Duvelisib in Patients With Relapsed/Refractory Peripheral T-cell Lymphoma: Final Results From the Phase 2 PRIMO Trial

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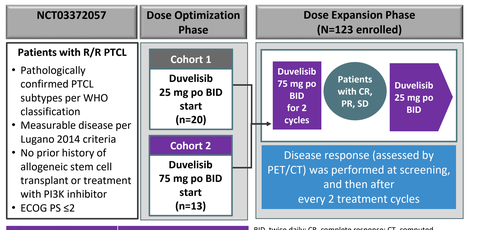
INTRODUCTION AND OBJECTIVES

- Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of aggressive lymphomas, with a poor prognosis and historical median overall survival of <6 months for relapsed or refractory (R/R) disease[1,2]
- In North America and Europe, the most common subtypes are PTCL-NOS (not otherwise specified), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL)[3]
- Currently approved single-agent therapies for R/R PTCL have modest overall response rates (ORR) (with the exception of brentuximab vedotin for CD30+ ALCL)[1]
- Duvelisib is a kinase inhibitor indicated for the treatment of adult patients with R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least 2 prior lines of systemic therapy. Limitations of Use: Duvelisib is not indicated or recommended for the treatment of any patients with CLL or SLL as initial or second-line treatment due to an increased risk of treatment-related mortality[4]
- PRIMO (NCT03372057) was an open-label, single-arm trial that evaluated safety and efficacy of duvelisib in R/R PTCL patients from the US, EU, UK, and Japan[5]

Please note that the data presented may be subject to change because of the ongoing data validation process.

PRIMO STUDY SCHEMA



Primary endpoint (dose expansion phase)	IRC-assessed ORR
Secondary endpoints	Safety, DOR, PFS, DCR (CR + PR + SD ≥8 weeks), OS, PK
Exploratory endpoints	PD and biomarkers

BID, twice daily; CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PK, pharmacokinetics; po, by mouth; PR, partial response; SD, stable disease; WHO, World Health Organization.

Eligible patients had to have ≥2 cycles of standard regimen and failed to achieve PR or better after ≥2 cycles or failed to achieve CR after completion of standard therapy or progressed after initial response. Each cycle was 28 days.
An eligibility criterion of a CD4 lymphocyte count ≥50/mm³ was added for the dose expansion phase.
Pneumocystis jirovecii prophylaxis was required; herpes simplex and varicella zoster virus prophylaxis were indicated as needed.

METHODS

- Eligibility criteria included adults with pathologically confirmed R/R PTCL after ≥2 cycles of at least 1 prior standard regimen and a CD4 lymphocyte count of ≥50/mm³
  - *Pneumocystis jirovecii* prophylaxis was required; herpes simplex and varicella zoster virus prophylaxis were recommended
- Based on dose optimization phase results, optimal dose was determined as duvelisib 75 mg twice daily (BID) for 2 cycles (to maximize disease control), then 25 mg BID (to mitigate late toxicities) until progressive disease (PD) or unacceptable toxicity
- The primary endpoint of the dose expansion phase was ORR by independent review committee assessment (Lugano 2014 criteria)
- Here we report the outcomes of the 123 patients from the PRIMO dose expansion phase (PRIMO-EP)

PATIENT DISPOSITION

Characteristic, n (%)	PRIMO-EP (N=123)
Patients withdrawn from treatment	123 (100)
PD	50 (40.7)
Adverse event	27 (22.0)
Other*	19 (15.4)
Clinical deterioration due to PD	11 (8.9)
Death	10 (8.1)
Termination of study by sponsor	3 (2.4)
Withdrawal of informed consent	2 (1.6)
Study drug interruption >42 days due to duvelisib-related toxicity	1 (0.8)

CR, complete response; SCT, stem cell transplant.
*Other: Intent to undergo SCT (total n=12: allogeneic, n=6; autologous, n=1; SCT type not disclosed, n=5), lack of efficacy (n=3), CR (n=1), patient decision (n=1), encephalopathy (n=1), second malignancy (n=1).

BASELINE CHARACTERISTICS

Characteristic	PRIMO-EP (N=123)
Median age (range), years	65 (21-92)
≥65 years, n (%)	66 (53.7)
Male, n (%)	67 (54.5)
Race, n (%)	
White	92 (74.8)
Asian	18 (14.6)
Black or African American	9 (7.3)
Other/missing	3 (2.4)/1 (0.8)
Median time from initial diagnosis (range), mo	18.20 (0.2, 195.5)
Median time from most recent R/R diagnosis (range), mo	1.15 (0, 142.9)
Baseline histology, n (%)	
PTCL-NOS	53 (43.1)
AITL	37 (30.1)
ALCL	20 (16.3)
Other*	13 (10.6)
Median no. of prior anticancer therapies (range)	2 (1, 9)
Stage at baseline, n (%)	
I	5 (4.1)
II	5 (4.1)
III	41 (33.3)
IV	71 (57.7)
Missing	1 (0.8)
Type of prior anticancer therapy, n (%)	
CHOEP/EPOCH	42 (34.1)
CHOP/R-CHOP	44 (35.8)
BV/BV-containing chemotherapy	47 (38.2)
Salvage chemo after CHOP/R-CHOP or CHOEP/EPOCH	43 (35.0)
Stem cell transplant	25 (20.3)

