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ORIGINAL RESEARCH

Retifanlimab Vs Avelumab in Patients with Metastatic Merkel Cell Carcinoma: A Cost Utility Analysis in Italy

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ABSTRACT

OBJECTIVE: Merkel cell carcinoma (MCC) is a very rare and aggressive neuroendocrine skin cancer, characterized by a 5-year survival rate of 13.5% in patients with distant metastases. This study aimed to evaluate the cost-utility of retifanlimab compared to avelumab in the treatment of metastatic MCC patients who had not received prior systemic therapies, from the perspective of the Italian National Health Service (SSN).

METHODS: A 7-day cycles partitioned survival model with three mutually exclusive health-states—progression-free, post-progression and death—was developed to compare lifetime clinical outcomes and costs for patients treated with retifanlimab versus avelumab in the Italian context. Progression-free survival and overall survival curves were modelled independently, with POD1UM-201 trial data used for retifanlimab efficacy. In the absence of direct head-to-head clinical trial data, avelumab efficacy was estimated using the hazard ratio obtained from a matching-adjusted indirect comparison. Following a previous National Institute for Health and Care Excellence submission, utility values were derived using a time-to-death approach, with health states defined as "$>$266 days to death", "35-266 days to death", and "$<$35 days to death". Direct healthcare costs, including drug acquisition and administration, disease monitoring, adverse event management, post-progression therapy, and end-of-life care, were sourced from Italian data. Costs and health outcomes were discounted at an annual 3% rate. Deterministic and probabilistic sensitivity analyses, along with scenario analysis, were conducted to assess the uncertainty of input parameters.

RESULTS: In the base case, retifanlimab demonstrated greater efficacy compared to avelumab, with 6.39 vs 3.42 life-years and 5.11 vs 2.68 quality-adjusted life-years (QALYs), at an additional cost of €12,228. The incremental cost-utility ratio was estimated at €5,037 per QALY gained. Sensitivity analyses confirmed the robustness of the base case results.

CONCLUSIONS: Retifanlimab can be considered a cost-effective option for Italian patients with metastatic MCC who have not received prior systemic therapies.

Keywords

Retifanlimab; Cost-utility analysis; Metastatic Merkel cell carcinoma; Italy

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine skin cancer [1]. It is primarily associated with Merkel cell polyomavirus (MCPyV) infection, ultraviolet radiation exposure and immunosuppression [1–4]. The disease most commonly affects elderly or immunocompromised individuals [2]. The prognosis of MCC is influenced by several factors including tumour stage, patient age, sex, and MCPyV status. Advanced stages are particularly associated with poor outcomes, with a 5-year survival rate of only 13.5% for stage IV disease [5].

Being a rare disease, MCC is associated with limited epidemiological data available in the literature. In Europe, the RARECARE database reported an incidence rate of 0.13 per 100,000 between 1995 and 2002 [6], while the Italian cancer registry reported an incidence rate of 0.34 per 100,000 between 2000 and 2010 [7].

In recent years, the standard treatment for metastatic MCC (mMCC) has undergone significant changes with the introduction of immunotherapy. Immune checkpoint inhibitors (ICIs), including avelumab and retifanlimab, which target programmed cell death protein-1 (PD-1), have shown substantial efficacy in clinical trials. Avelumab and retifanlimab were both evaluated in phase II, open-label, single-arm, multicenter trials involving mMCC patients [8,9].

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In the JAVELIN Merkel 200 trial – part B, avelumab, administered as first-line treatment, achieved an objective response rate of 39.7% in a cohort of 116 mMCC patients [8]. Similarly, retifanlimab, evaluated in the POD1UM-201 trial, demonstrated clinically significant activity in the entire cohort of 101 patients with advanced or metastatic MCC, resulting in an ORR of 53.5% and a median duration of response (DOR) of 25.3 months, with 71% of patients maintaining a response for over 12 months [9].

In Italy, avelumab is currently approved and reimbursed by the Italian Medicines Agency (AIFA) for the treatment of mMCC [10], while retifanlimab has received approval but is still undergoing evaluation for reimbursement.

While these advances in treatment are promising, the costs of ICIs, coupled with the resources needed for administration and patient monitoring, may represent an economic challenge. Consequently, evaluating the cost-effectiveness of these therapies is crucial for optimizing healthcare resource allocation and identifying the most effective treatment for both patients and the healthcare system.

This study aimed to assess the cost-utility of retifanlimab versus avelumab in the treatment of mMCC patients who had not received prior systemic therapies in Italy.

METHODS

Model structure

A newly developed partitioned survival model (PSM), based on the structure of the model submitted to the National Institute for Health and Care Excellence (NICE) for avelumab, was designed to assess and compare the clinical outcomes and costs of patients treated with retifanlimab and avelumab in the Italian context [11]. The analysis was conducted from the perspective of the Italian SSN with a lifetime horizon.

