



# European Dermatology Forum

## Guideline on the diagnosis and treatment of Merkel Cell Carcinoma

Developed by the Guideline Subcommittee of the  
**European Dermatology Forum**

### *Subcommittee Members:*

Prof. Dr. Celeste Lebbe, Paris (France)  
Prof. Dr. Jean-Jacques Grob, Marseille (France)  
Dr. Veronique del Marmol, Brussels (Belgium)  
Prof. Dr. Ketty Peris, Rome (Italy)  
Prof. Dr. Mark Middleton, Oxford (United Kingdom)  
Dr. Alessandro Testori, Milano (Italy)  
Prof. Dr. Claus Garbe, Tübingen (Germany)

Prof. Dr. Jürgen C. Becker, Graz (Austria)  
Dr. Josep Malvehy, Barcelona (Spain)  
Prof. Dr. Hubert Pehamberger, Vienna (Austria)  
Prof. Dr. Philippe Saiag, Vienna (Austria)  
Dr. Lars Bastholt, Odense (Denmark)  
Prof. Dr. Alexander Stratigos, Athens (Greece)

### *Members of EDF Guideline Committee:*

Prof. Dr. Werner Aberer, Graz (Austria)  
Prof. Dr. Martine Bagot, Paris (France)  
Prof. Dr. Nicole Basset-Seguin, Paris (France)  
Prof. Dr. Ulrike Blume-Peytavi, Berlin (Germany)  
Prof. Dr. Lasse Braathen, Bern (Switzerland)  
Prof. Dr. Sergio Chimenti, Rome (Italy)  
Prof. Dr. Alexander Enk, Heidelberg (Germany)  
Prof. Dr. Claudio Feliciani, Rome (Italy)  
Prof. Dr. Claus Garbe, Tuebingen (Germany)  
Prof. Dr. Harald Gollnick, Magdeburg (Germany)  
Prof. Dr. Gerd Gross, Rostock (Germany)  
Prof. Dr. Vladimir Hegyi, Bratislava (Slovakia)  
Prof. Dr. Michael Hertl, Marburg (Germany)  
Prof. Dr. Dimitrios Ioannides, Thessaloniki (Greece)  
Prof. Dr. Gregor Jemec, Roskilde (Denmark)  
Prof. Dr. Lajos Kemény, Szeged (Hungary)  
Dr. med. habil. Gudula Kirtschig, Nottingham (United Kingdom); Tübingen (Germany)  
Prof. Dr. Elke Weisshaar, Heidelberg (Germany)  
Prof. Dr. Sean Whittaker, London (United Kingdom)  
Prof. Dr. Fenella Wojnarowska, Oxford (United Kingdom)  
Prof. Dr. Marcus Maurer, Berlin (Germany)  
Prof. Dr. Kai Munte, Rotterdam (Netherlands)

Prof. Dr. Dieter Metze, Muenster (Germany)  
Prof. Dr. Gillian Murphy, Dublin (Ireland)  
PD Dr. Alexander Nast, Berlin (Germany)  
Prof. Dr. Martino Neumann, Rotterdam (Netherlands)  
Prof. Dr. Tony Ormerod, Aberdeen (United Kingdom)  
Prof. Dr. Mauro Picardo, Rome (Italy)  
Prof. Dr. Annamari Ranki, Helsinki (Finland)  
Prof. Dr. Johannes Ring, Munich (Germany)  
Prof. Dr. Berthold Rzany, Berlin (Germany)  
Prof. Dr. Rudolf Stadler, Minden (Germany)  
Prof. Dr. Sonja Ständer, Muenster (Germany)  
Prof. Dr. Wolfram Sterry, Berlin (Germany)  
Prof. Dr. Eggert Stockfleth, Bochum (Germany)  
Prof. Dr. Alain Taieb, Bordeaux (France)  
Prof. Dr. George-Sorin Tiplica, Bucharest (Romania)  
Prof. Dr. Nikolai Tsankov, Sofia (Bulgaria)  
Prof. Dr. Robert Knobler, Vienna (Austria)  
Prof. Dr. Annegret Kuhn, Muenster (Germany)  
Prof. Dr. Christos Zouboulis, Dessau (Germany)  
Prof. Dr. Torsten Zuberbier, Berlin (Germany)

### *Chairman of EDF Guideline Committee:*

PD Dr. Alexander Nast, Berlin (Germany)

Expiry date: 07/2018

---

*EDF Guidelines Secretariat to PD Dr. Alexander Nast:*

Bettina Schulze, Klinik für Dermatologie, Venerologie und Allergologie, Campus Charité Mitte,  
Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany  
phone: ++49 30 450 518 062, fax: ++49 30 450 518 911, e-mail: [bettina.schulze@charite.de](mailto:bettina.schulze@charite.de)

# **Diagnosis and Treatment of Merkel Cell Carcinoma. European Consensus-based Interdisciplinary Guideline**

On behalf of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC)

Celeste Lebbe<sup>1</sup>, Jürgen C. Becker<sup>2</sup>, Jean-Jacques Grob<sup>3</sup>, Josep Malvehy<sup>4</sup>, Veronique del Marmol<sup>5</sup>, Hubert Pehamberger<sup>6</sup>, Ketty Peris<sup>7</sup>, Philippe Saiag<sup>8</sup>, Mark R. Middleton<sup>9</sup>, Lars Bastholt<sup>10</sup>, Alessandro Testori<sup>11</sup>, Alexander Stratigos<sup>12</sup>, Claus Garbe<sup>13</sup>

<sup>1</sup> APHP University Department of Dermatology, Saint-Louis Hospital, INSERM U976 Paris, France

<sup>2</sup> University Department of Dermatology, Graz, Austria

<sup>3</sup> University Department of Dermatology, Marseille, France

<sup>4</sup> Melanoma Unit, Department of Dermatology, Hospital Clinic, Barcelona, Spain

<sup>5</sup> University Department of Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

<sup>6</sup> University Department of Dermatology, Vienna, Austria

<sup>7</sup> University Department of Dermatology, L'Aquila, Italy

<sup>8</sup> University Department of Dermatology, Université de Versailles-Saint Quentin en Yvelines, APHP, Boulogne, France

