Evaluation of proliferation biomarker serum thymidine kinase activity and prediction of early relapse in HR positive HER2 negative high risk early breast cancer: Analysis from the PENELOPE-B trial

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Background

- Nearly 30% of HR+ early breast cancer (eBC) patients (pts) will experience BC recurrence, many with incurable distant metastatic disease.
- There is currently no blood-based biomarker that can identify pts with residual disease and at high risk of recurrence before/during adjuvant therapy.
- Thymidine kinase (TK) is an enzyme that plays a key role in DNA replication during cell division[1].
- TK activity (TKa) is a validated biomarker for disease prognosis and therapy efficacy in metastatic breast cancer (mBC)[2].
- We investigated the prognostic utility of TKa in eBC using patient serum samples from the PENELOPE-B study (NCT01864746).

Patients and Methods

- PENELOPE-B (NCT01864746, GBG 78) was a phase III, multicenter, multinational, randomized, double-blind, placebo-controlled trial[3].
- 1250 HR+, HER2- eBC pts at high risk of relapse (CPS-EG score ≥3 or 2 with ypN+) after NACT received either Palbociclib (P) 125 mg or placebo (Pb) on days 1-21 every 4 weeks for 13 cycles, alongside standard ET.
- Serum samples were collected at baseline (BL), 6 months after starting therapy (C7), and end of treatment (EOT ~ 13 months after starting therapy).
- Samples were analyzed retrospectively for TKa with the FDA cleared DiviTum® TKa assay (Biovica) using DuA (DiviTum unit of Activity) as the measuring unit.
- The cutoff for defining high vs low TKa was 250 DuA. In previous mBC studies, a TKa threshold value above 250 DuA was significantly associated with likelihood of disease progression[4]. This same threshold value was applied to the PENELOPE-B sample set.
- TKa association with early invasive disease-free survival (iDFS) and distant disease-free survival (dDFS) was analyzed using restricted mean survival time (RMST) at a pre-specified timepoint of 1 year for BL TKa (as the proportional hazards assumption was violated) and Cox PH regression analysis for C7 TKa.
- The same method was also used to analyze the association of the CPS-EG score with early iDFS and dDFS using a cut-off score of ≤3 or >3.

Baseline TKa and iDFS

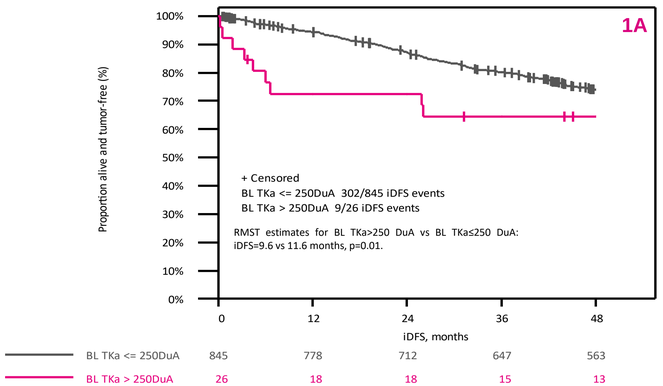

Figure 1A: BL TKa levels >250 DuA were significantly associated with invasive disease recurrence within the first 12 months of adjuvant therapy.

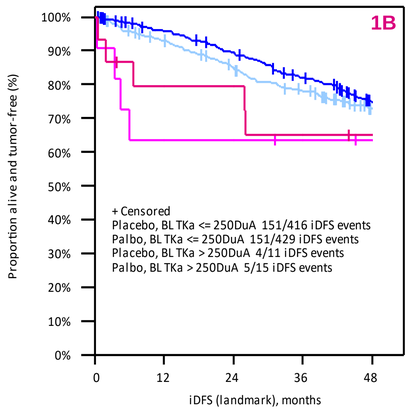

Figure 1B: No significant interaction was found between BL TKa>/≤250 DuA and treatment arm (p=0.51 for iDFS).

Cycle 7 TKa and iDFS

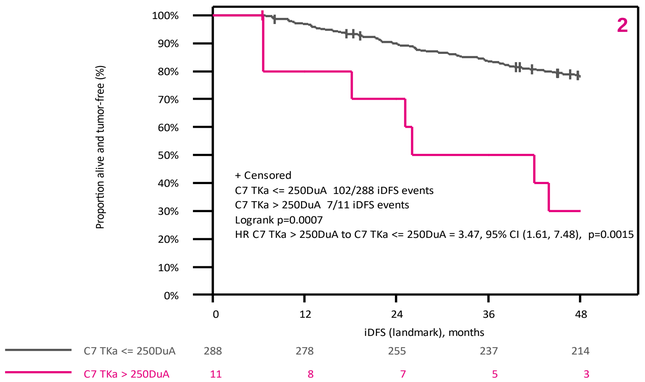

Figure 2. C7 TKa levels >250 DuA were significantly associated with both invasive and distant disease recurrence (Hazard ratio estimates for C7 TKa>250 DuA vs C7 TKa≤250 DuA)

	BL	C7	EOT
TKa RANGE	0-1025	20-4540	0-15360
TKa MEDIAN	81	70	82
TKa MEAN	102	126	177

Table 1: Range, Median, and Mean TKa values in DuA at BL, C7, and EOT

Results

- BL TKa levels were analyzed in a sample set of 871/1250 pts enrolled in PENELOPE-B (444 P+ET, 427 ET)
  - TKa dynamic changes were also analyzed in pts who had C7 (n=321) and EOT (n=367) samples.
- BL characteristics were representative and did not substantially differ between pts included and not
- Among these 871 pts, 311 pts had an iDFS event (P + ET, 156; ET alone, 155) with 45 of these pts recurring in the first year.
- BL TKa levels >250 DuA were significantly associated with both invasive and distant disease recurrence within the first 12 months of adjuvant therapy (Fig. 1A)
- No significant interaction was found between BL TKa>/≤250 DuA and treatment arm (Fig 1B)
- In early relapse pts who had a serum sample taken at the time of study discontinuation, 18/22 (82%) had an increase in TKa at the time of relapse as compared to BL.
- The CPS-EG score was not prognostic for early relapse within a year (RMST estimates for CPS-EG >3 vs CPS-EG≤3, iDFS=11.3 vs 11.6 months, p=0.12; dDFS=11.3 vs 11.7 months, p= 0.08).
- C7 TKa levels >250 DuA were significantly associated with both iDFS and dDFS (Fig. 2)
- No significant interaction with treatment was observed (iDFS: p(Cox)=0.24, dDFS: p(Cox)=0.35).
- EOT TKa levels >250 DuA did not correlate with either iDFS or dDFS.

Conclusions

- TKa was detectable in all pts w/BL analyzed, levels were significantly correlated with early disease recurrence.
- **BL TKa values >250 DuA were prognostic for early relapse within the 1st year of adjuvant therapy.**
- CPS-EG scores in contrast were not prognostic.
- Pts with early disease relapse had an increase in TKa levels at recurrence.
- **C7 TKa levels >250 DuA were significantly associated with both invasive and distant disease recurrence.**
- These findings warrant further investigation of serum TKa as a non-invasive dynamic biomarker that could be used to assess in "real-time" the presence of actively proliferating disease in adjuvant BC pts and to monitor response to treatment via serial serum TKa testing.

References

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