Combination of Immune and Genetic Biomarkers of Improved Efficacy to Buparlisib and Paclitaxel in Patients with SCCHN: BERIL-1 Sub-analysis

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Background

BERIL-1 Phase 2 clinical trial (Soulieres et al, CCR, 2018), previously evaluated the efficacy of Buparlisib + Paclitaxel, being one of the largest genomic landscape analyses to date in metastatic SCCHN.

With the recent approval of PD-1 in this indication, we sought to explore combination of genomic and immune infiltration biomarkers. The goal of our study was to identify predictive or prognostic biomarkers to support the current Phase 3 clinical trial, BURAN (NCT04338399), in the context of immune modulatory therapy.

Results

BERIL-1 Study Genomic Landscape

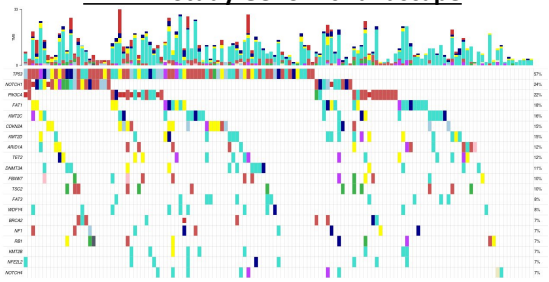


Figure 1. The genomic landscape observed within the BERIL-1 trial is consistent with the known landscape of SCCHN

Somatic interactions in SCCHN tumors

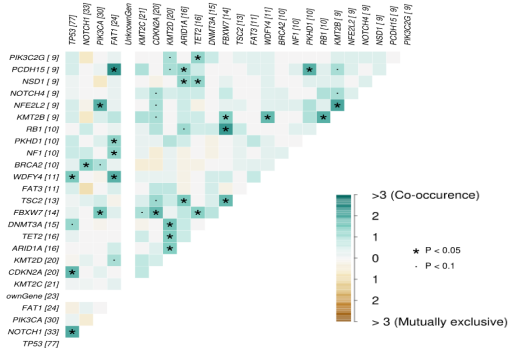
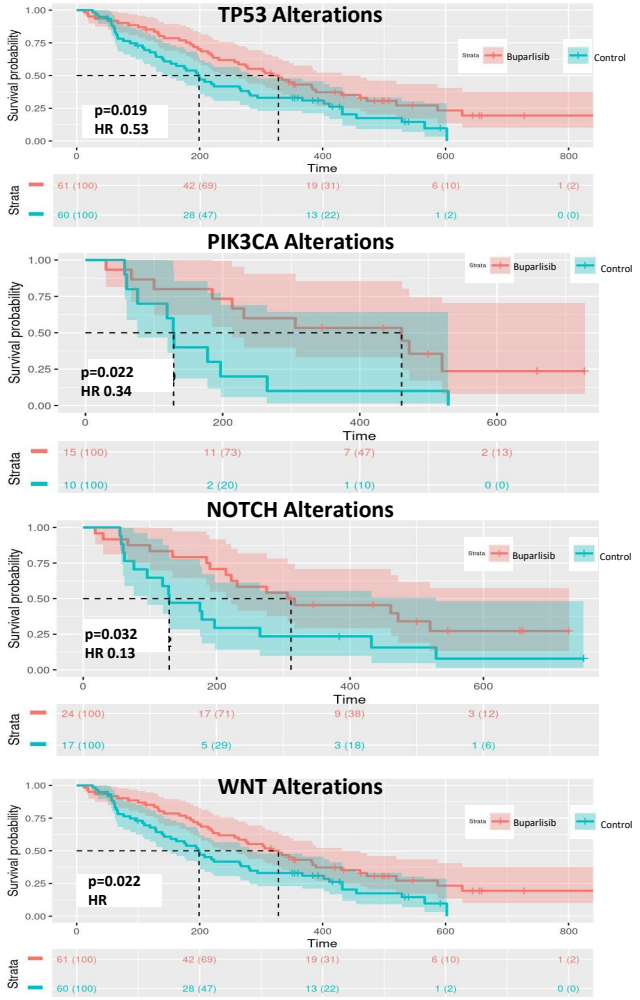


Figure 2. Most mutations that occur in the tumor are mutually exclusive. *TP53* and *NOTCH1* showed statistically significant co-occurrence within the tumor

