2021 3Q Areas of Interest for Pembrolizumab

- **Pembrolizumab in combination with an investigational agent(s). Innovative doublet or triplet combinations will be considered.**

2021 1Q Areas of Interest for Pembrolizumab

Bladder Cancer

Early Stage:

- Pembrolizumab combinations, including standard of care, chemotherapy, or novel agents, with strong biological and clinical rationale and have established safety:
    - for the treatment of both intermediate risk and high risk NMIBC including patients with varying prior exposure to BCG;
    - for BCG-intolerant patients or patients unable to receive BCG
    - bladder preservation strategies in MIBC
    - that potentially address pembrolizumab response or resistance pathways;
    - includes upper tract tumors;
- Incorporation of novel biomarker or translational strategies*

Late Stage:

- Pembrolizumab combinations that potentially address resistance pathways
- Incorporation of novel biomarker or translational strategies*
- Maintenance strategies

Breast Cancer

- Use of pembrolizumab after progression on prior PD-1/L1 inhibitor or other I/O
- Novel pembrolizumab combinations, such as with other I/Os, ADCs, TKIs, etc. (excluding adjuvant)
- Studies in clinically relevant biomarker subsets*

Colorectal Cancer

- Metastatic MSI-H or MSS colorectal cancers: pembrolizumab novel combinations (excluding chemo-only combinations, RT only combinations, or VEGF only combinations) with strong scientific/pre-clinical rationale, including groups with previous I/O exposure
- Locally advanced or metastatic rectal cancers: studies of pembrolizumab single agent or with novel combinations, including biomarker-defined groups
- Locally advanced or metastatic anal cancers: studies of pembrolizumab single agent or with novel combinations, in clinically relevant biomarker subsets, including but not limited to HPV.

GI/ Gastric Cancer

Esophageal and Gastric Cancer (Highest interest in MSS tumors)

- Pembrolizumab combination therapy, including novel agents, with strong biological and clinical rationale that potentially address resistance pathways:
    - In a neo-adjuvant/ adjuvant setting
    - Metastatic/ locally advanced disease
    - Previous IO exposure
    - HER2+ disease setting
- Incorporation of novel biomarker or translational strategies*
- Exploration and optimization of drug sequencing with pembrolizumab
- Innovative trial designs, consider risk stratification for relapse in the adjuvant setting where appropriate, utilizing novel biomarkers or assays

Pancreatic Cancer

- Pembrolizumab combinations with chemotherapy or novel agents, with strong biological rationale and pre-clinical evidence of activity in murine models. Evidence of acceptable safety profile for these combinations is recommended
- Innovative trial design for earlier stages of disease is of interest, including novel surrogate endpoints of efficacy, and novel assay development (ctDNA, liquid biopsy, etc.)
- Incorporation of novel biomarker or translational strategies, especially in metastatic disease*

Gynaecological Cancers

Ovarian cancer

- Combination therapies in recurrent ovarian cancer including novel investigational agents
- Particular interest in post IO / post PARPi
- Rare histologies
- Incorporation of novel biomarker or translational strategies including for monitoring response to treatment*

Cervical cancer

- Combination therapies in recurrent cervical cancer including novel investigational agents
- Rare histologies
- Pembrolizumab combinations including IO naive and IO refractory
- Incorporation of novel biomarker or translational strategies including for monitoring response to treatment*

Endometrial cancer

- Combination therapies in recurrent endometrial cancer including novel investigational agents
- Rare histologies
- Pembrolizumab combinations including IO naive and IO refractory
- Incorporation of novel biomarker or translational strategies including for monitoring response to treatment*

Vulvar cancer

- Combination therapies including novel investigational agents

Hematological Malignancies

Classical Hodgkin's Lymphoma

- Pembrolizumab monotherapy/combinations as maintenance (consolidative therapy) post Autologous Stem Cell Transplant
- Pembrolizumab as monotherapy or in combination in relapsed patients
- Pembrolizumab in combination in PD-1 refractory patients

