Immunotherapy in Colorectal cancer & MSI-High Solid Cancers

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Disclosures:

AMGEN : Speaker Bureau,

BAYER : Speaker Bureau and Consulting Programs

MMR-Deficiency and Immune Microenvironment

MMR system is a DNA integrity maintenance system leading to correction of single base nucleotide mismatches generated during DNA replication and recombination, Therefore maintains the genomic stability

The mechanism of MMR involves at least three different processes:

1. Recognition of single base replication errors is performed by the MutS*α:*

    a. MSH2-MSH6 heteroduplex or MSH2-MSH3 heteroduplex

2. Excision of the lagging strand from the mismatch by one of the MutL complexes:

    a. MLH1/PMS2 recruited by MutS protein

3. Re-synthesis of the excised-DNA and ligation by DNA polymerase and DNA ligase :

    a. MLH1 complexes with PMS2

    b. MSH2 complexes with MSH6

if MLH1 is negative→ PMS2 is negative

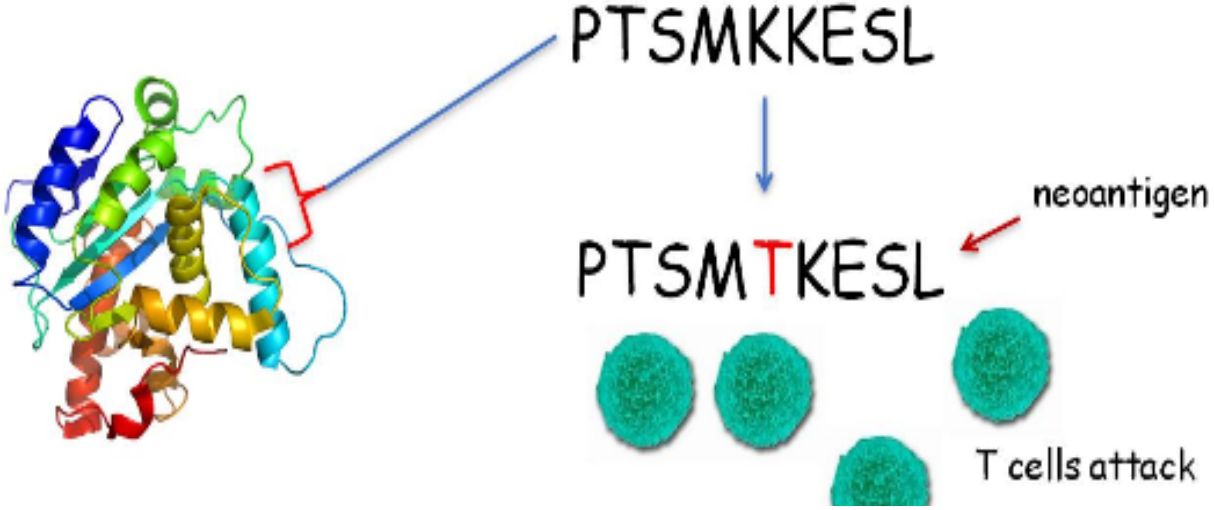
if MSH2 is negative → MSH6 is negative**.**

MMR-Deficiency and Immune Microenvironment

- Mismatch repair deficiency (MMR-D) referred to deficiency in proteins responsible for DNA repair such as MSH2, MSH6, MLH1, PMS2
- Therefore MMR deficiency leads to MSI-High phenotype
- MMR deficient /MSI-H cancers usually Harbor thousands of mutations leading to high mutational burden also known as hypermutated phenotype
- DNA Mutations generate Protein Neoantigens that are recognized by T-Cells

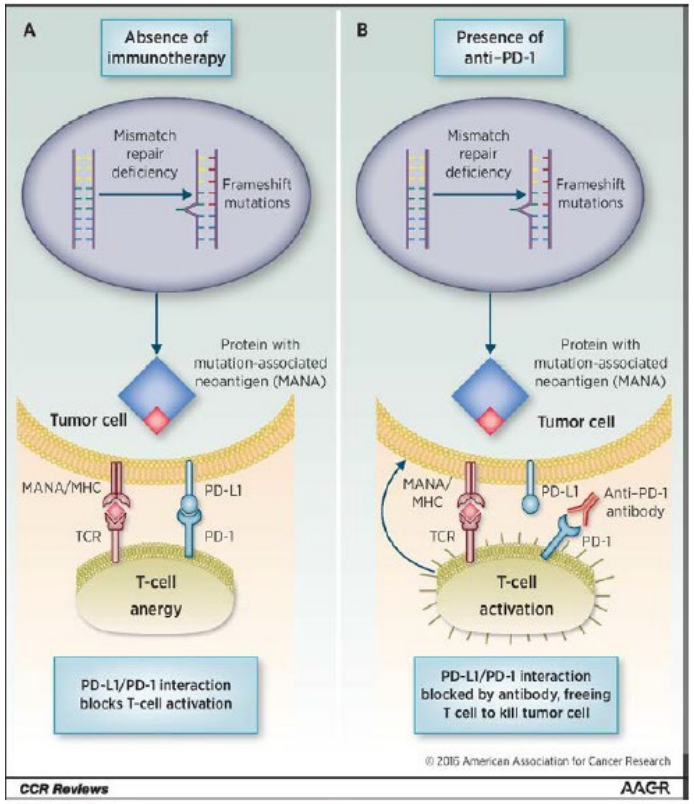
What is a Neoantigen?

- A peptide that undergoes mutation in cancer leading to immune system seeing this as foreign via MHC presentation



Rationale of Immunotherapy in MMR-D Cancers

- MSI-H Malignancies regardless of the tumor histology is associated with high mutational burden : Hypermutated phenotype
- High mutational burden leads to high Neoantigen expression
- High Neoantigen expression by itself recruits autologous immune recognition of cancer cell
- Therefore PD-1 inhibition on tumor Neoantigen specific T-cells can activate anti tumor immune response



Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

Tumor Type with MSI-High	
Small bowel tumors	25%
Endometrial cancers	16%
Colorectal cancers (all stages)	14%
Gastric cancers	6%
Cholangiocarcinoma	3-8%

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

MSI-H

Prevalence:

Stage	MSI-H
II	22%
III	12%
IV	3.5%

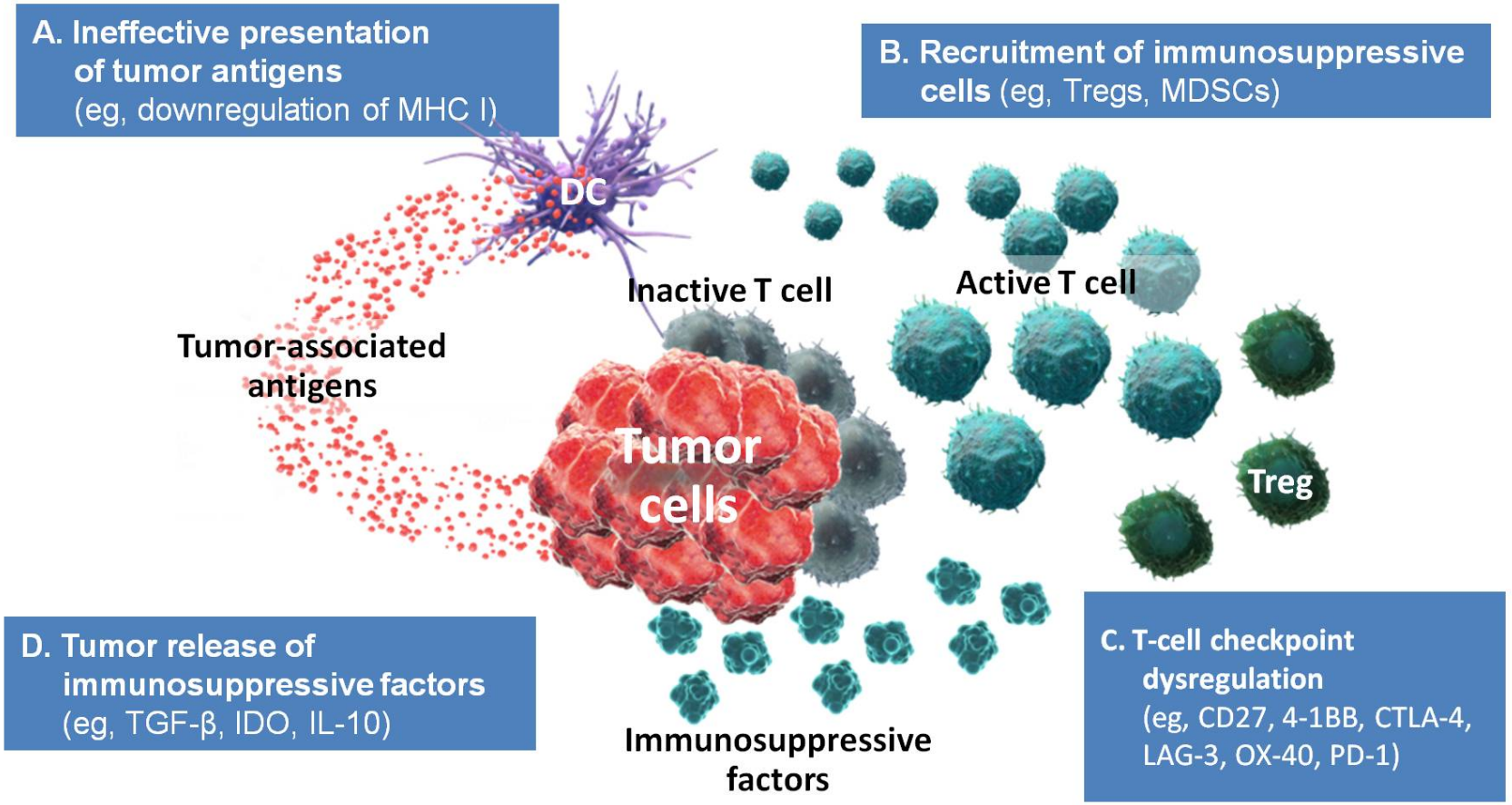
Unstable, MLH1/PMS2 (-) :

- 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

Biomarkers Identification

Ligand expression on tumor	Immunogenic microenvironment	Increased antigen presentation due to high DNA mutation load
PD-L1 Expression	Immune-Related Gene Expression (GEP) Signature	DNA Mismatch Repair Deficiency (MSI-H), DNA Polymerase mutation, others

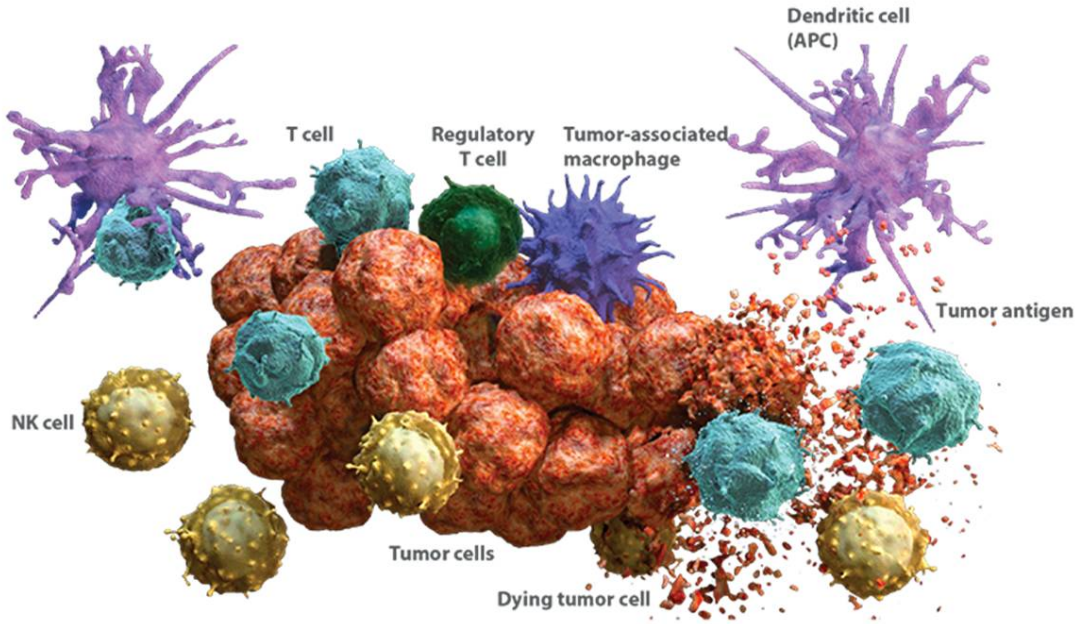
Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System



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.

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

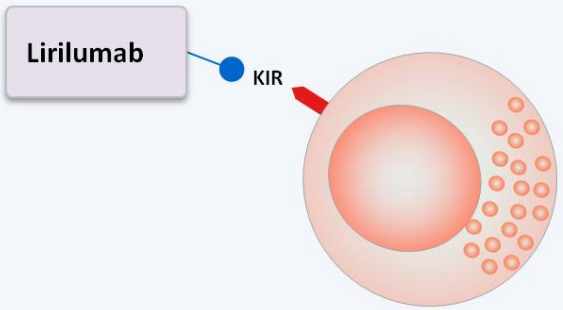
- The adaptive immune response is antigen specific and able to produce a durable response[1]
- **Cytotoxic T cells are essential anti-tumor effector cells** of the adaptive immune system[2,3]

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.

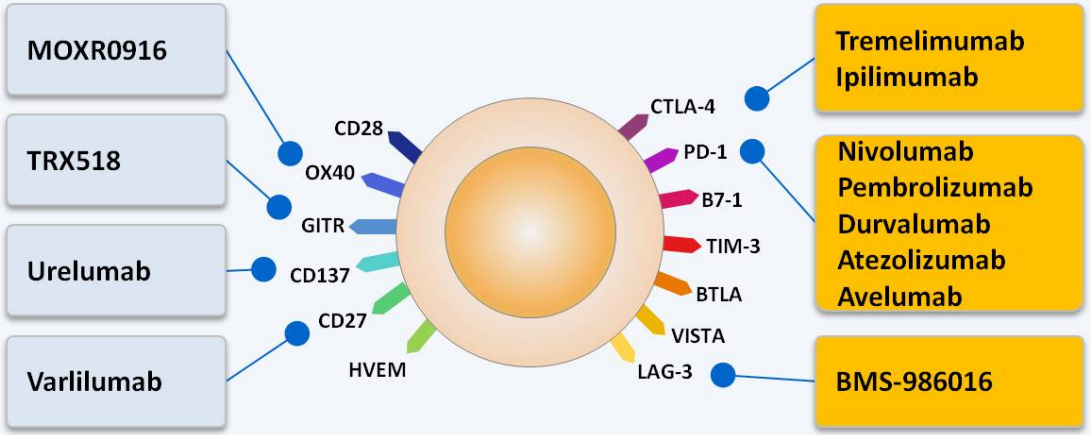
Targeting Checkpoints as an Approach to Cancer Therapy

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**

*

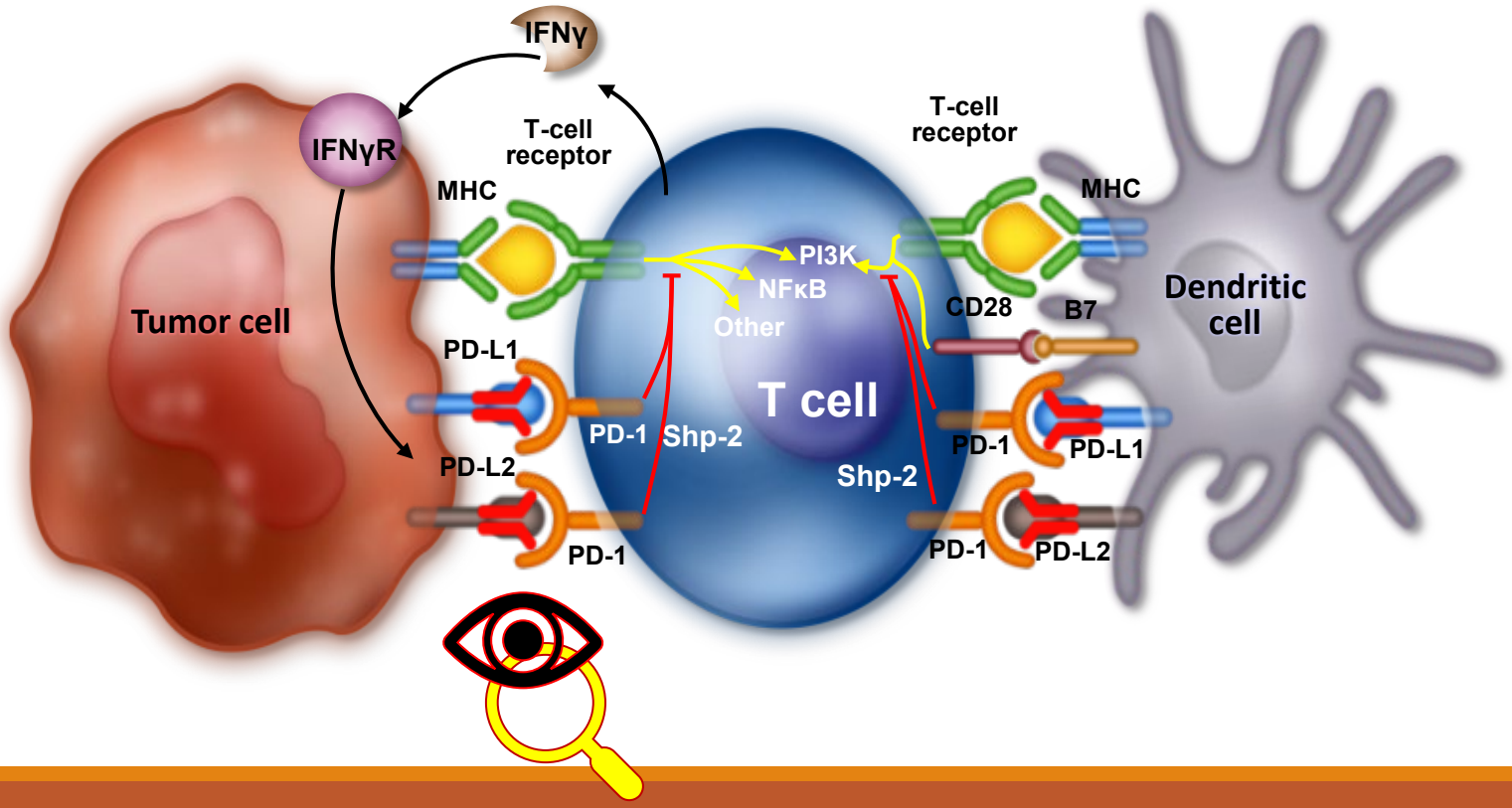
CTLA-4=cytotoxic T-lymphocyte antigen-4; GITR=glucocorticoid-induced TNFR family related gene; KIR=killer-cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene-3; NK=natural killer; PD-1=programmed death-1; PD-L1=programmed death ligand-1.

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.

Mechanism of Action of Immunotherapy

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

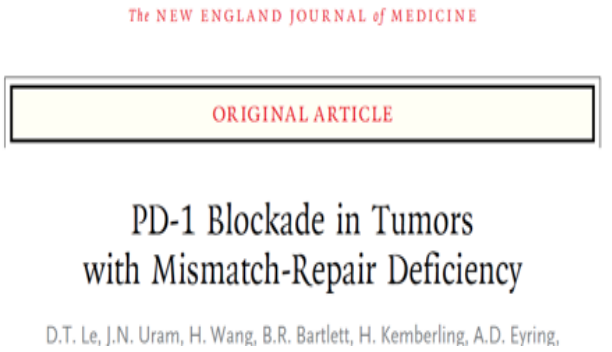
Binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[12–14]



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

(NEJM 2015)

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.

