Abstract # 4068

Predicting Overall Survival in Gastric Cancer Patients Randomized to Chemotherapy: A Re-evaluation of the ITACA-S Trial

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Background

- The Intergroup Trial of Adjuvant Chemotherapy in Adenocarcinoma of the Stomach (ITACA-S) evaluated the survival advantage of FOLFIRI followed by docetaxel and cisplatin in comparison to 5-FU/LV in patients with radically resected gastric cancer (GC).
- The trial found no clinical difference between the two regimens in the absence of molecular knowledge of the tumor.
- Class III β-tubulin (TUBB3) protein is a putative marker of resistance to taxane. Taxane binds to β tubulin, stabilizing microtubules and inducing cell-cycle arrest and apoptosis.
- Thymidine phosphorylase (TYMP) activates nucleoside analogues and is a reported marker of response to 5-FU.
- Multiplexed mass spectrometry proteomic analysis objectively quantifies TUBB3, TYMP and other actionable protein biomarkers from two formalin-fixed, paraffin-embedded (FFPE) tissue sections.

Hypotheses

- A TUBB3 protein cutoff of 750 amol/ug of total protein (predefined based on the assay's limit of detection) is predictive of overall survival (OS) in patients randomized to docetaxel.
- High expression of TYMP protein is a marker of response to 5-FU.

Methods

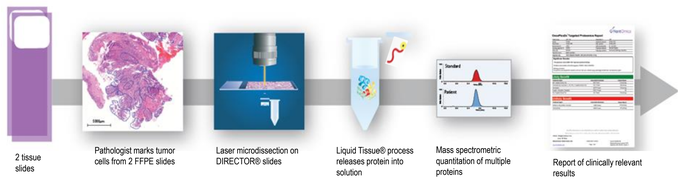

Figure 1: Archived tumor samples from the ITACA-S trial (n=247) were microdissected and solubilized for mass spectrometric quantification of TUBB3, TYMP and other proteins. The multiplexed proteomic assay is run in a CAP/CLIA clinical laboratory. The Gehan-Breslow-Wilcoxon test was used for survival comparisons.

Results

Taxane-treated GC patients with low TUBB3 protein expression (<750 amol/ug) survived longer

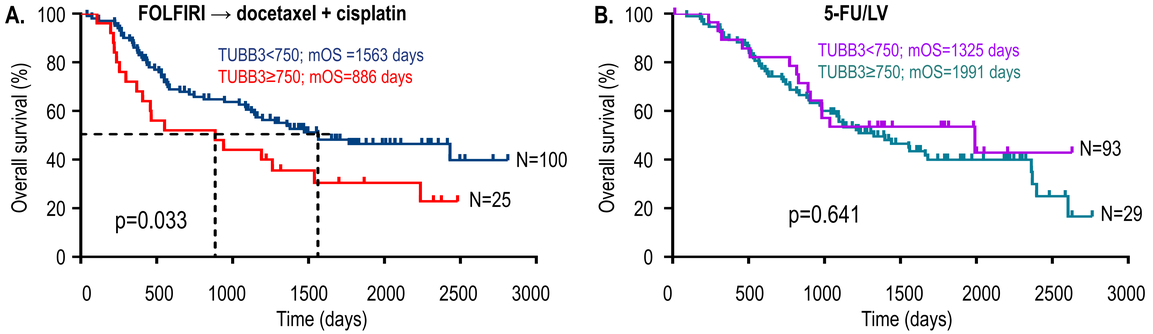

Figure 2: **A.** Among docetaxel-treated patients (n=125), those with TUBB3 levels below the cutoff (750 amol/ug; n=100) had nearly twice the median OS of patients with TUBB3 levels above the cutoff (n=25). **B.** There is no association between TUBB3 protein and overall survival in the 5-FU/LV arm.

TYMP protein >1335 amol/ug was associated with longer OS in 5-FU-treated patients

Longest survival with combined protein signature

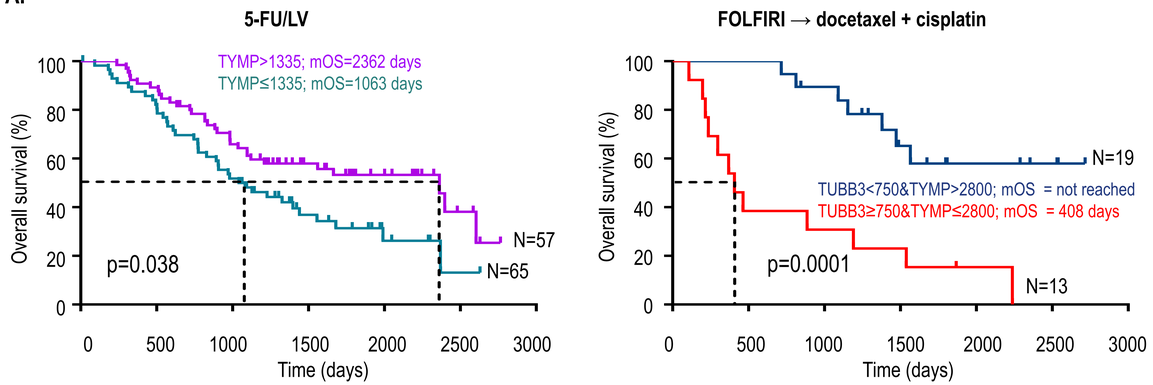

Figure 3: A. 5-FU/LV-treated patients (n=122) with TYMP protein expression above the cutoff (n=57) survived longer than those with lower TYMP levels (n=65). **B.** A combination of low TUBB3 and high TYMP expression predicted the longest survival in patients treated with FOLFIRI + docetaxel.

Conclusions

- Quantitative proteomic analysis of TUBB3 identified a subset of GC patients who benefitted from the addition of docetaxel to adjuvant chemotherapy in the ITACA-S trial.
- GC patients with high TUBB3 protein expression (≥ 750 amol/ug) had worse outcomes on a docetaxel-containing regimen than on chemotherapy without docetaxel.
- Ongoing analyses suggest that TUBB3 protein overexpression may also be predictive of docetaxel resistance in breast cancer patients. Similar TUBB3 protein cutoffs are expected to predict response to other types of microtubules inhibitors.
- Quantitative proteomic analysis of TYMP identified a subset of GC patients who benefitted from 5-FU/LV.
- A signature combining TUBB3 and TYMP protein expression predicted the longest survival in docetaxel-treated patients.
- Multiplexed proteomics identifies biomarkers for targeted therapy and chemotherapy that cannot be found with either genomic or immunohistochemistry analysis alone.

References

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Future Plans

Validate the study results in other indications including triple negative breast cancer and colorectal cancer.