

Decennale di
HIGHLIGHTS in
RADIOTERAPIA

*Update degli Studi
Practice Changing 2024*

Undicesima Edizione

In memoria di Renzo Corvò

**New evidence and practice
changing treatments in GI
tumors**

Giuditta Chiloiro, MD, PhD

*Fondazione Policlinico Universitario A. Gemelli
IRCCS*

Gemelli  
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore
Advanced Radiation
Therapy

ROMA

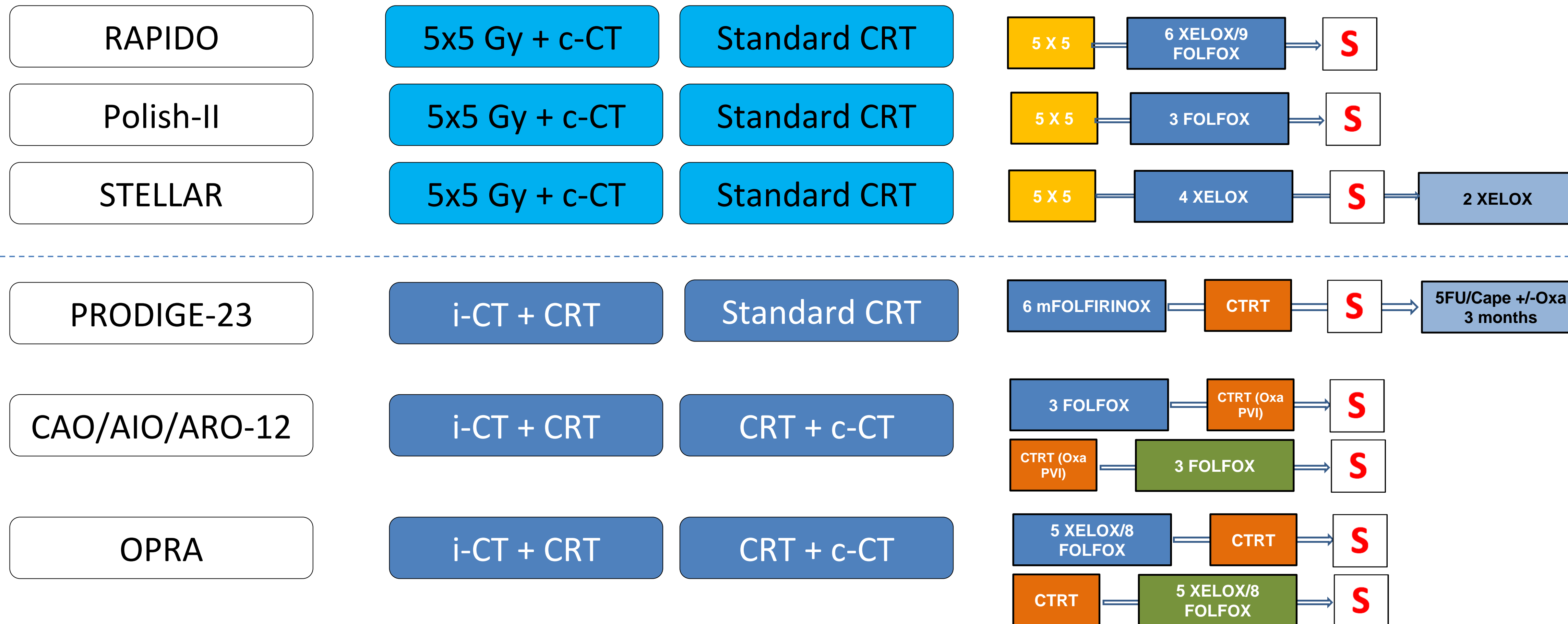
30-31 gennaio 2025
Starhotels Metropole



- Total Neoadjuvant Treatment (TNT)
- RT dose escalation
- Organ preservation
- Immunotherapy (MSI-H)



Total Neoadjuvant Therapy



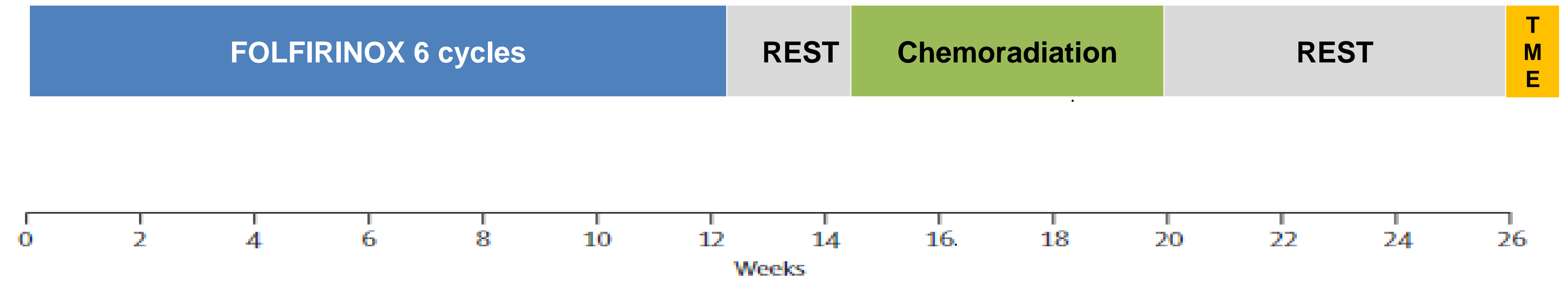
Total Neoadjuvant Therapy

RAPIDO	5x5 Gy + c-CT	Standard CRT
Polish-II	5x5 Gy + c-CT	Standard CRT
STELLAR	5x5 Gy + c-CT	Standard CRT
PRODIGE-23	i-CT + CRT	Standard CRT
CAO/AIO/ARO-12	i-CT + CRT	CRT + c-CT
OPRA	i-CT + CRT	CRT + c-CT

TNT Outcomes

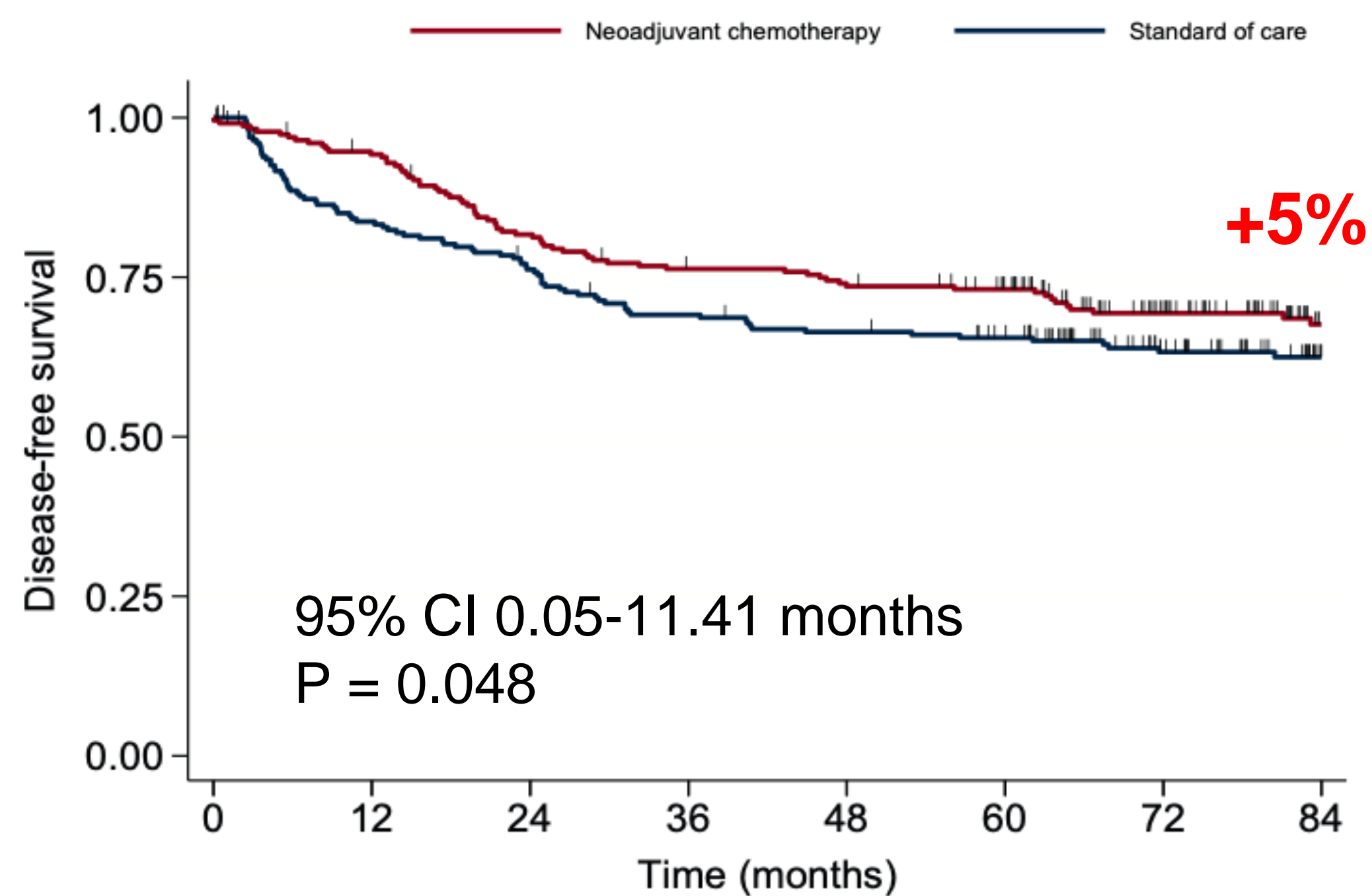
- **pCR** → improved
- **Local recurrence** → worst RAPIDO
- **Distant metastases** → improved
- **Disease free survival** → improved
- Overall Survival → **2024 news**

PRODIGE-23 trial



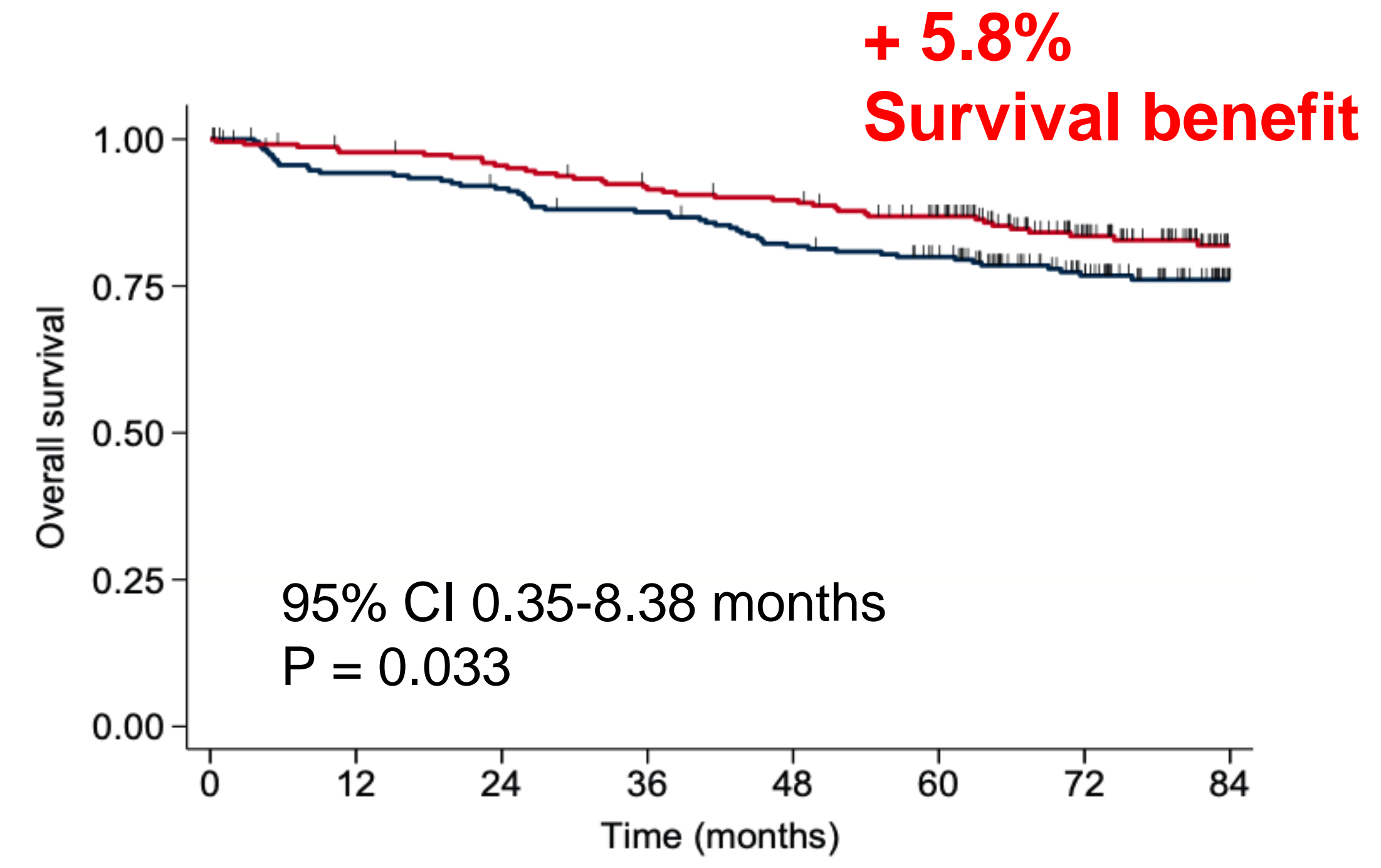
PRODIGE 23: 7-years follow up results

Disease free survival



Number at risk		0	12	24	36	48	60	72	84
Neoadjuvant chemotherapy	231	211	182	168	162	152	107	67	
Standard of care	230	190	172	155	148	140	100	64	

Overall survival



Number at risk		0	12	24	36	48	60	72	84
Neoadjuvant chemotherapy	231	218	212	201	196	179	127	79	
Standard of care	230	213	206	196	182	171	125	79	

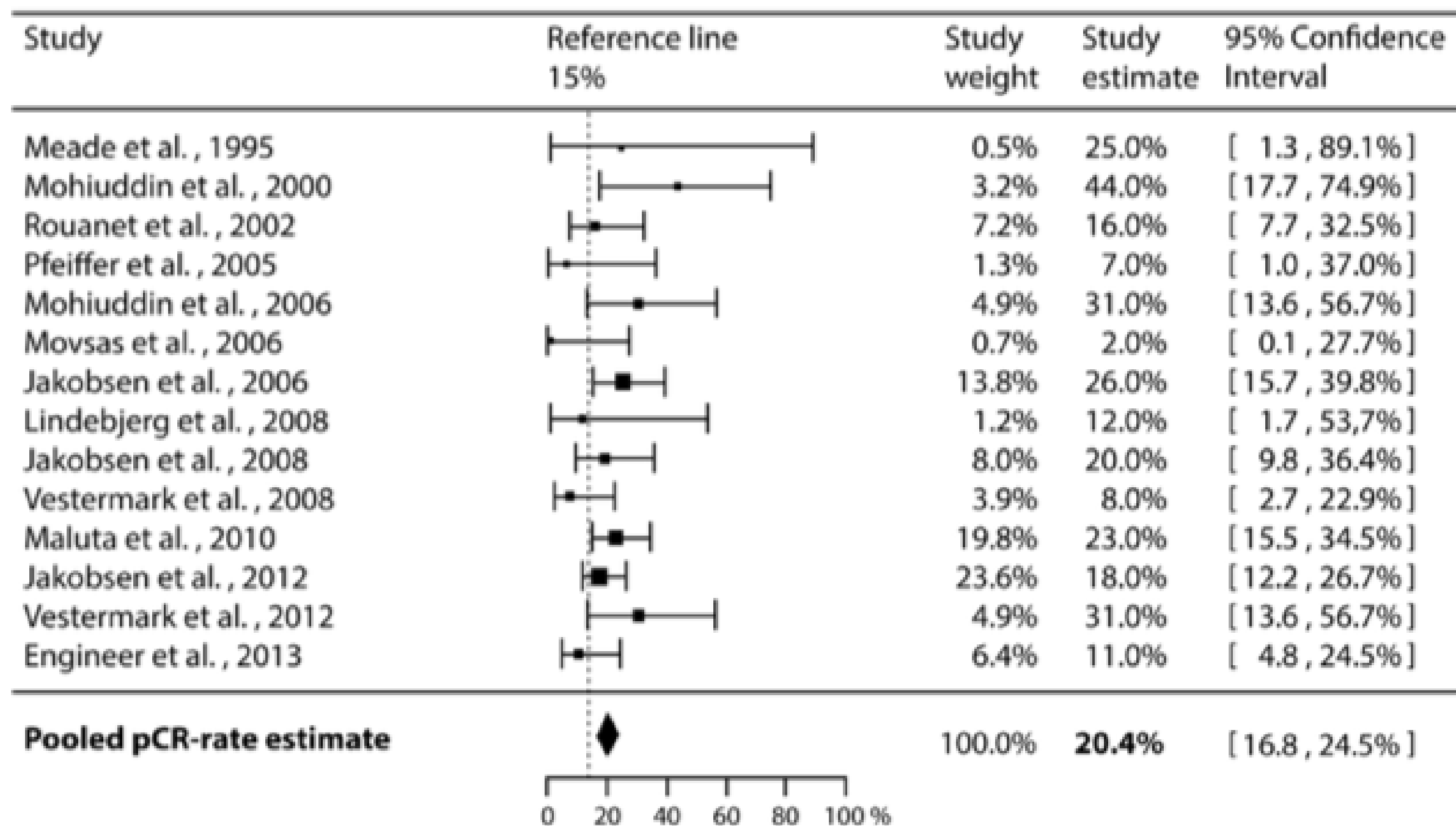
Total Neoadjuvant Therapy- to discuss:

- Induction versus consolidation
- High risk factors definition
- Standard Rt dose: 50.4 Gy

- Total Neoadjuvant Treatment (TNT)
- RT dose escalation
- Organ preservation
- Immunotherapy (MSI-H)



RT dose ≥ 60 Gy \rightarrow \uparrow pCR



- Non-operative management
- No clear impact on long term oncological outcomes
- Toxicity is **STILL** an issue

