BARCELONA 2024 ESMO congress

UNIVERSITY OF LEEDS

Systemic Therapy For Organ Preservation

Eyes To The Future

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Declaration of interests

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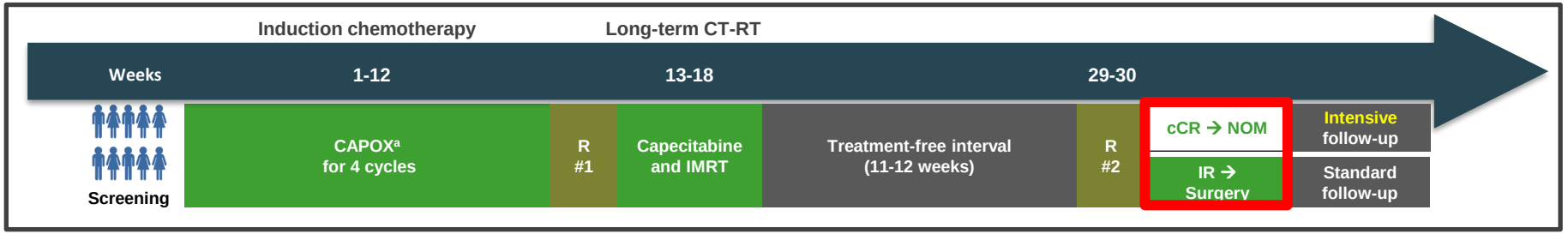
Background - organ preservation for rectal cancer

- Radical surgery using total mesorectal excision is an international standard of care for non-metastatic rectal cancer
- Phase 3 randomised trials demonstrate that neoadjuvant short course radiotherapy and long course fluoropyrimidine CRT reduces the risk of local recurrence
- ESMO guidelines recommend a risk-adapted approach to the use of radiotherapy based on the diagnostic pelvic MRI scan
- Around 15-30% of patients who receive neoadjuvant radiotherapy prior to surgery have a pathological complete response after radical surgery depending on the local extent of the disease
- Over the last 25 years there has been increasing interest whether patients who experience a complete clinical response can safely avoid surgery and the need for a temporary or permanent stoma

NO-CUT trial first results using TNT for organ preservation

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



CLINICAL OUTCOMES

- 26% Complete Clinical Response
- 20% Local regrowth after CCR at 10-25 months
- 97% Distant RFS at 30 months for complete response patients
- 77% Distant RFS at 30 months for all patients
- No data on Quality of Life / functional outcome

CONTEXT

- Consistent with current TNT results in pMMR rectal cancer
- Oncologically safe

CURRENT CLINICAL QUESTONS

- What is the best RT and chemotherapy sequence?
- What is be best (chemo) radiotherapy regimen?
- When should we use TNT for organ preservation?
- **How do we increase the CCR rate?**

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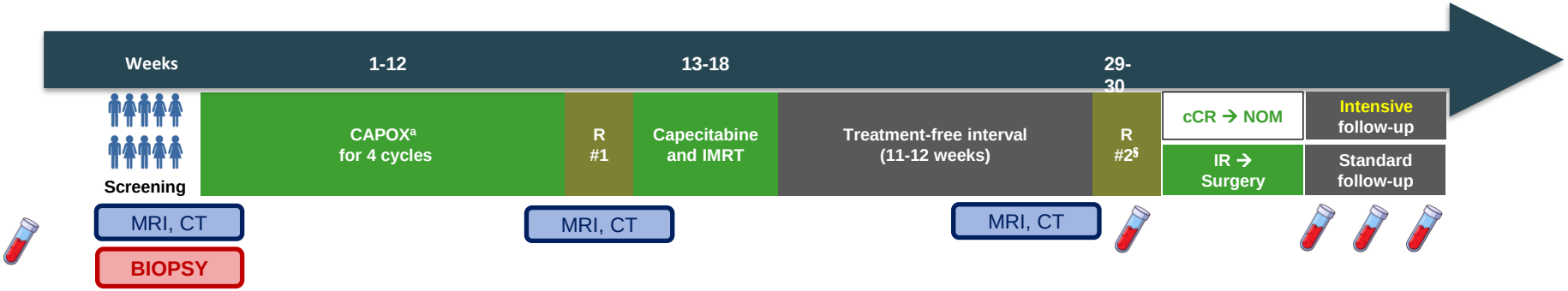
Amatu et al ESMO 2024

NO-CUT trial first results using TNT for organ preservation.



