HNPCC *25th Anniversary* annual meeting

October 13, 2016

Auditorium 1, Hvidovre Hospital

Forsknings- og Undervisningsbygningen

Impact of mismatch repair deficiency in the systemic treatment of colorectal cancer

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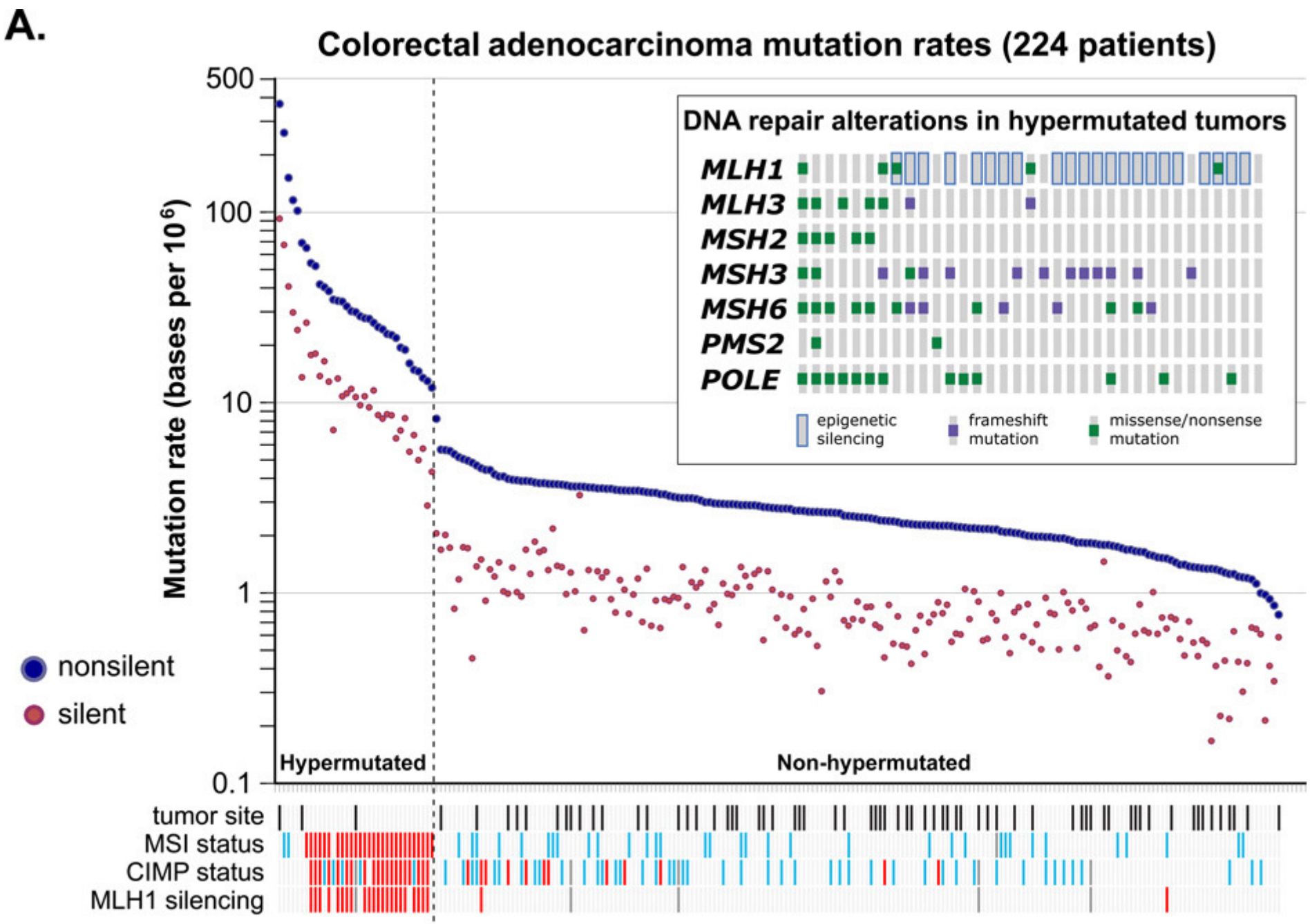
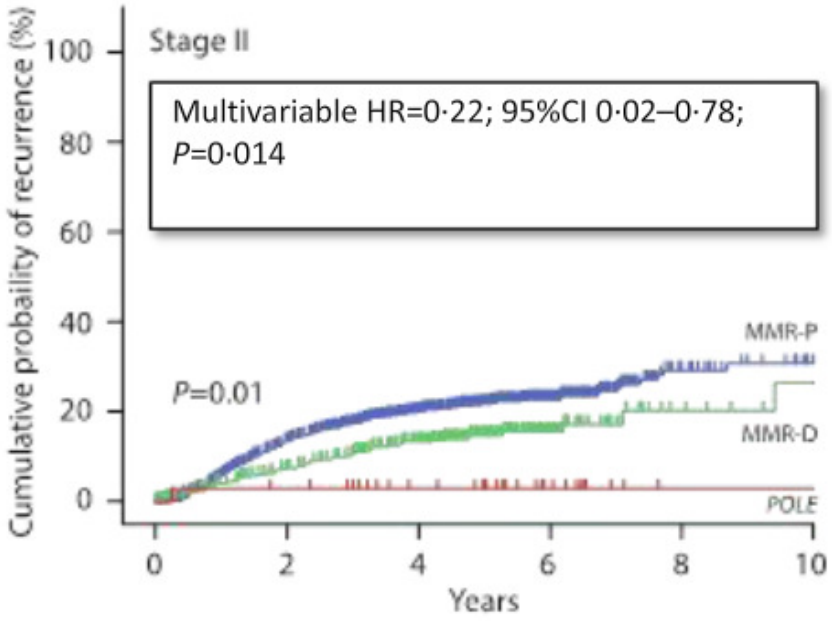
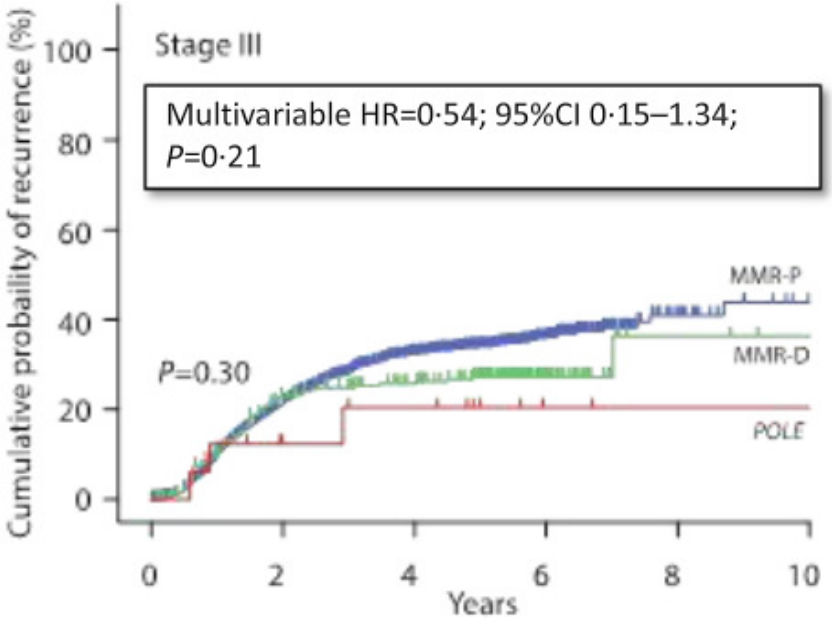


