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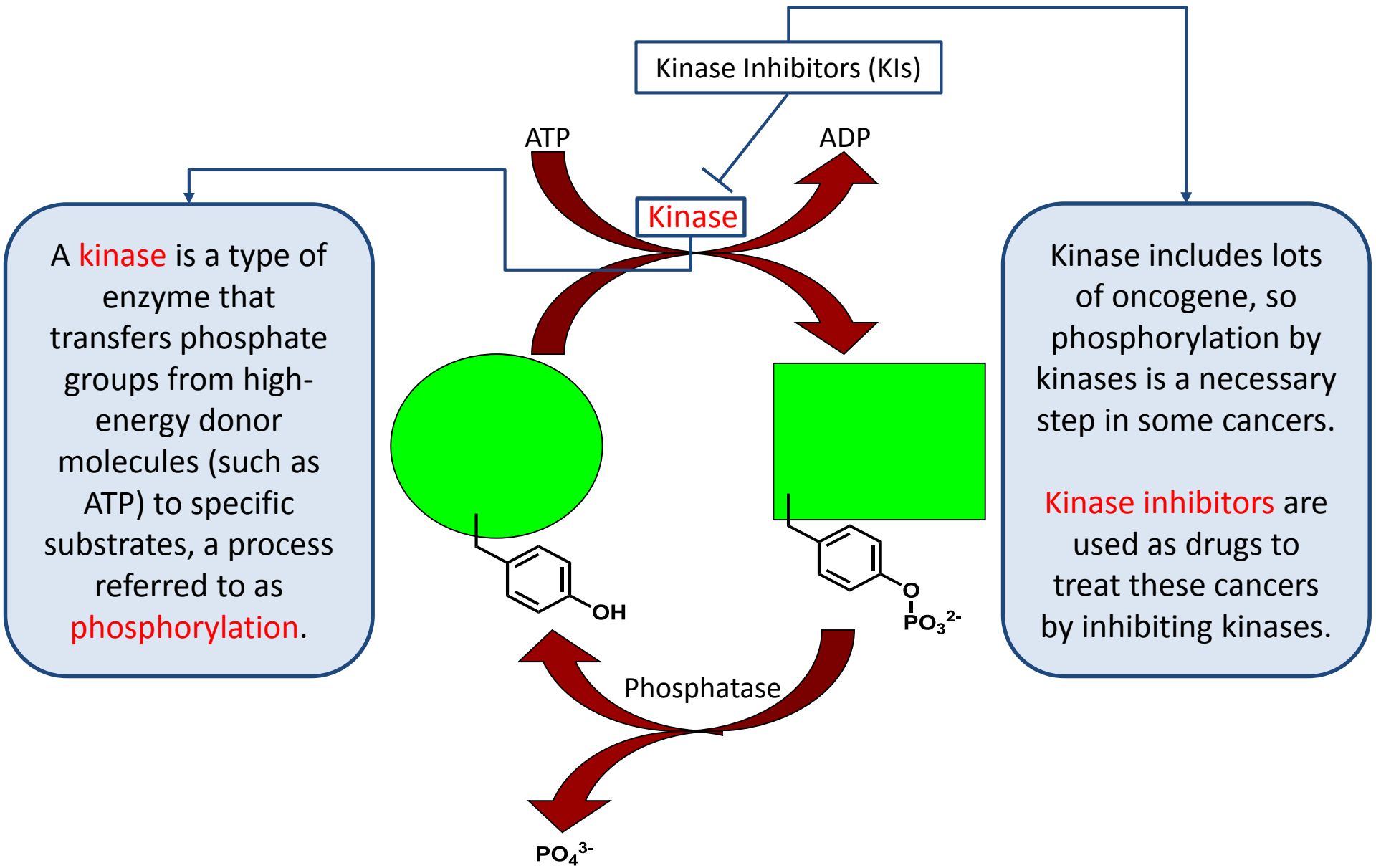
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Kinase Inhibitors (KIs)

ATP

ADP

Kinase

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.