<sup>9</sup> Department of Oncology, Oxford National Institute for Health Research Biomedical Research Centre, United Kingdom

<sup>10</sup> Department of Oncology, Odense University Hospital, Denmark

<sup>11</sup> Istituto Europeo di Oncologia, Divisione dermato-oncologica, Milan Italy

<sup>12</sup> 1<sup>st</sup> Department of Dermatology, University of Athens, A. Sygros Hospital, Athens, Greece

<sup>13</sup> University Department of Dermatology, Tuebingen, Germany

Address for correspondence:

Celeste Lebbe, MD PhD

Professor of Dermatology

Department of Dermatology

Hôpital Saint-Louis

1, Avenue Claude-Vellefaux

75010 Paris

France

E-Mail: [celeste.lebbe@sls.aphp.fr](mailto:celeste.lebbe@sls.aphp.fr)

## ABSTRACT

Merkel cell carcinoma is a rare tumour of the skin of neuro-endocrine origin probably developing from neuronal mechanoreceptors. A collaborative group of multidisciplinary experts from the European Dermatology Forum (EDF), The European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) was formed to make recommendations on MCC diagnosis and management, based on a critical review of the literature, existing guidelines and expert's experience. Clinical features of the cutaneous/subcutaneous nodules hardly contribute to the diagnosis of MCC. The diagnosis is made by histopathology, and an incisional or excisional biopsy is mandatory. Immunohistochemical staining contributes to clarification of the diagnosis. Initial work-up comprises ultrasound of the loco-regional lymph nodes and total body scanning examinations. The primary tumour should be excised with 1 - 2 cm margins. In patients without clinical evidence of regional lymph node involvement, sentinel node biopsy is recommended, if possible, and will be taken into account in a new version of the AJCC classification. In patients with regional lymph node involvement radical lymphadenectomy is recommended. Adjuvant radiotherapy might be considered in patients with multiple affected lymph nodes of extracapsular extension. In unresectable metastatic MCC mono- or poly-chemotherapy achieve high remission rates. However, responses are usually short lived. Treatment within clinical trials is regarded as a standard of care in disseminated MCC.

**Keywords:** Merkel cell carcinoma, diagnosis, surgical management, radiotherapy, systemic treatment.

## INTRODUCTION

These guidelines have been written under the auspices of the European Dermatology Forum (EDF) and the European Association of Dermato-Oncology (EADO) in order to assist clinicians in treating patients with Merkel cell carcinoma (MCC) in Europe. The paper was initiated due to advances in the histological diagnosis and the prognostic classification of MCC with implications for treatment selection. The guidelines address aspects of MCC management, from the clinical and histological diagnosis of primary tumour to the systemic treatment of advanced or metastatic disease. It is hoped that this set of guidelines will assist healthcare providers in managing their patients according to the current standards of care and evidence-based medicine. It is not intended to replace national guidelines accepted in their original country. These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may modify the conclusions or recommendations in this report. In addition, it may be necessary to deviate from these guidelines for individual patients or under special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent.

## **METHODS**

To construct this EDF-EADO-EORTC guideline, an extensive search with terms “Merkel cell carcinoma” using the PubMed, EMBASE and Cochrane Library databases was conducted (until December 31<sup>st</sup>, 2014). Articles included systematic reviews, pooled analyses and meta-analyses. The search was restricted to English-speaking language publications. We also searched for existing guidelines on Merkel cell carcinoma in the databases mentioned above as well as in relevant websites (national agencies, medical societies). A subgroup among the authors produced a working draft that was extensively discussed at a consensus meeting and thereafter through email communication. In addition, the panel

looked for concordances and differences among recently published guidelines<sup>1</sup>. Previous recommendations on distinct items (epidemiology, diagnosis, prognosis, treatment, and follow-up) were discussed extensively in view of the available evidence-based data. Items that were agreed upon by our expert panel were adapted within our guideline proposal with appropriate reference. Items that differed from previously published guidelines or were originally recommended by our working group were clearly stated as proposed by the EA-DO consensus group. The guideline draft was circulated between panel members from EADO, EDF, and EORTC before reaching its final form.

## **DEFINITION**

Merkel cell carcinoma (MCC) is a rare highly aggressive primary cutaneous carcinoma of the skin with epithelial and endocrine features. Its origin – neuroendocrine – are probably skin mechano-receptors; pluripotent stem cells or even lymphoid cells are likewise debated [3].

## **Epidemiology and Aetiology**

MCC annual age standardized incidence rate per million ranges from 2-4 in Europe and in the US to 8 /million PY in Australia. It increased from 1980 to 2000 in US and in Europe [4-7]. This can be related to a true increased incidence by itself or caused by aging of the population, increased sun exposure and/or improvement of diagnostic immunohistochemical tools as well as improved registration. MCC predominates in men (61.5%) and in elderly with a median age at diagnosis around 76 years, 71.6 % of patients being older than 70 [5, 7]. MCC is an aggressive disease with an overall 10-year survival for patients estimated to 57.3% in US [7] and 47% in Europe [5].

The main factors known to be involved in MCC pathogenesis are:

- UV radiation attested by a 8 times higher incidence in white compared to black, a correlation between incidence and UVB irradiation index, highest incidence rates in Australia and predominance on sun-exposed skin [8].
- Immunosuppression attested by a significantly increased risk in HIV patients and transplant recipients [9-11] and recent suggestion that high intra-tumoral T-lymphocyte infiltrates are associated with better survival [12, 13]. **Sofar no studies on the specific management of the immunosuppressive therapy in transplant patients diagnosed with MCC are available and minimization of immunosuppressors should be discussed on individual basis.**
- Merkel cell polyomavirus (MCPyV) DNA is a ubiquitous virus which can be detected in up to 80% cases using molecular techniques [14, 15] [16] [17] and in 97% using a recently available monoclonal anti large T antigen antibody [18]

## **DIAGNOSIS**

### **Clinical features of primary tumour**

MCC is a rapidly growing asymptomatic solitary, firm, non-tender, flesh-coloured to red tumour with nodular or plaque features, rarely ulcerated at first presentation. [19] The predominant sites are head and neck (53%) and extremities (34–35%); whereas trunk and oral and genital mucosa are involved in less than <10%. [7]

