

**PROPEL: A Multi-center Phase 2 Open-label Study  
of Pralatrexate with Vitamin B<sub>12</sub> and Folic Acid  
Supplementation in Patients with Relapsed or Refractory  
Peripheral T-cell Lymphoma (PTCL)**

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# PROPEL

Pralatrexate in Patients with  
Relapsed  
Or Refractory  
Peripheral T-cell  
Lymphoma

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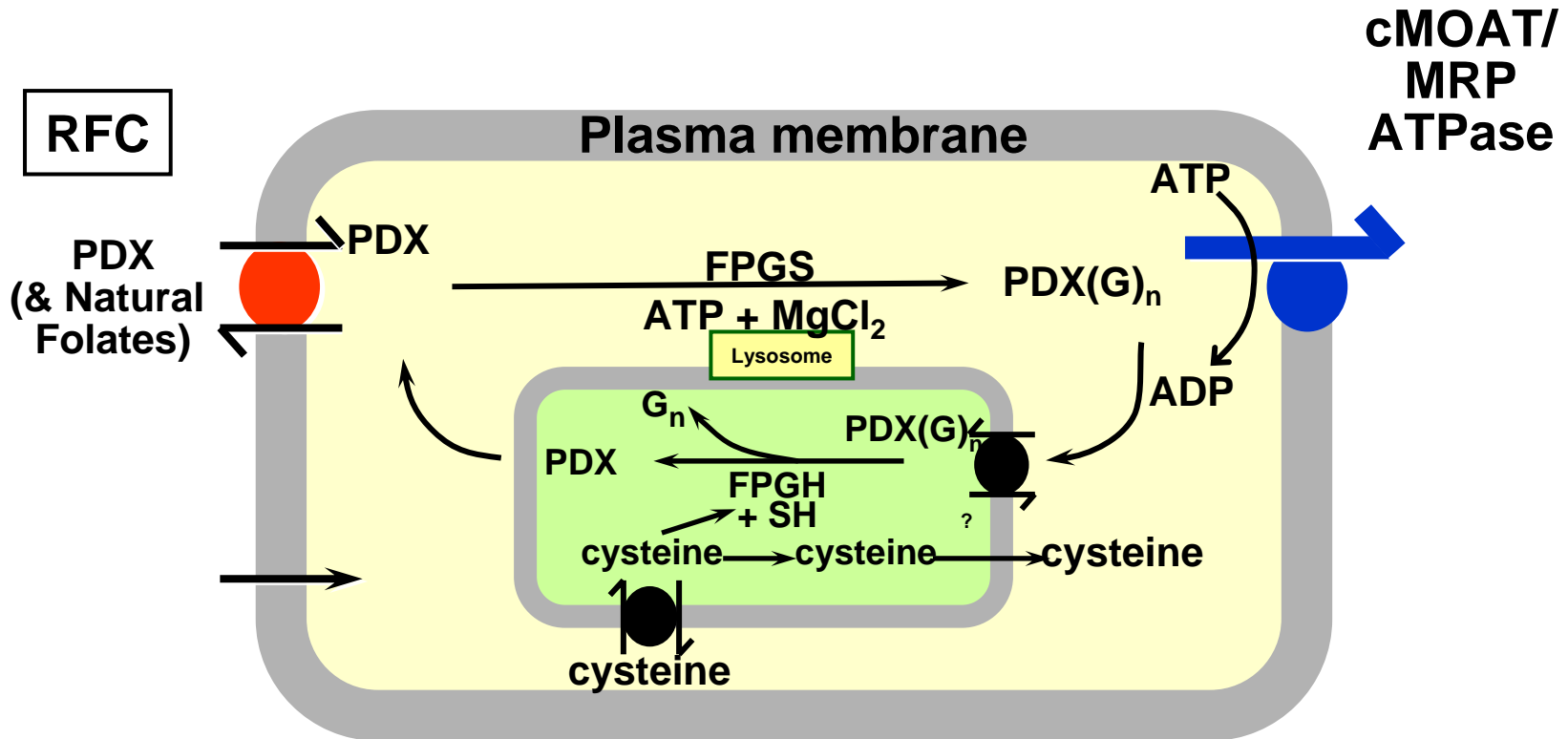
## Study Rationale

