Immunotherapy in Colorectal cancer

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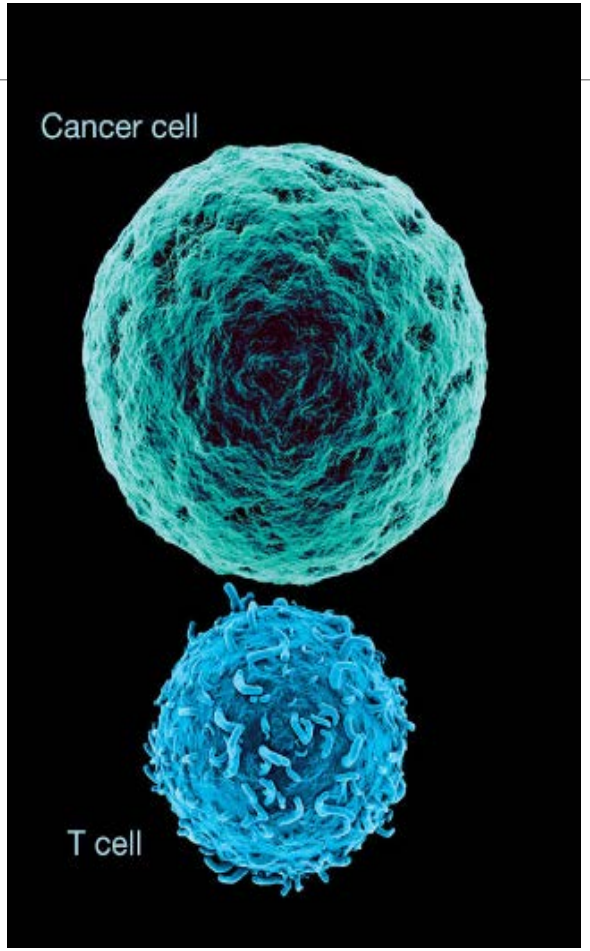


Introduction

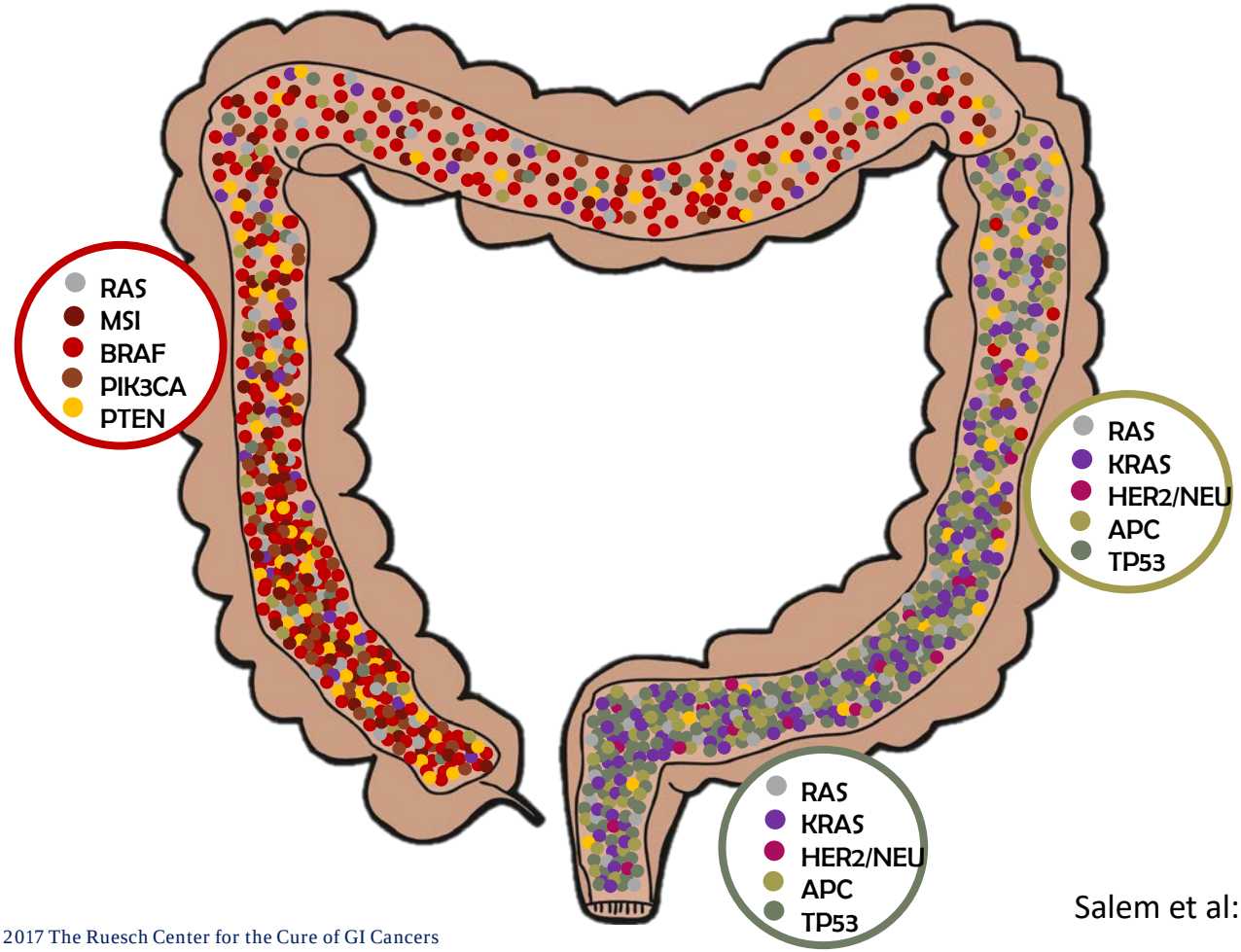
The Molecular and Immunologic landscape of Colorectal Cancer (CRC) had evolved the last decade.

Emphasis on precision Genomic-based medicine is able to provide a better understanding of CRC biomarkers that can be used to enhance successful treatment of patients with CRC

Identification of mutations in CRC in The EGFR signaling pathways involving all exons of *KRAS* and in *NRAS*, *BRAF*, *PIK3CA*, and *PTEN* helped to understand lack of response to anti-EGFR therapy.

Mismatch Repair protein identification in CRC not only may have predictive value in certain clinical setting but also a therapeutic implication.

Recent molecular biomarker data have shown the importance of microsatellite instability (MSI) testing, a marker of deficient mismatch repair (dMMR), for the selection of patients for immunotherapy



Salem et al: GI ASCO 2017

CRC and Mismatch Repair status

Sporadic MSI:

- 10-15% of all colon cancer
- Acquired hypermethylation of *MLH1* promoter
- More common than Lynch/HNPCC
- Leads to IHC profile: MLH1/PMS2 negative
- Lynch due to MLH1 germline mutation can have the same IHC profile

Unstable, MLH1/PMS2 (-) :

- BRAF V600E mutation in about 50% of sporadic unstable tumors, only rarely
- occurs in Lynch/HNPCC (so far, minority of those with PMS2 germline mutation;Senter, Gastroenterology, 2008)
- MLH1 methylation in most sporadic
- unstable tumors, only rarely in Lynch/ HNPCC

MMR-Deficiency and CRC Immune Microenvironment

MMR system is a DNA integrity maintenance system with is the correction of single base nucleotide mismatches (insertions or deletions) generated during DNA replication and recombination, thus maintaining the genomic stability

The mechanism of MMR involves at least three different processes:

1. Recognition of single base replication errors is performed by the MutSα (MSH2-MSH6 heteroduplex) or MutSβ (MSH2-MSH3 heteroduplex)

2. Excision of the lagging strand from the mismatch by one of the MutL complexes (mainly MutLα formed by MLH1/PMS2) recruited by MutS protein

3. Resynthesis of the excised-DNA and ligation by DNA polymerase delta and DNA ligase I

MLH1 complexes with PMS2

MSH2 complexes with MSH6

Therefore, if MLH1 is negative, PMS2 is usually negative and if MSH2 is negative, MHS6 is negative.

Corollary not necessarily true (MLH1 and MSH2 bind to other proteins as well)

MMR-Deficiency and CRC Immune Microenvironment

Mismatch Repair Deficient Tumors stimulates Immune system by Infiltration and Th1-associated environment

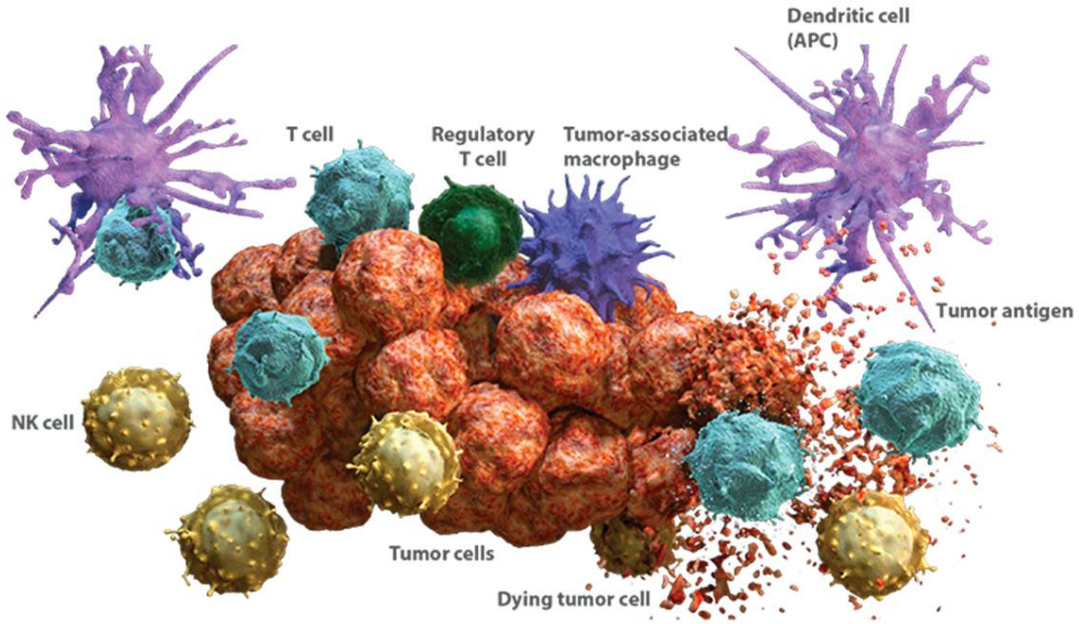
Several immune checkpoint ligands are upregulated in the dMMR tumor microenvironment : PD-1, PD-L1, cytotoxic T-lymphocyte associated protein 4 (CTLA- 4), lymphocyte-activation gene 3 (LAG-3) and IDO.

Thus, the active immune microenvironment appears to be counterbalanced by immune inhibitory signals that prevent tumor elimination

Immune infiltration directed → Neoantigens.

PD-L1 is also Upregulated on tumor cells and tumor-associated myeloid cells, and impairs T-cell-induced immune responses upon engaging its cognate co-inhibitory receptor, programmed cell death 1 (PD-1), which is always highly expressed on tumor-infiltrating lymphocytes (TILs)

Immune System: Able to Recognize and Eliminate Tumor Cells



INNATE IMMUNE RESPONSE

- The innate immune response is the body's first line of defense against pathogens and cancer[1]
- **Natural killer (NK) cells are essential innate effectors** of anti-tumor immunity[2]

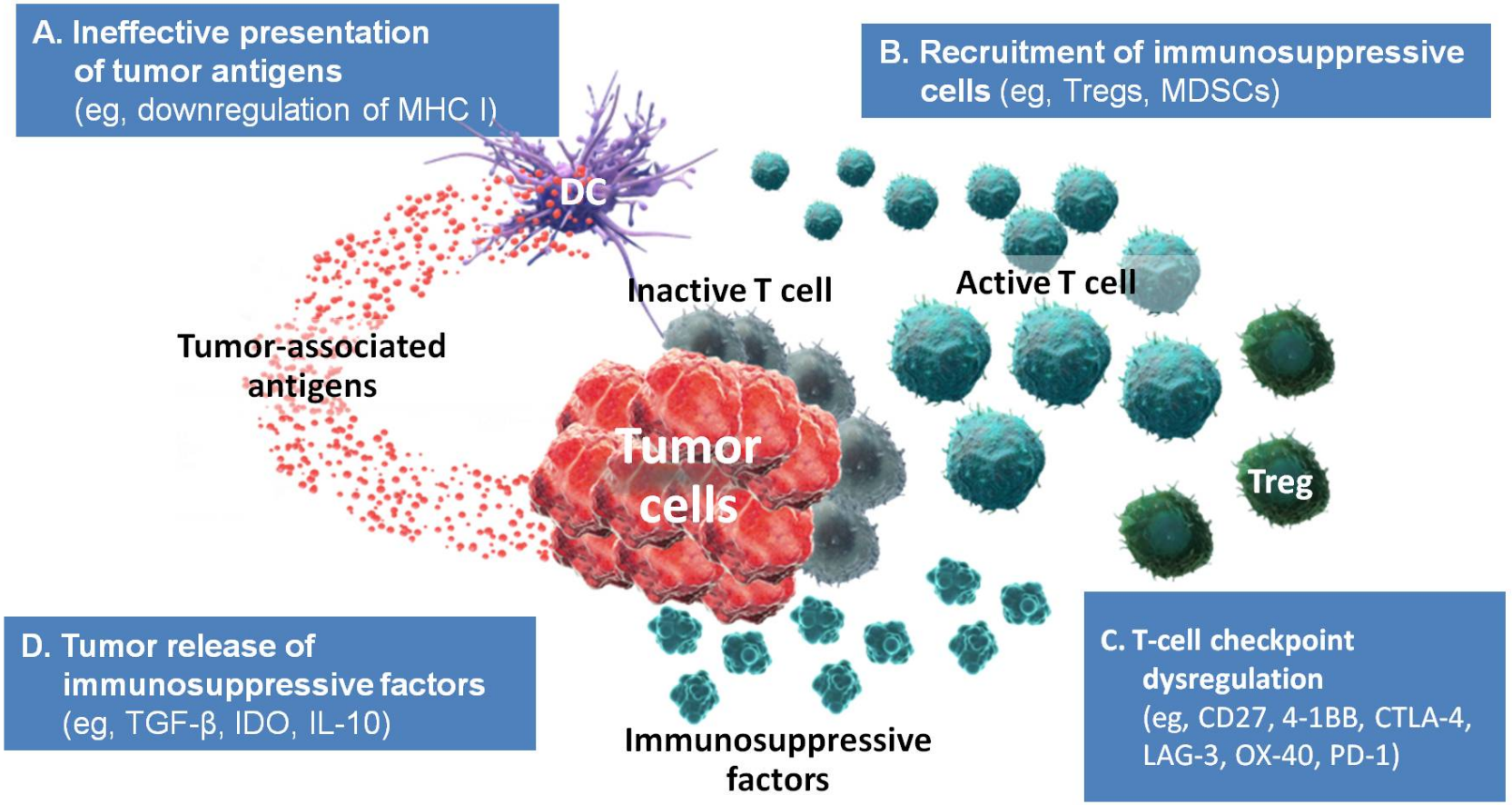
ADAPTIVE IMMUNE RESPONSE

- The adaptive immune response is antigen specific and able to produce a durable response[1]
- **Cytotoxic T cells are essential anti-tumor effector cells** of the adaptive immune system[2,3]

APC, antigen-presenting cell.

