Anti-cancer treatment schedule optimization based on tumor dynamics modelling incorporating evolving resistance

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Supplementary methods

1. Parameter estimate
To assist the setting of parameter values, the values of parameter describing tumor dynamics under anti-EGFR inhibitor ($D_1$) therapy were estimated by fitting the collected tumor sizes data\(^1\) using the first order conditional estimation method with interaction (FOCEI) implemented in NONMEM software, version 7.4.1 (ICON Development Solutions).

A non-linear mixed-effect model was developed. Parameters were assumed to be log-normally distributed and were expressed using equation (S1). $P_i$ represents the parameter of $i$th individual, $P_{pop}$ represents typical value of the parameter, and $\eta_i$ represents the random inter-individual variability (IIV) which was normally distributed with mean of 0 and variance of $\omega^2$. The residual error was characterized with a proportional error model as is shown in equation (S2), where $Obs$ represents observations, $IPRED$ represents individual predictions, and $\epsilon_i$ represents the proportional residual error which was assumed to be normally distributed with mean of 0 and variance of $\sigma_i^2$.

\[ P_i = P_{pop} \cdot e^{\eta_i} \]  
\[ Obs = IPRED \cdot (1 + \epsilon_i) \]

Assuming the tumor growth follows an exponential growth pattern, $k_{g1}$ was fixed as 0.03/week (=\ln2/(6.8 months $\cdot$ 4 weeks/month)) according to a previously reported median placebo tumor doubling time colorectal carcinomas, i.e. 6.8 months (range: 3 - 24 months)\(^2\). $k_{g2}$, as was assumed, was fixed as 0.021 /week (0.03-70%). The baseline levels of $TS$ and mutant $KRAS (M_{ctDNA1})$ were fixed according to real observations of each patient. For WT-$KRAS$ patients, the baseline of $T_{R1}$ were set to 0. For M-$KRAS$ patients, the baseline of $T_{R1}$ was estimated and the baseline of $T_{S}$ equals the difference between the observed baseline and estimated baseline $T_{R1}$.

2. Model in a evaluation cohort
The model used in the evaluation cohort was adjusted according to the findings of the study:
1) The detectable $EGFR$ L858R mutation or exon 19 deletion in ctDNA at the start of treatment indicates the tumor is sensitive to anti-EGFR inhibitor. Therefore, the sensitive clonal population ($T_s$) was assumed to carry one of these two mutations ($M_{ctDNA1}$);

2) L858R mutation or exon 19 deletion became undetectable when EGFR inhibitor ($D_1$) started and raised back again together with the newly developed $EGFR$ T790M mutation ($M_{ctDNA2}$) during treatment\(^3\), which indicates the emergence of treatment resistance. Therefore the acquired resistant clonal population under $D_1$ ($T_{R1}$) was assumed to carry both $M_{ctDNA1}$ and $M_{ctDNA2}$;

3) A hypothetical treatment next to anti-EGFR inhibitor ($D_2$) was incorporated and assumed to target T790M positive NSCLC cancer ($T_{R1}$). In the meantime, a third mutation ($M_{ctDNA3}$)
was able to be acquired which resulted in a third clonal population ($T_{R2}$) that were resistant to $D_2$.

More details of the model and the parameters are shown in Supplementary Fig. S1 and Supplementary Table S6.

The values of parameters regarding tumor dynamics were estimated using the collected time curves of tumor sizes as described above. The residual error was characterized with an additive error model as is shown in equation S3, where $Obs$ represents observations, $IPRED$ represents individual predictions, and $\varepsilon_2$ represents the additive residual error which was assumed to be normally distributed with mean of 0 and variance of $\sigma_2^2$. The parameter estimate results can be found in Supplementary Table S7.

\[
Obs = IPRED + \varepsilon_2 
\]  
(S3)

References

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Figure S1 The model structure that characterize the dynamics of tumor size and mutation concentrations in ctDNA from NSCLC patients.

