



IMS una oportunidad en cáncer colorrectal

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Disclosures

- Consultant/advisory/speaker: ROCHE, AMGEN, Sanofi, MERCK, MSD, SERVIER, BAYER, EISAI, Novartis, Astra-Zeneca, Lilly, Organon



- **Introducing MSI**



DNA Mismatch Repair System

- DNA Mismatch repair is a **highly conserved mechanism** involved in **restoring DNA integrity** after the occurrence of mismatching errors during DNA replication, recombination or iatrogenic damage
- **Four genes** regulate the MMR mechanism: mutL homologue 1 (**MLH1**), mutS homologue 2 (**MSH2**), mutS homologue 6 (**MSH6**) and postmeiotic segregation increased 2 (**PMS2**)
- The four proteins codified by these genes form **heterodimers**:
 - **MLH1/PMS2**
 - **MSH2/MSH6**

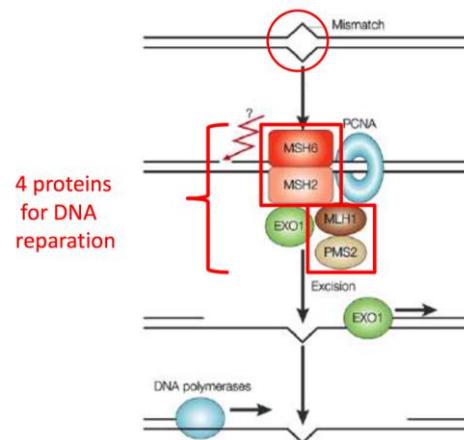




TABLE 3. Two Types of CRC

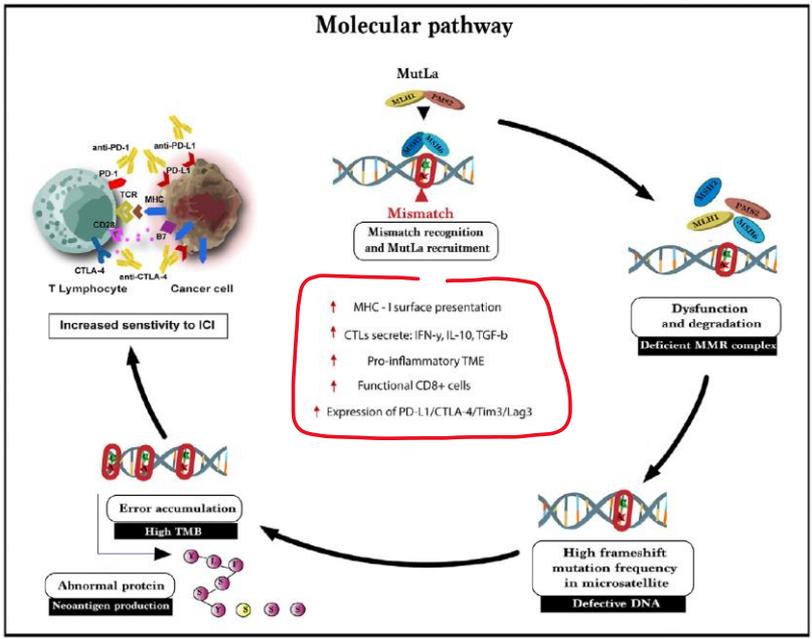
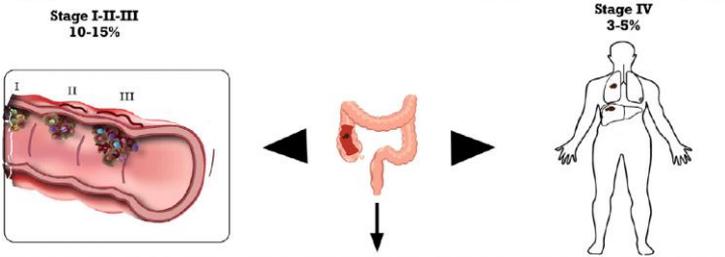
Genomic Parameter	Chromosomal Instability	Genetic Instability (MSI)
DNA ploidy	Aneuploid	Diploid
18q, 17p, 5q, 8p, 22q	Loss of genetic material, loss of heterozygosity	No loss of genetic material
Frequency: localized/mCRC	85% nonmetastatic and 95% metastatic	15% nonmetastatic and 5% metastatic
MMR system	Proficient MMR/MSS	Deficient MMR (hMSH2, hMLH1, hMSH6, hMSH3 alterations)/MSI
Frequent mutations	<i>RAS</i> mutation	<i>BRAF</i> ^{V600E} or <i>RAS</i> mutation
Origin	Sporadic or familial adenomatous polyposis	Sporadic or Lynch syndrome
Location	More frequent in left-side colon and rectum	More frequent in right-sided colon cancer
Tumor burden	Tumor mutation burden low	Tumor mutation burden high
Neoantigens	Few neoantigens	Many neoantigens
ICI efficacy	No apparent efficacy of ICIs	Efficacy of ICI

Abbreviations: CRC, colorectal cancer; MSI, microsatellite instability; mCRC, metastatic colorectal cancer; MMR, mismatch repair; MSS, microsatellite stability; ICI, immune checkpoint inhibitor.



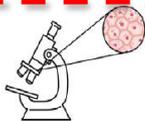
MSI colon cancer

MSI





Diagnostic Methods



Immunohistochemistry

MLH1, PMS2, MSH2, MSH6

- | | | | |
|---|--|--|--|
| S
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S | <ul style="list-style-type: none"> - Cost-effective - Widely accessible in practice - High sensibility - Low amount of tissue needed - Morphological evaluation - Identification of responsible gene | <ul style="list-style-type: none"> - Antibodies variability - False negative (missense mutations with catalytically inactive but antigenically intact mutant proteins) - Non-standardized method - Pre-analytical issues | W
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S |
|---|--|--|--|



qPCR-based MSI analysis

Panel Pentaplex
- BAT25, BAT26, BAT40, NR21, NR22, NR24 et NR27

Panel Bethesda
- BAT25, BAT26
- D5S346, D2S123, D17S250

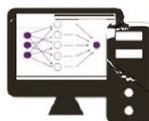
- | | | | |
|---|---|--|--|
| S
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S | <ul style="list-style-type: none"> - Consequence of inactivation - Guidelines with high consensus - Robust and highly reproducible - Combined molecular biology analyses possible | <ul style="list-style-type: none"> - Molecular biology platform (except Idylla) - Less cheap - No morphological control - At least 20% tumor cells - False negatives (biopsy, mucinous tumor) | W
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Routinely employed



