## 2024 Areas of Interest for Pembrolizumab

## Special Note: Diversity & Inclusion

We seek to foster diverse and inclusive representation within the individual Areas of Interest for each tumor type, and so encourage study concept submissions across our program which:

- Specifically focus on the outcome disparities in underrepresented populations
- Are led by non-academic programs/institutions
- Are conducted in under-represented regions or countries

### Home Administration

- Novel approaches for the administration of pembrolizumab in the home setting

## 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
- Pembrolizumab combinations with novel agents for bladder preservation strategies in MIBC

*Late Stage:*

- Novel combinations in patients with PD-1/PD-L1 refractory tumors (i.e., pembrolizumab plus olaparib, etc.)
  - Excluding VEGF/PDGFR TKI combinations
- Rechallenge strategies in patients previously exposed to PD-1/PD-L1 inhibitors in different disease settings
- Novel combinations for the perioperative management of MIBC patients

## Breast Cancer

- Novel pembrolizumab combinations, such as with other IOs, ADCs, TKIs, etc. in TNBC and HR+ breast cancer
  - Proposals addressing recurrence or progression following prior pembrolizumab therapy in TNBC are of special interest
  - Combinations with endocrine therapy +/- CDK4/6 inhibitors in HR+ breast cancer are not of interest
- Studies in clinically relevant biomarker subsets including HER2 low

## Colorectal Cancer

- Locally advanced MSI-H colon and rectal cancer:
  - Pembrolizumab novel combinations in locally advanced (Stage III) colon or (Stage II/III) rectal cancer with emphasis on neoadjuvant approaches that may be surgical sparing.
- MSI-H metastatic colorectal cancer
  - Pembrolizumab novel combinations in MSI-H mCRC refractory to IO monotherapy
- MSS colorectal cancers:
  - Pembrolizumab-based novel combinations for MSS mCRC with strong scientific/pre-clinical rationale (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 stage II/III rectal or stage III colon 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.
- Locally advanced or metastatic rectal 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

*Pancreatic Cancer*

- Pembrolizumab combinations with 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.

## Gynaecological Cancers

*Ovarian cancer*

- Frontline novel combinations with pembrolizumab especially for HRD(-) patients without PARPi
- Pembrolizumab combination therapies in recurrent ovarian cancer, with particular interest in post IO/post PARPi exposure setting
- Chemo-free regimens in recurrent setting
- IO and novel combinations after 2nd surgery
- Combination with immunomodulatory agents, bevacizumab and ADCs

- HER2 (+) and HER2 low/ultra-low ovarian cancer

*Cervical cancer*

- Pembrolizumab combination therapies in locally advanced cervical cancer
- Novel pembrolizumab combinations in IO naive and IO exposed settings, with particular interest in ADCs
- Chemo-free regimens in recurrent setting
- HER2 (+) and HER2 low/ultra-low cervical cancer

*Endometrial cancer*

- Novel combinations including pembrolizumab with TKIs, ADCs (e.g. Her2 low/positive), and other novel MOAs in both the IO naïve and IO exposed treatment settings

**Hematological Malignancies**

- Pembrolizumab in combination with agents with novel mechanisms of action

**Head & Neck Cancers**

*Recurrent/Metastatic HNSCC*

- Innovative combinations with pembrolizumab in R/M HNSCC
- Including PDL-1 negative populations
- Innovative combinations/strategies in IO experienced patients
- De-escalation strategies in HPV(+) OPSCC

*Locally Advanced HNSCC*

- New therapy approaches in post definitive setting, for patients who are eligible for salvage surgery
- Innovative chemo free combinations (e.g, IO + ADC, IO + IO, IO + TKI, etc.)
- Patients who progress within 6 months of definitive treatment
- Treatment sequence in locally advanced

*Cutaneous Squamous Cell Carcinoma (cSCC)*

- Innovative combinations with pembrolizumab in locally advanced (resectable), neoadjuvant and/or 1L recurrent/metastatic or unresectable locally advanced setting
- 2L PD-1/L1 experienced patient population

*Nasopharyngeal Carcinoma*

- Innovative combinations with pembrolizumab in EBV-associated NPC in locally advanced setting

*Salivary Gland and Thyroid Carcinomas*

- Innovative combinations (with strong rationale) with pembrolizumab in salivary gland and thyroid carcinomas

**Hepatobiliary Cancers**

*Hepatocellular Cancers*

- Strategies to improve pembrolizumab efficacy in advanced HCC including:
  - Uncommon subtypes
  - 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)
- Novel therapies after IO
- Strategies to improve pembrolizumab efficacy in advanced biliary cancer including:
  - Evaluate predictors of response to IO (blood-based markers, imaging, etc.)*

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

**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 combinations with TKI + pembrolizumab for genomic mutation driven cancers
  - 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

*SCLC*

- Novel pembrolizumab combinations in 1L
  - Determining mechanisms to improve response and outcomes in 1L based on biology of disease and known subtypes
  - Determining mechanisms of resistance
- 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 combinations for patients with melanoma, with emphasis on those with a described mechanism. Examples include, but are not limited to:
  - PD-1 +/- CTLA-4 resistant/refractory patients including those treated in adjuvant setting
  - Mucosal/acral melanoma
  - Uveal melanoma (not accepting pembro/lenvatinib doublet proposals)
  - Brain metastases (excluding leptomeningeal disease)
- Novel mechanisms of action are of particular interest (e.g., Novel TKIs, ADCs, immune-modulators, vaccines)
- Neoadjuvant (note patients must also receive adjuvant therapy as appropriate)

**Other Skin Cancers**

- Novel combinations in Merkel cell carcinoma (including neoadjuvant)
- Novel 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)
- Tumor agnostic approaches, both improving on current treatment and also in earlier line of treatment (if biomarker selected population is needed, please discuss with the RMSD/MSD Country Team before submission)
- Proposals with a strong translational rationale/evidence or component (e.g., neoadjuvant, enhancing MOA, overcoming resistance)
- Novel mechanistic combinations are of particular interest, including combinations with ADCs
- Doublet combinations with VEGF TKIs or olaparib are generally not of interest and should be discussed with the RMSD/MSD Country Team before submission

**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 (cc and Ncc) or risk groups, 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, including in neo-adjuvant setting for primary and metastatic resectable disease

**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, gamma delta T cells, natural killer (NK) cells, antigen presenting cells, exhausted T cells
            - Stromal cells: fibroblast reticular cells (FRCs), cancer associated fibroblasts (CAFs)
            - Tumor cells: intrinsic mechanisms that provide sensitivity or resistance to PD-1 inhibitors
        - Pathways: Immune trafficking, 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.
    - Development of models for response/resistance to anti-PD1:
        - Genome-wide CRISPR immune screens
        - Stroma/immune-tumor cell co-culture CRISPR screens
        - 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 novel combination partners, including antibody-drug conjugates and tumor intrinsic pathway inhibitors
    - Identify pathways and potential targets that modulate vasculature to enhance immune cell trafficking