Identification of potential immune biomarkers for GSK-3 inhibitor elraglusib (9-ING-41) in patients with relapsed/refractory metastatic cancer

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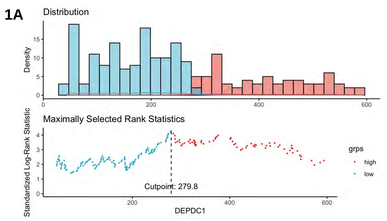
Abstract: #6426

ABSTRACT

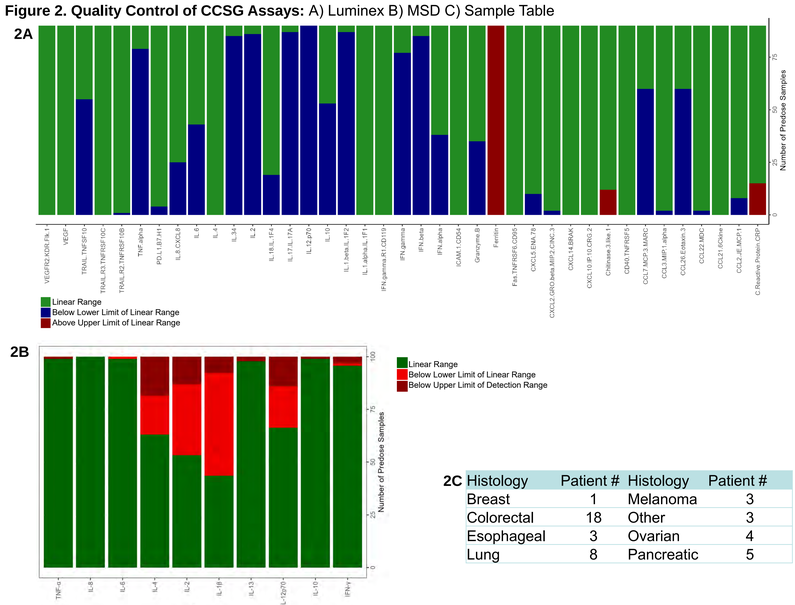
Elraglusib (9-ING-41), an inhibitor of GSK-3, is a potent antitumor and immune-modulatory agent in phase 2 clinical trials for the treatment of various cancers. Here, we examined the immune environment of elraglusib-treated cancer patients by measuring peripheral blood protein levels to explore whether the expression level of cytokines/chemokines/soluble cell receptors/growth factors (CCSG) is correlated with clinical outcome. Each was used as a binary predictor of overall and progression-free survival (OS and PFS) by optimal cutpoint determination using maximally selected rank statistics (Fig 1). Pre-dose plasma samples were obtained from 45 cancer patients with relapsed/refractory metastatic disease on the 1801 trial (NCT03678883), where they were treated with elraglusib (dose range: 1-15 mg/kg) either as a single agent (Part 1; n=21) or in combination with chemotherapy (Part 2; n=24). Using the Luminex platform, the expression of forty CCSG hypothesized to be linked to GSK-3 activity was assessed in pre-dose peripheral blood. Of those, four were found to be significant favorable markers (high level confers good outcomes) of OS and PFS, and eight were found to be significant unfavorable (high level confers poor outcomes) markers (Fig 3). Results at the time of abstract submission indicated that TNFRSF10C and CD95 were robust favorable OS markers and remained significant as the trial data matured (Fig 4). However, they are poor predictors of PFS. An MSD assay measuring ten cytokines was used to validate 9 of the original 40 CCSGs, many of which had many samples falling below the detection limit, in the same 45 patient samples. There was good agreement between the two assays, with IL-6 and IL-8 demonstrating significant stratification for OS and PFS in both assays (Fig 5 and 6). Colorectal cancer was the largest histologic group in the sample pool (n=18/45), and elraglusib has shown promise in pre-clinical models of colorectal cancer. Analysis of only the patients with colorectal cancer in the sample pool demonstrated that the stratification cutpoints determined from the entire cohort stratified the colorectal cancer subset well, and despite the small size of the cohort, many reached statistical significance (Fig 7). Examples shown here include favorable (CD95) and unfavorable (IL-1α and Granzyme B) CCSGs. The results of our multi-tiered exploratory study identified several putative biomarkers of elraglusib clinical benefit. This demonstrates the potential immunomodulatory mechanisms of elraglusib which will be used to inform further clinical development of elraglusib for the treatment of metastatic cancer.

