To quantify the association between tumor dynamics and overall survival across cancer types: a Bayesian Meta-Analysis

Assil Merlaud[1,2,3], Marion Kerioui[1,4], Jérémie Guedj[1], Davide Ronchi[5], René Bruno[2,6], Alyse Lin[7], Phyllis Chan[7], Benjamin Wu[7], Jin Y. Jin[7], Pascal Chanu[2,8], Julie Bertrand[1]

[1] Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, F-75018 Paris, France, [2] Institut Roche, Boulogne-Billancourt, France, [3] Clinical Pharmacology, Genentech-Roche, Paris, France, [4] MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK, [5] Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy, [6] Clinical Pharmacology, Genentech-Roche, Marseille, France, [7] Clinical Pharmacology, Genentech Inc. South San Francisco, USA, [8] Clinical Pharmacology, Genentech-Roche, Lyon, France

INTRODUCTION

- In oncology clinical trials, several endpoints are investigated including
  - Overall survival (OS): requiring long study duration
  - Other based on the tumor size measurement: with the Sum of Longest Diameters (SLD) of target lesions[1]
- Modelling both via survival function and tumor growth inhibition (TGI) could enable:
  - To better quantify the response of patient to treatment
  - To anticipate the treatment effect on OS using the TGI estimates
- kg (on-treatment growth constant of the SLD estimated by the Stein[2] TGI model) was shown to be a good explanatory variable of OS in different cancer types, using a two-stage TGI-OS approach[3,4]
  - No formal statistical framework to assess the heterogeneity in the impact of kg on OS across cancer types
  - Joint modelling known to provide unbiased estimate, especially for the biomarker-survival association parameter (β_{link})[5]

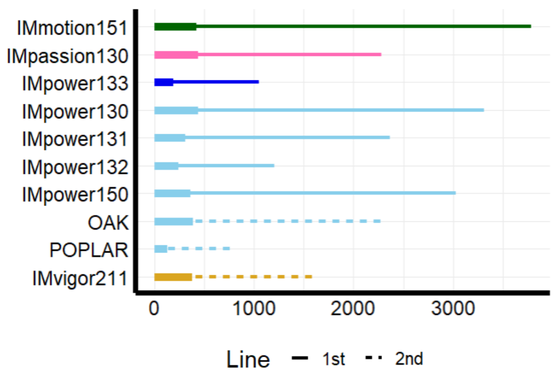
OBJECTIVES

- To assess whether the strength of the association between kg and OS is similar across cancer types
  ⇒ using a two-stage individual patient data meta-analysis (IP-DMA) with a joint modelling approach[6]

DATA

- Proprietary data - Hoffmann-La Roche: Treatment arm of 10 randomized clinical trials, investigating ≠ cancer types
- Similar population in terms of covariates across studies

Barplot of the number of patient with SLD per study (thick line) & number of SLD per study (thin line)



Cancer Type	Phase	Treatment
RCC	III	ATZ + BCZ
TNBC	III	ATZ + nab-PTX
SCLC	I/III	ATZ + CBP + etoposide
NSCLC	III	ATZ + CBP + nab-PTX
NSCLC	III	ATZ + CBP + nab-PTX
NSCLC	III	ATZ + CDDP/CBP + pemetrexed
NSCLC	III	ATZ + CBP + PTX + BCZ
NSCLC	III	ATZ
NSCLC	II	ATZ
mUC	III	ATZ

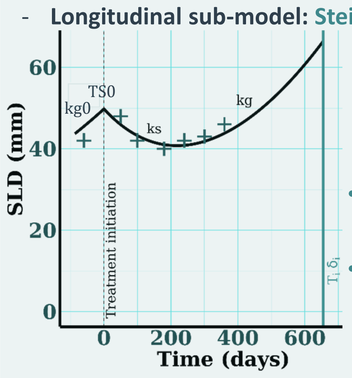
ATZ : Atezolizumab - BCZ : bevacizumab - CBP : carboplatin
CDDP : Cisplatin - PTX : Paclitaxel

