Duvelisib, an Oral Dual PI3K-δ,γ Inhibitor, Efficacy and Safety in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Rationale for the Phase 2 PRIMO Trial

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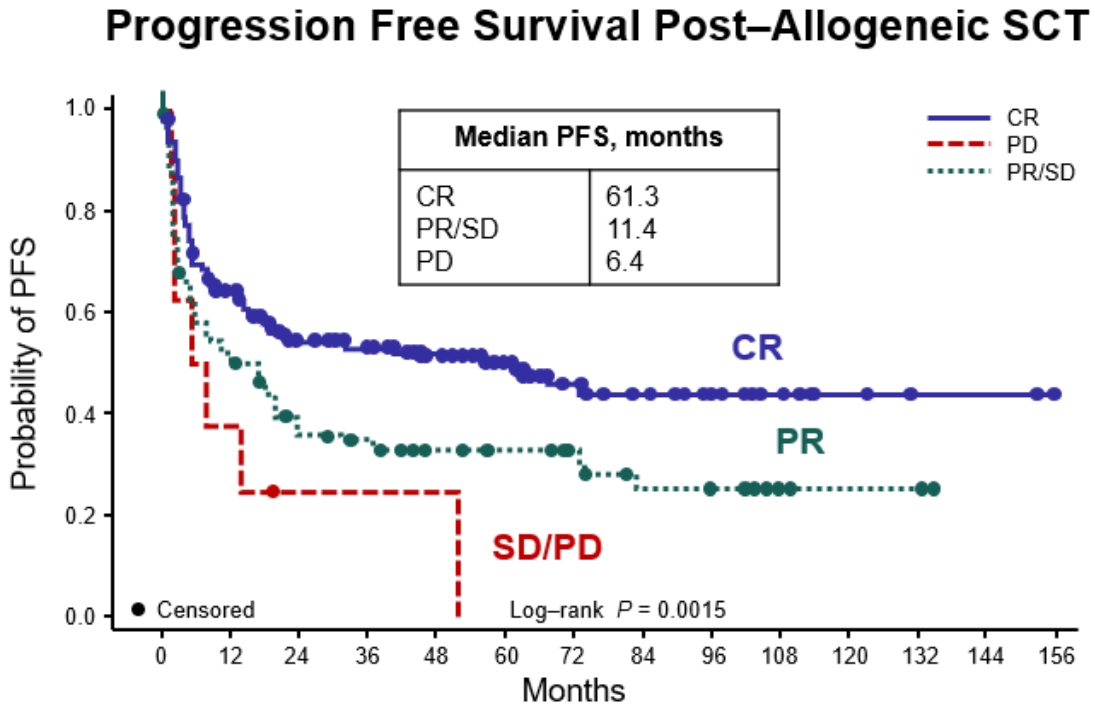
Introduction

- RR PTCL is an aggressive lymphoma with a poor prognosis, with a median overall survival of < 6 months[1]
- Most approved therapies for relapsed PTCL induce response rates of < 30% and median progression-free survival of < 4 months[2-6]

Drug	ORR, %	CR, %	Median PFS, months
Pralatrexate (N = 109)[2]	29	11	3.5
Romidepsin (N = 130)[3]	25	15	4
Belinostat (N = 120)[4]	26	11	1.6
Brentuximab (PTCL) (N = 34)[5]	41	24	6.4
Brentuximab (ALCL) (N = 58)[6]	86	57	14.6[a]

