Prognostic impact of type and location of germline *BRCA2* pathogenic or likely pathogenic variants (LP/PVs) in patients with HR+/HER2- advanced breast cancer: results from the multicenter real-world PAMBRACA study

PS1-11-28

Emma Zattarin[1,2], Elena Tenedini[2], Antonio Marra[3], Antonella Palazzo[4], Gaia Griguolo[5,6], Claudio Vernieri[7,8], Julian Etessami[3], Letizia Pontolillo[4,9], Giusy Landa[5,6], Arianna Daneri[10], Matteo De Monte[7,8], Riccardo Cuoghi Costantini[2], Ornella Ponzoni[1], Maria Grazia Razeti[10], Caterina Sposetti[7,11], Elena Barbieri[1], Martina Manni[1], Federica Caggia[1], Laura Cortesi[2,12], Giuseppe Curigliano[3,8], Emilio Bria[13,14], Valentina Guarneri[5,6], Massimo Dominici[1,2], Matteo Lambertini[10,15], Angela Toss[1,2]

1 Department of Medical Oncology, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy. 2 Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy. 3 Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, Milan, Italy. 4 Department of Medical Oncology, Comprehensive Cancer Center, Agostino Gemelli University Polyclinic (IRCCS), Rome, Italy. 5 Division of Oncology 2, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy. 6 Department of Surgery, Oncology and Gastroenterology, University of Padova, via Giustiniani 2, Padua 35128, Italy. 7 Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. 8 Department of Oncology and Hematology-Oncology, University of Milan, Via Festa del Perdono 7, 20122, Milan, Italy. 9 Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA. 10 Department of Medical Oncology, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy. 11 Dana Farber Cancer Institute and Harvard Medical School, Boston, USA. 12 Department of Medical Oncology, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy. 13 Università Cattolica del Sacro Cuore, Rome, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. 14 Ospedale Isola Tiberina – Gemelli Isola, Rome, Italy. 15 Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genoa, 16132 Genoa, Italy.

Background

The type and location of germline LP/PVs in the *BRCA1* and *BRCA2* genes influence the risk of developing breast cancer (BC) and its prognosis in the early setting (Toss et al. ASCO 2025). However, the clinical impact of different variants in patients (pts) with advanced BC (aBC) is unknown.

Methods

The PAMBRACA study is a multicenter retrospective study including *BRCA1* and *BRCA2* LP/PV carriers with HR+/HER2- aBC treated with endocrine therapy (ET) plus CDK4/6i. Some pts also received PARPi after progression on CDK4/6i plus ET. For this specific analysis, *BRCA1* carriers were excluded due to the limited sample size. We collected information on *BRCA2* variant type [insertion-deletion mutation (INDEL), single nucleotide variant (SNV), or copy number variation (CNV)], coding consequences, truncating vs non-truncating status, and exon location. The association between *BRCA2* LP/PV type/location and pt overall survival (OS) was explored.



Figure 1. Schematic representation of the *BRCA2* gene.

Funding: Funded by the European Union – Next Generation EU, Mission 4 Component 2 Investment 1.1 – CUP E53D23012810001

Results

72 pts with *BRCA2* LP/PV diagnosed with HR+/HER2- aBC were included. All pts received CDK4/6i+ET and 36 (50.0%) received PARPi for aBC. Detailed *BRCA2* type/location was available for 57 (79.2%), as shown in **Figure 2**. 5-year OS rate was 51% (95%CI 37-72). No *BRCA2* LP/PV type/location was associated with OS (**Figure 3**), even after adjusting for relevant covariates (INDEL vs SNV:p=0.203, frameshift vs nonsense: p=0.955, truncating vs not trunc:p=0.124, and exon 11 vs others:p=0.110). A n. of met. sites >3 (aHR 14.2, 95% CI 2.9-69.4, p = 0.001) and post-menopausal status (aHR 2.7, 95% CI 1.0-7.3, p = 0.056) were independently associated with poorer OS. No LP/PV type was associated with differences in PFS with CDK4/6i or PARPi (**Suppl.**).

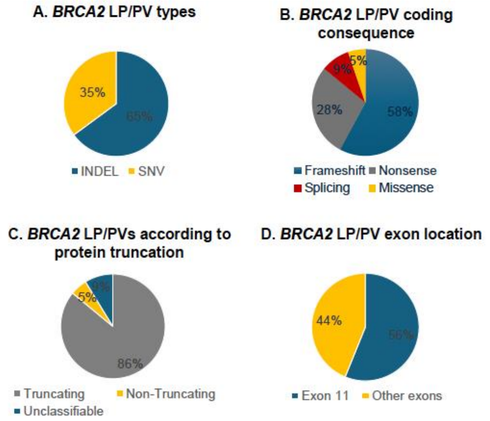


Figure 2. Distribution of *BRCA2* LP/PV type/location in the study.

Conclusions: In this cohort of pts with HR+/HER2- aBC harboring germline *BRCA2* LP/PV, neither the type nor the location of the LP/PV was associated with OS. Larger, prospective studies are warranted.

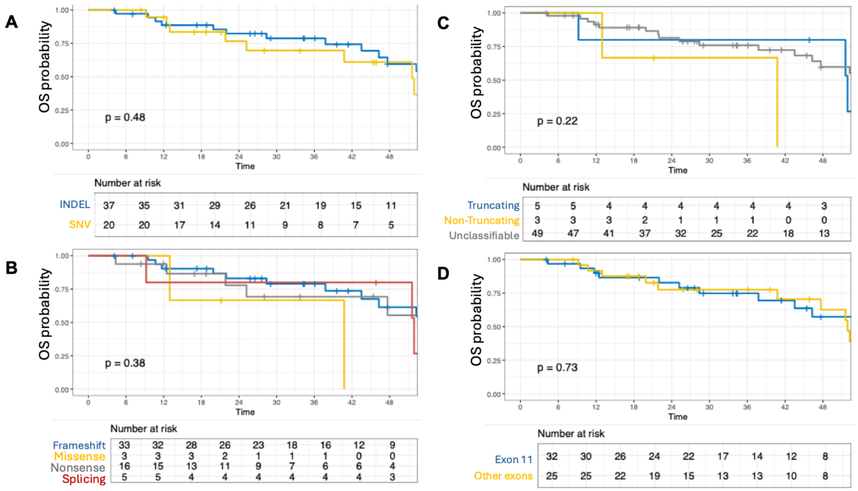


Figure 3. Kaplan-Meier curves of OS according to *BRCA2* LP/PV type/location.

PRESENTING AUTHOR: Professor Angela Toss

Email: atoss@unimore.it; ezattarin@unimore.it

@angela_toss @emmazattarin

Supplementary: