2023 ASCO ANNUAL MEETING

Preoperative Chemotherapy with Selective Chemoradiation versus Chemoradiation for Locally Advanced Rectal Cancer:

The PROSPECT Trial (Alliance N1048)

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ClinicalTrials.gov Identifier: NCT01515787

PRESENTED BY: Deb Schrag MD MPH FASCO, Attending, Gastrointestinal Oncology Service, Memorial Sloan Kettering NY, NY USA

PROSPECT Trial Summary:

Most intermediate risk rectal cancer patients can receive curative-intent treatment *without* pelvic chemoradiation.

PRESENTED BY: Deb Schrag MD MPH FASCO on behalf of the PROSPECT Investigators

Background: Rectal Cancer

- Globally ~800,000 new rectal cancer diagnoses in 2023; about half with locally advanced rectal cancer[1]

- Pelvic chemoradiation with either 5FU or capecitabine reduces **local pelvic recurrence-- a highly morbid outcome**[2]

- Neoadjuvant pelvic chemoradiation has been standard treatment for the past two decades[3]

1. Morgan E et al. Gut 2023
2. Fisher et al *JNCI* 1988; Douglas NEJM 1986; Folkesson J JCO 2005
3. Sauer *R et al NEJM* 2004

Curative Intent Treatment for Locally Advanced Rectal Cancer when PROSPECT began:

Pelvic Chemoradiation

5040 cGy with concurrent 5FU or capecitabine

5.5 weeks

~8 week recovery

Surgery

With Total Mesorectal Excision

4 to 6 day hospitalization

~6 week recovery

Adjuvant Chemo

(CAPOX or FOLFOX)

~16 weeks

PRESENTED BY: Deb Schrag MD MPH FASCO

PROSPECT Study Motivation

- Long term toxicity from pelvic chemoradiation:
  - Impaired bowel, bladder, and sexual function[1]
  - Increased risk of pelvic fracture and second malignancy[2]
  - Impaired marrow reserve[3]
  - Infertility and premature menopause[4]
    - Increasing diagnosis of rectal cancer before age 50[5]

1. Bruheim Int J Radiat Oncol Biol Phys 2010
2. Baxter N et al JAMA 2005
3. Chen MF et al Int J. Radiat. Oncol.Biol. Phys 2006
4. Ogilvy-Stuart AL Environ Health Perspect 1993
5.. Meyer JE et al Cancer 2010 and Sinicrope F *NEJM* 2022

Advances over the past two decades….

- Chemotherapy: FOLFOX[1]
- Surgical Technique: Total Mesorectal Excision[2]
- Screening: Fewer T4 and/or symptomatic tumors[3]
- Imaging: Pelvic MRI[4]

1. Goldberg R et al JCO 2004 and Andre T et a; NEJM 2004
2. Kapiteijn NEJM 2001
3. Knudsen JAMA 2021
4. Beets Tan RG et al, Radiology 2004

PROSPECT Trial Hypothesis (circa 2011):

- Neoadjuvant chemotherapy with FOLFOX and only *selective* use of pelvic chemoradiation will be noninferior to routine use of pelvic chemoradiation for locally advanced rectal cancer

