“BRAF and MEK Inhibition in Melanoma”

Grant McArthur MB BS PhD
Peter MacCallum Cancer Centre
Melbourne, Australia
Disclosure Information

• I have the following financial relationships to disclose
  —Research support from: Pfizer, Millennium & Novartis
Talk Overview

• Signaling by BRAF and MEK
• Clinical Efficacy of Inhibiting the BRAF/MEK pathway
• Toxicity of Inhibiting the BRAF/MEK pathway
• Resistance to BRAF inhibitors
Talk Overview

• Signaling by BRAF and MEK
• Clinical Efficacy of Inhibiting the BRAF/MEK pathway
• Toxicity of Inhibiting the BRAF/MEK pathway
• Resistance to BRAF inhibitors
The KIT/RAS/RAF/ERK Pathway and Therapeutic Targets in Melanoma

- **KIT**: Mutated in 2-3%
- **NRAS**: Mutated in 15%
- **BRAF**: Mutated in 35-45%
- **CDK4**: Amplified in 30%
- **CCND1**: Amplified in 10%
- **CDK2**: Amplified in 10-20%
- **MET**: Amplified in 10-20%
- **Mitogen-activated Protein Kinase (MEK)**
- **Extracellular Signal-Regulated Kinase (ERK)**
- **CDK2**: BCL2
- **Tyrosinase**
- **HMB45**
- **Mitf**
Multiple signals

- RTK
- GPCR

RAS

BRAF

MEK

ERK

- DUSP
- SPRY

Multiple outputs
Multiple signals

RTK — GPCR

RAS

BRAF

MEK

ERK

SPRY — Multiple outputs — DUSP
BRAF

V600E

CRAF → BRAF

Proliferation
Survival

BRAF

Proliferation
Survival
Talk Overview

• Signaling by BRAF and MEK
• Clinical Efficacy of Inhibiting the BRAF/MEK pathway
• Toxicity of Inhibiting the BRAF/MEK pathway
• Resistance to BRAF inhibitors
CT Response to BRAF Inhibition - Phase 1
PLX06/02 Study of Vemurafenib

A Best Overall Response

Flaherty et al, NEJM, 2010

Flaherty et al, NEJM, 2010
Pharmacodynamic analyses suggest >90% inhibition of pERK is required for response in BRAF^{V600E} melanoma patients.
**Survival- Phase 1 PLX06/02 Study**

**Figure 1. Overall survival.**

- Kaplan–Meier estimates of OS rate are presented in **Table 2**.

**Table 2. Kaplan–Meier Analysis of Overall Survival**

<table>
<thead>
<tr>
<th>Extension Cohort Time</th>
<th>Overall Survival Rate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>87.3</td>
<td>75.6–98.9</td>
</tr>
<tr>
<td>1 year</td>
<td>55.0</td>
<td>37.4–72.5</td>
</tr>
<tr>
<td>2 years</td>
<td>35.6</td>
<td>18.7–52.4</td>
</tr>
<tr>
<td>3 years</td>
<td>25.9</td>
<td>10.4–41.3</td>
</tr>
</tbody>
</table>

Kim et al, Society of Melanoma Research, 2012
Phase III BRIM3 Study design

Screening

- BRAF^{V600E} mutation

Stratification
- Stage
- ECOG PS (0 vs 1)
- LDH level (↑ vs nl)
- Geographic region

Randomization
N=675

Vemurafenib
960 mg po bid (N=337)

Dacarbazine
1000 mg/m^2 iv q3w (N=338)

Chapman, NEJM, 2011
Overall survival (Dec 30, 2010 cutoff)

Vemurafenib (N=336)
Est 6 mo survival 84%

Dacarbazine (N=336)
Est 6 mo survival 64%

Hazard ratio 0.37
(95% CI; 0.26 - 0.55)
Log-rank P<0.0001

Chapman, NEJM, 2011
BREAK-3 study design

**Screened**
- N = 733

**Enrolled**
- n = 250

3:1 randomization dabrafenib (150 mg po bid) or DTIC (1000 mg/m², IV, q3w).

