Diagnosis and Treatment of Melanocytic Lesions

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Dallas, Texas

Relevant Conflicts

• Consultant, Castle Biosciences, Myriad Genetics

Diagnosis and Treatment Today

• Most diagnoses made by routine histology
• New techniques available to assist when diagnostic difficulty
  – Special stains
  – Genetics
• Surgical recommendations changing; becoming less aggressive
• New medical therapy transforming melanoma treatment
• Genetic tests to assist in prognosis now available
Case History

- Middle aged woman with indurated plaque of left chest for months
- Gradually increasing in size
- No other relevant medical problems
S100: interpreted as positive; Diagnosis: Leiomyosarcoma.

CD34

SMA: interpreted as positive; Diagnosis: Leiomyosarcoma.
Revised Diagnosis: Desmoplastic Melanoma

- Immunoperoxidase staining not 100% reliable
- Sox-10, MITF: stain for melanocytes; stains nucleus; confirmatory stain for melanoma
- Useful in desmoplastic MM; HMB-45 and Mart-1 routinely negative
- Soft tissue neoplasms: may have bi- and multiphasic histologic morphology with aberrant staining patterns
- Biopsy not always same as excision
- “When dermatology and soft tissue neoplasia intersect, the outcome is often disastrous!” Beware!

Molecular Techniques for Diagnosis

- Histologic diagnosis of most melanomas straightforward
- In some cases, diagnosis may be elusive especially if biopsy not representative
- Techniques developed in efforts to make more definitive diagnoses
Fluorescence In Situ Hybridization

- Most cancers aneuploid
- Nucleic acid probes directed to specific genetic regions
  - 6p25, 6q23, 11q13, Cep 6 and 9p21
- Number of cells with over or under expression evaluated; percentages reported
- Caveats: may be focal; most data on obvious MM's; must be interpreted
- Only use in context of other features. NOT pathognomonic of malignancy!!
Genes on separate chromosomes

FISH in Atypical Spitzoid Lesions
- Gains in 6p25 or 11q13
- Homozygous 9p21 deletion clinically aggressive behavior
- Criteria for Atypical Spitzoid lesion not well defined, however
  - One person’s “atypical Spitz” another’s “garden variety” Spitz or melanoma

Comparative Genomic Hybridization

- Complete genome assessed
- Green tumor chromosomes hybridized with normal red chromosomes
- Green + Red = No color
  - Deletions: red
  - Additions: green
- Ratios ≤1 > computer analysis
- More objective than FISH

Array Based CGH

- Specific targeted DNA fragments
- Changes mapped directly onto genome
- Specific, sensitive, fast
- High throughput
- Identifies chromosome rearrangements that may be missed with karyotyping and FISH

Each dot is specific probe
Genetic “Profiling” of Melanocytic Lesions

- Specific gene mutations identified in melanoma and nevi
- Mitogen-Activated Protein (MAP) kinase pathway commonly affected: \textit{BRAF}, \textit{NRAS} and \textit{KIT} genes
- \textit{BRAF} gene mutated in 60% to 70% of malignant melanomas
- Others:
  - \textit{NRAS} (Rat sarcoma) [15%–20%]
  - c-\textit{kit} (26%–39%); MM on sun-damaged skin, acral and mucosal melanomas
  - CDK4 (<5%)
  - GNAQ: uveal melanomas

\textbf{BRAF Gene (Rapidly Accelerated Fibrosarcoma)}

- Three \textit{RAF} proteins: ARAF, BRAF, and CRAF
- B-raf: kinase; transports phosphate groups; activates or inactivates proteins
- Mutation: glutamic acid $\rightarrow$ valine at position 600, $^{\text{V600E}}$
  - 90% of all \textit{BRAF} mutations
- Increases kinase activity 10 fold; oncogene
- Detected by immunoperoxidase or PCR with Sanger or pyrosequencing
- New drugs inhibit BRAF and downstream proteins in MAP kinase pathway
Clinico-Pathologic-Genetic Spitz Nevus Variants

• Recent description of nevi with specific genes, clinical and histologic features
  – BAP-1 (3p21 deleted) epithelioid nevus
  – “Atypical Spitz tumor” with 11p gain +/-HRAS mutation
  – Spitz nevi with ALK fusion, other fusions (BRAF, RTK)

BAP-1 Mutations, Epithelioid Cell Nevi and Melanoma

• Mutations in BAP-1 (3p21 deletions) in uveal melanoma
  – BRCA associated protein-1; associated with histones; regulates homeobox expression
• Germline mutations in BAP-1 associated with familial melanoma
• Clones of large epithelioid cells; some Spitz and blue nevus-like melanoma
• + BRAF mutations
• No epidermal hyperplasia, no Kamino bodies, no clefting; large sheets of dermal epithelioid cells
Sclerosing Spitz Nevus with 11p Gain +/- HRAS Mutation

- Large bulky lesions
- Deep dermal sclerosis
- Desmoplasia
- Nests become single cells near base

Spitz Nevi with ALK (Anaplastic Lymphoma Kinase) Fusions
What are Gene Fusions?
• Hybrid genes formed from two separate genes
• Arise from translocation, interstitial deletion, or chromosomal inversion
• Often result in oncogenes or activation of proto-oncogenes

Spitz Nevus with ALK Fusion
• No HRAS mutations or loss of BAP1
• Two ALK fusions: TPM3-ALK and DCTN1-ALK
  – Anaplastic lymphoma kinase; when adjacent to protogenes, leads to activation and carcinogenesis
• Nevi are Polypoid, Amelanotic, Plexiform
New Genetic Tests on Horizon to Assist in Diagnosis

- Molecular test for difficult-to-diagnose melanoma cases
- 23 genes analyzed
- Additive molecular information distinct from FISH
- NOT substitute for clinicopathologic correlation
While New Techniques are Exciting, Beware of Over-relying on Them!

Test: FISH (Melanoma Panel)

Fluorescence in situ hybridization (FISH) of DNA probes for RREB1 (8q24.3), chromosome 6 centromere, MYB (8q23.3) and CCND1 (11q13.3) (Vysis, Ltd) was performed simultaneously on interphase nuclei from this specimen. The DNA probe for the RREB1 gene showed greater than 2 signals in 15 (60%) of 25 nuclei examined, which is above the normal limits of 10% for this probe. DNA probe for RREB1 and the centrometric region of chromosome 6 showed 14 (44%) of nuclei with a greater than 2:2 ratio for RREB1:6 centromere, which is above the normal limits of 45% for this ratio. A DNA probe for CCND1 showed greater than 2 signals in 10 (40%) of 25 nuclei examined, which is above the normal limit of 10% for this probe. These findings are consistent with an abnormal result and have been associated with a diagnosis of melanoma. The results of the remaining DNA probes in the melanoma panel are within normal limits.

COMMENTS:
A. There is a difficult case, and was discussed at our Dermatopathology Conference. Although a 2015 dermal component was present, the degree of melanocytic atypia was questionable. The patient was recommended for the Royal Free Hospital, London, for excisional biopsy. The patient was rechecked in 2016, and the case has been reviewed.

REFERENCES:
Slide Submitted for Consultation.
My diagnosis: SPITZ NEVUS, NOT MELANOMA

Beware of Over-reliance on New Techniques!
“It seems that currently there is a trend to overestimate the contribution of molecular investigations. In the same way that T-cell clonality is not a synonym for malignant disease or cutaneous lymphoma…, a positive FISH analysis or genetic instability in CGH within a melanocytic lesion is not equivalent to a malignant tumor.”
– Dummer R, Kerl K et al, Arch Dermatol, 2011

Tool vs Crutch
• Tool: something used by expert to enhance skills and produce something of greater value
• Crutch: something used by someone suffering a disability to survive or perform a function that others can perform well

*Beware of using new technology as a crutch rather than a tool!!!
What Is Nature Teaching Us About Spitzoid Lesions?

Case Report

- 10 yo AAF; expanding “mole”
- Present for years; increasing in size in past 6 months
- 2 months earlier, lesion bled
- Itching
- 1cm x 1.5cm
Diagnosis and Plan

• Malignant Melanoma With Spitzoid Features, 9.0mm In Thickness, Clark's Level IV
  – Case submitted to Myriad genetics for interest
  – Results: Likely Benign, -10.2
• Evaluated by Plastics and Surgical Oncology
• Plan:
  – Wide Local Excision
  – Sentinel lymph node biopsy
  – Full Thickness Skin Graft (donor site lower abdominal skin)

Node Status

• 5 out of 8 nodes were positive
• In spite of genetic studies, lesion still considered melanoma
• Submitted to Castle Biosciences; Class 2 result
• Test not validated for childhood melanoma, however
• Child without additional disease 3 years later
What if sentinel LN biopsy is positive in an “Atypical Spitzoid” Lesion?

Sentinel LN Metastasis is not Predictive of Poor Outcome in Problematic Spitzoid Tumors (Hung et al, Human Pathol 2013)
- 41 patients with atypical Spitzoid lesions
- Sentinel lymph node + in 26%
- 1 developed in transit mets; 0 developed distant disease over 57 months
- No deaths
- Age: 5-63 years

Sentinel Node Biopsy in Atypical Spitzoid Lesions (Ludgate, et al, 2014)
- 57 patients; 27 positive SLN
- All 27 alive and disease free for 42.8 months
- Positive SLN status: not a harbinger of poor prognosis in patients with atypical Spitzoid lesions
Should We Discard Diagnosis of Spitzoid Melanoma Especially in Children?

- “Brands” patient with malignant diagnosis; biologically benign but histologically aggressive
- Risk of unnecessary surgery
- Perhaps “Histologically Atypical Spitz Nevus” with comment that lesion may spread locally but rarely past regional node
- Not everything that spreads to lymph nodes is necessarily “malignant”
- Should we continue to perform sentinel LN biopsies in these cases?
- Perhaps Sophie Spitz was right: these lesions are “benign” juvenile melanomas

Genetic Testing to Assist in Prognosis of Melanoma

- FDA approved test developed by Castle Biosciences, Friendswood, Texas
- Formalin-fixed, paraffin-embedded tissue
- 31 genes from primary tumor; Gene Expression Profile (GEP)
- Validation algorithm; Class 1 (low) vs Class 2 (high) risk of developing metastatic disease within 5 years
- Potential “reflex” test for melanoma to suggest prognosis


GEP test workflow

RNA Isolation

cDNA generation and amplification (14X)

Microfluidics PCR gene card
28 discriminant gene targets and 3 control genes

Analysis of GEP with a proprietary algorithm to determine class and metastatic risk

Class 1
low metastatic risk

Class 2
high metastatic risk
Cellular functions represented in GEP signature

<table>
<thead>
<tr>
<th>Cellular function</th>
<th>Genes involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migration/chemotaxis/metastasis</td>
<td>CXCL14, SPP1, CLCA2, S100A9, S100A8</td>
</tr>
<tr>
<td>Cell surface receptors</td>
<td>TACSTD2, CLCA2, ROBO1</td>
</tr>
<tr>
<td>Chemokine/secreted molecules</td>
<td>CXCL14, MCP, SPP1</td>
</tr>
<tr>
<td>Differentiation/proliferation</td>
<td>CRABP2, SPRR3B, HG1</td>
</tr>
<tr>
<td>Gap junction/cellular adhesion</td>
<td>GJA1, DSC1, PPI</td>
</tr>
<tr>
<td>Extracellular functions</td>
<td>MGP, SPP1, CTS5</td>
</tr>
<tr>
<td>Structural proteins</td>
<td>KRT10B, KRT14</td>
</tr>
<tr>
<td>Lymphocytic invasion</td>
<td>LTA-4H</td>
</tr>
<tr>
<td>Transcription factor</td>
<td>TRIM29</td>
</tr>
<tr>
<td>Angiogenesis regulator</td>
<td>CXCL14</td>
</tr>
</tbody>
</table>

Where it Started: Uveal Melanoma

- Variable prognosis, no option of SLNB; 1st site of metastasis: liver
- 15 gene expression profile assay
- Significant differences in survival (Kaplan-Meir curve)
- Adopted by 90% of ocular oncologists
- Similar KM curve for cutaneous melanoma

Kaplan Meir Survival Curves
Currently, the only prognostic techniques for melanoma are AJCC criteria and Sentinel Lymph Node status

How Well Does AJCC Prediction Tool Work?

