Causal Modeling of CALGB 80405 (Alliance) Identifies Network drivers of Metastatic Colorectal Cancer


• CALGB 80405 is a recently-completed phase III clinical trial of FOLFOX and FOLFOX with randomly assigned capecitabine (cit) or bevacizumab (bev) in metastatic CRC (mCRC) patients.

• Hypothesis-free machine learning approaches to this study dataset can provide valuable insights into mCRC prognosis and management of mCRC progression.

• Causal modeling identifies the set of conditional dependencies between variables leading to outcomes.

• We built multivariate causal models of mCRC and examined the network drivers of mCRC survival.

MODEL 1: CLINICAL CAUSAL DRIVERS OF OS

- Clustering of NanoString data revealed three molecular clusters with upregulation of different signatures.

- BRAF mutation, RAS mutation, CMS4, and angiogenesis signature were the top molecular drivers of OS.

- Causal effects of 1st side on OS was found to be driven by a molecular pathway.

Model 2: Molecular Causal Drivers of OS

- Clustering of NanoString data revealed three molecular clusters with upregulation of different signatures.

- 1st side, ECOG performance score, concentrations of separate angiogenesis (AGS), hemoglobin (HGB), absolute neutrophil counts (ANC), lactate dehydrogenase (LDH) and metastases at intra-abdominal, lung, and liver were the strongest causal drivers of OS.

- Analysis of NanoString data:

  - For continuous variables, 3rd quartile values were used to compute HR.
  - For categorical variables, 2nd & 1st quartile values were used to compute HR.
  - Analysis of NanoString data:

    - Causal drivers of OS.

    - Identified causal drivers were validated in independent cohorts using univariate Cox proportional hazard model. HR, 95% CI, and p-value are shown in the plots below.

MODEL 3: CAUSAL DRIVER GENES OF OS

- ALOX5 and CDX2 were among the top causal driver genes of OS.

- The causal genes in the molecular pathways leading to OS are involved in ECM remodeling and angiogenesis, thereby corroborating the findings from Model 2.

Validation of Causal Drivers of OS

- Identified causal drivers were validated in independent cohorts using univariate Cox proportional hazard model. HR, 95% CI, and p-value are shown in the plots below.

RESULTS

CONCLUSIONS

- Bayesian causal modeling identified clinical and molecular driver genes (prognostic biomarkers) of OS for mCRC. The molecular drivers were validated in independent cohorts.

- 1st side, ECOG score, AST, LDH, HGB, and metastases (extra-abdominal, and liver) were the top clinical drivers of OS.

- BRAF & RAS mutations, CMS4, and angiogenesis ECM remodeling signature were top molecular drivers of OS.

- Consistent with previous studies, ALOX5 and CDX2 were identified as causal driver genes of OS.

- A molecular pathway between 1st side and OS was identified. Investigation into the molecular underpinnings of sidedness in driving OS is currently in progress.

- The availability of the measures for the drivers at baseline will allow better risk stratification at initiation of treatment.

- Additional research, including prospective studies, is necessary to confirm these findings.

Support: U01CA148021, U10CA148892, U10CA148881; El Lilly and Company, Genentech, Phase 4; ClinicalTrials.gov identifier: NCT00303580