Phase 1 Dose Escalation Study of MGC018, an anti-B7-H3 Antibody-Drug Conjugate (ADC), In Patients with Advanced Solid Tumors

Abstract #2631

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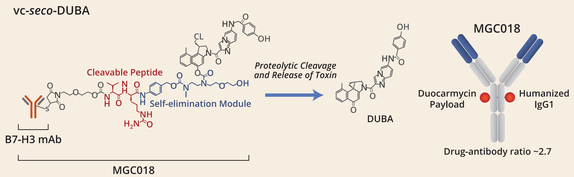
Background

MGC018: B7-H3 Directed ADC with Duocarmycin-based Linker Payload



- MGC018 is an anti-B7-H3 antibody-drug conjugate (ADC) with a duocarmycin payload
- vc-seco-DUocarmycin-hydroxyBenzamide Azaindole (DUBA) is a DNA alkylating agent
- DUBA cytotoxic activity is cell-cycle independent
- DUBA retains potency in multidrug-resistant cell lines
- Cleavable peptide linker – facilitates bystander effect
- Induces immunogenic cell death in preclinical models

DUBA Linker Payload provided and conjugated by *Byondis*.

Rationale for Targeting B7-H3 with MGC018

- B7-H3 is highly expressed in multiple solid tumors, with limited expression in normal tissue
- B7-H3 may play immune suppressive and tumor-autonomous roles that favor cancer growth
- B7-H3 is expressed by vascular endothelium and stroma in tumor microenvironment
- MGC018 is a novel ADC that delivers a potent duocarmycin-based DNA alkylating payload via native cysteines
- Duocarmycin DNA-targeted activity is directed to both dividing and non-dividing cells

Study Design and Objectives

- 3+3+3 Dose escalation design
- Six planned dose escalation cohorts: 0.5 to 5.0 mg/kg IV every three weeks
- Tumor response by investigator per RECIST v1.1 and PSA every 6 weeks (Dose Escalation)
- Tumor response by investigator every 9 weeks and PSA every 3 weeks (Cohort Expansion)
- Cohort Expansion at recommended Phase 2 dose (RP2D) to assess safety and tumor response (metastatic castration resistant prostate cancer (mCRPC), non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), triple-negative breast cancer (TNBC), melanoma)

Primary Objective

- Safety and maximum tolerated dose (or maximum administered dose)

Secondary Objectives

- Pharmacokinetics and immunogenicity
- Antitumor activity

Key Eligibility Criteria

Inclusion

- Patients with histologically proven, relapsed or refractory, unresectable locally advanced or metastatic solid tumors of any histology for whom no therapy with demonstrated clinical benefit is available (Dose Escalation)
- ≥ 18 years old; ECOG PS ≤ 2; life expectancy ≥ 12 weeks in Dose Escalation (24 weeks in Cohort Expansion); measurable disease as per RECIST v1.1
- Tumor tissue available to evaluate B7-H3 immunohistochemistry (B7-H3 expression not required for eligibility)

Exclusion

- Abnormal laboratory parameters (hematologic, renal, and/or liver function); clinically significant cardiovascular or pulmonary disease; patients with history of CNS metastasis must have completed treatment, be asymptomatic, and not have had CNS progression within 6 months; no history of leptomeningeal disease or spinal cord compression
- 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 Disease-Specific Criteria

- mCRPC that has progressed during or following 1 prior line of chemotherapy for metastatic disease, and if approved and available, no more than 2 prior lines of an anti-hormonal agent (e.g., abiraterone, enzalutamide) with a PSA value of at least 2 ng/mL and meeting at least one of the following:
  - Progression in measurable disease (RECIST v1.1)
  - Appearance of 2 or more new bone lesions according to Prostate Cancer Working Group 2 (PCWG2)
  - Rising PSA defined as at least 2 sequential rises in PSA (≥ 1 week apart) over a reference value (the last PSA [PSA ≥ 2 ng/mL] measured before the first rise in PSA) (as defined by the PCWG2)

Dose Escalation Results

Enrollment Status

Dose Escalation Complete (N=29)

- Maximum administered dose 4 mg/kg every 3 weeks
- RP2D defined as 3 mg/kg every 3 weeks

Cohort Expansion in mCRPC: Enrollment Ongoing

- *28 enrolled (of 40)*
- *Disease classification available for 20 of 28 patients: Bone only (7), mixed soft tissue + bone (9), soft tissue only (4)*

B7-H3 IHC Data

- 21 of 24 Patients with available tissue had samples evaluable for B7-H3 expression
- H-score: Median 190 (range 17–279); mean 175.7
- Vasculature score: Median 2+ (range 0–3+)

Data cutoff 03 May 2021.