- 11 patients died graded low risk by AJCC tool
  - All graded Class 2 by Gene Expression Profile (GEP)
- GEP: 10X more accurate
- GEP: independent prognostic variable in melanoma prognosis (Gerami, JAAD, May 2015)
GEP vs Sentinel LN Biopsy

- Sentinel LN biopsy, when positive, generally indicates worse prognosis
- Staging, not therapeutic, procedure
- When negative, patients may still develop metastases
  - 520 patients with negative SLNB
  - 83 (16.0%) with metastases at 23 months


SLN Status Identifies ≈30% of Patients Who Die From MM

Gene Expression Test Identifies 80% of Patients Who Die From Melanoma
Sentinel LN Biopsy

Gene Expression Profile

Is Sentinel Lymphadenectomy Cost Effective?

- "The cost of performing SLNB is great and only a small number will have disease identified that will alter treatment. These data call into question the appropriateness of SLNB for thin melanomas." Agnese, et al, Surgery, 2003.
- "We should continue attempts to identify molecular or proteomic markers associated with sufficient risk of regional metastases among patients with melanomas < 0.75 mm to identify those who should be offered the procedure. Until that time, recommendations for sentinel lymph node biopsy should not be extended to all T1b patients." Sabel, ASCO Post, 2013.
Is completion lymphadenectomy really needed in melanoma at all?

Melanoma surgery is trending the same as breast cancer surgery
If we could predict which patients with melanoma were more likely to metastasize, we could monitor and treat them differently.

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Patient #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70</td>
</tr>
<tr>
<td>Lesion site</td>
<td>Axial</td>
</tr>
<tr>
<td>Tumor thickness</td>
<td>0.13</td>
</tr>
<tr>
<td>Ulceration</td>
<td>No</td>
</tr>
<tr>
<td>Stage</td>
<td>IA</td>
</tr>
<tr>
<td>SLN status</td>
<td>Not assessed</td>
</tr>
<tr>
<td>AJCC 5-year survival estimate</td>
<td>95.7%</td>
</tr>
</tbody>
</table>

**DecisionDx-Melanoma Test Result, 5-year estimate**

- Class 1 result: 3% chance of metastasis
- Class 2 result: 69% chance of metastasis

Clinical outcome: Metastasis free at 6 years post-diagnosis (lung, then brain)
### Importance of Identifying who is at High Risk of Metastasis

- Stage I and II patients: conservative treatment and monitoring after SLN and wide excision
- Would other options be available if we could identify those more likely to develop metastases?
  - Adjunct chemotherapy with newer agents (Trial currently ongoing)
- Should we be offering this test on any patient with invasive melanoma?
- Will this become standard of care?
- What are medicolegal ramifications of not ordering test?
  - Could test be used for malpractice defense?
New Therapy for Widespread Disease

- BRAF inhibitors: diminish activating oncogenes
  - Interrupts the B-Raf/MEK step in activation pathway − B-Raf V600E mutation

- MEK inhibitors: diminish activating oncogenes
  - Inhibits mitogen-activated protein kinase enzymes MEK1 and/or MEK2

- PD-1 blockers: immune response “checkpoint” inhibition
  - Programmed death 1 (PD-1) receptor is down-regulator of T-cell mechanisms that limit immune responses against cancer
  - Removes inhibition of immune response; leads to anti-tumor activity

- CTLA-4 antibodies: immune response “checkpoint” inhibition
  - CTLA-4 inhibits T-cell responses

Conclusions

- Molecular testing of ever increasing importance in management of pigmented lesions
- Valuable for diagnosis, treatment and prognosis
- Surgery becoming less aggressive
- Medical therapy becoming more effective
- New GEP test could be first “reflex” test for cutaneous melanoma
Current Medical Management of Skin Malignancy:
The Dermatologist’s Perspective

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Clinical Adjunct Professor of Dermatology and Dermatopathology
Baylor University Medical Center
Texas Dermatology Associates, PA
April 2, 2016

Objectives

- Understand the evolving epidemiology of skin cancer
- Accurately identify patients at “high-risk” for skin malignancy
- Delineate newly identified familial melanoma cohorts
- Identify current risk reduction strategies for skin malignancy
- Discuss current medical therapies for managing early stage skin malignancy

Evolving Epidemiology

- Melanoma
- Non-melanoma skin cancer
Evolving Epidemiology

• Melanoma
  – In 2015 an estimated 74,000 U.S. men and women developed melanoma and 9,940 died from the disease
  – SEER data describe increasing incidence of 3% per year from 1992-2004
    • Including increased incidence of advanced tumor stage


Evolving Epidemiology

• Melanoma
  – Mortality rates stable over same time period
  EXCEPT for nonblack minorities, nodular MM and acral lentiginous MM

Shahk et al. J Natl Cancer Inst. 2015

Evolving Epidemiology

• Melanoma
  – Incidence in Rochester, MN, increasing in the following populations from 1970-2009:
    • Young women aged 18-39: 8-fold increase
    • Young men aged 18-39: 4-fold increase
    • Women aged 40-60: 24-fold increase
    • Men aged 40-60: 4.5-fold increase
  – Disease specific mortality decreased over time
  – BUT nearly 25% of deaths were from early stage disease

Evolving Epidemiology
• Melanoma
  – NOT increasing in children aged 0-17 in Rochester, MN


Evolving Epidemiology
• Study of melanoma prone families demonstrates dysplastic nevi are linked to risk of melanoma
• Risk of melanoma increases as number of dysplastic nevi increases


Evolving Epidemiology
• Population based study describes incidence of dysplastic nevi at 76 per 100,000 person-years
• Failed to detect an increased risk of subsequent NMSC or melanoma in this population, regardless of degree of atypia
• Not able to account for nevus counts

### Evolving Epidemiology-NMSC

- Study of Caucasian health professionals over time: Incidence of BCC is increasing in the US

![Graph showing the increase in incidence of BCC](image)


### Evolving Epidemiology-NSMC

- Factors associated with increased BCC risk
  - Family history of melanoma
  - History of painful or blistering sunburn
  - Blond or red hair color
  - Increased number of moles on upper extremities

- In this population BCC screening would be of highest value in men aged 50–60 years and women aged 55–65 years


### What patients are at increased risk of skin malignancy?

- Medication use
- Underlying disease
- Familial cancer syndromes
What medications may increase risk of NSMC?

- Voriconazole
  - In lung transplant recipients
    - Any exposure increased risk of SCC 2.6x
    - Dose dependent \( \rightarrow \) each 2 month interval increased risk 5x
  - In allogeneic hematopoietic stem cell recipients
    - Dose dependent increase
    - Confounder: immunosuppressive regimens


Does anti-TNF therapy in patients with psoriasis increase risk of NMSC?

- ESPRIT post marketing surveillance of patients with psoriasis treated with adalimumab
- 0.6 NMSC per 100 person-years in patients treated with adalimumab
- e.g. Follow 1000 people for 1 year, find 6 NMSC
- Limitations: No comparison to background population risk

Menter et al. JAAD. 2015.

Does anti-TNF therapy in patients with psoriasis increase risk of melanoma?

- Standardized incidence ratios:
  - 4.37 in psoriasis (>400% increase)
- Standardized mortality rate NOT increased
- Limitations:
  - Other treatments may increase risk

Does anti-TNF therapy in patients with autoimmune disease increase risk of NMSC?

- Standardized incidence ratios:
  - 1.39 in rheumatoid arthritis (~40% increase)
  - 1.76 in psoriasis (~75% increase)
  - 2.29 in crohn's (>100% increase)
- Standardized mortality rate NOT increased
- Limitations: NMSC incidence based on 1970's incidence rates


What special groups are at increased risk of skin malignancy?

- Disease:
  - Psoriasis
  - Rheumatoid arthritis
  - Inflammatory bowel disease
  - Chronic lymphocytic leukemia (CLL)
  - Non-Hodgkins lymphoma
- Treatment:
  - Solid organ transplant
  - Hematopoietic stem cell transplant
  - Methotrexate

From: The Risk of Cancer in Patients With Psoriasis: A Population-Based Cohort Study in the Health Improvement Network


Adjusted Hazard Ratio (aHR) for Cancer by Study Group. This Figure provides information on the adjusted hazard ratio (aHR) (95% CI) for any cancer except nonmelanoma skin cancer (NMSC) as well as individual cancers of interest in the overall, mild, and moderate-to-severe psoriasis groups. *Adjusted for age, sex. **Adjusted for age and sex and smoking status. ***Adjusted for age and sex, BMI, drinking and smoking status. "Adjusted for age, sex, and including clinical/"A indicates for age only. " Indicates only women. "Includes only women. "Indicates women 5 years or older. "CTCL indicates cutaneous T-cell lymphoma."
Cutaneous T cell Lymphoma and Psoriasis

• Is the increased risk real?
• Study evaluated primary care provider diagnostic codes

What about patients with other autoimmune disease?

• Retrospective cohort of patients with RA or IBD and history of NMSC
• 58 new NMSC per 1000 person-years
  - e.g. Follow 1000 people for 1 years, find 58 NMSC
• Methotrexate (MTX) exposure > 1yr gave hazard ratio of 1.6
  - e.g. MTX >1 yr increased risk of NMSC by 60% in this population
• Men and those with history of actinic keratoses had highest risk of NMSC


What about patients with lymphoma?

• Increased risk of NMSC, melanoma and rare skin malignancies in patients with CLL and NHL
  - CLL:
    • NMSC increased 8x
    • Melanoma increased 2-4x and 2x increased odds of death
    • Merkel cell carcinoma increased 8x

What about patients with lymphoma?

- Increased risk of NMSC, melanoma and rare skin malignancies in patients with CLL and NHL
  - NHL:
    - NMSC increased 8x
    - Melanoma increased 1.6x
    - Kaposi’s sarcoma increased 17x


What about solid organ transplant?

- Risk tends to parallel degree of immunosuppression
- Some immunosuppressive medications likely impute a higher risk
- Liver<Kidney<Lung<Heart
  - 80x risk of invasive SCC in renal transplant ~5 yrs out
  - Also increased risk of BCC, melanoma, Kaposi, merkel cell


What about solid organ transplant?