1. Dranoff G. *Nat Rev Cancer*. 2004;4:11-22. 2. Fernandez NC et al. *Nature Med*. 1999;5(4):405-411. 3. Ramarathinam L et al. *J Exp Med*. 1994;179(4):1205-1214.

Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System



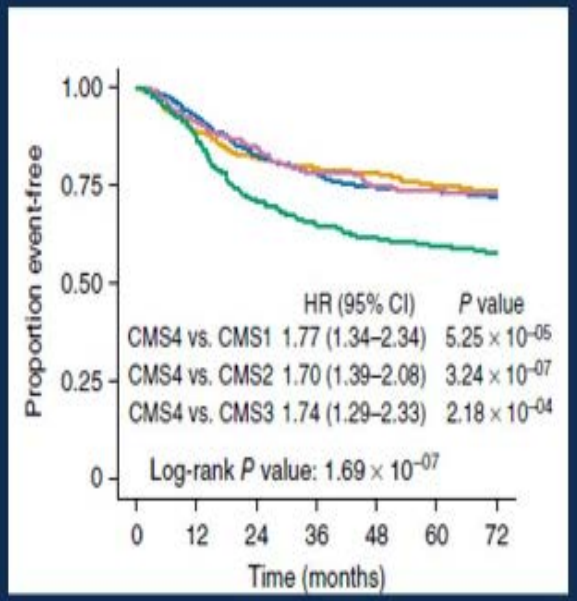
CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte antigen-4; DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; LAG-3, lymphocyte activation gene-3; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed death receptor-1; TGF-β, transforming growth factor beta; TIM-3, T cell immunoglobulin and mucin domain-3; Treg, regulatory T cell.

Vesely MD et al. Ann Rev Immunol. 2011;29:235-271.
Mellman I et al. Nature. 2011;480(7378):480-489.

Molecular markers that define high-risk stage II/III CRC

Cancer cell + Microenvironment markers: Gene expression CMS

RFS in 1,785 stage II/III CRC patients



CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI	CIN	CIN	CIN
	Epithelial	Epithelial	Mesechymal
	WNT/MYC	RAS mut	TGFß, angiogenesis
	EGFR high		
Immune infiltration			Stromal infiltration
Immune-activated	Immune-desert	Immune-desert	Immunosuppression
Right-sided	Left-sided	Right-sided	Both sides

Guinney et al, Nat Med 2015

Rationale of Immunotherapy in CRC MMR-D

Programmed death 1 (PD-1) pathway is a negative feedback system that represses Th1 cytotoxic immune responses and that, if unregulated, can damage the host.

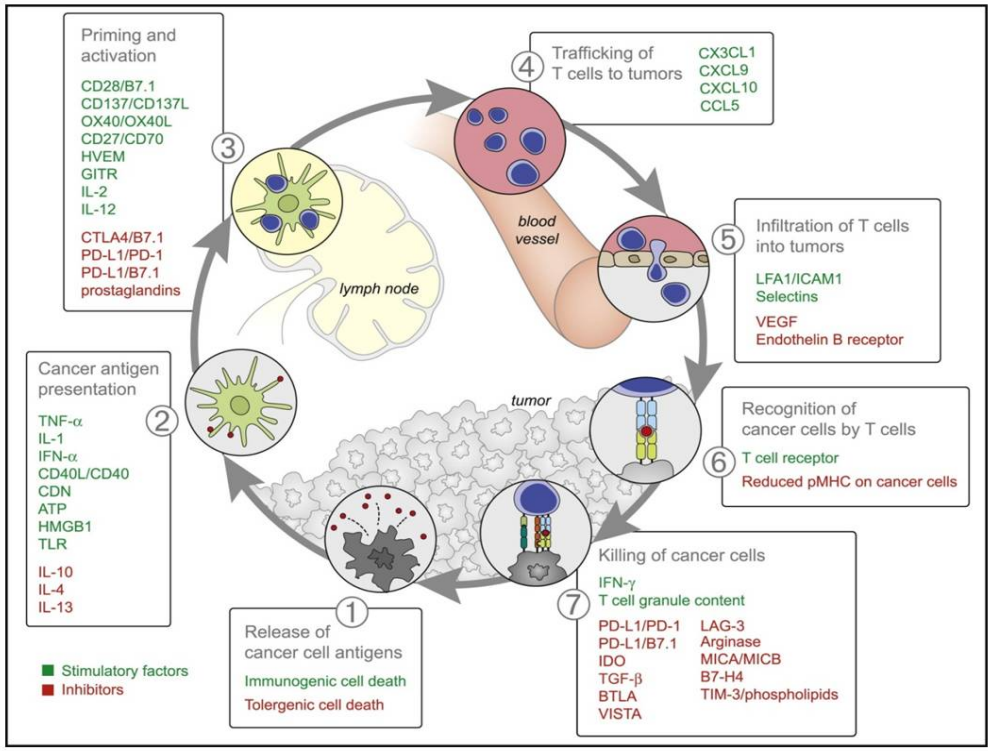
It is up-regulated in many tumors and in their surrounding microenvironment.

Blockade of this pathway with antibodies to PD-1 or its ligands has led to remarkable clinical responses in patients with many different types of cancer :

- Melanomas, non–small-cell lung cancer, renal-cell carcinoma, bladder cancer
- GI malignancies with MMR deficiency

The expression of PD-1 ligands (PD-L1 or PD-L2) on the surface of tumor cells or immune cells is an important — but not a definitive — predictive biomarker of response to PD-1 blockade.

Anti-Tumor Immune Response
Inhibition by Tumors

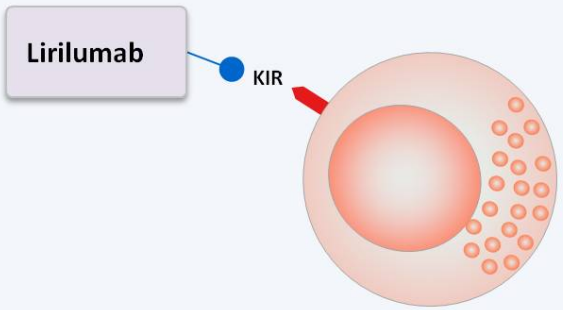


Chen DS, et al. Immunity. 2013;39:1-10.

1. Insufficient number of T cells are generated within the lymphoid compartment.
2. Insufficient number of T cells extravasate into the tumor.
3. T cells are inhibited in the tumor microenvironment.

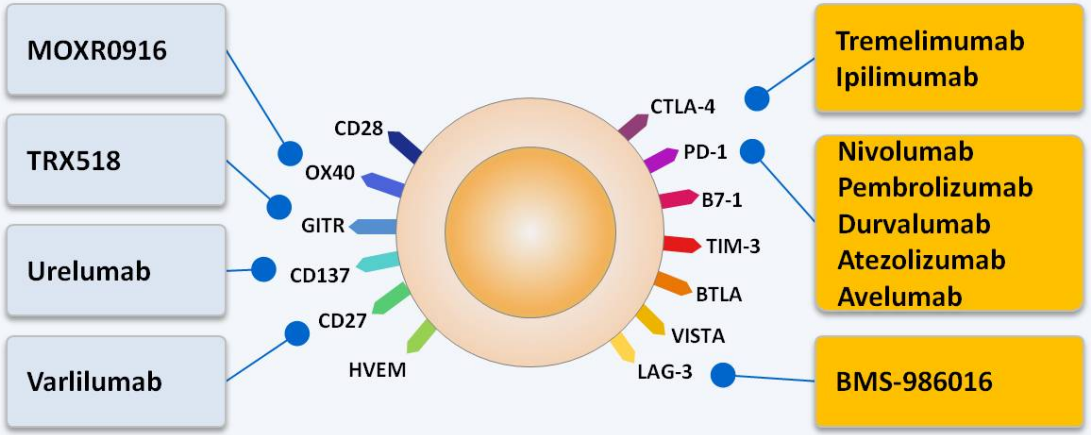
Targeting Checkpoints as an Approach to Cancer Therapy

Select Agents Targeting NK Cells (Innate Immunity)



Adapted from Pardoll et al.[1]

Select Agents Targeting T Cells (Adaptive Immunity)



Adapted from Mellman et al and Pardoll et al.[1,2]

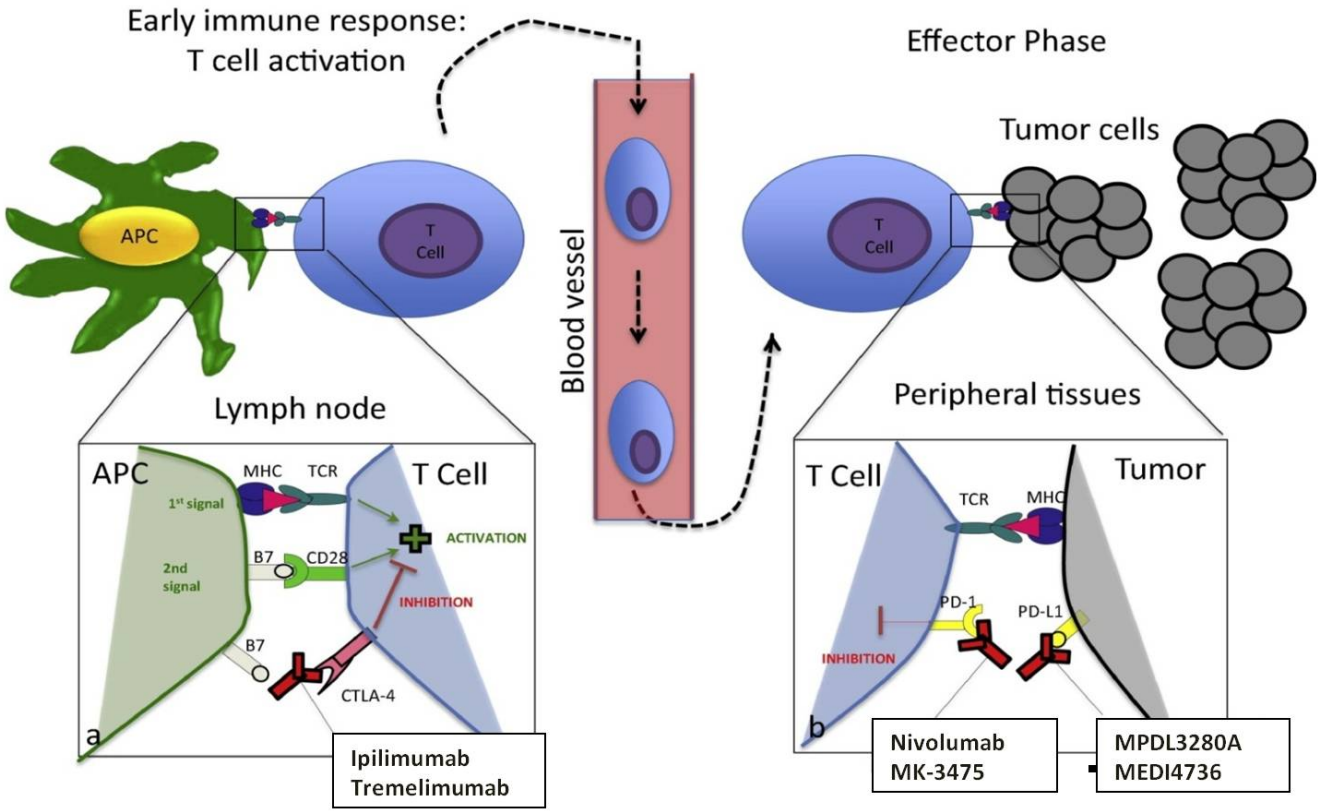
Blocking agents | **Stimulating agents**

*

CTLA-4=cytotoxic T-lymphocyte antigen-4; GITR=glucocorticoid-induced TNFR family related gene; KIR=killer-cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene-3; NK=natural killer; PD-1=programmed death-1; PD-L1=programmed death ligand-1.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264. 2. Mellman I et al. *Nature*. 2011;480(7378):480-489. 3. Clinicaltrials.gov.

