

Phase 1, First-in-Human Study of MGC026, a B7-H3–Targeted Antibody-Drug Conjugate (ADC) in Advanced Solid Tumors

Poster: #1020P

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INTRODUCTION

- The B7 homolog 3 (B7-H3) protein is overexpressed in multiple solid tumors including squamous cell carcinoma of the head and neck (SCCHN), and is associated with greater disease severity and poor outcomes^{1,2}
- MGC026 is a B7-H3–targeting antibody-drug conjugate (ADC) comprising the humanized antibody MGA017 site-specifically conjugated to a cleavable exatecan linker-payload via Fc glycans at asparagine 297.³ Following internalization, lysosomal cleavage releases exatecan, which inhibits topoisomerase I and induces cell death³
- Preclinically, MGC026 demonstrated dose-dependent cytotoxicity, bystander killing, and antitumor activity across multiple solid tumor models.³ No lung toxicity was observed in a cynomolgus monkey toxicology study,³ which may be due to glycan conjugation abolishing Fcγ receptor binding, thereby limiting nonspecific Fc-mediated uptake by alveolar macrophages
- Here, we report initial data from an ongoing phase 1 dose-escalation study in advanced solid tumors and initial SCCHN dose-expansion

METHODS

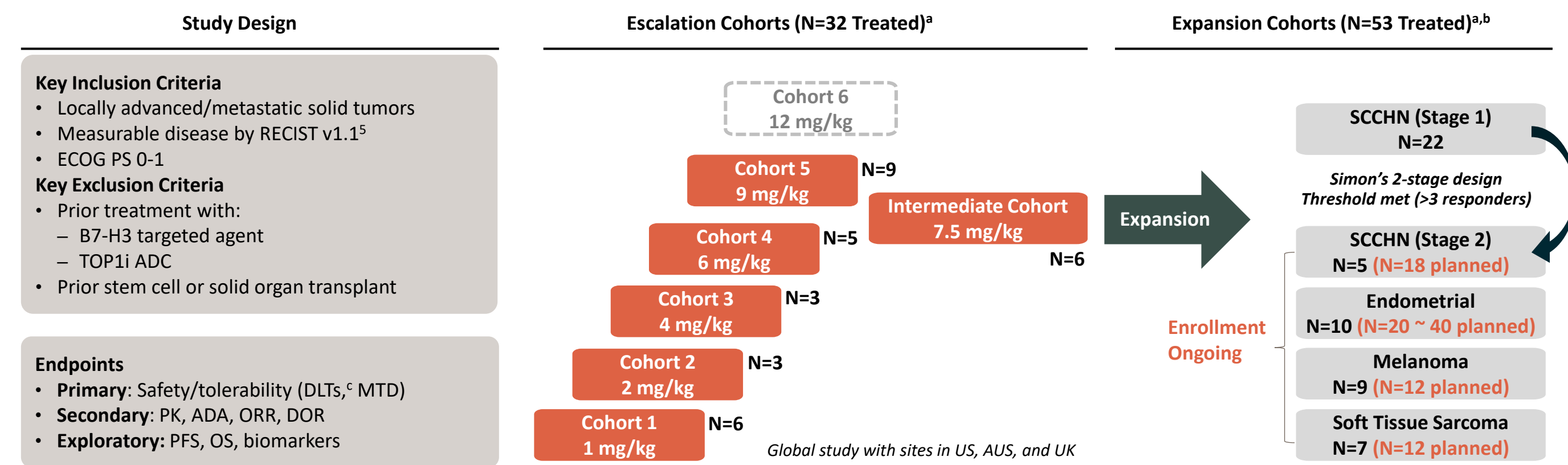
- This ongoing phase 1/1b, first-in-human, open-label, multicenter study evaluates MGC026 in dose-escalation and cohort-expansion (NCT06242470/CP-MGC026-01) (Figure 1)
- Eligible participants (≥18 years) had relapsed/refractory, unresectable, locally advanced or metastatic solid tumors. Eligible tumor types were based on reported prevalence of B7-H3 expression; prospective confirmation was not required
- Dose-escalation used the Keyboard Bayesian model-assisted design⁴ (target dose limiting toxicity [DLT] rate, 25%) with 6 planned dose levels. MGC026 was evaluated at 5 dose levels ranging from 1–9 mg/kg IV every 3 weeks (Q3W); the planned 12 mg/kg cohort was not opened for enrollment
- Maximum tolerated dose (MTD) was not formally established; based on available safety, efficacy, and PK data, 7.5 mg/kg was selected as the recommended dose for expansion (RDE)
- Dose expansion began after selection of the RDE, with up to 6 tumor-specific cohorts planned. The expansion cohorts received MGC026 at 7.5 mg/kg IV Q3W
- Tumors were assessed per RECIST v1.1⁵ every 9 weeks through Week 27, then every 12 weeks until progression, regardless of dose delays. Participants with metastatic castration-resistant prostate cancer (mCRPC) were assessed using the Prostate Cancer Clinical Trials Working Group 3 criteria⁶
- Safety was monitored throughout the study
- Population pharmacokinetics (PK) modeling and exposure-response analyses evaluated MGC026 ADC and unconjugated exatecan