The model included three mutually exclusive health states: i) pre-progression; ii) post-progression; iii) death. Transitions between states occurred in 1-week cycles, applying half-cycle correction. These states were defined based on the OS and progression-free survival (PFS) curves. The OS and PFS curves were modelled independently. A simplified diagram illustrating the model structure is shown in Figure 1.

Efficacy input

In the absence of direct head-to-head clinical trial, the efficacy of avelumab was estimated with the hazard ratio (HR) obtained from a matching-adjusted indirect comparison (MAIC) [12] which compared the individual patient data (IPD) from the open-label, single-arm, phase 2 POD1UM-201 trial (POD1UM-201, 2023, data on file) and the aggregate data

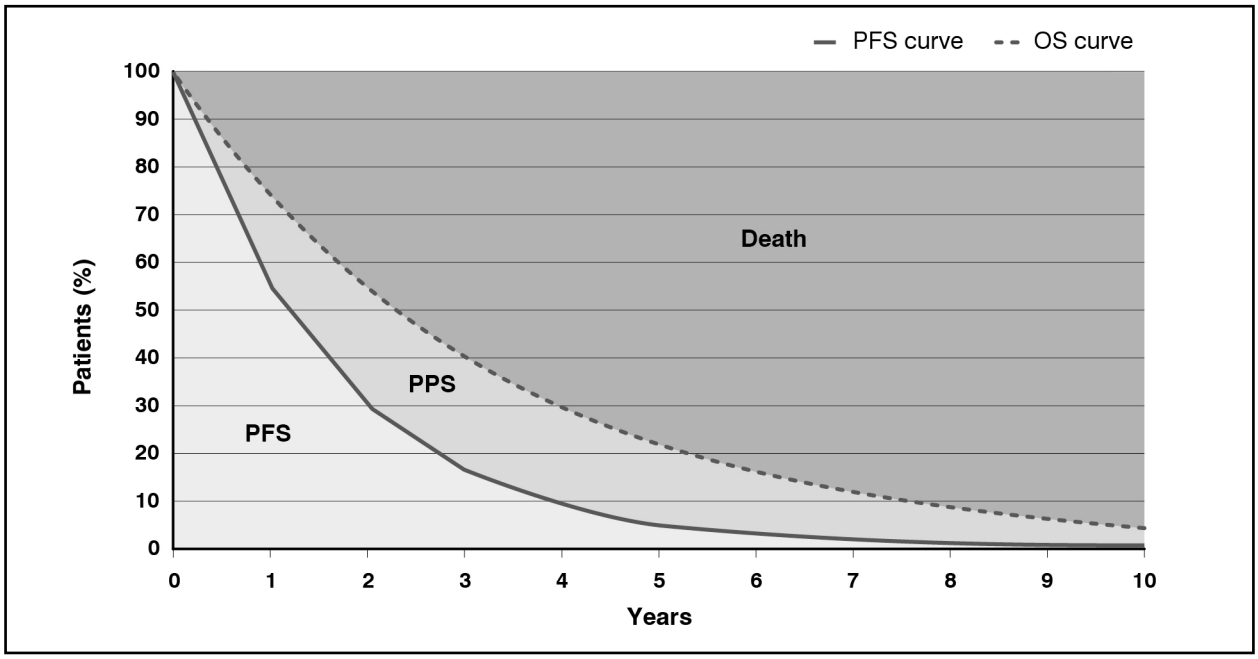

Figure 1. *Survival curves*
OS: overall survival; PFS: progression-free survival; PPS: post-progression survival

