Breaking New Ground: Neoadjuvant Trials in Advanced "Resectable" Melanoma

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MD Anderson Cancer Center
Spectrum of Advanced Disease

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

- Resectable (oligometastatic) stage IV disease
Definition of “Unresectability”

- Categorically / technically unresectable

- “Unresectable”
  - technically resectable
  - but not meaningful in terms of long term survival and regional disease control
Advanced Nodal Disease
Competing Risks

• Development of systemic (stage IV) disease
  - at least 50%
  - may be as high as 80%

• In basin failure
  - source of significant morbidity
  - difficult to treat
  - 20%-50% risk

• Toxicity of therapies

• Underlying co-morbidities
Advanced Stage III Melanoma
Management Goals

• Durable Local/Regional Control
  - long term survival
  - palliation
  - minimize morbidity and functional deficit

• Reduce the risk for distant failure
  - role of adjuvant therapy
Adjuvant Therapy for High risk Melanoma
FDA approvals and published phase III trials

• High dose Interferon (IIb, IIC, IIIa/b/c)
  - RFS benefit, minimal OS
  - high toxicity, long duration

• Pegylated Interferon (IIIa/b/c)
  - RFS only
  - moderate toxicity, longer duration

• Ipilimumab (10mg/kg)
  - modest RFS
  - high toxicity, short without maintenance

• Biochemotherapy (CVD / IL-2/ IFN)
  - RFS compared to HD IFN
  - high toxicity, shorter duration
Adjuvant Therapy for High risk Melanoma
Completed and future phase III trials

• DERMA Trial
  - Mage A3 ASCI vs placebo
  - stage IIIb/c

• ECOG 1609
  - Ipi (3mg) vs ipi (10mg) vs HD IFN
  - stage IIIb/c, IV m1a/b

• BRAF inhibitors vs placebo

• Anti PD-1 vs HD Interferon (planned to start)
The New / Evolving Landscape of Advanced Melanoma

- Recent approval of BRAF / MEK inhibitors and checkpoint blockade for unresectable stage III and stage IV disease
- Exciting data with combination checkpoint blockade therapy (most active)
- Recently reported randomized trial of Oncolytic Immunotherapy (T-VEC)
Biomarkers for Response and or Efficacy

- BRAF V600E, C-KIT, NRAS
- Ulceration
- Auto-immunity
- PDL-1 expression
- Extent of T cell infiltration
Neo-Adjuvant Therapy for Advanced Stage III and Stage IV Disease

Potential Benefits

• Ability to study tissue samples pre- and post-treatment
  • Biologic correlates/predictors of response & resistance
  • Endpoints: biologic, response rate, % pCR

• Endpoints may be achieved with a small number of patients

  • In-situ marker for response
  • Surgery more effective in the context of tumor responding to systemic therapy
Neo-Adjuvant Experience

• Combination chemotherapy
  - CVD
• Bio-chemotherapy
  - CVD(T), IL-2, Interferon
• High Dose Interferon
• Ipilimumab
Case Example (2)

• 69 yo female presented with bulky adenopathy in R axilla and R neck
• Biopsy showed metastatic melanoma - told by outside oncologist she had 3-6 months to live. Offered palliative radiation.
• Presented to MD Anderson, found to have BRAF mutation. Unresectable at presentation, treated with neoadjuvant BRAF/MEK x 8 weeks
• Re-staged - excellent response

Path = fibrosis, rare viable tumor cells

April 2014 (Pre-BRAF/MEK)

July 2014 (Post-BRAF/MEK)
Prospects for Neo-Adjuvant Approaches
Ipilimumab and Anti-PD-1
Neoadjuvant Trial Concepts

- Identify high risk groups who would be candidates for post-op adjuvant treatment (IIIIB/C and stage IV oligometastatic) - can justify higher toxicity regimens
- Access to tumor before, during, and after treatment
- Designed to have biologic events as primary endpoints (markers of response and resistance) - single arm for bio-marker - randomized phase II
Neoadjuvant Trial Concepts

- Randomized Phase II of Dabrafenib/Trametinib vs SOC (surgery + adjuvant): approved and funded, actively accruing
- Randomized Phase II of Ipi/Nivo vs Nivo alone: approved and funded will open by end of year
- Pembro/Peg intron vs Pembro alone: in development
- Neo-Adjuvant T-VEC will open soon
Patients with stage IIIB/IIIC or oligometastatic stage IV (<3 lesions), + BRAF mutation

**Randomize 2:1**

**BRAF/MEK vs. upfront surgery**

Arm A
Upfront surgery

Scheduled within 0-4 weeks

Surgical resection

Standard of care adjuvant therapy (interferon vs. observation)

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

Assess relapse-free survival, overall survival, toxicity

Pathologic assessment of tumor + research biopsy

**Clinical and radiographic follow up**

Assess relapse-free survival, overall survival, toxicity

**Blood draw and tumor biopsy**

Pre-treatment

On treatment biopsy / blood draw (arm B only)

