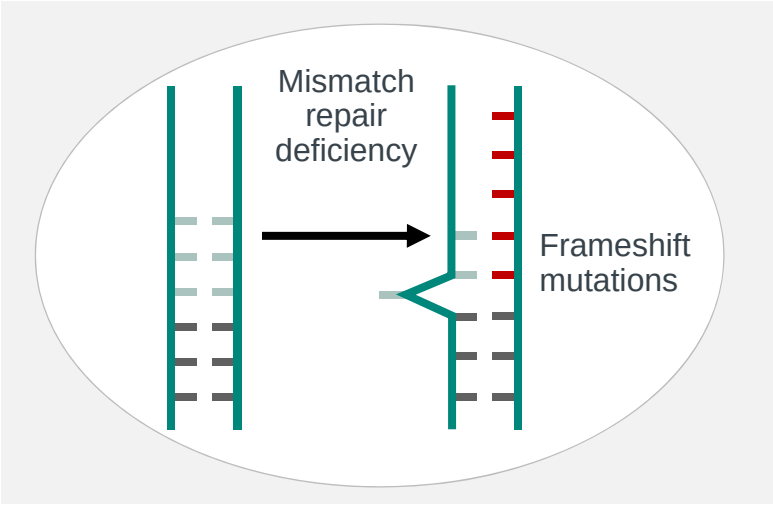
KEYTRUDA (pembrolizumab) Case Study

PD-1 Targeted Immunotherapy for MSI-H Cancer

FDA-ASCO-Friends Tissue-Agnostic Indications Workshop

DNA Microsatellites

- Small, repetitive sequences, principally of polyadenine tracts[1]
- Abundant throughout the genome; polymorphic between individuals, but unique and uniform in length in each person[1]
- Microsatellites are prone to mutations when there are deficiencies in DNA mismatch repair (dMMR)[2]



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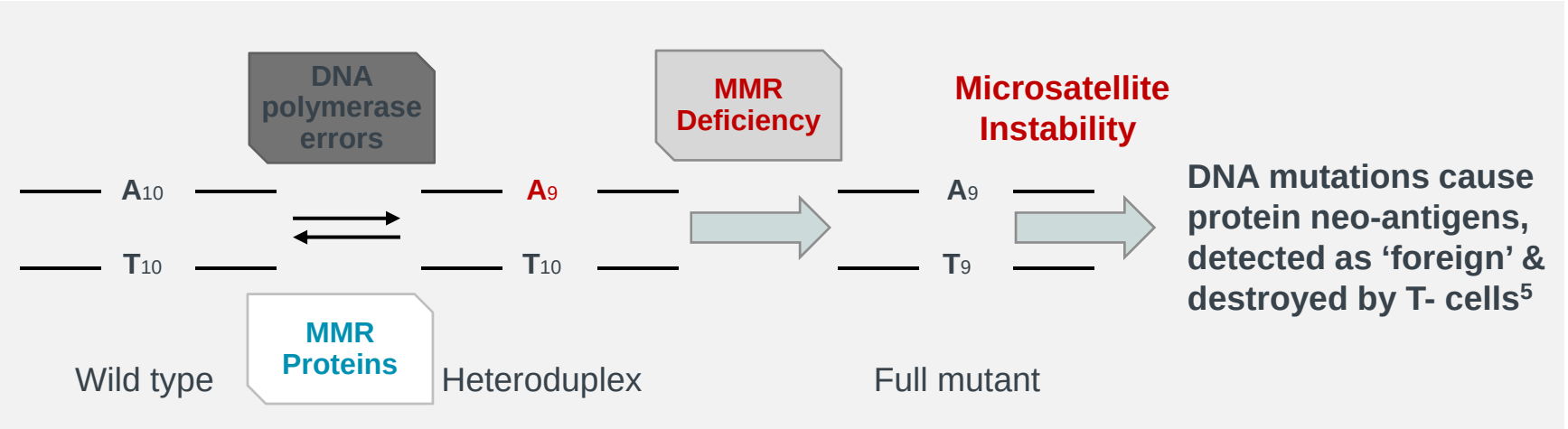
1. Boland CR, Goel A. *Gastroenterology.* 2010;138(6):2073–2087.
2. Gelsomino F, et al. *Cancer Treat Rev*. 2016;51:19-26.
3. Dudley JC, et al. *Clin Cancer Res.* 2016;22(4):813-820.

