2571

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Phase 2 Study of Retifanlimab (INCMGA00012) in Patients With Selected Solid Tumors (POD1UM-203)

Michele Maio,[1] Michael Schenker,[2] Jacques Medioni,[3] Slawomir Mandziuk,[4] Margarita Majem,[5] Gwenaelle Gravis,[6] Mark Cornfeld,[7] Sulabha Ranganathan,[7] Yubing Yao,[7] Howard Yeh,[8] Tibor Csoszi[9]

[1]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [2]Centrul de Oncologie Sf. Nectarie, Oncologie Medicala, Craiova, Romania; [3]Centre of Early Clinical Trials in Cancer, Hôpital Européen Georges-Pompidou, Universite de Paris, Paris, France; [4]Department of Clinical Oncology and Chemotherapy, Medical University of Lublin, Lublin, Poland; [5]Medical Oncology Department, Hospital de Sant Pau, Barcelona, Spain; [6]Department of Medical Oncology, Institut Paoli-Calmettes, Aix-Marseille Université, CRCM, Marseille, France; [7]Incyte Corporation, Wilmington, DE, USA; [8]Covance Clinical Development Services, Princeton, NJ, USA; [9]Hetényi Géza Kórház Onkológiai Központ, Szolnok, Hungary

Background

- Immunotherapy using checkpoint inhibitors (CPIs) such as programmed death 1/programmed death ligand 1 (PD-[L]1) are effective treatments for various tumor types[1]
- Retifanlimab (INCMGA00012) is an investigational humanized immunoglobulin G4k monoclonal antibody against human PD-1, designed to sustain/restore T-cell antitumor function, characteristic of the PD-1 inhibitor class[2,3]
- Clinical experience with retifanlimab has demonstrated pharmacology, safety, and clinical activity in multiple tumor types,[3–7] consistent with that reported with other PD-(L)1 antagonists
- The phase 2 POD1UM-203 study (NCT03679767) assessed efficacy and safety of retifanlimab in patients with selected solid tumors where CPI monotherapy is known to be highly active

Objectives

Primary

- Assessment of efficacy of retifanlimab in terms of objective response rate

Secondary

- Determination of duration of response, disease control rate, progression-free survival, overall survival (OS), safety, and pharmacokinetics (PK)

Exploratory

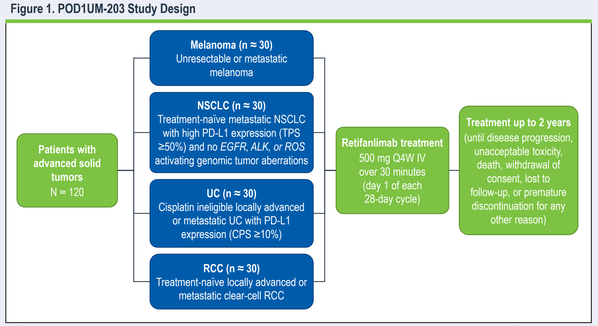
- Identification of biomarkers predictive of outcome or resistance to treatment, and immunogenicity of retifanlimab

Methods

Study Design

- Phase 2, open-label, multicenter study (**Figure 1**)

Figure 1. POD1UM-203 Study Design



CPS, combined positive score; IV, intravenous; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; Q4W, every 4 weeks; RCC, renal cell carcinoma; TPS, total proportion score; UC, urothelial cancer.

Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Patients ≥18 years of age with confirmed diagnosis of specific advanced solid tumors (melanoma, non-small cell lung cancer [NSCLC], urothelial cancer [UC], renal cell carcinoma [RCC])	• Previous treatment with any anti–PD-(L)1 therapy
• Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	• Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (defined as >10 mg of prednisone or equivalent)
• Eastern Cooperative Oncology Group performance status 0 or 1	• Known active central nervous system metastases and/or carcinomatous meningitis
• Adequate hematology, hepatic, and renal laboratory parameters	• Clinically significant cardiovascular or pulmonary conditions
	• Known active hepatitis A, B, or C infection
	• Active infections requiring systemic therapy

Assessments

- Response was assessed per RECIST v1.1 every 8 weeks (±7 days) during treatment
- Adverse events (AEs), graded by Common Terminology Criteria for Adverse Events version 5.0, were monitored throughout the study and for 28 (±7) days after the last dose of study treatment
  - Immune-related AEs were monitored for 90 days after the last dose of study treatment
- Blood samples for PK analysis were collected pre-infusion and 10 minutes post-infusion (±10 minutes) on day 1 of cycles 1, 2, 4, and 6
  - Additional PK samples were collected at 4 hours (±15 minutes) post-infusion on day 1 of cycle 1 and at any time on the day of end-of-treatment visit

