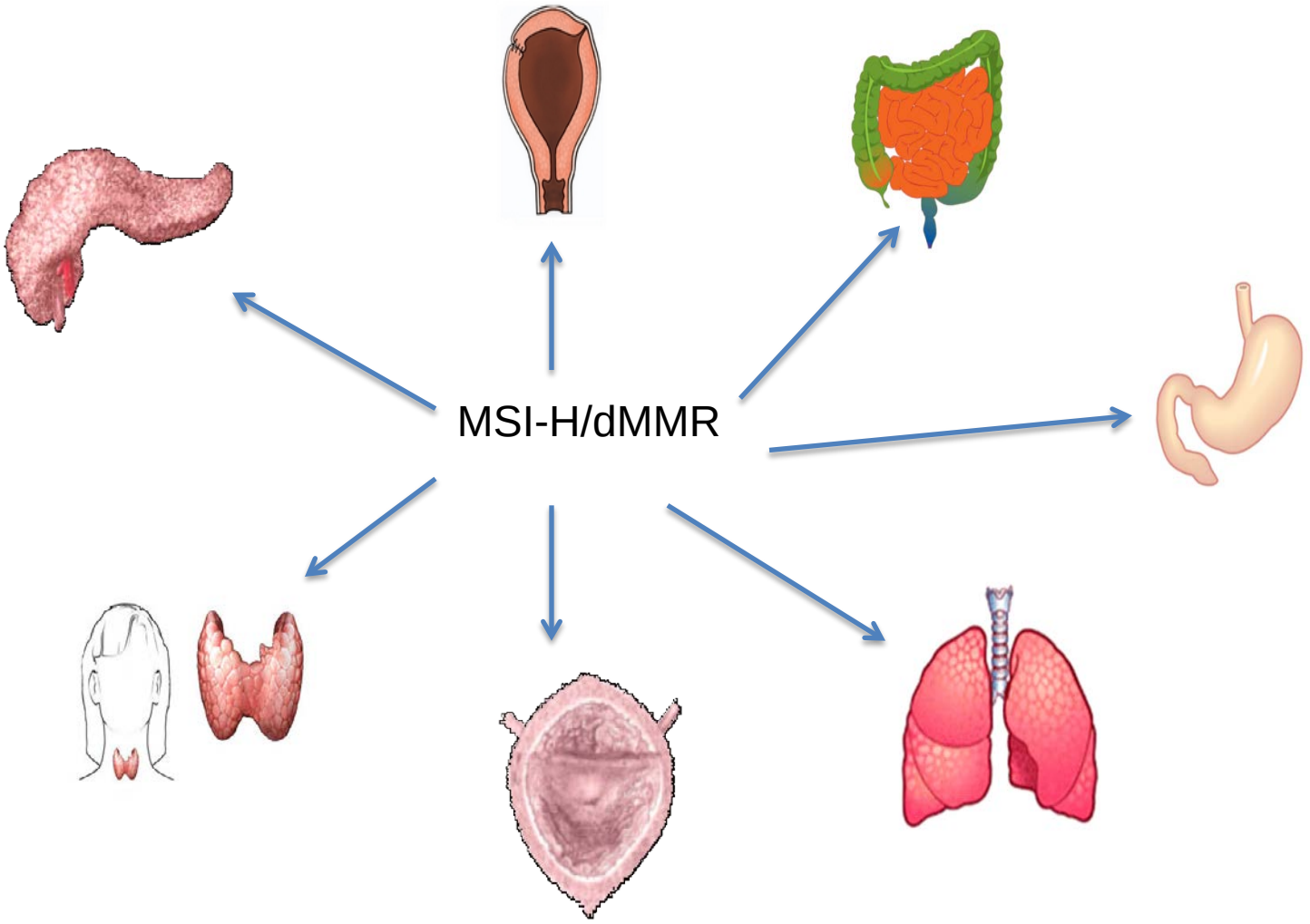
Approval of pembrolizumab (MSI-H/dMMR) and considerations for site-agnostic development of drugs in oncology

