First-in-human study of BG-C9074 (B7-H4–targeting ADC) in advanced solid tumors: dose escalation and safety expansion

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Key Takeaways

1. **BG-C9074 (B7-H4 ADC) demonstrated a favorable safety profile, with low rates of high-grade neutropenia and dose reductions, in patients with advanced solid tumors**

2. **Encouraging antitumor activity was observed across tumor types, particularly in ovarian cancer (OC)**

ADC, antibody–drug conjugate.

Background

- **B7-H4**, a transmembrane glycoprotein in the B7 superfamily, is minimally expressed in normal tissue but is upregulated in solid tumors including CCA, BC, OC, and EC[1,2]
- **BG-C9074** is an investigational topoisomerase I inhibitor ADC that targets B7-H4 with an innovative drug-linker design, a DAR of 6, and strong bystander effect
- **BG-C9074** is being investigated in a first-in-human phase 1a/1b, open-label, global, multicenter study alone and in combination with other anticancer therapies in patients with advanced solid tumors (NCT06233942)[3]

BG-C9074 B7-H4 ADC Molecular Design

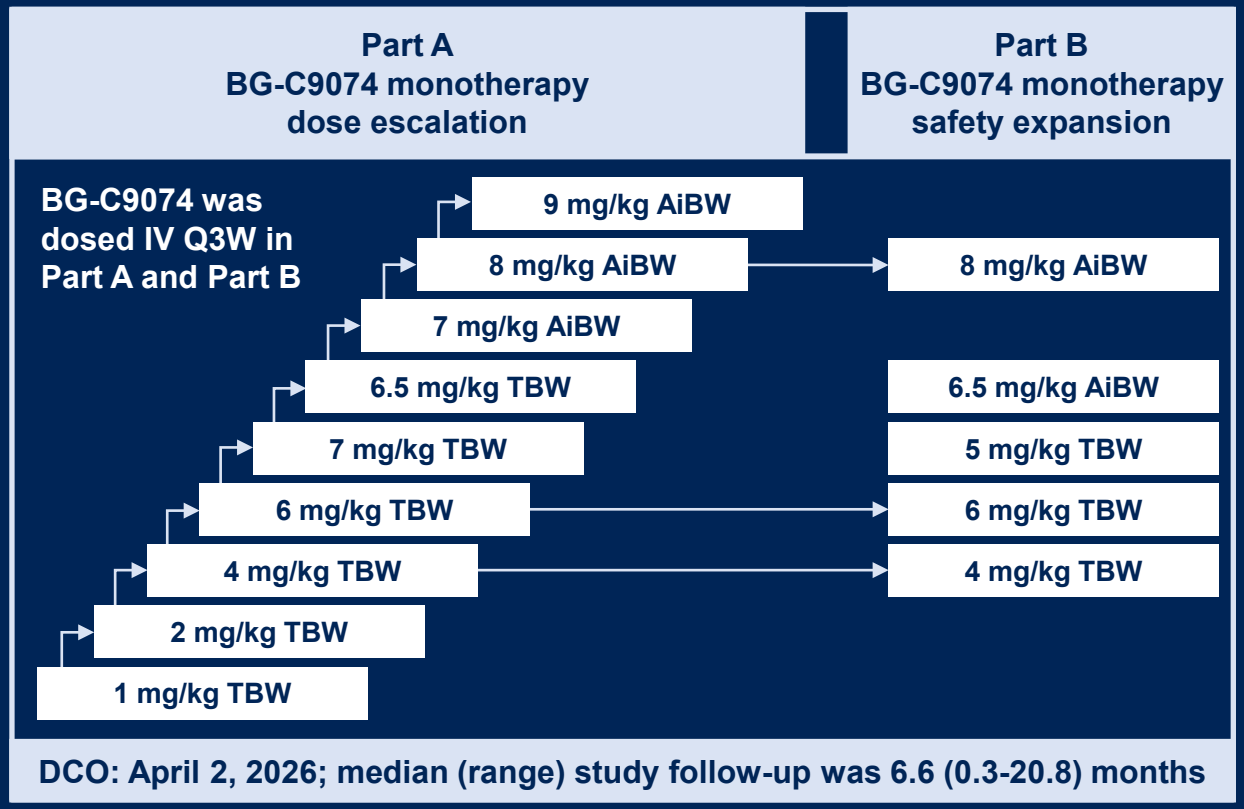
1. Dawidowicz M, et al. *Cancers (Basel)*. 2024;16:2519; 2. Zhou L, et al. *Front Immunol.* 2024;15:1426050; 3. ClinicalTrials.gov. Phase 1a/1b First-in-Human Study of BG-C9074 Alone and in Combination With Other Anticancer Therapies in Patients With Advanced Solid Tumors. NCT06233942. https://clinicaltrials.gov/study/NCT06233942.
BC, breast cancer; CCA, cholangiocarcinoma; DAR, drug-to-antibody ratio; EC, endometrial cancer.

