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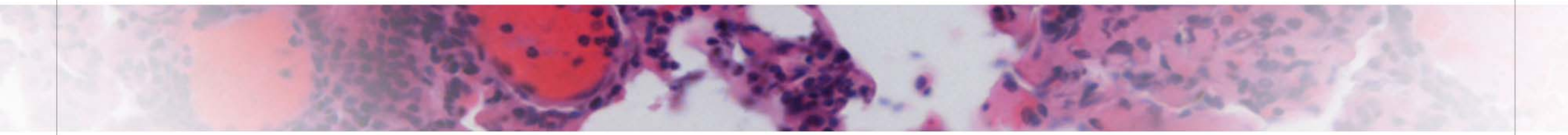


Early and Sustained Circulating Tumor DNA Response Dynamics After Loncastuximab Tesirine for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Poster slides, 65th ASH Annual Meeting and Exposition Meeting, December 9-12, 2023

Aggressive Lymphomas: Clinical and Epidemiological: Poster II
Sunday, December 10, 2023, 6:00 PM - 8:00PM (PST), San Diego Convention Center, Halls G-H

David M. Kurtz,[1*] Gregory Hogan,[2] Andre Schultz,[2] Jacob J. Chabon,[2] Ash A. Alizadeh,[1] Karin Havenith,[3] Sara Samari,[3] Tim Kopotsha,[3] Luqiang Wang,[4] Yajuan Qin,[4‡] Ying Wang,[4‡] and Serafino Pantano,[5]

[1]Department of Medicine, Divisions of Oncology and Hematology, Stanford University, Stanford, California, USA; [2]Foresight Diagnostics, Aurora, Colorado, USA; [3]ADC Therapeutics (UK) Ltd, London, United Kingdom; [4]ADC Therapeutics America, Inc., New Providence, New Jersey, USA; [5]ADC Therapeutics SA, Épalinges, Switzerland

[‡]Affiliation at the time of contribution to this research

Introduction

- Circulating tumor DNA (ctDNA) has emerged as a tool to characterize tumors and track minimal residual disease (MRD) in many malignancies, including diffuse large B cell lymphoma (DLBCL)
- Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]), an antibody–drug conjugate comprising an antibody targeting CD19 and a pyrrolobenzodiazepine (PBD) dimer cytotoxin, is an approved novel therapy for relapsed/refractory (R/R) DLBCL
- While ctDNA-MRD has been applied in the setting of CD19-targeted chimeric antigen receptor (CAR) T-cells, this has not been applied in the setting of treatment with Lonca

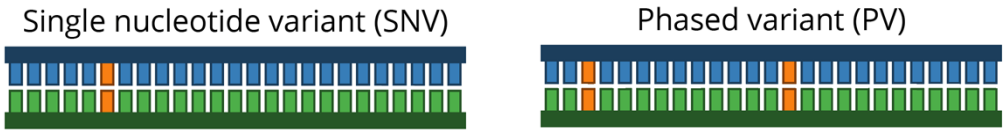
OBJECTIVE: To apply the ultrasensitive ctDNA-MRD detection method, phased variant enrichment and detection by sequencing (PhasED-Seq), to evaluate mutational profiles and ctDNA-MRD response dynamics with Lonca

CAR, chimeric antigen receptor; C2D1, Cycle 2 Day 1; ctDNA-MRD, circulating tumor DNA minimal residual disease; DLBCL, diffuse large B-cell lymphoma; EOT, end of therapy; Lonca, loncastuximab tesirine-lpyl; MRD, minimal residual disease; PBD, pyrrolobenzodiazepine; PhasED-Seq, phased variant enrichment and detection by sequencing; R/R, relapsed/refractory.

