DUVELISIB IN PATIENTS WITH RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMA: FROM THE PHASE 2 PRIMO TRIAL - IMPACT OF PRIOR THERAPY AND EXPANDED SAFETY ANALYSIS

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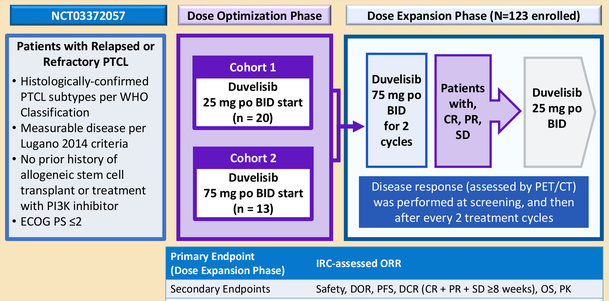
INTRODUCTION

- Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of aggressive lymphomas with poor prognosis; median overall survival (mOS) for relapsed/refractory (R/R) disease is <6 months [1,2]
- Current single agent therapies deliver modest overall response rates (ORR), typically <30% (except brentuximab vedotin (BV) in anaplastic large cell lymphoma (ALCL)[2]
- Duvelisib, an oral dual phosphatidylinositol 3-kinase (PI3K)-δ/γ inhibitor, is FDA approved for R/R chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) after ≥2 prior lines of systemic therapy
- The PRIMO trial (NCT03372057; sponsor: Secura Bio, Inc.) was a phase 2, open-label, single-arm trial evaluating duvelisib monotherapy in R/R PTCL

PRIMO PHASE 2 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

Eligible patients had to have received ≥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.

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; **ORR**, overall response rate; **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.

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

- PRIMO-EP eligibility: pathologically confirmed PTCL (WHO criteria) after ≥2 cycles of 1 prior standard regimen, and a CD4 lymphocyte count ≥50/mm³
- After dose optimization, the selected dose in the PRIMO-EP was DUV 75 mg BID for 2 cycles, to maximize disease control, followed by 25 mg BID, to mitigate late toxicities, until progressive disease (PD) or unacceptable toxicity
  - *Pneumocystis jirovecii* prophylaxis was required; herpes simplex and varicella zoster virus prophylaxis were strongly recommended
- The primary endpoint was ORR by IRC assessment (Lugano 2014 criteria)

PATIENT DISPOSITION

Characteristic	PRIMO-EP, n (%)
Discontinued study treatment	123 (100)
Progressive disease	50 (40.7)
Adverse event	27 (22.0)
Other‡	19 (15.4)
Clinical deterioration attributable to PD*	11 (8.9)
Death (on treatment or ≤30 days after last dose)	10 (8.1)
Study closure 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)

‡Other: Intent to undergo stem cell transplant (n=12), lack of efficacy (n=3), CR (n=1), patient decision (n=1), encephalopathy (n=1), second malignancy (development of B-cell malignancy, patient was on therapy for 57 days; n=1).
*Clinical deterioration attributable to PD was used by investigators when patients did not have a confirmed progressive disease at the time of decision to withdraw the patient from treatment.
††3 patients were on treatment (range 33.3–36.8 months) at time of study closure by sponsor.

BASELINE CHARACTERISTICS

Characteristic	PRIMO-EP (N=123), n (%)
Median age (range), years	65 (21-92)
≥65 years, n (%)	66 (53.7)
Male, n (%)	67 (54.5)
Median time from initial diagnosis (range), mos.	18.2 (0.2, 195.5)
Median time from most last R/R diagnosis (range), mos.	1.15 (0, 142.9)
Baseline histology, n (%)	
Peripheral T-cell lymphoma-NOS	53 (43.1)
Angioimmunoblastic T-cell lymphoma	37 (30.1)
Anaplastic large-cell lymphoma (ALCL)	20 (16.3)
Other*	13 (10.6)
Median no. of prior anticancer therapies (range)	2 (1, 9)
Disease stage at baseline‡, n (%)	
I	5 (4.1)
II	5 (4.1)
III	41 (33.3)
IV	71 (57.7)
Type of prior anticancer therapy, n (%)	
CHOP-based chemotherapy‡‡	83 (67.5)
BV/BV-containing chemotherapy	47 (38.2)
Salvage chemo after CHOP-based therapy	43 (35.0)
Autologous stem cell transplant	25 (20.3)
Romidepsin**	19 (15.4)
Pralatrexate	11 (8.9)
Primary refractory	
<CR to 1st line therapy	61 (49.6)
Best response to last therapy: SD, PD, relapse <6 mos from last dose	94 (76.4)

