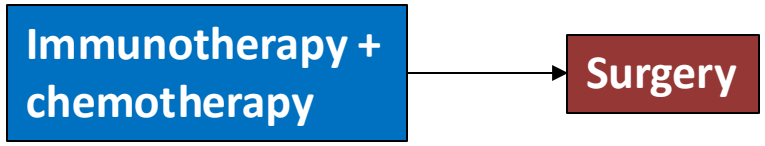
Peri-operative Therapy of Early-Stage Lung Cancer:
"Contribution of Components"

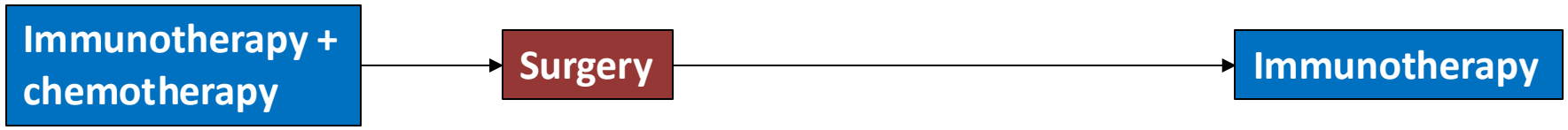
David R. Gandara, MD
University of California Davis Comprehensive Cancer Center
CMO, International Society Liquid Biopsy

Approaches incorporating Immunotherapy in Resectable NSCLC: Overview & Key Phase III Trials

Neoadjuvant
CheckMate 816



Perioperative
AEGEAN
KEYNOTE-671
CheckMate 77T



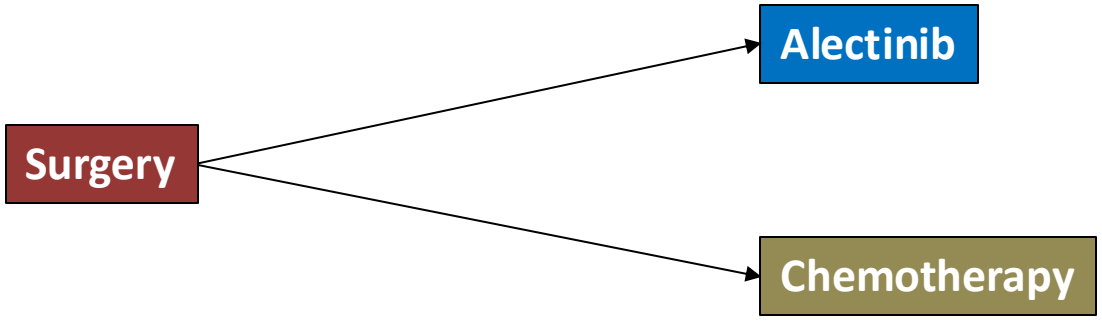
Adjuvant
IMpower010
KEYNOTE-091

[a]IMpower010: all patients;
KEYNOTE-091: recommended

Approaches With Targeted Therapies in Resectable NSCLC: *EGFR* and *ALK*

EGFR-mutated
ADAURA

ALK+
ALINA

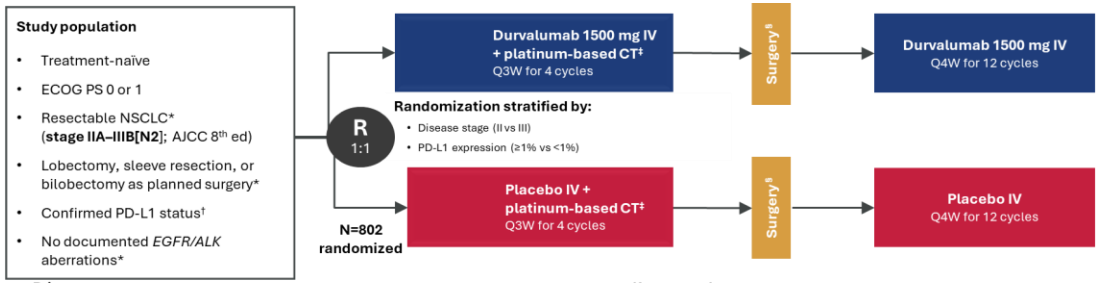


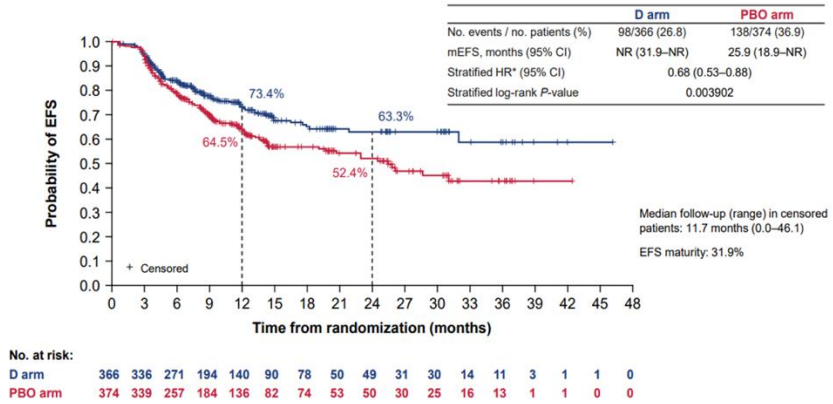
Key Phase III Trials in Early-Stage NSCLC: Neoadj only vs Adj Only vs Periop (Both)

	Perioperative				Neoadjuvant Only	Adjuvant Only	
Treatment Sequence					Neoadj ChemoIO x 3 cycles Surgery	Surgery Adj Chemo Adj IO	
Selected Trials	KN671	AEGEAN	NEOTORCH	CM 77T	CM816	Impower 010	KN091
Regulatory Decision	FDA Approval: neoadj pembro+ chemo→ pembro adj (≥4 cm or node +)				FDA Approval Nivo + Chemo:IB-IIIA (v7) and PD-L1	FDA Approval: Atezo: II-IIIA(v7) PD-L1 ≥1%	FDA Approval Pembro: Ib-IIIA (v7), any PD-L1
Neoadj Cycles	4	4	3	4	3	-	
Surgery proportion	82%	81%	82%	78%	83%	100%	
Receiving IO after Surgery	-	-	-	-	-	~ 84%	-
pCR	18%	17%	25%	25%	24%	-	
EFS/PFS/DFS HR	0.58	0.68	0.40	0.58	0.68	0.66 (PD-L1≥ 1% Stage II-IIIA)	0.76
OS HR (Interim)	0.72	-	0.62	-	0.62	0.71 (PD-L1≥ 1% Stage II-IIIA)	0.87

"Contribution of Components" - A Renewed Mandate from FDA

ODAC review of AEGEAN –A Perioperative Phase III Trial in Early-Stage NSCLC



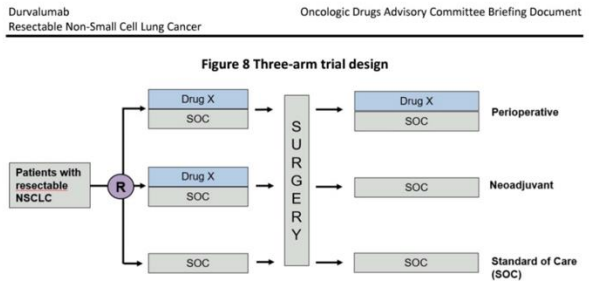


Heymach. *N Engl J Med.* 2023.

7. Draft Topics for Discussion by the Advisory Committee

- In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.
- Should FDA require that new trial design proposals for perioperative regimens include adequate within trial assessment of contribution of treatment phase?

In an 11 to 0 vote, the FDA's Oncologic Drugs Advisory Committee (ODAC) agreed that the FDA should mandate that new trial design proposals for perioperative regimens for resectable non–small cell lung cancer (NSCLC) include an adequate trial assessment of the contribution of each treatment phase.[1]

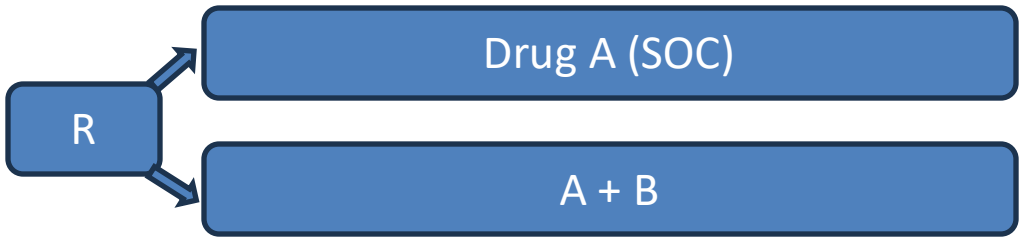


The incorporation of a new therapy into the neoadjuvant phase only rather than incorporation into the adjuvant phase only as the third arm in a 3-arm trial may be preferable because: (1) there may be stronger biologic rationale for antitumor activity in an intact tumor environment, (2) there are concerns for increased toxicities with longer duration adjuvant therapy relative to neoadjuvant therapy, and (3) some patients may achieve cure with neoadjuvant therapy and surgery alone. Thus, inclusion of an arm incorporating a new therapy in the neoadjuvant phase only may be the most reasonable choice to provide within trial information on the contribution of adjuvant treatment while preserving the ability to statistically test a potentially safe and effective addition of a new drug to only the neoadjuvant phase of therapy.

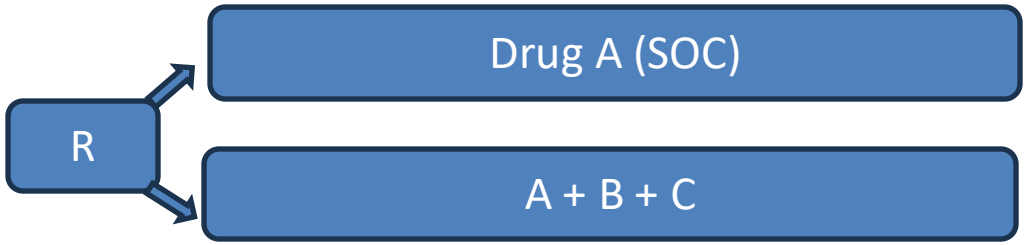
Contribution of Components in Drug & Regimen Development

Determination of the contribution of each component of a regimen to benefit observed

Contribution of Drug B is clear



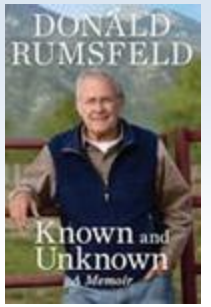
Contribution of B vs C vs B+C is unclear



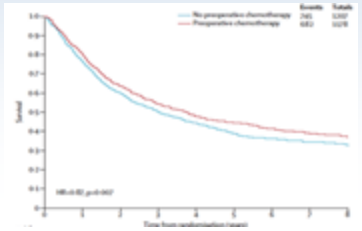
Assumptions

- **Drug A is FDA-approved & SOC**
- **Drugs B & C are investigational & not previously combined**

Early-Stage Immunotherapy Trials
What do we know that we know?



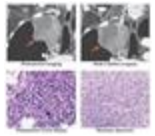
- **Known-Knowns:**
  - "Curative Intent" is the goal of therapy. Any approach that compromises this goal is unacceptable.
  - A variable proportion of Early-Stage NSCLC is cured with surgery alone. (Note impact of Stage migration ($7^{th} \rightarrow 8^{th}$)
  - Pre-op (Neo-Adjuvant) or Post-op Chemo (Adjuvant) improves OS (the cure rate) over surgery alone



Meta-Analysis of Neo- & Adjuvant Chemotherapy

	N	HR	P value
Neoadjuvant Trials	2385	0.87 (95% CI 0.78-0.96)	.007
Adjuvant Trials	8447	0.86 (95% CI 0.81-0.92)	<.0001

  - Pre-op checkpoint immunotherapy (CPI) alone is active but insufficient by itself. Combinations of ICI + Platinum-based chemo <u>can</u> improve EFS (& OS)



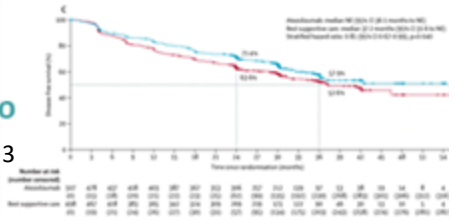
Major path response (mPR (Forde. NEJM 2018)

CM816
Nivo+Chemo→Surg

Forde et al., *NEJM*, 2022

  - Post-op chemo→CPI <u>can</u> also improve EFS (& OS)

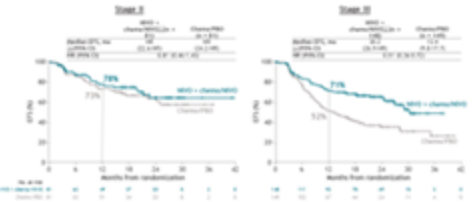
IMPOWER 010
Surg→ chemo→Atezo



Felip, Wakelee et al., *Lancet*, 2023

  - The impact of these therapies is greatest in Stage III NSCLC and least in Stage IB (or Stage II)
  - PD-L1 matters –Results better in PD-L1 positive

CM816
Nivo+Chemo→Surg
Stage II vs III

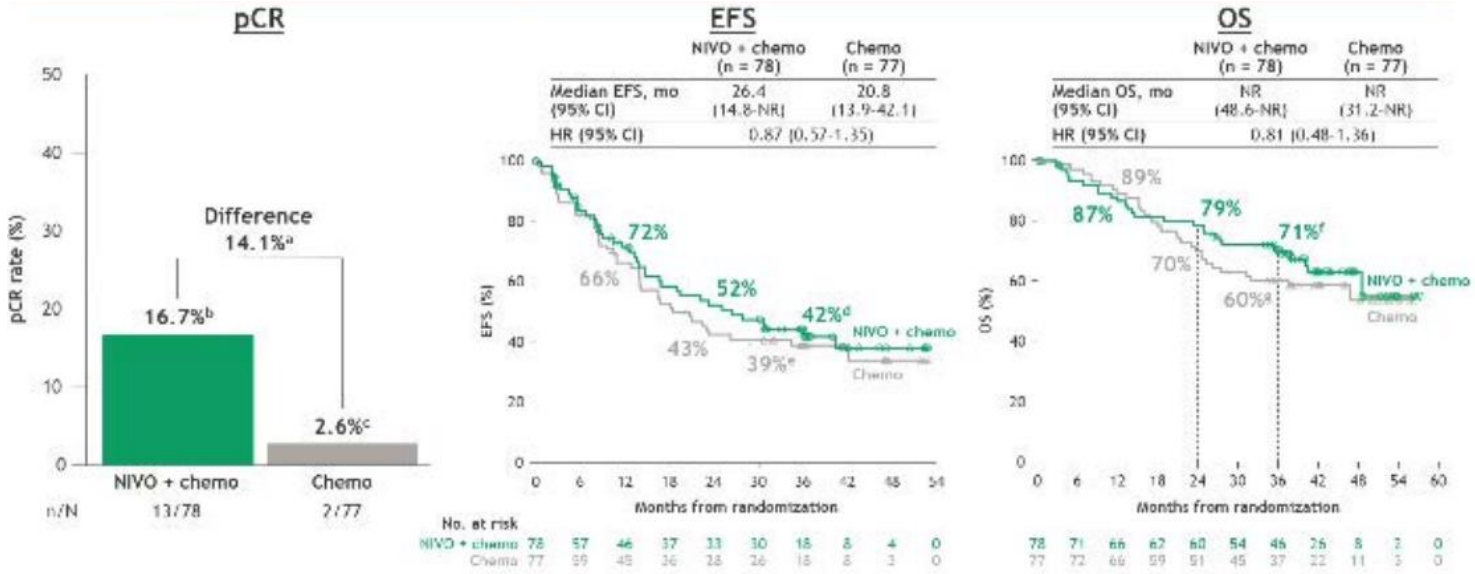


Forde et al., *NEJM*, 2022

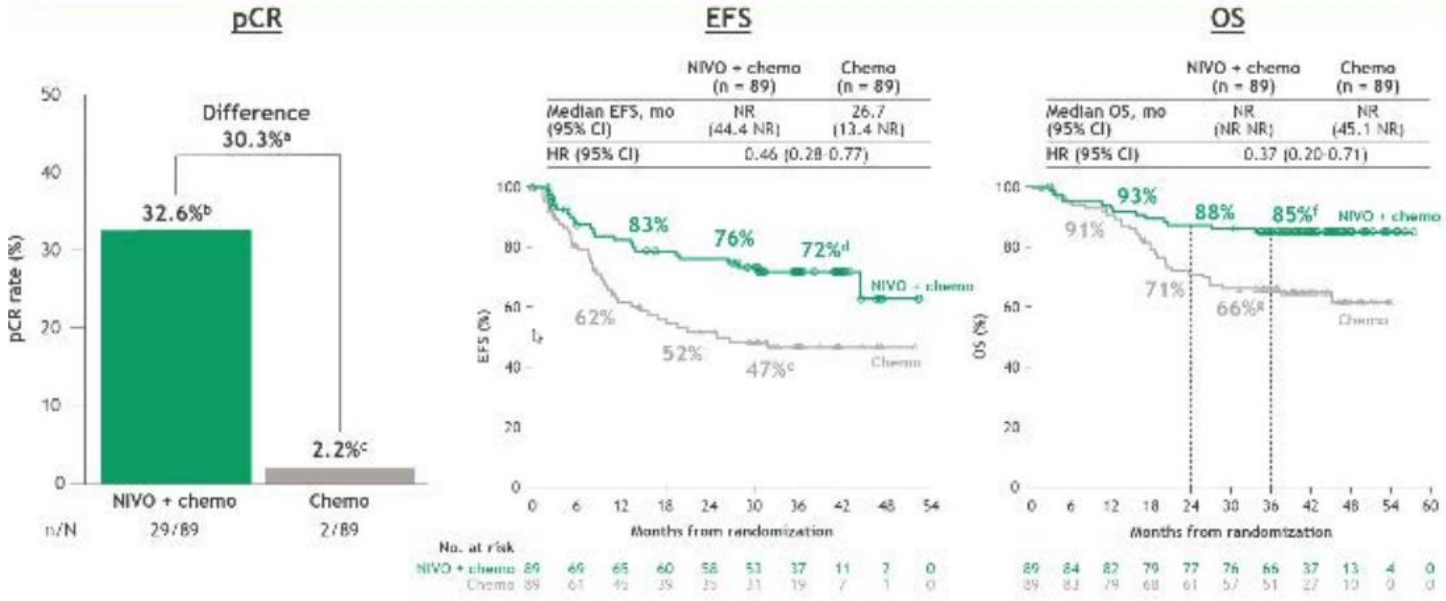
Gandara: ANCO CCU 2023

CheckMate 816: impact of PD-L1 expression

PD-L1<1%

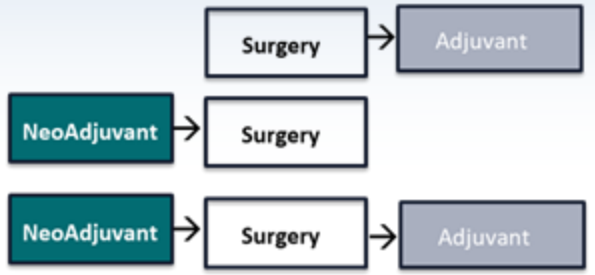


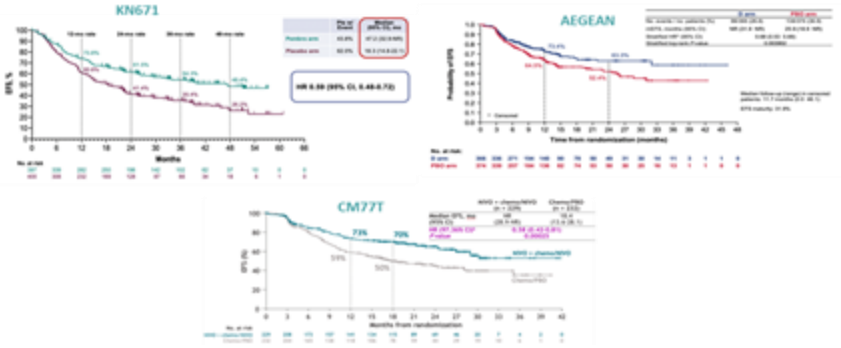
PD-L1≥1%



What we know that we don't yet know?

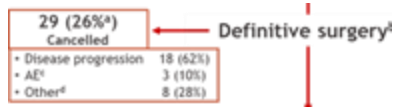
- **Known-Unknowns:**
  - Is Pre-op chemo-CPI superior to Post-op only?
    - Use caution in directly comparing trials. In some trials, patient populations are very heterogeneous (e.g., CM816)
  - Are Peri-operative approaches (Pre-op + Post-op) superior to Pre-op only or Post-op only?
    - Which patients require additional therapy after pre-op ICI-Chemo? This is the question: requires randomized trials
  - How much therapy is needed?; how much is too much & in whom? Variables: Stage subsets, Treatment regimen, Pneumonectomy rates (CM816: 17% & 21%), Biomarker subsets (e.g., PD-L1 score, KRAS G12C)





Nivo-Ipi arm of CM816

Nivo/Ipi: EFS (HR 0.77) & OS (HR 0.73) not significant
Nivo/Ipi Surgery cancelled: 26%