- **Dabrafenib**
  - 150 mg twice daily
  - n = 187

- **DTIC**
  - 1000 mg/m² IV every 3 weeks
  - n = 63

- **Dabrafenib**
  - 150 mg twice daily
  - n = 36
Primary endpoint: PFS Investigator-Assessed (June 2012)

Hazard ratio 0.37 (95% CI: 0.23–0.57); \( P < 0.0001 \)

Dabrafenib: median PFS 6.9 months

DTIC: median PFS 2.7 months

- On randomized study treatment at cut-off: dabrafenib 38%, DTIC 8%
- Median follow-up time: dabrafenib 10.5 months, and DTIC 9.9 months
- Median PFS following crossover was 4.4 months (n=35; 95% CI: 4.1, 6.3)
Overall survival by randomized treatment (December 2012)

- Percent alive at 15 months follow-up: dabrafenib 63%, DTIC 51%

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib</th>
<th>DTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of death/No. of patients randomized (%)</td>
<td>78/187 (42)</td>
<td>28/63 (44)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>18.2 (16.6, NR)</td>
<td>15.6 (12.7, NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.48, 1.21)</td>
<td></td>
</tr>
</tbody>
</table>
METRIC: Phase III Melanoma Study

BRAF mutation status
Using allele-specific PCR at RGI

Stratification factors
LDH (> ULN vs. < ULN) and
Prior chemotherapy (Yes vs. No)

Populations
ITT (all randomized patients) n=322;
Primary efficacy (subset of ITT) n=273

Primary endpoint
Progression-Free Survival (PFS) in
BRAF^{V600E} positive melanoma

Secondary endpoints
PFS in ITT
Overall Survival, Response rate and Safety

Screened (N=1059)

V600E/K mutation (n=322)

Trametinib 2mg QD (n=214)

Chemotherapy (n=108)

PFS

Trametinib 2mg QD

Chemotherapy = DTIC or paclitaxel
*Allowed after independent confirmation of progression

FSFV: Dec 2010,
LSFV: July 2011

Presented at: ASCO Annual Meeting 2012
METRIC Investigator-Assessed PFS – ITT

<table>
<thead>
<tr>
<th>Time From Randomization (Months)</th>
<th>Trametinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>214</td>
<td>108</td>
</tr>
<tr>
<td>1</td>
<td>205</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>163</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Number at risk
Trametinib 214 205 163 100 88 28 22 5 00
Chemotherapy 108 87 43 24 21 10 6 1 00

Events
Trametinib 118 (55)
Chemotherapy 77 (71)

Median (months)
Trametinib 4.8
Chemotherapy 1.5

HR (95% CI)
Trametinib 0.45 (0.33, 0.63)
Chemotherapy <0.0001

Proportion Alive and Progression-Free
METRIC Overall Survival – ITT

47% of the patients in the chemotherapy arm crossed over to trametinib
Updated Overall Survival Data
BRIM3 Study

McArthur et al, Lancet Oncology, 2014
Frequency of non-V600E BRAF mutations - Primary melanoma, Victoria, Australia
n=234

- V600E: 69%
- V600K: 20%
- L597: 5%
- K601E: 4%
- V600R: 1%
- V600D: 1%

M. Voskoboynik, C. Hewitt A. Dobrovic, A. Rynska, S. Wong, V. Mar
Melanoma BRAF Mutation: BRAF inhibitor + MEK-inhibitor

Best change in sum of target lesions

McArthur et al, ESMO 2013
Talk Overview

- Signaling by BRAF and MEK
- Clinical Efficacy of Inhibiting the BRAF/MEK pathway
- Toxicity of Inhibiting the BRAF/MEK pathway
- Resistance to BRAF inhibitors
### Selected adverse events (% of patients)

**Vemurafenib**

Median length of time on vemurafenib treatment: 4.2 months

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Vemurafenib, n=336</th>
<th>Dacarbazine, n=287</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>53</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>LFTs</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Cutaneous SCC</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Uveitis**</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Discontinuations due to AE: 7% vemurafenib; 4% dacarbazine

*Data from OS IA Dec 30, 2010, not updated for March 1, 2011 cutoff. **Data obtained from a manual count rather than a statistical output.
Photosensitivity

## Treatment-Related AEs in ≥ 10% of Dabrafenib Patients (June 2012)

<table>
<thead>
<tr>
<th>AE</th>
<th>Dabrafenib n (%)</th>
<th>DTIC n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>67 (36)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>50 (27)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>42 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Palmar-plantar hyperkeratosis</td>
<td>36 (19)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>56 (30)</td>
<td>0</td>
</tr>
<tr>
<td>SCC/KA</td>
<td>18 (10)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>36 (19)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (18)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>34 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>30 (16)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>27 (14)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Photosensitivity:** dabrafenib 4 (2%), DTIC 2 (4%)

KA, keratoacanthoma; SCC, squamous cell carcinoma
## Trametinib – Adverse Events (>15% of patients)

<table>
<thead>
<tr>
<th>Preferred Term (≥15% of subjects)</th>
<th>Trametinib n=211</th>
<th>Chemotherapy n=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>121 (57%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>91 (43%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>54 (26%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54 (26%)</td>
<td>27 (27%)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>40 (19%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (18%)</td>
<td>37 (37%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>36 (17%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (15%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>30 (14%)</td>
<td>23 (23%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (13%)</td>
<td>19 (19%)</td>
</tr>
</tbody>
</table>

### MEKi known events with Trametinib:
- Decreased Ejection Fraction / Ventricular dysfunction = 14 (7%)
- Chorioretinopathy = 1 (<1%)

**No reported case of cutaneous SCC or hyperproliferative skin lesions**
# Trametinib – Grade 3/4 AEs (> 1% of patients)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Trametinib</th>
<th>Chemotherapy</th>
<th>Trametinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (12%)</td>
<td>0</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (7%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (4%)</td>
<td>0</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferases increased</td>
<td>4 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0</td>
<td>0</td>
<td>4 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>0</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>0</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Dabrafenib + Trametinib: Key Treatment-Related Skin Toxicities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade ≥ 3, n (%)</th>
<th>Any grade event, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash/Skin toxicities¹</td>
<td>3 (2%)</td>
<td>61 (45%)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>0 (0%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>0 (0%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>0 (0%)</td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>

¹Skin toxicities include multiple terms
BRAF
V600E
Proliferation
Survival
CRAF
BRAF
BRAF-inhibitor
BRAF
V600E
Proliferation
Survival
CRAF
BRAF
BRAF-inhibitor
BRAF
V600E
Proliferation
Survival
Proliferation
Survival
Proliferation
Survival
Proliferation
Survival

Talk Overview

• Signaling by BRAF and MEK
• Clinical Efficacy of Inhibiting the BRAF/MEK pathway
• Toxicity of Inhibiting the BRAF/MEK pathway
• Resistance to BRAF inhibitors
Progression-free Survival BRIM3
(Censored at Crossover; February 2012 Survival Update)

Hazard ratio 0.38 (95% CI: 0.32–0.46)
Log-rank p<0.001

No. of patients at risk
Dacarbazine | 338 | 100 | 63 | 37 | 22 | 14 | 3 | 0 | 0
Zelboraf | 337 | 269 | 186 | 113 | 77 | 49 | 16 | 3 | 0

CI = confidence interval; PFS = progression-free survival.
Figure from Chapman PB, et al. Presented at ASCO 2012. Oral Presentation 8502.
Vemurafenib: Response is Homogeneous Progression is not
Testing on progression - multiple mechanisms of resistance