### **Histopathology [20]**

Diagnosis is based on incisional tumour biopsy. MCC generally consists in a solid nodular lesion in the dermis and subcutis. On haematoxylin examination MCC is characterized by a proliferation of uniform small round blue undifferentiated cells with large lobulated nuclei and scant cytoplasm, high mitotic rate and apoptotic bodies, and occasional necrosis. Immunohistochemistry is required for diagnosis (Table 1) and MCC is characterized by ex-

pression of both epithelial markers such as cytokeratin 20 with a characteristic paranuclear dot-like staining but also AE1/AE3 and CAM5.2 and by expression of neuroendocrine markers such as neuron-specific enolase (very sensitive but expressed by other neuroendocrine tumours), synaptophysin, and chromogranin A (more specific for MCC). The latter is the most commonly used marker with a diffuse cytoplasmic staining pattern. By contrast the following markers are generally negative: S-100 and HMB-45 expressed by melanoma, leukocyte common antigen and other lymphocyte markers expressed by lymphomas, CK7 and carcinoembryonic antigen expressed by sweat gland carcinomas and thyroid transcription factor1 (TTF-1) important for differential diagnosis with metastatic small cell lung cancer (SCLC) (see Table 1). The diagnostic value of Merkel cell polyomavirus detection using either molecular or immunohistochemical techniques is currently investigated [20]. In clinical practice a typical histology complemented with positive CK-20 and TTF-1 immunostaining is considered sufficient for diagnosis of MCC.

## **PROGNOSTIC CLASSIFICATION**

### **Clinical features (demography, primary tumour)**

Clinical unfavourable factors are male gender, location in head and neck or trunk as compared to upper limbs, size of the primary tumour [7] [5] and the presence of immunosuppression [21, 22].

### **Histological prognosis markers of the primary tumours**

So far there is no convincing demonstration of any histological prognosis marker in MCC.

The good prognostic value of low tumour depth, absence of lymph vascular invasion and more recently tumour infiltrating immune cells have been suggested and deserves further evaluation [13, 23, 24]. However it is well known from clinical practice that even a superficial MCC can metastasize and in the AJCC classification tumor depth is not regarded as a high risk feature [25].



## **Distant involvement**

The main prognostic factors are related to distant involvement. MCC tumours of localized stage carry the best prognosis (71% survival rate)[7]. In regional and distant disease five-year survival was 52% and 17%, respectively in a large European registry [5]; and 47.8% and 20.1% in the SEER study [7]

Lymph node status is the most important independent predictor [26] including occult microscopic nodal involvement which occurs in around one third of patients [2, 27]. Therefore the new AJCC classification based on 5823 prospectively enrolled MCC cases from the US National Cancer Data Base includes sentinel lymph node status which is considered as an important procedure in MCC management. Before sentinel lymph node biopsy, regional lymph node ultrasonography (US)[28] is recommended as well as initial work up with computerized tomography scanner (CT scan) or positron emission tomography – computed tomography (PET-CT).

## **AJCC classification [2]**

T1 are characterised by tumour size <2 cm (T1) while T2 (between 2 and 5cm) and T3 (more than 5cm) carries the same prognostic. The T4 category includes deeply invasive tumours (invading bone, muscle, fascia or cartilage) as in other AJCC staging systems.

Patients with nodal disease detected by pathologic examination but without detectable clinical involvement have micrometastatic or N1a nodal disease. Those who have clinically apparent regional lymph node disease, confirmed by pathologic evaluation, have macrometastatic or N1b nodal disease. N2 refers to the presence of in transit lesions. There are 3 categories of distant metastatic disease (M status) as in melanoma staging: M1a-distant skin, distant subcutaneous tissues, or distant lymph nodes; M1b-lung; and M1c-all other visceral sites. The stage and sub stages groups are summarized in table 2 with corresponding prognosis values.

## **PATIENT MANAGEMENT**

### **Preoperative staging**

Full body skin examination by an expert dermato-oncologist should be conducted. Lymph nodal clinical examination of all main nodal basins is done with particular carefulness to the loco regional nodes.

Ultrasound of the loco regional nodes and total body PET-CT will complete the instrumental staging

### **Primary and adjuvant treatment for clinically N0 disease**

There is no formal evaluation of excision margins in the literature, however the EA-DO/EORTC recommends a 1 to 2 cm excision margin taking into account functional considerations in the head/neck region and with complete histological inspection of the margins of the excised material using microscopically controlled surgery; however, it should be kept in mind, that the safety margin is more intended to remove microscopic satellite metastases than to ensure clear resection margins of the primary tumour. The benefit on survival of adjuvant radiotherapy of the tumour region (50 Gy and 10 more Gy on tumour bed) is highly suggested from retrospective studies and is therefore recommended [29-32]. Reconstruction should take into account further adjuvant radiotherapy.

Sentinel lymph node biopsy is recommended if possible, whatever the size of the tumour. If micro-metastasis is demonstrated, a therapeutic lymph node dissection is proposed although there are no prospective studies demonstrating its benefit in the literature.

If a sentinel node biopsy cannot be performed, regional follow up with ultrasound and clinical examination every 4 months should be planned.

Adjuvant irradiation (50 Gy) of the lymphatic drainage area has been shown in a prospective study to improve local control without improving survival [33]. Retrospective data from

the US National cancer database on 6955 patients conclude on the absence of survival benefit from adjuvant radiotherapy in stage III patients [32]. Therefore adjuvant radiotherapy of the lymphatic drainage area cannot be recommended in general after therapeutic node dissection but could be discussed in a multidisciplinary approach to improve local disease control mainly in case of extracapsular nodal involvement .

For elderly patients with poor performance status for whom surgery is not feasible, radiotherapy of tumours and positive lymph node can be discussed in a multidisciplinary approach.

