Comprehensive multiplatform biomarker analysis of 212 anal squamous cell carcinomas

Results

Figure 1. Distribution of cohort and patient specimens. 1A (above) shows the number of men and women retrospectively analyzed. The age range was 11 - 98, with the mean age of 58.9 years. 1B (below) shows a histogram of the age distribution. In total, twenty-seven specimens were collected from males and twenty-five from females.

Figure 2. Distribution of protein expression by IHC. The bar chart above shows distribution of therapeutic HER2,4 classified from lowest to highest. Bar, those marked in green correspond to biomarkers associated with agents on the NCCN algorithm. Biologic markers with the highest score (100%) were associated with treatment paradigms specific drug and/or drug classes, such as anti-HER2 monoclonal antibodies. The relationship is also expressed by the IHC. For example, HER2 overexpression is associated with probable resistance to fluorouracil and capecitabine. The table below the bar graph lists drug and drug classes associated with that biomarker’s protein expression. Absence of HER2 (33.2%, 61/186) implies a subset may derive benefit from alkylating drugs like temozolomide.

Figure 3. Distribution of mutations by either Sanger or NGS. Several mutations were detected involving the PIK3CA/PTEN pathway, including PIK3CA, PTEN, and AKT3. In all, 19/125 (15%) of anal squamous cell carcinomas showed dysregulation of the PIK3CA/PTEN/MTOR based on IHC (i.e. PTEN) and sequencing (i.e. AKT3, PIK3CA) analysis. Targeted agents along this pathway may be considered in future clinical trials. The high rate of PIK3CA mutations detected by IHC implies a subset may derive potential benefit from alkylating drugs. In total, twenty-seven specimens were detected in twenty-six specimens.

Figure 4. No Variants Detected. The table above shows the absence of mutations detected in the cohort. No significant (p < 0.05) differences were found between the (overall) primary tumor and the matched metastasis.

Figure 5 – Anal Cancer SH Distribution. The bar chart on the left shows distribution in SH (PIK3CA or PTEN). Higher percentages were detected in the HER family of receptors, indicating a potential benefit to HER inhibitors in addition. In addition, biomarkers showing no gene amplification such as MET, TOP2A and all indicate squamous cell carcinoma patients may benefit from MET-targeted therapy (e.g. crizotinib, alectinib), PI3K inhibitors, and ALK-targeted therapy (e.g. crizotinib) based on these SH results alone. One specimen with EGFR amplification also had concurrent ERBB2 (HER2) amplification. Other one specimen had EGFR amplification along with a mutation in ERBB2. Interestingly, all five specimens with EGFR amplification were from metastatic and not primary tumor samples.

Conclusions

- To the best of our knowledge, this is the most comprehensive molecular profiling review of anal squamous cell carcinomas.

- Overexpression of drug pumps, especially MRP1, may explain why advanced disease is resistant to conventional cytotoxic therapy. In addition, overexpression of biomarkers the presence of ABCs may explain the limited benefit of platinum and fluorouracil-based therapy, respectively, in advanced stage disease. Although MGMT overexpression is high, nearly 1/3 patients lack MGMT expression, which might indicate a role for use of alkylating agents. Further, MGMT overexpression (by IHC) may be relevant when considering emerging small molecule inhibition of MGMT. Caution is advised, though, when the lack of MGMT amplification.

- Our findings show new markers which may be considered when designing clinical trials. EGFR and ERBB2 (HER2) amplification by IHC may be used for targeted therapy/treatment of metastatic or primary advanced disease may guide patient selection when considering off-label use of targeted therapy.

- The high frequency of PIK3CA mutations warrants further investigation, in mutations can be targeted downstream in the PIK3CA/MTOR pathway. Although other mutations were rare, many were also targeted.

- The overall findings argue in favor of a role for comprehensive molecular profiling in advanced stage squamous cell carcinoma of the anus.

References