Results

Patients

- A total of 121 patients (35 melanoma, 23 NSCLC, 29 UC, 34 RCC) received ≥1 dose of retifanlimab and were included in the analyses (first patient first visit: January 9, 2019; last patient first visit: April 7, 2020)
- Patient demographics and disease characteristics are presented in **Table 1**
- At the data cutoff (April 15, 2021), 37 patients (30.6%) were on treatment
  - 84 out of 121 patients (69.4%) discontinued treatment; 55 (45.5%) due to progression disease (primary reason) and 18 (14.9%) due to AEs

Table 1. Baseline Demographics (Safety-Evaluable Population)

Variable	Melanoma (n = 35)	NSCLC (n = 23)	UC (n = 29)	RCC (n = 34)	Total (N = 121)
Age, median (range), years	69 (38–92)	69 (50–87)	72 (54–88)	66.5 (48–87)	70 (38–92)
≥65 years	21 (60.0)	14 (60.9)	23 (79.3)	19 (55.9)	77 (63.6)
≥75 years	15 (42.9)	4 (17.4)	11 (37.9)	7 (20.6)	37 (30.6)
Sex, n (%)					
Male	15 (42.9)	16 (69.6)	25 (86.2)	24 (70.6)	80 (66.1)
Female	20 (57.1)	7 (30.4)	4 (13.8)	10 (29.4)	41 (33.9)
Race, n (%)					
Caucasian	35 (100.0)	22 (95.7)	20 (69.0)	33 (97.1)	110 (90.9)
Asian	0	1 (4.3)	0	0	1 (0.8)
Other*	0	0	9 (31.0)	1 (2.9)	10 (8.3)

Data cutoff date: May 5, 2020.
*Includes Other and Missing.
NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; UC, urothelial cancer.

Antitumor Activity

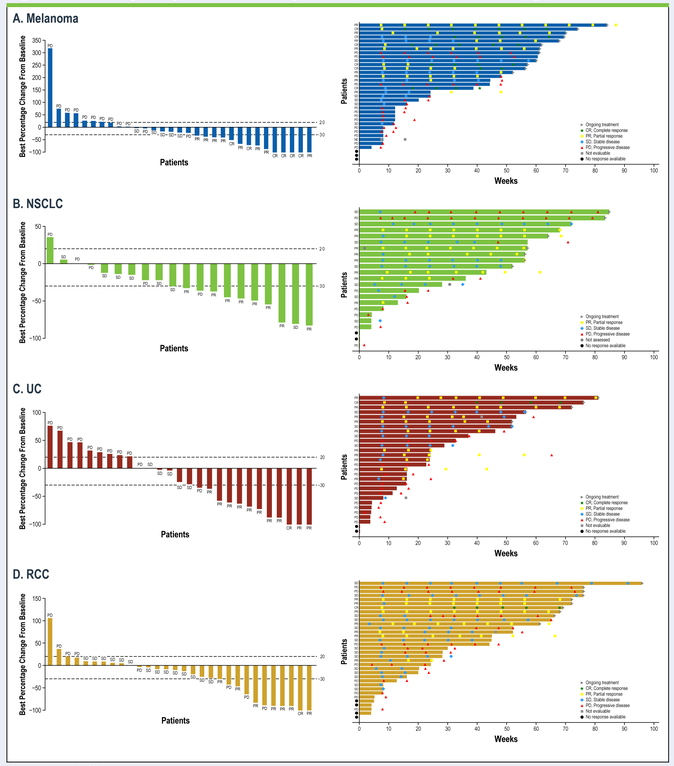
- The efficacy cutoff for the primary analysis occurred when all patients had been followed for at least 6 months from the time of initial treatment
- Confirmed RECIST v1.1 responses were observed in all tumor types and were durable (**Table 2**)
- After a median follow-up of 13.0 and 11.5 months, respectively, the median OS was more than 1 year in the melanoma and UC cohorts
  - The median OS was not reached in the NSCLC and RCC cohorts after a median follow-up of 12.2 and 15.0 months, respectively

