Immunotherapy for Metastatic Malignant Melanoma

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Survival in Melanoma by Stage

Stage I (n = 9175)

Stage II (n = 5739)

Stage III (n = 1528)

Stage IV (n = 1158)

THE CASE FOR CANCER IMMUNOTHERAPY

No new truly curative anticancer cytotoxic drug developed in the last 20 years (until recently)

The immune response is designed to identify and disable “escape routes” that cancers employ.
Too many escape routes?

Melanoma is among the most immunogenic of all solid cancers
TUMORS CREATE CHAOS

Disordered
Blood flow and vascular distribution
Stroma and immune milieu

Immune shaping
Create selection pressure so that cancers can evade immune destruction
Malignant “evolution”

Tumors go to great lengths
to evade or subvert the
immune response
Tumors Evade Immune Detection and Destruction

The immune response to tumor cells can be evaded by a number of mechanisms:

- Reduced antigen presentation
- Resistance to T-cell–mediated killing
- T-cell inhibition and anergy (e.g., by upregulation of coinhibitory molecules, including PD-L1)
- Treg-mediated immunosuppression
Cosignaling Molecules Contribute to Immune Regulation

- Cosignaling regulates T-cell activation
  - Signaling via costimulatory molecules (eg, CD28, GITR) promotes T-cell activation
  - Signaling via coinhibitory molecules (eg, PD-1, LAG-3), also termed "immune checkpoints," suppresses T-cell activation
- APCs can express the signaling partners of these costimulatory and coinhibitory molecules and direct T-cell function accordingly
Physiological Roles of Immune Checkpoint Pathways (cont)

CTLA-4 pathway\(^1,2\)
- Inhibits the activation of naïve and memory T cells at the lymph nodes, suppressing broad immune responses throughout the body

PD-1 pathway\(^1,2\)
- Acts at sites of inflammation and tumor immunosuppression, inhibiting tumor-specific immune responses
Metastatic Melanoma: Treatment Advances

Immunotherapy
Target host

Targeted Therapy
Target tumor
Ipilimumab, a CTLA-4 Blocking Monoclonal Antibody, Augments T-Cell Activation

T-cell Activation

T-cell Inactivation

T-cell Remains Active

Ipilimumab

- **CTLA-4 (cytotoxic T-lymphocyte associated antigen 4)**
  - a negative regulator of T cells
- **Ipilimumab:**
  - IgG1 monoclonal Ab
  - Block CTLA-4
  $\Rightarrow$ **Augments T cell activation** and proliferation.
- Allowing the immune system to maintain responsiveness against an antigen
- Overcoming various mechanisms of immune evasion
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O’Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.


Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

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Study 024: Phase III Placebo-Controlled Trial of First-line DTIC ± IPI

**SCREENING**
- Previously untreated, unresectable Stage III or IV melanoma (N = 502)

**INDUCTION**
- Ipilimumab 10 mg/kg q3w x4
  - Dacarbazine 850 mg/m² q3w x8
  - Placebo q3w x4

**MAINTENANCE**
- Ipilimumab 10 mg/kg q12w
  - Placebo q12w

- Week 1: Baseline tumor assessment
- Week 12: First scheduled Tumor assessment
- Week 24:
Study 024: Overall Survival

HR: 0.72
Median OS: 11.2 vs 9.1 months
p-value: <0.001
Metastatic Melanoma Response to Ipilimumab
Ipilimumab in Melanoma: Phase I/II Trials

- Durable responses (CR, PR, SD)
- Durable late responses (~10%)
- Learning curve toxicity management
- Immune-related toxicity correlates with clinical benefit
- Immunosuppressive treatment does not interfere with anti-tumor response
IPILIMUMAB South African EAP
# Baseline Characteristics of Treated Patients