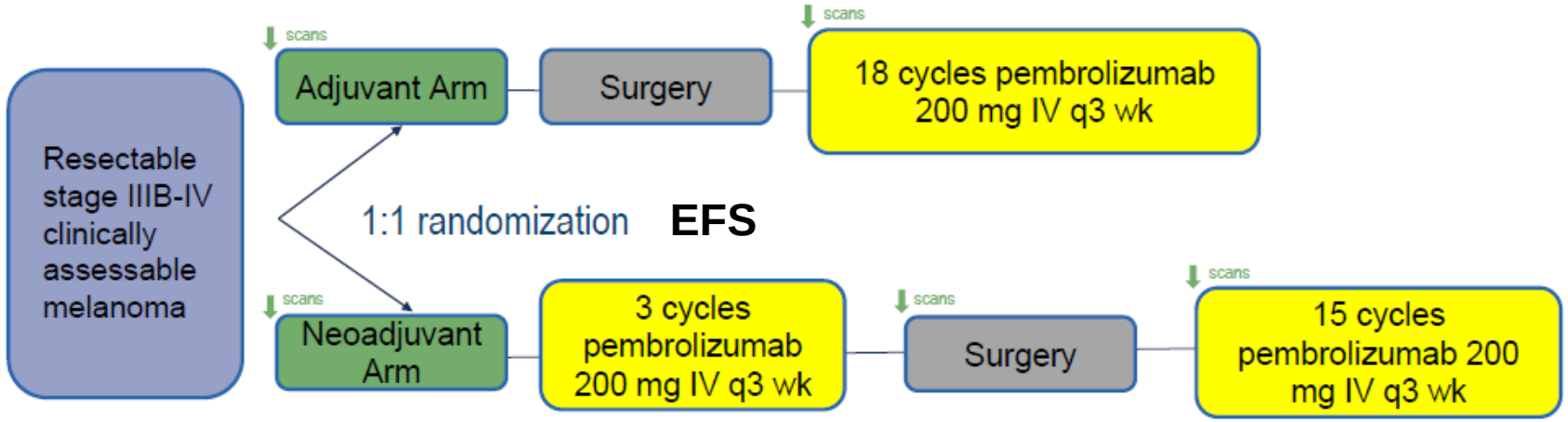


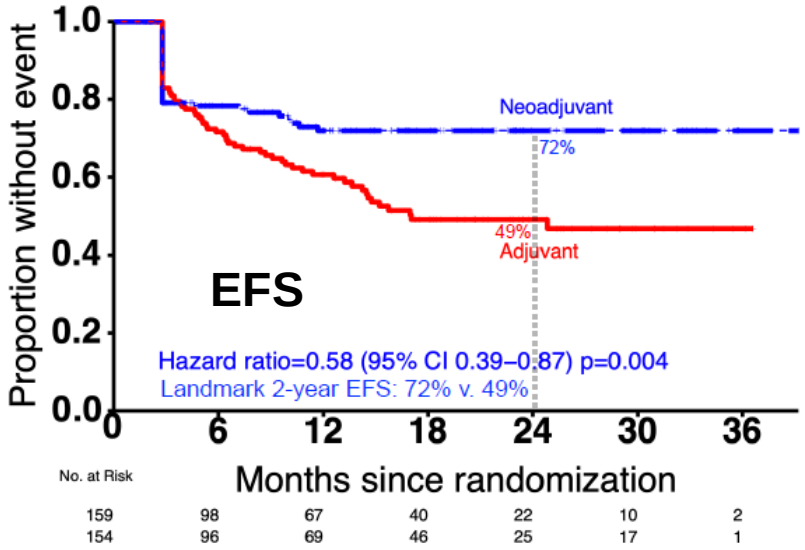
Awad: ESMO23

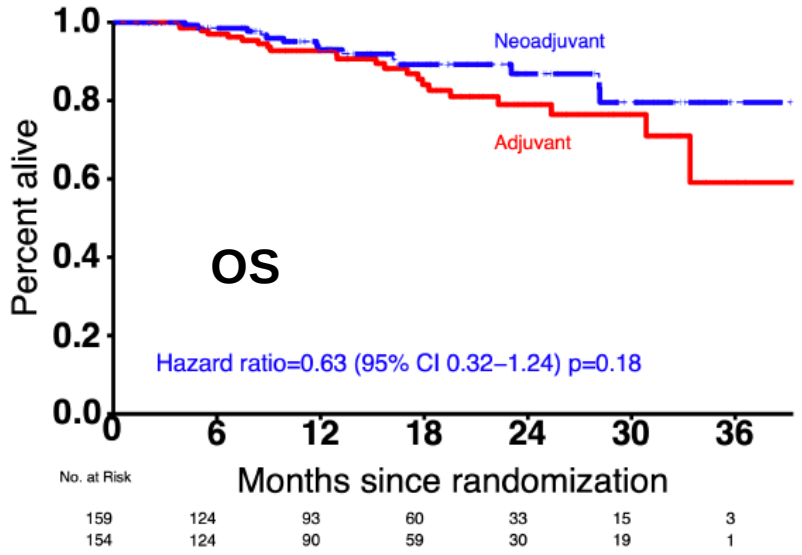
Gandara: ANCO CCU 2023

Neoadjuvant *vs*. Adjuvant Pembrolizumab for resectable stage III-IV Melanoma (SWOG S1801)

Mislabeling of the Neoadjuvant arm
-Actually Perioperative



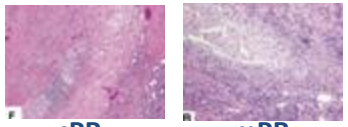




Patel S et al., ESMO 2022 & NEJM 2023

What else do we know that we don't yet know?

- **Known-Unknowns:**
  - What is the role of pathologic response after Pre-op therapy in determining long term outcomes or "cure"? Defining cPR vs mPR?
  - cPR portends a good prognosis after pre-op ICI/Chemo
  - Differentiating cPR from mPR

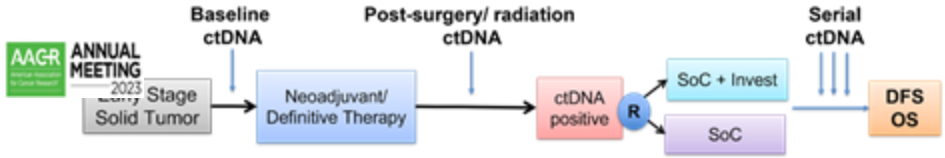


cPR mPR

Guidelines for Path Staging
Travis et al., *JTO*, 2020

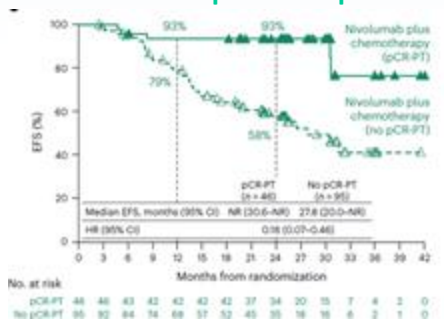
  - What is the role of plasma ctDNA in defining minimal residual disease (MRD) & how does this impact on long term outcomes or "cure"?
    - Are current MRD assays good enough to dictate post-op therapy? Escalation vs De-escalation vs Omission?

Proposed ctDNA trial design by FDA



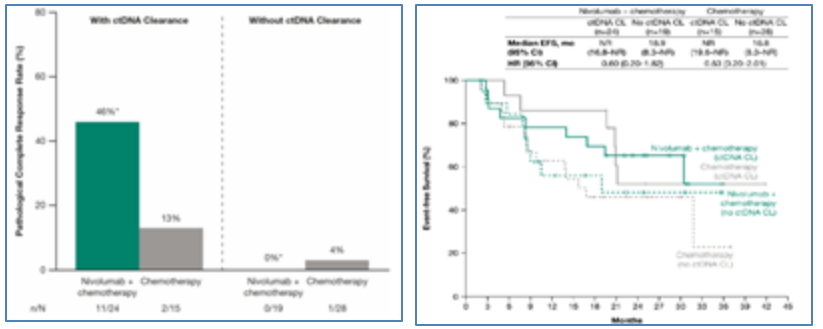
Vellanki: AACR 2023

CM816 –pCR vs no pCR

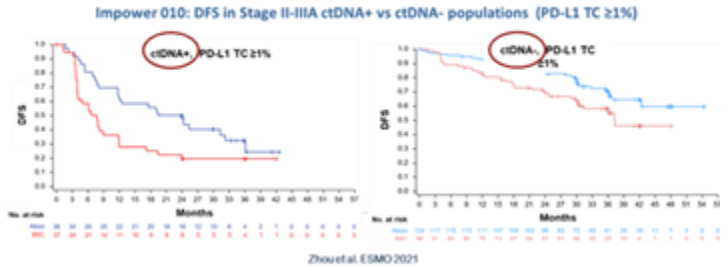


Deutsch et al., *Nat Med*, 2023

CM816 –pCR vs MRD

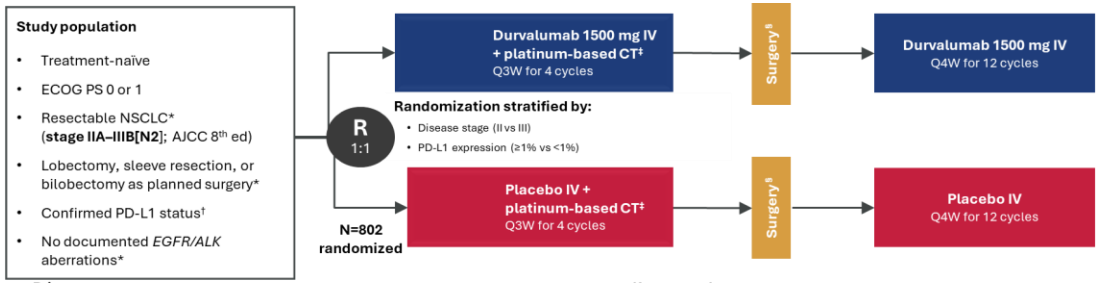


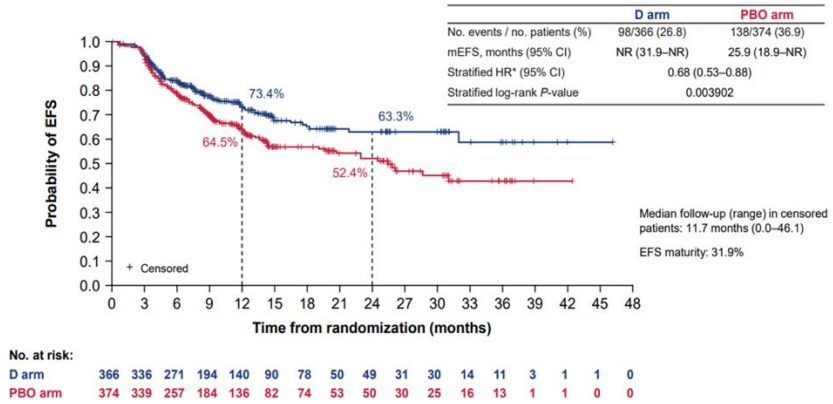
Forde et al., *NEJM*, 2022



"Contribution of Components" - A Renewed Mandate from FDA

ODAC review of AEGEAN –A Perioperative Phase III Trial in Early-Stage NSCLC



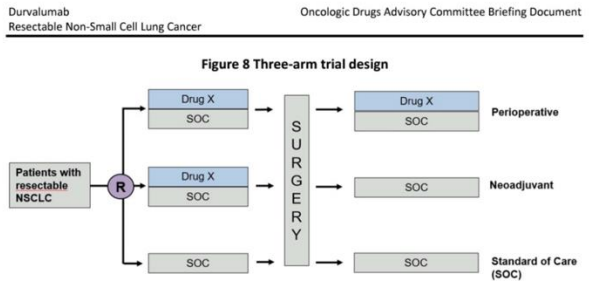


Heymach. *N Engl J Med.* 2023.

7. Draft Topics for Discussion by the Advisory Committee

- In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.
- Should FDA require that new trial design proposals for perioperative regimens include adequate within trial assessment of contribution of treatment phase?

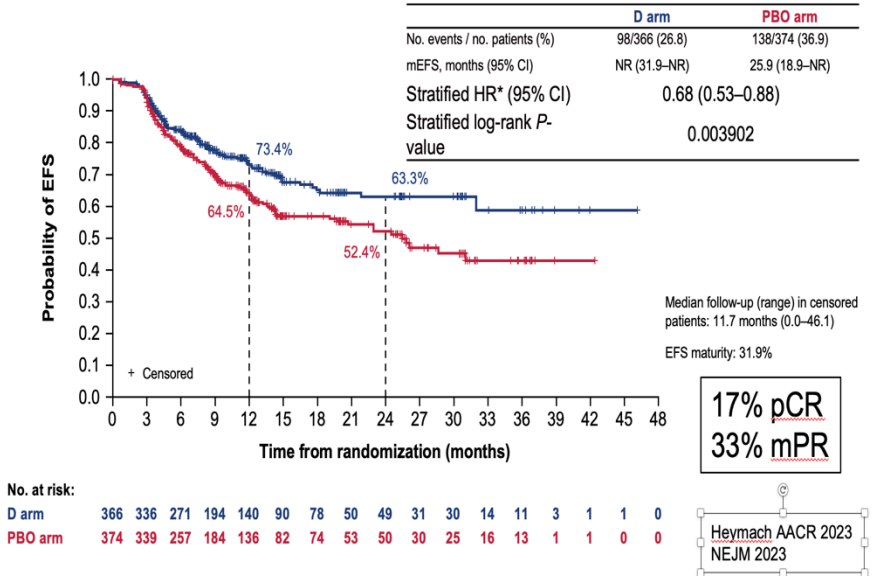
In an 11 to 0 vote, the FDA's Oncologic Drugs Advisory Committee (ODAC) agreed that the FDA should mandate that new trial design proposals for perioperative regimens for resectable non–small cell lung cancer (NSCLC) include an adequate trial assessment of the contribution of each treatment phase.[1]



