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Circulating tumor DNA assessment in patients with early-stage classical Hodgkin lymphoma treated with combination of brentuximab vedotin and nivolumab

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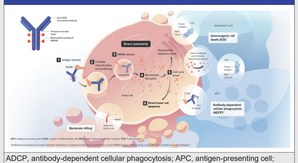
Conclusions

- The study showed that baseline circulating tumor DNA (ctDNA) was detectable in the majority of patients (34 of 36; 94%) with early-stage classical Hodgkin lymphoma (cHL) and that higher levels of ctDNA expression were associated with increased disease burden
- Treatment with brentuximab vedotin (BV), nivolumab, doxorubicin, and dacarbazine (AN+AD) reduced ctDNA levels, rendering them undetectable by end of treatment (EOT) in all patients
  - A limitation of the study was that ctDNA was not collected during long-term follow-up, and this could have limited the ability to predict relapse in long-term follow-up
- Identification of genetic alterations through ctDNA was consistent with alterations previous identified through tissue sequencing, suggesting that liquid biopsy has the potential to supplement tissue biopsy
- In 7 out of 34 patients (21%), decline in ctDNA levels was observed earlier than metabolic responses detected through imaging, suggesting the potential of ctDNA as an early indicator of treatment response
- The potential value of ctDNA as a biomarker for early detection and monitoring of treatment response in early-stage cHL should be further investigated. We plan to further explore the utility of ctDNA in the development of second-generation cluster of differentiation 30 (CD30)-directed antibody-drug conjugates (ADCs) SGN-35T and SGN-35C[1,2]

Introduction

- BV is an ADC approved in combination with doxorubicin, vinblastine, and dacarbazine for patients with cHL (**Figure 1**)[3]
- A previous study in patients with nonbulky early-stage cHL showed preserved efficacy and improved safety with BV plus doxorubicin and dacarbazine regimen after vinblastine was omitted[4]
- Results from the phase 2 SGN35-027 part C study have shown promising efficacy and tolerability with BV and nivolumab in combination with chemotherapy in patients with early-stage cHL in the first-line setting[5]
- Earlier results from the present study and in published literature suggested that ctDNA can be detected in patients with cHL, with molecular response potentially complementing imaging assessments[6,7]
- Here, we report on the use of an ultrasensitive assay for ctDNA detection in patients with early-stage cHL to explore its utility in this population

Figure 1: BV, a CD30-directed ADC consisting of 3 components: (1) an anti-CD30 monoclonal antibody (cAC10), (2) a protease-cleavable mc-vc linker, and (3) the microtubule-disrupting agent MMAE

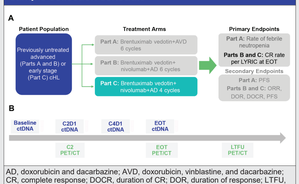


ADCP, antibody-dependent cellular phagocytosis; APC, antigen-presenting cell; CD30, cluster of differentiation 30; ICD, immunogenic cell death; mc-vc; maleimidocaproyl-valine-citrulline; MHC, major histocompatibility complex; MMAE, monomethyl auristatin E; TCR, T-cell receptor.

Methods

- SGN35-027 is an open-label, multipart, multicenter, phase 2 study (**Figure 2A**)
- The part C portion of the study enrolled patients with Ann Arbor stage I/II cHL without bulky disease (<10 cm in tumor diameter on computed tomography [CT])
- Patients received 4 cycles of BV 1.2 mg/kg, nivolumab 240 mg, doxorubicin 25 mg/m^2, and dacarbazine 375 mg/m^2 (AN+AD) intravenously on days 1 and 15 of each 28-day cycle
- Responses were assessed by positron emission tomography [PET]/CT according to Lugano classification[8] with LYRIC[9] at cycle 2 day 25-28 (C2) and at EOT, 30 to 37 days after last dose of study drug (**Figure 2B**)
- Plasma samples were collected at baseline, cycle 2 day 1 (C2D1), C4D1, and EOT. Samples from 36 patients were submitted for ctDNA analysis using phased variant enrichment and detection sequencing (PhasED-seq, Foresight Diagnostics, Boulder, CO), an ultrasensitive minimal residual disease assay for B-cell lymphomas (**Figure 2B**)
- PET/CT results were compared with ctDNA dynamic changes in patients with detectable baseline ctDNA

Figure 2: SGN35-027 part C study design and ctDNA sample collection schedule



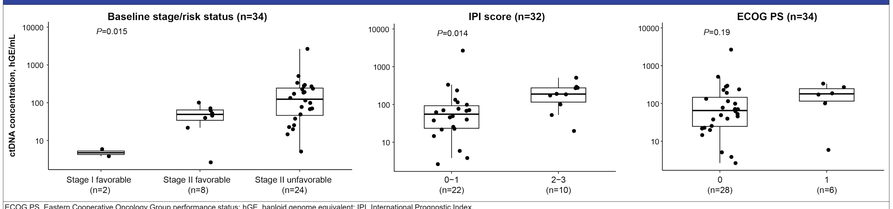
AD, doxorubicin and dacarbazine; AVD, doxorubicin, vinblastine, and dacarbazine; CR, complete response; DOCR, duration of CR; DOR, duration of response; LTFU, long-term follow-up; ORR, objective response rate; PFS, progression-free survival.

