Immunotherapy in colon cancer

Mridula Krishnan, MD

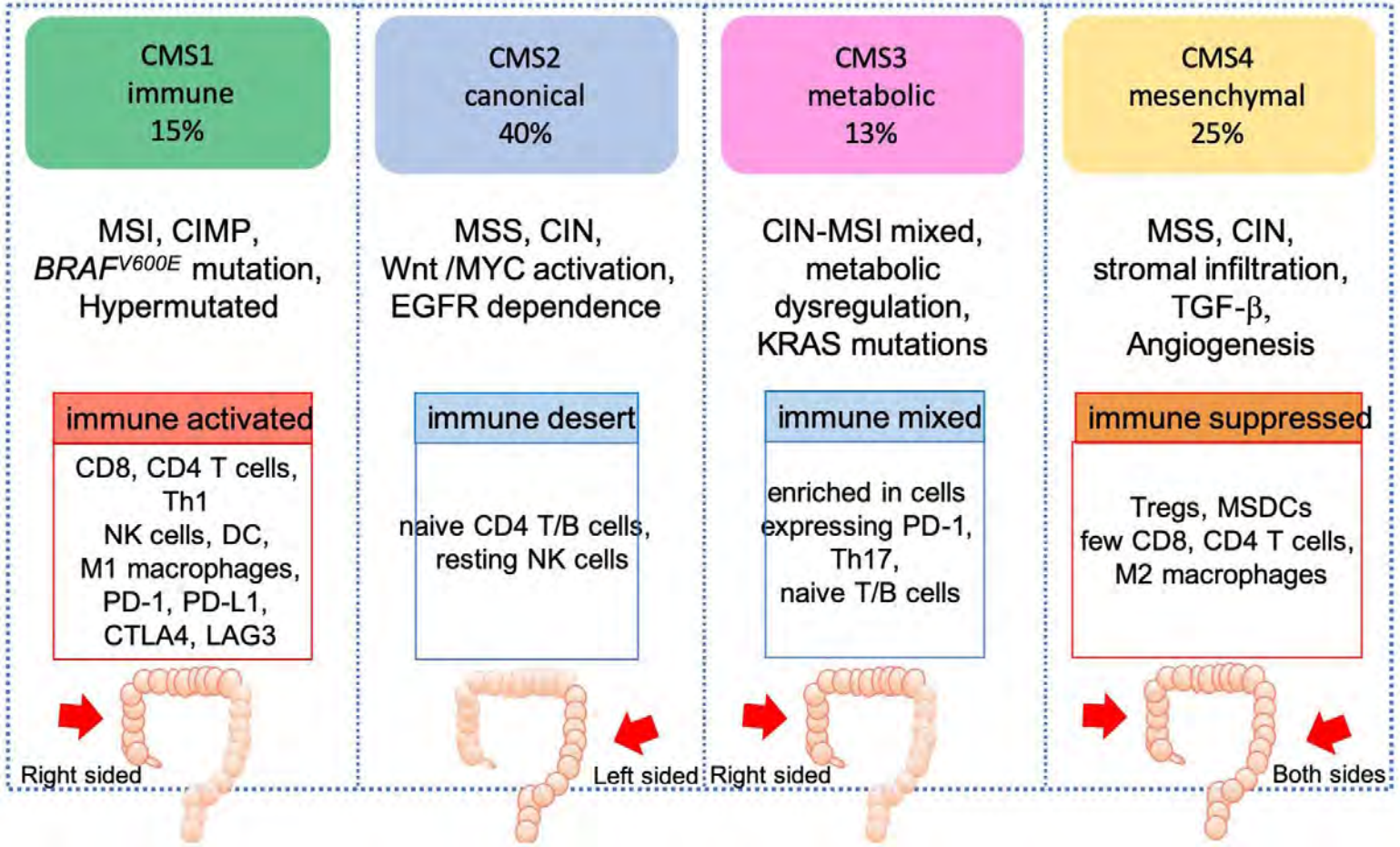
Hematology Oncology

University of Nebraska medical center

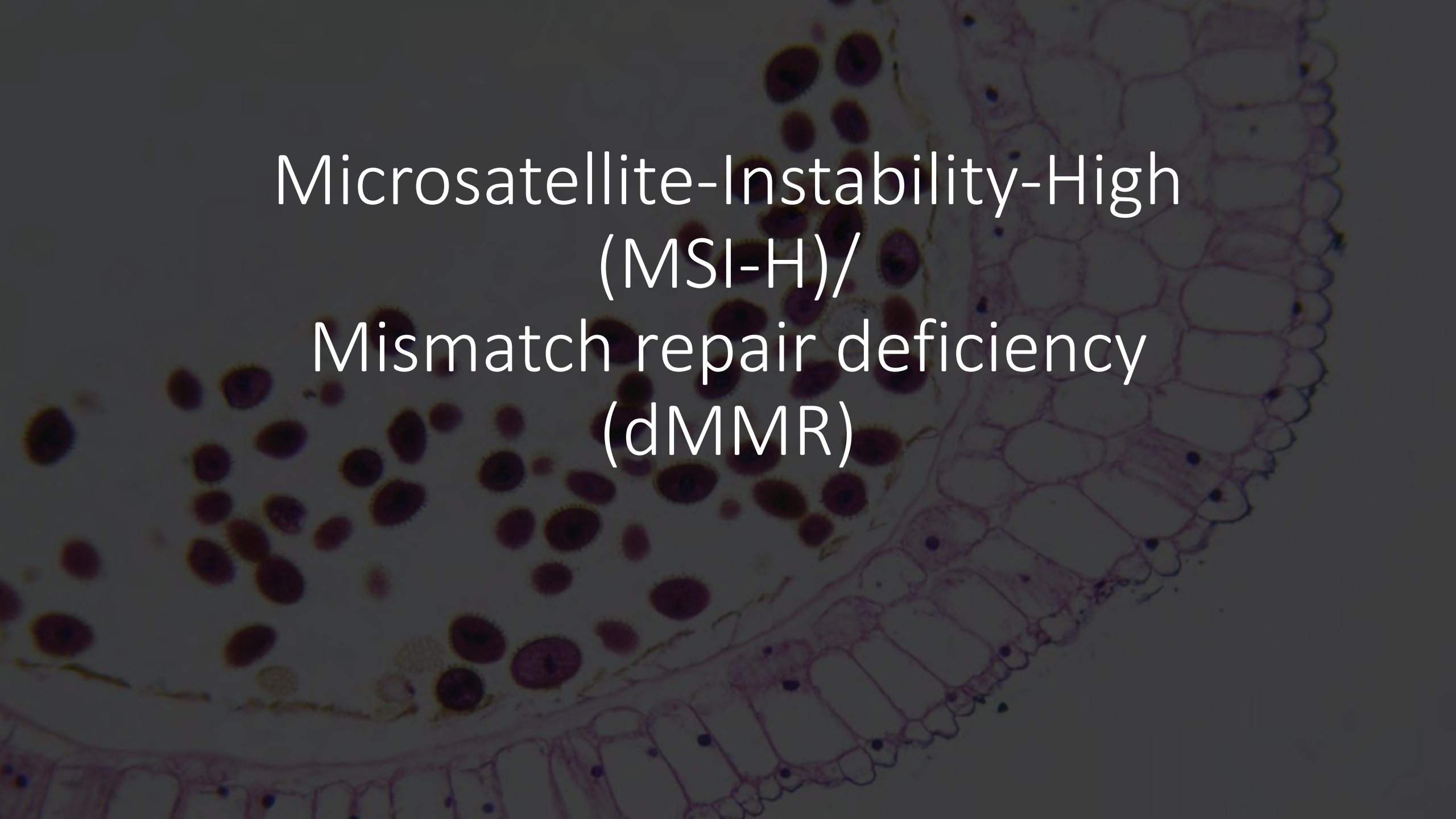
Objectives

- Role of immunotherapy in metastatic dMMR and MSI-H advanced CRC
- Role of Neoadjuvant immunotherapy - is this ready for prime time ?

Molecular classification of colon cancer



Martini G et al. Therapeutic Advances in Medical Oncology. 2020 Jul;12:1758835920936089.



Microsatellite-Instability-High (MSI-H)/ Mismatch repair deficiency (dMMR)

Introduction

- High microsatellite instability (MSI-H)/deficient mismatch repair (dMMR) phenotype is a distinct molecular signature across gastrointestinal cancers
- Highly immunogenic and heavily infiltrated by immune cells
- Uniquely vulnerable to therapeutic strategies enhancing immune antitumor response such as checkpoint inhibitors

Mechanism of dMMR

- Germline mutation of one of the genes ‘Lynch syndrome) – 25%
- Rest are sporadic (hypermethylation of MLH1 promoter gene)
- Right-sided tumors tend to be sporadic while rectal tumors tend to be associated with Lynch syndrome
- 15–20% of cases in stage II, 10–15% in sage III, and 4–5% in stage IV colon cancer

