Immunotherapy in Colorectal cancer & MSI-High Solid Cancers

Ahmed Zakari, MD
Associate Professor University of Central Florida, College of Medicine
Medical Director, Gastro Intestinal Cancer Program
AdventHealth Cancer Institute

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

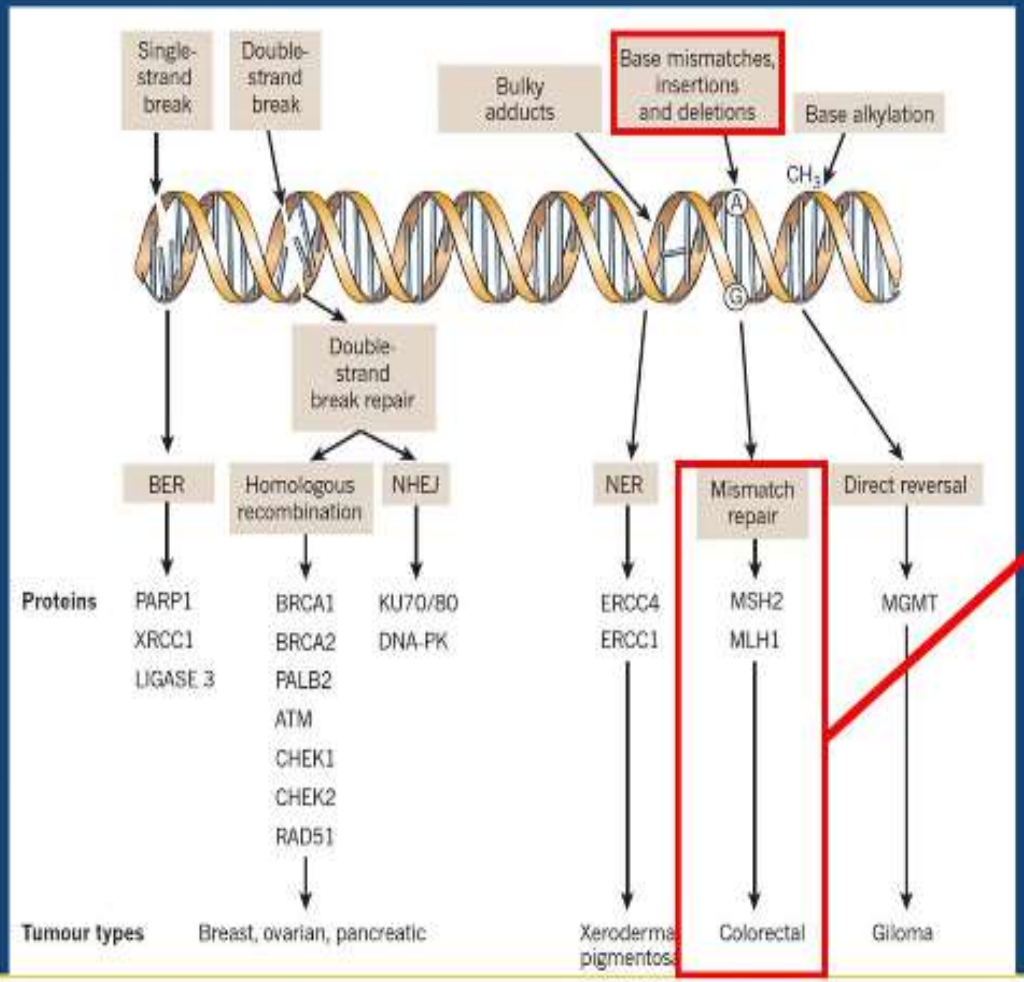
The mechanism of MMR involves at least three different processes:

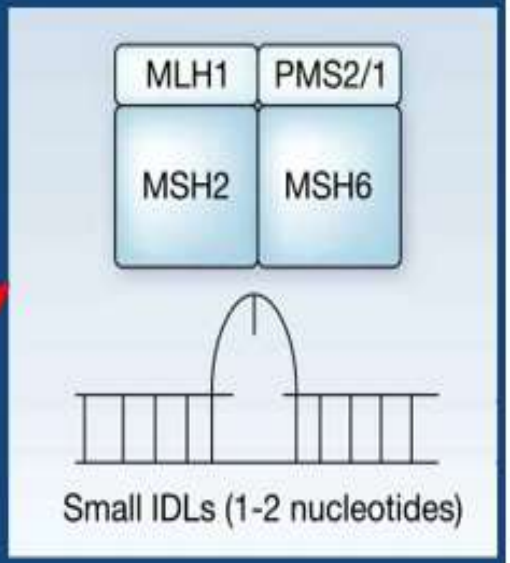
1. ***Recognition of single base replication errors is performed by the MutSα:***
    - ***a. MSH2-MSH6 heteroduplex or MSH2-MSH3 heteroduplex***
2. ***Excision of the lagging strand from the mismatch by one of the MutL complexes:***
    - ***a. MLH1/PMS2 recruited by MutS protein***
3. ***Re-synthesis 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.

DNA Repair Mechanisms





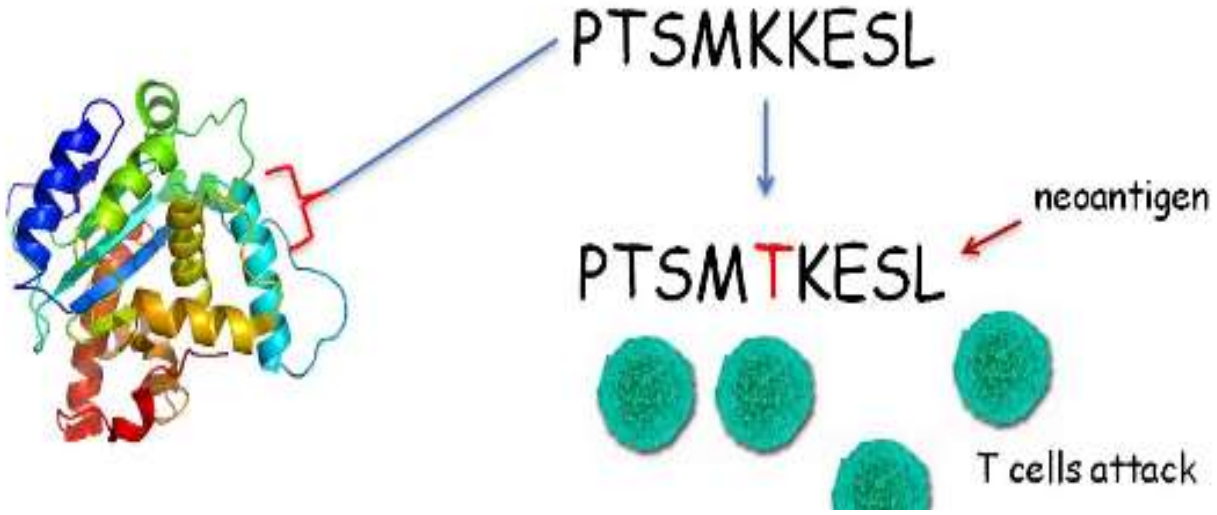
Lord Nature rev 2012

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*

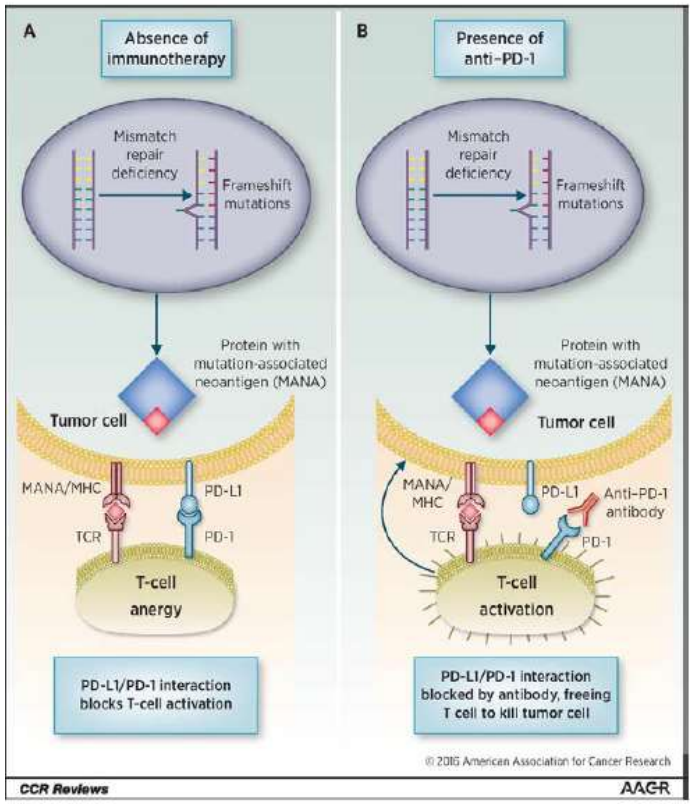
What is a Neoantigen?

- 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 : <u>Hypermutated phenotype</u>***
- ***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 (-) :

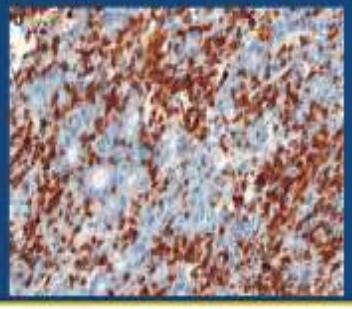
- *BRAF V600E mutation in about 50% of sporadic unstable tumors, only rarely*
- *occurs in Lynch/HNPCC (so far, minority of those with PMS2 germline mutation;Senter, Gastroenterology, 2008)*
- *MLH1 methylation in most sporadic*
- *unstable tumors, only rarely in Lynch/ HNPCC*

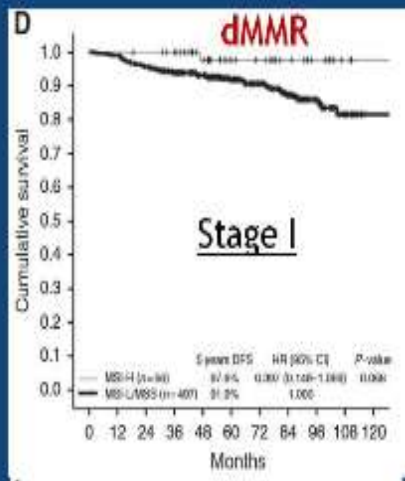
dMMR by Stage in CRC and Prognostic Impact

