U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Kane M. Belinostat Therapy and *UGT1A1* Genotype. 2023 Jul 20. In: Pratt VM, Scott SA, Pirmohamed M, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Belinostat Therapy and *UGT1A1* Genotype

Megan Kane, PhD[1]

Created: July 20, 2023.

Introduction

Belinostat (brand name Beleodaq) is a histone deacetylase (HDAC) inhibitor, approved for the treatment of relapsed or refractory peripheral T-cell lymphomas (PTCLs) (1). Belinostat targets 3 classes of HDACs (I, II and IV), resulting in higher levels of acetylation of both histone and non-histone proteins, thus reversing the changes in protein acetylation that are frequently disrupted during oncogenesis. Belinostat is administered as an infusion at a rate of 1000 mg/m^2 for 30 minutes on days 1–5 of a 21-day cycle (1).

Belinostat has a relatively short half-life and is primarily metabolized by uridine diphosphate (UDP)-glucuronosyltransferase 1A1 (UGT1A1)-mediated glucuronidation, with minor contributions from other UGT and cytochrome P450 (CYP) enzymes (1, 2). Genetic variation at the *UGT1A1* locus can result in decreased enzyme activity and thus increased exposure to belinostat. The US Food and Drug Administration (FDA)-approved drug label recommends a 25% decrease in dose for individuals who are known to be homozygous for the *UGT1A1*28* reduced function allele (Table 1) (1). Additional indications for dose reduction include grade 3 or 4 adverse reactions or significant decrease in neutrophil or platelet counts following belinostat administration (1). Some studies have suggested that other variant alleles may also lead to increased belinostat exposure, such as *UGT1A1*60*; however, no specific recommendations for dose reduction have been made for these alleles by either the FDA or other professional pharmacogenetic consortia. Belinostat should not be administered with other medications that can inhibit UGT1A1 function (1), such as nilotinib, ketoconazole, or ripretinib.

Table 1: The FDA (2023) Drug Label for Belinostat Dosage Recommendation based on *UGT1A1* Genotype

Genotype	Recommendation
*UGT1A1*28/*28*	Reduce the starting dose of belinostat to 750 mg/m^2

This table is adapted from (1).

Drug: Belinostat

Belinostat is a pan histone deacetylase inhibitor (HDACi) used in the treatment of relapsed or refractory PTCLs (1). Peripheral T-cell lymphomas encompass multiple subtypes that together represent 10–15% of all non-Hodgkin lymphomas. The PTCLs arise from the transformation of post-thymic T lymphocytes. (3) It is estimated that approximately 70% of individuals with PTCL either relapse or are refractory to first-line therapy (4). Classification and diagnostic criteria of the PTCL subtypes are described elsewhere (3, 5, 6, 7), but the 5-year

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Corresponding author.

overall survival rates vary significantly among these subtypes varying from 80–25% (4). The current indication and recommended use of belinostat is for refractory or relapsed PTCL; (1, 5) however, it has been investigated as a first-line agent for PTCL with other first-line therapies (8). Belinostat is one of several single agent options for refractory or relapsed PTCL recommended by the National Comprehensive Cancer Network (5).

Changes in gene expression are observed in most PTCL types, either owing to altered epigenetic regulation, gene fusion events, somatic genetic variation of genes involved in epigenetic regulation, or some combination of these events (9). The HDACs, key enzymes in the maintenance of protein acetylation, are also implicated in the pathogenesis of PTCL as well as other malignancies (10, 11). Protein acetylation has a role in epigenetics as well as modulation of many other cellular homeostatic processes (10).

Belinostat is referred to as a pan-HDACi as it can inhibit all 3 classes of HDAC isoforms in humans, impacting not only histone acetylation, but non-histone proteins as well (10). A loss of acetylation on histones is associated with condensation of the chromatin structure and reduced expression of the underlying genes (12). By inhibiting the removal of acetyl groups by HDACs, belinostat is thought to relax chromatin structure and affect the activity of non-histone nuclear proteins. This leads to expression of genes that were silenced during oncogenesis and facilitates pro-apoptotic cellular responses (10). In Phase I clinical trials in solid and hematologic malignancies, belinostat had a robust antitumor and anti-angiogenic effect, leading to phase II trials in both PTCL and cutaneous T-cell lymphoma (CTCL) (11, 13, 14).

Belinostat is administered intravenously at a dose of 1,000 mg/m^2 over 30 minutes once daily on days 1–5 of a 21-day cycle (1). It has an elimination half-life of 1.1 hours with a limited body tissue distribution; the majority of belinostat is bound to protein in plasma (1). Over 98% of belinostat is metabolized prior to excretion (15, 16). Belinostat is primarily metabolized through glucuronidation by UGT1A1 with minor contributions by UGT2B7, and the resulting metabolite is the major form detected in urine (1, 2, 15, 17). Additional metabolism of belinostat is carried out by CYP2A6, CYP2C9, and CYP3A4 to form belinostat amide and belinostat acid. However, the enzymes responsible for the formation of 2 other metabolites are currently unknown. (1, 16) The primary route of excretion of belinostat and its metabolites is through urine, with less than 10% of a single radiolabeled dose detected in the feces over 168 hours post-transfusion (15). Due to the significant role of UGT1A1 in the metabolism and elimination of belinostat, the FDA-approved drug label recommends a reduced dosage of 750 mg/m^2 for individuals with known UGT1A1 reduced function, specifically those who are homozygous for the *UGT1A1*28* allele (1). The FDA-approved drug label also cautions against concomitant use of belinostat with strong inhibitors of UGT1A1 (1).