Related Adverse Events ≥ 20%, All Grades

Fatigue, nausea, infusion related reaction, skin disorders, and neutropenia were most common

System Organ Class Preferred Term	0.5 mg/kg (N=3)	1.0 mg/kg (N=6)	2.0 mg/kg (N=7)	3.0 mg/kg (N=7)	4.0 mg/kg (N=6)	All (N=29)
AT LEAST ONE EVENT	3 (100%)	5 (83.3%)	6 (85.7%)	7 (100%)	6 (100%)	27 (93.1%)
Blood and lymphatic system disorders	0	1 (16.7)	2 (28.6)	3 (42.9)	2 (33.3)	8 (27.6)
Neutropenia	0	1 (16.7)	2 (28.6)	3 (42.9)	2 (33.3)	8 (27.6)
Gastrointestinal disorders	0	5 (83.3)	2 (28.6)	2 (28.6)	3 (50.0)	12 (41.4)
Nausea	0	2 (33.3)	2 (28.6)	1 (14.3)	3 (50.0)	8 (27.6)
General disorders and administration site conditions	2 (66.7)	2 (33.3)	2 (28.6)	4 (57.1)	5 (83.3)	15 (51.7)
Fatigue	1 (33.3)	1 (16.7)	2 (28.6)	4 (57.1)	3 (50.0)	11 (37.9)
Chills	1 (33.3)	0	2 (28.6)	0	4 (66.7)	7 (24.1)
Pyrexia	1 (33.3)	1 (16.7)	2 (28.6)	0	2 (33.3)	6 (20.7)
Injury, poisoning and procedural complications	0	0	2 (28.6)	5 (71.4)	2 (33.3)	9 (31.0)
Infusion-related reaction	0	0	2 (28.6)	5 (71.4)	2 (33.3)	9 (31.0)
Skin and subcutaneous tissue disorders	0	3 (50.0)	5 (71.4)	5 (71.4)	4 (66.7)	17 (58.6)
Skin hyperpigmentation	0	3 (50.0)	1 (14.3)	3 (42.9)	2 (33.3)	9 (31.0)
Palmar-plantar erythrodysaesthesia syndrome	0	0	3 (42.9)	3 (42.9)	2 (33.3)	8 (27.6)

Includes events with causality ratings of 'Possible', 'Probable' or 'Definite'. Subjects are counted once for each Preferred Term reported.
Data were extracted on 03May2021.

Grade ≥ 3 Related Adverse Events

Cytopenias were most common

System Organ Class Preferred Term	0.5 mg/kg (N=3)	1.0 mg/kg (N=6)	2.0 mg/kg (N=7)	3.0 mg/kg (N=7)	4.0 mg/kg (N=6)	All (N=29)
AT LEAST ONE EVENT	2 (66.7%)	2 (33.3%)	6 (85.7%)	4 (57.1%)	5 (83.3%)	19 (65.5%)
Blood and lymphatic system disorders	0	0	2 (28.6)	2 (28.6)	2 (33.3)	6 (20.7)
Neutropenia	0	0	2 (28.6)	2 (28.6)	2 (33.3)	6 (20.7)
Lymphopenia	0	0	1 (14.3)	1 (14.3)	1 (16.7)	3 (10.3)
General disorders and administration site conditions	0	0	0	0	2 (33.3)	2 (6.9)
Fatigue	0	0	0	0	2 (33.3)	2 (6.9)
Investigations	1 (33.3)	2 (33.3)	3 (57.1)	2 (28.6)	2 (33.3)	10 (34.5)
Lymphocyte count decreased	0	1 (16.7)	2 (28.6)	1 (14.3)	0	4 (13.8)
Neutrophil count decreased	0	1 (16.7)	1 (14.3)	0	0	2 (6.9)
Platelet count decreased	0	0	1 (14.3)	1 (14.3)	0	2 (6.9)
Lipase increased	1 (33.3)	0	0	0	1 (16.7)	2 (6.9)
White blood cell count decreased	0	1 (16.7)	0	0	1 (16.7)	2 (6.9)
Metabolism and nutrition disorders	0	0	2 (28.6)	0	0	2 (6.9)
Hypophosphataemia	0	0	2 (28.6)	0	0	2 (6.9)
Skin and subcutaneous tissue disorders	0	0	3 (42.9)	1 (14.3)	0	4 (13.8)
Palmar-plantar erythrodysaesthesia syndrome	0	0	1 (14.3)	1 (14.3)	0	2 (6.9)
Rash maculo-papular	0	0	2 (28.6)	0	0	2 (6.9)

