ESMO Translation Research Fellowship
(August 2010 – August 2012)

"Circulating tumor DNA in metastatic breast cancer"

Leticia De Mattos-Arruda

Final Report

Host Institute:	Institution Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital
Mentors:	Josep Tabernero/Joan Seoane
Project title:	"Circulating tumor DNA in metastatic breast cancer"
Home Institute:	Santa Casa de Misericórdia de Belo Horizonte, Faculdade de Ciências Médicas de Minas Gerais, Belo Horizonte, MG, Brazil

Rationale and Aim

Introduction

Traditionally, the study of many cancer biomarkers, including mutation status, has been based in archival tumor-tissue. The study of such biomarkers in the original tumor tissue biopsy depends on the availability and quality of the specimen and may not be representative of the disease due to intra-tumor heterogeneity [1, 2].

The development of novel techniques for the evaluation of blood-borne biomarkers (i.e. liquid biopsies) in cancer such as circulating tumor cells (CTCs) and circulating cell-free tumor DNA (ctDNA) have changed the translational arena. Circulating biomarkers might constitute representative readouts of both primary tumour and metastatic deposits, and provide ways to expedite the discovery and validation of clinically useful predictive biomarkers [3]. In fact, blood represents a potential source of circulating tumor material, which may complement or replace the available tissue and has shown to be less invasive and repeatable. Circulating blood biomarkers hold promise to be non-invasive real-time surrogates for tumor tissue-based biomarkers.

Circulating tumor DNA & massively parallel sequencing

ctDNA in plasma or serum has been widely investigated as potential non-invasive surrogates for tumor tissue biopsies [4-6]. The detection, quantification, and molecular characterization of plasma ctDNA have introduced new means for investigating the metastatic process and the mechanisms of therapeutic resistance, and for monitoring the emergence of treatment-resistant clones [3].

Massively parallel sequencing strategies of ctDNA seem to be feasible [5, 6]. Toward this end, more accurate information may be derived from the analyses of genomic alterations derived from ctDNA. Screening ctDNA for driver cancer genomic alterations may be more comprehensive and informative than single biopsies, because spatially geographic distinct clones derived from the same patient seem to be all found mixed

together in blood. Consequently, massively parallel sequencing of ctDNA may open the way to better understand the pathways that drive cancer metastasis and to personalize cancer therapy.

1st part

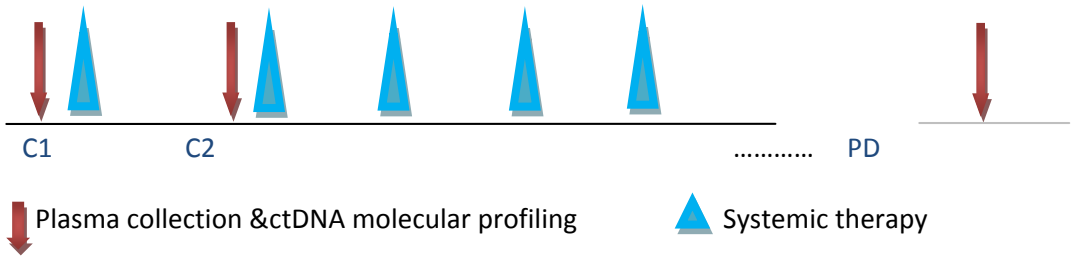
Initially, we were working with the Sequenom Mass Array (OncoCarta Panel platform version 1.0), which utilizes pre-designed and pre-validated mass spectrometric single nucleotide polymorphism genotyping technology for the parallel analysis of 238 simple and complex mutations across 19 common oncogenes.
Our aim was:

- To assess the feasibility of multiplex mutational detection with the OncoCarta Panel platform in plasma ctDNA and to match the somatic mutation profiling of both plasma ctDNA and patients' tumor tissue biopsies.
- To investigate if the measurement of plasma ctDNA quantitative and qualitative alterations have prognostic value in breast cancer metastatic patients.

Design

Observational study in which metastatic breast cancer patients with known specific mutations in archival tumor tissue biopsies were screened prospectively in 3 time points at the start of a new therapy, either standard or experimental for plasma ctDNA alterations (quantification and somatic mutation profiling) (Figure 1).

