



'Circulating tumor DNA to guide adjuvant therapy in colorectal cancer is ready for prime time. Agree or Disagree'

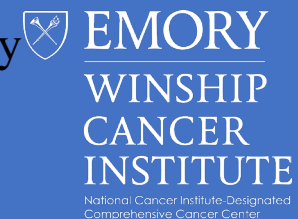
2022 Debates and Didactics

Haematology and Oncology

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Disclosures

Advisory role: Exelixis, Incyte, QED therapeutics

Research Support: AstraZeneca, Astella Pharmaceuticals, Ipsen, Merck, Eisai, BMS

No off- label uses of drugs will be presented.



Illustration by Chelsea O'Byrne

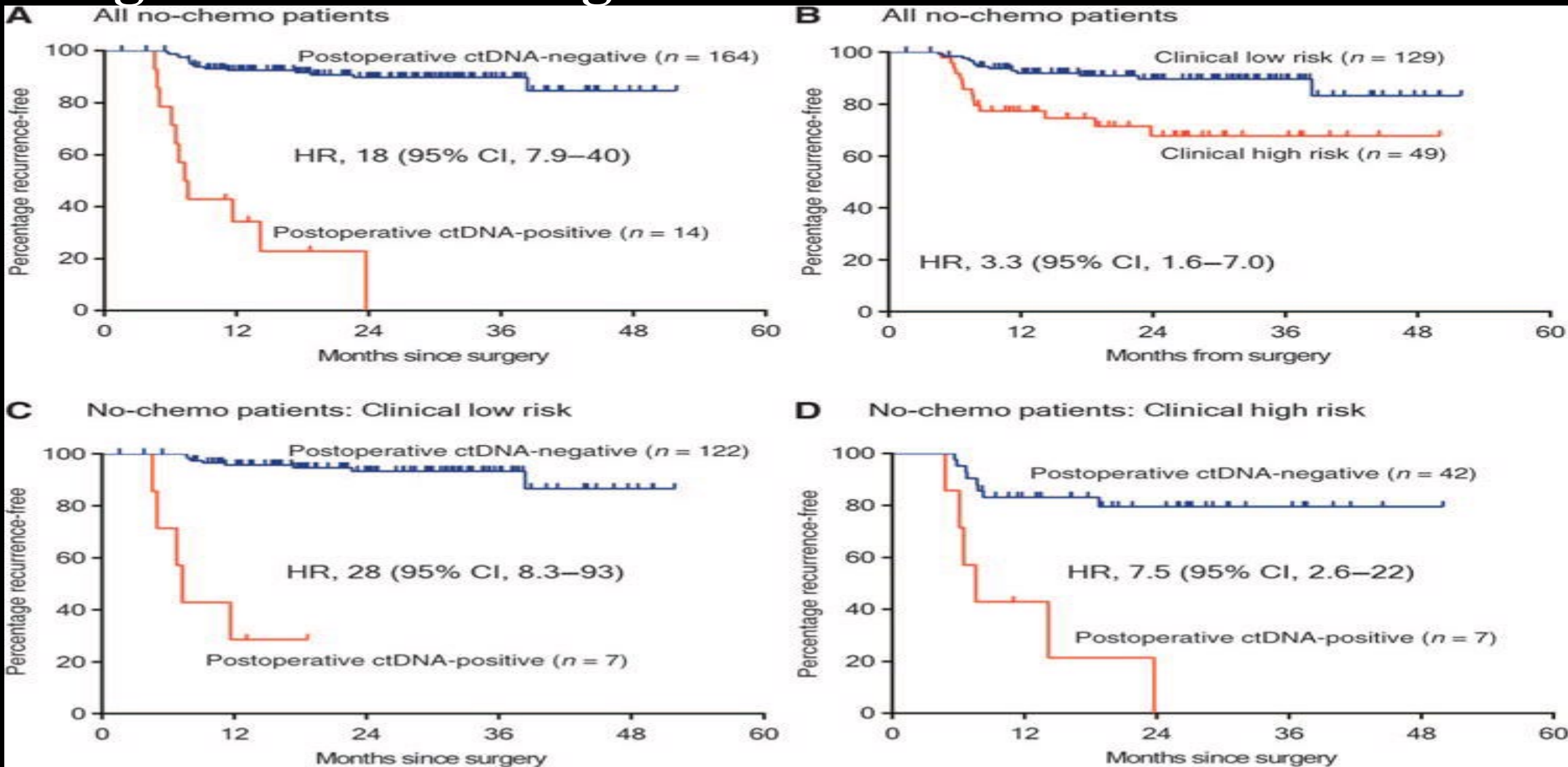
'Circulating tumor DNA to guide adjuvant therapy in colorectal cancer is ready for prime time. Agree or Disagree'

I WILL NOT MENTION THE ADDITIONAL COST!

Proposed Uses of ctDNA in Stage II and III Colon cancer

- Prognostication- Is my cancer going to come back?
- Prediction for adjuvant chemotherapy- What can we do to reduce the risk of recurrence
- De-escalation of adjuvant therapy - Do we really need that oxaliplatin or 6 months of 5FU
- Key references **DYNAMIC Study** and CIRCULATE- Japan (GALAXY)

