TITLE: Tumor Genomic Profiling in Breast Cancer Patients Using Targeted Massively Parallel Sequencing

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14. ABSTRACT

The overarching goal of this proposal is to use massively parallel sequencing to detect somatic genomic alterations in breast cancer tumor samples in order to identify genetic determinants of tumor behavior that may inform clinical decision-making. We have developed a targeted sequencing platform that interrogates ~450 genes that are known to be altered in breast cancer and other cancers. We ultimately plan to utilize this platform to study 150 tumor samples from women with ER+ breast cancer who have had early-, late- or no relapse following endocrine therapy. We have also sequenced tumor samples from patients with advanced breast cancer. To date, we have obtained metastatic tumor biopsies and successfully performed whole exome sequencing from more than 240 patients with metastatic breast cancer, as well as matched pre-treatment primary tissues in more than 130 of these patients. In 80 of these patients, clinically relevant genomic and molecular has been returned to the clinical team to aid with decision-making; in many cases, this information has impacted both treatment decisions as well as ultimate outcomes.
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1. INTRODUCTION:

Knowledge of genetic changes that occur in cancer cells should ultimately facilitate individualized approaches to cancer treatment. However, methods to systematically profile cancers for relevant genetic changes in the clinical setting remain underdeveloped. The overarching goal of this proposal is to use cutting-edge genomic technology (massively parallel sequencing) in patients with breast cancer to identify genetic determinants of tumor behavior that may inform clinical decision-making. Two unmet clinical challenges in breast cancer motivate this approach. The first is the need for improved biological understanding of early stage estrogen-receptor positive (ER+) tumors with a high risk of recurrence. Systematic genetic profiling of early stage ER+ tumors may identify specific subsets of breast cancer and predict which patients are most likely to relapse. Second, there is a clear need for novel therapeutic strategies in metastatic breast cancers that have become resistant to standard therapies. Systematic genetic characterization of these resistant cancers might teach us about new therapeutic strategies or guide the development of targeted drug combinations that may help to overcome cancer drug resistance. The aims of this study were to profile a clinically annotated cohort of 150 ER+ breast tumors to look for genetic differences in both early-recurring and late-recurring tumors. In addition, we sought to prospectively profile at least 50 patients with advanced breast cancer in order to study the impact of our approach in a setting that may ultimately inform clinical decision-making.

2. KEYWORDS:

Breast Cancer
Estrogen Receptor
Resistance
Recurrence
Massively Parallel Sequencing
Next Generation Sequencing
Targeted Sequencing
Whole Exome Sequencing
Genomics
Personalized Medicine
Precision Medicine

3. OVERALL PROJECT SUMMARY:

AIM #1: To perform genomic profiling across a clinically annotated cohort of ER+ breast tumors

The goal of this Aim was to establish a breast-cancer focused mutation profiling platform and use it to study an annotated collection of tumor samples from patients with ER+ breast cancers. During the course of this award, we successfully designed and constructed a targeted sequencing platform that can be used on FFPE tumor samples. This platform targets all known breast cancer related genes identified in large sequencing studies of breast cancer samples from the past several years, including several novel genomic alterations that we and others have recently identified in ER+ breast cancer samples. This platform is to be deployed on a cohort of tumor samples from patients with ER+ breast cancer who have had early recurrence, late recurrence, or
AIM 1A: To develop a breast cancer-focused massively parallel sequencing platform for FFPE samples

4 large sequencing studies (published in *Nature* in 2012) used whole exome and/or whole genome sequencing to catalogue the landscape of genomic alterations in primary, treatment-naïve breast cancers. In total, 819 primary breast cancers were sequenced across these 4 studies, of which 529 were ER+ (Table 1). A fifth study by Matthew Ellis and colleague reported the sequencing of 77 pretreatment tumor biopsies (46 whole genomes and 31 whole exomes) from patients with luminal breast cancer treated with a neoadjuvant aromatase inhibitor. This study was designed to identify genomic biomarkers that may predict response or intrinsic (de novo) resistance to endocrine therapy. Based on Ki67 levels in the surgical specimens, samples were stratified into AI-sensitive (Ki67 < 10%, n = 48) and AI-resistant samples (Ki67 > 10%, n = 29). Mutations in *MAP3K1* and possibly *GATA3* were associated with AI-sensitivity, while *TP53* mutations were associated with the AI-resistance. In the aggregate, these five studies have shed tremendous light onto the genomics of primary treatment-naïve breast tumors.

