Surgical Treatment of Melanoma Across the Disease Spectrum: Standards of Care and Evolving Paradigms

Merrick Ross, M.D.
Professor of Surgical Oncology
M.D. Anderson Cancer Center
Surgical Treatment of Melanoma Across the Disease Spectrum

Topics

• Stage I and II
  - SLN biopsy

• Stage III
  - completion dissection?
  - neo-adjuvant strategies for advanced nodal disease

• Stage IV
  - metastasectomy in the new melanoma landscape
The New Melanoma Landscape

- Recently approved systemic therapies for Stage IV
  - **B-Raf mutant**: Vemurafenib, dabrafenib, trametinib, dabrafenib / trametinib
  - Ipilimumab, anti-PD-1, (combination of anti-CTLA4 / anti-PD-1)
- Survival rates of resected Stage IV disease
- Novel intralesional agents (oncolytic immunotherapy)
- **Integration of Sentinel Lymph Node (SLN) biopsy**
  - the new Stage I / II disease
  - the new Stage III disease
Stage I and II Primary Melanoma

Components of Treatment

1. Wide excision
   - margins appropriate for thickness
   - reconstruction

2. Sentinel Node Biopsy
   - indications
   - technique
Lymph Node Involvement and Melanoma

- Regional nodes, most common site of first recurrence after wide excision of primary melanoma
  - 15%–50% chance for in-basin failure after dissection
  - > 50% chance for distant relapse
Sentinel Lymph Node Biopsy
Sentinel Node Biopsy
Goals

- Minimally invasive approach to nodal staging
- Improve the disease outcome for the node positive patients
  - survival
  - regional control

*Prevent the development of clinical nodal involvement*
Regional Control?
## Risk Factors for Regional Recurrence After Surgery Alone

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regional Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuhrmann, 2001</td>
<td>28%</td>
</tr>
<tr>
<td>Kretschmer, 2001</td>
<td>34%</td>
</tr>
<tr>
<td>Lee, 2000</td>
<td>30%</td>
</tr>
<tr>
<td>Shen, 2000</td>
<td>14%</td>
</tr>
<tr>
<td>Hughes, 2000</td>
<td>25%</td>
</tr>
<tr>
<td>Monsour, 1993</td>
<td>52%</td>
</tr>
<tr>
<td>Miller, 1992</td>
<td>12%</td>
</tr>
<tr>
<td>O’ Brien, 1991</td>
<td>24%</td>
</tr>
<tr>
<td>Calabro, 1989</td>
<td>17%</td>
</tr>
<tr>
<td>Bowsher, 1986</td>
<td>15%</td>
</tr>
<tr>
<td>Byers, 1986</td>
<td>16%</td>
</tr>
</tbody>
</table>

Weighted average:

$$\text{Weighted average:} \quad \frac{692 \text{ failures}}{3350 \text{ patients}} = 21\%$$
## Risk Factors for Regional Recurrence After Surgery Alone

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Regional Failure Rate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracapsular extension</td>
<td>31% - 63%</td>
<td>Lee, Calabro, Shen, Monsour</td>
</tr>
<tr>
<td>$\geq 4$ involved lymph nodes</td>
<td>22% - 63%</td>
<td>Lee, Calabro, Miller, Kretschmer</td>
</tr>
<tr>
<td>Lymph node $\geq 3$ cm</td>
<td>42% - 80%</td>
<td>Lee</td>
</tr>
<tr>
<td>Cervical lymph node location</td>
<td>33% - 50%</td>
<td>Lee, Bowsher, Monsour</td>
</tr>
</tbody>
</table>

30%–50% if high-risk features present
In-Basin Failure

Selective Lymphadenectomy vs ELND (Node Positive Only)

<table>
<thead>
<tr>
<th>% Nodal Failure</th>
<th>ELND</th>
<th>SLN</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>Slingluff, 1997</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>MDACC Study, 2003</td>
<td></td>
</tr>
</tbody>
</table>

MDACC Study, 2003
Does early treatment of lymph node disease improve survival?