METHODS

STAGE 1 – JOINT-MODEL TO ESTIMATE THE β_{link}^{s}

- **Development of the same structure of the joint model for each study s in terms of:**
  - Longitudinal sub-model for the SLD,
  - Link function between longitudinal and survival sub-models,
  - Survival sub-model for the OS,
  - Covariate model on survival sub-model
- **Estimation of the parameters for each study separately**
  - in a Bayesian framework using HMC algorithm in Stan[7]
  - for each parameter, use of the same non informative priors across studies
  - Prior in adequacy with previous work[8]

- **Longitudinal sub-model: Stein Model**

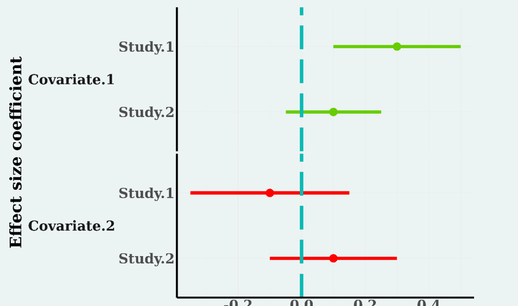


$$TS(t) = \begin{cases} if\ t \le 0 \\ TS0 \times e^{kg0 \times t} \\ if\ t > 0 \\ TS0 \times \left(e^{-ks \times t} + e^{kg \times t} - 1\right) \end{cases}$$

- Non linear mixed effect model (no IIV for kg0)
- constant residual error

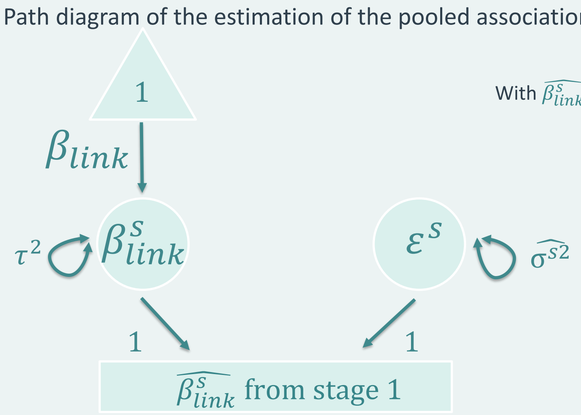
- **Link function:** log(kg) associated to a β_{link}^{s} regression coefficient
- Using the link function, investigation of **survival sub-model** as Accelerated Failure Time
  - Between: Exponential, Log-logistic, Log-normal, Weibull
  - Choice based on the minimization of the WAIC across studies

- Consideration of **covariates on survival**, among:
  1. White, Asian, Sex, Age, ECOG, CRP, Albumin, Number of Metastatic sites
  2. Incorporation in a full model per study
  3. Followed by a set of backward iteration to remove covariate with credibility interval that contained 0 accross all studies



STAGE 2 – RANDOM EFFECT META-ANALYSIS

- Path diagram of the estimation of the pooled association parameter β_{link} between the log(kg) and the survival[9]



$$\Rightarrow \widehat{\beta_{link}^{s}} = \beta_{link} + \nu^s + \varepsilon^s$$

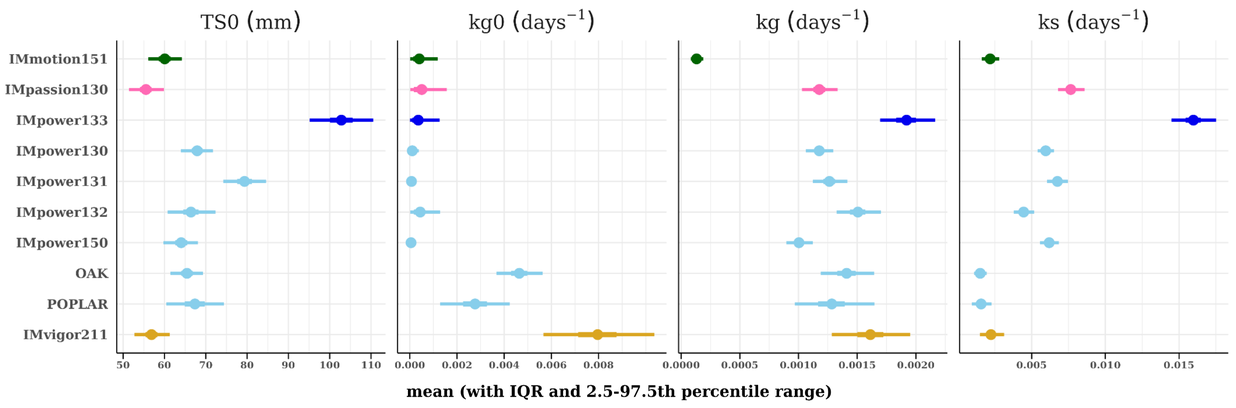
With $\widehat{\beta_{link}^{s}}$ the estimated β_{link}^{s} per study obtained with the joint model
β_{link} the mean population parameter of the link parameter
ν^s the between-study variation
$\nu^s \sim N(0, \tau^2)$ with τ^2 the between-study variance
ε^s the within-study variation
$\varepsilon^s \sim N(0, \widehat{\sigma^{s2}})$ with $\widehat{\sigma^{s2}}$ the sampling variance of the $\widehat{\beta_{link}^{s}}$
$\Rightarrow \beta_{link}^{s} \sim N(\beta_{link}, \widehat{\sigma^{s2}} + \tau^2)$

- $I^2 = \frac{\tau^2}{\tau^2 + E(\sigma^{s2})}$: proportion of heterogeneity that is not explained by the sampling error
- Meta-regression model: investigating either cancer types (NSCLC or not) or line of treatment (1st vs 2nd)

