

# **Study Design to Evaluate Dostarlimab in Locally-Advanced dMMR/MSI-High Rectal Cancer**

**February 9, 2023**

Oncologic Drugs Advisory Committee Meeting

GSK



## Introduction

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# dMMR/MSI-H Tumors Highly Susceptible to Checkpoint Inhibitors

- dMMR/MSI-H tumors
  - ↑ expression of PD-1 and PD-L1 in tumor tissues
  - ↑ tumor infiltrated lymphocytes
  - ↑ neoantigen due to high tumor mutation burden
- Subset of rectal cancer caused by this rare mutation
  - Well-established, predictive biomarker
  - NCCN guidelines recommend dMMR/MSI-H testing for all patients with rectal cancer<sup>1</sup>

# Dostarlimab: Established Anti-PD-1 Monoclonal Antibody for Advanced, Recurrent dMMR/MSI-H Tumors

- Accelerated approval for two indications in adults with dMMR solid tumors
  - Endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen
  - Any dMMR solid tumor that has progressed on or following prior treatment with no satisfactory alternative treatment options

# GARNET Single-Arm Trial: Dostarlimab Demonstrated Deep, Durable Response in 2L+ dMMR/MSI-H Solid Tumors

	N	ORR	Median DOR Months (range)	DOR Rate <sup>a</sup> at 12 Months (95% CI)	DOR Rate <sup>a</sup> at 24 Months (95% CI)
All evaluated advanced, metastatic dMMR/MSI-H tumors	327	44%	NR (1.2, 47.2+)	92% (86%, 96%)	85% (77%, 90%)
Advanced, metastatic dMMR/MSI-H Colorectal Cancer	105	43%	NR (2.8, 41.5+)	88% (74%, 95%)	Not Available

GARNET Phase 1 trial in locally advanced, or metastatic dMMR/MSI-H solid tumors that progressed following systemic anticancer therapy  
 ORR = Objective Response Rate; DOR = Duration of Response; NR = Not reached

# Ongoing Memorial Sloan Kettering Study Using Dostarlimab<sup>CO-6</sup> Monotherapy Earlier in Rectal Cancer Treatment Journey

## Memorial Sloan Kettering Cancer Center Study

- Neoadjuvant dostarlimab for patients with dMMR/MSI-H locally advanced rectal cancer (LARC)
- Demonstrated unprecedented efficacy
  - Clinical complete responses (cCR) in all patients following dostarlimab treatment
  - Sustained cCR, i.e., cCR12, for all eligible for 12-month evaluation following treatment
- All patients avoided adverse effects of standard of care

# GSK Designed Global Study with Endpoints that Align with MSK Study to Further Demonstrate Benefit of cCR12<sup>co-7</sup>

## GSK Planned Study 219369

- Enhance robustness, demonstrate reproducibility of MSK methods
- GSK and MSK results pooled to support accelerated approval
- Multi-site, single-arm, pivotal, Phase 2 study to establish efficacy of dostarlimab in dMMR/MSI-H LARC
- Primary endpoint cCR12
  - Literature shows cCR12 predicts long-term benefit, potentially curative **without** removing rectum
- Begin enrolling in April 2023

# Defining Clinical Complete Response – cCR and Clinical Complete Response for 12 Months – cCR12

## Stringent Criteria Define cCR

- Defined as absence of any abnormality, residual disease
- Based on endoscopic and MRI examinations
- Leads to non-operative approach, goal of organ preservation

## Durability for 12 months Defines cCR12

- Builds on cCR
- Careful monitoring with Non-operative Management
- Sustaining cCR for 12 months predicts 5-year outcomes including OS<sup>1</sup>



## Standard of Care

## Scientific Rationale Supporting cCR12

## MSK Study Design and Interim Results

## GSK Design of Phase 2 Study

## GSK Commitment to Accelerated Approval

## Conclusion

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## Treating dMMR/MSI-H Locally-Advanced Rectal Cancer

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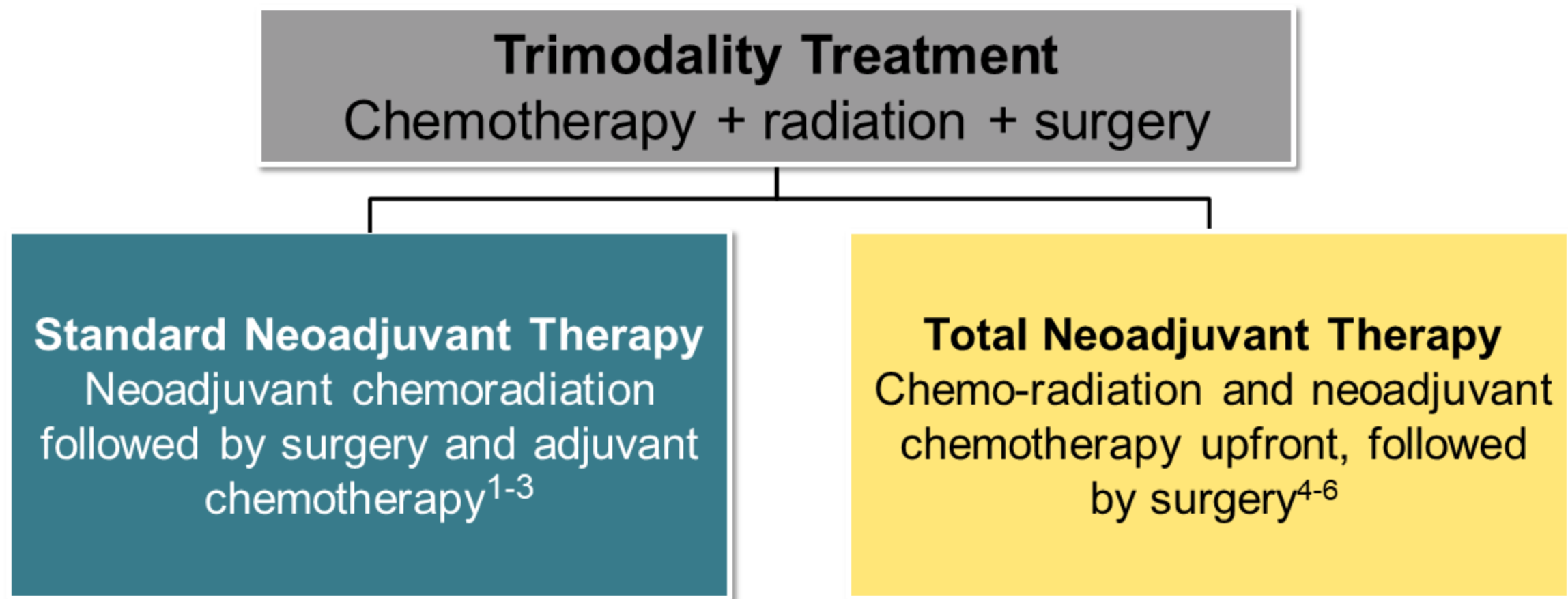
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# Locally Advanced dMMR/MSI-H Rectal Cancer Rare Form of Serious Disease