Adverse reactions associated with belinostat include hematologic toxicity, hepatotoxicity, tumor lysis syndrome, gastrointestinal toxicity, and embryo-fetal toxicity if used during pregnancy. Hematologic toxicities include thrombocytopenia, leukopenia, anemia, or a combination of these symptoms. Hepatotoxicity and liver function should be monitored prior to initiation of therapy and at the start of each round. Nausea, vomiting, and diarrhea can also occur during belinostat therapy. (1) The most frequently reported treatment-emergent adverse effects during clinical trials include nausea, fatigue, pyrexia, constipation, vomiting, and dizziness (11, 14). Tumor lysis syndrome (TLS) is a particular concern for individuals with advanced stage disease or high tumor burden; baseline hyperuricemia and bulky disease were associated with one individual experiencing grade 4 TLS and death due to multiorgan failure during clinical trial (1).

Some observed toxicities are indications for reduced dosage or discontinuation of belinostat. For hematologic toxicity, if the individual has a nadir absolute neutrophil count less than 0.5 x10^9/L or platelet count less than 25x10^9/L, the dosage should be decreased by 25% (1). Similarly, if a non-hematologic Common Terminology Criteria for Adverse Events (CTCAE) (18) Grade 3 or 4 adverse reaction is observed, decrease the dose by 25%; a recurrence of these adverse reactions after 2 dose reductions is an indication to discontinue belinostat (1).

Due to the genotoxic effects of belinostat, there is a risk of fetal harm when administered to a pregnant woman. The FDA-approved label recommends that females use effective contraception for 6 months following the last dose of belinostat and males whose partners are females of reproductive potential should also use effective contraception for 3 months following his last dose of belinostat (1). These recommendations are based on the mechanism of action of belinostat, as there are no available data on the use of this medication in pregnant women, nor were animal reproduction studies conducted with belinostat. (1) Additionally, there are no data regarding the excretion of belinostat into breast milk, how belinostat may affect a breastfed child, nor the effect on milk production; based on the potential adverse reaction to the breastfed child, nursing mothers are advised not to breastfeed until 2 weeks after the last belinostat dose (1).

Belinostat has not been proven to be safe or effective in pediatric individuals (1). In clinical trial data, individuals aged 65 and above had a higher response rate to belinostat versus individuals under 65 (36% versus 16%) (1, 11). However, no association was found between age of the individuals and rate of adverse reactions, indicating that age alone was not a risk factor for treatment-emergent adverse events (1). Moderate to severe hepatic impairment (as indicated by total bilirubin greater than 1.5 times the upper normal limit) was an exclusionary criterion for participation in clinical trials, but less severe hepatic impairment may increase exposure to belinostat (1, 11, 14). However, the FDA-approved label does not provide any alternative dosing recommendations for individuals with liver impairment (1).

Aberrations in protein acetylation and gene dysregulation are common across many types of cancer. The efficacy and safety of belinostat in other types of malignancies is an active area of investigation. It has been tested in acute promyelocytic leukemia, CTCL, B-cell lymphoma, advanced solid tumors including neuroendocrine and lung cancers, testicular germ cell tumors, and others (14, 19, 20, 21, 22, 23). Additionally, belinostat has been investigated as a potential therapy for atopic dermatitis (24, 25). Clinical trials involving belinostat can be found at ClinicalTrials.gov.

Gene: *UGT1A1*

The UGT enzymes (uridine diphosphate-glucuronosyltransferase, or UDP-glucuronosyltransferase) are a superfamily of enzymes that metabolize a wide range of lipophilic molecules such as bilirubin, steroids, toxins, and drugs. These enzymes mediate the process of glucuronidation, which is a phase II metabolic pathway during which glucuronic acid is conjugated to specific targets to convert them to water-soluble metabolites that can then be eliminated from the body (26).

The UGT genes are polymorphic, and genomic processes, such as variant splicing and epigenetic factors, likely contribute to their diversity. As a result, the substrates that the UGT enzymes catalyze are particularly variable (27). In humans, the UGT superfamily consists of 22 enzymes divided into 4 families, of which UGT1A is a member (28). The *UGT1A* gene locus is a cassette gene located on chromosome 2q37 in which common exons 2–5a and 5b are differentially spliced to unique first exons to form the 9 functional UGT1A family members (UGT1A1 and UGT1A3–UGT1A10) (29, 30). The *UGT1A1* promoter is differentially regulated compared to other UGT1As and consists of elements sensitive to xenobiotics (for example, pregnane X receptor and constitutive androstane receptor), hydrocarbons (for example, the aryl hydrocarbon receptor (AhR)), electrophilic nucleophiles and reactive oxygen species (for example, the nuclear factor 2 receptor), endobiotics and fatty acids (such as the glucocorticoid receptor), and a critical Thymine-Adenine-Thymine-Adenine (TATA) box that consists of polymorphic tandem repeats, $(TA)_{5-8}TAA$. Several Cytosine-phosphate-Guanine islands at the promoter further alter the affinity of nuclear receptors and therefore alter receptor activity.

Whereas many UGT enzymes overlap in the substrates they glucuronidate, UGT1A1 is the only enzyme that glucuronidates bilirubin, a yellow waste product produced during the catabolism of heme, a constituent of hemoglobin (31). When old or damaged red blood cells are broken down in the spleen, their hemoglobin is broken down to heme, which is then converted into bilirubin. The UGT1A1 enzyme converts this toxic,

insoluble form of bilirubin (unconjugated bilirubin) to its nontoxic form (conjugated bilirubin). Because conjugated bilirubin is water-soluble, it can be dissolved in bile and eliminated with solid waste. If bilirubin is not eliminated and instead accumulates to high levels (hyperbilirubinemia), it can cause a yellowish discoloration of the skin and eyes, a condition known as jaundice.