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tr>
<td><strong>Total</strong></td>
<td>108pts</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Median</td>
<td>59</td>
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<td>Range</td>
<td>27-86</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>73 (68%)</td>
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<td>35 (32%)</td>
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<td><strong>ECOG performance status</strong></td>
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<td>0</td>
<td>36 (33%)</td>
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<td>1</td>
<td>63 (58%)</td>
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<td>2</td>
<td>7 (6%)</td>
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<tr>
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<td>2 (3%)</td>
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## Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>1 year survival</th>
<th>2 year survival</th>
<th>3 year survival</th>
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<tbody>
<tr>
<td></td>
<td>N  Median</td>
<td>Lower Upper %</td>
<td>Lower Upper %</td>
<td>Lower Upper %</td>
</tr>
<tr>
<td>All</td>
<td>108 8,98</td>
<td>7,47 10,79 36%</td>
<td>26% 45% 20%</td>
<td>12% 27% 20%</td>
</tr>
<tr>
<td>Mucosal &amp; uveal</td>
<td>15 5,18</td>
<td>3,74 NA 8%</td>
<td>2% 13% 0%</td>
<td>0% 0% 0%</td>
</tr>
<tr>
<td>Cutaneous &amp; unknown</td>
<td>93 9,54</td>
<td>7,61 12,33 40%</td>
<td>30% 50% 23%</td>
<td>15% 32% 23%</td>
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</tbody>
</table>
Overall Survival of Cutaneous Met Melanoma

Impact on the tail of the curve!
Ipilimumab: Pooled Survival Analysis From Phase II/III Trials in Advanced Melanoma

Median OS: 11.4 mos (95% CI: 10.7-12.1)

3-yr OS rate: 22% (95% CI: 20-24)

Pts at Risk, n
Ipilimumab 1861 839 370 254 192 170 120 26 15 5 0

The interaction between the immune checkpoint receptor PD-1 and its ligands represents a potentially important tumor-specific immunomodulatory mechanism. By utilizing the PD-1 pathway, a tumor cell can prevent the activation of T-cells and therefore may block a key step that triggers the immune system.
PD-1 Receptor Blockade With Pembrolizumab

- Pembrolizumab is an antineoplastic agent, monoclonal antibody\(^1\).
- Pembrolizumab is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen-presenting or tumor cells.
  - By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates antitumor immunity\(^1\).

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APC = antigen-presenting cell; MHC = major histocompatibility complex; PD-1 = programmed death receptor 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

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1. [Insert local label.]
KEYNOTE-002: Pembrolizumab vs Chemotherapy in Ipi-Refractory Melanoma

Pt with advanced melanoma who progressed on or after Ipi (and targeted therapy, if BRAF V600+)
(N = 540)

Pembrolizumab
2 mg/kg IV q3w
(n = 180)

Pembrolizumab
10 mg/kg IV q3w
(n = 181)

Investigators’ choice of chemotherapy*
(n = 179)

Stratified by ECOG PS (0 vs 1); LDH (normal vs ≥ 110% ULN); BRAF status (wild type vs V600 mutant)

*Carboplatin + paclitaxel, paclitaxel alone, carboplatin alone, dacarbazine, or temozolomide. Pts with PD confirmed by independent central review could cross over to pembrolizumab treatment after the first 3-mo assessment.

Primary endpoint: PFS, OS
Secondary endpoints: ORR, DoR

KEYNOTE-002: Efficacy and Safety

- An international, randomized phase II study in pts with advanced melanoma with PD within 24 wks after ≥ 2 lpi doses
- Grade 3/4 toxicity incidence higher with chemotherapy (26%) vs pembrolizumab (11% at 2 mg/kg and 14% at 10 mg/kg)
- Most frequent adverse events of any grade (≥ 10%)
  - Pembrolizumab: fatigue, pruritus, and rash
  - Chemotherapy associated primarily with grade 1/2 fatigue, nausea, vomiting, anemia, reduced appetite, alopecia

KEYNOTE-006: Study Design

Stratified by ECOG PS (0 vs 1), line of therapy (1st vs 2nd), and PD-L1 status (positive* vs negative)

Unresectable stage III/IV melanoma, ≤ 1 prior therapy,† known BRAF status,‡ ECOG PS 0-1, no active brain metastases (N = 834)

Pembrolizumab 10 mg/kg IV Q2W for 2 yrs (n = 278)

