Trial in Progress — The PRIMO™ Study: A Phase 2 Study of Duvelisib Efficacy and Safety in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

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Poster 222b
Abstract TPS7590

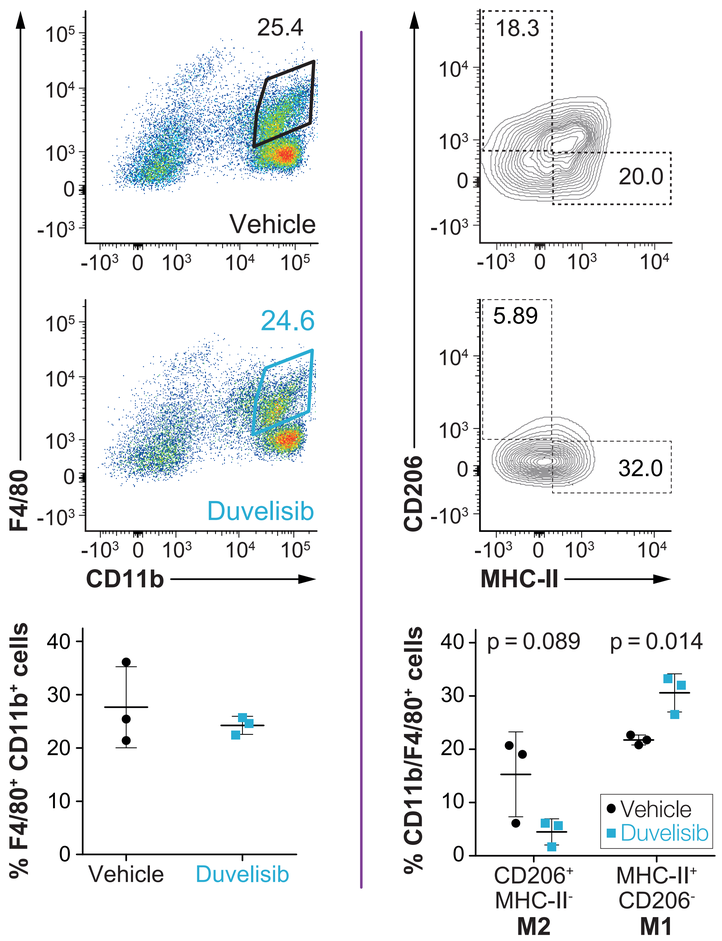
Background

- 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[1]
- In PTCL (n=16)[2], 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)[2], 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

Duvelisib, an oral dual inhibitor of PI3K-δ and PI3K-γ, changes macrophage polarization *in vivo*[2]



In the AITL PDX *in vivo* model, mice were engrafted with DFTL-78024 and treated with vehicle or duvelisib. **Left:** Quantification of splenic macrophages by F4/80 and CD11b staining. **Right:** Macrophage polarization in spleens is quantified by CD206 and MHC-II staining in vehicle- or duvelisib-treated animals. Duvelisib treatment increases the immunostimulatory M1 (MHC-II$^+$ CD206$^-$) population and decreases the immunosuppressive M2 (CD206$^+$ MHC-II$^-$) population. (Statistics: unpaired t-test)

Study Design

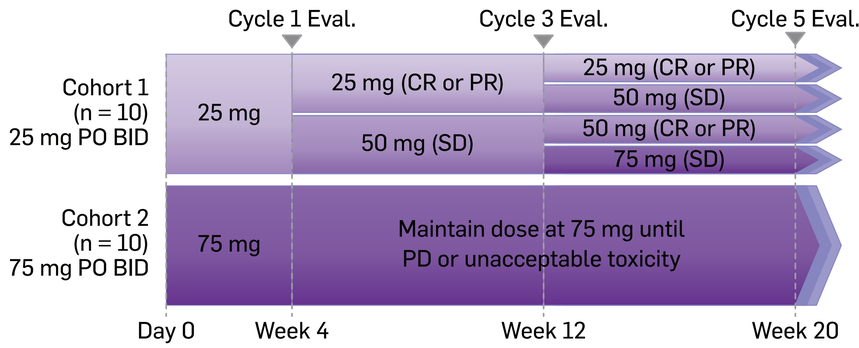
- This Phase 2 open-label study of duvelisib monotherapy is being conducted in adult patients (N = 120) with histologically confirmed PTCL subtypes: PTCL-NOS, AITCL, ALCL, and NKTL
- Study includes both a Dose Optimization Phase and an Expansion Phase
- **Primary objectives:** Identify the optimal dose of duvelisib and examine its efficacy, safety, and tolerability at the optimal dose
- Disease response measured by ^{18}FDG-PET-CT per an independent review committee utilizing the IWG criteria.

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



- All patients are treated at the optimal dose as determined in Dose Optimization Phase.

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

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ClinicalTrials.gov NCT03372057

Abbreviations: ^{18}FDG-PET-CT = positron emission tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose • AITL = angioimmunoblastic T-cell lymphoma • ALCL = anaplastic large cell lymphoma BID = twice daily • CD11b = cluster of differentiation molecule 11b CD206 = cluster of differentiation molecule 206 • CLL = chronic lymphocytic leukemia • CNS = central nervous system • CR = complete remission • CTCL = cutaneous T-cell lymphoma • DOR = duration of response • ECOG = Eastern Cooperative Oncology Group F4/80 = epidermal growth factor-like module-containing mucin-like hormone receptor-like 1 • ITT = Intent-to-Treat • IWG = International Working Group • MHC-II = major histocompatibility complex class II • NKTL = natural-killer/T-cell lymphoma • ORR = objective response rate OS = overall survival • pAKT = phospho-AKT • PD = progressive disease • PDX = patient-derived xenografts • PFS = progression-free survival • PI3K = phosphoinositide 3-kinase • PK = pharmacokinetic • PO = orally PR = partial response • PTCL = peripheral T-cell lymphoma PTCL-NOS = peripheral T-cell lymphoma not otherwise specified • R/R = relapsed/refractory • SD = stable disease • TCL = T-cell lymphoma • WHO = World Health Organization

References: 1) Flinn, et al. 2018. *Blood*. 131(8):877-887. doi: 10.1182/blood-201705-786566. [Epub 2017 Nov 30] **2)** Horwitz, et al. 2018. *Blood*. 131(8):888-898. doi: 10.1182/blood-2017-08-802470. [Epub 2017 Dec 12]

Presented at the 2018 American Society for Clinical Oncology Annual Meeting • Chicago, Illinois, USA • June 1-5, 2018