Nature. 2012 Jul 19; 487(7407): 330–337.

RESULTS – CRC RECURRENCE BY STAGE



No. at risk						
MMR-P	1735	1384	1074	268	58	38
MMR-D	426	357	286	70	17	12
POLE	34	32	24	10	1	1

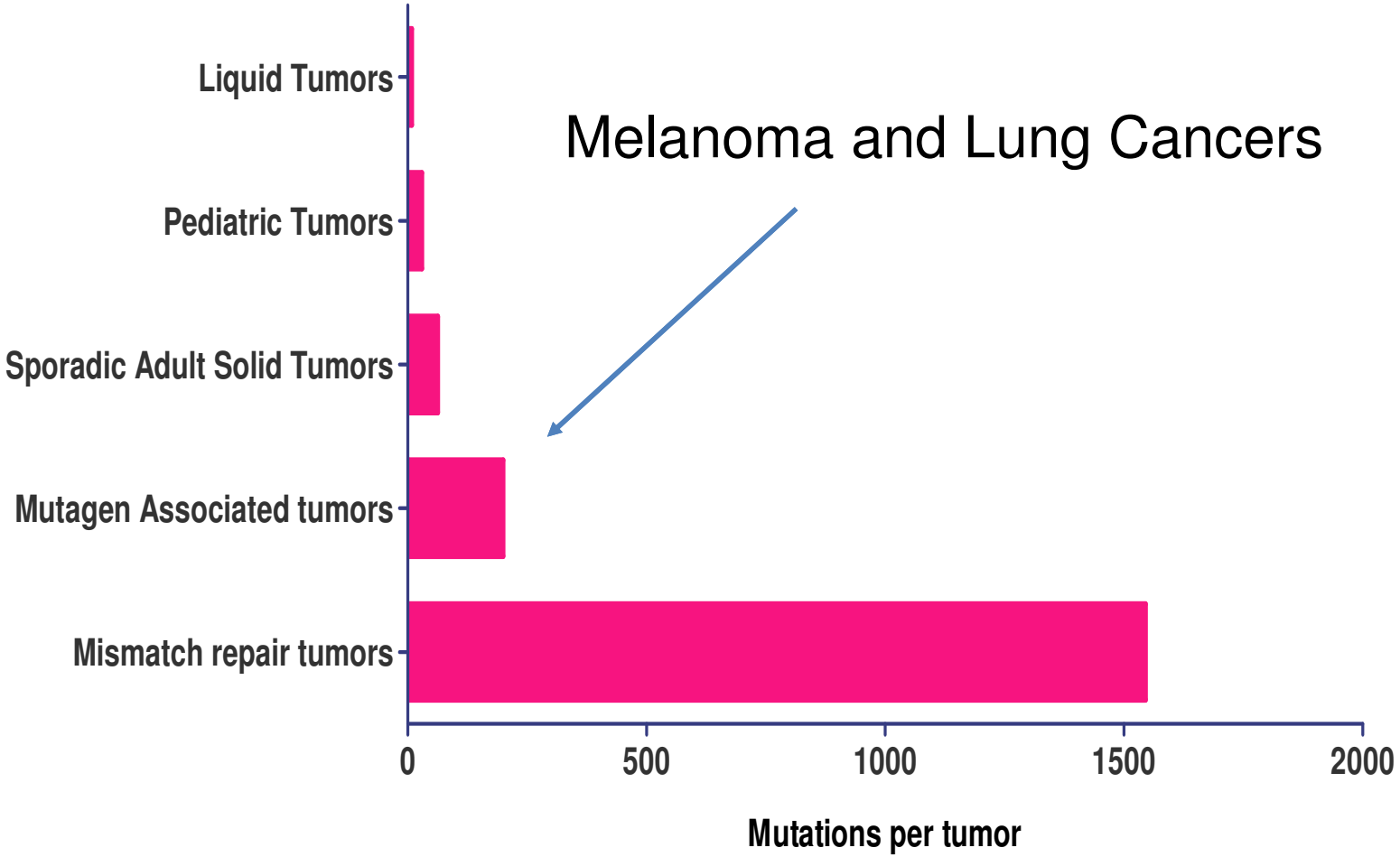


	2170	1602	1181	243	32	14
	263	189	157	30	4	2
	16	11	9	2	1	1

ESMO congress COPENHAGEN 2016

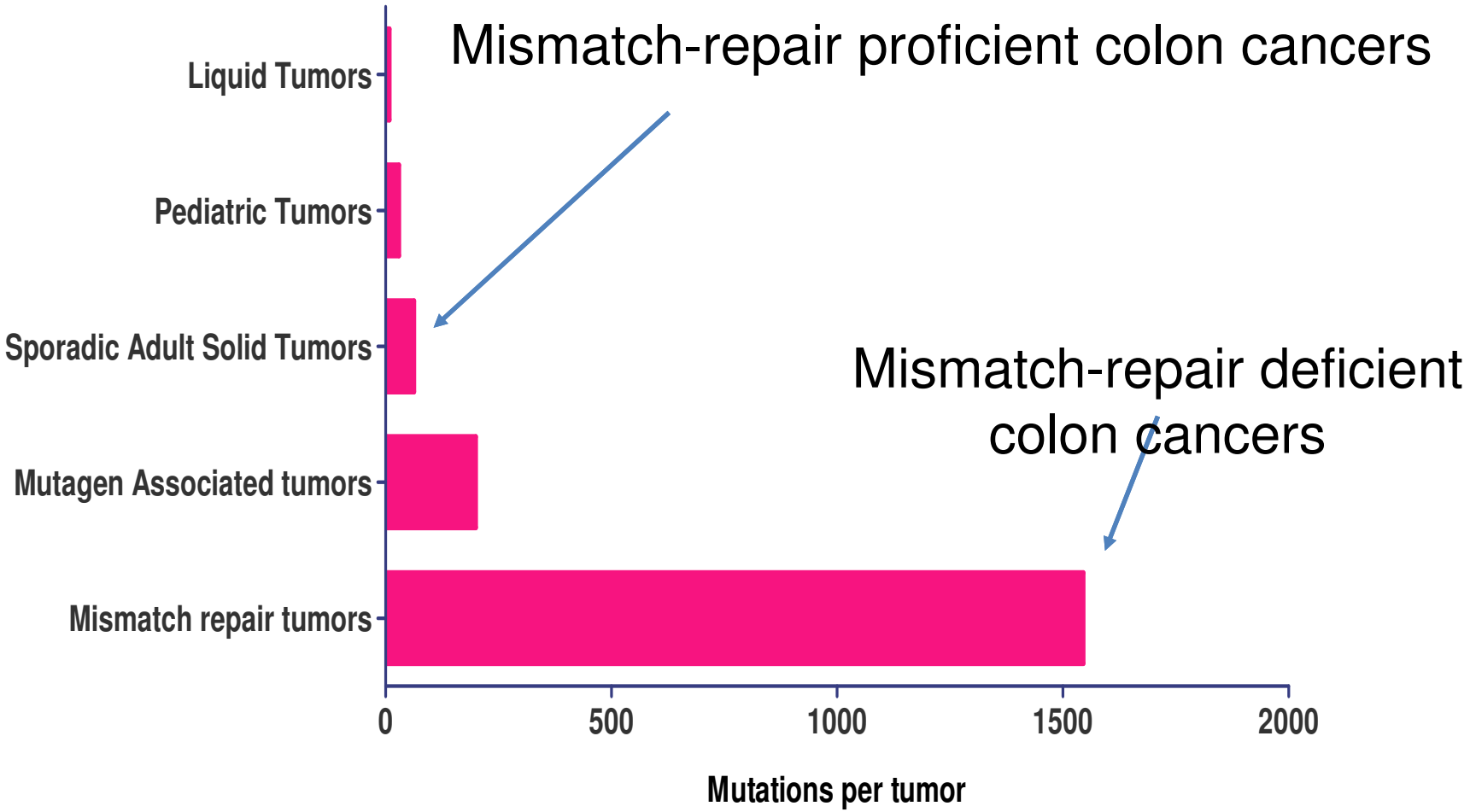
Domingo et al. *Lancet Gastro & Hepatology*, 2016

Mutations per tumor



ASCO 2015 & N Engl J Med May 30 2015

Mutations per tumor



ASCO 2015 & N Engl J Med May 30 2015

Hypothesis

- Mutations have been shown to encode proteins that can be recognized and targeted by the immune system
- Average tumor has dozens of somatic mutations; Mismatch repair deficient tumors harbor thousands of mutations
- Immune augmentation with PD-1 blockade may be highly effective in mismatch repair deficient tumors

ASCO 2015 & N Engl J Med May 30 2015

Mismatch Repair Deficiency

Microsatellite instability in tumor cells is due to deficient DNA mismatch repair:

- **germline** (Lynch syndrome) and/or **sporadic** mutations (MLH1, MSH2, MSH6, PMS2, EpCAM)
- **epigenetic silencing** (MLH1 hyper-methylation)

Study Design

Colorectal Cancers

Cohort A
Deficient in Mismatch Repair (n=25)

Cohort B
Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

Cohort C
Deficient in Mismatch Repair (n=21)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate

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Objective Responses (Sept 2015, N=63)

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	20	25	18
Objective Response Rate	55%	0%	55%
Disease Control Rate	90%	16%	72%