Metastatic disease with dMMR/MSI-H

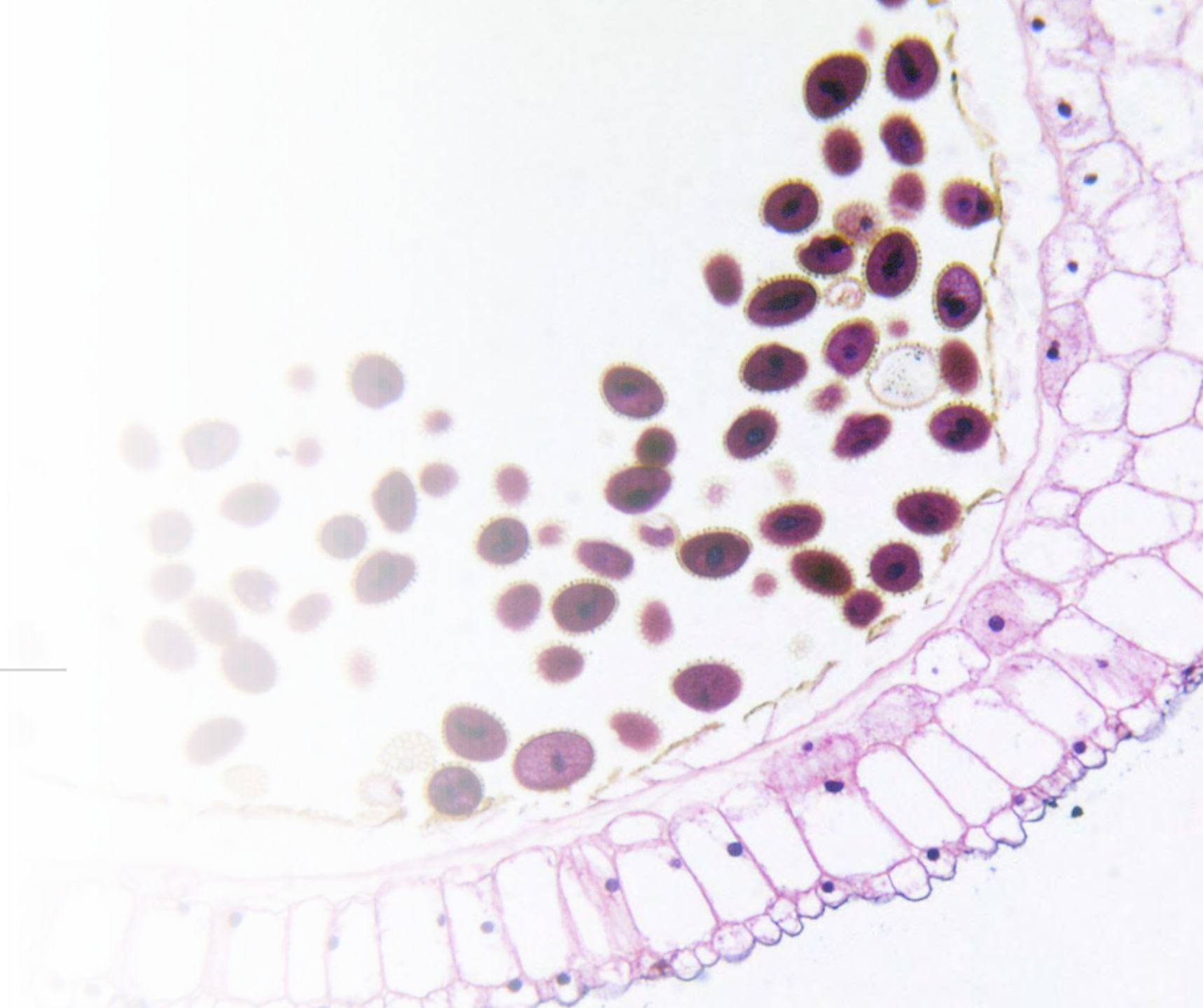


TABLE 2. Immune Checkpoint Inhibitors (Anti–PD-1 With or Without Anti–CTLA-4) and MSI/dMMR Colorectal Cancer

	Previous Systemic Treatment	No. of Patients	CR (%)	PR (%)	SD (%)	PD (%)	NE (%)	1-Year PFS (%)	1-Year OS (%)	2- or 3-Year PFS (%)	2- or 3-Year OS (%)	Median Follow-up Time (Months)
KEYNOTE-016[6]												
Pembrolizumab	≥ 1	28	11	46	32	4	7	—	—	—	—	8.7
KEYNOTE-164[13]												
Pembrolizumab, cohort A	≥ 2	61	3	30	18	46	3	34	72	42*	55*	31
Pembrolizumab, cohort B	≥ 1	63	8	25	24	40	3	41	76	37*	63*	24
KEYNOTE-177[19,22]												
Pembrolizumab	0	153	13.1	32	19.6	29.4	5.9	55	78	42**	61**	44.5
Chemotherapy with or without bevacizumab or cetuximab		154	3.9	29.2	42.2	12.3	12.3	38	74	11**	50**	44.4
CheckMate-142[12,16,24]												
Nivolumab	≥ 1	74	9	24	31	31	5	44	73	—	—	21
Nivolumab plus ipilimumab	≥ 1	119	13	32	21	12	2	71	85	60	71.4	30.9
Nivolumab plus ipilimumab	0	45	13	56	16	13	2	77	83	74*	79*	29.0
NIPICOL[17]												
Nivolumab plus ipilimumab	≥ 2	57	19	40	30	5	3	73	84	—	—	18.1
GARNET[14]												
Dostarlimab	≥ 1	69	36		—	—	—	—	—	—	—	—

Abbreviations: MSI, microsatellite instability; dMMR, mismatch repair deficiency; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; PFS, progression-free survival; OS, overall survival.
*Two-year survival rate.
**Three-year survival rate.