Pembrolizumab 10 mg/kg IV Q3W for 2 yrs (n = 277)

Ipilimumab 3 mg/kg IV Q3W x 4 doses (n = 256)

Assessments:
- Response at Wk 12, every 6 wks until Wk 48, then every 12 wks
- Survival every 12 wks

• Primary endpoints: PFS, OS

• Secondary endpoints: ORR, response duration, safety

*≥ 1% staining in tumor, adjacent immune cells by IHC (22C3 antibody).
†Excluding anti-CTLA-4, anti-PD-1, or anti-PD-L1 agents.
‡Prior anti-BRAF therapy not required if normal LDH levels, no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
KEYNOTE-006: Overall Response Rate With Pembrolizumab

- Greater ORR with KEYTRUDA 10 mg/kg every 3 weeks vs ipilimumab¹,a,b

**Response Rate (%)**

<table>
<thead>
<tr>
<th>Pembrolizumab 10 mg/kg Every 3 Weeks (N=277)</th>
<th>Pembrolizumab 10 mg/kg Every 2 Weeks (N=279)</th>
<th>Ipilimumab (N=278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6% CR</td>
<td>5% CR</td>
<td>1% CR</td>
</tr>
<tr>
<td>27% PR</td>
<td>29% PR</td>
<td>10% PR</td>
</tr>
<tr>
<td>33% ORR (95% CI, 27, 39)</td>
<td>34% ORR (95% CI, 28, 40)</td>
<td>12% ORR (95% CI, 8, 16)</td>
</tr>
</tbody>
</table>

Analysis cutoff date: 3 September 2014.

Independent radiology plus oncologist review using RECIST 1.1.
CR = complete response; ORR = overall response rate; PR = partial response.

¹. [Insert local label.]
KEYNOTE-006: Estimated OS With pembrolizumab$^{1,2}$

- 31% reduction in the risk of death with KEYTRUDA 10 mg/kg every 3 weeks vs ipilimumab
- 37% reduction in the risk of death with KEYTRUDA 10 mg/kg every 2 weeks vs ipilimumab
- The recommended dose of KEYTRUDA is 2 mg/kg every 3 weeks$^1$

Analysis cutoff date: 3 March 2015.

1. [Insert local label.]
KEYNOTE-006: Immune-Mediated AEs*

- **Pembrolizumab**
  - Thyroid abnormalities (hyperthyroidism, hypothyroidism, thyroiditis), pneumonitis, nephritis more common
  - Type 1 diabetes and uveitis only observed in pembrolizumab-treated pts
  - Hepatitis, myositis similar to rates with ipilimumab

- **Ipilimumab**
  - Colitis, hypophysitis more common

- Discontinuations ~ 5% in all arms
- ~ 10% of pts experienced grade 3/4 immune-mediated AEs
- No significant increase in incidence of immune-related AEs over time

*Not adjusted for exposure.
KEYNOTE-006
Conclusions

- Pembrolizumab associated with superior OS vs ipilimumab in pts with unresectable, stage III/IV melanoma with ≤ 1 previous line of therapy
  - Median OS for pembrolizumab not reached at median follow-up of 23 mos
- At 24 mos, ~ 30% of pembrolizumab-treated pts still alive and free of disease progression
- Pembrolizumab responses as durable as those with ipilimumab and continue to accrue, including CRs
- Long term safety profile for pembrolizumab remains favorable
- Investigators suggest that results confirm pembrolizumab as a standard of care for advanced melanoma

Phase III CheckMate 066: First-line Nivolumab vs Chemotherapy

Unresectable, treatment-naive stage III or IV melanoma; BRAF wild type; ECOG PS 0-1; 18 yrs of age or older (N = 418)

Nivolumab 3 mg/kg IV q2w + Placebo IV q3w (n = 210; 206 treated)

Placebo IV q2w + Dacarbazine 1000 mg/m² IV q3w (n = 208; 205 treated)

Treat until progression* or unacceptable toxicity

Stratified by PD-L1 status, M-stage

Primary endpoint: OS
Secondary endpoints: PFS, ORR, PD-L1 correlates

*Pts may be treated beyond initial RECIST v1.1–defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.

