Immunotherapy in Colorectal Cancer

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CCC MÜNCHEN
COMPREHENSIVE
CANCER CENTER

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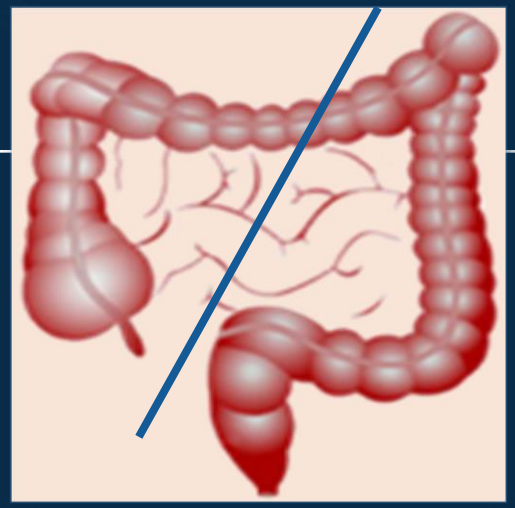
Distinct Molecular Biology in Right- vs. Left-Sided Tumors

Right Colon
20–40%

- Lower incidence
- More female
- Higher TMN
  larger tumors
  more mucinous
- Stronger immunogenicity
- Predominantly CIMP, MSI, BRAF
- Poor survival

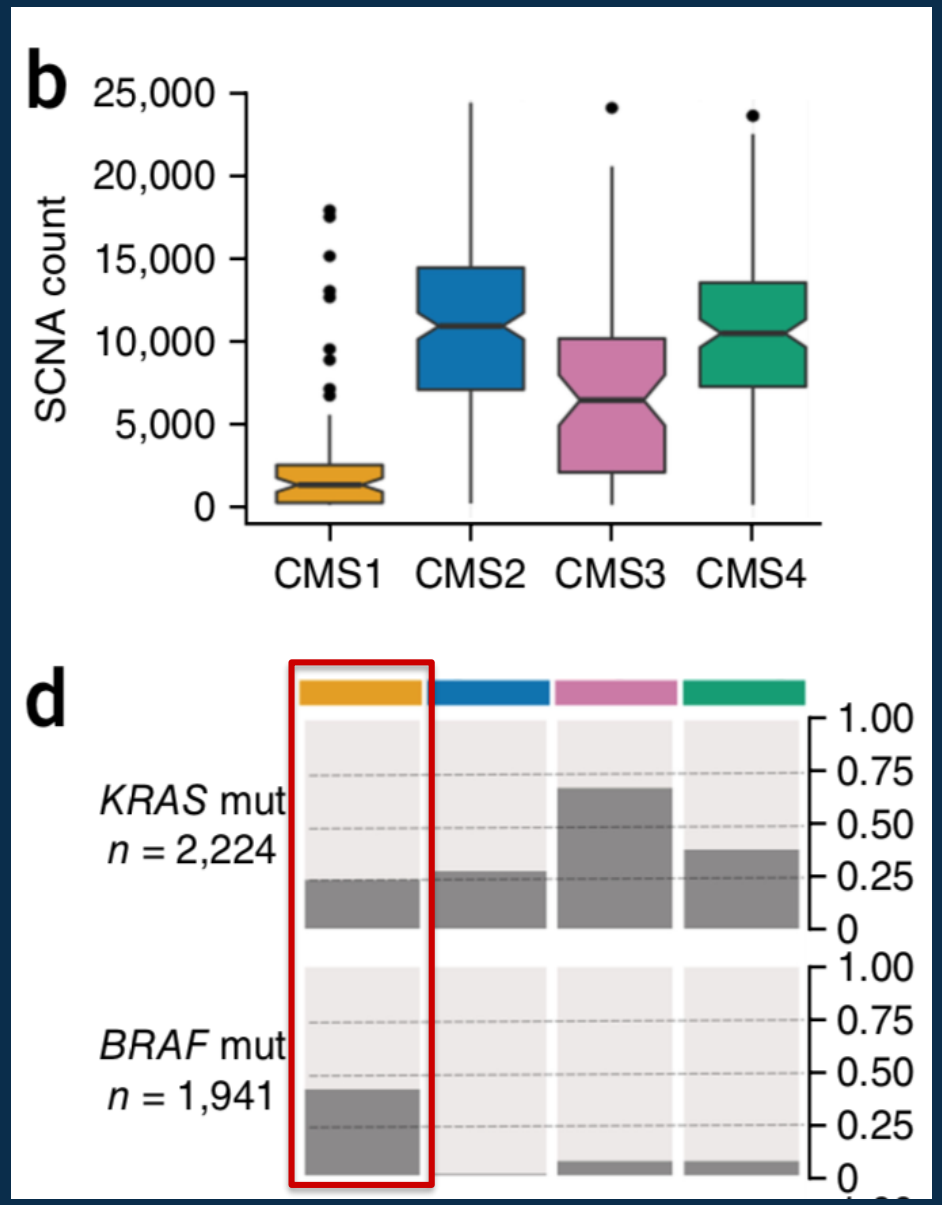


Left Colon + Rectum
60–80%

- More frequent
- More male
- Lower TNM
  smaller tumors
- Less immunogenic
- Predominantly chromosomal instability
- Better survival

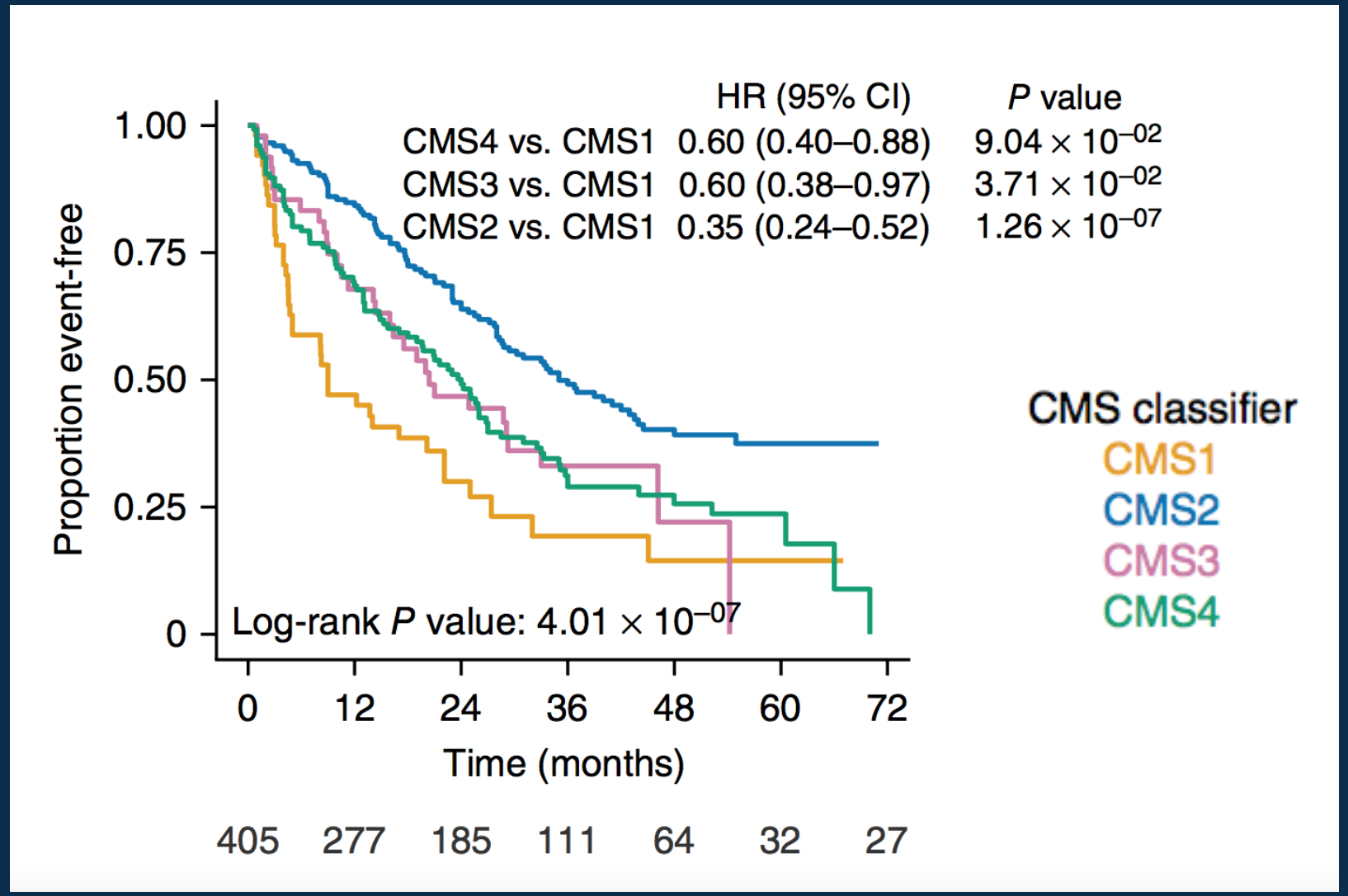
RAS mutation according to CMS subtype

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations	*KRAS* mutations		
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

