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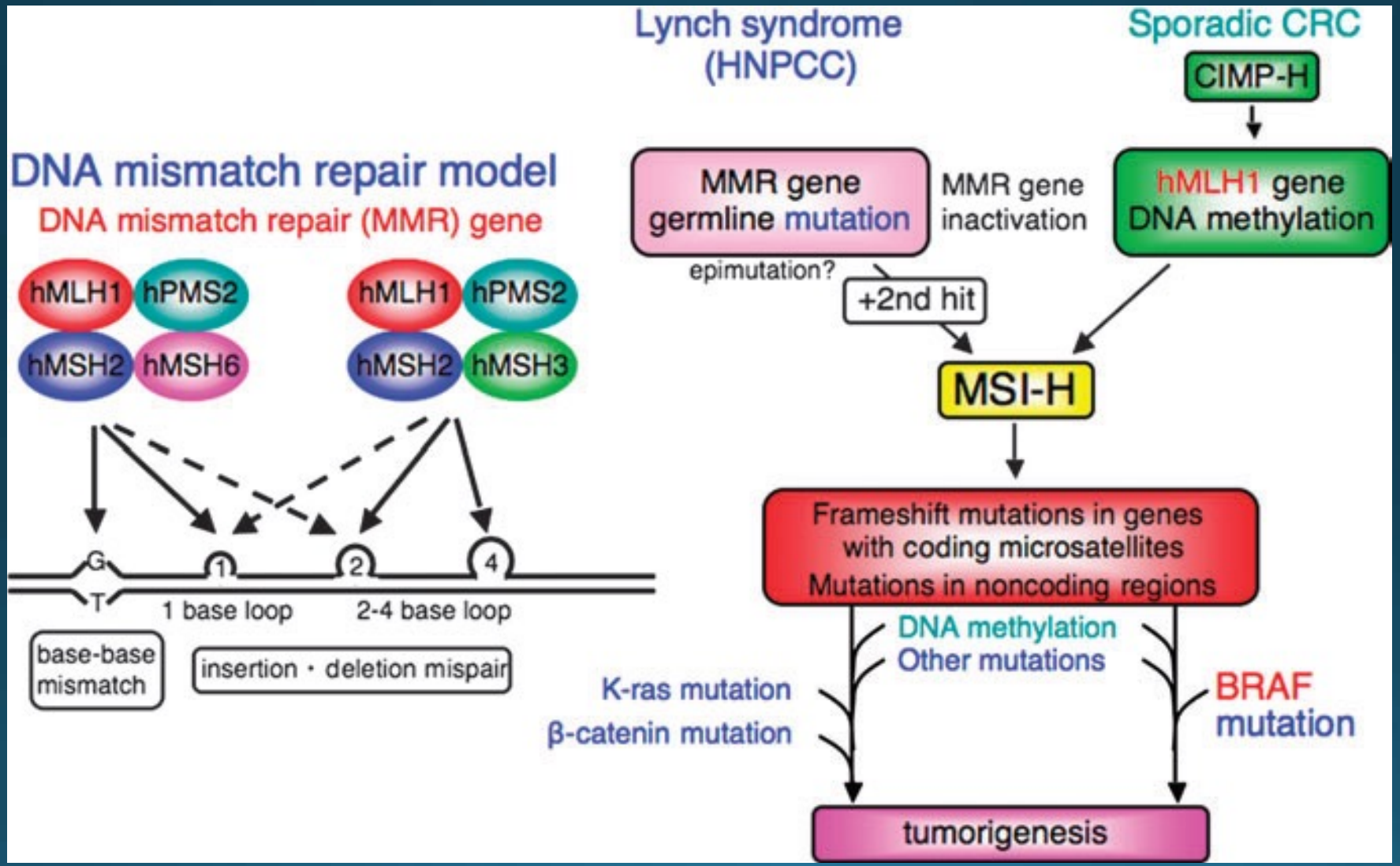
Checkpoint Inhibitors in GI Cancers

