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ORIGINAL ARTICLE

# Analysis of *UGT1A1* germline variants in patients with advanced breast cancer treated with trastuzumab-deruxtecan: results from the PROCURE Project

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**Background:** Although trastuzumab-deruxtecan (T-DXd) has demonstrated significant efficacy in advanced breast cancer, treatment discontinuation due to adverse events occurs in ∼20% of patients. Pharmacogenetic variants in uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) increase the toxicity risk for other antibody-drug conjugates using topoisomerase I inhibitors, but they remain unexplored for T-DXd.

**Material and methods:** The PROCURE Project is a translational study involving 26 Spanish institutions, investigating the association of germline pharmacogenomic variants with T-DXd toxicity for patients with HER2-positive or HER2-low advanced breast cancer. *UGT1A1**28 genotypes were determined in blood samples, and pharmacogenomic analyses were performed using the clinical data and adverse events extracted from the medical records of the patients. Additionally, stratified Cox models were used to quantify the risk of treatment discontinuation in the different *UGT1A1* genotypes.

**Results:** Between July 2022 and March 2024, a total of 292 patients with genetic and clinical information were enrolled in the study. At data cutoff, the median treatment duration with T-DXd was 12.0 months [95% confidence interval (CI) 10.5-14.1]. *UGT1A1* genotype distribution among patients was 43.2% wild-type (*1/*1), 46.2% heterozygous (*1/*28), and 10.3% homozygous (*28/*28). No association was observed between *UGT1A1* genotypes and the most common T-DXd adverse events. However, poor metabolizers (*28/*28) compared with extensive and intermediate metabolizers (*1/*1 and *1/*28, respectively) showed a trend toward higher incidence of neutropenia (13.3% versus <6%), as well as a higher incidence of grade ≥3 gastrointestinal toxicity (diarrhea and vomiting). The incidence of drug-induced pneumonitis/interstitial lung disease (ILD) was 11.0% (32/292). No association was observed between *UGT1A1*

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variants and the incidence of pneumonitis/ILD. Patients carrying *UGT1A1**28/*28 genotype showed a longer treatment duration (HR 0.47, 95% CI 0.23-0.93, $P = 0.03$) compared with *UGT1A1* wild-type patients.
**Conclusions:** In the PROCURE Project, *UGT1A1* variants, including the *28/*28 genotype, were not predictive of T-DXd–related adverse events in advanced breast cancer. The project highlights the need to identify alternative biomarkers to optimize toxicity risk stratification and guide personalized treatment strategies.
**Key words:** adverse events, breast cancer, pharmacogenetics, trastuzumab-deruxtecan, UGT1A1

## INTRODUCTION

Antibody-drug conjugates (ADCs) have significantly transformed the therapeutic landscape of breast cancer by enabling the selective delivery of cytotoxic agents to malignant cells, thereby enhancing efficacy while aiming to reduce systemic toxicity.[1] This targeted approach has led to the approval and widespread use of ADCs in various breast cancer subtypes, particularly those defined by HER2 expression.[2] However, the complex pharmacokinetics and pharmacodynamics of ADCs introduce substantial interindividual variability in both efficacy and toxicity profiles.[3] This variability underscores the importance of precision medicine approaches, including pharmacogenomics, to tailor treatment strategies and optimize patient outcomes.

A potential pharmacogenomic determinant relevant to ADC therapy is the uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) gene, which encodes the enzyme responsible for the glucuronidation and detoxification of SN-38, the active metabolite of irinotecan and camptothecine derivatives.[4] The *UGT1A1**28 polymorphism, particularly in the homozygous state, is associated with reduced enzymatic activity, leading to elevated systemic SN-38 levels and increased risk of adverse effects.[5] Clinical studies have shown that patients treated with the anti-Trop-2 SN-38 ADC sacituzumab govitecan and carrying the *UGT1A1**28/*28 genotype experience higher rates of severe hematologic and gastrointestinal toxicities, including grade $\geq$3 neutropenia, febrile neutropenia, anemia, and diarrhea.[6,7] The high prevalence of the *UGT1A1**28/*28 genotype, present in 10%-20% of the population,[8] supports the potential clinical utility of pretreatment pharmacogenetic testing to increase safety and personalize treatment.[9]