PRESENTED BY: Deb Schrag MD MPH FASCO

PROSPECT Study Summary

Recruitment 2012-2018 from 264 practice sites in the USA, Canada and Switzerland

Neoadjuvant Treatment for cT2N+, cT3N-, cT3N+ Rectal Cancer

R

1:1

Pelvic Chemoradiation
5040cGy in 5.5 weeks

FOLFOX 6 cycles
Chemoradiation if poor response or FOLFOX not tolerated

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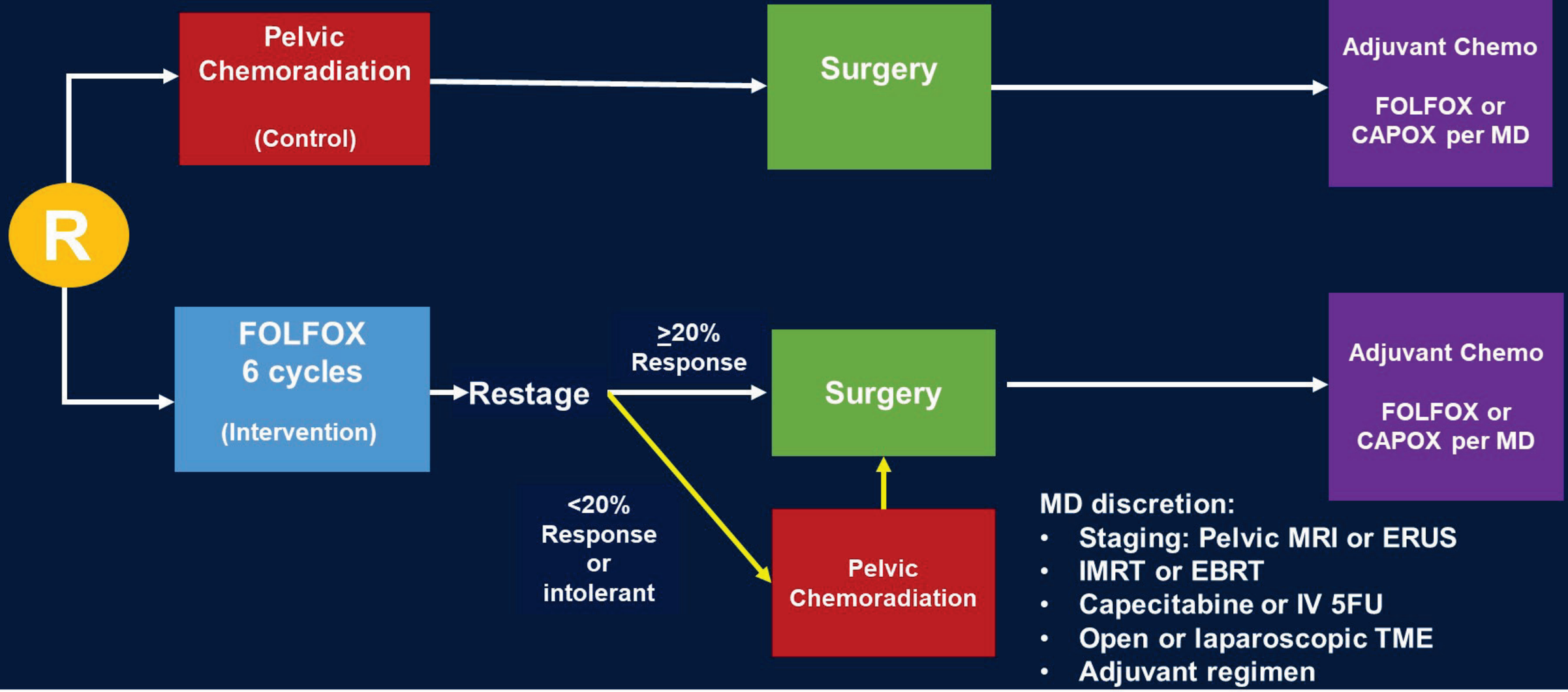
PROSPECT Study Full Schema



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PROSPECT Main Eligibility Criteria

Inclusion:

- Clinical Stage T2N+, T3N-, T3N+
- Chemoradiation is indicated
- Candidate for sphincter-sparing surgery

Exclusion:

- Tumor requiring an APR
- cT4 tumor
- ≥ 4 pelvic lymph nodes ≥ 1cm in short axis

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PROSPECT Study Endpoints

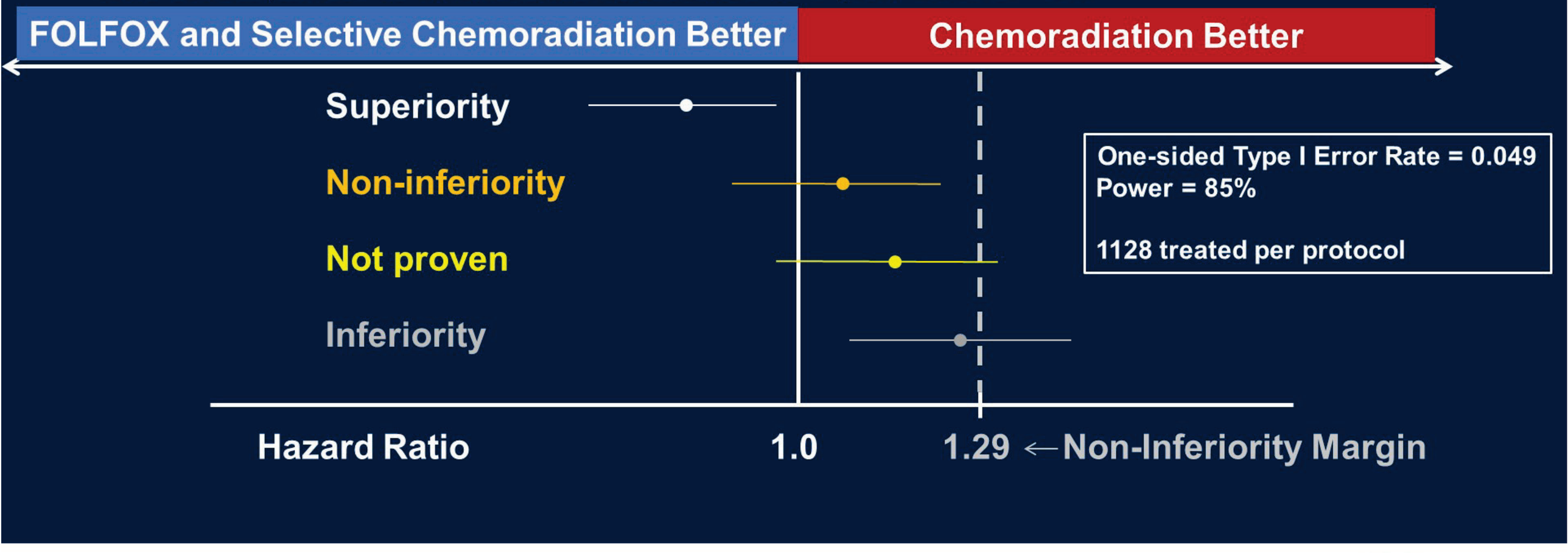
- **Primary Endpoint:**
  - Disease Free Survival

