Immunotherapy for dMMR metastatic colorectal cancer

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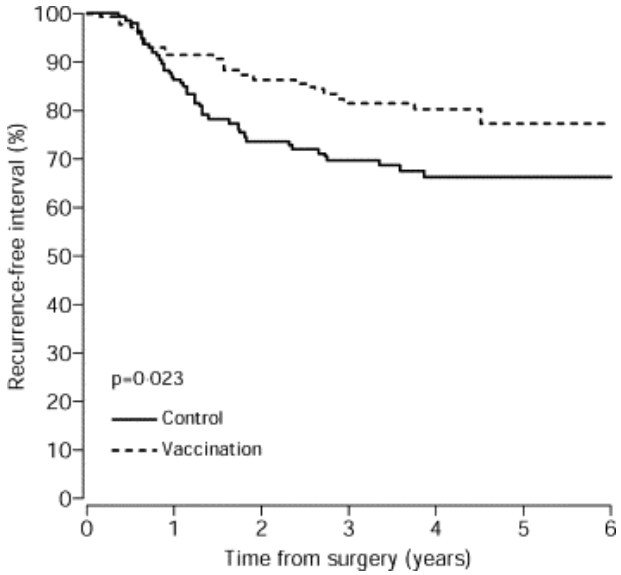
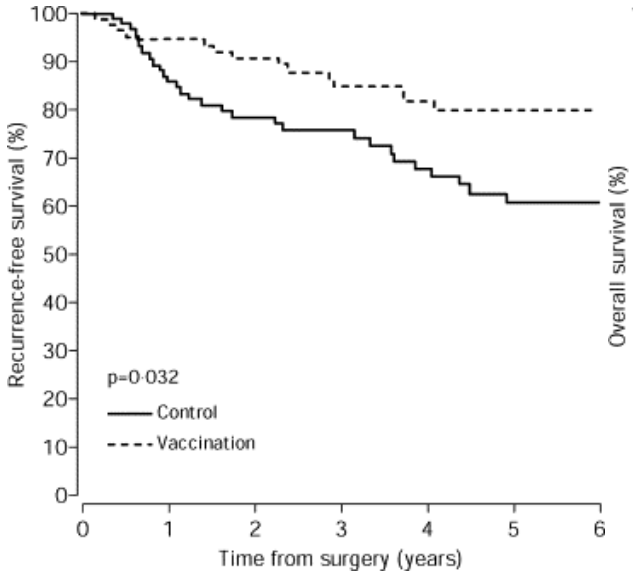
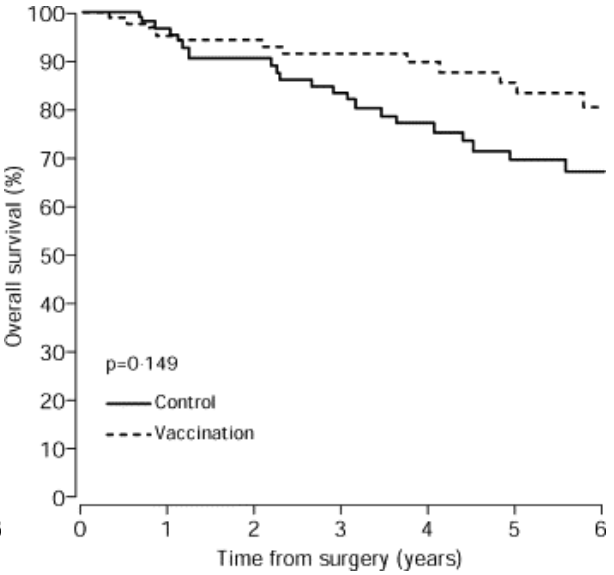
Active specific immunotherapy (ASI) in stage II-III colon cancer

