5043: Phase II study of the efficacy of retifanlimab (INCMGA00012) in penile squamous cell carcinoma (PSCC): ORPHEUS final analysis

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BACKGROUND

- PSCC is a rare tumor with a prevalence of 0.1-1 per 100,000 men in developed countries, although its incidence increases in low-income regions. Risk factors include HPV status (>50% of cases), immunosuppression, phimosis, or smoking [1,2].
- Surgery can be an effective option for localized disease, but PSCC is characterized by early lymphatic spread, and prognosis strongly decreases once metastasis has occurred [1,2]. The mainstay of treatment for advanced disease is platinum-based chemotherapy, but outcomes remain poor [1]. There is an unmet need for more effective and less toxic therapies for these patients.
- Most of PSCC patients present high levels of PD-1/PD-L1 [3]. Promising results have been reported with anti-PD-1/PD-L1 agents in different SCC, but evidence with immunotherapy is very limited in penile cancer. According to NCCN guidelines, only pembrolizumab is recommended for advanced PSCC as second line [2,4].
- Retifanlimab (INCMGA00012) is a PD-1 inhibitor that has demonstrated tolerability and preliminary efficacy in different solid tumors in clinical trials [5-7].
- ORPHEUS evaluates the efficacy and safety of retifanlimab in patients with unresectable locally advanced or metastatic PSCC previously treated or not with chemotherapy.

STUDY DESIGN

Multicenter (Spain, Italy), open-label, single-arm, phase II trial (NCT04231981).

Figure 1. ORPHEUS trial

Key inclusion criteria

- Male patients aged ≥18 years
- Radiological evidence of locally advanced unresectable or metastatic stage IV PSCC (T4 or N3 or M1)
- Pretreated patients should have received their last dose of chemotherapy ≥ 28 days from study entry.
- Naïve to any previous therapy with anti-PD-1 or anti-PD-L1/PD-L2 agents.
- ECOG performance status 0 - 1

Retifanlimab
500 mg I.V.
Q4W for up to 2 years

Tumor assessments per RECIST
- 8W during first 6 months and Q12W thereafter

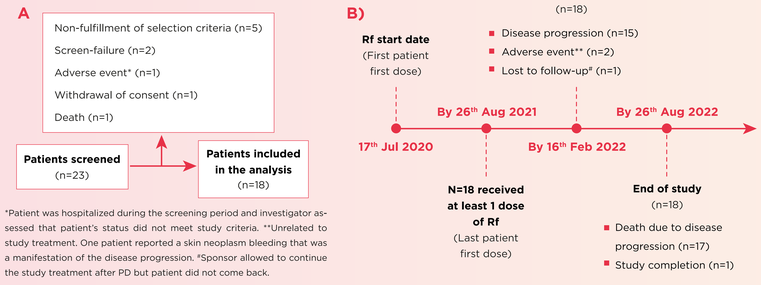
Safety assessments per NCI-CTCAE v.5.0

Until progressive disease, unacceptable toxicity, death, or consent withdrawal

- **Primary endpoint:** ORR by RECIST 1.1.
- **Secondary endpoints:** CBR, PFS, 6-month PFS, TTR, DoR, OS, maximum tumor shrinkage, incidence of TEAEs.

RESULTS

Figure 2. Recruitment (A) and study timeline (B)



*Patient was hospitalized during the screening period and investigator assessed that patient's status did not meet study criteria. **Unrelated to study treatment. One patient reported a skin neoplasm bleeding that was a manifestation of the disease progression. #Sponsor allowed to continue the study treatment after PD but patient did not come back.

RESULTS

Table 1. Patients' baseline characteristics

Baseline characteristics, n (%)	Overall (N=18)
Age, Median (Min; Max), years	66.5 (42; 81)
Caucasian	17 (94.4%)
ECOG	
0	7 (38.9%)
1	11 (61.1%)
PD-L1+*	
>1%	9 (52.9%)
>50%	3 (17.6%)
HIV+	1 (5.6%)
HPV+	1 (5.6%)
HPV-	3 (16.7%)
NA	14 (77.8%)
Time from diagnosis of penile cancer, median (Min; Max), years	1.0 (0.2;5.8)
Advanced disease at diagnosis	13 (72.2%)
Visceral involvement	9 (50.0%)
Previous surgical procedures for penile cancer	
Yes	15 (83.3%)
Lymphadenectomy	7 (38.9%)
N° of previous advanced disease treatment lines	
0	7 (38.9%)
1	6 (33.3%)
≥2	5 (27.8%)
Previous advanced disease treatment lines	
Yes	11 (61.1%)
Platinum-based regimes	10 (55.6%)
Radiotherapy	4 (22.2%)
Paclitaxel	1 (5.6%)

*Assessed by Ventana SP263 immunohistochemistry assay. Tumor samples were available from 17 patients.

