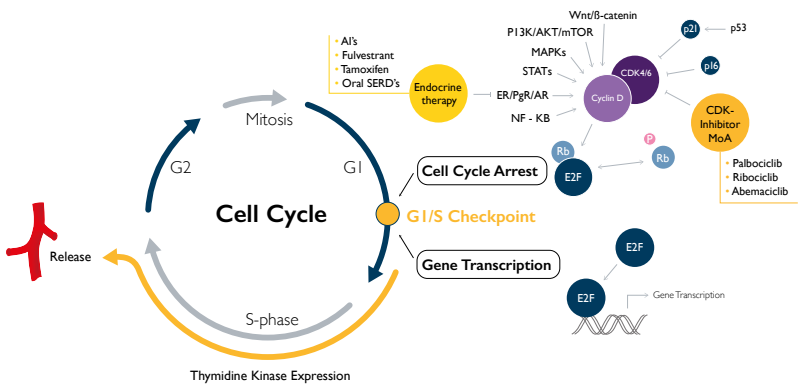
Background and Rationale

Thymidine Kinase (TK) plays a basic role in DNA synthesis and cell proliferation. The enzyme is highly cell cycle dependent and correlates with cell growth state.

TK activity (TKa) can provide an early indication in real-time of the effects on proliferation of oncology drugs by testing patient blood samples or cell lines.

TKa as a biomarker offers valuable information at all stages of drug development, from drug efficacy and dose response studies to patient selection. Incorporating TKa assessment into drug dose optimization studies can provide information about minimally effective dose selection to address the FDA's Project Optimus initiative.

FIG. 1 DiviTum® TKa – Scientific rationale for TKa as a proliferation biomarker



Objective

To review the drug development and clinical utility of TKa as a biomarker for predicting and monitoring therapy efficacy. Demonstrate TKa as a tool to measure efficacy of oncology pipeline compounds and drugs that target the cell cycle.

The DiviTum® TKa assay was used to measure circulating TKa levels both pre-treatment and at different time points on-treatment in serum or plasma samples from patients with metastatic breast cancer (MBC) treated with different therapies.

TKa as a PD biomarker addresses Project Optimus

TKa can be used as a pharmacodynamic biomarker to improve study endpoints. The launch of FDA's Project Optimus highlights the need to better identify the optimal dose for new drugs in development. TKa is a biomarker that can help address project optimus and the need by assessing the effects of drugs on cell proliferation in dose-response studies. Along with pharmacokinetic (PK) data, TKa levels can serve as a pharmacodynamic (PD) marker to help identify a minimally effective dose (MED). Fig. 2 represents a PK study to assess drug plasma concentration vs. time in relation to the MED and maximum tolerated dose (MTD). Fig. 3 represents the levels of TKa in patients treated at increasing drug doses with blood draws obtained at steady state. As the drug concentration increases, TK activity decreases. There is no additional cell proliferation suppression at dose level 4 vs dose level 3 despite the higher plasma drug concentration at dose level 4. The results suggest that dose level 3 is likely the optimal dose to test in dose expansion or phase 2 studies.

FIG. 2 Model of dose levels and drug concentration over time

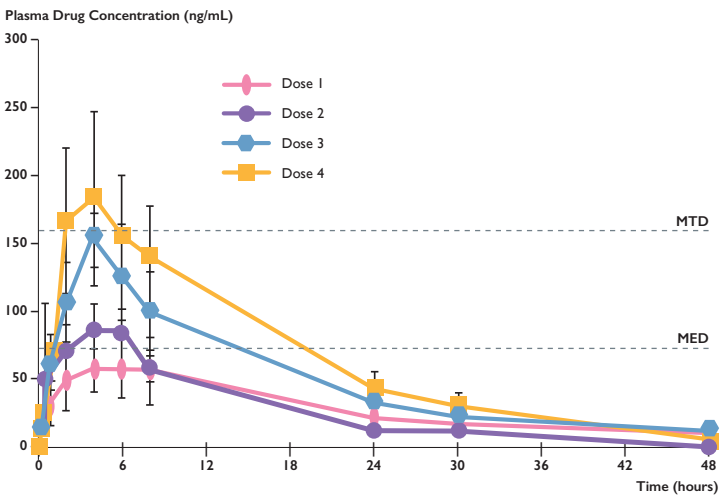
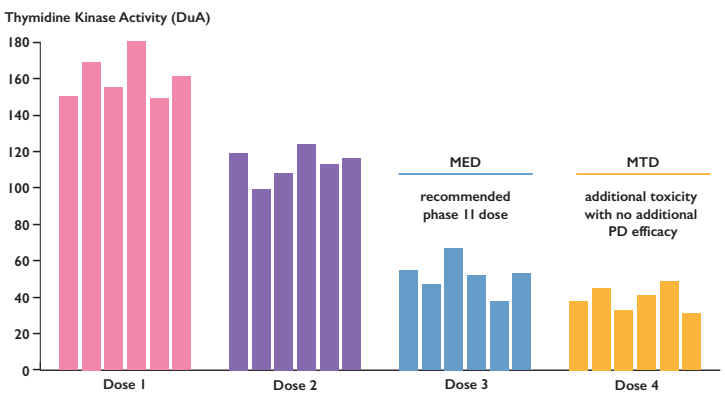