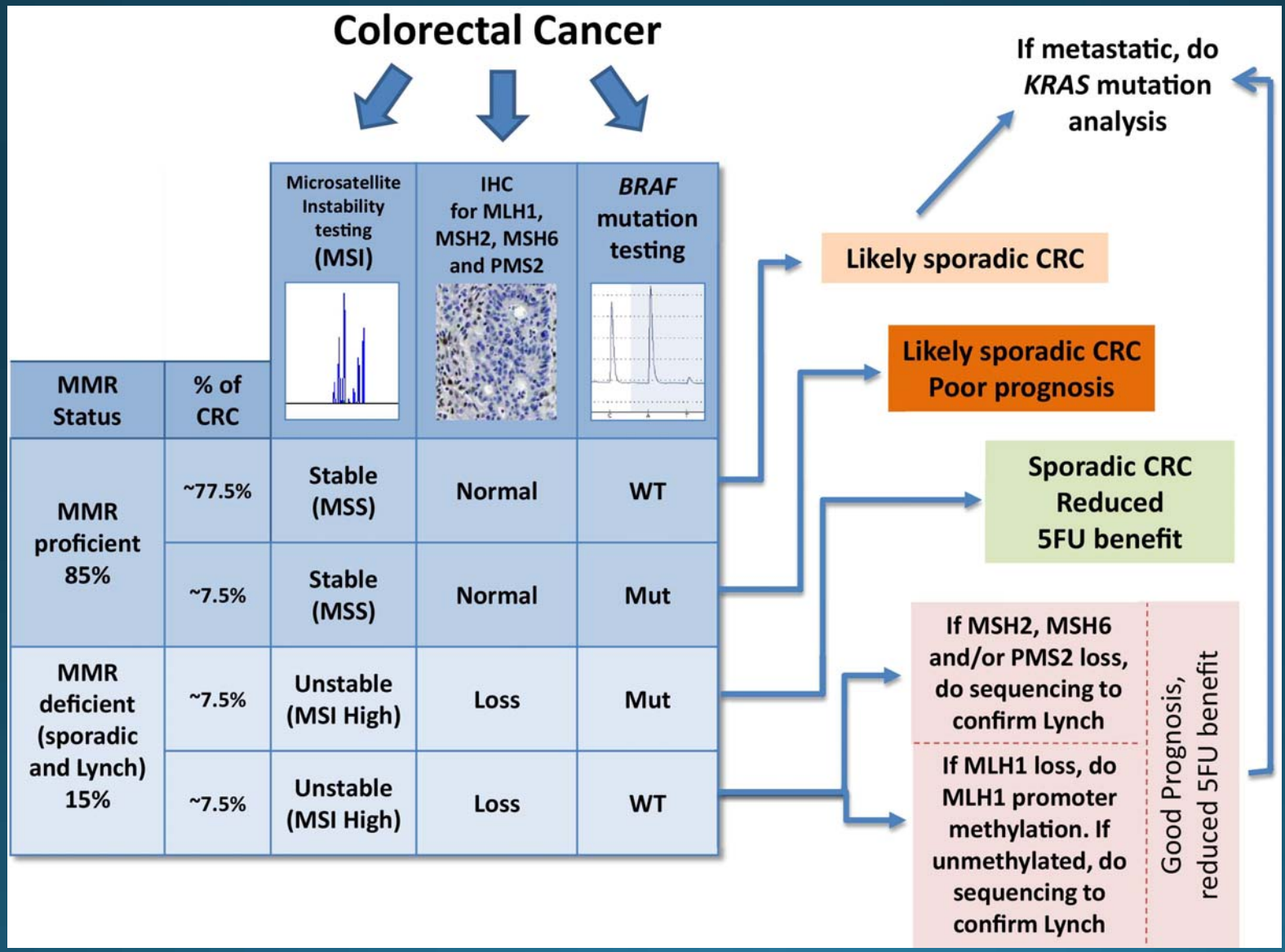
Disclosures

Contracted Research	Abbott Laboratories, AbbVie Inc, Apexigen, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Five Prime Therapeutics Inc, Forty Seven Inc, Genentech BioOncology, Gilead Sciences Inc, GlaxoSmithKline, Incyte Corporation, Kolltan Pharmaceuticals Inc, Leap Therapeutics Inc, Lilly, MacroGenics Inc, MedImmune Inc, Merck, Novartis Pharmaceuticals Corporation, OncoMed Pharmaceuticals Inc, Onyx Pharmaceuticals, an Amgen subsidiary, Pfizer Inc, Roche Laboratories Inc, Sanofi, Stemcentrx, Taiho Oncology Inc, Takeda Oncology, TG Therapeutics Inc.

Microsatellite instability



Microsatellite instability

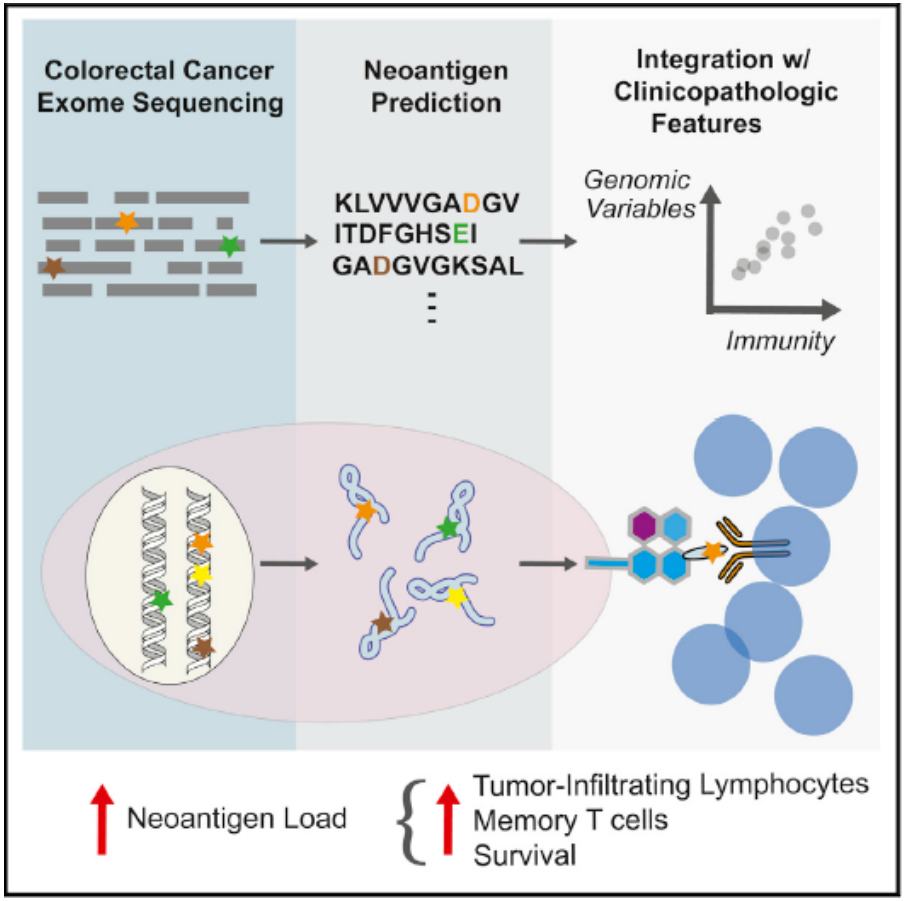


MSI in more than CRC

Cancer Type	General population risk	Lynch syndrome (MLH1 and MSH2 heterozygotes)	
		Risk	Mean age of onset
Colon	5.5%	52-82%	44-61 years
Endometrium	2.7%	25-60%	48-62 years
Stomach	< 1%	6-13%	56 years
Ovary	1.6%	4-12%	42.5 years
Hepatobiliary tract	< 1%	1.4-4%%	Not reported
Urinary tract	< 1%	1-4%	~55 years
Small bowel	< 1%	3-6%	49 years
Brain/central nervous system	< 1%	1-3%	~50 years
Sebaceous neoplasms	< 1%	1-9%	Not reported

