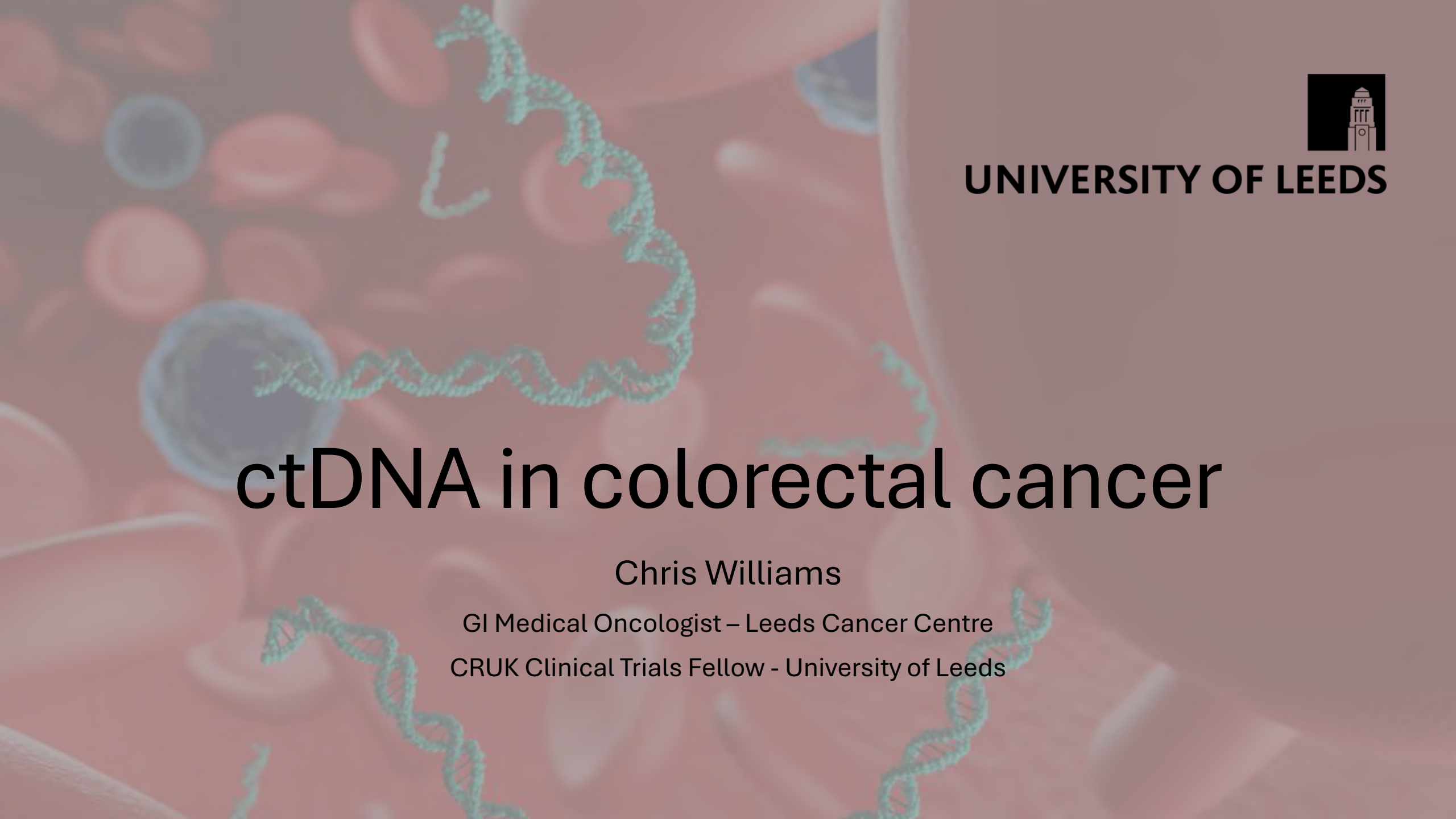

UNIVERSITY OF LEEDS

ctDNA in colorectal cancer

Chris Williams

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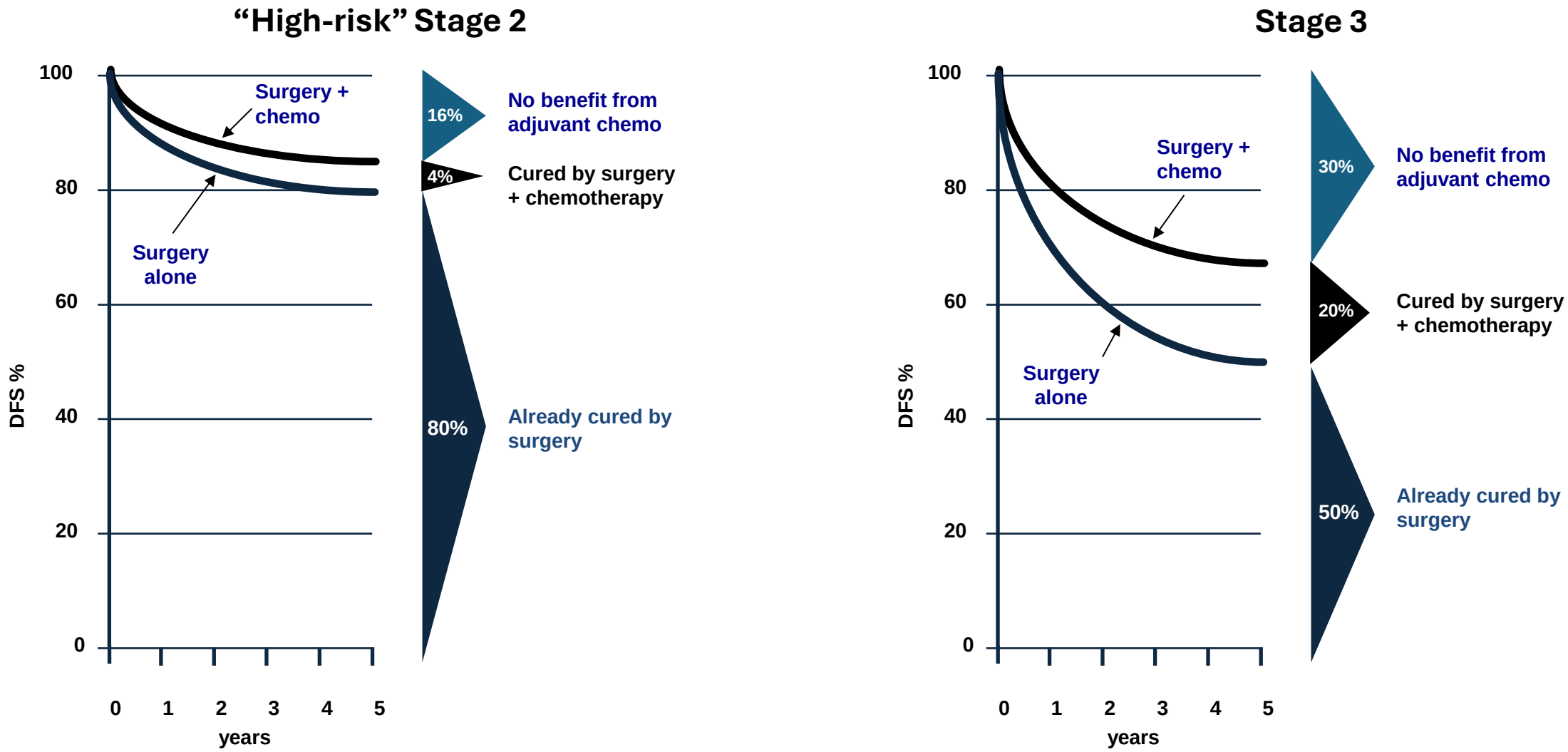
Disclosures

- Speaker Fees: Servier, Merck Serono, Roche Diagnostics
- CME: Tactics MD, MJH Life Sciences
- Research Funding: Roche Diagnostics, GSK
- Travel: IPSEN

Where might ctDNA have a role in CRC care?

