CUTANEOUS MALIGNANT MELANOMA

General Overview

- Malignant melanoma (MM) ranks 17th worldwide in incidence and 22nd in mortality (1)
- Incidence is higher in Europe and Oceania (MM ranks respectively 7th and 4th in incidence) (1)
- Risk factors: ultraviolet (UV) radiation (sun exposure, tanning beds), sunburn, multiple or dysplastic naevi and a medical history of melanoma
- Genetic mutations are rare but should be considered in case of multiple cutaneous MM, several family members with MM or associated tumor entities: FAMM (familial atypical multiple mole melanoma)-syndrome
- Various subtypes: superficial spreading melanoma, nodular melanoma, melanoma of unknown primary, acrolentigious melanoma, mucosal and uveal melanoma, blue naevus-like melanoma
- A-B-C-D rule: asymmetry – borders – color – diameter
- Risk of metastases increases with increasing Breslow thickness

Staging (AJCC 8th edition) and prognosis

- Work-up:
  - pT1a: no additional investigations – direct follow-up
  - pT1b-pT3a: CT thorax/abdomen/neck and/or US for locoregional LN metastases
  - ≥ pT3b: brain MRI and PET-CT
  - If cerebral metastases are suspected: brain MRI
  - Sentinel lymph node (LN) biopsy (SLNB) if:
    - Breslow thickness > 0.8mm (not if ≤ 0.8 mm and without ulceration)
    - At same time of wide local excision (WLE) to avoid LN drainage alterations - *vide infra.*

TNM-classification	
Tumor (T)	
T	**Breslow-thickness**
Tx	Primary tumor cannot be assessed
Tis	In situ
T0	No evidence of primary tumor
T1 T1a T1b	≤ 1.0 mm < 0.8 mm without ulceration < 0.8 mm with ulceration; 0.8 – 1.0 mm with or without ulceration
T2 T2a T2b	> 1.0 – 2.0 mm > 1.0 – 2.0 mm without ulceration > 1.0 – 2.0 mm with ulceration
T3 T3a T3b	> 2.0 – 4.0 mm > 2.0 – 4.0 mm without ulceration > 2.0 – 4.0 mm with ulceration
T4 T4a T4b	> 4.0 mm > 4.0 mm without ulceration > 4.0 mm with ulceration

Node (N)	
Nx	Regional lymph nodes (LN) cannot be assessed
N0	No positive regional LN
N1	1 LN or in-transit melanoma or (micro)satellite
N1a	Clinically occult
N1b	Clinically detectable
N1c	In-transit or (micro)satellite
N2	2-3 LN or in-transit melanoma or (micro)satellite
N2a	Clinically occult
N2b	Clinically detectable
N2c	In-transit or (micro)satellite
N3	≥ 4 LN; matted lymph nodes; in-transit melanoma or satellite lesions with positive LN
N3a	Clinically occult
N3b	Clinically detectable
N3c	In-transit or (micro)satellite
Metastasis (M)	
Mx	Metastases cannot be assessed
M0	No metastases found
M1	Metastases present
M1a	Distant soft tissue
M1b	Lungs
M1c	Other visceral organs
M1d	Central nervous system

AJCC 8th edition melanoma of the skin staging							
Clinical staging (cTNM)				**Pathological staging (pTNM)**			
Stage 0	Tis	N0	M0	**Stage 0**	Tis	N0	M0
Stage IA	T1a	N0	M0	**Stage IA**	T1a	N0	M0
Stage IB	T1b				T1b		
	T2a			**Stage IB**	T2a		
Stage IIA	T2b	N0	M0	**Stage IIA**	T2b	N0	M0
	T3a				T3a		
Stage IIB	T3b			**Stage IIB**	T3b		
	T4a				T4a		
Stage IIC	T4b			**Stage IIC**	T4b		
Stage III	Any T, Tis	≥ N1	M0	**Stage IIIA**	T1a/b-T2a	N1a, N2a	M0
				Stage IIIB	T0	N1b/c	
					T1a/b-T2a	N1b/c, N2b	
					T2b/T3a	N1a-2b	
				Stage IIIC	T0	N2b/c, N3b/c	
					T1a-3a	N2c, N3a/b/c	
					T3b/4a	≥ N1	
					T4b	N1a-2c	
				Stage IIID	T4b	N3a/b/c	
Stage IV	Any T	Any N	M1	**Stage IV**	Any T	Any N	M1

- T-category
  - Breslow thickness after complete excision
  - Mitotic rate is not included in the 8th edition of AJCC staging but important, so is the level of invasion, TILs and lymphovascular and neural invasion.

