The Development of MSI-H Cancer Therapy

Development of Anti-Cancer Drugs Forum
Tokyo , Japan, 18, February 2017

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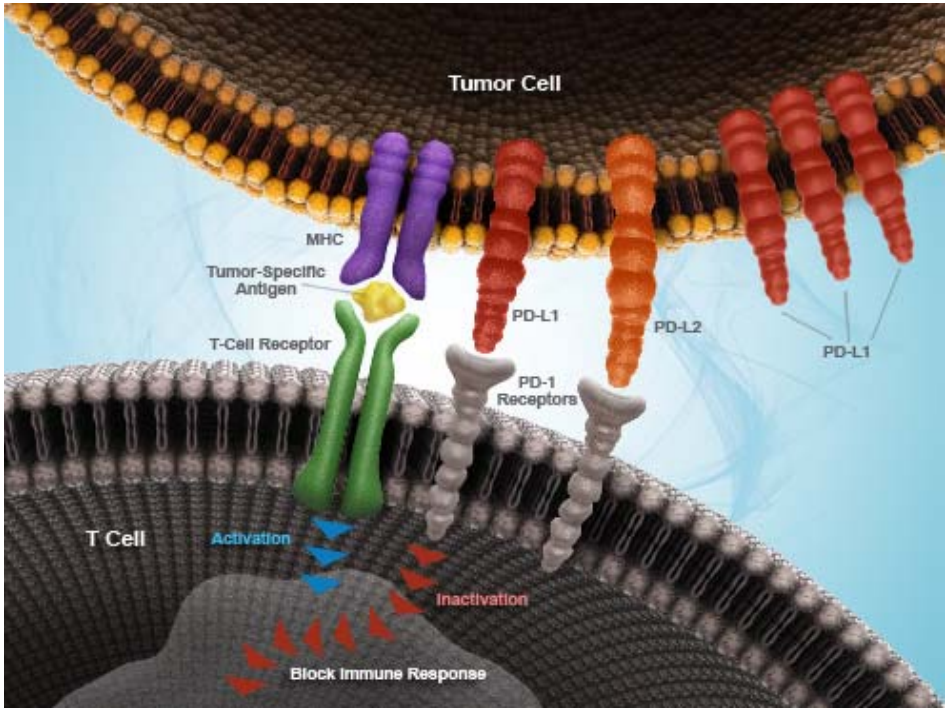
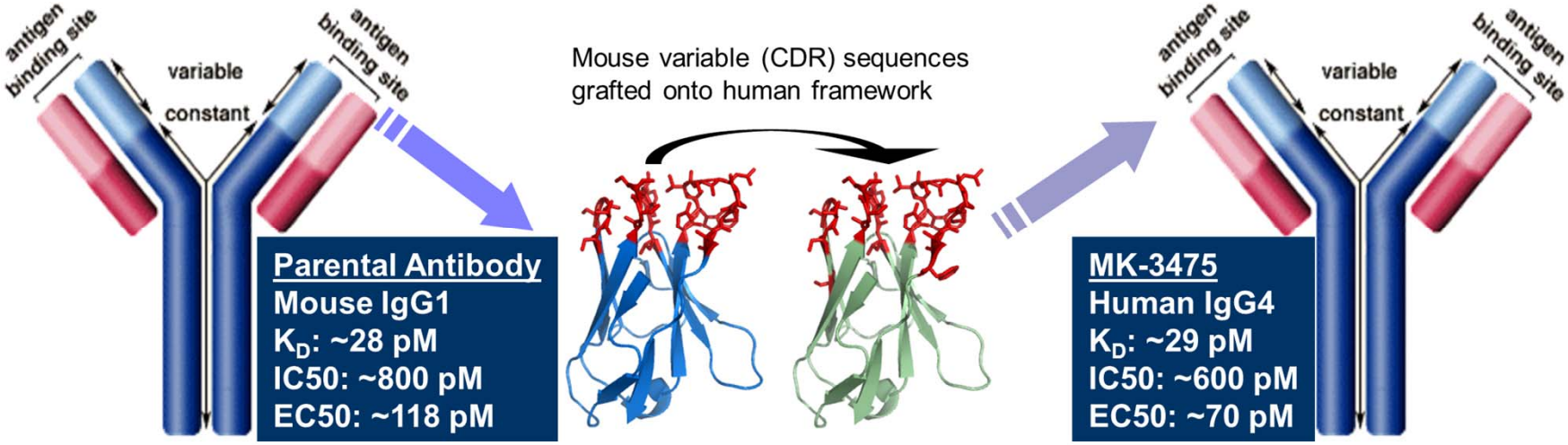
PD-L1 and PD-L2 Block T Cells from Attacking Cancer Cells

- PD-1 is an antigen expressed on the surface of activated T-cells
- PD-1 interacts with its ligands PD-L1 and PD-L2 expressed on cancer and surrounding cells
- This inhibits activation of T lymphocytes and prevents an anti-tumor immune response



PD-1 inhibition with Keytruda reactivates T cells to attack and kill cancer cells

Pembrolizumab is a Humanized IgG4, High-Affinity Anti-PD-1 Blocking Antibody



- No cytotoxic (ADCC/CDC) activity
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics

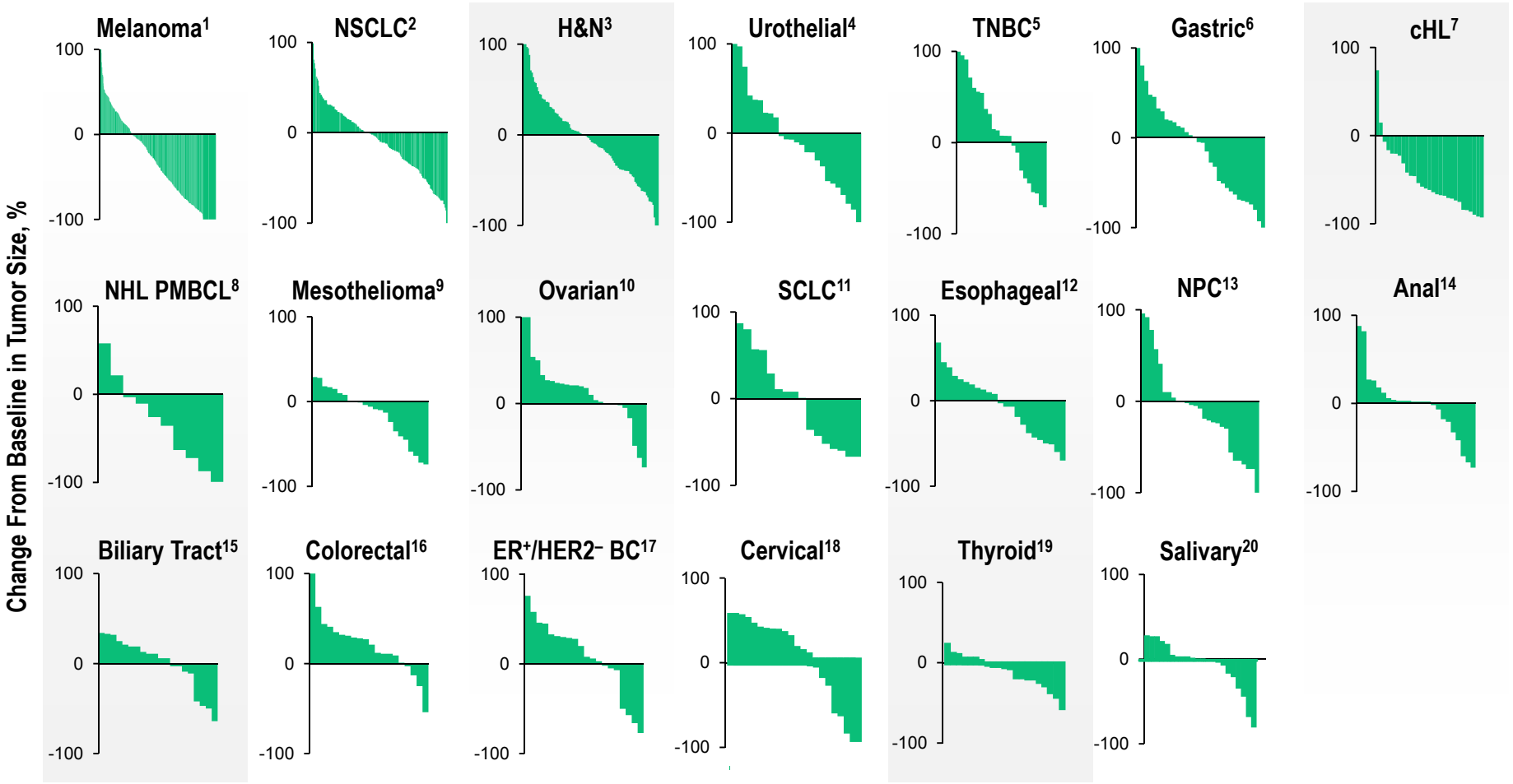
Presented by: Antoni Ribas ASCO 2013

KEYTRUDA Development Program

First anti-PD-1 to market in the US

- ✓ Approvals in Melanoma, Non-Small Cell Lung Cancer, (1L and 2L+ PD-L1+), Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
- ✓ Demonstrated overall survival
  - vs. ipilimumab in melanoma
  - vs. docetaxel in 2L+ PD-L1+ NSCLC
  - vs chemo in previously treated patients with advanced bladder cancer
- ✓ Data in first line NSCLC for both Monotherapy and in Combination with chemotherapy
- ✓ Clinical activity in more than 20 different tumor types
- ✓ More than 30 ongoing registration-enabling studies
- ✓ 5 FDA Breakthrough Designations

Keytruda Monotherapy Has Shown Activity in 20 Tumors



1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. O'Neil B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015; 18. Frenel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016.

Pembrolizumab Late Development Program

- Clinical trials are ongoing in common, uncommon, and rare cancers

Melanoma
1L (KN006)
2L (KN002)
Adjuvant (KN053/054)
1L + T-Vec (Amgen)
1L + IDO-1 (Incyte)

NSCLC
1L (KN024)
1L (KN042)
1L + pemetrexed non sq (KN189)
1L + pacitaxel sq(KN407)
2/3L (KN010)
Adjuvant (KN091)

Gastrointestinal
1L Gastric + chemo (KN062)
2L Gastric (KN061)
3L Gastric (KN059)
2L Esophageal (KN181)
3L Esophageal (KN180)
1L CRC MSI-high (KN177)
3L CRC MSI-high (KN164)

Hepatocellular
2L (KN224)
2L (KN240)

Head and Neck
1L + chemo/cetuximab (KN048)
2L (KN040)
3L (KN055)
2L Nasopharyngeal (KN122)