CXB Unique RT Technique : High RX dose/ small volume



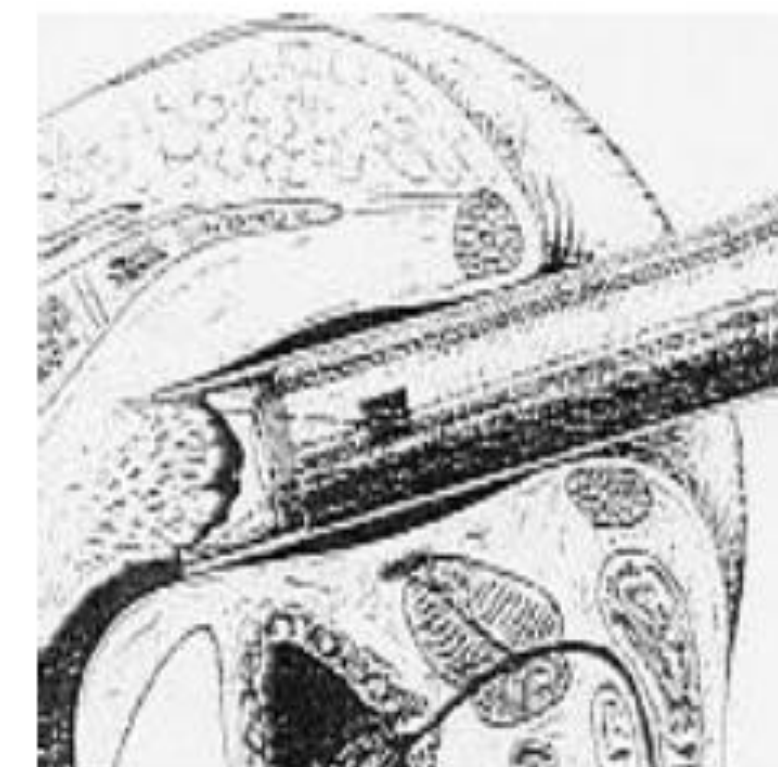
Contact X-ray 50 kV



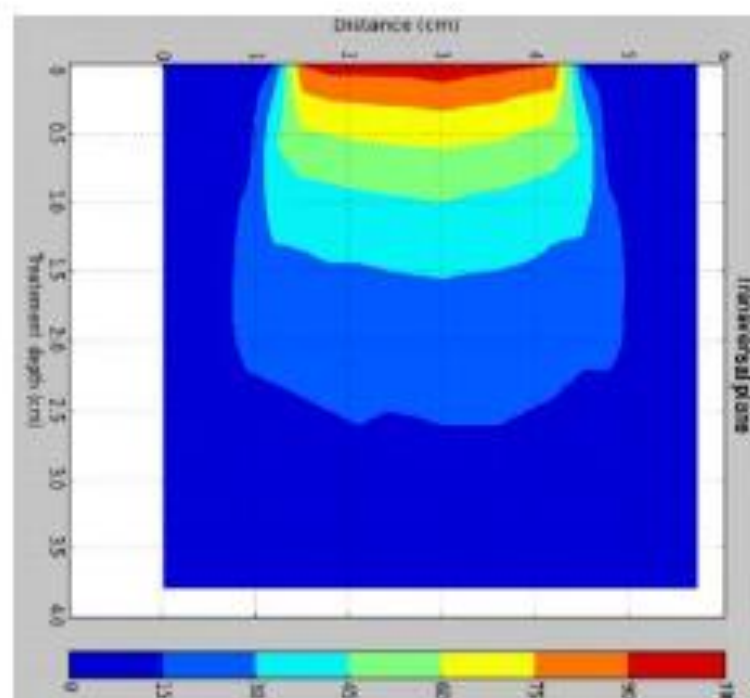
Ambulatory
Knee-chest position



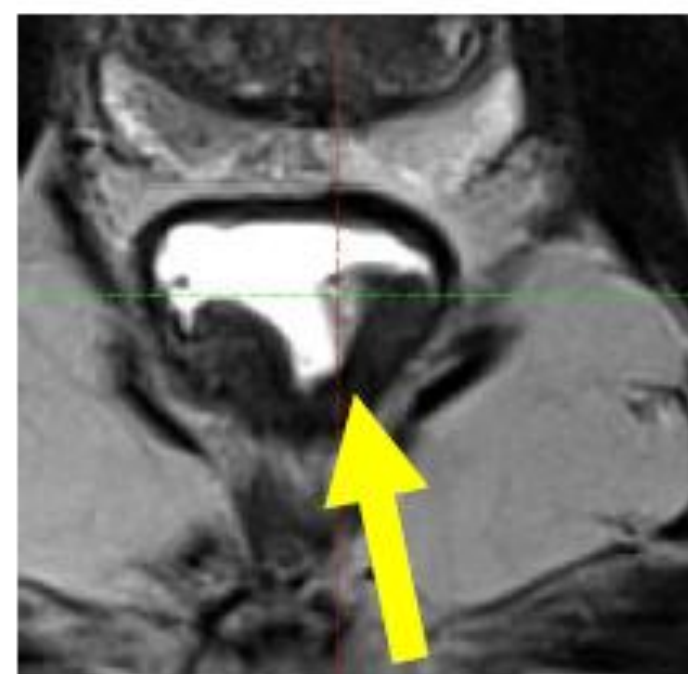
Precision
Eye guided
Applicator 3 cmØ



Endocavitary
30 Gy / 2 mn
fast - simple



Dose: Sharp fall off 50% : 5mm



T1-3 a/b < 5 cm
N0



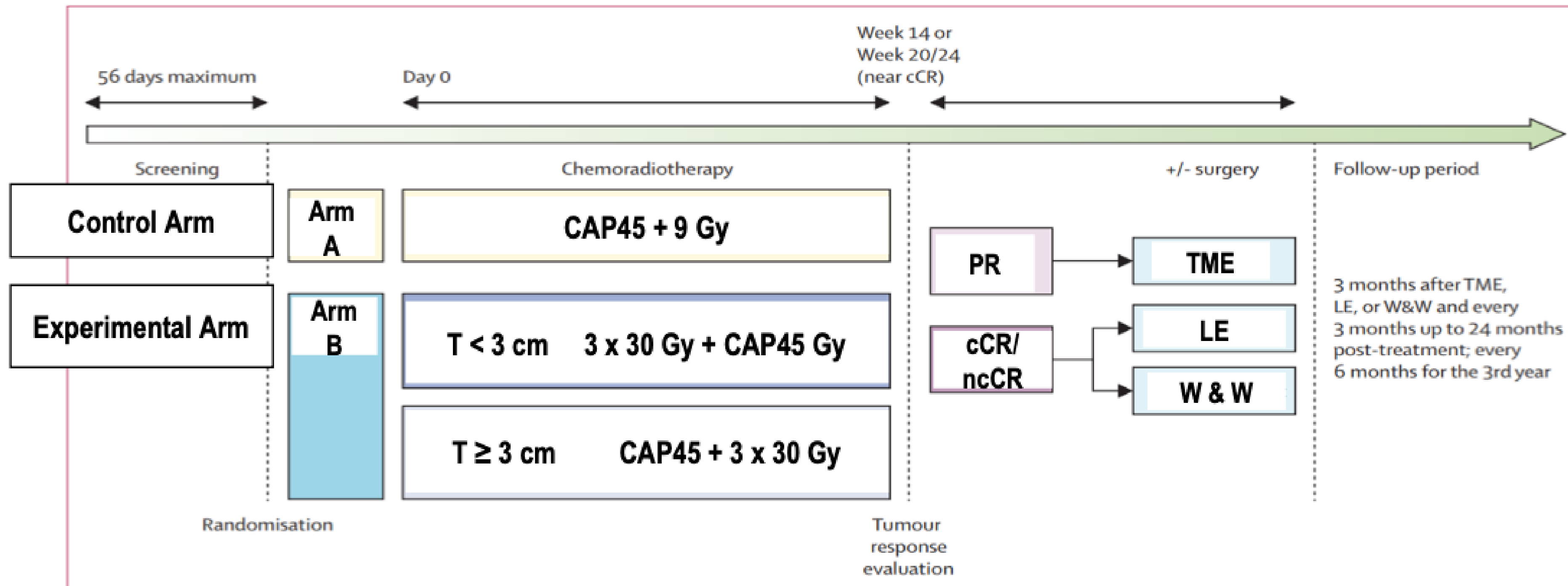
2.5 cm Ø 1/4 circumf.



Local control ≥ 85%

Gérard, et al. Eur J Cancer 2019

Phase III OPERA trial



Inclusion criteria:

- cT2-T3a/b
- diam <5cm
- N0-1
- <10 cm AV

July 2015 - June 2020

148 patients
randomised
(141 evaluable)

(**Arm A 69 – Arm B 72**)

Primary end-point:

- 3-yrs Organ Preservation

Organ preservation: updated results

BARCELONA 2024 **ESMO** congress

Organ preservation in early rectal adenocarcinoma: 5-year results of the randomized OPERA trial

Syrine Ben Dhia, MD et al. On behalf of ICONE

Antoine Lacassagne center, Nice, France 14/09/2024
Université Côte d'Azur

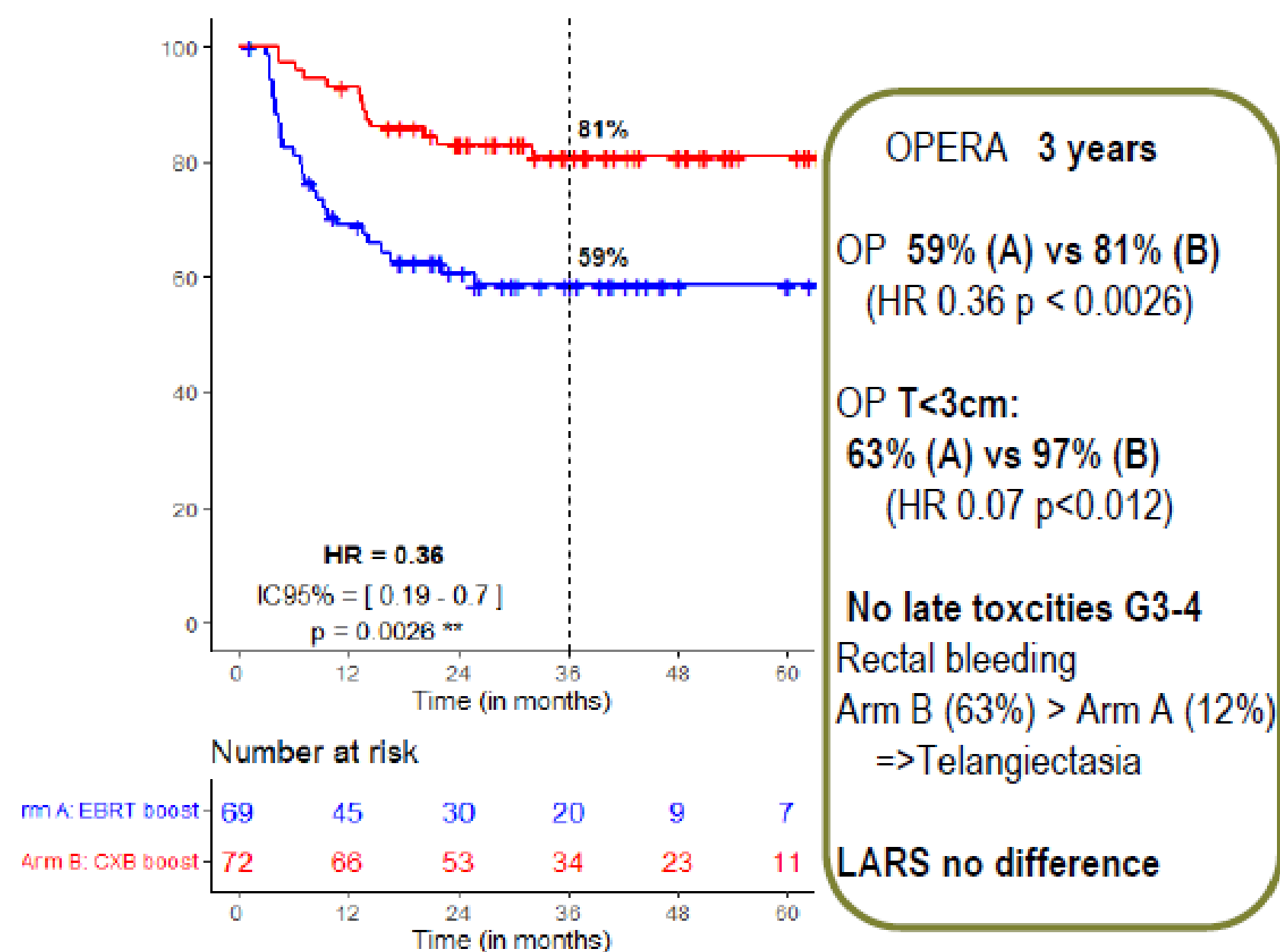


Syrine Ben Dhia

Organ preservation in early rectal adenocarcinoma: 5-year results of the randomized opera trial

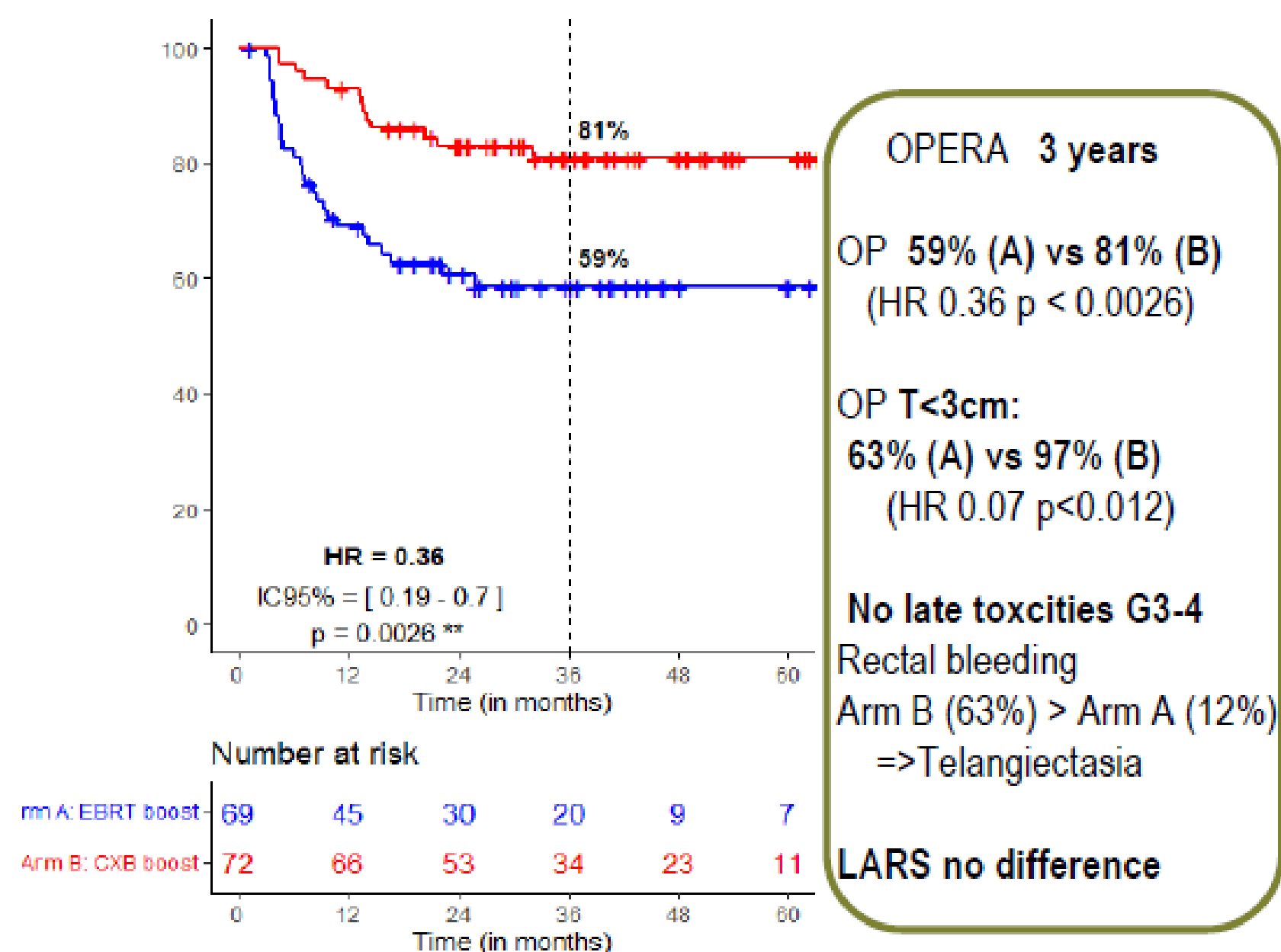
Phase III OPERA trial

141 Patients - Rectal preservation 3 years

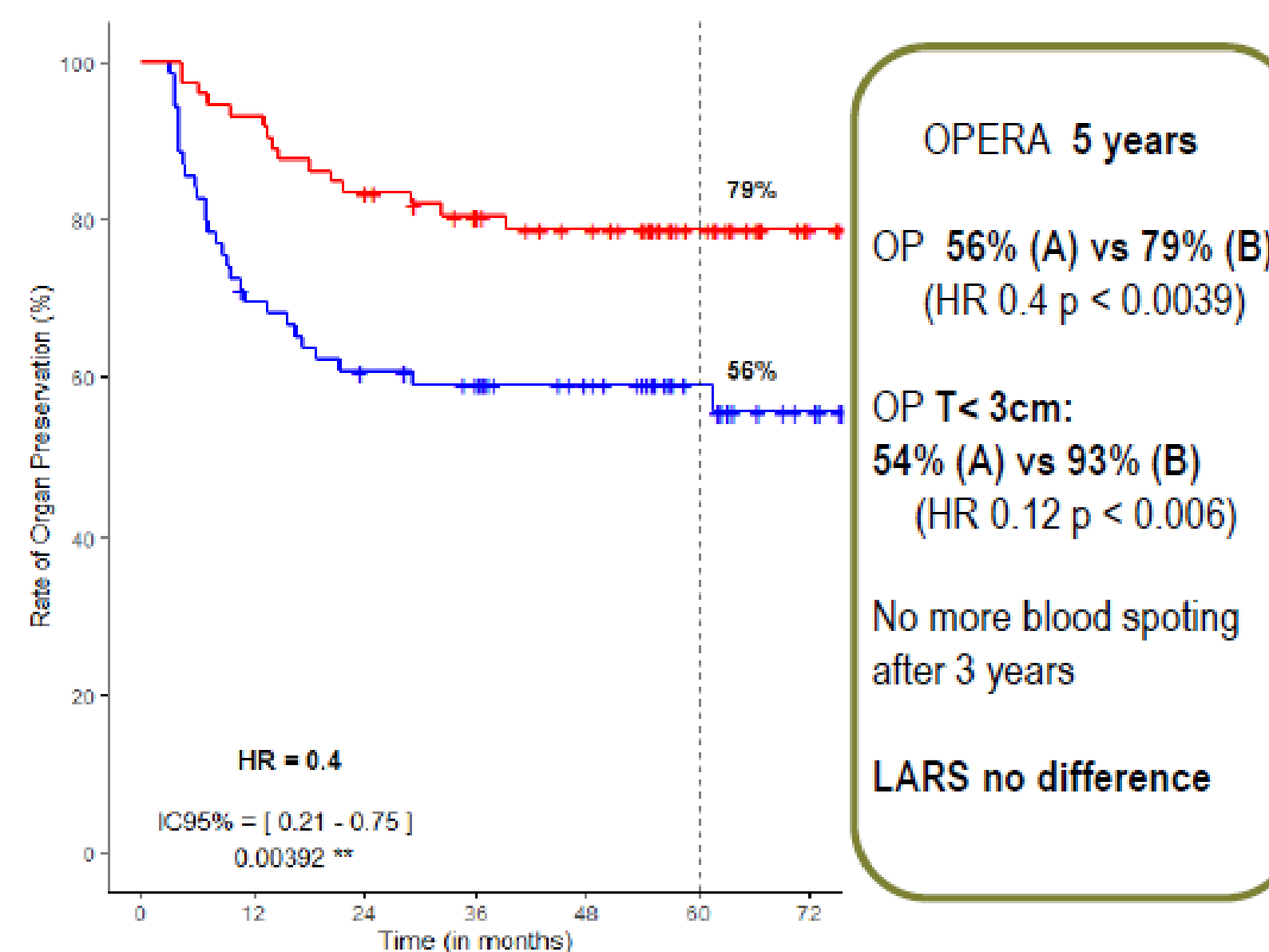


Primary end point

141 Patients - Rectal preservation 3 years

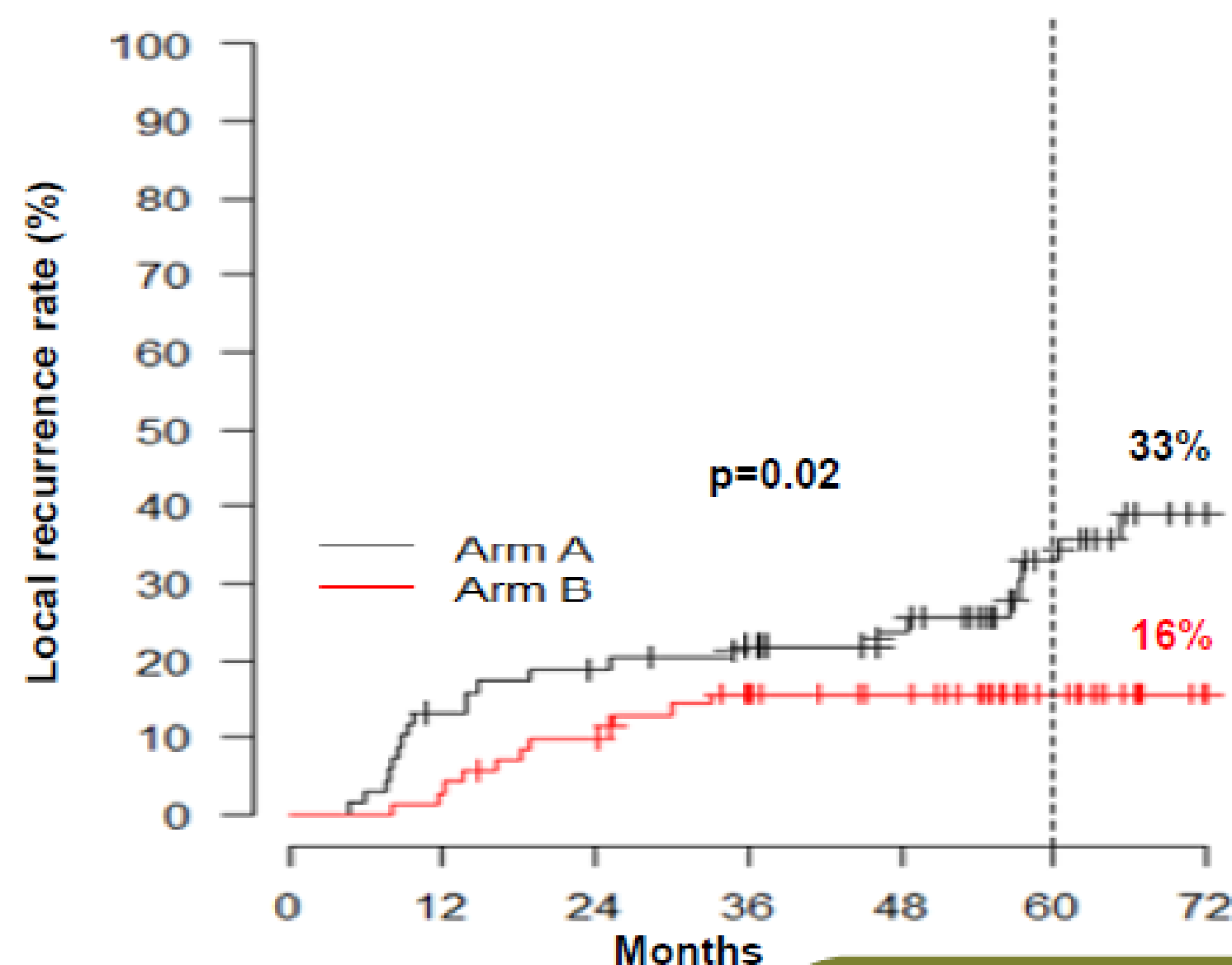


141 Patients - Rectal preservation 5 years

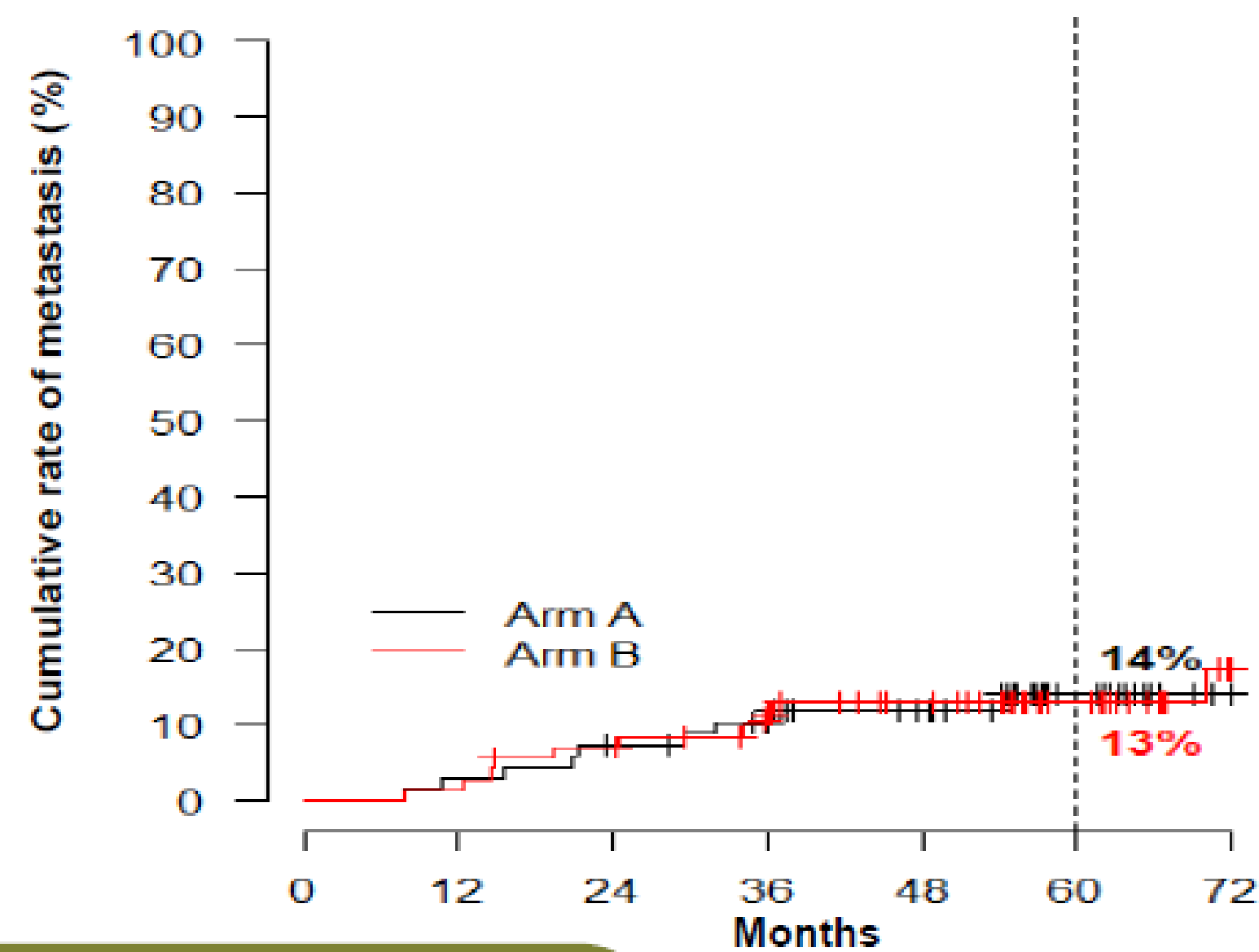


Secondary end points

Local recurrences at 5 year: 32 pts



Distant metastasis at 5 year: 20 pts



Local recurrence 16% (contact) vs 33% (control) ($p=0.02$)