- **Secondary Endpoints:**
  - Local recurrence
  - Overall survival
  - Complete (R0) surgical resection
  - Complete pathologic response
  - Toxicity-CTCAE and PRO-CTCAE
  - Quality of Life

Non-inferiority Hypothesis for Disease Free Survival

Non-inferiority could be claimed if the upper limit of the two-sided 90.2% confidence interval of the hazard ratio (HR) did not exceed 1.29.

This corresponds to an absolute difference in 5-year DFS of <5%



Characteristics of PROSPECT Participants

Recruitment: 264 Centers	FOLFOX and Selective Chemoradiation	Chemoradiation
N	585	543
Age Mean (SD)	57 (11)	57(11)
Sex		
Female	37%	32%
Male	63%	68%
Tumor location from the anal verge in cm (SD)	8 (3)	8 (3)
Baseline Staging Performed with MRI	84%	84%
Clinical Stage at Baseline		
cT2N+	11%	7%
cT3N-	39%	37%
cT3N+	50%	56%

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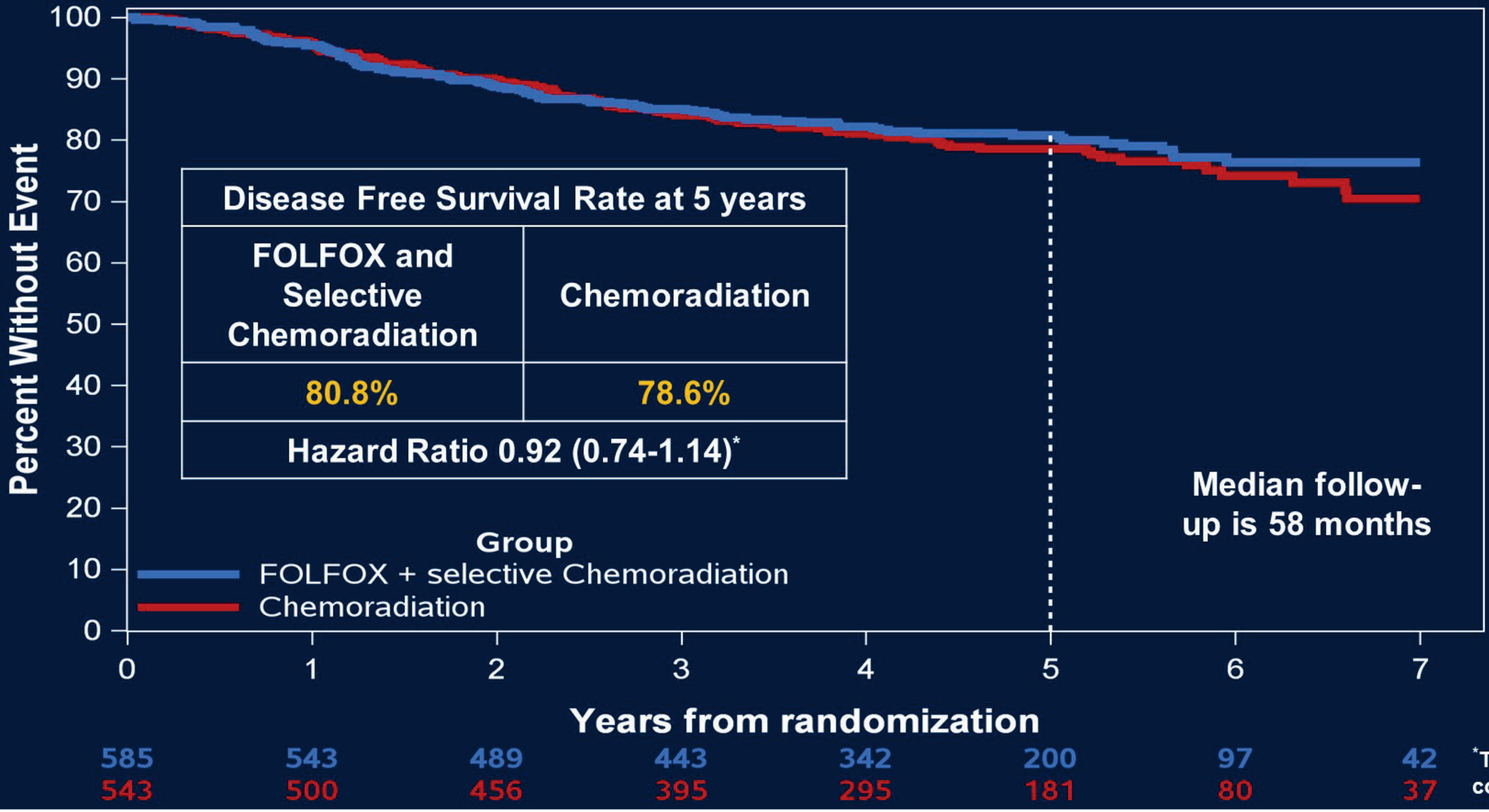
PROSPECT: Disease Free Survival