- Worse overall survival rates for subsequently diagnosed melanoma
- Worse melanoma related survival for advanced disease (Breslow level > 1.5mm)
- 20% of heart transplant patients at one center had a new diagnosis of skin cancer at 5 years post-transplant
- Up to 70% of heart transplant patients have had skin cancer by 20 years post-transplant

Hematopoietic Stem Cell Transplant (HSCT)

• Autologous transplant does not increase risk
• Allogeneic transplant increases risk (hazard ratio)
  – BCC 3x
  – SCC 18x
  – MM 5x
• Whole body irradiation necessary for increased BCC risk


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Hematopoietic Stem Cell Transplant (HSCT)

• Risk compared to renal transplant
  – BCC risk similar
  – SCC risk higher in renal transplant
  – MM risk 3x higher in HSCT

Hematopoietic Stem Cell Transplant (HSCT)

- Autologous transplant does not increase risk
- Allogeneic transplant increases risk (hazard ratio)
  - BCC 3x
  - SCC 18x
  - MM 5x
- Whole body irradiation necessary for increased BCC risk

USPTF Skin Cancer Screening 2016 Draft Recommendations

- Current evidence is insufficient to assess the balance of benefits and harms of visual skin cancer screening in adults.

USPTF Skin Cancer Screening Recommendations

- This recommendation applies to asymptomatic adults who do not have a history of premalignant or malignant skin lesions
Now what?!?

• Risk stratify
• Identify and screen high risk individuals

What is high risk?

• Disease:
  – Psoriasis
• Treatment:
  – TNF inhibitors
  – MTX
• Phenotype:
  – >5 Dysplastic nevi

What is very high risk?

• Disease:
  – Chronic lymphocytic leukemia (CLL)
  – Non-Hodgkins lymphoma
• Treatment:
  – Solid organ transplant
  – Hematopoietic stem cell transplant
  – Voriconazole
• Phenotype:
  – >100 nevi
  – >5 Dysplastic nevi and personal or family history of melanoma
• History:
  – Personal history of melanoma
Familial Melanoma Syndromes

• ~10% of patients with melanoma report a positive family history
• Familial melanoma due to identifiable germline mutation is uncommon
• Clues:
  – Early onset melanoma
  – Multiple primary cutaneous melanomas
  – Family history of melanoma in multiple family members on one side of family


BAP1 Tumor Syndrome

• BRCA1-associated protein 1
  – Intracellular deubiquitinase
  – Involved in cell division, signal transduction, gene expression, DNA repair, protein trafficking
  – Germline mutations
• Characteristic associated tumors include:
  – Uveal melanoma (aggressive)
  – Cutaneous melanoma
  – Mesothelioma
  – Renal Cell Carcinoma


BAP1 Tumor Syndrome

• Cutaneous findings:
  – Small, banal appearing flesh-colored to red-brown dome shaped to pedunculated papules
    • Histologically demonstrate findings similar to an atypical Spitz tumor
    • Loss of BAP1 staining
    • UNCLEAR if pre-malignant

Melanocytic BAP1-associated atypical intradermal tumor (MBAIT)

- No mitotic figures
- Prominent nuclear pseudoinclusions
- Large hyperchromatic nuclei and abundant cytoplasm
- No lamino bodies


BAP1 Tumor Syndrome

- Other tumors reported to occur at increased frequency
  - Basal cell carcinoma
  - Breast cancer
  - Ovarian tumors
  - Pancreatic cancer
  - Meningioma
  - Colon cancer
  - Hepatic cholangiocarcinoma


BAP1 Tumor Syndrome

- What to remember:
  - Uveal melanoma and cutaneous melanoma
  - “atypical Spitz tumors” (MBAIT’s)
  - Mesothelioma
  - Renal cell carcinoma
Familial Melanoma Syndromes

• Cowden’s Syndrome
  – PTEN mutations
  – 6% estimated lifetime risk of melanoma
  – Follicular thyroid cancer, breast carcinoma, endometrial carcinoma
• Other emerging syndromes:
  – TERT
  – MITF
  – POT1

Emerging Risk Reduction Techniques

• Nicotinamide
  – Phase 3, randomized, double blind, placebo controlled trial
  – Patients in Australia with 2 or more NSMC in past 5 years
  – After 12 months a 30% reduction in new SCC
  – After 12 months a 13% reduction in AKs
  – Returned to normal rates 6 months after discontinuation

Emerging Risk Reduction Techniques

• Painless PDT?
  – Daylight ALA PDT is well tolerated (pain score 2-3/10)
  – BF-200 ALA (an aminolevulinic acid nanoemulsion)
    • Non-inferiority when used for daylight PDT compared head-to-head with MAL daylight PDT
    • Pending FDA review

Chen et al. NEJM 2015.
Keratoacanthoma

Resurrecting a forgotten treatment

• May harbor HRAS mutations
  – Particularly in patients treated with BRAF inhibitor
• Wnt is a signaling protein involved in cellular differentiation
  – Wnt signaling activated during proliferation
  – Retinoic acid reverses Wnt activation
  – Molecular basis for retinoid treatment of KA
• p53 mutations in ~40%

Su F et al. NEJM 2012
Zito et al. Nat Commun 2014
Inflammatory response after injection
1 week after 3rd injection...
Bleomycin dose conversion: 1mg = 2 units

Kirby JS, JAAD 2009

Thank you!

johnrgriffin@gmail.com
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• Discuss current medical therapies for managing early stage skin malignancy

References

Advances in Molecularly-Based Targeted Therapy of Advanced Malignant Melanoma

Kevin B. Kim, MD
Clinical Director of Melanoma Clinical Research Program
California Pacific Medical Center
San Francisco, CA, USA

Dacarbazine Interleukin-2
• Response rate ~6-15%
• Durable response only in 5-10% of patients;
• Significant toxicity, such as capillary leak syndrome (IL-2)
• A median survival ~6-9 months

Treatment options were poor prior to Year 2011

Development of New Effective Therapies post-2011

* V600 mutation only
** previously treated with ipilimumab
Development of New Effective Therapies post-2011

Molecular targeted therapy

*V600 mutation only
**previously treated with ipilimumab

Melanoma has the highest mutation rate (Whole Exome Sequencing)

Melanoma: Whole Exome Sequencing

Melanoma has the highest mutation rate

Whole Exome Sequencing

MS Lawrence et al. Nature 2013

Melanoma: Whole Exome Sequencing

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Development of New Effective Therapies post-2011

Molecular targeted therapy

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Whole Exome Sequencing

MS Lawrence et al. Nature 2013

Melanoma: Whole Exome Sequencing

Melanoma: Whole Exome Sequencing

MS Lawrence et al. Nature 2013
BRAF is the most frequent mutation in melanoma

Significant reduction in FDG-metabolic activity after 2 weeks of BRAF inhibitor treatment

Vemurafenib: FDA Approval for BRAF V600-Mutant Melanoma
Despite the high response rate and OS benefit, the responses are not durable in most patients.

- **BRAF inhibitors**: median PFS ~6-7 months

Next approach: Combination of BRAFi and MEKi
Phase III study of Dabrafenib/Trametinib vs. Dabrafenib in BRAF V600 melanoma (COMBI-d)

- N=423 randomized
- Primary Endpoint = Investigator-assessed PFS
- Secondary Endpoints = OS, ORR, Duration of Response, Safety
- BRAF V600E/K
- Unresectable stage IIIC/IV
- Treatment naïve

Stratification:
- BRAF mut V600E/K
- LDH (>ULN v ≤ULN)

Dabrafenib + Trametinib
Dabrafenib + placebo
n=212
n=211

Modified from Long et al. JCO 2016

COMBI-d study showed Dabrafenib + Trametinib is superior to Dabrafenib alone

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Dabra/Trame</th>
<th>Dabra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med OS</td>
<td>11.0 mo</td>
<td>8.8 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.71 (95%CI: 0.55 - 0.92)</td>
<td>P = 0.0107</td>
</tr>
<tr>
<td>3-yr survival rate</td>
<td>51%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Modified from Long et al. Lancet 2015

Progression-free Survival

<table>
<thead>
<tr>
<th></th>
<th>Dabra/Trame</th>
<th>Dabra</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.67 (95%CI: 0.53 - 0.84)</td>
<td>P = 0.004</td>
</tr>
</tbody>
</table>

Modified from Long et al. Lancet 2015
COMBI-d Study: Response Rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR % (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib + Trametinib (n=211)</td>
<td>69 (62-75)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Dabrafenib + Placebo (n=212)</td>
<td>53 (46-60)</td>
<td></td>
</tr>
</tbody>
</table>

Complete response rate

- Dabrafenib + Trametinib (n=211): 16
- Dabrafenib + Placebo (n=212): 13

Stable disease, n (%)

- Dabrafenib + Trametinib (n=211): 24
- Dabrafenib + Placebo (n=212): 31

Duration of response

- Median: 12.9 vs. 18.6 months

**Phase III study of Dabrafenib/Trametinib vs. Vemurafenib in BRAF V600 melanoma (COMBI-v)**

- N=704 randomized
- Primary Endpoint = OS
- Secondary Endpoints = PFS, ORR, Duration of Response, Safety

**COMBI-v study showed**

Dabrafenib + Trametinib is superior to Vemurafenib alone

- Overall Survival
  - Med OS: 25.6 mo vs. 18.0 mo
  - HR: 0.66 (95% CI: 0.52 - 0.81)
  - P = 0.006
  - 2-yr survival rate: 51% vs. 38%
COMBI-v study showed Dabrafenib + Trametinib is superior to Vemurafenib alone.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Dabrafenib + Trametinib</th>
<th>Vemurafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med PFS</td>
<td>12.6 mo</td>
<td>7.3 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.61 (95% CI: 0.51-0.73)</td>
<td></td>
</tr>
</tbody>
</table>

Progression-free Survival

![Graph showing progression-free survival](image)

**COMBI-v Study: Response Rates**

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib + Trametinib (n=351)</th>
<th>Vemurafenib (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR % (95% CI)</td>
<td>66 (60-71)</td>
<td>53 (48-58)</td>
</tr>
<tr>
<td>p</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>CR rate, %</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>SD rate, %</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Duration of response, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>13.8 (11.2-18.1)</td>
<td>8.5 (7.4-8.7)</td>
</tr>
</tbody>
</table>

Modified from Robert et al. @JCO/ESMO Congress 2015
**Phase III COMBI-v study: Dabrafenib/Trametinib vs Vemurafenib**

Robert et al. NEJM 2014

- **Primary Endpoint:** Investigator-assessed PFS
- **Secondary Endpoints:** OS, ORR, Duration of Response, Safety
- **BRAF V600E/K Unresectable stage IIIC/IV Treatment naïve**
- **Stratification:** Staging, Geographic region

### Treatment Groups

- **Vemurafenib + Cobimetinib**
- **Vemurafenib + placebo**

Modified from Larkin et al. NEJM 2014

* Cobimetinib at 60 mg QD, 21 days on, 7 days off

---

**Phase III study of Vemurafenib/Cobimetinib vs Vemurafenib in BRAF V600 melanoma (Co-BRIM)**

- **N=495 randomized**
  - MAP V600E/K
  - Irresectable stage IIIIC/IV
  - Treatment naïve
- **Staging:** Investigator-assigned
- **Geographic region**

### Comparison Groups

- **Vemurafenib + Cobimetinib**
- **Vemurafenib + placebo**

n=248

n=247

Modified from Larkin et al. NEJM 2014

* Genentech-Roche Sponsored Study

---

**Co-BRIM study showed Vemurafenib + Cobimetinib is superior to Vemurafenib alone**

- **Progression-Free Survival**
  - **Med FFS:** 12.25 mo vs 7.2 mo
  - **HR:** 0.58 (95%CI: 0.46 - 0.72)
  - **P:** <0.001

Modified from Larkin et al. ASCO 2015

---
Co-BRIM study showed Vemurafenib + Cobimetinib is superior to Vemurafenib alone