Distant metastasis 13% (contact) vs 14% (control)

Disease-Free Survival 46% (contact) vs 73% (control) ($p=0.003$)

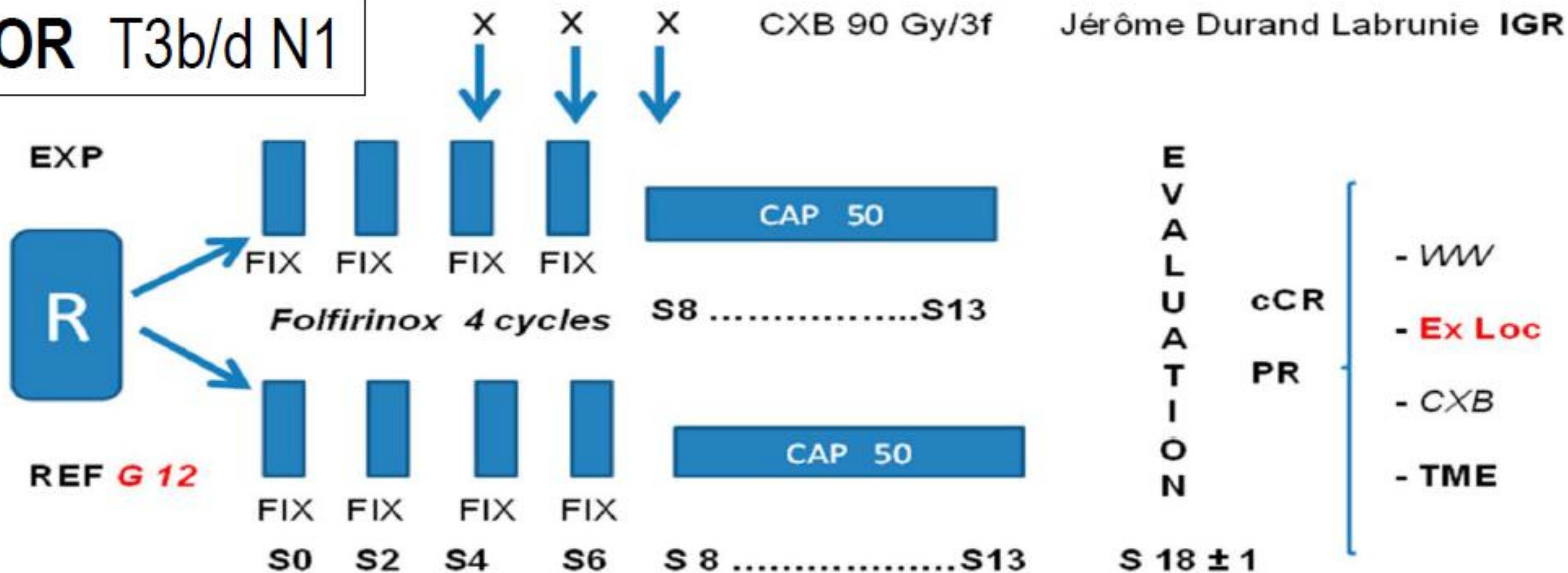
OS no difference

OPERA Conclusion *H Rutten (Lancet Gastro Hepatol 2023)*

TRESOR (FIX x4)

T2-T3 > 3.5 cm N0-N1 < 8 mm < 75 years **CXB boost?**

TRESOR T3b/d N1

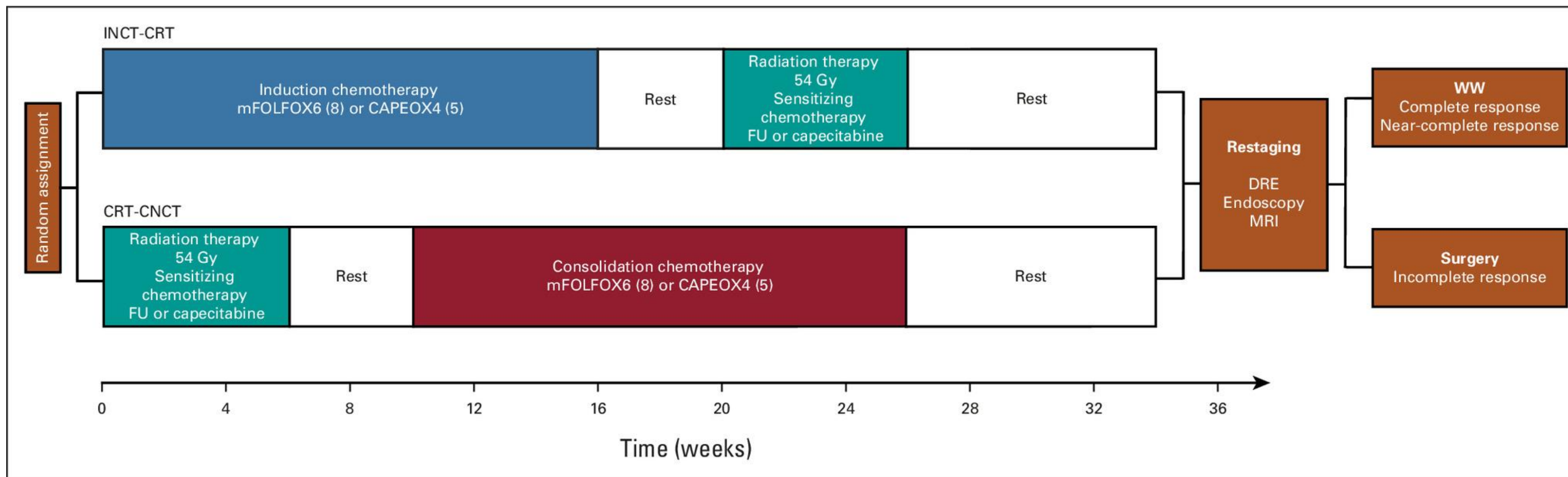


Ph III 3-year survival with organ preservation 60% vs. 40% : 200 pts

- Total Neoadjuvant Treatment (TNT)
- RT dose escalation
- **Organ preservation**
- Immunotherapy (MSI-H)



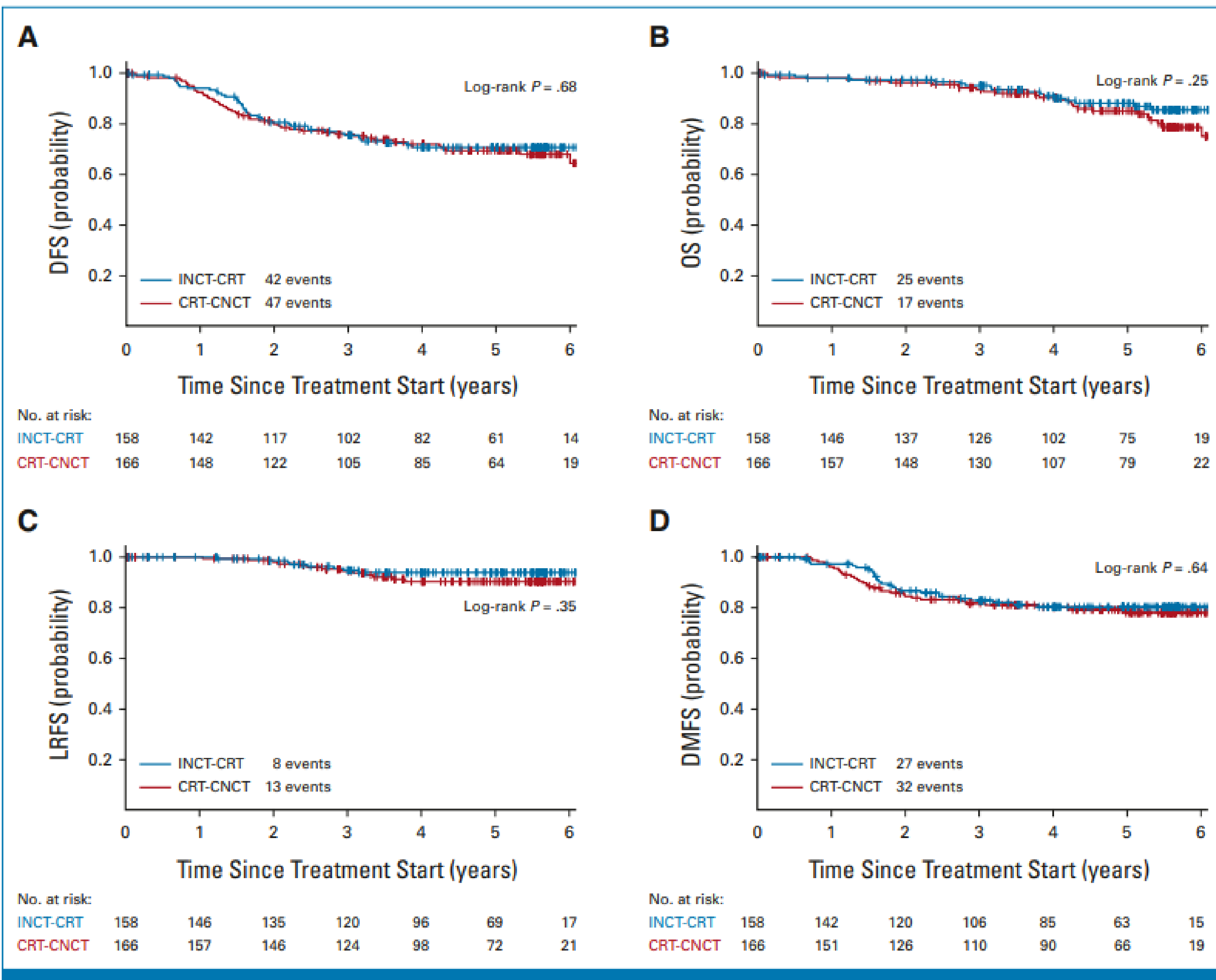
OPRA trial



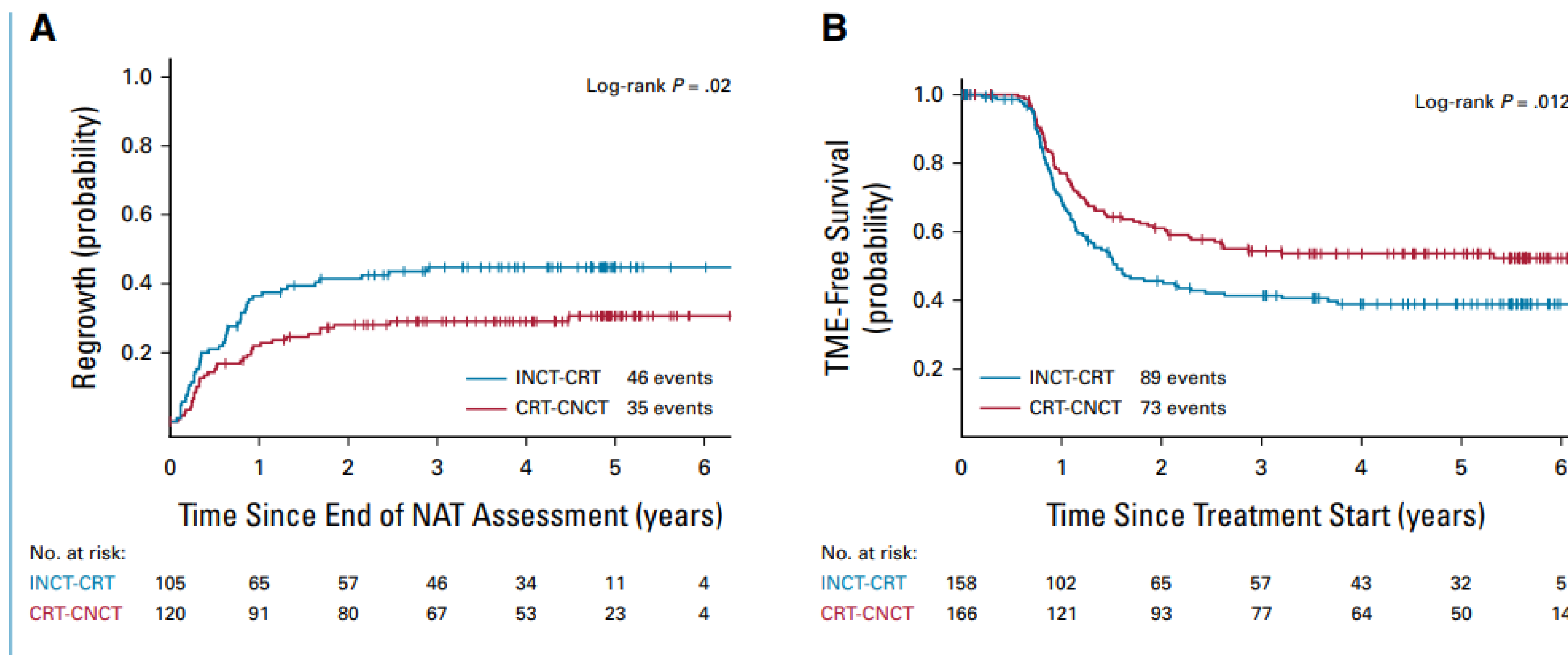
OPRA trial

Median FUP 51 mo

Primary end point: DFS



Secondary end point: TME-FS



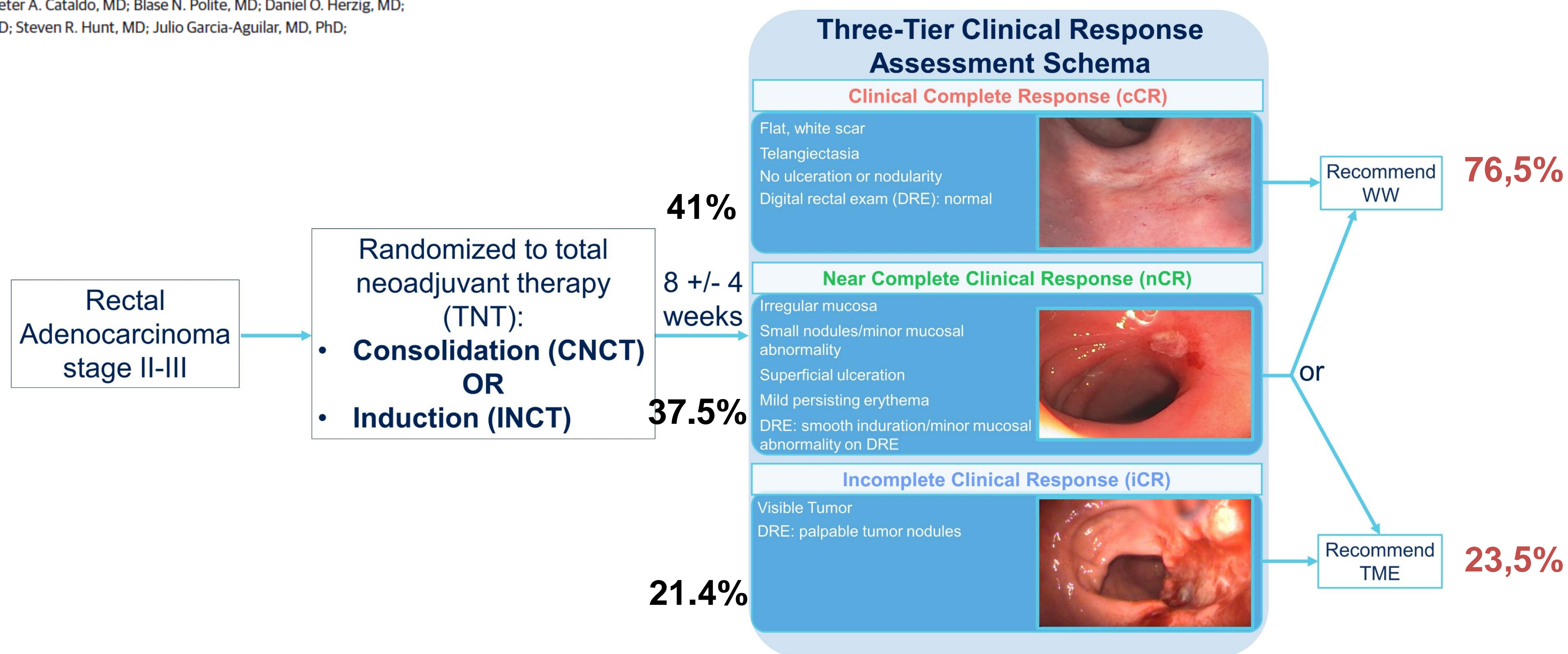
Regrowth:
Overall 36%: 44 InCT vs 29% CnCT
99% Regrowth within 2 years



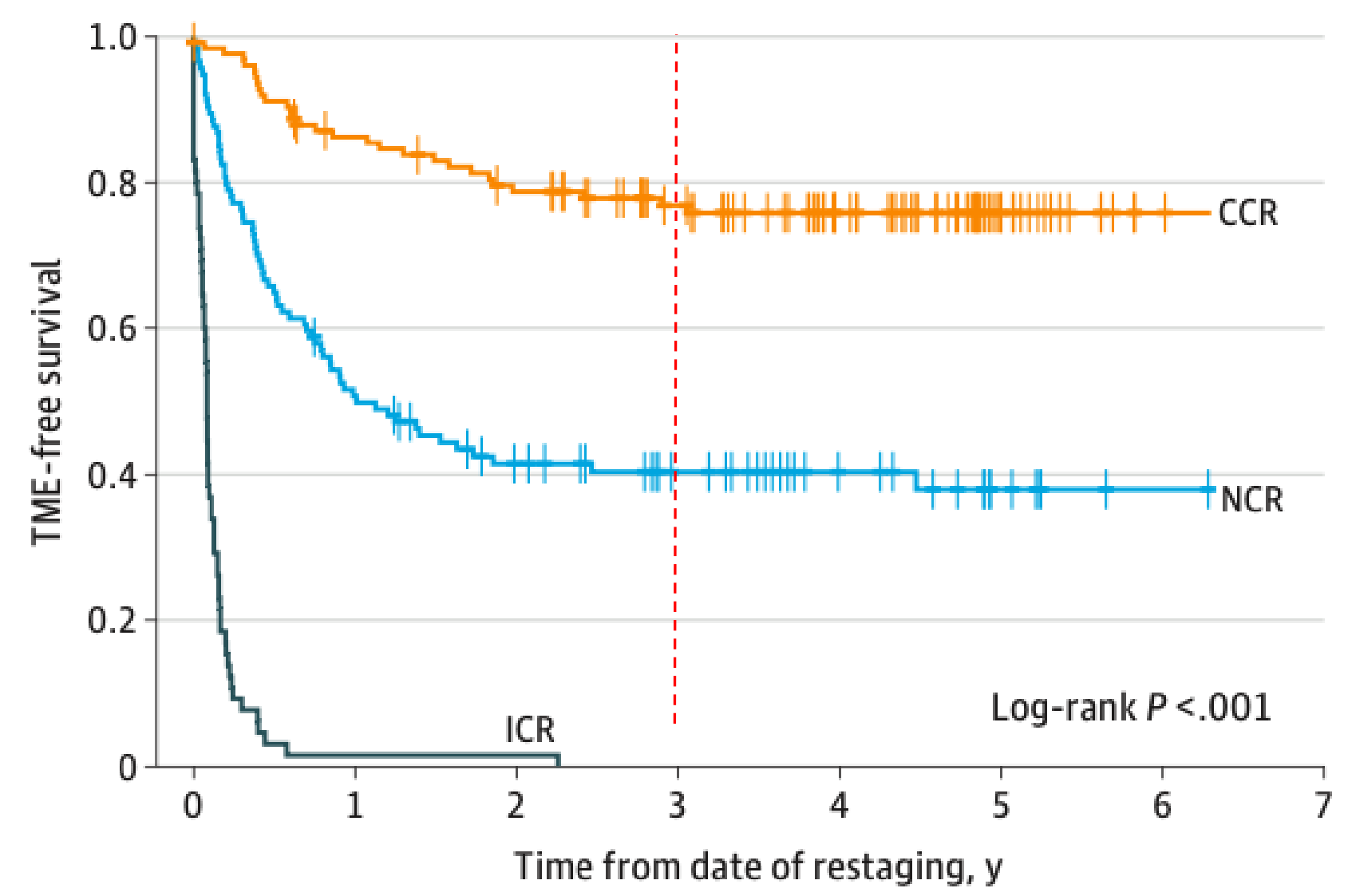
Original Investigation | Oncology

Organ Preservation and Survival by Clinical Response Grade in Patients With Rectal Cancer Treated With Total Neoadjuvant Therapy A Secondary Analysis of the OPRA Randomized Clinical Trial

Hannah M. Thompson, MD; Dana M. Omer, MD; Sabrina Lin, MS; Jin K. Kim, MD; Jonathan B. Yuval, MD; Floris S. Verheij, BSc; Li-Xuan Qin, PhD; Marc J. Gollub, MD; Abraham Jing-Ching Wu, MD; Meghan Lee, BS; Sujata Patil, PhD; Aram F. Hezel, MD; Jorge E. Marcet, MD; Peter A. Cataldo, MD; Blase N. Polite, MD; Daniel O. Herzig, MD; David Liska, MD; Samuel Oommen, MD; Charles M. Friel, MD; Charles A. Ternent, MD; Andrew L. Coveler, MD; Steven R. Hunt, MD; Julio Garcia-Aguilar, MD, PhD; for the OPRA Consortium



