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Genetic and Transcript Changesin Cereblon in IMiD-Treated Myeloma Patients

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Myeloma survival has been significantly improved by novel therapies over the past two decades. Immunomodulatory agents (IMiDs, Lenalidomide (LEN) and Pomalidomide (POM)) are a backbone of current treatment strategies. But myeloma (MM) remains incurable, because patients ultimately relapse.

IMiD drug resistance mechanisms are multifactorial, and can be either dependent or independent of IMiDs binding to Cereblon (CRBN) (a component of an E3 ligase) in tumor and immune cells. A small series of relapsed patients demonstrated sub-clonal mutation rates of 12% in CRBN and 10% in other CRBN pathway genes (Kortum *et al*, Blood 2016), but the clinical implication of this observation is unknown. In contrast, baseline gene expression of CRBN was not associated with clinical outcome to POM-DEX therapy (Qian *et al*, Leukemia & Lymphoma 2018). An integrated assessment of the burden of

different mechanisms of CRBN function loss, the selective pressure for their survival, and their effects on response to CRBN-modulating agents, is lacking.

For patients that progress on IMiD-based therapies, there is a need to develop drugs that will overcome their resistance. To appropriately target the right novel agents to the right patients, resistance mechanisms must be understood. A deeper understanding of the mechanistic basis for IMiD-specific resistance mechanisms is critical for differentiating new Cereblon modulating agents (eg CELMoDs) from the IMiDs.

Here, we present the largest comprehensive analysis of the burden of CRBN mutation or transcript variants in relapsed refractory myeloma (RRMM) patients. We analysed WGS and RNASeq data from 298 MM samples from 268 patients across 4 clinical trials (CC-4047-MM-010 (N=226), CC-4047-MM-013 (N=17), CC-220-MM-001 (N=45) and CC-122-ST-001MM2 (N=10), for whom outcome data were available. All patients had been exposed to LEN-based therapy and a subset (69/268) were also exposed to POM-based therapy.

The overall incidence of single nucleotide variants in CRBN was 17/298 (5.7%). The incidence of at least monoalleleic deletion at the CRBN gene locus was 21/298 (5.5%). CRBN has different transcript isoforms (Gandhi *et al*, BJHaem 2014). As high levels of isoform ENST00000424814.5, with deletion of exon 10, was previously correlated with poorer survival (Neri *et al*, Blood 2016), we assessed incidence of a high ratio (>2) of exon 10-deleted CRBN transcript to full length CRBN transcript. 92 samples had sufficient purity (>90% tumor cells) for this analysis. 13/92 samples (14.1%) had a high exon10-deleted transcript ratio. Overall, 43/268 (16.0%) patients had genetic or transcript variants in CRBN. In contrast, 27/514 (5.2%) newly diagnosed myeloma (NDMM) patients from the Myeloma Genome Project had genetic or transcript variants in CBRN; 2/514 (0.4%) had CRBN mutations, 11/514 (2.1%) had CRBN gene deletion and 14/514 (2.7%) had a high exon10-deleted transcript ratio. Thus, there was an increase in CRBN variants from NDMM to RRMM.

In patients exposed to LEN but not POM (219/268), there were 5 CRBN mutations, 14 monoallelic CRBN deletions and 13/92 patients with high exon10-deleted transcript ratio. In 69/268 patients exposed to POM (baseline from CC-220-MM-001 (N=35), CC-122-ST-001MM2 (N=10), or follow up samples from CC-4047-MM-010 (N=24)), there were 12 CRBN mutations in 8 patients (11.6%) and 7 CRBN deletions (10.1%), approximately double the incidence seen in the whole cohort. 3 CRBN deletions were homozygous, which was not observed in non-POM-exposed individuals. Sample purity was insufficient to measure transcript ratios.

In summary, 16.0% of RRMM patients that received LEN or POM have genetic or transcript variants in CRBN, a higher proportion than in NDMM. The impact of these aberrations on CRBN function, especially

related to binding of CRBN-modulating drugs, remains to be ascertained. Analysis of the correlation between CRBN variation and response to therapy, clinical outcomes, and the incidence and effect of mutation or copy loss of CRBN interactors (E3 Ligase members and regulators, CRBN substrates) is underway and will be presented.

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