**Supplementary Material**

# Monitoring of Dabrafenib and Trametinib in serum and self-sampled capillary blood in patients with BRAFV600-mutant melanoma

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**Supplementary Table S1. Characteristics of serum samples**

| Sample characteristic | No. of samples (patients) | % |
|---|---|---|
| **Total** | | |
| **(Hydroxy-)Dabrafenib** | **278 (27)** | 100 |
| included samples | 277 | 99.6 |
| excluded samples < LLOQ[a] | 1[b] | 0.4 |
| **Trametinib** | **266 (27)** | |
| included samples | 265 | 99.6 |
| excluded samples < LLOQ | 1[c] | 0.4 |
| **Samples / patient, median (range)** | | |
| **(Hydroxy-)Dabrafenib** | 10 (1 – 22) | |
| **Trametinib** | 8 (1 – 22) | |
| **(Hydroxy-)Dabrafenib**[d] | | |
| 150 mg q12h | 270 (27) | 97.5 |
| steady state samples | 267 (27) | 98.9 |
| *0-5 h post-dose* | 105 (17) | 39.3 |
| *5-10 h post-dose* | 27 (10) | 10.1 |
| *10-14 h post-dose* | 101 (16) | 37.8 |
| *> 14 h post-dose* | 34 (14) | 12.7 |
| non steady state samples | 3 (3) | 1.1 |
| 100 mg q12h | 7 (2) | 2.5 |
| steady state samples | 7 (2) | 2.5 |
| non steady state samples | 0 | |
| **Trametinib**[e] | | |
| 2 mg q24h | 214 (24) | 80.8 |
| steady state samples | 211 (24) | 98.6 |
| *0-10 h post-dose* | 61 (14) | 28.9 |
| *10-20 h post-dose* | 34 (7) | 16.1 |
| *20-30 h post-dose* | 115 (19) | 54.5 |
| *> 30 h post-dose* | 1 (1) | 0.5 |
| non steady state samples | 3 (3) | 1.4 |
| 1,5 mg q24h | 22 (2) | 8.3 |
| steady state samples | 22 (2) | 8.3 |
| *0-10 h post-dose* | 19 (2) | 86.4 |
| *10-20 post-dose* | 1 (1) | 4.6 |
| *20-30 h post-dose* | 2 (1) | 9.1 |
| *> 30 h post-dose* | 0 | |
| non steady state samples | 0 | |
| 1 mg q24h | 28 (5) | 11.0 |
| steady state samples | 28 (5) | 11.0 |
| *0-10 h post-dose* | 17 (4) | 60.7 |
| *10-20 post-dose* | 1 (1) | 3.6 |
| *20-30 h post-dose* | 10 (3) | 35.7 |
| *> 30 h post-dose* | 0 | |
| non steady state samples | 0 | |

a LLOQ, lower limit of quantification (6 ng/mL for dabrafenib, 10 ng/mL for hydroxy-dabrafenib, 2 ng/mL for trametinib)

b sample collected at 75 mg 12 h post-dose

c sample collected at 2 mg 30 min post-dose

d steady state assumed after continuous dosing for 14 days

e steady state assumed after continuous dosing for 14 days

**Supplementary Table S2. Characteristics of VAMS samples**

| Sample characteristic | No. of samples (patients) | % |
|---|---|---|
| **Total** | | |
| **Dabrafenib** | **169 (18)** | |
| at-home samples | 83 (9) | 49.1 |
| clinic samples | 86 (18) | 50.9 |
| included samples | 169 | 100 |
| excluded samples < LLOQ | 0 | 0 |
| excluded samples due to incorrect sampling | 8 | 4.7 |
| **Trametinib** | **158 (18)** | |
| at-home samples | 76 (8) | 48.1 |
| clinic samples | 82 (18) | 51.9 |
| included samples | 158 | 100 |
| excluded samples < LLOQ | 0 | 0 |
| excluded samples due to incorrect sampling | 8 | 5.1 |
| **Samples / patient, median (range)** | **6 (1 - 22)** | |
| **Dabrafenib** | | |
| 150 mg q12h | | |
| steady state samples | 145 | |
| non steady state samples | 4 | |
| *0-5 h post-dose* | 64 | |
| *5-10 h post-dose* | 34 | |
| *10-14 h post-dose* | 45 | |
| *> 14 h post-dose* | 7 | |
| 100 mg q12h | | |
| steady state samples | 16 | |
| non steady state samples | 0 | |
| *0.5 h post-dose* | 4 | |
| *5-10 h post-dose* | 5 | |
| *10-14 h post-dose* | 7 | |
| | | |
| **Trametinib** | | |
| 2 mg q24h | | |
| steady state samples | 116 | |
| non steady state samples | 0 | |
| *0-10 h post-dose* | 47 | |
| *10-20 h post-dose* | 41 | |
| *20-30 h post-dose* | 28 | |
| 1.5 mg q24h | | |
| steady state samples | 22 | |
| non steady state samples | 0 | |
| *0-10 h post-dose* | 17 | |
| *10-20 h post-dose* | 4 | |
| *20-30 h post-dose* | 1 | |
| 1 mg q24h | | |
| steady state samples | 16 | |
| non steady state samples | 4 | |
| *0-10 h post-dose* | 6 | |
| *10-20 h post-dose* | 11 | |
| *20-30 h post-dose* | 3 | |

**Supplementary Table S3. Steady state dabrafenib serum concentrations of all samples across all individuals**

| Dosing | time interval post-dose | per patient mean steady state dabrafenib serum concentration [ng/mL] | | | | number of patients contributing samples | number of samples* | samples per patient | |
|---|---|---|---|---|---|---|---|---|---|
| | | median | mean | IQR | SD | | | median | range |
| 100 mg q12h | 0-5 h | 307.50 | 307.50 | 137.50 | 194.45 | 2 | 2 (0) | 1 per patient | |
| | 10-14 h | 13.99 | 13.99 | | | 1 | 5 (0) | all from 1 patient | |
| 150 mg q12h | 0-5 h | 844.38 | 1070.05 | 703.67 | 585.44 | 17 | 105 (0) | 5 | 1-18 |
| | 5-10 h | 260.75 | 268.69 | 194.55 | 188.77 | 10 | 27 (0) | 2 | 1-7 |
| | 10-14 h | 45.03 | 58.00 | 24.95 | 40.26 | 16 | 101 (0) | 4.5 | 1-18 |
| | > 14h | 39.45 | 70.78 | 40.66 | 109.68 | 14 | 34 (0) | 1 | 1-7 |

* no sample was < LLOQ (6 ng/mL)

