A REVIEW AND UPDATE OF MELANOMA

Sanjay Awasthi, M.D.
Professor
Division Chief, Hematology & Oncology
Texas Tech University Health Sciences Center
Lubbock, Texas
I HAVE NO CONFLICTS OF INTEREST WITH RESPECT TO ANY CONTENT OF THIS PRESENTATION.

Sanjay Awasthi, M.D.
Tuesday April 14, 2015
Melanoma

- A highly lethal skin malignancy
- Rapidly increasing incidence
- Caused by
  - DNA damage due to sun exposure
  - Failure of immune surveillance
- Highly preventable
- Surgically curable when detected early
- Medically curable by immunotherapy
- At a cost...

![SEER Incidence and US Death Rates](chart.png)

SEER Incidence and US Death Rates
Melanoma of the Skin, Both Sexes
Joinpoint Analyses for Whites and Blacks from 1975-2013
and for Asian/Pacific Islanders, American Indian/Alaska Natives and Hispanics from 1982-2013

- Incidence
- Mortality

- White
- Black
- API
- AIAN
- Hispanic

Source: Incidence data for whites and blacks are from the SEER 9 registries (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indian/Alaska Natives and Hispanics are from the SEER 13 Areas (SEER 9 Areas, San Jose-Morgan Hill, Los Angeles, Alaska Native Registry and Rural Georgia). Mortality data are from US Mortality File, National Center for Health Statistics, CDC.

- Rates are age-adjusted to the 2000 US Std Population (10 age groups: 0-49 years P01-921)
- API = American Indian/Pacific Islander
- AIAN = American Indian/Alaska Native
- Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NA and exclude cases from the Alaska Native Registry. Mortality data for Hispanics exclude cases from Nebraska and Oklahoma.
UV-Induced DNA Mutations

Yagura T et al., Sensors 2011, 11, 4277-4294; doi:10.3390/s110404277

Melanomagenesis

- **Benign Nevus**: Basal layer of epidermis 1:5 ratio melanocyte:basal keratinocyte
- **Dysplastic Nevus**: Proliferation in clusters and separation from keratinocytes
- **Dysplasia**: Cytological and architectural atypia and partial anchorage independent growth (non-tumorigenic)
- **Radial Growth**: Increasing cytological and architectural atypia with radial growth without basement membrane invasion (limited tumorigenic)
- **Vertical Growth**: Infinite growth, neovascularization, basement membrane degradation, survival in dermis (tumorigenic)
- **Metastatic melanoma**: Cell motility, vascular invasion, survival in non-cutaneous tissue
Hereditary Melanoma

- 5-12% of patients have a family history of melanoma
- Hereditary melanomas are often
  - Early onset melanoma
  - Multiple primary melanomas
  - Across several generations on one side of the family
- Familial atypical multiple mole melanoma (FAMMM) syndrome
  - Melanoma in >1 first or second degree relative
  - High (often >50) total body nevi, some atypical
  - “...architectural disorder with asymmetry, subepidermal fibroplasia, and lentiginous melanocytic hyperplasia with spindle or epithelioid melanocytes gathering in nests of variable size and fusing with adjacent rete ridges to form bridges; variable dermal lymphocyte infiltration and the “shouldering” phenomenon wherein intraepidermal melanocytes extend alone or in groups beyond the main dermal component may also be present...”
CDKN2A (9p21)

- Cyclin-dependent kinase inhibitor 2A (aka MTS1, INK4A, CDKN2) is mutated in 25-40% of FAMMM kindreds
- Encodes two tumor suppressor proteins
  - P16INK4A (p16) using exon 1α
  - P14ARF using exon 1β
- Mutations occur most commonly in Exon 1α or 2
- Risk of melanoma
  - 14% by age 50 alternative years
  - 28% by age 80 years
- FAMMM-PC: Melanomas and pancreatic cancer
- Incidence of pancreatic cancer
  - In FAMMM without CDKN2A mutation: 6%
  - In FAMMM with CDKN2A mutation: 28%
- Penetrance for pancreatic cancers in CDKN2A mutant positive FAMMM kindreds ranges broadly from 11 to 60% depending on the specific mutation
Rarer Causes of Hereditary Melanoma

- **CDK4 (12q4)**
  - Exceedingly rare.
  - They occur at exon 2 codon 24 which is directly involved in binding of p16INK4A.
  - This mutation abrogates the ability of p16INK4A to inhibit CDK4-mediated Rb phosphorylation.

- **BRAF (7q34): Q608H mutant**

- **Rb1 (13q14.2): 7% of secondary neoplasms in survivors of retinoblastomas are melanomas**

- **CHEK2 (22q12.1)**
  - Possible association of brain tumor, sarcoma and melanoma

- **MC1R (melanocortin 1 receptor): variants are associated with fair skin, red hair and freckles. However, MC1R variants without this phenotype also predispose melanoma.**

- **MC1R (melanocortin 1 receptor): variants are associated with fair skin, red hair and freckles. However, MC1R variants without this phenotype also predispose melanoma.**

- **Xeroderma pigmentosum (XPA-G and XPV)**
  - *XPB (Werner Syndrome) – ERCC3 gene; high risk for acral or mucosal melanoma*
  - *XPC mutants have 5-20% incidence of melanoma, mostly lentigo maligna (which is otherwise seen in elderly with sun-damaged skin)*

- **BRCA2: RR 2.58**

- **BAP1: Uveal and cutaneous melanoma**

- **MITF**

- **Shelterin complex**

- **PTEN**
Somatic Mutations

- **Drivers**
  - **B-Raf**
    - 50% of melanomas
    - V600E (90%), V600E (5%)
  - **N-Ras**
    - 20% of melanomas
    - advanced melanomas
  - **cKit**
    - 11% of all melanomas have cKit mutations
    - Almost exclusively in nail beds, palms, soles, mucosa (10% of melanomas)
    - 10% of these have cKit mutations
    - Exons 11 and 13