- **Patients with peripheral T-cell lymphoma (PTCL) have a poor prognosis with current treatment paradigms**
- **New treatment options are needed for patients with PTCL, especially for those with relapsed or refractory disease**
- **Pralatrexate is a novel targeted antifolate designed to accumulate preferentially in cancer cells**
- **Pralatrexate has shown an encouraging response rate in patients with T-cell lymphoma in earlier studies<sup>1</sup>**
- **PROPEL was developed under the FDA Special Protocol Assessment (SPA) program**
- **Pralatrexate has US and EU orphan drug designation for T- cell non-Hodgkin's lymphoma (NHL) and FDA fast-track designation**

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## Pralatrexate Mechanism of Action

### RFC Mediates Tumor Selective Accumulation of Pralatrexate



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## Study

<b>Design</b>	<b>Phase 2 single arm, open label, multi-center, non-randomized, international</b>
<b>Target Population</b>	<b>Adult patients with relapsed or refractory PTCL</b>
<b>Number of Patients</b>	<b>Minimum of 100 evaluable patients</b>
<b>Treatment</b>	<b>Pralatrexate 30 mg/m<sup>2</sup> IV x 6 weeks followed by 1 week rest (7 week cycle) in combination with vitamin supplementation</b>
<b>Primary Endpoint</b>	<b>Response rate by IWC (CR + CRu + PR)</b>
<b>Secondary Endpoints</b>	<ul style="list-style-type: none"><li><b>• Duration of response</b></li><li><b>• Progression-free survival</b></li><li><b>• Overall survival</b></li></ul>

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## Key Eligibility Criteria

- **Pathological confirmation of PTCL**
  - Revised European American Lymphoma (REAL) World Health Organization (WHO) disease classification
- **Progressive disease after at least 1 prior treatment**
  - No restriction on maximum number of prior therapies
- **ECOG PS 0 – 2**
- **Adequate hematological, hepatic, and renal function**
  - Platelets  $\geq 100,000 \mu\text{L}$
  - ANC  $\geq 1,000 \mu\text{L}$
  - Bilirubin  $\leq 1.5 \text{ mg/dL}$
  - ALT/AST  $\leq 2.5 \times \text{ULN}$
  - Creatinine  $\leq 1.5 \text{ mg/dL}$

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## Eligible T-cell Lymphoma Histological Types

- **T/Natural killer (NK) cell leukemia/lymphoma**
- **Adult T-cell leukemia/lymphoma (human T-cell leukemia virus [HTLV] 1+)**
- **Angioimmunoblastic T-cell lymphoma**
- **Blastic NK lymphoma (with skin, lymph node, or visceral involvement)**
- **Anaplastic large cell lymphoma, primary systemic type**
- **PTCL – unspecified**
- **T/NK-cell lymphoma – nasal**
- **Enteropathy-type intestinal lymphoma**
- **Hepatosplenic T-cell lymphoma**
- **Extranodal peripheral T/NK-cell lymphoma – unspecified**
- **Subcutaneous panniculitis T-cell lymphoma**
- **Transformed mycosis fungoides**

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## Independent Central Review Assessments

- **Histologic confirmation of PTCL by independent central pathology review:**
  - **Cases that required further adjudication were referred to an adjudicator (Dr. Eric Hsi, Cleveland Clinic)**
- **A data monitoring committee performed safety assessments after 10, 35, and 65 patients had completed 1 cycle of therapy**
- **An independent central review team conducted the response assessments, which included:**
  - **Radiology (CT/MRI and PET scan)**
  - **Skin photography**
  - **All relevant clinical data**

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## Enrollment

### Total Accrual

- **115 Patients enrolled (August 2006 – April 2008)**
  - **80 (69%) US**
  - **26 (23%) Europe**
  - **9 ( 8%) Canada**

