CONSIDERATIONS IN DEVELOPMENT OF PEMBROLIZUMAB IN MSI-H CANCERS

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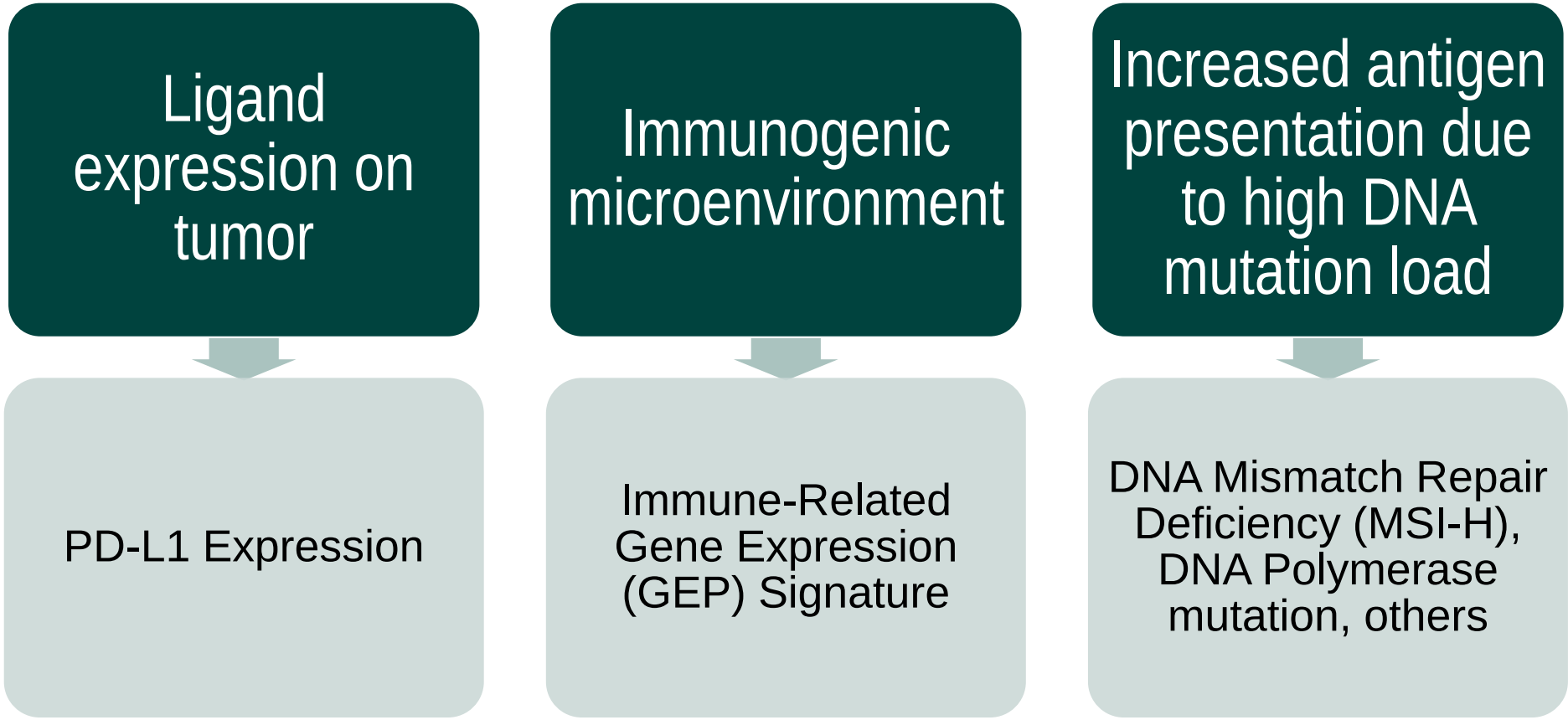
Microsatellite Instability-High Cancer - USPI