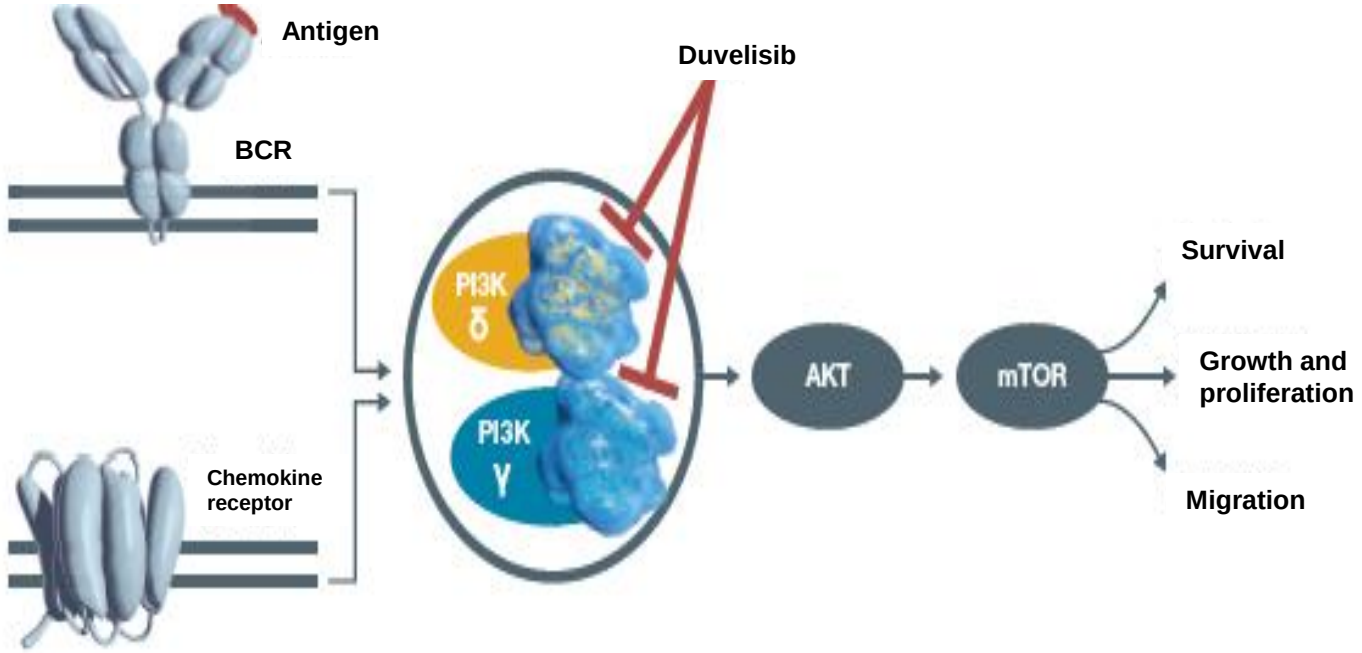
[a] Per IRC in subset of patients who achieved a CR.



1. Campo E, et al. *Blood.* 2011;117:5019-5032. 2. O'Connor OA, et al. *J Clin Oncol.* 2011;29:1182-1189. 3. Coiffier B, et al. *J Clin Oncol.* 2012;30:631-636. 4. O'Connor OA, et al. *J Clin Oncol.* 2015;33:2492-2499. 5. Horwitz SM, et al. *Blood.* 2014;123:3095-3100. 6. Pro B, et al. *J Clin Oncol.* 2012;30:2190-2196.

Duvelisib: a First-in-Class Oral Dual PI3K-δ,γ Inhibitor

- Duvelisib demonstrates a manageable safety profile and clinical activity over a broad range of hematologic malignancies
  - FDA approval for the treatment of RR CLL/SLL and FL in patients who have received ≥ 2 lines of prior therapy[1]
  - Granted Fast Track Designation by the FDA for the treatment of patients with PTCL who have received ≥ 1 prior therapy[2]
  - Being investigated in combination with other agents in multiple tumor types



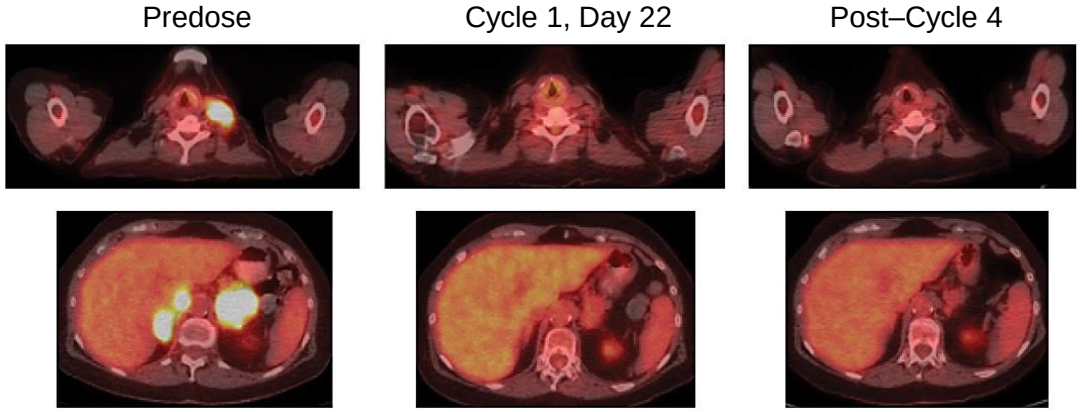
- In a phase 1 study, duvelisib demonstrated a manageable safety profile and clinical benefit in patients with PTCL[3,4]

1. Copiktra (duvelisib) [package insert]. Needham, MA: Verastem, Inc; 2018. 2. Verastem [press release]. http://investor.verastem.com/phoenix.zhtml?c=250749&p=irol-newsArticle&ID=2298618. Accessed June 12, 2019. 3. Flinn IW, et al. *Blood.* 2018;131:877-887. 4. Horwitz SM, et al. *Blood.* 2018;131:888-898.

