Microsatellite stable and instable (MSI-H) colorectal cancer – two different entities?

Dieter Köberle

UNIVERSITÄT BERN

St Claraspital
In besten Händen.

A history professor was diagnosed in 08.2022 with multiple liver metastases from a synchronous right-sided colon cancer with a BRAF (V600R) mutation

01/2024: A "cured" history professor with complete resolution of all tumor manifestations in excellent condition and without any side effects

...without scalpel, beam or chemo

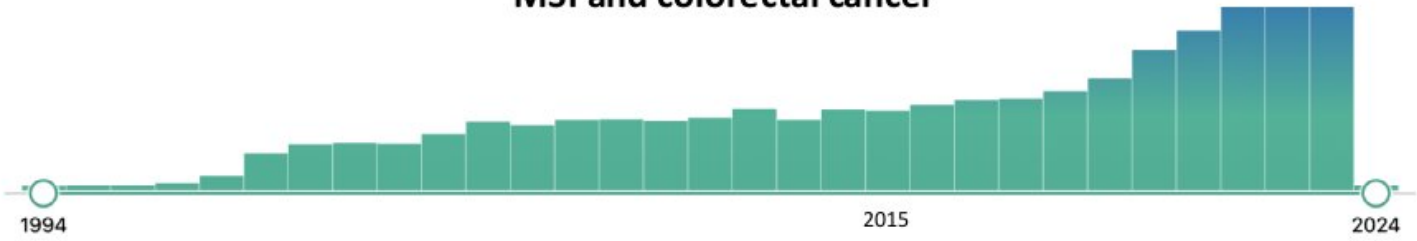
Microsatellite instable (MSI-H) colorectal cancer

BASICS

Immuno-Oncology

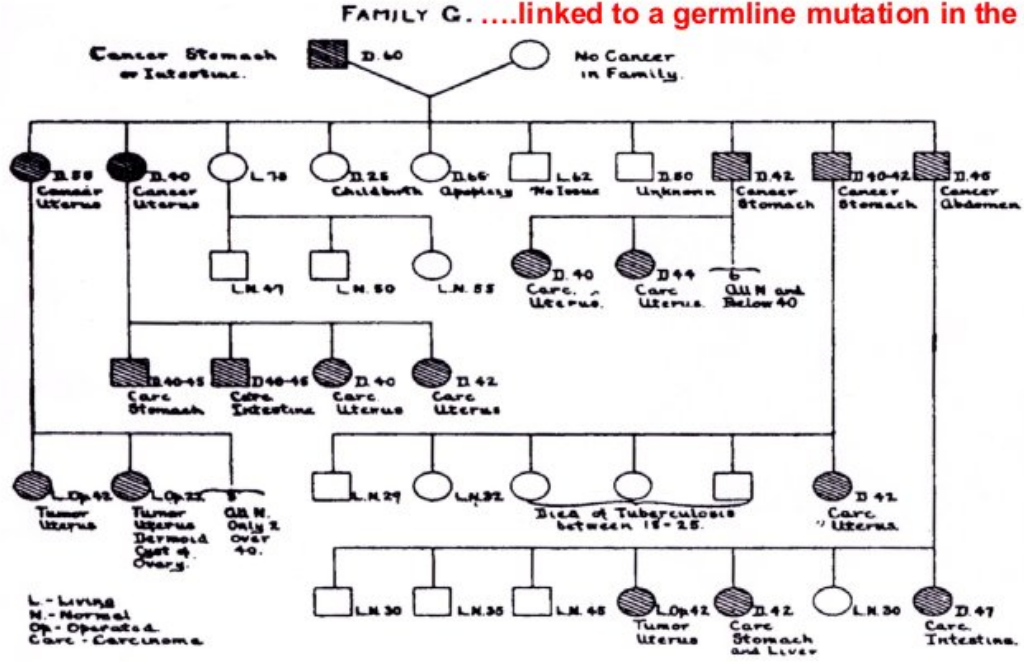
4,457 results

PUBMED SEARCH:
MSI and colorectal cancer



BASICS

- History and Biology
- Screening for Lynch Syndrome
- Testing
- 2 Different Entities?
- Biomarkers for Immuno-Oncology
- Impact of MSI on Prognosis and Chemotherapy Selection in Stage I-III



Aldred Warthin

Henry T. Lynch

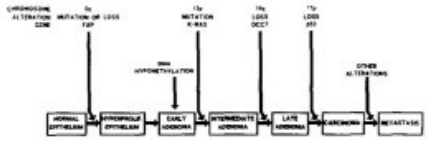
⇒ **Family History Taking:**
a very sensitive and cheap „screening“ method

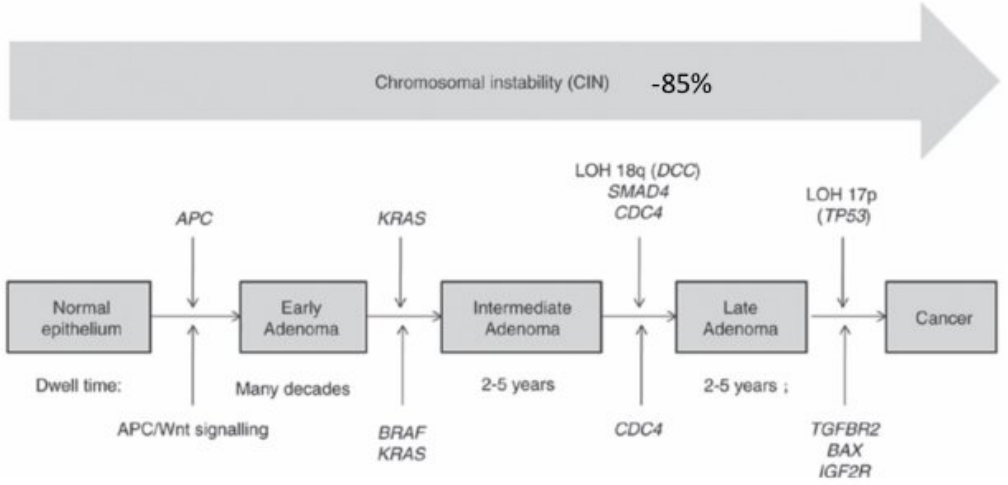
von HJ Müller

Cell, Vol. 61, 759–767, June 1, 1990, Copyright © 1990 by Cell Press

A Genetic Model for Colorectal Tumorigenesis

Eric R. Fearon and Bert Vogelstein
The Oncology Center
Program in Human Genetics
The Johns Hopkins University School of Medicine
Baltimore, Maryland 21231

