Preliminary Dose Escalation Results from a Phase 1/2, First-in-Human Study of MGC018 (Anti-B7-H3 Antibody-Drug Conjugate) in Patients with Advanced Solid Tumors

Abstract #308859

John Powderly[1], Sekwon Jang[2], Juniper Scribner[3], Deryk Loo[3], Chet Bohac[3], Alexander Spira[4], Manish Sharma[5]

[1]Carolina BioOncology, Huntersville, NC; [2]Inova Schar Cancer Institute Fairfax, VA; [3]MacroGenics, Inc., Rockville, MD; [4]Virginia Cancer Specialists, Fairfax, VA; [5]START Midwest, Grand Rapids, MI

bohacg@macrogenics.com

NCT03729596

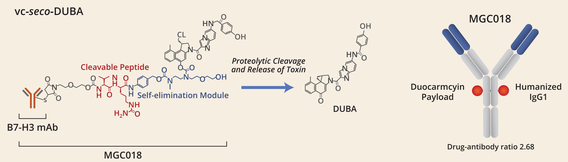
Background

High B7-H3 Expression Levels in Solid Tumors

Potential Indications	B7-H3 Positive*		2+ or Above	
Head and Neck Cancer	19/19	100%	19/19	100%
Kidney Cancer	77/78	99%	75/78	96%
Glioblastoma	65/66	98%	63/66	95%
Thyroid Cancer	34/35	97%	33/35	94%
Mesothelioma	41/44	93%	39/44	89%
Melanoma	132/146	90%	94/146	64%
Prostate Cancer	88/99	89%	51/99	52%
Pancreas Cancer	69/78	88%	45/78	58%
Bladder Cancer	134/156	86%	123/156	79%
Lung Cancer	324/379	85%	300/379	79%
Breast Cancer	189/249	76%	156/249	63%
Ovarian Cancer	59/79	75%	36/79	46%

*B7-H3 positivity reflects any grade staining (1-3+) via FFPE tumor microarray (cytoplasmic, membrane, and vasculature staining); B7-H3 is expressed on tumor as well as tumor vasculature.

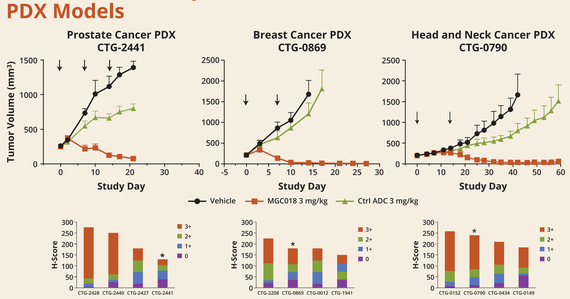
MGC018 Antibody-Drug Conjugate with Duocarmycin-based Linker Payload



- MGC018 is an anti-B7-H3 antibody-drug conjugate (ADC) with a duocarmycin payload
- vc-seco-DUocarmycin-hydroxyBenzamide Azaindole (DUBA) is a fully synthetic 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*.

Anti-Tumor Activity of MGC018 in Human Cancer PDX Models



Staining with goat anti-B7-H3 polyclonal Ab R&D Systems, Inc.

Rationale

- B7-H3 is highly expressed in multiple solid tumors, with limited expression in normal tissue
- MGC018 is a novel ADC that delivers a potent duocarmycin payload to dividing and non-dividing B7-H3-expressing cells

Study Design and Objectives

- Phase 1 study evaluates safety, dose-limiting toxicities (DLT), and maximum tolerated dose (MTD) of MGC018 in a dose escalation 3+3+3 design
- MGC018 dosed intravenously every 21 days (q3w)
- 6 dose escalation cohorts planned (0.5 to 5.0 mg/kg)
- Tumor response by investigator per RECIST v1.1 evaluated every 6 weeks for 1st 4 cycles and every 12 weeks thereafter
- Cohort expansion will enroll at the RP2D to assess safety and tumor response

Primary Objective

- Safety and MTD (or maximum administered dose)