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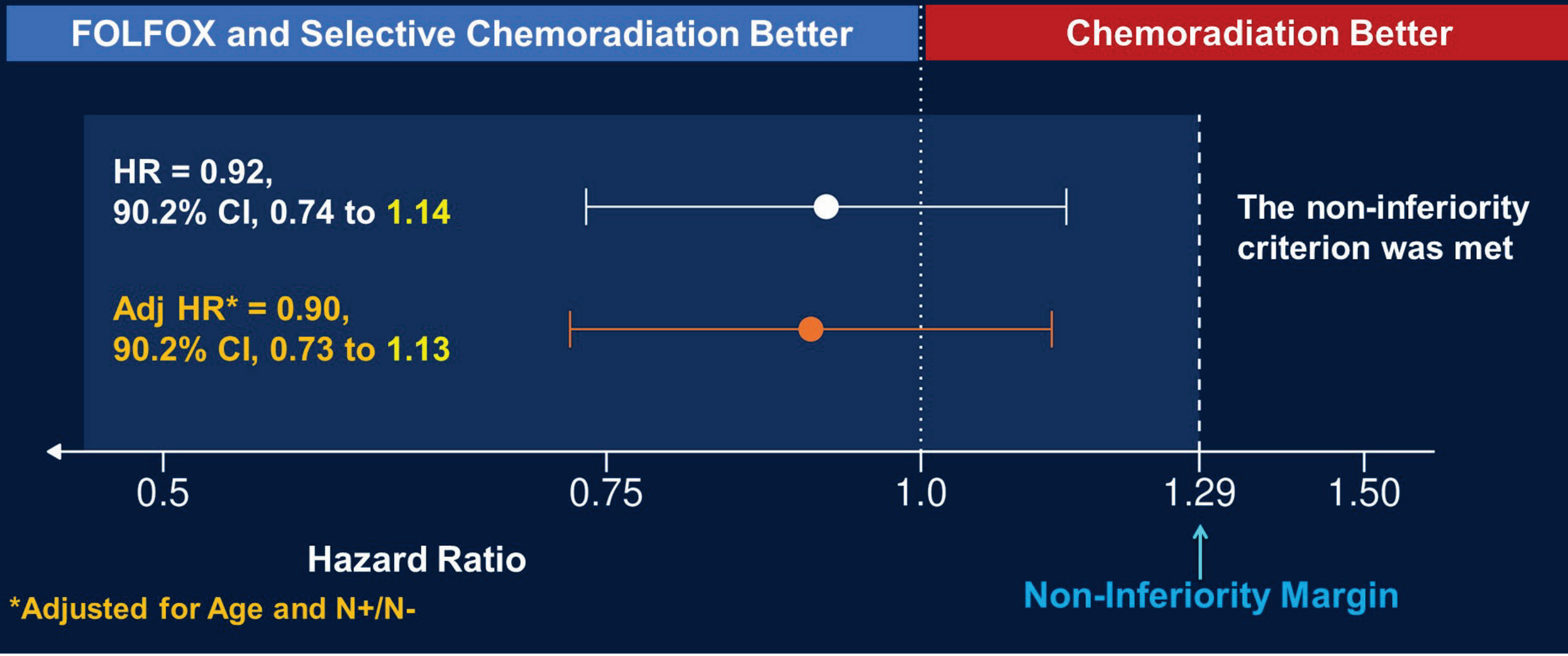
