Overall Survival: Metastatic Melanoma
Phase III Studies

1-year OS
25–35%\(^1\)

Ipi
24%\(^2\)
2010

1990

2-year OS
15%\(^1\)

Ipi
29%\(^4\) Ipi\(^a\)
2011

3-year OS
22%\(^3\)

Ipi\(^a\)
2012

4-year OS
30%\(^6\)

5-year OS
18%\(^5\) Ipi\(^a\)
2013

53%\(^11\) Dab + tram
48%\(^12\) Vem + cobi
55%\(^16\) Pembrolizumab
2014

GOAL \(\rightarrow\) NO DEATHS FROM MELANOMA

71%\(^{10}\) Pembrolizumab\(^c\)
74%\(^{11}\) Dab + tram\(^d\)
75%\(^{12}\) Vem + cobi
2015

64%\(^{15}\) Nivo + ipi (ph II)

44%\(^{17}\) Dab + tram
2016

35%\(^9\) Nivo (ph I)

\(\text{© Georgina V Long}\)

\(\text{a. Ipi} + \text{DTIC; b. BRAF WT only; c. Pooled pembrolizumab Q2W and Q3W 10mg/kg; d. Pooled Dab + tram data.}\)

Neoadjuvant Systemic Therapy in Melanoma

Professor Georgina Long
Melanoma Institute Australia
The University of Sydney
Royal North Shore Hospital

Oct 2016
Immune Cycle and Drug Targets

1. Recognize Tumour
   - Presence of antigen
   - APC present
   - Antigen processing & presentation occurs
   - Lack of inhibitors

2. Activation of Immune Cells
   (assume intact immune system)
   - T cells
   - NK Cells
   - T reg
   - Myeloid

3. Move to Target
   - Stroma – permissive (other immune cells, fibroblasts, angiogenesis)
   - Chemoattractants

4. Kill Target
   - Lack of Inhibitors
   - cellular (Treg, myeloid, tumour)
   - chemical (cytokines, IDO, metabolites)

Anti-PD-1

Targeted Therapy

Anti-CTLA4
Immune Cycle and Drug Targets

**Recognize Tumour**
- Presence of antigen
- APC present
- Antigen processing & presentation occurs
- Lack of inhibitors

**Kill Target**
- Cellular (Treg, myeloid, tumour)
- Chemical (cytokines, IDO, metabolites)

**Move to Target**
- Stroma – permissive (other immune cells, fibroblasts, angiogenesis)
- Chemoattractants

**Which combination? In who?**
- TVEC
- Vaccines
- RT
- Sting agonist
- CD137 agonist
- GITR agonist
- CSF1R
- LAG3 inhibitor
- TIM3 inhibitor
- GITR agonist
- TIGIT inhibitor
- IDO inhibitor
- Adenosine 2A receptor inhibitor
Neoadjuvant Model

Stage III Bulky Resectable
✓ Able to have:
  • Two Biopsies
  • Completion Dissection

PRE Bx (multiple core)
Screening 7-14 day
US nodal basin PET/CT

EDT Bx (multiple core)
Day 4-7
DRUG COMBINATION for 6-12 WEEKS
US week 4 and 8
US nodal basin PET/CT

Completion Dissection
Week 6-12
DRUG COMBINATION to 52 WEEKS
3 monthly CT
Endpoints

• Complete Pathological Response Rate
  
  Yet to correlate with the **ONLY** endpoint - Overall Survival

• Relapse Free Survival

• Opportunity Sub-studies
  – Toxicity
**Neoadjuvant Dabrafenib + Trametinib**

**Stage III Bulky Resectable (N=35)**
- BRAF$^{V600}$ mutation
- Able to have:
  - Two Biopsies
  - Completion Dissection

**Primary Endpoint:**
Pathological Response Rate

**Secondary Endpoint:**
- RECIST Response Rate
- RFS, OS
- Correlation of biomarkers with Outcome Endpoints

**Timeline:**
- **PRE Bx (multiple core)**
  - Screening 7-14 day
- **EDT Bx (multiple core)**
  - Day 4-7
- **Completion Dissection**
  - Week 12

**Procedure:**
- US nodal basin PET/CT
- Dabrafenib + Trametinib 52 WEEKS
- US week 4 and 8
- 3 monthly CT
Neoadjuvant Dabrafenib + Trametinib
Week 12 Response (n=19)

Pathological
CR = 47%

RECIST
CR = 47%

PET-FDG
CR = 53%

68% Improved Operability

Saw R et al ASCO 2016
Complete Response: Pathological, RECIST and PET

Baseline

Week 12

SOX 10 (melanoma) Baseline

CD68 (macrophage) Week 12

H&E

H&E

Saw R et al ASCO 2016
## Surgical Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>N= 19, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved Operability</td>
<td>13 (68%)</td>
</tr>
<tr>
<td>Wound Infection (requiring antibiotics)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Seroma (requiring intervention)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>New/Worse Clinical Lymphoedema</td>
<td>5 (26%)</td>
</tr>
</tbody>
</table>