Anti-PD1/PDL1 plus Anti-CTLA.4 to Influence the Lymphoid Compartment



Kyi C, et al. FEBS Lett. 2014;588:368-376

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.

PD-1 Blockade in Cancer with MMR- Deficiency

Le et al NEJM 2015:

- Phase II Trial for patients with MMR-D utilizing Pembrolizumab.
- 41 Patients with Metastatic Carcinoma with and Without MMR deficiency with Pembrolizumab between 2013-15
- Primary End Point: Immune Related ORR and PFS
- Pembrolizumab was administered intravenously at a dose of 10 mg per kilogram of body weight every 14 days
- The immune-related OR, PFS rate were :
  - 40% (4 of 10 patients) and 78% (7 of 9 patients), for MMR- deficient CRC
  - 0% (0 of 18 patients) and 11% (2 of 18 patients) for MMR-Proficient CRC .
- The median PFS and overall survival:
  - Not reached in the cohort with MMR-Deficient CRC
  - 2.2 and 5.0 months for MMR-Proficient (MSS) CRC

PD-1 Blockade in Cancer with MMR- Deficiency

Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.

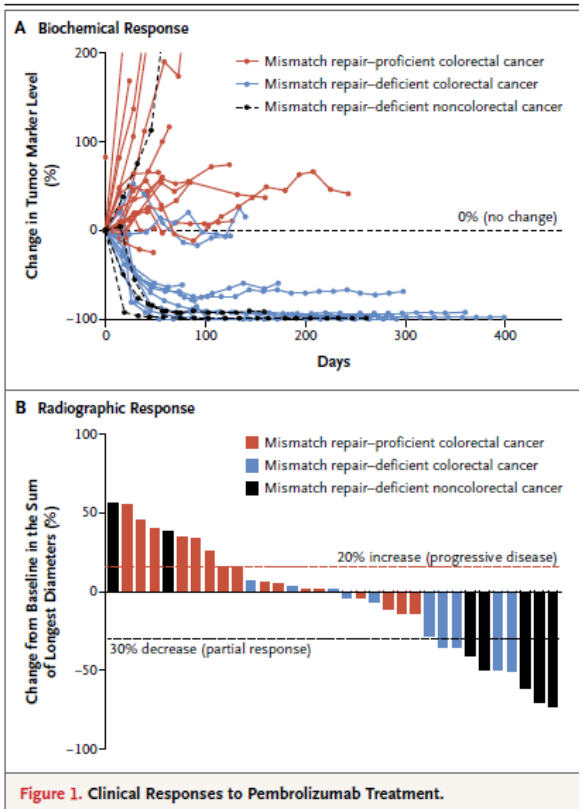
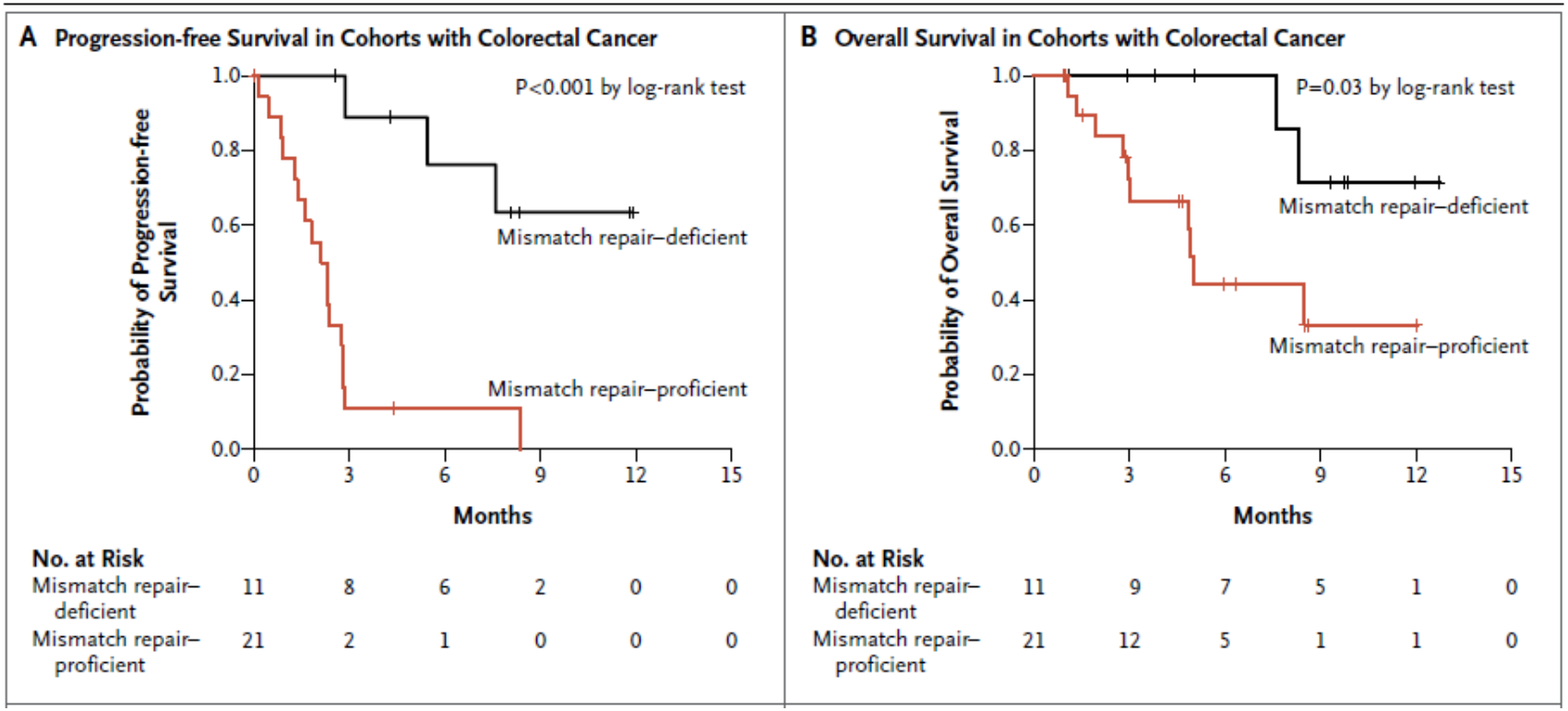
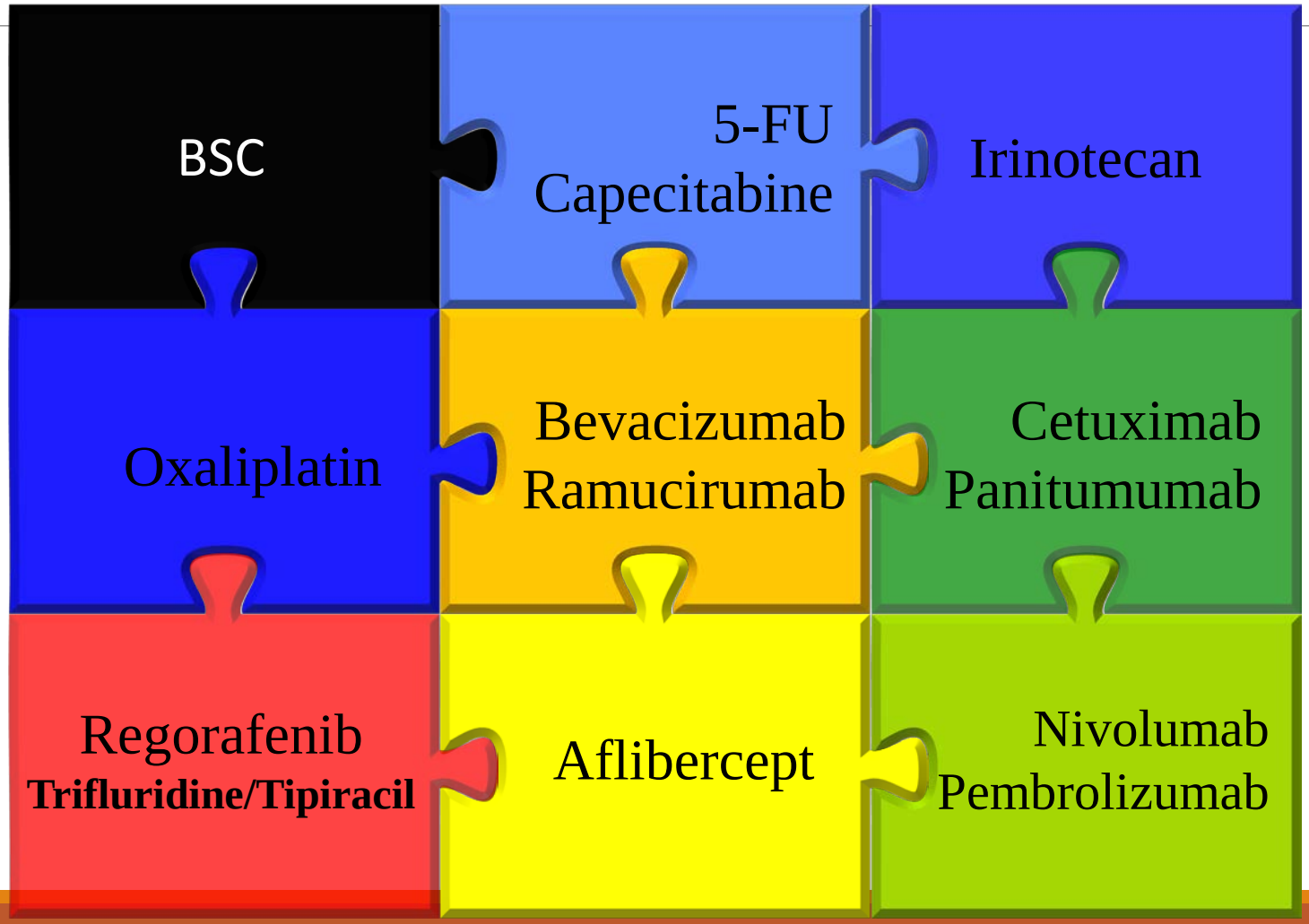
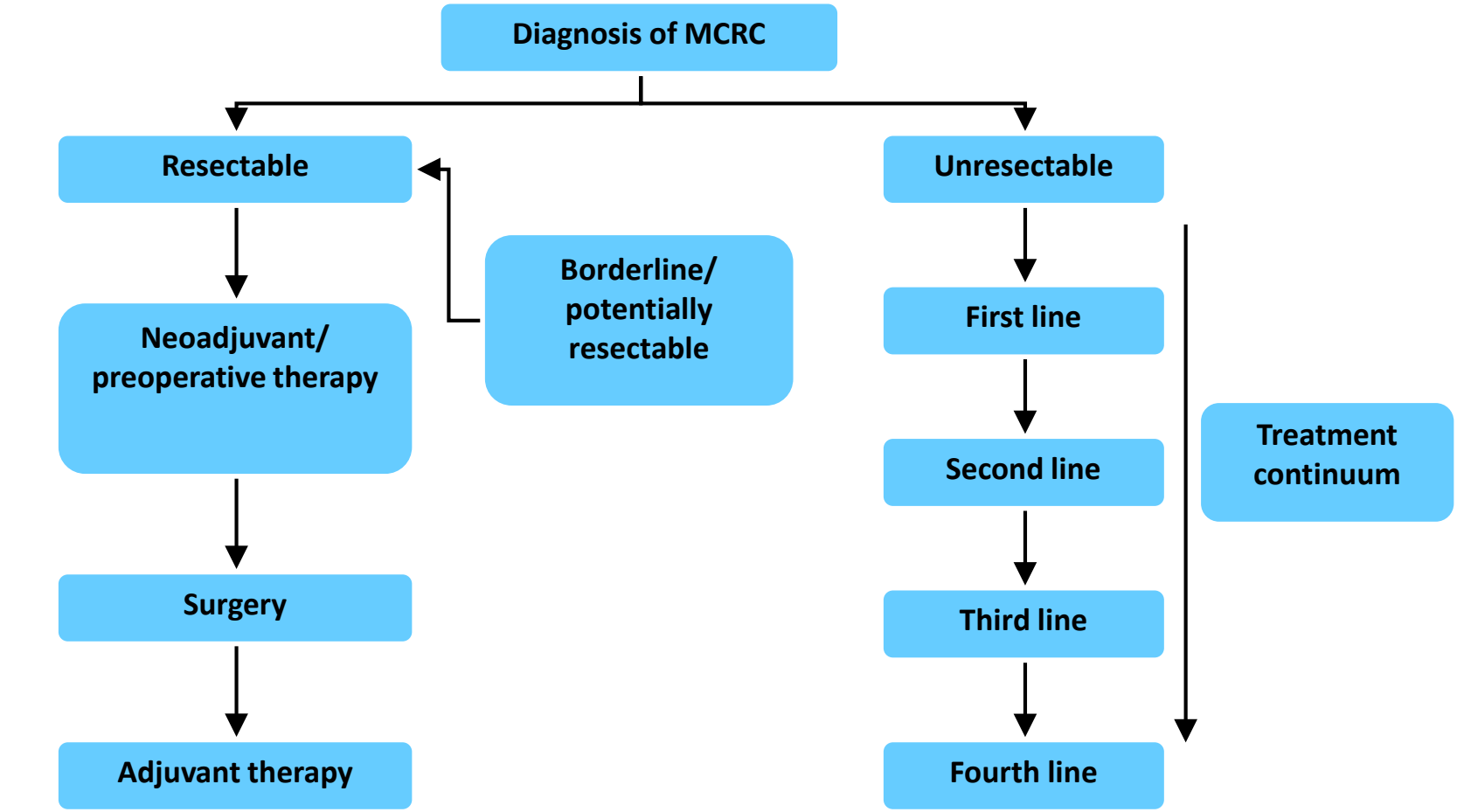


Figure 1. Clinical Responses to Pembrolizumab Treatment.