### Safety and Efficacy Populations

- **Baseline and safety analyses**
  - **111 patients received  $\geq 1$  dose of pralatrexate**
    - 4 patients did not receive pralatrexate
- **Efficacy analyses**
  - **109 evaluable patients**
    - 2 additional patients deemed not evaluable based on ineligible histology by central pathology review

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## Patient Characteristics

Category	Parameter	Pralatrexate Treated (N=111)	
		n	Percent
Gender	M/F	76 / 35	68% / 32%
Race	White	80	72%
	Black	14	13%
	Asian	6	5%
	Hispanic	9	8%
	Middle Eastern	1	<1%
	Unknown	1	<1%
Age (years)	< 65	71	64%
	≥ 65	40	36%
	Mean (range)	57.7	21 – 85 yrs
ECOG PS	0	43	39%
	1	49	44%
	2	19	17%

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## Histology

Histopathology	Per Independent Central Review (N=111)		Per Investigator (N=111)	
	n	Percent	n	Percent
<b>PTCL-unspecified</b>	<b>59</b>	<b>53%</b>	<b>51</b>	<b>46%</b>
<b>Anaplastic large cell lymphoma, primary systemic type</b>	<b>17</b>	<b>15%</b>	<b>17</b>	<b>15%</b>
<b>Angioimmunoblastic T-cell lymphoma</b>	<b>13</b>	<b>12%</b>	<b>18</b>	<b>16%</b>
<b>Transformed mycosis fungoides</b>	<b>12</b>	<b>11%</b>	<b>13</b>	<b>12%</b>
<b>Blastic NK lymphoma (with skin, lymph node, or visceral involvement)</b>	<b>4</b>	<b>4%</b>	<b>4</b>	<b>4%</b>
<b>T/NK-cell lymphoma-nasal</b>	<b>2</b>	<b>2%</b>	<b>1</b>	<b>&lt;1%</b>
<b>Extranodal peripheral T/NK-cell lymphoma unspecified</b>	<b>1</b>	<b>&lt;1%</b>	<b>2</b>	<b>2%</b>
<b>Adult T-cell leukemia/lymphoma (HTLV 1+)</b>	<b>1</b>	<b>&lt;1%</b>	<b>2</b>	<b>2%</b>
<b>T/NK-cell leukemia/lymphoma</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>
<b>Mycosis fungoides (not transformed)*</b>	<b>1</b>	<b>&lt;1%</b>	<b>0</b>	<b>0%</b>
<b>Inconsistent with T-cell lymphoma*</b>	<b>1</b>	<b>&lt;1%</b>	<b>0</b>	<b>0%</b>
<b>Aggressive T-cell lymphoma</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>
<b>Aggressive large cell T-cell lymphoma</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>

\*Two treated patients excluded from efficacy analysis

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## Prior Therapy

Number of prior systemic regimens	N = 111		
	Number of Regimens	n	Percent
1	23	21%	
2	30	27%	
3	23	21%	
4	14	13%	
≥ 5	21	19%	
<b>Median (range)</b>	<b>3.0 (1-12)</b>		
Number of prior regimens (including radiation and topical)	1	18	16%
	2	27	24%
	3	23	21%
	4	16	14%
	≥ 5	27	24%
	<b>Median (range)</b>	<b>3.0 (1-13)</b>	

**53% of patients were refractory to the most recent line of prior therapy**  
**25% of patients never had a response to any prior therapy**

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## Prior Systemic Therapy for PTCL

<b>Type</b>	<b>Pralatrexate (N=111)</b>	
	<b>n</b>	<b>Percent</b>
<b>CHOP</b>	<b>78</b>	<b>70%</b>
<b>Platinum-containing combination chemotherapy</b>	<b>45</b>	<b>41%</b>
<b>Non platinum-containing combination chemotherapy</b>	<b>43</b>	<b>39%</b>
<b>Single agent chemotherapy*</b>	<b>36</b>	<b>32%</b>
<b>Autologous SCT</b>	<b>18</b>	<b>16%</b>
<b>Bexarotene</b>	<b>15</b>	<b>14%</b>
<b>Steroids alone</b>	<b>8</b>	<b>7%</b>
<b>HyperCVAD</b>	<b>8</b>	<b>7%</b>
<b>Denileukin diftitox</b>	<b>7</b>	<b>6%</b>
<b>Systemic investigational agents</b>	<b>7</b>	<b>6%</b>
<b>Other (e.g., interferon, cyclosporine, alemtuzumab)</b>	<b>13</b>	<b>12%</b>

