# BioItaLEE – Comparative Biomarker Analysis of Liquid Biopsies and Paired Tissue Samples of Patients Treated With Ribociclib and Letrozole as First-line Therapy for Advanced Breast Cancer (ABC)

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## Introduction

- The addition of ribociclib (RIB) to endocrine therapy (ET) significantly improves the efficacy outcomes, including overall survival (OS), compared to ET alone in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC).[1-5]
- Currently, data on cyclin dependent kinase 4/6 inhibitors (CDK4/6i) predictive biomarkers are limited and inconclusive.[6, 7] ctDNA analysis is emerging as an attractive non-invasive approach to characterize tumor biology and its evolution overtime. Further studies are necessary to fully investigate the clinical utility and feasibility of liquid biopsy in this setting.[8, 9]

## Study Objectives

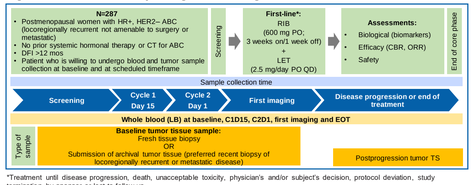
- The primary objective of the BioItaLEE phase 3b, multicenter (47 Italian centers), single-arm trial (NCT03439046) is to study ctDNA alterations, their evolution during treatment and their association with clinical outcome in postmenopausal endocrine sensitive and *de-novo* women with HR+, HER2– ABC receiving RIB and letrozole (LET) as first-line therapy. We recently presented the results of baseline ctDNA mutational status and its correlation with clinicopathological characteristics and response to treatment based on first imaging evaluation.[9] Here, we report a comparative single-nucleotide variant (SNV) analysis of baseline (pretreatment) ctDNA assessment by 2 next-generation sequencing (NGS) methods and tumor tissue DNA (tDNA) collected in the trial.

## Methods

### Biological Assessment in the Core Phase

- Biological samples such as pretreatment liquid biopsies (LBs) and tumor samples (TS) from metastatic site biopsy or primary tissue were collected prospectively in the trial (**Figure 1**).

**Figure 1. BioItaLEE Study Design and Biological Assessment in the Core Phase**




*Treatment until disease progression, death, unacceptable toxicity, physician's and/or subject's decision, protocol deviation, study termination by sponsor or lost to follow-up

ABC, advanced breast cancer; CBR, clinical benefit rate; C1D15, cycle 1 day 15; C2D1, cycle 2 day 1; CT, chemotherapy; DFI, disease free interval; EOT, end of treatment; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; LB, liquid biopsy; LET, letrozole; mo, month; ORR, overall response rate; PO, per oral; qd, once daily; RIB, ribociclib; TS, tissue sample.

### Next-Generation Sequencing (NGS) Analysis

- tDNA was extracted from tumor samples that had passed preanalytic screening (≥ 100 cells in H&E slides). The quantity and quality of tDNA were estimated via reverse transcription-polymerase chain reaction (RT-PCR) using the Quantifiler Trio DNA Quantification Kit (ThermoFisher Scientific). Samples with concentration ≥ 0.1 ng/µL and degradation index ≤ 10 were considered as suitable for NGS.
- Baseline ctDNA and tDNA were assessed by SNV analysis using the same 533-amplicon custom AmpliSeq HD panel.
- Baseline ctDNA was additionally analyzed by the Oncomine Pan-Cancer Cell-Free Assay (ThermoFisher Scientific) (**Table 1.**).