OH

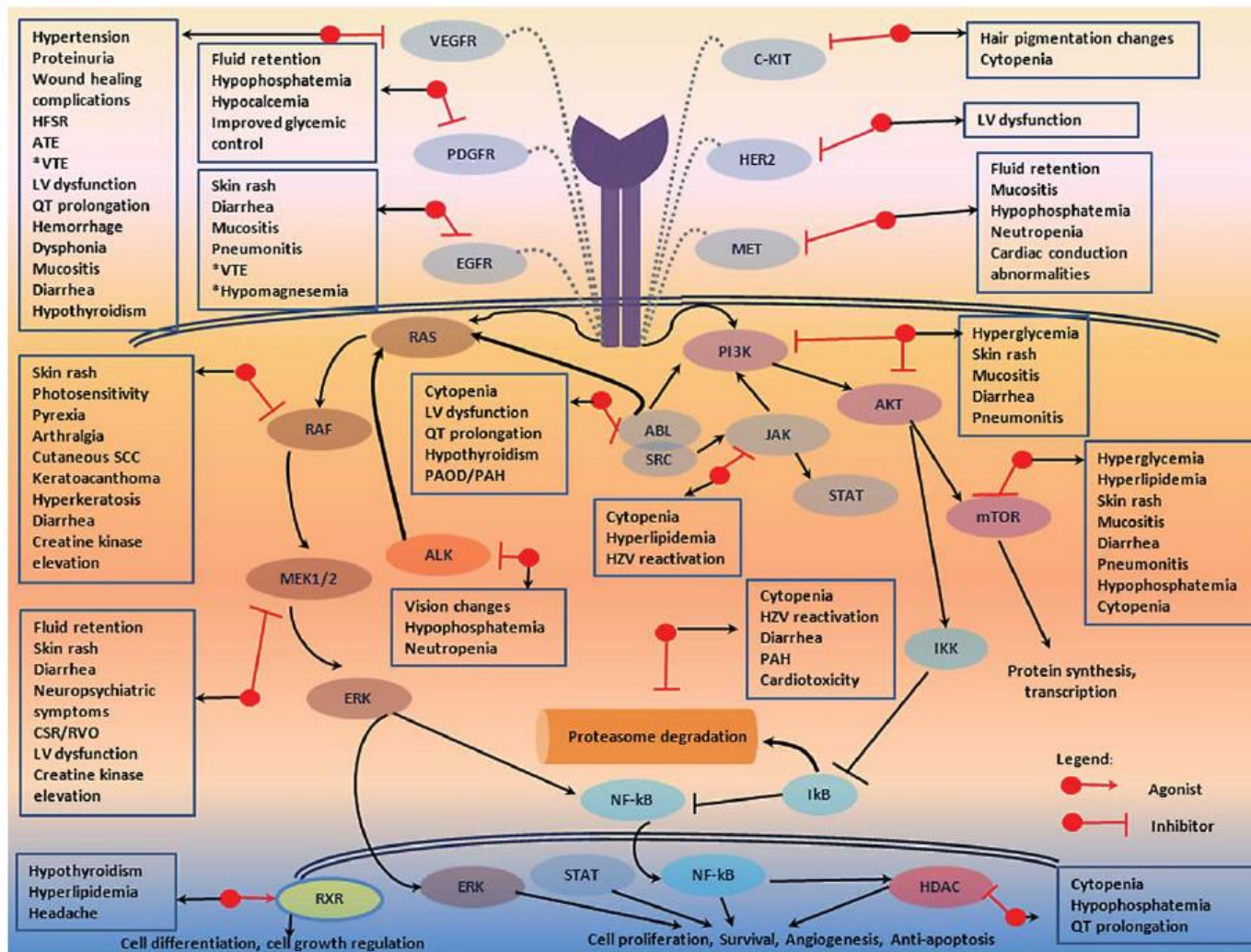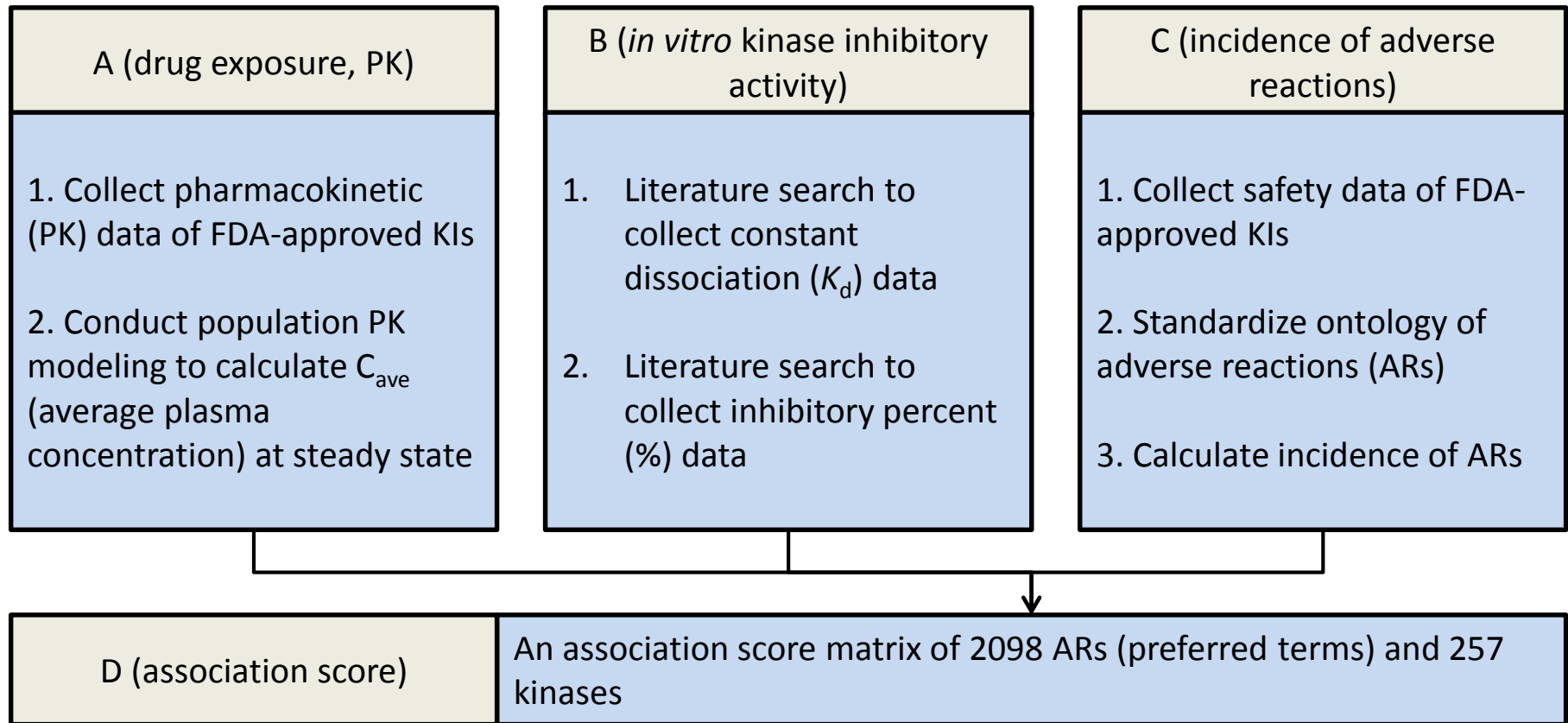