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Clinical and biochemical predictors of response to avelumab in patients with metastatic Merkel Cell Carcinoma (MCC)

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Abstract

Background: Merkel cell carcinoma (MCC) is a rare and highly aggressive cutaneous malignancy associated with poor prognosis. Immune checkpoint inhibitors (ICIs), including avelumab and pembrolizumab, have recently been approved as first-line treatment for metastatic MCC. Improved clinical outcomes in obese patients treated with ICIs, a phenomenon known as the "*obesity paradox*," have been reported across several tumor types. However, data in metastatic MCC patients remain limited, likely due to the rarity of this disease.

Patients and methods: This observational, hospital-based study investigated the role of clinical and biochemical markers as potential predictive factors of response to avelumab in patients with metastatic MCC. Patients treated at an Italian referral center for rare tumors between February 2019 and October 2025 were included. Clinicopathological characteristics, BMI, baseline laboratory parameters including neutrophil-to-lymphocyte ratio (NLR) and platelet (PLT) count, and response to avelumab were analyzed using prospectively collected data from an MCC system database.

Results: A total of 41 patients were included. Pre-treatment BMI ≥ 30 was significantly associated with longer progression-free survival (PFS) compared with BMI < 30 [BMI < 30 Group: median PFS, 5 months (95% CI: 3.0 – 22.0); BMI ≥ 30 Group: median PFS, not reached; p=0.031]. The multivariable Cox regression model confirmed these observations.

Conclusion: To our knowledge, this study represents one of the first investigations evaluating the predictive role of BMI in patients with metastatic MCC treated with first-line avelumab. Our findings are consistent with clinical observations of improved

outcomes in obese patients receiving ICIs across multiple tumor types. Advanced age, baseline immune impairment, and obesity-associated “inflammaging” may represent key factors influencing antitumor immune responses in patients with this rare clinical entity.

CHAPTER I

Background Rationale and Objectives

1.1 Epidemiology and Risk Factors

Merkel cell carcinoma (MCC) is a rare but highly aggressive primary tumor with both epithelial and neuroendocrine features, first described by Cyril Toker in 1972 as "trabecular carcinoma" [1]. Although it accounts for fewer than 1% of all cutaneous malignancies [2], its incidence has risen markedly in recent decades, largely driven by population aging, improved diagnostic accuracy, and a likely true increase in disease burden [3–13].

Age is a significant epidemiologic risk factor, with a median age at diagnosis of approximately 77 years, while MCC is rare in individuals younger than 50 years [2]. Incidence is nearly twice as high in men as in women and is substantially greater in non-Hispanic White populations compared with Black ones [14]. The area distribution mirrors cumulative ultraviolet (UV) exposure, which represents a pivotal risk factor, with predilection for sun-exposed skin.

Immunosuppression, related to HIV/AIDS, hematologic malignancies, or solid-organ transplantation, confers a several-fold risk elevation characterizing 6–12% of MCC cases [15–18].

At the molecular level, Merkel cell polyomavirus (MCPyV) is clonally integrated into the tumor genome and represents the etiological driver of approximately 80% of MCC in Europe and North America, while UV-driven, virus-negative MCC predominates in white

populations living in high-UV-exposed areas, including Australia [2,19,20].

1.2 Pathogenesis

From a pathogenetic perspective, MCC is characterized by two major molecular subtypes that arise through distinct etiological mechanisms but ultimately converge on the inactivation of the same key tumor suppressor pathways, namely retinoblastoma protein (RB1) and p53. The disruption of these pathways represents a central oncogenic event and underlies the aggressive biological behavior of the disease.

Most MCC cases are virus-positive and are driven by the clonal integration of MCPyV into the host genome. MCPyV is a small double-stranded DNA polyomavirus of 5.4 kilobases that is commonly detected as part of the normal cutaneous virome in healthy individuals. In MCC, viral integration occurs early during tumor development and is followed by constitutive expression of viral early genes [21–23]. These viral products include the large T antigen (LT) and small T antigen (sT). In contrast, late region genes, encoding the structural capsid proteins viral protein 1 (VP1) and viral protein 2 (VP2), are typically not expressed in tumor cells, as viral replication is no longer required for tumor maintenance [24].

A hallmark of virus-positive MCC is the presence of tumor-specific truncating mutations in the LT antigen. These mutations disrupt the helicase activity necessary for viral replication while preserving the ability of LT to bind and functionally inactivate RB1. In parallel, the sT antigen exerts oncogenic effects through multiple mechanisms, including disruption of Fbxw7-dependent proteostasis. This leads to the stabilization of oncogenic substrates and sustained activation of pro-survival signaling pathways [2,20]. As a consequence of these molecular events, virus-positive MCCs exhibit a relatively low

tumor mutational burden. However, these tumors remain highly immunogenic due to the stable and homogeneous expression of viral oncoproteins, which act as shared tumor antigens and can be recognized by the host immune system.

Conversely, virus-negative MCC is primarily associated with chronic UV radiation exposure. These tumors accumulate extensive UV-induced DNA damage and reach one of the highest tumor mutational burdens reported among human cancers [25]. The mutational landscape of virus-negative MCC is dominated by recurrent inactivating alterations in RB1 and TP53, consistent with canonical UV mutational signatures. In contrast to virus-positive tumors, immunogenicity in virus-negative MCC is driven by the large number of somatic mutations, which generate a broad repertoire of tumor-specific neoantigens [20].

Despite their distinct etiological origins, both virus-positive and virus-negative MCC converge on the functional inactivation of the RB1 and p53 tumor suppressor pathways. Loss of these critical regulators of cell-cycle control and genomic stability ultimately promotes uncontrolled cellular proliferation and tumor progression.

Importantly, both MCC subtypes are characterized by pronounced immunogenicity, albeit through different mechanisms: stable viral antigen expression in virus-positive tumors and extensive neoantigen generation in virus-negative tumors. This shared immunogenic profile provides a strong biological rationale for the remarkable sensitivity of MCC to immune checkpoint inhibition, which has fundamentally changed the therapeutic landscape of this cancer [26].

1.3 Clinical Presentation

MCC typically presents as a solitary, firm, painless, rapidly enlarging erythematous-violaceous nodule or plaque [2]. The primary tumor shows a predilection for sun-exposed areas, including the head and neck, upper and lower extremities; however, any cutaneous location may be involved. In 0.8–14% of patients, the primary lesion is occult, and the disease presents with nodal or distant metastasis [3,7,20]. Dermoscopic examination reveals polymorphous and linear irregular vessels, with an erythematous background and milky-red areas; however, these findings overlap substantially with those of other non-pigmented malignancies, making histopathologic and immunohistochemical confirmation mandatory [27] (Figure 1A-B).

1.4 Diagnosis and Histopathology

Histologically, MCC presents as a dermal or subcutaneous proliferation of small round blue cells, characterized by scant cytoplasm, finely granular “salt-and-pepper” chromatin, and a high mitotic rate, with a Ki-67 proliferation index often exceeding 70–80% [2]. Immunophenotypically, the diagnosis is supported by cytokeratin 20 (CK20) positivity, typically exhibiting a perinuclear dot-like staining pattern, along with the co-expression of synaptophysin, chromogranin A, and CD56. Conversely, negativity for thyroid transcription factor 1 (TTF-1), S100 protein, and melanocyte antigen Melan-A helps to exclude morphologically similar entities, including small cell lung carcinoma and melanoma [2,20].

1.5 Staging and Prognosis

The 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system presents the standard framework for MCC staging [28]. Primary tumor (T) definitions are consistent between clinical and pathological assessments. Nodal staging (N) distinguishes disease detected clinically or radiologically from histologic confirmation obtained through sentinel lymph node biopsy (SLNB), lymphadenectomy, or fine-needle aspiration [2]. Distant metastases (M) are categorized mirroring that of melanoma: M1a for cutaneous, subcutaneous, or distant lymph nodes metastases; M1b for lung; and M1c for other visceral sites [20].

Prognosis depends on both tumor- and host-related factors. Adverse features include larger tumor size (greater than 2 centimeters), head and neck location, and host immunosuppression, as well as pathological features such as increasing thickness and lymphovascular invasion [2,20]. Nodal risk rises with tumor diameter, from approximately 14% for lesions measuring 0.5 cm to over 36% for tumors ≥6 cm. Overall survival (OS) strongly depends on stage: five-year OS is about 50% for localized disease, 35% for regional involvement, and 13% for distant metastases. Occult nodal metastases are found in roughly one-third of patients at diagnosis, and outcomes are superior when disease is detected by SLNB compared with clinically evident nodal involvement [20].
At presentation, around 65% of patients have localized disease, 26% nodal metastases, and 8% distant metastases [2].

1.6 Therapeutic Landscape

For localized disease, wide local excision with 1–2 cm margins, if anatomically feasible, followed by adjuvant radiotherapy, represents the therapeutic standard. This multimodal approach reduces local recurrence, improves locoregional control, and may confer OS benefit, particularly in patients with negative prognostic factors.

As stated, SLNB is essential for accurate staging: when positive, it prompts consideration of Complete Lymph Node Dissection (CLND) and/or nodal basin radiotherapy. As no overall survival benefit has been demonstrated for routine CLND compared with radiotherapy alone, CLND is generally reserved for macroscopic nodal disease, whereas radiotherapy remains the cornerstone of nodal management [2,20].

In advanced MCC, platinum–etoposide chemotherapy historically represented the standard systemic approach, achieving high initial response rates exceeding 50%. However, these responses were short-lived, with a median progression-free survival (PFS) of only 3–4 months and no demonstrable OS benefit, thereby restricting its role to palliation [29].

The therapeutic landscape has since been revolutionized by the introduction of immune checkpoint inhibitors (ICIs), a class of agents that target immune checkpoint pathways—key regulatory mechanisms of the immune system that, when activated, attenuate antitumor immune responses.

ICIs act by modulating inhibitory regulatory pathways that physiologically limit T-cell activation and prevent autoimmunity. Among these, the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis plays a central role in peripheral immune tolerance. PD-1 is expressed on activated T lymphocytes, B cells, and natural killer (NK) cells and, upon engagement with its ligands PD-L1 or PD-L2, transduces

inhibitory signals that reduce T-cell proliferation, cytokine secretion, and cytotoxic effector function. Tumor cells and cells of the tumor microenvironment (TME) frequently exploit this pathway through PD-L1 overexpression, thereby inducing functional exhaustion of tumor-infiltrating lymphocytes and enabling immune escape [30].

Blockade of the PD-1/PD-L1 interaction with ICIs restores antitumor immune activity by reinvigorating exhausted T cells, enhancing clonal expansion, cytokine production, and tumor cell killing [31,32]. In immunogenic tumors, such as MCC, this strategy is particularly effective, as pre-existing antitumor immune responses can be rapidly reactivated once inhibitory signaling is relieved.

Among ICIs, avelumab, a fully human IgG1 monoclonal antibody directed against PD-L1, was the first agent to demonstrate efficacy and durable activity, with the JAVELIN Merkel 200 trial reporting an Objective Response Rate (ORR) of 33% as second-line treatment after chemotherapy and a median OS of 12.9 months. In the first-line setting, efficacy was even greater, with an ORR of ~40% and complete responses in ~16% of patients [33].

Avelumab disrupts PD-1/PD-L1–mediated inhibitory signaling, thereby reactivating antigen-specific T-cell responses within the MCC TME. By preventing PD-L1 engagement with PD-1 on activated T lymphocytes, avelumab enhances T-cell proliferation, cytokine production, and cytotoxic effector function, effectively reversing adaptive immune resistance. Distinct from other PD-L1 inhibitors, avelumab preserves an intact Fc domain that can engage Fcγ receptors on NK cells, enabling antibody-dependent cellular cytotoxicity (ADCC) against PD–L1–expressing tumor cells and contributing to sustained antitumor immune control in MCC [34].

Additional ICIs have demonstrated substantial efficacy: pembrolizumab, an IgG4 isotype antibody that targets PD-1receptor of lymphocytes, achieved an ORR of ~56% in treatment-naïve advanced MCC [35], while nivolumab (another anti-PD-1 monoclonal antibody) reached ORRs of up to ~68% in smaller prospective series [36].

Collectively, these data support PD-1/PD-L1 blockade as the guideline-endorsed first-line systemic therapy for advanced disease, marking a paradigm shift from transient cytotoxic benefit to durable immunologic control [2,20].

1.7 Prognostic factors of response

ICIs, and particularly the anti–PD-L1 antibody avelumab, have substantially improved outcomes for patients with metastatic MCC. However, durable benefit is achieved only in a subset of patients, and both primary and acquired resistance remain major barriers to long-term disease control.