Andre T, Cohen R, Salem ME et al. American Society of Clinical Oncology Educational Book. 2022 Apr 26;42:233-41.

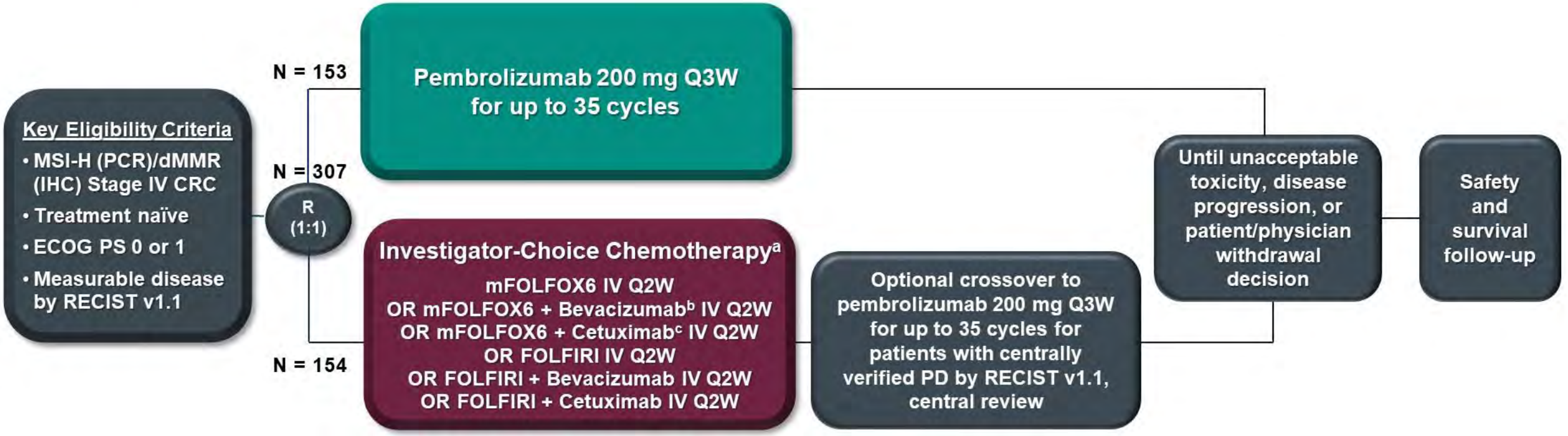
First approval for front line therapy in CRC

ORIGINAL ARTICLE

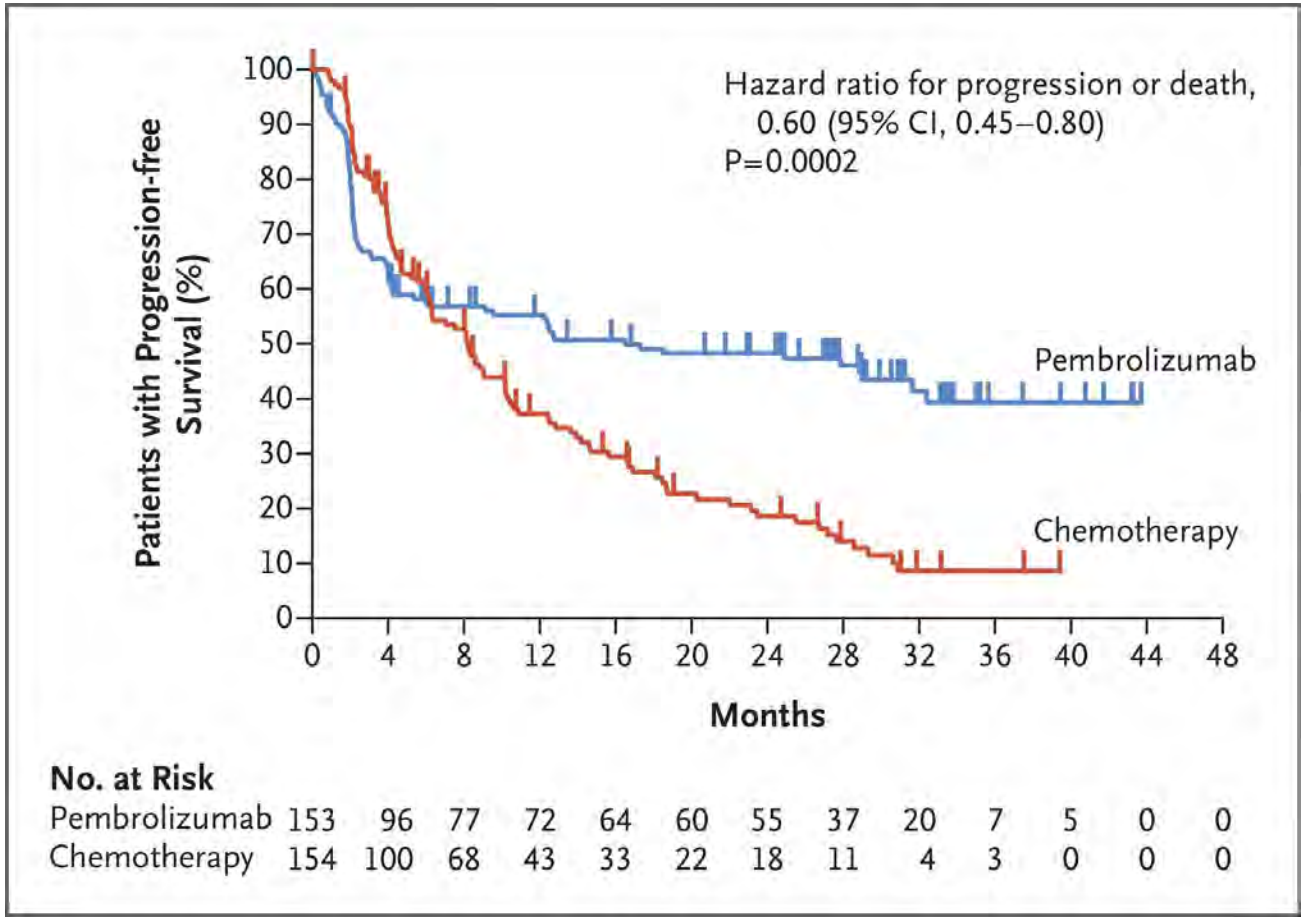
Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