Objective response rate: 40.0% with nivolumab vs 13.9% with chemo ($P < .001$)
Significantly better OS with nivolumab vs dacarbazine

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.1
0
0.2
Proportion Alive and Progression Free

Nivo + Ipi (n = 314)  Nivo (n = 316)  Ipi (n = 315)

Median PFS, mos (95% CI)  11.5 (8.9-16.7)  6.9 (4.3-9.5)  2.9 (2.8-3.4)

HR (99.5% CI) vs Ipi  0.42 (0.31-0.57)*  0.57 (0.43-0.76)*  –

HR (95% CI) vs Nivo  0.74 (0.60-0.92)*  –  –

*Stratified log-rank P < .00001 vs Ipi.
†Exploratory endpoint.
Combination Immunotherapy

- ipilimumab + nivolumab
  - melanoma 60% response versus single agent responses 44% (nivo), 19% (ipi)
  - 12% CR
  - 80% two year survival
## Combination Immunotherapies

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Mechanisms of Action</th>
<th>Phase</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>Anti-PD1 + anti-CTLA-4</td>
<td>I/II</td>
<td>Gastric, TNBC, PA, SCLC, Bladder, Ovarian</td>
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<tr>
<td></td>
<td></td>
<td>II/III</td>
<td>Melanoma, RCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>SCLC, GBM, NSCLC</td>
</tr>
<tr>
<td>Nivolumab + BMS-986016</td>
<td>Anti-PD1 + anti-LAG3</td>
<td>I</td>
<td>Solid tumors</td>
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<tr>
<td>Nivolumab + Viagenpumatucel-L</td>
<td>Anti-PD1 + vaccine</td>
<td>I</td>
<td>NSCLC</td>
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<tr>
<td>Nivolumab + urelumab</td>
<td>Anti-PD1 + anti-4-1ββ</td>
<td>I/II</td>
<td>Solid Tumors, B-Cell NHL</td>
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<td>Atezolizumab + MOXR0916</td>
<td>Anti-PD1 + anti-OX40</td>
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<td>Solid Tumors</td>
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<tr>
<td>Atezolizumab + varlilumab</td>
<td>Anti-PDL1 + anti-CD27</td>
<td>II</td>
<td>RCC</td>
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<tr>
<td>Atezolizumab + GDC-0919</td>
<td>Anti-PDL1 + IDO inhibitor</td>
<td>I</td>
<td>Solid Tumors</td>
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<tr>
<td>Epacadostat + atezolizumab, durvalumab, or pembrolizumab</td>
<td>IDO inhibitor + anti-PDL1 or anti-PD1</td>
<td>I/II</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>Pembrolizumab + T-Vec</td>
<td>Anti-PD1 + vaccine</td>
<td>III</td>
<td>Melanoma</td>
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<tr>
<td>Durvalumab + tremelimumab</td>
<td>Anti-PDL1 + anti-CTLA-4</td>
<td>I/II</td>
<td>Melanoma</td>
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<td></td>
<td>I/II/III</td>
<td>SCCHN</td>
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<td></td>
<td></td>
<td>II</td>
<td>Mesothelioma, UBC, TNBC, PA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>NSCLC, Bladder</td>
</tr>
</tbody>
</table>
Combination of PD-1, PDL-1 and CTLA-4 Blockade

• higher clinical response rates than single agent
  – melanoma, NSCLC, head and neck
• lower tolerability and higher discontinuation rates
• management of toxicity in broad patient populations in community settings
• dosing and sequence
• cost
Effective Surveillance, Recognition, and Intervention Minimizes the Potential Impact of AEs\textsuperscript{1,2}

Management of AEs

- Proactive monitoring
- Early recognition and reporting
- Appropriate management
- Vigilant follow-up

irAEs Are Associated With Immuno-oncology Therapies

The AEs described here represent some but not all irAEs that may occur with immune checkpoint inhibitor therapies.

irAEs Are Associated With Immuno-oncology Therapies

- **Hepatic**
  - Autoimmune hepatitis
  - ALT/AST increases

- **Renal**
  - Nephritis
  - Renal failure

- **Skin**
  - Macropapular rash
  - Pruritus

- **Endocrine**
  - Hypophysitis
  - Thyroiditis
  - Type 1 diabetes

- **Respiratory**
  - Pneumonitis

- **Gastrointestinal**
  - Colitis/diarrhea

- **Neuromuscular**
  - Peripheral sensory neuropathy

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*a The AEs described here represent some but not all irAEs that may occur with immune checkpoint inhibitor therapies.