Overall Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>PBO + Vem</th>
<th>Cobi + Vem</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>248</td>
<td>247</td>
</tr>
<tr>
<td>6</td>
<td>230</td>
<td>230</td>
</tr>
<tr>
<td>12</td>
<td>153</td>
<td>152</td>
</tr>
<tr>
<td>18</td>
<td>107</td>
<td>106</td>
</tr>
<tr>
<td>24</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Median follow-up: 18.5 months

OS events, n (%) 141 (56.9) 114 (46.2)
OS, median (95% CI), mo 17.4 (15.0-19.8) 22.3 (20.3-NE)
HR (95% CI) 0.70 (0.55-0.90)
P = 0.005

Modified from Atkinson et al. SMR Congress 2015

**coBRIM: Benefit of the Combination Was Seen in All Subgroups Assessed**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PBO + Vem</th>
<th>Cobi + Vem</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>248</td>
<td>247</td>
<td>22.3 vs 17.4</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>164</td>
<td>184</td>
<td>23.8 vs 19.8</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>80</td>
<td>58</td>
<td>21.8 vs 17.5</td>
</tr>
<tr>
<td>LDH level normal</td>
<td>138</td>
<td>130</td>
<td>NE vs 23.3</td>
</tr>
<tr>
<td>LDH ≥ ULN</td>
<td>104</td>
<td>112</td>
<td>14.8 vs 11.2</td>
</tr>
<tr>
<td>V600E</td>
<td>174</td>
<td>170</td>
<td>21.9 vs 17.5</td>
</tr>
<tr>
<td>V600K</td>
<td>32</td>
<td>24</td>
<td>24.1 vs 16.7</td>
</tr>
</tbody>
</table>

Modified from Atkinson et al. SMR Congress 2015

**NE**: not evaluable; **ULN**: upper limit of normal

**Phase III Co-BRIM study: Vemurafenib/Cobimetinib vs Vemuraf**

Modified from Larkin et al. NEJM 2014
Co-BRIM Study: Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Cobimetinib + Vemurafenib (n=247)</th>
<th>Vemurafenib + Placebo (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR % (95% CI)</td>
<td>69.6 (63.5-75.3)</td>
<td>50.0 (43.6-56.4)</td>
</tr>
<tr>
<td>CR rate, %</td>
<td>15.8</td>
<td>10.5</td>
</tr>
<tr>
<td>SD rate, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of response, months</td>
<td>Median (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.98 (11.1-16.6)</td>
<td>9.23 (7.5-12.8)</td>
</tr>
</tbody>
</table>

Larkin, Ascierto et al. NEJM 2014

coBRIM: Safety Profile of Cobimetinib and Vemurafenib Was Tolerable and Manageable

<table>
<thead>
<tr>
<th></th>
<th>PBO + Vem n = 246</th>
<th>Cobi + Vem n = 247</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, months</td>
<td>10.3</td>
<td>11.2</td>
</tr>
<tr>
<td>Treatment-related AEs, n (%)</td>
<td>232 (94)</td>
<td>237 (96)</td>
</tr>
<tr>
<td>Treatment-related grade 3-4 AEs, n (%)</td>
<td>122 (50)</td>
<td>142 (57)</td>
</tr>
<tr>
<td>Treatment-related grade 5 AEs, n (%)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Treatment discontinuation for related AEs, n (%)</td>
<td>16 (7)</td>
<td>31 (13)</td>
</tr>
</tbody>
</table>


Phase III Co-BRIM study: Vemurafenib/Cobimetinib vs Vemuraf Modified from Larkin et al. NEJM 2014
coBRIM: Potential Impact of Baseline Activities of Cell Signaling Pathways on Combined BRAF and MEK Inhibition1-5

PTEN

PI3K

ERAS

V600 mutations

AKT

CRAF

BRAF

Vemurafenib

MEK

Cobimetinib

pS6

ERK

K67

Baseline expression in tumors by IHC

IHC, immunohistochemistry; mTOR, mammalian target of rapamycin.

coBRIM: Baseline PTEN Loss Did Not Significantly Affect OS in Cobimetinib + Vemurafenib Arm

PTEN ≥ 50 (n = 116)
PTEN <50 (n = 37)
PTEN ≥ 50 (n = 101)
PTEN <50 (n = 39)

OS was selected based on bimodal distribution of PTEN expression.

Modified from Atkinson et al. SMR Congress 2015.

Combination of BRAFi + MEKi is superior to BRAFi alone

<table>
<thead>
<tr>
<th>Benefit of BRAFi/MEKi</th>
<th>COMBI-d (Dabra/Tram vs. Dabra)</th>
<th>COMBI-v (Dabra/Tram vs. Vemu)</th>
<th>Co-BRIM (Vemu/Cobi vs. Vemu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>PFS</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>OS</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Long et al. NEJM 2014; Long et al. JCO 2015
Robert et al. NEJM 2014; Robert et al. SMR Congress 2015
Larkin, Ascierto et al. NEJM 2014; Atkins et al. SMR Congress 2015
Clinical Efficacy of Combination of BRAFi + MEKi

<table>
<thead>
<tr>
<th>Benefit of BRAFi+MEKi</th>
<th>COMBi-d (Dabra/Tram vs. Dabra)</th>
<th>COMBi-v (Dabra/Tram vs. Vemu)</th>
<th>Co-ERIM (Vemu/Cobi vs. Vemu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>69% vs 53%</td>
<td>66% vs 53%</td>
<td>68% vs 45%</td>
</tr>
<tr>
<td>PFS</td>
<td>HR 0.67 Median 11.0 mo</td>
<td>HR 0.61 Median 12.6 mo</td>
<td>HR 0.58 Median 12.3 mo</td>
</tr>
<tr>
<td>Median OS</td>
<td>HR 0.71 Median 25.1 mo</td>
<td>HR 0.66 Median 25.6 mo</td>
<td>HR 0.70 Median 22.3 mo</td>
</tr>
</tbody>
</table>

Long et al. NEJM 2014; Long et al. JCO 2015
Robert et al. NEJM 2014; Robert et al. ASH Congress 2015
Larkin, Ascierto et al. NEJM 2014; Larkin et al. ASCO 2015; Atkinson et al. SMR Congress 2015

Systemic therapy for BRAF-mutant melanoma

- Molecular BRAF-targeting therapy has proven significant benefit (both PFS and OS)
- A combination of BRAF inhibitor and MEK inhibitor is now a standard therapy
- Should it be the first line therapy?
- Should be used as the second-line after immunotherapy?
- How to combine with immunotherapy with optimal sequence?

Escape mechanisms for BRAFi / MEKi resistance?

- Need to combine with PI3K / AKT / mTOR inhibitors? CDK inhibitors? RTK inhibitors?
Target: NRAS mutation

- Current ongoing studies for NRAS-mutant melanoma:
  - Phase III study of MEK162 vs. Dacarbazine
  - Phase III study of MEK162 + LEE011 (CDK4/6i)
  - Phase II study of Trametinib +/- GSK2141795 (AKTi)
  - Phase I study of Trametinib + Palbociclib (CDKi)

Mutations in Melanoma: Prevalence by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>BRAF Mutations</th>
<th>NRAS Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous w/o C.S.D.</td>
<td>50% BRAF</td>
<td>20% NRAS</td>
</tr>
<tr>
<td>Acral Melanoma</td>
<td>20% BRAF</td>
<td>10% NRAS</td>
</tr>
<tr>
<td>Mucosal Melanoma</td>
<td>3% BRAF</td>
<td>5% NRAS</td>
</tr>
<tr>
<td>Cutaneous C.S.D.</td>
<td>5% BRAF</td>
<td>10% NRAS</td>
</tr>
<tr>
<td>Acral:</td>
<td>11% Mut</td>
<td>25% Amp</td>
</tr>
<tr>
<td>Mucosal:</td>
<td>21% Mut</td>
<td>25% Amp</td>
</tr>
<tr>
<td>Skin C.S.D.</td>
<td>1-18% Mut</td>
<td>6% Amp</td>
</tr>
<tr>
<td>Uveal</td>
<td>Virtually No</td>
<td>Virtually No</td>
</tr>
<tr>
<td>BRAF/NRAS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Target: KIT mutation

- ~1-2% of all melanomas, but accounts for 10-20% of acral/mucosal melanomas

- KIT mutations occurring in exon 11 and 13 are likely to result in constitutive activation of KIT kinase
  - Mostly substitution mutations, compared to GISTs which tend to have more insertion/deletion mutation

- Three early phase II studies of imatinib revealed only 1 partial response among 63 pts with advanced melanoma.1-3
  - No selection of patients on the basis of the KIT aberration status.
  - The only responder had no KIT mutation, but had the highest protein expression.3
  - No definite association between the KIT expression level and clinical activity.3

1Ugurel et al. Br J Cancer 2005;
2Wyman et al. Cancer 2006;
**Target: KIT mutation**

- However, Phase II clinical studies of imatinib in pts with KIT aberration:1-3
  - Response rate 33-53% among patients with KIT mutation (esp. exon 11, 13)
  - No responses among KIT amplification only without mutation.3
  - Higher response rates among pts with recurrent hotspots of KIT gene (exon 11, 13) or a higher KIT mutant-to-wild type allele ratio (>1).2


**Target: KIT mutation**

- However, PFS (or TTP) of imatinib is short:
  - In the 3 studies, a median PFS ranges from 2.8 to 3.7 months in pts with KIT mutation and/or amplification.
  - A median PFS (or TTP) is ~4 months among pts with KIT mutation.

- Possible mechanism of resistance to KIT inhibitor
  - No secondary mutations found in tumor specimens at progression3
  - Pretreatment NRAS mutations may be possible causes in a few patients
    - 4 pts with KIT aberration/NRAS mutation had early PD, including 2 pts with KIT mutation/NRAS mutation
  - Secondary KIT mutations may confer resistance (in vitro)4


**Target: KIT mutation**

- Phase II study of sunitinib1:
  - 3 (2 confirmed) of 4 pts with KIT mutation had a clinical response including 1 CR
  - Only 1 of 6 pts with KIT amplification and/or overexpression had a unconfirmed PR.

- Phase II study of nilotinib2:
  - 2 of 3 pts with a KIT mutation and 0 of 6 pts with KIT amplification only had a PR

- Possibly newer generation KIT inhibitors be more effective?

**Target: KIT mutation**

- Current ongoing studies of KIT inhibitors:
  - Phase II studies of dasatinib
  - Phase II study of nilotinib
  - Phase III randomized study of masitinib vs. dacarbazine (primary endpoint = PFS)
  - Phase II study of PLX3397
  - Phase I study of imatinib + ipilimumab (all cancer types)


**Target: GNAQ/GNA11 mutation (Uveal)**

- ~80% of uveal melanoma contains either GNAQ or GNA11 mutation.\(^1\),\(^2\)
- GNA mutations activate the MAPK signaling pathway, possibly via MEK and/or PLC/\(\beta\)/PKC.\(^1,-3\)
- Preclinical data demonstrated the antitumor activity of MEK inhibition in GNAQ-mutant melanoma cell lines\(^1\).

- Van Raamsdonk, et al. NEJM 2010
- GNAQ siRNA results in pERK inactivation\(^1\)
- PKC\(i\) decreases cell viability\(^3\)

- AEB071 (\(\mu\)M)

**Target: GNAQ/GNA11 mutation (Uveal)**

- Phase I study of trametinib:
  - No objective responses observed among 16 pts with uveal melanoma, including 2 with GNAQ and 2 with GNA11 mutations.