Non-Hodgkin's Lymphoma

- Novel pembrolizumab containing combinations with non-chemotherapy agents in frontline and relapsed/ refractory settings in Diffuse Large B-Cell Lymphoma, Primary Mediastinal B-Cell Lymphoma, and Follicular Lymphoma
- Pembrolizumab in combination with cell therapy

Multiple Myeloma

- Novel pembrolizumab containing (no IMiD or carfilzomib) combinations with focus on bispecific Antibodies, Antibody-Drug Conjugates or new mechanisms of action in the relapsed/refractory setting

Head & Neck Cancers

Recurrent/Metastatic HNSCC

- Novel combinations in R/M HNSCC
    - Including PDL-1 negative populations
- Novel strategies after progression on anti-PD-1/PD-L1 (IO refractory)

- Studies focused on underrepresented populations in clinical trials (e.g. race, ethnicity)

Locally Advanced HNSCC

- Neo-adjuvant pembrolizumab + chemotherapy or novel combination in salvage surgery setting for recurrent HNSCC
- De-escalation strategies in locally advanced disease
    - Including HPV+ oropharynx cancer (OPC)
- Pembrolizumab + chemotherapy as induction therapy for LA HNSCC
- ChemoRT followed by adjuvant pembrolizumab in LA HNSCC (combination therapies + sequencing)
- Studies focused on underrepresented populations in clinical trials (e.g. race, ethnicity)

Nasopharyngeal Carcinoma

- Novel combinations with pembrolizumab + chemotherapy in EBV-associated NPC

Salivary Gland and Thyroid Carcinomas

- Novel strategies in combination with pembrolizumab in salivary gland and thyroid carcinomas

Hepatobiliary Cancers

Hepatocellular Cancers

- Neoadjuvant studies in early stages of HCC
- Strategies to improve pembrolizumab efficacy in advanced HCC including:
    - Uncommon subtypes
    - I/O refractory
    - Evaluate predictors of response to I/O (blood-based markers, imaging, etc.)*
- Child Pugh B group with pembrolizumab combinations (excluding TKI)
- Sequencing of therapy in advanced disease

Biliary Cancers

- Pembrolizumab combinations in preselected molecular subsets (including but not limited to IDH, FGFR, HER-2)
- Neoadjuvant/adjuvant studies in early stages of biliary cancer
- Strategies to improve pembrolizumab efficacy in advanced biliary cancer including
    - Uncommon subtypes
    - Evaluate predictors of response to I/O (blood-based markers, imaging, etc.)*

Thoracic Malignancies

NSCLC

- Novel neoadjuvant combinations
- Novel combinations in IO pre-exposed patients
    - I/O, I/O combinations, ADC combinations
    - Overcoming specific mechanism of resistance (e.g. LKB-1)
    - I/O exposed in the adjuvant and neoadjuvant setting
- Novel combinations in mutation driven patients
    - Novel TKI +pembrolizumab for non-EGFR, non-ALK mutation driven patients including KRAS mutant and others
    - Novel combinations with targeted ADC's (e.g. HER2, cMET) and T-cell engagers
- Novel combinations in 1L NCSLC including chemo free combinations in different biomarker subgroups (Leverage knowledge of tumor microenvironment to inform biologically rationale combination strategies)

SCLC

- Novel combinations in 1L
    - Determining mechanisms to improve response and outcomes in 1L based on biology of disease *or* with the use of novel markers such as ctDNA*
    - Determining mechanisms of resistance
    - Determining approach to treatment in setting of brain metastases
- Novel combinations in I/O pre-exposed patients

Mesothelioma

- Novel combination in 1L and in 2L I/O naive
    - Determining mechanisms to improve response and outcomes
- Novel combinations in I/O pre-exposed patients

Melanoma

- Novel combinations for patients with high-risk melanoma, with emphasis on those with a detailed/described mechanism. Examples include, but are not limited to:
    - PD-1/CTLA-4 resistant/refractory patients
    - Mucosal/Acral melanoma
    - Uveal melanoma
    - Brain metastases
- Neoadjuvant/adjuvant therapy
- Real world data on treatment patterns and outcomes in patients excluded from clinical trials

