Data-driven subtyping and differential glufosfamide benefit in pancreatic adenocarcinoma

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Introduction

- Glufosfamide couples a glucose moiety to an ifosfamide mustard to exploit tumor glucose transport and deliver an alkylator, with prior pancreatic cancer activity reported in early trials.
- Variation in baseline characteristics may identify subgroups with differential benefit.
- We applied bfLEAP™, an ensemble clustering and stability-selection framework, to a glufosfamide clinical dataset (TH-CR-302) to discover reproducible subpopulations and test treatment-by-subgroup interactions for overall survival (OS).

Methods

- A post hoc analysis of TH-CR-302, a randomized phase 3 clinical trial evaluating glufosfamide vs. best supportive care (BSC), was conducted using an ensemble clustering and stability-selection framework (bfLEAP®), to identify patient subgroups.
- A patient-to-patient similarity network was constructed from baseline demographics, screening labs, and pre-randomization clinical features.
- Clusters were then derived from this network by identifying recurring patient groupings. Patients without consistent groupings were not assigned a cluster.
- The primary endpoint was OS, with death as the event of interest.
- We identified clusters on pooled arms, then estimated arm-specific outcomes within clusters. Age and sex adjusted Cox models were used to evaluate the association between treatment assignment and OS. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

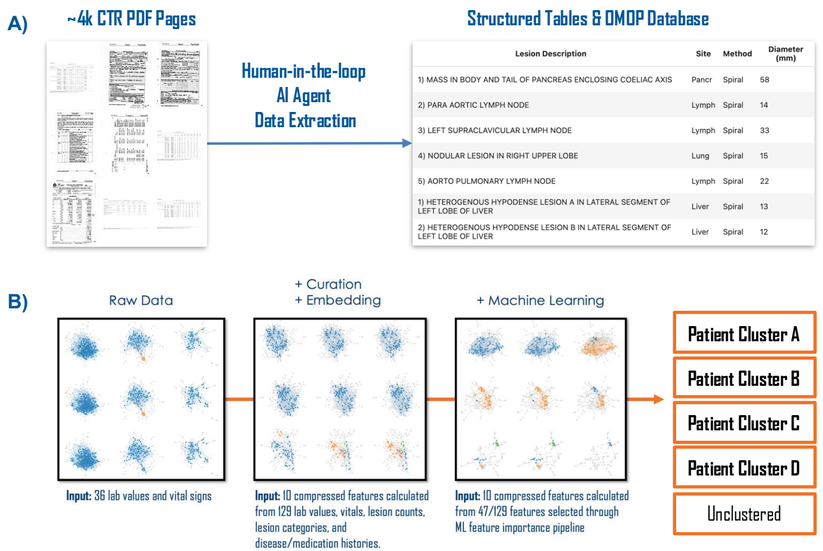

Figure 1. Data Extraction, Augmentation, and Clustering
A) Data was extracted from PDF-format Clinical Trial Reports using an AI Agent workflow with human-in-the-loop approval and statistical QC. Summary statistics in the CTR were reproduced as validation.
B) AI-assisted feature engineering and machine learning feature importance were used to identify a small subset of informative categorical features to build similarity networks and patient clusters. All features considered in this step were collected at screening.

Results

Figure 2. Overall survival, Adverse Event Grade and Tumor Differentiation by cluster

A) Overall survival by cluster was similar between the 4 subgroups.
B) Events grade 3-5 were more common in Clusters B and D. C). Moderately differentiated tumors were more common in Cluster A.

