A Phase 1, Open-Label, Dose Escalation Study of Enoblituzumab in Combination with Pembrolizumab in Patients with Select Solid Tumors

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Poster 024

Charu Aggarwal[1], Anthony Joshua[2], Robert Ferris[3], Scott Antonia[4], Osama Rahma[5], Anthony Tolcher[6], Roger B. Cohen[7], Yanyan Lou[8], Ralph Hauke[9], Nicholas Vogelzang[10], Dan Zandberg[11], Arash Kalebasty[12], Victoria Atkinson[13], Alex Adjei[14], Mahesh Seetharam[15], Ariel Birnbaum[16], Andrew Weickhardt[17], Vinod Ganju[18], Riva Bondarenko[19], Linda Peng[19], Tony Wu[19], Scott Currence[19], Jan Baughman[19], Ezio Bonvini[19], Stacie Goldberg[19], Jon Wigginton[19], Nehal Lakhani[20]

[1]University of Pennsylvania/Abramson Cancer Center, Philadelphia, PA; [2]St. Vincent's Hospital, Sydney, Australia; [3]University of Pittsburgh, Pittsburgh, PA; [4]Moffitt Cancer Center, Tampa, FL; [5]Dana Farber Cancer Institute, Boston, MA; [6]START, San Antonio, TX; [7]University of Pennsylvania, Philadelphia, PA; [8]Mayo Clinic, Jacksonville, FL; [9]Nebraska Cancer Specialists, Omaha, NE; [10]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [11]University of Maryland, Baltimore, MD; [12]Norton Cancer Institute, Louisville, KY; [13]University of Queensland, Brisbane, Australia; [14]Mayo Clinic, Rochester, MN; [15]Mayo Clinic, Scottsdale, AZ; [16]Rhode Island Hospital, Providence, RI; [17]Olivia Newton-John Cancer Research Institute, Melbourne, Australia; [18]Peninsula and Southeast Oncology, Frankston, Australia; [19]MacroGenics, Inc., Rockville, MD; [20]START Midwest, Grand Rapids, MI

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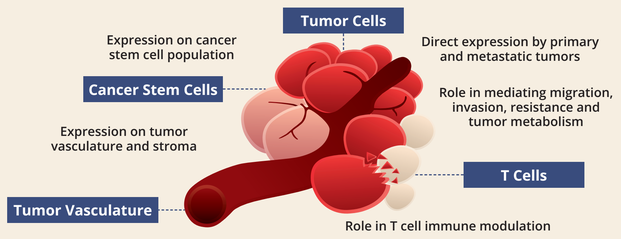
Background

Rationale for Targeting B7-H3 in Cancer



- B7-H3 expression associated w/adverse clinical features/outcome in various solid tumors
- B7-H3 expression may inversely correlate w/responsiveness to anti-PD-1 therapy*

* Yonesaka, et al., CCR, 2018

High Rate of B7-H3 Positivity Across Broad Range of Solid Tumors

Majority of B7-H3 positive tumors express high levels of B7-H3 (i.e., 2+ or above)

Fixed Tumor MicroArray	IHC Summary of >1,400 Tumor Tissue Samples Screened			
	B7-H3 Positive*		2+ or Above	
Potential Indications:				
Head and Neck	**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	**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%

Enoblituzumab + Pembrolizumab Combination Study Indications Evaluated

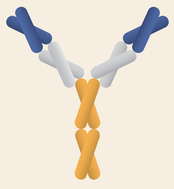
- Limited expression in normal tissue ➔ favorable profile for targeting B7-H3 with CD3 bispecific (orlotamab, SITC P305, P366) and/or ADC (MGC018, SITC P306)

*B7-H3 positivity reflects any grade staining via fixed tumor microarray; B7-H3 is expressed on tumor cells as well as tumor-associated vasculature.