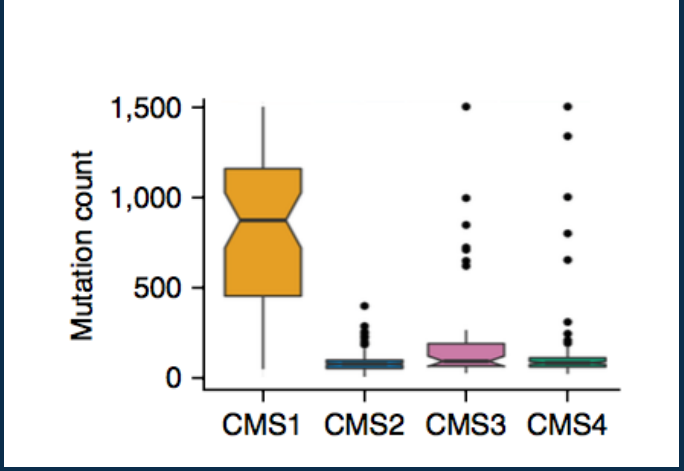


Guinney J, et al. Nature Med. 2015

Survival after relapse according to CMS subtype

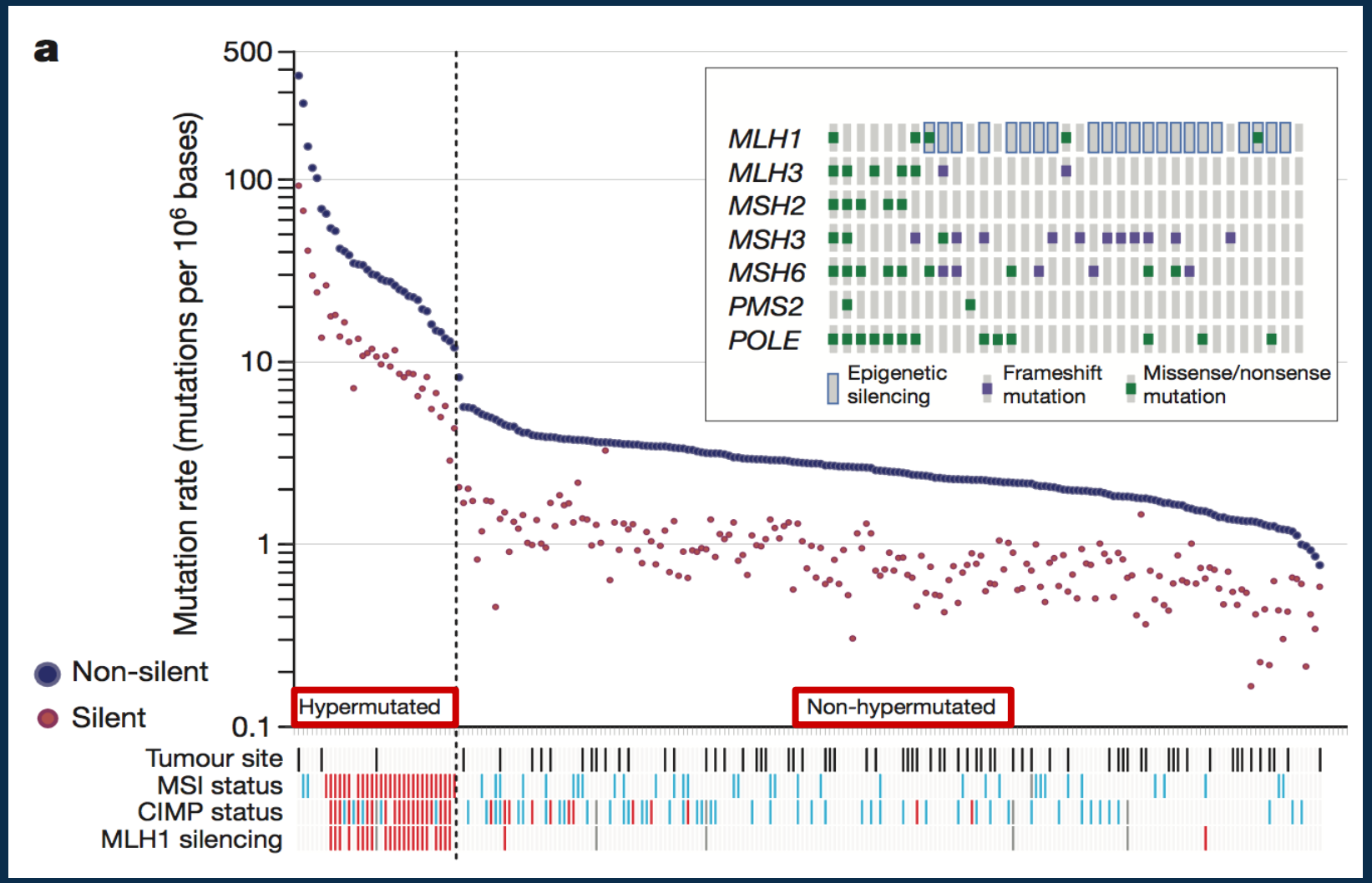


- **Best outcome in CMS2**
- **Worst outcome in CMS1**



Guinney J, et al. Nature Med. 2015

Hypermutated versus non-hypermutated CRC

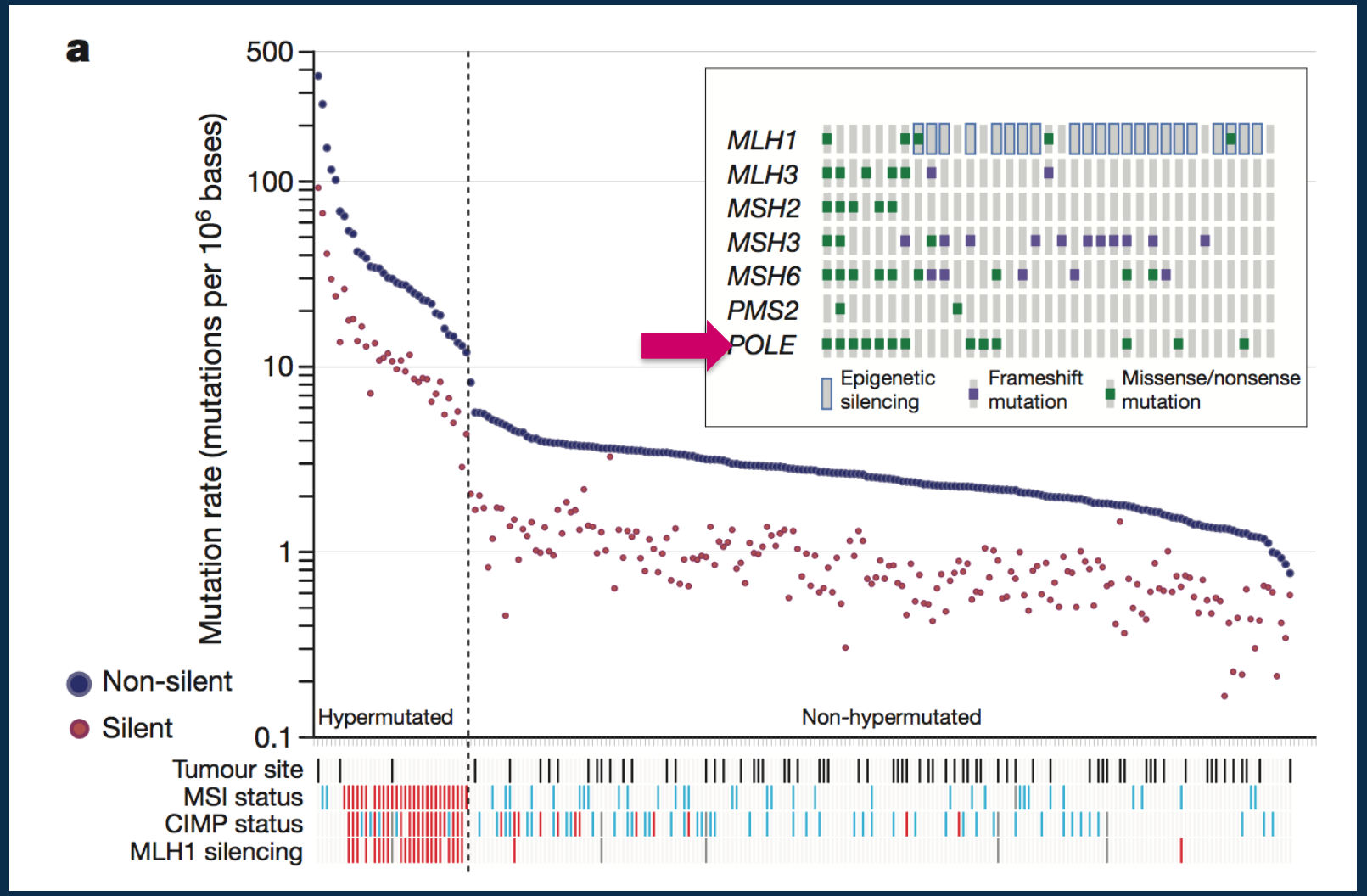


16% of CRCs hypermutated

- 75% MSI-high, usually with hypermethylation and MLH1 silencing

TCGA Nature 2012

POLE mutation associated with hypermutation

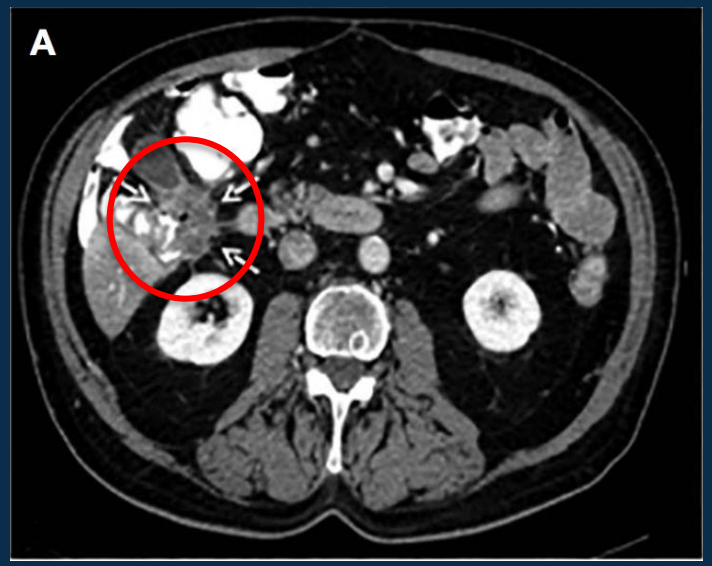


- 16% of CRCs hypermutated
  - 75% MSI-h, usually with hypermethylation and MLH1 silencing
- **Prevalence of a. 1%**
- POLE mutations are associated with ultramutated, but microsatellite-stable (MSS) phenotype

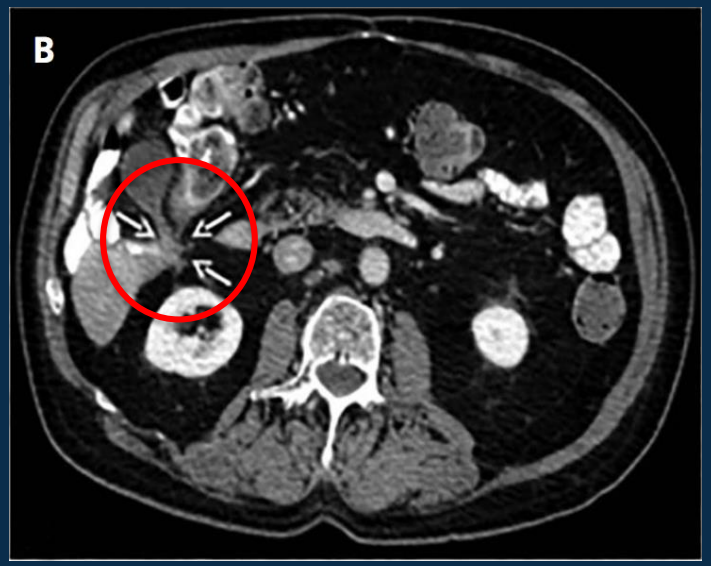
TCGA Nature 2012

POLE mutation: response to PD-1 inhibition

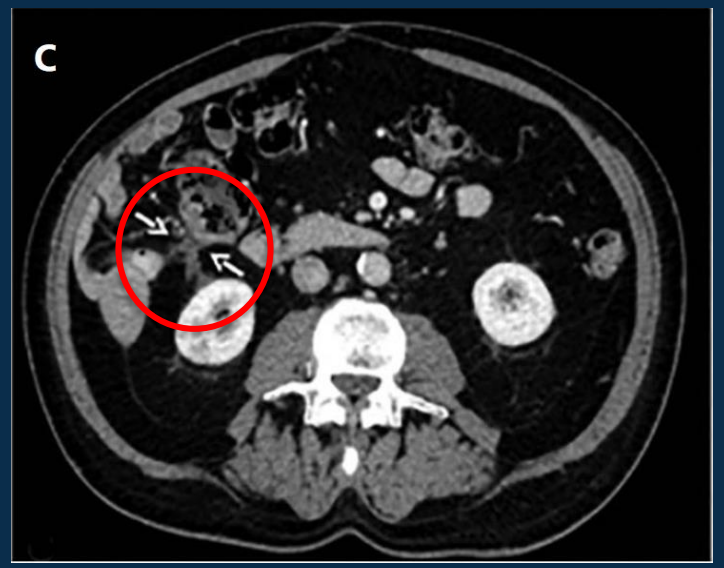
Before treatment



After 3 cycles Pembrolizumab



After 6 cycles Pembrolizumab



81 year old patient with recurrent right-sided colon cancer;

NGS-based analysis (FMI): TMB high (**122** mutations/megabase)

and $POLE^{V411L}$ mutation

Gong J, JNCCN 2017

Tumor mutational burden

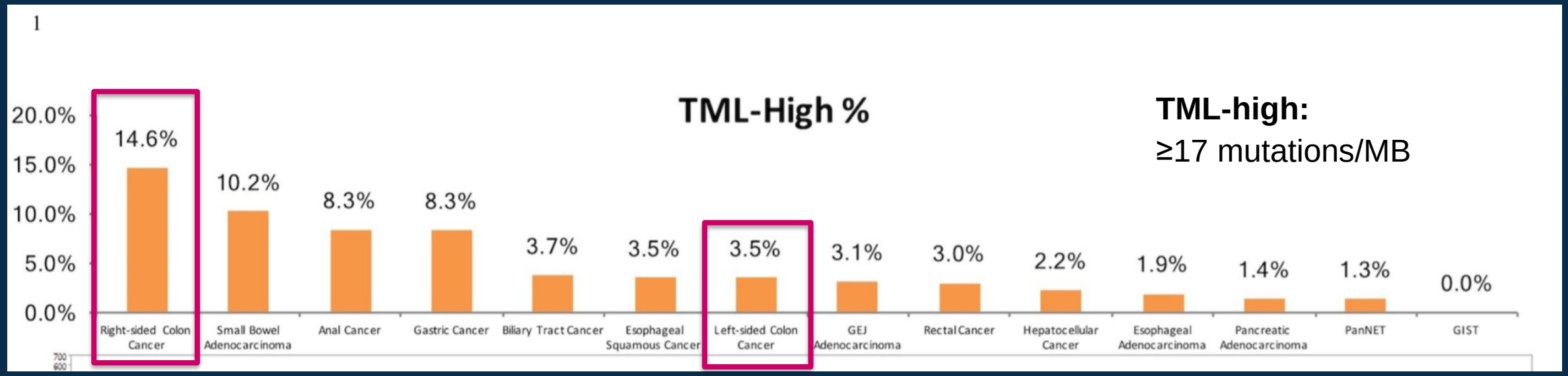
Determined by NGS-based panel sequencing

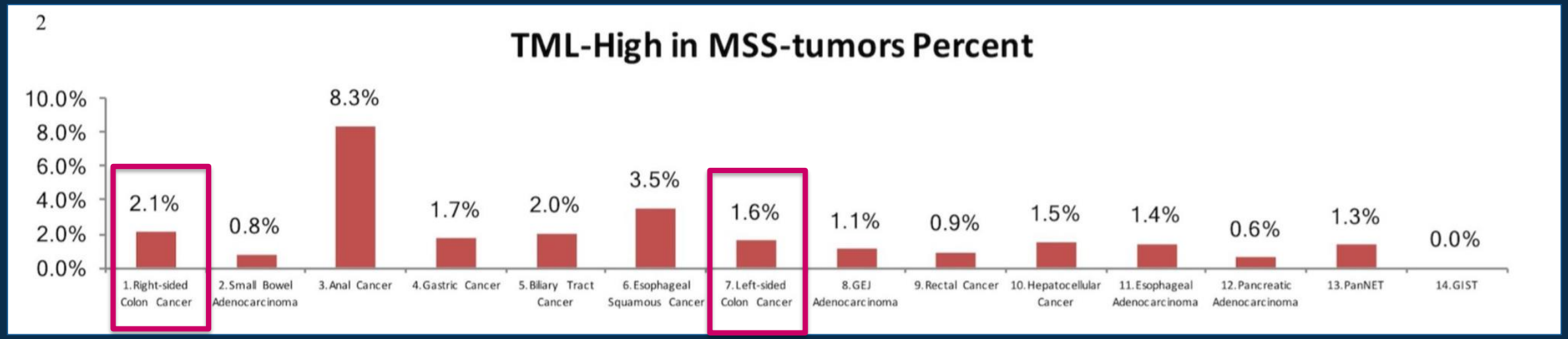
Efficacy of CPI according to TML

Correlation between Tumor Mutational Load and ORR with Anti–PD-1 or Anti–PDL1 therapy in 27 tumor types

Yarchoan NEJM 2017

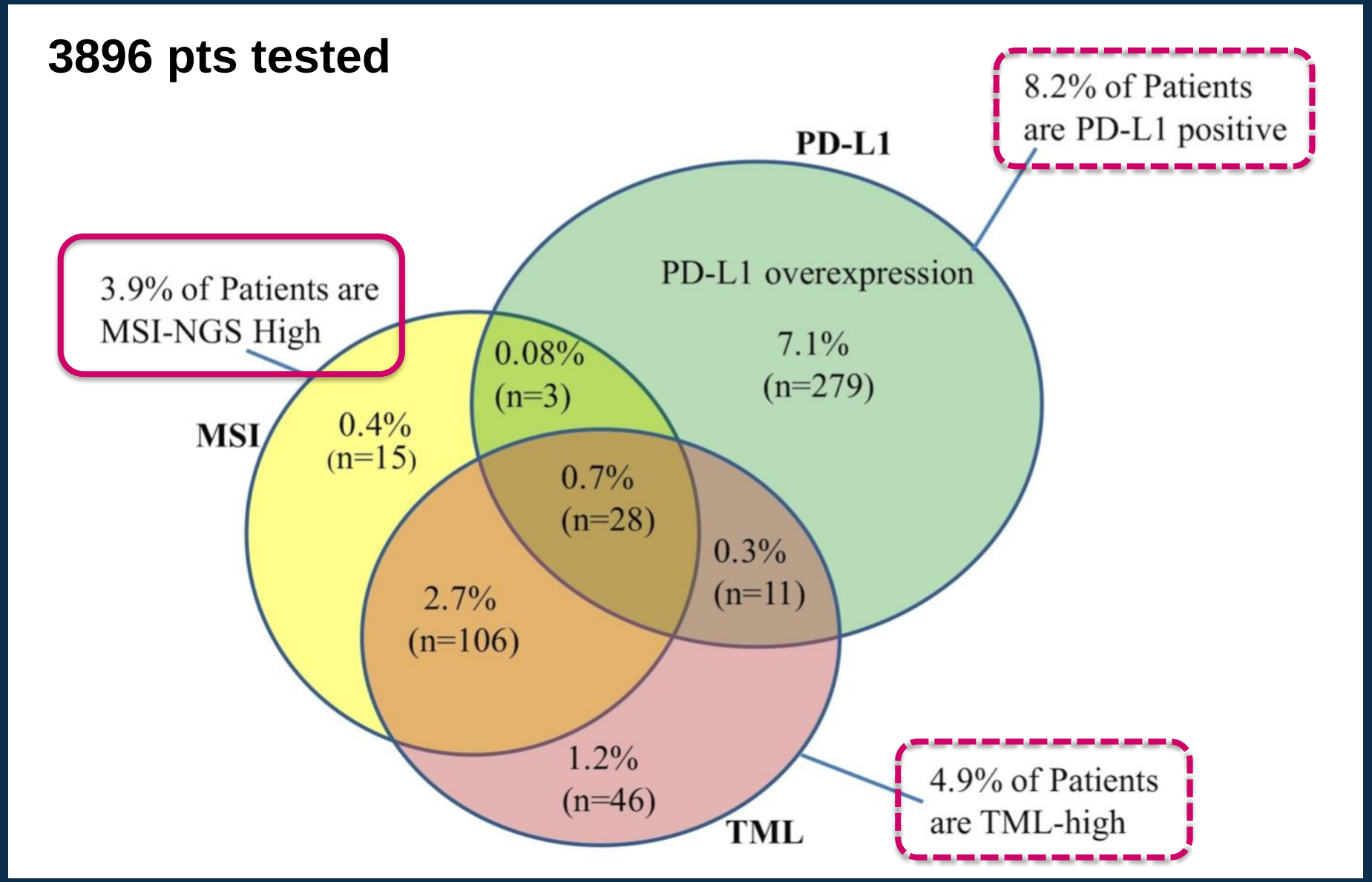
TML distribution across 14 gastrointestinal cancer types