Figure 1. Cutpoint Determination Process: A) Determining the rank statistic maximum and therefore cutpoint B) Maximally separated K-M curves



QUALITY CONTROL

Figure 2. Quality Control of CCSG Assays: A) Luminex B) MSD C) Sample Table



2C

Histology	Patient #	Histology	Patient #
Breast	1	Melanoma	3
Colorectal	18	Other	3
Esophageal	3	Ovarian	4
Lung	8	Pancreatic	5

INITIAL SCREEN

Identifying Prognostic CCSGa

Maximally Selected Rank Statistics

40 CCSG Luminex → OS → 33 CCSG with Successful OS and PFS Models → PFS

17 Statistically Significant OS Models
-5 Favorable CCSG
-13 Unfavorable CCSG

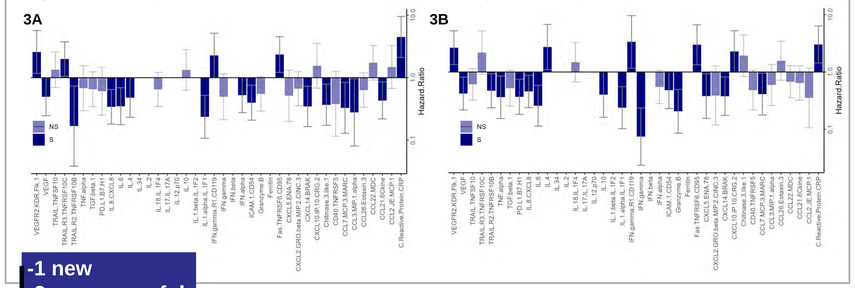
18 Statistically Significant PFS Models
- 6 Favorable CCSG
-14 Unfavorable CCSG

4 High CCSG=Favorable Markers for OS AND PFS
-VEGFR2
-IFNγ R1
-CRP
-CD95

8 High CCSG=Unfavorable Markers for OS AND PFS
-IL-6
-IL-8
-VEGF
-CCL7
-IL-1α
-CXCL14
-TRAIL R2
-CD54

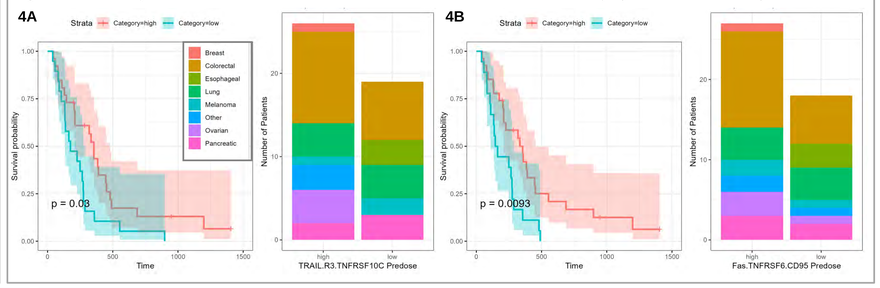
Iteratively Updated with Current Patient Data

Figure 3. Summary of Hazard Ratios for the Luminex Platform: A) for OS and B) for PFS



-1 new
-3 unsuccessful
-5 remeasured

Figure 4. Summary of Hazard Ratios for the Luminex Platform: OS for stratification by A) TNFRSF10C and B) CD95



CONFIRMATORY ASSAY

10 CCSG MSD → Maximally Selected Rank Statistics → OS, PFS

10 CCSG with Successful OS and PFS Models

9 Statistically Significant OS Models
-1 Favorable CCSG
-8 Unfavorable CCSG

6 Statistically Significant PFS Models
-6 Unfavorable CCSG

Iteratively Updated with Current Patient Data

6 Unfavorable Markers for OS AND PFS
-IL-1β
-IL-2
-IL-4
-IL-6
-IL-8
-TNFα

Figure 5. Assay Comparison: A) OS and B) PFS HR comparison for Luminex vs MSD assays

