ChemoTox
by Alpha Genomix Laboratories

Anticancer Medications Report

Patient: **Frederick Sanger**
Accession #:
Collection Date: **7/25/2017**

Ordered By: **Dr. Oncologist**
DOB: **8/31/1980**
Gender: **Male**

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POTENTIALLY IMPACTED MEDICATIONS FOR: FREDRICK SANGER

Category	Class	Standard Precautions	Use with Caution	Consider Alternatives
Anticancer Agents	Dihydropyrimidines	Capecitabine (Xeloda) Fluorouracil (Adrucil (iv); Carac (topical); Efudex (topical))		
	Histone Deacetylase Inhibitors		Belinostat (Beleodaq)	
	Protein Kinase Inhibitors	Gefitinib (Iressa)	Erlotinib (Tarceva) Nilotinib (Tasigna) Pazopanib (Votrient)	
	Taxanes	Paclitaxel (Taxol, Abraxane)		
	Thiopurines	Azathioprine (Azasan, Imuran) Mercaptopurine (Purinethol, Purixan) Thioguanine (Tabloid)		
	Topoisomerase inhibitors		Irinotecan liposomal (Onivyde)	Irinotecan (Camptosar)

GUIDANCE LEVELS

Based upon the patient's genotype, a medication has potentially reduced efficacy or increased toxicity or the patient has an increased risk for the indicated condition.

Based upon the patient's genotype, guidelines exist for adjusting dosage or increased vigilance or the patient has a moderate risk for the indicated condition.

Based on this patient's genotype, the medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

EVIDENCE LEVELS

Actionable: Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA,EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as new knowledge arises.

Informative: There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

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DOSING GUIDANCE FOR: FREDERICK SANGER

UGT1A1, DPYD, TPMT, MTHFR and CYP2C8 genotype and phenotype results are used to aid dose optimization and to reduce side effects but not to predict clinical outcomes to anticancer drugs. Hence they should not be used as predictive or prognostic biomarkers for anticancer drugs responses.

Azathioprine (Azasan, Imuran)

Evidence Level: **Actionable**

Normal Myelotoxicity Risk (TPMT *1/*1 Normal Metabolizer)

The genotype results predict that the patient has a normal TPMT activity. Start with a normal starting dose (e.g., 23 mg/kg/d), and adjust dose based on diseasespecific guidelines and myelosuppression. Allow 2 weeks to reach steady state after each dose adjustment.

Belinostat (Beleodaq)

Evidence Level: **Actionable**

Increased risk for belinostat toxicity (UGT1A1 *28/*28 Poor Metabolizer)

Since UGT1A1 metabolizes up to 90% of belinostat, patients homozygous for reduced function UGT1A1 alleles may have belinostat systemic exposures greater than those seen at doses of 1000 mg/m2 which is also the maximum tolerated dose. **Therefore, consider prescribing a lower starting dose of 750 mg/m2 to minimize dose-limiting toxicities.** It is also recommended to carefully monitor the patient for increased side effects and to titrate the drug according to the patient's tolerance.

Capecitabine (Xeloda)

Evidence Level: **Actionable**

Normal risk for fluoropyrimidine toxicity (DPYD *1/*1 Normal Metabolizer)

The genotype results predict that the patient has a normal Dihydropyrimidine dehydrogenase (DPD) activity. Unless other genetic, environmental, or other risk factors are present, the patient does not have an increased risk for dosedependent capecitabine toxicity. This genotype however, does not completely exclude toxicities from this drug. Use labelrecommended dosage and administration, and titrate the drug according to the patient's response.

Erlotinib (Tarceva)

Evidence Level: **Actionable**

Increased Risk of Hyperbilirubinemia (UGT1A1 *28/*28 Poor Metabolizer)

The genotype results predict a severely decreased UGT1A1 activity. The patient is expected to have a decreased capacity to conjugate bilirubin which is associated with mild hyperbilirubinemia. By inhibiting further UGT1A1 enzyme activity, erlotinib contributes to the increased susceptibility to unconjugated hyperbilirubinemia in subjects with this genotype. Consider prescribing erlotinib at standard doses and with caution. Monitor closely the patient for signs of hyperbilirubinemia.

Fluorouracil (Adrucil (iv); Carac (topical); Efudex (topical))

Evidence Level: **Actionable**

Normal risk for fluoropyrimidine toxicity (DPYD *1/*1 Normal Metabolizer)

The genotype results predict that the patient has a normal Dihydropyrimidine dehydrogenase (DPD) activity. Unless other genetic, environmental, or other risk factors are present, the patient does not have an increased risk for dosedependent fluorouracil toxicity; this genotype however, does not completely exclude toxicities from this drug. Use labelrecommended dosage and administration, and titrate the drug according to the patient's response.

Gefitinib (Iressa)

Evidence Level: **Actionable**

Normal Exposure to Gefitinib (CYP2D6 *4/*9 Intermediate Metabolizer)

Gefitinib undergoes extensive hepatic metabolism in humans by CYP3A4 and CYP2D6. CYP2D6 metabolizes gefitinib to its major active metabolite, Odesmethyl gefitinib. The patient's genotype predicts a normal exposure to gefitinib. Gefitinib can be prescribed at labelrecommended dosage and administration.