Figure 1. Timeline of ctDNA collection and therapy administration



Results

ning set, we analyzed samples from metastatic breast, colon and lung patients. We detected through the Sequenom Mass Array (OncoCarta Panel platform version 1.0) in plasma and matched ic mutation profiling of both plasma ctDNA and tumor tissue biopsies (Table 1).

sults for the training setting

sue	Tissue mutation	Sample type	Mutation
	PIK3CA H1047R	Plasma	No mutation detected
	PIK3CA E545K	Plasma	No mutation detected
	PIK3CA E542K	Plasma	PIK3CA E542K
	KRAS	Plasma	No mutation detected
	KRAS G12V	Plasma	KRAS G12V
	KRAS G13D	Plasma	KRAS G13D
	EGFR	Plasma	No mutation detected
	BRAFK601E	Plasma	BRAF K601E
	KRAS Q61L	Plasma	KRAS Q61L
	KRAS Q61L	Plasma	KRAS Q61L

spective setting, we collected blood from metastatic breast cancer patients at 3 time points and

s of the phosphatidylinositol-3-kinase (PI3K) pathway in metastatic breast cancer.

ows plasma ctDNA results and their corresponding mutation in tumor-tissue, and the treatment nts were receiving at the time of blood draw (Presented in part at the European Society for Medical (ESMO), Vienna, Austria, September 2012).

e and others [5, 6] have seen that it is possible to monitor the course of therapy in metastatic hrough the assessment of the somatic mutation detected in plasma ctDNA (Figure 2). The of mutant alleles detected in selected patients are in accordance with radiologic and biochemical (e.g. CA15.3 for breast cancer) and seem more sensitive indicators of disease status.

lasma ctDNA results for metastatic breast cancer patients with PI3K-pathway alterations in tumor-

Tissue PI3K-pathway alteration		Line of therapy	Administered Therapy	Best response	1st plasma sample (before starting a new line of therapy)	2nd plasma sample (after 1 month)
PI3K	H1047R	6	AKT inhibitor	SD	H1047R	WT
PI3K	E545K	4	PI3K alpha inhibitor	SD	N/A	WT
PI3K	E542K	6	Etoposide	early PD	E542K	N/A
PI3K	H1047R	4	Vinorelbine + trastuzumab	SD	H1047R	WT
PI3K	E545K	2	Capecitabine +/- sorafenibe	SD	E545K	WT
PI3K	H1047R	4	Letrozol+PI3K/mTOR inhibitor	SD	WT	WT
PI3K	H1047L	2	Tamoxifen	SD	WT	WT
PI3K	E545K*	4	Paclitaxel + anthracycline	SD	WT	N/A
PI3K	E545K	5	AKT inhibitor	early PD	H1047R	N/A
AKT1	E17K	2	Capecitabine	SD	WT	N/A
AKT1	E17K	4	AKT inhibitor	SD	AKT1 E17K	AKT1 E17K
PI3K	H1047R	5	PI3K inhibitor	SD	H1047R	WT
PI3K	H1047R	3	Afatinib + vinorelbin	SD	WT	WT
PI3K	G1049R	4	Capecitabine+ lapatinib	PR	WT	WT
PI3K	H1047R	5	Vinorelbine + trastuzumab	PR	H1047R	H1047R
PI3K	E110K	4	Paclitaxel + LCL161	PR	WT	WT

, not available, PR, partial response; SD, stable disease; PD, progressive disease; WT, wild-type. * Per Oncocarta: PIK3CA E545K. ** Primary tumor: ER+/HER2-, M1: HER+.

