Predicting Progression Free Survival (PFS) from Measurable Residual Disease (MRD) in Chronic Lymphocytic Leukemia (CLL)

Florencia A. Tettamanti[1], Holly Kimko[2], Shringi Sharma[3], Giovanni Di Veroli[1]

Systems Medicine, Clinical Pharmacology and Quantitative Pharmacology, Astrazeneca, Cambridge, UK[1], Systems Medicine, Clinical Pharmacology and Quantitative Pharmacology, Astrazeneca, Gaithesburg, MD, USA[2], Oncology, Clinical Pharmacology and Quantitative Pharmacology, Astrazeneca, San Francisco, California, USA[3]

Background

Whilst CLL remains an incurable disease, progressive treatment has resulted in prolonged survival with median progression-free survival (PFS_{med}) reaching 5 years in first-line CLL [1]. These improved outcomes increase the follow-up times required to assess the efficacy of novel regimens and therapies in clinical trials. Identifying shorter-term surrogate endpoints for use in clinical trials would permit more rapid assessment of improved therapies. Additionally, markers predictive of individual progression could inform personalized treatment.

MRD is detectable and often quantifiable remnant cancer cells following treatment. The association between MRD and survival outcomes in haematological cancers, including CLL, has often been reported [2,3]. However, limited quantitative analyses has been undertaken to establish the predictive power of MRD in relation to progression. Better understanding of the predictive ability of MRD and its features (e.g., presence/absence) may improve our prognostic potential at a trial and individual level. To this end, we collected published CLL data and conducted analyses to evaluate the potential of MRD to assess early futility of clinical trials and to predict individual risk of progression.

Objectives

To leverage available published data to :

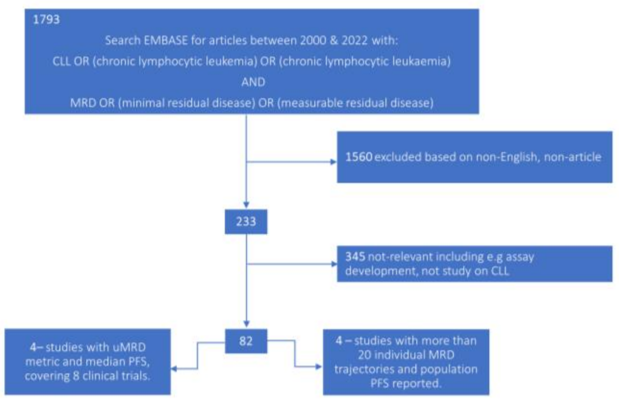
1. construct a model-based meta-analysis (MBMA) model to assess early futility of clinical trials from rates of undetectable MRD (uMRD).
2. assess whether individual MRD and study population PFS data were consistent with an underlying joint model.

Methods

Data Selection and Extraction

We conducted a systematic literature review as summarised in the consort diagram (**fig. 1**).

Fig. 1. Consort diagram



MBMA to predict PFS_{med} from uMRD rates

We calculated the relationship between uMRD rates (in %), and PFS_{med} using meta in R [4]:

$$PFS_{med} = \beta_0 + \beta_1\,\widehat{uMRD}.$$

Given an observed uMRD rate, $\widehat{\boldsymbol{uMRD}}$, in a study of n individuals, and using a normal approximation we determine the determine the distribution of uMRD rate:

$$\widetilde{uMRD} \sim N\left(\widehat{uMRD}, \frac{\widehat{uMRD}(100-\widehat{uMRD})}{n}\right).$$

Then, using eq (1), the distribution of PFS_{med}:

$$PFS_{med} \sim N\left(\beta_0 + \beta_1\widehat{uMRD}, \beta_1^2\frac{\widehat{uMRD}\left(100-\widehat{uMRD}\right)}{n}\right)$$

The probability of a related Phase III trial can be obtained by evaluating the cumulative area of distribution for desired median PFS.

Nonlinear Joint Model

For this analysis we used individual MRD trajectory data, and study population PFS. We adapted the standard joint modelling approach as follows.

