U.S. FOOD & DRUG ADMINISTRATION

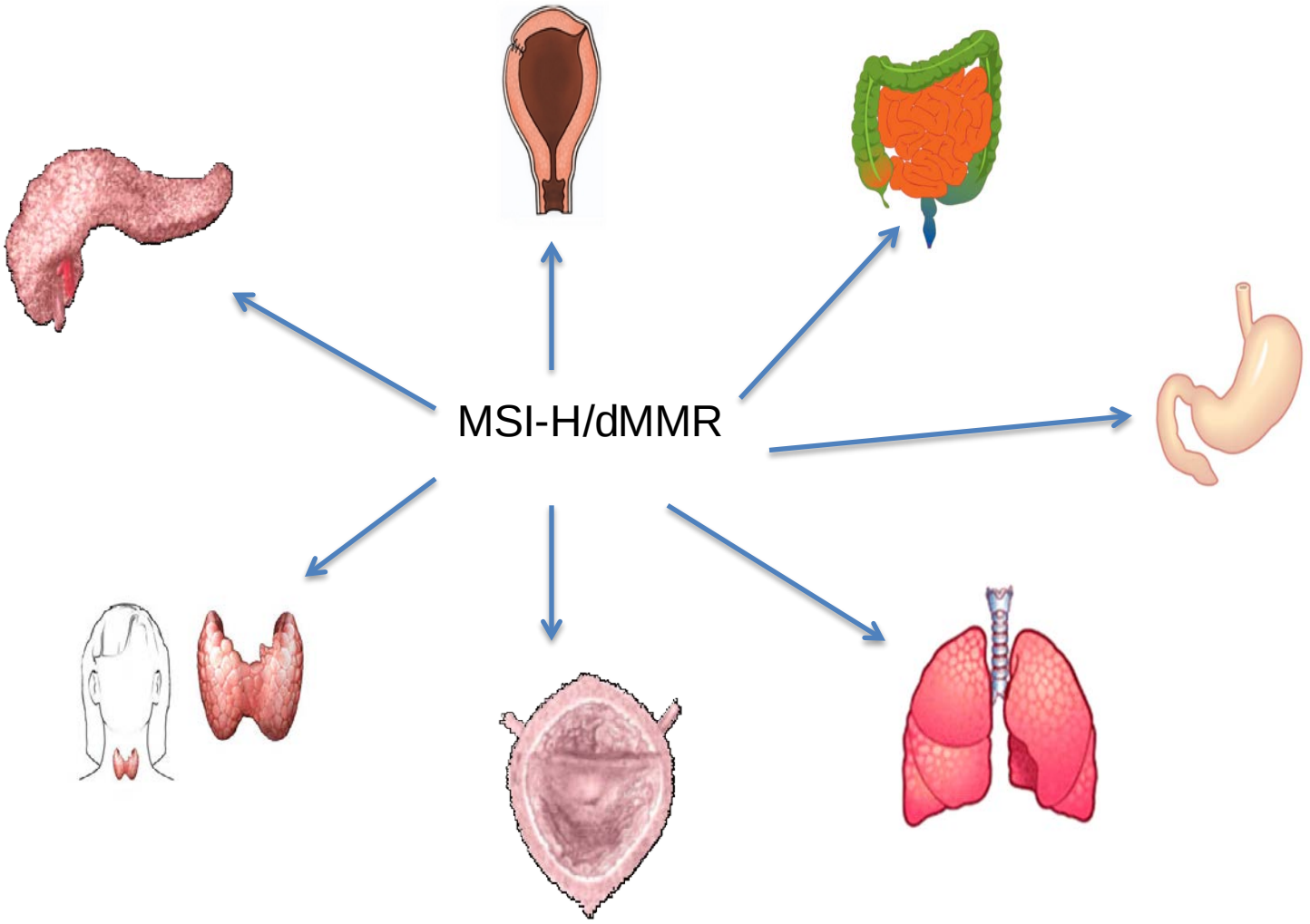
Approval of pembrolizumab for the treatment of MSI-H/dMMR cancers, agnostic of cancer type

