MGC018, an Anti-B7-H3 Antibody-Drug Conjugate (ADC), in Patients With Advanced Solid Tumors: Preliminary Results of Phase 1 Cohort Expansion

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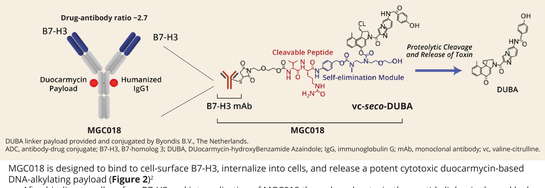
Background

- B7-homolog 3 (B7-H3) is highly expressed in multiple solid tumors, including prostate cancer, non–small cell lung cancer (NSCLC), breast cancer, melanoma, and squamous cell carcinoma of head and neck (SCCHN), with limited expression in normal tissue[1]
  - B7-H3 may play immune suppressive and tumor-autonomous roles that favor cancer growth
  - B7-H3 is expressed by tumor epithelium, tumor-associated vascular endothelium and stroma
- MGC018 is an investigational anti-B7-H3 antibody-drug conjugate (ADC) with a duocarmycin-based linker payload (**Figure 1**)[1]
  - Valine-citrulline-*seco*-DUocarmycin-hydroxyBenzamide-Azaindole (vc-*seco*-DUBA) is a DNA-alkylating agent
  - vc-*seco*-DUBA cytotoxic activity is cell cycle–independent
  - vc-*seco*-DUBA retains potency in multidrug-resistant cell lines
  - Cleavable peptide linker facilitates bystander effect
  - Induces immunogenic cell death in preclinical models

Figure 1. MGC018: B7-H3–Directed ADC With Duocarmycin-Based Linker Payload



DUBA linker payload provided and conjugated by Byondis B.V., The Netherlands.
ADC, antibody-drug conjugate; B7-H3, B7-homolog 3; DUBA, DUocarmycin-hydroxyBenzamide Azaindole; IgG, immunoglobulin G; mAb, monoclonal antibody; vc, valine-citrulline.

- MGC018 is designed to bind to cell-surface B7-H3, internalize into cells, and release a potent cytotoxic duocarmycin-based DNA-alkylating payload (**Figure 2**)[2]
  - After binding to cell-surface B7-H3 and internalization of MGC018 through endocytosis, the peptide linker is cleaved by lysosomal proteases, and the activated duocarmycin drug (DUBA) is formed (A, below)
  - vc-*seco*-DUBA binds to the minor groove of the DNA and alkylates DNA, disrupting the nucleic acid architecture, ultimately leading to cell death (A)
  - vc-*seco*-DUBA is membrane permeable and, if released by dying cells, can cause bystander killing of neighboring tumor cells, irrespective of B7-H3 expression (B)
  - DUBA DNA-targeted activity is directed to both dividing and nondividing cells because of bystander activity[3] (C)

Figure 2. MGC018 ADC Targets B7-H3 on Tumor Cells and Mediates Bystander Killing

Mode of Action

(A) Uptake of ADC by internalization and intracellular release of payload

(B) Proteolytic cleavage of payload in tumor microenvironment

(C) Diffusion of active payload to neighboring tumor cells

ADC, antibody-drug conjugate; B7-H3, B7-homolog 3.

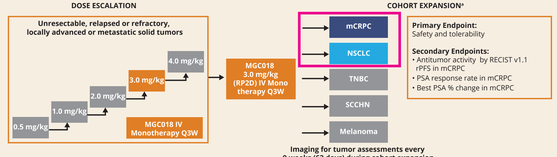
- MGC018 displayed potent antitumor activity in preclinical B7-H3–expressing tumor models of breast, ovarian, lung cancers, and melanoma, as well as in patient-derived xenograft models of breast, prostate, and head and neck cancers[1]
- MGC018 exhibited an acceptable safety profile with transient cytopenias and skin findings of dry skin and hyperpigmentation in cynomolgus monkeys after repeat-dose administration[1]
- Phase 1 dose escalation was completed[a]
  - There were 2 dose-limiting toxicities: 1 neutropenia Grade 4 at the 2 mg/kg dose cohort and 1 Grade 3 fatigue lasting over 72 hours in the 4 mg/kg dose cohort
  - The recommended Phase 2 dose (RP2D) was established as 3 mg/kg intravenously (IV) every 3 weeks (Q3W)
  - There was 1 confirmed partial response in a patient with melanoma, and 5/9 (55.5%) patients with >50% prostate-specific antigen (PSA) reduction in metastatic castration-resistant prostate cancer (mCRPC)
    - Anti-tumor activity was observed in three dose escalation patients with melanoma (target lesion sum reduction 24%, 28%, and 36%)
    - One patient with melanoma from the dose-escalation phase continues on study at 10 months with ongoing confirmed PR on imaging at 8 months