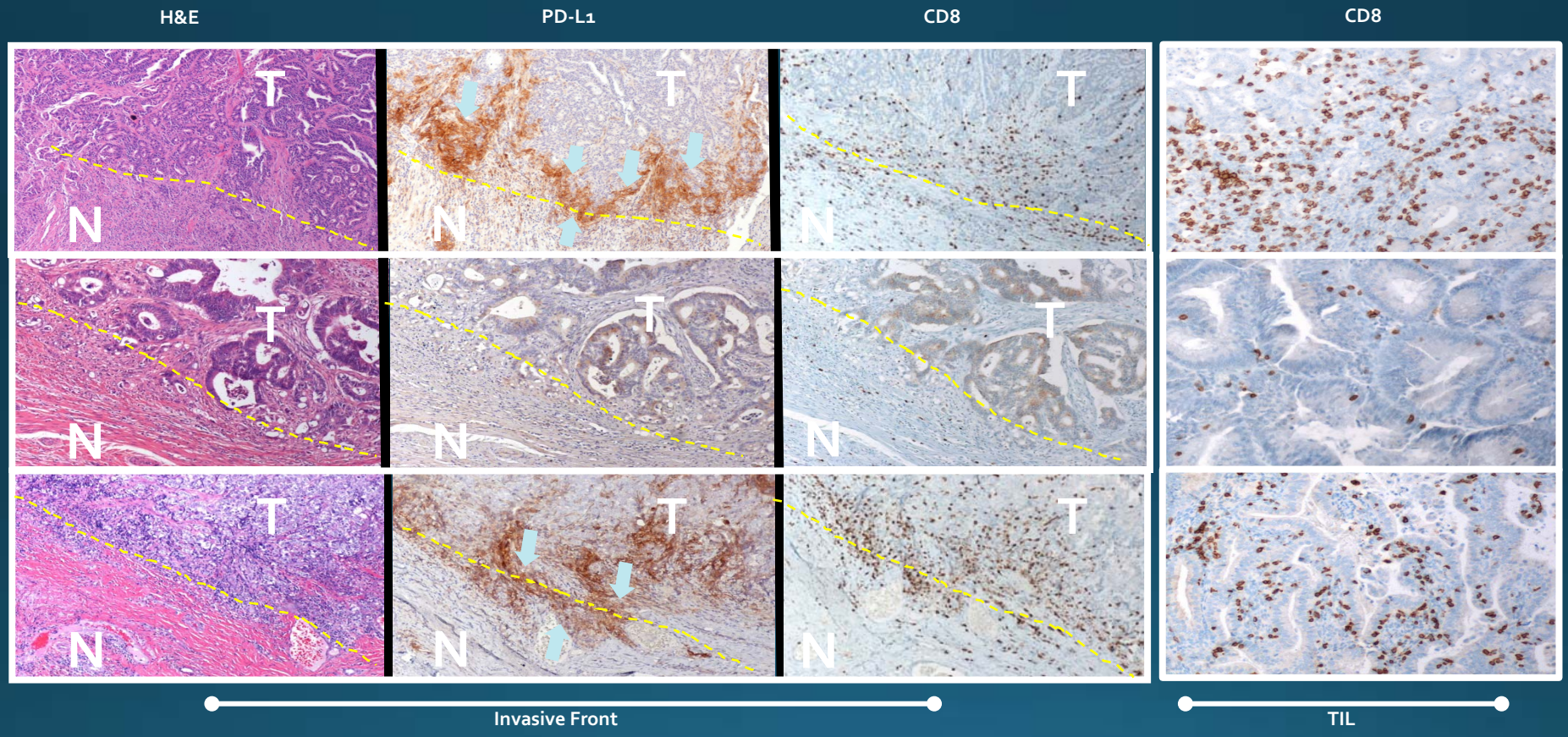
Hypermutation and Immuno-Oncology

- In CRC, MSI-H is associated with increases in immune infiltration and expression of immune checkpoint regulators[1,2]
- MSI-H is also associated with increased number of mutations per tumor
- Tumor mutations produce tumor-specific neoantigens, which when expressed on the tumor cell surface, are a target for T cells
  - May improve response to immunotherapy
- Elevated neoantigen load in CRC is associated with improved survival[2]

