FDA-AACR Workshop on

HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES

May 9, 2024, 9 a.m.–4 p.m.
The Bethesda Marriott | Bethesda, MD

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WELCOME

WELCOME AND INTRODUCTION

Elizabeth M. Jaffee, MD, FAACR
Sidney Kimmel Comprehensive Cancer Center

WORKSHOP OVERVIEW

Harpreet Singh, MD
U.S. Food and Drug Administration

THANK YOU TO OUR SUPPORTERS

American Association for Cancer Research

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May 9, 2024 | Bethesda, MD

SESSION 1: CURRENT LANDSCAPE FOR PERIOPERATIVE TRIAL DESIGNS

Current Therapeutic Landscape for Early-Stage Solid Tumors
Oladimeji Akinboro, MD, U.S. Food and Drug Administration

Biomarker-Guided Perioperative Clinical Trials
Valsamo Anagnostou, MD, PhD, Sidney Kimmel Comprehensive Cancer Center

Implementing Sequential, Multiple, Randomized (S.M.A.R.T.) Trial Designs
Kelley Kidwell, PhD, University of Michigan School of Public Health

SESSION 2A: OPTIMIZING PERIOPERATIVE TREATMENT REGIMENS

Optimizing the Regimen: Cooperative Group Perspective
Jhanelle Gray, MD, Moffitt Cancer Center

Cumulative and Long-Term Toxicity with Immunotherapy
Mark Yarchoan, MD, Sidney Kimmel Comprehensive Cancer Center

SESSION 2B: THE FUTURE OF REGISTRATIONAL TRIALS WITH MULTIPLE ARMS

Industry Perspective on Future Perioperative Trials: Efficacious vs Optimal Treatment
Minghua (Michael) Shan, PhD, Bayer Pharmaceuticals

Statistical Considerations for Future Perioperative Trials
Chi Song, PhD, U.S. Food and Drug Administration

SESSION 3: CONSIDERATIONS IN OTHER THERAPEUTIC AREAS

Where Do We Go from Here? Considerations for NSCLC and Other Therapeutic Areas
Harpreet Singh, MD, U.S. Food and Drug Administration

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May 9, 2024 | Bethesda, MD

Fireside Chat with FDA Division Directors

Harpreet Singh, MD
Oncology II

Angelo de Claro, MD
Hematologic Malignancies I

Nicole Gormley, MD
Hematologic Malignancies II

Laleh Amiri-Kordestani, MD
Oncology I

Steven Lemery, MD
Oncology III

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SESSION 1: CURRENT LANDSCAPE FOR PERIOPERATIVE TRIAL DESIGNS

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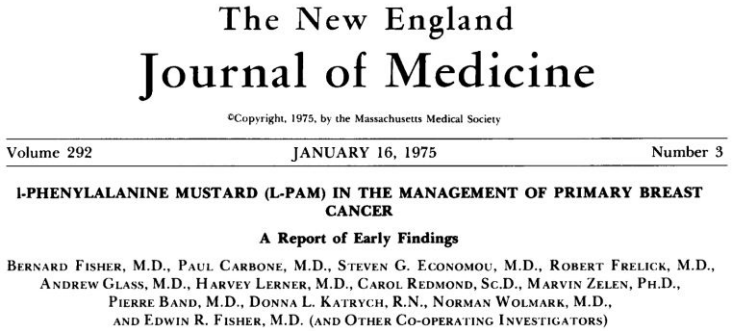
How Much is Enough?: Trial Designs for Treatment Regimens with Multiple Phases in Solid Tumors

Oladimeji (Ladi) Akinboro, MD, MPH
Office of Oncologic Diseases
FDA

May 9, 2024

Clinical benefit of adjuvant therapy first established in oncology in node-positive breast cancer based on multiple RCTs



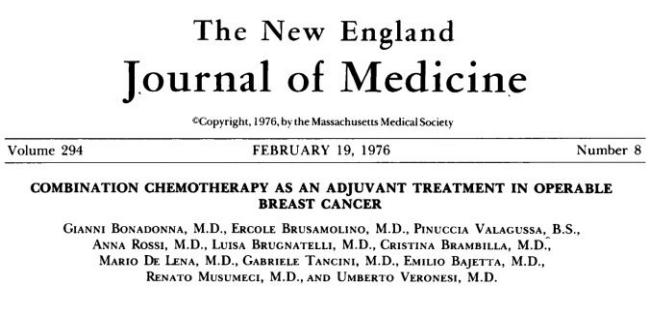
The New England
Journal of Medicine

Volume 292 JANUARY 16, 1975 Number 3

l-PHENYLALANINE MUSTARD (L-PAM) IN THE MANAGEMENT OF PRIMARY BREAST CANCER

A Report of Early Findings

BERNARD FISHER, M.D., PAUL CARBONE, M.D., STEVEN G. ECONOMOU, M.D., ROBERT FRELICK, M.D., ANDREW GLASS, M.D., HARVEY LERNER, M.D., CAROL REDMOND, SC.D., MARVIN ZELEN, PH.D., PIERRE BAND, M.D., DONNA L. KATRYCH, R.N., NORMAN WOLMARK, M.D., AND EDWIN R. FISHER, M.D. (AND OTHER CO-OPERATING INVESTIGATORS)



The New England
Journal of Medicine

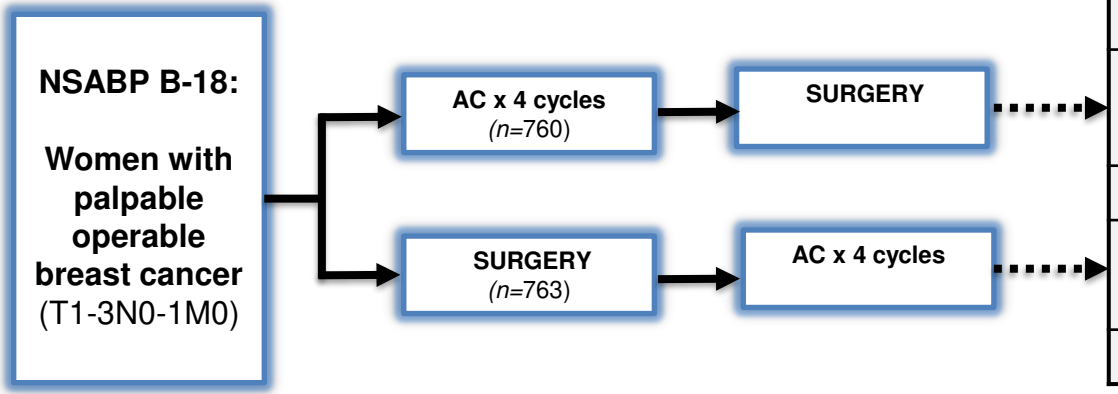
Volume 294 FEBRUARY 19, 1976 Number 8

COMBINATION CHEMOTHERAPY AS AN ADJUVANT TREATMENT IN OPERABLE BREAST CANCER

GIANNI BONADONNA, M.D., ERCOLE BRUSAMOLINO, M.D., PINUCCIA VALAGUSSA, B.S., ANNA ROSSI, M.D., LUISA BRUGNATELLI, M.D., CRISTINA BRAMBILLA, M.D., MARIO DE LENA, M.D., GABRIELE TANCINI, M.D., EMILIO BAJETTA, M.D., RENATO MUSUMECI, M.D., AND UMBERTO VERONESI, M.D.

- **Premise of Adjuvant Chemotherapy**:
  - Treatment and potential cure of micro-metastases
  - Favorable benefit-risk anticipated for appropriately selected patients i.e., those with high-risk/locally-advanced disease

Clinical efficacy of neoadjuvant therapy shown to be comparable to adjuvant therapy in breast cancer based on RCT evidence [1-3]



	Received lumpectomy	5-year DFS	5-year Distant DFS	5-year OS
Neoadjuvant	67%	66.7%	73.3%	79.6%
Adjuvant	60%	67.3%	73.2%	80.0%
p-value	-	0.99	0.70	0.83

- **Premise of Neoadjuvant Chemotherapy:**
  - Treatment and potential cure of micro-metastases
  - Potential downstaging, increased tissue conservation, and/or reduced surgical complications
  - Opportunity for pathologic assessment of treatment effect and development of correlative biomarkers

Abbreviations: AC=adriamycin (doxorubicin) plus cyclophosphamide; DFS=disease-free survival; *n*=number; OS=overall survival.

[1] Fisher B, et al. *J Clin Oncol.* 1997;15(7):2483-93. [2] Fisher B, et al. *J Clin Oncol.* 1998;16(8):2672-85. [3] Mauri D, et al. *J Natl Cancer Inst.* 2005;97(3):188-94.

Combined perioperative systemic regimens first established in oncology in lower esophageal/GEJ/gastric adenocarcinoma

RCT	Investigational therapy	Control arm	Investigational treatment phase(s)	Primary Endpoint(s)	Status/Readout
Multi-agent chemo					
STO5 (NCT00450205)	Bevacizumab + EOX	EOX	Neoadjuvant + Adjuvant	5-year OS	Negative

Contribution of phases not isolated in RCTs *though*:

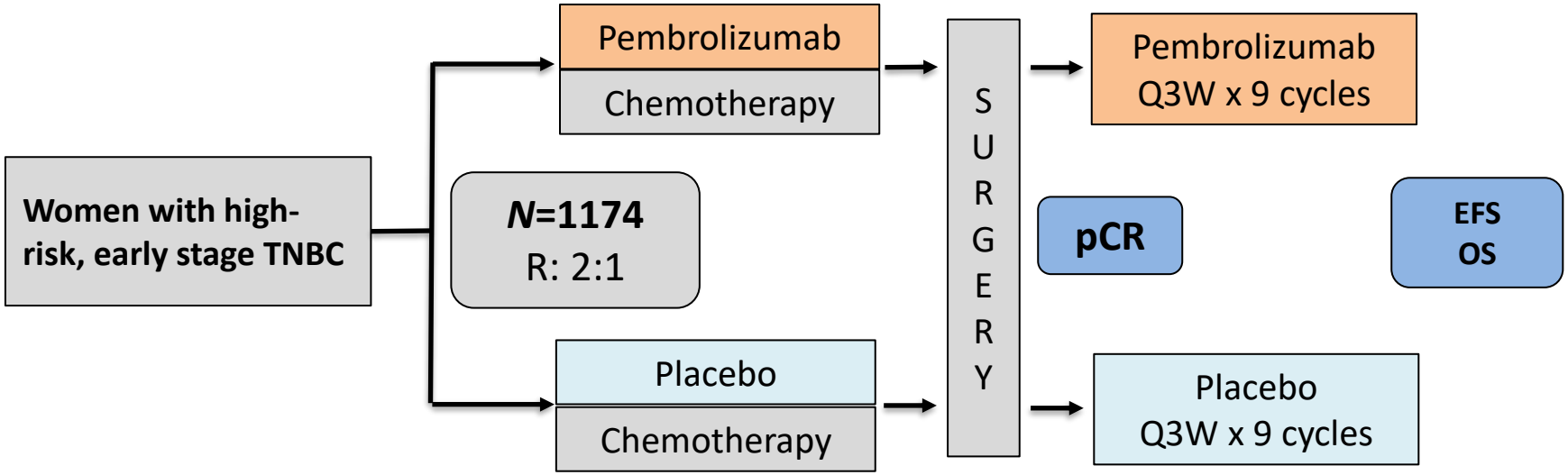
- Relatively limited duration of treatment: 2-4 cycles preop and 3-4 cycles postop
- OS primary endpoint

Abbreviations: AJCC=American Joint Committee on Cancer staging edition; CF=cisplatin plus continuous intravenous infusional 5-fluorouracil; chemo=chemotherapy; CX=cisplatin plus capecitabine; DFS=disease-free survival; ECF=epirubicin plus cisplatin plus continuous intravenous infusional 5-fluorouracil; ECX=epirubicin plus cisplatin plus capecitabine; EFS=event-free survival; FFCD=Fédération Francophone de Cancérologie Digestive; FLOT=Intravenous infusional 5-fluorouracil plus leucovorin plus oxaliplatin plus docetaxel; FNCLCC=Fédération Nationale des Centres de Lutte contre le Cancer; GEJ=gastroesophageal junction; ICI=immune checkpoint inhibitor; OS=overall survival; pCR=pathologic complete response; Q2W=every 2 weeks; Q3W=every 3 weeks; RCT(s)=randomized controlled trial(s); UICC=International Union again Cancer.

[1] Cunningham D, et al. *N Eng J Med,* 2006;355(1):11-20. [2] Ychou M et al. *J Clin Oncol,* 2011;29(13):1715-21. [3] Al-Batran S, et al. *Lancet Oncol,* 2019;393:491-503. [4] Cunningham D, et al. *Lancet Oncol.* 2017;18:357-70.