Predictive factors of ICI effectiveness in MCC remain incompletely understood, underscoring the need for reliable clinical, biochemical, and immunological biomarkers to guide patient stratification and therapeutic decision-making.

To date, response to ICIs has not shown a consistent association with MCPyV status or with UV-driven mutational signatures, despite the markedly distinct immunogenic landscapes of virus-positive and virus-negative MCC [37]. This apparent dissociation suggests that ICI responsiveness in MCC is not linked to a single tumor-intrinsic axis (viral antigenicity versus neoantigen load), but rather emerges from a broader interplay between tumor biology, the TME, and host systemic immune–metabolic factors [38]. Also PD-1/PD-L1 expression within tumor tissue has been explored as a potential predictor in some cohorts; however, results remain inconsistent, likely reflecting assay

heterogeneity, variability in immunohistochemical scoring thresholds, and substantial intratumoral and intertumoral heterogeneity [39,40].

The complexity of resistance to ICIs in MCC likely reflects the multifactorial nature of immune evasion. Mechanisms implicated across other tumor types—including impaired antigen presentation, T-cell exhaustion, TME remodeling, metabolic competition, and cytokine-mediated immunosuppression—are likely to play central roles in MCC but remain incompletely understood [41].

This gap underscores the need for comprehensive biomarker research integrating clinical, biochemical, genomic, transcriptomic, and immune-phenotypic variables.

Finally, emerging observations in oncology have highlighted the so-called "*obesity paradox*" whereby patients with elevated body mass index (BMI) appear to reach enhanced responses to ICIs across several malignancies [42]. Nevertheless, the rarity of MCC has limited the availability of tumor-specific data, leaving this potential association unexplored in this patient population.

1.8 Objectives

This doctoral project is grounded in the recognition of a significant unmet need in the current literature. One of the major challenges in metastatic MCC is the lack of reliable predictive biomarkers capable of identifying patients most likely to benefit from ICIs therapy. Although avelumab and other immunotherapies have substantially improved clinical outcomes, approximately half of patients with metastatic MCC do not achieve durable responses, and no validated clinical biomarkers are currently available to guide patient selection.

The study aims to address this unmet clinical need by focusing on readily accessible clinical parameters and circulating metabolic and inflammatory markers as candidate predictors of response in a prospective cohort of patients with metastatic MCC receiving avelumab. These parameters were selected based on accumulating evidence linking host metabolic status and systemic inflammation to immunotherapy responsiveness across multiple tumor types.

By exploring their potential role as analytically robust and clinically meaningful biomarkers, this project seeks to contribute to improved treatment stratification, earlier identification of non-responders, and ultimately better patient outcomes.

CHAPTER II

Materials and methods

2.1 Study design

This was an observational, hospital-based study designed to investigate the role of clinical and biochemical parameters as predictive biomarkers of immunotherapy response in patients with metastatic MCC treated with the ICI avelumab.

The study population included adult patients with a pathologically confirmed diagnosis of MCC and metastatic disease, who received avelumab as first-line therapy according to clinical choice and available treatment options. Patients were treated between February 2019 and October 2025 at the Sicilian Regional Center for the Prevention, Diagnosis and Treatment of Rare and Heredo-Familial Tumors, University Hospital Policlinico “Paolo Giaccone” of Palermo. Clinical data were collected in a prospectively updated MCC System database.

Pathological information collected for primary MCC included histological subtype, Ki-67 proliferation index (%), and chromogranin A expression, as reported in routine diagnostic pathology records. Clinical data included age, sex, disease stage at diagnosis, comorbidities, hepatic impairment (HBV- or HCV-correlated or from other cause), history of secondary malignancies, primary tumor site, number of metastatic sites, avelumab dosing, and treatment duration. Pre-treatment BMI, Neutrophil-to-Lymphocyte Ratio (NLR), and platelet count (PLT) were also recorded. NLR was calculated from baseline complete blood count values as the ratio between absolute neutrophil and lymphocyte counts. BMI was computed as weight in kilograms divided by height in

meters squared, and classified according to World Health Organization (WHO) criteria: normal weight (BMI =18.5–24.9), overweight (BMI = 25–29.9), and obese (BMI ≥30).

2.2 Endpoints and response assessment

The primary study endpoint was PFS, defined as the time from treatment initiation to disease progression, death from any cause, or last follow-up for censored patients. OS, defined as the time from treatment initiation to death from any cause, with patients alive at last follow-up censored, was also evaluated.

Tumor response to treatment was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.1), including progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR).

ORR, defined as the proportion of patients with a CR or PR per RECIST, was also calculated.

Associations between clinicopathological characteristics, BMI, NLR, PLT count, and clinical outcomes were analyzed. All clinical variables were anonymized and coded before analysis.

The study protocol received approval from the Ethics Committee of the University Hospital A.O.U.P. “Paolo Giaccone” of Palermo (approval number 1122). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.3 Statistical analysis

Descriptive analyses were performed to assess patients' characteristics. Differences between subgroups were assessed using Fisher's exact test. Pearson's correlation coefficient was used to evaluate the linear relationship between age and pre-treatment BMI.

The analysis of PFS and OS between groups was compared using the Kaplan-Meier method and log-rank test.

Univariable and multivariable Cox proportional hazards regression models were applied to identify independent prognostic factors for PFS and OS. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were reported. A two-sided P value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics Version 29.0 (IBM Corporation, Armonk, NY, USA).

CHAPTER III

Results

3.1 Baseline patient characteristics

From February 2019 to October 2025, 41 patients with metastatic MCC were included in the study. The median age of the overall population was 78 years (range, 31–91). Twenty-four patients (58.5%) were male, and 17 (41.5%) were female. All patients had a good performance status at treatment initiation, with 30 patients (73.2%) presenting an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 11 patients (26.8%) an ECOG performance status of 1.

Most patients had a relevant burden of comorbidities, with 27 patients (65.9%) presenting two or more concomitant conditions (cardiovascular, endocrinological, and/or other concomitant diseases). Hepatic impairment was reported in 4 patients (9.8%), whereas 12 patients (29.3%) had a history of a second solid or hematological malignancy.

Regarding tumor characteristics, the most frequent primary tumor site was the lower limb (41.5%), followed by head and neck (17.1%), upper limb (12.2%), trunk (9.8%), and unknown primary site (19.5%). Ki-67 proliferation index was available in 32 (78%) patients, with values ≥90% observed in 20 patients (48.7%), while chromogranin A expression was positive in 26 patients (63.4%).

At diagnosis, 21 patients (51.2%) presented with metastatic disease, while 19 patients (46.3%) had non-metastatic disease at initial presentation. Fewer than two metastatic sites were observed in 23 patients (56.1%), and lymph nodes represented the most common

site of metastasis (43.9%), either alone or in combination with other sites.

Baseline inflammatory and hematologic parameters were also assessed. NLR was ≥ 2 in 22 patients (53.7%), while platelet count was ≥ 207 $\times 10^9$/L in 28 patients (68.3%).

Based on baseline BMI, 32 patients (78.0%) were classified as non-obese (BMI <30), while 9 patients (22.0%) were classified as obese (BMI ≥30). In an exploratory analysis, age at avelumab initiation showed a weak inverse correlation with pre-treatment BMI (Pearson's r = −0.30, 95% CI [−0.56, 0.01]; p = 0.061). The detailed distribution of patient clinicopathological characteristics is reported in Table 1.

3.2 Outcome analysis

Overall, the median PFS was 13 months. At the time of data analysis, 22 events (progression or death) were observed in the overall cohort.

Notably, pre-treatment BMI ≥ 30 was significantly associated with longer PFS (p=0.031) (Figure 2). Median PFS was 5 months (95% CI: 3.0–22.0) in patients with BMI <30, whereas median PFS was not reached in patients with BMI ≥30.

Response to avelumab (CR/PR vs SD/PD) was significantly associated with longer PFS (p= 0.024) (Figure 3). No other prognostic factors (gender, ECOG performance status, Ki-67 (%), metastatic sites, metastatic stage at diagnosis, PLT, and NLR at baseline) were significantly associated with PFS.

In the overall population, the median OS was not reached. Nine (9) events (deaths) were recorded. The prognostic factors significantly associated with OS were the best response to avelumab (CR/PR vs SD/PD; p=0.003; median OS not reached vs 27.0 months [95% CI: 15.0–NR]) and ECOG performance status (≥1 vs 0; p=0.005; median OS 19.0 months

[95% CI: 4.0–NR] vs not reached) (Figure 4-5). No other prognostic factors were significantly associated with OS.

3.3 Objective response rate and timing of response

Overall, 21 of 41 patients (51.2%) achieved an objective response to avelumab, including 10 patients (24.4%) who achieved CRs and 11 patients (26.8%) who achieved PRs. SD was observed in 7 patients (17.1%), while PD occurred in 7 patients (17.1%). In 6 patients (14.6%), response assessment was still not available (Table 2).

The ORR was comparable between BMI subgroups, with responses observed in 16 of 32 patients (50.0%) in the BMI <30 group and in 5 of 9 patients (55.6%) in the BMI ≥30 group. CRs were more frequently observed among patients with BMI ≥30 (44.4%) compared with those with BMI <30 (18.8%), whereas PRs were more common in patients with BMI <30.

The median time to best response in the overall population was 3.6 months (range, 2.0–22.9). Patients with BMI <30 achieved best responses earlier, with a median time of 3.4 months (range, 2.0–19.4), whereas patients with BMI ≥30 showed a longer median time to best response of 8.4 months (range, 5.7–22.9).

3.4 Univariable and multivariable analysis

Table 3 summarizes the results of the univariable and multivariable prognostic factor analysis for PFS and OS. Variables included in the univariate analysis were: gender (male or female), age at avelumab start (≤ 75 or > 75 years), pre-treatment BMI (< 30 or ≥ 30),

performance status (1 or 0); metastatic sites (only lymph nodes or lymph nodes and/or other sites); metastatic at diagnosis (no or yes), best response to avelumab (CR/PR or SD/PD), pretreatment PLT count (< 207 or ≥ 207 × 109/L) and pre-treatment NLR (<2 or ≥ 2).

In univariable Cox regression analysis, baseline BMI ≥30 was associated with a statistically significant reduced risk of disease progression compared with BMI <30 (HR 0.553, 95% CI: 0.319–0.960). Also in the multivariable Cox regression model, BMI ≥30 emerged as an independent prognostic factor for longer PFS (HR 0.540, 95% CI: 0.294–0.991; p = 0.047).

Moreover, patients with metastatic involvement of lymph nodes and/or other sites had a significantly higher risk of progression compared with those with lymph node–only disease in univariable Cox regression (HR 2.642, 95% CI: 1.065–6.555; p=0.036). In the multivariable model, this association showed a similar direction but did not retain statistical significance (HR 2.375, 95% CI 0.943–5.985; p=0.067).

No statistically significant associations with PFS were observed for sex, age category (>75 vs ≤75 years), ECOG performance status, metastatic disease at diagnosis, or baseline PLT and NLR.

In the OS analysis, patients whose best response was SD/PD (vs CR/PR) had a significantly increased risk of death in univariable Cox regression (HR 8.043, 95% CI 1.699–38.062; p=0.009), and this association remained significant after multivariable adjustment (HR 17.251, 95% CI 2.145–138.717; p=0.007). This finding should be interpreted cautiously because the analysis is based on a small number of OS events, which increases the risk of model instability and overfitting.

Patients with ECOG performance status 1 (vs 0) had a significantly higher risk of death in univariable Cox regression (HR 5.660, 95% CI 1.706–18.773; p=0.005), and this association remained significant in the multivariable model (HR 12.720, 95% CI 2.192–73.814; p=0.005).

No other baseline clinical or laboratory variable was significantly associated with OS, in either univariable or multivariable analyses.

CHAPTER IV

Discussion

MCC is a rare and highly aggressive neuroendocrine malignancy that has long posed a therapeutic challenge [43].

Until a few years ago, chemotherapy represented the standard treatment for advanced MCC; however, outcomes were poor, with a median PFS of 3–4 months and a median OS of less than 10 months, alongside considerable toxicity [29,43].

The increased incidence of MCC among elderly and immunocompromised patients, together with the frequent presence of immune dysfunction, has long suggested a pivotal role of the immune system in MCC pathogenesis and progression [44].

More recently, immunotherapy has become the cornerstone of treatment for advanced and metastatic MCC, achieving durable responses in a subset of patients [2]. To date, three ICIs—avelumab, pembrolizumab, and nivolumab—as well as the combination of nivolumab and ipilimumab, have demonstrated antitumor activity in advanced MCC [35,45,46]. Avelumab was the first anti–PD-L1 agent approved for metastatic MCC, based on efficacy and safety results from the JAVELIN Merkel 200 trial [33,45]. A recent systematic review and non-comparative meta-analysis of real-world data on avelumab in advanced MCC found 12-month survival outcomes broadly consistent with JAVELIN Merkel 200 trial (12-month OS: 77.7% in stage III and 63.0% in stage IV; 12-month PFS: 53.3% and 39.3%, respectively), and provided additional effectiveness estimates for patients with stage III/locally advanced unresectable disease, a group underrepresented in pivotal trials [47].

