A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics (PK) of MGA012 (anti-PD-1 antibody) in Patients with Advanced Solid Tumors

Nehal Lakhani[1], Janice M. Mehnert[2], Drew Rasco[3], Michael Gordon[4], Joanna Lohr[5], Sharad Sharma[5], Hua Li[5], Ross LaMotte-Mohs[5], Paul Moore[5], Jichao Sun[5], Pepi Pencheva[5], Brad Sumrow[5], Jon Wigginton[5], John Powderly[6]

[1]START Midwest, Grand Rapids, MI; [2]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [3]South Texas Accelerated Research Therapeutics, San Antonio, TX; [4]Virginia P. Piper Cancer Care Network, Scottsdale, AZ; [5]MacroGenics, Inc., Rockville, MD; [6]Carolina BioOncology Institute, Huntersville, NC

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http://ir.macrogenics.com/events.cfm

Background

MGA012: Anti-PD-1 Monoclonal Antibody (mAb) with Favorable Design Features

- Humanized proprietary anti-PD-1 mAb
  - Hinge stabilized humanized IgG4
  - Benchmarks favorably against approved anti-PD-1 mAbs
- Anti-PD-1 becoming mainstay of cancer immunotherapy
- Basis for combination immunotherapy

MGA012: Favorable Preclinical Profile

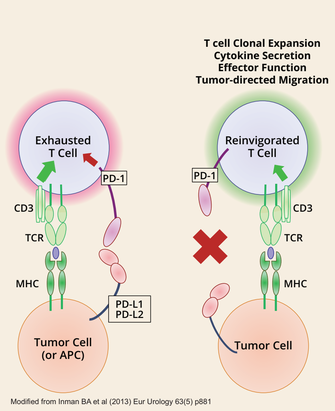
MGA012	MGA012 Compared to:	
	Nivolumab*	Pembrolizumab*
Affinity for human PD-1	>4x greater	>6x greater
Off-rate for human PD-1	~2x slower	~6x slower
Cell binding (MFI)	>	Equivalent
PD-L1/PD-L2 binding blockade	>	>
T-cell activation (IFNγ)	Equivalent	Equivalent
PK in cynomolgus monkeys	>	Equivalent

MGA012	Results
Tissue cross-reactivity	No unanticipated findings
Toxicology in cynomolgus monkeys: IV at 10, 40 or 150 mg/kg; QW x 4	Well tolerated at all doses No unanticipated findings NOAEL = 150 mg/kg
Predicted half-life in humans	~18 days

*Replicas of nivolumab and pembrolizumab produced at MacroGenics

Rationale for Targeting PD-1

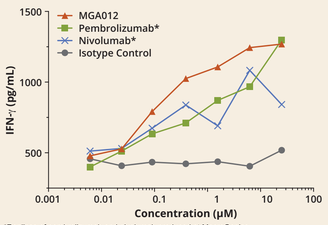
- Checkpoint receptors are subverted by tumors or APCs to evade immune system
  - Tumors induce state of immune suppression (TGF-β)
- PD-1 receptors are expressed on "exhausted" T cells
- Interactions with corresponding ligands negate anti-tumor T cell activity



Modified from Inman BA et al (2013) Eur Urology 63(5) p881

MGA012 Enhances Activation of SEB-stimulated Human T Cells

- Human PBMCs were pre-stimulated with 0.5 ng/mL SEB for 48h and re-stimulated for 48h in presence or absence of indicated mAbs
- IFNγ in supernatant was measured by ELISA



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Study Design

3+3 Design Dose Escalation (Complete)

- 10 mg/kg q2W
- 10 mg/kg q4W
- 3 mg/kg q2W
- 3 mg/kg q4W
- 1 mg/kg q2W

Expansion Cohorts (Ongoing; 3 mg/kg q2W)

- Endometrial
- Cervical
- Sarcoma
- NSCLC

Dosing Regimen: 1-hr IV infusion, q2W or q4W

Evaluations: 4-week Dose Limiting Toxicity (DLT) evaluation period; Efficacy per RECIST and irRECIST

Dose Expansion: MGA012 administered 3 mg/kg Q2W to checkpoint inhibitor-naïve patients with advanced solid tumors

Key Study Objectives

Primary Objective

- Characterize safety, tolerability, DLT, maximum tolerated dose (MTD) or maximum administered dose (MAD) of MGA012 when administered IV every two or four weeks to patients with relapsed/refractory unresectable locally-advanced or metastatic solid tumors

Secondary Objectives

- Characterize PK and immunogenicity of MGA012
- Investigate preliminary anti-tumor activity of MGA012 using both conventional RECIST 1.1 and immune-related RECIST (irRECIST)

Exploratory Objectives

- Explore relationships between PK, pharmacodynamics, patient safety, and anti-tumor activity of MGA012
- Investigate immune-regulatory activity of MGA012 in vivo, including various measures of T cell activation in peripheral blood and/or tumor biopsy specimens
- Determine PD-L1 expression via IHC staining of formalin-fixed, paraffin-embedded tumor biopsy specimens
- Determine relationships between membranous expression of PD-L1 on tumor cells, immune cell infiltration within biopsy specimens (e.g., $CD4^+$ and $CD8^+$ T cells), PD-L1 expression on immune cell infiltrate, and clinical response via IHC
- Characterization of T-cell repertoire using T-cell receptor spectratyping of peripheral blood mononuclear cells