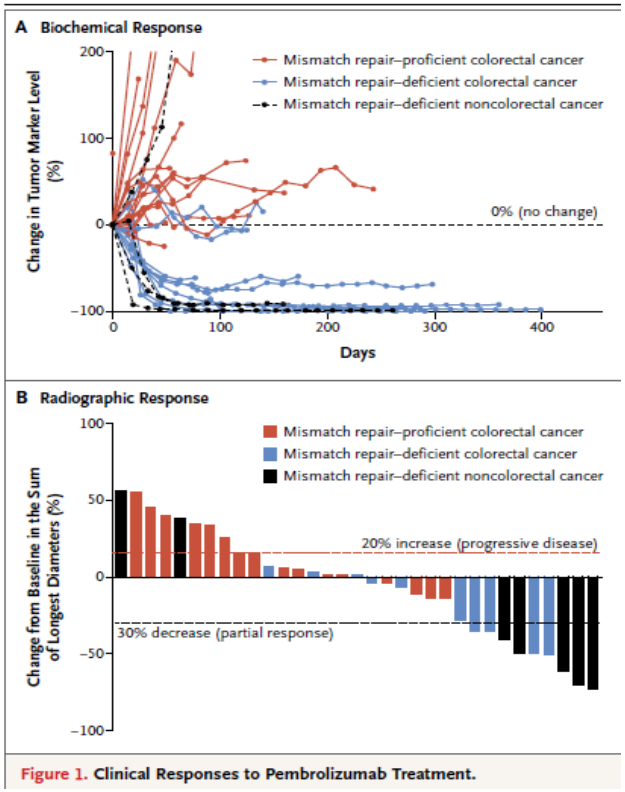
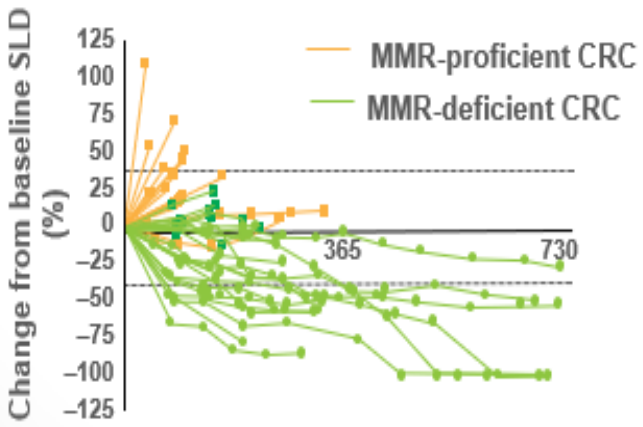
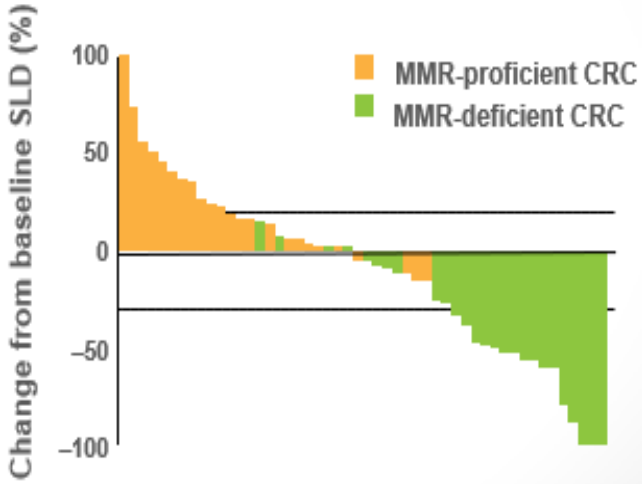


Figure 1. Clinical Responses to Pembrolizumab Treatment.

MSI-high tumours are responsive to PD-1 inhibitors

Pembrolizumab
(KEYNOTE 016, phase II)



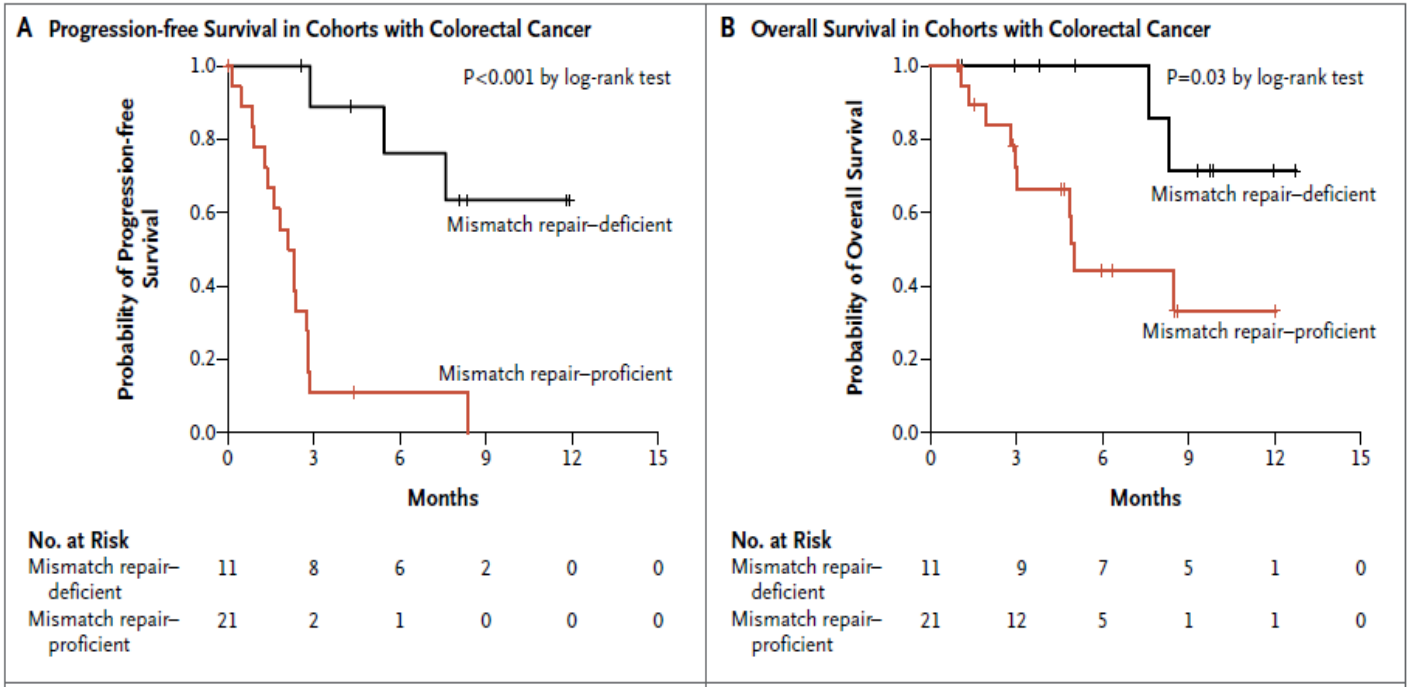


*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

1. Le et al. ASCO 2016;

PD-1 Blockade in Cancer with MMR- Deficiency

(NEJM 2015)



Pembrolizumab for MMR-D Cancers

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.
- ORR was 39.6% (95% CI: 31.7%–47.9%), with a CR in 11 patients (7.4%).
- The median duration of response was not reached
  - 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
- RR was 46% in those with other cancer types (Non-CRC)

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Colon Cancer

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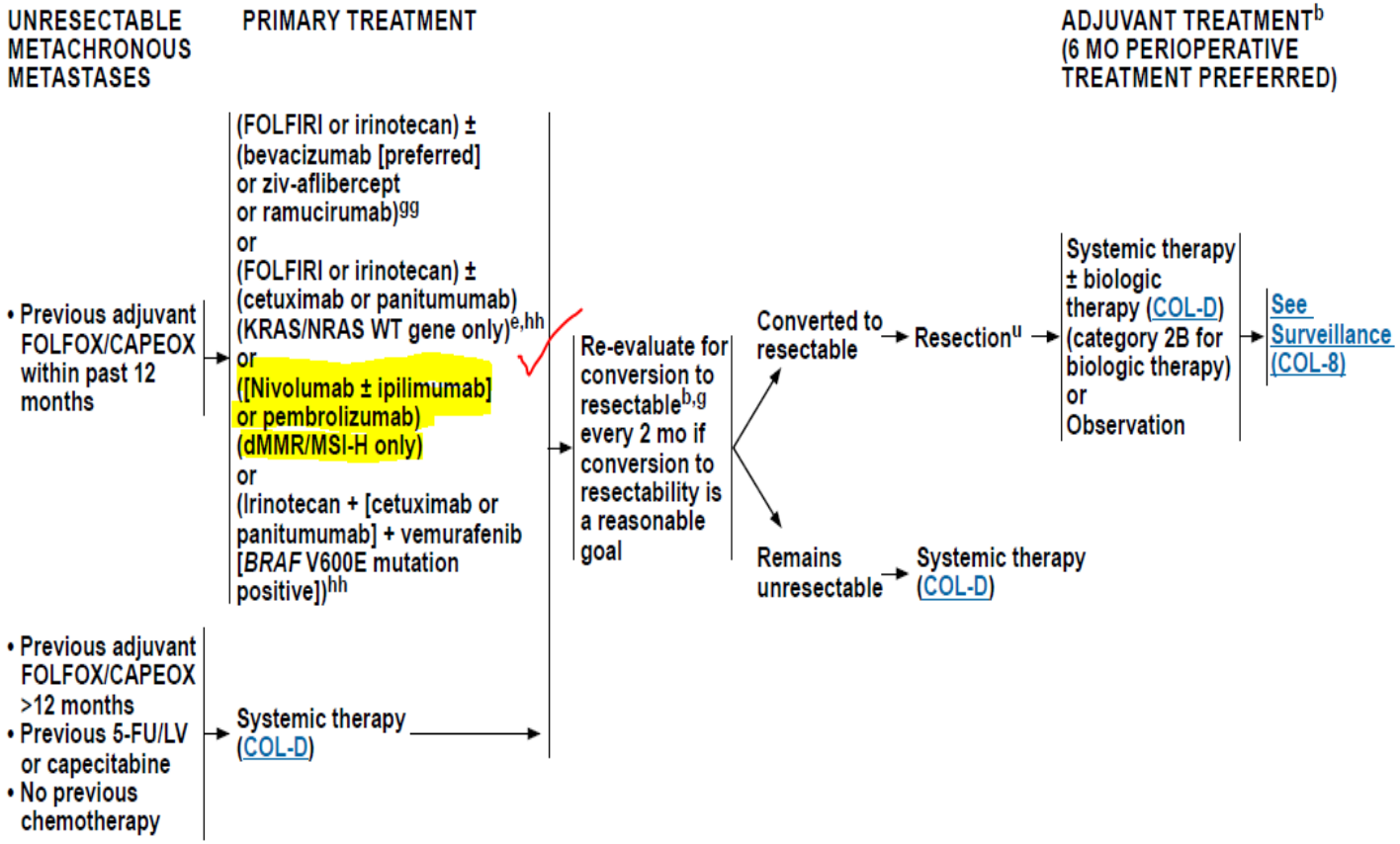
Discussion



