MELANOMA

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Dysplastic nevus

- Nevus of Clark, atypical mole
- Generally >5mm in largest dimension.
- Flat macules, slightly raised plaques with a “pebbly” surface, or target-like lesions with a darker raised center and irregular (notched), flat border.
- Variable in pigmentation (variegation)
- Appear just before puberty.
- Arise in continuity with centrally located compound nevus

Dysplastic nevus

- Histopathology
- Fusion and coalescence of nests of nevus cells in the epidermis.
- Single nevus cells with nuclear atypia are found in the basal layer (lentiginous hyperplasia).
- Nuclear enlargement, with irregular, often angulated, nuclear contours, and hyperchromasia
- Lymphocytic response is generally sparse
- Pigment released into dermis from dead cells (melanin incontinence)
- Linear fibrosis surrounding the involved epidermal rete ridge

Dysplastic nevus syndrome

- May have many such nevi over sun exposed and non-sun exposed surfaces
- 50% of those develop melanoma over lifetime

  50% have CDKN2A mutation at 9p21

  Depress RB gene, permitting cell cycle entry

Dysplastic nevus

A

Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

- Fig. 12-2A Accessed 07/16/2010

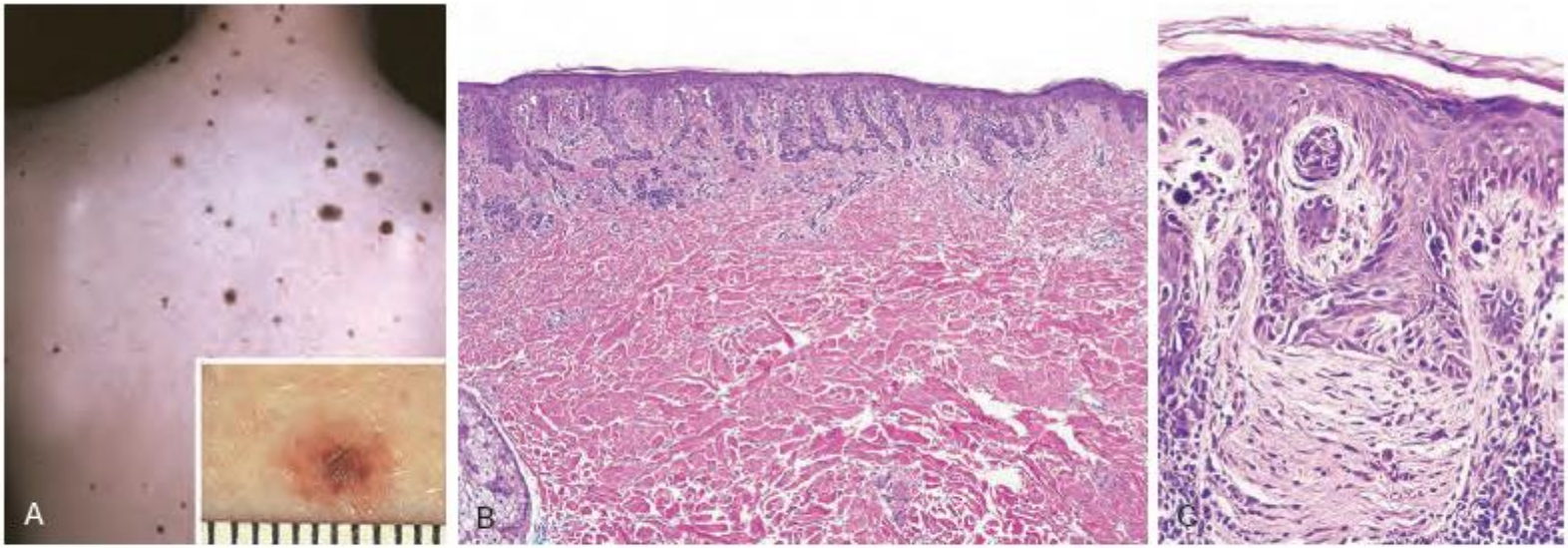
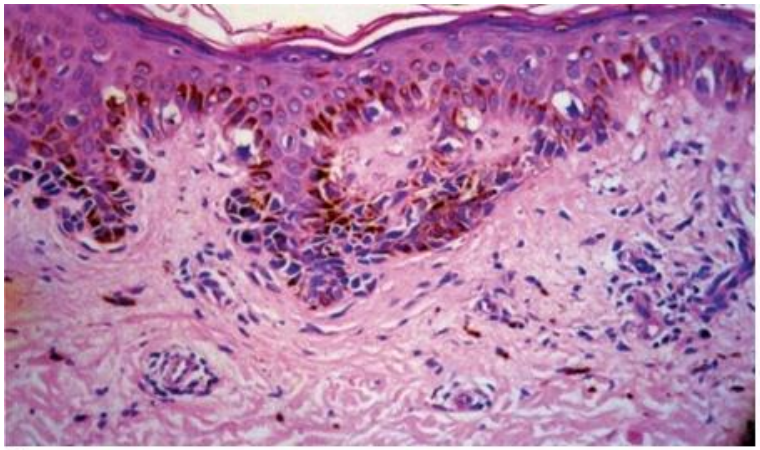
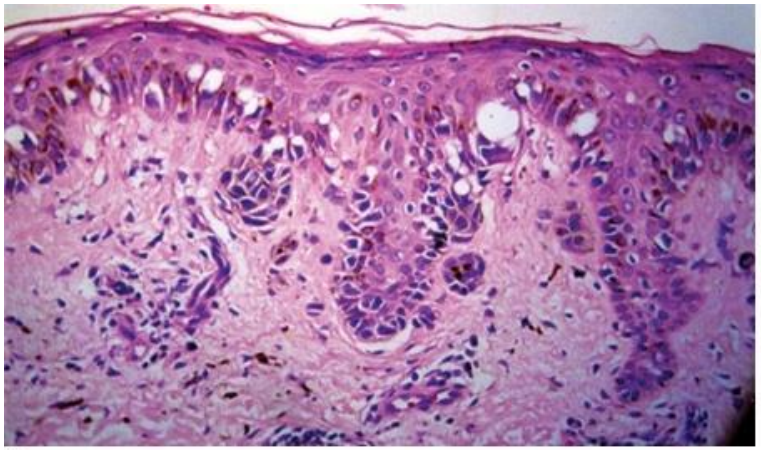


Figure 25-6 Dysplastic nevus. **A,** Numerous atypical nevi on the back. **B,** One such lesion (*inset A*) has a compound nevus component (*left*) and an asymmetric junctional nevus component (*right*). The former corresponds to the more pigmented and raised central zone and the latter to the less pigmented, flat peripheral rim of the lesion shown in **A. C,** An important feature is the presence of cytologic atypia (irregularly shaped, dark-staining nuclei). The dermis underlying the atypical cells characteristically shows linear, or lamellar, fibrosis.

