**Background**

- Duvelisib is an oral dual inhibitor of PI3K-δ and PI3K-γ being developed for the treatment of hematologic malignancies.
- In preclinical investigations, duvelisib potently killed TCL cell lines with constitutive phospho-AKT (S473) and reprogrammed tumor-associated macrophages from an immunosuppressive to immunostimulatory phenotype in PTCL mouse xenograft models.

**Duvelisib Monotherapy in TCL**

- In a Phase 1 study, duvelisib monotherapy demonstrated encouraging clinical activity and an acceptable safety profile.
- In PTCL (n=16), the ORR was 50.0% (3 CRs, 5 PRs), DOR ranging from 1.8-17.3 months, median PFS of 8.3 months, and median OS of 8.4 months.
- In CTCL (n=19), the ORR was 31.6% (including 6 PRs), DOR ranging from 1.6-3.5 months, median PFS of 4.5 months, and median OS not reached.
- These results suggest duvelisib monotherapy may provide a meaningful benefit in R/R PTCL, a population in need of new and effective therapies.

**Study Design**

- **Duvelisib, an oral dual inhibitor of PI3K-δ and PI3K-γ, changes macrophage polarization in vivo**

**Dose Optimization Phase (N = 20); 4 to 6 U.S. Study Centers**

**Cohort 1:** 25 mg PO BID, with potential sequential escalation to 50 mg PO BID, and then to 75 mg PO BID based on responses and tolerance of therapy.
- Dosing occurs continuously in 28-day cycles; patients evaluated at end of Cycle 1 and every 2 cycles thereafter:
  - CR or PR: Dose maintained
  - SD: Dose increased by 25 mg
  - PD: Duvelisib discontinued

**Cohort 2:** 75 mg PO BID until PD or unacceptable toxicity

**Expansion Phase (N = 100); ~40 Study Centers Globally**

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<tbody>
<tr>
<td>Cohort 1 (n = 10)</td>
<td>25 mg</td>
<td>25 mg (CR or PR)</td>
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<tr>
<td>25 mg PO BID</td>
<td>50 mg (SD)</td>
<td>50 mg (CR or PR)</td>
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<tr>
<td>25 mg PO BID</td>
<td>75 mg (SD)</td>
<td>75 mg (SD)</td>
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<tr>
<td>Cohort 2 (n = 10)</td>
<td>75 mg</td>
<td>Maintain dose at 75 mg until PD or unacceptable toxicity</td>
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**Outcome Measures**

- **Primary Endpoint**
  - IRC-assessed ORR — best response of CR or PR
- **Secondary Endpoints**
  - AEs and abnormal laboratory values
  - Duration of response
  - Progression-free survival
  - Disease control rate (i.e., CR + PR + SD ≥ 8 weeks)
  - Overall survival

**Exploratory Endpoints**

- Analysis of PTCL tumor pharmacodynamic markers
- Analysis of PTCL tumor prognostic markers
- Analysis of cytokines and non-tumor immune populations in relation to safety and efficacy

**Key Eligibility Criteria**

- Diagnosis of a pathologically confirmed histologic PTCL subtype, as defined by WHO:
  - PTCL-NOS
  - AITL
  - ALCL
  - » If CD30⁺, must have failed, be ineligible for, or be intolerant to brentuximab vedotin
  - NKTL
- Received ≥ 2 cycles of 1 prior regimen administered with curative intent and:
  - Failed to achieve PR or better after ≥ 2 cycles, or
  - Failed to achieve CR after ≥ 6 cycles, or
  - Progressed after initial response
- Measurable disease per IWG for PTCL
- ECOG performance score ≤ 2
- Washout of ≥ 14 days or 5 half-lives (whichever is longer) from PTCL-directed therapy
- No clinical evidence of transformation to more aggressive lymphoma subtype or CNS involvement by PTCL
- No prior history of allogeneic stem cell transplant or treatment with PI3K inhibitor
- No concurrent active malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix

**Now Enrolling**

For more information:

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ClinicalTrials.gov NCT03372057