Abstract S480:

Phase 1 Trial of CUDC-907, a Novel, Oral Dual Inhibitor of HDAC & PI3K: Updated Assessment of Patients with Relapsed or Refractory DLBCL, Including Double Expressor Lymphoma

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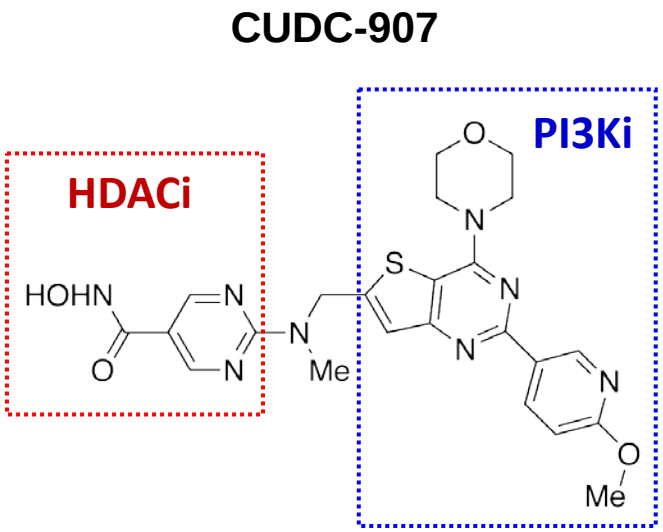
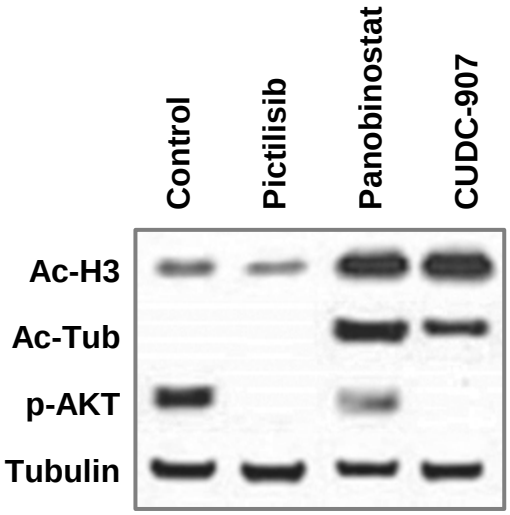
Presenter Disclosures

- Research Support
  - Curis Inc, Janssen, Novartis, Seattle Genetics
- Honoraria
  - Abbvie, Bayer, BMS, Celgene, Gilead, Incyte, Janssen, Novartis, Seattle Genetics, Takeda

