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Copy loss enrichment at metastatic disease progression in hormone receptor-positive (HR+)/HER2-negative metastatic breast cancer patients treated with endocrine therapy and CDK4/6 inhibition

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BACKGROUND

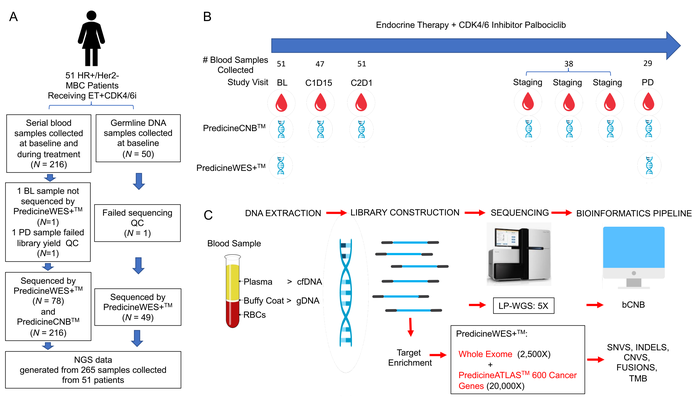
The development of a sensitive, cost-effective method to serially monitor for early signs of metastatic disease progression during treatment represents a critical unmet need.

To identify optimal approaches, we used two comprehensive NGS assays to profile somatic mutations and copy number variation in blood samples collected from HR+/HER2-negative metastatic breast cancer patients at baseline and during treatment with endocrine therapy and CDK4/6 inhibition (ET + CDK4/6*i*).

METHODS

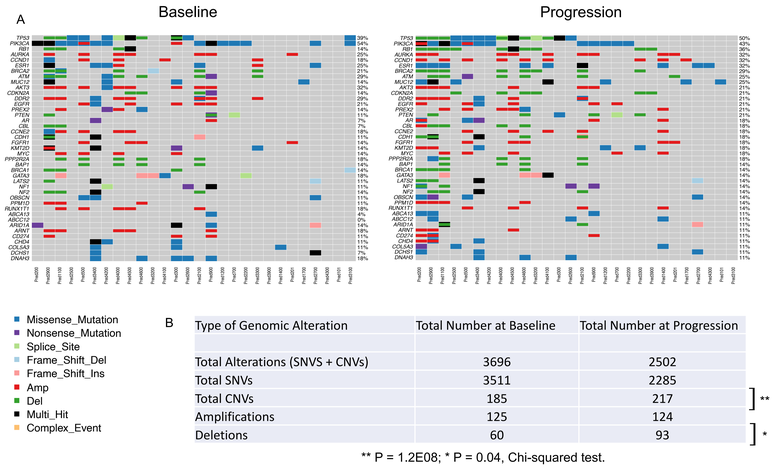
- Serial blood samples were evaluated from the Alt Dose Palbo trial (NCT03007979), a single-arm phase II study of palbociclib plus letrozole or fulvestrant on a weekly schedule of 5 days on/2 days off, in 28-day cycles, as the first- or second-line treatment.
- PredicineWES+^{TM}, a boosted whole exome sequencing (WES) assay that combines WES with deep coverage of 600 cancer genes targeted by the PredicineATLAS^{TM} panel, was used to generate exome-wide genomic profiles of somatic single nucleotide variation (SNV), indels and copy number variation (CNV), and to determine blood tumor mutation burden (bTMB) scores reflecting the number of mutations per megabase of DNA.
- PredicineCNB^{TM}, a low-pass whole genome sequencing (LP-WGS) assay, was used to generate blood copy number burden (bCNB) scores representing a comprehensive measure of copy number variation, including amplifications and deletions across all chromosome arms.

Figure 1: Study schema and NGS ctDNA analyses.
A) Study schema. B) Sample collection at baseline (BL), and during treatment at cycle 1 day 15 (C1D15), C2D1, Q3-month staging scans without progressive disease (PD), and at imaging detection of PD. C) NGS profiling with PredicineWES+^{TM} and PredicineCNB^{TM}.



RESULTS

Figure 2: Genomic alterations detected by PredicineWES+^{TM} in plasma at baseline and progression.
A) Heatmaps showing alterations in top-altered genes. B) Total number of SNVs vs. CNVs across all genes. C) Enrichment of specific genes at progression. N=28.