Prognostication- Stage II Colon Cancer



Prognostication-. This is
not a Cassandra Situation

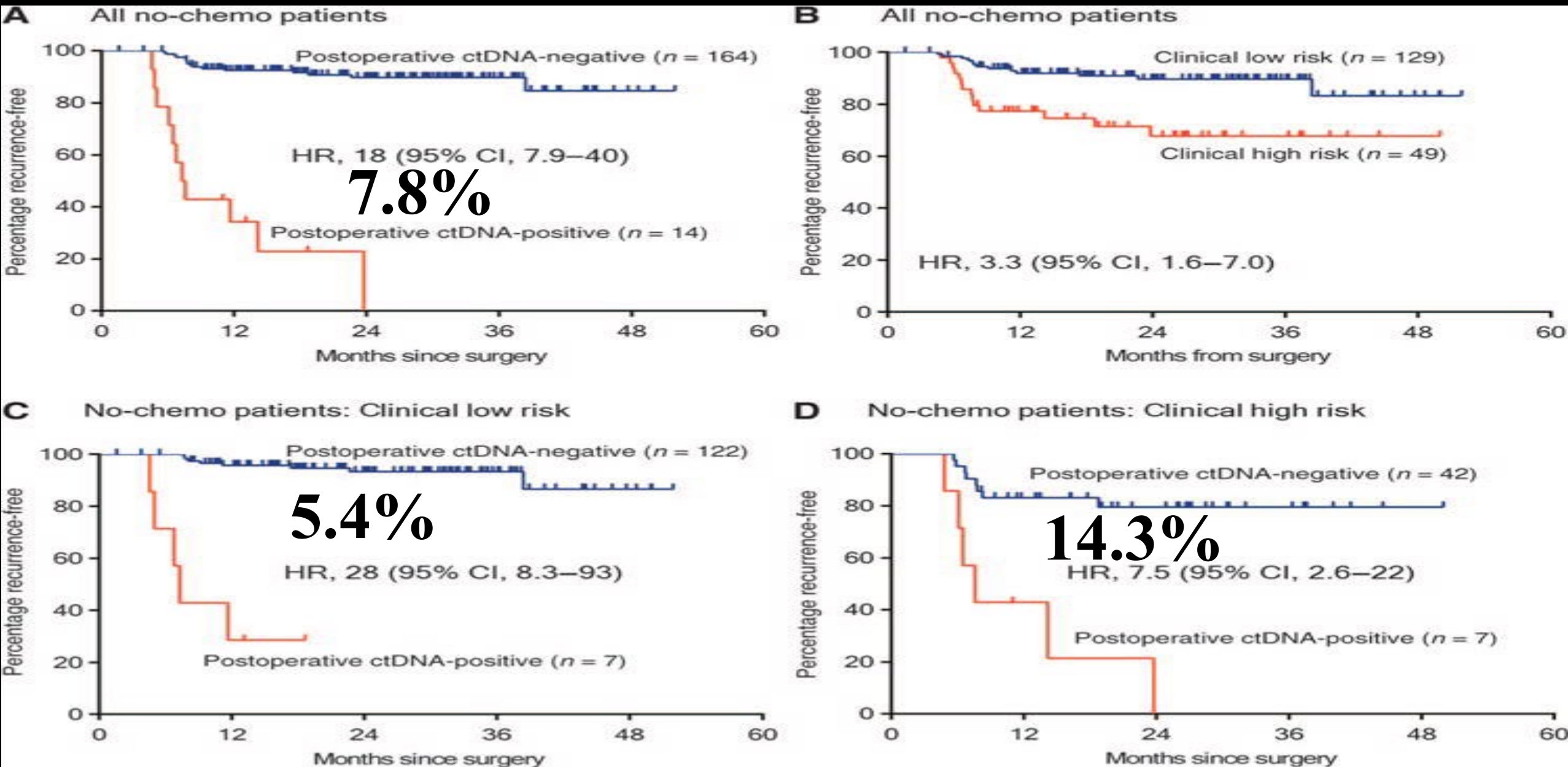


ctDNA for prognostication is overstated in Stage II Cancer

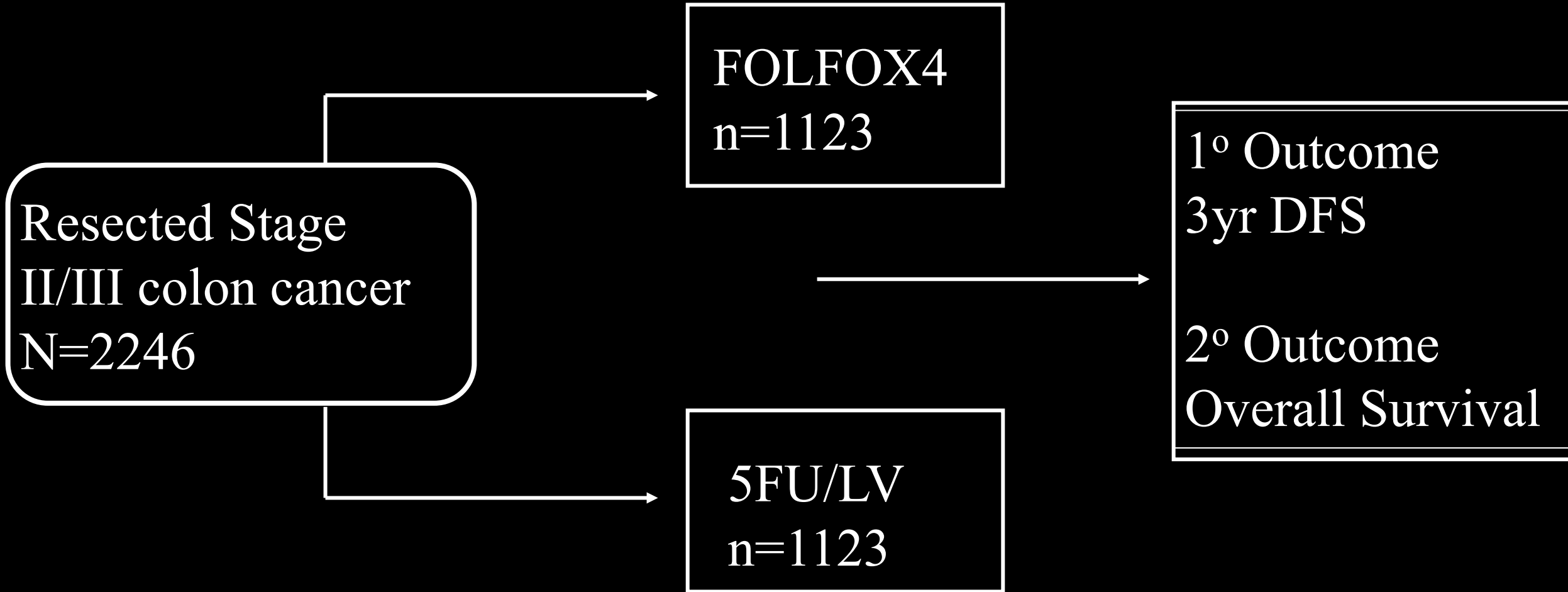
- 34 out of 230 patients (15%) developed recurrent disease
 - 85% of Stage II colon cancer cured with surgery only
- 20 of 230 patients (8%) were Post-op ctDNA +ve
 - 92% of Stage II colon cancer is post-op ctDNA –ve
- ctDNA positivity rate is only 50% of the overall recurrence rate

