



Phase 1 Trial of Oral CUDC-907, a Dual Inhibitor of HDAC and PI3K, in Patients with Refractory/Relapsed Lymphoma or Multiple Myeloma

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Introduction

Histone deacetylases (HDACs) and phosphatidylinositol 3-kinase (PI3K) pathways are validated therapeutic targets, as demonstrated by regulatory approvals of various agents for the treatment of certain lymphomas (HDACi or PI3Ki) and multiple myeloma (HDACi).

CUDC-907 is an orally bioavailable small molecule designed to target HDACs and PI3Ks in a single chemical entity. In preclinical studies, CUDC-907 potently inhibits tumor growth by inducing apoptosis and cell cycle arrest and also modulates the tumor microenvironment.

Safety and efficacy data from the completed dose escalation and ongoing expansion stages of the Phase 1 trial (CUDC-907-101) are presented showing the therapeutic potential of CUDC-907 administered as monotherapy in subjects with refractory or relapsed lymphoma and multiple myeloma (MM).

Enzymatic Inhibition

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

Study Design

Phase 1 open-label study in patients with relapsed/refractory lymphoma or MM

Primary Objective: To determine the maximum tolerated dose and recommended Phase 2 dose (RP2D) of oral CUDC-907

Secondary Objectives: To assess the safety, tolerability, PK, biomarkers of activity, and preliminary anti-cancer activity of CUDC-907

Ongoing dose escalation: 3+3 design testing 3 schedules of once daily dosing (QD, "5/2" & intermittent BIW or TIW) (completed)

- QD – 30 mg and 60 mg
- "5/2" (5 days on, 2 days off) – 60 mg
- Intermittent: BIW – 60, 90, 120 & 150 mg; TIW – 60, 90, 120 & 150 mg

Dose Expansion: 60 mg 5/2 and 120 mg TIW dose levels

Dose limiting toxicity (DLT) defined as

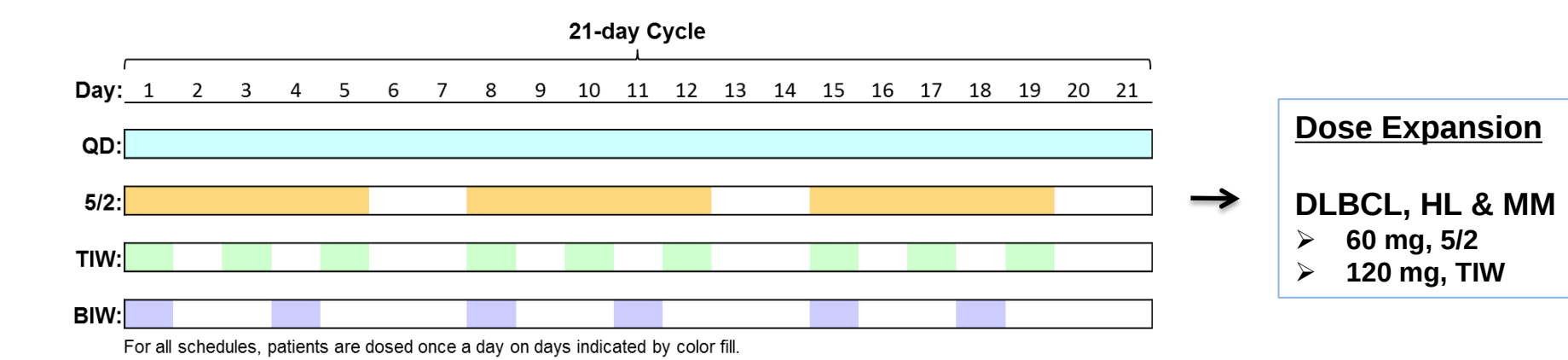
- Non-hematological Grade 3 AE, other than Grade 3 nausea or vomiting in subjects treated with less than optimal antiemetic therapy
- Any AE resulting in a dose delay ≥7 days
- Grade 4 neutropenia lasting ≥7 days, or ≥Grade 3 with fever >101.3°F (38.5°C) or infection
- Grade 4 thrombocytopenia ≥7 days,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

Study Population

- Histopathologically confirmed diagnosis of lymphoma or multiple myeloma that is refractory to or relapsed after ≥2 prior regimens
- Measurable or evaluable disease
- Age ≥ 18 years
- ECOG performance status ≤2

Assessments

- AEs were assessed until 30 days after the last dose of CUDC-907 & graded per NCI CTCAE v4.03
- Antitumor activity was assessed per Revised Response Criteria for Malignant Lymphoma, International Uniform Response Criteria for Multiple Myeloma
- Pharmacokinetic blood sampling occurred in Cycle 1 pre-dose & on Days 1, 8 & 15, as well as in Cycles 2–4 Day 1 & end of treatment. Additional sampling occurred on Cycle 1 Day 4 or 5 for patients assigned to the 5/2 schedule & on Cycle 1 Day 17 for those assigned to the BIW or TIW schedule
- PBMC & plasma biomarker samples were assessed in Cycle 1 on Days 1, 8 & 15 (all schedules); and additionally on Day 5 for patients on the 5/2 schedule
- Optional tumor sampling within 7 days prior to initiating CUDC-907 dosing & after CUDC-907 dosing