- Locally advanced rectal cancer defined as stage II or III disease
- > 20,000 individuals diagnosed with LARC annually in US<sup>1</sup>
  - 5% - 10% have distinct dMMR mutation<sup>2,3</sup>
- dMMR/MSI-H status varies across rectal tumor stages
  - Highest incidence in stage II tumors
  - Decreases with increasing stage, 10% in stage III, 5% in stage IV<sup>4-9</sup>

# Two Established Standards of Care for Locally Advanced Rectal Cancer Including dMMR/MSI-H



# Mortality and Significant Morbidities, Toxic Effects Associated with Standards of Care

- ~1/3 with locally advanced rectal cancer will die of distant metastases<sup>1,2</sup>
- Total mesorectal excision requires temporary colostomy, up to 30% permanent
- Colostomy issues include<sup>3</sup>
  - Social and physiological dysfunction
  - Depression
  - Stoma complications

# Surgery and Radiotherapy Impair Survivorship, Quality of Life for Patients with LARC

- Low anterior resection syndrome<sup>1</sup>
  - May occur in ~40% following partial or total resection of rectum
  - Fecal incontinence, urgency, diarrhea
- Sexual dysfunction can occur in as high as 79% of patients<sup>2,3</sup>
- Long-term urinary incontinence in 38% of patients<sup>4</sup>
- Second gynecologic malignancies<sup>5</sup>
  - Radiotherapy associated with 3-fold higher risk of developing uterine or ovarian cancer

# Non-Operative Management for Patients with Locally Advanced Rectal Cancer Who Achieve cCR after Neoadjuvant Therapy

## Non-Operative Management (NOM)

- Undertaken by centers with multidisciplinary teams to objectively determine cCR
- Careful monitoring to detect tumor regrowth over 5-year surveillance period
- Enables detection of any tumor regrowth, allows for timely treatment

# Standards of Care Result in Low Complete Response Rates for Locally Advanced Rectal Cancer Patients

	Neoadjuvant Chemoradiotherapy	Total Neoadjuvant Therapy
<b>Combined Complete Response Rate<sup>1</sup> (pCR+cCR12)</b>	21%	36%

pCR = pathological complete response; cCR = clinical complete response

- Majority of locally advanced rectal cancer patients not candidates for Non-operative Management
- Data in dMMR/MSI-H subpopulation less sensitive to chemotherapy



# High Unmet Need in Locally Advanced dMMR/MSI-H Rectal Cancer

- Rare form of rectal cancer generally treated with SoC
  - May be curative, but carries significant morbidity, long-term sequelae
- Need for a more efficacious treatment for this biomarker-selected population
  - Reduced morbidities
  - Potential for organ preservation with Non-operative Management



## Scientific Rationale Supporting cCR12 as Primary Endpoint

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# cCR Correlated with DFS3 in Neoadjuvant Chemoradiation Setting

- OPRA trial: Prospective, multi-center trial evaluating 3-tier clinical response in patients with LARC who underwent TNT<sup>1</sup>

	cCR n= 124 <sup>a</sup>	nCR n=113 <sup>a</sup>	iCR n=57
<b>DFS3</b>	<b>84%</b>	<b>76%</b>	<b>52%</b>
<b>Rate of organ preservation</b>	<b>79%</b>	<b>52%</b>	<b>9%</b>
<b>TME-Free DFS3</b>	<b>72%</b>	<b>44%</b>	<b>4%</b>