Over 150 genetic variants of *UGT1A1* have been reported (26, 31, 32). Of these, the available evidence indicates that 5 polymorphic variants are of clinical importance to UGT1A1 activity (*UGT1A1*6*, *UGT1A1*27*, *UGT1A1*28*, *UGT1A1*36*, *UGT1A1*37*), and 3 of these variants impact the tandem repeat of the TATA box ($[TA]_5TAA$ – *UGT1A1*36*, $[TA]_7TAA$ – *UGT1A1*28*, $[TA]_8TAA$ – *UGT1A1*37* (33)). The wild-type allele is called *UGT1A1*1,* which is associated with normal enzyme activity and the reference TATA box tandem repeat length ($[TA]_6TAA$) (Table 2).

As with all genetic variation, specific alleles or haplotypes vary in frequency across populations based on genetic ancestry and any history of evolutionary migration or bottleneck. To characterize the range of genetic variation in different groups of people, studies have used a mix of ethnic, racial, and geographic descriptors to group individuals with presumed common ancestry and shared genetic traits. Those descriptors are used interchangeably below based on the cited literature; however, the goal is to reflect a shared genetic background arising from common ancestry.

There are multiple genetic variations in the *UGT1A1* locus that decrease UGT1A1 enzyme activity and can lead to jaundice in the absence of exogenous substances, such as belinostat. The jaundice may be mild, as seen in Gilbert syndrome, or severe, as seen in Crigler-Najjar syndrome. (34)

The most common variant *UGT1A1* allele is *UGT1A1*28*, which is commonly found in African Americans (0.42–0.45 allele frequency, or 17–20% frequency of homozygosity in the population), Caucasians (0.26–0.31 allele frequency, or 6–9% homozygosity), and in Western and South Asian populations (0.26–0.33 allele frequency, or 6–10% homozygosity); however, it is less common in East and South-East Asian populations (0.09–0.16 allele frequency, or 0.8–2.5% homozygosity) (35, 36, 37). Within Caucasian and African American populations, the *UGT1A1*28* variant is a common cause of Gilbert syndrome (35, 38). The *UGT1A1*28* ($[TA]_7TAA$) variant contains an extra TA repeat within the TATA box promoter region (7 TA repeats compared with 6 in the wild-type allele) (39). This extra TA repeat decreases the rate of transcription initiation of the *UGT1A1* gene, leading to decreased enzyme activity and decreased glucuronidation of bilirubin (40). The data suggests that one copy of the *UGT1A1*28* allele results in an approximately 35% decrease in transcriptional activity, and 2 copies (**28/*28*, homozygous) results in an approximately 70% decrease, which is the genotype that the FDA has incorporated into the belinostat dosing label (1, 41, 42).

Another variant allele, UGT1A1*37 ($[TA]_8TAA$), has 8 TA repeats at the TATA box site, and results in reduced promoter activity of the gene to levels lower than the UGT1A1*28 allele. In contrast, the UGT1A1*36 ($[TA]_5TAA$) allele only has 5 repeats and is associated with increased promoter activity and a reduced risk of neonatal hyperbilirubinemia (a common and typically benign condition). Both UGT1A1*36 and UGT1A1*37 occur almost exclusively in populations of African origin, with estimated allele frequencies across African descent populations of 0.07 for **36* (TA_5) and 0.05 for **37* (TA_8) (gnomAD browser version 3.1.2, accessed 27 April 2023) (43). By comparison, the average frequency of these alleles across all populations in gnomAD is 0.01–0.02. The allele *UGT1A1*80* demonstrates strong linkage disequilibrium with both *UGT1A1*28* and **37* and is considered a surrogate marker for these alleles (33).

Other promoter variants have been reported in the phenobarbital-responsive enhancer module of the *UGT1A* locus. A T to G substitution, referred to as *UGT1A1*60*, results in decreased transcription of the gene and was found more frequently in individuals with mild hyperbilirubinemia (44), though other studies have reported no significant difference in total bilirubin concentration in individuals homozygous for *UGT1A1*60* versus wild-type homozygotes (45). The *UGT1A1*60* allele has been observed more frequently in individuals of African

descent versus European descent ('Caucasians') (46). It should be noted that the *UGT1A1*28* and **60* alleles are reported to be in linkage disequilibrium in multiple ethnic groups (46, 47), meaning an individual who has the higher number of TA repeats in the promoter (*UGT1A1*28*) is also likely to have the T to G substitution (*UGT1A1*60*) in the phenobarbital-responsive enhancer module region as well. Thus, it can be difficult to ascertain the individual contribution of these variants to total enzyme activity in vivo. The *UGT1A1*60* allele has a reported allele frequency of 0.47 in Caucasians (individuals of European descent) and 0.85 in Americans of African descent (46).

Another variant allele, *UGT1A1*6*, is more prevalent in East Asian populations, with an allele frequency of around 0.10–0.30 in Taiwanese, Chinese, Korean, and Japanese populations (37, 41, 48, 49). The *UGT1A1*6* allele is less common in South Eastern and Southern Asian populations, ranging from 0.027--0.12 in Thai, Malay, Indonesian, Vietnamese, and Indian population studies (37). This missense variant results in a glycine to arginine amino acid change at position 71 (p.Arg71Gly), and individuals who are homozygous for this allele have reduced UGT1A1 enzyme activity, which can cause Gilbert syndrome and prolonged neonatal jaundice (50, 51, 52, 53).

The *UGT1A1*27* (p.Pro229Gln) variant allele is located in exon 1 and has a minor allele frequency between 0.00011–0.0030 in those with Asian ancestry. It is associated with Gilbert's syndrome, post-irinotecan hyperbilirubinemia, and severe or life-threatening leukopenia or diarrhea during irinotecan therapy (54, 55). The allele is associated with a significant decrease in UGT1A1 substrate binding and catalytic activity (56).

