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A Phase II Study of Trastuzumab Plus Capecitabine with or Without Pertuzumab for HER2-positive Metastatic Breast Cancer as Second-line Treatment (PHEREXA)

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Background: Pertuzumab is a novel anti-HER2 antibody and is known to be active and well tolerated when combined with trastuzumab in patients with HER2-positive breast cancer. Capecitabine in combination with trastuzumab is more efficacious than capecitabine alone as second-line treatment of patients with HER2-positive metastatic breast cancer (MBC). The PHEREXA study is investigating the potential benefit of combining pertuzumab and trastuzumab plus capecitabine in patients with HER2-positive MBC whose disease has progressed during or following trastuzumab-based therapy in the first-line metastatic setting.

Materials and Methods: In this multicentre, open-label, Phase II trial, patients are randomised 1:1 to Arm A (trastuzumab: 8 mg/kg loading dose followed by a 6 mg/kg maintenance dose q3w; capecitabine: 1250 mg/m^2 twice daily for 14d q3w) or Arm B (trastuzumab: 8 mg/kg loading dose followed by a 6 mg/kg maintenance dose q3w; capecitabine: 1000 mg/m^2 twice daily for 14d and pertuzumab: 840 mg loading dose and 420 mg thereafter q3w). Enrolment began in January 2010 and 450 patients are to be recruited from approximately 150 sites in 19 countries. Eligible patients must have HER2-positive MBC (fluorescence or chromogenic *in situ* hybridisation-positive and/or immunohistochemistry 3+), which has progressed during or following trastuzumab-based therapy in the first-line metastatic setting, received prior taxane and a left ventricular ejection fraction (LVEF) of $\geqslant$50% at baseline. Exclusion criteria include prior treatment with capecitabine or pertuzumab, concurrent hormonal anticancer therapy and history of LVEF decline to <50% during or following prior trastuzumab therapy. The primary endpoint is independently assessed progression-free survival (PFS). Secondary endpoints include overall survival, PFS by investigator assessment, safety/tolerability and exploratory biomarkers. The study is being monitored by an independent safety monitoring committee; no untoward safety signals have been identified to date.

This study is registered at clinicaltrials.gov, NCT01026142.

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Modulating Effect of Microenvironment On Hormone Therapy of Breast Cancer

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Background: The most effective drugs for breast cancer are antiestrogen supplements such as tamoxifen (TAM). Loss of cell sensitivity to TAM may be associated with decrease of number of steroid receptors in breast tumors. Indeed, estradiol, pro-inflamatory cytokines and IFN-γ may modulate ER expression, but they are activated in different stages of malignization process, that's why their influence on receptor status will also have differences. Thus it will be important to investigate the impact of factors of cell microenvironment on ER expression, proliferation, apoptosis and cell cycle in MCF-7 cells on models of different breast cancer stages.

Materials and Methods: MCF-7 cells were cultured under standard conditions. For cocultivation was used a cell line MT-4 (human cell chronic lymphocytic leukemia) were used. Recombinant IFN-γ was added in concentration of 10 U / ml, TAM − 100 nM, E2 –10 nM, condition medium (C-medium) from T-lymphocytes − 1:1 with culture medium. Cell survival was determined by MTT test. The distribution of the cell population between the cell cycle stages was measured using flow cytometry. Expression of ER and EGF-R was visualised by immunocytochemistry (DAKO, USA).

Results: The results obtained have indicated that recombinant IFN-γ has got a cytostatic effect in comparison with a cytotoxic effect of TAM and a proliferative effect of estradiol. It was in suspension fraction that the increase of cell number for C-medium with E2, IFN-γ with E2, TAM with E2 and IFN-γ with TAM was shown. Decrease of the cell number in suspension fraction was demonstrated for IFN-γ, TAM, C-medium with TAM, while in adhesion fraction TAM, TAM with E2 and TAM with C-medium decreased the number of alive cells. IFN-γ, C-medium, IFN-γ with TAM, and TAM with C-medium have decreased cell number in S phase. IFN-γ and TAM increased cell number in G2/M phase, C-medium from T-lymphocytes and IFN-γ with TAM increased cell number in G0/G1 phase. In adhesion fraction apoptosis was stimulated by IFN-γ with E2, TAM, C-medium and E2 combined. IFN-γ and C-medium from T-lymphocytes stimulated ER expression in MCF-7 cells.

Conclusion: Perhaps TAM has become a first agent for target therapy. Thus, our data demonstrated that cell microenvironmental conditions (hormonal and humoral) have a strong influence on ER expression in breast cancer cell and as a result can modulate sensitiveness to antiestrogen therapy. Combination of antiestrogen therapy with balanced approach IFN-γ, activated T-cells and level of E2/Pr may being to commulative effect in antitumor treatment.