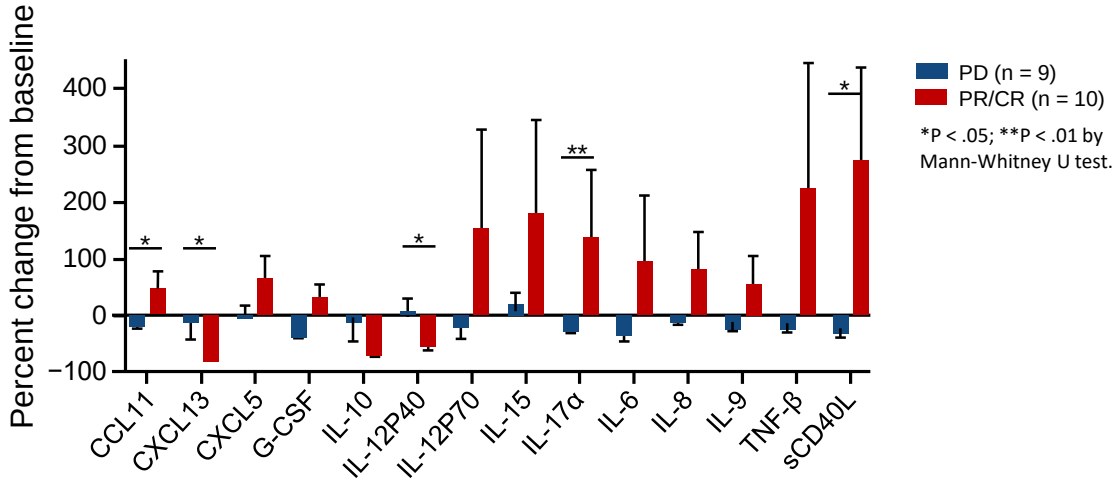
Duvelisib Activity in T-Cell Lymphoma

Clinical Correlates

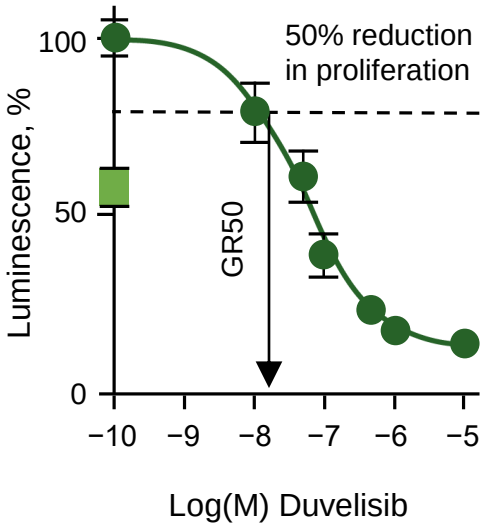
Rapid response to duvelisib in a patient with PTCL and PR