RESULTS

Study Design and Participants

- As of 1 September 2026, 85 participants were treated with MGC026, including 32 participants in the dose-escalation and 53 participants in the expansion cohorts, across 12 active sites (7 in the United States, 3 in Australia, and 2 in the United Kingdom) (Figure 1; Table 1)

Figure 1. MGC026 Phase 1 Trial Study Schema and Participants



*Participants received MGC026 Q3W IV for up to 35 cycles or until meeting a study treatment discontinuation criterion, whichever occurred first. Among the dose-expansion cohorts, efficacy analyses are presented for the SCCHN cohort only, as this cohort has the most mature data available at the time of analysis; data from other cohorts remain immature and are not yet suitable for efficacy evaluation. DLTs were assessed during the first cycle (Day 1) and/or Day 15. AE, adverse event; ADA, anti-drug antibodies; ADC, antibody-drug conjugate; B7-H3, B7 homolog 3; CRPC, castration-resistant prostate cancer; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SCCHN, squamous cell carcinoma of the head and neck; TOP11, topoisomerase I inhibitor.

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RESULTS, cont.

Table 1. Baseline Demographic and Disease Characteristics

Parameters	Dose-escalation cohorts (1–9 mg/kg) (n=32)	7.5 mg/kg cohorts ^a (n=59)	Dose-escalation + dose-expansion cohorts ^b (N=85)	SCCHN dose-expansion cohort (7.5 mg/kg) (n=27)
Age, median (range), years	65 (47–83)	63 (35–80)	64 (35–83)	61 (35–79)
Male, n (%)	21 (65.6)	36 (61.0)	51 (60.0)	21 (77.8)
Female, n (%)	11 (34.4)	23 (39.0)	34 (40.0)	6 (22.2)
Race, n (%)				
White	27 (84.4)	46 (78.0)	68 (80.0)	19 (70.4)
Black or African American	2 (6.3)	2 (3.4)	4 (4.7)	1 (3.7)
Asian	1 (3.1)	6 (10.2)	7 (8.2)	3 (11.1)
Unknown/Other	2 (6.3)	5 (8.5)	6 (7.1)	4 (14.8)
ECOG performance status, n (%)				
0	7 (21.9)	24 (40.7)	30 (35.3)	9 (33.3)
1	25 (78.1)	35 (59.3)	55 (64.7)	18 (66.7)
Tumor type, n (%)				
Bladder cancer	2 (6.3)	0	2 (2.4)	0
mCRPC	12 (37.5)	2 (3.4)	12 (14.1)	0
Colorectal cancer	3 (9.4)	2 (3.4)	3 (3.5)	0
Endometrial cancer	2 (6.3)	10 (16.9)	12 (14.1)	0
G/GE cancer	1 (3.1)	0	1 (1.2)	0
Melanoma	1 (3.1)	8 (13.6)	9 (10.6)	0
NSCLC	1 (3.1)	0	1 (1.2)	0
Ovarian cancer	2 (6.3)	0	2 (2.4)	0
Pancreatic cancer	3 (9.4)	1 (1.7)	3 (3.5)	0
Sarcoma	5 (15.6)	9 (15.3)	13 (15.3)	0
SCCHN	0	27 (45.8)	27 (31.8)	27 (100)
Disease status at initial diagnosis, n (%)				
Local resectable	14 (43.8)	24 (40.7)	36 (42.4)	10 (37.0)
Locally advanced unresectable	6 (18.8)	8 (13.6)	14 (16.5)	5 (18.5)
Metastatic	11 (34.4)	27 (45.8)	34 (40.0)	12 (44.4)
Unknown	1 (3.1)	0	1 (1.2)	0
Median (range) number of prior lines of therapy	4 (1–8)	3 (1–8)	3 (1–8)	3 (1–7)
Number of prior lines of therapy, n (%)				
Participants with available information on prior lines of therapy, n	32	51	77	22
1	3 (9.4)	4 (7.8)	7 (9.1)	1 (4.5)
2	2 (6.3)	10 (19.6)	12 (15.6)	2 (9.1)
3	8 (25.0)	20 (39.2)	24 (31.2)	10 (45.5)
4+	19 (59.4)	17 (33.3)	34 (44.2)	9 (40.9)
Prior systemic therapy, n (%)	32 (100)	58 (98.3)	84 (98.8)	27 (100)
Prior checkpoint inhibitor, n (%)	15 (46.9)	45 (76.3)	59 (69.4)	27 (100)