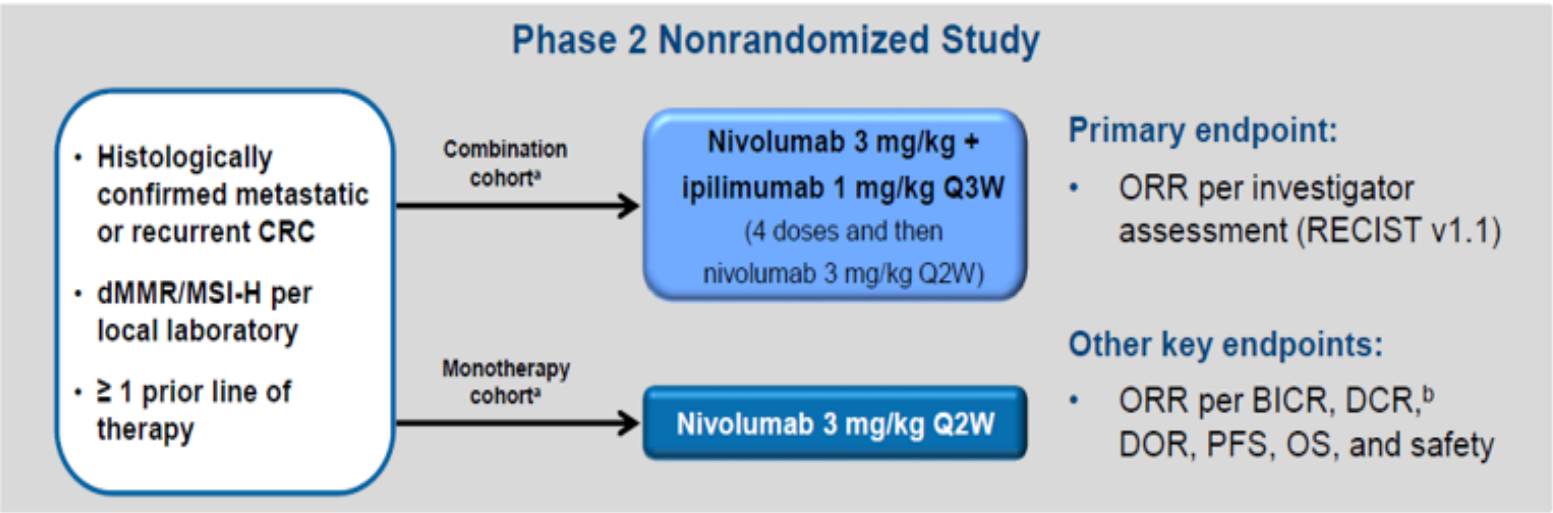
Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142

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

Nivolumab in MMR-D CRC *GI-ASCO 2018*

CheckMate-142 Study Design



- 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.

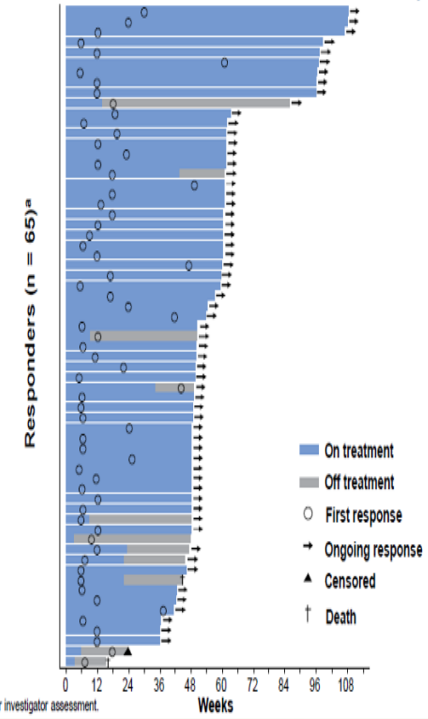
Response and Disease Control

Investigator-assessed	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
ORR[a], n (%) [95% CI]	27 (60) [44.3–74.3]
Best overall response, n (%)*	
CR	3 (7)
PR	24 (53)
SD	11 (24)
PD	6 (13)
Not determined	1 (2)
DCR[b], n (%) [95% CI]	38 (84) [70.5–93.5]

- Responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutation status, or diagnosis of Lynch syndrome
  - The ORR and DCR in patients with a *BRAF* mutation (n = 17) were 71% and 88%, respectively

Characterization of Response

Nivolumab + ipilimumab

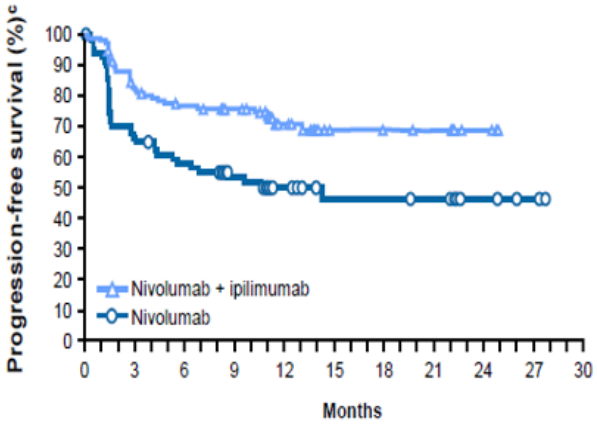


[a]Response per investigator assessment.

- 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

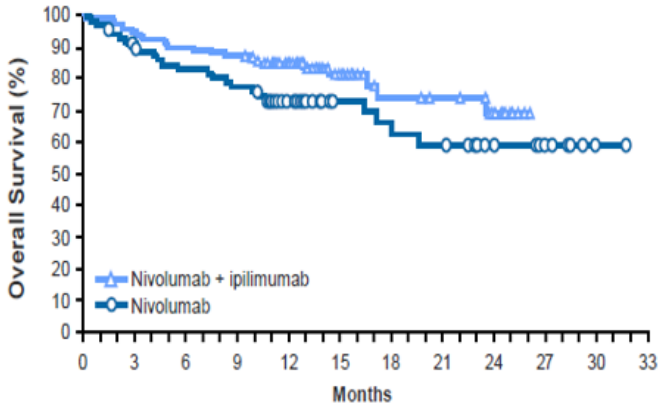
Checkmate 142 PFS and OS

	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]

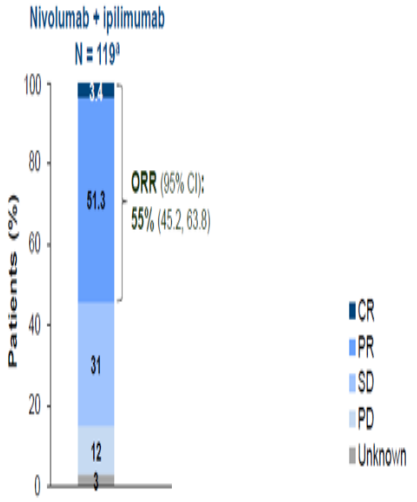
[a]Median follow-up was 13.4 months (range, 9–25). [b]Median PFS was not reached (95% CI, not estimable). [c]PFS per investigator assessment. [d]Median OS was not reached (95% CI, 18.0, not estimable).
[e]Median follow-up was 13.4 months (range, 10–32). [f]CheckMate-142 monotherapy and combination therapy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

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

Checkmate 142

(Nivo+ Ipi in MSI-H CRC previously Rx)

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]

Conclusion:

- Nivolumab + Ipilimumab provided a durable clinic in benefit in previously treated patient with MSI-H CRC
- meaningful improvement in quality of life were observed
- safety was manageable with low rate of discontinuation
- Nivolumab + Ipi will present a promising new treatment option for previously treated MSI-H CRC

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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

Michael J. Overman,[1] Francesca Bergamo,[2] Ray McDermott,[3] Massimo Aglietta,[4] Franklin Chen,[5] Fabio Gelsomino,[6] Ka Yeung Mark Wong,[7] Michael Morse,[8] Eric Van Cutsem,[9] Alain Hendlisz,[10] Bart Neyns,[11] Rebecca A. Moss,[12] Huanyu Zhao,[12] Z. Alexander Cao,[12] Shital Kamble,[12] Scott Kopetz,[1] Thierry André[13]