Table 2: Relative Enzymatic Activity of UGT1A1 Variants

Allele name	Variant	Relative activity	Potential impact on drug metabolism	CPIC functional status[e]
*UGT1A1*1*	None (promoter $[TA]_6TAA$)	100%[a]	Normal	Normal function
*UGT1A1*6*	p.Arg71Gly	70%[b]	Slower	Decreased function
*UGT1A1*27*	p.Pro229Gln	50% [c]	Slower	Decreased function
*UGT1A1*28*	Promoter $(TA)_7TAA$	65%[a]	Slower	Decreased function
*UGT1A1*36*	Promoter $(TA)_5TAA$	130%[a]	Faster	Increased function
*UGT1A1*37*	Promoter $(TA)_8TAA$	50%[a]	Slower	Decreased function
*UGT1A1*60*	c.-3279T>G	60%[d]	Slower	Normal function[f]

CPIC – Clinical Pharmacogenetics Implementation Consortium
[a] Activity level from (35)
[b] Activity level from (51)
[c] Activity level from (56)
[d] Activity level from (44)
[e] Functional status from (57)
[f] Functional status from (58)

Phenoconversion

Mismatch between an individual's genotype-predicted phenotype and actual phenotype, or "phenoconversion," results from extrinsic factors (namely, comedications or comorbidities) altering the expression or function of enzymes. Individuals harboring an intermediate metabolizer phenotype are typically more susceptible to phenoconversion as a function of compromised drug metabolism capacity, whereas poor metabolizers (PMs) are unlikely to undergo phenoconversion but are more likely to experience toxicity from low or absent drug metabolism capacity limiting clearance of toxic drug species (59). The FDA-approved label recommends avoidance of belinostat administration with UGT1A1 inhibitors, as this may result in an increased exposure of the individual to belinostat (1). Medications that inhibit UGT1A1 include nilotinib (60), ketoconazole (61), and

ripretinib along with other tyrosine kinase inhibitor drugs (62). This is highly relevant given the interest in belinostat therapy for multiple cancer types in a combination therapy approach (8, 22). The use of belinostat may, conversely, impact enzymatic activity and alter the effect of other comedications. Belinostat can interfere with rifampin-induced changes in gene expression such as the induction of CYP3A4 expression (63). Belinostat, however, did not significantly impact the metabolism of warfarin by CYP2C9 (64). Belinostat itself inhibits UGT enzymes, and thus may interfere with metabolism of other UGT substrates (65).

Linking *UGT1A1* Genetic Variation with Treatment Response

The primary mechanism of belinostat clearance is metabolism by UGT1A1 (2, 15, 66). Genetic variation in the *UGT1A1* locus can lead to a decrease in enzyme activity and thus increase an individual's exposure to belinostat, leading to a higher risk of adverse reactions. The FDA-approved drug label and initial clinical studies support a decrease in dose (750 mg/m^2) for individuals who are homozygous for the *UGT1A1*28* allele to minimize toxicities (1, 2). Given the FDA guidance to avoid belinostat and co-medication with UGT1A1 inhibitors, it is unclear why additional genetic variants with a known decrease in function are not indications for a dose decrease on the product label. Additional studies have suggested that the *UGT1A1*60* allele also results in decreased clearance of belinostat, both when it was the only detected variant but also when detected in *cis* with **28* (67, 68). Both *UGT1A1*28* and **60* have been shown to be associated with increased belinostat exposure and a higher risk of thrombocytopenia and neutropenia (67). However, it should be noted that the Clinical Pharmacogenetics Implementation Consortium (CPIC) reassessed the functional status of *UGT1A1*60* and determined it was a normal-function allele, as indicated by serum bilirubin concentrations (45, 58). The clinical function of *UGT1A1* alleles as assigned by CPIC, initially published with guidelines for atazanavir pharmacogenetics (33), are presented in Table 2.

Further clinical studies are needed to determine the role of both common and rare *UGT1A1* variants in belinostat metabolism and the risk of adverse reactions.

Genetic Testing

The NIH Genetic Testing Registry (GTR) has tests for belinostat response and UGT1A1 genetic variation. Variants impacting UGT1A1 enzyme activity affect both the coding sequence as well as the promotor region of UGT1A locus. The FDA-approved label does not recommend for or against genetic testing prior to belinostat therapy, but states that knowledge of *UGT1A1*28* genotype is sufficient indication to alter prescribing. No other clinical practice guidelines for translation of other genotypes to altered dosing are currently available. Liu and colleagues recommend *UGT1A1* genotyping before administering any medication that is metabolized by UGT1A1 (69). Indeed, germline testing for variation in *UGT1A1* along with 4 other pharmacogenes has been estimated to have impact on oncology care as significantly as somatic variant testing (70). As a result of the demonstrated impact on UGT1A1 activity and the increased risk of adverse reactions, Goey and Figg recommend *UGT1A1* genotyping for both **28* and **60* variant alleles when determining belinostat dose (68).

One pharmacogenetic study in an oncology clinical setting found that approximately 17% of individuals had a UGT1A1 PM phenotype, defined as having 2 decreased-function alleles (*UGT1A1*6* or **28*) (70). Genotyping for different lengths of the TA promoter alleles requires a high degree of precision, particularly given the multiple variant alleles reported for that position, thus it is important to consider the testing methodology when selecting a genetic test or reviewing testing results.

The *UGT1A1*28* allele has been reported to be in linkage disequilibrium with the **80* allele; however, the *UGT1A1*80* variant itself is not known to influence *UGT1A1* expression (71). Instead, *UGT1A1*80* has been suggested to serve as a proxy for **28* variant identification in some single nucleotide polymorphism-based genotyping assays (33, 70, 71).