Entry Criteria

Key Inclusion Criteria

- Dose escalation: histologically proven, locally advanced unresectable or metastatic solid tumors for whom no approved therapy with demonstrated clinical benefit is available or standard treatment was declined. Disease-specific criteria to be applied in Cohort Expansion
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy ≥12 weeks
- Measurable disease per RECIST 1.1
- Acceptable laboratory parameters

Key Exclusion Criteria

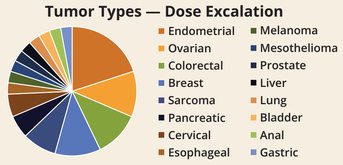
- Symptomatic central nervous system metastases
- Patients with prior immune checkpoint inhibitor (e.g., anti-PD-L1, anti-PD-1, anti-CTLA-4) are not eligible in Cohort Expansion
- History of known or suspected autoimmune disease with specific exceptions
- Treatment with any systemic anti-neoplastic therapy, or investigational therapy within 4 weeks; radiation therapy or corticosteroid treatment within 2 weeks
- Clinically significant cardiovascular or pulmonary disease

Results

Patient Demographics — Dose Escalation

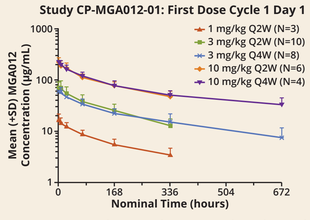
- Broad array of tumor types evaluated
- 24 female, 13 male
- Median age 63 years
- 7 of 37 (19%) have prior checkpoint exposure

Tumor Types — Dose Excalation



Preliminary Pharmacokinetic Analysis

Study CP-MGA012-01: First Dose Cycle 1 Day 1

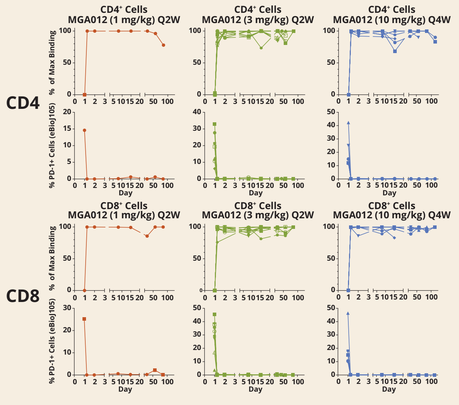


Dose (mg/kg)		C_{max} (μg/mL)	AUC_{INF} (h•μg/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	$T_{1/2}$ H
1	N	3	3	3	3	3
	Mean	15.5	3439	0.304	87.3	216.8
	SD	4.8	928	0.077	12.1	45.9
	%CV	31	27	25	14	21
3	N	18	18	18	18	18
	Mean	70.7	17096	0.200	84.4	401.5
	SD	19.9	6784	0.070	37.8	346.0
	%CV	16	40	35	45	86
10	N	10	10	10	10	10
	Mean	232.4	63906	0.169	86.4	422.3
	SD	52.3	18566	0.050	21.0	167.9
	%CV	38	29	30	24	40

- For 3 mg/kg and 10 mg/kg dose levels:
  - C_{max} and AUC_{inf} are dose proportional
  - $T_{1/2}$ (β) approximately 17 days
  - Achievement of steady-state in approximately 85 days
- For 1 mg/kg dose level:
  - MGA012 showed faster elimination; however, only 3 patients evaluated

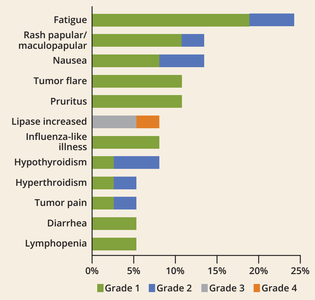
T-cell Receptor Occupancy

- Full and sustained receptor occupancy of MGA012 at all dose levels evaluated on both $CD4^+$ and $CD8^+$ T-cells
- Complete loss of competing fluorescently labeled anti-PD-1 staining (eJBio105 clone) at all dose levels



Preliminary Safety Results

Treatment-related AEs in ≥2 Patients



Summary of Adverse Events (AEs)