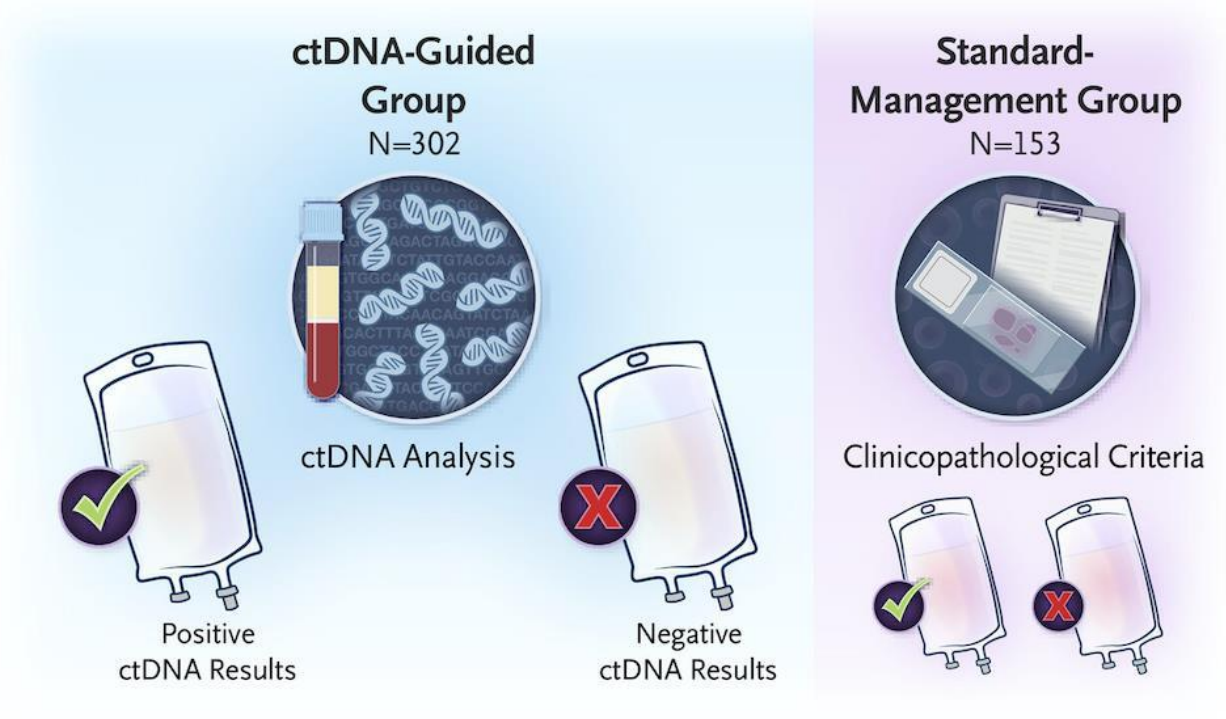
- *Early detection*
- ctDNA-guided adjuvant therapy
  - Treatment de-escalation
  - Treatment escalation
- Risk stratification for neoadjuvant therapy
- Monitoring biomarker during (palliative) therapy
- Dynamic biomarker assessment

ctDNA-guided adjuvant therapy: What's wrong with the status quo?



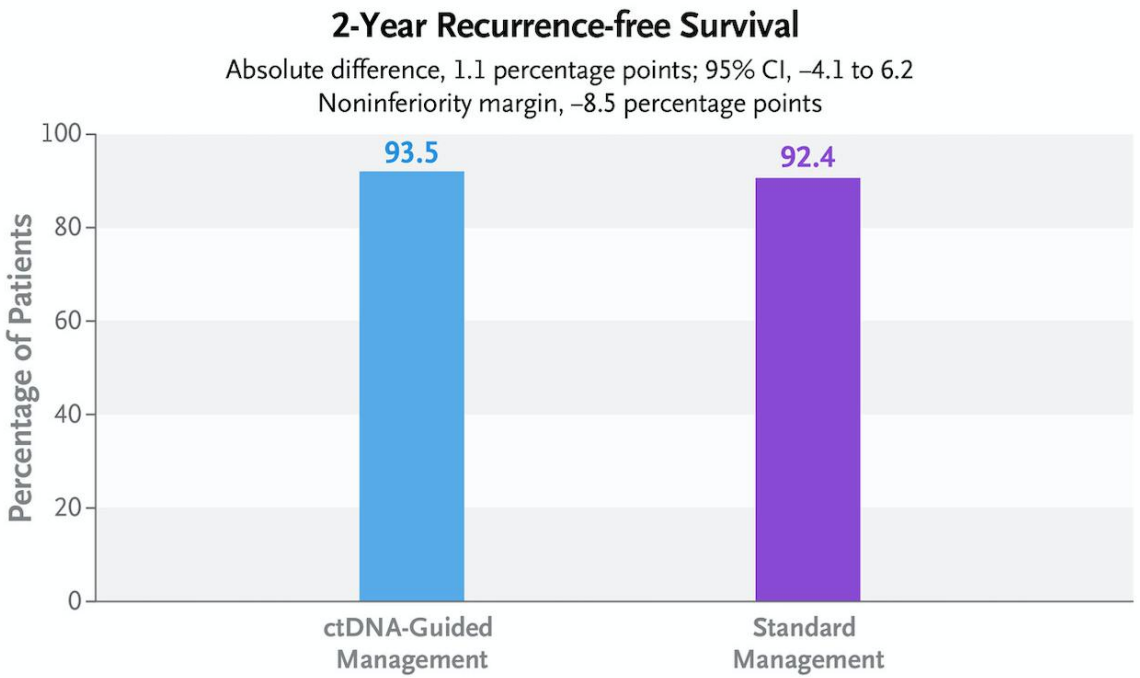
ctDNA-guided adjuvant therapy: DYNAMIC

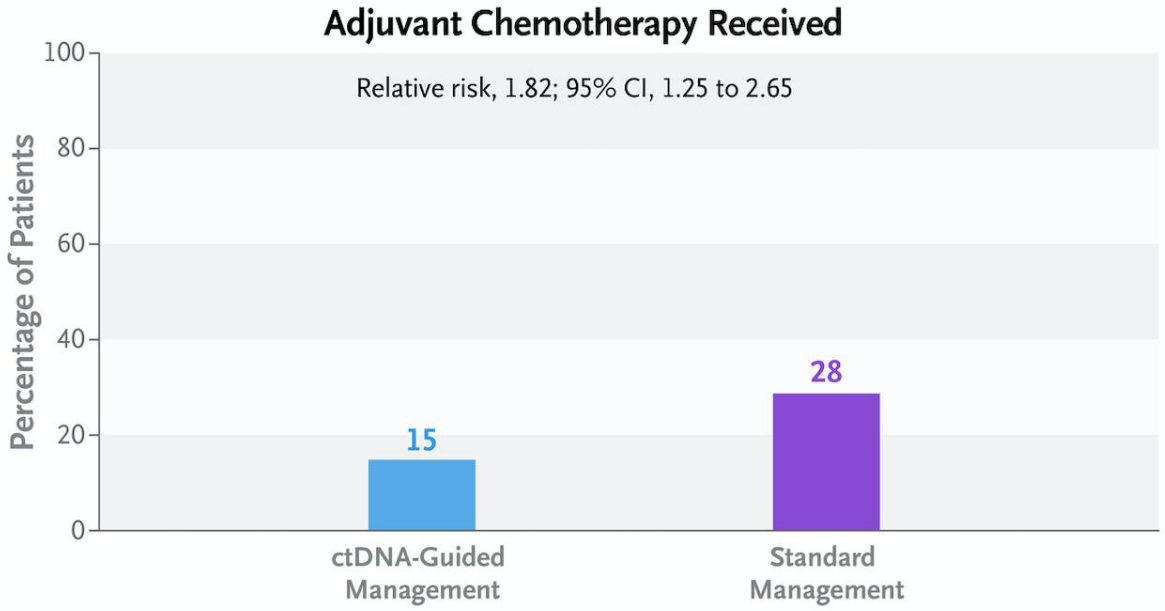
- Phase II RCT, non-inferiority
- Stage II colon or rectal (no neoadj Rx)
- Randomisation 2:1
  - ctDNA-guided vs SOC
  - Chemo regimen: physician's choice
- Tumour-informed ctDNA
  - 4 and 7 weeks post-op
- 1º endpoint: RFS at 2yrs
- Key 2º endpoint: Rx with adj chemo