As described in our original research proposal, we developed an enriched set of genes including these new significantly altered genes identified in breast cancer, as well as numerous other novel cancer genes that have recently been identified. In total, this design included all of the exons from 435 genes, selected introns to identify translocations from 22 genes, more extensive tiling across the entirety of 23 genes, and the promoter of the *TERT* gene. The resultant list of genomic coordinates were optimized and a set of baits were designed and synthesized. We completed testing and implementing of this platform, as described in our original research proposal.

More recently, we identified several novel alterations in ER+ breast tumors, including translocations in *ESR1*, the gene that encodes the estrogen receptor (Wagle, Garraway, and Arteaga, unpublished results). Given the potential importance of ESR translocations in ER+ breast cancer, we then further modified our bait design to include genomic coordinates across select introns in ESR1. In addition, two papers from the Broad Institute published in *Nature* in 2013 highlighted several novel cancer genes not previously identified as significant in cancer. All of these alterations were also added to our targeted sequencing panel design, and a 2nd iteration (v2.0) was then developed. This v2.0 targeted sequencing panel is particularly well suited to profiling ER+ breast tumors.

**TASKS:**
- Design and optimization of breast-cancer specific platform (Month 1 – Month 4): **COMPLETE**
AIM 1B: **To perform genomic profiling across a clinically annotated cohort of ER+ breast tumors**

In this aim, we proposed to use our breast-cancer focused platform to profile a cohort of early stage ER+ breast tumors that have recurred after adjuvant therapy, including patients with late relapse, early relapse, and no relapse at 10 years. IRB approval was obtained to obtain and sequence these samples, and approval from the DFCI Breast Cancer User Committee for use of these tissues was also obtained. Due to delays in the sequencing platform development, user committee approval, and limitations of funding sources to perform the sequencing on all 150 samples, this aim has not yet been completed. Additional funding sources are presently being obtained, and, once funding is in place, sequencing of these tumors samples will commence.

**REVISED MILESTONES:**

- All sequencing completed by *June 2017*
- Statistical analysis completed by *September 2017*

AIM #2: **To assess the feasibility of prospective sequencing in patients with advanced breast cancer**

In this Aim, we proposed to apply massively parallel sequencing to patients with advanced breast cancer. The goal here was to study the feasibility of our approach in a setting that may ultimately inform clinical decision-making. This will serve as a proof-of-principle for how genomics could be used prospectively for cancer precision medicine – to uncover somatic genetic changes that impact the treatment and prognosis of patients with breast cancer. Because of the delay in implementing the new targeted sequencing platform, we established a more comprehensive platform that incorporates whole exome sequencing and transcriptome sequencing (RNASeq) in patients with advanced breast cancer. This platform includes all targets in the v2.0 targeted sequencing panel described above, but is more comprehensive in that it can detect mutations, insertions/deletions, copy number alterations, and translocations in all genes in the genome, as well as genome-wide expression.