Table 2. Summary of Overall Response (RECIST v1.1)

Variable	Melanoma (n = 35)	NSCLC (n = 23)	UC (n = 29)	RCC (n = 34)
Objective response rate, n (%)	14 (40.0)	8 (34.8)	11 (37.9)	8 (23.5)
95% CI	23.9–57.9	16.4–57.3	20.7–57.7	10.7–41.2
Best objective response, n (%)				
Complete response	6 (17.1)	0	1 (3.4)	1 (2.9)
Partial response	8 (22.9)	8 (34.8)	10 (34.5)	7 (20.6)
Stable disease	5 (14.3)	7 (30.4)	5 (17.2)	14 (41.2)
Progressive disease	12 (34.3)	6 (26.1)	11 (37.9)	8 (23.5)
Not evaluable	4 (11.4)	2 (8.7)	2 (6.9)	4 (11.8)
Disease control rate, n (%)	19 (54.3)	15 (65.2)	16 (55.2)	22 (64.7)
95% CI	36.6–71.2	42.7–83.6	35.7–73.6	46.5–80.3
Median progression-free survival, months (95% CI)	3.6 (1.8–NR)	4.4 (1.8–NR)	5.7 (1.8–13.6)	5.4 (2.3–11.4)
Median overall survival, months (95% CI)	14.7 (8.7–NR)	NR (5.2–NR)	15.2 (7.7–NR)	NR (NR–NR)
Median duration of response, months (95% CI)	NR (5.9–NR)	NR (1.9–NR)	11.5 (2.2–NR)	NR (2.8–NR)

Data cutoff date: April 15, 2021.
CI, confidence interval; NR, not reached; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial cancer.

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



Data cutoff date: April 15, 2021.
Upper limit of dotted line indicates a criterion for progressive disease (≥20% increase in sum of target lesion diameters) and lower limit indicates a criterion for partial response (≥30% decrease in sum of target lesion diameters).
NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; UC, urothelial cancer.

Safety and Tolerability

Table 3. Summary of Adverse Events (Safety-Evaluable Population)

Adverse Event, n (%)	N = 121
Treatment-emergent adverse event (all grade, treatment-related and -unrelated)	206 (87.6)
Treatment-related adverse event	68 (56.2)
Grade ≥3 adverse event (treatment-related and -unrelated)	46 (38.0)
Grade ≥3 treatment-related adverse event	11 (9.1)
Serious adverse event (all grade, treatment-related and -unrelated)	31 (25.6)
Serious treatment-related adverse event	5 (4.1)*
Adverse event leading to drug discontinuation (all grade, treatment-related and -unrelated)	13 (10.7)
Treatment-related adverse event leading to drug discontinuation	3 (2.5)†
Adverse event leading to drug interruption (all grade, treatment-related and -unrelated)	23 (19.0)
Treatment-related adverse event leading to drug interruption	14 (11.6)‡
Adverse event leading to death (all grade, treatment-related and -unrelated)	6 (5.0)
Treatment-related adverse event leading to death	0

Data cutoff date: September 23, 2020.
*Due to hepatocellular injury (n = 2 events), and acute kidney injury, infusion reaction, and hypophysitis (n = 1 event each).
†Due to pneumonitis, blood creatinine increased, and hepatocellular injury (n = 1 event each).
‡Due to rash (n = 3 events), arthralgia (n = 2 events), hepatocellular injury (n = 2 events), and acute kidney injury, alanine aminotransferase increased, anemia, asthenia, blood creatinine increased, decreased appetite, diarrhea, myalgia, pneumonia, pruritus, rash macular, rash papular, and wheezing (n = 1 event each).

- The most common treatment-emergent AEs (TEAEs; >10% incidence) were asthenia (17.4%), arthralgia (14.9%), decreased appetite (14.0%), pruritus (12.4%), rash (10.7%), and urinary tract infection (10.7%)
  - The majority of TEAEs were low grade (grade ≤2); 3 patients had treatment-related drug discontinuations for grade 2 azotemia, grade 3 blood creatinine increased, and grade 3 hepatocellular injury (n = 1 event each)

Table 4. Immune-Related Adverse Events

Adverse Event, n (%)	N = 121 Any Grade	Grade ≥3
Any immune-related adverse event	23 (19.0)	2 (1.7)
Endocrine disorders*	12 (9.9)	0
Rash†	8 (6.6)	1 (0.8)
Pruritus‡	3 (2.5)	0
Other§	7 (5.8)	1 (0.8)

Data cutoff date: September 23, 2020.
*Endocrine disorders includes the following MedDRA terms: hypothyroidism and hyperthyroidism.
†Rash includes the following MedDRA terms: rash, rash erythematous, rash maculopapular, and rash pustular.
‡Pruritus includes the following MedDRA terms: pruritus and pruritus generalized.
§Other includes 1 event each of acute kidney injury, hypophysitis, myositis, pancreatitis, polyarthritis, pneumonitis, and uveitis.
MedDRA, Medical Dictionary for Regulatory Activities.