Study Design and Methods

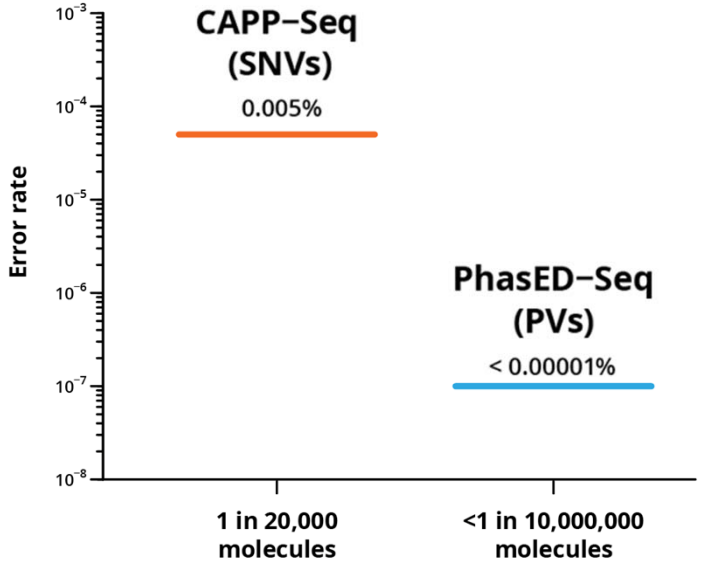
- The LOTIS-2 study (NCT03589469) evaluated the efficacy of Lonca in R/R DLBCL after ≥2 lines of prior systemic therapy
- Samples from 33 patients were profiled by PhasED-Seq (Foresight Diagnostics) to represent a range of best responses to therapy
- Baseline plasma + PBMC were used to identify tumor-specific PVs
  - ctDNA-MRD levels and mutational genotypes were identified before treatment, after 1 cycle of treatment (C2D1), and at EOT

A.



- Genotyping PVs on a single cfDNA molecule improves limit detection of ctDNA-MRD
- Background error rate is reduced and sensitivity is increased by approximately 100 times when genotyping PVs versus SNVs

B.



Kurtz et al, *Nature Biotechnol.* 2021;39(12):1537-1547 (PMID 34294911)
Foresight LDT validation data (data on file)
C2D1, cycle 2, day1; CAPP-Seq, cancer personalized profiling by deep sequencing; cfDNA, circulating free DNA; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; Lonca, loncastuximab tesirine-lpyl; MRD, minimal residual disease; PBMC, peripheral blood mononuclear cells; PhasED-Seq, phased variant enrichment and detection by sequencing; PV, phased variant; R/R, relapsed/refractory; SNV, single nucleotide variant.

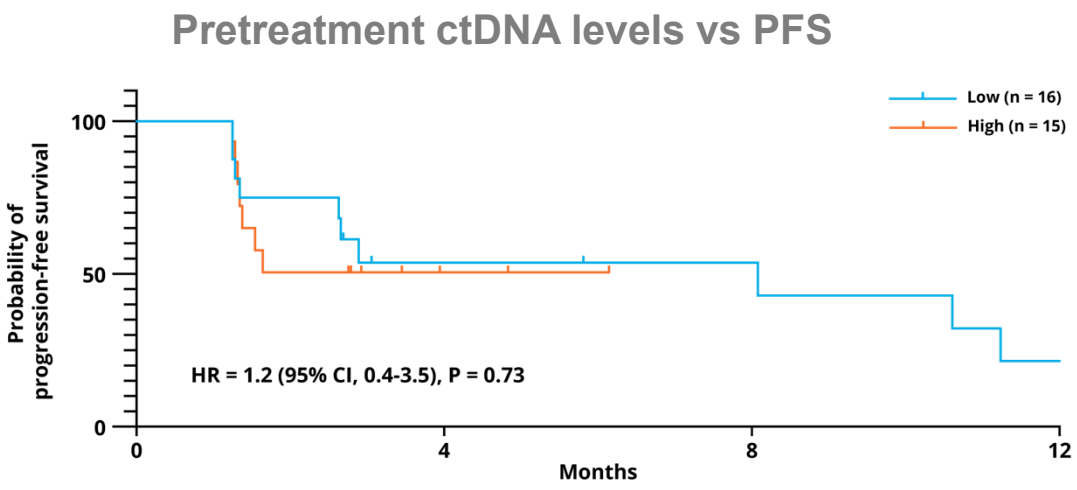
Patient Characteristics and Best Overall Response

