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## Frequency of *MET* and *PIK3CA* copy number elevation and correlation with outcome in early stage breast cancer

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### Abstract

**Purpose**—To determine the frequency and association with relapse-free survival (RFS) of *MET* and *PIK3CA* copy number elevations in early stage breast cancer.

**Methods**—Tumor DNA was extracted from 971 formalin-fixed paraffin-embedded early breast cancers for molecular inversion probes arrays. Data was segmented using the SNP-FASST2 segmentation algorithm. Copy number gains were called when copy number of each segment was greater than 2.3 or 1.7 respectively. RFS was estimated by Kaplan-Meier. Cox proportional hazards models were fit to determine independent associations of copy number with RFS.

**Results**—82 (8.44%) and 134 (13.8%) of tumors had *MET* or *PIK3CA* copy number elevation respectively, and 25.6% with *MET* copy number elevation had *PIK3CA* copy number elevation. Patients with either *MET* or *PIK3CA* high copy number tended to have poorer prognostic features (larger tumor size, higher grade, and hormone receptor negativity). Both, *MET* and *PIK3CA* high copy number were more likely to occur in triple negative disease ( $P=0.019$  and  $<0.001$ , respectively). At a median follow-up of 7.4 years, there were 252 recurrences. Five-year RFS were 63.5%, and 83.1% for *MET* high copy number and *MET* normal/low copy number respectively, ( $P=0.06$ ); and 73.1%, and 82.3% for *PIK3CA* high copy number and *PIK3CA* normal/low copy number respectively, ( $P=0.15$ ). High copy number for either gene was not an independent predictor of RFS.

**Conclusion**—High copy number of *MET* or *PIK3CA* was associated with poorer prognostic features and triple negative disease. Co-amplification was frequent. Patients with high *MET* copy number tumors tended to have a worst RFS.

### Keywords

*MET*; *PIK3CA*; gene copy number; breast cancer; prognosis

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## INTRODUCTION

The hepatocyte growth factor (HGF) and its receptor, the transmembrane tyrosine kinase MET interaction leads to formation of phosphorylated MET which activates downstream effectors such as PI3K (Phosphatidylinositol-3 kinase)/AKT, PLC  $\gamma$  (Phospholipase C  $\gamma$ ), RAS-MAPK (mitogen-activated protein kinase), c-Src and STATs (signal transducer and activator of transcription) to promote cell proliferation, survival motility, and invasion, as well as morphogenic changes that in normal cells stimulate tissue repair and regeneration but are also co-opted during tumor growth.<sup>1-8</sup> MET over-expression, with or without gene amplification, has been reported in a variety of human cancers including breast, lung, and gastrointestinal malignancies.<sup>9-11</sup> Further, high levels of HGF and/or MET correlate with poor prognosis in several tumor types, including breast, ovarian, cervical, gastric, head and neck, and non-small cell lung cancer.<sup>10,12-15</sup>

The PI3K pathway plays a key role in cell growth, protein translation, autophagy, metabolism, and cell survival.<sup>16-18</sup> Thus, tight regulation of the PI3K pathway is paramount to ensure that cellular inputs are integrated for appropriate cellular outcomes. The PI3K pathway is downstream of most growth factor tyrosine kinase receptors including MET, EGFR, HER2 and IGFR that have been implicated in breast cancer. PI3K signaling is deregulated through a variety of mechanisms, including overexpression or activation of TKR, activating mutations, gene amplification of *PIK3CA* and *AKT* isoforms, as well as loss of the negative regulators PTEN and INPP4B.<sup>19,20</sup> Other forms of deregulation and aberrations of this pathway have been implicated not only in breast cancer development and progression, but also in resistance to targeted therapies directed to tyrosine kinase receptors and hormone receptors.<sup>20-23</sup> As a result, multiple drugs targeting the PI3K pathway are in early clinical trials as mono or combination therapies in breast cancer.<sup>18,24</sup>

In breast cancer, reported aberrations in the PI3K pathway have been mostly restricted to detection of activating mutations and loss of suppressors, and data in MET receptor aberrations have been limited in the disease. The purpose of this study was to determine the frequency and association with relapse-free survival (RFS) of *MET* and *PIK3CA* copy number elevations and their interaction in a large cohort of early stage breast cancer.