CUDC-907: Chemically Designed Oral, Dual Inhibitor of HDAC and PI3K

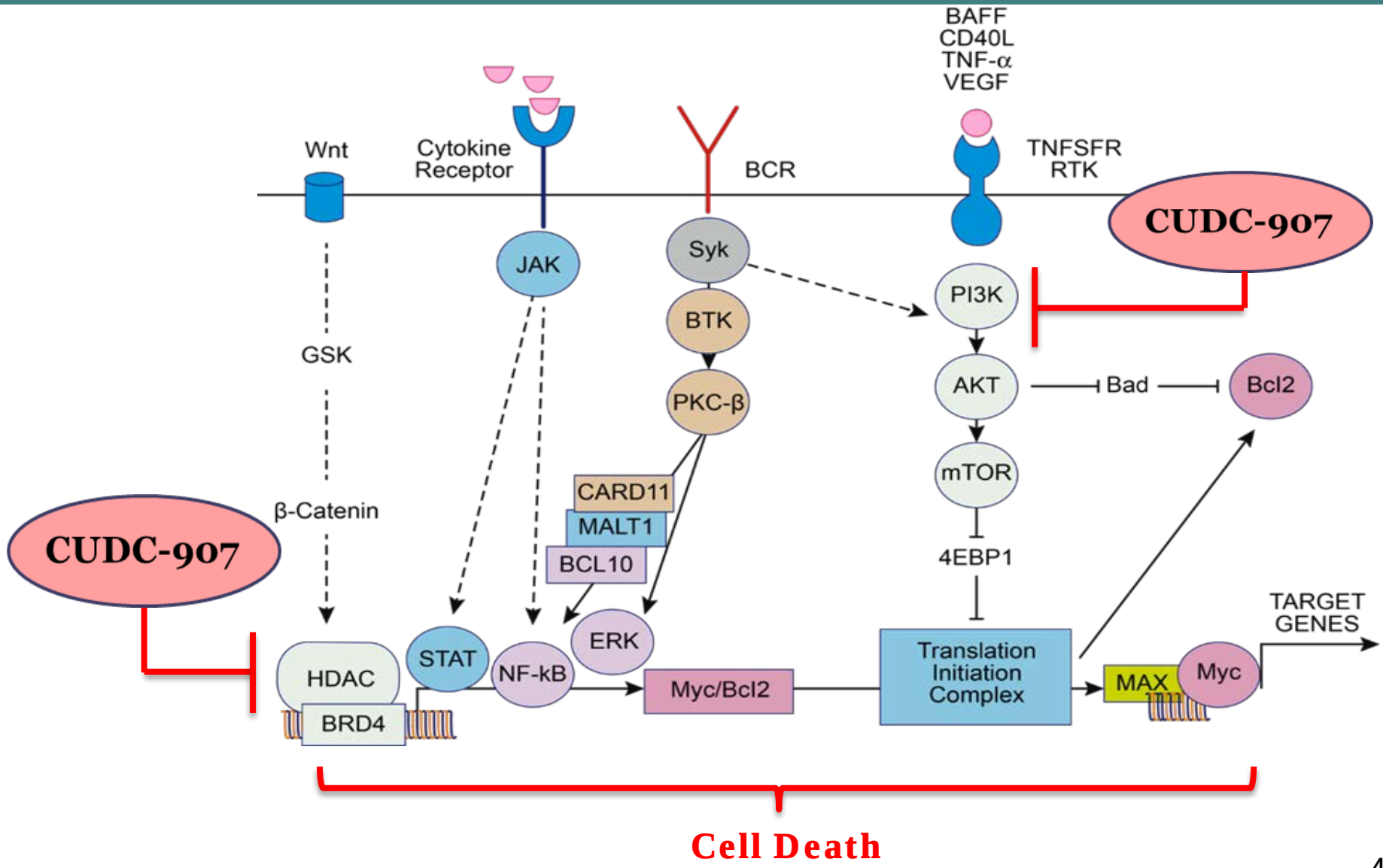
- First in class, rationally designed, dual inhibitor of HDAC (class I and II) and PI3K (class I α, β, and δ)
- Potential to overcome drug resistance by suppressing critical oncogenic networks