Primary end point: 3 year OP



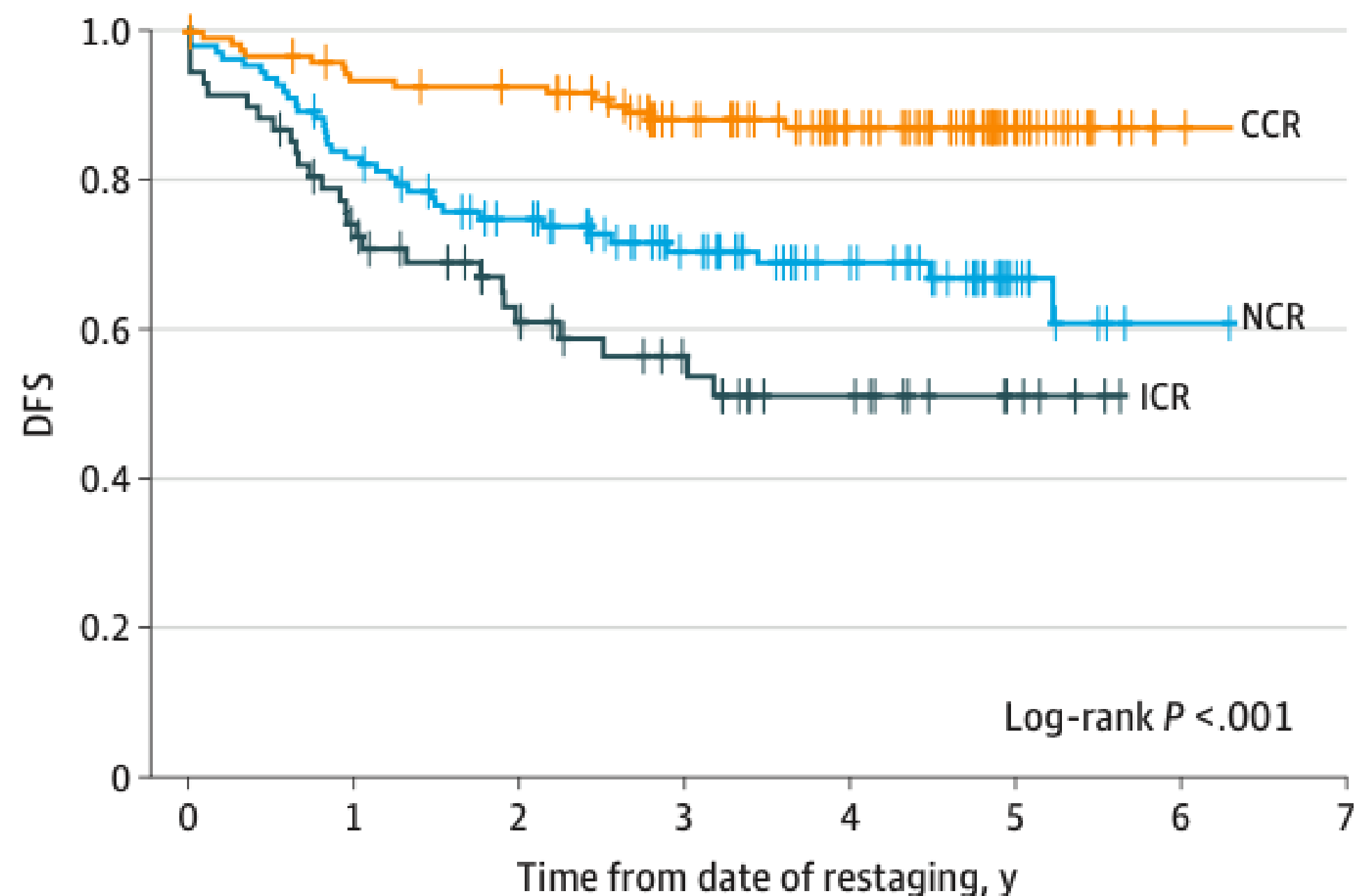
77%

40%

0%

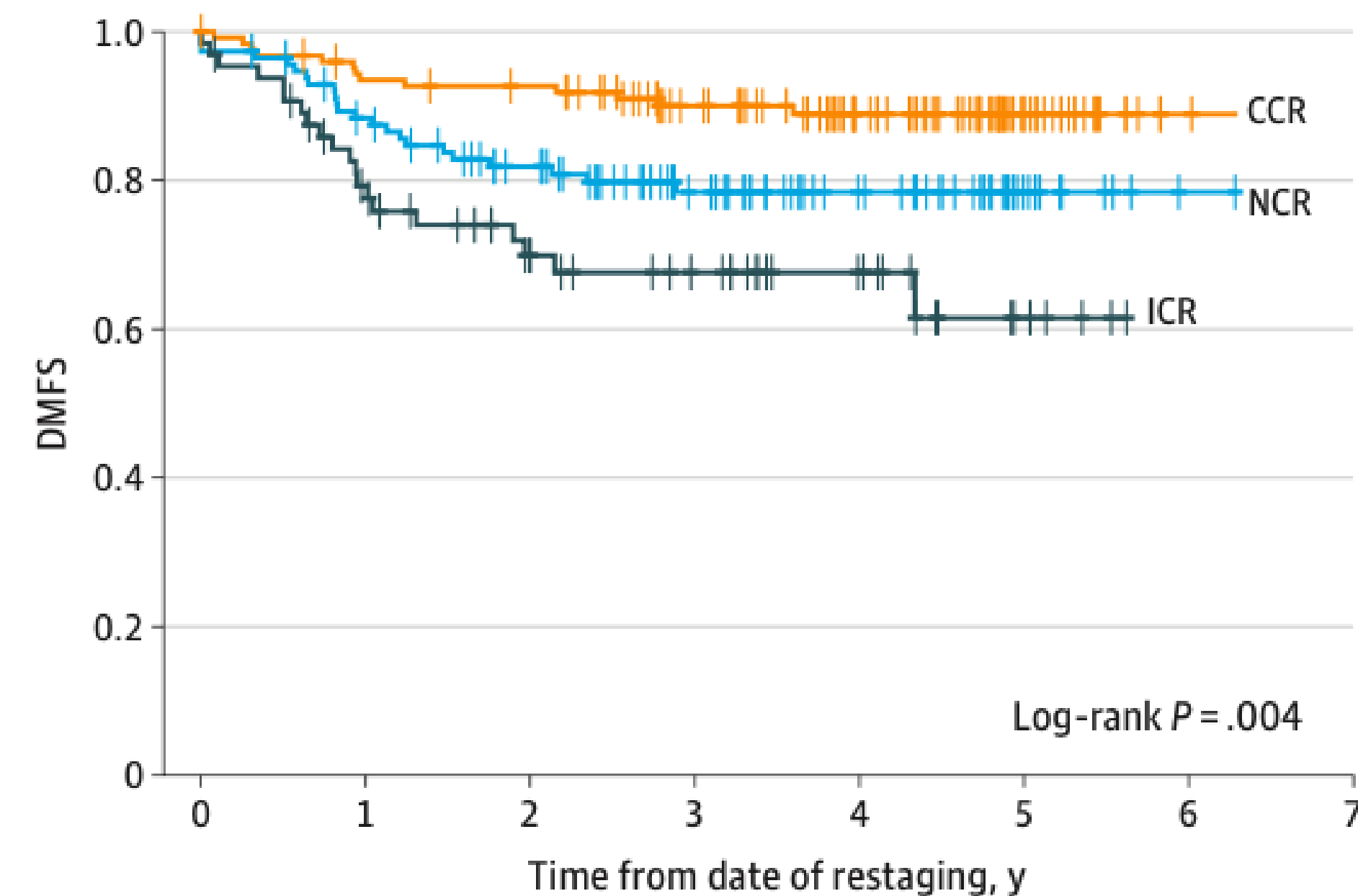
No. at risk	0	1	2	3	4	5	6	7
CCR	125	104	93	77	54	19	4	
NCR	114	57	41	31	19	9	4	
ICR	65	1	1	0	0	0	0	

Disease free survival



No. at risk	0	1	2	3	4	5	6	7
CCR	125	113	110	89	65	26	6	
NCR	114	92	75	55	37	14	6	
ICR	65	45	29	21	13	5	0	

Distant Metastases free survival



No. at risk	0	1	2	3	4	5	6	7
CCR	125	114	111	90	66	27	6	
NCR	114	97	81	59	39	16	6	
ICR	65	47	32	25	16	5	0	



Total Neoadjuvant Treatment (TNT) including Non-Operative Management (NOM) for Proficient Mismatch Repair Locally Advanced Rectal Cancer (pMMR LARC): First Results of NO-CUT Trial

Amatu A.¹, Zampino M. G.², Bergamo F.³, Mosconi S.⁴, Sibio D.¹, Gerardi M. A.², Prete A. A.³, Filippone F. R.⁴, Ferrari G.¹, Borin S.², Galuppo S.³, Mariano S.¹, Tosi F.¹, Bonazzina E.¹, Patelli G.^{1,5,6}, Ghezzi S.¹, Lazzari L.⁶, Bencardino K.¹, Sartore-Bianchi A.^{1,5}, and Siena S.^{1,5}
on behalf of the NO-CUT Trial Cooperative Group

¹ Grande Ospedale Metropolitano Niguarda, Milan, Italy

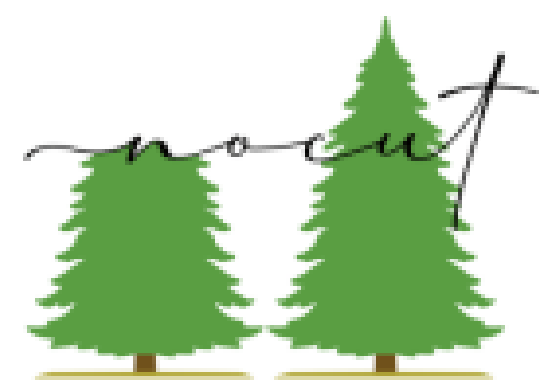
² Istituto Europeo Oncologia IRCCS, Milan, Italy

³ Istituto Oncologico Veneto IRCCS, Padua, Italy.

⁴ ASST Papa Giovanni XXIII, Bergamo, Italy

⁵ Università degli Studi di Milano, Milan, Italy

⁶ IFOM ETS The AIRC Institute of Molecular Oncology



NO-CUT Trial
EudraCT 2017-3671-60

presented by **Alessio Amatu, MD**

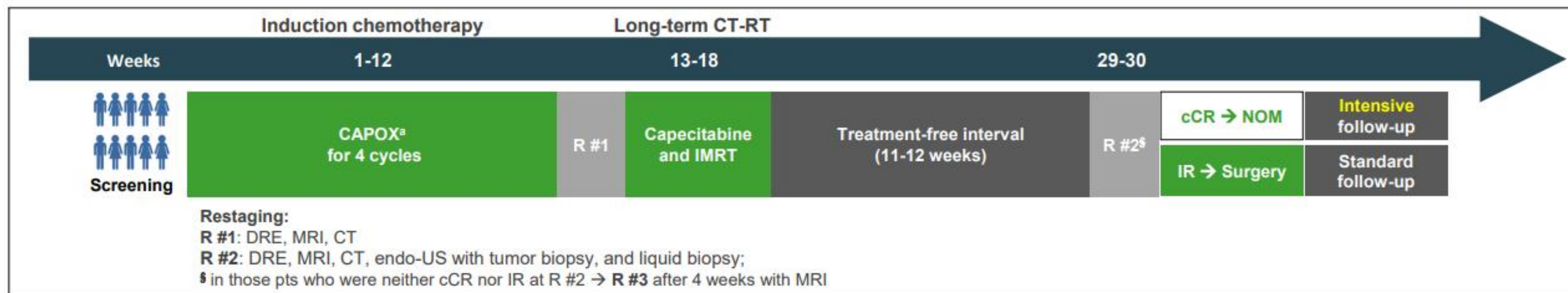
ESMO 2024 Congress, Presidential Symposium Eyes to the Future, September 16, 2024



NO-CUT TRIAL design



180 patients with mid/low cT3-4 and/or cN1-2, cM0, pMMR/MSS, rectal adenocarcinoma; ECOG PS 0-1, fit for surgery



- Primary endpoint:** % of patients alive and distant relapse free at 30 months (DRFS₃₀, H₀: 75% and H₁: 82%); at least 44 NOM patients were needed, with an $\alpha = 10\%$ and $\beta = 20\%$ to reject H₀
- Secondary endpoints:** cCR rate, organ preservation rate in NOM patients

Abbreviations: **cCR** = clinical complete response; **CT**: computed tomography scan with contrast medium of chest, abdomen, and pelvis; **CT-RT**: chemo-radiotherapy; **DRE**: digital rectal examination; **endo-US**: endoscopic Ultrasound; **IMRT**: intensive modulated radiation therapy; **IR**: incomplete response; **pMMR**: proficient mismatch repair; **MRI**: magnetic resonance imaging with contrast medium of pelvis; **NOM**: non-operative management; **R**: restaging. ^a FOLFOX 6 cycles if not eligible to CAPOX.

Clinical tumor response to TNT

		cCR (%)	IR (%)	p-value
Number of patients		46 (26)	134 (74)	-
Tumor location	Low	26 (36)	47 (64)	0.017
	Medium	20 (19)	87 (81)	
Clinical T stage	T1	2 (100)	0 (0)	0.004
	T2	5 (39)	8 (61)	
	T3	37 (28)	96 (72)	
	T4	2 (6)	30 (94)	
Clinical TNM stage	II	9 (45)	11 (55)	0.065
	III	37 (23)	123 (77)	

- 26% patients achieved cCR and proceeded with NOM
- 90% patients who had IR underwent surgery
- T stage was confirmed as a clinical predictor of cCR
- Tumor location (low) was associated with response

Abbreviations: **cCR** = clinical complete response; **IR**: incomplete response; **NOM**: non-operative management.



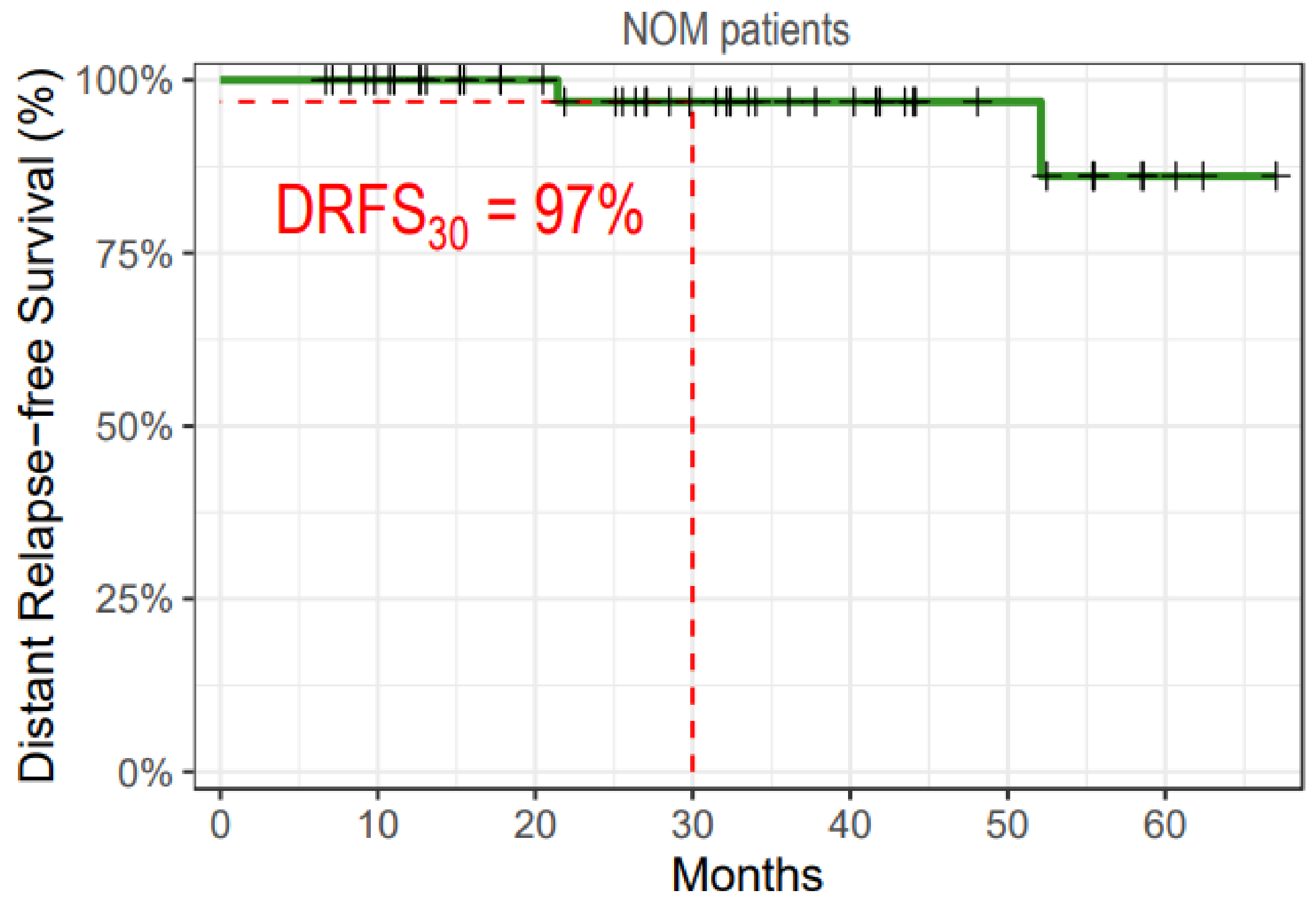
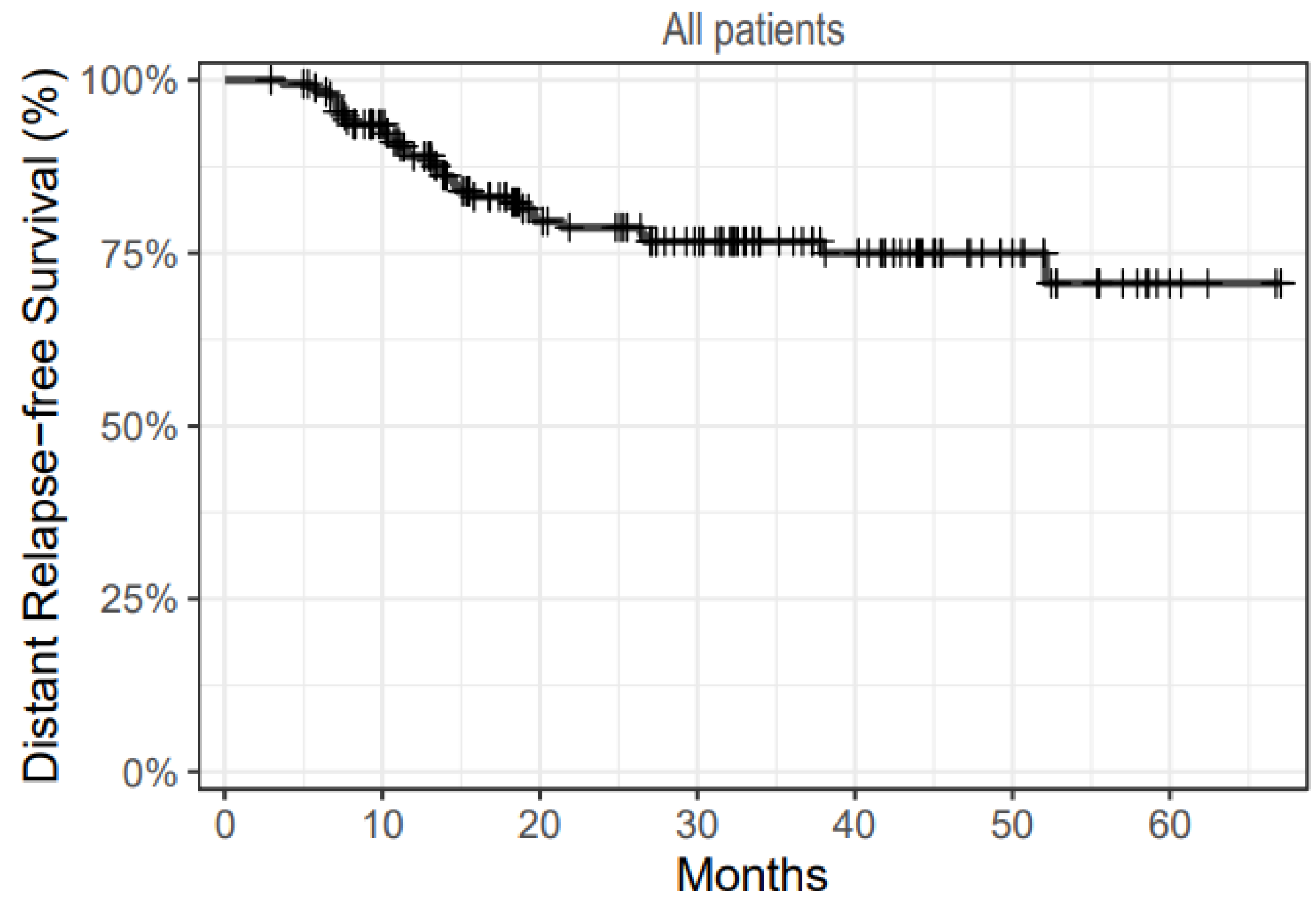
Alessio Amatu

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NO-CUT Trial
 EudraCT 2017-3671-60

Primary Objective: Distant Relapse-Free Survival in NOM patients



Primary endpoint (Distant Relapse-Free Survival at 30 months, DRFS₃₀) was met:

- In NOM pts (n = 46) DRFS₃₀ 96.9% (95%CI 91.0-100.0)
- In all pts (n = 180) DRFS₃₀ 76.7% (95%CI 69.8-84.2)