Trastuzumab-deruxtecan (T-DXd), an ADC approved for the treatment of HER2-positive and HER2-low breast cancer, employs a distinct topoisomerase I inhibitor payload different from SN-38, and the influence of *UGT1A1* variants on its metabolism has not been explored.[10] Despite its potent antitumor activity and unique mechanism of action, T-DXd is associated with a distinct toxicity profile characterized by gastrointestinal disturbances, myelosuppression, and a notable risk of interstitial lung disease (ILD) or pneumonitis, which can be life-threatening.[11] Multiple large trials and meta-analyses have reported ILD in 10%-15% of patients, with grade $\geq$3 events in 1%-2% and ILD-related mortality in 1%-1.4% of patients.[12] Regarding neutropenia, grade $\geq$3 occurs in 13%-28% of patients and grade $\geq$3 anemia in 8%-13%, with thrombocytopenia and leukopenia being less common (5%-8%).[13] Gastrointestinal toxicities are also frequent, with nausea (44%-73%), vomiting (20%-34%), diarrhea (22%-32%), constipation (11%-22%), and decreased appetite (29%-60%) being the most common events of any grade.[13] Although grade $\geq$3 gastrointestinal toxicities such as nausea (4%-6%), vomiting (1%-5%), and diarrhea (1%-3%) are less frequent, they can still impact quality of life and may necessitate supportive care or drug dose adjustments.[14] The overall T-DXd safety profile is consistent across different tumor types, although higher doses, non-Caucasian ethnicity, and use in nonbreast cancer indications are associated with a greater risk of severe adverse events.[14-16] Consistently, up to 20% of patients may discontinue T-DXd due to adverse events.[13]

The PROCURE Project, a multicenter translational research initiative involving 26 Spanish institutions, was launched to explore the impact of germline pharmacogenomic variants on the toxicity of T-DXd-treated patients. Through this investigation, the study aims to assess the broader utility of pharmacogenomic profiling in the context of advanced breast cancer and contribute to the evolving framework of individualized therapy. As ADCs become increasingly central to breast cancer treatment, integrating pharmacogenomic insights and proactive toxicity management will be crucial to maximizing therapeutic benefit while minimizing harm.

## MATERIAL AND METHODS

### *Study population*

The PROCURE Project included female patients with advanced HER2-positive or HER2-low breast cancer treated with T-DXd between July 2022 and March 2024. Patients were recruited from 26 Spanish hospitals participating in the study. To be eligible for inclusion, patients had to (i) have received at least 1 dose of T-DXd for its currently approved indications; (ii) have had genomic, clinical, and safety information reported in the electronic case report form (eCRF); and (iii) have had a minimum follow-up period of 3 weeks to assess early-onset toxicities. Given the exploratory nature of the study, the inclusion was restricted to female patients to have a more homogeneous cohort and avoid potential confounding factors due to sex differences. The study was designed to be retrospective-prospective, allowing the inclusion of patients who had already discontinued treatment for whom clinical data could be gathered from the medical records. Patients who had initiated T-DXd before institutional approval of the study and had discontinued treatment for any reason were enrolled retrospectively; all other patients were enrolled

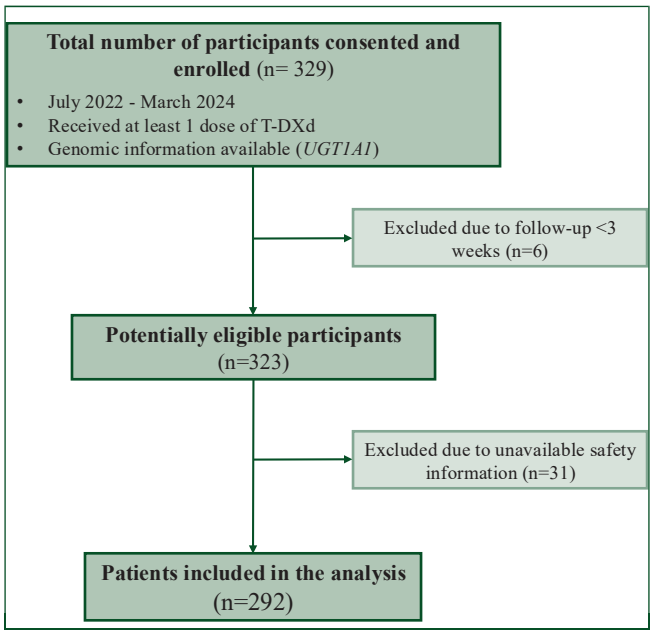


**Figure 1. Flowchart overviewing patient eligibility and study inclusion.**
T-DXd, trastuzumab-deruxtecan.

prospectively. Figure 1 summarizes patient inclusion, exclusions, and eligibility for analysis.

Demographic and clinical variables, including age, treatment duration, baseline comorbidities, and prior treatments, were collected from electronic medical records. The adverse events were assessed locally by the participating sites and investigators. Patients were treated according to standard local practice, and the use of prophylactic and supportive drugs (e.g. antiemetic or antidiarrheal) was at the physician's discretion.

