Abstract 257:

Phase 1 Trial Testing Single Agent CUDC-907, a Novel, Oral Dual Inhibitor of HDAC & PI3K: Initial Assessment of Patients with RR DLBCL, Including Double Expressor Lymphoma

Anas Younes[1], Jesus G. Berdeja[2], Manish R. Patel[3], Kevin R. Kelly[4], Ian W. Flinn[2], John F Gerecitano[1], Sattva S. Neelapu[5], Amanda R. Copeland[1], Amy Akins[3], Myles Clancy[6], Anna Ma[6], Kaiming Sun[6], Ze Tian[6], Jing Wang[6], Jaye Viner[6], and Yasuhiro Oki[5]

[1]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York City, NY
[2]Sarah Cannon Research Institute, Nashville, TN
[3]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL
[4]University of Southern California Keck School of Medicine, Los Angeles, CA
[5]Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX
[6]Curis, Inc, Lexington, MA

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Presenter Disclosures

- Research Support
  - Curis, Inc, Janssen, Novartis, Seattle Genetics
- Honoraria
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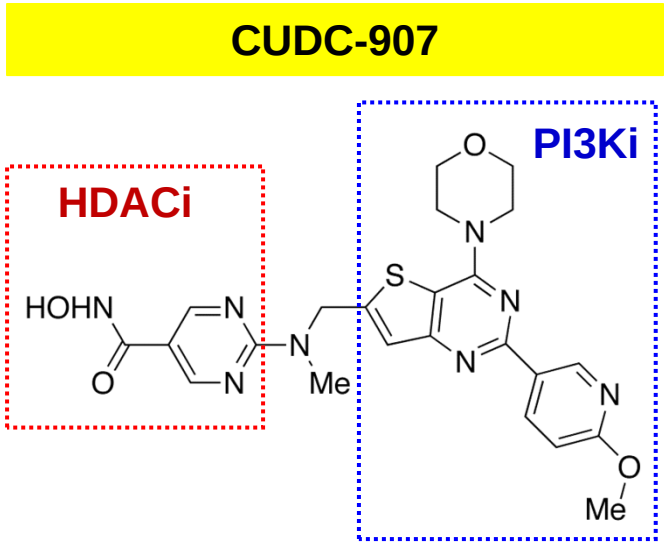
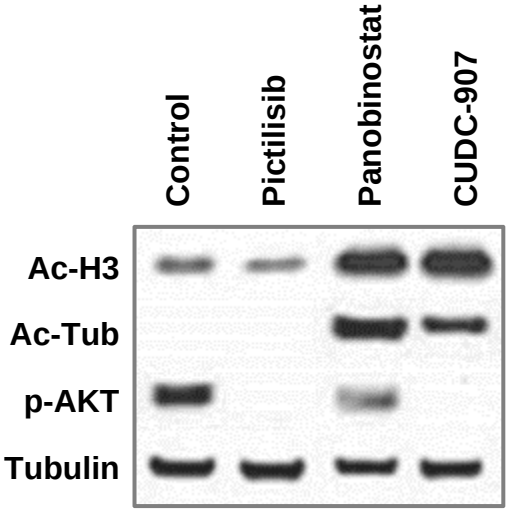
CUDC-907: Chemically Designed Oral, Dual Inhibitor of HDAC and PI3K

- **First in class, rationally designed, dual inhibitor of HDAC and PI3K**
- **Potential to overcome drug resistance by suppressing critical oncogenic networks**

