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Colorectal cancer with microsatellite instability and immunotherapies

by Prof. David Tougeron and Dr. Sebastian Stintzing

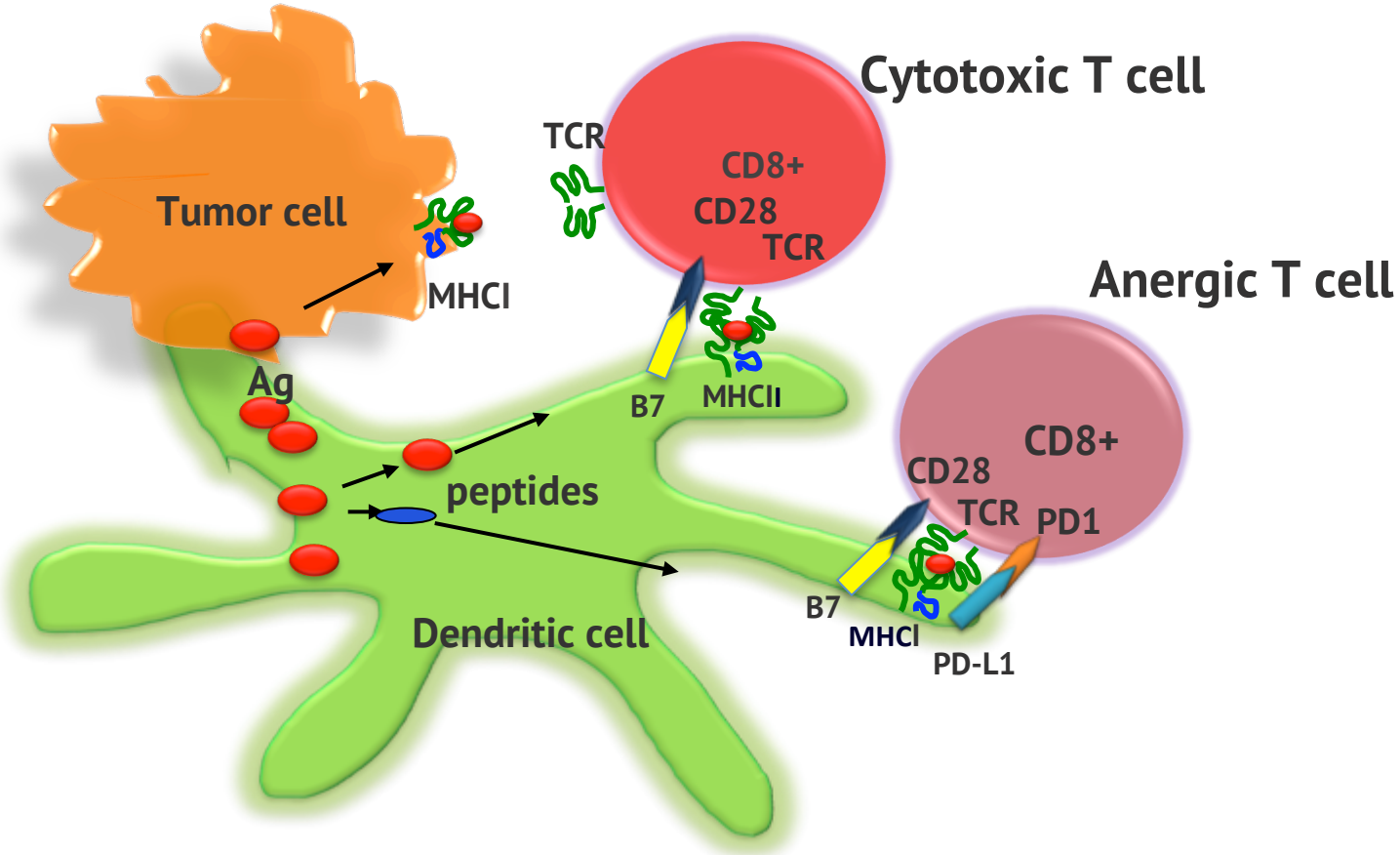
COLORECTAL CANCER WITH MICROSATELLITE INSTABILITY AND IMMUNOTHERAPIES

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, et al. N Engl J Med 2015;372:2509-20