- N-category
  - Assessment of regional lymph nodes and non-nodal regional sites, e.g. (micro)satellite and in-transit metastases
  - Microsatellite = metastasis adjacent or deep to, but not connected to the primary tumor <2 cm from primary; satellite if ≥ 2 cm.
  - 'Matted nodes' if two or more LN appear joined together.
- Prognostic factors:
  - Poor: tumor thickness, increased mitotic rate, ulceration, positive SLNB, extracapsular extension of tumor out of LN, elevated LDH and S100
  - Favorable: TILs
- 5Y-OS: stage I-II (65-100%), stage III (41-71%), stage IV (9-28%)

Treatment

TREATMENT OF LOCAL DISEASE

- Wide local excision (WLE) with safety margins, which depend on the Breslow thickness: 0.5 cm for *in situ*, 1 cm for Breslow thickness ≤ 2 mm, and 2 cm for > 2 mm.
  - WLE only after confirmation of MM-diagnosis after original excision
  - Smaller safety margins can be allowed in functional or cosmetic area's (joints, face); in these cases, option for Mohs micrographic surgery
- Radiotherapy (RT):
  - Can be curative for lentigo maligna, in cases where surgery is unacceptable
  - In rare palliative cases, where excision is not possible due to severe comorbidities (= non curative)

TREATMENT OF LOCOREGIONAL DISEASE

- No indication for elective LN dissection or RT to LN
- In rare palliative cases, RT can be considered.
- SLNB for each tumor ≥ pT1b + WLE

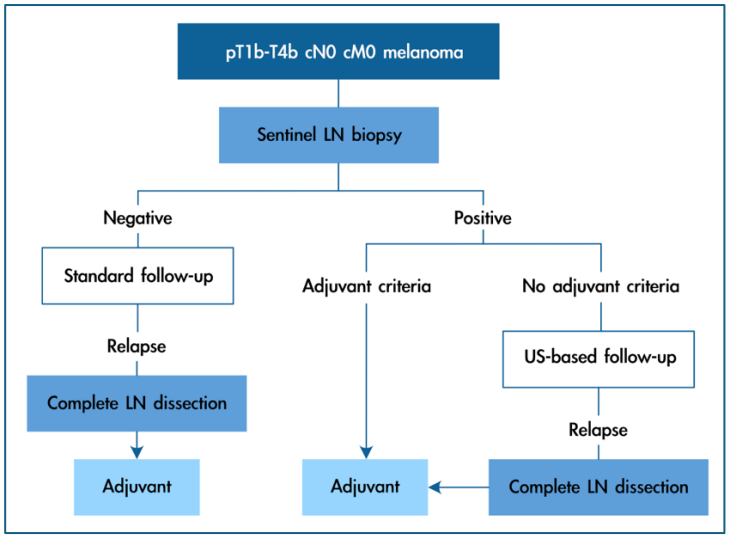

Figure 1: treatment algorithm for stage I-III melanoma

ADJUVANT TREATMENT

- Not recommended for stage I/IIA melanoma after complete resection
- Adjuvant systemic therapy:
  - BRAFwt: 1 year adjuvant anti-PD-1 monotherapy (2)

    - BRAFmt: 1 year adjuvant dabrafenib/trametinib (preferred) (3) OR anti-PD-1 monotherapy (2)
- Adjuvant RT: not standard

TREATMENT IN STAGE IV

- Resectable oligometastatic disease: local therapy (surgery) + systemic adjuvant therapy (4, 5).
- Non-resectable:
    - Immunotherapy: combination (nivolumab + ipilimumab) (6) or anti-PD-L1 monotherapy (nivolumab or pembrolizumab) or anti-PD-L1/LAG3 (Opdualag) (7)
        - 1L choice, also in BRAFmt, however expected to change to 'run in' with targeted therapy if symptomatic (vide what's new) (8)
    - Targeted therapy:
        - BRAFmt: encorafenib/binimetinib (preferred due to less toxicity), dabrafenib/trametinib, vemurafenib/cobimetinib (9, 10)
        - Other: KIT-inhibitors (if activating KIT mutation), entrectenib/larotrectinib (if NTRK gene fusion)