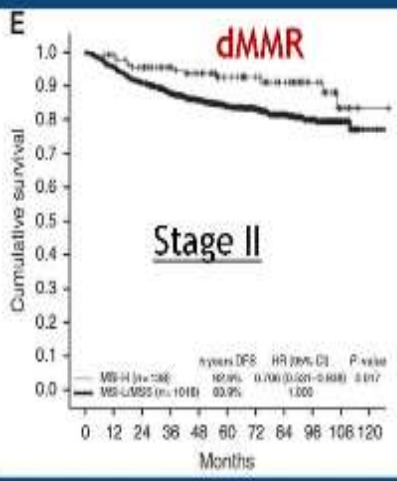
Stage Distribution

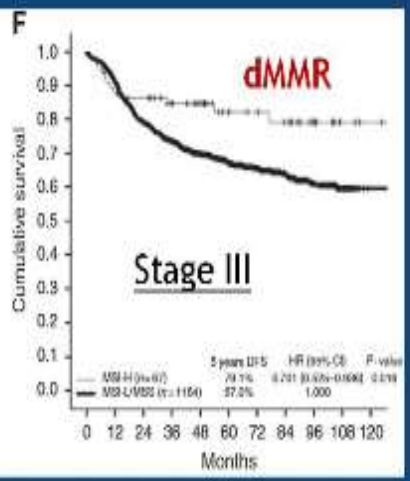
Stage	MSI-H
II	22%
III	12%
IV	3.5%

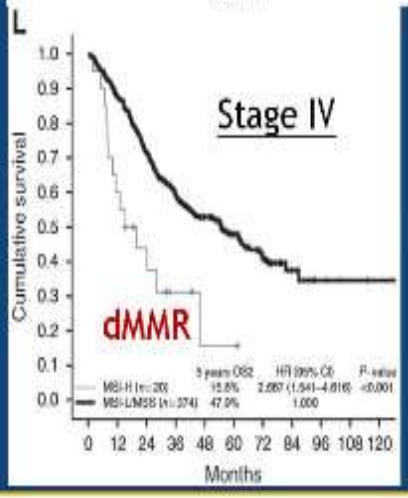
MSI-high tumor: anti-CD3 Ab

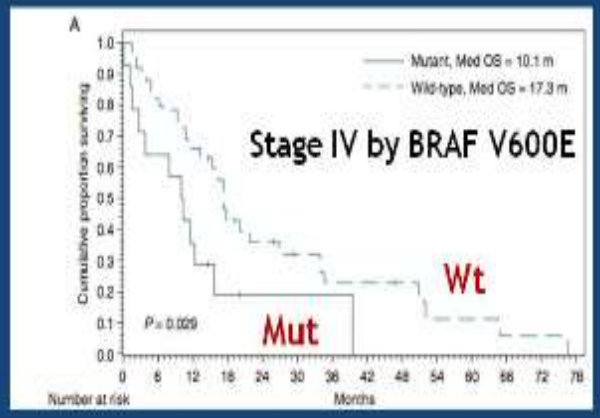






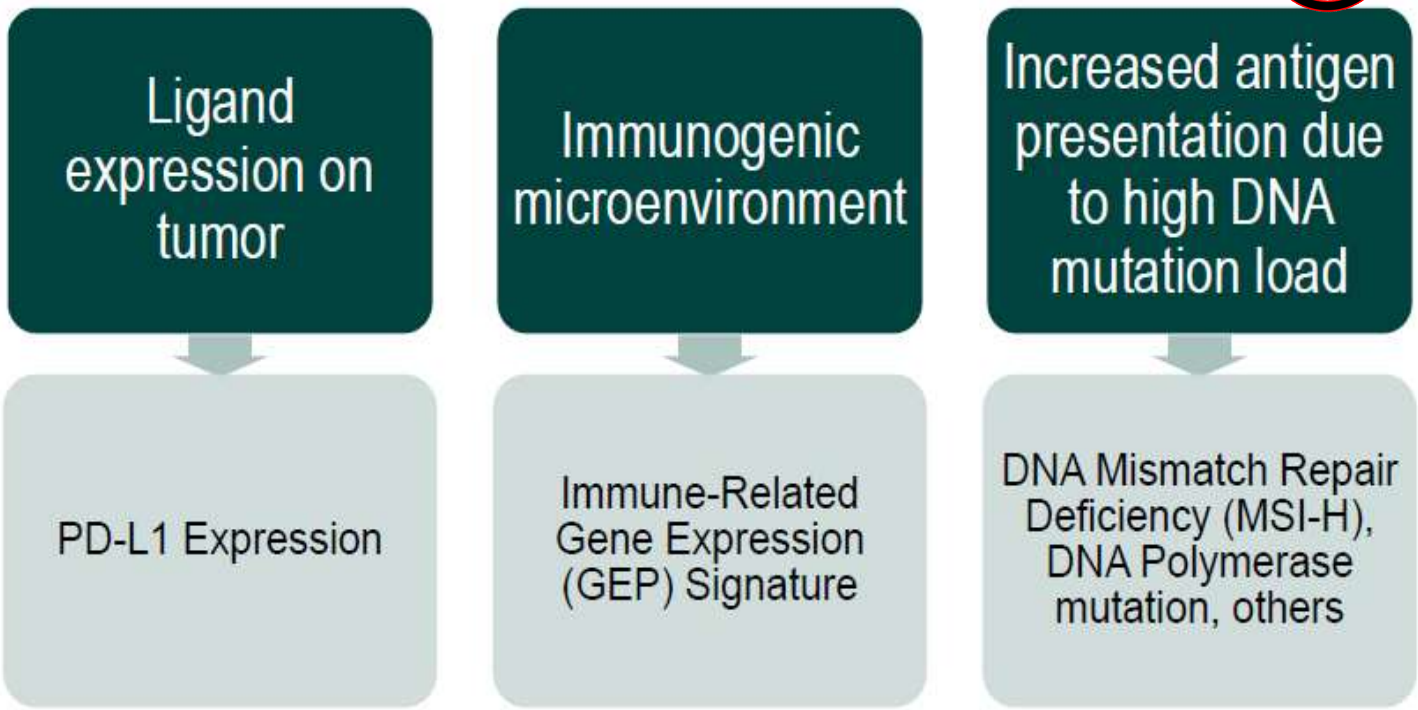




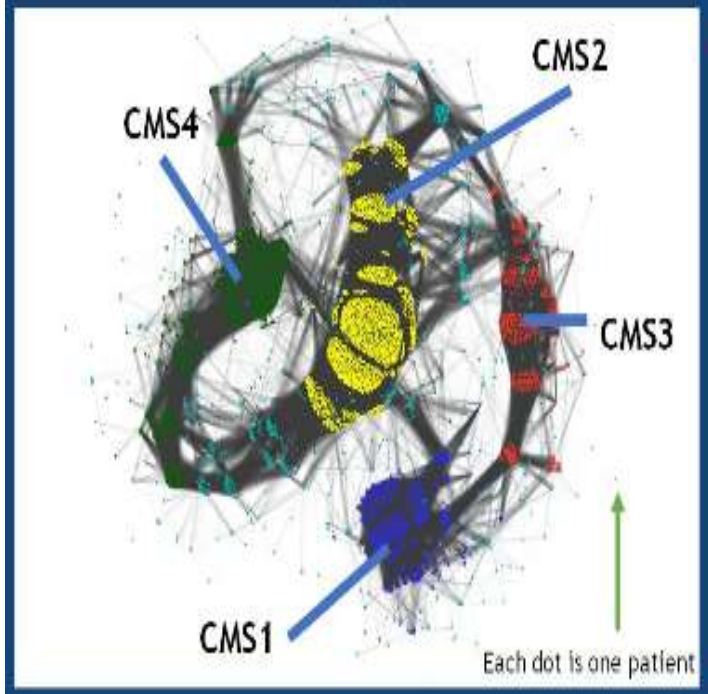


Tejpar S, 2009; Kaanpman R, 2009; Kim S-K 2015; Goldstein JBD 2014

Biomarkers Identification

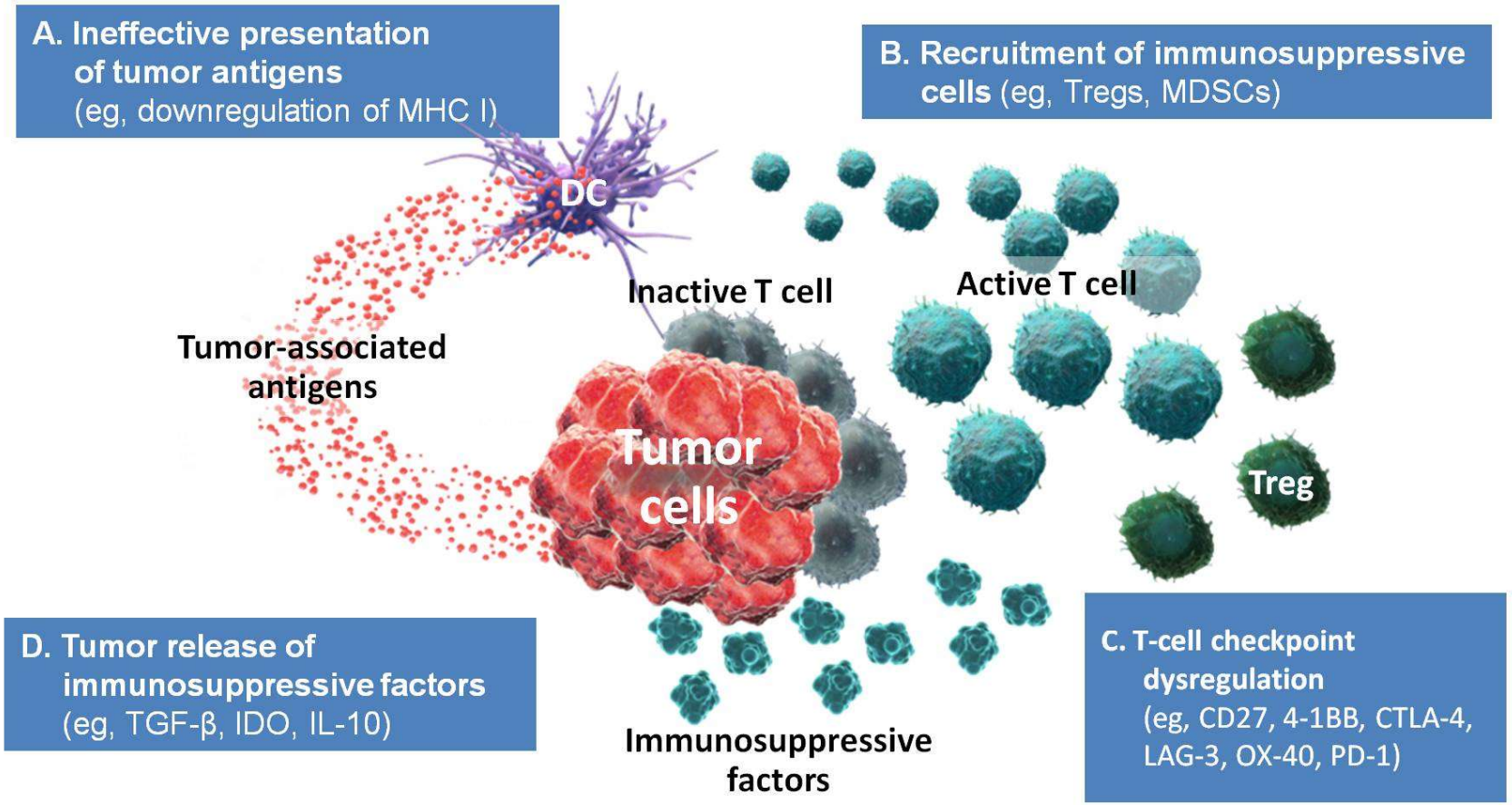


Biomarkers Identification : CMS



CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high Hypermutation	SCNA high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis
Worse survival after relapse	Better survival after relaspe		Worse relapse-free and overall survival

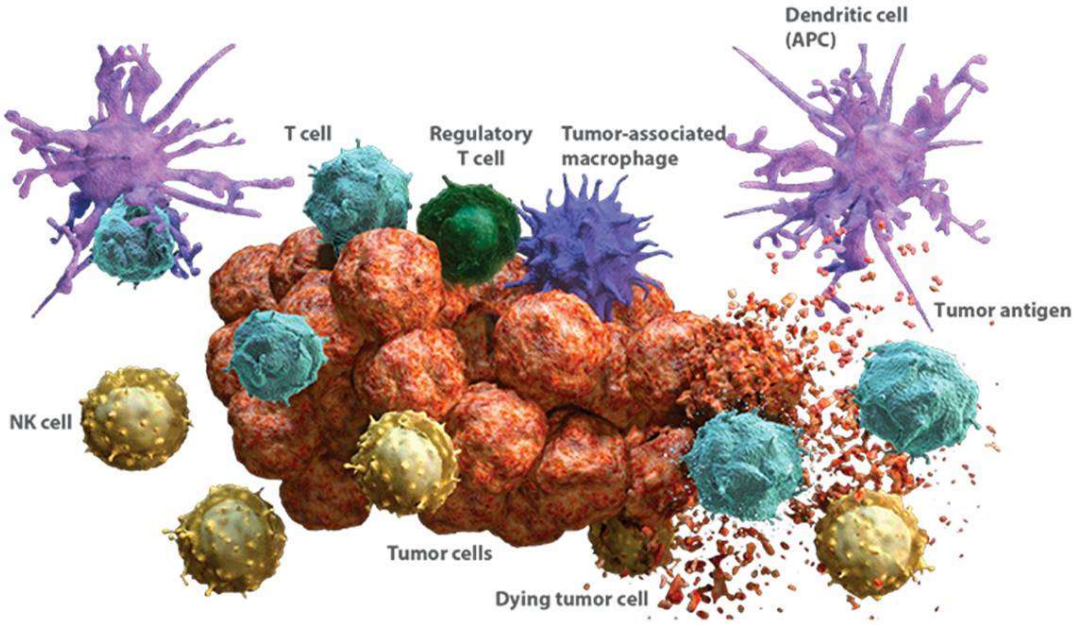
Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System



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

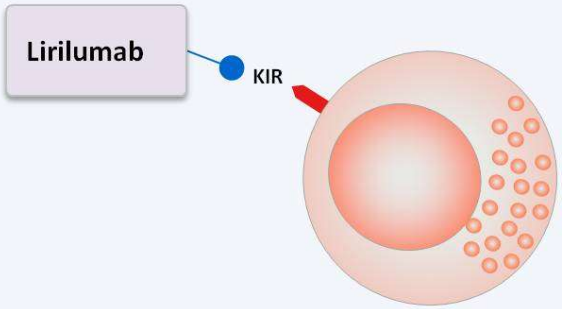
- The adaptive immune response is antigen specific and able to produce a durable response[1]
- **Cytotoxic T cells are essential anti-tumor effector cells** of the adaptive immune system[2,3]

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.