Restaging CT scans every 3 months with blood draws

Blood draw and tumor biopsy at relapse
Endpoints

• Primary – relapse-free survival (at 1 year)
• Secondary
  - overall survival
  - pathologic complete response rate (pCR)
  - safety of dabrafenib and trametinib in this population
  - biomarkers (tumor-based and blood-based)

Ipilimumab + Nivolumab
Neoadjuvant Trial Concept

Melanoma Medical Oncology and Surgical Oncology
MD Anderson Cancer Center
Winter 2015
Patients with stage IIIB/IIIC or oligometastatic stage IV (<3 lesions), BRAF wt or mutant

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Neoadjuvant Nivolumab (3 doses)</th>
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<tbody>
<tr>
<td></td>
<td>Restaging via CTs followed by surgical resection</td>
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<tr>
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<td>Pathologic assessment with correlative studies</td>
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<td>Adjuvant Nivolumab x 6 months</td>
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<td>Follow up with restaging q 12 weeks</td>
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<table>
<thead>
<tr>
<th>Arm B</th>
<th>Neoadjuvant Ipilimumab &amp; Nivolumab (2 doses)</th>
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<tr>
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<td>Restaging via CTs followed by surgical resection</td>
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<tr>
<td></td>
<td>Adjuvant Nivolumab x 6 months</td>
</tr>
<tr>
<td></td>
<td>Follow up with restaging q 12 weeks</td>
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</tbody>
</table>

Randomize 1 nivo:1 ipi/nivo

n=20

Blood draw and tumor biopsy Pre-treatment

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

Blood draw and tumor harvested at surgery

Restaging CT scans q 12 weeks
With blood draws

Blood draw and tumor biopsy at relapse
Endpoints

• Primary endpoint:
  – Pathologic/biomarker analysis
    • Pathologic markers: residual cancer burden\textsuperscript{1}, % tissue necrosis, quantification of mitotic activity by phosphohistone H3\textsuperscript{2}
    • Immune analyses

• Secondary endpoints: Overall response rate, progression free survival, overall survival, safety analyses

2: Nielsen et al. Mod Pathol 2013; 26: 404-13
Pembrolizumab + Pegylated Interferon Neoadjuvant Trial Concept

Melanoma Medical Oncology and Surgical Oncology
MD Anderson Cancer Center
Patients with stage IIIB/IIIC or oligometastatic stage IV (<3 lesions), BRAF wt or mutant

**Randomization of Pembro alone vs Pembro + Peg**

**Arm A**
Neoadjuvant Pembro (4 cycles)

8 weeks

Restaging via CTs followed by surgical resection

Pathologic assessment with correlative studies

Follow up with restaging q 12 weeks

Adjuvant Pembro x 18 months
Followed by Peg

**Arm B**
Neoadjuvant Peg + Pembro (4 cycles)

8 weeks

Restaging via CTs followed by surgical resection

Adjuvant ?

Follow up with restaging q 12 weeks

**Follow up with restaging q 12 weeks**

Blood draw and tumor biopsy
Pre-treatment

On treatment biopsy / blood draw (prior to dcycle 3)

Blood draw and tumor harvested at surgery

Restaging CT scans q 12 weeks
With blood draws

Blood draw and tumor biopsy at relapse

N=?
Endpoints

• Primary endpoint:
  – Pathologic response/biomarker analysis
    • Pathologic markers: residual cancer burden\(^1\), % tissue necrosis, quantification of mitotic activity by phosphohistone H3\(^2\)
    • Immune analyses: see proposal for full details (done with J Wargo in collaboration with P Sharma and J Allison)

• Secondary endpoints: Overall response rate, progression free survival, overall survival, safety analyses, change in PDL-1 expression and correlation with response
Neo-Adjuvant T-VEC

- OPTiM trial met primary endpoint of DR
- Borderline OS endpoint secondary endpoint
  - subset of Stage IIIb/c and M1a OS advantage
- Resectable stage IIIb/c and M1a

- Randomized phase 2 of surgery followed by adjuvant vs pre-op T-VEC 12 weeks

T-VEC Responses in Injected And Uninjected Lesions
Primary overall survival

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<tr>
<th>Events/N (%)</th>
<th>Median (95% CI), months</th>
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<tr>
<td>T-VEC</td>
<td>189/295 (64)</td>
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<tr>
<td>GM-CSF</td>
<td>101/141 (72)</td>
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HR = 0.79 (95% CI: 0.62, 1.00)  
Unadjusted log-rank P = 0.051

Patients at risk:

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<thead>
<tr>
<th>T-VEC</th>
<th>GM-CSF</th>
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<tr>
<td>295</td>
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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)

Treatment Strategies for Advanced Melanoma

Take Home Messages

- Multi-disciplinary input is critical
- Initial therapy should not be recommended in isolation, but as part of a comprehensive plan
- Combinatory strategies are rational and offer the promise of future advancement
- Neoadjuvant trials hold the promise of insights into rational and more personalized treatment strategies