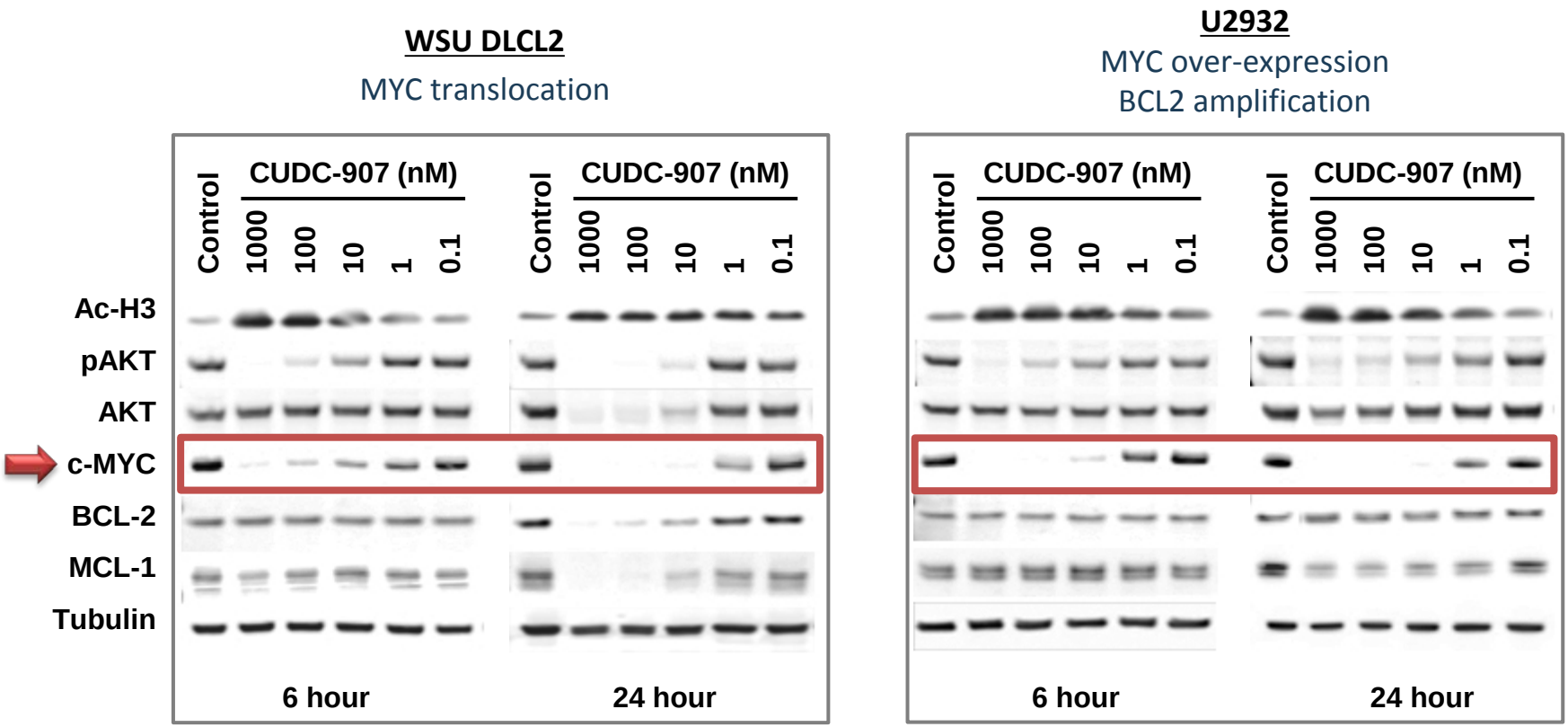
Enzyme	HDAC					PI3K			
Isotype	1	2	3	6	10	Alpha	Delta	Beta	Gamma
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

Proposed Mechanism of CUDC-907



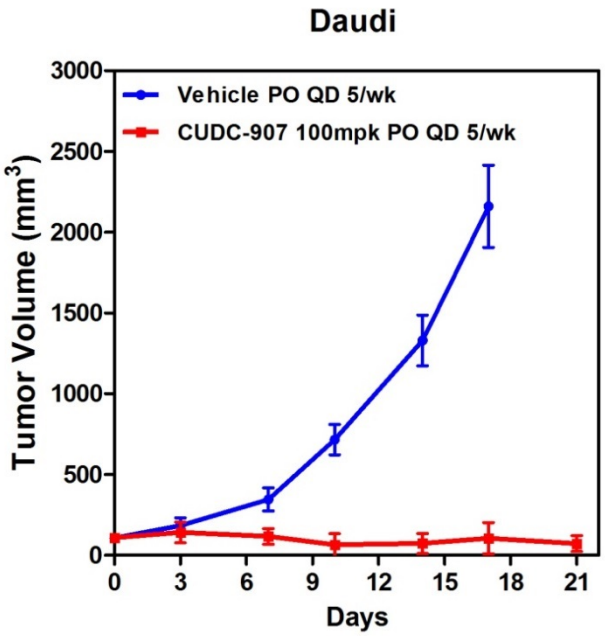
Mehta-Shah and Younes, Semin Hematol. 2015

CUDC-907 Decreases MYC Protein Levels in DLBCL Cell Lines



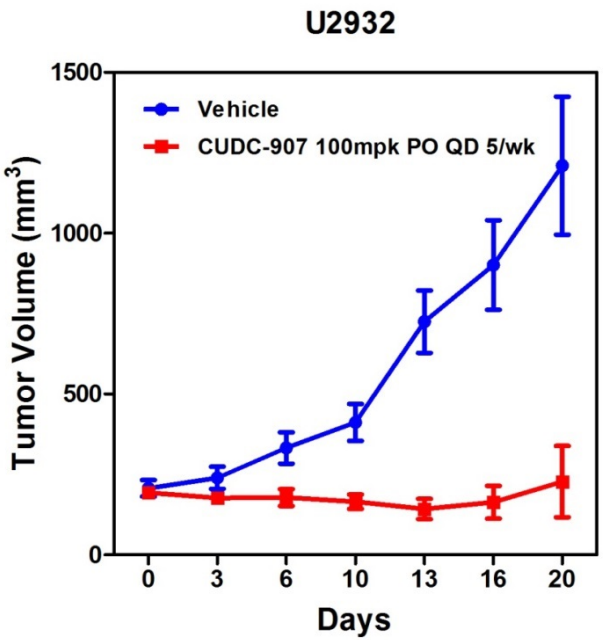
In Vivo Efficacy in MYC+ Xenograft Models