**Supplementary Table S4. Steady state hydroxy-dabrafenib serum concentrations of all samples across all individuals**

| Dosing | time interval post-dose | per patient mean steady state hydroxy-dabrafenib serum concentration [ng/mL] | | | | number of patients contributing samples | number of samples (n < LLOQ) | samples per patient | |
|---|---|---|---|---|---|---|---|---|---|
| | | median | mean | IQR | SD | | | median | range |
| 100 mg q12h | 0-5 h | 341.59 | 341.59 | 218.87 | 309.53 | 2 | 2 (0) | 1 per patient | |
| | 10-14 h | 37.21 | 37.21 | | | 1 | 5 (0) | all from 1 patient | |
| 150 mg q12h | 0-5 h | 973.74 | 1210.67 | 753.64 | 780.51 | 17 | 105 (0) | 5 | 1-18 |
| | 5-10 h | 387.57 | 533.49 | 194.88 | 554.28 | 10 | 27 (0) | 2 | 1-7 |
| | 10-14 h | 76.01 | 87.26 | 51.43 | 39.68 | 16 | 101 (1) | 4.5 | 1-18 |
| | > 14 h | 59.63 | 166.26 | 32.94 | 400.91 | 14 | 34 (0) | 1 | 1-7 |

**Supplementary Table S5. Steady state trametinib serum concentrations of all samples across all individuals**

| Dosing | time interval post-dose | per patient mean steady state trametinib serum concentration [ng/mL] | | | | number of patients contributing samples | number of samples (n < LLOQ) | samples per patient | |
|---|---|---|---|---|---|---|---|---|---|
| | | median | mean | IQR | SD | | | median | range |
| 1.0 mg q24h | 0-10 h | 10.75 | 10.96 | 3.33 | 4.06 | 4 | 17 (0) | 3 | 1-10 |
| | 10-20 h | 13.80 | 13.80 | | | 1 | 1 (0) | only 1 sample | |
| | 20-30 h | 5.89 | 6.06 | 0.56 | 0.58 | 3 | 10 (0) | 2 | 1-7 |
| 1.5 mg q24h | 0-10 h | 13.07 | 13.07 | 2.87 | 4.06 | 2 | 19 (0) | 9.5 | 1-18 |
| | 10-20 h | 8.92 | 8.92 | | | 1 | 1 (0) | only 1 sample | |
| | 20-30 h | 6.94 | 6.94 | | | 1 | 2 (0) | all samples from 1 patient | |
| 2 mg q24h | 0-10 h | 17.50 | 18.09 | 5.82 | 5.31 | 14 | 62 (1*) | | |
| | 10-20 h | 12.57 | 12.79 | 3.03 | 2.34 | 7 | 34 (0) | | |
| | 20-30 h | 11.19 | 10.75 | 2.40 | 2.13 | 19 | 115 (0) | | |

* sample was collected 30 min post dose

**Supplementary Table S6. Observed concentrations of dabrafenib, hydroxy-dabrafenib and trametinib vs. covariates**

| Compound | Covariate | groups | serum $C_{min}$ [ng/mL] median | IQR | mean | SD | n | p-value |
|---|---|---|---|---|---|---|---|---|
| Dabrafenib | sex | male | 39.3 | 24.3 | 36.5 | 15 | 9 | 0.174 |
| | | female | 52.9 | 77.8 | 75.5 | 48 | 7 | |
| | age above 65 | no | 43.5 | 19.6 | 54.9 | 37.3 | 9 | 1 |
| | | yes | 42.9 | 21.1 | 51.9 | 41.8 | 7 | |
| | BMI (kg/m$^2$) | < 30 | 42.9 | 21.4 | 46.5 | 34.4 | 11 | 0.377 |
| | | >= 30 | 54 | 76 | 69.1 | 44.8 | 5 | |
| | moderate CYP2C8 inhibitor | no | 44.3 | 28.7 | 58.9 | 49 | 9 | 0.689 |
| | | yes | 47.4 | 17.4 | 46.9 | 15 | 6 | |
| | P-gp inhibitor | no | 52.9 | 86.2 | 77.8 | 54.6 | 7 | 0.351 |
| | | yes | 41.8 | 9.9 | 42.4 | 13.8 | 9 | |
| | P-gp inducer | no | 48 | 38.3 | 60.9 | 46.1 | 10 | 0.594 |
| | | yes | 41.8 | 9.86 | 40.4 | 9.31 | 5 | |
| | PPI | no | 51.6 | 35.4 | 63.1 | 43.1 | 13 | 0.305 |
| | | yes | 32.4 | 9.42 | 32.4 | 13.3 | 2 | |
| Hydroxy-dabrafenib | sex | male | 72.9 | 38.7 | 77.3 | 41 | 9 | 0.837 |
| | | female | 68.3 | 37.5 | 86 | 44 | 7 | |
| | age above 65 | no | 77.6 | 69.7 | 92.7 | 47.7 | 9 | 0.252 |
| | | yes | 55.6 | 29.1 | 66.2 | 27 | 7 | |
| | BMI (kg/m$^2$) | < 30 | 72.9 | 35.9 | 73.6 | 32.6 | 11 | 0.583 |
| | | >= 30 | 68.3 | 86 | 97.6 | 56.5 | 5 | |
| | moderate CYP2C8 inhibitor | no | 78 | 46.2 | 89.4 | 45 | 9 | 0.864 |
| | | yes | 76.6 | 57 | 86.3 | 38 | 6 | |
| | P-gp inhibitor | no | 78 | 53.8 | 100 | 44.9 | 7 | 0.351 |
| | | yes | 70.2 | 28 | 77.3 | 34.4 | 9 | |
| | P-gp inducer | no | 90.9 | 62.6 | 101 | 44.1 | 10 | 0.099 |
| | | yes | 56.6 | 19.5 | 62.1 | 14.3 | 5 | |
| | PPI | no | 78 | 65.7 | 93.1 | 41.1 | 13 | 0.171 |
| | | yes | 53.7 | 16.5 | 53.7 | 23.3 | 2 | |
| Trametinib | sex | male | 11.2 | 2.51 | 10.6 | 1.61 | 13 | 0.692 |
| | | female | 11.3 | 2.01 | 11.1 | 3.08 | 6 | |
| | age above 65 | no | 11.3 | 1.6 | 10.6 | 1.7 | 12 | 0.865 |
| | | yes | 10.9 | 2.88 | 10.9 | 2.81 | 7 | |
| | BMI | < 30 | 11.4 | 1.2 | 11.2 | 2.18 | 12 | 0.219 |
| | | >= 30 | 9.79 | 2.28 | 9.93 | 1.84 | 7 | |
| | P-gp inhibitor | no | 11.3 | 2.86 | 10.9 | 2.52 | 11 | 0.657 |
| | | yes | 10.9 | 1.85 | 10.5 | 1.59 | 8 | |
| | P-gp inducer | no | 11.7 | 0.95 | 11.5 | 1.81 | 11 | 0.027 |
| | | yes | 9.68 | 2.56 | 9.3 | 2.03 | 7 | |
| | PPI | no | 11.5 | 2.58 | 10.8 | 2.43 | 14 | 0.574 |
| | | yes | 10.9 | 1.1 | 10.7 | 1.22 | 4 | |

