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A Phase 1 Study of INCMGA00012, a PD-1 Inhibitor, in Patients With Advanced Solid Tumors: Preliminary Results for Patients With Advanced Cervical Cancer (POD1UM-101)

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Introduction

- Cervical cancer is the fourth most common cause of cancer-related deaths in women worldwide[1]
- Recurrent or metastatic cervical cancer is incurable with limited treatment options and poor prognosis with median survival of 8–13 months[2,3]
- Programmed cell death 1 (PD-1) inhibitors have demonstrated clinical efficacy in human papillomavirus (HPV)–related tumors with a response rate of 14.3% in patients with pretreated programmed cell death ligand 1 (PD-L1)–positive metastatic cervical cancer[4]
- INCMGA00012 is an investigational humanized immunoglobulin G4 monoclonal antibody against human PD-1 that prevents the interaction between PD-1 and its ligands to sustain/restore T-cell antitumor function[5]
- The ongoing cohort-expansion phase of the first-in-human POD1UM-101 study (NCT03059823) has previously reported favorable safety profile and encouraging preliminary antitumor activity in patients with non-small cell lung cancer and endometrial cancer[6]
- The present analysis reports updated safety and activity data from INCMGA00012 in the cohort of patients with previously treated advanced cervical cancer

Objectives (Expansion Phase)

Primary

- Safety and tolerability

Secondary

- Pharmacokinetics and immunogenicity (previously reported), antitumor activity by objective response rate, duration of response, progression-free survival, and overall survival

Exploratory

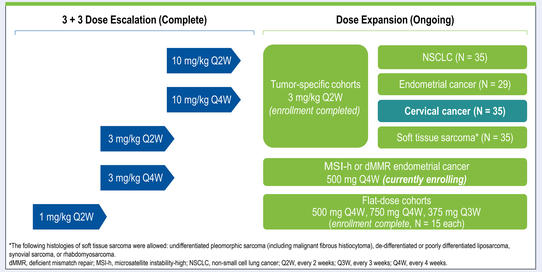
- Determination of PD-L1 expression and immune cell infiltration and their relationship to clinical response

Methods

Study Design

- Phase 1, open-label, dose-escalation, and cohort-expansion study **(Figure 1)**
- Patients in tumor-specific cohorts received INCMGA00012 at 3 mg/kg every 2 weeks (Q2W) as an intravenous infusion up to 26 cycles (a cycle being defined as 4 weeks)
- An additional cohort in microsatellite instability-high or deficient mismatch repair endometrial cancer is ongoing at the flat dose (recommended phase 2 dose) of 500 mg every 4 weeks

Figure 1. POD1UM-101 Study Design



*The following histologies of soft tissue sarcoma were allowed: undifferentiated pleomorphic sarcoma (including malignant fibrous histiocytoma), de-differentiated or poorly differentiated liposarcoma, synovial sarcoma, or rhabdomyosarcoma.
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.

Eligibility Criteria (Cervical Cancer Cohort)

Inclusion

- Patients ≥18 years of age with unresectable, locally advanced, or metastatic cervical cancer who have progressed during or following 1–5 prior treatments
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group performance status 0 or 1
- Adequate organ function and bone marrow reserve
- Tumor specimen collection for retrospective central PD-L1 expression testing

Exclusion

- Patients with symptomatic or untreated central nervous system metastases
- Prior treatment with immune checkpoint inhibitor
- Clinically significant cardiovascular, gastrointestinal, or pulmonary conditions
- High dose of systemic corticosteroids or immunosuppressant drugs within 14 days prior to study drug initiation
- History of suspected autoimmune disease

Evaluations

- Safety and tolerability were evaluated based on adverse events (AEs) per Common Terminology Criteria for Adverse Events 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 assessed by the investigator every 8 weeks for the first 24 weeks and every 12 weeks thereafter, per RECIST v.1.1; treatment post progression was allowed per immune-related RECIST (irRECIST)
- PD-L1 status was determined retrospectively on available tissues by immunohistochemistry (IHC) using the PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA)

Results

Patients

- As of September 23, 2019, the data cutoff date, 35 patients were enrolled in the cervical cancer cohort and treated with INCMGA00012
- Patient demographics and disease characteristics are presented in **Table 1**
- At the data cutoff, 6 patients (17%) were on treatment; 1 patient (3%) completed study treatment
  - 28 of 35 patients (80%) discontinued treatment, primarily (60%) owing to progression; 11% discontinued owing to AEs

Drug Exposure

- Patients received a median (range) of 10 (1–47) infusions of INCMGA00012 3 mg/kg Q2W
- Median (range) duration of treatment was 4.4 (0.03–21.4) months