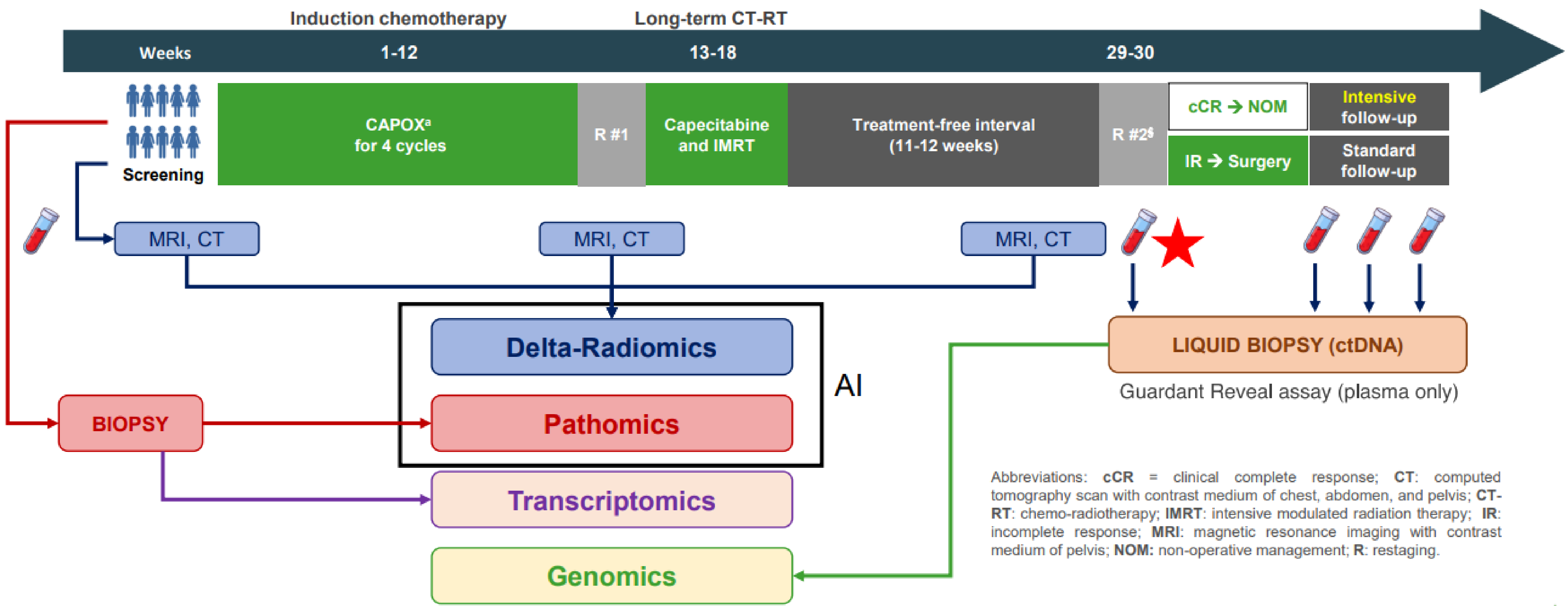
Alessio Amatu

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Translational multi-omics programme

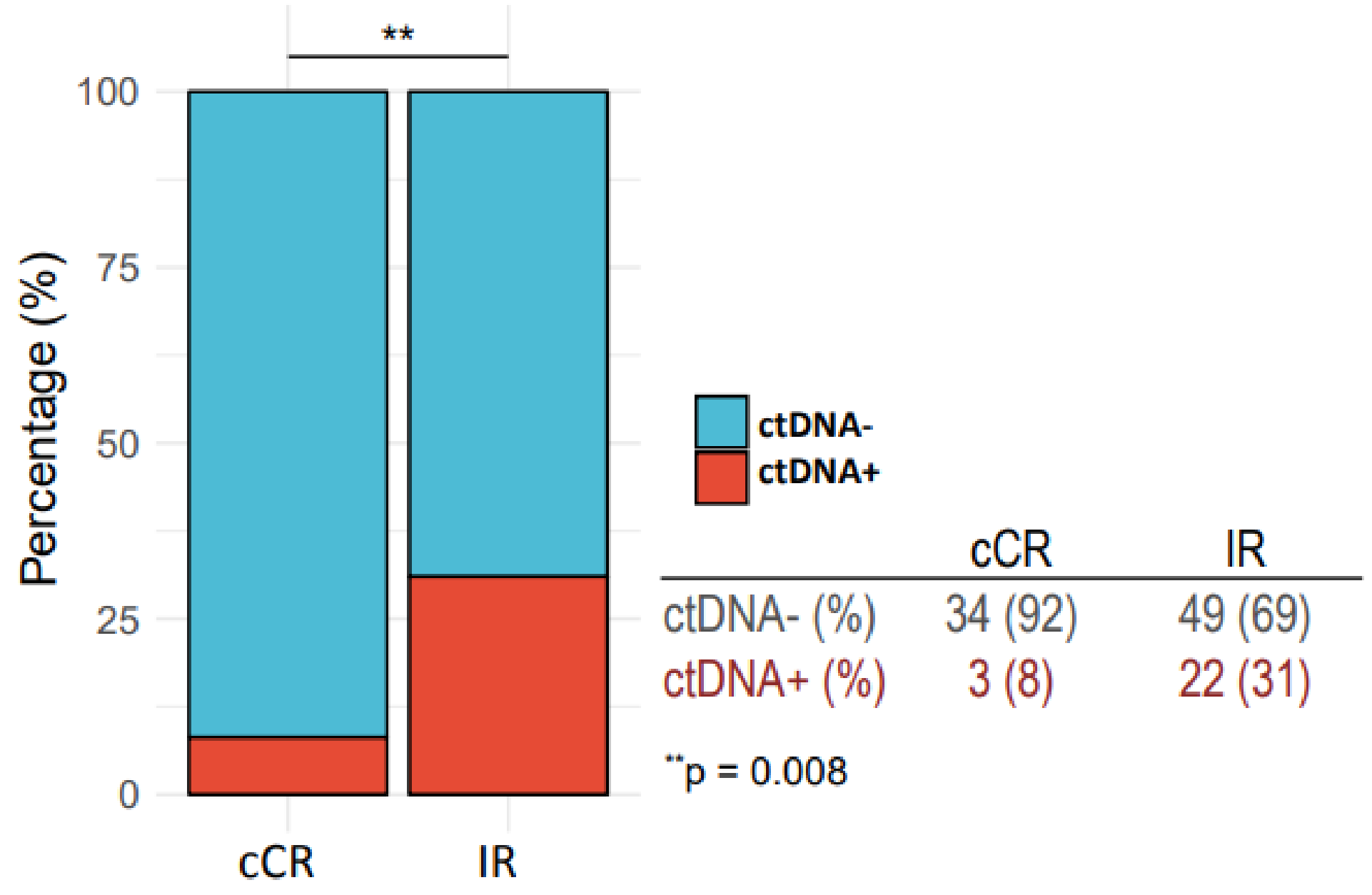
Identification of multi-omics biomarkers predictive of outcome



Abbreviations: **cCR** = clinical complete response; **CT**: computed tomography scan with contrast medium of chest, abdomen, and pelvis; **CT-RT**: chemo-radiotherapy; **IMRT**: intensive modulated radiation therapy; **IR**: incomplete response; **MRI**: magnetic resonance imaging with contrast medium of pelvis; **NOM**: non-operative management; **R**: restaging.

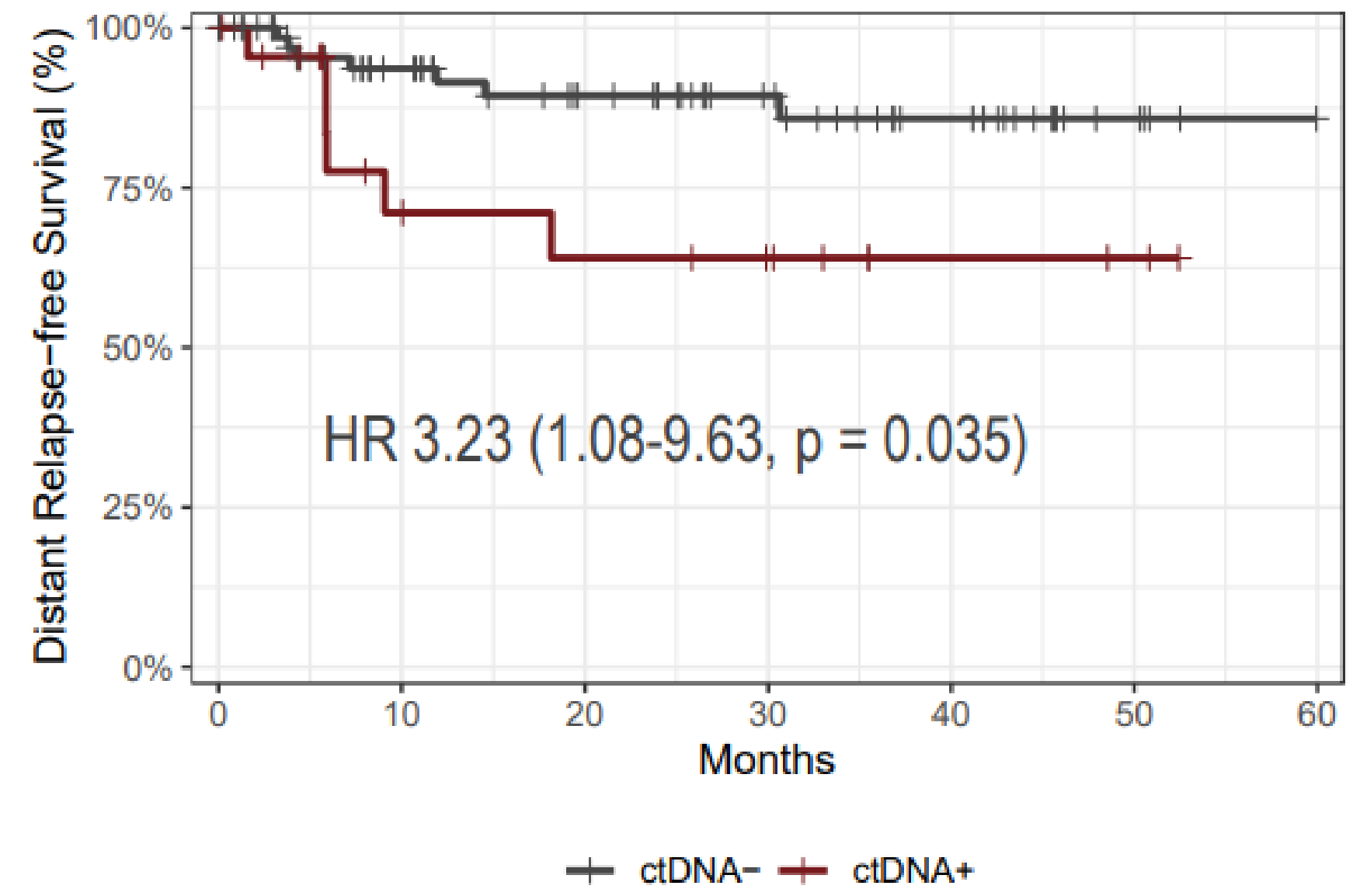
ctDNA status after TNT predicts clinical response and DRFS

ctDNA status according to clinical response (cCR vs IR)



- In 108 evaluable patients, absence of ctDNA was significantly associated with tumor response

DRFS in overall population according to ctDNA status

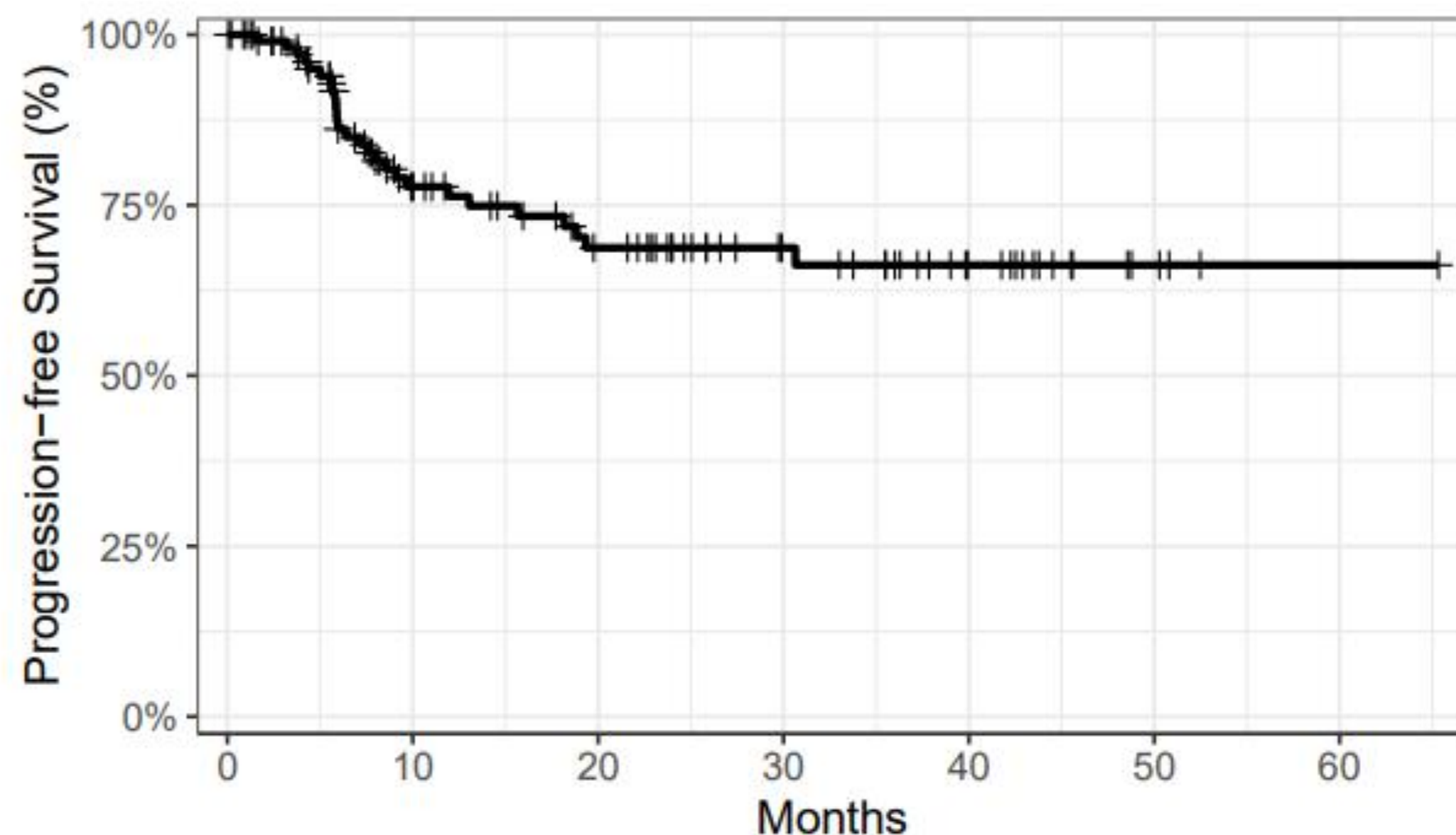


- Patients with ctDNA+ had an increased risk for distant-relapse, regardless of surgery

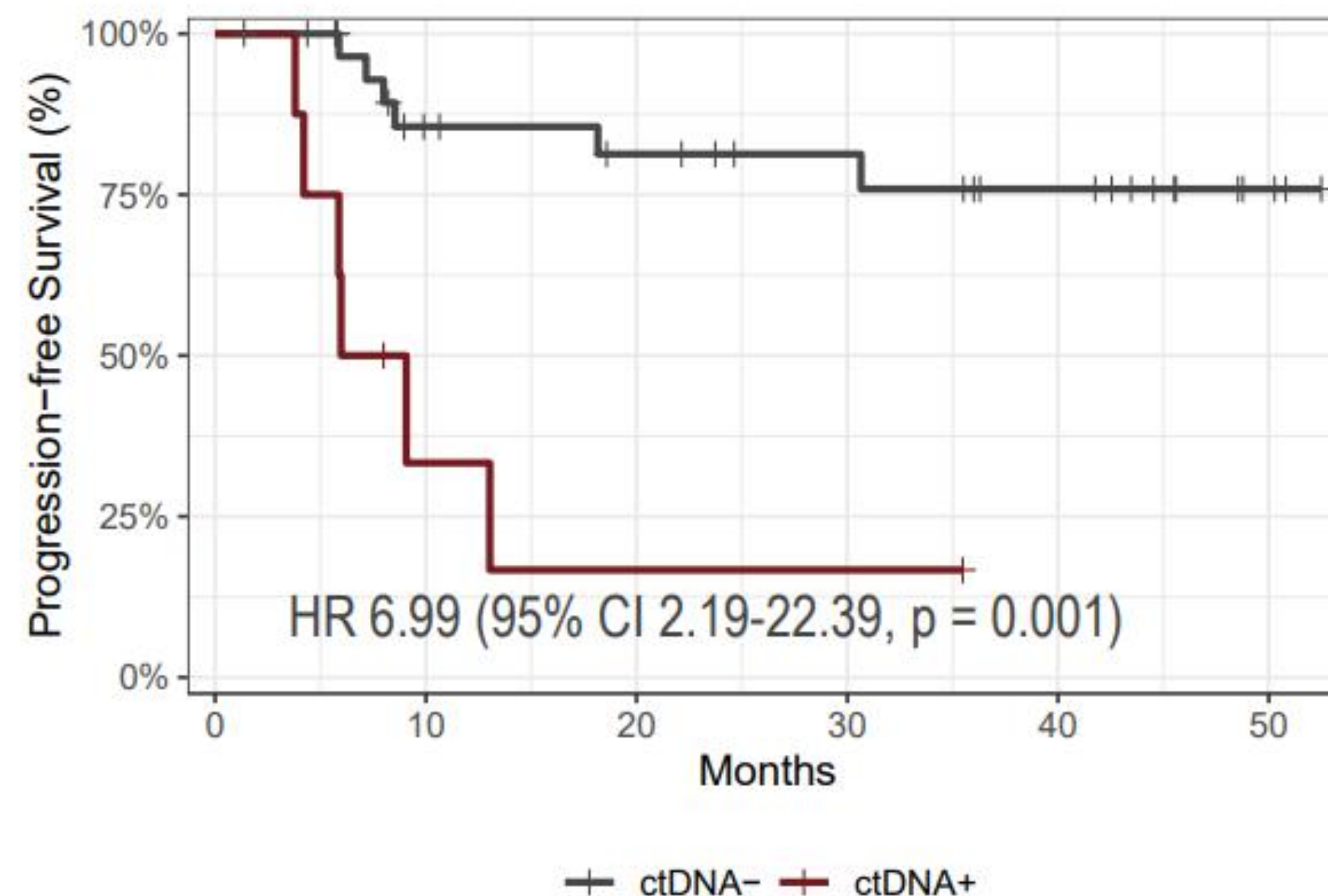
DRFS	ctDNA-	ctDNA+
2-year	89.4% (81.6-97.9)	64% (44.3-92.5)
3-year	85.8% (76.0-96.9)	64% (44.3-92.5)

ctDNA status after surgery in IR patients predicts PFS

PFS after surgery (n=121)



PFS according to ctDNA status after surgery (n=43)



- In the 121 patients who undergo rectal surgery, 2y- and 3y-PFS rate was 68.7% (95% CI 59.2-69.8) and 66.2% (95% CI 56.1-78.2)
- Patients with ctDNA+ after surgery had a significant increased risk for progression



Radiation Oncology: Bridging the Care Gap
3-7 May 2024 | Glasgow, UK





Best Clinical Paper



ESTRO 2024 11:51 **Best Clinical Paper: Organ preservation in rectal cancer: the GR...** Armadillo

Pr Véronique VENDRELY
CHU Bordeaux

Organ preservation in rectal cancer: the GRECCAR12 randomized phase 3 trial (NCT02514278)

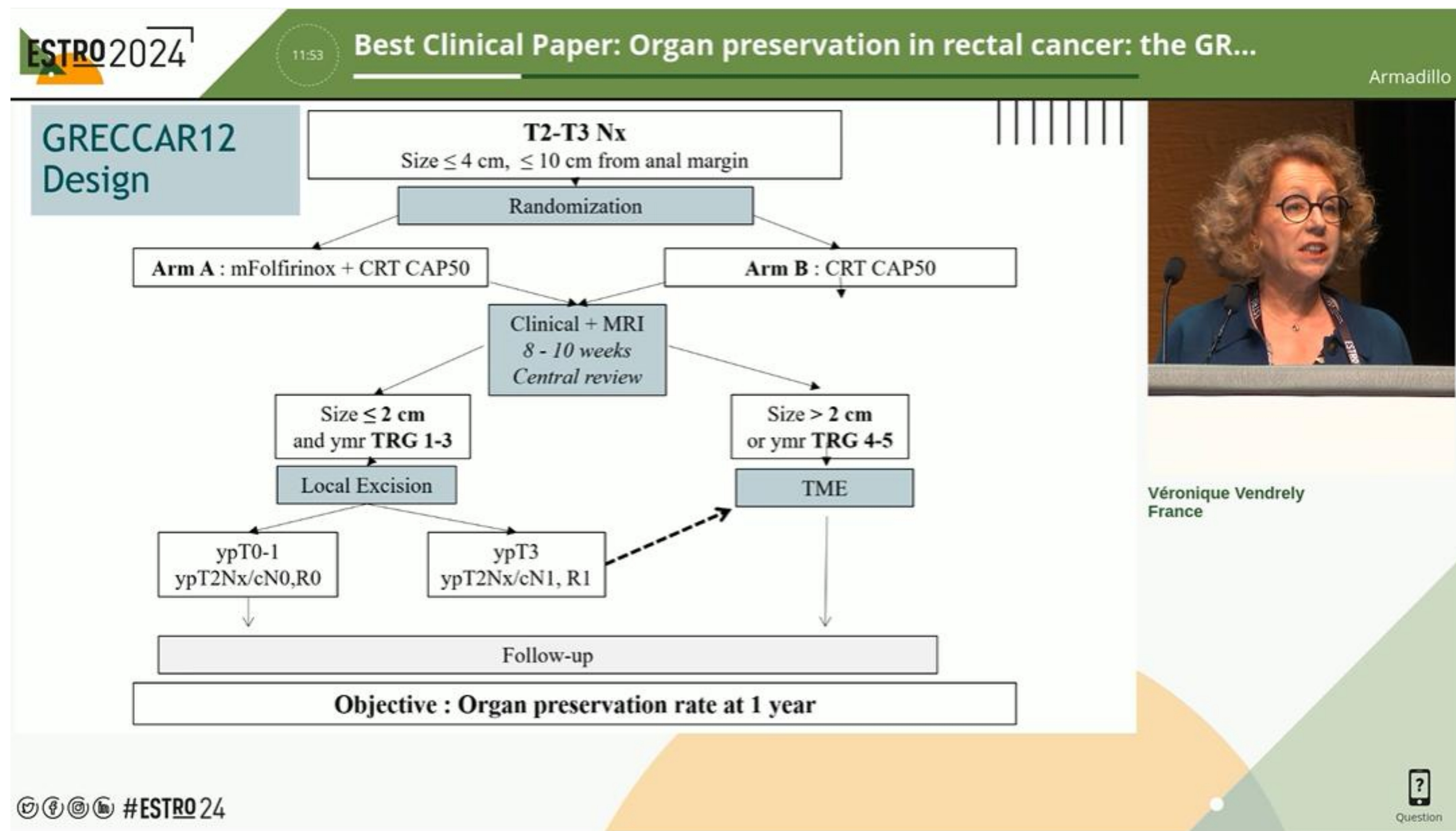
Véronique Vendrely
France

 universit  de BORDEAUX  CENTRE HOSPITALIER UNIVERSITAIRE BORDEAUX  

 #ESTRO24 

GRECCAR2 limitations:

- » Failed to improve functional outcomes
- » 20% M rates in both arms

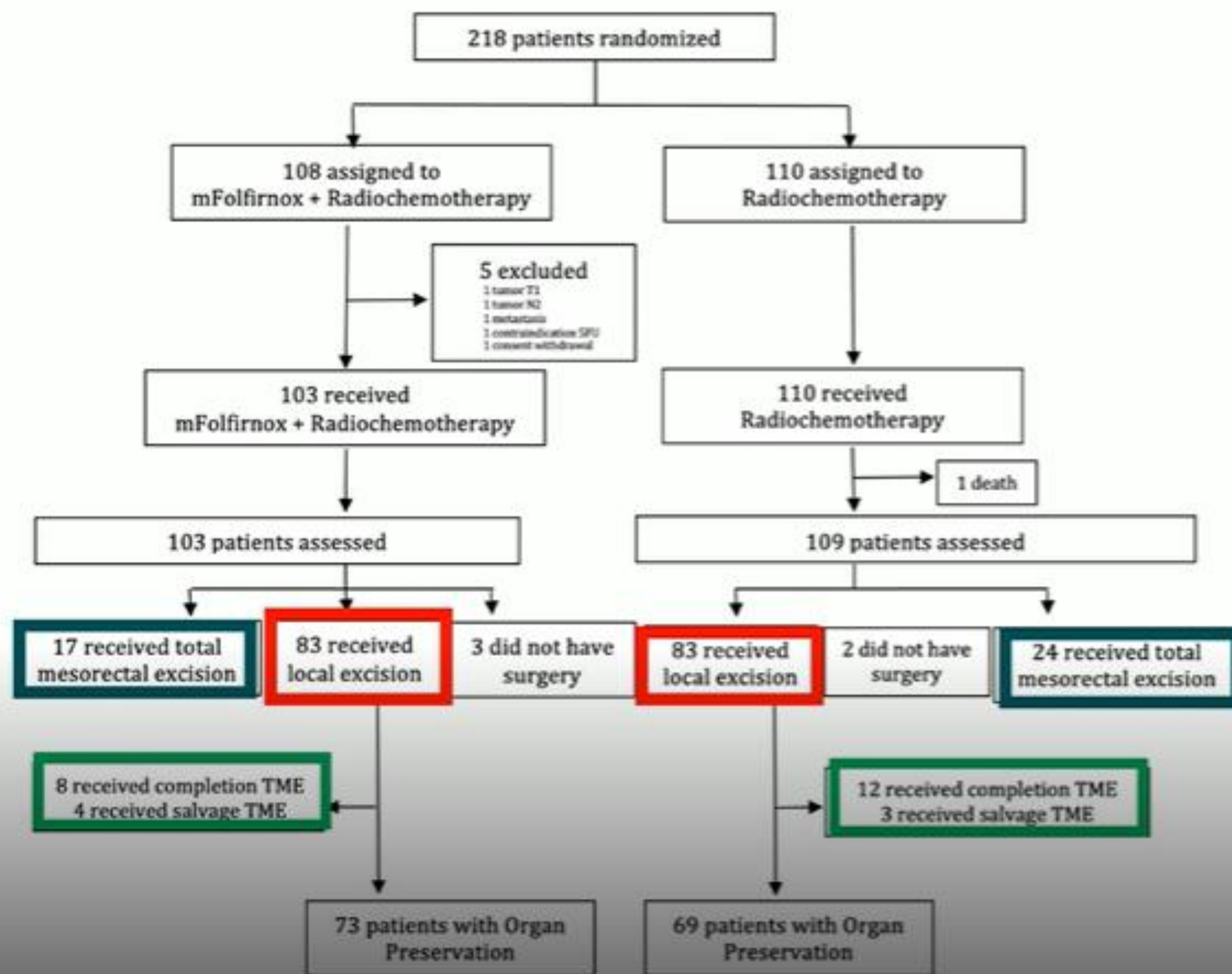




11:55

Best Clinical Paper: Organ preservation in rectal cancer: the GR...

Armadillo



Véronique Vendrely
France

Primary endpoint: rectal preservation at 1 year

Overall, Organ Preservation was possible for 142 patients (67%)

- 73 patients (71.6%) in experimental arm
- 69 patients (62.7%) in control arm
- **HR: 1.88 [0.99;3.57]**

Reason of non-OP	(n=29)	(n=40)
Initial TME	17	24
Completion TME	8	12
Salvage TME for recurrence	5	3
TME for morbidity	0	0
Death before surgery	0	1

Pathological results

	Total	CT-CRT (n=100)	CRT (n=107)	OR
ypT0	94	54 (54%)	40 (37%)	2.19 [1,19;4,02]
ypT1	35	14 (14%)	21 (19.6%)	
ypT2	62	27 (27%)	35 (32.7%)	
ypT3	16	5 (5%)	11 (10.3%)	

Highly significant difference regarding complete pathological results / almost significant regarding organ preservation



Véronique Vendrely
France



Were patients properly selected before initial TME ?



Size >2cm
ymr TRG 4-5

	CT-RTCT (n=17)	RTCT (n=24)
ypT0	7 (41.2%)	6 (25%)



Véronique Vendrely
France

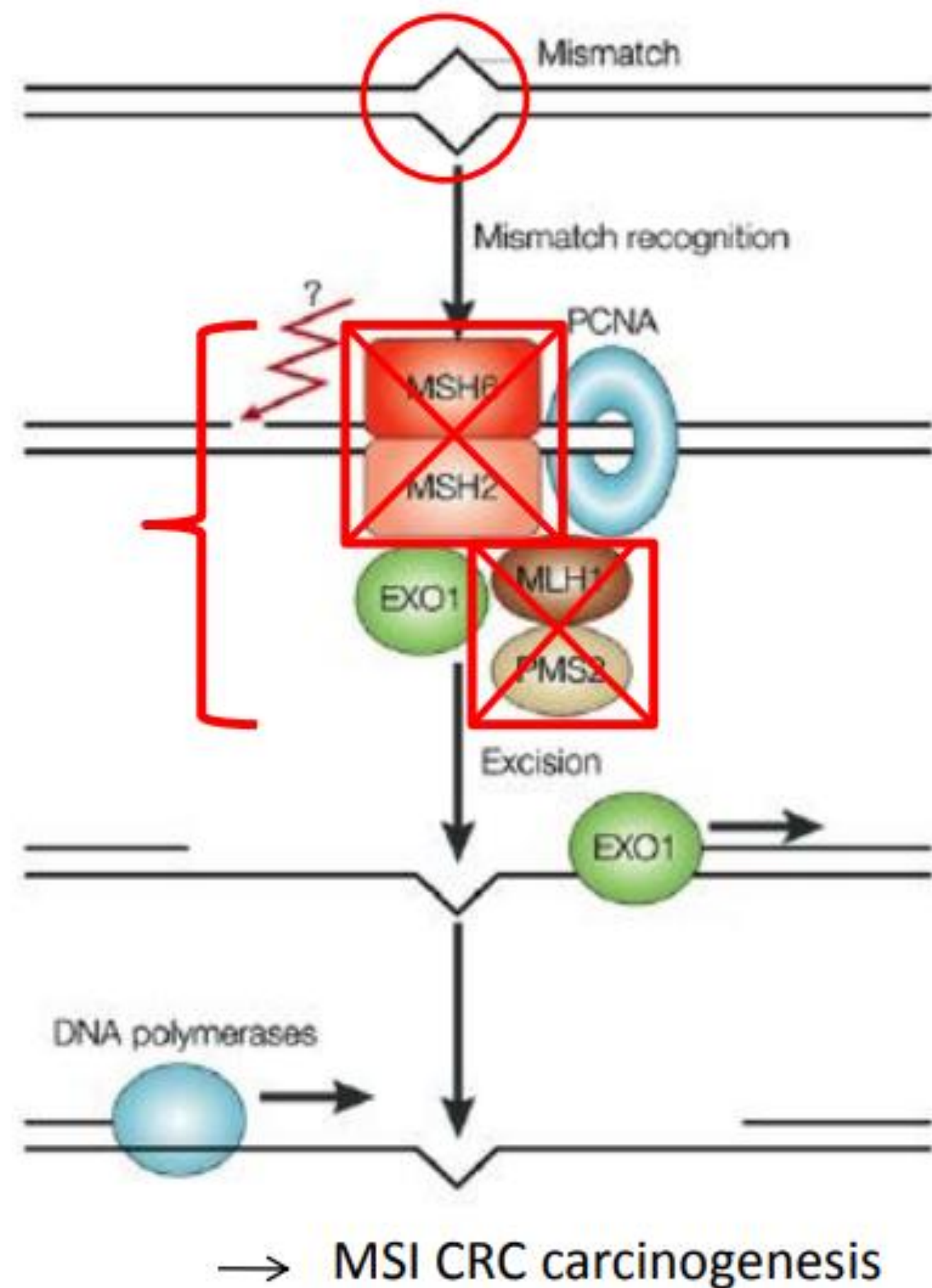


- Total Neoadjuvant Treatment (TNT)
- RT dose escalation
- Organ preservation
- Immunotherapy (MSI-H)



Deficient MMR system

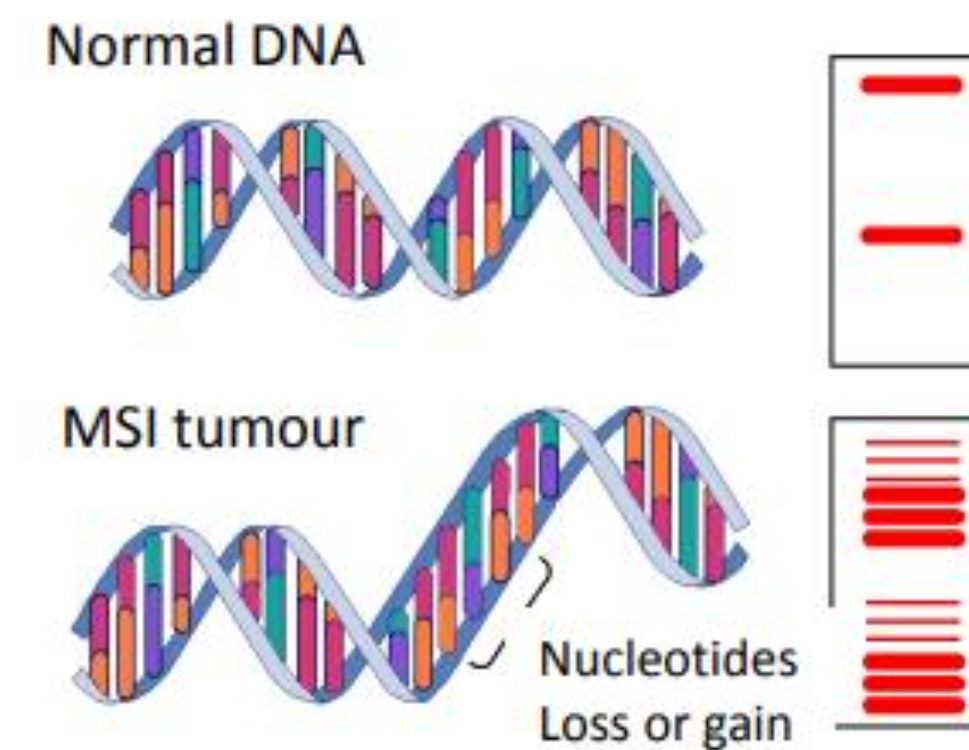
4 proteins
for DNA
reparation



Rectal cancer 3-5%

Colon 15%

Molecular profile Microsatellite Instability



BARCELONA
2024 **ESMO** congress

Long-Term Survival and Organ Preservation with Pembrolizumab in Localized MSI-H/dMMR Solid Tumors

Kaysia Ludford MD/MSc, Michael LaPelusa MD, Wei Qiao PhD, Jane Varkey Thomas MD, Nancy You MD/MHSc, Selvi Thirumurthi MD/MS, Dipen Maru MD, Bryan Iorgulescu MD/MPH, Scott Kopetz MD/PhD, Michael J. Overman MD.

Barcelona, Spain, 9/14/2024

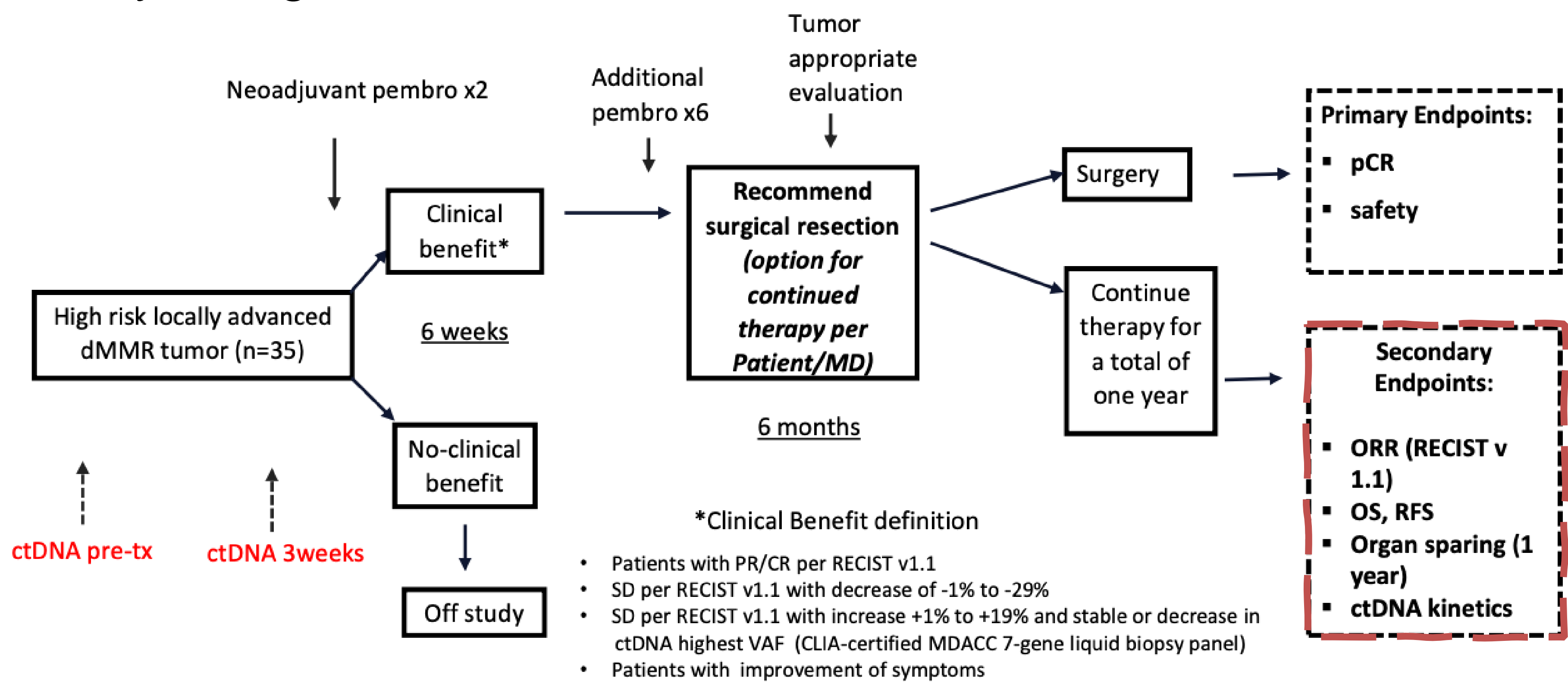


Kaysia Ludford

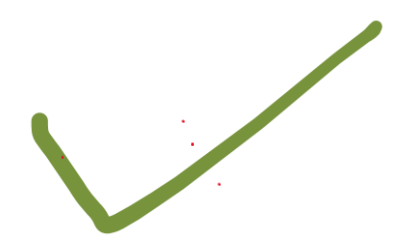
Long-term survival and organ preservation with pembrolizumab in localized MSI-H/dMMR solid tumors

3 years FUP

Study design



pCR 65%



Ludford, J Clin Onc 2023

Results

☐ Median follow up 2.9 years (range 0-3.8 years)

☐ Best ORR: 82% (n=33)

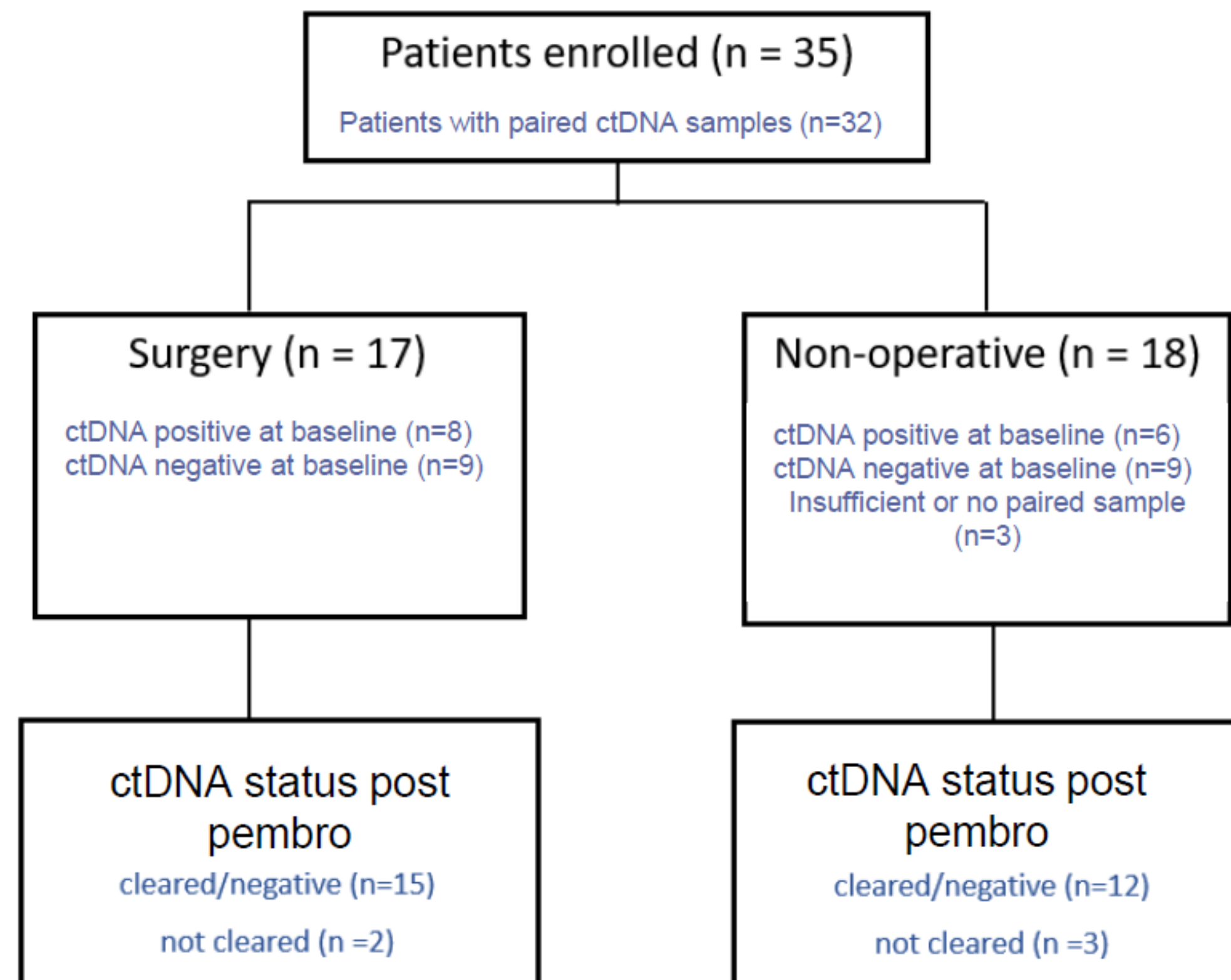
CR	39.4%
PR	42.4%
SD	18.2%

☐ 17/17 surgically resected patients remain cancer free (median follow up: 35 months)

☐ 14/18 non-operative patients alive with organ intact (median follow up 27.5 months)

- 2 died (reported in original report)
- 2 lost to follow up (1 international pt; 1 died 2.5 yrs after being lost to follow up)