\*other than denileukin diftitox or bexarotene

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## Summary of Response by Central Review: IWC

<b>69% of responders did so after Cycle 1</b>		<b>Pralatrexate (N=109)</b>		
		<b>n</b>	<b>Percent</b>	<b>95% CI</b>
<b>Best Response</b>	<b>CR+CRu+PR</b>	<b>29</b>	<b>27%</b>	<b>19-36</b>
	<b>CR</b>	<b>10</b>	<b>9%</b>	
	<b>CRu</b>	<b>1</b>	<b>&lt;1%</b>	
	<b>PR</b>	<b>18</b>	<b>17%</b>	
	<b>SD</b>	<b>23</b>	<b>21%</b>	
	<b>PD</b>	<b>40</b>	<b>37%</b>	
	<b>UE</b>	<b>3</b>	<b>3%</b>	
	<b>ND: off-treatment in C1</b>	<b>14</b>	<b>13%</b>	



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## Duration of Response by Central Review: IWC

**An accurate estimate of the median duration of response cannot be reported at this time due to the current length of follow up**

Duration of Response*	n= 29	
	n (%)	n still on treatment
> 3 months	17 (59%)	6
≤ 3 months	12 (41%)	1

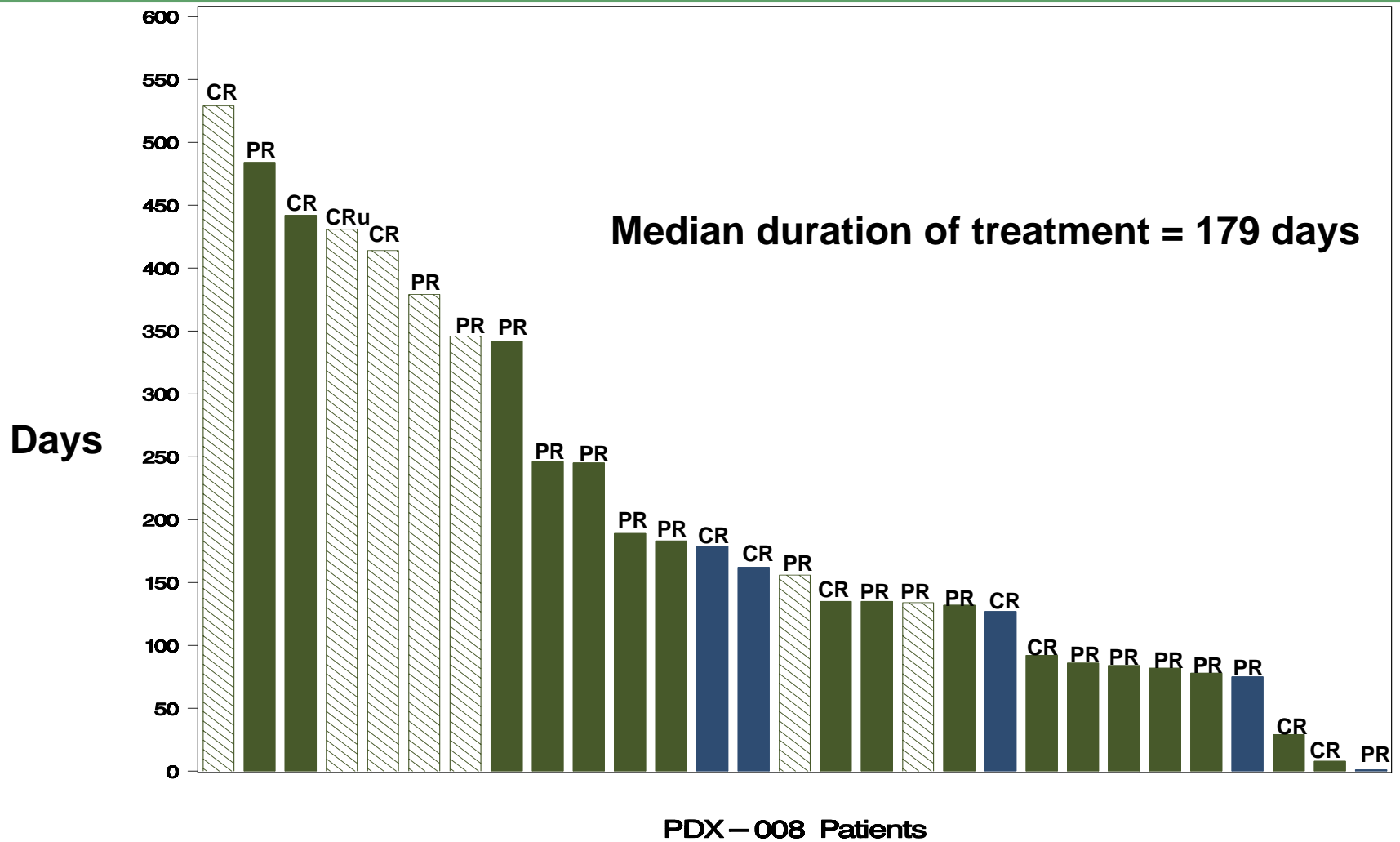
**Assessment of response occurs at the conclusion of every odd cycle**