- **Passengers**
  - **PI3K (AKT3, PTEN (20-30%))**
  - **P16/Rb**
    - p16 in 40% of advanced tumors
    - Cyclin-D 20%
    - CDK4 in 5%
  - **FAS**
  - **EGF**
# CNA in Cutaneous vs. Ocular Melanoma

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**Cutaneous**

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**Ocular**
Mutations in Cutaneous vs. Ocular Melanoma

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Prevention

- **Sunscreen**
  - *1621 patient 10 year trial, Australia*
  - Regular sunscreen vs. observation
  - *Overall melanoma incidence was decreased but (HR 0.5: 0.24-1.02, p 0.051)*
  - *Invasive melanoma incidence is decreased by regular sunscreen use (HR 0.27 : 0.08-0.97)*
  - *Higher SPF may lead to behavioral increase in sun exposure*

- **Tanning Beds**
  - *Meta-analysis 27 studies*
  - *Overall RR 1.20 (95% CI, 1.08 -1.34).*
  - *Before age 35 RR 1.87 (95% CI, 1.41 to 2.48)*
  - *1.8% increase in risk of melanoma for each additional session of sunbed use per year.*

- **Statins**
  - *27 cases in 39,426 subjects*
  - *59/19,872 with statin*
  - *68/19544 without*
  - *No significant effect on risk overall*

Benefit of Screening by PCP

- Prospective Cohort, France, self-assessed high-risk
- Contacted by mail to consult their GP for skin examination
- Efficacy: patient participation and the # melanomas detected
- 3745 invited
- 61% underwent a skin exam
- Best participation was people over 60 and men over 50 compared with all other subgroups (72.4% vs 49.6%, p<0.001; and 66% vs 52.4%, p<0.001, respectively).
- Six melanomas (160/100 000)
- Potential benefit of
  - Targeted screening strategy in primary care
  - Annual reminder

Clinical Presentation

- **Anatomic Sites**
  - Skin (Head & neck, Trunk, Extremities, Palms/Soles/Nails)
  - Eye (retinal, uveal)
  - Mucous membranes (aerodigestive tract, genitourinary tract)

- **Signs**
  - 30% from previously normal skin
  - New mole
  - Change in color, shape or elevation or old mole.

- **Symptoms**
  - Itching
  - Bleeding
  - Pain (rare)
  - Symptoms related to organ site of primary or metastatic involvement

Melanoma Stage at Diagnosis

- 115,913 adults
- Whites 98.6%
- Men 56.6%
- Age 40-64: 45%; >65: 43%
- Sites
  - Head/face: 28%
  - Trunk: 29.8%
  - Upper limbs: 25%
  - Lower limb: 17%
- In-situ or localized: 92.5%
- Regional or distant: 7.5%

Physical Signs of Cutaneous Melanoma

- Seborreic keratosis
- Atypical nevus
- Blue nevus
- Spitz nevus
- Borderline lesions
  - Atypical melanocytic proliferation (AMP)
  - Superficial melanocytic tumor of uncertain significance (SAMPUS)
  - Melanocytic tumor of uncertain malignant potential (MELTUMP)
  - Atypical Spitz tumor
  - Atypical cellular blue nevus

http://www.plasticsurgery.co.za/skin-cancer/
Diagnostic Modalities

- Visual inspection and dermoscopy
- Reflectance confocal microscopy uses a low-power 830 nm laser to create a 30x three-dimensional image
- Multispectral imaging (Melafind, SIAscope, MoleMate)
  - One computer-based optical imaging device (MelaFind®, 2011)
  - For use by dermatologist, not intended for lesions with a diagnosis of melanoma or likely melanoma.
  - Accessible, pigmented lesions with a diameter 2-22 mm without scar or fibrosis and intact skin, >1 cm from the eye, and not on acral, palmar, plantar, mucosal, or subungual areas.
- Smartphone applications
- **BIOPSY**
  - Depends on clinical suspicion
  - No shave, incision
  - Only excision
  - Imaging Assistance
    - Ultrasound
    - Dermoscopy
    - Epiluminescence microscopy
    - Laser / digital microscopy
    - Light-scattering
Histological Characteristics of Prognostic Significance

- Thickness
- Depth of invasion
- Histological subtype
- Growth phase
- Ulceration
- Mitotic rate
- Angiolympathic invasion
- Desmoplasia
- Neurotropism
- Margins

- IHC
  - S100
  - MART-1 (MelanA)
  - GP100 (HMB45 or NKI-betab)
  - MITF
  - Tyrosinase (T311)

- FISH
- CGH
- Cytogenetics
Confirmation of Histological Diagnosis

- Immunohistochemistry
  - S100
  - MART-1 (MelanA)
  - GP100 (HMB45 or NKI-betab)
  - MITF
  - Tyrosinase (T311)
Clinical Subtypes of Melanoma

- **Superficial Spreading (SSM):** Majority (~70%), they generally arise in a pre-existing nevus and slowly evolve over 1-5 years. They have deeply pigmented spots or ‘lacy’ areas with patches of amelanotic ‘regression’ and notched or indented periphery in the background of a brown junctional nevus.

- **Nodular (NM):** Second most common (15-30%), They often start in uninvolved truncal skin. They are more common in men. They are darker, and more uniformly colored and raised than SSM and may resemble a blood blister. 5% are amelanotic. Their growth is more aggressive, often 6-12 months.