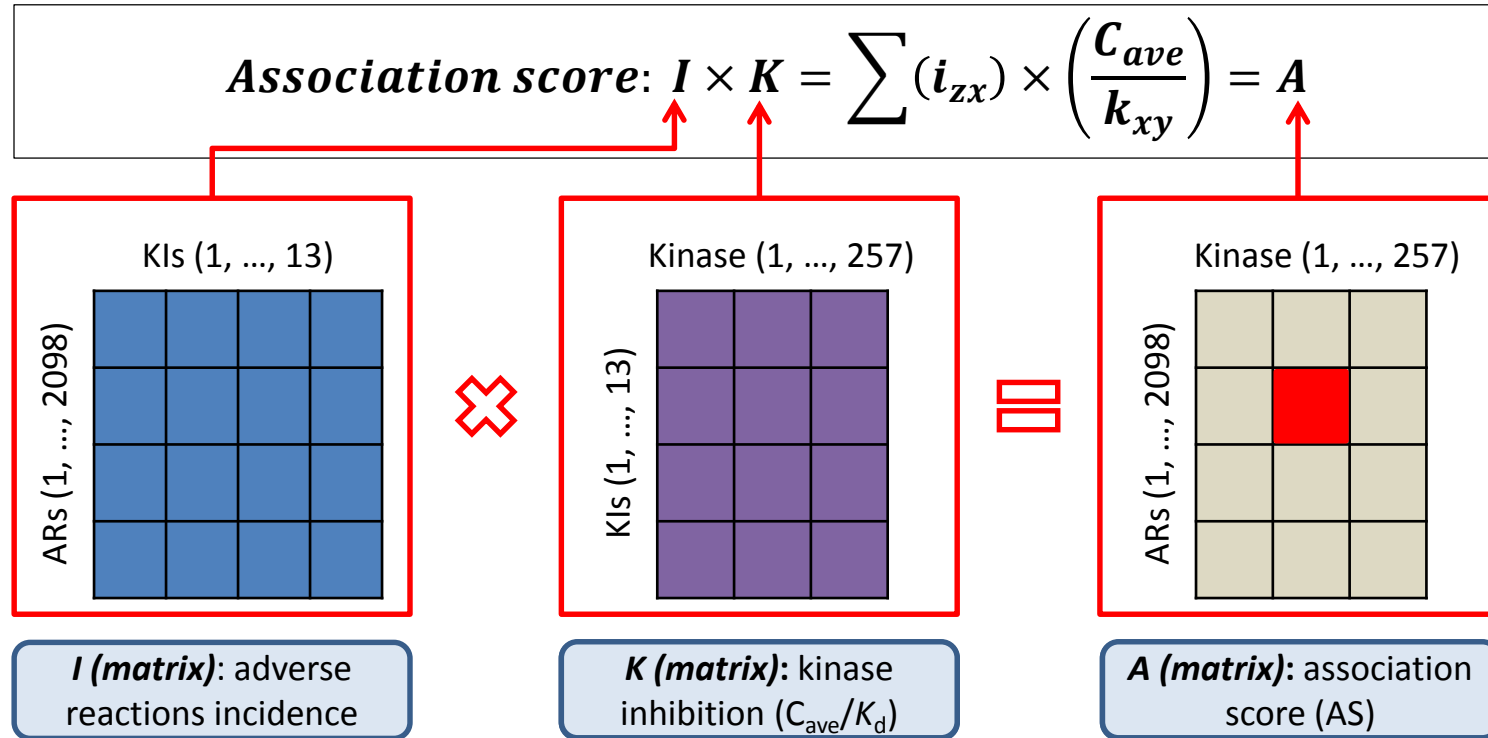PO_3^{2-}