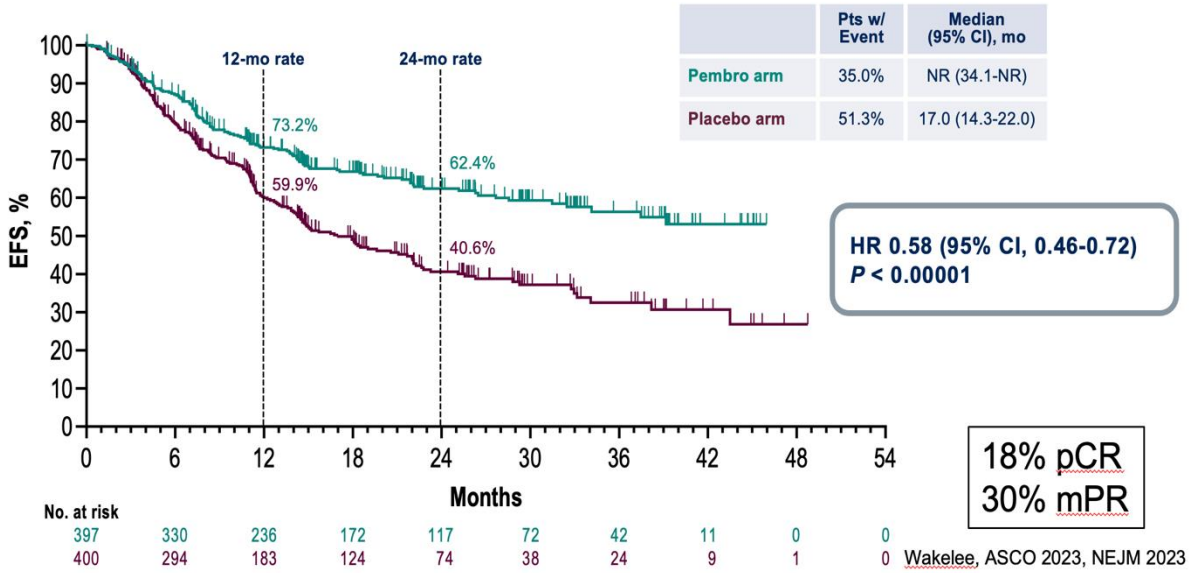
The incorporation of a new therapy into the neoadjuvant phase only rather than incorporation into the adjuvant phase only as the third arm in a 3-arm trial may be preferable because: (1) there may be stronger biologic rationale for antitumor activity in an intact tumor environment, (2) there are concerns for increased toxicities with longer duration adjuvant therapy relative to neoadjuvant therapy, and (3) some patients may achieve cure with neoadjuvant therapy and surgery alone. Thus, inclusion of an arm incorporating a new therapy in the neoadjuvant phase only may be the most reasonable choice to provide within trial information on the contribution of adjuvant treatment while preserving the ability to statistically test a potentially safe and effective addition of a new drug to only the neoadjuvant phase of therapy.

Peri-Operative IO Trials
EFS from AEGEAN, KN671 & CM77T

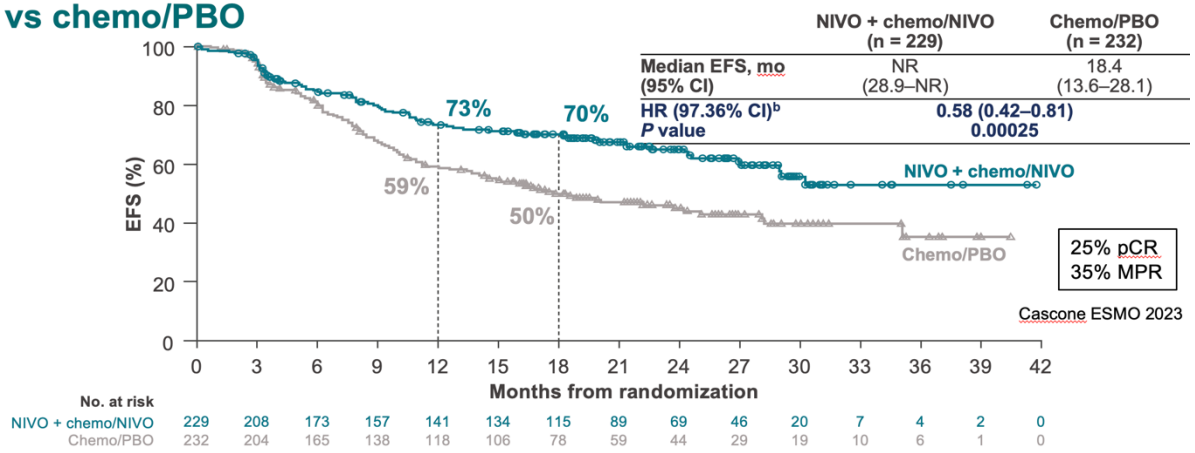
AEGEAN: EFS using RECIST v1.1 (BICR) (mITT)
First planned interim analysis of EFS



KN671 - EFS



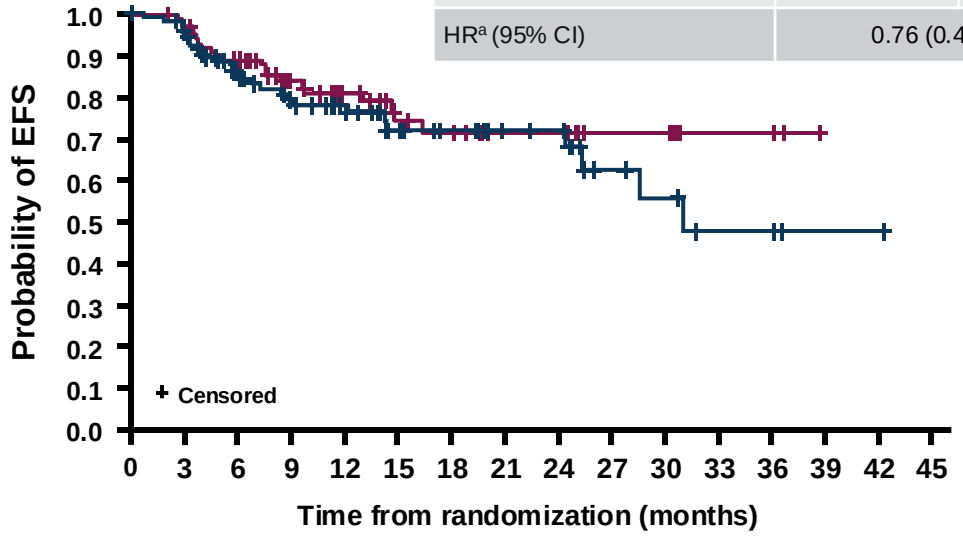
CM77T Primary endpoint:
EFS[a] per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO



- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41–0.76

AEGEAN: EFS (BICR) by Disease Stage (mITT) –Prespecified Subgroup Analysis

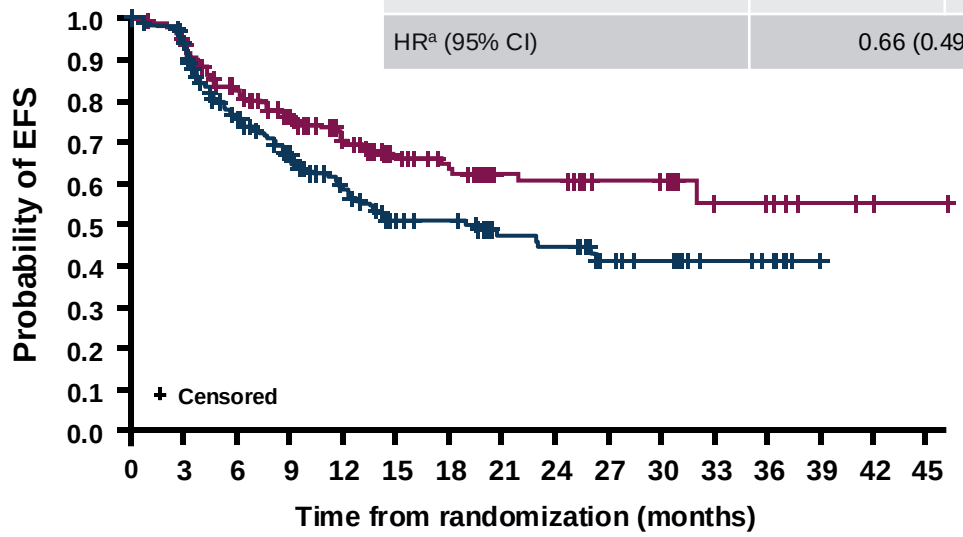
Stage II	D arm	PBO arm
No. events / no. patients (%)	21/104 (20.2)	28/110 (25.5)
mEFS, months (95% CI)	NR (NR–NR)	31.1 (25.4–NR)
HR[a] (95% CI)	0.76 (0.43–1.34)	



No. at risk:

D arm	104	96	82	56	43	27	24	17	17	12	12	4	4	0	0	0
PBO arm	110	102	81	59	47	31	26	19	18	10	8	5	5	1	1	0

Stage III	D arm	PBO arm
No. events / no. patients (%)	76/261 (29.1)	110/264 (41.7)
mEFS, months (95% CI)	NR (31.9–NR)	19.5 (12.2–26.2)
HR[a] (95% CI)	0.66 (0.49–0.88)	



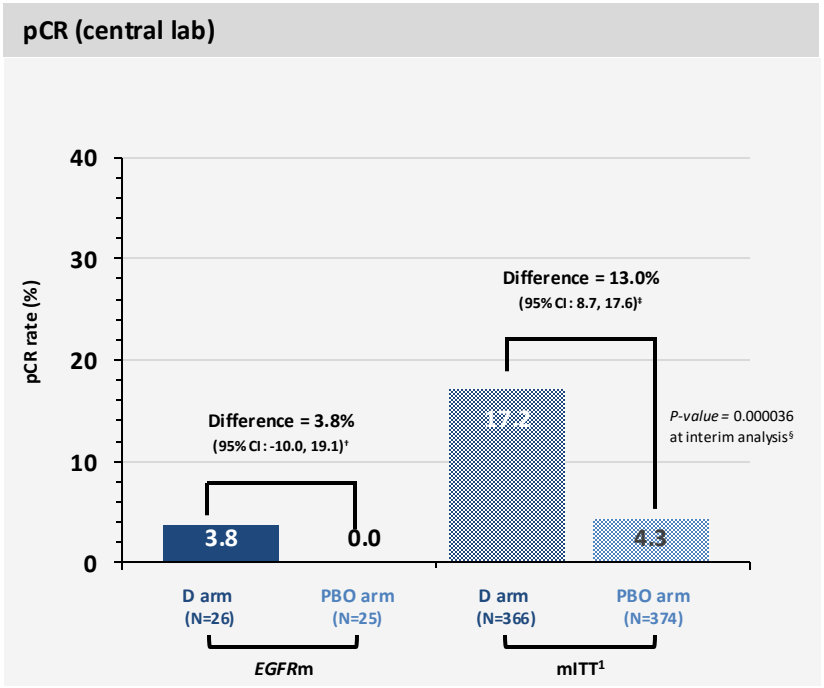
No. at risk:

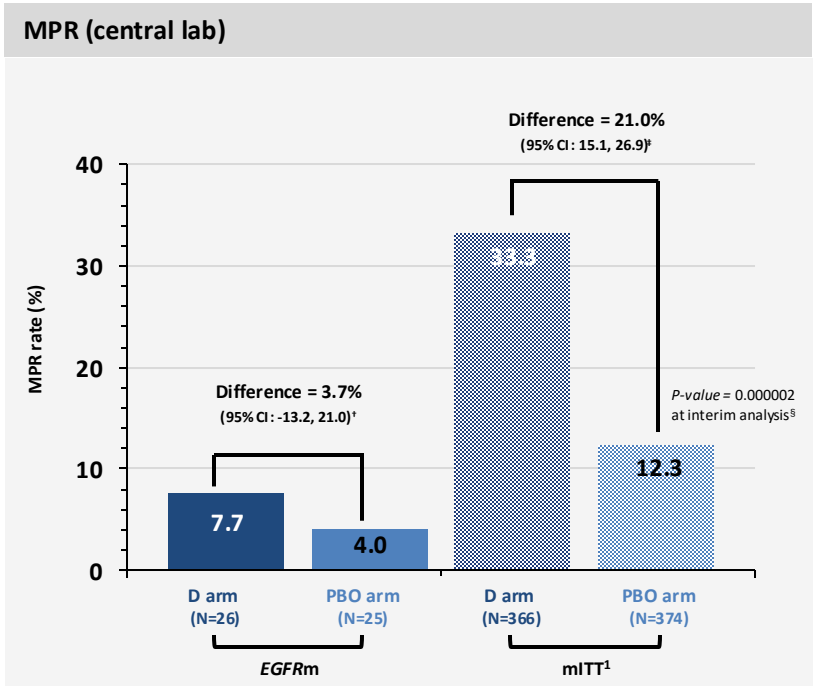
D arm	261	239	189	138	97	63	54	33	32	19	18	10	7	3	1	1
PBO arm	264	237	176	125	89	51	43	32	32	20	17	11	8	0	0	0

DCO: Nov 10, 2022 (N=740)

Heymach JV, et al. *N Engl J Med*. 2023

AEGEAN: Pathologic Response in *EGFR*m vs ITT population





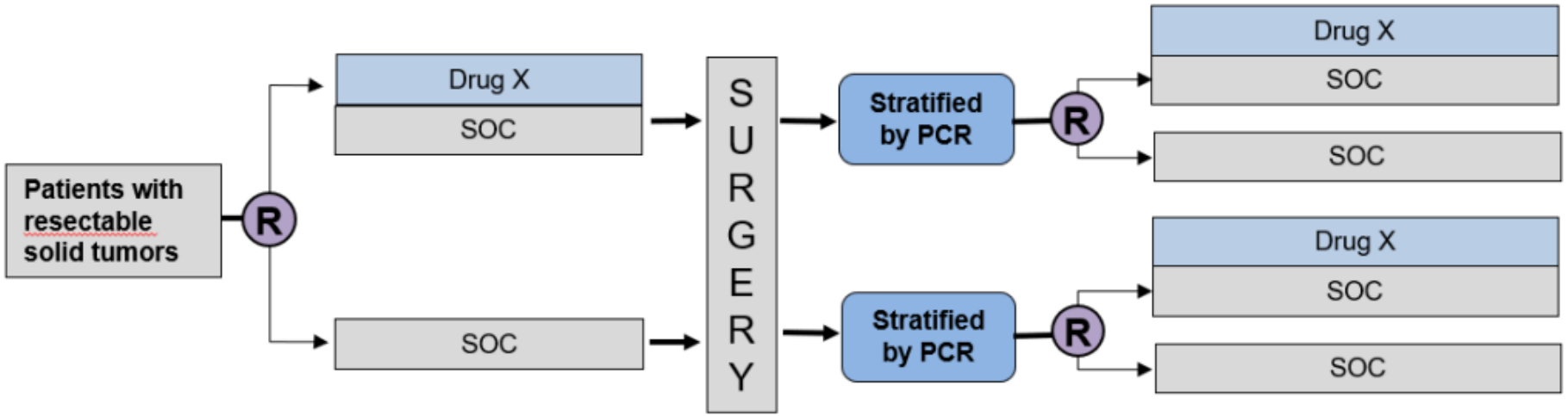
*Pre-planned analysis; pathological response assessed using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumour bed.[2] pCR = a lack of any viable tumour cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = ≤10% viable tumour cells in lung primary tumour after complete evaluation of the resected lung cancer specimen. Patients were classified as non-responders if they were not eligible for assessment (including those with R2 resection margins by local assessment) or they did not have a surgical specimen. †CIs calculated by unstratified Miettinen and Nurminen method. ‡CIs calculated by stratified Miettinen and Nurminen method. §No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; n=740 [data shown]); statistical significance in the mITT population was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; P-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test).

[1]Heymach JV, et al. *Cancer Res* 2023;83 (8_Supplement):CT005;
[2]Travis WD, et al. J Thorac Oncol 2020;15:709-40

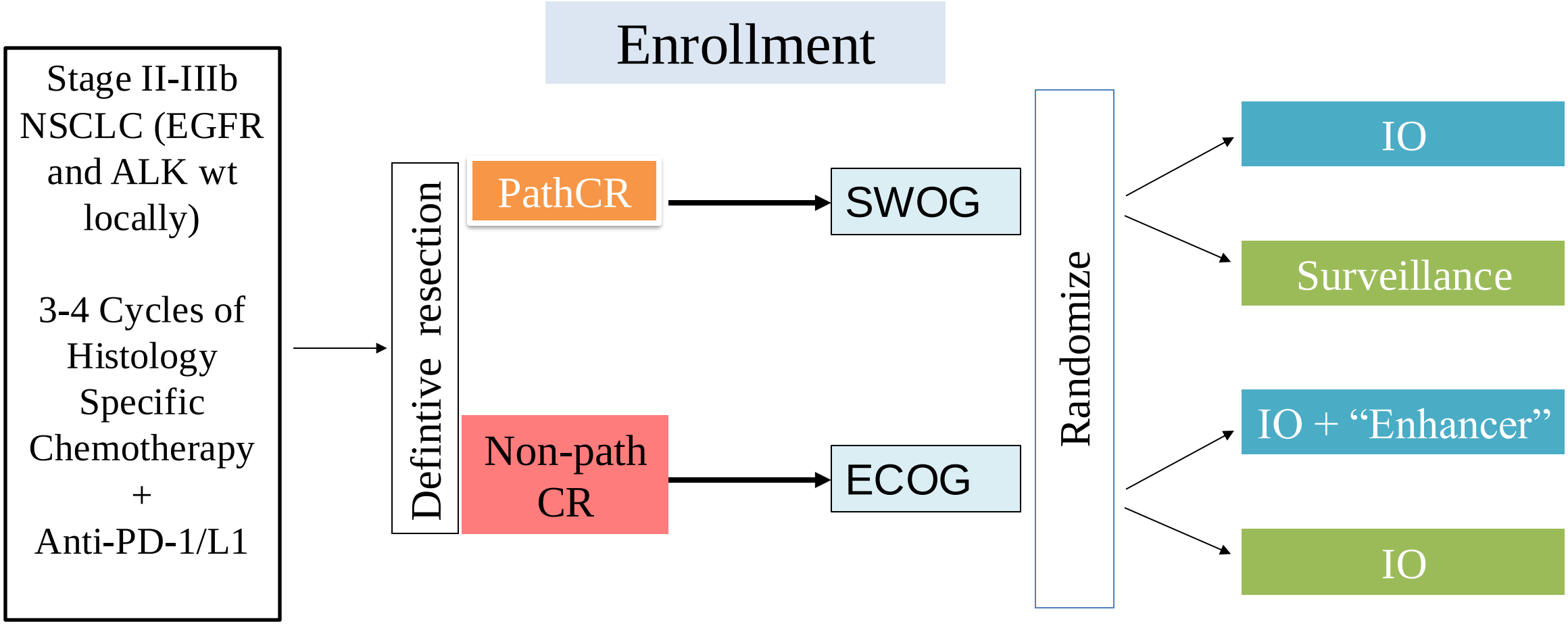
Harpole D, et al. WCLC 2023

Contribution of Components based on Biomarker (e.g. pCR)

Figure 10 Trial design with re-randomization for resectable NSCLC



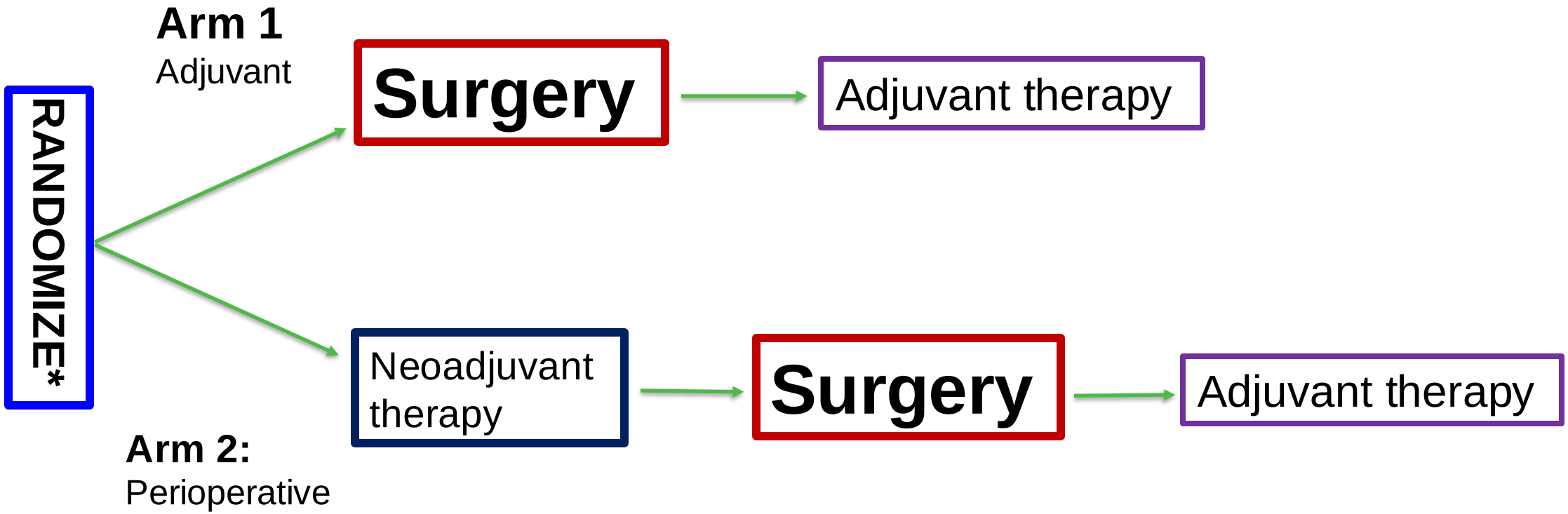
ECOG/SWOG CLEAR-INSIGHT



EA5231 (CLEAR) PI: Dwight Owen; S2414 (INSIGHT) PI: Jeremy Cetnar

Perioperative versus adjuvant systemic therapy in patients with resectable non-small cell lung cancer (PROSPECT-LUNG): PIs Daniel Morgensztern (Alliance), Raid Ajumaily (SWOG)

