# Biomarker Development and Optimization
## dMMR/MSI-H Tissue Agnostic FDA Approval

## Industry Perspective

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# Regulatory Considerations

- FDA  draft guidance for industry, “Tissue Agnostic Development in Oncology”, is the first to be issued by a health authority.
- EU guidance or guidance from any other health authorities on tissue agnostic development in oncology is currently not available.
- FDA guidance is based upon scientific concepts and FDA experience in review of tissue agnostic indications.
- Some concepts may be applicable for global tissue agnostic development.

# FDA Draft Guidance for Industry "Tissue Agnostic Development in Oncology" Issued October 2022

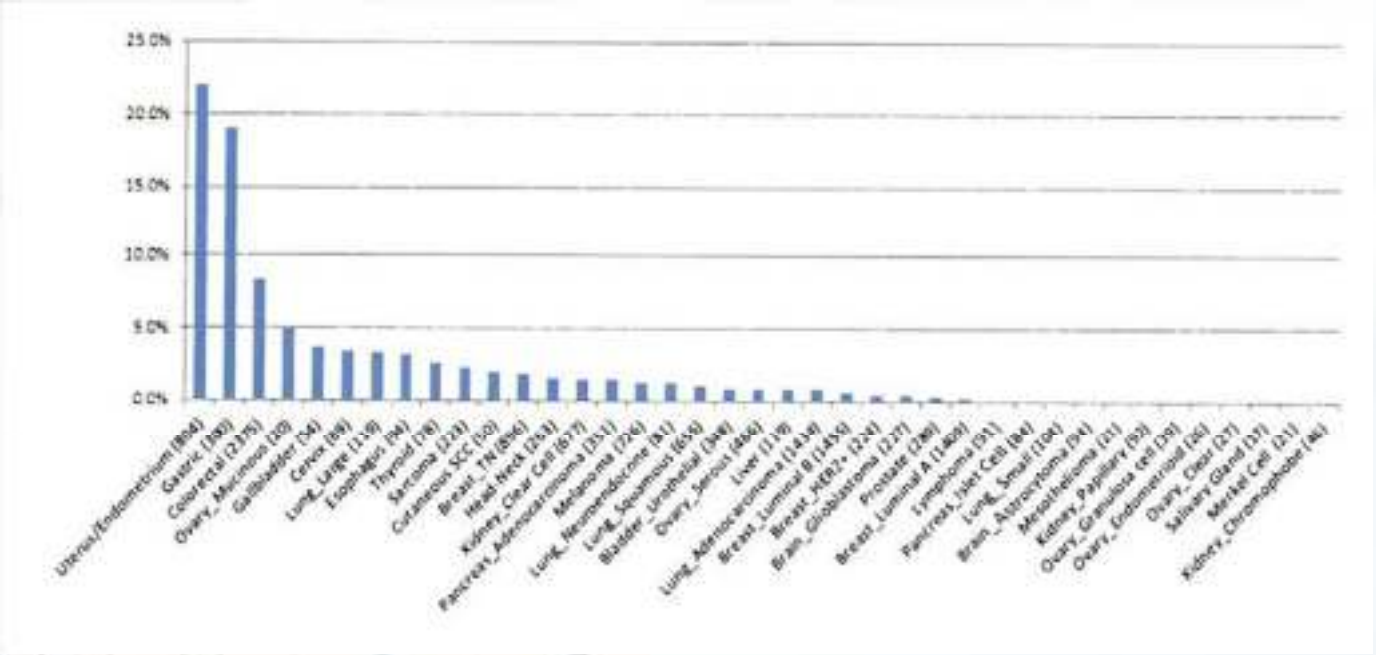
- Tissue agnostic drug development in oncology:
- Increased understanding of oncology disease pathways enables tissue agnostic drug development.
- Knowledge of biology of cancer and response to the drug necessary for effective tumor agnostic program.
- Tissue agnostic development can target:
  - Intrinsic alterations or receptors: NTRK (neurotropic receptor tyrosine kinase)
  - Factors extrinsic to the cancer: tumor microenvironment