Up to 10% of patients who were ctDNA –ve still developed recurrent disease

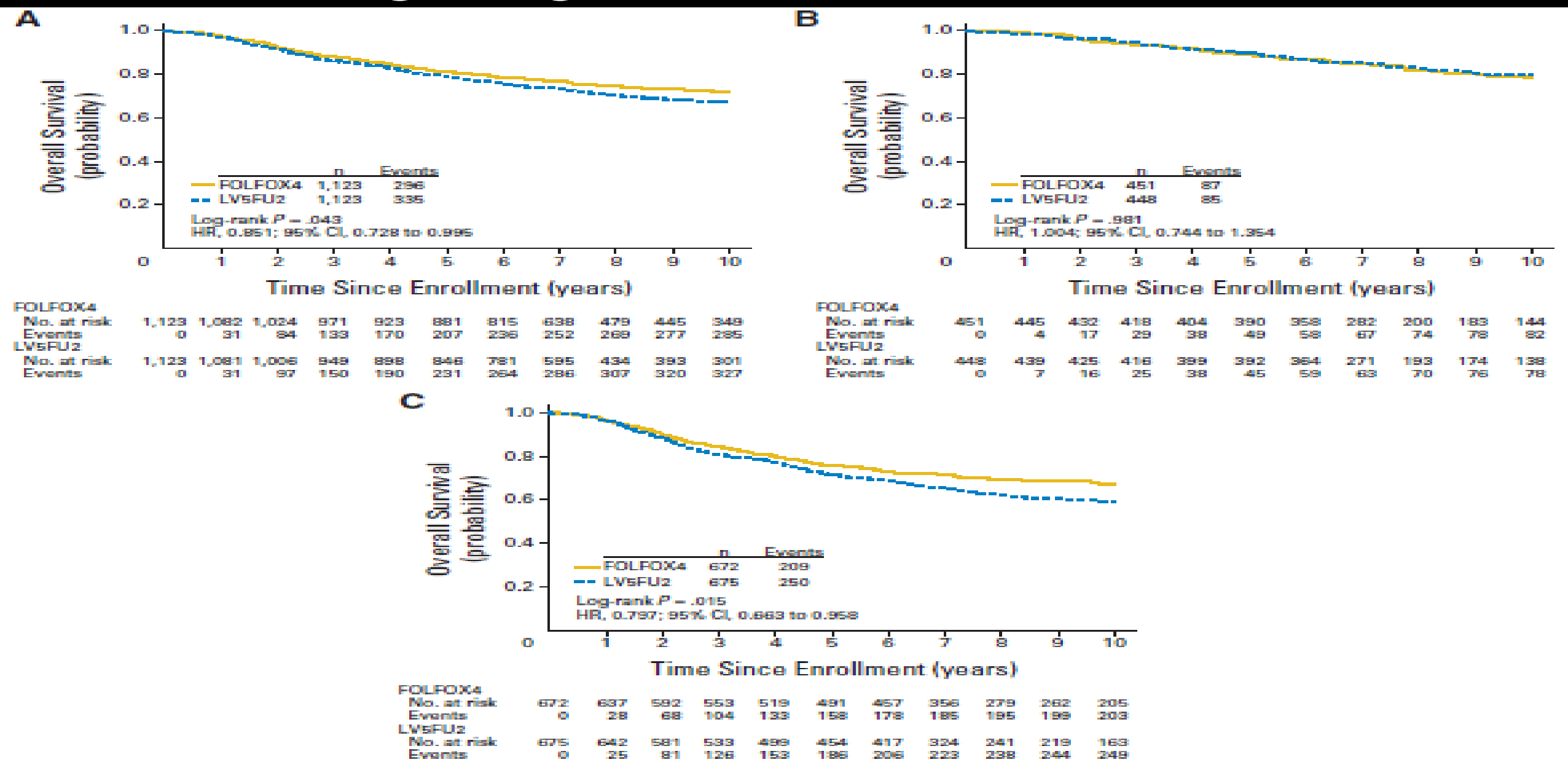
Prognostication for Stage II Colon Cancer- key numbers