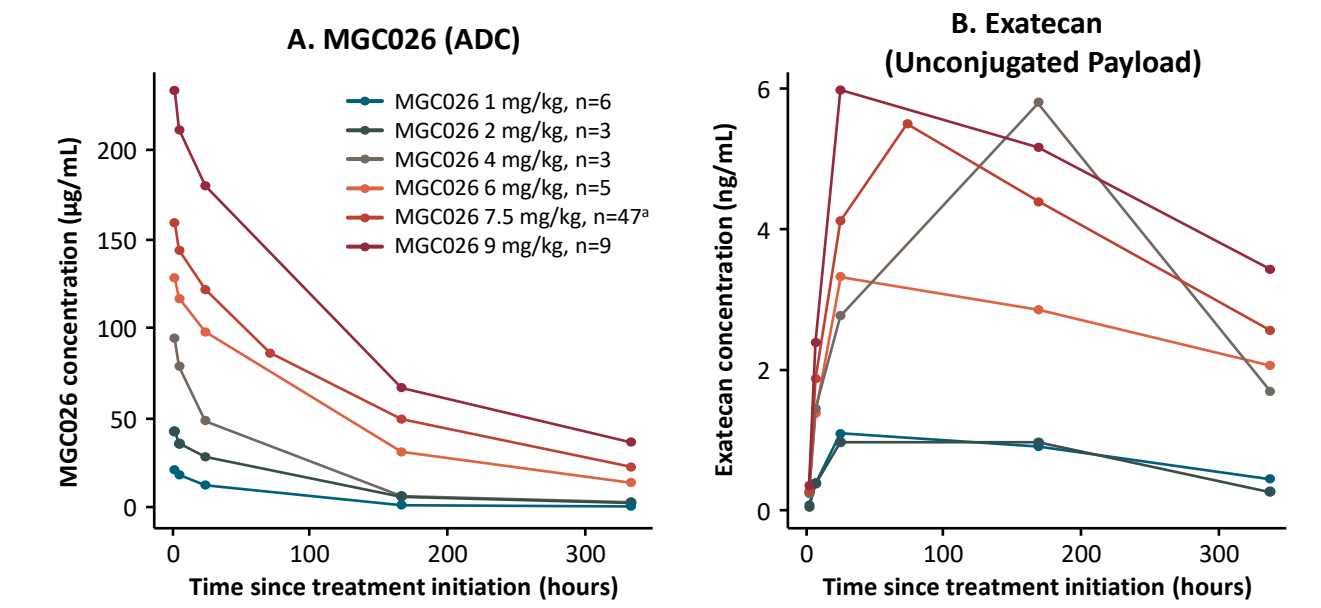
^aIncludes the intermediate dose-escalation cohort (7.5 mg/kg; n=6) and all the dose-expansion cohorts (n=53). ^bIncludes all participants from the dose-escalation cohorts (n=32) and participants from dose-expansion cohorts, including SCCHN (n=27) and endometrial cancer (n=10), melanoma (n=9), and soft tissue sarcoma (n=7). Based on NCI-CTCAE version 5.0. ^cIncludes events with causality assessments of 'Possible', 'Probable', or 'Definite'. ^dThe SAEs occurring in 8 of 12 participants were: anemia (n=4), pneumonia (n=4), febrile neutropenia (n=1), fatigue (n=2), aspartate aminotransferase (n=2), sepsis (n=2), and pulmonary embolism (n=2). AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- Among the 32 participants treated in the dose-escalation cohorts, the median number of prior lines of therapy was 4 (range, 1–8); and the median exposure was 13.4 weeks (range, 1.1–87.1).
- In the dose-expansion cohorts, 53 participants were treated with MGC026: 27 had SCCHN, 10 had endometrial cancer, 9 had melanoma, and 7 had soft tissue sarcoma (Figure 1; Table 1)
- Among the dose-expansion cohorts, efficacy results are presented for the SCCHN expansion cohort, which had the most mature data at the cutoff. Efficacy data from the other expansion cohorts remain immature and are not presented herein

Pharmacokinetics

- A dose-dependent increase in MGC026 exposure was observed for the ADC and unconjugated payload (Figure 2)

Figure 2. Pharmacokinetics Exposure for MGC026 (A) and Unconjugated Payload (B) by Dose Level



^aThe 7.5 mg/kg group includes participants from the intermediate dose-escalation cohort and the dose-expansion cohorts with available pharmacokinetics data. ADC, antibody drug conjugate.

