Regulatory Considerations for Tissue Agnostic Development

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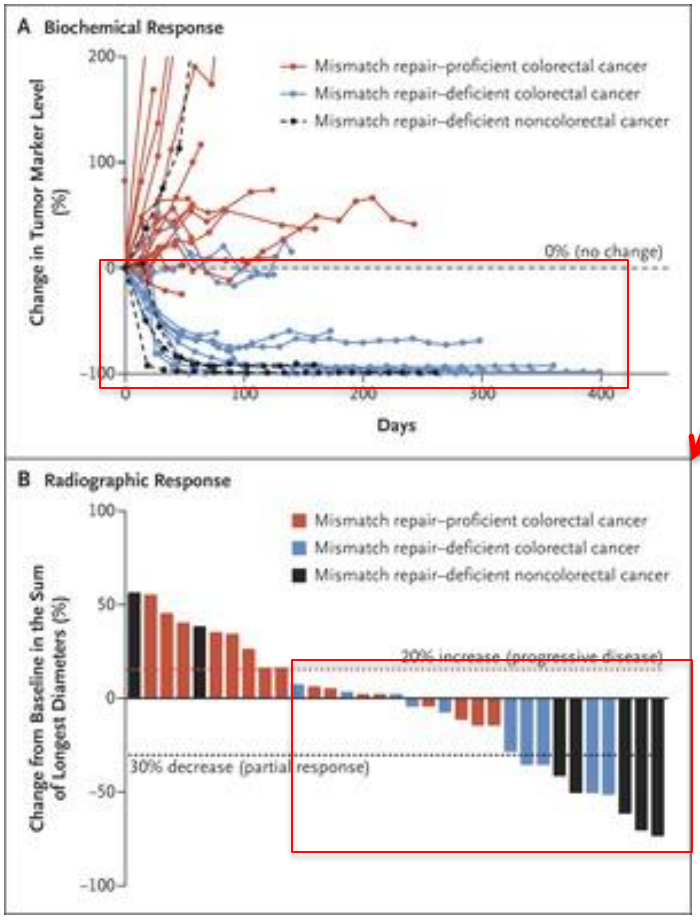
A regulator's perspective on the MSI-H/MMRd tissue agnostic approval of pembrolizumab

ASCO 2015 (Study KN016)