Enoblituzumab: Fc-optimized, Anti-B7-H3 Antibody

Candidate:
- Humanized, Fc-optimized anti B7-H3 antibody

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



Key Clinical Programs:
- Phase 1b combination study (with pembrolizumab) enrolled
- Investigator-sponsored study ongoing in neoadjuvant prostate cancer (SITC P338)
- Combination study with anti-PD-1 (MGA012*) planned

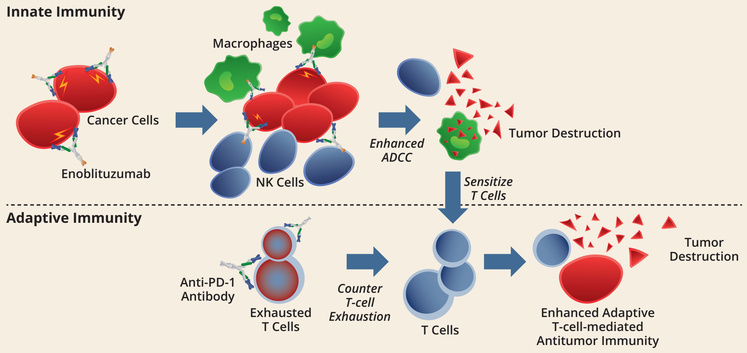
*Also known as INCMGA00012; see SITC P669, P313, P336.

Rationale to Combine Enoblituzumab with Anti-PD-1

<u>Hypothesis</u>: 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 Fc-optimized antibody (margetuximab, anti-HER2) combined with pembrolizumab benchmarked favorably vs. historical anti-PD-1 monotherapy experience in gastric carcinoma[1]
- Preliminary data indicates enoblituzumab can modulate T-cell repertoire in treated patients
  - Enhanced peripheral T-cell clonality and clone abundance[2]
  - Enhanced local T-cell infiltration in prostate cancer[3]
- Combined targeting of B7-H3 and PD-1/PD-L1 in preclinical tumor models can mediate greater antitumor activity than either single agent alone[4]
- 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[5]

Coordinate engagement of innate and adaptive immunity to mediate tumor regression



1. Presented at ASCO 2018, 4030. **2.** Unpublished. **3.** Presented at SITC 2018, P338. **4.** Lee, et al., Cell Research, 2017. **5.** Hsu, et al., J Clin Invest, 2018.

Methods

Enoblituzumab + Pembrolizumab Study Design

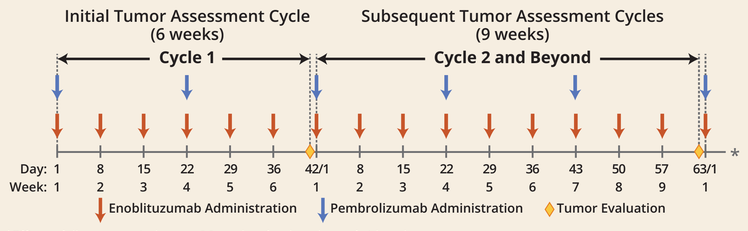
Dose Escalation + Expansion

Dose Escalation
(Dosing completed, No MTD defined)

Cohorts 1–3
3, 10, 15 mg/kg enoblituzumab + 2 mg/kg pembrolizumab
B7-H3 Positive Tumors
3+3+3 Design

Dose Expansion
- NSCLC (anti-PD-1/PD-L1 Naïve, PD-L1<1%)
- NSCLC (Post anti-PD-1/PD-L1)
- SCCHN (anti-PD-1/PD-L1 Naïve)
- SCCHN (Post anti-PD-1/PD-L1)
- Melanoma (Post anti-PD-1/PD-L1)
- Urothelial (Post anti-PD-1/PD-L1)

Dosing and Cycle Schedule



*Efficacy follow-up period: up to 96 weeks after last dose of either drug.

Results

Safety Profile

Drug-Related Adverse Event (≥5% of Patients)	Number (%) of Patients	
	All Grades Total (N=133)	≥ Grade 3 (N=133)
Any adverse event	115 (86.5)	36 (27.1)
Infusion-related reaction	73 (54.9)	9 (6.8)
Fatigue	37 (27.8)	2 (1.5)
Rash	14 (10.5)	1 (0.8)
Nausea	12 (9.0)	0
Pyrexia	12 (9.0)	0
Lipase increased	11 (8.3)	8 (6.0)
Arthralgia	10 (7.5)	0
Decreased appetite	9 (6.8)	2 (1.5)
Diarrhea	9 (6.8)	1 (0.8)
Hypothyroidism	8 (6.0)	0
Anemia	7 (5.3)	1 (0.8)
Pneumonitis	7 (5.3)	2 (1.5)
Chills	7 (5.3)	0