**Primary and locoregional approach followed by adjuvant therapy for clinically N+ node (with cytological or histological confirmation and negative TDM or TEP CT imaging)**

The combination of surgery and radiotherapy of the tumour region will be performed as described below. Therapeutic node dissection of the basin will be performed eventually followed by adjuvant radiotherapy if indicated. As already stated retrospective data strongly suggest that adjuvant radiotherapy does not impact overall survival but only local disease control. Therefore it will be discussed in extensive disease on a case by case multidisciplinary approach [32]. Adjuvant immunotherapeutic trials have been initiated and whenever possible patients should be treated within a clinical trial. For elderly patients with poor performance status for whom surgery is not feasible, radiotherapy of tumours and lymph node can be discussed in a multidisciplinary approach.

***Treatment of extra-nodal locoregional disease: Surgery/ radiation therapy/ electrochemotherapy/ isolated limb infusion***

Satellite or in-transit metastases around the primary site should be removed surgically if the number, size and location allows a complete removal of the metastatic sites. RT alone

or in combination with chemotherapy may be used as an alternative option when surgery is not feasible. RT is particularly helpful as a palliative treatment, in order to relieve pain.

Electrochemotherapy is a relatively new treatment modality which can find indication in locally advanced lesions [34].

Isolated hyperthermic limb perfusion represents an important therapeutic option when the local progression could include in the treatment proposals the indication for amputation [35, 36]. In solid tumours with such a locoregional diffusion on limbs, isolated limb perfusion with tumour necrosis factor and alkeran has demonstrated in most solid tumours to save as much as 70% of limbs otherwise undergoing to amputation. A less invasive approach to treat locally advanced disease in the limbs is represented by isolated limb infusion. The efficacy is usually 10-15% less beneficial than with the classic approach but less invasive with reduced complications.

### **Follow up**

There is no evaluation of the best follow-up strategy. Once loco regional disease is under control from the surgical point of view, the proposal can be characterized by clinical examinations and nodal ultrasound every 4 months during the first 3 years then every 6 months for up to 5 years.

CT or PET CT might be proposed every year for 5 years.

### **Metastatic stage**

Except for surgery of isolated metastasis, there is no established curative treatment for metastatic MCC. In a recent American registry chemotherapy was not associated with MCC relapse or survival [37] and no therapy is currently approved in this situation by FDA or EMEA.

Various regimens used to treat small cell lung cancer thought to be a neuroendocrine tumour, have been evaluated in small series or case reports and are summarized in Desch et al [38]. These regimens combine in various ways carboplatin, cisplatin, and etoposide, cyclophosphamide with vincristine, doxorubicin, prednisone, bleomycin, or 5-fluorouracil. Initial regression is frequent with response rate up to 75% [39] [40, 41] [38] but of short duration with median overall survival rate of 9 months and high toxicity in elderly patients.

Among these regimens, one of the most frequently used for patients with good performance status is a combination of platinum and etoposide (cisplatin 60-80 mg/m<sup>2</sup> IV on day 1 **plus** etoposide 80-120 mg/m<sup>2</sup> IV on days 1-3 every 21-28 days **or** carboplatin AUC 5 IV on day 1 **plus** etoposide 80-100 mg/m<sup>2</sup> IV on days 1-3 every 28 days:

([http://www.nccn.org/professionals/physician\\_gls/pdf/scll.pdf](http://www.nccn.org/professionals/physician_gls/pdf/scll.pdf))

On the other hand monotherapies using anthracyclines, liposomal anthracyclines or etoposide have also led to anecdotal responses with less toxicity and can also be considered in a case by case approach. Best supportive care or palliative radiotherapy can be discussed in patients with poor performance status.

Enrolment in clinical trials should be encouraged and should aim to evaluate innovative therapies such as immunotherapy including anti CTLA4 and anti PDL1/PD-1, pan tyrosine kinase inhibitors and somatostatin analogues. If the physicians, patients or family members need detailed information about the ongoing clinical trials in MCC, the following site provides this immediately: [http://ec.europa.eu/research/health/medical-research/cancer/fp7-projects/immomec\\_en.html](http://ec.europa.eu/research/health/medical-research/cancer/fp7-projects/immomec_en.html)

- [1]. Becker JC, Assaf C, Vordermark D, Reske SN, Hense J, Dettenborn T, et al. Brief S2k guidelines--Merkel cell carcinoma. *J Dtsch Dermatol Ges* 2013;11 Suppl 3:29-36, 31-8.
- [2]. Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol* 2010;63(5):751-61.
- [3]. Van Keymeulen A, Mascré G, Youseff KK, Harel I, Michaux C, De Geest N, et al. Epidermal progenitors give rise to Merkel cells during embryonic development and adult homeostasis. *J Cell Biol* 2009;187(1):91-100.
- [4]. Hussain SK, Sundquist J, Hemminki K. Incidence trends of squamous cell and rare skin cancers in the Swedish national cancer registry point to calendar year and age-dependent increases. *J Invest Dermatol* 2010;130(5):1323-8.
- [5]. Reichgelt BA, 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(4):579-85.

