P669

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First-in-Human Phase 1 Study of INCMGA00012 in Patients With Advanced Solid Tumors: Interim Results of the Cohort Expansion Phase

Janice M. Mehnert,[1] Anthony M. Joshua,[2] Nehal Lakhani,[3] Udai Banerji,[4] Drew W. Rasco,[5] Iwona Lugowska,[6] Monika Tomaszewska-Kiecana,[7] Elena Garralda,[8] Deanna L. Kornacki,[9] Bradley J. Sumrow,[10] Nawel Bourayou,[9] Chuan Tian,[9] John Powderly[11]

[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [2]Kinghorn Cancer Centre, St Vincents Hospital, Sydney, Australia; [3]START – Midwest, Grand Rapids, MI, USA; [4]The Royal Marsden, London, UK; [5]START – South Texas Accelerated Research Therapeutics, LLC, San Antonio, TX, USA; [6]Early Phase Clinical Trials Unit, Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland; [7]BioVirtus Research Site, Otwock, Poland; [8]Vall D'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [9]Incyte Corporation, Wilmington, DE, USA; [10]MacroGenics, Inc, Rockville, MD, USA; [11]Carolina BioOncology Institute, Huntersville, NC, USA

Introduction

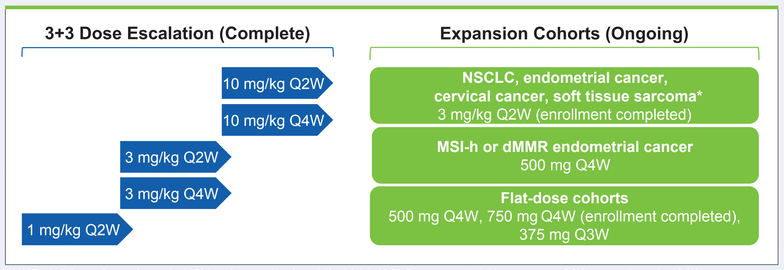
- In recent years, programmed cell death 1 (PD-1) inhibitors have quickly become an important treatment approach in different cancer settings[1]
- INCMGA00012 (also known as MGA012) is a humanized, hinge-stabilized immunoglobulin G4 (IgG4) monoclonal antibody that blocks the interaction of PD-1 with programmed cell death ligands 1 and 2 (PD-L1 and PD-L2), interrupts PD-1 signaling, enhances antigen-induced interferon-γ release, and has a favorable preclinical profile[2]
- The first-in-human phase 1 study (NCT03059823) evaluates INCMGA00012 monotherapy in patients with advanced solid tumors
  - Results of the dose-escalation portion have previously been presented[3]
  - Here we report the interim results from the cohort expansion portion of this study

Objectives

- To evaluate safety, pharmacokinetics, and preliminary antitumor activity of INCMGA00012 (body-weight and flat dosing) in selected solid tumors

Methods

Figure 1. Overall Study Design



dMMR, deficient mismatch repair; MSI-h, microsatellite instability-high; NSCLC, non-small cell lung cancer; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.
* The following histologies of soft tissue sarcoma are allowed: undifferentiated pleomorphic sarcoma (including malignant fibrous histiocytoma), de-differentiated or poorly differentiated liposarcoma, synovial sarcoma, or rhabdomyosarcoma.

Eligibility Criteria (Cohort Expansion Phase)

- Tumor-specific cohorts: patients with unresectable, locally advanced, or metastatic non-small cell lung cancer (NSCLC), endometrial cancer, cervical cancer, and soft tissue sarcoma who have progressed during or following 1–5 prior treatments
  - Patients with NSCLC and known targetable aberrations (*EGFR, ALK, ROS1*) should have received all approved therapy known to confer clinical benefit prior to enrollment
  - Endometrial cancer patients (in the weight-based dosing group) were eligible regardless of microsatellite instability-high (MSI-h) or deficient mismatch repair (dMMR) status
  - Sarcoma cohort was limited to selected subtypes **(Figure 1)**
- Flat-dose cohorts: patients with carcinoma of any tumor histology that has progressed during or following 1–5 prior treatments consistent with the standard of care for respective tumor types
- All patients must have had measureable disease per Response Evaluation Criteria in Solid Tumors (RECIST v1.1), Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function and bone marrow reserve, and available tumor specimen for retrospective determination of PD-L1 expression
- Patients were excluded if they had symptomatic or untreated central nervous system metastases; prior treatment with immune checkpoint inhibitor (eg, anti–PD-1/PD-L1, anti-cytotoxic T-lymphocyte–associated protein 4); clinically significant cardiovascular, gastrointestinal, or pulmonary conditions; high dose of systemic corticosteroids or immune suppressive drugs within the 14 days prior to study drug initiation; or history of suspected autoimmune disease

