Phase 2/3 Open-label Trial of Enoblituzumab in Combination with MGA012, with and without Chemotherapy, in the Treatment of Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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Fernanda I. Arnaldez[1], Charu Aggarwal[2], Scott Currence[1], Jan Baughman[1], Paul Moore[1], George Blumenschein[3], Jon M. Wigginton[1], Robert Ferris[4]

[1]MacroGenics, Inc. Rockville, MD; [2]Penn Medicine, Philadelphia, PA; [3]MD Anderson Cancer Center, Houston, TX; [4]Hillman Cancer Center, UPMC, Pittsburgh, PA

arnaldezf@macrogenics.com

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Background

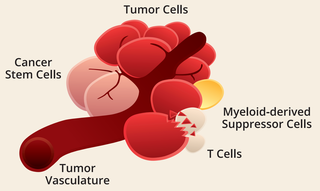
Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- SCCHN accounts for >500,000 new cases and nearly 300,000 deaths annually worldwide as of 2012[1]
- Patients with recurrent/metastatic (R/M) SCCHN have a poor prognosis with median overall survival (OS) of <1 year[2], remaining an unmet medical need
- PD-1 and PD-L1 blockade has demonstrated antitumor activity in advanced SCCHN; pembrolizumab has shown efficacy in first-line treatment of R/M SCCHN[3]
- A recent study of enoblituzumab combined with pembrolizumab showed this combination is feasible with an acceptable toxicity profile[4]. While studies of monotherapy pembrolizumab in this population report responses below 17%[5], the overall response rate of PD-1/PD-L1 inhibitor-naïve patients (post platinum) in patients receiving enoblituzumab plus pembrolizumab was 33% (6/18) including 1 confirmed CR and 5 confirmed PRs[6], suggesting a cooperative mechanism and providing rationale for further development of this combination in patients with recurrent/metastatic SCCHN

Rationale

Targeting B7-H3 in Cancer

Associated with adverse clinical features and outcome in various solid tumors

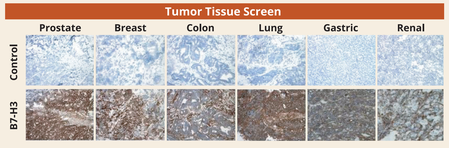


Expression on:
- Primary tumor & metastases
- Cancer stem cells
- Tumor stroma and vasculature

Potential immunological role
- Inhibition of T-cell activation
- Correlated with lack of response to anti-PD-1 therapy

Tumor-autonomous role
- Migration & invasion
- Tumor metabolic advantage
- Associated with chemotherapy resistance

B7-H3: IHC on Tumor Tissue

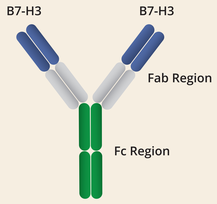


Confirmed High Penetrance in Broad Set of Solid Tumors

Fixed Tumor MicroArray	IHC Summary of Samples Screened			
	B7-H3 Positive		2+ or Above	
Lead Potential Indications:				
Head and Neck	19/19	100%	19/19	100%
Kidney Cancer*	77/78	99%	75/78	96%
Lung Cancer	226/272	83%	211/272	78%
Breast Cancer**	119/164	73%	115/164	70%
Prostate Cancer	88/99	89%	51/99	52%
Melanoma	66/70	94%	32/70	46%
Bladder	14/20	70%	9/20	45%
Other Potential Indications:				
Glioblastoma	65/66	98%	63/66	95%
Thyroid Cancer	34/35	97%	33/35	94%
Mesothelioma	41/44	93%	39/44	89%
Pancreas Cancer	69/78	88%	45/78	58%
Ovarian Cancer*	59/79	75%	36/79	46%

*Also target expression in tumor vasculature. **Triple negative: 8/17 positive, 2+ or above (47%).

