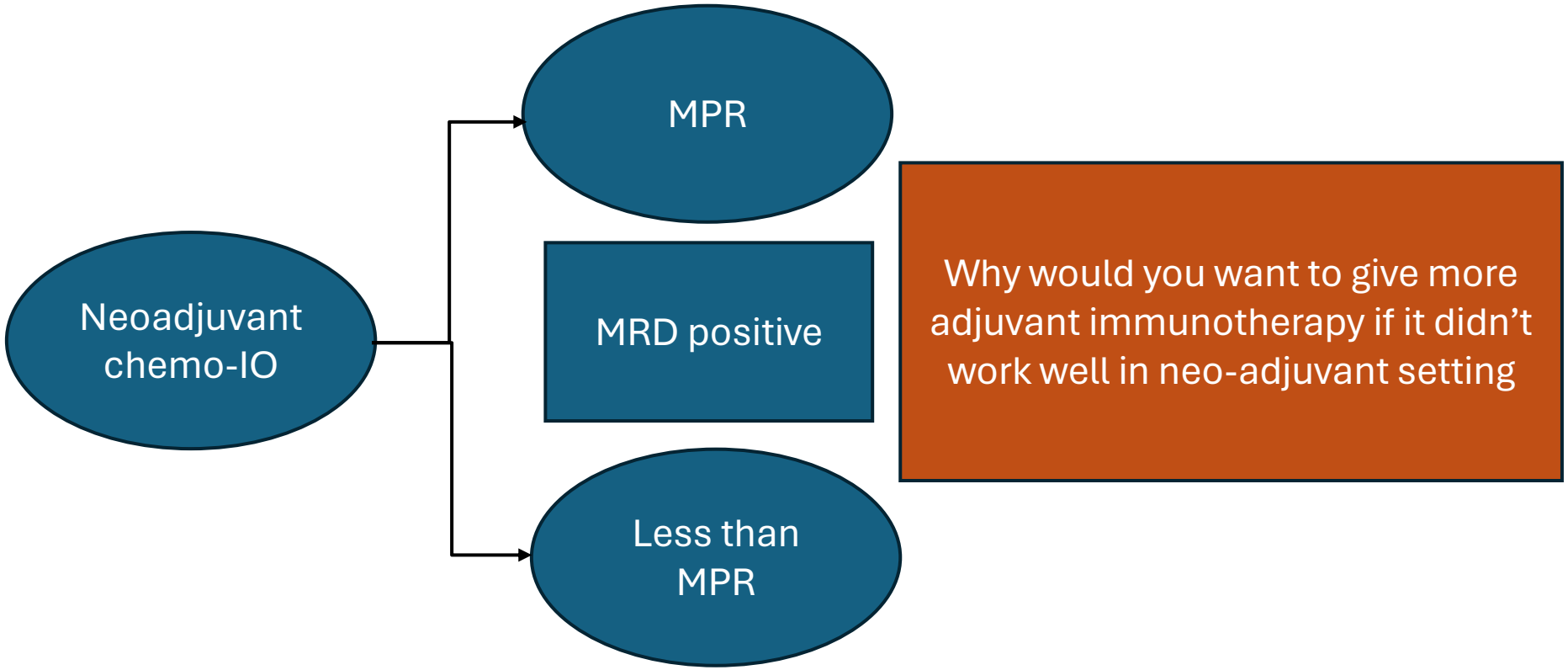
Wakelee et al NEJM 2023

Factors that may contribute to the decision for adjuvant therapy?