$C_{min}$, trough concentration; IQR, interquartile range; SD, standard deviation; BMI, body mass index; PPI, proton pump inhibitor

**Supplementary Table S7. Co-medication of all patients stratified by potential to induce or inhibit CYP3A4 or CYP2C8**

| Drug | CYP3A4 | Strength | CYP2C8 | Strength | Reference* |
|---|---|---|---|---|---|
| **Strong CYP3A4 or CYP2C8 inhibitors / inducers** | | | | | |
| Thiamazole | inhibitor | strong | - | - | (1) |
| **Moderate CYP3A4 or CYP2C8 inhibitors / inducers** | | | | | |
| Amlodipine | inhibitor | unknown | inhibitor | moderate | (1) |
| Clindamycin | inhibitor | moderate | - | - | (1) |
| Fluvastatin | inhibitor | unknown | inhibitor | moderate | (1) |
| Irbesartan | inhibitor | unknown | inhibitor | moderate | (1) |
| Levothyroxine | - | - | inhibitor | moderate | (1) |
| Spironolactone | - | - | inhibitor | moderate | (1) |
| **Weak CYP3A4 or CYP2C8 inhibitors / inducers** | | | | | |
| Candesartan | - | - | inhibitor | weak | (1) |
| Fenofibrate | - | - | inhibitor | weak | (1) |
| **CYP3A4 or CYP2C8 inhibitors / inducers of unknown strength** | | | | | |
| Atrovastatin | - | - | inhibitor | unknown | (1) |
| Hydrocortisone | inducer | unknown | inducer | unknown | (1) |
| Methylprednisolone | inducer | unknown | inducer | unknown | (1) |
| Omeprazole | inhibitor/inducer | unknown | - | - | (1) |
| Prednisolone | inducer | unknown | - | - | (1) |
| Prednisone | inducer | unknown | inducer | unknwon | (1) |
| Simvastatin | - | - | inhibitor | unknown | (1) |
| **Comedication without known effects on CYP3A4 or CYP2C8 metabolism** | | | | | |
| Acetylcysteine | - | - | - | - | (1) |
| Acetylsalicylic acid | - | - | - | - | (1) |
| Allopurinol | - | - | - | - | (1) |
| Amiloride | - | - | - | - | (1) |
| Bendroflumethiazide | - | - | - | - | (1) |
| Bisoprolol | - | - | - | - | (1) |
| Calcium | - | - | - | - | (1) |
| Calcium citrate | - | - | - | - | (1) |
| Carvedilol | - | - | - | - | (1) |
| Ceftriaxone | - | - | - | - | (1) |
| Clonidine | - | - | - | - | (1) |
| Denosumab | - | - | - | - | (1) |
| Digitoxin | - | - | - | - | (1) |
| Duasterid | - | - | - | - | (1) |
| Edoxaban | - | - | - | - | (1) |
| Enalapril | - | - | - | - | (1) |
| Estradiol | - | - | - | - | (1) |
| Hydrochlorothiazide | - | - | - | - | (1) |
| Ibuprofen | - | - | - | - | (1) |
| Ipilimumab | - | - | - | - | (1) |
| Iron | - | - | - | - | (1) |
| Lamotrigine | - | - | - | - | (1) |
| Levocetiricin | - | - | - | - | (1) |
| Levomepromazine | - | - | - | - | (1) |
| Lorazepam | - | - | - | - | (1) |
| Magnesium | - | - | - | - | (1) |
| Metformin | - | - | - | - | (1) |

| | | | | | |
|---|---|---|---|---|---|
| Metoprolol | - | - | - | - | (1) |
| Moxonidine | - | - | - | - | (1) |
| Mycophenolate mofetil | - | - | - | - | (1) |
| Nivolumab | - | - | - | - | (1) |
| Olmesartan | - | - | - | - | (1) |
| Omega 3 fatty acids | - | - | - | - | (1) |
| Pantoprazole | - | - | - | - | (1) |
| Penicillin | - | - | - | - | (1) |
| Phenprocoumon | - | - | - | - | (1) |
| Pravastatin | - | - | - | - | (1) |
| Quetiapine | - | - | - | - | (1) |
| Ramipril | - | - | - | - | (1) |
| Rivaroxaban | - | - | - | - | (1) |
| Selenium | - | - | - | - | (1) |
| Sitagliptin | - | - | - | - | (1) |
| Tacrolimus | - | - | - | - | (1) |
| Tamsulosin | - | - | - | - | (1) |
| Tilidin | - | - | - | - | (1) |
| Tiotropium | - | - | - | - | (1) |
| Torasemide | - | - | - | - | (1) |
| Triameteren | - | - | - | - | (1) |
| Trimipramine | - | - | - | - | (1) |
| Valsartan | - | - | - | - | (1) |
| Venlafaxine | - | - | - | - | (1) |
| Vitamin D3 | - | - | - | - | (1) |
| Vitamin E | - | - | - | - | (1) |
| Xipamide | - | - | - | - | (1) |

* (1) www.drugbank.ca

**Supplementary Table S8. Co-medication of all patients stratified by potential to induce or inhibit P-glycoprotein**

| Drug | Reference* |
|---|---|
| **P-glycoprotein inhibitors** | |
| Amlodipine | (1) |
| Atrovastatin | (1) |
| Bisoprolol | (1) |
| Candesartan | (1) |
| Carvedilol | (1) |
| Fluvastatin | (1) |
| Lamotrigine | (1) |
| Omeprazole | (1) |
| Simvastatin | (1) |
| Tacrolimus | (1,2,3) |
| Venlafaxine | (1) |
| **P-glycoprotein inducers** | |
| Acetylsalicylic acid | (1) |
| Hydrocortisone | (1) |
| Levothyroxine | (1) |
| Methylpredinsolone | (1) |
| Prednisolone | (1) |
| Spironolactone | (1) |
| **Co-medication without known effects on P-glycoprotein** | |
| Acetylcysteine | (1) |
| Allopurinol | (1) |
| Amiloride | (1) |
| Bendroflumethiazide | (1) |
| Calcium | (1) |
| Clindamycin | (1) |
| Clonidine | (1) |
| Denosumab | (1) |
| Digitoxin | (1) |
| Dutasterid | (1) |
| Edoxaban | (1) |
| Enalapril | (1) |
| Fenofibrate | (1) |
| Fluticasone | (1) |
| Formoterol | (1) |
| Hydrochlorothiazide | (1) |
| Ibuprofen | (1) |
| Ipilimumab | (1) |
| Irbesartan | (1) |
| Iron | (1) |
| Iron (II) glycine sulphate | (1) |
| Lacosamide | (1) |
| Levetiracetam | (1) |
| Levocetiricin | (1) |
| Levomepromazine | (1) |
| Lorazepam | (1) |
| Magnesium | (1) |
| Metformin | (1) |
| Metoprolol | (1) |
| Moxonidine | (1) |