nCR = near Complete Response; iCR = incomplete Clinical Response

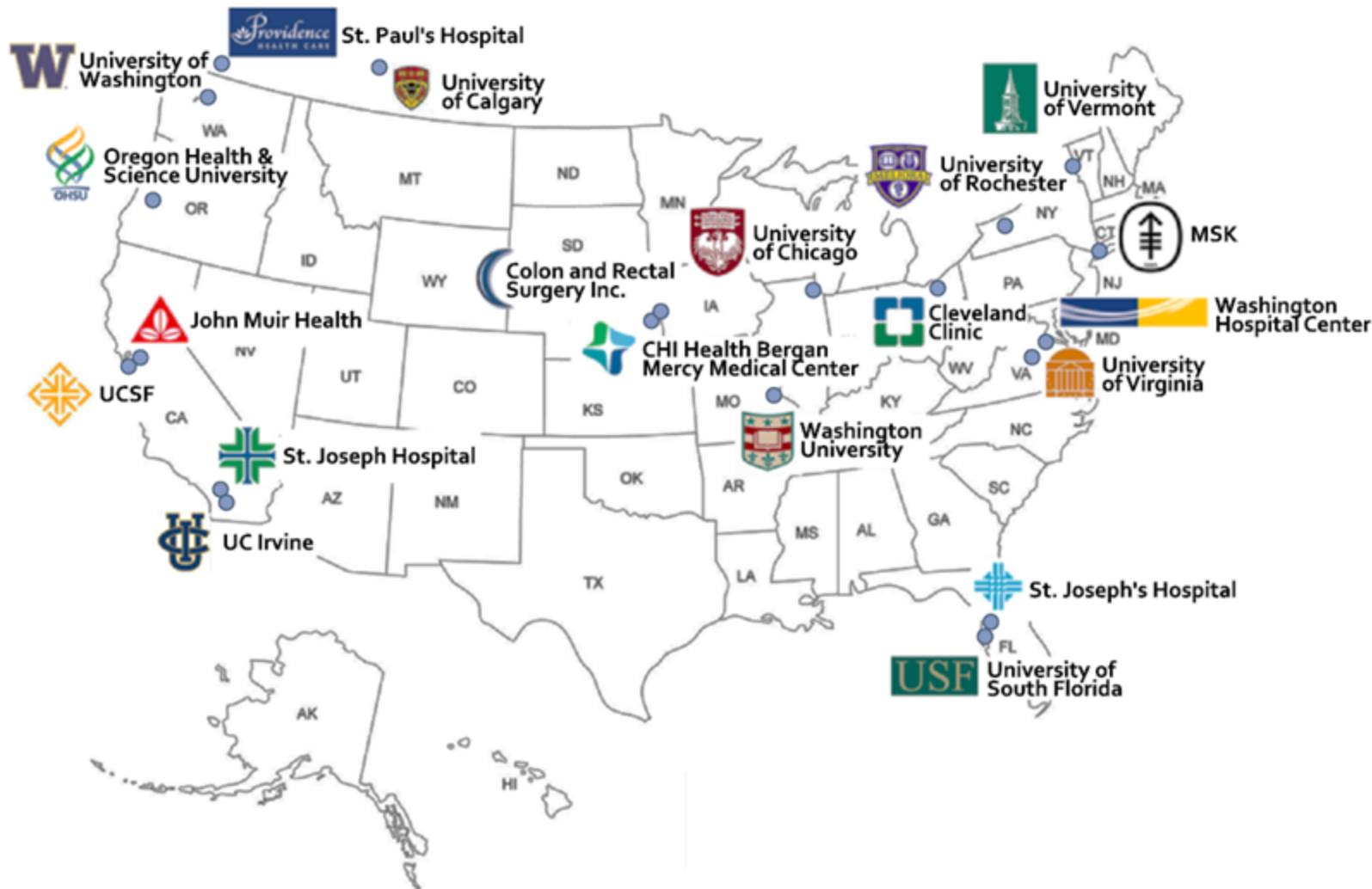
Disease-Free Survival (DFS3) represents continuation of response for 3 consecutive years

TME = total mesorectal excision

1. Thompson et al, 2021

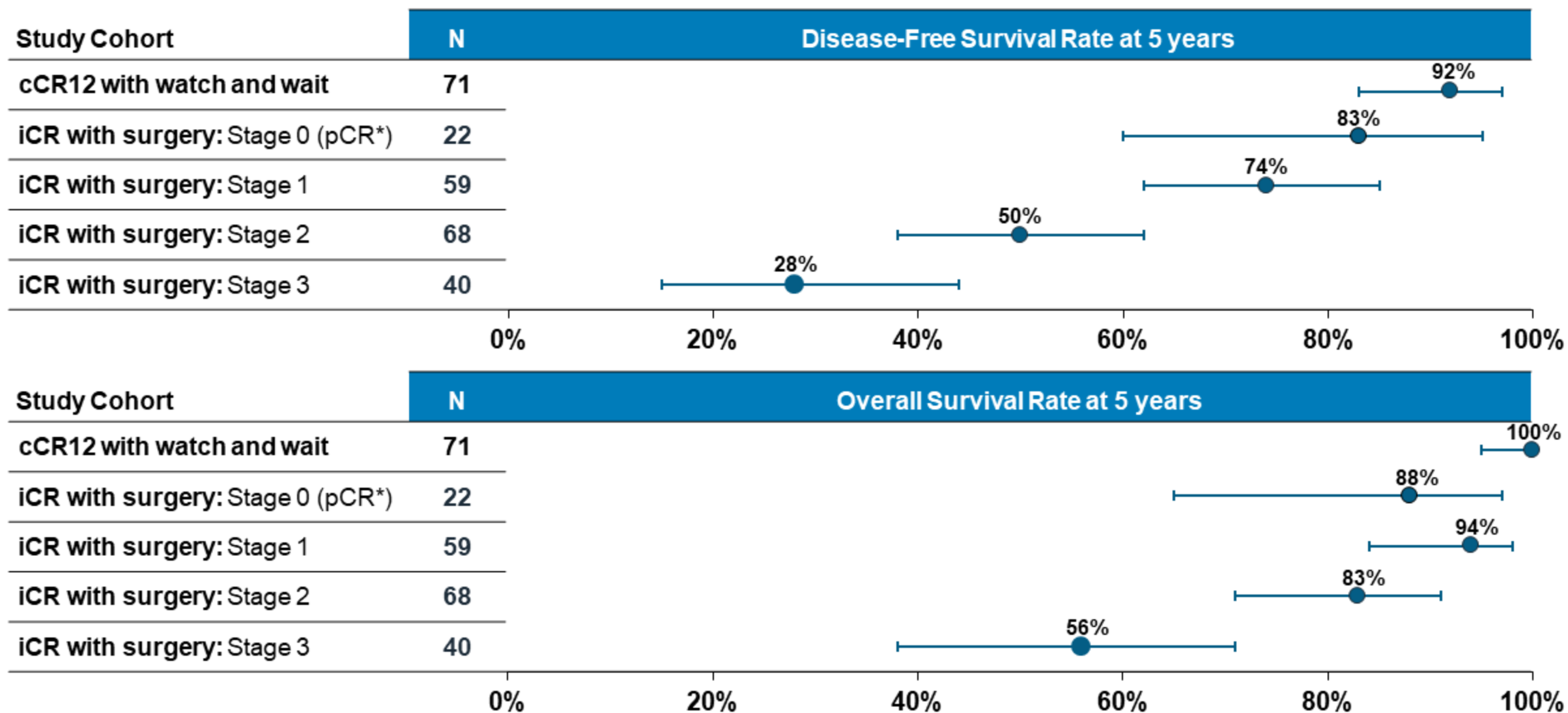
a. Patients with cCR and nCR offered Non-operative Management; OPRA = Organ Preservation Rectal Adenocarcinoma trial