Nevertheless, as observed in other malignancies, only approximately half of patients with

metastatic MCC respond to immune checkpoint blockade, and a considerable proportion eventually develop acquired resistance. Consequently, there is an urgent need to identify predictive factors of immunotherapy response and to better understand the mechanisms of tumor immune escape following ICI treatment [48].

In this context, readily accessible host-related variables, including clinical and metabolic parameters, may provide complementary prognostic and predictive information beyond tumor-centered biomarkers [49].

On this topic, recent pan-cancer analyses evaluating outcomes in patients treated with ICIs have reported an association between obesity (BMI ≥30) and improved survival compared with patients with a BMI <30. This phenomenon, termed "*obesity paradox*", was observed across multiple tumor types, including non–small cell and small cell lung cancer, renal cell carcinoma, bladder cancer, breast cancer, gastric cancer, colorectal cancer, endometrial cancer, sarcoma, and others [42].

In the dermatological field, Incorvaia et al. investigated the prognostic and predictive role of BMI in combination with circulating soluble immune checkpoints in patients with metastatic melanoma treated with anti-PD-1 therapy. The authors observed that overweight patients (BMI ≥ 25) achieved significantly improved clinical outcomes, particularly when associated with low baseline levels of soluble PD-1, identifying BMI and circulating immune checkpoints as interconnected predictive factors of response to ICIs [50].

In the present study, we investigated the role of selected clinicopathological and biochemical parameters in patients affected by metastatic MCC treated with avelumab. In our survival analyses, obese MCC patients (BMI ≥ 30) had improved PFS compared with patients with overweight or normal weight (BMI < 30). Baseline clinical

characteristics in our cohort were comparable between BMI groups, suggesting that the observed association between BMI and PFS was not driven by major baseline imbalances. In univariable Cox regression analysis, pre-treatment BMI ≥30 was associated with a significantly reduced risk of disease progression compared with BMI <30. Notably, this association remained significant after adjustment for potential confounders in the multivariable model, underscoring the robustness of the observed effect.

Although counterintuitive, since obesity is a recognized risk factor for cancer development, this finding suggests that host metabolic states may modulate the efficacy of PD-1/PD-L1 blockade in ways that differ from their impact on natural disease course.

MCC patients are frequently characterized by a compromised immune system, not only as a result of physiological age-related immune aging [51], but also due to the high prevalence of additional immunosuppressive conditions [52]. In this already vulnerable immunological setting, obesity could represent an additional factor capable of modulating immune function.

Obesity is well known to be associated with a chronic low-grade systemic inflammatory state, sustained by continuous production of pro-inflammatory cytokines and adipokines, which profoundly alter the adipose tissue microenvironment and extend their effects systemically [53–55]. Rather than enhancing immune activity, this persistent inflammatory stimulation may lead to progressive immune dysregulation.

Specifically, prolonged exposure to inflammatory signals has been shown to promote functional exhaustion of T lymphocytes, characterized by impaired effector function and increased expression of inhibitory immune checkpoints within the PD-1/PD-L1 axis, ultimately resulting in reduced immune competence, a phenomenon known as

"*inflammaging*" [55]. In parallel, obesity promotes a pro-inflammatory remodeling of adipose tissue, including M1 macrophage polarization and increased cytokine release, further amplifying systemic inflammation [56].

As a consequence, obese individuals may exhibit a paradoxical immune phenotype, in which chronic inflammation coexists with impaired antitumor immune surveillance. Specifically, T cell exhaustion, often associated with increased PD-1 expression, can make antitumor immunity more dependent on PD-1/PD-L1–mediated suppression. As a result, tumors may become more sensitive to immune checkpoint inhibition. Therefore, PD-L1 blockade may be particularly effective when tumor-infiltrating T cells are already present and checkpoint signaling is the main barrier to effector function, allowing T-cell reinvigoration and, in some cases, durable tumor control.

Such immune–metabolic interplay may contribute to the association observed between obesity and improved outcomes in immunotherapy-treated MCC [56].

However, these mechanistic considerations remain hypothesis-generating in our cohort, as we did not directly assess systemic inflammatory cytokine profiles or T-cell exhaustion phenotypes.

Nevertheless, the interpretation of the obesity paradox warrants caution. In patients with advanced cancer, a lower BMI may reflect pre-treatment frailty and cancer-related weight loss. In particular, pre-treatment unintentional weight loss, sarcopenia, and cachexia are common in metastatic settings and have been consistently associated with impaired treatment tolerance, reduced immune competence, and poorer survival outcomes, independently of tumor immunobiology. Consequently, patients classified as non-obese at baseline may include individuals with occult cancer-related catabolic

status or higher symptom burden, which could lead to shorter PFS regardless of PD-L1 pathway dependence.

Furthermore, BMI is a surrogate of adiposity and does not capture body composition. Patients with a similar BMI may differ substantially in skeletal muscle mass and visceral fat distribution.

To mitigate these concerns, future studies should incorporate objective markers of nutritional and inflammatory status (e.g., baseline weight change, albumin, C-reactive protein, prognostic nutritional index), as well as imaging-based estimates of muscle mass and adiposity, and evaluate BMI both as a continuous variable and in interaction with cachexia-related parameters [57–59].

In line with this approach, recent evidence based on computed tomography (CT)-derived body composition analyses suggests that the obesity paradox observed in patients receiving ICIs may be more accurately explained by differences in adipose tissue distribution rather than by BMI alone. Specifically, higher subcutaneous and visceral adipose tissue indices—but not intermuscular fat—have been associated with improved PFS and OS, highlighting the heterogeneous biological role of distinct adipose compartments [60].

Given the routine availability of baseline staging CT imaging in our institution, future work on this cohort will incorporate CT-derived body composition measures—such as skeletal muscle index and subcutaneous/visceral adipose tissue indices—to disentangle BMI from sarcopenia/cachexia and refine the interpretation of BMI-related associations.

Notably, in our cohort, patients with BMI ≥30 had a longer time to best response than those with BMI <30. This finding may suggest that, in obese patients, antitumor immune activation following PD-L1 blockade may occur more gradually, yet result in more sustained disease control. A delayed but durable immune response has been described in other immunotherapy-treated populations and may reflect differences in immune priming, metabolic signaling, or effector T-cell dynamics within the TME [61]. These observations may support the importance of prolonged treatment exposure and adequate follow-up when evaluating immunotherapy outcomes in obese patients with metastatic MCC [62].

This study has some limitations, including the small sample size, which reflects the rarity of metastatic MCC, and its observational design. However, all patients were consecutively enrolled at a single referral center, ensuring a relatively homogeneous dataset and limiting potential selection bias. Additionally, BMI represents an imperfect surrogate for obesity, as it does not distinguish between lean mass and adipose tissue [50]. Future prospective studies involving larger cohorts and more precise assessments of body composition are warranted to validate these findings. If confirmed, BMI and body composition–related parameters could contribute to a pragmatic risk stratification framework in metastatic MCCs treated with avelumab, ideally integrated with immunological and tumor-related features to improve clinical decision-making.

CHAPTER V

Conclusions

MCC is a highly immunogenic malignancy that predominantly affects older and immunocompromised individuals—patient groups in whom therapeutic options have historically been limited and outcomes poor. The advent of ICIs has substantially reshaped the treatment landscape, enabling durable disease control in a meaningful proportion of cases; nevertheless, long-term benefit remains limited to a subset of patients, and robust biomarkers to guide prognosis and clinical decision-making are still lacking.

Within this real-world cohort of metastatic MCC treated with avelumab, baseline obesity (BMI ≥30) was associated with prolonged PFS, supporting the clinical relevance of host-related factors and extending the "*obesity paradox*" observation to this rare malignancy. Although BMI is an imperfect marker of adiposity and does not capture body composition or longitudinal weight change, it may nonetheless reflect broader host factors—including nutritional reserve, frailty, and systemic inflammation—that shape immune competence and treatment tolerance. Overall, these findings suggest that readily available baseline measures may aid risk stratification and support the hypothesis that metabolic–inflammatory status may modulate antitumor immunity in MCC.

Larger, multicenter studies incorporating CT-based body-composition parameters and circulating inflammatory/nutritional biomarkers are needed to validate the association, clarify underlying mechanisms, and improve clinical applicability.

Tables and Figures

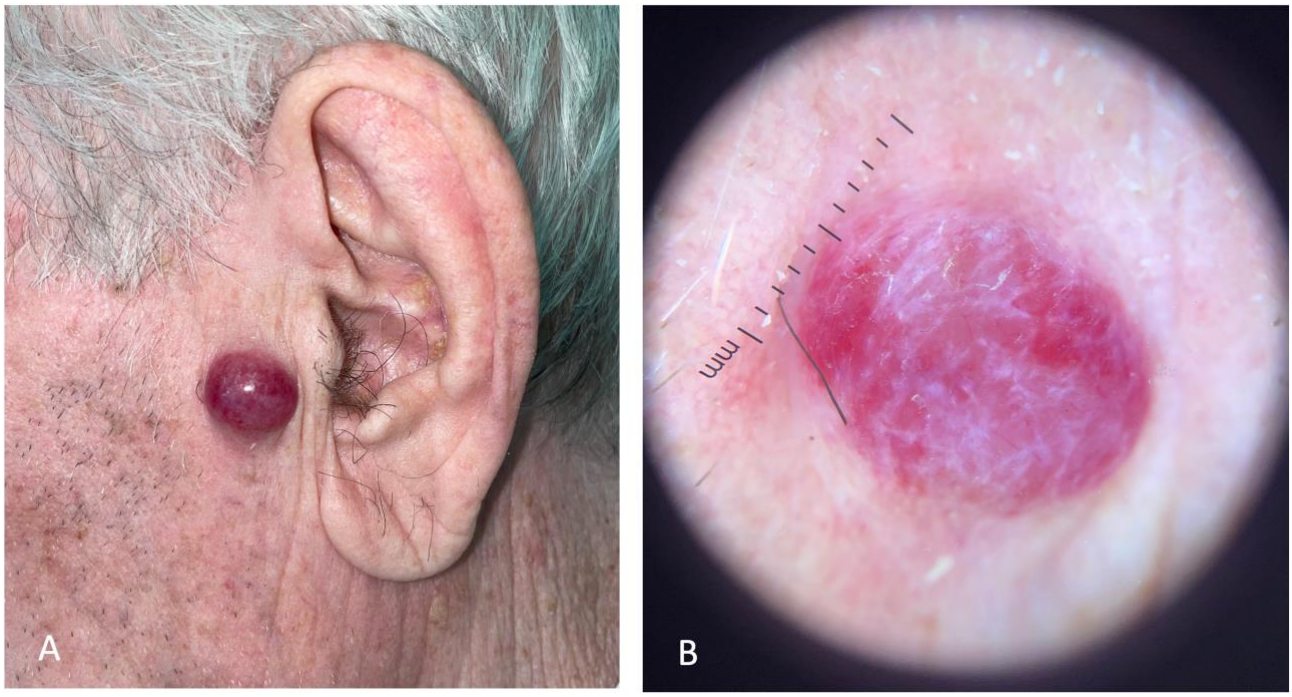

Figure 1. A) MCC appears as a solitary, firm, painless, rapidly enlarging violaceous nodule in the left preauricular region of a male patient; B) dermoscopic examination (10×) reveals irregular vessels, with an erythematous background and milky-red areas.

