

Supplementary Document

Evaluation of patient-reported severity of hand-foot syndrome under
capecitabine using a Markov modeling approach

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NONMEM code of the final model

\$PROBLEM Capecitabin HFS mCTMM

\$INPUT

ID ; No. of the patient

TIME ; Therapy cycle no. as time unit

DV ; No AE -> DV = 1, otherwise DV = 2-4 (grades 1-3)

AMT ; Probability for AE compartments

CMT ; 1-4 = AE compartments

DOSEDAY ; Absolute dose per day

EVID

MDV

AGE

SEX

MAMMA ; tumor entity: mamma carcinoma

COLON ; tumor entity: colorectal cancer

OTHER ; other tumor entity

MONO ; Capecitabin monotherapy yes/no

\$DATA HFS_total.csv

\$SUBROUTINES ADVAN6 TOL = 4

\$MODEL

NCOMP = 4

COMP = (G0) ; No AE

COMP = (G1) ; Mild AE

COMP = (G2) ; Moderate AE

COMP = (G3) ; Severe AE

\$ABB COMRES = 1

\$PK

IF(NEWIND.NE.2) THEN

PSDV = 0

COM(1) = 0

ENDIF

PRSP = PSDV ; Previous DV

IF(TIME.EQ.0) F1 = 1

IF(PRSP.EQ.1) COM(1) = 0

IF(PRSP.EQ.2) COM(1) = 1

IF(PRSP.EQ.3) COM(1) = 2

IF(PRSP.EQ.4) COM(1) = 3

F1=0

F2=0

F3=0

F4=0

IF(COM(1).EQ.0) F1 = 1

IF(COM(1).EQ.1) F2 = 1

IF(COM(1).EQ.2) F3 = 1

IF(COM(1).EQ.3) F4 = 1

;--- mCTMM model parameters

MET = THETA(4)*EXP(ETA(2)) ; Mean equilibration time

ET1 = ETA(1)

\$DES

A1 = THETA(1)+ET1 + THETA(5)*(DOSEDAY-3000) ; alpha_1 with linear dose effect

B2 = THETA(2) ; beta_2

B3 = THETA(3) ; beta_3

; Logit of the cumulative probabilities

LGE1 = A1 ; >=Grade 1

LGE2 = LGE1 + B2 ; >=Grade 2

LGE3 = B3 + LGE2 ; Grade 3

; Cumulative probabilities

PGE1 = EXP(LGE1)/(1+EXP(LGE1)) ; >=Grade 1

PGE2 = EXP(LGE2)/(1+EXP(LGE2)) ; >=Grade 2

PGE3 = EXP(LGE3)/(1+EXP(LGE3)) ; Grade 3

; Probabilities

P0 = (1-PGE1) ; Probability of grade 0

P1 = (PGE1-PGE2) ; Probability of grade 1

P2 = (PGE2-PGE3) ; Probability of grade 2

P3 = PGE3 ; Probability of grade 3

; Transfer rate constants

L01 = 1/(MET*(1+P0/P1))

L10 = L01 *P0/P1

L12 = 1/(MET*(1+P1/P2))

L21 = L12 *P1/P2

L23 = 1/(MET*(1+P2/P3))

L32 = L23 *P2/P3

; Differential equations for the probability of each grade

$$DADT(1) = L10*A(2) - L01 *A(1) ; \text{Grade 0}$$

$$DADT(2) = L01*A(1)+L21*A(3)-(L10+L12)*A(2) ; \text{Grade 1}$$

$$DADT(3) = L12*A(2)+L32*A(4)-(L21+L23)*A(3) ; \text{Grade 2}$$

$$DADT(4) = L23*A(3) - L32 *A(4) ; \text{Grade 3}$$

\$ERROR

;--- Redefine variables from \$DES

$$A1X = THETA(1) + ET1+ THETA(5)*(DOSEDAY-3000)$$

$$B2X = THETA(2)$$

$$B3X = THETA(3)$$

$$LGE1X = A1X$$

$$LGE2X = LGE1X + B2X$$

$$LGE3X = B3X + LGE2X$$

$$PGE1X = \text{EXP}(LGE1X)/(1+\text{EXP}(LGE1X))$$

$$PGE2X = \text{EXP}(LGE2X)/(1+\text{EXP}(LGE2X))$$

$$PGE3X = \text{EXP}(LGE3X)/(1+\text{EXP}(LGE3X))$$

$$POX = (1-PGE1X)$$

$$P1X = (PGE1X-PGE2X)$$

$$P2X = (PGE2X-PGE3X)$$

$$P3X = PGE3X$$

; --- Define Y

$$POX = A(1) ; \text{Probability of observing grade 0}$$

$$P1X = A(2) ; \text{Probability of observing grade 1}$$

P2X = A(3) ; Probability of observing grade 2

P3X = A(4) ; Probability of observing grade 3

IF(DV.EQ.1.AND.CMT.EQ.0) Y=P0X

IF(DV.EQ.2.AND.CMT.EQ.0) Y=P1X

IF(DV.EQ.3.AND.CMT.EQ.0) Y=P2X

IF(DV.EQ.4.AND.CMT.EQ.0) Y=P3X

; Cumulative probabilities

CUP0 = P0X

CUP1 = CUP0 + P1X

CUP2 = CUP1 + P2X

CUP3 = CUP2 + P3X

; Start of simulation

IF(ICALL.EQ.4) THEN

IF(CMT.EQ.0) THEN

CALL RANDOM (2,R)

IF(R.LE.CUP0) DV = 1

IF(R.GT.CUP0.AND.R.LE.CUP1) DV = 2

IF(R.GT.CUP1.AND.R.LE.CUP2) DV = 3

IF(R.GT.CUP2) DV = 4

ENDIF

ENDIF

; End of simulation

; Store DV

PSDV = DV

\$THETA

(1.81) ; 1 alpha_1

(-1000000, -1.8,0) ; 2 beta_2

(-1000000, -2.08,0) ; 3 beta_3

(0, 1.09) ; 4 MET

(0.00083) ; Dose effect

\$OMEGA

1.25 ; IIV alpha_1

0.294 ; IIV MET

\$COV PRINT=E MATRIX=R

\$ESTIMATION MAXEVAL=9999 METHOD=1 LAPLACE LIKE PRINT=1 NOABORT SIG=2

;\$SIM (7776) (8877 UNIFORM) ONLYSIM NOPREDICTION