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Analysis of *MET* Genetic Aberrations in Patients With Breast Cancer at MD Anderson Phase I Unit

Debora de Melo Gagliato¹, Denis L. Fontes Jardim¹, Gerald Falchook¹, Chad Tang^{1,2}, Ralph Zinner¹, Jennifer J. Wheler¹, Filip Janku¹, Vivek Subbiah¹, Sarina A. Piha-Paul¹, Siqing Fu¹, Kenneth Hess³, Sinchita Roy-Chowdhuri⁴, Stacy Moulder⁵, Ana M. Gonzalez-Angulo⁵, Funda Meric-Bernstam¹, and David S. Hong¹

¹Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX

²Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

³Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

⁴Department of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

⁵Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

MET aberrations were associated with adverse tumor pathologic features, such as high grade and hormone receptor negativity in a cohort of breast cancer patients referred to a Phase I program. Additionally, patients with *MET* aberrations had inferior overall survival from Phase I consult compared with wild-type patients. These findings are quite provocative, identifying a subset of patients at a particularly high risk for worse survival outcomes.

Background—c-*MET* is a receptor tyrosine kinase whose phosphorylation activates important proliferation pathways. *MET* amplification and mutation have been described in various malignancies, including breast cancer (BC), and c-*MET* overexpression is associated with worse survival outcomes in patients with BC. We describe *MET* mutation and amplification rates in a BC cohort of patients referred to a Phase I Unit.

Methods—We reviewed the electronic medical records of all patients with advanced BC tested for *MET* amplification, mutation, or both who were referred to the Department of Investigational Cancer Therapeutics at MD Anderson.

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Address for correspondence: Debora de Melo Gagliato, MD, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515, Holcombe Blvd, Houston, TX 77030, dgagliato@gmail.com.

Disclosure

The other authors have stated that they have no conflicts of interest.

Results—A total of 107 patients with advanced BC were analyzed for *MET* mutation/variant (88 patients) or amplification (63 patients). Of these, 49 were tested for both genetic abnormalities. Three of 63 patients (4.7%) demonstrated *MET* gene amplification by fluorescence in situ hybridization (2 in primary tissue; 1 in metastatic site). *MET* mutation/variant was detected in 8 of 88 patients (9%). High-grade tumors were characteristic of all patients harboring *MET* amplification and were present in 7 of 8 (87.5%) of those with *MET* mutation. Metastatic sites were greater in *MET*-amplified compared with wild-type patients (median of 7 vs. 3 sites). Five of 8 patients (62.5%) with *MET* mutations had triple negative BC compared with 46% in controls. In addition, patients with positive test results for *MET* aberrations (n = 11) had inferior overall survival (OS) from Phase I consult compared with wild-type patients (n = 37), although this was not statistically significant (median OS = 9 vs. 15 months, *P* = .43).

Conclusions—In this cohort of patients with BC who were referred to our Phase I Department, *MET* aberrations were associated with higher metastatic burden and high-grade histology. We could not demonstrate differences in survival outcomes because of a small sample size.

Keywords

c-MET inhibitors; *MET* amplification; Metastatic breast cancer; *MET* mutation; Personalized therapy

Introduction

Largely expressed in epithelial/endothelial cells, c-MET is a receptor tyrosine kinase (RTK) encoded by the *MET* proto-oncogene.¹ On binding with the hepatocyte growth factor (HGF), the c-MET receptor dimerizes, autophosphorylates, and activates downstream pathways, including mitogen-activated protein kinase, phosphatidylinositol 3-kinase, and signal transducer and activator of transcription.^{2,3} Once activated, these proliferation pathways promote cell invasiveness and metastasis.^{4,5}

Various studies have demonstrated a correlation between c-MET activation and cancer pathophysiology. The altered level of activated *MET* RTK may play an important role in cancer development. Deregulated signaling can occur secondary to gene amplification, protein overexpression, activating mutations, increased autocrine or paracrine ligand-mediated stimulation, or interaction with other active cell-surface receptors.^{6,7}

Germline point mutations in the *MET* oncogene are involved in the tumorigenesis of papillary renal cell carcinoma.^{8,9} However, *MET* mutations occur with low frequency in other tumor types,^{10,11} and only some mutant alleles have been proven to cause malignant transformation after constitutive receptor activation.¹²

