The challenges of combinations of targeted agents in oncology

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Disclosures

- **Interests**: employed by Sanofi
- **Conflicts of interest**: None
- Experimental data of the non-approved drugs pimastertib, SAR245408, SAR245409, and SAR405838 will be shown
The challenges of combinations from a drug developer’s perspective

1. What to combine – and for whom?
   - Lessons from combining a MEK inhibitor with a PI3K inhibitor or an HDM2 inhibitor

2. Challenges in clinical development:
   - Drug-drug interactions
   - Trial design
   - Regulatory requirements
   - Commercial consequences

3. Is there a scientific basis for 2 vs. Many?
   - The complexity of cancer likely requires higher-order combinations

4. A potential future – multiplexed drugs
Blocking both PI3K & MAPK pathways with potent inhibitors of Class I PI3Ks (SAR245408 & SAR245409) and MEK1/2 (Pimasertib) may lead to greater tumor cell death versus each agent alone.

<table>
<thead>
<tr>
<th>In vitro activity profile (IC50, nM)</th>
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</thead>
<tbody>
<tr>
<td><strong>Family</strong></td>
</tr>
<tr>
<td><strong>PI3K</strong></td>
</tr>
<tr>
<td>Class IA</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Class IB</td>
</tr>
<tr>
<td>PI3K related</td>
</tr>
</tbody>
</table>

SAR245408: formerly XL147
SAR245409: formerly XL765
Pimasertib or MSC1936369B or AS703026

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Pimasertib + PI3Ki combination in dual KRAS/PIK3CA mt CRC PDX models – Efficacy

CR-IGR-0023M (KRAS G12D / PI3K E542K)

CR-LRB-0008M (KRAS G12V / PI3K E545K)

CR-IGR-0032P (KRAS G12D / PI3K E545K)*

Pimasertib + PI3Ki combination in dual KRAS/PIK3CA mt PDXs upon combination therapy

Potent anti-tumor activity in KRAS/PIK3CA mt PDXs upon combination therapy

WIN 2014 Symposium • 23-24 June • Paris • France
Combination of a MEK inhibitor, pimasertib (MSC1936369B), and a PI3K/mTOR inhibitor, SAR245409, in patients with advanced solid tumors: Results of a phase Ib dose-escalation trial. ASCO 2013, Rebecca Suk Heist et al.

- In Phase 1, 53 pts treated, DLTs skin rash, asthenia (Gr 3)
- Four expansion cohorts (18 pts each): dual KRAS/PIK3CA mutated (mt) colorectal cancer (CRC), triple-negative breast cancer, KRAS mt non-small cell lung cancer (NSCLC) and BRAF mt melanoma.
- 4 partial responses: KRAS mt CRC (n=1) and low-grade ovarian cancer (n=3, 1 KRAS mt/PIK3CA mt and 2 wild-type).
Pimapsertib and SAR245409 combination phase Ib trial: activity in low grade serous ovarian cancer

Tumor percentage size change, LGSOC patients

Clinical activity in patient 104-0002

3/12/2012

6/17/2013

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S Sidhu et al., AACR 2013
SAR405838 and pimasertib: complementary induction of cell death mediators
An enhancer compound library screen identified MEK inhibitors as synergistic combination partners for SAR405838

Performed at Zalicus, Inc. (Cambridge, MA)

Run SAR405838 in pairwise combinations (200 compound enhancer library of SOC and targeted mechanisms)

Clear hit: MEK is the most significantly enriched enhancer target in the screen

Context: Synergy observed in p53 WT cells that exhibit MAPK pathway activation

Cytostasis converted to complete cytotoxicity

C32: B-Raf mutant, PTEN null melanoma

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S Rowley et al., AACR 2014
Validation of screening results: extension to additional Ras/Raf mutant contexts and clinically relevant MEK inhibitors

**Synergy results using Ray Design methodology**
*Ras/Raf mutant, p53 WT cell lines*

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Mutation</th>
<th>Tumor type</th>
<th>SAR405838 + pimasertib</th>
<th>SAR405838 + trametinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT1197</td>
<td>Nras</td>
<td>Bladder</td>
<td>Synergy</td>
<td>Synergy</td>
</tr>
<tr>
<td>KU-19-19</td>
<td>Nras</td>
<td>Bladder</td>
<td>Synergy</td>
<td>Trend to synergy</td>
</tr>
<tr>
<td>SKMEL103</td>
<td>Nras</td>
<td>Melanoma</td>
<td>Synergy</td>
<td>Synergy</td>
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<tr>
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<tr>
<td>UACC62</td>
<td>Braf</td>
<td>Melanoma</td>
<td>Trend to synergy</td>
<td>Trend to synergy</td>
</tr>
<tr>
<td>C32</td>
<td>Braf</td>
<td>Melanoma</td>
<td>Synergy</td>
<td>Synergy</td>
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<tr>
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<td>CRC</td>
<td>Synergy</td>
<td>Synergy</td>
</tr>
<tr>
<td>NCI-H460</td>
<td>Kras</td>
<td>NSCLC</td>
<td>Inconclusive</td>
<td>Synergy</td>
</tr>
</tbody>
</table>

**Isobologram: HT1197**
*SAR405838 + pimasertib*

Jean-Paul Nicolas, Françoise Hervé, Laurent Dassencourt, Fanny Windenberger

**WIN 2014 Symposium • 23-24 June • Paris • France**

S Rowley et al., AACR 2014
SAR405838 and pimasertib: complementary induction of cell death mediators
Development Considerations

- Drug-Drug interactions: pharmacology, safety, and efficacy considerations for choosing combinations
- Trial design considerations: getting the right combination dose
- Regulatory guidance: “Because co-development generally will provide less information about the individual new investigational drugs, it may present greater risk compared to clinical development of an individual drug”
  [Codevelopment of Two or More New Investigational Drugs for Use in Combination. FDA Guidance to Industry, June 2013]
- Commercial considerations:
  - Investment in development increases, as there are more dose cohorts, patient selection, biomarkers, etc
  - Risk in development is not decreased
  - The ideal combination partner may not be accessible
The complexity of cancer likely requires higher-order combinations

Triple combination of HDM2i + PI3Ki + MEKi caused more growth inhibition than any two-way combination of these agents

Hanahan and Weinberg, Cell, 2000 Jan 7;100(1):57-70

Saiki et al, Oncotarget, 2014 Apr 30;5(8):2030-43
One injection – 5 genes silenced in vivo in lung

5 siRNAs targeting different genes

Data from Daniel G. Anderson, MIT, with permission

5 EC genes silenced 60-80% with total dose 0.25 mg/kg
Nanoparticles carrying miR-34a or siRNA targeting Kras delay lung tumor progression

Data from Daniel G. Anderson, MIT, with permission
RNA Combination Therapy Delivered to NSCLC Model

- Kras\(^{G12D}\) activation and p53 loss drives NSCLC

Data from Daniel G. Anderson, MIT, with permission
Acknowledgements

- Dan Anderson and colleagues, MIT
- SAR and pimasertib PIs, patients, and families
- Merck Serono Oncology
- Sanofi Oncology