Secondary Objectives

- PK and immunogenicity
- Antitumor activity

Key Eligibility Criteria

Inclusion

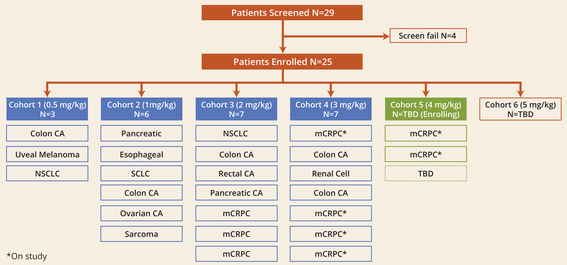
- Patients with histologically proven, relapsed or refractory, unresectable locally advanced or metastatic solid tumors of any histology
- Patients for whom no therapy with demonstrated clinical benefit is available
- Tumor tissue available to evaluate B7-H3 IHC (B7-H3 expression not required for eligibility)

Exclusion

- Abnormal laboratory parameters (hematologic, renal, and/or liver function)
- Untreated or symptomatic central nervous system metastasis
- Treatment with any systemic chemotherapy within 3 weeks (radiotherapy within 2 weeks)
- Clinically significant cardiovascular or pulmonary disease

Results

Enrollment Status



*On study

- 25 patients enrolled as of 06 May 2020
- 23 patients included in safety and efficacy assessment of Cohorts 1–4
- 18 patients (1 with metastatic castration-resistant prostate cancer [mCRPC]) with measurable disease evaluated per RECIST v1.1
- 6 patients with mCRPC with bone only disease

Safety Summary

Related Adverse Events ≥ 10%, All Grades

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)	All (N=23)
AT LEAST ONE EVENT	3 (100)	4 (66.7)	7 (100)	7 (100)	21 (91.3)
Blood and lymphatic system disorders	0	1 (16.7)	2 (28.6)	3 (42.9)	6 (26.1)
Neutropenia	0	1 (16.7)	2 (28.6)	3 (42.9)	6 (26.1)
Lymphopenia	0	0	1 (14.3)	2 (28.6)	3 (13.0)
Gastrointestinal disorders	0	4 (66.7)	2 (28.6)	2 (28.6)	8 (34.8)
Nausea	0	2 (33.3)	2 (28.6)	1 (14.3)	5 (21.7)
Vomiting	0	1 (16.7)	2 (28.6)	1 (14.3)	4 (17.4)
General disorders and administration site conditions	2 (66.7)	2 (33.3)	2 (28.6)	5 (71.4)	11 (47.8)
Fatigue	1 (33.3)	1 (16.7)	2 (28.6)	4 (57.1)	8 (34.8)
Chills	1 (33.3)	1 (16.7)	2 (28.6)	1 (14.3)	5 (21.7)
Pyrexia	1 (33.3)	0	2 (28.6)	0	3 (13.0)
Injury, poisoning and procedural complications	0	0	2 (28.6)	5 (71.4)	7 (30.4)
Infusion related reaction	0	0	2 (28.6)	5 (71.4)	7 (30.4)
Investigations	1 (33.3)	3 (50.0)	4 (57.1)	4 (57.1)	12 (52.2)
Neutrophil count decreased	0	1 (16.7)	1 (14.3)	3 (42.9)	5 (21.7)
Lymphocyte count decreased	0	1 (16.7)	2 (28.6)	1 (14.3)	4 (17.4)
Platelet count decreased	0	0	1 (14.3)	2 (28.6)	3 (13.0)
Skin and subcutaneous tissue disorders	0	3 (50.0)	5 (71.4)	5 (71.4)	13 (56.5)
Skin hyperpigmentation	0	3 (50.0)	1 (14.3)	3 (42.9)	7 (30.4)
Palmar-plantar erythrodysaesthesia syndrome	0	0	3 (42.9)	2 (28.6)	5 (21.7)
Pruritus	0	1 (16.7)	1 (14.3)	2 (28.6)	4 (17.4)
Rash maculo-papular	0	0	2 (28.6)	1 (14.3)	3 (13.0)

[1]Includes events with causality ratings of 'Possible', 'Probable' or 'Definite'. [2]Subjects are counted once for each Preferred Term reported. (Note: 1 pt at 1.0 mg/kg and 3.0 mg/kg experienced angioedema; both AEs were Grade 2 and resolved to baseline.)

