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Real-world insights: Neoadjuvant KEYNOTE-522 regimen in triple-negative breast cancer patients with germline BRCA mutations.

Monique Celeste Tavares, Romualdo Barroso-Sousa, Laura Testa, Flavia Cavalcanti Balint, Solange Moraes Sanches, Fernanda Madasi Pinheiro, Jose Bines, Vladmir Cordeiro Lima Sr., Rafael Dal Ponte Ferreira, Daniela Dornelles Rosa, Zenaide Silva de Souza, Daniele Assad Suzuki, Debora De Melo Gagliato, Carlos Henrique dos Anjos, Bruna M. Zucchetti, Anezka Carvalho Rubin de Celis Ferrari, Mayana Lopes De Brito, Maria Marcela F. Monteiro, Maria Del Pilar Estevez-Diz, Renata Colombo Bonadio; A.C. Camargo Cancer Center, São Paulo, Brazil; Grupo Dasa, Brasilia, Brazil; Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil; Instituto Nacional de Câncer Josér Alencar Gomes da Silva - INCA, Rio De Janeiro - RJ, Brazil; Instituto Nacional de Câncer; LACOG (Latin American Cooperative Oncology Group), Rio De Janeiro, Brazil; Hospital Moinhos de Vento, Porto Alegre, Brazil; Hospital Sírio-Libanês, Brasília, Brazil; Hospital Beneficência Portuguesa, São Paulo, Brazil; Hospital Sírio-Libanês, São Paulo, Brazil; DASA Oncology, Hospital 9 De Julho, São Paulo, Brazil; DASA Oncologia - Hospital Santa Paula, São Paulo, Brazil; DASA Oncology - Clínica AMO, Salvador, Brazil; Instituto do Câncer do Ceara, Fortaleza, Brazil; Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background: Triple-negative breast cancer (TNBC) is the most immunogenic subtype and is highly prevalent among patients (pts) with germline BRCA1/2 mutations (gBRCAm). Regardless of mutation status, the current standard treatment for early-stage TNBC is chemotherapy combined with pembrolizumab, as per the KEYNOTE-522 protocol. **Methods:** Data were collected from pts diagnosed with early-stage TNBC treated according to the KEYNOTE-522 regimen at ten cancer centers from July 2020 to December 2024. Epidemiological data and treatment outcomes of pts with gBRCAm were compared to those with BRCA wild-type/unknown (BRCAwt). **Results:** A total of 413 pts were analyzed, of whom 320 (82%) underwent germline testing; 49 (12.7%) had a gBRCAm, including 45 (91%) with BRCA1 and 4 (9%) with BRCA2 mutations. Pts with gBRCAm were younger (median 39 vs. 44 years, P<0.001) and more likely to be premenopausal (80.8% vs. 65.6%, P=0.045) and have grade 3 tumors (91% vs. 80%, P=0.214) than BRCAwt pts. Stage II disease was the most common in both groups (71.4% vs. 70%, P=0.315). Regarding treatment, gBRCAm pts were more frequently treated with dose-dense AC (doxorubicin and cyclophosphamide) (66% vs. 54%, P=0.160) and underwent mastectomy more often (93.9% vs. 35.9%, P=0.001). Only 2% of gBRCAm pts experienced disease progression during neoadjuvant therapy compared to 5% of BRCAwt pts (P=0.491).Pathological complete response (pCR; ypT0-Tis ypN0) rates were 73% in gBRCAm pts compared to 61% in BRCAwt pts (P=0.114). Residual cancer burden (RCB) 0-1 occurred in 83.7% vs. 76.6% (P=0.345). Subgroup analysis by disease stage revealed pCR rates of 74.3% in stage II gBRCAm pts versus 65.2% in BRCAwt pts (P=0.334), and 72.7% in stage III gBRCAm pts compared to 45.3% in BRCAwt pts (P=0.113).Grade 3 or higher adverse events (AEs) occurred in 50% of gBRCAm pts versus 34.9% of BRCAwt pts (P=0.055), with more frequent neutropenia (32.6% vs. 19.5%, P=0.041), diarrhea (6.1% vs. 1.6%, P=0.079), and immune-related AEs (12.2% vs. 7.4%, P=0.259). There were no significant differences in drug discontinuation rates due to toxicity (28% vs. 22%, P=0.327). **Conclusions:** Pts with gBRCAm exhibited high pCR rates with the KEYNOTE-522 regimen, achieving pCR rates over 70% even in stage III disease. Further research is needed to optimize treatment strategies in this population, including potential de-escalation approaches. Research Sponsor: None.