On the other hand, *MET* amplification has been observed in many diverse neoplasias, such as gastric, esophageal,¹³ medulloblastoma,¹⁴ glioblastoma,¹⁵ and lung cancers.¹⁶ *MET* amplification leads to protein overexpression and constitutive activation of the kinase domain.¹⁷ There is also evidence that *MET* amplification occurs more frequently in metastatic tumors, suggesting that this event may play a role later in the oncogenic process.^{18,19}

Overexpression of c-MET has been shown to contribute to the development of the invasive phenotype during BC progression. Beviglia et al²⁰ examined c-MET receptor expression in human BC cells in vivo and in cultured cell lines, showing that poorly differentiated and invasive cell lines expressed high levels of the receptor and ligation by HGF was associated with increased motility and invasiveness. Additional evidence demonstrates that basal-like BCs are characterized by elevated tyrosine phosphorylation of c-MET.^{21,22} Another study showed overexpression of c-MET in BC primary tumors being strongly associated with worse disease-free survival (8 months) compared with tumors without c-MET overexpression (53 months; $P = .037$; relative risk, 3.0; confidence interval, 1.1–8.3).²³ Thus, the HGF/c-MET axis seemingly plays a significant role in BC tumor progression.

Despite the plethora of data linking *MET* aberrations with cancer development and progression, little is known about how *MET* mutations or amplifications affect clinical practice. We therefore sought to describe the cohort of patients with BC who were referred to our Phase I Clinical Trials Program and had their tumor tissue evaluated for *MET* mutation/variant, gene amplification, or both.

Patients and Methods

Patients

We reviewed the electronic medical records of all patients with advanced BC tested for *MET* amplification, mutation or both, who were referred to the Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program) at The University of Texas MD Anderson Cancer Center from May 2010 to March 2013. Patients were eligible for inclusion in the data analysis if a primary diagnosis of BC was histologically confirmed and a tumor sample was sent to assess *MET* mutation and amplification. This study and all associated treatments were conducted in accordance with the guidelines of the MD Anderson Institutional Review Board. Because this was a retrospective study, informed consent was waived.

Tissue Samples and Mutational Analysis

MET mutation was investigated in archival formalin-fixed, paraffin-embedded tissue blocks or material from fine-needle aspiration biopsies obtained from diagnostic or therapeutic procedures. All histologies were centrally reviewed at MD Anderson. *MET* mutation or variant analysis was performed in different Clinical Laboratory Improvement Amendment–certified laboratories as part of a gene panel analysis or in a single test. These included assessment of 182 genes using a targeted next-generation sequencing Foundation One platform (Foundation Medicine, Cambridge, MA), 46 genes in an Ion Torrent next-generation sequencing procedure (Baylor College of Medicine Cancer Genetics Laboratory, Houston, TX), and 53 genes using a Sequenom Mass ARRAY platform (Knight Diagnostics, Portland, OR) or a polymerase chain reaction–based primer extension assay assessing mutational hot spots in the *MET* gene in the Division of Pathology and Laboratory Medicine at MD Anderson.

MET amplification was analyzed via fluorescence in situ hybridization (FISH) at MD Anderson or Baylor's Cancer Genetic Laboratory. Copy numbers were expressed as gene copy number in relation to CEP7, a gene located near the centrosome of the same chromosome. *MET* was considered amplified when the c-MET/CEP7 signal ratio was ≥ 2.0 or when this ratio was < 2.0 but there were > 20 copies of c-MET signals and/or clusters in $> 10\%$ of the tumor nuclei counted.

Treatment and Evaluation

Patients with advanced breast cancer (BC) who were referred to the Phase I Clinic and met inclusion criteria were enrolled in clinical trials judged to be clinically appropriate by attending physicians. Treatment continued until disease progression, withdrawal of consent by the patient, clinical judgment deeming the necessity of removing a patient from a clinical trial, or development of unacceptable toxicity or death. Clinical assessments were performed as specified in each protocol, typically before the initiation of therapy and then at a minimum at the beginning of each new treatment cycle. Treatment response was assessed using computed tomography scans, magnetic resonance imaging, or positron emission tomography scans at baseline before treatment initiation and then every 2 cycles (6–8 weeks). All radiographs were read in the Department of Radiology at MD Anderson and were reviewed in the Department of Investigational Cancer Therapeutics tumor measurement clinic. Responses were categorized using the Response Criteria in Solid Tumors (RECIST)^{24,25} on the basis of specific protocol requirements and were reported as best response.