NGS- based method

- | | | | |
|---|---|--|--|
| S
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S | <ul style="list-style-type: none"> - Multi markers evaluable - Wide choice of panels - Low amount of tissue needed - TMB estimation - Discrimination sporadic vs Lynch | <ul style="list-style-type: none"> - Expensive - Not routinely available - Long tumouround time - Not specific guidelines - Tumor cell content may affect the results - To be compared to reference techniques | W
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Artificial Intelligence

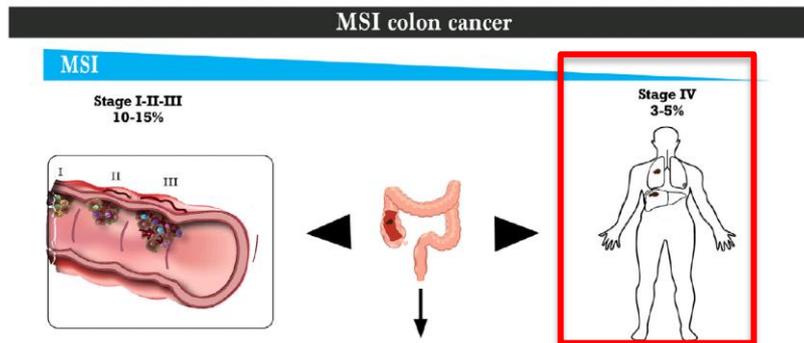
- | | | | |
|---|---|---|--|
| S
T
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H
S | <ul style="list-style-type: none"> - Multi markers evaluable - Cost-effective - Reduced resource-utilization - Efficient pre-screening tool | <ul style="list-style-type: none"> - Not routinely available - Not specific guidelines - To be compared to reference techniques - No discrimination sporadic vs Lynch | W
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ctDNA- based method

- | | | | |
|---|--|---|--|
| S
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S | <ul style="list-style-type: none"> - Feasible in case of scarce tissue material - Minimally invasive - Easily repeatable to monitor disease evolution and treatment response - Capable to detect tumor heterogeneity | <ul style="list-style-type: none"> - Not routinely available - Not specific guidelines - To be validated in prospective trials - To be compared to reference techniques | W
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|---|--|---|--|

Future application



- **Scientific evidence: Main clinical trials**

KEYNOTE 016: Phase II study for MSI-H/dMMR cancer

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Lubner, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zahner, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhajani, T. Husbner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

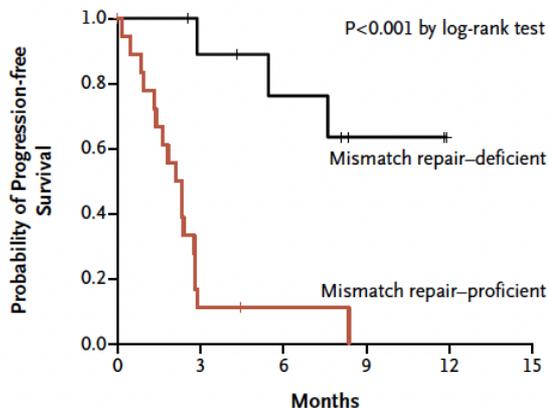
N ENGL J MED 372:26 NEJM.ORG JUNE 25, 2015

Table 2. Objective Responses According to RECIST Criteria.

Type of Response

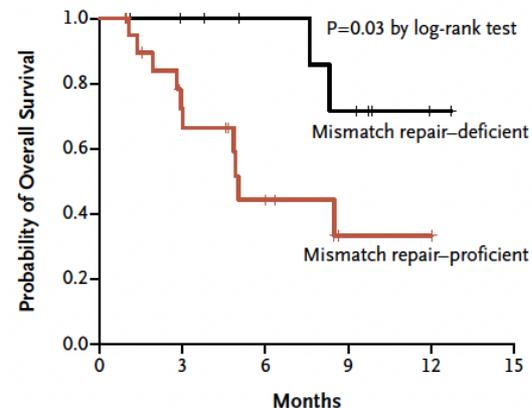
- Complete response — no. (%)
- Partial response — no. (%)
- Stable disease at week 12 — no. (%)
- Progressive disease — no. (%)
- Could not be evaluated — no. (%)‡
- Objective response rate (95% CI) — %
- Disease control rate (95% CI) — %§
- Median duration of response — wk
- Median time to response (range) — wk

A Progression-free Survival in Cohorts with Colorectal Cancer



No. at Risk	0	3	6	9	12	15
Mismatch repair-deficient	11	8	6	2	0	0
Mismatch repair-proficient	21	2	1	0	0	0