## MATERIALS AND METHODS

### Patients and tumor samples

Adequate tumor DNA from formalin-fixed paraffin-embedded (FFPE) tissue blocks, clinical history, and follow-up data of 1,003 patients diagnosed with early breast cancer between 1985 and 1999 were identified from the Early Stage Breast Cancer Repository (ESBCR) at MD Anderson Cancer Center. Clinical information (including patient's age, race/ethnicity, stage, tumor size, lymph node status, nuclear grade, hormone receptor (HR) status) and primary treatment (including surgery, radiotherapy therapy, chemotherapy, and endocrine therapy) was extracted from the medical records.

### Molecular inversion probes and copy number

Tumor DNA was extracted from FFPE tissues and processed for copy number analyses. Briefly, 5-10 (5- $\mu$ m) macrodissected tumor sections containing > 80% tumor cells per protocol were pooled and treated three times with proteinase K in ATL Tissue Lysis Buffer™ (Qiagen, Valencia, CA). Following lysis, samples were applied to uncoated Argylla Particles™ (Argylla Technologies, Tucson, AZ) and processed according to manufacturer recommendations (<http://www.argylla.com>). For 129 cases, DNA from non-tumor bearing lymph nodes, stored as FFPE, was isolated as an internal germline reference for the population. Tumor and normal DNA at 10 ng/ $\mu$ L was shipped to the Affymetrix™

MIP laboratory for copy number measurement. The laboratory was blinded to all sample and subject information including identity of duplicates. Data from the MIP high-density arrays are deposited at the National Center for Biotechnology Information (NCBI) (GSE31424).

Nexus Copy Number v5.1 (BioDiscovery, El Segundo, CA) was used for processing the MIP data of these patients' samples. Nexus Copy Number segmented the data using the SNP-FASST2 segmentation algorithm, and called copy number gains or losses when the estimated copy number of each segment was greater/less than 2.3/1.7 for *MET* and *PIK3CA* respectively. Each sample has, in general, a different set of segments. Common segments were derived in order to perform analyses, with a size of 77,487 of the union of all segment break-points for 971 samples. In order to reduce the dimensionality of the data, similar procedures were followed for the CGH regions. We clustered consecutive segments if no two segments within the cluster had different gain/loss calls for at least 97% of the samples. This simple criterion yielded 3378 segments with common breakpoints across all 971 samples.

### Statistical Analysis

Patient characteristics were tabulated and described by their medians and ranges by copy number (high vs. normal/low) with a chi-square test or Wilcoxon's rank sum test as appropriate. Relapse free-survival (RFS) was measured from the date of diagnosis to the date of first local/distant metastasis or last follow-up. Patients who died before experiencing a disease recurrence were considered censored at their date of death in the analysis. Survival outcomes were estimated according to the Kaplan-Meier product limit method. Using log rank statistics, groups were compared between high copy number and normal/low copy number groups for *MET*, *PIK3CA* and their co-amplifications as well as other important clinical variables. Three multivariate Cox proportional hazard models were developed. The first model incorporated *MET*, *PIK3CA*, copy number and their interaction. The second and third models incorporated either *MET* copy number or *PIK3CA* copy number and other prognostic clinical variables. Models were based on a backward selection procedure where all variables of interest were first included in a full model for screening and only variables with  $P < 0.1$  were retained.  $P$ -values less than 0.05 were considered statistically significant. Analysis was performed by using R 2.11.2. (R Development Core Team, 2010, Vienna, Austria).

## RESULTS

Table 1 illustrates the patient and tumor characteristics as well as the therapy received by *MET* and *PIK3CA* copy number groups. Eighty-two (8.44%) were found to have elevated *MET* copy number, 134 (13.8%) had elevated *PIK3CA* copy number respectively, 25.6% of tumors with elevated *MET* copy number, also had elevated *PIK3CA* copy number, and 15.7% of tumors with elevated *PIK3CA* copy number, also had elevated *MET* copy number (Figure 1). Patients with tumors harboring either *MET* or *PIK3CA* high copy number tended to have more aggressive prognostic features including larger tumor size, higher tumor grade, and negative hormone receptors. There were no significant differences on adjuvant chemotherapy or radiation therapy. However, more patients with normal/low copy number in either *MET* or *PIK3CA* received adjuvant endocrine therapy ( $P=0.003$  and  $<0.000$ , respectively). Elevated *MET* or *PIK3CA* copy number were more likely to occur in triple negative disease ( $P=0.019$  and  $<0.001$ , respectively).