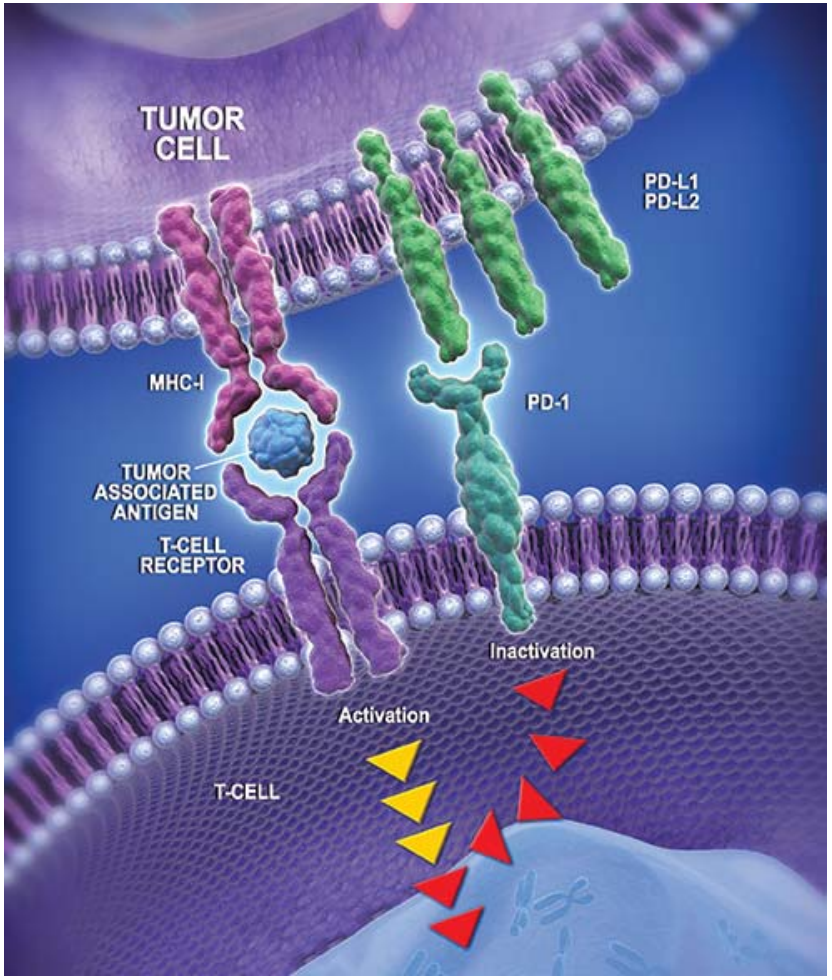


1. Llosa NJ, et al. *Cancer Discov*. 2015;5:43–51.
2. Giannakis M, et al. *Cell Reports*. 2016;15:857–865.

Baseline PD-L1 Expression and CD8 T-Cell Infiltration



PD-1 Pathway

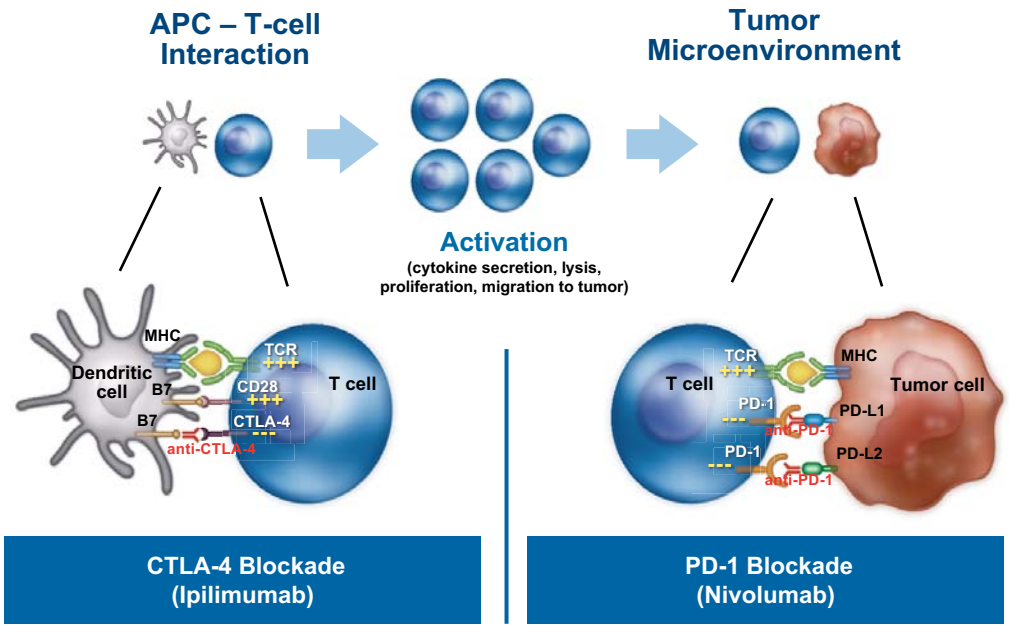


- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function[1]
- PD-L1 expression on tumor cells and macrophages suppresses immune surveillance, permitting neoplastic growth[2]

1. Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704. 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64.

Ipilimumab and Nivolumab Mechanisms of Action

- PD-1 expression on TILs is associated with decreased cytokine production and effector function[1]
- Nivolumab is a fully human IgG4 immune checkpoint inhibitor antibody
  - Binds PD-1 receptors on T cells
  - Disrupts PD-L1/PD-L2 signaling to restore antitumor immunity[2-4]
- Nivolumab and the anti-CTLA-4 antibody, ipilimumab, enhance T-cell antitumor activity through distinct but complementary mechanisms[1-3,5]
- The combination of nivolumab and ipilimumab has demonstrated deep and durable responses in solid tumors[6,7]

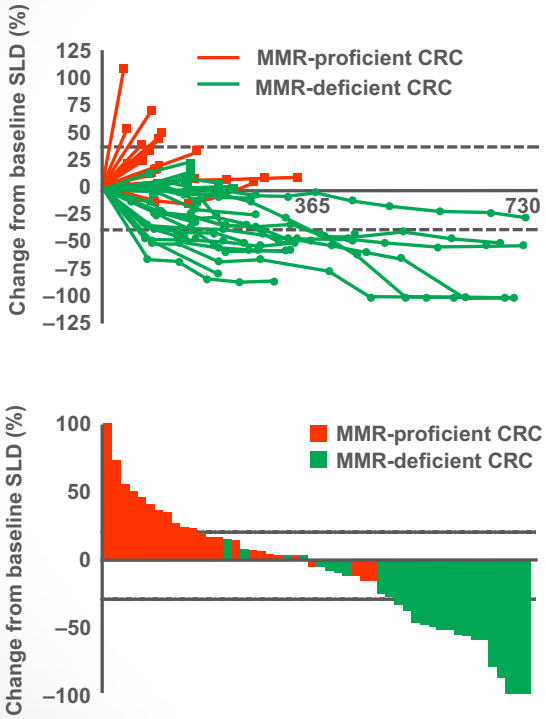


1. Hamid O, et al. *Exp Opin Biol Ther.* 2013;13:847–861.
2. Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167–3175.
3. Wang C, et al. *Cancer Immunol Res.* 2014;2:1–11.
4. Topalian SL, et al. *N Engl J Med.* 2012;366:2443–2454
5. Pardoll D, et al. *Nat Rev Cancer*. 2012;12:252-264.
6. Wolchok J, et al. *N Engl J Med*. 2013;369:122–133.
7. Postow MA, et al. *N Engl J Med*. 2015;372:2006–2017.

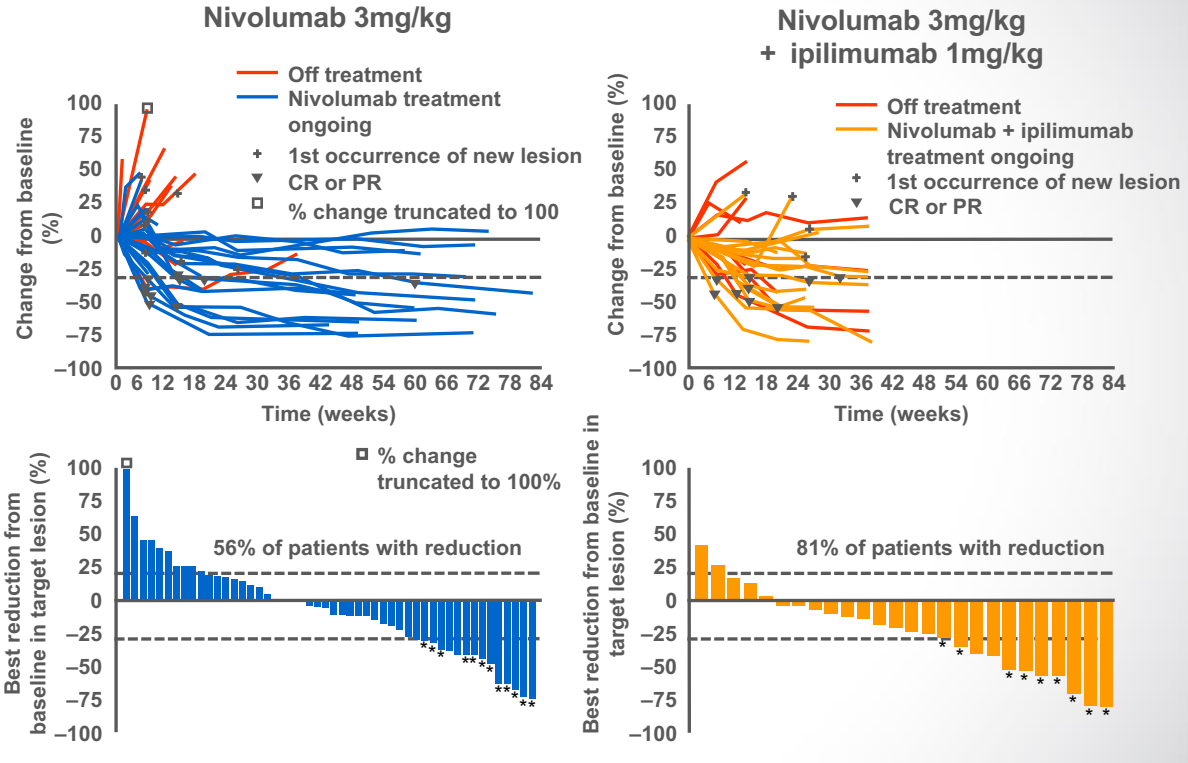
APC = antigen-presenting cell; MHC = major histocompatibility complex; TCR = T-cell receptor