Resistance to BRAF inhibition does not involve mutation in BRAF itself

A. MEK-dependent progression
- NRAS mutations
- NRAS<sup>Q61</sup>
- COT overexpression
- CRAF
- BRAF<sup>V600E</sup>
- MEK1/2 mutations
- MEK
- ERK
- Survival

B. MEK-independent progression
- RTK ligand overexpression
- RTK ligand
- PI3K
- PIK3CA mutation
- AKT

Resistance to BRAF inhibition does not involve mutation in BRAF itself

Heterogeneity of ERK phosphorylation at progression

- Recovery of ERK and MEK phosphorylation at disease progression was observed in some but not all patients

McArthur ASCO, 2011
Overcoming Resistance to BRAF inhibition

A. MEK-dependent progression

NRAS mutations

NRAS\textsuperscript{Q61}

COT overexpression

COT

CRAF

BRAF\textsuperscript{V600E}

BRAF\textsuperscript{V600E} truncation

BRAF\textsuperscript{V600E} amplification

MEK1 mutations

MEK

ERK

P

Survival

Dabrafenib
Vemurafenib

Trametinib
Cobimetinib

Acknowledgements

Keith Flaherty
Paul Chapman
Keith Nolop
Axel Hauschild
Nick Choong
Antoni Ribas
Jeff Sosman

Kevin Kim
Igor Puzanov
Joe Grippo
Gideon Bollag
Richard Lee
Rene Gonzalez

Study Coordinators

Patients & their families
PD-1 and ipilimumab in sequence

Antoni Ribas, M.D., Ph.D.
Professor of Medicine
Professor of Surgery
Professor of Molecular and Medical Pharmacology
Director, Tumor Immunology Program, Jonsson Comprehensive Cancer Center (JCCC)
University of California Los Angeles (UCLA)
Chair, Melanoma Committee at SWOG
PD-1/PD-L1 inhibiting reagents in clinical development

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Class</th>
<th>$K_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab (MDX1106, BMS936558, BMS-ONO)</td>
<td>IgG4 fully human antibody</td>
<td>3 nM</td>
</tr>
<tr>
<td></td>
<td>MK-3475 (lambrolizumab, Merck)</td>
<td>IgG4 engineered humanized antibody</td>
<td>29 pM</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab (CT-011, CureTech-Teva)</td>
<td>IgG1 humanized antibody</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>AMP-224 (Amplimmune-GSK)</td>
<td>Fc-PD-L2 fusion protein</td>
<td>-</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS935559 (MDX-1105, BMS-ONO)</td>
<td>IgG4 fully human antibody</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MPDL3280A (Genentech)</td>
<td>IgG1 engineered fully human antibody</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MEDI4736 (MedImmune, AZ)</td>
<td>IgG1 engineered fully human antibody</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MSB0010718C (Merck-Serono)</td>
<td>NA</td>
<td>-</td>
</tr>
</tbody>
</table>
Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haijing Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollias, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Szol, M.D.

27% ORR

28% ORR

18% ORR

Nivolumab

Safety and Tumor Responses with MK-3475 (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Keeford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elssasser-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmieleowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

ORR: 38%

Highest dose ORR: 52%
(by RECIST 1.1 with confirmation assessed by ICR)

MK-3475
Clinical activity of MK-3475 in a patient progressing to 3 prior lines of therapy

Baseline: April 13, 2012
April 9, 2013

72-year-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab

A. Ribas, ASCO 2013
Clinical activity in a patient with a metastatic desmoplastic melanoma

54 yrs old male with desmoplastic melanoma after progressing on ipilimumab

A. Ribas, ASCO 2013

B. Chmielowski M.D., Ph.D.
Paul Tumeh M.D.
MK-3475 (lambrolizumab) single agent therapy: Maximum Change From Baseline in Tumor Size
(Independent Central Review per RECIST 1.1)

Ribas et al. ASCO 2013
Time to Response and On-Study Duration
(Independent Central Review per RECIST 1.1)

Individual Patients Treated With MK-3475

IPI-Pretreated
IPI-Naive
Complete Response
Partial Response
On Study

The median duration of response had not been reached at the time of analysis, with median follow-up time of 11 months.