B Overall Survival in Cohorts with Colorectal Cancer



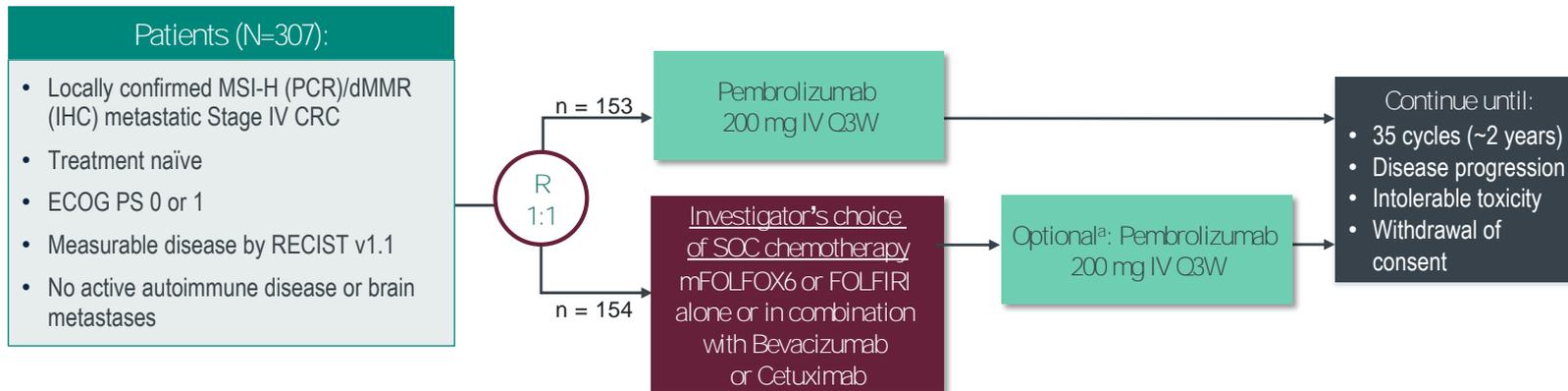
No. at Risk	0	3	6	9	12	15
Mismatch repair-deficient	11	9	7	5	1	0
Mismatch repair-proficient	21	12	5	1	1	0

KEYNOTE 177: Phase III study in 1st line MSI-H/dMMR CRC



Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Plant, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Diaz, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Fares, P. Mainello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*



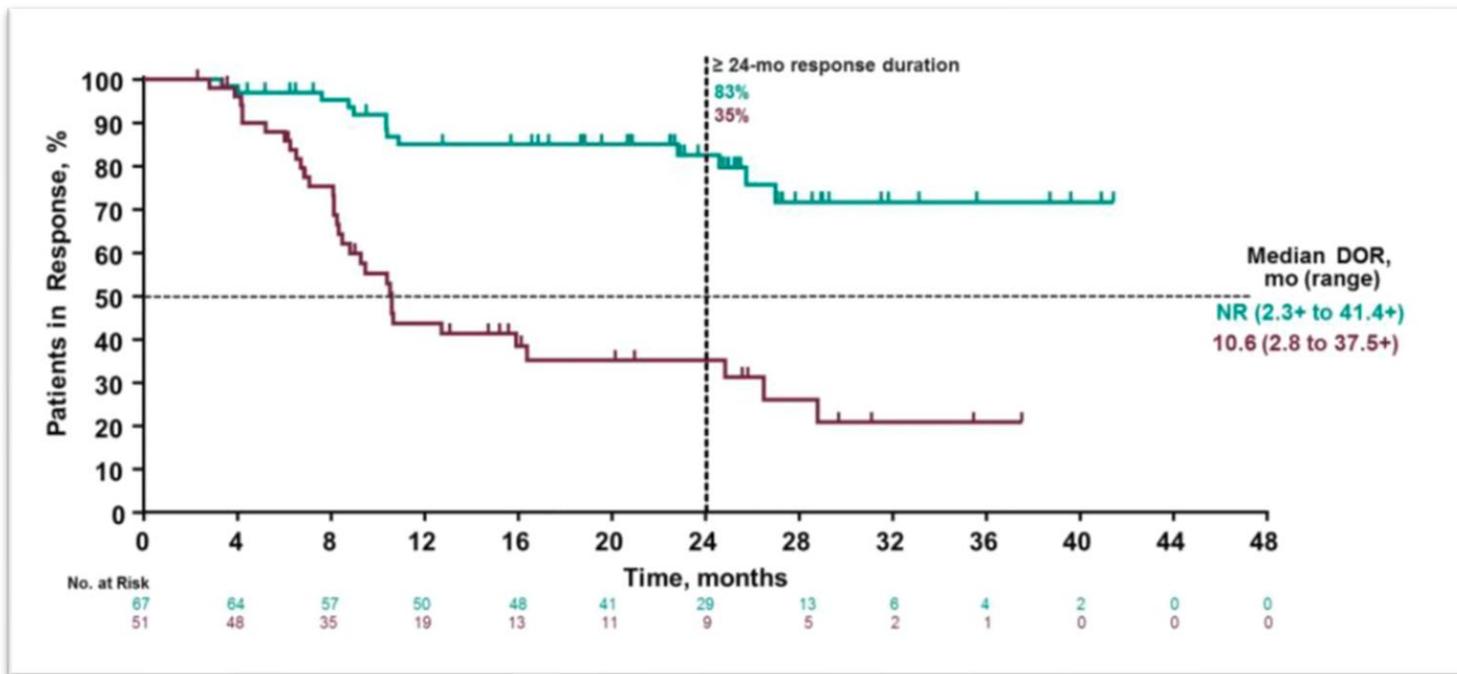
Primary Endpoints
<ul style="list-style-type: none"> PFS per RECIST v1.1 by BICR OS

Secondary Endpoints
<ul style="list-style-type: none"> ORR per RECIST v1.1 by BICR PFS2 HRQOL Safety

*Crossover to Pembrolizumab for patients with centrally verified PD by RECIST v1.1, central review



KEYNOTE 177: PFS





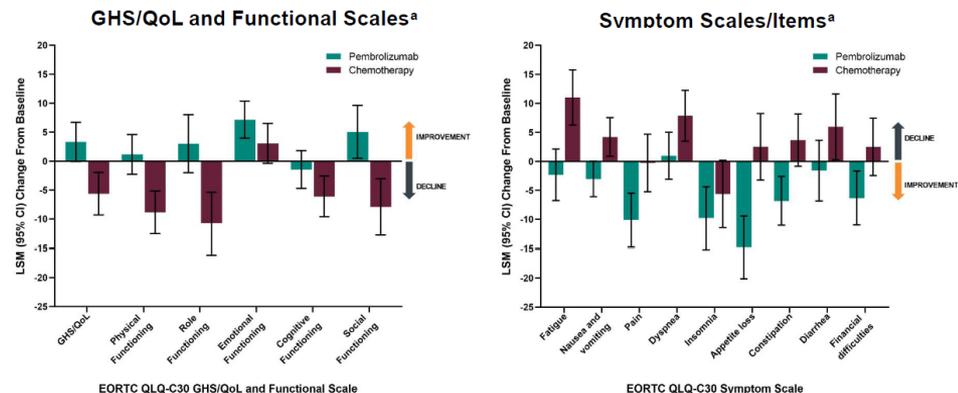
KEYNOTE-177: Update PFS and Overall Survival

