

Oncologic Drugs Advisory Committee Meeting

Introductory Comments

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February 9, 2023

Dostarlimab

- **Product Class:** Programmed death receptor-1 (PD-1)-blocking monoclonal antibody
- **Current approvals (Accelerated Approval):**
 - deficient mismatch repair (dMMR) recurrent or advanced solid tumors
 - dMMR recurrent or advanced endometrial cancer
- **Proposed Indication:**
 - dMMR/microsatellite instability high (dMMR/MSI-H) locally advanced rectal cancer (LARC)
- **Proposed Approval Pathway:** Accelerated Approval

RESEARCH SUMMARY

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Cercek A et al. DOI: 10.1056/NEJMoa2201445

CLINICAL PROBLEM

Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.

RESULTS

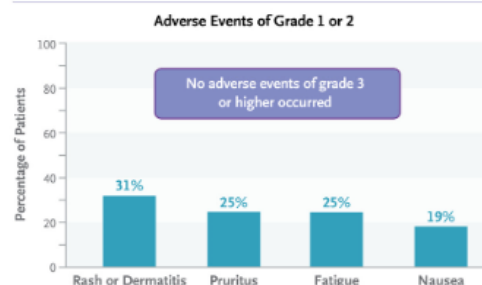
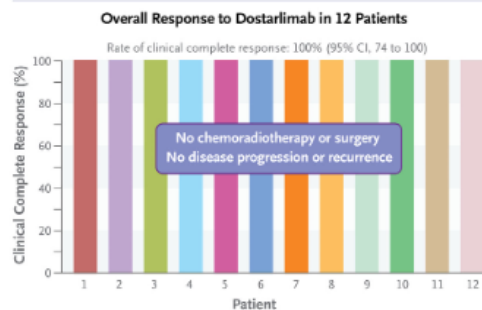
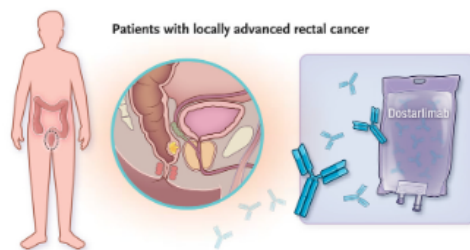
Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

Safety: No adverse events of grade 3 or higher have occurred. The most common adverse events of grade 1 or 2 included rash or dermatitis, pruritus, fatigue, and nausea.

LIMITATIONS AND REMAINING QUESTIONS

- The study was small and limited to a single institution, and most of the patients were White.
- Longer-term follow-up is needed to evaluate the duration of response.

Links: [Full Article](#) | [NEJM Quick Take](#) | [Editorial](#)



CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.

Design: Single-arm trial

Patients: Stage II/III dMMR/MSI-H rectal cancer

Treatment: Neoadjuvant dostarlimab 500 mg IV mg every 3 weeks for 6 months

Assessment: MRI, PET-CT, endoscopy

Results:

- 12/30 patients completed treatment
- **100% clinical complete response (cCR)**
- No adverse events of Grade ≥ 3 reported

Outline

- Meeting Purpose
- Rectal Cancer Overview
- Proposed Dostarlimab Clinical Development Program
- Discussion Topics

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Meeting Purpose

- Discuss and provide input on adequacy of proposed strategy to demonstrate the safety and effectiveness of dostarlimab as treatment for dMMR/MSI-H LARC
 - Single arm trials in the curative-intent setting
 - Clinical endpoints to characterize benefits and risks of treatment
 - Measures to obtain data to support safe & effective use of dostarlimab, if approved
 - heterogeneity of LARC population
 - heterogeneity in expertise to implement surgery-sparing treatment

