Brain metastases and actionable genetic alterations with sacituzumab govitecan versus docetaxel in metastatic non-small cell lung cancer: subgroups of the phase III EVOKE-01 trial

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Conclusions

- In this post hoc analysis of the EVOKE-01 study, numerically higher overall survival (OS) and no difference in progression-free survival (PFS) were observed with sacituzumab govitecan (SG) compared with docetaxel in subgroups of patients with brain metastases at baseline and patients with prior treatment for actionable genomic alterations (AGAs)
  - OS in patients with brain metastases and those with AGAs who received SG was comparable to or trending better than that observed in patients treated with SG from the overall EVOKE-01 study population[1]; however, OS in those treated with docetaxel was numerically lower than in patients treated with docetaxel from the overall study population[1]
  - PFS values were lower in both treatment arms in the brain metastases and AGA subgroups compared with the overall study population[1]
- Data from EVOKE-01 show that SG has activity in subgroups of patients with brain metastases and AGAs

Plain Language Summary

- Non-small cell lung cancer (NSCLC) that has spread throughout the body is hard to treat. In many patients, their cancer gets worse even if treatment initially helped
- Some patients have NSCLC cancers that have DNA changes that can be targeted with specific drugs or treatments against the cancer. These types of DNA changes are called "actionable genomic alterations". However, "targeted treatments" often stop working
- In many patients, NSCLC spreads to the brain, and these patients are particularly in need of better treatments
- In the EVOKE-01 study, researchers used a treatment called sacituzumab govitecan, or SG, and compared it with a type of chemotherapy called docetaxel to see if SG would be helpful for patients who have already been treated for NSCLC that has spread throughout the body
  - In EVOKE-01, researchers found that patients who took SG lived about the same amount of time or a little longer than patients who took docetaxel, and many benefited from SG treatment
- Sometimes there are specific subsets of patients among a wider group of patients who benefit from a treatment. Here, we looked at a subset of patients from the EVOKE-01 study, to see if SG helped patients with NSCLC that has spread to the brain or if SG helped patients who previously had treatment for actionable genomic alterations
- We found that patients with previously treated NSCLC that has spread to the brain or has been treated for actionable genomic alterations who took SG tended to live longer than those who took docetaxel

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Introduction

- Patients with metastatic NSCLC (mNSCLC) have limited treatment options after progression on platinum-based chemotherapy,[2] and standard-of-care docetaxel provides suboptimal efficacy that comes with notable treatment-related adverse events,[1,3] leaving an unmet need for more effective treatment options
  - While targeted therapy has improved outcomes for patients with AGA, acquired resistance and subsequent disease progression is common.[5] These patients need effective therapies after progression on platinum-based chemotherapy and targeted therapy[1,4]
  - Treatment of patients with brain metastases presents an additional challenge; brain metastases are estimated to occur in 40% of patients with NSCLC at some point in their disease course and are associated with limited survival, poor outcomes, and impaired quality of life[6-8]
- The phase 3 EVOKE-01 (NCT05089734) study compared SG, a trophoblast cell-surface antigen 2–directed antibody-drug conjugate, with docetaxel in patients with mNSCLC who progressed after platinum-based chemotherapy and anti–programmed death (ligand)-1 (PD-[L]1) treatment
  - A numerical, but not statistically significant, improvement in OS was observed with SG compared with docetaxel (hazard ratio [HR], 0.84; 95% CI, 0.68–1.04), and the SG group had fewer grade ≥3 adverse events and adverse event–related discontinuations compared with docetaxel[1]
- Here we investigate efficacy in the EVOKE-01 study in subgroups of patients with brain metastases and patients with AGAs

Methods

- Eligible patients (age ≥18 years) had stage IV NSCLC with progression on/after a platinum-based chemotherapy and anti–PD-(L)1 therapy, as well as targeted treatment for any known AGAs
  - Patients with previously treated brain metastases were eligible if central nervous system disease was stable for ≥4 weeks before enrollment, there was no evidence of new or enlarging brain metastases, and they were taking ≤10 mg/day of prednisone (or its equivalent)
  - Patients with known AGAs were required to have prior treatment with an appropriate tyrosine kinase inhibitor
- Patients were randomized 1:1 (stratified by histology, best response to last anti–PD-[L]1–containing regimen, and receipt of AGA treatment) to receive SG (10 mg/kg IV, days 1 and 8) or docetaxel (75 mg/m^2 IV, day 1) in 21-day cycles until progression or unacceptable toxicity
- The primary endpoint of EVOKE-01 was OS, and key secondary endpoints included investigator-assessed PFS and objective response rate (ORR)
- In this post hoc analysis, descriptive statistics were used to evaluate the primary and secondary endpoints for the subgroup of patients with known brain metastases at baseline and a separate subgroup of patients with known AGAs at baseline