[1]MD Anderson Cancer Center, Houston, TX; [2]Istituto Oncologico Veneto - IRCSS, Padova, Italy; [3]St. Vincent's University Hospital, Dublin, Ireland; [4]University of Torino, Turin, Italy; [5]Novant Health Oncology Specialists, Winston-Salem, NC; [6]University Hospital of Modena, Modena, Italy; [7]The University of Sydney, Sydney Medical School, Sydney, Australia; [8]Duke University Office of Research Administration, Durham, NC; [9]University Hospitals Gasthuisberg - Leuven, Leuven, Belgium; [10]Institut Jules Bordet, Brussels, Belgium; [11]Universitair Ziekenhuis Brussel, Brussels, Belgium; [12]Bristol-Myers Squibb, Princeton, NJ; [13]Hôpital Saint-Antoine and Sorbonne Universités, UMPC Paris 06, Paris, France

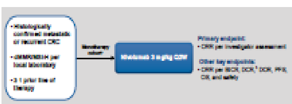
Background

- 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)	52.0 (27–77)
Male, n (%)	44 (59)	30 (57)	14 (67)
ECOG performance status, n (%)			
0	32 (43)	21 (40)	11 (52)
1	42 (57)	32 (60)	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	13 (18)	12 (23)	1 (5)
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 (1–79)	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

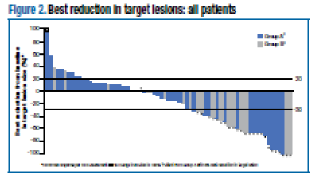
- ORR by BICR was 34% (95% CI, 23.2, 45.7) with nivolumab monotherapy, and 62% of patients had disease control (Table 3)
  - Median time to response was approximately 2.8 months across all groups
  - Clinical benefit was observed across all groups

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 (1.4+ to 31.6+)	NR (4.6+ to 27.2+)	NR (1.4+ to 31.6+)
Median duration of SD (range), months	8.3 (4.3–40)	8.5 (4.1–40)	5.3 (2.6–40)

- 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



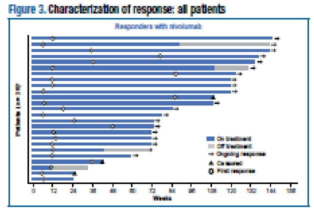
- CR rates increased in all patients with longer follow-up (Table 4)
- Similar trends in CR were observed in groups A and B

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

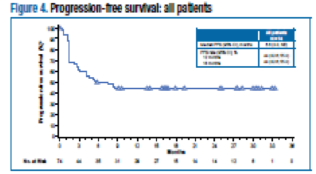
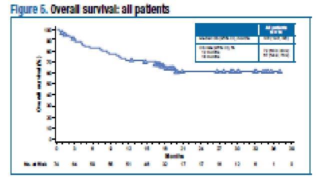


Figure 5. Overall survival: all patients



- 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

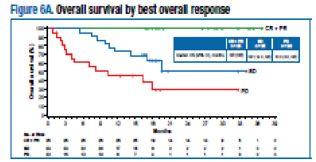
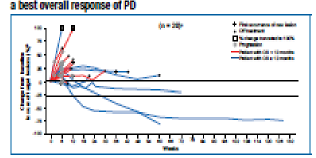


Figure 6B. Antitumor activity after initial progression in patients with a best overall response of PD



Safety

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

Table 5. Safety summary

Patients, n (%)	All patients N = 74	
	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

TRAE = treatment-related adverse event

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

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3. Le DT, et al. *Science* 2017;357:409–413.
4. Tougeron D, et al. *Ann Oncol* 2017;28:(suppl 5) Abstract 533P.
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- All authors contributed to and approved the presentation; writing and editorial assistance was provided by Bridget Sackey Aboagye of Chrysalis Medical Communications, Inc, funded by Bristol-Myers Squibb

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Presented at the 2018 ASCO Gastrointestinal Cancers Symposium; January 18–20, 2018; San Francisco, CA

Email: MOverman@mdanderson.org

Overview of Trials included MSI-H Cancers

Study	Design and Patient Population	Number of patients	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	≥1 prior regimen

ORR per Tumor Type MSI-H

		Objective response rate		DOR range
	N	n (%)	95% CI	(months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)

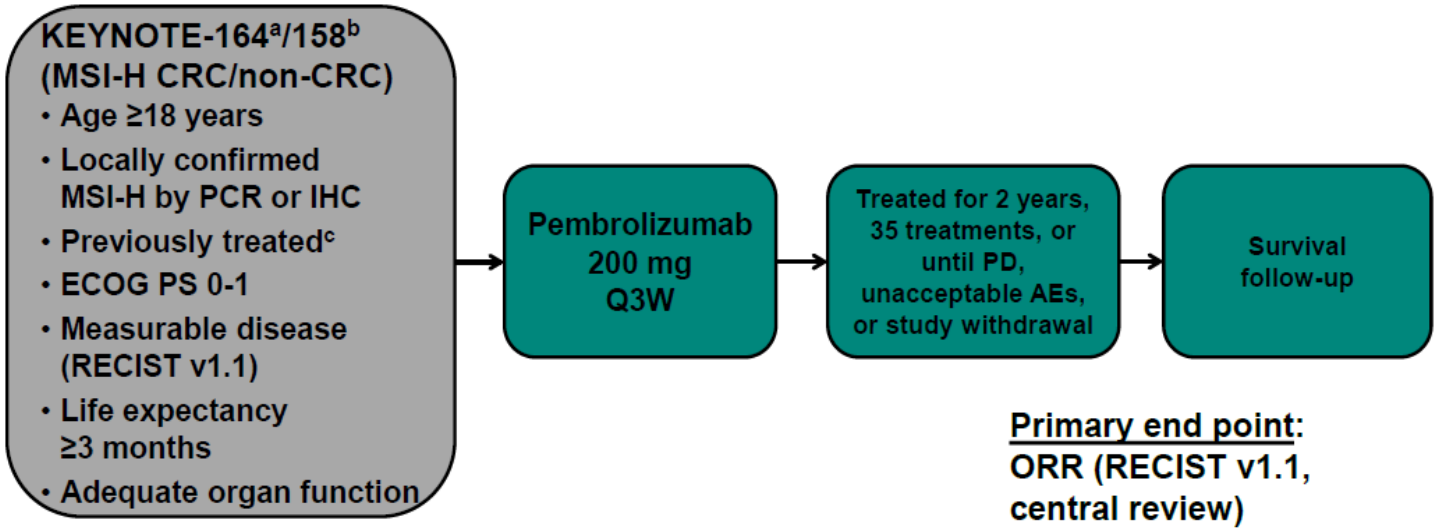
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

KEYNOTE-164 Cohort B: Pembrolizumab for Patients With Advanced Microsatellite Instability High (MSI-H) Colorectal Cancer (#3514)

D.T. Le[1]; P. Kavan[2]; T. W. Kim[3]; M. Burge,[4]; E. Van Cutsem[5]; H. Hara[6]; P. Boland[7]; J. L. Van Laethem[8]; R. Geva[9]; H. Taniguchi[10]; T. Crocenzi[11]; M. R. Sharma[12]; C. E. Atreya[13]; L. A. Diaz, Jr[14]; L. W. Liang[15]; P. Marinello[15]; T. Dai[15]; B. O'Neil[16a]

PD-1 Blockade in Cancer with MMR- Deficiency

Global Phase 2 Studies KEYNOTE-164 and KEYNOTE-158: Study Design



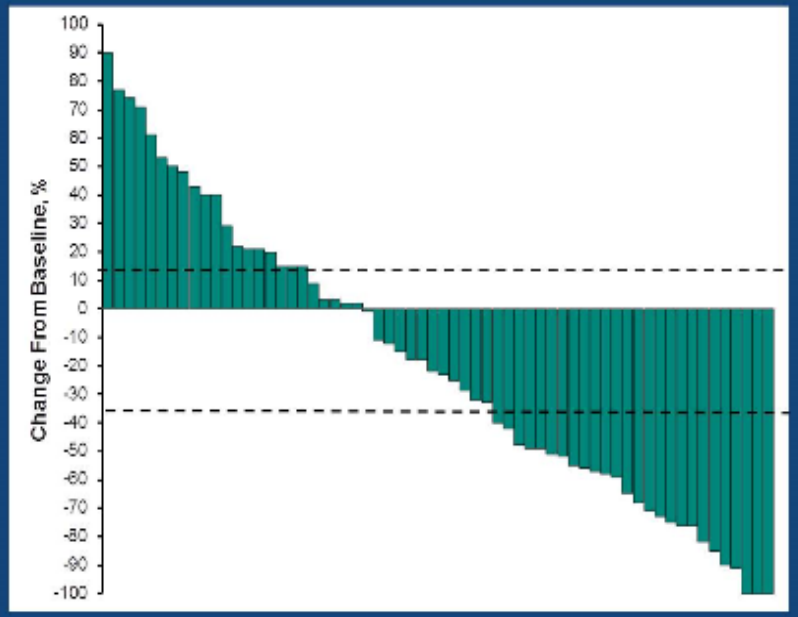
Primary end point:
ORR (RECIST v1.1, central review)

Secondary end points:
DOR, PFS, OS, safety

[a]Histologically confirmed, advanced, unresctable or metastatic CRC; previous treatment with approved therapies including fluoropyrimidine, oxaliplatin, and irinotecan.
[b]Histologically or cytologically confirmed, advanced, incurable non-CRC solid tumor; patients must have progressed on or be intolerant to standard therapies.
[c]≥2 prior therapies and ≥1 prior therapy for MSI-H CRC and non-CRC, respectively.
Clinicaltrials.gov: NCT02460198 and NCT02628067