TRANSLATIONAL RESEARCH

Pre-treatment biopsy, standard imaging, sequential bloods

ctDNA +ve after TNT prognostic

Higher pre-treatment leucocyte score predictive of high CCR

Pre-treatment CRIS-E score predictive of low CCR

COMMENTS

Blood sample post CapOx, pre TNT would be of interest

What is the clinical benefit of ctDNA +ve after TNT?

Important signals to predict CCR using TNT to help guide patient selection

Amatu et al ESMO 2024

Changing the treatment paradigm in rectal cancer - smarter kinder non-surgical treatments to replace radical surgery and a stoma

We are now entering a new era where systemic and radiotherapy-based treatments alone or in combination **have the potential to change the treatment paradigm** within the next 5-10 years

An increasing body of evidence demonstrates that **active surveillance of a complete response after non-surgical treatments can be safely surgically salvaged**

Promising but relatively small studies of new treatments and technologies are reporting **complete clinical response rates (CCR) of 30-60%** and sometimes higher

To accelerate progress we are uniquely placed to

- develop new treatments underpinned by a **strong scientific rationale**
- test promising new treatments in **randomised trials against standard(s) of care**
- understand response and resistance and associated mechanisms to make **biologically informed decisions to select patients** for standard and novel treatments
- **avoid over-treatment**
- **offer organ preservation strategies to patients who want this approach**

Organ preservation approaches

Planned organ preservation

Very early disease cT1, sm1 cN0	cT1-2; cT3a/b if middle or high cN0 (cN1 if high) MRF clear; no EMVI
Standard of care TEM +/- perioperative CRT	**Standard of care** TME alone

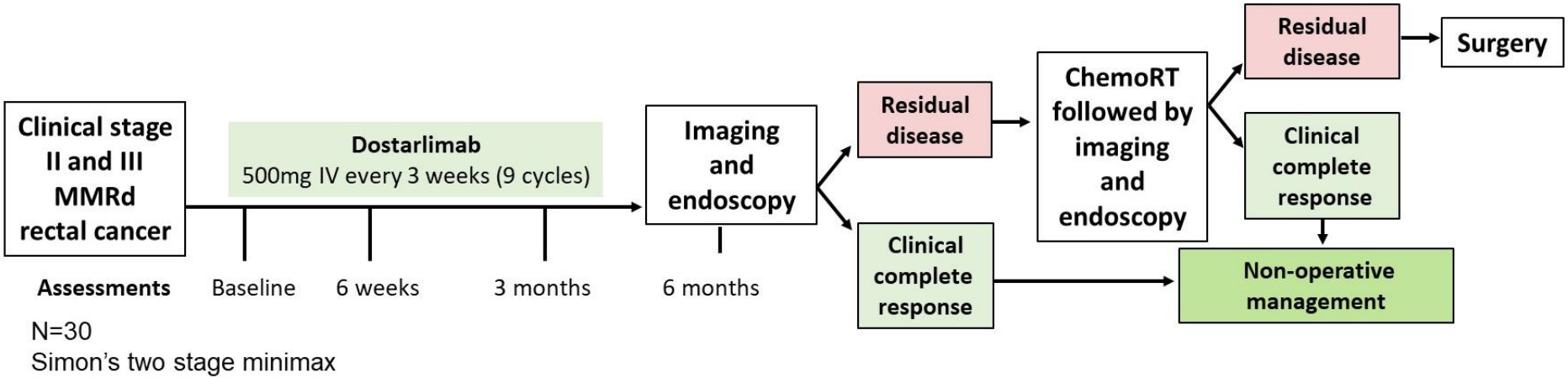
Planned organ preservation

cT3a/b very low levators clear MRF clear cT3a/b in mid or high rectum, cN1-2 (not extranodal), no EMVI	cT3c/d or very low, levators not threatened, MRF clear. cT3c/d mid rectum, cN1-N2 (extranodal), EMVI +ve	cT3 with MRF involved cT4b, levators threatened, lateral node +ve
Standard of care TME alone if high quality or plus SCPRT/CRT	**Standard of care** SCRT or CRT followed by TME	**Standard of care** CRT or SCPRT + FOLFOX followed by TME