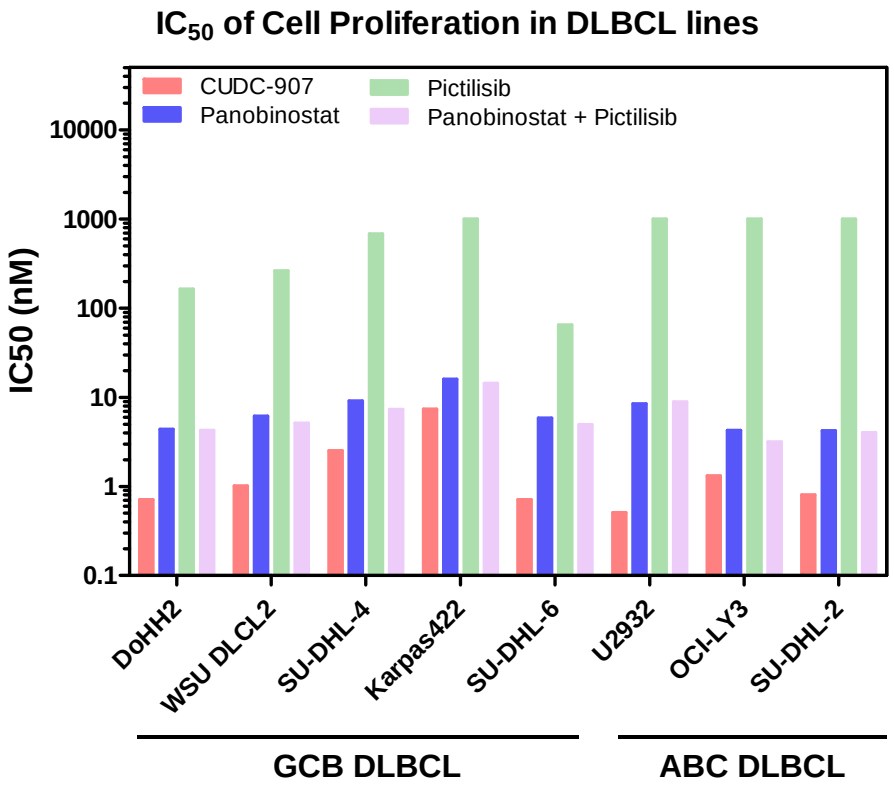




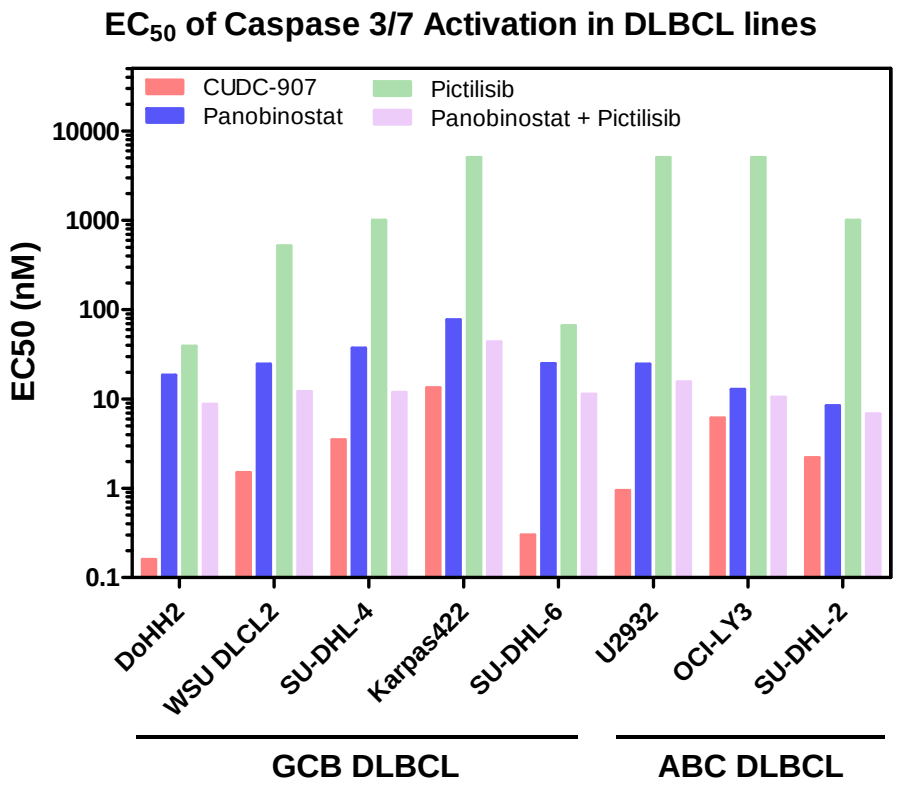
Enzyme	HDAC					PI3K			
Isotype	1	2	3	6	10	Alpha	Delta	Beta	Gamma
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