Ribas et al. ASCO 2013
## Drug-Related Adverse Events

**Observed in >5% of Patients (N = 135)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades, n (%)</th>
<th>Grade 3-4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>107 (79.3)</td>
<td>17 (12.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41 (30.4)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>28 (20.7)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>28 (20.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27 (20.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (11.9)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (10.4)</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>13 (9.6)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (9.6)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (9.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>12 (8.9)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>11 (8.1)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>11 (8.1)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (8.1)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (6.7)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (5.2)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>
Frequent development of vitiligo (skin depigmentation) in responding patients
PD-1 blockade with single agent MK-3475 improving other skin conditions
PD-1 blockade with single agent MK-3475 leading to the disappearance of a pigmented birth mark
Nivolumab + Ipilimumab combination therapy: Best Responses in Concurrent Cohorts (WHO response criteria)

After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients continue to respond as of Feb 2013.

Wolchok et al. ASCO 2013
WHO waterfalls with combination nivolumab + ipilimumab or single agent MK-3475

The “depth of the response” is in part an artifact of how the data is presented when using WHO (bidimensional measurements) in a waterfall plot.
## Treatment-Related Adverse Events (≥10% of all patients)

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event</th>
<th>Concurrent All Cohorts (n=53)</th>
<th>Sequenced All Cohorts (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr</td>
<td>Gr 3-4</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>49 (93)</td>
<td>28 (53)</td>
</tr>
<tr>
<td>Rash</td>
<td>29 (55)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>25 (47)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (38)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (34)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (21)</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>11 (21)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>ALT</td>
<td>11 (21)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Lipase</td>
<td>10 (19)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Amylase</td>
<td>8 (15)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (11)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>6 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (11)</td>
<td>0</td>
</tr>
</tbody>
</table>

Presented by J. Wolchok, ASCO 2013
What is the decision making for 1st line treatment of advanced melanoma?

- BRAF testing
  - Positive
  - Negative
- “Growth kinetics”
  - Slow
  - Fast
What is the decision making for 1st line treatment of advanced melanoma?

**Predictive factors for response to PD-1/L-1 blockade**

- Positive
- Negative

**BRAF testing**

- Positive
- Negative

**“Growth kinetics”**

- Slow
- Fast
Conclusions

• PD-1/PD-L1 blockade therapy should be used as single agent in patients who have a chance of responding to this therapy

• Combination therapies with PD-1/PD-L1 blockade should only be used in patients with a low likelihood of a tumor response to single agent therapy
Combination Checkpoint Blockade Therapy for Melanoma

Jedd Wolchok

Ludwig Center at Memorial Sloan-Kettering Cancer Center, New York
Ipilimumab Augments T-Cell Activation and Proliferation

Adapted from O’Day et al. Plenary session presentation, abstract #4, ASCO 2010.
Patients at Risk

| Patients | 4846 | 1786 | 612 | 392 | 200 | 170 | 120 | 26 | 15 | 5 | 0 |

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS Rate (95% CI): 21% (20–22%)

Hodi et al., ESMO, 2013
Immune-Related Adverse Events

- Rash
- Colitis/enteritis
- Elevated AST/ALT
- Thyroiditis
- Adrenal insufficiency
- Hypophysitis

Severity is inversely related to vigilance of surveillance. If detected early, most are easily treated and reversible.
Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

Sznol et al., ASCO, 2013
Tumor Burden in Patients with Melanoma Receiving Nivolumab 3 mg/kg

Change in target lesions from baseline (%)

Weeks since treatment initiation

Change in target lesions from baseline (%)

Weeks since treatment initiation

Sznol et al., ASCO, 2013
Select Drug-Related Adverse Events (≥1%) Occurring in Melanoma Patients Treated with Nivolumab

- **Select AE:** AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention

<table>
<thead>
<tr>
<th>Category</th>
<th>Any Grade % (n)</th>
<th>Grade 3-4 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any select AE</td>
<td>54 (58)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Skin</td>
<td>36 (38)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18 (19)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>13 (14)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>7 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>6 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
MK-3475: Maximum Change From Baseline in Tumor Size

Ribas et al., ASCO, 2013
Clinical Activity, MK-3475

Baseline: April 13, 2012

April 9, 2013

72-year-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab

Images courtesy of A. Ribas, UCLA.