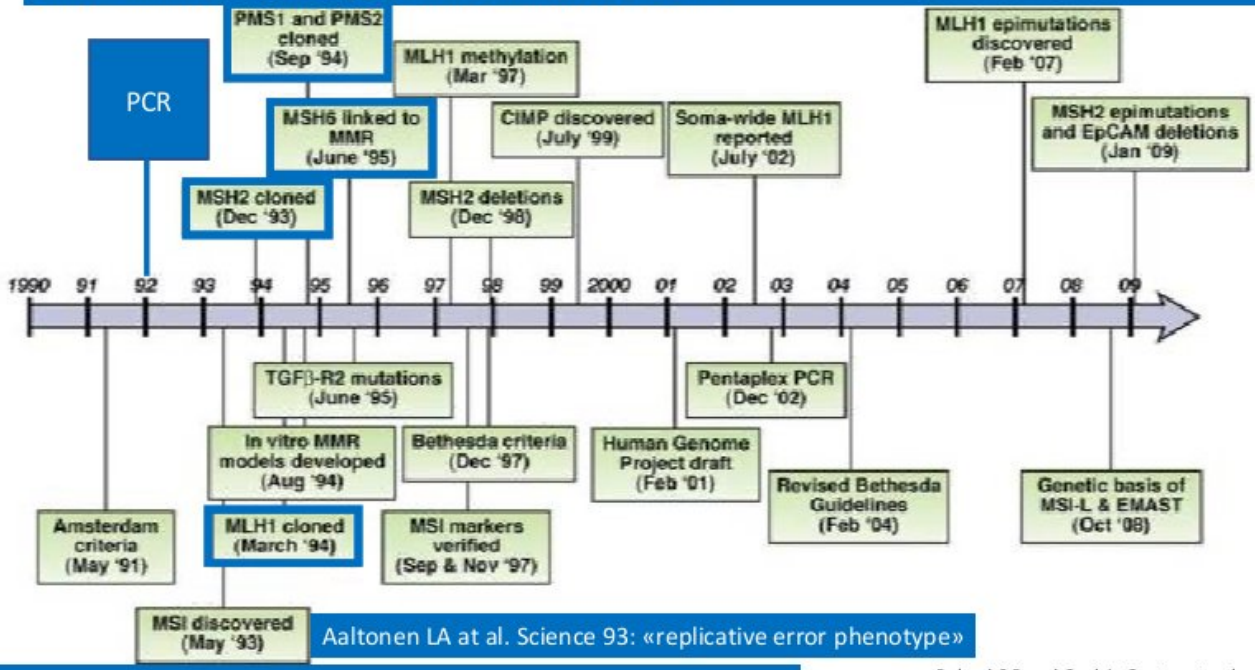




Nguyen HT et al; *Oncology Letters 2018*

MSI research associated with colorectal cancer from 1990 to 2010

A series of investigations led to the realization that MSI arises from defects in the DNA mismatch repair (MMR) system and the identification of the 4 genes that cause Lynch syndrome

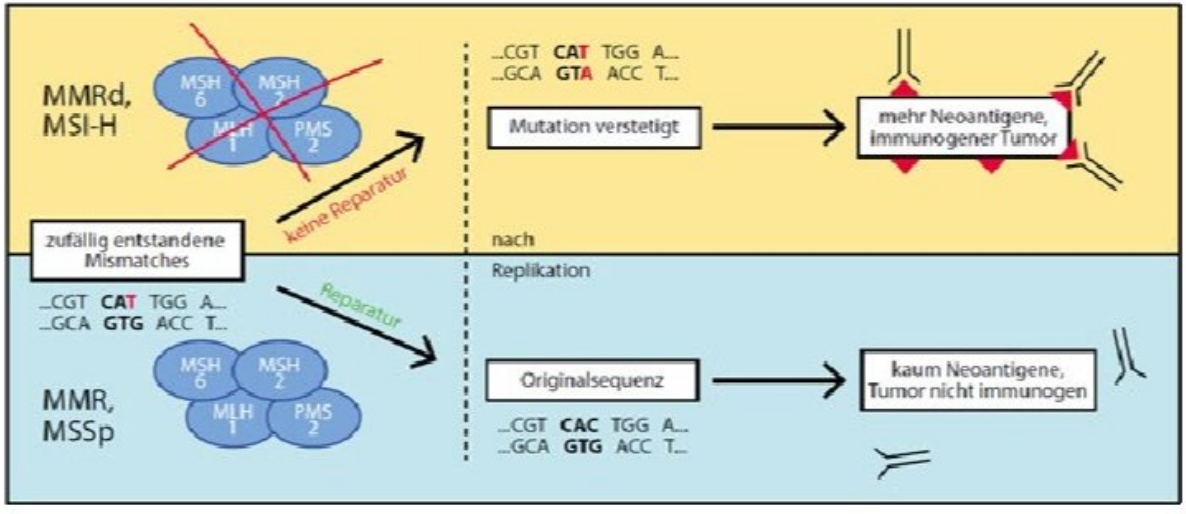


Aaltonen LA at al. Science 93: «replicative error phenotype»

Ionov Y et al. Nature 93: "ubiquitous somatic mutations at simple repeated sequences"