Tie et al. NEJM, 2022

ctDNA-guided adjuvant de-escalation: DYNAMIC





Tie et al. NEJM, 2022

ctDNA-guided adjuvant de-escalation: DYNAMIC

Table 2. Treatment Delivery and Adherence.*

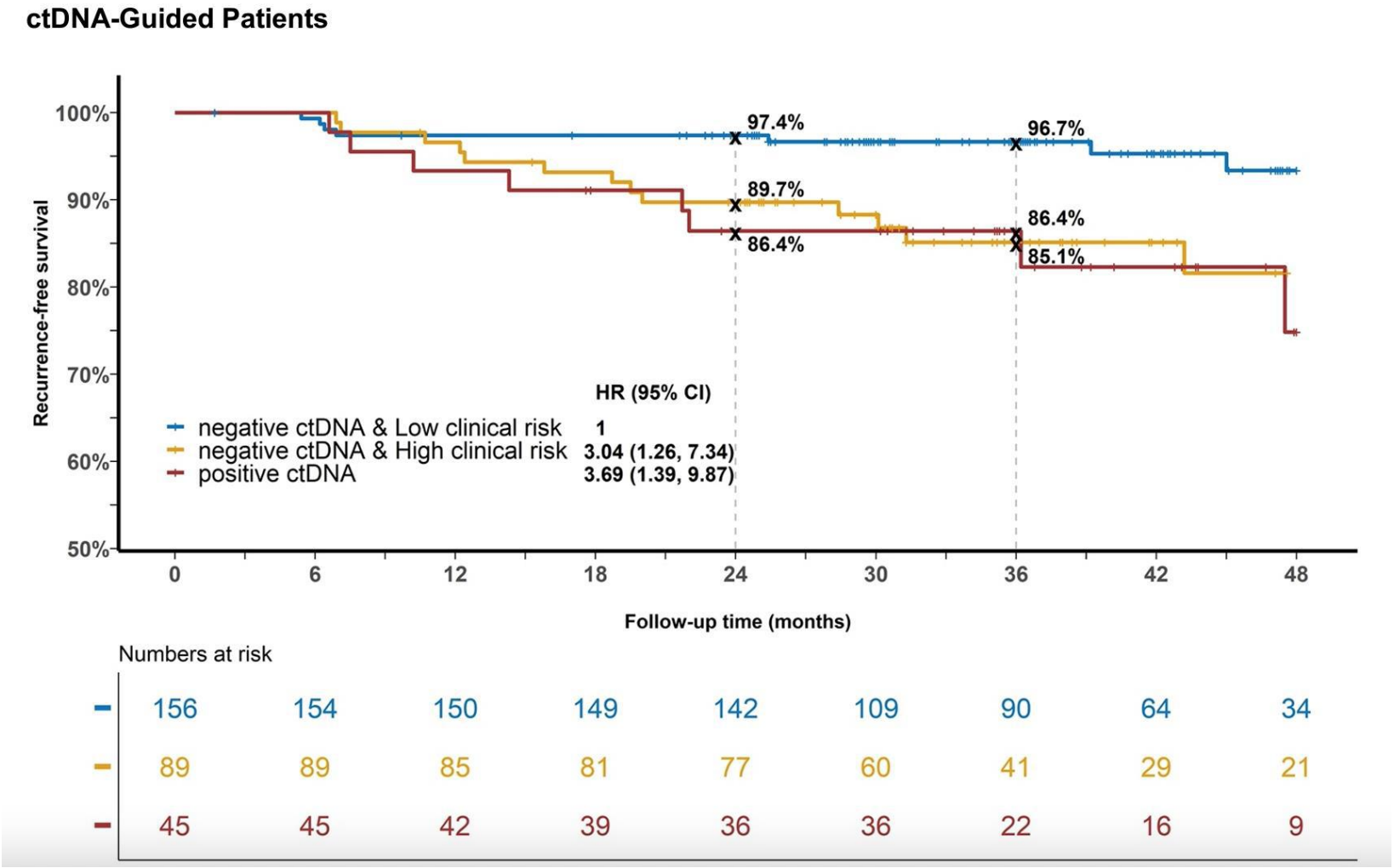
Treatment Characteristic	Standard Management (N=147)	ctDNA-Guided Management (N=294)	Relative Risk (95% CI)
Adjuvant chemotherapy received — no. (%)			
No	106 (72)	249 (85)	
Yes	41 (28)	45 (15)	1.82 (1.25–2.65)
Chemotherapy regimen received — no./total no. (%)			
Oxaliplatin-based doublet	4/41 (10)	28/45 (62)	
Single-agent fluoropyrimidine	37/41 (90)	17/45 (38)	2.39 (1.62–3.52)
Median time from surgery to start of chemotherapy (IQR) — days	53 (49–61)	83 (76–89)	
Median treatment duration (IQR) — wk	24 (21–24)	24 (19–24)	
Reason for stopping chemotherapy — no./total no. (%)			
Completion of planned treatment	32/41 (78)	38/45 (84)	
Disease relapse	1/41 (2)	0/45 (0)	
Patient request	1/41 (2)	1/45 (2)	
Toxic effects	7/41 (17)	6/45 (13)	
Percentage of full dose delivered			
Mean	77±26	74±24	
Median (IQR)	84 (64–100)	78 (56–100)	

Tie et al. NEJM, 2022

ctDNA-guided adjuvant de-escalation: DYNAMIC

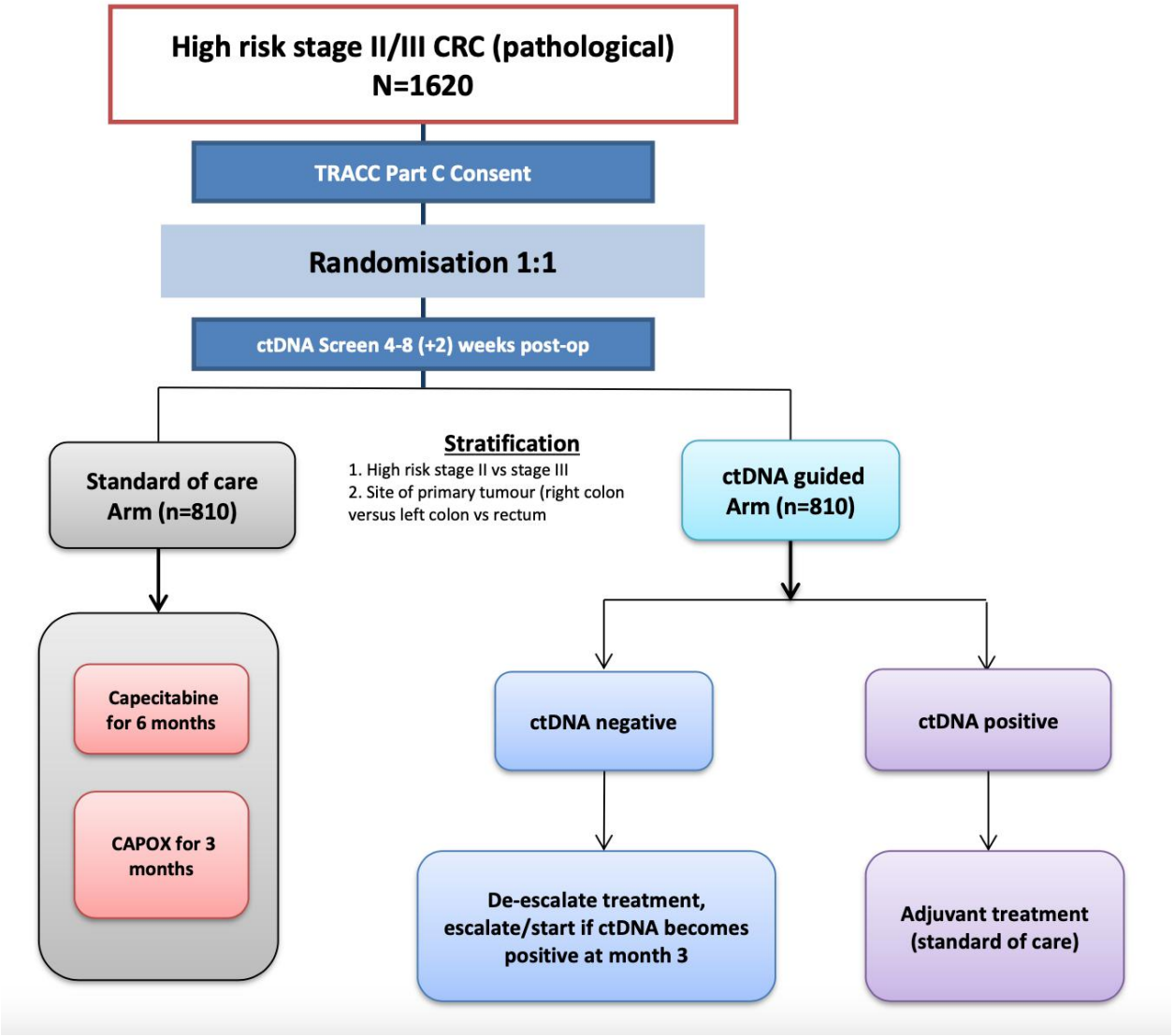
Stage II “high-risk disease” = pMMR and ≥1:

- pT4
- Poor tumour differentiation
- Lymph node yield <12
- Lymphovascular invasion
- Tumour perforation, or bowel obstruction



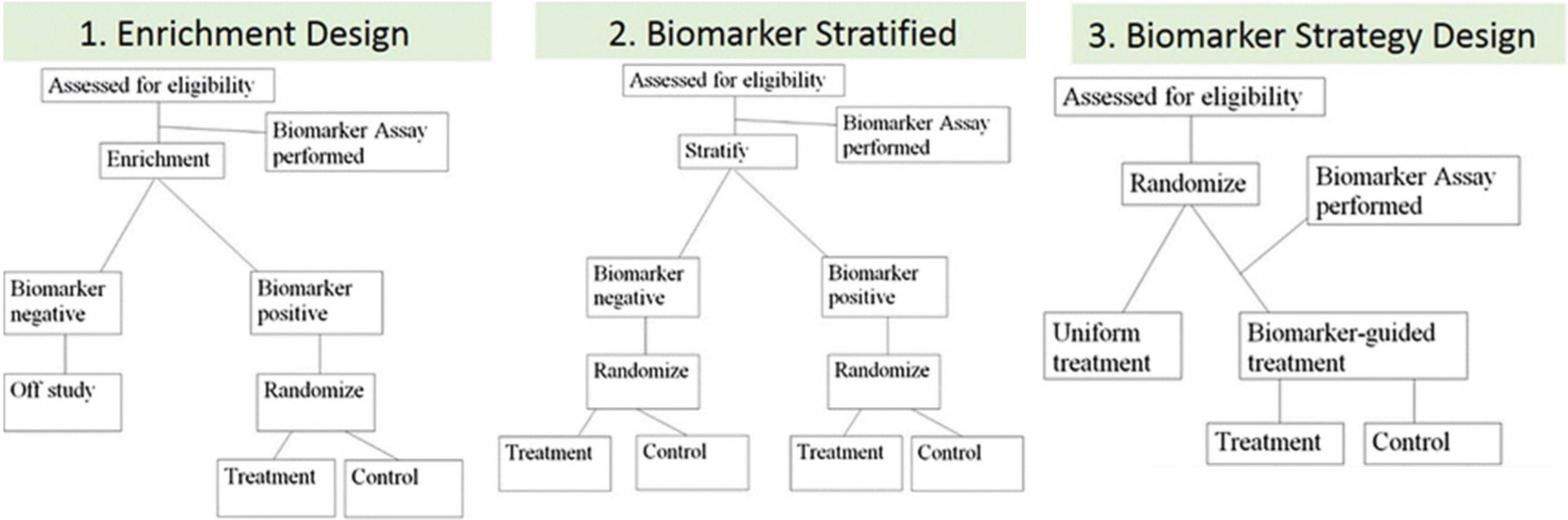
Tie et al. NEJM, 2022

ctDNA-guided adjuvant de-escalation: TRACC



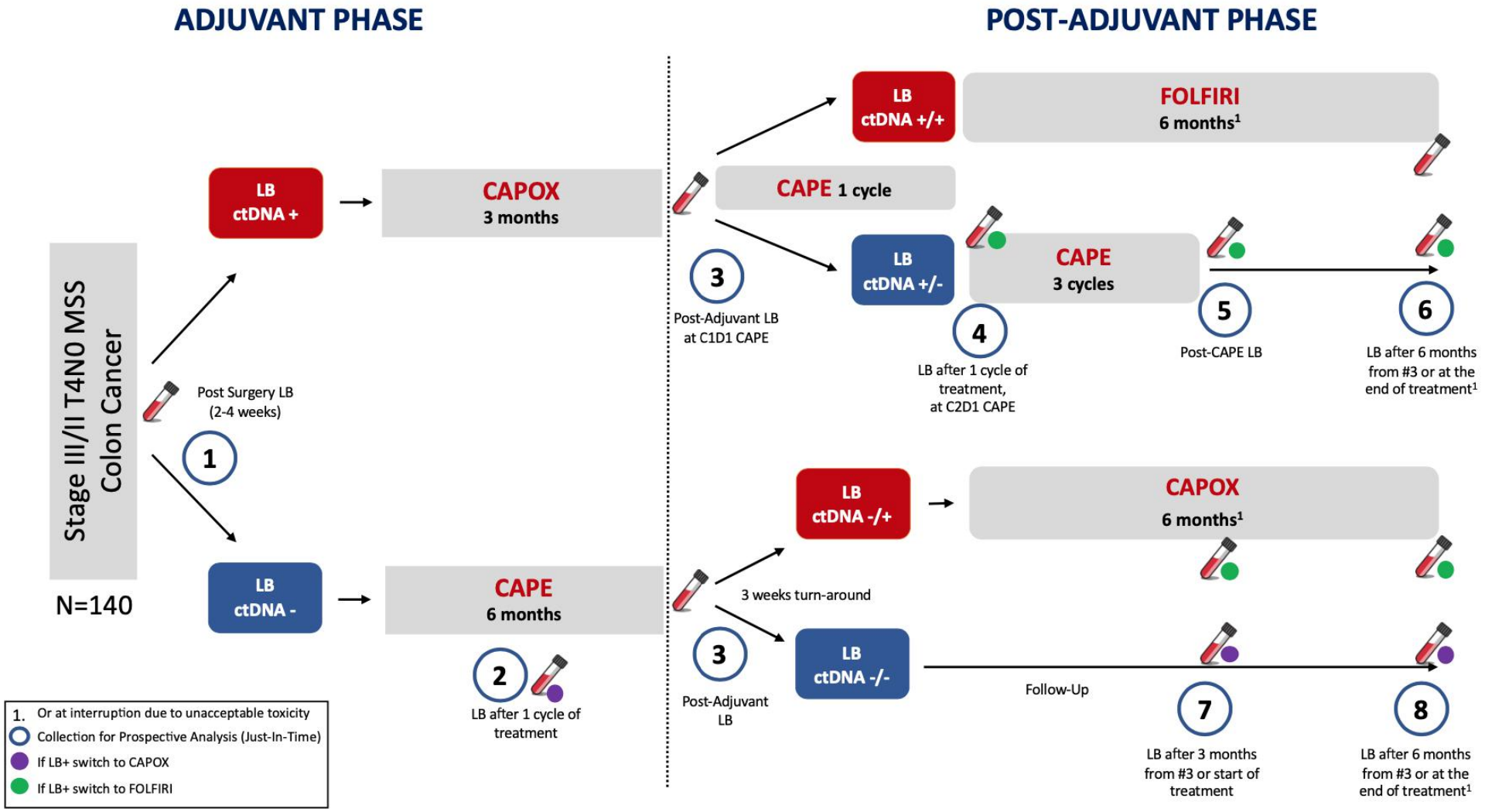
- Phase III non-inferiority RCT
- Tumour-naïve ctDNA at 4-8 weeks post-op (Guardant Reveal®)
- 1º endpoint: 3yr DFS

