A liquid biomarker – Thymidine Kinase Activity – reflecting proliferation rate provides unique guidance for predicting therapy efficacy and monitoring of advanced breast cancer

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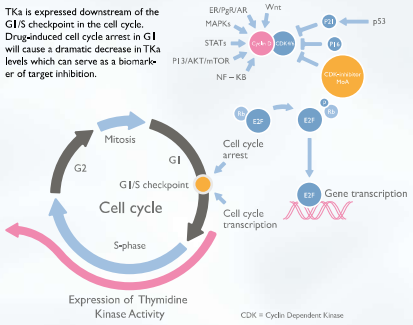
Background and Rationale

- Thymidine kinase (TK) is an enzyme that plays a key role in DNA replication and is tightly linked to cell proliferation rate. Its presence or absence can serve as a biomarker of active cell proliferation or cell cycle arrest - "a liquid Ki67".
- TK activity (TKa) can provide an early indication in real-time of the biologic activity of oncology drugs from patient blood samples.
- DiviTum® TKa is an ELISA-based assay that can accurately measure TKa levels in serum or plasma samples. The DiviTum® TKa assay is FDA cleared and CE labeled for clinical use.

Fig. 1 DiviTum® TKa - Scientific rationale for use as a predictive and efficacy biomarker of anti-proliferative oncology drugs



Objective

Evaluate the clinical utility of TKa as a biomarker for predicting and monitoring therapy efficacy in metastatic breast cancer (MBC). Measure response to Endocrine Therapy (ET) with or without CDK4/6 inhibitors.

Method

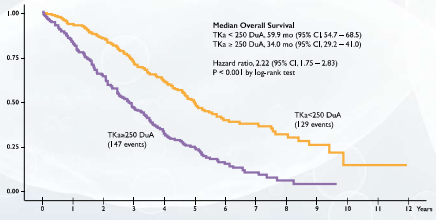
Circulating TKa was measured at different time points in serum or plasma samples from patients with MBC treated with ET +/– CDK4/6 inhibitors. TKa was measured with the DiviTum® TKa assay (Biovica, Sweden) and clinically validated in the SWOG S0226 study with samples collected at baseline and at 2, 3, 4 and 7 months on therapy.

Postmenopausal patients diagnosed with hormone receptor positive (HR+) MBC treated with ET + CDK4/6i had samples collected at different timepoints including baseline (screening), at cycle 1 day 15 and cycle 2 day 1 (day 28) establishing a TKa pattern for the first treatment cycle.

Clinical Study Results mono ET

DiviTum® TKa provides clinically meaningful information for patients with HR+ MBC. Low TKa levels provide such a high NPV (97% Negative Predictive Value) for rapid progression that such patients might forego additional therapy added to single agent ET.

Fig. 2 DiviTum® TKa – Median Overall Survival for TKa high vs low in the SWOG S0226 study



Serum baseline (BL) levels of TKa in HR+ MBC patients treated with endocrine therapy (ET) demonstrate that TKa can predict short vs. long PFS and OS. In MBC, a BL TKa value of <250 DuA is significantly correlated with longer PFS (HR=1.76, p<0.0001) and OS (HR=2.38, p<0.0001) independent of patient and disease characteristics. Low levels of TKa monitored during endocrine therapy of MBC predict a low risk of disease progression within 30 or 60 days enabling the opportunity to reduce the frequency of imaging examinations.

Clinical Study Results TKa vs ctDNA

Circulating TKa is less complex and more convenient to measure than ctDNA and early data demonstrate that TKa can further improve the predictive precision of CDK4/6 inhibitor efficacy in MBC.

TKa demonstrates greater separation between patterns than ctDNA as demonstrated in Fig. 3 and 4.

In the prospective BioltaLEE study, TKa was compared vs ctDNA in 287 postmenopausal women with HR+ MBC. Early sTKa dynamic patterns are strongly predictive of PFS. Pattern 2 with high sTKa levels at C2D1 following initial decrease at C1D15 was associated with higher risk of progression versus the pattern 1 with low sTKa levels at both time points (HR, 2.89; 95% CI, 1.57, 5.31; P = 0.0006), while the pattern 3 with high sTKa levels at C1D15 was associated with the shortest PFS (HR, 5.65; CI: 2.84, 11.2; P < 0.0001).

