

**The YODA Project
Research Proposal Review**

The following page contains the final YODA Project review
approving this proposal.

The YODA Project
Research Proposal Review - Final
(Protocol #: 2018-3321)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | Yes |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Approve |

Comments:

No additional comments.

**The YODA Project
Research Proposal Review**

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and
the original submitted proposal.

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2018-3321)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | No |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Not Approve |

Comments:

The aims state that "Part of data will be used for model development, remaining part will be used for external validation." However, the methods imply that this validation is uncertain: "Some of the data may be reserved to perform an external validation of the mode."
The investigators should reconcile these statements and clarify their validation plan.

Principal Investigator

First Name: Pascal
Last Name: Chanu
Degree: PharmD
Primary Affiliation: Genentech
E-mail: pascal.chanu@roche.com
Phone number: +33(0)647715016
Address: 27bis quai Paul Sedallian, 69009, Lyon, FRANCE
27bis quai Paul Sedallian
City: Lyon
State or Province: Rhône
Zip or Postal Code: 69009
Country: France

General Information

Key Personnel (in addition to PI):

First Name: Pascal
Last name: Chanu
Degree: PharmD
Primary Affiliation: Institut Roche (Roche group)

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_signed_0.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s):

1. [NCT02076009 - Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone \(DRd\) vs Lenalidomide and Dexamethasone \(Rd\) in Subjects With Relapsed or Refractory Multiple Myeloma](#)
2. [NCT02136134 - Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone \(DVd\) vs Bortezomib and Dexamethasone \(Vd\) in Subjects With Relapsed or Refractory Multiple Myeloma](#)
3. [NCT01615029 - An Open Label, International, Multicenter, Dose Escalating Phase I/II Trial Investigating the Safety of Daratumumab in Combination With Lenalidomide and Dexamethasone in Patients With Relapsed or Relapsed and Refractory Multiple Myeloma](#)
4. [NCT00574288 - Daratumumab \(HuMax®-CD38\) Safety Study in Multiple Myeloma - Open Label, Dose-escalation Followed by Open Label, Single-arm Study](#)
5. [NCT01985126 - An Open-label, Multicenter, Phase 2 Trial Investigating the Efficacy and Safety of Daratumumab in Subjects With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy \(Including a Proteasome Inhibitor and IMiD\) or Are Double](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Evaluation of longitudinal serum M protein (or free light chain) to predict survival in patients with relapsed/refractory multiple myeloma

Narrative Summary:

Longitudinal tumor size models were developed and model-based estimates of tumor growth inhibition (TGI) metrics were found predictive biomarkers of clinical outcome PFS (progression free survival) and OS (overall survival). These analyses were conducted in various cancer types with successful prediction of OS in independent Phase 3 studies based on Phase 2 TGI data (Claret et al, 2009, Claret et al 2013, Bruno et al, 2014). The link between TGI metrics and OS/PFS is assumed to be disease specific and treatment independent. The proposed study will evaluate the longitudinal dynamics of M-protein or free light chain (FLC) levels to derive TGI metrics and predict survival in multiple myeloma.

Scientific Abstract:

Background: Metrics derived by longitudinal tumor growth inhibition (TGI) modeling is an early predictive biomarker of long-term survival for several cancer types (Claret et al, 2009, Claret et al 2013, Bruno et al, 2014). Similar to tumor burden for solid tumors, serum M-protein (and/or involved FLC) levels are part of response criteria for Multiple Myeloma (MM) patients, and thus their dynamic change can predict the long-term clinical benefit (OS, PFS). Tumor growth inhibition (TGI) capture treatment effect and can predict OS (PFS) in drug-independent models. This framework can support Phase1/2 GO/NO GO decisions and the study design of Ph3 clinical trials, which use survival endpoints as primary endpoint.

Objective: Development of survival model linking OS (or PFS) to TGI metrics derived from longitudinal serum M-protein data in patients with relapsed/refractory MM and baseline prognostic factors.

Study Design and Participants: Participants will be patients with relapsed/refractory MM who have participated in the following clinical trials: NCT00574288, NCT01615029, NCT01985126, NCT02076009, NCT02136134. Part of data will be used for model development, remaining part will be used for external validation.

Main Outcome Measures: OS/PFS parametric model for MM

Statistical Analysis: A TGI model will be developed to describe the dynamic change of serum M-protein (or involved FLC) and translate it into TGI metrics. A parametric model for OS (PFS) will be developed to describe the survival time distribution as a function of TGI metrics and prognostic factors.