Phase II Study of Selumetinib vs Temozolomide in Uveal Melanoma

**Selumetinib** (n = 47 evaluable for response)
- Gnaq mutant
- Gna11 mutant
- Gnaq/11 WT

**Temozolomide/Dtic** (n = 46 evaluable for response)
- Gnaq mutant
- Gna11 mutant
- Gnaq/11 WT

* Exon 4 mutation assessed and absent

**Tumor Regression:** 50%
**RECIST Response:** 15%

**Tumor Regression:** 4%
**RECIST Response:** 0%

**Initial Tx with Selumetinib** (n = 46 evaluable for response)
- Gnaq mutant
- Gna11 mutant
- Gnaq/11 WT

**TMZ/DTC → Selumetinib** (n = 35 evaluable for response)
- Gnaq mutant
- Gna11 mutant
- Gnaq/11 WT

* Exon 4 mutation assessed and present

**Tumor Regression:** 50%
**RECIST Response:** 15%

**Tumor Regression:** 3%
**RECIST Response:** 0%

---

**Phase II Study of Selumetinib vs Temozolomide in Uveal Melanoma**

**PFS**

**Overall Population**
- Selumetinib (n = 47)
- Temozolomide (n = 46)

15.9 weeks (95% CI, 8.4 – 23.1) vs 7.0 weeks (95% CI, 4.3 – 8.4)
**HR 0.48 (95% CI, 0.30 – 0.80)**
*p = 0.005*

**Exon 5 Gg/11 Mutation Positive**
- Selumetinib (n = 38)
- Temozolomide (n = 42)

15.4 weeks (95% CI, 8.1 – 16.9) vs 7.0 weeks (95% CI, 4.3 – 11.9)
**HR 0.55 (95% CI, 0.34 – 0.87)**
*p = 0.011*

---

Modified from 2013 ASCO meeting: Carvajal et al. (Abstract CRA9003)

---

**Phase II Study of Selumetinib vs Temozolomide in Uveal Melanoma**

**Modified from 2013 ASCO meeting: Carvajal et al. (Abstract CRA9003)**
SUMIT: a Phase III, randomized, placebo-controlled, double-blind trial (NCT01974752)

**Primary endpoint**
- PFS by central review (RECIST 1.1)

**Secondary endpoints include**
- ORR, OS, DoR, safety and tolerability

**Exploratory endpoint**
- MEK pathway mutations in GNAQ/GNA11

**Key inclusion criteria**
- mUM (histologically or cytologically confirmed)
- \( \geq 1 \) lesion measurable at baseline
- ECOG PS 0–1
- Life expectancy >12 weeks

**Key exclusion criteria**
- Previous systemic anticancer therapy (may have prior surgery, or intra-hepatic or non-systemic therapy)

Protocol amended to ensure all randomized patients had the opportunity to complete 14-week minimum follow-up (two post-baseline tumor assessments)

BICR, blinded independent central review; bid, twice daily; DoR, duration of response; DTIC, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; mUM, metastatic uveal melanoma; ORR, objective response rate; OS, overall survival; Pbo, placebo; PO, orally; q6wk, every 6 weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1

Selumetinib 75 mg bid PO + DTIC 1000 mg/m² IV on Day 1 of every 21-day cycle

Pbo bid PO + DTIC 1000 mg/m² IV on Day 1 of every 21-day cycle

Administered until objective disease progression (BICR), intolerable toxicity, or another discontinuation criteria; scanning schedule q6wk

Randomized 3:1, stratified by the presence/absence of liver metastases

Patients with mUM, with no prior systemic therapy

Optional open-label treatment: selumetinib +/- DTIC (data not shown)

**Progression-free survival (primary endpoint)**

There was a numerical improvement in median PFS with Sel + DTIC compared with Pbo + DTIC by site-based review

HR 0.49 (95% CI 0.28, 0.84)
2-sided p=0.0102

Sel + DTIC (n=97) Pbo + DTIC (n=32)

Events, n (%) 77 (79) 26 (81)

Median, mo 3.8 2.1

Progression free at 3/6 mo 56%/16% 26%/14%

**Best tumor response by central review**

Partial response recorded for three patients

Pbo + DTIC
No responses recorded

Modified from Carvajal et al. SMMR Congress 2015
Target: GNAQ/11 mutation

- Current ongoing studies for uveal melanoma:
  - Phase II studies of AEB071 (PKCi)
  - Phase II study of MEK162 + AEB071
  - Phase II study of trametinib +/- GSK2141795 (AKTi)
  - Phase II study of vorinostat

Target: NRAS mutation

- ~20% of melanomas harbor NRAS mutation.
- Prognosis of patients with NRAS-mutant melanoma is poor.¹
- There are no established therapies NRAS mutant melanoma
- MEK inhibitors have an activity in NRAS mutant melanoma?

¹ Jakob, Bassett, Ng, et al. Cancer 2011
MEK162: PFS – NRAS-/BRAF-mutant

Lack of cell cycle arrest with MEK inhibition centered on a CDK4-Rb axis.

This results led to a phase I/II study of MEK162 + LEE011 in NRAS-mutant melanoma

Target: NRAS mutation

- Current ongoing studies for NRAS-mutant melanoma:
  - Phase III study of MEK162 vs. dacarbazine
  - Phase III study of MEK162 + LEE011 (CDK4i)
  - Phase III study of trametinib +/- GSK2141795 (AKTi)
  - Phase I study of trametinib + palbociclib (CDK4i)
Future direction in melanoma targeted therapy

(BRAF mutant melanoma)

- Is the combination of RAFi and MEKi be better than a RAF inhibitor alone in pts with BRAF mutation?
  - Yes for PFS and now OS
  - It is the backbone of BRAF targeted therapy
- Can genomic and epigenetic data potentially predict the clinical benefit of different targeted therapy combinations?

<table>
<thead>
<tr>
<th>Other alterations</th>
<th>Potential combination with</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN2A deletion</td>
<td>CDK4 inhibitor</td>
</tr>
<tr>
<td>PI3K deletion</td>
<td>PIK3 (alpha) inhibitor</td>
</tr>
<tr>
<td>PIK3/akt activation</td>
<td>Akt inhibitor</td>
</tr>
<tr>
<td>Activated RTKs</td>
<td>MEK inhibitor</td>
</tr>
<tr>
<td>Stromal HGF upregulation</td>
<td>EGFR inhibitor</td>
</tr>
<tr>
<td>PS3</td>
<td>MDM2 inhibitor</td>
</tr>
</tbody>
</table>

Future direction in melanoma targeted therapy

- Do patients with BRAF-mutated melanoma need continued BRAF inhibition while on subsequent therapy after prior BRAF inhibitor?
- Will the maintenance therapy with immunotherapy be beneficial after response to BRAF-targeted therapy?
- Does the combination of BRAFi and immunotherapeutic agents improve survival and a cure rate???
  - Dabrafenib + Ipilimumab (ongoing)
  - Vemurafenib + anti-PDL1 antibody (ongoing)
  - Dabrafenib +/- Trametinib + Pembrolizumab (ongoing)
  - Dabrafenib + Trametinib + anti-PDL1 antibody (ongoing)
  - And many more to come...

Future direction in melanoma targeted therapy

- Advances in genomic sequencing and proteomic analysis will facilitate the clinical development of targeted drugs.
- Strategic selection of patients with appropriate (or potential predictive) biomarkers in phase I and II studies
- Close collaboration with basic scientists (preclinical data/correlative data) is essential.
- Collection of tumor / blood samples for correlative biomarker studies is a MUST.
  - Close collaboration with surgeons and interventional radiologists
  - Dedicated research personnel in the planning and execution of the sample collection
  - Robust, user-friendly pathology molecular and clinical database
Dacarbazine
Interleukin-2
Ipilimumab
Vemurafenib*
Dabrafenib*
Trametinib*
*BRAF V600 mutation only
**previously treated with Ipilimumab

• Median survival is ~2 years; 5-year survival rate > 20%
• Need to optimally combine or sequence these drugs!
• Need to find effective targeted therapy for non-BRAF-mutant melanomas
• Need to discover predictive biomarkers for clinical benefit!
Update on Cutaneous T-Cell Lymphomas

Estil A. Vance, M.D.

Skin Tumor Conference
4-2-16

Disclosures

I am on the Celgene Speakers Bureau, speaking approximately 5 times yearly.
**CTCL EPIDEMIOLOGY**

- ~1000 new cases annually in U.S.
  - Comprises 2.2% of all lymphomas
  - Incidence increasing
- Estimated prevalence 16,000 to 20,000 in U.S.
- Two times more common in men than women
- More common in blacks than whites
- Majority of patients 45 to 65 years of age at time of diagnosis

---

**WHO/EORTC Classification of Primary CTCL**

|-------------------------|-----------------------------|-------------------|-----------------------|--------------------------|----------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|

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**Primary Cutaneous T-Cell Lymphoma (CTCL)**

- Mycosis fungoides (MF)
  - Most common T-Cell lymphoma of the skin
  - MF and Sézary comprise 55% of all CTCL
  - Isolated patches, plaques, and/or tumors
  - Classic histopathologic features
    - Superficial dermal infiltrate of malignant lymphocytes
    - Cerebriform nuclei within malignant lymphocytes
    - Epidermotropism (Pautrier’s microabscesses)
  - Early stage lesions include reactive benign T-lymphocytes
Histopathologic Appearance of MF

Upper dermal infiltrate of small lymphocytes with presence of Pautrier’s microabscesses in epidermis

Immunophenotyping of MF

- Helper-Memory Cells: CD4, CD45RO+
- Pan-T markers: CD2, CD3, CD5+
- Infiltrating T cells: CD8+ (immune response to the tumor cells)
- Loss of markers: CD7 (may be seen in benign conditions 10-20%)
- CD30 may be present in 30%

Membrane Proteins of the Malignant T Cell

- CD3 and T-cell receptor
- CD4 (TH 2 subtype)
- CD45RO (Memory T Cell)
- LFA-1
- CCR4
- CD26 (-) Depeptidyl peptidase IV
- CD7 (-)
- CD25 (+)/(-)
- CLA (Cutaneous Lymphoid Antigen)
CLA expressing T-cells: Cutaneous T-cells (Skin Homing)

- 16% of circulating T-cells in normal controls
- CLA is also expressed on all granulocytes, monocytes, dendritic cells
- The ligand for CLA is E-selectin-1, expressed at low levels on all blood vessels in the skin
- E-selectin is upregulated in lesional skin of CTCL and any inflamed skin lesion

Immunogenotyping: TCR pattern

- TCR alpha/beta or TCR gamma/delta
- Dominant Clone (Southern Blot or PCR)
  - false + possible
  - Utility unknown
  - 50% Stage IA will have a PCR+ circulating clone
  - Complete clinical remissions: 1/3+ PCR

CTCL Staging Evaluations

- Physical exam
- Blood: CBC w/ differential, LFTs, s-IL2R, β2-microglobulin, LDH, flow cytometry, UA
- Chest X-ray (PA & LAT)
- CT abdomen & pelvis (more valuable in >IIa)
- Lymph node biopsy when warranted
- Bone marrow if circulating cells present
### CTCL Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin Disease</th>
<th>Adenopathy</th>
<th>Pathology*</th>
<th>Visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Patch/plaque (&lt;10% body surface area)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ib</td>
<td>Patch/plaque (≥10% body surface area)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIA</td>
<td>Patch/plaque</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIb</td>
<td>Tumors</td>
<td>+&lt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>Generalized erythroderma</td>
<td>+&lt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVa</td>
<td>Patch/plaque, tumors, or erythroderma</td>
<td>+&lt;</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IVb</td>
<td>Patch/plaque, tumors, or erythroderma</td>
<td>+&lt;</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

* = uninvolved node, reactive node, or dermatopathic node with small clusters (<6 cells) of convoluted cells.
+ = dermatopathic node with large clusters (≥6 cells) of convoluted cells or lymph node effacement.

