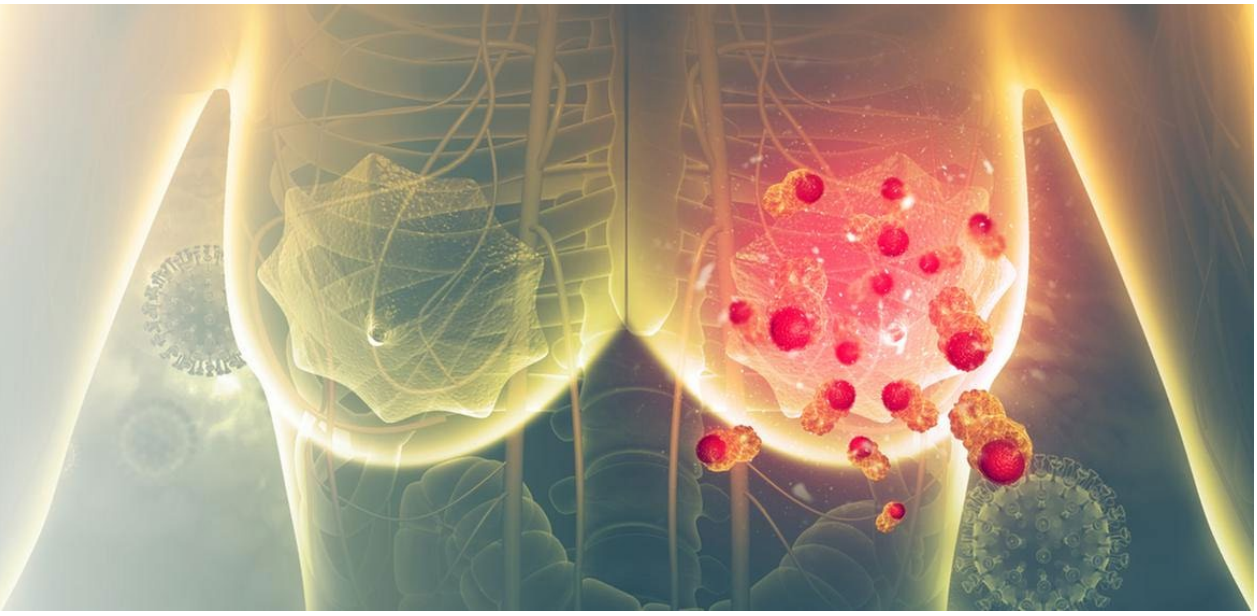
MOLECULAR HEALTH

Advanced & metastatic breast carcinoma

What to do in case of endocrine resistance?

Endocrine resistance is common in advanced breast cancer: Tumor genetic analyses using liquid biopsy could reveal therapeutic options here. Prof. Nicholas Turner, The Institute of Cancer Research, UK, presented helpful studies at the EBCC[a].[1]



In hormone receptor-positive (HR+) advanced breast cancer, endocrine-based therapy with aromatase inhibitor and CDK4/6[b] inhibitor is the standard of care supported by the guidelines. [2,3] However, most patients develop resistance to endocrine therapies after an initial response; 15-20% even have primary resistance. The consequence: few treatment options with unfavorable prognosis.[4]

Analysis of circulating tumor DNA (ctDNA) from plasma (liquid biopsy) provides comprehensive insights into primary and acquired resistance to endocrine therapies.[1,4]

Detect therapy-relevant biomarkers and resistances with ctDNA

According to Prof. Turner, the following mutations, for example, which can be detected by ctDNA analysis, are associated with a therapeutic consequence:[1]

ESR1 mutations as resistance markers for aromatase inhibitors.

Mutations of the estrogen receptor alpha (ESR1[c]) gene result in ligand-independent signaling activation of the estrogen receptor (ER).[5,6] Retrospective ctDNA analyses of prospective studies such as SoFEA, EFECT, or BOLERO-2 demonstrated:[7-9]

- ESR1 mutations occur frequently with aromatase inhibitor therapy in the metastatic setting (30% of patients).[7]
- In the presence of an ESR1 mutation, continued aromatase inhibitor therapy is associated with a worse prognosis.[7-9]
- HR+ advanced breast cancer with an ESR1 mutation respond better to anti-estrogen therapy with fulvestrant or to a combination of fulvestrant and the mTOR[d] inhibitor everolimus in follow-up therapy.[7-9]
- Therefore, aromatase inhibitor therapy is inappropriate for patients with proven ESR1 mutation, according to Prof. Turner. Endocrine therapy with fulvestrant should be given instead.[1]