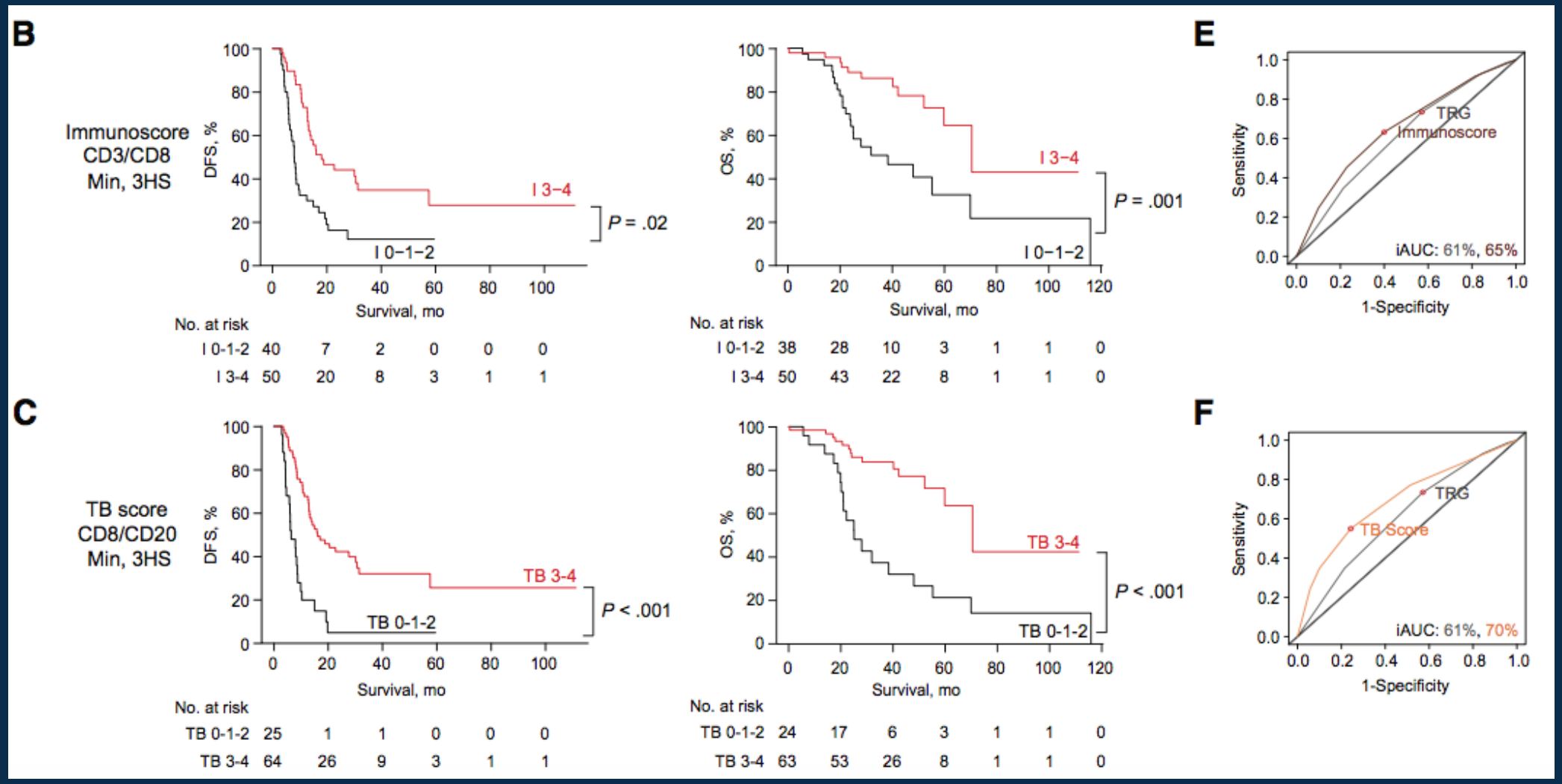
Salem Mol Cancer Res 2018

TML, MSI and PDL-1 in 14 different GI cancer sites



Salem Mol Cancer Res 2018

Immunoscore correlates with DFS and OS in mCRC



Evaluation of **153 mCRC** patients after complete resection of 441 metastases: evaluation of immune infiltration of metastases in relation to DFS and OS

Mlecnik B…Galon J, JNCI 2018

Prediction of response to check-point inhibitors

Parameter	Prediction of response to CPI
MMRd (MSI-high)	upfront determination recommended
POLE mutation	rare (1%), predicts response to CPI
Tumor mutational load (TML)	additional relevance unclear
PD-L1	does not predict response to CPI
Immunoscore	prognostic relevance

Immunotherapy in mCRC

MSI high predicts response to check-point inhibitors

PD-L1 expression is not a predictor

Keynote 016: Pembrolizumab in MMRd CRC

Study Design

Colorectal Cancers

Cohort A
Deficient in Mismatch Repair (n=28)

Cohort B
Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

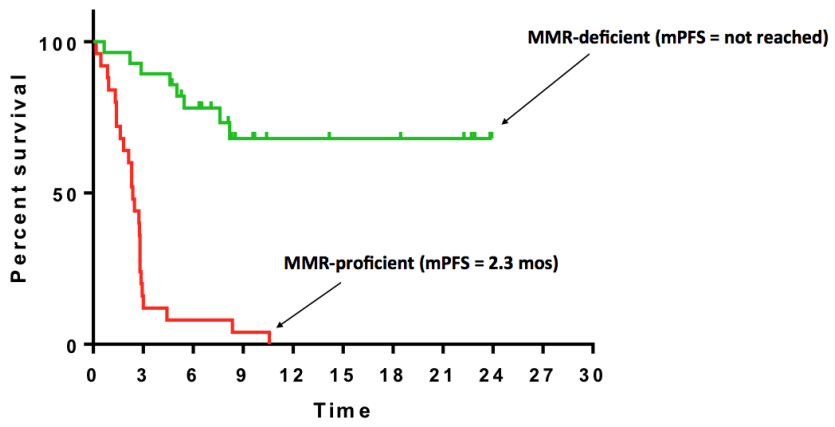
Cohort C
Deficient in Mismatch Repair (n=30)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Here we report and update from the original 13 CRC Cohort A patients reported at ASCO 2015

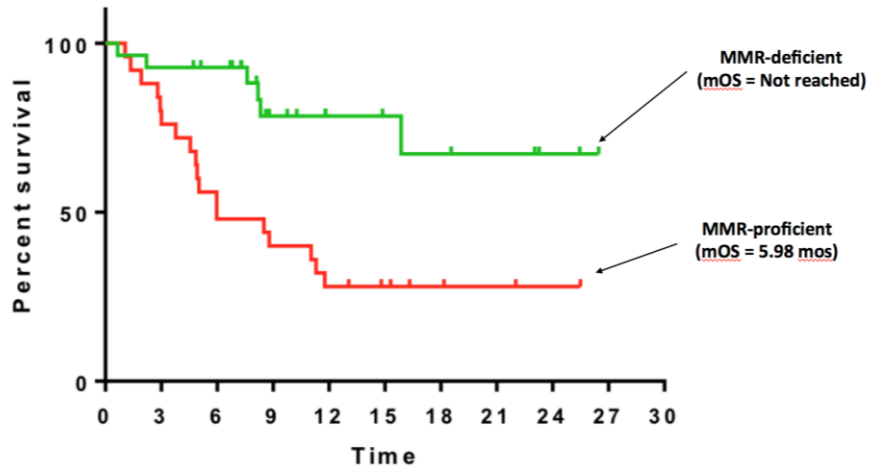
Study Summary

Type of Response-no (%)	MMR-deficient CRC n=28	MMR-proficient CRC n=25
Objective Response Rate (%)	57%	0%
Disease Control Rate (%)	89%	16%
Progression-free Survival (mos)	Not Reached	2.3
Overall Survival (mos)	Not Reached	5.98