**Patients receiving subsequent therapy (including SCT) before PD is documented are censored**

\*Duration of response is measured from first day of documented response to PD or death.

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## Duration of Treatment in Responders by Central Review: IWC



- On Treatment (N=7)
- Off Treatment, Subsequent SCT (N=5)
- Off Treatment (N=17)

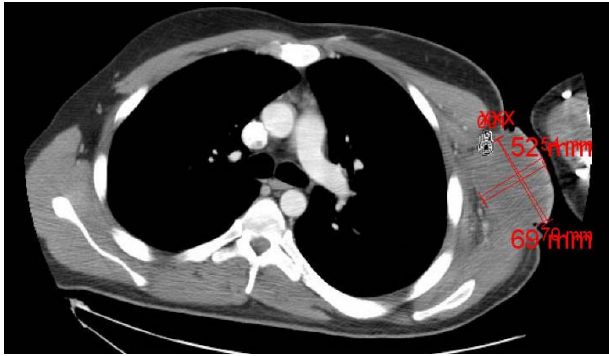
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## Summary of Response by Investigator Assessment

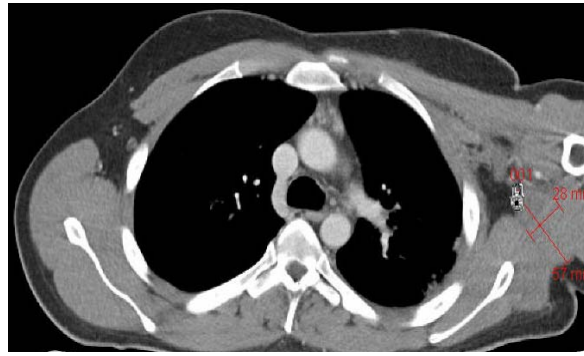
		Pralatrexate (N=109)		
		n	Percent	95% CI
Best Response	CR+CRu+PR	42	39%	29-48
	CR	14	13%	
	CRu	4	4%	
	PR	24	22%	
	SD	21	19%	
	PD	40	37%	
	UE	1	< 1%	
	ND: off-treatment in C1	5	5%	

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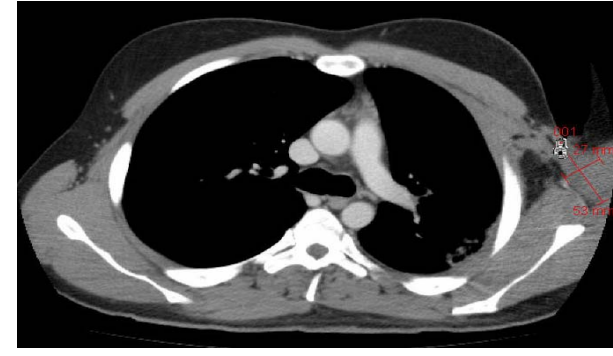
## Patient with Anaplastic Large Cell Lymphoma



