PK/PD relationship of the monoclonal anti-BAFF antibody tabalumab in combination with bortezomib in patients with previously treated multiple myeloma: comparison of serum M-protein and serum Free Light Chains as predictors of Progression Free survival

Pascal Chanu,[1] Rene Bruno,[1] Laurent Claret,[1] David B. Radtke,[3] Susan P. Carpenter,[2] James E. Wooldridge,[3] Damien M. Cronier[4]

[1]Pharsight Consulting Services, Lyon and Marseille, France; [2]Applied Molecular Evolution, San Diego, USA; [3]Eli Lilly and Company, Indianapolis, USA; [4]Eli Lilly and Company, Windlesham, UK

ABSTRACT

Objectives: The serum levels of M-protein were recently used in a PK/PD modeling study as a surrogate for tumor burden in multiple myeloma (MM) patients. The decrease in serum M-protein after 8 weeks of treatment proved successful as a predictor of progression-free survival (PFS) and overall survival (OS) (2,3). However, patients with oligo- or non-secretory disease cannot be included in such analyses. Alternatively, involved serum Free Light Chains (iFLC) can be measured in a greater number of MM patients (4,5), and could represent a useful tool to predict survival in a broader patient population. Here we present a PK/PD study aimed at comparing the use of M-protein and iFLC as surrogates for MM tumor burden and as a predictor of PFS.

Methods: Tabalumab is a human mAb that neutralizes membrane-bound and soluble B cell activating factor (BAFF). A combination of tabalumab and bortezomib (BTZ) was evaluated in a Phase 1 study in multiple myeloma patients (6,7). The serum levels of tabalumab, M-protein and iFLC were connected in PK/PD models by Non Linear Mixed Effect Modeling (8). The predicted decrease in serum levels of M-protein and iFLC were used to predict PFS using a previously published model (3).

Results: The PK of tabalumab was described by a 2-compartment model with mixed clearance. The PD model previously developed for M-protein (2) proved adequate to describe both M-protein and iFLC serum levels, with parameter estimates for iFLC reflective of their faster turn over. The models predicted a different dose-response relationship of tabalumab for the decrease in serum M-protein or iFLC at week 8 of treatment. However, the decrease in the serum levels of both M-prot and iFLC were predictive of preliminary PFS results in the patient population.

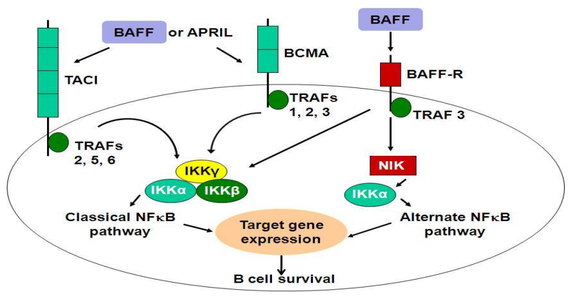
Conclusions: The time course of serum levels of M-protein and iFLC were successfully described by the PK/PD models developed in this study. The models characterized a different dose-response relationship for the activity of tabalumab on the 2 biomarkers. Both M-protein and iFLC responses were, however, predictive of PFS in the patient population.

BACKGROUND

BAFF (B-cell Activating Factor of the Tumor Necrosis Factor Family)

- BAFF binds to 3 receptors on plasma cells in marrow: BCMA, TACI and BAFF-R. There is evidence that BAFF is involved in B cell malignancies and multiple myeloma (MM) (1)

Figure 1. Pathways involved in BAFF-mediated B cell survival



Adapted from F. Mackay & C Ambrose, Cytokine & Growth Factor Rev. 2003;14:311-24; Neri P, et al. Clin Cancer Res. 2007;13:5903-9; Moreaux J, et al. Blood. 2004;103:3148-57; Novak AJ, et al. Blood. 2004;103:689-94; Briones J, et al. Exp Hematol. 2002;30:135-41.

Tabalumab is a monoclonal anti-BAFF antibody

Tabalumab was tested in a phase 1 study in combination with bortezomib IV in patients with previously treated MM (Fig. 2)

Figure 2. Study Design

Dose escalation

3 pt. cohorts + 3 pts. if DLT* occurs (up to 30 pts.)
Cycle=21 days

Dose levels 1-5: 1mg, 10 mg, 30 mg, 100 mg, and 300 mg.