Dysplastic nevus



E



F

E. The nuclei of the melanocytes are atypical and enlarged, characteristic of epithelioid melanocytic dysplasia. F. Melanocytes are in linear array, characteristic of lentiginous melanocytic dysplasia. The melanocytes are not as enlarged as in the area of epithelioid dysplasia.

(Photomicrographs used with permission from Wallace H. Clark, Jr.)

Fig. 123-2 Accessed 07/20/2010

Lentigo maligna

- A large, very irregular and asymmetric macule
- Sun exposed areas
- Median age 65 years-old
- 5-10% of cutaneous melanomas
- Rare in non-whites
- Lentiginous spread.
- There is striking variegation of pigmentation (tan, brown, dark brown, black).
- A desmoplastic variant may not be pigmented.
- Neurotization of cells in dermis.
- <u>This is malignant melanoma in situ</u>

Lentigo maligna

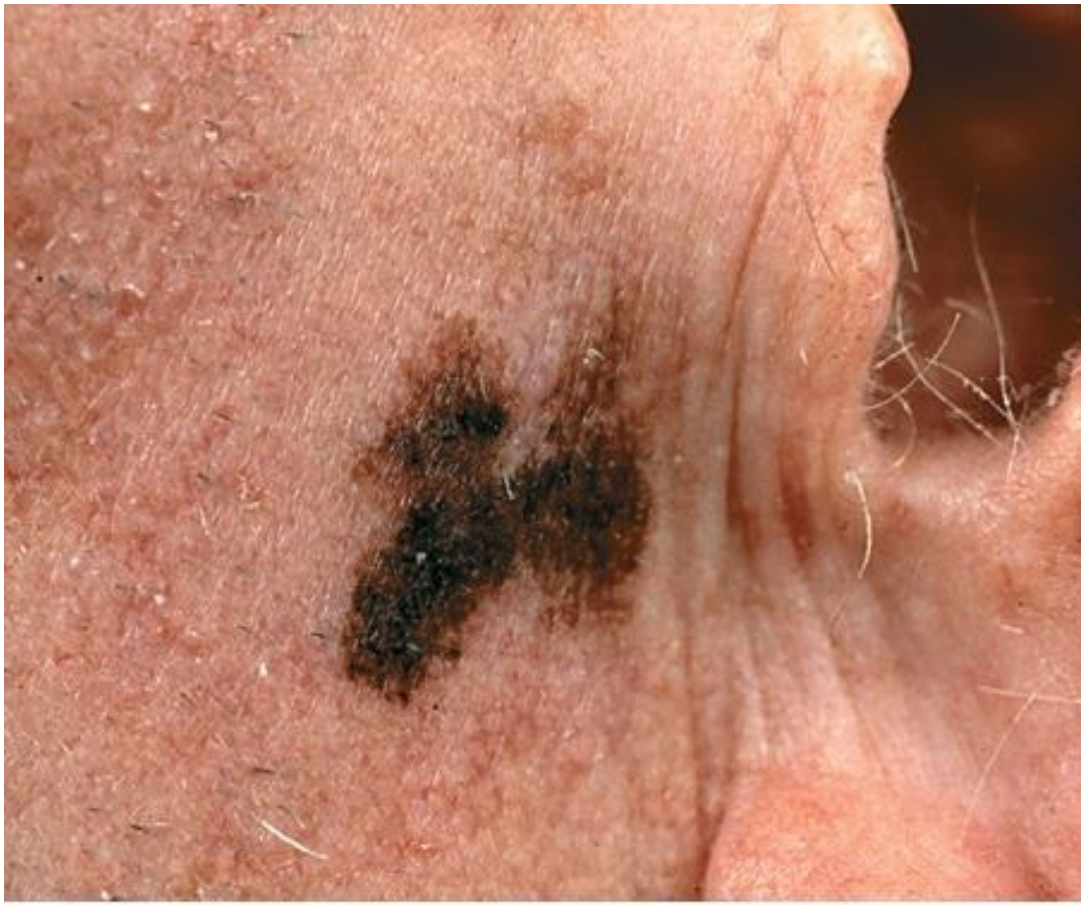


Fig. 12-7 Accessed 07/16/2010

Malignant melanoma

- ABCDE of melanoma
- Asymmetric
- Border is irregular
- Color variable
- <1% are not pigmented
- Diameter enlarged
- >10mm in largest dimension
- Enlarging lesion (particularly if rapid)

Diagnostic criteria

- If a pigmented skin lesion has enlarged, the positive likelihood ratio (LR+) for melanoma is 11, while the LR- is 0.2.
- Asymmetry
- Irregular border
- Irregular (variegated) pigmentation
- Increasing diameter in a skin lesion are associated with an LR+ of 8.3 for melanoma.
- If all five criteria are present, the LR+ is 98 for melanoma.

Malignant melanoma

- Occurs in sun exposed areas of skin
- Periodic severe sunburns early in life are the most important risk factor.
- Large cells with prominent nucleoli form poorly defined nests. Single cells are present in the epidermis.
- Both upward invasion in the epidermis as well as downward invasion into the dermis may be seen.
- 10% familial melanoma
- Young age
- Multiple dysplastic nevi
- Xeroderma pigmentosum predisposes

