

Background

- The Intergroup Trial of Adjuvant Chemotherapy in Adenocarcinoma of the Stomach (ITACA-S) evaluated the survival advantage of postoperative sequential chemotherapy with FOLFIRI followed by docetaxel plus cisplatin in comparison to therapy with 5-FU/LV in patients with radically resected gastric cancer (GC).
- Results of the ITACA-S trial showed no clinical difference when choosing between chemotherapy agents in the treatment of gastric cancer in the absence of molecular intelligence.
- We retrospectively evaluated the relationship between survival and expression of class III β -tubulin (TUBB3) protein (Figure 2) using selected reaction monitoring mass spectrometry (SRM-MS) in ITACA-s prospective randomized trial.
- A cutoff for TUBB3 was prospectively defined based on the proteomic assay's limit of detection (TUBB3=750 amol/ug).

Hypothesis

- Determine whether a pre-defined cutoff of TUBB3>750 amol/ug by SRM-MS analyses is predictive of overall survival (OS) in GC patients from ITACA-s trial

Methods

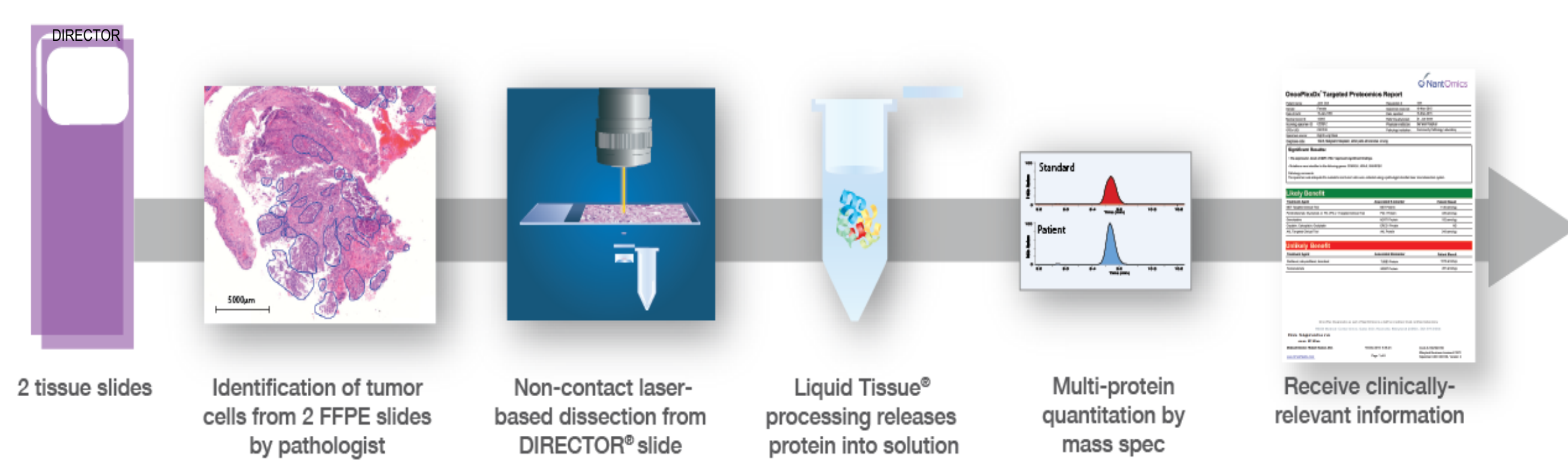


Figure 1: Mass spectrometry is used to quantify proteins expressed by solubilized formalin-fixed, paraffin-embedded (FFPE) tumor samples. More than 250 quantitative proteomic assays for relevant oncology biomarkers have been built, 35 of which are currently run in a CAP/CLIA clinical laboratory. Tumor samples from the ITACA-s randomized trial have been retrospectively analyzed to define protein cutoff levels predictive of response to chemotherapies. The Mantel-Cox log-rank test was used for survival comparisons.