Additionally, *UGT1A1* genotyping may reveal variants that are associated with Gilbert syndrome or Crigler-Najjar syndrome type 1 or type 2. More information and resources for these conditions are available through MedGen. While more clinical data may be needed on belinostat metabolism, studies have shown that variants associated with Gilbert syndrome or Crigler-Najjar syndrome type 2 not only impact bilirubin metabolism, but multiple exogenous substances as well (31, 33, 56, 72).

The *UGT1A1* Gene Interactions with Medications Used for Additional Indications

Variation in *UGT1A1* and its promoter region are associated with risks of adverse reactions for a range of medications.

- Multiple medications used in oncology are metabolized by UGT1A1 including irinotecan, nilotinib, and sacituzumab govitecan; decreased UGT1A1 activity may lead to increased exposure to these medications with a higher risk of adverse reactions, adjusted dosing may be necessary based on *UGT1A1* genotype.
- The human immunodeficiency virus type 1 protease inhibitor, atazanavir, inhibits UGT1A1 activity and may lead to increased indirect plasma bilirubin concentration; UGT1A1 PMs may experience jaundice leading to discontinuation of therapy (33)
- A medication used for acromegalia, pegvisomant, caused liver injury in individuals who were positive for *UGT1A1*28* (26)

Additional information on gene-drug interactions for *UGT1A1* are available from PharmGKB, CPIC and the FDA (search for "UGT1A1").

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2023 Statement from the US Food and Drug Administration (FDA):

Patients with Reduced UGT1A1 Activity

Reduce the starting dose of Beleodaq to 750 mg/m^2 in patients known to be homozygous for the UGT1A1*28 allele.

[….]

Pharmacogenomics

UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 20% of the black population, 10% of the white population, and 2% of the Asian population are homozygous for the UGT1A1*28 allele. Additional reduced function alleles may be more prevalent in specific populations.

Because belinostat is primarily (80 -90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced UGT1A1 activity (e.g., patients with UGT1A1*28 allele). Reduce the starting

[1] *The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.*

dose of Beleodaq to 750 mg/m^2 in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities.

Please review the complete therapeutic recommendations that are located here: (1)

Nomenclature for selected *UGT1A1* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*UGT1A1*1*	$(TA)_6TAA$	NM_000463.2:c.-53_-52TA[7]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs3064744
*UGT1A1*6*	211G>A Gly71Arg	NM_000463.2:c.211G>A (NM_001072.4:c.862-6536G>A)	NP_000454.1:p.Gly71Arg	rs4148323
*UGT1A1*27*	Pro229Gln	NM_000463.3:c.686C>A	NP_000454.1:p.Pro229Gln	rs35350960
*UGT1A1*28*	$(TA)_7TAA$	NM_001072.4:c.862-6800AT[8]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs3064744
*UGT1A1*36*	$(TA)_5TAA$	NM_001072.4:c.862-6800AT[6]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs3064744
*UGT1A1*37*	$(TA)_8TAA$	NM_001072.4:c.862-6800AT[9]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs3064744
*UGT1A1*60*	-3263T>G -3279T>G	NM_001072.4:c.862-10021T>G	Not applicable—variant occurs in a non-coding region	rs4124874
*UGT1A1*80*	c.-364C>T	NM_007120.2:c.868-7110C>T	Not applicable—variant occurs in a non-coding region	rs887829

Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (73).
UGT Allele nomenclature and definitions are available from (32)
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
dbSNP - database of single nucleotide polymorphisms

Acknowledgments

The author would like to thank Ben Kong, PharmD, Clinical Pharmacist, Oregon Health & Science University, Knight Cancer Institute, Portland, Oregon, USA; Natalie Reizine, MD, Assistant Professor of Medicine, University of Illinois Cancer Center, Chicago, IL, USA; and Tristan Sissung, PhD, MS, Staff Scientist, Clinical Pharmacology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA for reviewing this summary.

References

1. BELEODAQ- belinostat injection, powder, lyophilized, for solution. East Windsor, NJ, USA: Acrotech Biopharma Inc; 2023. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2e8ef36b-71fa-4492-a16f-577d5f7d111d
2. Wang, L.Z., J. Ramirez, W. Yeo, M.Y. Chan, et al., Glucuronidation by UGT1A1 is the dominant pathway of the metabolic disposition of belinostat in liver cancer patients. PLoS One, 2013. 8(1): p. e54522. PubMed PMID: 23382909.