- **Disease control rate** was achieved by 6 (33.3%) patients (3 PR + 3 SD) (**Table 2** and **Figure 3**).

Table 2. Efficacy endpoints, n (%)

Clinical Benefit rate (CBR)	Overall (N=18)
PR*	3 (16.7%)
SD≥24w	1 (5.6%)
SD<24w	2 (11.1%)
PD	11 (61.1%)
NE	1 (5.6%)
Objective Response Rate (ORR)	
Yes	3 (16.7%)
[95% CI] (Wilson)	[5.8%;39.2%]
TTR, median (Min; Max), mo	1.9 (1.7;2.4)
DoR, median (Min; Max), mo	3.3 (1.8;8.5)

*Partial responses were radiologically confirmed in 2 patients.

Figure 3. Best percentage change in sum of lesions

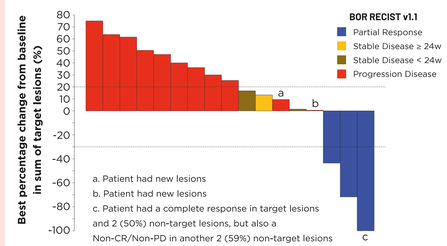


Figure 4. Progression free survival (A) and overall survival (B)

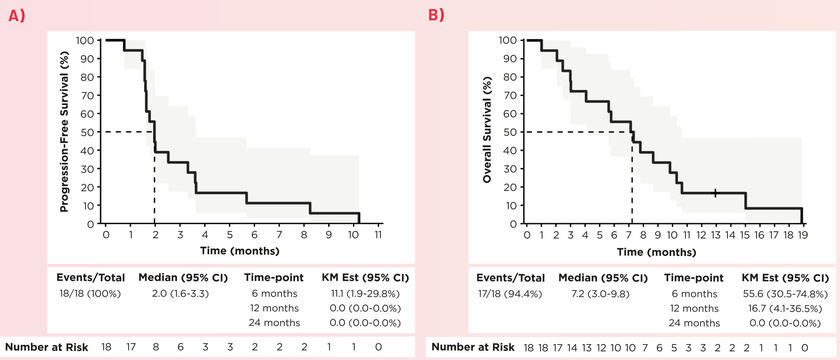


Table 3. TEAEs and related TEAEs by grade (G)

Overall (N=18) n (%) (by PT)	TEAEs Any	TEAEs G3	TEAEs G4	Related TEAEs Any	Related TEAEs G3
TEAEs	**14 (77.8)**	**4 (22.2)**	**2 (11.1)**	**5 (27.8)**	**1 (5.6)**
Haematologic	**3 (16.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Leukocytosis	1 (5.6)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)
Anaemia	2 (11.1)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)
Non-haematologic*	13 (72.2)	4 (22.2)	2 (11.1)	5 (27.8)	1 (5.6)
Fatigue	5 (27.8)	1 (5.6)	0 (0)	4 (22.2)	1 (5.6)
Decreased appetite	2 (11.1)	1 (5.6)	0 (0)	1 (5.6)	1 (5.6)
Cellulitis	2 (11.1)	1 (5.6)	0 (0)	0 (0)	0 (0)
Groin infection	2 (11.1)	1 (5.6)	0 (0)	0 (0)	0 (0)
Pseudomonas infection	2 (11.1)	1 (5.6)	0 (0)	0 (0)	0 (0)
Rash	2 (11.1)	0 (0)	0 (0)	1 (5.6)	0 (0)
Xerosis	1 (5.6)	0 (0)	0 (0)	1 (5.6)	0 (0)
Ejection fraction decreased	1 (5.6)	0 (0)	1 (5.6)	0 (0)	0 (0)
Hypercalcaemia of malignancy	1 (5.6)	0 (0)	1 (5.6)	0 (0)	0 (0)

* No treatment-related G4 TEAEs nor TEAEs > G4 were reported. Serious TEAEs occurred in 5 (27.8%) patients, TEAES leading to study discontinuation occurred in 2 (11.1%) patients, and TEAEs leading to death in 1 (5.6%) patient, but none of them were related to retifanlimab.