Assessments

- Safety and tolerability were evaluated based on adverse events (AEs) per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
  - AEs of special interest include grade ≥3 infusion-related reactions or cytokine release syndrome; grade ≥2 immune-related AEs; and abnormal liver enzymes that meet the criteria for potential Hy's law
- Response was assessed by the investigator every 8 weeks for the first 24 weeks and every 12 weeks thereafter, per RECIST version 1.1; treatment post progression was allowed per immune-related RECIST (irRECIST)
- For pharmacokinetic evaluations, serum concentrations of INCMGA00012 were monitored using an enzyme-linked immunosorbent assay
- PD-L1 status was determined retrospectively on available tissues by immunohistochemistry (IHC) using the PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA, USA)

Results

Patients

- As of the September 23, 2018 data cutoff, 132 patients were enrolled and treated with INCMGA00012 3 mg/kg every 2 weeks (Q2W) in tumor-specific cohorts (35 NSCLC, 34 cervical cancer, 34 sarcoma, 29 endometrial cancer) **(Table 1)**
- Additionally, 15 patients with different tumor types were enrolled in each flat-dose cohort of 500 mg every 4 weeks (Q4W) and 750 mg Q4W
- Overall, 107/162 (66%) patients had discontinued treatment as of the data cutoff, primarily due to radiographic progression (40%) and clinical progression (11%)

Table 1. Baseline Demographics (Safety-Evaluable Population [N=162])

Variable	INCMGA00012 3 mg/kg Q2W: NSCLC (n=35)	Cervical Cancer (n=34)	Soft Tissue Sarcoma (n=34)	Endometrial Cancer (n=29)	INCMGA00012 500 mg Q4W (n=15)	INCMGA00012 750 mg Q4W (n=15)
Median (range) age, y	63 (37–75)	52 (29–81)	44 (18–86)	64 (46–84)	60 (36–76)	56 (30–82)
Gender, n (%)						
Female	12 (34)	34 (100)	15 (44)	29 (100)	9 (60)	8 (53)
Male	23 (66)	0	19 (56)	0	6 (40)	7 (47)
Race, n (%)						
White	34 (97)	30 (88)	29 (85)	23 (79)	11 (73)	12 (80)
Other	1 (3)	4 (12)	5 (15)	6 (21)	4 (27)	3 (20)
ECOG PS*, n (%)						
0	1 (3)	16 (47)	15 (44)	7 (24)	7 (47)	5 (33)
1	34 (97)	17 (50)	18 (53)	22 (76)	8 (53)	10 (67)
MSI status, n (%)						
MSI-h	N/A	N/A	N/A	4 (14)	N/A	N/A
MSS				4 (14)		
Unknown				21 (72)		
PD-L1 expression, n (%)						
TPS ≥1%	8 (23)†	8 (24)	1 (3)	3 (10)	0	0
TPS 0%	16 (46)	13 (38)	31 (91)	22 (76)	0	0
Unknown‡	11 (31)	13 (38)	2 (6)	4 (14)	15 (100)	15 (100)

ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-h, microsatellite instability-high; MSS, microsatellite stable; N/A, not applicable; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q4W, every 4 weeks; TPS, tumor proportion score.
* 1 patient with cervical cancer and 1 with soft tissue sarcoma had ECOG PS of 2.
† Of 8 patients with TPS ≥1%, 4 had TPS 1–49% and 4 had TPS ≥50%.
‡ Analysis ongoing, or unavailable data at the time of analysis.

