ERK Inhibition: Is it Feasible?

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I have no financial relationships to disclose
Rational for Targeting RAS-RAF-ERK Pathway

- High frequency of activating RAS or BRAF mutations found in cancer
- Selective BRAF and MAP-ERK kinase (MEK) inhibitors efficacious in melanoma
- Majority of responses are transient
- ERK1/2 kinase inhibitors have antitumor activity in MAPK inhibitor-naïve and inhibitor-resistant cells containing resistant BRAF or RAS mutations
ERK Screening Strategy

Initiated assay: 2003

**Approach: Biochemical Assay (active ERK2)**

Kinase activity inhibition assay:
active ERK2 + compounds

ERK2 Kinase activity inhibition

SCH 720349

ERK2 $IC_{50} = 0.53 \mu M$

CDK2 $IC_{50} = 0.63 \mu M$

**Approach: Binding Assay (inactive ERK2)**

Inactive ERK2 + compounds

activate ERK2 with MEK

ERK2 Kinase activity inhibition

SCH 746514

A-ERK2 $IC_{50} = 2 \mu M$

CDK2 $IC_{50} > 10 \mu M$

Good kinase selectivity

<table>
<thead>
<tr>
<th>Kinase</th>
<th>$IC_{50}$ (uM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL</td>
<td>&gt;10</td>
</tr>
<tr>
<td>AKT1</td>
<td>&gt;10</td>
</tr>
<tr>
<td>CDK2</td>
<td>&gt;10</td>
</tr>
<tr>
<td>B-RAF</td>
<td>&gt;10</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;10</td>
</tr>
<tr>
<td>EPHB4</td>
<td>&gt;10</td>
</tr>
<tr>
<td>P38</td>
<td>&gt;10</td>
</tr>
<tr>
<td>IGF1R</td>
<td>&gt;10</td>
</tr>
<tr>
<td>IRAK4</td>
<td>&gt;10</td>
</tr>
<tr>
<td>JAK2</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>
Development of ERK Inhibitors

SCH 746514
ERK2 IC$_{50}$ = 2 uM
Issue: Potency

SCH 772984
ERK2/1 IC$_{50}$ = 1/4 nM
Prolif Colo-205 IC$_{50}$ = 11 nM
SCH772984 (ERKi) Profile

- Potent ERK inhibitor (enzyme and cell)
- Good kinase selectivity profile
- ATP competitive

![Structure of SCH772984](image)

**Kinome Selectivity**

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERK1</td>
<td>0.001</td>
</tr>
<tr>
<td>ERK2</td>
<td>0.004</td>
</tr>
<tr>
<td>CDK2</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>MEK1</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>CRAF</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>p38b</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>GSK3b</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>RSK2</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>CAMK4</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>MST2</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>PKCa</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>ROCK2</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

Selective against 320 kinases

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**Binding**

<table>
<thead>
<tr>
<th></th>
<th>ERK2</th>
<th>MEK1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>K&lt;sub&gt;D&lt;/sub&gt; (nM)</td>
<td>K&lt;sub&gt;D&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>GSK1120212</td>
<td>No binding</td>
<td>7 ± 2.7</td>
</tr>
<tr>
<td>SCH772984</td>
<td>0.48 ± 0.14</td>
<td>No binding</td>
</tr>
</tbody>
</table>
SCH772984: Novel Dual Mechanism of Inhibition

• MEK phosphorylation residues T202/Y204 & T185/187 of ERK

• SCH772984 does not bind or inhibit MEK
SCH772984 Binding to ERK2 Induces Conformation Change

Unbound ERK2

ERK2 bound to ERK inhibitor
SCH772984 Binding to ERK2 Induces Conformation Change: Dual Mechanism of Inhibition

ERK2 / SCH772984 complex

- Binds active site of ERK & inhibits kinase activity
- Distorts conformation / hinders MEK ability to phosphorylate ERK
- pERK can be used as biomarker for target engagement
Targeting RAS–ERK signalling in cancer: promises and challenges

Ahmed A. Samatar and Poulakis I. Poulakakos

Abstract | The RAS–RAF–MEK–ERK signalling pathway is hyperactivated in a high percentage of tumours, most frequently owing to activating mutations of the KRAS, NRAS and BRAF genes. Recently, the use of compounds targeting components of ERK signalling, such as RAF or MEK inhibitors, has led to substantial improvement in clinical outcome in...
Tumors with RAF / RAS Mutations are Sensitive to ERKi
ERKi Induces Tumor Regressions in Melanoma Tumor Xenograft Model