Towards the beginning of the grant term, we established a pipeline for prospective whole exome sequencing from FFPE tumor samples to support clinical decision making (and clinical trial enrollment) for appropriately consented patients with advanced cancers at the Dana-Farber Cancer Institute (DFCI) known as CanSeq. We initially conducted a pilot study on 16 patients that enabled optimization of various aspects of our emerging clinical sequencing pipeline, including sample acquisition, DNA extraction, sequencing, and analysis. The somatic and germline alterations were analyzed using a heuristic algorithm called PHIAL. This algorithm applies a categorization framework that incorporates the degree of actionability and level of evidence for that action. A similar algorithm was also been developed for germline alterations. We also developed a customized report that streamlines the results of these algorithms for presentation to a Cancer Genomics Evaluation Committee, a multi-disciplinary “genomics tumor board” whose purpose was to make decisions about the interpretation and clinical actionability of somatic and germline alterations. Somatic analysis of the first 16 patients demonstrated at least one plausibly actionable somatic alteration linked to an approved or experimental therapy in 15 out of 16 cases. This work was published in Nature Medicine in 2014 (Van Allen, Wagle, et al, 2014).
Building on the foundation established by CanSeq, our prospective sequencing approach for patients with metastatic breast cancer has continued to evolve over the past few years. Patients at DFCI with metastatic ER+ breast cancer are asked to enroll on an IRB-approved metastatic breast cancer biopsy protocol (#05-246). Under this protocol, 3-6 frozen core biopsies are collected from metastatic lesions and are available for genomic testing. For all patients, we simultaneously obtain a tube of blood as a source of germline DNA. Thus, this protocol allows prospective whole exome and transcriptome sequencing of metastatic biopsies from patients with advanced ER+ breast cancer – both for retrospective analysis and prospective return of results, when appropriate.

In 2014, during the course of this award, I transitioned from a post-doctoral fellow in Levi Garraway’s laboratory to an independent faculty member in the Department of Medical Oncology at Dana-Farber Cancer Institute. In this new independent faculty role, I am a member of the new Dana-Farber/Brigham and Women’s/Broad Institute Center for Cancer Prevision Medicine (CCPM). As part of the CCPM, I developed a novel infrastructure and workflow to conduct this research project, based on the experiences gained over the past few years. This is detailed in Figure 1. This workflow enables the acquisition of multiple clinical and research

Figure 1. Modified workflow for prospective genomic profiling and studies of resistance for patients with ER+ metastatic breast cancer.
biopsies from patients with metastatic breast cancer with the return of relevant clinical information (including genomic sequencing) to the clinician and patient. The remaining tissues are available for genomic and molecular analyses, as shown in Figure 1. In this way, this new workflow serves both Aim 2A and 2B. Prospective enrollment using this new workflow began in June 2015.

**AIM 2A: To assess the clinical impact of prospective genomic profiling in advanced breast cancer**

Under the new Center for Cancer Precision Medicine workflow, described above (Figure 1), we have collected **111 metastatic biopsies from 105 patients** with ER+ metastatic breast cancer. 6 cores were taken per biopsy on average (range 1-12). The number of biopsies with sufficient material for each test and success rates is shown in Figure 2. In **3/94 biopsies (3%)**, pathology found a tumor type other than breast cancer. Of the remaining testable samples, **10% changed ER or HER2 status**. Both of these findings highlight that in more than 10% of patients with advanced breast cancer, the routine pathologic evaluation of metastatic biopsies has clinically relevant implications.

![Center for Cancer Precision Medicine Metastatic Breast Cancer Study](image)

**Figure 2.** Yield of ER+ metastatic tumor biopsies for various analyses. In more than 90% of patients, there was sufficient tissue for pathological evaluation, receptor testing, and massively parallel sequencing.
To date, we have completed targeted sequencing for 80 of these patients and this information has been returned to physicians to aid with clinical decision-making. Of these 80 patients, more than 70% had alterations in at least one of 5 genes that are entry criteria for ongoing clinical trial at our institution. This includes 46% with PIK3CA mutations, 23% with ESR1 ligand-binding domain mutations, 9% with ERBB2 mutations, 9% with FGFR1/2 amplifications, and 1% with AKT1 mutations. Beyond these, there were additional alterations identified that were relevant to other targeted therapies. We recently presented this data at the 2016 ASCO Annual Meeting (Wagle et al, ASCO Annual Meeting 2016).

Physicians have now begun to act on this information. As shown in Figure 3, physicians have the opportunity to use the results they receive to enroll patients on several clinical trials that have particular genomic alterations as entry criteria. We are in the process of developing additional trials to be included in the list of potential options. As an example, one patient with resistant metastatic breast cancer was found to have an ERBB2 activating mutation in her metastatic tumor.