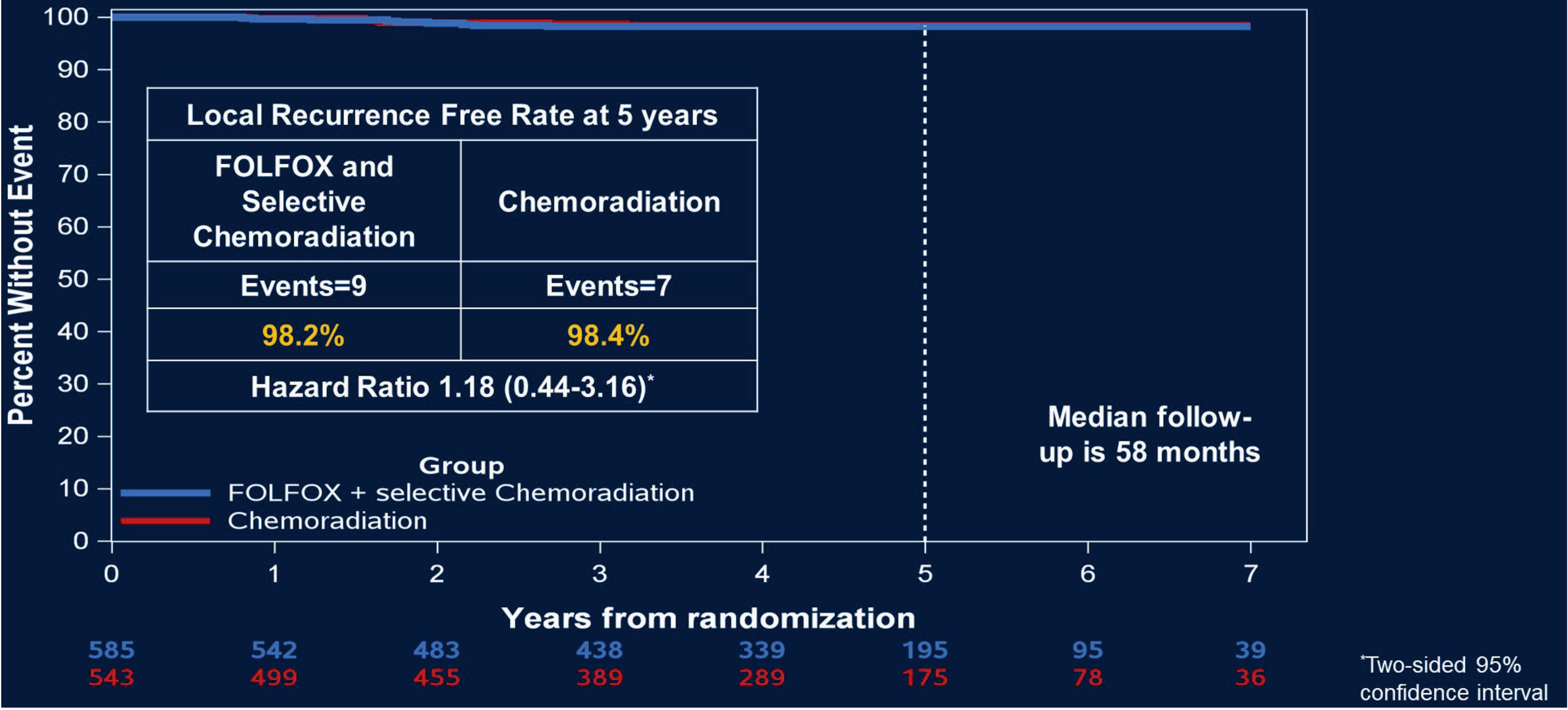
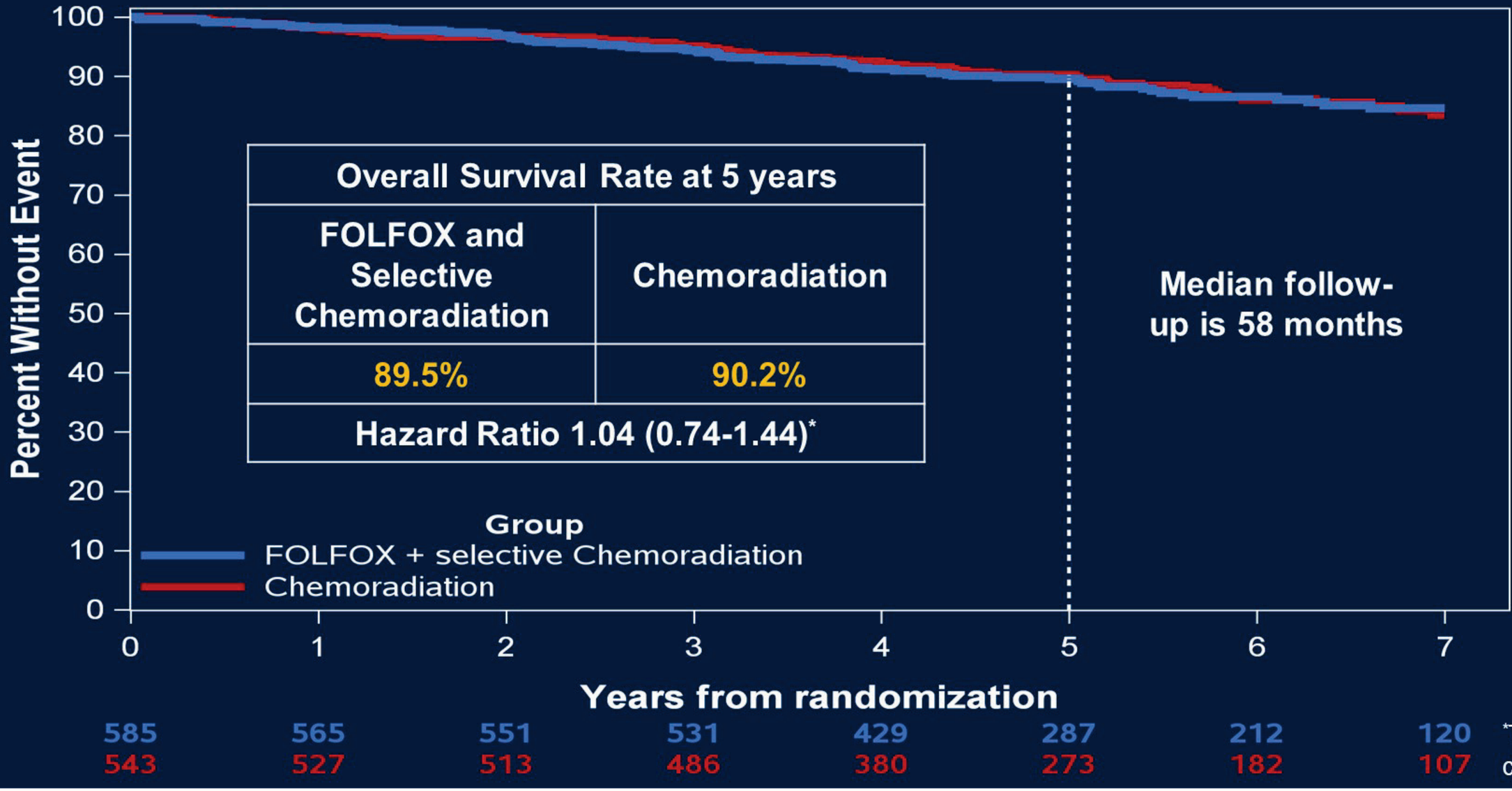
PROSPECT: Disease Free Survival