17/19 (89%) Pyrexia or Pyrexia Syndrome
Neoadjuvant Dabrafenib + Trametinib
3/19 Patients Recurred (1 death)

Patient 1 Recurred 24 weeks Local + Distant

Saw R et al ASCO 2016
Neoadjuvant Dabrafenib + Trametinib
3/19 Patients Recurred

Patient 2

Pathological

<table>
<thead>
<tr>
<th>CR</th>
<th>Non-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

RECIST

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

PET-FDG

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9</td>
<td>1</td>
<td>PD</td>
</tr>
</tbody>
</table>

Recurred 48 weeks
Local only

Saw R et al ASCO 2016
Neoadjuvant Dabrafenib + Trametinib
3/19 Patients Recurred

Patient 3

Pathological
- CR
- Non-CR

RECIST
- CR
- PR
- SD
- PD

PET-FDG
- CR
- PR
- SD
- PD

Recurred 53 weeks
Distant Only

Saw R et al ASCO 2016
Baseline T Cell Subsets in Blood

**Progressors**

- CD4+ T cells
- CD8+ T cells
- CD4-/CD8- T cells

**Non-Progressors**

- CD4+ T cells
- CD8+ T cells
- CD4-/CD8- T cells

- TH1
- TH2
- TH17
Immunotherapy
Do we NEED Neoadjuvant Therapy?
## Schedule of immunotherapy and surgery

<table>
<thead>
<tr>
<th></th>
<th>Day 17</th>
<th>Day 19</th>
<th>Day 21</th>
<th>Day 23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NeoAdj clg</strong></td>
<td><img src="img1" alt="Day 17" /></td>
<td><img src="img2" alt="Day 19" /></td>
<td><img src="img3" alt="Day 21" /></td>
<td><img src="img4" alt="Day 23" /></td>
</tr>
<tr>
<td><strong>NeoAdj Txt</strong></td>
<td><img src="img5" alt="Day 17" /></td>
<td><img src="img6" alt="Day 19" /></td>
<td><img src="img7" alt="Day 21" /></td>
<td><img src="img8" alt="Day 23" /></td>
</tr>
<tr>
<td><strong>Adj clg</strong></td>
<td><img src="img9" alt="Day 17" /></td>
<td><img src="img10" alt="Day 19" /></td>
<td><img src="img11" alt="Day 21" /></td>
<td><img src="img12" alt="Day 23" /></td>
</tr>
<tr>
<td><strong>Adj Txt</strong></td>
<td><img src="img13" alt="Day 17" /></td>
<td><img src="img14" alt="Day 19" /></td>
<td><img src="img15" alt="Day 21" /></td>
<td><img src="img16" alt="Day 23" /></td>
</tr>
</tbody>
</table>

Slide courtesy M Teng, QIMR
Neoadjuvant vs Adjuvant anti-PD-1+anti-CD137 therapy:
Superior eradication of 4T1.2 & E0771 metastases

Slide courtesy M Teng, QIMR
Neoadjuvant immunotherapy → strong early expansion & maintenance of tumour-specific CD8+ T cells in blood.
Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab (OpACIN) in Resectable Stage III

N=20

stage III palpable melanoma no in-transit metastases the last 6 months

PBMC tumor biopsy HLA typing PET/CT + CT MRI brain

-4 0 6 12 18 weeks

Adjuvant arm

4x ipi 3mg/kg + nivo 1mg/kg q3wk

Neoadjuvant arm

2x ipi + nivo

2x ipi + nivo

Blank et al ESMO 2016
### Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Adjuvant (n=8)</th>
<th>Neo-adjuvant (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, years, +/-SD</strong></td>
<td>53 +/- 7y</td>
<td>55 +/- 12y</td>
</tr>
<tr>
<td><strong>Sex – male (n)</strong></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>WHO 0 (n)</strong></td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td><strong>No. of BL lymph nodes (median)</strong></td>
<td>2 (1-4)</td>
<td>1 (1-5)*</td>
</tr>
<tr>
<td><strong>Stage IIIB/IIIC (No. of patients)</strong></td>
<td>7/1</td>
<td>7/3</td>
</tr>
<tr>
<td><strong>LDH normal (n)</strong></td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td><strong>CRP normal (n)</strong></td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td><strong>ALC normal (n)</strong></td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

* based on estimation of pathology report

Blank et al ESMO 2016
### Response To Treatment (Neo-adjuvant Arm Only)