![Trials for Patients with Metastatic Breast Cancer](image)

**Figure 3.** Based on the results of sequencing, physicians have the option of enrolling patients on clinical trials that have particular genomic alterations as entry criteria.

![Case Studies - Patient 315](image)

**Figure 4.** Example where prospective genomic profiling identified an ERBB2 activating mutation in a patient with advanced breast cancer which led to enrollment on a clinical trial of neratinib + fulvestrant, with excellent response.
biopsy. This led her physician to enroll her on a clinical trial of neratinib and fulvestrant, which requires an activating ERBB2 mutation for enrollment. She has had an excellent response to therapy, and continues on this clinical trial at present (see Figure 4).

In summary, we have shown that metastatic biopsy program for cancer precision medicine in breast cancer is feasible, with >90% of biopsies yielding sufficient tissue for pathology, receptors, and targeted sequencing. Multiple clinically relevant genomic and molecular alterations are identified in metastatic biopsies – with implications for choice of next therapy, clinical trial eligibility, and novel drug targets. This includes identifying a cancer other than breast cancer (3%), a change in ER or HER2 status (10%), and somatic alterations that are entry criteria for clinical trials of targeted therapies (>70%). We plan to continue collection of serial biopsies from enrolled patients, and utilize clinically relevant pathological, genomic, and molecular information for clinical decision-making and trial enrollment.

**TASKS:**
- Protocol activation (Month 1 – Month 3): COMPLETE
- Patient enrollment (Month 4 – Month 36): COMPLETE
- Sample acquisition (Month 4 – Month 36): COMPLETE
- Genomic profiling (including DNA extraction, library construction, sequencing, and validation) (Month 4 – Month 36): COMPLETE
- Interpretation of genomic alterations and reporting to physicians/patients (Month 4 – Month 36): COMPLETE
- Analysis of feasibility and clinical impact (Month 4 – Month 36): COMPLETE

**MILESTONES:**
- Protocol activated and patient enrollment begins by Month 4: COMPLETE
- Sequencing of first 5-10 patients completed and reported to physician/patient by Month 9: COMPLETE
- Analysis of feasibility and clinical impact of first 5-10 patients by Month 12: COMPLETE
- Sequencing of first 20 patients completed and reported to physician/patient by Month 18: COMPLETE
- Analysis of feasibility and clinical impact of first 20 patients by Month 21: COMPLETE
- Sequencing of at least 50 patients completed and reported to physician by Month 33 COMPLETE
- Analysis of feasibility and clinical impact of 50 patients by Month 36 COMPLETE

**AIM 2B: To use whole-exome sequencing to identify genomic mechanisms of therapeutic resistance**

The goal of this aim was perform whole exome sequencing in breast cancer patients who develop resistance to targeted therapies (e.g., endocrine therapies, anti-Her2 therapies, PI3K inhibitors, mTOR inhibitors) in order to identify novel resistance mechanisms. In addition to the 111 biopsies above, we were able to obtain an additional 72 metastatic tumor biopsies and matched blood samples that were obtain from Dana-Farber patients between 2006 and 2014, including 27
biopsies that have been collected since the start of this grant term. Of these 183 metastatic biopsies, we have been able to obtain matched pre-treatment primary tissues from 77 patients, resulting in 77 “trios” of primary, metastatic, and normal tissues from the same patient (Figure 5). Whole exome and transcriptome sequencing of all tissues from 63 of these trios has now been completed, and analysis is underway. We are also in the process of obtaining and sequencing the pretreatment samples from the remaining patients, and expect to ultimately have pre-treatment and post-resistance analysis on at least 100 patients with ER+ metastatic breast cancer.

While systematic analysis of these trios is currently underway, to date we have completed a preliminary landscape analysis of whole exome sequencing from 100 endocrine-resistant metastatic biopsies. This analysis highlights several genes that are recurrently altered at different times.
rates than in primary breast cancer (Figure 7). In many cases, these genes are acquired in the resistant tumors and not detected in the corresponding pre-treatment biopsies. For example, Figure 8 illustrates a patient who acquires several genomic alterations that can result in resistance to endocrine therapy, including loss of ER and loss of RB1. Several additional resistance candidates have been identified in this initial analysis. The preliminary results for this study was presented at the 2016 ASCO Annual Meeting (Wagle et al, 2016). A manuscript is currently in preparation.

