Biomarker Development and Optimization

dMMR/MSI-H and TMB-H Tissue Agnostic FDA Approvals for KEYTRUDA® (pembrolizumab)

Sid Mathur
Merck & Co., Inc., Rahway, NJ, USA

Ingredients enabling tissue agnostic drug development paradigms

Advances in diagnostic technology

Advances in drug development

Legislative support

Industry willing to take more risk

Surrogate Endpoints

Strong/innovative leadership from regulator

Patient Advocacy groups

Timeline for tissue-agnostic FDA approvals for pembrolizumab

May 2017

KEYTRUDA MSI-H/dMMR tissue agnostic approval

June 2020

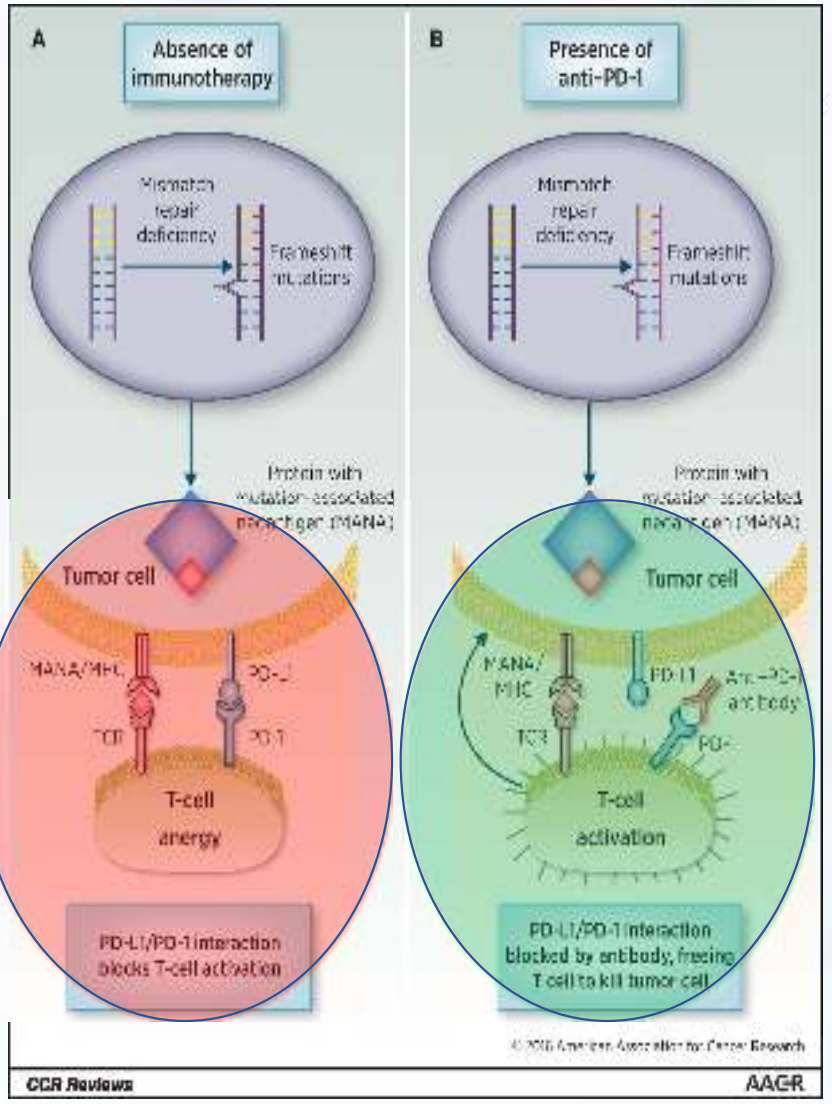
KEYTRUDA TMB-H tissue agnostic approval

MSI-H phenotype may confer responsiveness to PD-1 inhibition independent of histology

- PD-1 is an antigen expressed on the surface of activated T-cells and interacts with its ligands PD-L1 and PD-L2 expressed on cancer and surrounding cells. This inhibits activation of T lymphocytes and prevents an anti-tumor immune response

PD-1 blockade reactivates T cells to attack and kill cancer cells

- 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



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

Key aspects of FDA review

- Whether the presence of MSI-H/dMMR represents a unique biomarker that predicts response to pembrolizumab and is consistent in this predictability across tumor types
  - MSI-H/dMMR patients have higher tumor mutational burden. Higher ORR in MSI-H versus MSS patients was not due to PD-L1 expression differences between the MSI-H I and MSS states. Mutational load/MSI-H I appeared to be independent of inflammation or PD-L1 expression
  - In pooled dataset of 149 patients across 5 trials and 15 different tumor types, ORR was 39.6% (95% CI: 31.7, 47.9) with 78% of responding patients experiencing a DOR of more than 6 months. ORR was similar among CRC patients [ORR 36% (95% CI: 26, 46) and non-CRC patients [ORR 46% (95% CI: 33, 59)]
- Whether one or more companion diagnostic devices were required to select the indicated patient population in order to ensure safe and effective use of pembrolizumab
  - Local MSI/MMR testing was used to enroll majority of patients in the trials. While in certain tumors where pembrolizumab was already approved (e.g., lung, melanoma), MSI-H/dMMR testing may not be essential, in others like pancreatic cancer or CRC, accurate MSI/MMR testing was key to identify patients for pembrolizumab treatment versus alternates. For a tissue agnostic indication, it was determined that having accurate and reproducible tests in clinical practice was needed. At the time of pembrolizumab approval, 2 post-marketing commitments to develop CDx tests were issued
- Other items: Evaluation of efficacy consistency based on pembrolizumab dosage regimens as well as extrapolation of efficacy results to pediatric patients with MSI-H cancers

TMB-H as tissue-agnostic biomarker
No standardization existed for calling TMB-H

There are other mechanisms to generate high mutational load beyond loss of DNA MMR function. Therefore, limiting pembrolizumab tissue agnostic approval to patients with MSI-H/dMMR tumors would potentially leave patients behind

- For any biomarker that is a continuous variable, like TMB, a cutoff is needed for that biomarker to be used to select patients for treatment
- There was no standard definition of a TMB-H patient at the time of the MSI-H/ dMMR approval
- FDA wanted to avoid the confusion that arose with PD-L1 IHC when multiple PD-1/PD-L1s were approved with different CDx IHC assays with different cut-points, different clones, etc.
- A harmonized cutoff was needed to develop a TMB-H CDx

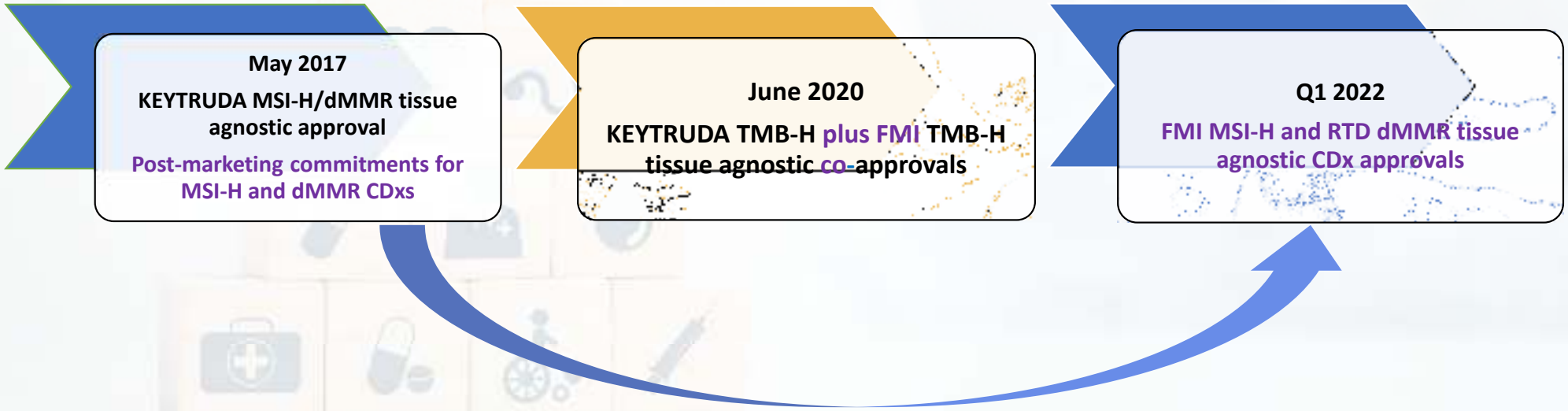
Previous MSD experience: PD-L1: data driven, but decision made within company – e.g., TPS≥1%, TPS ≥50%, CPS ≥1