Data were extracted on 03May2021.

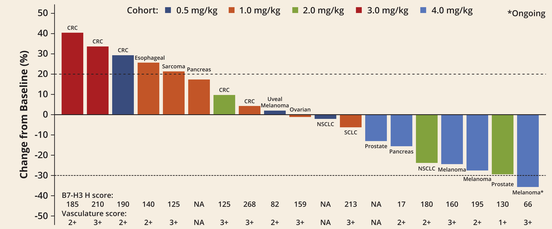
Treatment-Emergent Adverse Events

Manageable Safety Profile

Patients Experiencing at Least One Adverse Event	0.5 mg/kg (N=3)	1.0 mg/kg (N=6)	2.0 mg/kg (N=7)	3.0 mg/kg* (N=7)	4.0 mg/kg (N=6)	All (N=29)
Adverse Event	3 (100%)	6 (100%)	7 (100%)	7 (100%)	6 (100%)	29 (100%)
Treatment-Related Adverse Event[1]	3 (100)	5 (83.3)	6 (85.7)	7 (100)	6 (100)	27 (93.1)
Adverse Event ≥ Grade 3[2]	3 (100)	4 (66.7)	7 (100)	5 (71.4)	5 (83.3)	24 (82.8)
Treatment-Related Adverse Event ≥ Grade 3[2]	2 (66.7)	2 (33.3)	6 (85.7)	4 (57.1)	5 (83.8)	19 (65.5)
Serious Adverse Event	1 (33.3)	1 (16.7)	3 (42.9)	2 (28.6)	2 (33.3)	9 (31.0)
Dose-limiting Toxicity	0	0	1 (14.3)[3]	0	1 (16.7)[4]	2 (6.9)
Event that Resulted in Study Discontinuation	1 (33.3)	2 (33.3)	3 (42.9)	4 (57.1)	2 (33.3)	10 (34.5)
Event that Resulted in MGC018 Withdrawal	1 (33.3)	1 (16.7)	3 (42.9)	4 (57.1)	2 (33.3)	11 (37.9)
Event that Resulted in MGC018 Dose Reduction	0	0	1 (14.3)	2 (28.6)	2 (33.3)	5 (17.2)
Event that Resulted in MGC018 Interruption	1 (33.3)	0	1 (14.3)	5 (71.4)	5 (83.3)	12 (41.4)
Fatal Adverse Event (pneumonitis/pneumonia)	1 (33.3)	0	0	0	0	1 (3.4)
Adverse Event of Special Interest (AESI) – Infusion Reaction	0	0	2 (28.6)	5 (71.4)	2 (33.3)	9 (31.0)

[1]Includes events with causality assessments of 'Possible', 'Probable' or 'Definite'. [2]Based on CTCAE criteria version 4.0.3. [3]Grade 4 neutropenia resolved to baseline. [4]G3 fatigue > 72 hours. *Amendment during 3.0 mg/kg dose level applied to allow dose modification.
Data were extracted on 03May2021.