- Patients received a median (min; max) of 3.0 (1.0; 13.0) cycles during 12.1 (4.0; 57.9) weeks. Mean relative dose intensity was 96.6%.
- At data cut-off (26th Aug 2022), after a follow-up of 7.2 (1.0; 18.9) months, no patients remained on therapy.

CONCLUSIONS

- Retifanlimab in monotherapy displayed signals of clinical activity in patients with advanced or metastatic PSCC.
- Safety profile was consistent with previous data, with no treatment-related serious AEs nor deaths.
- The present results serve as a proof-of-concept to develop novel strategies of combination therapy or validation studies with larger sample size, pending the identification of suitable biomarkers for patient selection.
- These findings could pave the way for immunotherapy development in this orphan genitourinary tumor.

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Abbreviations: PSCC: penile squamous cell carcinoma; HPV: human papillomavirus; PD-1: programmed cell death protein 1; PD-L1: PD-1 ligand; NCCN: National Comprehensive Cancer Network; ECOG: Eastern Cooperative Oncology Group; Rf: retifanlimab; Q4W/Q8W/Q12W: every 4/8/12 weeks; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR: objective response rate; RECIST: Response Evaluation Criteria In Solid Tumors; CBR: clinical benefit rate; PFS: Progression-free survival; TTR: time to response; DoR: duration of response; OS: overall survival; PD: progression disease; PR: partial response; HIV: human immunodeficiency virus; NA: not available; SD: stable disease; w: week; CI: confidence interval; mo: months; n (%): number of patients (percentage based on N); N: number of patients in the population; AEs: adverse events; TEAEs: Treatment Emergent AEs; PT: preferred term.

Lay language summary – ORPHEUS for ASCO 2023

Phase II study of the efficacy of retifanlimab (INCMGA00012) in penile squamous cell carcinoma (PSCC): ORPHEUS final analysis.

Penile squamous cell carcinoma (PSCC) is the most common tumor type among all penile cancer cases. However, it is a rare disease with an occurance of lower than 1 case per 100,000 men in developed countries. Because of the low incidence, only a few studies worldwide are currently investigating this disease.

Although surgery can be an effective option for early disease, patient survival is very low once metastasis has occurred. In the advanced stage, platinum-based chemotherapy is the preferred treatment option, but toxicity is high, and outcomes remain poor. Therefore, new therapeutic strategies for patients with advanced disease are urgently needed.

According to recent studies, most patients with advanced penile cancer have high levels of a protein called PD-L1 that helps tumor cells to reproduce and promotes tumor growth. Targeting this protein with immunotherapy (drugs against PD-L1) has shown a clinical benefit in patients with other tumor types.

The ORPHEUS study evaluated whether retifanlimab, a new drug that targets PD-L1, could reduce tumor size and increase survival in penile cancer patients with advanced disease or metastasis.

The study enrolled 18 men with advanced or metastatic PSCC who were then observed for 7.2 months (range from 1.0 to 18.9 months). They had a median age of 66.5 years old. Patients recieved retifanlimab intravenously every 4 weeks for up to 2 years of treatment. The study results showed that, among these 18 patients, 6 of them (which accounts for a 33.3%) responded to the treatment. Specifically, 3 patients had a reduction in tumor size and 3 patients had a stable disease without any significant progression of the tumor. The remaining patients had a progression in their disease. The median progression free survival, which is the time during and after the treatment that a patient lives with the disease but it does not get worse, was 2 months. The median overall survival, which is the time elapsed from the end of the treatment until the patient's death, was 7.2 months. Regarding the safety profile of retifanlimab, the most common side effects related to the treatment in these patients were fatigue and decreased appetite.

In summary, during treatment with retifanlimab, one third of the patients with advanced or metastatic PSCC displayed signals of clinical activity, and the safety profile was consistent with previous studies. These findings could help to develop new treatment strategies for this rare tumor that currently has limited treatment options.