Enoblituzumab



- Investigational humanized, Fc-optimized anti-B7-H3 antibody

Function/MoA
- Enhances Fc-mediated activies, including ADCC
- **Increases** binding to activating **FcγR, CD16A**, including low-affinity allele
- **Decreases** binding to inhibitory **FcγR, CD32B**
- Potential coordinate engagement of innate and adaptive immunity

MGA012

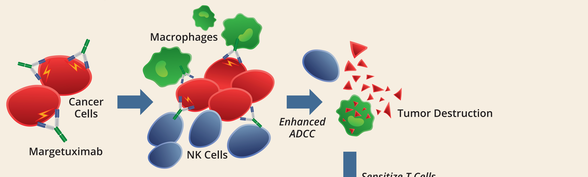
- MGA012 (also known as INCMGA00012) is an investigational anti-PD-1 monoclonal antibody with a tolerable safety profile and activity signal consistent with other agents in its class[8] demonstrated in early studies

Rationale for Combination

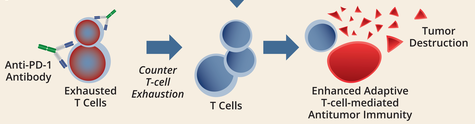
Hypothesis: Coordinate engagement of innate and adaptive immunity with enoblituzumab and anti-PD-1 may mediate greater antitumor activity than either single agent alone
- Activity of investigational Fc-optimized antibody (margetuximab, anti-HER2) combined with pembrolizumab benchmarked favorably vs. historical anti-PD-1 monotherapy experience in gastric carcinoma[9]
- Preliminary data indicates enoblituzumab can modulate T-cell repertoire in treated patients
  - Enhanced peripheral T-cell clonality and clone abundance[10]
  - Enhanced local T-cell infiltration in prostate cancer[11]
- Combined targeting of B7-H3 and PD-1/PD-L1 in preclinical tumor models can mediate greater antitumor activity than either single agent alone[12]
- NK cells may express PD-1, and PD-1/PD-L1 interaction can impair NK cell function
  - PD-1/PD-L1 blockade can enhance NK cell function and preclinical antitumor activity[13]

Coordinate engagement of innate and adaptive immunity to mediate tumor regression

Innate Immunity

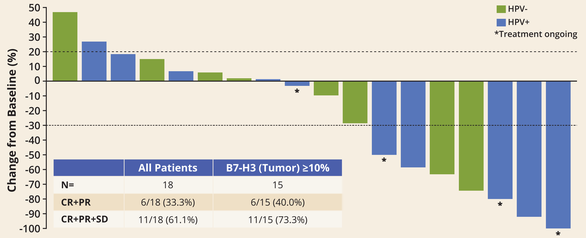


Adaptive Immunity



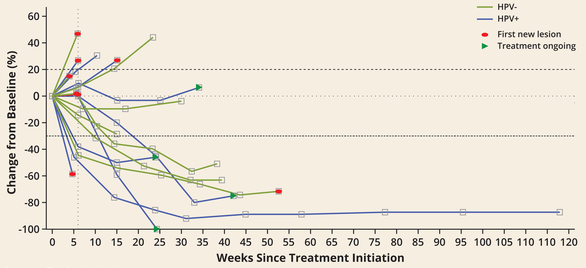
Phase 1 Antitumor Activity in SCCHN Patients, Anti-PD-1/PD-L1 Naïve

Tumor regression in patients with SCCHN, irrespective of HPV status



	All Patients	B7-H3 (Tumor) ≥10%
N=	18	15
CR+PR	6/18 (33.3%)	6/15 (40.0%)
CR+PR+SD	11/18 (61.1%)	11/15 (73.3%)

Durable objective responses and disease stabilization

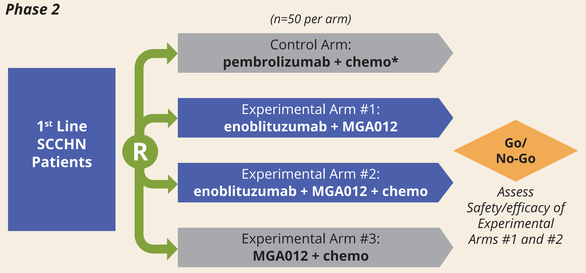


Data cut-off 12 October 2018.

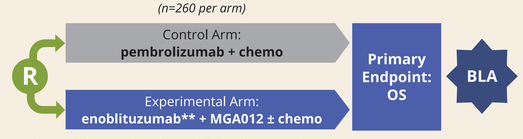
Phase 2/3 Study Design

Planned Initiation of Global Study in 4Q2019

Phase 2



Phase 3



* Investigator choice carboplatin or cisplatin, plus 5-FU. **Pending chronic tox study.

