Clinical Trial Design: Immunofolate in Non-Small Cell Lung Cancer

Study Title:

Efficacy and Safety of Immunofolate in Combination with PD-1 Inhibitors in Advanced Non-Small Cell Lung Cancer

Primary Objective:

To evaluate the progression-free survival (PFS) in patients with advanced or metastatic NSCLC treated with Immunofolate in combination with PD-1 inhibitors (e.g., nivolumab or pembrolizumab) compared to PD-1 inhibitors alone.

Secondary Objectives:

- To assess overall survival (OS) in both treatment arms.
- To evaluate the objective response rate (ORR) and duration of response (DoR).
- To assess immune biomarkers in the tumor microenvironment, such as PD-L1 expression, tumor mutational burden (TMB), and T-cell infiltration.
- To evaluate safety and tolerability of Immunofolate in combination with PD-1 inhibitors (e.g., nivolumab or pembrolizumab).

Study Population:

Inclusion Criteria:

- Adult patients (>=18 years) with histologically or cytologically confirmed advanced/metastatic NSCLC.
- No prior treatment with immune checkpoint inhibitors.
- ECOG performance status of 0 or 1.
- Measurable disease by RECIST 1.1.
- Adequate organ function (e.g., liver, kidney, bone marrow).
- Ability to provide informed consent.

Exclusion Criteria:

- Active autoimmune diseases or history of autoimmune disorders.
- Uncontrolled infection or other severe, uncontrolled medical conditions.
- History of severe hypersensitivity reactions to PD-1 inhibitors.
- Prior treatment with systemic chemotherapy, targeted therapy, or other immune-modulating agents for advanced NSCLC.
- Brain metastasis or leptomeningeal disease.

Treatment Arms:

Arm 1 (Experimental): Immunofolate + PD-1 inhibitor (nivolumab or pembrolizumab)

- Immunofolate: Oral administration of Immunofolate at a defined dose, given daily.
- PD-1 Inhibitor: Standard dosing of nivolumab (240 mg every 2 weeks) or pembrolizumab (200 mg every 3 weeks).

Arm 2 (Control): PD-1 inhibitor (nivolumab or pembrolizumab) alone

- PD-1 Inhibitor: Standard dosing of nivolumab or pembrolizumab, as above.

Treatment Duration:

Induction Phase: Patients will receive the assigned treatment (Immunofolate + PD-1 inhibitor or PD-1 inhibitor alone) until disease progression, unacceptable toxicity, or withdrawal of consent.

Follow-up Phase: Patients will be monitored for disease progression every 8 weeks for the first 6 months, then every 12 weeks thereafter. Survival will be followed until the final analysis.

Endpoints:

Primary Endpoint:

- Progression-Free Survival (PFS) based on RECIST 1.1 criteria.

Secondary Endpoints:

- Overall Survival (OS).

- Objective Response Rate (ORR).

- Duration of Response (DoR).

- Safety: incidence and severity of treatment-related adverse events (AEs), including immune-related AEs.

- Immunologic Biomarkers: Analysis of tumor tissue and blood samples for PD-L1 expression, TMB, and immune cell infiltration (e.g., CD8+ T cells, T-regs).

Statistical Analysis:

Sample Size: 150 patients (75 per treatment arm).

- This sample size will provide sufficient power (80%) to detect a clinically meaningful difference in PFS with a significance level of 0.05.

Analysis Plan:

- PFS and OS will be analyzed using Kaplan-Meier survival curves and compared between groups using a log-rank test.

- Subgroup analyses will be performed to assess the effects of PD-L1 expression, TMB, and other relevant biomarkers.

- Safety will be assessed by descriptive statistics and adverse event reporting.

Trial Timeline:

Screening Period: 2-4 weeks.

Treatment Period: 12 months (with treatment until disease progression or unacceptable toxicity).

Follow-Up Period: Minimum of 12 months for survival data.

Safety Monitoring:

An independent Data Monitoring Committee (DMC) will review interim safety data every 6 months.

Patients will be closely monitored for any immune-related adverse events (irAEs), including

pneumonitis, colitis, hepatitis, and endocrinopathies.

Biomarker and Correlative Studies:

- Blood and tumor biopsies will be collected for analysis of immune biomarkers at baseline and during treatment, such as:
  - Tumor mutational burden (TMB).
  - PD-L1 expression on tumor cells.
  - T-cell and myeloid cell markers (CD8, CD4, PD-1, CTLA-4, etc.).
  - Cytokine profiling to assess immune activation.