The path forward in immunotherapies- combinations:
But can we afford them?

Prof Grant McArthur
Peter MacCallum Cancer Centre
University of Melbourne
Disclosure Information

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  • Research support from: Pfizer, Celgene & Ventana
  • Consultant: Provectus
Combination approaches to treating melanoma.

BRAF<sup>V600E</sup> → Dabrafenib/Vemurafenib

MEK → Trametinib/Cobimetinib

Melanoma Proliferation & Survival

CTLA-4 Blockade

Dendritic cell → T cell

B7 CD28 + + +

B7 CTLA-4

anti-CTLA-4

PD-1 Blockade

T cell → Tumor cell

TCR MHC

PD-1 PD-L1

PD-1 PD-L2

anti-PD-1
Host and Tumor Cell Intrinsic Biology is Important in Cancer.

McArthur & Ribas, J Clinical Oncology, 2013
Response to BRAF-inhibition

Increase MDA Expression
- gp100
- MART-1
- Tyrosinase

Decrease Immunosuppressive Factors
↓ IL-6
↓ IL-10
↓ TGF-β

PD-L1
TIM-3
Dying Melanoma
Induction of PD-L1 Expression by the EML4-ALK Oncoprotein and Downstream Signaling Pathways in Non–Small Cell Lung Cancer

Keiichi Ota,1 Koichi Azuma,2 Eiji Iwama,1 Taishi Harada,1 Koichiro Matsumoto,1 Shinzo Takamori,3 Masayoshi Kage,4 Tomoaki Hoshino,2 Yoichi Nakanishi,1 and Isamu Okamoto1

1Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 2Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan; 3Department of Surgery, Kurume University School of Medicine, Fukuoka, Japan; 4Department of Diagnostic Pathology, Kurume University Hospital, Fukuoka, Japan;
Clear evidence in cell lines and patients of regulation of PD-L1 expression by EML4-ALK
There is a need to study PD-L1 expression of EML4-ALK tumours to ALK-inhibitors in vivo in patients.
Clear evidence in cell lines and patients of regulation of PD-L1 expression by EML4-ALK
There is a need to study PD-L1 expression of EML4-ALK tumours to ALK-inhibitors in vivo in patients.
Upregulation of PD-L1 and CD8 T-cells in melanoma patients following BRAF inhibition
Clinical Trials of ALK and PD-1/PD-L1 inhibitors are needed

- 4 trials of BRAF/MEK inhibitors and PD-1/PD-L1 inhibitors in melanoma
  - Dabrafenib/Trametinib + Pembrolizumab
  - Dabrafenib/Trametinib + Nivolumab
  - Dabrafenib/Trametinib + MEDI4736
  - Vemurafenib/Cobimetinib + Atezolizumab
Combination approaches in immuno-oncology

CTLA-4 Blockade

PD-1 Blockade
Regulation of the Cancer-Immunity Cycle

Chen D & Mellman I, Immunity, 2013
Types of Toxicity to Oncology Drugs

Conventional toxicity

Immune-related toxicity

Financial toxicity!
Cost of New Melanoma Therapies in the USA - $US

There is strong argument to pay according to effectiveness
Inequities in Access to Cancer Therapies

- **anti-PD-1 for melanoma**
  - Dec 2015

- **PD-1 Monotherapy Reimbursed**
- **PD-1 Monotherapy Access**
- **PD-1 + CTLA-4 Combination**

© 2009 www.outline-world-map.com
Nivolumab + Ipilimumab in Melanoma: PFS (Intent-to-Treat)

### Median PFS, months (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.4)</td>
</tr>
</tbody>
</table>

### HR (99.5% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>vs. IPI</th>
<th>vs. NIVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.74 (0.60–0.92)**</td>
</tr>
<tr>
<td>NIVO</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>IPI</td>
<td>--</td>
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</tr>
</tbody>
</table>

### No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>NIVO + IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>141 months</td>
<td>151</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>65 months</td>
<td>124</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>24 months</td>
<td>54</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>12 months</td>
<td>47</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>6 months</td>
<td>47</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>3 months</td>
<td>47</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>1 month</td>
<td>47</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>0 months</td>
<td>47</td>
<td>24</td>
<td>4</td>
</tr>
</tbody>
</table>

However!

- No overall survival data available in the public domain at this point.
- 55% rate of Grade 3-4 treatment-related adverse events
- Study was designed to compare nivo+ipi toipi but clinically nivo+ipi versus nivo is the relevant comparison.

Wolchok et al, ASCO, 2015
Cost-Effectiveness of Nivolumab in combination with Ipilimumab in patients with unresectable advanced melanoma in Australia

M Bohensky, H Kim, A Gorelik, D Liew

The University of Melbourne
Bristol Myers Squibb Australia
Key findings

• Comparing Nivo+Ipi to Ipi
  • $US38,000 per life year gained
  • $US45,000 per QALY gained

• Within ICER acceptable to NICE/PBAC
  (UK $US45,000 / Aus $US 54,000 )
Limitations

- Clinically, and health economically, the most relevant comparison is nivo + ipi vs nivo.
- Only a model - no overall survival data at this point.
- Model used the relationship between PFS and OS based predominantly on BRAF & MEK inhibitors. IO agents maybe different.
- Details of costings of toxicity not provided to give a clinician confidence of the accuracy.
We need a 6th way to fight cancer: Innovative health econnomics!