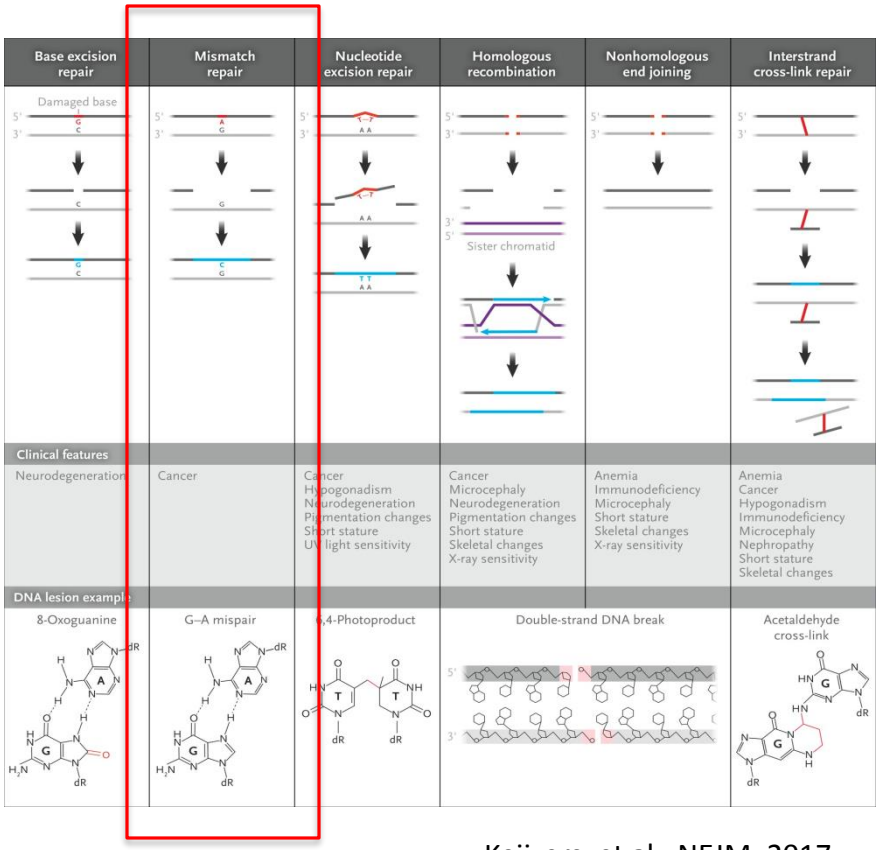
adapted from Le et al., NEJM, 2015

- irORR (Le et al., 2015)
  - 4 of 10 (CRC)
  - 7 of 9 (non-CRC)

- GI oncology monotherapy approvals:
  - Regorafenib (CRC) - 2012
  - Ramucirumab (gastric) - 2014
  - TAS-102 (CRC) - 2015

Mismatch repair deficiency (dMMR):

Usually results in microsatellite instability



Keijzers, et al., NEJM, 2017

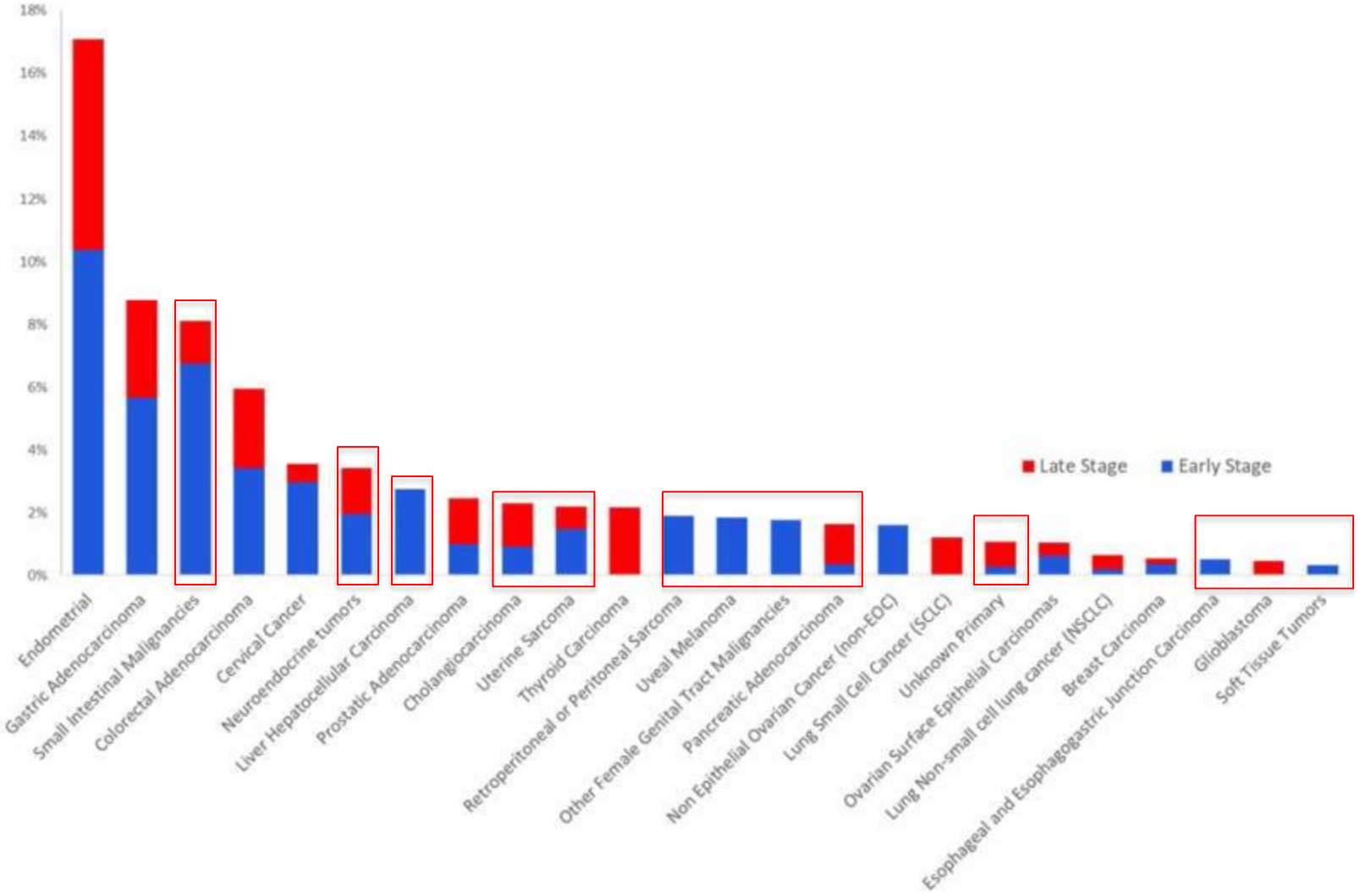
- Causes of dMMR:
  - Mutation in DNA repair proteins
    - e.g., Lynch syndrome
  - Inactivation of DNA repair proteins
- (usually) diagnosed with IHC

