Non-synonymous single nucleotide polymorphisms (nsSNPs) in non receptor tyrosine kinases (nRTKs) may serve as oncologic targets and predictive biomarkers, with significant lesions described in various nRTK regions including the tyrosine kinase domain (TKD).

Next Generation Sequencing (NGS) allows the entire coding sequence to be evaluated. This facilitates the identification of novel lesions.

We searched all nsSNPs in 14 nRTKs in the tumors of patients (pts) at our institution that received NGS with Caris Life Sciences\(^1\) from 2013-2015 with a diagnosis of advanced breast, colon or lung cancer.

Substitutions were classified as either within or extra-TKD; in the case of JAK1-3, pseudokinase domain lesions were also identified.

In order to predict the pathogenicity of nsSNPs, \textit{in silico} analysis with PolyPhen-2 (Harvard)\(^2,3\) was completed.

13% of breast, colon, and lung tumors harbored an nRTK nsSNP that was predicted-damaging by \textit{in silico} analysis.

68% of these mutations occurred outside of the TKD, with an additional 9% in JAK1-3 pseudokinase domain.

NGS can identify nsSNPs in various nRTK regulatory domains that warrant further characterization.

Further work is needed to determine how these pnsSNPs affect function and if they are clinically actionable.

169/356 (47%) of patients had \(\geq 1\) nRTK lesion (range 0-8).

245 variants were found including 200 nsSNPs and 45 known pathogenic (PATH) mutations:

- PIK3CA (19 breast, 13 colon, 5 NSCLC)
- AKT1 (5 breast)
- pnsSNPs were found in 14/14 nRTKs.

52/200 (26%) nsSNPs were predicted-damaging (pnsSNPs) among 49 pts (6 breast, 13 colon and 30 NSCLC).

The nRTKs most frequently predicted damaging:

- Breast: SRC (2/2 variants were pnsSNPs) and ABL2 (1/5)
- Colon: ABL1 (5/10), JAK3 (3/27) and CDK12 (2/8)
- NSCLC: JAK3 (6/20), BTK (5/8), ABL1 (3/12), JAK2 (3/11), CDK12 (3/9) and JAK1 (3/3).

Of 180 nsSNPs with \textit{in silico} results:

- 68% were extra-TKD (29/122 variants were pnsSNPs)
- 23% within the TKD (13/42)
- 9% in pseudokinase domains of JAK1-3 (10/16). Notably, 8/10 pseudokinase domain pnsSNPs were in NSCLC pts (3 JAK1, 2 JAK2 and 3 JAK3).

### METHODS

We searched all nsSNPs in 14 nRTKs in the tumors of patients (pts) at our institution that received NGS with Caris Life Sciences\(^1\) from 2013-2015 with a diagnosis of advanced breast, colon or lung cancer.

Substitutions were classified as either within or extra-TKD; in the case of JAK1-3, pseudokinase domain lesions were also identified.

In order to predict the pathogenicity of nsSNPs, \textit{in silico} analysis with PolyPhen-2 (Harvard)\(^2,3\) was completed.

### RESULTS

#### SNPs by nRTK

<table>
<thead>
<tr>
<th>nRTK</th>
<th>Number of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>10</td>
</tr>
<tr>
<td>ABL2</td>
<td>1</td>
</tr>
<tr>
<td>AKT1</td>
<td>3</td>
</tr>
<tr>
<td>AKT2</td>
<td>1</td>
</tr>
<tr>
<td>AKT3</td>
<td>3</td>
</tr>
<tr>
<td>BTK</td>
<td>5</td>
</tr>
<tr>
<td>JAK1</td>
<td>3</td>
</tr>
<tr>
<td>JAK2</td>
<td>6</td>
</tr>
<tr>
<td>JAK3</td>
<td>3</td>
</tr>
<tr>
<td>SRC</td>
<td>2</td>
</tr>
<tr>
<td>CDK2</td>
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</tr>
<tr>
<td>CDK4</td>
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<tr>
<td>CDK6</td>
<td>3</td>
</tr>
<tr>
<td>PIK3CA</td>
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</tr>
</tbody>
</table>

### CONCLUSIONS

- 13% of breast, colon, and lung tumors harbored an nRTK nsSNP that was predicted-damaging by \textit{in silico} analysis.
- 68% of these mutations occurred outside of the TKD, with an additional 9% in JAK1-3 pseudokinase domain.
- NGS can identify nsSNPs in various nRTK regulatory domains that warrant further characterization.
- Further work is needed to determine how these pnsSNPs affect function and if they are clinically actionable.

### REFERENCES


### DISCLOSURES: Presenting authors, Srishti Sareen and Matthew Stein received travel scholarships from Caris Life Sciences to attend ASCO Annual Meeting 2017.