Feasibility of a platform trial based on molecular analysis in rare gynecologic cancers

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Objective: The aim of this study was to determine whether enough actionable mutations exist in rare gynecologic cancers to justify the design of a platform trial.

Method: We compiled all molecular profiling data performed at Caris Life Sciences through July 2019. Actionable mutations were identified in all nonepithelial and rare epithelial ovarian cancers, rare uterine, neuroendocrine gynecologic, and vulvar cancers.

Results: We identified 2,870 rare gynecologic cancers. Actionable mutations in stromal tumors (n = 244) included PIK3CA (8%), ARID1A (8%), and 20 other actionable mutations (<5% each). Actionable mutations in germ cell tumors (n = 43) included ARID1A (42%), PIK3CA (19%), TMB-high (14%), FBXW7 (11%), PTEN (10%), CDKN2A (9%), NF1 (9%), and 17 other actionable mutations (<8% each). Among 1,136 rare epithelial ovarian cancers, actionable mutations in mucinous vulvar cancers (n = 153) included KRAS (58%), ARID1A (48%), CDKN2A (14%), PIK3CA (12%), copy number amplification (CNA) of HER2 (10%), and 23 other actionable mutations (<8% each). Actionable mutations in low-grade serous tumors (n = 307) included ARID1A (22%), KRAS (21%), BRAF (12%), and 17 other actionable mutations (<7% each). Actionable mutations in endometrioid tumors (n = 119) included ARID1A (80%), PTEN (31%), PIK3CA (30%), KRAS (19%), PIK3R1 (14%), TMB-high (11%), and 32 other actionable mutations (< 8% each). Actionable mutations in clear cell ovarian cancers (n = 396) included ARID1A (87%), PIK3CA (43%), KRAS (10%), and 30 other actionable mutations (<7% each). Actionable mutations in ovarian cancers (n = 316) included ARID1A (30%), PIK3CA (7%), and 35 other actionable mutations (<7% each) including 1 BRAF fusion (50%) and several CNAs. Among 1,259 rare uterine cancers, 558 sarcomas, 485 serous cancers, and 216 clear cell cancers were identified. Actionable mutations in uterine sarcomas included ARID1A (13%), PTEN (7%), and 27 other actionable mutations (<6% each), including gene fusions in NTRK3, BRAF, and ALK. Actionable mutations in uterine serous cancers included ARID1A (41%), PIK3CA (32%), FBXW7 (20%), and actionable mutations in 27 other genes, CNAs, and fusion events (≤10% each). Actionable mutations in uterine clear cell cancers included ARID1A (61%), PIK3CA (34%), PTEN (17%), FBXW7 (12%), 32 other actionable mutations (≤10% each). Actionable mutations in 120 gynecologic neuroendocrine tumors included ARID1A (37%), PIK3CA (19%), PTEN (18%), and 28 other actionable mutations (<9% each). Actionable mutations in 68 vulvar cancers included PIK3CA (19%), CDKN2A (18%), TMB-high (10%), ARID1A (10%), and 20 other actionable mutations (<10% each).

Conclusion: A variety of actionable mutations are present among all rare gynecologic cancers, but mutations specific to individual histologies are not reliably present. This supports molecular profiling to identify potential targets and supports a platform trial strategy to study rare gynecologic cancers.

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