- **Acral Lentiginous (AL):** They occur on palms, soles and nailbeds. They occur in Asians and dark skinned patients, without history of sun exposure. The majority are on the sole of the foot of older people, often developing over 1-3 years into 2-3 cm irregular bordered lesions with elevation, ulceration or fungation.

- **Desmoplastic Melanoma (DM):** These are rare. They may be without or with histological presence of other more common melanoma histologies. They are usually amelanotic, often misdiagnosed as scar tissue, dermatofibroma, or other spindle cell tumor. They are typically HMB-45 negative.

- **Lentigo Maligna (LM):** These are infrequent (4-10%). They occur almost always on face, head or hands. A typical presentation is on the face of a Caucasian woman, present for many years. They have significant color variation, convoluted edges and areas of regression. They have a distinct biology and have low likelihood of metastasis.
Workup for Stage II-IV

- **Laboratory Testing**
  - Serum LDH
  - CMP
  - CBC
  - ESR
  - TSH
  - RF, ANA, ESR
  - Vitamin D

- **Radiological Staging**
  - MRI Brain with contrast
  - Whole Body PET-CT
  - Record all sites of metastases
  - Measure several target lesions

- **Genetic Testing for Germline Mutations**: Depending on suspicion
TNM Staging

- **T**: Thickness, ulceration, mitoses
  - **T1**: \(< 1.00 \text{ mm}\)
  - **T2**: 1.01 to 2.00 mm
  - **T3**: 2.01-4; 2.01 – 4.00 mm
  - **T4**: > 4 mm
  - **A vs. B**: ulceration; mitosis in T1

- **N**:
  - **N1**: 1 node (a: micrometastasis; b: macrometastasis)
  - **N2**: 2-3 (a: micrometastasis; b: macrometastasis; c: in-transit, satellites)
  - **N3**: 4+ (or matted nodes, **or** in-transit met/satellite with >1 metastatic nodes)

- **M**:
  - **M1a**: Met to distant nodes, skin or subcutaneous tissue
  - **M1b**: Lung
  - **M1c**: All other visceral metastases

LDH elevated

Surgical Therapy

Prior to the 1930s, radiotherapy was used routinely for locally advanced melanoma. Surgical therapy significantly improved outcomes and these continued to improve with time. The value of surgical resection of lymph node metastases was recognized...


Margins of Resection

- Randomized, open-label multicenter UK trial
- Breslow > 2 mm on trunk or limbs (excluding palms or soles)
- 1992-2001, randomized 1:1 to 1 (n=453) or 3 cm (n=447) margins
- Median follow-up 8.8 years
- 194 deaths in 1 cm group vs. 165 in the 3 cm group ([HR] 1.24 [95% CI 1.01-1.53]; p=0.041).
- Surgical complications 8 vs. 15% in 1 vs. 3 cm

1 cm excision margin is inadequate for cutaneous melanoma with Breslow thickness greater than 2 mm on the trunk and limbs.

Nodal Management

The real test of prophylactic node dissection for melanoma will come when an accurate comparison is made between prophylactic node dissection in patients with the nodes microscopically positive at the time of surgery, and patients who undergo local excision initially and node dissection later when the nodes become clinically enlarged. This comparison will also determine whether any chance for a cure is lost while waiting for nodes containing microscopic metastases to become palpable. Until this comparison can be made, the value of prophylactic node dissection for melanoma remains unproved.8

Necessity for Lymph Node Dissection

- Elective Lymph Node Dissection for Stage II
  - *No advantage in 4 RCTs*
    - Veronesi, 1977, 1982
    - Sim et al., 1987, 1986
    - Balch et al., 1996
    - Cascinelli et al., 1998

- Rationale for SNL for > 1.2 mm Thickness (Stage IIA-IIIA)
  - *The first draining node for metastasis*
  - Iodosulfan-Blue / $^{99}$Tc-99
  - *Thickness vs. SNL-positivity*
    - < 1.5 mm: 4%
    - >1.5 – 4 mm: 22%
    - > 4 mm: 27%
Long Term Follow-up of the MSLT-I Study
SLN Guidelines - ASCO

- Meta-analysis of 73 studies from 1990-2011
- SLN biopsy is an acceptable method for lymph node staging of most patients with newly diagnosed melanoma.

Recommendations:
- 1-4mm: SLN biopsy is recommended for patients with intermediate-thickness melanomas (1-4mm Breslow thickness) of any anatomic site;
- SLN biopsy in this population provides accurate staging.
- >4mm may be recommended for staging purposes and to facilitate regional disease control.
- < 1 mm: insufficient evidence to support routine SLN biopsy although it may be considered in selected cases with high risk features when staging benefits outweigh risks of the procedure.
- Completion lymph node dissection (CLND) is recommended for all patients with a positive SLN biopsy and achieves good regional disease control.
- CLND following a positive SLN biopsy: MSLT II
  - Wong et al., J. Clin Oncol. 2012; 30(23):2912-2918
Surgery for Resectable Stage IIIB

- Biopsy primary / node
- Resect primary with wide-excision
- Radical lymphadenectomy
- Consider SNL for other draining node sites
- Aim:
  - *Negative Margins for primary / resectable satellites*
  - *Nodal clearance with negative margins*
Adjuvant Therapy After Resection of Stage III

- Radiation: TROG 02.01 (N Z 217)
  - Showed that among stage III melanoma patients with nodal metastasis, adjuvant radiation therapy (RT) to lymph node (LN) basin after nodal dissection reduces LN field relapse rate,
  - But without an overall survival (OS) benefit.

- Systemic
  - Interferon-α2B
    - Improved DFS (OS in ¼ studies)
    - Questionable benefit of first month high-dose treatment
  - PEG-IFN (Sylatron)
    - Improved DFS, not OS (except possibly in ulcerated N1)
  - Ipilimumab
EORTC 18952: Adjuvant Interferon in Resected IIB and III melanoma

- n=1388
- IFN 10 MU, 5x/wk x 4 wk, then either
  - 10 MU 3x/wk x 13 mo
  - 5 MU 3x/wk x 25 mo vs. observation
- 11 yr f/u
- RFS, HR of 0.94 vs. 0.84 for 12 vs. 24 mo (p = 0.06)
  - In ulceration group,
    - RFS 0.82 (p = 0.16) versus 0.61 (p = 0.0008)
    - OS 0.80 (p = 0.13) versus 0.59 (p = 0.0007).
  - In stage IIB/III-N1, RFS 0.85 versus 0.62
- Superiority of 25-mo IFN schedule
- Ulceration is overriding predictive factor for IFN-sensitivity.

Interferon Adjuvant Therapy: Sunbelt Trial

- ECOG 1694 indicated that high dose interferon adjuvant therapy conferred overall survival advantage.
- Previous meta-analyses showed that IFN improves OS 3% (NNT 29).
- The sunbelt trial tested HDI adjuvant in 3619 patients with 1 pos SLN.
- It found no survival benefit for adjuvant HDI:
  - 5-year OS in Obs = 74.8% and in HDI = 71.4%.
  - 5-year DFS in Obs = 67.1% and in HDI = 70.9% in the HDI group.
- Ulceration predicted improved DFS (not OS) in patients treated with HDI.
- Molecular staging by RT-PCR had no prognostic significance.

Treatment of Patients with Unresectable Stage III or IV Melanoma

- Median Survival: historically, ~11 mo (wide range depending on site of disease and LDH)

- Systemic Therapy
  - *Chemotherapy*
  - *Immunotherapy*
    - Cytokines
    - Cellular therapy
    - Vaccines
    - Immune checkpoint
  - *Targeted Small Molecules*
  - *Combinations*

- Local therapies
  - Resection of oligometastatic disease
  - Radiation of oligometastatic disease
  - Physical/chemical ablation
  - Organ perfusion
  - Intraliesional oncolytic virus
  - Many others
### Chemotherapy of Melanoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Ref</th>
<th>Phase</th>
<th>Treatment</th>
<th>n</th>
<th>Stage</th>
<th>PS</th>
<th>Prior OR Tx (CR+PR)</th>
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<th>PR</th>
<th>SD</th>
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<th>OS (mo)</th>
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<td>Sosman et al.</td>
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<td>50%</td>
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<td>Docetaxel / Vinorelbine / GM-CSF</td>
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<td>4%</td>
<td>18%</td>
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<td>4%</td>
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<td>O’Day et al.</td>
<td>III</td>
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<td>325</td>
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<td>N</td>
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<td>22%</td>
<td>49%</td>
<td>5%</td>
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<td>Flaherty et al.</td>
<td>III</td>
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<td>1%</td>
<td>17%</td>
<td>39%</td>
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<td>0%</td>
<td>17%</td>
<td>60%</td>
<td>23%</td>
<td>70%</td>
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<td>Flaherty et al.</td>
<td>III</td>
<td>Paclitaxel / Carbo / Sorafenib</td>
<td>393</td>
<td>IIIB-IV</td>
<td>0-1</td>
<td>Y</td>
<td>20%</td>
<td>1%</td>
<td>20%</td>
<td>41%</td>
<td>29%</td>
<td>84%</td>
<td>5  11</td>
</tr>
<tr>
<td>2013</td>
<td>Ott et al.</td>
<td>I</td>
<td>Paclitaxel / Temozolomide / Oblimersen</td>
<td>32</td>
<td>IV</td>
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<td>6%</td>
<td>34%</td>
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<td>Paclitaxel (nano) / Carbo</td>
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<td>6%</td>
<td>44%</td>
<td>50%</td>
<td>25%</td>
<td>3  10</td>
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</table>
Chemotherapy: Dacarbazine vs. nab-paclitaxel

- Chemotherapy-naïve patients with stage IV melanoma
- Nab-paclitaxel 150 mg/m² d 1, 8, 15 q 4 wk vs DTIC 1000 mg/m² q 3 wk
- 529 patients: nab-paclitaxel (n = 264) or dacarbazine (n = 265).
  - ECOG PS 0 (71%)
  - M1c stage disease (65%)
- Median PFS 4.8 vs. 2.5 mo. favoring nab-paclitaxel HR 0.792 (95.1% CI 0.631-0.992; P = 0.044).
- The median OS was 12.6 vs. 10.5 mo. favoring nab-paclitaxel (HR 0.897, 95.1% CI 0.738-1.089; P = 0.271).
- ORR 15% versus 11% (P = 0.239)
- Grade ≥3 toxicity
  - Nab-paclitaxel: neuropathy 25% and neutropenia 20%
  - Dacarbazine neutropenia 10%

Immunotherapy of Melanoma: Rationale

- The skin is an immune organ
- Melanocytes exist in close contact with dendritic cells and lymphocytes
- Escape from immune surveillance plays a key role in melanomagenesis
- Melanoma expresses multiple antigens recognized by T-cells
- Melanoma cells are immunogenic
- Melanomas are often heavily infiltrated by immunocytes
- Melanomas are very susceptible to interventions targeted at cellular immunity

### T-cell activating antigens in melanoma

<table>
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<tr>
<th>Cancer/Testis</th>
<th>Melanocytic</th>
<th>Mutated</th>
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<td>MAGE-1</td>
<td>gp100</td>
<td>b-catenin</td>
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<td>MAGE-3</td>
<td>MART1 (Melan-A)</td>
<td>CKD-4</td>
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<td>BAGE</td>
<td>TRP1 (gp75)</td>
<td>MUM-1</td>
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<td>GAGE</td>
<td>TRP2</td>
<td>Tyrosinase</td>
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<tr>
<td>GnT-V</td>
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<tr>
<td>p15</td>
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<tr>
<td>NY-ESO-1</td>
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</tbody>
</table>
Immunotherapy of Melanoma
Humoral Immunity

■ Vaccines
  - Cells/tissue
  - Cell extracts
  - Recombinant proteins
  - Peptides

■ Though none are approved for therapy, novel approaches to identify particularly immunogenic peptides that affects specific T-cell subsets may yet yield vaccines that have significant activity alone and especially in combinations. Stay tuned...
Immunotherapy of Melanoma: Generalized Immunostimulation by Cytokines

- Interferon-alpha: shown effective in an adjuvant setting
- HD-IL2: The first curative immunotherapy
  - *Landmark NCI 374 pt study*
    - OR 16%
    - CR 6%
    - PR 10%
- GM-CSF: limited effectiveness alone, but could enhance combinations
Immunotherapy of Melanoma
Cellular Immunity: TIL + HD-IL2

- Dendritic cell – several approaches in development, some promising
- T-Cell - Tumor infiltrating lymphocytes (TIL)
  - Very Effective
    - ORR 56%, 22% CR
    - Of those in CR, 93% alive at 5 years
    - 3 yr Survival 36%
    - 5 yr survival 29%
  - Drawbacks
    - Selected population
    - Myeloablation
    - Toxic
    - Logistical issues

Abnormal peptides (antigens) on cancer cell and antigen-presenting cells activate T-cell receptors (TCR) on T-lymphocytes.

This initiates intracellular signals that cause T-cell proliferation, cytokine secretion.

Consequent expansion of immunocytes kills cancer cells.

Some of the same processes cause autoimmune disease in which normal cells are also killed.
Immunotherapy of Melanoma

Cellular Immunity: Checkpoint

- TCR transmits down-stream signals through PI3K and AKT
- TCR is co-simulated by the activation of an associated receptor, CD28.
- CD80 and CD86, membrane proteins expressed on antigen-presenting cells, are the stimulatory ligands for the CD28 receptor that associates with TCR in the T-cell membrane.
- Activation of CD28 upon binding to CD80 or CD86 markedly amplifies signaling down-stream of TCR.
- CTLA4 binds and sequesters CD80 and CD86, thus prevents CD28 and TCR activation.
- Activation of CTLA4 results in intracellular activation of protein phosphatases SHP and PTP2A that inactivate CD28 as well as AKT.
- CTLA4 activation inhibits T-helper cells and enhances immunosuppressive T\(^\text{reg}\) cells.
Immunotherapy of Melanoma

Cellular Immunity: Checkpoint

- Binding of PD1 to its ligands PD-L1 (CD274) and PD-L2 (CD273) activate SHP, inhibiting AKT and other kinase pathways.
- PD1 expression is induced after T-cell activation.
- PD1 activation serves to inhibit inflammatory/immune responses in peripheral tissues, such as cancers.
- PD1 is expressed on tumor-infiltrating lymphocytes.
- The PD-L1 is expressed on cancer cells.
Single Agent Ipilimumab in Pre-treated Stage IIIB & IV Melanoma

- N= 676 HLA-A*0201-positive pre-treated, stage III or IV melanoma,
- Randomized 3:1:1
  - ipilimumab 3 mg/kg/3 wk x 4 plus gp100 (403 patients): Median OS 10 mo
  - ipilimumab 3 mg/kg/3 wk x 4 (137): Median OS 10.1 mo
  - gp100 alone (136): Median OS 6.4 mo
- Grade 3 or 4 irAE: 10 to 15%; 14 deaths related to the study drugs

Ipilimumab + Dacarbazine in Stage IIIB & IV Melanoma

- Unresectable stage III/IV, untreated
- 87% ECOG 0, 13% ECOG 1
- 85% normal LDH
- 93% M1
- Randomized 1:1
  - DTIC 850 mg/m² (n = 250) q 3 wk x 8 + Ipi 10 mg/kg q 3 wk x 4
  - DTIC 850 mg/m² (n = 250) q 3 wk x 8 + Placebo
- Maintenance ipilimumab or placebo every 12 weeks beginning at week 24.
- 5 yr survival
  - 18.2% (95% CI, 13.6% to 23.4%) I+D
  - 8.8% (95% CI, 5.7% to 12.8%) I+P (P = .002)
- A survival plateau began at approximately 3 years.
- During maintenance, Skin irAE predominated in survivors

Pembrolizumab after Ipilimumab Failure in Stage IIIB & IV Melanoma

- Randomized Phase II Multicenter
- PD within 24 wk after 2 or more doses of ipi and if Braf-mutation positive, progressed on Braf-I and/or ipi
- Randomly assigned (1:1:1)
  - pembro 2 mg/kg (n=280) q 3 wk
  - Pembro 10 mg/kg (n=181) q 3 wk
  - Investigator-choice chemo (179)
- PFS, compared with chemo
  - 34% at 6 mo, Pembro 2 mg/kg (HR 0.57, 95% CI 0.45-0.73; p<0.0001)
  - 38% at 6 mo, Pembro 10 mg/kg (0.50, 0.39-0.64; p<0.0001)
  - 16% at 6 mo chemo.
- Treatment-related grade 3-4 adverse events
  - 11% in the pembro 2 mg/kg
  - 14% in the pembro 10 mg/kg
  - 26% in the chemo
- AE grade 3-4
  - Pembro: fatigue, edema, myalgia (1-5%)
  - Pembro (10 mg/kg): hypopituitarism, colitis, diarrhea, decreased appetite, hyponatremia, and pneumonitis (1% each)
  - Chemo: anemia (5%), fatigue (5%), neutropenia (4%), and leucopenia (4%).