\[ T_S, T_{R1}, \text{ and } T_{R2} \] represent the sizes of the three tumor clonal populations, respectively. \( k_{g1}, k_{g2}, k_{g3} \) represent the net growth rates of three clonal populations. \( k_{s1} \) and \( k_{s2} \) represent the tumor decay rate due to treatments. \( k_{M1} \) and \( k_{M3} \) represent the mutation rate constant from drug susceptible clonal population to drug resistant clonal population during the course of anti-EGFR inhibitor \((D_1)\) and the hypothetical treatment \((D_2)\), respectively. \( k_{M2} \) and \( k_{M4} \) represent the transition rate constant from drug resistant clonal population to drug susceptible clonal population upon the withdrawal of treatments. \( k_1, k_2, k_3, \text{ and } k_4 \) represent the shedding rate constant of ctDNA which carries mutations.
Figure S2. Model evaluation results on the time-courses of tumor diameters (a) and EGFR mutation concentrations including L858R mutation/exon 19 deletion (b) and T790M mutation (c) collected from a previous clinical study where patients with non-small cell lung cancer were treated with anti-EGFR inhibitor icotinib/gefitinib.
Figure S3. The simulated total tumor burden (a,c,e) and mutation concentrations (b,d,f) under continuous treatment (a,b), intermittent treatment (8-week treatment and 4-week suspension) (c,d), and adaptive treatment with the second hypothetical drug (ctDNA limits for drug adjustment: 5 and 10 fragments/ml, monitor frequency: 12 weeks) (e,f) for 100 colorectal cancer patients. Median total tumor sizes (black lines), $M_{ctDNA1}$ (light sea green lines), and $M_{ctDNA2}$ (salmon lines) were plotted together with corresponding 90% prediction intervals. Median PFS (black dashed vertical line), $T_{TS-TSO}$ (red dashed vertical line), and $T_{mutant_{test}}$ (blue dash vertical line) were also shown in the figure.
Figure S4. Simulated time curves from sensitivity analysis.
Simulated time-curves of tumor burden (a,c,e,g,i,k) and $M_{ctDNA}$ concentrations (b,d,f,h,j,l) based on each parameter setting under continuous treatment (a-d), intermittent treatment (8-week treatment and 4-week suspension) (e-h), and adaptive treatment (ctDNA limits for drug adjustment: 5 and 10 fragments/ml, monitor frequency: 12 weeks) (i-k). Every parameter increased by 50% (a,b,e,f,i,j) or decreased by 50% one at a time (c,d,g,h,k,l).
Figure S5. Relative change (Δ) of predicted minimum total tumor size (a), of total tumor size at the last simulated time point (180 weeks) (b), and of M_{ctDNA1} or M_{ctDNA2} concentrations at the last simulated time point (180 weeks) (c) compared with using original parameters in the sensitivity analysis.
Figure S6. When fixing $k_{M2}$ and $k_{M4}$ to zero, the predicted median progression-free survival (PFS) (a) and the time until the tumor size had grown back to the baseline level ($T_{S<TS0}$) (b) of evaluated regimens.
**Figure S7.** When fixing $k_{M2}$ and $k_{M4}$ to zero, the simulated time-curves of total tumor burden and each clonal population (a,d,g), mutation concentrations (b,e,h), and dosing strategies (c,f,i) of a typical subject with metastatic colorectal cancer undergoing continuous treatment (a,b,c), intermittent treatment (8-week treatment and 4-week suspension) (d,e,f), and adaptive treatment with the second hypothetical drug (ctDNA limits for drug adjustment: 5 and 10 fragments/ml, monitor frequency: 12 weeks) (g,h,i).
Estimated PFS (black dashed vertical line), $T_{\text{TS-TS0}}$ (red dashed vertical line), and $T_{\text{mutant_test}}$ (blue dash vertical line) are also shown in the figure.
Figure S8. When fixing $k_{M2}$ and $k_{M4}$ to zero, model predicted total tumor burden and each clonal population (a) and mutant KRAS concentrations (b) under a regimen of 20-week treatment and 20-week suspension.
Figure S9 The simulated total tumor burden under continuous treatment (a) and intermittent treatment (8-week treatment and 4-week suspension) (b) for 100 colorectal cancer patients with detectable KRAS mutation pre-treatment. Median total tumor sizes (black lines) were plotted along with 90% prediction intervals. Median PFS (black dashed vertical line) and TS<TS0 (red dashed vertical line) were also shown in the figure.
|                               | WT-KRAS patients | M-KRAS patients |
|-------------------------------|------------------|-----------------|
| Number of patients           | 25               | 3               |
| Gender (Male (%))            | 15 (60%)         | 0 (0%)          |
| Age (years) (median (range)) | 59 (42-78)       | 56 (48-78)      |
| TS₀ (mm²) (median (range))   | 5649 (396-38006) | 1714 (1312-1849) |
| Baseline mutant KRAS (fragments/ml) (median (range)) | 0 | 411 (23-810) |
| PFS (week) (median (range))  | 23 (7-52)        | 7 (7-11)        |
| Mutant KRAS detectable time (week) (median (range)) | 22 (5-34) (N=9) | 0 |