Other Skin Cancers

- Novel combinations in Merkel cell carcinoma (including neoadjuvant)
- Advanced basal cell carcinoma

Innovative Strategies

- Pembrolizumab-based combinations in rarer tumor types with a high unmet medical need (primary brain tumors, sarcomas, neuroendocrine tumors and adrenocortical carcinomas remain a key focus for the program)
- Pembrolizumab + lenvatinib, pembrolizumab + olaparib, and innovative pembrolizumab combinations
- Proposals with a strong translational rationale/evidence or component (e.g. neoadjuvant)

Prostate Cancer

- Neoadjuvant or adjuvant studies of pembrolizumab as monotherapy and in combination (combinations including, but not limited to, novel immune modulating agents, including agonists and antagonists for TGFß, olaparib and nano-particle delivery therapeutics)
- Combinations in other lines of therapy, including but not limited to, oncolytic viral agents, radiation, PARP inhibition, and agents targeting the CDK-12 pathway
- Novel combinations of pembrolizumab for small cell / neuroendocrine-like differentiated disease
- Studies that include objectives to investigate biological mechanisms of pembrolizumab response or resistance
- Studies evaluating biochemical failure

Renal Cell Carcinoma

- Pembrolizumab combinations with novel mechanisms of action. Combinations of interest include but not limited to metabolic pathways, epigenetic pathways, targeting of the myeloid compartment and other emerging immune and non-immune pathways
- Pembrolizumab combination studies in patients with renal cell carcinoma regardless of histology, including patients with localized disease and advanced disease where the primary tumor is in situ
- Concepts in treatment naïve, as well as in patients who have received prior treatment (including IO/IO or IO/TKI combinations or sequenced treatment)
- Studies which include objectives to investigate biological mechanisms of pembrolizumab response or resistance

Preclinical

- Evaluation of PD-1 Pathway Mechanism of Action
    - Understand the mechanistic basis for response/resistance to anti-PD-1. There is particular interest in studies assessing:
        - Cell Types
            - Immune cells: B cells (investigation of the role of PD-1 signaling in the humoral response), gamma delta T cells, natural killer (NK) cells, antigen presenting cells, exhausted T cells
            - Associated cells: Fibroblast reticular cells (FRCs), cancer associated fibroblasts (CAFs)
            - Tumor cells: intrinsic mechanisms that provide sensitivity or resistance to PD-1 inhibitors
            - Cancer Stem Cells.
        - Pathways
            - Angiogenesis, hypoxia, epithelial-mesenchymal transition (EMT), antigen presentation and machinery, TGFbeta
            - Immune exhaustion vs. immune senescence as it relates to response to pembro and/or other cancer immunotherapies.
- Pembrolizumab combinations
    - Identify mechanisms of action associated with reported clinical response to anti-PD-1 combination treatment (reverse translational studies)
    - Targeting the tumor-stromal-immune cell axis:
        - Identify mechanisms of action that modulate the tumor stroma
        - Identify mechanisms of action that modulate vasculature to enhance immune cell trafficking
        - Mechanical and biophysical aspects of the tumor micro-environment
        - Evaluate the contribution of tumor intrinsic pathways to immune escape
        - Identify mechanisms of action that modulate immune suppressive cell function natural killer (NK) cells, B cells (including tumor resident B cells), myeloid cells (MDSCs, DCs, TAMs)

*Please note that IISP studies must have a clinical efficacy primary (or co-primary) endpoint

Critical Timelines:

- October 9, 2020: Post AOI to Engagezone
- December 7- January 19, 2021: Submission window for concept summary submission to US RMSD or oncmisp@msd.com
- February 5, 2021: Reviews due from PDT
- February 10, 2021: Concept summary reviews complete and all investigators notified
- March 10, 2021: Full concept submissions due
- March 24, 2021: Assignments sent to reviewers

- April 14, 2021: Concept reviews due
- April 27, 2021: Initial scoring results sent internally
- May 10-21, 2021: MISP review committee meetings
- June 2021: Final concept decisions