Data cutoff: February 19, 2021

	Pembrolizumab N = 153	Chemotherapy N = 154
Progression-free survival^a		
Number of events, n (%)	86 (56.2)	117 (76.0)
Median, mo (95% CI)	16.5 (5.4-38.1)	8.2 (6.1-10.2)
12-mo PFS rate, %	55.3	38.0
36-mo PFS rate, %	42.3	11.1
Overall response rate, n (%) [95% CI]^a	69 (45.1) [37.1-53.3]	51 (33.1) [25.8-41.1]
Best overall response, n (%)^a		
Complete response	20 (13.1)	6 (3.9)
Partial response	49 (32.0)	45 (29.2)
Stable disease	30 (19.6)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable/No assessment ^b	9 (5.8)	19 (12.3)
Duration of response, median (IQR), mo	Not reached (36.1-NR)	10.6 (8.1-28.8)
Response duration ≥36 months, %	76%	24%
Median duration of response (range), months²	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
Response duration of ≥24 months, %	83.5%	33.6%

Change in Score From Baseline to Prespecified Week 18

EORTC QLQ-C30 GHS/QoL, Functional, and Symptom Scales/Items

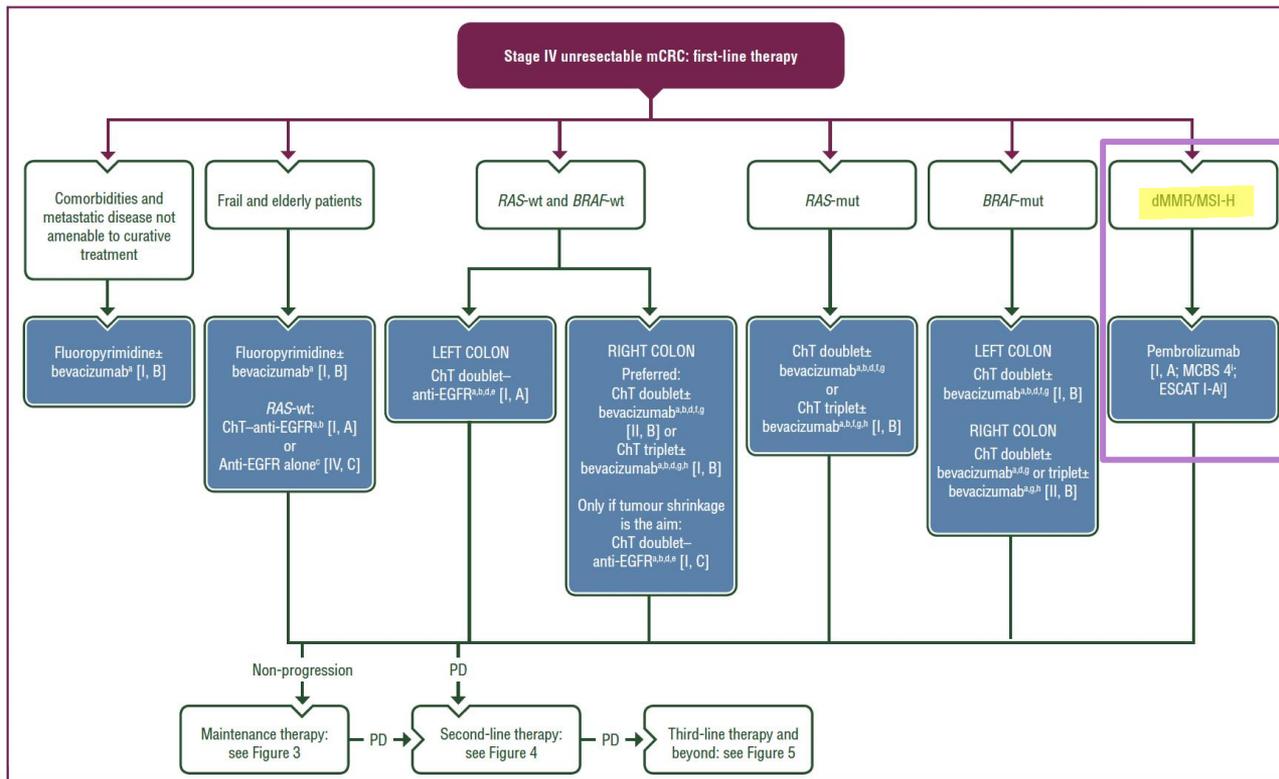


1. Andre et al. Presented at ASCO 2021. 2. Shiu et al. Presented at ASCO-GI 2021. 3. Andre et al. *N Engl J Med* 2020;383:2207-18. 4. Diaz et al. *Lancet Oncol*. 2022; 23(5):659-670



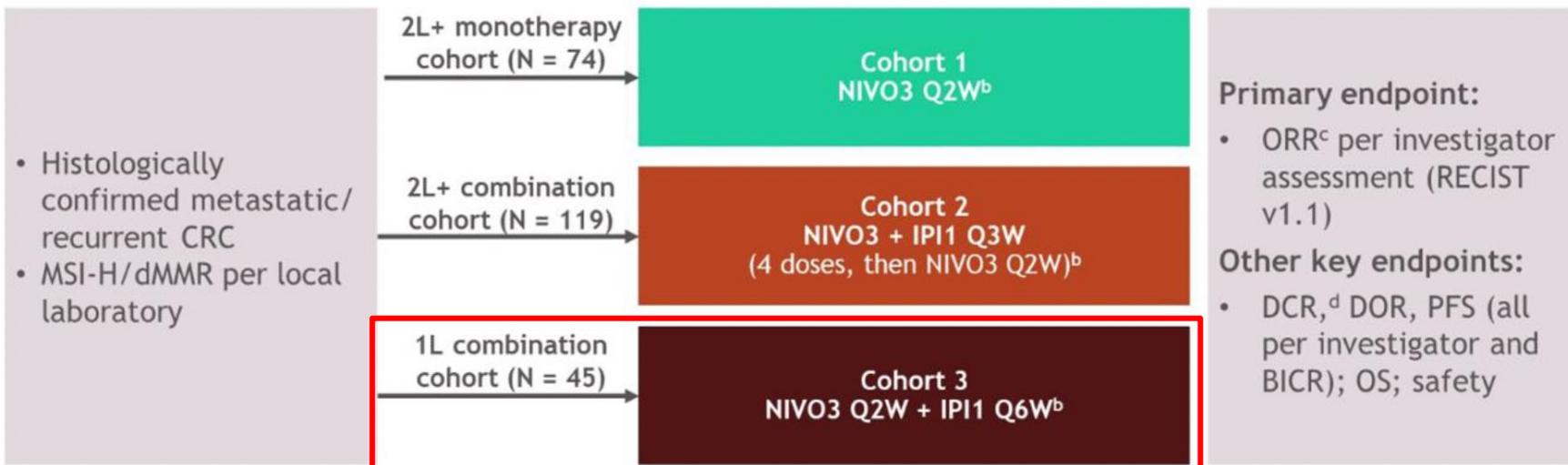
Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]