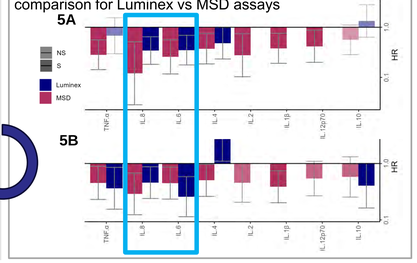
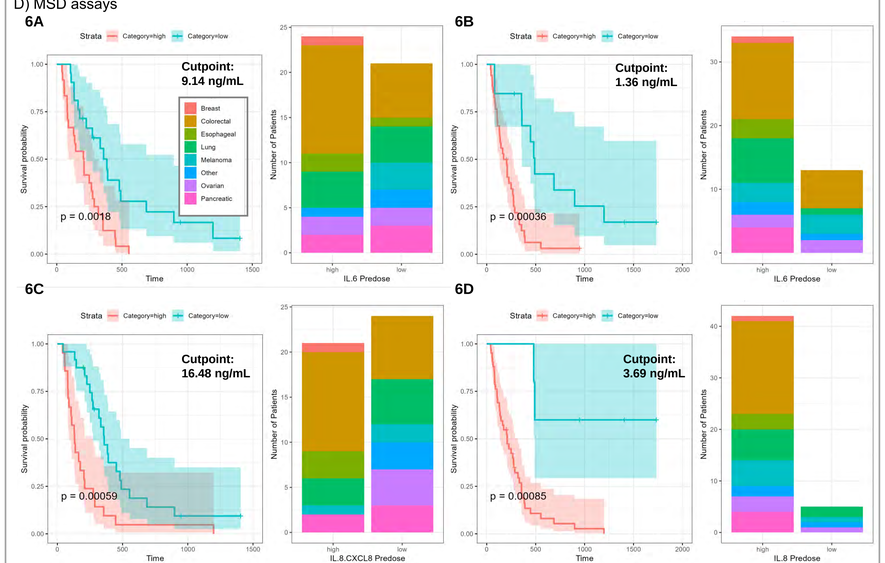
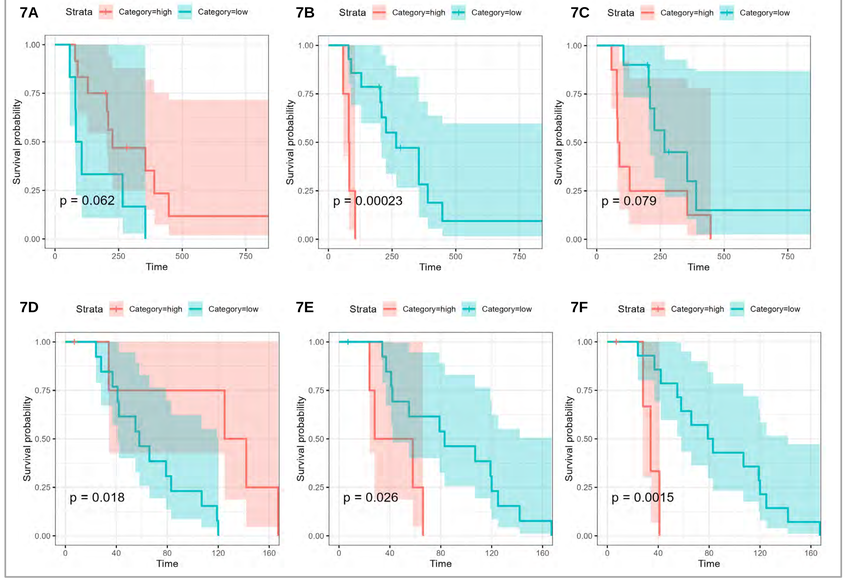


Figure 6. IL-6 and IL-8 Stratification: OS using IL-6 using A) Luminex and B) MSD assays. OS for IL-8 using C) Luminex and D) MSD assays



COLORECTAL BIOMARKERS

Figure 7. Colorectal Cancer Stratification with Luminex Assay: OS stratification using A) CD95, B) IL-1α, and C) Granzyme B. PFS stratification using D) CD95, E) \, and F) Granzyme B.



CONCLUSIONS

Preliminary results of our exploratory study identified plasma levels of CCSGs prior to elraglusib monotherapy or combination treatment as potential biomarkers associated with improved clinical outcomes in cancer patients with relapsed/refractory metastatic disease.

- Stratification seems to work for multiple histologies
- The colorectal cancer subset is significantly stratified by several CCSGs

CITATIONS

Kassambara A, Kosinski M, Biecek P (2021). _survminer: Drawing Survival Curves using 'ggplot2'_. R package version 0.4.9, <https://CRAN.R-project.org/package=survminer>.
H. Wickham. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016.
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