TS₀, baseline tumor size; PFS, progression-free survival; WT-KRAS patients, patients who were identified to be initially KRAS wild-type; M-KRAS patients, patients who had detectable mutant KRAS pre-treatment.
Table S2: Parameter estimates of the tumor dynamics model based on the dataset collected from patients with metastatic colorectal cancer

| Parameters                      | Estimate (RSE)                                      | IIV (CV%) [shrinkage] |
|---------------------------------|----------------------------------------------------|-----------------------|
| **WT-KRAS patients**            |                                                    |                       |
| $T_{S,0}$ (mm$^2$)              | $T_{S,0}^{obs}$ (fixed)                            |                       |
| $T_{R1,0}$ (mm$^2$)             | 0 (fixed)                                         |                       |
| **M-KRAS patients**             |                                                    |                       |
| $T_{S,0}$ (mm$^2$)              | $T_{S,0}^{obs} - T_{R1,0,Est}$                     |                       |
| $T_{R1,0}$ (mm$^2$)             | 1830 (17%)                                        | 0 (fixed)             |
| $k_{g1}$ (/week)                | 0.03 (fixed)                                      | 68.6% [14%]           |
| $k_{g2}$ (/week)                | 0.7 $\cdot$ $k_{g1}$ (fixed)                      |                       |
| $k_{s1}$ (/week)                | 0.127 (5%)                                        |                       |
| $k_{M1}$ (/week)                | 0.0459 (18%)                                      |                       |
| Residual error                  |                                                   |                       |
| Prop (CV%)                      | 21.7% (11%)                                       |                       |

$T_{S,0}^{obs}$, observed total tumor size, $T_{R1,0,Est}$, estimated baseline of $T_{R1}$, WT-KRAS patients, patients who were identified to be initially KRAS wild-type; M-KRAS patients, patients who had detectable mutant KRAS pre-treatment. RSE, relative standard error, CV, coefficient of variation, IIV, inter-individual variability, Prop, proportional residual error.

Relative standard errors (RSEs) of parameter estimates were all within an acceptable range (<30%).
**Table S3** Characteristics of the dataset collected from patients with non-small cell lung cancer (NSCLC)

|                           | Values                                      |
|---------------------------|---------------------------------------------|
| Number of patients        | 16                                          |
| $T_{S0}$ (mm) (median (range)) | 33.92 (16.97-87.96)                        |
| Baseline EGFR L858R mutation/exosome 19 deletion concentration (copies/ml) (median (range)) | 438.75 (42-9555.56)                        |
| PFS (months) (median (range)) | 12 (4-25)                                  |
| EGFR T790M mutation detectable time (months) (median (range)) | 10.5 (3-27.5)                              |

$T_{S0}$, baseline tumor size; PFS, progression-free survival
**Table S4** The results of each evaluated schedule in patients who were identified to be initially *KRAS* wild-type

| Schedules | Median PFS* (90% interval) (weeks) | Median $T_{TS-TS0}$ (90% interval) (weeks) | Median $T_{\text{mutant test}}$ (90% interval) (weeks) |
|-----------|-----------------------------------|------------------------------------------|--------------------------------------------------|
| Continuous schedule (standard of care) | 36 (32-44) | 52 (36-72) | 18 (8-52.6) |
| Intermittent schedules

$D_1$ was administered for $N$ weeks and suspended for $M$ weeks. Total treatment time was 180 weeks.