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

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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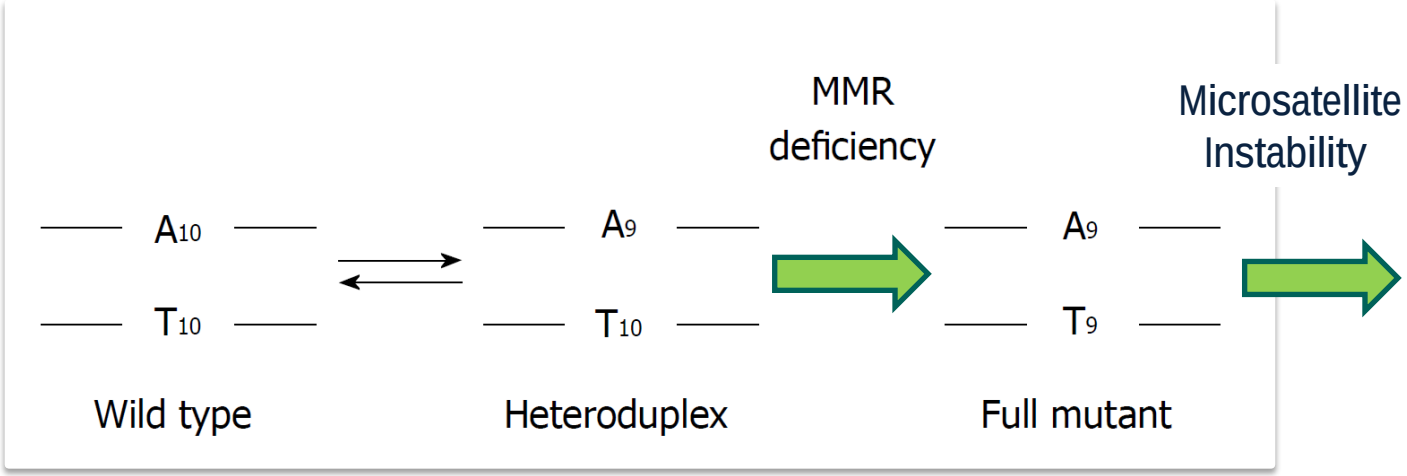
MSI-H Cancer Has a High Mutational Burden

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

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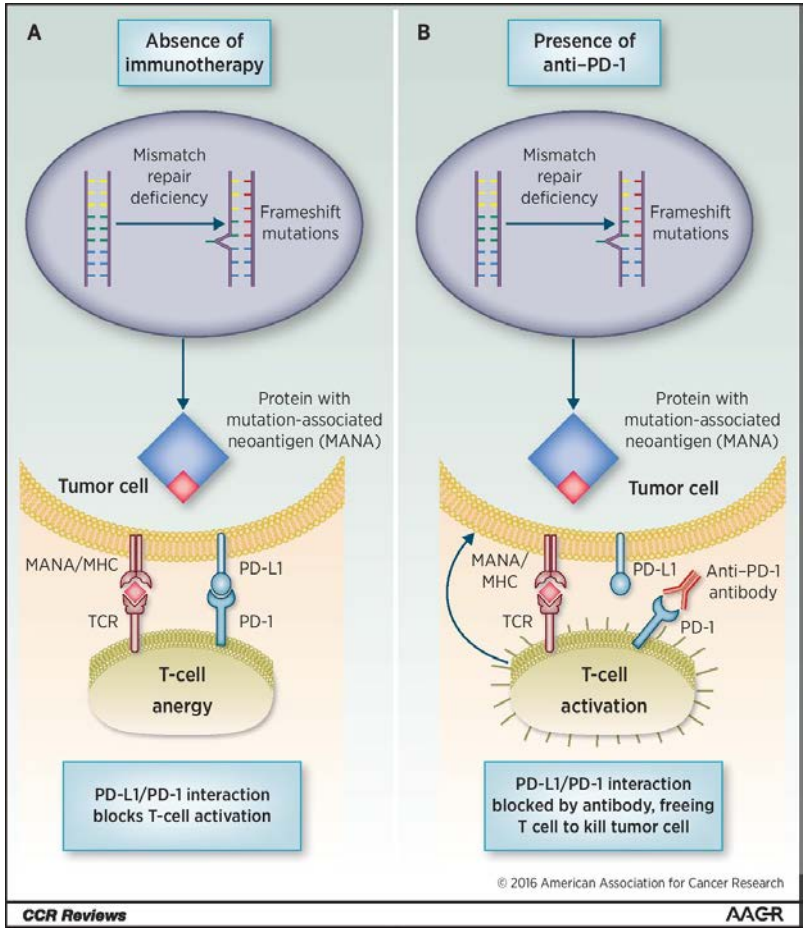
Rationale and Hypothesis