Safety

Dose escalation

- Three participants treated during dose escalation experienced DLTs:
 - In cohort 1 (1 mg/kg): grade 3 alanine aminotransferase increased in 1 participant
 - In cohort 5 (9 mg/kg): grade 3 febrile neutropenia and grade 4 thrombocytopenia in 1 participant; and grade 4 nonfebrile neutropenia in 1 participant

Overall safety

- Overall, adverse event (AE) distribution is shown in Table 2
- Grade ≥3 treatment-related AEs (TRAEs) occurred in 43 of the 85 (50.6%) participants
 - The most common grade ≥3 TRAEs were anemia and neutropenia (Figure 3)
 - Gastrointestinal TRAEs were mainly grade ≤2 and manageable (Figure 3)
- No interstitial lung disease (ILD)/pneumonitis, ocular toxicities, or unexpected toxicities were observed
- Two fatal treatment-emergent AEs (TEAEs) were reported; neither was treatment-related

Table 2. Overall Summary of Adverse Events

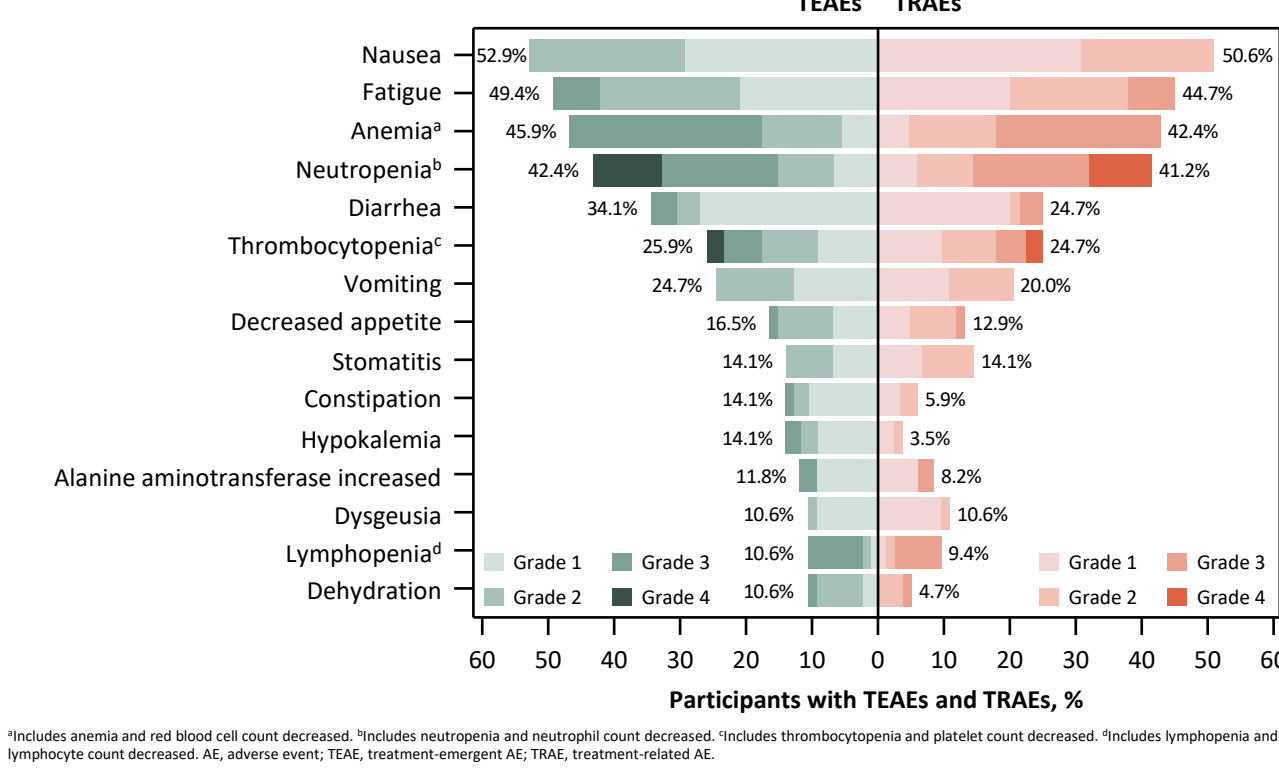
AE, n (%)	Dose-escalation cohorts (1–9 mg/kg) (n=32)	7.5 mg/kg cohorts ^a (n=59)	Dose-escalation + dose-expansion cohorts (N=85) ^b	SCCHN dose-expansion cohort (7.5 mg/kg) (n=27)
TEAE	31 (96.9)	54 (91.5)	79 (92.9)	24 (88.9)
TEAE grade ≥3 ^c	22 (68.8)	37 (62.7)	54 (63.5)	18 (66.7)
TRAE ^d	28 (87.5)	50 (84.7)	72 (84.7)	23 (85.2)
TRAE grade ≥3 ^{c,d}	19 (59.4)	29 (49.2)	43 (50.6)	13 (48.1)
SAE	9 (28.1)	20 (33.9)	27 (31.8) ^e	13 (48.1)
Fatal AE (not treatment related)	1 (3.1)	2 (3.4)	2 (2.4)	1 (3.7)
TRAE of special interest ^f	1 (3.1)	0	1 (1.2)	0
Infusion-related reaction	1 (3.1)	0	1 (1.2)	0
TRAE leading to MGC026 dose interruption	15 (46.9)	19 (32.2)	30 (35.3)	7 (25.9)
TRAE leading to MGC026 dose reductions	8 (25.0)	13 (22.0)	20 (23.5)	9 (33.3)
TRAE leading to MGC026 discontinuation	4 (12.5)	0	4 (4.7)	0

