Introduction:

Despite potential life-changing morbidity and mortality, there are no validated biomarkers for identifying patients at risk of developing serious immune-related adverse events (irAE) from immune checkpoint inhibitor (ICI) therapy. Autoimmune conditions and irAE both involve loss of tolerance to endogenous antigens with similar clinical manifestation.

We have previously shown that individuals with irAE have higher baseline IgG autoantibody (autoAb) levels with a greater increase in IgG and IgM autoAb after ICI administration, compared to those without irAE. Other studies have identified associations and potential mechanistic relationships between the gut microbiome and development of irAE.

We hypothesize that changes in intestinal microbiome composition, autoAb profiles, and peripheral immunophenotype with ICI therapy are associated with the development of irAE and are influenced by immunosuppressive treatment for irAE.

STUDY OBJECTIVES

Primary Objective

• To assess the feasibility of evaluating intestinal microbiome composition, autoAb profiles and peripheral blood immunophenotype in patients treated with ICI-based combination immunotherapy.

Endpoint: The project will be deemed feasible if > 50% of patients have biospecimens (stool and blood samples) collected at ≥ 2 time-points (Figure 1).

Secondary Objectives

• To assess:
  - Baseline intestinal microbiome composition with the development of significant irAE (≥ Grade 2 CTCAE v5.0 and/or requiring systemic immunosuppression).
  - Baseline autoAb profiles with the development of significant irAE.
  - Baseline peripheral blood immunophenotype with the development of significant irAE.
  - Early changes in intestinal microbiome composition, autoAb profile, and peripheral immunophenotype on ICI-based combination immunotherapy with the development of significant irAE.
  - Tumor genomic profile by whole exome sequencing (WES) with development of significant irAE.
  - To evaluate changes in intestinal microbiome composition, autoAb profile, and peripheral blood immunophenotype from baseline to the development of significant irAE (≥ Grade 2 CTCAE v5.0 and/or requiring systemic immunosuppression); and from onset of irAE to resolution (≤ Grade 1 CTCAE v5.0).

STUDY DESIGN

• INSPECT-IO is a prospective Princess Margaret Cancer Centre initiative [NCT04107311].

• Whole blood and stool samples are collected from all patients at baseline (≥ 28 days prior to ICI), an early timepoint (2 – 6 weeks after starting ICI) and at end of treatment (≥ 28 days after completion of ICI) as shown in Figure 1.

• Additional blood and stool samples are collected within 96 hours of onset, and upon resolution of every significant irAE (≥ grade 2 by CTCAE v5.0 or requiring systemic immunosuppression).

Study enrolment is ongoing with 38 patients to date and a target accrual of 74 patients.

SAMPLE ANALYSIS

• Shotgun sequencing will be used to determine gut microbial taxonomic and metagenomic composition from stool samples.

• AutoAb profiling will be performed by multiplex proteomic arrays and immunophenotyping will be done using flow cytometry.

• Archival tumor tissue and organ-specific tissue biopsies for histologic irAE diagnosis will be stored for WES and other molecular analyses.

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