Microsatellite Mutations are Usually Corrected by MMR Machinery

- During replication, incorrect DNA alignment and polymerase errors can lead to insertions/deletions[1]
- Mismatch repair proteins ***MLH1, MSH2, MSH6, PMS2*** correct these errors[2]
- MMR deficiency due to loss of repair protein expression or function causes MSI phenotype[1]

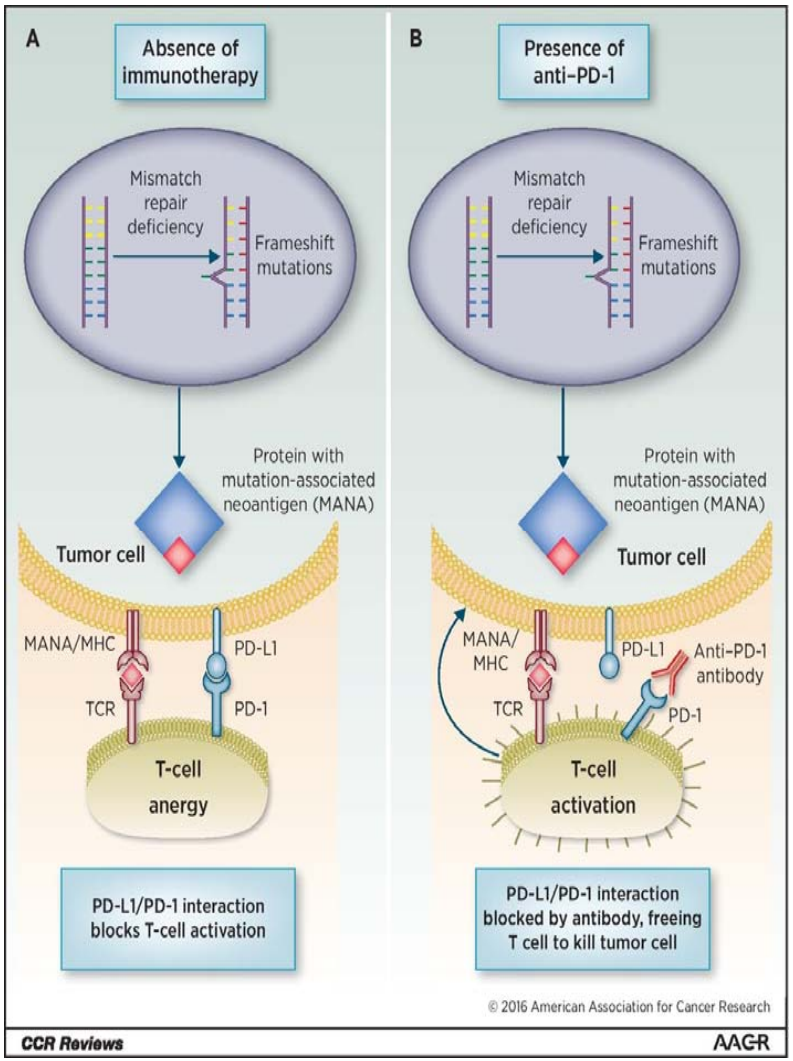


Adapted from Chung et al. 2003; Kirkpatrick et al. 1997.[3,4]

1. Sinicrope FA, et al. *Clin Cancer Res*. 2012;18(6):1506-512.
2. Gelsomino F, et al. *Cancer Treat Rev* . 2016; 19-26.
3. Chung DC, et al. *Ann Intern Med*. 2003;138(7):560-570.
4. Kirkpatrick DT, et al. *Nature.* 1997;387(6636):929-931.
5. Yarchoan M, et al. *Nature Rev Cancer.* 2017;17(4):209-222.

