## C-025

# CDKN2C IN MULTIPLE MYELOMA: BIOLOGICAL AND CLINICAL IMPLICATIONS

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**Introduction:** *CDKN2C* (*p18*$^{INK4c}$) is a negative regulator of the G1/S transition point, and alterations of this cyclin-dependent kinase inhibitor (CKI) may result in cell-cycle progression suggesting that its cellular function is important in myeloma biology. Deletions of *CDNK2C* have been previously identified in myeloma cell lines and we have been able to extend this analysis further by defining the role of *CDKN2C* inactivation in primary patient material.

**Materials and Methods:** We analyzed 78 cases using the Affymetrix SNP mapping and U133 plus 2.0 expression arrays. Copy number, loss of heterozygosity analysis and supervised hierarchical clustering were performed using dChipSNP.

**Result:** High resolution gene mapping allowed the identification of one small homozygous deletion at 1p32.3. This region contains the transcript *CDKN2C*. We found 3 homozygous deletions (median size 0.43 Mb; range 0.39-1.74 Mb) and 9 hemizygous deletion at the same region comprising 15% of all cases. The expression pattern of *CDKN2C* was examined in the total data set. The distribution of the expression patterns highlights the strong correlation of low expression of *CDKN2C* with homozygous deletion. In addition, three cases with hemizygous deletion and 29% cases without alterations of 1p32.3 also expressed *CDKN2C* at a similar low level. We correlated the expression level of *CDKN2C* with a proliferation index (PI). The three cases with homozygous deletion of *CDKN2C* grouped together with the most proliferative myelomas, consistent with the biological function of a CKI. We looked at the impact of the PI on progression free survival (PFS) and overall survival (OS), and found that the group with high PI had a worse outcome than the group with low PI (median, 15 versus 25 months; $P$=0.1). We examined the impact of copy number change at *CDKN2C* on outcome and found that the cases which were intact at this region had an improved PFS compared to cases with loss of either one or two copies of *CDKN2C* (median, 13 versus 22 months; $P$=0.1).

**Conclusions:** We have identified inactivation of *CDKN2C* as being an important mechanism of deregulation of the G1/S transition in presenting clinical material.