Outline

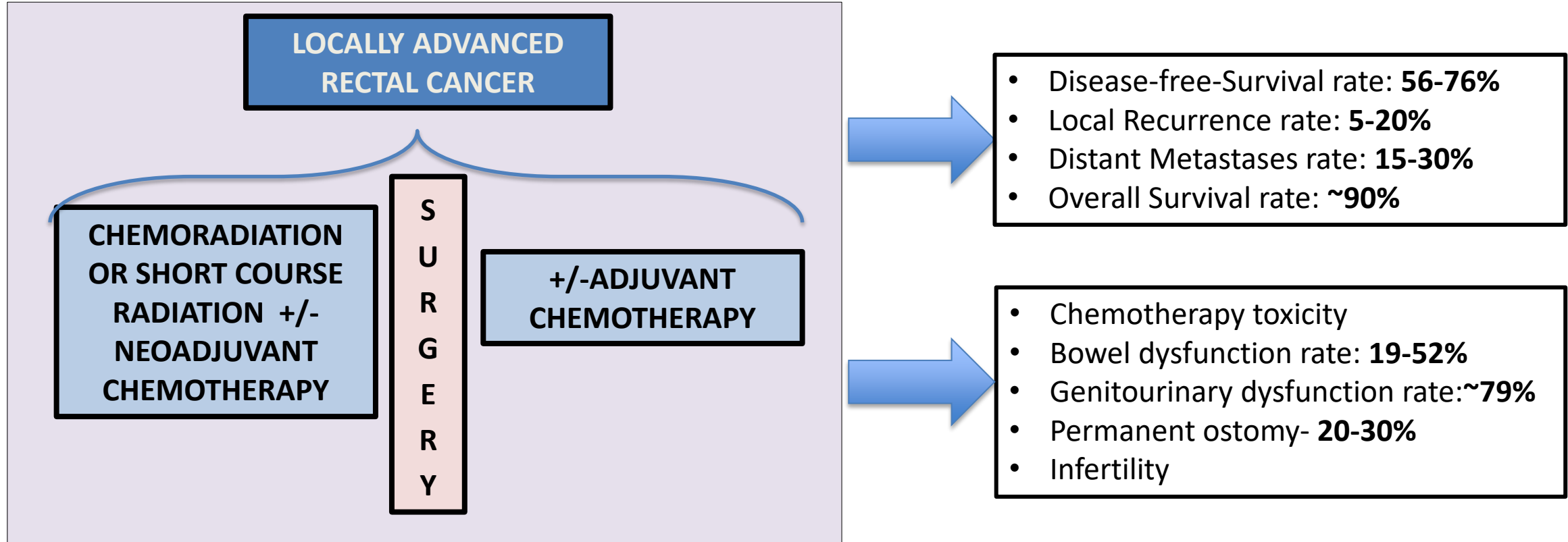
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Rectal Cancer

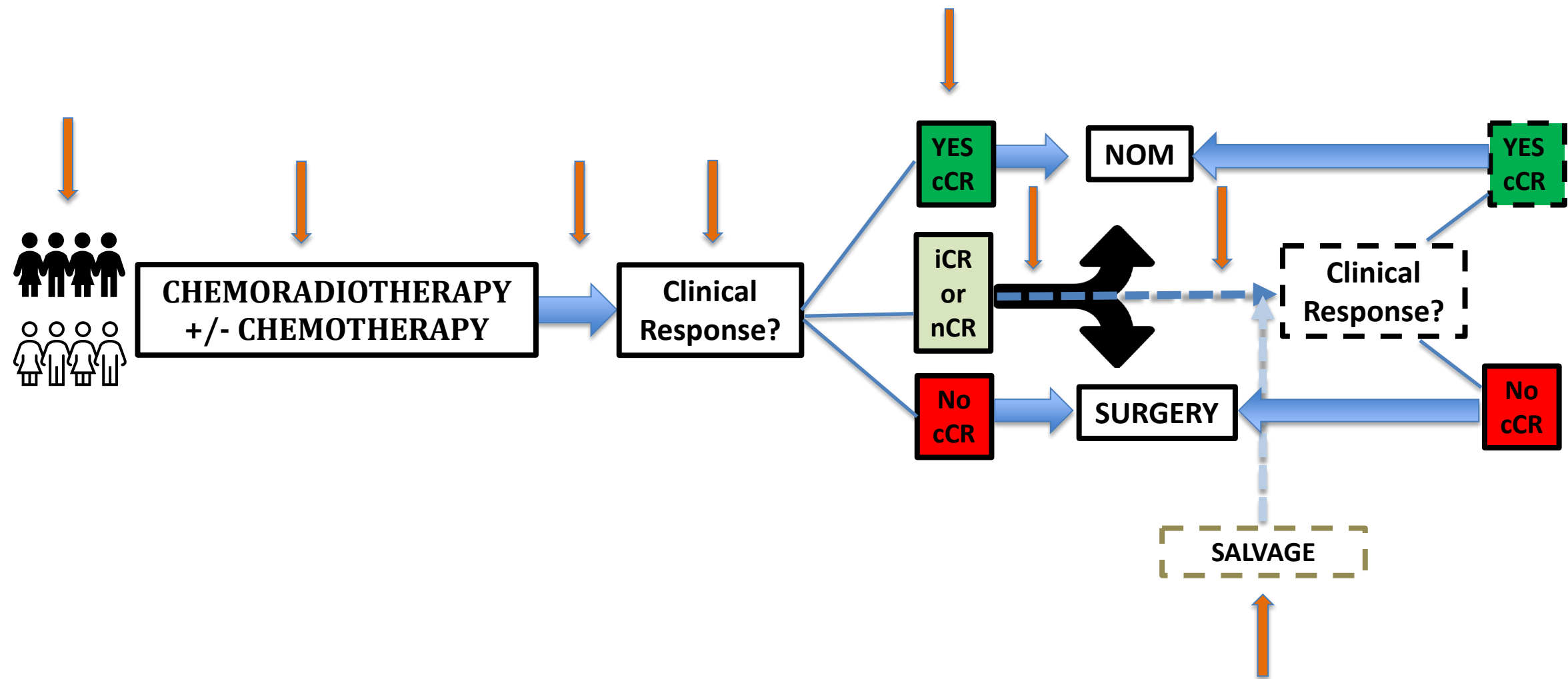


- Incidence: 46,050 cases/year (U.S)
- dMMR/MSI-H **colorectal cancer (CRC)** incidence 12-20%
- dMMR/MSI-H **rectal cancer** incidence unknown – range 2.7-21%
- Treatments for rectal cancer
 - **Stage I:** Surgery
 - **Stage II-III:** Multi-modality therapy
 - **Stage IV:** Chemotherapy, targeted therapy

Treatment & Outcomes- Historical Experience



Non-Operative Management- Historical Experience



cCR- clinical complete response; iCR- incomplete response; nCR- near complete response; NOM – non-operative management

Outcomes from Non-Operative Management



IWWD Study- 880 Patients (cCR)	MSKCC Study- 113 Patients (cCR)	OPRA Trial 224 patients (cCR)
Local Regrowth rate- 25% Overall Survival at 5y- 85%	Local Regrowth rate- 20% Organ preservation rate- 81% Overall Survival rate at 5y- 73%	cCR rate- 74 vs 76% Regrowth rate - 28%/40% Organ preservation rate 3y- 53%/41% Overall Survival at 3y- >90%/>90%

Summary- NOM in LARC

- **NOM Studies heterogenous**
 - Uncertainty regarding:
 - Patient selection
 - Chemotherapy & Radiation protocols
 - Clinical response definition & assessment methods
 - Follow-up protocols-
 - Variable long-term outcomes studied
 - Challenges in interpreting outcomes
- **Benchmarks for NOM not established**
 - Unclear relationship of cCR to long-term outcomes of benefit
 - Unclear significance of cCR in setting of chemoradiation vs. radiation-free treatment

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Evidentiary Standard for Approval

- **Evidentiary Approval Standard**
 - Safety and Effectiveness demonstrated in adequate and well-controlled trials
- **Approval Pathways**
 - Accelerated Approval (AA)
 - Improvement over available therapy
 - Effect on surrogate endpoint or intermediate clinical endpoint reasonably likely to predict clinical benefit
 - Traditional Approval
 - Demonstrate effects on symptom, function, survival

Oncology Approvals in Non-Metastatic Setting



- **FDA approvals in early (non-metastatic) curative-intent setting**
 - Randomized controlled trials
 - Based on established endpoints of clinical benefit (e.g., disease-free survival [DFS], event-free survival [EFS], overall survival [OS])
 - Traditional approval granted
 - **Exception:** BCG- unresponsive non-muscle invasive bladder cancer
- **For planned AA submissions in curative-intent setting**
 - Relationship between ‘novel endpoint’ and endpoints denoting clinical benefit should be characterized

Approvals in Non-Muscle Invasive Bladder Cancer

- **Basis for Approval**
 - Complete response rate in single arm trials
 - Inadequate therapy to serve as comparators for randomized trials
 - Delay of standard of care (SOC) considered benefit due to high morbidity (and mortality) associated with cystectomy
- **Preceding Approvals**
 - Stakeholder discussion & agreement on endpoint, trial design, treatment assessment & follow-up
 - Public workshop & Publication
 - FDA guidance issued