Results

Patient Demographics and Baseline Characteristics

- Of the 603 patients randomized in EVOKE-01 (SG, n = 299; docetaxel, n = 304), 74 (12%) had known brain metastases at baseline and 44 (7%) had a known AGA at baseline (**Table 1**)
- Median (range) age was 59 (31–79) years for patients with brain metastases and 63 (40–79) years for patients with AGAs. Baseline characteristics are shown in **Table 1**

Table 1. Baseline Characteristics

	Patients with brain metastases at baseline (n = 74)		Patients with known AGA at baseline (n = 44)	
	SG (n = 35)	Docetaxel (n = 39)	SG (n = 19)	Docetaxel (n = 25)
Age (years), median (range)	61 (31–79)	59 (38–74)	67 (43–79)	59 (40–77)
Sex, n (%)				
Male	26 (74)	25 (64)	8 (42)	12 (48)
Female	9 (26)	14 (36)	11 (58)	13 (52)
Race, n (%)				
Asian	3 (9)	4 (10)	2 (11)	8 (32)
Black	0	1 (3)	0	0
White	18 (51)	28 (72)	13 (68)	11 (44)
Other[a]	14 (40)	6 (15)	4 (21)	6 (24)
Previous lines of therapy, n (%)				
1	20 (57)	18 (46)	0	0
2	10 (29)	14 (36)	6 (32)	11 (44)
≥3	5 (14)	7 (18)	13 (68)	14 (56)
Histology, n (%)				
Squamous	4 (11)	4 (10)	0	2 (8)
Nonsquamous[b]	31 (89)	35 (90)	19 (100)	23 (92)
Best response to last prior immune therapy[c]				
CR/PR	14 (40)	18 (46)	6 (32)	11 (44)
SD/PD	21 (60)	21 (54)	12 (63)	14 (56)
Brain metastases at baseline, n (%)	35 (100)	39 (100)	4 (21)	7 (28)
Received prior therapy for AGA, n (%)	4 (11)	7 (18)	19 (100)	25 (100)
Gene with AGA, n (%)[d]				
EGFR	1 (3)	4 (10)	6 (32)	13 (52)
KRAS	2 (6)	2 (5)	7 (37)	7 (28)
MET	1 (3)	0	4 (21)	1 (4)
ROS1	0	0	1 (5)	2 (8)

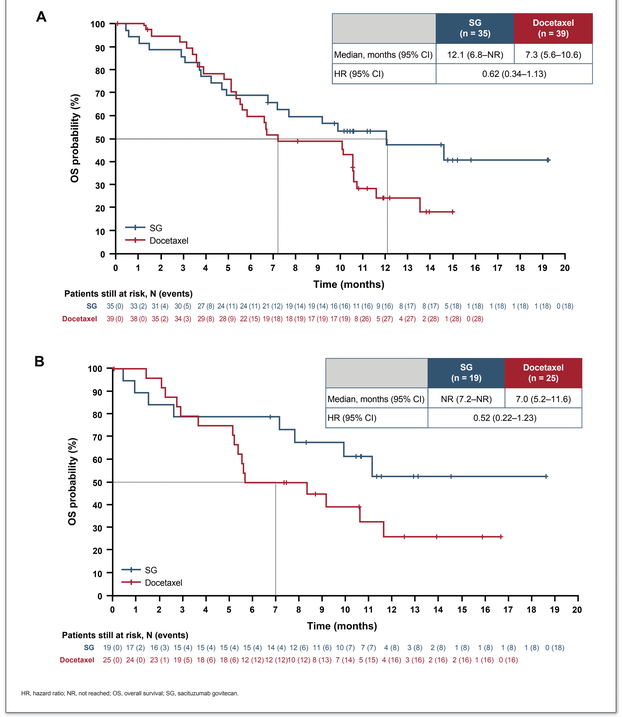
[a]Includes race reported as "other" or race not reported. [b]Histologies not otherwise specified were included in the nonsquamous group. [c]Best response was not available for 1 patient with known AGAs from the SG group. [d]Patients with multiple types of AGA were counted once for each type. Genes that were identified in >2 patients are listed in the table. Additional AGAs identified in the brain metastases subgroup were in *ALK* (docetaxel, n = 1) and "other" (docetaxel, n = 1), which includes genes that could not be identified; and in the AGA subgroup: *ALK* (SG, n = 1; docetaxel, n = 1), *BRAF* V600E (SG, n = 1; docetaxel, n = 1), *NTRK* (SG, n = 1), *RET* (SG, n = 1; docetaxel, n = 1), and 5 AGAs categorized as "other" (SG, n = 2; docetaxel, n = 3).
AGA, actionable genomic alteration; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

Results

Efficacy

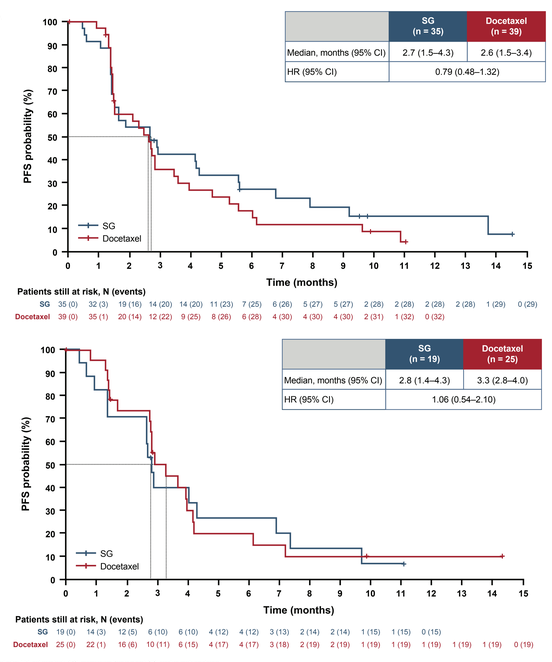
- As of 29 November 2023, median OS was numerically higher with SG compared with docetaxel for patients with brain metastases and for patients with AGAs (**Figure 1**)
  - Median (95% CI) OS for patients with brain metastases was 12.1 (6.8–not reached [NR]) months with SG and 7.3 (5.6–10.6) months with docetaxel (HR, 0.62; 95% CI, 0.34–1.13)
  - Median (95% CI) OS for patients with AGAs was NR (7.2–NR months) with SG and 7.0 (5.2–11.6) months with docetaxel (HR, 0.52; 95% CI, 0.22–1.23)
- PFS was similar with SG and docetaxel for patients with brain metastases and for patients with AGAs (**Figure 2**)
- ORR was numerically higher with docetaxel for patients with brain metastases and for patients with AGAs compared with SG (**Table 2**)

Figure 1. OS in Patients With Known Baseline (A) Brain Metastases and (B) AGAs



HR, hazard ratio; NR, not reached; OS, overall survival; SG, sacituzumab govitecan.

Figure 2. PFS in Patients With Known Baseline (A) Brain Metastases and (B) AGAs



HR, hazard ratio; NR, not reached; PFS, progression-free survival; SG, sacituzumab govitecan.

Table 2. Summary of Efficacy in Patients With Brain Metastases and Patients With AGAs

	Patients with brain metastases at baseline (n = 74)		Patients with known AGA at baseline (n = 44)	
	SG (n = 35)	Docetaxel (n = 39)	SG (n = 19)	Docetaxel (n = 25)
ORR, % (95% CI)[a]	8.6 (1.8–23.1)	10.3 (2.9–24.2)	10.5 (1.3–33.1)	12.0 (2.5–31.2)
Best overall response, n (%)				
PR	3 (8.6)	4 (10.3)	2 (10.5)	3 (12.0)
SD	14 (40.0)	17 (43.6)	9 (47.4)	13 (52.0)
PD	14 (40.0)	14 (35.9)	4 (21.1)	6 (24.0)
Not evaluable	3 (8.6)	0	1 (5.3)	0
Not assessed	1 (2.9)	4 (10.3)	3 (15.8)	3 (12.0)
DCR, % (95% CI)[a,b]	48.6 (31.4–66.0)	53.8 (37.2–69.9)	57.9 (33.5–79.7)	64.0 (42.5–82.0)

[a]2-sided CI based on Clopper-Pearson method. [b]Proportion of patients who achieve a CR, PR, or SD.
AGA, actionable genomic alteration; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.