ARTICLE - Plasma Cell Disorders

Adjusting for subsequent therapies in the TOURMALINE-MM1 study shows clinically meaningful improvement in overall survival with addition of ixazomib to lenalidomide and dexamethasone

Karthik Ramasamy,[1] Nizar J. Bahlis,[2] Shaji K. Kumar,[3] Arun Kumar,[4] Holly Cranmer,[5] Bingxia Wang,[4] Jonathan Dabora,[6] Richard Labotka,[4] Paul G. Richardson[7] and Philippe Moreau[8]

[1]Oxford University Hospitals NHS Foundation Trust and Oxford Translational Myeloma Center, University of Oxford, Oxford, UK; [2]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, Alberta, Canada; [3]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [4]Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA; [5]Takeda UK, London, UK; [6]Takeda Pharmaceuticals America, Inc., Lexington, MA, USA; [7]Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA and [8]University Hospital Hôtel Dieu, Nantes, France

Correspondence: K. Ramasamy
karthik.ramasamy@ndorms.ox.ac.uk

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Supplementary Material

Inverse probability of censoring weights (IPCW)[1,2]

The IPCW method artificially censors switchers (i.e., patients receiving subsequent therapies) at the time of treatment switch, and then weights each patient's contribution to the estimation based on the patient's propensity for switching to subsequent therapy, predicted by baseline and time-dependent covariates. Estimates obtained using this pseudo population then have causal interpretation free of the impact of the subsequent therapy. The IPCW are estimated using logistic models on the whole dataset with the binary outcome of censoring at the time of switching to a subsequent therapy (0 if not censored, 1 if censored) as the response, and study treatment and baseline/time-varying characteristics as covariates.[3] Individual logistic regression models (for both numerator and denominator of the inverse censoring weight) started with all pre-specified covariates, which included both the time-fixed and time-varying covariates: region (North America *vs.* others), age (<75 *vs.* ≥75), race (white *vs.* non-white), Eastern Cooperative Oncology Group score (0 or 1 *vs.* 2), relapse and/or refractory (relapsed *vs.* refractory *vs.* relapsed and refractory), type of myeloma (IgA *vs.* other), percentage of plasma cells (≤30 *vs.* >30; missing), presence of extramedullary plasmacytomas (yes *vs.* no), presence of lytic bone lesions (yes *vs.* no), cytogenetic abnormalities (high risk *vs.* others), prior lenalidomide (yes *vs.* no), prior thalidomide (yes *vs.* no), prior proteasome inhibitor (yes *vs.* no), number of line therapies (1 *vs.* 2 or 3), baseline hemoglobin, baseline platelets, creatinine clearance (median), albumin (median), lactate dehydrogenase (median), β2 microglobulin (median), and corrected calcium (median); duration of exposure, disease progression status at each study visit, hemoglobin value at each study visit and progression/relapse, platelets value at each study visit and progression/relapse, M-protein value at progression/relapse, type of subsequent therapy with proteasome inhibitor, types of subsequent

therapy with immunomodulatory drugs. Each logistic model was shrunk until no covariate in the model had a *P* value more than 0.1. Covariates remaining in any of the individual models were retained in all the logistic models. Stabilized weights were used for the analyses. A stratified weighted Cox model was used to estimate the hazard ratio (HR), and the Chi-squared test was used to generate the *P* value for treatment effect. The Cox model results were used to generate the survival curves.

Marginal structural model (MSM)[4]

A logistic model on the whole data from both arms with a switch to a subsequent therapy (0 if not switched, 1 if switched) as the response, and study treatment and pre-specified baseline/time-varying characteristics as covariates was used to calculate the inverse probability of treatment switching weight (IPTW). Separately, to adjust for possible bias caused by informative censoring, a logistic model on the whole data from both arms with censoring (0 if not censored, 1 if censored) as the response, and study treatment and baseline/time-varying characteristics as covariates was used to calculate the IPCW. Afterwards, IPTW and IPCW were multiplied for each patient at each observed timepoint to get the combined inverse probability weight for each patient. Like the IPCW method, individual logistic regression model building started with all covariates, and was shrunk until no covariate in the model had a *P* value more than 0.1. Stabilized weights were re-scaled using a similar approach as described for the IPCW method.

A stratified Weighted Cox model that has treatment, indictor function for the switch to subsequent therapy, and an interaction of the previous two variables was used to estimate the HR. Chi-squared test for HR=1 as the null hypothesis was used to generate the *P* value.

Rank preserving structural failure time model (RPSFTM)[3,5]

The RPSFTM method adjusts the survival times for the switchers using an acceleration factor (calculated through g-estimation) such that they represent the predicted survival time had the patient not switched and received subsequent therapies. As there was no protocol-defined crossover in this study, we followed a similar implementation approach as in the "treatment group" approach described in the literature.[6-8] Following this we assumed that:

1. Patients in the IRd arm continued to derive similar benefit until death/censor post study treatment discontinuation as when they were on-treatment, and
2. Patients in the Rd arm post discontinuation derived the same survival benefit as patients in the IRd arm (common treatment effect assumption).

Based on the above assumptions, the acceleration factor was estimated and then used to estimate the counterfactual survival time from subsequent therapy to death/censor and thus overall counterfactual survival time if patients would not have switched to a subsequent therapy for patients in the Rd arm. Recensoring is applied as explained in Latimer *et al.*[9] where the recensoring cut-off was the longest survival time in this study. A stratified Cox proportional hazards model was used to estimate the HR, and a stratified log-rank test was used to generate the *P* value, by using randomization stratification factors. The Kaplan-Meier estimates for counterfactual survival time were used to generate the survival curves.

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