Proposed Dostarlimab Clinical Studies

Design	N	1° endpoints	2° endpoints
Study 19288 (Study 1): <ul style="list-style-type: none"> Single-institution, single-arm 	30	<ul style="list-style-type: none"> ORR cCR12 (AA) 	
Study 219369 (Study 2): <ul style="list-style-type: none"> Multicenter, single-arm 	100	<ul style="list-style-type: none"> cCR12 (AA) 	<ul style="list-style-type: none"> cCR36 EFS-3y
		EFS, ORR, TME-3 years, disease-specific survival (DSS), DSS-5years, OS, OS-5 years	
Study 219606 (Study 3): <ul style="list-style-type: none"> Randomized study of perioperative dostarlimab vs. adjuvant chemotherapy dMMR/MSI-H locally advanced colon cancer 	711	<ul style="list-style-type: none"> EFS 	<ul style="list-style-type: none"> EFS-2y EFS-3y pCR OS

ORR- overall response rate; TME – total mesorectal excision; pCR – pathological complete response

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Topic 1

Adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment.

- Use of single arm trial in the curative-intent setting
- Evaluating long-term outcomes- no comparator arm
- NOM outcomes in LARC include radiation

Topic 2

Adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab.

- Historical data on cCR rate as endpoint for LARC
- Magnitude/durability of cCR rate reasonably likely to predict clinical benefit
- EFS evaluation in a single-arm trial for LARC

Topic 3

Study population with Stage II/III dMMR/MSI-H rectal cancer for a NOM approach.

- LARC comprises heterogenous population
- Trial design considerations to characterize benefits & risks across population

Topic 4

Potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

- Patient selection and management may vary across treatment settings; impact on clinical outcomes

VOTE

Will the data from the proposed single arm trials enrolling a total of 130 patients, be sufficient to characterize the benefits and risks of dostarlimab in the curative-intent setting for patients with dMMR/MSI-H LARC?



Dostarlimab Development in dMMR/MSI-H Locally Advanced Rectal Cancer

Oncologic Drugs Advisory Committee Meeting
February 9, 2023

Sandra J. Casak, MD
Division of Oncology 3 / Office of Oncologic Diseases



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Outline

- Background
- Dostarlimab development in dMMR/MSI-H LARC
- Topics for discussion



Outline

- Background
- Dostarlimab development in deficient mismatched repair dMMR/MSI-H LARC
- Topics for discussion

Background: Rectal Cancer

- US 2023 ~ 46,050 new cases/year
- dMMR/MSI-H **colorectal cancer (CRC)** incidence 12-20%
 - More common in right-sided CRC tumors
 - Incidence:
 - Stage 1-2: 10-32%
 - Stage 3-4: 5-16%
- dMMR/MSI-H **rectal cancer** incidence unknown – range 2.7-21%

American Cancer Society Colorectal Cancer Statistics, 2023; Bonneville R. JCO Precision Oncology 2017; Cercek A, Clin Cancer Res 2020; Papke D, NEJM 2022; Swets M, Histopathology 2022

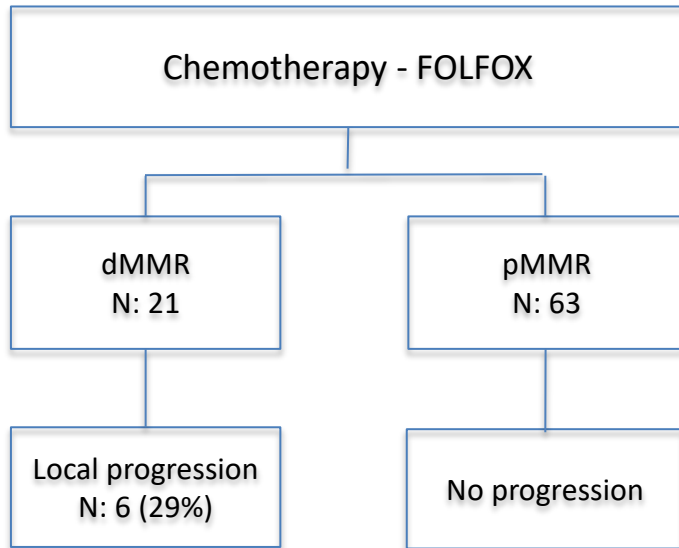
Locally Advanced Rectal Cancer- Standard of Care Treatment



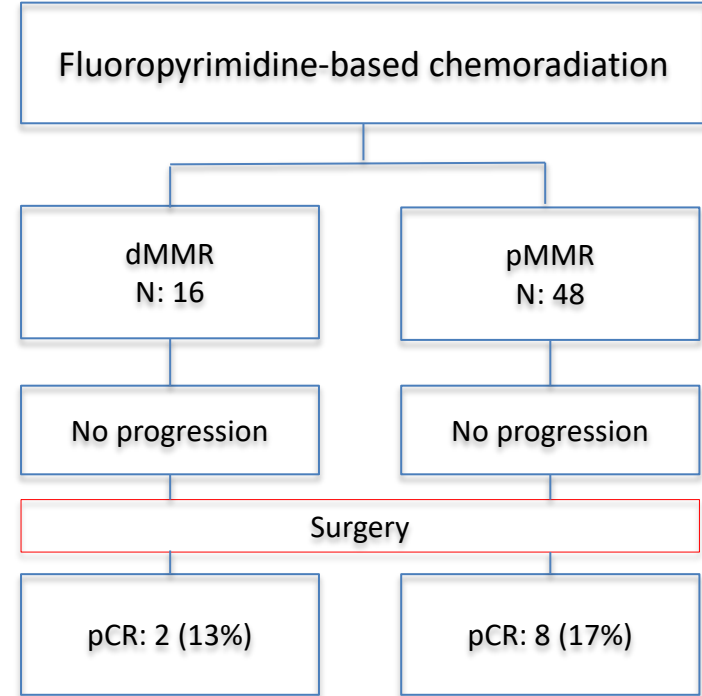
- **Treatment:**
 - Multimodality treatment (fluoropyrimidine-based chemotherapy, radiotherapy, and surgery)
 - Curative intent
- **Clinical Outcomes:**
 - 5% - 20% local recurrence
 - 15% - 30% distant metastases
 - DFS-3y 56% (POLISH II) to 76% (PRODIGE-23)
 - OS-3y ~ 90% (PRODIGE-23 and RAPIDO)

Standard of Care – Predictive Role of dMMR/MSI-H in Locally Advanced Rectal Cancer

- Retrospective review database 2003-2018
- Comparison with matched controls based on MMR status



FOLFOX: fluorouracil, leucovorin, oxaliplatin; pMMR: proficient mismatch repair; pCR: pathologic complete response



Standard of Care – Predictive Role of dMMR/MSI-H in Locally Advanced Rectal Cancer



MD Anderson Cancer Center (MDACC) retrospective series

- dMMR Stage 2/3 – 30 patients treated with neoadjuvant fluoropyrimidine-based chemotherapy and radiation
- 29 patients underwent surgery
- 8 (27.6%) pCR
- 1 cCR – declined surgery

de Rosa N, J Clin Oncol 2016

Clinical Outcomes Following Standard of Care

- Bowel dysfunction – low anterior resection syndrome 19-52%
- Genitourinary and sexual dysfunction ~79%
- Permanent ostomy ~20-30%
- Infertility

Croese A, Intl J Surg 2018; Saito S, EJSO, 2016; Pietrangeli A, J Exp Clin Cancer Research, 2009; Lange M, BJS 2008; Back E, BJS 2021; Lemini R BMC Surgery 2021;