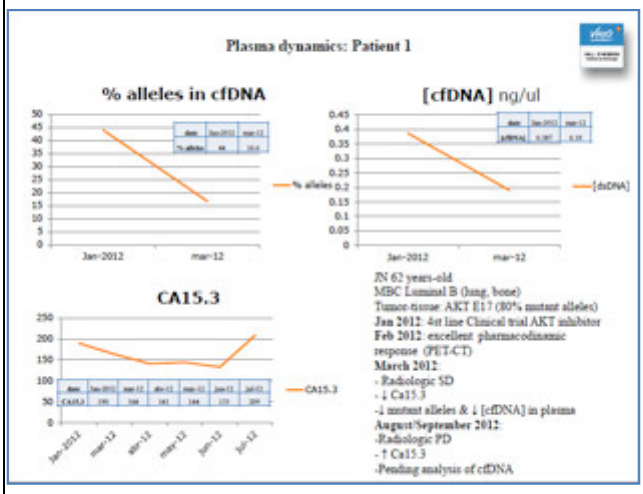
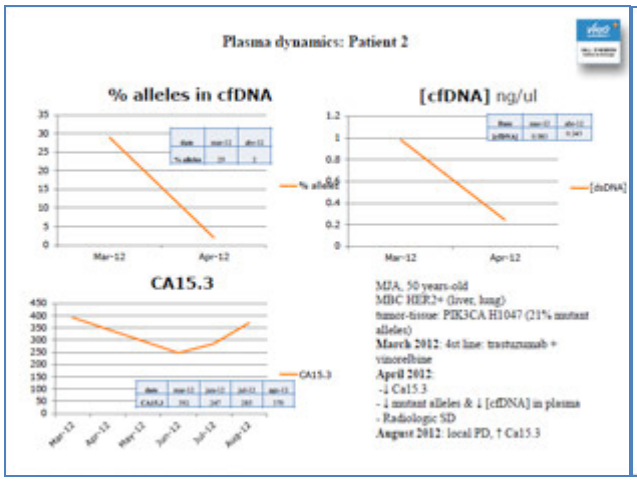
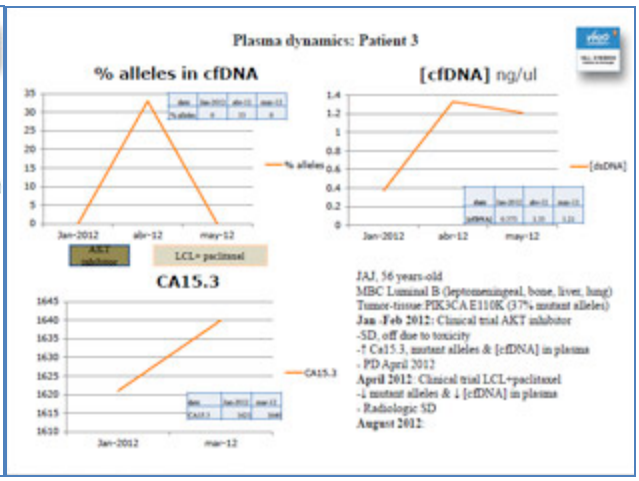


Figure 2. Assessment of ctDNA in the plasma for 3 selected patients with metastatic breast cancer. The graphs depict tumor dynamics as per concentration of total DNA [DNA] and the frequency of mutant alleles [% mutant alleles]. Both parameters are in accordance with radiologic and biochemical responses.





2nd part

In the second part of the project, we worked with massively parallel sequencing in tumor tissue and plasma-derived ctDNA. The use of massively parallel sequencing through "liquid biopsies" should provide means to uncover potential actionable targets and mechanisms of therapeutic resistance. This may provide ways to better select and monitor patients for specific targeted therapies.

Our aim was:

- To perform massively parallel sequencing in tumor tissue and ctDNA to decode genomic aberrations of metastatic or advanced breast cancer patients throughout patient treatment.
- To determine whether the collection of mutations detected in plasma ctDNA are representative of those obtained from the analysis of the tumor tissue, and if ctDNA can be used as a surrogate for tumor tissue.

Results of the feasibility study in collaboration with the Memorial Sloan-Kettering Cancer Center, New York, NY will be presented as a *Poster Discussion Session* at San Antonio Breast Cancer meeting (SABCS), San Antonio, Texas, December 2013.
Title: "Longitudinal Massively Parallel Sequencing Analysis of Circulating Cell-Free Tumor DNA".

Future perspectives

Our goal now is to perform massively parallel sequencing of ctDNA in specific populations of cancer patients in order to discover predictive and prognostic molecular aberrations. In parallel with the analysis of the ctDNA of cancer patients, we aim to perform pre-clinical work with circulating biomarkers and patient-derived xenograft models. In fact, patient-derived xenograft models and the study of "liquid biopsies" may reproduce the molecular characteristics of the patients, powerfully modeling human cancer for biomarker discovery and potentially guiding personalized therapeutic decisions [7][8].

List of Publications Resulting from the Grant

1. **De Mattos-Arruda L,** Cortes J, Santarpia L, Vivancos A, Tabernero J, Reis-Filho JS, Seoane J: Circulating tumour cells and cell-free DNA as tools for managing breast cancer. *Nat Rev Clin Oncol* 2013, 10(7):377-389.
2. Serra V, Vivancos A, Puente XS, Felip E, Silberschmidt D, Caratu G, Parra JL, **De Mattos-Arruda L,** Grueso J, Hernandez-Losa J *et al*: Clinical response to a lapatinib-based therapy of a Li-Fraumeni Syndrome patient with a novel HER2-V659E mutation. *Cancer Discov* 2013.
3. **De Mattos-Arruda L,** Bidard FC, Won H, Cortes J, Ng C, Peg V et al. Establishing the origin of metastatic deposits in the setting of multiple primary malignancies: the role of massively parallel sequencing. Molecular Oncology 2013 (accepted)
4. **De Mattos-Arruda L,** Rodon J. Pilot Studies for Personalized Cancer Medicine: First Steps for Putting the Patient at Center Stage for Treatment Selection. The Oncologist 2013 (in press).
5. **De Mattos-Arruda L,** Cortes J: Use of Pertuzumab for the Treatment of HER2-Positive Metastatic Breast Cancer. *Advances in therapy* 2013, 30(7):645-658.
6. **De Mattos-Arruda L,** Tabernero J, Seoane J, Cortes J: Circulating tumour cells in early breast cancer. *Lancet Oncol* 2012, 13(9):e370; author reply e370.
7. Azim HA, Jr., Kroman N, Paesmans M, Gelber S, Rotmensz N, Ameye L, **De Mattos-Arruda L,** Pistilli B, Pinto A, Jensen MB *et al*: Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013, 31(1):73-79 *(Collaborative work with Dr. Hatem Azim, 2010 ESMO Translational Fellowship recipient).*
8. **De Mattos-Arruda L,** Cortes J: Advances in first-line treatment for patients with HER-2+ metastatic breast cancer. *Oncologist* 2012, 17(5):631-644.
9. Serrano C, Cortes J, **De Mattos-Arruda L**, Bellet M, Gomez P, Saura C, Perez J, Vidal M, Munoz-Couselo E, Carreras MJ *et al*: Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. *Ann Oncol* 2012, 23(4):897-902.
10. **De Mattos-Arruda L,** Cortes J: Breast cancer and HSP90 inhibitors: is there a role beyond the HER2-positive subtype? *Breast* 2012, 21(4):604-607.
11. Cortes J, Calvo E, Gonzalez-Martin A, Dawood S, Llombart-Cussac A, **De Mattos-Arruda L**, Gomez P, Silva O, Perez EA, Rugo HS *et al*: Progress against solid tumors in danger: the metastatic breast cancer example. *J Clin Oncol* 2012, 30(28):3444-3447.
12. **De Mattos-Arruda L,** Olmos D, Tabernero J: Prognostic and predictive roles for circulating biomarkers in gastrointestinal cancer. *Future Oncol* 2011, 7(12):1385-1397.
13. **De Mattos-Arruda L,** Elattar I, Azim HA, Jr.: Circulating tumor cells in metastatic breast cancer: the need for a standardized approach. *Ann Oncol* 2011, 22(1):234.
14. **De Mattos-Arruda L,** Dienstmann R, Tabernero J: Development of molecular biomarkers in individualized treatment of colorectal cancer. *Clinical colorectal cancer* 2011, 10(4):279-289.