Thierry André, M.D., Kai-Keen Shiu, F.R.C.P., Ph.D., Tae Won Kim, M.D., Ph.D., Benny Vittrup Jensen, M.D., Lars Henrik Jensen, M.D., Ph.D., Cornelis Punt, M.D., Ph.D., Denis Smith, M.D., Rocio Garcia-Carbonero, M.D., Ph.D., Manuel Benavides, M.D., Ph.D., Peter Gibbs, M.D., Christelle de la Fouchardiere, M.D., Fernando Rivera, M.D., Ph.D., et al., for the KEYNOTE-177 Investigators*

KEYNOTE-177 Study Design
(NCT02563002)

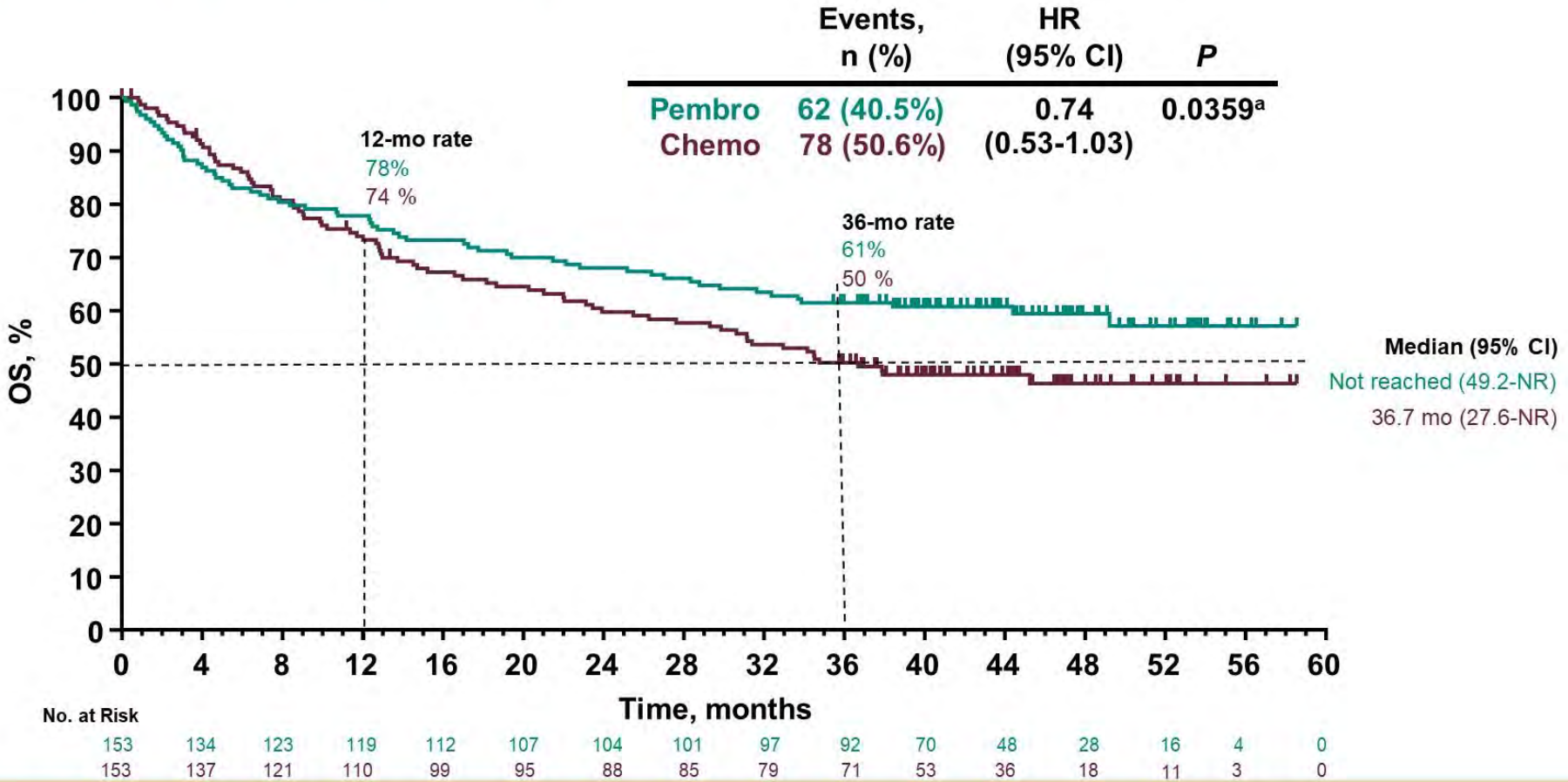


- Dual-primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR



Andre T et al. N Engl J Med 2020; 383:2207-2218
DOI: 10.1056/NEJMoa2017699

Overall Survival



CheckMate 142 NIVO3 + IPI1 1L cohort study design

- CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC[a]

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory
- No prior treatment for metastatic disease

→ NIVO3 Q2W + IPI1 Q6W[b]

Primary endpoint:

- ORR per investigator assessment (RECIST v1.1)

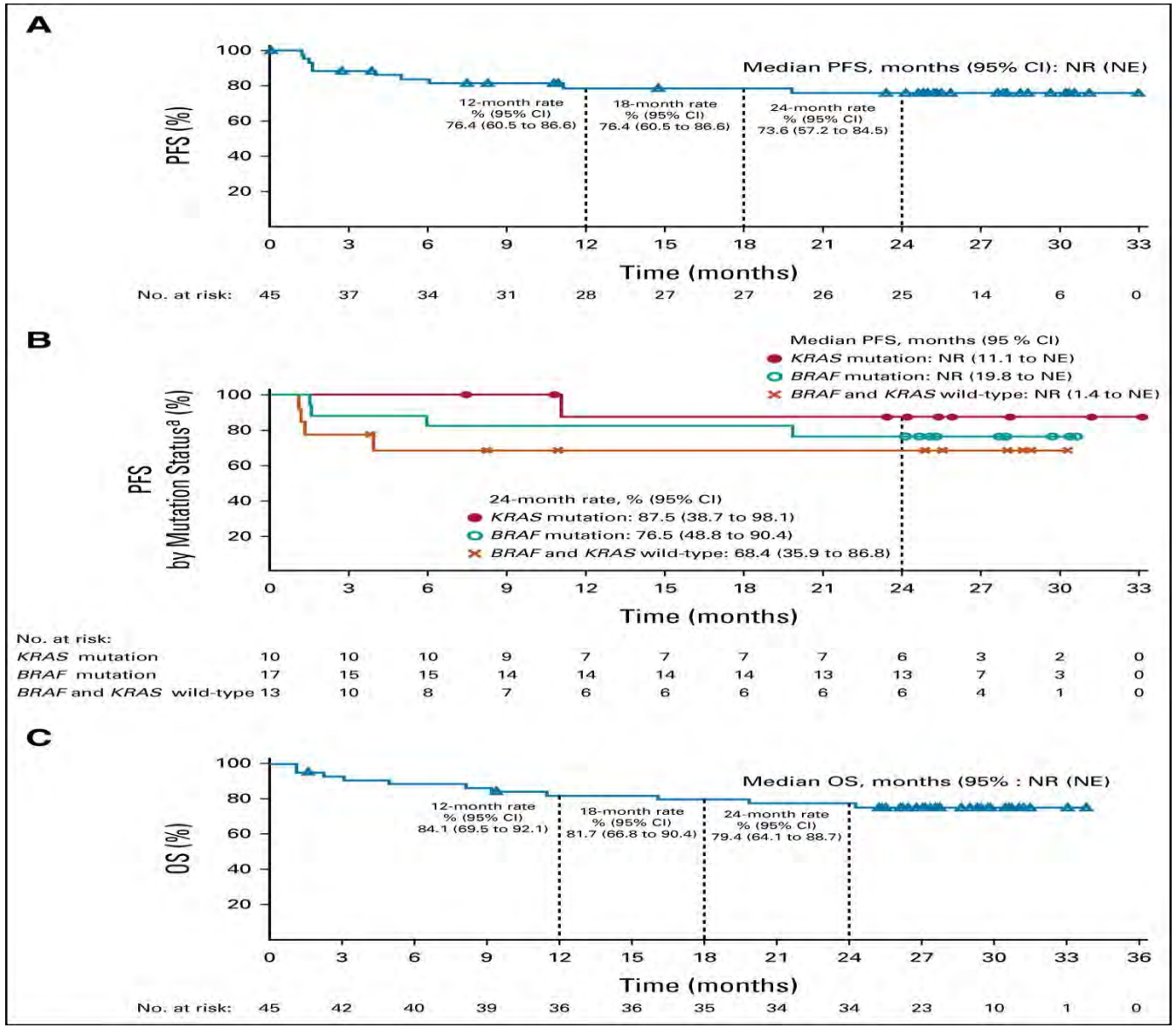
Other key endpoints:

- ORR per BICR, DCR,[c] DOR, PFS, OS, and safety

- At data cutoff (October 2019), the median duration of follow-up was 29.0 months (range, 24.2–33.7)[d]

[a]ClinicalTrials.gov number, NCT02060188. [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end. [c]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients. [d]Median follow-up was defined as time from first dose to data cutoff. BICR, blinded independent central review; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; NIVO3, nivolumab 3 mg/kg; IPI1, ipilimumab 1 mg/kg; PR, partial response; SD, stable disease.

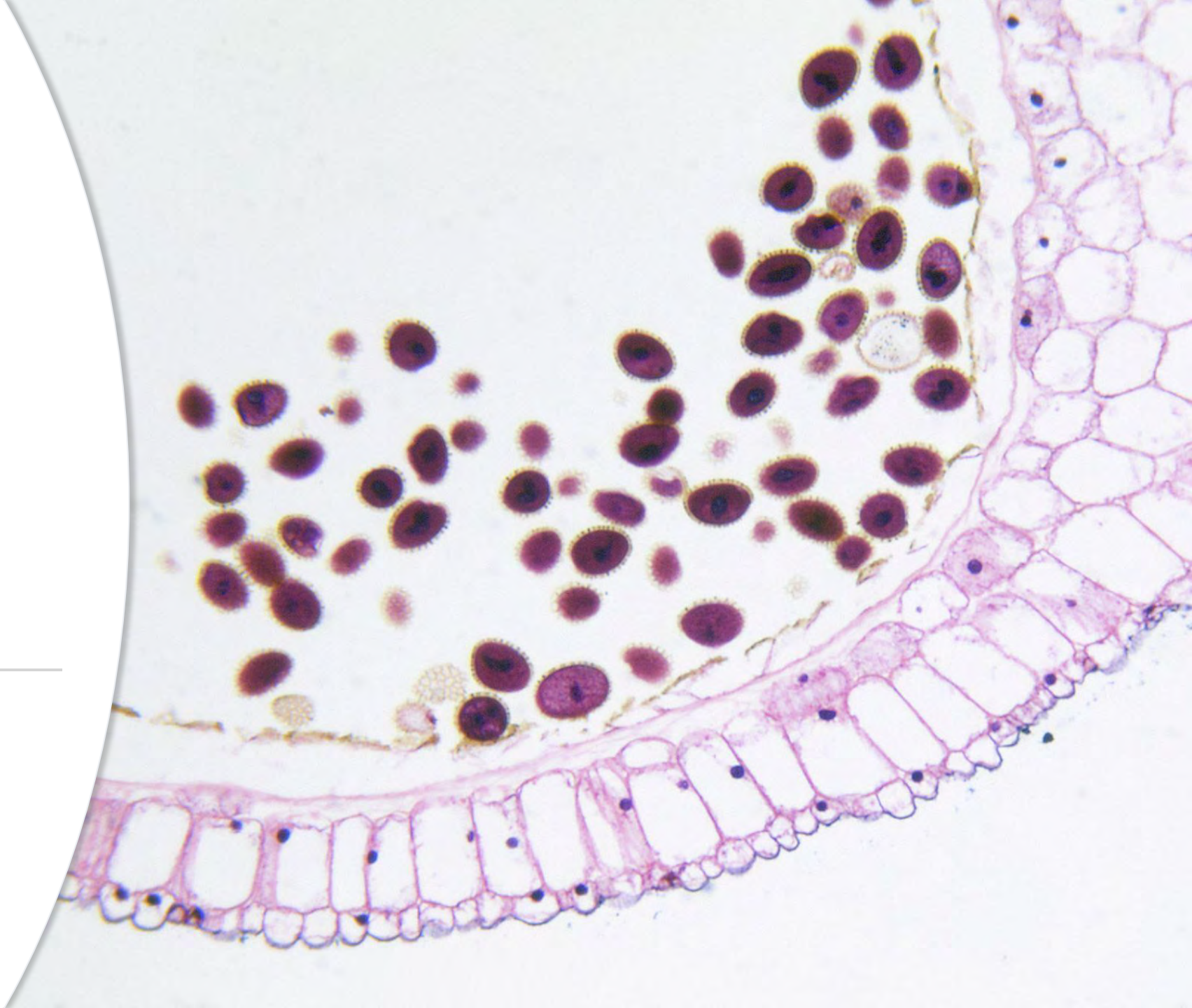
Lenz et al. JCO 2021



Lenz HJ et al. Journal of Clinical Oncology. 2022 Jan 10;40(2):161-70.