Schedule

Cycle #	1	2	3	4	5	6	7	8
Bortezomib	X	X	X	X	X	X	X	X
Tabalumab	X	X	X		X		X	
Dexamethasone**	X	X	X	X	X	X	X	X

*DLT=dose limiting toxicity:
- ≥Grade 3 nonhematological toxicity
- Thrombocytopenia with platelets <10,000/μL on ≥2 occasions despite transfusion support
- Grade 4 neutropenia lasting >5 days +/or neutropenic fever ≥101 F
- >7-day delay in ability to receive Day 1 dose for Cycle 2 due to toxicity

Therapy	Administration	Days of Indicated Cycles
Bortezomib	1.3 mg/m²	Days 1, 4, 8, and 11
Tabalumab	30 min-infusion	Day 1 or Day 2 in Part B1 for DDI assessment
**Dexamethasone	20 mg po	Days 1, 2, 4, 5, 8, 9, 11, and 12

Part A Dose Escalation → Part B1 Tabalumab on Day 2 → Part B2 Safety Expansion → Part B3** + dexamethasone**

Tabalumab 100 mg i.v.

STUDY OBJECTIVES

To develop a PK/PD model describing the effect of tabalumab and bortezomib on the M-protein and involved Free Light chains (iFLC) serum levels in patients with MM

To compare the decrease in serum M-protein and iFLC serum levels at week 8 as predictors of Progression Free Survival in MM patients

METHODS

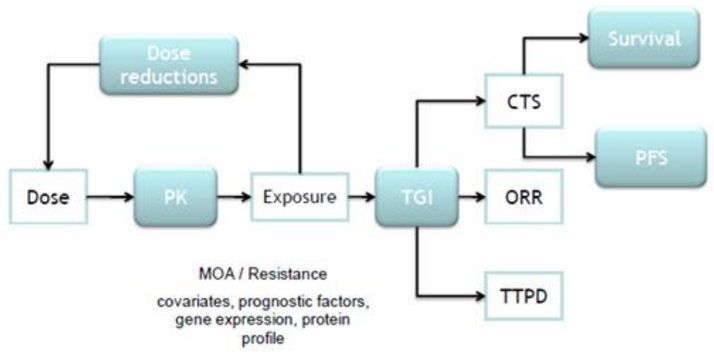
Study population

The analysis was conducted using PK and PD data collected from a subset of 45 patients enrolled in all parts of the study:

Dose (mg)	Patients included in the analysis	Patients with PK data available	Patients with detectable M-protein in serum	Patients with detectable FLCs in serum
1	3	3	3	3
10	4	4	1	4
30	5	5	3	5
100	28	28	19	28
300	5	5	3	5
Total	45	45	29	45

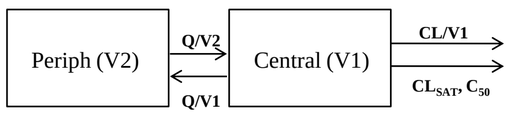
Drug-disease modeling framework

The modeling framework used in this study is similar to that previously used for dexamethasone, pomalinomide and lenalinomide in MM (3)



Pharmacokinetics

Tabalumab: a 2-compartment model with mixed clearance was selected to describe the time course of tabalumab serum levels. This model was used to generate steady state AUC estimates used as input to the M-protein and iFLC longitudinal models



Bortezomib: The dose in mg was used as input to the TGI model

Serum M-protein and iFLC longitudinal model

The time course of serum M-protein and iFLC was described using the same structural model, previously used for serum M-protein in MM patients (2), wherein Biom(t) is either M-protein or iFLC:

$$\frac{dExposure_{Taba}}{dt} = u_{Taba}(t) - Kp_{Taba} \cdot Exposure_{Taba}(t)$$

$$\frac{dExposure_{BTZ}}{dt} = u_{BTZ}(t) - Kp_{BTZ} \cdot Exposure_{BTZ}(t)$$

$$\frac{dBiom}{dt} = KL \cdot Biom(t) - KD_{Taba}(t) \cdot Exposure_{Taba}(t) \cdot Biom(t) - KD_{BTZ}(t) \cdot Exposure_{BTZ}(t) \cdot Biom(t)$$

$$KD_{Taba}(t) = KD_{0,Taba} \cdot e^{-\lambda_{Taba} \cdot t}$$

$$KD_{BTZ}(t) = KD_{0,BTZ} \cdot e^{-\lambda_{BTZ} \cdot t}$$

$$Biom(0) = BASE$$

Survival model

The change from baseline in the serum levels of M-protein and iFLC at week 8 were used as markers of the level of tumor growth inhibition and used as input to predict PFS in the patients receiving 100 mg in the study.