Boland C.R and Goel A; Gastroenterology 2010

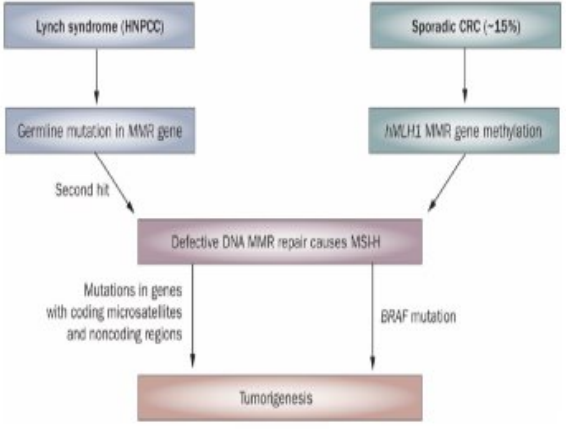
MSI is caused by deficiencies in MMR



dMMR = deficient DNA mismatch repair (MMR) <-> MSI-H phenotype

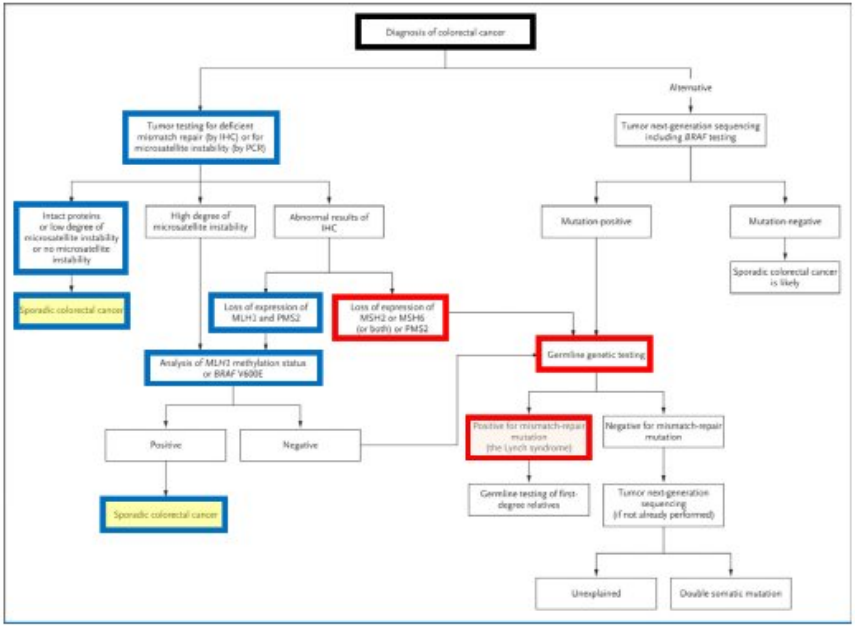
pMMR = proficient MMR <-> MSS phenotype

Distinct molecular pathways for the development of defective DNA MMR + MSI-H in CRC



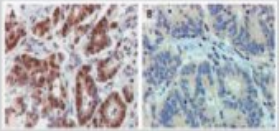
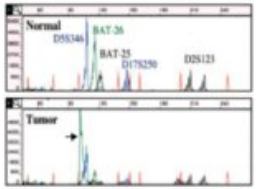
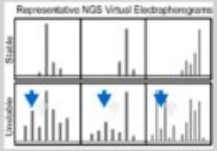
Sinicrope et al; Nat Rev Clin Oncol 2010

Algorithm for Lynch-Syndrome Testing in patients with a new diagnosis of CRC



Sinicrope FA; NEJM 2018

Determination of MSI and MMR Status

Type of Analysis	Measurement and Classification	Considerations
IHC 	• IHC detects the presence or absence of tumor MMR proteins using antibodies against MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*; visual score • dMMR is the loss of expression of at least one MMR protein in tumor cell	• Guidelines recommend confirmation of IHC results by PCR (93%–97% concordance with PCR) • IHC is a useful screening test for Lynch syndrome
PCR 	• Detects the functional failure of tumor MMR proteins, resulting in instability in microsatellite allele length • Two reference panels are used: (1) the Bethesda panel: BAT25 and BAT26 (mononucleotide markers), D5S346, D2S123, and D17S250 (dinucleotide markers) and (2) the Promega panel: BAT25, BAT26, NR21, NR24, and NR-27 (mononucleotide markers) • The MSI phenotype is defined by the presence of at least two unstable markers compared with healthy tissue or at least three unstable markers in the absence of healthy tissue	• Guidelines recommend confirmation of PCR results by IHC (> 93%–97% concordance with IHC)
NGS 	• NGS detects the MSI phenotype and/or mutation rate (mutational load) in a tumor sample • MSI is determined by a number of markers analyzed	• In development • Potential to offer one-step sequencing for other common mutations (i.e., *BRAF* and *RAS*, *HER2* amplification, and many other genes)

Abbreviations: MSI, microsatellite instability; dMMR, mismatch repair deficiency; IHC, immunohistochemistry; PCR, polymerase chain reaction; NGS, next-generation sequencing.

André T; *ASCO Educational Book 2022*

TWO different Subtypes of Colorectal Cancer

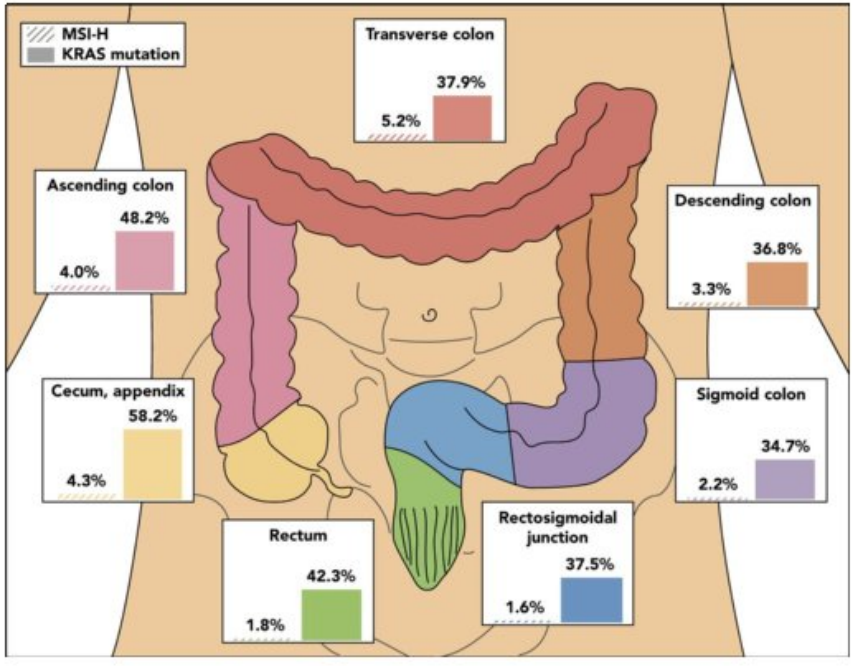
Genomic Parameter	Chromosomal Instability	Genetic Instability (MSI)
DNA ploidy	Aneuploid	Diploid
18q, 17p, 5q, 8p, 22q	Loss of genetic material, loss of heterozygosity	No loss of genetic material
Frequency: localized/mCRC	85% nonmetastatic and 95% metastatic	15% nonmetastatic and 5% metastatic
MMR system	Proficient MMR/MSS	Deficient MMR (hMSH2, hMLH1, hMSH6, hMSH3 alterations)/MSI
Frequent mutations	*RAS* mutation	*BRAF*^{V600E} or *RAS* 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; MMS, microsatellite stability; ICI, immune checkpoint inhibitor.