3. Stuver, R., Z.D. Epstein-Peterson, W.T. Johnson, N. Khan, et al., Current Treatment of Peripheral T-cell Lymphoma. Oncology (Williston Park), 2022. 36(5): p. 293-305. PubMed PMID: 35576176.
4. Wolska-Washer, A., P. Smolewski and T. Robak, Advances in the pharmacotherapeutic options for primary nodal peripheral T-cell lymphoma. Expert Opin Pharmacother, 2021. 22(9): p. 1203-1215. PubMed PMID: 33524268.
5. NCCN Clinical Practice Guidelines in Oncology, T-Cell Lymphomas, 1.2023, 5 January 2023. Network, N.C.C.; [Cited 21 April 2023]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1483
6. Swerdlow, S.H., E. Campo, S.A. Pileri, N.L. Harris, et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, 2016. 127(20): p. 2375-90. PubMed PMID: 26980727.
7. Campo, E., E.S. Jaffe, J.R. Cook, L. Quintanilla-Martinez, et al., The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood, 2022. 140(11): p. 1229-1253. PubMed PMID: 35653592.
8. Johnston, P.B., A.F. Cashen, P.G. Nikolinakos, A.W. Beaven, et al., Belinostat in combination with standard cyclophosphamide, doxorubicin, vincristine and prednisone as first-line treatment for patients with newly diagnosed peripheral T-cell lymphoma. Exp Hematol Oncol, 2021. 10(1): p. 15. PubMed PMID: 33602316.
9. Saleh, K., J.M. Michot and V. Ribrag, Updates in the Treatment of Peripheral T-Cell Lymphomas. J Exp Pharmacol, 2021. 13: p. 577-591. PubMed PMID: 34188559.
10. Zhang, Q., S. Wang, J. Chen and Z. Yu, Histone Deacetylases (HDACs) Guided Novel Therapies for T-cell lymphomas. Int J Med Sci, 2019. 16(3): p. 424-442. PubMed PMID: 30911277.
11. O'Connor, O.A., S. Horwitz, T. Masszi, A. Van Hoof, et al., Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol, 2015. 33(23): p. 2492-9. PubMed PMID: 26101246.
12. Gallinari, P., S. Di Marco, P. Jones, M. Pallaoro, et al., HDACs, histone deacetylation and gene transcription: from molecular biology to cancer therapeutics. Cell Res, 2007. 17(3): p. 195-211. PubMed PMID: 17325692.
13. Steele, N.L., J.A. Plumb, L. Vidal, J. Tjornelund, et al., A phase 1 pharmacokinetic and pharmacodynamic study of the histone deacetylase inhibitor belinostat in patients with advanced solid tumors. Clin Cancer Res, 2008. 14(3): p. 804-10. PubMed PMID: 18245542.
14. Foss, F., R. Advani, M. Duvic, K.B. Hymes, et al., A Phase II trial of Belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. Br J Haematol, 2015. 168(6): p. 811-9. PubMed PMID: 25404094.
15. Calvo, E., G. Reddy, V. Boni, L. Garcia-Canamaque, et al., Pharmacokinetics, metabolism, and excretion of (14)C-labeled belinostat in patients with recurrent or progressive malignancies. Invest New Drugs, 2016. 34(2): p. 193-201. PubMed PMID: 26769244.
16. Campbell, P. and C.M. Thomas, Belinostat for the treatment of relapsed or refractory peripheral T-cell lymphoma. J Oncol Pharm Pract, 2017. 23(2): p. 143-147. PubMed PMID: 26921086.
17. Dong, D., T. Zhang, D. Lu, J. Liu, et al., In vitro characterization of belinostat glucuronidation: demonstration of both UGT1A1 and UGT2B7 as the main contributing isozymes. Xenobiotica, 2017. 47(4): p. 277-283. PubMed PMID: 27180825.
18. Institute, N.C. *Common Terminology Criteria for Adverse Events (CTCAE)*. 19 April 2021; Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
19. Valiuliene, G., I. Stirblyte, D. Cicenaite, A. Kaupinis, et al., Belinostat, a potent HDACi, exerts antileukaemic effect in human acute promyelocytic leukaemia cells via chromatin remodelling. J Cell Mol Med, 2015. 19(7): p. 1742-55. PubMed PMID: 25864732.
20. Puvvada, S.D., H. Li, L.M. Rimsza, S.H. Bernstein, et al., A phase II study of belinostat (PXD101) in relapsed and refractory aggressive B-cell lymphomas: SWOG S0520. Leuk Lymphoma, 2016. 57(10): p. 2359-69. PubMed PMID: 26758422.

21. Balasubramaniam, S., C.E. Redon, C.J. Peer, C. Bryla, et al., Phase I trial of belinostat with cisplatin and etoposide in advanced solid tumors, with a focus on neuroendocrine and small cell cancers of the lung. Anticancer Drugs, 2018. 29(5): p. 457-465. PubMed PMID: 29420340.
22. Luu, T., P. Frankel, J.H. Beumer, D. Lim, et al., Phase I trial of belinostat in combination with 13-cis-retinoic acid in advanced solid tumor malignancies: a California Cancer Consortium NCI/CTEP sponsored trial. Cancer Chemother Pharmacol, 2019. 84(6): p. 1201-1208. PubMed PMID: 31522242.
23. Lobo, J., C. Guimaraes-Teixeira, D. Barros-Silva, V. Miranda-Goncalves, et al., Efficacy of HDAC Inhibitors Belinostat and Panobinostat against Cisplatin-Sensitive and Cisplatin-Resistant Testicular Germ Cell Tumors. Cancers (Basel), 2020. 12(10). PubMed PMID: 33050470.
24. Liew, W.C., G.M. Sundaram, S. Quah, G.G. Lum, et al., Belinostat resolves skin barrier defects in atopic dermatitis by targeting the dysregulated miR-335:SOX6 axis. J Allergy Clin Immunol, 2020. 146(3): p. 606-620 e12. PubMed PMID: 32088305.
25. Quah, S., G. Subramanian and P. Sampath, Repurposing Belinostat for Alleviation of Atopic Dermatitis. Dermatol Ther (Heidelb), 2021. 11(3): p. 655-660. PubMed PMID: 33852133.
26. Steventon, G., Uridine diphosphate glucuronosyltransferase 1A1. Xenobiotica, 2020. 50(1): p. 64-76. PubMed PMID: 31092094.
27. Meech, R., D.G. Hu, R.A. McKinnon, S.N. Mubarokah, et al., The UDP-Glycosyltransferase (UGT) Superfamily: New Members, New Functions, and Novel Paradigms. Physiol Rev, 2019. 99(2): p. 1153-1222. PubMed PMID: 30724669.
28. Mackenzie, P.I., K.W. Bock, B. Burchell, C. Guillemette, et al., Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. Pharmacogenet Genomics, 2005. 15(10): p. 677-85. PubMed PMID: 16141793.
29. van Es, H.H., A. Bout, J. Liu, L. Anderson, et al., Assignment of the human UDP glucuronosyltransferase gene (UGT1A1) to chromosome region 2q37. Cytogenet Cell Genet, 1993. 63(2): p. 114-6. PubMed PMID: 8467709.
30. Sissung, T.M., R. Barbier, L.M. Cordes and W.D. Figg, *UGT1A1 Polymorphisms and Mutations Affect Anticancer Drug Therapy*, in *Handbook of Therapeutic Biomarkers in Cancer*, S.X. Yang and J.E. Dancey, Editors. 2021: New York.
31. Strassburg, C.P., Pharmacogenetics of Gilbert's syndrome. Pharmacogenomics, 2008. 9(6): p. 703-15. PubMed PMID: 18518849.
32. UGT Official Nomenclature: UGT1A and UGT2B haplotypes and SNPs tables., [Cited March 2018]. Available from: https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/
33. Gammal, R.S., M.H. Court, C.E. Haidar, O.F. Iwuchukwu, et al., Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther, 2016. 99(4): p. 363-9. PubMed PMID: 26417955.
34. Bhandari, J., P.K. Thada and D. Yadav, *Crigler Najjar Syndrome*, in *StatPearls*. 2023: Treasure Island (FL).
35. Beutler, E., T. Gelbart and A. Demina, Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci U S A, 1998. 95(14): p. 8170-4. PubMed PMID: 9653159.
36. Hall, D., G. Ybazeta, G. Destro-Bisol, M.L. Petzl-Erler, et al., Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. Pharmacogenetics, 1999. 9(5): p. 591-9. PubMed PMID: 10591539.
37. Huang, M.J., P.L. Chen and C.S. Huang, Bilirubin metabolism and UDP-glucuronosyltransferase 1A1 variants in Asians: Pathogenic implications and therapeutic response. Kaohsiung J Med Sci, 2022. 38(8): p. 729-738. PubMed PMID: 35942604.
38. Guillemette, C., Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. Pharmacogenomics J, 2003. 3(3): p. 136-58. PubMed PMID: 12815363.
39. ClinVar: UGT1A1*28, [Cited March 20, 2018]. Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/12275/