Grade ≥ 3 Related Adverse Events

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)	All (N=23)
AT LEAST ONE EVENT	2 (66.7)	2 (33.3)	7 (100)	3 (42.9)	14 (60.9)
Blood and lymphatic system disorders	0	0	2 (28.6)	2 (28.6)	4 (17.4)
Neutropenia	0	0	2 (28.6)	2 (28.6)	4 (17.4)
Lymphopenia	0	0	1 (14.3)	1 (14.3)	2 (8.7)
Gastrointestinal disorders	0	1 (16.7)	0	0	1 (4.3)
Gastrointestinal inflammation	0	1 (16.7)	0	0	1 (4.3)
Investigations	1 (33.3)	2 (33.3)	4 (57.1)	2 (28.6)	9 (39.1)
Lymphocyte count decreased	0	1 (16.7)	2 (28.6)	1 (14.3)	4 (17.4)
Blood alkaline phosphatase increased	0	0	1 (14.3)	1 (14.3)	2 (8.7)
Neutrophil count decreased	0	1 (16.7)	1 (14.3)	0	2 (8.7)
Platelet count decreased	0	0	1 (14.3)	1 (14.3)	2 (8.7)
Lipase increased	1 (33.3)	0	0	0	1 (4.3)
White blood cell count decreased	0	1 (16.7)	0	0	1 (4.3)
Respiratory, thoracic and mediastinal disorders	1 (33.3)	0	0	0	1 (4.3)
Pneumonitis	1 (33.3)	0	0	0	1 (4.3)
Skin and subcutaneous tissue disorders	0	0	3 (42.9)	1 (14.3)	4 (17.4)
Palmar-plantar erythrodysaesthesia syndrome	0	0	1 (14.3)	1 (14.3)	2 (8.7)
Rash maculo-papular	0	0	2 (28.6)	0	2 (8.7)
Stasis dermatitis	0	0	1 (14.3)	0	1 (4.3)

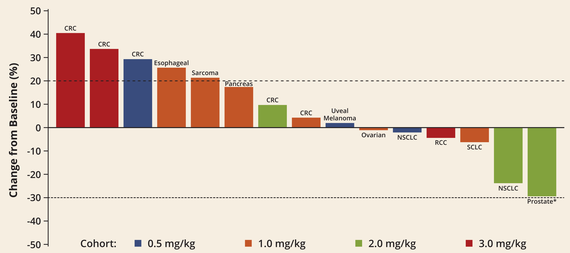
Overall Summary of Treatment-Emergent Adverse Events

Patients Reporting 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)	All (N=23)
Adverse Event	3 (100)	6 (100)	7 (100)	7 (100)	23 (100)
Treatment-Related Adverse Event [1]	3 (100)	4 (66.7)	7 (100)	7 (100)	21 (91.3)
Adverse Event ≥ Grade 3 [2]	3 (100)	4 (66.7)	7 (100)	4 (57.1)	18 (78.3)
Treatment-Related Adverse Event ≥ Grade 3 [2]	2 (66.7)	2 (33.3)	7 (100)	3 (42.9)	14 (60.9)
Serious Adverse Event	1 (33.3)	1 (16.7)	3 (42.9)	0	5 (21.7)
Event that Resulted in Study Discontinuation	1 (33.3)	1 (16.7)	3 (42.9)	0	5 (21.7)
Event that Resulted in Drug MGC018 Withdrawal	1 (33.3)	1 (16.7)	3 (42.9)	1 (14.3)	6 (26.1)
Event that Resulted in Drug MGC018 Dose Reduction	0	0	1 (14.3)	2 (28.6)	3 (13.0)
Event that Resulted in Drug MGC018 Interrupted	1 (33.3)	0	2 (28.6)	5 (71.4)	8 (34.8)
Fatal Adverse Event (pneumonitis)	1 (33.3)	0	0	0	1 (4.3)
Adverse Event of Special Interest (AESI) – Infusion Reaction	0	0	2 (28.6)	5 (71.4)	7 (30.4)

[1]Includes events with causality assessments of 'Possible', 'Probable' or 'Definite'. 'Based on CTCAE criteria version 4.0.3.
*Amendment applied to allow dose modification.

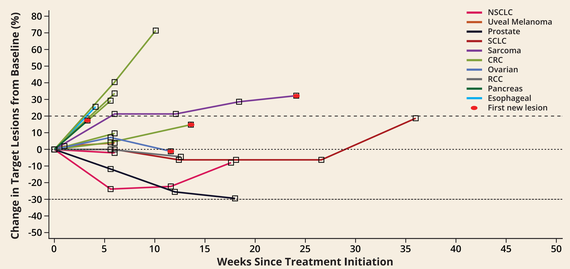
- 3 treatment-related serious adverse events occurred in 3 patients: pneumonitis in a patient with concurrent bacterial pneumonia; non-infectious gastroenteritis; and stasis dermatitis in a patient with chronic venous insufficiency
- One DLT; Grade 4 neutropenia resolved to baseline
- No febrile neutropenia observed

Best Percent Change of Target Lesions by MGC018 Dose Level and Tumor Type in the Evaluable Population[1]



[1]Patients who received at least one dose and had at least one post-baseline tumor evaluation. *mCRPC Pt #1. Data were extracted on 06MAY2020.