**Table 1. Molecular Analysis Performed by NGS Testing**

| NGS Testing | BioItaLEE AmpliSeq HD Custom Panel | | Oncomine Pan-Cancer Cell-Free Assay (ThermoFisher Scientific) |
|---|---|---|---|
| **Sample tested** | Baseline LB (ctDNA) | Baseline TS | Baseline LB (ctDNA) |
| **Mean coverage and LOD** | 23000 X<br>0.1%<br>(for 10 ng of cfDNA input) | 12000 X<br>0.1%<br>(for 5 ng of tDNA) | 32000 X<br>0.1%<br>(for 10 ng of cfDNA input) |
| **No. of genes tested for SNV** | 39 | | 44 |
| **Genes analyzed** | ***AKT1, APC,*** *ATM, CDH1, CCND1, CCNE1, CDK4, CDK6, CDH1, CDKN2A,* ***EGFR, ERBB2, ERBB3,*** *ERBB4,* ***ESR1, FGFR1,*** *GATA3,* ***HRAS, KIT,*** *KMT2C,* ***KRAS, MAP2K1,*** *MAP2K4 , MAP3K1,* ***MET,*** *MLH1, NF1, NOTCH1,* ***NRAS, PDGFRA, PIK3CA,*** *PIK3R1, RB1, RUNX1,* ***PTEN, RET,*** *SRC, TBX3,* ***TP53*** | ***AKT1,*** *ALK,* ***APC,*** *AR, ARAF, BRAF, CHEK2, CTNNB1, DDR2,* ***EGFR, ERBB2, ERBB3, ESR1,*** *FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2,* ***KIT, KRAS, MAP2K1,*** *MAP2K2,* ***MET,*** *MTOR,* ***NRAS,*** *NTRK1, NTRK3,* ***PDGFRA, PIK3CA, PTEN,*** *RAF1,* ***RET,*** *ROS1, SF3B1, SMAD4, SMO,* ***TP53*** |

- Eighteen genes highlighted in bold are the common ones in the 2 NGS panels used for baseline ctDNA testing. However, not all the amplicons assessed within the same gene by the 2 methods are overlapping.

### Comparison Analysis

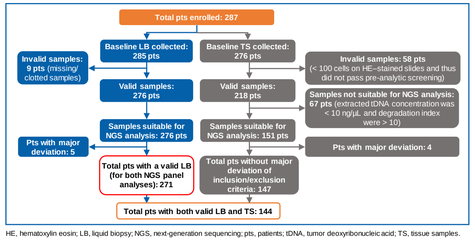
- The results of the SNV analysis, not considering variant of unknown significance, obtained for LB samples using the 533-amplicon custom AmpliSeq HD panel were compared to those obtained for TS. Moreover, the results of the SNV analysis obtained for LB samples using the 533-amplicon custom AmpliSeq HD panel were compared to those obtained for LB samples using the Oncomine Pan-Cancer Cell-Free Assay (considering overlapping amplicons only).
- The Cohen's kappa statistic (agreement/disagreement index) (based on categories from study by Altman DG: Practical statistics for medical research. 1st edition. Oxford: Chapman and Hall 1991; 1-611) was computed, together with its 95% confidence interval (CI), in order to determine a global assessment of agreement between the results.
- The McNemar's test was performed to test the hypothesis that the proportion of pts with an SNV was equivalent between the 2 NGS analyses; *P*-values were reported.
- The distributions of *PIK3CA* variant allele frequency in "concordant positive" (LB+/TS+), "concordant negative" (LB-/TS-) and "discordant" (LB+/TS-, LB-/TS+) were evaluated, and the statistical difference was estimated by Wilcoxon-Mann-Whitney test.
- A comparison between the gene-level mutation frequencies observed in the BioItaLEE cohort (baseline LB [n = 271] and TS [n = 144]) with the frequencies observed in TCGA cohort (breast invasive carcinoma [TCGA, provisional], ER+/HER2– subset [n = 590]), was performed. Of all the mutations called, only the subset overlapping with the regions covered by custom panel were included in the analyses. For both datasets, only mutations reported in the COSMIC database were included. The differences in observed frequencies were tested by Fisher's exact test, and *P*-values were corrected using the Benjamini Hochberg method.

## Results

### Patient characteristics and disposition

- From February to December 2018, 287 postmenopausal women were enrolled.
- Baseline LB and TS were collected from 285 and 276 pts, respectively. Matched LB and TS samples were available for 144 evaluable pts (**Figure 2**).

**Figure 2. Consort Diagram**




HE, hematoxylin eosin; LB, liquid biopsy; NGS, next-generation sequencing; pts, patients; tDNA, tumor deoxyribonucleic acid; TS, tissue samples.

- Baseline TS were collected from a metastatic site (33.3%) and primary tumors (66.7%). In more than half of the cases (54.2%, n = 78), TS were collected from a recent sampling (within 60 days from the start of study treatment), while 27.8% (n = 40) of the samples were taken from semi-recent (between 6 months and D61 from C1D1) and 18% (n = 26) from archival tissues (> 6 months from C1D1). Notably, 51% of enrolled pts had *de novo* metastatic disease at study inclusion.
- Patient demographics and baseline characteristics of patient population (n = 144) are listed in **Table 2**.