Vaccination with autologous tumor + BCG versus observation







All patients, n = 254
Stage II n = 170
Stage III n = 84

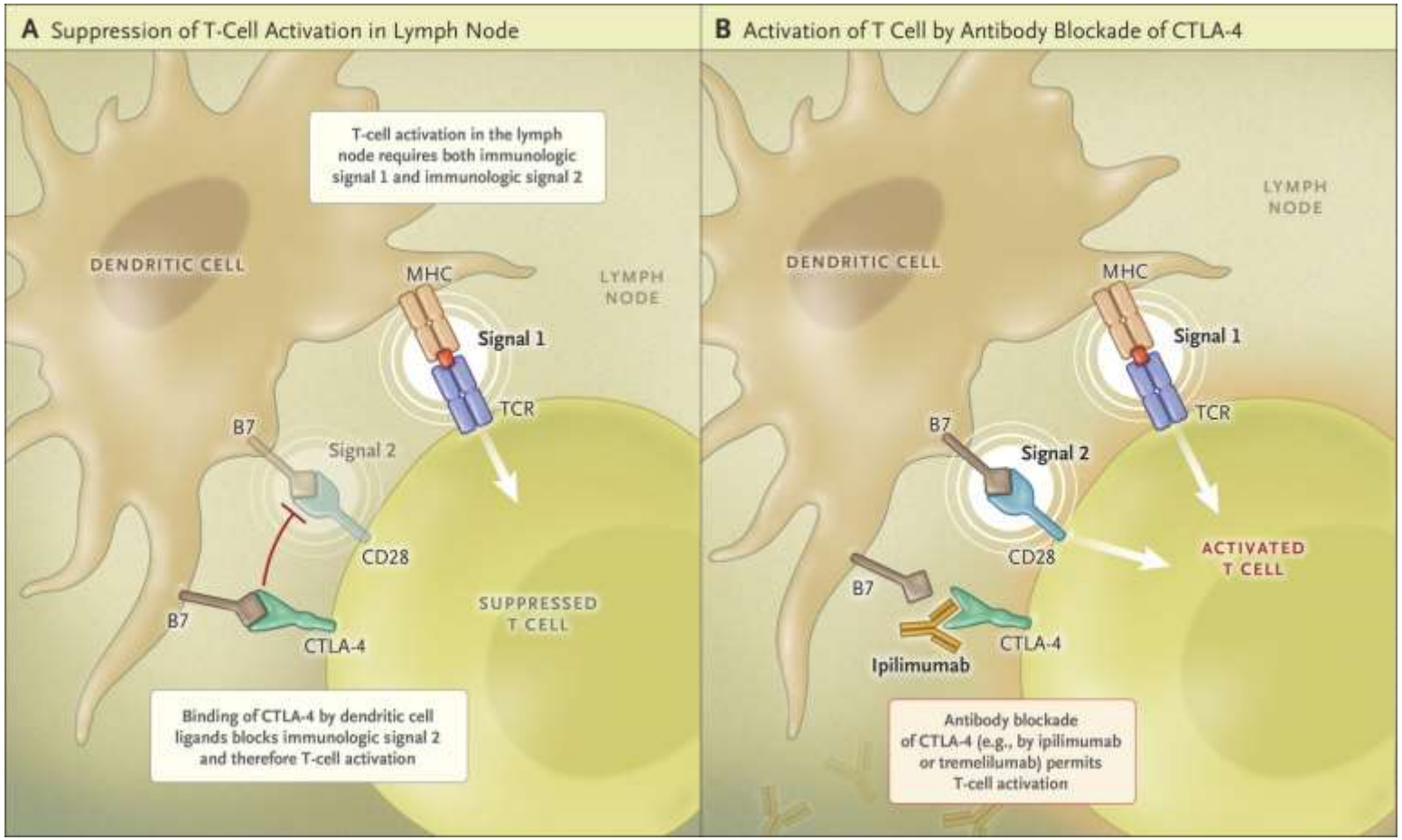
Stage II, RFS

Stage II, OS

ASI: significant benefit for stage II patients in RFS, trend in OS

Vermorken et al. Lancet 1999

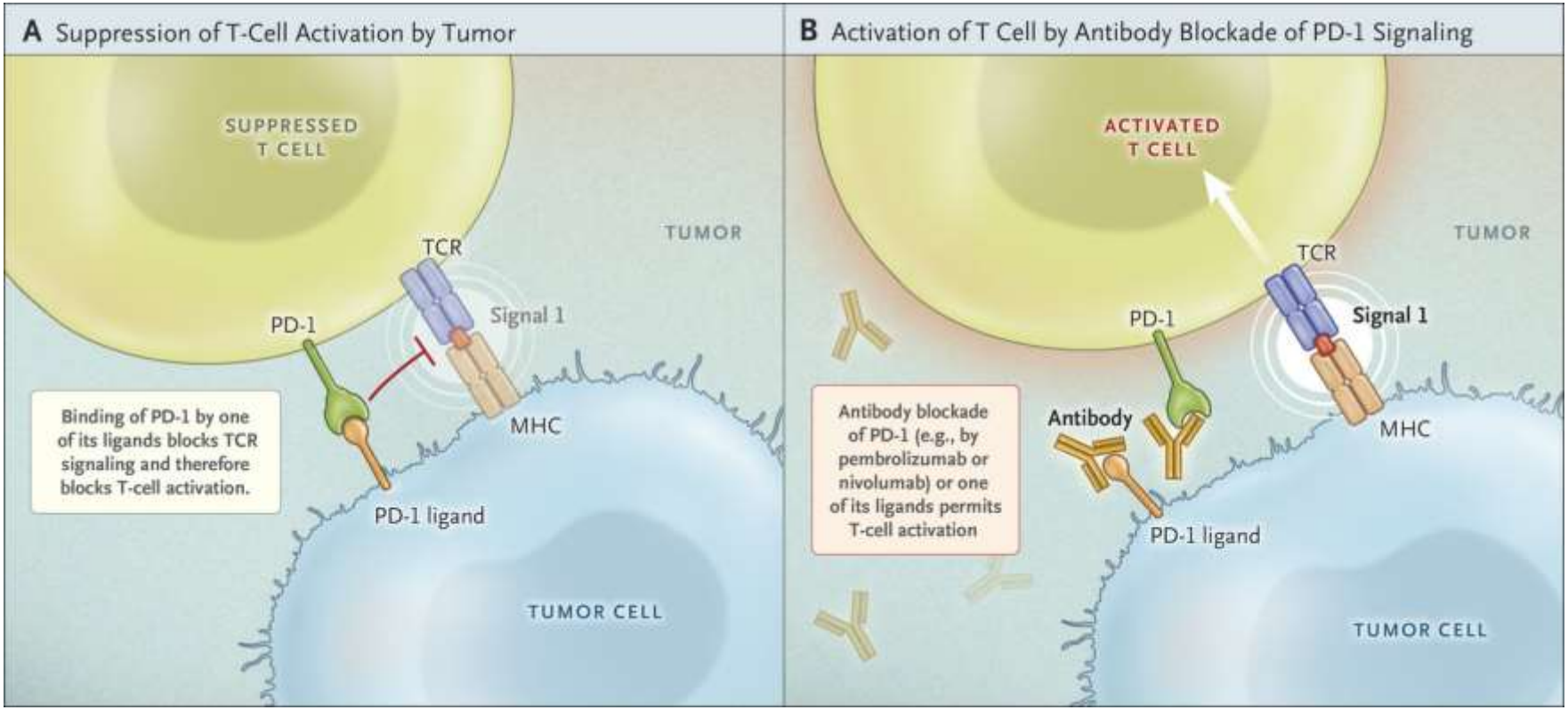
Releasing the brakes on cancer immunotherapy



T cell activation in the lymphnode requires 2 immunological signals

Ribas et al. NEJM 2015

Releasing the brakes on cancer immunotherapy



During long-term antigen exposure, Programmed Death 1 (PD-1) receptor is expressed by T cells, which suppresses T cell activation

Ribas et al. NEJM 2015

Deficient Mismatch Repair (dMMR) in CRC

- Deficient MMR system allows persistence of mismatch mutations, especially in regions of repetitive DNA (microsatellites), causing microsatellite instability (MSI)
- MSI in CRC: hereditary (mutations) and sporadic (hypermethylation MLH1)
- Only approx.5% of patients with metastatic CRC have MSI tumors, and their poor prognosis is driven by *BRAF* mutation status[1,2]
- MSI tumors are immunogenic[3]
- Pembrolizumab, Nivolumab: anti-programmed death 1 (PD-1) immune checkpoint inhibitors

Hypothesis:

- PD-1 blockade is more effective in MSI tumors than in MSS tumors

[1]Koopman M et al. Br J Cancer 2009
[2]Venderbosch S et al. Clin Cancer Res 2014
[3]Smyrk T et al. Cancer 2001

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

- Pembrolizumab 10 mg/kg i.v. every 2 weeks
- Treatment-refractory metastatic cancer, 3 cohorts:
  - dMMR CRC
  - pMMR CRC
  - dMMR non-CRC