Baseline and dynamic sTKa changes provided independent information.

Fig. 3 Three TKa patterns predict PFS in MBC

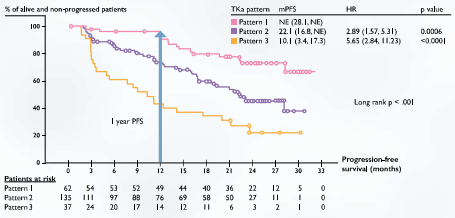
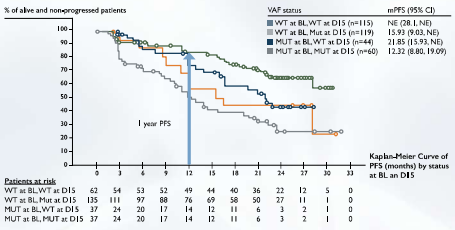
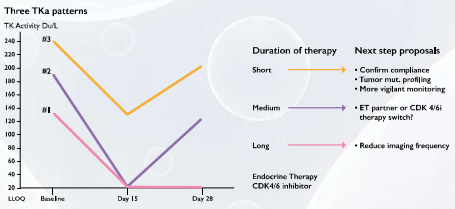


Fig. 4 Four ctDNA patterns predict PFS in MBC



Clinical Study Results CDK4/6i's

Fig. 5 TKa patterns predict duration of CDK4/6i therapy in HR+ MBC patients



Patients achieving a complete TKa suppression two weeks (C1D15) into CDK4/6i treatment, sustained at 4 weeks (C2D1) of treatment, have a long duration of therapy with very few patients progressing in the first 12 months when treated in the 1st line (Fig 5. Pattern #1). In contrast, patients whose TKa levels never fall below the LLOQ (Lower Limit of Quantification) of the DiviTum® TKa assay have a much worse outcome with a median PFS of 10.1 months with 1st line CDK4/6i therapy (Pattern #3).

Clinical Study Results TKa vs CA 15-3

- As demonstrated in the large SWOG S0226 study, baseline (BL) TKa is highly prognostic in patients with HR+ MBC initiating first-line systemic ET, (low BL TKa = superior prognosis, Fig 2.)
- TKa measured in serum at 2, 3, 4 and 7 months post initiation of ET predicts outcome at all time points.
- BL CA 15-3 is not prognostic for PFS at baseline but is prognostic after 3 cycles of treatment.

Conclusions

- TKa patterns provide clinical utility by predicting and monitoring the efficacy of ET with or without CDK4/6 inhibitors.
- TKa is a clinically useful drug efficacy and disease monitoring biomarker that can provide unique information about the proliferative status of a patient's disease.
- Low DiviTum® TKa values provide clinically meaningful information and routine monitoring of TKa patterns and levels in HR+ MBC can enhance and augment other monitoring tools and imaging frequency can be reduced.

Ongoing Studies

Studies address the use of TKa for imaging reduction, CDK4/6i dose reduction with confirmation of efficacy/sustained cell proliferation suppression and monitoring of MBC.

TK IMPACT – Prospective, real-time study at WashU, US. DiviTum® TKa is used to provide information for imaging frequency decisions. Patient blood serum samples are collected at baseline, weeks 2, 4, 6, 8, every 4 weeks up to week 24, and then every 12 weeks thereafter until disease progression. n=40.

PDM-MBC – Prospective monitoring and imaging reduction study at Christie hospital, Manchester, UK and 4 centers in Sweden. The study will also address a biomarker algorithm for improved predictive precision and monitoring of MBC. n=100.

TIRESIAS – Identification and monitoring of resistance to first-line treatment with CDK 4/6 inhibitors in combination with ET in patients with metastatic luminal breast cancer through non-invasive biomarkers. Prospective multi-center study in Italy. n=150.

YALE MBC – Prospective, real-time, clinical trial to study the correlation between DiviTum® TKa levels and medication non-compliance, potential drug-drug interaction issues, and the effects of medication dose reductions in the care of MBC patients receiving CDK4/6 inhibitor therapy. n=120.

Contact info@biovica.com for a full list of ongoing clinical studies or to discuss studies to include DiviTum® TKa measurements.

Acknowledgements

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DiviTum® TKa

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