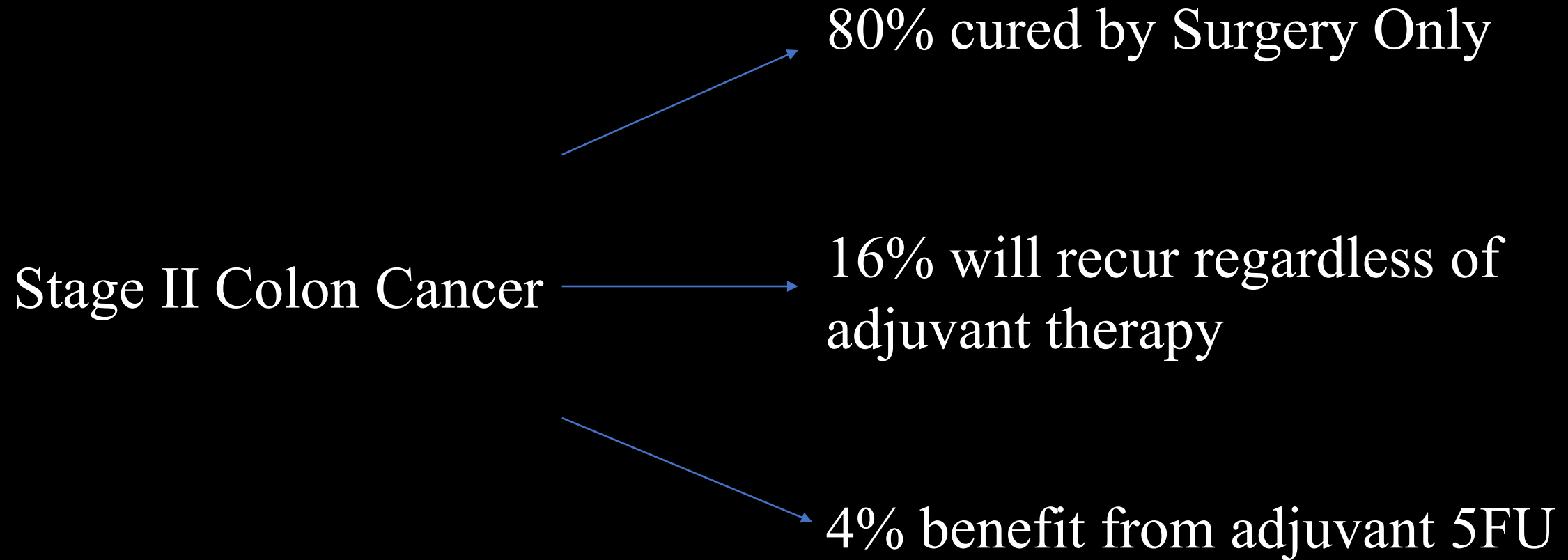
Adjuvant Therapy in Colon Cancer: MOSAIC study



What are we getting from FOLFOX?