Progression-free Survival



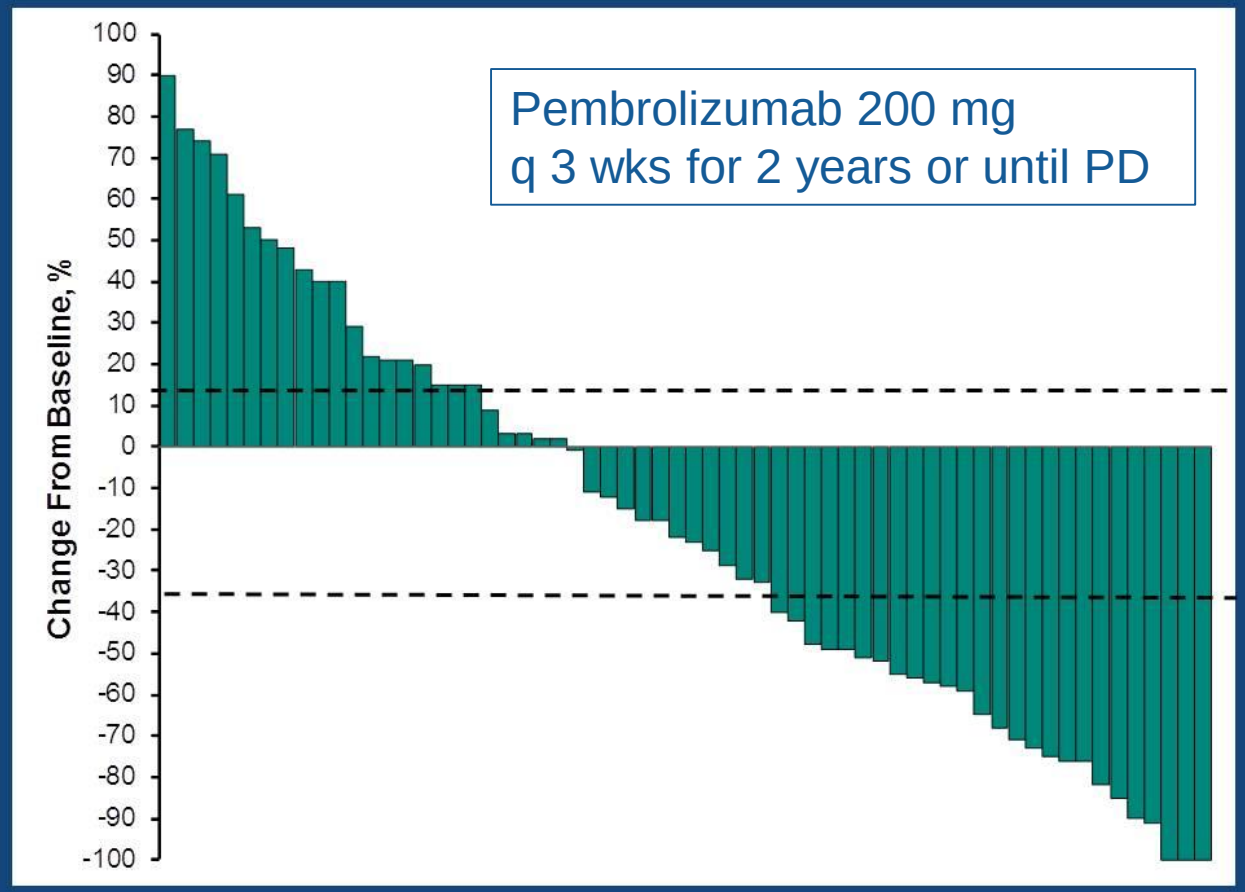
Overall Survival



Dung T. Le, et al. ASCO 2016, #103

KEYNOTE 164: Chort B

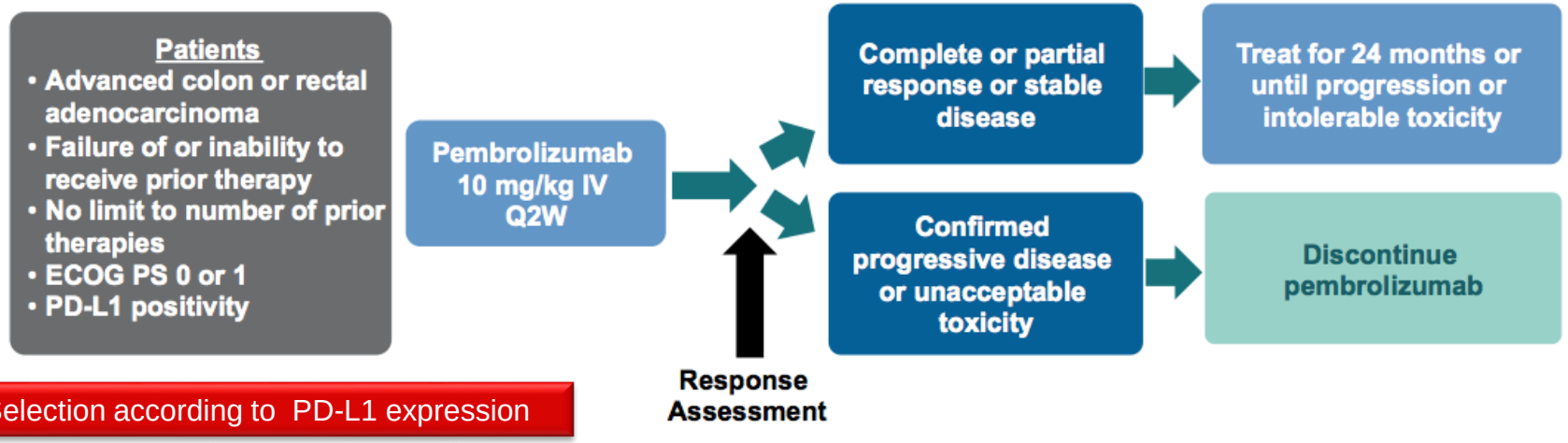
Best Percentage Change From Baseline in Target Lesion Size (RECIST v1.1)



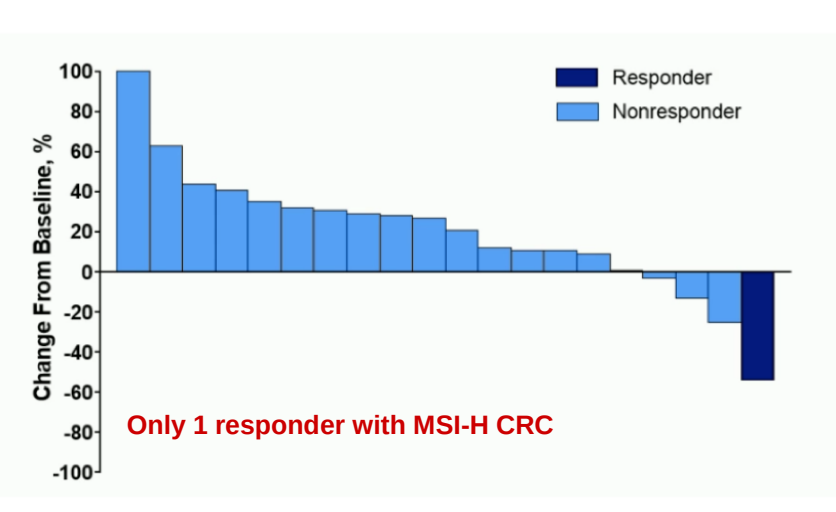
- Median duration of follow-up: 12.6 months (range, 0.1-15.4)
- ORR: 32% (95% CI, 21%-45%)
  - 2 CR, 18 PR
- Median duration of response: not reached (2.1+ to 13.2+ months)
  - 15 (75%) patients had duration of response ≥6 months