40. Bosma, P.J., J.R. Chowdhury, C. Bakker, S. Gantla, et al., The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med, 1995. 333(18): p. 1171-5. PubMed PMID: 7565971.
41. Chapter 1 - Principles of Pharmacogenomics: Pharmacokinetic, Pharmacodynamic, and Clinical Implications., Y.W. Francis Lam, L.H.C.; [Cited March 2018]. Available from: https://www.sciencedirect.com/science/book/9780123919182
42. Barbarino, J.M., C.E. Haidar, T.E. Klein and R.B. Altman, PharmGKB summary: very important pharmacogene information for UGT1A1. Pharmacogenet Genomics, 2014. 24(3): p. 177-83. PubMed PMID: 24492252.
43. Karczewski, K.J., L.C. Francioli, G. Tiao, B.B. Cummings, et al., The mutational constraint spectrum quantified from variation in 141,456 humans. Nature, 2020. 581(7809): p. 434-443. PubMed PMID: 32461654.
44. Sugatani, J., K. Yamakawa, K. Yoshinari, T. Machida, et al., Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. Biochem Biophys Res Commun, 2002. 292(2): p. 492-7. PubMed PMID: 11906189.
45. Pasternak, A.L., K.R. Crews, K.E. Caudle, C. Smith, et al., The impact of the UGT1A1*60 allele on bilirubin serum concentrations. Pharmacogenomics, 2017. 18(1): p. 5-16. PubMed PMID: 27967321.
46. Innocenti, F., C. Grimsley, S. Das, J. Ramirez, et al., Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups. Pharmacogenetics, 2002. 12(9): p. 725-33. PubMed PMID: 12464801.
47. Maruo, Y., C. D'Addario, A. Mori, M. Iwai, et al., Two linked polymorphic mutations (A(TA)7TAA and T-3279G) of UGT1A1 as the principal cause of Gilbert syndrome. Hum Genet, 2004. 115(6): p. 525-6. PubMed PMID: 15378351.
48. Akaba, K., T. Kimura, A. Sasaki, S. Tanabe, et al., Neonatal hyperbilirubinemia and a common mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene in Japanese. J Hum Genet, 1999. 44(1): p. 22-5. PubMed PMID: 9929972.
49. Zhang, X., J.F. Yin, J. Zhang, S.J. Kong, et al., UGT1A1*6 polymorphisms are correlated with irinotecan-induced neutropenia: a systematic review and meta-analysis. Cancer Chemother Pharmacol, 2017. 80(1): p. 135-149. PubMed PMID: 28585035.
50. Akaba, K., T. Kimura, A. Sasaki, S. Tanabe, et al., Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. Biochem Mol Biol Int, 1998. 46(1): p. 21-6. PubMed PMID: 9784835.
51. Yamamoto, K., H. Sato, Y. Fujiyama, Y. Doida, et al., Contribution of two missense mutations (G71R and Y486D) of the bilirubin UDP glycosyltransferase (UGT1A1) gene to phenotypes of Gilbert's syndrome and Crigler-Najjar syndrome type II. Biochim Biophys Acta, 1998. 1406(3): p. 267-73. PubMed PMID: 9630669.
52. Maruo, Y., K. Nishizawa, H. Sato, Y. Doida, et al., Association of neonatal hyperbilirubinemia with bilirubin UDP-glucuronosyltransferase polymorphism. Pediatrics, 1999. 103(6 Pt 1): p. 1224-7. PubMed PMID: 10353933.
53. Boyd, M.A., P. Srasuebkul, K. Ruxrungtham, P.I. Mackenzie, et al., Relationship between hyperbilirubinaemia and UDP-glucuronosyltransferase 1A1 (UGT1A1) polymorphism in adult HIV-infected Thai patients treated with indinavir. Pharmacogenet Genomics, 2006. 16(5): p. 321-9. PubMed PMID: 16609363.
54. Koiwai, O., M. Nishizawa, K. Hasada, S. Aono, et al., Gilbert's syndrome is caused by a heterozygous missense mutation in the gene for bilirubin UDP-glucuronosyltransferase. Hum Mol Genet, 1995. 4(7): p. 1183-6. PubMed PMID: 8528206.
55. Ando, Y., H. Saka, M. Ando, T. Sawa, et al., Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res, 2000. 60(24): p. 6921-6. PubMed PMID: 11156391.
56. Udomuksorn, W., D.J. Elliot, B.C. Lewis, P.I. Mackenzie, et al., Influence of mutations associated with Gilbert and Crigler-Najjar type II syndromes on the glucuronidation kinetics of bilirubin and other UDP-