- Prof. David Tougeron, Department of Gastroenterology, Poitiers University Hospital, France
- Dr. Sebastian Stintzing, Department of Hematology and Oncology at the University Hospital Munich of the University of Munich, Germany

IMMUNOSURVEILLANCE AND IMMUNE CHECKPOINTS



- **Cytotoxic T cell** is the most important immune cell for cancer immunosurveillance
- In order to be activated, a T lymphocyte needs an association of triggering signals:
  - recognition of tumor antigen coupled with major histocompatibility complex (MHC)
  - activating co-stimulatory molecules (B7/CD28)
- Inhibiting co-stimulatory molecules, called **immune checkpoint**, prevent excessive T cell activation and induce T cell energy

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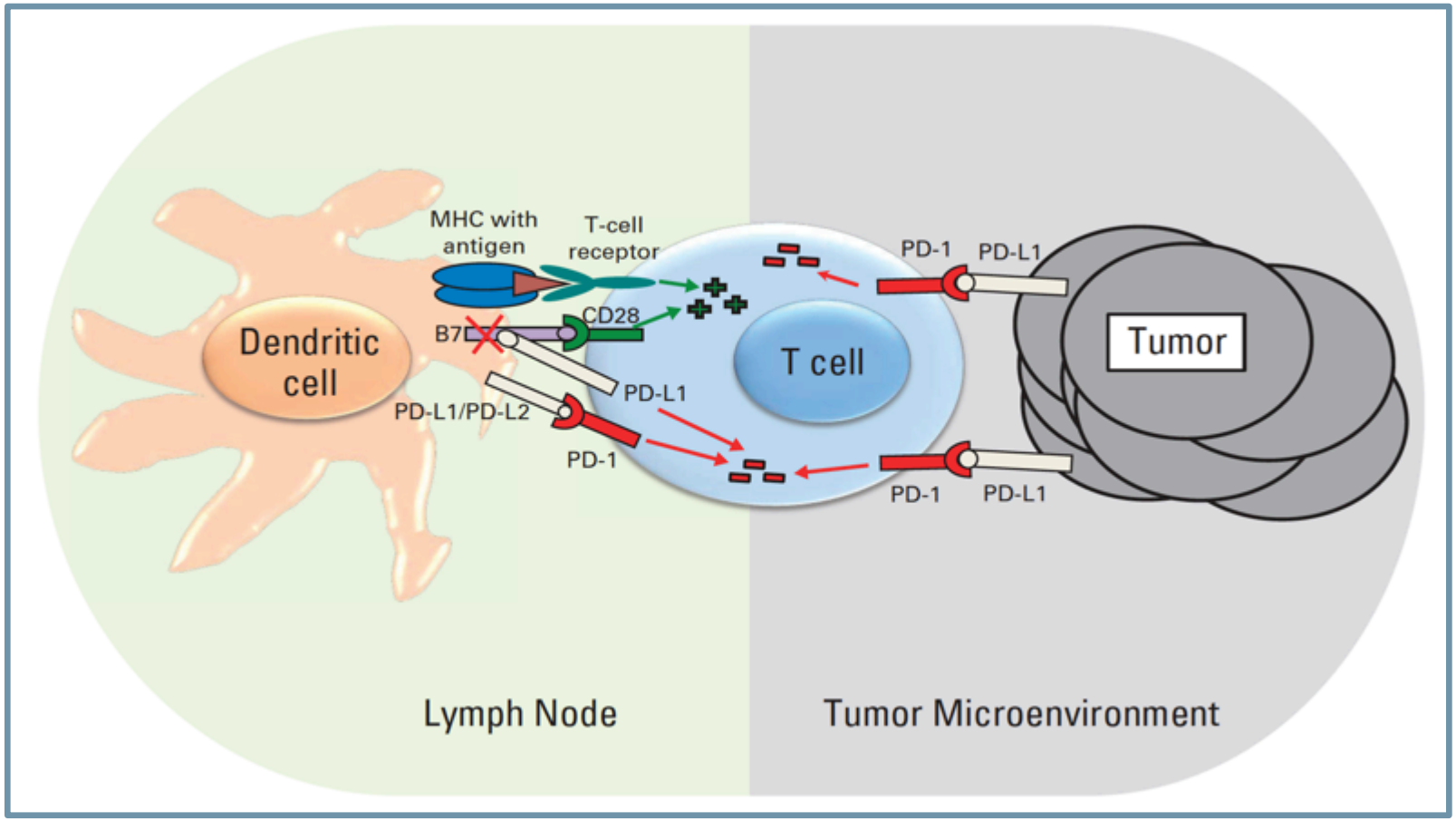
IMMUNES CHECKPOINTS (PD-L1 / PD-1)