Steven Lemery, MD, MHS
Associate Director, DOP2

Traditional development paradigm

- Based on tumor type, e.g.,
  - Previously untreated pancreatic cancer
  - HCC after previous sorafenib treatment
- Based on a biomarker within a tumor type, e.g.,
  - HER-2 positive breast or gastric cancer
  - RAS wild-type colorectal cancer

MSI-H/dMMR, not the organ, defines the indication



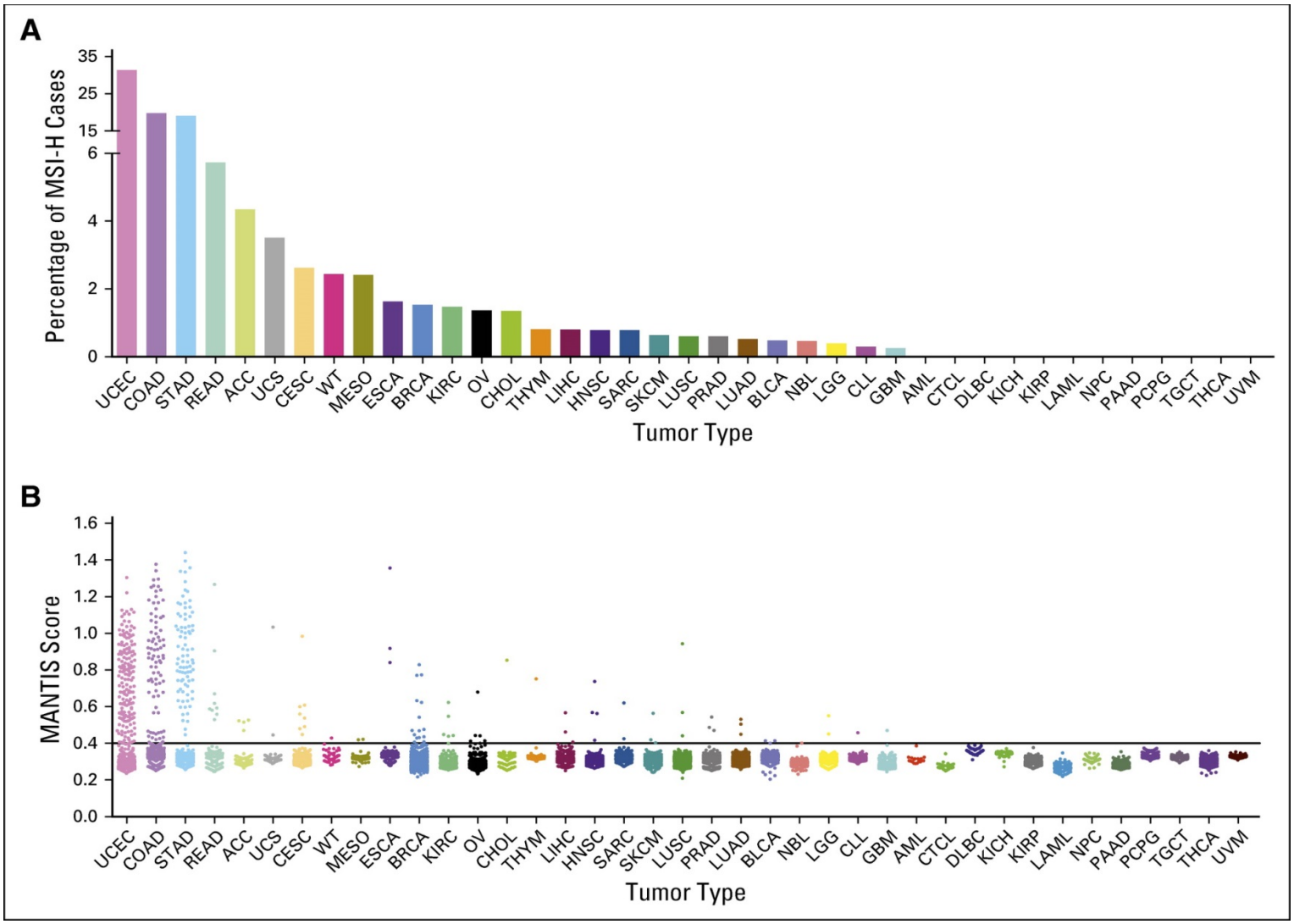
What is MSI-H/dMMR?