Microsatellite Instability (MSI-H)

Measurable "phenotype" of dMMR

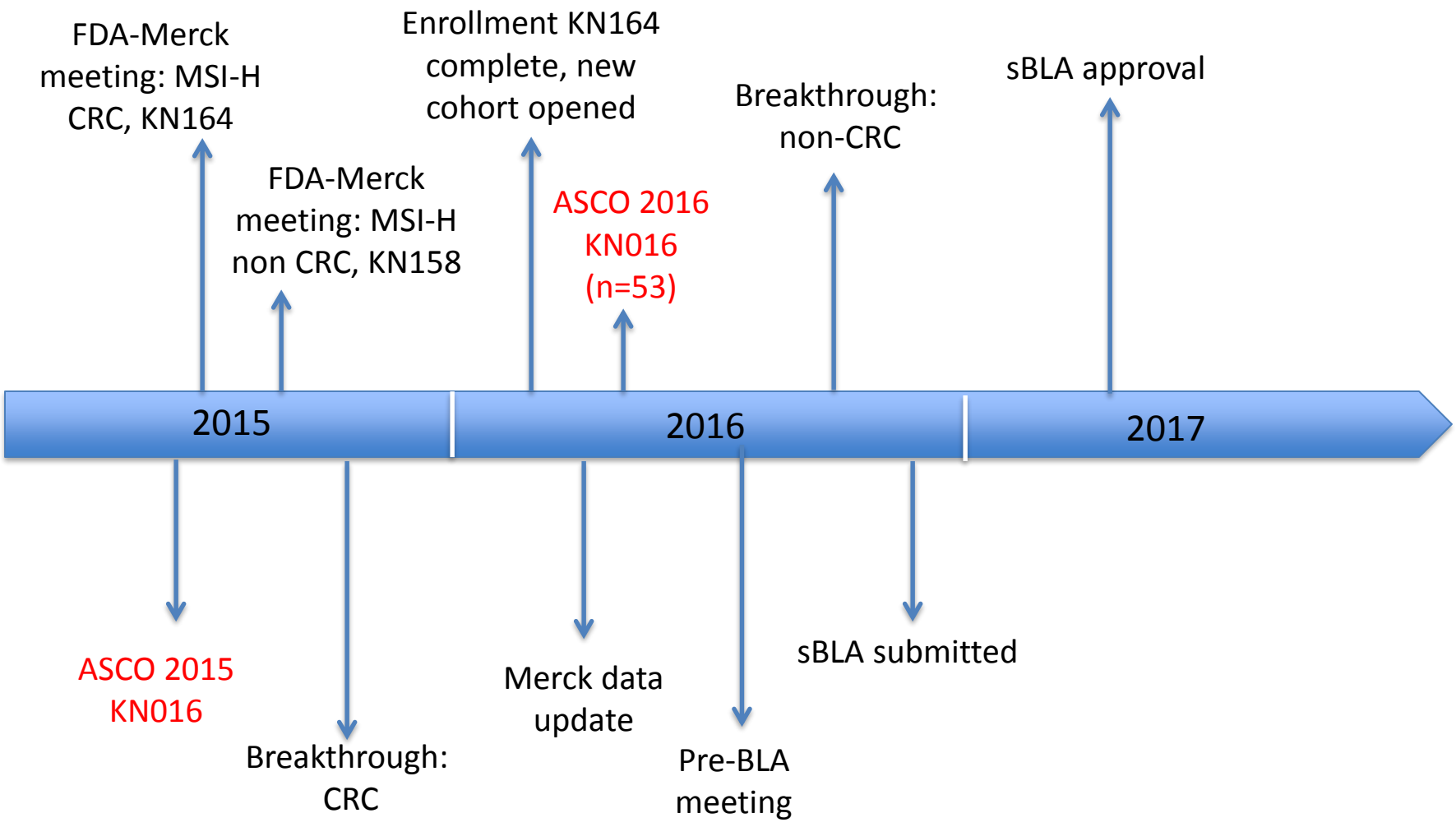
- Microsatellite = short repeats of DNA
- Length variable from person to person
- MSI can occur with spontaneous gains or loss of nucleotides in microsatellites
- Detect with PCR or NGS
- MSH-H associated with increased tumor-mutation burden