Exposure and Safety

- Patients received a median (range) of 6 (1–24) infusions of INCMGA00012 3 mg/kg Q2W, 2 (1–8) infusions of 500 mg Q4W, and 3 (1–7) infusions of 750 mg Q4W

Table 2. Summary of AEs (Safety-Evaluable Population [N=162])

AE, n (%)	3 mg/kg Q2W (n=132)	500 mg Q4W (n=15)	750 mg Q4W (n=15)
AE (all grade, related and unrelated)	108 (82)	15 (100)	13 (87)
Treatment-related AE	65 (49)	8 (53)	6 (40)
Grade ≥3 AE (related and unrelated)	46 (35)	5 (33)	5 (33)
Grade ≥3 treatment-related AE	12 (9)	1 (7)	0
Serious AE (all grade, related and unrelated)	33 (25)	3 (20)	3 (20)
Serious treatment-related AE	9 (7)	1 (7)	1 (7)
Non-fatal AEs leading to discontinuation	7* (5)	1† (7)	0
AEs leading to death (all were unrelated to treatment)	5‡ (4)	1§ (7)	0
AESI	16 (12)	3 (20)	2 (13)

AE, adverse event; AESI, AE of special interest; Q2W, every 2 weeks; Q4W, every 4 weeks.
* 1 grade 4 and 2 grade 3 colitis (n=3 total); grade 3 brain edema, grade 3 transaminase increased, grade 2 myocarditis, and grade 1 peripheral edema (n=1 each).
† Grade 2 bilateral iritis.
‡ Cardiac failure and pulmonary hypertension (n=1); cardiovascular insufficiency, hemiparesis, nephritis, pneumothorax (n=1 each).
§ Sepsis.

Table 3. Adverse Events of Special Interest

AE, n (%)	3 mg/kg Q2W (n=132)	500 mg Q4W (n=15)	750 mg Q4W (n=15)
Colitis	3 (2)	0	0
Infusion-related reaction	3 (2)	0	0
Liver function abnormality*	3 (2)	2 (13)	0
Endocrine disorders	2 (2)	1 (7)	2 (13)
Rash†	2 (2)	0	0
Diarrhea	1 (1)	0	0
Hyperglycemia	1 (1)	0	0
Myocarditis	1 (1)	0	0
Nephritis	1 (1)	0	0
Pain in extremity	1 (1)	0	0

AE, adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks.
* Liver function abnormality includes the following Medical Dictionary for Regulatory Activities (MedDRA) terms: autoimmune hepatitis, cholangitis, alanine aminotransferase increased, blood bilirubin increased, and transaminases increased.
† Rash includes the following MedDRA terms: rash and rash maculopapular.

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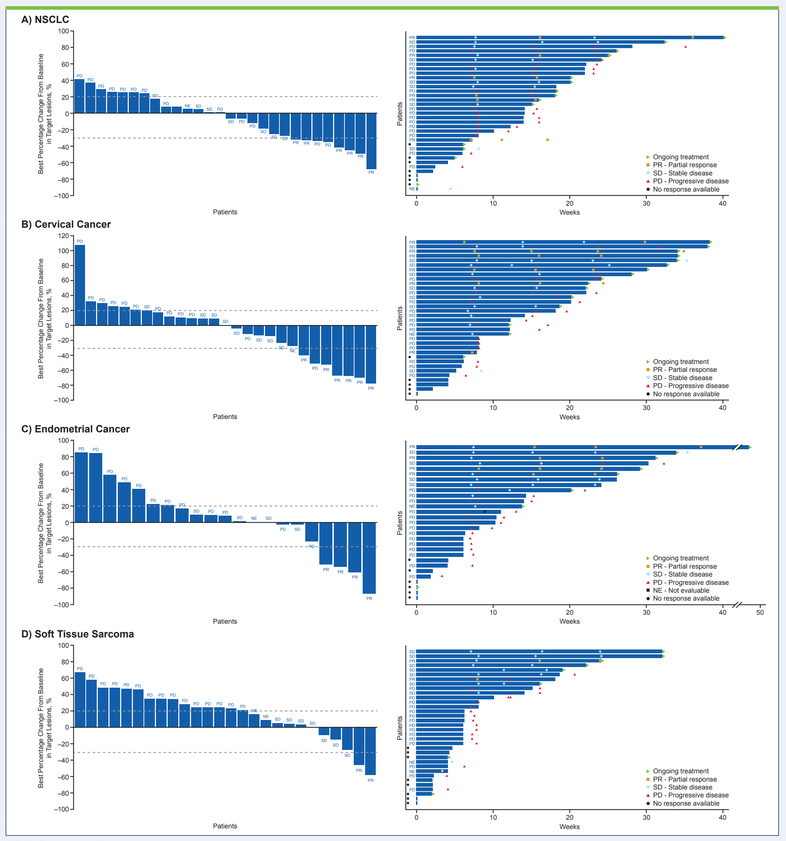
Interim Antitumor Activity