MSI-H Phenotype May Confer Responsiveness to PD-1 Inhibition Independent of Histology

- Hypothesis: Since the target is immune cells, PD-1 inhibition is effective in treating any MSI-H cancer
  - Regardless of tumor histology high neoantigen expression leads to autologous immune recognition of cancer cells, and cytotoxic T-lymphocyte rich microenvironment within the tumor
  - Blocking PD-1 on tumor neoantigen-specific T cells may activate anti-tumor immune responses

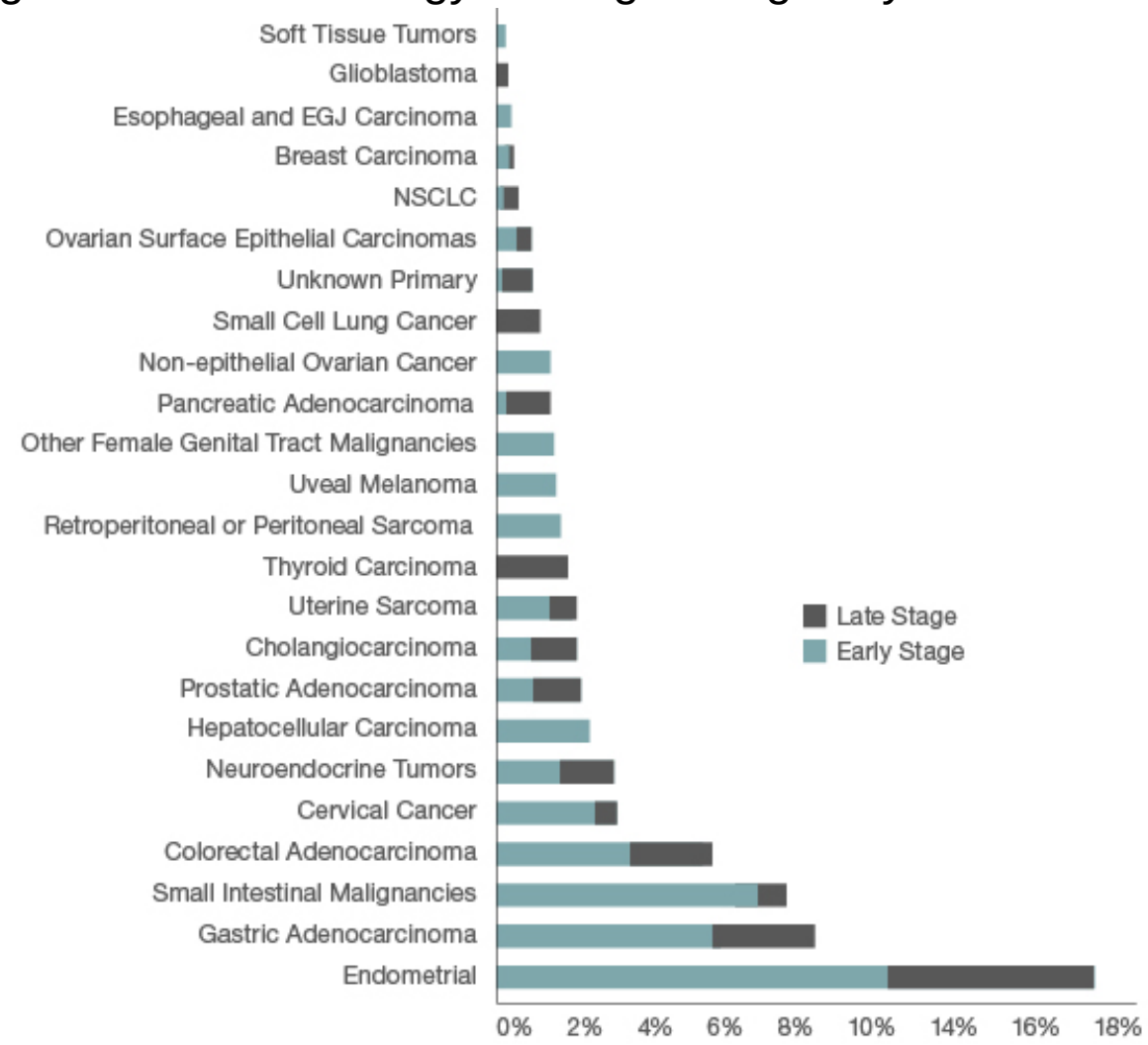


Dudley JC et al. *Clin Cancer Res* 2016;22:813-820

MSI-H Cancer: Disease Background and Testing Guidelines

MSI-H is Observed in Multiple Cancer Types

Cancers that are more likely to be MSI-H (i.e., prevalence ~5% or higher) include those of the gastrointestinal and gynecological organ systems