# Multiple Institutions Across North America Participated in the OPRA Trial



- ✓ Created consensus criteria that standardized evaluation, determination of cCR
- ✓ Able to prospectively implement non-operative management in patients who achieve cCR

# Sustained cCR (cCR12) Predictive of Long-Term Clinical Outcomes Including 5-year DFS and OS



# Neoadjuvant Anti-PD-1 Therapy Consistently Achieves High Rates of CR in dMMR/MSI-H Colorectal Tumors

Phase II Study	Tumor	Classification	Anti-PD-1	N	CR
Cercek, 2022	Rectal	Stage II-III	Dostarlimab	12	100% <sup>a</sup>
ESMO 2022 (NICHE-2)	Colon	Stage I-III	Nivolumab+Ipilimumab	112	67% <sup>b</sup>
Ludford 2023	CRC	Stage II-III	Pembrolizumab	27	65% <sup>c</sup>
Hu, 2022	CRC	Stage III	Toripalimab	17	65% <sup>b</sup>
Chalabi, 2020 NICHE	Colon	Stage I-III	Nivolumab+Ipilimumab	20	60% <sup>b</sup>
Retrospective Study	Tumor	Classification	Anti-PD-1	N	CR
Pei, 2022	CRC	Stage II-III	Sintilimab	10	100% <sup>b</sup>
Ludford, 2021	CRC	Stage III-IV	Anti-PD-1 ± Anti-CTLA4	14	93% <sup>b</sup>
Wang, 2022	Rectal	Stage I-III	Anti-PD-1	29	83% <sup>a,b</sup>
Zhang, 2022	CRC	Stage II-III	Anti-PD-1	32	78% <sup>a,b</sup>

Complete Response (CR) assessment based on accepted evaluation method for the tumor type

a. Clinical CR assessment; b. Pathological CR assessment; c. Among 17 of 27 patients who underwent surgery

# Growing Consensus for Nonoperative Management and cCR in Large, Prospective Rectal Cancer Trials

- Patients express unwillingness to be randomized to surgery vs non-operative management following cCR

Country	N	Tumor	Phase	Design	Primary Endpoint	Secondary Endpoints
<b>US</b> (Janus)	312	MSS/MMRp Rectal Cancer Stage II or III	Ph 2	Randomized, two-arm, open-label (Chemo: Triplet vs Doublet)	<b>cCR</b>	DFS, OS, Organ-preservation- Time
<b>Japan</b> (ENSEMBLE)	608	M0 resectable MSS/MMRp -Rectal Cancer	Ph 3	Randomized, two-arm, open-label (SCRT+CAPOXIRI vs SCRT+CAPOX)	Organ preservation adapted DFS	<b>cCR</b> , Recurrence rate, LRFS, OS
<b>Germany</b> (ACO)	702	Rectal Cancer Stage III	Ph 3	Randomized, two-arm, single-blind (SCRT+ chemo vs CRT+chemo)	Organ preservation	<b>cCR</b> , OS

# Data Support Ability to Successfully Intervene with Surgery in Event of Tumor Regrowth

- Majority of patients can undergo surgical intervention, achieve favorable outcomes
- OPRA Disease Free Survival rates
  - Similar for patients who had TME at restaging compared to patients who had TME at regrowth
- Same operation at regrowth as after total neoadjuvant therapy
- Data and experience support long-term clinical outcomes, including disease free survival