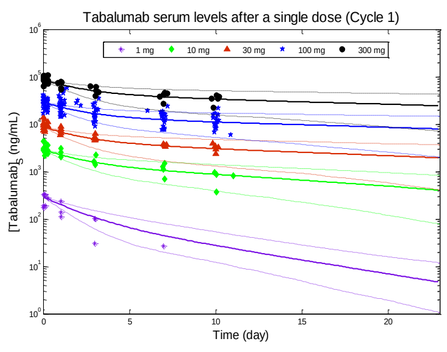
Two alternate models tested: one previously developed for dexamethasone alone and one for dexamethasone in combination with lenalinomide (3)

RESULTS

Tabalumab pharmacokinetics

The PK of tabalumab was adequately captured by the PK model over the 1-300 mg dose range studied (Fig. 3).

Figure 3. VPC of the tabalumab PK model and parameter estimates



Parameter Description	Estimate (%SEE)	%IIV (%SEE)
CL (L/day)	0.15 (11.2)	56% (20.8)
V1 (L)	3.4 (4.0)	25% (26.4)
Q (L/day)	0.7 (13.3)	---
V2 (L)	2.9 (7.9)	29% (35.3)
CL_{SAT} (L/day)	1.2 (112)	---
C_{50} (ng/mL)	161 (125)	---
σ_{prop} (%CV)	18.4 (26)	
σ_{add} (ng/mL)	47.4 (44)	

Serum M-protein levels

The time course of the change in M-protein levels in serum was adequately described by the model in the patient population (Fig. 4)

The model could separate the effect of tabalumab and bortezomib and predicted a dose-dependent effect of tabalumab on the change from baseline of serum M-protein levels at week 8 (Fig. 5)

The Posterior Predictive Check (PPC) performed on the change from baseline at week 8 in the 100 mg dose group indicates that the model is qualified (Fig. 5)

Figure 4. Example of model fit to individual serum M-protein data

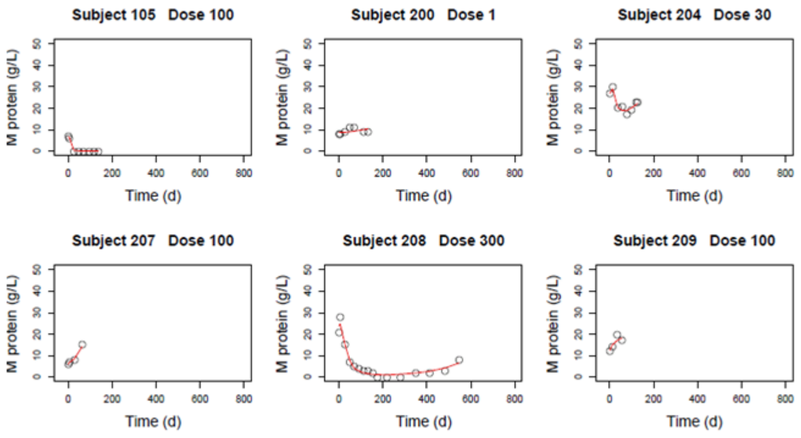
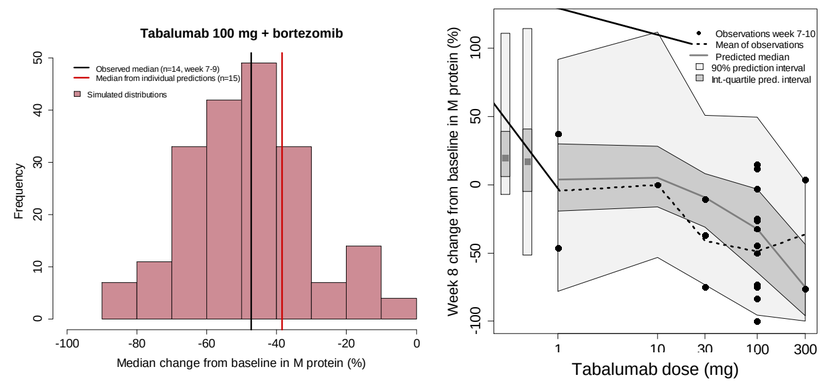


Figure 5. PPC – predicted relative change in serum M-protein levels at week 8 at the dose of 100 mg (left panel) and over the 1-300 mg dose range (right panel)



Involved serum Free Light Chains levels

The same structural model previously adopted to describe the time course of serum M-protein adequately described the time course of iFLC in the patient population (Fig. 6), and could also separate the anti-myeloma activity of bortezomib from that of tabalumab