A Progression-free Survival in Cohorts with Colorectal Cancer
Probability of Progression-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
P<0.001 by log-rank test
Mismatch repair–deficient
Mismatch repair–proficient
0
3
6
9
12
15
Months
No. at Risk
Mismatch repair–deficient 11 8 6 2 0 0
Mismatch repair–proficient 21 2 1 0 0 0
B Overall Survival in Cohorts with Colorectal Cancer
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
P=0.03 by log-rank test
Mismatch repair–deficient
Mismatch repair–proficient
0
3
6
9
12
15
Months
No. at Risk
Mismatch repair–deficient 11 9 7 5 1 0
Mismatch repair–proficient 21 12 5 1 1 0


BSC
5-FU
Capecitabine
Irinotecan
Oxaliplatin
Bevacizumab
Ramucirumab
Cetuximab
Panitumumab
Regorafenib
Trifluridine/Tipiracil
Aflibercept
Nivolumab
Pembrolizumab

Management of MCRC: An Evolving Treatment Algorithm



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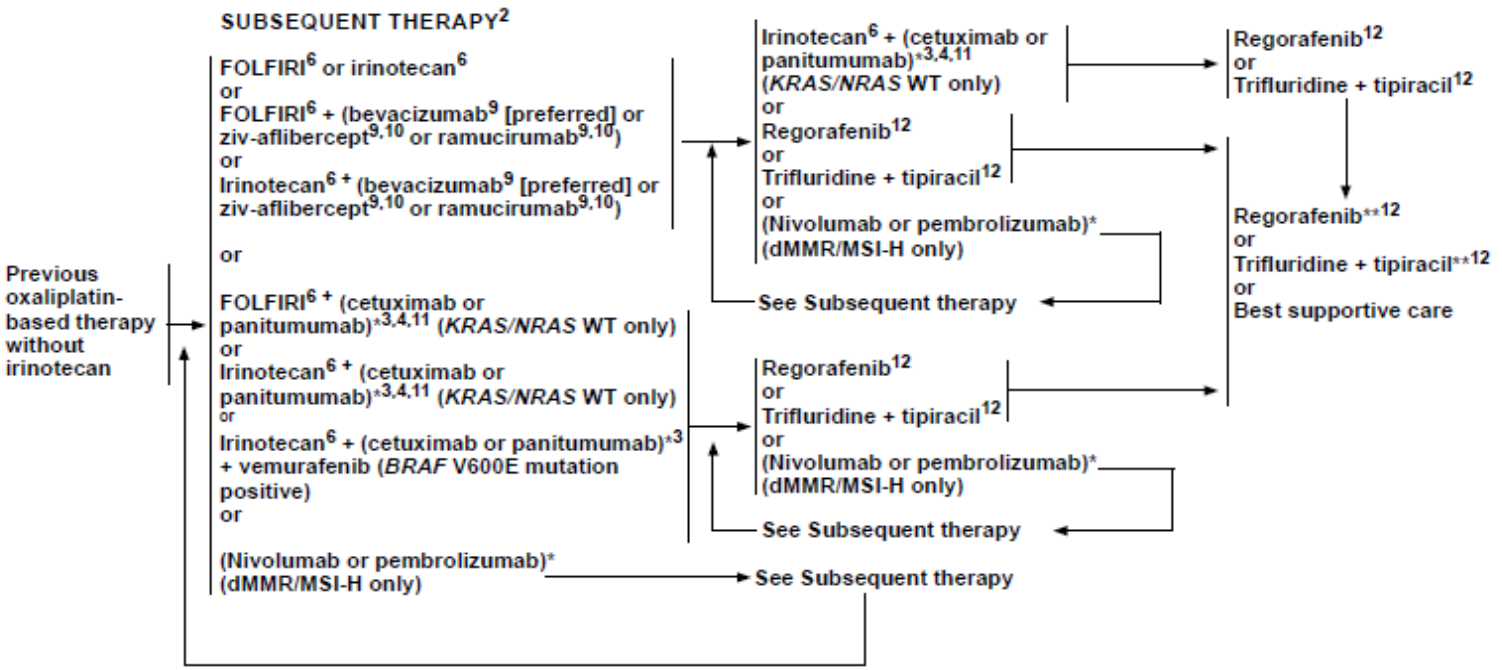
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[1]



*if neither previously given
**if not previously given

See footnotes COL-D 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[1]

INITIAL THERAPY[2]

Patient appropriate for intensive therapy

- FOLFOX ± bevacizumab
  or
  CAPEOX ± bevacizumab
  or
  FOLFOX + (cetuximab or panitumumab)[3-5]
  (*KRAS*/*NRAS* WT and left-sided tumors only)
  → Progression → See COL-D 2 of 10
- or
  FOLFIRI[6] ± bevacizumab
  or
  FOLFIRI[6] + (cetuximab or panitumumab)[3-5]
  (*KRAS*/*NRAS* WT and left-sided tumors only)
  → Progression → See COL-D 3 of 10
- or
  FOLFOXIRI[6] ± bevacizumab → Progression → See COL-D 4 of 10
- or
  5-FU/leucovorin (infusional preferred) ± bevacizumab[7]
  or
  Capecitabine ± bevacizumab[7]
  → Progression → See COL-D 5 of 10

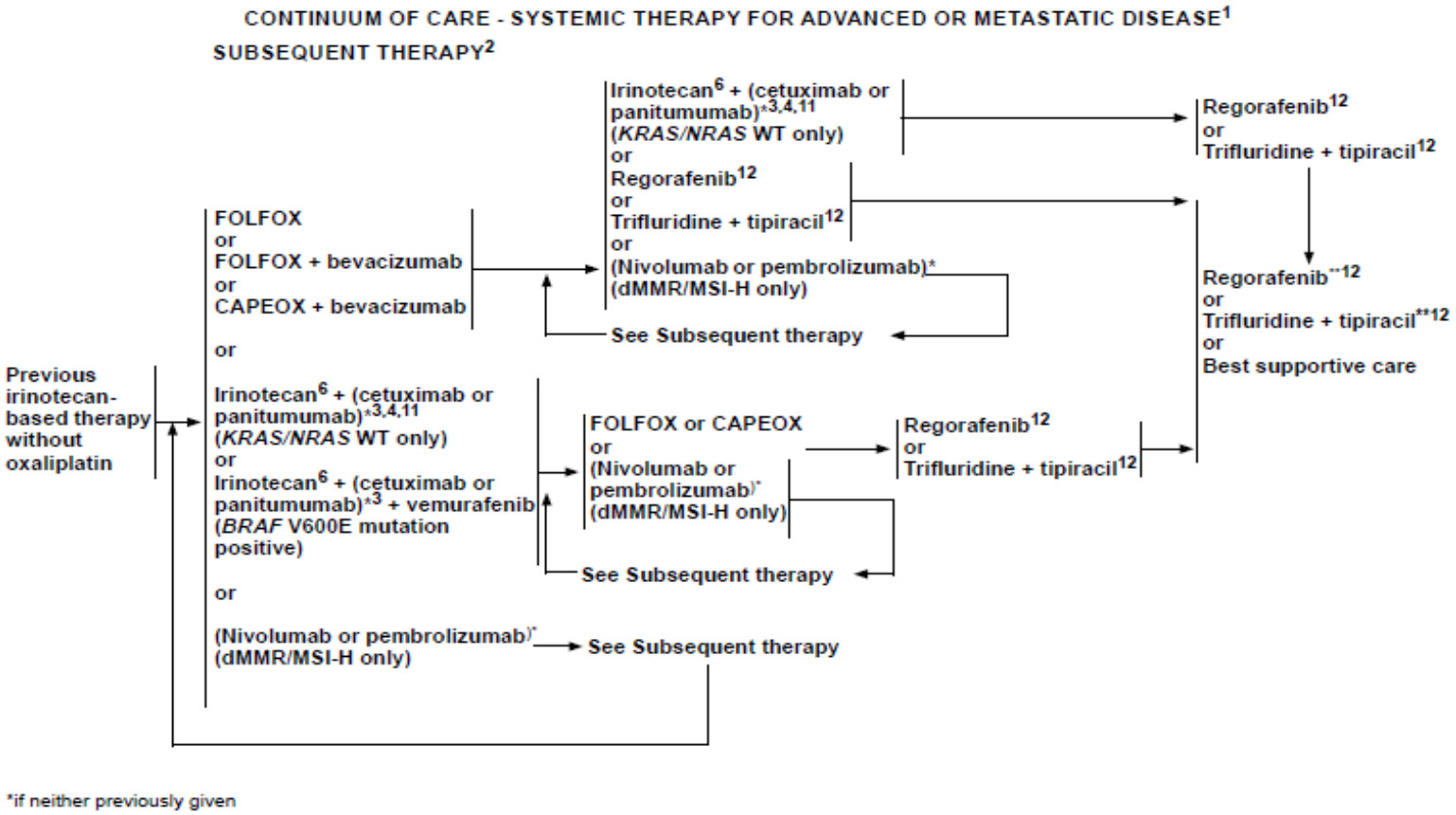
Patient not appropriate for intensive therapy[2]

- Infusional 5-FU + leucovorin ± bevacizumab
  or
  Capecitabine ± bevacizumab
  or
  (Cetuximab or panitumumab)[3-5]
  (category 2B) (*KRAS*/*NRAS* WT and left-sided tumors only)
  or
  (Nivolumab or pembrolizumab)
  (dMMR/MSI-H only)[3]

  → Improvement in functional status → Consider initial therapy as above[8]

  → No improvement in functional status → Best supportive care
  See NCCN Guidelines for Palliative Care

See footnotes COL-D 6 of 10



*if neither previously given

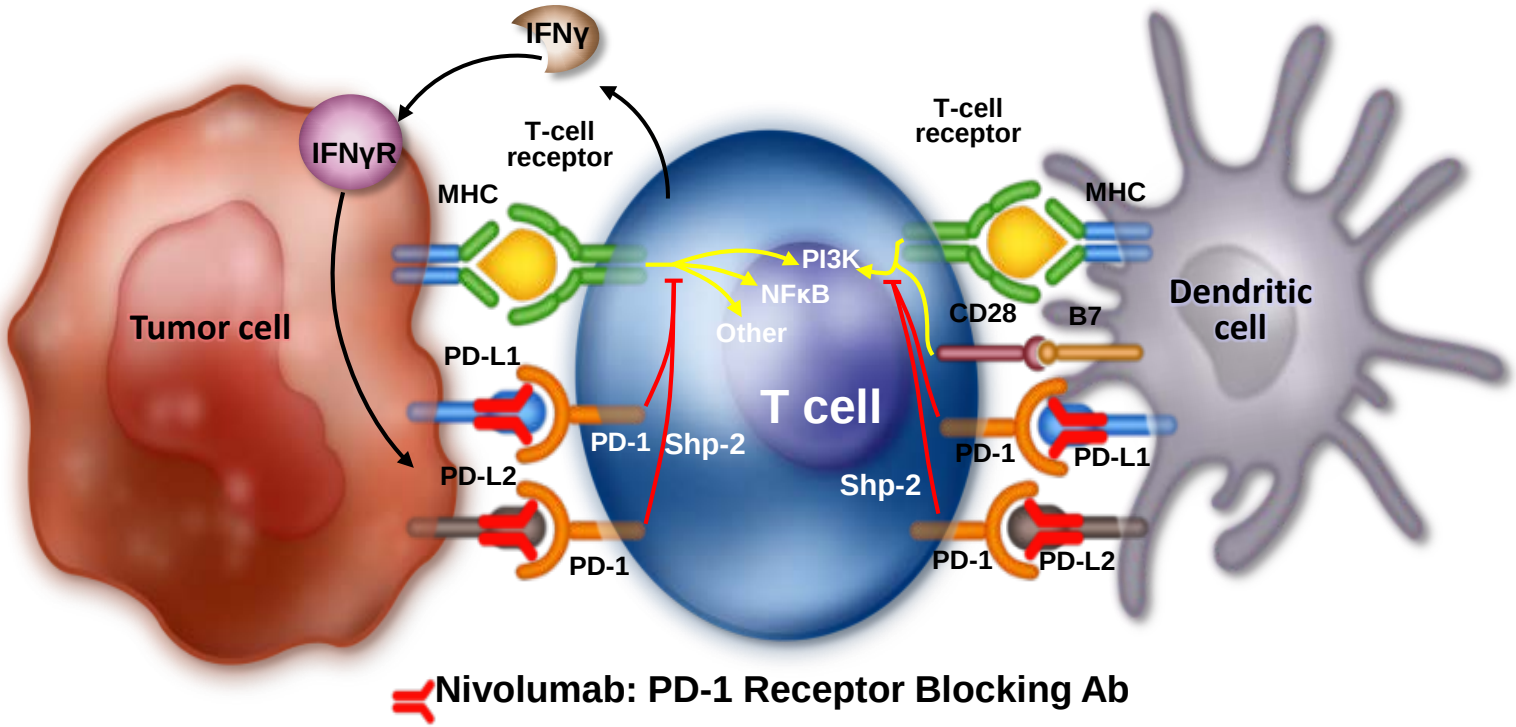
Table 1. Key immunotherapy trials in metastatic colorectal cancer (CRC).