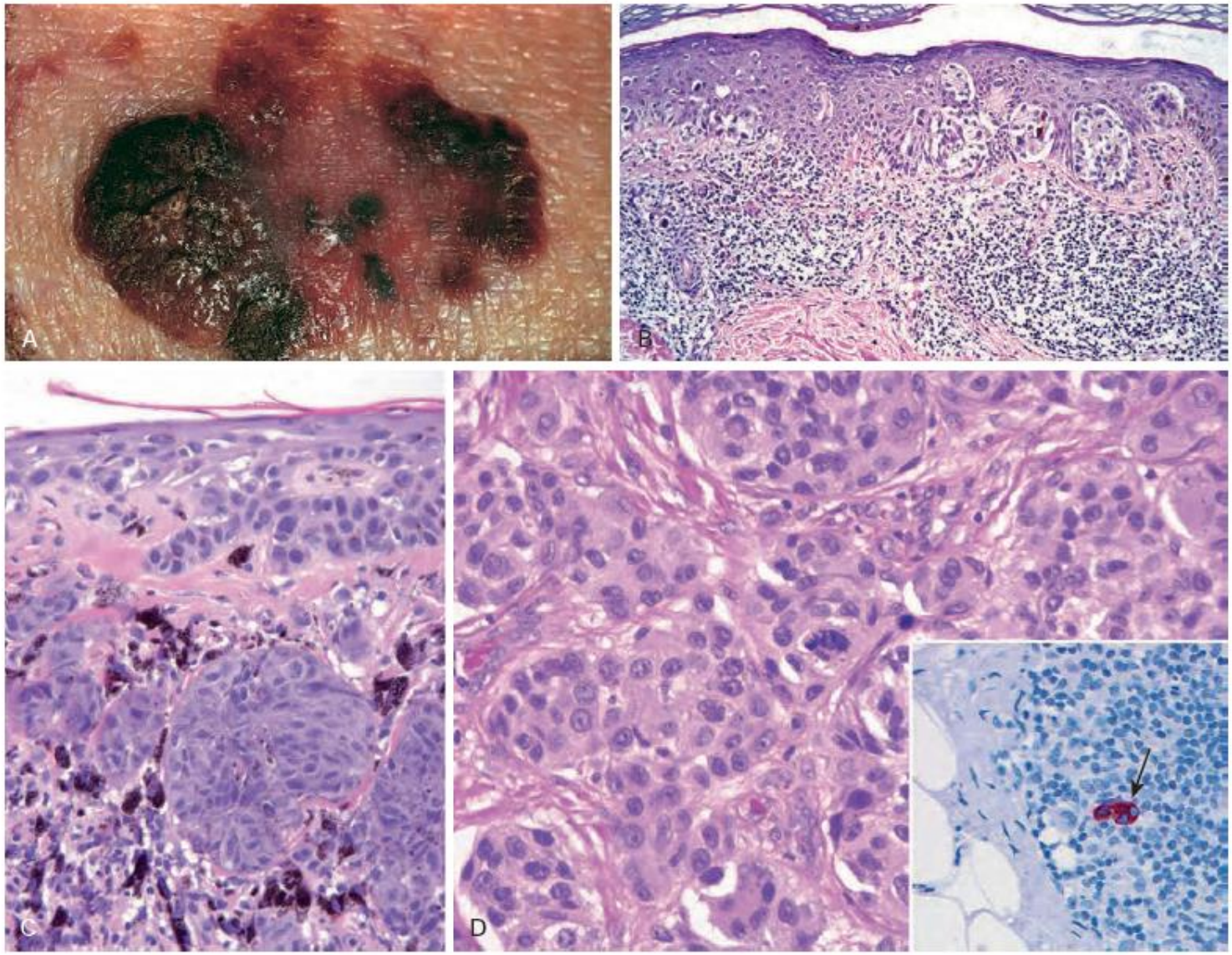


Figure 25-8 Melanoma. **A,** Typical lesions are irregular in contour and pigmentation. Macular areas correlate with the radial growth phase, while raised areas correspond to nodular aggregates of malignant cells in vertical growth phase. **B,** Radial growth phase, showing irregular nested and single-cell growth of melanoma cells within the epidermis and an underlying inflammatory response within the dermis. **C,** Vertical growth phase, demonstrating nodular aggregates of infiltrating cells. **D,** High-power view of melanoma cells. The *inset* shows a sentinel lymph node with a tiny cluster of melanoma cells *(arrow)* staining for the melanocytic marker HMB-45. Even small numbers of malignant cells in a draining lymph node may confer a worse prognosis.

Malignant melanoma

- Activating mutations in BRAF, a serine/threonine kinase that is downstream of RAS, are seen in 40-50%
- Activating mutations in N-RAS occur in an additional 15% to 20% of tumors.
- Activate P13K/AKT pathway as PTEN at 10q23.31 lost
- PI3K/AKT pathway mutations common.
- 70% TERT amplification (telomerase reactivated)
- Create new binding sites for ETS transcription factors, which are known to be up-regulated by BRAF signaling

Malignant melanoma

- Loss of CDKN2A gene at 9p21
- 40% of hereditary cases show this abnormality.
- 10% of sporadic cases
- Codes for p16 (inhibit CDK4 and CDK6)
- De-represses RB, permitting cell cycle entry.
- Also codes for $p14^{arf}$.
- Loss of $p14^{arf}$ removes inhibition of MDM2 and accelerates p53 degradation.
- Loss of CDK4 gene at 12q14.1 also noted in <u>familial melanoma</u>.
- De-represses RB, permitting cell cycle entry.

Malignant melanoma

- CTLA-4 expression evades immunologic surveillance by turning off T-cell.
- Impaired apoptosis as terminal step.

Malignant melanoma

- Uveal melanoma associated with mutations of GNAQ at 9q21.2 (25%) and GNA11 (55%) at 19p13.3
- GNAQ encodes the α-subunit of a heterotrimeric G-protein that couples transmembrane domain receptors to intracellular signaling pathways (remain activated).
- GNA11 encodes for a member of the q-class of G-protein alpha subunits and signals through PLC and PKC.
- No GTP to GDP conversion