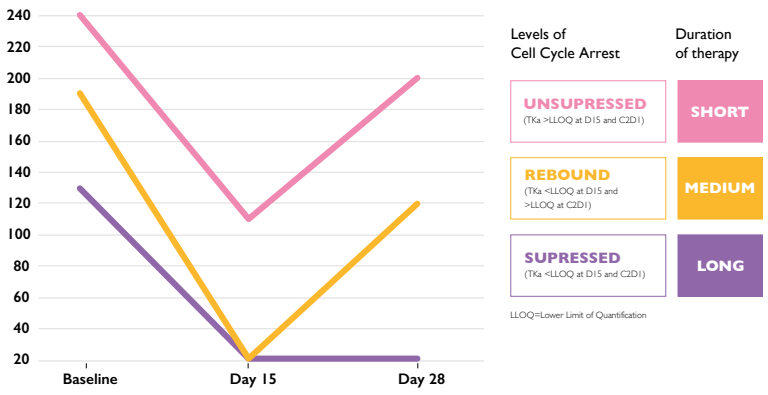
FIG. 3 Increasing drug doses associated with reductions in TKa levels



TKa as a biomarker in a clinical perspective

In clinical studies TKa has demonstrated the ability to predict drug response. HR+ MBC patient levels of serum TKa at baseline, Day 15 and Day 28 during first cycle of endocrine therapy and CDK4/6i. Levels below LLOQ of the DiviTum® TKa assay set as complete suppression of TKa/cell cycle arrest.

FIG. 4 TKa patterns predict duration of CDK4/6i therapy in HR+ MBC patients



Patients achieving a complete TKa suppression two weeks into CDK4/6i treatment, sustained at 4 weeks of treatment, have a long duration on therapy with very few patients progressing in the first 12 months (Fig 4 Suppressed). 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 less than a year (Unsuppressed).

	BioltaLEE R+L I st line	PalboAlt P+L/F I st line	PYTHIA P+F 2nd line
UNSUPPRESSED	10 month	4 month	5 month
REBOUND	22 month	21 month	13 month
SUPPRESSED	Not reached	34 month	17 month
Patients (n)	287	54	124

R = Ribociclib P = Palbociclib L = Letrozole F = Fulvestrant
Median PFS in months.

UNSUPPRESSED:
Incomplete suppression of TKa at Day 15 and Day 28

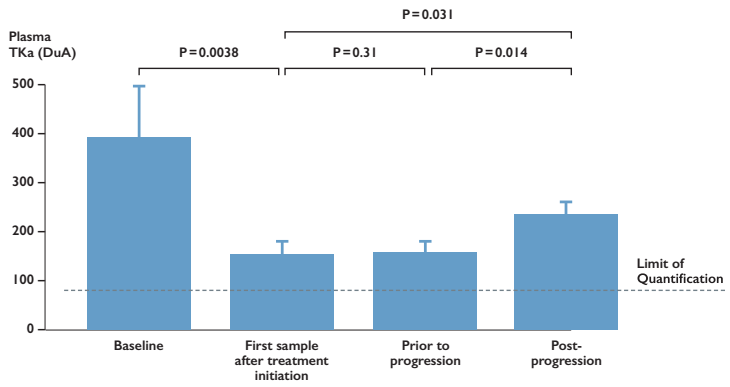
REBOUND:
Complete suppression of TKa at Day 15, rebound >assay LLOQ at Day 28

SUPPRESSED:
Complete suppression of TKa at Day 15 and Day 28

In total, 6 clinical HR+ MBC studies have presented results that support TKa as a biomarker of early prediction of patient response to CDK4/6 inhibition. TKa can be used as a readout for successful drug target engagement, for biomarker-driven patient selection and enrichment in drug development clinical trials.

After initiation of samuraciclib treatment, a CDK7 inhibitor, a significant reduction in TKa levels in blood from metastatic breast cancer patients was observed, indicating inhibition of cell cycle progression. For patients on samuraciclib therapy and with stable disease before progression, TKa levels were significantly lower than pre-treatment (p=0.0038), as shown in Fig 5. Post-progression TKa levels increased to significantly higher levels than during therapy including the last sample measured before progression (p=0.014).

FIG. 5 TKa levels over time correlating to progression



Conclusions

- TKa is a translational biomarker that bridges results between preclinical and clinical studies, providing fundamental information for drug development decision making
- TKa can identify the minimally effective dose - addressing Project Optimus guidelines
- TKa can be used to select patients most likely to respond to therapy based on their TKa profile

Acknowledgements:
We thank all patients participating in clinical trials for generating evidence for the clinical utility of DiviTum® TKa and the physicians & researchers conducting the trials and publishing the data.

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The biomarker thymidine kinase

reflecting proliferation rate and drug efficacy in solid tumors

can provide guidance in drug development and address Project Optimus

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