Drug(s)	Target	Population	Patients	Response Rate	Identifier
Trials for MSI-H CRC					
Pembrolizumab	PD-1	Refractory MSI-H CRC	25	57%	Le et al. [30]
Nivolumab	PD-1	Refractory MSI-H CRC	47	26%	NCT02060188 [31]
Nivolumab + Ipilimumab	PD-1 + CTLA-4	Refractory MSI-H CRC	30	33%	
Trials for MSS CRC					
Pembrolizumab	PD-1	Refractory MSS CRC	28	0%	Le et al. [30]
Nivolumab + Ipilimumab	PD-1 + CTLA-4	Refractory MSS CRC	20	5%	NCT02060188 [31]
Trials of Various CRC Sub-Types					
Tremelimumab	CTLA-4	Refractory CRC	49	2%	Chung et al. [28]
Nivolumab	PD-1	Refractory CRC	19	0%	Topalian et al. [32]
BMS-936559	PD-L1	Refractory CRC	18	0%	Brahmer et al. [33]
Atezolizumab + Bevacizumab	PD-L1	Refractory CRC	14	7%	NCT01633970 [34]
Atezolizumab + FOLFOX/bev		Metastatic CRC (70% first line)	30	40% (total) 48% (first-line)	
Atezolizumab + Cobimetinib	PD-L1 MEK	Refractory CRC (30% MSS, 70% unknown)	23	17% (3 MSS, 1 unknown)	NCT01988896 [35]

Nivolumab Mechanism of Action

PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function[11]

Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[12–14]



Nivolumab in MMR-D CRC

CheckMate-142 Study Design

Phase 2 Nonrandomized Study

- Histologically confirmed metastatic or recurrent CRC
- dMMR/MSI-H per local laboratory
- ≥ 1 prior line of therapy

Combination cohort[a] → Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses and then nivolumab 3 mg/kg Q2W)

Monotherapy cohort[a] → Nivolumab 3 mg/kg Q2W

Primary endpoint:

- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:

- ORR per BICR, DCR,[b] DOR, PFS, OS, and safety

- Median follow-up in the combination therapy cohort (N = 119) was 13.4 months (range, 9–25)[c]
- Results of the monotherapy cohort (N = 74) with a similar median follow-up of 13.4 months (range, 10–32) are also presented[1,c]

[a]Enrollment was staggered with additional patients being enrolled if ≥ 7 of the first 19 centrally confirmed MSI-H patients had a confirmed response (CR or PR). CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison. [b]Patients with a CR, PR, or SD for ≥12 weeks. [c]Defined here as the time from first dose to data cutoff.

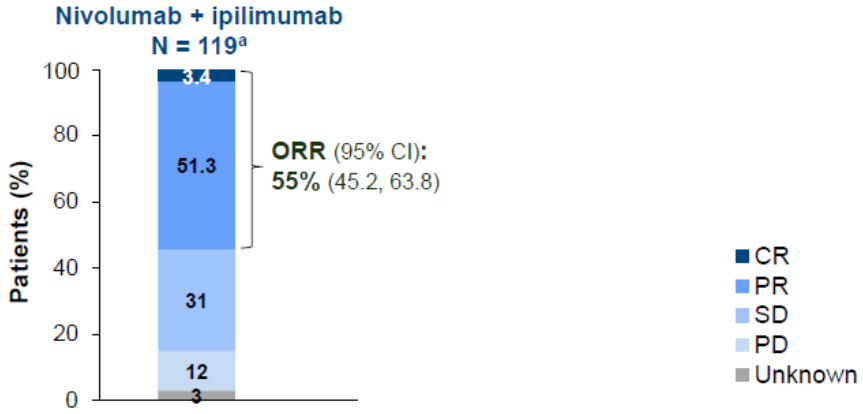
1. Overman MJ, et al. *Lancet Oncol* 2017;18:1182–1191.

Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142

Thierry André,[1] Sara Lonardi,[2] Ka Yeung Mark Wong,[3] Heinz-Josef Lenz,[4] Fabio Gelsomino,[5] Massimo Aglietta,[6] Michael Morse,[7] Eric Van Cutsem,[8] Ray McDermott,[9] Andrew Graham Hill,[10] Michael B. Sawyer,[11] Alain Hendlisz,[12] Bart Neyns,[13] Magali Svrcek,[1] Rebecca A. Moss,[14] Jean-Marie Ledeine,[15] Z. Alexander Cao,[14] Shital Kamble,[14] Scott Kopetz,[16] Michael J. Overman[16]

[1]Hôpital Saint Antoine and Sorbonne Universités, UMPC Paris 06, Paris, France; [2]Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; [3]The University of Sydney, Sydney Medical School, Sydney, Australia; [4]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [5]University Hospital of Modena, Italy; [6]University of Torino, Turin, Italy; [7]Duke University Office of Research Administration, Durham, NC; [8]University Hospitals Gasthuisberg - Leuven, Leuven, Belgium; [9]St Vincent's University Hospital, Dublin, Ireland; [10]Tasman Oncology Research Pty Ltd, Southport, Queensland, Australia; [11]Cross Cancer Institute, Edmonton, AB, Canada; [12]Institut Jules Bordet, Brussels, Belgium; [13]Universitair Ziekenhuis Brussel, Brussels, Belgium; [14]Bristol-Myers Squibb, Princeton, NJ; [15]Bristol-Myers Squibb, Braine-l'Alleud, Belgium;[16]MD Anderson Cancer Center, Houston, TX

Investigator-Assessed Response and Disease Control

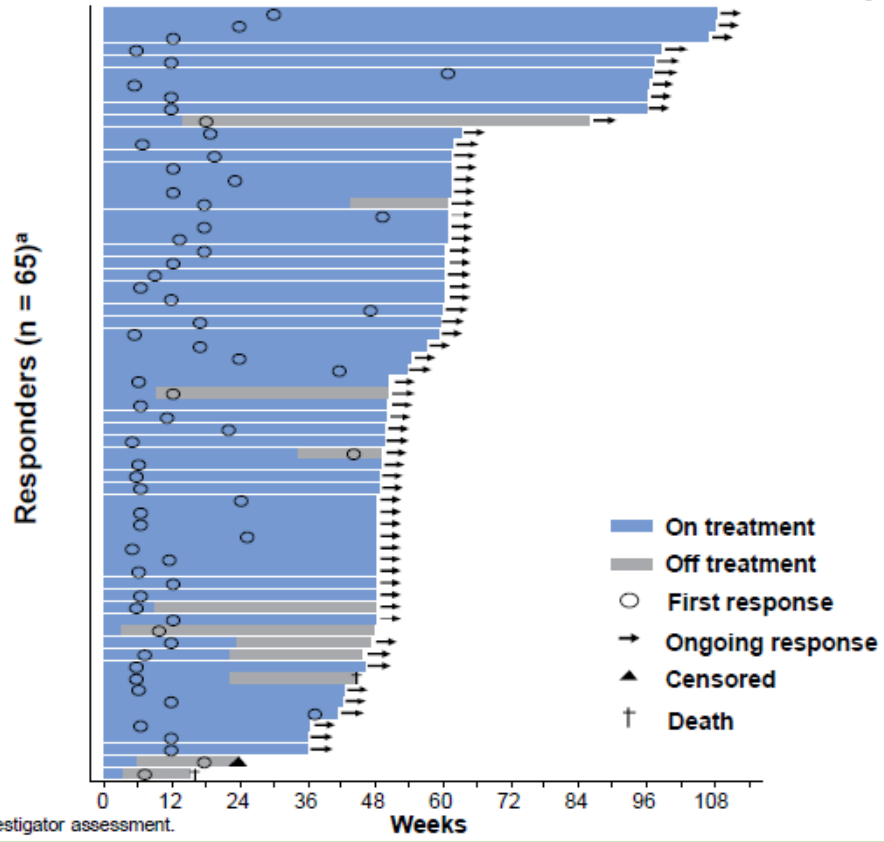


- DCR[b] was 80% (95% CI: 71.5, 86.6) with combination therapy and 69% (57.1, 79.2) with monotherapy[1,d]
- Combination therapy provided a numerically higher ORR, including CRs, and DCR relative to monotherapy during a similar follow-up period[d]

[a]Median follow-up was 13.4 months (range, 9–25). [b]Disease control was defined as patients with a CR, PR, or SD for ≥12 weeks. [c]Median follow-up was 13.4 months (range, 10–32).
[d]CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.
1. Overman MJ et al. *Lancet Oncol* 2017;18:1182–1191.

Characterization of Response

Nivolumab + ipilimumab

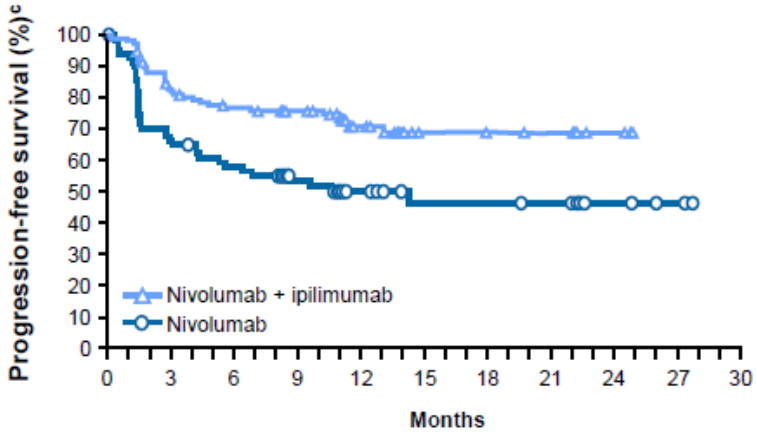


[a]Response per investigator assessment.

- Median time to response was 2.8 months (range, 1–14)
- Responses were durable:
  - Median DOR was not reached
  - 94% of responders had ongoing responses at data cutoff

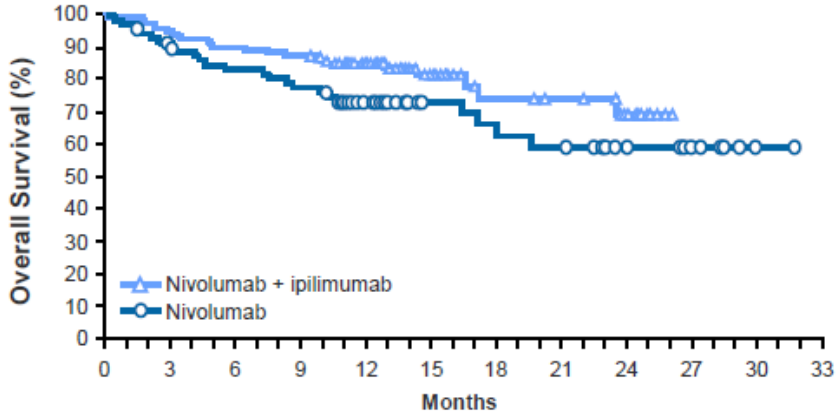
Progression-Free and Overall Survival

	Nivolumab + ipilimumab[a,b]
9-month rate (95% CI), %	76 (67.0, 82.7)
12-month rate (95% CI), %	71 (61.4, 78.7)



No. at Risk											
Nivolumab + ipilimumab	119	95	86	78	39	12	11	10	3	0	0
Nivolumab	74	48	41	32	17	12	12	11	6	3	0

	Nivolumab + ipilimumab[a,d]
9-month rate (95% CI), %	87 (80.0, 92.2)
12-month rate (95% CI), %	85 (77.0, 90.2)



119	113	107	104	78	33	19	17	11	0	0	0
74	64	59	55	37	21	19	17	11	6	1	0

- With similar follow-up, combination therapy provided improved PFS and OS relative to monotherapy[a,e,f]

[a]Median follow-up was 13.4 months (range, 9–25). [b]Median PFS was not reached (95% CI, not estimable). [c]PFS per investigator assessment. [d]Median OS was not reached (95% CI, 18.0, not estimable).
[e]Median follow-up was 13.4 months (range, 10–32). [f]CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.