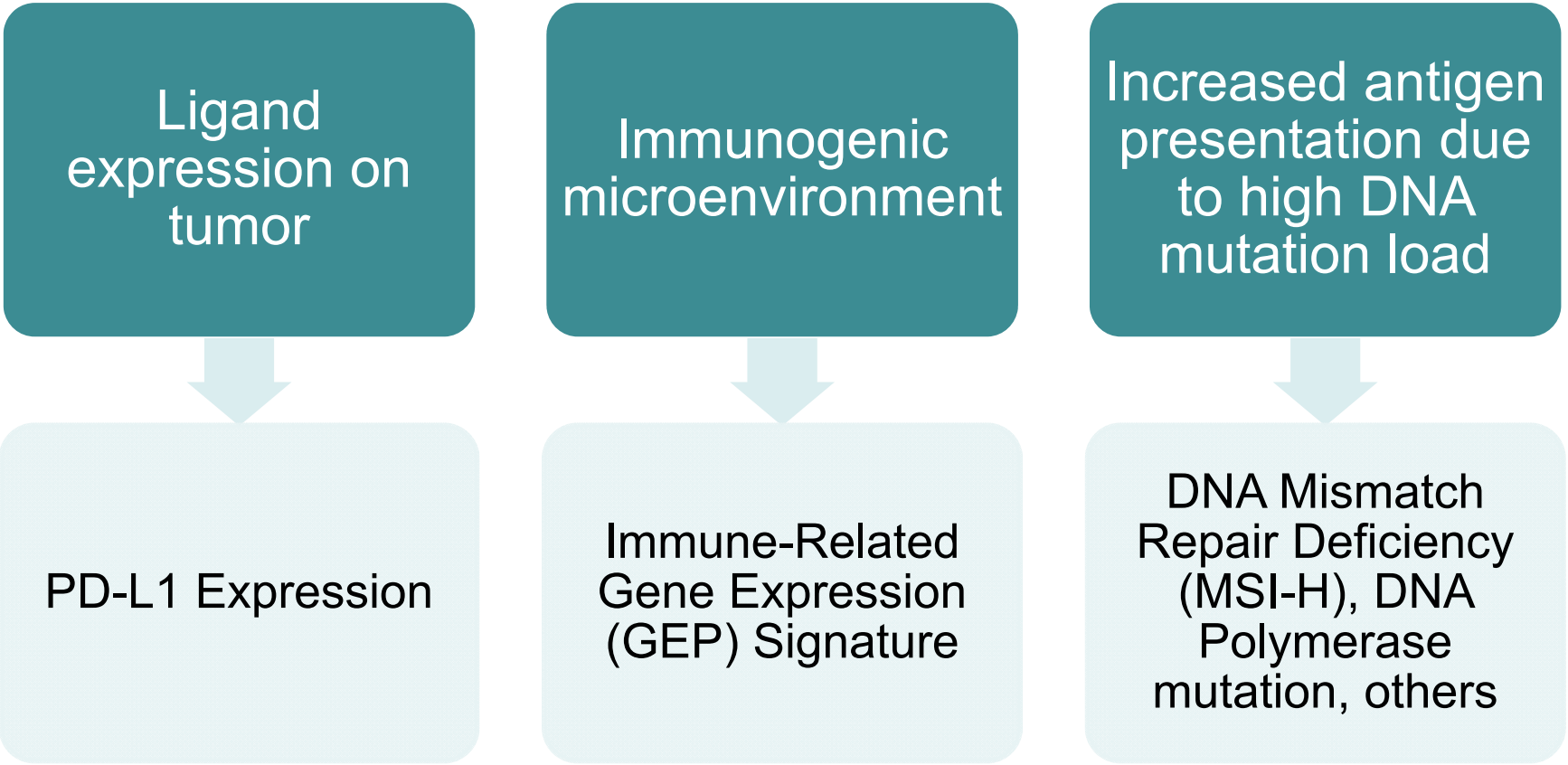
Hematological Malignancies
3L HL (KN087)
rrHL + brent. ved. (KN204)
2L NHL rrPMBCL (KN170)
1L MM + len/dex (KN185)
3L rrMM + pom/dex (KN183)

Bladder
1L (KN052)
1L (KN361)
2L NIBC (KN057)
2L (KN045)

Triple Negative Breast
2L+ (KN086)
2L/3L (KN119)

Other
2L Advanced Cancers (KN158)
2L Ovarian (KN100)
2L Prostate (KN199)
1L Renal Cell Carcinoma (KN427)
1L + Axitinib Renal Cell Carcinoma (KN426)

Biomarker Program to Identify Cancers Likely to Respond to Pembrolizumab Therapy



Goal is to identify patients most likely to benefit from treatment

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KEYNOTE (KN) 016

- Demonstration of clinical efficacy in a biomarker-defined population

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ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Dung T. Le, M.D., Jennifer N. Uram, Ph.D., Hao Wang, Ph.D., Bjarne R. Bartlett, B.S., Holly Kemberling, R.N., Aleksandra D. Eyring, M.Pharm., Andrew D. Skora, Ph.D., Brandon S. Luber, Sc.M., Nilofer S. Azad, M.D., Dan Laheru, M.D., Barbara Biedrzycki, Ph.D., C.N.R.P., Ross C. Donehower, M.D., Atif Zaheer, M.D., George A. Fisher, M.D., Ph.D., Todd S. Crocenzi, M.D., James J. Lee, M.D., Ph.D., Steven M. Duffy, M.D., Richard M. Goldberg, M.D., Albert de la Chapelle, M.D., Ph.D., Minori Koshiji, M.D., Ph.D., Feriyl Bhaijee, M.D., Thomas Huebner, M.D., Ralph H. Hruban, M.D., Laura D. Wood, M.D., Ph.D., Nathan Cuka, M.D., Drew M. Pardoll, M.D., Ph.D., Nickolas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Shibin Zhou, M.D., Ph.D., Toby C. Cornish, M.D., Ph.D., Janis M. Taube, M.D., Robert A. Anders, M.D., Ph.D., James R. Eshleman, M.D., Ph.D., Bert Vogelstein, M.D., and Luis A. Diaz, Jr., M.D.

May 30, 2015 | DOI: 10.1056/NEJMoa1500596

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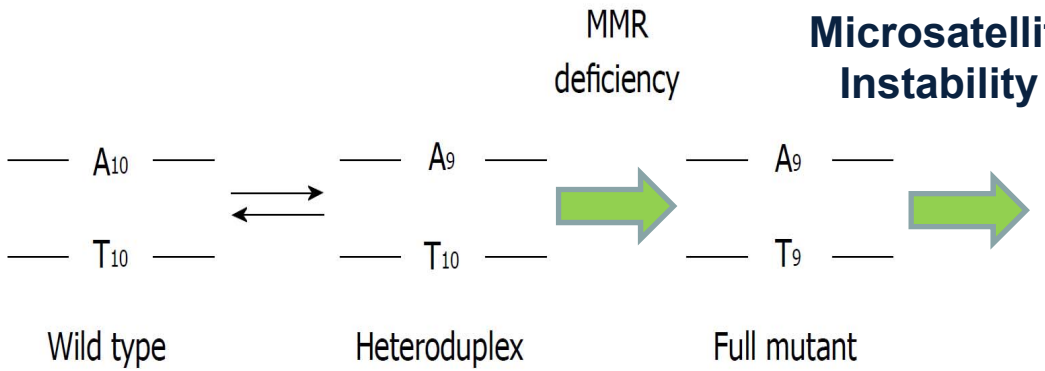
MSI-H Cancer Has a High Mutational Burden