Pembrolizumab in Treatment-naïve Stage III B & IV Melanoma

- Open label study, 655 patients, 581 with measurable disease
- Treated with pembrolizumab
  - 10 mg/kg/d q 2 wk
  - 10 mg/kg/d q 3 wk
  - 2 mg/kg/d
- Efficacy
  - ORR 33%
  - 12 Mo PFS rate 35%
  - Median OD 23 mo
- Grade 3 or 4 treatment-related AEs occurred in 14%.
- 2 vs 3 wk, 2mg/kg vs 10 mg/kg were similar.
- Possible higher response at 10mg/kg q 2 wk, NS.

Nivolumab after Ipilimumab Failure in Stage IIIB & IV Melanoma

- Multicenter randomised, open label phase III
- Stage IV, progressed after ipilimumab, or ipilimumab+B-Raf inhibitor
- Randomized 2:1 nivolumab 3 mg/kg q 2 weeks vs. dacarbazine 1000 mg/m(2) q 3 weeks vs. carbo-taxol (AUC6 – 175/m2) until progression or toxicity
- Nivo (n=272) v chemo (n=133)
- ORR
  - Nivo: 31.7% [95% CI 23.5-40.8] (n=120)
  - Chemo: 10.6% [3.5-23.1] (n=47)
- AE (3-4):
  - Nivolumab: lipase (3), LFT (2), Anemia (2), Fatigue (2)
  - Chemo: Neutropenia (14) Thrombocytopenia (6) Anemia (5)
- SAE: Nivo (12) v Chemo (9); no deaths.

Weber et al., Lancet Oncol. 2015 Apr;16(4):375-84.
## Ipilimumab vs Ipilimumab + GM-CSF: Results

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>GM-CSF + Ipilimumab (n = 123)</th>
<th>Ipilimumab (n = 122)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>19 (15.5)</td>
<td>18 (14.8)</td>
<td>–</td>
<td>.880</td>
</tr>
<tr>
<td>▪ CR</td>
<td>2 (1.6)</td>
<td>0 (0)</td>
<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>▪ PR</td>
<td>17 (13.8)</td>
<td>18 (14.8)</td>
<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>26 (21.1)</td>
<td>23 (18.9)</td>
<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>3.1</td>
<td>3.1</td>
<td>0.92</td>
<td>.569</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>17.5</td>
<td>12.7</td>
<td>0.64</td>
<td>.014</td>
</tr>
<tr>
<td>1-yr OS, %</td>
<td>68.9</td>
<td>52.9</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Nivolumab + Ipilimumab in Treatment Naïve Melanoma

- 945 previously untreated patients with unresectable stage III or IV melanoma randomized (1:1:1) to Ipi vs. Nivo vs. Nivo + Ipi

- Median PFS
  - Nivo+Ipi: **11.5** mo [8.9 to 16.7]
  - Ipi: **2.9** mo [2.8 to 3.4]; HR: 0.42 [99.5% CI, 0.31 to 0.57; P<0.001]
  - Nivo: **6.9** mo [4.3 to 9.5] with nivolumab HR(v Ipi) 0.57 [99.5% CI, 0.43 to 0.76; P<0.001].
  - PD-L1 *Pos*: Nivo+Ipi or Nivo: PFS 14.0 mo (*EQUAL*)
  - PD-L1 *Neg*: Nivo+Ipi v Nivo: PFS 11.2 v 5.3.

- AE 3 or 4: Nivo-16.3% ; Ipi 27.3% Nivo-Ipi 55.0%; 27.3%

Ipilimumab for Adjuvant Therapy in Stage III Melanoma

- Double-blind, phase 3 trial, 951 patients, 19 countries, Stage III cutaneous melanoma
  - excluding lymph node metastasis ≤1 mm or in-transit metastasis, completely excised with adequate surgical margins
  - No prior systemic therapy for melanoma
  - 2008-2011

- Randomized 1:1 to Placebo vs. 10 mg/kg ipilimumab q 3 wk x 4, then q 3 mo x 3 y
  - Median follow-up of 2.74 years (IQR 2.28-3.22),
  - 528 recurrence-free survival events (234 in the ipilimumab group vs 294 in the placebo group).

- Grade 3-4 immune-related adverse events
  - GI (16%), hepatic (11%) and endocrine (8%).
  - 52% discontinued due to AE, 39% during first 4 doses
  - 5 deaths due to irAE (1%), 3 colitis, 1 myocarditis, 1 Guillain-Barré syndrome.