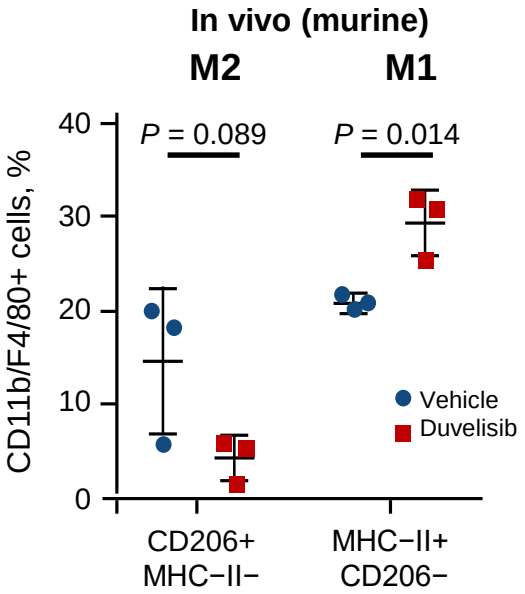


Cytokine changes associated with response to duvelisib



Preclinical Duvelisib Activity





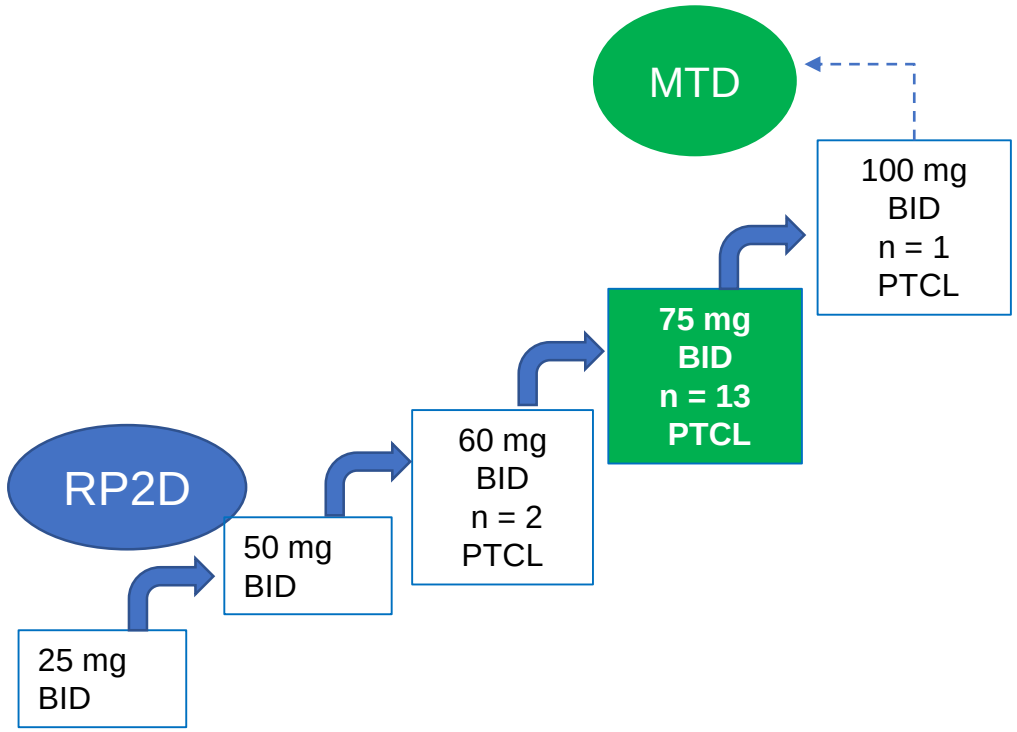
- Duvelisib exhibited potent activity against some T-cell lymphoma cell lines in vitro
- Duvelisib stimulated a change in the distribution macrophages from an immunosuppressive (M2) to immunostimulatory (M1) phenotype in PTCL mouse xenograft models

Horwitz SM, et al. *Blood.* 2018;131:888-898.

Duvelisib Monotherapy: Clinical Activity in PTCL

Phase 1 Trial[1,2]

Patients with RR PTCL: N = 16



	Duvelisib 75 mg BID (n = 13)	All PTCL (N = 16)
ORR, n (%)	**7 (54)**	**8 (50)**
[95% CI]	**[25.1-80.8]**	**[24.7-75.3]**
Best overall response, n (%)		
Complete response	2 (15)	3 (19)
Partial response	5 (38)	5 (31)
Stable disease	1 (8)	1 (6)
Progressive disease	5 (38)	6 (37)
Unknown	0	1 (6)
Median time to response (range), mo	1.9	1.9 (1.6-3.5)
Median PFS (95% CI), mo	8.3	8.3 (1.4-NR)
Median OS (95% CI), mo	16.2	8.4 (4.3-NR)

- Response to duvelisib was observed across a spectrum of PTCL subtypes
  - 3 CRs in EATL, AITCL, and PTCL-NOS
  - 5 PRs in AITCL, ALCL, PTCL-NOS, and SPTCL (n = 2)

1. Horwitz SM, et al. *Blood.* 2018;131:888-898. 2. Flinn IW, et al. *Blood.* 2018;131:877-887.

Duvelisib Monotherapy: Select TEAEs of Interest

Phase 1 Trial[1,2]