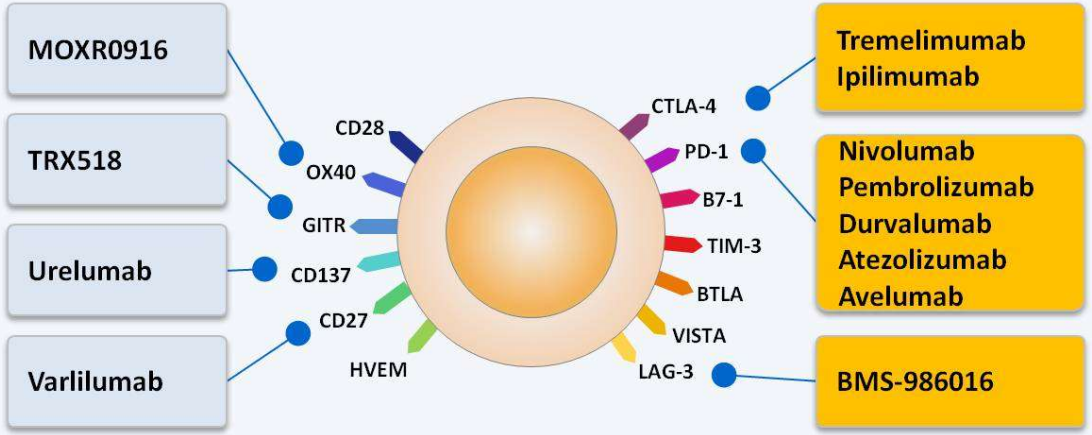
Targeting Checkpoints as an Approach to Cancer Therapy

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**

*

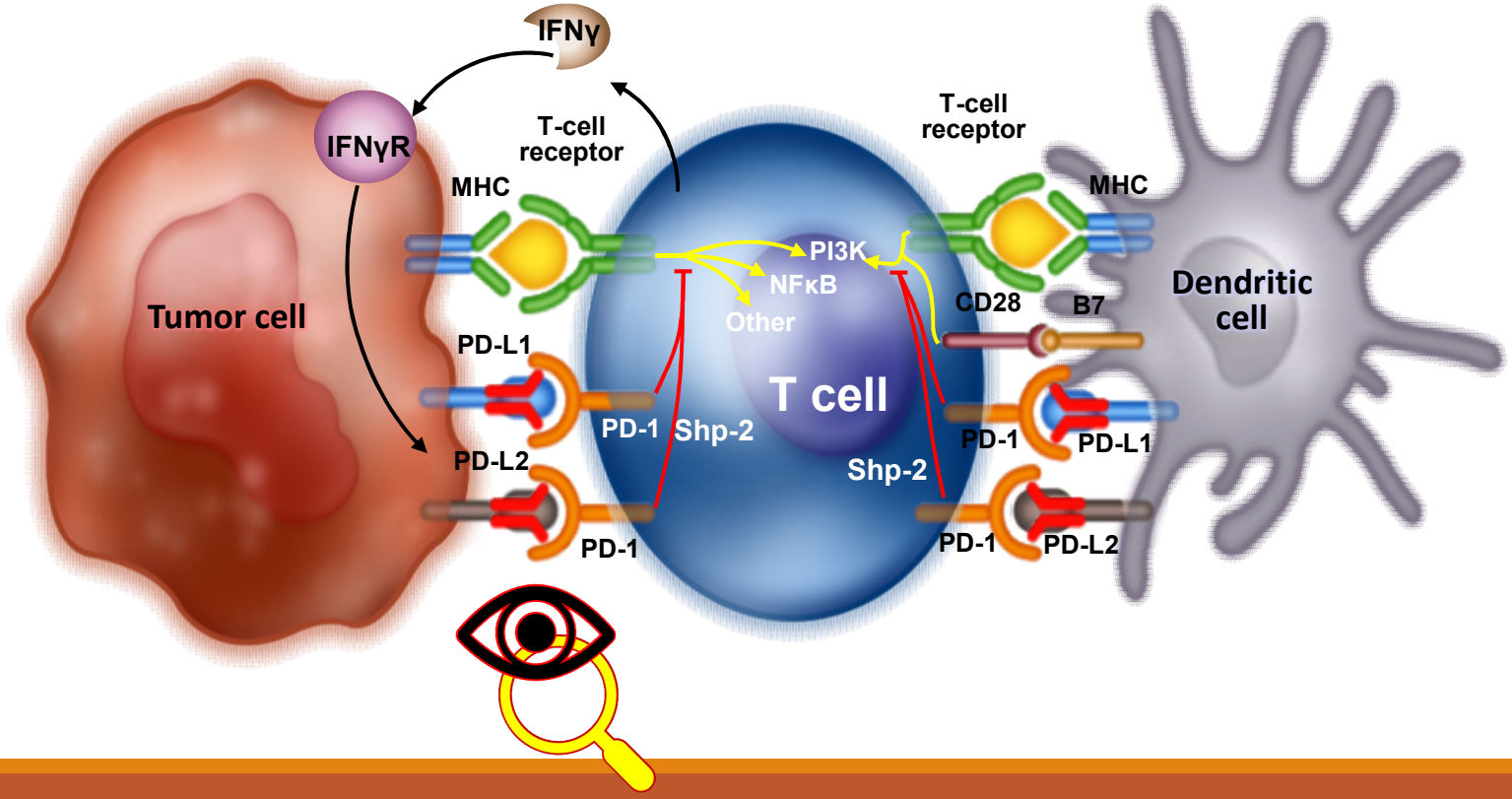
CTLA-4=cytotoxic T-lymphocyte antigen-4; GITR=glucocorticoid-induced TNFR family related gene; KIR=killer-cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene-3; NK=natural killer; PD-1=programmed death-1; PD-L1=programmed death ligand-1.

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]

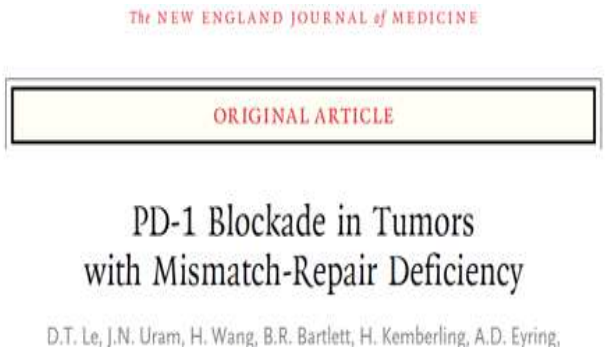
Binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[12–14]



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.

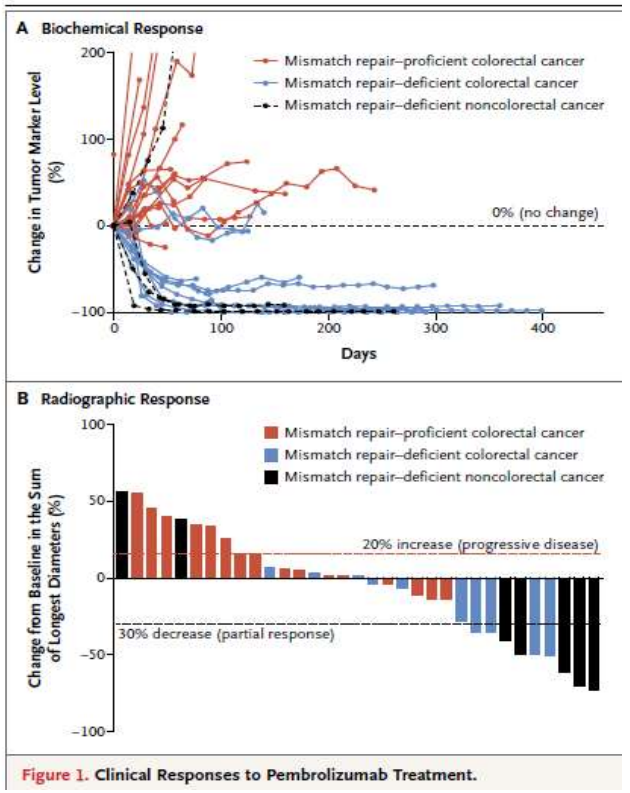
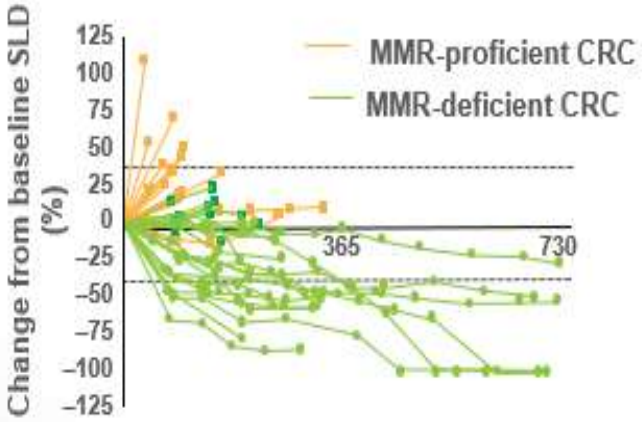
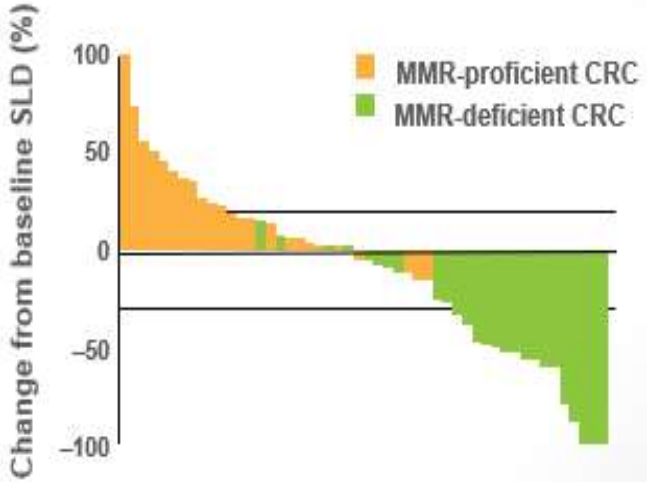


Figure 1. Clinical Responses to Pembrolizumab Treatment.