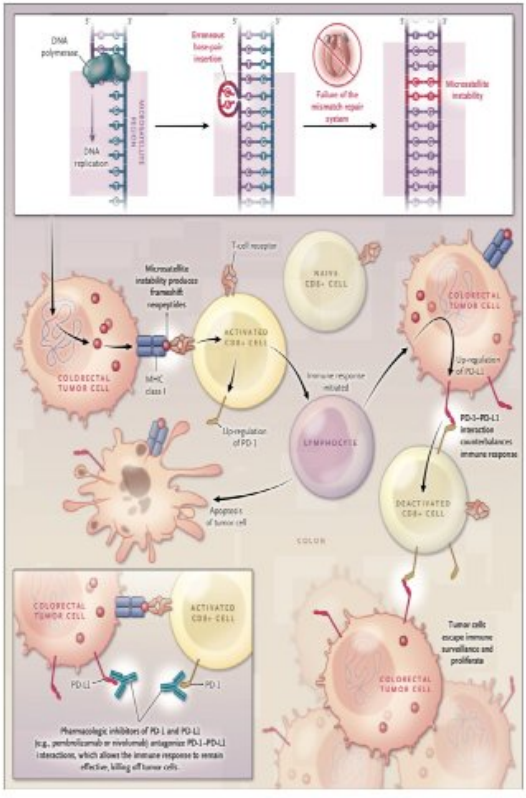
André T; *ASCO Educational Book 2022*

MSI and KRAS mutation prevalence according to primary CRC site

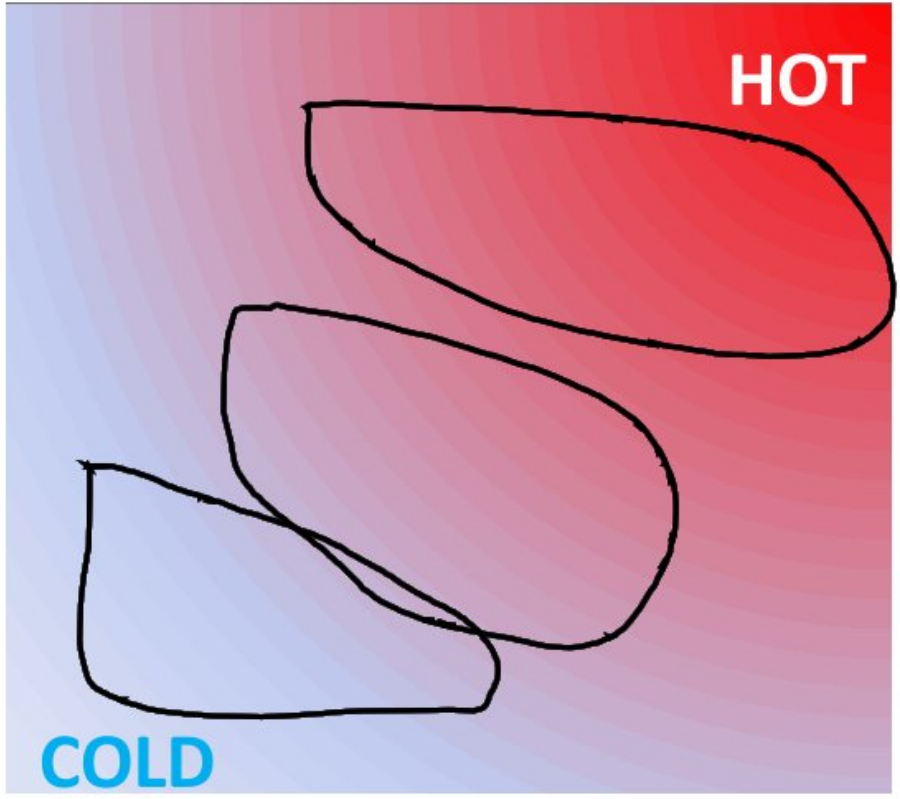
(numbers refer to metastatic disease)



Journal of the National Comprehensive Cancer Network 19, 3; 10.6004/jnccn.2020.7619



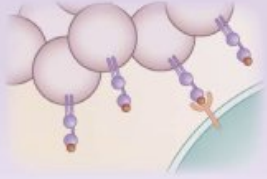
Sinicrope et al; *N Engl J Med* 2018



Yarchoan M et al; *N Engl J Med* 2017

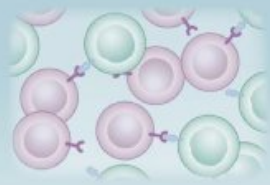
Potential biomarkers of CRC immunotherapy