PIK3CA mutations as a therapy-relevant biomarker for PIK3CA inhibitors.[1,10]

PIK3CA[e]-Mutations can be addressed in the EU with the approved PIK3CA inhibitor alpelisib as of this year.[10,11] Overall, PIK3CA mutations are present in approximately 40% of patients with HR+, HER2[f] breast cancer. In the pivotal SOLAR-1 study, alpelisib in combination with fulvestrant achieved a significant effect on progression-free survival (PFS) compared to placebo and fulvestrant in patients with PIK3CA-mutated, HR+, HER2- advanced breast cancer who received prior endocrine therapy.[10]

Alterations in RB1 or FGFR as resistance markers in CDK4/6 inhibitors

Under CDK4/6 inhibitor therapy, clonal selection and the development of resistance mechanisms, such as inactivating RB1[g] or activating FGFR[h] mutations, could be detected by ctDNA analysis[12] If RB1 mutations were present prior to initiation of therapy with a CDK4/6 inhibitor, such patients will not benefit from CDK4/6 inhibitor therapy.[13] This would allow the identification of patients with primary resistance to CDK4/6 inhibitors. However, in his presentation, Prof. Turner highlighted that these mutations are rare and testing has not been widely established.[1]

In the clinic: Selection of targeted therapies using ctDNA

The plasmaMATCH study documents the potential benefit of therapy monitoring for routine clinical practice using ctDNA analysis for the first time. During the course of therapy, the occurrence of defined addressable mutations was detected, appropriate targeted therapy options were selected, and the benefit of treatment was recorded: In addition to ESR1 mutations, mutations in the HER2 or AKT1[i] genes were analyzed.[14] These have been described in advanced breast cancer, but occur less frequently than the ESR1 mutation.[13,15-17] The study divided patients with previously treated advanced breast cancer into 1 of 4 treatment cohorts based on mutation profile:[14]

- **Cohort A:** increased dose of fulvestrant in ESR1 mutations
- **Cohort B:** Neratinib (pan-HER tyrosine kinase inhibitor) for HER2 mutations; for ER+ breast carcinoma plus standard dose fulvestrant.
- **Cohort C** (only ER+): Capivasertib (selective AKT inhibitor) for AKT1 mutations plus standard dose of fulvestrant
- **Cohort D:** Capivasertib for AKT1 mutations (only ER) or PTEN mutations

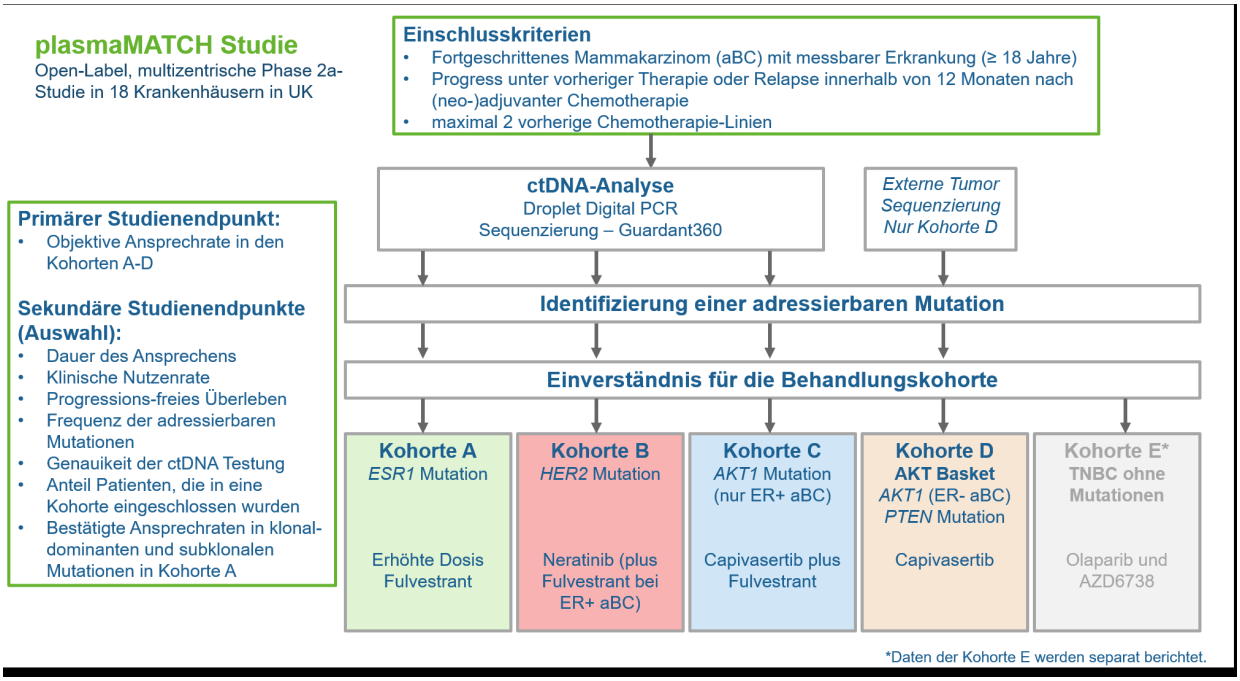
The primary study endpoint was the confirmed objective response rate in the 4 treatment cohorts. In Cohorts B and C, the primary study endpoint achieved response rates of 25% and 22%, respectively.[14] Liquid Biopsy can, therefore, **easily and quickly find rare, therapy-relevant mutations** such as HER2 and AKT1 mutations, Prof. Turner said. This knowledge makes it possible to initiate appropriate and potentially effective therapy in patients with breast cancer.[1,14]