Methods – Study Design of Phase 1a

Phase 1a Dose-Escalation and Safety Expansion Parts of Phase 1a/1b Study

Key eligibility criteria for the monotherapy dose-escalation and safety expansion phases

- ≥18 years
- Confirmed advanced, metastatic, or unresectable solid tumors, irrespective of B7-H4 expression
  - **Dose escalation** included HR+/HER2− BC, CCA, EC, sqNSCLC, TNBC, or OC
  - **Safety expansion** included HR+/HER2− BC, TNBC, or OC[a]
- ECOG PS ≤1
- Prior treatment with B7-H4 targeting ADC not permitted



Endpoints for the dose-escalation phase

- **Primary:** safety/tolerability, MTD, RDFE
- **Secondary:** ORR, DOR, DCR, PK, ADAs
- **Exploratory:** PFS, exploratory biomarkers

[a]CAA and sqNSCLC were discontinued after dose escalation.

ADA, anti-drug antibody; AiBW, adjusted ideal body weight; DCR, disease control rate; DCO, data cutoff; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR+/HER2−, hormone receptor positive/human epidermal growth factor receptor 2 negative; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RDFE, recommended dose for expansion; sqNSCLC, squamous non-small cell lung cancer; TBW, total body weight; TNBC, triple-negative breast cancer.

Results – Baseline Characteristics

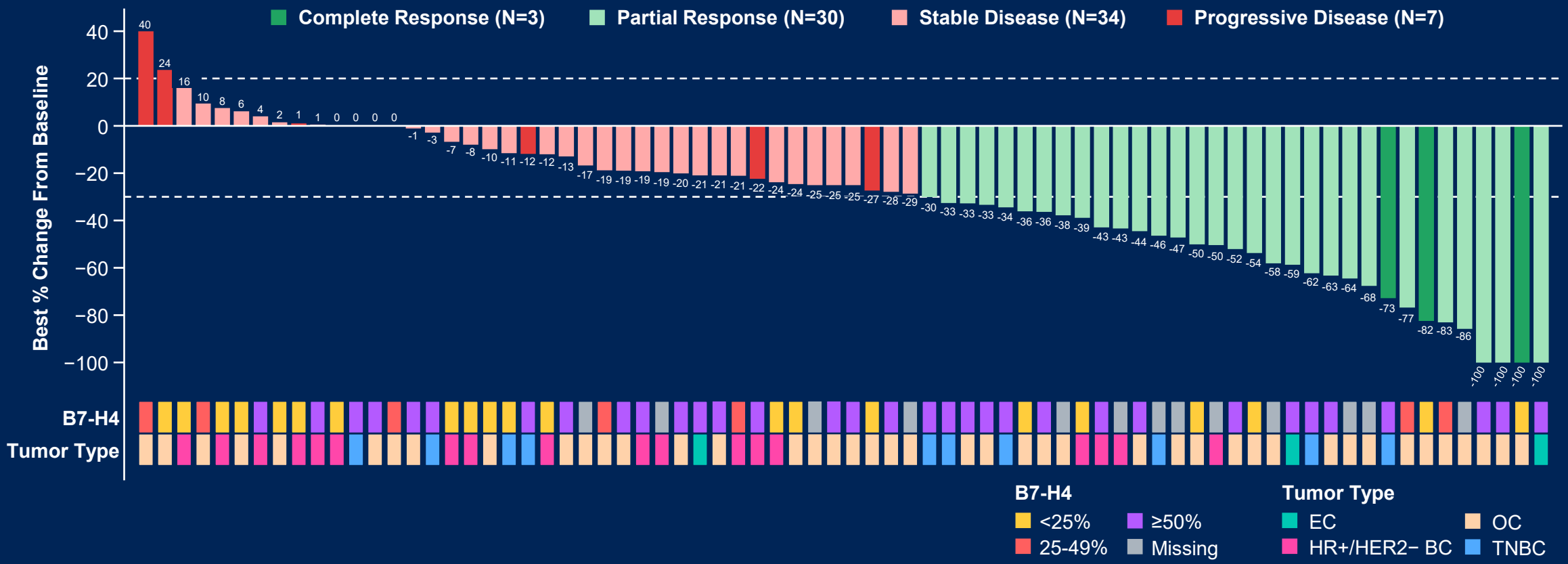
Patients Were Heavily Pretreated With a Median of Four Prior Lines of Therapy