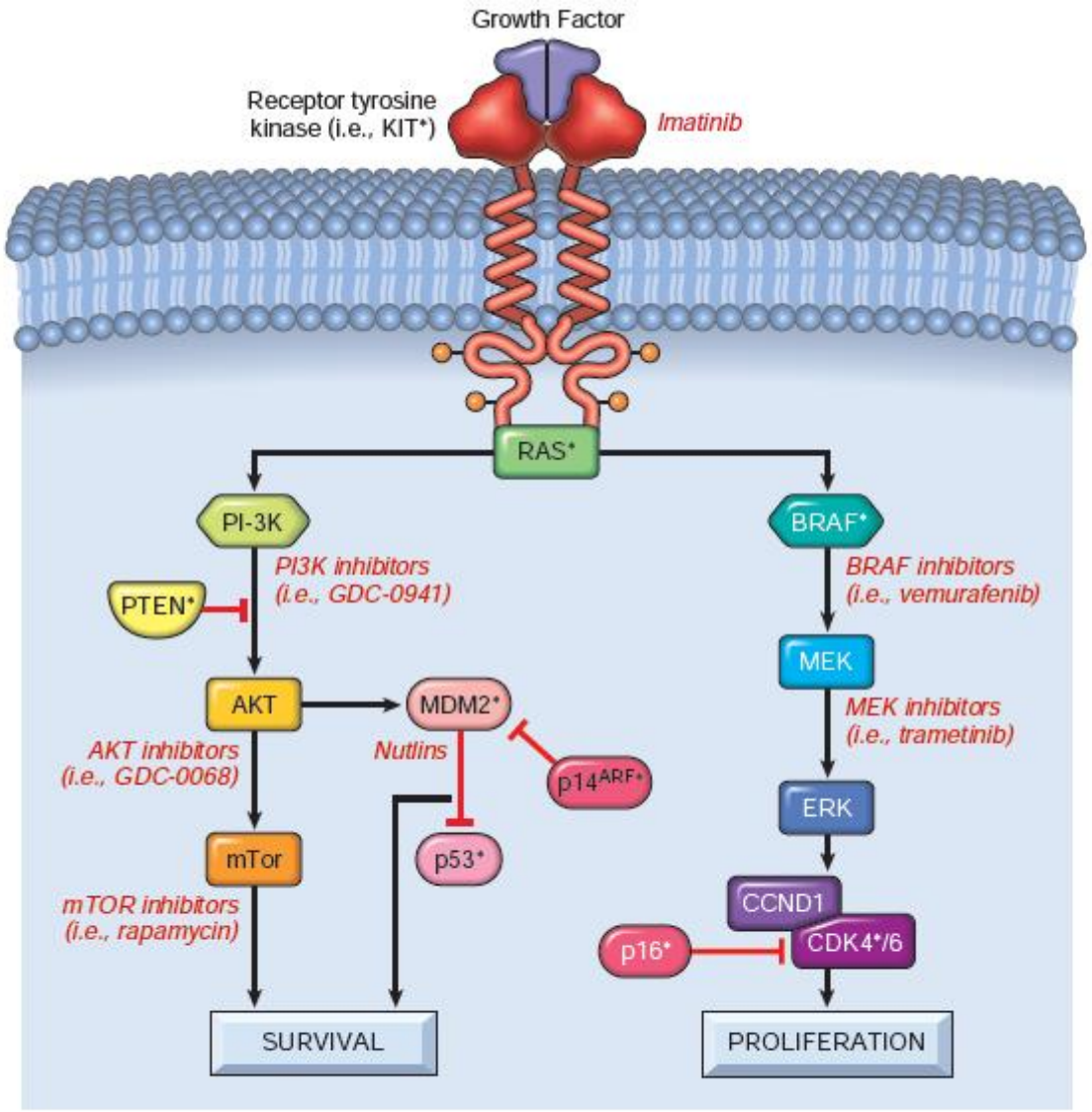


Figure 25-7 Pathways important in melanoma. Growth factors activate signaling circuits involving receptor tyrosine kinases (e.g., KIT), RAS, and two key downstream pathways that include the serine/threonine kinase BRAF and the phospholipid kinase PI3K. Proteins indicated by asterisks are mutated in melanoma. Components of these pathways that are being targeted by drugs are indicated.

Malignant melanoma

- Acral melanoma that occurs on feet is not related to sun exposure, and is usually seen in darker pigmented individuals.
- 8% of cases
- Not related to sun exposure
- Median age 65 years-old
- Principal melanoma in Africans, Asians
- Presents in nail bed (subungual)
- Thumb or great toe usual sites
- BRAF (15%), N-RAS (15%), C-KIT (15%) mutations.
- KIT at 4q12 lies upstream of RAS

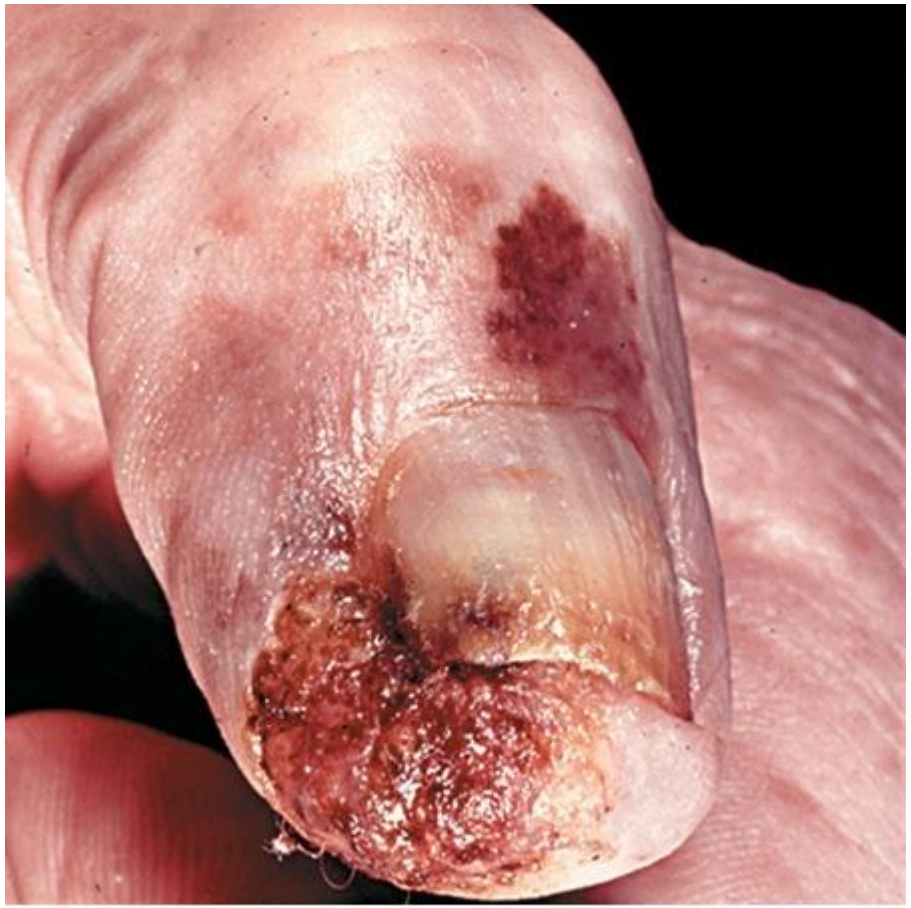
Malignant melanoma

- Intermittent intense UVB exposure (Freckling)
- BRAF (10%), N-RAS (10%), C-KIT (2%) mutations.
- Melanoma not related to sun exposure and not acral is associated with BRAF (50%), N-RAS(20%), but no C-KIT mutations.
- 20% also have PTEN mutations
- Melanoma arising from mucosal surfaces is associated with BRAF (5%), N-RAS (15%), and C-KIT(20%) mutations.

Malignant melanoma

- BRAF part of the RAS/RAF/MAPK/MEK family.
- Mutant BRAF V600E up-regulates cyclin D1 and down-regulates p27 KIPI, a cell cycle inhibitor
- Regulates BCL-2 and MCL-1 apoptotic proteins
- Down-regulates immunological differentiation antigens (Melan-1, MART-1).
- Activated KIT mutations initiate cell signaling via MAP/MEK/ERK, PI3K/AKT, and JAK/STAT pathways.

Acral lentiginous melanoma



A

Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

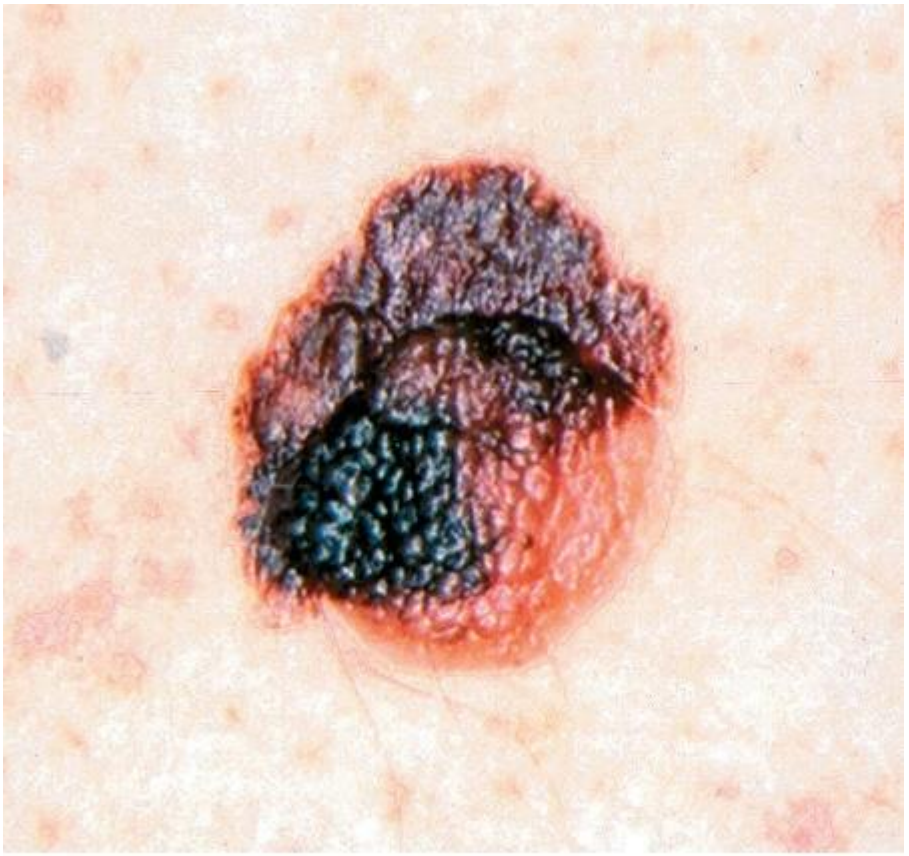
Lentiginous component on the dorsal skin of the thumb: macular, sharply and ill-defined brown and grey-bluish spots. Subungual and distal ulcerated nodular component.