FDA approval on May 23, 2017

Traditional paradigm for approvals for in oncology

- 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



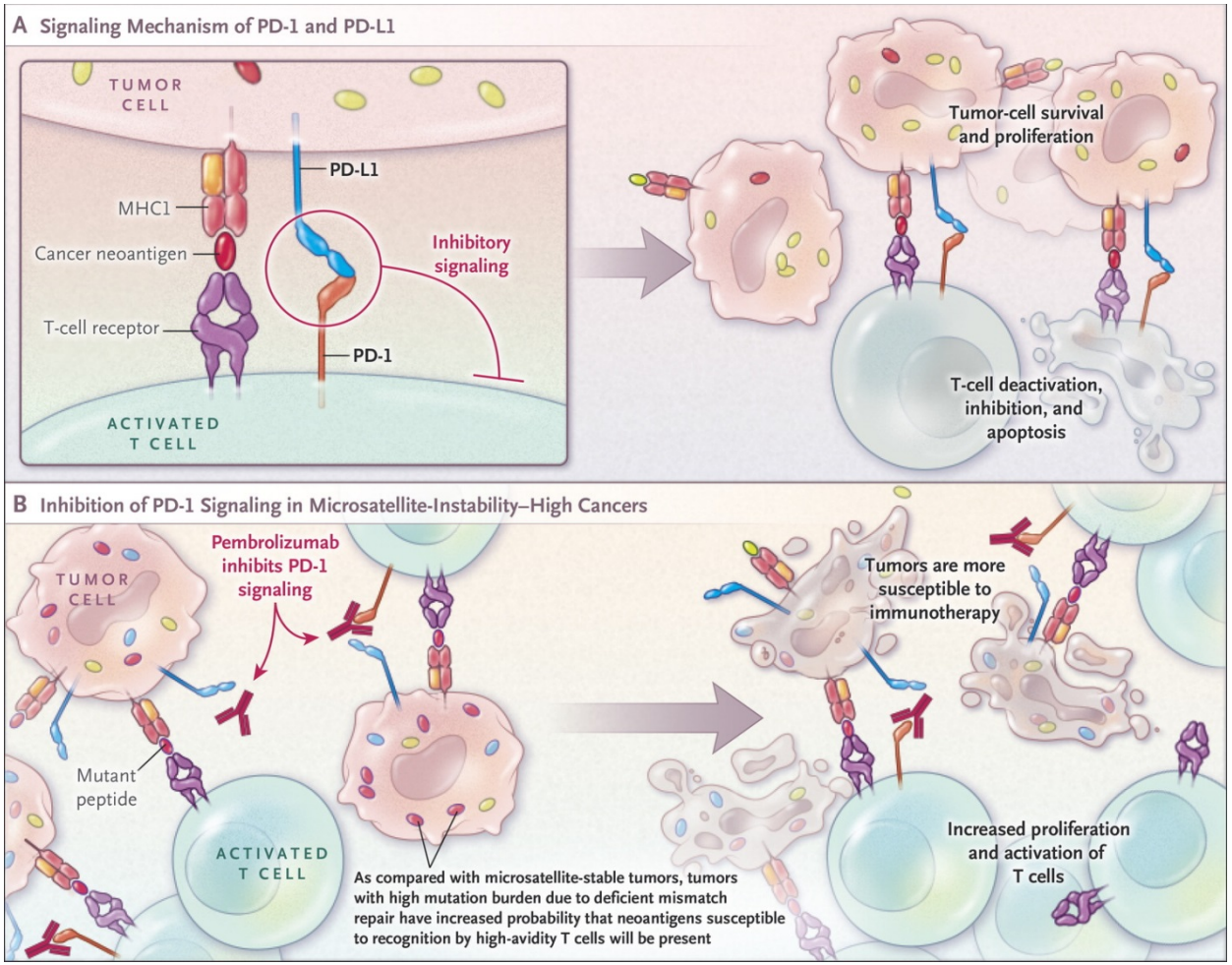
What is MSI-H/dMMR?

- 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?