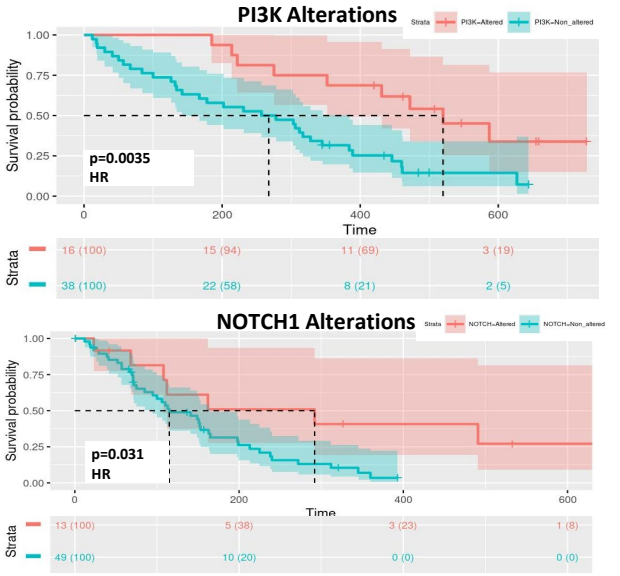
High Immune Infiltration with Genetic Pathway Alterations Associate with Improved Response Between Treatment Arms



*All observations for OS were also statistically significant for PFS

Figure 3. Patients harboring genetic alterations in TP53, PIK3CA, NOTCH and WNT pathways with high levels of immune infiltration showed significantly improved therapeutic response to Buparlisib when compared to the control group. The response of the combined biomarker was improved over that of either individual biomarker. Abbreviations: HR, Hazard Ratio; OS, Overall Survival; PFS, Progression Free Survival.

High Immune Infiltration with Genetic Alterations Associate with Improved Response Within Buparlisib Treatment Arm



*All observations for OS were also statistically significant for PFS & not observed in control

Figure 4. Patients with either PI3K or NOTCH1 mutations and high immune infiltration at baseline showed improved therapeutic response within the Buparlisib treatment arm. Neither individual biomarker showed statistically relevant therapeutic response.

TP53 Mutants with High TMB Associate with Improved Response Across Treatment Arms

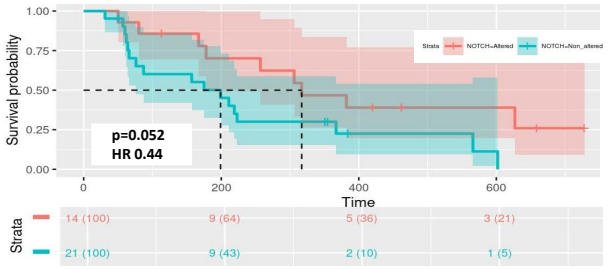


Figure 5. High Tumor Mutational Burden (TMB) associated with worse overall survival to Buparlisib. However, when combined with TP53 mutations at baseline, high TMB showed improved response when compared to placebo.

Buparlisib Does Not Alter The Mutational Landscape of Patients Throughout The Duration of Treatment

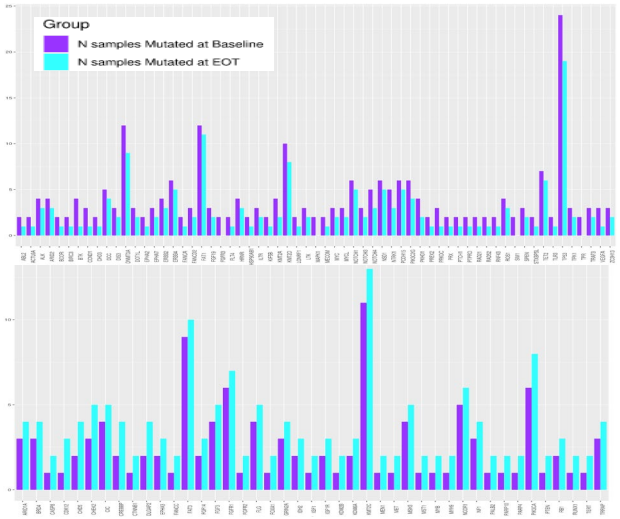


Figure 6. There were no statistical differences between mutations observed at baseline and EOT within the Buparlisib treatment arm in those subjects that had matched ctDNA samples available.

Conclusions

- **BERIL-1 data set consistently showed genomic alterations known within SCHHN. Mutations within the tumor were predominantly mutually exclusive.**
- **High immune infiltration at baseline when combined with mutations in known SCCHN cancer pathways within the indication showed significant improvement in therapeutic response both across treatment arms as well as within the Buparlisib treatment arm.**
- **Combination of immune and genomic biomarkers showed improved HR compared to biomarkers alone supporting the hypothesis that subjects with genomic alterations would benefit from Buparlisib combined with immune modulatory therapies.**
- **Buparlisib has not been shown to alter the mutational rate of subjects from baseline to EOT.**