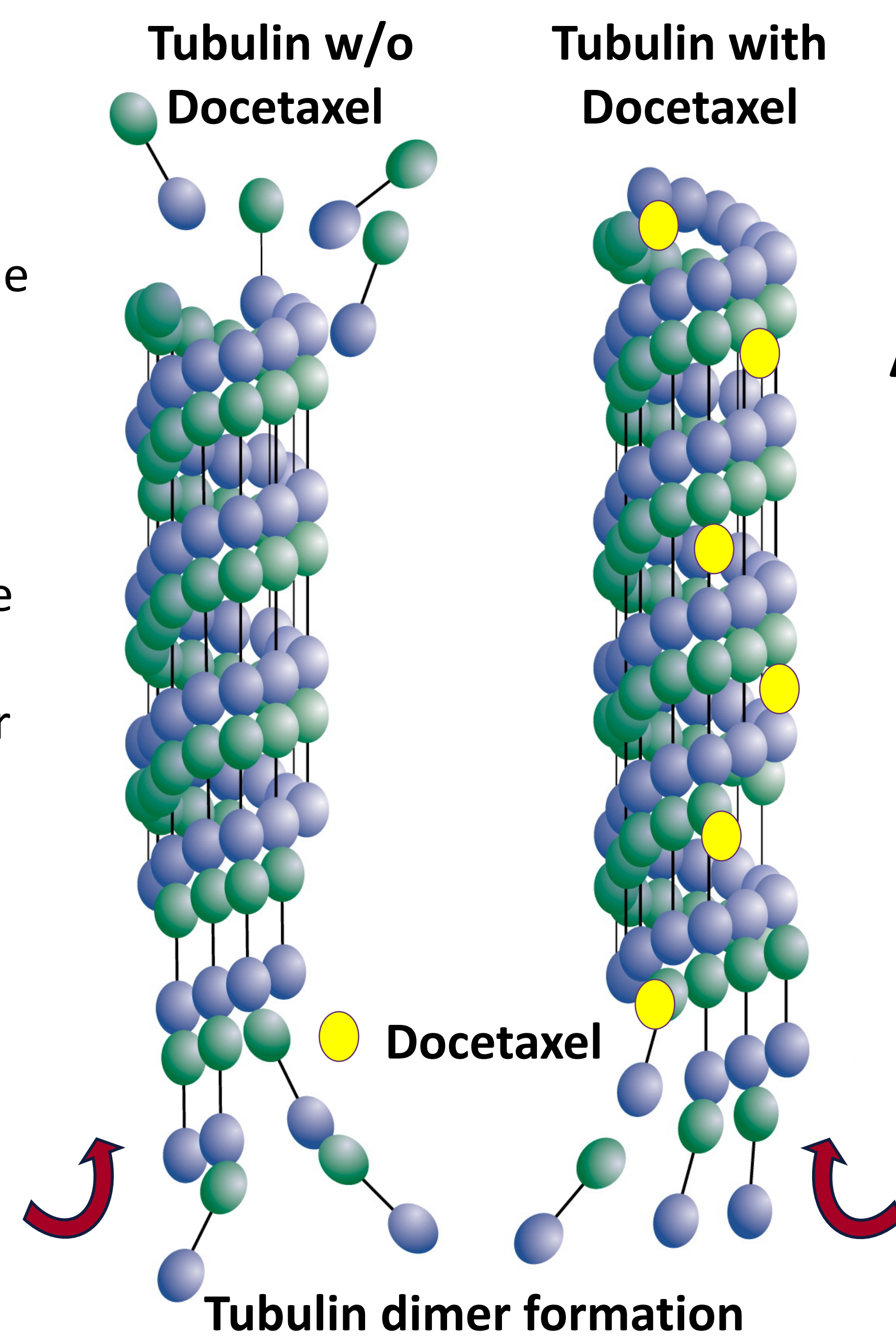


Figure 2: Taxane binds to β tubulin, stabilizing microtubules & inducing cell-cycle arrest and apoptosis.