Tumor neoantigens



- TMB
- POLE/POLD
- MSI-H/dMMR

Pre-existing immunoresponse

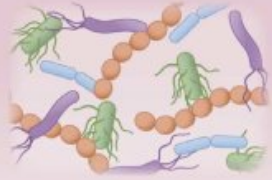


- TILs
- Immunoscore
- Cold/hot
- PD-L1

Gene mutations

- B2M
- KRAS/NRAS

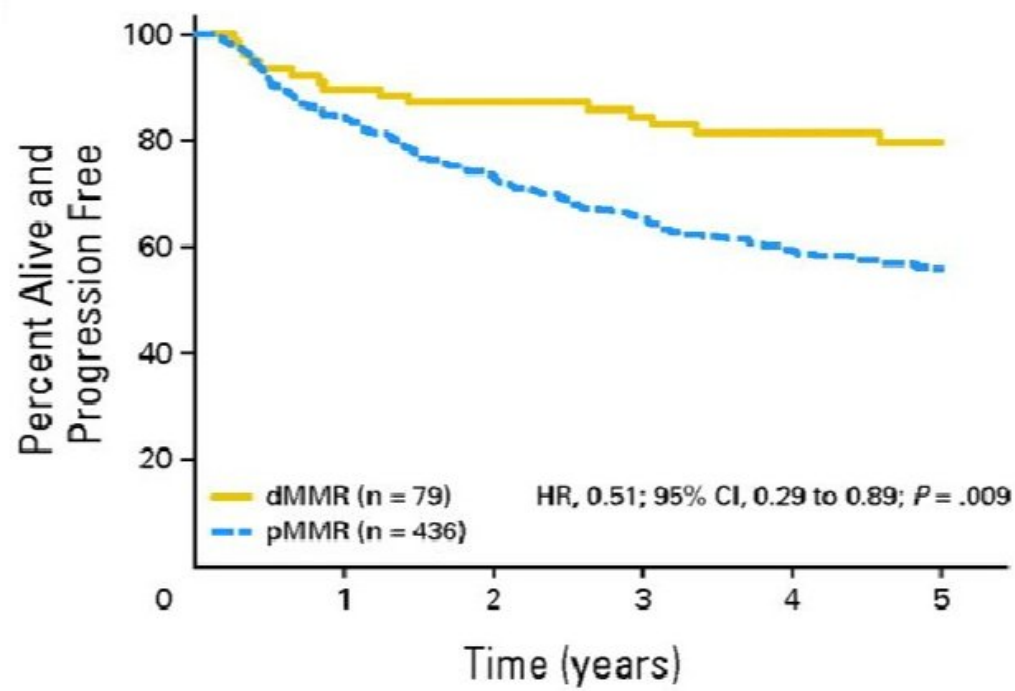
Gut microbiota

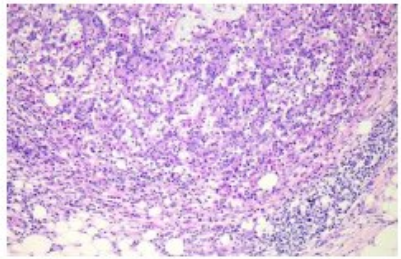


- B. pseudolongum
- L. Johnsonii
- Olsenella sp.
- A. Muciniphila

Fan A et al: Int. J. Biol. Sci. 2021

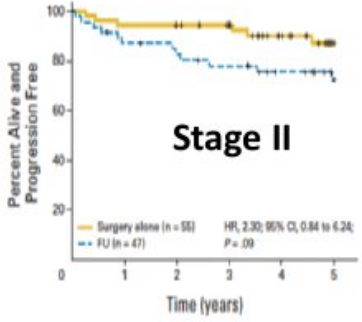
Prognosis in early stages (II-III) is better in MSI-H/dMMR CRC

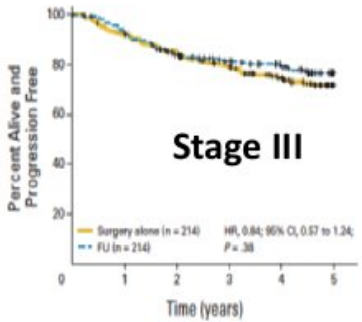




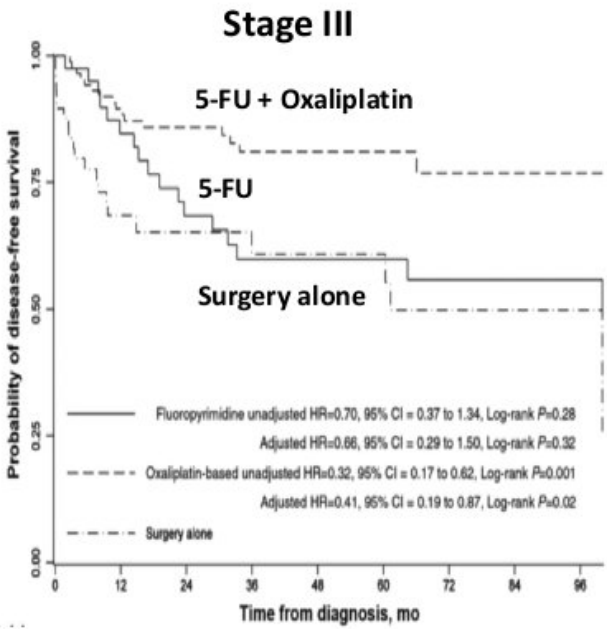
Sargent et al; J Clin Oncol 2010

MSI as a predictor of response to chemotherapy





Sargent et al; J Clin Oncol 2010



Tougeron et al; J Nat Cancer Inst 2016

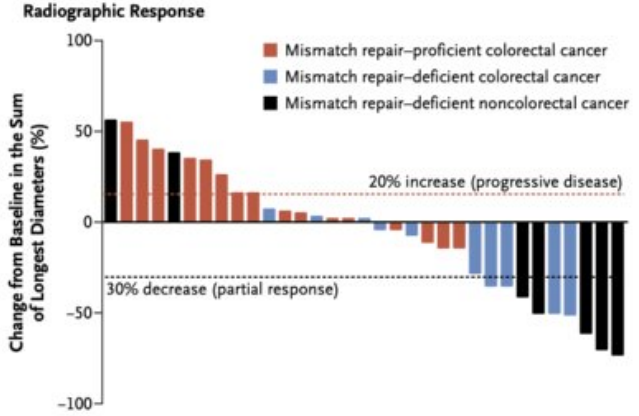
Immuno-Oncology

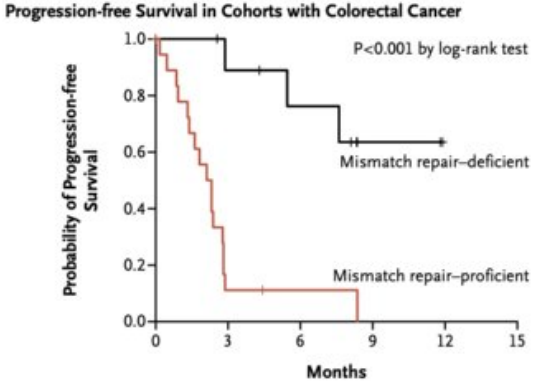
- I-O is a treatment standard in first-line treatment of MSI-H mCRC
- Neoadjuvant treatment of locally advanced CRC
- Questions around I-O treatments
- The history professor

