3 February 2026
EMA/OD/0000284336
EMADOC-360526170-2927172
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Zynyz (retifanlimab)
Treatment of anal cancer
EU/3/20/2343

Sponsor: Incyte Biosciences Distribution B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance	Retifanlimab
Other name	--
International Non-Proprietary Name	Retifanlimab
Tradename	-
Orphan condition	Treatment of anal cancer
Sponsor's details:	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 BP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Incyte Biosciences Distribution B.V.
COMP opinion	10 September 2020
EC decision	10 October 2020
EC registration number	EU/3/20/2343
Type II variation procedural history	
Rapporteur / Co-rapporteur	Peter Mol / Selma Arapovic Dzakula
Applicant	Incyte Biosciences Distribution B.V.
Application submission	29 January 2025
Procedure start	22 February 2025
Procedure number	EMA/VR/0000247788
Invented name	Zynyz
Proposed therapeutic indication	Zynyz is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with metastatic or with inoperable locally recurrent squamous cell carcinoma of the anal canal (SCAC).
CHMP opinion	29 January 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Elisabeth Johanne Rook / Alexandru Mihail Simion
Sponsor's report submission	15 July 2025
COMP discussion	20-22 January 2026
COMP opinion (adoption via written procedure)	3 February 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2020 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing retifanlimab was considered justified based on clinical data in patients progressing after platinum-based chemotherapy who achieved durable partial or complete responses;
- the condition is chronically debilitating due to any combination of a mass, non-healing ulcer, pain, bleeding, itching, discharge, faecal incontinence and fistulae and life-threatening due to a 5-year survival around 80%;
- the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing retifanlimab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with advanced and metastatic anal cancer who relapsed following standard platinum-based chemotherapy regimen achieved durable responses. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing retifanlimab as an orphan medicinal product for the orphan condition: treatment of anal cancer.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Tumours of the anal canal are a sub-group of digestive system tumours (WHO, 5th Edition 2016). They are split into benign and malignant tumours. Greater than 90% of the cases of carcinoma of the anal canal are squamous cell carcinoma (SCAC) (Eng et al 2014), followed by adenocarcinoma.

Important causal factor of SCAC is anal infection with carcinogenic human papillomavirus infection (HPV). Immune-compromised patients, such as with Human immunodeficiency virus (HIV) infections,

are a specific population of risk of SCAC. Most patients diagnosed in the sixth decade of life or later, although this maybe early in patients with HIV.

Most patients with anal cancer present with rectal bleeding. Diagnosis can be delayed because this bleeding is often misdiagnosed as haemorrhoids. Genital warts are not always present, leaving the underlying HPV infection silent. Other symptoms include rectal pain and/or mass sensation and tenesmus, occurring in approximately 30% of patients (Ryan et al 2000).

The approved therapeutic indication "ZYNYZ is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with metastatic or with inoperable locally recurrent squamous cell carcinoma of the anal canal (SCAC)" falls within the scope of the designated orphan condition "Treatment of anal cancer".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor discussed the chronically debilitating nature of the disease. Patients with locally recurrent disease or distant disease frequently experience pain, sacral involvement, symptomatic bulky necrotic lymphadenopathy, and destructive anal canal involvement as a result of local tumour effects (Eng et al 2014). Recurrent disease is also accompanied by considerable morbidity including incontinence, impaired sexual function, and diarrhoea, which lead to a reduced quality of life, and are related not just to the disease but also to complications of treatment with chemotherapy and radiotherapy (Glynne-Jones et al 2014, Pan et al 2018). Advanced SCAC is chronically debilitating, with multiple toxicities associated with prior therapies including diarrhoea, obstructions, compromised motility, perforations, malabsorption, myelosuppression, colostomies and fistulas (Bentzen et al 2013, Li et al 2017, Pessia et al 2020).

Approximately 10%-20% of patients suffer distant relapse and 10% present with de novo metastatic disease. In these Stage IV patients group the median progression free survival (PFS) and overall survival (OS) following standard-of-care platinum-based chemotherapy is short (Rao et al 2021).

The COMP has previously accepted that the clinical course of anal cancer is chronically debilitating due to any combination of a mass, non-healing ulcer, pain, bleeding, itching, discharge, faecal incontinence and fistulae and life-threatening due to an overall 5-year survival around 80%.

Number of people affected or at risk

The sponsor proposed a prevalence of approximately 2.0 in 10,000. The sponsor conducted an updated review of the literature and of cancer databases to cover the period from the orphan drug designation submission (May 2020) to May 2025.