Results

Multiplexed Targeted Proteomics Identify GC Patients Who May Benefit from Docetaxel

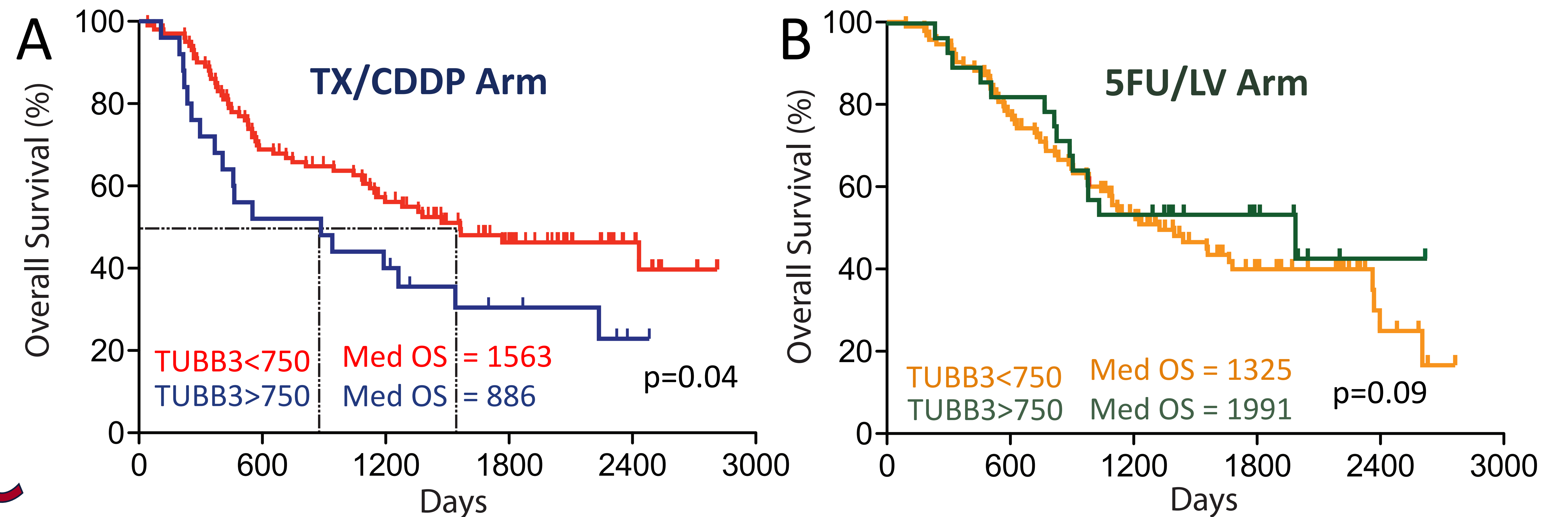


Figure 3: A) Among GC patients treated with docetaxel-containing chemotherapy (n=125), those with TUBB3 levels below the cutoff (750 amol/ μ g of total protein) had nearly twice the median overall survival (OS) as patients with TUBB3 levels above the cutoff (1563 vs 886 days, p=0.04). **B)** There is no significant association between TUBB3 protein expression and overall survival in the 5-FU/LV arm.

GC patients with TUBB3 protein expression above 750 amol/ug had worse outcomes on a Docetaxel-containing regimen