| | |
|---|---|
| Mycophenolate mofetil | (1) |
| Nivolumab | (1) |
| Olmesartan | (1) |
| Omega 3 fatty acids | (1) |
| Pantoprazole | (1) |
| Penicillin | (1) |
| Phenprocoumon | (1) |
| Potassium | (1) |
| Potassium citrate | (1) |
| Pravastatin | (1) |
| Quetiapine | (1) |
| Ramipril | (1) |
| Rivaroxaban | (1) |
| Salmeterol | (1) |
| Selenium | (1) |
| Sitagliptin | (1) |
| Tamsulosin | (1) |
| Thiamazole | (1) |
| Tilidin | (1) |
| Tiotropium | (1) |
| Torasemide | (1) |
| Triamteren | (1) |
| Trimipramine | (1) |
| Valsartan | (1) |
| Vitamin D3 | (1) |
| Vitamin E | (1) |
| Xipamide | (1) |

* (1) www.drugbank.ca

(2) Saeki T, Ueda K, Tanigawara Y, Hori R, Komano T. Human P-glycoprotein transports cyclosporin A and FK506. J Biol Chem. 1993 Mar 25;268(9):6077-80. PMID: 7681059.

(3) Singh H, Agarwal V, Chaturvedi S, Misra DP, Jaiswal AK, Prasad N. Reciprocal Relationship Between HDAC2 and P-Glycoprotein/MRP-1 and Their Role in Steroid Resistance in Childhood Nephrotic Syndrome. Front Pharmacol. 2019 May 22;10:558. doi: 10.3389/fphar.2019.00558. PMID: 31191307; PMCID: PMC6540828

**Supplementary Table S9. Error metrics for the individual predictions using empirical Bayesian estimates**

| Compound | MPE [%] | MAPE [%] | MRD |
|---|---|---|---|
| Dabrafenib | -5.45 | 23.68 | 1.34 |
| Hydroxy-Dabrafenib | 26.76 | 43.8 | 1.60 |
| Trametinib | 3.9 | 15.5 | 1.23 |

**Supplementary Table S10. Summarized MAP estimates for $AUC_\tau$ and trough concentrations of dabrafenib and hydroxy-dabrafenib**

| ID | pause / dose reduction / discontinuation due to AE | average predicted DAB $AUC_\tau$ [ng·h /mL] 150mg q12h | average predicted OH-DAB $AUC_\tau$ [ng·h /mL] 150mg q12h | sum of predicted $AUC_\tau$ | average predicted DAB $C_{min}$ [ng/mL] 150mg q12h | average observed DAB $C_{min}$ [ng/mL] | average predicted OH-DAB $C_{min}$ [ng/mL] 150mg q12h | average observed OH-DAB $C_{min}$ [ng/mL] | sum of observed $C_{min}$ [ng/mL] |
|---|---|---|---|---|---|---|---|---|---|
| DT001 | | 5296 | 5450 | 10746 | 29.10 | 28.7 | 62.00 | 50.61 | 79.31 |
| DT002 | | 7809 | 4090 | 11899 | 121.36 | 115.2 | 82.73 | 74.02 | 189.22 |
| DT003 | | 6002 | 6200 | 12202 | 37.30 | 41.4 | 78.30 | 78.98 | 120.38 |
| DT004 | | 5676 | 5750 | 11426 | 41.42 | 41.8 | 82.08 | 70.16 | 111.96 |
| DT005 | | 6240 | 17810 | 24050 | 51.85 | - | 510.00 | - | |
| DT006 | | 6478 | 8210 | 14688 | 54.00 | 54.0 | 156.00 | 141.56 | 195.56 |
| DT007 | p | 10535 | 11930 | 22465 | 183.21 | - | 362.14 | - | |
| DT008 | d | 4720 | 6040 | 10760 | 20.50 | - | 67.50 | - | |
| DT009 | r | 4460 | 5040 | 9500 | 39.50 | 20.0 | 84.50 | 72.90 | 92.90 |
| DT010 | | 3610 | 4480 | 8090 | 14.12 | - | 36.55 | - | |
| DT011 | d | 8304 | 5250 | 13554 | 120.63 | 154.7 | 110.13 | 102.80 | 257.50 |
| DT012 | | 5423 | 4370 | 9793 | 36.06 | 45.8 | 51.00 | 56.61 | 102.41 |
| DT013 | | 6974 | 7800 | 14774 | 63.25 | - | 137.50 | - | |
| DT014 | | 3145 | 2490 | 5635 | 50.69 | 23.0 | 46.10 | 37.19 | 60.19 |
| DT015 | | 6371 | 6800 | 13171 | 67.71 | 69.8 | 128.43 | 122.33 | 192.13 |
| DT017 | | 6027 | 6930 | 12957 | 40.64 | - | 101.73 | - | |
| DT018 | | 5944 | 5500 | 11444 | 42.00 | - | 78.59 | - | |
| DT019 | | 5709 | 5590 | 11299 | 46.04 | 44.3 | 92.05 | 55.16 | 99.46 |
| DT020 | | 5796 | 6820 | 12616 | 28.50 | 34.4 | 80.40 | 83.13 | 117.53 |
| DT021 | d | 3245 | 6320 | 9565 | 10.50 | 5.5 | 62.50 | 15.36 | 20.86 |
| DT022 | | 5100 | 4180 | 9280 | 78.63 | 20.8 | 61.75 | 78.00 | 98.80 |
| DT023 | | 8331 | 7890 | 16221 | 119.69 | 129.6 | 197.69 | 170.93 | 300.53 |
| DT024 | | 6400 | 4330 | 10730 | 45.00 | 52.9 | 53.00 | 50.08 | 102.98 |
| DT025 | | 3608 | 5860 | 9468 | 30.00 | - | 97.00 | - | |
| DT026 | r | 4999 | 6440 | 11439 | 32.00 | 14.0 | 88.57 | 37.21 | 51.21 |
| DT027 | | 6350 | 8540 | 14890 | 42.29 | 51.7 | 141.43 | 151.71 | 203.41 |
| DT028 | | 8566 | 9380 | 17946 | 298.00 | - | 468.00 | - | |