Characteristic	All patients n (%)	BMI < 30 n (%)	BMI ≥ 30 n (%)	p-value
No. of Patients (%)	41 (100)	32 (78.0)	9 (22.0)	
Gender				
Male	24 (58.5)	20 (62.5)	4 (44.4)	0.45
Female	17 (41.5)	12 (37.5)	5 (55.6)	
Age (years), median (range)	78 (31-91)	78 (31-91)	75 (36-85)	
Age category				
<75 y	15 (36.6)	11 (34.4)	4 (44.4)	0.701
≥75 y	26 (63.4)	21 (65.6)	5 (55.6)	
ECOG				
0	30 (73.2)	24 (75.0)	6 (66.7)	0.68
1	11 (26.8)	8 (25.0)	3 (33.3)	

No. of Comorbidities				
<2	14 (34.1)	12 (37.5)	2 (22.2)	0.692
≥2	27 (65.9)	20 (62.5)	7 (77.8)	
Hepatopathy				
No	29 (70.7)	22 (68.8)	7 (77.8)	0.706
Yes	4 (9.8)	4 (12.5)	0 (0.0)	
Unknown	8 (19.5)	6 (18.8)	2 (22.2)	
Second Tumor				
No	28 (68.3)	22 (68.8)	6 (66.7)	1.00
Yes	13 (31.7)	10 (31.2)	3 (33.3)	
Primary site				
Head and neck	7 (17.1)	6 (18.8)	1 (11.1)	0.756
Trunk	4 (9.8)	2 (6.2)	2 (22.2)	
Upper limb	5 (12.2)	4 (12.5)	1 (11.1)	
Lower limb	17 (41.5)	14 (43.8)	3 (33.3)	
Unknown	8 (19.5)	6 (18.8)	2 (22.2)	
Ki-67 (%)				
<90	12 (29.3)	9 (28.1)	3 (33.3)	0.494
≥90	20 (48.8)	17 (53.1)	3 (33.3)	
Unknown	9 (22.0)	6 (18.8)	3 (33.3)	
Chromogranin-A				
Negative	4 (9.8)	3 (9.4)	1 (11.1)	0.625
Positive	26 (63.4)	19 (59.4)	7 (77.8)	
Not specified	11 (26.8)	10 (31.2)	1 (11.1)	
Metastatic at diagnosis				
No	19 (46.3)	17 (53.1)	2 (22.2)	0.133
Yes	21 (51.2)	14 (43.8)	7 (77.8)	
N. of metastatic sites				
<2	23 (56.1)	19 (59.4)	4 (44.4)	0.471
≥2	18 (43.9)	13 (40.6)	5 (55.6)	
Common site of metastasis				
Lymph nodes	18 (43.9)	14 (43.8)	4 (44.4)	1.0
Others	23 (56.1)	18 (56.2)	5 (55.6)	
NLR				
<2	14 (34.1)	10 (31.2)	4 (44.4)	0.527
≥2	22 (53.7)	17 (53.1)	5 (55.6)	
Unknown	5 (12.2)	5 (15.6)	0 (0.0)	
PLT (x10^9/L)				
<207	8 (19.5)	6 (18.8)	2 (22.2)	0.464
≥207	28 (68.3)	21 (65.6)	7 (77.8)	
Unknown	5 (12.2)	5 (15.6)	0 (0.0)	

Table 1. Patients' and disease characteristics

	All patients	BMI < 30	BMI ≥ 30
No. of Patients (%)	41 (100.0)	32 (78.0)	9 (22.0)
Time to Best Response, Median (range), months	3.6 (2.0–22.9)	3.4 (2.0–19.4)	8.4 (5.7–22.9)
Overall Response (CR + PR), No. (%)	21 (51.2)	16 (50.0)	5 (55.6)
Best Response, No. (%)			
CR	10 (24.4)	6 (18.8)	4 (44.4)
PR	11 (26.8)	10 (31.2)	1 (11.1)
SD	7 (17.1)	4 (12.5)	3 (33.3)
PD	7 (17.1)	6 (18.8)	1 (11.1)
Unknown	6 (14.6)	6 (18.8)	0 (0.0)

Table 2. Objective responses and timing of responses to avelumab.

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

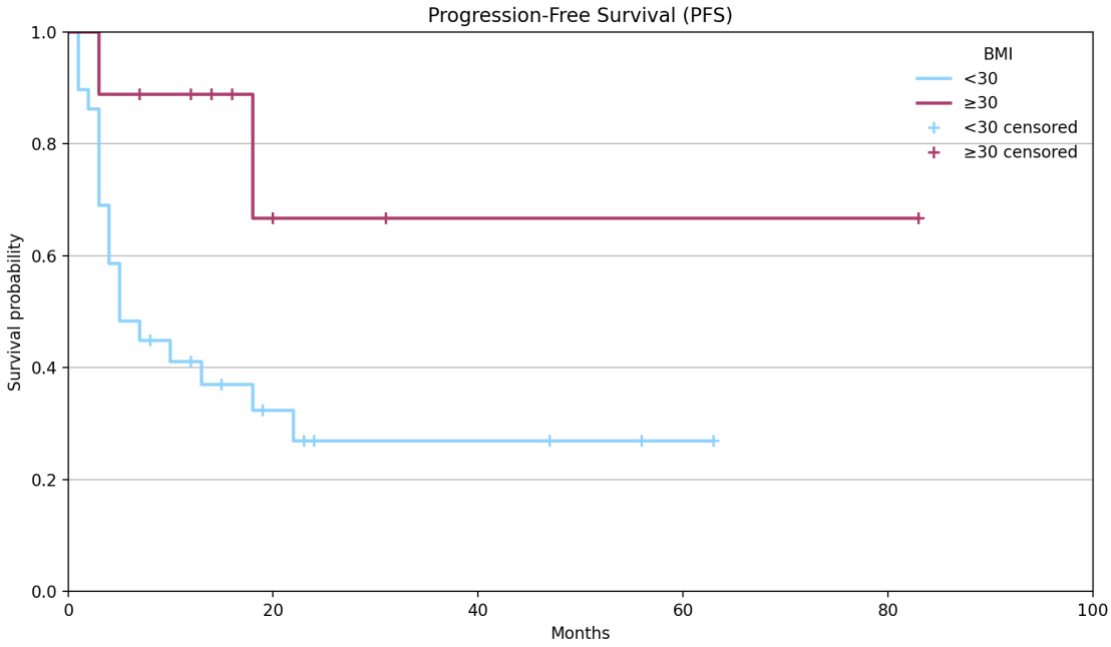

Figure 2. Progression-Free Survival according to BMI.

BMI: body mass index

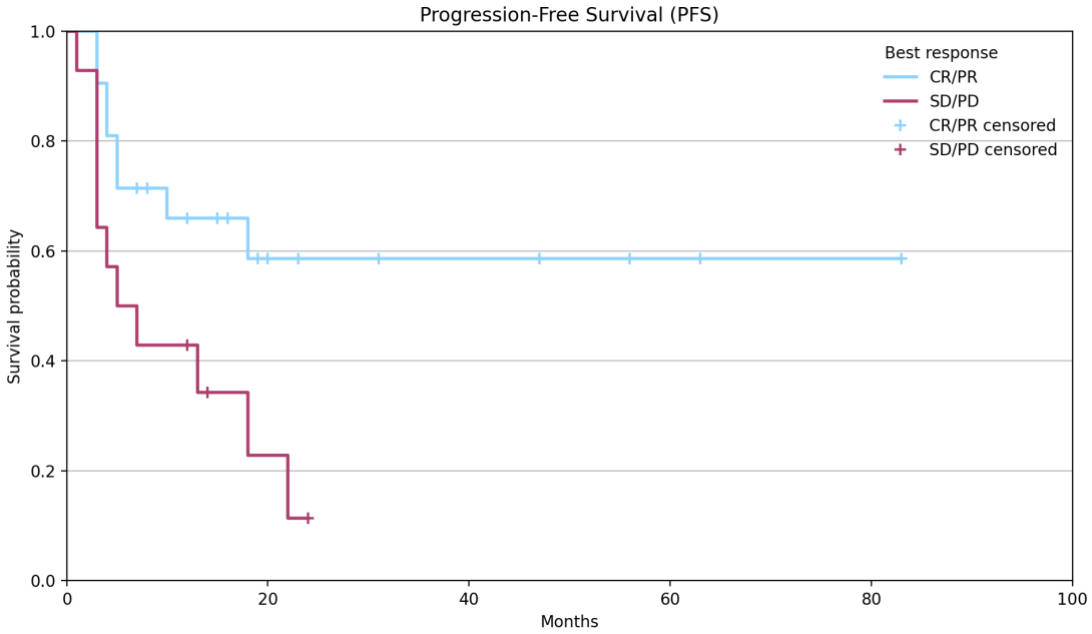

Figure 3. Progression-Free Survival according to best response.

CR: complete response; PR, partial response; SD: stable disease; PD: progressive disease.

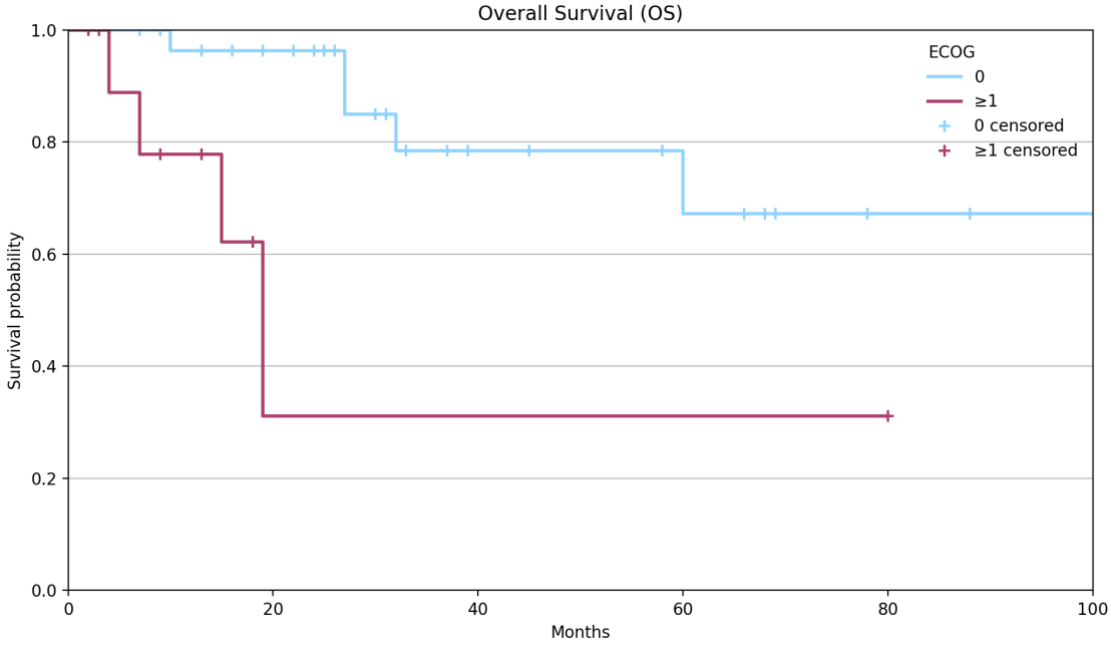

Figure 4. Overall survival according to ECOG performance status.

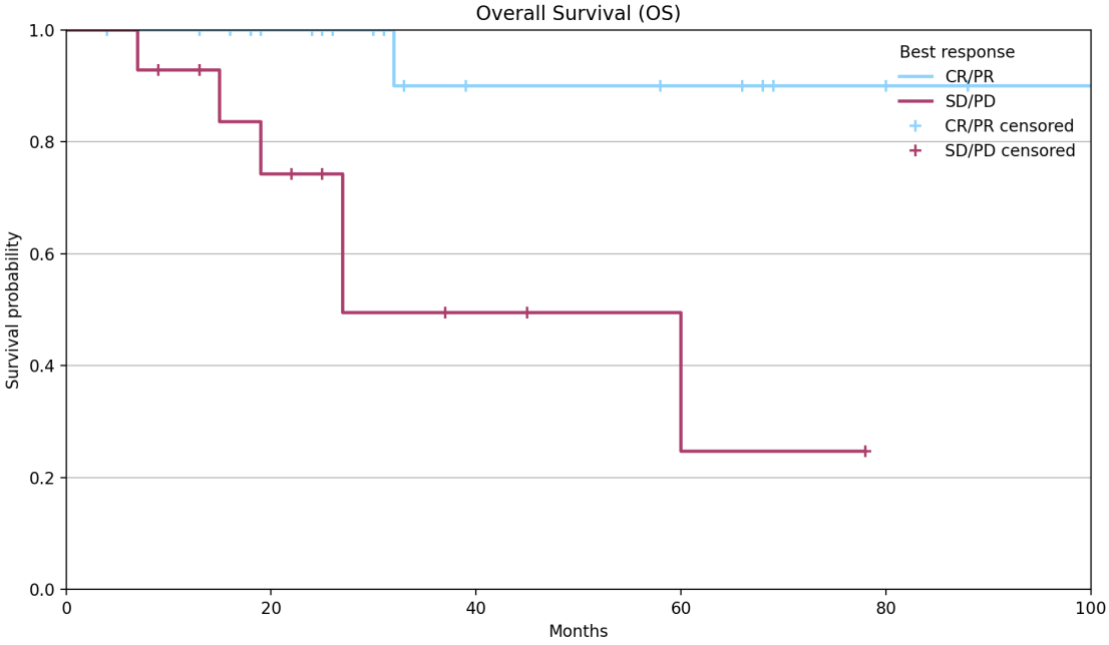

Figure 5. Overall survival according to to best response.