Fig. 12-14A Accessed 07/16/2010

Malignant melanoma

- Radial growth describes the horizontal spread of melanoma within the epidermis.
- Lentigo maligna (5-10%)
- Median age 65 years-old
- Sun exposed skin
- Indolent
- Superficial spreading type (70%)
- Sun exposed skin
- Ages 30-50 years-old
-

Malignant melanoma

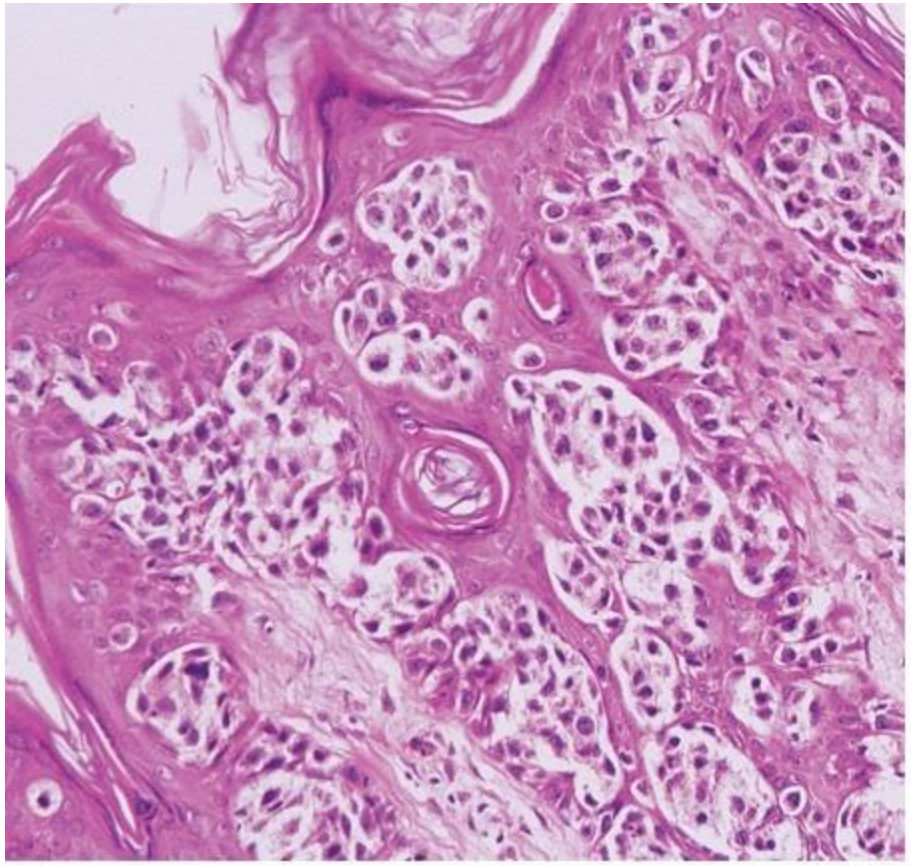


The upper dark brown portion with a pinkish rim of this lesion is a dysplastic nevus.

The variegated blue-black and pink plaque in the lower half of the lesion is the superficial spreading melanoma (0.9-mm thickness) arising within the dysplastic nevus.

Fig. 12-3 Accessed 07/16/2010

Radial growth phase



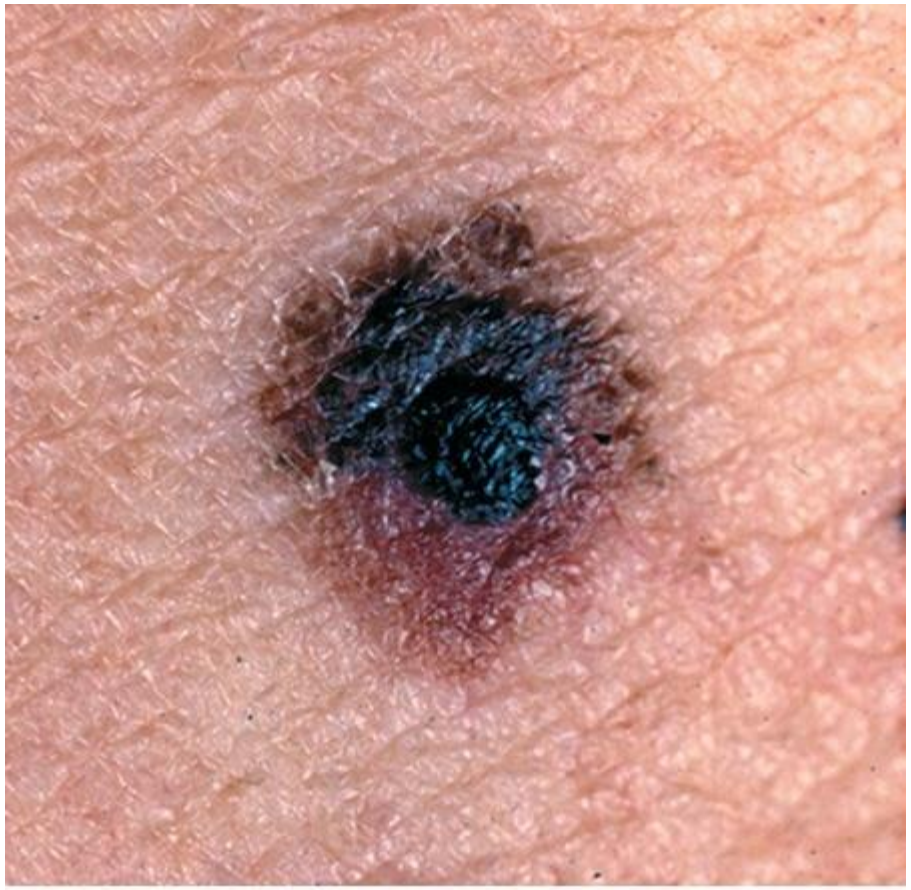
This superficial spreading tumor shows intra-epidermal growth. In this photomicrograph, the pagetoid distribution is evident in the epidermis. The cells are relatively uniform and have an abundance of dusty, fine pigment. These relatively large melanoma cells are frequently referred to as epithelioid cell type.