Immune-Related Adverse Events of Special Interest (AESI)	Number (%) of Patients	
	All Grades Total (N=133)	≥ Grade 3 (N=133)
Pneumonitis	5 (3.8)	2 (1.5)
Myocarditis	2 (1.5)	1 (0.8)
Diarrhea	1 (0.8)	1 (0.8)
Adrenal insufficiency	1 (0.8)	1 (0.8)
Colitis	1 (0.8)	0

- Drug-related AE:
  - Leading to treatment discontinuation: 6.8%
  - Leading to death: 0.8% (1 patient with pneumonitis)
- Nature of events consistent with enoblituzumab or pembrolizumab alone

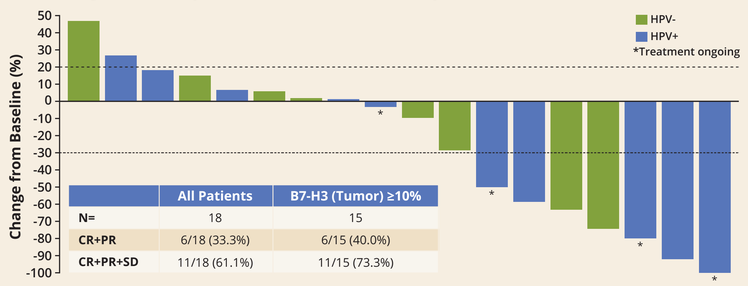
Summary of Overall Best Response Status (RECIST)

	Anti-PD-1/PD-L1 Naïve		Prior Anti-PD-1/PD-L1			
Indication	SCCHN	NSCLC	SCCHN	NSCLC	Urothelial Cancer	Cutaneous Melanoma
Total Treated Patients	21	16	24	25	21	14
Age (years) Mean ± SD Median (Range)	62.8 ± 9.13 65.0 (44–74)	65.7 ± 7.75 65.0 (50–79)	62.7 ± 9.99 62.0 (34–76)	64.2 ± 8.73 63.0 (50–83)	67.1 ± 9.39 70.0 (40–79)	60.5 ±15.24 63.0 (25–79)
Gender Female Male	3 (14.3) 18 (85.7)	8 (50.0) 8 (50.0)	2 (8.3) 22 (91.7)	10 (40.0) 15 (60.0)	6 (28.6) 15 (71.4)	3 (21.4) 11 (78.6)
Response Evaluable	18	14	19	21	17	13
PR (confirmed)	6/18 (33.3%)	5/14 (35.7%)	0	1/21 (4.8%)	1/17 (5.9%)	1/13 (7.7%)
SD	5/18 (27.8%)	8/14 (57.1%)	9/19 (47.4%)	12/21 (57.1%)	8/17 (47.1%)	5/13 (38.5%)
PD	7/18 (38.9%)	1/14 (7.1%)	10/19 (52.6%)	7/21 (33.3%)	8/17 (47.1%)	6/13 (46.2%)
NE	0	0	0	1/21 (4.8%)	0	1/13 (7.7%)

PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Evaluable.

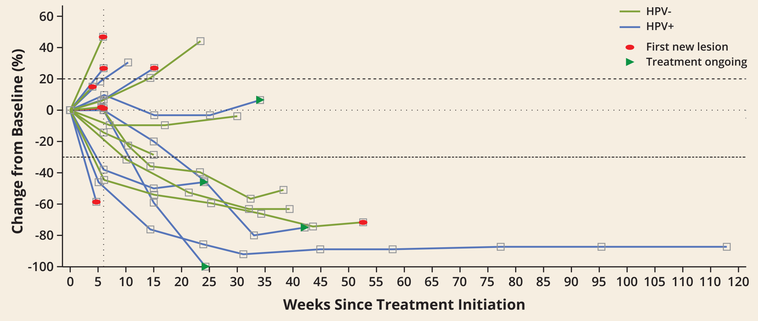
Antitumor Activity in SCCHN Patients, Anti-PD-1/PD-L1 Naïve