At a median follow-up of 7.5 years (range 0-21.1 years), there were 252 recurrences. Table 2 summarizes the 5-year RFS by *MET* and *PIK3CA* copy number and by other patient and tumor characteristics. Five-year RFS was 63.5%, and 83.1% for *MET* high copy number and *MET* normal/low copy number respectively, ( $P=0.06$ ); and 73.1%, and 82.3% for *PIK3CA*

high copy number and *PIK3CA* normal/low copy number respectively, ( $P=0.15$ ) (Figures 2A and 2B). To evaluate the interaction of coordinate gene copy elevations in *MET* and *PIK3CA*, patients were classified into four groups: normal/low both *PIK3CA* and *MET* copy number, high both *PIK3CA* and *MET* copy number, *MET* high copy number and *PIK3CA* high copy number. No statistically significant difference in 5-year RFS estimates was found ( $P=0.137$ ) (Figure 2C).

The Kaplan-Meier survival curves by *MET* and *PIK3CA* gene copy number and breast cancer subtype are presented in Figure 3. When looking at *MET* copy number, patients with HR-positive and high *MET* copy number breast cancer had a significant lower 5-year RFS compared with patients with HR-positive and normal/low *MET* copy number breast cancer (76.4% vs. 85.4%,  $P=0.034$ ). There was a trend to worse 5-year RFS in patients with HER2-positive and high *MET* copy number breast cancer compared with patients with HER2-positive and normal/low *MET* copy number breast cancer (64.3% vs. 77.2%,  $P=0.061$ ). No difference was seen in triple receptor-negative disease ( $P=0.80$ ). When looking at *PIK3CA* copy number, there were no differences in 5-year RFS estimates by breast cancer subtype. Exploratory survival analysis to evaluate the interaction of high gene copy number in both *MET* and *PIK3CA* by breast cancer subtypes showed no statistically significant difference in 5-year RFS estimates (data not shown).

Table 3 summarizes the multivariate models *MET*, *PIK3CA*, copy number and their interaction. The results were consistent with the RFS univariate analysis. Overall, patients with tumors harboring high *MET* copy number tended to be at higher risk to develop a recurrence compared to patients with tumors with normal/low *MET* copy number (HR:1.53, 95% CI:0.98-2.38,  $P=0.06$ ). High *PIK3CA* copy number was not an independent predictor risk for recurrence (HR:1.3, 95% CI:0.91-1.86,  $P=0.147$ ), nor was the interaction of both *MET* and *PIK3CA* high copy number (HR:0.7, 95% CI:0.28-1.77,  $P=0.458$ ). When looking at patients with hormone receptor-positive breast cancer, patients with tumors with high *MET* copy number were more likely to develop recurrences (HR:1.86, 95% CI:1.07-3.25,  $P=0.029$ ). In multivariate models including patient and tumor characteristics, *MET* or *PIK3CA* high copy number were not independent predictors of RFS after adjustment for age, stage, nodal status, tumor size and breast cancer subtype (HR:1.21, 95% CI:0.8-1.82,  $P=0.357$ , and HR:1.29, 95% CI:0.85-1.94,  $P=0.229$ ).

## DISCUSSION

The purpose of this study was to determine the frequency of *MET* and *PIK3CA* copy number in breast cancer and their associations with patient outcome. We found that 82 (8.44%) and 134 (13.8%) of tumors had elevated *MET* or *PIK3CA* copy number respectively, and 25.6% of tumors had both *PIK3CA* and *MET* high copy number and that high copy number of *MET* or *PIK3CA* was associated with poorer prognostic features and triple negative disease. Patients with tumors harboring elevated *MET* copy number tended to have worse 5-year RFS, ( $P=0.06$ ). High copy number for either gene was not an independent predictor of RFS.