Burkitt Lymphoma



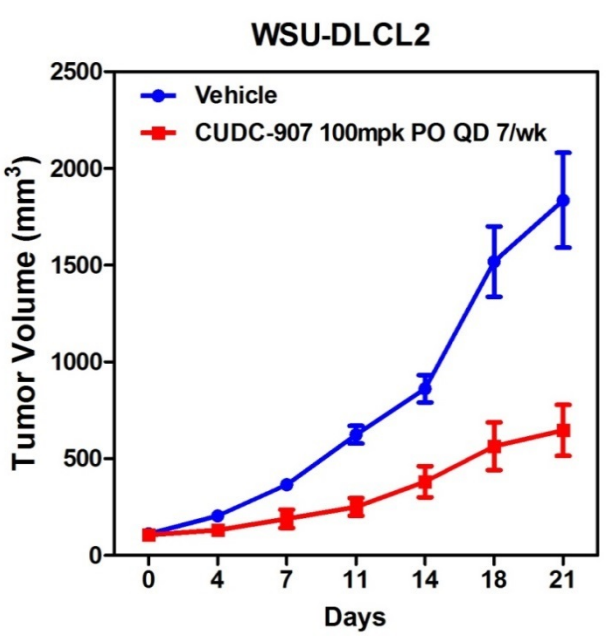
MYC translocation

ABC DLBCL



MYC over-expression
BCL2 amplification

GCB DLBCL



MYC & BCL2 translocations

CUDC-907-101 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

Criteria for DLT & Response-evaluable Population

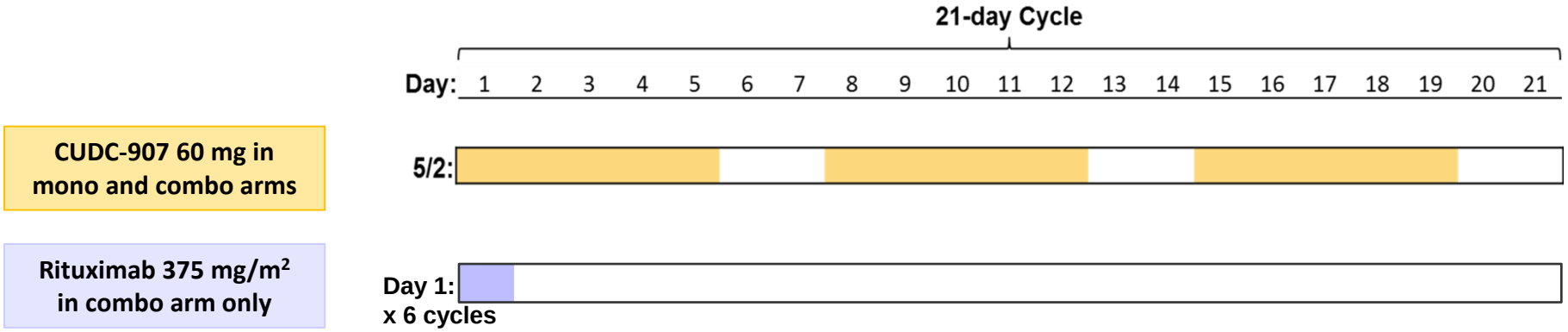
- Dose Limiting Toxicity
  - Non-hematological Grade 3 AE, other than Grade 3 nausea or vomiting treated with sub-optimal antiemetic
  - AE resulting in a dose delay ≥7 days
  - Grade 4 neutropenia ≥7 days, or ≥Grade 3 with fever >101.3°F (38.5°C) or infection
  - Grade 4 thrombocytopenia ≥7 days, or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