Microscopic

Macroscopic
MSLT I: Trial Design

Melanoma ≥1 mm or ≥ Clark IV

Randomization

Wide excision alone 40% 60% Wide excision + SLN

SLN +

Occult Stage III

CLND for Recurrence Immediate CLND

SLN -

DSS: Primary Endpoint
DFS: Secondary Endpoint

No recurrence: observation

Observation
## Melanoma Specific Survival – Node+

Final Dataset (intent to treat)

<table>
<thead>
<tr>
<th>Group</th>
<th># Event / Total N</th>
<th>Estimate S(t) ± SE % 5-year</th>
<th>Estimate S(t) ± SE % 10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBS, had nodal recur.</td>
<td>48/87</td>
<td>57.5 ± 5.4</td>
<td>41.5 ± 5.6</td>
</tr>
<tr>
<td>SNB+</td>
<td>70 / 193</td>
<td>69.8 ± 4.4</td>
<td>62.1 ± 4.8</td>
</tr>
</tbody>
</table>

- **HR**: 0.56
- **95% C.I.** (0.37 - 0.84)
- **Log Rank P=0.006**
Unraveling Heterogeneity of Stage I/II Melanoma

5-Year Survival Rate by T-Classification System

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td></td>
<td>95 ± 0.4</td>
<td>97 ± 1.1</td>
</tr>
<tr>
<td>T1b</td>
<td>&gt;</td>
<td>91 ± 1.0</td>
<td>95 ± 1.5</td>
</tr>
<tr>
<td>T2a</td>
<td>&gt;</td>
<td>89 ± 0.7</td>
<td>95 ± 0.6</td>
</tr>
<tr>
<td>T2b</td>
<td>&gt;</td>
<td>77 ± 1.7</td>
<td>86 ± 2.0</td>
</tr>
<tr>
<td>T3a</td>
<td></td>
<td>79 ± 1.2</td>
<td>85 ± 1.5</td>
</tr>
<tr>
<td>T3b</td>
<td>&gt;</td>
<td>63 ± 1.5</td>
<td>76 ± 2.5</td>
</tr>
<tr>
<td>T4a</td>
<td></td>
<td>67 ± 2.4</td>
<td>76 ± 3.6</td>
</tr>
<tr>
<td>T4b</td>
<td></td>
<td>45 ± 1.9</td>
<td></td>
</tr>
</tbody>
</table>

*Stage-appropriate use of SLN biopsy
SLN Biopsy
Multi-Disciplinary Components

• Pre-operative lymphoscintigraphy
  - accurate technique
  - accurate reading
  - surgeon to look at images

• Surgical approach
  - injection of radio-colloid and blue dye
  - removal of all SLN’s
  - images in the room

• Pathological evaluation
  - serial sections and immuno-stains
Constellation of Node Positive Disease

New Stage IIII
AJCC Stage III 5-Year Survival by Tumor Burden, # of Nodes, and Primary Tumor Ulceration

<table>
<thead>
<tr>
<th>Ulceration</th>
<th>No. of Nodal Micrometastases (+/- SE)</th>
<th>No. of Nodal Macrometastases (+/- SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>1 81.5±1.73.2±3.38.0±8.51.6±7.46.6±7.45.4±9.</td>
<td>1 51.6±7.46.6±7.45.4±9.</td>
</tr>
<tr>
<td></td>
<td>(777) (246) (46) (75) (67) (50)</td>
<td>(75) (67) (50)</td>
</tr>
<tr>
<td>Present</td>
<td>56.6±2.953.9±4.234.0±8.349.4±6.237.7±6.229.2±6.7</td>
<td>49.4±6.237.7±6.229.2±6.7</td>
</tr>
<tr>
<td></td>
<td>(531) (223) (49) (88) (93) (68)</td>
<td>(88) (93) (68)</td>
</tr>
</tbody>
</table>

Balch, Gershenwald, Soong et al., J Clin Oncol, May 2010
7th ed. AJCC Database - Regional LN Paradigm Shift

- Macroscopic: 19% (N=560)
- Microscopic: 81% (N=2334)
Incidence of Positive SLN: AJCC Stage Grouping

Consensus Threshold: 5%-8%
Stage III (Sentinel node positive) 

Consider baseline imaging for staging (category 2B) and to evaluate specific signs or symptoms (CT, PET/CT, MRI) 

Complete Lymph node dissection
Rationale for CLND

- Probability of + NSLN (Staging)
- Improved regional control
- Improved survival
- Less morbidity
Only patients with non-sentinel lymph node involvement can derive benefit from CLND
10%-20% have additional nodes involved by routine histology

A selective approach to completion dissection is rational!