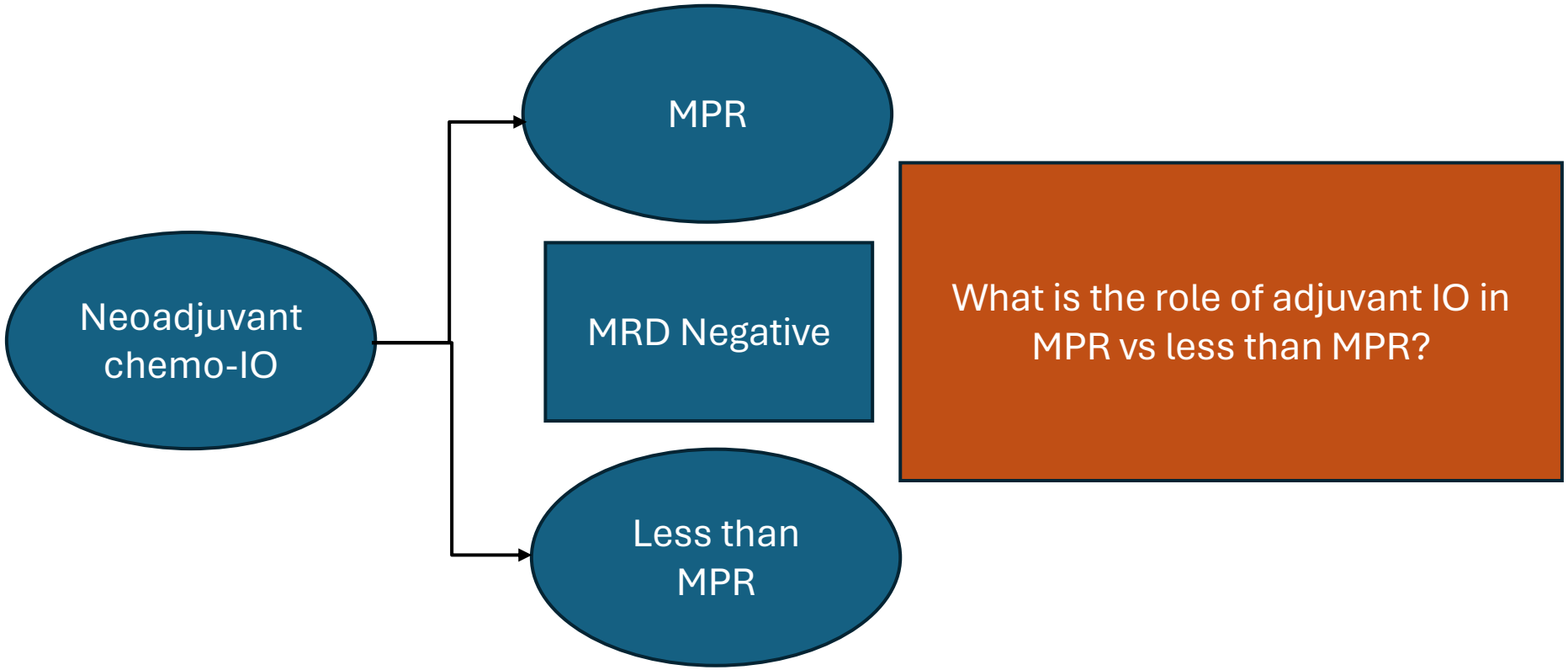
- Pathologic response
  - CPR: With excellent survival outcome from CM816, these patient may not need further adjuvant IO
  - MPR: Unclear if adjuvant IO provide additional benefit
  - Less than MPR: KN671 suggested improvement of survival with neo-adjuvant IO followed by IO
- MRD
  - Presence
  - Absence

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

More adjuvant IO for MRD positive??