CT October 3, 2006



CT March 2, 2007



CT April 13, 2007



October 16, 2006



January 2, 2007



January 29, 2007

**Patient refractory to CHOP, DHAP and ICE  
Received pralatrexate for 127 days prior to autologous SCT**

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## Response Analyses by Key Subsets

		Pralatrexate (N = 109)			
		n	Percent	Response Rate IWC Percent	95% CI
Region	North America	85	78%	28%	19-39
	Europe	24	22%	21%	7-42
Age	< 65	70	64%	24%	15-36
	≥ 65	39	36%	31%	17-48
Prior systemic therapy	1 regimen	23	21%	26%	10-48
	2 regimens	29	27%	21%	8-40
	> 2 regimens	57	52%	30%	18-43
Prior transplant	Yes	18	17%	33%	13-59
	No	91	83%	25%	17-35
Histology	PTCL NOS	59	54%	31%	19-44
	Angioimmunoblastic	13	12%	8%	0-36
	Anaplastic LC	17	16%	29%	10-56
	Transformed MF	12	11%	25%	5-57
	Other	8	7%	25%	3-65

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## Adverse Events $\geq$ Gr 3 Occurring in $\geq$ 3% of Patients (n=111)

	Any Grade	Grade 3	Grade 4
<b>Mucosal inflammation*</b>	<b>70%</b>	<b>17%</b>	<b>4%</b>
<b>Thrombocytopenia**</b>	<b>41%</b>	<b>14%</b>	<b>19%<sup>1</sup></b>
<b>Nausea</b>	<b>40%</b>	<b>4%</b>	<b>0%</b>
<b>Fatigue</b>	<b>36%</b>	<b>5%</b>	<b>2%</b>
<b>Anemia**</b>	<b>34%</b>	<b>16%</b>	<b>2%</b>
<b>Neutropenia**</b>	<b>24%</b>	<b>13%</b>	<b>7%</b>
<b>Dyspnea</b>	<b>19%</b>	<b>7%</b>	<b>0%</b>
<b>Hypokalemia**</b>	<b>15%</b>	<b>4%</b>	<b>1%</b>
<b>Abnormal LFTs*</b>	<b>13%</b>	<b>5%</b>	<b>0%</b>
<b>Abdominal pain</b>	<b>11%</b>	<b>4%</b>	<b>0%</b>
<b>Leukopenia**</b>	<b>11%</b>	<b>3%</b>	<b>4%</b>
<b>Febrile Neutropenia</b>	<b>5%</b>	<b>5%</b>	<b>0%</b>
<b>Sepsis</b>	<b>5%</b>	<b>3%</b>	<b>2%</b>
<b>Hypotension</b>	<b>5%</b>	<b>3%</b>	<b>1%</b>

\*includes 6 MedDRA preferred terms \*\*includes 2 MedDRA preferred terms \*\*\*includes 3 MedDRA preferred terms

1- Only 5 patients had platelet count < 10,000  $\mu$ L

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## Summary and Conclusions

- **PROPEL is the largest prospective study ever conducted in patients with relapsed or refractory PTCL**
  - **Patients in the study received a median of 3 prior systemic regimens (range 1-12)**
- **PROPEL established that pralatrexate has impressive clinical activity in patients with relapsed or refractory PTCL**
  - **Central independent review of all relevant clinical data revealed durable CRs and PRs**
  - **Responses were seen irrespective of the amount of prior therapy**
- **Mucosal inflammation and thrombocytopenia were the most common Grade 3 - 4 AEs**
- **Pralatrexate-based combinations may provide a novel platform for future upfront T-cell treatment programs**

# Acknowledgements

**Thank you to all patients, their families and the PROPEL Study Team**

## Investigators and Institutions

Study Chair: **Owen A. O'Connor** – Columbia University

**Steve Horwitz** – Memorial Sloan Kettering

**Barbara Pro** – MD Anderson

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