PROSPECT: Freedom from Local Recurrence



PROSPECT: Overall Survival



Surgical and Pathologic Endpoints

Secondary endpoints in participants who completed Surgery	FOLFOX and Selective Pelvic Chemoradiation N=535	Pelvic Chemoradiation N=510
Complete (R0) Rectal Resection	99%	97%
Low Anterior Resection Rate	98%	98%
Pathologic Complete Response	22%	24%
Positive Radial margin	1.2%	1.5%

Adjuvant Treatment and Therapy Duration

Adjuvant treatment in patients who had surgery	FOLFOX and Selective Pelvic Chemoradiation N=535	Pelvic Chemoradiation N=510
Received any adjuvant chemotherapy	82%	83%
Median duration (IQR) from randomization to last dose of postoperative therapy (weeks)	35 (33, 39)	37 (34, 40)

Use of Pelvic Chemoradiation in patients randomized to FOLFOX

9% (53/585) of participants randomized to FOLFOX received neoadjuvant chemoradiation either because:

- Restaging demonstrated clinical response <20% or
- They did not tolerate at least 5 cycles of FOLFOX

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PROSPECT: Clinician-Reported Toxicity

Most severe toxicity during observation period based on CTCAE v. 4.0	FOLFOX and Selective Chemoradiation 12 weeks* 535 patients	Chemoradiation 6 weeks 510 patients
Neoadjuvant grade ≥3 adverse events	41%	23%
Adjuvant grade ≥3 adverse events	25%	39%

*22 weeks if also treated with chemoradiation

During Neoadjuvant treatment:

- More diarrhea in the RT group
- More neuropathy in the FOLFOX group

During Adjuvant treatment:

- More diarrhea in the RT group
- More neuropathy in the RT group

Patient-Reported Adverse Events During Neoadjuvant Treatment

% Reporting Severe PRO-CTCAE Scores	Neoadjuvant Treatment	
	FOLFOX and Selective Chemoradiation 12 weeks (22 weeks if also 5FUCRT)	Chemoradiation 6 weeks
Anxiety	11%	6%
Appetite Loss	22%	9%
Constipation	27%	11%
Depression	10%	3%
Diarrhea	6%	20%
Dysphagia	12%	1%
Dyspnea	7%	1%
Edema	2%	2%
Fatigue	42%	20%
Mucositis	11%	2%
Nausea	21%	7%
Neuropathy	19%	5%
Pain	22%	18%
Vomiting	4%	2%