PhasEDseq is a new method to detect ctDNA through phased variants to tumor fractions on the order of ppm.[10] Quantitative levels of ctDNA were measured in hapoid genome equivalents (hGEs) per mL.

Results

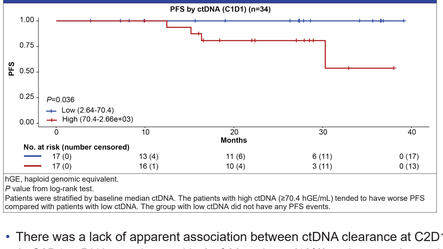
- Baseline ctDNA was detectable in 34 of 36 patients (94%)
- ctDNA concentration was higher in patients with greater disease burden, indicated by baseline stage/risk status (*P*=0.015) and International Prognostic Score (*P*=0.014) (**Figure 3**)
- A numerical trend was seen toward worse progression-free survival (PFS) in patients with high baseline ctDNA (**Figure 4**)
- ctDNA levels decreased in all patients after 1 cycle of treatment (**Figure 5**)

Figure 3: Baseline ctDNA was detected in 94% of patients with early-stage cHL and appeared to be associated with higher disease burden



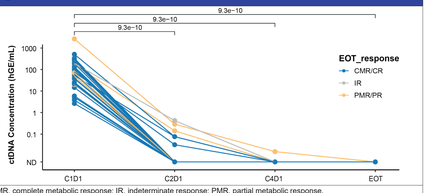
ECOG PS, Eastern Cooperative Oncology Group performance status; hGE, haploid genome equivalent; IPI, International Prognostic Index.
P value from Wilcoxon rank-sum test (two groups) or Kruskal-Wallis test (more than two groups).

Figure 4: Patients with high baseline ctDNA had a numerical trend toward worse PFS



hGE, haploid genomic equivalent.
P value from log-rank test.
Patients were stratified by baseline median ctDNA. The patients with high ctDNA (≥70.4 hGE/mL) tended to have worse PFS compared with patients with low ctDNA. The group with low ctDNA did not have any PFS events.

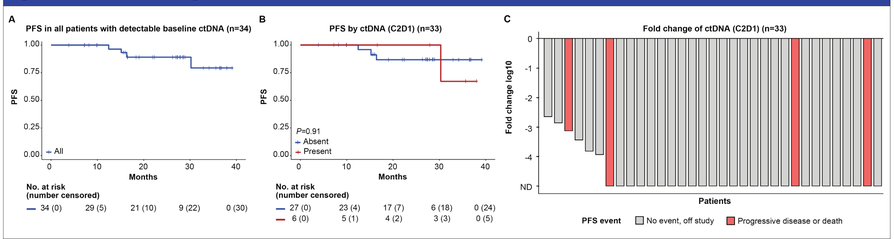
Figure 5: ctDNA concentration decline after treatment with AN+AD



CMR, complete metabolic response; IR, indeterminate response; PMR, partial metabolic response.
P value from Wilcoxon signed-rank test.
Absolute ctDNA concentration was quantified as mutant hGE/mL plasma. ctDNA levels reported as not detected were assumed to be 0; for visualization purposes, a minimal concentration was added.

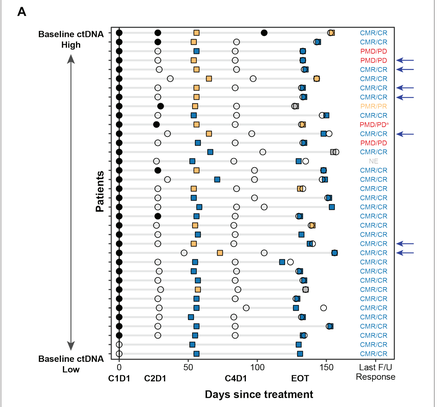
- There was a lack of apparent association between ctDNA clearance at C2D1 and PFS (**Figure 6**)
- At C2D1, ctDNA was detected in 6 of 33 patients (18%) and was undetectable in 27 of 33 patients (82%) (**Figure 7A**)
- At C2 interim PET/CT, 18 of 34 patients (53%) achieved complete metabolic response (CMR); of these, 17 patients had ctDNA samples evaluable, with 16 patients having undetectable ctDNA (**Figure 7B**)
- At C2 interim PET/CT, the remaining 16 of 34 patients (47%) achieved partial metabolic response (PMR); of these, 5 patients had detectable ctDNA, and 11 had undetectable ctDNA (**Figure 7B**)
  - All 11 patients with undetectable ctDNA achieved CMR at later time points
- At C4D1, only 1 patient continued to have detectable ctDNA
- At EOT, PET/CT showed that 26 of 34 patients (76%) achieved CMR, 5 achieved PMR, and 3 achieved indeterminate response (IR); none had detectable ctDNA at EOT (**Figure 7B**)
- OncoPrint of ctDNA was available for 31 patients, indicating that the most frequent genetic alterations occurred in *IGLL5* (55%), *TNFAIP3* (42%), and *STAT6* (42%) (**Figure 8**)