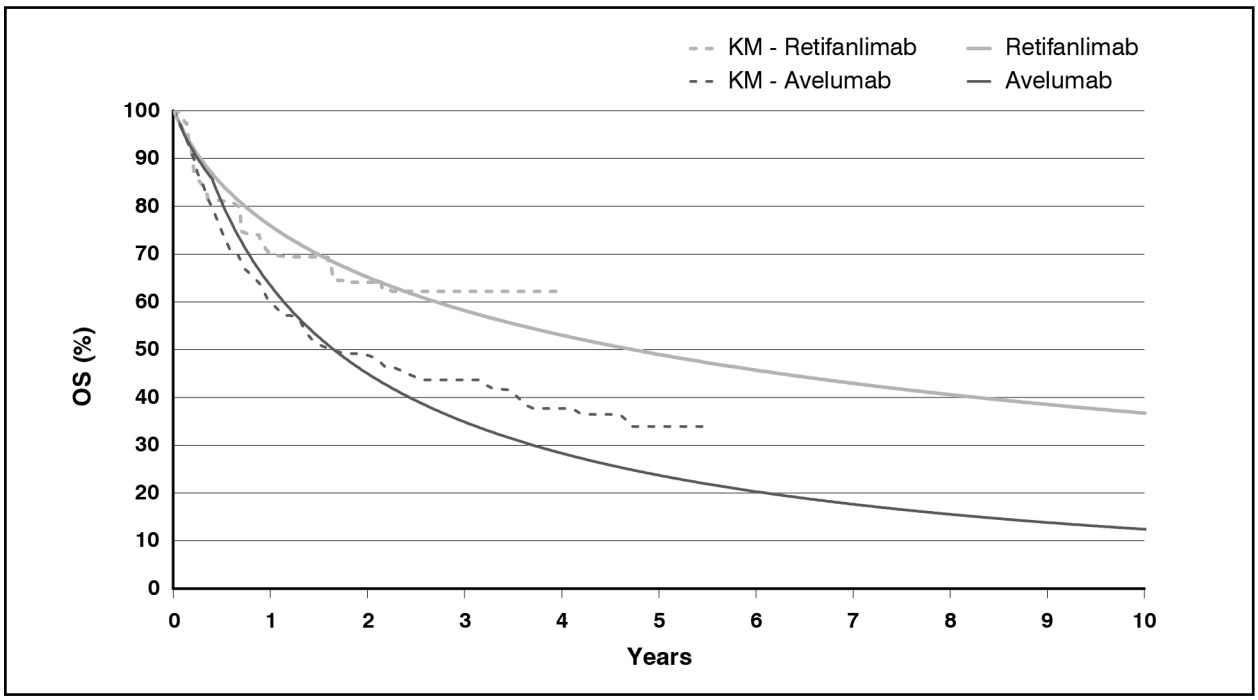

Figure 2. *Long-term overall survival (OS) prediction*
KM: Kaplan-Meier

from the JAVELIN Merkel 200 – part B trial [8,13]. To ensure comparability, IPD from the POD1UM-201 trial were adjusted for key prognostic factors defined by clinical experts, including age (<65 years), ECOG status, MCPyV status, PD-L1 status, presence of visceral metastasis, and the site of the primary tumor. Patients with locoregional disease were excluded from the analysis [12]. The HR results from the piecewise constant hazard model for OS and PFS using weighted data are presented in the Supplementary Material Table S1.

OS and PFS curves are illustrated in Figure 2 and Figure 3. Regarding OS for retifanlimab, the log-normal, Gompertz, and generalized gamma distributions had similar AIC and BIC values. In the base case, the log-normal distribution was selected because it provided more conservative survival estimates compared to the other two distributions (Supplemen-