MSI-high tumours are responsive to PD-1 inhibitors

Pembrolizumab (KEYNOTE 016, phase II)[1,*]



Nivolumab ± ipilimumab (CheckMate-142, phase II)[2]



*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

1. Le et al. ASCO 2016; 2. Overman et al. ASCO 2016

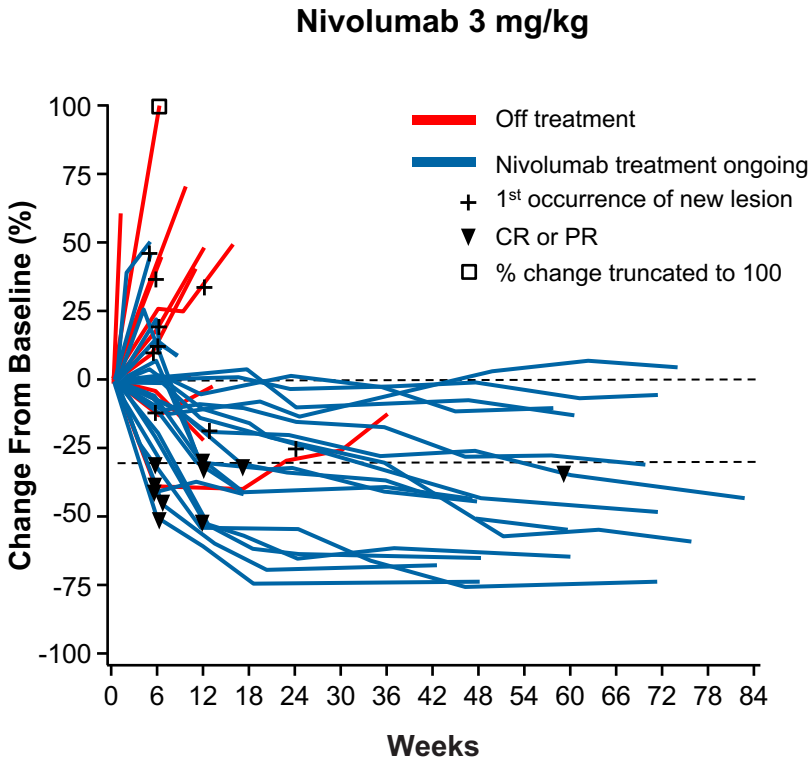
Type of Response-no (%)	**MMR-deficient CRC n=28**	**MMR-proficient CRC n=25**
Complete Response	3 (11)	0 (0)
Partial Response	13 (46)	0 (0)
Stable Disease (Week 12)	9 (32)	4 (16)
Progressive Disease	1 (4)	11 (44)
Not Evaluable[1]	2 (7)	10 (40)
Objective Response Rate (%)	16 (57)	0 (0)
95% CI	39 - 73	0 -13
Disease Control Rate (%)	25 (89)	4 (16)
95% CI	73 - 96	6 - 35
Median Follow Up (mos)	9.3	6

[1]Patients were considered not evaluable if they did not undergo a 12 week scan

Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab Monotherapy

	Nivolumab 3 mg/kg (n = 47)[a]
ORR, n (%) (95% exact CI)	12 (25.5) (15.4, 38.1)
Complete response	0
Partial response	12 (25.5)
Stable disease	14 (29.8)
Progressive disease	17 (36.2)
Unable to determine	4 (8.5)
Median time to response, mo (range)	2.12 (1.3–13.6)
Median duration of response, mo (range)	NE (0.0[b]–15.2[b])

[a]Patients with ≥ 12 weeks of follow-up
[b]Includes censored observations
CR = complete response; NE = not estimable; PR = partial response



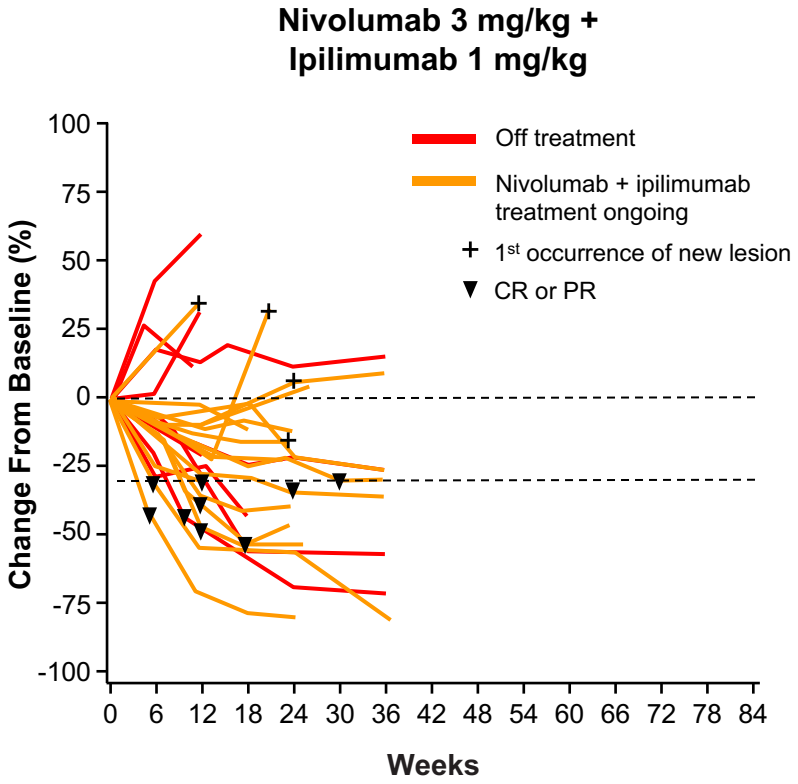
Horizontal reference line indicates 30% reduction

Overman ASCO 2016

Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab + Ipilimumab

	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 27)[a]
ORR, n (%) (95% exact CI)	9 (33.3) (18.6, 50.9)
Complete response	0
Partial response	9 (33.3)
Stable disease	14 (51.9)
Progressive disease	3 (11.1)
Unable to determine	0
Median time to response, mo (range)	2.73 (1.2–6.9)
Median duration of response, mo (range)	NE (NE–NE)

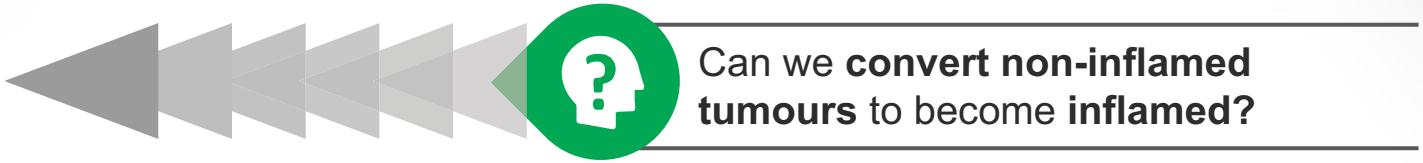
[a]Patients with ≥ 12 weeks of follow-up
[b]Includes censored observations
CR = complete response; NE = not estimable; PR = partial response