- **PD-1/PD-L1** interaction allows for negative feedback on the immune response regulating effector T cell responses in peripheral tissues and leads to peripheral T cell tolerance
- PD-L1 expression is up-regulated on a wide range of cancer cells to allow immunosurveillance escape

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ANTI-PD-1 AND ANTI-PD-L1

TARGET	BLOCKADE AGENT	MOLECULAR PROPERTY	PHASE	EVALUATED CANCER	COMPANY
PD-1	CT-011 (pidilizumab)	Humanized IgG1	II	Hematologic cancer, melanoma	CureTech
	MK-3475 (pembrolizumab)	Humanized IgG4	III	Advanced solid tumors, Melanoma, NSCLC	Merck & Co
	BMS-936558 (nivolumab)	Fully human IgG4	III	Melanoma, RCC, NSCLC, HNSCC, Advanced solid tumors	Bristol-Myers Squibb
	AMP-224	PD-L2 fusion protein	I	Advanced solid tumors	Amplimmune/ GlaxoSmithKline
PD-L1	BMS-936559	Fully human IgG4	I	Advanced solid tumors	Bristol-Myers Squibb
	MEDI4736	Humanized IgG	I/III	Advanced solid tumors NSCLC	MedImmune
	MPDL3280A	Fully human IgG4	I/II	Melanoma, RCC, NSCLC, Bladder cancer, Advanced solid tumors	Roche
	MSB0010718C	Fully human IgG4	I/II	Advanced solid tumors, Merkel cell carcinoma	Merck & Co

Several **immune checkpoint inhibitors** (ICIs) have been developed so as to prevent negative regulations of the host immune system

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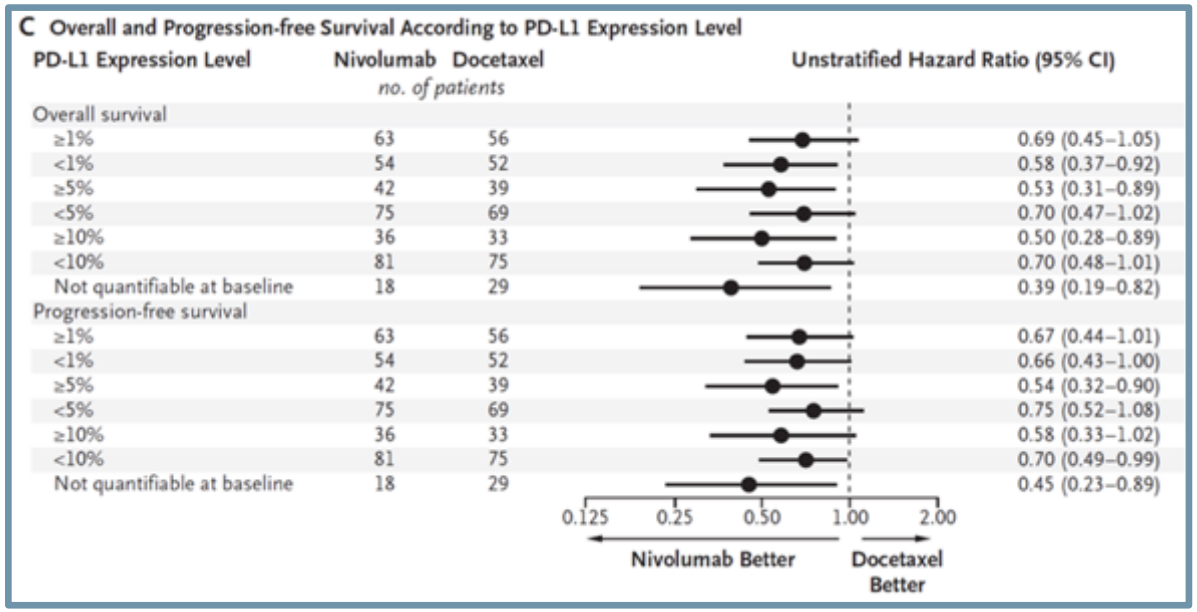
Zheng P et al. Biomark Cancer 2015