ctDNA adjuvant trial designs



Dobbin et al. J Immunotherapy of Cancer, 2016

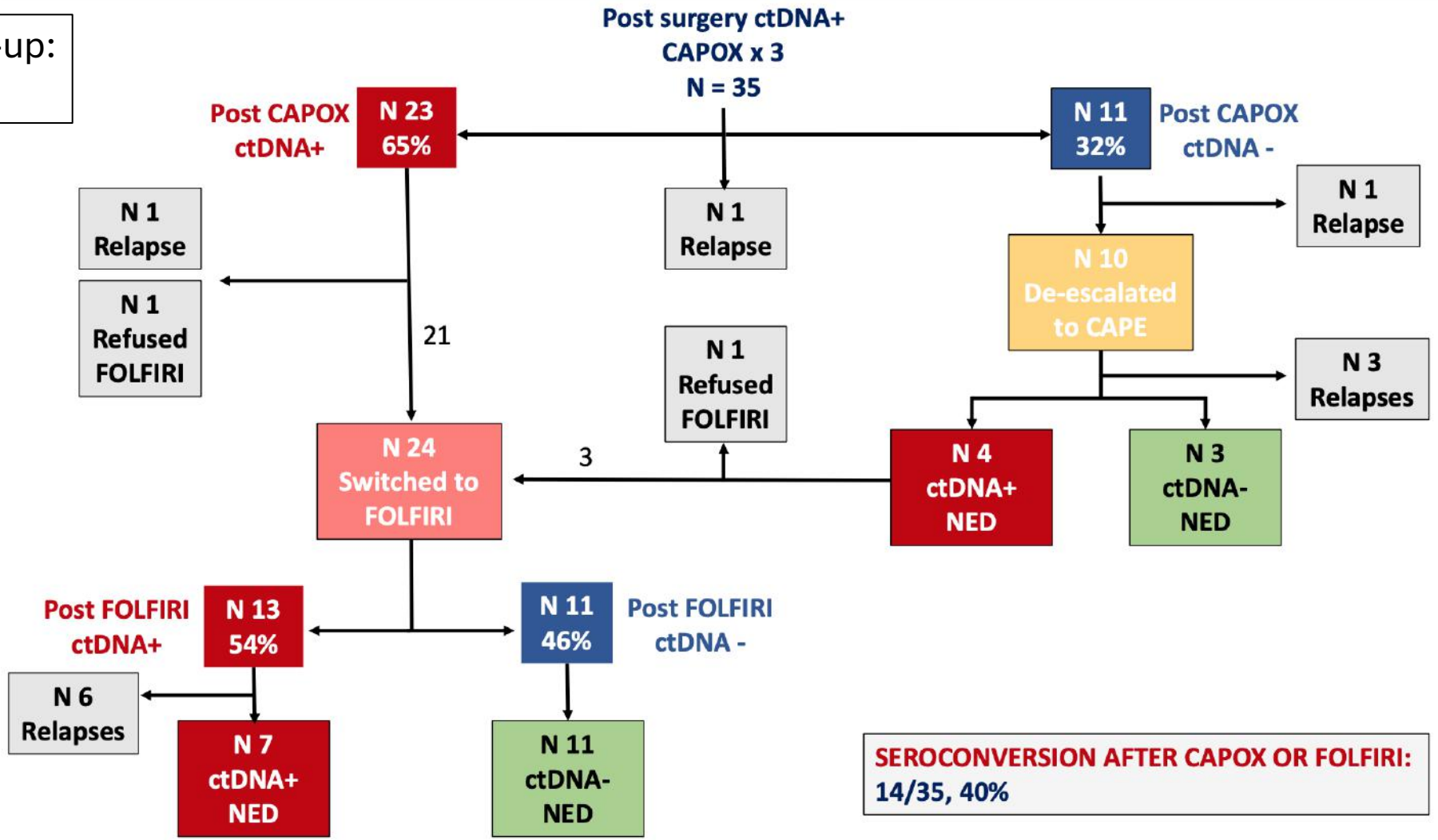
ctDNA-guided adjuvant escalation: PEGASUS



Lonardi et al. ESMO Congress, 2023

ctDNA-guided adjuvant escalation: PEGASUS

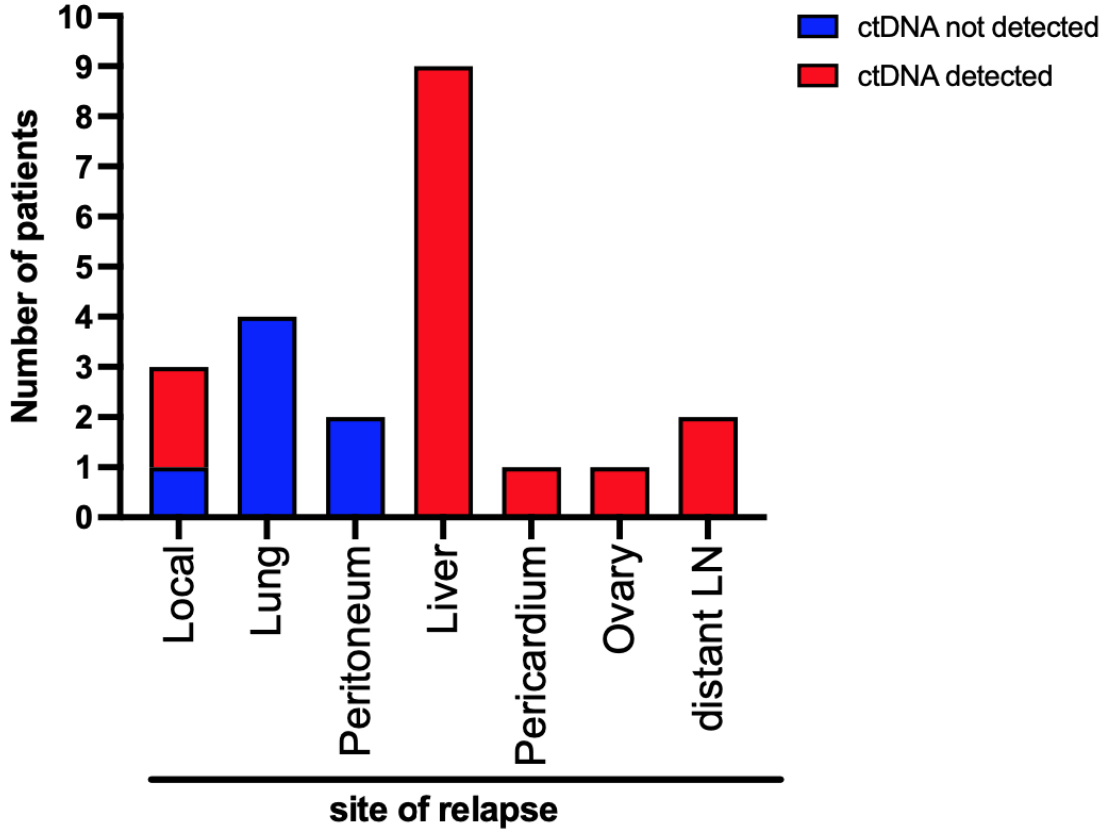
Median follow-up:
24.2 months



Lonardi et al. ESMO Congress, 2023

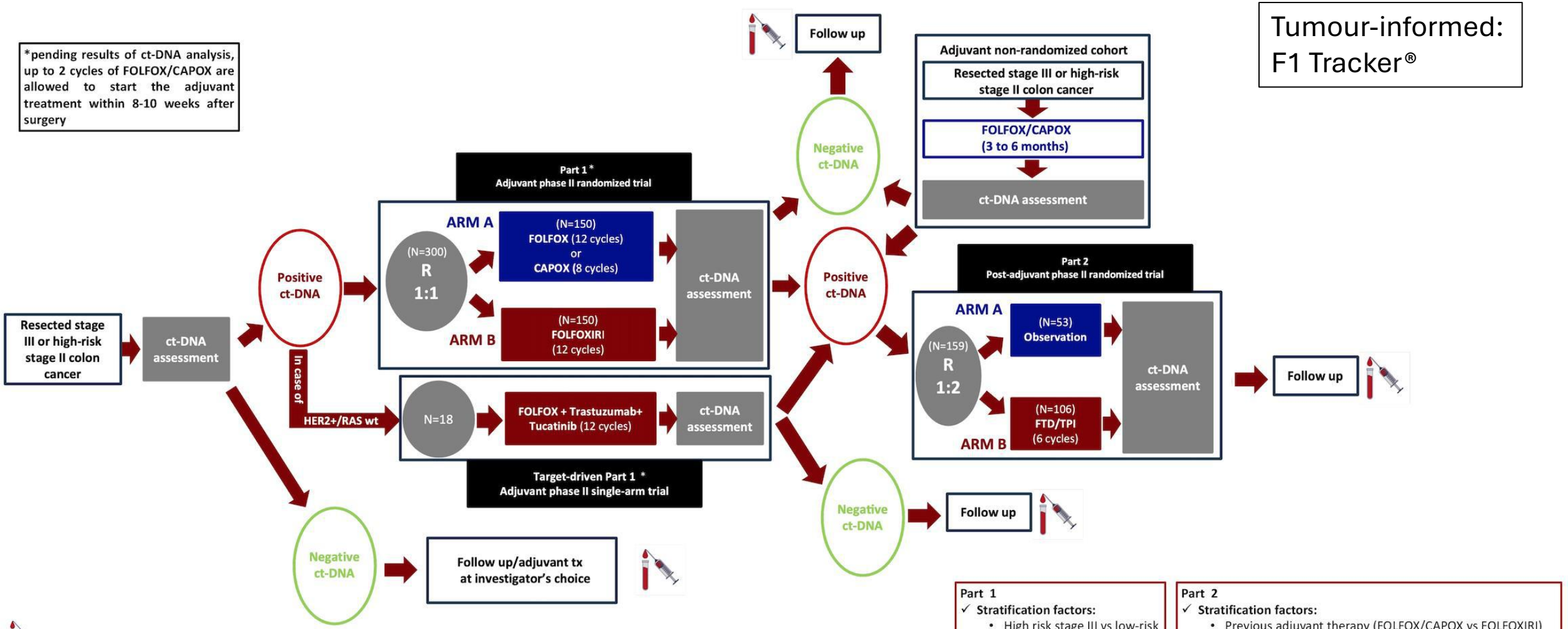
(PEGASUS additional learning point)

