Exploratory ctDNA Analyses for the EVOKE-01 Study in Metastatic Non–Small Cell Lung Cancer

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Conclusions

- Exploratory ctDNA analyses performed for the EVOKE-01 NSCLC study identified no potential predictive biomarkers for SG
- ctDNA was prognostic for OS in both treatment arms, with undetectable ctDNA at baseline associated with the longest survival (median not reached)
- ctDNA clearance at C2D1 supports SG's antitumor activity in NSCLC
  - Greater ctDNA clearance at this point was also prognostic for OS with both treatment arms
- Oncogenic driver alterations of *KRAS* mutations were frequent (20% of patients) in the study and had a negative prognostic effect
- Deleterious *TP53* mutations were observed in 68% of patients and were a negative prognostic biomarker in both arms; patients with *KEAP1*/*STK11* mutations (independent of *TP53* mutation status) had the worst OS

References: **1.** Zografos E, et al. *Cancers*. 2022;14:4954. **2.** Zaman FY, et al. *Cancers*. 2023;15:2425. **3.** Black JRM, et al. *Nat Med*. 2025;31:70-6. **4.** Trodelvy. Package insert. Gilead Sciences, Inc; March 2025. **5.** Paz-Ares LG, et al. *J Clin Oncol*. 2024;42:2860-72.

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Introduction

- In non–small cell lung cancer (NSCLC), circulating tumor DNA (ctDNA) analysis is an important tool to complement assessment of clinical efficacy and identify molecular alterations that may be prognostic or predictive of treatment[1-3]
- Sacituzumab govitecan (SG) is a first-in-class Trop-2-directed antibody-drug conjugate that delivers SN-38 to cells that express Trop-2; SG is approved in previously treated metastatic breast cancer that is either triple negative or hormone receptor positive, human epidermal growth factor receptor 2 negative[4]
- EVOKE-01 (NCT05089734), a randomized, open-label, phase 3 study, compared SG and docetaxel in metastatic NSCLC that had progressed on or after receiving platinum-based chemotherapy and anti–programmed cell death protein (ligand) 1 (PD-[L]1) treatment[5]
  - Although statistical significance was not met at final analysis, SG showed numerical improvement in the primary endpoint of overall survival (OS) in comparison with docetaxel
- Determining the prognostic value of ctDNA levels and molecular alterations detected in ctDNA is important to predicting outcomes, guiding treatment decisions, and improving patient care
- Here, we report data from exploratory analyses conducted to assess the prognostic/predictive value of ctDNA and genomic alterations in EVOKE-01

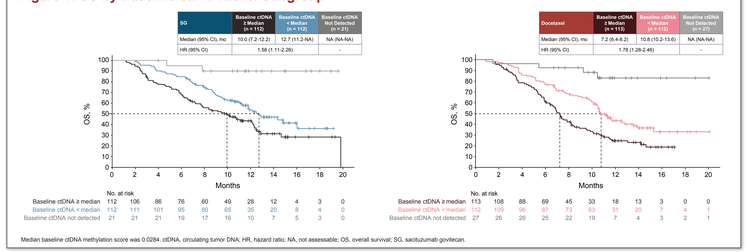
Methods

- Exploratory biomarker analyses were conducted in the ctDNA biomarker-evaluable population (BEP) comprising 497 patients and representing 82% of the intent-to-treat (ITT) population
- Cell-free DNA was extracted from blood collected at baseline and cycle 2 day 1 (C2D1)
- Baseline ctDNA and ctDNA clearance (relative reduction of ctDNA from baseline to C2D1) were analyzed to determine their association with clinical outcomes, including OS, progression-free survival (PFS), and best overall response (BOR)
- The Guardant Infinity™ assay (Palo Alto, CA, USA), a tumor-agnostic platform, was used to quantify ctDNA by detecting tumor-specific methylation patterns in plasma-derived ctDNA, estimating ctDNA fractions, and identifying gene alterations
  - ctDNA levels and gene variants from a comprehensive panel (≈ 800 genes) were reported based on predefined thresholds and metrics as previously described
  - Additional information on oncogenic driver alterations or deleterious mutations collected from study sites was also used in some analyses
  - Oncogenic driver alterations of interest were those identified in the literature as activating in NSCLC and included alterations of *EGFR* (exon 19 and 20 indels, L858R, L861Q, T790M, G719A, G724S, S768I, and C797S), *KRAS* (G12A, G12C, G12D, G12F, G12V, G13C, G13D, G13F, Q61H, Q61L, and Q61R), *ERBB2* (amplification, exon 20 insertions), *BRAF* (V600E), *MET* (exon 14 skipping) and *ALK*, *ROS1*, *RET*, and *NTRK1/2/3* (gene fusions)
- ctDNA levels (conveyed as methylation score) and clearance were calculated as follows:
  - Region-level ctDNA fractions were calculated as the ratio between the counts of differentially methylated regions and universally methylated regions for regions identified from testing a large cohort of nontumor and tumor samples
  - Sample-level ctDNA fractions were determined by averaging the top 100 region-level ctDNA fractions
  - The sample-level percentage reduction in ctDNA was calculated as the percentage decrease from the baseline value to the on-treatment value
- Baseline ctDNA and ctDNA clearance were used to define subgroups for analyses:
  - Baseline ctDNA subgroups: < median ctDNA fraction, ≥ median ctDNA fraction, and ctDNA not detected
  - ctDNA clearance subgroups: < 50% reduction and ≥ 50% reduction from baseline to C2D1, and ctDNA low (ctDNA not detected at either baseline or C2D1)
- Clinical data used in the biomarker analyses were from the study's final analysis (cutoff date: November 29, 2023)