Brief Project Background and Statement of Project Significance:

Model-based approaches has been valuable in drug development by integrating early clinical data to enhance learning and reduce the risk/cost of large confirmatory clinical trials. For oncology drug development, the decision-making in early phases often relies on the observation of short-term tumor shrinkage and achievement of ORR while regulatory decision for drug approval depends on long-term survival improvement (OS or PSF). Despite a qualitative association between the short-term endpoint and long-term endpoints, ORR estimates obtained from early phase clinical trials are imprecise (due to small sample size) and uninformative to support Phase 3 design of clinical trials with survival endpoints as primary objective. Therefore, the proposed Modeling & Simulation framework to improve the predictions of long-term survival benefit.

For ORR and early evaluation of antitumor activity, RECIST criteria is used for solid tumors, where tumor size is originally measured by imaging techniques on a continuous scale and transformed into 4 categories (complete

response, partial response, stable disease, progressive disease). This categorization facilitates clinical interpretation of measured tumor size but has limitations as based on point estimate of categorized response. First, transforming a continuous variable into a categorical one results in loss of information. Second, RECIST assessment is categorized based on the best response at initial scan with subsequent scan only needed to confirm complete or partial response. Consequently, dynamic characteristics related to tumor progression, including natural tumor growth, treatment-related tumor shrinkage, and treatment-related resistance are generally not taken into account.

Instead of ORR, significant efforts have been made in the past decade to develop longitudinal tumor size models by leveraging all individual longitudinal tumor size information collected. These models, at a minimum, capture the competing rates of tumor size growth and shrinkage. Based on the models, several tumor growth inhibition (TGI) metrics: change in tumor size (CTS) at specified early time point, time to tumor growth (TTG), and tumor growth rate (KG) can be derived and linked to survival endpoints. This model-based approach has been applied to predict clinical response and OS in cancer patients for a variety of clinical settings (Claret et al, 2009, Claret et al 2013, Bruno et al, 2014).

In MM, M-protein (or involved FLC) are produced in excessive amounts by malignant plasma cells. The reduction of M-protein and normality of FLC ratio are part of the International Myeloma Working Group Uniform Response Criteria to assess response. Unlike tumor size for solid tumors, subject to a maximum of five target lesions per RECIST and based on imaging result assessed every 6-8 weeks, M-protein/FLC represents the total body burden and is measured in blood. Given the potentially better data quality and quantity with M-protein, we will evaluate the use of TGI modeling based on longitudinal M-protein (or FLC) data to predict long-term survival outcomes in MM patients as reported in previous analyses (Jonsson et al, 2015).

Specific Aims of the Project:

The overall objective of this study is to assess whether the routine short-term measurement of M-protein (or FLC) could be used to predict long-term survival benefit for MM subjects under treatment.

Our specific aims are:

- 1) Develop longitudinal models for M-protein (or FLC) by utilizing data from MM clinical studies of NCT00574288, NCT01615029, NCT01985126, NCT02076009, NCT02136134 to derive TGI metrics;
- 2) develop parametric survival models by establishing the link between TGI metrics and OS (or PFS) and by identifying baseline patient prognostic factors for OS (or PFS).

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Patient-level data from Studies NCT00574288, NCT01615029, NCT01985126, NCT02076009 and NCT02136134. The following clinical and laboratory variables are requested:

1. Time posted the first treatment
2. Serum M protein over time
3. FLC over time
4. OS (1=evt, 0= censor)
5. PFS (1=evt, 0= censor)
6. Treatment arm
7. Study
8. Line of therapy
9. Refractory or relapsed status
10. Baseline ECOG
11. ISS
12. RISS
13. Prior therapy
14. Age
15. Baseline body weight

16. Baseline creatinine
17. Baseline LDH
18. Baseline Hemoglobin (g/L)
19. Baseline Albumin (g/L)

Main Outcome Measure and how it will be categorized/defined for your study:

OS (or PFS) parametric model for MM disease

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

TGI metrics derived from individual M-protein (or FLC) data over time.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Baseline prognostic factors

Statistical Analysis Plan:

The Modeling & Simulation framework employed here is based on: a drug-dependent TGI model and a drug independent (disease dependent) survival model. Treatment effect is captured by the TGI metrics which can be considered as biomarkers and known as very good predictors of survival outcomes.