A. Cervantes^{1,2}, R. Adam³, S. Roselló^{1,2}, D. Arnold⁴, N. Normanno⁵, J. Taieb^{6,7}, J. Seligmann⁸, T. De Baere^{9,10,11}, P. Osterlund^{12,13}, T. Yoshino¹⁴ & E. Martinelli¹⁵, on behalf of the ESMO Guidelines Committee^{*}





CheckMate 142: non-randomized, phase II trial evaluating efficacy and safety of nivo-based therapies in patients with MSI-H MCRC





First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study

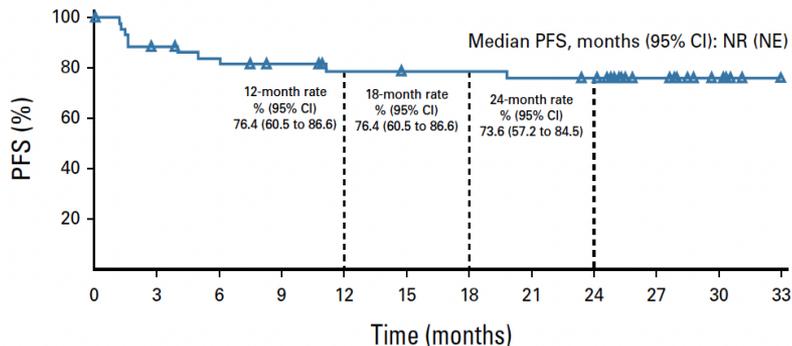
Heinz-Josef Lenz, MD¹; Eric Van Cutsem, MD, PhD²; Maria Luisa Limon, MD³; Ka Young Mark Wong, PhD⁴; Alain Hendlisz, MD, PhD⁵; Massimo Aglietta, MD, PhD⁶; Pilar García-Alfonso, MD⁷; Bart Neyns, MD, PhD⁸; Gabriele Luppi, MD⁹; Dana B. Cardin, MD¹⁰; Tomislav Dragovich, MD, PhD¹¹; Usman Shah, MD¹²; Sandzhar Abdullaev, MD, PhD¹³; Joseph Grisar, MS¹⁴; Jean-Marie Ledigne, MS¹⁵; Michael James Overman, MD¹⁶; and Sara Lonardi, MD¹⁷

TABLE 2. ORR, Best Overall Response, DCR, and Median DOR (N = 45)

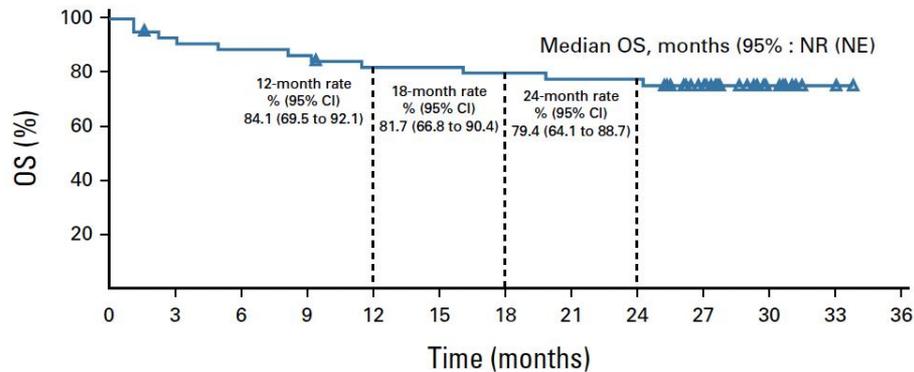
Response	Investigator Assessed	BICR Assessed
ORR, ^a No. (%)	31 (69)	28 (62)
95% CI	53 to 82	46.5 to 76.2
ORR by <i>BRAF</i> and/or <i>KRAS</i> mutation status, ^b No. (%)		
<i>BRAF</i> and <i>KRAS</i> wild-type (n = 13)	8 (62)	7 (54)
<i>BRAF</i> mutation (n = 17)	13 (76)	14 (82)
<i>KRAS</i> mutation (n = 10)	8 (80)	7 (70)
Best overall response, ^c No. (%)		
CR	6 (13)	11 (24)
PR	25 (56)	17 (38)
SD	7 (16)	8 (18)
PD	6 (13)	7 (16)
Not determined	1 (2)	2 (4)
DCR, ^d No. (%)		
95% CI	70.5 to 93.5	63 to 89
Median DOR, months (range) ^e	NR (1.4+ to 29.0+)	NR (3.3+ to 29.0+)

First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study

Heinz-Josef Lenz, MD¹; Eric Van Cutsem, MD, PhD²; Maria Luisa Limon, MD³; Ka Yeung Mark Wong, PhD⁴; Alain Hendilisz, MD, PhD⁵; Massimo Aglietta, MD, PhD⁶; Pilar Garcia-Alfonso, MD⁷; Bart Neyns, MD, PhD⁸; Gabriele Luppi, MD⁹; Dana B. Cardin, MD¹⁰; Tomislav Dragovich, MD, PhD¹¹; Usman Shah, MD¹²; Sandzhar Abdullaev, MD, PhD¹³; Joseph Gricar, MS¹³; Jean-Marie Ledoine, MS¹³; Michael James Overman, MD¹⁴; and Sara Lonardi, MD¹⁵



