Localization of Non-Receptor Tyrosine Kinase (nRTK) Variants in Solid Tumor Patients Using Next-Generation Sequencing (NGS)

Srishti Sareen, Matthew K Stein, Lindsay K Morris, Saradasri Karri, Kruti Patel, David Shibata, Ari M Vanderwalde, Lee S Schwartzberg, Mike G Martin

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

The University of Tennessee WEST Cancer Center — Methodist Healthcare Family

BACKGROUND

- 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.

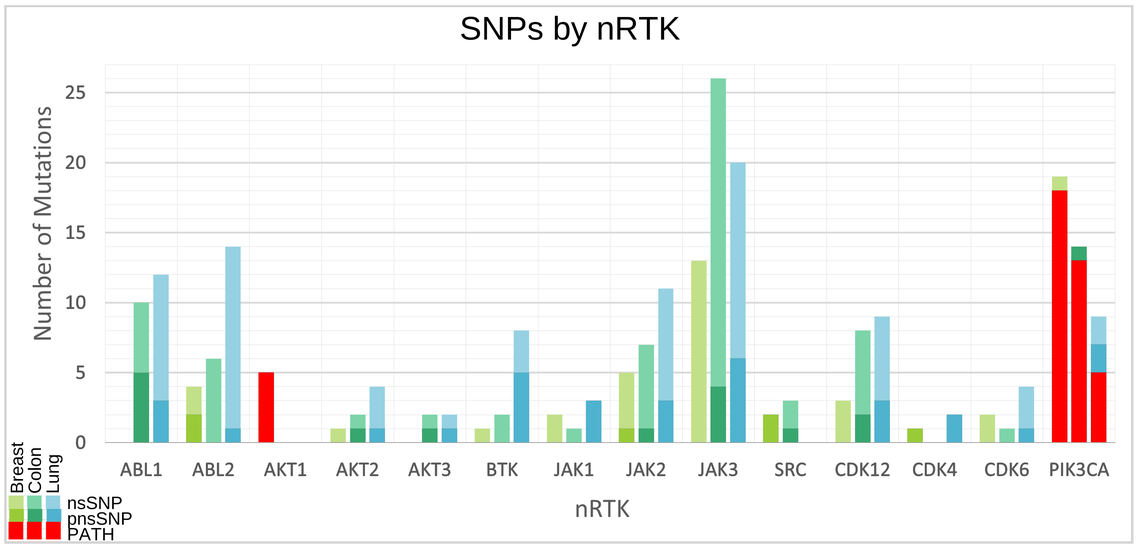
METHODS

- 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, *in silico* analysis with PolyPhen-2 (Harvard)[2,3] was completed.

RESULTS

VARIABLE	NUMBER (%)
Patients	**356**
Cancer type	
Breast	79 (22%)
Colon	110 (31%)
Non-small cell Lung	156 (44%)
Small cell Lung	11 (3%)
Median age	**61 (range 26-86)**
Sex	
Female	206 (58%)
Male	150 (42%)
Race	
White	220 (62%)
Black	124 (35%)

- 169/356 (47%) of patients had ≥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 *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).

CONCLUSIONS

- 13% of breast, colon, and lung tumors harbored an nRTK nsSNP that was predicted-damaging by *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

[1] **Caris Life Sciences**. (2016). http://www.carislifesciences.com

[2] **Adzhubel IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR**. PolyPhen 2. *Nat Methods; 7(4): 248-249*. (2010). http://genetics.bwh.harvard.edu/pph2/

[3] **Hahn AW, Giri S, Patel D, et al.** Next-generation sequencing and in silico analysis facilitate prolonged response to pazopanib in a patient with metastatic urothelial carcinoma of the renal pelvis. *J Natl Compr Canc Netw; 2015(13): 1181-1185. (2015).*

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

INQUIRIES: Please contact
•M.K. Stein, mstein3@uthsc.edu
•M.G. Martin, mmartin@westclinic.com