Best Percent Change of Target Lesions in Evaluable Population[1]



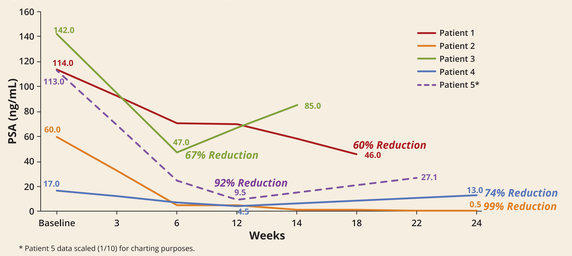
[1]Patients who received at least one dose and had at least one post-baseline tumor evaluation. CRC = Colorectal cancer. NA = Not available.
Data were extracted on 03MAY2021.

Activity in Melanoma Patients

Patient	Prior Radiation/ Surgery	B7-H3 H Score (Vasculature Score)	Line of Therapy	Treatment	Duration of Therapy	Reason for MGC018 Discontinuation	Best Response in Target Lesions
Patient #1 3 target lesions (lung, liver, chest wall) Non-target pelvic nodes and perirectal/lung lesions	Radiation and Surgery	160 (3+)	1	Nivolumab	10/18 – 07/19		
			2	Ipilimumab	08/19 – 09/19		
			2	Nivolumab	08/19 – 02/20		
			2	Relatlimab	11/19 – 02/20		
			3	Carboplatin/Taxol	04/20 (1 dose)	SAE hematuria/ thrombocytopenia	
			4	**MGC018**	**05/20 – 07/20**		**-24%**
Patient #2 4 target lesions (2 lung, hilar node, soft tissue) Non-target bilateral lung lesion	Surgery	195 (2+)	1	Pembrolizumab	03/20 – 07/20		
			2	Ipilimumab + Nivolumab	07/20 – 08/20		
			3	**MGC018**	**10/20 – 03/21**	PD	**-28%**
Patient #3 2 target lesions (skin) Non-target multiple lower extremity lesions	Radiation and Surgery	66 (3+)	1	Ipilimumab	02/15 – 05/15		
			2	Pembrolizumab	08/15 – 10/17		
			3	Ipilimumab	06/18 – 08/18		
			4	Nivolumab	10/18 – 09/20		
			5	**MGC018**	**10/20 – 04/21**	N/A, ongoing	**cPR (-36%)**

PD = progressive disease; cPR = confirmed partial response; N/A = not applicable.
Data were extracted on 03May2021.

Update on mCRPC PSA Responders from ASCO 2020

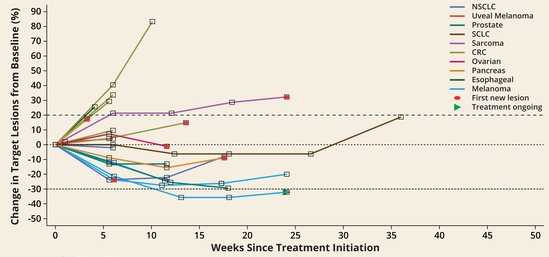


* Patient 5 data scaled (1/10) for charting purposes.

Patient (Dose)	B7-H3 H Score (Vasculature Score)	Line of Therapy	Treatment	Duration of Therapy (# months)	MGC018 Best Response	MGC018 PSA Reduction	MGC018 Time to Progression (# months)	Reason for MGC018 Discontinuation
Patient #1 **2 mg/kg** One target lesion (lymph node); non-target abdominal adenopathy and bone lesions	130 (1+)	1	Docetaxel	4				
		2	Enzalutamide	24				
		3	Prostvac	5				
		4	Abiraterone	6				
		5	Nivolumab	9				
		6	**MGC018**	**4**	**SD (-29%)**	**-60%**	**Unknown (>4)**	**Patient decision due to numerous clinic visits**
Patient #2 **3 mg/kg** Bone only disease	N/A (insufficient invasive tumor)	1	Docetaxel	6				
		2	Abiraterone	4				
		3	Enzalutamide	12				
		4	Radium 223	6				
		5	**MGC018**	**6**	**SD**	**-99%**	**6**	**New skull lesions on CT scan obtained for head injury; skull lesions not seen on baseline bone scan: no baseline head CT**
Patient #3 **3 mg/kg** Bone only disease	250 (2+)	1	Docetaxel	8				
		2	Provenge	2				
		3	Enzalutamide	6				
		4	Abiraterone	9				
		5	**MGC018**	**3**	**SD**	**-67%**	**Not yet progressed (7)**	**Palmar plantar erythrodysesthesia**
Patient #4 **3 mg/kg** Bone only disease	279 (2+)	1	Abiraterone	Unknown				
		2	Nivo + Rucaparib	Unknown				
		3	**MGC018**	**5**	**SD**	**-74%**	**Not yet progressed (7)**	**Pericardial effusion**
Patient #5 **3 mg/kg** Bone only disease	215 (1+)	1	Docetaxel	4				
		2	Provenge	12				
		3	Enzalutamide	7				
		4	Abiraterone	7				
		5	Docetaxel	4				
		6	**MGC018**	**3**	**SD**	**-92%**	**Initiated subsequent therapy (6)**	**Increasing PSA**