TGI model

Longitudinal M-protein (or FLC) will be analyzed using non-linear mixed effects modeling in NONMEM. Two model structures will be tested:

1. Simplified TGI model by Claret et al 2013
2. Bi-exponential model by Stein et al, 2011

Those models will be used to derive metrics: tumor size ratio to baseline at week 8 (TS ratio, with model 1), Time to Growth (TTG, with model 1) and KG (growth rate constant, with model 2). There will be no formal further development of the TGI models because they are already established and only meant to derive TGI metrics but there could still be some model optimization (random effects, error model), candidate models will then be selected based on the minimum objection function ($-2 \times \log \text{likelihood}$).

Survival model

1. TGI metrics will be merged with survival data (OS/PFS) i.e. survival time and information on death/progression events, censoring, potential baseline prognostic factors.
2. The impact of individual baseline prognostic factors and TGI metrics on OS/PFS will be explored using Kaplan-Meier and Cox regression analyses using `survfit` and `coxph` functions, respectively in R. The univariate Cox survival analysis (`coxph` function in R) will be performed to screen relevant prognostic factors prior to parametric modeling.
3. The survival analysis will be performed in R using a parametric survival modeling approach using the `survreg` function in R. The probability density function that best describes the observed survival times will be selected among normal, lognormal, Weibull, logistic, log-logistic, and exponential using the difference in Akaike information criterion (AIC) of the alternative models. A "full" model will be built by including all significant covariates screened in the Cox univariate analysis with a significance level of $p < 0.05$ per the log-likelihood ratio test where the difference in $-2 \times \log \text{likelihood}$ (score) between alternative models follows a χ^2 distribution. The score indicates the level of significance for the association between a covariate and OS (or PFS): the higher the score, the more significantly this covariate is associated with OS (or PFS). Then a backward stepwise elimination will be carried out. At each elimination step, one covariate will be removed from the model. If the reduced model (without this removed covariate) becomes significantly worse ($p < 0.01$), the removed covariate stays in the model. The relative influence of each remaining covariate on the model will be re-evaluated by deleting it from the reduced model on an individual basis with a significance level of $p < 0.01$. The backward elimination will result in the final model, in which all covariates will be significant.
4. The predictive performance of the model will be assessed by posterior predictive checks.
5. Some of the data may be reserved to perform an external validation of the model.

Project Timeline:

The project is expected to be completed 1 year after data availability.

1. Completion of contract: July 2018
2. Obtain de-identified dataset: Aug-September 2018
3. Analysis and report submitted to YODA: March 2019
4. Circulating of abstract targeting ASH 2019 to YODA: April 2019
5. Circulating of paper to YODA targeting xxx Journal: July-Aug 2019

Dissemination Plan:

The obtained model may be potentially used by the scientific community:

1. Characterize the link between (TGI) metrics as biomarkers to capture treatment effect and predict for OS/PFS benefit in "drug-independent" survival models
2. Simulate survival outcomes for any new therapy for which TGI metrics will be determined.

The resulting model(s) will be published and made available to the community.

1. Circulating of abstract targeting ASH 2019 to YODA: April 2019
2. Circulating of paper to YODA targeting xxx Journal: July-Aug 2019

Target journals are:

Clinical Pharmacology & Therapeutics (CPT)

CPT: Pharmacometrics & Systems Pharmacology (CPT: PSP)

Bibliography:

Bruno R, Mercier F and Claret L. Evaluation of Tumor Size Response Metrics to Predict Survival in Oncology Clinical Trials. *Clin Pharmacol Ther* 95:386-393, 2014

Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, Fagerberg J, Bruno R. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics *Journal of Clin Oncol*, 27, 4103-4108, 2009.

Claret L, Gupta M, Han K, Joshi A, Sarapa N, He J, Powell B and Bruno R. Evaluation of Tumor-Size Response Metrics to Predict Overall Survival in Western and Chinese Patients With First-Line Metastatic Colorectal Cancer. *Journal of Clin Oncol*, 31, 2110-2114, 2013.

Jonsson F, Ou Y, Claret L, Siegel D, Jagannath S, Vij R, Badros A, Aggarwal S, Bruno R. A Tumor Growth Inhibition Model Based on M-Protein Levels in Subjects With Relapsed/Refractory Multiple Myeloma Following Single-Agent Carfilzomib Use. *Clinical Pharmacology Therapeutics: Pharmacometry and System Pharmacology*, 4, 711-719, 2015.

Stein WD, Gulley JL, Schlom J, Madan RA, Dahut W, Figg WD, et al. Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. *Clin Cancer Res*, 17(4), 907-917, 2011.