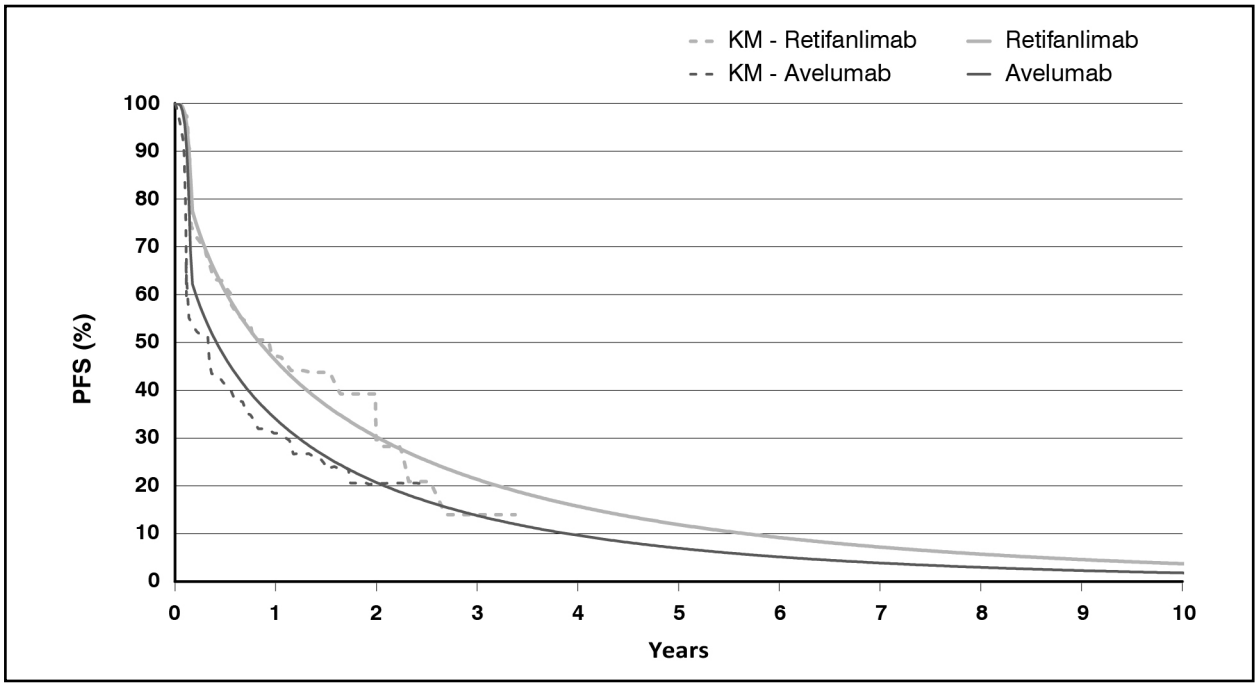

Figure 3. *Long-term progression-free survival (PFS) prediction*
KM: Kaplan-Meier

tary Material Table S2). The impact of this assumption was further evaluated in the scenario analysis. Despite analytic tests indicating that the proportional hazards assumption was not violated, visual assessment of the Kaplan-Meier plot (Figure 2) suggested evidence of a deviation from the proportional hazards assumption and time-dependent hazard ratios were therefore used. Time-dependency was implemented by splitting the follow-up time into two intervals and calculating a single constant HR within each interval. A 5-month split was chosen based on visual assessment of the cumulative hazard plot. Thus, the OS curve for avelumab was modelled with two distinct HRs: 1.092 during the first 5 months and 2.243 for the subsequent period [12]. The impact of this assumption was further investigated in the scenario analysis.

The PFS curve for retifanlimab was modelled using a time-dependent distribution, as visual inspection of the Kaplan-Meier curve (Figure 3) revealed a high risk of progression and death during the initial months, which subsequently decreased. The assumption of proportional hazards in the analysis of PFS was not satisfied and time-dependent hazard ratios were therefore used. A 2-month split was chosen based on visual assessment of the cumulative hazard plot. Thus, the PFS curve for avelumab was estimated using HRs of 2.145 for the first 2 months and 1.168 for the subsequent period [12].

Utilities

For the utility estimation, the model employed a time-to-death approach, assigning utility values based on the remaining time until death, measured in days. Based on OS data, three distinct health states were defined: i) >266 days to death; ii) 35-266 days to death; iii) <35 days to death. This methodology aligns with the approach used by NICE, which is considered effective in capturing the decline in utility values as patients approach the end of life.

Furthermore, the analysis included the impact of severe adverse events (AE) on patients' quality of life by adjusting for utility decrements associated with these events and their duration (Supplementary Material Table S3). The data for utility decrements were primarily sourced from the avelumab submission to NICE [11] or, when unavailable, relevant literature was consulted [14]. Utility decrements were applied as a one-off reduction at the beginning of the simulation.

Cost input

This analysis was conducted from the perspective of the Italian SSN, considering only direct healthcare costs, including drug acquisition and administration, post-progression therapies, patient monitoring, management of AEs, and end-of-life care. The main inputs are summarized in Table I, with further data provided in the Supplementary Material (Table S4 and Table S5). Costs and health outcomes were discounted at an annual 3% rate. All costs are presented in 2024 values.

Drug acquisition and administration

For avelumab the ex-factory prices net of mandatory discount [15], was considered. The price of retifanlimab was assumed to be equivalent to the cost of the highest-priced PD-1 inhibitor in Italy, rounded up to the nearest thousand (Supplementary Material Table S6).

Cost item		Unit cost (€)	References
Avelumab (200 mg)[1]		985.55	AIFA – Lists of Class A and Class H medications [15]
IV administration		37.10	DRG 410 (day hospital) reduced by 90% [19]
Disease monitoring PFS (weekly)		24.41	Italian National Tariff [19]
Disease monitoring PPS (weekly)		22.99	Italian National Tariff [19]
Post-progression therapies (one-off)		1,484	Harms et al. [30], D'Angelo et al. [13], Decreto 10/2012 [19]
AE management (one-off)	• Retifanlimab	494.45	Mickisch et al. [23], DRG 139, 297, 90, 395 [19]
	• Avelumab	176.52	
End of life (one-off)		4,023.69	Scaccabarozzi et al. [24]

Table I. *Cost input*

[1] Ex-factory price net of mandatory discounts

AE: adverse event; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival

The dosing regimen for avelumab followed the indications in the Summary of Product Characteristics (SmPC) [16], while for retifanlimab, the regimen was based on the POD1UM-201 trial protocol [17] and its SmPC [18], with treatment continuing for a maximum of 2 years.

Treatment and administration costs were calculated by multiplying the number of patients in each cycle, derived from the PFS curve, by the respective drug acquisition and administration costs. Drug wastage was not considered in the analysis. For intravenous or subcutaneous drug administrations, the cost per administration was determined using the national tariff (DRG 410) for day-hospital settings [19], adjusted by a 90% reduction [20].

