MULTI-OMIC PROFILING OF METASTATIC LESIONS TO GUIDE TREATMENT SELECTION: THE SIDE OUT 2 TRIAL EXPERIENCE

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Study Primary Objective

The aim of this prospective pilot study was to explore if treatment selection based on Multi-omic Profiling (MoP) provides clinical benefits superior to empiric treatment selection in progressive metastatic breast cancers (MBC).

Methods

Trial design: The Side Out 2 trial (clinicaltrials.gov ID NCT01919749) was an open-label, multicenter pilot study which used the molecular profile of target lesions to guide treatment selection. Therapeutic regimens were selected only from FDA approved compounds.

Patient Population: Between 2014 and 2016, four US sites enrolled 32 previously treated MBC patients.

Key Eligibility Criteria:

- ✓ Age ≥18 years;
- ✓ ECOG of 0-1;
- ✓ Absence of symptomatic CNS metastasis;
- ✓ Adequate organ and bone marrow function;
- ✓ Documented diagnosis of metastatic breast cancer with measurable disease accessible to biopsy;
- ✓ Progression of disease on ≥ 1 prior chemotherapeutic and/or hormonal regimen(s) for advanced disease within 6 months of treatment initiation.

Response Rate Criteria: Growth Modulation Index (GMI) was used to assess patients' response to treatment based on tumor response by RECIST 1.1.

PFS_B/PFS_A ratio ≥ 1.3 = benefit for patient.

To meet the primary objective, ≥ 30% of patients must reach a GMI score ≥ 1.3 (PMID:25209003).

Study workflow

Consenting/Screening/Enrollment:
MBC patient with disease progression, clear documentation of time between treatments, and documented progression on the most recent treatment.

Tissue Collection and Multi-Omic Analysis:
Multi-omic analysis of the metastatic lesion;
- RNA-Seq & Exome Sequencing;
- Immunohistochemistry of 7 predictive markers*;
- LCM-RPPA based protein singling network analysis of 12 FDA approved drug targets and downstream substrates**.

Target(s) Found

Yes → Patient receives treatment based on identified target(s).

No → Patient receives treatment based on physician choice.

Disease Assessment Using RECIST Criteria:
Patients are assessed every 7 ± 1 weeks during the GMI monitoring window until disease progression or treatment discontinuation.

If progression is not observed at the end of therapy, patients are assessed every 3 months until progression.

At disease progression an optional second biopsy may be performed.

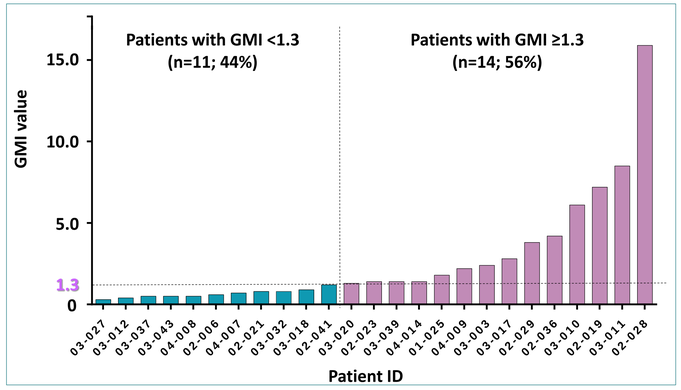
*IHC markers: Androgen (AR), Estrogen (ER), and Progesterone (PR) Receptor; SPARC; TOP2A; TOPO1, and Thymidylate Synthase (TS).
**LCM-RPPA markers: ALK; pAKT S473; pc-Abl Y735; pEGFR Y1068; pERB2 Y1248; pERB3 Y1289; pERK 1/2 T202/Y204; pp70S6K T389; pPDGFR Y751; PTEN; pRet Y905; pSrc Y527.

Results

Enrollment overview

Patient Summary	Number of Patients
Enrolled	32
Treated based on MoP	29
Treated with standard of care	3
Evaluable for GMI window	25

Patient outcome based on GMI score



- ✓ Of the 25 patients, 14 (56%) met or exceeded a GMI of 1.3.
- ✓ The most frequently selected treatments were: Irinotecan based on TOPO1 expression (n = 12; single agent n = 5) and Capecitabine based on TS expression (n = 10; single agent n = 3).
- ✓ Seven patients received endocrine therapy, 3 of whom were treated with Everolimus and Exemestane.
- ✓ Based on HER2 amplification/pathway activation, HER2 targeted agents were given to 5 patients.