Glufosfamide Best Supportive Care

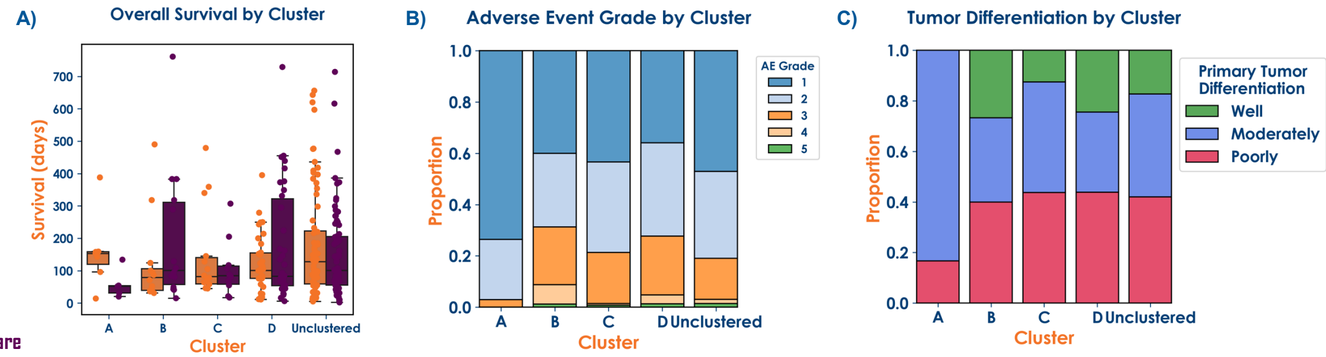

Figure 3. Observed notable lab differences between Clusters

A) Patient in cluster A had the lowest median glucose levels.
B-C) Neutrophil and monocyte counts were higher among glufosfamide recipients in Cluster A.

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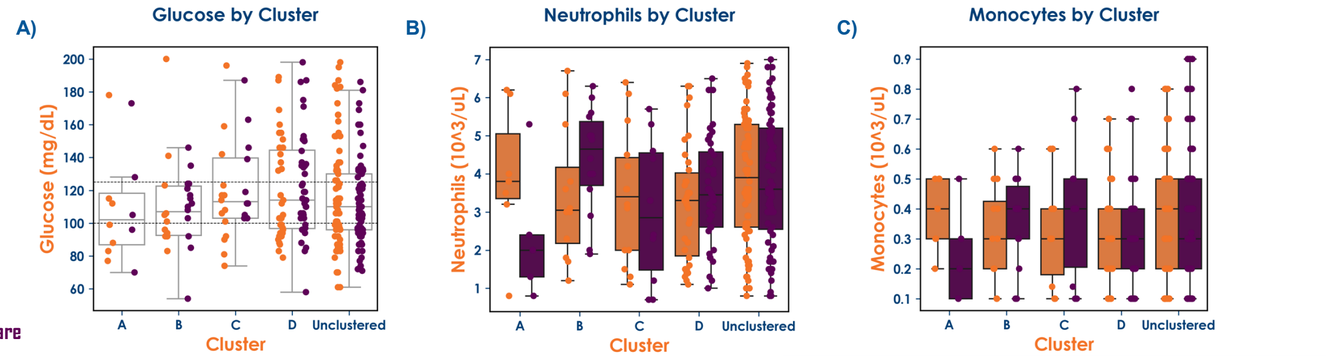
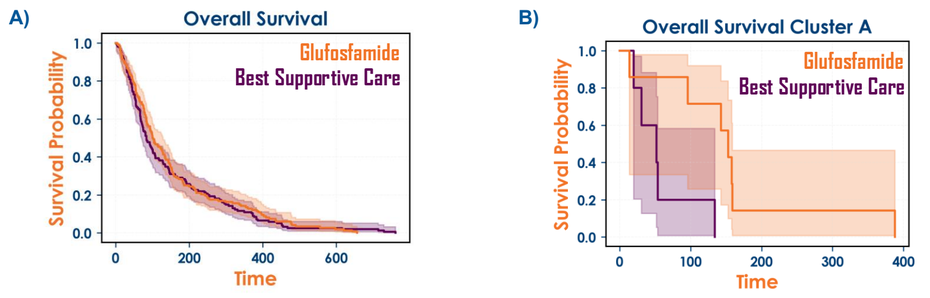


Figure 4. Overall Survival
A-B) Subjects in Subgroup A (n=12) demonstrated an almost 3x increase in mean survival from the control to treatment arms. (58.2 vs 149.3 days, t-test p=0.065)



Group	Median Survival	95% CI Lower	95% CI Upper
Best Supportive Care	84.0	70.0	102.0
Glufosfamide	102.0	85.0	129.0

Group	Median Survival	95% CI Lower	95% CI Upper
Best Supportive Care	52.0	20.0	134.0
Glufosfamide	153.0	14.0	159.0

Conclusions

Ensemble approaches like bfLEAP™ can successfully identify patient subgroups within existing glufosfamide clinical trial data. Treatment effect heterogeneity was identified amongst clusters, identifying possible early predictors of outcomes.

These findings highlight the potential of data driven clustering approaches to refine patient stratification and guide the development of personalized treatment strategies.

Acknowledgements & COI

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