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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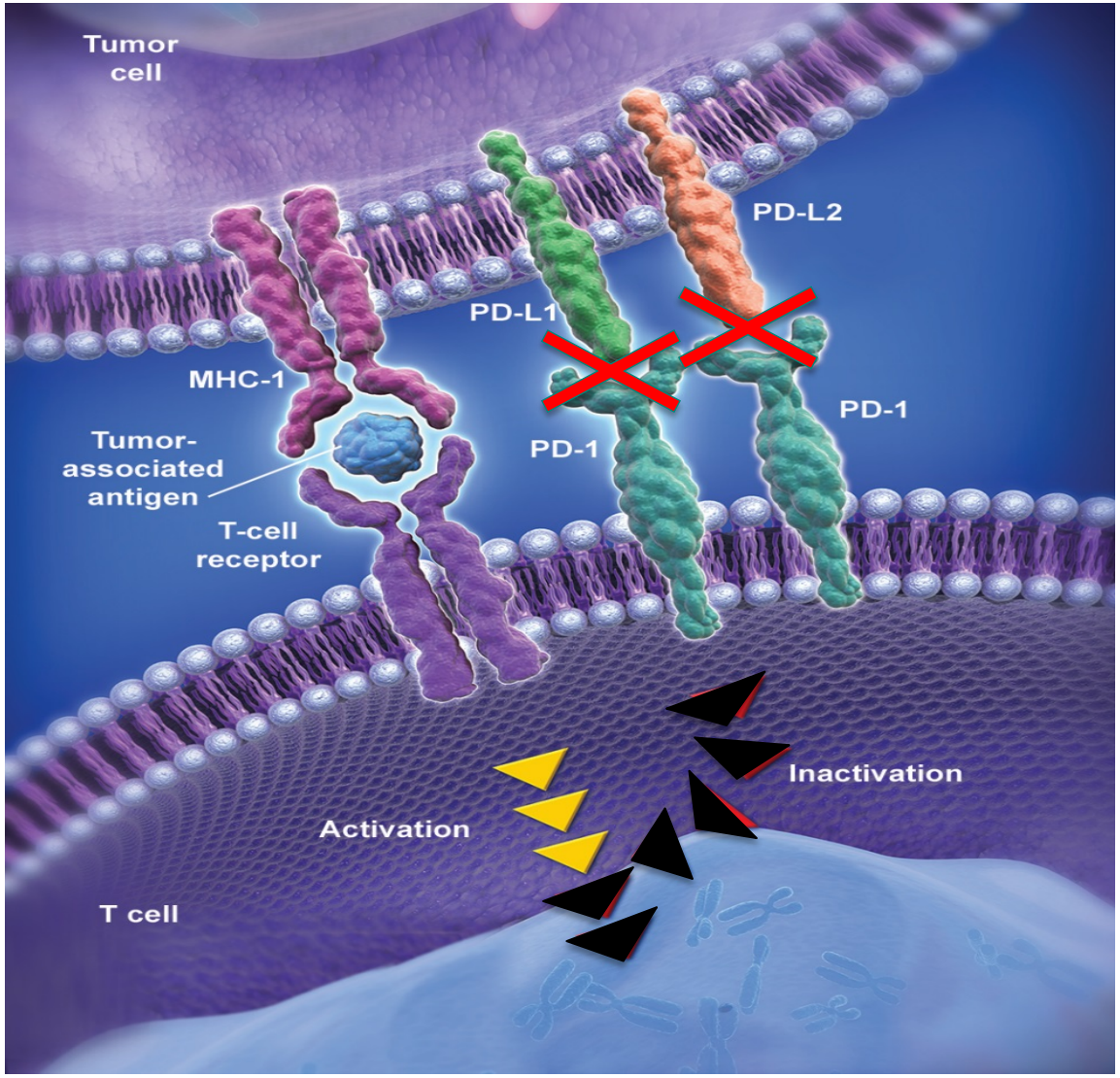
Biological Rationale for Tumor-Agnostic Approach

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



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KEYNOTE (KN) 016 Investigator-Initiated Trial

MSD-sponsored, investigator-initiated trial at Johns Hopkins University – detection of efficacy signal 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 Tumor Phenotype Associated with Efficacy in Colorectal and Non-Colorectal Patients Treated with Pembrolizumab

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

- Initiated in 2013, sponsored by Johns Hopkins- Sidney Kimmel Comprehensive Cancer Center in collaboration with MSD