KEYNOTE 164 ASCO 2018

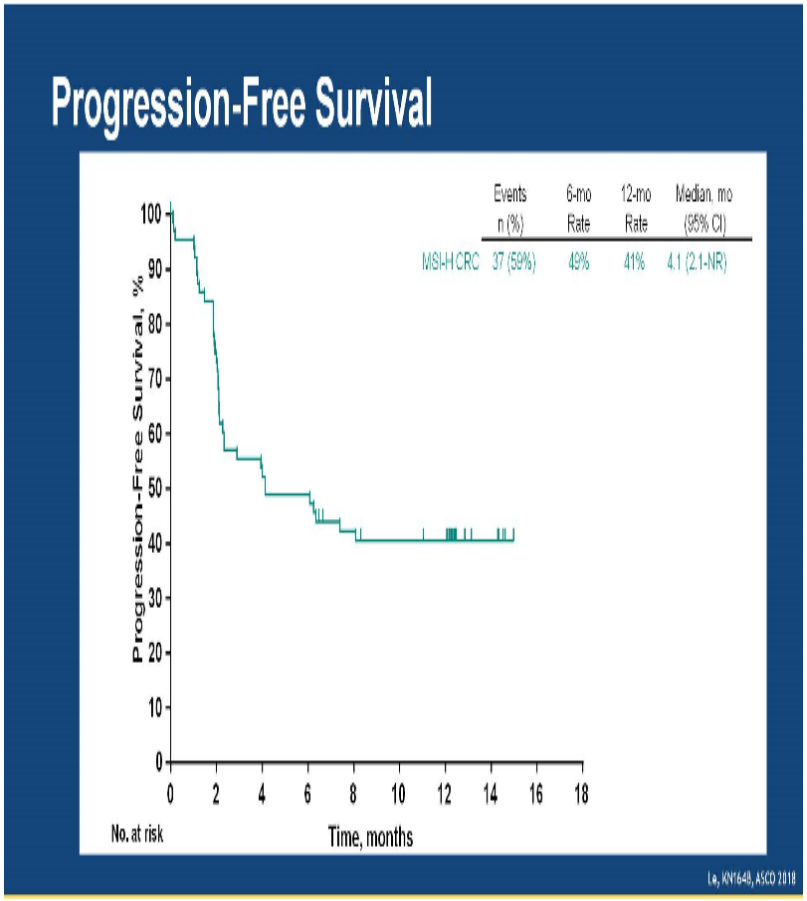
Best Percentage Change From Baseline in Target Lesion Size (RECIST v1.1)

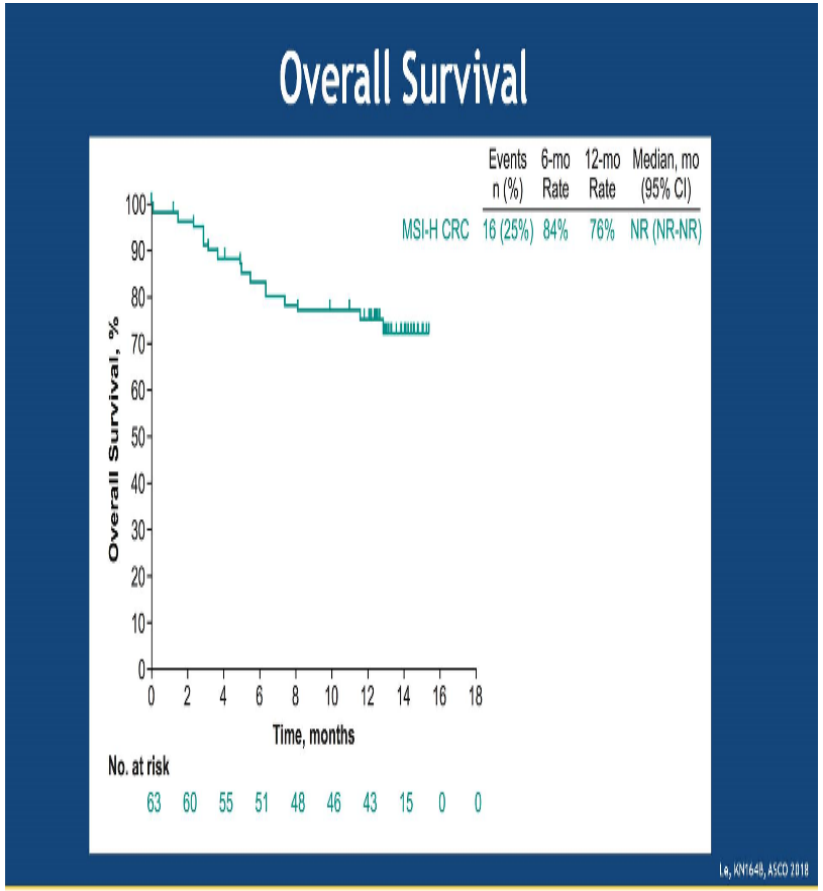


- Median duration of follow-up: 12.6 months (range, 0.1-15.4)
- ORR: 32% (95% CI, 21%-45%)
  - 2 CR, 18 PR
- Median duration of response: not reached (2.1+ to 13.2+ months)
  - 15 (75%) patients had duration of response ≥6 months

Le, KN164B, ASCO 2018

KEYNOTE 164 ASCO 2018



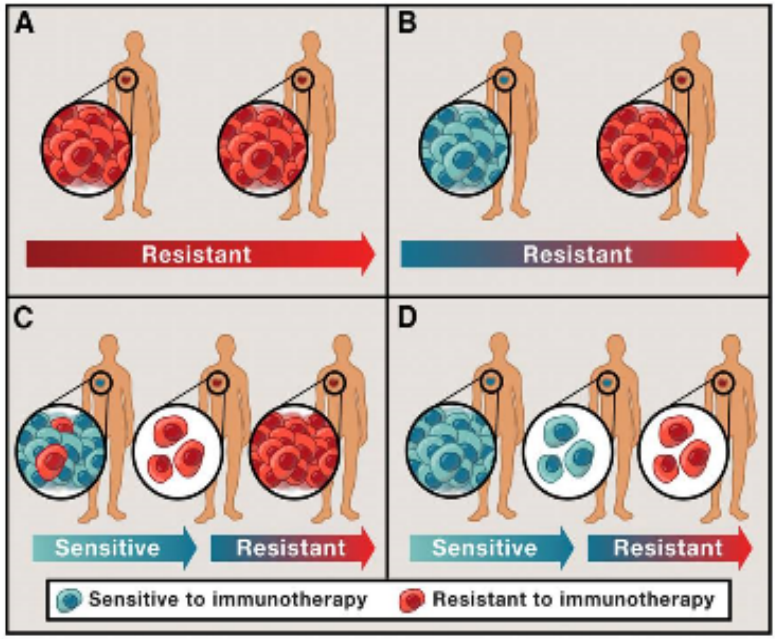


	Chemotherapy and Biologics	Pembrolizumab		Nivolumab
				Basket trial MSI-H
ORR %				31.1 %
Best Overall response				
CR				
PR				
SD				
Unable assess				
Disease control %				69%

Resistance Mechanism of Immunotherapy

Intrinsic Resistance Mechanisms to Immunotherapy

Scenarios that intrinsic resistance can be developed

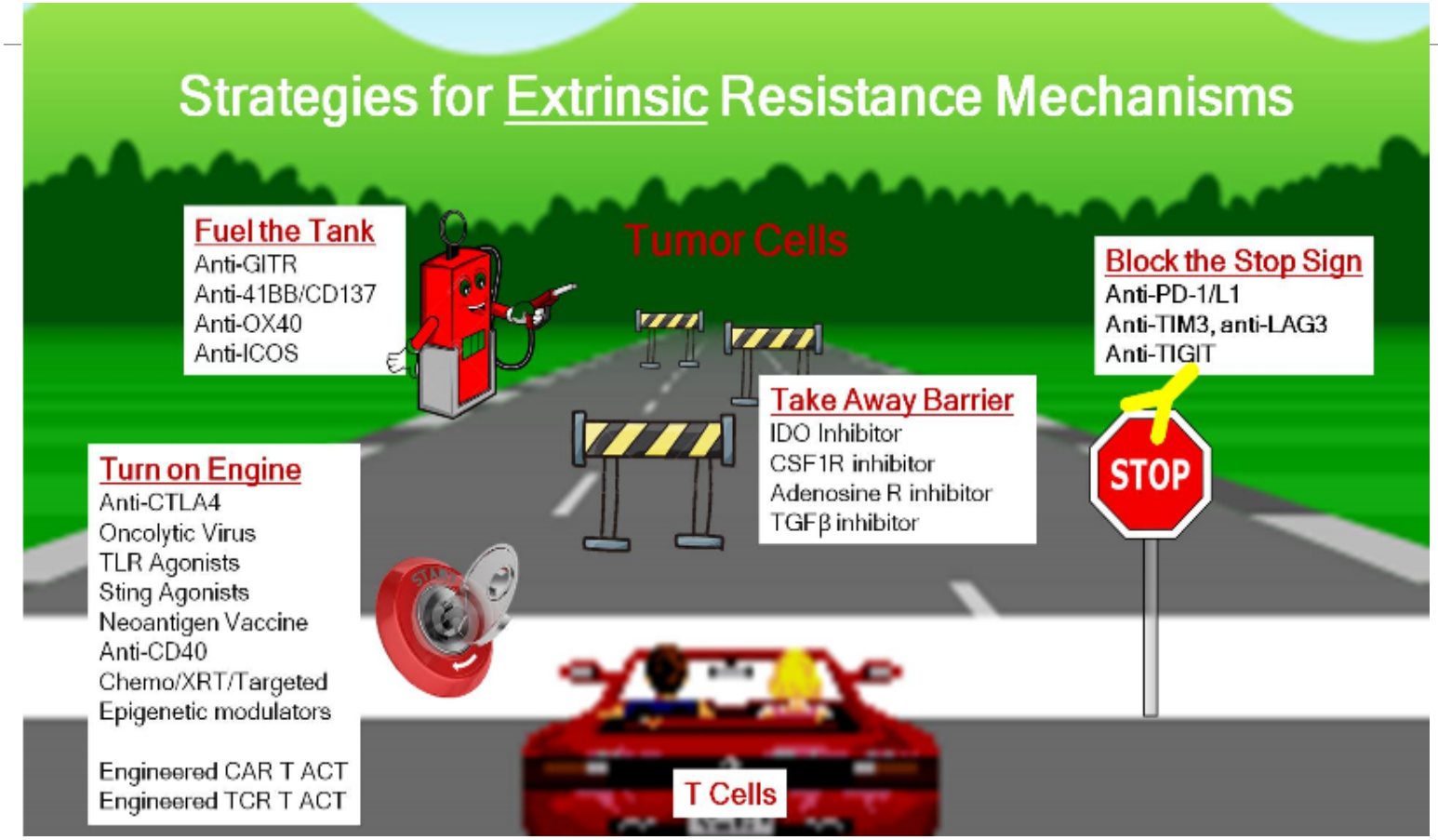


Primary resistance:
Immune escape mechanisms that exist in the non-responding patients

Acquired resistance:
Immune escape mechanisms that developed after an initial response

Sharma, Hu-Lieskovan, Wargo, Ribas. Cell, 2017
Hu-Lieskovan and Ribas. Cancer Journal. 2017

Resistance Mechanism of Immunotherapy



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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).