DAB, dabrafenib; OH-DAB, hydroxy-dabrafenib

**Supplementary Table S11. Summarized MAP estimates for $AUC_\tau$ and trough concentrations of trametinib**

| ID | pause / dose reduction / discontinuation due to AE | predicted $AUC_\tau$ [ng ·h /mL] 2 mg q24h | predicted $C_{min}$ [ng/mL] 2 mg q24h | average observed $C_{min}$ [ng/mL] |
|---|---|---|---|---|
| DT001 | | 313.09 | 10.51 | 10.1 |
| DT002 | | 358.36 | 12.66 | 12.6 |
| DT003 | | 287.59 | 9.53 | 11.2 |
| DT004 | r | 326.00 | 11.51 | 11.8 |
| DT005 | d | 546.25 | 20.17 | - |
| DT006 | | 334.62 | 11.67 | 11.9 |
| DT007 | | 331.39 | 11.54 | - |
| DT008 | d | 326.05 | 11.36 | 9.2 |
| DT009 | r | 342.83 | 12.02 | 11.9 |
| DT010 | | 300.6 | 10.34 | 9.1 |
| DT011 | d | 442.00 | 15.76 | 15.9 |
| DT012 | | 228.19 | 7.27 | 7.2 |
| DT013 | | 450.43 | 16.60 | - |
| DT014 | | 325.51 | 11.37 | 10.7 |
| DT015 | | 337.89 | 11.81 | 11.8 |
| DT017 | r | 399.45 | 14.43 | 6.7 |
| DT018 | r | 252.2 | 8.43 | 7.7 |
| DT019 | r | 335.72 | 11.53 | 6.9 |
| DT020 | r | 339.07 | 11.90 | 5.6 |
| DT021 | d | 327.27 | 11.37 | 11.2 |
| DT022 | | 343.38 | 12.04 | 12.1 |
| DT023 | | 349.24 | 11.79 | 11.3 |
| DT024 | | 247.34 | 8.06 | 6.2 |
| DT025 | | 371.33 | 13.00 | - |
| DT026 | | 303.18 | 9.09 | 9.7 |
| DT027 | | 304.02 | 10.39 | 11.7 |
| DT028 | | 251.78 | 8.35 | - |

**Supplementary Table S12. Clinical adverse events documented at least once**

| | No. of patients (%) | | | | |
|---|---|---|---|---|---|
| Max. CTCAE grade per patient | 0 | 1 | 2 | 3 | ≥ 4 |
| Abdominal pain | 23 (85.2) | 4 (14.8) | | | |
| Arthralgia | 21 (77.8) | 6 (22.2) | | | |
| Asthenia | 25 (92.6) | 1 (3.7) | 1 (3.7) | | |
| Bradycardia | 26 (96.3) | 1 (3.7) | | | |
| Cephalgia | 24 (88.9) | 3 (11.1) | | | |
| Constipation | 25 (92.6) | 2 (7.4) | | | |
| Cough | 21 (77.8) | 6 (22.2) | | | |
| Diarrhoea | 21 (77.8) | 5 (18.5) | | 1 (3.7) | |
| Dry skin | 19 (70.4) | 7 (25.9) | 1 (3.7) | | |
| Dysgeusia | 26 (96.3) | 1 (3.7) | | | |
| Dyspnea | 20 (74.1) | 7 (25.9) | | | |
| Edema | 22 (81.5) | 5 (18.5) | | | |
| Fatigue | 20 (74.1) | 5 (18.5) | 2 (7.4) | | |
| Flatulence | 26 (96.3) | 1 (3.7) | | | |
| Flu-like symptoms | 17 (63.0) | 9 (33.3) | 1 (3.7) | | |
| Folliculitis / cellulitis | 25 (92.6) | 2 (7.4) | | | |
| Hair loss | 25 (92.6) | 2 (7.4) | | | |
| Impaired vision | 26 (96.3) | 1 (3.7) | | | |
| Loss of appetite | 22 (81.5) | 5 (18.5) | | | |
| Muscle cramps | 25 (92.6) | 2 (7.4) | | | |
| Myalgia | 17 (63.0) | 10 (37.0) | | | |
| Nail dystrophy | 25 (92.6) | 2 (7.4) | | | |
| Nausea | 20 (74.1) | 6 (22.2) | 1 (3.7) | | |
| Neoplasms of the skin | 24 (88.9) | 3 (11.1) | | | |
| Paronchyia | 26 (96.3) | 1 (3.7) | | | |
| Parotitis | 26 (96.3) | 1 (3.7) | | | |
| Pruritus | 20 (74.1) | 6 (22.2) | 1 (3.7) | | |
| Pyrexia | 22 (81.5) | 4 (14.8) | | 1 (3.7) | |
| Reduced LVEF | 21 (77.8) | 5 (18.5) | 1 (3.7) | | |
| Skin rash | 22 (81.5) | 5 (18.5) | | | |
| Stomatitis | 26 (96.3) | 1 (3.7) | | | |
| Urinary tract infection | 26 (96.3) | | 1 (3.7) | | |
| Vertigo | 25 (92.6) | 2 (7.4) | | | |
| Vomiting | 24 (88.9) | 2 (7.4) | 1 (3.7) | | |
| Weight gain | 25 (92.6) | 1 (3.7) | 1 (3.7) | | |
| Weight loss | 25 (92.6) | 2 (7.4) | | | |
| Xerostomia | 24 (88.9) | 3 (11.1) | | | |

CTCAE, Common Terminology Criteria for Adverse Events; LVEF, left ventricular ejection fraction

**Supplementary Table S13. Laboratory adverse events documented at least once**

| | No. of patients (%) | | | | |
|---|---|---|---|---|---|
| Max. CTCAE grade per patient | 0 | 1 | 2 | 3 | ≥ 4 |
| Alkaline phosphatase elevated | 9 (33.3) | 16 (59.3) | 2 (7.4) | | |
| ALT elevated | 23 (85.2) | 4 (14.8) | | | |
| Anemia | 4 (14.8) | 21 (77.8) | 2 (7.4) | | |
| AST elevated | 20 (74.1) | 6 (22.2) | 1 (3.7) | | |
| Bilirubin elevated | 26 (96.3) | 1 (3.7) | | | |
| Creatine phosphokinase elevated | 7 (25.9) | 11 (40.7) | 5 (18.5) | 4 (14.8) | |
| creatinine elevated | 15 (55.6) | 12 (44.4) | | | |
| Gamma glutamyl transferase elevated | 21 (77.8) | 3 (11.1) | 1 (3.7) | 2 (7.4) | |
| Hyponatremia* | 20 (74.1) | 6 (22.2) | | | |
| Leucopenia | 12 (44.4) | 12 (44.4) | 1 (3.7) | 2 (7.4) | |
| Lipase elevated | 13 (48.1) | 9 (33.3) | | 5 (18.5) | |
| Lymphopenia* | 14 (51.9) | 3 (11.1) | 7 (25.9) | 2 (7.4) | |
| Neutropenia | 20 (74.1) | 4 (14.8) | 2 (7.4) | 1 (3.7) | |
| Thrombocytopenia | 25 (92.6) | 2 (7.4) | | | |