MSI-high tumours are responsive to PD-1 inhibitors

Pembrolizumab
(KEYNOTE 016, phase II)





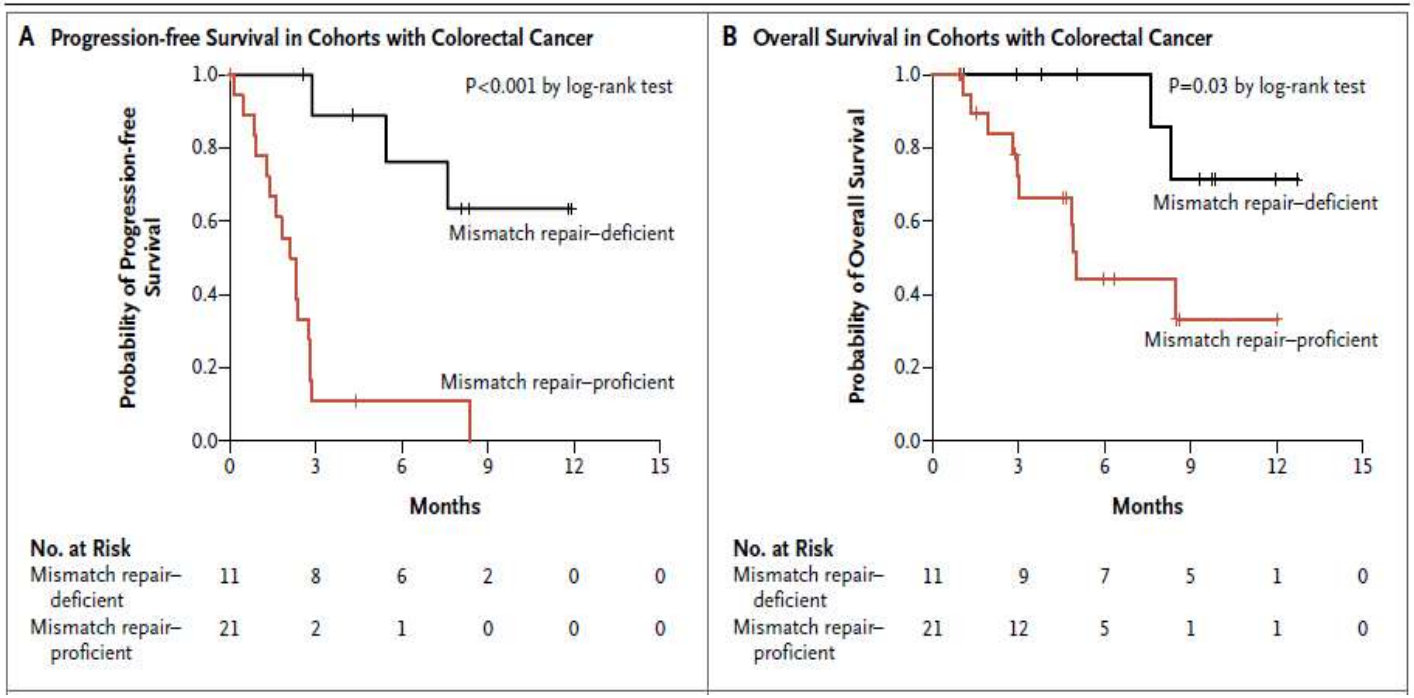
*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

1. Le et al. ASCO 2016;

PD-1 Blockade in Cancer with MMR- Deficiency

(NEJM 2015)

PD-1 BLOCKADE IN MISMATCH-REPAIR DEFICIENCY



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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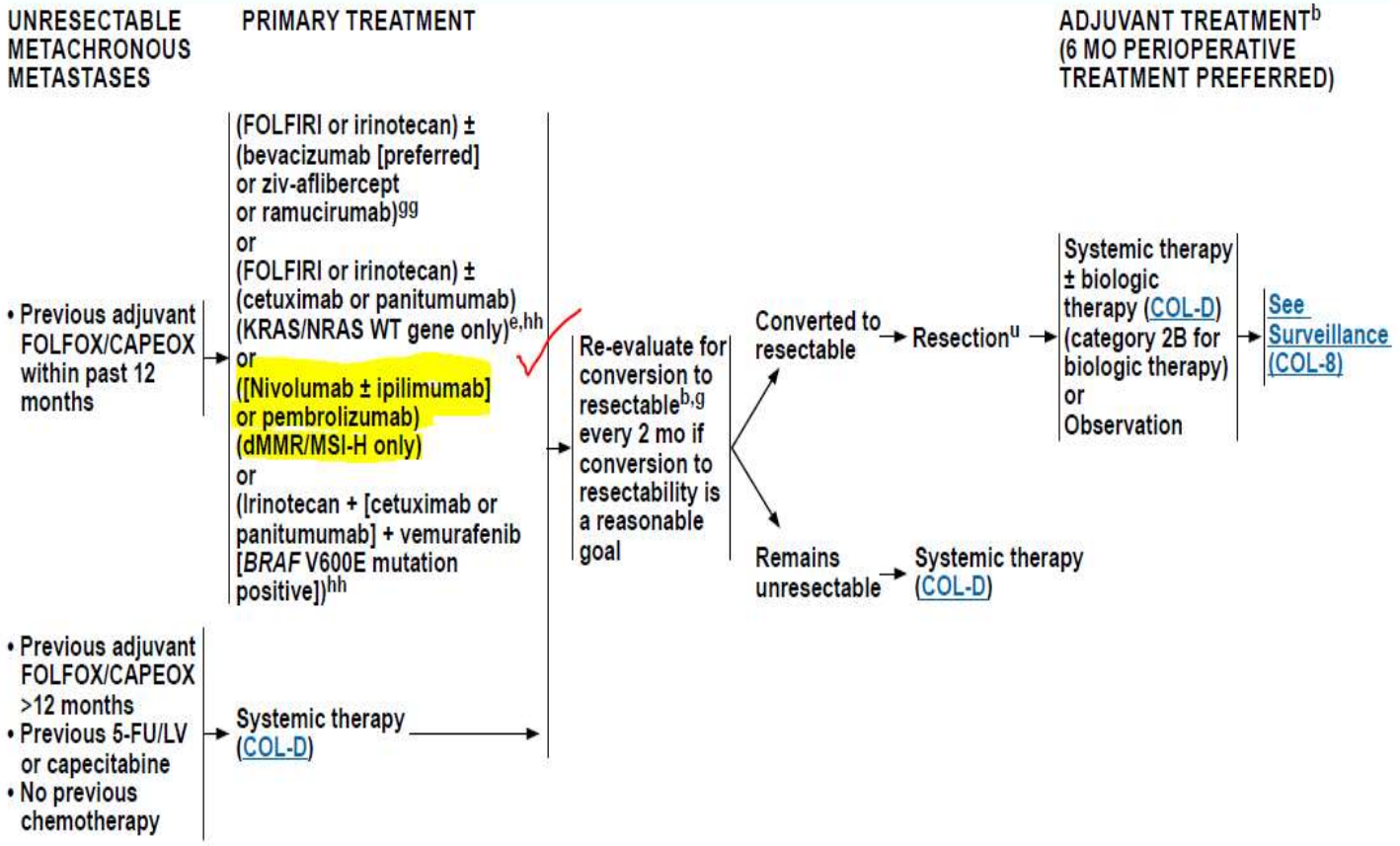


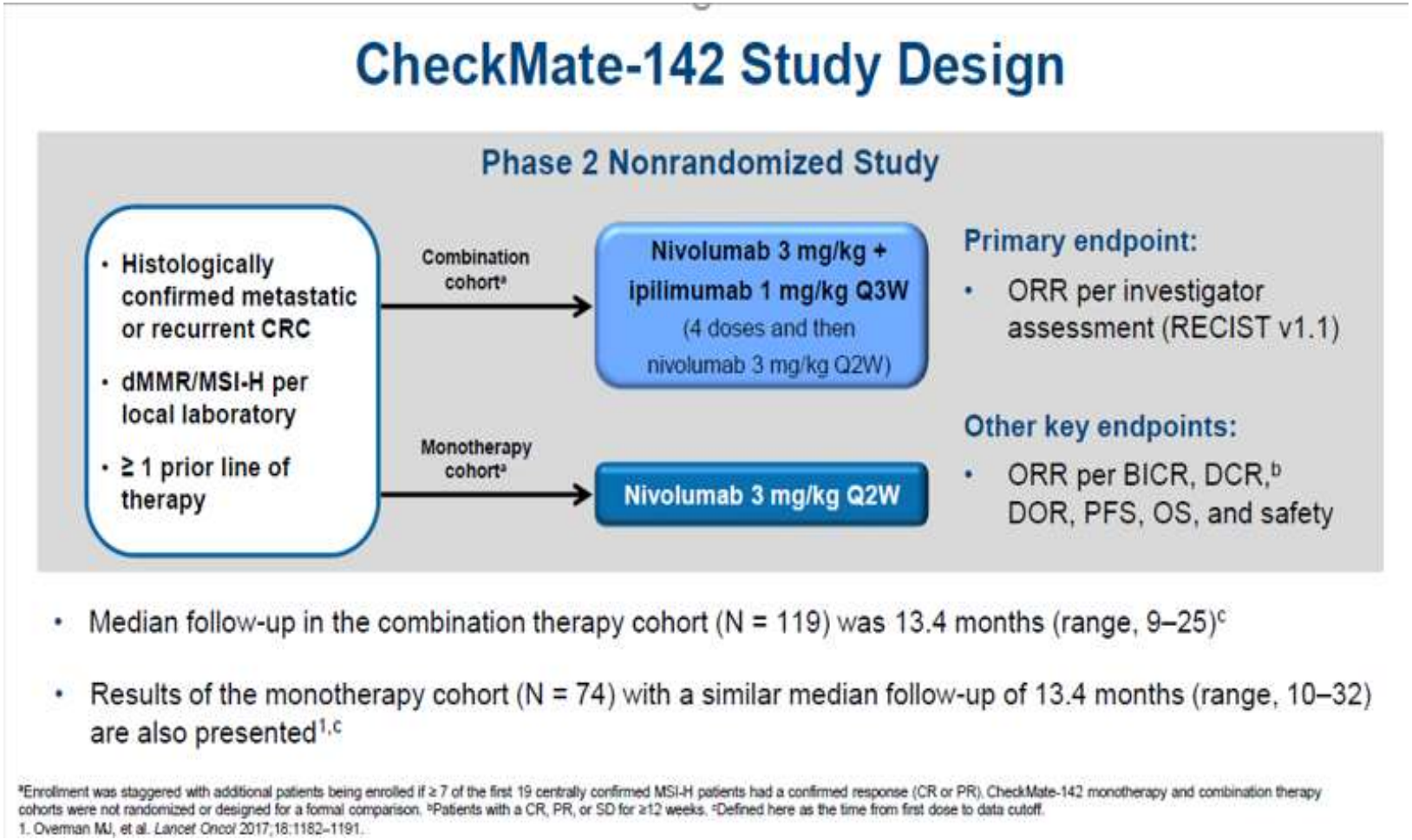
Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142