Pooled ORR in MSI-H Cancers

	N=149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

The Future of Immuno-oncology in MSI-H malignancies

Where we go from here :

- Search for more Biomarkers : Lymphocyte Infiltrate, TMB..
- Understanding Resistance Mechanism:
- New Clinical trials for First Line therapy for Metastatic CRC or Optimizing adjuvant therapy for Stage III CRC
- The Role of ctDNA in stratification of Stage II CRC and the utilization of ImmunoRx

The COMMIT Trial Stage IV CRC MMRd

Randomized Study of mFOLFOX6/Bevacizumab +/- Atezolizumab or Atezolizumab Monotherapy in Patients with d-MMR Metastatic Colorectal Cancer (COMMIT)	
NCI Trial Number	NCT 02912559
Trial Type	Phase III randomized 3-arm trial
Sponsor	NRG-GI004/SWOG-S1610/ NCI
Primary Outcome	Progression-free survival
Secondary Outcome	OS, ORR, safety profile, surgical conversion rate, DCR, duration of response and stable disease
Patient Population (Inclusion Criteria / Exclusion Criteria)	• Metastatic CRC; first-line • d-MMR by IHC in CLIA-lab
Number of Patients Needed to Accrue	325 (347 total)
Status	Currently Accruing

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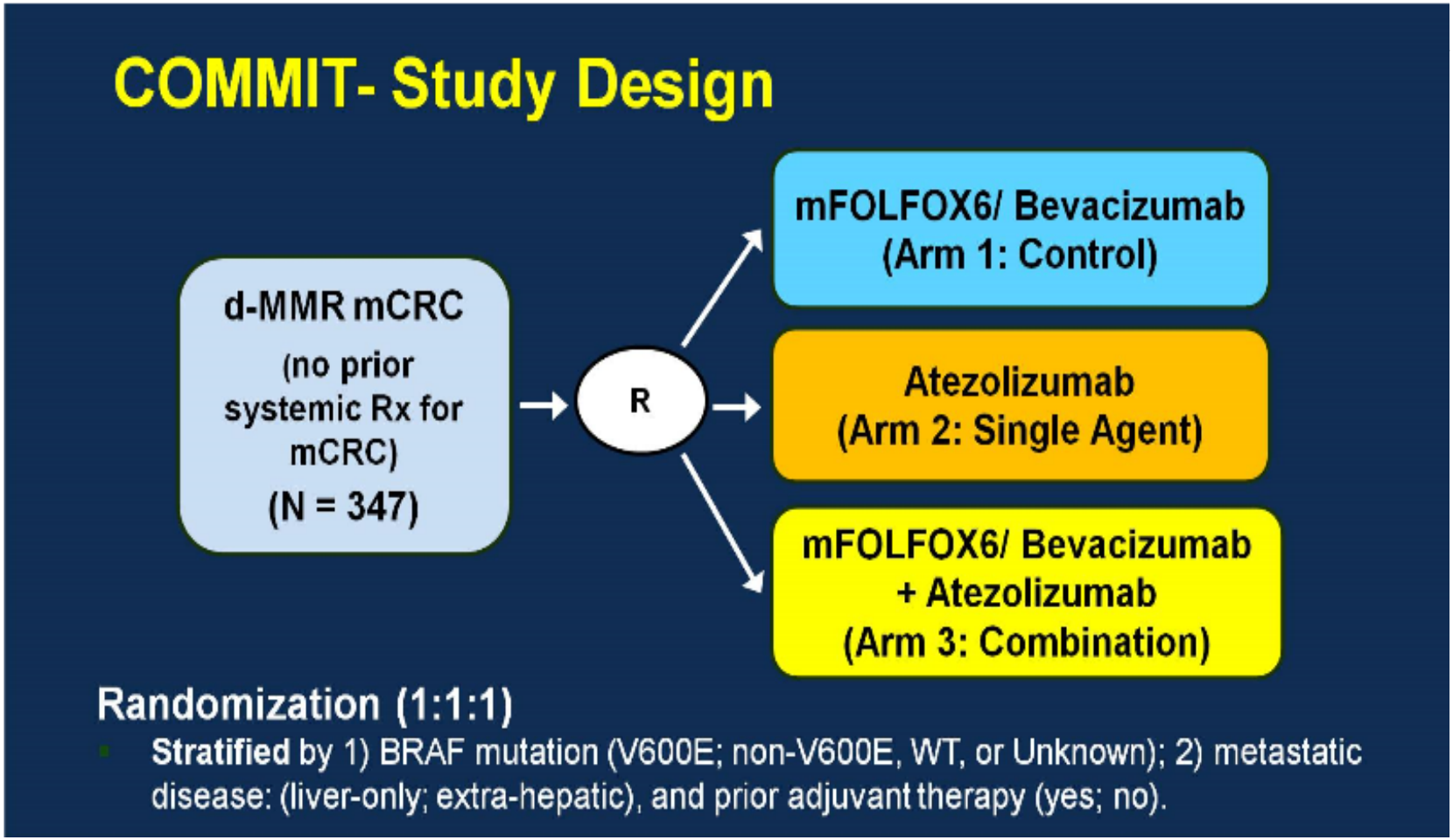
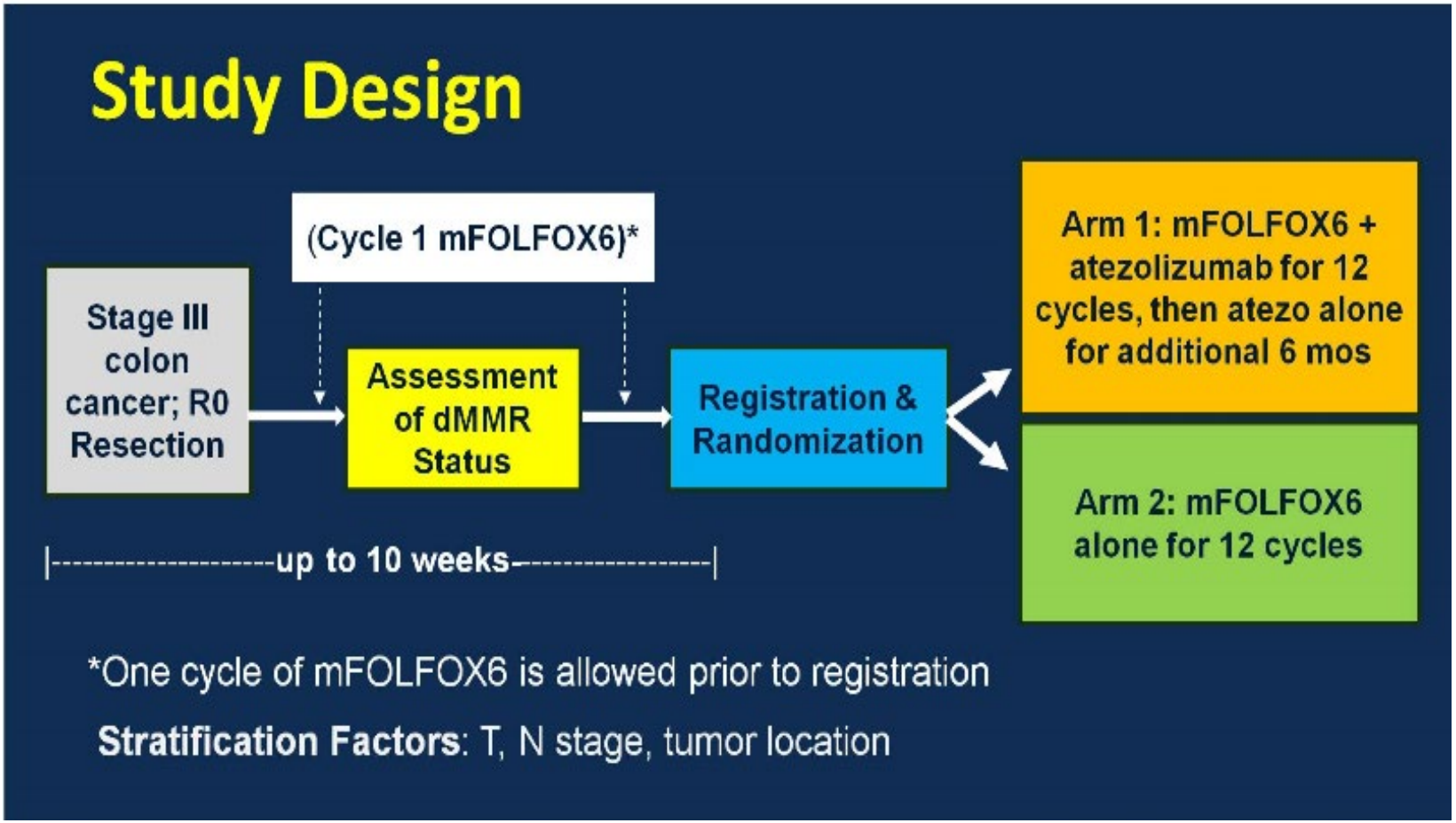
The COMMIT Trial Stage IV CRC MMRd