Objectives

- Primary objectives of Phase 1 cohort expansion were safety and tolerability
- Secondary objectives were antitumor activity of MGC018 administered IV as monotherapy in patients with advanced solid tumors, as well as radiographic progression-free survival (rPFS), PSA response rate, and best PSA percent change in patients with mCRPC

Methods

Figure 3. Study Design



[a]Enrollment for the mCRPC, NSCLC, and TNBC cohorts opened in 2020, whereas the SCCHN and melanoma cohorts opened in May 2021.
IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non–small cell lung cancer; PSA, prostate-specific antigen; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; rPFS, radiographic progression-free survival; SCCHN, squamous cell cancer of head and neck; TNBC, triple-negative breast cancer.

- This Phase 1/2 study involved a 3+3+3 dose-escalation design followed by Phase 1 cohort expansion[2-4]
- During cohort expansion, patients with relapsed or refractory, unresectable mCRPC, metastatic NSCLC, locally advanced or metastatic triple-negative breast cancer (TNBC), metastatic or recurrent unresectable SCCHN, or locally advanced or metastatic melanoma received MGC018 at the RP2D of 3 mg/kg IV Q3W, established during dose escalation based on the review of the safety, tolerability, and pharmacokinetic data[a]
- MGC018 3 mg/kg was administered IV over 60 minutes on Days 1 and 22 of Cycle 1 and every subsequent 42-day cycle thereafter
- To manage toxicity, dose interruption of up to ≥21 days and dose reductions were allowed
- In the cohort expansion, tumor response by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was evaluated every 9 weeks for all patients. rPFS and PSA were assessed Q3W in mCRPC patients using Prostate Cancer Working Group 2 (PCWG2) criteria

Key Eligibility for Phase 1 Cohort Expansion

Inclusion

- Patients with histologically proven, relapsed or refractory, unresectable locally advanced or metastatic solid tumors
- Patients with mCRPC that progressed during or after 1 prior line of chemotherapy for metastatic disease, and if approved and available, no more than 2 prior lines of an antihormonal agent (e.g., abiraterone, enzalutamide) with a PSA value of at least 2 ng/mL and meeting at least 1 of the following:
  - Progression in measurable disease (RECIST version 1.1)
  - Appearance of 2 or more new bone lesions according to PCWG2
  - Rising PSA defined as at least 2 sequential rises in PSA (≥1 week apart) over reference value (last PSA [PSA ≥2 ng/mL] measured before first rise in PSA) (as defined by PCWG2)
- Patients with metastatic NSCLC who have failed standard cytotoxic, targeted, and biologic or checkpoint inhibitor therapy, with no more than 2 prior lines of cytotoxic chemotherapy
- Patients with locally advanced or metastatic TNBC that has progressed during or after at least 1 systemic therapy; American Society of Clinical Oncology/College of American Pathologists guidelines should be followed for establishing TNBC diagnosis
- Patients with SCCHN that has progressed during or following at least one systemic therapy for metastatic or recurrent unresectable disease, with no more than 2 prior lines of cytotoxic chemotherapy
- Patients with melanoma that has progressed during or following at least one systemic treatment for unresectable locally advanced or metastatic diseases, including patients intolerant of or refused standard therapy
- Patients for whom no therapy with demonstrated clinical benefit available is allowed
- Archival or formalin-fixed paraffin-embedded tumor tissue available to evaluate B7-H3 immunohistochemistry (B7-H3 expression not required for eligibility)
- Eastern Cooperative Oncology Group performance status of ≤2