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 /Ipilimumab in MMR-D CRC

Check mate 142 GI-ASCO 2018

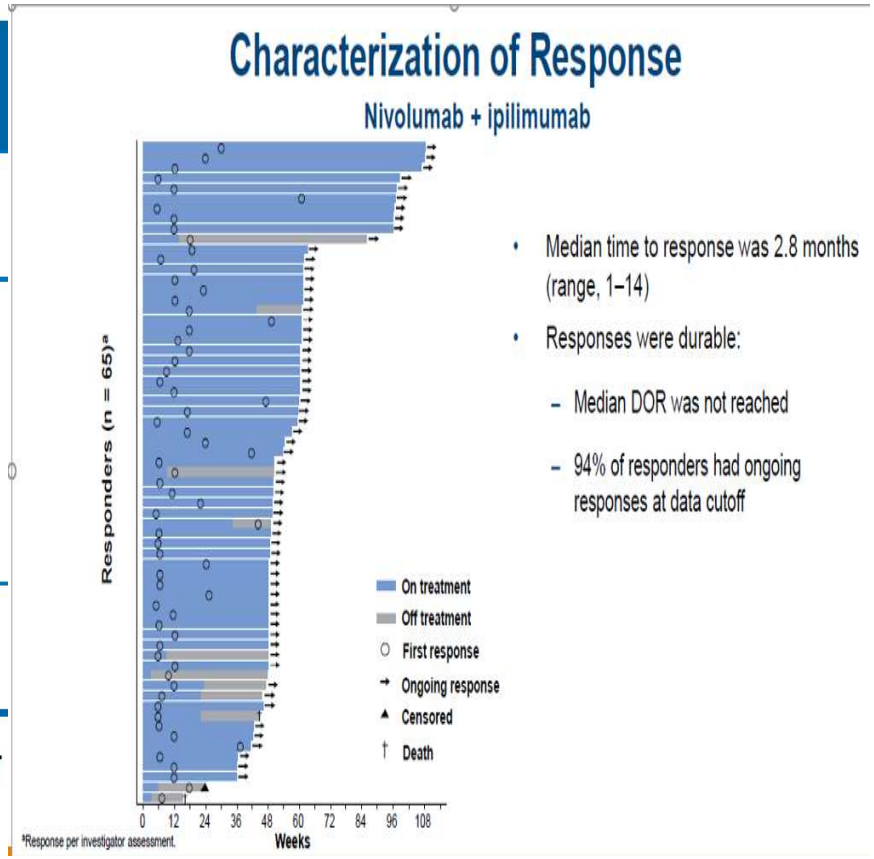


Response and Disease Control

Check mate 142 GI-ASCO 2018

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]

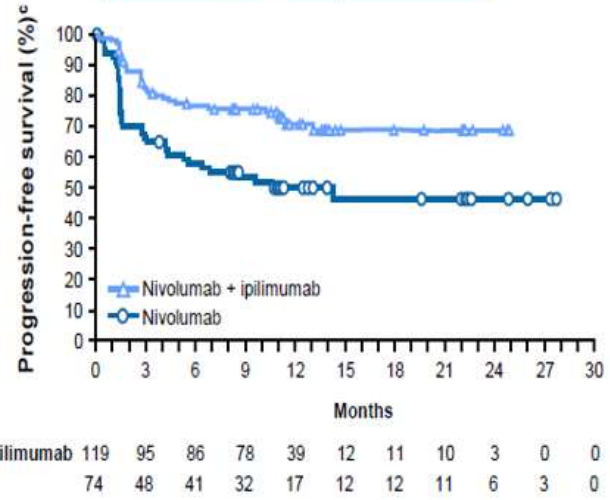
- Responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutation status, or diagnosis of Lynch syndrome
  - The ORR and DCR in patients with a *BRAF* mutation (n = 17) were 71% and 88%, respectively



- 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

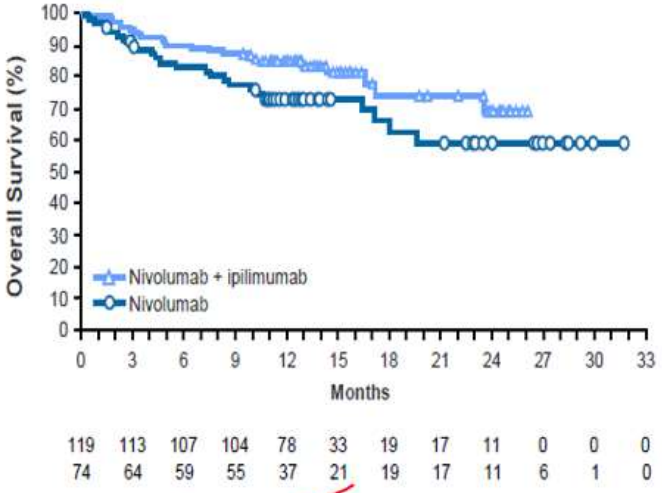
Checkmate 142 PFS and OS

	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]

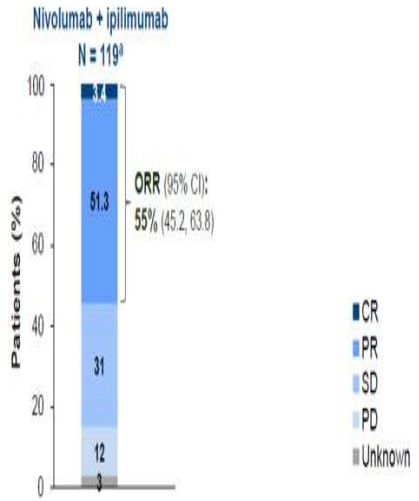
[a]Median follow-up was 13.4 months (range, 9–25). [b]Median PFS was not reached (95% CI, not estimable). [c]PFS per investigator assessment. [d]Median OS was not reached (95% CI, 18.0, not estimable).
[e]Median follow-up was 13.4 months (range, 10–32). [f]CheckMate-142 monotherapy and combination therapy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

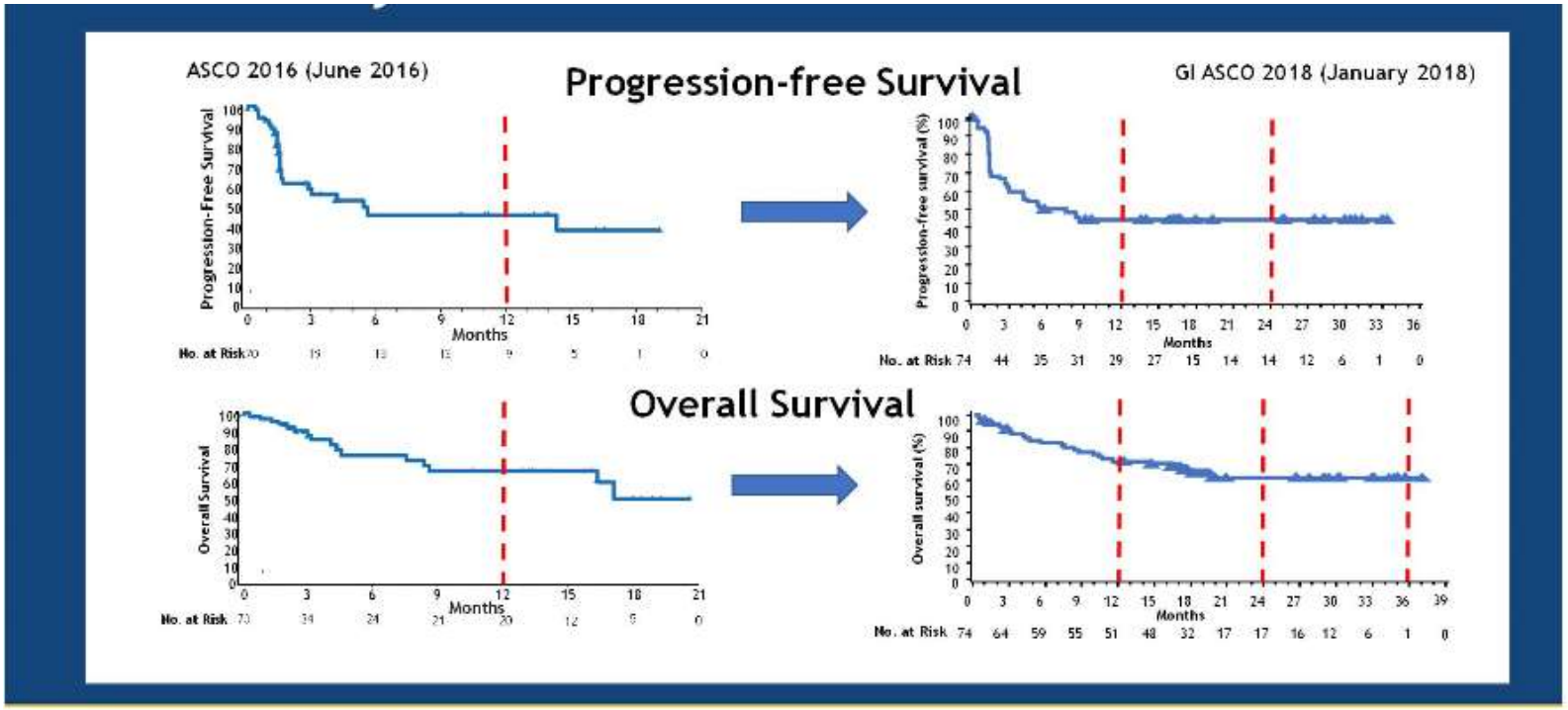


- DCR[b] was 80% (95% CI: 71.5, 86.6) with combination therapy and 69% (57.1, 79.2) with monotherapy[1,d]
- Combination therapy provided a numerically higher ORR, including CRs, and DCR relative to monotherapy during a similar follow-up period[d]

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***

Durability of Response of Nivolumab in MSI-H CRC

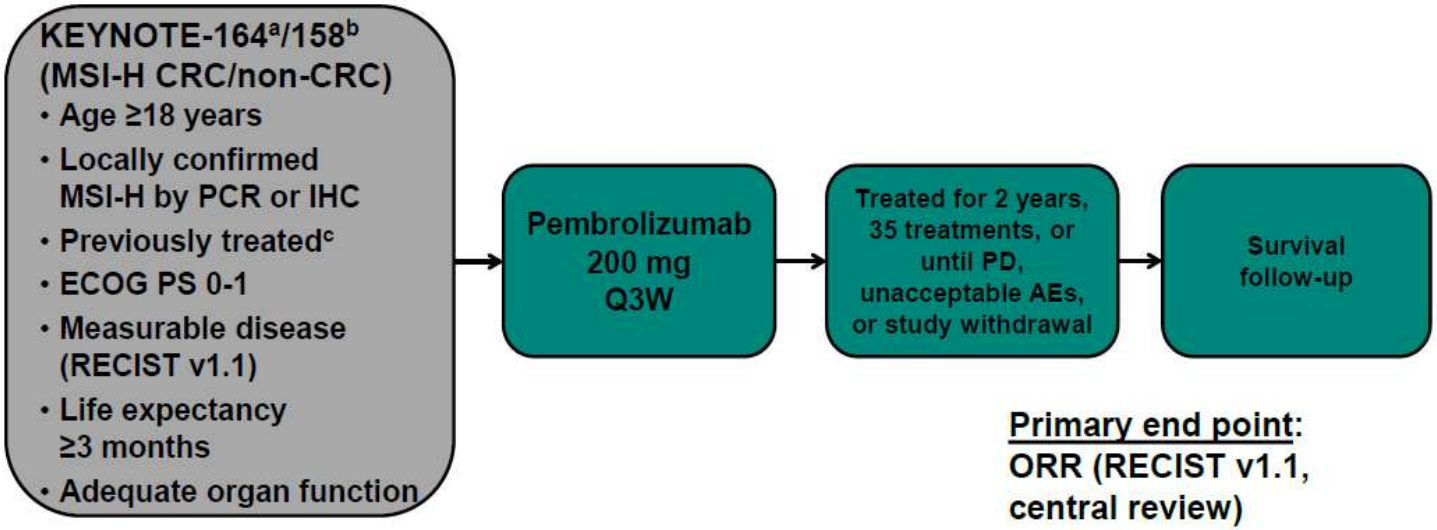


KEYNOTE-164 Cohort B: Pembrolizumab for Patients With Advanced Microsatellite Instability High (MSI-H) Colorectal Cancer (#3514)