OTHER

- In-transit metastases: surgery, RT, laser ablation, cryotherapy, intralesional injections, electrochemotherapy, hyperthermic isolated limb perfusion
- Brain metastases: RT (mainly stereotactic) and systemic options (combination immunotherapy, BRAF + MEK-inhibitors

REIMBURSEMENT

- Ipilimumab (3mg/kg q3w, max 4 doses)
    - Inoperable or metastatic MM in patients with ECOG 0-1 (monotherapy or in combination with nivolumab)
- Nivolumab (monotherapy/maintenance: 240mg q2w/480mg q4w; combination 1mg/kg q3w)
    - Inoperable or metastatic MM (monotherapy or combined with ipilimumab)
    - Adjuvant in stage IIB/C or node-positive or metastatic melanoma after complete resection (monotherapy)
- Pembrolizumab (200mg q3w/400mg q6w)
    - Inoperable or metastatic MM (monotherapy)
    - Adjuvant in stage IIB/C or III MM after complete resection (monotherapy)
- Dabrafenib/trametinib (respectively, 150mg 2dd and 2mg 1dd)
    - Adjuvant in stage III MM with BRAFV600Emt
    - Inoperable or metastatic MM with BRAFV600Emt
- Cobimetinib/vemurafenib (respectively, 60mg 1dd (3 weeks on, 1 week off) and 480 mg 2dd)
    - Inoperable or metastatic MM with BRAFV600Emt
- Encorafenib/binimetinib (respectively, 450mg 1dd, 45mg 2dd)
    - Inoperable or metastatic MM with BRAFV600Emt
- Opdualag (nivolumab + relatlimab) (flat dosing 480/160mg)
    - First-line inoperable or metastatic MM with PD-L1 <1% (monotherapy)
- Imatinib (400mg/day)
    - Reimbursed irrespective of the therapeutic line if activating KIT mutation.
- Entrectenib (600mg/day)
    - For locally advanced/metastatic malignancies with NTRK fusion, no prior NTRK inhibitor use, and no viable alternative treatments.

Follow-up

	Stage IA	Stage IB*-IIA	Stage IIB-IIIC	Stage IIID	Stage IV resected/complete remission
Year 1-3					
Clinical examination	6 months	(3)-6 months	3 months	3 months	3 months
US regional LN	/	6 months	3-6 months	3-6 months	3-6 months
Laboratory LDH, S100	/	3-6 months	3-6 months	3-6 months	3-6 months
Imaging**	/	/	6 months	3-6 months	3 months
Year 4-10					
Clinical examination	12 months	6 months	6 months	6 months	6 months
US regional LN	/	/	/	/	/
Laboratory LDH, S100	/	/	/	/	/
Imaging**	/	/	/	/	/
Year > 10					
Clinical examination	12 months	12 months	12 months	12 months	12 months
US regional LN	/	/	/	/	/
Laboratory LDH, S100	/	/	/	/	/
Imaging**	/	/	/	/	/

Based on European consensus-based interdisciplinary guideline for melanoma (2022, EDF, EADO, EORTC) (PMID 35570085)
* For sentinel node biopsy stages patients US regional LN can be omitted
** Imaging: CT or PET-CT - MRI brain

What's new?

- To be expected: immune checkpoint inhibitors in the neoadjuvant setting (11). CAVE not yet in the clinics! With important implications towards SNB-protocol.
- "Run in" with BRAF/MEK-inhibition during a short period: 8 or 12 weeks; after which continuous therapy with immune checkpoint inhibitors until progressive disease seems favorable (in comparison to the alternative regimen). Cfr Secombit trial (8) and ImmunoCobiVem phase II study (12).
- Advent of TIL therapy in first line metastatic disease/upcoming clinical trial TIL + pembrolizumab in first line
- Novel immunmodulating drugs such as anti-TIGIT

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