No. at risk: 45 37 34 31 28 27 27 26 25 14 6 0

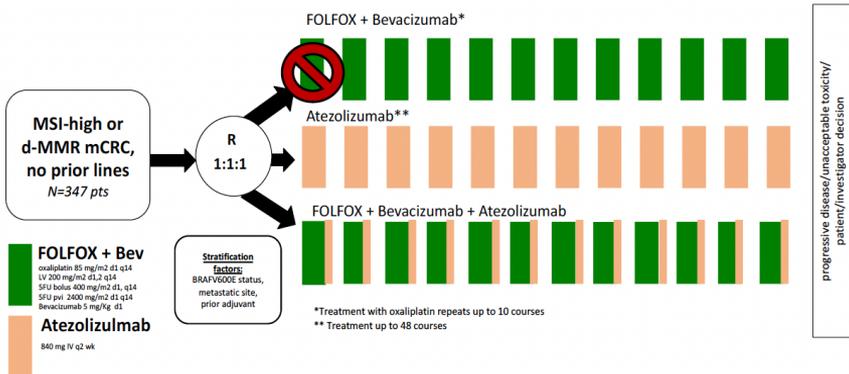


No. at risk: 45 42 40 39 36 36 35 34 34 23 10 1 0

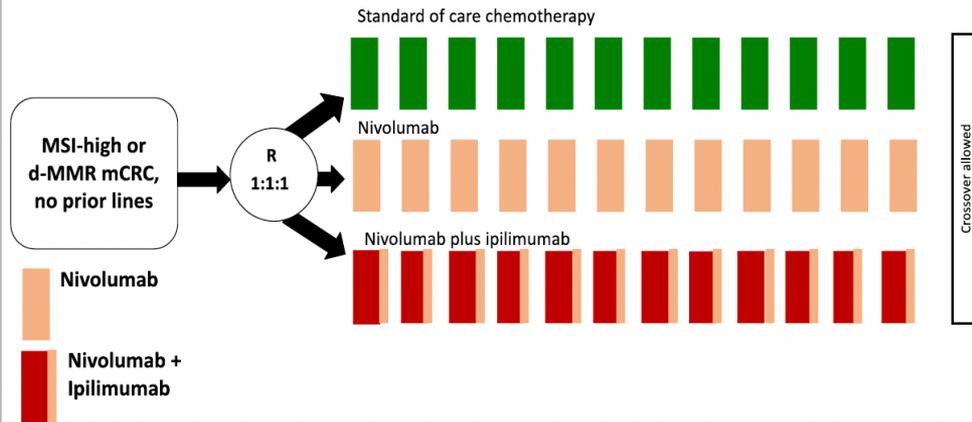
CHALLENGES: Ongoing trails combining ...



NRG-GI004/SWOG-1610 1-L trial design

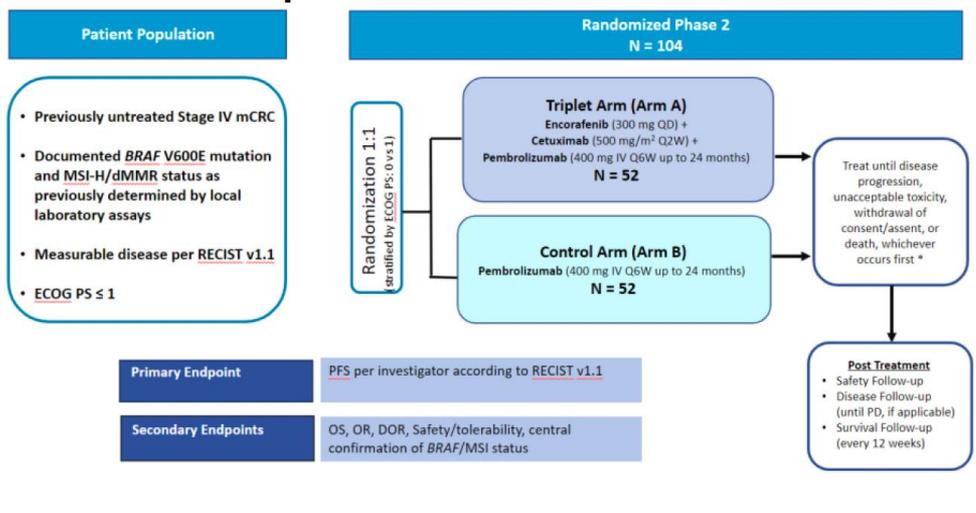


CA209-8hw trial design

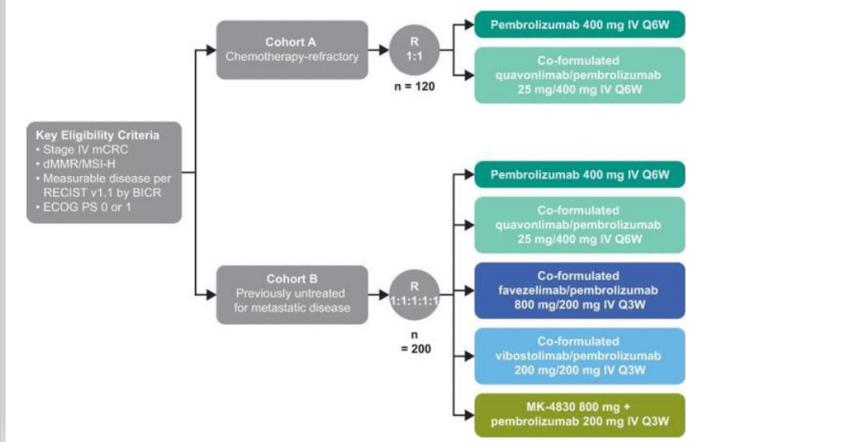


CHALLENGES: Ongoing trails combining ...