Tumor regression in patients with SCCHN, irrespective of HPV status



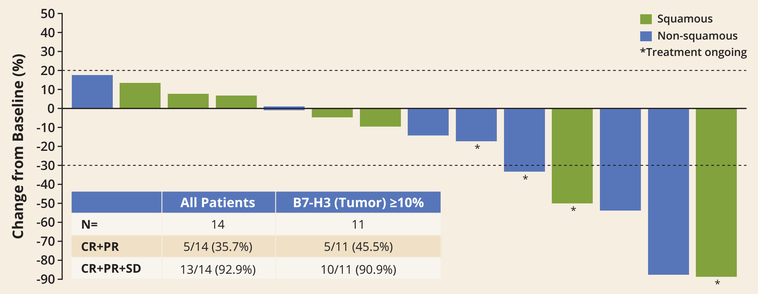
Antitumor Activity in SCCHN Patients, Anti-PD-1/PD-L1 Naïve

Durable objective responses and disease stabilization



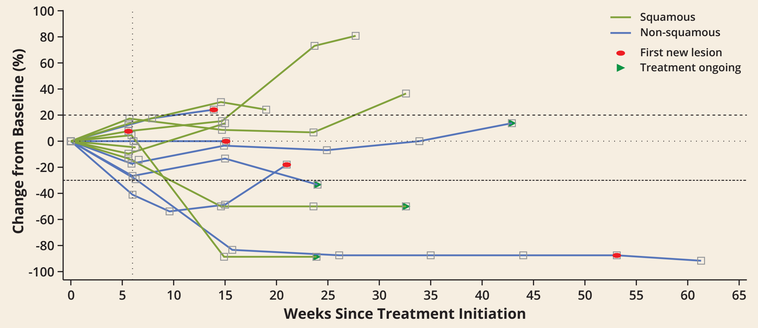
Antitumor Activity in NSCLC Patients, Anti-PD-1/PD-L1 Naïve, PD-L1<1%

Tumor regression in NSCLC patients who are PD-L1 negative (*i.e.*, <1%)



Antitumor Activity in NSCLC Patients, Anti-PD-1/PD-L1 Naïve, PD-L1<1%

Durable objective responses and disease stabilization



Enoblituzumab + Pembrolizumab Combination Benchmarks Favorably

SCCHN	Study Results			
Agent (Study)	**Enoblituzumab + Pembrolizumab**	**Nivolumab (CM-141)[1]**	**Pembrolizumab (KN-012)[2]**	**Pembrolizumab (KN-040)[3]**
N	18	240	174	247
ORR	33.3%	13%	16%	15%

NSCLC	Study Results			
Agent (Study)	**Enoblituzumab + Pembrolizumab**	**Nivolumab (CM-057)[4]**	**Pembrolizumab (CM-017)[5]**	**Pembrolizumab (KN-001)[6]**
Histology	Both	Non-Squamous	Squamous	Both
N	14	108	54	87
ORR	35.7%	9%	17%	8%

1. Ferris, et al., 2016, *N Eng J Med* 375: 1856. **2.** Keytruda® package insert. **3.** Cohen, et al., 2017, ESMO LBA45. **4.** Borghaei, et al., 2015, *NEJM*. **5.** Brahmer, et al., 2015, *NEJM*. **6.** Garon, et al., 2015, *NEJM*.

Data cutoff (all analyses) 12 October 2018

Conclusions

- Enoblituzumab/pembrolizumab combination demonstrates acceptable safety profile
- Rate of immune-related adverse events comparable to experience w/anti-PD-1 monotherapy
- In anti-PD-1/PD-L1 naïve patients treated with enoblituzumab/pembrolizumab, objective response rates benchmark favorably with historical experience with anti-PD-1 monotherapy
  - SCCHN (post platinum chemotherapy): 33.3%
  - NSCLC (PD-L1 <1%): 35.7%
- Further investigation of enoblituzumab + anti-PD-1 combination is warranted in patients with SCCHN and NSCLC, including in combination with chemotherapy
- Given expression patterns of B7-H3, further investigation of combination of enoblituzumab and anti-PD-1 is warranted in other tumor types, including both checkpoint-naïve and experienced populations

The Sponsor thanks the patients and their families for participating in this study.