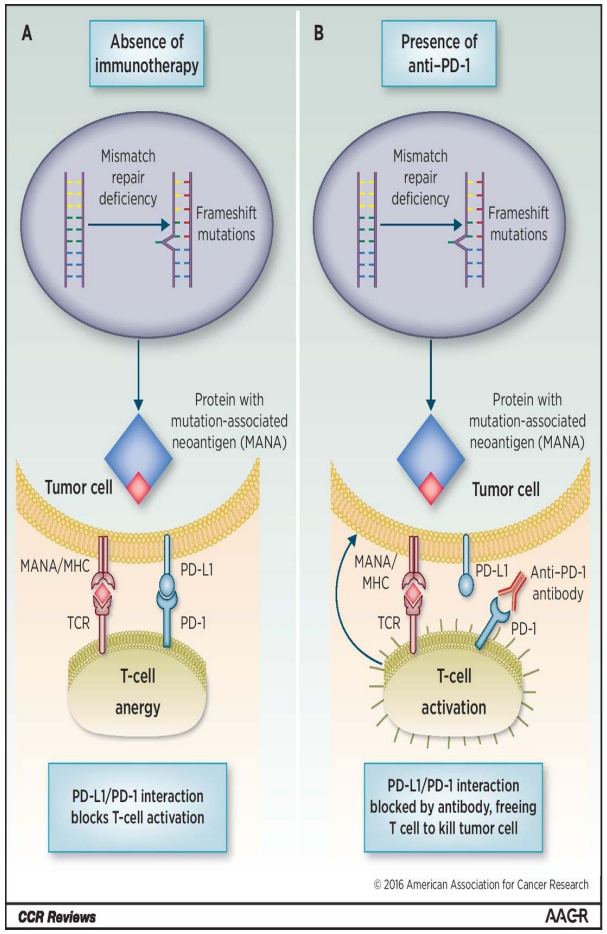
- Mismatch repair (MMR) deficiency refers to deficiency in proteins responsible for DNA MMR: MSH2, MSH6, MLH1, PMS2.
- MMR deficiency leads to the MSI-H phenotype.
- MMR deficient/MSI-H cancers harbor thousands of mutations (i.e., high mutational burden; hypermutated phenotype).



DNA mutations lead to protein neo-antigens, detected as 'foreign' & recognized by T-cells

Rationale and Hypothesis

- Hypothesis: Pembrolizumab is effective in treating any MSI-H cancer
  - MSI-H cancer, regardless of tumor histology, is associated with a high mutational burden (hypermutated phenotype)
  - High mutational burden leads to high neoantigen expression
  - High neoantigen expression leads to autologous immune recognition of cancer cells
  - By blocking PD-1 on tumor neoantigen-specific T cells, pembrolizumab can activate anti-tumor immune responses



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

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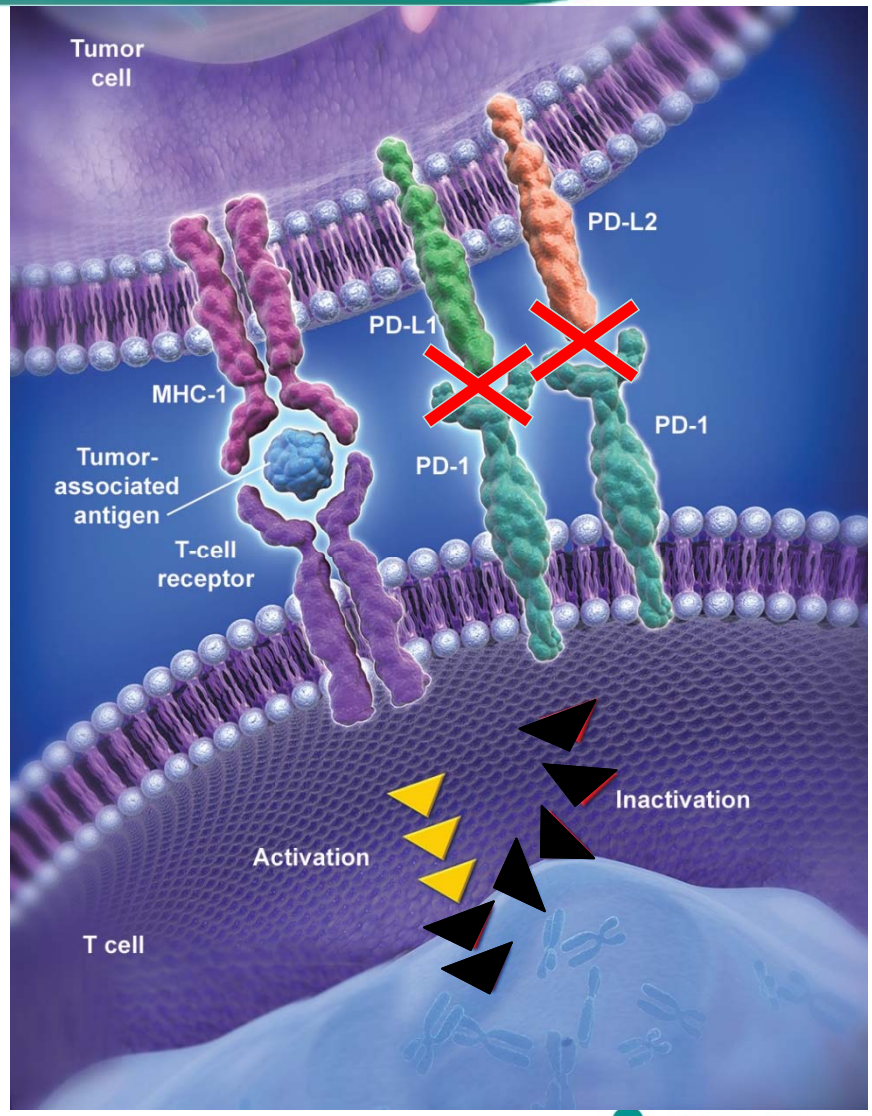
Biological Rationale for Tumor-Agnostic Approac