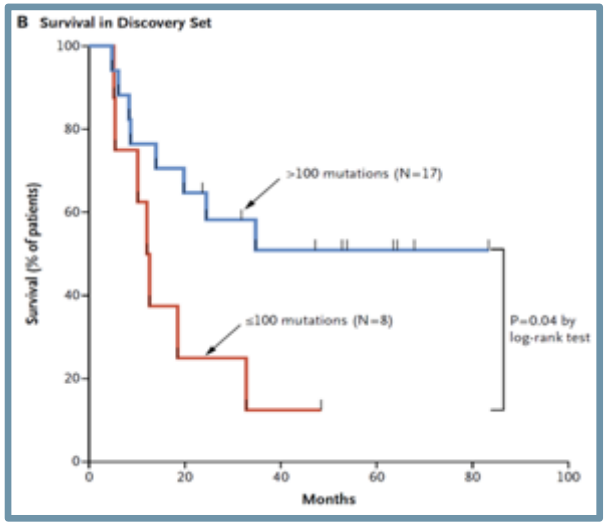
BIOMARKERS OF ANTI-PD-1 AND ANTI-PD-L1 EFFICACY

1. PD-L1 expression can predict anti-PD-1 and anti-PD-L1 efficacy


C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)

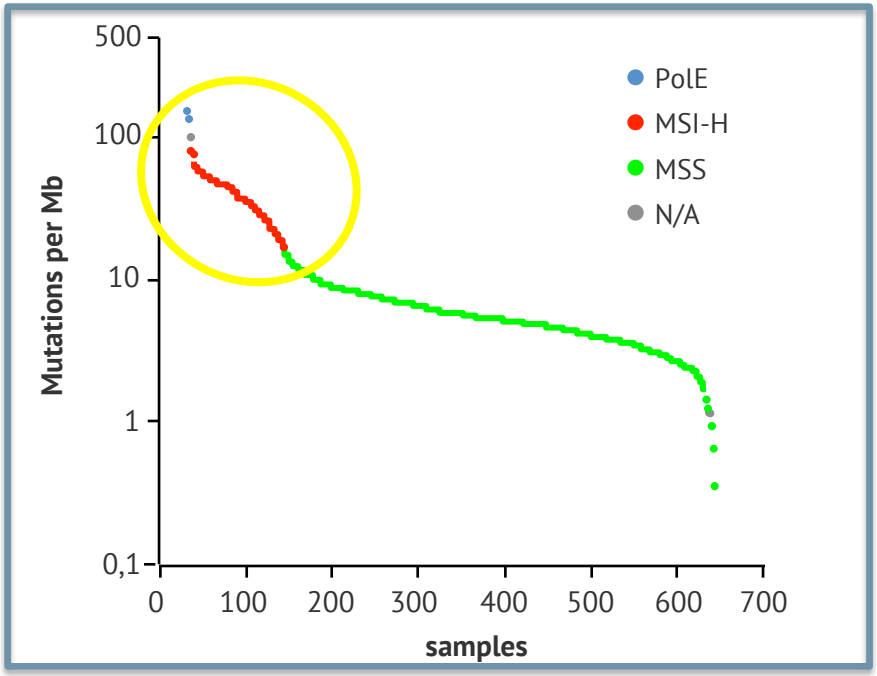
2. Tumor mutational load can predict anti-PD-1 and anti-PD-L1 efficacy