- MSI-H = microsatellite instability
- dMMR = deficient mismatch repair
- Causes of dMMR/MSI-H:
  - Mutation in DNA repair proteins
    - Can occur in Lynch syndrome
  - Inactivation of DNA repair proteins

Why does this matter?

- Impairment in mismatch repair causes
  - ↑↑↑ mutations in tumors
  - Some mutations (neo-antigens) may be targeted by immune system
- Pembrolizumab can facilitate immune system response in some MSI-H/dMMR cancers

MSI-H in different tumor types



Bonneville et al., JCO Precision Oncology, 2017

Initial Interaction with Merck

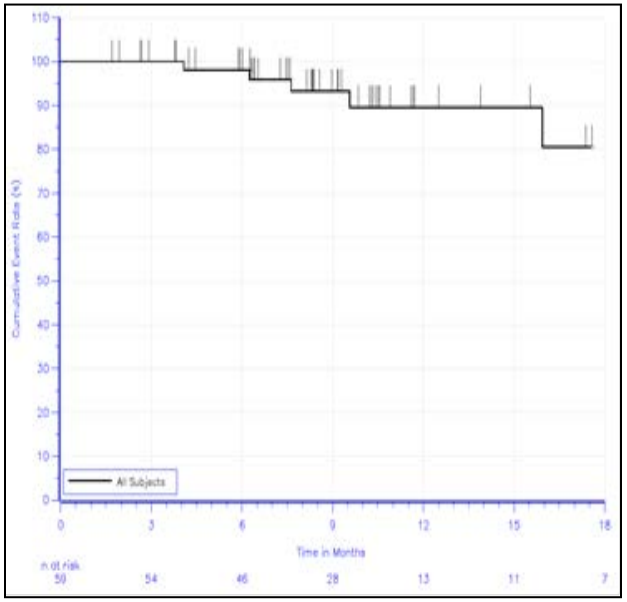
- FDA discussed KN-16 with Merck in May 2015
  - ORR:
    - 4/10 MSI-H CRC
    - 5/7 MSI-H other tumors
    - 0/18 MSS CRC
  - Discussed design of KN-164 (MSI-H CRC)
    - FDA recommended enrolment of patients with other MSI-H GI cancers
    - FDA recommended that Merck submit a BTDR.

Pre-BLA regulatory history

Date	Event
Jul 2015	FDA and Merck met to discuss development in MSI-H non-CRC
Oct 2015	BTDR granted for MSI-H CRC
Mar 2016	Enrollment in KN-164 complete; new cohort to be opened
Apr 2016	Merck provided FDA an update of development program
Jul 2016	Pre-BLA meeting: FDA informed Merck that Agency amenable to TA indication
Oct 2016	BTDR granted for MSI-H non CRC

Data supporting pembrolizumab approval

	N	Objective response rate	
		n (%)	95% CI
CRC	90	32 (36%)	(26%, 46%)
Non-CRC	59	27 (46%)	(33%, 59%)
Endometrial cancer	14	5 (36%)	(13%, 65%)
Biliary cancer	11	3 (27%)	(6%, 61%)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)
Pancreatic cancer	6	5 (83%)	(36%, 100%)
Small intestinal cancer	8	3 (38%)	(9%, 76%)
Breast cancer	2	PR, PR	
Prostate cancer	2	PR, SD	
Bladder cancer	1	NE	
Esophageal cancer	1	PR	
Sarcoma	1	PD	
Thyroid cancer	1	NE	
Retroperitoneal adenocarcinoma	1	PR	
Small cell lung cancer	1	CR	
Renal cell cancer	1	PD	



KM-DOR in 59 responding patients

Source: Keytruda labeling, BLA submission, FDA review documents

Pembrolizumab MSI-H approval considerations

- Strong scientific/biological rationale
- Compelling clinical data
- Extensive history of clinical use / safety profile
- Favorable risk/benefit profile with similar ORR in other indications
- Approved for patients without available therapies