CR: complete response; PR, partial response; SD: stable disease; PD: progressive disease.

	PFS Univariable HR (IC95%)	p-value	PFS Multivariable HR (IC95%)	p-value	OS Univariable HR (IC95%)	p-value	OS Multivariable HR (IC95%)	p-value
BMI (≥30 vs <30)	0.553 (0.319–0.960)	**0.035**	0.540 (0.294–0.991)	**0.047**	0.638 (0.280–1.453)	0.285	—	—
Gender (M vs F)	0.556 (0.241–1.283)	0.169	—	—	0.669 (0.211–2.117)	0.494	—	—
Age (>75 vs ≤75 years old)	1.31 (0.50-3.45)	0.584	—	—	1.68 (0.32-8.66)	0.537	—	—
ECOG Performance status (1 vs 0)	1.912 (0.814–4.492)	0.137	—	—	5.660 (1.706–18.773)	**0.005**	12.720 (2.192–73.814)	**0.005**
Metastatic Sites (Lymph nodes and/or others sites vs only lymph nodes)	2.642 (1.065–6.555)	**0.036**	2.375 (0.943–5.985)	0.067	2.771 (0.734–10.466)	0.133	—	—
Metastatic at diagnosis (yes vs no)	1.042 (0.458–2.371)	0.922	—	—	0.939 (0.297–2.972)	0.915	—	—
Best Response (SD/PD vs CR/PR)	2.360 (0.903–6.165)	0.080	—	—	8.043 (1.699–38.062)	**0.009**	17.251 (2.145–138.717)	**0.007**
PLT (≥207 vs < 207 × 10^9/L)	0.77 (0.27-2.21)	0.626	—	—	0.46 (0.10-2.07)	0.315	—	—
NLR (≥2 vs <2)	0.92 (0.35-2.41)	0.865	—	—	0.54 (0.12-2.40)	0.420	—	—

Table 3. Univariable and multivariable Cox proportional hazards regression analyses evaluating the association between clinical, pathological, and laboratory variables and PFS and OS in patients with MCC treated with avelumab. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs).

Biblography

1. Toker, C. Trabecular Carcinoma of the Skin. *Arch. Dermatol.* 1972, *105*, 107, doi:10.1001/archderm.1972.01620040075020.
2. Gauci, M.-L.; Aristei, C.; Becker, J.C.; Blom, A.; Bataille, V.; Dreno, B.; Del Marmol, V.; Forsea, A.M.; Fargnoli, M.C.; Grob, J.-J.; et al. Diagnosis and Treatment of Merkel Cell Carcinoma: European Consensus-Based Interdisciplinary Guideline – Update 2022. *Eur. J. Cancer* 2022, *171*, 203–231, doi:10.1016/j.ejca.2022.03.043.
3. Fondain, M.; Dereure, O.; Uhry, Z.; Guizard, A.V.; Woronoff, A.S.; Colonna, M.; Molinie, F.; Bara, S.; Velten, M.; Marrer, E.; et al. Merkel Cell Carcinoma in France: A Registries-based, Comprehensive Epidemiological Survey. *Journal of the European Academy of Dermatology and Venereology* 2018, *32*, 1292–1296, doi:10.1111/jdv.14798.
4. Rubió-Casadevall, J.; Hernandez-Pujol, A.M.; Ferreira-Santos, M.C.; Morey-Esteve, G.; Vilardell, L.; Osca-Gelis, G.; Vilar-Coromina, N.; Marcos-Gragera, R. Trends in Incidence and Survival Analysis in Non-Melanoma Skin Cancer from 1994 to 2012 in Girona, Spain: A Population-Based Study. *Cancer Epidemiol.* 2016, *45*, 6–10, doi:10.1016/j.canep.2016.09.001.
5. Samuel, R.J.; Matthews, A.G.; Holme, S.A. Merkel Cell Carcinoma in Scotland 2000-10. *British Journal of Dermatology* 2015, *173*, 1073–1075, doi:10.1111/bjd.13869.
6. Reichgelt, B.A.; Visser, O. Epidemiology and Survival of Merkel Cell Carcinoma in the Netherlands. A Population-Based Study of 808 Cases in 1993–2007. *Eur. J. Cancer* 2011, *47*, 579–585, doi:10.1016/j.ejca.2010.11.002.
7. Zaar, O.; Gillstedt, M.; Lindelöf, B.; Wennberg-Larkö, A. -M.; Paoli, J. Merkel Cell Carcinoma Incidence Is Increasing in Sweden. *Journal of the European Academy of Dermatology and Venereology* 2016, *30*, 1708–1713, doi:10.1111/jdv.13698.
8. Jacobs, D.; Huang, H.; Olino, K.; Weiss, S.; Kluger, H.; Judson, B.L.; Zhang, Y. Assessment of Age, Period, and Birth Cohort Effects and Trends in Merkel Cell

Carcinoma Incidence in the United States. *JAMA Dermatol.* 2021, *157*, 59, doi:10.1001/jamadermatol.2020.4102.

9. Paulson, K.G.; Park, S.Y.; Vandeven, N.A.; Lachance, K.; Thomas, H.; Chapuis, A.G.; Harms, K.L.; Thompson, J.A.; Bhatia, S.; Stang, A.; et al. Merkel Cell Carcinoma: Current US Incidence and Projected Increases Based on Changing Demographics. *J. Am. Acad. Dermatol.* 2018, *78*, 457-463.e2, doi:10.1016/j.jaad.2017.10.028.
10. Freeman, M.B.; Holman, D.M.; Qin, J.; Lunsford, N.B. Merkel Cell Carcinoma Incidence, Trends, and Survival Rates among Adults Aged ≥50 Years from United States Cancer Statistics. *J. Am. Acad. Dermatol.* 2019, *80*, 1154–1156, doi:10.1016/j.jaad.2018.10.045.
11. Kieny, A.; Cribier, B.; Meyer, N.; Velten, M.; Jégu, J.; Lipsker, D. Epidemiology of Merkel Cell Carcinoma. A Population-based Study from 1985 to 2013, in Northeastern of France. *Int. J. Cancer* 2019, *144*, 741–745, doi:10.1002/ijc.31860.
12. Garbutcheon-Singh, K.B.; Curchin, D.J.; McCormack, C.J.; Smith, S.D. Trends in the Incidence of Merkel Cell Carcinoma in Victoria, Australia, between 1986 and 2016. *Australasian Journal of Dermatology* 2020, *61*, doi:10.1111/ajd.13131.
13. Youlden, D.R.; Soyer, H.P.; Youl, P.H.; Fritschi, L.; Baade, P.D. Incidence and Survival for Merkel Cell Carcinoma in Queensland, Australia, 1993-2010. *JAMA Dermatol.* 2014, *150*, 864, doi:10.1001/jamadermatol.2014.124.
14. Albores-Saavedra, J.; Batich, K.; Chable-Montero, F.; Sagy, N.; Schwartz, A.M.; Henson, D.E. Merkel Cell Carcinoma Demographics, Morphology, and Survival Based on 3870 Cases: A Population Based Study. *J. Cutan. Pathol.* 2010, *37*, 20–27, doi:10.1111/j.1600-0560.2009.01370.x.
15. Asgari, M.M.; Sokil, M.M.; Warton, E.M.; Iyer, J.; Paulson, K.G.; Nghiem, P. Effect of Host, Tumor, Diagnostic, and Treatment Variables on Outcomes in a Large Cohort With Merkel Cell Carcinoma. *JAMA Dermatol.* 2014, *150*, 716, doi:10.1001/jamadermatol.2013.8116.
16. Tadmor, T.; Liphshitz, I.; Aviv, A.; Landgren, O.; Barchana, M.; Polliack, A. Increased Incidence of Chronic Lymphocytic Leukaemia and Lymphomas in Patients with <scp>M</Scp> Erkel Cell Carcinoma – a Population Based Study of

335 Cases with Neuroendocrine Skin Tumour. *Br. J. Haematol.* 2012, *157*, 457–462, doi:10.1111/j.1365-2141.2012.09087.x.

17. Howard, R.A.; Dores, G.M.; Curtis, R.E.; Anderson, W.F.; Travis, L.B. Merkel Cell Carcinoma and Multiple Primary Cancers. *Cancer Epidemiology, Biomarkers & Prevention* 2006, *15*, 1545–1549, doi:10.1158/1055-9965.EPI-05-0895.
18. Lanoy, E.; Costagliola, D.; Engels, E.A. Skin Cancers Associated with HIV Infection and Solid-organ Transplantation among Elderly Adults. *Int. J. Cancer* 2010, *126*, 1724–1731, doi:10.1002/ijc.24931.
19. von der Grün, J.; Winkelmann, R.; Meissner, M.; Wieland, U.; Silling, S.; Martin, D.; Fokas, E.; Rödel, C.; Rödel, F.; Balermpas, P. Merkel Cell Polyoma Viral Load and Intratumoral CD8+ Lymphocyte Infiltration Predict Overall Survival in Patients With Merkel Cell Carcinoma. *Front. Oncol.* 2019, *9*, doi:10.3389/fonc.2019.00020.
20. Lugowska, I.; Becker, J.C.; Ascierto, P.A.; Veness, M.; Blom, A.; Lebbe, C.; Migliano, E.; Hamming-Vrieze, O.; Goebeler, M.; Kneitz, H.; et al. Merkel-Cell Carcinoma: ESMO–EURACAN Clinical Practice Guideline for Diagnosis, Treatment and Follow-Up. *ESMO Open* 2024, *9*, 102977, doi:10.1016/j.esmoop.2024.102977.
21. Moens, U.; Prezioso, C.; Pietropaolo, V. Genetic Diversity of the Noncoding Control Region of the Novel Human Polyomaviruses. *Viruses* 2020, *12*, 1406, doi:10.3390/v12121406.
22. Bopp, L.; Wieland, U.; Hellmich, M.; Kreuter, A.; Pfister, H.; Silling, S. Natural History of Cutaneous Human Polyomavirus Infection in Healthy Individuals. *Front. Microbiol.* 2021, *12*, doi:10.3389/fmicb.2021.740947.
23. Schowalter, R.M.; Pastrana, D. V.; Pumphrey, K.A.; Moyer, A.L.; Buck, C.B. Merkel Cell Polyomavirus and Two Previously Unknown Polyomaviruses Are Chronically Shed from Human Skin. *Cell Host Microbe* 2010, *7*, 509–515, doi:10.1016/j.chom.2010.05.006.
24. Yang, R.; Lee, E.E.; Kim, J.; Choi, J.H.; Kolitz, E.; Chen, Y.; Crewe, C.; Salisbury, N.J.H.; Scherer, P.E.; Cockerell, C.; et al. Characterization of ALTO-Encoding Circular RNAs Expressed by Merkel Cell Polyomavirus and Trichodysplasia

Spinulosa Polyomavirus. *PLoS Pathog.* 2021, *17*, e1009582, doi:10.1371/journal.ppat.1009582.

25. Harms, P.W.; Vats, P.; Verhaegen, M.E.; Robinson, D.R.; Wu, Y.-M.; Dhanasekaran, S.M.; Palanisamy, N.; Siddiqui, J.; Cao, X.; Su, F.; et al. The Distinctive Mutational Spectra of Polyomavirus-Negative Merkel Cell Carcinoma. *Cancer Res.* 2015, *75*, 3720–3727, doi:10.1158/0008-5472.CAN-15-0702.
26. Becker, J.C.; Stang, A.; Schrama, D.; Ugurel, S. Merkel Cell Carcinoma: Integrating Epidemiology, Immunology, and Therapeutic Updates. *Am. J. Clin. Dermatol.* 2024, *25*, 541–557, doi:10.1007/s40257-024-00858-z.
27. Korecka, K.; Badiu, I.M.; Tschandl, P.; Akay, B.N.; Apalla, Z.; Hofmann-Wellenhof, R.; Kittler, H.; Kremer, N.; Lanssens, S.; Longo, C.; et al. Dermoscopy in Merkel Cell Carcinoma—A Multicenter Retrospective Study of the International Dermoscopy Society. *Int. J. Dermatol.* 2025, doi:10.1111/ijd.70213.
28. Amin, M.B.; Greene, F.L.; Edge, S.B.; Compton, C.C.; Gershenwald, J.E.; Brookland, R.K.; Meyer, L.; Gress, D.M.; Byrd, D.R.; Winchester, D.P. The Eighth Edition <scp>AJCC</Scp> Cancer Staging Manual: Continuing to Build a Bridge from a Population-based to a More "Personalized" Approach to Cancer Staging. *CA Cancer J. Clin.* 2017, *67*, 93–99, doi:10.3322/caac.21388.
29. Nghiem, P.; Kaufman, H.L.; Bharmal, M.; Mahnke, L.; Phatak, H.; Becker, J.C. Systematic Literature Review of Efficacy, Safety and Tolerability Outcomes of Chemotherapy Regimens in Patients with Metastatic Merkel Cell Carcinoma. *Future Oncology* 2017, *13*, 1263–1279, doi:10.2217/fon-2017-0072.
30. Gaiser, M.R.; Bongiorno, M.; Brownell, I. PD-L1 Inhibition with Avelumab for Metastatic Merkel Cell Carcinoma. *Expert Rev. Clin. Pharmacol.* 2018, *11*, 345–359, doi:10.1080/17512433.2018.1445966.
31. Tumeh, P.C.; Harview, C.L.; Yearley, J.H.; Shintaku, I.P.; Taylor, E.J.M.; Robert, L.; Chmielowski, B.; Spasic, M.; Henry, G.; Ciobanu, V.; et al. PD-1 Blockade Induces Responses by Inhibiting Adaptive Immune Resistance. *Nature* 2014, *515*, 568–571, doi:10.1038/nature13954.
32. Huang, A.C.; Postow, M.A.; Orlowski, R.J.; Mick, R.; Bengsch, B.; Manne, S.; Xu, W.; Harmon, S.; Giles, J.R.; Wenz, B.; et al. T-Cell Invigoration to Tumour

Burden Ratio Associated with Anti-PD-1 Response. *Nature* 2017, *545*, 60–65, doi:10.1038/nature22079.