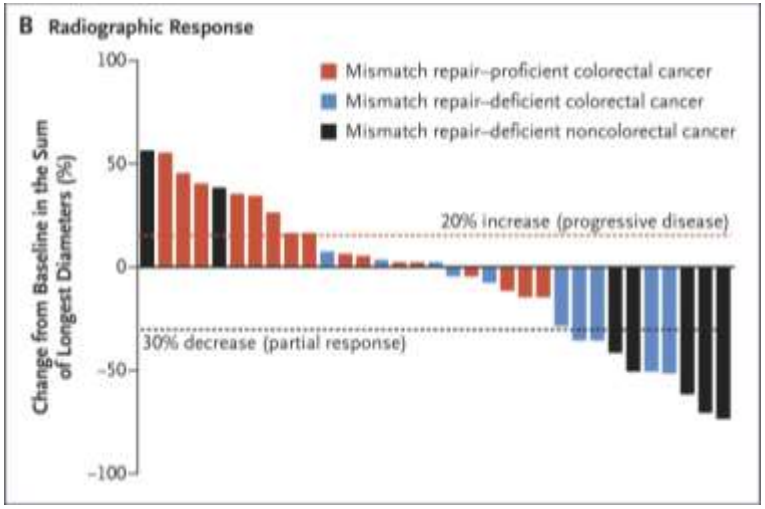
Le et al. NEJM 2015

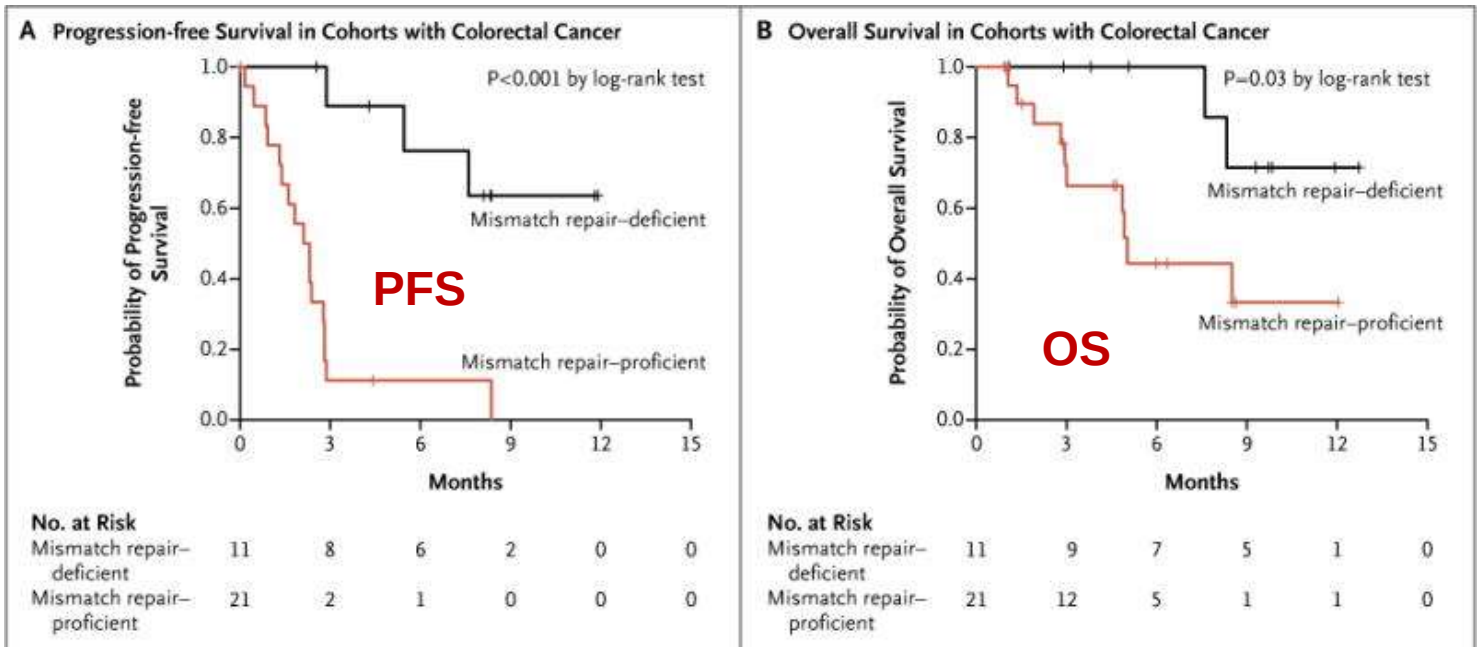
PD-1 blockade by pembrolizumab in metastatic CRC