- PD-1 blockade with pembrolizumab can restore effective anti-tumor immunity in MSI-H cancer, regardless of cancer type



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Pembrolizumab Therapy of MSI-H Cancer

- MSI-H cancer represents a unique, biomarker-identified disease with a common immunobiology
- MSI-H cancers are readily identifiable using locally available assays (e.g., PCR, IHC)
- MSI-H – associated with worse prognosis in advanced CRC; limited data in MSI-H gastric and endometrial cancer – worse prognosis (or unclear association with prognosis) in advanced-stage disease

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Programmed death-1 blockade in mismatch repair deficient colorectal cancer

Dung T. Le, Jennifer N. Uram, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Nilofer S. Azad, Daniel Laheru, Ross C. Donehower, Todd S. Crocenzi, Richard Goldberg, George Fisher, James Lee, Tim Greten, Minori Koshiji, Peter Kang, Bob Anders, James Eshleman, Bert Vogelstein and Luis A. Diaz, Jr.

PRESENTED AT: ASCO ANNUAL MEETING '16

Study Design

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=28)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=30)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability
- Here we report and update from the original 13 CRC Cohort A patients reported at ASCO 2015

Key Eligibility for Cohorts A & B

- Histologically proven metastatic or locally advanced mismatch repair deficient colorectal solid tumor malignancy
  - **IHC** showing deficiency in MLH1, MSH2, MSH6, or PMS2
  - or microsatellite instability detected by **PCR** (instability in 2 or more loci); locally testing acceptable
- Measurable disease
- Patients with colon cancer must have received at least two prior cancer therapy regimens.
- ECOG Performance Status of 0-1
- No prior anti-PD-1/PD-L1/PD-L2, anti-CD137, anti-OX-40, anti-CD40, anti-CTLA4

D Le ASCO 2016

Demographics

Characteristic	MMR-deficient CRC n=28	MMR-proficient CRC n=25
Median Age (range)– years	49 (26-75)	62 (32-79)
Gender-female no. (%)	13 (46)	9 (36)
ECOG PS-zero	5 (18)	7 (28)
Liver Mets	14 (50)	15 (60)
Median Prior Regimens	3	4
Lynch Syndrome		
Yes	15 (54)	0 (0)
No	2 (7)	25 (100)
Unknown	11 (39)	0 (0)

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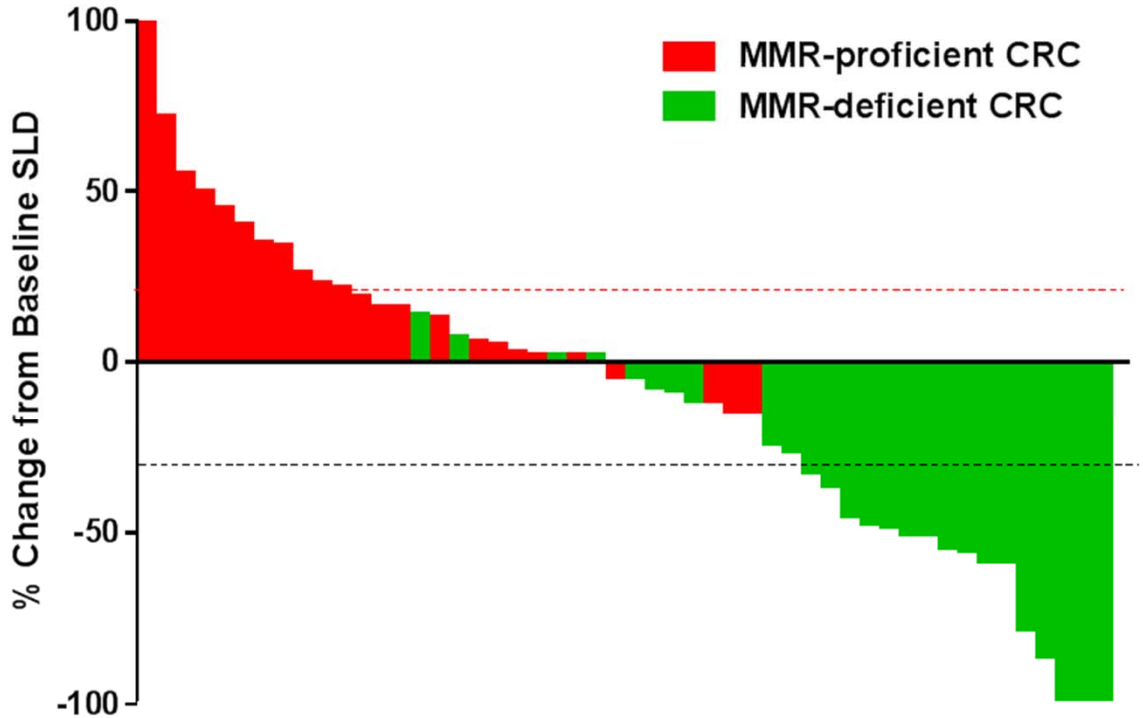
Best Radiographic Response