## **MSK Study:** ***Design and Interim Results***

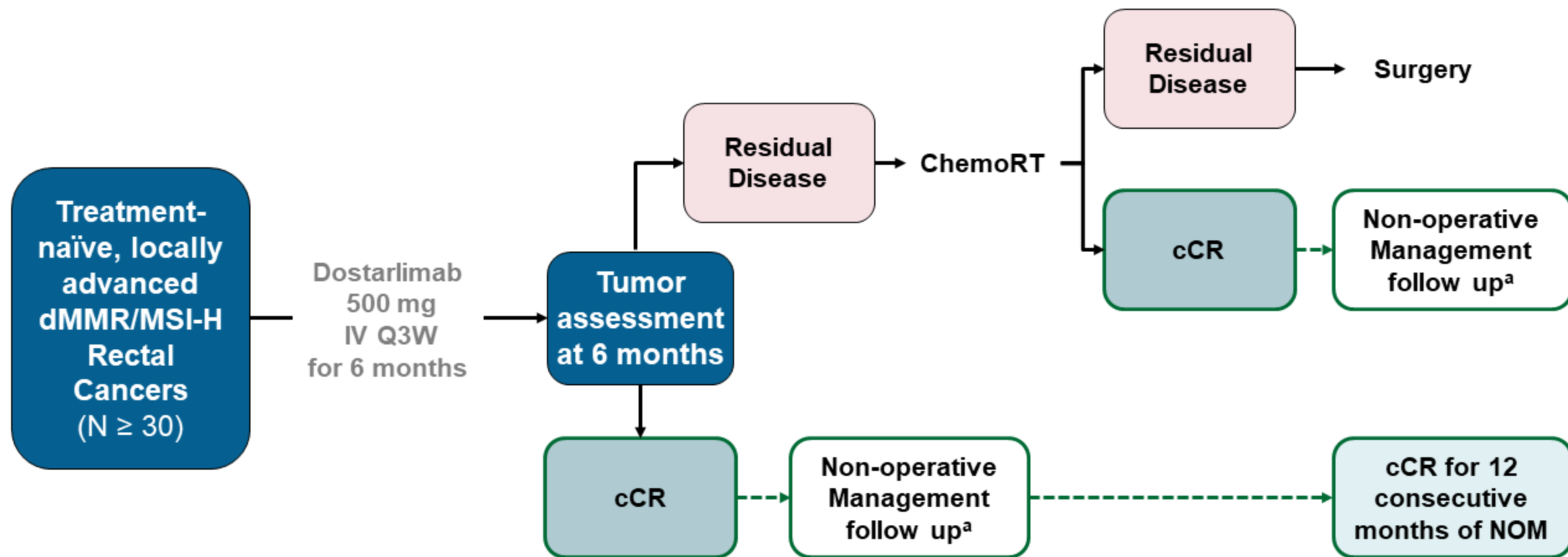
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# MSK Study: Ongoing, Open-Label, Single-Arm, Phase 2 Study



**cCR = Clinical Complete Response, defined as no evidence of residual disease by endoscopy, digital rectal exam, or rectal-specific MRI and no evidence of metastatic disease**

*Evaluated at 18 months*

# MSK Study Co-Primary Endpoints

- Overall Response Rate (ORR)
  - Complete Response (CR), near CR (nCR) and Partial Response (PR)
- cCR12 **or** pCR
  - Sustained cCR for 12 consecutive months after dostarlimab, evaluated at 18-month timepoint
  - Determined by multidisciplinary team
  - Pathologic complete response in patients who require surgery

# MSK Study: Non-Operative Management, Intense Monitoring to Confirm Continued cCR at Each Evaluation

- Assessments every 4 months for 2 years, every 6 months in years 3 to 5
  - More frequent than standard clinical practice
  - Includes imaging, endoscopic exams, biopsies, blood tests
- Similar to OPRA surveillance approach<sup>1</sup>

# MSK Study: Patients Representative of Locally Advanced dMMR/MSI-H Rectal Cancer Population

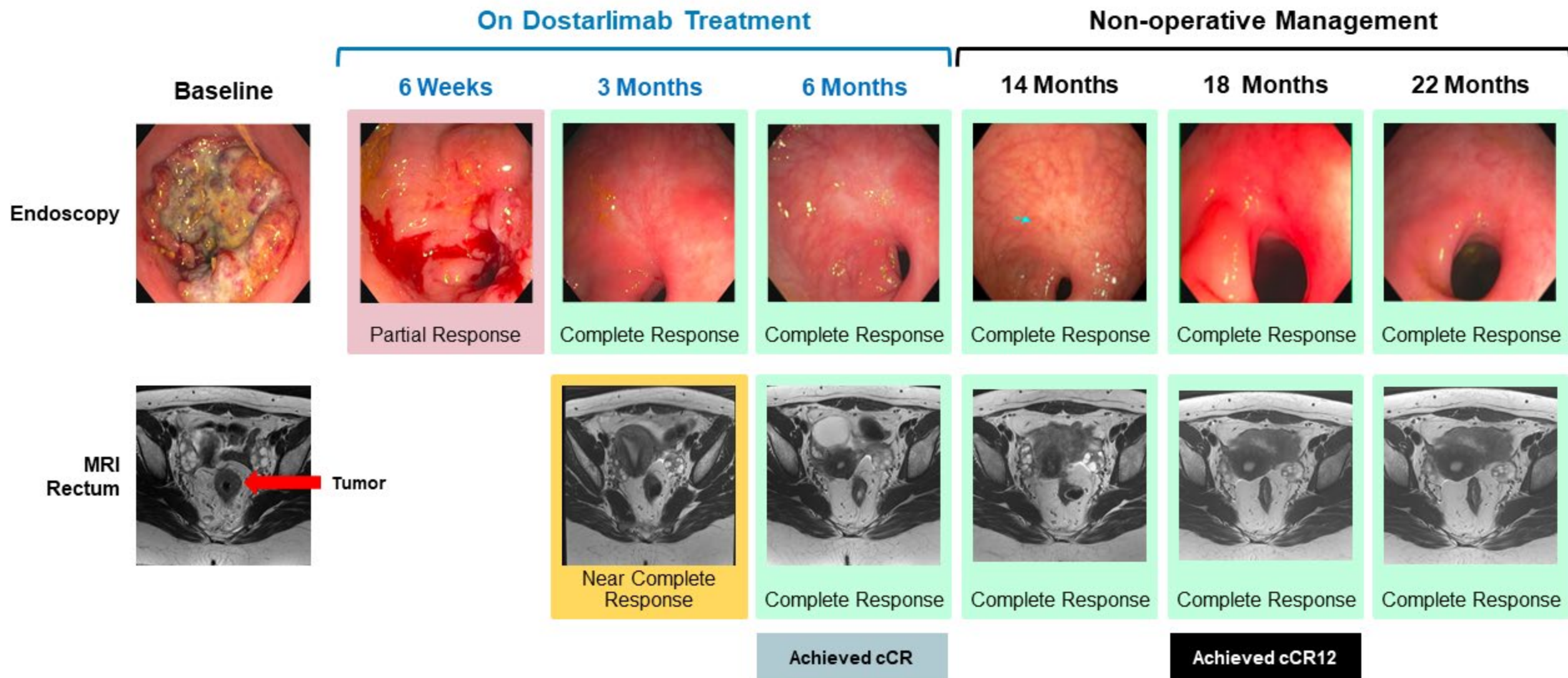
Characteristic	N=18
Female	67%
Age, median years (range)	54 (26 –78)
Race	
White non-Hispanic	66%
Black or African American	17%
Asian-Far East/Indian Subcontinent	17%
Ethnicity	
Hispanic	6%
Tumor Staging	
T1 or T2	22%
T3, T4	78%
Nodal Status	
Positive	94%
Negative	6%
Tumor Mutational Burden, mean (range)	67 (36 – 106)