Ribas et al., ASCO, 2013
MPDL3280A Phase Ia: Tumor Burden Over Time (Melanoma)

Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

Hamid et al., ASCO, 2013
### Phase I Study: Schedule

#### Concurrent Cohorts

<table>
<thead>
<tr>
<th>Ipilimumab once every 3 weeks (4 doses)</th>
<th>Ipilimumab once every 12 weeks (8 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ↓ ↓ ↓</td>
<td>↓ ↓ ↓ ↓</td>
</tr>
<tr>
<td>Weeks 0 3 6 9 12 15 18 21 24 36 48 60 72 84 96 108</td>
<td></td>
</tr>
<tr>
<td>↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑</td>
<td></td>
</tr>
<tr>
<td>Nivolumab once every 3 weeks (8 doses)</td>
<td>Nivolumab once every 12 weeks (8 doses)</td>
</tr>
</tbody>
</table>

- First tumor assessment at 12 weeks

#### Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every 2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks

- Tumor assessments by mWHO and immune-related response criteria
- Data as of Feb 2013 for 86 patients
# Treatment-Related Select Adverse Events

<table>
<thead>
<tr>
<th>Select Adverse Event</th>
<th>Concurrent Regimen All Cohorts (n=53)</th>
<th>Sequenced Regimen All Cohorts (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr</td>
<td>Gr 3-4</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (6)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>7 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>3 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Skin</td>
<td>37 (70)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20 (38)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>12 (23)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Lipase</td>
<td>10 (19)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Amylase</td>
<td>8 (15)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
### Clinical Activity: Sequenced Regimen

<table>
<thead>
<tr>
<th>Nivolumab (mg/kg)</th>
<th>Response Evaluable Patients n</th>
<th>CR n</th>
<th>PR n</th>
<th>Objective Response Rate % [95% CI]</th>
<th>Aggregate Clinical Activity Rate % [95% CI]</th>
<th>≥80% Tumor Reduction at 8 wk n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14 [2-43]</td>
<td>0</td>
</tr>
</tbody>
</table>

- With sequenced nivolumab after prior ipilimumab, 20% of patients had confirmed objective responses.
- 13% of patients had ≥80% tumor reduction at their first scheduled 8-week tumor assessment (rapid and deep responses).
Best Responses in All Evaluable Patients in Sequenced Cohorts

Patients who had radiographic progression with prior ipilimumab treatment.

Patients who had stable disease with prior ipilimumab treatment.
### Clinical Activity: Concurrent Regimen

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
<th>Response Evaluable Patients n</th>
<th>CR n</th>
<th>PR n</th>
<th>Objective Response Rate % [95% CI]</th>
<th>Aggregate Clinical Activity Rate % [95% CI]</th>
<th>≥80% Tumor Reduction at 12 wk n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>3</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td></td>
<td>21 [5-51]</td>
<td>50 [23-77]</td>
<td>4 (29)</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>17</td>
<td>3</td>
<td>6</td>
<td></td>
<td>53 [28-77]</td>
<td>65 [38-86]</td>
<td>7 (41)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>5</td>
<td></td>
<td>40 [16-68]</td>
<td>73 [45-92]</td>
<td>5 (33)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td></td>
<td>50 [12-88]</td>
<td>83 [36-100]</td>
<td>0</td>
</tr>
<tr>
<td>Concurrent</td>
<td>52</td>
<td>5</td>
<td>16</td>
<td></td>
<td></td>
<td>40 [27-55]</td>
<td>65 [51-78]</td>
<td>16 (31)</td>
</tr>
</tbody>
</table>