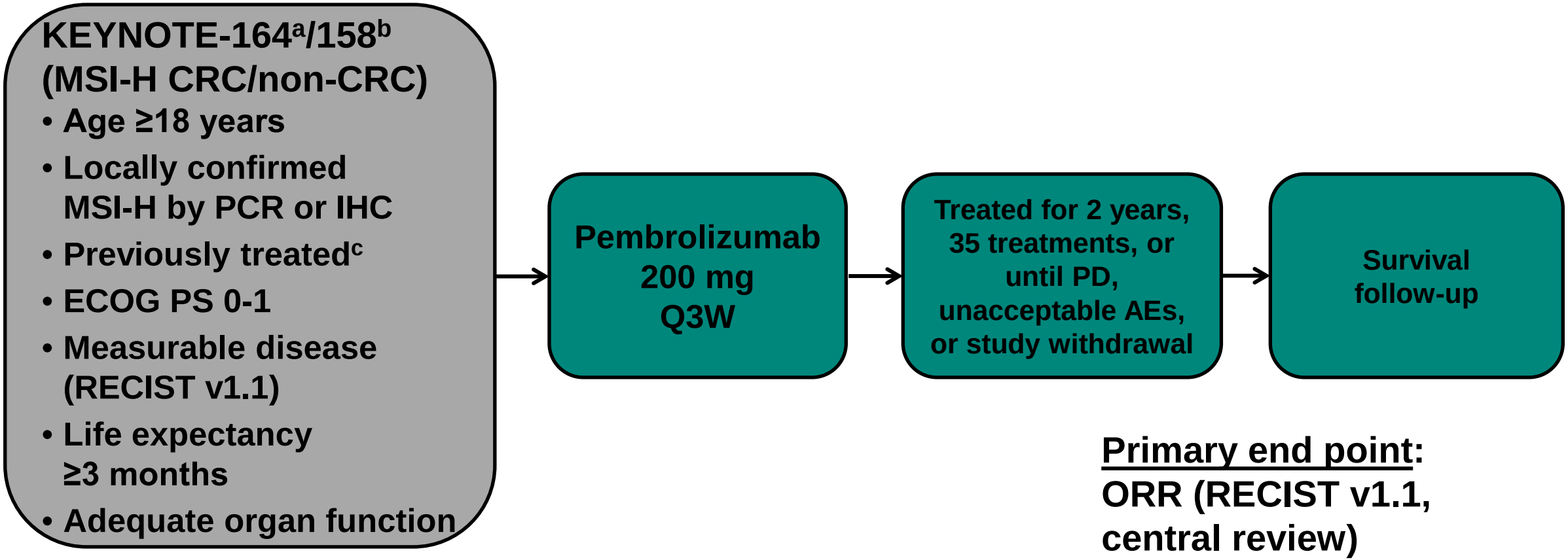
Colorectal Cancers		Non-Colorectal Cancers
Cohort A Deficient in Mismatch Repair (n=40)	Cohort B Proficient in Mismatch Repair (n=25)	Cohort C Deficient in Mismatch Repair (n=40)

- MSI-H identified by IHC (deficiency of MLH1, MSH2, MSH6, or PMS2), or by PCR (instability in ≥2 loci)

- Primary endpoint: ORR
- Secondary endpoints: PFS by RECIST v1.1, and OS

Le D et al, NEJM 2015; Diaz L et al, ASCO 2016

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

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)

Overview of Trials Included in MSI-H

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

Tumor Agnostic Approach

Prevalence of MSI-H prohibits conduct of randomized controlled trials by tumor type

Looking for a consistent, durable treatment effect which supports utility of pembrolizumab across multiple tumor types

- Primary efficacy endpoint across trials: ORR
- Key secondary efficacy endpoint: Duration of response

Analysis approach: Pooled across all trials and across all tumor types to examine consistency of effect