In Vitro Efficacy in DLBCL Cells

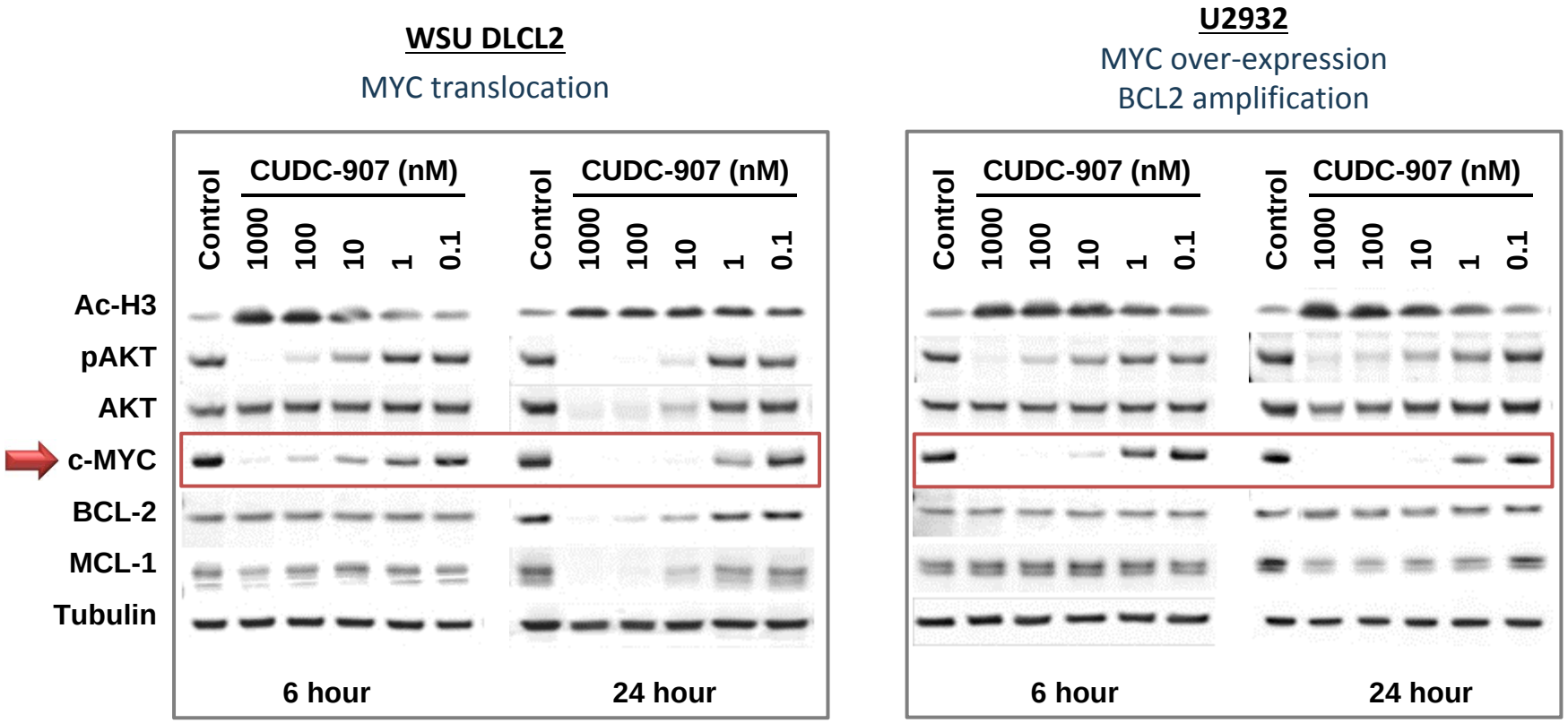
Anti-proliferation



Apoptosis Induction

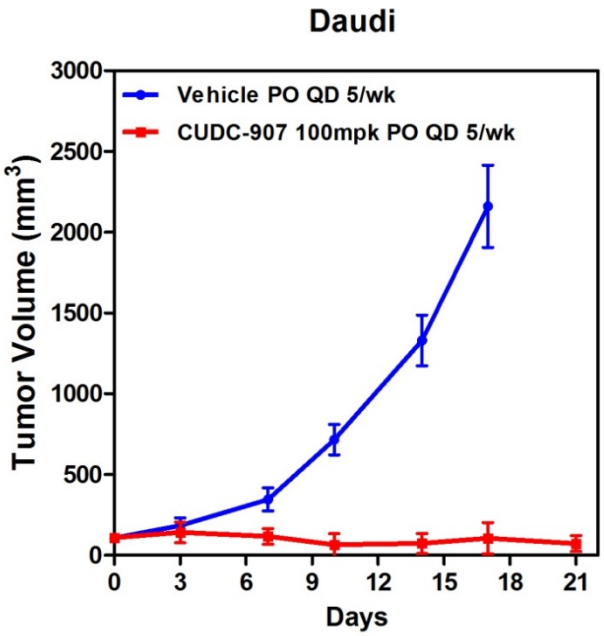


CUDC-907 Decreases MYC Protein Levels in DLBCL Cells



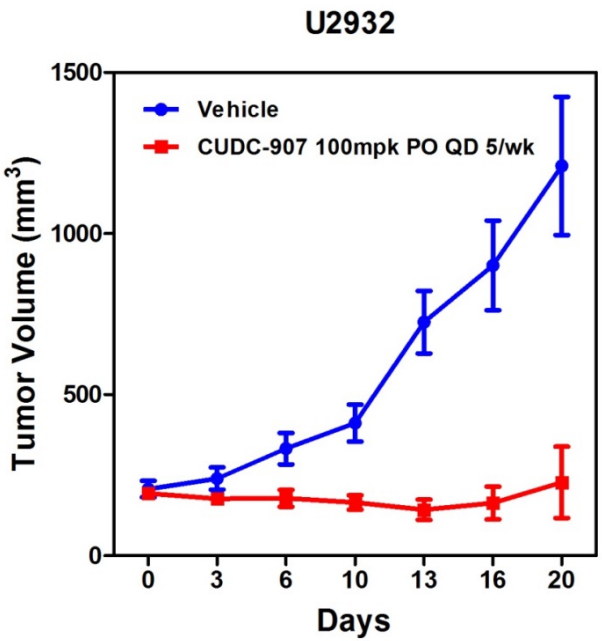
In Vivo Efficacy in MYC+ Xenograft Models

Burkitt Lymphoma



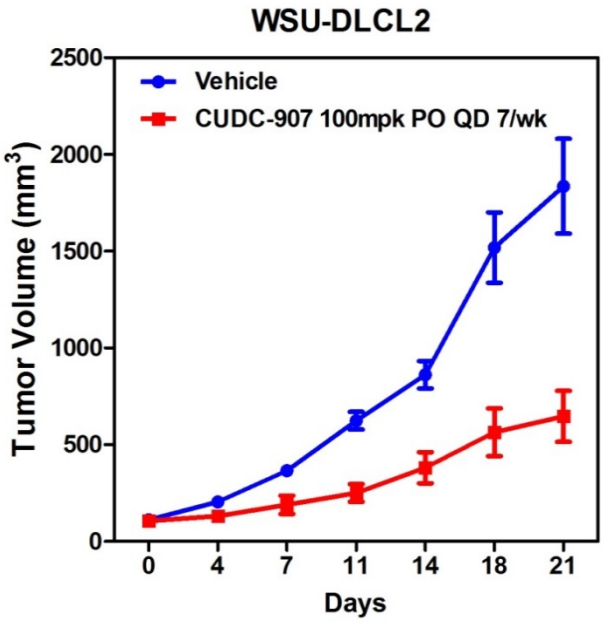
MYC translocation
TP53 (G266E)

ABC DLBCL



MYC over-expression
BCL2 amplification
TP53 (C176Y)

GCB DLBCL



MYC & BCL2 translocations
TP53 (R248Q)
EZH2 (Y646F)