The iFLC model, however, did not predict a dose-dependent effect on the change from baseline of iFLC at week 8 (Fig. 7)

Figure 6. Example of model fit to individual iFLC data

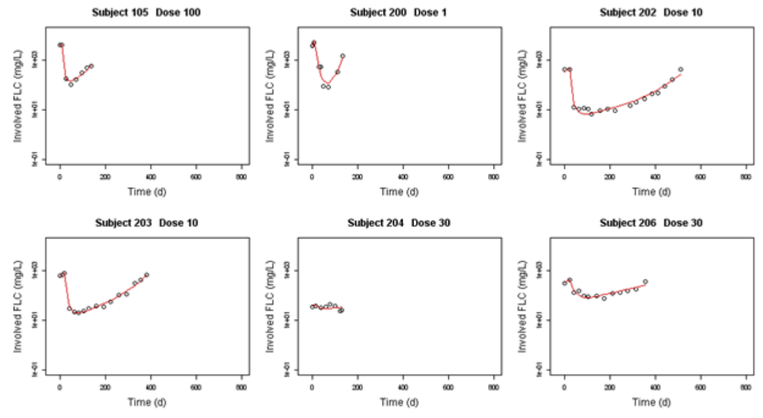
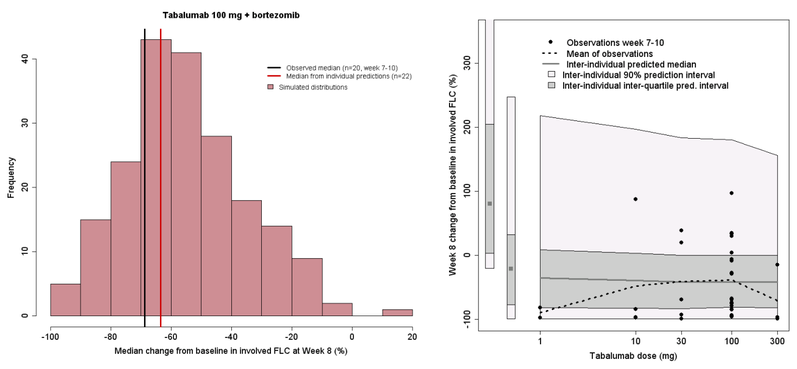


Figure 7. PPC – predicted relative change in iFLC levels at week 8 at the dose of 100 mg (left panel) and over the 1-300 mg dose range (right panel)

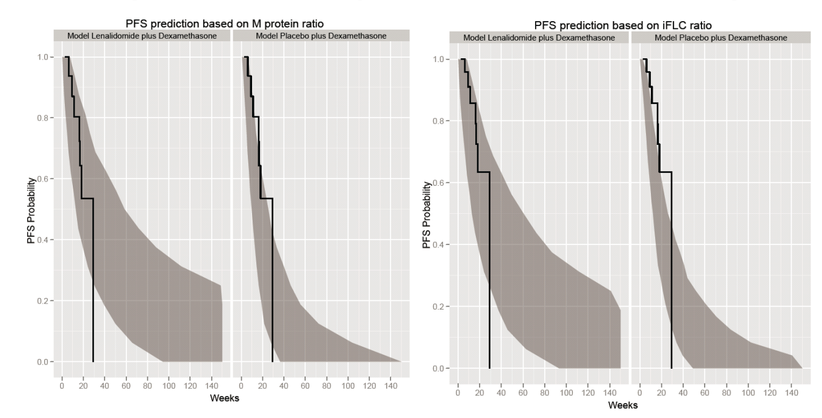


Prediction of Progression Free Survival

The model developed previously for dexamethasone in combination with lenalinomide was a better predictor of preliminary PFS in the study than that developed for dexamethasone administered alone (Fig. 8)

Using this model, the change from baseline in the serum levels of M-protein and iFLC were equally predictive of the PFS observed in the study at the dose of 100 mg

Figure 8. Observed vs. predicted PFS at the dose of 100mg



CONCLUSIONS

- The time course of the serum levels of M-protein and iFLC in this study were successfully described by the same structural PK/PD model
- Both M-protein and iFLC responses were predictive of preliminary PFS in the patient population. However, the two models characterized a different dose-response relationship for the activity of tabalumab on M-protein and iFLC serum levels
- As a result, a double blinded randomized phase 2 study is currently ongoing to test the efficacy of tabalumab at the dose of 100 and 300 mg versus placebo
- The effect of dexamethasone addition in a sub-group of patients remains unaccounted for in this analysis

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