Fig. 124-10 Accessed 07/20/2010

Malignant melanoma

- Vertical growth phase refers to downward growth of lesion into deeper dermis.
- Nodular appearance
- Absence of neurotization
- Depth of invasion (Breslow thickness) associated with metastatic potential and survival
- Nodular form (no radial growth phase)
- Median age 55 years-old
- Sun exposed areas

Malignant melanoma



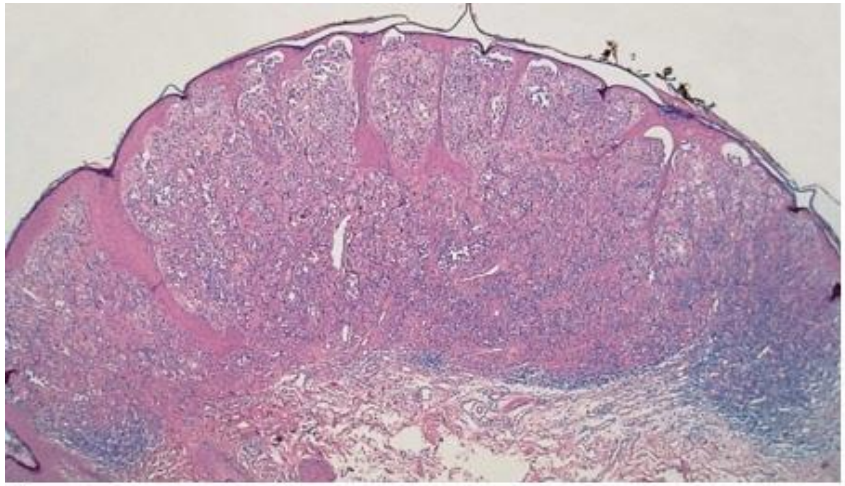
A

An only minimally flat-topped, elevated, asymmetric and irregular plaque with variegate color (brown, black) with sharply demarcated margins. The surface is also irregular with a cobblestone pattern. This is radial growth (laterally).

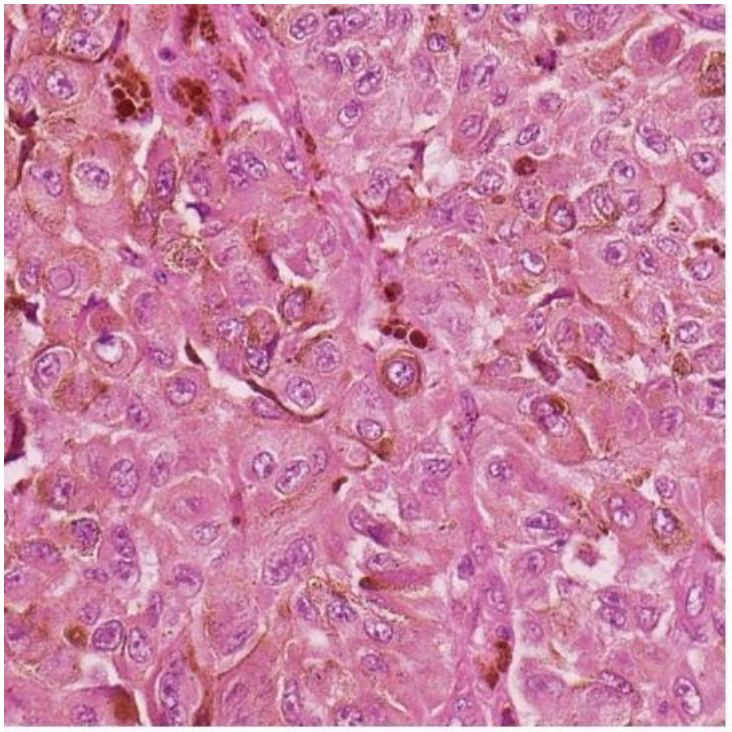
In the center there is a small black, dome-shaped nodule. This is the switch to the vertical growth phase.

Fig. 12-11A Accessed 07/16/2010

Vertical growth phase



A



B

A. Low-powered photomicrograph demonstrating a dome-shaped expansile tumor located in the upper dermis. B. High-powered photomicrograph reveals nests of anaplastic epithelioid cells in the tumo**r.**

Fig. 124-17 Accessed 07/20/2010

Malignant melanoma

- Breslow thickness
- Distance from granular layer or depth of ulcer to the deepest continguous melanoma
- More accurate than older Clark level.
- Ulceration predisposes to metastasis.
- Satellite or in-transit (intralymphatic) metastases poor prognostic feature.
- Elevated LDH levels poor prognostic feature.

Malignant melanoma

- Good prognostic features
- Tumor involving an extremity
- Tumor <0.75mm thick
- Radial growth pattern
- Low tumor cell mitotic rate

Malignant melanoma

- Excisional skin biopsy completely removes the tumor.
- Curative if the tumor is small, thin, <1 mitosis/mm^3, and 2cm tumor free margins can be obtained.
- Incisional biopsy is performed if the tumor is large. The thickest area should be sampled (if flat, the darkest area).
- Resected lesions (Stages I-III) rarely recur

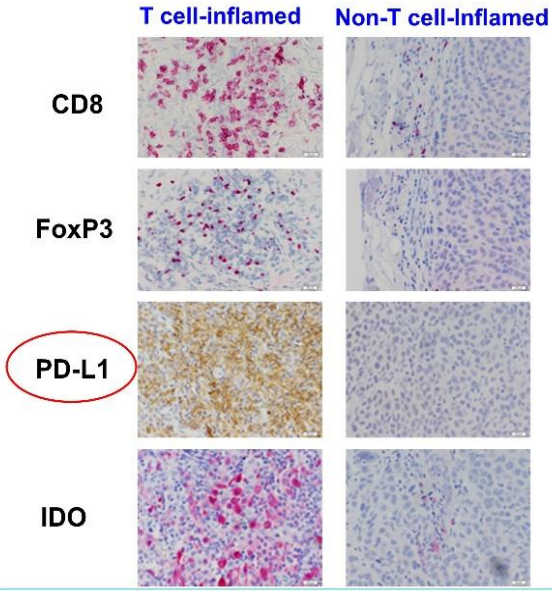
Malignant melanoma

- If nodes clinically negative and lesion >1.0mm thick or mitotic index >1/mm^3, sentinel node biopsy.
- If sentinel node positive, (therapeutic) lymphadenectomy.
- Then, adjuvant therapy with CTLA-4 and PD-1 antibodies
- PD-L1 affects tumor micro-environment
- PD-1 receptor is expressed on activated lymphocytes and modulates T-cell exhaustion.
- Blockade may reactivate lymphocytes with anti-tumor activity.