Exclusion

- Abnormal laboratory parameters (hematologic, renal, and/or liver function)
- Clinically significant cardiovascular or pulmonary disease
- Evidence of pleural or pericardial effusion
- CNS metastases that are symptomatic, require treatment, and/or are progressing within 6 months
- History of leptomeningeal disease or spinal cord compression
- Treatment with any systemic chemotherapy, biologic, investigational agents, or mediastinal/pelvic radiation within 4 weeks; small molecule–targeted or kinase inhibitors within 14 days; prior therapy with B7-H3-targeted agent (prior radioligand within 6 months in mCRPC cohort expansion)

Cohort Expansion Results

- As of August 16, 2021, 86 of 88 patients enrolled in cohort expansion had received MGC018 (mCRPC, n=40; NSCLC, n=21; TNBC, n=16; melanoma, n=9)
  - 37 of 88 patients (42%) discontinued treatment: PD was most common cause of treatment discontinuation (n=25), followed by AEs (n=6), physician decision (n=1), and death (n=1)
  - 51 of 88 patients (58%) patients continued to receive MGC018
- Baseline characteristics of patients with mCRPC or NSCLC are included in **Table 1**
- 93% of mCRPC patients had B7-H3 H-score ≥160 and 60% of NSCLC patients had a B7-H3 H-score ≥130
- Data cutoff as of August 16, 2021

Table 1. Baseline Patient Characteristics

Characteristic	mCRPC (n=40)	NSCLC (n=21)
Age, years		
Mean ± SD	69.7 ± 7.02	60.7 ± 8.13
Median (range)	70.0 (52.0, 83.0)	62.0 (48.0, 75.0)
Gender, n (%)		
Female	0	12 (57.1)
Male	40 (100)	9 (42.9)
Ethnicity, n (%)		
Not Hispanic or Latino	36 (90.0)	19 (90.5)
Hispanic or Latino	1 (2.5)	0
Not Reported	3 (7.5)	2 (9.5)
ECOG performance status, n (%)		
0	17 (42.5)	0
1	23 (57.5)	19 (90.5)
2	0	2 (9.5)
No. of prior therapies for advanced disease, median (range)	3 (2-7)	2 (1-5)
Prior chemotherapy, n (%)	40 (100)	20 (95.2)
Prior anti-PD-1/PD-L1, n (%)	7 (17.5)	15 (71.4)
Prior TKI, n (%)	7 (17.5)	7 (33.3)
Next generation hormonal therapy, n (%)	40 (100)	N/A
B7-H3 score (vasculature score), median (range)[a]	1 (0-3)	2 (0-3)
B7-H3 score (H-score), median (range)[a]	222.5 (24-300)[b]	139 (0-205)[c]
Baseline PSA (ng/mL)	(n=39)	
Mean ± SD	269.9 ± 693.83	NA
Median (range)	89.8 (5.3, 4302.0)	

[a]Recombinant anti-CD276 antibody, SP206 (Abcam, Toronto, Ontario, CA). [b]30 of 41 with H-scores reported. [c]15 of 21 with H-scores reported.
B7-H3, B7-homolog 3; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; NA, not applicable; NSCLC, non–small cell lung cancer; PD-1, programmed death-protein 1; PD-L1, programmed death-ligand 1; PSA, prostate-specific antigen; SD, standard deviation; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer.