	OC (n=63)	TNBC (n=18)	HR+/HER2− BC (n=28)	EC (n=3)	Total (N=112)
Median (range) age, years	57.0 (19.0-79.0)	56.0 (38.0-71.0)	57.0 (37.0-72.0)	68.0 (66.0-77.0)	57.0 (19.0-79.0)
Sex, n (%)					
Female	63 (100.0)	18 (100.0)	28 (100.0)	3 (100.0)	112 (100.0)
ECOG PS, n (%)					
0	34 (54.0)	10 (55.6)	17 (60.7)	1 (33.3)	62 (55.4)
1	29 (46.0)	8 (44.4)	11 (39.3)	2 (66.7)	50 (44.6)
Median (range) prior lines of therapy	3 (0-12)	4 (2-12)	5 (1-13)	3 (2-9)	4 (0-13)
Prior anticancer drug therapy, n (%)					
Bevacizumab	52 (82.5)	3 (16.7)	3 (10.7)	1 (33.3)	59 (52.7)
PARP	31 (49.2)	1 (5.6)	1 (3.6)	0 (0.0)	33 (29.5)
TOP1 inhibitor	5 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.5)
TOP1 inhibitor ADC	4 (6.3)	9 (50.0)	8 (28.6)	0 (0.0)	21 (18.8)
Non-TOP1 inhibitor ADC	6 (9.5)	2 (11.1)	1 (3.6)	0 (0.0)	9 (8.0)
Mirvetuximab soravtansine	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)

PARP, poly(ADP-ribose) polymerase; TOP1, DNA topoisomerase I.

Results – Antitumor Activity in BC, OC, EC (1/2)

Responses at Target Dose Range of 5 mg/kg TBW to 8 mg/kg AiBW Were Observed Across Tumor Types



Results – Antitumor Activity in BC, OC, EC (2/2)

Confirmed ORR was 36.5% across tumor types, 39.5% in OC, and 40.0% in TNBC

Responses across tumor types at 5 mg/kg TBW to 8 mg/kg AiBW	OC (n=4	
Confirmed ORR, n (%)	17 (39.5)	
95% CI[a]	25.0-55.6	
Unconfirmed ORR, n (%)	21 (48.8)	
95% CI[a]	33.3-64.5	26.2
DCR, n (%)	40 (93.0)	9 (90.0)
95% CI[a]	80.9-98.5	55.5-99.7