Patient Characteristics*		Number (%)
Age (median)		65, range 25-83
Stage	I-II	10 (32)
	III-IV	21 (68)
IPI	0-1	9 (29)
	2	6 (19)
	3	13 (42)
	4-5	3 (10)
Diagnosis	DLBCL, NOS	26 (84)
	PMBCL	2 (6)
	HGBCL with *MYC* and *BCL2/BCL6*	3 (10)
Cell of origin	GCB	9 (29)
	ABC	6 (19)
	Not evaluable	16 (52)
Prior LOT (median)		3, range 2-7
Response	CR	6 (19)
	PR	14 (45)
	PD	11 (35)

*Includes only 31/33 (94%) of patients successfully genotyped.

ABC, activated B-cell; CR, complete response; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; GCB, germinal center B-cell; HGBCL, high grade B-cell lymphoma; IPI, international prognostic index; Lonca, loncastuximab tesirine-lpyl; LOT, lines of therapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B cell lymphoma; PR, partial response.

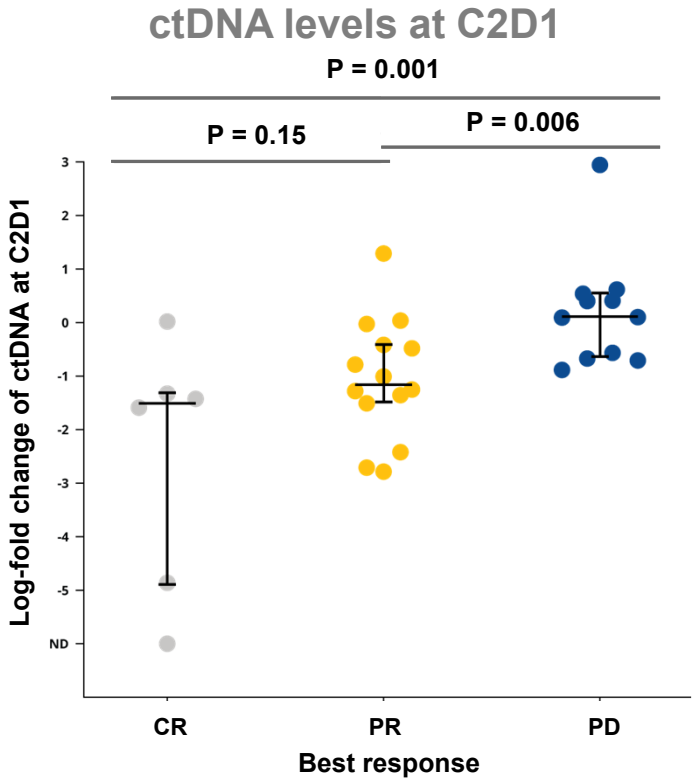
Results: On-Treatment ctDNA is Prognostic for Outcomes After Lonca



- PVs were successfully genotyped from pretreatment plasma in 31/33 (94%) patients
- All subsequent analyses were conducted on these 31 patients, who represented a range of best responses to therapy:
  - 6 CR, 14 PR, and 11 PD
  - Median concentration of pretreatment ctDNA in patients was 141 hGE/mL (range, 0.4-3608 hGE/ml)
  - When dividing patients into those with high vs low pretreatment ctDNA levels, based on the median value, the pretreatment levels were not prognostic of progression-free survival
    - HR = 1.2 (95% CI, 0.4–3.5), P = 0.73
- Both the absolute levels and the change in ctDNA at C2D1 were prognostic for response to treatment (PFS and OS)

C2D1, Cycle 2 Day 1; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; hGE, haploid genome equivalents; HR, hazard ratio; Lonca, loncastuximab tesirine-lpyl; PFS, progression-free survival; PD, progressive disease; PR, partial response; PV, phased variant.