Figure 6: Tumor ctDNA change from C2D1 and PFS



hGE, haploid genomic equivalent.
P values from log-rank test.
Absolute ctDNA concentration was quantified as mutant hGE/mL plasma. ctDNA levels reported as not detected were assumed to be 0; for visualization purposes, a minimal concentration was added. ctDNA change at C2D1 from baseline was calculated as log10 (on-treatment level/pretreatment ctDNA level) for visualization in waterfall plots.

Figure 7: ctDNA status and PET/CT assessment over time (n=36)



B

Interim
PET/CT vs. C2D1 ctDNA

	PET+	PET-
ctDNA+	5	1
ctDNA-	11	16

EOT
PET/CT vs. EOT ctDNA

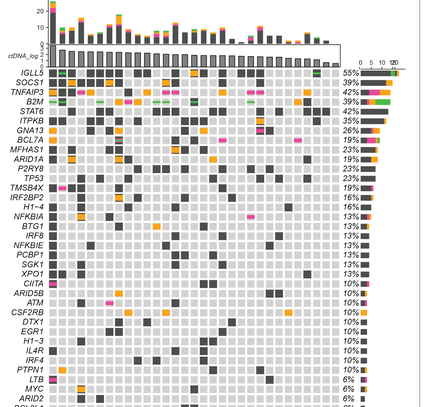
	PET+	PET-
ctDNA+	0	0
ctDNA-	8[b]	25

PET/CT Status
CMR/CR
IR
PMR/PR

ctDNA Status
Absent
Present

CR, complete response; F/U, follow-up; IR, indeterminate response; MCL, mantle cell lymphoma; NE, not evaluable; PD, progressive disease; PMD, progressive metabolic disease; PR, partial response.
Seven patients had ctDNA clearance at C2D1 but PMR at interim PET/CT and later converted to CMR on EOT PET/CT; these patients are indicated by an arrow (→) next to their last follow-up response.
[b]Patient died from MCL, not PD on cHL.
[a]PET/CT at EOT showed PMR for 5 patients and IR for 3 patients. Subsequently, 4 of the 5 patients with PMR converted to CMR, and 1 patient developed a secondary primary malignancy. Of the patients with IR, 2 converted to CMR, and 1 converted to PMR.

Figure 8. Genetic alterations detected by ctDNA



Gene Name	Function
IGLL5	Tumor suppressor gene
SOCS1	JAK/STAT signaling
TNFAIP3	NFkB signaling pathway
B2M	Antigen presentation
STAT6	JAK/STAT signaling
ITPKB	PI3K-AKT signaling
GNA13	G-protein coupled receptor signaling
BCL7A	lymphomagenesis
MFHAS1	lymphomagenesis
ARID1A	Chromatin regulation, SWI/SNF complex
P2RY8	G-protein coupled receptor the promote the clustering of activated B cells
TP53	Tumor suppressor gene

SNV, single nucleotide variation.
Denominator of the prevalence calculation uses number of patients with ≥1 reported SNV (n=31) at baseline.

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References: 1. Hamblett KJ, et al. *Mol Cancer Ther.* 2023;22(suppl 12):C132. **2.** Hamblett KJ, et al. *Blood.* 2023;142(suppl 1):1440. **3.** Adcetris (brentuximab). Prescribing information. Seagen Inc. **4.** Abramson JS, et al. *Blood Adv.* 2023;7:1130-1136. **5.** Abramson JS. Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Abstract 460. **6.** Abramson JS. Oral presentation at: 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, CA, and virtual. Abstract 611. **7.** Lynch RC, et al. *Blood.* 2023;141:2576-2586. **8.** Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068. **9.** Cheson BD, et al. *Blood.* 2016;128:2489-2496. **10.** Kurtz MK, et al. *Blood.* 2019;134(suppl 1):552.

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