Results

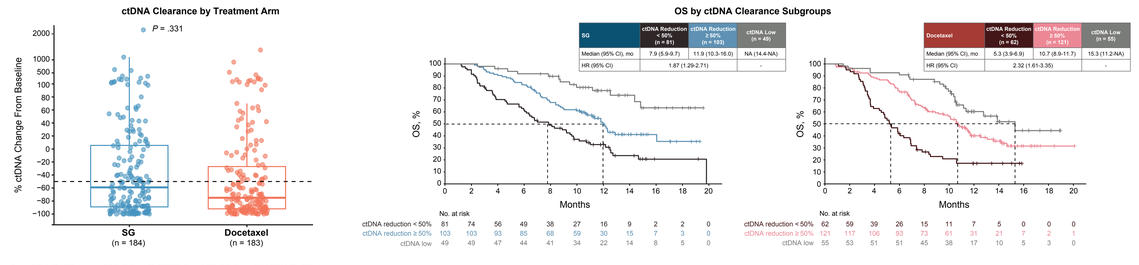
- Baseline characteristics were similar between the ctDNA BEP and ITT populations
- Baseline samples were available for 497 patients, of whom 477 had samples available at C2D1, representing 79% of the ITT population
  - Baseline ctDNA was not detected in 48/497 patients (9.7%), and in a similar number of patients across treatment arms, for 21 and 27 patients for SG and docetaxel, respectively
- Levels of ctDNA were similar in SG and docetaxel arms at both baseline and C2D1
- Median OS was slightly longer in the ctDNA BEP than in the ITT population with both SG (12.2 vs 11.1 months, respectively) and docetaxel (10.2 vs 9.8 months, respectively)
  - The between-treatments hazard ratio (HR [95% CI]) was 0.78 (0.62-0.99) in the ctDNA BEP and 0.84 (0.68-1.04) in the ITT population
- Median OS was the longest (not assessable [NA] in either arm) in patients with no detectable ctDNA at baseline, and longer in patients with < median of 0.0284 than in those with ≥ median tumor methylation score for samples with ctDNA detected at baseline (**Figure 1**)
- Consistent with OS data, median PFS was the longest (8.3 and 7.5 months with SG and docetaxel, respectively) in patients with no detectable ctDNA, and was longer in patients with ctDNA level < median than in those with ctDNA level ≥ median
  - Median PFS was 4.6 vs 4.0 months (HR 1.40; 95% CI, 1.05-1.87) for < median vs ≥ median ctDNA level subgroups with SG
  - Median PFS was 5.4 vs 2.9 months (HR 1.80; 95% CI, 1.33-2.42) for < median vs ≥ median ctDNA level subgroups with docetaxel
- Overall, ctDNA reduction was observed at C2D1 compared with baseline (**Figure 2**)
  - Median ctDNA reduction was 59% and 75% with SG and docetaxel, respectively (P = .331)
  - Pearson's X^2 test also supported a similar proportion of patients with no detectable ctDNA at baseline and C2D1, < 50% vs ≥ 50% reduction in categories between the treatment arms
- Median OS was the longest (NA with SG and 15.3 months with docetaxel) in patients with undetected ctDNA at either time point, and longer in patients with ≥ 50% ctDNA reduction than in patients with < 50% ctDNA reduction (**Figure 2**)
- PFS was also longer in patients with ≥ 50% ctDNA reduction than in those with < 50% ctDNA reduction
  - Median PFS was 2.7 vs 5.6 months (HR 2.07; 95% CI, 1.51-2.84) for < 50% vs ≥ 50% ctDNA subgroups, respectively with SG
- Median PFS was 1.7 vs 4.2 months (HR 2.11; 95% CI, 1.51-2.96) for < 50% vs ≥ 50% ctDNA subgroups, respectively with docetaxel
- No trend was noted for baseline ctDNA and BOR in either treatment arm (**Figure 3**)
  - Baseline ctDNA levels were similar in patients with stable disease (SD) or progressive disease (PD), regardless of treatment
  - Baseline ctDNA levels were slightly lower among patients who experienced partial response (PR) with docetaxel than SG
- Median ctDNA reduction was greatest among patients who experienced PR, followed by patients with SD, and the lowest in patients with PD as BOR (**Figure 3**)
  - ctDNA clearance was similar in patients with PR in both the SG and docetaxel treatment arms