ALT, alanine aminotransferase; AST, aspartate aminotransferase

* data not available for one patient

**Supplementary Table S14. Dose reductions and treatment discontinuations**

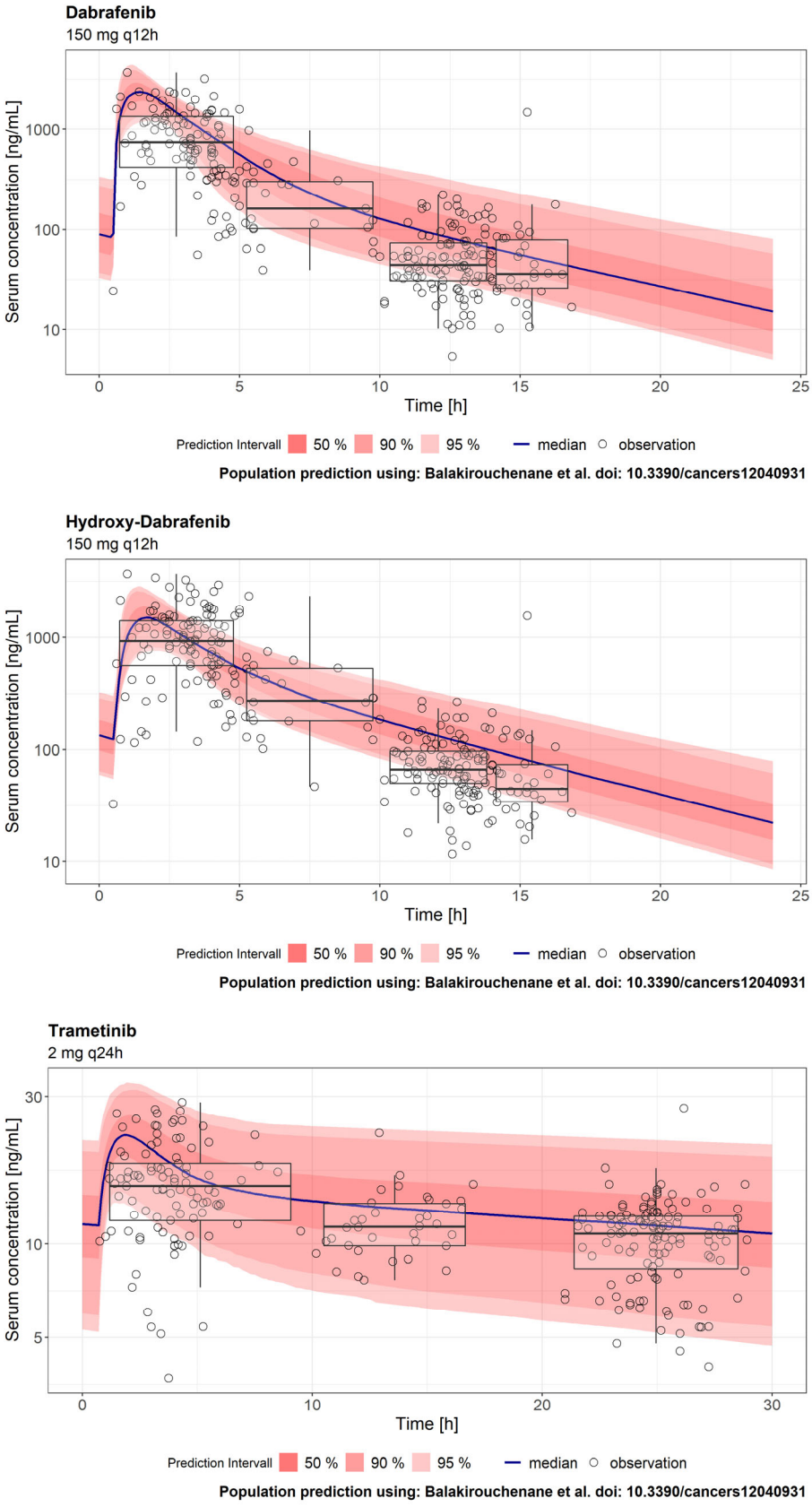
| | permanent treatment discontinuation n (%) | | temporary treatment discontinuation n (%) | | dose reduction n (%) | |
|---|---|---|---|---|---|---|
| | dabrafenib | trametinib | dabrafenib | trametinib | dabrafenib | trametinib |
| none | 19 (70.4) | 18 (66.7) | 17 (63.0) | 17 (63.0) | 24 (88.9) | 21 (77.8) |
| adverse events | 2 (7.4)* | 3 (11.1)* | 3+3** (22.2) | 4+4*** (29.6) | 2+1 (11.1) | 1+5 (22.2) |
| end of adjuvant therapy | 3 (11.1) | 3 (11.1) | - | - | - | - |
| other reason | 3 (11.1) | 3 (11.1) | 4** (14.8) | 2 (7.4) | - | - |

* two patients had permanent treatment discontinuation of dabrafenib *and* trametinib, one patient only of trametinib