Phosphatase

PO_4^{3-}

Background

FIGURE 1. Toxicities 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.

Grace K. Dy and Alex A. Adjei, CA Cancer J Clin 2013; 63: 249–279

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

A (drug exposure, PK)	B (*in vitro* kinase inhibitory activity)	C (incidence of adverse reactions)
1. Collect pharmacokinetic (PK) data of FDA-approved KIs 2. Conduct population PK modeling to calculate C_{ave} (average plasma concentration) at steady state	1. Literature search to collect constant dissociation (K_d) data 2. Literature search to collect inhibitory percent (%) data	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

$$\textbf{\textit{Association score}}: \textbf{\textit{I}} \times \textbf{\textit{K}} = \sum(\textbf{\textit{i}}_{zx}) \times \left(\frac{\textbf{\textit{C}}_{ave}}{\textbf{\textit{k}}_{xy}}\right) = \textbf{\textit{A}}$$

KIs (1, ..., 13)

ARs (1, ..., 2098)

Kinase (1, ..., 257)

KIs (1, ..., 13)

Kinase (1, ..., 257)

ARs (1, ..., 2098)

I (matrix): adverse reactions incidence

K (matrix): kinase inhibition (C_{ave}/K_d)

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.

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

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

Reference for inhibitory percent data:
Uitdehaag JC et al. PLoS One. 2014 Mar; 9(3): e92146

Reference for K_d data:
Davis MI et al. Nat Biotechnol. 2011 Oct; 29(11): 1046-51
Karaman MW et al. Nat Biotechnol. 2008 Jan; 26(1): 127-32

An Example

To identify kinases associated with hypertension

Kinase (1, ..., 266)

ARs (1, ..., 2098)
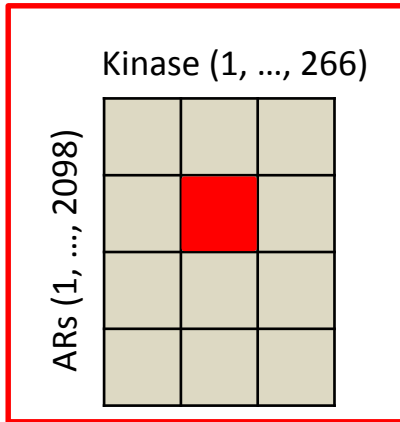
Preliminary identified kinases leading to hypertension: VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR α, PDGFR β, TTK, ... (27 kinases in total)

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.

Kinase	# Inhibition
VEGFR2	6
FLT1	6
FLT4	6
PDGFRA	6
PDGFRB	5
FGFR2	5
KIT	4
FGFR3	3
FGFR1	2
RAF1	2
AURKC	1

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

KINASE: A Web App to Query the Results

Results