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

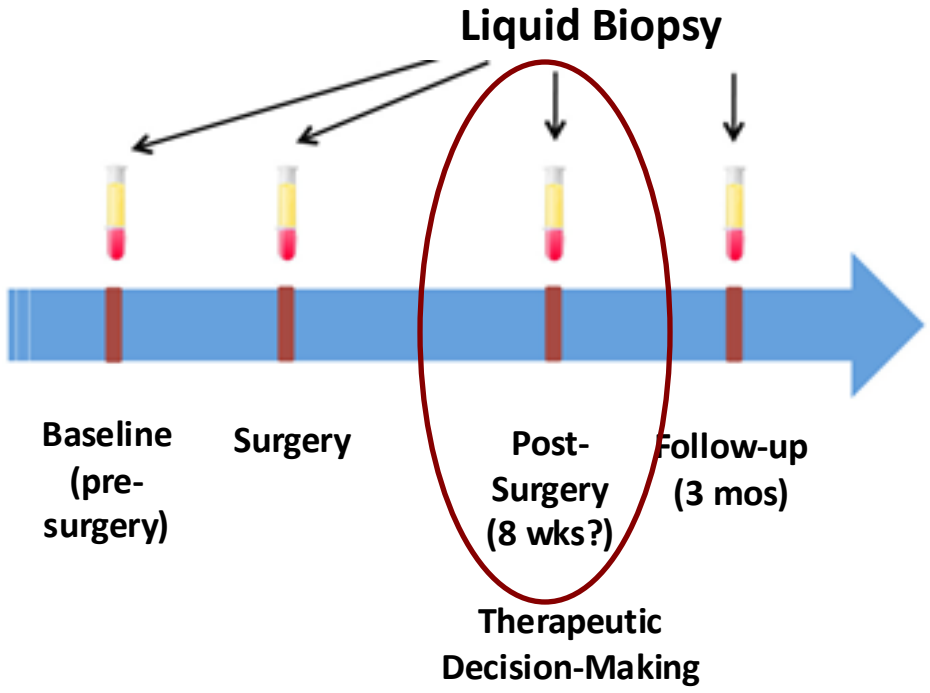


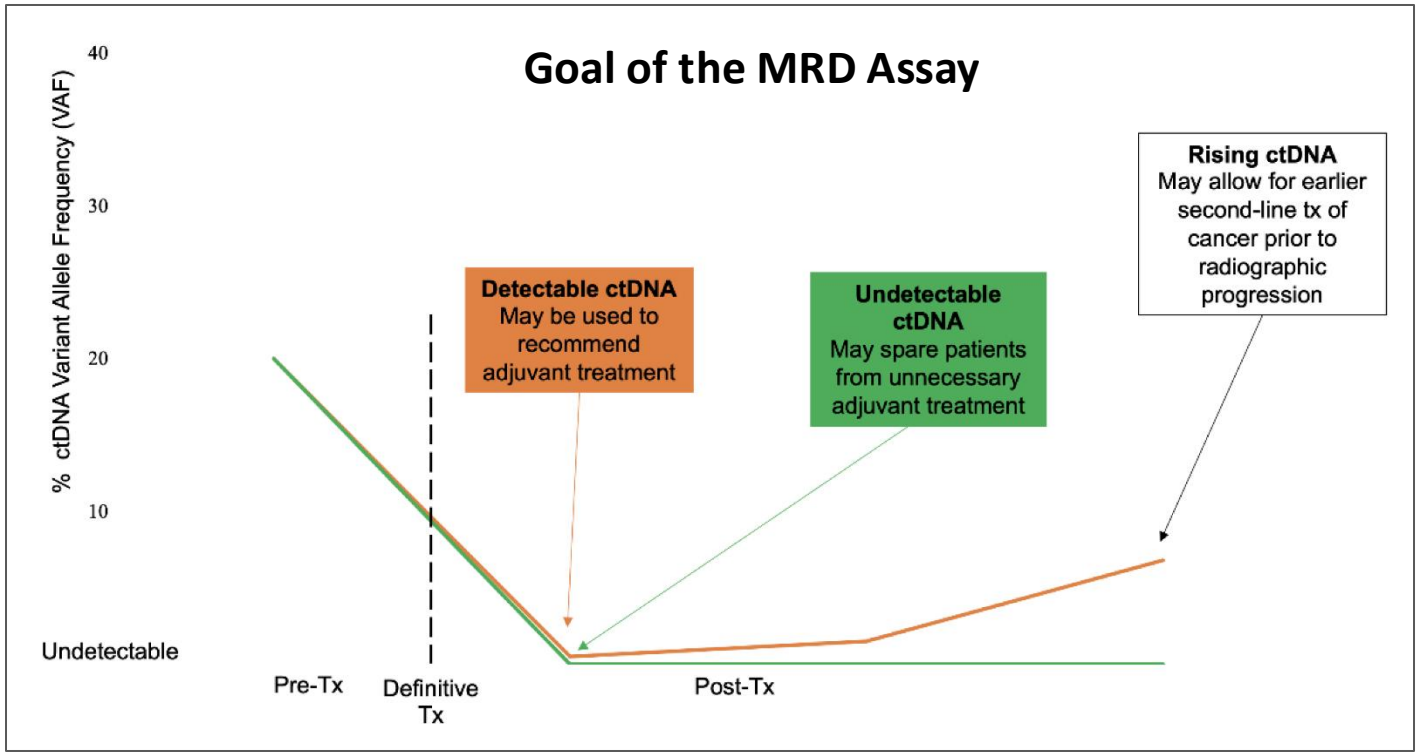
*Histologically-confirmed IIA – IIIB NSCLC

Co-primary objectives: wrEFS; OS

Secondary objectives: resection rates; R0 resection rates; AEs resulting in treatment discontinuation, hospitalization, death; association between pCR and rwEFS; rwEFS post 3-years from randomization among patients who remain event-free at 3 years

Algorithm for Liquid Biopsy Analysis of Minimal Residual Disease (MRD) post-surgery in Early-Stage NSCLC





from Ulrich et al. Cancers 2021

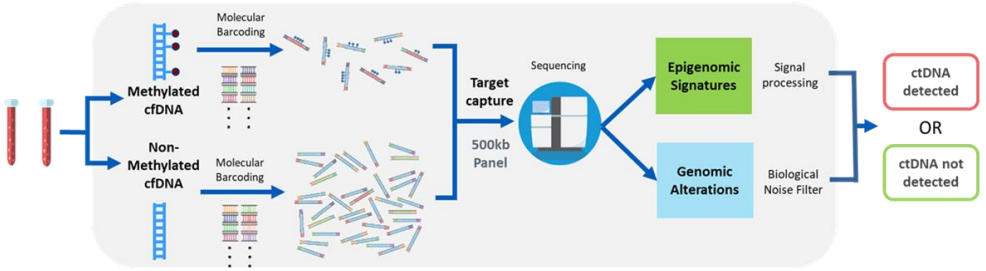
Gandara: from Liquid Biopsy in Precision Medicine 2022 (adapted)

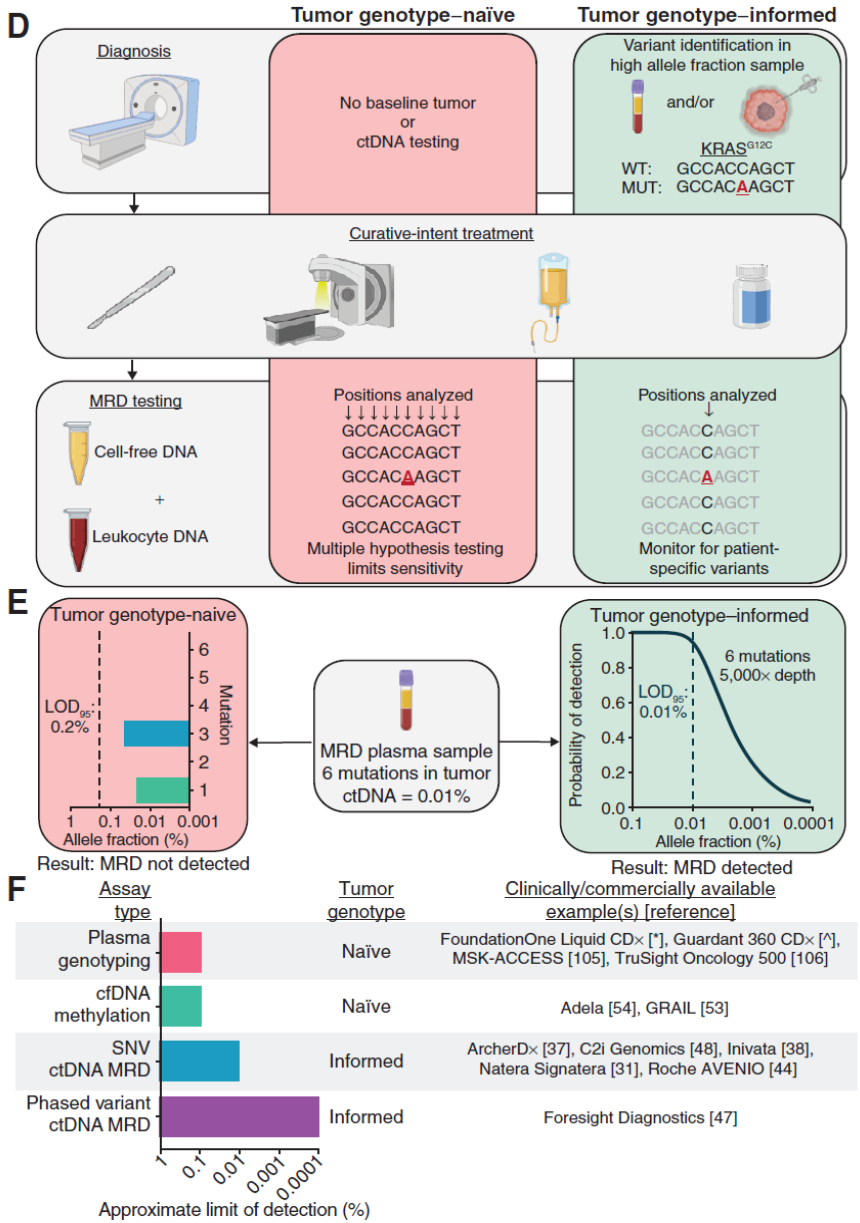
Liquid Biopsy Approaches to MRD

Parameter	Tissue-naive	Tissue-informed	Plasma-informed
Adequacy of Tumor Tissue Sample	Not required	Practical limitation	Not required
Sensitivity	MRD-specific assays improve	Lower LOD	MRD-specific assays improve
Specificity	CHIP requires filtering algorithm	Tumor specific	Improved by baseline ctDNA
Emergent Variants	Detects	Unable to assess	Detects
Resistance Variants	Detects	Unable to assess	Detects
Turn Around Time	Much shorter	Longer	Much shorter

Gandara. ISLB 2023

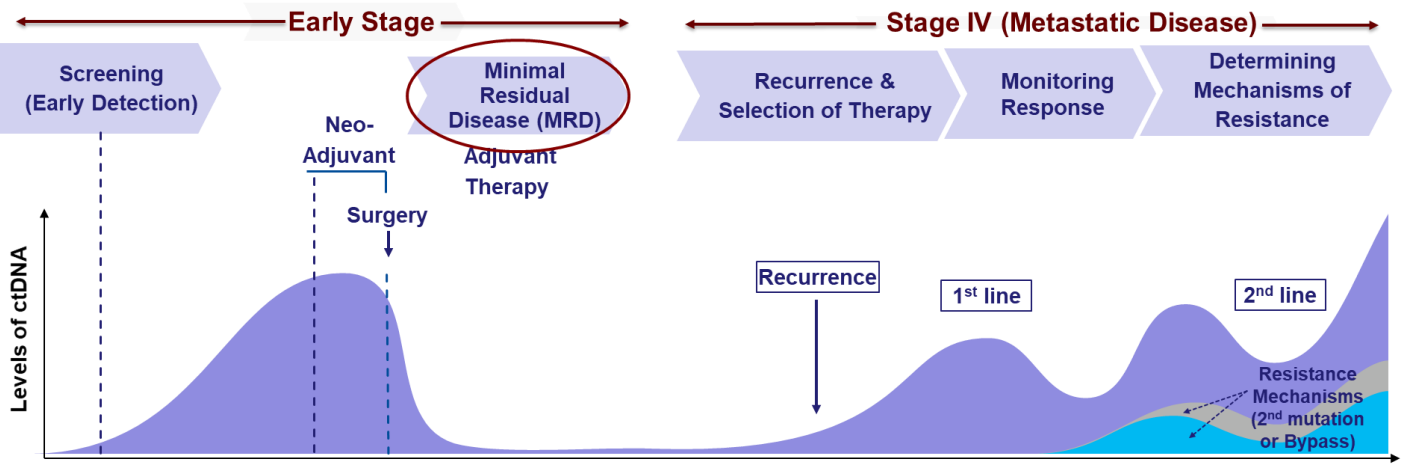
Guardant REVEAL: MRD assay integrating genomic & epigenomic analysis

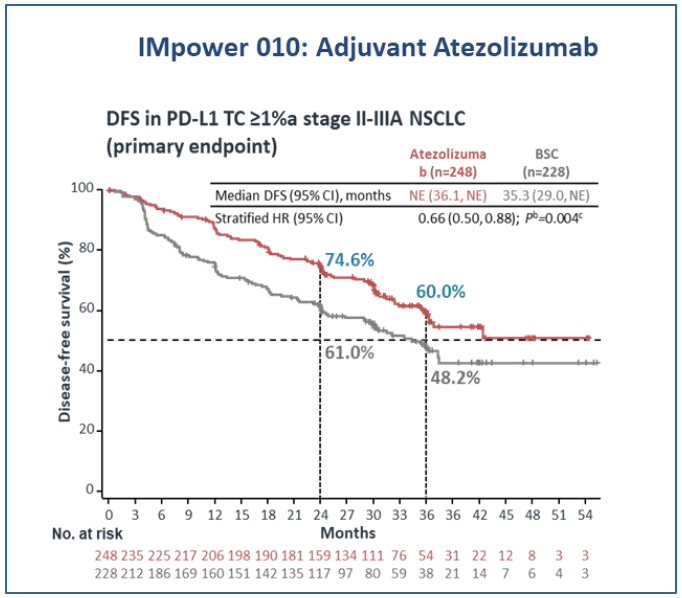


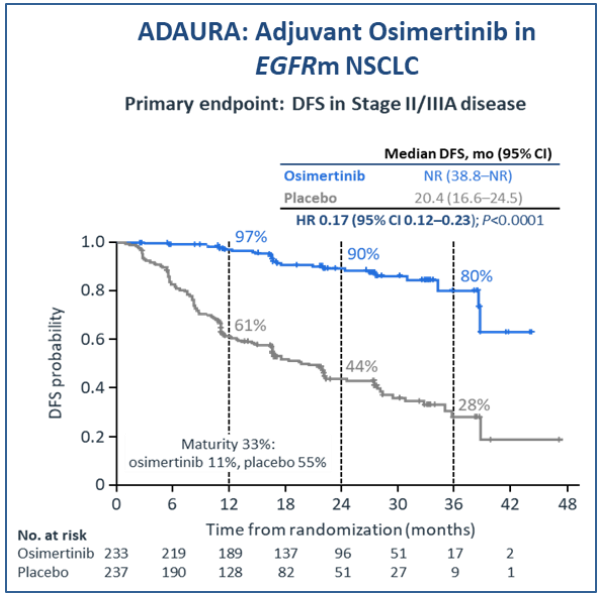


Molding (Diehn) Cancer Discov 2021; Pellini et al. JCO 2022

Two landmark trials in the adjuvant NSCLC space- IMpower010 and ADAURA: Can plasma ctDNA analysis for MRD define who benefits and who does not?