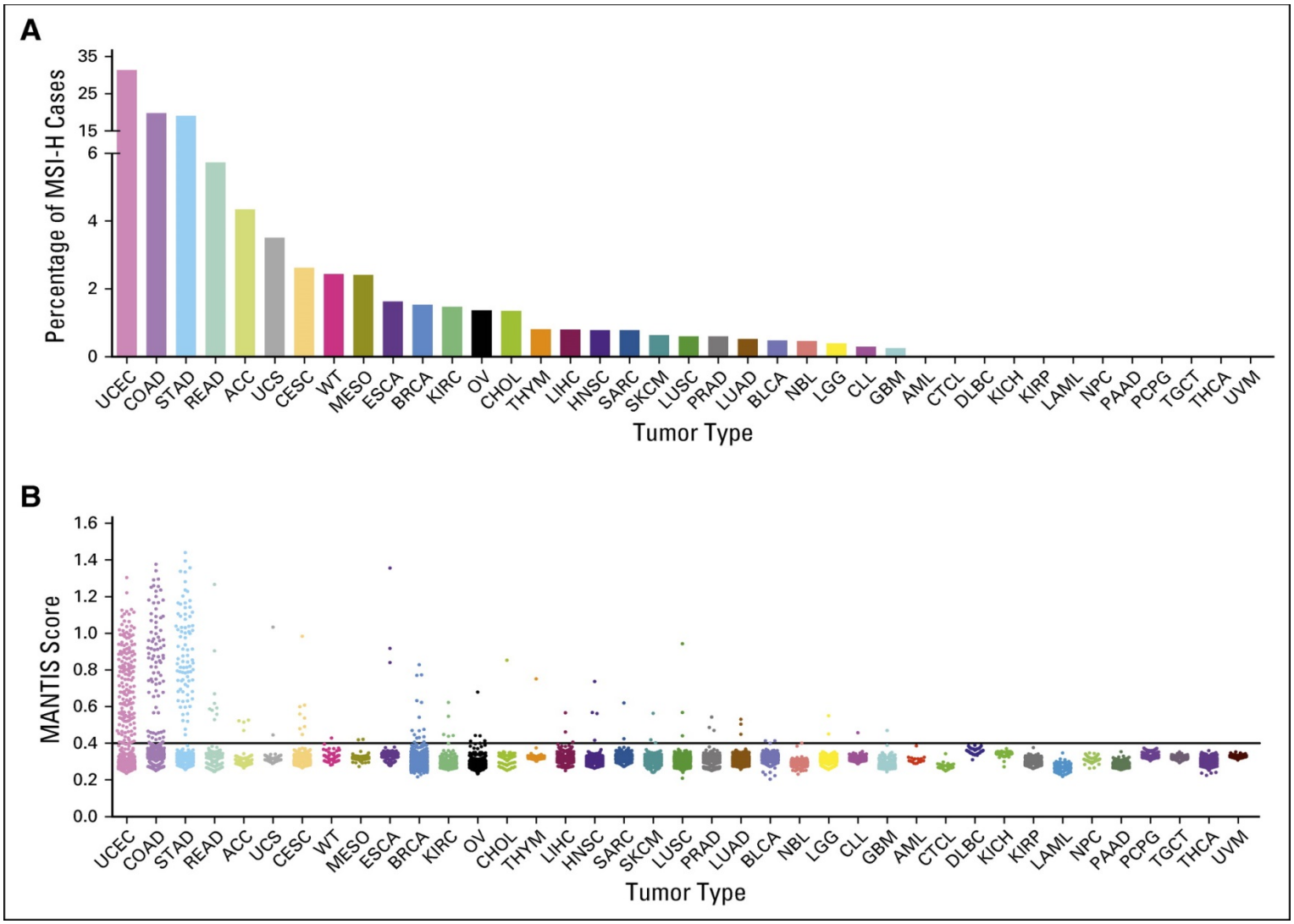
- Impairment in mismatch repair causes
  - Greatly increased number of mutations in tumors
  - Some mutations (neo-antigens) may be targeted by immune system
- Pembrolizumab can facilitate immune system attack in some MSI-H/dMMR cancers

Mechanism of Action



Lemery et al., NEJM, 2017

MSI-H in different tumor types



Bonneville et al., JCO Precision Oncology, 2017

Data supporting pembrolizumab approval

Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

Lemery, NEJM, 2017

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

Post-approval

- Accelerated approval requirement
  - Assess clinical effects in larger number of patients and longer duration
    - Including children
- Approval commitments
  - Develop tests to identify MSI-H and dMMR in tumor samples

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?
- Adjuvant use?
- GBM?