Figure 1. OS by Baseline ctDNA Level Subgroup



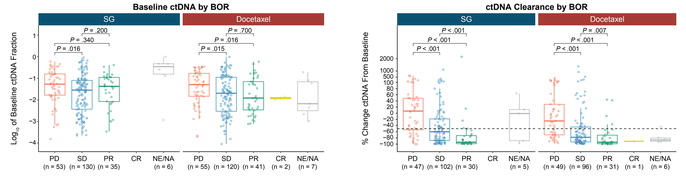
Median baseline ctDNA methylation score was 0.0284. ctDNA, circulating tumor DNA; HR, hazard ratio; NA, not assessable; OS, overall survival; SG, sacituzumab govitecan.

Figure 2. ctDNA Clearance



ctDNA, circulating tumor DNA; HR, hazard ratio; NA, not assessable; OS, overall survival; SG, sacituzumab govitecan.

Figure 3. Baseline ctDNA and Clearance by BOR

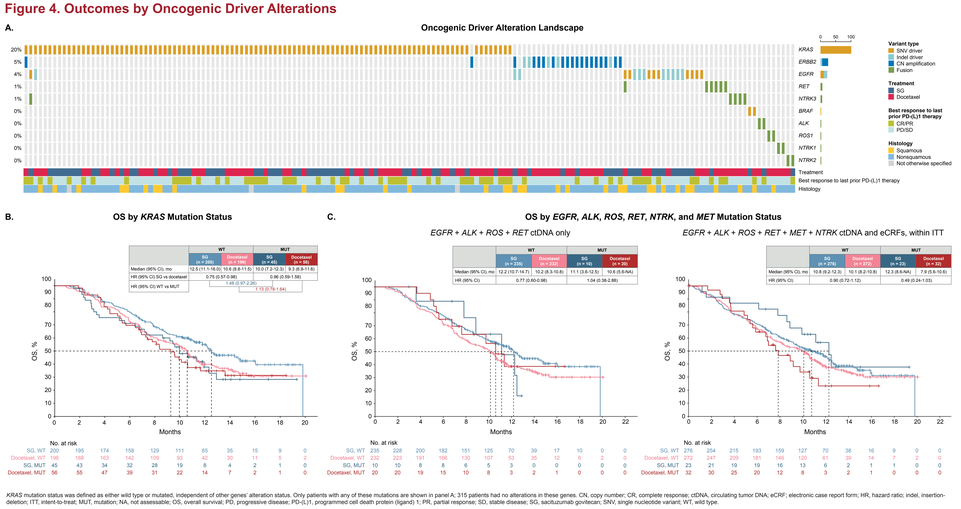


BOR, best overall response; CR, complete response; ctDNA, circulating tumor DNA; NA, not assessable; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

Results (continued)

- Most oncogenic driver alterations were detected for *KRAS* and occurred in 20% of patients with baseline ctDNA (**Figure 4A**)
- Median OS was longer with wild-type vs mutant *KRAS*, irrespective of treatment (**Figure 4B**)
- Small numbers of oncogenic driver alterations in *ALK*, *EGFR*, *RET*, and *ROS1* from ctDNA analysis limited OS interpretations. Further analysis, including mutational data (eg, alterations in *MET* and *NTRK*) collected from study sites showed a numerical OS benefit with SG vs docetaxel (**Figure 4C**). These analyses were limited by the small number of patients and no statistical significance
- Frequency of oncogenic driver alterations in EVOKE-01 was lower than in the overall NSCLC population
  - Per study design, patients had to have prior treatment with chemotherapy and anti–PD-(L)1 therapy, as well as targeted therapy, if they had known actionable genomic alterations

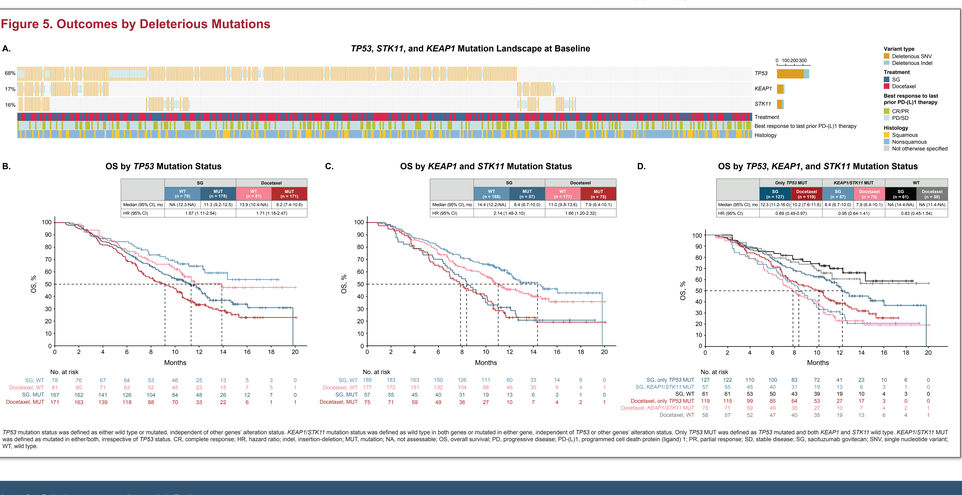
Figure 4. Outcomes by Oncogenic Driver Alterations



KRAS mutation status was defined as either wild type or mutated, independent of other genes' alteration status. Only patients with any of these mutations are shown in panel A; 315 patients had no alterations in these genes. CN, copy number; CR, complete response; ctDNA, circulating tumor DNA; eCRF; electronic case report form; HR, hazard ratio; indel, insertion-deletion; ITT, intent-to-treat; MUT, mutation; NA, not assessable; OS, overall survival; PD, progressive disease; PD-(L)1, programmed cell death protein (ligand) 1; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; SNV, single nucleotide variant; WT, wild type.

- Deleterious mutations of *TP53*, *KEAP1*, and *STK11* were frequent (**Figure 5A**)
  - Most patients (387; 76% of BEP) had ≥ 1 mutation among *TP53*, *KEAP1*, and *STK11*
  - *TP53* mutations occurred in 338/497 patients (68% of BEP), and 246 patients (49% of BEP) had *TP53* mutations but no mutations to *KEAP1* and *STK11*
  - 40 patients (8% of BEP) had mutations to *KEAP1* and/or *STK11* but no *TP53* mutations
- Median OS was longer with wild-type vs mutant *TP53*, irrespective of treatment (**Figure 5B**)
- Similarly, median OS was longer in patients with wild-type *KEAP1* and/or *STK11* than in those with either of these genes mutated, regardless of *TP53* status, other mutations, or treatment (**Figure 5C**)
- Patients harboring tumors with wild-type *TP53*, *KEAP1*, and *STK11* had the longest survival, with median OS not assessable (**Figure 5D**)
- Median OS favored SG over docetaxel in patients with only *TP53* mutant (wild-type *KEAP1*/*STK11*) (**Figure 5D**)
- Patients with CR/PR had a similar number of mutations in *TP53*/*KEAP1*/*STK11* as patients with PD/SD as best response to last prior PD-(L)1 therapy

Figure 5. Outcomes by Deleterious Mutations



TP53 mutation status was defined as either wild type or mutated, independent of other genes' alteration status. *KEAP1*/*STK11* mutation status was defined as wild type in both genes or mutated in either gene, irrespective of *TP53* or other genes' alteration status. Only *TP53* MUT was defined as *TP53* mutated and both *KEAP1* and *STK11* wild type. *KEAP1*/*STK11* MUT was defined as mutated in either/both, irrespective of *TP53* status. CR, complete response; HR, hazard ratio; indel, insertion-deletion; MUT, mutation; NA, not assessable; OS, overall survival; PD, progressive disease; PD-(L)1, programmed cell death protein (ligand) 1; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; SNV, single nucleotide variant; WT, wild type.