Utilizing H&E Images and Digital Pathology to Predict Response to Buparlisib in SCCHN

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Introduction

This study aimed to assess a novel methodology for identifying recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) patients likely to benefit from combination Buparlisib + paclitaxel treatment. We focused on AI-based structuring and analysis of H&E images to identify spatial features associated with clinical outcomes.

Analysis focused on the following:

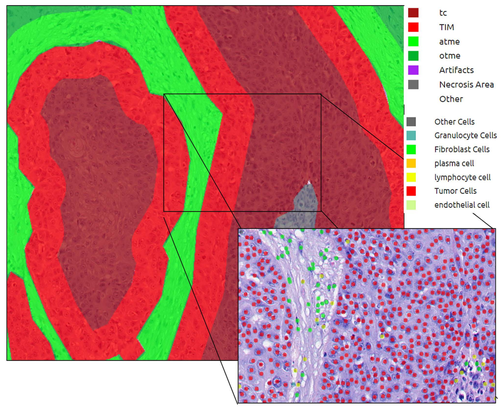
- Predictive value of Tumor-Infiltrating Lymphocytes (TILs) in treatment response.
- Impact of tumor-related inflammation by assessment of granulocyte-tumor cell interactions within the tumor invasive margins and microenvironment.
- Development of a novel spatial feature-based method to identify potential Buparlisib responders

Methods

- **Study Design:** BERIL-1 (NCT01852292) was a multicenter, randomized, double-blind, placebo-controlled phase II trial evaluating Buparlisib + paclitaxel or placebo + paclitaxel in recurrent or metastatic SCCHN patients.
- **AI Image Analysis:** H&E-stained whole slide images (WSI) were scanned at 40x. A deep learning model was developed to identify tumor, necrotic, and stromal regions in addition to fibroblasts, endothelial cells, and immune cells.
- **Spatial Biomarker Evaluation:** Histopathological biomarkers from 144 subjects (73 in treatment & 71 in placebo arms) were assessed for overall survival (OS) as an endpoint.
- **Statistical Analysis:** Cox proportional hazards models were used to compute HR and associated 95% CI for OS. Significance of survival curves for subgroups, defined by spatial biomarkers, were calculated by log rank test.

Image analysis

- The deep learning model accurately classified tumor, necrotic, and stromal areas, as well as fibroblast, endothelial, and immune cells (plasma cells, lymphocytes, granulocytes), as compared to human pathologist annotations.



Visualization of the cell and area classifications models
Tumor area = TC + TIM
TME = aTME + oTME
***TIM = Tumor invasive margin - 60µm wide region internal to the tumor-stroma border**
***TC = Tumor center – the area internal to the tumor invasive margin**
***aTME = Adjacent TME - 60µm wide region external to the tumor-stroma border**
***oTME= Outer TME - the area outside the adjacent TME**

Predicted

Reference	Tumor	Stroma	Necrosis	Nerve	Other
Tumor	85%	11.3%	1.1%	0	2.5%
Stroma	3.4%	92.8%	0.8%	0.5%	2.6%
Necrosis	9.4%	6.9%	80.9%	0	2.8%
Nerve	0	5%	0	90.6%	4.4%
Other	7.3%	11.6%	0.6%	0.2%	80.3%

Accuracy of the area segmentations model

Predicted

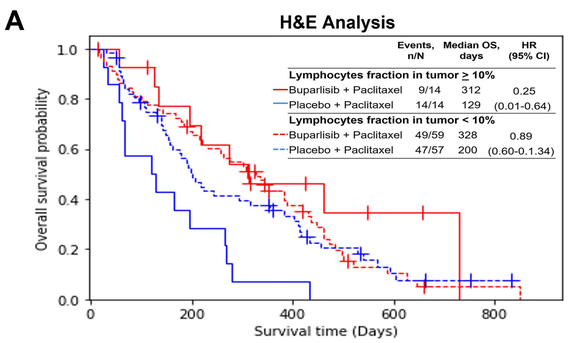
Reference	Tumor	Lymphocyte	Fibroblast	Plasma	Granulocyte	Endothelial
Tumor	76.6%	1.8%	2.2%	0.2%	0.1%	0.1%
Lymphocyte	1.2%	83.5%	1.95%	3.2%	0.7%	0.1%
Fibroblast	4.9%	2.8%	70.6%	0.5%	0.1%	1.7%
Plasma	1.1%	21.1%	6%	61.9%	0.1%	0
Granulocyte	1.3%	9.7%	0.7%	0.1%	70.7%	0.1%
Endothelial	4.2%	5.2%	23.3%	0.4%	0.4%	48.2%