- [6]. Girschik J, Thorn K, Beer TW, Heenan PJ, Fritschi L. Merkel cell carcinoma in Western Australia: a population-based study of incidence and survival. *Br J Dermatol* 2011;165(5):1051-7.
- [7]. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. *J Cutan Pathol* 2010;37(1):20-7.
- [8]. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol* 2003;49(5):832-41.
- [9]. Lanoy E, Costagliola D, Engels EA. Skin cancers associated with HIV infection and solid-organ transplantation among elderly adults. *Int J Cancer* 2010;126(7):1724-31.
- [10]. Lanoy E, Dores GM, Madeleine MM, Toro JR, Fraumeni JF, Jr., Engels EA. Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. *AIDS* 2009;23(3):385-93.
- [11]. Koljonen V, Kukko H, Tukiainen E, Bohling T, Sankila R, Pukkala E, et al. Incidence of Merkel cell carcinoma in renal transplant recipients. *Nephrol Dial Transplant* 2009;24(10):3231-5.
- [12]. Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T, Joensuu H. Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. *J Natl Cancer Inst* 2009;101(13):938-45.
- [13]. Sihto H, Bohling T, Kavola H, Koljonen V, Salmi M, Jalkanen S, et al. Tumor infiltrating immune cells and outcome of Merkel cell carcinoma: a population-based study. *Clin Cancer Res* 2012;18(10):2872-81.
- [14]. Kassem A, Technau K, Kurz AK, Pantulu D, Loning M, Kayser G, et al. Merkel cell polyomavirus sequences are frequently detected in nonmelanoma skin cancer of immunosuppressed patients. *Int J Cancer* 2009;125(2):356-61.
- [15]. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008;319(5866):1096-100.
- [16]. Becker JC, Houben R, Ugurel S, Trefzer U, Pfohler C, Schrama D. MC polyomavirus is frequently present in Merkel cell carcinoma of European patients. *J Invest Dermatol* 2009;129(1):248-50.
- [17]. Paik JY, Hall G, Clarkson A, Lee L, Toon C, Colebatch A, et al. Immunohistochemistry for Merkel cell polyomavirus is highly specific but not sensitive for the diagnosis of Merkel cell carcinoma in the Australian population. *Hum Pathol* 2011;42(10):1385-90.
- [18]. Rodig SJ, Cheng J, Wardzala J, DoRosario A, Scanlon JJ, Laga AC, et al. Improved detection suggests all Merkel cell carcinomas harbor Merkel polyomavirus. *J Clin Invest* 2012;122(12):4645-53.
- [19]. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol* 2008;58(3):375-81.
- [20]. Kuwamoto S. Recent advances in the biology of Merkel cell carcinoma. *Hum Pathol* 2011;42(8):1063-77.
- [21]. Brewer JD, Shanafelt TD, Otley CC, Roenigk RK, Cerhan JR, Kay NE, et al. Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol* 2012;30(8):843-9.
- [22]. Tarantola TI, Vallow LA, Halyard MY, Weenig RH, Warschaw KE, Grotz TE, et al. Prognostic factors in Merkel cell carcinoma: analysis of 240 cases. *J Am Acad Dermatol* 2013;68(3):425-32.
- [23]. Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: histologic features and prognosis. *Cancer* 2008;113(9):2549-58.
- [24]. Sihto H, Joensuu H. Tumor-infiltrating lymphocytes and outcome in Merkel cell carcinoma, a virus-associated cancer. *Oncoimmunology* 2012;1(8):1420-1421.
- [25]. Izikson L, Helm T, Sroa N, Zeitouni NC. Clinical stage of Merkel cell carcinoma and survival are not associated with Breslow thickness of biopsied tumor. *Dermatol Surg* 2012;38(8):1351-6.
- [26]. Bichakjian CK, Lowe L, Lao CD, Sandler HM, Bradford CR, Johnson TM, et al. Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. *Cancer* 2007;110(1):1-12.
- [27]. Gupta SG, Wang LC, Penas PF, Gellenthin M, Lee SJ, Nghiem P. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. *Arch Dermatol* 2006;142(6):685-90.

- [28]. Righi A, Asioli S, Caliendo V, Macripo G, Picciotto F, Risio M, et al. An ultrasonography-cytology protocol for the diagnostic management of regional nodes in a subset of patients with Merkel cell carcinoma of the skin. *Br J Dermatol* 2013;168(3):563-570.
- [29]. Veness MJ, Perera L, McCourt J, Shannon J, Hughes TM, Morgan GJ, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. *ANZ J Surg* 2005;75(5):275-81.
- [30]. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol* 2006;142(6):693-700.
- [31]. Maubec E. Sentinel node biopsy in the initial evaluation of 87 patients with Merkel cell carcinoma. In: ASCO; 2014; Chicago; 2014.
- [32]. Bhatia S. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: Survival analysis of 6,908 cases from the National Cancer Data Base. In: ASCO; 2014; 2014.
- [33]. Jouary T, Leyral C, Dreno B, Doussau A, Sassolas B, Beylot-Barry M, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. *Ann Oncol* 2012;23(4):1074-80.
- [34]. Scelsi D, Mevio N, Bertino G, Occhini A, Brazzelli V, Morbini P, et al. Electrochemotherapy as a new therapeutic strategy in advanced Merkel cell carcinoma of head and neck region. *Radiol Oncol* 2013;47(4):366-9.
- [35]. Grandpeix C, Bonvalot S, Petrow P, Fraitag S, Gounod N, Avril MF. [Continued complete remission of Merkel cell carcinoma with in-transit metastasis after treatment with isolated limb perfusion regional chemotherapy]. *Ann Dermatol Venerol* 2006;133(8-9 Pt 1):700-3.
- [36]. Zeitouni NC, Giordano CN, Kane JM, 3rd. In-transit Merkel cell carcinoma treated with isolated limb perfusion or isolated limb infusion: a case series of 12 patients. *Dermatol Surg* 2011;37(3):357-64.
- [37]. Asgari MM, Sokil MM, Warton EM, Iyer J, Paulson KG, Nghiem P. Effect of host, tumor, diagnostic, and treatment variables on outcomes in a large cohort with Merkel cell carcinoma. *JAMA Dermatol* 2014;150(7):716-23.
- [38]. Desch L, Kunstfeld R. Merkel cell carcinoma: chemotherapy and emerging new therapeutic options. *J Skin Cancer* 2013;2013:327150.
- [39]. Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Cancer* 1999;85(12):2589-95.
- [40]. Tai P, Yu E, Assouline A, Lian JD, Joseph K, Miale T, et al. Multimodality management for 145 cases of Merkel cell carcinoma. *Med Oncol* 2010;27(4):1260-6.
- [41]. Tai PT, Yu E, Winkquist E, Hammond A, Stitt L, Tonita J, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. *J Clin Oncol* 2000;18(12):2493-9.

---

## SUMMARY

The present EDF-EADO-EORTC guidelines represent a European consensus-based interdisciplinary set of recommendations (S2 level) addressing all aspects of management of MCC, from the diagnosis of primary tumour to the systemic treatment of locally advanced or metastatic disease. The recommendations are based on current standards of care, existing guidelines and expert panel opinion. A summary of these guidelines is provided in Table 3.

---

## VALIDITY PERIOD

These guidelines are planned to be updated at least every three years.