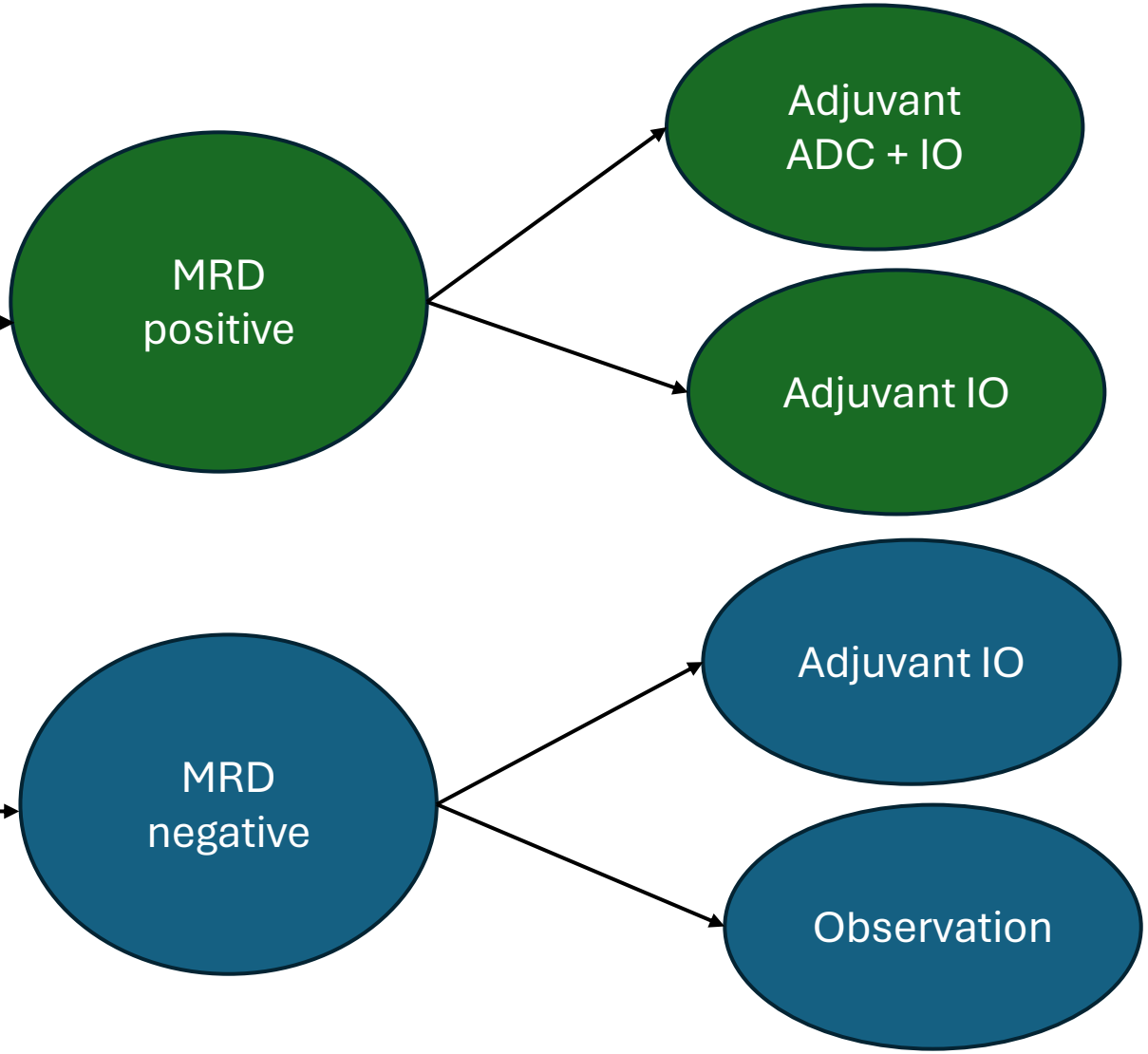
More adjuvant IO for MRD positive??