In ICI/targeted therapy era: Combined perioperative '*regimen*' first approved in early-stage TNBC

KEYNOTE-522 [1]: *Not designed to isolate contribution of phases* [2]

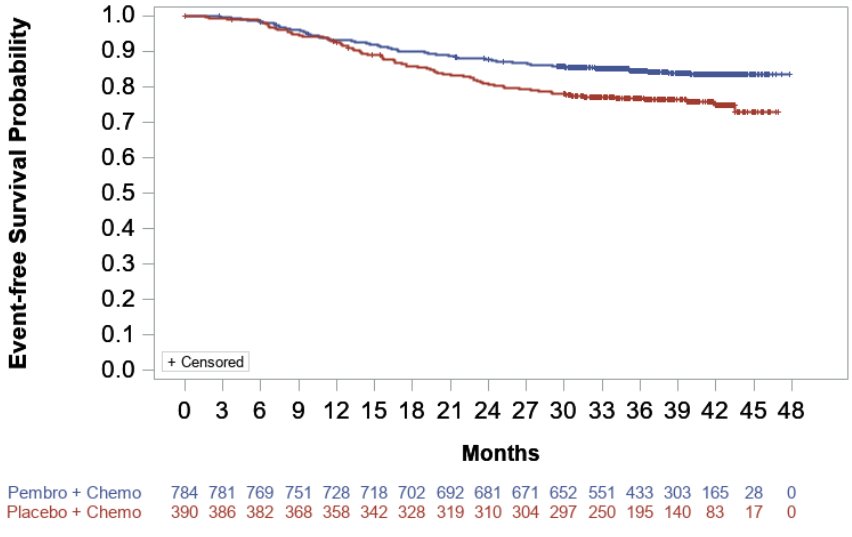


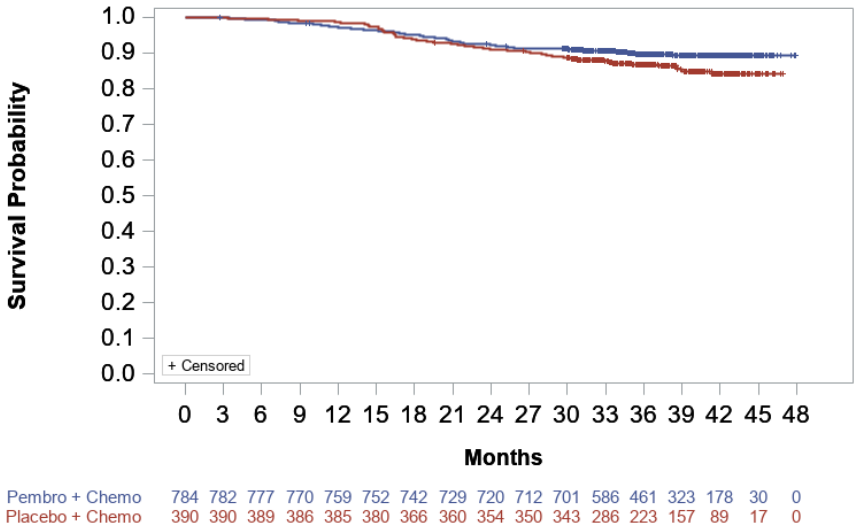
Primary endpoints: pCR and EFS
Key secondary endpoint: OS

Abbreviations: EFS=event-free survival; ICI=immune checkpoint inhibitor; *N*=number; OS=overall survival; pCR=pathologic complete response; R=randomization; Q3W=every 3 weeks; R=randomization: TNBC=triple-negative breast cancer.

[1] Schmid P, et al. *N Eng J Med.* 2022;386(6):556-67. [2] Shah M, et al. *Clin Cancer Res.* 2022;28(4):5249-53.

KEYNOTE-522: Improved EFS but additional toxicity (irAEs) with the investigational combined perioperative *'regimen'* [1, 2]





	EFS			OS		
	Events (95% CI)	HR (95% CI)	*p*-value	Events (95% CI)	HR (95% CI)	*p*-value (IF)
Pembrolizumab + Chemotherapy (*n*=784)	16%	0.63 (0.48, 0.82)	0.00031	10%	0.72 (0.51, 1.02)	- (45%)
Placebo + Chemotherapy (*n*=390)	24%			14%		

Abbreviations: CI=confidence interval; EFS=event-free survival; HR=hazard ratio; IF=information fraction; imAEs=immune-mediated adverse events; OS=overall survival.

[1] Schmid P, et al. *N Eng J Med.* 2022;386(6):556-67. [2] Shah M, et al. *Clin Cancer Res.* 2022;28(4):5249-53.

Active investigational landscape of ICI-based regimens for resectable NSCLC

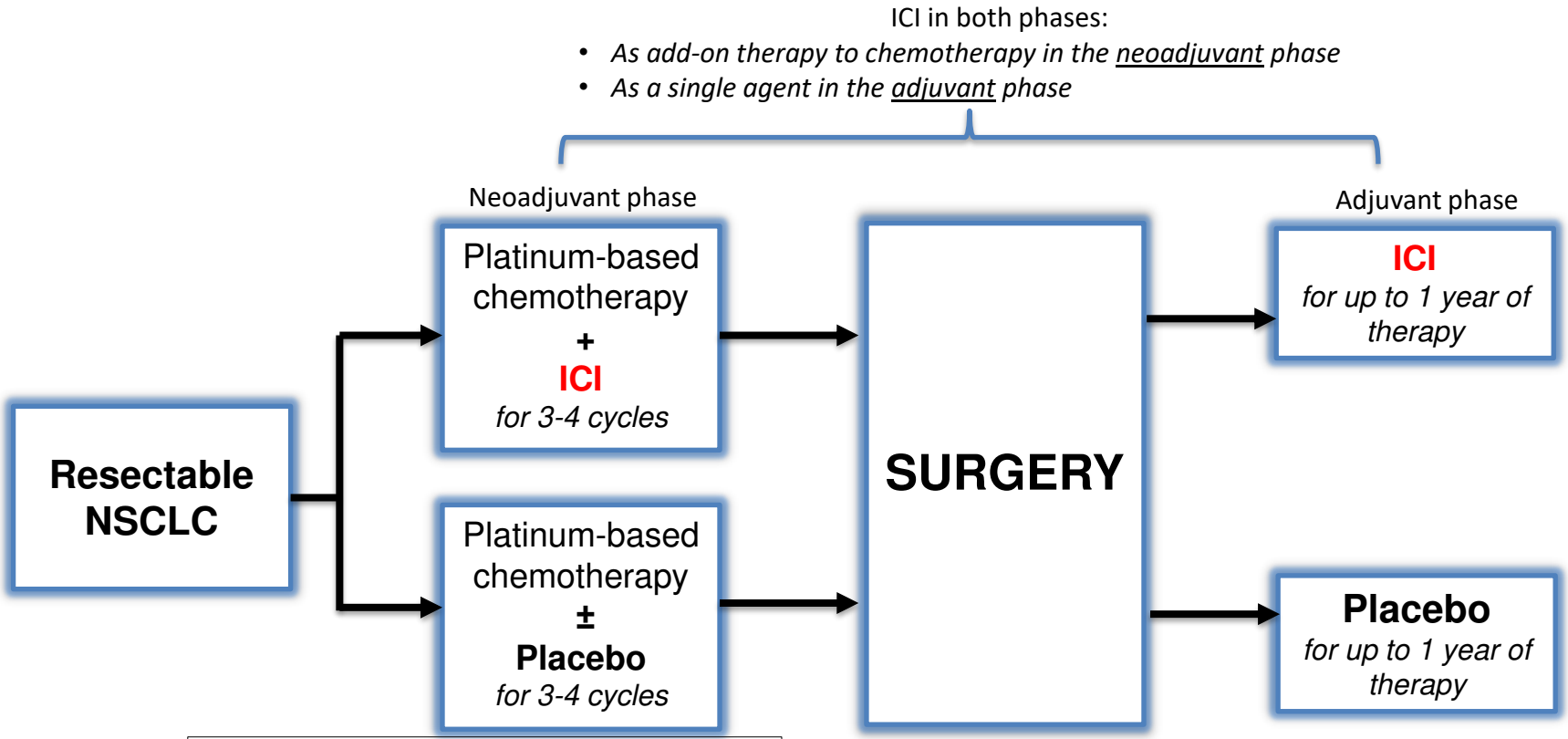
RCT	Investigational ICI	Treatment phase(s)	Primary Endpoint(s)	Status/Readout
IMpower030 (NCT03456063)	Atezo + chemo → Atezo	Neoadjuvant + Adjuvant	EFS	Ongoing
IMpower010 (NCT02486718)	Atezo	Adjuvant	DFS [a]	FDA-approved [b]
SKYSCRAPER-15 (N				
AEGEAN (NCT0380				
MERMAID-I (NCT04				
BR.31 (NCT0227337				
CheckMate-816 (NC				proved
CheckMate-77T (NC				
ANVIL (NCT0259594				
KEYNOTE-671 (NCT				proved
KEYNOTE-091 (NCT				proved [c]
BTCRC-LUN18-153 (				
NCT04316364 (ex-U				
NCT05116462 (ex-U				
RATIONALE 315 (NCT04379635; ex-U.S/China-only)	*Tislelizumab*	*Neoadjuvant + Adjuvant*	*EFS, MPR*	*Ongoing*
NEOTORCH (NCT04158440; ex-U.S/China-only)	*Toripalimab*	*Neoadjuvant + Adjuvant*	*EFS, MPR [a]*	*Ongoing*

PD(L)-1 Pandemonium

Abbreviations: Atezo=atezolizumab; chemo=platinum-based chemotherapy; DFS=disease-free survival; Durva=durvalumab; EFS=event-free survival; ICI=immune checkpoint inhibitor; MPR=major pathologic response; Nivo=nivolumab; NSCLC=non-small cell lung cancer; pCR=pathologic complete response; PD(L)-1=programmed death (ligand) -1; Pembro=pembrolizmab; RCTs=randomized controlled trials.
[a] Overall survival included in the protocol prespecified statistical testing strategy to control overall Type I error. [b] Approved for those who are PD-L1-positive. [c] Approved for patients who received prior chemotherapy.

Uncertainties due to study design

What is the relative contribution of the neoadjuvant and adjuvant ICI on efficacy endpoints?
Are patients being overtreated?



Abbreviations: ICI=immune checkpoint inhibitor; NSCLC=non-small cell lung cancer.

Anti-PD-(L)1-based regimens in resectable NSCLC [a] :

Apparent comparable EFS/DFS treatment effect sizes across neoadjuvant-only RCT vs. perioperative RCTs

		CheckMate-816 (Neoadjuvant only)		KEYNOTE-671 (Neoadjuvant + Adjuvant)		AEGEAN [1, b] (Neoadjuvant + Adjuvant)		CheckMate-77T [2, c] (Neoadjuvant + Adjuvant)	
		Nivo + Chemo (*n*=179)	Chemo (*n*=179)	Pembro + Chem/Pembro (*n*=397)	Placebo + Chemo/Placebo (*n*=400)	Durva + Chemo/Durva (*n*=366)	Placebo + Chemo/Placebo (*n*=374)	Nivo + Chemo/Nivo (*n*=229)	Placebo + Chemo/Placebo (*n*=232)
Stage (PD-L1)		IB-IIIA [d]		II-IIIB [e]		II-IIIB [e]		II-IIIB [e]	
EFS	Median, months (95% CI)	31.6 (30.2, NE)	20.8 (14.0, 26.7)	NR (34.1, NE)	17.0 (14.3, 22.0)	NR (31.9, NE)	25.9 (18.9, NE)	NR (28.9, NE)	18.4 (13.6, 28.1)
	HR (95% CI)	**0.63 (0.45, 0.87)**		**0.58 (0.46, 0.72)**		**0.68 (0.53, 0.88)**		**0.58 (0.42, 0.81)**	
	p-value (alpha)	0.0052 (0.0262)		< 0.0001 (0.0092)		0.004 (0.009)		0.00025	
OS	Median, months (95% CI)	-	-	NR (NE, NE)	52.4 (45.7, NE)	-	-	-	-
	HR (95% CI)	0.57 (0.38, 0.87)		0. (0.56, 0.93)		-		-	
	p-value (alpha)	0.0079 (0.0033)		0.0103 (0.0109)		-		-	

Abbreviations: Atezo=atezolizumab; chemo=platinum-based chemotherapy; CI=confidence interval; Durva=durvalumab; EFS=event-free survival; HR=hazard ratio; IQR=inter-quartile range; *n*=number; NA=not applicable; NE=not estimable; Nivo=nivolumab; NR=not reached; NSCLC=non-small cell lung cancer; OS=overall survival; pCR=pathologic complete response; PD-(L)1=programmed death (ligand) 1; Pembro=pembrolizumab; TC=tumor cells.

[1] Heymach J,et al. *N Eng J Med*, 2023;398(18):1672-84. [2] Cascone T. ESM0 2023; LBA1.

[a] Based on data provided in the product labels for the respective anti-PD-(L)-1-based agents except where specific references are cited. [b] Results at the first interim analysis of AEGEAN. [c] Results at the interim analysis of CheckMate-77T. [d] Based on the American Joint Committee on Cancer TNM 7th staging edition. [e] Based on the American Joint Committee on Cancer TNM 8th staging edition.