Le, 2017

MSI-H/dMMR Testing Guidelines

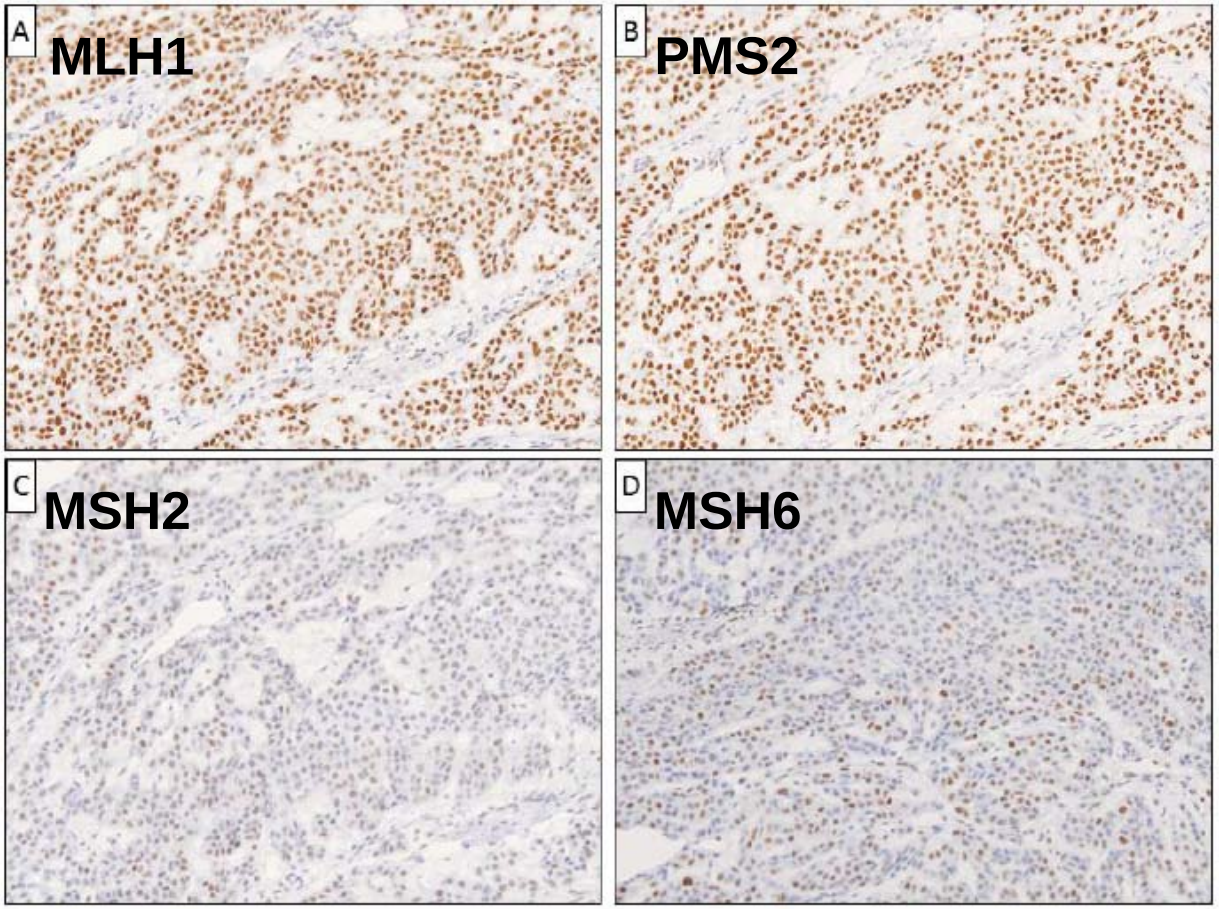
NCCN Guidelines version 1.2016 for Colorectal Cancer: Lynch Syndrome, Stage II disease, and all patients with metastatic disease

- IHC for dMMR and PCR for MSI are different assays measuring the same biologic effect
- IHC/MMR & PCR/MSI tests are widely used, and readily available in the US (EU)
- NGS platforms available more recently for Colorectal Cancer and Lynch Syndrome testing
- Class II assays cleared for IHC and NGS
- These testing guidelines informed the testing approach used in Merck MSI-H cancer trials:

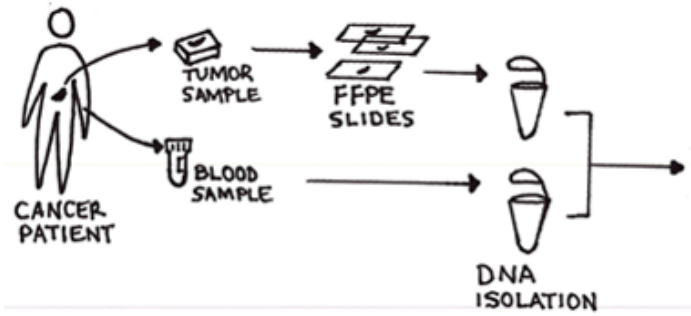
Test	Reagents to targets	Result Indicative of MSI-H
IHC	***Antibodies to:*** MLH1/MSH2/MSH6/PMS2	Any 1 (or more) of 4 proteins absent
PCR	***PCR probes to:*** • BAT25, BAT26, NR21, NR24, Mono27 ***OR*** • BAT25, BAT26, Di 5S346, Di 2S123, Di 17S250	≥ 2 of 5 loci differ in size from corresponding normal loci

IHC-Based dMMR Assay

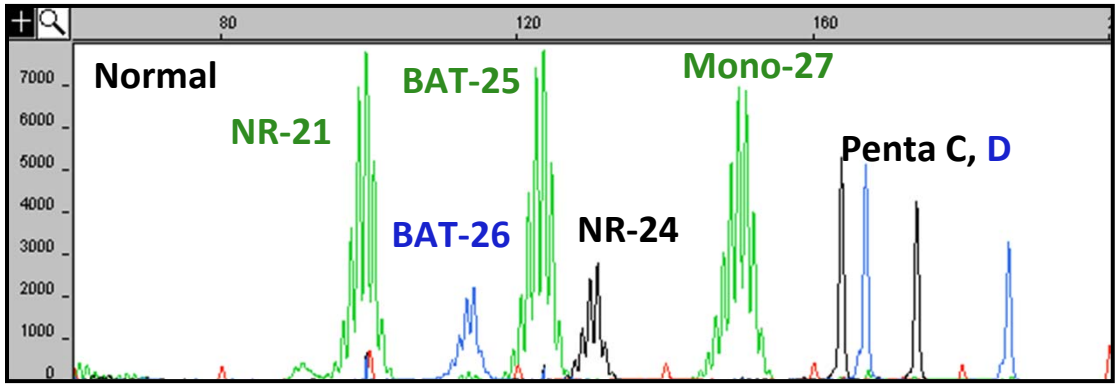
dMMR when at least one of four MMR proteins are absent