### Risk Evaluation and Management Strategy (REMS)

#### Gastrointestinal
- Any changes in normal bowel habits or changes from baseline (eg, last week, last visit)
  - Diarrhea
  - Abdominal pain
  - Blood or mucus in stool with or without fever
  - Peritoneal signs consistent with bowel perforation
  - Ileus

#### Liver
- Elevations in liver function tests
  - AST >2.5 times upper limit of normal (ULN)
  - ALT >2.5 times ULN
  - Total bilirubin >1.5 times ULN

#### Skin
- Pruritus
- Rash (Maculopapular Rash)
- Viteligo

#### Neurologic
- Monitor for symptoms of motor and sensory neuropathy
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia

#### Endocrine
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries
Kinetics of appearance of immune-related adverse event

Adverse Events

- **CTLA-4**: Rash, diarrhea, hepatitis, endocrine
  - 24% grade 3/4 (1)

- **PD-1/PD-L1**: Rash, fatigue, arthralgias, pneumonia
  - 6-12% grade 3/4 (2-4)

- **Chemotherapy**: Alopecia, nausea, myelosuppression
  - ~50% grade 3/4 (5)

References:

1. Hodi et al. *NEJM* 2010
3. Topalian et al. *NEJM* 2012
5. Kelly et al. *JCO* 2001
Conclusions on Anti-PD1 Antibodies

- Anti-PD1 antibodies pembrolizumab and nivolumab are more active than ipilimumab\textsuperscript{a,b,c,d}

- Analyses of QoL presented at SMR 2015 showed
  - Superior QoL with single-agent use of an anti-PD1 antibody vs single-agent ipilimumab\textsuperscript{c}
  - Similar QoL with nivolumab/ipilimumab combination vs single-agent ipilimumab\textsuperscript{d}

- Data from the CheckMate 067 trial suggest the tumor microenvironment may hold clues as to whether a PD1 inhibitor could be used alone or with ipilimumab in the frontline setting, although this is not entirely clear at this time and more data is needed\textsuperscript{a}

Immunotherapy Summary

Immunotherapy continues to grow in importance in the care of patients with melanoma.
Response patterns to immunotherapy agents vary but can be durable.
Vigilance for adverse events by the patient, their family, and their healthcare team important.
Growing evidence indicates that chemotherapy treatment and the use of corticosteroids for immune-related toxicities do not reduce the efficacy of immunotherapies.
Patients education about expectations with immunotherapy is also important.
Treatment of Advanced Malignant Melanoma 2016. Standard of care

- BRAF V600E  Positive
  - Vemurafenib (+ - Cobimet)
  - Dabrafenib + Trametinib
  - Ipilimumab
  - Pembrolizumab / Nivolumab
  - T-VEC
  - Clinical trials

- BRAF V600E  Negative
  - Pembrolizumab/Nivolumab
  - Ipilimumab
  - Ipilimumab + Nivolumab
  - T-VEC
  - Clinical trials
Future Directions

Combination strategies including immunotherapy are currently being evaluated

Targeted agents + immunotherapy

Multiple immunotherapeutic agents

Patients selection using clinical and biological biomarkers

Identification of additional tumor subtypes that can be effectively treated with immunotherapy
“In your case, Dave, there are choices, surgery, outpatient immunotherapy, anti BRAF, anti MEK, anti PDI or whatever is in the box that our lovely Carol is holding”. 
‘THANK YOU’

SANDTON ONCOLOGY CENTRE
Ipilimumab
Major benefit is in durable tumor regressions

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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