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Background: The heterogeneous fates of MBC preclude our understanding of both resistance to therapy and escape from cancer immunoediting. Here, we performed a comprehensive molecular analysis of lethal MBC patients (pts), interrogating both the malignant and immune tumor microenvironment (TME) compartments, and T-cell receptor (TCR) repertoires, across multiple metastases (mets).

Methods: Multi-platform profiling of mets (N = 182 mets to 22 organs, 5-36 mets/pt), primary tumors (pr) (N = 6) and ctDNA from body fluids (4.7/pt) in 10 warm autopsies of MBC pts (5 ER+/HER2-, 3 ER+/HER2+, 1 ER-/HER2+, 1 ER-/HER2-), included exome seq (N = 86), shallow whole genome seq (N = 168), RNA seq (N = 61), ultra-deep targeted seq (TS) (N = 243), TCRseq (N = 70) and IHC (N = 102). State-of-the-art bioinformatics was applied to the data.

Results: Mutation (mut) burden landscape varied between pts (11,579 mut, median 255.41 mut/pt) and across mets within each pt (median 122 mut/met); was greater than TCGA mut burden (median 63.5 mut/pr, $p = 4.927 \times 10^{-14}$). Landscape of mut and predicted neo-antigen were dominated by stem (present in all mets/pt) or clade (some mets/pt), but not private (one met/pt). TS data confirmed that all pr tumors contained the clonal ancestors of 10 pts, and characterized ctDNA bathing organs. Copy number alteration profiles were remarkably similar across mets in 9 of the 10 pts, except in a ER+/HER2- pt, whose mets shared a common ancestor (1q gain/16q loss), then early sub-clonal evolution occurred. Mets were grouped into phylogenetic clades that share common genomic ancestry and accumulated previously unknown mutation signatures. Mets evolved as communities of clones as a fraction of the metastatic stem and clade mutations were sub-clonal. Immune TME was either homogeneous in a particular metastatic clade, or different across mets to a particular organ. Stem and clade clonotypes prevailed across TCR landscape within each pt. TCR repertoires revealed adaptive immune responses to co-evolve with the metastatic genomes.

Conclusions: The genomic and immune landscapes demonstrate an unprecedented integrated view of the heterogeneous landscape of genomic aberrations, TME features and T-cell adaptive immune responses in lethal MBC.