The study was approved by the institutional research ethics board (reference number 2022/173).

### *UGT1A1 genotyping*

To evaluate the potential association between *UGT1A1* genetic variants and T-DXd-related toxicity, blood samples were collected from all study participants, and germline DNA was extracted. The time point for blood extraction was at least 3 weeks after the first dose of T-DXd, although for patients who had already discontinued T-DXd, the blood sample was collected afterwards. The primary genotyping method involved Sanger sequencing of the *UGT1A1* promoter region, allowing for the detection of the number of TA repetitions of rs306474 and defining *28 and the less common alleles *36 and *37. In addition, a fluorescent probe-based assay directed to rs887829 (a polymorphism in almost complete linkage disequilibrium with rs306474) was used to validate the *UGT1A1**28 genotype. In brief, for Sanger sequencing, the primers used were 5′-AAG CGG GGG TAC AGT TGT GTT C-3′ and 5′-AAG AAT ACA GTG GGC AGA GAC AG-3′. Validation of genotyping was carried out using the KASP SNP Genotyping System (LGC Biosearch Technologies, Novato, CA), a fluorescent (FRET)-based assay using competitive allele-specific PCR, according to the vendor's instructions, with custom probes. Concordance between both techniques ensured the accuracy and reproducibility of the results.

### *Study endpoints*

The primary endpoint of the PROCURE Project was the proportion of all-grade adverse events reported in patients treated with T-DXd according to their *UGT1A1* genotype (*1/*1 extensive metabolizers, *1/*28 intermediate metabolizers, *28/*28 poor metabolizers). The secondary endpoints included the proportion of grade ≥3 adverse events (AE), the incidence of ILD, and treatment duration and discontinuation (for all causes and specifically due to safety reasons) across the three *UGT1A1* genotype categories.

### *Statistical analysis*

Descriptive statistical analyses were performed to characterize the study population and to summarize key clinical and genetic variables. Categorical variables were reported as absolute values and percentages, whereas continuous variables were expressed as the median range. Logistic regression models were used to investigate the association between clinicopathological factors and the percentage of grade ≥3 adverse events, as well as the association between *UGT1A1* genotypes and adverse events in terms of odds ratios (ORs) with 95% confidence interval (95% CI) and *P* values derived from the Wald test. Missing at random values in clinical data were imputed using the chained equations method with the *mice* R package (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.107695).[17] However, no imputation was conducted on safety or genetic data. Sensitivity analysis was performed without data imputation. As an exploratory analysis, Kaplan—Meier curves and stratified Cox models (stratified by HER2 status: HER2-positive versus HER2-low) were used to compare time to treatment discontinuation with T-DXd (including disease progression, toxicity, or any other cause) across the different *UGT1A1* genotypes. The log-rank test was used to estimate *P* values. Additionally, cumulative incidence functions were used to estimate treatment discontinuation specifically due to safety reasons in a competing-risks setting, with treatment discontinuation for other reasons as a competing event. The median follow-up time was calculated using the reverse Kaplan—Meier method. Due to the exploratory nature of the study, no formal hypothesis testing was performed to avoid inflating the overall type I error rate due to multiple comparisons. All *P* values are considered exploratory and should be interpreted accordingly. All analyses were conducted using R statistical software (version 4.3.1, The R Foundation).

## RESULTS

### *Patient characteristics*

Between July 2022 and March 2024, a total of 329 female patients enrolled in the study had genomic data available. Among them, 292 (88.8%) were considered eligible for this