<table>
<thead>
<tr>
<th>Pat ID</th>
<th>Courses</th>
<th>Radiologic response (CT scans, mm)</th>
<th>Pathologic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>2</td>
<td>31 x 50 → 18 x 31</td>
<td>pCR</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>23 x 36 → 17 x 23 &amp; 22 x 24 → 9 x 12</td>
<td>pCR</td>
</tr>
<tr>
<td>19</td>
<td>2</td>
<td>24 x 40 → 19 x 24</td>
<td>pCR</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>22 x 40</td>
<td>(&lt;1mm)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>21 x 47</td>
<td>(0.5mm)</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>9 x 10</td>
<td>(sporadic tumor cells)</td>
</tr>
<tr>
<td>14</td>
<td>4</td>
<td>18 x 19, 25, 37, ND</td>
<td>micrometastasis (sporadic tumor cells)</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>28 x 40</td>
<td>micrometastasis of 9mm within 33mm metastasis (75% necrosis)</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>22 x 40</td>
<td>LNs 35mm, 2mm, 1mm, 0.5mm, 0.1mm</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>11 x 18 → 17 x 25</td>
<td>LNs 30mm, 13mm, 6.0mm, 3.5mm</td>
</tr>
</tbody>
</table>

**Pathological CR 30%**

**Relapse:**
- 2 Neoadjuvant Arm (SD)
- 3 Adjuvant Arm

Blank et al ESMO 2016
## Immunotherapy Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades (n)</th>
<th>Grade 3/4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Elevated Lipase</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Adrenal Insufficiency</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

16/18 Grade 3/4
6/18 recovered
12/18 ongoing – 8 endocrinopathies

Blank et al ESMO 2016
AJCC Melanoma Staging 8th Edition

Melanoma Specific Survival Stage III Melanoma

Gershenwald-Scolyer AJCC 8th Edition

Stage, 5 yr OS

IIIA, 93%
IIIB, 83%
IIIC, 69%
IIID, 32%
OpACIN-NEO

stage III measurable melanoma
no in-transit metastases the last 6 months

R

2x ipi 3mg/kg + nivo 1mg/kg q3wk

2x ipi 1mg/kg + nivo 3mg/kg q3wk

surgery

2 x ipi 3mg/kg

2x nivo 3mg/kg

PBMC

PBMC tumor biopsy
HLA typing
PET/CT + CT
MRI brain

PBMC

PBMC

PBMC

PBMC CT or PET/CT

weeks

-4
0
3
6
12
Targeted Therapy  Immunotherapy
BRAF inhibition

CD8

CD4

BASELINE

Responding Day 7

Melanoma Ag ↑

Progression

Melanoma Ag ↓

J Wilmott, G V Long & R A Scolyer CCR 2012
Frederick-Wargo CCR 2013
*Wilmott et al I immun 2013
Favorable T cell ratios with BRAFi/MEKi (Early-During Treatment Biopsies)

Slide Courtesy C Blank
Combine Or Sequence?
Targeted & Immune Therapies

Targeted Therapy  Immunotherapy

Immunotherapy  Targeted Therapy

SHORT

©Georgina V Long
Neoadjuvant Sequencing Study

For all 3 study arms:

Stage III resectable melanoma
V600 BRAF mutation
N=60

= Anti PD1 pembrolizumab IV 2mg/kg
(Q3W from week 12-52 in all arms)

G V Long MIA
Clinical Trials App

ClinicalTrials Refer Melanoma
Conclusions

• D+T $\rightarrow$ 50% pCR, Improved Surgery
• Ipi+Nivo $\rightarrow$ 20% pCR
• Superior Efficacy vs Adjuvant?
• Translational platform $\rightarrow$ efficient assessment of combinations
Acknowledgements

- Patients and Families
- National and International Colleagues and Scientists working in Melanoma
- Melanoma Institute Australia and Trials Team
  - Maria Gonzales, Tracy Liaw, Maria Cruzado, Kate Willis, Sarah Lane, Libby Emmett, Elizabeth Liniker, Rajat Rai, Ines Silva, Kazi Nahar, Anna Hoadley, Georgia Cairns, Lydia Visintin
  - John Thompson, Robyn Saw, Jonathon Stretch, Andrew Spillane, Kerwin Shannon, Omgo Nieweg, Ken Lee, Sydney Ch’ng
- Australian Genome Project
MIA Surgical Team

Robyn Saw
Omgo Nieweg
Jonathan Stretch
Angela Hong
Dioma Damien
MIA Clinical Trials Team
Translational Research
# AJCC Melanoma Staging 8th Edition

<table>
<thead>
<tr>
<th>When T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the pathological stage group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a/b–T2a</td>
<td>N1a or N2a</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T1a/b–T2a</td>
<td>N1b/c or N2b</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2b/T3a</td>
<td>N1a–N2b</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1a–T3a</td>
<td>N2c or N3a/b/c</td>
<td>M0</td>
<td>IIIC</td>
</tr>
<tr>
<td>T3b/T4a</td>
<td>Any N ≥N1</td>
<td>M0</td>
<td>IIIC</td>
</tr>
<tr>
<td>T4b</td>
<td>N1a–N2c</td>
<td>M0</td>
<td>IIIC</td>
</tr>
<tr>
<td>T4b</td>
<td>N3a/b/c</td>
<td>M0</td>
<td>IIID</td>
</tr>
<tr>
<td>Any T, Tis</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
</tr>
</tbody>
</table>

Gershenwald-Scolyer AJCC 8th Edition