### Altered Genes by Patient (Biomarker Analysis Set)

- At least 1 SNV was found in 72.9% (n = 105) and 44.4% (n = 64) of TS and LB, respectively. Of note, 34.0% (n = 49) of TS and 20.7% (n = 24) of LB exhibited > 1 alteration.
- The SNVs found in > 2% of TS samples analysis vs corresponding data observed on LB are included in **Table 3**.
- The following oncoplot represents the pattern, co-occurrence, and type of genomic alterations found both in baseline TS and in LB for genes (n = 18) having alteration frequency ≥ 1% in TS or LB (**Figure 3**).

### Genomic Concordance Analysis Between Baseline Tissue and Liquid Biopsy Samples (n = 144)

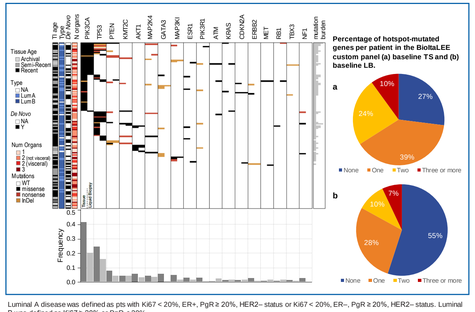
- SNV gene alterations found in baseline TS and LB were compared and their agreement was evaluated.
- The concordance for altered genes found in at least 2% of pts is detailed in **Table 3**.
- The overall concordance in terms of single gene alteration by pts between LB and TS was moderate (K = 0.51, CI: 0.44-0.58, P < 0.0001) mostly due to negative findings in LB. For *PIK3CA*, 18.8% (n = 27) of pts had concordant-positive status (LB+/TS+), 58.3% (n = 84) had concordant-negative status (LB-/TS-), and 23% (n = 33) had discordant status (21.5% [n = 31] had with LB- /TS+, and only 1.4% [n = 2] with LB+/TS-).
- The calculation of an overall concordance in terms of SNVs observed in pts' samples (K "adjusted") confirmed a moderate concordance (K "adjusted" = 0.48; CI: 0.39, 0.56).
- Assessment of agreement in patient subgroups showed that the concordance remained moderate independent of the timing of tissue sampling (archival, semi-recent, and recent) and location of the metastatic sites. In addition, agreement between TS and LB results seems to be better (K = 0.64, good) in pts with > 3 organs affected by metastases and worst in pts with Ki67 ≤ 20% (K = 0.37, fair); this suggests to explore more deeply the potential impact of tumor burden and aggressiveness on ctDNA release.

**Table 2. Demographic and Baseline Characteristics of pts With Valid Baseline LB and TS**

| Demographic Variable | | Biomarker Analysis Set (N = 144) |
|---|---|---|
| **Median age, years (range)** | | 67.0 (47-86) |
| **Age category, years, n (%)** | < 65<br>≥ 65 | 55 (38.2)<br>89 (61.8) |
| **ECOG performance status, n (%)** | 0<br>1<br>2 | 105 (72.9)<br>37 (25.7)<br>2 (1.4) |
| **Metastatic disease status, n (%)** | *De novo*<br>Recurrent | 74 (51.4)<br>70 (48.6) |
| **Estrogen/progesterone positive status, n (%)** | Both ER+ and PgR+<br>ER+ only<br>PgR+ only<br>Not assessable | 125 (86.8)<br>15 (10.4)<br>2 (1.4)<br>2 (1.4) |
| **Ki67, n (%)** | < 20%<br>≥ 20%<br>Missing | 46 (31.9)<br>91 (63.2)<br>7 (4.9) |
| **Metastatic sites, n (%)** | Bone<br>Bone only<br>Visceral<br>Liver<br>Lung<br>Liver and lung<br>Other visceral<br>CNS<br>Lymph nodes<br>Skin<br>Breast<br>Other | 103 (71.5)<br>26 (18.1)<br>60 (41.7)<br>15 (10.4)<br>45 (31.3)<br>51 (35.4)<br>12 (8.3)<br>0<br>96 (66.7)<br>4 (2.8)<br>11 (7.6)<br>12 (8.3) |
| **Number of organs of interest involved by metastases by patient, n (%)** | One organ<br>Bone<br>Liver and lung<br>Neither bone nor liver or lung<br>Two organs<br>Liver and lung included (visceral)<br>Liver and lung not included (nonvisceral)<br>Three organs<br>No organ of interest involved | 46 (31.9)<br>30 (20.8)<br>4 (2.8)<br>12 (8.3)<br>69 (47.9)<br>23 (16.0)<br>46 (31.9)<br>28 (19.4)<br>1 (0.7) |
| **Tumor type** | Luminal A<br>Luminal B<br>Unknown | 33 (22.9)<br>104 (72.2)<br>7 (4.9) |

ER /PgR and Ki67 data are not centrally assessed but are obtained from local pathology reports.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.