Horizontal reference line indicates 30% reduction

Overman ASCO 2016

How can we best treat the other 95% of CRC tumours that are MSS: combination approaches

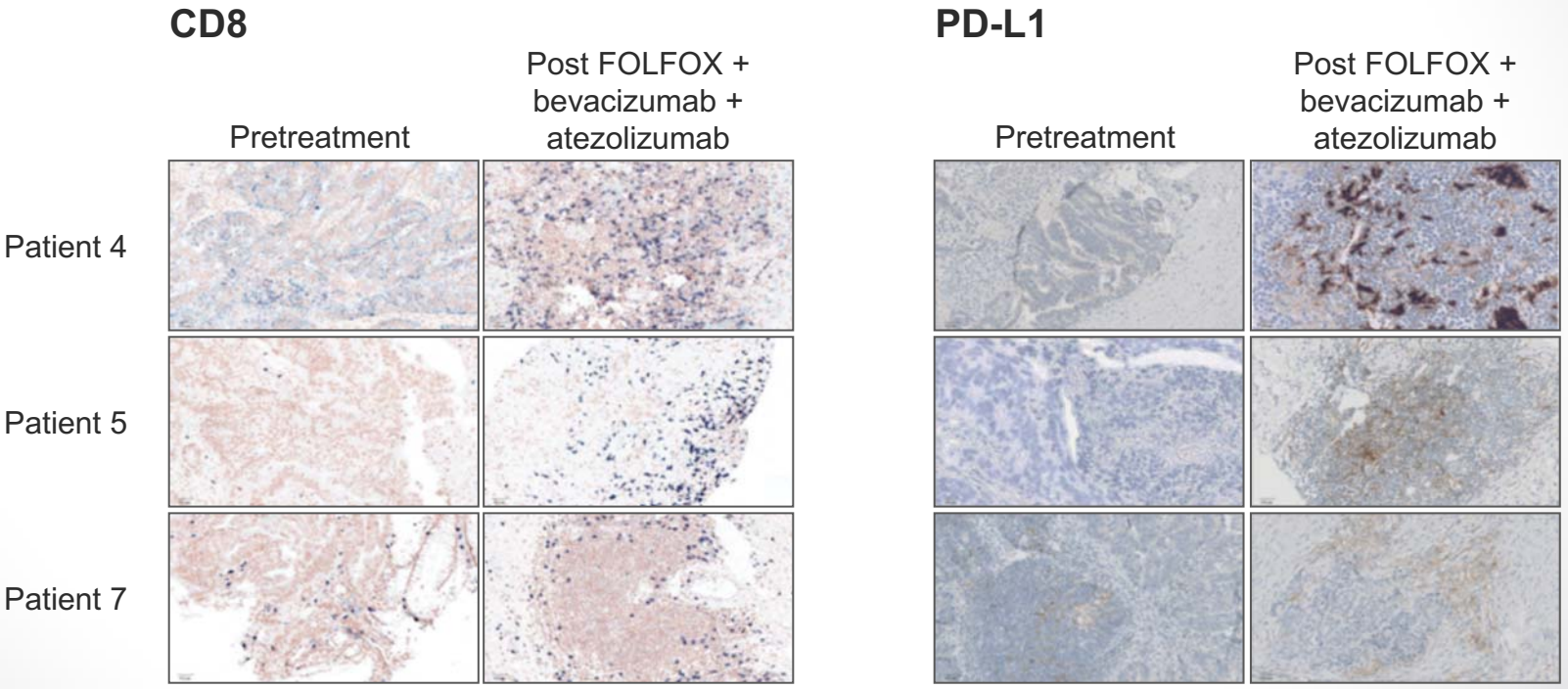


INFLAMED	IMMUNE EXCLUDED	IMMUNE DESERT
CD8+ T cells infiltrated, but non-functional	CD8+ T cells accumulated but not efficiently infiltrated	CD8+ T cells absent from tumour and periphery
Accelerate or remove brakes on T cell response	Bring T cells in contact with cancer cells	Increase number of antigen-specific T cells or increase antigen presentation

Kim and Chen. Ann Oncol 2016
Hegde et al. Clin Cancer Res 2016

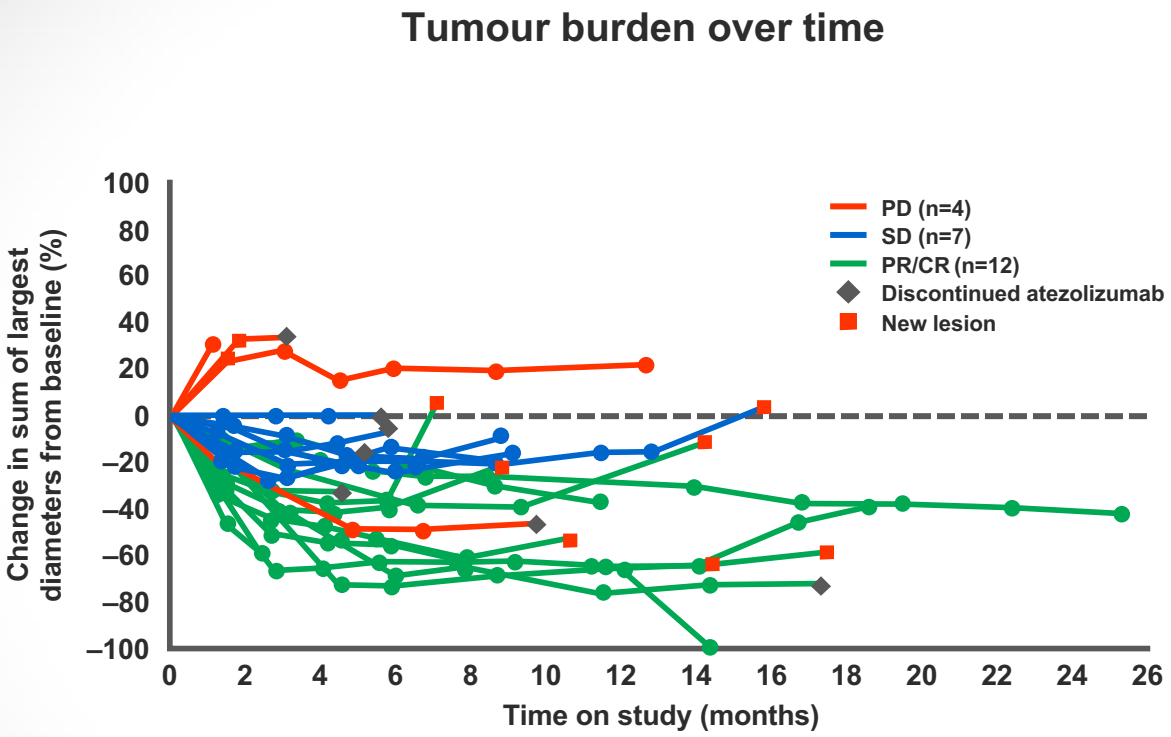
Combined chemotherapy plus Bevacizumab may create a favourable microenvironment for immunotherapy