MSI-H in different tumor types



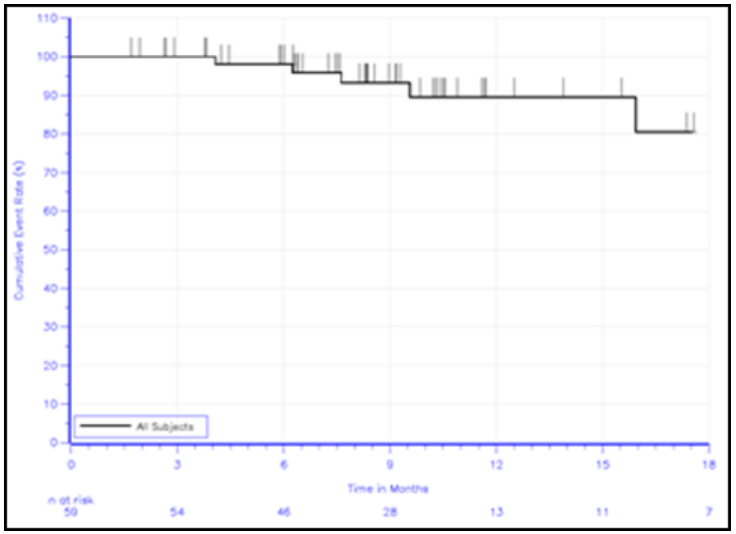
Le et al., Science 2018

(Partial) development timeline



Background: data supporting pembrolizumab MSI-H/dMMR approval

	N	ORR N (%)	95% CI
CRC	**90**	**32 (36%)**	**(26, 46)**
Non-CRC	**59**	**27 (46%)**	**(33, 59)**
Endometrial	14	5 (36%)	(13, 65)
Biliary	11	3 (27%)	(6, 61)
Gastric/GEJ	9	5 (56%)	(21, 86)
Pancreatic	6	5 (83%)	(36, 100)
Small Int.	8	3 (38%)	(9, 76)
Breast	2	PR, PR	
Prostate	2	PR, SD	
Bladder	1	NE	
Esophageal	1	PR	
Sarcoma	1	PD	
Thyroid	1	NE	
Retroperitoneal	1	PR	
SCLC	1	CR	
RCC	1	PD	