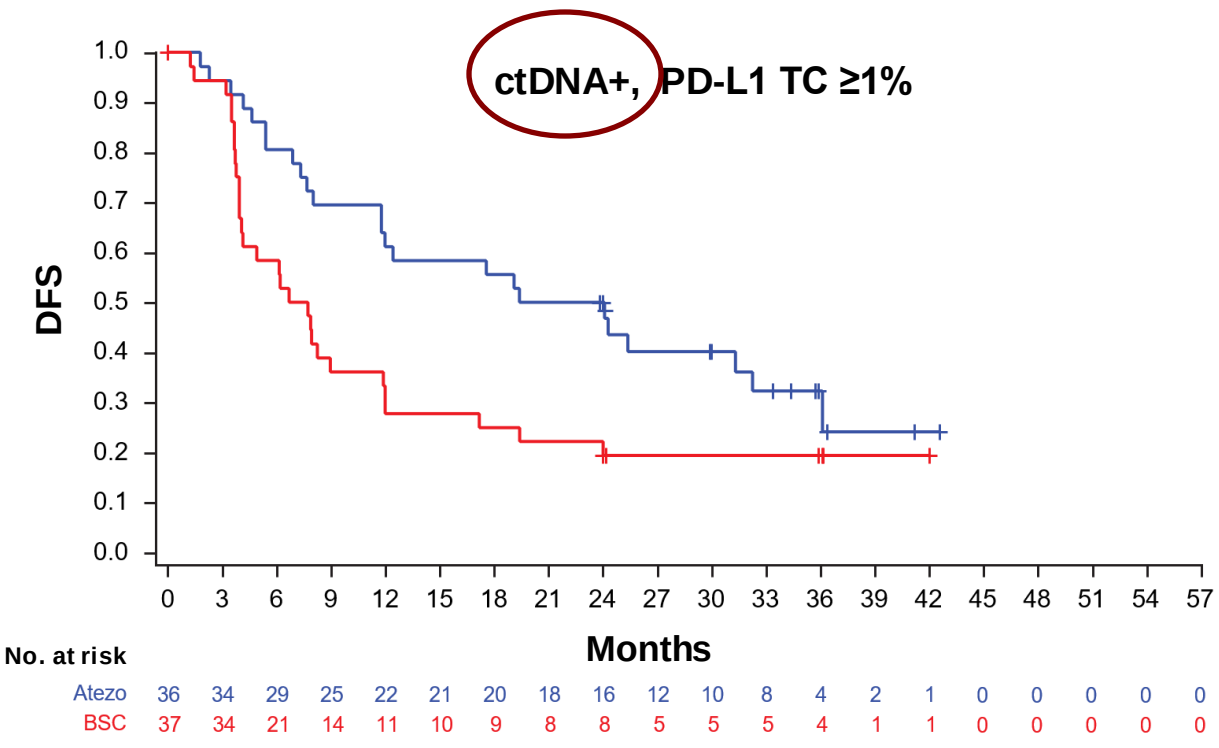




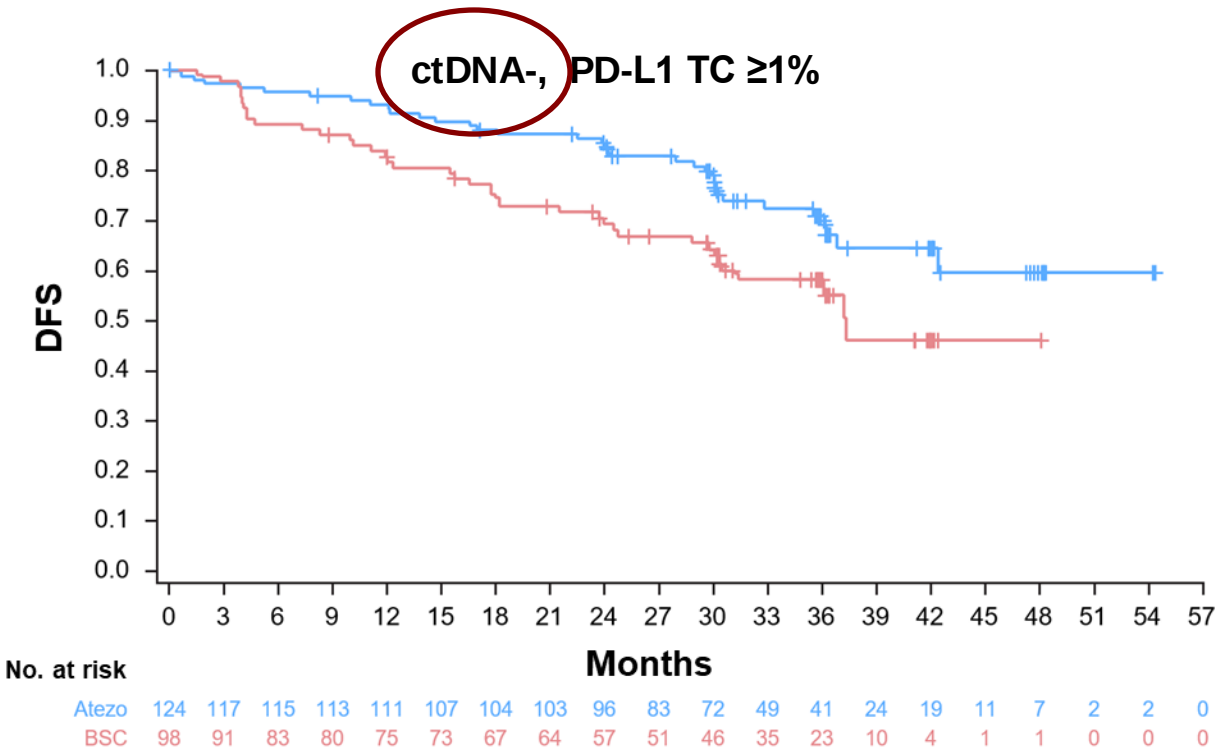
- Is MRD detection by plasma ctDNA only prognostic in these trials? (poor outcome regardless of therapeutic intervention)
- Is MRD detection by plasma ctDNA predictive for outcome with therapeutic intervention?
  - Do only patients with positive MRD after surgery benefit from these therapies?

Wu et al. N Engl J Med 2020; . Felip et al. Lancet 2021.

IMpower010: DFS in Stage II-IIIA ctDNA+ vs ctDNA- populations (PD-L1 TC ≥1%)



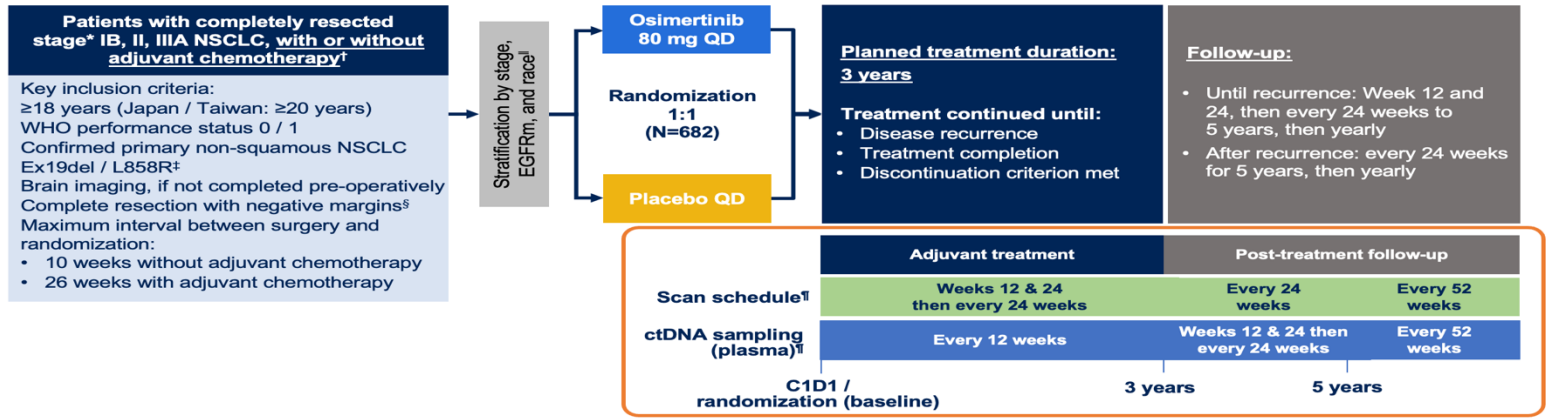
ctDNA+	PD-L1 TC ≥1%	
	Atezo (n=36)	BSC (n=37)
mDFS, mo	21.8	7.2
HR (95% CI)	0.54 (0.31, 0.93)	

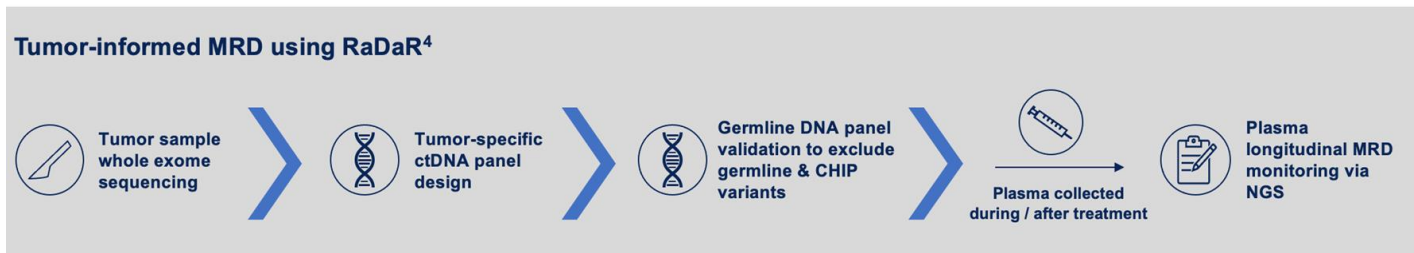


ctDNA–	PD-L1 TC ≥1%	
	Atezo (n=124)	BSC (n=98)
mDFS, mo	NR	37.3
HR (95% CI)	0.57 (0.36, 0.90)	

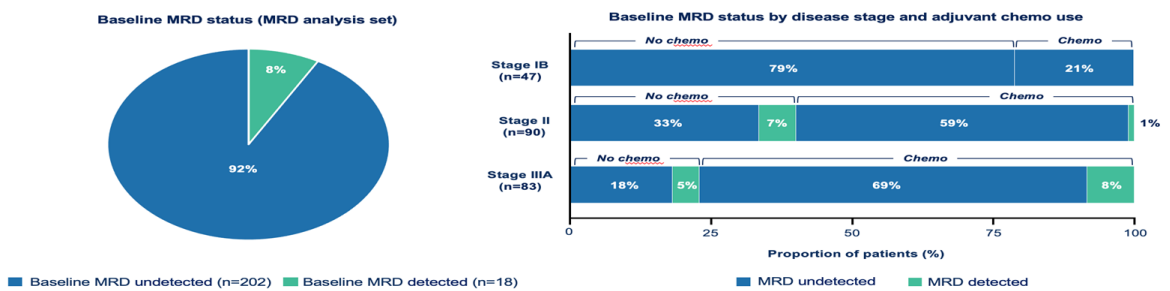
Zhou et al. ESMO 2021

ADAURA: Molecular residual disease (MRD) analysis of osimertinib among patients with resected EGFR-mutated Stage IB–IIIA NSCLC

