

Perform genotyping at least 48h before treatment start.

DPYD risk variant	Effect
c.1129-5923C>A G(rs75017182, c.1236G>A/HapB3)	Decreased function allele (Affects mRNA splicing)
c.2846A>T (rs67376798)	Decreased function allele (Affects co-factor binding Asp949Val)
c.1679T>G (rs55886062)	Nonfunctional allele (Affects protein stability Ile560Ser)
c.1905+1G>A (rs3918290)	Nonfunctional allele (Affects mRNA splicing)

DPYD risk variant carrier

No risk variant carrier

DPYD risk variant	Dose adjustment
One DPYD risk allele e.g. c.2846A>T/= or c.1905+1G>A/=	50% of standard Dose
Two decreased function alleles e.g. c.2846A>T/c.2846A>T or c.1129-5923C>G/c.2846A>T	25% of standard Dose
One decreased function and one nonfunctional allele e.g. c.1905+1G>A/c.1129-5923C>G or c.2846A>T/c.1679T>G	No FP-chemotherapy recommended
Two nonfunctional alleles eg. c.1905+1G>A/c.1905+1G>A or c.1679T>G/c.1905+1G>A	No FP-chemotherapy recommended

DPYD risk variant	Dose adjustment
No DPYD risk allele	100% of standard dose

Use infusional 5-FU instead of Capecitabine if possible.
Start treatment with genotype-adjusted dose.

Treat following cycles according to standard care.

Capecitabine

5-FU

Titrate treatment to toxicity to avoid underdosing

5-FU TDM

Pre-analytical considerations
Suitable time windows for blood collection: a) 24h infusion : 18-20h after start of infusion b) 48h infusion: 18-42 h after start of infusion c) 7 days infusion: 18-48h after start of infusion
The 5-FU infusion pump must not be empty, otherwise incorrectly low 5-FU concentrations will be measured (The 5-FU half-life is only about 20min!)
The blood samples must be mixed with a 5-FU stabilizer immediately after collection, mix well.
Any irregularities during infusion which could lead to incorrectly low 5-FU concentrations (e.g. infusion rate slowed down, infusion paused) should be reported.

5-FU AUC (mg*h/L)	Dose adjustment in the next cycle in %
> 40	30% lower
37 - 39	25 % lower
34 - 36	20% lower
31 - 33	10 % lower
20 - 30	No change required
17 - 19	10% higher
14 - 16	20% higher
08 - 13	25 % higher
< 8	Repeat the previous dose to exclude possible pre-analytical errors. If repeated AUC < 8 : Dose adjustment: 30% higher