^aIncludes the intermediate dose-escalation cohort (7.5 mg/kg; n=6) and all the dose-expansion cohorts (n=53). ^bIncludes all participants from the dose-escalation cohorts (n=32) and participants from dose-expansion cohorts, including SCCHN (n=27) and endometrial cancer (n=10), melanoma (n=9), and soft tissue sarcoma (n=7). Based on NCI-CTCAE version 5.0. ^cIncludes events with causality assessments of 'Possible', 'Probable', or 'Definite'. ^dThe SAEs occurring in 8 of 12 participants were: anemia (n=4), pneumonia (n=4), febrile neutropenia (n=1), fatigue (n=2), aspartate aminotransferase (n=2), sepsis (n=2), and pulmonary embolism (n=2). AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

SCCHN cohort

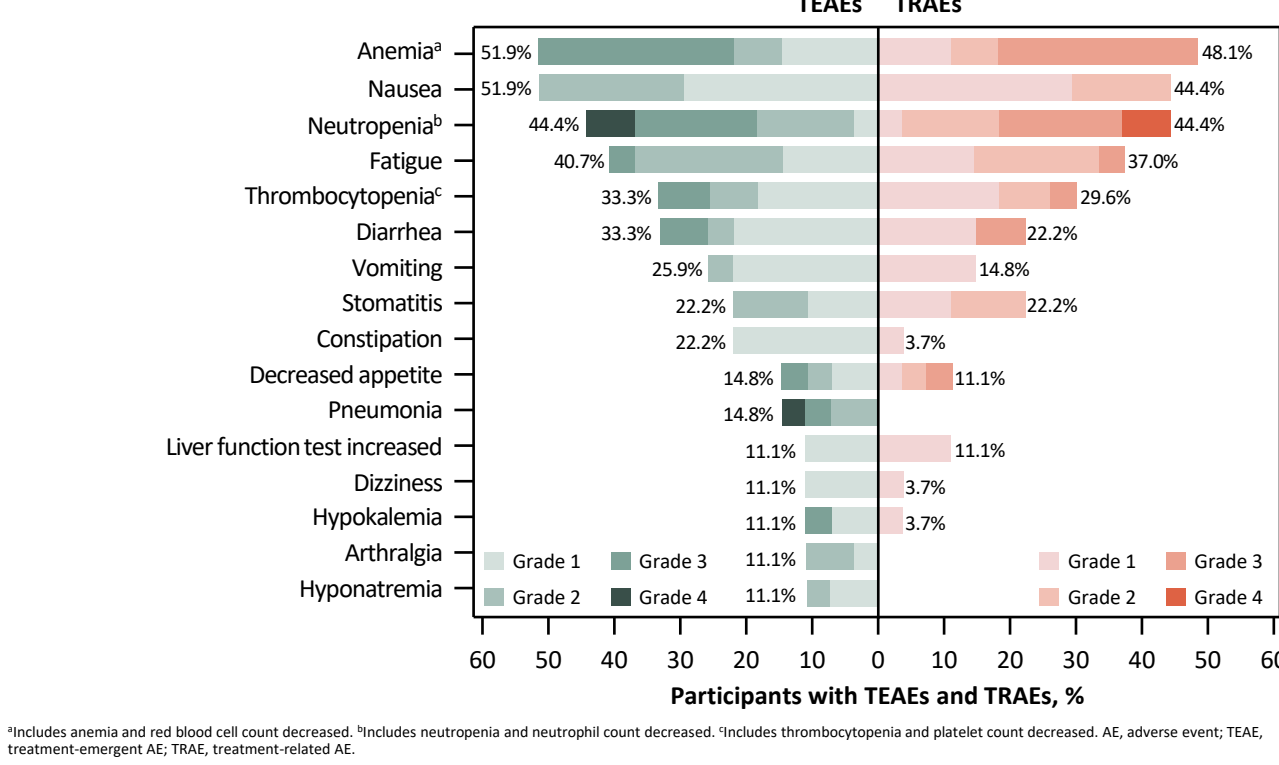
- The AE profile in the SCCHN cohort (Figure 4) was similar to that of the overall safety population (Figure 3)
 - No participants in the SCCHN cohort discontinued study treatment due to AEs (Table 2)

