Background

- The WHO recognizes multiple variant histologies of urothelial carcinoma (vUC), many of which have been associated with poor outcomes compared with UC (UC).
- Prior studies have identified molecular differences between variant vUC and UC through targeted techniques, for example, HER2 gene amplification in micropapillary histology or CDH1 loss in plasmacytoid histology.
- We aimed to explore molecular differences between urothelial carcinoma and UC using multiplatform profiling.

Methods

- 23 micropapillary (MP), 16 plasmacytoid (P), 16 nested (N), 6 clear cell (CC), and 2 giant cell (GC) variant UC specimens were tested between 2012 to 2018 via a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ) that included gene sequencing (Sanger or next generation sequencing [NGS]), gene expression (immunohistochemistry [IHC]), and intrinsic profiling (EPI and PI3K-AKT). Percentages of select molecular aberrations according to histologic subtype are shown in Table 1.
- The rates of DNA damage repair (DDR) mutations was low in MP, P and GC compared with UC. However, the rate of DDR mutations in sarcomatoid vUC was comparable to UC.
- The WHO recognizes multiple variant histologies of urothelial carcinoma, including MP and P, among others.
- Further studies are needed to confirm these findings, and may lead to the development of novel molecularly targeted therapies.

Results

- The rates of DNA damage repair (DDR) mutations was low in MP, P, N, and GC compared with UC. However, the rate of DDR mutations in sarcomatoid vUC was comparable to UC.
- CISH HER2 amplification was seen in 27.3% MP compared with only 10.4% UC (p=0.005).
- Compared to UC, PD-L1 IHC was positive in a higher proportion of S (55.6% vs. 23.1%, p=0.002). However, PD-L1 IHC was positive in lower rates among other vUC subtypes.
- Tumor mutational burden was high in a lower proportion of most vUC compared to UC. 18.4% UC vs. 14.3% MP (p=0.7), 9% P (p=0.25), and 8.5% S (p=0.88). In the limited GC samples, TMB was high in 50%.
- There were more ARID1A mutations detected in MP than UC (100% [3 specimens] v. 41.3%, p=0.044), and more CDKN2A mutations in P than UC (50% [4 specimens] v. 2%, p=0.001).

Conclusions

- Aggressive variant histology UCs have a differential profile of molecular aberrations compared to UC.
- Several of these differences are in molecular targets that are under active investigation in the treatment of UC, such as DNA damage repair, HER2, and FGFR.
- Other differences are in biomarkers associated with response to checkpoint inhibitors, such as PD-L1 expression and TMB.
- Further studies are needed to confirm these findings, and may support therapy development for these rare, aggressive UC subtypes.

References