Conference presentations:

1. **De Mattos-Arruda L**, Cortes J, Saura C, Nuciforo P, Bidard F-C, Won H, Weigelt B, Berger M, Seoane J, Reis-Filho J Longitudinal Massively Parallel Sequencing Analysis of Circulating Cell-Free Tumor DNA (to be presented as a *Poster Discussion Session* at San Antonio Breast Cancer meeting (SABCS), San Antonio, Texas, December 2013).
2. BRAFV600 serum/plasma analysis: Predictive value of survival in melanoma treated with BRAF inhibitors. Gonzalez Cao M, Martin Algarra S, Muñoz E, Mayo de las Casas C, Jose Luis Manzano Cortes J, … **De Mattos-Arruda L….**, et al. (to be presented as a Poster at 2013 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference, October 19-23 in Boston, Massachusetts, US).
3. **De Mattos-Arruda L**, Siu LL, Cortes J, Berge Y, Razak ARA, Rodon Ahnert J, et al. Phase I dose-escalation, open-label study of HSP990 administered orally in adult patients with advanced solid malignancies. J Clin Oncol 31, 2013 (suppl; abstr 2561^) (Poster).
4. **De Mattos-Arruda L**, Cortes J, Aura C, Gregori J, Caratú G, Saura C, Oliveira M, Tabernero J, Seoane J & Vivancos A. Breast cancer (BC) and the study of intratumoral heterogeneity through PI3K pathway-biomarkers. (Abstract 2952, presented at the European Society for Medical Oncology (ESMO), Vienna, Austria, September 2012) (Poster).
5. Bendell J, Roda D, Mateo J, Hollebecque A, **De Mattos-Arruda L**, Meng R, et al. Phase Ib Dose Escalation Study of the Akt Inhibitor GDC-0068 with Docetaxel or mFOLFOX6 in Patients with Advanced Solid Tumors. (Abstract 458, European Society for Medical Oncology (ESMO), Vienna, Austria, September 2012) (Poster).
6. **De Mattos-Arruda L**, Cortes J, Aura C, Oliveira M, Navarro A, Caratu G, et al. Analysis of the intratumoral heterogeneity of PIK3CA mutant alleles in breast cancer (BC): Implications for the luminal (LUM) phenotype. J Clin Oncol 30, 2012 (suppl; abstr 10511) (Poster Discussion).
7. Oliveira M, Navarro A, **De Mattos-Arruda L**, Sánchez-Ollé G, Bellet M, Balmaña J et al. PI3K pathway (PI3Kp) dysregulation and response to pan-PI3K/AKT/mTOR/dual PI3K-mTOR inhibitors (PI3Kpi) in metastatic breast cancer (MBC) patients (pts). J Clin Oncol 30, 2012 (suppl; abstr 509) (Clinical Science Symposium).
8. Navarro A, Oliveira M, **De Mattos-Arruda L** Sánchez-Ollé G, Bellet M, Balmaña J et al. Prognostic significance of PI3K pathway (PI3Kp) dysregulation in metastatic breast cancer (MBC) patients (pts). J Clin Oncol 30, 2012 (suppl; abstr 566) (Poster).
9. Torrejon D, Di Cosimo S, Sanchez-Olle G, Balmaña J, Bellet M, Gomez P … **De Mattos-Arruda L** ...et al. Presentation and treatment of HER2-positive metastatic breast cancer patients already treated with adjuvant trastuzumab. J Clin Oncol 30, 2012 (suppl; abstr 619) (Poster).
10. **De Mattos-Arruda L**, Cortes J, Sánchez-Pla A, Aura C, Ortega V, Sánchez-Ollé G et al. Assessment of the intratumoral heterogeneity in metastatic breast cancer (MBC) through the analysis of the frequency of PIK3CA mutant alleles. IMPAKT Breast Cancer Conference - Brussels, Belgium, 2012 (Poster).
11. Vidal M, Di Cosimo S, Torrejon D, Saura C, Gómez-Pardo P, Pérez-Garcia J, Muñoz-Couselo E, Bellet M, Sanchez-Olle G, **De Mattos-Arruda L** et al. Survival Outcome with Bevacizumab: Activation of the Phosphatidylinositol-3 Kinase (PI3K) Pathway Due to PIK3CA Mutations or PTEN Loss Makes a Difference. San Antonio Breast Cancer Symposium, EUA, 2011 (Poster).
12. Oliveira M, **De Mattos-Arruda L**, Sánchez-Ollé G, Graña B, Cortes J, Perez-Garcia J. et al. Prognostic implications o phosphatidylinositol 3-kinase (PI3K) pathway alterations in metastatic triple- negative breast cancer (mTNBC). J Clin Oncol 29: 2011 (suppl; abstr 1081) (Poster).
13. **De Mattos-Arruda L,** Oliveira M, Sánchez-Ollé G, Moreno-Fernandez D, Graña B, Cortes J et al. Metastatic breast cancer (MBC) subtypes have different overall survival (OS) according to phosphathidylinositol-3-kinase (PI3K) pathway status. J Clin Oncol 29: 2011 (suppl; abstr e21130).