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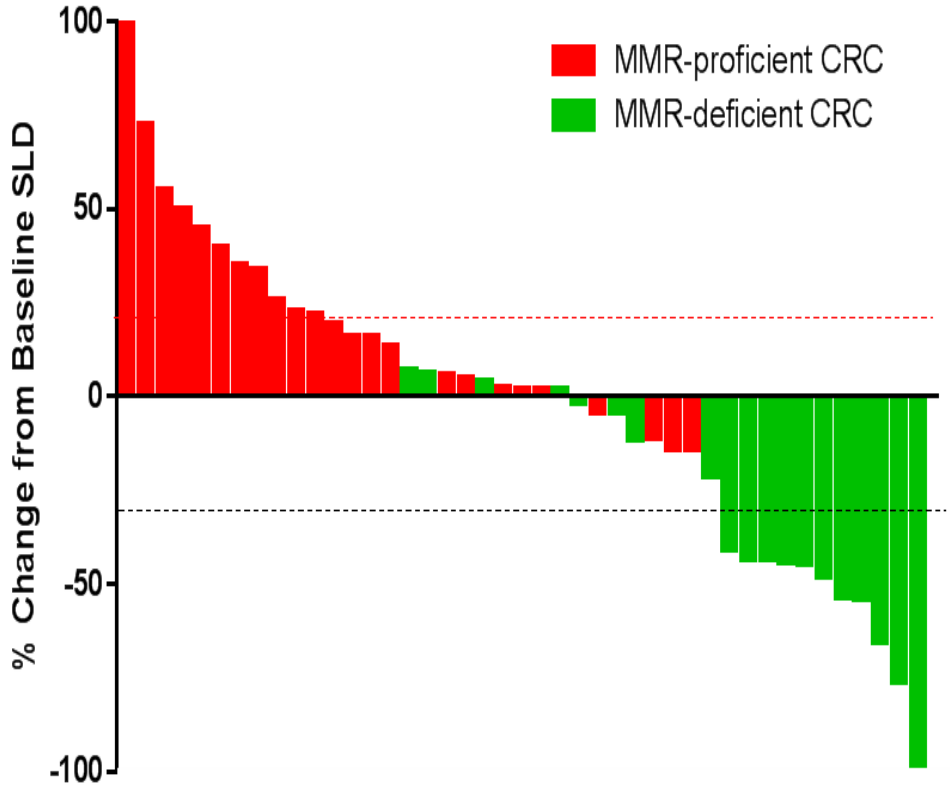
Target Lesions: CRC Cohorts



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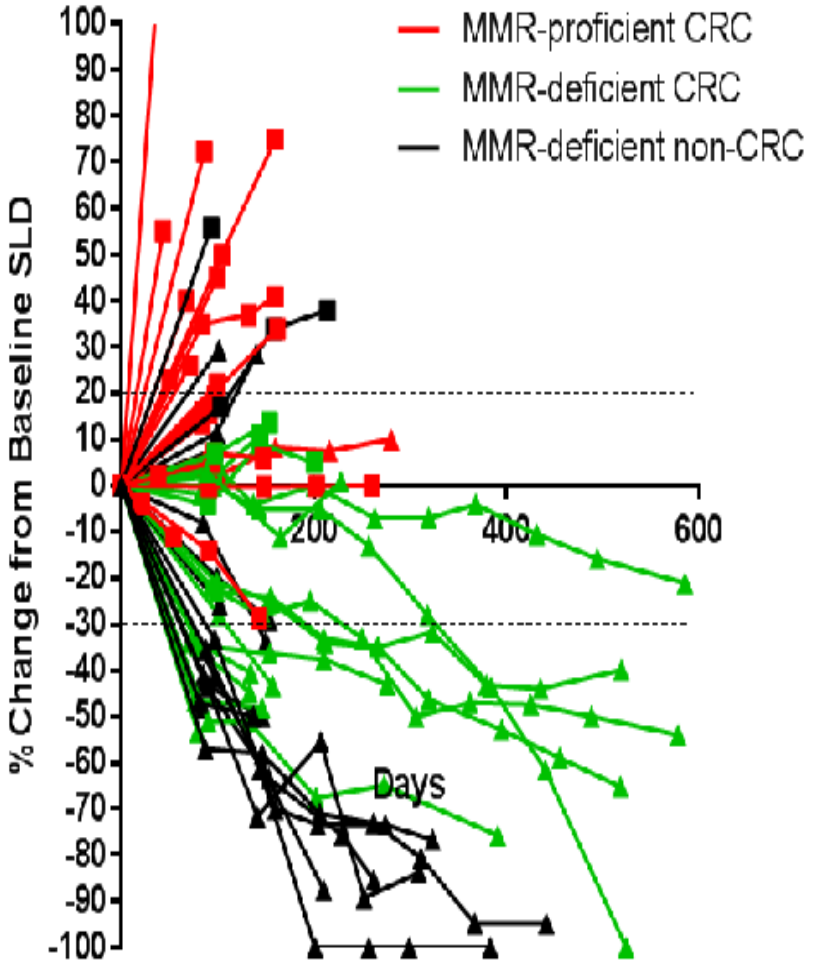
Duration of Response