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



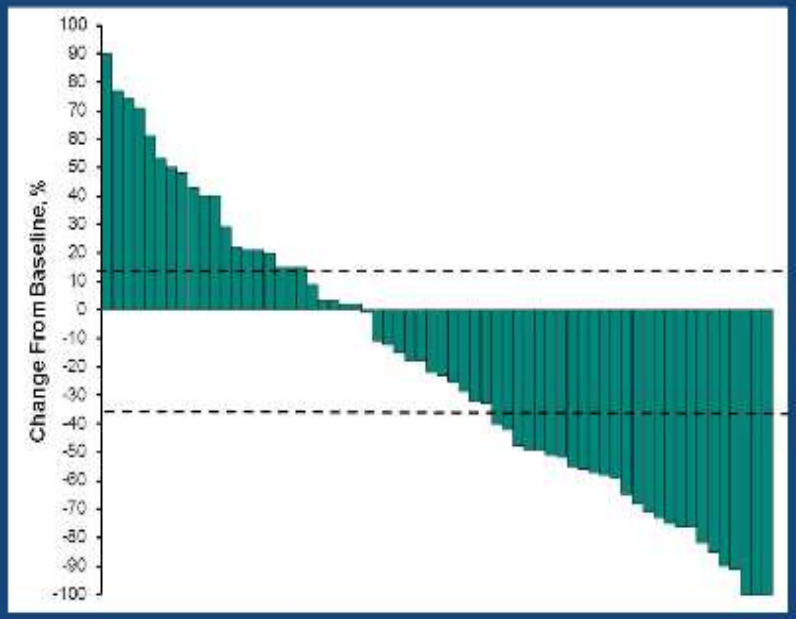
Primary end point:
ORR (RECIST v1.1, central review)

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

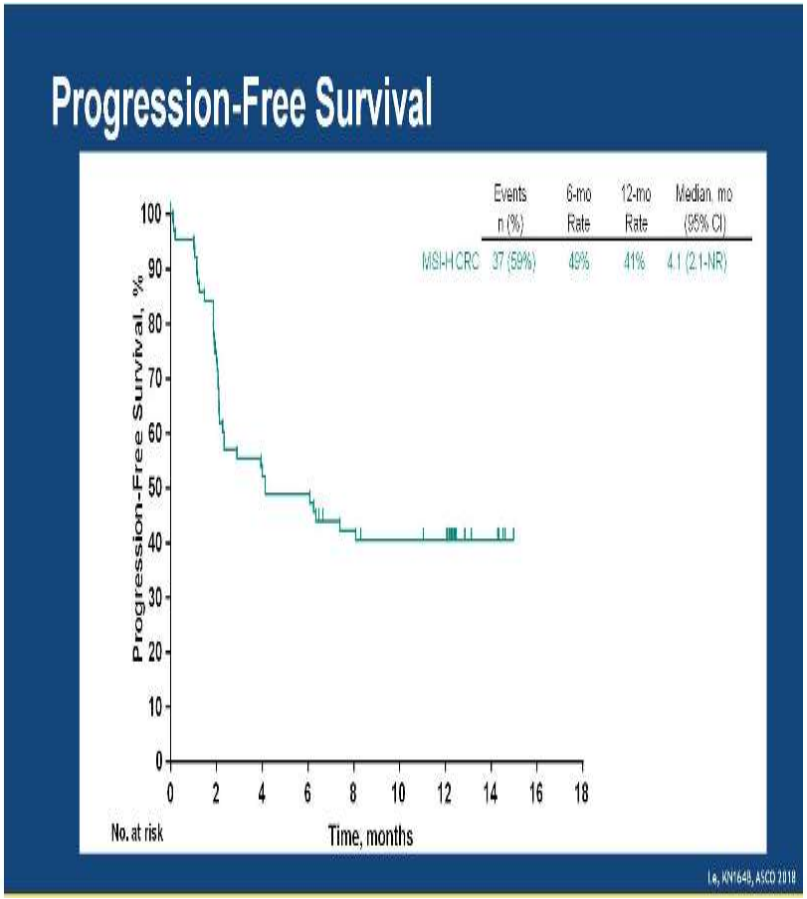
Best Percentage Change From Baseline in Target Lesion Size (RECIST v1.1)

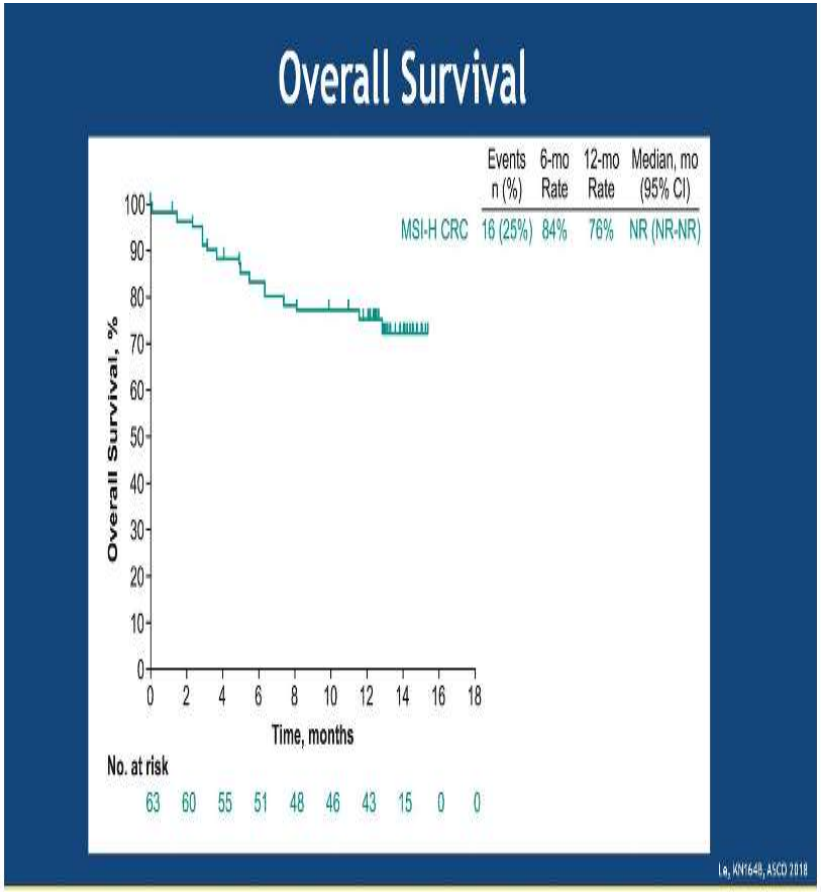


- Median duration of follow-up: 12.6 months (range, 0.1-15.4)
- ORR: 32% (95% CI, 21%-45%)
  - 2 CR, 18 PR
- Median duration of response: not reached (2.1+ to 13.2+ months)
  - 15 (75%) patients had duration of response ≥6 months

Le, KN164B, ASCO 2018

KEYNOTE 164 ASCO 2018





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%

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

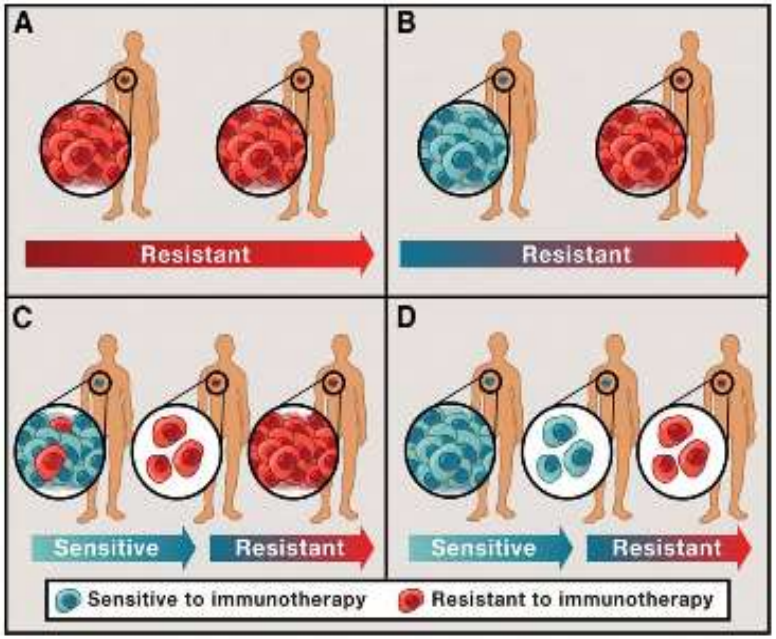
		Objective response rate		DOR range
	N	n (%)	95% CI	(months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)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

Resistance Mechanism of Immunotherapy

Intrinsic Resistance Mechanisms to Immunotherapy

Scenarios that intrinsic resistance can be developed

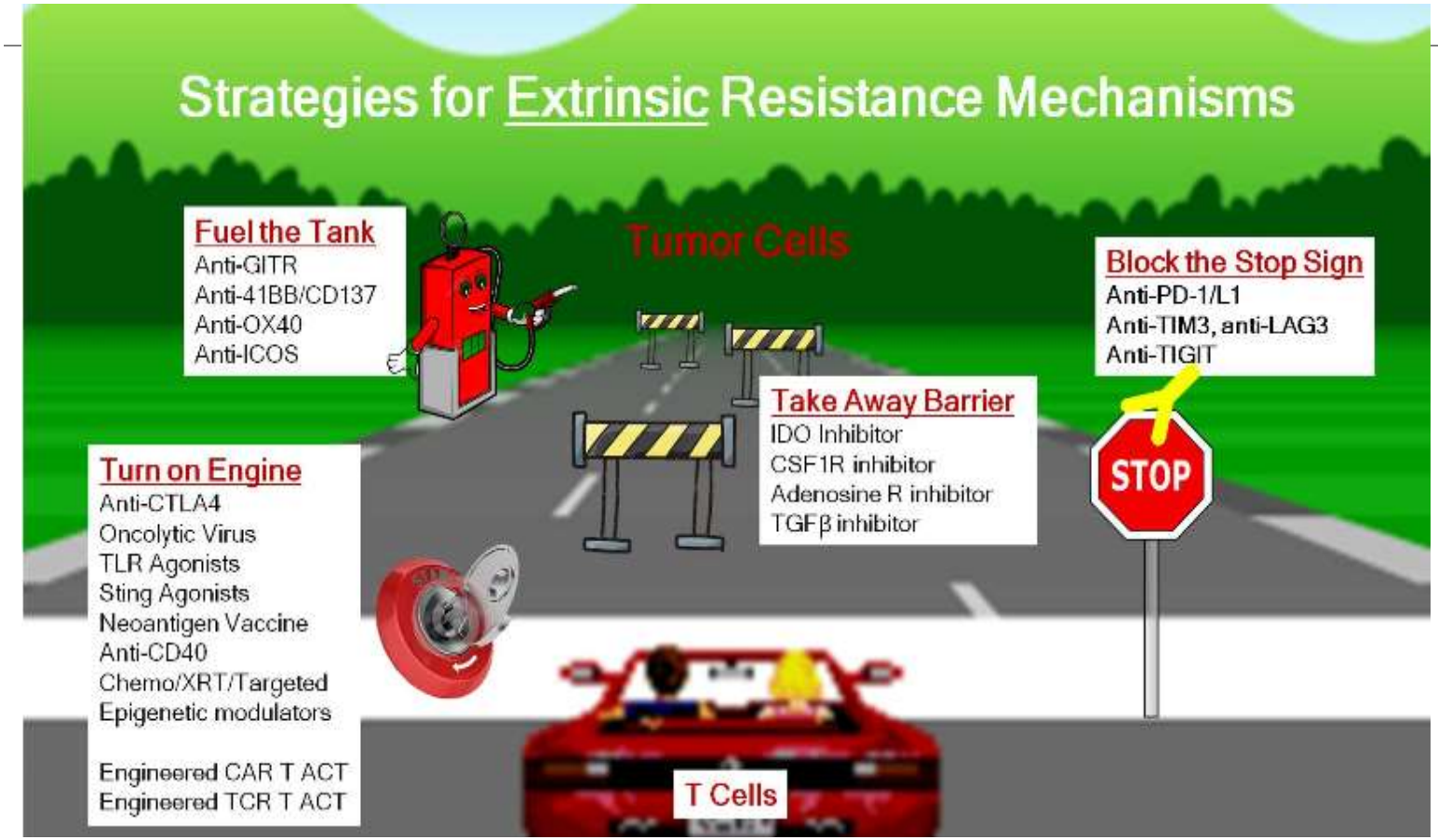


Primary resistance:
Immune escape mechanisms that exist in the non-responding patients

