2022 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 with established safety profile:
- for the treatment of high risk and/or intermediate risk NMIBC including patients with varying prior exposure to BCG; or
- in PD-1/PD-L1 experienced patients; or
- in upper tract tumors; or
- for BCG-intolerant patients or patients unable to receive BCG

Late Stage:

- Novel pembrolizumab-containing combinations in patients with PD-1/PD-L1 refractory tumors
- Excluding pembrolizumab and VEGF/PDGFR TKI combinations
- Rechallenge strategies in patients previously exposed to PD-1/PD-L1 inhibitors in different disease settings

Breast Cancer

- Use of pembrolizumab in combination with novel agents after progression on prior pembrolizumab therapy in advanced TNBC (excluding adjuvant)
- Novel pembrolizumab combinations, such as with other IOs, ADCs, TKIs, etc. excluding CDK4/6 inhibitors in HR+
- Studies in clinically relevant biomarker subsets*

Colorectal Cancer

- Metastatic MSI-H -CRC Tumors:
- Pembrolizumab novel combinations in treatment naïve and those exposed to prior IO therapy
- MSS colorectal cancers: pembrolizumab novel combinations with strong scientific/pre-clinical rationale, including groups with previous IO exposure
- Excluding chemo-only combinations, RT only combinations, or VEGF only combinations
- Novel strategies to help identify responsive sub-groups of MSS mCRC that are more likely to respond to pembrolizumab based combination therapy
- Locally advanced or metastatic rectal cancers: studies of pembrolizumab single agent or with novel combinations, including translational strategies to identify responsive subgroups.
- Locally advanced or metastatic anal cancers: studies of pembrolizumab single agent or with novel combinations.

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:
- Metastatic/locally advanced disease
- Previous IO exposure
- HER2+ disease setting

Pancreatic Cancer

- Pembrolizumab combinations with chemotherapy or novel agents, with strong biological rationale and pre-clinical evidence of activity in preclinical models. Evidence of an acceptable safety profile for these combinations is recommended.
- Incorporation of novel translational strategies in metastatic disease*

Gynaecological Cancers

Ovarian cancer

- Pembrolizumab combination therapies in recurrent ovarian cancer including novel investigational agents
- Particular interest in post IO/post PARPi
- Rare histologies may be considered if not already addressed by our company programs

Cervical cancer

- Pembrolizumab combination therapies in locally advanced/metastatic/recurrent cervical cancer including novel investigational agents
- Rare histologies may be considered if not already addressed by our company programs
- Therapeutic vaccines in combination with pembrolizumab may be considered if not already addressed by our company programs
- Pembrolizumab combinations including IO naive and IO exposed

Endometrial cancer

- Pembrolizumab combination therapies in locally advanced/metastatic/recurrent endometrial cancer including novel investigational agents
- Rare histologies may be considered if not already addressed by our company programs
- Pembrolizumab combinations including IO naive and IO exposed (including post-pembrolizumab/lenvatinib)
- Pembrolizumab combinations in the neoadjuvant setting for endometrial cancer

Hematological Malignancies

- Pembrolizumab monotherapy in unfit and/or elderly patients
- Pembrolizumab in combination with cellular therapy or as maintenance following cellular therapy
- Pembrolizumab in combination with agents with novel mechanisms of action
- Pembrolizumab as monotherapy or in combination in rare lymphomas (e.g. PTLD, PCNSL, PTCL, CTCL etc.)

Head & Neck Cancers

Recurrent/Metastatic HNSCC

- Novel pembrolizumab combinations in R/M HNSCC
- Including PDL-1 negative populations
- Novel strategies after progression on anti-PD-1/PD-L1 (IO refractory)
- HPV virus specific T cells + pembrolizumab

Locally Advanced HNSCC

- Neoadjuvant pembrolizumab + chemotherapy or novel combination in post salvage surgery setting for recurrent HNSCC

- De-escalation strategies in locally advanced disease
- Including HPV+ and oropharynx cancer (OPC)
- Novel chemo free combinations IO + IO
- Pembrolizumab + chemotherapy as induction therapy for locally advanced HNSCC sequencing chemo after IO
- Definitive chemoRT followed by pembrolizumab in locally advanced HNSCC (including combination therapies or sequencing after IO)

Cutaneous Squamous Cell Carcinoma (cSCC)

- Novel combinations with pembrolizumab in locally advanced, neoadjuvant and/or 1L Recurrent/Metastatic setting
- 2L PD-1/L1 refractory patient population

Nasopharyngeal Carcinoma

- Novel combinations with pembrolizumab 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

- Strategies to improve pembrolizumab efficacy in advanced HCC including:
- Uncommon subtypes
- Novel first line combinations, including bevacizumab containing triplets
- Evaluate predictors of response to IO (blood-based markers, imaging, etc.)*
- Ways to combat resistance to IO or IO combinations
- Sequencing of therapy in advanced disease