33. D'Angelo, S.P.; Lebbé, C.; Mortier, L.; Brohl, A.S.; Fazio, N.; Grob, J.-J.; Prinzi, N.; Hanna, G.J.; Hassel, J.C.; Kiecker, F.; et al. First-Line Avelumab in a Cohort of 116 Patients with Metastatic Merkel Cell Carcinoma (JAVELIN Merkel 200): Primary and Biomarker Analyses of a Phase II Study. *J. Immunother. Cancer* 2021, *9*, e002646, doi:10.1136/jitc-2021-002646.
34. Sharma, A.N.; Shah, K.S.; Sharma, A.A.; Yu, S.S. Avelumab in the Treatment of Advanced Merkel Cell Carcinoma: A Systematic Review. *Dermatologic Surgery* 2024, *50*, 407–411, doi:10.1097/DSS.0000000000004107.
35. Nghiem, P.T.; Bhatia, S.; Lipson, E.J.; Kudchadkar, R.R.; Miller, N.J.; Annamalai, L.; Berry, S.; Chartash, E.K.; Daud, A.; Fling, S.P.; et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *New England Journal of Medicine* 2016, *374*, 2542–2552, doi:10.1056/NEJMoa1603702.
36. Topalian, S.L.; Bhatia, S.; Amin, A.; Kudchadkar, R.R.; Sharfman, W.H.; Lebbé, C.; Delord, J.-P.; Dunn, L.A.; Shinohara, M.M.; Kulikauskas, R.; et al. Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial. *Journal of Clinical Oncology* 2020, *38*, 2476–2487, doi:10.1200/JCO.20.00201.
37. Kacew, A.J.; Dharaneeswaran, H.; Starrett, G.J.; Thakuria, M.; LeBoeuf, N.R.; Silk, A.W.; DeCaprio, J.A.; Hanna, G.J. Predictors of Immunotherapy Benefit in Merkel Cell Carcinoma. *Oncotarget* 2020, *11*, 4401–4410, doi:10.18632/oncotarget.27823.
38. Goh, G.; Walradt, T.; Markarov, V.; Blom, A.; Riaz, N.; Doumani, R.; Stafstrom, K.; Moshiri, A.; Yelistratova, L.; Levinsohn, J.; et al. Mutational Landscape of MCPyV-Positive and MCPyV-Negative Merkel Cell Carcinomas with Implications for Immunotherapy. *Oncotarget* 2016, *7*, 3403–3415, doi:10.18632/oncotarget.6494.
39. Knepper, T.C.; Montesion, M.; Russell, J.S.; Sokol, E.S.; Frampton, G.M.; Miller, V.A.; Albacker, L.A.; McLeod, H.L.; Eroglu, Z.; Khushalani, N.I.; et al. The Genomic Landscape of Merkel Cell Carcinoma and Clinicogenomic Biomarkers

of Response to Immune Checkpoint Inhibitor Therapy. *Clinical Cancer Research* 2019, *25*, 5961–5971, doi:10.1158/1078-0432.CCR-18-4159.

40. Cortellini, A.; Bersanelli, M.; Buti, S.; Cannita, K.; Santini, D.; Perrone, F.; Giusti, R.; Tiseo, M.; Michiara, M.; Di Marino, P.; et al. A Multicenter Study of Body Mass Index in Cancer Patients Treated with Anti-PD-1/PD-L1 Immune Checkpoint Inhibitors: When Overweight Becomes Favorable. *J. Immunother. Cancer* 2019, *7*, 57, doi:10.1186/s40425-019-0527-y.
41. Spyrou, N.; Vallianou, N.; Kadillari, J.; Dalamaga, M. The Interplay of Obesity, Gut Microbiome and Diet in the Immune Check Point Inhibitors Therapy Era. *Semin. Cancer Biol.* 2021, *73*, 356–376, doi:10.1016/j.semcancer.2021.05.008.
42. Yoo, S.-K.; Chowell, D.; Valero, C.; Morris, L.G.T.; Chan, T.A. Outcomes Among Patients With or Without Obesity and With Cancer Following Treatment With Immune Checkpoint Blockade. *JAMA Netw. Open* 2022, *5*, e220448, doi:10.1001/jamanetworkopen.2022.0448.
43. Becker, J.C.; Stang, A.; DeCaprio, J.A.; Cerroni, L.; Lebbé, C.; Veness, M.; Nghiem, P. Merkel Cell Carcinoma. *Nat. Rev. Dis. Primers* 2017, *3*, 17077, doi:10.1038/nrdp.2017.77.
44. Kaae, J.; Hansen, A. V.; Biggar, R.J.; Boyd, H.A.; Moore, P.S.; Wohlfahrt, J.; Melbye, M. Merkel Cell Carcinoma: Incidence, Mortality, and Risk of Other Cancers. *JNCI Journal of the National Cancer Institute* 2010, *102*, 793–801, doi:10.1093/jnci/djq120.
45. Kaufman, H.L.; Russell, J.; Hamid, O.; Bhatia, S.; Terheyden, P.; D'Angelo, S.P.; Shih, K.C.; Lebbé, C.; Linette, G.P.; Milella, M.; et al. Avelumab in Patients with Chemotherapy-Refractory Metastatic Merkel Cell Carcinoma: A Multicentre, Single-Group, Open-Label, Phase 2 Trial. *Lancet Oncol.* 2016, *17*, 1374–1385, doi:10.1016/S1470-2045(16)30364-3.
46. Kim, S.; Wuthrick, E.; Blakaj, D.; Eroglu, Z.; Verschraegen, C.; Thapa, R.; Mills, M.; Dibs, K.; Liveringhouse, C.; Russell, J.; et al. Combined Nivolumab and Ipilimumab with or without Stereotactic Body Radiation Therapy for Advanced Merkel Cell Carcinoma: A Randomised, Open Label, Phase 2 Trial. *The Lancet* 2022, *400*, 1008–1019, doi:10.1016/S0140-6736(22)01659-2.

47. Freitag, A.; Lan, Z.; Moradian, H.; Rutherford, M.; Kwon, C.; Kearney, M. Avelumab Real-World Use in Advanced Merkel Cell Carcinoma: A Systematic Review and Non-Comparative Meta-Analysis. *Future Oncology* 2026, 1–14, doi:10.1080/14796694.2025.2610172.
48. Russo, A.; Incorvaia, L.; Malapelle, U.; Del Re, M.; Capoluongo, E.; Vincenzi, B.; Chiari, R.; Cortesi, L.; Danesi, R.; Florena, A.M.; et al. The Tumor-Agnostic Treatment for Patients with Solid Tumors: A Position Paper on Behalf of the AIOM- SIAPEC/IAP-SIBioC-SIF Italian Scientific Societies. *Crit. Rev. Oncol. Hematol.* 2021, *165*, 103436, doi:10.1016/j.critrevonc.2021.103436.
49. Trevellin, E.; Bettini, S.; Pilatone, A.; Vettor, R.; Milan, G. Obesity, the Adipose Organ and Cancer in Humans: Association or Causation? *Biomedicines* 2023, *11*, 1319, doi:10.3390/biomedicines11051319.
50. Incorvaia, L.; Rinaldi, G.; Badalamenti, G.; Cucinella, A.; Brando, C.; Madonia, G.; Fiorino, A.; Pipitone, A.; Perez, A.; Li Pomi, F.; et al. Prognostic Role of Soluble PD-1 and BTN2A1 in Overweight Melanoma Patients Treated with Nivolumab or Pembrolizumab: Finding the Missing Links in the Symbiotic Immune-Metabolic Interplay. *Ther. Adv. Med. Oncol.* 2023, *15*, 175883592311518, doi:10.1177/17588359231151845.
51. Papa, V.; Li Pomi, F.; Borgia, F.; Vaccaro, M.; Pioggia, G.; Gangemi, S. Immunosenescence and Skin: A State of Art of Its Etiopathogenetic Role and Crucial Watershed for Systemic Implications. *Int. J. Mol. Sci.* 2023, *24*, 7956, doi:10.3390/ijms24097956.
52. Harms, P.W.; Harms, K.L.; Moore, P.S.; DeCaprio, J.A.; Nghiem, P.; Wong, M.K.K.; Brownell, I. The Biology and Treatment of Merkel Cell Carcinoma: Current Understanding and Research Priorities. *Nat. Rev. Clin. Oncol.* 2018, *15*, 763–776, doi:10.1038/s41571-018-0103-2.
53. Santoni, M.; Massari, F.; Bracarda, S.; Procopio, G.; Milella, M.; De Giorgi, U.; Basso, U.; Aurilio, G.; Incorvaia, L.; Martignetti, A.; et al. Body Mass Index in Patients Treated with Cabozantinib for Advanced Renal Cell Carcinoma: A New Prognostic Factor? *Diagnostics* 2021, *11*, 138, doi:10.3390/diagnostics11010138.
54. Vincenzi, B.; Badalamenti, G.; Armento, G.; Silletta, M.; Spalato Ceruso, M.; Catania, G.; Napolitano, A.; Maltese, G.; Valeri, S.; Incorvaia, L.; et al. Body Mass

Index as a Risk Factor for Toxicities in Patients with Advanced Soft-Tissue Sarcoma Treated with Trabectedin. *Oncology* 2018, *95*, 1–7, doi:10.1159/000487266.

55. Wang, Z.; Aguilar, E.G.; Luna, J.I.; Dunai, C.; Khuat, L.T.; Le, C.T.; Mirsoian, A.; Minnar, C.M.; Stoffel, K.M.; Sturgill, I.R.; et al. Paradoxical Effects of Obesity on T Cell Function during Tumor Progression and PD-1 Checkpoint Blockade. *Nat. Med.* 2019, *25*, 141–151, doi:10.1038/s41591-018-0221-5.
56. Assumpção, J.A.F.; Pasquarelli-do-Nascimento, G.; Duarte, M.S.V.; Bonamino, M.H.; Magalhães, K.G. The Ambiguous Role of Obesity in Oncology by Promoting Cancer but Boosting Antitumor Immunotherapy. *J. Biomed. Sci.* 2022, *29*, 12, doi:10.1186/s12929-022-00796-0.
57. Kim, S.; Yoon, S.; Park, I.; Lee, J.L.; Jeong, H.; Ko, Y.; Kim, K.W.; Kim, S.Y. Body Composition and Immunotherapy Outcomes in Patients with Advanced Urothelial Carcinoma. *BMC Cancer* 2025, *25*, 1853, doi:10.1186/s12885-025-15131-7.
58. Lee, J.H.; Hyung, S.; Lee, J.; Choi, S.-H. Visceral Adiposity and Systemic Inflammation in the Obesity Paradox in Patients with Unresectable or Metastatic Melanoma Undergoing Immune Checkpoint Inhibitor Therapy: A Retrospective Cohort Study. *J. Immunother. Cancer* 2022, *10*, e005226, doi:10.1136/jitc-2022-005226.
59. Guo, H.; Lin, X.-Y.; Feng, S.; Wang, C.; Yuan, L.-Q.; Sheng, X.-G.; Li, D.-P. Prognostic Value of Obesity in Patients with Cancer Treated with Immune Checkpoint Inhibitors: An Updated Meta-analysis and Systematic Review. *Mol. Clin. Oncol.* 2023, *20*, 5, doi:10.3892/mco.2023.2703.
60. Lou, J.; Guo, Y.; Li, L.; Yang, Y.; Liu, C.; Zheng, C.; Yang, L. Explanation of the Obesity Paradox of Immunotherapy in Cancer Patients Using CT-Derived Adipose Composition Parameters: A Systematic Review and Meta-Analysis. *Int. Immunopharmacol.* 2025, *144*, 113699, doi:10.1016/j.intimp.2024.113699.
61. Hodi, F.S.; O'Day, S.J.; McDermott, D.F.; Weber, R.W.; Sosman, J.A.; Haanen, J.B.; Gonzalez, R.; Robert, C.; Schadendorf, D.; Hassel, J.C.; et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine* 2010, *363*, 711–723, doi:10.1056/NEJMoa1003466.