	dMMR CRC	pMMR CRC	dMMR non-CRC
N	11	21	9
previous regimens 1 2 ≥3	 0 3 (27%) 8 (73%)	 0 4 (19%) 17 (81%)	 1 (11%) 5 (56%) 3 (33%)
mutation status BRAF wildtype KRAS wildtype	 8 (73%) 6 (55%)	 11 (52%) 13 (62%)	 4 (44%) 4 (44%)
Lynch syndrome	9 (82%)	0	4 (44%)
Response rate	**40%**	**0%**	**71%**
Disease control rate	**90%**	**11%**	**71%**
Updated results Le et al. ASCO 2016			
N	28	25	
Response rate	**50%**	**0%**	
Disease control rate	**89%**	**16%**	

Le et al. NEJM 2015

Pembrolizumab in metastatic CRC





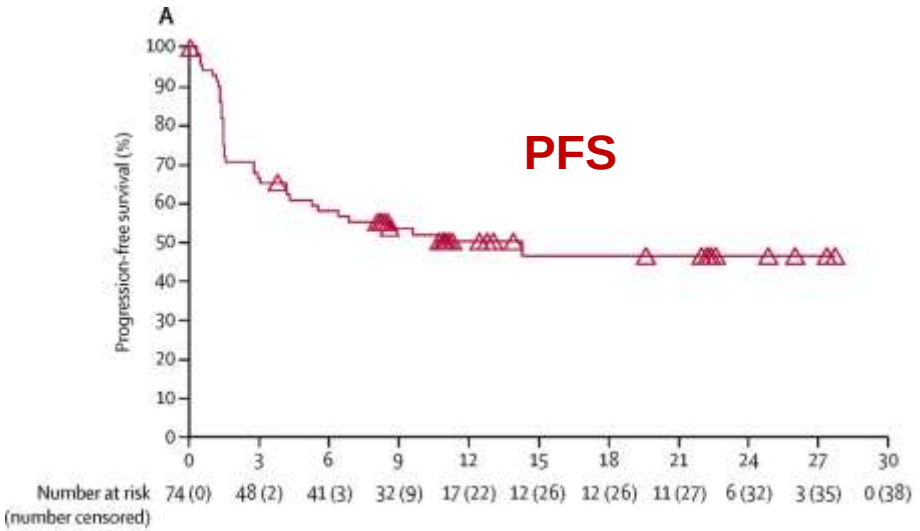
Le et al. NEJM 2015

Nivolumab in dMMR metastatic CRC

- Checkmate142: nivolumab 3 mg/kg every 2 weeks, n = 74
- Progression on/intolerant for ≥ 1 previous line of treatment, including fluoropyrimidine and oxaliplatin or irinotecan
- Response rate 31%, DCR 69%
- Median PFS 14.3 months, 1-year PFS 50%, 1-year OS 73%
- No association of response with PD-L1 expression, *KRAS/BRAF* mutation status, or Lynch syndrome
- dMMR status centrally not confirmed in 14 (19%) patients, but responses observed in 3 (21%) of these patients

Overman et al. Lancet Oncol 2017

Nivolumab in dMMR metastatic CRC



N = 74	N (%)
previous regimens	
0	1 (1%)
1	11 (15%)
2	22 (30%)
≥3	40 (54%)
mutation status	
KRAS/BRAF wt	29 (39%)
BRAF mutation	12 (16%)
KRAS mutation	26 (35%)
unknown	7 (9%)
PD-L1 expression	
≥1%	21 (28%)
<1%	47 (64%)
unknown	6 (8%)
Lynch syndrome	
yes	27 (36%)
no	28 (38%)
unknown	19 (26%)