- Immune-related AEs led to dose delay in 5 patients (4.1%), but none led to treatment discontinuation and/or dose interruption

Pharmacokinetics

Table 5. Comparison of Retifanlimab PK Parameters After First Dose and at Steady State From POD1UM-101 and POD1UM-203

	POD1UM-101 (60-Minute Infusion)	POD1UM-203* (30-Minute Infusion)	POD1UM-203* (30-Minute Infusion)
First dose			
C_{max}, mg/L	168 ± 51.6	148 ± 39.7	139 ± 29.5
	159	143	136
Steady state			
C_{max}, mg/L	219 ± 65.7	202 ± 83.4	140 ± 54.9
	203	189	119
Trough, mg/L	58.7 ± 26.8	43.3 ± 44.0	49.5 ± 20.4
	52.9	33.5	46.7

Data cutoff date: May 5, 2020.
Values are presented as mean ± standard deviation and geometric mean.
*Two production processes were used to manufacture retifanlimab during the course of the study and evaluated for PK independently.
C_{max}, maximum plasma drug concentration; PK, pharmacokinetics.

- PK parameters from POD1UM-203, which is the first retifanlimab clinical study to evaluate a shorter 30-minute infusion time, were similar to those observed in POD1UM-101, that evaluated a longer 60-minute infusion time

Conclusions

- **Retifanlimab demonstrated antitumor activity in patients with melanoma, NSCLC, UC, or RCC that is consistent with published results for other PD-(L)1 inhibitors[8–14]**
- **Retifanlimab was generally well-tolerated with a safety profile that is also characteristic of the PD-(L)1 inhibitor class[15]**
- **Clinical and PK results show that the more convenient 30-minute infusion schedule is acceptable**
- **These results support further clinical development of retifanlimab as monotherapy and in combination with novel agents**

Disclosures

Maio: Advisor/board member – *Alfasigma, Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly & Company, GSK, Incyte Corporation, Merck Serono, MSD, Pierre Fabre, Roche, Sanofi*; Stock ownership – *Epigen Therapeutics, Theravance*; Honoraria – *Alfasigma, Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly & Company, GSK, Merck Serono, MSD, Pierre Fabre, Roche, Sanofi, Sciolone Pharmaceuticals*. **Schenker:** Research funding – *AbbVie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, Daiichi Sankyo, Eli Lilly & Company, Gilead, GSK, Incyte Corporation, Merck Serono, MSD, Mylan, Pfizer, Pharma Mar, Regeneron, Roche, Tesaro*. **Medioni:** Consulting/advisory role – *AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo*; Travel expenses – *MSD, Pfizer, Roche*. **Mandziuk:** Nothing to disclose. **Majem:** Advisor/board member – *Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, MSD, Roche, Sanofi*; Honoraria – *Bristol Myers Squibb, Eli Lilly & Company, MSD, Pierre Fabre*; Travel accommodation – *Eli Lilly & Company, MSD*. **Gravis:** Consulting/advisory role – *AstraZeneca, Bayer, Bristol Myers Squibb, Ipsen, Janssen, MSD Oncology, Pfizer, Sanofi/Aventis*; Speakers' Bureau – *Amgen, Astellas Pharma, Bristol Myers Squibb, Ipsen, Janssen Oncology, MSD Oncology, Sanofi/Aventis*; Travel accommodation – *Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen Oncology, Pfizer, Sanofi*. **Yeh:** Nothing to disclose. **Csoszi:** Consulting/advisory role – *Novartis*; Speakers' bureau – *Ipsen, Janssen-Cilag*; Travel accommodation – *Pfizer, Sanofi*. **Cornfeld, Ranganathan, and Yao:** Employment and stock ownership – *Incyte Corporation*.

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