**Introduction** Multiple Myeloma (MM) evolution and heterogeneity is interesting for its potential translational relevance. Recent studies using bulk sequencing of Smoldering MM cells obtained from Bone Marrow (BM) report recurring CNA patterns. By analyzing single-CMMCs isolated from enriched peripheral blood, we show here, for the first time in MM, evidence of frequent convergent lesions, i.e. alterations developed independently across different evolutionary branches, including CNAs often found in MM and previously reported as common truncal alterations.

**Methods** Peripheral blood samples (4.0 ml) were obtained from n=3 patients with MM. CMMCs were enriched with CellSearch® AutoPrep® using a custom kit with anti-CD138 or anti-CD138/CD38 antibody-conjugated ferrofluids for positive enrichment and CD38-PE, CD19/CD45-APC immunofluorescent staining for detection. Cell enumeration was based on the co-localization of nuclear DAPI staining and CD38-PE on CellSearch CTAII®. Single CMMCs (CD38+/CD19- and CD45-/DAPI+) and White Blood Cells (WBCs: CD38-/CD19+ or CD45+/DAPI+) were then isolated with DEPArray NxT system. Single-cell genomic DNA was amplified using Ampli™ Whole Genome Amplification (WGA) kit, Illumina®-compatible libraries were obtained using Ampli™ LowPass kit and the process was automated on a Hamilton STARlet Liquid handler. Multiplexed, low-pass whole-genome sequencing was performed on HiSeq 2500 Illumina® platform. Genome-wide single-cell Low-Pass Copy Number Alteration (LPCNA) analysis was performed using the cloud-based bioinformatic suite MSBiosuite (Menarini Silicon Biosystems).

**Results** 186/215 (86%) single CMMCs passed QC criteria and were included in the analysis. Single WBCs were also included as normal controls. Cumulatively, CNA profiles of single CMMCs showed patterns typical of MM, including 1q gain, 13 monosomy, sub-chromosomal gain or trisomy 3, 5, 7, 9, 11, 15, 21. Intra-patient single-cell profiling surprisingly revealed convergent lesions, i.e. alterations developed independently across different evolutionary branches, along with conserved (common truncal), and divergent alterations (found only in specific sub-clusters). In addition, in one patient, we found evidence that 1q gain, 13q deletion and 6p gain were actually sub-clonal, in contrast with recent publications reporting them as truncal early-onset lesions.

**Conclusions** Single CMMCs CNA profiling reveals patterns of frequent convergent alterations developed independently through branched evolution, undetectable through bulk sequencing.