## Ipilimumab for Adjuvant Therapy in Stage III Melanoma

### Study Details


### Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ipilimumab</th>
<th>Placebo</th>
<th>Hazard Ratio (95% or 99% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>162/475</td>
<td>214/476</td>
<td>0.72 (0.59–0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III A</td>
<td>24/98</td>
<td>22/88</td>
<td>0.98 (0.46–2.09)</td>
<td>0.07</td>
</tr>
<tr>
<td>III B</td>
<td>68/213</td>
<td>85/207</td>
<td>0.75 (0.50–1.14)</td>
<td></td>
</tr>
<tr>
<td>III C with 1–3 positive lymph nodes</td>
<td>34/69</td>
<td>45/83</td>
<td>1.00 (0.56–1.80)</td>
<td></td>
</tr>
<tr>
<td>III C with ≥4 positive lymph nodes</td>
<td>36/95</td>
<td>62/98</td>
<td>0.48 (0.28–0.81)</td>
<td></td>
</tr>
<tr>
<td>No. of positive lymph nodes</td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>1</td>
<td>65/217</td>
<td>82/220</td>
<td>0.79 (0.52–1.21)</td>
<td></td>
</tr>
<tr>
<td>2 or 3</td>
<td>61/163</td>
<td>70/158</td>
<td>0.83 (0.53–1.30)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>36/95</td>
<td>62/98</td>
<td>0.48 (0.28–0.81)</td>
<td></td>
</tr>
<tr>
<td>Type of positive lymph node</td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Microscopic</td>
<td>54/210</td>
<td>76/193</td>
<td>0.61 (0.39–0.96)</td>
<td></td>
</tr>
<tr>
<td>Macroscopic</td>
<td>108/265</td>
<td>138/283</td>
<td>0.80 (0.58–1.11)</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Yes</td>
<td>73/197</td>
<td>110/203</td>
<td>0.64 (0.44–0.94)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79/257</td>
<td>88/244</td>
<td>0.80 (0.54–1.20)</td>
<td></td>
</tr>
<tr>
<td>Lymph-node and ulceration status</td>
<td></td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Microscopic and ulceration</td>
<td>28/99</td>
<td>43/88</td>
<td>0.54 (0.29–0.99)</td>
<td></td>
</tr>
<tr>
<td>Macroscopic and ulceration</td>
<td>45/98</td>
<td>67/115</td>
<td>0.76 (0.46–1.23)</td>
<td></td>
</tr>
<tr>
<td>Microscopic and no ulceration</td>
<td>21/104</td>
<td>29/97</td>
<td>0.62 (0.30–1.29)</td>
<td></td>
</tr>
<tr>
<td>Macroscopic and no ulceration</td>
<td>58/153</td>
<td>59/147</td>
<td>0.90 (0.56–1.45)</td>
<td></td>
</tr>
</tbody>
</table>

---

**Graph:**

[Graph showing the hazard ratio and P values for different subgroups.]

---

**Reference:**

Safety/Efficacy Anti-PD1/AntiPDL1

- Meta-analysis, 51 trials, 6,800 patients
- Overall adverse
  - Melanoma 16% (95% CI: 6%-28%)
  - NSCLC 11% (95% CI: 8%-14%)
  - RCC 20% (95% CI: 11%-32%)
- Responses: PD-L1 pos vs. neg
  - 41.4% versus 26.5%
  - RR = 1.92 (95% CI: 1.53-2.41, P < 0.001).
- Better than other immunotherapies
  - Response rate  
    \[ (RR = 2.89, \text{95\% CI: } 2.46-3.40, \text{P < 0.001}) \]
  - Death risk  
    \[ (HR= 0.53; \text{95\% CI: } 0.48-0.57; \text{P < 0.001}) \]
  - AE  
    \[ (RR = 0.49, \text{95\% CI: } 0.30-0.80, \text{P = 0.004}) \]

The efficacy and safety of anti-PD-1/PD-L1 antibodies for treatment of advanced or refractory cancers: a meta-analysis.
Zhang T1,2, Xie J3, Arai S2,4, Wang L5, Shi X6, Shi N7, Ma F2, Chen S2, Huang L1, Yang L1, Ma W5, Zhang B8, Han W9, Xia J10, Chen H8, Zhang Y1,5,11,12.
Autoimmune Adverse Effects of Immunotherapy

- Colitis (Ipi)
- Hepatitis
- Thyroiditis
- Hypophysitis
- Pneumonitis (Niv/Pem)
- Nephritis
- Iritis/Uveitis
- Vasculitis
- Meningitis
- Pancreatitis
- Pericarditis
- Polymyositis
- Polymyalgia rheumatica
- Psoriasis
- Temporal Arteritis
- Vasculitis
- ANY IMMUNE TOXICITY (15%)
Vitiligo

- Meta-analysis
- 5,737 patients 1995-2013
  - Cumulative incidence 3.4%
  - PFS benefit – HR 0.51 [0.32-0.82]
  - OS benefit – HR 0.25 [0.10-0.61]

Teulings et al., JCO.2014.57.4756
Management of Autoimmune Toxicities

- Monitoring (Liver, kidney, lung thyroid, adrenal, testis, pituitary)
- Clinical recognition (caution in considering invasive testing)
- Immunosuppression
  - Early treatment
  - Gradual tapering
  - Combinations
- Delay therapy
- Discontinue of therapy
- Long-term monitoring for delayed adverse effects
# Systemic Immunosuppressives

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cort/Hold</td>
<td>Cort/DC</td>
<td>Cort/DC</td>
<td>Cort/DC</td>
</tr>
<tr>
<td>Prednisone 20 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone 1 mg/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infilximab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Selection of second line immunosuppressives

- Vigilance
  - Signs of first-line failure
  - Adverse effects of corticosteroids
  - Evidence of opportunistic infections

- According to Known Uses
  - Uveitis: CyA
  - Nephritis: cyclophosphamide
  - Hepatitis:
    - Calcineurin inhibitor (unless cholestasis present)
    - Consider MMF as first-line in those with contraindications to steroids or renal insufficiency
  - Dermatitis
    - Tacrolimus (topical)
  - Colitis:
    - Calcineurin inhibitor
    - Infliximab
    - Adjuncts: sulfasalazine, budesonide
Second Line
Immunosuppressives: Which Ones and When