KM-DOR in 59 responding patients

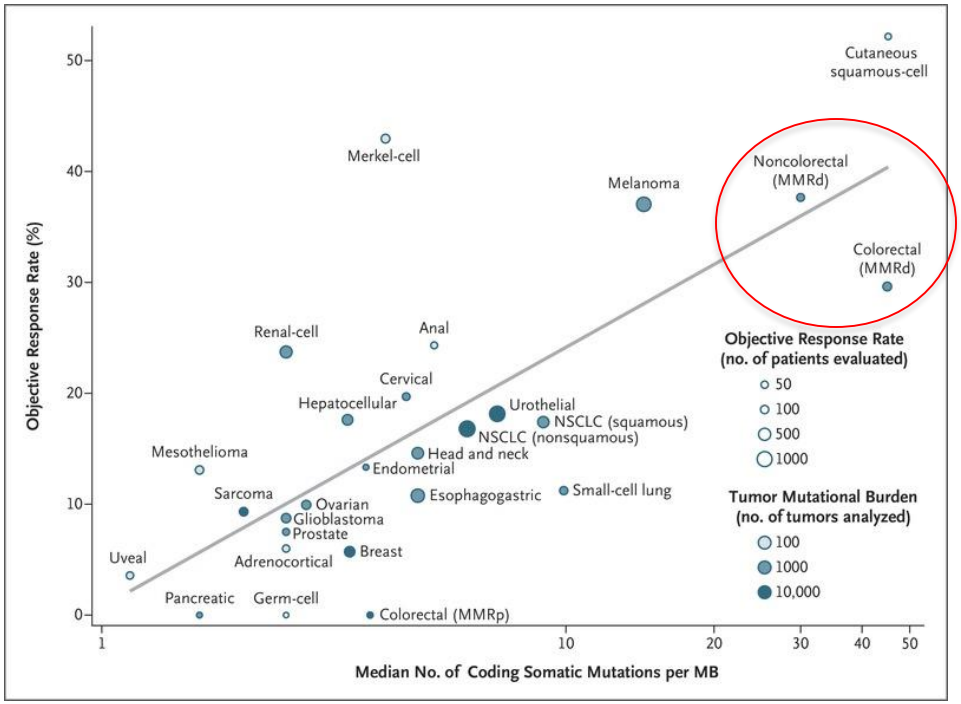
At time of approval, responses observed in *at least* 14 MSI-H/dMMR tumor types; many ongoing

Source: Keytruda labeling, BLA submission, FDA review documents

Pembrolizumab MSI-H approval considerations

- Biology
- Clinical data
- Approved for patients without available therapies (unmet need)
- Post-approval requirements