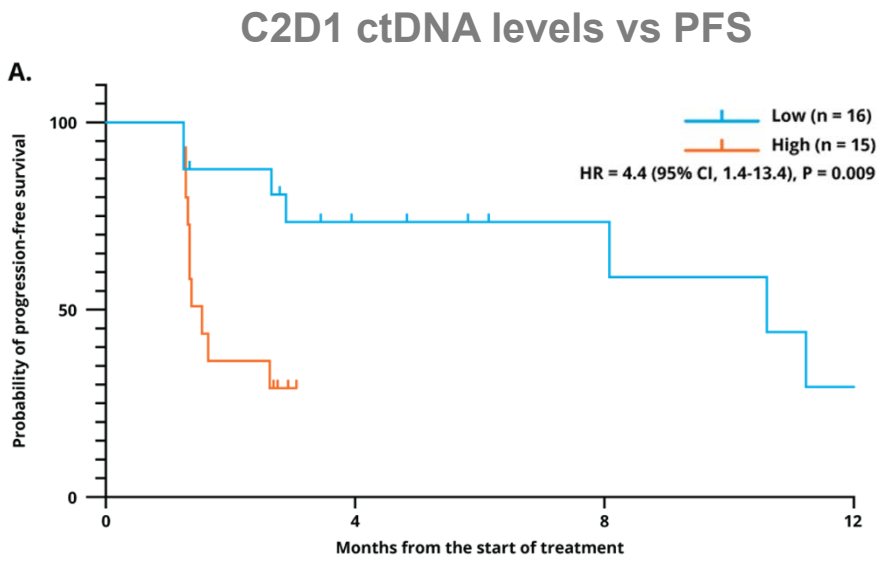
Results: On-Treatment ctDNA is Prognostic for Outcomes After Lonca

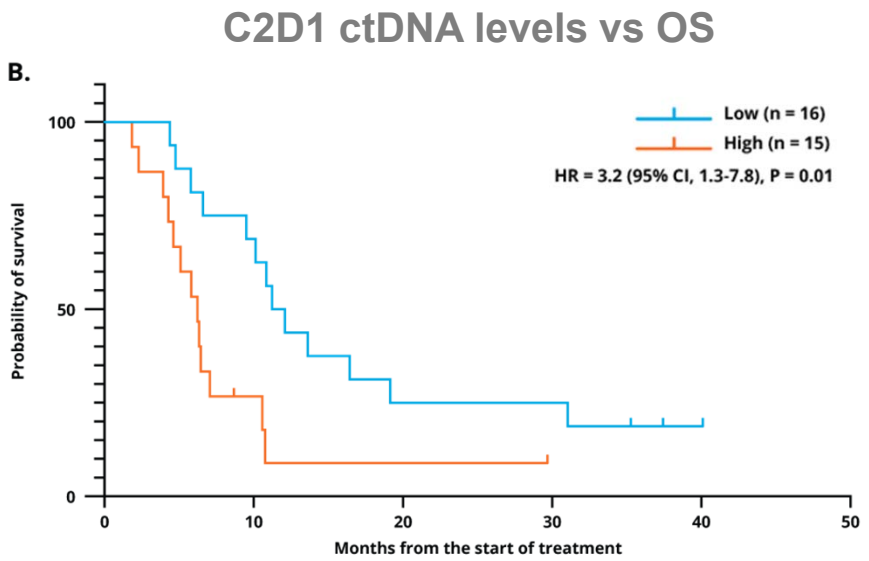


- Patients achieving either a CR or a PR had a significantly greater reduction in their ctDNA levels at C2D1 than those failing to respond
  - CR vs PD, median LFC, 1.5 vs 0.1, P = 0.001
  - PR vs PD, median LFC, 1.1 vs 0.1, P = 0.006
- Patients achieving a CR or a PR did not have significantly different changes in ctDNA at C2D1 (P = 0.15)

C2D1, cycle 2 day 1; CR, complete response; ctDNA, circulating tumor DNA; LFC, log-fold change; PD, progressive disease; PR, partial response.