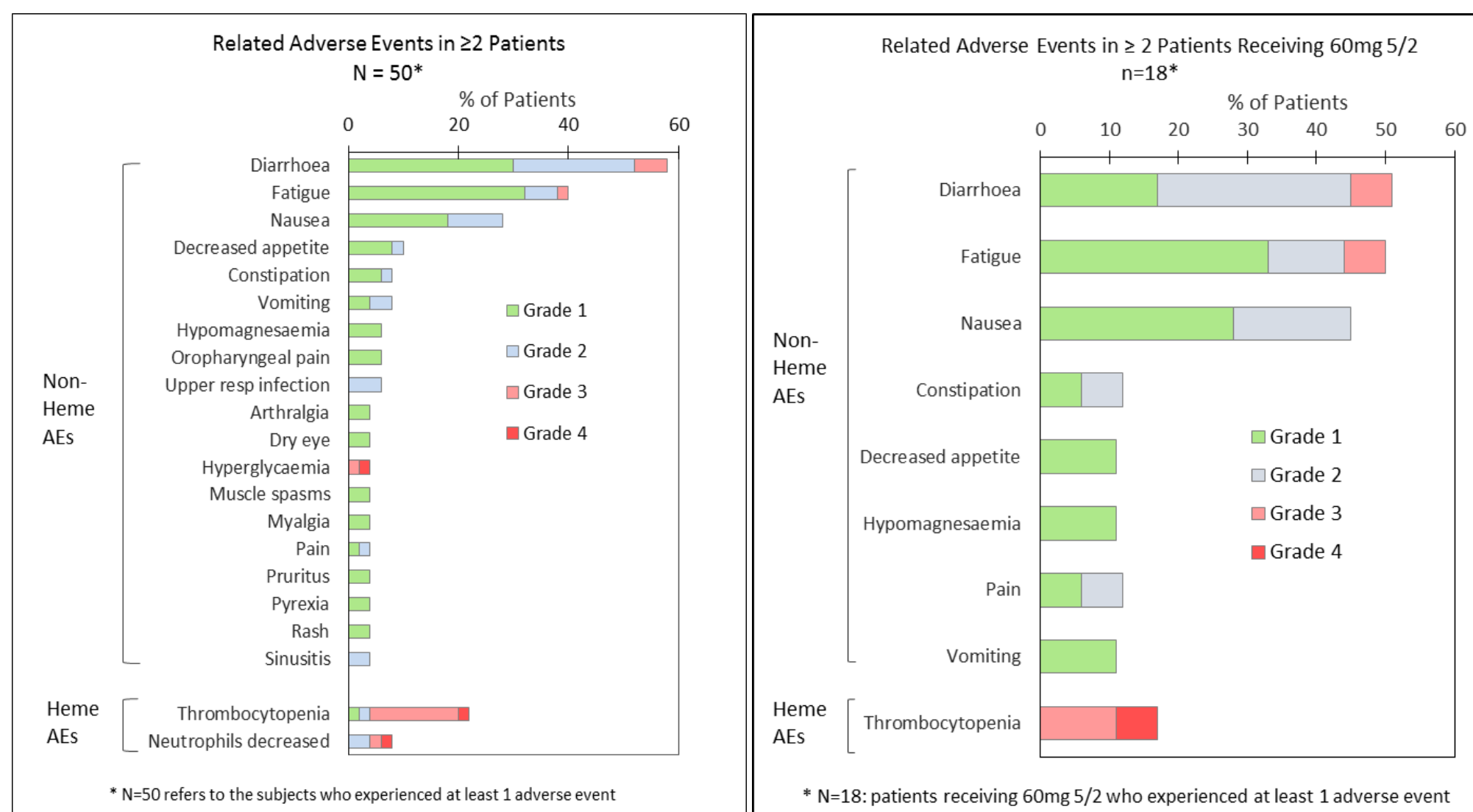
Patient Characteristics & Disposition

Characteristics & Disposition	Overall N=57
Male, Female	40, 17
Age (median), yrs	61
Disease Type n (%)	
Diffuse large B-cell lymphoma (DLBCL)	9 (16)
t-FL/DLBCL	7 (12)
Hodgkin Lymphoma (HL)	14 (25)
T-Cell Lymphoma	3 (5)
Multiple Myeloma (MM)	9 (16)
Other	15 (26)
Prior Treatment	
No. prior regimens [median (range)]	5 (2-10)
Prior HDACi exposure n (%)	6 (11)
Prior PI3Ki exposure n (%)	5 (9)
No. Discontinued Study Treatment n (%)	
Progressive Disease	22 (39)
Physician Decision	10 (18)
Adverse Event	6 (10)
Withdrawal of Consent	3 (5)
Other**	2 (4)

*At the time of data cut-off, 14 patients (25%) were on treatment

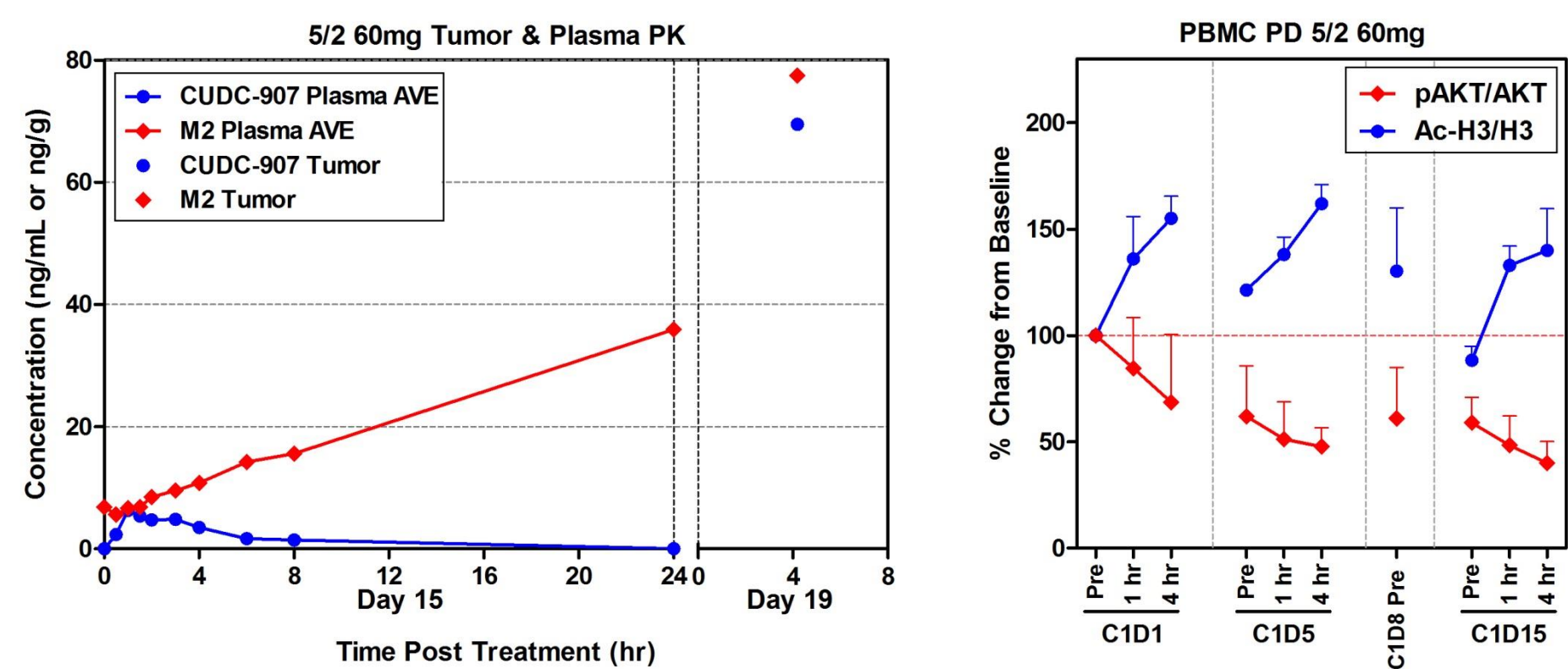
**Decision to undergo BMT (1), clinical signs of PD (1)