# Considerations for Tumor Agnostic Development

## Pembrolizumab FDA 2017 approval for Unresectable/Metastatic MSI-H/dMMR Tumors

- **Understanding of biology and drug mechanism of action**
- DNA mismatch repair pathway previously (MSI-H/dMMR) characterized in colon cancer and Lynch syndrome.
- High mutations/MSI-H had been identified in other tumors
- Natural history information available for some MSI-H tumors
- Link demonstrated between MSI-H and response to checkpoint inhibitors
- MSI-H/dMMR appears in various solid tumors
  - Prevalence varies-highest prevalence endometrial, GI, colorectal tumors

# Prevalence of MSI-H Differs Across Tumors



# FDA Draft Guidance for Industry "Tissue Agnostic Development in Oncology" Points to consider

- May be necessary to generalize treatment effect in some tumors based upon data to tumors with lower prevalence of same molecular alteration.
- Assess potential differences in response across tumor types with same molecular alteration.
- Dose justification may be required. Some tumor types could require dose adjustment for specific toxicity: i.e. drug with hepatoxicity may require lower dose for HCC in tumor agnostic indication.
- Single-arm tumor agnostic studies may be acceptable to support approval for patients with advanced or metastatic cancers if results are clinically meaningful.
  - Randomized trials challenging due to differences in standard-of-care control arms across tumor types.
- FDA postmarketing requirement for MSI-H tumor agnostic accelerated approval: Expand same KN158 single-arm study with additional patients, including with tumors of lower frequency; 25 children and duration of response for at least 12 months.

# Tumor Types/Population Selection

- Study subjects with MSI-H/dMMR in various solid tumors enrolled in multi-tumor “basket studies”.
- FDA guidance states that patients with high prevalence of biomarker tumor be studied in adequate numbers to describe the treatment effect.
  - Pembrolizumab MSI-H study had highest representation of colorectal tumors, followed by endometrial and GI tumors.
    - Several MSI-H CRC-only studies included, increasing representation.
- ORR was similar across tumor types-Allowed for generalizability to lower prevalence MSI-H/dMMR tumors.
- Pembrolizumab had well-characterized safety profile: No dosing restrictions for different tumors.

# FDA Draft Guidance for Industry "Tissue Agnostic Development in Oncology

- Clinical Trial Considerations:
- Contemporaneous development of tumor agnostic indication with separate development program for a specific tumor type requires consideration of how inclusion of molecularly alteration-positive subjects in tumor-specific results would impact efficacy.
  - Example: MSI-H/dMMR tumor agnostic and MSI-H colorectal cancer.

# Issues to Address for Future Tumor Agnostic Development

- Nonclinical pharmacology studies should include cell lines from cancers of different origins.
- No need to conduct nonclinical studies in all tumors considered for the tumor agnostic development program.
- May be possible to supplement nonclinical pharmacology studies to support FIH with nonclinical or clinical data from different drugs studied in tumors with same molecular alteration.
- Subject selection for clinical development can be guided by initially studying the drug in smaller subgroup(s) of the population or by excluding certain subgroups.
- Studies should enroll patient population with sufficient representation of tumor types.
- Pediatric development should be included with tissue agnostic programs.
- ICH guidance should be followed as appropriate for all stages of the tumor agnostic development program.

# Diagnostic Considerations

- Molecular alterations may vary in complexity from simple genetic alterations or complex phenotypic alterations such as for MSI-H tumors.
- Accurate and reliable tests are necessary for identification of patients irrespective of tumor type.
- FDA and other health authorities may require a companion or complementary diagnostic that may differ from the test used to screen and enroll patients.
- A tissue agnostic companion diagnostic should provide sufficient evidence of test performance across a number of tumor types.
- Postmarketing commitments for diagnostic development may be imposed.

# Thank you