Statistical Analysis

Patient characteristics, including demographics, tumor type, *MET* mutation or amplification status, and associated genetic abnormalities were summarized using frequency distributions and percentages. Time to treatment failure (TTF) was defined as the interval from the start of therapy to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, physician judgment, or death. Overall survival (OS) was assessed starting from the date of the first appointment in the Phase I Clinic using Kaplan–Meier curve analysis and compared with the log-rank statistic. All statistical analyses were carried out using S+ software, version 8.2 (TIBCO Software Inc, Houston, TX).

Results

Patient Characteristics

A total of 107 patients with advanced BC were analyzed for *MET* mutation/variant (88 patients) or amplification (63 patients). Among these patients, 49 were tested simultaneously for both genetic abnormalities. Their median age at diagnosis was 47 years (range, 31–72 years). Among all groups, most patients were white. The number of prior therapies received before Phase I referral was similar among groups. Detailed patient characteristics according to *MET* status are shown in Table 1. In the entire patient cohort, 46 patients were classified as having triple negative BC, defined by lack of estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) expression.

MET Abnormalities

Three of 63 patients (4.7%) demonstrated *MET* gene amplification by FISH, in the primary tissue in 2 and in the metastatic site in 1. *MET* mutation/variant was detected in 8 of 88 patients (9%). Among patients who were found to have a *MET* mutation, half were tested using primary tissue and half had testing of a metastatic site. The copy number of the *MET* gene in relation to *CEP7* in *MET*-amplified patients ranged from 2.22 to 5.0 (Table 2). Of the 8 mutation/variants detected, 5 were N375S, which is considered to be germline.²⁶ In addition, 2 patients had T1010I and 1 patient had a M362T mutation (Table 2).

Comparison of Clinical and Mutational Characteristics

Patients with tumors harboring *MET* amplification were diagnosed at a younger age compared with control patients, with a median age at diagnosis of 39 years. Twenty-five percent of patients (2/8) and 33% of patients (1/3) whose tumor tissue was found to have *MET* mutation and amplifications were black, respectively, compared with 12% of patients without *MET* aberrations (10/80 patients in the nonmutated group and 7/60 in the nonamplified group) (Table 1).

All patients with *MET* amplification or mutation were classified as having invasive ductal carcinoma tumors. All tumors harboring *MET* amplification and 87.5% (7/8) of those with *MET* mutation were classified as high grade (Table 2). In contrast, patients without *MET* mutation or amplification had fewer high-grade tumors (43/77 [56%] in the nonmutated group and 36/58 [62%] in the nonamplified group). Only 2 of 8 patients with *MET* mutations were positive for progesterone receptor and estrogen receptor.

The median number of organs involved with metastatic disease in the nonamplified group was 2 (0–6). In contrast, patients with *MET* amplification had a median of 7 organs involved with metastatic disease. When trying to identify a pattern of metastatic sites, we found that patients with *MET* abnormalities more frequently presented with metastatic disease to the lymph nodes, compared with patients without *MET* aberrations, who presented with a greater proportion of individuals without nodal disease involvement (80.7% and 100% for *MET* mutation and amplification, respectively, compared with 70% and 67% for nonmutated and nonamplified cases, respectively).

Concomitant Mutations

MET amplification and mutation were mutually exclusive in the 49 patients tested for both abnormalities simultaneously. Five of 11 patients (45%) with *MET* aberrations had concomitant mutations in other genes, including TP53 mutation (1 patient), PIK3CA mutation (3 patients), and HER2 gene overexpression or amplification (1 patient) (Table 3).

Outcomes on Phase I Protocols

Of the 107 study patients tested for *MET* amplification or mutation, irrespective of result, 76 (71%) were included in at least 1 Phase I protocol. The median TTF of *MET*-positive patients (n = 8) treated in their first Phase I protocol was 1.7 months (range, 0.5–7.8 months) compared with 3.6 months (range, 0.2–27.3 months) for the group testing negative for at least 1 *MET* abnormality (n = 68). Of the 8 patients testing positive for a *MET* abnormality

who were enrolled in different Phase I protocols, only 1 had a partial response defined by RECIST criteria. That patient had a *MET* amplification and was enrolled on a protocol combining bevacizumab, temsirolimus, and carboplatin.