Table 1. Baseline Demographics and Disease Characteristics of the Cervical Cancer Cohort (Safety-Evaluable Population)

Variable	N = 35
Age, median (range), y	51 (29–81)
Race, n (%)	
White	31 (89)
Other*	4 (11)
ECOG PS,† n (%)	
0	17 (49)
1	17 (49)
Histology, n (%)	
Squamous	18 (51)
Adenocarcinoma	15 (43)
Adenosquamous	1 (3)
Missing	1 (3)
PD-L1 expression,‡ n (%)	
TPS ≥1%	17 (49)
TPS <1%	12 (34)
Unknown	6 (17)
Prior systemic therapy, n (%)	
Any	35 (100)
Prior platinum	35 (100)
Prior bevacizumab	7 (20)
Prior radiotherapy, n (%)	32 (91)
Prior surgery, n (%)	19 (54)

*Includes black (n = 1), Asian (n = 1), and other (n = 2).
†One patient had ECOG PS of 2.
‡Results based on central testing. For patients with unknown status, either no tumor tissue was received (n = 2) or the sample was not evaluable (n = 4).
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

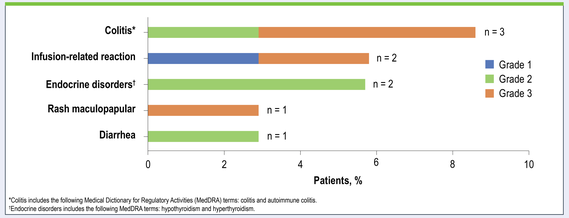
Safety and Tolerability

Table 2. Summary of Adverse Events for the Cervical Cancer Cohort (Safety-Evaluable Population)

Adverse Events, n (%)	N = 35
Adverse event (all grade, treatment-related and -unrelated)	34 (97)
Treatment-related adverse event	24 (69)
Grade ≥3 adverse events (treatment-related and -unrelated)	17 (49)
Grade ≥3 treatment-related adverse event	6 (17)
Serious adverse events (all grade, treatment-related and -unrelated)	11 (31)
Serious treatment-related adverse event	4 (11)
Adverse events leading to discontinuation	5 (14)
Adverse events leading to death (unrelated to treatment)*	1 (3)
Adverse events of special interest	8 (23)

*One patient had an adverse event of cardiac failure that led to a fatal outcome.

Figure 2. Adverse Events of Special Interest (Maximum Grade)



*Colitis includes the following Medical Dictionary for Regulatory Activities (MedDRA) terms: colitis and autoimmune colitis.
†Endocrine disorders includes the following MedDRA terms: hypothyroidism and hyperthyroidism.

Antitumor Activity

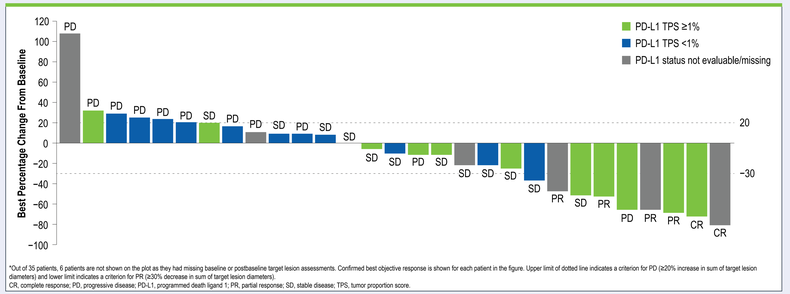
- Confirmed responses per RECIST were observed in 6 of the 35 treated patients **(Table 3)**
  - Out of the 6 responders, 3 had PD-L1–positive tumors (remaining 3 were not evaluable [NE]/missing)
  - An additional 12 patients had stable disease for an overall disease control rate of 51%
- The best percentage change from baseline in target lesion size is shown in **Figure 3**
- Treatment durations of individual evaluable patients are shown in **Figure 4**
  - Median duration of response was not reached (95% confidence interval, 10.3–NE months)
  - Five of the 6 responders remain on treatment
  - Responses have been followed for a median (range) of 12 (9.3–18.3) months

Table 3. Summary of Overall Response in the Cervical Cancer Cohort (per RECIST v1.1)

Variable	N = 35
Objective response rate (95% CI), %	17.1 (6.6–33.6)
Best objective response, n (%)	
Complete response	2 (6)*
Partial response	4 (11)*
Stable disease	12 (34)
Progressive disease	13 (37)
Missing	4 (11)†
Median duration of response (95% CI), months	NE (10.3–NE)
Median progression-free survival (95% CI), months	3.6 (1.8–5.4)
Median overall survival (95% CI), months	NE (12.1–NE)