glucuronosyltransferase 1A substrates. Pharmacogenet Genomics, 2007. 17(12): p. 1017-29. PubMed PMID: 18004206.
57. UGT1A1 Allele Functionality Table, CPIC; [Cited 22 June 2023]. Available from: https://files.cpicpgx.org/data/report/current/allele_function_reference/UGT1A1_allele_functionality_reference.xlsx
58. CPIC. *CPIC Guideline for Atazanavir and UGT1A1, March 2017 Update*. 2017 13 Feb 2023; Available from: https://cpicpgx.org/guidelines/guideline-for-atazanavir-and-ugt1a1/.
59. Shah, R.R. and R.L. Smith, Addressing phenoconversion: the Achilles' heel of personalized medicine. Br J Clin Pharmacol, 2015. 79(2): p. 222-40. PubMed PMID: 24913012.
60. Miura, M., Therapeutic drug monitoring of imatinib, nilotinib, and dasatinib for patients with chronic myeloid leukemia. Biol Pharm Bull, 2015. 38(5): p. 645-54. PubMed PMID: 25947908.
61. Yong, W.P., J. Ramirez, F. Innocenti and M.J. Ratain, Effects of ketoconazole on glucuronidation by UDP-glucuronosyltransferase enzymes. Clin Cancer Res, 2005. 11(18): p. 6699-704. PubMed PMID: 16166450.
62. Lv, X., Z. Wang, Z. Wang, H. Yin, et al., Inhibition of human UDP-glucuronosyltransferase enzyme by ripretinib: Implications for drug-drug interactions. Toxicol Appl Pharmacol, 2023. 466: p. 116490. PubMed PMID: 36963523.
63. Abbott, K.L., C.S. Chaudhury, A. Chandran, S. Vishveshwara, et al., Belinostat, at Its Clinically Relevant Concentrations, Inhibits Rifampicin-Induced CYP3A4 and MDR1 Gene Expression. Mol Pharmacol, 2019. 95(3): p. 324-334. PubMed PMID: 30622215.
64. Agarwal, N., J.P. McPherson, H. Bailey, S. Gupta, et al., A phase I clinical trial of the effect of belinostat on the pharmacokinetics and pharmacodynamics of warfarin. Cancer Chemother Pharmacol, 2016. 77(2): p. 299-308. PubMed PMID: 26719074.
65. Wang, X., Z. Wang, Z. Wang, X. Chen, et al., Inhibition of human UDP-glucuronosyltransferase enzyme by belinostat: Implications for drug-drug interactions. Toxicol Lett, 2021. 338: p. 51-57. PubMed PMID: 33290829.
66. Bailey, H., J.P. McPherson, E.B. Bailey, T.L. Werner, et al., A phase I study to determine the pharmacokinetics and urinary excretion of belinostat and metabolites in patients with advanced solid tumors. Cancer Chemother Pharmacol, 2016. 78(5): p. 1059-1071. PubMed PMID: 27744565.
67. Goey, A.K., T.M. Sissung, C.J. Peer, J.B. Trepel, et al., Effects of UGT1A1 genotype on the pharmacokinetics, pharmacodynamics, and toxicities of belinostat administered by 48-hour continuous infusion in patients with cancer. J Clin Pharmacol, 2016. 56(4): p. 461-73. PubMed PMID: 26313268.
68. Goey, A.K. and W.D. Figg, UGT genotyping in belinostat dosing. Pharmacol Res, 2016. 105: p. 22-7. PubMed PMID: 26773202.
69. Liu, D., Q. Yu, Q. Ning, Z. Liu, et al., The relationship between UGT1A1 gene & various diseases and prevention strategies. Drug Metab Rev, 2022. 54(1): p. 1-21. PubMed PMID: 34807779.
70. Reizine, N.M., K. Danahey, T.M. Truong, D. George, et al., Clinically actionable genotypes for anticancer prescribing among >1500 patients with pharmacogenomic testing. Cancer, 2022. 128(8): p. 1649-1657. PubMed PMID: 35090043.
71. Bravo-Gomez, A., S. Salvador-Martin, P. Zapata-Cobo, M. Sanjurjo-Saez, et al., Genotyping of UGT1A1*80 as an Alternative to UGT1A1*28 Genotyping in Spain. Pharmaceutics, 2022. 14(10). PubMed PMID: 36297516.
72. Argevani, L., C. Hughes and M.J. Schuh, Dosage Adjustment of Irinotecan in Patients with UGT1A1 Polymorphisms: A Review of Current Literature. Innov Pharm, 2020. 11(3). PubMed PMID: 34007623.
73. Kalman, L.V., J. Agundez, M.L. Appell, J.L. Black, et al., Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. Clin Pharmacol Ther, 2016. 99(2): p. 172-85. PubMed PMID: 26479518.

License