Assessment of risk for non-sentinel node metastases
CLND for melanoma

Completion LND - positive NSLN

- The strong independent prognostic significance of a positive NSLN has been confirmed by four separate studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># + NSLN</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghaferi</td>
<td>2009</td>
<td>71</td>
<td>1.92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weiner</td>
<td>2010</td>
<td>60</td>
<td>1.76</td>
<td>0.03</td>
</tr>
<tr>
<td>Brown</td>
<td>2010</td>
<td>51</td>
<td>2.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pasquali</td>
<td>2014</td>
<td>353</td>
<td>1.34</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- CLND is a great (though very expensive and morbid) staging tool.
CLND for melanoma

Completion LND - positive NSLN

All patients

Two nodes positive only

Ariyan C, Ann Surg Oncol 2009; 16(1):186
CLND for melanoma

Clinical equipoise: Prevailing practice

• A review of the NCDB identified 2942 melanoma patients with a positive sentinel node treated 2004-2005.
• Only half of these patients went on to completion lymph node dissection.
• Predictors of CLND included treatment at an NCI designated cancer center, non lower extremity primary tumors, and age < 75.

What is the fractional benefit of the CLND above what is achieved by just removing the involved SLN(s)?
Patients with MM $\geq 1\text{mm}$ ($n=4650$)

- SLNB
  - SLNB positive ($n=930$)
  - SLNB negative ($n=3720$)

Exclusion criteria
- Patients refusal

Randomization ($n=558$)

Follow-up

Arm A: Observation* ($n=279$)

Radical Lymphadenectomy and Follow-up* ($n=279$)

German Trial Design (DeCOG-SLT)
Melanoma - specific survival

Arm A: 84.3% (78.8%; 89.8%)
Arm B: 82.7% (76.6%; 88.8%)

HR (Arm B vs. Arm A) 1.01 (0.64; 1.59)  
p=0.98

Leiter, ASCO 2015

DeCOG study – secondary endpoint
<table>
<thead>
<tr>
<th>Tumor load</th>
<th>Arm A (Observation) N = 233</th>
<th>Arm B (Radical LAD) N = 240</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SN per patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>158</td>
<td>174</td>
<td>0.124</td>
</tr>
<tr>
<td>2 - 3</td>
<td>67</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>&gt; 3</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Histological criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;E positive</td>
<td>144</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Immunhisto. pos. (S100, HMB45, Melan A)</td>
<td>73 31.3%</td>
<td>77 32.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 6.9%</td>
<td>23 9.6%</td>
<td></td>
</tr>
<tr>
<td>not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Size of metastases in the SLN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single cells / &lt;0,5 mm</td>
<td>76 32.6%</td>
<td>68 28.3%</td>
<td>0.276</td>
</tr>
<tr>
<td>0,5 - 1,00 mm</td>
<td>82 35.2%</td>
<td>85 35.4%</td>
<td></td>
</tr>
<tr>
<td>1,01 - 2,00 mm</td>
<td>43 18.5%</td>
<td>48 20.0%</td>
<td></td>
</tr>
<tr>
<td>2,01 - 5,00 mm</td>
<td>12 5.2%</td>
<td>11 4.6%</td>
<td></td>
</tr>
<tr>
<td>5,01 - ...mm</td>
<td>4 1.7%</td>
<td>3 1.3%</td>
<td></td>
</tr>
<tr>
<td>others</td>
<td>16 6.9%</td>
<td>25 10.4%</td>
<td></td>
</tr>
</tbody>
</table>

64-68% of Pts with ≤ 1mm of SLN tumor burden
CLND for melanoma

Clinical equipoise: MSLT-II trial

Positive SLN
N=1755

Stratify by extent of nodal involvement

Completion LND

Observation

Therapeutic LND

Observation (with nodal basin U/S)

Nodal recurrence only
No nodal recurrence only

Observation

IRB 09-112
Nodal Basin Control According to Randomized Treatment Arm

Cumulative Incidence of Nonsentinel-Node Metastasis

Years after Randomization

Observation
Dissection
Overall Melanoma-Specific Survival According to Treatment Arm

![Graph showing survival rates for melanoma patients under different treatments.]