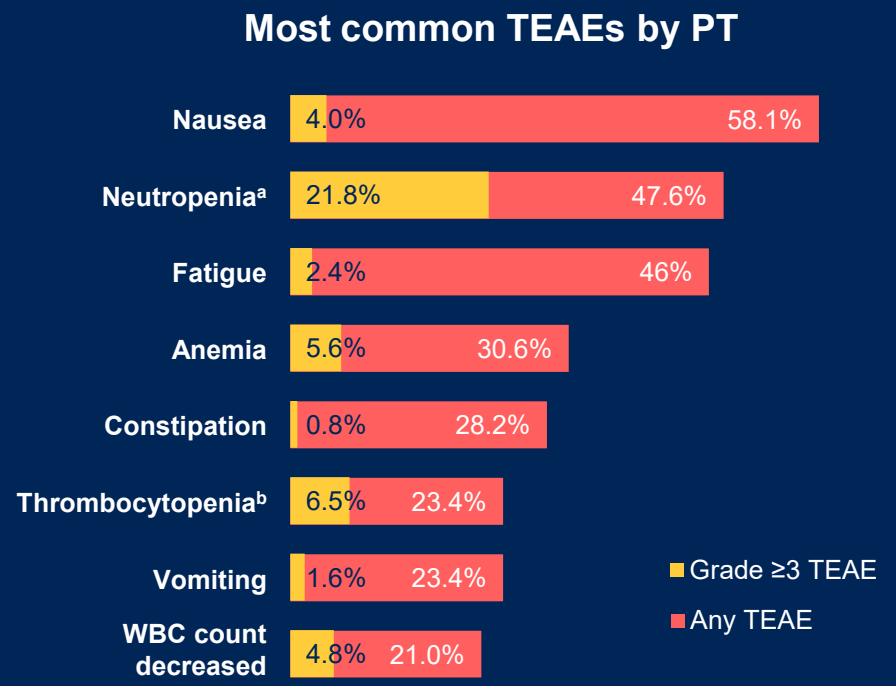
Responses at 6.5, 7, 8 mg/kg AiBW only	OC phase 1a (N=22)
Best Overall Response, n (%)	
CR	2 (9.1)
PR	8 (36.4)
SD	12 (54.5)
PD	0 (0.0)
Confirmed ORR, n (%) 95% CI[a]	10 (45.5) 24.4-67.8
Unconfirmed ORR, n (%) 95% CI[a]	12 (54.5) 32.2-75.6
DCR (CR + PR + SD), n (%) 95% CI[a]	22 (100.0) 84.6-100.0

[a]95% CI was estimated using the Clopper–Pearson method. [b]One response was confirmed after DCO date.
CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Results – Safety

Overall, BG-C9074 Monotherapy Was Well Tolerated With Low Rates of Dose Reductions

n, %	TBW		AiBW				Total (N=124)
	1-4 mg/kg (n=31)	5-7 mg/kg (n=50)	6.5 mg/kg (n=15)	7 mg/kg (n=6)	8 mg/kg (n=16)	9 mg/kg (n=6)	
Any TEAE	30 (96.8)	49 (98.0)	15 (100.0)	6 (100.0)	16 (100.0)	6 (100.0)	122 (98.4)
Grade ≥3 TEAEs	5 (16.1)	22 (44.0)	7 (46.7)	4 (66.7)	9 (56.3)	5 (83.3)	52 (41.9)
Grade ≥3 treatment-related TEAEs	2 (6.5)	19 (38.0)	4 (26.7)	2 (33.3)	7 (43.8)	5 (83.3)	39 (31.5)
Any TESAEs	5 (16.1)	12 (24.0)	4 (26.7)	2 (33.3)	3 (18.8)	2 (33.3)	28 (22.6)
TEAEs leading to study treatment dose reductions	0 (0.0)	13 (26.0)	1 (6.7)	2 (33.3)	4 (25.0)	3 (50.0)	23 (18.5)
DLT, n	0	5	0	1	0	2	8



- DLTs with TBW dosing included platelet count decreased (n=3), febrile neutropenia (n=1), and fatigue (n=1)
- DLTs with AiBW dosing included neutropenic infection (n=1), nausea (n=1), and unexplained death (n=1)

Adverse events were graded for severity using CTCAE v5.0.