**Table 1. Baseline demographic characteristics of the PROCURE cohort ($N = 292$ patients)**

| Clinicopathologic variables | | Overall ($N = 292$) | *UGT1A1* genotypes | | |
|---|---|---|---|---|---|
| | | | *1/*1 ($n = 126$) | *1/*28 ($n = 135$) | *28/*28 ($n = 30$) |
| Age, years (median, range) | | 58 (34-94) | 58 (38-85) | 58 (36-94) | 58 (34-82) |
| Race | Caucasian | 261 (89.4%) | 113 (89.7%) | 125 (92.6%) | 23 (76.7%) |
| | Black or African American | 10 (3.4%) | 6 (4.8%) | 1 (0.7%) | 2 (6.7%) |
| | Asian | 4 (1.4%) | 2 (1.6%) | 1 (0.7%) | 1 (3.3%) |
| | Other | 5 (1.7%) | 2 (1.6%) | 1 (0.7%) | 2 (6.7%) |
| | Not reported | 12 (4.1%) | 3 (2.4%) | 7 (5.3%) | 2 (6.7%) |
| Stage at BC diagnosis | I-III | 159 (54.5%) | 71 (56.3%) | 74 (54.8%) | 14 (43.3%) |
| | IV (*de novo*) | 133 (45.5%) | 55 (43.7%) | 61 (45.2%) | 16 (53.3%) |
| HR status | Positive | 191 (65.4%) | 91 (72.2%) | 83 (61.5%) | 14 (43.3%) |
| | Negative | 101 (34.6%) | 35 (27.8%) | 52 (38.5%) | 16 (53.3%) |
| HER2 IHC | 0+ | 9 (3.1%) | 5 (4.0%) | 4 (3.0%) | 0 (0.0%) |
| | 1+ | 28 (9.6%) | 11 (8.7%) | 14 (10.4%) | 3 (10.0%) |
| | 2+ | 93 (31.8%) | 39 (31.0%) | 44 (32.6%) | 10 (33.3%) |
| | 3+ | 144 (49.3%) | 63 (50.0%) | 64 (47.4%) | 16 (53.3%) |
| | Not available | 18 (6.2%) | 8 (6.3%) | 9 (6.7%) | 1 (3.3%) |
| Number of prior metastatic lines | 1-2 | 162 (55.5%) | 75 (59.5%) | 70 (51.9%) | 17 (56.7%) |
| | 3+ | 130 (44.5%) | 51 (40.5%) | 65 (48.1%) | 13 (43.3%) |
| Starting dose of T-DXd | 4.4 mg/kg | 23 (7.9%) | 12 (9.5%) | 10 (7.4%) | 1 (3.3%) |
| | 5.4 mg/kg | 269 (92.1%) | 114 (90.5%) | 125 (92.6%) | 29 (96.7%) |

BC, breast cancer; HR, hormone receptor; IHC, immunohistochemistry; T-DXd, trastuzumab-deruxtecan; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1

analysis as they had clinical and safety information available and a minimum follow-up period of 3 weeks after the first dose of T-DXd. Supplementary Table S1 (available at https://doi.org/10.1016/j.esmoop.2026.107695) shows the partial missing data among patients included in the analysis. Briefly, the median age of this latter population was 58 years (range 34-94), 62% (181/292) were hormone-receptor positive, and most patients received 5.4 mg/kg as a starting dose of T-DXd (93.5%; 273/292). Table 1 shows the main characteristics of the study population.

### Treatment exposure and safety profile

At data cutoff (January 2025), the median duration of T-DXd treatment was 12.0 months (95% CI 10.5-14.1) and the median follow-up time was 18.3 months (95% CI 15.4-20.5). By this date, the most common all-grade adverse events were asthenia (49.0%), nausea (43.8%), and alopecia (21.2%). The incidence of drug-induced pneumonitis/ILD in our study was 11.0% (32/292), with 20 grade 1 events, 10 grade 2 events, and 3 grade 3 events. Grade $\geq$3 adverse events occurred in 21.9% of patients, mainly neutropenia (6.8%) and asthenia (4.5%) (Table 2). Supplementary Tables S2 and S3 (available at https://doi.org/10.1016/j.esmoop.2026.107695) show the association between clinicopathological factors and the percentage of grade $\geq$3 adverse events. No grade 5 events were reported in the study. Treatment discontinuation occurred in 130 (44.9%) of patients, 55 (42.3%) due to safety reasons (nausea/vomiting, asthenia, and ILD being the most frequent AE leading to discontinuation), and 75 (57.7%) due to disease progression.

### UGT1A1 genotypes and T-DXd-induced toxicity

Regarding *UGT1A1* variant groups, 43.2% (126/292) of patients with *1/*1 genotype were classified as extensive metabolizers; 46.2% (135/292) *1/*28 and 0.3% (1/292) *1/*37 patients were classified as intermediate metabolizers; and 10.3% (30/292) *28/*28 homozygous patients were classified as poor metabolizers. Overall, no significant association was observed between *UGT1A1* genotypes and the most common adverse events (Table 3), with all comparisons showing $P$ values $> 0.05$. Compared with other genotypes, *UGT1A1* poor metabolizers showed numerically higher rates of neutropenia (13.3% versus <6%) and leukopenia (6.7% versus <2.5%), as well as a higher incidence of grade $\geq$3 gastrointestinal toxicity (diarrhea and vomiting), although differences were not statistically significant. No association was observed between *UGT1A1* variants and the incidence of ILD/pneumonitis.

The percentage of patients with dose reduction in the *1/*1, *1/*28, and *28/*28 subgroups was 34.1%, 30.6%, and 40.1%, respectively. Treatment discontinuation due to adverse events—occurred in 15.3% of patients with the *1/*1 genotype, 13.4% with *1/*28, and 0.0% with *28/*28 (Table 3).

### UGT1A1 genotypes and treatment duration

Overall, 133 patients (45.5%) had discontinued T-DXd at the data cutoff. The primary reasons for treatment discontinuation were disease progression or death (67.7%), safety-related events (15.8%), treatment completion (14.3%), and investigator or patient decision (2.3%). Patients with *UGT1A1* *28/*28 genotype showed a numerically higher median time of treatment duration (17.3 months, 95% CI, 13.1—NR) compared with patients with *1/*1 genotype (11.6 months, 95% CI 9.1-14.1) and *1/*28 genotype (11.9 months, 95% CI 9.5-18.0) (Figure 2). There was a statistically significant difference in the time to treatment discontinuation in patients with *UGT1A1* *28/*28 genotype (stratified HR 0.47, 95% CI 0.23-0.93, $P = 0.03$) when

**Table 2. Most frequent treatment-emergent adverse events**

| Adverse events | Any grade | | Grades 1-2 | | Grade ≥3[a] | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| Any | 245 | 83.9 | 181 | 62.0 | 64 | 21.9 |
| Asthenia | 143 | 49.0 | 130 | 44.5 | 13 | 4.5 |
| Nausea | 128 | 43.8 | 123 | 42.1 | 5 | 1.7 |
| Alopecia | 62 | 21.2 | 61 | 20.9 | 1 | 0.3 |
| Diarrhea | 59 | 20.2 | 56 | 19.2 | 3 | 1 |
| Constipation | 58 | 19.9 | 58 | 19.9 | 0 | 0 |
| Vomiting | 54 | 18.5 | 49 | 16.8 | 5 | 1.7 |
| Neutropenia | 50 | 17.1 | 30 | 10.3 | 20 | 6.8 |
| Anemia | 33 | 11.3 | 29 | 9.9 | 4 | 1.4 |
| ILD/pneumonitis | 32 | 11.0 | 29 | 10.0 | 3 | 1 |
| Headache | 25 | 8.6 | 25 | 8.6 | 0 | 0 |
| Abdominal pain | 21 | 7.2 | 19 | 6.5 | 2 | 0.7 |
| Decreased appetite | 19 | 6.5 | 19 | 6.5 | 0 | 0 |
| Mucositis | 19 | 6.5 | 19 | 6.5 | 0 | 0 |
| Rash | 19 | 6.5 | 19 | 6.5 | 0 | 0 |
| Cough | 18 | 6.2 | 18 | 6.2 | 0 | 0 |
| Dysgeusia | 17 | 5.8 | 17 | 5.8 | 0 | 0 |
| Dyspepsia | 17 | 5.8 | 16 | 5.5 | 1 | 0.3 |
| Thrombocytopenia | 17 | 5.8 | 15 | 5.1 | 2 | 0.7 |
| Dyspnea | 16 | 5.5 | 12 | 4.1 | 4 | 1.4 |
| Hyporexia | 15 | 5.1 | 15 | 5.1 | 0 | 0 |
| Dizziness | 14 | 4.8 | 14 | 4.8 | 0 | 0 |
| Pyrosis | 12 | 4.1 | 12 | 4.1 | 0 | 0 |
| Back pain | 11 | 3.8 | 11 | 3.8 | 0 | 0 |
| Epigastralgia | 11 | 3.8 | 11 | 3.8 | 0 | 0 |
| Epistaxis | 11 | 3.8 | 11 | 3.8 | 0 | 0 |
| Arthralgia | 10 | 3.4 | 10 | 3.4 | 0 | 0 |
| Insomnia | 9 | 3.1 | 9 | 3.1 | 0 | 0 |
| Myalgia | 9 | 3.1 | 9 | 3.1 | 0 | 0 |
| Neuropathy | 9 | 3.1 | 9 | 3.1 | 0 | 0 |
| Upper respiratory tract infection | 9 | 3.1 | 8 | 2.8 | 1 | 0.3 |

ILD, interstitial lung disease.
[a]No grade 5 events were reported in the study.

compared with patients with *UGT1A1* *1/*1. The difference was not statistically significant for patients with *UGT1A1* *1/*28 genotype (stratified HR 0.86, 95% CI 0.58-1.28, $P = 0.46$). Similar results were observed when analyzing discontinuations specifically due to adverse events (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.107695).

## DISCUSSION

The findings from the PROCURE Project add to the growing landscape of research investigating the role of pharmacogenetics in predicting adverse events associated with ADCs in breast cancer. In our study, we did not find an association between *UGT1A1* genetic variants and the incidence of adverse events in patients with advanced breast cancer treated with T-DXd.