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

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 (ongoing)
  - 60 mg 5/2 monotherapy in patients with RR DLBCL, HL, or MM
  - 60 mg 5/2 + rituximab 375 mg/m^2 (R-907) combination patients with RR DLBCL



Patients receive treatment once a day on days indicated by color fill

Demographics & Study Disposition: Safety Population

Characteristics & Disposition	Overall (N=75)
Male, n (%)	50 (67)
Age, median years (range)	61 (20-85)
Histology, n (%)	
Diffuse large B-cell lymphoma (DLBCL)	31 (41)
Transformed follicular lymphoma (t-FL/DLBCL)*	11 (15)
Hodgkin Lymphoma (HL)	16 (21)
Multiple Myeloma (MM)	9 (12)
Other lymphoma**	19 (25)
Prior Therapies	
No. prior regimens [median (range)]	4 (1-9)
HDAC inhibitor, n (%)	9 (12)
PI3K inhibitor, n (%)	3 (4)

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

**Includes T-cell (n=4), lymphoplasmacytic (n=3), small lymphocytic (n=3), mantle cell (n=3), follicular (n=2), marginal zone (n=2), Burkitt (n=1), and gray-zone (n=1)

Demographics & Study Disposition: DLBCL Population

Characteristics & Disposition	*de novo* DLBCL (n=20)	t-FL/DLBCL* (n=11)	Overall (N=31)
Male, n (%)	16 (80)	7 (64)	23 (74)
Age, median years (range)	58 (20-77)	71 (49-85)	64 (20-85)
Primary refractory, n (%)**	3 (15)	2 (18)	5 (16)
Prior Therapies			
No. prior regimens [median (range)]	3 (2-9)	3 (2-6)	3 (2-9)
Stem cell transplant, n (%)	7 (35)	3 (27)	10 (32)
Radiation therapy, n (%)	8 (40)	1 (9)	9 (29)
HDAC inhibitor, n (%)	1 (5)	-	1 (3)
Treatment received			
CUDC-907 monotherapy, n (%)	14 (70)	11 (100)	25 (81)
CUDC-907 + rituximab, n (%)	6 (30)	-	6 (19)
Response Evaluable*, n (%)**	13 (65)	8 (73)	21 (68)

N=21 patients were evaluable for disease response. N=10 patients discontinued treatment prior to completing their first post-baseline response assessment