Brahmer J et al. N Eng J Med 2015 ; Snyder A et al. New Eng J Med 2014

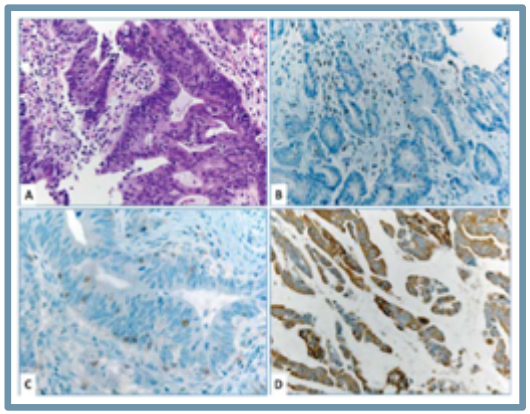
COLORECTAL CANCERS WITH MICROSATELLITE INSTABILITY (DMMR CRC)

1. dMMR CRC represent 12% of CRC and are associated with high mutation load



2. High expression of PD-1 ans PD-L1 in dMMR CRC

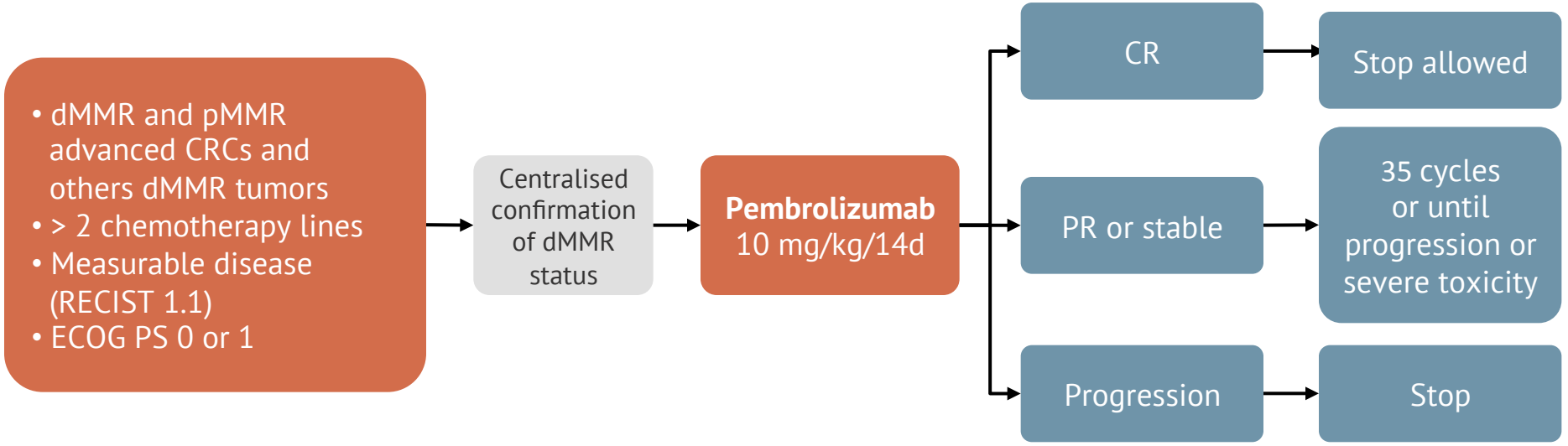
Colon Cancer subtypes (N=87)	PD-1 expression (TILs) (% and range)	PD-L1 (tumor cells) (%)	Concurrent PD-1/PD-L1 expression (%)
MSS colon cancers (n=60)	39% (1-11)	13%	4%
MSI-H colon cancers (n=27)	77% (1->20)*	38%*	32%*



Gatalica Z, Cancer Epidemiol Biomarkers Prev 2014 ; Le DT, N Eng J Med 2015, Giannakis M et al. ASCO 2015

ANTI-PD-1 AND DMMR CRC

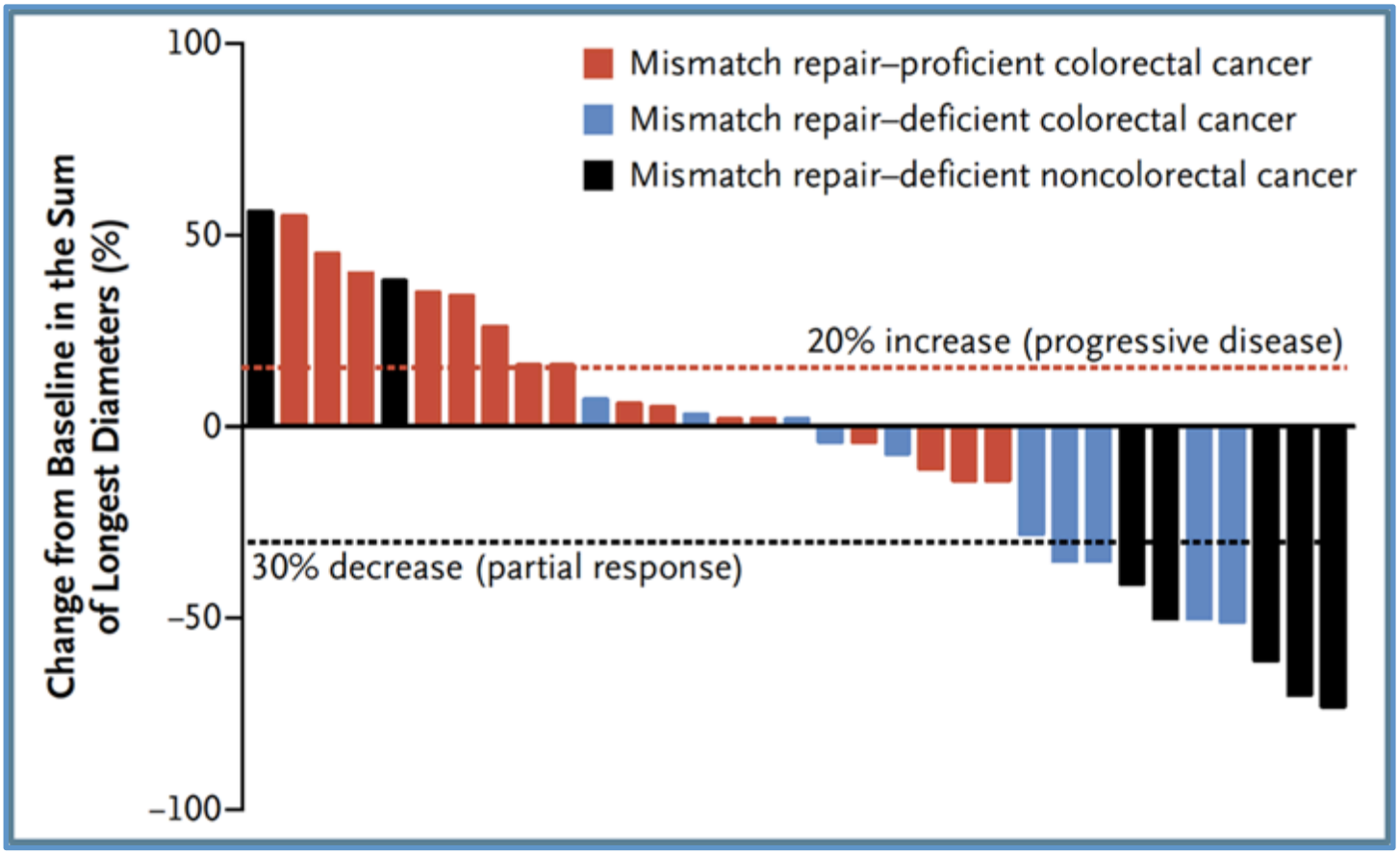
- Phase II
- 41 patients with chemoresistant metastatic CRC
- Pembrolizumab 10 mg/kg every 14 days



- **Tumor response evaluation**: at week 12 then every 8 weeks
- **Primary endpoint: objective response according immune-related response criteria (irRC)**
- **Secondary endpoints: i**PFS, OS, safety