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

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

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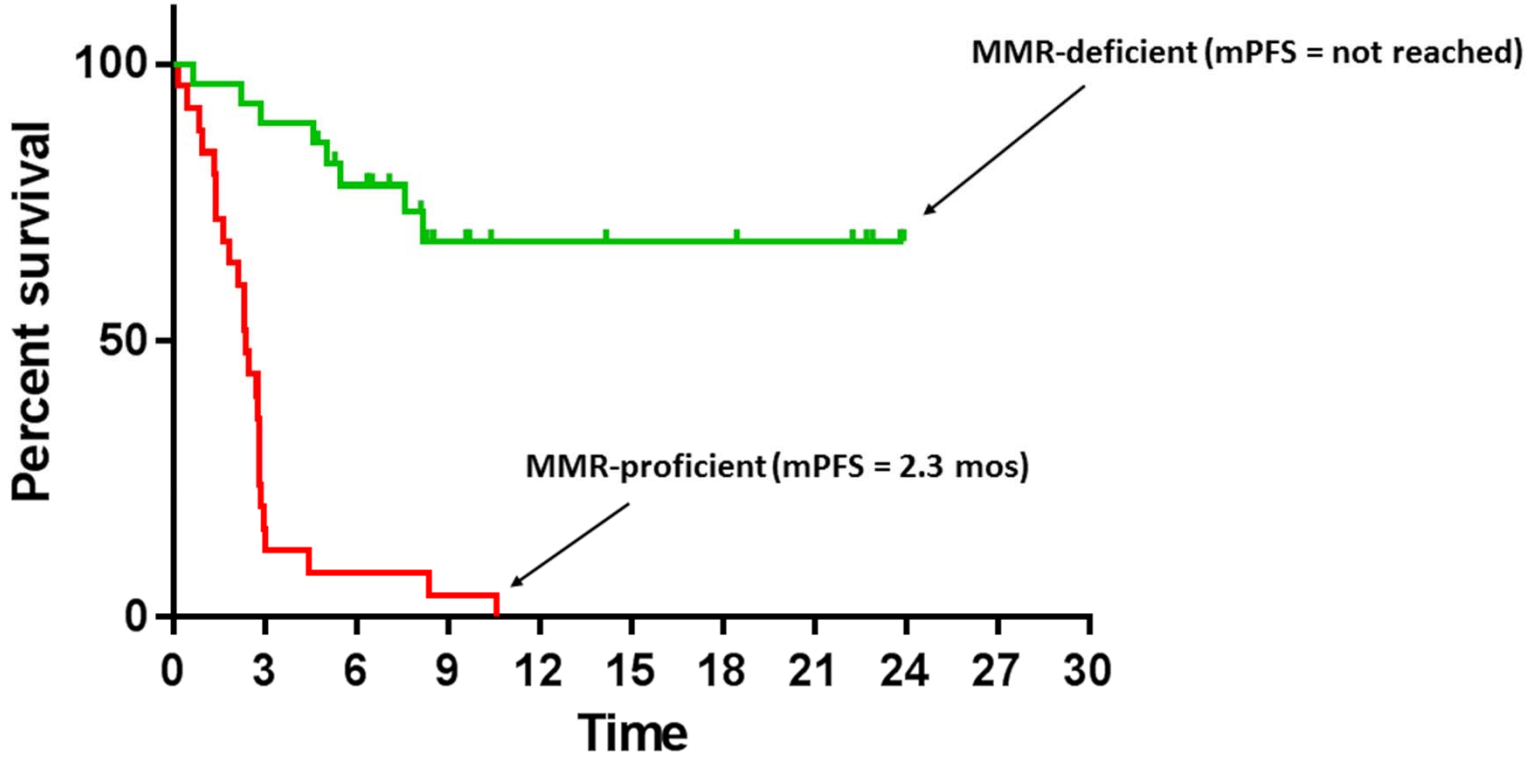
Progression-free Survival



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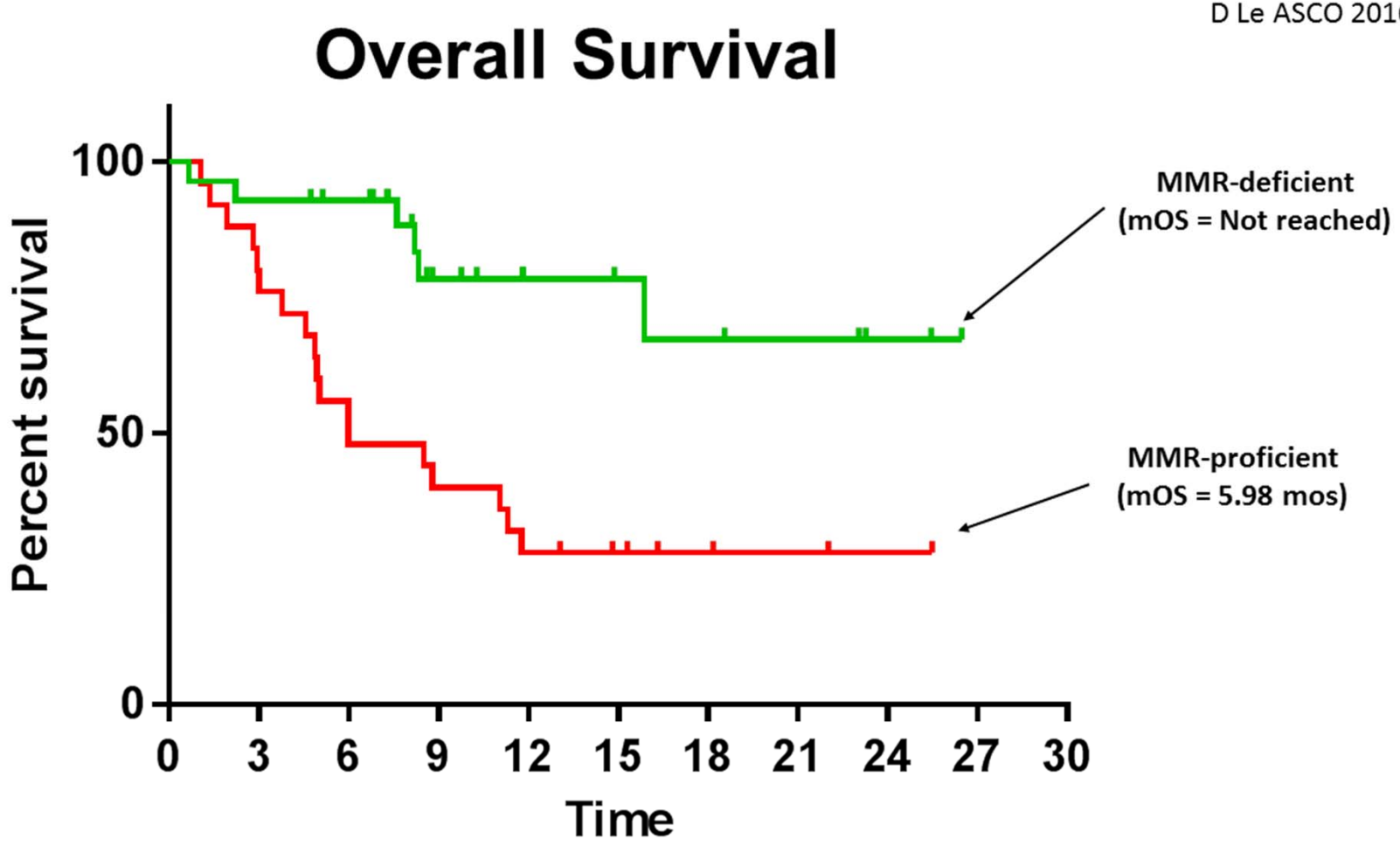