Existing literature strongly supports the relevance of *UGT1A1* polymorphisms—particularly the *28/*28 genotype—as predictors of toxicity in SN-38–based therapies such as irinotecan and sacituzumab govitecan.[5,18,19] In the ASCENT trial of sacituzumab govitecan, exploratory analyses confirmed higher rates of grade ≥3 hematologic toxicity in *UGT1A1* poor metabolizers, prompting regulatory recommendations for closer monitoring and supportive care in these patients.[7,20]

Despite these precedents, our study reveals no significant association between *UGT1A1* genotype and the risk of treatment-related adverse events in patients receiving T-DXd, an ADC whose cytotoxic payload may bypass UGT1A1 metabolism.[21] However, given the limited size of the *28/*28 subgroup, these findings should be interpreted with caution. The exploratory nature of the analyses precludes definitive conclusions regarding the absence of an association. The preclinical pharmacokinetic evaluations of T-DXd in cynomolgus monkeys showed that the major pathway of excretion for DXd is the fecal route.[22] Dxd is a substrate of organic anion transporting polypeptides, P-gp, and breast cancer resistance protein. These findings are consistent with the known pharmacokinetic profile of T-DXd, which employs a membrane-permeable derivative of exatecan, a topoisomerase I inhibitor structurally distinct from SN-38.[23] After internalization and lysosomal degradation of the antibody-drug complex, the payload is released intracellularly, leading to potent bystander cytotoxic effects.[24] However, it is also hypothesized that the payload's membrane permeability contributes to systemic exposure and off-target effects in a manner unrelated to traditional hepatic detoxification pathways.[21]

This pharmacodynamic distinction may explain the absence of UGT1A1-related associations with T-DXd toxicity and suggests the need to investigate alternative pharmacogenomic or

**Table 3. Association between *UGT1A1* genotypes and key adverse events**

| Adverse events | Any grade | | | Grade ≥3 | | |
|---|---|---|---|---|---|---|
| | *1/*1 ($n = 126$) | *1/*28 ($n = 135$) | *28/*28 ($n = 30$) | *1/*1 ($n = 126$) | *1/*28 ($n = 135$) | *28/*28 ($n = 30$) |
| Overall gastrointestinal | 61.1% ($n = 77$) | 48.9% ($n = 66$) | 53.3% ($n = 16$) | 5.6% ($n = 7$) | 1.5% ($n = 2$) | 10.0% ($n = 3$) |
| Nausea | 50.0% ($n = 63$) | 38.5% ($n = 52$) | 43.3% ($n = 13$) | 3.2% ($n = 4$) | 0.7% ($n = 1$) | 0% ($n = 0$) |
| Diarrhea | 23.0% ($n = 29$) | 17.0% ($n = 23$) | 20.0% ($n = 6$) | 0.8% ($n = 1$) | 0.7% ($n = 1$) | 3.3% ($n = 1$) |
| Vomiting | 20.6% ($n = 26$) | 16.3% ($n = 22$) | 20.0% ($n = 6$) | 2.4% ($n = 3$) | 0% ($n = 0$) | 6.7% ($n = 2$) |
| Overall hematological | 27.0% ($n = 34$) | 25.2% ($n = 34$) | 30.0% ($n = 9$) | 7.9% ($n = 10$) | 9.6% ($n = 13$) | 0% ($n = 0$) |
| Neutropenia | 17.5% ($n = 22$) | 17.8% ($n = 24$) | 10.0% ($n = 3$) | 6.3% ($n = 8$) | 8.1% ($n = 11$) | 0% ($n = 0$) |
| Anemia | 14.3% ($n = 18$) | 8.1% ($n = 11$) | 13.3% ($n = 4$) | 2.4% ($n = 3$) | 0.7% ($n = 1$) | 0% ($n = 0$) |
| Thrombocytopenia | 4.8% ($n = 6$) | 5.2% ($n = 7$) | 13.3% ($n = 4$) | 0% ($n = 0$) | 1.5% ($n = 2$) | 0% ($n = 0$) |
| Leukopenia | 2.4% ($n = 3$) | 2.2% ($n = 3$) | 6.7% ($n = 2$) | 1.6% ($n = 2$) | 0.7% ($n = 1$) | 0% ($n = 0$) |
| Lymphopenia | 0% ($n = 0$) | 1.5% ($n = 2$) | 0% ($n = 0$) | 0% ($n = 0$) | 0% ($n = 0$) | 0% ($n = 0$) |
| ILD/pneumonitis | 12.7% ($n = 16$) | 9.6% ($n = 13$) | 10% ($n = 3$) | 0.8% ($n = 1$) | 1.5% ($n = 2$) | 0% ($n = 0$) |
| Dose reduction (any reason) | 34.1% | 30.6% | 40.1% | - | - | - |
| Treatment discontinuation due to adverse events (cumulative incidence at 18 months) | 15.3% | 13.4% | 0.0% | - | - | - |