Approach to defining a TMB-H cutoff

- A three-part approach for selection of a pan-tumor TMB-H cutoff was defined in discussions with FDA:
  1. Examination of **biological data** (relationship between TMB and inflammation in the TME), independent of a particular anti-PD-1 agent or associated response data
  2. **Balance enrichment** across histologies while capturing a meaningful portion of the responders (**sensitivity**)
  3. **Harmonization** with FOCR, pharma and diagnostics around a single TMB cutoff value for pursuit of a tissue-agnostic indication

MSD

Timeline for tissue-agnostic Rx and CDx approvals



Challenges: Developing an MSI-H algorithm that works across tumors

- During MSI-H pan tumor CDx development, FMI MSI caller went through a significant update - changed from Principal Component Analysis to Fraction-Based
- Update allowed F1CDx to support tissue agnostic indication, whereas it was previously optimized for CRC and endometrial carcinoma

- During this time, analytical and clinical validation for the MSI-H CDx were paused
- FMI and MSD collaborated on cutoff development, utilizing tumor bank samples (independent of CDx AV/CV samples). Cutoff was selected using an orthogonal PCR based method, developed on training set(s) and confirmed using test set(s)

Challenges: Establishing clinical validation for MSI-H/dMMR tissue-agnostic CDx submissions

Studies leading to Rx approval	Studies with samples available for CDxs
KEYNOTE-016	X
KEYNOTE-164	KEYNOTE-164
KEYNOTE-012	X
KEYNOTE-028	X
KEYNOTE-158	KEYNOTE-158

- There was a high proportion of missing data for both CDxs (~63%). This was due to:
  - Not all clinical samples were available for CDx testing (e.g., samples not available or lack of consent for retrospective MSI/MMR central testing)
  - A significant number of non-evaluable MSI/MMR CDx results due to aspects like cut-slide stability of samples for IHC assessment and sample quality/QC criteria for NGS assessment
- Robust imputation analyses were conducted as sensitivity analyses to account for missing or non-evaluable MSI/MMR CDx data in the 2 CDx submissions

Things to consider for future development

- Utilizing a centralized (CDx) test in the clinical trial may help obtain homogeneous biomarker assessments as well as help develop a standardized test that can be quickly deployed commercially upon drug approval
- There may be instances where due to unmet medical need and certain factors*, local testing may be preferred in the trial
  - In such cases, it is advisable to retain clinical samples (including screen fails if applicable) for bridging studies needed to develop CDx and to define certain minimum parameters labs needs to follow
- Tissue agnostic indications need extensive analytical validation which can take longer if the biomarker has low prevalence
- Teams should consider the impact of the new EU IVD regulation (IVDR) on choice of assay(s) used (e.g., in-house tests or centralized test(s)) in the trial and impact to timelines and resources
  - In-house tests are exempt from IVDR if they follow Article 5(5) exemptions
  - Centralized test may need to obtain approval (if used in trial for medical management, e.g., patient selection) from member states before being used in the trial
- Obtaining regulator feedback in EU may be challenging for diagnostic development and validation

*e.g., availability of local testing coupled with central testing solution not being ready/available for trial initiation

Thank you

Cause and effect of microsatellite instability