Perioperative anti-PD-(L)1-based regimens in NSCLC [a]:

EFS/DFS treatment effect sizes comparable across trials

		CheckMate-816 (Neoadjuvant only)		KEYNOTE-671 (Neoadjuvant + Adjuvant)		AEGEAN [1, b] (Neoadjuvant + Adjuvant)		CheckMate-77T [2, c] (Neoadjuvant + Adjuvant)		KEYNOTE-091 [d] (Adjuvant only)		IMpower010 [e] (Adjuvant only)	
		Nivo + Chemo (*n*=179)	Chemo (*n*=179)	Pembro + Chem/Pembro (*n*=397)	Placebo + Chemo/Placebo (*n*=400)	Durva + Chemo/Durva (*n*=366)	Placebo + Chemo/Placebo (*n*=374)	Nivo + Chemo/Nivo (*n*=229)	Placebo + Chemo/Placebo (*n*=232)	Pembro (*n*=506)	Placebo (*n*=504)	Atezo (*n*=248)	Placebo (*n*=228)
Stage (PD-L1)		IB-IIIA [f]		II-IIIB [g]		II-IIIB [g]		II-IIIB [g]		II-IIIA [f]		II-IIIA [f] (PD-L1 ≥ 1% TC)	
EFS/DFS	Median, months (95% CI)	31.6 (30.2, NE)	20.8 (14.0, 26.7)	NR (34.1, NE)	17.0 (14.3, 22.0)	NR (31.9, NE)	25.9 (18.9, NE)	NR (28.9, NE)	18.4 (13.6, 28.1)	58.7 (39.2, NE)	34.9 (28.6, NE)	NR (36.1, NE)	35.3 (29.0, NE)
	HR (95% CI)	**0.63 (0.45, 0.87)**		**0.58 [h] (0.46, 0.72)**		**0.68 (0.53, 0.88)**		**0.58 (0.42, 0.81)**		**0.73 (0.60, 0.89)**		**0.66 (0.50, 0.88)**	
	p-value (alpha)	0.0052 (0.0262)		< 0.0001 (0.0092)		0.004 (0.009)		0.00025		-		0.004	
OS	Median, months (95% CI)	-	-	NR (NE, NE)	52.4 (45.7, NE)	-	-	-	-	-	-	NR [6, k] (NE, NE)	NR [6, k] (NE, NE)
	HR (95% CI)	0.57 [i] (0.38, 0.87)		0.72 [j] (0.56, 0.93)		-		-		-		0.71 [6, k] (0.49, 1.03)	
	p-value (alpha)	0.0079 (0.0033)		0.0103 (0.0109)		-		-		-		-	

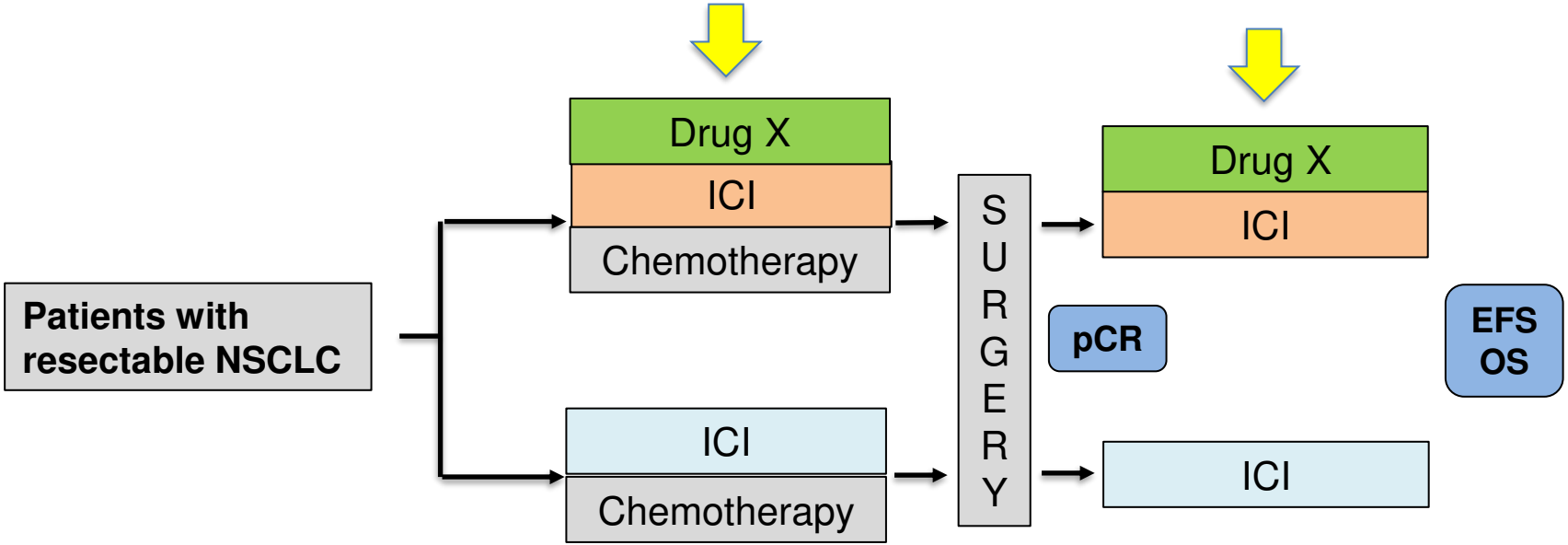
Abbreviations: Atezo=atezolizumab; chemo=platinum-based chemotherapy; CI=confidence interval; DFS=disease-free survival; Durva=durvalumab; EFS=event-free survival; HR=hazard ratio; IQR=inter-quartile range; *n*=number; NA=not applicable; NE=not estimable; Nivo=nivolumab; NR=not reached; NSCLC=non-small cell lung cancer; OS=overall survival; pCR=pathologic complete response; PD-(L)1=programmed death (ligand) 1; Pembro=pembrolizumab; TC=tumor cells.

[1] Heymach J,et al. *N Eng J Med,* 2023;398(18):1672-84. [2] Cascone T. ESM0 2023; LBA1. [3] Wakelee H, et al. *N Eng J Med,* 2023;389(6):491-503. [4] O'Brien M, et al. *Lancet Oncol.* 2022;23:1274-86. [5] Felip E, et al. *Lancet.* 2021;398:1344-57. [6] Felip E, et al. *Ann Oncol.* 2023;34(10):907-19.

[a] Based on data provided in the product labels for the respective anti-PD-(L)-1-based agents except where specific references are cited. [b] Results at the first interim analysis of AEGEAN. [c] Results at the interim analysis of CheckMate-77T. [d] At IA2 for patients in KEYNOTE-091 who received prior adjuvant chemotherapy (86% of the overall intention-to-treat population in both arms). [e] All patients in IMpower010 received prior adjuvant chemotherapy. [f] Based on the American Joint Committee on Cancer TNM 7th staging edition. [g] Based on the American Joint Committee on Cancer TNM 8th staging edition. [h] EFS results at the interim analysis for EFS which corresponds with the pre-specified first interim analyses for OS. [i] In CheckMate-816, 26% of patients had died at the time of EFS interim analysis. [j] In KEYNOTE-671, OS results as of the pre-specified second interim analysis. [k] In Impower010, 19% of patients had died at the time of DFS interim analysis and the OS HR was based on an exploratory analysis.

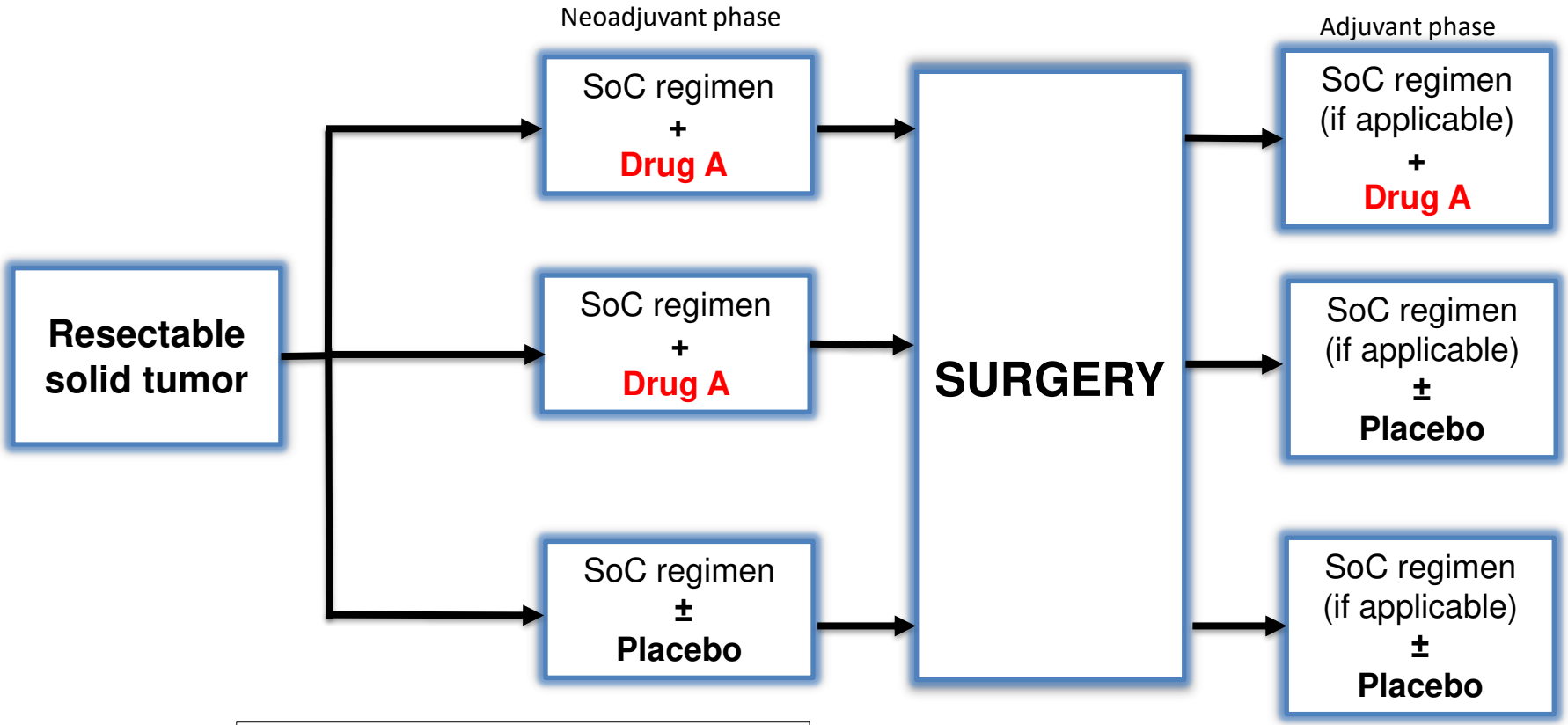
Add-on Designs in Resectable NSCLC

- Despite remaining questions on optimal regimen and concern for overtreatment, add-on designs are being proposed
- Raises potential for increased toxicity with unknown benefit



Abbreviations: EFS=event-free survival; ICI=immune checkpoint inhibitor; NSCLC=non-small cell lung cancer; OS=overall survival; pCR=pathologic complete response.

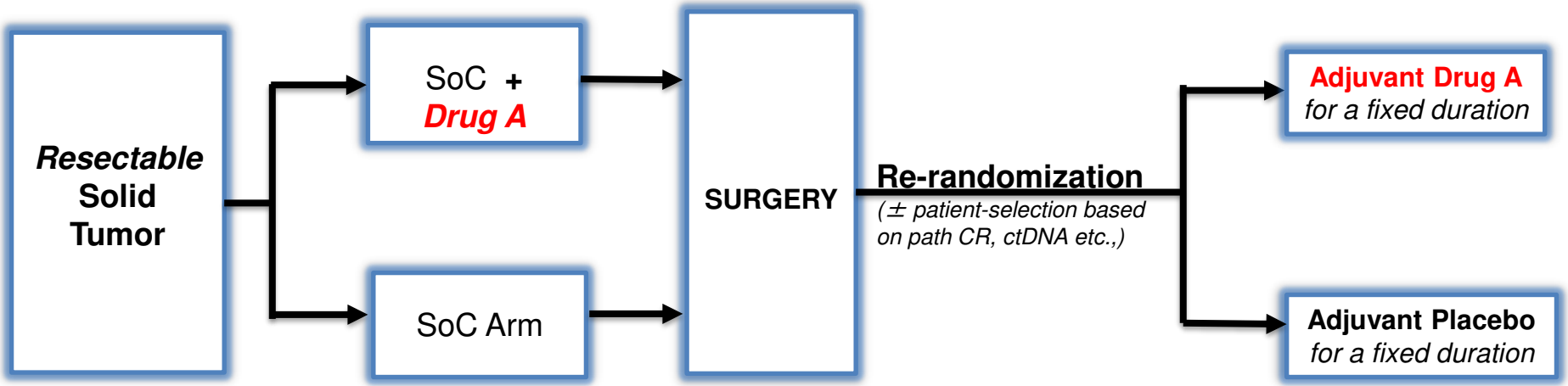
Three-arm design of perioperative trials evaluating new product '*Drug* A' as add-on to SoC



Abbreviations: SoC=standard of care.

Alternative trial designs to isolate the treatment effects of neoadjuvant and adjuvant phases

- Upfront randomization to receive investigational regimen *vs* SoC in neoadjuvant phase
- Re-randomization to investigational product *vs.* placebo/SoC in adjuvant phase



Abbreviations: ctDNA=circulating tumor deoxyribonucleic acid; path CR=pathologic complete response; SOC=standard of care.

Well-designed patient-centric perioperative trials ***that isolate contributions of neoadjuvant and adjuvant treatment phases*** present several opportunities including…

- Clinical benefit of each treatment phase in '*add-on*' and *'replacement'* therapeutic strategies
- Clear assessment of the added toxicity of the additional/prolonged therapy that may be unnecessary for some patients
- Development of early endpoints of clinical benefit, e.g., path CR, for regulatory purposes
- Development of biomarkers, e.g., ctDNA, to aid treatment optimization strategies in perioperative treatment settings

Abbreviations: ctDNA=circulating tumor deoxyribonucleic acid; path CR=pathologic complete response.