- **Dissection**
  - At 1 year: 824
  - At 2 years: 759
  - At 3 years: 654
  - At 4 years: 510
  - At 5 years: 389
  - At 6 years: 275
  - At 7 years: 191
  - At 8 years: 128
  - At 9 years: 83
  - At 10 years: 39

- **Observation**
  - At 1 year: 931
  - At 2 years: 856
  - At 3 years: 734
  - At 4 years: 564
  - At 5 years: 425
  - At 6 years: 304
  - At 7 years: 217
  - At 8 years: 151
  - At 9 years: 95
  - At 10 years: 55

**P = 0.55**
Surgical Morbidity of Lymphadenectomy
Microscopic vs Palpable disease (MSLT-1)

• Compared morbidity of formal dissection in node positive patients
  - SLN positive vs delayed for palpable nodal disease

• Hospital stay
  - shorter for SLN positive patients

• Symptomatic lymphedema
  - less in SLN positive group, 12% vs 20%, p=.04

Reasons for CLND after Positive SLNBx

- complete staging
  - need 2 positive nodes for high priority adjuvant trial of Anti-PD-1 vs IFN
  - number of + nodes and presence of non-SLN involvement prognostic

- Improved regional disease control and less post-dissection morbidity for patients with non-sentinel node involvement
Completion Node Dissection

Conclusions

• No direct evidence that CLND provides a survival benefit

• SLN biopsy may be therapeutic for the patients with only SLN disease (80% of the SLN+ patients)

• Prognosis in patients with non-SLN involvement is particularly unfavorable

• A selective approach based on predicted risk of non-SLN involvement is rational

• Improved regional disease control and accurate staging may be the only benefits of CLND
## Working Model
### Predicting Risk for Additional Positive Nodes

<table>
<thead>
<tr>
<th>Score*</th>
<th>No. of pts in group</th>
<th>No. additional pos LN</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-2</td>
<td>126</td>
<td>5</td>
<td>126</td>
<td>4.0</td>
</tr>
<tr>
<td>3-4</td>
<td>126</td>
<td>28</td>
<td>126</td>
<td>22.0</td>
</tr>
<tr>
<td>5+</td>
<td>30</td>
<td>14</td>
<td>30</td>
<td>46.7</td>
</tr>
</tbody>
</table>

*Score = sum of
Breslow thickness (0 or 1 for ≤ 2 mm or > 2 mm, respectively),
SLN focus (0, 1, 2, or 3 for ≤ 0.5, >0.5 and ≤ 2, >2 and ≤ 10, or > 10 mm, respectively)
Number of SLNs harvested (0, 1, or 2 for ≥ 3, 2, or 1 respectively)
Melanoma

**CLINICAL/PATHOLOGIC STAGE**

- Stage III (Sentinel node positive)

**WORKUP**

- Consider baseline imaging for staging (category 2B) and to evaluate specific signs or symptoms (CT scan, PET/CT, MRI)

**PRIMARY TREATMENT**

- Discuss and offer complete lymph node dissection
Spectrum of Advanced Disease

• Nodal disease (Stage IIIb/c)
  - with or without known primary
  - resectable vs “unresectable”

• Limited local/satellite/intransit metastases
  - stage IIIb: intransit only
  - stage IIIc: with nodes

• Resectable (oligometastatic) stage IV disease
Resectable Stage III and Selected Oligometastatic Stage IV Melanoma

Standard of care

- Upfront Surgery
- Selective use of adjuvant nodal basin irradiation (stages III b/c)
- Systemic adjuvant therapy
  - resected stage III: interferon, ipilimumab, or clinical trial
  - resected stage IV: clinical trial or observation
Advanced Stage III Melanoma Management Goals

• Durable Local/Regional Control
  - long term survival
  - palliation (expectant palliation)
  - minimize morbidity and functional deficits

• Reduce the risk for distant failure
Stage III patients have a high risk of recurrence after upfront surgery—70%.