In addition to this study on ER+ metastatic breast cancer, we had access to metastatic tumor biopsies collected from patients enrolled on a phase II study evaluating the combination of lapatinib and trastuzumab in patients with metastatic HER2+ breast cancer. The total study accrual was 116 patients and a baseline tumor biopsy was required at time of study entry. By design, patients had varying degrees of prior trastuzumab exposure. We performed deep whole exome sequencing (WES) on metastatic frozen tumors and matched normal tissue from 65 patients plus 54 matched archival FFPE primary samples. The two most significant recurrently mutated genes in this cohort were PIK3CA (n=22; 34%) and TP53 (n=36; 55%). As shown in Figure 9, compared to 120 primary, treatment-naïve HER2+ tumors sequenced in the TCGA study, there was no significant difference in the incidence of point mutations and indels in TP53 and PIK3CA (55% and 34%, respectively). However, the incidence of ERBB2 (HER2) mutations was significantly increased (14% vs 2%, p = 0.002). There was no significant difference in the mutation rates in ERBB3, ERBB4, and EGFR.

HER2 mutations have previously been identified in ~2% of primary HER2- cancers and <2% of primary HER2+ cancers (CBio portal). In our study, we identified a somatic HER2 mutation in 9 out of 65 metastatic biopsies (14%), 5 of which were in the kinase domain (Figure 5). The HER2 L755S mutation (found in 3 patients) is a well-described activating mutation in HER2 that results in resistance to lapatinib and sensitivity to irreversible inhibitors (e.g. neratinib). The remaining 2 kinase domain mutations have not been described previously. They were present at low allelic fractions, both in patients who received prior trastuzumab. Characterization of these mutations is currently underway. 4 additional patients, 2 of whom received prior trastuzumab, had uncharacterized mutations in other domains of HER2 at low allelic fractions.

Additional recurrently mutated genes occur at much lower frequencies and are being confirmed. In addition, an analysis to identify genes that may contribute to resistance to trastuzumab is being conducted by comparing matched metastatic and primary biopsies from the 46 patients who received prior anti-Her2 therapy prior to the metastatic biopsy.
The results for these studies on HER2+ metastatic breast cancer patients were presented in a Poster Highlights session at the 2014 ASCO Annual Meeting (Wagle et al, 2014b) and in a Poster Highlights session with an oral presentation at the 2014 San Antonio Breast Cancer Symposium (Wagle et al, 2014b). A manuscript is currently in preparation.

In summary, we have performed comprehensive next-generation sequencing on more than 130 sets of metastatic biopsies and matched pretreatment biopsies from patients with metastatic breast cancer. Going forwards, we plan to continue our analysis of whole exome and transcriptome data from these cohorts. We will integrate this sequencing data with clinical information to identify potential mechanisms of resistance to specific agents, and then perform functional and mechanistic testing of key alterations to further elucidate the landscape of resistance mutations in metastatic breast cancer.

**TASKS:**
- Whole exome sequencing of patients with acquired resistance to targeted therapies (Month 9 – Month 36): **COMPLETE**

**MILESTONES:**
- Whole exome sequencing on first 3-6 patients with acquired resistance completed by Month 16: **COMPLETE**
- Whole exome sequencing of at least 15 patients with acquired resistance completed by Month 33: **COMPLETE**
4. KEY RESEARCH ACCOMPLISHMENTS:

- Development of a novel targeted sequencing platform that includes ~450 genes that are significantly altered in breast cancer and other cancers, including novel unpublished alterations that we have recently identified in ER+ breast cancers
- Development of a prospective whole exome sequencing pipeline that includes sequencing from FFPE samples, analysis, curation, and interpretation of clinically relevant somatic and germline alterations, discussion of key findings by the Cancer Genome Evaluation Committee, and return of results to physicians and patient (Van Allen, Wagle, et al, Nature Medicine, 2014)
- Implementation of a novel Cancer Precision Medicine infrastructure and workflow that involves the acquisition of metastatic research biopsies with triage of samples for clinical pathology and receptor testing, clinical targeted sequencing (with return of results), whole exome and transcriptome sequencing, single cell transcriptome sequencing, and cell line generation, as well as cell free DNA analysis. The initial patient to utilize this workflow was biopsied in June 2015; to date we have obtained 111 metastatic biopsies over the past year. More than 90% of biopsies yielded sufficient tissue for pathology, receptors, targeted sequencing, and whole exome and transcriptome sequencing (Wagle et al, ASCO Annual Meeting 2016).
- Return of results to treating physicians, including pathology, receptor status, and targeted sequencing results from metastatic biopsies for 80 patients to date, with multiple clinically relevant genomic and molecular alterations are identified. This includes identifying a cancer other than breast cancer (3%), a change in ER or HER2 status (10%), and somatic alterations that are entry criteria for clinical trials of targeted therapies (>70%). This information has impacted clinical decision making in many instances, and there are several examples of therapeutic response as a result of these decisions (Wagle et al, ASCO Annual Meeting 2016).
- Whole exome sequencing of 100 ER+ metastatic breast cancer, plus 77 matched archival primary samples (Wagle et al, ASCO Annual Meeting 2016). Sequencing analysis has demonstrated:
  - The mutational landscape in resistant ER+ metastatic breast cancer differs significantly from ER+ primary breast cancer.
  - Multiple potential resistance mechanisms to endocrine therapy were identified.
  - When resistant metastatic biopsies were compared to matched treatment-naïve primary tumors from the same patient, many biologically and clinically relevant genes were found to be acquired in the metastatic setting.
- Whole exome sequencing of 65 HER2+ metastatic breast cancer, plus 54 matched archival primary samples (Wagle et al, ASCO Annual Meeting 2014; Wagle et al San Antonio Breast Cancer Symposium 2014). Sequencing analysis has demonstrated:
  - PIK3CA and TP53 were significantly recurrently mutated in these tumors, at the same rate as in primary, treatment-naïve HER2+ breast cancer
  - The prevalence of PIK3CA and TP53 mutations was similar in the metastatic samples from those patients who received prior trastuzumab and those who were trastuzumab naïve, though some metastatic biopsies in patients who received prior trastuzumab had mutations of interest not detected in the corresponding primaries
Somatic HER2 mutations in patients with HER2+ MBC treated seem to occur at a higher rate than in primary HER2+ breast cancer, and may be involved in resistance to trastuzumab and lapatinib

5. CONCLUSION:
To date, we have made significant progress on this research project. Although not yet fully completed, this work has already provided new knowledge that informs the development of novel treatment strategies in breast cancer. For Aim 1, we expect to utilize the targeted sequencing panel we have developed to profile 150 early stage ER+ breast cancers in the near future. For Aim 2, we have completed our stated goal of performing and returning whole exome and targeted sequencing on 50 patients with advanced breast cancer, and have extended the cohort to more than 80 patients. We have also collected and sequencing metastatic biopsies and matched pretreatment samples on our stated goal of at least 15 patients, and have extended this to more than 130 patients. We expect to complete the analysis on these cohorts shortly. Once complete, we hope to be able to better determine how best to use targeted therapies in advanced breast cancer, and to develop novel strategies to overcome resistance mechanisms. If widely deployed, implementation of this approach may open new opportunities to link cancer genomics with molecular features, clinical outcomes, and treatment response in patients with breast cancer. This approach may ultimately impact clinical practice by offering a categorical means to identify genetic changes affecting genes and pathways targeted by existing and emerging drugs, thereby speeding the advent of cancer precision medicine.
6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. Manuscripts:

   (1) Lay Press:

   None

   (2) Peer-Reviewed Scientific Journals:


   (3) Invited Articles:


   (4) Abstracts:


at a major cancer center. 2013 ASCO Annual Meeting, Chicago, IL, May 31- June 4, 2013. [Poster Discussion]


b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

**Regional**

2015

“Translational Genomics and Precision Cancer Medicine” Invited Talk
Department of Pathology
Boston University School of Medicine
Boston, MA

2015

“Cancer Care as a Model for Precision Medicine” Invited Talk
MIT Collaborative Series
Massachusetts Institute of Technology

2016

“Cancer Precision Medicine” Invited Talk
MIT-CHIEF Series
Massachusetts Institute of Technology

**National**

2013

“CanSeq: The Use of Whole Exome Sequencing To Guide the Care of Cancer Patients” Invited Talk
62nd Meeting of the National Cancer Institute Director’s Consumer Liaison Group (DCLLG)
National Cancer Institute
Washington, DC
2013
“Identification of New Targets and Pathways in Cancer: Translating Basic Discoveries into the Clinic”
American Association of Cancer Research Annual Meeting 2013 Washington, DC
2013
“Genomic and Molecular Profiling: What We Know and What's Coming”
Clinical Care in Oncology for the Advanced Practice Provider American Society of Clinical Oncology 2013 Pre-Meeting Chicago, IL
2013
“Genomic Testing for All Cancer Patients at Dana-Farber Cancer Institute, Brigham & Women’s Hospital, and Boston Children’s Hospital”
Next Generation Diagnostics Summit 2013 Washington, DC
2013
“Clinical and Translational Cancer Genomics”
Vanderbilt Ingram Cancer Center Nashville, TN
2013
“Clinical Genomics and Precision Cancer Medicine”
Norris Cancer Center Grand Rounds University of Southern California Los Angeles, CA
2014
“Clinical Genomics and Precision Cancer Medicine”
Abramson Cancer Center University of Pennsylvania Philadelphia, PA
2014
“Clinical Genomics and Precision Cancer Medicine”
Center for Molecular Oncology Memorial Sloan-Kettering Cancer Center New York, NY
2014
“How Can We Move Forward with Combination Targeted Therapies in a Breast Cancer Genomically-Driven Trial?”
2015
“Assigning Clinical Meaning to Cancer Genome Data”
American Association of Cancer Research Annual Meeting 2015 Washington, DC
2015
“CanSeq: Whole Exome Sequencing to Guide the Care of Cancer Patients”
American Association of Cancer Research Annual Meeting 2015 Washington, DC
2015
“Understanding response and resistance to anti-cancer therapies through the study of extraordinary responders”
American Association of Cancer Research Precision Medicine Series:
Integrating Clinical Genomics and Cancer Therapy
Salt Lake City, UT
2015  “Assigning Clinical Meaning to Cancer Genome Data for Cancer Precision Medicine”
AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics
Boston, MA
2015  “Cancer Precision Medicine”
NCI Cancer Research Network Workshop
National Cancer Institute
Bethesda, MD
2015  “Insights from the Study of Extraordinary Responders”
American Society of Hematology Annual Meeting 2015
Orlando, FL
2015  “Translational Genomics” Poster Discussion Session
San Antonio Breast Cancer Symposium 2015
San Antonio, TX
2016  “The Metastatic Breast Cancer Project”
NCCN IRB Director’s Forum
Orlando, FL
2016  “Assigning Clinical Meaning to Cancer Genome Data for Cancer Precision Medicine”
2016 American College of Medical Genetics Annual Clinical Genetics Meeting
Tampa, Florida

**National Abstract Oral Presentations**

2014  “Whole exome sequencing (WES) of HER2+ metastatic breast cancer (MBC) from patients with or without prior trastuzumab (T): A correlative analysis of TBCRC003”
San Antonio Breast Cancer Symposium 2014
San Antonio, TX

**International**

2013  “Tumor Genomic Profiling: Targeted versus Whole Exome Sequencing”
1st International Congress on Controversies in Personalized Oncology (CONPO)
Barcelona, Spain
2013  “Clinical and Translational Breast Cancer Genomics”
The 3rd Global Cancer Genomics Consortium Symposium: From Oncogenomics to Cancer Care
Lisbon, Portugal
2013  “Clinical Cancer Genomics and Precision Cancer Medicine”
Translational Genomics Symposium
National Institute of Genomic Medicine (INMEGEN)
7. INVENTIONS, PATENTS AND LICENSES:

Nothing to report.