Molecular characteristics of metastatic lesions and treatment

Subject ID	GMI	Receptor Status	Metastatic site	Targets	Treatment
02-03-027	0.3	ER+;PR-;HER2-	Omentum	AR; ER; TOPO1	Irinotecan; Megestrol Acetate
02-03-012	0.4	ER+;PR+;HER2-	Liver	AR; ER; TOPO1; TS	Capecitabine; Irinotecan; Megestrol Acetate
02-03-037	0.5	ER+;PR+;HER2-	Liver	TOPO1	Irinotecan
02-03-043	0.5	ER+;PR-;HER2-	Liver	TUBB3	Eribulin
02-04-008	0.5	ER+;PR+;HER2-	Chest wall/Skin	ER; p-p70S6K	Everolimus; Exemestane
02-02-006	0.6	ER+;PR-;HER2-	Lymph node	p-AKT; p-ERB2; p-ERB3; p-ERK; TS	Capecitabine; Lapatinib
02-04-007**	0.7	ER+;PR-;HER2-	Chest wall/Skin	ER; p-ERB2; p-ERK; TOPO1; TUBB3	Eribulin; Irinotecan; Lapatinib; Letrozole
02-02-021	0.8	ER+;PR-;HER2-	Omentum	ER; p-p70S6K	Everolimus; Exemestane
02-03-032	0.8	ER-;PR-;HER2-	Chest wall/Skin	TUBB3	Eribulin
02-03-018	0.9	ER+;PR-;HER2-	Liver	Thymidine Phosphorylase (TYMP)	Capecitabine
02-02-041	1.2	ER-;PR-;HER2-	Chest wall/Skin	TOPO1	Irinotecan
02-03-020	1.3	ER+;PR-;HER2-	Liver	ER; p-p70S6K	Everolimus; Exemestane
02-02-023	1.4	ER-;PR-;HER2-	Liver & Lymph node*	EZH2*; Survivin*; TOPO1; TS; TUBB3*	Capecitabine; Irinotecan; Paclitaxel
02-03-039	1.4	ER-;PR-;HER2+	Lung	TOPO1; HER2; p-ERB2; p-ERK	Irinotecan; Trastuzumab
02-04-014	1.4	ER+;PR-;HER2-	Lung	TOPO1	Irinotecan
02-01-025	1.8	ER+;PR-;HER2-	Lymph node	TS	Capecitabine
02-04-009	2.2	ER+;PR+;HER2-	Abdominal mass	AR; ER; TS; AR; TUBB3	Capecitabine; Megestrol Acetate; Vinorelbine
02-03-003	2.4	ER+;PR-;HER2-	Liver	SPARC	Paclitaxel
02-03-017	2.8	ER+;PR-;HER2-	Liver	TS; p-EGFR; p-ERB2; p-ERB3; p-ERK	Capecitabine; Lapatinib
02-02-029	3.8	ER-;PR-;HER2- ***	Chest wall/Skin	TOPO1	Irinotecan
02-02-036	4.2	ER+;PR-;HER2-	Liver	TOPO1; TS	Capecitabine; Irinotecan
02-03-010	6.1	ER+;PR+;HER2-	Liver	TOPO1	Irinotecan
02-02-019	7.2	ER-;PR-;HER2+	Chest wall/Skin	p-EGFR; p-ERB2; p-ERB3/ERBB3; p-ERK; HER2; TUBB3	Docetaxel; Pertuzumab; Trastuzumab
02-03-011	8.5	ER-;PR-;HER2-	Liver	TOPO1; TS	Capecitabine; Irinotecan
02-02-028	15.9	ER+;PR-;HER2-	Chest wall/Skin	TS	Capecitabine

* A second biopsy was collected from the same patient after recurrence; ** Metastatic lesion from a male breast tumor; *** Data retrieved from whole exome sequencing analysis.

Conclusions

- ✓ This study confirmed the unique role of MoP in selecting effective treatments for MBC.
- ✓ This approach provided clinical benefits for 56% of previously treated MBC patients, which met the primary objective of the study.
- ✓ This study also suggests that irinotecan may be an under-developed drug for MBC patients.
- ✓ As such, this approach merits further investigation.