Only 3 patients were treated in Phase I protocols that contained a c-MET inhibitor; 2 of them had a *MET* mutation/variant (N375S and T1010I). All patients enrolled in a c-MET inhibitor clinical trial presented with disease progression as the best response. No patient had a response to treatment.

Analysis of Survival of MET-Positive Patients

For survival analysis, we compared the group of patients who tested positive for a *MET* mutation/variant or amplification (*MET*-positive group, 11 patients) with patients who tested negative for both abnormalities (*MET*-negative group, 38 patients). The median OS from the day that patients were initially seen in our Phase I Clinic was 9 months for *MET*-positive patients and 15 months for *MET*-negative patients (hazard ratio, 1.5; 95% confidence interval, 0.6–3.8; $P = .43$) (Figure 1).

Discussion

We detected *MET* gene amplification in 3 of 63 patients (4.7%) and a *MET* genetic variant in 8 of 88 patients (9%) with BC. These were mutually exclusive among patients who were tested simultaneously for both abnormalities. Of note, patients with *MET* amplification were diagnosed at a younger age and had higher-grade tumors with a greater median number of organs with metastatic disease compared with wild-type patients. High-grade tumors were more frequent in the *MET*-mutated patient cohort.

Although the small sample size precludes drawing definitive conclusions, patients with *MET*-positive BC are particularly challenging for Phase I treatment because of their lower response to drugs and shorter survival. Of note, patients with *MET* aberrations who were enrolled in Phase I clinical trials had a shorter median TTF compared with patients without *MET* alterations (1.7 vs. 3.6 months). These findings are in line with preclinical data linking *MET* as a resistance pathway for a variety of targeted agents, including inhibitors of epidermal growth factor,²⁷ BRAF,²⁸ and vascular endothelial growth factor.²⁹

Basal-like BC tumors are putatively enriched for gene sets that are overrepresented in transcriptional signatures regulated by *MET*.²² Tissue microarray analyses have shown c-MET immunoreactivity to be higher in basal-like cases of human BC than in other BC subtypes. It is known that most patients with basal-like BC lack or show low levels of estrogen and progesterone receptor positivity and lack HER2 protein overexpression and HER2 gene amplification.³⁰ Although we do not have information on molecular subtypes of BC identified through gene expression profiling in our patient population, the 5 patients with triple negative BC whose tumor tissue was found to have *MET* mutation might be analogous to patients with the basal-like molecular BC subtype.³¹

Preclinically, an animal model demonstrated a causal role for the *MET* gene in the onset of mammary tumors with basal characteristics, including metaplasia, absence of progesterone

receptor, HER2 expression, and expression of cytokeratin 5.³² Furthermore, analysis of *MET* expression in a cohort of human BC samples showed that tumors with the highest levels of *MET* correlated with the basal subtypes.³³ In addition, it has been demonstrated that c-met expression was an independent predictor of recurrence and death in triple negative BC.³⁴

Patients with *MET* aberrations treated in a Phase I Program had inferior, although not statistically significant, survival outcomes compared with the remainder of the patients in our cohort. The small number of patients in our study potentially limits the statistical power needed to discriminate meaningful differences among groups. Evidence suggests that *MET* aberrations are associated with poor survival outcomes in various cancers. Many efforts have been made to characterize the effects of sustained *MET* activation in inhibition of apoptosis and metastasis in preclinical models.^{4,35} *MET* expression might be associated with resistance to treatment in patients with BC, even in a cohort of individuals co-expressing ErbB2, for whom a highly effective treatment, such as trastuzumab, is available.^{36,37}

Inferior survival outcomes have been described in patients with BC with *MET* alterations. Lengyel et al²³ evaluated expression of the c-MET and HER2 RTKs and the c-MET ligand hHGF/scatter factor in primary BC and their lymph node metastases, using both conventional immunohistochemistry and immunofluorescence. They demonstrated that c-MET overexpression identified by both methods was associated with a high risk of disease progression. Median disease-free survival in patients with c-MET overexpressing tumors was 8 months compared with 53 months when c-MET expression was low ($P = .037$; hazard ratio, 3.0).²³

A group of researchers at MD Anderson evaluated protein levels of c-MET and p-cMET in 257 patients with BC by using reverse-phase protein array. They demonstrated that c-MET and p-cMET levels were significant prognostic factors for recurrence-free survival and OS.³⁸

We observed that our patients harboring *MET* aberrations had a trend toward higher pathologic grade tumors compared with those without *MET* alterations. In non-small cell lung cancer, Ai et al³⁹ demonstrated that c-MET protein expression rates were significantly more frequent in poorly differentiated tissues compared with well and moderately differentiated tissues ($P < .05$).