Biliary Cancers

- Pembrolizumab combinations in preselected molecular subsets (including but not limited to IDH, HER-2)
- Strategies to improve pembrolizumab efficacy in advanced biliary cancer including:
- Evaluate predictors of response to IO (blood-based markers, imaging, etc.)*

Thoracic Malignancies

NSCLC

- Novel neoadjuvant pembrolizumab combinations
- Novel pembrolizumab combinations in IO pre-exposed patients
- IO combinations, including ADC combinations
- Overcoming specific mechanism of resistance (e.g. LKB-1)
- IO exposed in the early stage and locally advanced disease
- Novel pembrolizumab combinations in mutation driven cancers
- Novel TKI + pembrolizumab for non-EGFR, non-ALK mutation driven cancers including KRAS mutant and others
- Novel combinations with targeted ADCs (e.g. HER2, cMET) and T-cell engagers
- Novel pembrolizumab combinations in 1L NSCLC including chemo free combinations in different biomarker subgroups or PD-L1 expression levels (leverage knowledge of tumor microenvironment to inform biological rationale for combination strategies)

SCLC

- Novel pembrolizumab combinations in 1L

- Determining mechanisms to improve response and outcomes in 1L based on biology of disease
- Determining mechanisms of resistance
- Determining approach to treatment in setting of brain metastases
- Novel pembrolizumab combinations in IO pre-exposed patients

Mesothelioma

- Novel pembrolizumab combinations in 1L and in 2L IO naïve
- Determining mechanisms to improve response and outcomes
- Novel pembrolizumab combinations in IO pre-exposed patients

Melanoma

- Novel pembrolizumab combinations for patients with high-risk melanoma, with emphasis on those with a detailed/described mechanism. Examples include, but are not limited to:
- Anti-PD-1/L1 +/- anti-CTLA4 resistant/refractory patients including those previously treated in adjuvant setting
- Mucosal/Acral melanoma
- Uveal melanoma (excluding pembrolizumab + lenvatinib doublet proposals)
- Brain metastases
- Neoadjuvant therapy (excluding pembrolizumab + lenvatinib doublet proposals)

Other Skin Cancers

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

Innovative Strategies

- Pembrolizumab-based combinations in underserved tumor types with a high unmet medical need (primary brain tumors, sarcomas, neuroendocrine tumors and adrenocortical carcinomas remain a key focus for the program)
- Novel mechanistic combinations are of particular interest
- Proposals with a strong translational rationale/evidence or component (e.g. neoadjuvant, enhancing MOA, overcoming resistance)

Note: doublet combinations with VEGF TKIs should be discussed with the RMSD/MSD Country Team before submission

Prostate Cancer

- Neoadjuvant studies of pembrolizumab as monotherapy and in combination; combinations including, but not limited to, novel immune modulating agents, and other novel mechanisms of action (e.g., TRT)
- Combinations in other lines of therapy, including but not limited to, oncolytic viral agents, radiation, PARP inhibition, and multikinase inhibitors
- Studies evaluating the biochemical failure setting
- Studies in elderly (>80 years) population and underserved minority groups
- Novel combinations of pembrolizumab for small cell/neuroendocrine-like differentiated disease
- Studies that include objectives to investigate biological mechanisms of pembrolizumab response or resistance

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 or oligometastatic disease and advanced disease where the primary tumor is in situ
- IO refractory and post IO disease setting (including IO/IO or IO/TKI combinations or post adjuvant 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
- Pathways
- Angiogenesis, hypoxia, epithelial-mesenchymal transition (EMT), antigen presentation and machinery, cytokine/chemokine expression, immune checkpoints, immune exhaustion vs. immune senescence as it relates to response to pembrolizumab and/or other cancer immunotherapies.
- Organoids/3D models for immunotherapy response

- Pembrolizumab combinations
- Identify mechanisms of action associated with reported clinical response to anti-PD-1 combination treatment (reverse translational studies)
- Identify additive, synergistic, and/or antagonistic mechanisms of action between pembrolizumab and anti-tumor antigen antibody-drug conjugates (ADCs)
- Targeting the tumor-stromal-immune cell axis:
- Identify role of tumor stroma in cancer progression; potential stromal targets
- Identify pathways and potential targets that modulate vasculature to enhance immune cell trafficking
- Evaluate the contribution of tumor intrinsic pathways to immune escape
- Identify mechanisms of action that modulate immune suppressive cells B cells (including tumor resident B cells), myeloid cells (MDSCs, DCs, TAMs)
- Models of combination drug discovery
- Genome-wide CRISPR immune screens
- Stroma/immune-tumor cell co-culture CRISPR screens
- Organoids/3D models for immunotherapy response

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