- With 1 mg/kg nivolumab + 3 mg/kgb ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences
Best Responses in All Evaluable Patients in Concurrent Cohorts

Change in target lesions from baseline (%)
Rapid and Durable Changes in Target Lesions

1 mg/kg nivolumab + 3 mg/kg ipilimumab

First occurrence of new lesion

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown
Preliminary Survival of Patients Treated With Concurrent Regimen

1-year Survival: 82%
95% CI (69.0%; 94.4%)

Patients at Risk

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg + 3 mg</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>14</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All concurrent regiment</td>
<td>53</td>
<td>47</td>
<td>36</td>
<td>29</td>
<td>19</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Died/Treated

- 1 mg/kg nivolumab + 3 mg/kg ipilimumab
- Died/Treated: 2/17
- All concurrent regimen
- Died/Treated: 9/53
Evaluating PD-L1 status as a candidate biomarker

![Graph showing objective response rate for different treatment groups.]

- **Nivolumab monotherapy** (Grosso et al. ASCO 2013): 3/21 (-), 7/17 (+)
- **Combination nivolumab plus ipilimumab**: 9/22 (-), 6/13 (+)
- **Sequenced nivolumab after ipilimumab**: 1/13 (-), 4/8 (+)

**Positivity rate** = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy)

Callahan et al., ASCO, 2013
Evaluating ALC as a candidate biomarker

Low ALC rate = 20% (8/41, monotherapy), 27% (14/52, combination therapy), and 21% (6/28, sequenced therapy)

Callahan et al., ASCO, 2013
Increased frequency of activated \((\text{ki}67^+)\) CD\(^+_4\) and CD\(^+_8\) T cells with concurrent nivolumab + ipilimumab

Callahan et al., ASCO, 2013
Increased frequency of activated (ICOS⁺) CD4⁺ and CD8⁺ T cells with concurrent nivolumab + ipilimumab

Callahan et al., ASCO, 2013
Ki67 staining of CD8+ T cells

**COHORT 1 (0.3 NIVO, 3 IPI)**
n=6

**COHORT 2/8 (1 NIVO, 3 IPI)**
n=15

**COHORT 3 (3 NIVO, 3 IPI)**
n=3

**COHORT 2A (3 NIVO, 1 IPI)**
n=9

**COHORT 6 (1 NIVO)**
n=7

**COHORT 7 (3 NIVO)**
n=8

Maggie Callahan
ICOS Staining of CD8+ T cells by Cohort

- **COHORT 1 (0.3 NIVO, 3 IPI)**
  - n=6

- **COHORT 2/8 (1 NIVO, 3 IPI)**
  - n=15

- **COHORT 2A (3 NIVO, 1 IPI)**
  - n=9

- **COHORT 3 (3 NIVO, 3 IPI)**
  - n=3

- **COHORT 6 (1 NIVO)**
  - n=7

- **COHORT 7 (3 NIVO)**
  - n=8

Maggie Callahan

---

Memorial Sloan Kettering Cancer Center
Phenotype of activated peripheral blood CD8^+ T cells after combination

Selected Marker

CTLA-4

ICOS

PD-1

Nivolumab

Pre-treatment

Day 7 post treatment

Callahan et al., ASCO, 2013
Metastatic Melanoma Patients Have Increased MDSC

Summary

• Checkpoint blockade is an effective treatment with durable responses in melanoma

• Intense study of both predictive and pharmacodynamic biomarkers of response and toxicity will allow for more intelligent patient selection and novel target discovery.

• Combination therapy will be necessary for immunotherapy to achieve full potential (other immune modulators, vaccines, radiation, chemotherapy, targeted therapy, anti-angiogenic therapy).

• Combined checkpoint blockade may allow constraints for monotherapy to be overcome and is now being studied in phase 2 and phase 3 trials for melanoma.