62. Chiou, V.L.; Burotto, M. Pseudoprogression and Immune-Related Response in Solid Tumors. *Journal of Clinical Oncology* 2015, *33*, 3541–3543, doi:10.1200/JCO.2015.61.6870.

Scientific Products

Peer-reviewed articles published in international journals during the PhD project period

1: Custurone P, Li Pomi F, Lentini M, Vaccaro M, Borgia F. An unpleasant segmental facial lesion: Unilateral nevoid telangiectasia. J Cosmet Dermatol. 2022 Nov;21(11):6492-6493. doi: 10.1111/jocd.15207. Epub 2022 Jul 19.

2: Borgia F, Li Pomi F, Vaccaro M, Alessandrello C, Papa V, Gangemi S. Oxidative Stress and Phototherapy in Atopic Dermatitis: Mechanisms, Role, and Future Perspectives. Biomolecules. 2022 Dec 19;12(12):1904. doi: 10.3390/biom12121904.

3: Borgia F, Custurone P, Li Pomi F, Vaccaro M, Alessandrello C, Gangemi S. IL-33 and IL-37: A Possible Axis in Skin and Allergic Diseases. Int J Mol Sci. 2022 Dec 26;24(1):372. doi: 10.3390/ijms24010372.

4: Peterle L, Macca L, Li Pomi F, Vaccaro F, Borgia F, Vaccaro M. An impressive case of alopecia universalis after COVID-19 vaccination: a coincidental finding or a consequence? Eur Rev Med Pharmacol Sci. 2023 Jan;27(1):437-441. doi:10.26355/eurrev_202301_30900

5: Di Bartolomeo L, Vaccaro F, Irrera N, Borgia F, Li Pomi F, Squadrito F, Vaccaro M. Wnt Signaling Pathways: From Inflammation to Non-Melanoma Skin Cancers. Int J Mol Sci. 2023 Jan 13;24(2):1575. doi: 10.3390/ijms24021575.

6: Di Bartolomeo L, Borgia F, Pedaci FA, Li Pomi F, Vaccaro M, Filippeschi C, Guarneri F, Oranges T. Dermoscopy features of infantile perianal pyramidal protrusion. Pediatr Dermatol. 2023 Sep-Oct;40(5):890-893. doi:10.1111/pde.15270. Epub 2023 Feb 8.

7: Di Bartolomeo L, Li Pomi F, Vaccaro M, Borgia F, Lentini M. Eruptive papules on axillary folds of an adolescent. Pediatr Dermatol. 2023 Jul-Aug;40(4):727-729. doi: 10.1111/pde.15268. Epub 2023 Feb 8.

8: Li Pomi F, Papa V, Borgia F, Vaccaro M, Allegra A, Cicero N, Gangemi S. Rosmarinus officinalis and Skin: Antioxidant Activity and Possible Therapeutical Role in Cutaneous Diseases. Antioxidants (Basel). 2023 Mar 9;12(3):680. doi: 10.3390/antiox12030680.

9: Borgia F, Li Pomi F, Alessandrello C, Vaccaro M, Gangemi S. Potential Role of Innate Lymphoid Cells in the Pathogenesis and Treatment of Skin Diseases. J Clin Med. 2023 Apr 21;12(8):3043. doi: 10.3390/jcm12083043.

10: Papa V, Li Pomi F, Borgia F, Vaccaro M, Pioggia G, Gangemi S. Immunosenescence and Skin: A State of Art of Its Etiopathogenetic Role and Crucial Watershed for Systemic Implications. Int J Mol Sci. 2023 Apr 27;24(9):7956. doi: 10.3390/ijms24097956.

11: Li Pomi F, Macca L, Peterle L, Romeo P, Vaccaro M, Borgia F. Photodynamictherapy for intergluteal warts in a child affected by Rett syndrome. Photodiagnosis Photodyn Ther. 2023 Jun;42:103620. doi: 10.1016/j.pdpdt.2023.103620. Epub 2023 May 22.

12: Peterle L, Sanfilippo S, Borgia F, Li Pomi F, Vadalà R, Costa R, Cicero N, Gangemi S. The Role of Nutraceuticals and Functional Foods in Skin Cancer: Mechanisms and Therapeutic Potential. Foods. 2023 Jul 7;12(13):2629. doi: 10.3390/foods12132629.

13: Macca L, Li Pomi F, Ingrasciotta Y, Morrone P, Trifirò G, Guarneri C. Hidradenitis suppurativa and psoriasis: the odd couple. Front Med (Lausanne). 2023 Jul 7;10:1208817. doi: 10.3389/fmed.2023.1208817.

14: Papa V, Li Pomi F, Borgia F, Genovese S, Pioggia G, Gangemi S. "Mens Sana in Cute Sana"-A State of the Art of Mutual Etiopathogenetic Influence and Relevant Pathophysiological Pathways between Skin and Mental Disorders: An Integrated

Approach to Contemporary Psychopathological Scenarios. Cells. 2023 Jul 12;12(14):1828. doi: 10.3390/cells12141828.

15: Di Bartolomeo L, Li Pomi F, Borgia F, Vaccaro F, Guarneri F, Vaccaro M. Role of Capillaroscopy in Early Diagnosis of Ionizing Radiation Damage in Healthcare Professionals. Medicina (Kaunas). 2023 Jul 24;59(7):1356. doi: 10.3390/medicina59071356

16: Peterle L, Sanfilippo S, Tonacci A, Li Pomi F, Borgia F, Gangemi S. Common pathogenetic traits of atopic dermatitis and autism spectrum disorders, potential connections and treatments: trivial Th2 inflammation or much more? Front Immunol. 2023 Jul 27;14:1201989. doi: 10.3389/fimmu.2023.1201989.

17: Li Pomi F, Peterle L, Vaccaro M, Borgia F. Daylight photodynamic therapy for cutaneous leishmaniasis in a pediatric setting: A case report and literature review. Photodiagnosis Photodyn Ther. 2023 Dec;44:103800. doi: 10.1016/j.pdpdt.2023.103800. Epub 2023 Sep 19

18: Li Pomi F, Vaccaro M, Peterle L, Borgia F. Photodynamic therapy for severe acne. Photodiagnosis Photodyn Ther. 2024 Feb;45:103893. doi: 10.1016/j.pdpdt.2023.103893. Epub 2023 Nov 10.

19: Macca L, Vaccaro F, Li Pomi F, Borgia F, Irrera N, Vaccaro M. Kyrle disease: a case report and literature review. Eur Rev Med Pharmacol Sci. 2023 Nov;27(21):10705-10715. doi: 10.26355/eurrev_202311_34351.

20: Li Pomi F, Vaccaro F, Borgia F, Irrera N, Vaccaro M. Cutaneous adverse events following treatment with third-generation EGFR tyrosine kinase inhibitors. Ital J Dermatol Venerol. 2024 Apr;159(2):212-214. doi:10.23736/S2784-8671.23.07781-2. Epub 2024 Jan 23. PMID: 38261309.

21: Li Pomi F, Vaccaro M, Pallio G, Rottura M, Irrera N, Borgia F. Tirbanibulin 1% Ointment for Actinic Keratosis: Results from a Real-Life Study. Medicina (Kaunas). 2024 Jan 28;60(2):225. doi: 10.3390/medicina60020225.

22: Li Pomi F, Motolese A, Paganelli A, Vaccaro M, Motolese A, Borgia F. Shedding Light on Photodynamic Therapy in the Treatment of Necrobiosis Lipoidica: A Multicenter Real-Life Experience. Int J Mol Sci. 2024 Mar 23;25(7):3608. doi: 10.3390/ijms25073608.

23: Li Pomi F, Papa V, Borgia F, Vaccaro M, Pioggia G, Gangemi S. Artificial Intelligence: A Snapshot of Its Application in Chronic Inflammatory and Autoimmune Skin Diseases. Life (Basel). 2024 Apr 16;14(4):516. doi: 10.3390/life14040516.

24: Li Pomi F, Peterle L, d'Aloja A, Di Tano A, Vaccaro M, Borgia F. Anti-aging Effects of Tirbanibulin 1% Ointment: A Real-Life Experience. Dermatol Ther (Heidelb). 2024 Jun;14(6):1683-1696. doi: 10.1007/s13555-024-01178-0. Epub 2024 May 14.

25: Papa V, Li Pomi F, Borgia F, Vaccaro M, Pioggia G, Gangemi S. Alarmins in cutaneous malignant melanoma: An updated overview of emerging evidence on their pathogenetic, diagnostic, prognostic, and therapeutic role. J Dermatol. 2024 Jul;51(7):927-938. doi: 10.1111/1346-8138.17278. Epub 2024 May 22.

26: Li Pomi F, Macca L, Vaccaro M, Lentini M, Borgia F. Eruptive blue nevi of the scalp mimicking melanoma metastases. Ital J Dermatol Venerol. 2024 Aug;159(4):472-473. doi: 10.23736/S2784-8671.24.07719-3. Epub 2024 Jun 17.

27: Galeano M, Vaccaro F, Irrera N, Caradonna E, Borgia F, Li Pomi F, Squadrito F, Vaccaro M. Melanoma and cannabinoids: A possible chance for cancer treatment. Exp Dermatol. 2024 Jul;33(7):e15144. doi: 10.1111/exd.15144.

28: Li Pomi F, Macca L, d'Aloja A, Rottura M, Vaccaro M, Borgia F. Conventional versus daylight photodynamic therapy for recalcitrant hand warts: Efficacy, safety and

recurrence. Photodiagnosis Photodyn Ther. 2024 Dec;50:104360. doi:10.1016/j.pdpdt.2024.104360. Epub 2024 Oct 9.

29: Li Pomi F, Vaccaro F, Ieni A, Borgia F, Vaccaro M. Angiolymphoid hyperplasia with eosinophilia of the ear. Ital J Dermatol Venerol. 2025 Feb;160(1):65-67. doi: 10.23736/S2784-8671.24.07966-0. Epub 2024 Nov 4.

30: Li Pomi F, d'Aloja A, Rottura M, Vaccaro M, Borgia F. The Skin-Lightening Power of Tirbanibulin 1% Ointment. Dermatol Ther (Heidelb). 2025 Jan;15(1):95-110. doi: 10.1007/s13555-024-01310-0. Epub 2024 Nov 30.

31: Rizzi A, Li Pomi F, Inchingolo R, Viola M, Borgia F, Gangemi S. Alarmins in Chronic Spontaneous Urticaria: Immunological Insights and Therapeutic Perspectives. Biomedicines. 2024 Dec 4;12(12):2765. doi:10.3390/biomedicines12122765.

32: Papa V, Li Pomi F, Minciullo PL, Borgia F, Gangemi S. Skin Disorders and Osteoporosis: Unraveling the Interplay Between Vitamin D, Microbiota, and Epigenetics Within the Skin-Bone Axis. Int J Mol Sci. 2024 Dec 28;26(1):179. doi: 10.3390/ijms26010179.

33: Li Pomi F, D'Aloja A, Di Tano A, Vaccaro M, Borgia F. Pediatric genital warts successfully treated with photodynamic therapy. Dermatol Reports. 2025 May 23;17(2):9979. doi: 10.4081/dr.2024.9979. Epub 2024 Nov 4.

34: Li Pomi F, d'Aloja A, Valguarnera D, Vaccaro M, Borgia F. Exploring Anti- Aging Effects of Topical Treatments for Actinic Keratosis. Medicina (Kaunas). 2025 Jan 24;61(2):207. doi: 10.3390/medicina61020207.

35: Papa V, Li Pomi F, Di Gioacchino M, Mangifesta R, Borgia F, Gangemi S. Mast Cells and Microbiome in Health and Disease. Front Biosci (Landmark Ed). 2025 Mar 20;30(3):26283. doi: 10.31083/FBL26283.