22 relapses: 10 in ctDNA negative and 12 in ctDNA positive patients



Lonardi et al. ESMO Congress, 2023

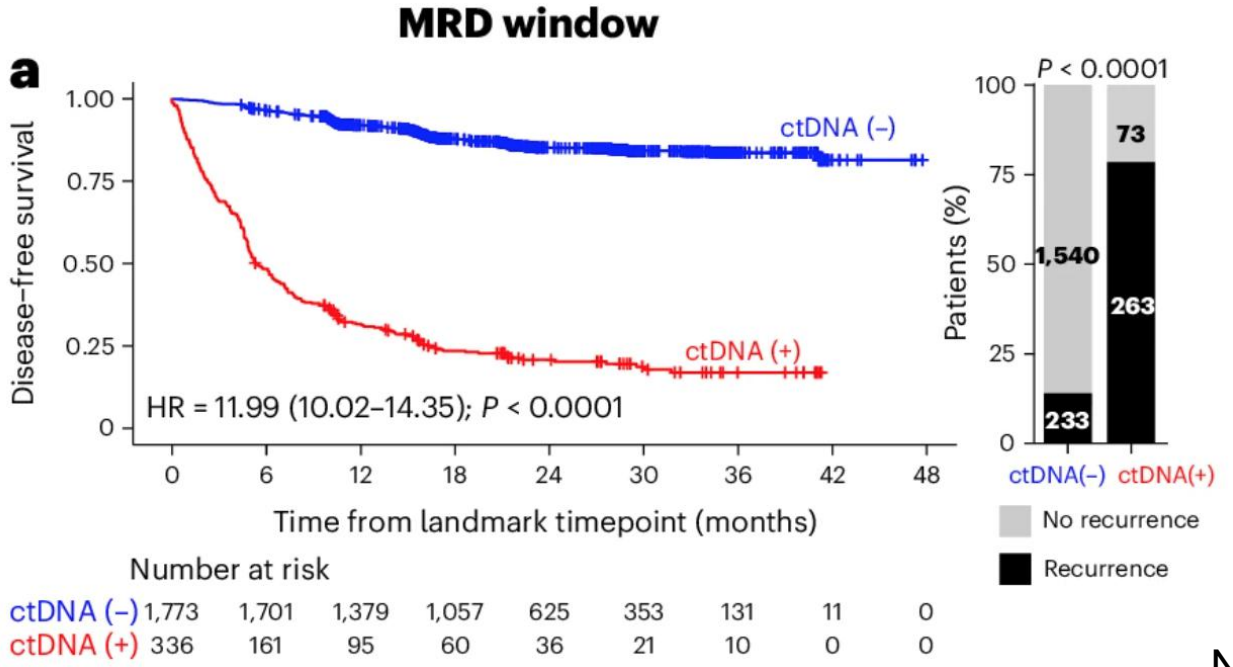
ctDNA-guided adjuvant escalation: ERASE-CRC



Conca et al. ASCO Annual Meeting, 2024

ctDNA-guided adjuvant escalation: CIRCULATE

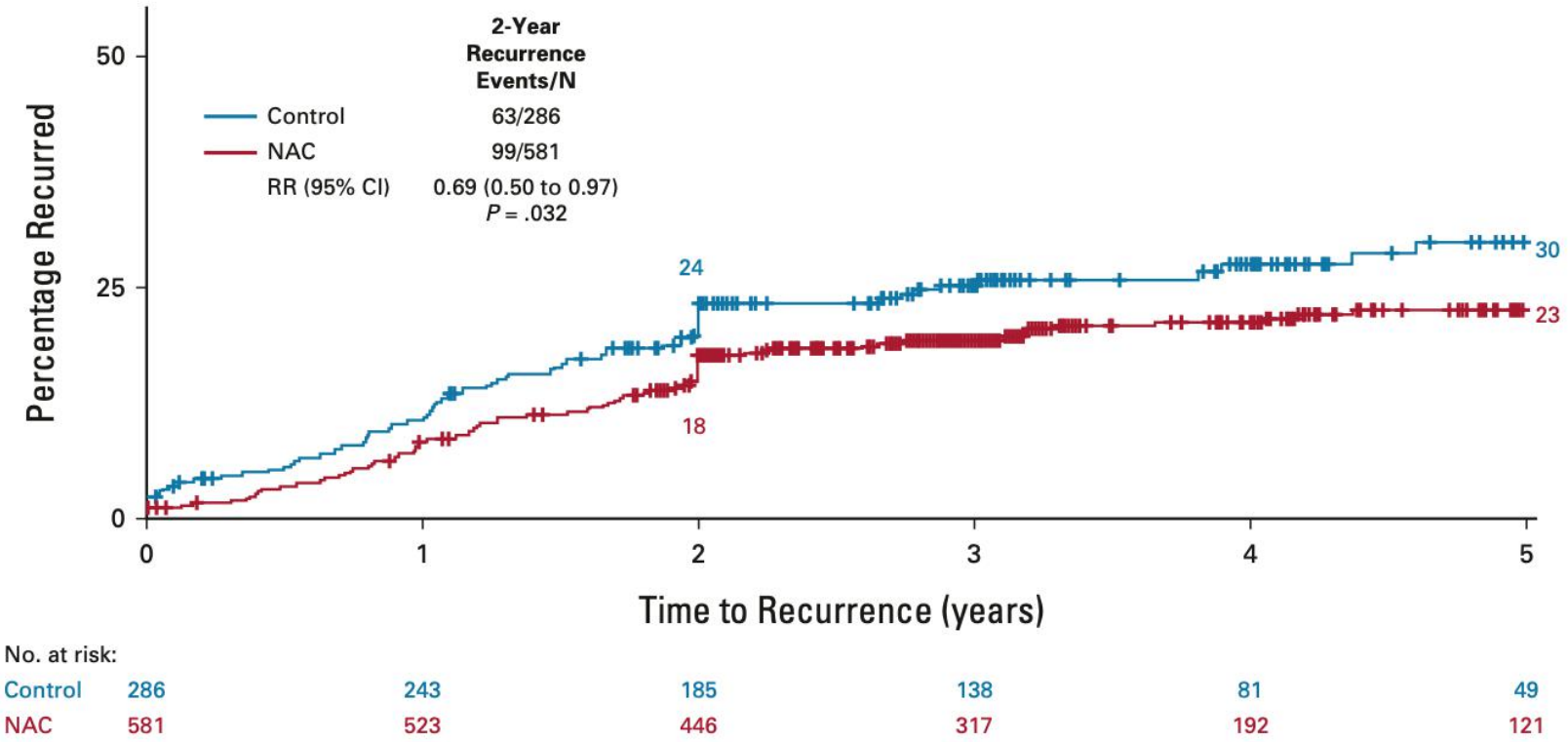
- Multinational ctDNA-based trials using Signatera® tumour-informed assay
- GALAXY (observational study within CIRCULATE-Japan) first to publish



Nakamura et al. Nat Med, 2024

ctDNA risk stratification at baseline

FOxTROT 1: Neoadjuvant chemo vs STS
Abs diff 3yr DFS in pMMR subgroup = 5.3%



Risk stratification for neoadjuvant SACT in colon cancer

- Nodal sampling not possible
- PET-CT and MRI not helpful
- CT staging currently used to estimate pathological staging

Strategies to improve risk stratification:

- CT-specific risk factors
- TILs quantification
- ?ctDNA

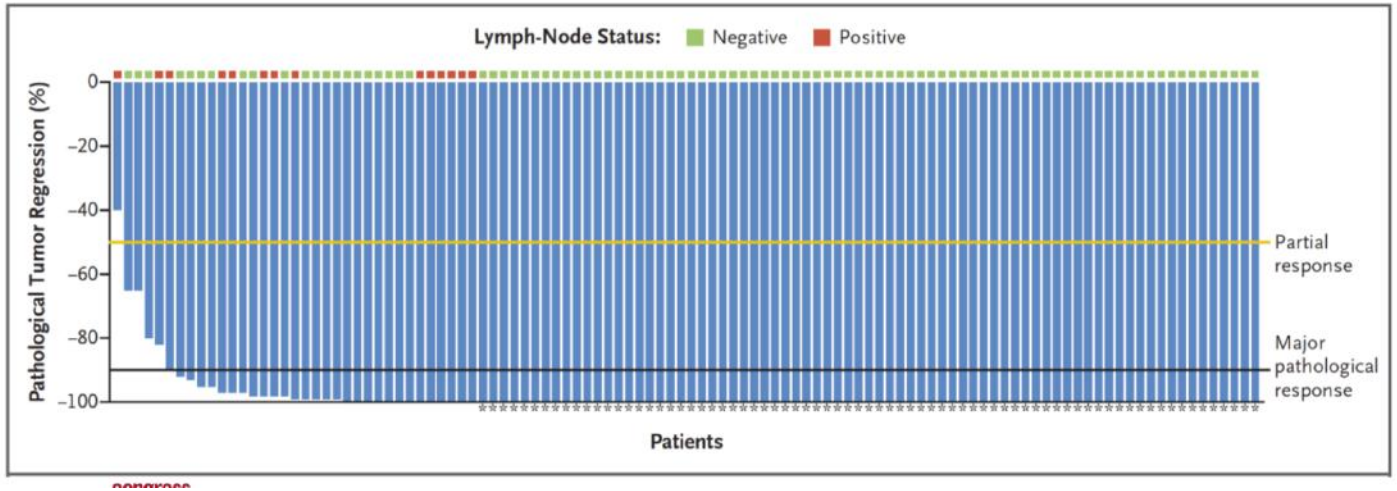
Morton et al. JCO, 2023

ctDNA risk stratification at baseline

Pathologic responses in NICHE-2

Pathologic response in **98%** of 111 patients in efficacy analysis

- Major pathologic response (≤10% residual viable tumor): **95%**
- Pathologic complete response: **68%**



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Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

Myriam Chalabi, M.D., Ph.D., Yara L. Verschoor, M.D., Pedro Batista Tan, M.Sc., Sara Balduzzi, Ph.D., Anja U. Van Lent, M.D., Ph.D., Cecile Grootscholten, M.D., Ph.D., Simone Dokter, M.Sc., Niké V. Büller, M.D., Ph.D., Brechtje A. Grotenhuis, M.D., Ph.D., Koert Kuhlmann, M.D., Ph.D., Jacobus W. Burger, M.D., Ph.D., Inge L. Huibregtse, M.D., Ph.D., Tjeerd S. Aukema, M.D., Ph.D., Eduard R. Hendriks, M.D., Steven J. Oosterling, M.D., Ph.D., Petur Snaebjornsson, M.D., Ph.D., Emile E. Voest, M.D., Ph.D., Lodewyk F. Wessels, Ph.D., Regina G. Beets-Tan, M.D., Ph.D., Monique E. Van Leerdam, M.D., Ph.D., Ton N. Schumacher, Ph.D., José G. van den Berg, M.D., Ph.D., Geerard L. Beets, M.D., Ph.D., and John B. Haanen, M.D., Ph.D.

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- PET CT and MRI not helpful
- CT staging currently used to estimate pathological staging

Strategies to improve risk stratification:

- CT-specific risk factors
- TILs quantification
- ?ctDNA

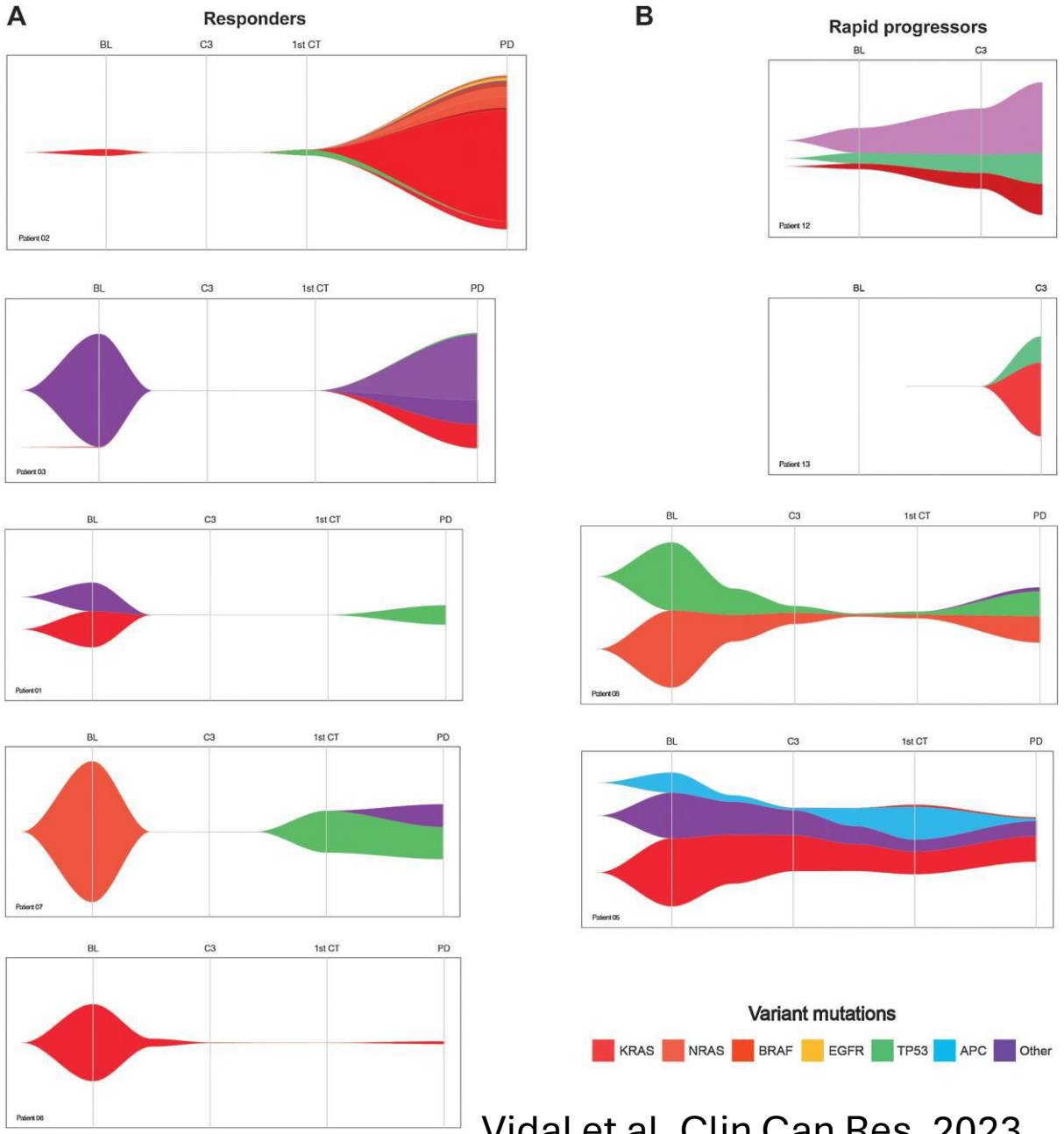
Chalabi et al. NEJM, 2024

ctDNA risk stratification at baseline: PLATFORM-B

- Obs study of ctDNA alterations during 1st line chemo+anti-EGFR

- Quantifying ctDNA: “trunk_ctDNA”
  - VAF of most abundant variant ⇒ ?proxy for overall tumour burden

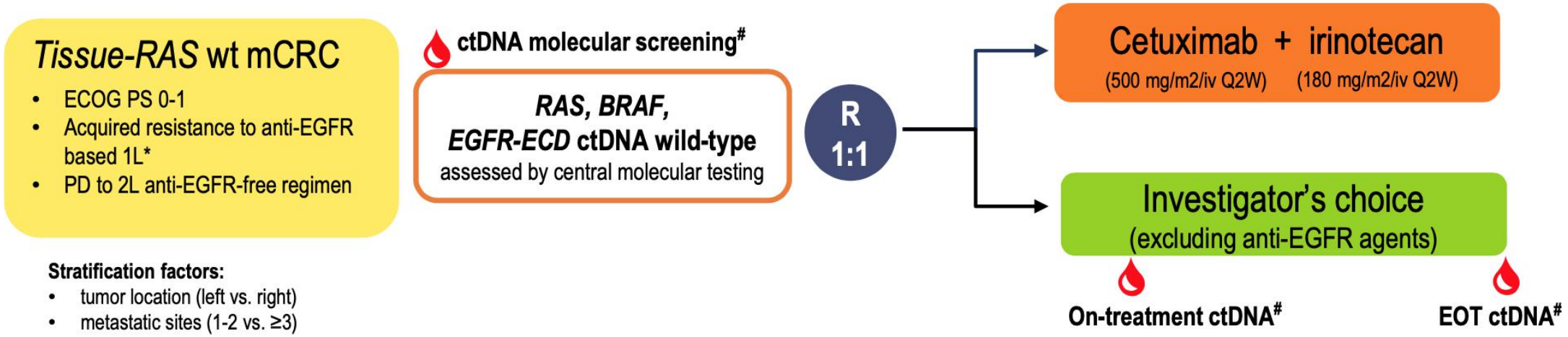
(Tumour-naïve assay)