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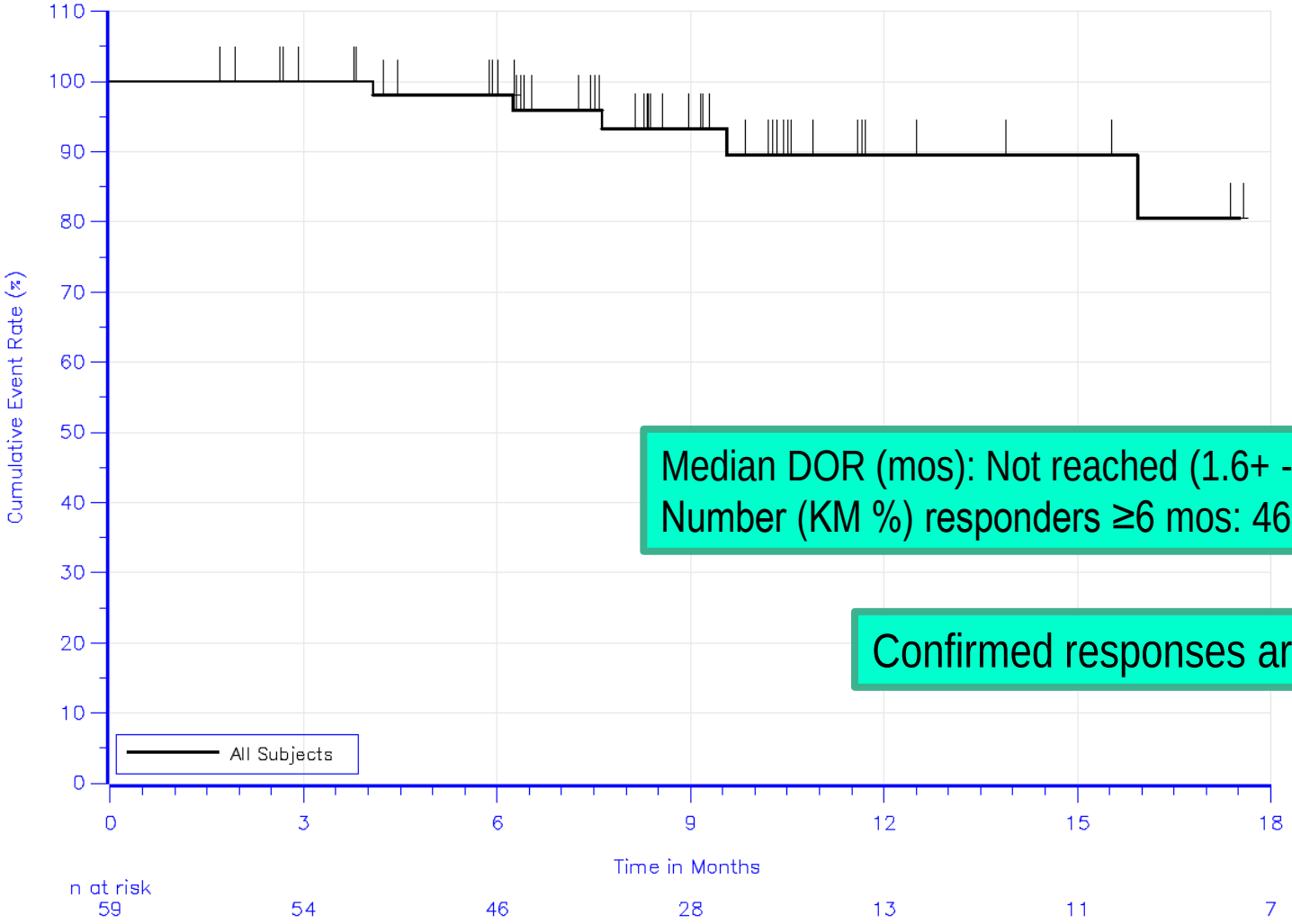
Pooled ORR Results for Patients with MSI-H/dMMR Cancer

	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%

Source: USPI

Pooled DOR Results for Patients with MSI-H/dMMR Cancer



Median DOR (mos): Not reached (1.6+ - 22.7+)
Number (KM %) responders ≥6 mos: 46 (78%)

Confirmed responses are durable

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Results by Tumor Type for Patients with MSI-H/dMMR Cancer

		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.

Source: USPI

Results by Tumor Type for Patients with MSI-H/dMMR Cancer (continued)

		Objective response rate		DOR range
	N	n (%)	95% CI	(months)
Non-CRC (continued)	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

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

Source: USPI

Pembrolizumab Addresses Unmet Need in MSI-H/dMMR Cancer Population

- 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)
- The low prevalence of the MSI-H phenotype in uncommon or rare cancers preclude RCTs for individual types of MSI-H cancers
- Pembrolizumab addresses an unmet medical need with a favorable benefit risk profile in previously treated patients with advanced MSI-H cancer

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 indications

- Study design for providing evidence of clinical efficacy - Low prevalence of biomarker in uncommon or rare cancers may prevent conduct of RCTs for individual tumor types defined by biomarker in a timely manner
- Identification of study population

THANK YOU

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