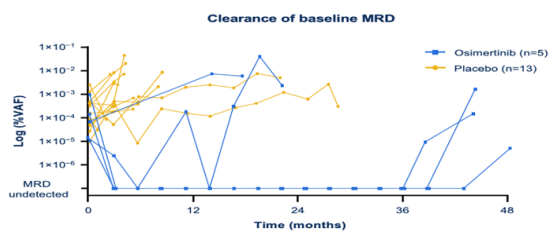




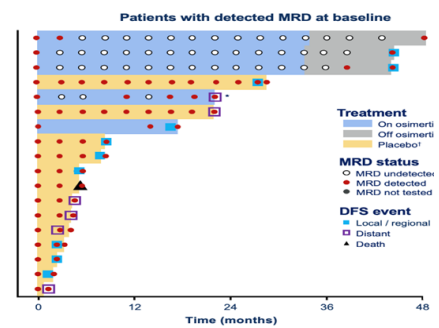
Majority of patients were MRD undetected at baseline



Detected MRD at baseline was associated with poor outcomes



- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD



T. John. ASCO 2024

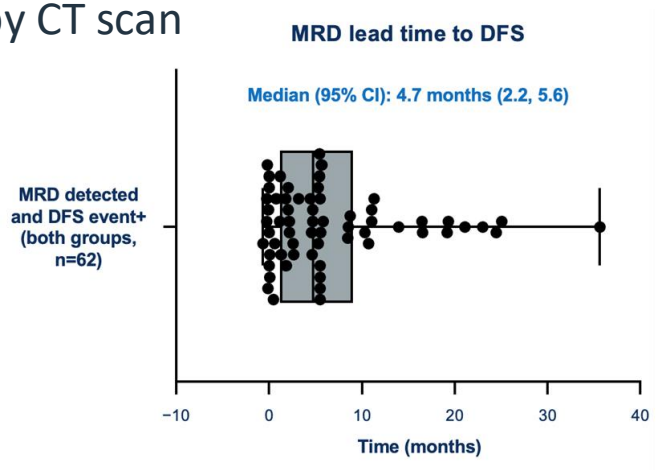
ADAURA: Molecular residual disease analysis of osimertinib among patients with resected EGFR-mutated Stage IB–IIIA NSCLC

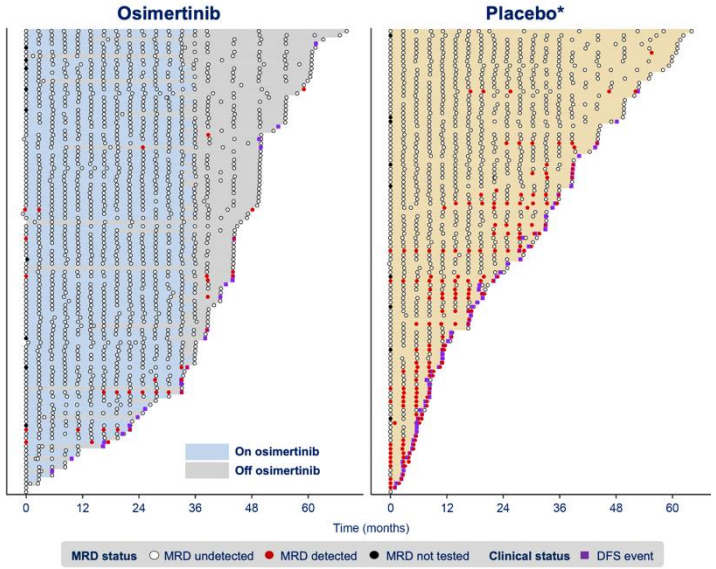
Long-Term Follow up over 5 years

MRD events were eventually detected in:

- 13% of osimertinib group (15/112)
- 49% of the placebo group (53/108)

MRD by ctDNA was detected earlier than by CT scan





Summary

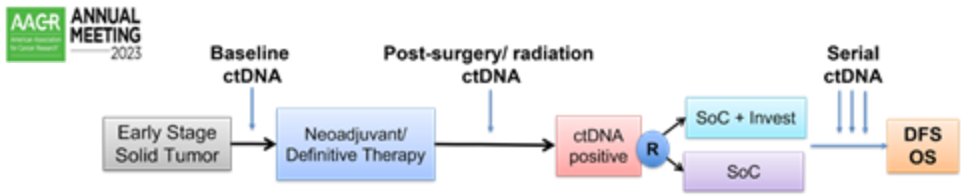
- These long-term observations do not assist in the primary goal of MRD assays,
- Primary Goal is to guide therapeutic decision-making after surgery (must be done within about 8-12 weeks)

John T, et al. ASCO 2024. Abstract 8005.

Relationship of pCR to Plasma ctDNA in the setting of Neoadjuvant Chemo-Immunotherapy of Early-Stage NSCLC

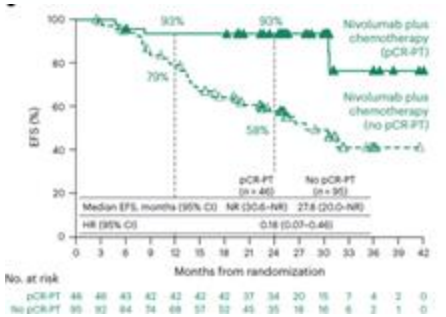
- **What is the role of plasma ctDNA in defining minimal residual disease (MRD) & how does this impact on long term outcomes or "cure"?**
  - **Are current MRD assays good enough to dictate post-op therapy? Escalation vs De-escalation vs Omission?**

Proposed trial design by FDA



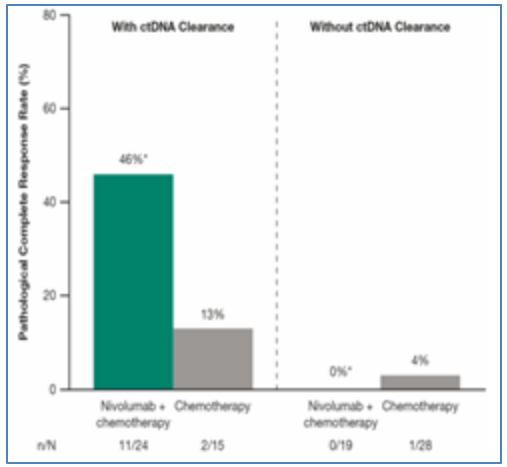
Vellanki: AACR 2023

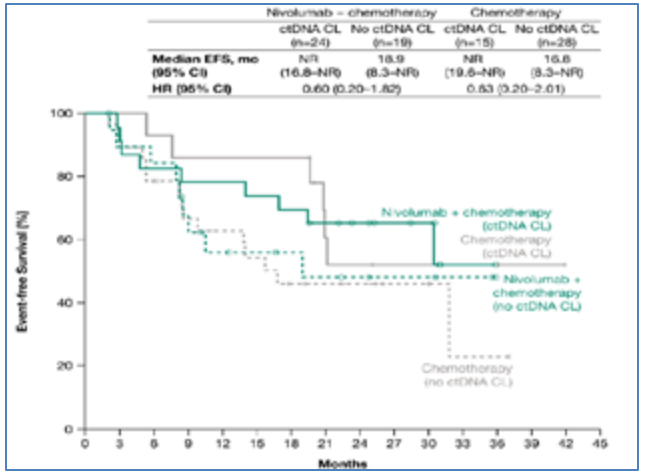
CM816 –pCR vs no pCR



Deutsch et al., *Nat Med*, 2023

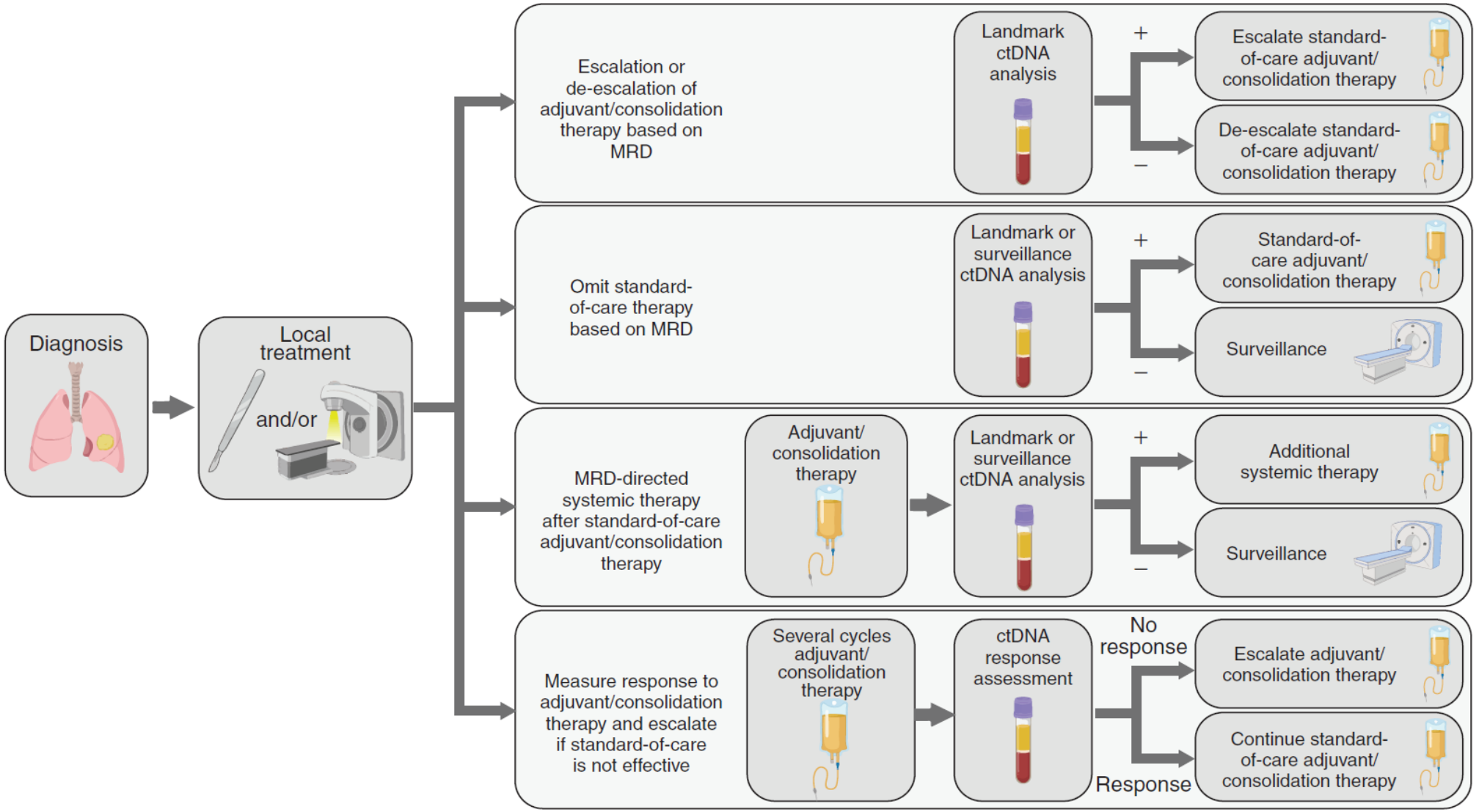
CM816 –ctDNA Clearance vs No Cl





Forde et al., *NEJM*, 2022

MRD-related Prospective Clinical Trial Designs



Pellini (Chaudhuri). JCO 2022

International Society of Liquid Biopsy (ISLB) Annual Congress
Denver, November 23-25, 2024