Finalised: February 2015, Next update planned: February 2018

## TABLES

**Table 1. Immunohistochemistry, adapted from Becker et al [1]. Becker JC, Assaf C, Vordermark D, Reske SN, Hense J, Dettenborn T, et al. Brief S2k guidelines--Merkel cell carcinoma. J Dtsch Dermatol Ges 2013;11 Suppl 3:29-36, 31-8.**

	MCC	Lymphoma	Melanoma	SCLC*
CK 20	+	-	-	-
Neuron-Specific-Enolase	+ <sup>#</sup>	-	-	+/-
Chromogranin A (CgA)	+/-	-	-	+/-
Huntingtin interacting protein 1 (HIP1)	+	+/-	-	-
Vimentin	-	+	+	-
Melan-A/MART-1	-	-	+	-
Leukocyte common Antigen (LCA)	-	+	-	-
Thyroid Transcription Factor-1 (TTF-1)	-	-	-	+



---

\* SCLC small cell lung cancer

**Table 2 Staging classification of MCC (adapted from Lemos et al 2010) [2]. Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol 2010;63(5):751-61.**

Stage	T	N	M	5 years survival (%)
O	TIS	N0	M0	
IA	T1	pN0	M0	79
IB	T1	cN0	M0	60
IIA	T2/T3	pN0	M0	58
IIB	T2/T3	cN0	M0	49
IIC	T4	N0	M0	47
IIIA	Any T	N1a	M0	42
IIIB		N1b/N2	M0	26
IV		Any N	M1	18

TO, no primary tumour, TIS (in situ)

---

T1 primary tumour diameter <2cm, T2 comprise between 2 and 5 cm, T3 more than 5 cm

NO, no regional node metastasis, cNO, nodes not clinically detectable but no pathologic examination, pNO, nodes negative both clinically and by pathologic examination

N1a micrometastasis, N1b macrometastasis, N2 in transit metastasis.

**Table 3. Summary of Management Recommendations on MCC by EDF-EADO-EORTC  
Expert Panel**

---

*Diagnostic and staging recommendations:*

- The diagnosis of MCC is primarily based on histological and immunohistochemical features.
- A biopsy and histologic confirmation should be performed in all clinically suspicious lesions
- The diagnosis of MCC should prompt a complete examination of the entire skin and palpation of the regional lymph nodes for nodal involvement
- Initial work up consists in ultrasound of the loco regional nodes as well as computerized tomography scanner (CT scan) or Positron Emission Tomography – Computed Tomography (PET CT).
- Sentinel lymph node biopsy is recommended if possible and is taken into account in the new AJCC classification

*Treatment recommendations:*

- Surgical excision with 1 to 2 cm margins taking into account functional considerations in the head/neck region is recommended followed by adjuvant therapy of the tumour region
- In case of lymph node involvement, the preferred treatment is a regional lymph node dissection. Adjuvant RT will be discussed in cases where multiple nodes are affected or if extracapsular involvement is observed
- Satellite or in-transit metastases around the primary site should be removed surgically if a complete removal of the metastatic sites is feasible. Electrochemotherapy or RT with or without chemotherapy may be used as an alternative option when surgery is not feasible.

---

### **Addendum 1: Surgical aspects of lymph node dissection in nodal disease**

The neck dissection consists in the ablation of the nodes of the 5 levels. The parotid; the scalp between the eye and the mastoid regions. But not all investigators proceed with the dissection of the five levels of nodes if the metastatic nodes are not directly in the parotid gland. Similarly the indication of performing the dissection of the submental mandibular (level I-II) nodes can be avoided when the metastases lie in the posterior triangle (V level) nodes.

There are 3 levels of dissection in the groin. Superficial groin dissection captures node-bearing tissue between the superficial fascia and the fascia lata, in a triangular area bound by the adductor longus medially, the Sartorius laterally, and the inguinal ligament superiorly, also called the Scarpa triangle. The fascia lata is continuous with the fascia overlying the Sartorius and adductors, an easily identifiable plane defining the deep border of dissection and the roof of the femoral canal. The tissue superficial to the fascia lata has the greatest number of inguinal nodes, draining most of the cutaneous portion of the lower extremity. A deep groin dissection includes the same areas, but also encompasses the tissue within the femoral sheath, deep to the fascia lata, containing few more deep inguinal nodes, as well as several lymphatic channels. This requires skeletonisation of the femoral vessels and increased associated morbidity. Both areas of dissection include excision of Cloquet's node at the superior end of the dissection along the femoral canal, usually located between the femoral vein and the Cooper's ligament. The saphenous vein is usually sacrificed in both cases, but surgeons may also decide to preserve it as usually it does not compromise the approach of radical surgery. The iliac and obturator dissection accompanies the groin dissection, it involves the dissection of both the obturator and the nodes

---

along the external iliac vessels from the inguinal ligament to the origin of the internal iliac artery. This technique requires skeletonisation of the external iliac vessels until the bifurcation of the common iliac vessels.

The dissection in this area is associated with significant morbidity. Overall morbidity rates have been reported between 17% and 90%, with incidence of wound infection of 13–33%, seroma formation, skin flap necrosis, and long lasting limb lymphedema. It is important to mention that this wide range for morbidity can be also due to lack of uniform evaluation criteria.

The axillary dissection is characterized by the dissection of the nodes lying between the medial aspect of the dorsal muscle, to the lateral aspect of the minor pectoralis muscle representing the first level of Berg nodes, followed by the dissection of the nodes lying below the minor pectoralis muscle representing the second level of Berg nodes and concluding the dissection of the nodes lying between the medial aspect of the minor pectoralis muscle and the subclavian tendon which is just in correspondence of the axillary vein entering in the chest wall and representing the limit of the third level of Berg nodes. The minor pectoralis muscle can be easily preserved without compromising the quality of the radical surgery. The procedure should be completed by excising the Rotter nodes located in the space in between the two pectoralis muscles and the nodes between the axillary vein and the subclavian fossa.

