Role of RIZ1 delP 704 polymorphism in metastatic breast cancer patients treated with exemestane

S. Gagno[1], M.R. D'Andrea[2], C. Zanusso[1], E. Dreussi[1], L. Giodini[1], R. Roncato[1], M. Montico[1], E. Cecchin[1], M. Mansutti[3], S. Saracchini[4], D. Sartori[5], M. Medici[6], A. Rocca[7], G. Benedetti[8], P. Sandri[9], A. Pellegrino[10], A. Fabbri[11], L. Gianni[12], F. Riccardi[13], I. Spagnoletti[14], R. Meo[15], V. Amoroso[16], E. Cretella[17], A.M. Baldelli[18], G. Toffoli[1]

[1]Experimental and Clinical Pharmacology Unit, CRO-National Cancer Institute, Aviano, Italy
[2]A.C.O. San Filippo Neri, Dept. of Clinical Oncology, Rome, Italy
[3]Santa Maria della Misericordia Hospital, Dept. of Oncology, Udine, Italy
[4]A.O. Santa Maria Degli Angeli, Dept. of Oncology, Pordenone, Italy
[5]Azienda ULSS n.13, Dept. of Oncology, Mirano-Dolo-Noale, Italy
[6]Azienda ULSS n.12, Dept. of Oncology, Venice, Italy
[7]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Dept. of Oncology, Meldola, Italy
[8]Azienda ASUR - zona territoriale 9, Dept. of Oncology, Macerata, Italy
[9]S.Maria dei Battuti Hospital, Dept. of Oncology, San Vito al Tagliamento, Italy
[10]S. Pietro Fatebenefratelli Hospital, Dept. of Oncology, Rome, Italy
[11]ASL Viterbo – Belcolle Hospital, Dept. of Oncology, Viterbo, Italy
[12]Infermi Hospital, Dept. of Oncology, Rimini, Italy
[13]Cardarelli Hospital, Dept. of Oncology, Naples, Italy
[14]Sacro Cuore di Gesù FateBeneFratelli, Dept. of Oncology, Benevento, Italy
[15]Presidio Maria delle Grazie, Dept. of Oncology, Cerreto Sannita, Italy
[16]Spedali Civili Brescia, Dept. of Oncology, Brescia, Italy
[17]Azienda sanitaria Ospedale centrale di Bolzano, Dept. of Oncology, Bolzano, Italy
[18]A.O. San Salvatore, Dept. of Oncology, Pesaro, Italy

Background: Estrogens sustain growth of estrogen receptor positive (ER+) breast cancer (BC) cells. ER activity is enhanced by several co-activators, including RIZ1, encoded by the tumor suppressor *PRMD2* gene. RIZ1 is a zinc finger protein representing a specific ERα co-activator. ERα function is strongly enhanced by RIZ1, which promotes optimal estrogen response in several tissues. Due to its critical role, polymorphisms on this gene, as well as on *ESR1* gene, coding for ERα, could affect estrogen activity. Estrogens are synthesized by aromatase, which is the target of several inhibitor drugs, including exemestane. Unfortunately, in a subset of ER+ MBC patients, exemestane is not effective and, in some cases, even toxic. Several germ-line single nucleotide polymorphisms (SNPs) have been described in *PRMD2* and *ESR1* genes. SNPs in this estrogens pathway, by affecting estrogens activity, could be responsible for the different treatment outcomes.

Aims: Our study aimed at investigating the predictive value of SNPs on *PMRD2* and *ESR1* genes in terms of Response Rate (RR) in ER+ MBC patients treated with exemestane as first-line hormone therapy.

Methods: This multicenter study enrolled 302 patients with ER+ MBC or locally-advanced BC with complete clinical data. For RR assessment, patients having a Complete Response (CR) or a Partial Response (PR) were compared with patients showing a Stable Disease (SD) or Progression Disease (PD) according to RECIST criteria. Multivariate statistical analyses for the associations between SNPs and clinical outcome were performed by logistic regression model. 95%CI and p-values underwent an internal validation by re-sampling trough the application of bootstrap analysis with 1000 replications.

Results: In this study we found an association between RR and the insertion/deletion (indel) polymorphism RIZ1_delP704 (rs2308040), which causes the insertion of a Proline residue at position 704 of the protein. Indeed, according to the recessive model, patients bearing the homozygous insertion (Pro/Pro) genotype had a higher probability of being responsive to exemestane therapy (OR_{DOM}=2.23, 95%CI 1.25-4.00, p=0.007) than Del/Del or Del/Pro patients.

Conclusions: This study pointed out the predictive role of RIZ1_delP704 (rs2308040) Pro/Pro genotype in the RR of MBC patients treated with the aromatase inhibitor exemestane. Once validated, this pharmacogenetic marker might be useful for treatment personalization.