Figure 3. Adverse Events Occurring in ≥10% of Participants in Overall Safety Population (N=85)



^aIncludes anemia and red blood cell count decreased. ^bIncludes neutropenia and neutrophil count decreased. ^cIncludes thrombocytopenia and platelet count decreased. ^dIncludes lymphopenia and lymphocyte count decreased. AE, adverse event; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Figure 4. Adverse Events Occurring in ≥10% of Participants in the SCCHN Cohort Expansion (N=27)



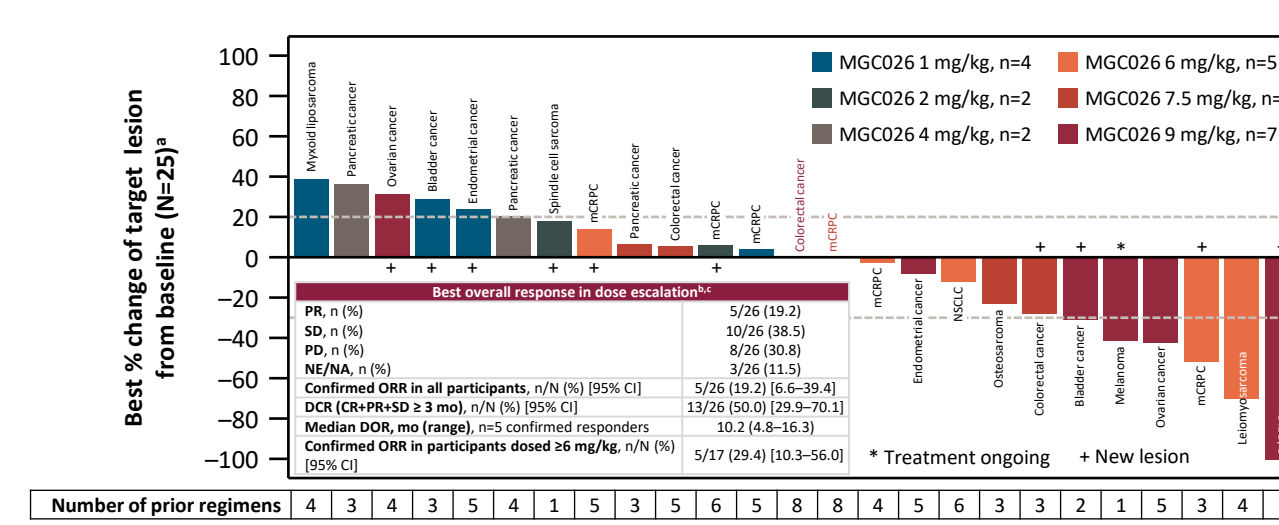
^aIncludes anemia and red blood cell count decreased. ^bIncludes neutropenia and neutrophil count decreased. ^cIncludes thrombocytopenia and platelet count decreased. AE, adverse event; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Efficacy