### **Disclosure of Potential Conflicts of Interests**

Dr. Bastholt reports personal fees from Astra-Zeneca, personal fees from Bristol Myers Squibb, personal fees from Roche, personal fees from Merck, outside the submitted work; Dr. Becker reports personal fees from Amgen, personal fees from LEO, personal fees from

---

MSD, personal fees from Merck Serono, personal fees from Roche, personal fees from Glaxo Smith Kline, outside the submitted work; Dr. Garbe reports personal fees from Amgen, grants and personal fees from Bristol Myers Squibb, grants and personal fees from Glaxo Smith Kline, personal fees from Merck, personal fees from Novartis, grants and personal fees from Roche, outside the submitted work; Dr. Grob reports personal fees from Meda, personal fees from LEO, personal fees from Galderma, personal fees from Almirall, personal fees from Roche, outside the submitted work; .Dr. Lebbé reports personal fees from Bristol Myers Squibb, personal fees from Merck, personal fees from Roche, personal fees from Novartis, personal fees from Glaxo Smith Kline, personal fees from Amgen, outside the submitted work; .Dr. Malvey reports personal fees from LEO, personal fees from Almirall, personal fees from MEDA, personal fees from ISDIN, outside the submitted work; Dr. del Marmol reports personal fees from LEO, personal fees from Roche, personal fees from MEDA, personal fees from AbbVie, outside the submitted work; Dr. Middleton reports personal fees from Millenium, personal fees from Amgen, personal fees from Roche, personal fees from Merck, personal fees from Glaxo Smith Kline, personal fees from Bristol Myers Squibb, outside the submitted work; Dr. Pehamberger reports personal fees from LEO, personal fees from Almirall, personal fees from Roche, personal fees from Bristol Myers Squibb, outside the submitted work; Dr. Peris reports personal fees from LEO, personal fees from MEDA, personal fees from Roche, personal fees from Novartis, personal fees from AbbVie, outside the submitted work; .Dr. Saiag reports personal fees from Merck, during the conduct of the study; personal fees from Bristol Myers Squibb, personal fees from Glaxo Smith Kline, personal fees from Merck, personal fees from Novartis, grants and personal fees from Roche, outside the submitted work; Dr. Stratigos reports personal fees from LEO, personal fees from Novartis, personal fees from Roche, personal fees from MEDA, grants from Janssen-Cilag, personal fees from Pfizer, personal fees from AbbVie,

---

outside the submitted work; Dr.Tesstori declared that he has no conflict of interests. Dr.

Zalaudek reports personal fees from Bristol Myers Squibb and LEO, during the conduct of the study; personal fees from LEO, personal fees from Almirall, personal fees from Roche, personal fees from Bristol Myers Squibb, outside the submitted work

# Conflicts of interests – Lars Bastholt

The Work Under Consideration for Publication					
		Astra Zeneca	BMS	Roche	Merck
1	Grant	no	no	no	no
2	Consulting fee or honorarium	no	no	no	no
3	Support for travel to meetings for the study or other purposes	no	no	no	no
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	no	no	no
5	Payment for writing or reviewing the manuscript	no	no	no	no
6	Provision of writing assistance, medicines, equipment, or administrative support	no	no	no	no
7	Other	no	no	no	no

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	no	no	no	no
2	Consultancy	Yes	Yes	Yes	Yes
3	Employment	no	no	no	no
4	Expert testimony	no	no	no	no
5	Grants/grants pending	no	no	no	no
6	Payment for lectures including service on speakers bureaus	no	no	no	no
7	Payment for manuscript preparation	no	no	no	no
8	Patents (planned, pending or issued)	no	no	no	no
9	Royalties	no	no	no	no
10	Payment for development of educational presentations	no	no	no	no
11	Stock/stock options	no	no	no	no
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Yes	Yes	Yes	Yes
13	Other (err on the side of full disclosure)	no	no	no	no



\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	no	no	no

Conflicts of interests – Claus Garbe

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	Amgen	BMS, GSK	MSD; Novartis	Roche
2	Consultancy	Amgen	BMS, GSK	MSD, Novartis	Roche
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	BMS	GSK	Roche	
6	Payment for lectures including service on speakers bureaus	Amgen	BMS, GSK	MSD, Novartis	Roche
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	BMS	Roche		
13	Other (err on the side of full disclosure)	no			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			

## Conflicts of interests

Jean Jacques Grib

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	0			
2	Consulting fee or honorarium	0			
3	Support for travel to meetings for the study or other purposes	0			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	0			
5	Payment for writing or reviewing the manuscript	0			
6	Provision of writing assistance, medicines, equipment, or administrative support	0			
7	Other				

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	Meda, Leo, galderma, almirall	Unrelated to SCC GSK, Roche, BMS, Merck, celgene,		
2	Consultancy	0			
3	Employment	0			
4	Expert testimony	0			
5	Grants/grants pending	0			
6	Payment for lectures including service on speakers bureaus	0			
7	Payment for manuscript preparation	0			
8	Patents (planned, pending or issued)	0			
9	Royalties	0			
10	Payment for development of educational presentations	Linked to SCC/KA Almirall	Unrelated to SCC GSK, Roche, BMS		
11	Stock/stock options	0			
12	Travel/accommodations/meeting expenses unrelated	0	Unrelated to SCC GSK, Roche,		

	to activities listed**				
13	Other (err on the side of full disclosure)	Institutional funding from approx.. 20 pharma companies (fee for service for commercial clinical trials)			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No			

Conflicts of interests Celeste Lebbe

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant				
2	Consulting fee or honorarium				
3	Support for travel to meetings for the study or other purposes				
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like				
5	Payment for writing or reviewing the manuscript				
6	Provision of writing assistance, medicines, equipment, or administrative support				
7	Other				

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	BMS	MSD	ROCHE	Novartis, GSK Amgen
2	Consultancy			Roche	GSK
3	Employment				
4	Expert testimony				
5	Grants/grants pending				
6	Payment for lectures including service on speakers bureaus				
7	Payment for manuscript preparation				
8	Patents (planned, pending or issued)				
9	Royalties				
10	Payment for development of educational presentations				
11	Stock/stock options				
12	Travel/accommodations/meeting expenses unrelated to activities listed**			Support to go to the ASCO and ESMO meeting in 2014	
13	Other (err on the side of full)				

	disclosure)				
--	-------------	--	--	--	--

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?				