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- Angela James

AACR

- Rukiya Umoja
- Jon Retzlaff
- Nicholas Warren
- Tristen Tellman

FDA-AACR Workshop on

HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES

May 9, 2024 | Bethesda, MD

Biomarker-Guided Perioperative Clinical Trials: The emerging role of liquid biopsies

Valsamo Anagnostou, MD, PhD
Associate Professor
Leader, Precision Oncology Analytics
Co-leader, Molecular Tumor Board & Lung Cancer Precision Medicine Center of Excellence
Director, Thoracic Oncology Biorepository, Sidney Kimmel Cancer Center
Johns Hopkins School of Medicine, Baltimore, MD

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Disclosure Information

Valsamo Anagnostou

I have the following relevant financial relationships to disclose:

Consultant for: Astra Zeneca and Neogenomics

Grant/Research support (to Johns Hopkins University) from: Astra Zeneca, Personal Genome Diagnostics, Delfi Diagnostics, Bristol Myers Squibb

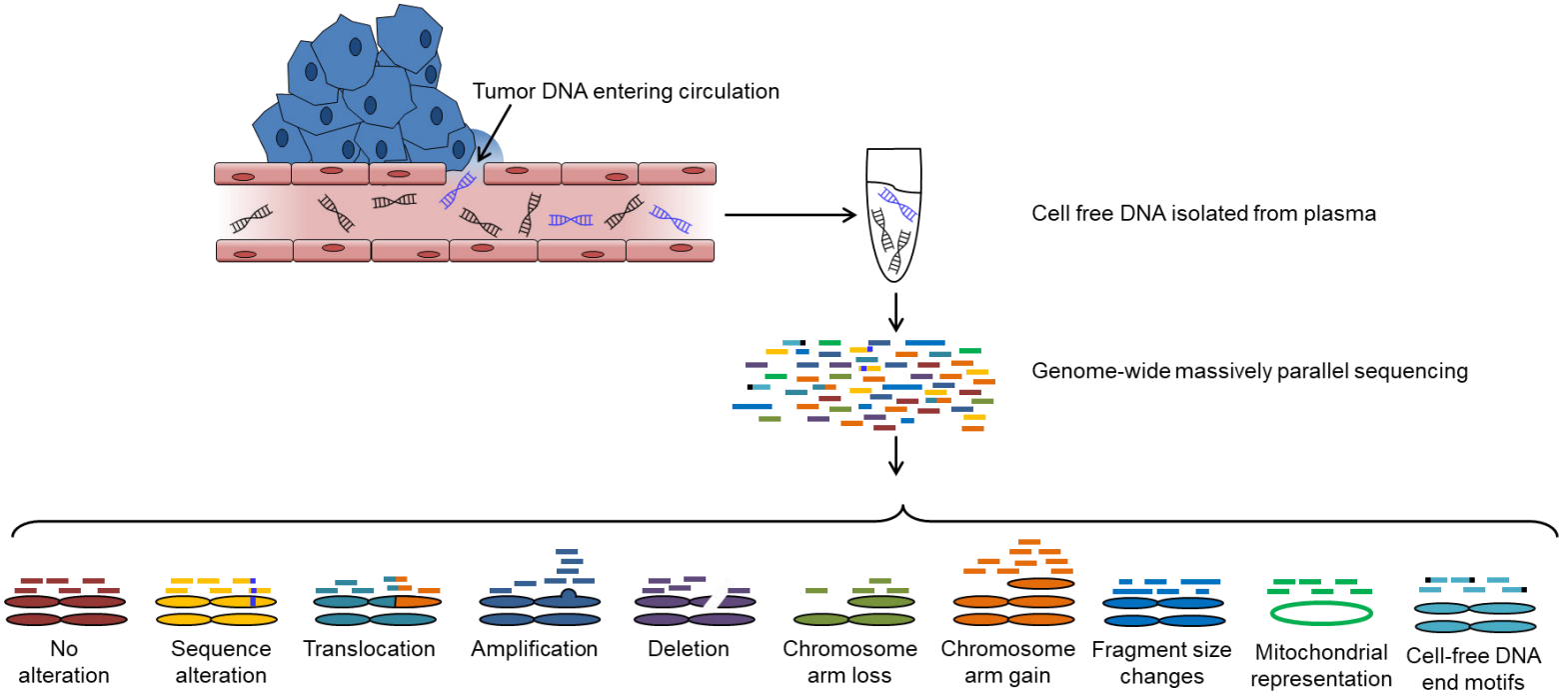
Honoraria from: Foundation Medicine, Personal Genome Diagnostics

- and -

My additional financial relationship disclosures are:

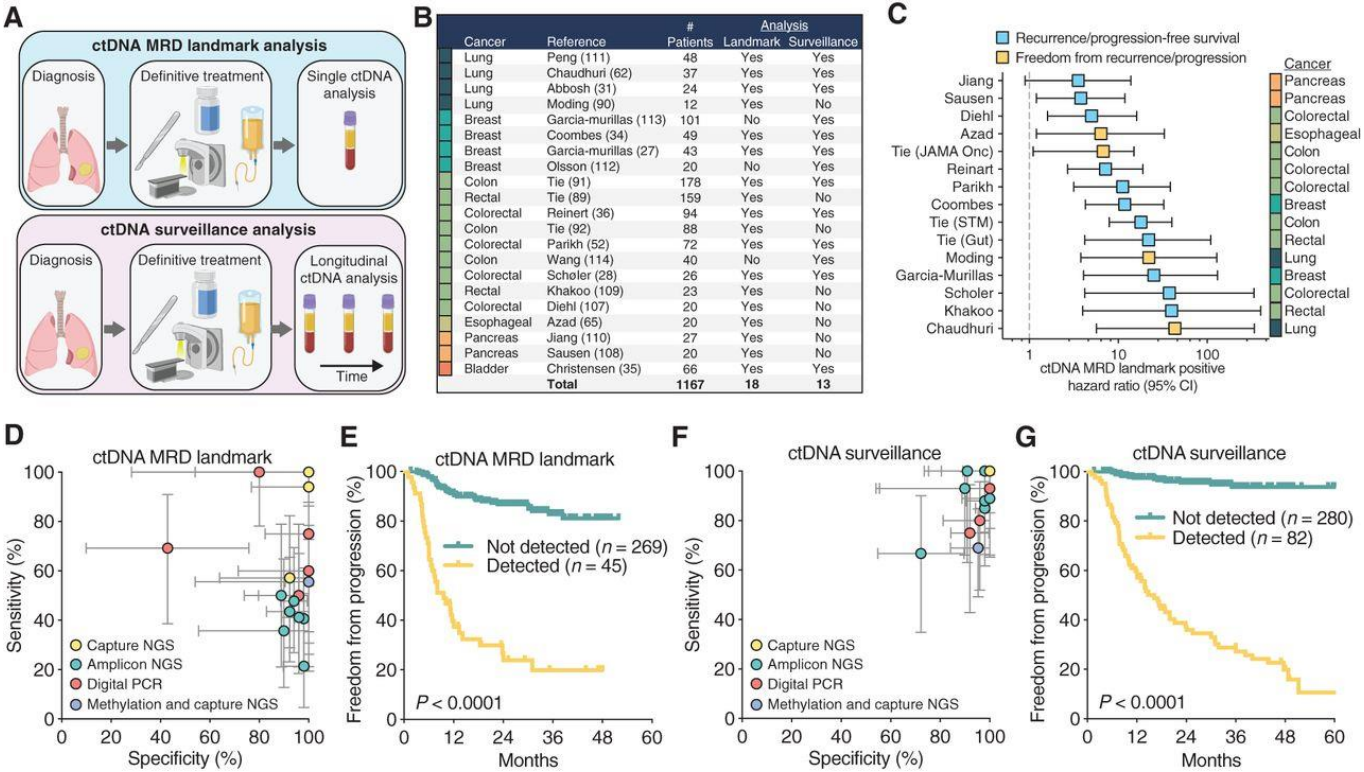
I am an inventor on patent applications (63/276,525, 17/779,936, 16/312,152, 16/341,862, 17/047,006 and 17/598,690) submitted by Johns Hopkins University related to cancer genomic analyses, ctDNA therapeutic response monitoring and immunogenomic features of response to immunotherapy that have been licensed to one or more entities. Under the terms of these license agreements, the University and inventors are entitled to fees and royalty distributions.

Liquid biopsy approaches for sensitive and specific detection of cancer



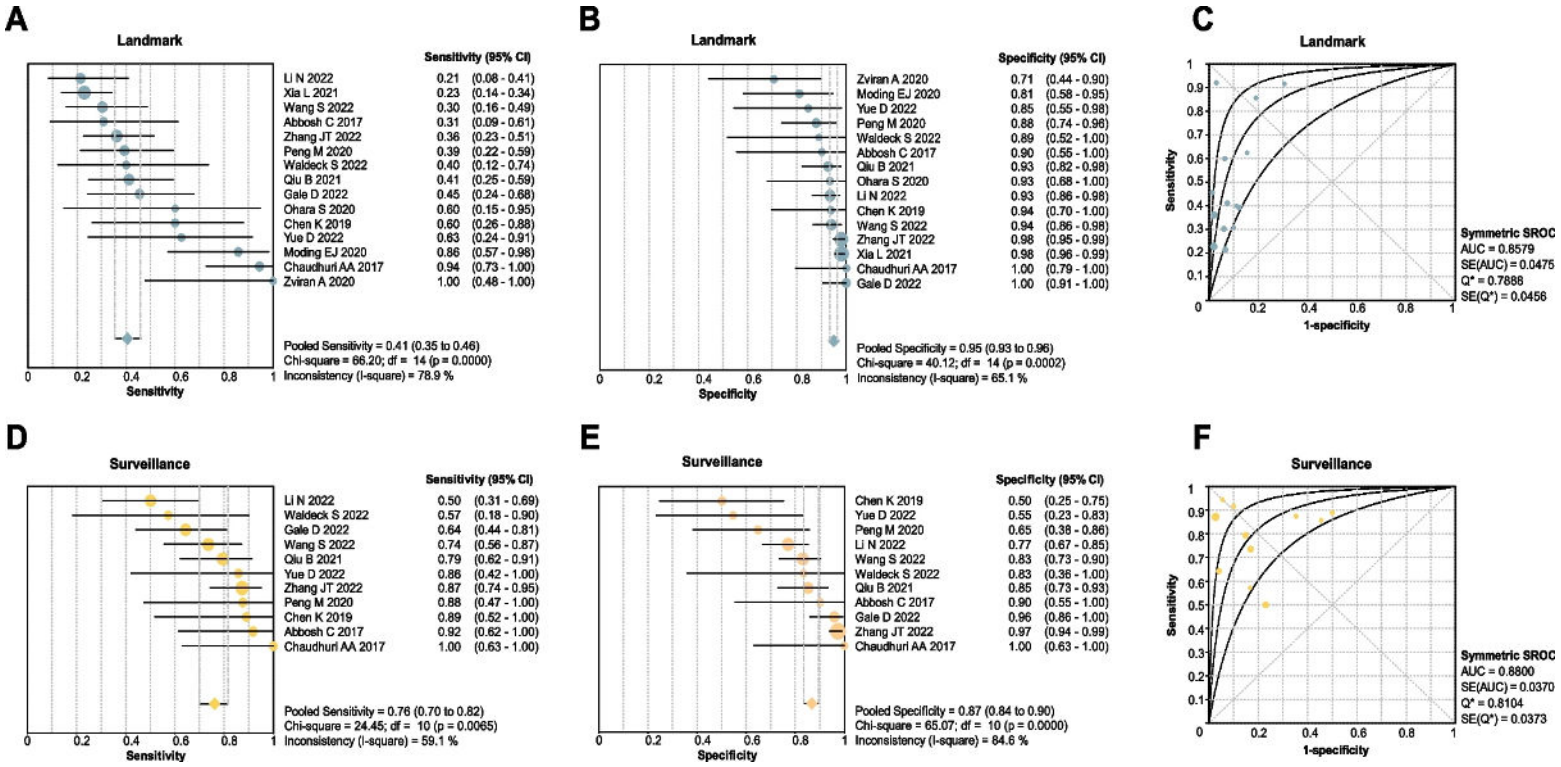
Bruhm et al., *Nat Genet*, 2023, Mattox et al., *Cancer Discov*, 2023, Wang et al., *PNAS*, 2023, Sivapalan et al., *Clin Can Res*, 2023, Foda et al., *Cancer Discov*, 2023 Cohen et al., *Nat Biotechnol*, 2021, Cristiano et al., *Nature*, 2019, Anagnostou et al., *Can Res*, 2019, 2020, Cohen et al., *Science*, 2018, Phallen et al., *Science TM*, 2017

ctDNA MRD is prognostic



Moding et al., *Cancer Discov,* 2021

Clinical sensitivity of ctDNA MRD



Zhong et al., *BMC Medicine*, 2023

Landmark ctDNA MRD for NSCLC

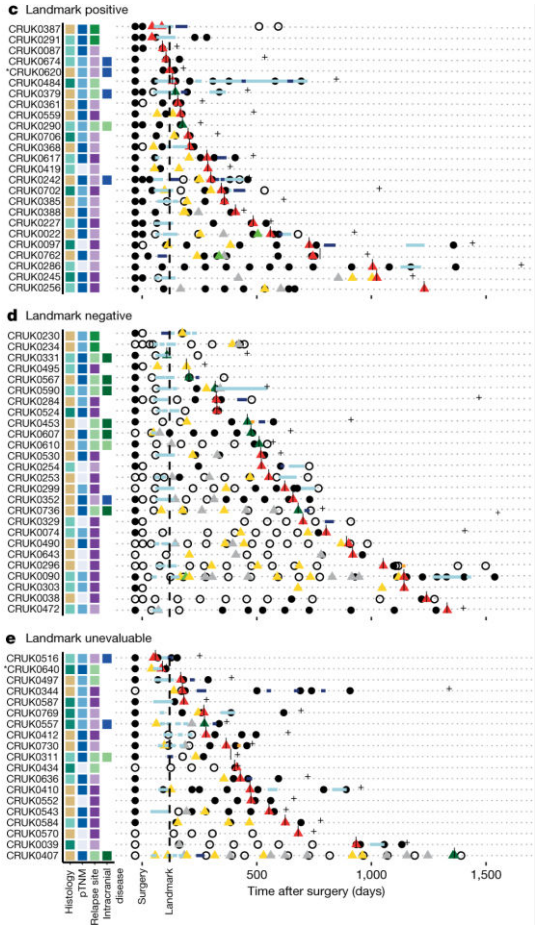
ctDNA MRD+
Recurrence +
(n=25)