Deregulation of MET receptor activity occurs in a wide spectrum of human cancers, as a result of germline SNPs, somatic mutations, gene amplification, protein overexpression, and autocrine circuits driven by HGF.<sup>24</sup> In breast cancer, reports have been small and restricted to assessment of protein overexpression of the MET receptor as well as its ligand HGF in tumor tissues.<sup>13-15,26,27</sup> The estimated rate of MET protein overexpression has been 20-30%,<sup>26,27</sup> and as in several other tumor types, increased expression of MET receptor or its ligand HGF in breast cancer correlates with increased aggressiveness of disease and an overall poorer prognosis.<sup>14,25,26</sup> Initial work assessing immunoreactive (ir)-HGF

concentrations in tumor extracts of 258 primary human breast cancers using an enzyme-linked immunosorbent assay showed that ir-HGF level was correlated with large tumor size ( $P=0.05$ ). Patients with high ir-HGF concentration had a significantly shorter relapse-free ( $P=0.001$ ) and overall survival ( $P=0.001$ ) rates. ir-HGF level was an independent predictor of relapse-free ( $P=0.041$ ) and overall survival ( $P=0.036$ ).<sup>14</sup> In a smaller cohort of 91 tumors, high MET receptor expression by immunofluorescence in patients with positive and negative lymph nodes correlated with lower 5-year survival rate ( $P=0.008$ , and  $P=0.006$  respectively).<sup>27</sup> A small study of 40 primary breast cancers detecting MET and HGF by immunofluorescence and immunohistochemistry showed that MET levels did not correlate with established poor prognostic factors. However, overexpression of MET correlated with disease progression ( $P=0.037$ ). They also showed that when accounting for HER2 status, MET overexpression identified a subset of patients with adverse outcomes independently of HER2 positivity.<sup>26</sup> Our study is the first one to report *MET* gene copy number, its distribution by tumor subtype and correlation with patient outcome. In our analysis, patients with high *MET* copy number had larger tumors, of higher grade, and negative hormone receptors. Two interesting findings should be highlighted: the higher proportion of triple-negative disease with this aberration, and the prognostic value of copy number in breast cancer, especially in hormone receptor-positive disease. This is important since we continue to need new therapeutic targets that activate signaling in triple receptor-negative breast cancer, and MET receptor inhibition could contribute to cell proliferation, survival and invasion. On the other hand, in our search for mechanisms of therapy resistance to endocrine therapy, MET signaling should be investigated. Lastly, we need to define the frequency of MET protein overexpression and its correlation with other aberrations such as gene amplification and activating mutations. Comprehensive work in our institution is on-going to answer this question.

In breast cancer, reported aberrations in the PI3K pathway have been mostly restricted to detection of activating mutations and loss of tumor suppressors and the data on *PIK3CA* gene amplification being limited.<sup>21,28,29</sup> In a series of 92 primary breast cancers, investigators used quantitative real-time PCR to measure gene copy number and reported that 8.7% (8 of 92) of the tumors harbored a gain of *PIK3CA* gene copy number suggesting that gene amplification is not the main molecular mechanism in activating the PI3K-driven tumorigenesis pathway in breast cancer.<sup>30</sup> In a second cohort of breast cancers, researchers reported that 10 of 161 tumors had *PIK3CA* gene amplification, and half of them also had an activation mutation in the gene suggesting that an additive effect of point mutation and copy number gain can contribute to oncogenesis.<sup>31</sup> In our large cohort of early breast cancers, we also showed that 13.8% of all breast cancers have elevated *PIK3CA* copy number. However, assessing breast cancer subtypes, 28% of triple negative breast cancers had a high *PIK3CA* copy number suggesting that gene amplification in conjunction with loss PTEN and INPP4B may contribute to PI3K pathway activation in this subtype. However, basal breast cancers have a greater frequency of copy number aberrations, thus determining whether *PIK3CA* (or *MET*) amplification is a tumor “driver” remains to be determined. Previous to our report, the largest tumor set in which *PIK3CA* amplification was assessed, consisted of 292 invasive breast cancers, from which 209 were tested and 28 were found to be amplified (13.4%).<sup>32</sup> In this work the investigators looked at other PI3K pathway aberrations and correlated them with breast cancer molecular subtype and outcome. Mutations and copy number gains were almost exclusive events with only 1 cancer encompassing both mutation and copy number gain of the *PIK3CA* gene. Neither mutations nor copy number gain were associated with clinicopathological parameters, breast cancer molecular subtype or outcome.<sup>32</sup>

Lastly we demonstrated that 26% of *MET*-amplified tumors also have *PIK3CA* amplification, a higher frequency than predicted by chance implying that coaberrations in the PI3K and MET pathways occur at sufficient frequency that could contribute to patient



outcomes. Further studies including comprehensive analysis of large cohorts of breast cancers (i.e. TCGA- The Cancer Genome Atlas) to determine frequencies of mutations, copy number, methylation, translational changes in PI3K pathway-related genes and *MET* alone and in combination to determine the frequency of coaberrations in the pathways across multiple modalities are on-going in our group.