Adjuvant therapy options are not optimal: controversy with high dose interferon, peg-intron and high dose ipilimumab.

Nodal basin irradiation has significant risk of lymphedema.

Delay in the treatment of the micrometastatic disease.
Neoadjuvant Therapy → Surgery → Adjuvant Therapy

Potential Advantages

• Tumor shrinkage → Decreased surgical morbidity
  - better regional disease control
  - avoid the morbidity of adjuvant XRT

• Destruction of micro-metastases → Prevent distant disease spread

• Objective measure of patient’s response to therapy → Personalization of adjuvant therapy

• Potential pathway for new drug evaluation/registration
Adjuvant therapy

Targeted Therapy

Immunotherapy

Pre-1998
1998-2011
2011-2015

Approvals w/o (+) randomized trials
No approvals
Approvals: 10 for metastatic disease, 2 adjuvant

1996 HD Interferon

1975 DTIC
1998 HD-IL2

2011
2012
2013
2014
2015

Ipilimumab

Peg IFN

Dabrafenib
Trametinib
Dabrafenib
Ipilimumab
Nivolumab
Nivolumab
Ipilimumab

Vemurafenib

Trametinib

Pembrolizumab

Vemurafenib

Bio-chemotherapy

US approval for metastatic disease,
adjuvant timeline

Personalizing clinical management & understanding/overcoming resistance
Poor Outcomes for Clinical Stage III Melanoma

8th Edition AJCC Draft

Clinical Stage IIIIC MDACC Historical Controls (n=144)
SOC: Surgery +/- Adjuvant

Activity of Dabrafenib + Trametinib in Stage IV

- 617 patients, median PFS 11.1 months, median OS 25.6 months
- Overall response rate 67%, Disease control rate 91%
  - Very favorable outcomes in patients that achieved a CR (16%)
  - Best predictors of CR: ↓ Sum of diameters & < 3 metastatic sites

Hypothesis: More frequent CRs and durable responses in Stage III

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>OS rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>CR</td>
<td>100</td>
<td>95% (91–99)</td>
</tr>
<tr>
<td>PR</td>
<td>316</td>
<td>83% (79–88)</td>
</tr>
<tr>
<td>SD</td>
<td>150</td>
<td>51% (43–60)</td>
</tr>
<tr>
<td>PD</td>
<td>35</td>
<td>38% (25–59)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>16</td>
<td>14% (2–86)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>PFS rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>CR</td>
<td>100</td>
<td>90% (84–96)</td>
</tr>
<tr>
<td>PR</td>
<td>316</td>
<td>51% (46–57)</td>
</tr>
<tr>
<td>SD</td>
<td>150</td>
<td>21% (15–30)</td>
</tr>
<tr>
<td>PD</td>
<td>35</td>
<td>0%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>16</td>
<td>25% (5–100)</td>
</tr>
</tbody>
</table>

Long et al, Lancet Oncology, In Press
Case Example (1)

- 47 yo female with prior hx of R arm melanoma presented with bulky adenopathy in R axilla (? resectable). Biopsy - melanoma (BRAF mut)
- Treated with neoadjuvant BRAF/MEKi x 8 weeks with excellent radiologic response
  
  Path = fibrosis, no viable tumor cells (pCR)

October 2013 (Pre-BRAF/MEKi)  
December 2013 (Post-BRAF/MEKi)
Lymph node with extensive fibrosis and melanin deposition in the extracapsular tissue
Neoadjuvant BRAF and MEK Inhibition

Neoadjuvant and Adjuvant Dabrafenib and Trametinib Compared to Upfront Surgery in Patients With Clinical Stage III or Oligometastatic Stage IV Melanoma (Combi-Neo)

Phase 2 Randomized Trial vs Standard of Care of Surgery + Adjuvant
Patients with stage IIIB/IIIC or oligometastatic stage IV (<3 lesions), + BRAF mutation