Chemo plus immunotherapy ? Ongoing trials

Early stage/locally advanced MSI high CRC



- A number of retrospective studies and post hoc analysis have evaluated the role of MMR as a prognostic and predictive biomarker in stage II–III CRC
- Favorable prognosis of stage II dMMR colon cancer and lack of benefit from adjuvant chemotherapy
- Oxaliplatin-based chemotherapy may be considered for high-risk stage II disease
- Three to six months of oxaliplatin-based chemotherapy per usual standards is recommended for patients with dMMR stage III colon cancer

Table 3. Predictive and prognostic value of MSI from two ACCENT pooled analysis.

	Treatment	5-year OS		HR	95% CI	*p*
		dMMR	pMMR			
Stage II						
Sargent *et al.*[50]	Surgery alone (*n* = 307)	90%	78%	0.27	0.10–0.74	0.011
	5-FU (*n* = 1155)	88%	87%	0.87	0.61–1.26	0.469
Stage III						
Sargent *et al.*[50]	Surgery alone (*n* = 264)	59%	54%	0.69	0.35–1.36	0.283
	5-FU (*n* = 2723)	77%	71%	0.79	0.65–0.97	0.023
Cohen *et al.*[51]	Surgery alone (*n* = 202)	73%	53%	0.58	0.21–1.63	0.2648
	FP-based (*n* = 204)	74%	67%	0.60	0.28–1.25	0.1459
	FP + oxaliplatin (*n* = 4250)					
	N1	89.9%	87.1%	0.65	0.45–0.93	0.0132
	N2	69.1%	72.1%	1.22	0.94–1.59	0.1403
	Low risk*	91.6%	88.7%	0.63	0.42–0.95	0.0186
	High risk*	69.8%	72.6%	1.13	0.88–1.45	0.3424
	Surgery ± FP-based	dMMR: 73% *versus* 74% (*n* = 49)		1.27	0.34–4.81	0.7218
	FP-based ± oxaliplatin	dMMR: 75.6% *versus* 85.0% (*n* = 185)		0.52	0.28–0.93	0.0254

*Low risk: T1-3N1, high risk: T4 and/or N2.
95% CI, 95% confidence interval; dMMR, deficient mismatch repair; FP, fluoropyrimidine; HR, hazard ratio; MSI, microsatellite instability; OS, overall survival; pMMR, proficient mismatch repair; 5-FU, 5-fluorouracil.

What about neoadjuvant immunotherapy in CRC?

- NICHE phase II trial – 21 patients with MSI/dMMR CRC received dual checkpoint ICI 4 weeks proir to surgery
- Path CR was observed in 20/20 patients (CI : 86-100%)

Chalabi M et al. Nat Med 2020

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

Kaysia Ludford, MD[1,2]; Won Jin Ho, MD[3]; Jane V. Thomas, MD[2]; Kanwal P.S. Raghav, MBBS[2]; Mariela Blum Murphy, MD[2]; Nicole D. Fleming, MD[4]; ...

35 patients

54% colon

23% rectal

14 underwent surgery and 70% had path CR

Ludford et al. Ann oncol. 2021

ORIGINAL ARTICLE

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

Andrea Cercek, M.D., Melissa Lumish, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.A., Jinru Shia, M.D., Michelle Lamendola-Essel, D.H.Sc., Imane H. El Dika, M.D., Neil Segal, M.D., Marina Shcherba, M.D., Ryan Sugarman, M.D., Ph.D., Zsofia Stadler, M.D., Rona Yaeger, M.D., et al.

- Patients with stage II and III dMMR rectal cancer received neoadjuvant Dostarlimab for a total of 6 months
- Patients with cCR underwent a watch and wait strategy
- Among 11 paitents, the cCR rate was 100% with single agent Dostarlimab

- What is the best regimen to use?
- Optimal duration of therapy
- How are we sure of path CR?
- Can we also resect metastasis if limited to one site?
- Will all these questions be answered by a phase 3 trial for locally advanced rectal cancers?

Important take home points

- All CRC's should be tested for MSI H/dMMR status
- ICI's have significantly impacted treatment of MSI high disease
- Some patients may have primary resistance to ICI therapy
- Neoadjuvant ICI should be considered for dMMR tumors