| N (weeks) | M (weeks) | 48 (24-80) | 56 (24-112.8) | 28 (8-92.8) |
|-----------|-----------|------------|---------------|-------------|
| 4         | 4         | 12 (12-72.6) | 24 (12-96) | 32 (8-112.4) |
| 8         | 4         | 44 (32-60) | 60 (36-104.2) | 20 (8-80) |
| 8         | 8         | 38 (16-64) | 60 (32-113.2) | 24 (8-93.2) |
| 8         | 12        | 20 (16-20) | 40 (20-116.4) | 28 (8-108) |
| 12        | 4         | 40 (32-56) | 60 (36-92.2) | 24 (8-68.4) |
| 12        | 8         | 40 (20-60) | 60 (36-112.2) | 28 (8-88) |
| 12        | 12        | 24 (20-49.0) | 64 (24-116.2) | 32 (8-100.4) |
| 12        | 16        | 24 (20-28) | 52 (24-108.4) | 32 (8-96) |

Adaptive schedules with a hypothetical second treatment

$D_1$ was continuously given, and suspended and switched to $D_2$ when the ctDNA measurement increased to higher than UP fragment/ml. Treatment switched back to $D_1$ when ctDNA measurement decreased back to lower than LOW fragment/ml. Total treatment time was 180 weeks.

| LOW (fragment/ml) | UP (fragment/ml) | Monitoring frequency of ctDNA (weeks) |
|-------------------|------------------|--------------------------------------|
| 5                 | 10               | 4                                    |
| 5                 | 15               | 4                                    |
| 5                 | 20               | 4                                    |
| 5                 | 25               | 4                                    |
| 10                | 15               | 4                                    |
| 10                | 20               | 4                                    |
| 10                | 25               | 4                                    |
| 5                 | 10               | 8                                    |

| 62 (36-118.4) | 124 (45.2-170.8) | 100 (36-169.2) |
| 60 (32-116.4) | 132 (45.8-176)  | 108 (36-172) |
| 60 (32-112.4) | 124 (46.8-180)  | 102 (36-168) |
| 60 (32-112.4) | 120 (44-172.4)  | 102 (36-168.2) |
| 56 (32-124)   | 124 (47.2-172.8) | 108 (42.4-172.8) |
| 56 (32-108.4) | 120 (47.8-172.2) | 108 (44-176) |
| 56 (32-108.8) | 114 (44-172.2)  | 110 (44-175.8) |
| 60 (32-112.4) | 120 (44.8-96)   | 96 (40-163.2) |
Disease progression was defined by WHO criteria

$D_1$, anti-EGFR inhibitor; $D_2$, a hypothetical second treatment to which the newly acquired clone is susceptible; PFS, Progression-free survival; $T_{\text{mutant test}}$, time until detectable mutation; $T_{\text{TS-TSO}}$, the time until the tumor size had grown back to the baseline level; ctDNA, circulating tumor DNA

| $D_1$ | $D_2$ | $T_{\text{TS-TSO}}$ | PFS (44-166) | $T_{\text{mutant test}}$ (44-166) |
|-------|-------|----------------------|-------------|-------------------------------|
| 5     | 15    | 8                    | 60 (32-104.8)| 120 (44-169)                 |
| 5     | 20    | 8                    | 56 (32-100.4)| 120 (44-168)                 |
| 5     | 25    | 8                    | 56 (32-104.4)| 116 (44.8-168)              |
| 10    | 15    | 8                    | 60 (32-104.4)| 120 (44-168)                 |
| 10    | 20    | 8                    | 56 (32-108.4)| 120 (44-164.4)              |
| 10    | 25    | 8                    | 56 (32-104.8)| 118 (44.2-160)              |
| 10    | 10    | 12                   | 64 (32-108)  | 128 (44-164)                 |
| 5     | 15    | 12                   | 60 (36-120)  | 124 (44-176)                 |
| 5     | 20    | 12                   | 60 (32-104.2)| 120 (44-157.6)              |
| 5     | 25    | 12                   | 60 (32-104)  | 120 (44-156)                 |
| 10    | 15    | 12                   | 62 (32-108.2)| 124 (44-176)                 |
| 10    | 20    | 12                   | 60 (32-108)  | 120 (44-157.6)              |
| 10    | 25    | 12                   | 60 (36-104.2)| 120 (44-156)                 |

*Disease progression was defined by WHO criteria*

$D_1$, anti-EGFR inhibitor; $D_2$, a hypothetical second treatment to which the newly acquired clone is susceptible; PFS, Progression-free survival; $T_{\text{mutant test}}$, time until detectable mutation; $T_{\text{TS-TSO}}$, the time until the tumor size had grown back to the baseline level; ctDNA, circulating tumor DNA
Table S5 Predicted progression-free-survival and time until detectable mutation in the sensitivity analysis.

