Utility of the microflex LT platform in the development of serum proteomic companion diagnostic (CDx) tests in NSCLC

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Long Abstract:

Clinical oncology assays using mass spectrometry have exclusively been run on instrument platforms designed for use in research (RUO) laboratories. RUO instruments (autoflex™ III and autoflex SPEED) have been historically used for measurement of serum proteomic profiles in NSCLC. Here, we employ the microflex™ LT (LT), a MALDI-TOF MS which is a component of Bruker's FDA cleared MALDI Biotyper CA system, for development of a CDx test. The companion diagnostic test, BDX004, is currently under development as part of a global, randomized, double-blind Phase 2 clinical study, FOCAL. BDX004 will be used prospectively to select previously untreated, EGFR mutation-positive patients with advanced NSCLC to receive one of two treatments: (1) the combination of ficlatuzumab (a humanized monoclonal antibody against hepatocyte growth factor) and an EGFR tyrosine kinase inhibitor (TKI), or (2) an EGFR TKI with placebo. In the present study, we evaluated the LT through comparative studies with RUO MALDI-TOF instruments utilizing samples from patients previously diagnosed with NSCLC. In summary, we found that, under common laboratory procedures, the LT produces results equivalent to research grade MALDI-TOF MS instrumentation. In initial studies, the microflex LT showed similar resolution ($R > 600$ at 6632.1 m/z) and sensitivity ($S/N \geq 50$ with 500 fmoles BSA in 100 laser shots) performance parameters as the autoflex series research instruments ($R > 800$ at 6632.1 m/z and $S/N \geq 50$ with 500 fmoles BSA in 250 laser shots). The LT was qualified with several independent sample sets [n = 4 (8 replicates; 2000 spectra/replicate), n = 67 (3 replicates; 2000 spectra/replicate), and n = 20 (3 replicates; 2000 spectra/replicate)] and achieved 100%, >97%, and 100% concordance with reference data sets previously acquired on the autoflex platforms. As expected, due to the lower laser repetition rate of the LT's nitrogen laser, the acquisition speed was slower on the LT as compared to the

autoflex instruments by a factor of two. However, the slower acquisition speed is partially compensated for with increased sensitivity, which is particularly evident in the reference sample mass spectra which have signal-to-noise ratios ~1.5 greater than those acquired on the autoflex platform. The LT has now been used to evaluate >300 additional samples in NSCLC patients and achieved results with similar concordance with results obtained through research grade RUO MALDI-TOF MS instrumentation. Based on these studies, the microflex LT appears to be suitable for measurement of serum proteomic profiles in NSCLC and the resultant data suggest that the inclusion of the microflex LT in CDx test development has the potential to expand the utility of MALDI-based testing in the clinic.