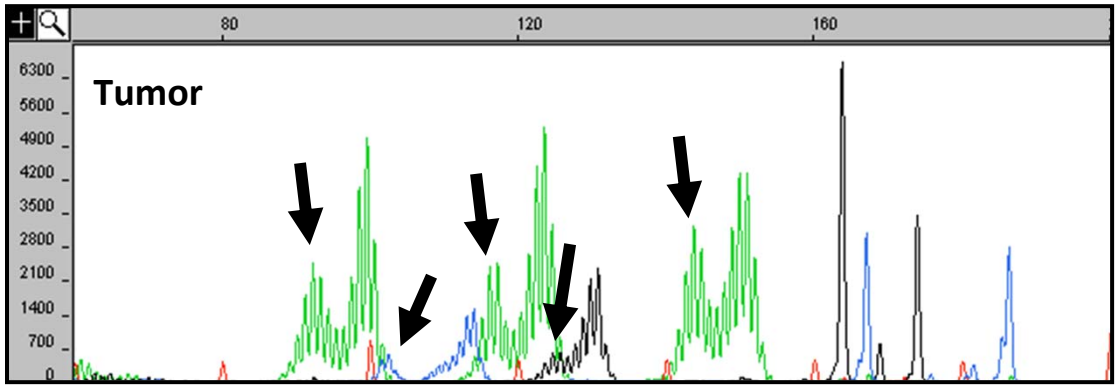


PCR-Based MSI Assay



MSI-H if ≥ 2 of 5 loci differ in size from corresponding normal loci





Courtesy:
James Eshleman

sBLA Submission, Approval, and Post-marketing Commitments

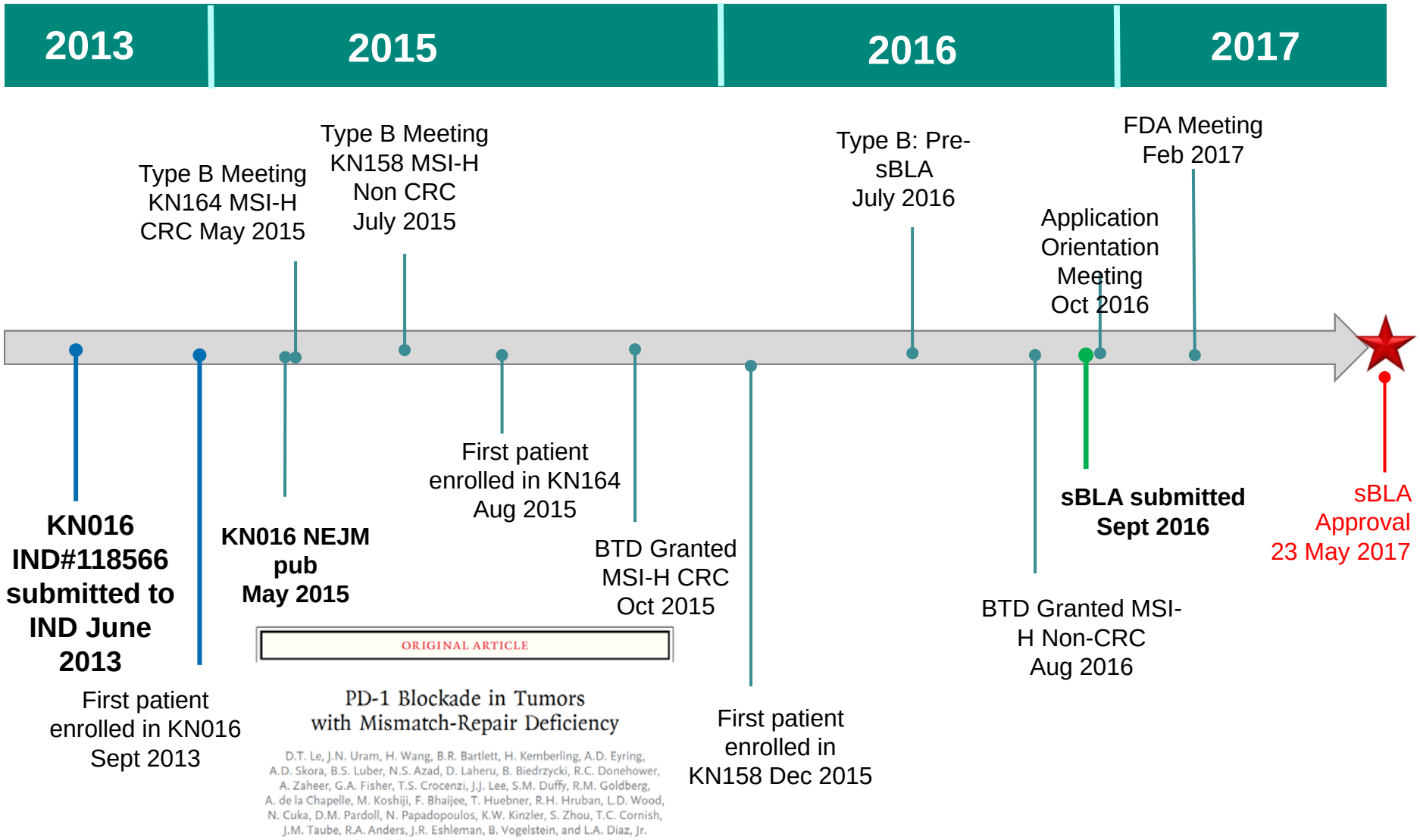
FDA Feedback Informed Pembrolizumab Clinical Development in MSI-H Cancer

- May 2015, FDA meeting for KEYNOTE-164
  - To discuss design of KEYNOTE-164 with FDA:
  - FDA encouraged Merck to enroll patients with MSI-H small intestinal and other gastrointestinal malignancies in a dedicated protocol, in order to expedite development in this population

- July 2015, FDA meeting for KEYNOTE-158 (Basket Trial)
  - To discuss design of KEYNOTE-158 with FDA
  - Included cohort of MSI-H solid tumors (except colorectal cancer)

- On May 23, 2017, the U.S. FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

