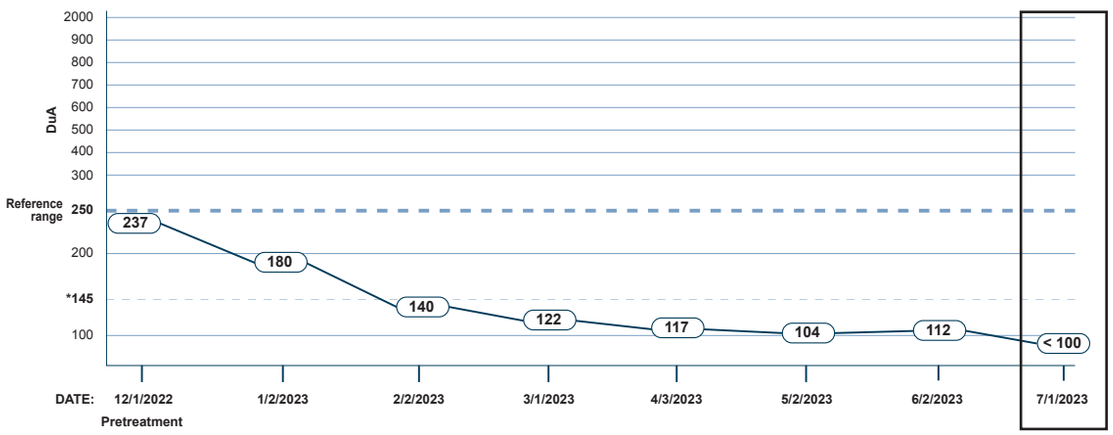
SAMPLE PATIENT PROFILES AND ASSESSMENTS

Innovative Tumor TKactivity (TKa) Profile Test for early prognosis and prediction of mBC treatment outcomes in postmenopausal HR+ mBC patients[1-5,*]

The DiviTum® TKa test has been validated for use only with serum samples from postmenopausal women previously diagnosed with HR+ metastatic breast cancer (mBC).

Example of patient on endocrine therapy (ET)



*< 145 DuA for patients treated with CDK4/6 inhibitor.

Potential interpretation:

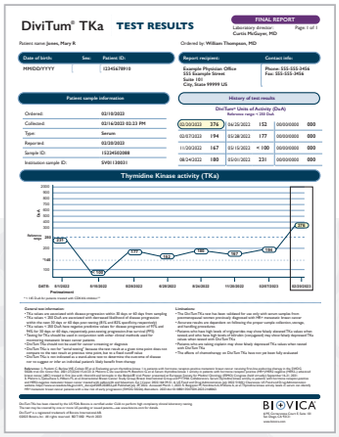
- Patient's baseline DiviTum TKa level is < 250 DuA, which is associated with better prognosis in HR+ mBC patients starting first-line ET (progression-free survival [PFS] of 17 vs 11 months and overall survival of 58 vs 30 months)[1,2,†]
- Baseline and on-therapy levels < 250 DuA are also associated with decreased likelihood of disease progression within 30 days or 60 days post testing[1]

Assessment:

- Clinicians can consider repeating DiviTum TKa test to continue monitoring treatment response

TKa = thymidine kinase activity; DuA = DiviTum Units of Activity.
*Unique predictive profiles based on *Treatment Response Patterns*.
†In a randomized phase III trial, postmenopausal HR+ mBC treated with first-line ET where patients randomized to receive either anastrozole or anastrozole + fulvestrant. There were 694 patients enrolled, and 454 patients had samples available for DiviTum TKa assessment.

DiviTum® TKa

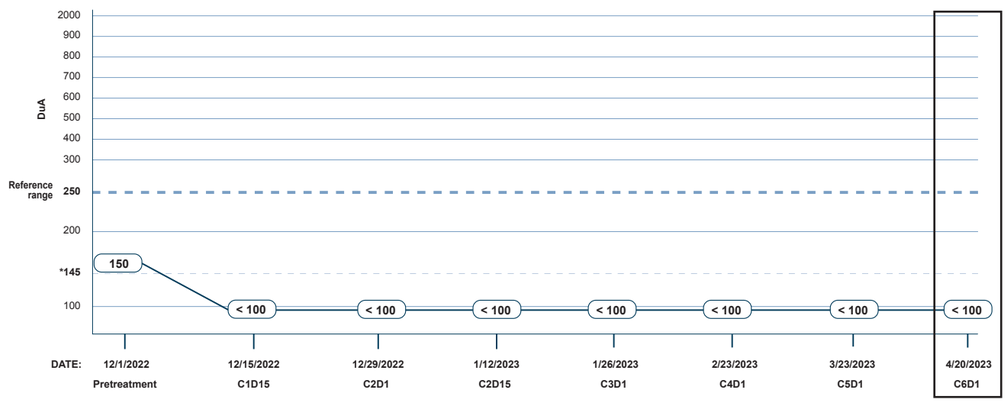

DiviTum® TKa TEST RESULTS

Example of Test Report

Examples of patients on CDK4/6 inhibitor and endocrine therapy

Profile 1

DiviTum TKa level < 145 DuA on day 15—and DiviTum TKa level remained below < 145 on cycle 2, day 1—even after stopping the CDK4/6 inhibitor for 1 week.