Le DT et al. New Eng J Med 2015

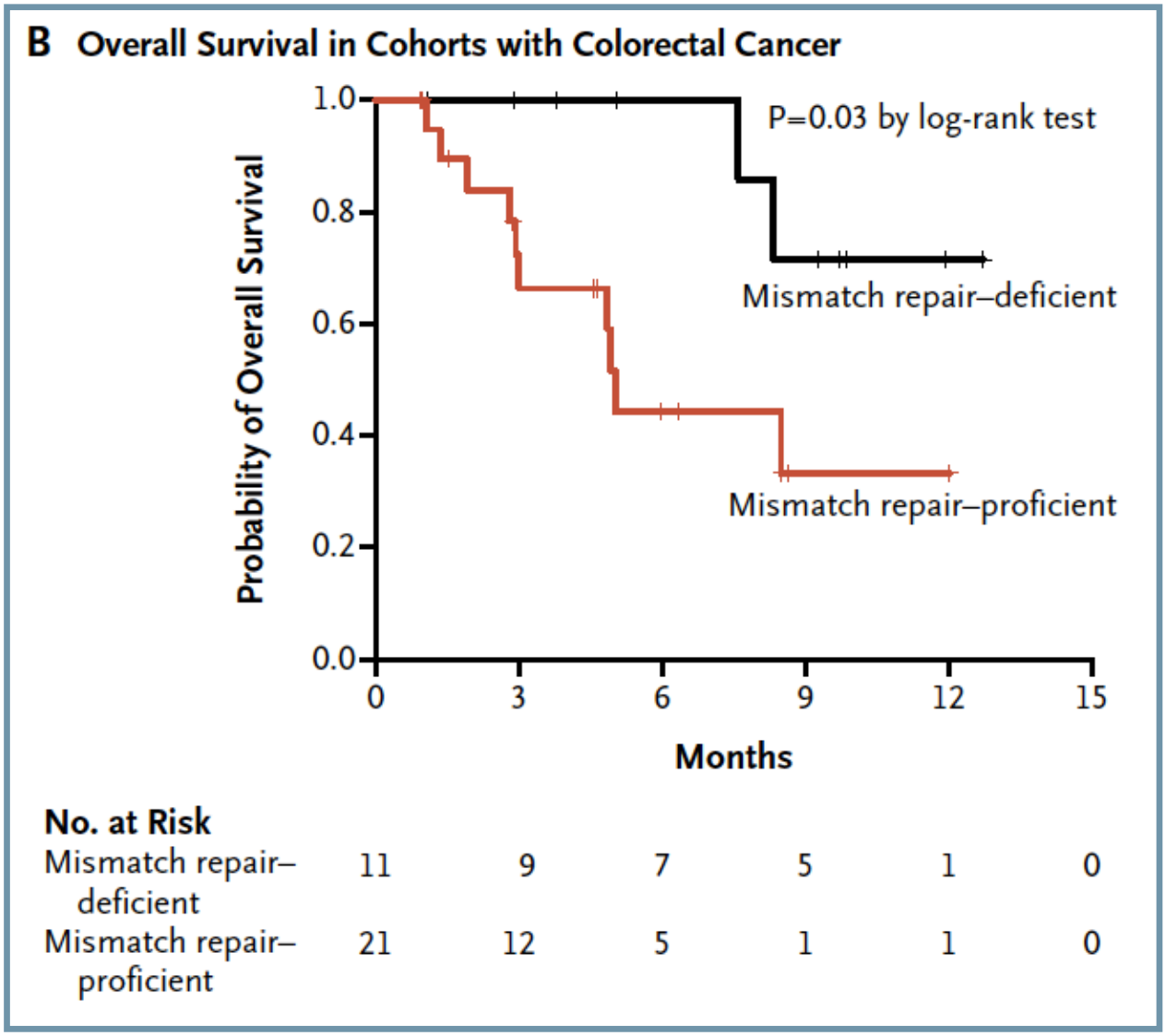
ANTI PD-1 AND DMMR CRC



	OR (%)	Stable (%)
pMMR CRC (n=18)	0	11
dMMR CRC (n=10)	**40**	**90**
dMMR non CRC (n=7)	71	71