Design of the plasmaMATCH study

The phase 2a plasmaMATCH study included 1,051 patients with previously treated advanced breast cancer (Fig. 1):[14]

- Results of ctDNA analysis were available in 1,034 patients.
- One or more addressable mutations were found in 357 patients.
- A total of 135 patients were assigned to one of the cohorts by ctDNA testing; of these, 84, 21, 18, and 19 patients were assigned to cohorts A, B, C, or D, respectively.
- For example, the patients who were not included were not eligible, decided not to be included themselves (or by decision of the treating physician), or the deadline for inclusion in the cohort had passed.

Fig. 1: Study design of the plasmaMATCH study. Modified according to Turner et al., 2020.[1,14]



Read in the **publication** by Turner et al. (2020) the results of the plasmaMATCH study.

> The Kommission Mamma [Breast Cancer Commission] of the AGO (Arbeitsgemeinschaft Gynäkologische Onkologie [Gynecological Oncology Working Group]) recommends mutation testing of genes such as PIK3CA, ESR1 and HER2 in metastases and plasma in metastatic breast carcinoma.[2]

Possible strategy for avoiding resistance: triple combination therapy

According to Prof. Turner, triple combination therapies of PIK3CA inhibitor, endocrine therapy with fulvestrant, and CDK4/6 inhibitors could prevent the development of resistance in endocrine-pretreated breast cancer.[1] This is indicated by previous experiments in cell lines and mouse models.[18] The recently published results of a phase Ib trial also underscore the importance of this therapeutic approach: the triple combination therapy of palbociclib, taselisib, and fulvestrant was responded to by 37.5% of patients with pretreated PIK3CA-mutated, ER+ advanced breast cancer.[19]

Deciding therapy intensification using PIK3CA inhibitor based on ctDNA level?

Suitable patients for triple combination therapy could be selected by determining ctDNA levels after treatment initiation.[1] For example, retrospective analysis of the PALOMA-3 trial showed that patients had a poor prognosis when ctDNA levels (mainly PIK3CA) were not reduced with CDK4/6 inhibitor and endocrine-based therapy.[20] In this case, intensification of therapy with PIK3CA inhibitor might be useful. A corresponding study is being planned.[1]

Early molecular detection of minimal residual disease with ctDNA

Furthermore, studies show that across all subtypes of breast cancer, high ctDNA levels were associated with a high risk of recurrence.[21, 22] Some resistance mutations can be detected approximately 6 months prior to clinical progression. Other mutations, such as RB1 mutations, which may occur with CDK4/6 inhibitor therapy, were not detectable in ctDNA until shortly before relapse. With the help of a ctDNA analysis, a therapeutic intervention could be initiated at an early stage if a "molecular relapse" is detected. Clinical studies are also desired for this, according to Prof. Turner.[1]

Abbreviations

a EBCC: 12th European Breast Cancer Conference
b DK4/6: Cycline-dependent kinases 4/6
c ESR1: Estrogen receptor alpha
d mTOR: mechanistic target of rapamycin
e PIK3CA: Phosphatidylinositol 4,5-bisphosphate 3-kinase
f HER2: human epidermal growth factor receptor 2
g RB1: Retinoblastoma protein
h FGFR: fibroblast growth factor receptors
i AKT1: AKT Serine/Threonine Kinase 1
j PTEN: Phosphatase And Tensin Homolog

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