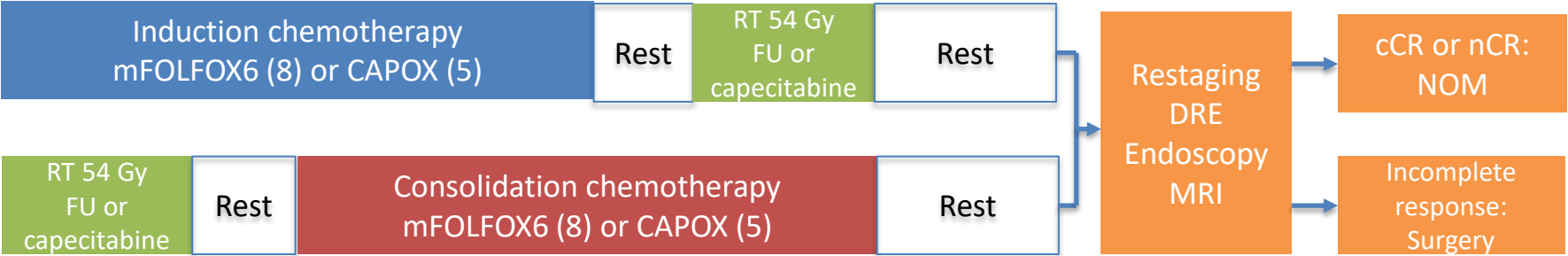
Non-Operative Management

- Heterogeneity across studies limit the interpretation of data - differences in:
 - study population (tumor location, stage, etc.)
 - outcomes studied
 - chemoradiation and chemotherapy regimens
 - schedules of assessments, imaging protocols, follow-up protocols
- Limited evidence from randomized controlled studies
 - unclear relationship between cCR and long-term outcomes

Non-Operative Management- Outcomes

- cCR 10-78%
- International Watch and Wait Database – 880 patients with cCR
 - Local regrowth 25% (88% in the first 2 years)
 - OS-5y 85%
- MSKCC – 113 patients with cCR
 - 20% (n: 22 patients) local regrowth
 - 81% (93 patients) rectum preservation
 - 18% (20 patients) total mesorectal excision [TME] for management of relapse
 - OS-5y 73%

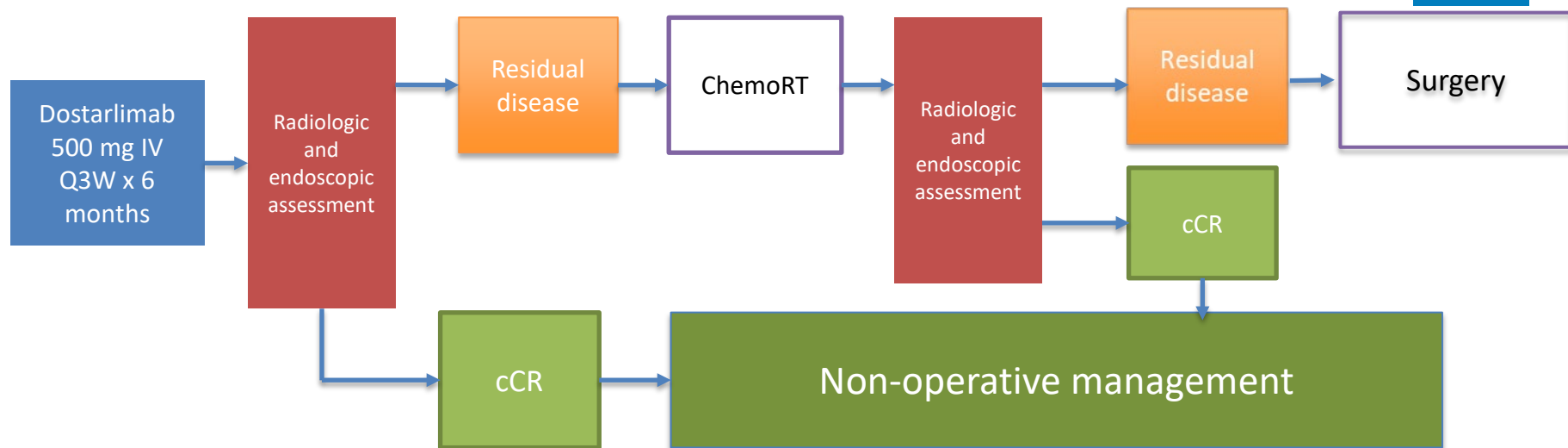
Non-Operative Management– OPRA Trial



Tumor Regrowth		
NOM (n: 225)		Surgery (n: 79)
Induction (n: 105)	Consolidation (n: 120)	6%
40%	27%	

Garcia Aguilar J, J Clin Oncol 2022

MSKCC Study 19-288 (NCT04165772)



- 14 patients with dMMR Stage 2 and 3 LARC
- 100% cCR after dostarlimab treatment
- 4 patients sustained response at Month 12

Treatment of LARC: Summary

- Standard of care:
 - Multimodality (chemotherapy, radiotherapy, and surgery)
 - Treatment is with curative intent.
- Outcomes: Dependent on population, treatment strategy, endpoint definition
- Treatment-related morbidity and sequelae