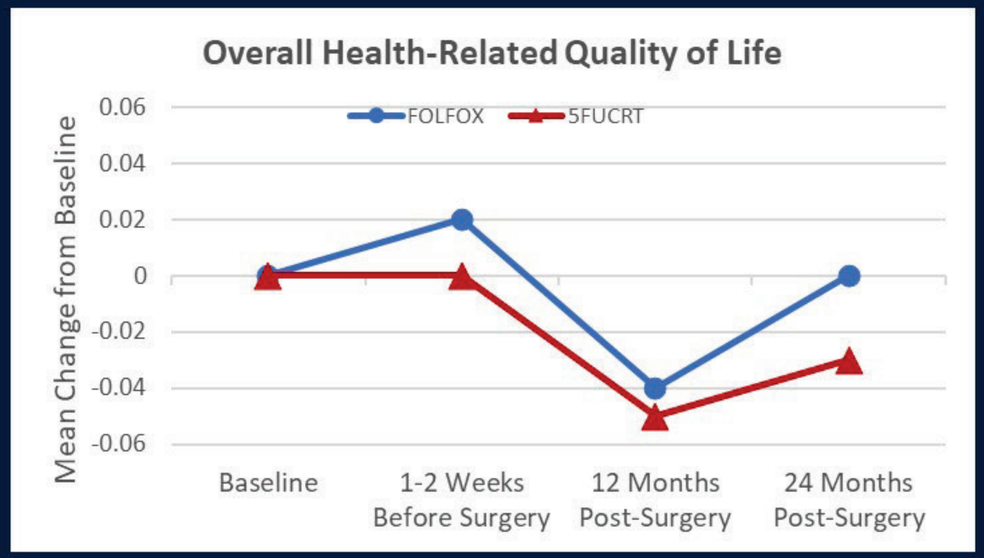
Values represent % with PRO-CTCAE composite scores ≥3 which were worse than each patient's baseline score (n=940).

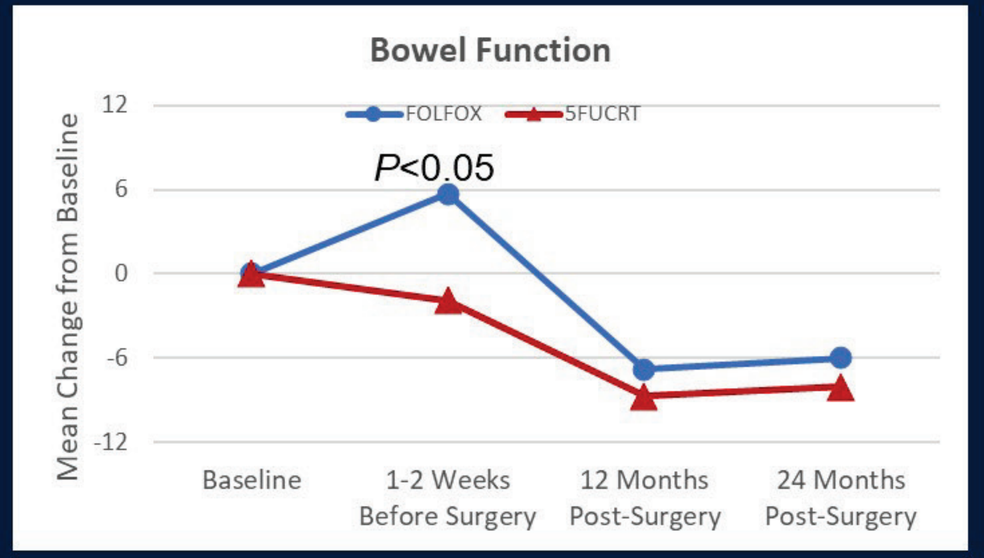
Patient-reported Severe Adverse Events at 12 months

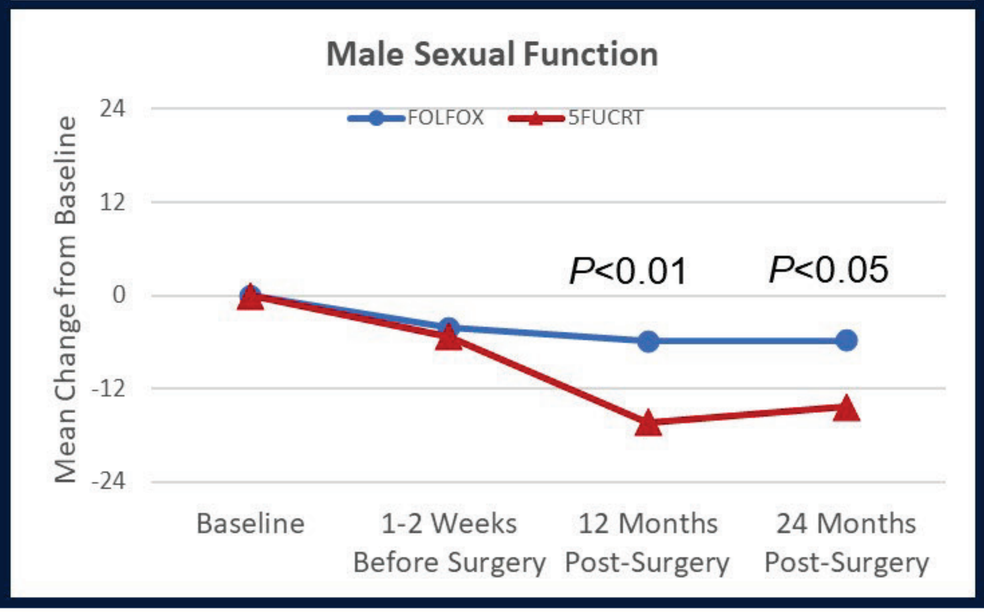
	Severe Adverse Symptoms at 12 months	
% Reporting Severe PRO-CTCAE Scores	FOLFOX and Selective Chemoradiation	Chemoradiation
Anxiety	3%	2%
Appetite Loss	1%	1%
Constipation	3%	4%
Depression	2%	3%
Diarrhea	2%	4%
Dysphagia	1%	0%
Dyspnea	0%	0%
Edema	1%	1%
Fatigue	3%	7%
Mucositis	0%	0%
Nausea	1%	0%
Neuropathy	3%	8%
Pain	5%	4%
Vomiting	0%	0%