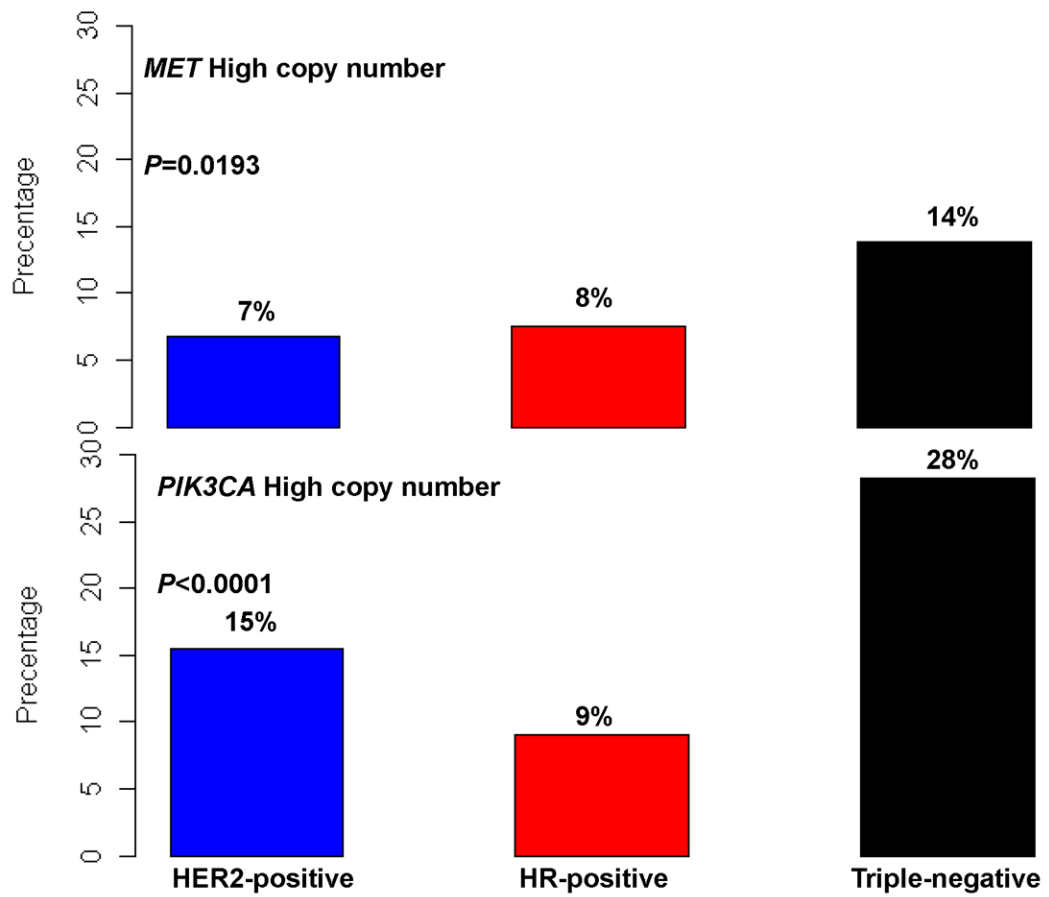
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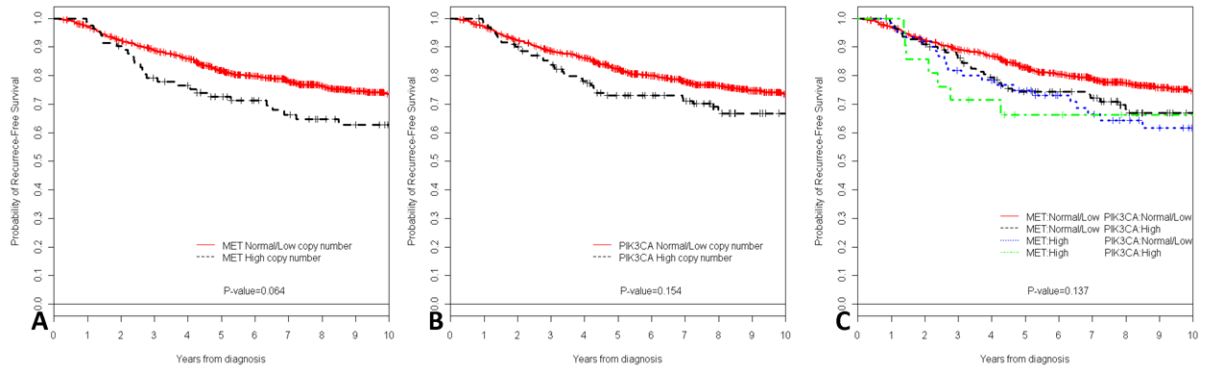