# MSK Study: All Patients Attained cCR Following Dostarlimab Monotherapy

- No patient has required chemotherapy, radiation or surgery
- All adverse events Grade 1 or 2
- Safety profile in line with other checkpoint inhibitors

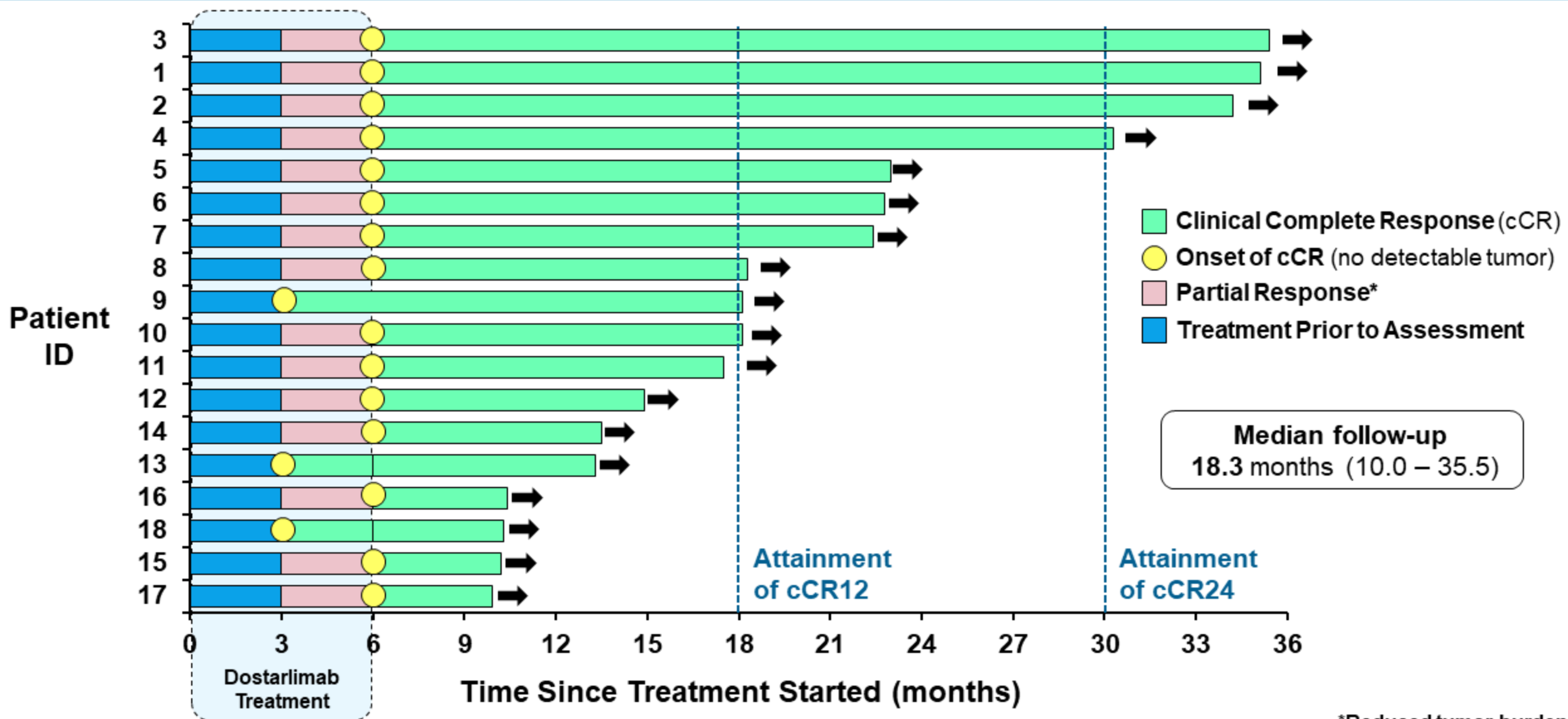


# Serial Imaging Illustrates Sustained Clinical Complete Response Following Dostarlimab Treatment<sup>CO-31</sup>



# MSK Study: Enduring Duration of Response

[18 Patients Reported at ASCO 2022, Updated Through Dec 2022]





# MSK Study: dMMR/MSI-H LARC is Highly Responsive to Neoadjuvant Monotherapy with Dostarlimab<sup>CO-33</sup>

- Significant short-term benefits require long-term data, additional patient exposure
  - Help demonstrate durability
  - Increase understanding of ability to retreat in event of recurrence
- Need for clinical study to corroborate MSK results
  - Confirm unprecedented efficacy with dostarlimab
  - Eliminate tumors demonstrated by cCR
  - Collect data to confirm cCR12 predicts for long-term benefit