Results: Levels of ctDNA at C2D1 are Prognostic for PFS and OS

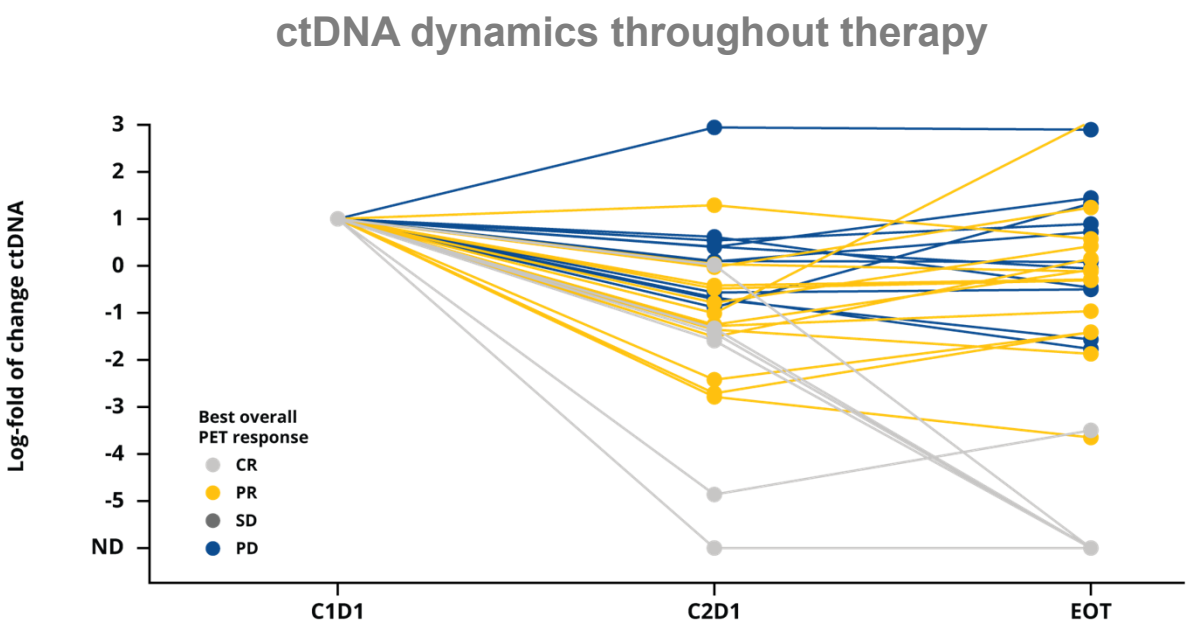




- When dividing patients at the median into those with high vs low levels of ctDNA at C2D1, lower levels of ctDNA were significantly associated with PFS (Figure A) and OS (Figure B)
  - PFS: HR = 4.4 (95% CI, 1.4–13.4), P = 0.009
  - OS: HR = 3.2 (95% CI, 1.3–7.8), P = 0.01