ILD, interstitial lung disease.

clinical biomarkers that may better stratify patients by toxicity risk. In this regard, prior studies have proposed associations between polymorphisms in genes related to immune response (e.g. MUC5, FCGR2A) and susceptibility to ILD or hypersensitivity reactions in patients receiving ADCs, although these findings remain preliminary and largely unvalidated.[25,26] The broader integration of germline pharmacogenomics and host-specific biomarkers, such as cytokine profiles or HLA haplotypes, could significantly advance the field by identifying patients at elevated risk for severe toxicities like ILD, which remain a limiting factor for continued T-DXd use in a subset of patients.[27,28]

As the number of ADCs incorporating topoisomerase I inhibitors continues to grow, the potential clinical relevance of UGT1A1 testing is likely to expand accordingly.[9] Although *UGT1A1* polymorphisms, particularly the *28/*28 genotype, have demonstrated clear predictive value for toxicity in ADCs utilizing SN-38, such as sacituzumab govitecan, their role in newer ADCs with different topoisomerase I payloads remains an area of active investigation. Many of these emerging agents, including derivatives of exatecan and other camptothecin analogues, share metabolic pathways or overlapping mechanisms of toxicity that could still be influenced by UGT1A1-mediated glucuronidation to varying degrees.[9] Consequently, the application of *UGT1A1* genotyping may serve not only as a toxicity risk stratification tool for existing therapies but also as a foundational biomarker in the early clinical development of novel ADCs.

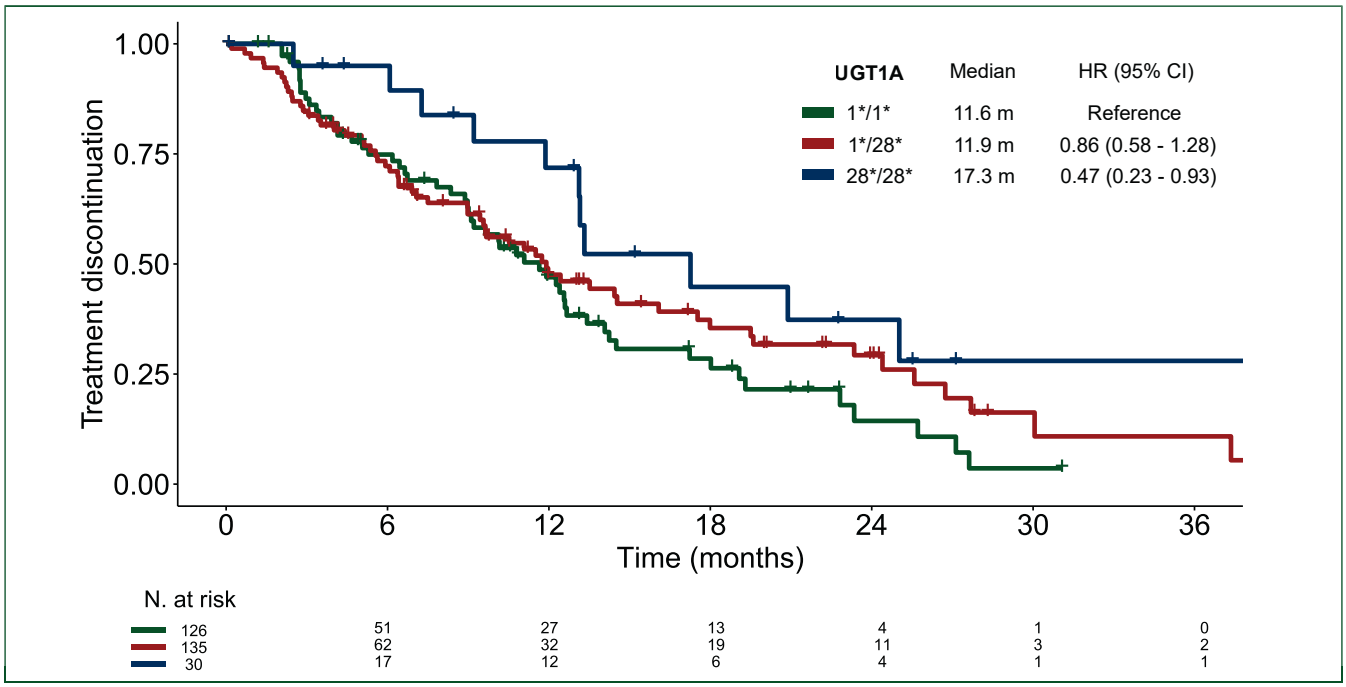


**Figure 2. Kaplan–Meier curves and hazard ratios (HRs) for time to treatment discontinuation according to UGT1A1 groups.**
CI, confidence interval.