Pembrolizumab MSI-H/dMMR approval

- Granted accelerated approval
  - ORR/DOR data post-approval
  - Over 400 patients with at least 25 tumors enrolled
- AA requirement: advantage over available therapy
  - CRC: prior FP, oxaliplatin, irinotecan
  - Other solid tumors: progressed on available therapies and no satisfactory options
    - *This requirement does not apply to regular approval*
- Companion IVD PMCs

TA approval/development considerations

1. How many tumor types should be evaluated?
2. Extrapolation to non-studied tumor types/pediatrics?
3. Accelerated versus regular approval?
4. How will residual uncertainty be managed?
   - e.g., if a drug is ineffective for a particular rare-tumor biomarker
     - Pre-approval
     - Post-approval (e.g., trials, registries, RWD)

How many tumor types should be evaluated?

- No “one size fits all” answer
  - Does the totality of evidence support approval?
  - Were common tumor types studied?
  - Was effect generally consistent among tumors?
  - Is approach scientifically supportable?

Extrapolation* – Yes, if appropriate

- Pembrolizumab:
  - At time of approval, responses observed in *at least* 14 MSI-H/dMMR tumor types
  - No pattern indicating a qualitative effect of tumor type on response

Pediatrics: Pembrolizumab – MSI-H

- Dose of pembrolizumab established in children
- Pembrolizumab approved in children with cHD
- Biology of MSI-H (e.g., increased mutation burden) expected to be similar in children

TA – General Pediatric Considerations

- Consider formulations *early* during development
- Initiate pediatric trials early
  - Establish dose in all age groups
  - Consider enrolling patients age 12 years or older in adult trials

Chuk et al., CCR, 2017

Approval Considerations

- RCTs to assess OS in rare biomarker(+) tumor types with unprecedented effects on ORR and DOR
  - May not be feasible
  - Probably not ethical in refractory setting
- For pembrolizumab, OS/PFS improvements in other cancers with similar ORR and high TMB (e.g., melanoma, NSCLC)
- FDA took similar approach with crizotinib for ROS1-postive NSCLC

Uncertainty

- Absolute certainty regarding drug effect will not exist for every biomarker-tumor-drug combination
  - Sponsors need to make the case that the approach is appropriate based on scientific/clinical data
- Absolute certainty *also* does not exist in tumor-specific approvals

How to address uncertainty

- Pre-market: Is data package sufficient (FDA approval decision)
  - Substantial evidence standard
- Post-market trials (e.g., for pembrolizumab)
- Real world-data?

Pre-market data requirements

- Sufficient data to make a risk-benefit determination
- Sufficient data that the effect is “real”
- Influenced by
  - magnitude of benefit
  - known toxicity profile
  - unmet need / lack of available therapies
  - risk to patient of no treatment

The future for MSI-H?

- Earlier treatment?
  - First-line metastatic CRC?
  - Adjuvant use
  - ? Role for first-line in other tumor-types
- Identify patients less likely to respond
- How to treat patients who progress

Ongoing questions / issues

- What is the best test?
  - IHC, PCR, NGS (or combination)
- Identification of more people with Lynch syndrome
- Will benefit continue to endure after stopping pembrolizumab?
- GBM in patients after TMZ?
  - Safety in patients with CNS disease

TA beyond MSI-H/PD-1

- NTRK fusions?
  - Breakthrough designation publically announced for two drugs
  - Very rare in common tumors
  - Common in certain ultra-rare tumors
- TMB
  - How would indication (e.g., TMB cut-off) be defined?
  - Are IVD tests comparable?

Risks of TA Development / Trials

- Could *slow* drug development
  - By diverting resources from more common biomarker-positive tumor types (e.g., via site selection)
  - Enrollment challenges for rare diseases
- Could increase development costs
  - e.g., increased sites, number of patients screened, etc.

How will TA approval impact development for biomarker negative populations?

- e.g., should MSI-H patients be excluded from clinical trials of single agent PD-1 inhibitors?
  - If not, how to assess whether an effect is driven solely by biomarker-positive population?

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Thank you!

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