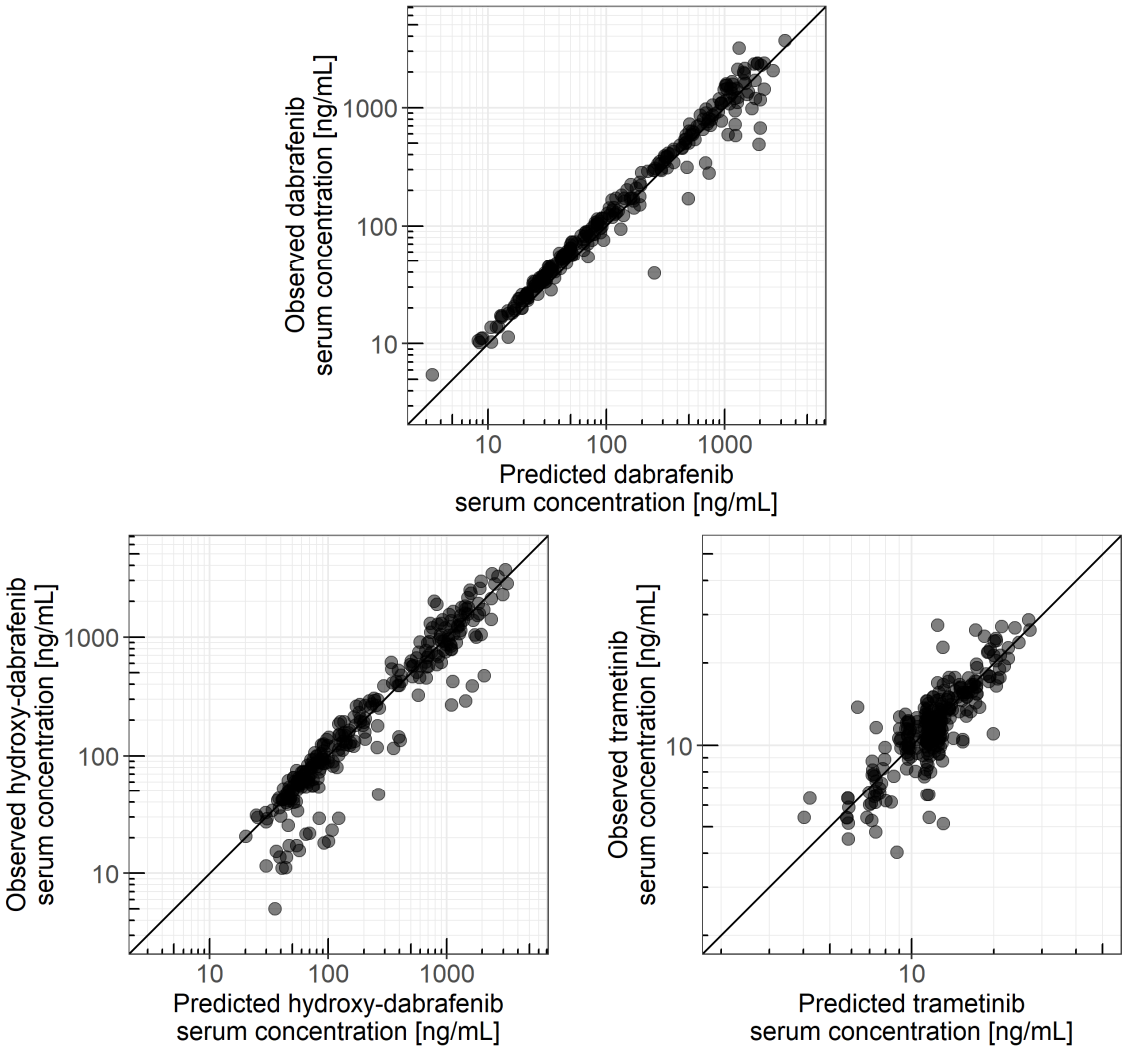
** one patient had temporary treatment discontinuation before *and* during the study

*** two patients additionally had temporary treatment discontinuations for other reasons

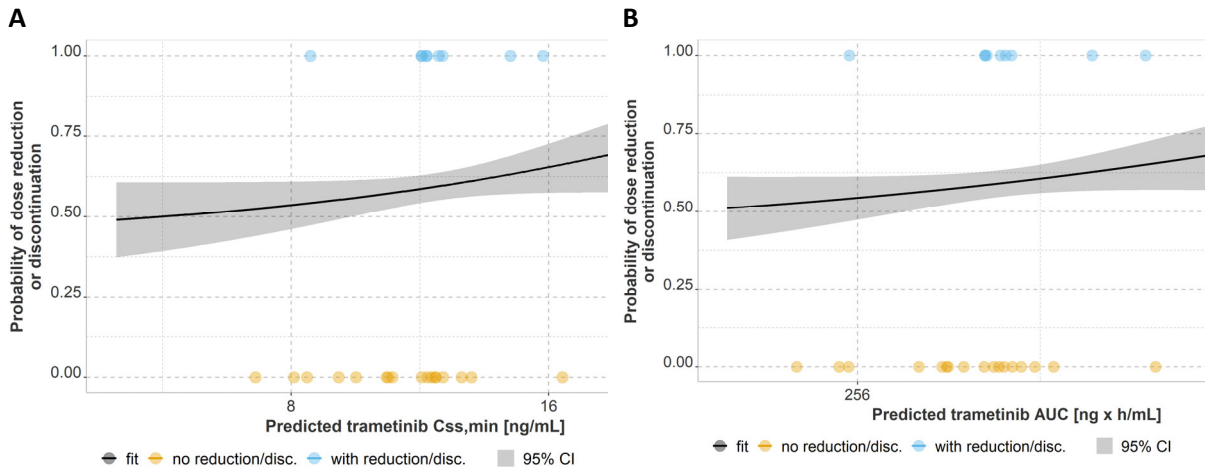
\+ refers to patients with temporary treatment discontinuations or dose reductions *prior* to observation in the study



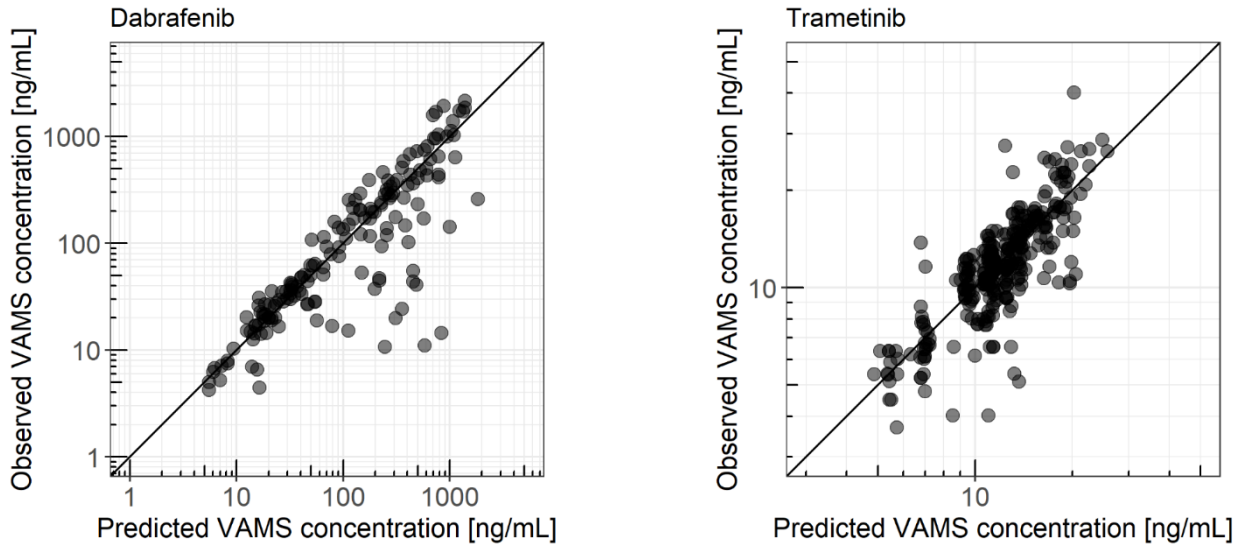

**Supplementary Figure S1. Simulated steady state pharmacokinetics vs. observed data.** Patient characteristics and dosages were used to simulate steady state pharmacokinetics with IIV on 1000 virtual patients. Simulated data was overlaid with the observed data.




**Supplementary Figure S2. Individual observed vs. individual predicted serum concentrations.** Empirical Bayesian estimates were used for prediction of dabrafenib, hydroxy-dabrafenib and trametinib serum concentrations.

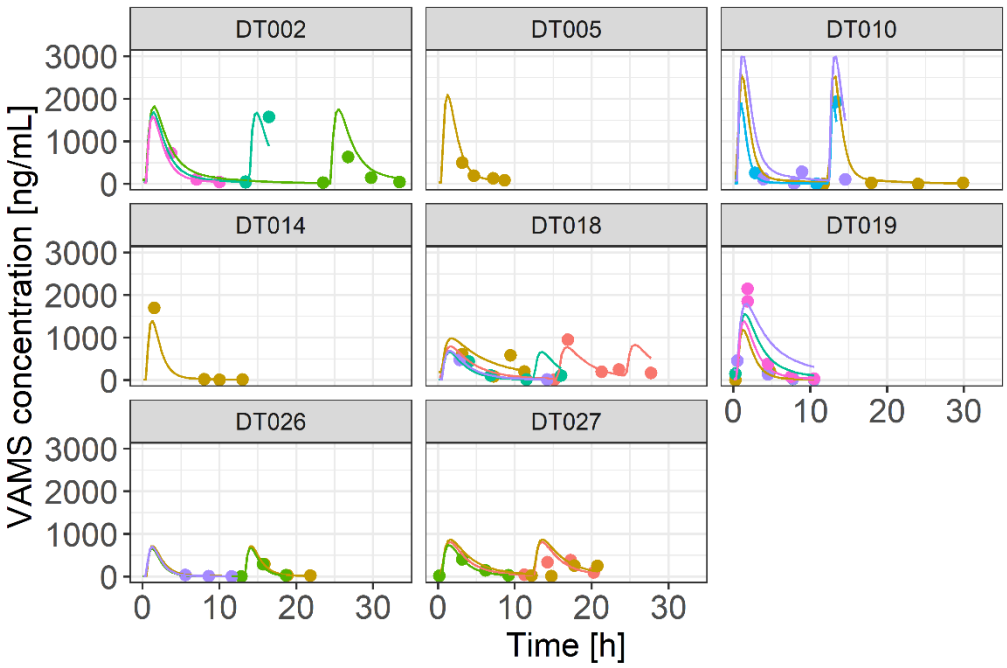



**Supplementary Figure S3. Trametinib exposure vs. probability of dose reduction or treatment discontinuation.** Logistic regression was used for analysis. **A:** Predicted trough concentration as exposure surrogate; intercept: -0.349, effect of $C_{min}$: 0.06178 (p-value: 0.0798) **B:** Predicted $AUC_{\tau}$ as exposure surrogate; intercept: -0.436, effect of $AUC_{\tau}$: 0.0024 (p-value: 0.0988)

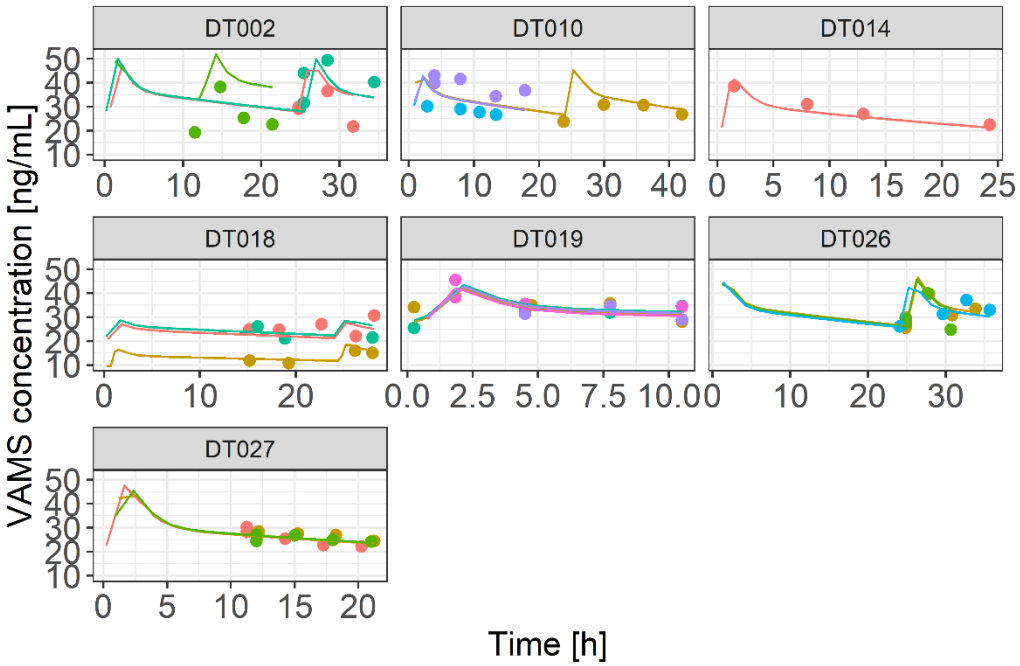



**Supplementary Figure S4. Individual predicted vs. observed VAMS concentrations.** Prediction of dabrafenib and trametinib concentrations was performed by using the consolidated datasets.

**A**




**B**




**Supplementary Figure S5. At-home sampled VAMS concentration-time profiles.** Points are individual measured VAMS concentrations; lines represent the fitted concentration time curve using the MAP approach. Different colours indicate different occasions of at-home sampling of the same patient. **A:** At-home sampled dabrafenib VAMS concentrations (90 samples, 8 patients). **B:** At-home sampled trametinib VAMS concentrations (84 samples, 7 patients). DT018 was not in steady state on one occasion. DT018 and DT019 received 1 mg and 1.5 mg q24h of trametinib, respectively. DT005 was on dabrafenib monotherapy.