Development Timeline of KEYTRUDA in MSI-H Cancer



Pembrolizumab Response by Tumor Type - FDA Filing (15 tumor types)

		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

Pembrolizumab Response by Tumor Type - FDA Filing (15 tumor types) - 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

Pediatric Strategy, PMRs, and PMCs

MSI-H Pediatric Considerations

- Expectation that disease biology of MSI-H cancer in adults will be similar to disease biology in children (e.g., children with congenital dMMR syndromes) → extrapolation of pembrolizumab efficacy to the pediatric population
- Accepted pediatric dose
- A ongoing study which is enrolling pediatric patients is being conducted to satisfy a requirement for accelerated approval

PMR to Verify Clinical Benefit in the Tumor-Agnostic Indication

- Longer follow-up with pembrolizumab in MSI-H cancer patients
- Greater number and variety of tumor types, including at least 124 patients with CRC and 300 patients with non-CRC, including a sufficient number of patients with prostate cancer, thyroid cancer, small cell lung cancer; and ovarian cancer; and 25 children
- To characterize response rate and duration, patients will be followed for at least 12 months from the onset of response

MSI-H US Approval 23 May 17: Included Post Marketing Commitments (PMCs)

- Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an **immunohistochemistry based** *in vitro* diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are *mismatch repair deficient*.

- Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a **nucleic acid-based** *in vitro* diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are *microsatellite instability high*.

CDx development after drug approval: Rationale, challenges

- Lemery, et al., 2017 http://www.nejm.org/doi/pdf/10.1056/NEJMp1709968
- CDx test(s) were not co-developed.
  - MSI-H / dMMR as a prognostic determinant for colorectal cancer recurrence was available for decades in medical practice
  - FDA approved this indication without approved CDx tests.…because of the high unmet medical need…the high response rate, and the known safety profile
- 2 CDx assays to be developed as part of PMCs
  - Tests are clinically, biologically synonymous, but measure different substrates
    - IHC, to support dMMR
    - nucleic acid-based, to support MSI-H
- Post-trial development of a CDx is challenging
  - sample availability is a major hurdle as limited tumor tissue was collected from trials,limited number of tumor blocks for IHC

Harmonization with other National Health Authorities

MSI-H Pan Tumor Approval in Japan

- Approved on December 21, 2018 by PMDA
- Approved under Conditional Early Approval System (CEAS)

MSI-H Pan Tumor Worldwide Registration Status (22 approvals)

Country	Approval Date
Argentina	11/15/2018
Aruba	6/19/2017
Bahrain	1/8/2018
Curacao	6/29/2017
Egypt	3/6/2018
Israel	2/6/2018
Jamaica	7/26/2017
Japan	12/21/2018
Jordan	12/12/2018
Kuwait	7/5/2018
Lebanon	12/20/2017
Oman	2/8/2018
Palestine	1/14/2019
Paraguay	12/11/2018
Peru	6/27/2017
Philippines	10/26/2018
Qatar	5/2/2018
Russia	2/26/2019
Taiwan	11/30/2018
UAE	12/25/2017
Ukraine	6/21/2018
United States	5/23/2017

Histology-Independent Indication Development in EU

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 13 December 2018
2 EMA/CHMP/755489/2018
3 Committee for Human Medicinal Products (CHMP)

4 Concept paper on the revision of the guideline on the
5 evaluation of anticancer medicinal products in man

- Presenting the main features and principles of new designs (mainly basket trials). Because regulatory experience is limited in this field for the time being, the guidance on this topic is only focusing on main aspects and principles.

Adopted by CHMP for release for consultation	13 December 2018
Start of public consultation	14 January 2019
End of consultation (deadline for comments)	14 April 2019

Clear interest in scientific concept

The European View: Possible in Theory, Challenging in Practice

- The concept of histology-independent indications
  - Requires in-depth knowledge about the mechanism of and at least strong plausibility across subgroups
  - Need to explore heterogeneity of effects (interactions, resistance mechanisms)
  - Multiple therapeutic contexts, evidence of positive benefit-risk balance
  - Easier when high unmet need across subgroups
  - Challenging when competing against available options with established clinical utility (e.g. survival) in some subgroups; indirect comparisons (rare diseases, lack of historical data); extrapolation

Challenges to translate scientific concept into current regulatory framework

Thank You