Clinical sensitivity 49%

ctDNA MRD-
Recurrence +
(n=26)

51% discordance

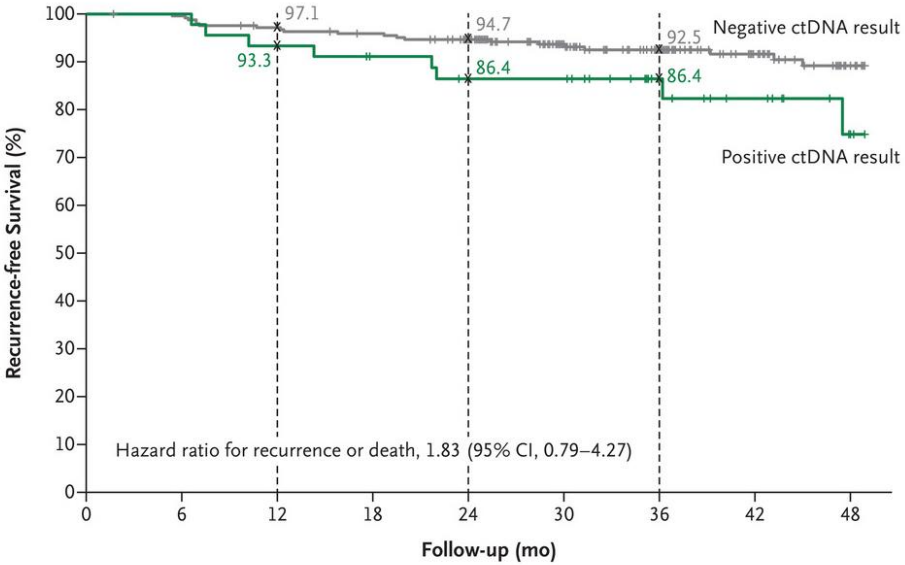
ctDNA in-evaluable
Recurrence +
(n=19)



- Tumor-informed anchored multiplex PCR enrichment
- Assay sensitivity using a 50-variant panel at 0.01% VAF was > 90% at DNA input > 20 ng
- LOD 95 VAF 0.008% (80 PPM)
- **Landmark ctDNA MRD assessed within 120 days of surgery: 25% ctDNA MRD+**
- **Clinical sensitivity 49% (fraction of ctDNA MRD+ among those who recurred)**
- Landmark ctDNA MRD+ patients had a hazard ratio of 5.3 for OS and a hazard ratio of 6.8 for freedom from relapse relative to MRD- (P<0.001)
- Landmark-positive patients had the longest lead times (228 days)
- Patients relapsing in the first year of surgery are more likely to be MRD positive

Abbosh et al., *Nature*, 2023

What does ctDNA MRD “-” mean?

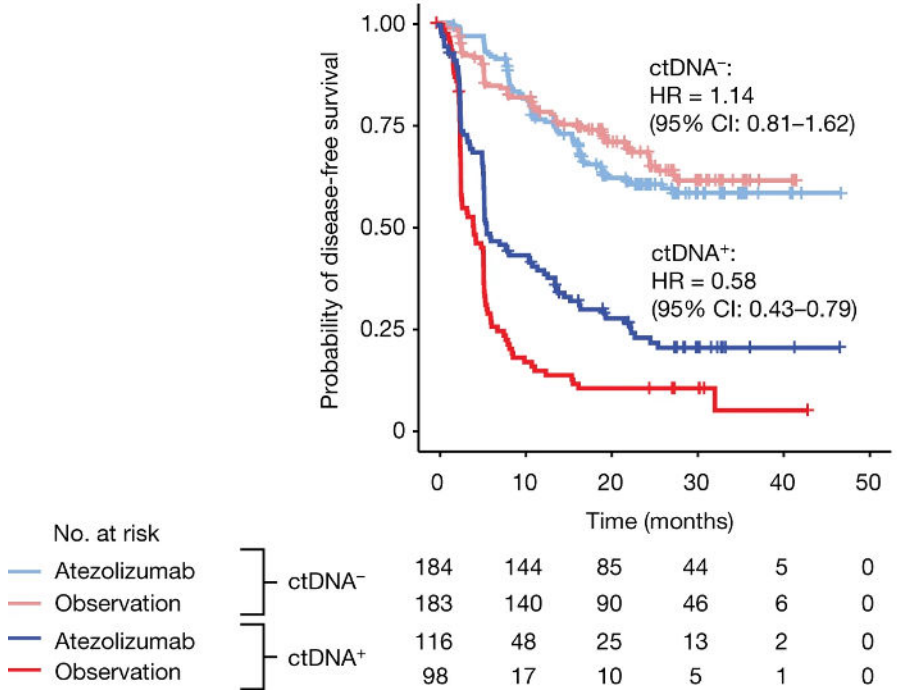


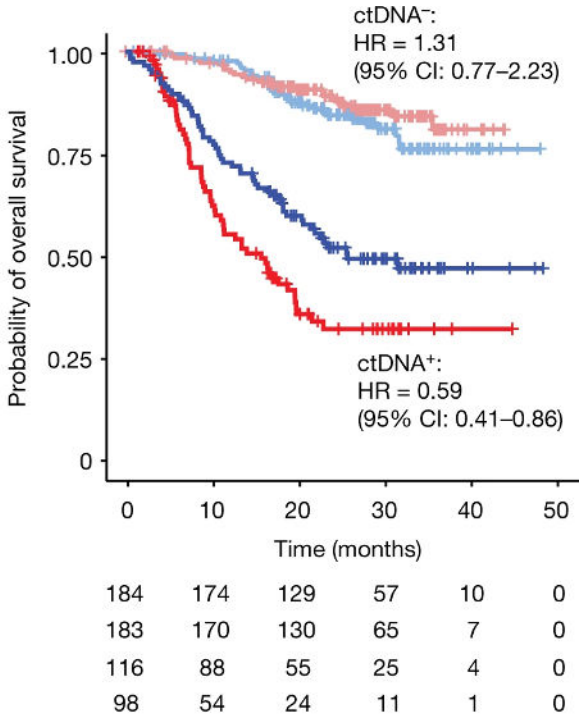
No. at Risk									
Negative ctDNA result	246	244	236	231	220	169	131	93	55
Positive ctDNA result	45	45	42	39	36	36	22	16	9

- In the ctDNA-guided group of the DYNAMIC trial, recurrence or death occurred in 15 of 246 ctDNA-negative patients (6%).
- **A fraction of ctDNA MRD-negative patients experience disease recurrence.**

Tie et al., *NEJM,* 2022

IMvigor010: ctDNA MRD is predictive for adjuvant immunotherapy





Powles et al., *Nature*, 2021

IMpower-010: Adjuvant IO may delay ctDNA MRD emergence

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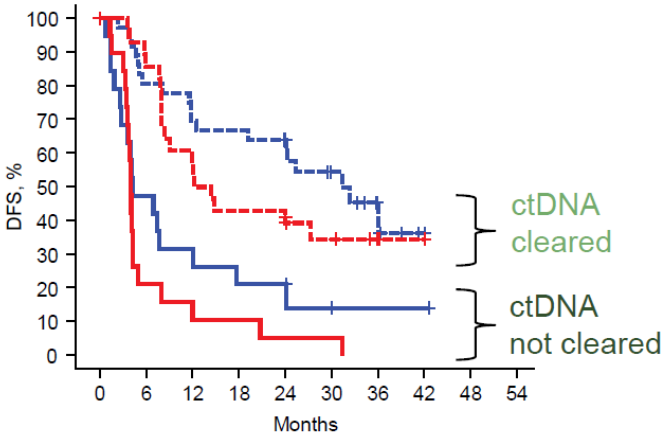
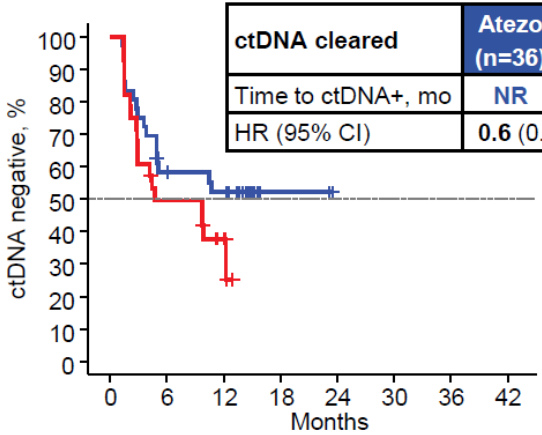
DFS by treatment arm and post-chemo ctDNA clearance status



ctDNA cleared	Atezo (n=36)	BSC (n=28)
mDFS, mo	31.3	13.3
HR (95% CI)	**0.7** (0.37, 1.34)	

ctDNA not cleared	Atezo (n=19)	BSC (n=20)
mDFS, mo	4.2	3.9
HR (95% CI)	**0.67** (0.34, 1.32)	

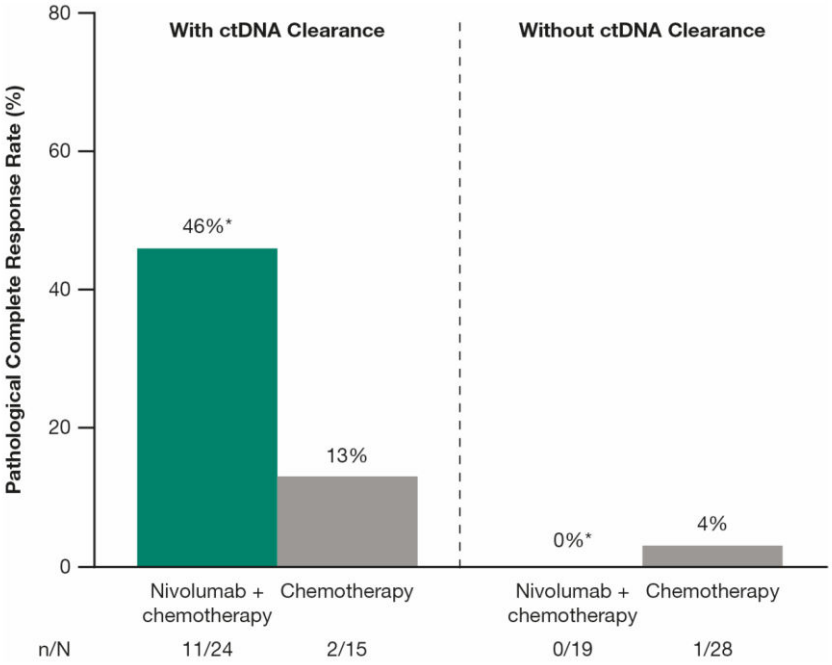
Time to ctDNA+ by treatment arm



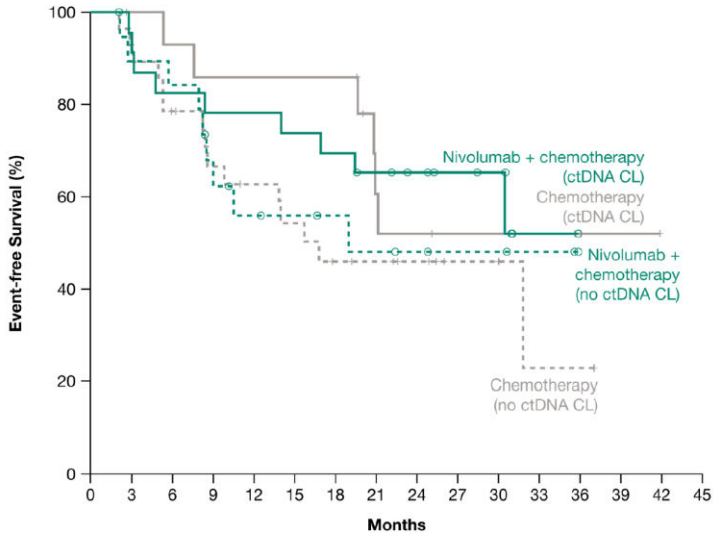
ctDNA cleared	Atezo (n=36)	BSC (n=28)
Time to ctDNA+, mo	NR	4.7
HR (95% CI)	**0.6** (0.31, 1.17)	