NEJM 2015

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

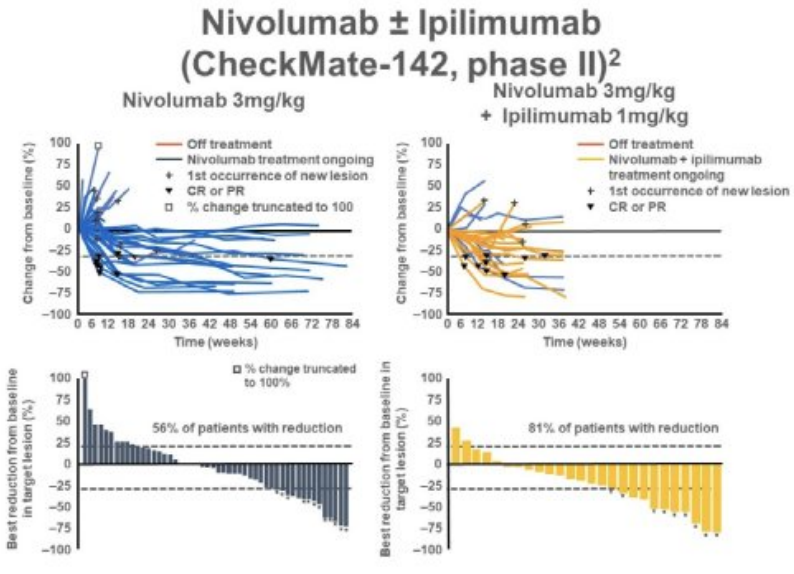
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, 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.

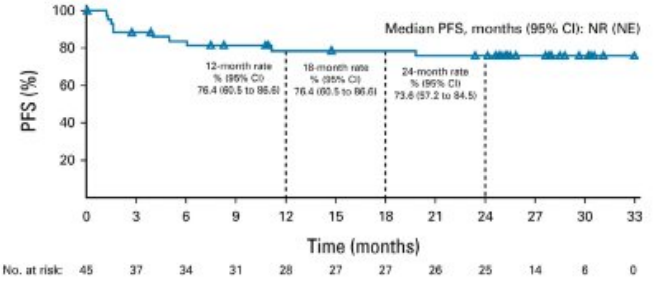


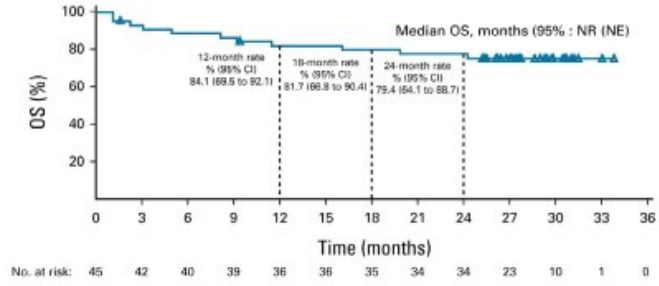


This study showed for the first time that mismatch-repair status predicts clinical benefit of immune checkpoint blockade with pembrolizumab

MSI-H CRCs are responsive to PD(L)-1 inhibitors
Combination inhibitors treatment appears to be more potent







Lenz et al; J Clin Oncol 2022

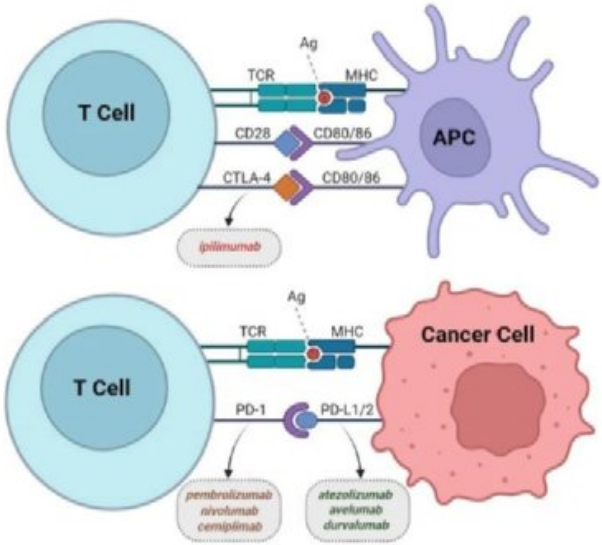
THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2018

Illustrations: Niklas Elmehed

James P. Allison • Tasuku Honjo

"for their discovery of cancer therapy by inhibition of negative immune regulation"

THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

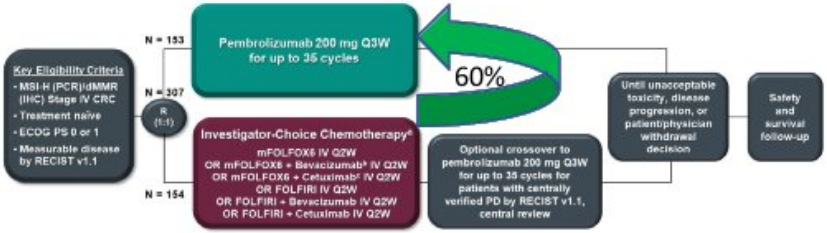


Immune Checkpoint Inhibitors

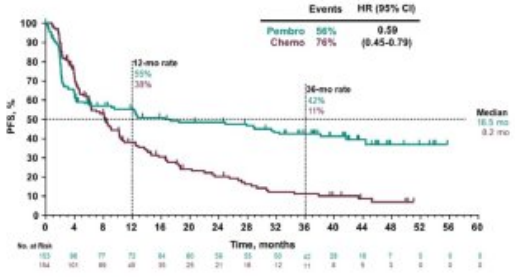
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

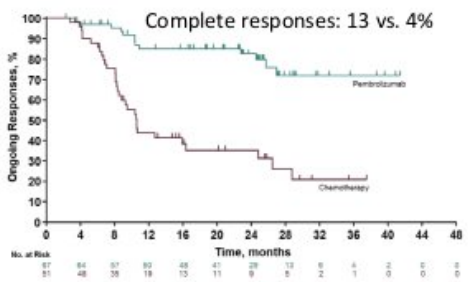
KEYNOTE-177 Study Design
(NCT02563002)



