Approved AOIs for 2024:

Pembrolizumab:

- Characterization of intra-tumoral myeloid-lineage populations, including neutrophils, and their biology from immune suppression to antigen presentation, in the context of response or resistance to pembrolizumab
- Analysis of PD-1/PD-L1 function in tumor biology
- Mechanisms of immune cell trafficking and exclusion from tumors
- Determination of the tumor architecture and interactions between tumor and immune cells

Note : New clinical trial submissions will only be considered if they involve the use of either Belzutifan or sacituzumab tirumotecan (sac-TMT) in combination.

Belzutifan:

- Analyses of HIF2A inhibition in the context of tumor biology including mechanisms of response and resistance:
- Effect of tumor genetic and biological interactions between tumor signaling pathways and HIF2A biology and inhibition
- Effect of HIF2A inhibition on the tumor immune response
- Mechanisms of tumor resistance to HIF2A inhibition
- Mechanisms of tumor response to HIF2A inhibition
- Mechanisms of interaction between inhibition of HIF2A and standard of care treatment

Sacituzumab tirumotecan (sac-TMT)/ADCs:

- Mechanisms of response and resistance to sac-TMT either alone or in combination with pembrolizumab or other standard-of-care agents.
- Mechanisms to overcome resistance to sac-TMT either alone or in combination with pembrolizumab or other standard-of-care agents.
- Mechanisms of response and resistance to approved antibody-drug conjugates (ADCs) alone and/or in combination with pembrolizumab or other SOC chemotherapies.

Note: In the context of OTSP, it is strongly encouraged to collect and analyse samples at confirmed radiological/clinical progression or at the end of treatment. Refer to the MISP sac-TMT AOIs for information on tumor types of interest. Please note that IISP proposals competing with or duplicating any registration trial for sac-TMT will not be supported.

ctDNA-related areas:

- Retrospective temporal analyses of ctDNA as a surrogate for monitoring of minimal residual disease burden in the neoadjuvant or adjuvant setting.
- Retrospective temporal analyses of ctDNA as a predictor of treatment response or progression
- ctDNA as a tool to investigate tumor genetics, biology, or evolution.

Note: It is not recommended to conduct studies that involve the use of ctDNA assays for prospective clinical trial enrollment or for on-treatment patient clinical decision making. Furthermore, studies utilizing non-commercial ctDNA assays are also discouraged.

General Considerations

We advised you to consult with your field-based team to discuss tumor types that are of interest.

- Submissions employing longitudinal patient sampling, including trials conducted in the neoadjuvant setting, are strongly encouraged.
- Patient selection or clinical decision making using experimental biomarker assays or technology that are not regulatory agency-approved will require additional discussion.
- Submissions focused on the following areas are discouraged:
    - Pipeline compounds not approved for investigator studies
    - Technology development, implementation, or validation
    - Therapeutic agents for combination studies that:
        - Have shown no monotherapy activity in phase I or II studies
        - Do not have a phase II recommended dose or an established safety profile
        - Are repurposed agents from non-oncology therapeutic areas
    - Phase I studies
    - Tumor vaccines
    - CART-T or other cellular therapies
    - Pediatric studies
    - Studies aimed at studying or modulating the microbiome
    - Studies that are purely *in vitro* or *in vivo* mouse models
    - Biomarker identification or validation