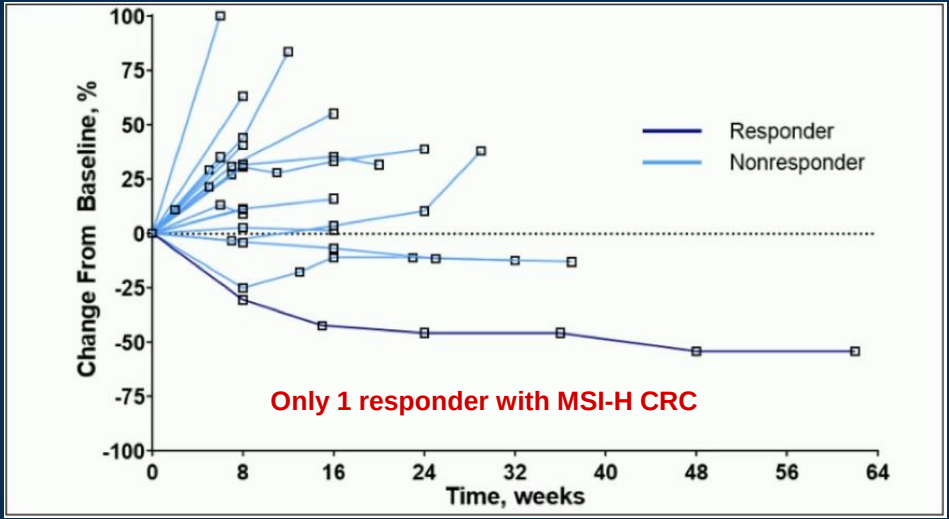
Le, KN164B, ASCO 2018

KEYNOTE-028: Phase 1b multicohort study of Pembrolizumab for PD-L1+ advanced CRC



Selection according to PD-L1 expression





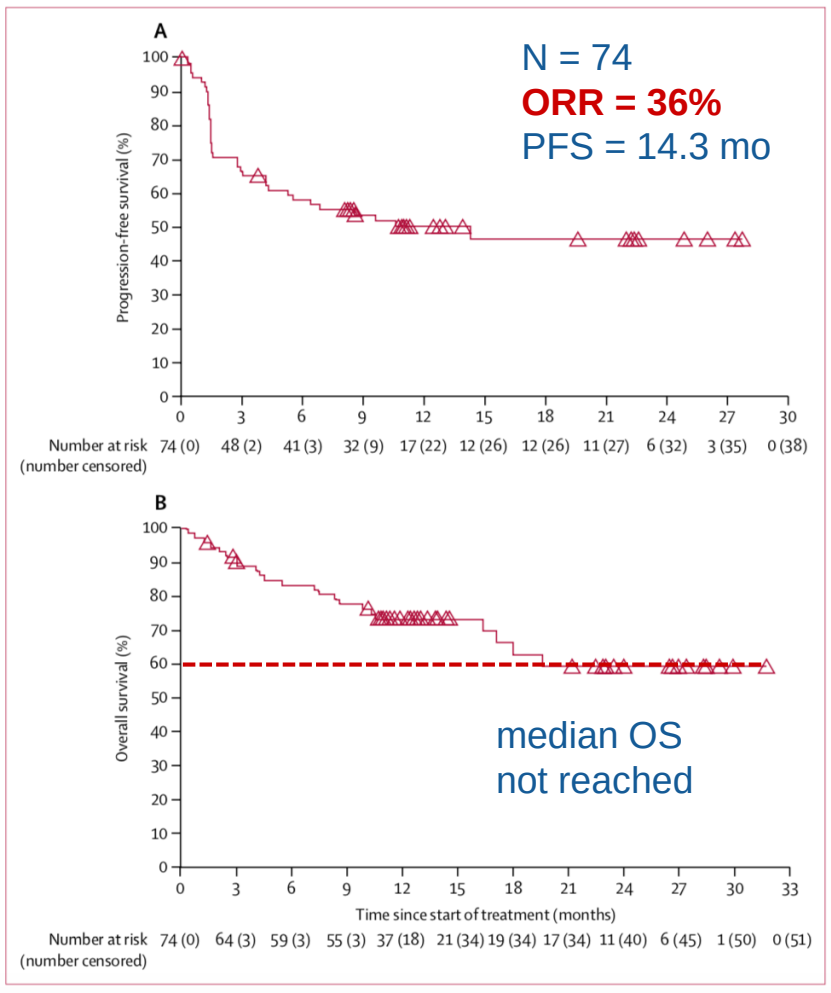
Conclusion

PD-L1 expression does not predict response to CPI

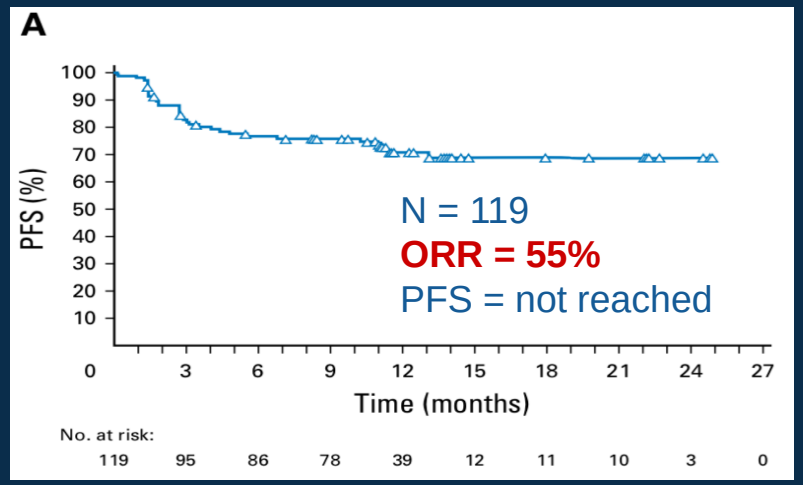
O'Neil et al, ESMO 2015 (Abstract #502)

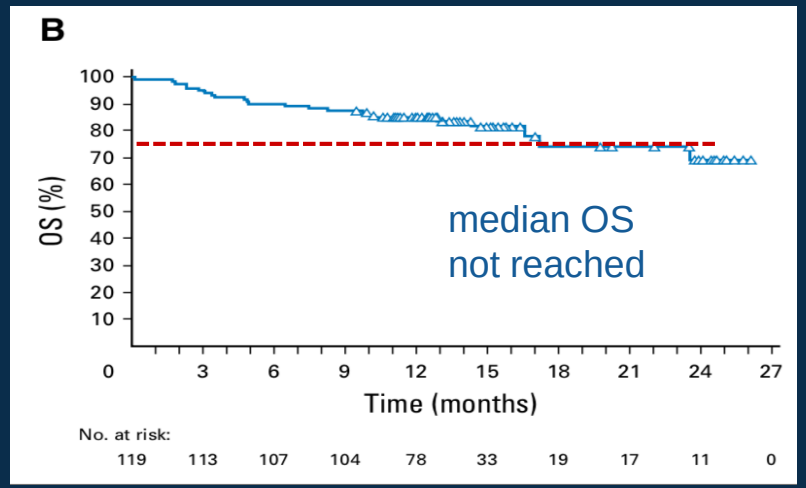
CheckMate 142: Nivolumab in MMRd mCRC

Nivolumab 3mg/kg



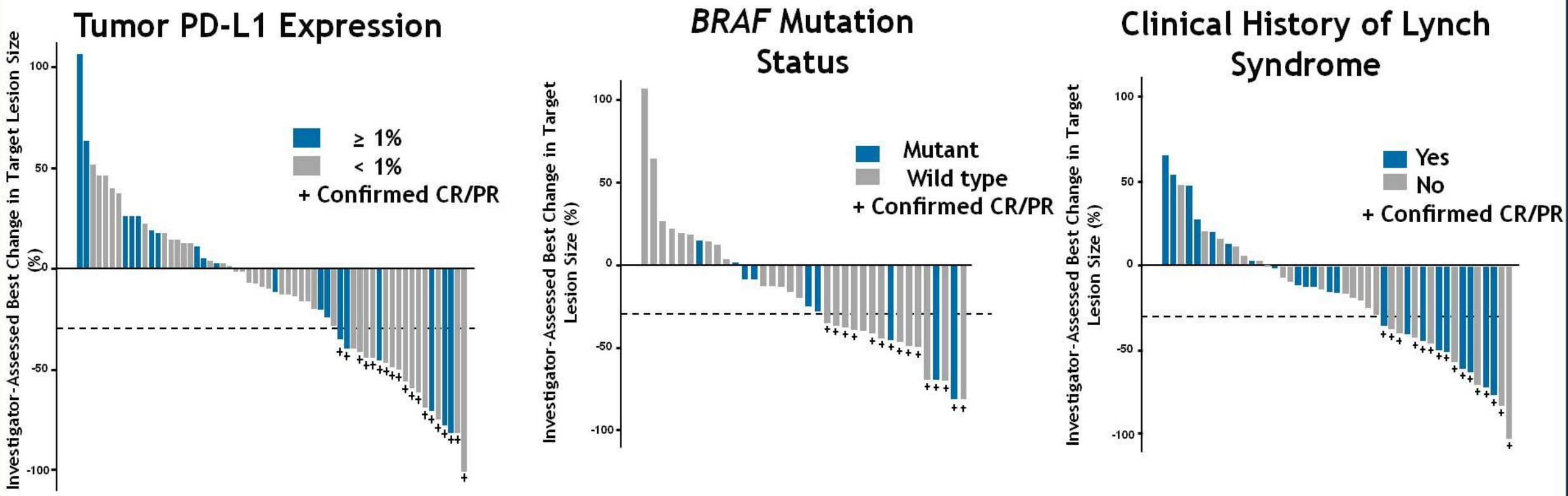
Nivolumab 3mg/kg + **Ipilimumab** 1mg/kg





Overman MJ, Lancet Oncol 2017
Overman MJ, JCO 2017

Reduction in Target Lesions Regardless of PD-L1 Expression, BRAF or Lynch History