Felip et al., presented at *ESMO Immuno-Oncology*, 2022

Pre-op ctDNA clearance predicts pCR and EFS with neoadjuvant chemo-IO

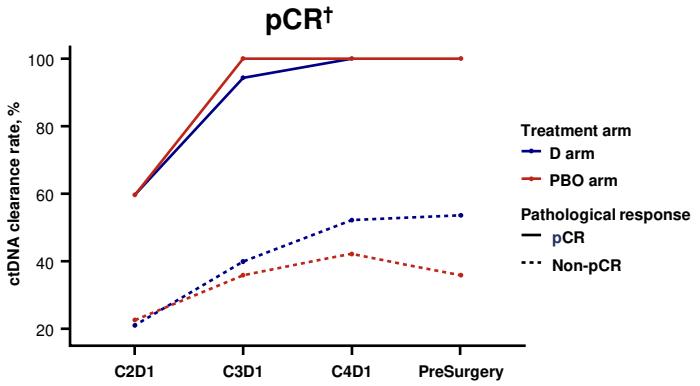


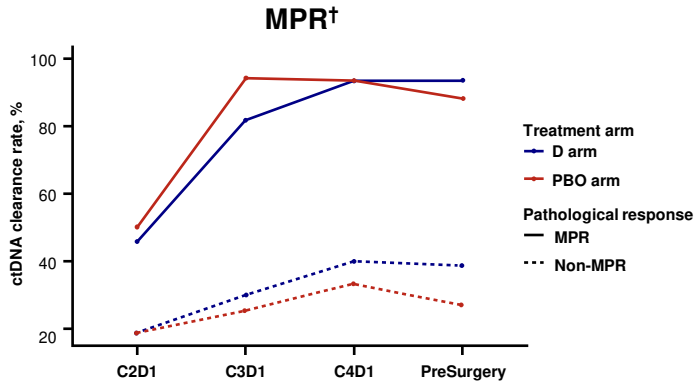
	Nivolumab + chemotherapy		Chemotherapy	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
Median EFS, mo (95% CI)	NR (16.8–NR)	18.9 (8.3–NR)	NR (19.6–NR)	16.8 (8.3–NR)
HR (95% CI)	0.60 (0.20–1.82)		0.63 (0.20–2.01)	



Forde et al., *NEJM*, 2022

Pre-op ctDNA clearance predicts pCR





- Patients without ctDNA clearance were unlikely to achieve pCR (NPV > 84.0% at C2D1 in both arms)
- Patients who achieved ctDNA clearance in the D arm vs the PBO arm were more likely to achieve pCR (PPV = 50.0% vs 14.3% at C2D1)

Predictive value of ctDNA clearance at different timepoints for pCR

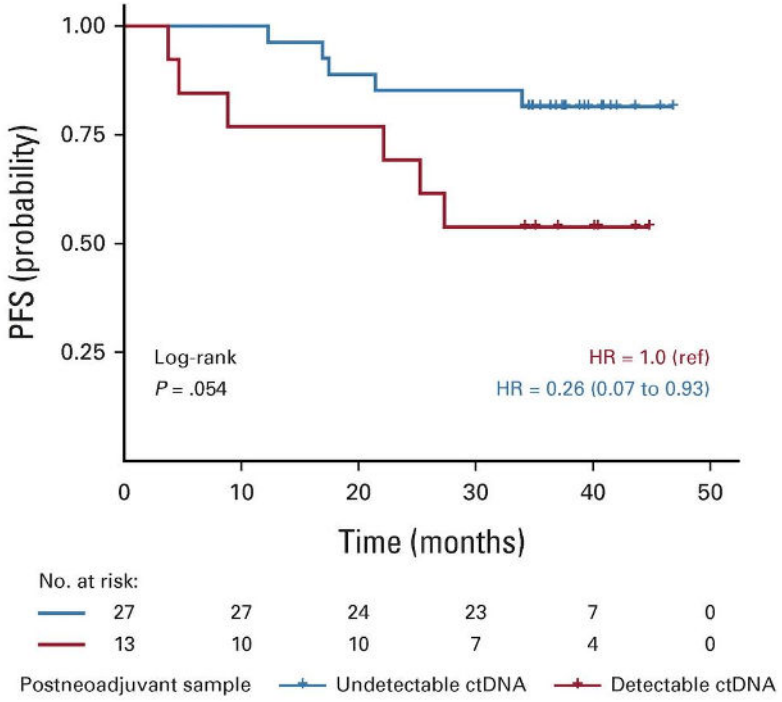
D arm	pCR	
	PPV	NPV
C2D1	50.0%	84.9%
C3D1	43.6%	97.1%
C4D1	40.5%	100.0%
PreSurgery	41.5%	100.0%

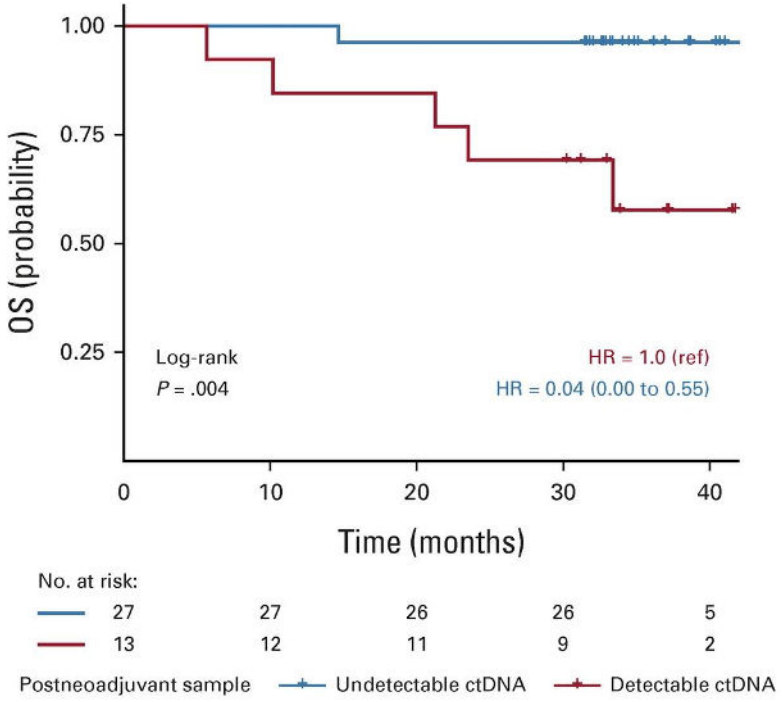
PBO arm	pCR	
	PPV	NPV
C2D1	14.3%	96.9%
C3D1	18.2%	100.0%
C4D1	18.2%	100.0%
PreSurgery	19.4%	100.0%

*In the BEP, pCR (25.6% vs 6.3%) and MPR (44.4% vs 18.8%) rates were higher in the D arm vs the PBO arm. †The plots include all evaluable patients at each timepoint. NPV, negative predictive value; PPV, positive predictive value.

Reck et al., *presented at ESMO 2023*

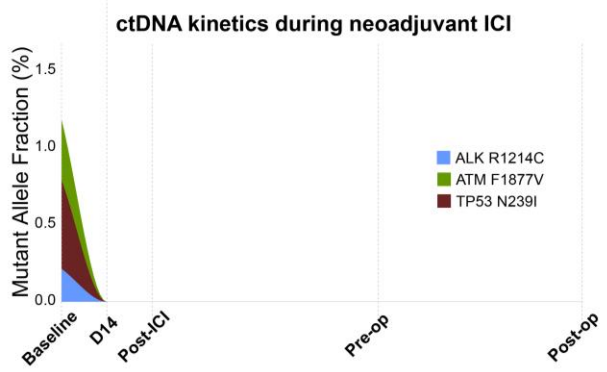
Post-neoadjuvant IO ctDNA clearance is associated with overall survival