CCR

“Opportunist ” organ preservation strategy

PD-1 blockade in dMMR locally advanced rectal cancer



dMMR
<10% of rectal cancer patients

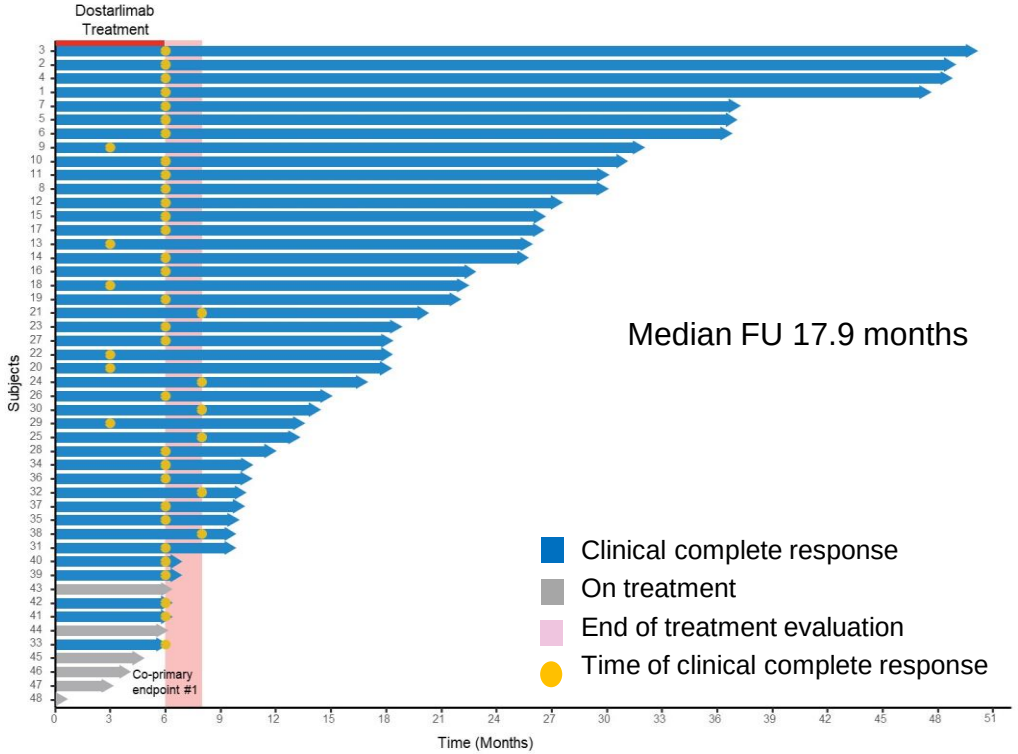
Primary Objectives
- Overall response rate of PD-1 blockade with or without chemoradiation
- Pathologic complete response (pCR) or clinical complete response (cCR) rate at 12 months after PD-1 blockade with or without chemoradiation

Secondary Objective
- Safety and tolerability

Cercek et al. NEJM 2022

Individual response to PD-1 blockade with dostarlimab

ID	Age	T stage	N stage	FU Months	Overall response
1	38	T4	N+	23.8	CR
2	30	T3	N+	20.5	CR
3	61	T1/2	N+	20.6	CR
4	28	T4	N+	20.5	CR
5	53	T1/2	N+	9.1	CR
6	77	T1/2	N+	11.0	CR
7	77	T1/2	N+	8.7	CR
8	55	T3	N+	5.0	CR
9	68	T3	N+	4.9	CR
10	78	T3	N-	1.7	CR
11	55	T3	N+	4.7	CR
12	27	T3	N+	4.4	CR
13	26	T3	N+	0.8	CR
14	43	T3	N+	0.7	CR