**Figure 3. Oncoplot: Pattern and Type of Genomic Alterations in Pts With Valid Baseline LB and TS**




Luminal A disease was defined as pts with Ki67 < 20%, ER+, PgR≥ 20%, HER2– status or Ki67 < 20%, ER–, PgR ≥ 20%, HER2– status. Luminal B was defined as Ki67≥ 20% or PgR < 20%.
LB, liquid biopsies; Lum A, luminal A; Lum B, luminal B; N, number; NA, not applicable; TS, tissue samples; WT, wild type.

**Table 3. Concordance Analysis in Single Gene Alteration by pts Between LBs and TS (n = 144)**

| Cohen's kappa Values | < 0.20 | 0.21-0.40 | 0.41-0.60 | 0.61-0.80 | 0.81-1.0 |
|---|---|---|---|---|---|
| **Quality** | Poor | Fair | Moderate | Good | Very good |

| Gene | TS, % (n) | LB, % (n) | K Cohen's (95% CI) | McNemar P-Value | LB+ /TS+ % (n) | LB+ /TS- % (n) | LB- /TS+ % (n) | LB- /TS- % (n) |
|---|---|---|---|---|---|---|---|---|
| ***PIK3CA*** | 40.3 (58) | 20.1 (29) | 0.48 (0.34, 0.62) | < 0.0001 | 18.8 (27) | 1.4 (2) | 21.5 (31) | 58.3 (84) |
| ***TP53*** | 24.3 (35) | 16.0 (23) | 0.44 (0.27-0.62) | 0.0186 | 11.1 (16) | 4.9 (7) | 13.2 (19) | 70.8 (102) |
| ***PTEN*** | 7.6 (11) | 4.2 (6) | 0.56 (0.28, 0.85) | 0.1250 | 3.5 (5) | 0.7 (1) | 4.2 (6) | 91.7 (132) |
| ***KMT2C*** | 4.2 (6) | 4.2 (6) | 0.83 (0.59, 1.00) | 1.0000 | 3.5 (5) | 0.7 (1) | 0.7 (1) | 95.1 (137) |
| ***MAP2K4*** | 4.2 (6) | 3.5 (5) | 0.72 (0.41, 1.00) | 1.0000 | 2.8 (4) | 0.7 (1) | 1.4 (2) | 95.1 (137) |
| ***ATM*** | 0.7 (1) | 2.1 (4) | 0.49 (-0.11-1.00) | 0.5000 | 0.7 (1) | 1.4 (2) | 0 | 97.9 (141) |
| ***AKT1*** | 5.6 (8) | 2.8 (4) | 0.48 (0.13, 0.83) | 0.2188 | 2.1 (3) | 0.7 (1) | 3.5 (5) | 93.8 (135) |
| ***MAP3K1*** | 4.9 (7) | 1.4 (2) | 0.43 (0.03, 0.83) | 0.0625 | 1.4 (2) | 0 | 3.5 (5) | 95.1 (137) |
| ***ESR1*** | 2.8 (4) | 1.4 (2) | -0.02 (-0.04, 0.00) | 0.6875 | 0 | 1.4 (2) | 2.8 (4) | 95.8 (138) |
| ***GATA3*** | 5.6 (8) | 0.7 (1) | 0.21 (-0.14, 0.56) | 0.0156 | 0.7 (1) | 0 | 4.9 (7) | 94.4 (136) |
| ***ERBB2*** | 2.1 (3) | 0.7 (1) | 0.49 (-0.11, 1.00) | 0.5000 | 0.7 (1) | 0 | 1.4 (2) | 97.9 (141) |
| ***PIK3R1*** | 2.8 (4) | 0.7 (1) | -0.01 (-0.03, 0.01) | 0.3750 | 0 | 0.7 (1) | 2.8 (4) | 96.5 (139) |
| **Overall** | | | **0.51 (0.44, 0.58)** | **< 0.0001** | | | | |
| **Overall "adjusted"** | | | **0.48 (0.39, 0.56)** | **< 0.0001** | | | | |

