Recent Advances in Melanoma Therapy

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Annual Incidence and Deaths from Skin Cancer in the United States

Cancer Mortality Rates by State Economic Area

Melanoma, White Males, 1970-94

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Survival in Melanoma by Stage

![Image of survival curves for melanoma stages]

GNAQ 32% G11 45%
NRAS 15% BRAF 28%
NRAS 18% BRAF 57%
C-Kit 5% - 10% NRAS 25% BRAF 10%
C-Kit 10% - 20% NRAS 15%


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**Phase III BRIM3 Study design**

**Screening**
- BRAF<sup>V600E</sup> mutation

**Stage**
- ECOG PS (0 vs 1)
- LDH (↑ vs nl)
- region

**Randomization**
N=675

- **Vemurafenib**
  - 960 mg po bid (N=337)

- **Dacarbazine**
  - 1000 mg/m<sup>2</sup> iv q3w (N=338)

**Summary of confirmed objective response rates**

<table>
<thead>
<tr>
<th></th>
<th>ASCO 2011</th>
<th>ASCO 2012 (post-hoc)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTIC</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>No. of evaluable pts</td>
<td>(n=220)</td>
<td>(n=219)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>2.3</td>
<td>3.6</td>
</tr>
<tr>
<td>ORR, %</td>
<td>5.5</td>
<td>48.4</td>
</tr>
<tr>
<td>CR, %</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>PR, %</td>
<td>5.5</td>
<td>47.5</td>
</tr>
</tbody>
</table>

<sup>*</sup>Censored at crossover

**Progression-free survival (February 01, 2012 cut-off) censored at crossover**

- **Vemurafenib** (n=337)
- **Dacarbazine** (n=338)

**Overall survival (February 01, 2012 cut-off) censored at crossover**

- **Vemurafenib** (n=337)
- **Dacarbazine** (n=338)

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**Overall survival by baseline characteristic (February 01, 2012 cut-off) censored at crossover**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of patients</th>
<th>Favors vemurafenib</th>
<th>Favors dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>675</td>
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<tr>
<td>Age:</td>
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<td></td>
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<tr>
<td>&lt;65 years</td>
<td>514</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>161</td>
<td></td>
<td></td>
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<tr>
<td>Sex:</td>
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</tr>
<tr>
<td>Female</td>
<td>294</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>381</td>
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<td></td>
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<tr>
<td>ECOG status:</td>
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<tr>
<td>0</td>
<td>459</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>216</td>
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<td></td>
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<tr>
<td>Disease stage:</td>
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<tr>
<td>IIIc</td>
<td>33</td>
<td></td>
<td></td>
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<tr>
<td>MTa</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTb</td>
<td>127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTc</td>
<td>441</td>
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<td></td>
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<tr>
<td>LDH:</td>
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<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>391</td>
<td></td>
<td></td>
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<tr>
<td>Elevated</td>
<td>284</td>
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</tr>
</tbody>
</table>

Hazard ratio and 95% confidence interval

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**Enhanced Antitumor Activity with Combination**

**BRAF<sup>V600E</sup> human melanoma xenograft**

Unpublished Data

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**Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations**

Keith T. Flaherty, M.D., Jeffrey R. Iffert, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hadimi, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nagappa Ibrahim, M.D., Rogier Knoberizer, M.D., Howard A. Eisen, M.D., Gerald Fischke, M.D., M.B., Alain Aljouz, M.D., Karl Lesot, M.D., Georgina V. Long, M.D., Igra Putzanos, M.D., M.S.C.I., Peter Lebechcz, M.D., Ph.D., Agn Singh, M.G., Shonda Little, M.P.H., Peng Sun, M.D., Alicia Alfred, Ph.D., Danielle Ouellet, Ph.D., Kevin B. Kim, M.D., Kwan Pat, M.D., M.B.A., and Jeffrey Winer, M.D., Ph.D.

September 29, 2012: DOI:10.1056/NEJMoa1201095

Abstract | Article | References
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**Progression-Free Survival**

- Med (mos): 5.8
- HR (95% CI): 0.56 (0.37, 0.87), 0.006
- P Value: 0.005
- PFS rate: 9%
- Median follow up time: 14 months

**Investigator-assessed Maximum Tumor Reduction Part B BRAFi naïve melanoma patients (N=77)**

- Dose levels: dabrafenib/trametinib (mg BID/mg QD)
  - 75/1
  - 150/1
  - 150/1.5
  - 150/2

**Maximum percent reduction from baseline measurement**

**The NEW ENGLAND JOURNAL of MEDICINE**

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

- Melanoma 28%
- Renal Cell 27%
- NSCLCa 18%
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Conclusions

- Unprecedented advances in melanoma therapy
- BRAF inhibitors may be the primary choice for BRAF mt patients
  - Testing
  - Resistance to therapy
- Immunological Therapies
  - Ipilimumab
  - PD-1 (PD-L1)
- Anti-angiogenic
- Chemotherapy