# SUPPLEMENTARY MATERIAL

**Supplementary Table S1.** Summary of design characteristics of the clinical trials used either for model development or external validation.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | **MODEL DEVELOPMENT DATASET** | | **VALIDATION DATASET** |
| **Study** | | **JEAL** | **JMES** |
| **Phase** | | II | III | III |
| **Design** | | Multicenter randomized, double blinded | Multicenter randomized, open label | Multicenter randomized, double blinded |
| **Disease** | | Locally advanced or metastatic pancreatic cancer | | |
| **Dosing Schedule** | **Dose** | Gemcitabine i.v infusion  (30-60 min) 1000 mg/m2 | Gemcitabine i.v infusion  (30-60 min) 1250 mg/m2 | Gemcitabine i.v infusion  (30-60 min) 1000 mg/m2 |
| **Cycle** | 28 days/cycle.  Given once a week x3 + 1week rest | 21 days/cycle.  Given once a week x2 + 1week rest | 28 days/cycle.  Given once a week x3 + 1week rest |
| **Duration** | | 33 months | 28 months | 21 months |
| **Patients** | | 58 | 227 | 275 |
| **Gender** | **Female** | 59% | 46.50% | 43% |
| **Male** | 41% | 53.50% | 57% |
| **Age** | **Median** | 62 | 63 | 61 |
| **Range** | 34-85 | 28-82 | 34-86 |
| **Origin** | **Caucasian** | 92% | 89.70% | N.R |
| **Other** | 8% | 10.30% | N.R |
| **ECOG PS** | **0** | 32% | 31.60% | 37% |
| * **1** | 68% | 68.40% | 63% |
| **Disease Stage** | **II** | 2% | N.R | 6% |
| **III** | 9% | N.R | 4% |
| **IV** | 89% | 91.10% | 90% |
| **NODB** | **1** | 48% | | 42% |
| **2** | 39% | | 58%\* |
|  | **3** | 8% | | \* |
|  | **4** | 3% | | \* |
|  | * **5** | 2% | | \* |
| **NLSB** | **1** | 38% | | N.R |
|  | **2** | 27% | | N.R |
|  | **3** | 16% | | N.R |
|  | **4** | 10% | | N.R |
|  | * **5** | 9% | | N.R |

The overall survival data presented in Wendling et al1, and used for validation purposes, correspond to the control arm of a Phase III study2, in which patients with advanced metastatic pancreatic cancer, were treated with either gemcitabine + aflibercept or gemcitabine plus placebo (treatment arm analyzed by Wendling et al-).

ECOG=Eastern Cooperative Oncology Group; PS=Performance Status; NODB=Number of organs damaged with tumour lesions at baseline; NLSB=Number of tumour lesions at baseline; N.R=Not Reported. \* The number of organs damaged in the validation dataset was reported in two categories; (i) for 1 or (ii) for 2 or more lesions.

## References Supplementary File I

Wendling T, Mistry H, Ogungbenro K, Aarons L. (2016) Predicting survival of pancreatic cancer patients treated with gemcitabine using longitudinal tumour size data. Cancer Chemother Pharmacol (2016) 77:927–938

Rougier P, Riess H, Manges R, Karasek P, Humblet Y, Barone C, Santoro A, Assadourian S, Hatteville L, Philip PA (2013) Randomised, placebo-controlled, double-blind, parallel-group phaseIII study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. Eur J Cancer 49(12):2633–2642

**Supplementary Table S2.** Summary of model development based on -2LL values

|  |  |  |
| --- | --- | --- |
| **Model Description** | | **-2LL** |
| ***OS Model*** | Exponential | 2652.019 |
| Gompertz | 2576.734 |
| Weibull | 2523.067 |
| ***TS + OS Joint Model*** | Exponential tumour growth  Drug effect: AUC metabolite  Survival weibull. | 2009.633 |
| Exponential tumour growth  Drug effect: AUC metabolite **+resistance**  Survival weibull. | 1989.065 |
| Exponential tumour growth  Drug effect: AUC metabolite+resistance  Survival weibull **+ link TS0** | 1975.909 |
| Exponential tumour growth  Drug effect: AUC metabolite+resistance  Survival weibull + **link predicted TS** | 1945.23 |
| ***Covariate analysis*** | **Number of lesions on TS0** | 1778.758 |
| **Number of organ damaged on TS0** | 1751.865 |
| **Patient ECOG status on β** | 1733.784 |

**Supplementary Table S3.** Population Parameters Estimates

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Estimate (2.5th -97.5th)**  **Pooled dataset (n=285)**  **Final model parameters** | **Estimate**  **Subset I (n=72)** | **Estimate**  **Subset II (n=213)** |
| **TS model** |  |  |  |
|  | 6.04 (5.65-6.66)  0.299(0.208-0.363)  0.123(0.06-0.23) | 6.27  0.272  0.161 | 6.06  0.29  0.157 |
| *Kp (wk-1)* | 0.0103(0.003-0.0104) | 0.0043 | 0.0088 |
| *Slope (wk x AUC)-1\** | 0.00058 (0.00014-0.0067) | 0.0003 | 0.0005 |
| *KR (wk-1)* | 0.0162(0.013-0.129) | 0.016 | 0.0177 |
| *ISV\_TS0 (%)* | 40 (33-48) | 37 | 39 |
| *ISV\_Kp (%)* | 87(82-176) | 133 | 90 |
| *ISV\_Slope (%)* | 86(80-202) | 80 | 96 |
| *Residual error (log(cm))* | 0.276 (0.191-0.332) | 0.19 | 0.308 |
| **OS model** |  |  |  |
|  | 0.0126 (0.009-0.015) | 0.0135 | 0.0124 |
| *(wk-1)* | 1.63 (1.5-2.02)  0.433 (0.112-0.652) | 1.75  0.514 | 1.67  0.335 |
| *(log(cm)-1)* | 0.618 (0.419-1.02) | 0.514 | 0.648 |

Parameters are listed as estimates with 95% confidence intervals obtained from 500 bootstrap analyses in parenthesis (just within the pooled dataset). Estimates of inter-subject variability (ISV) are shown as coefficients of variation. θNLSB, θNODB, θECOG ,are parameters quantifying the covariate effects of the NLSB and NODB on TS0, and the ECOG status on the parameter.

\*Units of AUC of gemcitabine metabolite in white blood cells (wk·picomol/106 cells).