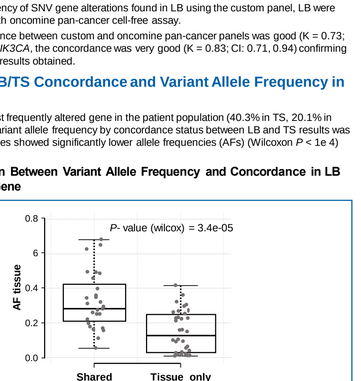
### Concordance Analysis Between Custom and Oncomine Pan-cancer NGS Panels

- To verify the consistency of SNV gene alterations found in LB using the custom panel, LB were additionally tested with oncomine pan-cancer cell-free assay.
- The overall concordance between custom and oncomine pan-cancer panels was good (K = 0.73; CI: 0.64, 0.81). For *PIK3CA*, the concordance was very good (K = 0.83; CI: 0.71, 0.94) confirming the validity of ctDNA results obtained.

### Correlation of LB/TS Concordance and Variant Allele Frequency in *PIK3CA* Gene

- For *PIK3CA*, the most frequently altered gene in the patient population (40.3% in TS, 20.1% in LB), an analysis of variant allele frequency by concordance status between LB and TS results was done. Discordant cases showed significantly lower allele frequencies (AFs) (Wilcoxon *P* < 1e 4) (**Figure 4**).

**Figure 4. Correlation Between Variant Allele Frequency and Concordance in LB vs TS for *PIK3CA* Gene**



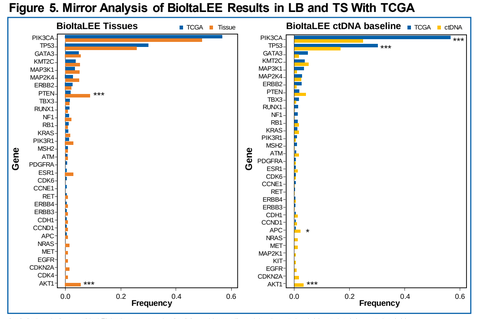

### Mirror Analysis With TCGA

- The mutation frequencies in BioItaLEE TS cohort were overall consistent with TCGA. However, a significantly increased mutation rate in *PTEN* and *AKT* as compared to TCGA was detected (*P* < 0.001), in line with genomic studies of metastatic breast cancer cohorts.[10,11] *PIK3CA* and TP53 mutation rate was lower in LB cohort than in TCGA (*P* < 0.001), mainly due to low/undetectable ctDNA content in a significant proportion of pts. Nevertheless, APC (*P* < 0.05) and AKT1 (*P* < 0.001) were mutated at higher rate than in TCGA (**Figure 5**).
- To be noted that in 144 pts with both a valid LB and TS, 22 distinct *PIK3CA* variants with different AFs were observed, suggesting both clonal and subclonal alterations.

### Altered Genes in the Patient Population Without a Valid Matched Tumor Sample

- Of the 127 pts with a valid LB but without a matched TS, 47.2% (n = 60) had at least an SNV, 15% (n = 19) had 2 alterations and 4% (n = 5) had 3 or more alterations. Significantly, 24.4% (n = 31) had a *PIK3CA* alteration.

**Figure 5. Mirror Analysis of BioItaLEE Results in LB and TS With TCGA**




Statistical analysis: two-sided Fisher's exact test, Benjamini–Hochberg adjusted *P*-value. *= *P* < 0.05; **= *P* < 0.01; ***= *P* < 0.001.

## Conclusions

- In our study, gene mutations were more frequently found in TS rather than LB, supporting the strategy of querying the tissue to complement ctDNA in case of negative results.
- The ultra-deep NGS approach used for TS in this study enabled agreement between TS and LB results. LB+ findings with TS- results were rare.
- Overall, mutation prevalence in TS (in 66.7% of the cases represented by primary tumor samples) was comparable with that found in the TCGA primary BC database. The differences in mutation prevalence of some genes may be due to the different timing of the tumor sampling in our study (80.6% of all biopsies were sampled within 6 months from study enrollment), and the presence of a high proportion of pts with *de novo* metastatic disease in our cohort (51% of all the TS are from biopsies of pts with *de novo* metastatic disease).
- Discordance in *PIK3CA* status between TS and LB is associated with lower AFs in TS, likely due to subclonal events, which may lead to undetectable mutation in ctDNA.

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