**Arm A**
Upfront surgery

Scheduled within 0-4 weeks

Surgical resection

Standard of care adjuvant therapy (interferon vs. observation)

Pathologic assessment of tumor + research biopsy

Assess relapse-free survival, overall survival, toxicity

**Arm B**
Neoadjuvant BRAFi/MEKI

Neoadjuvant BRAF/MEK x 8 weeks

Restaging via CTs followed by surgical resection

Adjuvant BRAF/MEK x 44 weeks

Clinical and radiographic follow up

**Clinical and radiographic follow up**

Blood draw and tumor biopsy

Pre-treatment

On treatment biopsy / blood draw (arm B only)

Blood draw and tumor biopsy at surgery

Restaging CT scans every 3 months with blood draws

Blood draw and tumor biopsy at relapse

Clinical and radiographic follow up

Pathologic assessment of tumor + research biopsy

Assess relapse-free survival, overall survival, toxicity

n=28

n=56
Excellent Responder: 79% decrease by RECIST and Pathologic CR

Poor Responder: 23% decrease by RECIST and viable tumor at surgery
Neoadjuvant and Adjuvant D+T Significantly Improved RFS over SOC

HR 60.2
95% CI (6.7-7965)
P<0.0001
Patients with pCR had improved RFS compared to those without pCR.
Neoadjuvant and Adjuvant Checkpoint Blockade in Patients With Clinical Stage III or Oligometastatic Stage IV Melanoma (NCT02519322)

Nivolumab vs Ipi / Nivo

Phase 2 randomized trial
Tumor Burden Change From Baseline from CheckMate-067

NIVO + IPI
Median change: -51.9%

NIVO
Median change: -34.5%

IPI
Median change: +5.9%

Confirmed responder
30% reduction in tumor burden by RECIST v1.1

Presented by J. Wolchok ASCO 2015
Patients with stage IIIB/IIIC or oligometastatic stage IV (≤3 lesions)

Randomize 1 nivo:1 ipi/nivo
Stratified by Stage (IIIB/IIIC/M1A vs M1B/M1C) and PDL1 status

Arm A
Neoadjuvant Nivolumab (4 doses)

Restaging via CTs followed by surgical resection

Follow up with restaging q 12 weeks x 2 years

Adjuvant Nivolumab x 6 months

Pathologic assessment with correlative studies

Arm B
Neoadjuvant Ipilimumab & Nivolumab (3 doses)

Restaging via CTs followed by surgical resection

Follow up with restaging q 12 weeks x 2 years

Adjuvant Nivolumab x 6 months

2015-0041: Neoadjuvant Checkpoint

n=20

On treatment biopsy / blood draw (prior to dose 2 and dose 3)

Blood draw and tumor biopsy Pre-treatment

Blood draw and tumor biopsy at relapse

Restaging CT scans q 12 weeks

Research blood draws

Follow up with restaging q 12 weeks x 2 years

n=20
Intralesional Therapy (Oncolytic Immunotherapy): Goals

• Locally ablative therapy for local disease control
  – High, local concentration
  – Palliation/symptom control

• Induction of systemic host immune antitumor activity
  – Augment the local injected response
  – Response in distant and uninjected regional metastases
  – Systemic adjuvant response (treat micrometastases)
  – Limited systemic toxicity
  – Durable response
Drug Agencies in US and Europe Approve T-VEC

October 27, 2015

- T-VEC: US approval for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

December 16, 2015

- T-VEC: EU approval for Stages III B, IIIC, IVM1a metastatic melanoma
Lesion-level and patient-level responses to T-VEC

Lesion type: injected

Lesion type: uninjected non-visceral

Lesion type: uninjected visceral

Percentage Change From Baseline

Tumor area change: ≥ 25%  > -50% to < 25%  -100% to ≤ -50%

To be included in the lesion-level response analysis, lesions were required to have at least 2 measurements. For the patient-level response analysis, only patients with at least 1 lesion represented in the corresponding waterfall plot were included. Responses were per investigator.