Safety

- The median number of doses (range) received in expansion safety cohort by all 86 patients was 3.0 (1.0-8.0); patients with mCRPC received 3.5 (1.0-8.0) doses, those with NSCLC received 3.0 (1.0-7.0) doses, TNBC 2.0 (1.0-6.0) doses, and melanoma 2.0 (1.0-2.0) doses
- There were 3 COVID-19-positive treatment-emergent adverse events (TEAE) in expansion cohort; 1 patient had a Grade 5 event as a result of COVID-19 infection
- 83 Patients (96.5%) experienced TEAEs, which were treatment related in 78 patients (90.7%; **Table 2**)
- 48 Patients (55.8%) had Grade ≥3 TEAEs, which were treatment related in 43 patients (50.0%; **Table 2**)
- 29 Patients (33.7%) reported at least 1 serious TEAE, 24 of which were considered treatment related (**Table 2**)
- There were 2 deaths (**Table 2**)
  - One mCRPC patient with a PSA decrease of 50% on study day 62 was admitted for Grade 4 thrombocytopenia on rivaroxaban, declined therapeutic platelet transfusion and was discharged to home; Grade 5 of unknown etiology event occurred 42 days after last (second) dose of MGC018 (treatment-related adverse event [TRAE]; **Table 2**).
  - The other patient had mCRPC with stable disease and a PSA decrease of 50% and had Grade 5 event at 5 months due to COVID-19 infection (TEAE; **Table 2**)
- 5 TEAEs leading to drug discontinuation occurred in 4 patients with mCRPC (pleural effusion, dyspnea exertional, thrombocytopenia, PPE, and orthostatic hypotension); 3 TEAEs in 2 patients with NSCLC (pleural effusion, PPE, and abdominal pain); and 1 TEAE in a patient with TNBC (neutropenia)
- TEAEs leading to dose reductions occurred in patients with mCRPC (30%), NSCLC (19.0%), and TNBC (12.5%)
- Dose interruptions (including infusion interruption and dose delay) occurred in patients with mCRPC (55.0%), NSCLC (52.4%), TNBC (31.3%), and melanoma (33.3%)

Table 2. Overall Summary of Adverse Events

	Safety population (N=86)[a]	
	Treatment emergent, n (%)	Treatment related, n (%)
Any AE	83 (96.5)	78 (90.7)
Any Grade ≥3 AE	48 (55.8)	43 (50.0)
Any SAE	29 (33.7)	24 (27.9)
Any deaths	2 (2.3)	1 (1.2)[b]
AE of special interest (AESIs)	11 (12.8)	NA
AEs leading to MGC018 discontinuation	7 (8.1)	6 (7.0)
AEs leading to MGC018 dose reductions	18 (20.9)	18 (20.9)
AEs leading to MGC018 interruption	41 (47.7)	39 (45.3)

[a]86 patients include 9 patients in the melanoma cohort. [b]Grade 5 event of unknown etiology.
AE, adverse event; N/A, not available; SAE, serious adverse event.

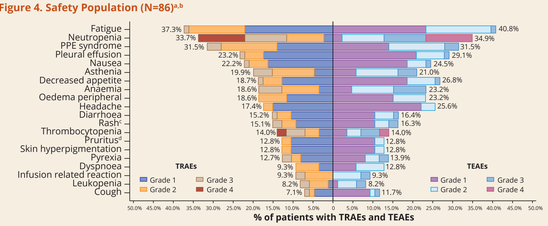
- The most common (≥20%) TRAEs were fatigue (37% all grades; 1% Grade ≥3), neutropenia (34% all grades; 22% Grade ≥3), palmar-plantar erythrodysesthesia syndrome (31% all grades; 4% Grade ≥3), pleural effusion (23% all grades; 1% Grade ≥3), and nausea (22% all grades; 1% Grade ≥3), and asthenia (20% all grades; 5% Grade ≥3) (**Table 3** and **Figure 4**)
- The most common (>10%) AEs of special interest were PPE (23.3%) and pleural effusion (27.9%)
- Febrile neutropenia was not reported
- Serious TRAEs that occurred in at least 2 patients were pyrexia (4%), pleural effusion (4%), dyspnea exertional (2%), anemia (2%), and thrombocytopenia (2%)

Table 3. Treatment-Related Adverse Events Reported in ≥10% of Patients[a]