RESULTS

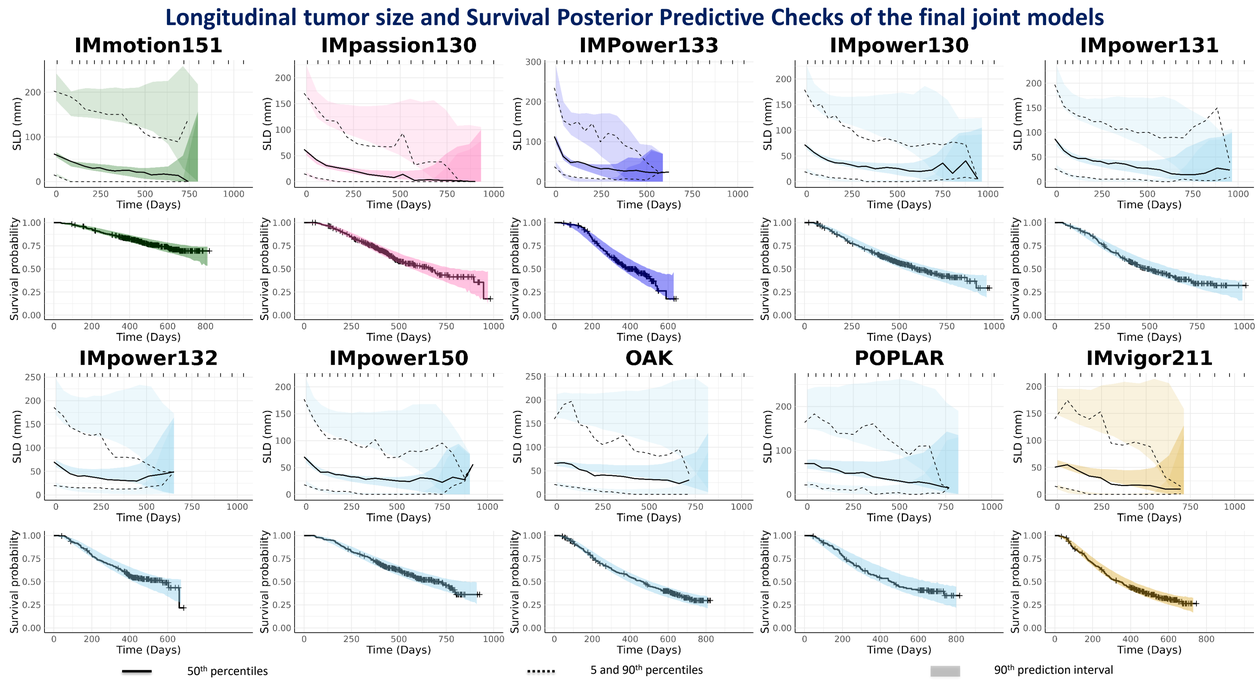
STAGE 1

Estimates of the longitudinal parameters of the joint model of each study (posterior mean and 95% credibility interval (CI))



- Longitudinal parameters of the joint model differed for each study
  - Kg0 is unidentifiable in seven studies
  - Variability of parameter estimates between study
  - Tumor growth under treatment faster for SCLC patient than for RCC patients
  - Conversely shrinkage induced by treatment was stronger for SCLC patient than for RCC patients
- Selected survival sub-model: Lognormal
- Selected covariates deteriorating the survival: High Number of metastatic sites, ECOG & CRP
- Selected covariates improving the survival: Asian & High Albumin

Longitudinal tumor size and Survival Posterior Predictive Checks of the final joint models

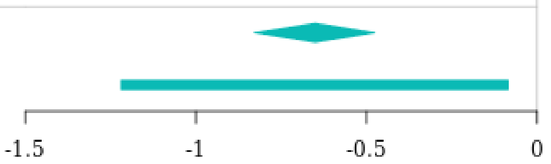


- With notable differences between studies (e.g. Immotion151 and IMpower133) , the same joint model replicated correctly the data at the individual and population level

STAGE 2

Forest plot of the β_{link} parameter estimates and the 95% prediction interval of the estimated β_{link}

study	estimate	95% CI
IMmotion151	-0.186	[-0.304, -0.067]
IMpassion130	-0.420	[-0.524, -0.315]
IMPower133	-0.662	[-0.833, -0.491]
IMpower130	-0.730	[-0.861, -0.598]
IMpower131	-0.880	[-1.007, -0.753]
IMpower132	-1.021	[-1.274, -0.767]
IMpower150	-0.741	[-0.886, -0.597]
OAK	-0.568	[-0.672, -0.464]
POPLAR	-0.683	[-0.874, -0.492]
IMvigor211	-0.702	[-0.802, -0.601]
β_{link}	**-0.650**	**[-0.829, -0.476]**
β_{link} *Prediction*	**-0.650**	**[-1.219, -0.085]**
Heterogeneity (tau): 0.24 [0.13, 0.42]		**I^2 = 92%**



- Increase of kg significantly associated with an increase of risk of death, across cancer types
- For any new study, a kg divided by 2 is expected to translate into an increase of the survival time within 6% to 132% in any cancer
  ⇒ High heterogeneity of the magnitude of this association across studies
  ⇒ Not explained by neither cancer types or line of treatment

DISCUSSION

- kg significantly associated with the risk of death regardless of study and cancer types
- The IPD-MA enabled to quantify a large β_{link} heterogeneity across studies: needs further investigation

⇒ Might by due to the use of SLD: aggregate the information of individual lesion coming from several organs

- Modelling the dynamics of the individual lesions within a patient in the context of joint model has been proposed[8,10] which enabled to quantify a β_{link} at the organ level and demonstrate a large variability across location

⇒ Using this model in the context of an IPD-MA will enable us to explore the impact of organ-specific tumor dynamics on the risk of death across cancer types, in a desire to bridge predictive capabilities among clinical trial

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