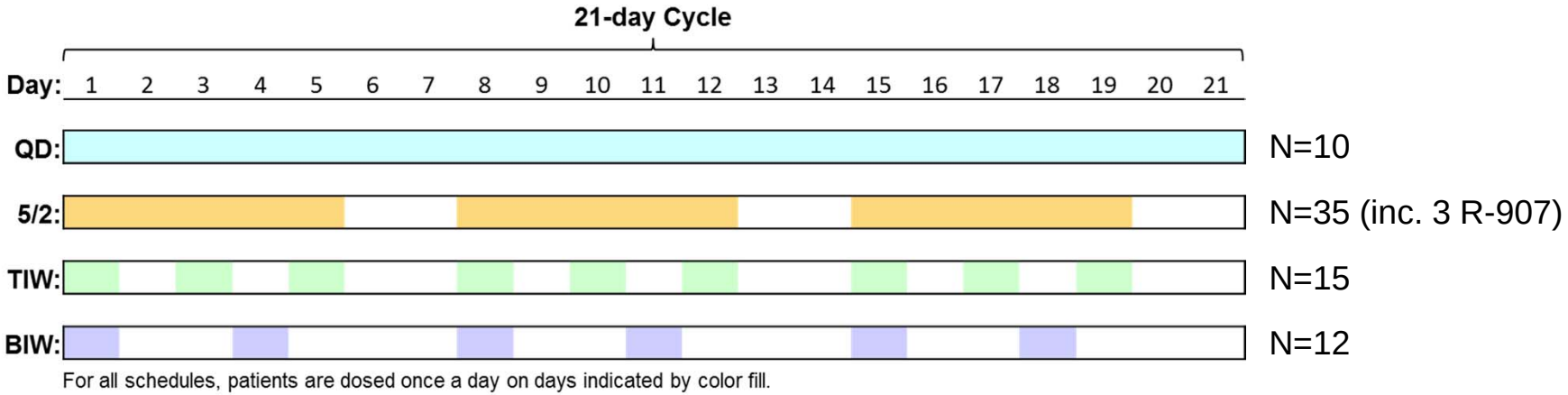
CUDC-907 Phase 1 Trial Design

- Objectives
  - Primary: MTD, RP2D
  - Secondary: Safety and tolerability, pharmacokinetics, biomarkers, anti-cancer activity

- Study Population
  - Histopathologically confirmed relapsed or refractory lymphoma or multiple myeloma after ≥2 prior regimens
  - Measurable or evaluable disease
  - Age ≥ 18 years
  - ECOG performance status ≤2

Dosing

- Oral, once daily dosing (21-day cycles)
  - Dose Escalation Phase
    - QD: 30 or 60 mg
    - BIW or TIW: 60, 90, 120 or 150 mg
    - 5/2 (5 days on, 2 days off): 60 mg
  - Dose Expansion Phase
    - 60 mg 5/2 monotherapy in patients with RR DLBCL, HL or MM
    - 60 mg 5/2 + rituximab 375 mg/m^2 (R-907) in patients with RR DLBCL



Criteria for DLT & Response-evaluable Population

- Dose Limiting Toxicity
  - Non-hematological Grade 3 AE, other than Grade 3 nausea or vomiting treated with sub-optimal antiemetic
  - AE resulting in a dose delay ≥7 days
  - Grade 4 neutropenia ≥7 days, or ≥Grade 3 with fever >101.3°F (38.5°C) or infection
  - Grade 4 thrombocytopenia ≥7 days, or ≥Grade 3 with significant bleeding

- Response-evaluable Population
  - Received at least 1 dose of study drug and underwent 1 post-baseline disease assessment

Demographics & Study Disposition: All Patients

Characteristics & Disposition	Overall (N=72)
Male, n (%)	50 (69)
Age, median years (range)	64 (22-85)
Histology, n (%)	
Diffuse large B-cell lymphoma (DLBCL)	25 (35)
Transformed follicular lymphoma (t-FL/DLBCL)*	9 (13)
Hodgkin Lymphoma (HL)	17 (24)
Multiple Myeloma (MM)	9 (13)
Other lymphoma**	21 (29)
Prior Therapies	
No. prior regimens [median (range)]	3 (1-9)
HDAC inhibitor, n (%)	9 (13)
PI3K inhibitor, n (%)	3 (4)

*High grade or composite low-high grade disease per local pathology report

**Includes T-cell (n=5), lymphoplasmacytic (n=3), small lymphocytic (n=3), mantle cell (n=3), follicular (n=2), marginal zone (n=2), Burkitt (n=1), unspecified B-cell (n=1), and gray-zone (n=1)