1. Overman MJ, et al. *Lancet Oncol* 2017;18:1182–1191.

Conclusions

- Nivolumab + ipilimumab provided durable clinical benefit in previously treated patients with dMMR/MSI-H mCRC
  - High ORR (55%) and durable responses (median DOR not reached)
  - Median PFS and OS not reached with median follow-up of 13 months; 85% of patients alive at 1 year
- Meaningful improvements in quality of life were observed
- Safety was manageable with a low rate of discontinuation due to TRAEs
- Indirect comparisons in CheckMate-142 suggest that nivolumab + ipilimumab provides improved clinical benefit relative to nivolumab monotherapy
- Nivolumab + ipilimumab represents a promising new treatment option for patients with previously treated dMMR/MSI-H mCRC

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Nivolumab in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: Long-Term Survival According to Prior Line of Treatment From CheckMate-142

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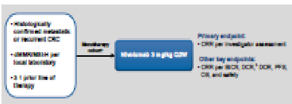
Background

- Approximately 4% of patients with metastatic colorectal cancer (mCRC) have a deficiency in the DNA mismatch repair system (dMMR) that leads to high microsatellite instability (MSI-H)[1–4]
- Nivolumab demonstrated meaningful clinical benefit in patients with dMMR/MSI-H mCRC[5]
  - With 13 months of follow-up, ORR was 32% per blinded independent central review (BICR); 73% of patients were alive at 1 year
  - FDA granted accelerated approval based on notable clinical benefit (ORR per BICR 28%; median DOR not reached) in a subset of patients that has progressed following chemotherapy with a fluoropyrimidine, oxaliplatin, and irinotecan[6]
- Here we present BICR-assessed efficacy and safety results with 21 months of follow-up for the nivolumab monotherapy cohort as well as subanalyses by prior chemotherapy with a fluoropyrimidine, oxaliplatin, and irinotecan

Study Design

- CheckMate-142 is an ongoing, multi-cohort, phase 2 trial investigating the efficacy and safety of nivolumab-based therapies in patients with mCRC
- Between March 12, 2014, and March 16, 2016, 74 patients with locally determined dMMR/MSI-H mCRC were enrolled in the monotherapy cohort[5]

Figure 1. CheckMate-142 monotherapy cohort study design



Assessments

- Tumor assessments were performed using CT or MRI per RECIST v1.1
  - Evaluated: at baseline; every 6 weeks for 24 weeks; every 12 weeks until disease progression or discontinuation
  - Response was assessed by BICR
  - Treatment beyond progression was permitted if the patient tolerated and benefited from study treatment per investigator assessment
- Safety assessments were performed continually while patients were on treatment and for ≥ 100 days following discontinuation per CTCAE v4.0

Results

Patient Characteristics and Disposition

- The median age was 52 years and 16% of patients had a *BRAF* mutation (Table 1)
  - Patients in group A (n = 53) had received ≥ 3 prior chemotherapies, including a fluoropyrimidine, oxaliplatin, and irinotecan
  - Patients in group B (n = 21) had not received prior treatment with all 3 of these chemotherapies (fluoropyrimidine, oxaliplatin, and irinotecan)
    - Most (≥ 85%) patients had received prior fluoropyrimidine and oxaliplatin; 10% of patients had received prior therapy with irinotecan

Table 1. Demographics and baseline characteristics

	All patients N = 74	Group A N = 53	Group B N = 21
Median age (range), years	52.5 (26–79)	53.0 (26–79)	53.0 (27–77)
Male, n (%)	44 (59)	30 (57)	14 (67)
ECOG performance status, n (%)			
0	32 (43)	21 (40)	11 (52)
1	41 (55)	31 (58)	10 (48)
Disease stage at diagnosis, n (%)			
I–III	41 (55)	31 (58)	10 (48)
IV	33 (45)	22 (42)	11 (52)
Mutation status, n (%)			
BRAF/KRAS wild type	29 (39)	21 (40)	8 (38)
BRAF mutation	12 (16)	6 (11)	6 (29)
KRAS mutation	27 (36)	22 (42)	5 (24)
Unknown	6 (8)	4 (8)	2 (10)
Clinical history of Lynch syndrome, n (%)			
Yes	28 (38)	20 (38)	8 (38)
No	27 (36)	15 (28)	12 (57)
Unknown	19 (26)	18 (34)	1 (5)
Prior lines of therapy, n (%)			
0	1 (1)	0	1 (5)
1	11 (15)	1 (2)	10 (48)
2	22 (30)	15 (28)	7 (33)
≥ 3	40 (54)	37 (70)	3 (14)
Prior therapies received, n (%)			
Fluoropyrimidines (5-FU/capecitabine)	73 (99)	53 (100)	20 (95)
Oxaliplatin	71 (96)	53 (100)	18 (86)
Irinotecan	55 (74)	53 (100)	2 (10)
VEGF inhibitor	57 (77)	45 (85)	12 (57)
EGFR inhibitor	31 (42)	27 (51)	4 (19)
Regorafenib	12 (16)	12 (23)	0 (0)
Other	11 (15)	9 (17)	2 (10)

- At the median follow-up of 21 months (range, 17–40), 39% of patients were still on treatment (Table 2)

Table 2. Patient disposition and exposure

	All patients N = 74	Group A n = 53	Group B n = 21
Median number of nivolumab doses (range)	28.5 (1–78)	27.0 (1–77)	32.0 (1–78)
Continuing treatment, n (%)	29 (39)	22 (42)	7 (33)
Discontinued treatment, n (%)	45 (61)	31 (58)	14 (67)
Reasons for treatment discontinuation, n (%)			
Disease progression	31 (42)	23 (43)	8 (38)
AE related to study drug	7 (9)	5 (9)	2 (10)
AE unrelated to study drug	1 (1)	0	1 (5)
Other	6 (8)	3 (6)	3 (14)

Efficacy

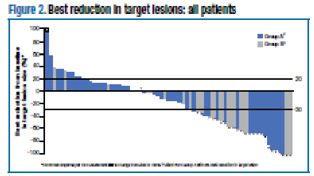
- ORR by BICR was 34% (95% CI, 23.2, 45.7) with nivolumab monotherapy, and 62% of patients had disease control (Table 3)
  - Median time to response was approximately 2.8 months across all groups
  - Clinical benefit was observed across all groups

Table 3. Response, disease control, and durability

	All patients N = 74	Group A n = 53	Group B n = 21
ORR, n (%)	25 (34)	14 (26)	11 (52)
[95% CI]	[23.2, 45.7]	[15.3, 40.3]	[29.8, 74.3]
Best overall response, n (%)			
CR	7 (9)	4 (8)	3 (14)
PR	18 (24)	10 (19)	8 (38)
SD	23 (31)	16 (30)	7 (33)
PD	22 (30)	19 (36)	3 (14)
Unable to determine	4 (5)	4 (8)	0
Disease control, n (%)	46 (62)	29 (55)	17 (81)
[95% CI]	[50.1, 73.2]	[40.4, 68.4]	[58.1, 94.6]
Median DOR (range), months	NR (1.6+ to 31.6+)	NR (4.6+ to 27.3+)	NR (1.6+ to 31.6+)
Median duration of SD (range), months	8.3 (4.3–NR)	8.5 (4.1–NR)	5.3 (2.6–NR)

- Most patients (60%) had a reduction in tumor burden from baseline with nivolumab monotherapy (Figure 2)

Figure 2. Best reduction in target lesions: all patients



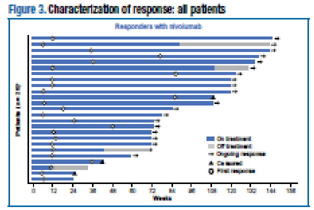
- CR rates increased in all patients with longer follow-up (Table 4)
- Similar trends in CR were observed in groups A and B

Table 4. Response and disease control with longer follow-up in all patients

	All patients N = 74	
	13-Month follow-up	21-Month follow-up
ORR, n (%)	24 (32)	25 (34)
[95% CI]	[22.0, 44.3]	[23.2, 45.7]
Best overall response, n (%)		
CR	2 (3)	7 (9)
PR	22 (30)	18 (24)
SD	25 (34)	23 (31)
PD	21 (28)	22 (30)
Not determined	4 (5)	4 (5)
Disease control, n (%)	47 (64)	46 (62)

- Nivolumab continued to provide clinically meaningful and durable responses (Figure 3)
  - 80% of responders had ongoing responses at data cutoff
  - 64% had responses lasting ≥ 12 months

Figure 3. Characterization of response: all patients



- Median PFS was 6.6 months in all patients (Figure 4)
  - Median PFS was 4.2 months and not reached in groups A and B, respectively
  - 12- and 18-month PFS rates were 41% (group A) and 52% (group B)
- Median OS was not reached in all patients (Figure 5)
  - Median OS was not reached in groups A or B
  - 12-month OS rate was 68% (group A) and 81% (group B)
  - 18-month OS rate was 66% (group A) and 70% (group B)

Figure 4. Progression-free survival: all patients

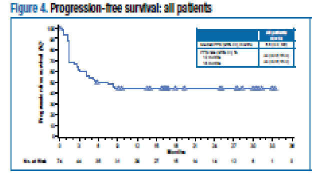
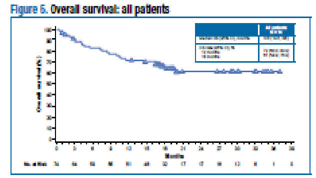


Figure 5. Overall survival: all patients



- Best overall response to nivolumab treatment correlated with overall survival (Figure 6A)
- Patients with a best overall response of PD who had a reduction in or stabilization of target lesions were more likely to survive ≥ 12 months (Figure 6B)

Figure 6A. Overall survival by best overall response

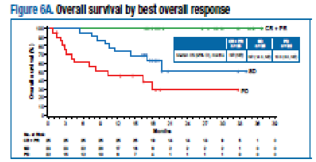
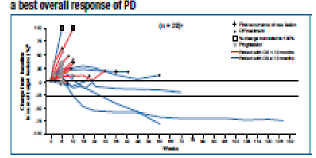


Figure 6B. Antitumor activity after initial progression in patients with a best overall response of PD



Safety

- No new safety signals were reported with long-term follow-up (Table 5); safety was consistent across subgroups evaluated

Table 5. Safety summary

	All patients N = 74	
Patients, n (%)	Any grade	Grade 3–4
Any TRAE	54 (73)	15 (20)
Any serious TRAE	10 (14)	9 (12)
Any TRAE leading to discontinuation	6 (8)	5 (7)
TRAEs reported in ≥ 10% of patients		
Fatigue	17 (23)	1 (1)
Diarrhea	16 (22)	1 (1)
Pruritus	12 (16)	0
Lipase increased	9 (12)	6 (8)
Rash	8 (11)	0

Conclusions

- Nivolumab continued to provide durable clinical benefit with long-term follow-up (21 months) in previously treated patients with dMMR/MSI-H mCRC
  - PFS and OS rates demonstrated continued stability
  - CR rate increased with longer follow-up
  - Median DOR and OS were not reached
- Durable clinical benefit with deepening of response was observed regardless of prior chemotherapy with a fluoropyrimidine, oxaliplatin, and irinotecan
- No new safety signals were reported with long-term follow-up
- Results support ongoing evaluation of nivolumab-based therapy in the first-line setting

References

1. Koopman M, et al. *Br J Cancer* 2009;100:266–273.
2. Vanderbosch S, et al. *Clin Cancer Res* 2014; 20: 5322–5330.
3. Le DT, et al. *Science* 2017;357:409–413.
4. Tougeron D, et al. *Ann Oncol* 2017;28(suppl 5):Abstract 533P.
5. Overman MJ, et al. *Lancet Oncol* 2017;18:1182–1191.
6. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2018.

Acknowledgments

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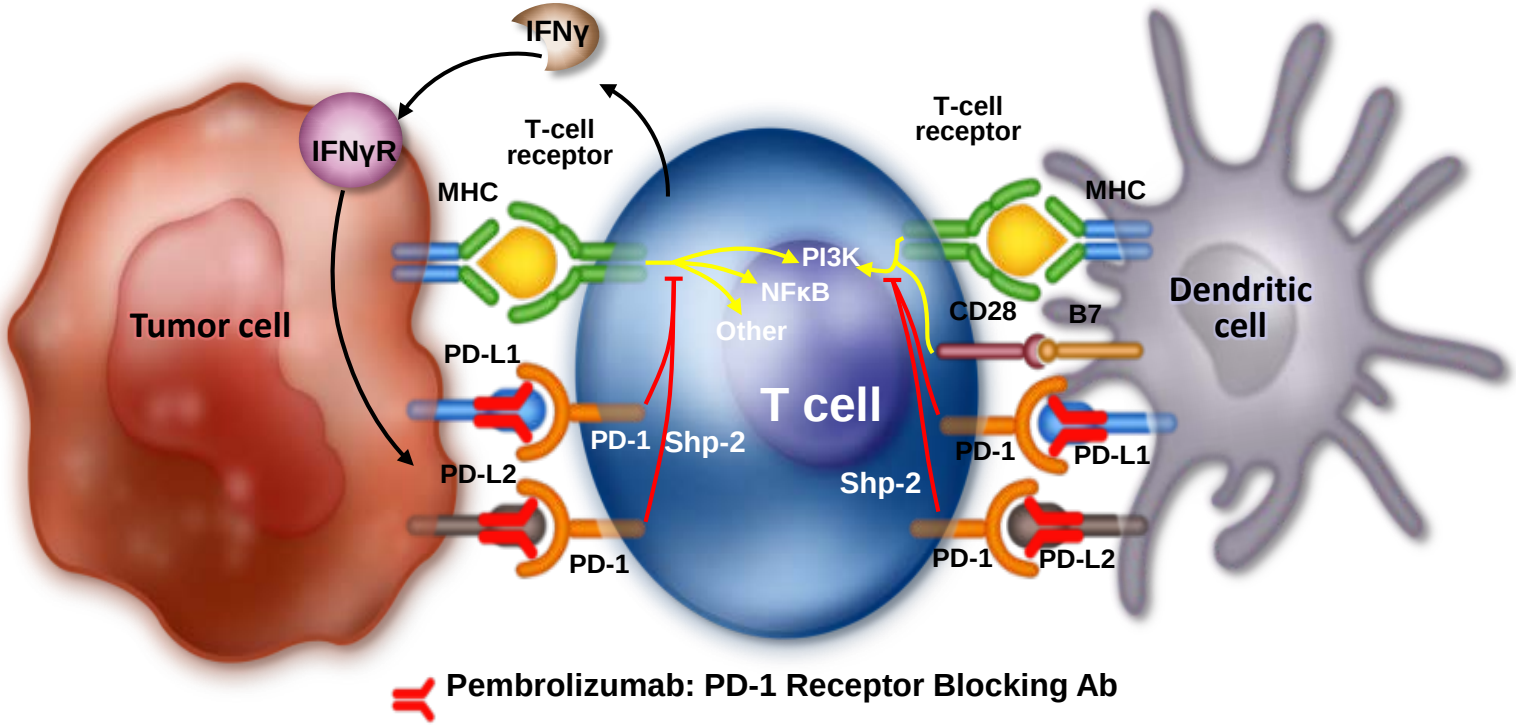
Pembrolizumab Mechanism of Action

PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function[11]

Pembrolizumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[12–14]



Pembrolizumab for MMR-D CRC

KEYNOTE -016, -164, -012, -028, and -158

Patients received pembrolizumab at 200 mg every 3 weeks or 10 mg/kg Q2 weeks for up to 24 months or until unacceptable toxicity or PD

90 patients had colorectal cancer and 59 patients had 14 other cancer types.