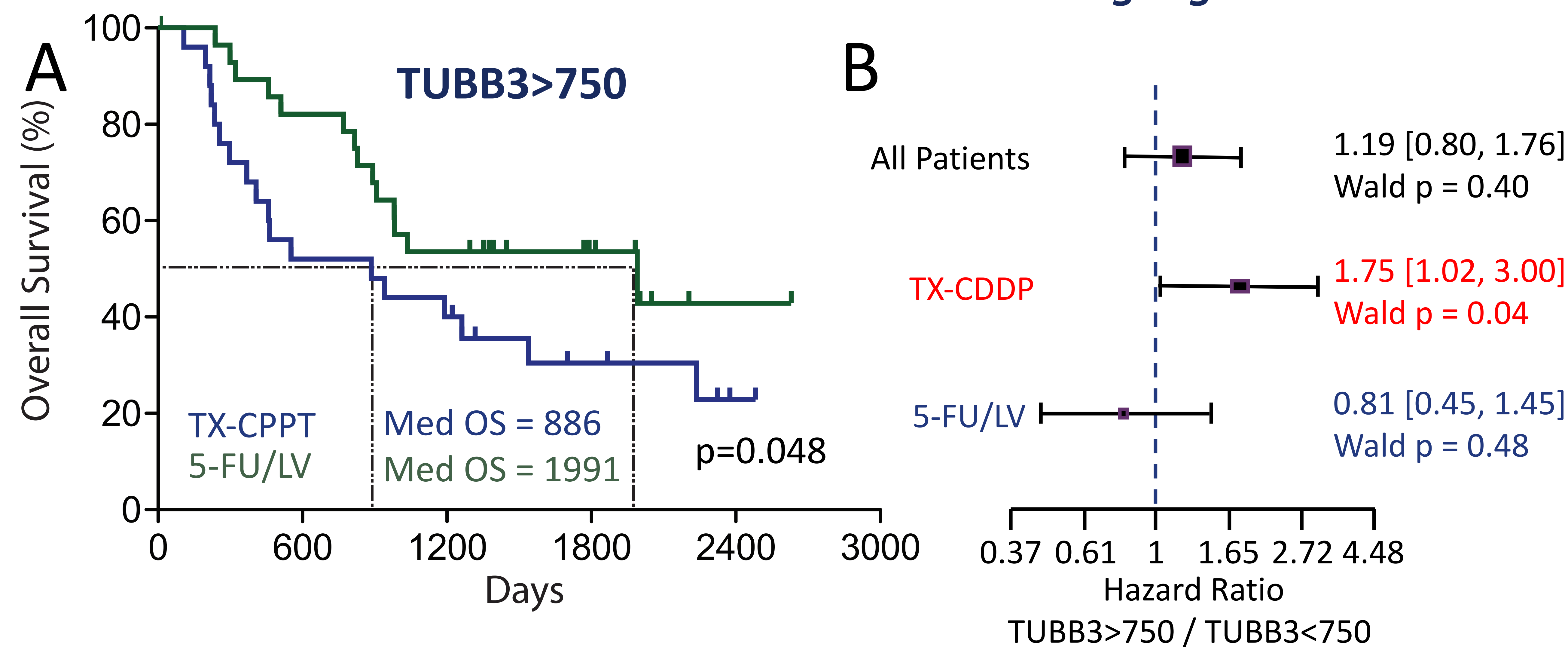


Figure 4: A) Among patients with high TUBB3 levels (>750 amol/ug), those treated without docetaxel survived longer than patients in the docetaxel arm (OS=1991 vs 886 days, p=0.048). **B)** Univariate Cox Model: OS, binary TUBB3

Conclusion

- Quantitative proteomic analysis of multiple biomarkers – for both targeted therapy as well as chemotherapy – is able to successfully identify actionable protein levels that cannot be found by genomic analysis alone.
- Quantitative proteomic analysis of TUBB3 expression identified a subset of GC patients who benefitted from the addition of docetaxel to adjuvant chemotherapy in the ITACA-s trial.
- GC patients with TUBB3 expression above 750 amol/ug had worse outcomes on a docetaxel-containing regimen than on chemotherapy without docetaxel.
- Using this cutoff, we have identified patients who overexpressed TUBB3 and subsequently responded to taxane chemotherapy
- Personalized chemotherapy based on the TUBB3 biomarker is promising and warrants broader evaluation.