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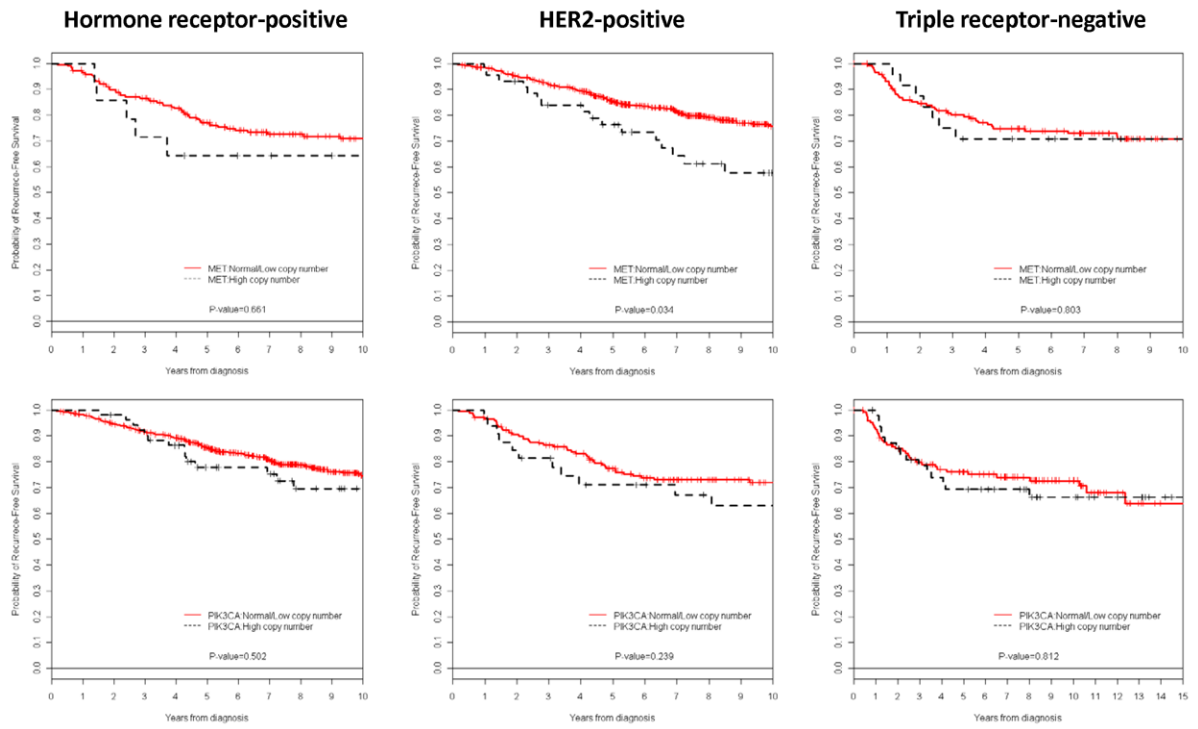