B

Type of Genomic Alteration	Total Number at Baseline	Total Number at Progression	
Total Alterations (SNVS + CNVs)	3696	2502	
Total SNVs	3511	2285	
Total CNVs	185	217	**
Amplifications	125	124	
Deletions	60	93	*

** P = 1.2E08; * P = 0.04, Chi-squared test.

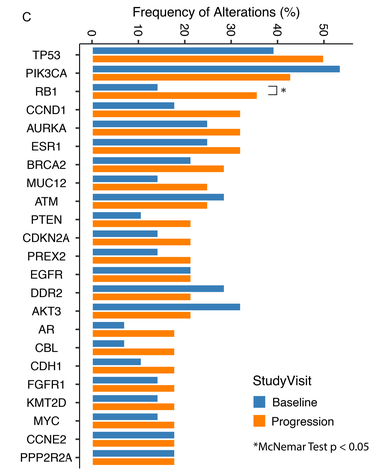


Figure 3: bTMB and bCNB levels at baseline and progression.
No significant differences were observed in median bTMB or bCNB at baseline vs. progression.

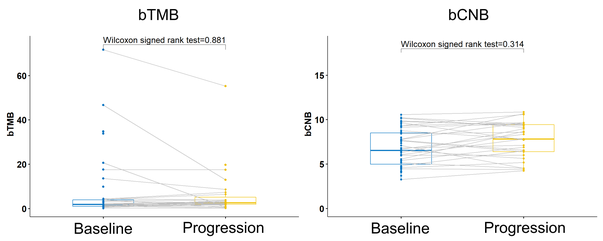


Figure 4: Comparison of ctDNA dynamics as measured by ctDNA fraction and bCNB during treatment and progression.
Serial blood samples from 4 patients were analyzed by PredicineATLAS^{TM} to derive ctDNA fraction values and by PredicineCNB^{TM} to derive bCNB scores at baseline, C1D15, D2D1, staging, and progression timepoints. Similar dynamics were observed using both NGS metrics.

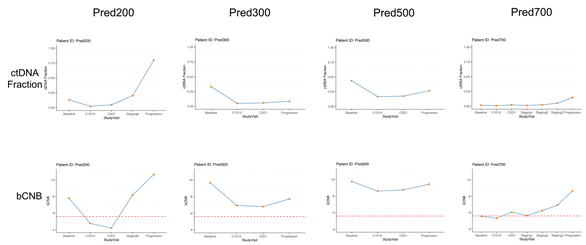
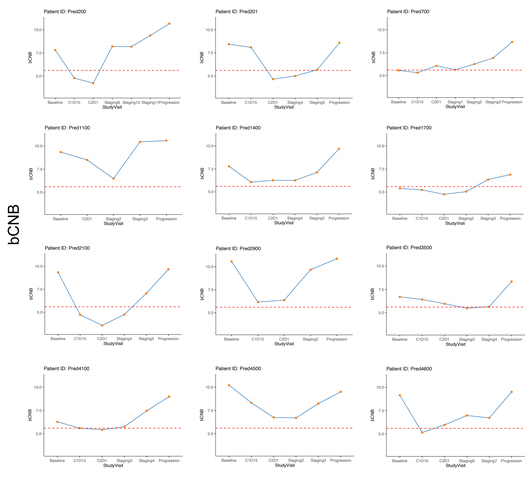


Figure 5: bCNB increases before radiographic detection of clinical progression.
Serial analysis of bCNB during treatment revealed decreases at C1D15 and/or C2D1, followed by increases that preceded imaging detection of progressive disease in 12/18 (66.7%) of patients for whom staging blood samples were analyzed.



SUMMARY OF RESULTS

Profiling using PredicineWES+^{TM} in plasma at baseline vs. progression revealed:

- Enrichment of specific variants at progression.
- Decrease in total # of SNVs at progression.
- Increase in total # of CNVs (primarily copy loss events) at progression.
- No change in median bTMB levels.

Serial monitoring of bCNB at baseline and during treatment demonstrated:

- Decreased bCNB levels following the initiation of treatment.
- Increased bCNB levels that preceded radiographic detection of progressive disease.
- No change in median bCNB levels at baseline vs. progression.

CONCLUSIONS

WES in plasma is a highly sensitive, comprehensive NGS approach for detecting individual variants at baseline and during treatment, some of which are significantly enriched at progression. However, NGS assays designed around specific variants to monitor for disease progression are costly. Dynamic changes in CNVs during treatment can be detected prior to radiographic detection of relapse using a shallow LP-WGS assay. This approach constitutes a promising cost-effective method to serially monitor for early signs of metastatic disease progression during treatment.

FUTURE DIRECTIONS

- Evaluate bCNB dynamics to detect disease progression in extended cohorts of patients undergoing treatment for metastatic breast cancer and other malignancies.
- Determine lead time over radiographic imaging.
- Establish clinical utility by evaluating whether early treatment change based on serial bCNB improves patient outcomes.

Andrew A. Davis reports serving on an advisory board for Pfizer, Inc. Contact information: aadavis@wustl.edu