Evaluation of circulating VEGF-based biomarkers in INTEGRATE: A Randomised Phase II Double-Blind Placebo-Controlled Study of Regorafenib in Refractory Advanced Oesophageo-Gastric-Arcic (AOGC) – A study by the Australasian Gastrointestinal Trials Group

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Abstract #64

To understand an exploratory analysis of blood-based biomarkers identified as predictive and/or prognostic of REG treatment effect in the INTEGRATE trial. We report the findings here on the first part of this analysis.

Methods

Sample Size 145 patients had blood samples evaluable from a total study population of 141 eligible patients (97 REG, 50 placebo) randomised from 32 centres. Clinical Endpoints: REG was used to determine the predictive and/or prognostic effect of these biomarkers.

Processed Blood: Blood samples were collected from patients at BL (pre-treatment). REG was used to determine the predictive and/or prognostic effect of these biomarkers.

Baseline NLR

• A higher neutrophil:lymphocyte ratio (NLR) at BL was a significant predictor of worse PFS (p=0.007).

Baseline VEGF

• High BL levels of IL-8 and worse PFS (p=0.047).
• High BL levels of IL-8 and worse PFS (p=0.047).

Baseline biomarkers individual and in combination (in a multivariate model).

Results

• There was no convincing statistical evidence that any BL plasma biomarkers were associated with worse PFS.
• The geographical regions differed according to BL levels of:
  • VEGF-A (higher in ANZ/CAN)
  • VEGF-B (higher in Korea)
  • VEGF-D (higher in Korea) and
  • sVEGFR-1 (higher in ANZ/CAN)
  • When patients were treated with chemotherapy (Zhang 2014).

Conclusions

• High NLR at BL is an independent prognostic factor for worse PFS and OS in patients with gastric cancer.
• High plasma VEGF-A, IL-8 and sVEGFR-1 were significantly associated with poorer prognosis for PFS – however not significant after adjusting for NLR and age.
• A very strong correlation between plasma levels of VEGF-A and VEGF-C was found.
• A significant REG treatment effect by geographical region, was not explained by differences in BL biomarker studied.
• A predictive blood based biomarker for REG remains elusive.

A broader exploratory biomarker study including blood biomarkers beyond the VEGF axis and tissue based biomarkers is ongoing. Results will inform the biomarker study of the INTEGRATE II trial commencing in 2016.

Summary

• This was an exploratory biomarker evaluation to clarify REG RD efficacy results of the INTEGRATE trial and inform a future Phase II trial by identifying response sub-populations.

• High NLR was associated with different geographical regions in the distribution of different biomarkers.
• High NLR is associated with worse PFS in gastric cancer, as reported by others.
• High BL levels of IL-8 and sVEGFR-1 were also found to be adverse prognostic factors for gastric cancer.
• High BL levels of VEGF-A and sVEGFR-1 were not found to be adverse predictors of REG efficacy.
• Of the plasma biomarkers analysed at BL, none modified the effect of REG in those patients.

• This study confirms a higher NLR at BL is a significant prognostic factor for PFS and OS, as found in other gastric cancer trials (Zhang 2014).