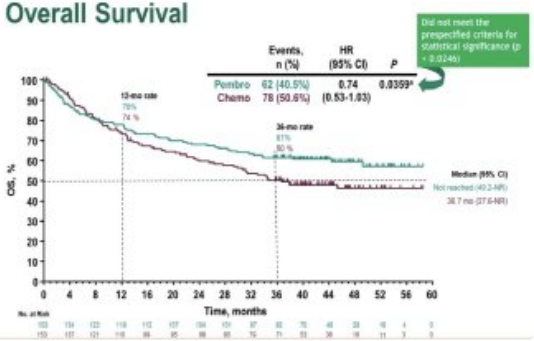
Progression-Free Survival



Duration of Response

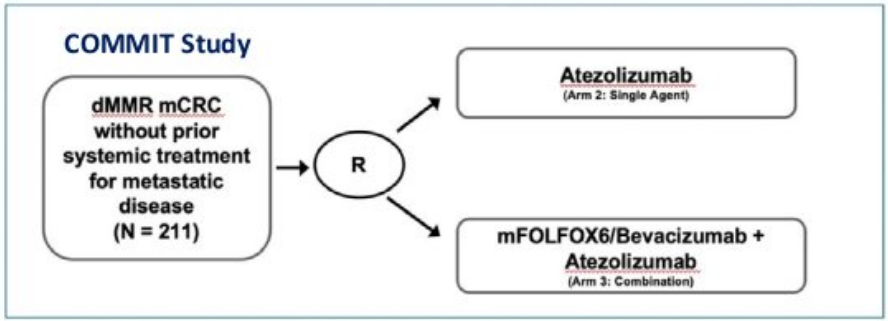


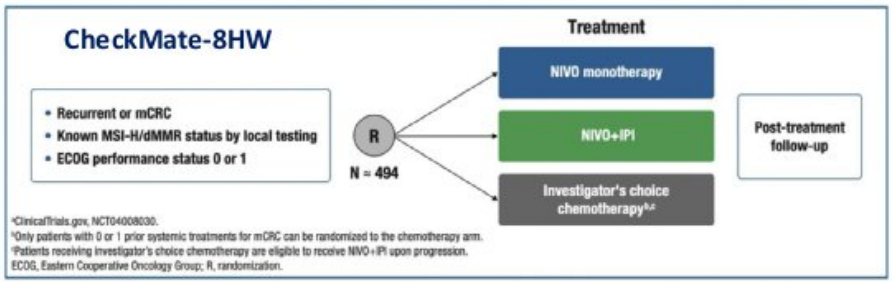
Overall Survival



This study showed superiority of pembrolizumab to combination chemotherapy + mAb and established a new treatment standard for MSI-H metastatic CRC

Not all MSI-High/dMMR tumors are created equal





Options:

Checkpoint-Inhibitor alone

Chemotherapy + Checkpoint-Inhibitor

Checkpoint-Inhibitor alone

Combination of 2 Checkpoint-Inhibitors

Chemotherapy alone (poor comparator)

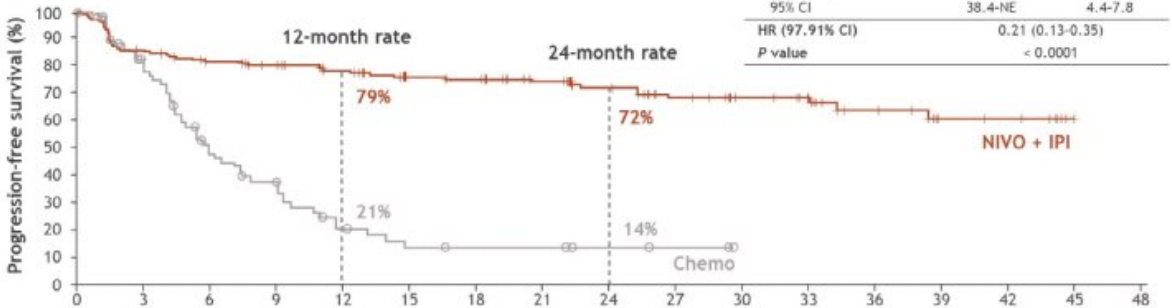
IPI + Nivo from Checkmate 8HW

ASCO Gastrointestinal Cancers Symposium

CheckMate 8HW: first results of 1L NIVO + IPI vs chemo

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	

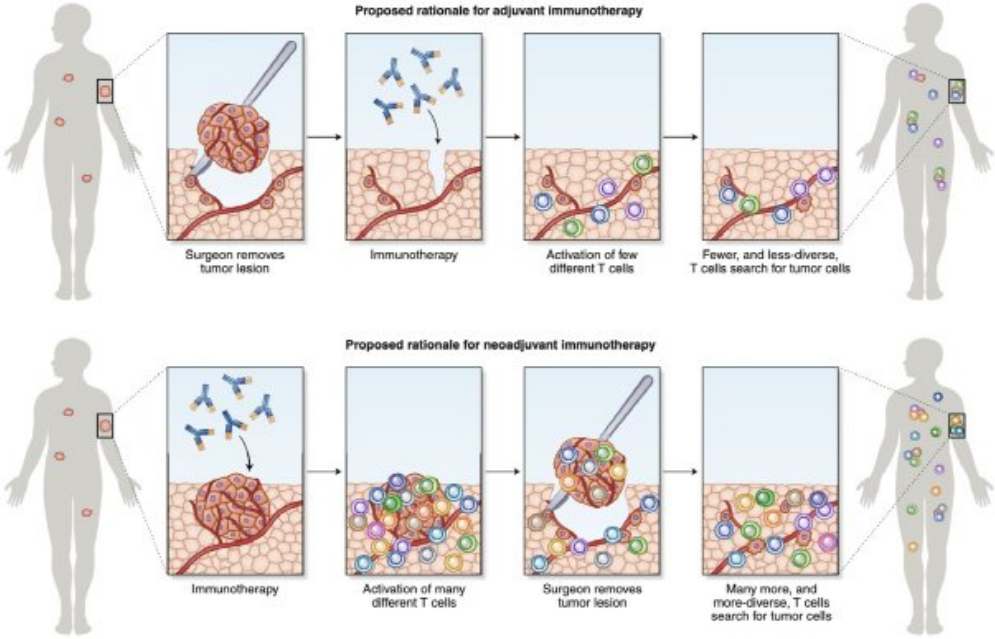


No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

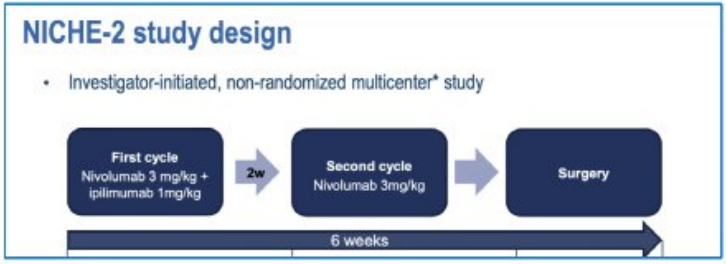
[a]Per BICR. [b]Median follow-up, 24.3 months.