Le DT et al. New Eng J Med 2015

ANTI PD-1 AND DMMR CRC

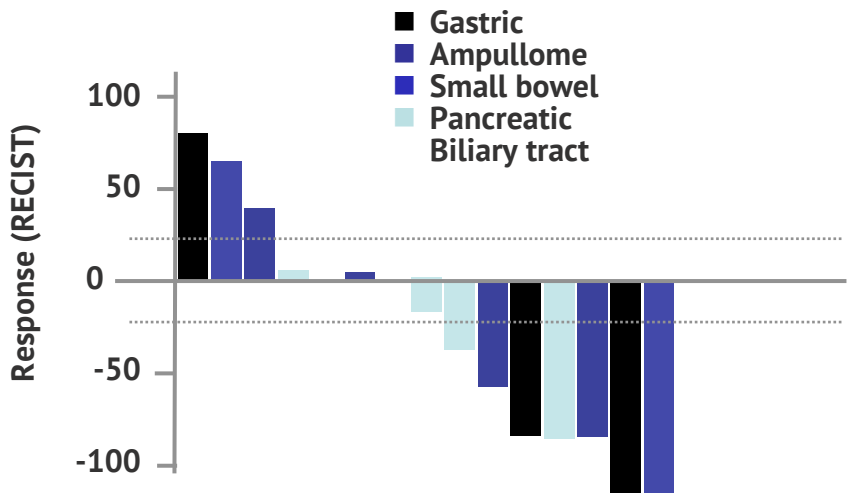


Le DT et al. New Eng J Med 2015

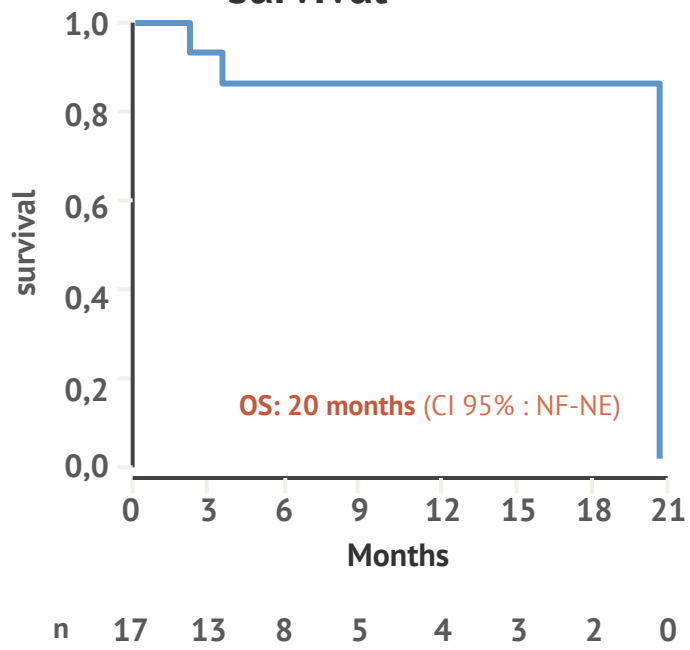
PROSPECTIVE COHORTE OF PEMBROLIZUMAB IN DMMR NON-CCR

- Response rate: 47% (n=8)
- Disease control rate: 76% (n=13)

Objective response



Overall survival



Le DT et al. ASCO GI 2016

CONCLUSION - DISCUSSION

- **High efficacy of anti-PD-1 in dMMR CRC**
- **But**:
  - small non-randomized phase II trial, confirmatory studies are needed
  - possibility to combine with chemotherapy/radiotherapy/targeted therapies?
  - predictive biomarkers (PD-1/PD-L1 **expression**)?
  - management of immune related sides effects
  - evolution of treatment response with immune checkpoints
  - cost

- **Perspective:**
  - ongoing trial: KEYNOTE-177 (first line **pembrolizumab in dMMR CRC**) and CheckMate-142 (nivolumab plus ipilimumab in dMMR chemoresistant CRC)
  - **Combination with cytotoxic chemotherapy**

⇒ Awaiting FDA approval

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