☐ No additional progression events beyond the 6 pts in original report

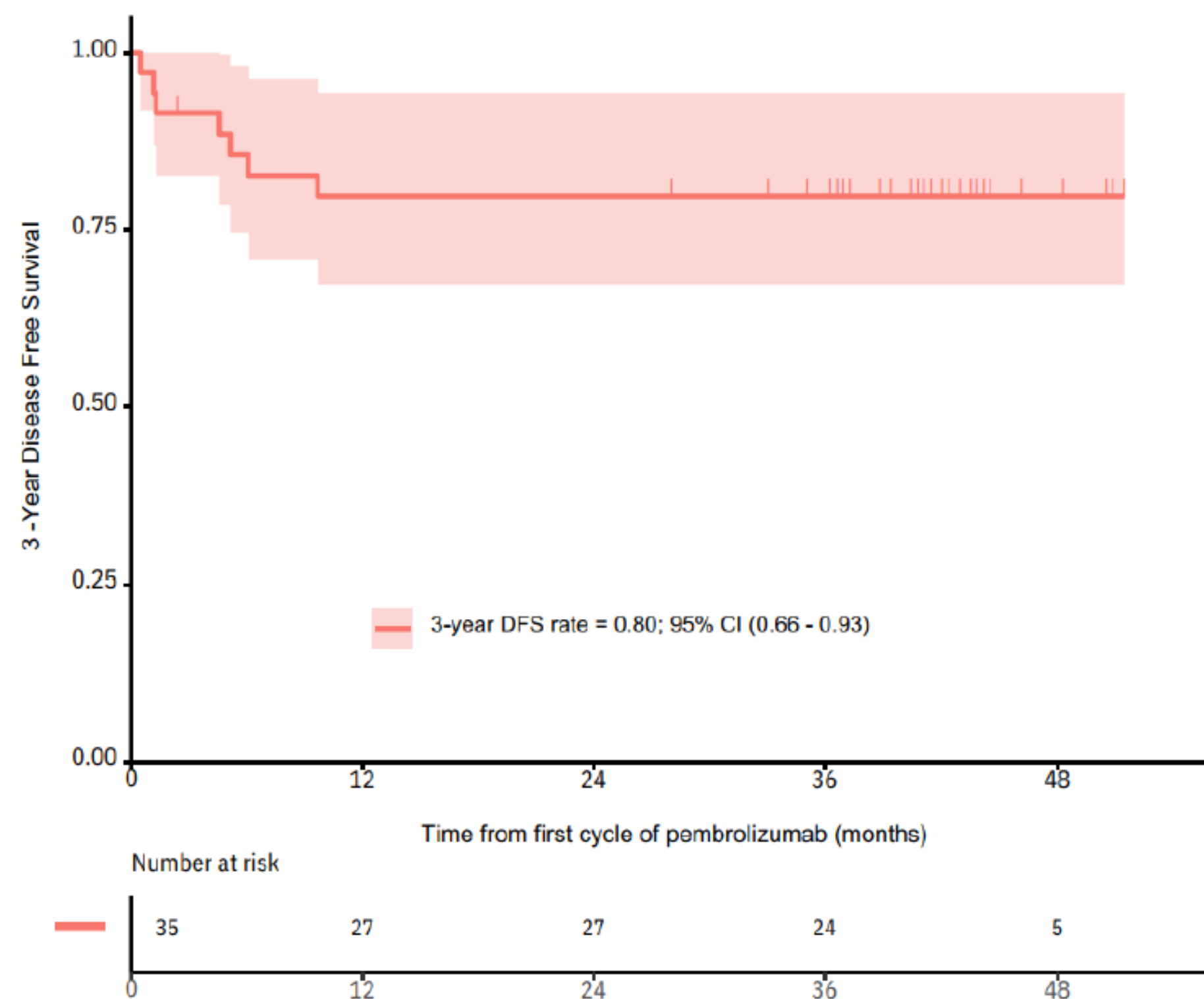


n= 19 colon, 8 rectal, 2 pancreatic, 2 duodenal, 1 each: ampullary, meningioma, endometrial, gastric

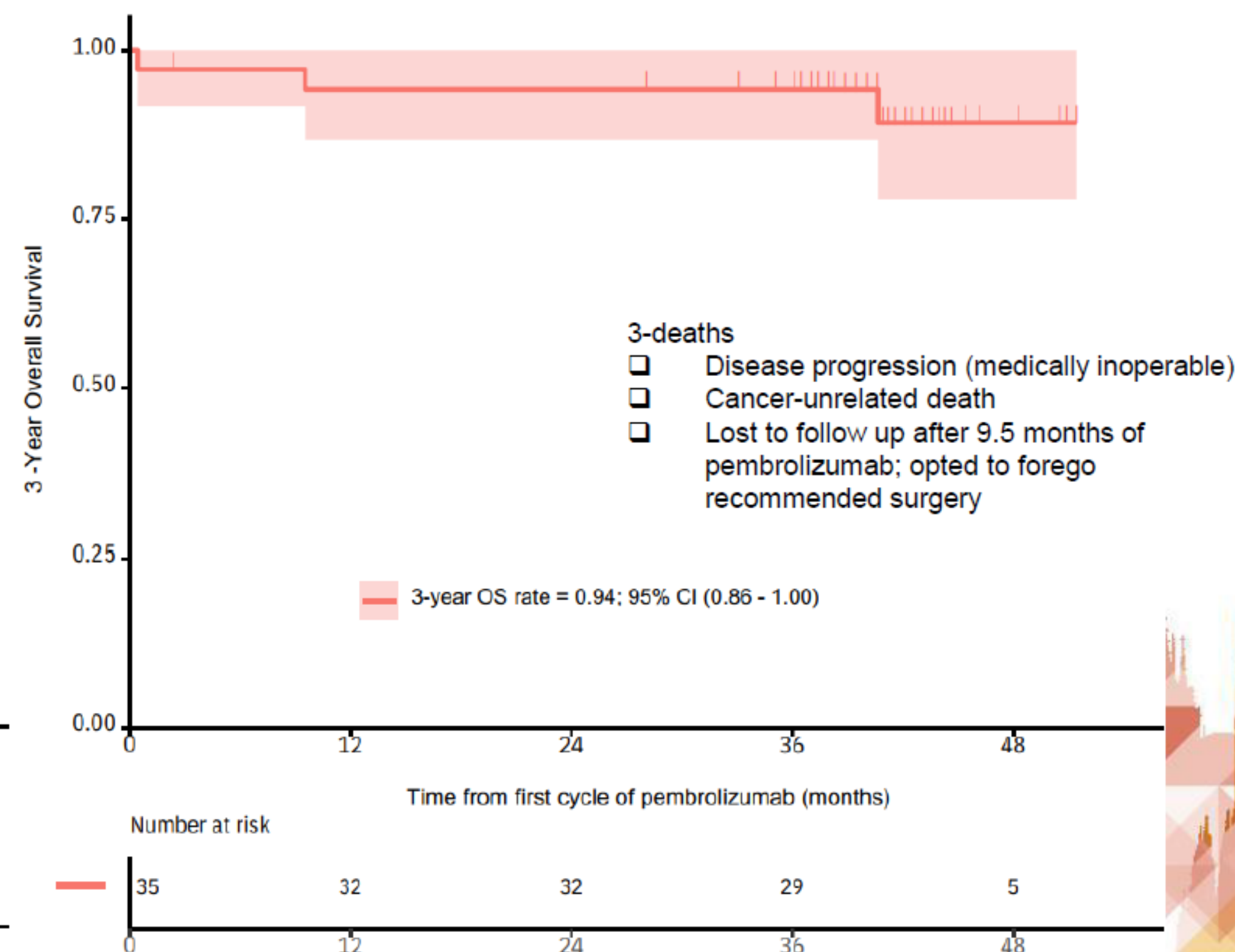
BARCELONA 2024 **ESMO** congress

Results

3-year DFS rate among all patients

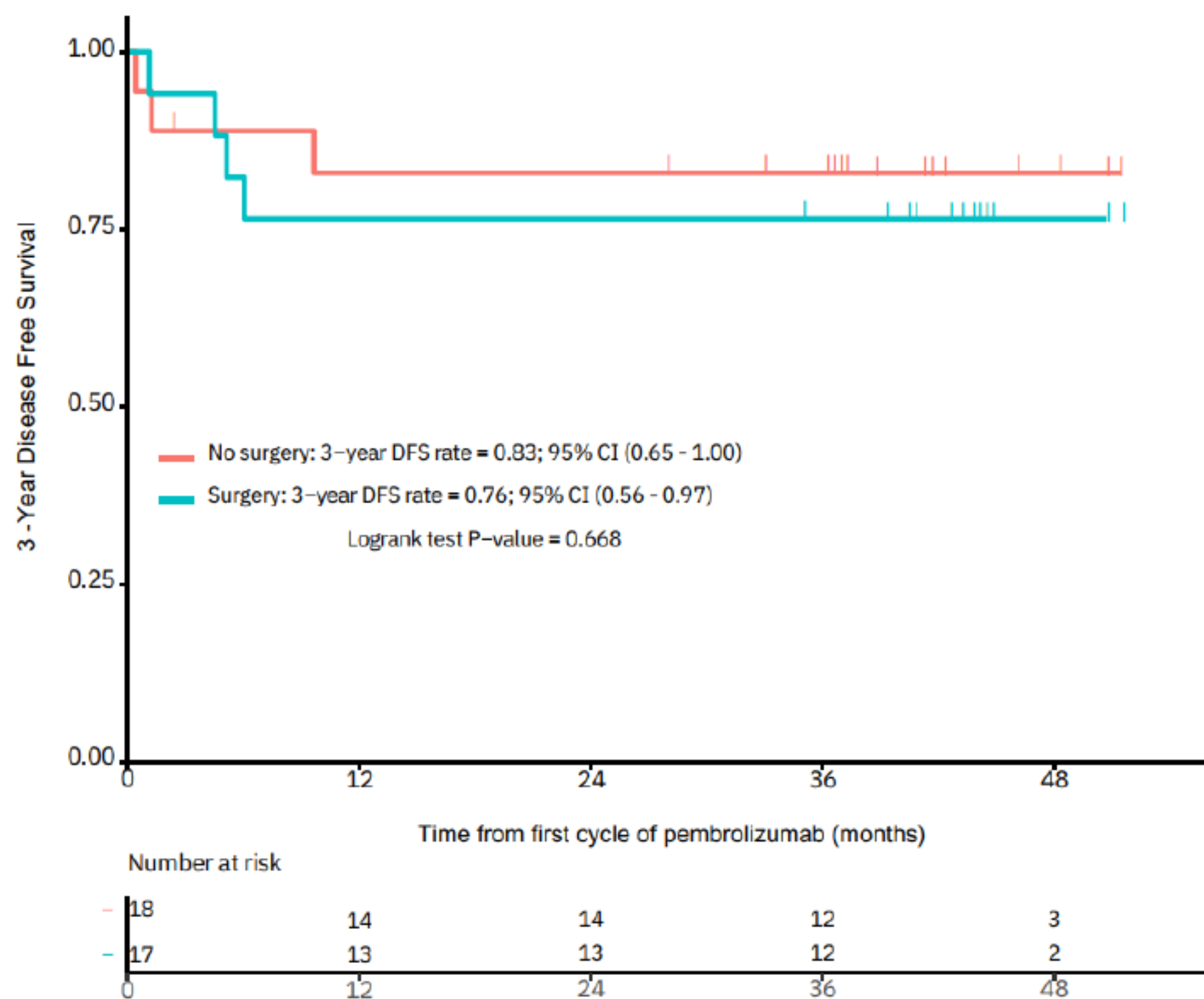


3-year OS rate among all patients

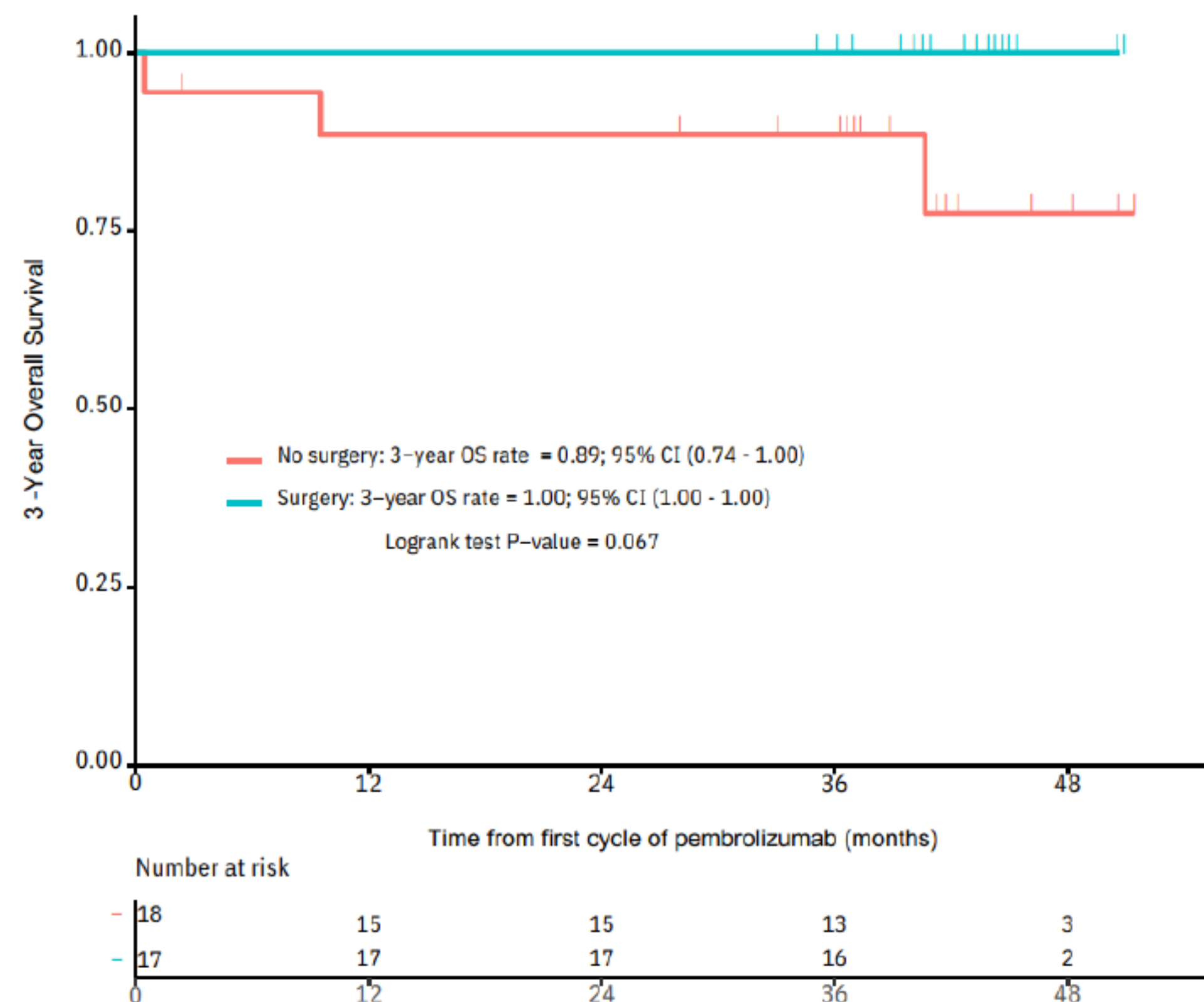


Results

3-year DFS rate by management strategy

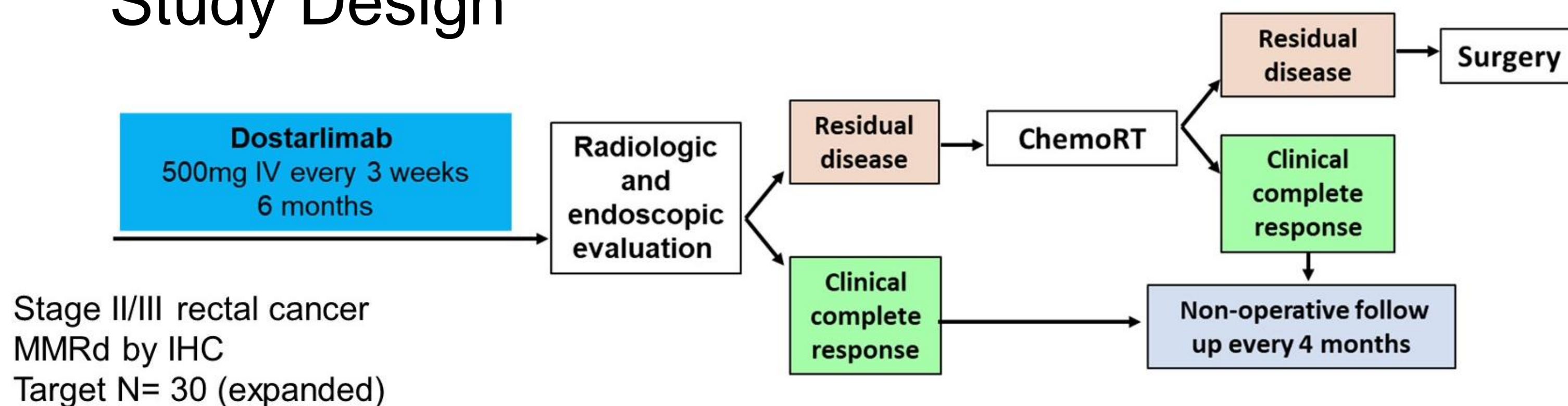


3-year OS rate by management strategy



Dostarlimab for dMMR LARC: phase II trial

Study Design



cCR 100%

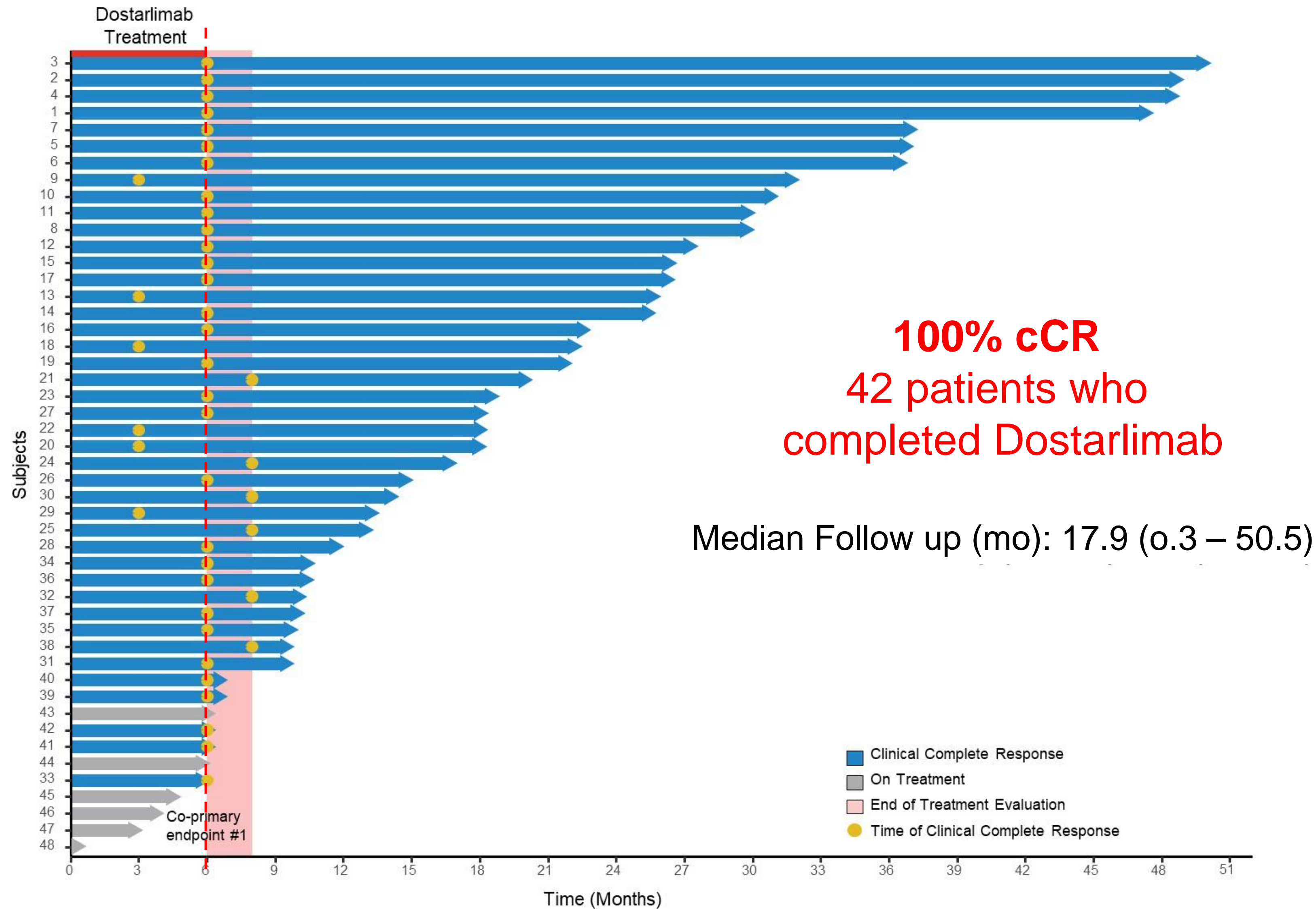
Primary Endpoints:

- ORR after completion of PD-1 alone or in combination with chemoRT
- pCR or sustained cCR for 12 mo after completion of PD1 alone or in combination with chemoRT

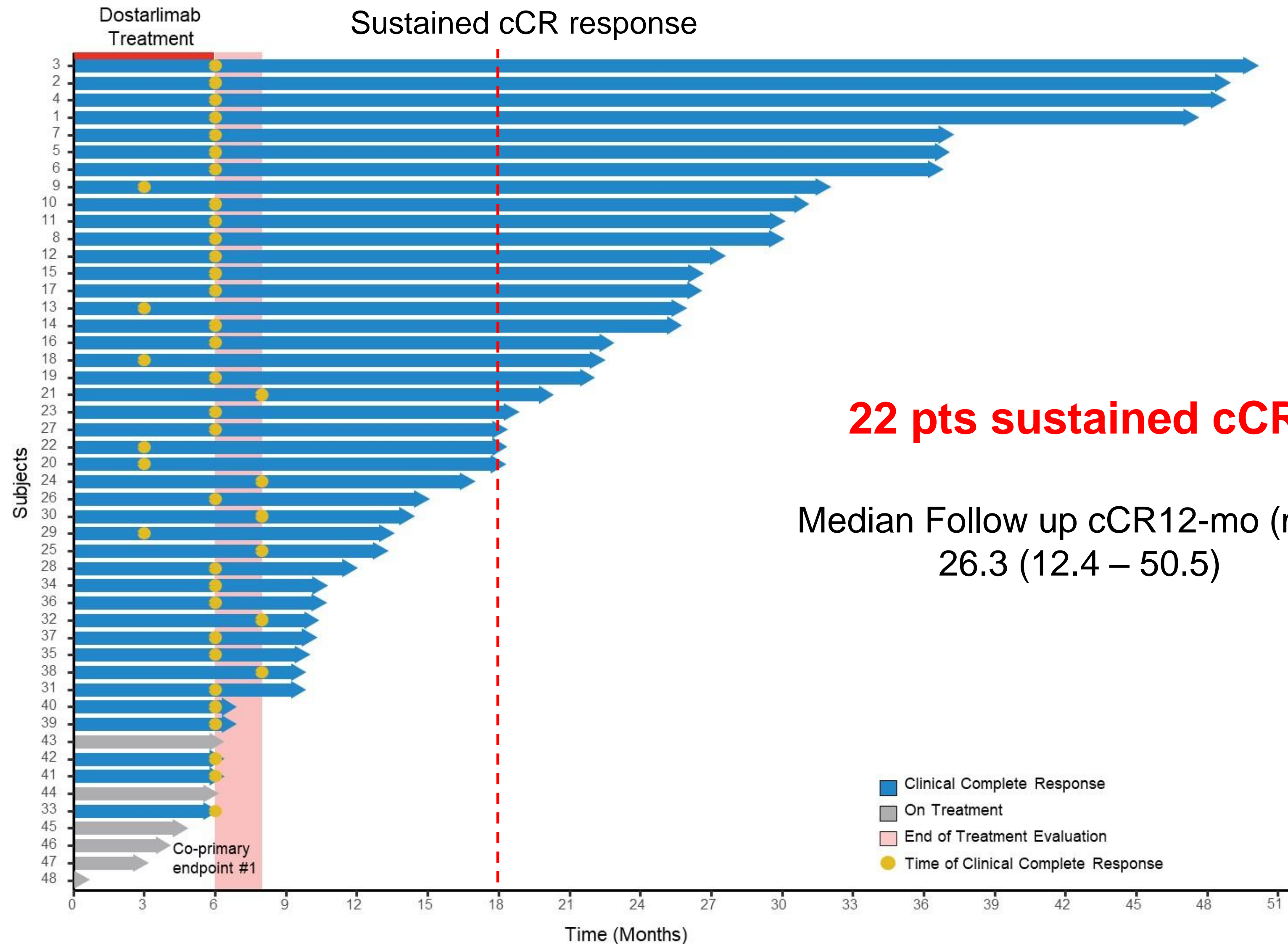
Sample Collection: ctDNA, biopsy, imaging