Additional Prognostic information from Blood: B0- no or <5% atypical cells present, B1- <1000 Sezary cells/microliter, B2->1000 Sezary/microliter

### CTCL Survival By Stage

![CTCL Survival By Stage](image)

### Immune response to CTCL

- Percentage of CD8+ lymphocytes in skin correlates directly with survival and inversely with stage
- CD4/CD8 ratios in skin biopsies increase with stage
- Cyclosporin
  - Rapid dissemination
  - Transformation and dissemination

References:
- Kreis et al. JAAD. 1980; 16: 1130-40
- Vonderheid et al. JAAD. 1987; 17: 40-52
- Hoppe et al. JAAD. 1993; 22: 448-450
Principles of Therapy

- The Long Game
- Attempt to improve or augment antitumor immune response and avoid drugs early on that might suppress this.
- Decrease immune milieu that may be tumor stimulatory
- Therapeutic goals more often palliation than aggressive attempts to eradicate disease
- Combine skin directed therapy with systemic and immunomodulatory where possible
- Be mindful of infectious risks
  - Barrier compromise even if no real immune suppression
- Surveillance for transformation and secondary malignancies
- Paradigm shifts are easier for you than the patients

Types of Treatment for MF

- Palliative: directed at symptoms
- Skin-directed therapy
- Biological Response Modifiers
- Targeted Toxins
- Systemic Cytotoxic Therapy
- Vaccinations - Immunotherapy

FDA Approved Therapy

1987 Only nitrogen mustard, velban, and methotrexate approved
1987 Photopheresis approved for erythrodermic CTCL
1998 ONTAK® (DAB-IL-2) approved
1999 Approval of oral bexarotene (Targretin® capsules)
2000 Approval of topical bexarotene (Targretin® gel)
2006 Vorinostat, 2 prior systemic therapies
2009 Romidepsin approved, at least 1 prior therapy
2011 Pralatrexate, at least 1 prior systemic therapy*
2011 Brentuximab vedotin**
2006 Vorinostat, 2 prior systemic therapies
2013 Valchlor (topical mechlorethamine 0.02% gel)

* Still PTCL indication, **CD30+ transformation, not approved PCALCL
Skin-Directed Treatment Options for CTCL

- Topical Therapy
  - Corticosteroids, Retinoids, Vitamin D
- Topical Chemotherapy
  - Nitrogen Mustard, BCNU
- Phototherapy
  - sunlight, UVB, PUVA, PUVA Plus interferon or retinoid
- Electron Beam & local XRT

Topical Nitrogen Mustard for MF

- Mechanism of action: DNA alkylation, possible delayed type hypersensitivity (TH1) response
- Aqueous or ointment base, applied to skin once daily - Previously required compounding
  - Continue for 2-3 months after CR (longer maintenance does not decrease relapse rate)
- Mechlorethamine 0.02% gel approved

Bexarotene Gel

- Early stage CTCL (IA–IIA)
- Overall response rate (ie. 50% reduction): 63%
- Clinical complete response rate 21%
- Median time to onset of response: 20 weeks
- Durable responses: 61+ weeks
- Most common adverse event: irritation (87%)
### Imidazoquinolones

- Imiquimod and resiquimod
- Toll-like receptor agonists
- TLR7 Imiquimod, TLR7 and 8 resiquimod
- Resiquimod - Rook et al 2015

<table>
<thead>
<tr>
<th>Data</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 enrolled, 12 completed</td>
<td></td>
</tr>
<tr>
<td>11/12 responded (&gt;50% reduction skin involvement)</td>
<td></td>
</tr>
<tr>
<td>4/5 with follicular MF responded</td>
<td></td>
</tr>
<tr>
<td>Primarily mild skin toxicity</td>
<td></td>
</tr>
</tbody>
</table>

Successful therapy associated with decline in malignant clone and recruitment PCD, benign T-cell, and NK to area

---

### Resiquimod

![Resiquimod](image)

Figure 2: Resiquimod is an effective therapy for early stage MFs. Changes from baseline in CD8+ T cells (A) and CD8+ T cells recruited to the skin (B) in 12 patients treated with resiquimod for 16 weeks. Filled bars show naïve CD8+ T cells and filled bars show recruited CD8+ T cells. The x-axis shows the time points at which the skin biopsies were taken. The y-axis shows the percentage of CD8+ T cells in the skin. The data were analyzed using the Kruskal-Wallis test. Significant differences were observed at 14 weeks in the treatment group vs. the control group, and the recruited CD8+ T cells. The data are presented as mean ± SEM.

---

### Resiquimod

![Resiquimod](image)

Figure 3: Reduction of benign and malignant T-cell clones in patients treated with resiquimod. The data are presented as mean ± SEM. Significant differences were observed between the groups at 14 weeks. The data were analyzed using the Kruskal-Wallis test. Significant differences were observed at 14 weeks in the treatment group vs. the control group, and the recruited CD8+ T cells. The data are presented as mean ± SEM.
Narrowband (NB) vs PUVA for MF (IA & IB)

- **N= 56 patients (21 NB; 35 PUVA)**
- **Efficacy:**
  - NB CR 17/21 (81%); PR 4/21 (19%); PD 0
  - PUVA CR 25/35 (71%); PR 10/35 (29%); PD 0
- **The mean relapse-free interval**
  - NB: 24.5 months (range, 2-66 months)
  - PUVA: 22.8 months (range, 1-43 months)
- **UVB not ideal for folliculotropic, tumor stage, dark complexion**

EBRT for MF

- **Total skin EBRT**
  - 6-9 MeV electrons via linear accelerator
  - 6 field technique: ant, post, 4 oblique fields
  - 1.5-2.0 Gy per fraction over 9-10 wks
  - Total dose: 30-36 Gy
- **Localized EBRT**
  - Tumors: 9-12 MeV with 2 cm margins
  - Total dose: 20-30 Gy
- **Method of action:** targets lymphocytes, most radiosensitive cell

Total Skin EBRT

- **Adverse effects**
  - Acute skin effects: burning erythema, edema
  - Chronic skin effects: xerosis, superficial atrophy, telangiectasia, dyspigmentation
  - Alopecia, loss of nails (usually regrow)
  - Heat intolerance due to the suppression of sweat gland production (usual duration, 6-12 mos)
  - Increased SCC and BCC
- **Other therapies may play a role**
CTCL: Systemic Therapy

- Tretinoin capsules
- Bexarotene capsules
- Acitretin capsules
- Methotrexate
- Prednisone/chlorambucil
- Interferon
- Zanomibumab
- Alemtuzumab
- Romidepsin
- Vorinostat
- Extracorporeal photochemotherapy
- Other biologic modifiers
- Denileukin diftitox
- Combination chemotherapy
- Bortezomib
- Pegylated liposomal Doxorubicin
- Praltrexate

Photopheresis for MF/Sézary Syndrome

CTCL protocol: one 3-hour treatment on 2 consecutive days, every 2-4 weeks

Proposed mechanism of action

- Induces apoptosis of lymphocytes
- Converts monocytes to immature dendritic cells
- Dendritic cells engulf lymphocytes and present tumor antigen to cytotoxic T cells


ECPP (Extracorporeal Photopheresis)

- Associated with increased APC’s.
- Response rates of up to 60%.
- Patients responding tend to have:
  - Circulating tumor cells.
  - Circulating CD8+ cells (cytotoxic T-cells)
- May be combined with:
  - IFN-α, γ - IL-12
  - Retinoids - GM-CSF
**ECPP (Extracorporeal Photopheresis)**

- Good response to ECPP
- Erythroderma
- Relatively low (closer to normal) peripheral CD4 : CD8
- Normal LDH
- CTCL patients who are erythrodermic with a relatively intact immune system are optimal candidates for ECP

**Retinoids and Photopheresis**

- Retinoids increase:
  - production of IFN-\(\gamma\) and IL-12
  - T-cell activation (CD25 expression)
- Photopheresis increases:
  - CD8+ T-cells
  - APCs
  - Apoptosis

**Cytokine Therapy**

- Interferon alpha and gamma
- Granulocyte-macrophage colony stimulating factor
  - IL-2
  - IL-12
- Anti-interleukins: all-7, all-10, and all-15
Oral Retinoids for MF/Sézary Syndrome

Specific retinoid receptor ligands that influence critical pathways for cell proliferation, differentiation, and apoptosis

<table>
<thead>
<tr>
<th>Retinoid</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>25-50 mg/d</td>
</tr>
<tr>
<td>Bexarotene*</td>
<td>300 mg/m² BSA/day</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>1 mg/kg/d</td>
</tr>
</tbody>
</table>

* FDA-approved for CTCL in December 1999


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Targretin Capsules In CTCL

300 mg/m²/day is optimal initial dose, when dose-related safety profile considered

Though optimistic goal in most
Prompt and durable responses remarkable in heavily pretreated population with few if any remaining treatment options
Patients benefited regardless of tumor response

---

### Response Rates by TNM Staging According to PEC for 300 mg/m²/day Initial Dose (N = 84 Patients)

<table>
<thead>
<tr>
<th>TNM Clinical Stage</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>50% (2/4)</td>
</tr>
<tr>
<td>IB</td>
<td>52% (11/21)</td>
</tr>
<tr>
<td>IIA</td>
<td>67% (20/30)</td>
</tr>
<tr>
<td>IIB</td>
<td>57% (13/23)</td>
</tr>
<tr>
<td>III</td>
<td>32% (6/19)</td>
</tr>
<tr>
<td>IVA</td>
<td>44% (4/9)</td>
</tr>
<tr>
<td>IVB</td>
<td>40% (2/5)</td>
</tr>
</tbody>
</table>

---
Oral Targretin 300 mg/m²/d
Median Days to Response

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset 1st response</td>
<td>57 (27-114)</td>
<td>180 (14-197)</td>
</tr>
<tr>
<td>Onset best response</td>
<td>87 (27-153)</td>
<td>180 (15-197)</td>
</tr>
<tr>
<td>Days disease control</td>
<td>210 (120-210)</td>
<td>299 (57-299)</td>
</tr>
</tbody>
</table>

Targretin Capsules In CTCL
Most Common Laboratory Abnormalities

- Hypertriglyceridemia and Hypercholesterolemia
  - 2.6% incidence of pancreatitis
  - Gemfibrozil increased bexarotene plasma levels and is not recommended for use with Targretin capsules

- Thyroid axis alteration (central hypothyroidism)
  - Leukopenia/Neutropenia
  - Elevation liver function tests
  - All reversible at discontinuation

Targretin Capsules In CTCL Package
Insert Laboratory Monitoring

- Fasting lipids before treatment, weekly until response is established (usually 2-4 weeks), and then every 8 weeks
- LFTs at baseline; after 1, 2 and 4 weeks of treatment; and then at least every 8 weeks if stable
- Baseline thyroid tests should be obtained and patients monitored during treatment
- WBC count with differential at baseline and periodically during treatment
ONTAK
Pivotal Phase III Clinical Trial
Objective Tumor Response by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Complete response</th>
<th>Clinical complete response</th>
<th>Partial response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ib n=16</td>
<td>44%</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>IIa n=10</td>
<td>30%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>IIb n=19</td>
<td>32%</td>
<td>18%</td>
<td>13.4%</td>
</tr>
<tr>
<td>III n=11</td>
<td>21%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>IVa n=15</td>
<td>6.6%</td>
<td>13.4%</td>
<td></td>
</tr>
</tbody>
</table>

Complete response/ Clinical complete response  Partial response

Retinoids (bexarotene, ATRA)
Butyrates

IL-2R Upregulation

ONTAK Safety Profile

Significant Adverse Events*

Safety Evaluated in 143 Patients
- Flu-like symptoms (91%)
- Acute hypersensitivity-type reactions (69%)
- Asthenia (66%)
- Nausea/vomiting (64%) (which led to dehydration in some patients)
- Hypoalbuminemia (83%)
- Infections (48%)
- Vascular leak syndrome (27%)

* Every AE associated with ONTAK therapy was included in package insert, regardless of causality assigned by investigating physician.
Ontak Patient Management Issues

For older patients, low threshold for evaluation LVEF. Cautious use in patients with renal insufficiency. Edema is generally better tolerated than orthostasis/hypotension. Cautious fluid administration may avert spiraling renal function.
Adhere to albumin guidelines
Dexamethasone premedication.