Irinotecan (Camptosar)

Evidence Level: **Actionable**

Increased risk for irinotecan toxicity (UGT1A1 *28/*28 Poor Metabolizer)

The genotype results predict that the patient has a decreased UGT1A1 activity at 30% of normal, and will likely have impaired elimination of active and toxic irinotecan metabolite SN38. The patient has a high risk of neutropenia, diarrhea, and asthenia when treated with moderate or high doses of irinotecan. Dose decreases as well as delayed treatment in subsequent cycles may be needed.

Doses < 180 mg/m2
No changes in dosing recommended. Use labelrecommended dosage and administration and titrate the drug according to the patient's tolerance to treatment.

Doses between 180 mg/m2 and 230 mg/m2
Irinotecan doses may be associated with a significant increase in toxicity risk. **Dose reduction up to 30% can be considered** in these patients depending upon the degree of hematological toxicity, nausea and diarrhea.

Doses >240 mg/m2
Not recommended in this patient.

Irinotecan liposomal (Onivyde)

Evidence Level: **Actionable**

Increased Risk of Irinotecan Liposomal (Onivyde) Toxicity (UGT1A1 *28/*28 Poor Metabolizer)

The patient carries two decreased function alleles and has decreased UGT1A1 activity (30% of normal). The patient has an increased risk of neutropenia, diarrhea, and asthenia when treated with standard doses of irinotecan liposomal (Onivyde). Patient should be monitored closely for any of these signs. **Consider a lower starting dose of 50 mg/m2 in patients who are homozygous for UGT1A1 *28 allele (or homozygous for other decreased function alleles such as *6, *27, *37).**

Onivyde, a liposomal formulation of irinotecan, cannot substitute for other drugs containing irinotecan.

Mercaptopurine (Purinethol, Purixan)

Evidence Level: **Actionable**

Normal risk for myelotoxicity (TPMT *1/*1 Normal Metabolizer)

The genotype results predict that the patient has a normal TPMT activity. Start with normal starting dose (e.g., 75 mg/m2 /d or 1.5 mg/kg/d), and adjust doses without any special emphasis on mercaptopurine compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.

Nilotinib (Tasigna)

Evidence Level: **Actionable**

Increased risk of hyperbilirubinemia (UGT1A1 *28/*28 Poor Metabolizer)

Carriers of UGT1A1 alleles that reduce enzyme activity are expected to have a decreased capacity to conjugate bilirubin which is associated with mild hyperbilirubinemia. By inhibiting further UGT1A1 enzyme activity, nilotinib contributes to the increased susceptibility to unconjugated hyperbilirubinemia in subjects carrying reduced UGT1A1 function alleles. Monitor serum liver tests (ALT, AST, and bilirubin) more carefully. Nilotinib dose can be adjusted based on bilirubin levels.

Paclitaxel (Taxol, Abraxane)

Evidence Level: **Actionable**

Normal risk for peripheral neuropathy (CYP2C8 *1A/*1A Normal Metabolizer)

Unless other genetic and non genetic factors are present, the genotype results predict that the patient has normal CYP2C8mediated paclitaxel metabolism and typical risk for paclitaxelinduced
peripheral neuropathy. Use labelrecommended dosage and administration and follow standard precautions for monitoring the risk of peripheral neuropathy.

Pazopanib (Votrient)

Evidence Level: **Actionable**

Increased risk of hyperbilirubinemia (UGT1A1 *28/*28 Poor Metabolizer)

Carriers of UGT1A1 alleles that reduce enzyme activity are expected to have a decreased capacity to conjugate bilirubin which is associated with mild hyperbilirubinemia. By inhibiting further UGT1A1 enzyme activity, pazopanib contributes to the increased susceptibility to unconjugated hyperbilirubinemia in subjects carrying reduced UGT1A1 function alleles. Monitor serum liver tests (ALT, AST, and bilirubin) more carefully. Dose can be adjusted based on bilirubin levels.

Thioguanine (Tabloid)

Evidence Level: **Actionable**

Normal risk for myelotoxicity (TPMT *1/*1 Normal Metabolizer)

The genotype results predict that the patient has a normal TPMT activity. Start with the normal starting dose. Adjust doses of thioguanine, and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady state after each dose adjustment.

TEST DETAILS FOR: FREDRICK SANGER

Gene	Genotype	Phenotype	Alleles Tested
CYP2C8	*1A/*1A	Normal Metabolizer	*2, *3, *4
CYP2D6	*4/*9	Intermediate Metabolizer	*2, *4, *4M, *6, *9, *10, *11, *12, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication)
DPYD	*1/*1	Normal Metabolizer	*2A, *9A, *9B, rs67376798 A, *13
TPMT	*1/*1	Normal Metabolizer	*2, *3A, *3B, *3C, *4
UGT1A1	*28/*28	Poor Metabolizer	*6, *27, *28

Disclaimer: Only a physician, pharmacist or other healthcare professional should advise a patient on the use of information in this report.
Methodology: Array based assays detect listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Limitations: This test will not detect all the known mutations that result in altered or inactive tested genes. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has intermediate or high sensitivity phenotypes due to the presence of an undetected polymorphism or due to drugdrug interactions.

Laboratory Certification: CLIA #11D2071408