- Increases in PD-L1 expression on immune cells are observed on-treatment (4/7)
- Baseline PD-L1 levels were not predictive of response



Wallin et al. AACR 2016

Atezolizumab plus Bevacizumab and/or FOLFOX in mCRC: phase Ib



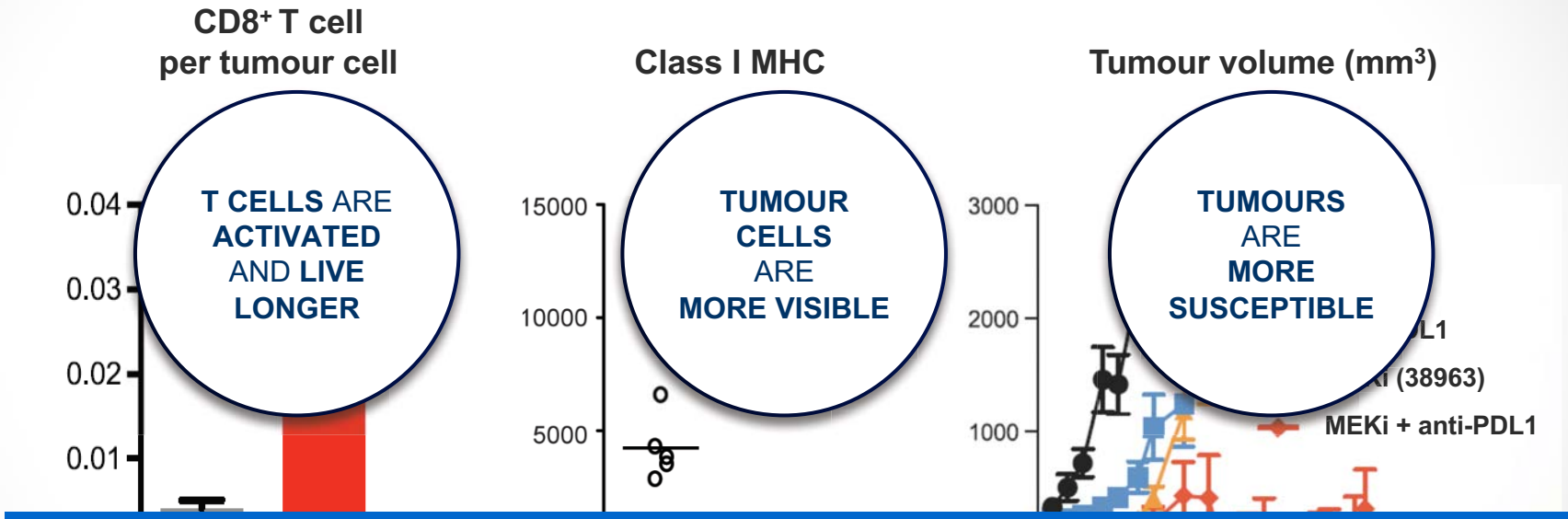
Patient number	ORR	mPFS	DOR
23	52%	14.1 months	11.4 months

- 3/9 patients treated beyond 15 months continue to be on treatment
- No unexpected toxicities were observed

Wallin et al. AACR 2016

MEK inhibition has a direct effect on T cells and the tumour microenvironment

- MEK inhibition alone can result in **intratumoural T-cell accumulation** and **MHC Class I upregulation**
- MEK inhibition and anti-PD-L1 are synergistic in xenograft models



A more favourable tumour microenvironment from MEK inhibition may help to unlock the full anti-tumour potential of PD-L1 inhibition

Ebert et al. Immunity 2016

Cobimetinib▼ + Atezolizumab in MSS mCRC (phase Ib)

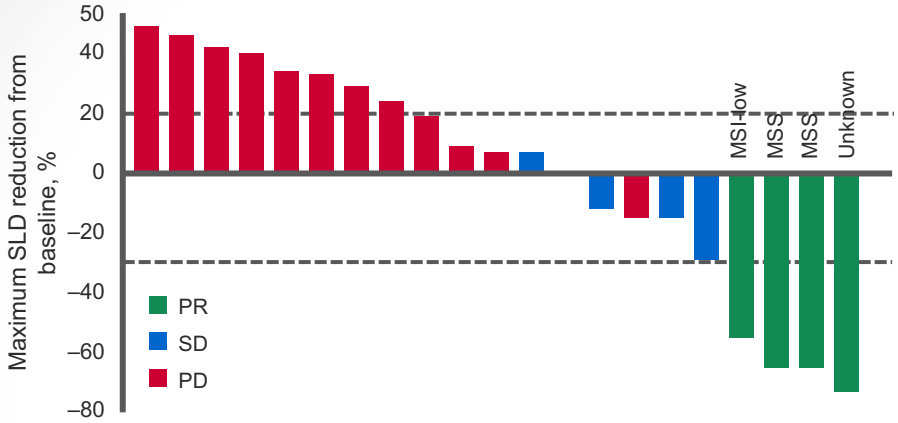
- Open-label, multicentre study including microsatellite stable (MSS) CRC tumours
- **Eligibility:** ECOG PS 0–1, measurable disease per RECIST v1.1
- **Primary endpoint:** dose limiting toxicity
- **Secondary endpoints:** DoR, AEs, C_{max}/C_{min} of atezolizumab and cobimetinib, ORR according to RECIST, PFS, OS

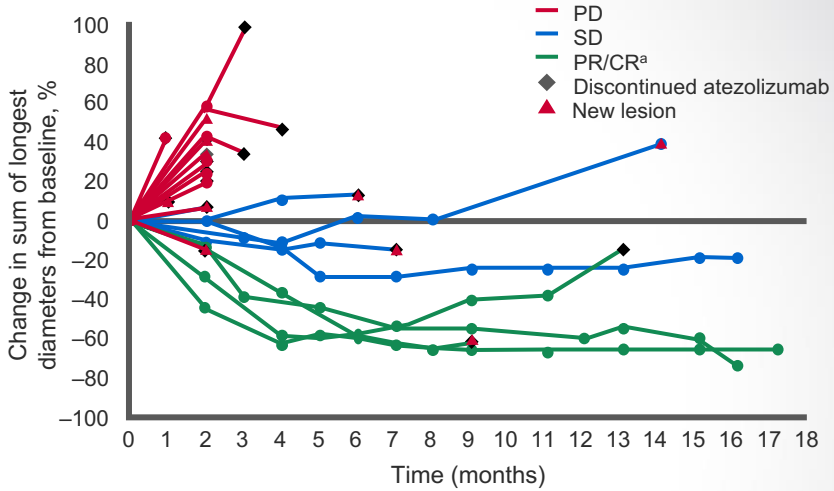
▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory authorities in your country according to your national requirements.

*One KRAS WT and two KRAS MT patients
clinicaltrials.gov identifier NCT01988896

Bendell et al. ASCO 2016
Desai et al. ESMO 2016

Cobimetinib + Atezolizumab efficacy: change in tumour burden



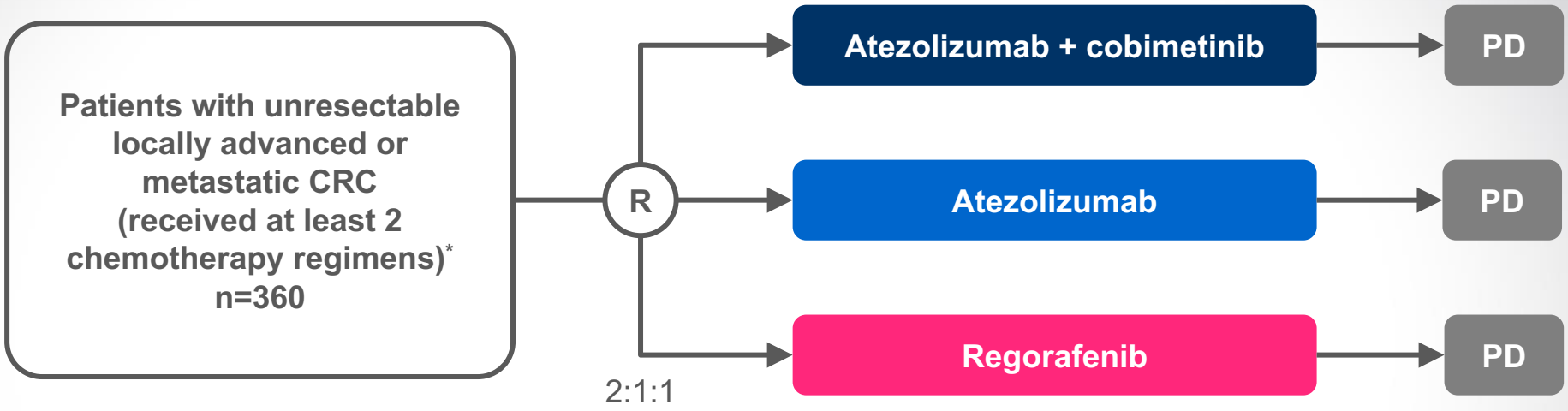


- Four patients had partial responses (confirmed per RECIST v1.1); responses are ongoing in two of these patients
- Median duration of response was not reached (range: 5.4–14.9+ months)
- Tumour volume reduction was not associated with PD-L1 status: TC3 (n=1, PD), TC0 (n=18), NA (n=4)

[a]Confirmed per RECIST v1.1

Bendell et al. ASCO 2016
Desai et al. ESMO 2016

Ongoing phase III trial of Cobimetinib and Atezolizumab in chemotherapy-refractory mCRC (COTEZO – IMBlaze 370)



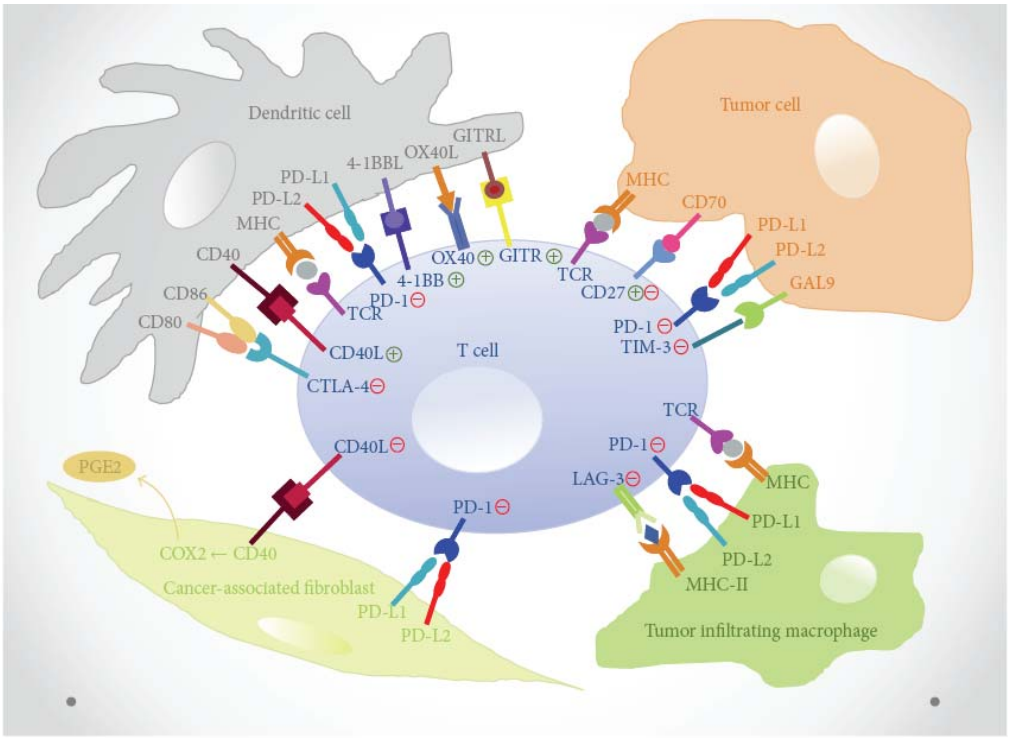
- Primary endpoint = OS

*Experienced disease progression or was intolerant to at least two systemic chemotherapy regimens including fluoropyrimidines, irinotecan, or oxaliplatin

NCT02788279

Emerging Strategies: Immunotherapy for mCRC

Immune checkpoint molecules in CRC pathogenesis[1]



Immunotherapies in clinical studies for mCRC[1,2]

- **Immune checkpoint inhibitors**
  - **PD-1 inhibitors**
  - **PD-L1 inhibitors**
  - **CTLA-4 inhibitors**
  - **LAG-3 inhibitors**
- **Vaccines**

1. Reprinted with permission from: Jacobs J, et al. *J Immunol Res*. 2015;2015:158038; 2. Koido S, et al. *World J Gastroenterol.* 2013;19: 8531-8542.