Data suggests that PO-1 and its ligands PO-1/PD-12 mediate immune evasion in CLL. However, recent work (Ding et al, Blood 2017) demonstrates that pembrolizumab (pemb) alone is ineffective in patients [pemb, DFS 2.4 months]. In 5 pts with relapsed/refractory (r/r) CLL, 3 responded to combination of rituximab / nivolumab (azure ASH, 2016). A key interaction exists between PSK signaling and immune checkpoint surveillance which by which PSK decreases PO-1 tumor expression.

We therefore hypothesized synergistic activity with PO-1 + PSK blockade. We tested the safety and activity of umbralisib, a next generation high-specificity PI3K inhibitor, in combination with pemb and the glycoprotein non-CD19 mAb, umbralisib in r/r CLL and RT, representing the first reported combination of a PI3K inhibitor with a PI3K inhibitor.

**Study Design**

- Phase I/II dose escalation (3+3 design), multicenter study to assess the safety and efficacy of pemb combination with umbralisib and umbralisib (UTX) in pts with relapsed or refractory and CLL (NCT05132186).
- Prior BTK, MANTLE, PACE, CLEVER, and ECOG-ACRIN E1612 trials.
- Mean age: 65.5 years (range 24–84 years).

**Study Objectives**

- To determine the safety of umbralisib + pemb in CLL and RT pts
- To evaluate efficacy (ORR, PFS)
- To determine the immunophenotypic and cytokine profiles of 8 T cells in subjects

**Key Eligibility Criteria**

- Must have relapsed or refractory CLL or RT
- Must be ≥18 years old
- ECOG PS 0–1
- Must have at least 10% of CD23+ B-cells
- CD23+ B-cells ≥10% of CD19

**Primary Objective**

- Efficacy: In PO-1 dose-escalation (5+5 design), multicenter study to assess the safety and efficacy of pemb combination with umbralisib and umbralisib (UTX) in pts with relapsed or refractory and CLL (NCT05132186).

**Secondary Objectives**

- To determine the safety of umbralisib + pemb in CLL and RT pts
- To evaluate efficacy (ORR, PFS)
- To describe the immunophenotypic and cytokine profiles of 8 T cells in subjects

**Key Eligibility Criteria**

- Must have relapsed or refractory CLL or RT
- Must be ≥18 years old
- ECOG PS 0–1
- Must have at least 10% of CD23+ B-cells
- CD23+ B-cells ≥10% of CD19

**Primary Objective**

- Efficacy: In PO-1 dose-escalation (5+5 design), multicenter study to assess the safety and efficacy of pemb combination with umbralisib and umbralisib (UTX) in pts with relapsed or refractory and CLL (NCT05132186).