Objective response rate on blinded independent central radiologist review according to Response Evaluation Criteria in Solid Tumors 1.1 was 39.6% (95% confidence interval = 31.7%–47.9%), with a complete response in 11 patients (7.4%).

The median duration of response was not reached, with durations ranging from 1.6+ to 22.7+ months

Responses lasting ≥ 6 months in 78% of responders.

Response rates were 36% in patients with colorectal cancer and 46% in those with other cancer types.

Pembrolizumab for MMR-D CRC

Table 2. Key ongoing/planned trials in MSI-H CRC.

Patient Population	Treatment	Primary Endpoint	Identifier
Metastatic: Refractory (Cohort A); or ≥1 Prior Therapy (Cohort B)	Pembrolizumab Monotherapy	Objective Response Rate	Keynote 164 NCT02460198
1st Line Metastatic	Pembrolizumab monotherapy vs. Standard of Care Chemotherapy	Progression-Free Survival	Keynote 177 NCT02563002
1st Line Metastatic	Atezolizumab vs. Atezolizumab + FOLFOX + Bevacizumab vs. FOLFOX + Bevacizumab	Progression-Free Survival	NRG-GI004/S1610 NCT02997228
Stage III	Atezolizumab + FOLFOX vs. FOLFOX alone	Disease-Free Survival	Alliance A021502 NCT02912559

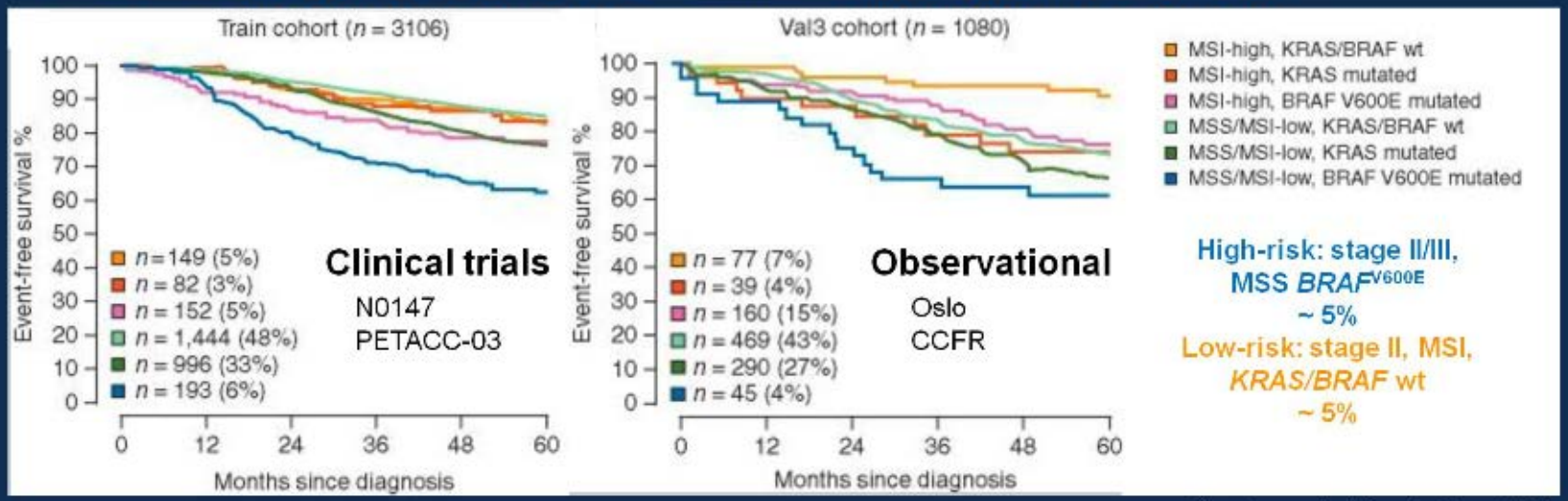
Table 3. Combinatorial immunotherapy trials in progress.

Drug(s)	PD-1/PD-L1 Partner (Target)	Description	Identifier
CRC Specific or CRC Expansion Studies			
Atezolizumab	Cobimetinib (MEK), Bevacizumab (VEGF-A)	Phase I—Metastatic CRC	NCT02876224
Pembrolizumab	Cetuximab (EGFR)	Phase Ib/II—Pre-treated CRC	NCT02713373
Atezolizumab	Capecitabine, Bevacizumab (VEGF-A)	Randomized Phase II Refractory CRC	NCT02873195
Durvalumab	Cediranib (VEGFR, c-kit)	Phase I/II—Refractory CRC Expansion	NCT02484404
Pembrolizumab	Nintedanib (VEGFR, PDGFR, FGFR)	Phase I/II—CRC	NCT02856425
Pembrolizumab	Napabucasin (STAT3)	Phase I/II Refractory CRC	NCT02851004
Pembrolizumab	Oral azacitidine (DNMT), Romidepsin (HDAC1/2)	Phase I—Pre-treated MSS CRC	NCT02512172
Pembrolizumab	Azacitidine (DNMT), Epacadostat (IDO-1)	Phase I/II Refractory MSS CRC and NSCLC	NCT02959437
Nivolumab	Epacadostat (IDO-1)	Phase I/II—Solid tumors, CRC	NCT02327078
Pembrolizumab	Poly-ICLC (TLR-3)	Phase I/II—MSS CRC	NCT02834052
Nivolumab	Varlilumab (CD-27)	Phase I/II—Solid tumors, CRC	NCT02335918
Durvalumab	Pexidartinib (CSF-1R)	Phase I—Pre-treated pancreas and CRC	NCT02777710
Atezolizumab	CPI-444 (Adenosine-A2A)	Phase I—Solid tumors, MSI-H CRC	NCT02655822
Nivolumab	Chemoradiation	Phase I/II—Locally advanced rectal cancer	NCT02948348
Durvalumab	Tremelimumab (CTLA-4), Radiation	Phase II—NSCLC and CRC with liver metastases	NCT02888743
Pembrolizumab	Tumor infiltrating Lymphocytes, IL-2, cytoxan, fludarabine	Phase II—digestive tumors, CRC arm	NCT01174121
Phase I Studies in Solid Tumors			
Durvalumab	Selumetinib (MEK)	Phase I—Solid Tumors	NCT02586987
Pembrolizumab	Aflibercept (VEGF-A/B, PIGF)	Phase I—solid tumors	NCT02298959

Molecular markers in CRC

Molecular markers that define high-risk stage II/III CRC

Cancer cell markers: MSI status, *KRAS/BRAF*^{V600E} mutations



Dienstmann et al, Annals Oncol 2017

Future of Immunotherapy in CRC MMR-Deficient

Where do we go From here?

After the FDA Approval of PD-1 Inhibitors in Metastatic CRC MMR-D

Pembro Vs Chemotherapy for Metastatic CRC , MMR-D

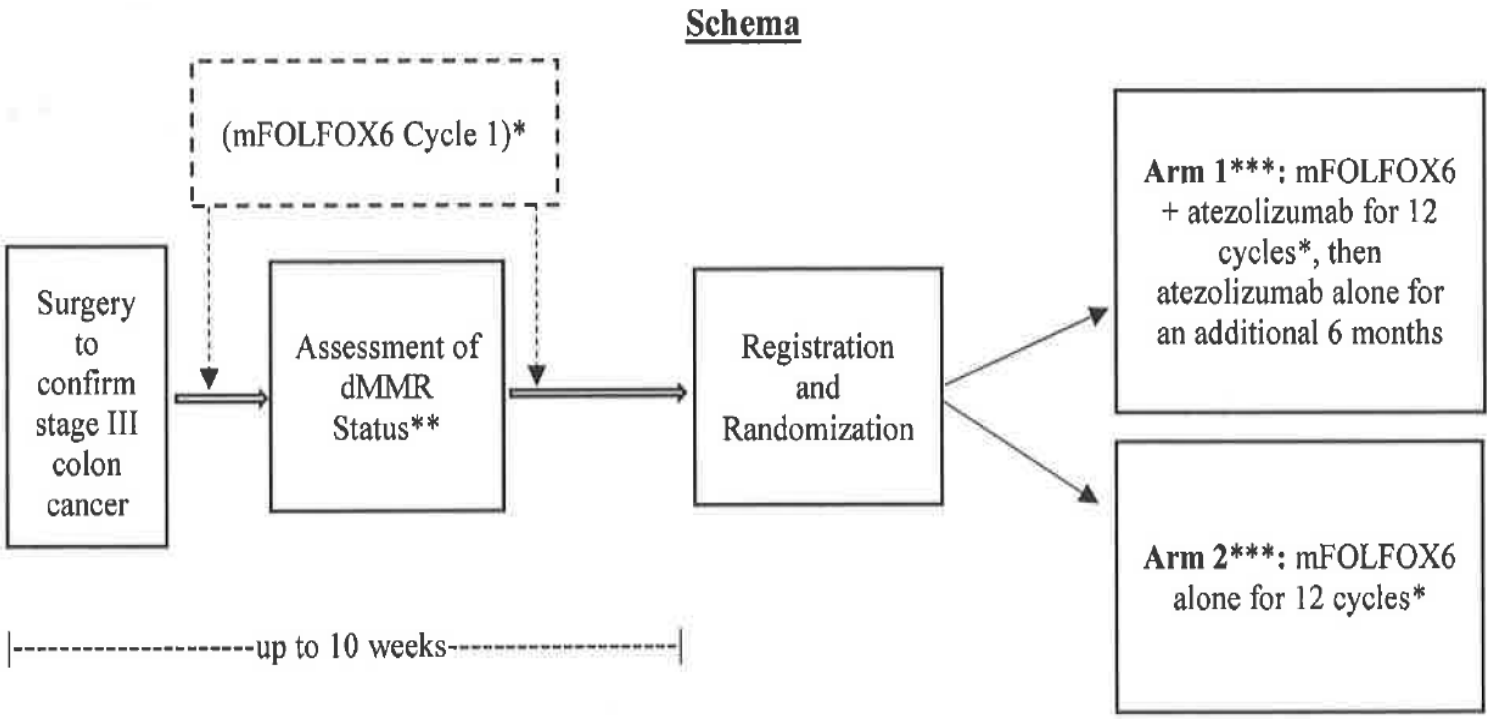
KEYNOTE-177: Randomized phase III study of pembrolizumab versus investigator-choice chemotherapy for mismatch repair-deficient or microsatellite instability-high metastatic colorectal carcinoma

270 patients will be randomly assigned to 200 mg of pembrolizumab every 3 weeks or investigator's choice of 1 of 6 chemotherapy regimens chosen prior to randomization. Treatment is to continue until disease progression, unmanageable toxicity

Investigators are hoping to show that frontline treatment with the PD-1 inhibitor pembrolizumab can improve progression-free survival (PFS) compared with standard-of-care chemotherapy in patients with mismatch repair-deficient or microsatellite instability-high (MSI-H) colorectal cancer (CRC).