SEAMARK 1L phase 2 randomized trial

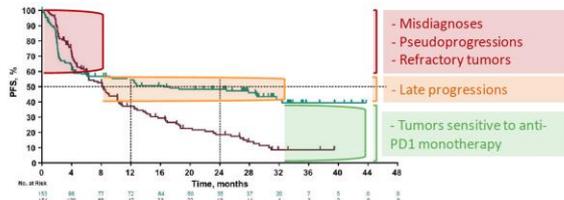


KEYSTEP-008 1L phase 2 randomized trial





Open Questions in MSI mCCR:



Who should be treated with anti-PD1 alone?

Who should be treated with anti-PD1 + anti-CTLA4?

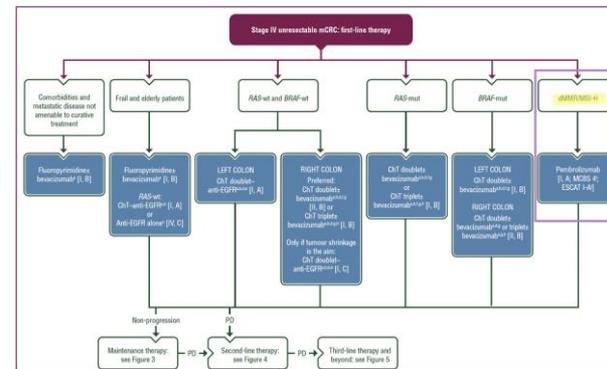
Who should be treated with other compounds?

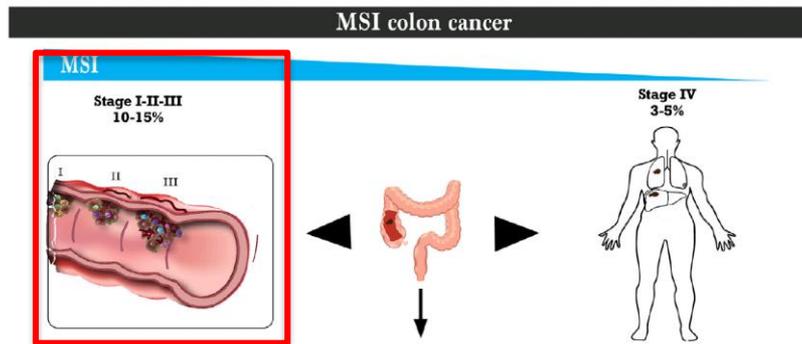
How patients should be managed under ICIs (management of post-IO residual lesions)?

André et al., ASCO 2021

Take Away:

- Test ALL metastatic CRC patients for MSI
- Pembrolizumab: SOC 1 Line for all MSI patients



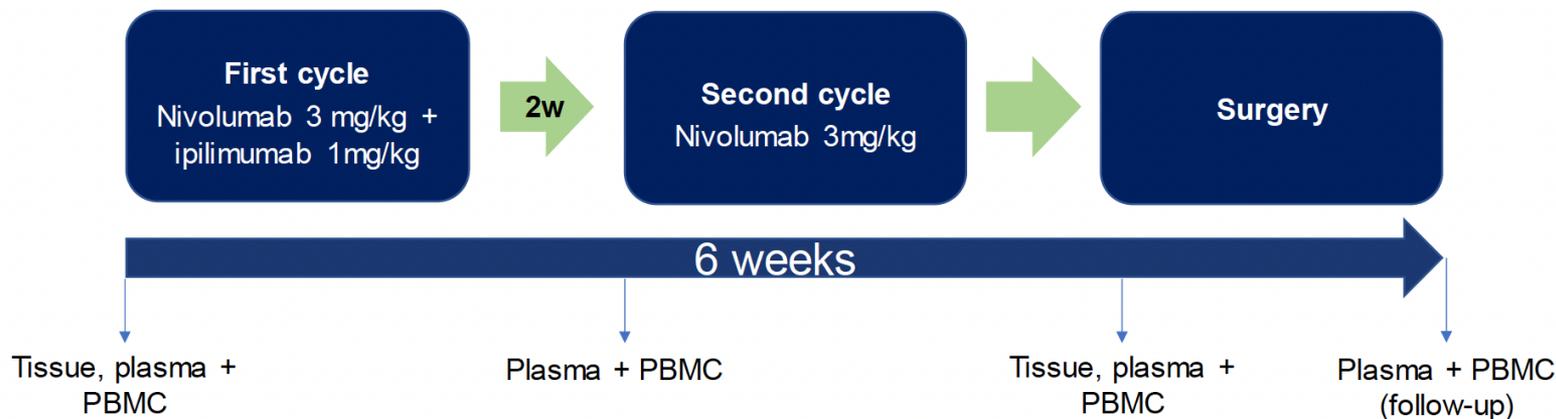


- **Scientific evidence: Main clinical trials**



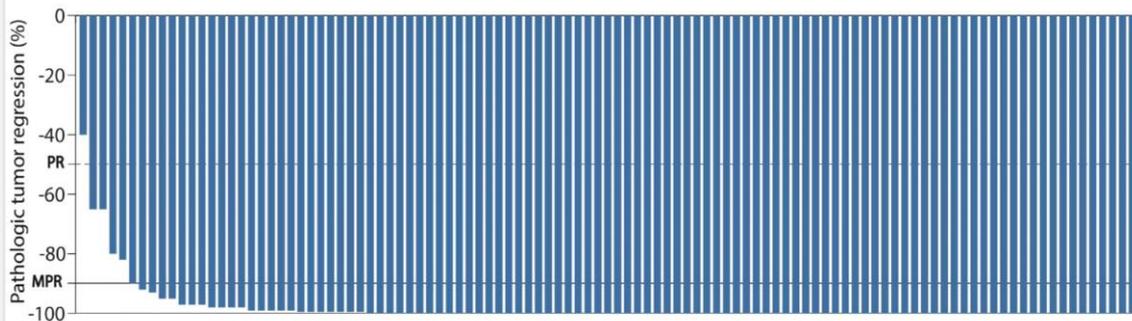
NICHE-2 study design – dMMR only

- Investigator-initiated, non-randomized multicenter* study
- Locally advanced dMMR colon cancers