Dose escalation

- As of data cutoff, among 26 response-evaluable participants in the dose-escalation cohorts (all doses):
 - Five achieved a confirmed partial response (PR) with an objective response rate (ORR) of 19.2%; 10 had stable disease (SD). Disease control rate (DCR, defined as complete response [CR] + PR + SD ≥3 months) was 50.0% (13/26) (Figure 5)
 - Median duration of response (DOR) was 10.2 months (range, 4.8–16.3) (Figure 5)
 - All 5 confirmed responders received doses ≥6 mg/kg and represented 5 different tumor types (Figure 5)
 - Among the 17 response-evaluable participants treated at ≥6 mg/kg, confirmed ORR was 29.4%

Figure 5. Best Percent Change of Target Lesions by MGC026 Dose Level and Tumor Type in the Response-Evaluable Population

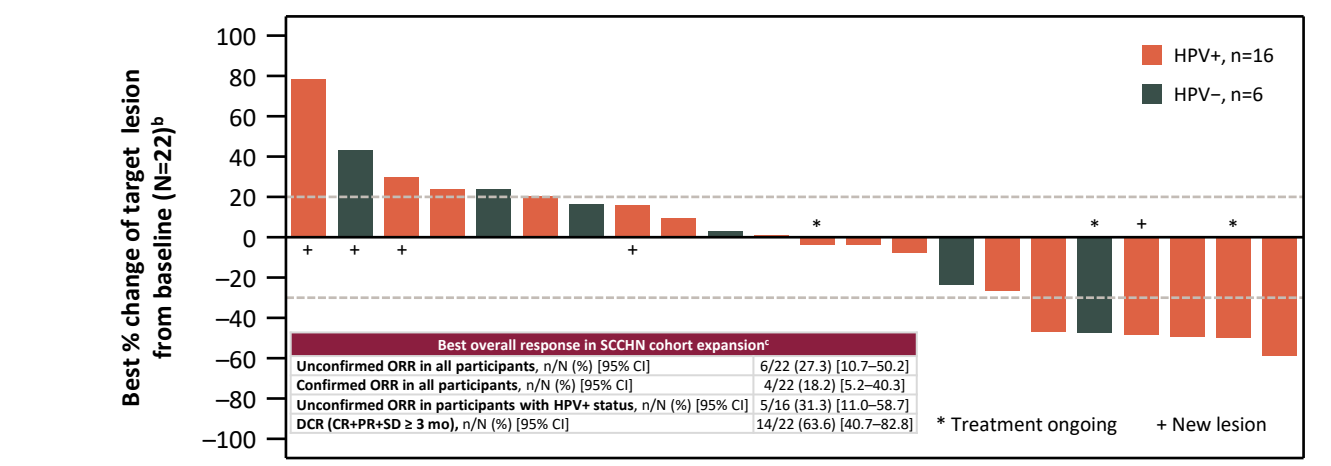


^aParticipants who received ≥1 dose and had measurable disease at both baseline and post-baseline. ^bParticipants who received ≥1 dose and had measurable disease at baseline. ^cOne participant had measurable disease at baseline and therefore is included in the DCR table, but this participant did not have a post-baseline tumor assessment; accordingly, this participant is not included in the waterfall plot. ^dBest overall response: CR, complete response; DCR, disease control rate; DOR, duration of response; G/GE, gastric or gastroesophageal junction cancer; mCRPC, metastatic castration-resistant prostate cancer; NA, not available; NE, not evaluated; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