Vidal et al. Clin Can Res, 2023

ctDNA: dynamic biomarker assessment in CITRIC

multicenter, randomized, open-label, phase II study



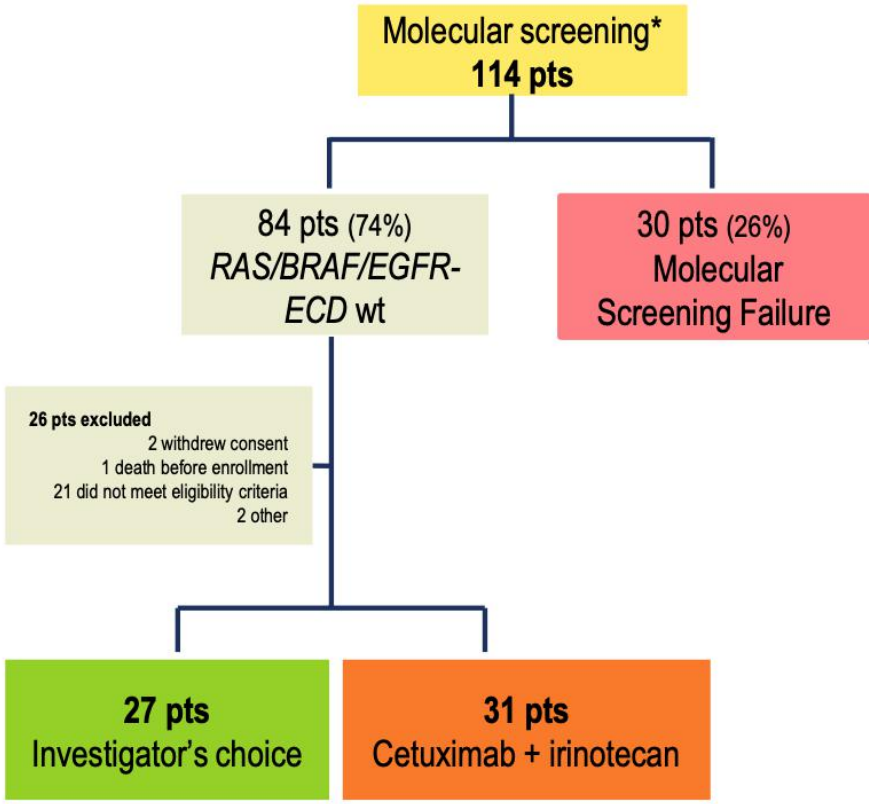
Primary endpoint: ORR (investigator assessed)
Secondary endpoints: DCR, DDC, TTF, PFS, OS, safety

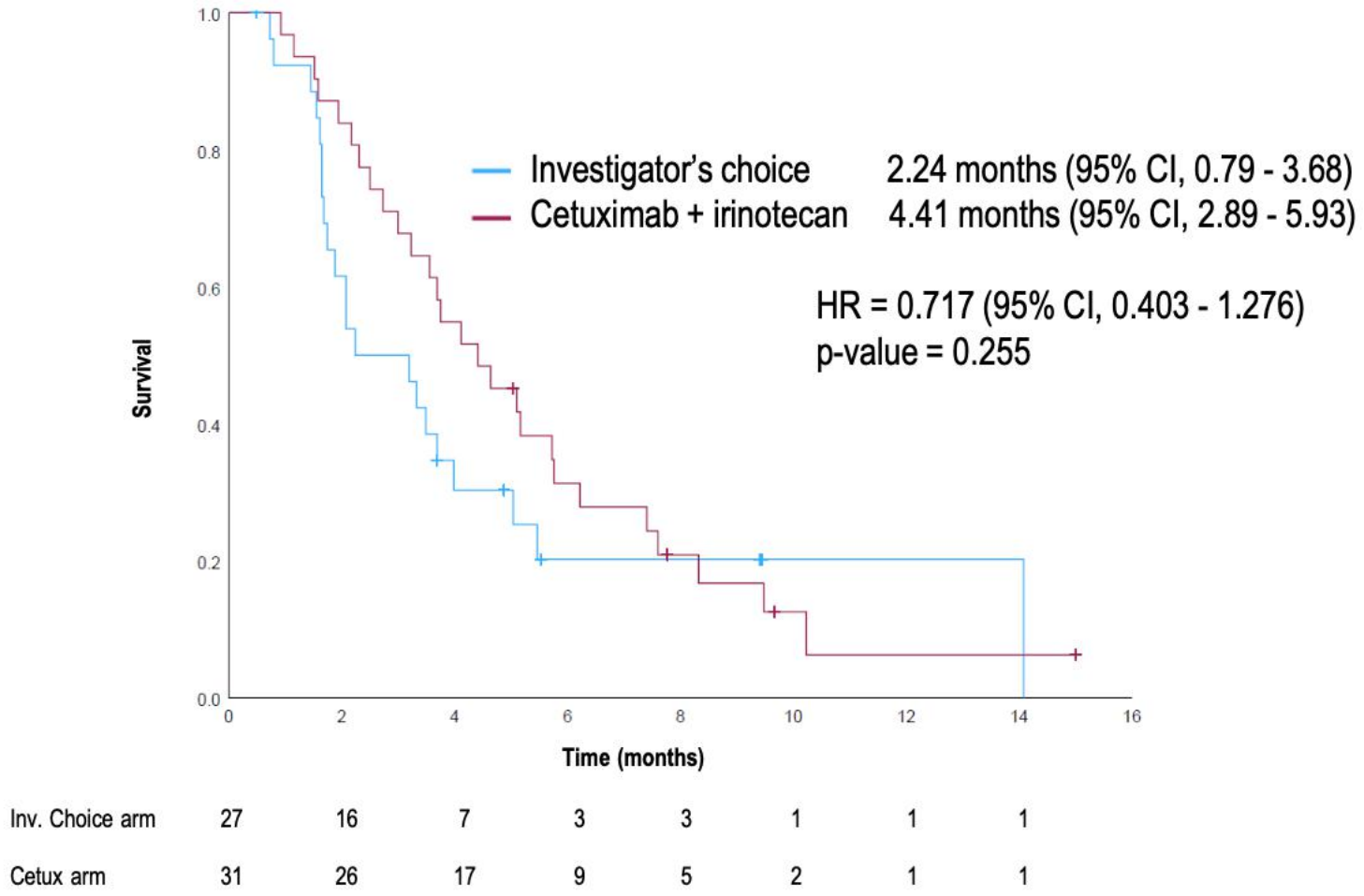
Statistical considerations:

- Designed to detect a difference of 27% between cetuximab arm (30%) and investigator's choice arm (3%)
- Accepting an alpha risk of 0.10 and a beta risk of 0.2 in a two-sided Fisher's exact test, 28 patients per arm need to be included

Santos et al. ESMO Congress, 2024

ctDNA: dynamic biomarker assessment in CTIRIC

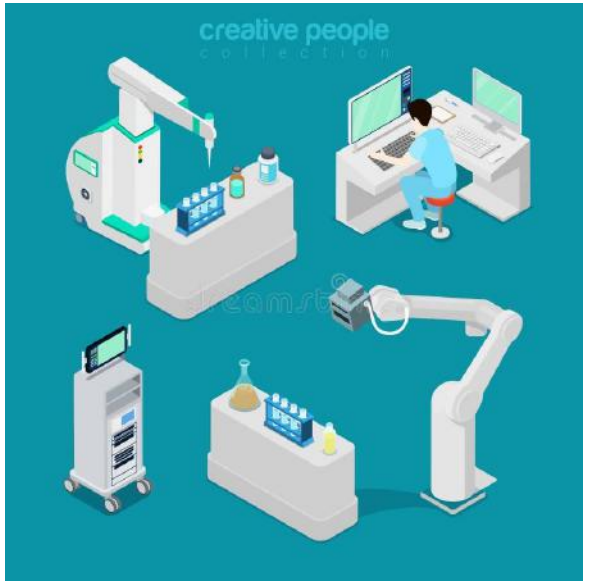




Santos et al. ESMO Congress, 2024

Future challenges

- Validation
- Integration with existing and novel biomarkers
- Differing assays
- Evolving technology
- Cost-effectiveness analyses
- “Pre-early uptake”
- Funding of NICE approvals



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NHS
The Leeds Teaching Hospital
NHS Trust

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