Merkel-cell carcinoma: ESMO–EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Clinical classification of MCC of the skin according to the UICC TNM (eighth edition)

T (primary tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour ≤2 cm in greatest dimension
T2	Tumour >2 cm but ≤5 cm in greatest dimension
T3	Tumour >5 cm in greatest dimension
T4	Tumour invades deep extradermal structures, i.e. cartilage, skeletal muscle, fascia or bone
N (regional LNs)	
NX	Regional LNs cannot be assessed
N0	No regional LN metastasis
N1	Regional LN metastasis
N2	In-transit metastasis[a] *without* LN metastasis
N3	In-transit metastasis[a] *with* LN metastasis
M (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Skin, subcutaneous tissues or non-regional LN(s)
M1b	Lung

M1c	Other site(s)

LN, lymph node; MCC, Merkel-cell carcinoma; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

[a]In-transit metastasis is a discontinuous tumour distinct from the primary lesion and located between the primary lesion and the draining regional LNs or distal to the primary lesion.

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Supplementary Table S2. pTNM pathological classification of MCC of the skin according to the UICC TNM (eighth edition)

pTNM pathological classification	
pN0	Histological examination of a regional lymphadenectomy specimen will ordinarily include six or more LNs. If the LNs are negative but the number ordinarily examined is not met, classify as pN0.
pNX	Regional LNs cannot be assessed
pN0	No regional LN metastasis
pN1	Regional LN metastasis
pN1a	(sn) microscopic metastasis detected on SLNB
pN1a	Microscopic metastasis detected on node dissection
pN1b	Macroscopic metastasis (clinically apparent)
pN2	In-transit metastasis[a] *without* LN metastasis
pN3	In-transit metastasis[a] *with* LN metastasis

The pT category corresponds to the T category.

LN, lymph node; MCC, Merkel-cell carcinoma; pTNM, pathological tumour–node–metastasis; SLNB, sentinel lymph node biopsy; sn, sentinel node; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

[a]In-transit metastasis is a discontinuous tumour distinct from the primary lesion and located between the primary lesion and the draining regional LNs or distal to the primary lesion.

Supplementary Table S3. Clinical stage grouping of MCC of the skin according to the UICC TNM (eighth edition)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2, T3	N0	M0
IIB	T4	N0	M0
III	Any T	N1, N2, N3	M0
IV	Any T	Any N	M1

MCC, Merkel-cell carcinoma; Tis, carcinoma *in situ*; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

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Supplementary Table S4. Pathological stage grouping of MCC of the skin according to the UICC TNM (eighth edition)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2, T3	N0	M0
IIB	T4	N0	M0
IIIA	T0	N1b	M0
	T1-4	N1a, N1a(sn)	M0
IIIB	T1-T4	N1b, N2, N3	M0
IV	Any T	Any N	1

MCC, Merkel-cell carcinoma; sn, sentinel node; Tis, carcinoma *in situ*; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

Supplementary Table S5. ESMO-MCBS table for new therapies/indications in MCC

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[a]
Avelumab	Adult patients with metastatic MCC	JAVELIN Merkel 200 (Part A – pretreated patients)[2-8] Phase II NCT02155647	Single arm	ORR: 33.0% Median DoR: 40.5 months 5-year survival: 26%[b]		QoL was not a prespecified endpoint	4[c] (Form 3)
Avelumab	Adult patients with metastatic MCC	JAVELIN Merkel 200 (Part B – treatment-naive patients)[6-11] Phase II NCT02155647	Single arm	ORR: 39.7% Median DoR: 18.2 months Median PFS: 4.1 months		QoL was not a prespecified endpoint	4[c] (Form 3)

				1-year survival: 60%			
Pembrolizumab[d]	Adult and paediatric patients with recurrent, locally advanced or metastatic MCC	KEYNOTE-017[12-14] Phase II NCT02267603	Single arm	ORR: 58% Median DoR: NR (>9 months) Median PFS: 16.8 months 3-year survival: 59.4%			3 (Form 3)

CI, confidence interval; DoR, duration of response; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; HR, hazard ratio; MCC, Merkel-cell carcinoma; NR, not reached; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QoL, quality of life.

[a]ESMO-MCBS version 1.1[15] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[b]Prior to the use of immunotherapies targeting PD-1 or its major ligand, PD-L1, patients with advanced MCC had an expected 5-year survival of 14%-27%.[16]

[c]MCBS score upgraded based on expanded access and real-world experience.

[d]FDA approved, not EMA approved.

Supplementary Table S6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

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