Incidence

Squamous cell carcinoma of the anal canal is a rare cancer, accounting for < 3% of digestive system cancers (Ghosn et al 2015, Islami et al 2017, Rao et al 2021). Approximately 40,000 new cases of anal cancer estimated in 2012 globally (Islami et al 2017). It is estimated that there were approximately 81,779 people living with anal cancer in the United States in 2021, with an estimate of 10,930 new cases with 2030 deaths in 2025 (SEER 2025). The incidence rate is 2.2 per 100,000 people, with a higher incidence in women (2.5 per 100,000) than men (1.6 per 100,000; SEER 2025). In European countries, the incidence rate varies from 1 per 100,000 men and women in the UK to 3 per 100,000 in

Switzerland (Pessia et al 2020). According to the ECIS, about 9,901 new cases of anal cancer were diagnosed in the EU-27 in 2022 (ECIS 2022). This corresponds to a crude incidence rate of 2.2 per 100,000 in the EU-27 (ECIS 2022). In European countries, the incidence rate varies from 1 per 100,000 men and women in the UK to 3 per 100,000 in Switzerland (Pessia et al 2020).

Although SCAC is rare, the incidence is increasing, due to sexual transmission of oncogenic strains of HPV (Ghosn et al 2015, Nelson et al 2013, Symer and Yeo 2018). In Europe, there has been an increase of SCAC from 0.595 per 100,000 per person-years from 1999 to 2002 to 0.728 per 100,000 person-years from 2003 to 2007 (RARECARENet 2020). The incidence has increased over 2.9% and about 1.9 times for men and 1.5 times for women around 2020 compared from decade 1992-2001 (Pessia 2020). This trend is also noted particularly in developed countries: the incidence of SCAC more than doubled between 1988 to 1992 and 2008 to 2012, in men and women, when data were pooled from 7 high income countries in North America, Europe, and Oceania (Kang et al 2018). The incidence rate will increase from around 1,900 cases per year in 2023-2025 to around 2,400 cases per year in 2038-2040, rise by 14%. The incidence rate will increase more in women than men (Cancer Research UK 2025). The increasing incidence of anal carcinoma is particularly evident in HIV positive patients (Abramowitz et al 2009, Moureau-Zabotto et al 2017, Piketty et al 2012).

According to the GLOBOCAN 2022 (GLOBOCAN 2022a), 54,306 newly diagnosed anal cancer cases were estimated worldwide (United States: 9024, Europe: 14219, UK: 1929, and Japan: 1091). In the US, in the SEER 22 database (2017-2021), the highest number of new cases of anal cancer was recorded in the age group of 60 to 64 years.

Survival

Treatment of localized SCAC has not advanced in decades even though clinical outcomes remain suboptimal. The standard of care is fluoropyrimidine-based chemotherapy in combination with radiotherapy, with a 5-year disease-free survival rate of approximately 60% (Ajani et al 2008, Bartelink et al 1997, Flam et al 1996, Nigro et al 1974). The 5-year overall survival (OS) improved from 64% in 1980 to 75% in 2010, with a statistically significant difference (P=0.046) (Sekhar 2017). The prognosis of metastatic anal cancer patients is poor with a 5-year relative survival rate of 30%; (Rao et al 2021). Surgery as a primary therapeutic option has generally been abandoned because comparable survival without the need for permanent colostomy can be achieved with these regimens (Glynne Jones et al 2014, Maurel et al 2011, Moureau-Zabotto et al 2017, NCCN 2023, Nigro et al 1983). Relapse after primary treatment occurs in up to 40% of patients within 5 years, and the prognosis for those who experience relapse or who present with de novo metastatic disease is poor (Gunderson et al 2012).

Prevalence

According to the GLOBOCAN 2022, 42,168 1-year prevalent anal cancer cases (prevalence proportions 0.53 per 100,000) worldwide with 8743 1-year prevalent cases (prevalence proportions 2.0 per 100,000), 22,279 3-year prevalent cases (prevalence proportions 5.0 per 100,000), and 32,726 5-year prevalent cases (prevalence proportions 7.4 per 100,000) in EU-27 (GLOBOCAN 2022b).

Estimation of the prevalence

Since direct prevalence data was not found in the literature search conducted for anal cancer in Europe at the time of the orphan drug maintenance report, an indirect calculation of prevalence is presented below. According to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation" (COMP/436/01) and assuming a stable incidence and disease

duration, the prevalence (P) can be calculated as P = I x D, where: I = incidence and D = mean disease duration.

The estimates derived from ECIS database were used for the recalculation of the estimated prevalence of in the EU.

- According to ECIS, about 9 901 new cases of anal cancer were diagnosed annually in Europe in 2022;
- Given the 5-year overall survival rate ranges 64% to 75% for SCAC (Roa et al 2021, Sekhar 2017, a 10-year mean disease duration is estimated, and;
- Eurostat estimates a population of 477.9 million for the EU-27 in 2022

The prevalence calculation is presented in the table below (see Table 1).

Table 1. Estimated prevalence of SCAC in the EU-27

Estimated annual incident cases in Europe	**Disease mean duration**	**Total population in the EU-27**	**Estimated prevalence per 10,000 persons in the EU-27**
9 901	10 years	477,900,000	2.07

The COMP agreed with the methodology used and proposed figure of approximately 2 in 10,000 persons.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are no medicinal products authorised for the treatment of squamous cell carcinoma of the anal canal.