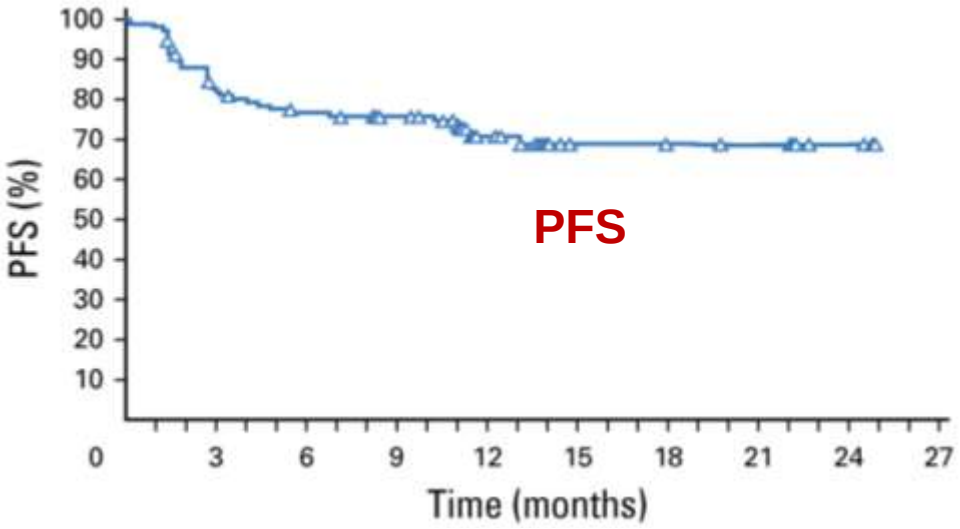
Overman et al. Lancet Oncol 2017

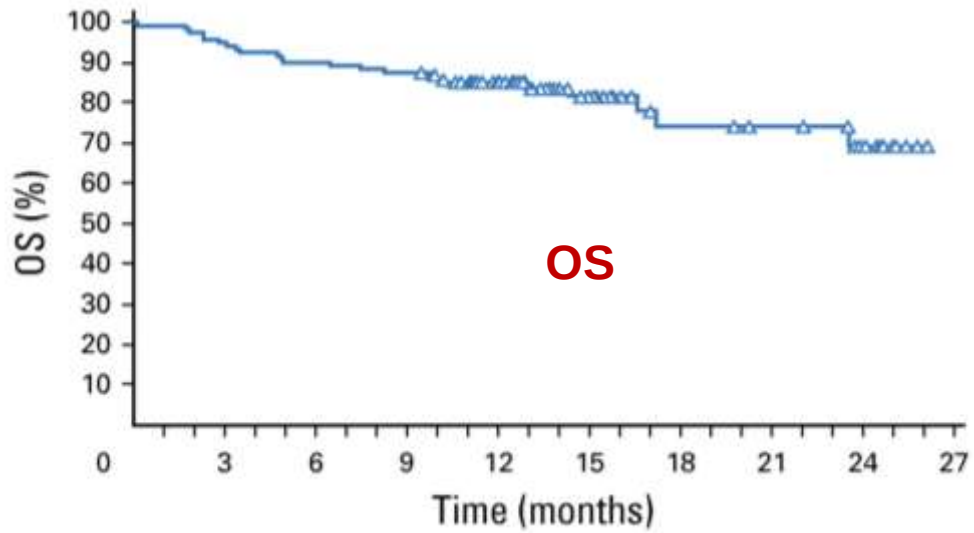
Nivolumab + Ipilimumab in dMMR metastatic CRC

- Checkmate142: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 wks (4 doses), followed by nivolumab 3 mg/kg every 2 weeks, n = 119
- Progression on/intolerant for ≥ 1 previous line of treatment, including fluoropyrimidine and oxaliplatin or irinotecan
- Response rate 55%, DCR 80%
- 1-year PFS 71%, 1-year OS 85%
- No association of response with PD-L1 expression, *KRAS/BRAF* mutation, or Lynch syndrome

Overman et al. J Clin Oncol 2018

Nivolumab + Ipilimumab in dMMR metastatic CRC





N = 119	N (%)
previous regimens	
0	1 (1%)
1	27 (23%)
2	43 (36%
≥3	48 (40%)
mutation status	
KRAS/BRAF wt	31 (28%)
BRAF mutation	29 (24%)
KRAS mutation	44 (37%)
unknown	15 (13%)
PD-L1 expression	
≥1%	26 (22%)
<1%	65 (55%)
unknown	28 (24%)
Lynch syndrome	
yes	35 (29%)
no	31 (26%)
unknown	53 (45%)