BRAF mutant model

- Vehicle
- ERKi 12.5 mpk
- ERKi 25 mpk
- ERKi 50 mpk

Graph showing tumor volume over days of treatment with different treatments.
ERKi Induces Tumor Regressions in Pancreatic KRAS Mutant Tumor Xenograft Model
Mechanisms of resistance to BRAF inhibitors

Response 15 weeks

Resistance 23 weeks

Resistant Mechanisms to RAFi

- RTK activation
- RAS mutation
- RAFi (PLX4032, GSK2118436)
- BRAF amplification
- BRAF variant expression
- MEK mutation

- Can ERK inhibitor overcome resistance conferred by RAF inhibitors?

Wagle et al., JCO 2011
ERKi Overcomes Resistance to BRAF Inhibitors (Vemurafenib)

A375 (BRAF\textsuperscript{V600E} mutant melanoma)

(Acquired KRAS\textsuperscript{G13D})

A375 (BRAF\textsuperscript{V600E} mutant melanoma)

SCH772984 µM

pERK

ERK
ERKi Overcomes Resistance to MEK Inhibitor (Trametinib)

KRAS$^{G13D}$ mutant colon cancer

(Acquired MEK1$^{G128D/L215P}$)

KRAS$^{G13D}$ mutant colon cancer

Viability (% control)

GSK1120212 log [M]

SCH772984 log [M]
Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nageotte Ibrahim, M.D., Ragini Kudchodkar, M.D., Howard A. Burris III, M.D., Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D., Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I., Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H., Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D., Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

ABSTRACT

BACKGROUND
Resistance to therapy with BRAF kinase inhibitors is associated with reactivation of the mitogen-activated protein kinase (MAPK) pathway. To address this problem, we conducted a phase 1 and 2 trial of combined treatment with dabrafenib, a selective BRAF inhibitor, and trametinib, a selective MAPK kinase (MEK) inhibitor.

METHODS
In this open-label study involving 247 patients with metastatic melanoma and BRAF V600 mutations, we evaluated the pharmacokinetic activity and safety of oral dabrafenib (75 or 150 mg twice daily) and trametinib (1, 1.5, or 2 mg daily) in 85
ERKi Overcomes Resistance to the Combination of BRAFi and MEK Inhibitors in BRAF Mutant Melanoma

A101D parental (BRAF<sup>V600E</sup> Mutant)

A101D BR+MR (BRAF <sup>V600E</sup> Mutant)

<table>
<thead>
<tr>
<th></th>
<th>A101D parental</th>
<th>A101D BR+MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLX4032 (10 μM)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GSK1120212 (1 μM)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SCH772984 (2 μM)</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Blots:**
- pERK
- ERK
- pRSK
- RSK
- Actin
Trametinib (MEKi) activity in BRAF inhibitor naïve patients

Confirmed Response Rate: 25%
Median PFS: 4.0 months

Kim, Kefford, Pavlick et al. J Clin Oncol. 2013
Trametinib (MEKi) not Effective in Patients Who Had Prior BRAFi Therapy

Confirmed Response Rate: 5%

Kim, Kefford, Pavlick et al. J Clin Oncol. 2013
Clinical Utility for ERK Inhibitors

- Target RAF / MEK inhibitors refractory tumors

- Develop ERK inhibitor in combination
  - ERKi + RAFi
  - ERKi + MEKi
  - ERKi + PI3Ki
  - ERKi + BRAFi + MEKi

- Sequential treatment with MAPK pathway inhibitors to prevent / delay resistance:

- ERK Inhibitors may address a large unmet medical needs: NSCL, Pancreatic cancers, NRAS mutant melanoma
ERK Inhibition: Is it Feasible?

YES (preclinical)
Summary

- SCH772984 is a first-in-class novel, potent & selective ERK inhibitor that demonstrates:
  - Potency & selectivity
  - a unique dual mechanism of action
  - *in vivo* anti-tumor activity in BRAF/RAS mutant tumors
  - activity in resistance settings with ERK reactivation

- ERKi and BRAFi combination results in enhanced anti-tumor activity

- ERK inhibitors in clinical trials: MK8353, BVD-0994 & GDC-0994
Thank you for your attention!