Alliance Trial A021502

Randomized Trial of Standard of care chemoRx Vs Combined Atezolizumab as adjuvant Therapy for Stage III Colon Cancer with MMR-Deficient



Adjuvant Therapy Decision-Making: General Principles

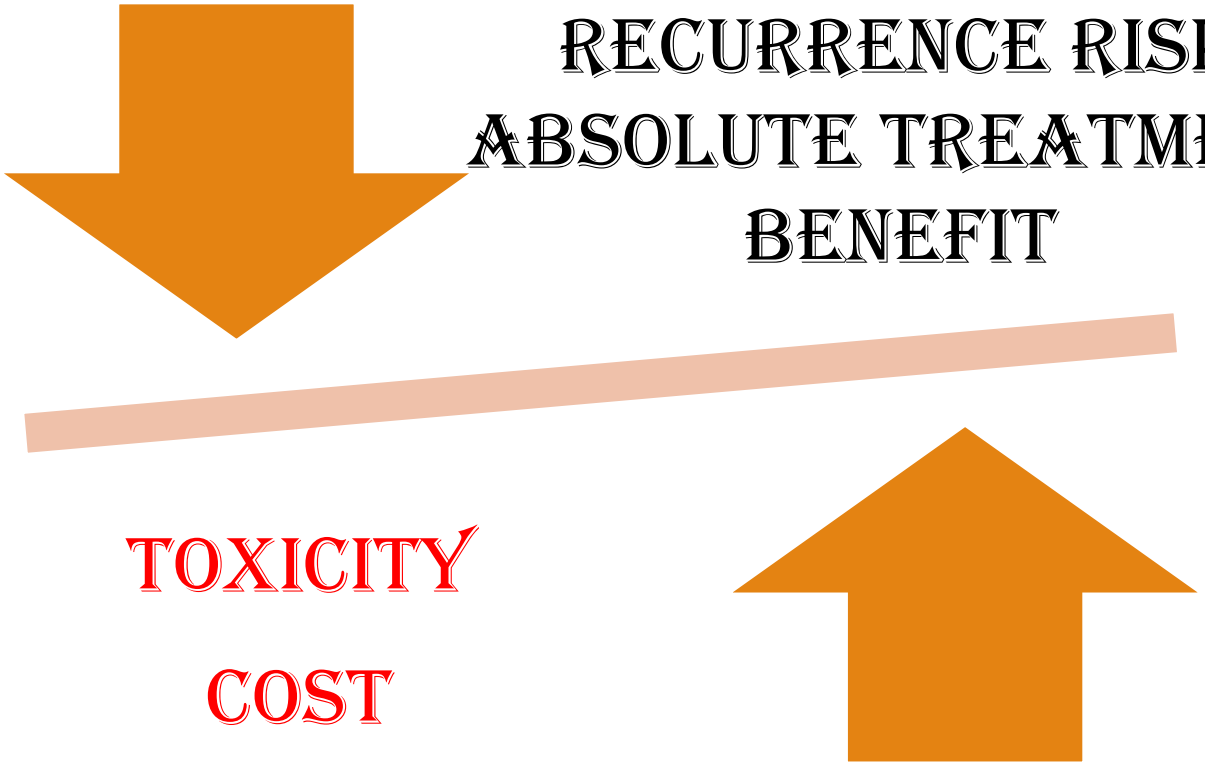
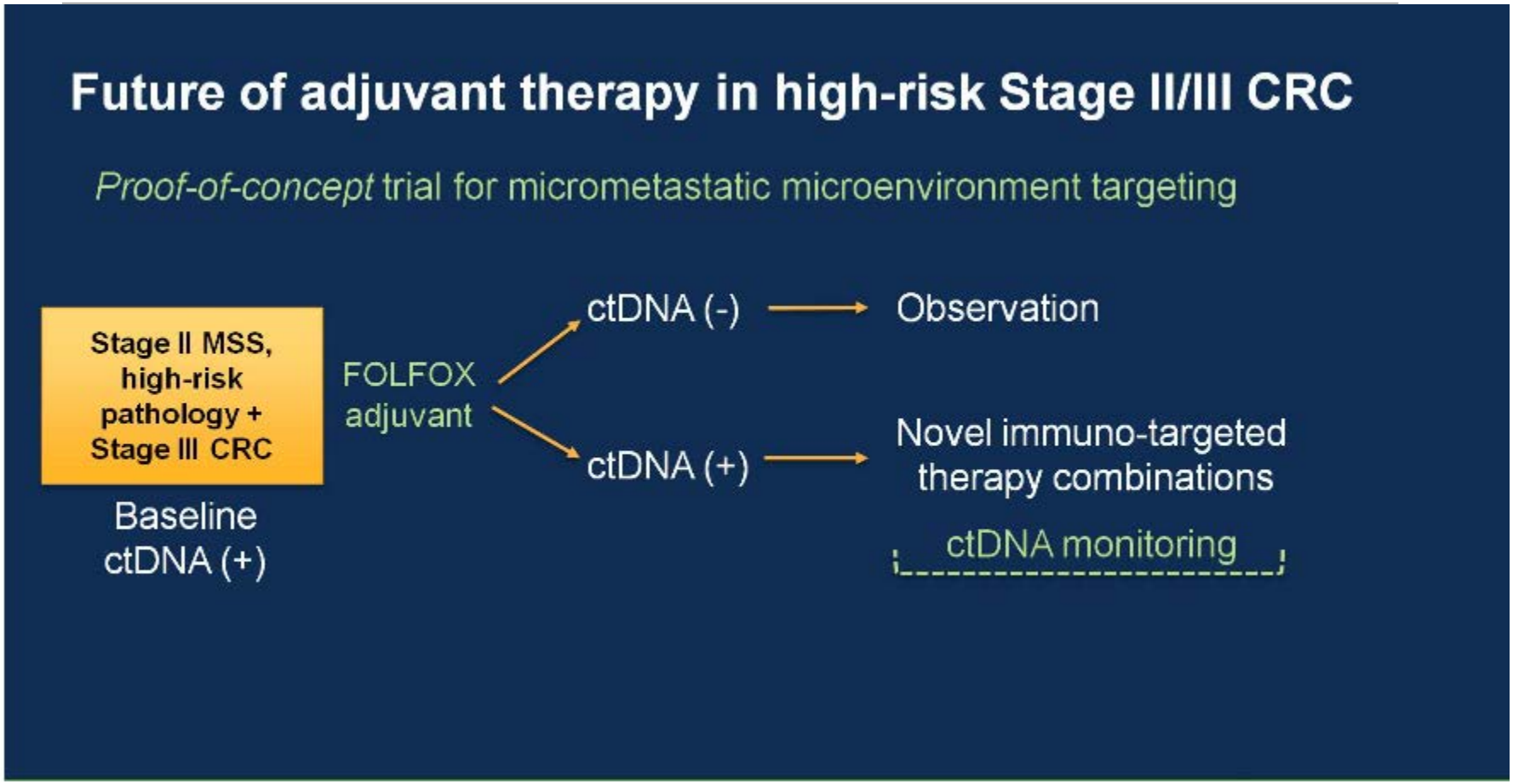


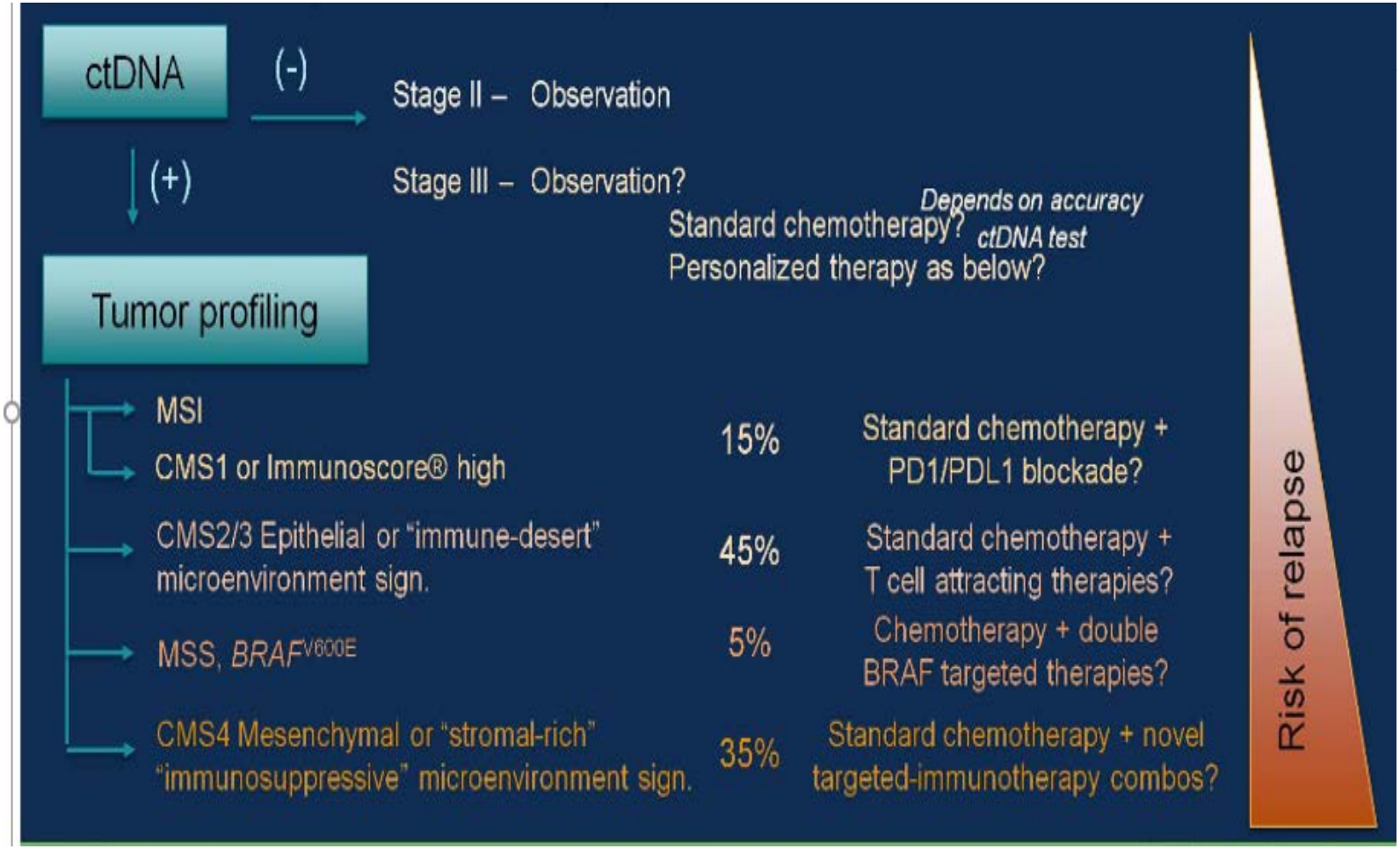
Table 1: Ongoing clinical trial with immune-checkpoint inhibitors alone or in a combination regimen according to mismatch repair status for different solid tumors. Last updated, April 2017.

Experimental arm	Active comparator regimen	Disease	Setting	Phase	Comments	ClinicalTrials.gov Identifier
Atezolizumab + FOLFOX	FOLFOX	CRC	Adjuvant, stage III	3	CT plus IO up to 25 courses	NCT02912559
Pembrolizumab	FOLFOX FOLFIRI Bevacizumab Cetuximab	CRC	IV	3	KEYNOTE-177 IO for up to 35 treatments	NCT02563002
GVAX° Pembrolizumab Cyclophosphamide	Single arm	CRC	Advanced	2	MMRp	NCT02981524
AZD9150 [§] Durvalumab	Single arm	Pancreatic, NSCLC, and MMRd CRC	Advanced	2	—	NCT02983578
Pembrolizumab Poly-ICLC[+]	Single arm	MMRp CRC	IV	1/2	IO for 1 year	NCT02834052
DS-8273[^] Nivolumab	NA	MMRp CRC	IV	1	—	NCT02991196
Nivolumab	Single arm	Hypermutated malignancies	Recurrent or refractory disease	1/2	Pediatric patients (12 months to 18 years of age) Biallelic MMRd[*]	NCT02992964
Nivolumab	Single arm	mCRPC with mutations in DNA repair defects[#]	IV	2	ImmunoProst Trial IO until progression or unacceptable toxicity	NCT03040791
Avelumab Ad-CEA vaccine Standard of care	FOLFOX Bevacizumab Capecitabine	CRC	IV	2	CT and IO with maintenance	NCT03050814
Pembrolizumab	Single arm	High-grade gliomas, diffuse intrinsic pontine gliomas, or hypermutated brain tumors	NA	2	IO for 34 courses	NCT02359565

FOLFOX: Fluorouracil, Leucovorin, and Oxaliplatin combination regimen. CRC: colorectal cancer. CT: chemotherapy. IO: immunotherapy. FOLFIRI: Fluorouracil, Leucovorin, and Irinotecan. MMRp: mismatch repair proficient profile. MMPd: mismatch repair deficient profile. NSCLC: non-small cell lung carcinoma. mCRPC: metastatic castration-resistant prostate cancer; °GVAX, cancer vaccine composed of irradiated tumor cells genetically modified to secrete granulocyte-macrophage colony-stimulating factor; [§] AZD9150, antisense oligonucleotide inhibitor of STAT3; [+]Poly-ICLC (carboxymethylcellulose, polyinosinic-polycytidylic acid, and poly-L-lysine double-stranded RNA), ligand of TLR3; [^]DS-8273a, anti-human death receptor 5 (DR5) agonistic antibody; [*]patients must have evidence of biallelic mismatch repair deficiency either in their tumor tissue (by immunohistochemistry or sequencing) or in their germline (by sequencing) and/or evidence of hypermutant malignancy by whole exome sequencing with a mutation load > 100 per exome; [#]the germline and somatic DRD (BRCA1, BRCA2, ATM, PTEN, CHEK2, RAD51C, RAD51D, PALB2, MLH1, MSH2, MSH6, and PMS2) will be assessed by T-NGS of metastatic sites or by liquid biopsy.

Future of Immunotherapy in CRC MMR-Deficient




ctDNA
(-)
Stage II – Observation
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Stage III – Observation?
Standard chemotherapy?
Depends on accuracy ctDNA test
Personalized therapy as below?
Tumor profiling
MSI
CMS1 or Immunoscore® high
15%
Standard chemotherapy + PD1/PDL1 blockade?
CMS2/3 Epithelial or "immune-desert" microenvironment sign.
45%
Standard chemotherapy + T cell attracting therapies?
MSS, BRAFV600E
5%
Chemotherapy + double BRAF targeted therapies?
CMS4 Mesenchymal or "stromal-rich" "immunosuppressive" microenvironment sign.
35%
Standard chemotherapy + novel targeted-immunotherapy combos?
Risk of relapse

Conclusion

CRC Immunotherapy after the approval of 2 drugs as immune checkpoints inhibitors will have a positive impact on Median survival of patients with Metastatic CRC MMR-Deficient

Need to continue to identify Predictive Biomarkers for Response to checkpoints inhibitors which may explain lack of response and resistance to Immunotherapy in CRC

Combination Chemo-Immunotherapy Trials will lead to better optimization of first Line therapy in Selected CRC

Combination of novel agents co-stimulatory CD137 with PD-1 Inhibitors is appealing