The costs of premedication (e.g., paracetamol) and any concomitant treatments were assumed to be included in the drug administration tariff. It was also assumed that patients would undergo the following tests prior to each drug administration: complete blood count, liver function, renal function, and thyroid function. The costs associated with these tests were estimated using the national tariffs for outpatient specialist services [19].

Post-progression therapies

The treatments administered following disease progression were assumed to consist of one infusion of chemotherapy every 21 days in a hospital setting. The expenses associated with post-progression therapies were applied as a one-time cost with no assumed effect on survival outcomes.

Based on clinical trial data, it was estimated that 77.1% of patients receiving retifanlimab (POD1UM-201, 2023, data on file) and 88.9% of patients receiving avelumab [13] would undergo post-progression therapies. The duration of this therapy was assumed to be 2.9 months, in line with the average duration of second-line chemotherapy reported in a recent systematic review [21]. The cost of each infusion was estimated using the national tariff (DRG 410) for day-hospital settings [19].

Patient monitoring

The model's assumptions regarding the type and frequency of monitoring visits and tests (Supplementary Material Table S5) were based on the guidelines outlined in the Regional Healthcare Plan of Campania [22] and supplemented by expert clinical opinion (Expert Opinion). In the absence of specific data, it was assumed that patients receiving either retifanlimab or avelumab would have an equivalent frequency of monitoring and resource utilization. The associated resource costs were estimated using the national tariffs for outpatient specialist services [4].

Adverse event management

The model included only grade ≥3 AEs that occurred in more than one patient, as events of lower severity were considered to have a minimal impact on costs. AEs data for retifanlimab were obtained from the POD1UM-201 trial (POD1UM-201, 2023, data on file), while data for avelumab were sourced from the JAVELIN Merkel 200 – part B trial [8] (Supplementary Material Table S5).

The mean per-patient cost for AE management was calculated by multiplying the frequency of each event by its corresponding management cost (Supplementary Material Table S4), derived from relevant literature [23] or from national tariffs [19]. For AEs that did not require hospitalization, it was assumed that a specialist consultation would be sufficient, with associated costs estimated based on national tariffs for outpatient specialist services [19].

End-of-life

The cost of end-of-life care were applied to all patients at the time of death. In the absence of specific data, a value sourced from the literature was used [24]. This expense, representing terminal care during the last 3 months of life, was incorporated as a one-time cost in the cycle in which death occurred.

Sensitivity analyses

A univariate deterministic sensitivity analysis (DSA) was performed to identify key drivers and assess sources of uncertainty in the model's input parameters. Each parameter was varied by ±20% from the base case value or within its defined range.

To evaluate the overall uncertainty across all model parameters, a probabilistic sensitivity analysis (PSA) was conducted with 1,000 iterations. In each iteration, parameters were varied simultaneously and randomly, according to their probability distributions and the model outputs were recalculated.

Scenario analysis

A range of scenario analyses were carried out to test the robustness of base-case results. Specifically:

- Discount rates of 0%, 1.5%, and 5%.
- Retifanlimab efficacy based on unweighted IPD.
- Alternative parametric distributions for the retifanlimab OS curve.
- OS curve for avelumab estimated using a single HR of 0.615.
- 5-year and 10-year time horizons.
- Progression-based approach for the utility estimation (0.827 for pre-progression and 0.742 for post-progression health states [25]).

	Retifanlimab	Avelumab	Δ
Overall costs (€)	161,585	149,357	12,228
• Drug	145,809	136,105	9,704
• Administration	3,301	4,475	-1,174
• AE	494	177	318
• Monitoring PFS	2,451	1,673	778
PPS	5,360	2,522	2,839
• Post-progression therapy	907	790	117
• End of life	3,261	3,615	-354
Total LYs	6.39	3.42	2.98
Total QALYs	5.11	2.68	2.43
ICER (€/LY gained)		4.107	
ICER (€/QALY gained)		5.037	
INMB (€)[1]		67,881	

Table II. *Cost-utility results in the base case analysis*
[1] Calculated considering a willingness-to-pay of €33,000 per QALY
AE: adverse event; INMB: Incremental Net Monetary Benefit; LY: life-years; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life-years