Summary

- PD-1 blockade with pembrolizumab is highly active in MRD metastatic colorectal cancer
- Complete and durable responses are seen in more than 50% of patients
- Currently, 5 patients (18%) have reached the two year mark and anti-PD-1 has been held. These patients are under active surveillance.
- Single agent studies with pembrolizumab in 1st line MRD metastatic colorectal cancer are actively recruiting

PD-1 Blockade in Mismatch Repair Deficient Cancer Independent of Tumor Histology

Luis Diaz, Jr., Jennifer Durham, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Nilo Azad, Tianna Dauses, Daniel Laheru, James Lee, Todd Crocenzi, Richard Goldberg, George Fisher, Tim Greten, Christian Meyer, Amanda Nickles Fader, Deborah Armstrong, Minori Koshiji, Bert Vogelstein, and Dung Le

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University of Pittsburgh, Pittsburgh, PA
National Cancer Institute, Bethesda, MD
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Study Design

L Diaz, ASCO 2016

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability

Study Design

L Diaz, ASCO 2016

Cohort C
Deficient in Mismatch Repair (n=21)

Ongoing Expansion (n=+50)

Non-Colorectal Cancers Deficient in Mismatch Repair (n=30)

L Diaz, ASCO 2016

Key Eligibility for Cohort C

- Histologically proven metastatic or locally advanced mismatch repair deficient non-colorectal solid tumor malignancy
  - -mismatch repair deficiency documented by **IHC** showing deficiency in MLH1, MSH2, MSH6, or PMS2 or microsatellite instability detected by **PCR** (instability in 2 or more loci); testing performed locally
- Measurable disease
- Progressive disease
- Received at least 1 prior therapy
- ECOG 0-1
- Adequate renal, hepatic, bone marrow reserve
- Brain mets allowed if treated and stable (no imaging required)
- No prior anti-PD-1/PD-L1/PD-L2, anti-CD137, anti-OX-40, anti-CD40, anti-CTLA4
- No HIV, hepatitis B, hepatitis C
- No autoimmune disease or active steroids

Baseline Characteristics

L Diaz, ASCO 2016

Characteristic	MMR-deficient non CRC n=30 (%)
Median Age (range)– years	56 (36-92)
Gender-female no. (%)	14 (47)
ECOG PS-zero	6 (20)
Primary-location	
Endometrial	9 (30)
Ampullary/biliary	7 (23)
Pancreatic	4 (13)
Small bowel	4 (13)
Gastric	3 (10)
Other (prostate, thyroid, sarcoma)	3 (10)
Metastatic	30 (100)
Liver Mets	16 (53)
Median Prior Regimens	2
Germline mutation or Lynch Syndrome	
Yes	5 (17)
No	7 (23)
Unknown	18 (60)

Responses

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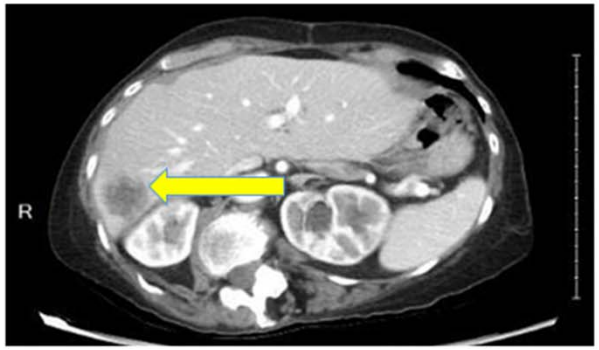
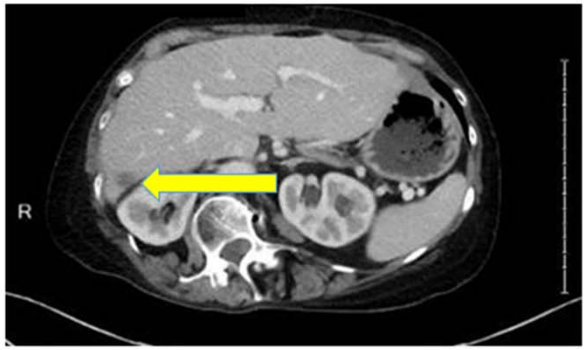
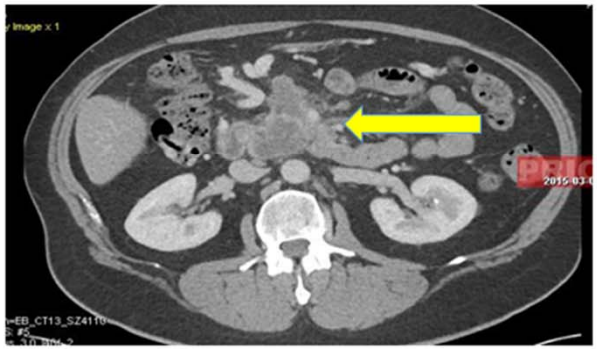
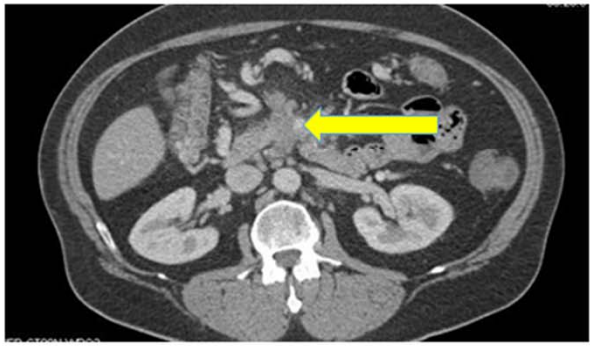
Endometrial