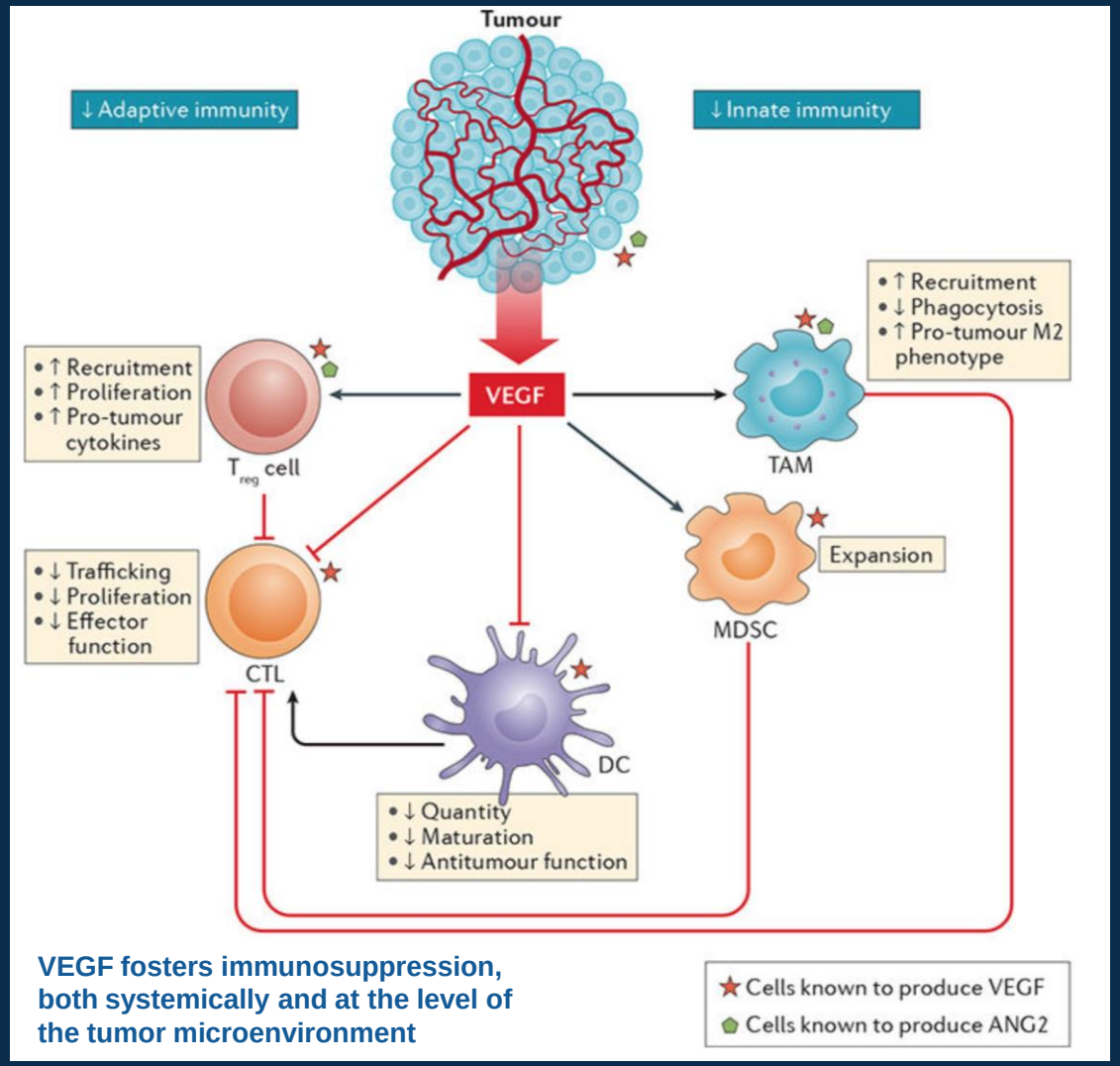


CheckMate 142

Overman et al. Lancet Onc 2017

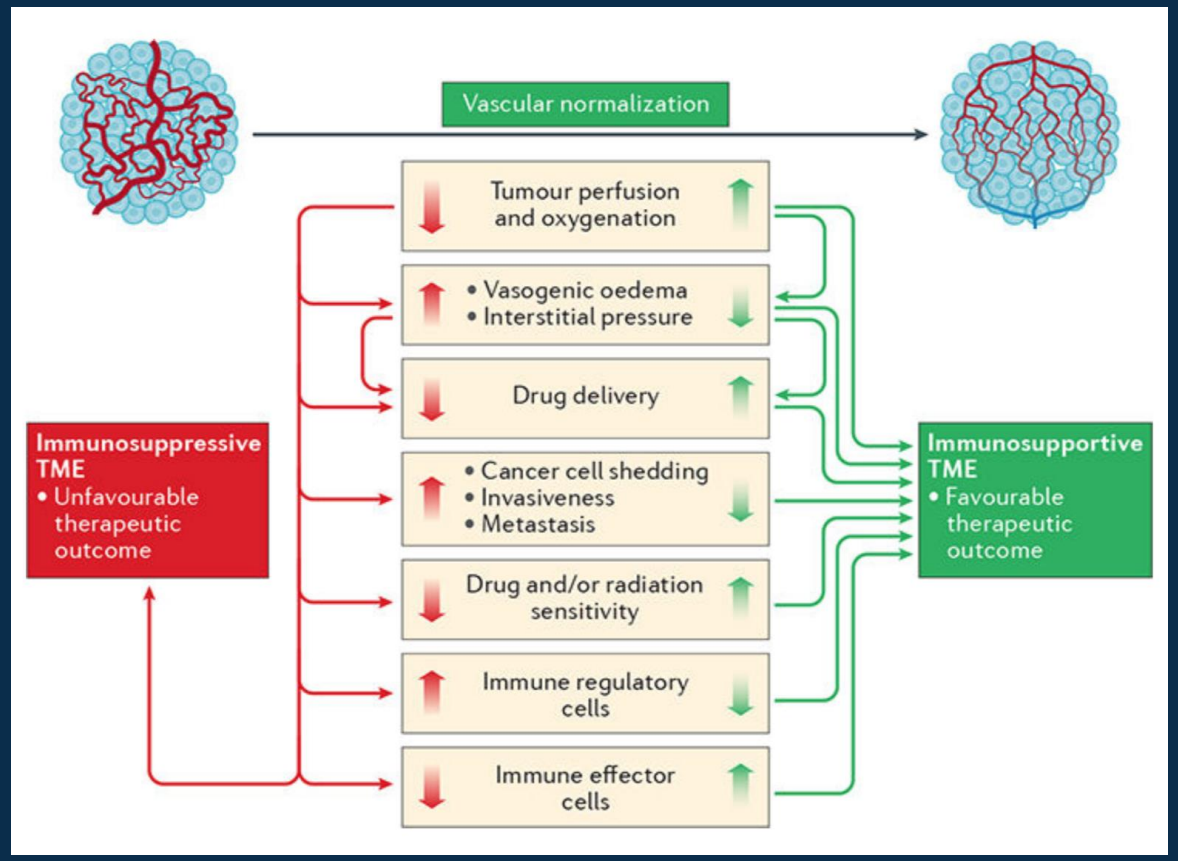
New avenues of CPI-based research

Hypothesis: abnormal tumor vasculature is associated with a decrease in innate and adaptive immunity



VEGF fosters immunosuppression, both systemically and at the level of the tumor microenvironment

Vascular normalization by use of anti-VEGF agents



Fukumura D, et al. Nat Rev Clin Oncol 2018

Combination of CPIs with Bevacizumab

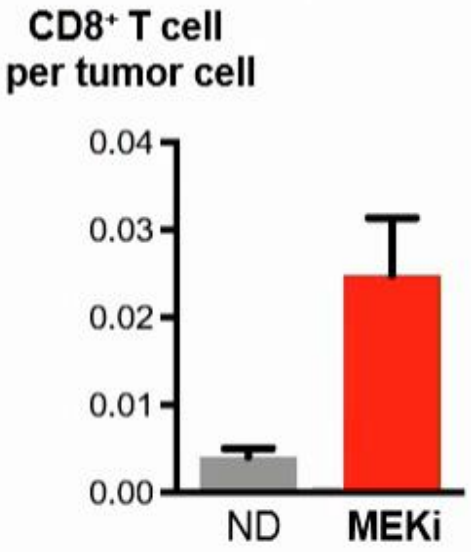
Study	Regimen	Target	Study population	Phase
CheckMate 9X8 (NCT03414983)	FOLFOX + **Bevacizumab** + **Nivolumab** vs FOLFOX + Bevacizumab	**PD1**	1st-line mCRC (MMR not specified)	Phase II/III
ElevatION (NCT03176264)	mFOLFOX6 + **PDR001 + Bevacizumab**	**PD1**	1st-line mCRC (pMMR)	Phase I
BACCI (NCT02873195)	Capcitabine + **Bevacizumab + Atezolizumab** vs Capecitabine + Bevacizumab	**PD-L1**	Refractory/ metastatatic CRC (MMR not specified)	Phase II

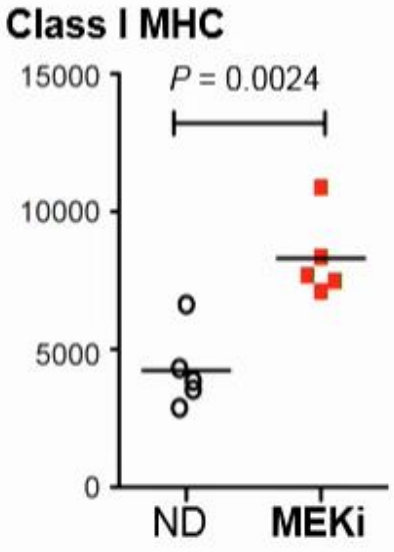
Synergistic interaction of CPI with bevacizumab in:
renal cancer and hepatocellular cancer

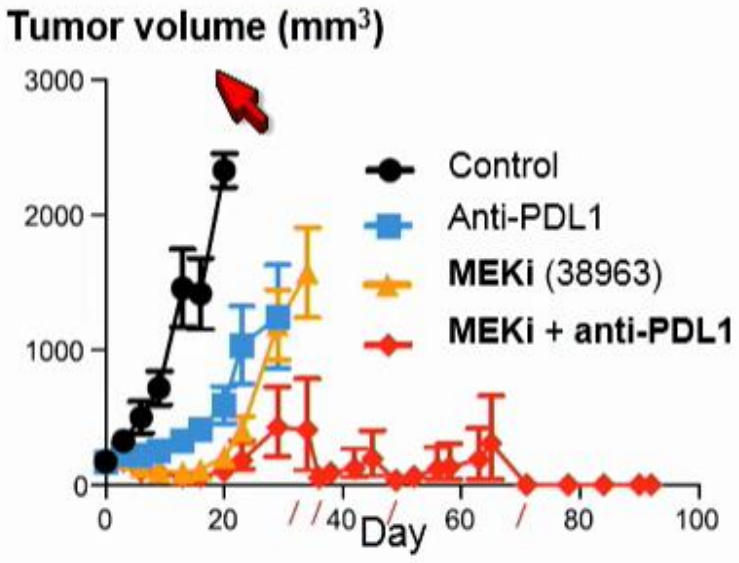
Modified according to Michael Morse ASCO 2018

PD-L1 and MEK Inhibition: A Rational Combination

- MEK inhibition alone can result in **intratumoral T-cell accumulation** and **MHC I upregulation**, and synergizes with an anti-PDL1 agent to promote **durable tumor regression**[1]





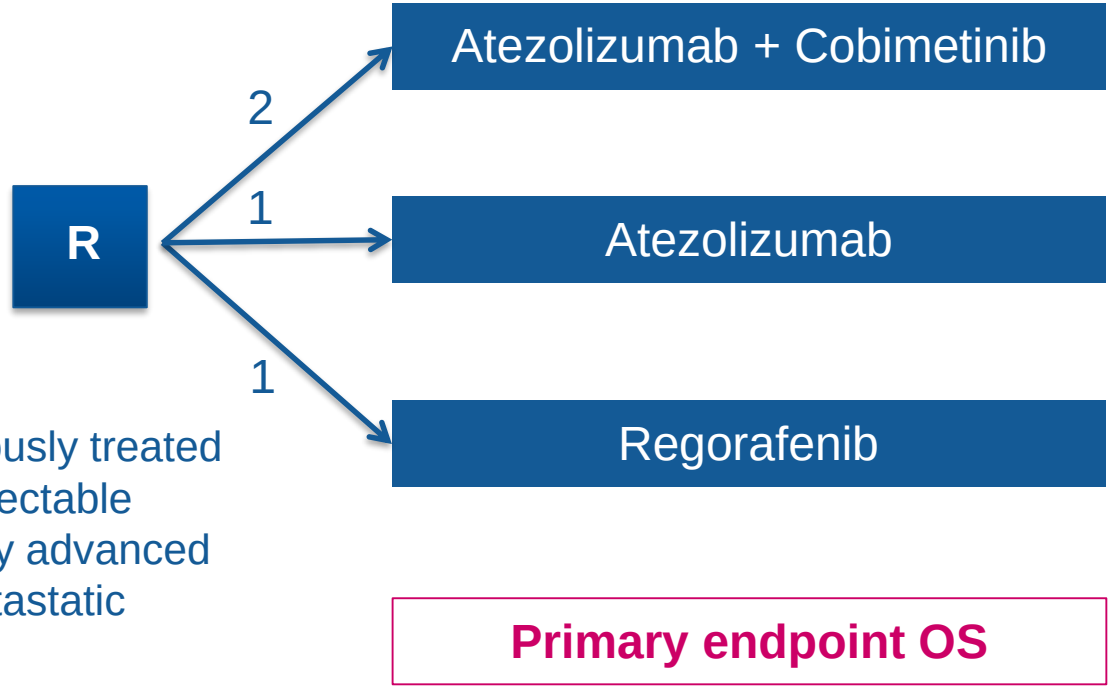


- To examine the possible benefits of MEK inhibition with an anti-PDL1 agent, we evaluated cobimetinib + atezolizumab in patients with advanced solid tumors

MHC, major histocompatibility complex; ND, no drug (vehicle alone).
CT26 (KRASmt) CRC models. 1. Ebert et al. *Immunity* 2016.