Baseline, 6 weeks, 3 mo, 6 mo and q4 mo during NOM

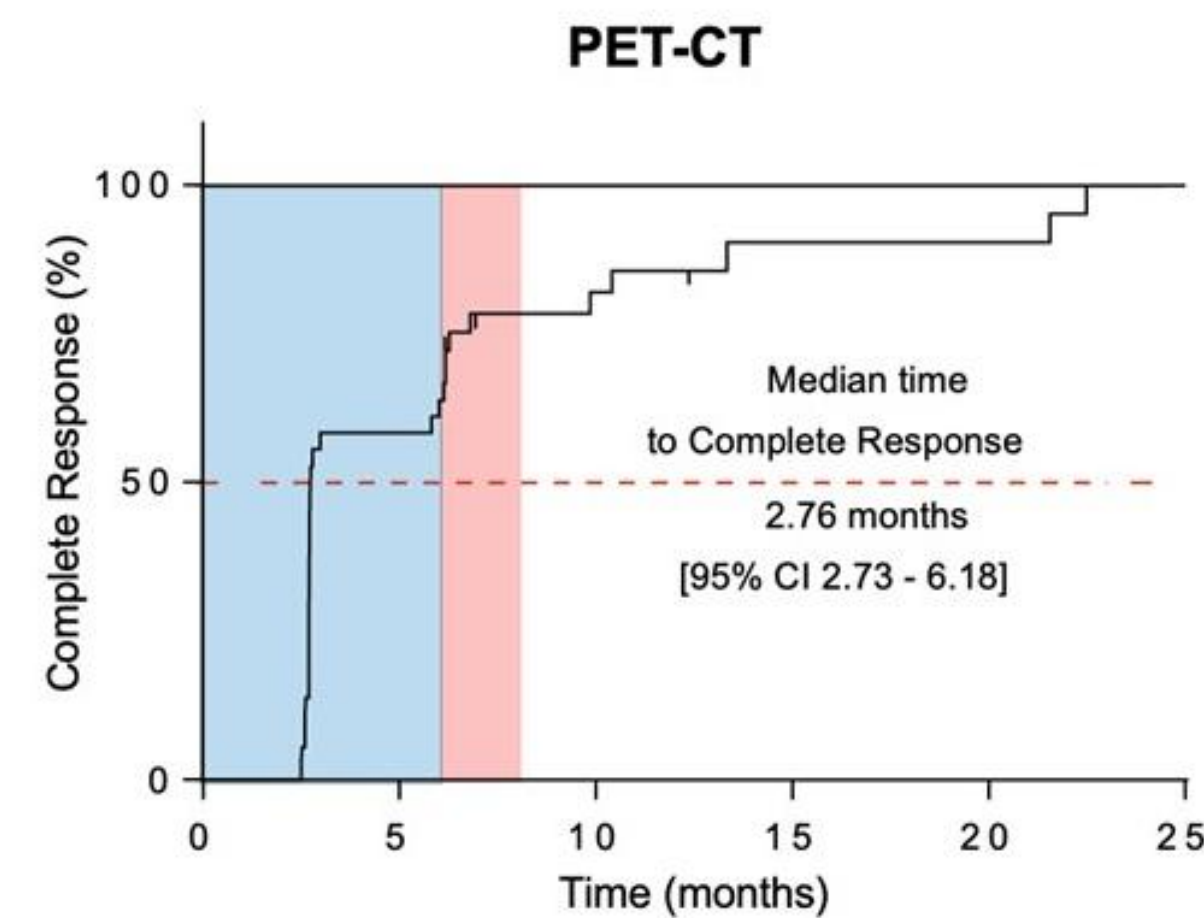
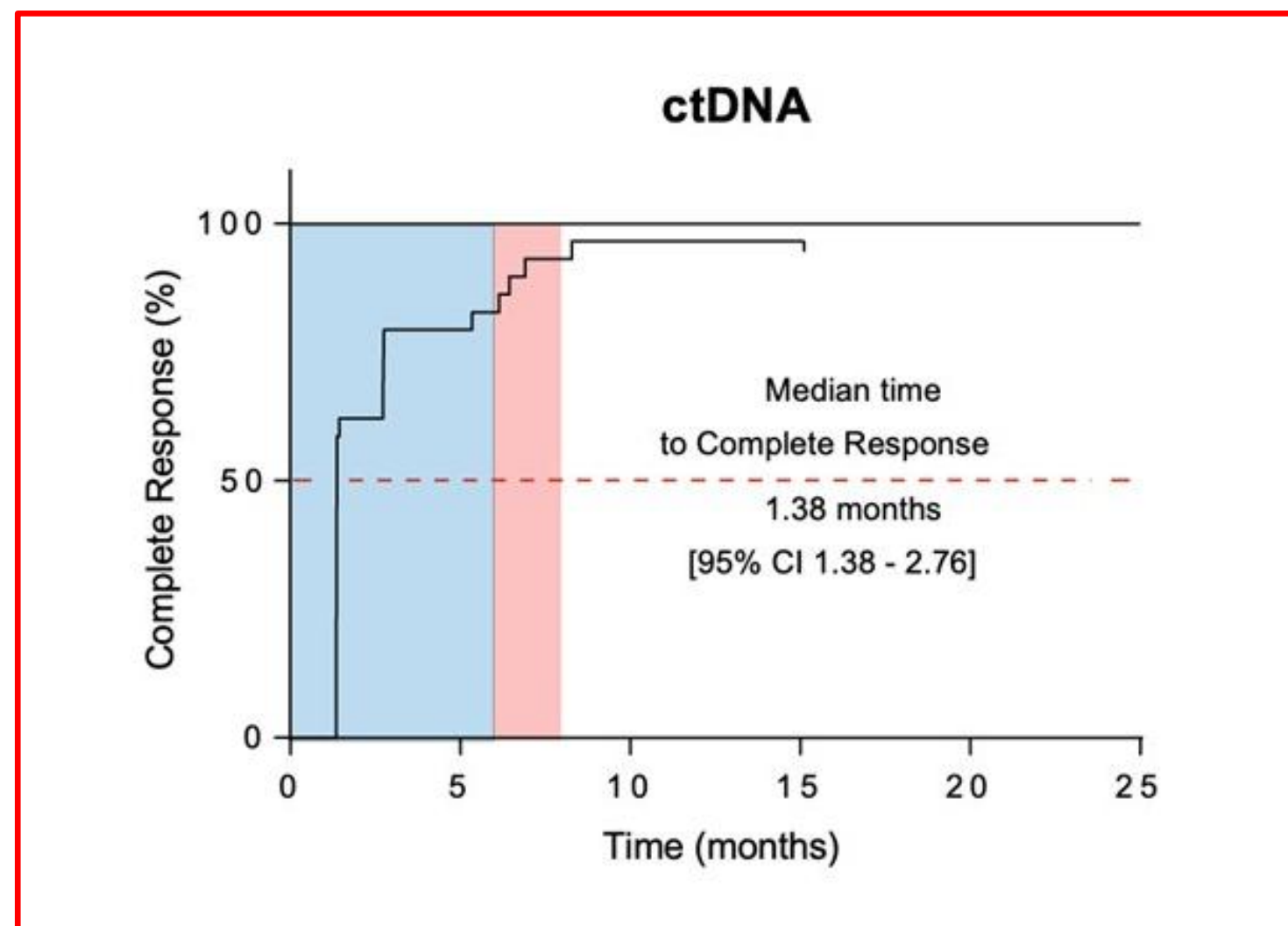
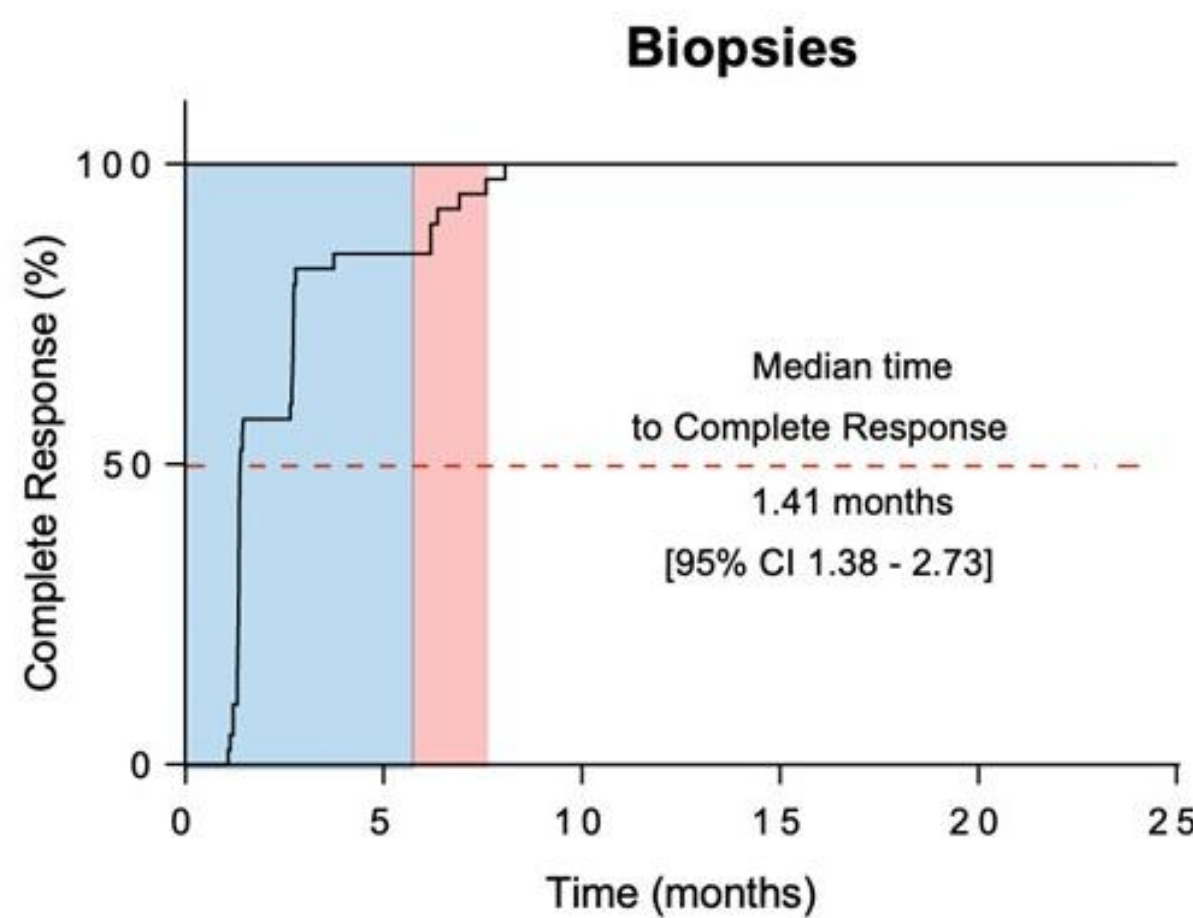
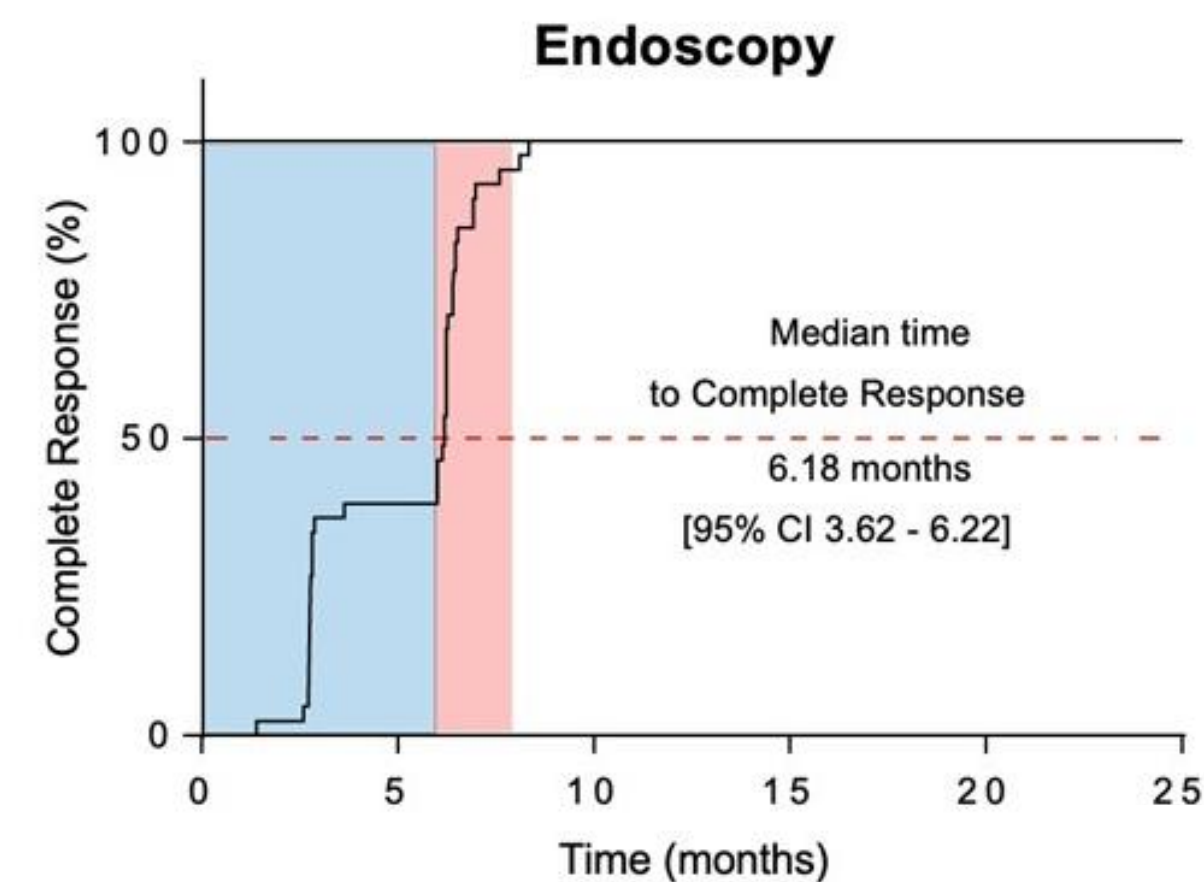
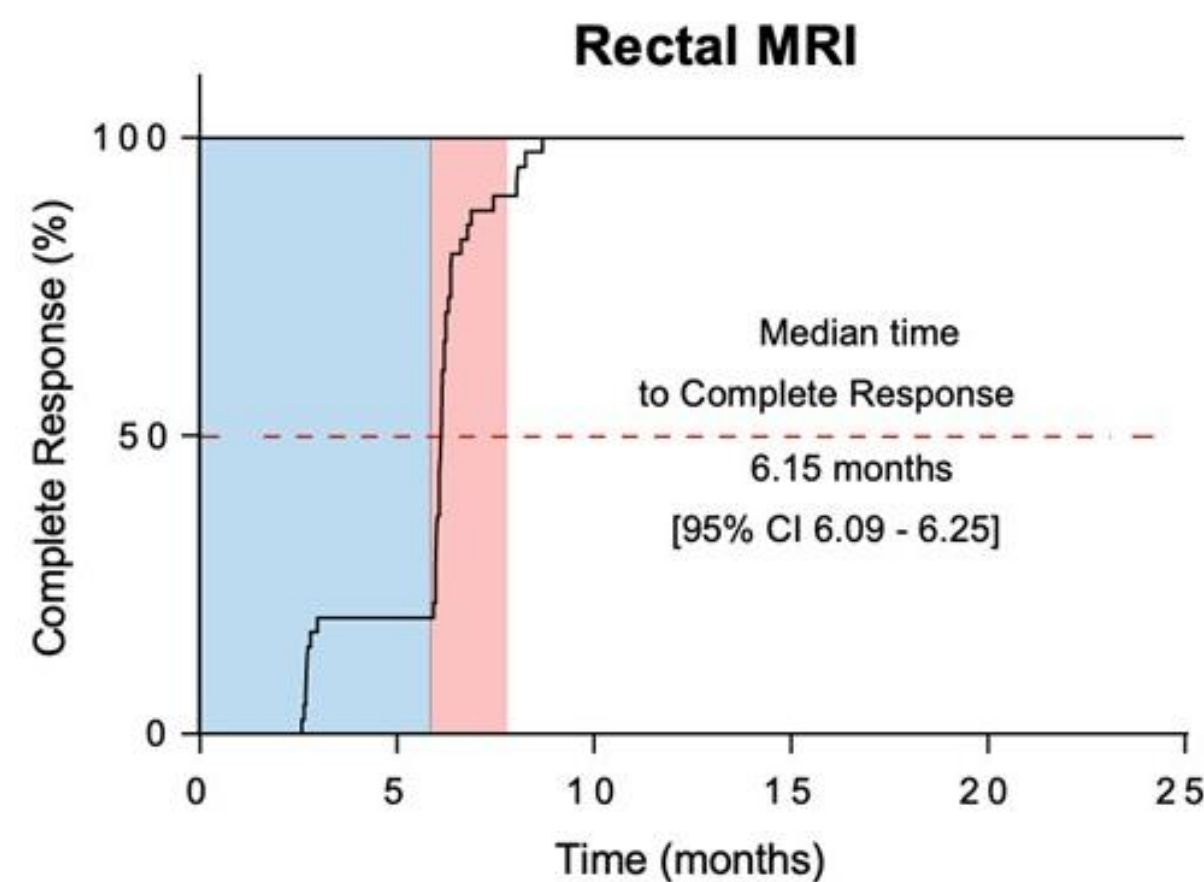
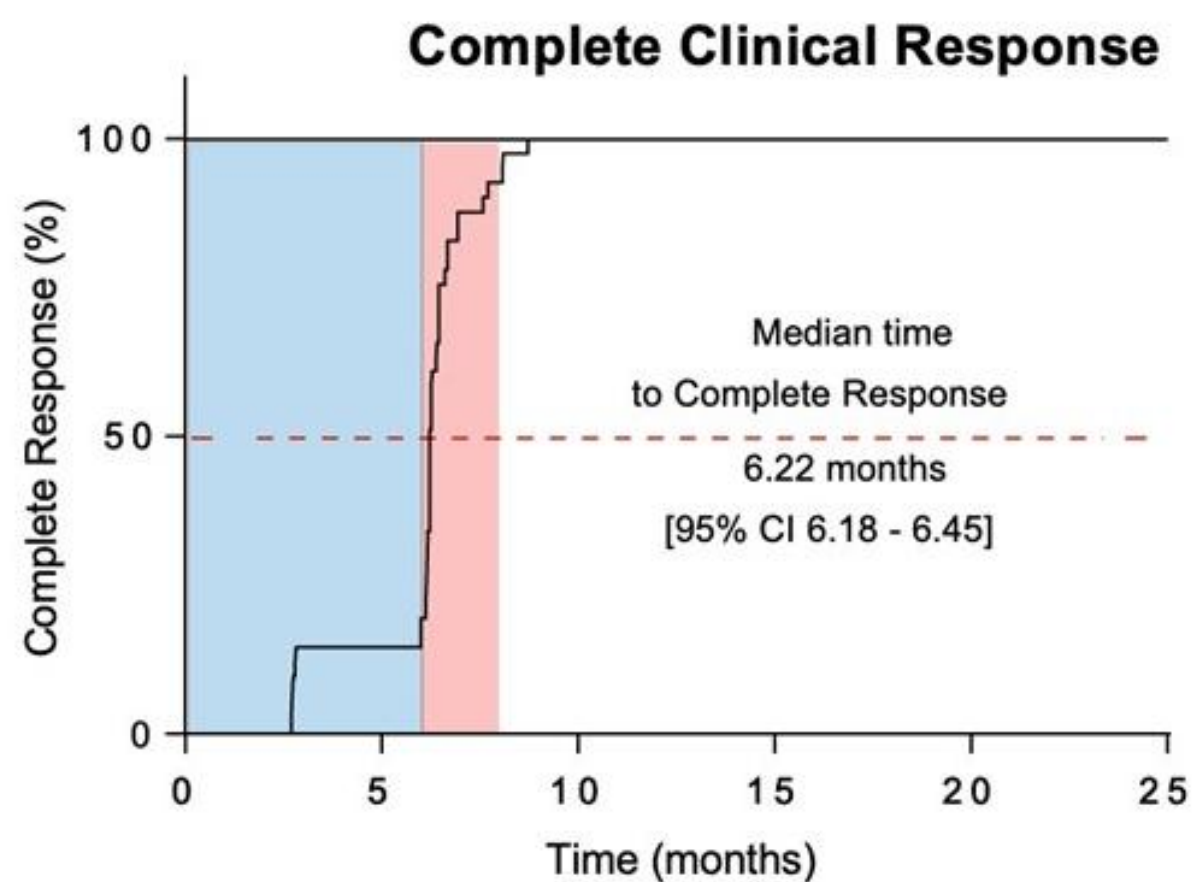
Duration of response



Duration of response



Time to cCR response



Time on Treatment
End of Treatment Evaluation



- **Total Neoadjuvant Treatment (TNT):**
 - Improve OS (Prodige-23 trial)
- **RT dose escalation:**
 - confirm the improvement of OP (CXT)
 - best results $T < 3\text{cm}$
- **Organ preservation:**
 - TNT to improve OP
 - Similar survival outcomes Ind-Con CT
 - OP $>$ Con CT
 - OP no detrimental on survival outcomes
 - ctDNA: high risk feature of distant recurrences
- **Immunotherapy (MSI-H):**
 - Long term results



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