Poster 292P

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Serum thymidine kinase 1 activity in patients with hormone receptor positive (HR+)/HER2 negative (HER2-) advanced breast cancer (aBC) treated in first line with ribociclib and letrozole in the BioItaLEE trial

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CONCLUSION

- TKa appears to be a prognostic and predictive biomarker in patients with HR+/HER2– aBC treated with RIB + LET as first-line therapy
- Stratifying patients based on TKa baseline value and dynamic changes under treatment may help to predict response to treatment and outcomes
  - Lack of TKa decrease at D15 may identify patients with primary resistance to treatment and poor prognosis
  - TKa rebound at C2D1 may indicate early tumor adaptation to RIB + LET treatment, but patients still have good prognosis
  - Persistent TKa decrease may identify patients with sustained CDK4/6 inhibition and excellent prognosis
- Baseline and dynamic TKa changes provided independent information
- Further randomized studies are warranted to confirm the data and the clinical utility of this biomarker
- Analyses of disease progression/end of treatment results, as well as combined results from TKa and ctDNA analyses are ongoing

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INTRODUCTION

- Combination treatment with the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor ribociclib (RIB) and endocrine therapy (ET) significantly improves efficacy outcomes compared to ET alone in patients with HR+, HER2– aBC[1–5]
- However, validated predictive biomarkers are needed in order to identify those patients that will derive the most benefit from treatment with RIB and ET
- Thymidine kinase 1 (TK1) is a cytosolic enzyme with a role in DNA synthesis and cell proliferation[6]
  - TK1 activity is downstream of the CDK4/6 pathway, which makes it a potential marker of CDK4/6 inhibitor efficacy[6]
  - TK1 activity can be measured in serum as a readout of tumor proliferation[7]

OBJECTIVE

- To assess serum TK1 activity (TKa) as a prognostic and predictive biomarker of response to first-line treatment with RIB + letrozole (LET) in patients with HR+, HER2– aBC

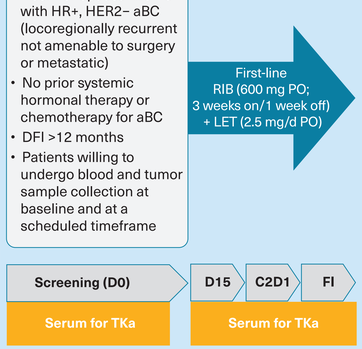
METHODS

- BioItaLEE is a phase 3b, multicenter, single arm trial (NCT03439046) studying multiple potential biomarkers of response, their evolution during treatment, and their association with clinical outcomes in postmenopausal women with endocrine-sensitive HR+, HER2– aBC receiving RIB + LET as first-line therapy in Italy

METHODS (CONT...)

- The focus of this work is one of the secondary endpoints of the trial: the measurement of TKa levels and their association with clinical outcome
  - Sera were collected at baseline (D0), day 15 of cycle 1 (D15), day 1 of cycle 2 (C2D1) and at first imaging (FI, 12 weeks) (**Figure 1**)

Figure 1. Study design with focus on serum collection for TKa



Serum samples were also collected at time of progression and/or end of treatment but were not analyzed in this work. DFI: disease-free interval; PO, orally.

- TKa was determined by a refined ELISA-based method, the DiviTum® assay (Biovica, Uppsala, Sweden), with a working range of 20–4000 DiviTum units (Du)/L and a limit of detection (LOD) of 20 Du/L
- The prognostic role of TKa level at baseline was evaluated
- The predictive role of TKa dynamics was explored by defining three patterns (P):
  - P1: TKa <LOD at D15 and C2D1
  - P2: TKa <LOD at D15 and >LOD at C2D1
  - P3: TKa >LOD at D15
- The association between TKa levels at different time points and progression-free survival (PFS) was assessed by multivariate Cox models

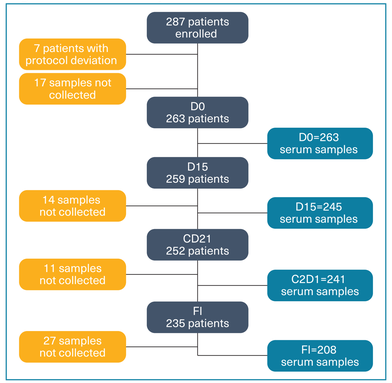
RESULTS

- Overall, 287 postmenopausal patients were enrolled across 47 Italian centers (**Table 1**)
- Serum samples were collected at each time point (**Figure 2**)
  - 93.2% of patients had matched valid serum samples collected at screening and D15; 88.2% at screening, D15 and C2D1, and 74.9% at all time points (screening, D15, C2D1 and FI)

Table 1. Patient characteristics

Characteristic	N=263
Age (years), median (range)	66.0 (47–86)
Proportion of patients aged ≥70 years, n (%)	93 (35.4)
Disease characteristics, n (%)	
Luminal A	74 (28.1)
Luminal B	173 (65.8)
Unknown	16 (6.1)
De novo metastatic	105 (39.9)
Disease Free Interval (years) in relapsed patients, median (range)	10.0 (0–27)
Patients with bone only disease, n (%)	62 (23.6)
Presence of visceral metastases, n (%)	114 (43.3)
Follow-up (months), median (range)	26.9 (22.3–32.3)
PFS (months), median (95% CI)	23.4 (20.8, not estimable)