	Patients With Hematologic Malignancies[1]		Patients With TCL[2]
	Duvelisib 25 mg BID (n = 66)	Duvelisib 75 mg BID (n = 124)	Duvelisib[a] (n = 35)
All grades, n (%)			
ALT or AST increased	23 (35)	59 (48)	20 (57)
Diarrhea	33 (50)	49 (39)	11 (31)
Neutropenia	21 (32)	23 (18)	7 (20)
Colitis	6 (9)	7 (6)	4 (11)
Grade ≥ 3, n (%)			
ALT or AST increased	12 (18)	29 (23)	14 (40)
Diarrhea	10 (15)	12 (10)	0
Neutropenia	17 (26)	18 (14)	6 (17)
Colitis	5 (8)	4 (3)	2 (6)

[a] 27 patients (77%) with TCL were treated at the MTD of oral duvelisib (75 mg) twice daily on a 28-day cycle. The other 8 patients received 25 mg (n = 1), 50 mg (n = 1), 60 mg (n = 4),or 100 mg (n = 2) twice daily.

- Duration of exposure was not equivalent between 25 and 75 mg BID groups

1. Verastem Oncology. Data on file. 2. Horwitz SM, et al. *Blood.* 2018;131:888-898.

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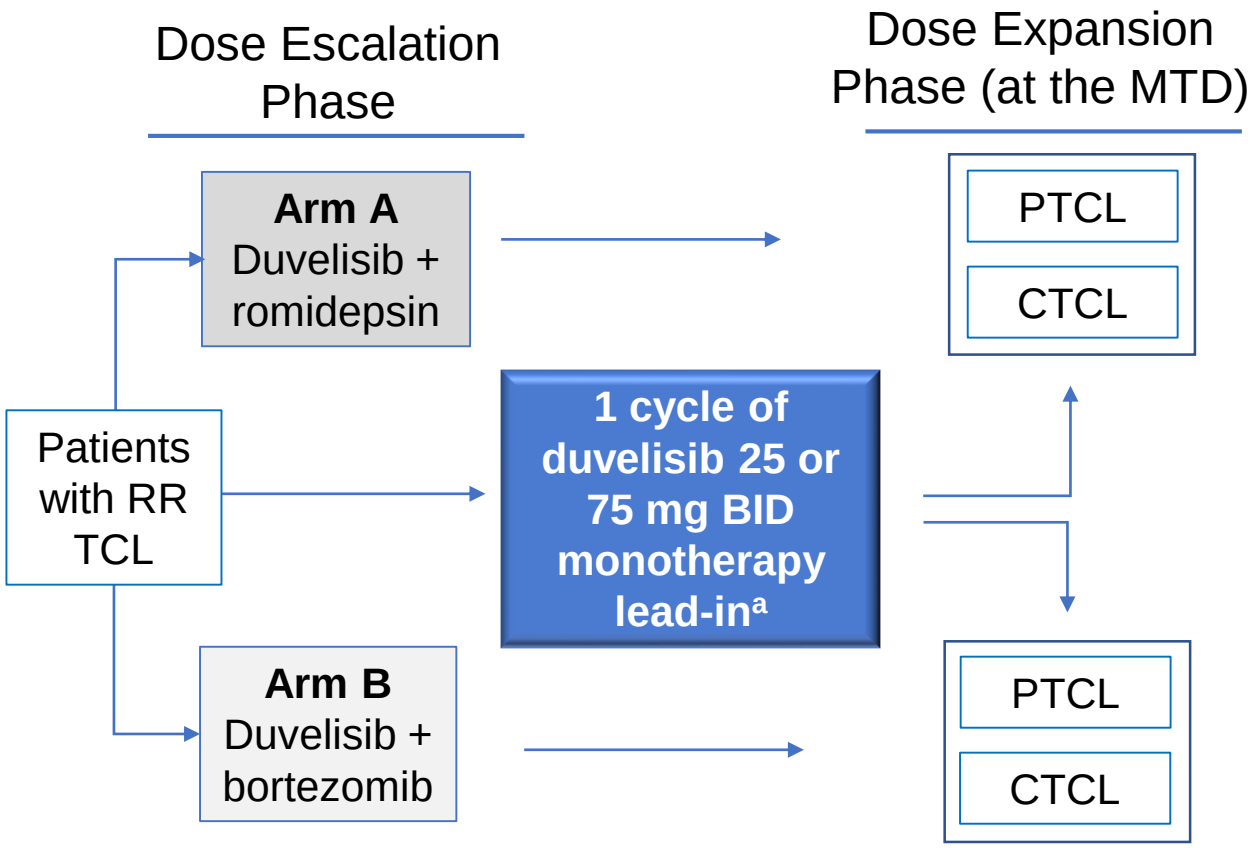
Efficacy of Duvelisib Monotherapy Lead-In to Combination Therapy