8. REPORTABLE OUTCOMES:

Nothing to report.

9. OTHER ACHIEVEMENTS:

a) Promotion to Assistant Professor of Medicine at Dana-Farber Cancer Institute and Harvard Medical School

In July 2014, I was appointed as an independent faculty member in Department of Medical Oncology at Dana-Farber, with my own laboratory and translational research program in breast cancer. In November 2015, I was promoted to Assistant Professor in Medicine at Harvard Medical School. I also serve as an inaugural faculty member in the new Center for Precision Cancer Medicine at DFCI and I was appointed as an Associate Member of the Broad Institute of Harvard and MIT.

b) Over the course of this award, I have obtained several awards and grants, several of which are related to the preliminary data generated by this award (indicated with an *):

*2013 – 2015  *Systematic genomic profiling of endocrine-resistant breast cancer
Landon Foundation-AACR INNOVATOR Award for Research in Personalized Cancer Medicine (Wagle)
Principal Investigator

2014 – 2015  Exceptional Responses in Cancer
Next Generation Fund of the Broad Institute of Harvard and MIT
(Wagle) Principal Investigator

*2014 – 2016  Identifying resistance mechanisms in ER+ breast cancer by translational genomics
Dana-Farber/Harvard SPORE in Breast Cancer Career Development Award
(Wagle) Principal Investigator
*2015 – 2018 Identifying resistance mechanisms in ER+ breast cancer by translational genomics
Susan G. Komen Career Catalyst Research Grant
(Wagle) Principal Investigator

*2015 – 2017 Elucidating mechanisms of resistance to selective estrogen receptor degraders (SERDs) in ER+ metastatic breast cancer through translational genomics
V Foundation Martin D. Abeloff V Scholar Award (Wagle)
Principal Investigator

*2016 – 2018 Identifying mechanisms of response and resistance to selective estrogen receptor degraders (SERDs) in ER+ metastatic breast cancer
Breast Cancer Alliance Exceptional Project Grant (Wagle)
Principal Investigator

*2016 – 2019 Overcoming resistance to combined ER and CDK4/6 inhibition in breast cancer
AACR NextGen Grant for Transformative Cancer Research (Wagle)
Principal Investigator

2016 – 2017 Tumor and Germline Genomic Analysis in Young Patients with Metastatic Breast Cancer
Broad Ignite Grant (Wagle)
Principal Investigator

*2016 – 2018 Identifying mechanisms of resistance in ER+ metastatic breast cancer through translational genomics
Novartis Drug Development Program (Wagle)
Principal Investigator

*2016 – 2018 Elucidating Mechanisms of Intrinsic and Acquired Resistance to Combined ER and CDK4/6 Inhibition in Metastatic Breast Cancer
Mary Kay Foundation Grant (Wagle)
Principal Investigator

10. TRAINING AND PROFESSIONAL DEVELOPMENT:
I continue to be advised by an exceptional group of mentors to help guide me in my research and my career development. My primary scientific mentor is Dr. Levi Garraway, a visionary physician-scientist with an extraordinary scientific track record who has served as an outstanding personal and professional role model. I have also continued to be mentored by a committee comprised of world-class experts in breast cancer translational research and cancer genomics, who have provided invaluable guidance over the course of this award. My training has also been enhanced by my training environment. I have had the opportunity to attend multiple weekly and monthly seminars and courses as well as present my work in them. In addition, I have had the opportunity to attend numerous scientific meetings over the past few years, including the San
Antonio Breast Cancer Symposium, the ACRR Annual Meeting, the ASCO Annual Meeting, the AACR-EORTC-NCI Meeting on Molecular Targets and Cancer Therapeutics, and several meetings and workshops of the NHGRI Clinical Sequencing Exploratory Research Consortium.

11. REFERENCES:


