Immunotherapy Predictive Biomarkers in Metastatic Breast Cancer

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ABSTRACT
Background: We queried whether comprehensive genomic profiling (CGP) of mBC subtypes could identify biomarkers that have been linked to responsiveness to immunotherapy (IO) treatments.

Methods: DNA was extracted from 3,871 mBC (1,288 ER+/HER2-, 1,969 HER2 amplified (amp) and 643 TNBC. CGP was performed using a hybrid-capture assay. Tumor mutational burden (TMB) was determined on 0.83-1.14 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci in 564 cases. PD-L1 on TILs in subsets was determined by IHC (Ventana SP142).

Results: Patient ages were similar. Genomic alterations (GA)/tumor were similar ranging from 5.9 to 7.3. MTOR pathway targets were commonly observed in mBC. TNBC, CDH1 and ESRI GA most frequent in ER+/HER2- cases. ERBB2 short variant (SV) mut were most frequent in ER+/HER2- and HER2 amp and not seen in TNBC. Other kinase targets were uncommon except for FGFR1 GA in ER+/HER2-, BRCA1/2 GA least frequent in HER2 amp. AR was amplified in 1% of all mBC. Markers of potential IO benefit: CD274 (PD-L1) amp (1-3%), BRAF GA (1-4%), TMB of ≥10 mut/Mb (8-12%), TMB of ≥20 mut/Mb (2-3%), MSI-High (0.1-0.4%), PBRM1 GA (1%) and low (1-10%) or high (0-20%) PD-L1 staining. Potential markers of resistance: inactivating GA in STK11 (2-1%) and MDM2 amplification (3-6%).

Conclusions: In addition to guiding targeted therapy selection, CGP shows potential to identify GA linked to resistance and response to IO in mBC. The demonstrations of clinical benefit of immunotherapy in mBC supports the need for the development of biomarkers used to guide the use of ICPI drugs for these patients.

MATERIALS AND METHODS

DNA was extracted from 40 μm of FFPE sections

Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer

Hybrid-capture-based sequencing using adaptor ligation-based libraries

Mean coverage depth >600X

Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed

Tumor mutational burden (TMB) calculated from 0.83-1.14 Mb sequenced DNA

RESULTS

• Patient ages and GA/tumor were similar
• MTOR pathway targets were common and lowest in TNBC
• CDH1 and ESRI GA most frequent in ER+/HER2- cases
• ERBB2 short variant (SV) mut were most frequent in ER+/HER2- and HER2 amp
• Other kinase targets were uncommon except for FGFR1
• BRCA1/2 GA least frequent in HER2 amp

Markers of potential IO benefit:
- CD274 (PD-L1) amp (1-3%)
- BRAF GA (1-4%)
- TMB of ≥10 mut/Mb (8-12%)
- TMB of ≥20 mut/Mb (2-3%)
- MSI-High (0.1-0.4%)
- PBRM1 GA (1%) and low (1-10%) or high (0-20%) PD-L1 staining

Potential markers of potential IO resistance:
- Inactivating GA in STK11 (2-1%)
- MDM2 amplification (3-6%)

CONCLUSIONS

- In addition to guiding targeted therapy selection, CGP shows potential to identify GA linked to response and resistance to IO in mBC
- The demonstrations of clinical benefit of immunotherapy in mBC supports the need for the development of biomarkers used to guide the use of ICPI drugs for these patients