First, we fit an MRD dynamic model to individual data using a non-linear mixed effects approach implemented in Monolix [5]:

$$\frac{d}{dt}M_d(t) = -Dexp(-dt), \qquad \frac{d}{dt}M_g(t) = gM_g\left(1-\frac{M_g}{K}\right)$$

$$\text{and } M(t) = M_d(t) + M_g(t),$$

where $M(t)$ is MRD; M_d and M_g are respectively the sub-population fraction of cancer cells that are exponentially dying or growing subject to logistic growth; d is tumor death rate constant; g represents the net growth rate; and K is the carrying capacity of the system.

Then, for individuals in a study, we constructed the proportional hazard function, and PFS:

$$h_{l,m,n}(t) = \left(\frac{k_l}{\lambda_l}\right)\left(\frac{t}{\lambda_l}\right)^{k_l-1}\exp\left(\alpha_{l,m}f_{m,n}(t)\right)$$

$$PFS_{l,m,n}(t) = exp\left(-\int_0^t h_{l,m,n}(s)ds\right)$$

where (k_l,λ_l) define the baseline hazard function for study l; $\alpha_{l,m}$ is the association parameter for study l of the m^{th} joint function and $f_{m,n}$(t) is the m^{th} joint function evaluated for individual n. We assessed the goodness-of-fit using the residual sum of squares between the mean of the PFS across individuals and the observed PFS of the study. We considered 3 competing PFS models:

1. **Model 1:** $f_1 = 0$, a model independent of MRD.
2. **Model 2:** $f_2 = M(0)$, a model informed by baseline MRD value.
3. **Model 3:** $f_3 = \frac{log(M(t))}{log\,M(0)}$, a model informed by the normalized instantaneous MRD value.

f_2 and f_3 were evaluated in Monolix® (24). Joint model selection and parameter estimation were done by an Approximate Bayesian Computation rejection algorithm in MATLAB [6,7].

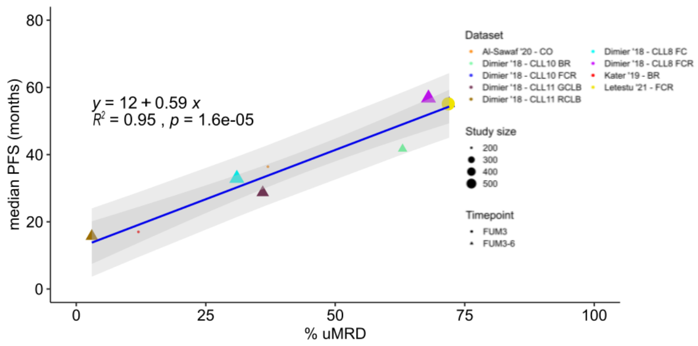
Results

MBMA to predict PFS_{med} from uMRD rates

We identified 4 papers of phase 3 clinical trials which reported PFS_{med} and uMRD rates. The trials encompassed data from 2689 patients, covering a wide range of chemotherapies with diverse mode of actions. Patient demographics were comparable and all but one clinical trial, Kater '19, was in treatment naïve cohorts.

We found a significant relationship between uMRD rates and PFS_{med}, with 95% of variability in PFS_{med} explained by uMRD rates (**fig 2**).

Fig 2 uMRD rates at 3-6 months and PFS_{med} are strongly correlated. Dark grey ribbon 95% CI of the mean, light grey 95% PI. TREATMENT: BR, bendamustine and rituximab; FC, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab; G-Clb, obinutuzumab plus chlorambucil; R-Clb, rituximab plus chlorambucil. CO: Chlorambucil-Obinutuzumab.



Excluding the study in relapsed refractory patients, minimally impacted the model parameters and the observed change was within the range observed when removing any other study (data not shown).

Verification of MBMA

We verified the meta-regression model on two additional small studies with different treatment and patient cohorts (**Table 1**).

Table 1. Summary of MBMA predictions using 2 small studies. uMRD in %, PFS_{med} in months.