Single centre study

No observed >= Grade 3 toxicity

Cercek et al. NEJM 2022

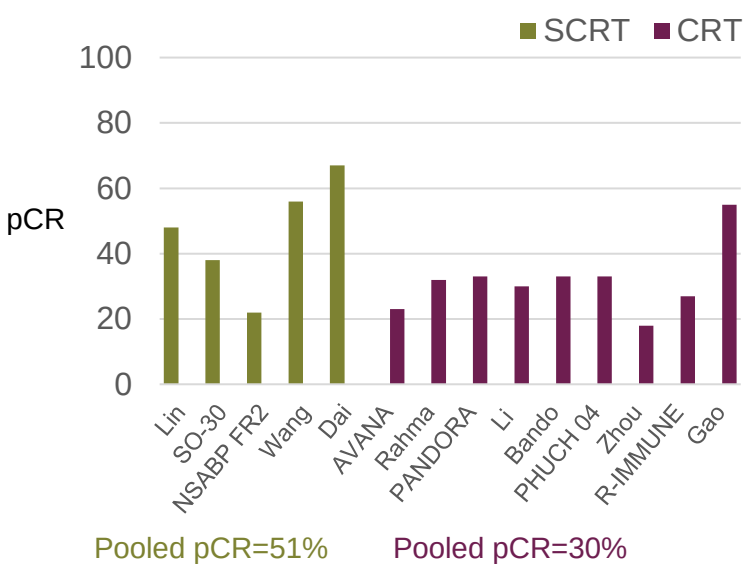
Cercek et al. ASCO 2024

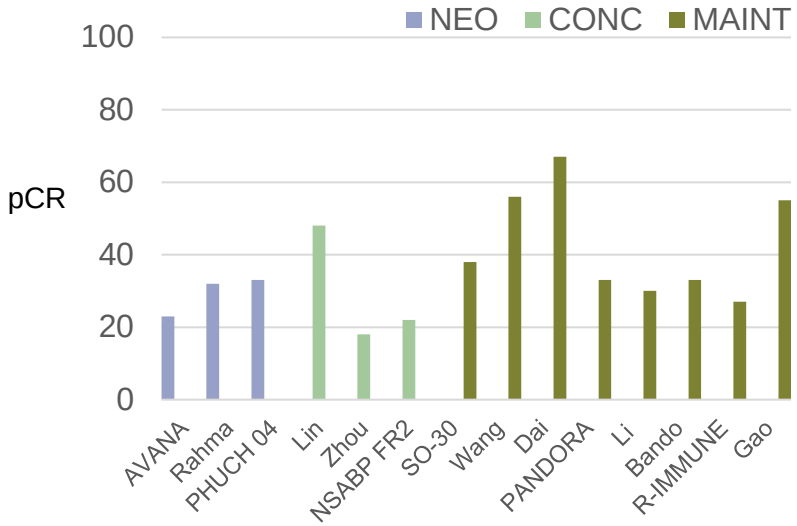
Efficacy and safety of neoadjuvant chemoradiotherapy combined with immunotherapy in pMMR locally advanced rectal cancer

N= 533 patients, median sample size 43 (21-101); 84-100% pMMR/MSS

Eight Immunotherapy agents

20% Grade 3 toxicity in nine trials of immunotherapy and CRT





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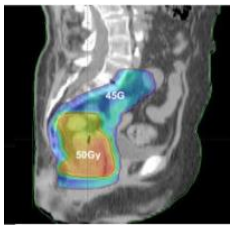
Yang et al Frontiers in Immunology 2024

OPERA Phase III Trial - early stage rectal cancer

Planned organ preservation

cT1-2; cT3a/b if middle or high cN0 (cN1 if high) MRF clear; no EMVI

SoC - TME alone



Very low distant failure rate

cT2/ cT3a/ cT3b cN0/ cN1 with lymph nodes<8mm <5cm in size

Capecitabine 825mg/m2 bd 5d/wk

45Gy in 25F

25Gy/5F

If <3cm
90Gy/3F/4weeks

Capecitabine 825mg/m2 bd 5d/wk

45Gy in 25F

If >=3cm
90Gy/3F/4weeks

3-year organ preservation rate

- 59% CRT
- **81% CRT + Contact** - (HR 0·36, 95% CI 0·19–0·70 (p=0·0026)