BV, brentuximab vedotin; **CHOEP**, cyclophosphamide, doxorubicin, vincristine, etoposide, + prednisone; **CHOP**, cyclophosphamide, doxorubicin, vincristine, + prednisone; **EPOCH**, etoposide, prednisone, vincristine, cyclophosphamide, + doxorubicin
*Additional other histologies with n>1: follicular helper T, Epstein-Barr virus-related PTCL, natural killer cell lymphoblastic lymphoma, intestinal TCL.
†One patient is missing data for baseline disease stage.
‡CHOP/CHOEP/EPOCH (33 patients received etoposide in their first line of therapy).
**One additional patient had prior belinostat.

EFFICACY OUTCOMES IN THE PRIMO-EP

- Overall response rate (ORR): 48%; complete response (CR): 33%
- Median progression-free survival (mPFS): 3.4 months
- Median overall survival (mOS): 12.4 months
- Median duration of response (mDOR): 7.9 months
- AITL subgroup: ORR 62%, CR 51%, mDOR 11.7 months, mPFS 8.3 months, mOS 18.1 months
- Nineteen patients (15%) received stem cell transplantation after PRIMO (11/12 with planned SCT at time of treatment discontinuation plus 8 additional patients)

EFFICACY OUTCOMES BY NUMBER OF PRIOR REGIMENS

Efficacy outcome*	1 prior line, (n=34)	2 prior lines, (n=29)	≥3 prior lines, (n=59)
ORR, n (%)	10 (29.4%)	19 (65.5)	29 (49.2)
CRR , n (%)	6 (17.6)	15 (51.7)	19 (32.2)
Median DOR (95% CI), mos.	6.5 (1.9, –)	11.7 (2.1, 22.7)	7.9 (1.9, –)
Median PFS (95% CI), mos.	1.9 (1.7, 8.3)	9.0 (3.6, 22.7)	3.0 (1.7, 3.7)
Median OS (95% CI), mos.	30.2 (12.4, –)	22.7 (11.5, –)	7.3 (4.7, 10.9)

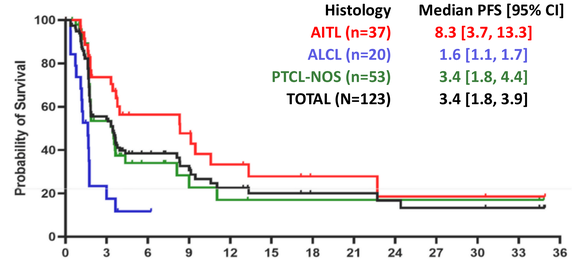
*One patient was missing data for number of prior lines of therapy.

EFFICACY OUTCOMES BY PRIOR ANTICANCER THERAPY

Prior therapies, n/N (%)	CR	PR	SD
CHOP-based therapy (CHOP/R-CHOP or CHOEP/EPOCH) (n=83)	27/83 (32.5)	12/83 (14.5)	4/83 (4.8)
BV or BV/chemo (n=47)	16/47 (34.0)	4/47 (8.5)	3/47 (6.4)
Salvage chemo after CHOP-based therapy, (n=43)	19/43 (44.2)	3/43 (7.0)	0
Autologous SCT (n=25)	6/25 (24.0)	7/25 (28.0)	1/25 (4.0)
Romidepsin* (n=19)	6/19 (31.6)	2/19 (10.5)	0

*One additional HDACi (belinostat) was used in one additional patient.

PROGRESSION-FREE SURIVAL BY HISTOLOGY



Number at risk:

AITL	37	23	13	11	7	5	3	3	2	2	2	1	0
ALCL	20	3	1	0									
PTCL-NOS	53	20	8	5	3	2	2	2	2	2	2	2	0
TOTAL	123	50	24	17	11	8	6	6	5	4	4	3	0

ADVERSE EVENTS: ANY GRADE IN ≥20% OF PATIENTS; GRADE ≥3 IN ≥5% OF PATIENTS — BY TREATMENT PERIOD

TEAE (any grade) in ≥20% of patients, n (%)	Cycles ≤2 (N=123)	Cycles >2–6 (n=63)	Cycles >6 (n=25)	Overall TEAE rate (any grade)
Neutropenia	35 (28.5)	14 (22.2)	4 (16.0)	41 (33.3)
AST increased	35 (28.5)	18 (28.6)	1 (4.0)	44 (35.8)
ALT increased	31 (25.2)	22 (34.9)	1 (4.0)	46 (37.4)
Diarrhea	25 (20.3)	16 (25.4)	8 (32.0)	41 (33.3)
Thrombocytopenia	23 (18.7)	8 (12.7)	7 (28.0)	32 (26.0)
Leukopenia	23 (18.7)	5 (7.9)	1 (4.0)	25 (20.3)
Fatigue	19 (15.4)	8 (12.7)	6 (24.0)	32 (26.0)