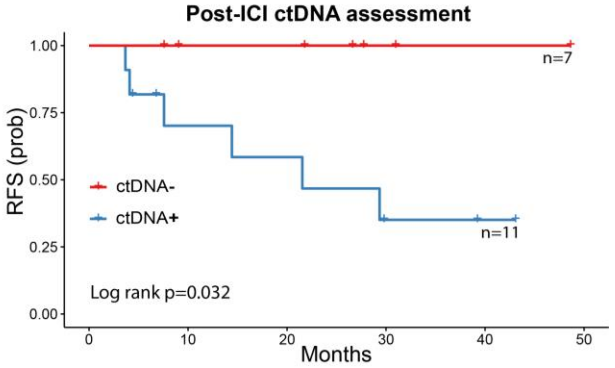


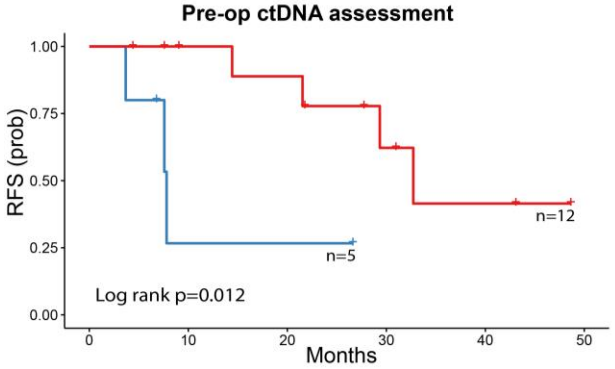


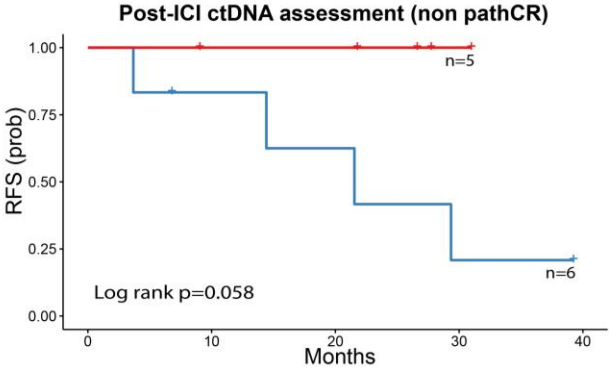
Provencio et al., *JCO,* 2022

ctDNA assessment may help refine the heterogeneity of non pCR



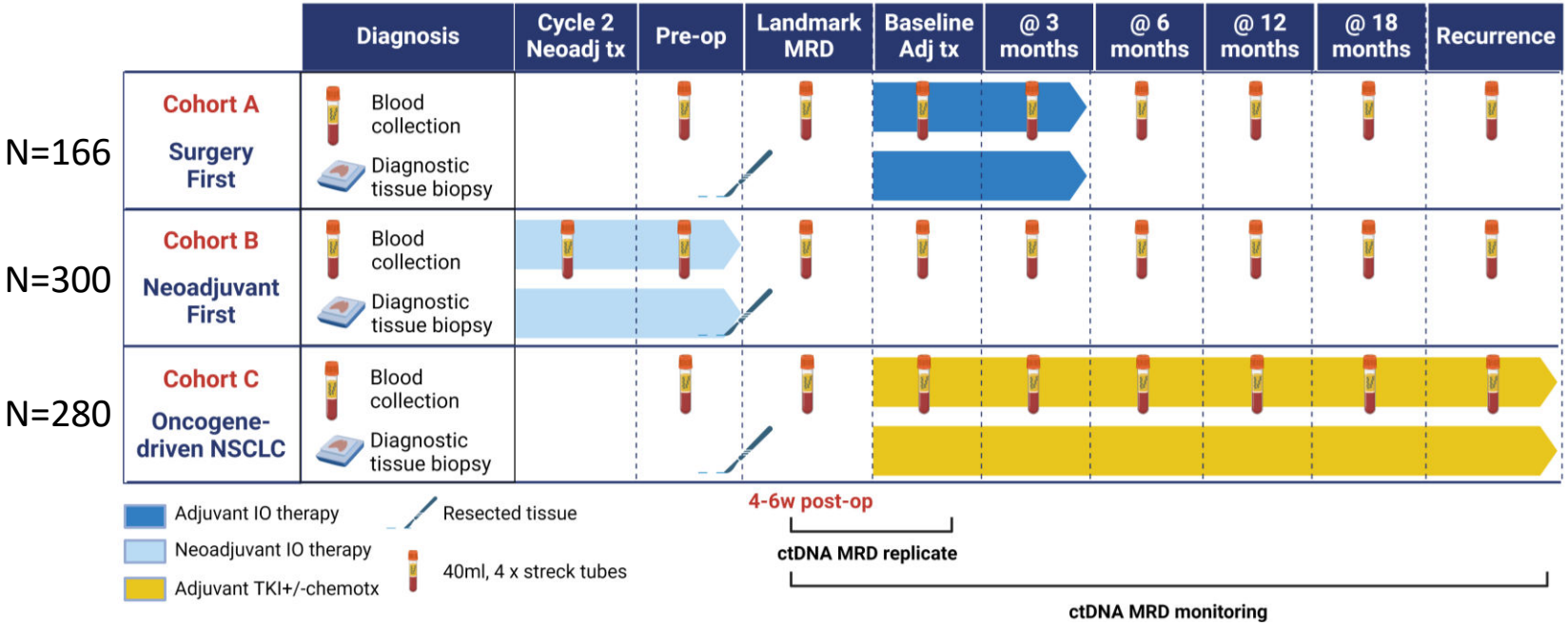






Kelly, Landon et al., *Nat Med,* 2024

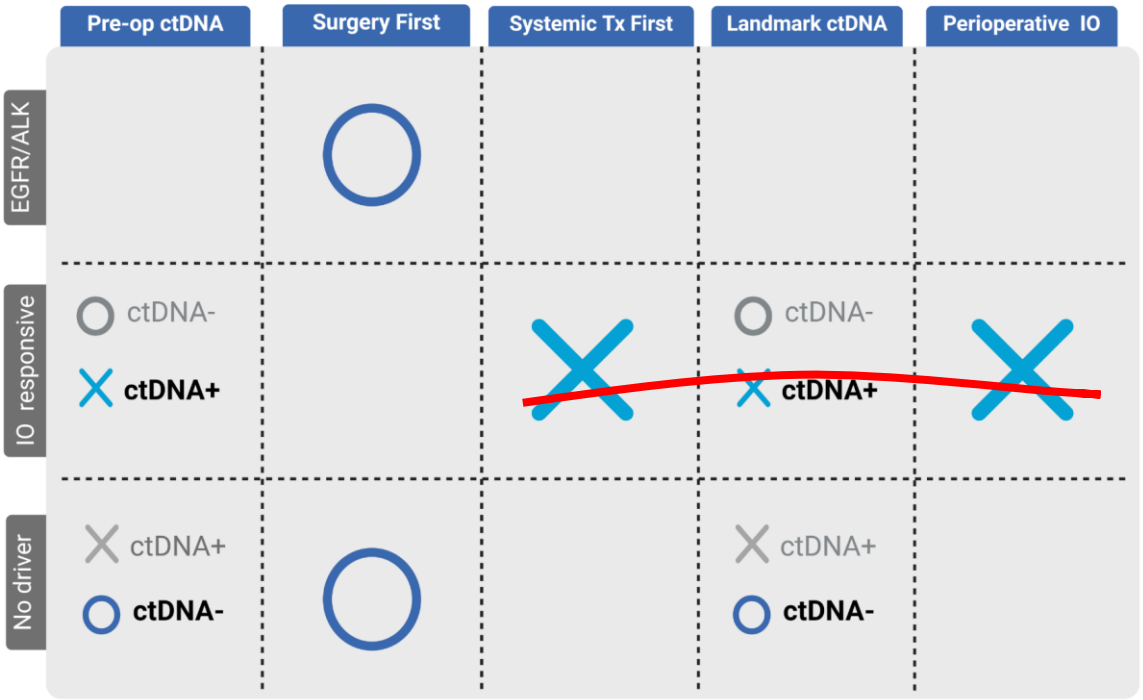
The Tic Tac Toe trial



Primary endpoint: ctDNA MRD correlation with 2-year DFS/EFS rate

Secondary endpoint: ctDNA MRD correlation with 2-year OS rate

ctDNA MRD holds promise in navigating the evolving therapeutic landscape of early stage cancers



- ctDNA MRD may inform stratification and enrichment strategies in clinical trials for patients with early stage cancers.
- ctDNA MRD assays continue to evolve and are reaching an analytical sensitivity suitable for clinical implementation.
- Critical need to validate the clinical sensitivity of ctDNA MRD.

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@ValsamoA @MolecularOncLab @HopkinsThoracic @Hopkins_MTB

FDA-AACR Workshop on

HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES

May 9, 2024 | Bethesda, MD

SMART Cancer Clinical Trials

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FDA U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research

Disclosure Information

Kelley Kidwell

I have the following relevant financial relationships to disclose:

Grant/Contract support from PCORI, FDA, NIH.

Co-owner of smart-workshops.com

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How Do Providers Treat Individuals?

- Ongoing care and follow up
- Therapies are not set in stone
- Therapies can be changed, intensified, discontinued
- Treatment decisions can be based on health progress, treatment adherence, side effects, and patient choice
- Follow-up therapy based on experience, guidelines, clinical trials

Dynamic Treatment Regimen

- DTR, a.k.a. adaptive intervention, adaptive treatment strategy, stepped care, treatment policies
- Sequence of **individually tailored decision rules** that specify whether, how and/or when to alter the intensity, type, dose or delivery of intervention at critical decision points in the course of care, prevention, implementation, or education
- **Guide/Formula for treatment**
- **Evidence-based**
- Goal: operationalize sequential decision making with the aim of improving clinical practice

DTR Example: Chronic Lymphocytic Leukemia

- First start with combination treatment I+O+V.
- If there is not minimal residual negative disease with complete remission at one year, continue I maintenance therapy.
- If there is minimal residual negative disease with complete remission at one year, then discontinue I therapy.

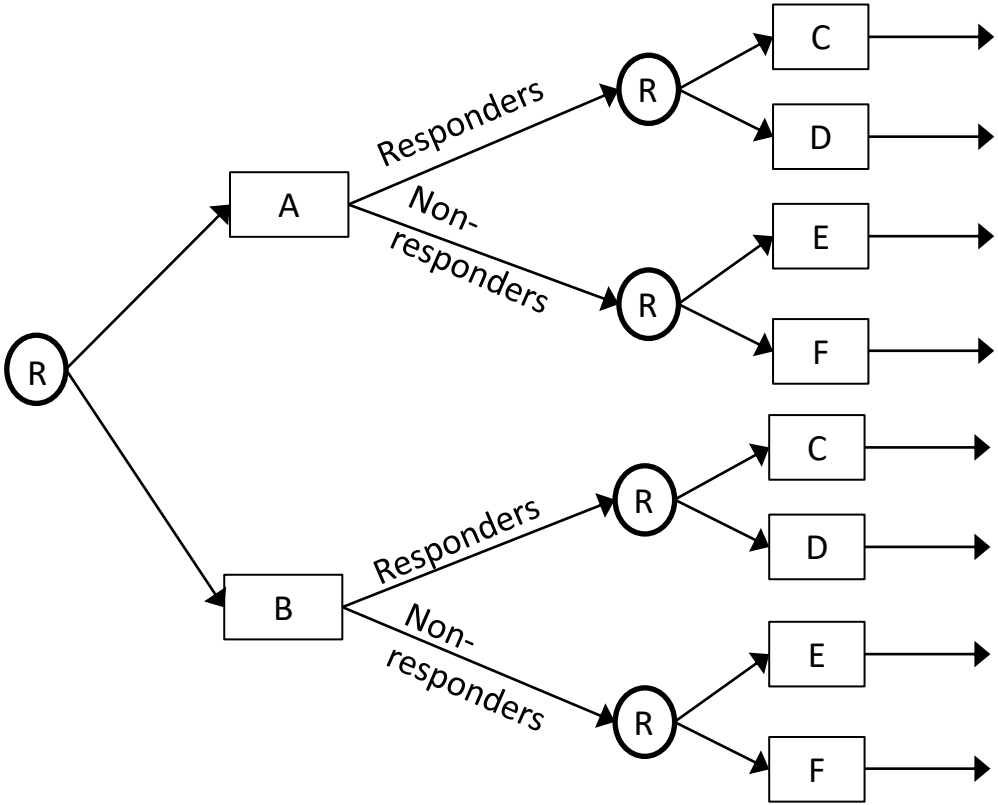
Questions to Consider to Develop DTR

1. What is the best **first-line** intervention?
2. What is the best **measure of response** to see if the intervention is successful?
3. When is the best **time to measure response** to the initial intervention?
4. What is the best **subsequent** treatment among **non-responders**?
5. What is the best **subsequent** treatment among **responders**?

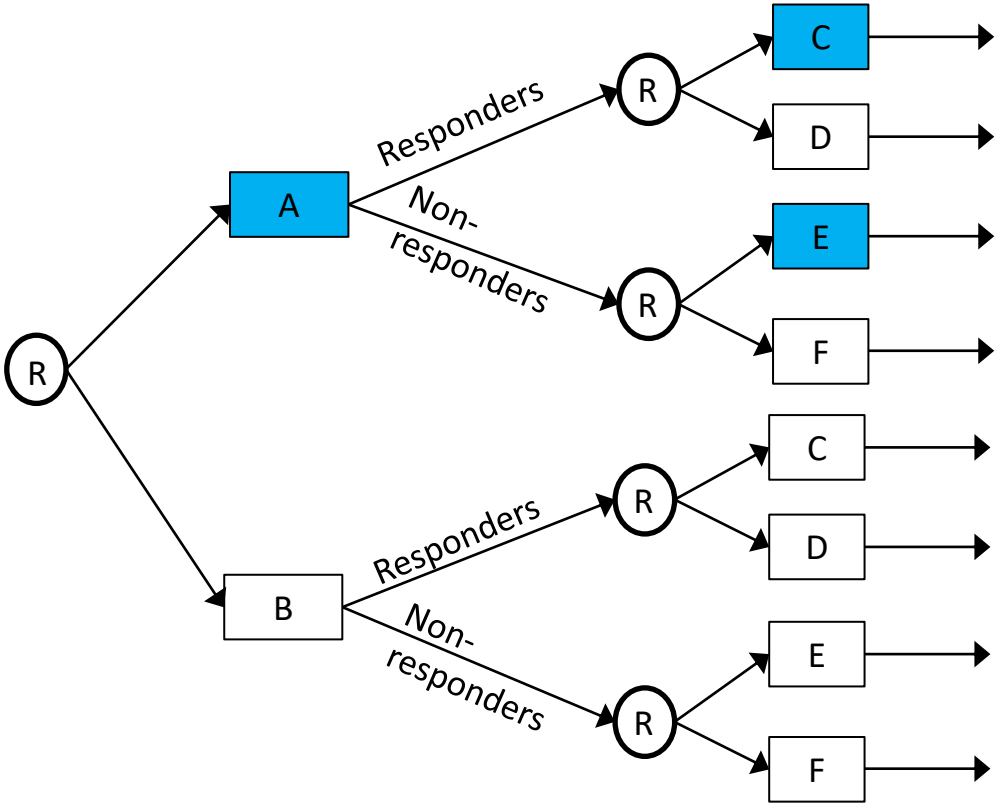
S.M.A.R.T.

- **S**equential, **m**ultiple **a**ssignment, **r**andomized **t**rial
- A type of **multi-stage randomized design**
- Trial participants are randomized to a set of treatment options at **critical decision points** over the course of treatment
  - Critical decisions occur in short time frame
- **All individuals** participate in all stages of the trial
- Subsequent randomization is based on information leading up to that point
- DTRs embedded in design
- Goal: **Develop/Construct effective DTRs**

