Abstract #287

NantHealth/NantOmics

# Clinical trial screening of CDKN2A genomic alterations in patients with Pancreatic cancer and Hepatobiliary cancers requires greater precision than somatic sequencing alone.


CONTRIBUTING RESEARCHERS

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## BACKGROUND

The TAPUR Study is a phase II multi-basket study that evaluates the anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations known to be drug targets. Results in two cohorts of pancreatic cancer and gall bladder patients each with *CDKN2A* loss or mutation were reported at ASCO 2018. The conclusion was that monotherapy with palbociclib is not associated with clinical activity in these patients. This may be a false conclusion if the genomic targets were absent in these patients.

## METHODS

A total of 158 GI pts (P = 123, GB = 20, Bile Duct = 15) with deep whole exome sequencing (WES, >200x coverage) of tumor and blood samples, and whole transcriptomic sequencing (RNA-Seq) (~200x$10^6$ reads per tumor) were available for this analysis from a commercial database. Variant calling was performed through joint probabilistic analysis of tumor and normal DNA reads, with germline status of variants being determined by heterozygous or homozygous alternate allele fraction in the germline sample. Gene expression levels were determined with BowTie alignments and RSEM quantification.

## RESULTS

There were 26 somatic variants, 1 of which is not expressed, and there are 12 germline variants, with one sample overlapping with a germline and a somatic variant (p.A148T and p.A76Rfs*44).
Counting all 11 germline variants as false positives, a total 37 of 158 samples would be positive for CDKN2A mutant status, a rate of 23% (17%-31% CI). 11 germline and one unexpressed DNA variant would be false positives, for a false positive rate of 32% (18%-50% CI). However, if the 8 common germline variants are excluded, the call rate is 29/158 = 18% (12%-25% CI). The false positive rate is 4/22 = 18% (12%-40% CI).

CDKN2A SOMATIC VARIANTS

| Coding_Change | Variant | Class |
|---|---|---|
| c.139_150+1del | __c.139_150+1del__ | Splice Site |
| c.457+1G>A | __c.457+1G>A__ | Splice Site |
| c.225dupC | __p.A76Rfs*44__ | Frame Shift |
| c.225_238del | __p.A76Tfs*39__ | Frame Shift |
| c.257C>A | __p.A86D__ | Missense |
| c.346_347ins | __p.D116Afs*6__ | Frame Shift |
| c.80_81del | __p.E27Gfs*16__ | Frame Shift |
| c.181G>T | __p.E61*__ | Nonsense |
| c.164G>A | __p.G55D__ | Missense |
| None | __p.G69Gfs*101__ | Frame Shift |
| c.247C>T | __p.H83Y__ | Missense |
| c.247C>T | __p.H83Y__ | Missense |
| c.47_50del | __p.L16Pfs*9__ | Frame Shift |
| c.185_208del | __p.L62_E69del__ | In-Frame Del. |
| c.341C>G | __p.P114R__ | Missense |
| None | __p.P94L__ | Missense |
| c.172C>T | __p.R58*__ | Nonsense |
| c.172_173ins | __p.R58Pfs*62__ | Frame Shift |
| c.238C>T | __p.R80*__ | Nonsense |
| c.238C>T | __p.R80*__ | Nonsense |
| c.19delA | __p.S7Afs*19__ | Frame Shift |
| c.228delC | __p.T77Lfs*69__ | Frame Shift |
| c.83_100del | __p.V28_E33del__ | In-Frame Del. |
| c.240_245delins | __p.V82Rfs*64__ | Frame Shift |
| c.387C>A | __p.Y129*__ | Nonsense |
| c.132delC | __p.Y44*__ | Frame Shift |
| c.131_132ins | __p.Y44*__ | Frame Shift |

CDKN2A_ GERMLINE VARIANTS

| Protein_Change |
|---|
| p.G63R |
| p.A148T |
| p.A148T |
| p.A57V |
| p.A148T |
| p.A148T |
| p.A148T |
| p.A148T |
| p.A148T |
| p.G101W |
| p.A148T |
| p.G63R |

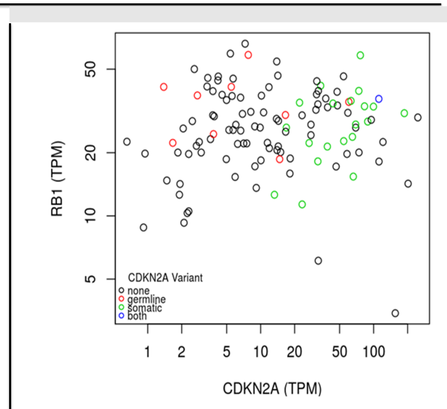


FIGURE 1: RNAseq, true somatic CDKN2A variants had significantly higher TPM counts than germline variants (T-test p=0.0002).

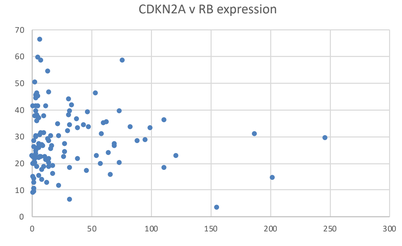


FIGURE 2: RNAseq, RB was consistently expressed and RB status was not dependent on CDKN2A status

## CONCLUSIONS

Somatic only sequencing would have identified 37/158 patients as TAPUR eligible
Population AF filtering at 0.5% would have removed 8 patients

Matched germline:somatic sequencing further reduced the pool to 25/158 patients as true CDKN2A variants (15.8%)

4 patients (3%) would have been incorrectly considered TAPUR eligible

True somatic CDKN2A variants had significantly higher TPM counts than germline variants (T-test p=0.0002).

RB was expressed in all cases at some level by RNAseq, and this RB loss is an unlikely explanation for lack of clinical activity of palbociclib in this population