A Phase 1b/2 Study of BRAF Inhibitor (BRAFi) Encorafenib (ENCO) Plus MEK Inhibitor (MEKi) Binimetinib (BINI) in Cutaneous Melanoma Patients Naive to BRAFi Treatment


Presented By Ryan Sullivan at 2015 ASCO Annual Meeting
Oncogenic BRAF Mutations in Melanoma

- BRAF V600 mutations present in 40–50% of patients
- Single-agent small-molecule inhibition of BRAF and MEK improves survival compared with chemotherapy\(^1\)–\(^3\)
- Combined BRAF and MEK inhibition improves survival compared with single-agent BRAF inhibitors\(^4\)–\(^6\)

Encorafenib in Melanoma

- ATP-competitive RAF kinase inhibitor
- Phase 1:
  - DLTs: HFS, pain, fatigue, asthenia, diarrhea/rash/headache, facial paresis/confusion, pain/neuralgia
  - $T_{1/2}$ 3 hours
  - MTD 450 mg QD; RP2D 300 mg QD

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DLT, dose-limiting toxicity; HFS, hand-foot skin reaction; PD, progressive disease; PR, partial response; GD, once daily; MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose; SD, stable disease; UNK, unknown.


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Binimetinib in Melanoma

- Potent and highly selective allosteric, ATP-uncompetitive inhibitor of MEK1/2
- $T_{1/2}$ 7–8 hours
- RP2D 45 mg BID
- Phase 2 trial in BRAF/NRAS-mutant melanoma:
  - 8 responders in 41 BRAF-mt patients (20%), median PFS 3.6 months
CMEK162X2110: Phase 1b/2 Trial of Encorafenib and Binimetinib

- Phase 1b/2 design
- MTD was not declared
- RP2D:
  - Encorafenib 450 and 600 mg QD
  - Binimetinib 45 mg BID
Phase 1b/2 Trial of Encorafenib and Binimetinib

- 55 BRAFi-naive, BRAF-mutant patients were treated as part of Phase 1b (n=13) and Phase 2 (n=42) portions of the study
- Median exposure 9.7 months

<table>
<thead>
<tr>
<th>ENCO (mg QD)</th>
<th>BINI (mg BID)</th>
<th># Patients Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;400</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>400 or 450</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td><strong>600</strong></td>
<td><strong>45</strong></td>
<td><strong>39</strong></td>
</tr>
<tr>
<td>800</td>
<td>45</td>
<td>2</td>
</tr>
</tbody>
</table>

BINi, Binimetinib; ENCO, Encorafenib.
Data cut-off: January 7, 2015.

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years at screening</td>
<td>Median 54.0</td>
</tr>
<tr>
<td></td>
<td>Range 23.0–86.0</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (65.5)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (34.5)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>31 (56.4)</td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>21 (38.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LDH, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;ULN</td>
<td>32 (58.2)</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>21 (38.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41 (74.5)</td>
</tr>
<tr>
<td>1</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td>BRAF subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>V600E</td>
<td>49 (89.1)</td>
</tr>
<tr>
<td>V600K</td>
<td>5 (9.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>
Response

CR, complete response; DCR, disease control rate; ORR, overall responder rate.

*26 of 39 patients assigned to ENCO 600 mg were dose reduced to ENCO 450 mg as per protocol.
*Additional patients received ENCO 50 mg + BNI 45 mg (n=3), ENCO 100 mg + BNI 45 mg (n=1),
ENCO 200 mg + BNI 45 mg (n=1), or ENCO 600 mg + BNI 45 mg (n=2).

Response confirmation is not required. RECIST v1.1 was used to evaluate response.

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Response

70-year-old man

- Previously untreated, recurrent, and metastatic melanoma
- Commenced ENCO 450 mg QD and BINI 45 mg BID on March 18, 2013; response initially noted on April 11, 2013
- Patient remained on study for ~13 months until progression
Progression-Free Survival

Median, months [95% CI]
11.3 [7.4, 14.6]

PFS (%)

0 20 40 60 80 100

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

Time (months)

Number of patients at risk
55 51 44 36 28 23 20 14 8 6 5 3 3 3 3 2 0

CI, confidence interval.

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Progression-Free Survival by LDH

Median, months [95% CI]
LDH ≤ULN: 20.0 [11.0; ne]
LDH >ULN: 6.8 [5.0; 11.3]

Number of patients at risk
LDH ≤ULN: 32 30 27 22 20 16 14 10 8 6 5 3 3 3 2 0
LDH >ULN: 21 19 16 13 8 7 6 4 0 0 0 0 0 0 0 0

Censored - LDH at baseline

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# Safety

All-cause AEs reported in $\geq 25\%$ of ENCO 600 mg group

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ENCO 400/450 mg + BINI 45 mg N = 9</th>
<th>ENCO 600 mg + BINI 45 mg N = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grade 3/4 n (%)</td>
</tr>
<tr>
<td>Total</td>
<td>9 (100)</td>
<td>5 (55.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased*</td>
<td>3 (33.3)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>CPK increased</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased*</td>
<td>4 (44.4)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>2 (22.2)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
*Only one patient with bilirubin elevation.

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# Safety

All-cause AEs of special interest

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ENCO 400/450 mg + BINI 45 mg</th>
<th>ENCO 600 mg + BINI 45 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grade 3* n (%)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Chorioretinopathy</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal pigment epithelium detachment</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis aceniform</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Palmar-plantar ES</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasm*</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*ES, erythrodysesthesia
*No events were Grade 4.
†Total neoplasm benign, malignant and unspecified (including cysts and polyps).
Monitoring of Ocular AEs

- Extensive monitoring of ocular toxicity was performed in this study
  - Full ophthalmological examinations were performed at screening, C1D15, C2D1, C2D15, Day 1 of all subsequent Cycles, and end of trial, and included:
    - Slit lamp examination, visual acuity testing, visual field testing (IOP), OCT and indirect fundoscopy (with dilation) with attention to retinal abnormalities (especially CSR and RVO)
  - For patients with clinical suspicion of retinal changes, additional assessments of fluorescein angiography and/or focal ERG (where feasible) were recommended to be performed at the discretion of the treating physician
  - Patients with Grade 1 CSR were allowed to continue treatment with binimetinib and generally had resolution of subretinal fluid and visual symptoms over time

C, cycle; CSR, central serous retinopathy; D, day, ERG, electrotretinography; IOP, intraocular pressure; OCT, optical coherence tomography; RVO, retinal vein occlusion


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Summary and Conclusions

- Combination of encorafenib and binimetinib is well tolerated and shows promising activity for BRAFi-naive, BRAF-mutant melanoma
- RP2D of encorafenib in this combination is higher than single-agent RP2D (450 mg daily vs 300 mg daily)
- Response rate and PFS consistent with other BRAFi/MEKi combinations
- Lower rates of pyrexia and photosensitivity differentiate this combination from other MEK/BRAF inhibitor combinations\(^1\),\(^2\)
- Further evaluation of this combination is underway
  - Phase 3 COLUMBUS (ENCO+BINI vs ENCO vs vemurafenib)

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