Percent Change of Target Lesions by Tumor Type



Tumor Responses with MGC018

- Reduction of pleural-based tumor in NSCLC patient following progression after 5L of prior therapy

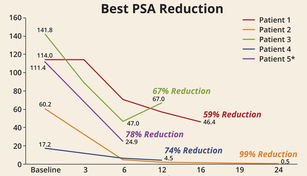
Line of Tx	Treatment	Cycles	Duration of Therapy (Months)	Best Response
1	Carboplatin+Paclitaxel+Bevacizumab	4	2	SD
2	Nivolumab	40	16	SD
3	MK-7162 (IDO1 inhibitor)	3	2	SD
4	APG-1252 (Bcl-2 inhibitor)	2	1	PD
5	Pembrolizumab (MK-3475)	2	1	PD
6	MGC018	2	2	SD (≈24%)

- Greater than 50% PSA decline following MGC018 in heavily pre-treated mCRPC

Patient (Dose)	Line of Therapy	Treatment	Duration of Therapy (months)	MGC018 Response
Patient #1	1	Docetaxel	4	SD (-29%); 59% PSA Decline
2 mg/kg	2	Enzalutamide	24	
One target lesion (lymph node), abdominal adenopathy & bone lesions	3	Prostvac	5	
	4	Abiraterone	6	
	5	Nivolumab	6	
	6	**MGC018**	**4**	
Patient #2	1	Docetaxel	6	SD (Ongoing); 99% PSA Decline
3 mg/kg	2	Abiraterone	4	
Bone only disease	3	Enzalutamide	12	
	4	Radium 223	6	
	5	**MGC018**	**3**	
Patient #3	1	Docetaxel	8	SD (Ongoing); 67% PSA Decline
3mg/kg	2	Provenge	2	
Bone only disease	3	Enzalutamide	6	
	4	Abiraterone	9	
	5	**MGC018**	**1.5**	
Patient #4	1	Abiraterone	Unknown	SD (Ongoing); 74% PSA Decline
3 mg/kg	2	Nivolumab + Rucaparib	Unknown	
Bone only disease	**3**	**MGC018**	**1.5**	
Patient #5	1	Docetaxel	4	SD (Ongoing); 78% PSA Decline
3mg/kg	2	Provenge	12	
Bone only disease	3	Enzalutamide	7	
	4	Abiraterone	7	
	5	Docetaxel	4	
	6	**MGC018**	**1.5**	

Patient 1 had 59% PSA reduction with near partial response, and several patients with ongoing stable disease.

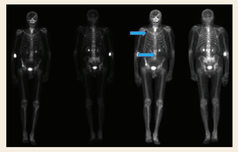
Best PSA Reduction



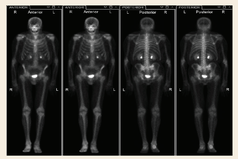
*Patient 5 Scaled for Charting Purposes: Baseline PSA 1,114 ng/mL dropped to 249 ng/mL on Week 6

- Patient 2: 99% PSA reduction with substantial improvement in metastatic bone lesions of thoracic/lumbar spine, ribs, sternum, and pelvis

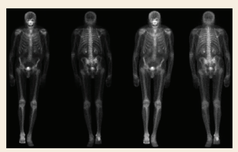
November 13, 2019



February 7, 2020



May 1, 2020



B7-H3 IHC Data

- 18 of 23 patients had tissue samples evaluable for B7-H3 expression
- H-score: Median 200 (range 82–279)
- Vasculature score: Median 2+ (range 0–3+)

Conclusions

- MGC018 has an acceptable safety profile to date with manageable hematologic and skin toxicity
  - 1 DLT occurred at 2 mg/kg, resolved to baseline
- Preliminary evidence of anti-tumor activity with radiologic improvement in heavily pretreated patients:
  - NSCLC
  - mCRPC with rapid PSA reduction
- Enrollment ongoing at 4 mg/kg q3w
- Planned dose expansion in mCRPC

Presented at the ASCO20 Virtual Scientific Program, May 29–31, 2020