ORR vs. TMB



Adapted from Yarchoan et al., NEJM 2017

Unique TA development considerations

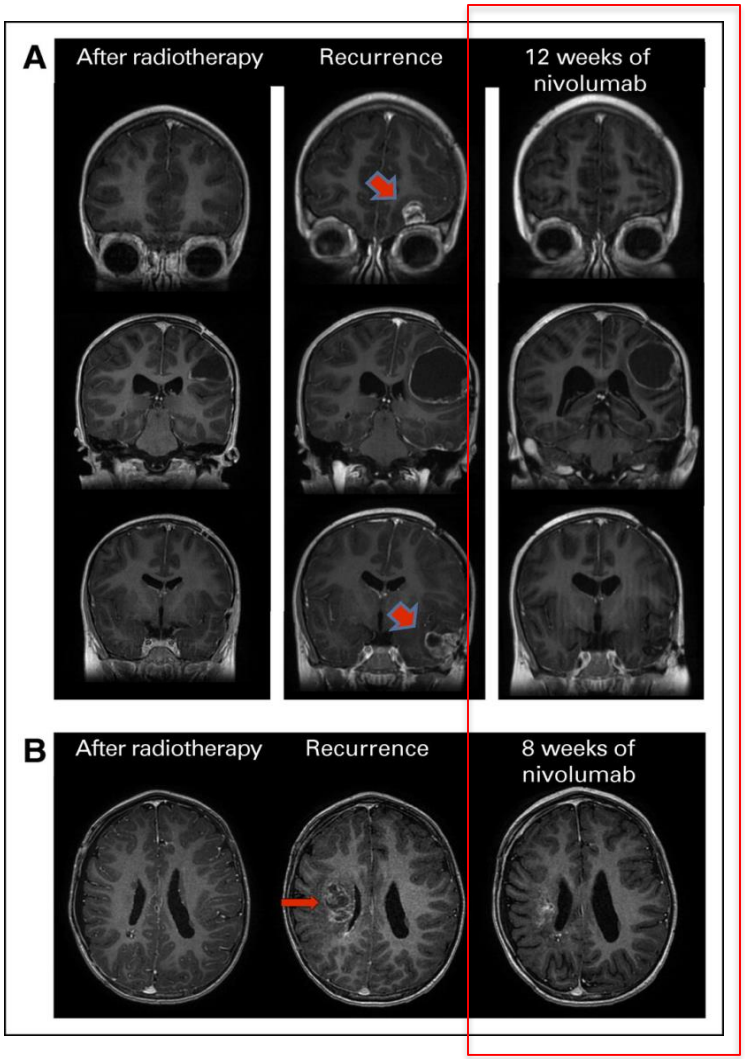
1. Pediatrics
2. In Vitro Diagnostic Devices (IVD)
3. Disease vs. indication
4. Drug development considerations

Pediatrics

Examples of biomarker-positive tumors in children

- MSI-H/MMRd (CMMRd-related cancers)
- NTRK-fusion (infantile fibrosarcoma, papillary thyroid, mesoblastic nephroma)
- ALK-fusion (lymphoma, myofibroblastic tumors)
- ROS-1 (myofibroblastic tumors)

Anti-PD-1 in congenital mismatch repair deficiency (CMMRd)



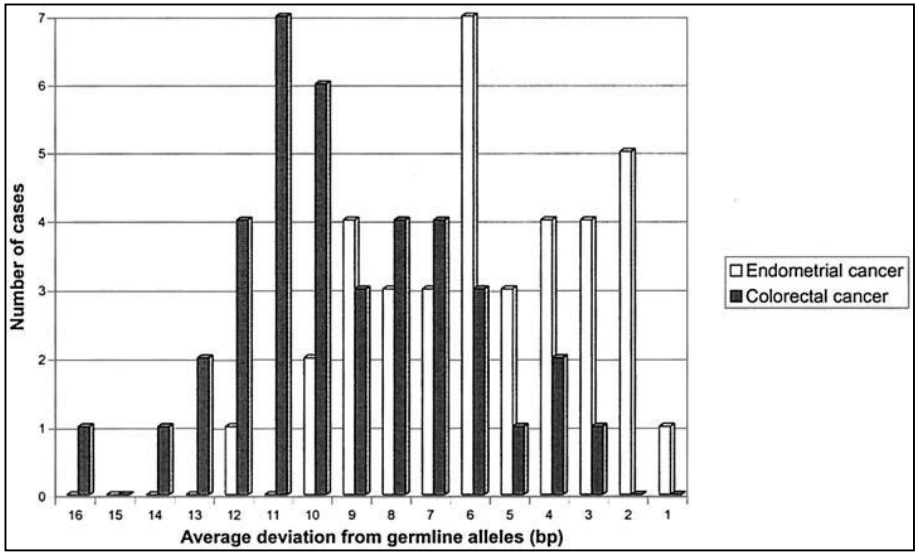
- Although rare, patients potentially can benefit
  - Risk of CNS swelling (T2 flair images) in high-grade GBM
  - Limitation of use and PMR for pediatric CNS tumors

Adapted from Bouffet et al., JCO, 2016 (gadolinium enhanced T1 sequences)

