PI3K/PTEN/Akt/mTOR pathway aberrations and co-incidence of hormone receptors and HER2 in 19,784 diverse solid tumors

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Abstract

Background: Molecular aberrations in the phosphatidylinositol 3-kinase (PI3K) pathway have been documented across cancers, especially *PIK3CA* mutations and mutation or loss of PTEN. These alterations may be relevant to therapies targeting the PI3K/PTEN/Akt/mTOR signaling pathway.

Methods: Molecular profiling was performed on 19,784 tumors (>40 cancer types) at a CLIA-certified laboratory. Tests included next generation sequencing (NGS), protein expression (immunohistochemistry), and gene amplification (FISH or CISH).

Coverage	
Gene	**Amino Acids Covered**
PIK3CA	75-118, 336-353, 418-555, 692-729, 979-1068
PTEN	1-27, 165-267, 280-342
AKT1	16-47

Results: Frequency and type of *PIK3CA, AKT1* and *PTEN* mutations were collated across cancers. Aggregate gene mutation rates (47 genes), protein expression rates (18 proteins), and copy number (5 biomarkers) were measured. Comparison of frequencies and correlations across cancers identified lineage-specific differences, and co-incidences of associated biomarkers, which will be described. Of note, endometrial, breast, cervical, anal squamous cell, and bladder cancers had the highest *PIK3CA* mutation rate (37%, n=1600; 31%, n=2282; 29%, n=284; 28%, n=67, 22%, n=303, respectively). Patterns in *AKT1* and *PTEN* mutation rates differed by cancer, as did PTEN loss - hepatocellular, 57%, prostate, 52%, and endometrial 50% loss. Co-mutation of *PTEN* and *PIK3CA* occurred in 1.5% of breast, 0% of prostate, and 12% of endometrial cancers. Of interest, PIK3CA mutations and PTEN loss co-occurred frequently, e.g. 31% of *PIK3CA* mutated patients also have a PTEN loss.
PIK3CA mutations across cancers were distributed 43% in exon 9, 33% in exon 20, and 24% in other exons. Distribution of *PIK3CA* mutations by cancer type varied and occurred more frequently in the presence of HER2 protein expression or copy number increase (p=0.0001) and more frequently in the presence of hormone receptor overexpression (androgen receptor (AR), progesterone receptor (PR), and estrogen receptor (ER)) (p=0.0335). PTEN loss was seen in 27% of patients with and 30% without HER2 overexpression or amplification (p=0.004).

Conclusions: Patterns of biomarker co-alterations across cancers may provide new insights relevant to targeted therapy and may be crucial to optimizing combination treatments.

Co-Incidence of Biomarker Aberrations in the presence or absence of PIK3C*A* or PTEN Mutations

Table 1. A. Aggregate differences in gene mutation rates, protein expression rates, and copy number were measured and are shown between PIK3C*A* WT and PIK3C*A* MT patients and between PTEN WT and PTEN MT cases. **B.** Total mutations identified out of total cases tested, each, for PIK3C*A* or PTEN.

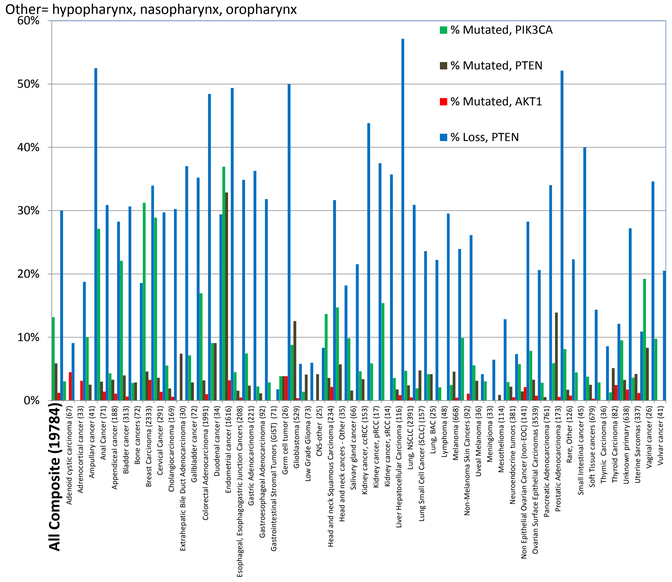
A.	Next Gen Seq, % Mutated												IHC, % Protein Expression above threshold, unless noted								ISH	
Biomarker	TP53	BRAF	KRAS	HRAS	FBXW7	FGFR2	HNF1A	ATM	CTNNB1	ERBB2	PTEN	PIK3CA	PTEN loss	TOP2A	AR	ER	PR	MGMT	PGP	TS	HER2	HER2	cMET
PIK3CA WT	49	3.8	16	0.5	2	1	1	3	2	1	5	n/a	29	73	16	23	13	58	17	49	6	3.5	1.4
PIK3CA MT	35	2.1	21	1.0	6	3	2#	4	7	2	16	n/a	31	86	29	44	33	54	12	52	11	6.4	0.2
PTEN WT	47	3.6	17	0.5	2	1	1	3	2	1	n/a	12	74	73	18	24	14	58	17	49	7	4.1	1.3
PTEN MT	34	4.1#	19#	0.4#	6	7	5	5	12	2	n/a	33	27	84	23	49	42	42	10	60	4	0.9	0.2

All differences are significant (p value<0.05), unless indicated with a #.