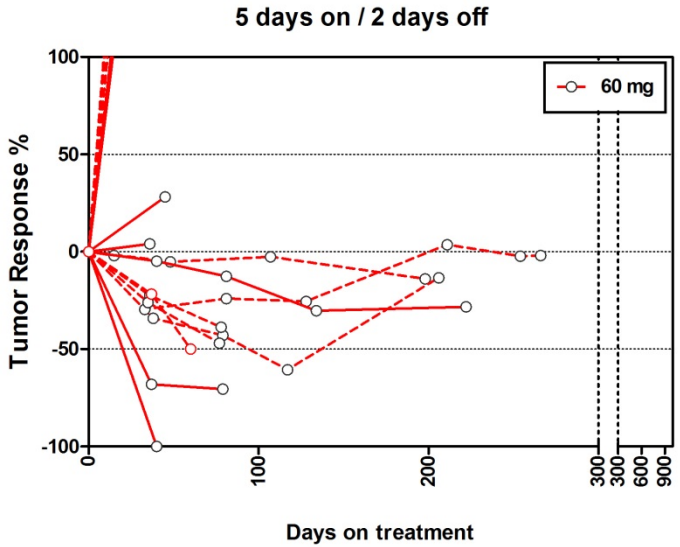
DLTs & RP2D Selection

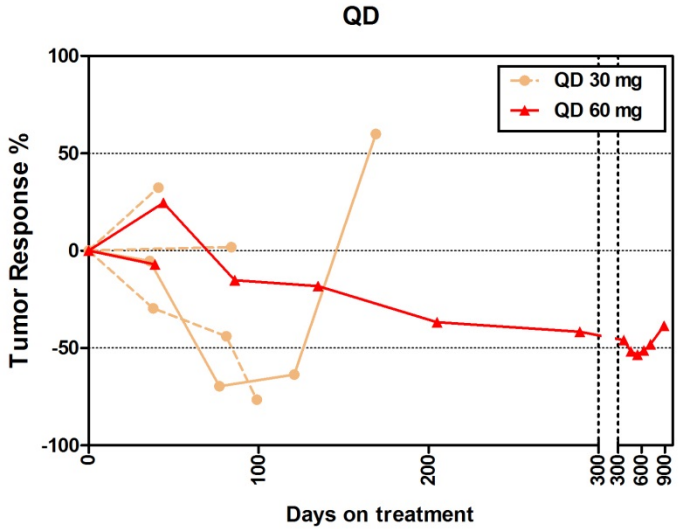
- 4 DLTs at the highest doses tested for QD and intermittent (BIW, TIW) dosing groups
  - 60 mg QD: G3 diarrhea, G4 hyperglycemia*
  - 150 mg BIW: G3 hyperglycemia**
  - 150 mg TIW: G3 diarrhea*

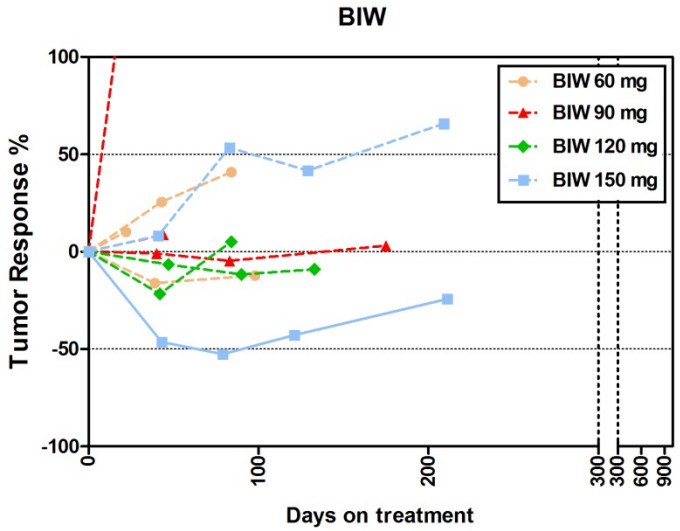
- 60 mg 5/2 selected as RP2D
  - Tolerability comparable to that of other schedules
  - Responses tend to occur earlier than with other schedules
  - No DLTs

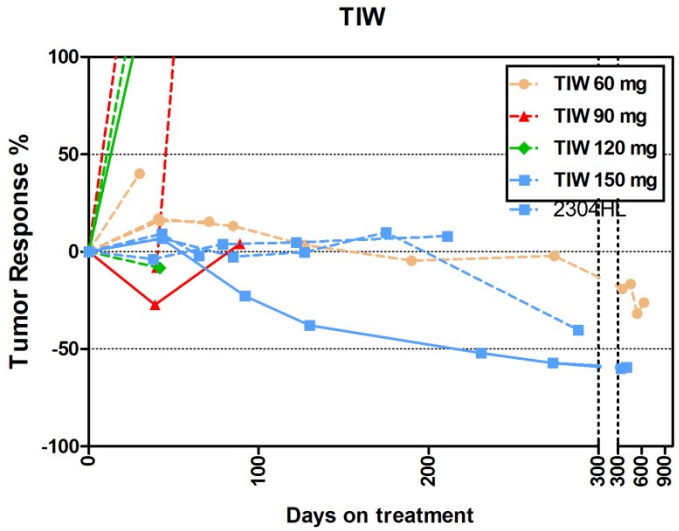
*Subjects with RR HL, **Subject with RR DLBCL

