

TDM-based tailored dosing of durvalumab in lung cancer patients - a comprehensive population pharmacokinetic-pharmacoeconomic evaluation. *Clinical Pharmacokinetics*.

Fenna de Vries^{1,2}, Eric J.F. Franssen, Arthur A.J. Smit, Dirk Jan A.R. Moes, Anthonie J. van der Wekken, Thijs Oude Munnink, Jeroen J.M.A. Hendriks, Daphne W. Dumoulin, Stijn L.W. Koolen, Wietske Kievit, Michel M. van den Heuvel, Rob ter Heine.

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SUPPLEMENTAL MODEL CODE

```
$PROBLEM DURVALUMAB
$INPUT (...)
$Data (...)
$SUBROUTINE ADVAN6 TOL=4

$MODEL
COMP = (CENTRAL)
COMP = (PERI)
COMP = (AUCSS)
COMP = (AUC1)
COMP = (AUCTOTAL)

$PK
;--- COVARIATES
FLASEX = 0
IF (SEX.EQ.0) FLASEX = 1

ADA = 0 ; NO ADA

ALB = 39.5 * EXP(ETA(1)) ; ALBUMIN
CRCL = 85.9 * ((WT / 63.75)**0.75) * EXP(ETA(2)) ; CREATININE CLEARANCE
TUMORSIZE = 50.8 * EXP(ETA(3)) ; TUMOR SIZE
SPDL1 = 139 * EXP(ETA(4)) ; SOLUBLE PDL1

;--- PK
D1 = (1 / 24) ; 1 H INFUSION

; -- CL, Q and VMAX ARE PER DAY
CL = 0.232 * (1 - 0.035 * (ALB - 38)) * (1 + 0.00149 * (CRCL - 85.65)) * (0.937**FLAECOG) * (0.857**FLASEX) *
    (1 + 0.00178 * (TUMORSIZE - 74.8)) * ((WT / 69.8)**0.389) * EXP(ETA(5))
VM = 0.824 * (1 + 0.00336 * (SPDL1 - 124.8))
V1 = 3.51 * (0.835**FLASEX) * ((WT / 69.8)**0.406) * EXP(ETA(6))
V2 = 3.45 * (0.795**FLASEX) * EXP(ETA(7))
Q = 0.476 * THETA(1)
KM = 0.344

S1 = V1

K10 = CL / V1
K12 = Q / V1
K21 = Q / V2

K10I = K10
K12I = K12
K21I = K21
V1I = V1
VMI = VM

$DES
; --- PK
C1 = A(1) / V1

DADT(1) = -K10 * A(1) - K12 * A(1) - ((VM * C1) / (KM + C1)) + K21 * A(2)
```

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DADT(2) = -K21 * A(2) + K12 * A(1)

FLAAUCSS = 0

IF (T.GE.252) FLAAUCSS = 1

FLAAUC1 = 0

IF (T.LT.28) FLAAUC1 = 1

DADT(3) = C1 * FLAAUCSS

DADT(4) = C1 * FLAAUC1

\$ERROR

IPRED = F

IF (CMT.EQ.1) Y = F + (F * ERR(1)) + ERR(2)

AUCSS = A(3)

AUCFIRST = A(4)

\$MIX

P(1) = 0.75 ; ECOG 0

P(2) = 0.25 ; ECOG 1

NSPOP = 2

\$THETA

1 FIX ; 1 DUMMY

\$OMEGA ; (CV²)

0.0113 ; 1 IIV ALB

0.0314 ; 2 IIV CRCL

0.281 ; 3 IIV TUMORSIZE

0.692 ; 4 IIV SPDL1

\$OMEGA BLOCK(3) CORRELATION

0.0729 FIX ; 5 IIV CL

0.279 0.0437 ; 6 CL-V1 IIV V1

0 0.560 0.113 ; 7 CL-V2 V1-V2 IIV V2

\$SIGMA

0.0454 ; PROP ERR

0.09 ; ADD ERR

\$SIMULATION ONLYSIM SUBPROBLEMS = 1 (2252) (74292)