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

**Patient never experienced complete or partial response on any prior therapy

***Patient completed at least one post-baseline disease assessment

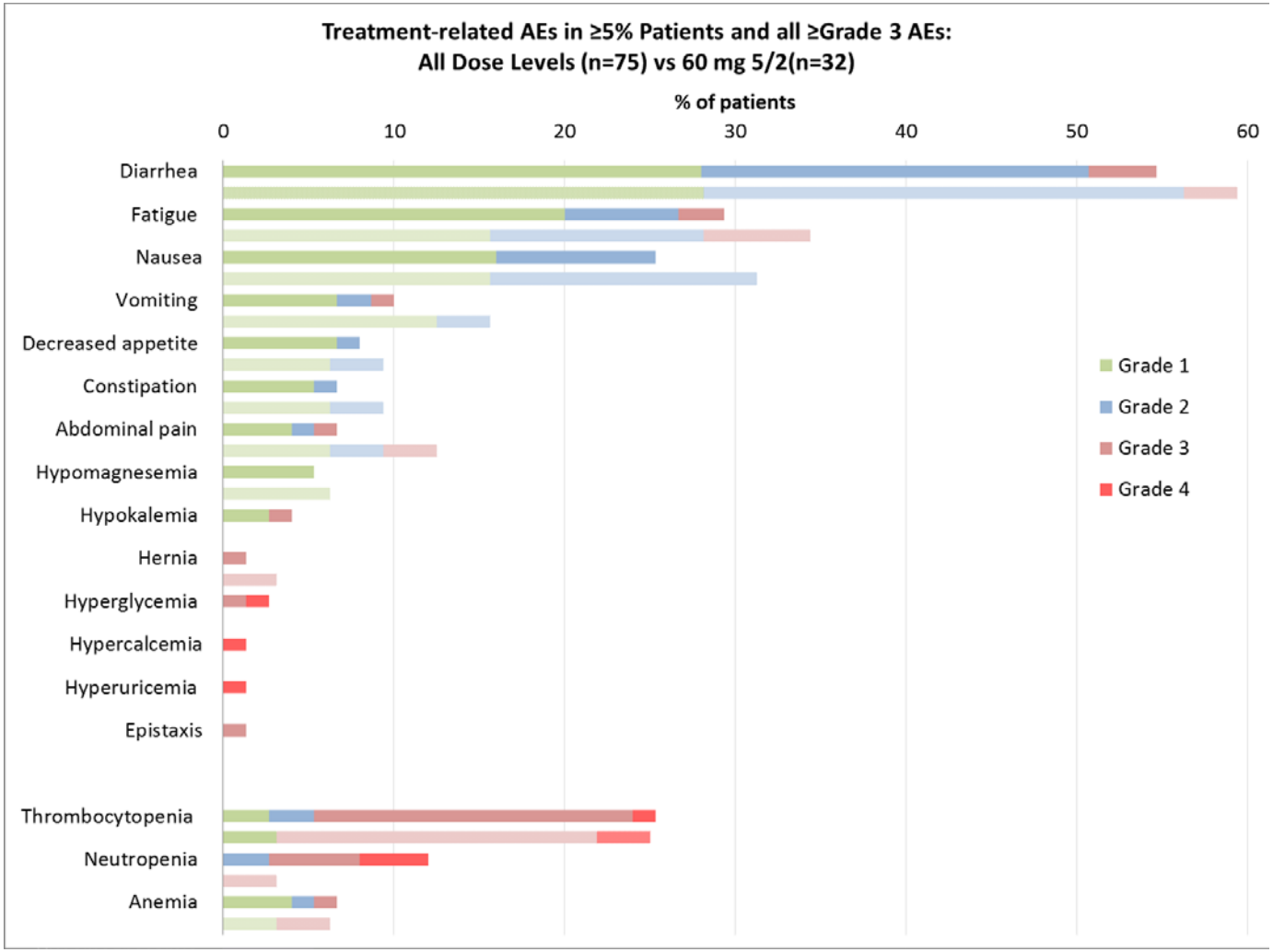
DLTs & RP2D Selection

- 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

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



Most common AEs:

All dose levels

- Diarrhea (55%)
- Fatigue (29%)
- Nausea (25%)
- Thrombocytopenia (25%)
- Neutropenia (12%)

RP2D (60mg 5/2)

- Diarrhea (59%)
- Fatigue (34%)
- Nausea (31%)
- Thrombocytopenia (25%)
- Vomiting (16%)
- Abdominal pain (13%)

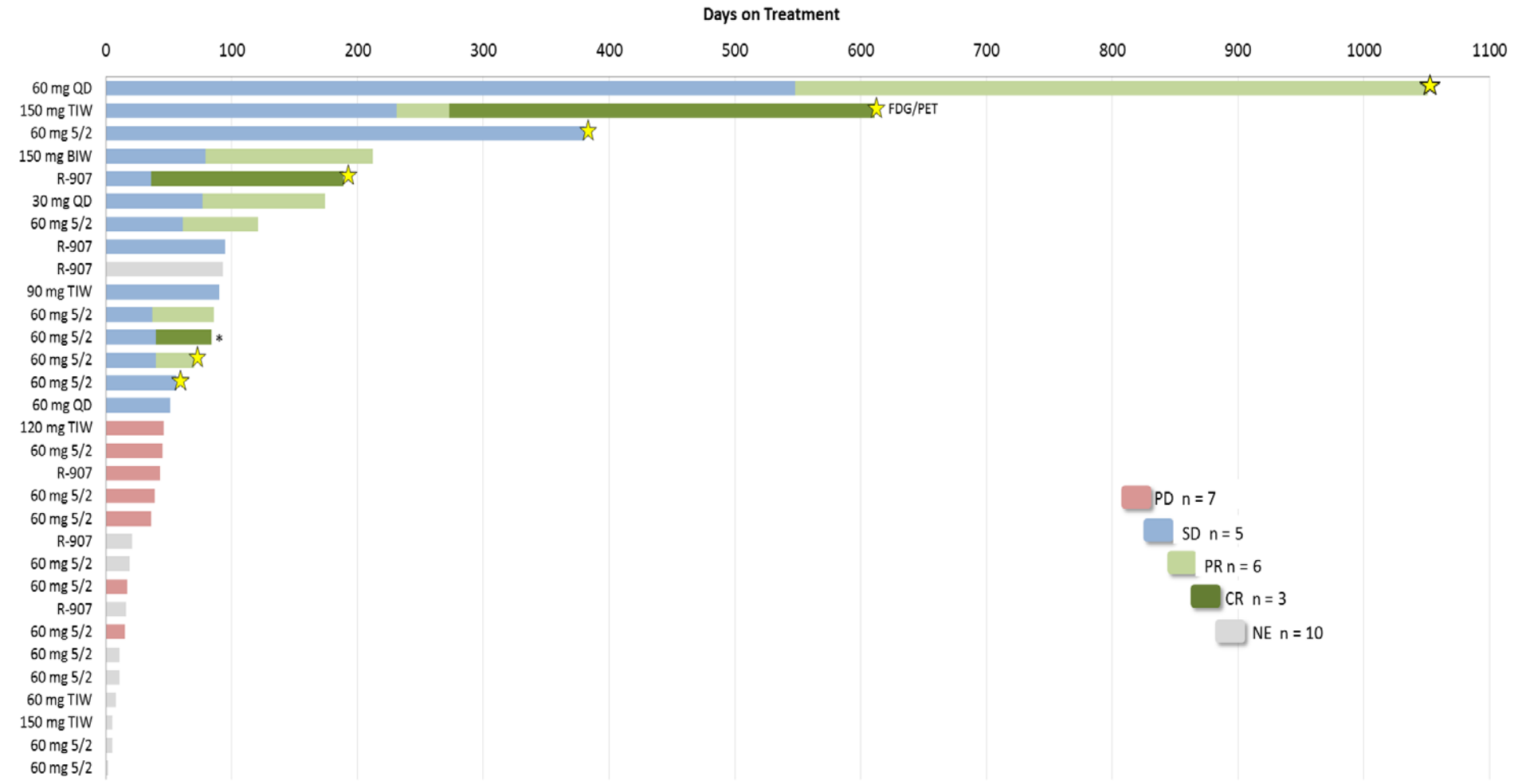
NOTE: lighter color on bottom row per AE denotes 60 mg 5/2 dose

Best Response in RR DLBCL: CUDC-907 monotherapy

Indication	N	Best Response, N (%)					Median Treatment Duration, months (range)**
		CR	PR	SD	PD	NE*	
Overall DLBCL	25	2 (8)	6 (24)	4 (16)	6 (24)	7 (28)	1.4 (<1-35)
MYC+	8	2 (25)	2 (25)	1 (13)	-	3 (38)	4.2 (<1-20)
MYC-	4	-	1 (25)	-	2(50)	1 (25)	0.5 (<1-6)
MYC?	13	-	3 (23)	3 (23)	4 (31)	3 (23)	1.4 (<1-35)