Pancreatic





Baseline **Week 12**

Objective Responses

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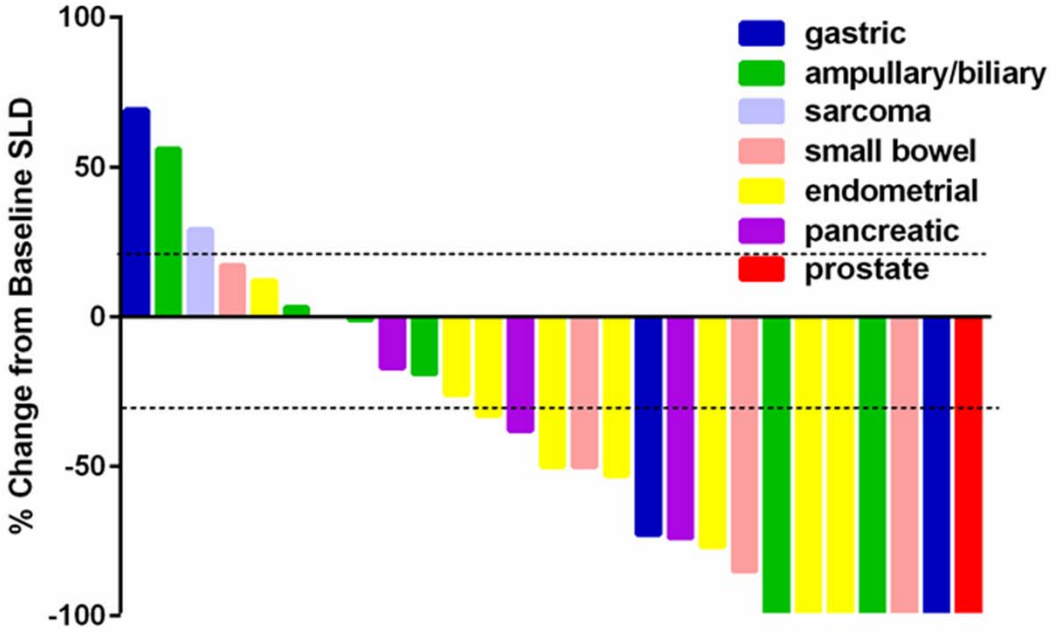
Type of Response-no (%)	MMR-deficient non CRC n=30
Complete Response	9 (30)
Partial Response	7 (23)
Stable Disease (Week 12)	5 (17)
Progressive Disease	7 (23)
Not Evaluable[1]	2 (7)
Objective Response Rate (%)	16 (53)
95% CI	36-70
Disease Control Rate (%)	21 (70)
95% CI	52 - 83
Median Follow Up	10 mos

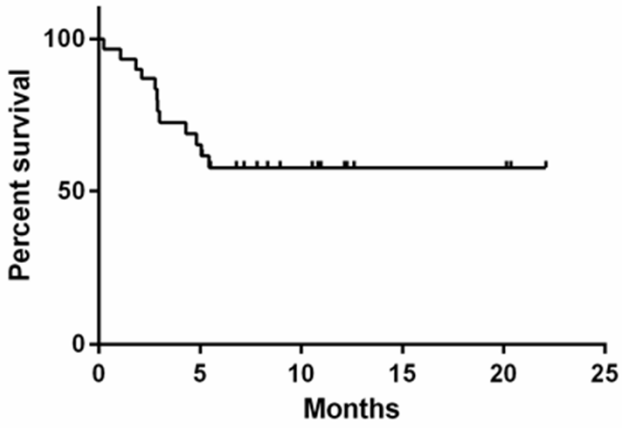
[1]Patients were considered not evaluable if they did not undergo a 12 week scan

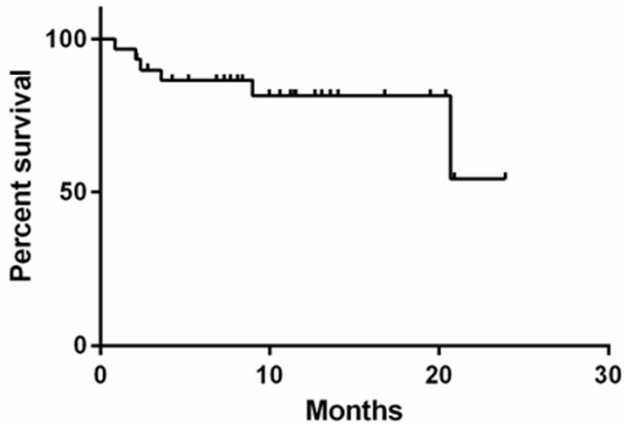
L Diaz, ASCO 2016

Target Lesion Measurements



Progression-Free and Overall Survival





PFS = Non-estimable (NE)
PFS rate (1 yr) = 57%

OS = Non-estimable (NE)
OS rate (1 yr) = 81%

Conclusions

- Mismatch repair deficiency can be determined using existing commercially available tests.
- Mismatch repair deficient cancers are responsive to checkpoint blockade with anti-PD1.
- Durable clinical responses are noted across tumors with mismatch repair deficiency including endometrial, gastric, duodenal, pancreatic, ampullary, and biliary cancers.
- Expected toxicities are manageable.

Ongoing Clinical Studies

- A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects With Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164)
  - Locally confirmed MMR deficient or MSI status
- A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)
  - Any advanced solid tumor, with the exception of colorectal carcinoma (CRC), which is Microsatellite Instability (MSI)-High (MSI-H)

Conclusions

- There is a strong biological rationale for anti-PD-1 pembrolizumab therapy of MSI cancer, regardless of tumor histology
- Clinical trials have demonstrated durable clinical efficacy of pembrolizumab for the treatment of MSI-H colorectal and non-colorectal cancer
- Challenges in drug development for a tumor-agnostic indication
  - Study design for providing evidence of clinical efficacy (vs traditional randomized controlled studies)
  - Identification of study population