| Parameters | Continuous schedule | Intermittent schedule | Adaptive schedule |
|------------|---------------------|-----------------------|------------------|
|            | PFS (weeks)         | (8-week treatment and 4-week suspension) | (ctDNA limits for drug adjustment: 5 and 10 fragments/ml, monitor frequency 12 weeks) |
| $k_{g1}$   | Increase 50%: 36 (-8) | Decrease 50%: 48 (+4) | Increase 50%: 96 (+32) |
| $k_{g2}$   | 28 (-8) 52 (+16)    | 32 (-12) 84 (+40)    | 56 (-8) 76 (+12) |
| $k_{g3}$   | - -                | - -                  | 60 (-4) - |
| $k_{s1}$   | - -                | - -                  | 32 (-12) 60 (-4) |
| $k_{s2}$   | - -                | - -                  | - -       |
| $k_{M1}$   | 32 (-4) 44 (+8)    | 36 (-8) 60 (+16)    | 84 (+20) 44 (-20) |
| $k_{M2}$   | - -                | 48 (+4) 40 (-4)     | - 60 (-4) |
| $k_{M3}, k_{M4}$ | - -                | - -                  | - -       |
| $k_{c}$    | - -                | - -                  | - -       |
| $H$        | - -                | - -                  | 96 (+32) |
| $K_{T50}$  | - -                | - -                  | No result |
| $k_{\text{max}_1}$ | - -                | - -                  | No result |
| $k_{\text{max}_2}$ | - -                | - -                  | No result |

$T_{\text{mutant\_test}}$ of $M_{ctDNA1}$ (weeks) | $T_{\text{mutant\_test}}$ of $M_{ctDNA2}$ (weeks) |

| Parameters | Increase 50% | Decrease 50% | Increase 50% | Decrease 50% | Increase 50% | Decrease 50% |
|------------|--------------|--------------|--------------|--------------|--------------|--------------|
| $k_{g1}$   | 20 (+4)      | -            | 24 (+4)      | -            | 120 (-48)    | 180 (+12)    |
| $k_{g2}$   | -            | 20 (+4)      | -            | 28 (+8)      | 108 (-60)    | No result    |
| $k_{g3}$   | -            | -            | -            | -            | 120 (-48)    | No result    |
| $k_{s1}$   | 24 (+8)      | 12 (-4)      | 32 (+12)     | 16 (-4)      | No result    | 72 (-96)     |
| $k_{s2}$   | -            | -            | -            | -            | No result    | 108 (-60)    |
| $k_{M1}$   | 12 (-4)      | 32 (+16)     | 16 (-4)      | 44 (+24)     | No result    | 144 (-24)    |
| $k_{M2}$   | -            | -            | -            | -            | No result    | 132 (-36)    |
| $k_{M3}$   | -            | -            | -            | -            | 120 (-48)    | No result    |
| $k_{M4}$   | -            | -            | -            | -            | No result    | 132 (-36)    |
| $k_{c}$    | -            | -            | -            | -            | -            | 132 (-36)    |
| $H$        | 20 (+4)      | 12 (-4)      | 28 (+8)      | 16 (-4)      | -            | 120 (-48)    |
| $K_{T50}$  | 28 (+12)     | 8 (-8)       | 32 (+12)     | 8 (-12)      | 180 (+12)    | 96 (-72)     |
| $k_{\text{max}_1}$ | 20 (+4)      | -            | 24 (+4)      | -            | 180 (+12)    | -            |
| $k_{\text{max}_2}$ | -            | -            | -            | 132 (-36)    | -            | -            |

PFS, Progression-free survival; $T_{\text{mutant\_test}}$, time when mutation concentration became detectable; $M_{ctDNA1}$, KRAS mutation; $M_{ctDNA2}$, the second hypothesis mutation; -, result same as that under the original parameter setting; No result, the mutant gene concentrations did not reach the detectable limit (5 fragments/ml) by the end of simulation time (180 week).

