

## Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency – Summary of Pre-treatment Dosing Recommendations

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April 2023

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## **Functional Status of DPYD Variant Alleles**

Table 1 – Reduction in DPD activity associated with known *DPYD* variants

| DPYD Variant*  | Activity<br>Score** | Functional<br>Status <sup>3</sup> *** | Reduction in DPD Enzymatic Activity – Heterozygous carriers <sup>3</sup> | Reduction in DPD Enzymatic Activity – Homozygous carriers <sup>11</sup> |
|--|---------------------|---------------------------------------|--|---|
| Wild-type e.g. c.1627A>G (DPYD*5) c.85T>C (DPYD*9A)  | 1                   | Normal activity                       | None   | None  |
| <b>c.2846A&gt;T</b> (D949V, rs67376798)  | 0.5                 | Decreased activity                    | 30%  | 50%   |
| c.1236G>A<br>(rs56038477, E412E);<br>same variant as<br>c.1129-5923C>G<br>(rs75017182)<br>haplotype B3 (HapB3) | 0.5                 | Decreased<br>activity                 | 35%  | 20-70%  |
| c.1905+1G>A<br>( <i>DPYD</i> *2A,<br>IVS14+1G>A,<br>rs3918290)   | 0                   | No activity                           | 50%  | 100%  |
| <b>c.1679T&gt;G (</b> <i>DPYD</i> * <b>13</b> , 1560S, rs55886062)   | 0                   | No activity                           | 68%  | 75%   |

<sup>\*</sup>Various versions of nomenclature are used for *DPYD* variants; the most commonly used are bolded



<sup>\*\*</sup> Individual variant allele activity scores; see Appendix 2 for a definition of Activity Score

<sup>\*\*\*</sup>Variant allele definitions and assignment of allele function can be found in the *DPYD* Allele Functionality Table (<a href="https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/">https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/</a>)

## **Genotype-Guided Dosing Recommendations for Planned Fluoropyrimidine Treatment**

Table 2 – Initial Genotype-Guided Fluoropyrimidine Dosing Recommendations by DPYD Variant

| DPYD Variant 1              | DPYD Variant 2                       | Activity<br>Score <sup>a</sup> | <i>DPYD</i> Metabolizer <sup>b</sup> | Starting Dose Recommendation <sup>c</sup>   |
|-----------------------------|--------------------------------------|--------------------------------|--------------------------------------|---|
| any normal function variant | any normal function variant          | 2                              | Normal                               | No dose adjustment  |
| c.1905+1G>A (*2A)           | any normal function variant          | 1                              | Intermediate                         | Reduce <sup>c</sup> starting dose by 50%  |
| c.1905+1G>A (*2A)           | c.1905+1G>A (*2A)                    | 0                              | Poor                                 | Avoid use of 5-FU or 5-FU prodrug-based regimens.   |
| c.1905+1G>A (*2A)           | c.1129-5923C>G,<br>c.1236G>A (HapB3) | 0.5                            | Poor                                 | Avoid use of 5-FU or 5-FU prodrug-based regimens.  If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring |
| c.1905+1G>A (*2A)           | c.1679T>G (*13)                      | 0                              | Poor                                 | Avoid use of 5-FU or 5-FU prodrug-based regimens.   |
| c.1905+1G>A (*2A)           | c.2846A>T                            | 0.5                            | Poor                                 | Avoid use of 5-FU or 5-FU prodrug-based regimens.  If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring |
| c.1679T>G (*13)             | any normal function variant          | 1                              | Intermediate                         | Reduce <sup>d</sup> starting dose by 50%  |
| c.1679T>G (*13)             | c.1679T>G (*13)                      | 0                              | Poor                                 | Avoid use of 5-FU or 5-FU prodrug-based regimens.   |