Radiotherapy with concomitant 5-FU (5-fluorouracil) and MMC (Mytomycin-C) is recommended as standard of care first-line therapy for patients with localised SCCA, with a 5-year disease-free survival rate of approximately 60% (Bartelink et al 1997, Ajani et al 2008, Flam et al 1996).

Surgery as a primary therapeutic option has generally been abandoned because comparable survival without the need for permanent colostomy can be achieved with these regimens (Glynne-Jones et al 2014, Maurel et al 2011, Moureau-Zabotto et al 2017, NCCN 2023, Nigro et al 1983). Approximately 10%-20% of patients with anal cancer will require a pre-treatment colostomy (Rao et al, 2021).

The first-line standard of care for locally advanced or metastatic stage IV SCAC is platinum-based chemotherapy with a carboplatin-paclitaxel combination (Giani et al 2013, Glynne-Jones et al 2014, Moureau-Zabotto et al 2017, NCCN 2023).

There is no established systemic therapy for patients with SCAC whose disease has progressed on initial systemic treatment. Most practice guidelines, including those of the European Society of Medical Oncology, the American Society of Colon and Rectal Surgeons, the French Intergroup, and the

Association of Coloproctology of Great Britain & Ireland, do not include specific recommendations for therapy following first-line platinum chemotherapy (Glynne-Jones et al 2014, Gollins et al 2017, Moureau-Zabotto et al 2017, Stewart et al 2018). See Table below for ESMO recommendations fir advanced anal cancer (SCAC).

Figure 1. ESMO treatment algorithm for advanced anal cancer (source Rao et al, 2021)

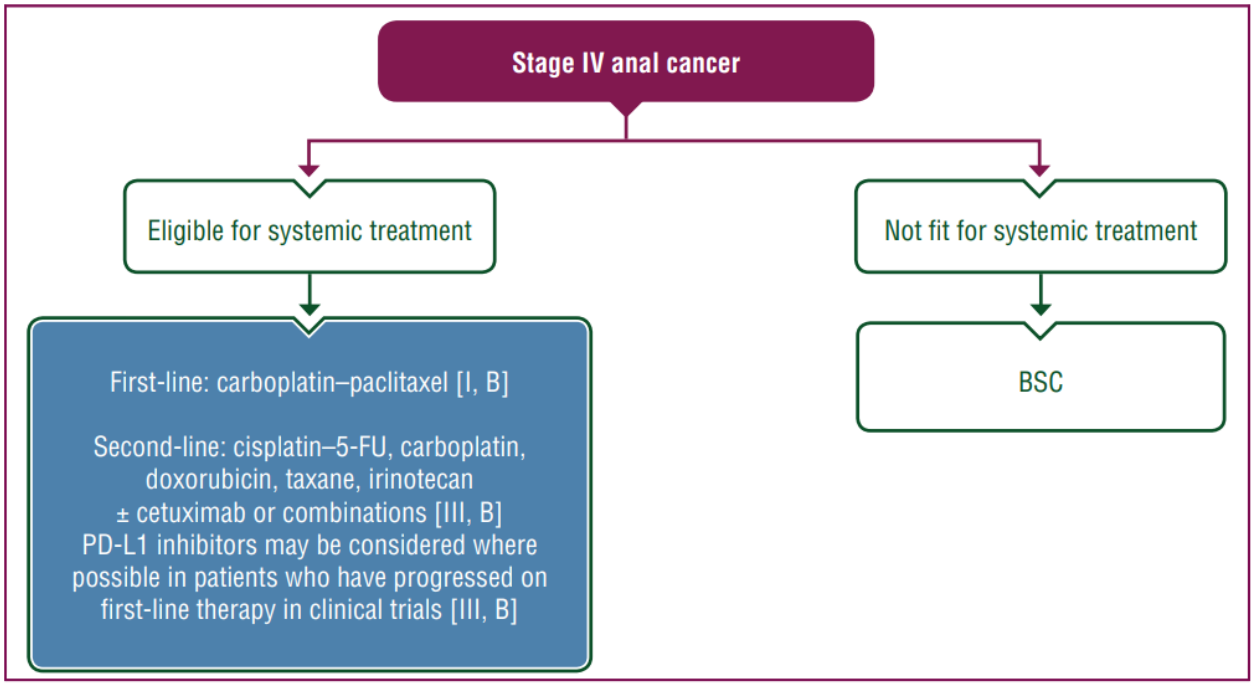

Figure 3. Treatment algorithm for advanced anal cancer.
Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
5-FU, 5-fluorouracil; BSC, best supportive care; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Significant benefit

Not applicable.

4. COMP position adopted on date

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of anal cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to bleeding, pain, itching, tenesmus, discharge, faecal incontinence and fistulae.
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Zynyz, retifanlimab, INN for Treatment of anal cancer (EU/3/20/2343) is not removed from the Community Register of Orphan Medicinal Products.