Non-Operative Management: Summary

- Evidence for NOM
 - retrospective studies of chemotherapy + radiotherapy in highly specialized centers
 - no standardized approach for patient selection, treatment strategy, cCR definition and assessment, other outcomes, monitoring protocols, etc.
- Major risk – non-salvageable local regrowth or metastases
- Uncertain long-term outcomes



Outline

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- Dostarlimab development in dMMR/MSI-H LARC
- Topics for discussion

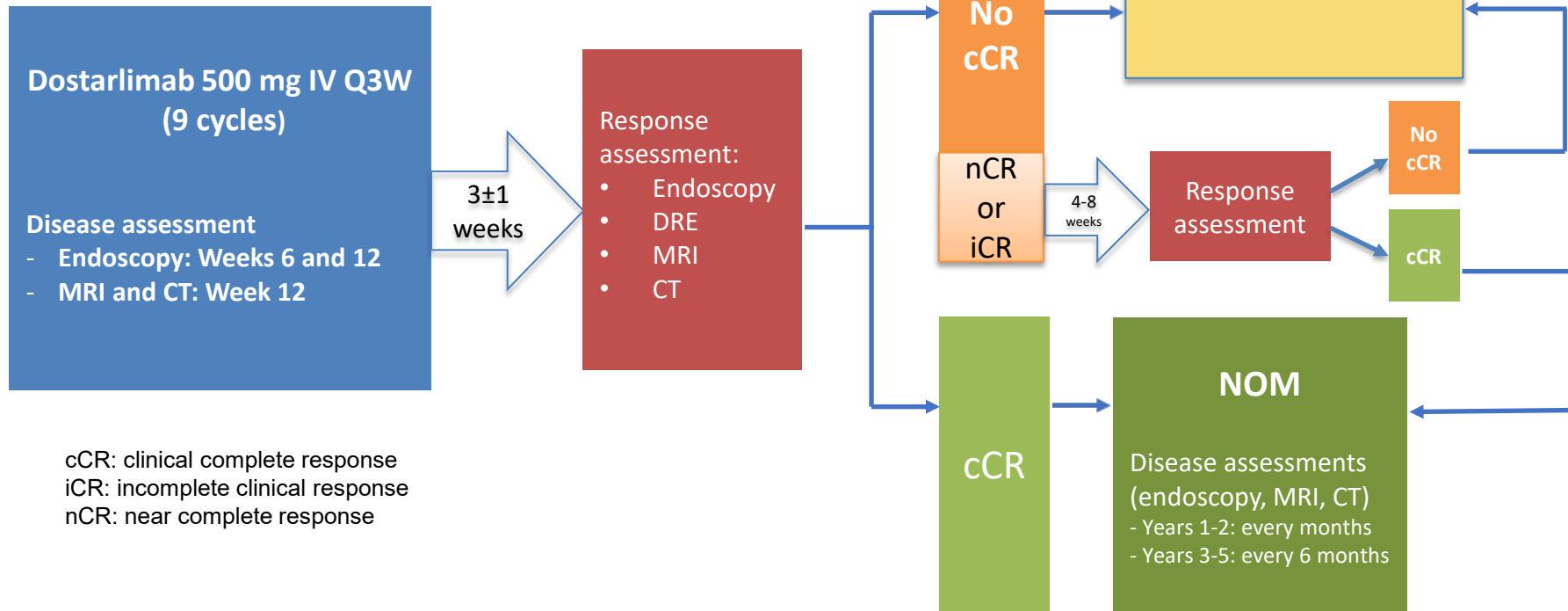
Dostarlimab for the treatment of patients with locally advanced, treatment-naïve mismatch-repair deficient (dMMR) or microsatellite-instability-high (MSI-H) rectal cancer

Proposed Data Package for a Future BLA Submission

Design/population	N pts	Primary endpoints	Secondary endpoints
Study 19288 (Study 1): <ul style="list-style-type: none"> Single-institution, single-arm 	30	ORR and cCR12	
Study 219369 (Study 2): <ul style="list-style-type: none"> Multicenter, single-arm 	100	cCR12	<ul style="list-style-type: none"> cCR36 EFS-3y
		Additional endpoints: EFS, ORR, TME-3 years, disease-specific survival (DSS), DSS-5years, OS, OS-5 years	
Study 219606 (Study 3): <ul style="list-style-type: none"> Randomized study in dMMR/MSI-H locally advanced colon cancer perioperative dostarlimab vs. adjuvant chemotherapy 	711	EFS	<ul style="list-style-type: none"> EFS-2y EFS-3y pCR OS