Across the pond- Quick And Simple And Reliable- QUASAR



MOSAIC Study Summary for Stage II Colon Cancer

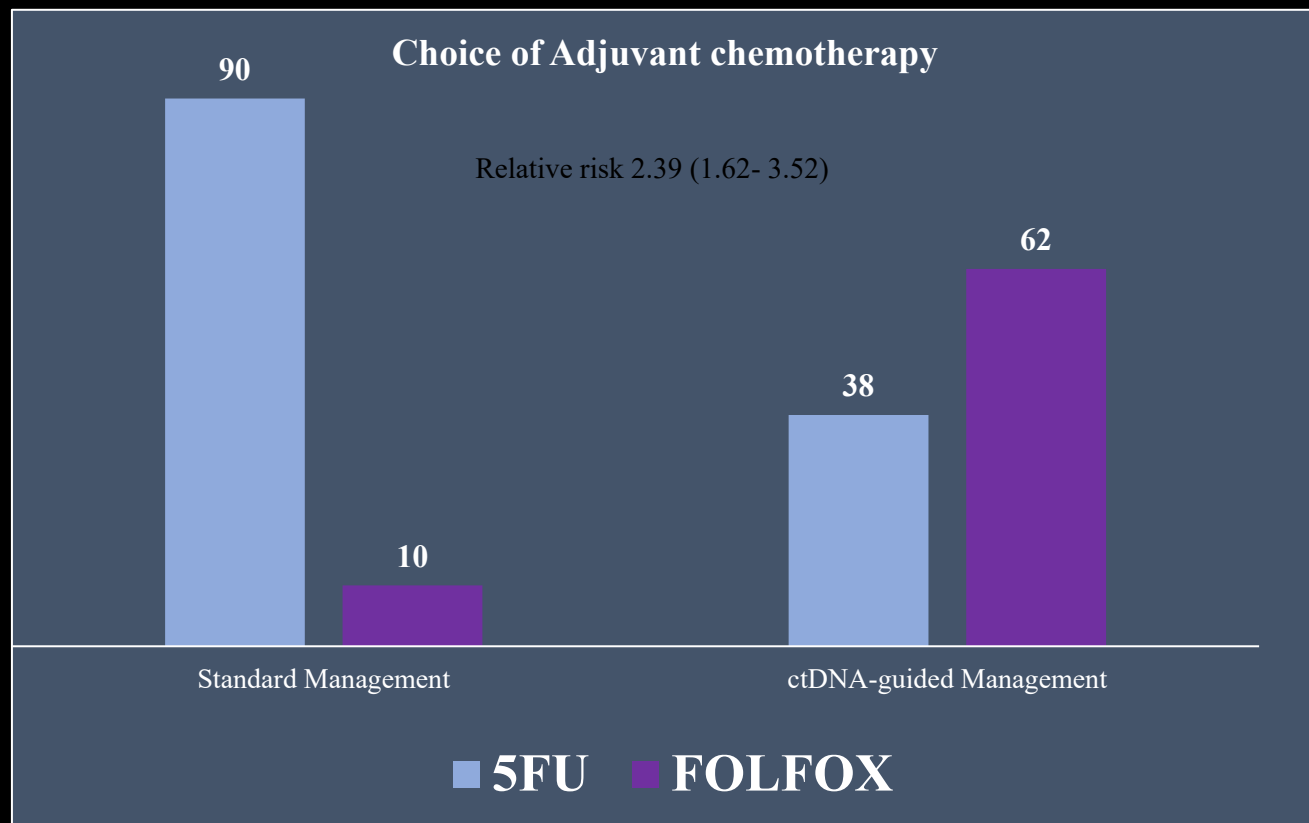
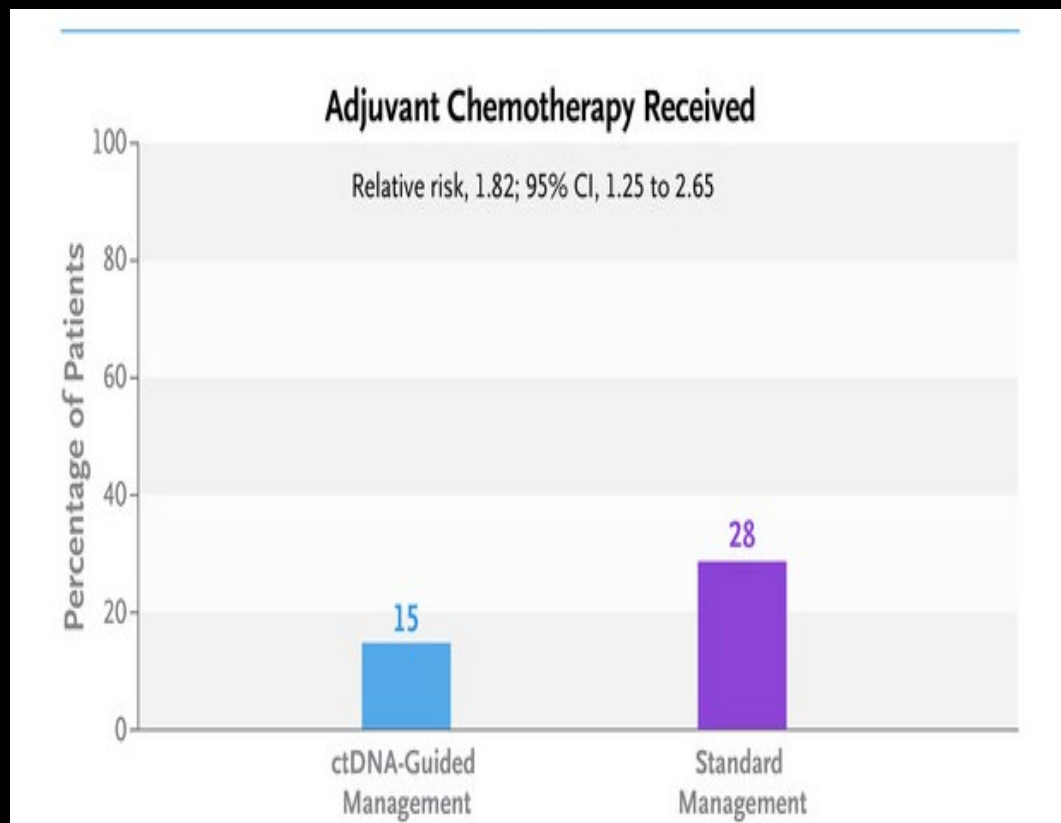
Stage	5FU	FOLFOX	HR	HR95% CI	P Value
All Stage II (n=448)					
3-yr DFS (%)	84.7	87.1	0.89	0.68- 0.16	0.390
5-yr OS (%)	90.0	89.0	1.00	0.74 to 1.35	0.980
Low risk Stage II (n=223)					
3-yr DFS (%)	87.9	88	1.02	0.68-1.53	0.904
5-Yr OS (%)	92.3	90.5	1.17	0.73- 1.87	0.516
High Risk Stage II (n=222)					
3-yr DFS (%)	81.3	86.3	0.79	0.55- 1.13	0.194
5-yr OS (%)	87.5	87.6	0.89	0.60- 1.32	0.579

ctDNA and Chemotherapy in Stage II Colon Cancer- DYNAMIC

Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Standard Management (N=147)	ctDNA-Guided Management (N=294)	Overall (N=441)
Male sex — no. (%)	81 (55)	154 (52)	235 (53)
Median age (range) — yr	62 (28–84)	65 (30–94)	64 (28–94)
Age group — no. (%)			
≤70 yr	113 (77)	207 (70)	320 (73)
>70 yr	34 (23)	87 (30)	121 (27)
ECOG performance-status score — no./total no. (%)†			
0	124/147 (84)	226/293 (77)	350/440 (80)
1	20/147 (14)	65/293 (22)	85/440 (19)
2	3/147 (2)	2/293 (1)	5/440 (1)
Type of center — no. (%)			
Metropolitan	121 (82)	240 (82)	361 (82)
Regional	26 (18)	54 (18)	80 (18)
Primary tumor site — no. (%)‡			
Left side	78 (53)	126 (43)	204 (46)
Right side	69 (47)	168 (57)	237 (54)
Tumor stage — no. (%)			
T3	127 (86)	250 (85)	377 (85)
T4	20 (14)	44 (15)	64 (15)
Poor tumor differentiation — no. (%)	17 (12)	43 (15)	60 (14)
Lymph node yield <12 — no. (%)	7 (5)	13 (4)	20 (5)
Tumor perforation — no. (%)	7 (5)	7 (2)	14 (3)
Bowel obstruction — no./total no. (%)†	18/147 (12)	26/291 (9)	44/438 (10)
Lymphovascular invasion — no. (%)	38 (26)	82 (28)	120 (27)
Deficient mismatch repair — no. (%)	27 (18)	59 (20)	86 (20)
Clinical risk group — no./total no. (%)§			
High	60/147 (41)	116/293 (40)	176/440 (40)
Low	87/147 (59)	177/293 (60)	264/440 (60)
Median time from surgery to randomization (IQR) — days	33 (28–41)	32 (28–39)	32 (28–39.5)

DYNAMIC STUDY HIGHLIGHTS



7% of patients were ctDNA –ve but developed recurrent disease

18% of patients with ctDNA +ve colon cancer still developed recurrence or died within 3 years despite chemotherapy

'Treating only the patients who had detectable ctDNA reduced the percentage of patients who received adjuvant therapy as compared with standard management and did not compromise recurrence-free survival'- Tie et al, 2022

For ctDNA-ve patients, RFS was 85% for patients with high-risk colon cancer

3yr RFS was 91.2 vs 92.7% for standard treatment vs ctDNA guided treatment approach

18% of patients with ctDNA +ve colon cancer still developed recurrence or died within 3 years despite chemotherapy

Summary

If a patient with Stage II colon cancer comes to clinic.