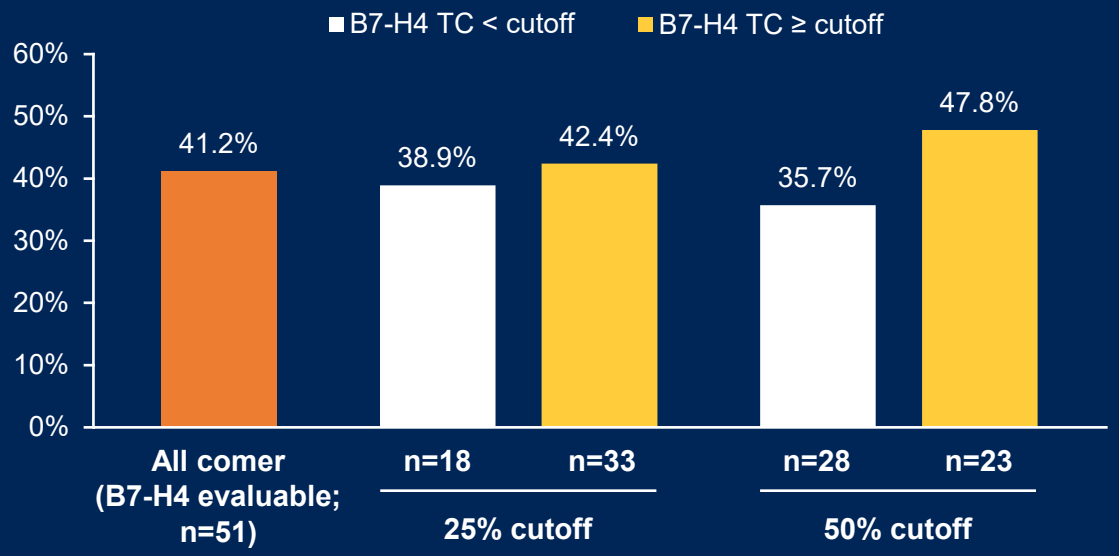
[a]Neutropenia included the terms neutrophil count decreased, neutropenia, febrile neutropenia, and neutropenic infection. [b]Thrombocytopenia included the terms platelet count decreased and thrombocytopenia.

CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; PT, preferred term; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; WBC, white blood cell.

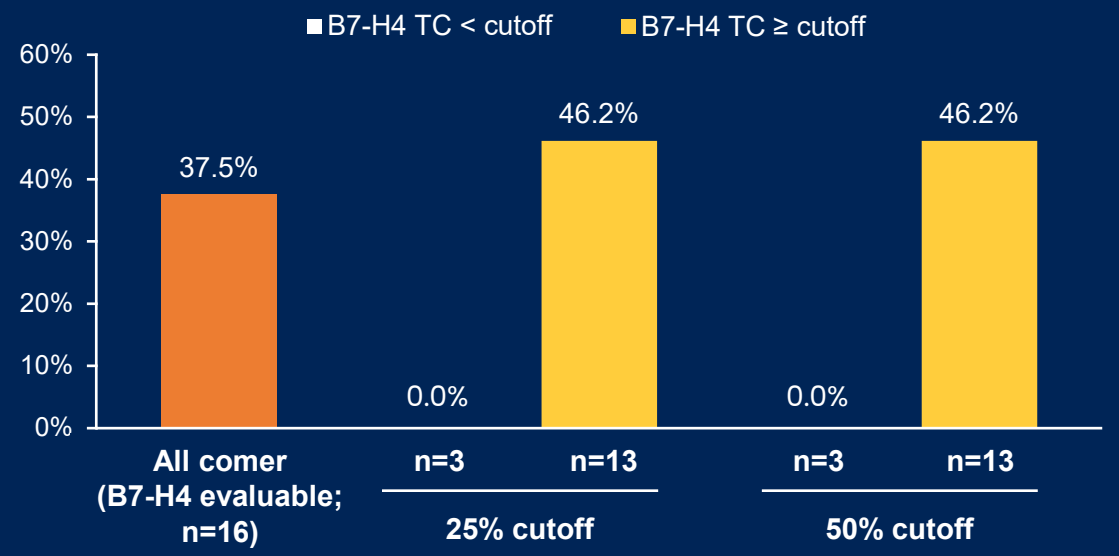
Results – Biomarkers

No Consistent Association of Responses With B7-H4 Expression Across Tumor Types Was Observed

uORR in B7-H4 subgroups in OC across all dose levels



uORR in B7-H4 subgroups in TNBC across all dose levels



- In OC, responses were observed across all levels of B7-H4 expression
- In TNBC, most enrolled patients had high B7-H4 expression, and all responses occurred in this subgroup

TC, tumor cells; uORR, unconfirmed objective response rate.

Key Takeaways

BG-C9074 demonstrated a favorable safety profile and promising antitumor activity in patients with advanced solid tumors

- Preliminary antitumor activity was particularly promising in OC, the most represented tumor type, and also encouraging in TNBC
  - In OC, clinical responses were observed across all levels of B7-H4 expression, supporting an all-comer approach to subsequent development of BG-C9074
  - 81% of patients with TNBC and available biomarker data had high B7-H4 expression, and all responses were observed in that group; analysis will continue in a larger dataset
- Dose expansion and dose optimization are ongoing to inform registration-enabling studies