Malignant melanoma

- CTLA-4 primes T-cell
- LAG-3 expression not relevant
- Nivolumab and relatlimab as first line therapy.
- Patients who respond to administration of CTLA-4 antibodies (10%) may remain tumor free for long periods.
- Enables recognition of self-antigens
- Nivolumab with dabrafenib/trametinib in BRAF V600+ unresectable melanoma as well as if CNS metastases present

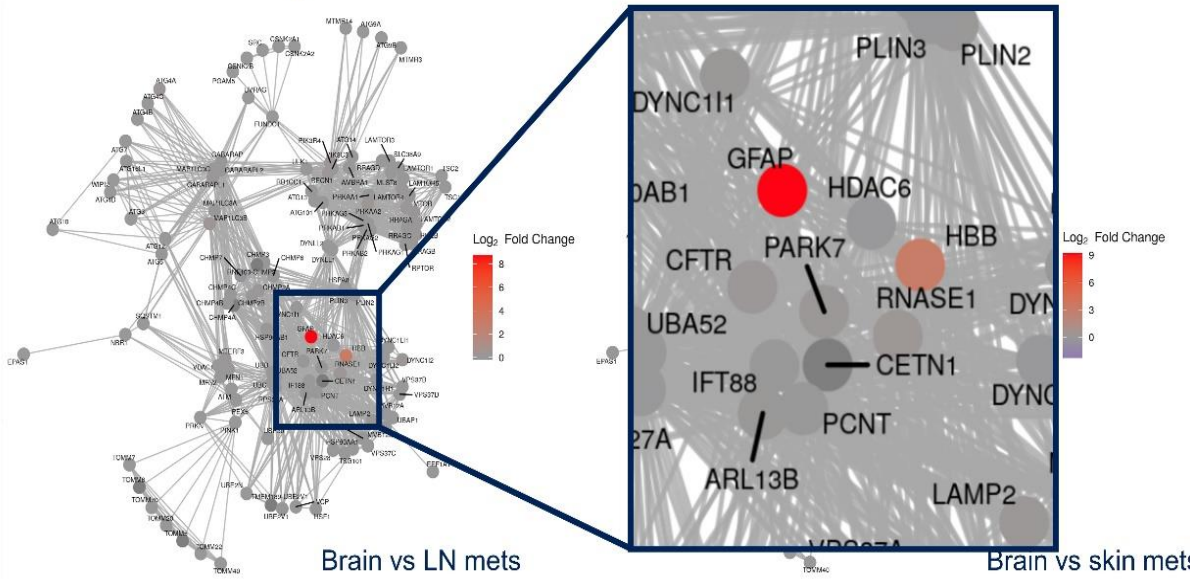
Immune-inhibitory Tregs, PD-L1, and IDO are associated with a CD8$^+$ T cell infiltrate



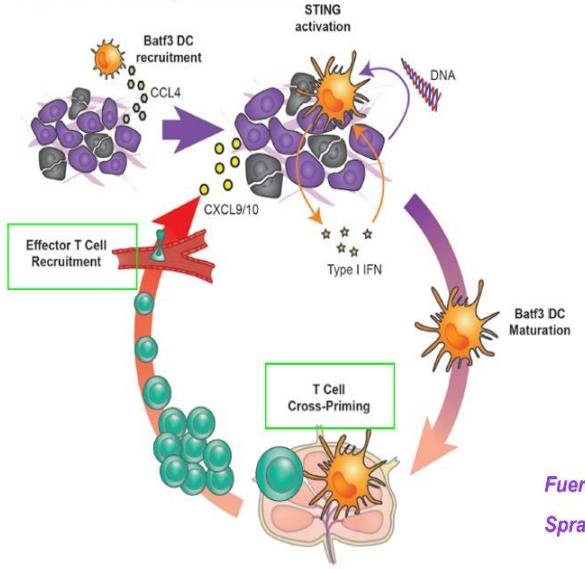
- Immune-intrinsic negative feedback loop
- CD8$^+$ T cell-derived IFN-γ upregulates PD-L1 and IDO, and CCL22 recruits Tregs
- Suggested paradigm to restore CD8$^+$ T cells already in tumor through blocking negative regulation

Spranger et al., Science Trans. Med. 2013

Upregulation of autophagy signaling is driven by increased expression of *GFAP* and *HBB* in MBM

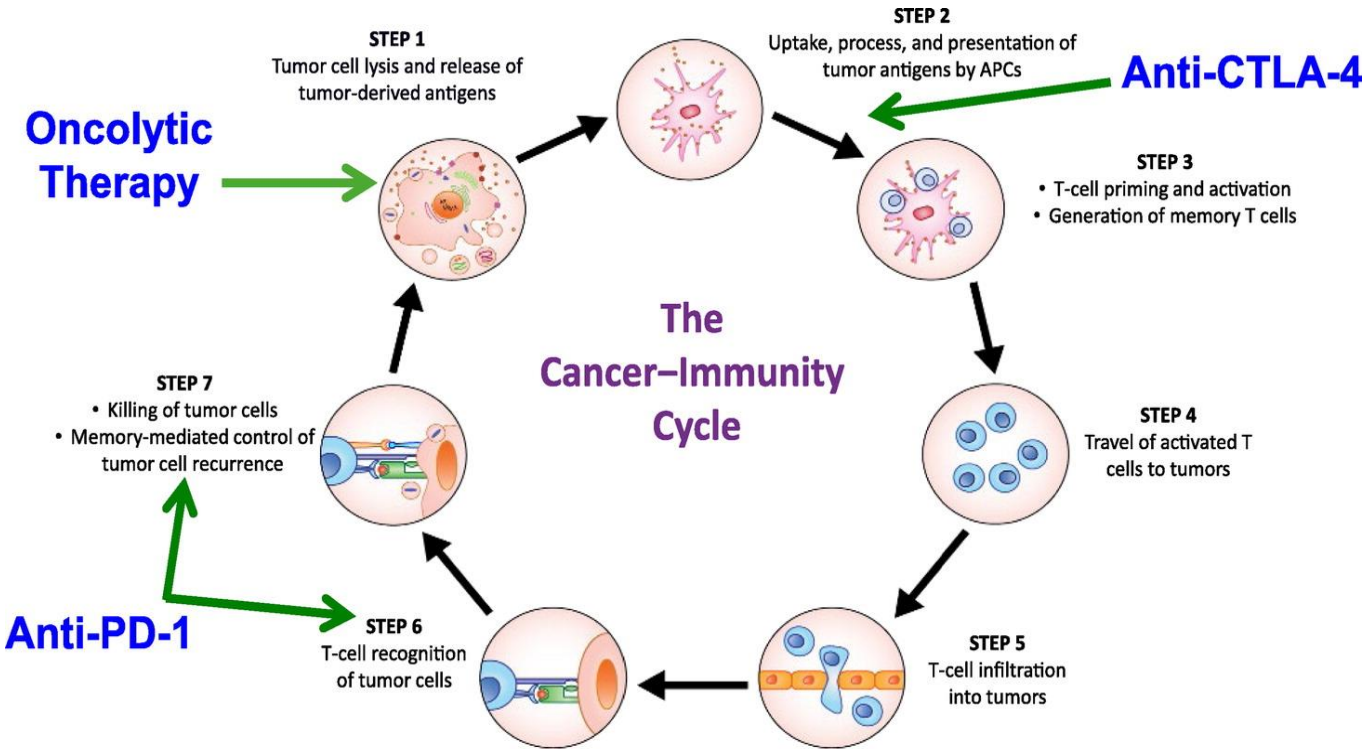


Batf3-lineage dendritic cells are involved in both the priming phase and the effector phase of anti-tumor CD8+ T cell response



Fuertes et al; J. Exp. Med. 2011

Spranger et al, Nature. 2015; Cancer Cell 2017



https://ascopubs.org/doi/full/10.1200/EDBK_79437

Malignant melanoma

- Vitamin D levels inversely associated with disease extent and survival
- CD8+ T cells isolated from patients recognize autologous tumor cells
- Gp100 peptide based vaccines may delay progression.
- 10% response to vaccine
- β-catenin activation sufficient for resistance to immunotherapy

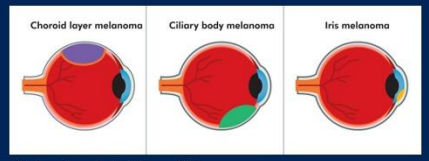
Malignant melanoma

- Metastatic melanoma patients treated with bio-chemotherapy and maintenance immunotherapy who have a normal LDH level or skin or nodes as their metastatic sites may have durable remission of their disease.
- Antibiotic therapy may lower response to tyrosine kinase inhibitors
- Microbiome downregulates CD4, upregulates CD8

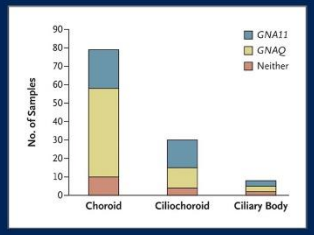
Malignant melanoma

- Isolated limb perfusion at 42C with melphalan or thiotepa chemotherapy is given with interferon-α and TNF after regional lymphadenectomy.
- Regression of visceral metastases is seen with combination chemotherapy (cisplatin, carmustine, dacarbazine, tamoxifen or cisplatin vinblastine, dacarbazine) and biologic therapy with interferon-α or IL 2.

Uveal Melanoma (UM)



Chattopadhyay C et al. *Cancer* 2016.

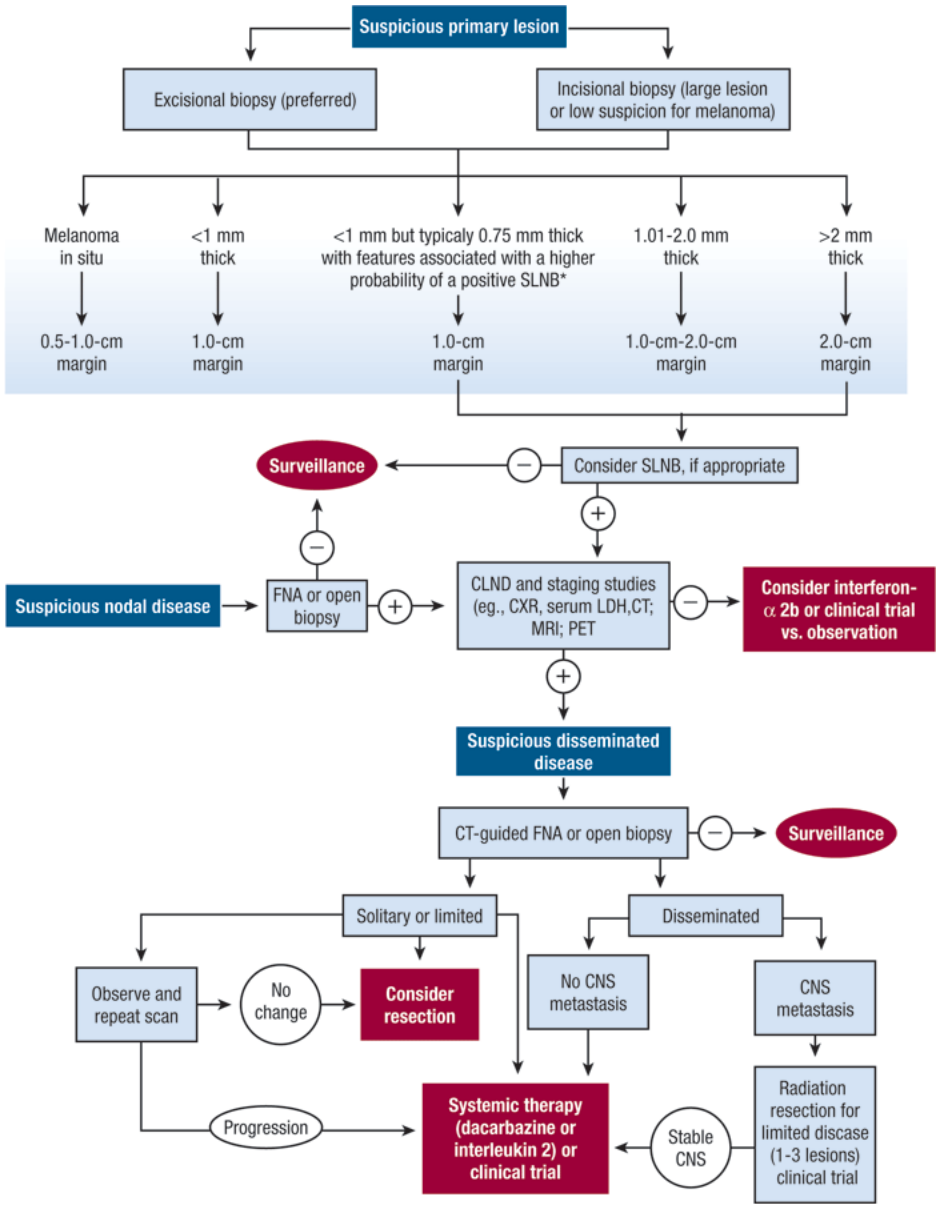


Van Raamsdonk CD et al. *N Engl J Med* 2010.

- Distinct biology from cutaneous melanoma
- Propensity for liver metastasis
- No standard therapy once metastatic
- Poor OS, median ~12 months
- Expression of gp100

Malignant melanoma

- End and limited-stage ocular melanoma managed by close observation.
- Radiation may be employed.
- Enucleation if:
- Tumor is growing in a blind eye
- Melanoma involves more than half the iris or involves the anterior chamber
- Extraocular extension.



Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

Fig. 124-20 Accessed 07/20/2010