Grade 1-2 rectal bleeding

- 2% CRT
- 63% CRT + Contact (p<0.0001)

Local recurrence

- 23% CRT
- 15% CRT + Contact (p=0·59)

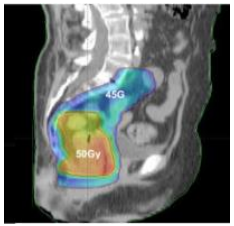
Gerard et al Lancet Gastro Hep 2023

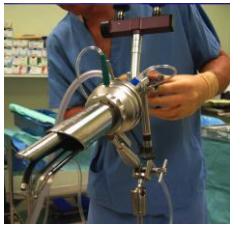
STAR TREC Phase II/III Organ Preservation Trial

Planned organ preservation

cT1-2; cT3a/b if middle or high cN0 (cN1 if high) MRF clear; no EMVI

SoC - TME alone





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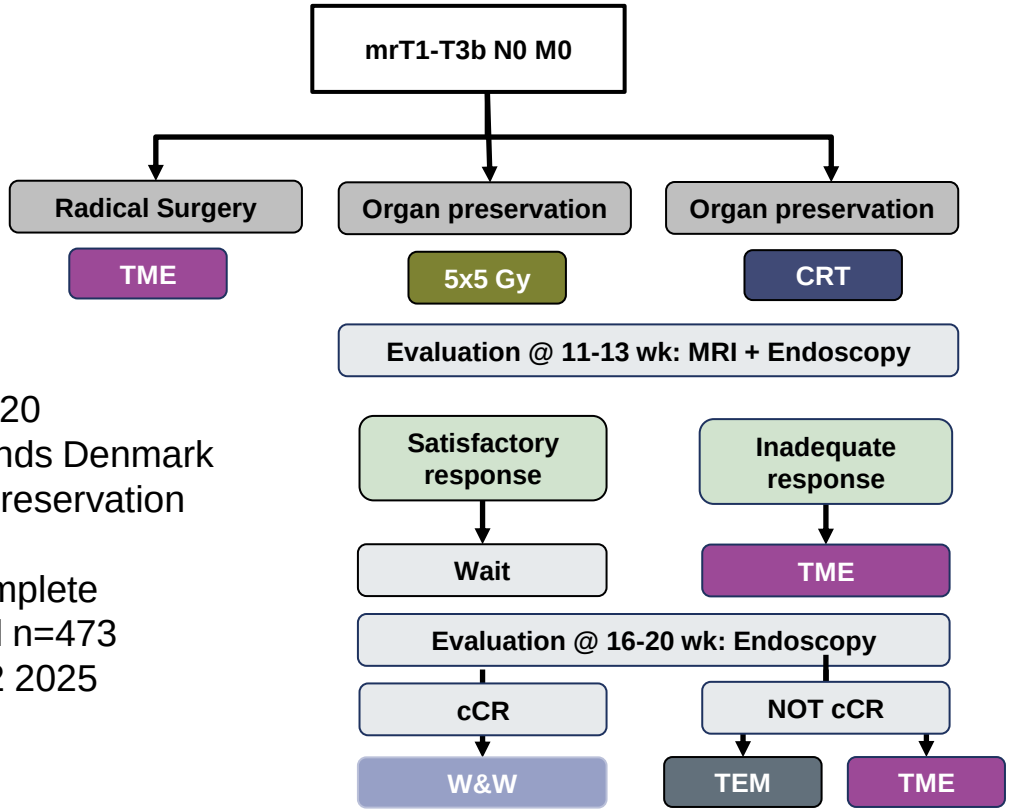