## **GSK Study 219369**

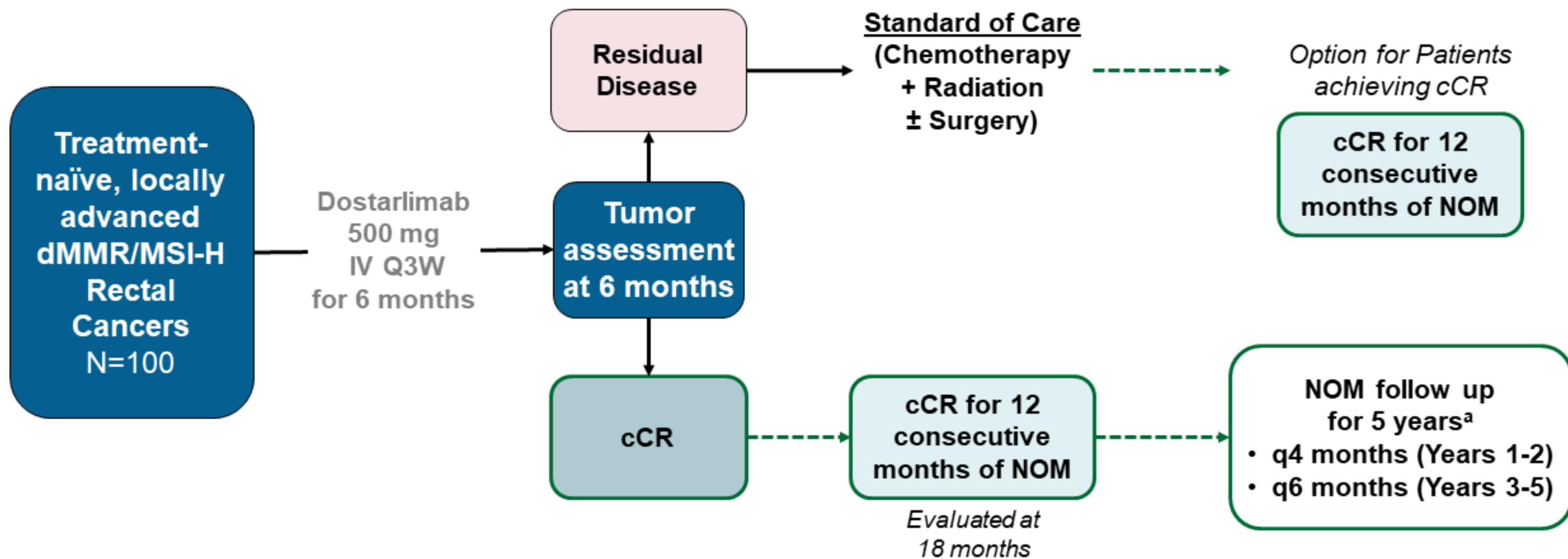
### **Design of Phase 2 Study**

**Ivan Diaz-Padilla, MD, PhD**

Vice President, Oncology Clinical Development  
GSK

# Study 219369 Design Aligned with MSK Study in Global Population to Demonstrate Reproducibility

Study design reflects input from > 30 global key opinion leaders specializing in rectal cancer



a. Tumor assessments (Digital rectal exam, CT CAP, rectal MRI, endoscopy, biopsy [when applicable])

# Appropriateness of Single Arm Study Design

- Imbalance in frequency, nature of toxicity profiles between dostarlimab and standard of care
  - Anticipate high drop-out rate in control arm
- Efficacy of dostarlimab widely reported
  - MSK reports 100% cCR
  - Patients, physicians reluctant to participate in randomized trial
- Only enrolling patients with dMMR/MSI-H LARC
  - Rare tumor with limited numbers of confirmed patients

# Study 219369 Inclusion Criteria Intended to Enroll Representative Patient Population

- Key enrollment criteria will mirror MSK study
  - $\geq 18$  years of age
  - Histologically confirmed rectal cancer
  - Clinical stage II or III (T3–4, N0 or T any, N+)
  - dMMR/MSI-H status
  - Without metastatic or recurrent disease
- Broad global participation
  - > 45 clinical sites, multidisciplinary teams
  - Key centers in the US, Europe and rest of the world

## Study 219369

## Prespecified Primary and Select Secondary Endpoints

	Endpoint	Definition
Primary	<b>cCR12</b> by ICR	Proportion who maintain cCR for 12 months after 6 months of dostarlimab treatment (assessed at 18-month timepoint)
Key Secondary	<b>EFS3</b> by Investigator	Proportion alive and event free at 3 years from first dose of dostarlimab
	<b>cCR36</b> by ICR	Proportion who maintain cCR for 36 months after end of dostarlimab treatment (assessed at 42-month timepoint)
Other Secondary	<b>OS5</b>	Defined as being alive at 5 years from first dose of dostarlimab
	<b>DSS5</b>	Defined as not dying due to disease at 5 years from first dose of dostarlimab

# Design to Evaluate Dostarlimab Monotherapy as a Cure for dMMR/MSI-H Locally Advanced Rectal Cancer

## Need and Opportunity

- Improve cure rates with a better-tolerated therapy, avoids debilitating morbidities

## Study Design

- Design supported by data with thorough planning and preparation
- Global expert support and collaboration with academic institutions, patient advocacy groups, regulators

## Study Objectives

- Additional data in larger patient population
- Confirm efficacy, safety, tolerability of dostarlimab monotherapy for patients with this rare form of rectal cancer



## **GSK Commitment to Accelerated Approval**

**Hesham A. Abdullah, MD, MSc**

Senior Vice President,  
Global Head of Oncology Development  
GSK



## GSK Phase 2 Study and Long-Term MSK Data Designed to Support Accelerated Approval in dMMR/MSI-H LARC

- Primary endpoint reasonably likely to predict for survival benefit
  - Sustained cCR, i.e., cCR12
- Longer-term outcomes from MSK study will be available
- Submission to include data on benefit-risk in  $\geq 130$  patients
- Goal is to provide potentially curative therapy and survivorship without devastating, long-term effects of standard of care