Adverse Events



- AEs have been reversible with standard therapeutic interventions, dose holds and/or dose reductions
- The most common G3/4 related AEs reported in 2 or more patients were:
 - Thrombocytopenia & neutrophils decreased (hematologic)
 - Diarrhea, hyperglycaemia & fatigue (non-hematologic)
- DLTs consisting of diarrhea & hyperglycaemia occurred in 3 patients assigned to the highest doses tested on QD & intermittent (BIW or TIW) schedules
 - G3 diarrhea: 60 mg QD & 150 mg TIW dose groups
 - G4 hyperglycaemia: 60 mg QD & 150 mg BIW dose groups
- 5/2 60 mg & TIW 120 mg dosing was found to be reasonably tolerated while still achieving objective responses. Further assessment in the Expansion Phase is ongoing in patients with DLBCL, HL, & MM.

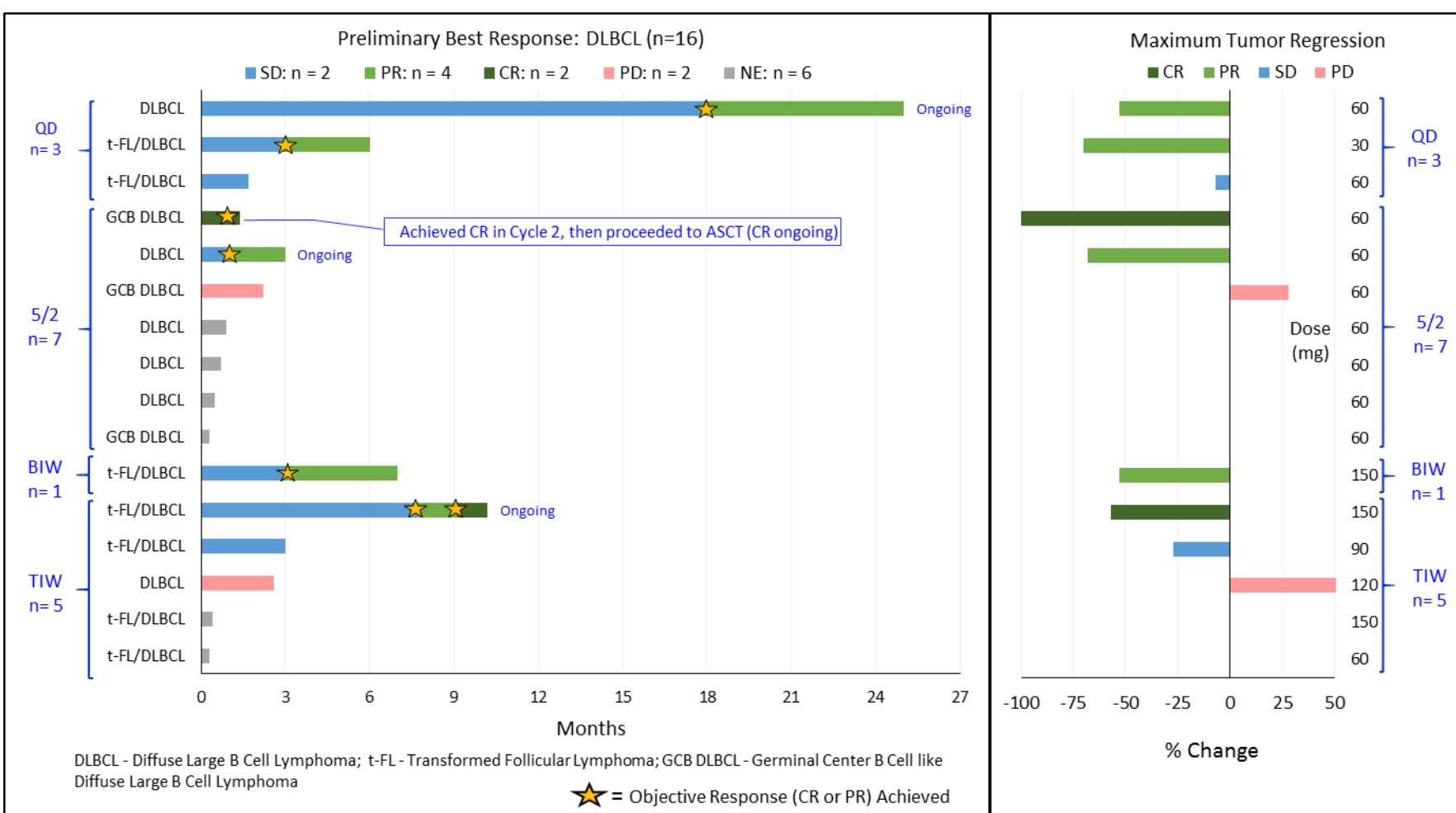
PK - PD



- Plasma PK on day 15 is represented by the average of data from 14 patients (5/2 schedule, 60 mg)
- M2 is a metabolite of CUDC-907
- Tumor PK represents a single tumor sample obtained from the right axillary lymph node of a patient dosed on the 5/2 schedule (60 mg)
- PBMC PD represents the average of qualified samples from the first 3 patients (5/2 schedule, 60 mg)
 - Analysis of additional PBMC samples from other patients is ongoing

