160 CIRCULATING TUMOR DNA FOR MEASURABLE RESIDUAL DISEASE (MRD) DETECTION IN MULTIPLE MYELOMA PATIENTS UNDERGOING CAR T-CELL THERAPY

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Background Measurable residual disease (MRD) is an important predictor of survival outcomes in both newly diagnosed and relapsed/refractory multiple myeloma (MM). Currently, it is assessed by bone marrow aspirate, either using next-generation sequencing or multi-color flow cytometry. However, not only does it require an invasive procedure, it may not capture the spatial heterogeneity of the tumor. Here, we apply cell-free DNA liquid biopsies via Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) to detect circulating tumor DNA (ctDNA) and quantitatively track in MM patients undergoing anti-BCMA CAR T-cell therapy.

Methods We performed CAPP-Seq for the detection of ctDNA using a MM-specific gene panel, which we previously developed.[1] A total of 252 plasma, germline and tumor samples from 28 patients receiving BCMA directed standard of care CAR-T therapy (idecabtagene vicleucel, n=23 or ciltacabtagene autoleucel, n=5) were sequenced to assess the dynamics of ctDNA. Clinical MRD was performed on day 90 (+/- 15 days) after CAR infusion by ClonoSeq (Adaptive Biotechnologies), or by multiparametric flow cytometry (Mayo Clinic) in patients without a trackable sequence for ClonoSeq. The clinical MRD and ctDNA levels at matched timepoints were assessed for correlation. These metrics were also correlated with patient outcomes.

Results Using CAPP-Seq, a median of 90 SNVs (range 2–264) were detected per case; 24/28 patients (86%) had a sufficient number of variants for tumor monitoring. On day 90, 14 patients had evaluable plasma. For clinical MRD, 24/28 patients were submitted for identification of trackable sequences by ClonoSeq including 6 patients who already had identified clones during prior therapy; 8/24 patients (33%) failed the identification of dominant sequences. For these patients, MRD flow cytometry was sent on day 90. Overall, 16 patients had clinical MRD data (ClonoSeq, n=13; flow, n=3). For patients who had both day 90 ctDNA and clinical MRD (n=14), there was a significant correlation in quantification by respective measures (rho=0.71, p=0.007; figure 1A). Kaplan-Meier analysis showed progression-free survival (PFS) significantly correlated with day 90 ctDNA level (p=0.03; figure 1B) as well as clinical MRD (p=0.008).

Conclusions MRD has emerged as an important prognostic biomarker in MM. However, current methods depending on bone marrow aspirates limit the frequency of assessment. ctDNA assessment by CAPP-Seq can quantitatively follow the disease burden and assess MRD. ctDNA-MRD levels correlate with clinical MRD, and ctDNA negativity on day 90 is associated with improved PFS. ctDNA-MRD can potentially provide comparable information to clinical bone marrow MRD.

REFERENCE

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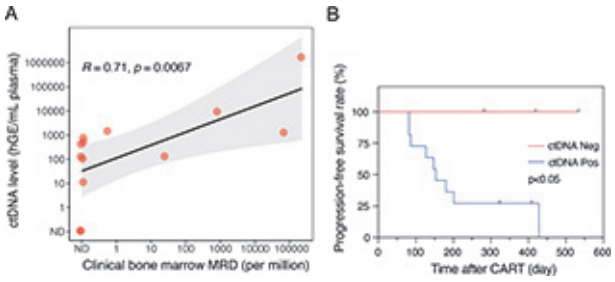
Ethics Approval This study has obtained ethics approval by Stanford IRB under protocol number of #18329 and #5019.

All the participants gave informed consent before taking part.



Abstract 160 Figure 1 Assessment of MRD by circulating tumor DNA. (A) Correlation between day 90 ctDNA level and clinical bone marrow MRD assay (ClonoSeq, n=11; MRD flow, n=3). (B) Kaplan-Meier curve of progression-free survival (PFS) according to the ctDNA positivity at day 90.

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