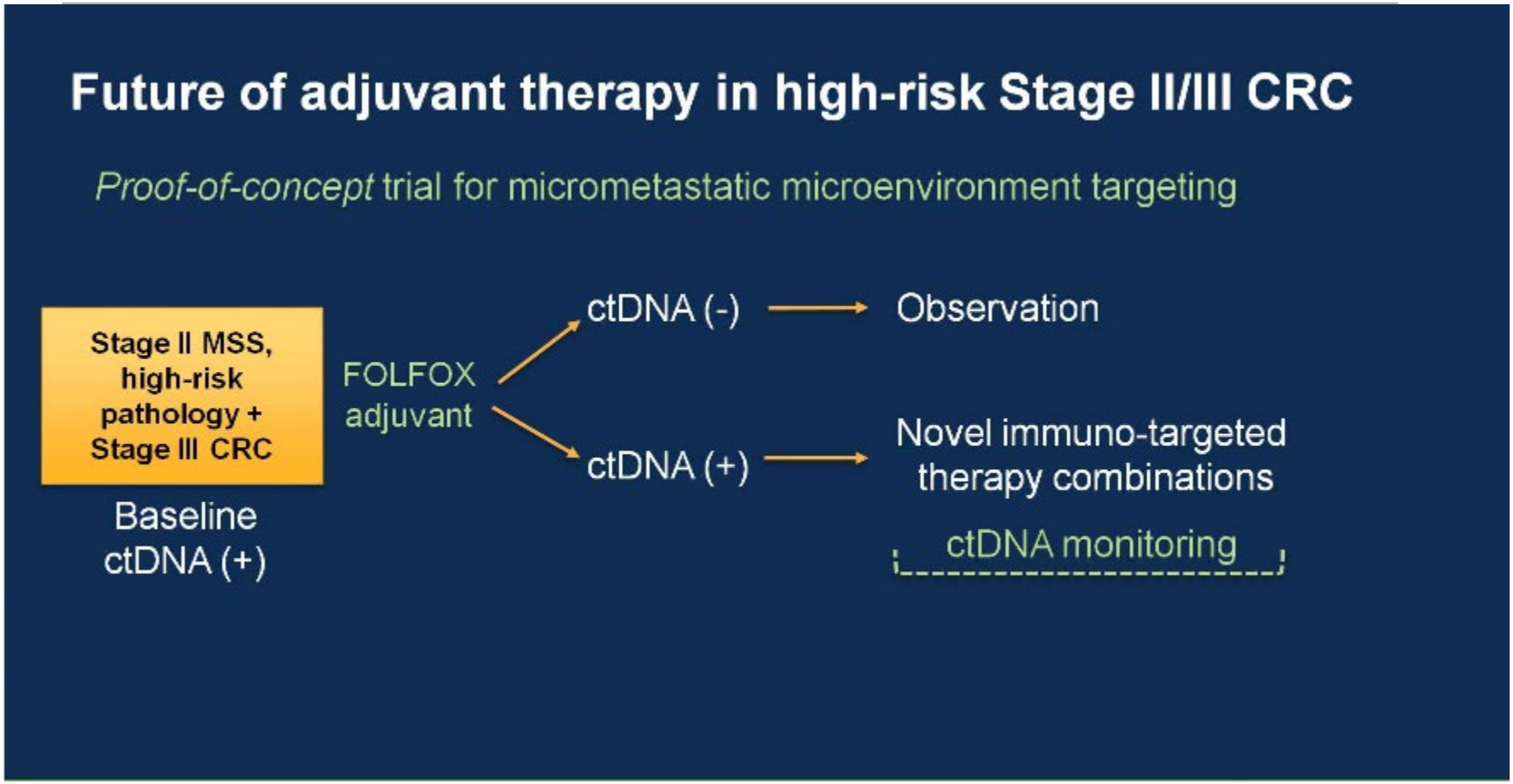
The ATOMIC Trial stage III CRC MMRd

mFOLFOX6 with or without Atezolizumab in Patients with Stage III Colon Cancer and Deficient DNA Mismatch Repair (ATOMIC)	
NCI Trial Number	NCT02912559
Trial Type	Phase III Adjuvant Trial
Sponsor	Alliance A021502/ NCI
Primary Outcome	Disease-free survival
Secondary Outcome	OS, adverse event profile
Patient Population (Inclusion Criteria / Exclusion Criteria)	• Resected stage III adenocarcinoma (any T, $N_{1-2}M_0$). • d-MMR by IHC (local or reference lab)
Number of Patients Needed to Accrue	557 (700 total)
Status	Currently Accruing

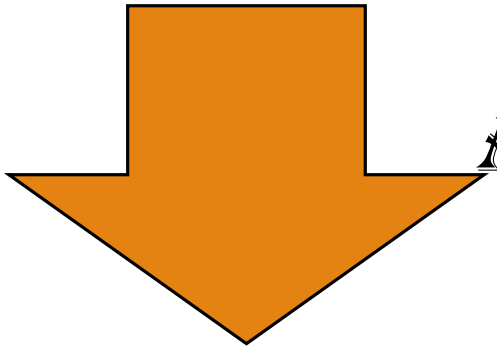
The ATOMIC Trial stage III CRC MMRd



Future of Immunotherapy in CRC MMR-Deficient

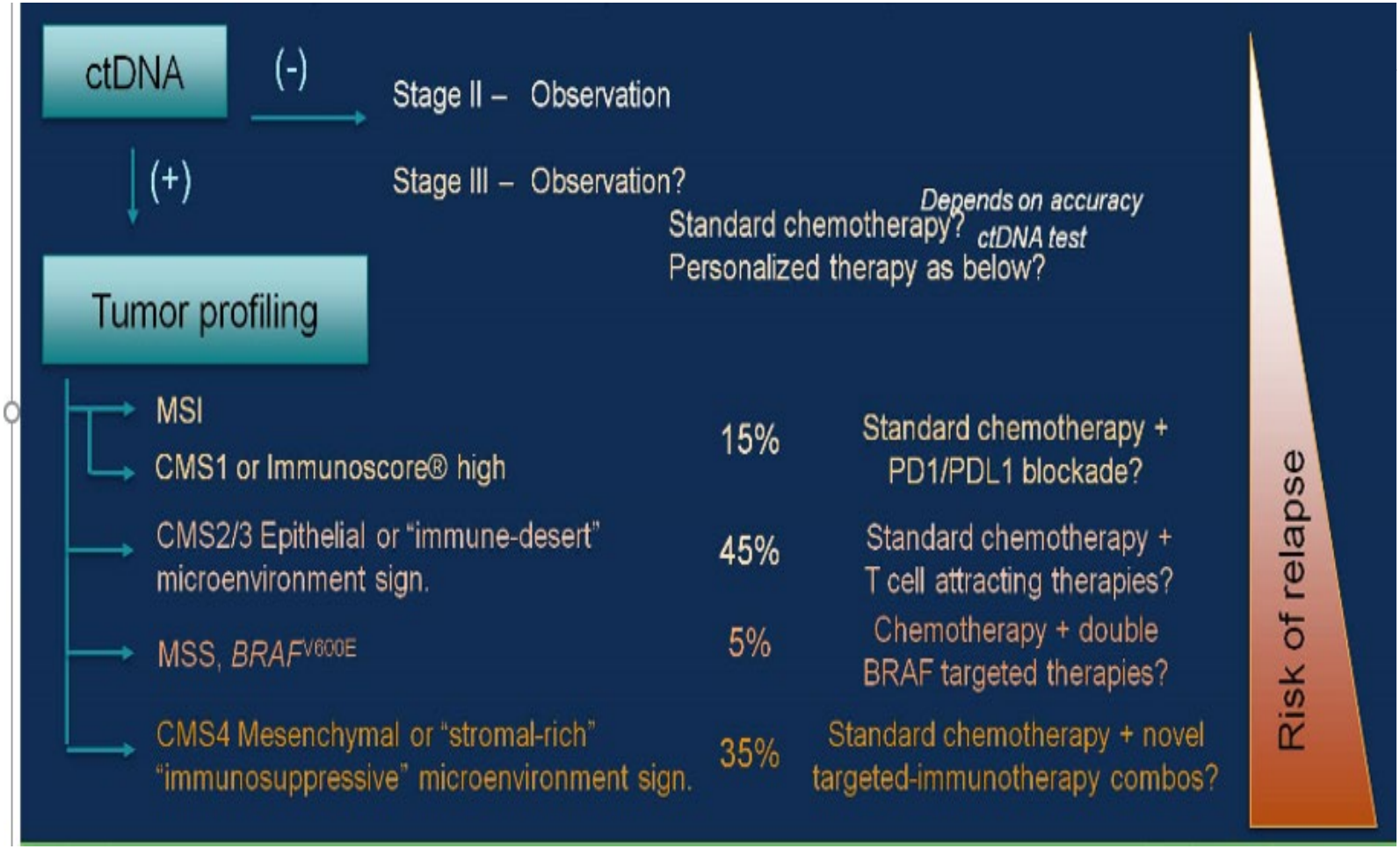


Treatment Decision-Making



RECURRENCE RISK
ABSOLUTE TREATMENT BENEFIT

TOXICITY
COST


ctDNA
(-)
Stage II – Observation
(+)
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

- Immunotherapy with the the FDA approval of 2 PD-1 Inhibitors (Pembrolizumab/ Nivolumab) and CTLA-4 Inhibitor (Ipilimumab) will certainly have a positive impact on Median survival of patients with Metastatic CRC and NON-CRC MMR-Deficient
- Need to continue to identify Predictive Biomarkers for Response to checkpoints inhibitors and help explain lack of response and resistance to Immunotherapy in some the MSI-H Malignancies
- 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