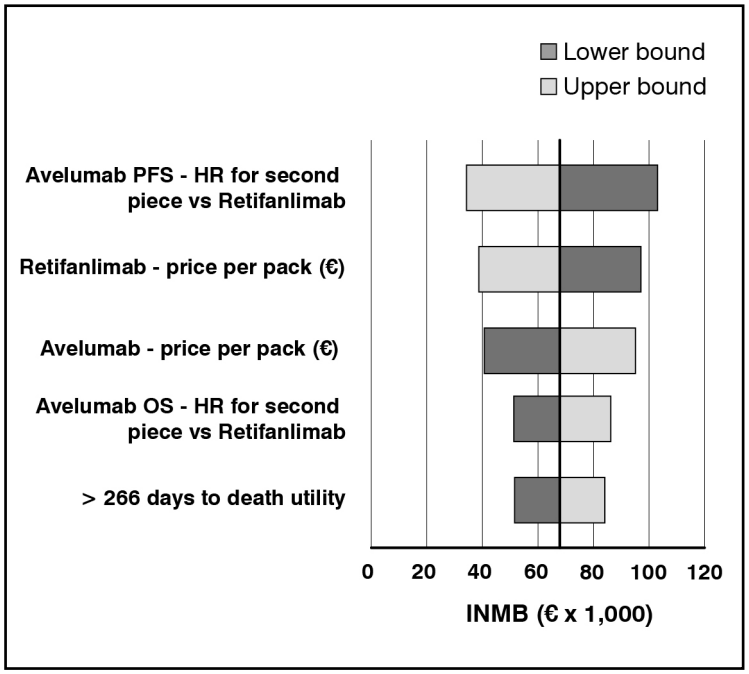

Figure 4. *DSA (tornado chart): incremental net monetary benefit*
HR: hazard ratio; INMB: Incremental Net Monetary Benefit; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life-years

RESULTS

Base case analysis

Retifanlimab demonstrated significantly improved efficacy outcomes compared to avelumab. Specifically, retifanlimab provided an additional 6.39 life-years (LYs) and 5.11 quality-adjusted life-years (QALYs), compared to 3.42 LYs and 2.68 QALYs with avelumab (Table II and Supplementary Material Table S6). This resulted in an incremental gain of 2.98 LYs and 2.43 QALYs in favour of retifanlimab. The overall costs for retifanlimab were €161,585 compared to €149,357 for avelumab, leading to an additional cost of €12,228. As a result, the incremental cost-utility ratio (ICER) was estimated at €4,107 per LY gained and at €5,037 per QALY gained. The detailed breakdown of costs is provided in Table II.

In particular, the model estimated that retifanlimab reduced drug administration costs by 26%. On the other hand, monitoring costs were higher with retifanlimab due to longer survival. These estimates are likely conservative, as we assumed three CT scans per year for both pre- and post-progression.

Sensitivity analyses

The results of the DSA are presented using a tornado diagram, highlighting the key model parameters influencing the incremental net monetary benefit (INMB) (Figure 4). This was computed considering a willingness to pay of €33,000 per QALY, in line with the drug reimbursement threshold reported in Italy [26]. The analysis showed that the INMB was sensitive to variations in drug pricing and the HRs used to estimate avelumab's efficacy.

In the PSA, the incremental cost-effectiveness plane (Figure 5) showed that all simulations fell within the eastern quadrants, indicating that retifanlimab was more effective than avelumab. Additionally, 43.0% of the simulations were in the south-east quadrant, indicating that retifanlimab was dominant (more effective and less costly).