Key Study Objectives

Primary Objectives

Phase 2:
- To select the preferred enoblituzumab + MGA012 regimen (with or without chemotherapy) for further evaluation in Phase 3, in comparison to pembrolizumab + chemotherapy, based primarily upon evaluation of Investigator-assessed overall response rate (ORR) and safety

Phase 3:
- To compare the OS of patients treated with enoblituzumab + MGA012 (with or without chemotherapy, according to the preferred regimen selected in Phase 2) to patients treated with pembrolizumab + chemotherapy

Secondary Objectives/Endpoints

Phase 2:
- Investigator-assessed progression-free survival (PFS), disease control rate (DCR), duration of response (DoR), and OS
- Safety
- PK of enoblituzumab and MGA012, including PPK and exposure-response analyses
- Immunogenicity of enoblituzumab and MGA012

Phase 3:
- Investigator-assessed PFS, ORR, DCR, and DoR
- OS and Investigator-assessed ORR, PFS, DCR, and DoR in subpopulations pre-defined by PD-L1 and/or B7-H3 expression
- Safety
- Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)

Exploratory Objectives/Endpoints

- Relationships between PK, pharmacodynamics, patient safety, and antitumor activity of the enoblituzumab + MGA012 combination with and without concurrent chemotherapy
- Relationships between PD-1, PD-L1, and B7-H3 expression on tumor cells and response

Entry Criteria

Key Inclusion Criteria

- Histologically proven, recurrent or metastatic SCCHN not curable by local therapy
- No prior systemic therapy for SCCHN in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior of given as part of multimodal treatment for locally advanced disease)
- Primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx
- HPV test results available (positive and negative eligible)
- ECOG performance status of 0 or 1
- Adequate end organ function

Key Exclusion Criteria

- Progressive disease within 6 months of completion of curatively intended systemic treatment for locoregionally advanced SCCHN
- Radiation or other non-systemic therapy within 2 weeks of randomization
- Diagnosis of immunodeficiency, or use of immunosuppresive therapy within 14 days of first dose of study drug

References

1. Siegel R, Naishadham D, and Jemal A, Cancer statistics, 2013. CA Cancer *J. Clin*, 2013. 63(1): p. 11-30. **2.** Price KA and Cohen EE, Current treatment options for metastatic head and neck cancer. Curr Treat Options *Oncol*, 2012. 13(1): p. 35-46. **3.** Keynote 048. 1200/JCO.2019.37.15_suppl.6000 *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 6000-6000. **4.** Aggarwal C et al, Open-Label, Dose Escalation Study of Enoblituzumab in Combination with Pembrolizumab in Patients with Select Solid Tumors. 33rd Annual Meeting of The Society for Immunotherapy of Cancer Washington, DC, USA November 7–11, 2018. **5.** Cohen EE, Harrington KJ, Tourneau C, Dinis J, Licitra L, Ahn M, et al., Head and Neck Cancer, Excluding Thyroid. 2017 Annual Congress of the European Society for Medical Oncology. **6.** Mehnert J et. al. 33rd Annual Meeting of The Society for Immunotherapy of Cancer Washington, DC, USA November 7–11, 2018. **7.** Yanesaka et al, *Clinical Cancer Research* 2018. **8.** Mehnert J et. al. 33rd Annual Meeting of The Society for Immunotherapy of Cancer, Washington, DC, USA November 7–11, 2018. **9.** Catenacci D et al, Margetuximab Plus Pembrolizumab in *ERBB2*-Amplified PD-L1+ Gastroesophageal Adenocarcinoma Post Trastuzumab. *American Society of Clinical Oncology*, June 1-5, 2018. **10.** Unpublished. **11.** Shenderov E et al, Phase II Neoadjuvant and Immunologic Study of B7-H3 Targeting with Enoblituzumab in Localized Intermediate- and High-Risk Prostate Cancer. 33rd Annual Meeting of The Society for Immunotherapy of Cancer, Washington, DC, USA November 7–11, 2018. **12.** Lee YH et al, Inhibition of the B7-H3 immune checkpoint limits tumor growth by enhancing cytotoxic lymphocyte function. *Cell Res* 2017 Aug;27(8): 1034-1045. **13.** Hsu J et al, Contribution of NK cells to immunotherapy mediated by PD-1/PD-L1 blockade. *J Clin Invest*. 2018;128(10):4654–466.

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