1. Do I need ctDNA assessment to judge their prognosis? – No.

- Overall, 7.8% will be ctDNA +ve

- About 5% for low risk and about **15% for high risk**

2. Do I need ctDNA assessment to determine if they need adjuvant chemotherapy?- No

- Our current treatment algorithms work fine

- Similar 3-year DFS with ctDNA approach vs Standard approach

- COBRA will tell us what to do with ctDNA+ve low risk dxs

3. For high-risk Stage II Colon Cancer. Do you need ctDNA testing- No

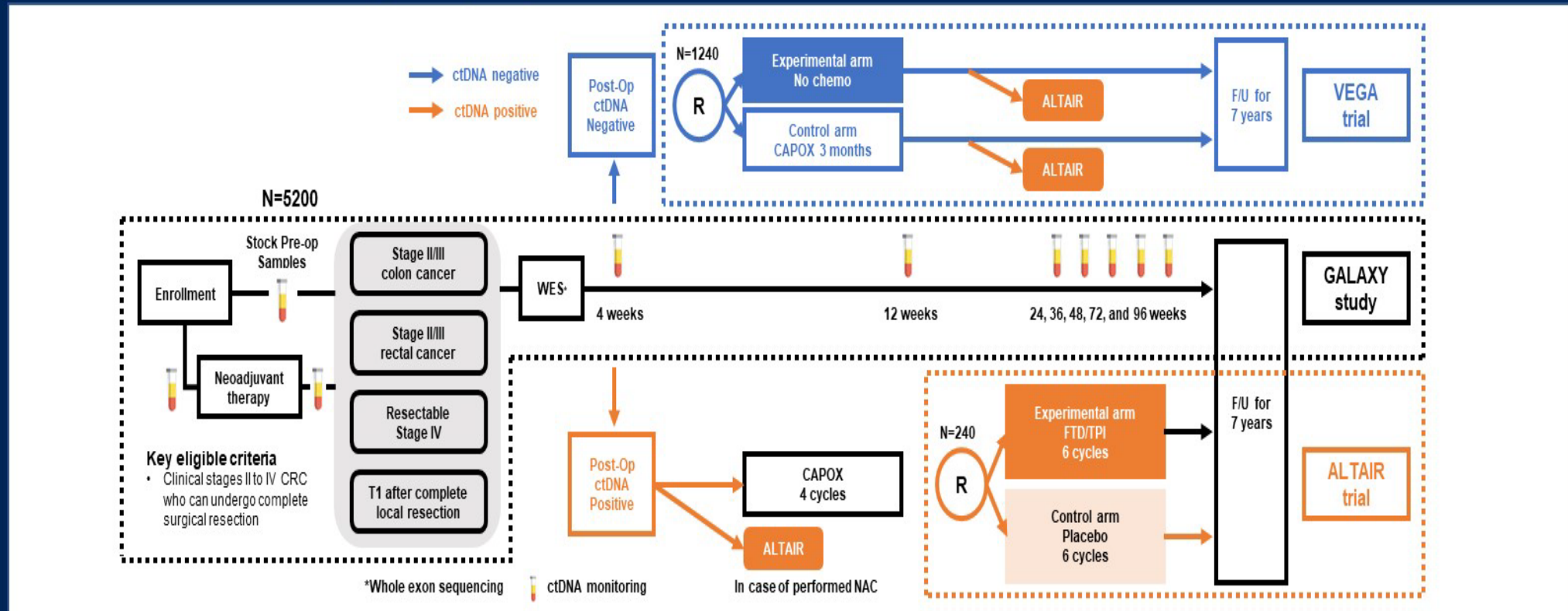
- But- 3yr DFS of 76% vs 92% for adjuvant 5FU vs FOLFOX if ctDNA +ve