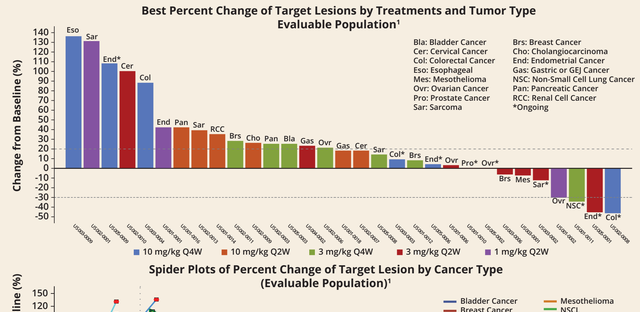
Patients Reporting at Least 1	1 mg/kg Q2W (N=3)	3 mg/kg Q2W (N=10)	3 mg/kg Q4W (N=10)	10 mg/kg Q2W (N=8)	10 mg/kg Q4W (N=6)	Total (N=37)
AE	3 (100)	10 (100)	10 (100)	8 (100)	6 (100)	37 (100)
Treatment-Related AE[1]	2 (66.7)	9 (90.0)	4 (40.0)	5 (62.5)	4 (66.7)	24 (64.9)
AE ≥ Grade 3[2]	2 (66.7)	8 (80.0)	4 (40.0)	4 (50.0)	4 (66.7)	22 (59.5)
Treatment-Related AE[1] ≥ Grade 3[2]	0	4 (40.0)	0	0	0	4 (10.8)
Serious AE	2 (66.7)	2 (20.0)	2 (20.0)	1 (12.5)	2 (33.3)	9 (24.3)
Treatment-Related Serious AE[1]	0	1 (10.0)	0	0	0	1 (2.7)
AESIs	0	3 (30.0)	1 (10.0)	0	1 (16.7)	5 (13.5)

[1]Includes events with causality assessments of 'Possible', 'Probable' or 'Definite'
[2]Based on CTCAE criteria version 4.0
Treatment-related SAE: Aphasia in the context of new brain metastases
*Data as of 23-Sept-2017

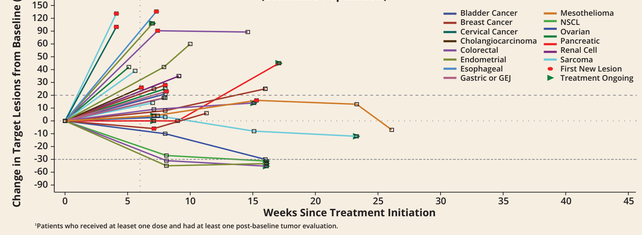
- MGA012 demonstrated acceptable tolerability with no DLTs at completion of Dose Escalation
- MAD – 10 mg/kg Q2W; no MTD exceeded or defined
- Most common treatment-related AEs include fatigue (n=9, 24.3%), rash (n=5, 13.5%), nausea (n=5, 13.5%), tumor flare (n=4, 10.8%), and pruritus (n=4, 10.8%)
- Treatment-related Grade ≥3 AEs occurred in 4/37 (10.8%) patients, including increased lipase (n=3) and vulvovaginal ulceration/inflammation (n=1)
- A single treatment-related SAE of aphasia reported, which occurred in setting of new brain metastases
- Immune-related AEs limited to rash (n=5, 13.5%), hypothyroidism (n=3, 8.1%), hyperthyroidism (n=2, 5.4%), vaginal ulceration/inflammation (n=1, 2.7%), and infusion-related reaction (n=1, 2.7%)

Preliminary Efficacy Results

Best Percent Change of Target Lesions by Treatments and Tumor Type Evaluable Population[1]



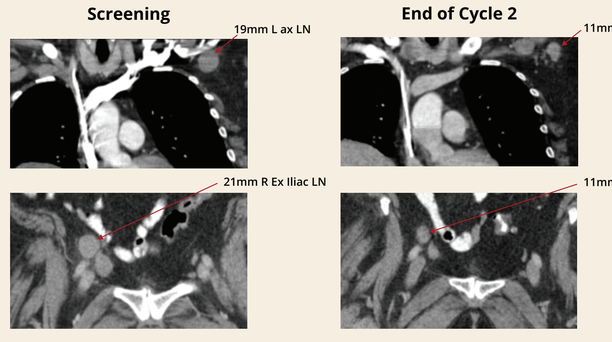
Spider Plots of Percent Change of Target Lesion by Cancer Type (Evaluable Population)[1]



[1]Patients who received at leaset one dose and had at least one post-baseline tumor evaluation.

- Thirty-one response-evaluable patients at data cutoff (10 Oct 2017)
- Two confirmed partial responses (uterine papillary serous carcinoma and MSI-H colorectal carcinoma)
- Two unconfirmed partial responses (squamous cell lung carcinoma and ovarian carcinoma)
- Nine patients with stable disease as best response
- Others had radiographic progressive disease or clinical progression

Patient Vignette



- 64-yr-old female with uterine papillary serous carcinoma (3 mg/kg q2W)
- Prior treatments: TAH-BSO with 6 cycles of adjuvant carboplatin + taxol
- Target lesions: 19 mm L axillary lymph node; 21 mm R Ext Iliac lymph node
- Scans demonstrate 45% and 40% decreases in tumor burden at end of Cycles 2 and 4, respectively
- Patient remains on study, currently on Cycle 6

Conclusions

- MGA012 has demonstrated:
  - An acceptable safety profile
  - Predictable PK/PD
  - Early evidence of anti-tumor activity
- Dose Expansion ongoing in tumor-specific cohorts at 3 mg/kg q2W in U.S., Europe, Australia, New Zealand
- Future trials planned for combination testing of MGA012 with T-cell re-directed, CD-3 based DART® molecules

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