	Safety population (N=86)[b]	
	Any grade, n (%)	Grade ≥3, n (%)
Fatigue	32 (37.2)	1 (1.2)
Neutropenia	29 (33.7)	19 (22.1)
Palmar-plantar erythrodysesthesia syndrome	27 (31.4)	3 (3.5)
Pleural effusion	20 (23.3)	1 (1.2)
Nausea	19 (22.1)	1 (1.2)
Asthenia	17 (19.8)	4 (4.7)
Anemia	16 (18.6)	5 (5.8)
Decreased appetite	16 (18.6)	1 (1.2)
Edema peripheral	16 (18.6)	0
Headache	15 (17.4)	0
Diarrhea	13 (15.1)	1 (1.2)
Thrombocytopenia	12 (14.0)	6 (7.0)
Pyrexia	11 (12.8)	2 (2.3)
Pruritus	11 (12.8)	0
Rash	11 (12.8)	2 (2.3)
Skin hyperpigmentation	11 (12.8)	0

[a]Patients are counted only once by preferred term. [b]86 patients include 9 patients in melanoma cohort.

Figure 4. Safety Population (N=86)[a,b]

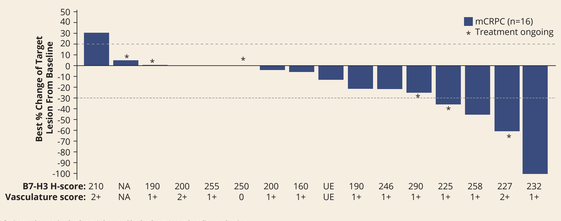


[a]Patients are counted only once by preferred term. [b]86 patients include 9 patients in melanoma cohort. [c]Includes MedDRA preferred terms of rash and maculopapular rash.
[d]Includes MedDRA preferred terms of pruritis and generalized pruritis.
PPE, palmar-plantar erythrodysesthesia.

Efficacy

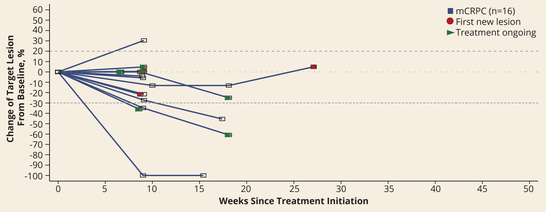
- A total of 32 treated patients had first 9-week imaging and were evaluable for tumor response (mCRPC, n=16; NSCLC, n=16):
  - 8 of 32 Patients (25%) had reductions in target lesion sums from baseline of more than 30% (partial response): 4 patients with mCRPC (2 confirmed PR [cPR] and 2 unconfirmed PR [uPR]) (**Figures 5** and **6**) and 4 patients with NSCLC (4 uPR) (**Figures 7** and **8**). An additional NSCLC patient had 30% reduction in target lesion sum; however, non-target lesions not evaluated due to obstruction of bronchus and overall response not evaluable.
  - Best overall response rates were 25% (4 of 16) in both the mCRPC and the NSCLC cohorts
    - For 4 PRs in mCRPC cohort, mean B7-H3 H-score was 236
    - For 4 PRs in NSCLC cohort, mean B7-H3 H-score was 162 (1 PR had B7-H3 H-score unevaluable)
  - In mCRPC cohort, 10 of 16 patients had reductions in target lesion sums from baseline (**Figures 5** and **6**)
  - In NSCLC cohort, 13 of 16 patients had reductions in target lesion sums from baseline (**Figures 7** and **8**)
  - 13 of 32 Patients (40.6%) continued on treatment

Figure 5. Best Percent Change of Target Lesions in mCRPC Cohort (Tumor Response-Evaluable Population)[a]



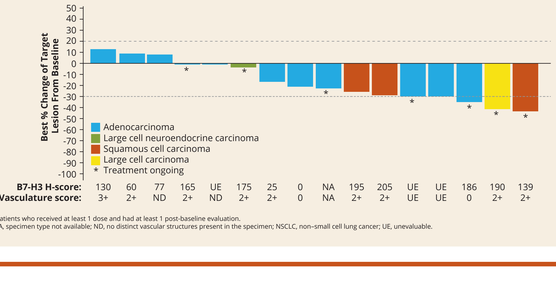
[a]Patients who received at least 1 dose and had at least 1 post-baseline evaluation.
mCRPC, metastatic castration-resistant prostate cancer; NA, not available; UE, unevaluable due to insufficient viable tumor.

Figure 6. Percent Change of Target Lesions in mCRPC Cohort (Tumor Response-Evaluable Population)[a]



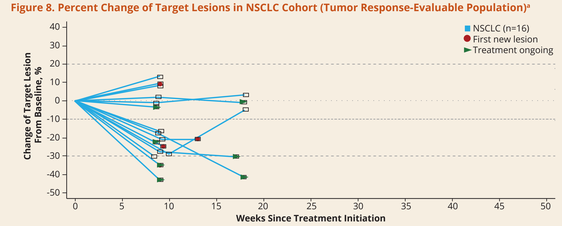
[a]Patients who received at least 1 dose and had at least 1 post-baseline tumor evaluation.
mCRPC, metastatic castration-resistant prostate cancer.

Figure 7. Best Percent Change of Target Lesions in NSCLC Cohort (Tumor Response-Evaluable Population)[a]



[a]Patients who received at least 1 dose and had at least 1 post-baseline evaluation.
NA, specimen type not available; ND, no distinct vascular structures present in the specimen; NSCLC, non–small cell lung cancer; UE, unevaluable.

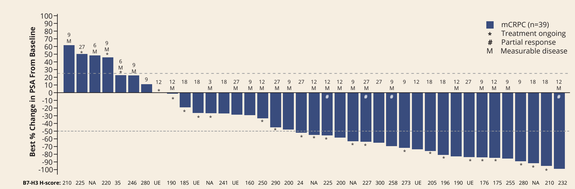
Figure 8. Percent Change of Target Lesions in NSCLC Cohort (Tumor Response-Evaluable Population)[a]



[a]Patients who received at least 1 dose and had at least 1 post-baseline tumor evaluation.
NSCLC, non–small cell lung cancer.

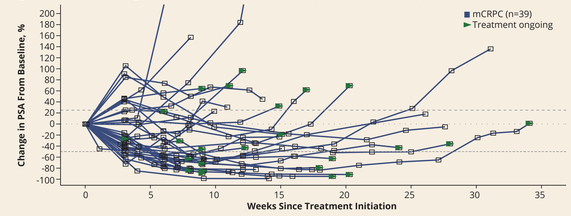
- In mCRPC cohort, 39 patients were evaluable for PSA response (**Figures 9** and **10**):
  - 21 of 39 Patients (53.8%) had reductions in PSA from baseline of more than 50%
  - 24 of 39 Patients (61.5%) remained on treatment

Figure 9. Best Percent Change of PSA in mCRPC Cohort (PSA Response-Evaluable Population)[a]



One patient with measurable disease and 3 weeks on study is not added because only baseline PSA had been performed.
Numbers above bars are numbers of weeks since first dose.
[a]Patients who received at least one dose and had at least 1 post-baseline PSA evaluation.
M, measurable disease by RECIST v1.1; mCRPC, metastatic castration-resistant prostate cancer; NA, not available; PSA, prostate-specific antigen; UE, unevaluable.

Figure 10. Percent Change of PSA in mCRPC Cohort (PSA Response-Evaluable Population)[a]



Two patients off-scale had PSA increases >200%.
[a]Patients who received at least 1 dose and had at least 1 post-baseline PSA evaluation.
mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

Conclusions

- MGC018 continued to demonstrate activity in multiple tumor types, including mCRPC and NSCLC in cohort expansion and mCRPC, NSCLC, and melanoma in dose escalation
- B7-H3 is highly expressed in mCRPC and NSCLC with responses seen across varying levels of expression
- Results to date have demonstrated a manageable safety profile with a low rate of treatment discontinuation due to AEs (6 of 86 pts in the expansion cohort to date). In future studies, alternative starting dosages may be explored to optimize the total number of doses administered and overall treatment duration.
- Enrollment is ongoing in TNBC, SCCHN, and melanoma cohorts

References

1. Scribner JA, et al. *Mol Cancer Ther*. 2020;19(11):2235-2244.
2. Powderly J, et al. *J Immunother Cancer*. 2018;6(suppl 1):P306.
3. Powderly JD, et al. *J Clin Oncol*. 2020;38(suppl 15; abstr 3071).
4. Jang S, et al. *J Clin Oncol*. 2021;39(suppl 15; abstr 2631).

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Disclosures

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