- Let's wait for OS numbers

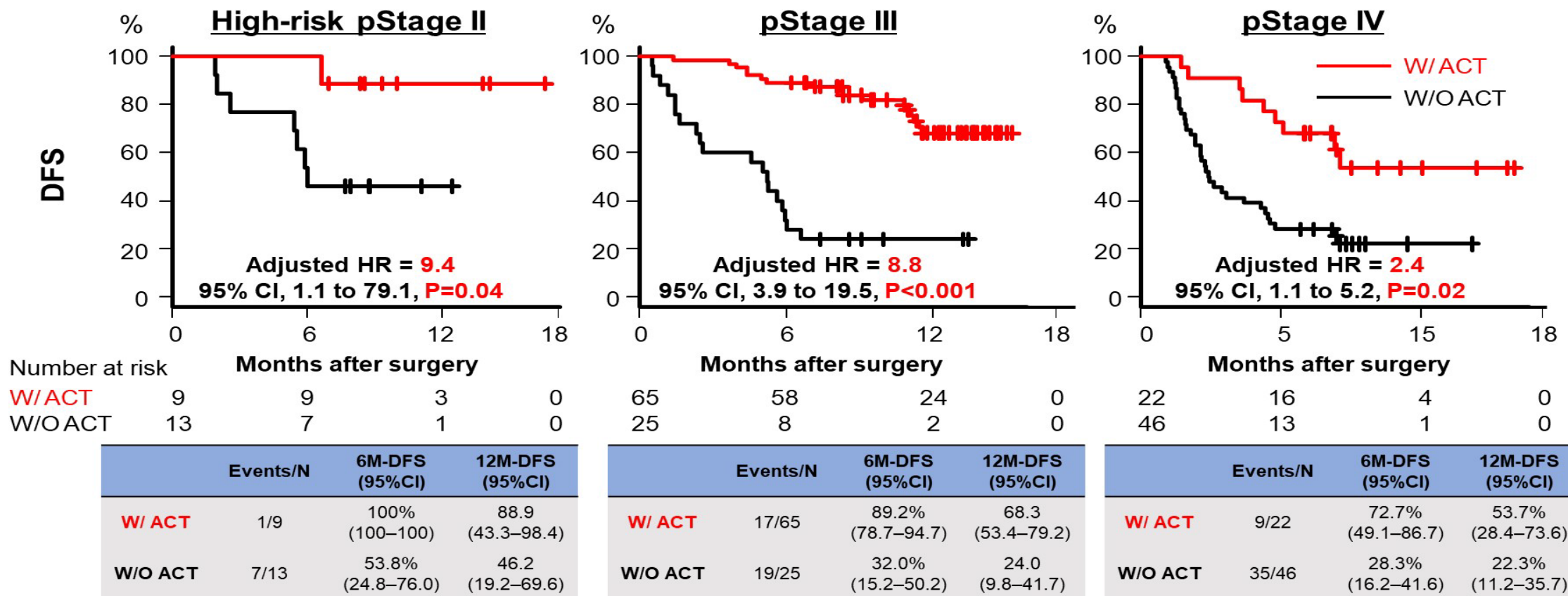
- ALTAIR may provide information about post chemo ctDNA+ve dxs

ctDNA in Stage III disease- Circulate-Japan/GALAXY read out

Schema of CIRCULATE-Japan project



DFS by pStage in post-op-4w ctDNA positive population



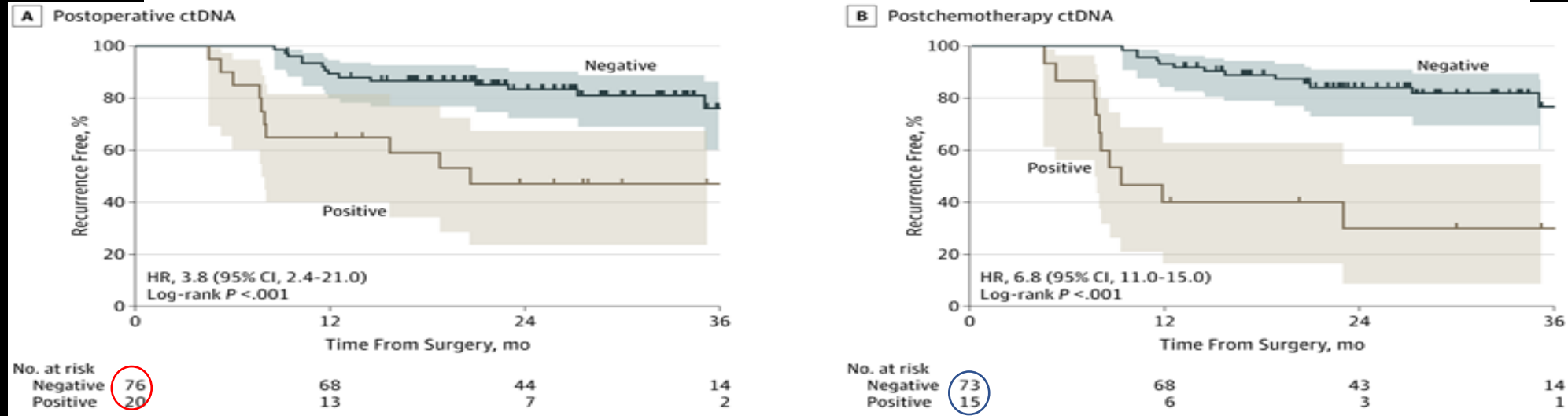
HR was adjusted by sex, and performance status. ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval. DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