Tissue agnostic IVD considerations

- Pembrolizumab
  - Clinical experience with IHC/PCR testing
  - PMCs for IVDs
- Assess performance across tumors
- Is more than one device desirable, e.g.?
  - NGS for rare biomarkers
  - IHC (or other) if high prevalence

MSI testing CRC vs endometrial



Kuisman et al., Am J Path, 2002

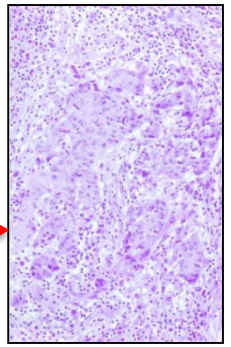
- Differences in allelic shifts in CRC vs. EC in certain BAT markers
- May influence sensitivity of PCR

Is MSI-H/MMRd a new disease state?

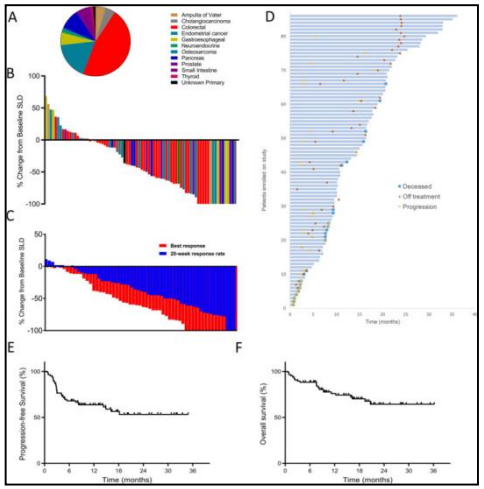
Arguments for MSI-H as one disease

MSI-H tumors share

- Histological characteristics, e.g.,
  - Lymphocytic infiltration
  - Medullary-type patterns
- Increased TMB, and
- Response to checkpoint inhibition



Alexander et al., Am J Pathol. 2001



Le et al., Science, 2017

Arguments against a tissue agnostic indication as a single disease

- MMRd not only molecular finding
  - Other oncogenic aberrations may differ in different cancers

- Differences in natural history, e.g.,
  - FOLFOX
    - A treatment for colon cancer
    - Unlikely to be effective for GBM
  - NTRK-positive infantile fibrosarcoma ≠ NTRK-positive NSCLC

Development / Regulatory Considerations

- Uncertainty regarding effects on different tumor types
- Could impact trials of the drug in non-biomarker selected patients
- FDA has used principles of TA development to support non-TA approvals
- Other

FDA applied principles of TA development to BRAF/MEK inhibitors

- NSCLC (D+T), n = 93
- Anaplastic thyroid cancer (D+T), n = 23
- Erdheim-Chester Disease (V), n = 22

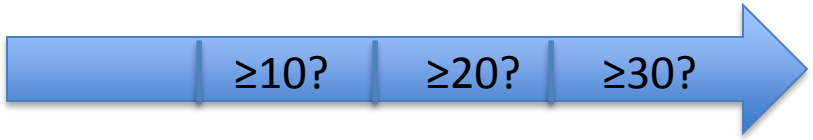
Tissue Agnostic Development Considerations

- Randomized controlled trials in rare biomarker (+) tumor types with unprecedented effects on response
  - May not be feasible
  - Probably not ethical in refractory setting
- For pembrolizumab, ↑ survival or PFS in other cancers with similar response rate and high mutation burden, e.g.,
  - Melanoma
  - NSCLC

Future challenges with TA development (what if biomarker is quantitative?)

How to define an indication with a quantitative biomarker?

TMB (how many mutations per megabase?)



How will different IVD CDx's classify patients?

IVD#1: TMB = 22 mut/Mb

IVD#2: TMB = 16 mut/Mb

……but the preferred anti -PD-1 on formulary is approved for a TMB of 18 mut/Mb *with IVD#3*

Other challenges

Drug combination Trials?