| DPYD Variant 1                       | DPYD Variant 2                       | Activity<br>Score <sup>a</sup> | <i>DPYD</i><br>Metabolizer <sup>b</sup> | Starting Dose Recommendation <sup>c</sup>   |
|--------------------------------------|--------------------------------------|--------------------------------|---|---|
| c.1679T>G (*13)                      | c.1129-5923C>G,<br>c.1236G>A (HapB3) | 0.5                            | Poor                                    | Avoid use of 5-FU or 5-FU prodrug-based regimens.  If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring |
| c.1679T>G (*13)                      | c.2846A>T                            | 0.5                            | Poor                                    | Avoid use of 5-FU or 5-FU prodrug-based regimens.  If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring |
| c.1129-5923C>G,<br>c.1236G>A (HapB3) | any normal function variant          | 1.5                            | Intermediate                            | Reduce <sup>d</sup> starting dose by 50%  |
| c.1129-5923C>G,<br>c.1236G>A (HapB3) | c.1129-5923C>G,<br>c.1236G>A (HapB3) | 1                              | Intermediate                            | Reduce <sup>d</sup> starting dose by 50%  |
| c.1129-5923C>G,<br>c.1236G>A (HapB3) | c.2846A>T                            | 1                              | Intermediate                            | Reduce <sup>d</sup> starting dose by 50%  |
| c.2846A>T                            | any normal function variant          | 1.5                            | Intermediate                            | Reduce <sup>d</sup> starting dose by 50%  |
| c.2846A>T                            | c.2846A>T                            | 1                              | Intermediate                            | Reduce <sup>d</sup> starting dose by 50% <sup>e</sup>   |

<sup>&</sup>lt;sup>a</sup> Activity score is calculated as the sum of the two individual variant allele activity scores (1=fully functional, 0.5=reduced function, and 0=non-functional)

Adapted from the 2017 CPIC Guidelines and Supplementary Tables. **CPIC guidelines and content are subject to updates and modifications, refer to cpicpgx.org for most current content.** 



<sup>&</sup>lt;sup>b</sup> Likely phenotype; extent to which the variant alleles influence enzyme activity

<sup>&</sup>lt;sup>c</sup> For standard dosing of 5-FU or capecitabine. Excludes low (metronomic) dosing as this was not represented in studies; dose adjustments in these patients should be based on clinical judgement.

<sup>&</sup>lt;sup>d</sup> Followed by titration of dose based on toxicity. Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities.

e May require > 50% dose reduction in starting dose for carriers of this genotype, based on case reports

Initial Genotype-guided Fluoropyrimidine Dosing Recommendations by Hetero/Homozygous State

Table 3 - Initial Fluoropyrimidine Dosing Recommendations for <u>Heterozygous</u> Carriers of a *DPYD* Variant Allele<sup>a</sup>:

| DPYD Variant                      | Starting Dose Recommendation <sup>b</sup> |
|-----------------------------------|---|
| c.1905+1G>A (*2A)                 | Reduce <sup>c</sup> starting dose by 50%  |
| c.1679T>G (*13)                   | Reduce <sup>c</sup> starting dose by 50%  |
| c.1129-5923C>G, c.1236G>A (HapB3) | Reduce <sup>c</sup> starting dose by 50%  |
| c.2846A>T                         | Reduce <sup>c</sup> starting dose by 50%  |

Table 4 - Initial Fluoropyrimidine Dosing Recommendations for <u>Homozygous</u> Carriers of *DPYD* Variant Alleles:

| DPYD Variant                      | Starting Dose Recommendation <sup>b</sup>             |
|-----------------------------------|---|
| c.1905+1G>A (*2A)                 | Avoid use of 5-FU or 5-FU prodrug-based regimens.     |
| c.1679T>G (*13)                   | Avoid use of 5-FU or 5-FU prodrug-based regimens.     |
| c.1129-5923C>G, c.1236G>A (HapB3) | Reduce <sup>c</sup> starting dose by 50%              |
| c.2846A>T                         | Reduce <sup>c</sup> starting dose by 50% <sup>d</sup> |

<sup>&</sup>lt;sup>a</sup> Does not refer to carriers of compound or double heterozygous variant alleles.

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<sup>&</sup>lt;sup>b</sup> For standard dosing of 5-FU or capecitabine. Excludes low (metronomic) dosing as this was not represented in studies; dose adjustments in these patients should be based on clinical judgement.

<sup>&</sup>lt;sup>c</sup> Followed by titration of dose based on toxicity. Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities.

<sup>&</sup>lt;sup>d</sup> May require > 50% dose reduction in starting dose for carriers of this genotype, based on case reports