Outcome Of Systemic Therapies

• Most studies are small (~15 patients) and uncontrolled. One randomized trial
• No standardized response criteria
• Response rates variable (19-58%) depending upon prior treatment and response criteria
• Responses not durable (median TTP 2 to 13 months)
• No impact on survival

Nucleoside Analogs

Includes Fludarabine, Cladribine, Gemcitabine, Pentostatin
All are active
Toxicities include:
  Increased T-cell immune deficiency
  Myelosuppression
  Neurotoxicity
  Renal Toxicity (TTP/HUS-Pentostatin)
  Pancreatic (Pentostatin)
Gemcitabine

When given at 1000/m$^2$ days 1,8,15 of 28
Overall response 68% with CR 8%
Durations of CR and PR were 15/10 mos.
8/11 with Sezary responded.
TTP possible

Vorinostat Indication

Approved for relapse, persistence, or progression after 2 prior systemic therapies

Vorinostat Demonstrated a 30% Objective Response Rate in the Pivotal Study

- Objective response defined as a ≥50% decrease in SWAT score for at least 4 weeks.
- One patient with stage IIB CTCL had a complete clinical response.

Efficacy evaluated using stringent criteria
Patients with 0% to 49% decrease in SWAT scores were considered nonresponders.
Vorinostat: Some Safety Information

Pulmonary embolism, deep vein thrombosis
Dose-related thrombocytopenia and anemia
QTc prolongation has been observed.
Vorinostat and coumarin = prolongation of PT and INR.
Severe thrombocytopenia and GI bleeding have been reported with concomitant use of vorinostat and other HDAC inhibitors (eg, valproic acid).
Monitor platelet count every 2 weeks for the first 2 months.
GI Disturbance: Recommend 2 liters fluid/day.
Hyperglycemia.
Contraindicated in pregnancy and breast-feeding.
Caution in hepatic impairment.

Romidepsin

HDAC inhibitor
Approved for CTCL after one prior systemic therapy
Weekly infusion over 3 hours for 3 weeks of a 4 week cycle
2 large single arm multi-center studies
Primarily stage IIB or greater
Median 2 prior systemic therapies
34-35% ORR, 6% CR, Duration of response 15 and 11 mos
Median time to response was 2 months
Most common SAE was infection (8% and 32%)
Nausea (57%/71%) and asthenia (54% and 64%) common
QTc monitoring, optimize Mg and K
EBV, Hepatitis B reactivation, TLS reported

Romidepsin- Efficacy/Composites

From Whitaker et al, JCO 2010, Piekarz et al, JCO 2009
Romidepsin - Blood Clearance

Fig 1. Sezary cell counts for six of the 13 patients with a higher blood tumor burden (Sezary cells at > 1,000/μL and/or Sezary cells > 20% of lymphocytes at baseline.

Belinostat

Pan-HDAC inhibitor
Investigated in 29 patients with CTCL after one prior systemic therapy
1000 mg/m² daily for 5 days of a 21 day cycle
Patients had received a median of one prior skin directed therapy and 4 prior systemic therapies
Overall RR was 14% for CTCL (35% for PTCL)
Significant nausea and vomiting reported
1 episode Vfib reported
May be used in transformed disease

Methotrexate

Response rates approaching 50% realized with up to 25 mg orally weekly (median)
May be combined with IFNα (MTX 10 mg/m² biweekly, IFNα 9 mU tiwk for 6-12 mos, 74%CCR)
Combined with monthly ECPP
Remember hepatic surveillance approaching 2 grams (Derm)
Pralatrexate

- Novel antifolate with high affinity for the RFC-1
  - RFC expression is induced by various oncogenes
  - Highly expressed on malignant tissue
  - Principal transporter through which folates and antifolates enter cells
  - Allows drug to selectively accumulate in tumor cells
- For PTCL, preclinical studies demonstrate superior activity compared with methotrexate
  - 10-fold greater cytotoxicity in lymphoma cell lines
  - Enhanced regression of lymphoma tumors transferred to SCID mice
  - Cell-line remission in vivo correlated with RFC-1 expression

Pralatrexate Response Rates

<table>
<thead>
<tr>
<th>n</th>
<th>Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>45%</td>
</tr>
<tr>
<td>41</td>
<td>51%</td>
</tr>
<tr>
<td>13</td>
<td>8%</td>
</tr>
<tr>
<td>54</td>
<td>41%</td>
</tr>
</tbody>
</table>

Optimal Dose/Schedule: 15 mg/m² administered 3 out of 4 weeks

Pralatrexate Treatment-Related Adverse Events at Optimal Dose/Schedule

<table>
<thead>
<tr>
<th>Adverse Events (AEs)</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal inflammation</td>
<td>48%</td>
<td>17%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>31%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Optimal Dose/Schedule: 15 mg/m² administered 3 out of 4 weeks
Pralatrexate in CTCL
Phase I Conclusions

- Pralatrexate demonstrated high activity in patients with heavily pretreated relapsed/refractory CTCL.
  - ORR (at optimal dose and schedule) = 45%
  - PFS (at optimal dose and schedule) = Not reached
- Toxicity generally acceptable at the optimal dose/schedule.
  - Mucosal inflammation = 48% (primarily Grade 1/2)
  - Absence of Grade 3/4 neutropenia
  - Single event of Grade 3 thrombocytopenia
- Pralatrexate should be evaluated in earlier lines of therapy and also in combination with other therapeutics in CTCL.


Pralatrexate Treatment- Progression Free Survival


Pralatrexate- Hematologic

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralatrexate</td>
<td>15 mg/m²</td>
<td>IV</td>
<td>qw for 3 wks per 4-wk schedule</td>
</tr>
</tbody>
</table>

Supplementation to potentially reduce hematologic toxicity and mucositis

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₁₂</td>
<td>1 mg</td>
<td>IM</td>
<td>q8-10w</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1.0-1.25 mg</td>
<td>PO</td>
<td>qd</td>
</tr>
</tbody>
</table>

- Vitamin B₁₂
  - Initiate no more than 10 weeks prior to first dose of pralatrexate
  - Subsequent injections may be given same day as therapy
- Folic acid
  - Initiate during the 10-day period preceding the first dose of pralatrexate
  - Continue during full course of therapy and for 30 days after last dose
- Low dose Leucovorin
Liposomal Pegylated Doxorubicin

Response rates reported ranging from 40-90%
25 patients with advanced MF (IIB-IVB)
receiving 40 mg/m2 every 4 weeks- OR 50%
with median PFS 5 mos
Generally well tolerated

Bortezomib

Initial 12 evaluable patients.
Overall response rate 67% with 2 CR and 6 PR
Dosed at 1.3 mg/m2 days 1,4,8,11.
All responses durable from 7 to >14 mos.
Only neuropathy and thrombocytopenia (g3).

Alemtuzumab

Particular activity in SS
Low doses 10-15 mg SC tiwk until Sezary
count<1000 cells/μL, OR 86-100%
Requisite antibiotic prophylaxis
Lenalidomode

RR 28% with median TTP 10 mos
Started at 10 mg PO daily x21 days with 5 mg escalation/cycle to max 25 mg/day
Significant cutaneous flares seen if started at higher doses

LENALIDOMIDE

Zanolimumab

Human anti-CD4 Ab.
Objective responses in up to 56% of patients.
Duration of response approaching 81%.
Prominent side effect: rash.
Anti-CCR4: Mogamulizumab (Poteligeo®)

CCR4 important for skin homing of malignant cells
Expressed on tumors and immune suppressors, such as Tregs
Phase I (Kyowa) CTCL/PTCL
ORR 37%: 47% in SS (8/17), 29% in MF (7/21)
Phase I, ATL/PTCL,
ORR 31% (5/16), 13% 2 CR, 19% 3 PR
Clinical response even at lowest dose
• Phase II in relapsed ATL,
  27 pts ORR 13 (50%), CR 8 (31%), PR 5 (19%)

BMT

Autologous BMT has been done producing short remissions.
Initial case reports showed some durable remissions to allogeneic BMT.
Successes with RIST are reported.
Successful demonstration of GVL by DLI effect.
TRM at one year approximately 20%.
Incorporation of TSEB in some instances may reduce suppurative complications, but requires substantial planning.

Allogeneic Peripheral Stem Cell Transplant for CTCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (age, yrs)</th>
<th>Conditioning Regimen</th>
<th>GVHD prophylaxis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soligo 2003</td>
<td>N = 3 (51-60)</td>
<td>Fludarabine, TBI</td>
<td>CSA, MMF</td>
<td>3 CR: 18 and 24 mo, 1 dead d+73</td>
</tr>
<tr>
<td>Molina 2003, 2005</td>
<td>N = 8 (21-59)</td>
<td>Fludar/Melph n = 4 Cyclophos/TBI n = 3 Cyclophos/Busulfan</td>
<td>CSA n = 8 MTX n = 4 MMF n = 6</td>
<td>8 CR: 6 alive (33-106 mo), 2 dead (sepsis)</td>
</tr>
<tr>
<td>Guitart 2002</td>
<td>N = 3 (27-39)</td>
<td>Cyclophos/Mesna, TBI</td>
<td>CSA, steroid, +/- MMF</td>
<td>3 CR: 15, 52, 60 mo</td>
</tr>
<tr>
<td>Masood 2002</td>
<td>N = 1 (37)</td>
<td>Cyclophos, TBI</td>
<td>MTX, CSA</td>
<td>CR: 24 mo</td>
</tr>
<tr>
<td>Koeppel 1994</td>
<td>N = 1 (31)</td>
<td>Cyclophos, TBI</td>
<td>MTX, CSA, steroid</td>
<td>CR: 72 mo</td>
</tr>
</tbody>
</table>

BMT- Lymphoma Working Party EBMT

Retrospective study looking at 113 patients with MF (24 with Sezary) receiving allo BMT between 1997 and 2007. 45% sibling and 55% MUD. 76% RIST and 24% MAC (TBI 40%). OS 56% at 1 year and 44% at 3 years, and 38% 5 yr. PFS 34% 1 year, 28% 3yr, 25% 5yr RIST reduced NRM without increase in relapse. MrD better than MUD (OS RR 4.0 and PFS 2.7). 15 patients alive and well after DLI at last F/U despite relapse NRM at one year was 22% and associated strongly with poor PS at BMT and myeloablative conditioning regimen. TBI associated with lower PFS.