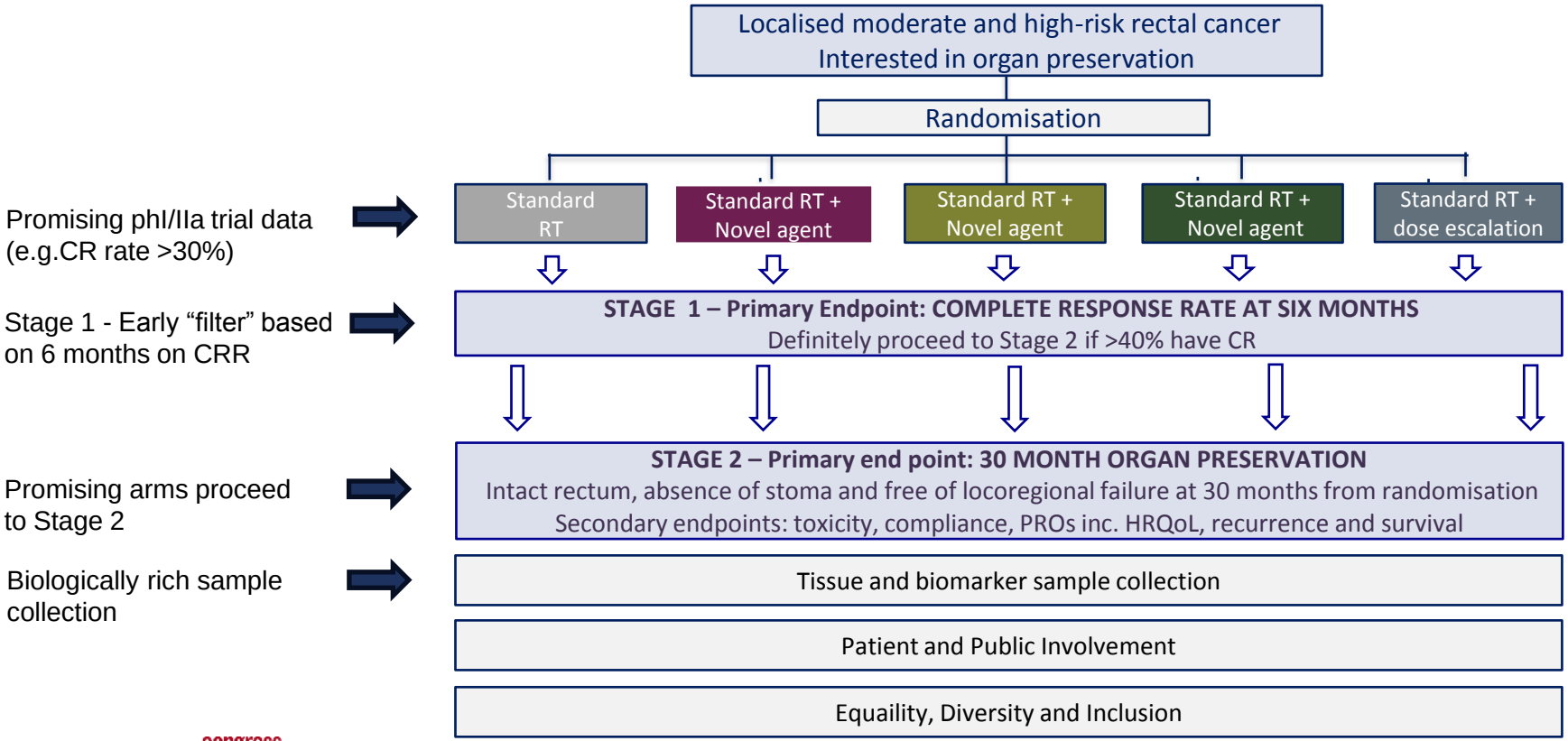


Phase II n=120
UK Netherlands Denmark
60% organ preservation

Phase III complete
Total accrual n=473
Results Q1/2 2025

Rambouts et al BMJ Open 2017

Innovative adaptive clinical trial platforms



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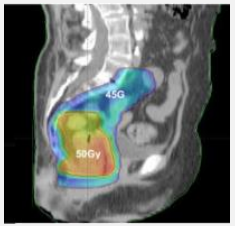
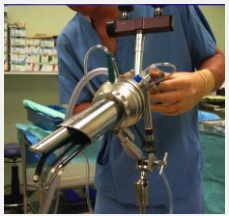
Accelerating progress in the organ preservation paradigm