PAPER	TREATMENT	SIZE	OBS. uMRD	OBS. PFS_{MED}	PRED. PFS_{MED} (95%PI)
Abrisqueta '13	FCRM+R	59	76	60	57 (47 -67)
Ritgen '04	Allo-SCT	9	29	48	29 (20-38)
	Auto-SCT	26	100	NR	71 (60-83)

Predicting probability of technical success of clinical trial with MBMA

Given a Phase 2 clinical trial of 50 subjects, receiving chemotherapy, had a uMRD rate of 65% then, $PFS_{med} \sim N\left(12 + 0.59 \times 65, 0.59^2\left(\frac{65\times(100-65)}{50}\right)\right)$.

Hence, the probability of achieving a median PFS of at least 50 months is 54%.

Joint Modelling to predict PFS from MRD

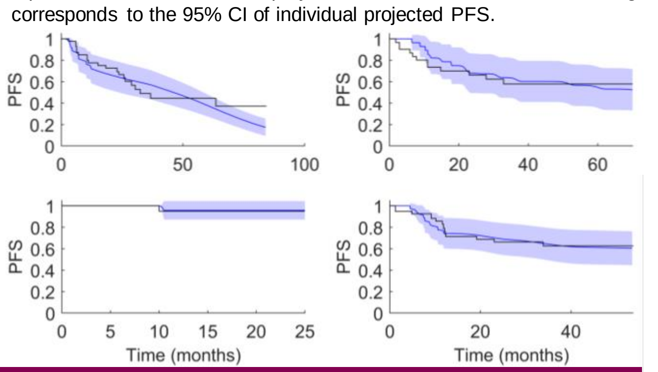
We identified 4 papers, each with 1 study, which reported PFS curves and individual MRD trajectories. The median study size was 35 (range 27-42), and patient demographics were similar across all studies. In three studies, non-naïve patients received allo-SCT. In the remaining study, patients received continuous ibrutinib and ublituximab in combination, until MRD became undetectable.

Individual MRD dynamics were adequately captured by the MRD dynamic sub-model (data not shown). In all but one study, Model 3 was the most strongly supported by the data (BF_{31}>20 and BF_{32}≥2, **Table 2**). For, Roeker '22, no single model was better supported by the data although the joint model using the continuous metric was the least well supported (BF_{21}=1, BF_{31} BF_{32}≤01, **Table 2**). Model 3 simulations are shown in **fig 3**.

Table 2. Summary of Bayes Factor, BFij. BFij corresponds to the ratio of the probability of Model i to the probability of Model j given the data.

PAPER	BF_{21}	BF_{31}	BF_{32}
Logan '13	23	80	4
Ritgen '08	32	76	2
Roeker '22	1	0.05	0.04
Tournilhac '21	29	49	2

Fig 3. Simulation with parameter set corresponding to minimal r_{ss} value for Model 3. Black-line represents observed PFS, blue line represents mean of the projected PFS and the shaded region corresponds to the 95% CI of individual projected PFS.



Conclusions

- We constructed a meta-regression model that can be used to predict PFS_{med} from uMRD rates with reasonable confidence, permitting the evaluation of technical success of a clinical trial in chemotherapies.
- We have shown that, in a joint modelling framework, the incorporation of MRD metrics could improve PFS prediction.
- Future access to more comprehensive data may address the limitations of our study and improve our findings.

References: 1) Ou Y Frontiers in Oncology 2022 12.2) Kwok M. et al. Blood. 2016;128(24):2770–3 3) Santacruz R et al, Haematologica. 2014;99(5):873–80 4) Balduzzi S, et al How to perform a meta-analysis with R: a practical tutorial. Evidence Based Mental Health. 2019. 153-60.5) http://lixoft.com/products/monolix/; 2018 6) Csilléry K et al Trends in Ecology & Evolution. 2010 Jul 1;25(7):410–8 7) https://www.mathworks.com 2022

Work supported by AstraZeneca

Presented at the PAGE Meeting, Rome, 25-28 June 2024