TEAE (grade ≥3) in ≥5% of patients, n (%)	Cycles ≤2 (N=123)	Cycles >2-6 (n=63)	Cycles >6 (n=25)	Overall TEAE rate (grade ≥3)
Neutropenia	17 (13.8)	8 (12.7)	3 (12.0)	22 (17.9)
ALT increased	16 (13.0)	14 (22.2)	0	26 (21.1)
AST increased	15 (12.2)	8 (12.7)	1 (4.0)	21 (17.1)
Macropapullar Rash	7 (5.7)	4 (6.3)	0	10 (8.1)
Thrombocytopenia	5 (4.1)	5 (7.9)	2 (8.0)	11 (8.9)
Lymphopenia	5 (4.1)	5 (7.9)	1 (4.0)	9 (7.3)
Diarrhea	4 (3.3)	5 (7.9)	5 (20.0)	12 (9.8)
Hypokalemia	1 (0.8)	0	3 (12.0)	4 (3.3)
Hypoxia	1 (0.8)	0	2 (8.0)	3 (2.4)

ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

AESI	Any grade	Median (range) time to onset (any event), days	AESI resulting in d/c*	Median (range) duration (any event), days	AESI resulting in death
Any AESI, n (%)	108 (87.8)	N/A	27 (22.0)	-	4 (3.3)
Colitis	3 (2.4)	223 (202-522)	1 (0.8)	10 (5, 17)	0
Cutaneous reactions	44 (35.8)	58 (1, 507)	1 (0.8)	12 (1, 273)	0
Diarrhea	41 (33.3)	65 (1, 616)	7 (5.7)	9 (1, 113)	0
Infections	51 (41.5)	56 (1, 930)	8 (6.5)	15 (1, 122)	2 (1.6)
Neutropenia	41 (33.3)	36 (1, 420)	1 (0.8)	8 (2, 155)	0
Pneumonia	8 (6.5)	43 (11, 644)	1 (0.8)	13 (2, 57)	0
Pneumonitis	2 (1.6)	33 (20, 71)	1 (0.8)	14 (1, 15)	1 (0.8)
Elevated aminotransferase	55 (44.7)	49 (1, 288)	10 (8.1)	9 (1, 274)	1 (0.8)

*d/c, discontinuation

TEAES WITH DOSE MODIFICATION OR DEATH

- TEAEs leading to dose hold or dose reduction were seen in 37.6% and 3.0% of patients, respectively
- TEAEs (excluding PD) resulting in death: n=10; of these, 4 were considered to be treatment-related (cryptococcosis, Epstein-Barr virus-associated lymphoproliferative disorder, pneumonitis, and sepsis), and only 2 were infections (sepsis and cryptococcosis)
- Non-treatment-related TEAEs resulting in death: cardiac arrest, gastrointestinal hemorrhage, hepatic failure, hypoxia, suicide, and vascular dementia

CONCLUSIONS

- **In a heavily treated, R/R population, duvelisib efficacy outcomes did not show a consistent pattern based on prior lines of therapy**
- **Notably, patients with more heavily pretreated disease (where unmet need may be greatest) demonstrated numerically favorable outcomes**
- **For R/R PTCL, a 75 mg BID dose was administered for the first 2 cycles (CLL/SLL indicated dose: 25 mg BID). Although there is a different dosing regimen for PTCL, generally there was no consistent pattern of higher rates of persisting or emerging AEs with longer treatment duration**
- **Rates of diarrhea showed a modest trend of increase; however, there was no increase in rates of colitis**
- **Rate of fatal infectious AEs was very low, and lower than in B-cell malignancy data**
- **Incidences of elevated aminotransferases were manageable with dose modification, and were not a leading cause of discontinuation**
- **These data support the tolerability of this regimen (75 mg BID for 2 cycles followed by 25 mg BID) in R/R PTCL**
- **Based on AITL subgroup efficacy, the sponsor has initiated a randomized, phase 3 trial (TERZO™, NCT06522737) investigating duvelisib in a homogeneous R/R nodal T-follicular helper cell lymphoma population**

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CONTACT

For further inquiries or information about the PRIMO or TERZO studies, please scan the QR code

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