BV, brentuximab vedotin; CHOEP, cyclophosphamide + doxorubicin + vincristine + etoposide + prednisone; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; DLBCL, diffuse large B-cell lymphoma; EPOCH, etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin; mo, month; R-CHOP, rituximab + CHOP; TCL, T-cell lymphoma.
*Other histologies: follicular helper T (n=4), Epstein-Barr virus-related PTCL (n=2), natural killer cell lymphoblastic lymphoma (n=2), intestinal TCL (n=2), 1 each of primary cutaneous gamma delta TCL, subcutaneous panniculitis-like TCL, and DLBCL. One DLBCL was not in alignment with inclusion criteria.

DUVELISIB EXPOSURE IN PRIMO-EP (N=123)

Characteristic	PRIMO-EP (N=123)
Median relative dose intensity (range), %	97.7 (2.7, 151.2*)
Mean treatment duration, weeks	19.2
Median treatment duration (range), weeks	8.29 (0.1, 160.0)
Treatment duration categories, n (%)	
Treatment duration of ≤2 cycles (≤56 days)	54 (43.9)
Treatment duration of >2 to 4 cycles (57 to 112 days)	30 (24.4)
Treatment duration of >4 cycles (>112 days)	39 (31.7)
Patients with any dose reduction, n (%)	42 (34.1)
Patients with any dose hold, n (%)	59 (48.0)

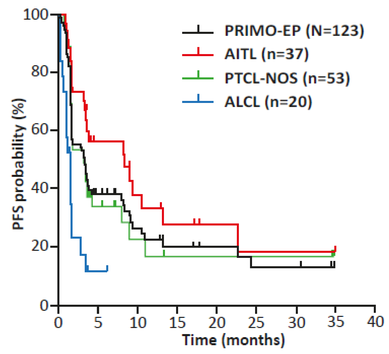
*The dose was re-escalated to 75 mg BID after C3D1 in 8 patients; per protocol the dose could be re-escalated based on response assessment and safety.
Dose hold is defined as dose held for duvelisib and dose interrupted for duvelisib.

EFFICACY OUTCOMES

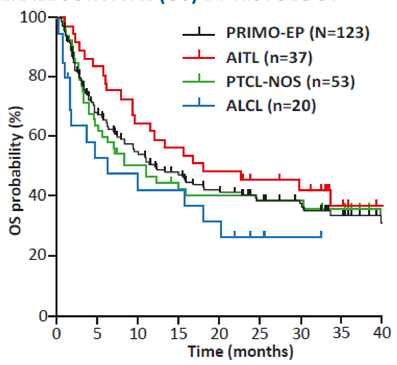
Efficacy outcome	PRIMO-EP (N=123)	AITL (n=37)	PTCL-NOS (n=53)	ALCL (n=20)
ORR, n (%)	59 (48.0)	23 (62.2)	26 (49.1)	3 (15.0)
CR, n (%)	41 (33.3)	19 (51.4)	16 (30.2)	3 (15.0)
Median DOR (95% CI), mo	7.89 (6.41, 20.96)	11.70 (7.29, NC)	7.39 (2.00, NC)	1.97 (1.87, NC)
Median duration of CR (95% CI), mo	7.89 (6.41, 22.74)	11.70 (5.45, NC)	7.39 (6.41, NC)	1.97 (1.87, NC)
Median time to response (range), mo	1.77 (0.5, 3.7)	1.81 (1.4, 3.7)	1.74 (0.5, 3.0)	1.71 (1.6, 3.5)
Median PFS (95% CI), mo	3.45 (1.84, 3.94)	8.34 (3.68, 13.34)	3.45 (1.77, 4.37)	1.64 (1.12, 1.74)
Median follow-up time for PFS, mo	6.24	-	-	-
Median OS (95% CI), mo	12.35 (8.38, 22.70)	18.07 (9.56, NC)	11.04 (5.09, 30.42)	6.34 (1.84, 20.14)
Median follow-up time for OS, mo	35.45	-	-	-
SCT after PRIMO,* n (%)	19 (15.4)	4 (10.8)	10 (18.9)	3 (15.0)
Allogeneic/autologous/ not disclosed	15/2/2	4/0/0	7/2/1	2/0/1

CR, complete response; DOR, duration of response; mo, month; NC, not calculated; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant.
*There were 11/12 with planned SCT at time of duvelisib treatment discontinuation plus 8 additional patients who received SCT.