Considering the adverse survival outcomes observed in this single-center cohort of patients harboring *MET* aberrations, an untimely identification of those individuals might be of relevance at an early onset of metastatic disease. Recruiting them to Phase I protocols that include a *MET* inhibitor can result in better tumor control, more prolonged progression-free intervals, and perhaps an impact on OS. Particularly in the triple negative BC group, this strategy might be of relevance, because these patients often experience a more dramatic disease course, with deterioration of performance status and fewer treatment strategies compared with patients with hormone receptor and HER2-positive BC.

Study Limitations

Our study is limited because it is primarily descriptive rather than reporting the results of a series of controlled experiments. Other weaknesses are that it was largely retrospective with a variety of different methods of molecular analysis. Second, there is a referral bias; the patients selected for testing had aggressive disease and were referred for enrollment in a Phase I clinical trial after developing resistance to BC standard therapy. Third, a major limitation is the lack of matched normal tissue to confirm that the reported mutations are somatic. Because we did not compare *MET* genetic alterations with c-MET receptor expression levels, comparisons with previous studies were limited. Last, there were limitations in tissue availability and an expected evolution in the technologies used for measuring tumor parameters. Despite these drawbacks, this work provides important clues about the genetic makeup of these patients with advanced BC. More important, the study results are hypothesis generating, forming the basis for future studies.

Conclusions

MET genetic alterations are present in a small subset of patients with BC, and they presented to our Phase I Clinical Trials Program with unfavorable clinicopathologic features, such as higher tumor grade, less positivity for hormone receptors, and a greater number of metastatic disease sites. This BC subgroup is currently a challenging population, and further studies are necessary to confirm the inferior survival rate of patients with fewer responses to treatment in current Phase I clinical protocols.

Clinical Practice Points

- In breast cancer (BC), the Hepatocyte Growth Factor (HGF)/c-MET axis seems to play an important role. Overexpression of c-MET has been shown to contribute to the development of the invasive phenotype during BC progression and was associated with inferior survival.
- More aggressive and proliferative BC subtypes, such as basal-like, are characterized by elevated tyrosine phosphorylation of c-MET.
- In this study, patients with advanced BC and *MET* genetic aberrations referred to Phase I Department had younger age at diagnosis, higher proportion of high grade tumors, higher number of organs involved with metastatic disease and higher proportion of triple negative BC subtype when compared to wild type patients.
- These patients also presented inferior overall survival (OS) from Phase I consult compared with wild-type patients.
- These findings foment future studies evaluating *MET* aberrations in patients referred to Phase I protocols. Development of specific strategies to improve survival endpoints in this particularly poor risk cohort of patients is warranted.

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Figure 1.

OS According to MET Status From Presentation to the Phase I Clinic. Kaplan–Meier OS Curves for Patients With BC According to *MET* Status Starting From Presentation in a Phase I Clinic

Abbreviations: CI = confidence interval; HR = hazard ratio.

Table 1

Demographic Characteristics and Metastatic Sites in Patients Stratified by *MET* Mutation and Amplification Status