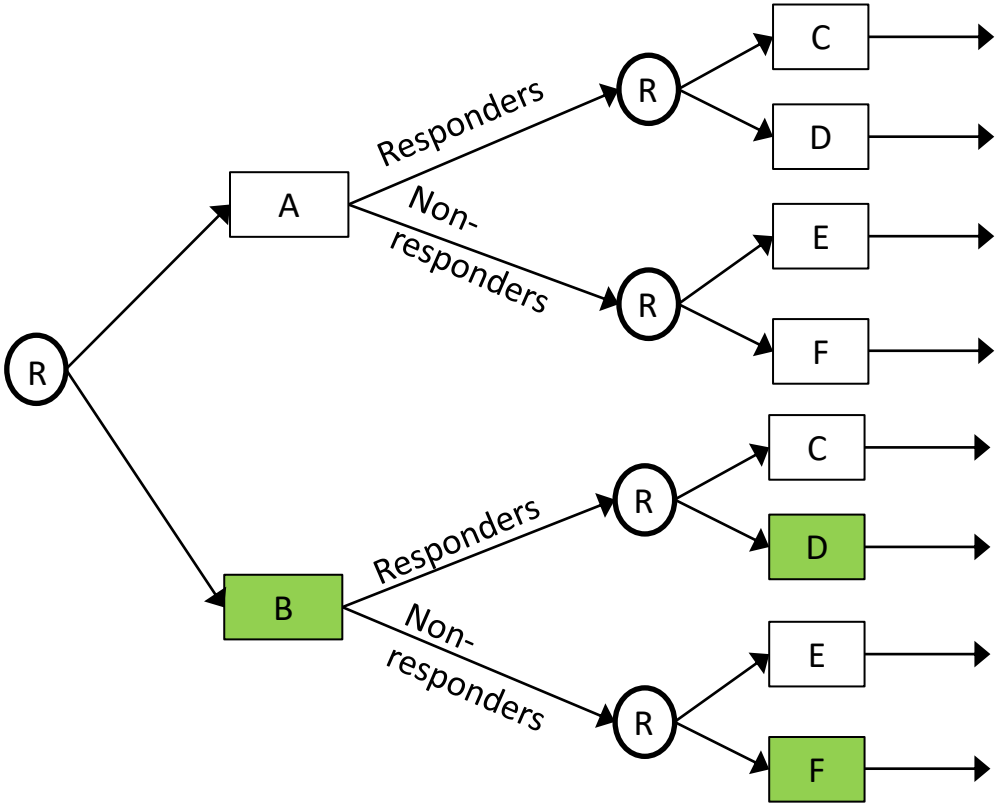
SMART Design: Example 1



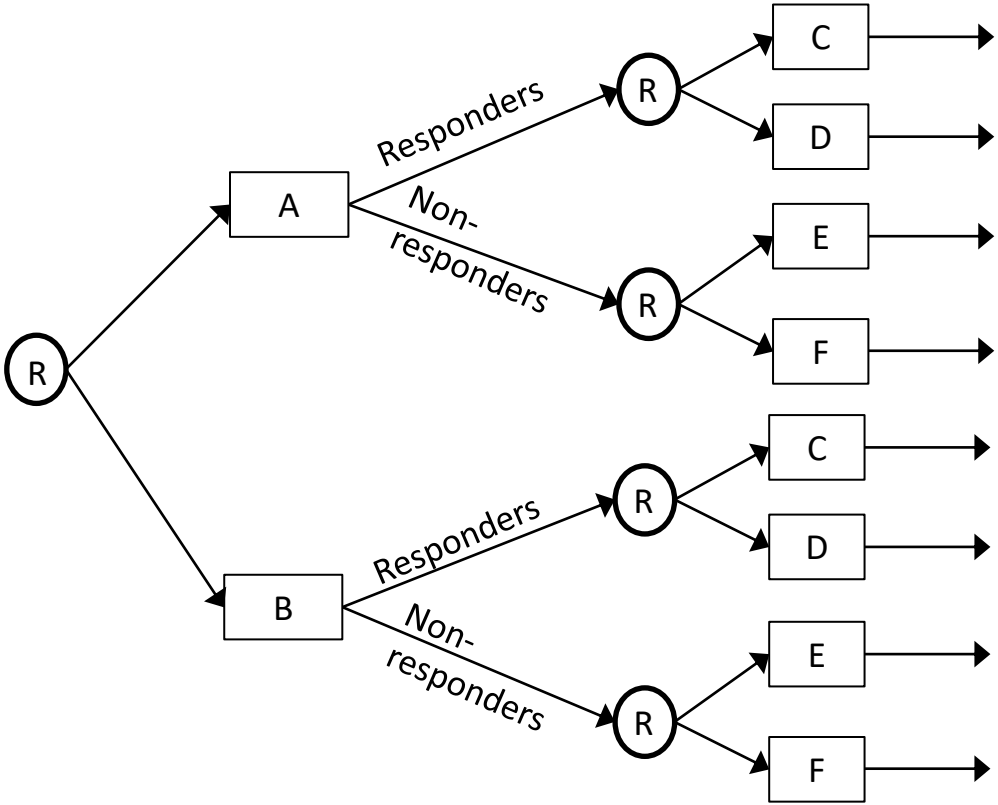
Embedded DTRs: Example 1



Embedded DTRs: Example 2



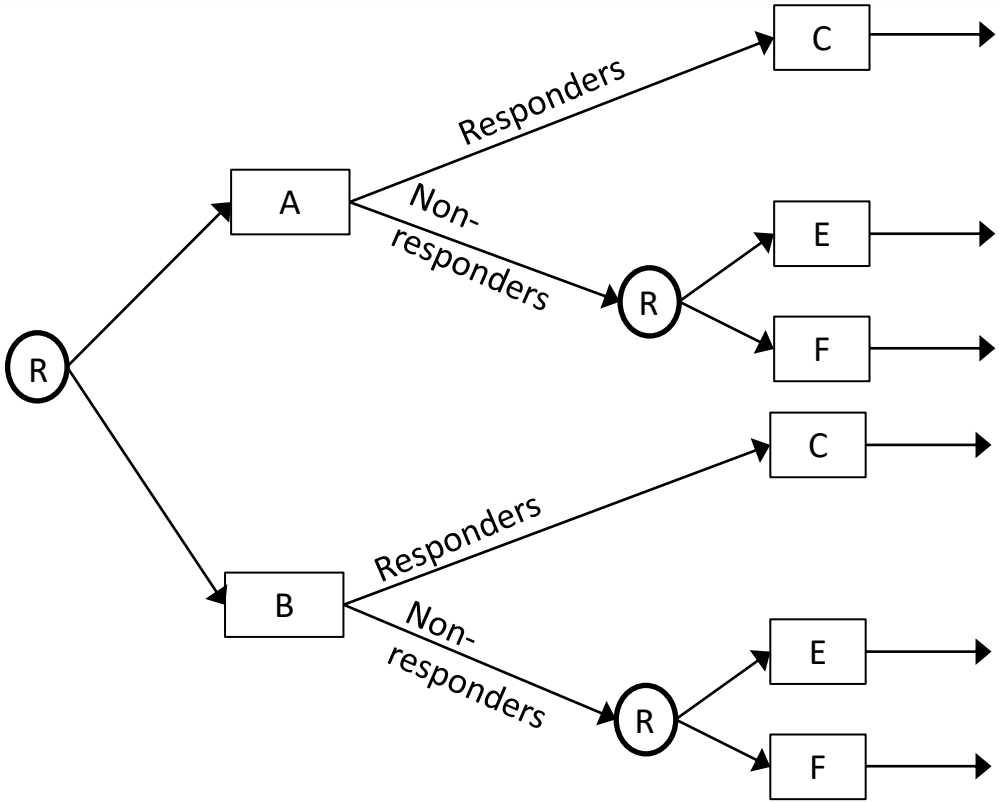
Number of Embedded DTRs: 8



A,C,E
A,C,F
A,D,E
A,D,F

B,C,E
B,C,F
B,D,E
B,D,F

SMART Design: Example 2, DTRs=4



A,C,E
A,C,F

B,C,E
B,C,F

SMART Benefits

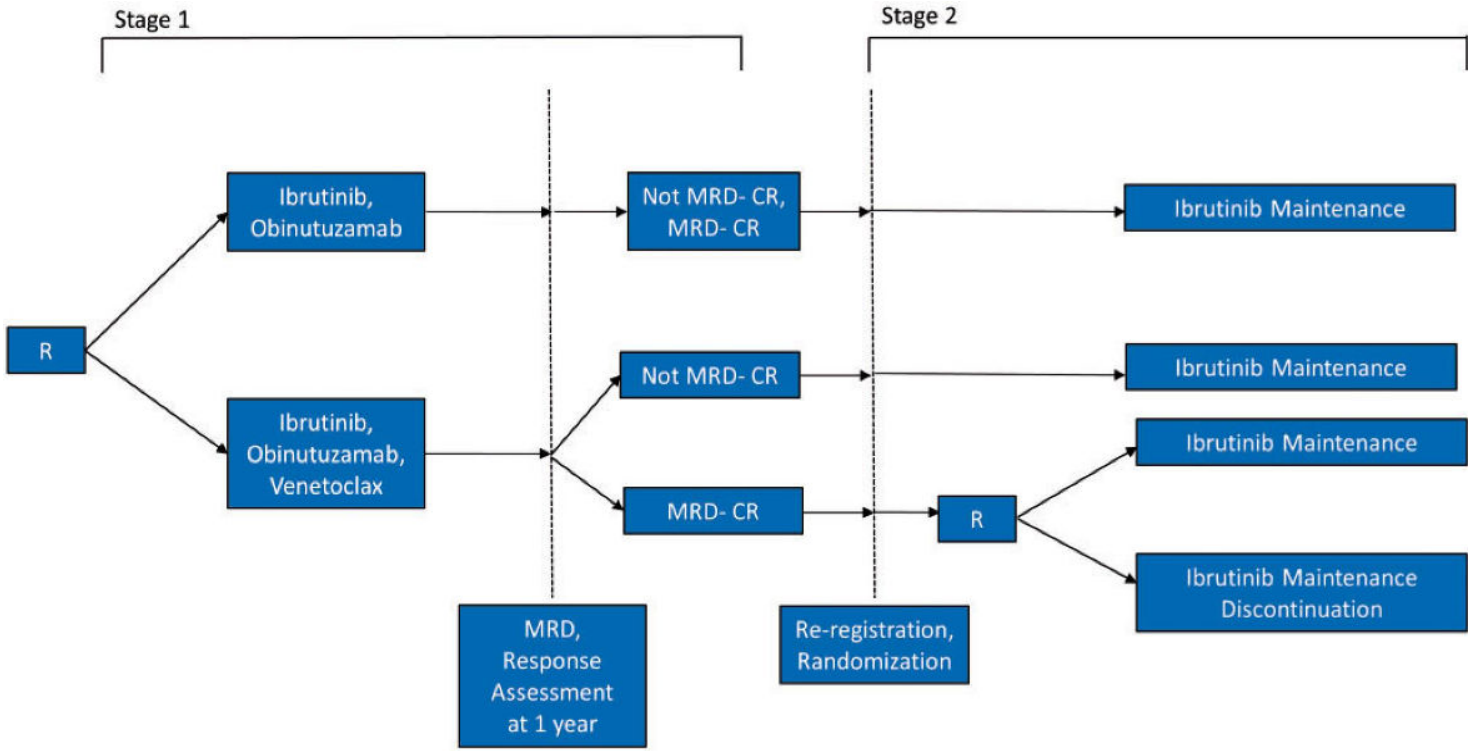
- **Delayed Effects** – treatment synergies or antagonisms
- **Prescriptive Effects** – initial treatment may elicit symptoms to better match individual to subsequent treatment
- **Sample Selection Effects** – individuals who enroll in, remain in or are adherent in a SMART may be different from those in other designs

SMART Example: Precursor to A041702

- Related to NCT03737981
- Design considered for Alliance trial A041702
- Outcome: Progression Free Survival (PFS)
- Objectives:
  - Does ibrutinib (I) + venetoclax (V) + Obinutuzumab (O) with ibrutinib maintenance (IM) have superior PFS compared to I+O+IM
  - Does treatment strategy of I+V+O+IM for patients without minimal residual disease complete response or I+V+O+IM discontinuation for patients with minimal residual disease complete response have superior PFS compared to I+O+IM
- N = 488

Ruppert et al. Annals of Oncology 30: 542–550, 2019 doi:10.1093/annonc/mdz053

SMART: 2 randomizations in sequence



Ruppert et al. Annals of Oncology 30: 542–550, 2019 doi:10.1093/annonc/mdz053

Why a SMART design?

- **Simultaneously address the effectiveness of treatments at each stage and the effectiveness of embedded adaptive interventions**
- Which sequential treatments work better than standalone treatment?
- Investigate the interplay between treatment strategies and disease development.
- Allows those who are doing well on initial therapy to stay on it.
- **Approximate clinical care**

Embedded Treatment regimens

1. Receive I+O, followed by IM [regardless of minimal residual disease complete response at one year].
2. Receive I+V+O, followed by IM [regardless of minimal residual disease complete response at one year].
3. Receive I+V+O, followed by IM if no minimal residual disease complete response at one year and discontinue IM if minimal residual disease complete response.

Comparing 3 vs 1 can determine if more aggressive initial therapy and discontinued therapy for patients with best responses is superior to less aggressive initial therapy with continued therapy for all patients.

Common SMART Study Aims

1. Minimal residual disease complete response rates between I+O vs. I+V+O at 1 year.

Comparison of initial treatments

2. Among those who start with I+V+O and reach minimal residual disease complete response, is PFS better for those who receive IM or discontinue IM?

Comparison of 2nd stage strategies

3. Estimate embedded (dynamic) treatment regimen effects and identify the most promising. Explore moderators of first and second stage treatment.

Building/comparing DTRs

Sample Size & Analysis Depends on Aim

- Aims that do not consider DTRs, use standard methods
  - Two arm comparison as usual
  - May need to up weight sample size by proportion of (non-)responders / subset data for analysis

- Aims that include DTRs: SMART specific methods
  - Account for restricted randomization, simultaneous estimation of DTR effects
  - Various applets and R packages exist (see https://d3c.isr.umich.edu/available-software/)

Logistics

- Consent (to potential multiple randomizations) once at start of SMART
- Randomize upfront or sequentially
- Consider viable DTRs: tolerability, missed response assement

- In analysis: do not compare treatment pathways; compare DTRs
  - SMART designs do not inherently increase bias to trial

SUMMARY

- **Dynamic treatment regimens** are evidence-based guidelines for clinical practice
- A **SMART** is a clinical trial design that can provide evidence for effective DTRs
- The **sample size** of a SMART is highly dependent on the primary aim; analytic methods depend on the objective
- **R packages and applets** are available to help in design and analysis for a SMART: (https://d3c.isr.umich.edu/software/ & other R packages e.g. DTR)

Resources: Articles & Texts

- Website
  - https://d3c.isr.umich.edu/experimental-designs/sequential-multiple-assignment-randomized-trials-smarts/
- Articles:
  - Kidwell KM, Almirall D. *Sequential, Multiple Assignment, Randomized Trial Designs*. JAMA. 2023;329(4):336–337. doi:10.1001/jama.2022.24324
  - Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. *A "SMART" design for building individualized treatment sequences.* The Annual Review of Clinical Psychology, 2012. 8:21-48.
  - Almirall, D., Nahum-Shani, I., Sherwood, N.E., Murphy, S.A. *Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research*. Translational behavioral Medicine, 2014. 4(3):260-274.
- Texts:
  - **Adaptive Treatment Strategies in Practice: Planning Trials and Analyzing Data for Personalized Medicine**. Ed. Kosorok & Moodie. 2016. ASA-SIAM.
  - **Dynamic Treatment Regimes: Statistical Methods for Precision Medicine**. Tsiatis, Davidian, Holloway, Laber. 2020. CRC Press.

Thank you!

Interested in learning more?

https://smart-workshops.com

- SMART Workshop, June 13-14, 10-330 ET – recorded if cannot attend synchronously
  - https://smart-workshops.com/smart-design-info
- Small sample SMART Workshop, Aug 13-14, 10-330 ET – recorded if cannot attend synchronously
  - https://smart-workshops.com/snsmart-design-info

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SESSION 1: CURRENT LANDSCAPE FOR PERIOPERATIVE TRIAL DESIGNS

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Session 1 Panel Discussion

- Feasibility of S.M.A.R.T trial designs
- Regulatory perspective on perioperative trials
- Patient-centric perioperative trials
- Industry perspective on perioperative trials
- Impact on clinicians' treatment decisions