Figure 2. Serum sample attrition chart



- Median (range) TKa in serum samples was 74.8 Du/L (19–9412) at baseline, 19.0 Du/L (19–1953) at D15 (below the LOD), 48.1 Du/L (19–3689) at C2D1 and 31.5 Du/L (19–11622) at FI (**Figure 3**)
  - At screening, 88.2% of patients had TKa levels above the LOD, while this percentage was 15.1% at D15, 71.4% at C2D1 and 59.6% at FI
- High TKa (value >median) at baseline was associated with poor prognosis (HR for disease progression 2.21; 95% CI 1.45,3.37; p=0.0002) (**Figure 4**)
- TKa levels at other time points were also of prognostic value
  - Median PFS (95% CI) was 28.1 months (22.11, not estimable) for patients with low TKa (<LOD) and 10.1 months (3.42,17.3) for patients with high TKa at D15
  - Median PFS (95% CI) was not estimable (27.9, not estimable) for patients with low TKa (<median) and 16.1 months (12.1,20.8) for patients with high TKa at C2D1
- TKa values varied along serum collection time points with complex dynamics
  - A decrease in TKa <LOD was observed in 208/245 (84.9%) patients at D15, rebounding in most cases at C2D1 with TKa >LOD in 172/241 (71.4%) patients

Figure 3. TKa levels at different sample collection time points in the study

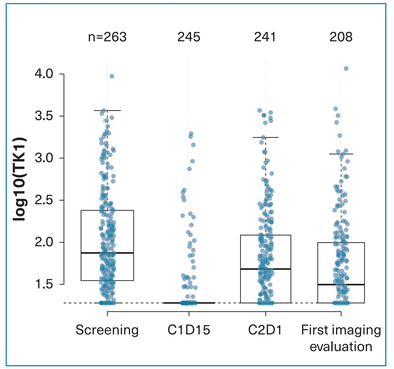
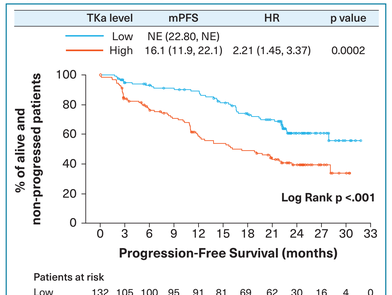


Figure 4. PFS stratified by TKa level at baseline (high [value >median] vs low)



Dots represent censored events. Patients at risk are patients who have no censored observation and have not experienced a progression or death event at the appropriate timepoint

- Three main TKa dynamic patterns were identified, which were strongly predictive of PFS (**Figure 5**)
  - TKa <LOD at D15 and >LOD at C2D1 (P2) was associated with a worse outcome compared with TKa <LOD at both time points (P1) (HR for disease progression 2.89; 95% CI 1.57,5.31; p=0.0006)
  - TKa >LOD at D15 (P3) was associated with an even shorter PFS when compared with P1 (HR for disease progression 5.65; 95% CI 2.84,11.23; p<0.0001)
- Further prognostic information was provided by combining patient stratification by TKa level at baseline (high vs low) with dynamic patterns at different time points (**Table 2** and **Figure 6**)
  - For patients in P2, high TKa (>median) at baseline correlated with a worse PFS compared with low TKa at baseline (TKa high vs low: HR for disease progression 3.47; 95% CI 1.64,7.36; p=0.0012)
  - A high TKa value at baseline also correlated with worse PFS in patients in P3 (TKa high vs low: HR 6.19; 95% CI 2.84,13.52; p<0.0001); however, this observation must be interpreted with caution as the vast majority of patients in P3 had high TKa at baseline and only 3/37 patients had low levels
  - There was no significant difference for patients in P1 in this regard (TKa high vs low: HR 1.02; 95% CI 0.31, 3.34; p=0.9755)

Figure 5. PFS stratified by TKa dynamic patterns

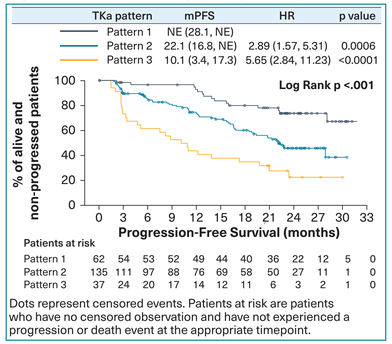


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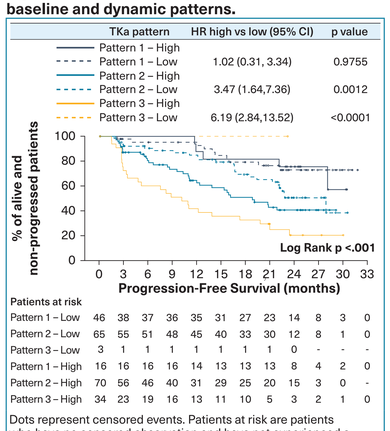
Table 2. Median PFS (95% CI) stratified by combined TKa levels at baseline and dynamic patterns

Low TKa (<median) at D0			High TKa (>median) at D0		
Pattern 1 (n=46)	Pattern 2 (n=65)	Pattern 3 (n=3)	Pattern 1 (n=16)	Pattern 2 (n=70)	Pattern 3 (n=34)
NE (NE,NE)	22.80 (19.38,NE)	NE (NE,NE)	NE (22.11,NE)	16.13 (11.96,NE)	9.46 (3.29,17.28)

NE: not estimable.

Figure 6. PFS stratified by combined TKa levels at baseline and dynamic patterns.



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Presenting Author Disclosures

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