Major pathologic response in 95% of patients; 67% pCR



Median time from first treatment to surgery = 5.4 weeks

N: 107

Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease

- 3 patients received adjuvant CTx
- 5 patients >70 years
- 6 patients refused

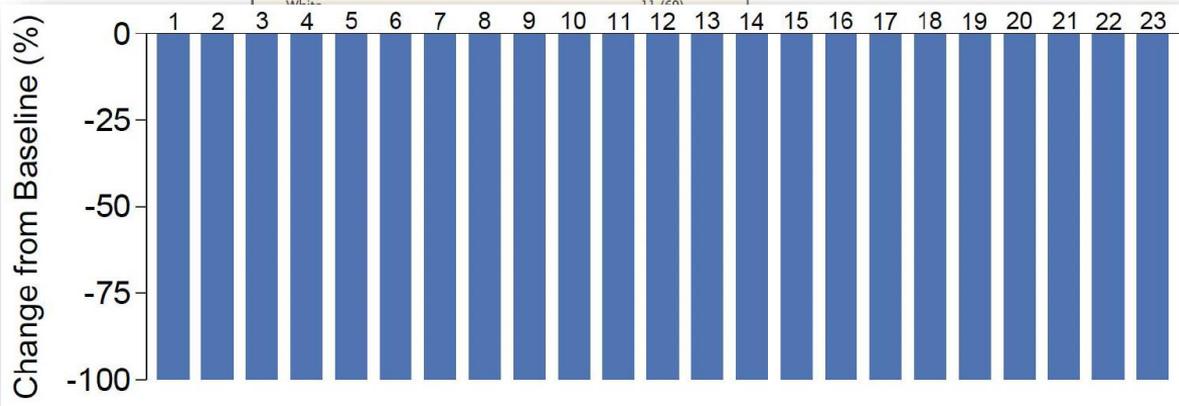
ORIGINAL ARTICLE

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

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

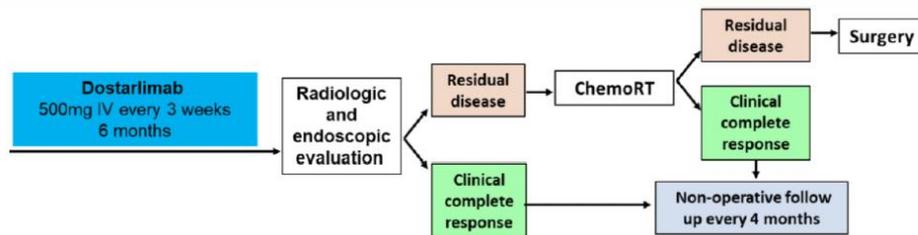
Table 1. Demographic and Disease Characteristics of the Patients at Baseline.

Characteristic	Value
Patients enrolled — no. (%)	16 (100)
Female sex — no. (%)	10 (62)
Median age (range) — yr	54 (26–78)
Race — no. (%)*	13 (81)



surgery and radiotherapy:

Organ preservation in rectal cancer

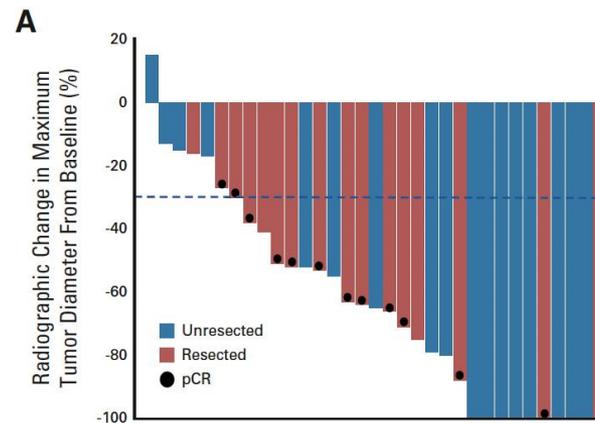




Characteristic	No. (%)
Age at diagnosis, year	
Mean	57
Median (range)	62 (25-90)
Sex	
Female	15 (43)
Male	20 (57)
Race	
White	33 (94)
Other	2 (6)
ECOG PS	
0-1	33 (94)
2	2 (6)
Tumor types	
Colon adenocarcinoma	19 (54)
Rectal adenocarcinoma	8 (23)
Pancreatic adenocarcinoma	2 (6)
Duodenal adenocarcinoma	2 (6)
Other ^a	4 (11)
Clinical stage^b	
II	8 (23)
III	26 (74)
Etiology of dMMR	
Sporadic	19 (54)
Lynch syndrome	16 (46)
Resectability	
Resectable	26 (74)
Unresectable	9 (26)

Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors

Kaysia Ludford, MD^{1,2}; Won Jin Ho, MD³; Jane V. Thomas, MD²; Kanwal P.S. Raghav, MBBS²; Mariela Blum Murphy, MD²; Nicole D. Fleming, MD⁴; Michael S. Lee, MD²; Brandon G. Smaglo, MD²; Y. Nancy You, MD²; Matthew M. Tillman, MD²; Carlos Kamiya-Matsuoka, MD⁵; Selvi Thirumurthi, MD²; Craig Messick, MD⁵; Benny Johnson, DO²; Eduardo Vilar, MD, PhD⁶; Arvind Dasari, MBBS²; Sarah Shin, BS²; Alexei Hernandez, BS²; Xuan Yuan, MD²; Hongqui Yang²; Wai Chin Foo, MD⁹; Wei Qiao, MS, PhD¹⁰; Dipen Maru, MD⁹; Scott Kopetz, MD, PhD²; and Michael J. Overman, MD²





Open Questions in MSI early stage CCR:

How much IO is enough

- Mono vs dual inhibition
- Duration

Is IO curing ?

Can we de-escalate ?

- Rectal cancer (surgery, CH/RT)
- Colon cancer (chemotherapy)

Take Away:

- **Highest response rates**
- **Neoadjuvant IO: high rates cCR, pCR**
- **De-escalation of treatments**

**foro
debate
oncología**

Zaragoza 26-29 septiembre 2023



GRACIAS iii

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