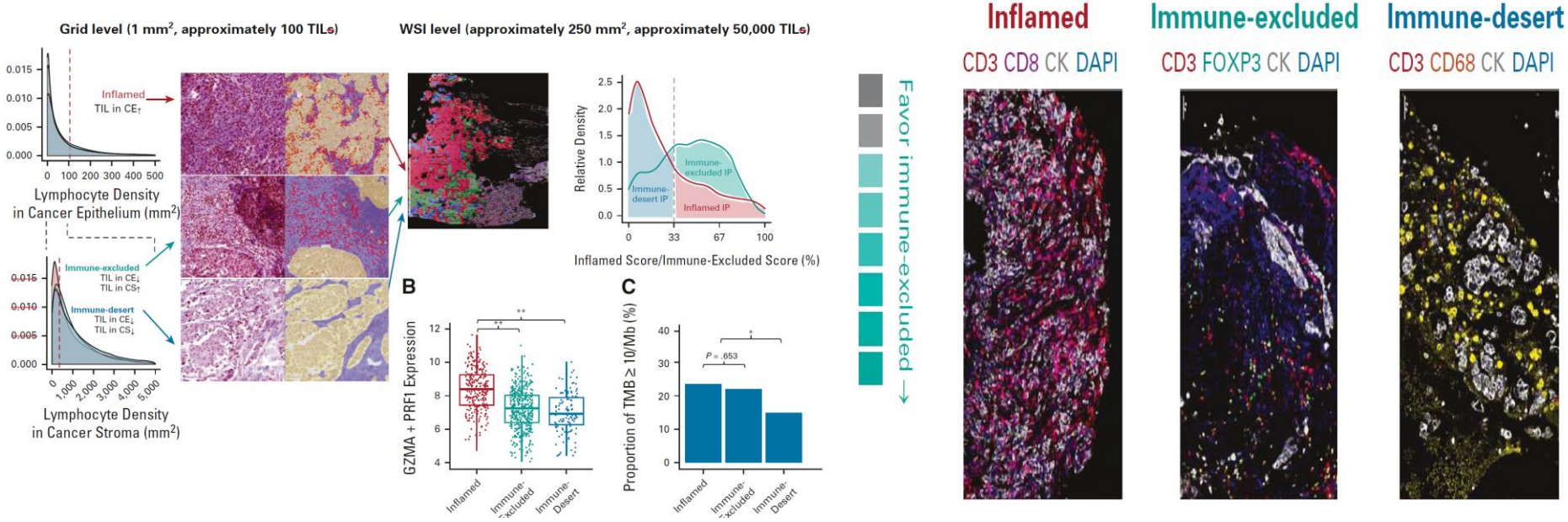
Potential new study

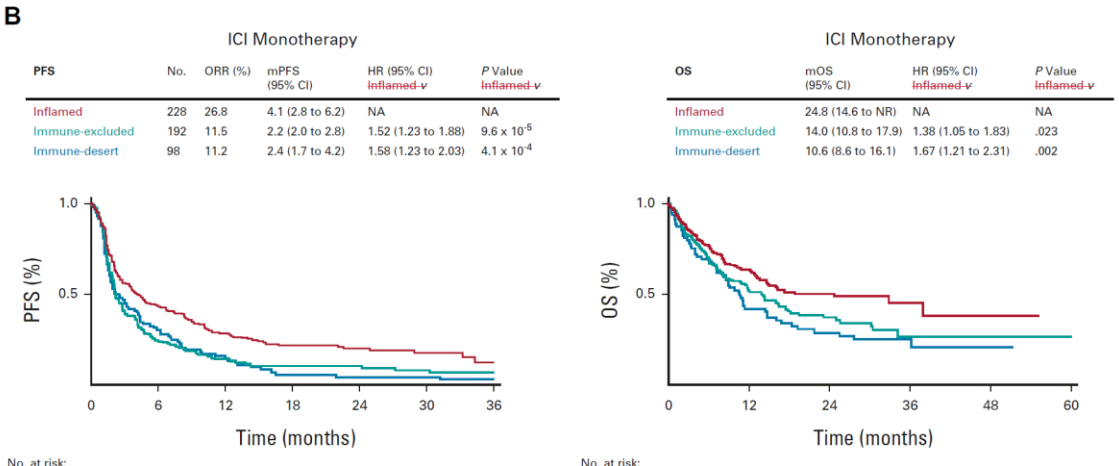
- Stage III (higher chance of MRD positive)
- Completed chemo-IO
- Completed surgery
- MPR/Less than MPR

Stratification:
MRP vs less than MRP
PDL1<1% vs >1%



Potential new biomarker: AI-assisted analysis of tumor infiltrate lymphocyte





Park (Mok) et al JCO 2022

Summary

- Biomarker
  - Adjuvant IO: PDL1>50% benefit the most, and no benefit with PDL1<1%. Debatable for PDL11-49%
  - Neoadjuvant chemo-IO: Lesser benefit with PDL1<1%
  - TMB is unlikely to be helpful but pending on further analysis.
- MRD
  - Diverse technology and shouldn’t be view as a single entity
  - MRD positive is a strong poor prognostic factor
  - Key factors that may impact on selection of patient for adjuvant IO
    - Pathologic response :CPR, MPR, Less than MPR
    - MRD: Positive vs negative
  - Excellent survival outcome in CPR group from CM816 (no adjuvant therapy)
  - Need future study to define the role of MRD in patients with MPR/less than MPR

What really matter: Afternoon tea

Faculty for ESMO course on
EGFR mutation, Jan 2024

蘭芳園
LAN FONG YUEN

Nearest location at Nathan Road