IMblaze 370: primary endpoint not reached

N = 363



Previously treated
Unresectable
Locally advanced
or metastatic
CRC

	Atezo + Cobi	Atezo	Reg
ORR, %	**2.7**	**2.2**	**2.2**
OS, mo	**8.9**	**7.1**	**8.5**

OS A+C vs Reg: HR 1.00, p=0.987
OS Atezo vs Reg: HR 1.19

PFS A+C vs Reg: HR 1.25, p=0.987
PFS Atezo vs Reg: HR 1.39

Cobimetinib: MEK inhibitor
Atezolizumab: PD-L1 inhibitor

Bendell et aL. ESMO 2018

NICHE-Study in early stage colon cancer

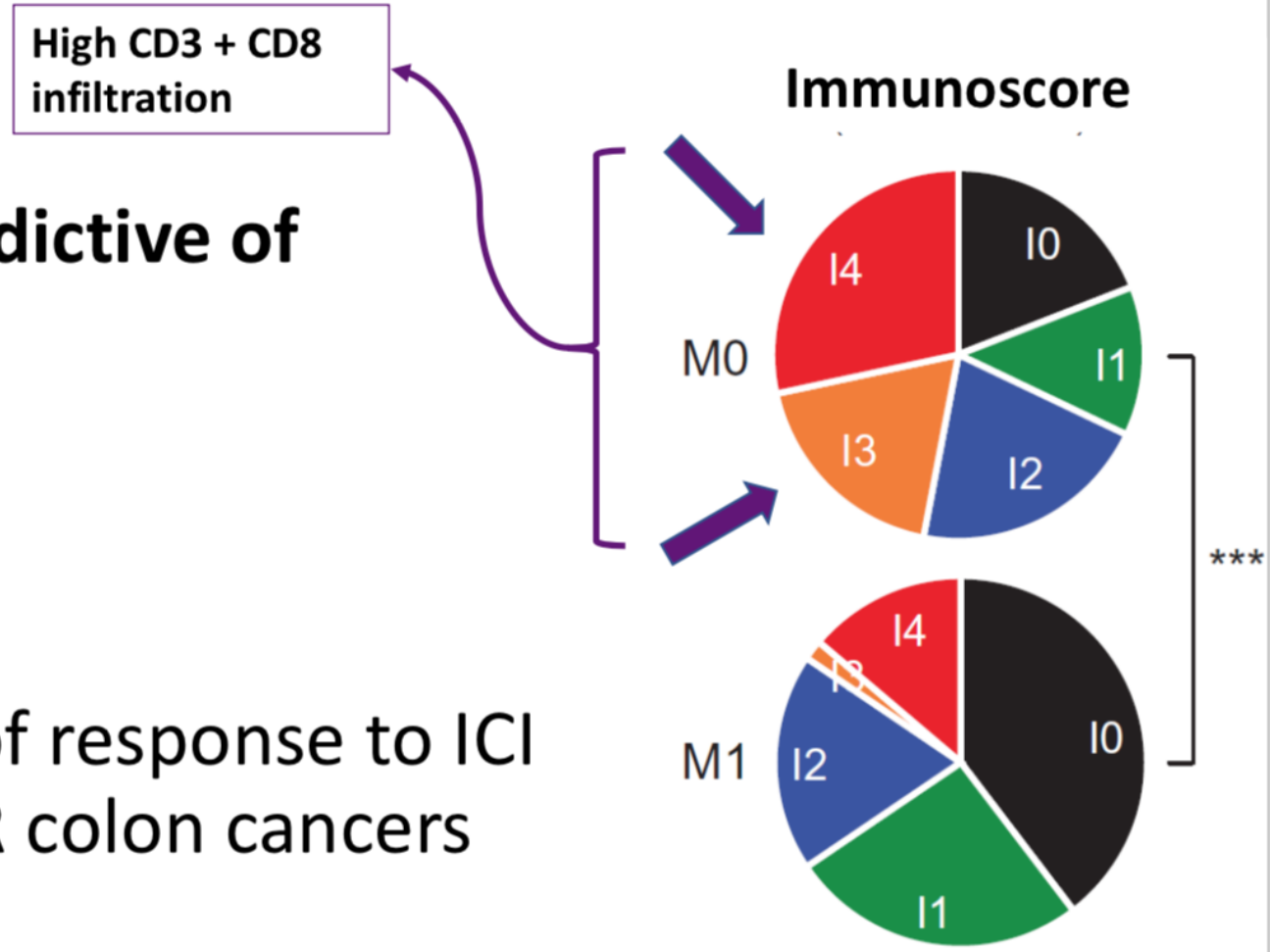
Rationale

Pre-existing T-cell response predictive of response to ICI

- Non-metastatic CRC: 50%
- Metastatic CRC: 15%

Hypothesis: higher probability of response to ICI in early stage dMMR and pMMR colon cancers

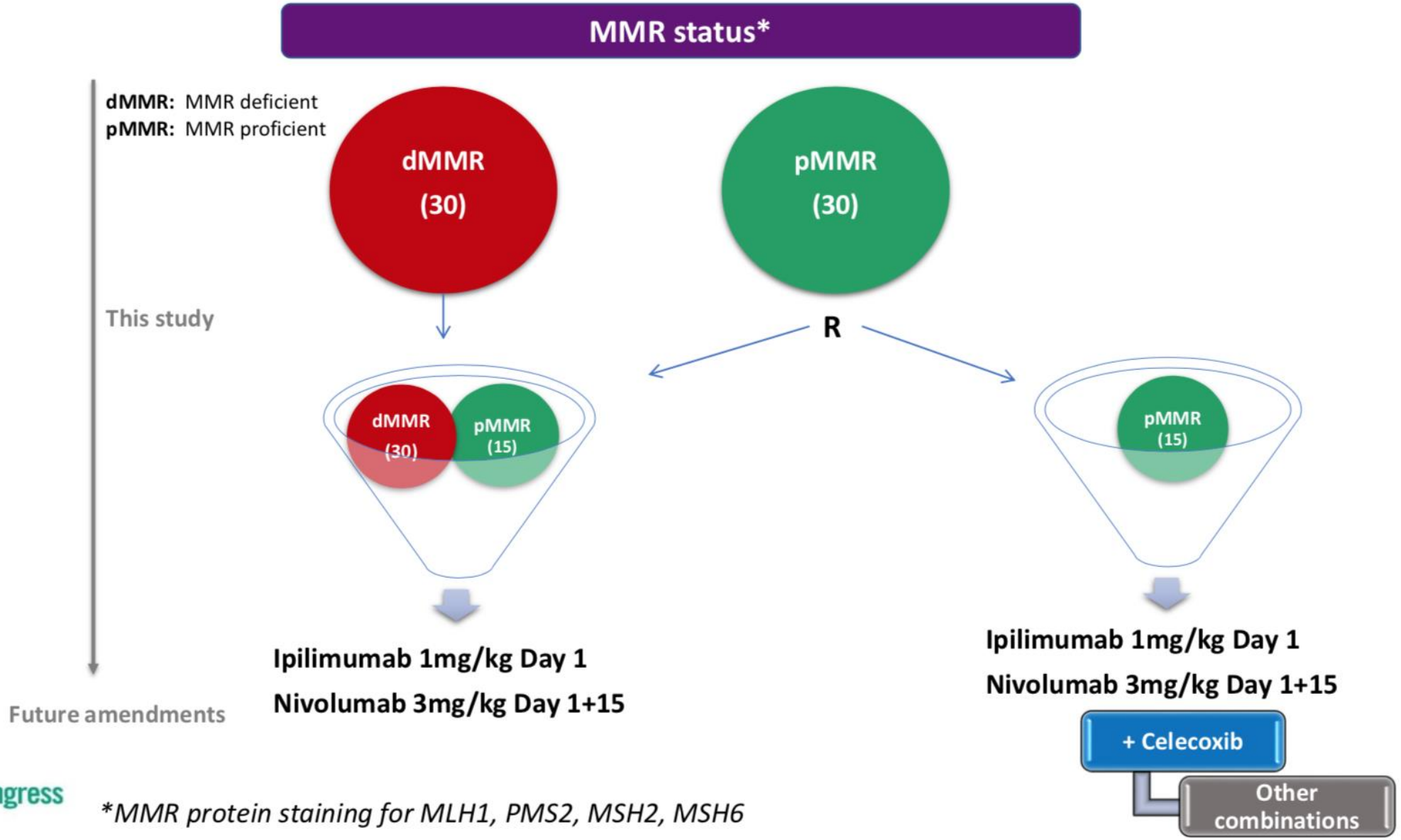
Primary endpoint = feasibility



Colorectal cancer
M0 = non-metastatic
M1 = metastatic

Myriam Chalabi et al. ESMO 2018

NICHE – pre-operative adaptive design



**MMR protein staining for MLH1, PMS2, MSH2, MSH6*

efficacy - major response in 100% of dMMR tumors

dMMR (n=7)		
Pre-treatment clinical stage	Pathological stage at resection	Residual vital tumor
cT2N2a	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT3N0	ypT0N0	0 %
cT3N2a	ypT1N0	1 %
cT4aN2a	ypT2N0	2 %
cT4aN1a	ypT3N1	2 %

pMMR (n=8)		
Pre-treatment clinical stage	Pathological stage at resection	Residual vital tumor
cT3N1a	ypT3N2	85 %
cT3N0	ypT3N0	90 %
cT2N0	ypT3N1	90 %
cT2N0	ypT3N0	90 %
cT3N1b	ypT3N1	90 %
cT3N1b	ypT3N2	95 %
cT3N0	ypT3N0	100%
cT2N0	ypT2N0	100 %

MUNICH 2018 ESMO congress

*Major pathological response = <10% residual vital tumor
Residual vital tumor %: average of scores by two independent pathologists

but no response in pMMR

Summary

- dMMR (MSI-high) is associated with high tumor mutational burden and predicts response to CPI
- Upfront determination of MMR-status is highly recommended, while CPI are not yet registered for mCRC
- POLe mutation is a rare event and also appears to predict response to CPI
- PD-L1 expression, Lynch-Syndrome or BRAF-mutation do not affect outcome in immunotherapy of MMRd mCRC
- The potential role of TML in CPI-response prediction still needs to be defined