Summary of Therapies for CTCL/SS

Skin-directed therapies: highly effective in the early stages of MF
Relapses common
The challenge: develop systemic targeted therapies with minimal adverse effects capable of inducing meaningful remissions Current therapeutic goal: do no harm, prevent disease progression Comparison trials needed to prioritize systemic therapy

CONCLUSIONS and QUESTIONS
Practical Updates in the Surgical Management of Cutaneous Malignancies

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Surgical Oncology
Baylor University Medical Center

Melanoma

Risk Factors

- Skin type
- Age
- Gender
- Previous melanoma
- Sunlight exposure
- Family history
- Atypical mole and melanoma syndrome
Clinical Presentation

Pathologic Factors

• Clark level (extent of penetration in dermis)
• Breslow thickness (depth of invasion)
• Ulceration
• Mitotic rate

<table>
<thead>
<tr>
<th>Classification of Melanoma</th>
<th>Breslow Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin</td>
<td>&lt; 1mm</td>
</tr>
<tr>
<td>Intermediate Thickness</td>
<td>1-4 mm</td>
</tr>
<tr>
<td>Thick</td>
<td>&gt; 4mm</td>
</tr>
</tbody>
</table>
Management of Local Disease

- Local Control: Wide local excision

WHO Melanoma Group: 1991

- Prospective, randomized trial
- 512 patients with a primary melanoma < 2mm thick
- Randomized to 1cm or 3cm margin

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Margin (cm)</th>
<th>N</th>
<th>Breslow Thickness</th>
<th>Local Recurrence</th>
<th>Overall Survival</th>
<th>Followup (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO¹</td>
<td>1991</td>
<td>1 vs 3</td>
<td>632</td>
<td>&lt;2</td>
<td>NS</td>
<td>NS</td>
<td>9</td>
</tr>
<tr>
<td>Sweden²</td>
<td>2000</td>
<td>2 vs 5</td>
<td>989</td>
<td>&lt;2mm</td>
<td>NS</td>
<td>NS</td>
<td>11</td>
</tr>
<tr>
<td>Intergroup³</td>
<td>2001</td>
<td>2 vs 4</td>
<td>740</td>
<td>1-4mm</td>
<td>NS</td>
<td>NS</td>
<td>10</td>
</tr>
<tr>
<td>France⁴</td>
<td>2003</td>
<td>2 vs 5</td>
<td>362</td>
<td>&lt;2mm</td>
<td>NS</td>
<td>NS</td>
<td>16</td>
</tr>
<tr>
<td>UKMSG⁵</td>
<td>2004</td>
<td>1 vs 3</td>
<td>900</td>
<td>&gt;2mm</td>
<td>1cm margin</td>
<td>increased risk</td>
<td>NS</td>
</tr>
<tr>
<td>Sweden⁶</td>
<td>2011</td>
<td>2 vs 4</td>
<td>936</td>
<td>&gt;2 mm</td>
<td>NS</td>
<td>NS</td>
<td>6.7</td>
</tr>
<tr>
<td>MDACC/Moffitt⁷</td>
<td>1998</td>
<td>&lt;= 2 vs &gt;2</td>
<td>278</td>
<td>&gt;4mm</td>
<td>NS</td>
<td>NS</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*All of these patients were treated with a 1 cm margin


Other Prospective, Multi-Institutional, Randomized Clinical Trials

1. 1 mm stage I primary cutaneous melanoma. Comparison of excision with margins of 1 or 3 cm. JAMA 1988.
2. 2 survival groups: 1 cm and 3 cm. JAMA 2000.
5. 5 Intergroup study: 2cm and 4cm. Arch Surg. 2001.
**Recommendations for Excision Margins**

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Excision Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ 0.5-1cm</td>
<td></td>
</tr>
<tr>
<td>&lt; 1mm 1 cm</td>
<td></td>
</tr>
<tr>
<td>1-2 mm 1-2 cm</td>
<td></td>
</tr>
<tr>
<td>2-4 mm 2 cm</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 mm 2 cm</td>
<td></td>
</tr>
</tbody>
</table>

**Special Anatomic Considerations**

- Fingers and toes – Amputation
- Sole of foot
  - Preserve deep fascia for skin graft
  - Consider weight-bearing areas
- Breast - mastectomy not indicated
- Umbilicus – may need to be resected if melanoma is in the vicinity
- Scalp and Face

**Management of the Draining Nodal Basin**

- Melanoma commonly metastasizes to regional lymph nodes
  - Usually the first site of metastasis
- Prior to 1990
  - Lymph Node Dissection
    - Observation vs nodal dissection for clinically evident disease for >1mm thick

Lateral Neck Dissection

- May include superficial parotidectomy
- Risks
  - Bleeding
  - Infection
  - Transient nerve damage
  - Permanent nerve damage

Axillary Lymph Node Dissection

- Levels I-III
- Risks
  - Bleeding / Infection
  - Seroma
  - Injury to Nerves
  - Lymphedema
  - Shoulder problems

Inguinal Lymph Node Dissection

- Superficial/Deep
- Risks
  - Bleeding
  - Infection
  - Seroma
  - DVT
  - Lymphedema
  - Hernia
WHO Elective Lymph Node Dissection Trial

- Prospective, randomized
- Melanoma of the trunk at least 1.5 mm thick
- 5 year survival
  - 66.7% ELND vs 51.3% Observation
  - Patients with occult regional metastasis had 48.2% 5-year survival vs 26.6% 5 yr survival for patients who developed palpable disease

Cassinelli. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomized trial. The Lancet 1998

Intergroup Melanoma Trial

- Prospective, multi-institutional trial
- 1-4 mm thick melanomas: ELND vs Observation
  - No difference in survival between both groups overall
- Subset analysis
  - Better survival for ELND group
    - Younger than 60 years
    - No ulceration
    - 1-2 mm thick
    - Extremity melanoma
Sentinel Lymph Node Biopsy

- 1990: First experience
- 223 patients
- Status of the sentinel lymph node reflects the status of the entire regional lymph node basin.
- False negative rate 1%


Morbidity of SLN Biopsy vs CLND

<table>
<thead>
<tr>
<th>Complications</th>
<th>SLN alone (%)</th>
<th>SLN + CLND (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound separation</td>
<td>0.24</td>
<td>1.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1.08</td>
<td>6.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe infection</td>
<td>0</td>
<td>1.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>0.66</td>
<td>11.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hematoma/seroma</td>
<td>2.31</td>
<td>5.9</td>
<td>0.0002</td>
</tr>
<tr>
<td>Total complications</td>
<td>4.6</td>
<td>23.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


Morbidity of SLN Biopsy vs CLND

<table>
<thead>
<tr>
<th>Location</th>
<th>SLN alone (%)</th>
<th>SLN + CLND (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>2.4</td>
<td>10</td>
<td>0.008</td>
</tr>
<tr>
<td>Axilla - Total complications</td>
<td>4</td>
<td>19.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>0.3</td>
<td>4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Groin - Total Complications</td>
<td>8.1</td>
<td>51.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>1.5</td>
<td>31.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Multicenter Selective Lymphadenectomy Trial (MSLT-1)

- WLE + Observation vs. WLE + SLN biopsy with immediate lymphadenectomy if the node was positive
- Mean 10 yr disease-free survival was significantly better in SLN group for patients with intermediate thickness and thick melanomas
- Patients in the SLN group with intermediate thickness melanomas and nodal metastasis experienced a better 10 yr distant disease-free survival and melanoma-specific survival.
- Sentinel node status is the strongest prognostic indicator


Risk of Positive SLN

<table>
<thead>
<tr>
<th>Thickness (mm)</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thinf:&lt;0.75</td>
<td>Rare</td>
</tr>
<tr>
<td>Thinf:0.75-1.0</td>
<td>5</td>
</tr>
<tr>
<td>Intermediate: 1-4</td>
<td>8-30 (risk increases with increasing thickness)</td>
</tr>
<tr>
<td>Thick:&gt;4</td>
<td>40 (also at risk of systemic spread)</td>
</tr>
</tbody>
</table>

The Role of SLN for Thin Melanomas

- <0.75mm
  - 2.7% positive SLN
- 0.75-1mm
  - 6.2% positive SLN

- High-risk features
  - Ulceration
  - Mitotic rate 1/mm² or greater
  - Clark level IV/V

Who Should Have a Sentinel Lymph Node Biopsy?

<table>
<thead>
<tr>
<th>Breslow depth</th>
<th>SLN biopsy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>No</td>
</tr>
<tr>
<td>&lt;= 0.75 mm thick</td>
<td>Consider if high-risk features are present</td>
</tr>
<tr>
<td>0.76-1 mm</td>
<td>Consider if no high-risk features</td>
</tr>
<tr>
<td>1 mm or greater</td>
<td>Offer if high-risk features are present</td>
</tr>
</tbody>
</table>

Positive Sentinel Lymph Node

• 18% of patients will have additional positive nodes
  – Size of SLN metastasis
  – Distribution of metastasis in the SLN (subcapsular vs. parenchymal)
  – Number SLN involved
  – Tumor thickness and ulceration


Multicenter Selective Lymphadenectomy Trial (MSLT-II)

• Prospective, randomized trial
• Compares patients with sentinel lymph node metastases to undergo immediate completion lymph node dissection vs nodal basin ultrasound surveillance.

• Closed to accrual
• Estimated completion date: 2022
Summary of the Initial Surgical Management of Patients with Melanoma

- History and Physical with special emphasis on nodal basins
- Wide local excision
  - Should NOT be performed prior to the sentinel lymph node biopsy if indicated
- Sentinel lymph node biopsy when appropriate
- Completion lymph node dissection if the sentinel lymph node is positive

Principles of Complete Lymph Node Dissection

- Anatomically complete dissection of involved nodal basin
- In the groin consider elective iliac and obturator lymph node dissection if clinically positive inguinal nodes or >=3 inguinal nodes are positive
- Iliac and obturator lymph node dissection is indicated if pelvic CT is positive or if Cloquet’s node is positive
- For primary melanomas of the head and neck with clinically or microscopically positive lymph nodes in the parotid gland, a superficial parotidectomy and appropriate neck dissection of draining nodal basins is recommended.

Follow up and Surveillance

- Melanoma in situ or <1mm thick
  - Skin exam every 6 months for 2 years, annually thereafter
- 1-4 mm thick with a negative sentinel lymph node or thin melanoma with high-risk features
  - Skin and nodal exam every 3-4 months x 3 years, every 6 months during years 3 and 4, annually thereafter
  - CT and LDH
- Stage III disease
  - PET scan or CT is performed prior to completion lymph node dissection
  - Consider CT or PET every 6-12 months
  - MRI brain
- Medical oncology referral when appropriate
Principles of Excision

- Obtain histologically negative margins
- NCCN Recommendation: Every effort should be made to perform SLNB prior to definitive excision
  - Wide excision with 1-2 cm margins
  - May consider Mohs techniques if they do not interfere with SLNB
- Reconstruction involving extensive undermining of tissue should be delayed until margins are verified and SLNB is performed
- If adjuvant radiation is planned, minimize extensive tissue movement to expedite initiation of radiation therapy.
Other Skin Cancers

- Dermatofibrosarcoma protuberans
- Cutaneous leiomyosarcoma
- Squamous cell carcinoma

Thank you!!

- Christine.Landry@Baylorhealth.edu