36: Li Pomi F, d'Aloja A, Vaccaro M, Borgia F. Photodynamic therapy for flat warts arising on a tattoo. Photodiagnosis Photodyn Ther. 2025 Jun;53:104574. doi: 10.1016/j.pdpdt.2025.104574. Epub 2025 Apr 3.

37: Li Pomi F, Gammeri L, Borgia F, Di Gioacchino M, Gangemi S. Oxidative Stress and Skin Diseases: The Role of Lipid Peroxidation. Antioxidants (Basel). 2025 May 7;14(5):555. doi: 10.3390/antiox14050555.

38: Scuruchi M, Speranza D, Bruschetta G, Vaccaro F, Galeano M, Pallio G, Vaccaro M, Borgia F, Li Pomi F, Collino M, Irrera N. Protein Kinase CK2 Inhibition Represents a Pharmacological Chance for the Treatment of Skin Diseases. Int J Mol Sci. 2025 Jun 4;26(11):5404. doi:10.3390/ijms26115404.

39: Li Pomi F, d'Aloja A, Rottura M, Vaccaro M, Borgia F. Tirbanibulin 1% Ointment for the Treatment of Hyperkeratotic Actinic Keratosis. J Dermatol. 2025 Sep;52(9):1395-1403. doi: 10.1111/1346-8138.17845. Epub 2025 Jul 2.

40: Li Pomi F, d'Aloja A, Vitale M, Rottura M, Irrera N, Vaccaro M, Borgia F. Efficacy of 5-Fluorouracil 4% Cream in the Treatment of Hyperkeratotic Actinic Keratosis: A Single-Center Retrospective Real-World Study. Dermatol Ther (Heidelb). 2025 Aug 16. doi: 10.1007/s13555-025-01518-8.

41: Vaccaro F, Mannino F, Santarpia M, Cullotta C, Galeano M, Borgia F, Li Pomi F, Arcoraci V, Lentini M, Franchina M, Vaccaro M, Pallio G, Irrera N. Genistein and Curcumin Inhibit Proliferation and Invasiveness in BRAFV600E Mutant and Wild-Type Melanoma Cells: Insights into Their Anticancer Effects. Biomedicines. 2025 Aug 10;13(8):1954. doi: 10.3390/biomedicines13081954.

42: Li Pomi F, Vaccaro M, Vitale M, Alaimo R, Borgia F. JAK Inhibitors in Down Syndrome: Alopecia Areata Resolution and Vitiligo Improvement with Baricitinib. Acta Derm Venereol. 2025 Sep 10;105:adv44081. doi: 10.2340/actadv.v105.44081.

43. Paganelli A, Michelerio A, Collina MC, Pilla MA, Spadafora M, Longo C, Dattola A, Richetta AG, Pellacani G, Pezzini C, Mandel VD, DI Tullio F, Conti A, Motolese A, Marani A, DE Pace B, Megna A, Condorelli AG, Arginelli F, Persechino F, Garbarino F, Ambrosio L, Scala E, Vassallo C, Motolese A; Study Group on Cutaneous Vascular Diseases and Skin Ulcers of the Italian Society of Dermatology and Sexually Transmitted Diseases (SIDeMaST). Clinical management of pigmented purpuric dermatoses: evidence from a survey among the Study Group on Cutaneous Vascular Diseases of the Italian Society of Dermatology and Venereology. Ital J Dermatol Venerol. 2025 Oct;160(5):406-412. doi: 10.23736/S2784-8671.25.08243-X. PMID: 41041874.

44. Casella R, Li Pomi F, Borgia F, Nettis E, Gangemi S. Shared Immunopathogenic Mechanisms in Chronic Spontaneous Urticaria, Vitiligo, and Hashimoto's Thyroiditis: The Role of Oxidative Stress and Vitamin D. Life (Basel). 2025 Sep 29;15(10):1535. doi: 10.3390/life15101535. PMID: 41157208; PMCID: PMC12565167.

45. La Barbera G, Ciodaro F, Luppino G, Li Pomi F, Loteta S, Miceli G, Cusmano C, Chirico V, Alibrandi A, Chimenz R, Visalli C, Borgia F, Conti G. Ear involvement in patients affected by juvenile idiopathic arthritis. Joint Bone Spine. 2025 Nov 1;93(3):106002. doi: 10.1016/j.jbspin.2025.106002. Epub ahead of print. PMID: 41183588.

46. Li Pomi F, Papaianni V, Vitale M, Cutuli F, Randazzo B, Vaccaro M, Borgia F. Cutaneous Leishmaniasis Successfully Treated with Photodynamic Therapy: A Case Series. Photodiagnosis Photodyn Ther. 2026 Jan 10:105346. doi: 10.1016/j.pdpdt.2026.105346. PMID: 41525920.

47. Li Pomi F, Di Leo G, Genovese S, Borgia F, Gangemi S. Redox Network Dysfunction: Integrating Ferroptosis and Cuproptosis Across Human Diseases. Antioxidants (Basel). 2025 Dec 23;15(1):24. doi: 10.3390/antiox15010024. PMID: 41596083; PMCID: PMC12838178.

Oral presentations, posters, and abstracts presented at national and international conferences during the PhD period

- Speaker at 97th National Congress of SiDeMaST, Naples, Italy, 2023. Oral presentation: "Antimicrobial Photodynamic Therapy for Intergluteal Warts in a Child with Rett Syndrome."
- Poster Presentation, 97th National Congress of SiDeMaST, Naples, Italy, 2023. "Dermoscopy Features of Infantile Perianal Pyramidal Protrusion."
  Authors: L. Di Bartolomeo, F. Borgia, F.A. Pedaci, F. Li Pomi, M. Vaccaro, C. Filippeschi, F. Guarneri, T. Oranges.
- Oral Communication, 97th National Congress of SiDeMaST, Naples, Italy, 2023. "A Case of Lymphedematous Mucinosis Associated with Obesity."
  Authors: A. Motolese, L. Macca, F. Li Pomi, F. Guarneri, M. Vaccaro.
- Poster Presentation, 97th National Congress of SiDeMaST, Naples, Italy, 2023. "Role of Wnt Signaling Pathways in the Pathogenesis of Non-Melanoma Skin Cancer."
  Authors: L. Di Bartolomeo, F. Vaccaro, N. Irrera, F. Borgia, F. Li Pomi, F. Squadrito, M. Vaccaro.
- Speaker at 98th National Congress of SiDeMaST, Giardini Naxos (ME), Italy, 2024.
  Oral presentation: "Cutaneous Adverse Events Following Treatment with Third-Generation EGFR Tyrosine Kinase Inhibitors."
- Poster Presentation, 98th National Congress of SiDeMaST, Giardini Naxos (ME), Italy, 2024. "Real-Life Experience with Tirbanibulin 1% Ointment for the Treatment of Actinic Keratosis."
  Authors: F. Li Pomi, M. Vaccaro, F. Vaccaro, F. Borgia.
- Poster Presentation, 98th National Congress of SiDeMaST, Giardini Naxos (ME), Italy, 2024. "Anti-Aging Effect of Tirbanibulin 1% Ointment."
  Authors: F. Li Pomi, M. Vaccaro, F. Vaccaro, F. Borgia.
- Oral Communication, 98th National Congress of SiDeMaST, Giardini Naxos (ME), Italy, 2024. "Pulsed Dye Laser for the Treatment of Unilateral Nevoid

Telangiectasia."

Authors: F. Li Pomi, M. Ventimiglia, M. Patalano, F. Borgia.

- Poster Presentation, EADV Congress, Amsterdam, The Netherlands, 2024. "Tirbanibulin 1% Ointment for Actinic Keratosis: Results from a Real-Life Study."

  Authors: F. Li Pomi, L. Peterle, A. D'Aloja, A. Di Tano, M. Vaccaro, F. Borgia.
- Poster Presentation, EADV Congress, Amsterdam, The Netherlands, 2024. "Anti-Aging Effects of Tirbanibulin 1% Ointment: A Real-Life Experience."

  Authors: F. Li Pomi, L. Peterle, A. D'Aloja, A. Di Tano, M. Vaccaro, F. Borgia.
- Oral Communication, 11th Melanoma Congress in conjunction with the 21st EADO Congress, Athens, Greece, 2025. "Tirbanibulin 1% Ointment for the Treatment of Hypertrophic Actinic Keratosis."
- Poster Presentation, EADV Symposium, Prague, Czech Republic, 2025. "The Skin-Lightening Power of Tirbanibulin 1% Ointment."

  Authors: F. Li Pomi, A. D'Aloja, M. Vaccaro, F. Borgia.
- Invited Speaker, Workshop "Update in Diagnosis and Therapy of Cutaneous Immunopathologies," VIII National Congress Dies Panormitanae atque Magnae Graeciae, Italy, 2025. Oral presentation: "Vitiligo: From Pathogenesis to Clinical Management."
- Invited Speaker, 22nd Annual Congress of the European Society for Photodynamic Therapy, Brussels, Belgium, 2025.

  Oral presentation: "Photodynamic Therapy for Necrobiosis Lipoidica."
- Poster Presentation, 22nd Congress of the European Society for Photodynamic Therapy, Brussels, Belgium, 2025. "Photodynamic Therapy for Flat Warts on a Tattooed Area: A Tattoo-Conservative Approach."

  Authors: F. Borgia, F. Li Pomi.
- Poster Presentation, 22nd Congress of the European Society for Photodynamic Therapy, Brussels, Belgium, 2025. "Daylight Photodynamic Therapy for Pediatric Cutaneous Leishmaniasis: A Case Series."

  Authors: F. Li Pomi, S.P. Cannavò, F. Borgia.

- Invited Speaker, XIV International Congress of Dermatology, Rome, Italy, 2025. Oral presentation: “JAK Inhibitors in Down Syndrome: Alopecia Resolution and Vitiligo Improvement with Baricitinib.”
- Oral Communication, XIV International Congress of Dermatology, Rome, Italy, 2025.
  “The Skin-Lightening Power of Tirbanibulin 1% Ointment.”
  Authors: F. Li Pomi, A. D’Aloja, M. Rottura, M. Vaccaro, F. Borgia.
- Oral Communication, XIV International Congress of Dermatology, Rome, Italy, 2025. “Tirbanibulin 1% Ointment for the Treatment of Hypertrophic Actinic Keratosis
  Authors: F. Li Pomi, A. D’Aloja, M. Vaccaro, F. Borgia.
- Poster Presentation, EADV Congress, Paris, France, 2025. “Tirbanibulin 1% Ointment for Solar Lentigines on the Dorsal Hands.”
  Authors: F. Li Pomi, A. D’Aloja, M. Vaccaro, F. Borgia.
- Poster Presentation, EADV Congress, Paris, France, 2025. “Photodynamic Therapy for Cutaneous Leishmaniasis.”
  Authors: F. Li Pomi, S.P. Cannavò, V. Papaianni, F. Marielli, M. Vaccaro, F. Borgia.
- Poster Presentation, EADV Congress, Paris, France, 2025. “Photodynamic Therapy for Pediatric Genital Warts.”
  Authors: F. Li Pomi, M. Vaccaro, F. Borgia.
- Invited Speaker, Workshop “Atopic Dermatitis and Alopecia Areata: The Importance of Integrated Management,” Palermo, Italy, 2025. Oral presentation: “Systemic Therapy of Atopic Dermatitis.”
- Oral Communication, National Congress I Percorsi Pediatrici, Letojanni, Italy, 2025. “Photodynamic Therapy for Pediatric Cutaneous Leishmaniasis.”
  Authors: F. Li Pomi, M. Vaccaro, M. Vitale, F. Cutuli, B. Randazzo, F. Borgia.
- Poster Presentation, National Congress I Percorsi Pediatrici, Letojanni, Italy, 2025. “Photodynamic Therapy for Pediatric Genital Warts.”
  Authors: F. Li Pomi, M. Vaccaro, F. Borgia.
- Oral Communication, National Congress I Percorsi Pediatrici, Letojanni, Italy, 2025. “Real-Life Experience in the Management of Infantile Hemangiomas: A

Retrospective Analysis of a Cohort of 16 Patients."
Authors: F. Borgia, F. De Luca, L. Bruno, L. Oreto, F. Marielli, F. Li Pomi, M. Vaccaro.

Awards and Honors

- Winner of the "Best Poster" Award for the contribution "Photodynamic Therapy for Flat Warts Arising on a Tattoo" at the 22nd Annual Congress of the European Society for Photodynamic Therapy, Brussels, Belgium, May 30–31, 2025.
- Recipient of the 16th Pediatric Research Award "Stretto di Messina" (Best Poster category) for the poster "Photodynamic Therapy for Pediatric Cutaneous Leishmaniasis."