- According to side effects
  - GI side-effects of MM make it less appropriate for hepatitis, pancreatitis or colitis
  - Tacrolimus may not be tolerated by those with Hypophysitis
  - Avoid azathioprine in those with cytopenias, pancreatitis or hepatitis
  - Avoid infliximab in those with lymphoproliferative disorders

- According to pharmacokinetics
  - CyA, hepatic clearance, not appropriate for severe hepatitis with elevated bilirubin
  - MM, renal clearance, not appropriate for low creatinine clearance
  - Avoid azathioprine in those with dysfunctional GI absorption

- Potency and onset of action
  - Azathioprine is more appropriate for maintenance
  - Calcineurin inhibitors are most potent oral agents
**Infliximab**

- Anti-TNFα antibody

**Mechanism of Action**
  - Neutralizes extracellular TNFα
  - Inhibits numerous inflammatory and autoimmunity mechanisms through inhibition of cytokines

**Indications**
  - Inflammatory bowel disease
  - More active in Crohn’s disease than U.C.
  - Rate or remission of 66% (30% placebo) in patients with acute steroid-refractory U.C. at 8 weeks (little effect seen earlier).

**Pharmacology**
  - 5 mg/kg i.v. q 2 week till remission
  - 10 mg/kg is not more effective
  - High frequency of anti-infliximab alloantibodies decrease efficacy

**Toxicity**
  - Class toxicity of increase in malignancy
  - Particularly lymphoma
  - May cause interstitial pneumonitis

---

Intralesional Therapy: TVEC

- Talimogene laherparepvec (T-VEC): herpes simplex virus type 1-derived oncolytic immunotherapy
- Selectively replicates within tumors and produces GM-CSF
- Randomized comparison of T-VEC vs. GM-CSF in stage IIIB to IV melanoma
- 436 patients
- Durable response rate:
  - T-VEC: 16.3% (95% CI, 12.1-20.5)
  - GM-CSF: 2.1% (95% CI, 0-4.5)
- Overall response rate:
  - T-VEC: 26.4% (95% CI 21.4-31.5)
  - GM-CSF: 5.7% (95% CI, 1.9-9.5)
- Median OS was
  - TVEC: 23.3 months (95% CI, 19.5-29.6 mo) with T-VEC and
  - GMCSF: 18.9 months (95% CI, 16.0 to 23.7 months)
  - HR 0.79 (95% CI, 0.62-1.00; p = 0.051)
- AE: Generally mild cytokine release syndrome

GM-CSF /Polypeptide Vaccine Adjuvant Therapy

- Randomized, placebo-controlled multi-institution
- 815 patients completely resected high risk stage III or IV
- Grouped by human leukocyte antigen (HLA) -A2 status.
  - HLA-A2 positive were randomized to GM-CSF, PV, both, or placebo;
  - HLA-A2 negative were randomized to GM-CSF or placebo
- Treatment lasted for 1 year or until recurrence
- There were no significant improvements in OS or RFS

Targeting Signaling Downstream of Ras
Targeting Signaling Downstream of Ras

- **BRAF**
  - mutated at V600 in ~45-50% of melanoma
  - V600E > V600K > V600D
  - *BRAF* inhibitors
    - Vemurafenib
    - Dabrafenib

- **Targeting MEK to Overcome Braf Resistance**
  - Alternative activation of the MEK-ERK Pathway
  - MEK1 over-expression, mutation or alternative pathway activation
  - N-Ras mutations
  - Additional mutations in B-Raf
  - PDGFRb, IGFR1, PI3K activation
  - MEK Inhibitors
    - Trametinib
BRAFi + MEKi in Treatment-naive BRAFV600 Mutation Positive Patient

- Analysis of Phase I and II study for OS in BRAF inhibitor-naive
  - *Dabrafenib 150 mg twice daily*
  - *Trametinib 2 mg daily*
- PFS: 44, 22 and 18% at 1, 2 and 3 y
- OS:
  - 72, 60 and 47%, at 1, 2 and 3 y
  - OS at 3 years was 63% in patients CR
- At 3 years was 62% survival in patients nl LDH
- Median > 2 y
- PFS > 3 years
- Prolonged survival associated with mets in fewer than 3 organ sites

Quality of Life Vemurafenib vs. Dabrafenib/trametinib in First Line

- Open-label, randomized phase III, 704 patients BRAF V600
- Randomized 1:1
  - dabrafenib 150 mg bid + trametinib 2 mg q d (n=352)
  - vemurafenib 960 mg q.d (n=352)
- Combination was significantly better with respect to
  - EORTC QLQ-C30 global health
  - EORTC QLQ-C30 pain
  - Disease progression,

Stereotactic Body RT for Oligometastatic Melanoma

- n=56 lesions in 32 patients, median f/u 1.9 y
- Sites
  - 15 musculoskeletal
  - 14 liver
  - 14 lung
  - 11 abdominal
  - 2 extra abdominal lymph nodes.
- Median single-fraction equivalent dose 43 Gy
- CR was achieved in 49 lesions (86%)
- 43 lesions maintained CR at median of 22 months.
Adjuvant Radiotherapy for H&N Muscosal Melanoma

- Retrospective, 39 patients (2000-2015)
- 27 patients underwent adjuvant radiation
- Baseline characteristics were similar in those without or with adjuvant RT
- Local Control at 2 y higher with the adjuvant RT (66.8% vs. 11.8%, P = 0.003)
- Overall survival at 2 y was unaffected (52.8% vs. 42.3%, P = 0.537)
Brain Radiation

- Concurrent Immunotherapy
- Brain necrosis with BRAF/MEKi
- Increase in size of lesions
THANK YOU