B.	PIK3CA	PTEN
MT/Total	2548/19784	1108/18885
% Total	13.2%	5.9%

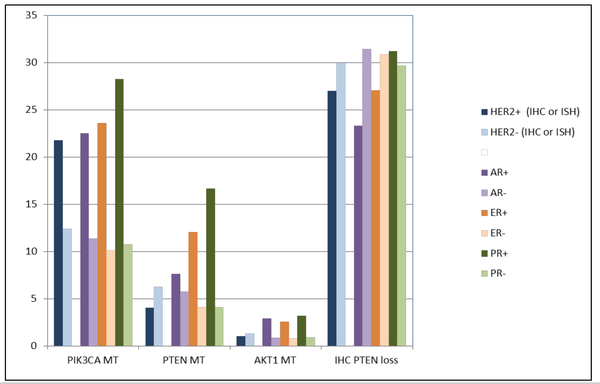
PIK3CA, PTEN, AKT1 Mutation and PTEN Loss by Lineage

Figure 1. Percent PIK3CA, *PTEN*, AKT1 mutation and PTEN loss were compared across cancers.
Total cases by lineage are indicated in parentheses. Total cases tested=19784.
CNS-other =neuroblastoma, medulloblastoma, ependymoma, ganglioglioma; Head and neck cancers – Other= hypopharynx, nasopharynx, oropharynx



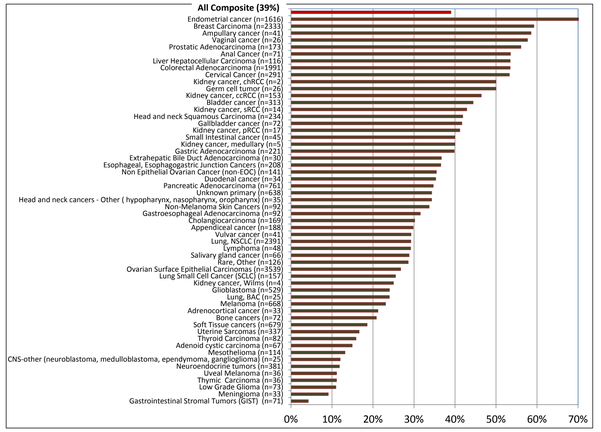
Frequency of *PIK3CA*, *AKT1*, and *PTEN* mutations or PTEN loss in presence/absence of hormone receptors or HER2

Figure 2.



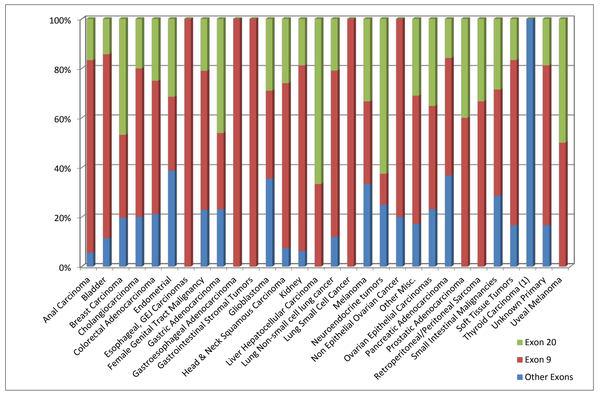
Incidence of any PI3K/AKT1/mTOR pathway aberrations, by lineage

Figure 3.



PIK3CA Mutations by Exon and Lineage

Figure 4. Distribution of PIK3C*A* mutations in helical, kinase, or other regions differ by subtype. All non-exon 9 or 20 mutations are grouped as 'Other'.



Conclusions

- 13.2% (2548/19356) of patients with diverse cancers have PIK3C*A* mutations; 33% of these mutations are found in the kinase domain and 43% in the helical domain.
- 5.9% of tumors (1108/18885) have PTEN mutations; 30% (5510/18366) have PTEN loss. The total number of patients with any PI3K/AKT/mTOR pathway aberration is 39%.
- Multiple aberrations, including but not limited to mutations in KRAS, BRAF, CTNNB1, TP53, and APC or altered expression of TS, MGMT, HER2, and hormone receptors may co-exist with PIK3C*A* or PTEN anomalies.
- PIK3C*A* mutation, PTEN mutation and PTEN loss are found in an important subset of multiple tumor types and may be targeted by inhibitors. Optimization of the drug used may require determining the specific types of aberration seen, e.g., helical versus kinase domain (PIK3C*A*) versus PTEN aberration.
- Since multiple anomalies may co-exist with PIK3C*A* or PTEN alterations, patients may require customized combinations of targeted agents to overcome resistance pathways.

References

1. Dienstmann, R, et al. (2014) "Picking the point of inhibition: a comparative review of PI3K/AKT/mTOR pathway inhibitors." Mol Cancer Ther; 13(5) 2014.
2. Janku, F et al. (2014) "Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors". Cell Reports; 6, 2014.