*< 145 DuA for patients treated with CDK4/6 inhibitor.

Potential interpretation:

- A DiviTum TKa level < 145 DuA on day 15 that is sustained on day 28—even after a CDK4/6 inhibitor treatment interruption—may indicate persistent CDK4/6 inhibition and cell cycle arrest during the scheduled 1-week break
- Consistently low TKa levels suggest stable disease
- Data suggest that patients with DiviTum TKa Profile 1 *Treatment Response Pattern* will have an extended PFS[3-5,*]

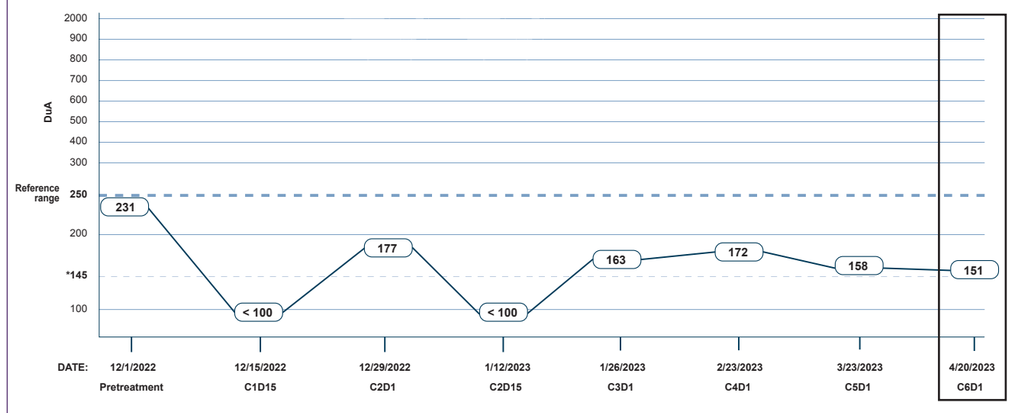
Assessment:

- Clinicians may consider reducing frequency of routine CT scans—if there are no clinical signs of disease progression—and DiviTum TKa levels remain low

*In a study of 287 HR+/HER2– mBC patients receiving first-line therapy with ribociclib + letrozole, almost no patients with this DiviTum TKa *Treatment Response Pattern* (n = 62) progressed for 1 year. Median PFS has not yet been reached in this group after 27 months of follow-up.[4,5]

Profile 2

DiviTum TKa level is < 145 DuA on day 15, but on cycle 2, day 1, the TKa level increased during the 1-week drug holiday to > 145 DuA.



*< 145 DuA for patients treated with CDK4/6 inhibitor.

Potential interpretation:

- An observed DiviTum TKa rebound > 145 DuA after a CDK4/6 inhibitor treatment interruption is compatible with a recovery in tumor cell proliferation during the scheduled 1-week break
- TKa levels consistently < 250 DuA indicate low likelihood of disease progression
- Data suggest that patients with DiviTum TKa Profile 2 *Treatment Response Pattern* will have a shorter PFS compared to Profile 1[3-5,*]

Assessment:

- Clinicians may consider an alternative dosing schedule for the current CDK4/6 inhibitor, which reduces the length of the drug holiday, or switching to a different CDK4/6 inhibitor that is dosed continuously[6]

*In a study of 287 HR+/HER2– mBC patients receiving first-line therapy with ribociclib + letrozole, median PFS with this DiviTum TKa *Treatment Response Pattern* (n = 135) was 22 months.

DiviTum TKa is an in vitro diagnostic device intended for the semiquantitative measurement of thymidine kinase activity (TKa) in human serum. The assay is to be used as an aid in monitoring disease progression in previously diagnosed hormone receptor positive (HR+), metastatic, postmenopausal female breast cancer patients. A TKa value of < 250 DiviTum Units of Activity (DuA) is associated with the decreased likelihood of disease progression within 30 days or 60 days post testing for patients on endocrine therapy. DiviTum TKa results should be used in conjunction with other clinical methods for monitoring breast cancer.

