**Validation of covariates in Shiny app & simulation result of different SEX using NONMEM followed by our calculation method.**

- Covariate validation in predicted duration of severe neutropenia from 50 simulations in R – result from shiny app

For each GCSF regimen, the range of covariate was entered to see the range of duration affected by covariate.

\* *p* value was determined by objective function value using log likelihood ratio test in stepwise-regression step.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Run** | **Median (range)** | **Median of Duration** | | ***p* value** |
|  |  | **GCSF1** | **GCSF7** |  |
| GCSF | 0 or 1 | 105 | 142 | < 0.0001 |
| ANC | 3.5 (0.7-13.8) | 91-120 | 122-165 | < 0.0001 |
| BUN | 14 (5-59) | 101-109 | 141-141 | < 0.01 |
| SEX | 0 or 1(male) | 105 | 142 | < 0.01 |
| HCT | 32.5 (20.6-44.6) | 105-106 | 141-143 | < 0.01 |
| log p53 fold change | 3.2 (0.3-42.9) | 99-109 | 141-145 | < 0.05 |
| WBC | 4.9 (1.7-18.3) | 104-106 | 141-142 | < 0.05 |

- Further investigation to check 95% PI for different Sex – result from shiny app

|  |  |  |
| --- | --- | --- |
|  | **Median of Duration (95% PI)** | |
| **SEX** | **GCSF1** | **GCSF7** |
| Female | 105 (5-166) | 142 (21-229) |
| Male | 105 (6-166) | 142 (25-229) |

-Validation in NONMEM, followed by our previous calculation for duration of severe neutropenia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **-**Female |  |  |  |  |  |  |
|  | SEX | Level | Mean | SD | Lower95 | Upper95 |
| data100 | 0 | 100 | 34.32 | 42.40 | 26.01 | 42.63 |
| data140 | 0 | 140 | 68.58 | 86.81 | 51.56 | 85.59 |
| data200 | 0 | 200 | 79.22 | 40.88 | 71.20 | 87.23 |
| data260 | 0 | 260 | 97.78 | 35.02 | 90.92 | 104.64 |
| data300 | 0 | 300 | 99.33 | 38.17 | 91.85 | 106.82 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| -Male |  |  |  |  |  |  |
|  | SEX | Level | Mean | SD | Lower95 | Upper95 |
| data100 | 1 | 100 | 44.56 | 44.00 | 35.94 | 53.19 |
| data140 | 1 | 140 | 82.63 | 84.50 | 66.07 | 99.19 |
| data200 | 1 | 200 | 92.72 | 38.45 | 85.18 | 100.25 |
| data260 | 1 | 260 | 111.84 | 32.11 | 105.54 | 118.13 |
| data300 | 1 | 300 | 114.21 | 34.90 | 107.37 | 121.05 |

**Calculation method**

1. For each dose (dataXXX), we simulated 100 runs.

2. From all runs, duration was calculated by Excel by each run, from finding starting time and ending time. If ANC was not recovered till the last time, we set the ending time as 300hrs (last time in simulation dataset). Herein, since we simulated 24 hour interval dataset, we found X time point when Y=0.5K (by connecting each continuous two time points) by excel function. <- Sheet1 in ‘SIM\_Dur\_calculation.xlsx’

3. If starting time or ending time show more than twice (fluctuate), the earliest time and latest time was set up as starting time point (left) and ending time point (right) of severe neutropenia, respectively. <- Sheet ‘Left’ and ‘Right’ in ‘SIM\_Dur\_calculation.xlsx’

4. Duration of neutropenia for each run was calculated as ‘right-left’. <- Sheet ‘Dur’ in ‘SIM\_Dur\_calculation.xlsx’

3. If severe neutropenia does not happen at all, duration was set as 0. <- ‘PKPD\_5Dose\_SIM\_Male\_Dur\_includezero.csv’

4. Summarized statistics were obtained from all 100 runs: mean, standard deviation, 2.5 percentile and 97.5 percentile to show 95% CI, following R codes (R codes for summary was provided by Dr. Junan Li, who is biologist & statistician in the project).

```

n<-length(Dur)

m<-mean(Dur)

n

m

sd(Dur)

error <- qnorm(0.975)\*sd(Dur)/sqrt(n)

left <- mean(Dur)-error

right <- mean(Dur)+error

left

right

paste("95% CI is ",left,right)

SEX<-1

Level<-100

Mean<-m

SD<-sd(Dur)

Lower95<-left

Upper95<-right

data100<-c(SEX,Level,Mean,SD, Lower95, Upper95)

data100

```