**Figure 1.** Distribution of *MET* and *PIK3CA* copy number by breast cancer subtype.





**Figure 2.** Kaplan-Meier relapse-free survival curves of all patients and *MET* (A) copy number, *PIK3CA* (B) copy number, and *MET* and *PIK3CA* copy number (C).



**Figure 3.** Kaplan-Meier relapse-free survival curves of patients by breast cancer subtype and *MET* or *PIK3CA* copy number.

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Table 1

Patient and Tumor Characteristics

Characteristic	ALL		MET copy number				PI3KCA copy number			
	N=971	%	High	%	Normal/Low	P-value	High	%	Normal/Lost	P-value
<b>Age at Diagnosis</b>										
Min	25	--	28	--	25	--	25	--	25	--
Median	53	--	52	--	53.5	--	51	--	54	--
Max	87	--	86	--	87	0.3899	84	--	87	0.0387
<b>Tumor size</b>										
<2cm	566	58.29	34	41.46	532	59.84	62	46.27	504	60.22
>=2cm	369	38	46	56.1	323	36.33	69	51.49	300	35.84
<b>Nodal Status</b>										
Positive	383	39.44	34	41.46	349	39.26	38	28.36	345	41.22
Negative	565	58.19	47	57.32	518	58.27	93	69.4	472	56.39
<b>Grade</b>										
1	92	9.47	4	4.88	88	9.9	5	3.73	87	10.39
2	477	49.12	35	42.68	442	49.72	50	37.31	427	51.02
3	336	34.6	41	50	295	33.18	72	53.73	264	31.54
<b>Estrogen Receptor</b>										
Negative	293	30.18	38	46.34	255	28.68	71	52.99	222	26.52
Positive	666	68.59	44	53.66	622	69.97	62	46.27	604	72.16
<b>Progesterone Receptor</b>										
Negative	406	41.81	42	51.22	364	40.94	80	59.7	326	38.95
Positive	555	57.16	40	48.78	515	57.93	53	39.55	502	59.98
<b>HER2</b>										
Negative	764	78.68	68	82.93	696	78.29	102	76.12	662	79.09
Positive	207	21.32	14	17.07	193	21.71	32	23.88	175	20.91
<b>Breast Cancer Subtype</b>										
HER2-positive	207	21.32	14	17.07	193	21.71	32	23.88	175	20.91

Characteristic	ALL		MET copy number				PI3KCA copy number				
	N=971	%	High N=82	%	Normal/Low N=889	%	P-value	High N=134	%	Normal/Lost N=837	P-value
Hormone receptor-positive	583	60.04	44	53.66	539	60.63		53	39.55	530	63.32
Triple receptor negative	173	17.82	24	29.27	149	16.76	0.0193	49	36.57	124	14.81
<b>Menopausal Status</b>											
Peri/pre-menopausal	312	32.13	28	34.15	284	31.95		49	36.57	263	31.42
Post-menopausal	624	64.26	52	63.41	572	64.34	0.8363	80	59.7	544	64.99
<b>Stage</b>											
I	304	31.31	18	21.95	286	32.17		32	23.88	272	32.5
II	662	68.18	64	78.05	598	67.27	0.0694	101	75.37	561	67.03
<b>Histology</b>											
Ductal	898	92.48	78	95.12	820	92.24		128	95.52	770	92
Other	58	5.97	3	3.66	55	6.19	0.4914	2	1.49	56	6.69
<b>MET</b>											
High copy number	82	8.44	--	--	--	--		21	15.67	61	7.29
Normal/Low copy number	889	91.56	--	--	--	--		113	84.33	776	92.71
<b>PIK3CA</b>											
High copy number	134	13.8	21	25.61	113	12.71		--	--	--	--
Normal/Low copy number	837	86.2	61	74.39	776	87.29	0.0021	--	--	--	--
<b>Chemotherapy</b>											
No	480	49.43	38	46.34	442	49.72		62	46.27	418	49.94
Anthracycline-based	323	33.26	26	31.71	297	33.41		49	36.57	272	32.74
Anthracycline and Taxane-based	114	11.74	12	14.63	102	11.47	0.6496	14	10.45	100	11.95
<b>Radiation Therapy</b>											
Yes	410	42.22	38	46.34	372	41.84		47	35.07	363	43.37
No	535	55.1	43	52.44	492	55.34	0.5805	84	62.69	451	53.88
<b>Endocrine Therapy</b>											
Yes	422	43.46	23	28.05	399	44.88		36	26.87	386	46.12
No	522	53.76	58	70.73	464	52.19	0.003	95	70.9	427	51.02
											<0.0001