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



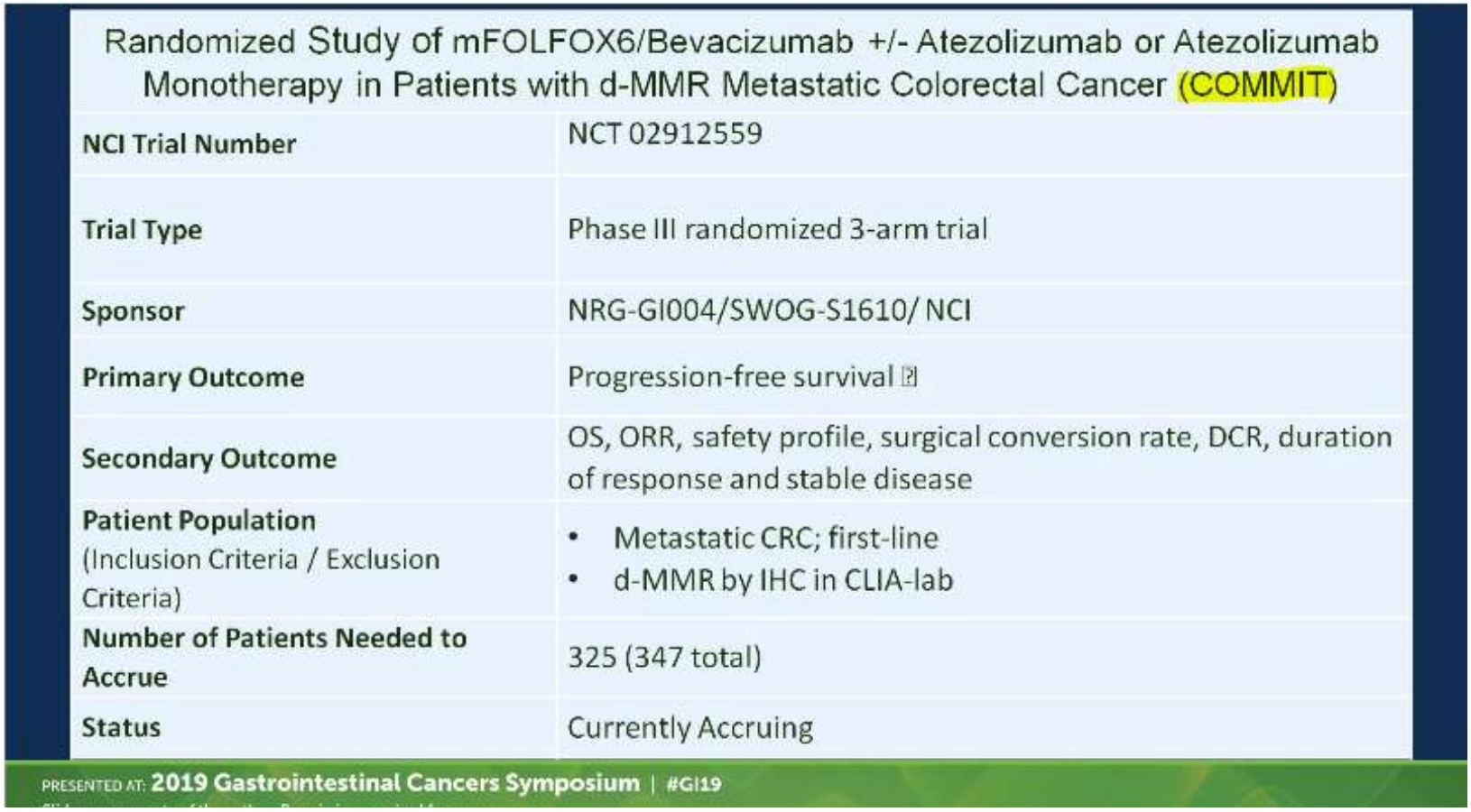
GI-ASCO 2019 **SH LIESKOVan**

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***

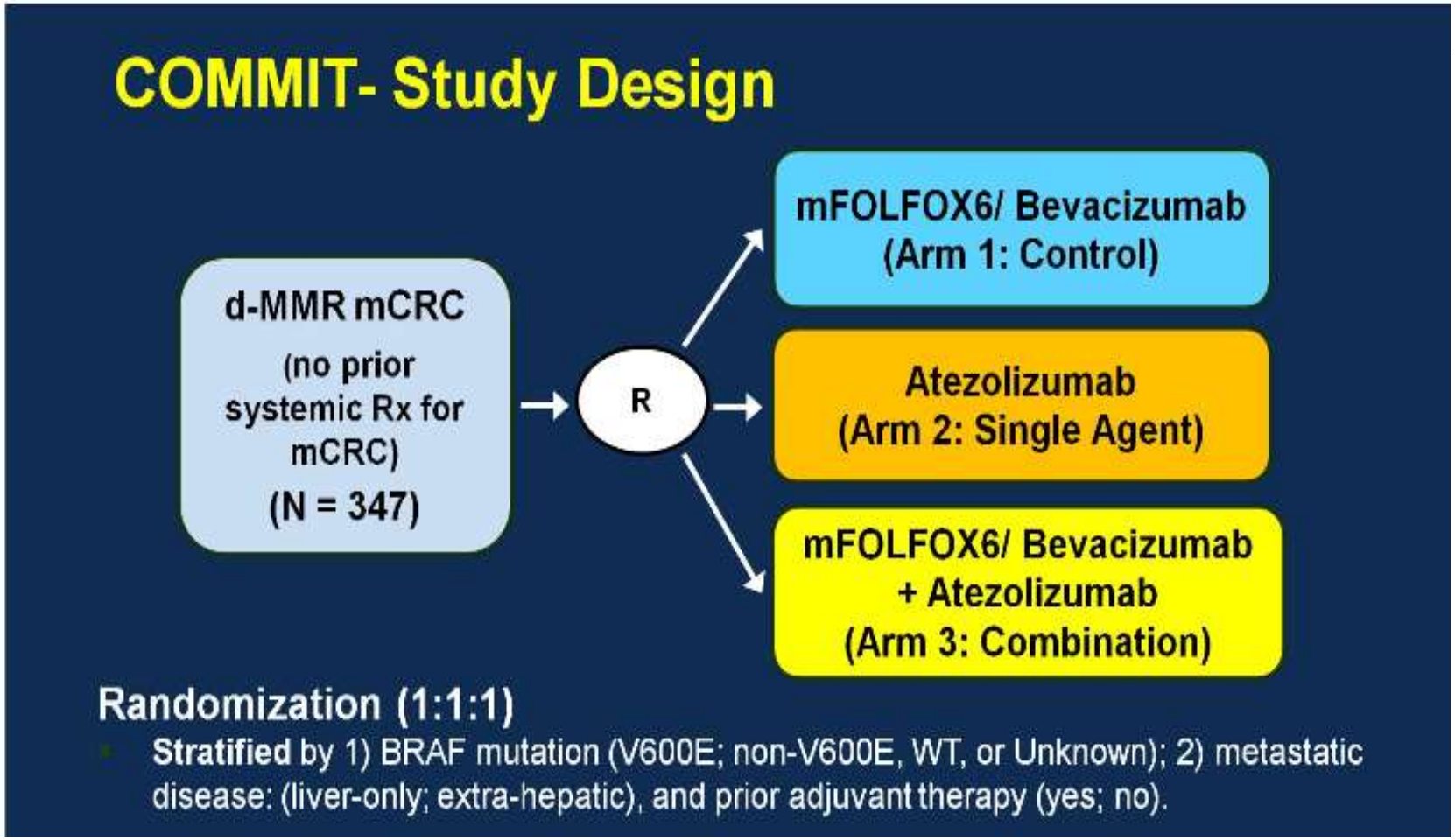
The COMMIT Trial Stage IV CRC MMRd



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

PRESENTED AT: **2019 Gastrointestinal Cancers Symposium** | #GI19

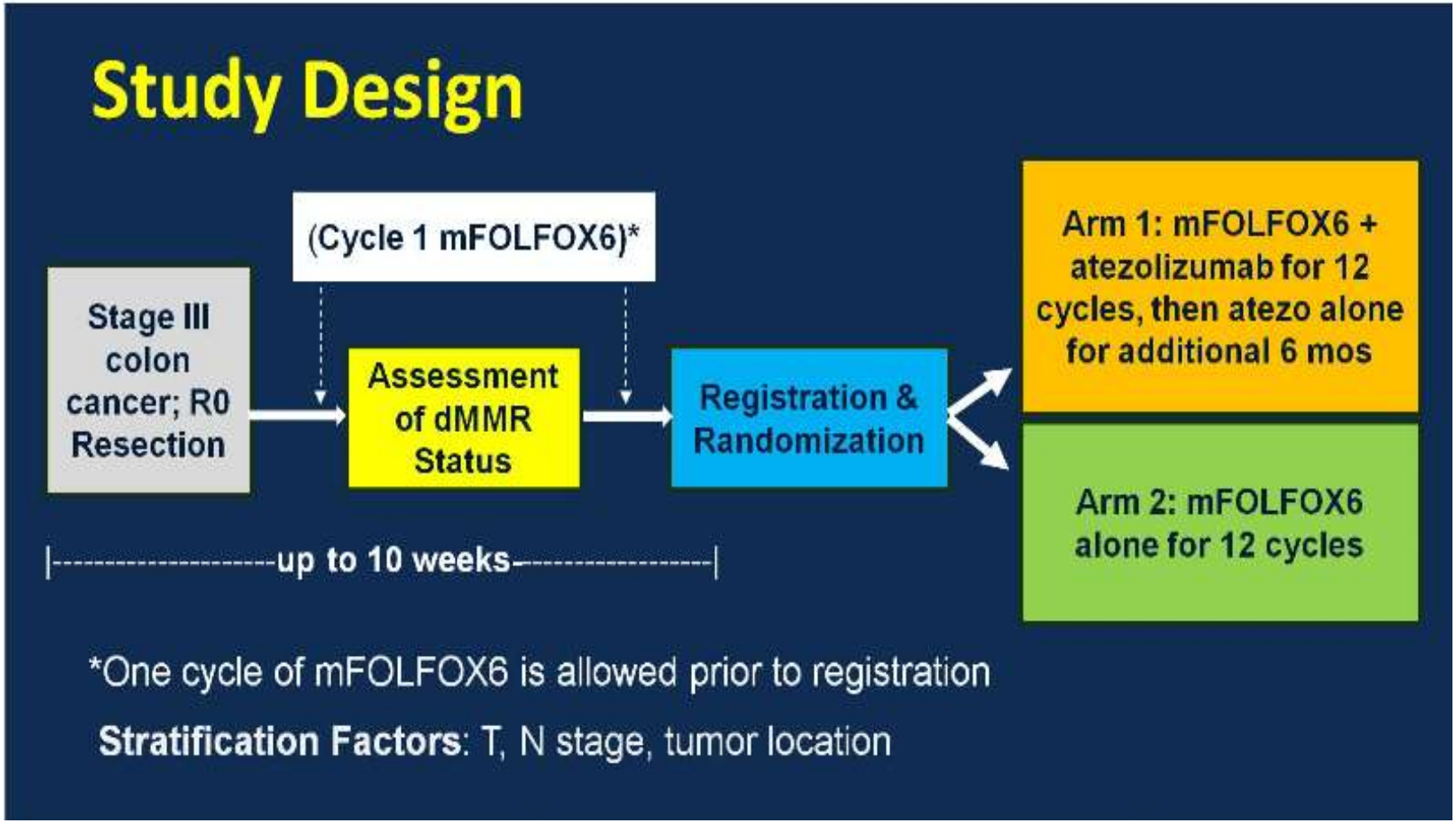
The COMMIT Trial Stage IV CRC MMRd



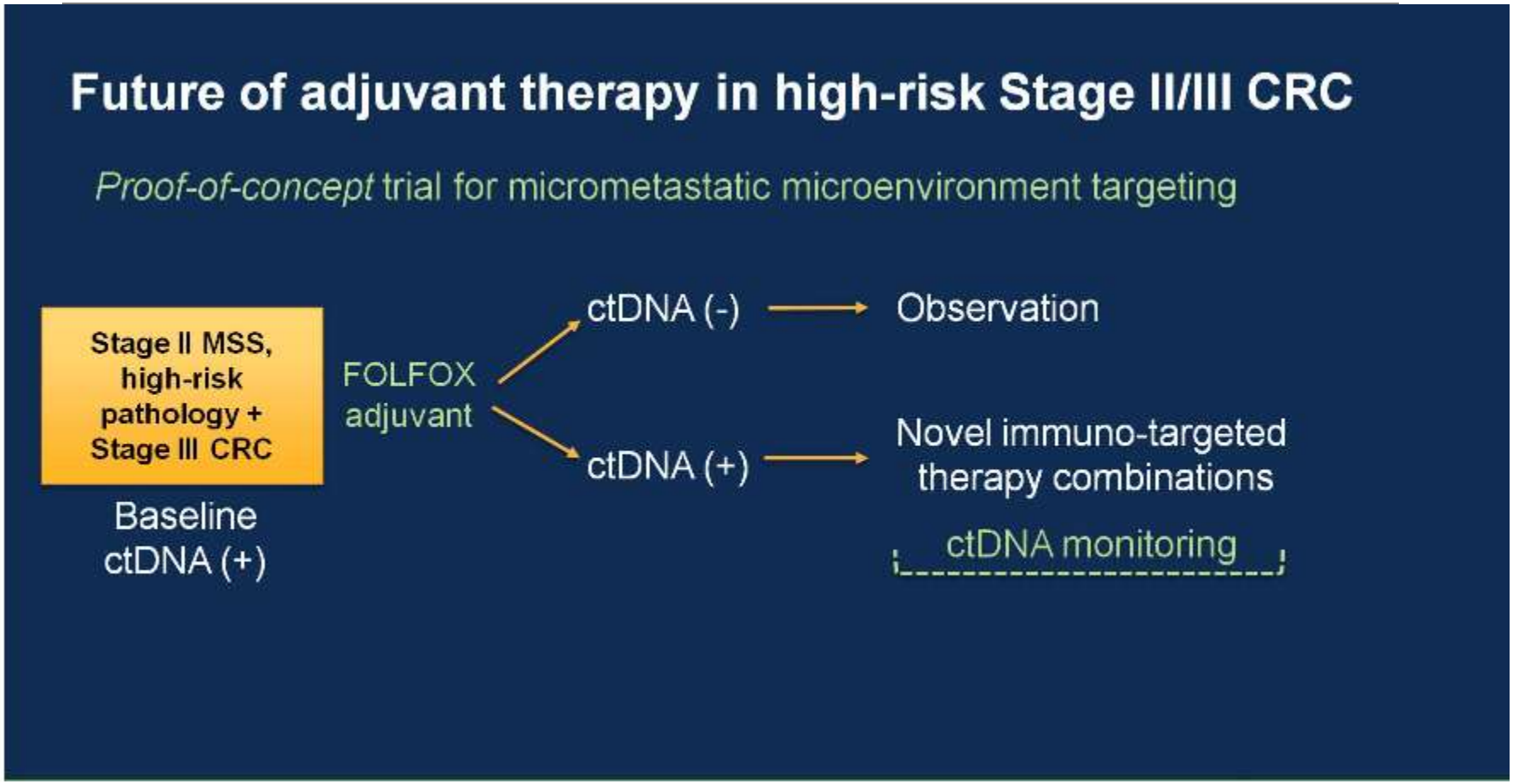
The ATOMIC Trial stage III CRC MMRd

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

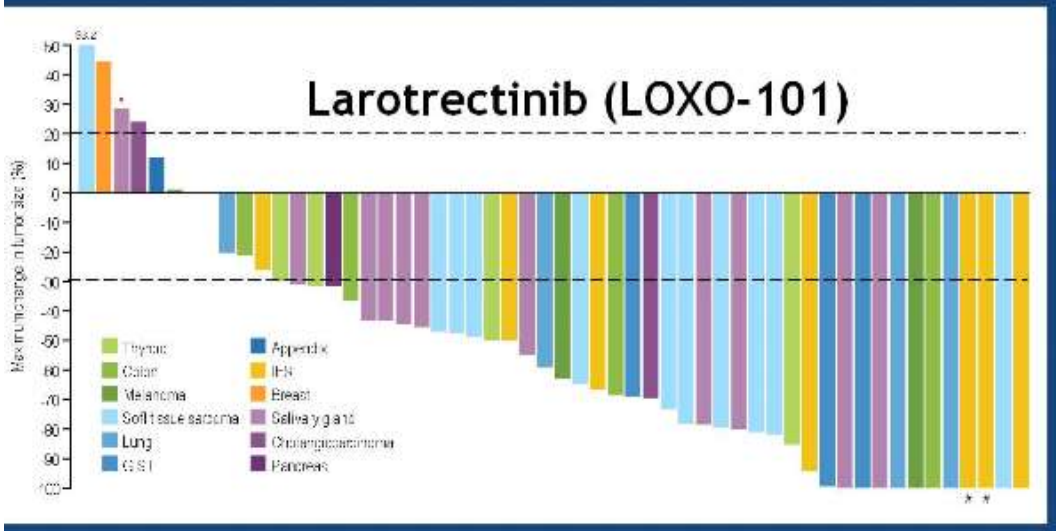


Future of Immunotherapy in CRC MMR-Deficient