TREATMENTS



Standard chemotherapy agents

Immuotherapy



Novel agents

Science

Samples

Study Team

Statistics

Innovate

Collaborate

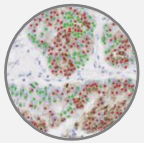
Personalise

Patients

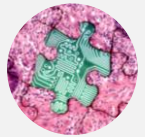
BIOLOGY

Circulating biomarkers

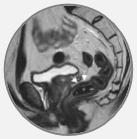
Immune



Pathology



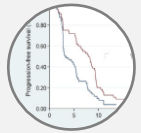
AI



Imaging

Microbiome

Radiobiology



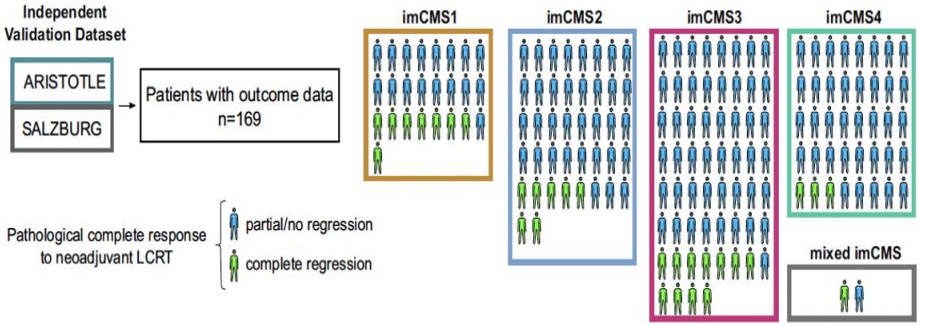
Clinical outcomes

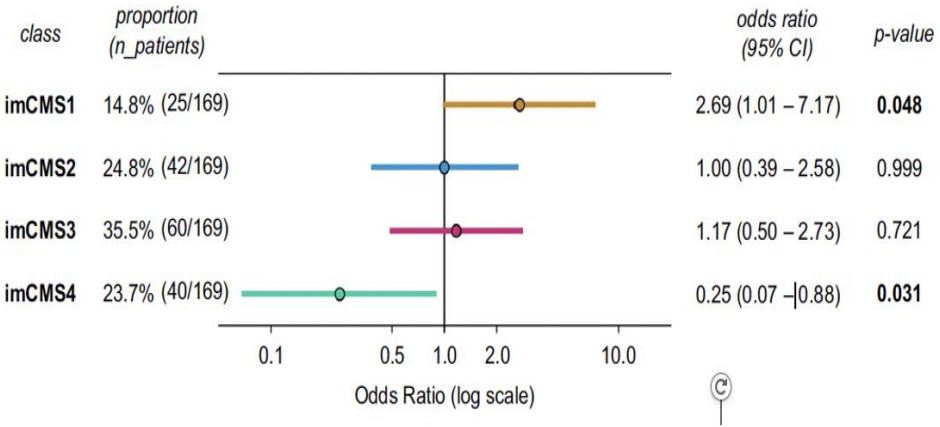
Future personalised and stratified treatments for organ preservation treatment

Clinically-led risk-adaption
- Avoid overtreatment (early stage and “blanket” use of TNT)

Multiomic Federated learning
- Securely co-train artificial intelligence models in pathology and radiology
- Cheaper, predictive biomarkers

Prediction of CCR to risk stratify
- Deep learning image based histopathological models
- imCMS4 - poor outcome with high stromal content
- imCMS1 - good outcome





Lafarge et al NPJ Precision Oncology 2024

Eyes to the Future - changing the treatment paradigm in rectal cancer

- Within the next 10-15 years we can together change the treatment paradigm for rectal cancer patients
- Organ preservation will become an established treatment approach using smarter kinder non-surgical treatments, offered to the majority of patients
- Multiomics and AI will provide the predictive tools to develop and select the optimal non-surgical treatments for individual patients
- Novel approaches will accelerate the development of new systemic therapies
- Clinical trials will establish optimal treatments, long term safety and the kindest treatments for patients

Acknowledgements

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Yorkshire Cancer Research

Leeds Hospitals Charity

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Thank you!

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