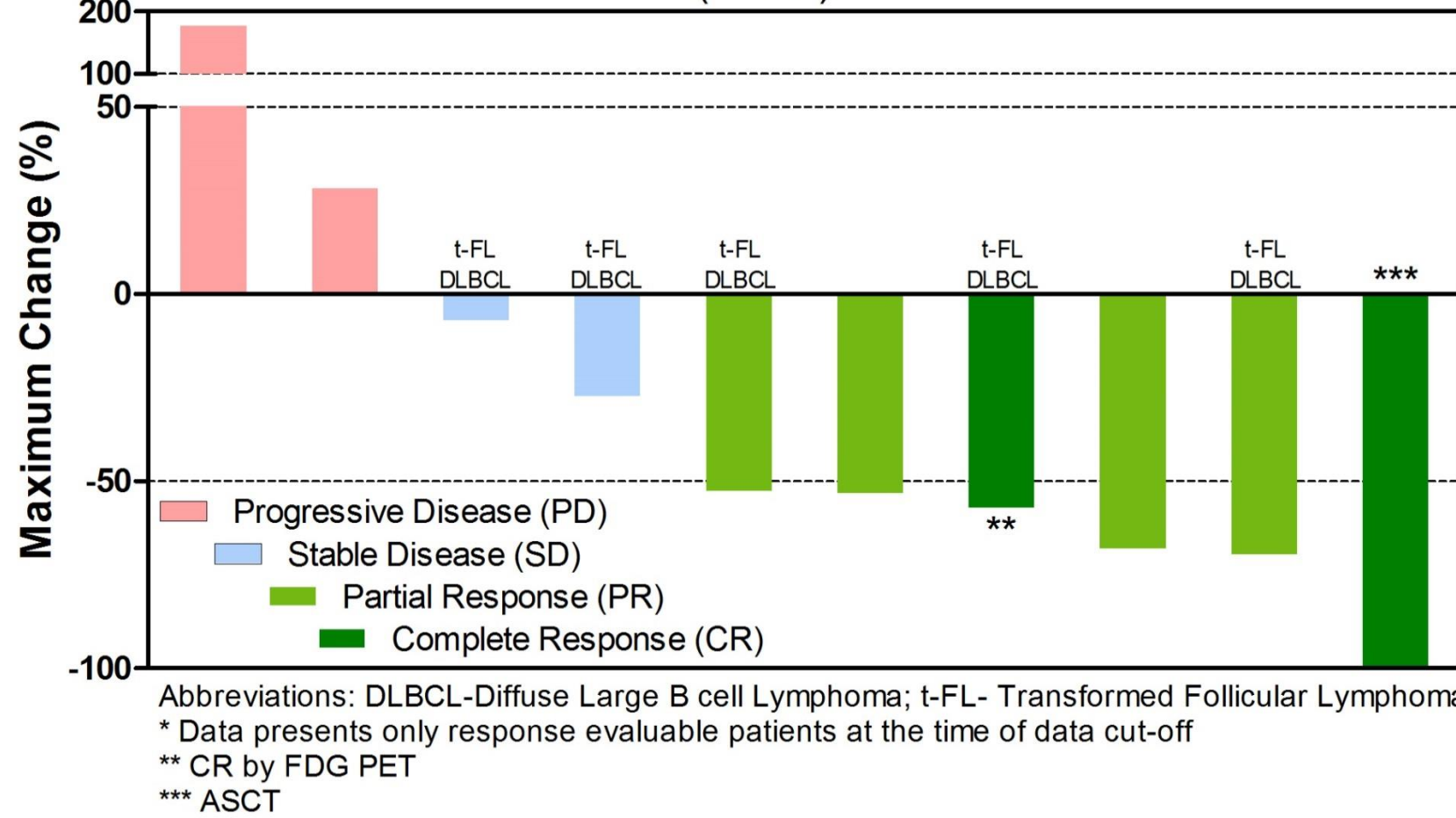
Activity in RR DLBCL

RR DLBCL – Duration on Treatment



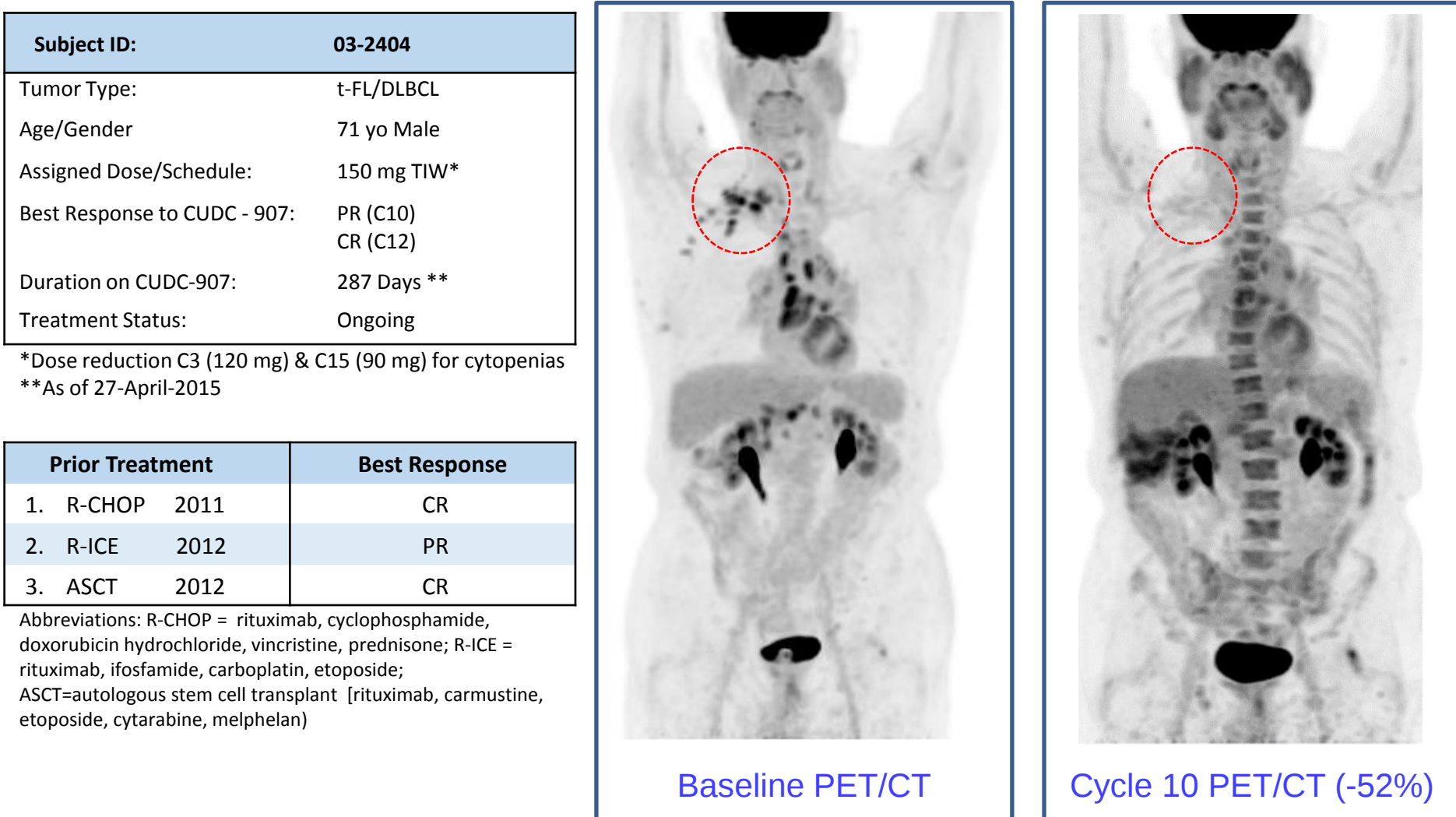
10 of 16 patients with DLBCL were evaluable for disease response; 6 patients were NE due to withdrawal from study before completing Cycle 1 and/or before being assessed for response due to AE (2, hypercalcaemia [rel day 8, unrelated] & sepsis [rel day 5, unrelated]); early clinical progression (2, rel days 16 & 17); withdrawal of consent (1, rel day 5); or restaging pending (1).