Figure 2. Best Percentage Change From Baseline in Target Lesions (Left) and Duration of Treatment (Right)



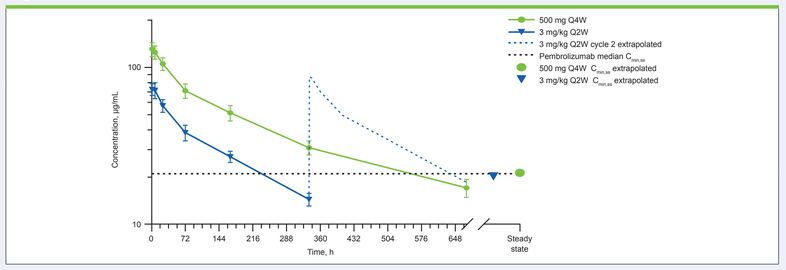
NSCLC, non-small cell lung cancer.

- Responses were also observed in the tumor-agnostic, flat-dosing expansion cohorts (ovarian, breast, and endometrial cancer)

Pharmacokinetics

- The pharmacokinetics of the 500-mg Q4W flat dose schedule were comparable with weight-based dosing at 3 mg/kg Q2W **(Figure 3)** and provided comparable trough exposure to that reported for pembrolizumab[4]
- The half-life observed with the 3 mg/kg Q2W and 500 mg Q4W was 17 days and 14 days, respectively

Figure 3. INCMGA00012 Pharmacokinetics



$C_{min,ss}$, minimum steady-state plasma drug concentration during a dosage interval; Q2W, every 2 weeks; Q4W, every 4 weeks.

Conclusions

- In the cohort expansion portion of this Phase 1 study, INCMGA00012 has been generally well tolerated in both weight-based and flat dosing schedules
- Immune-related AE profile is acceptable and as expected for a PD-1/PD-L1 inhibitor
- This interim analysis shows confirmed RECIST responses in all tumor-specific expansion cohorts
- Pharmacokinetic properties with flat dosing are favorable for further development
- This study is being expanded to evaluate safety of the 500-mg Q4W dose in a larger cohort of MSI-h or dMMR endometrial cancer patients, as well as a Q3W flat dosing regimen in a tumor-agnostic population
- INCMGA00012 is being investigated as monotherapy and in combination with other treatment modalities in clinical trials – 5 of which are also presented at SITC 2018 (P336, P313, P304, P305, P306)

Disclosures

JMM has served as a consultant for Amgen, Boehringer Ingelheim, and Merck Sharp & Dohme; and received honoraria from EMD Serono and Genentech. AMJ has no disclosures to declare. NL is a PI on trials supported by ALX Therapeutics, Amgen, Arqule, Ascentage, Apexian, Asana Biosciences, Formation Biologics, Beigene, Constellation Pharma, CytomX, Daiichi Sankyo, Forty Seven, Inc, InhibRx, Incyte, MacroGenics, Inc, Loxo, Livzon Mabpharm, Merck, Northern Biologics, Pfizer, Regeneron, Symphogen, and TaiRx, Inc. UB has served as a consultant for Astex Pharmaceuticals and Phoenix Solutions, and received honoraria from Lilly. DWR has served as a consultant for Boehringer Ingelheim, Lilly, and TaiRx, Inc. IL has received honoraria from Bristol-Myers Squibb and Roche, and has served on the speaker bureau for Bristol-Myers Squibb. MT-K has no disclosures to declare. EG has served as a consultant for Boehringer Ingelheim, Janssen, and Roche. DLK, NB, and CT are paid employees and stockholders at Incyte Corporation. BJS is a paid employee and stockholder at MacroGenics, Inc. JP has served as a consultant for AstraZeneca/MedImmune, Bristol-Myers Squibb, Curis, Genentech/Roche, and TopAlliance BioSciences Inc; served on the speaker bureaus for Bristol-Myers Squibb, Dendreon, Genentech/Roche, and Merck; is an employee of BioCytics and Carolina BioOncology Institute; and owns stock or other ownership interests in BioCytics, Bluebird Bio, Carolina BioOncology Institute, Juno Therapeutics, Kite Pharma, Lion Biotechnologies, and ZIOPHARM Oncology.

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