Overman et al. J Clin Oncol 2018

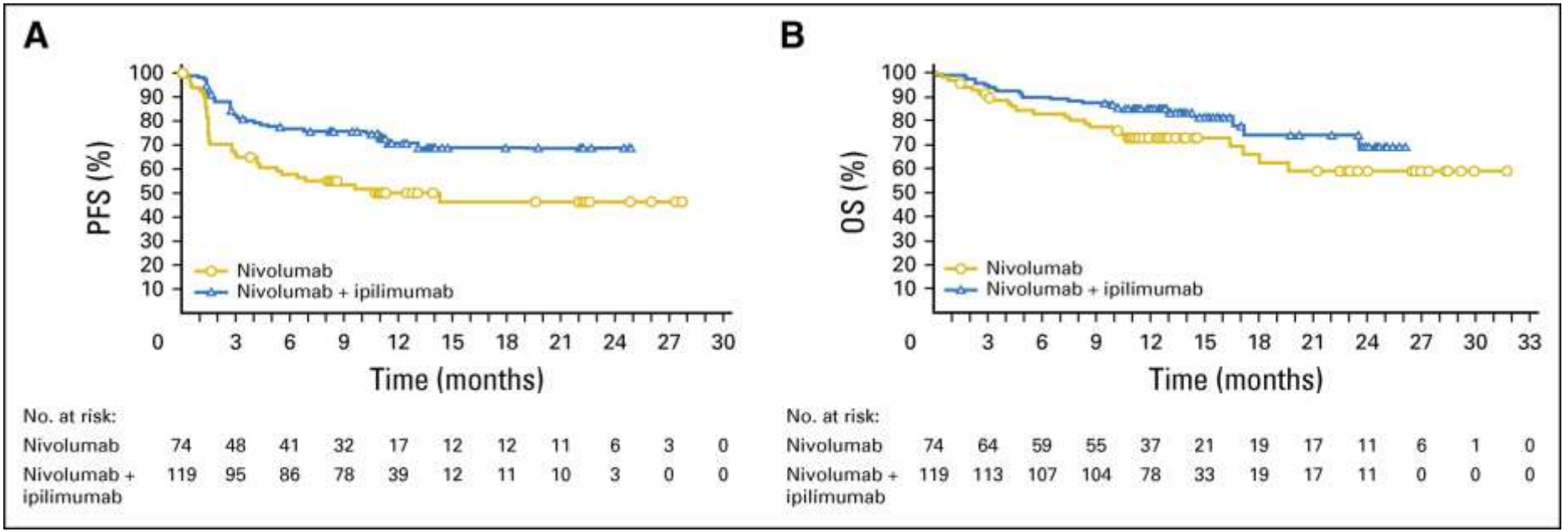
Non-randomised comparison of 3 studies in dMMR metastatic CRC

	Keynote 164 pembrolizumab	Checkmate 142 nivolumab	Checkmate 142 nivolumab + ipilimumab
n	61	74	119
≥ 2 prior regimens	90%	84%	76%
BRAF mutation	15%	16%	24%
Response rate	26.6%	31.1%	55%
Disease control rate	50.8%	69%	80%
1-year PFS	34%	50%	71%
1-year OS	72%	73%	85%

Diaz et al. ASCO 2017
Overman et al. Lancet Oncol 2017
Overman et al. J Clin Oncol 2018

Nivolumab vs nivolumab + ipilimumab in dMMR metastatic CRC

non-randomised data!



Overman et al. J Clin Oncol 2018

Conclusions

- Excellent results in the small subgroup of dMMR CRC patients
- Suggestion of superior results for anti-PD-1 + anti-CTLA4
- Randomised studies in 1st line dMMR metastatic CRC are ongoing:
  Phase 3: pembrolizumab vs standard of care, with cross-over
  Phase 2: 1st line nivolumab + ipilimumab
- Pembrolizumab: FDA approval for MSI tumors (2017), not in Europe
- Nivolumab: FDA approval for dMMR CRC (2017), not approved by EMA (January 2018)
- Future: not only release the brakes, but also step on the gas!

Keynote177 study

- Phase 3 randomized study in 1st line with standard systemic treatment versus pembrolizumab, with option of cross-over
- Primary endpoint: PFS, n = 270, closed for accrual January 2018

- Accrual in NL over 1.5 years in 4 centers: 15 (8 in 1 center)
- Update 2017 guideline CRC: dMMR and *RAS/BRAF* mutation status should be tested prior to initiation of 1st line systemic therapy!
- Studies in dMMR CRC and compassionate use program are ongoing in NL