Maximum Target Lesion Changes: DLBCL (n=10*)



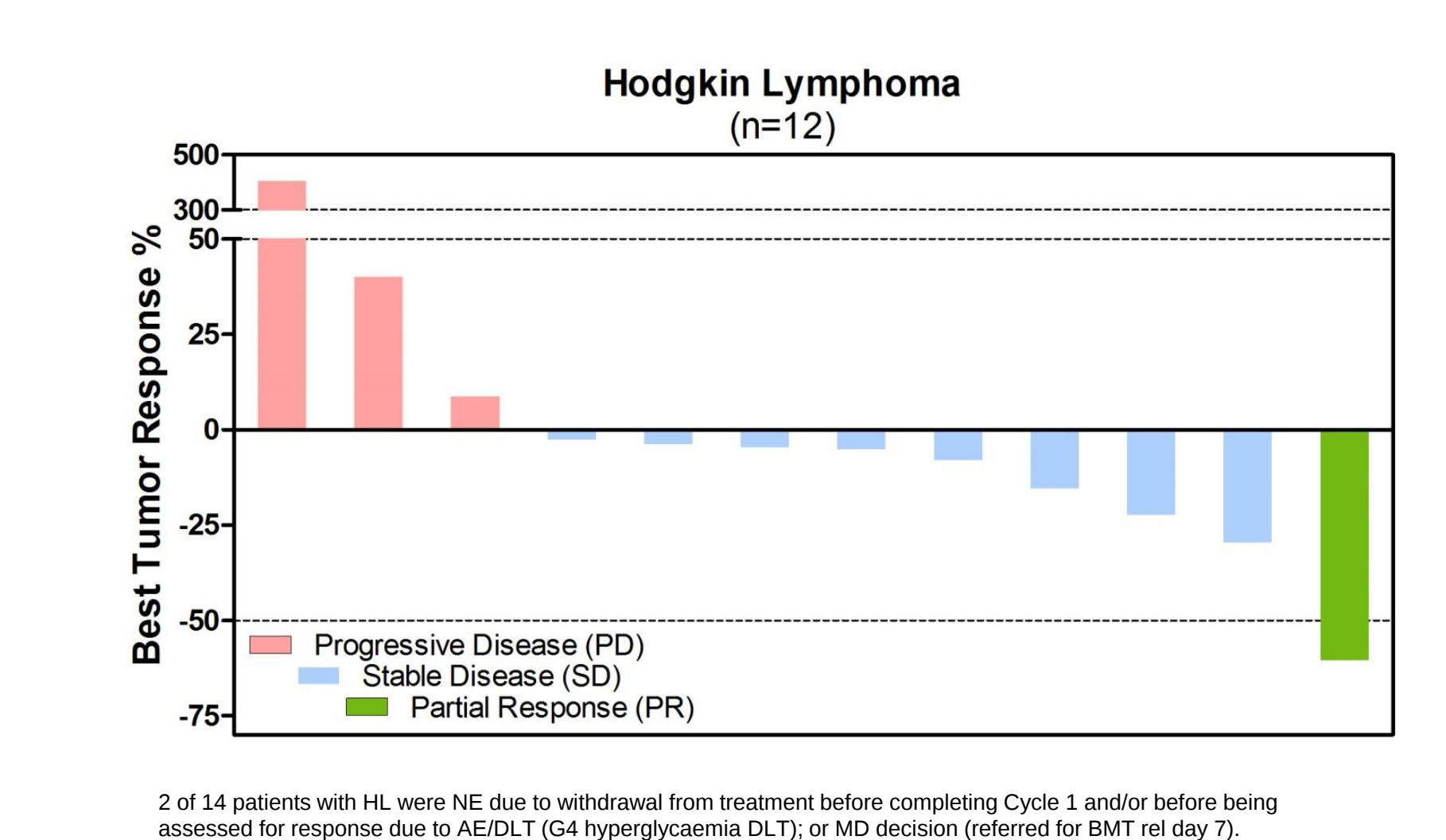
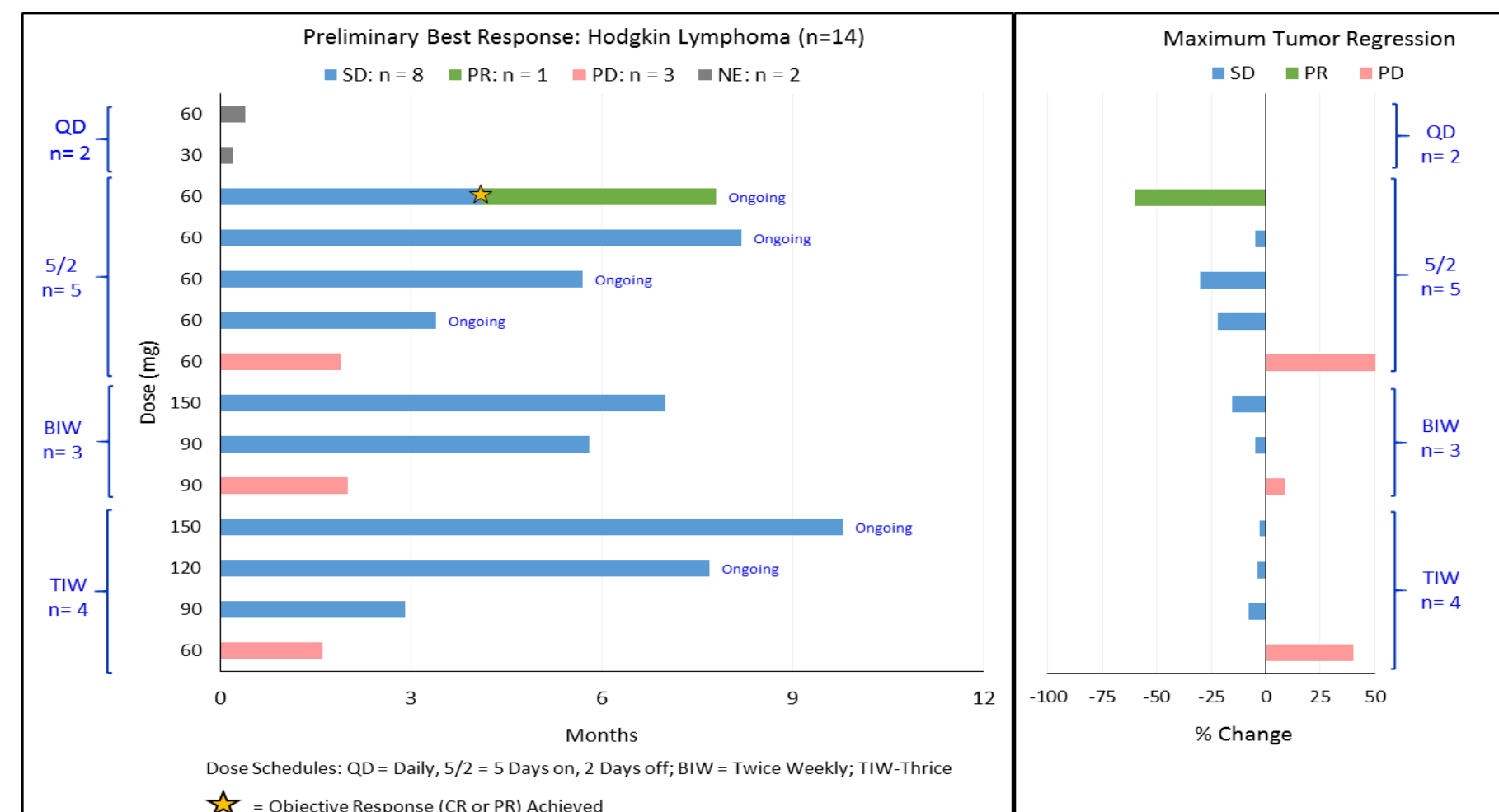
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RR t-FL/DLBCL: Case Report

