Combined Population PK Modeling and Disproportionality Analyses to Assess the Association between Kinase Inhibition and Adverse Reactions

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Kinase Inhibitors
Background

A kinase is a type of enzyme that transfers phosphate groups from high-energy donor molecules (such as ATP) to specific substrates, a process referred to as phosphorylation.

Kinase includes lots of oncogene, so phosphorylation by kinases is a necessary step in some cancers.

Kinase inhibitors are used as drugs to treat these cancers by inhibiting kinases.
Adverse Reactions of KIs

Background

Figure 1. Toxocities Associated With Signal Transduction Inhibitors.*Associated predominantly with monoclonal antibodies. ATE indicates arterial thromboembolism; CSR, central serous retinopathy; HZV, herpes zoster virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PAOD, progressive arterial occlusive disease; RVO, retinal vein occlusion; SCC, squamous cell cancer; VTE, venous thromboembolism.
Aim and Methods Outline

Aim: to assess the association between kinase inhibition and adverse reactions

A (drug exposure, PK)
1. Collect pharmacokinetic (PK) data of FDA-approved KIs
2. Conduct population PK modeling to calculate $C_{\text{ave}}$ (average plasma concentration) at steady state

B (in vitro kinase inhibitory activity)
1. Literature search to collect constant dissociation ($K_d$) data
2. Literature search to collect inhibitory percent (%) data

C (incidence of adverse reactions)
1. Collect safety data of FDA-approved KIs
2. Standardize ontology of adverse reactions (ARs)
3. Calculate incidence of ARs

D (association score)
An association score matrix of 2098 ARs (preferred terms) and 257 kinases
**Association Score Matrix**

**Methods**

**Association score:** 

\[ I \times K = \sum (i_{zx}) \times \left( \frac{C_{ave}}{k_{xy}} \right) = A \]

- **I (matrix):** adverse reactions incidence
- **K (matrix):** kinase inhibition \( \left( \frac{C_{ave}}{K_d} \right) \)
- **A (matrix):** association score (AS)

**Limitation**

A false positive may be included when a high association score was obtained with a high AR incidence but moderate kinase inhibition.

**Solution**

After identifying AR associated KIs, only keep the preliminary identified kinases (by association score) which can be inhibited with > 95% activity by any identified KIs.
# Data from 17 Kinase Inhibitors

## Results

<table>
<thead>
<tr>
<th>Kinase Inhibitors (KIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Axitinib (Inlyta)</td>
</tr>
<tr>
<td>2 Pazopanib (Votrient)</td>
</tr>
<tr>
<td>3 Sorafenib (Nexavar)</td>
</tr>
<tr>
<td>4 Vandetanib (Caprelsa)</td>
</tr>
<tr>
<td>5 Crizotinib (Xalkori)</td>
</tr>
<tr>
<td>6 Erlotinib (Tarceva)</td>
</tr>
<tr>
<td>7 Gefitinib (Iressa)</td>
</tr>
<tr>
<td>8 Lapatinib (Tykerb)</td>
</tr>
<tr>
<td>9 Bosutinib (Bosulif)</td>
</tr>
<tr>
<td>10 Dasatinib (Sprycel)</td>
</tr>
<tr>
<td>11 Imatinib (Gleevec)</td>
</tr>
<tr>
<td>12 Nilotinib (Tasigna)</td>
</tr>
<tr>
<td>13 Sunitinib (Sutent)</td>
</tr>
<tr>
<td>14 Cabozantinib (Cometriq)</td>
</tr>
<tr>
<td>15 Ponatinib (Iclusig)</td>
</tr>
<tr>
<td>16 Regorafenib (Stivarga)</td>
</tr>
<tr>
<td>17 Afatinib (Gilotrif)</td>
</tr>
</tbody>
</table>

### 17 KIs

1. Incidence of adverse reactions (ARs)
2. Inhibitory percent (%) data against 283 kinases

### 13 KIs

1. Pharmacokinetic (PK) data
2. Dissociation constant ($K_d$) data against 257 kinases


An Example
To identify kinases associated with hypertension

<table>
<thead>
<tr>
<th>Kinase</th>
<th># Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR2</td>
<td>6</td>
</tr>
<tr>
<td>FLT1</td>
<td>6</td>
</tr>
<tr>
<td>FLT4</td>
<td>6</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>6</td>
</tr>
<tr>
<td>PDGFRB</td>
<td>5</td>
</tr>
<tr>
<td>FGFR2</td>
<td>5</td>
</tr>
<tr>
<td>KIT</td>
<td>4</td>
</tr>
<tr>
<td>FGFR3</td>
<td>3</td>
</tr>
<tr>
<td>FGFR1</td>
<td>2</td>
</tr>
<tr>
<td>RAF1</td>
<td>2</td>
</tr>
<tr>
<td>AURKC</td>
<td>1</td>
</tr>
</tbody>
</table>

Preliminary identified kinases leading to hypertension: VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR α, PDGFR β, TTK, ...
(27 kinases in total)

Identify hypertension associated KIs: pazopanib, axitinib, regorafenib, sorafenib, vandetanib, cabozantinib (6 KIs in total)

Only keep preliminary identified kinases which can be inhibited with > 95% activity by any identified 6 KIs.
Results

4279 associations involving 534 ARs (preferred terms) and 140 kinases were identified.

Well-established pairs of kinase inhibition and ARs were confirmed:

- hypertension – VEGFR2;
- rash – EGFR/HER4;
- conjunctivitis – EGFR;
- fluid retention;
- diarrhea – EGFR;
- pulmonary hypertension – ABL;
- QT prolongation – VEGFR;
- proteinuria – VEGFR.

Visualize the results using a web app: [https://jzliu.shinyapps.io/KINASE](https://jzliu.shinyapps.io/KINASE)
KINASE: A Web App to Query the Results

Results

Kinase Inhibitory Network Associated Side Effects (KINASE)

Please select an ontology for adverse reactions

- Standardized PT (preferred term)
- HLT (higher level term)
- SOC (System Organ Class)
- CMQ (Customized MedDRA Query)

Please select a standardized PT

hypertension

hypertension is the selected adverse reaction (AR)

6 of KIs that are potentially associated with the selected AR

Association between kinase inhibition and ARs

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Adverse reaction</th>
<th>Count</th>
<th>Expected count</th>
<th>False discovery rate (FDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT1</td>
<td>hypertension</td>
<td>255768.301130283</td>
<td>200918.133767855</td>
<td>0</td>
</tr>
<tr>
<td>FLT4</td>
<td>hypertension</td>
<td>128519.207268873</td>
<td>98487.1029497328</td>
<td>0</td>
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<tr>
<td>KIT</td>
<td>hypertension</td>
<td>1215382.9182246</td>
<td>940403.226488005</td>
<td>0</td>
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<tr>
<td>PDGFR A</td>
<td>hypertension</td>
<td>697179.965188529</td>
<td>534696.591386896</td>
<td>0</td>
</tr>
<tr>
<td>PDGFR B</td>
<td>hypertension</td>
<td>1732664.23809598</td>
<td>1368662.23517691</td>
<td>0</td>
</tr>
</tbody>
</table>

Showing 1 to 5 of 11 entries
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