# Conflicts of interests –JOSEP MALVEHY

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	LEO	ALMIRALL	MEDA	
2	Consultancy	LEO	ALMIRALL	MEDA	
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	ALMIRALL	MEDA	ISDIN	
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	LEO	ALMIRALL	ISDIN	
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	ALMIRALL	MEDA	
13	Other (err on the side of full disclosure)	no			



\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			

Conflicts of interests -- Véronique DEL MARMOL

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	NO			
2	Consulting fee or honorarium	NO			
3	Support for travel to meetings for the study or other purposes	NO			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	NO			
5	Payment for writing or reviewing the manuscript	NO			
6	Provision of writing assistance, medicines, equipment, or administrative support	NO			
7	Other	NO			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	LEO	MEDA	ROCHE	ABBVIE
2	Consultancy				
3	Employment	NO			
4	Expert testimony	NO			
5	Grants/grants pending	NO			
6	Payment for lectures including service on speakers bureaus	NO	NO	NO	ABBVIE
7	Payment for manuscript preparation	NO			
8	Patents (planned, pending or issued)	NO			
9	Royalties	NO			
10	Payment for development of educational presentations	NO			
11	Stock/stock options	NO			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	NO			
13	Other (err on the side of full disclosure)	NO			

\* This means money that your Institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	NO			

## Conflicts of interests

The Work Under Consideration for Publication					
		Mark Middleton	Name	Name	Name
1	Grant	No			
2	Consulting fee or honorarium	No			
3	Support for travel to meetings for the study or other purposes	No			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No			
5	Payment for writing or reviewing the manuscript	No			
6	Provision of writing assistance, medicines, equipment, or administrative support	No			
7	Other	No			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership				
2	Consultancy	Millenium, Amgen, Roche, Merck, GSK, AZ, BMS			
3	Employment	No			
4	Expert testimony	No			
5	Grants/grants pending	No			
6	Payment for lectures including service on speakers bureaus	No			
7	Payment for manuscript preparation	No			
8	Patents (planned, pending or issued)	No			
9	Royalties	No			
10	Payment for development of educational presentations	BMS			
11	Stock/stock options	No			
12	Travel/accommodations/meeting expenses unrelated	BMS, Merck			

	to activities listed**				
13	Other (err on the side of full disclosure)	Institutional funding from approx.. 20 pharma companies (fee for service for commercial clinical trials)			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No			

Conflicts of interests

*Hugert Pechamberger*

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	No			
2	Consulting fee or honorarium	No			
3	Support for travel to meetings for the study or other purposes	No			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No			
5	Payment for writing or reviewing the manuscript	No			
6	Provision of writing assistance, medicines, equipment, or administrative support	No			
7	Other	No			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	LEO	Almirall	Roche	BMS
2	Consultancy	LEO	Almirall	Roche	BMS
3	Employment	No			
4	Expert testimony	No			
5	Grants/grants pending	No			
6	Payment for lectures including service on speakers bureaus	No			
7	Payment for manuscript preparation	No			
8	Patents (planned, pending or issued)	No			
9	Royalties	No			
10	Payment for development of educational presentations	No			
11	Stock/stock options	No			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	BMS	LEO	Roche	
13	Other (err on the side of full disclosure)	No			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No			

# Conflicts of interests – Ketty Peris

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	LEO	Meda	Roche	Novartis
2	Consultancy	LEO	Meda	Roche	
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	LEO	Meda	Roche	
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	Meda	Roche	Abbvie
13	Other (err on the side of full disclosure)	no			



\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			

Conflicts of interests

*Philippe Saia*

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	0			
2	Consulting fee or honorarium	0			
3	Support for travel to meetings for the study or other purposes	MSD			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	0			
5	Payment for writing or reviewing the manuscript	0			
6	Provision of writing assistance, medicines, equipment, or administrative support	0			
7	Other	0			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	Roche-Genentec	GSK	Novartis	BMS, Merck
2	Consultancy	GSK			
3	Employment	0			
4	Expert testimony	0			
5	Grants/grants pending	Roche			
6	Payment for lectures including service on speakers bureaus	GSK	Roche		
7	Payment for manuscript preparation	GSK			
8	Patents (planned, pending or issued)	0			
9	Royalties	0			
10	Payment for development of educational presentations	0			
11	Stock/stock options	0			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Roche-Genentec	GSK	Novartis	BMS, Merck
13	Other (err on the side of full)	0			

	disclosure)				
--	-------------	--	--	--	--

\* This means money that your institution received for your efforts.  
 \*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	0			

Conflicts of interests – Alexander J. Stratigos

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other				

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	LEO			
2	Consultancy	novartis	roche	LEO	MEDA
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	Jannsen-Cilag			
6	Payment for lectures including service on speakers bureaus	MSD	Pfizer	LEO	Roche
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	MacGraw Hill (Pediatric dermatology atlas)			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	Jannsen-Cilag	Abbvie	

13	Other (err on the side of full disclosure)				
----	--	--	--	--	--

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			

## Conflicts of interests

*Alessandro Testoni*

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	NO			
2	Consulting fee or honorarium	NO			
3	Support for travel to meetings for the study or other purposes	NO			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	NO			
5	Payment for writing or reviewing the manuscript	NO			
6	Provision of writing assistance, medicines, equipment, or administrative support	NO			
7	Other				

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	GSK	BMS	AMGEN	ROCHE
2	Consultancy	NO			
3	Employment	NO			
4	Expert testimony	NO			
5	Grants/grants pending	NO			
6	Payment for lectures including service on speakers bureaus	NO			
7	Payment for manuscript preparation	NO			
8	Patents (planned, pending or issued)	NO			
9	Royalties	NO			
10	Payment for development of educational presentations	NO			
11	Stock/stock options	NO			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	NO			
13	Other (err on the side of full disclosure)	NO			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	NO			

Conflicts of interests for Jürgen C. Becker, Translational Dermato-Oncology, DKTK Essen

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant				
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	no			
2	Consultancy	Amgen	Leo	MSD	GSK
3	Employment	no			
4	Expert testimony	Novartis			
5	Grants/grants pending	BI			
6	Payment for lectures including service on speakers bureaus	Amgen	MerckSerono		
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Roche	Amgen	MerckSerono	
13	Other (err on the side of full	no			



disclosure)				
-------------	--	--	--	--

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships				
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no		