Toxicity and managing issues with antibody-drug conjugates and last-generation approved kinase inhibitors for breast cancer in patients with suspected Gilbert´s disease. Illarramendi J, Arraras JI, Salgado J, De La Cruz S, Zabalegui A, Illarramendi JJ. Services of Hematology, Medical Oncology and Clinical Biochemistry. University Hospital of Navarra. Pamplona. Spain.

Introduction: Antibody-drug conjugates (ADC) and last-generation approved kinase inhibitors (KI) have been a major advance to improve survival in patients (p.) with breast cancer (BC). There is limited knowledge on the use of ADC and KI in BC p. with GD. Prescribing information from regulatory agencies include some useful guidance on this context, but several issues complicate their application. We aim to analyze our experience on this subject in real-world conditions.

Methods: Retrospective study. Single-center, academic institution. Studied ADC: sacituzumab govitecan (SGV), trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-Dxd). Studied KI: palbociclib (PALB) and tucatinib (TUC). Suspected GD was defined on standard clinical findings. Major endpoints for toxicity have been therapy suspension for adverse events, life-threatening episodes and unexpected toxicities.

Results: 23 patients (p.) included. Some p. received several ADC and or KI. T-DM1 in 12 p. (164 cycles, 1 p. ongoing), T-Dxd in 1 p. (35 cycles, ongoing), SGV in 1 p. (2 cycles, ongoing), PALB in 12 p. (98 cycles), TUC in 2 p. (9 cycles, 1 p. ongoing). The SGV p. was included after pharmacogenomics disclosed a heterozygous variant in UGT1A1 (*1*28). She is a 78-year woman who needed dose adjustment for neutropenia, without major toxicities so far. Among T-DM1 p. , 9/12 had bilirubin elevations during therapy (7 grade 1, 2 grade 2), and T-DM1 was suspended in 1 p. for this reason. Among PALB therapy, 3 p. developed hyperbilirubinemia, and therapy was suspended in 1 p. for long-lasting transaminitis. The p. on T-Dxd developed grade 1 hyperbilirubinemia without major toxicities. Both p. on TUC developed further bilirubin elevations (1 grade 1, 1 grade 2) even with reduced doses of TUC, but without other major toxicities.

Conclusions: T-DM1, T-Dxd and PALB were used in this context without major concerns. Use of TUC was problematic as expected, since TUC is a strong inhibitor of UGT1A1. Although p. with GD were excluded from pivotal SGV trials, its use may be considered in absence of significant homozygous variants of UGT1A1, but further knowledge on this subject is needed.

Keywords: breast cancer, Gilbert´s disease, sacituzumab-govitecan, tucatinib, trastuzumab-deruxtecan, palbociclib.