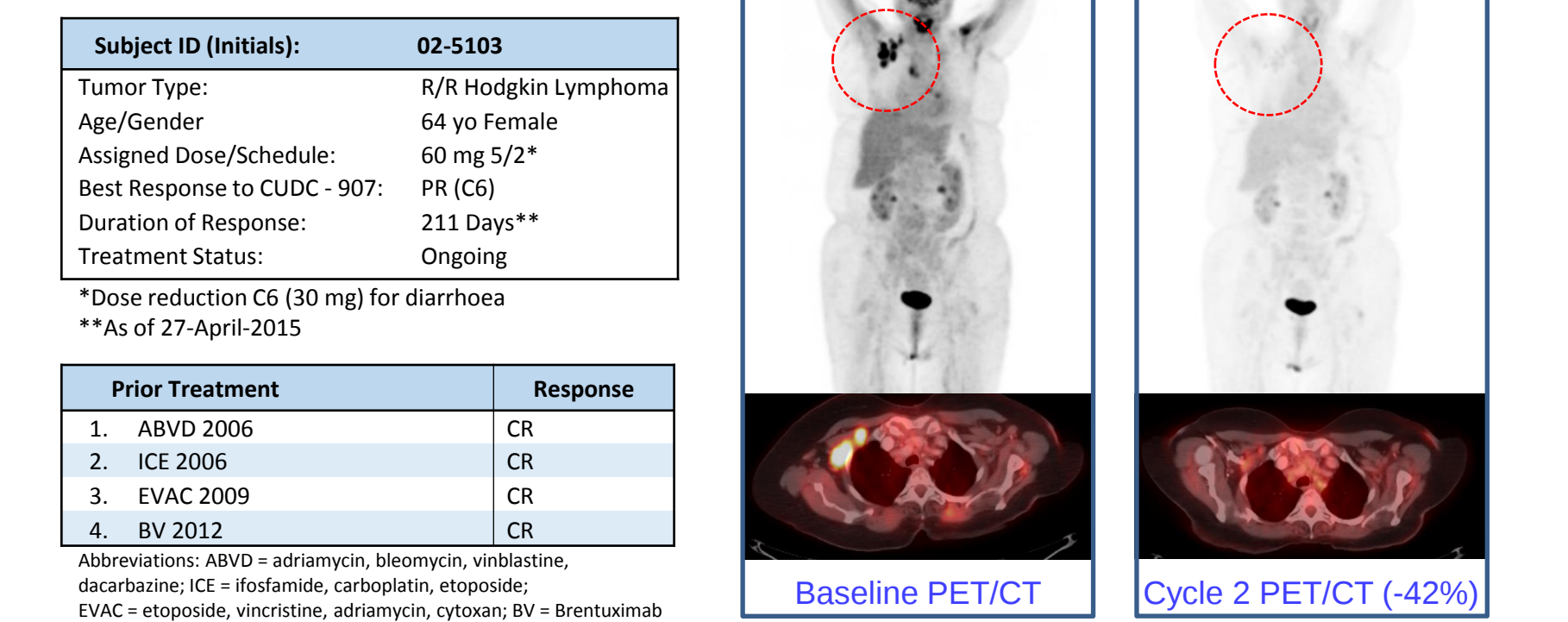


Activity in RR HL

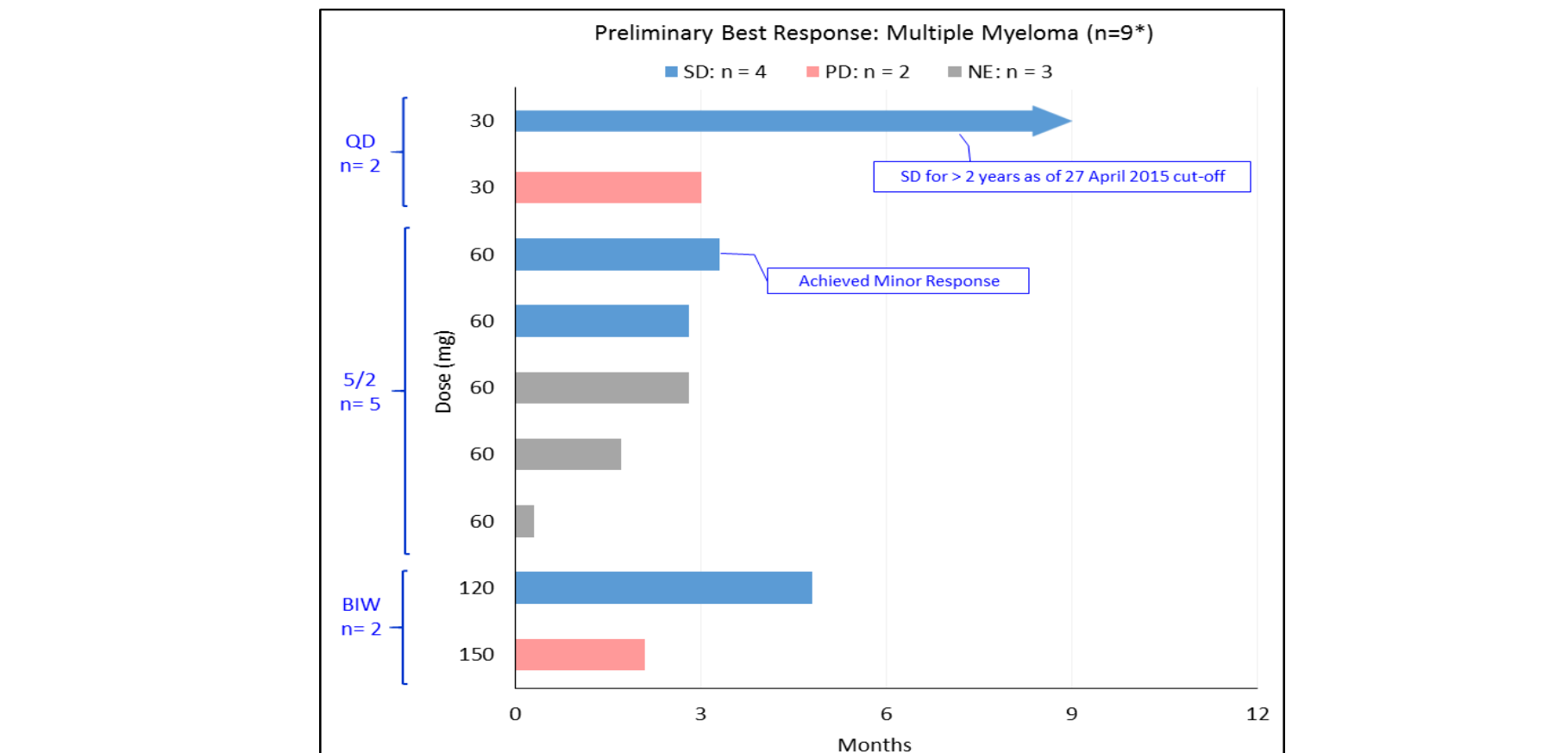
RR HL – Duration on Treatment



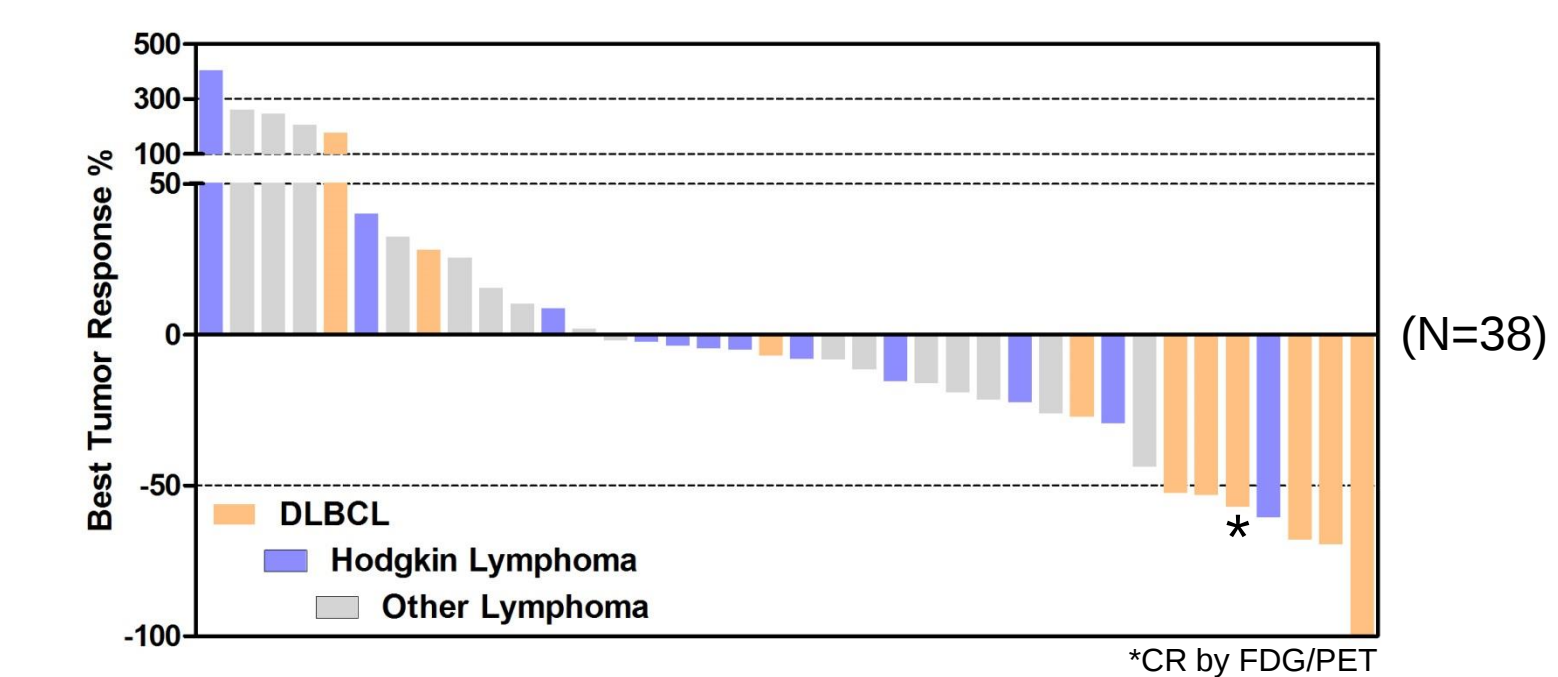
RR HL: Case Report



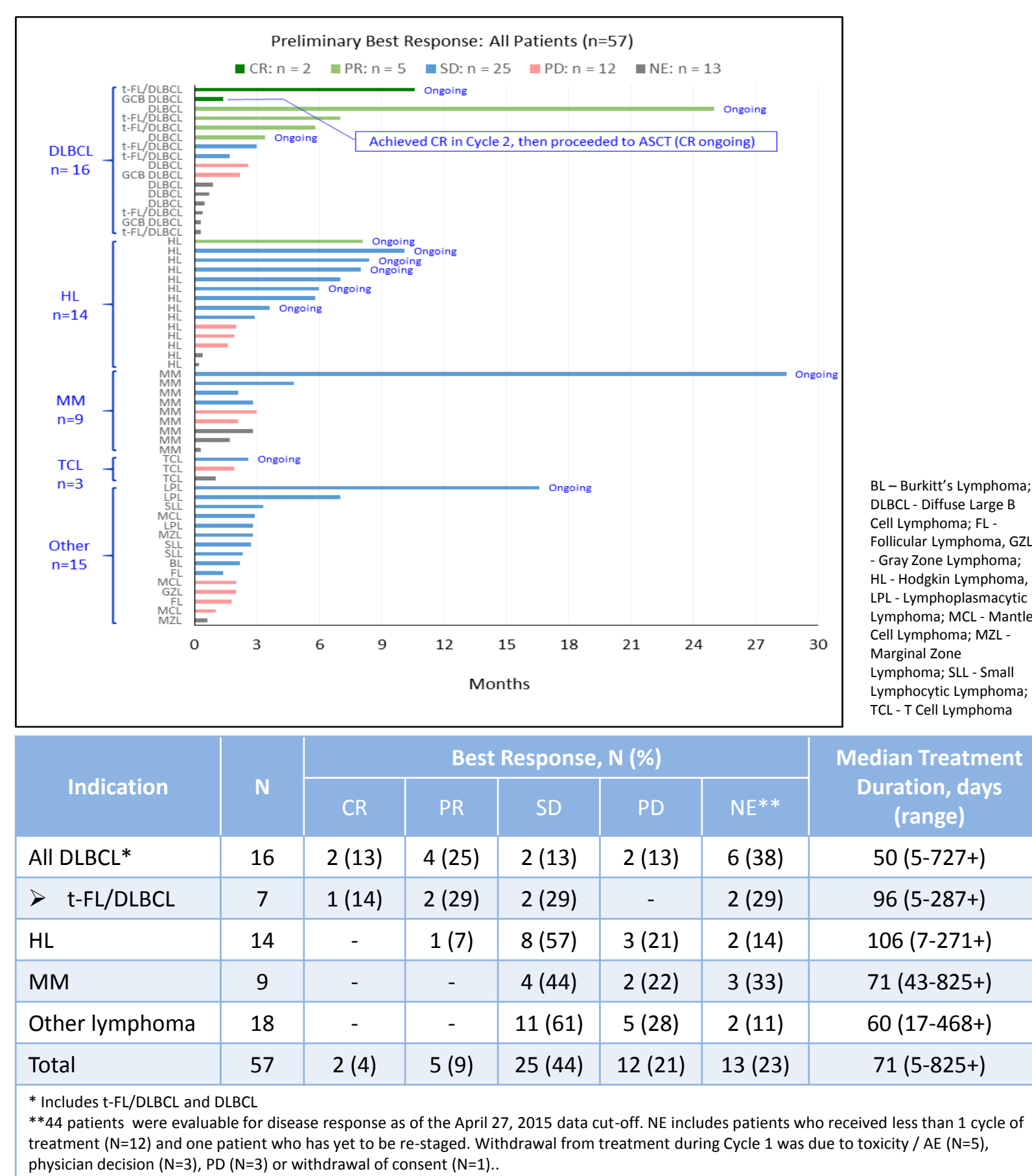
Activity in Multiple Myeloma



Activity in All Lymphoma



Summary: Best Response Assessment



Conclusions

- The dose escalation phase of this Phase 1 study has been completed. The ongoing expansion phase of is evaluating the safety and tolerability of CUDC-907 at RP2D of 60 mg 5/2 and 120 mg TIW in patients with RR DLBCL, HL & MM. ClinicalTrials.gov Identifier: [NCT01742988](https://clinicaltrials.gov/ct2/show/study/NCT01742988)
- CUDC-907 has been shown to be reasonably tolerated with self-limiting AEs that most commonly consist of G1-2 diarrhoea, fatigue, nausea and thrombocytopenia.
- Objective responses have occurred on all dosing schedules and across all investigational sites. Among the response-evaluable patients:
 - RR DLBCL: 6 objective responses (2 CRs, 4 PRs) were observed. Median treatment duration in these patients is 3 months (range: 1.6 - 24.2+ months, ongoing). Long-term responders have included patients with t-FL/DLBCL, one with a triple hit status involving MYC, BCL-2 and BCL-6.
 - RR HL: 1 objective response (1 PR) was observed. Median treatment duration in these patients is 5.4 months (range: 1.1 – 9+ months, ongoing).
 - MM: Minor response was observed 1 patient. Median treatment duration in these patients is 3 months (range: 1.5 – 27.5+ months, ongoing).
- An expansion arm of the trial is currently enrolling patients with DLBCL to treatment with CUDC-907 in combination with standard dose rituximab.
- A Phase 2 trial of CUDC-907 in combination with rituximab in patients with RR DLBCL who are not eligible for high dose chemotherapy is expected to be initiated in 2015.
- A Phase 1 trial evaluating CUDC-907 in patients with advanced/relapsed solid tumors (60 mg 5/2 and 120 mg TIW doses and schedules) is ongoing. ClinicalTrials.gov Identifier: [NCT02307290](https://clinicaltrials.gov/ct2/show/study/NCT02307290)

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