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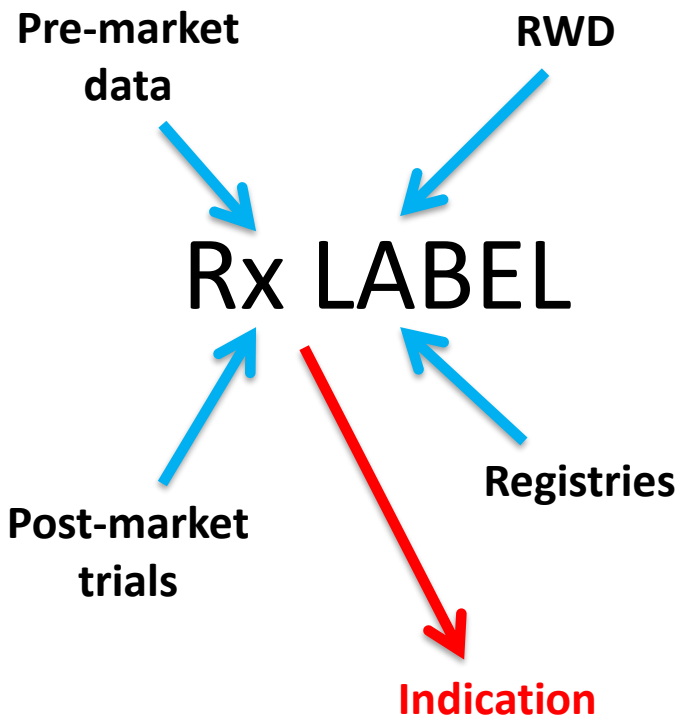
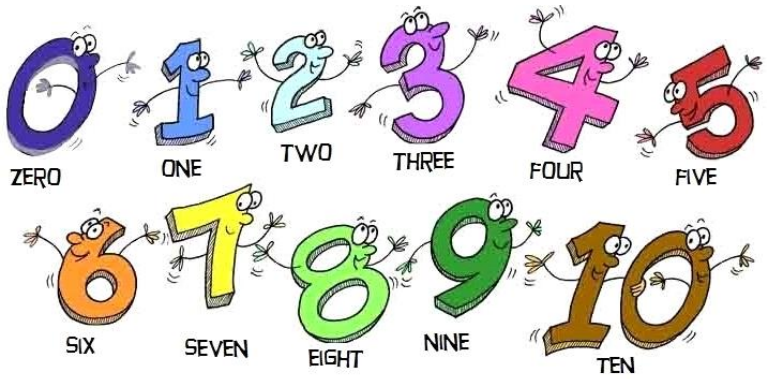
Product Labeling?



Other Questions

How many tumors???



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Different pathways?

- Fast Track
- Breakthrough
- Accelerated approval

Unmet Need

How will TA approval impact development for biomarker negative populations?

e.g., should patients with “neo-antigen” positive tumors be excluded from clinical trials of single agent checkpoint inhibitors?

- If not, how to assess whether an effect is driven solely by biomarker-positive population?
- At a minimum, the biomarker should be identified in these trials.
- What if the investigational drug was a cytotoxic drug or a multi-target TKI?
  - Presence of the biomarker may not matter

Hypothetical Example

- ORR in biomarker "+" tissue agnostic population = 50%
- How to consider results or design of randomized trials in a single cancer type (non-biomarker selected) with
  - ORR of 1% in biomarker negative group
  - ORR of 5% in biomarker negative group
  - ORR of 10%, in biomarker negative group, etc.
- *And* a biomarker "+" incidence rate in that cancer type of
  - 1%
  - 5%
  - 10%
  - 30%, etc.

Summary

The TA approval of pembrolizumab

- Facilitated faster access for patients with unmet need
- Was granted without every tumor type being studied
  - Including children
  - Post-marketing data forthcoming
- Was granted without a companion in vitro diagnostic device
  - PMCs
- Created new opportunities *and* challenges

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