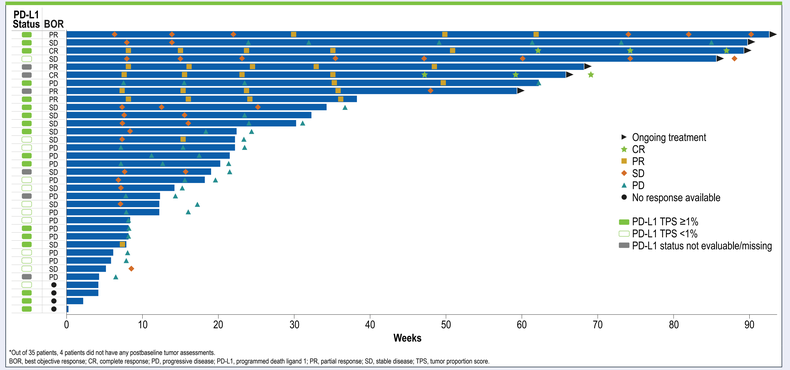
*Confirmed responses.
†Patients had no postbaseline assessment available.
CI, confidence interval; NE, not evaluable; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 3. Best Percentage Change From Baseline in Target Lesion Size (Sum of Diameters) for Individual Patients*



*Out of 35 patients, 6 patients are not shown on the plot as they had missing baseline or postbaseline target lesion assessments. Confirmed best objective response is shown for each patient in the figure. Upper limit of dotted line indicates a criterion for PD (≥20% increase in sum of target lesion diameters) and lower limit indicates a criterion for PR (≥30% decrease in sum of target lesion diameters).
CR, complete response; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportion score.

Figure 4. Duration of Treatment and Best Objective Responses*



*Out of 35 patients, 4 patients did not have any postbaseline tumor assessments.
BOR, best objective response; CR, complete response; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportion score.

Conclusions

- **INCMGA00012 was generally well tolerated in patients with locally advanced metastatic cervical cancer and has shown consistent safety profile with previously reported data[5,6]**
  - **Immune-related AEs were consistent with available clinical experience with PD-1/PD-L1 inhibitors**
- **Preliminary activity in the cohort of patients with previously treated recurrent or metastatic cervical cancer is encouraging and consistent with previously reported activity from immune checkpoint inhibitors in this setting[4]**
  - **Durable confirmed responses were achieved in 17.1% of patients (2 complete responses, 4 partial responses)**
  - **Disease control rate was 51%**
- **Further clinical investigation of INCMGA00012 in cervical cancer is warranted**

Disclosures

Mehnert: Consultant – *Amgen, Boehringer Ingelheim, Merck Sharp & Dohme*; honoraria – *EMD Serono, Genentech*. **Paz-Ares:** Leadership – *EMA SAG, Genomica*; honoraria – *Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Incyte, Lilly, Merck Serono, MSD, Novartis, Pfizer, PharmaMar, Roche/Genentech, Sysmex*; travel, accommodations, expenses – *AstraZeneca, AstraZeneca Spain, Bristol-Myers Squibb, Lilly, MSD, Pfizer, Roche*. **Banerji:** Honoraria – *Astellas, Astex, Eli Lilly, Janssen, Karus Therapeutics, Novartis, Phoenix Solutions, Vermalis*; funding for phase 1 investigator-initiated trials – *AstraZeneca, BTG International, Carrick Therapeutics, Chugai, Onyx Pharmaceuticals, Verastem*; employment – *Institute of Cancer Research, London*, which is involved in the development of PI3K, HSP90, HDAC, AKT, ROCK, RAF, CHK1, and HSF1 inhibitors. **Lakhani:** Principal investigator on trials supported: *ALX Therapeutics, Amgen, ArQule, Ascentage, Apexian, Asana Biosciences, Beigene, Constellation Pharma, CytomX, Daiichi Sankyo, Formation Biologics, Forty Seven, Inc, Inhibrx, Incyte Corporation, MacroGenics, Inc, Livzon Mabpharm, Loxo Merck, Northern Biologics, Pfizer, Regeneron, Symphogen, TaiRx, Inc*. **Ochsenreiter:** Honoraria for lectures and advice: *AstraZeneca, Bristol-Myers Squibb, Glenmark, Incyte, Ipsen, Macrogenics, Merck, MSD*; travelling support – *Bristol-Myers Squibb, Ipsen, Merck, Pfizer*. **Kornacki, Tian, Condamine,Bourayou:** Employment and stock ownership – *Incyte Corporation*. **Pikiel, Kryzhanivska, Arkenau, González:** Nothing to disclose.

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