Data were extracted on 03May2021.

Percent Change of Target Lesions



Data were extracted on 03May2021.

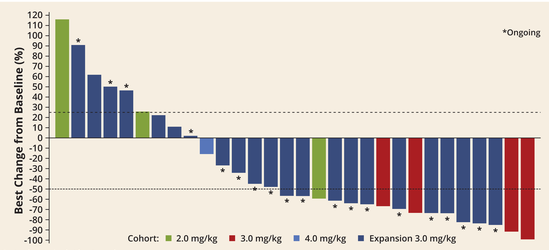
mCRPC Patients with < 50% PSA Reduction

Patient (Dose)	B7-H3 H Score (Vasculature Score)	Line of Therapy	Treatment	Duration of Therapy (# months)	MGC018 Best Response	MGC018 PSA Change	Reason for MGC018 Discontinuation
Patient #6 **2 mg/kg** Bone only disease	245 (2+)	1	Docetaxel	4			
		2	Sipuleucel-T	2			
		3	Abiraterone	18			
		4	**MGC018**	**1.5**	**SD**	**+70%**	**Stasis dermatitis**
Patient #7 **2 mg/kg** Bone only disease	N/A (insufficient tumor)	1	Enzalutamide	Unknown			
		2	Docetaxel	4			
		3	Abiraterone	12			**Palmar plantar erythrodysesthesia/ maculopapular rash**
		4	Radium 223	2			
		5	**MGC018**	**1.5**	**SD**	**+25%**	
Patient #8 **4 mg/kg** Bone only disease	No biopsy available	1	Docetaxel	5			
		2	Enzalutamide	8			
		3	**MGC018**	**2**	**SD**	**-12%**	**Patient decision**
Patient #9 **4 mg/kg** Periaortic lymph node Bone disease	Not performed	1	Enzalutamide	24			
		2	Docetaxel	3			
		3	Cabazitaxel	3			
		4	Tesetaxel	1			**DLT Grade 3 fatigue > 72 hours**
		5	**MGC018**	**.25**	**Not evaluable**	**Unknown**	

Data were extracted on 03May2021.

Best Percent Change in PSA: Dose Escalation and Cohort Expansion

>50% PSA Reduction in 11/22 (50%) mCRPC Expansion Patients; (16/31 [52%] in Escalation + Expansion)



Patients who received at least one dose.
Data were extracted on 03MAY2021.

Conclusions

- Acceptable safety profile with manageable hematologic and skin toxicity
  - Recommended Phase 2 dose = 3 mg/kg
- Anti-tumor activity observed in 3 dose escalation melanoma patients
  - Reductions in target lesion sums of 24%, 28%, and 36% (cPR, remains on treatment 6 mos.)
- Preliminary mCRPC cohort expansion results as of data cutoff (03 May 2021)
  - > 50% PSA reduction in 11/22 (50%) patients
  - Of 13 patients with measurable disease, 6 not yet evaluable, 7 had first 9-week imaging
    - Of the 7 patients, 4 had reductions in target lesion sums of 13%, 21%, 27%, and 35% (uPR)
    - 12 of 13 patients remain on treatment
- Ongoing enrollment in mCRPC, TNBC, NSCLC, SCCHN, and melanoma

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