Selection of Courses & Workshops Attended During the Fellowship

2010 - 12^{o} ECCO - AACR - EORTC - ESMO Workshop on Methods in Clinical Cancer Research. Special grant of Ontario Institute of Cancer Research. Flims, Switzerland.
2012 - IMPAKT Breast Cancer Conference**-**Brussels, Belgium, 2012.
2012 - Training Course of IMPAKT Breast Cancer Conference**-**Brussels, Belgium, 2012
2011 & 2012 - ASCO Annual Meeting, American Society of Clinical Oncology, Chicago, USA.
2012 - ESMO Congress, Vienna, AU.

Awards and prizes

2010 - 12^{o} ECCO - AACR - EORTC - ESMO Workshop on Methods in Clinical Cancer Research, Flims, Switzerland. Special grant of Ontario Institute of Cancer Research.
2012 - Susan G. Komen for the Cure® travel grant. IMPAKT Breast Cancer Conference**-**Brussels, Belgium,
2012 - *Merit Award* of ASCO Conquer Cancer Foundation, American Society of Clinical Oncology, Chicago, US, 2012.
2012 - ESMO 2012 Congress Travel Grant, Vienna, Au 2013 - *Merit Award* of ASCO Conquer Cancer Foundation, American Society of Clinical Oncology
Chicago, US, 2013.
2013 - AACR Scholar-In-Training Award, San Antonio Breast Cancer symposium, San Antonio, TX, US.

Other research projects:

- Vall d' Hebron Hospital, Breast Cancer Center and Drug Development Programme. Co-investigator of phase I, II and III trials (Ongoing).
- A Phase Ib, Open-label, Dose-Escalation Study Of The Safety And Pharmacology Of GDC-0068 In Combination With Either Docetaxel Or Fluoropyrimidine Plus Oxaliplatin In Patients With Advanced Solid Tumors. Co-Investigator (Ongoing).
- A Phase I Dose Escalation, Multi-Center, Open-label Study of HSP990 Administered Orally in Adult Patients With Advanced Solid Malignancies. Co-Investigator (Completed).
- A Two-Part, Adaptive, Randomized trial of Ridaforolimus in Combination with Dalotuzumab Compared to Exemestane or Compared to Ridaforolimus or Dalotuzumab Monotherapy in Estrogen Receptor Positive Breast Cancer Patients. Co-Investigator (Ongoing).
- A Randomized, Phase II, Multicenter, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Metmab And/Or Bevacizumab in Combination With Paclitaxel in Patients With Metastatic, Triple Negative Breast Cancer. Co-Investigator (Ongoing).
- A Randomized Study Evaluating the Efficacy and Safety of Continued Or Re-induced Bevacizumab in Combination with Chemotherapy for Patients With Local Recurrent or Metastatic Breast Cancer After First Line Chemotherapy and Bevacizumab Treatment. Co-Investigator (Ongoing).
- A Phase. Ib/II, Open Label, Multi-center Study Evaluating the Safety and Efficacy of BKM120 in Combination With Trastuzumab in Patients With Relapsing HER2 Overexpressing Breast Cancer Who Have Previously Failed Trastuzumab. Co-Investigator (Completed).
- A multicentric case-control study to determine the effect of pregnancy on breast cancer outcome in women with history of breast cancer. Co-Investigator (Completed) *(Collaborative work with Dr. Hatem Azim, 2010 ESMO Translational Fellowship recipient).*
- 12^{o} ECCO - AACR - EORTC - ESMO Workshop on Methods in Clinical Cancer Research - Flims, Switzerland, June 2010. Project title: **"**A phase 1/2 study of trastuzumab-DM1 (T-DM1) combined with nonpegylated liposomal doxorubicin (NPLD) in HER2-positive metastatic breast cancer (MBC) patients who have progressed on a HER2 directed therapy"(Completed).