Tumor Response by Dose & Schedule

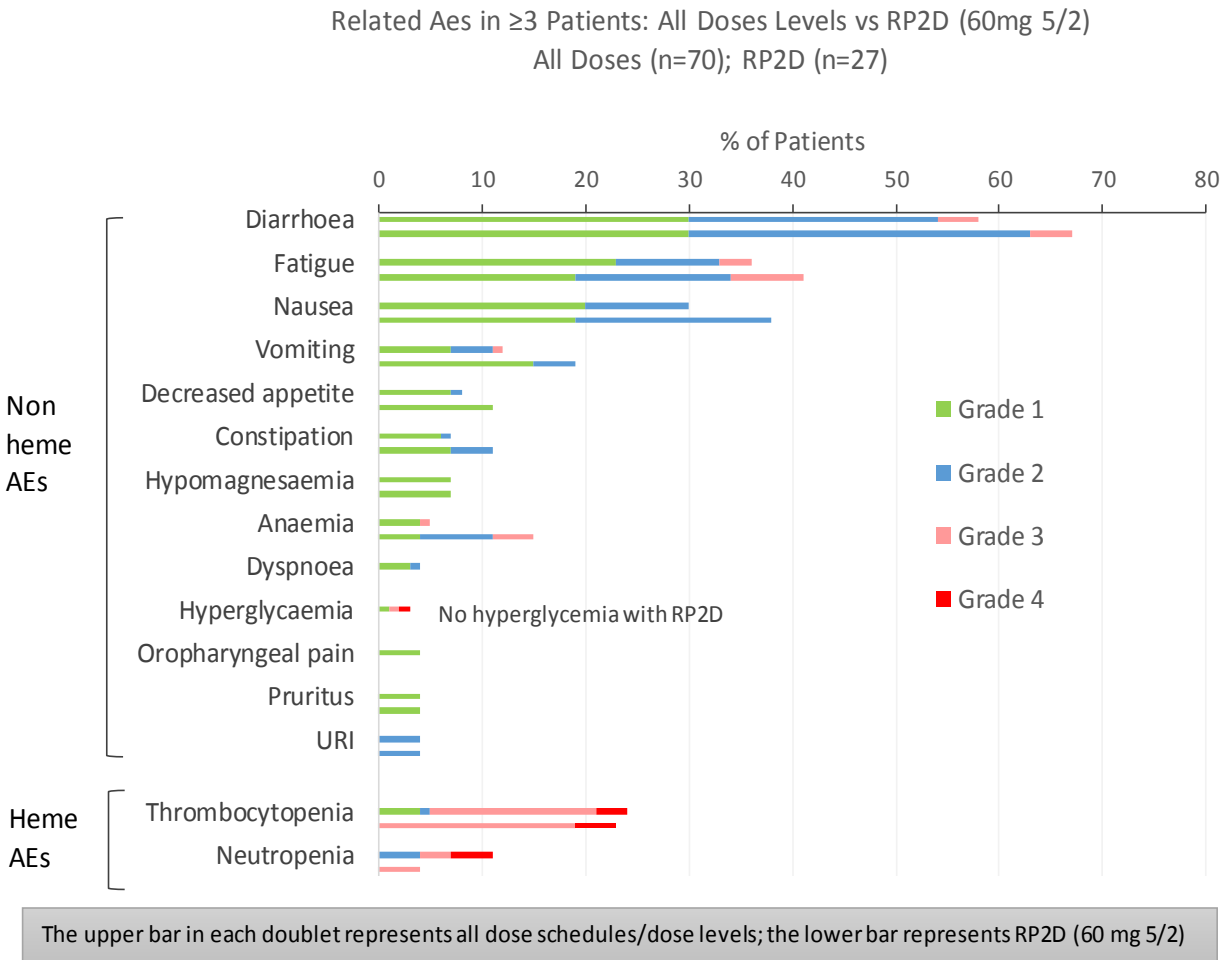








Treatment-Related Adverse Event Frequency: All Doses/Schedules *vs* RP2D (60 mg 5/2)



Most common AEs:

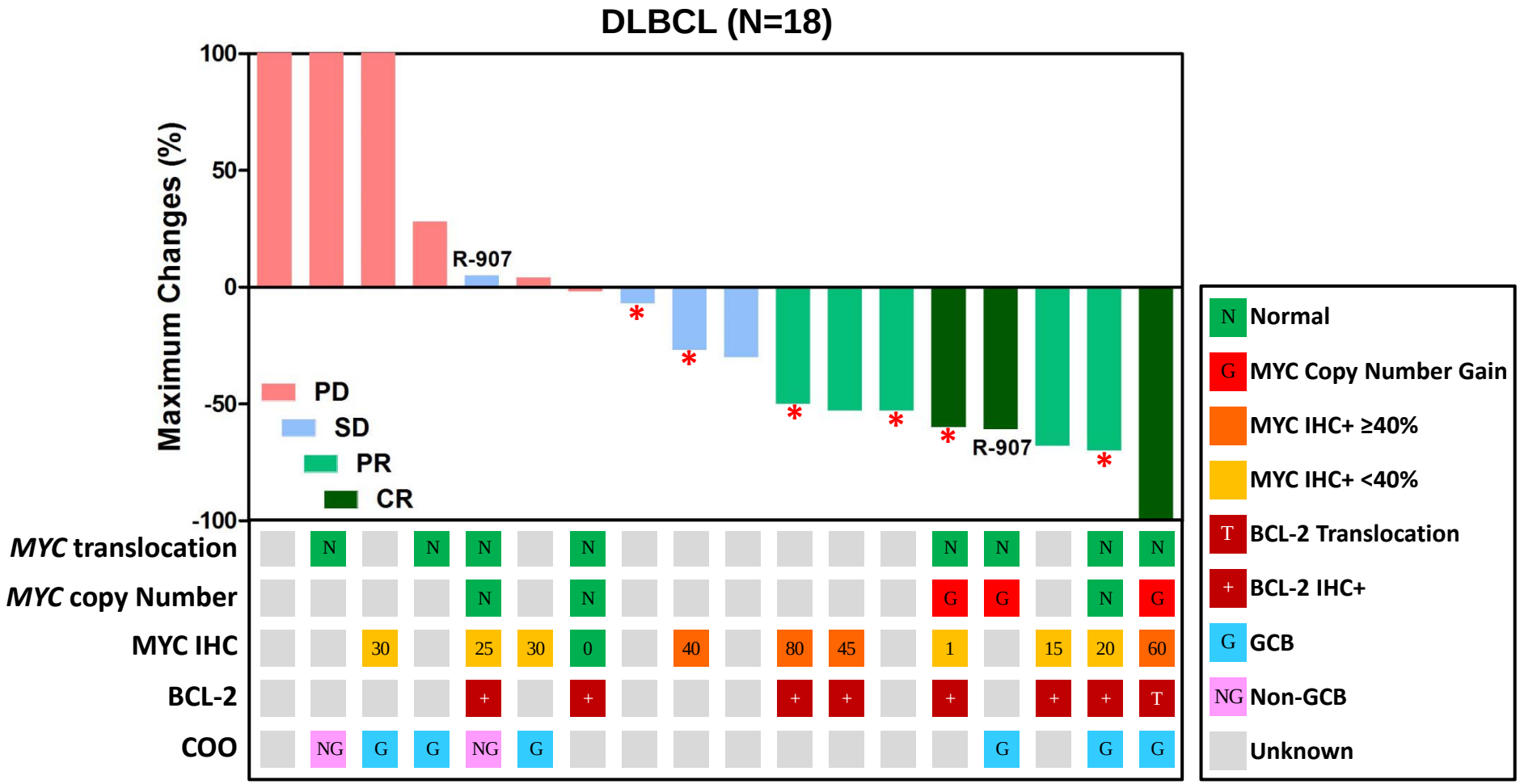
All dose schedules

- Diarrhea (59%)
- Fatigue (36%)
- Nausea (30%)
- Thrombocytopenia (24%)
- Neutropenia (11%)

RP2D (60mg 5/2)

- Diarrhea (67%)
- Fatigue (41%)
- Nausea (37%)
- Thrombocytopenia (22%)
- Vomiting (19%)
- Anemia (15%)

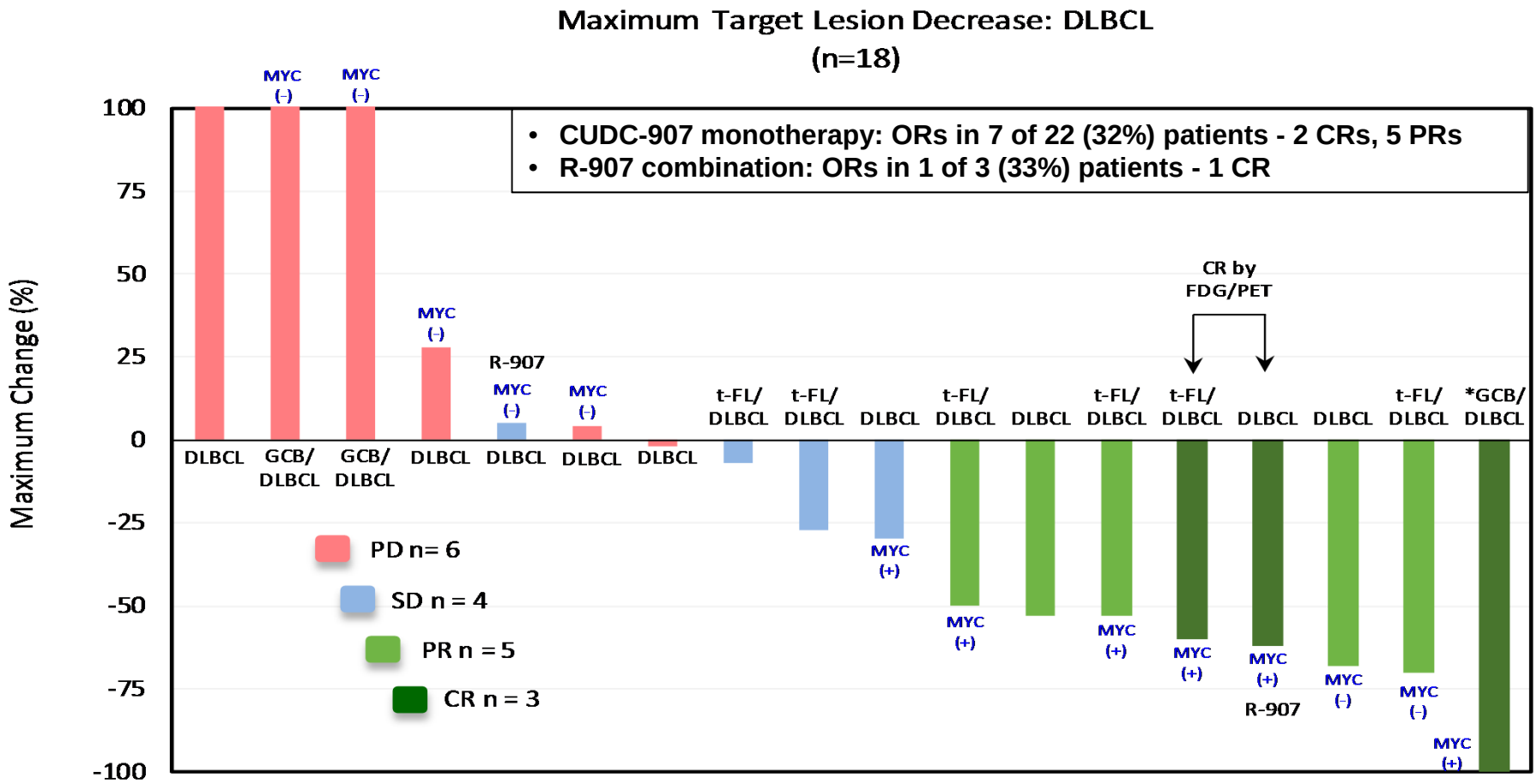
Exploratory Biomarker Analysis in RR DLBCL: MYC, BCL-2 and COO



Note: 18 of 25 patients were evaluable for disease response.
7 of 25 patients discontinued treatment prior to completing their first post-baseline response assessment.

* t-FL/DLBCL

RR DLBCL Maximum Target Lesion Change



DLBCL - Diffuse Large B Cell Lymphoma; t-FL - Transformed Follicular Lymphoma; GCB DLBCL - Germinal Center B Cell like Diffuse Large B Cell Lymphoma

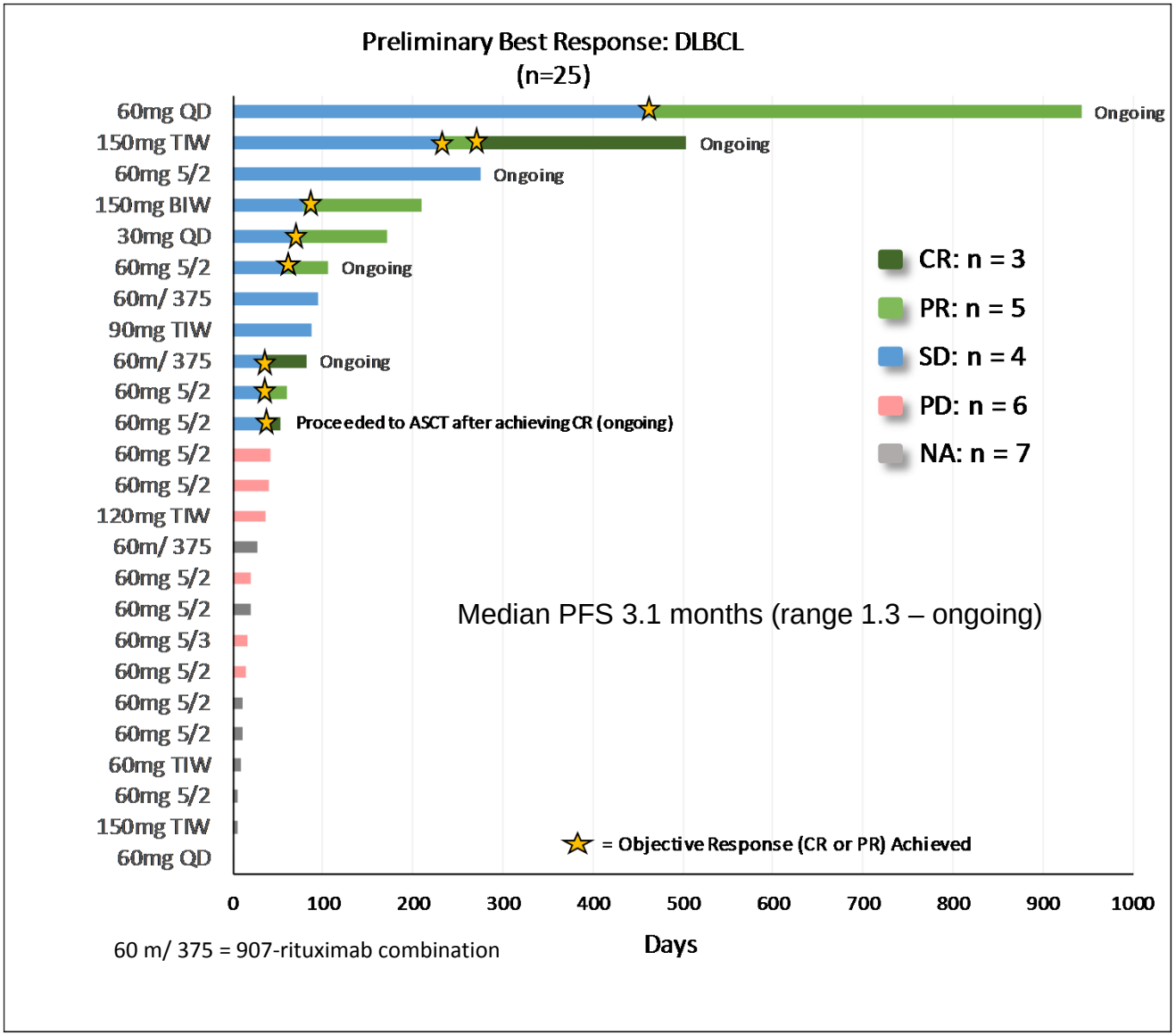
MYC (+): ≥ 40% expression by IHC; or translocation or copy number gain (3-4 copies) by FISH

R-907 = rituximab + CUDC-907

* Achieved CR Cycle 2, proceeded to ASCT (CR ongoing)

Note: 18 or 25 patients were evaluable for disease response. 7 of 25 patients discontinued treatment prior to completing their first post-baseline response assessment.

RR DLBCL Response by Treatment Duration



Conclusions

- Orally administered CUDC-907 is reasonably tolerated with self-limiting AEs that most commonly consist of G1-2 diarrhea, fatigue, nausea, and thrombocytopenia
- Objective responses in patients with RR DLBCL on all dosing schedules with CUDC-907 monotherapy (including those with MYC+ and DE disease)
  - ITT: 7/22 patients (32%)
  - Response-evaluable: 7/16 patients (44%)
- Ongoing Phase 1 expansion testing CUDC-907 at RP2D of 60 mg 5/2 +/- rituximab with extensive biomarker analysis (ClinicalTrials.gov: NCT01742988)
- Phase 2 study will further evaluate CUDC-907 +/- rituximab in patients with RR DLBCL exhibiting *MYC* translocation or copy number gain, MYC protein overexpression

In Press

- Lancet Oncology “Phase 1 safety and dose escalation of CUDC-907, a first-in-class, oral, dual inhibitor of HDAC and PI3K in relapsed or refractory lymphoma and multiple myeloma”

Acknowledgments

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