LARC: locally advanced rectal cancer; ORR: overall response rate; cCR12: complete response at Month 12; EFS: event-free survival; TME: total mesorectal excision; DSS: disease-specific survival; OS: overall survival; pCR: pathological complete response

Study 219369 (Study 2)



Study 2: Endpoints

- **Primary endpoint:** cCR12
 - no evidence of residual disease by endoscopy or rectal-specific MRI
 - no evidence of metastatic disease
 - as assessed by Independent Central Review (ICR) 12 months after nine cycles of dostarlimab
- **Key secondary endpoints**
 - cCR36 (maintenance of cCR for 36 months) by ICR
 - EFS-3y (alive and free of disease progression precluding surgery, local recurrence, and distant recurrence) by Investigator (INV).
 - OS-5y



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- Background
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- Topics for discussion

Topics for discussion

- Adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment
- Adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses.
- Study population with Stage II/III LARC dMMR/MSI-H for a NOM approach
- Potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

Topics for Discussion

- Adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment
- Adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses of these.
- Study population with Stage II/III LARC dMMR/MSI-H for a NOM approach
- Potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

Topic #1

Discuss the adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment

- Inadequate assessment of time-to-event endpoints and symptoms or function
- Absence of data to define benchmark for success
- Feasibility of a randomized controlled trial

Topic #1

Discuss the adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment

- Use of single arm trial in the curative-intent setting
- Evaluating long-term outcomes w/o comparator arm

Topics for Discussion

- Adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment
- Adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses of these.
- Study population with Stage II/III LARC dMMR/MSI-H for a NOM approach
- Potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

Topic #2

Discuss the adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses

- Uncertain relationship between response and long-term outcomes
- EFS assessment without concurrent control
- NOM is supported mostly by non-randomized, retrospective trials, with marked heterogeneity

Topic #2

Discuss the adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses

- Historical data on cCR rate as endpoint for LARC therapies
- Magnitude/durability of cCR reasonably likely to predict clinical benefit
- Interpretability of EFS as an endpoint of clinical benefit in a single-arm trial

Topics for Discussion

- Adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment
- Adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses of these.
- Study population with Stage II/III LARC dMMR/MSI-H for a NOM approach
- Potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

Topic #3

Discuss the study population with Stage II/III LARC dMMR/MSI-H for a NOM approach

- Positive lymph nodes, large tumors, Lynch syndrome, etc. may confer a higher risk of recurrence
- Differences in institutional practices for selection of patients for NOM

Topic #3

Discuss the study population with Stage II/III LARC dMMR/MSI-H for a NOM approach

- LARC comprises a heterogeneous population
- Trial design considerations to characterize benefits and risks across population

Topics for Discussion

- Adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment
- Adequacy of the proposed clinical endpoints (i.e., cCR rate, EFS), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses of these.
- Study population with Stage II/III LARC dMMR/MSI-H for a NOM approach
- Potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

Topic #4

Discuss the potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

- High volume centers with surgical expertise and specialization in LARC
 - higher rates of sphincter preservation, decreased rates of postoperative morbidity and mortality, lower rates of local recurrence, and improved survival
- Multidisciplinary teams recommended
- Early recognition of recurrences may increase successful long-term outcomes

Topics #4

Discuss the potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes

- Discuss the potential impact of the variability in care and expertise across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes and generalizability of study results.

Presentation summary

- GSK plans to develop dostarlimab as a single agent for the *treatment of patients with locally advanced, treatment-naïve mismatch-repair deficient (dMMR) or microsatellite-instability-high (MSI-H) rectal cancer.*
- Uncertainties surrounding NOM
- Uncertainties on data package including single-arm data to adequately characterize a risk:benefit assessment.

Voting Question

Will the data from the proposed single arm trials enrolling a total of 130 patients be sufficient to characterize the benefits and risks of dostarlimab in the curative intent setting for patients with dMMR/MSI-H LARC?



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