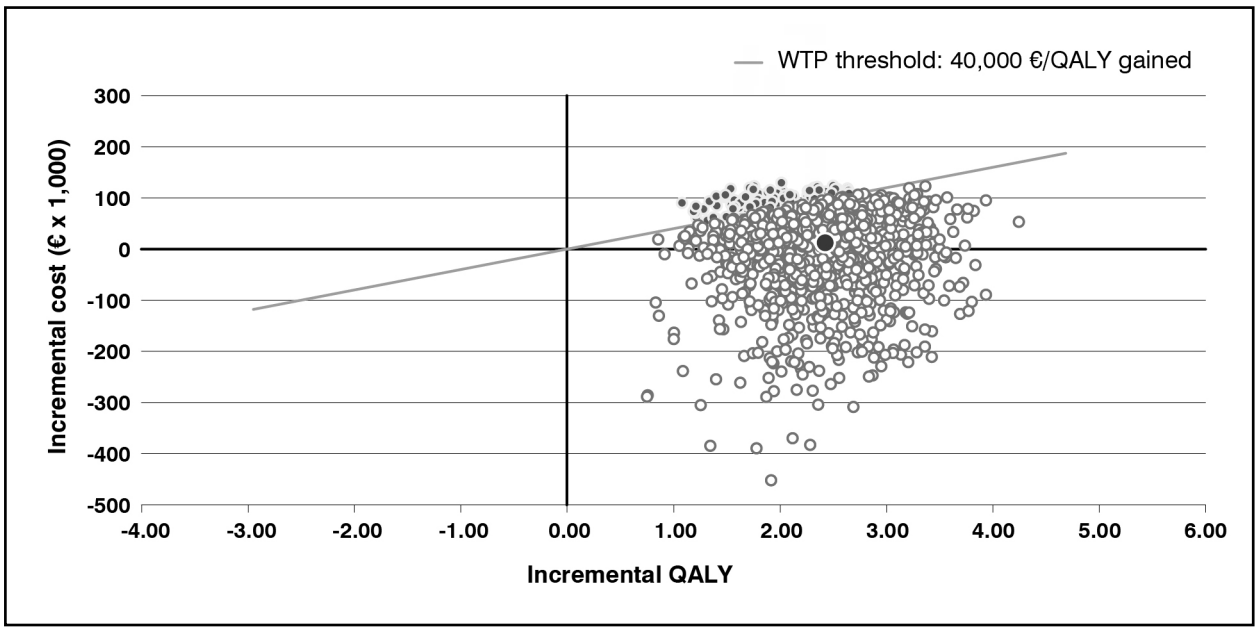

Figure 5. *PSA (scatterplot): incremental cost-effectiveness plane*
QALY: quality-adjusted life-years; WTP: willingness-to-pay

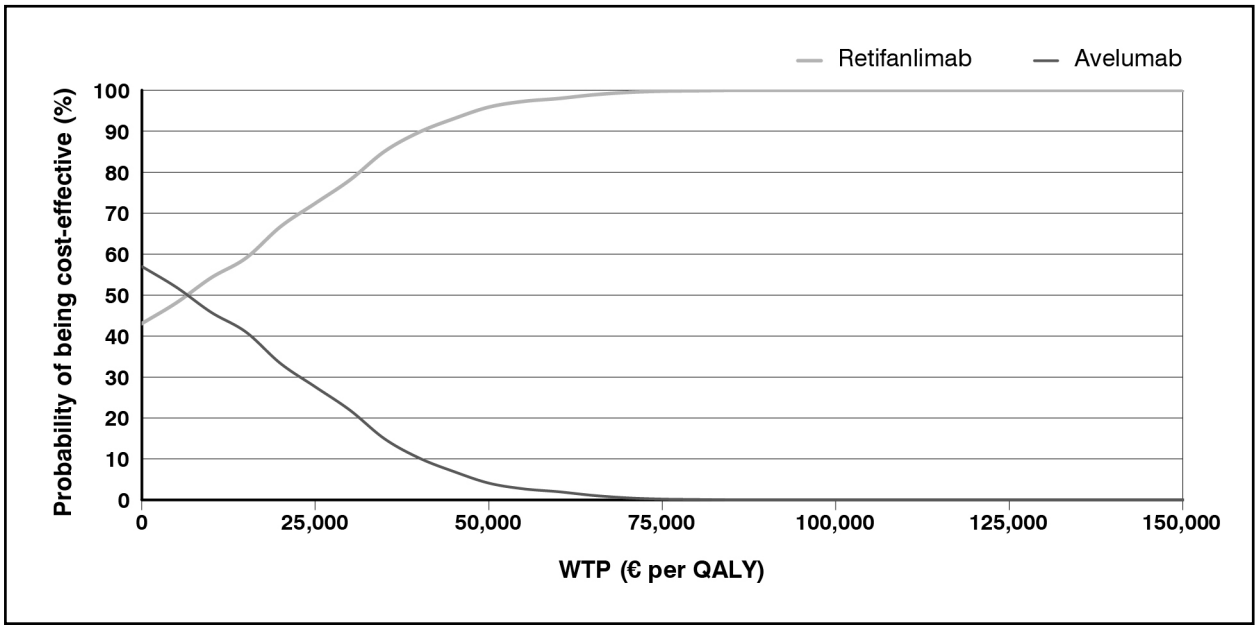

Figure 6. *PSA: cost-effectiveness acceptability curve*
QALY: quality-adjusted life-years; WTP: willingness-to-pay

In the cost-effectiveness acceptability curve (Figure 6), the probability of retifanlimab being cost-effective increased with higher willingness-to-pay (WTP) thresholds. At a WTP threshold of €40,000 per QALY gained, the probability reached 89.8%.

Scenario analysis

The scenario analysis confirmed the base case results, with the ICER varying within the established range of minimum and maximum values. Among the scenarios investigated (Table III), retifanlimab was found to be dominant in the scenario where unweighted IPD were used to model its efficacy. Conversely, shortening the time horizon to 5 years increased the estimated ICER to €42,157 per QALY gained. Notably, the assumptions regarding the parametric distribution used to extrapolate efficacy data beyond the trial follow-up had minimal impact on the estimated ICER, which ranged from €5,037 to €9,185 per QALY gained.