Neoadjuvant treatment might be more potent than adjuvant



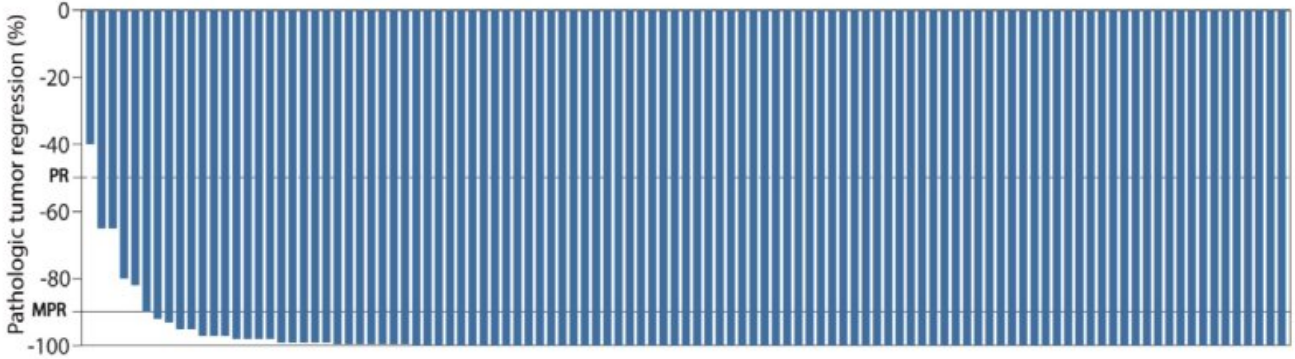
Versluis et al; Nat Medicine 2020

Neoadjuvant treatment in MSI-H CRC is highly effective



Grad 3/4 AES was observed in 3% (3/112 pts)

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



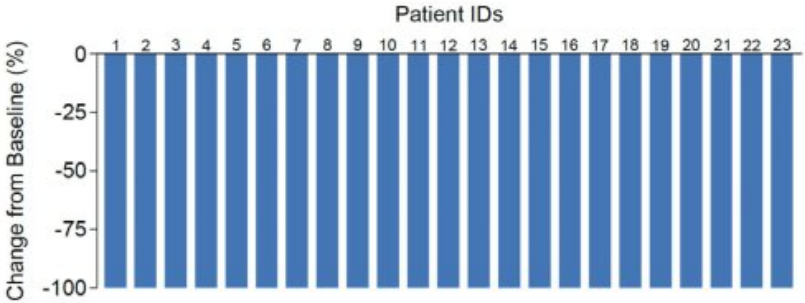
Chalabi et al. ESMO 2022

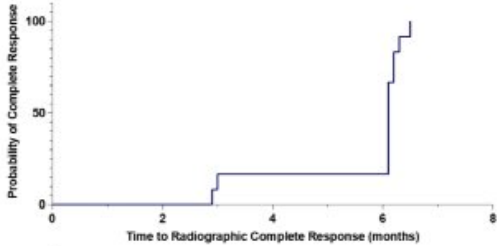
PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

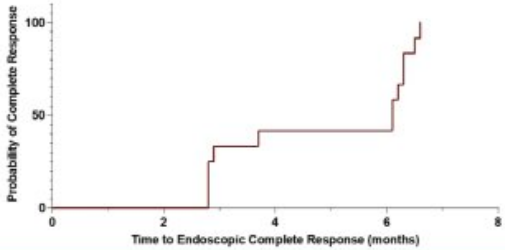
Cercek A et al NEJM 2022; Cercek A et al. JSMO 2023

Patients with stage II/III dMMR rectal cancer received 9 doses of a checkpoint-inhibitor (Dostarlimab)

Non-operative follow-up was done if complete response was detected, otherwise CRT → Surgery







23/23 patients achieved a complete response

Is durable disease control in check-point blockade responders reality?

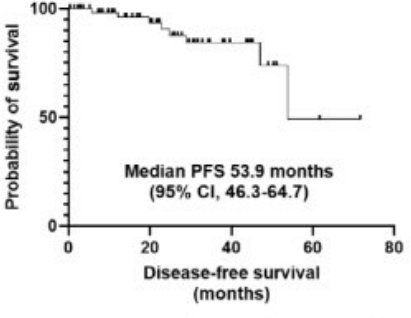
How long do we have to treat? What are the associated treatment costs?

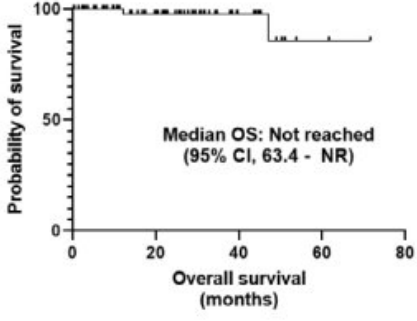
MD Anderson Cancer Center experience:

121 pts with MSI metastatic CRC received I-O therapy (2014-22)

64 pts (53%) had sustained response and I-O was stopped after 2 yrs

23 months after stopping: 56/64 pts had no disease recurrence





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Pembrolizumab 200 mg q 3 weeks for 2 years (36 treatments): 343.332 CHF (SL)

What is the future role of surgery in patients with MSI-H CRC and major response to checkpoint-inhibitor therapy?

We need to learn together how to integrate immuno-oncology into best practice

Long-lasting, complete remission was achived by treatment with an checkpoint-inhibitor (monotherapy). His tumor was MSI-H (Non-Lynch).

Conclusions

- MSI-H/dMMR is a distinct subtype of CRC based on many multiple features.
- Frequency is different according to tumor stage (15% in stage II-III/5% in stage IV) and localisation within the colorectum.
- MSI-H/dMMR is a very strong biomarker for the selection of immunotherapy.
- Immunotherapy is already standard of care in first-line treatment of MSI-H /dMMR CRCs.
- Promising phase II data suggest that immunotherapy will play a dominant role in the treatment of early stage MSI-H/ dMMR CRCs.
- The future role of surgery and radiotherapy remains to defined if major remission is achieved by immunotherapy.
- New treatment options (e.g. new combinations, bispecific mAbs…) will emerge.