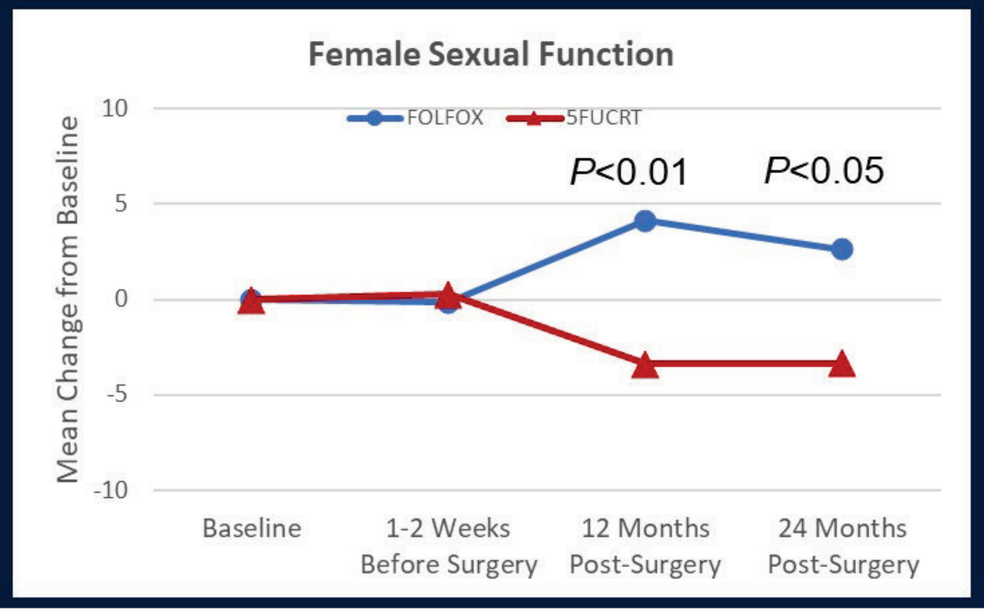
Values represent % with PRO-CTCAE composite scores ≥3 which were worse than each patient's baseline score (n=531).

PROSPECT: Quality of Life Evaluation









Quality of Life: Trend, but no significant difference between groups

Bowel function and sexual function favor FOLFOX group

N-373

Positive values represent improvement compared to baseline

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Limitations

- Excluded high risk patients: distal, T4 tumors, multiple enlarged nodes
- Not all patients had MRI staging
- We may still be overtreating some patients

Caveat: *While conducting this trial, new approaches have emerged*

- **Shorter courses of adjuvant FOLFOX[1]**
- **Short course radiation[2]**
- **Total neoadjuvant therapy[3]**
- **Non-operative management[4]**
- **Immuno-ablative therapy for MSI-high patients[5]**

1. Grothey A NEJM 2018
2. Bahdoer R Lancet 2001
3. Cercek A Jama Oncol 2022
4. Habr-Gama A, Dis Colon Rectum 1998
5. Cercek A, NEJM 2022

PROSPECT Trial Conclusion

Neoadjuvant FOLFOX, with only selective use of pelvic chemoradiation, is a safe and effective treatment option for patients with cT2N+, cT3N-, or cT3N+ rectal cancer

PRESENTED BY: Deb Schrag MD MPH FASCO

THANK YOU, Collaborating Investigators and Research Professionals

NCI National Clinical Trials Network
a National Cancer Institute program

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

PROSPECT Publications

The NEW ENGLAND JOURNAL of MEDICINE

Schrag D, Shi Q, Weiser MJ et al

Preoperative Treatment of Locally Advanced Rectal Cancer

www.nejm.org/doi/full/10.1056/NEJMoa230326

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Journal of Clinical Oncology®

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Basch EB, Dueck AL et al

Patient-Reported Outcomes During and After Treatment for Locally Advanced Rectal Cancer

ascopubs.org/doi/full/10.1200/JCO.23.00903

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