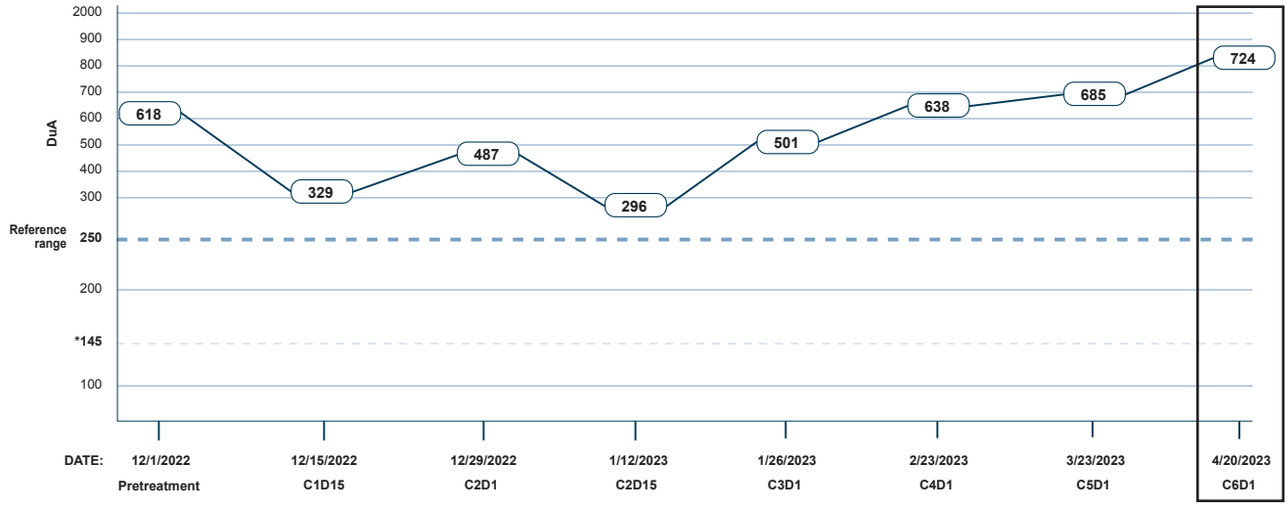
The DiviTum TKa test has been validated for use only with serum samples from postmenopausal women previously diagnosed with HR+ metastatic breast cancer. Accurate results are dependent on following the proper sample collection, storage, and handling procedures (see Instructions for Use, MA0016_F). Assay variability may be up to 12%.[7] The effects of chemotherapy on DiviTum TKa have not yet been fully evaluated.

DiviTum® TKa

Example of patient on CDK4/6 inhibitor and endocrine therapy

Profile 3

DiviTum TKa level never dropped < 145 DuA at any time point, indicating that tumors are still proliferating and treatment is not working optimally.



*< 145 DuA for patients treated with CDK4/6 inhibitor.

Potential interpretation:

- Data suggest that a patient with DiviTum TKa Profile 3 *Treatment Response Pattern* will have shorter duration on treatment and reduced PFS[3-5,*]
- Steadily increasing TKa levels suggest likelihood of disease progression

Assessment:

- Clinicians may consider:
  - Confirming medication compliance/patient is not currently taking a concomitant medication that could potentially interfere with CDK4/6 inhibitor efficacy
  - Confirming absence of tumor mutations that could potentially cause resistance to CDK4/6 inhibitors
  - Closer monitoring, as disease is more likely to progress in < 1 year[3-5,*]

*In a study of 287 HR+/HER2– mBC patients receiving first-line therapy with ribociclib + letrozole, median PFS with this DiviTum TKa *Treatment Response Pattern* (n = 37) was 10 months.

Vigilant monitoring. DiviTum TKa.

References: 1. Bergqvist M, Nordmark A, Williams A, et al. Thymidine kinase activity levels in serum can identify HR+ metastatic breast cancer patients with a low risk of early progression (SWOG S0226). *Biomarkers.* 2023. doi:10.1080/1354750X.2023.2168063. **2.** Paoletti C, Barlow WE, Cobain EF, et al. Evaluating serum thymidine kinase 1 in patients with hormone receptor-positive metastatic breast cancer receiving first-line endocrine therapy in the SWOG S0226 trial. *Clin Cancer Res.* 2021;27(22):6115-6123. **3.** Malorni L, Tyekucheva S, Hilbers FS, et al; International Breast Cancer Study Group; Breast International Group and PYTHIA Collaborators. Serum thymidine kinase activity in patients with hormone receptor-positive and HER2-negative metastatic breast cancer treated with palbociclib and fulvestrant. *Eur J Cancer.* 2022;164:39-51. **4.** Malorni L, De Laurentiis M, Bianchini G, et al. 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. Poster presented at: European Society for Medical Oncology (ESMO) Congress (held virtually); September 16-21, 2021. **5.** Malorni L, De Laurentiis M, Bianchini G, et al. 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. Supplemental poster presented at: European Society for Medical Oncology (ESMO) Congress (held virtually); September 16-21, 2021. **6.** Krishnamurthy J, Luo J, Suresh R, et al. A phase II trial of an alternative schedule of palbociclib and embedded serum TK1 analysis. *NPJ Breast Cancer.* 2022;8(1):35. **7.** US Food and Drug Administration. July 2022 510(K) Clearances. US Food and Drug Administration website. https://www.accessdata.fda.gov/cdrh_docs/pdf20/K202852.pdf. Published July 29, 2022. Accessed March 1, 2023.

DiviTum® TKa

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