PROGRESSION-FREE SURVIVAL (PFS) BY HISTOLOGY



OVERALL SURVIVAL (OS) BY HISTOLOGY



ALL-CAUSALITY TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs) OCCURRING IN ≥15% OF PATIENTS

TEAE	PRIMO-EP (N=123), n (%)
Patients with any TEAE	120 (97.6)
Alanine aminotransferase increased	46 (37.4)
Aspartate aminotransferase increased	44 (35.8)
Neutrophil count decreased	41 (33.3)
Diarrhea	41 (33.3)
Platelet count decreased	32 (26.0)
Fatigue	32 (26.0)
Anemia	31 (25.2)
Pyrexia	31 (25.2)
Nausea	30 (24.4)
White blood cell count decreased	25 (20.3)
Constipation	20 (16.3)
Serum lactate dehydrogenase increased	19 (15.4)
Maculopapular rash	19 (15.4)

ALL-CAUSALITY GRADE ≥3 TEAEs OCCURRING IN ≥5% OF PATIENTS

TEAE	PRIMO-EP (N=123), n (%)
Alanine aminotransferase increased	26 (21.1)
Neutrophil count decreased	22 (17.9)
Aspartate aminotransferase increased	21 (17.1)
Diarrhea	12 (9.8)
Platelet count decreased	11 (8.9)
Rash, maculopapular	10 (8.1)
Lymphocyte count decreased	9 (7.3)
Anemia	7 (5.7)

GRADE ≥3 TREATMENT-RELATED TEAEs OCCURRING IN ≥5% OF PATIENTS

TEAE	PRIMO-EP (N=123), n (%)
Alanine aminotransferase increased	25 (20.3)
Aspartate aminotransferase increased	20 (16.3)
Neutrophil count decreased	18 (14.6)
Diarrhea	10 (8.1)
Rash, maculopapular	10 (8.1)
Platelet count decreased	7 (5.7)

ADVERSE EVENTS OF SPECIAL INTEREST

Adverse event of special interest	PRIMO-EP (N=123)	
	Any grade, n (%)	Grade ≥3, n (%)
Alanine/aspartate aminotransferase elevation	55 (44.7)	30 (24.4)
Infections*	51 (41.5)	16 (13.0)
Cutaneous reactions	44 (35.8)	13 (10.6)
Diarrhea	41 (33.3)	12 (9.8)
Neutropenia	41 (33.3)	22 (17.9)
Pneumonia	8 (6.5)	5 (4.1)
Pneumonitis	2 (1.6)	1 (0.8)
Colitis	4 (3.3)	2 (1.6)

*There were no cases of *Pneumocystis jirovecii* pneumonia in study.

TEAEs RESULTING IN DOSE HOLD, DOSE REDUCTION, OR DEATH

- Patients with TEAEs resulting in dose hold: 55 (44.7%)
- Patients with TEAEs resulting in dose reduction: 12 (9.8%)
- Patients with TEAEs resulting in discontinuation: 41 (33.3%) patients (excluding PD)

TEAE* resulting in death (excluding PD)	PRIMO-EP (N=123), n
Cryptococcosis†	1
Epstein-Barr virus–associated lymphoproliferative disorder†	1
Pneumonitis†	1
Sepsis†	1
Cardiac arrest	1
Gastrointestinal hemorrhage	1
Hepatic failure	1
Hypoxia	1
Suicide	1
Vascular dementia	1

AE, adverse event.
*TEAE: AE that emerges or worsens in the period from date of first dose to 30 days after the date of last dose.
†TEAEs with a relationship of possible, probable, or definite per investigator are considered related to study treatment.

CONCLUSIONS

- The outcomes of the 123 patients in PRIMO-EP demonstrated an ORR of 48%, a complete response (CR) rate of 33%, and a median duration of response of 7.89 months, with 15% of patients continuing to stem cell transplant; these results compare favorably to currently approved single-agent options
  - **Notably, efficacy in the AITL subgroup stands out with ORR 62%, CR 51%, median PFS 8.34 months, and median OS 18.07 months**
- Adverse events were generally manageable with per-protocol dose modifications and were consistent with those observed previously
- PRIMO-EP results confirm duvelisib to be a promising agent for this disease with a high unmet need, poor prognosis, and limited effective treatment options[1,2]
- Based on these results, the sponsor is initiating a randomized phase 3 study in the EU/UK to investigate duvelisib in R/R nodal follicular helper T-cell lymphoma (TERZO™: NCT06522737; EU CT: 2024-516605-23-00)

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