The application of a multigene NGS assay in homologous recombination deficiency tracking.

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Background: Several tumor types have been efficiently treated with PARP inhibitors, a class of proteins involved in DNA repair pathway, which are approved for the treatment of ovarian, breast, prostate, and pancreatic cancer. The BRCA1/2 genes are essential for homologous recombination, and tumors which carry this type of mutations appear to have a defective homologous recombination pathway as a result of the loss of the second non mutated allele in the tumor. However, both epigenetic changes and mutations in many other genes involved in the HR pathway, including Fanconi anemia genes and the ARID1A, ATM, ATRX, BAP1, BARD1, BLM, BRIP1, CHEK1/2, MRE11A, NBN, PALB2, RAD50, RAD51, WRN may be responsible for the HRD phenomenon. In addition to mutational status, useful for the detection of the patients that would benefit from PARPi treatment could be the presence of certain genomic scars in the tumor, such as the loss of heterozygosity (LOH).

Methods: In this study 406 samples from patients with various tumor types were analyzed using a targeted NGS assay for the analysis of 513 genes associated with targeted and immuno-oncology therapies. This assay detects relevant SNVs, indels, CNVs, gene fusions, splice variants in addition to TMB and MSI simultaneously. It also measures genomic instability using sample-level LOH in addition to the analysis for 31 HR related gene alterations. Moreover, the %gLOH was also calculated by the OncoScan™ CNV Assay in 25 samples in order to compare the results obtained by these two methodologies. Results: An HR gene mutation was detected in 20.93% of the tumors analyzed, with BRCA1/2 genes being the most prevalent HR altered genes detected in 5.17% of the tumors. The majority of the non BRCA1/2 HR mutations were in ARID1A (4.18%), ATRX (2.21%) and ATM (1.97%) genes. The %gLOH was highly correlated with the presence of mutations in the BRCA1/2 genes since 76.19% (16/21) of the tumors harboring such alterations had a high %LOH value (p = 0.007). Additionally, the LOH status was highly correlated to the presence of TP53 mutations, while a negative correlation to KRAS mutations was observed. Furthermore, there was no association of %LOH and TMB value in our cohort. Lin’s Concordance Correlation Coefficient was 0.93 for the 25 evaluable samples examined simultaneously by both assays, indicating an almost perfect agreement. Conclusions: A high rate of HR mutations was detected in ovarian, breast and prostate which is consistent with the PARPi approval in these tumor types. The presence of BRCA1/2 mutations was highly associated with increased LOH value whereas it did not correlate to other HR mutations. Additionally, the pancancer presence of HR gene alterations indicates that the use of such genes as biomarkers of platinum and PARPi treatments should be evaluated in a wider range of tumor types. In conclusion the addition of analysis of the gLOH seems to be useful for the detection of additional patients eligible for PARPis. Research Sponsor: None.