Accuracy of the cell classification model

Spatial biomarker analysis results

Overall survival of patients above vs. below 10% TILs in Tumor

A



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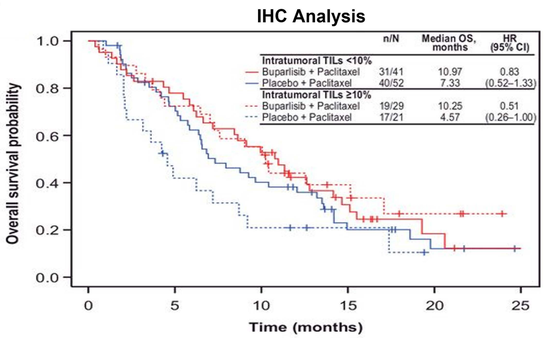
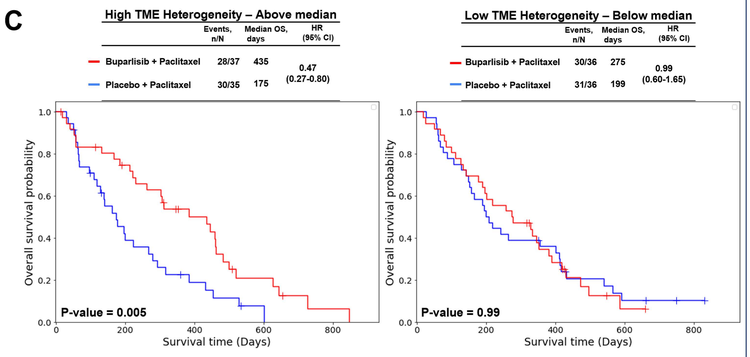


- **A-B - Tumor Infiltrating Lymphocytes (TILs):** Patients with ≥10% TILs in tumor area (TA) showed improved overall survival compared to the control arm, suggesting TILs as a potential prognostic marker for Buparlisib treatment outcomes. H&E analysis showed consistent ability to detect those patients with TILs in the TA and was able to produce better predictive HRs when compared to traditional IHC analysis.

Overall survival of patients with high vs. low TME heterogeneity

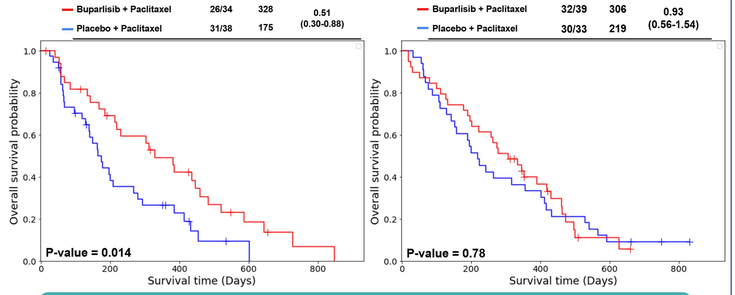
C



- **C - TME Heterogeneity:** High but not low cellular heterogeneity in the TME correlated with improved overall survival in combination therapy, highlighting the importance of TME complexity in treatment response.

Overall survival of patients with high vs. low granulocytes fraction in the TIM

D



- **D - Granulocytes Fraction in the Tumor Invasive Margins (TIM):** High percent of granulocytes, rather than low in the TIM was associated with improved overall survival in patients receiving Buparlisib + paclitaxel compared to the control, suggesting a potential role of granulocytes in treatment efficacy.

Conclusion

This study underscores the utility of H&E-based image analysis in identifying potential candidates for Buparlisib + paclitaxel therapy among metastatic SCCHN patients. The results presented highlight the ability of H&E analysis to identify similar features as traditional biomarkers as well as features that would be challenging to detect by traditoinal assays. These findings provide insights into the MOA of buparlisib as well as valuable information towards a better patient selection strategy for future studies. Validation and further investigation are necessary to inform personalized oncology treatment strategies.

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