INTRODUCTION

Despite major progress in the molecular characterization of ovarian cancers (OC), women with recurrent, advanced stage OC continue to be treated with cytotoxic chemotherapy agents that achieve poor overall response rates. This contrasts with the treatment paradigm for other cancers, where outcomes have been improved by selecting treatment based upon “actionable” genomic alteration(s) that are in drug-targetable pathways. There is a need to determine if molecular profiling for OC patients can improve treatment outcomes by informing therapy choices. Such a profile should comprehensively identify “actionable” genetic aberrations as well as measure expression levels of proteins that are drug targets/response biomarkers.

As part of molecular profiling analyses performed for recurrent ovarian cancer patients to inform selection of their next treatment, the presence of mutations or alterations (e.g., copy number (CN) changes) in ~200 genes that encode proteins that are key mediators in oncogenic and tumor suppressive pathways were determined using a validated exon-capture next-gen sequencing platform provided in a CLIA-certified laboratory setting. The expression of target proteins for some FDA-approved therapies was also measured. Comparisons of high grade serous (HGS) to non-HGS histology tumors are described.

SUMMARY AND CONCLUSIONS

1. Genomic analysis of mostly recurrent specimens from advanced stage ovarian cancer patients revealed that non-HGS and HGS cancers are molecularly distinct but contain genetic alterations in similar cancer pathways.

2. A median of 3 (range 0–7) “actionable” alterations were detected/tumor. >30% harbored alterations in key genes involved in HR DNA repair (HRR), RAS-MAPK, and the cell cycle that are targetable by drugs in clinical development (Fig 2 and 4).

3. Co-existing alterations in >1 pathway were found in 58% of the specimens and may impact responses to agents targeting only one pathway (Fig 4).

4. Low PTEN, p16, and RB protein levels are found in 9-17% of specimens and are not only associated with genomic aberrations (Fig 3).

5. 88 of the 99 specimens contained genetic alterations amenable to targeted therapies (Fig 4). Ten patients received such treatment (Fig 5).

6. Best responses were observed in the patients with endometrioid and clear cell ovarian cancers bearing mutations in KRAS and/or PIK3CA and WT TP53. Long term remission was observed with PARP inhibitor treatment in a HGS patient with a somatic BRCA2 mutation (Fig 5).

7. More clinical trials of targeted agents are needed to establish the value of profile-informed drug selection in the larger population.