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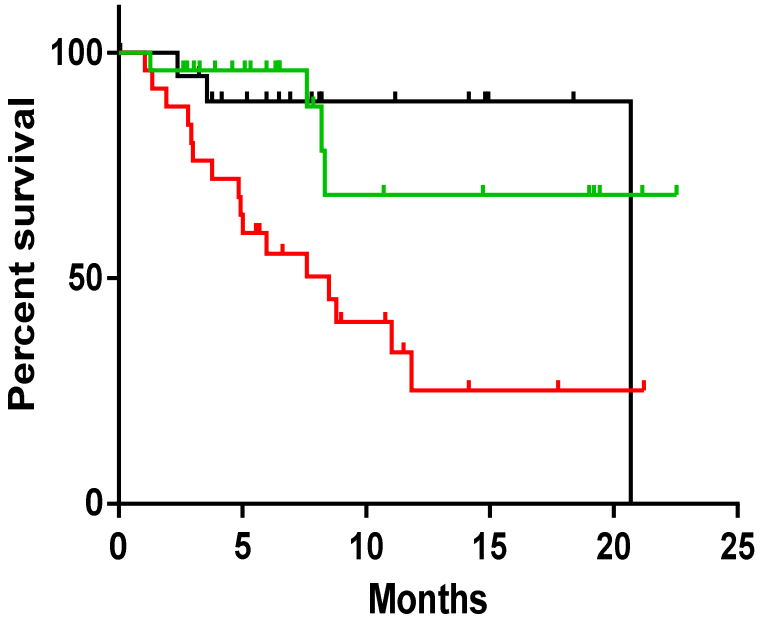
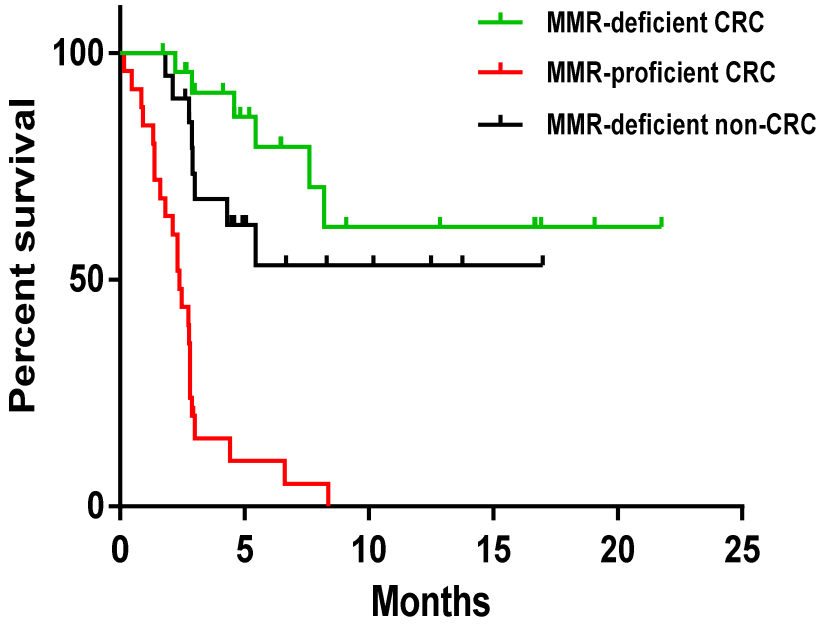
Surival Curves (October 2015)



Overall Survival



Progression-Free Survival

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Keynote 177

Study Treatment

Keynote 177

Pembrolizumab Arm

- Pembrolizumab 200 mg IV Q3W

Standard of Care Arm

- Investigator's choice of one of the following Q2W:
  - mFOLFOX6
  - mFOLFOX6 + bevacizumab
  - mFOLFOX6 + cetuximab
  - FOLFIRI
  - FOLFIRI + bevacizumab
  - FOLFIRI + cetuximab

Keynote 177

- First-line treatment
- Immunohistochemistry or DNA MSI
- Essential to identify patients at the MDT conference
- Herlev
- Odense
- Vejle

Take home

- Immunotherapy - a revolution for the one in twenty patients with metastastic dMMR colorectal cancer
- Be aware of both sporadic cases and Lynch Syndrome patients – the possibility of trials
- Pathologists identifies the patients
- MDT conferences

Future perspective (hope)