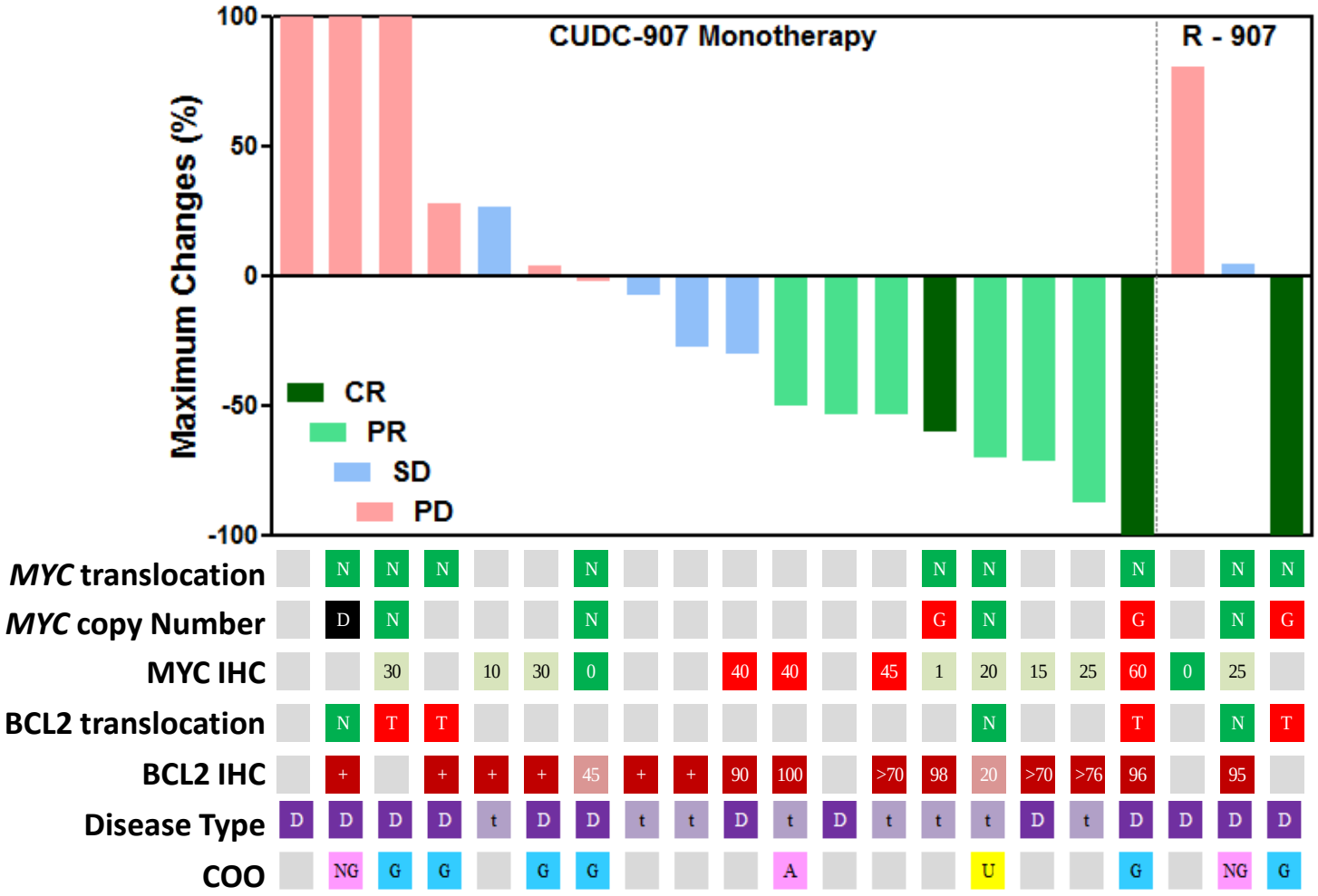
*N=18 patients were evaluable for disease response. N=7 patients discontinued treatment prior to completing their first post-baseline response assessment due to withdrawal of consent (n=4), unrelated AEs (n=2), and too early to evaluate (n=1)
**5 patients ongoing treatment as of 15 March 2016
+ = per local or central pathology report including ≥40% expression per IHC, translocation per FISH, or copy number (3-4) gain by FISH
- = local or central pathology report <40% expression per IHC and no translocation or copy number gain by FISH
? = local or central pathology report unavailable for IHC and/or FISH results

RR DLBCL Response by Treatment Duration (n=31)



N=21 patients were evaluable for disease response. N=10 patients discontinued treatment prior to completing their first post-baseline assessment
R-907 = patients receiving CUDC-907 60 mg 5/2 + rituximab 375 mg/m2
*Achieved CR in C2, proceeded to ASCT (CR ongoing)
☆ = treatment ongoing (n=6)

Responses and SD in RR DLBCL: 6 MYC+ (3CR, 2PR, 1SD) and 4 DE (1CR, 2PR, 1SD)



Note: 21 of 31 patients were evaluable for disease response.
10 of 31 patients discontinued treatment prior to completing their first post-baseline response assessment.

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: 8/25 patients (32%); Response-evaluable: 8/18 patients (44%)
  - MYC+ ITT: 4/8 patients (50%); Response-evaluable: 4/5 patients (80%)
- Ongoing Phase 1 expansion testing CUDC-907 at RP2D of 60 mg 5/2 +/- rituximab with extensive biomarker analysis (NCT01742988)
- Phase 2 study will further evaluate CUDC-907 +/- rituximab in patients with RR DLBCL exhibiting *MYC* gene translocation or copy number gain, or MYC protein overexpression **(NCT02674750)**

Acknowledgments

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