T-VEC Responses in Injected And Uninjected Lesions

Cycle 1

Cycle 13
**Primary overall survival**

<table>
<thead>
<tr>
<th>Survival</th>
<th>T-VEC</th>
<th>GM-CSF</th>
<th>Difference % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-mo</td>
<td>73.7%</td>
<td>69.1%</td>
<td>4.6 (-4.7, 13.8)</td>
</tr>
<tr>
<td>24-mo</td>
<td>49.8%</td>
<td>40.3%</td>
<td>9.5 (-0.5, 19.6)</td>
</tr>
<tr>
<td>36-mo</td>
<td>38.6%</td>
<td>30.1%</td>
<td>8.5 (-1.2, 18.1)</td>
</tr>
<tr>
<td>48-mo</td>
<td>32.6%</td>
<td>21.3%</td>
<td>11.3 (1.0, 21.5)</td>
</tr>
</tbody>
</table>

Events/N (%)

<table>
<thead>
<tr>
<th></th>
<th>Medians (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-VEC</td>
<td>189/295 (64) 23.3 (19.5, 29.6)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>101/141 (72) 18.9 (16.0, 23.7)</td>
</tr>
</tbody>
</table>

HR = 0.79 (95% CI: 0.62, 1.00)

Unadjusted log-rank P = 0.051


HR, hazard ratio.
Exploratory OS subgroup analysis by disease stage

Stage IIIB/C, IV M1a

HR: 0.57 (95% CI: 0.40, 0.80)
Log rank: P < 0.001 (descriptive)

Stage IV M1b/c

HR: 1.07 (95% CI: 0.75, 1.52)
Log rank: P = 0.71 (descriptive)
Neo-Adjuvant T-VEC

- Resectable stage IIIb/c and M1a, N=150

- Randomized phase 2 trial of standard of care upfront surgery + adjuvant vs pre-op T-VEC 12 weeks followed by surgery

Combination Trials of Oncolytic Immunotherapy and Anti-CTLA-4 or Anti-PD-1 are ongoing
Neoadjuvant Therapy for Advanced Resectable Melanoma
Where are we Now and Where are we Going?

- A growing international interest has emerged in designing and completing neoadjuvant trials
- Ideal model for discovering and validating biomarkers of response and resistance
  - easy access for serial tissue acquisition
- Improved regional disease control and survival outcomes will lead to new treatment paradigms
- Novel combinations to “raise the tail of the curve” in the stage IV setting will be tested in the neoadjuvant setting
- The first International Neoadjuvant Consortium was held in November at the SMR
Surgery for Stage IV Disease

Why?

• Ten new approvals in last 5 years

• Robust response with BRAF inhibition, but not durable

• Low response rate with ipilimumab

• High response rate with combination checkpoint blockade but significant toxicity

• Surgery well tolerated, 100% response rate
Surgery for Stage IV melanoma: Patient selection

• Curative intent
  - *can a complete resection be performed?*
  - symptoms?
  - morbidity of planned surgery?
  - associated co-morbidity?

• Favorable biology?
  - target the right patient population

• Palliation
  - improve quality of life
  - candidates for effective systemic therapy
SWOG S9430: Phase II Trial – Complete Resection for Stage IV Melanoma

- Prospective registry - surgical resection, stage IV
- 1996-2005, 18 centers
- 77 patients enrolled
  - 8 pts: not completely resected to NED
  - 3 pts: no tumor in specimen
  - 2 pts: locoregional disease only
- 64 patients included in primary analysis
  - median age 54y, M:F ≈2:1
  - sites: any visceral, 31%; non-visceral only, 69%
  - >1 site resected, 22%
  - 11 received some type of systemic adjuvant (8 IFN)
- Median RFS, 5mos; median OS, 21mos

Sosman et al., Cancer 2011
SWOG S9430 – Overall Survival
Patients Completely Resected

Sosman et al., Cancer 2011
Canvaxin Stage IV Placebo-Controlled Randomized Trial

- Two sites, 5 nodules, complete resection, no brain mets within 6 months of surgery
- NED based on repeat staging within 45 days of randomization
- Trial stopped by DSMB short of planned accrual April 2005 after 2nd interim analysis
- 38 months median and 40% 5-year survival!