C2D1, cycle 2 day 1; CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

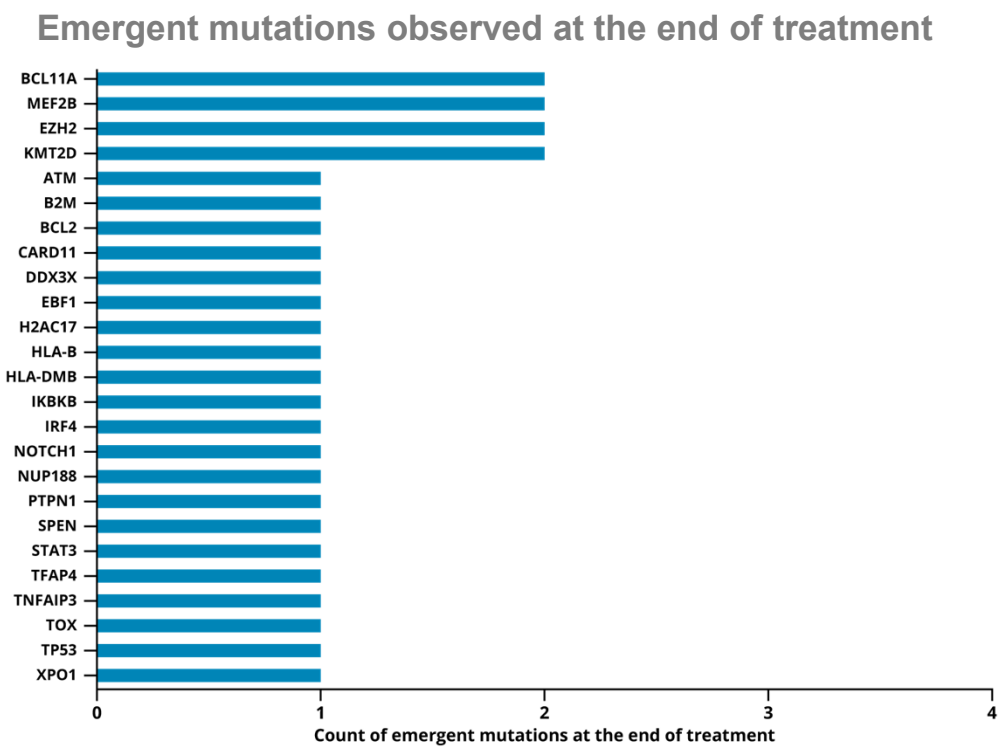
Results: Molecular Response to Lonca Continues to Deepen Beyond C2D1 in Patients Achieving a CR



- For patients with CR as best response, 5 of 6 patients cleared their ctDNA-MRD to undetectable levels by the end of treatment, as compared with only 1 of 6 patients at C2D1.
  - This suggests deepening responses beyond C2D1. In contrast, 0 of 10 patients with PR and 0 of 15 patients with PD cleared their ctDNA-MRD.
- The patient with a CR who did not show a deepening of molecular response was the only patient with a CR who ended treatment for radiographic disease progression
- All other patients with a CR ended treatment for other reasons (eg, toxicity, transplant, or persistent complete remission)

C1D1, cycle 1, day 1; C2D1, cycle 2 day 1; ctDNA, circulating tumor DNA; CR, complete response; EOT, end of treatment; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

Results: Emergent mutations observed at EOT do not include mutations in CD19



- We assessed ctDNA for mutations across our genotyping panel, including *CD19*, prior to treatment with Lonca and at the time of progression in all patients
- Only 1 mutation in *CD19* (*R363C*) was observed in a pretreatment sample; this patient achieved a PR followed by PD after 3 cycles of treatment with persistence of the mutation in *CD19*
- In this cohort, no emergent mutations in *CD19* were observed at the end of treatment (0/31). However, mutations in several other genes were observed at the end of treatment but not in the ctDNA collected prior to therapy. These mutations were present at high relative variant allele frequency in the relapse sample, suggesting clonal selection during treatment
  - Few genes demonstrated recurrent emergent mutations at the end of treatment, indicating the absence of specific patterns emerging at relapse

ctDNA, circulating tumor DNA; Lonca, loncastuximab tesirine-lpyl; EOT, end of treatment; VAF, variant allele frequency.

Conclusions

- ctDNA molecular response assessment using PhasED-Seq is prognostic for outcomes in patients receiving Lonca monotherapy
- ctDNA levels as early as C2D1 can predict outcomes and are indicative of a fast response to Lonca. Furthermore, molecular responses can deepen with additional cycles
- While emergent mutations can be detected after Lonca, *CD19* alterations do not appear to be a common emergent mechanism of resistance
- In this exploratory study, ctDNA-MRD predicts Lonca efficacy and outcomes and should be further considered as a universal biomarker in DLBCL

ctDNA, circulating tumor DNA; DLBCL, diffuse large B cell lymphoma; Lonca, loncastuximab tesirine-lpyl; MRD, minimal residual disease; PhasED-Seq, phased variant enrichment and detection by sequencing.