Luminal, i.e., estrogen receptor-positive (ER+) breast cancer (BC) is an heterogeneous disease in terms of tumor progression, therapy response, and relapse. Additional biomarkers with a prognostic and predictive impact could facilitate advanced patient stratification and may reveal new therapeutic options for individual patients suffering from BC.

Patients and Methods

Generation of NSG based MXD4−/− hematopoietic stem cells (HSC) were isolated from the umbilical cord blood and transplanted into neonatal NOD.Cg-Prkdcscid Il2rgtm1Wjl/Tg (NSG) mice 3 hours post 1 Gy irradiation as previously described. BC samples were transplanted in 7-8 weeks old humanized female NSG mice together with a 0.18 mg 17β-estradiol pellet (Innovative Research of America). In addition, 3 previously established, patient-derived xenograft (PDX) models (PT-F2, PT-F3, and PT-S4) provided by Elisabeth Marangoni (Institute Curie, Paris, France), and 2 PDX models (PT-C1C and PT-E2) provided by Andreas Trumpf (H-Stein, Heidelberg, Germany) were also used. Differences between tumor weight of wild type (mmd2+) and amplified (mmd2+++) hPDX models were assessed by Student's t-test. For the functional assays in vitro, ZR-75-1 BC cells were treated with the mmd2 inhibitor AMG232. Cell proliferation and apoptosis were analyzed by flow cytometry, a scratch assay was performed to analyze migration cell capacity over time, and Dunnnett's multiple comparisons test was applied.

GeparTrios patient cohort for mmd2+ assessment: For this study we selected tissue specimens previously diagnosed as Luminal BC from the GeparTrios (NCT00544765) trial. All patients within the trial received an anthracycline/taxane based neoadjuvant chemotherapy. Dual color FISH was applied on pathologic xenograft specimens to monitor mmd2+ and the cere12 region (mmd2+ score 1 corresponding to normal and score 2-3 corresponding to gain expression). Association with DFS and OS were analyzed by Cox regression models with 95% confidence interval (CI) and presented as Kaplan-Meier curves.

Primary objective: Identification and validation of biomarkers associated with successful engraftment, augmented tumor growth, and enhanced metastatic potential of xenotransplantation into humanized mice.

Secondary objective: Retrospective validation and correlation of aforementioned markers with clinical outcomes of Luminal BC patients within the GeparTrios trial.

The tumor weight in all four hPDX-mmd2+++ was significantly increased compared to hPDX-mmd2++ (Fig. 2A & B; p < 0.0003). In addition, the hPDX-mmd2+++ showed a significantly enhanced potential to develop lung metastasis compared to hPDX-mmd2++ (11/14 vs 1/10, respectively, p = 0.0011; data not shown).

An mmd2 gene amplification propels growth and progression of ER+ BC in a preclinical humanized xenograft NSG mouse model.

mmd2 inhibition of ER+ BC cells in vitro reduces cell proliferation and migration and induces cell apoptosis.

An unfavorable impact of mmd2 gain on survival outcome of Luminal BC patients is mainly caused within the Luminal-A BC subcohort.

Prospective studies are required to verify the suitability of mmd2 for advanced Luminal BC stratification and therapeutic targeting of ER+ BC.

References


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