New Merging Data on MMR-Deficient Cancers: NTRK Fusions

Targeting Tropomyosin receptor kinase (TRK) fusions (High Rate in MSI-high CRC)



Characteristics	NTRK rearranged (n = 13) No. (%)
MSI status	
MSS (n=162)	3 (23.1)
MSI-high (n=26)	10 (76.9)
NA	0

38% of MSI-high CRC
1.9% of MSS CRC

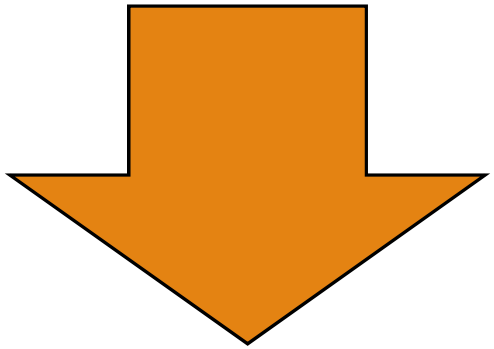
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Michael Overman

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Hyman ASCO 2017, Pietrantonio et al. JNCI 2017

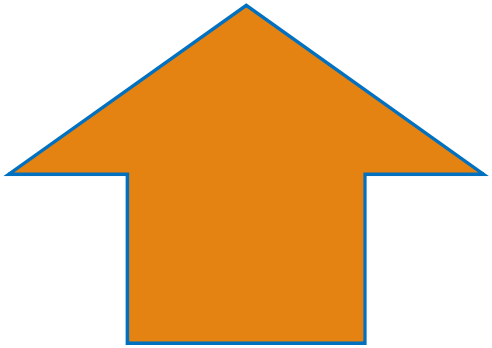
Treatment Decision-Making

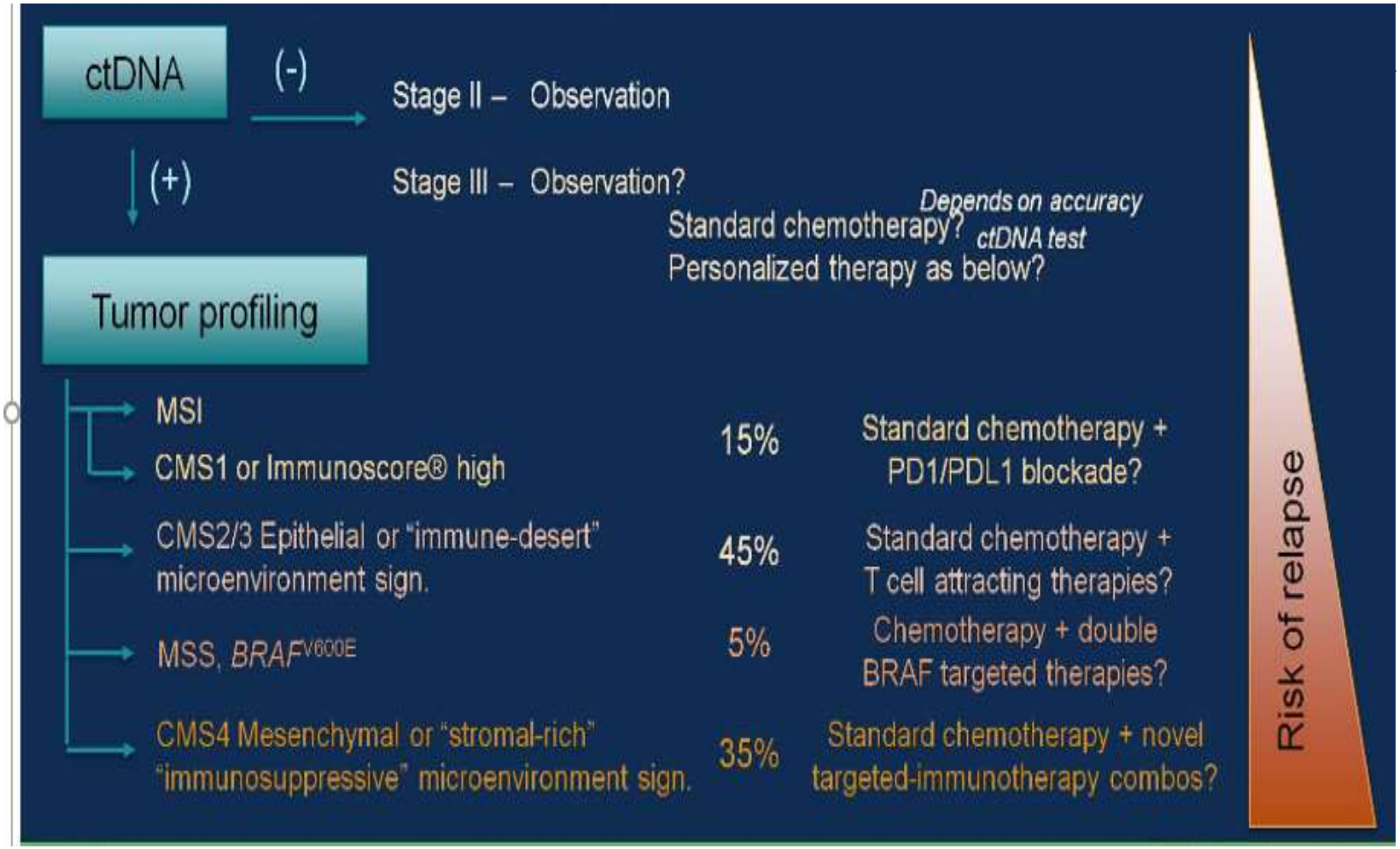


PROGRESSION OF DZ
ABSOLUTE TREATMENT BENEFIT

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***