Incorporating pharmacogenetic screening into ADC trials could facilitate the identification of vulnerable subpopulations, optimize dose selection, and support individualized treatment planning—thereby reinforcing the broader integration of precision medicine in oncology.[29]

The numerically higher median treatment duration observed in patients with the *UGT1A1* *28/*28 genotype (17.3 months) compared with *1/*1 (11.6 months) and *1/*28 (11.9 months) suggests a potential pharmacogenomic effect on outcomes with trastuzumab-deruxtecan. Because UGT1A1 metabolizes SN-38—structurally related to the more potent DXd payload—the reduced enzyme activity associated with *28/*28 may alter drug exposure, contributing to the longer treatment duration and delayed discontinuation seen in this group, although prospective evidence remains limited.[9] Overall, these findings suggest that *UGT1A1* *28/*28 may be linked to prolonged therapy and potentially modified drug metabolism, warranting further investigation to clarify its clinical relevance.

In the context of precision oncology, the identification of reliable biomarkers for treatment-related toxicity is essential not only for guiding supportive care strategies but also for informing therapeutic decision-making, including dose modifications and treatment selection. Biomarker-driven de-escalation strategies, which aim to minimize overtreatment while maintaining efficacy, are becoming increasingly prominent in oncology. For example, de-escalation trials in HER2-positive early breast cancer (e.g. APT, ATEMPT, PERSEPHONE) have successfully used clinical and molecular markers to identify subgroups of patients who may benefit from reduced treatment intensity without compromising outcomes.[30-32] In the setting of metastatic disease, where cumulative toxicity poses a substantial burden, there is a compelling rationale for extending this approach to ADCs, particularly when predictive markers of both efficacy and toxicity are available.

Our study has certain limitations that should be acknowledged. First, as an observational study, intersite variability in toxicity grading and reporting may introduce bias. Due to the retrospective nature of this study, there may be significant variability and inconsistency in the reporting of toxicity across centers and the use of prophylactic measures (data not collected). Moreover, it is unclear whether the standardized Common Terminology Criteria for Adverse Events v5.0 criteria were consistently applied by all the participating sites. Second, the study may be underpowered to detect small or modest genotype-toxicity associations, particularly for low-frequency variants. Third, our study is based on the Mediterranean population and lacks the representation of other ethnic groups. This makes the cohort homogenous, although the validity of our results in other ethnic groups must be considered cautiously. Future studies should incorporate multi-omic approaches—including transcriptomic and proteomic profiling—and consider prospective validation of candidate variants in larger, ethnically diverse populations. Fourth, our study lacks pharmacokinetic samples that could potentially complement a correlation analysis with *UGT1A1* variants. The PROCURE Project is an ongoing study, and an amendment is planned to collect pharmacokinetic samples in the newly enrolled patients. Lastly, the limited number of poor metabolizers *UGT1A1* *28/*28 warrants interpreting the results in this group with caution. Despite the small number, it is in accordance with the expected prevalence in the Mediterranean population, and very similar to the exploratory analyses of the ASCENT trial with sacituzumab govitecan that included 34 poor metabolizers out of 243 patients.[7]

The PROCURE Project's strengths lie in its robust multicenter design, sample size, diverse patient population reflective of real-world clinical practice, and comprehensive genotyping approach. By combining *UGT1A1* testing with a genome-wide SNP array that is currently under analysis, we laid the groundwork for future discovery of novel pharmacogenomic markers beyond candidate gene approaches. Moreover, the inclusion of patients who discontinued treatment early due to toxicity ensures that high-risk individuals are adequately represented, a limitation often encountered in clinical trial cohorts.

In conclusion, our results indicate that *UGT1A1* polymorphisms, specifically the *28/*28 genotype, are not predictive of T-DXd—related adverse events in patients with HER2-positive or HER2-low advanced breast cancer. These findings contrast with the established role of UGT1A1 in SN-38—based therapies and suggest that the mechanisms of toxicity in T-DXd therapy are independent of UGT1A1-mediated metabolism. The absence of a clear pharmacogenomic predictor for T-DXd toxicity underscores the urgent need for continued biomarker discovery efforts. Identifying reliable predictors of ILD and other treatment-related adverse events will be crucial to support the implementation of personalized ADC therapy and to enable biomarker-guided de-escalation strategies in metastatic breast cancer.

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