Characteristic	Not Mutated (n = 80)	Mutated (n = 8)	Not Amplified (n = 60)	Amplified (n = 3)
Age at diagnosis, years: median	48 (31–72)	43 (36–57)	47 (31–70)	39 (34–47)
Prior therapies: median (range)	3 (0–12)	2.5 (0–6)	3 (0–10)	4 (2–13)
Ethnicity (%)				
Asian/American Indian	4 (5)	1 (12.5)	2 (3)	1 (33.3)
Black	10 (12.5)	2 (25)	7 (12)	1 (33.3)
Hispanic	10 (12.5)	0	6 (10)	0
White	56 (70)	5 (62.5)	45 (75)	1 (33.3)
Histology (%)				
IDC	62 (77)	7 (87.5)	48 (80)	3 (100)
ILC	11 (14)	0	5 (8)	0
Metaplastic	4 (5)	1 (12.5)	5 (8)	0
Adenocarcinoma NOC	3 (4)	0	2 (4)	0
Metastasis (%)				
No. metastasis sites: median (range)	3 (1–7)	3 (2–5)	2 (0–6)	7 (4–7)
Liver	50 (63)	5 (62.5)	34 (56)	2 (67)
Lungs	25 (31)	4 (50)	16 (26)	3 (100)
Bone	49 (61)	5 (62.5)	33 (53)	3 (100)
CNS	15 (18.5)	1 (12.5)	7 (11.5)	1 (33)
Peritoneum	4 (5)	0	2 (3)	2 (67)
Lymph nodes	56 (70)	7 (87.5)	40 (67)	3 (100)
Site of mutational analysis				
Primary tumor	42 (53)	4 (50)	25 (42)	2 (67)
Metastatic tumor	38 (47)	4 (50)	35 (58)	1 (33)

Abbreviations: CNS = central nervous system; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; NOC = not otherwise classified.

Table 2Histologic and Genetic Characteristics in Patients Stratified by *MET* Mutation and Amplification Status

Characteristic (%)	Not Mutated (n = 80)	Mutated (n = 8)	Not Amplified (n = 60)	Amplified (n = 3)
HER2	4 (3/80)	12.5 (1/8)	5 (3/60)	0/3
PI3KCA	32 (25/78)	25 (2/8)	25 (13/52)	33 (1/3)
KRAS	1.5 (1/71)	0/8	0/42	0/3
EGFR	1.5 (1/63)	0/8	2 (1/59)	0/2
p53	36 (16/44)	12.5 (1/8)	50 (9/18)	50 (1/2)
NRas	3 (2/67)	0/8	6 (2/36)	0/3
C-kit	2 (1/53)	0/2	3 (1/31)	0/1
% ER+	54 (43/80)	12.5 (2/8)	52 (31/60)	67 (2/3)
% PR+	31 (39/80)	12.5 (2/8)	42 ((25/60)	67 (2/3)
PTEN				
Loss	26 (6/23)	0/4	16 (7/43)	1/2
Weak	9 (2/23)	0/4	5 (2/43)	0/2
No loss	65 (15/23)	100 (4/4)	79 (34/43)	1/2
Grade				
Low	5 (4/77)	0	2 (1/58)	0/3
Medium	32 (24/77)	12.5 (1/8)	36 (21/58)	0/3
High	63 (49/77)	87.5 (7/8)	62 (36/58)	100 (3/3)

Abbreviations: EGFR = epidermal growth factor receptor; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.

Table 3

Histology and Mutation Status of Patients With *MET* Mutation and Amplification, and Their Response to Phase I Protocols

Patient No.	Histology	Mutation/Copy No.	Concomitant Mutations	Phase I Protocol	Best Response	TTF (mo)
c-Met mutated						
1	IDC, ER/PR–	N375S	TP53	Anti-mesothelin	PD	1.4
2	Metaplastic	N375S	–	None	–	–
3	IDC, ER/PR–	N375S	Her2 amplification, PIK3CA	c-MET inhibitor	PD	1.5
4	IDC, ER/PR+	T1010I	–	c-MET inhibitor	PD	1.4
5	IDC, ER/PR–	T1010I	–	Dasatinib + VPA	PD	0.5
6	IDC, ER/PR	N375S	–	None	–	–
7	IDC, ER/PR–	M362T	–	None	–	–
8	IDC, ER/PR+	N375S	PIK3CA	Anastrozole + erlotinib	SD	6.2
c-Met amplified						
9	IDC, ER/PR+	4.35	–	Dasatinib + VPA	SD	7.8
10	IDC, ER/PR+	5.0	PIK3CA	Carboplatin + Bevacizumab + temsirolimus	PR	6.0
11	IDC, ER/PR–	2.11	–	None	–	–

Abbreviations: ER = estrogen receptor; IDC = invasive ductal carcinoma; PD = progressive disease; PR = progesterone receptor; SD = stable disease; TTF = time to treatment failure; VPA = valproic acid.