**Table 2**  
Five-year relapse-free survival estimates by copy number and patient and tumor characteristics

	N	Events	5 Year RFS Estimates		P-Value
			Survival	95% CI	
All	971	252	81.00%	(78.5%, 83.6%)	
<b>MEI copy number</b>					
High	82	29	72.60%	(63.5%, 83.1%)	
Normal/Low	889	223	81.80%	(79.3%, 84.5%)	0.0637
<b>PI3KCA copy number</b>					
High	134	44	73.10%	(65.7%, 81.3%)	
Normal/Low	837	208	82.30%	(79.7%, 85.1%)	0.154
<b>Subtype</b>					
HER2-positive	207	62	76.30%	(70.5%, 82.5%)	
Hormone receptor-positive	583	137	84.70%	(81.7%, 87.8%)	
Triple receptor-negative	173	49	74.20%	(67.8%, 81.3%)	0.071
<b>Age at Diagnosis</b>					
<50	371	123	77.40%	(73.2%, 81.9%)	
>=50	595	129	83.30%	(80.3%, 86.5%)	0.0003
<b>Tumor size</b>					
<2cm	566	116	86.50%	(83.6%, 89.5%)	
>=2cm	369	123	73.90%	(69.4%, 78.7%)	<0.0001
<b>Nodal Status</b>					
Positive	383	113	86.60%	(83.7%, 89.5%)	
Negative	565	130	73.90%	(69.5%, 78.6%)	<0.0001
<b>Grade</b>					
1	92	22	85.00%	(77.8%, 92.9%)	
2	477	113	83.30%	(79.9%, 86.9%)	
3	336	95	77.50%	(73.0%, 82.2%)	0.249
<b>Menopausal Status</b>					
Peri/pre-menopausal	312	101	76.30%	(71.5%, 81.3%)	

	N	Events	5 Year RFS Estimates		P-Value
			Survival	95% CI	
Post-menopausal	624	140	83.90%	(81.0%, 87.0%)	0.0009
<b>Stage</b>					
I	304	43	91.90%	(88.8%, 95.1%)	
II	662	209	76.00%	(72.7%, 79.5)	<0.0001
<b>Histology</b>					
Ductal	898	235	80.70%	(78.0%, 83.4)	
Other	58	14	85.30%	(76.3%, 95.2%)	0.826
<b>Chemotherapy</b>					
No	480	102	85.20%	(81.9%, 88.6%)	
Anthracycline-based	323	110	75.50%	(70.9%, 80.5%)	
Anthracycline and Taxane-based	114	24	81.60%	(74.6%, 89.2%)	0.001
<b>Radiation Therapy</b>					
Yes	410	109	82.50%	(78.8%, 86.4%)	
No	535	134	80.60%	(77.2%, 84.2%)	0.645
<b>Endocrine Therapy</b>					
Yes	422	79	87.30%	(84%, 90.6%)	
No	522	164	76.80%	(73.1%, 80.6%)	0.0008



**Table 3**

Multivariate Cox proportional hazard model including MET, PIK3CA copy number and their interaction

	<b>Hazard Ratio</b>	<b>95% Confidence Intervals</b>	<b>P-value</b>
<b>All Tumors</b>			
MET Normal/Low copy number	1		
MET High Copy number	1.53	0.98-2.38	0.06
PIK3CA Normal/Low copy number	1		
PIK3CA High Copy number	1.3	0.91-1.86	0.147
MET and PIK3CA high copy number	0.7	0.28-1.77	0.458
<b>HER2-positive</b>			
MET Normal/Low copy number	1		
MET High Copy number	0.92	0.29-2.95	0.886
PIK3CA Normal/Low copy number	1		
PIK3CA High Copy number	1.3	0.67-2.52	0.43
MET and PIK3CA high copy number	2.68	0.4-18.16	0.312
<b>Hormone receptor-positive</b>			
MET Normal/Low copy number	1		
MET High Copy number	1.86	1.07-3.25	0.0287
PIK3CA Normal/Low copy number	1		
PIK3CA High Copy number	1.25	0.7-2.23	0.4418
MET and PIK3CA high copy number	0.59	0.12-2.89	0.515
<b>Triple receptor-negative</b>			
MET Normal/Low copy number	1		
MET High copy number	1.33	0.51-3.43	0.56
PIK3CA Normal/Low copy number	1		
PIK3CA High copy number	1.17	0.6-2.3	0.645
MET and PIK3CA high copy number	0.61	0.12-2.95	0.535