# Confirmatory Phase 3 Trial in Stage II / III dMMR/MSI-H Population Completes Data Conversion Package

- Longer follow up from Memorial Sloan Kettering study
- Follow up for long-term survival from GSK pivotal study
- Data from separate large randomized Phase 3 study
  - Under discussion with FDA
  - Patients with dMMR/MSI-H perioperative colon cancer

# Study in Locally Advanced dMMR/MSI-H Colon Cancer Confirms Phase 2 Locally Advanced dMMR/MSI-H Rectal Cancer Study

## Highly-Similar Diseases

- Colon and rectal cancer have similar symptomatology, biology
- Known responsiveness to systemic therapies, including immunotherapies

## Biomarker-Selected Population

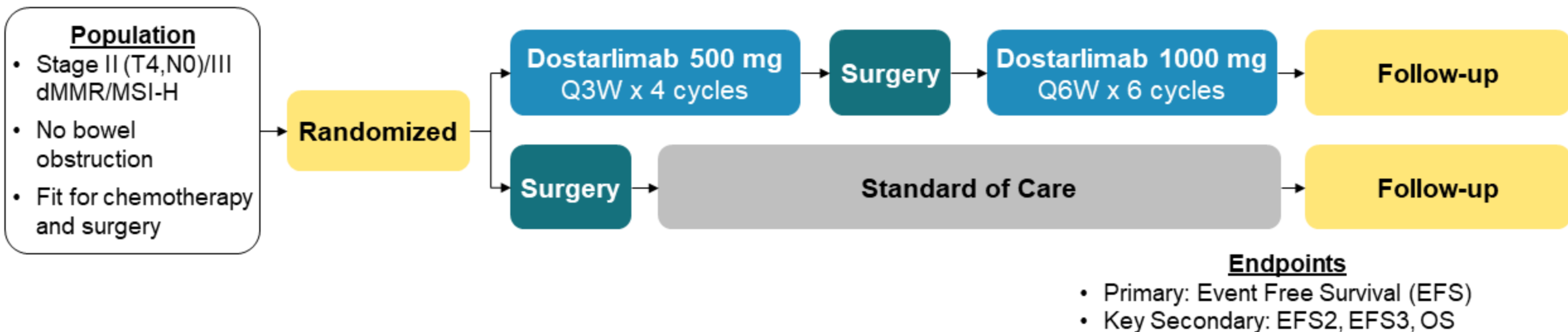
- Enroll homogeneous population with dMMR/MSI-High tumors
- Overlap in disease staging between colon and rectal studies – stage II and III

## Responsiveness to Anti-PD-1

- High immune cell infiltrates, highly responsive to anti PD-1 therapies
- Dostarlimab effective in dMMR tumors, regardless of tissue origin

Randomized study in locally advanced **dMMR/MSI-H colon cancer** is closest setting where benefit in locally advanced **dMMR/MSI-H rectal cancer** can be confirmed in a controlled study

# Preliminary Schematic for Confirmatory, Phase 3 Study in Locally Advanced dMMR/MSI-H Stage II / III Colon Cancer



- Randomized, open label study investigating whether perioperative dostarlimab could replace standard of care
- Incidence of colon cancer supports randomized design
  - Enables formal comparison of dostarlimab monotherapy against standard of care in a dMMR/MSI-H population

## GSK Phase 2 Study Appropriately Evaluates Benefit of Dostarlimab in Locally Advanced dMMR/MSI-H Rectal Cancer

- Study population selected given sensitivity of early stage dMMR rectal cancer to immunotherapy
- Phase 2 design offers non-operative management for patients cCR
  - Undertaken with appropriate and intense monitoring
- Sustained cCR for 12 months is primary endpoint
  - Shown to be predictive of favorable long-term outcomes
- Verification of benefit from longer-term outcomes from MSK and GSK studies, proposed, randomized Phase 3 study in colon cancer



## Conclusion

**Gordana Vlahovic, MD, MHS**

Vice President, Medicines Development Lead  
GSK

# Study 219369 Design Supports Accelerated Approval, Demonstrating Benefit of NOM as New Treatment Paradigm

ODAC Questions	Data to Resolve Question
<i>Appropriateness of single-arm studies to evaluate benefit-risk</i>	<ul style="list-style-type: none"> <li>MSK study: Unprecedented efficacy, ability to avoid treatment-associated morbidities with standard of care widely reported</li> <li>Randomization to SoC would result in dropouts and missing data as patients unwilling to accept life-limiting AEs of SoC in rare population</li> </ul>
<i>Adequacy of cCR12 and EFS3 to characterize benefit</i>	<ul style="list-style-type: none"> <li>cCR is stringent, well-defined and accepted endpoint for LARC</li> <li>Sustaining cCR for 12 months predicts 5-year outcomes including OS</li> <li>MSK results, additional evidence from multiple global studies using cCR and NOM</li> </ul>
<i>Appropriateness of study population</i>	<ul style="list-style-type: none"> <li>dMMR/MSI-H tumors highly susceptible to checkpoint inhibitors</li> <li>Demonstrated anti-PD-1 efficacy in various dMMR/MSI-H tumors</li> </ul>
<i>Impact from inter-site variability on outcomes</i>	<ul style="list-style-type: none"> <li>Protocol standardization and training</li> <li>Consensus evaluation of cCR by multi-disciplinary approach</li> </ul>
<i>Study 219369 with MSK characterizes benefit-risk (N=130)</i>	<ul style="list-style-type: none"> <li>Application will include long-term safety, response and survival data               <ul style="list-style-type: none"> <li>cCR12, cCR36, EFS3, OS results</li> </ul> </li> </ul>