ctDNA monitoring of metastatic melanoma patients receiving immunotherapy

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Background & objectives

Signal transduction inhibition as well as Immune-Checkpoint Inhibition (ICI) have revolutionized the treatment of patients with metastatic melanoma. A radiological assessment following RECIST 1.1 criteria is the current standard definition of resistance. Nevertheless, the subsequent treatment switch can be too late to improve patient´s overall survival. Analysis of circulating tumor components in blood, such as circulating tumor DNA (ctDNA), shows promising potential to close this gap. Here, we monitored ctDNA in blood samples from patients with metastatic melanoma receiving immune checkpoint inhibition (ICI) therapy.

Methods

The mutational landscape is being examined in over 250 time points of 42 metastatic melanoma patients (stage IV) receiving ICI, using the Plasma SeqSensei™ technology, which includes a PCR-based amplification of five mutations (BRAF, EGFR, KRAS, NRAS, PIK3CA), and was applied to peripheral blood samples obtained before and during the course of immunotherapy. The underlying technology is intended for the ultra-sensitive detection and quantification of clinically relevant somatic mutations in plasma DNA by assigning a unique identifier (UID) to each DNA molecule prior to sequencing. Patients were subdivided into: (i) Responder (PR= Partial Remission; SD= Stable Disease; CR=Complete Remission) within the first 6 months from baseline); (ii) Non-responder (time points: 3 months before progression to 3 months after progression).

Results

Plasma SeqSensei™ allowed the discrimination of a truly mutated template sequence from sequence variations andhigh sensitivity down to 0.07% mutant allele fractions (MAF) and an absolute detection limit of 7 mutant molecules (MM). Changes in ctDNA levels during therapy

correlated with treatment response, where increasing ctDNA was predictive for disease progression and decreasing ctDNA was predictive for treatment response. Increasing ctDNA levels predicted disease progression earlier than routine radiologic scans (median: 7 weeks). Cerebral metastasis was not always reflected in ctDNA levels. A discrepancy between MAF and MM/mL could be observed, which might be related to adverse autoimmune events. An in-depth computational analysis of the patient-specific courses will be presented at the congress.

Conclusion

Our study shows the feasibility of ctDNA monitoring in metastatic melanoma patients receiving ICI therapy, which might be integrated into an update of the RECIST criteria in the near future.