Parameter	Base Case	Investigated scenarios	ΔCost (€)	ΔQALY	ICER (€ per QALY)
Discount rate	3.0%	0%	5,497	3.18	1,727
		1.5%	9,099	2.77	3,287
		5%	15,796	2.06	7,656
Retifanlimab efficacy data	Weighted IPD	Unweighted IPD	-9,286	2.49	Dominant
OS curve extrapolation for retifanlimab	Log-normal	Weibull	12,086	2.38	5,088
		Log-normal	12,228	2.43	5,037
		Exponential	15,498	1.69	9,185
		Gamma	11,968	2.27	5,264
		Log-logistic	12,147	2.41	5,042
		Generalized gamma	11,739	1.99	5,905
		Gompertz	11,219	1.73	6,468
OS curve HR for avelumab	Time-dependent approach	Single HR	11,838	2.02	5,873
Utility	Time-to-death approach	Progression-based approach	12,228	2.19	5,584
Time horizon	Lifetime	5 years	30,063	0.71	42,157
		10 years	15,694	1.53	10,273

Table III. *Scenario analysis results*
HR: hazard ratio; IPD: individual patient data; OS: overall survival; QALY: quality-adjusted life-years

DISCUSSION

This analysis compared the long-term clinical and economic outcomes of retifanlimab versus avelumab in patients with mMCC who had not received prior systemic therapies, from the Italian SSN perspective.

In the base-case analysis, retifanlimab was cost-effective offering significant clinical benefits over avelumab, both in terms of LYs and QALYs. Furthermore, the ICERs for retifanlimab of €4,107 per LY gained and €5,037 per QALY gained fall well below commonly accepted thresholds. While Italy lacks formal ICER acceptability thresholds, the Italian Society of Health Economics (AIES) suggests an informal range of €25,000–40,000 per QALY [27]. Notably, evidence suggests that the ICER significantly influences the outcomes of pricing and reimbursement negotiations with AIFA when it exceeds €40,000/QALY [26].

Sensitivity and scenario analyses also confirmed the robustness of the base case results. Even when key factors such as drug pricing and PFS HR varied, retifanlimab remained cost-effective across most scenarios. Notably, retifanlimab was dominant in 43.0% of the simulations in the PSA and in the scenario analysis where efficacy was modelled using unweighted IPD. Although retifanlimab generally incurred higher costs than avelumab, it consistently offered significant improvements in patients' quality of life, justifying its additional cost and potential adoption in clinical practice. The analysis focused on mMCC patients; however, retifanlimab has a broader indication than avelumab, as it also includes patients with recurrent, locally advanced MCC that is not amenable to curative surgery or radiation therapy.

To the best of our knowledge, this is the first economic assessment on retifanlimab and no further analyses were identified in the literature.

This analysis employed a newly developed model, derived from the structure of the avelumab model submitted to NICE. However, several limitations must be acknowledged. First, the lack of direct clinical trials comparing retifanlimab with avelumab may affect the certainty of the efficacy assessment. To address this limitation, an indirect comparison was performed using the MAIC, which is recognized as an appropriate and valid methodology in cases where direct comparisons are unavailable. The MAIC allows for reliable estimates of treatment efficacy by adjusting for differences in baseline characteristics between studies, ensuring more robust and clinically relevant results [28].

Moreover, the short follow-up duration in the clinical trials required extrapolation to estimate long-term outcomes. Although extrapolation is standard practice, it relies on assumptions that may not fully reflect real-world dynamics, highlighting the need for extended follow-up data.

Additionally, the utility values were derived from the avelumab submission to NICE. Although these values are widely accepted, they may not entirely represent the Italian healthcare context.

The absence of real-world evidence further limits the applicability of these findings. While clinical trial data provide valuable insights, integrating real-world data in future analyses would enhance the robustness and relevance of these results.

Lastly, future evaluations of retifanlimab should adopt the ISPOR Value Flower framework [29] to provide a more comprehensive assessment of its value. This approach extends beyond traditional cost-effectiveness measures by including broader societal benefits such as improved patient productivity, enhanced treatment adherence, and equitable access to care [29]. Key dimensions, including the value of hope, the insurance value, and the real option value, should also be considered to capture psychological, financial, and future therapeutic benefits associated with the treatment [29]. Assessing retifanlimab's role in advancing scientific innovation and addressing societal impacts [29], such as indirect costs and caregiver burden, will further enrich its economic and societal evaluation.

CONCLUSION

The results of this cost-utility analysis provide strong support for considering retifanlimab as a highly cost-effective treatment option compared to avelumab, particularly in light of its demonstrated clinical benefits and its alignment with the commonly accepted economic threshold in Italy.

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Conflict of interests
GG, CP, and MP are employees of AdRes HE&OR which has received project funding from Incyte Biosciences Italy.

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