Acknowledgments

I am extremely grateful for the opportunity that ESMO and Amgen gave me with the Translational Research Fellowship.

I would like to acknowledge all people that have contributed directly and indirectly to this project and have contributed to my academic background as a scientific physician.

To all my colleagues, friends and collaborators from Vall d' Hebron Institute of Oncology/ Vall d' Hebron University Hospital.

A special acknowledgement:
To Jose Baselga who gave me opportunity to work at the Vall d' Hebron University Hospital.
To Javier Cortes who has mentored me at the breast cancer outpatient clinic and clinical trials.
To our collaborators, Johann De Bono (Royal Marsden Hospital, UK), and Jorge S Reis-Filho/Britta Weigelt (Memorial Sloan-Kettering Cancer Center, New York, NY).

And to my mentors Prof. Joan Seoane, for giving me a unique opportunity at his laboratory and for always guiding me and Dr. Josep Tabernero for his wonderful support.

Personal statement

I am a Brazilian medical oncologist and translational/ clinical investigator at the Translational Research Programme/Breast Cancer Center of Vall d'Hebron University Hospital, Barcelona. I have been conducting translational research projects and cutting edge clinical trials since 2009, after my residency in Medical Oncology.

From 2010 to 2012, I was involved with the European Society for medical Oncology (ESMO) Translational Research Fellowship, in which I started investigating the biology and molecular profiling of plasma circulating free DNA and circulating tumor cells in the metastatic breast cancer setting. With my enthusiasm and perseverance, and with the support of my mentors, I pioneered the programme of circulating biomarkers at Vall d'Hebron Hospital. Given its initial success, this programme now includes other cancer types in addition to breast cancer.

Based on the recent publications on massively parallel sequencing analysis of human cancers and my experience with the use of this technology for the analysis of primary breast cancers and metastasis, I have realized that intra-tumor genetic heterogeneity is one of the major challenges we currently face. In fact, I believe that understanding the impact of intra-tumor genetic heterogeneity on the biology and clinical behavior of breast cancers is absolutely essential for the realization of the potentials of precision medicine.

Given my involvement in the circulating biomarkers program at Vall d'Hebron University Hospital, one of the questions that fascinate me is whether massively parallel sequencing analysis of tumor DNA from plasma samples would constitute an alternative to sequencing of DNA extracted from biopsies, in particular for patients with metastatic disease, given that different metastatic deposits from the same patient have been shown to have distinct constellations of genetic aberrations and that biopsies of metastatic deposits are not uncommonly too risky to be performed. My vision is that 'liquid biopsies' may constitute an excellent means for the discovery of biomarkers, disease monitoring and tailoring the therapy of patients.

References

1. Gerlinger M, Rowan AJ, Horswell S et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012; 366: 883-892.
2. Swanton C. Intratumor heterogeneity: evolution through space and time. Cancer Res 2012; 72: 4875-4882.
3. De Mattos-Arruda L, Cortes J, Santarpia L et al. Circulating tumour cells and cell-free DNA as tools for managing breast cancer. Nat Rev Clin Oncol 2013; 10: 377-389.
4. Forshew T, Murtaza M, Parkinson C et al. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. Sci Transl Med 2012; 4: 136ra168.
5. Murtaza M, Dawson SJ, Tsui DW et al. Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. Nature 2013; 497: 108-112.
6. Dawson SJ, Rosenfeld N, Caldas C. Circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med 2013; 369: 93-94.
7. Eichhorn PJ, Rodon L, Gonzalez-Junca A et al. USP15 stabilizes TGF-beta receptor I and promotes oncogenesis through the activation of TGF-beta signaling in glioblastoma. Nat Med 2012; 18: 429-435.
8. Zhang L, Ridgway LD, Wetzel MD et al. The identification and characterization of breast cancer CTCs competent for brain metastasis. Sci Transl Med 2013; 5: 180ra148.

Photograph: Leticia De Mattos-Arruda