SCCHN dose expansion

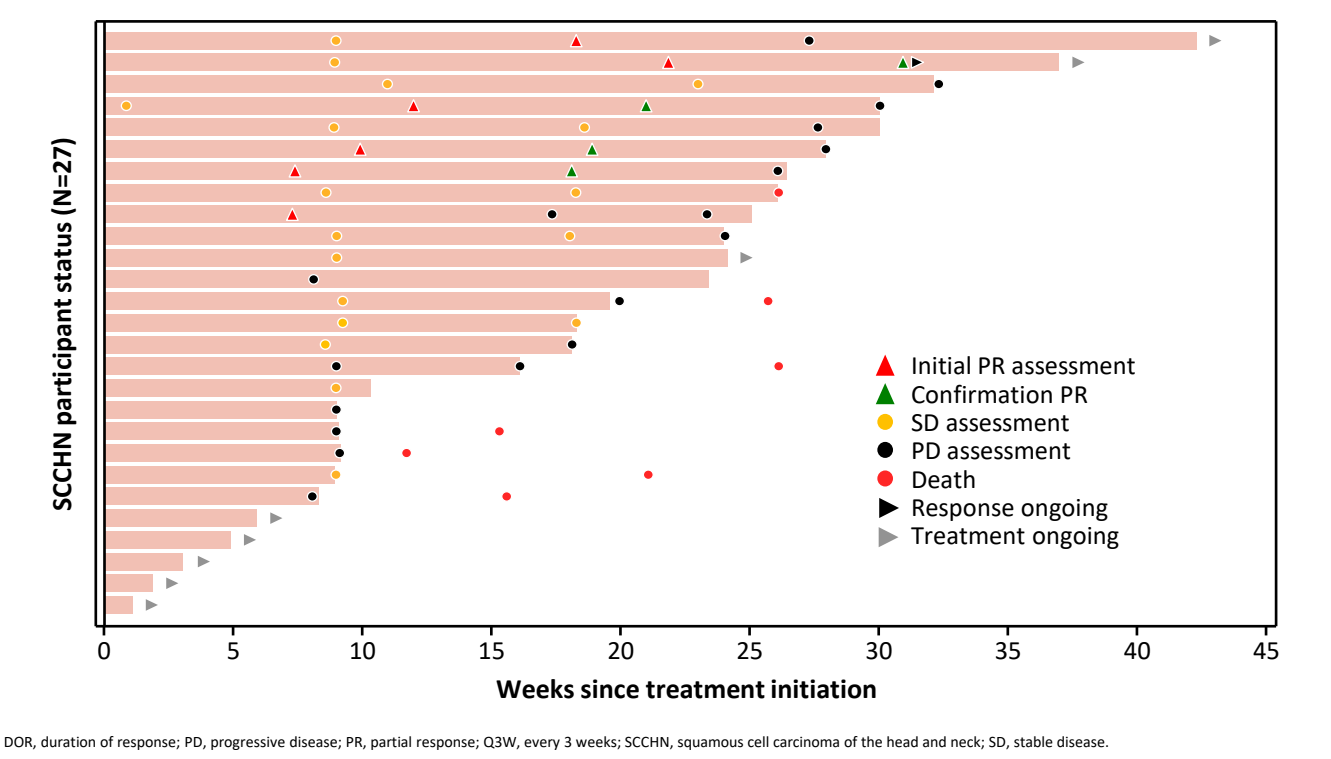
- Among 22 response-evaluable participants with SCCHN in the dose-expansion cohort (Figure 6):
 - Six participants (27.3%) achieved a PR as their best overall response (BOR; 4 confirmed and 2 unconfirmed)
 - Four participants achieved a confirmed PR (ORR, 18.2%); 12 had SD. DCR was 63.6%
- Among the 16 response-evaluable participants in the SCCHN cohort with positive human papilloma virus (HPV) status, 5 participants (31.3%) achieved a PR as their best overall response (BOR; 4 confirmed and 1 unconfirmed)
- As of the data cutoff, 8 participants with SCCHN in the dose-expansion cohort remained on treatment, with treatment duration extending beyond 30 weeks for 2 participants (Figure 7)

Figure 6. Best Percent Change of Target Lesions in Response-Evaluable Participants With SCCHN by HPV Status^a in the Dose-Expansion Cohort



^aHPV status was based on available electronic data capture-recorded results; when prior HPV testing results were unavailable, p16 immunohistochemistry was used as a surrogate based on tumor-tissue availability. p16 expression was assessed using the Cytokeratin antibody (Ventana/Roche), with positivity defined as moderate-to-strong nuclear and cytoplasmic staining in ≥70% of viable tumor cells. ^bParticipants who received ≥1 dose and had measurable disease at both baseline and post-baseline. ^cParticipants who received ≥1 dose and had measurable disease at baseline. ^dBest overall response: CR, complete response; DCR, disease control rate; DOR, duration of response; HPV, human papillomavirus; NA, not available; ORR, objective response rate; PD, progressive disease; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Figure 7. Assessment of Tumor Response Over Time in the SCCHN Cohort Expansion (7.5 mg/kg Q3W)



DOR, duration of response; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

CONCLUSIONS

- Interim phase 1 findings demonstrated a manageable safety profile for MGC026
 - The most common grade ≥3 TRAEs were hematologic
 - No treatment-related discontinuations in the SCCHN cohort
 - No ILD/pneumonitis, ocular toxicities, or unexpected toxicities were observed
- MGC026 also demonstrated encouraging antitumor activity in heavily pretreated participants with advanced solid tumors
 - Responses during dose escalation had a median duration of 10.2 months
 - In the SCCHN expansion cohort, BOR was 27% (6/22 PRs, including 2 unconfirmed)
- Enrollment is ongoing in tumor-specific cohorts
- Together these findings support further clinical development of MGC026 in a range of potential indications, including evaluation of combination regimens in earlier lines of therapy