Phase 1 Duvelisib + Romidepsin/Bortezomib Combination Study[1,2]



	Patients With PTCL Who Responded After 1 Cycle of Duvelisib Monotherapy Lead-In (n = 16)	
	Duvelisib 75 mg BID (n = 9)	Duvelisib 25 mg BID (n = 7)
ORR, n (%)	4 (44)	4 (57)
Best overall response, n (%)		
CR	2 (22)	2 (29)
PR	2 (22)	2 (29)

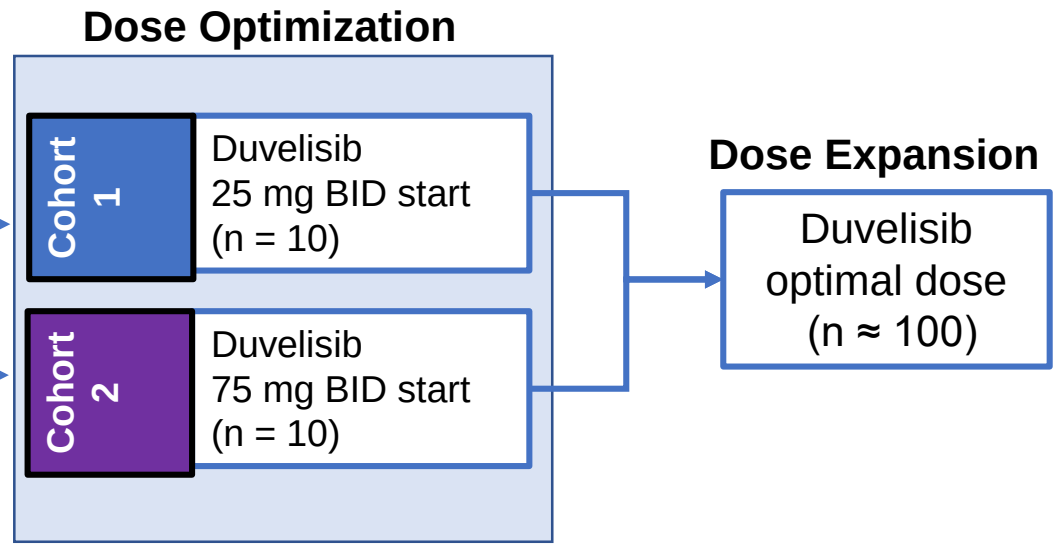
[a] In the dose escalation phase, the MTD of duvelisib in combination with romidepsin or bortezomib was 75 mg BID and 25 mg BID, respectively. Patients who did not achieve CR on duvelisib alone at the end of cycle 1 proceeded to combination therapy.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02783625. Accessed June 12, 2019. 2. Horwitz SM, et al. *Blood.* 2018:132(suppl 1) [abstract 683].

PRIMO: Phase 2 Study of Duvelisib Monotherapy in Relapsed or Refractory PTCL

Patients With Relapsed or Refractory PTCL[a]

- Histologically confirmed PTCL subtype: PTCL-NOS, AITCL, ALCL, or NKTL
- Measurable disease per IWG for PTCL
- No transformation to aggressive lymphoma
- No prior history of allogeneic stem cell transplant or treatment with PI3K inhibitor
- ECOG PS ≤ 2



The expansion phase is ongoing, with ≈ 40 study centers open in the United States; additional sites planned for Germany, Italy, UK, and Japan

Primary objectives: identify the optimal dose of duvelisib and examine its efficacy, safety, and tolerability at the optimal dose

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

[a] Received ≥ 2 cycles of 1 prior regimen administered with curative intent and did not achieve PR or better after ≥ 2 cycles, or did not achieve CR after ≥ 6 cycles, or progressed after initial response.

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03372057. Accessed June 12, 2019.

Conclusions

- Duvelisib—a dual PI3K-δ,γ inhibitor—represents a potential new therapy for the treatment of T-cell lymphomas
- In phase 1 studies, duvelisib 25 or 75 mg BID demonstrated encouraging clinical activity in patients with relapsed or refractory PTCL, with responses observed across a spectrum of subtypes
- The dose optimization phase of the ongoing phase 2 PRIMO study will identify the optimal regimen of duvelisib monotherapy in relapsed or refractory PTCL and characterize the efficacy and tolerability of duvelisib in ≈ 100 patients