*With original parameters, the predicted PFS were 36, 44, and 64 weeks under continuous, intermittent, and adaptive schedule, respectively, and the predicted $T_{\text{mutant\_test}}$ were 16, 20, and 168 weeks, respectively.*
Table S6 Parameters values of the developed model characterizing the dynamics of tumor size and mutation concentrations in NSCLC patients

| Parameters | Description | Typical Values | Ref. |
|------------|-------------|----------------|------|
| $T_{S,0}$ (mm) | Baseline of $T_S$ | 35 | Data |
| $T_{R1,0}$ (mm) | Baseline of $T_{R1}$ | 0 | Mutation was assumed to be acquired during treatment |
| $T_{R2,0}$ (mm) | Baseline of $T_{R2}$ | 0 | |
| $M_{ctDNA1,0}$ (copies/ml) | Baseline of $EGFR$ L858R mutation or exon 19 deletion ($M_{ctDNA1}$) | 450 | |
| $M_{ctDNA2,0}$ (copies/ml) | Baseline of $EGFR$ T790M mutation ($M_{ctDNA2}$) | 0 | |
| $M_{ctDNA3,0}$ (copies/ml) | Baseline of a third hypothetical mutation ($M_{ctDNA3}$) | 0 | |
| $k_{g1}$ (/month) | Growth rate constant of $T_S$ | 0.07 | Estimated |
| $k_{g2}$ (/month) | Growth rate constant of $T_{R1}$ | 0.049 | |
| $k_{g3}$ (/month) | Growth rate constant of $T_{R2}$ | 0.035 | |
| $k_{s1}$ (/month) | Tumor shrinkage rate constant due to $D_1$ (anti-EGFR inhibitor) | 0.8 | Estimated |
| $k_{s2}$ (/month) | Tumor shrinkage rate constant due to $D_2$ (the second hypothetical treatment) | 0.8 | $k_{s1}$ |
| $k_{M1}$ (/month) | Mutation rate from $T_S$ to $T_{R1}$ when $D_1 = 1$ | 0.6 | Estimated |
| $k_{M2}$ (/month) | Mutation rate from $T_{R1}$ to $T_S$ when $D_1 = 0$ | 0.4 | Lower than $k_{M1}$ |
| $k_{M3}$ (/month) | Mutation rate from $T_{R1}$ to $T_{R2}$ when $D_2 = 1$ | 0.6 | $k_{M1}$ |
| $k_{M4}$ (/month) | Mutation rate from $T_{R2}$ to $T_{R1}$ when $D_2 = 0$ | 0.4 | $k_{M2}$ |
| $H$ | Hills coefficient | 5 | Visually matching the slope of T790M mutation time-courses |
| $KT_{50}$ (mm) | The size of tumor that provide half-maximal shedding rate of ctDNA | 30 | |
| $k_{max,1}$ (copies/ml/(month*mm)) | Maximum shedding rate of $M_{ctDNA1}$ | 120 | |
| $k_{max,2}$ (copies/ml/(month*mm)) | Maximum shedding rate of $M_{ctDNA2}$ | 50 | |
| $k_{max,3}$ (copies/ml/(month*mm)) | Maximum shedding rate of $M_{ctDNA3}$ | 50 | |
| Symbol | Description                                      | Value |
|--------|--------------------------------------------------|-------|
| $k_e$  | ctDNA eliminate rate constant                    | 2     |
| IIV$_B$ ($\omega_1$) | Standard deviation of IIV of baselines | 0.6   |
| IIV$_{kg}$ ($\omega_2$) | Standard deviation of IIV of $k_g$ | 0.2   |

cDNA, circulating tumor DNA; IIV, inter-individual variability
Table S7 Parameter estimates of the tumor dynamics model based on the dataset collected from patients with NSCLC

| Parameters   | Estimate (RSE%) | IIV (CV%) [shrinkage] |
|--------------|-----------------|-----------------------|
| $T_{\text{s,0}}$ (mm) | $T_{\text{S}_0,\text{obs}}$ (fixed) |                       |
| $T_{R1,0}$ (mm) | 0 (fixed) |                       |
| $k_{g1}$ (/month) | 0.0675 (45%) | 105.4% [6%] |
| $k_{g2}$ (/month) | $0.7 \cdot k_{g1}$ (fixed) | - |
| $k_{31}$ (/month) | 0.835 (23%) | 74% [3%] |
| $k_{M1}$ (/month) | 0.553 (28%) | - |
| Residual error | - |                       |
| Add (mm) | 2.67 (34%) |                       |

RSE, relative standard error; CV, coefficient of variation; IIV, inter-individual variability; Add, additive residual error