Limitations of GALAXY study

The GALAXY is unwieldy

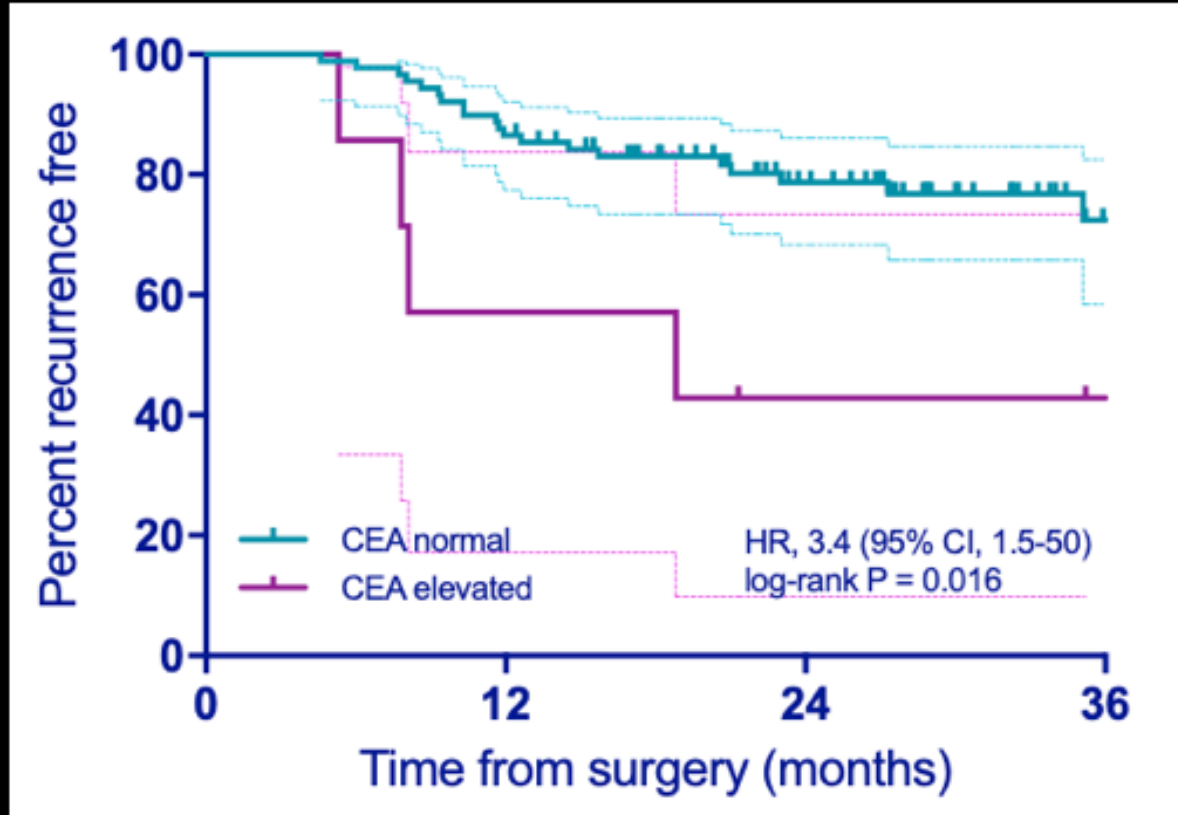
- Observational study
- Heterogenous- colon and rectal Stage I-IV disease
- Limited actionable information

Circulating Tumor DNA Analyses as Markers of Recurrence Risk and Benefit of Adjuvant Therapy for Stage III Colon Cancer



CEA tells a similar story

Post-op CEA



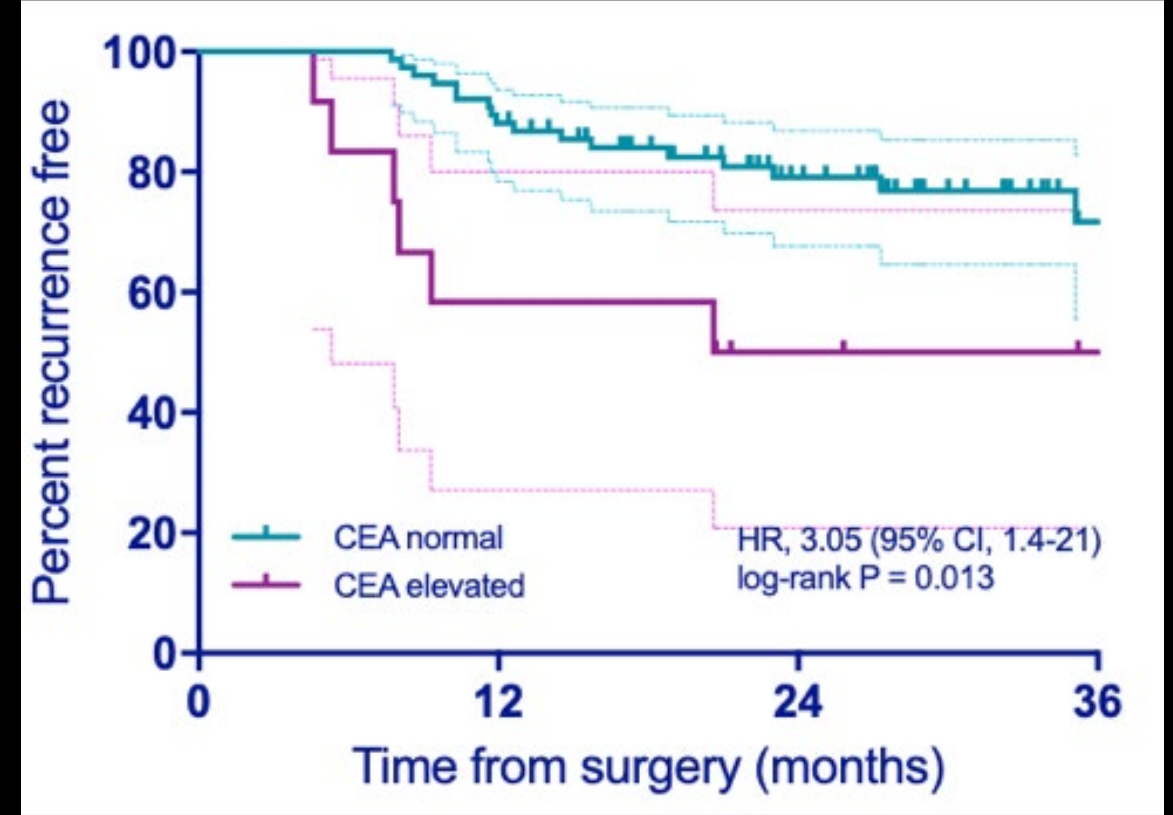
Neg 89
Pos 7

78
5

50
3

16
2

Post-chemo CEA



Neg 76
Pos 12

68
8

43
5

14
3

Summary

- ctDNA assays offer complementary, not supplementary information about prognosis in Stage II and Stage III colon cancer
- In stage II Colon Cancer, MRD assessment may help reduce the rate of use of adjuvant chemotherapy, but the standard treatment pathway provides similar survival outcomes
- ctDNA highlights a problem we are aware of- current adjuvant therapy is inadequate. We know this already
- Based on the available data, today, ctDNA assessment is not ready for guiding adjuvant therapy for most patients with stage II/III Colon cancer. Let the data mature.
- And I have not mentioned the additional costs!



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