Exploration of the Impact of the Treatment Mechanism of Action on the Surrogate Relationship between Progression Free Survival and Overall Survival in Metastatic Colorectal Cancer

MSR21

Heather Poad, Sam Khan, Lorna Wheaton, Anne Thomas, Michael Sweeting and Sylwia Bujkiewicz. University of Leicester, Leicester, UK.

Aim

To determine whether treatment's mechanism of action affects the surrogate relationship between progression free survival (PFS) and overall survival (OS) in metastatic colorectal cancer (mCRC).

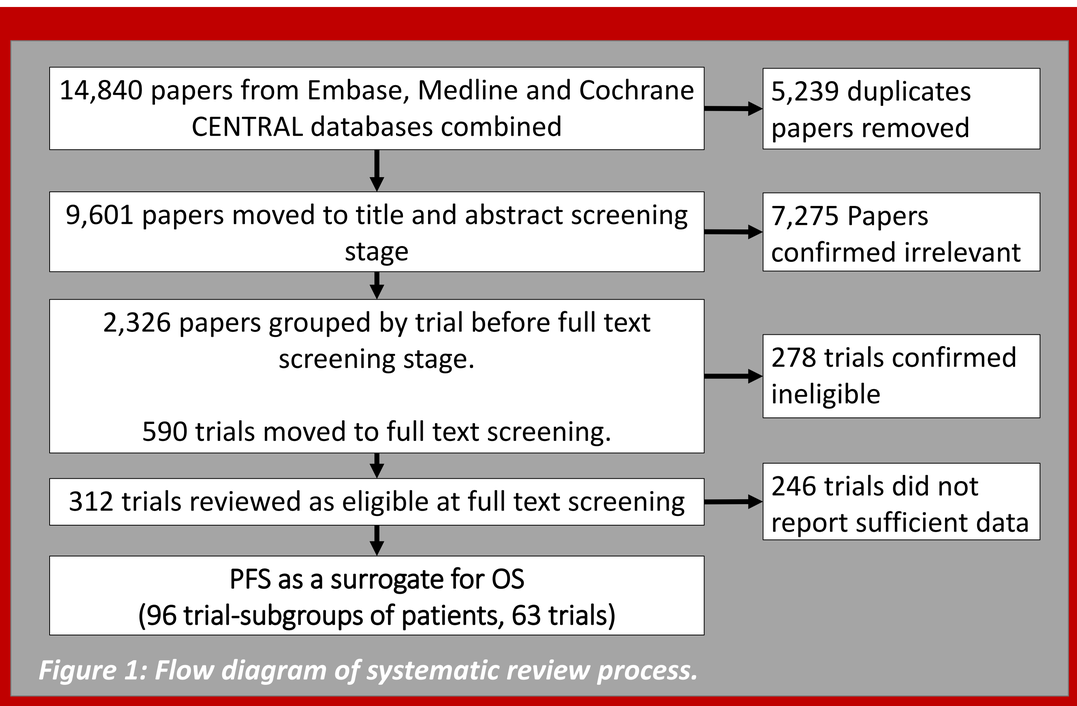

Figure 1: Flow diagram of systematic review process.

Systematic Review

A systematic literature review was conducted to identify all randomised controlled trials (RCTs) of any pharmacological therapies for mCRC that were published between 1st January 2003 and 3rd April 2020 (PROSPERO registration CRD42020167075). The process is described in Figure1. Trials included reported treatment effects on PFS and OS. Data was separated into trial-subgroups depending the KRAS status of patients.

Statistical Methods

The surrogate relationship between PFS and OS was evaluated in an overall analyses including all RCTs using the Daniels and Hughes method [1, 2].

Trials were then classified by the mechanism of action of the experimental arm. To evaluate the surrogate relationship between PFS and OS according to the mechanism of action a subgroup analyses of data within each class and a hierarchical method combining all data were used [3].

Analysis was completed using R and WinBUGs.

Criteria for assessing the strength of the surrogate relationship

Surrogacy was assessed using the following three criteria, with visual example in Figure 2:

- **Slope: 95% CrI (Credible Interval) does not include 0**
- **Intercept: 95% CrI to include 0**
- **Conditional Variance: 95% CrI to be small and close to 0**

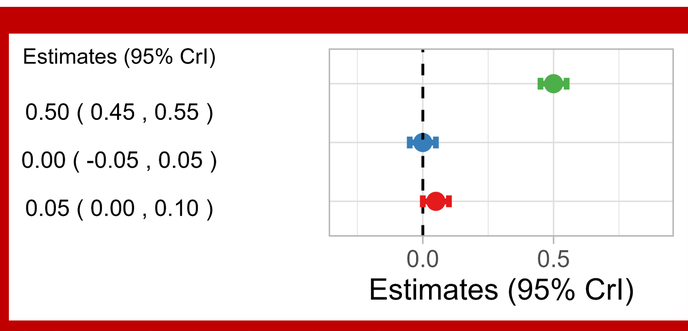

Figure 2: Example forest plot & values that show a strong surrogate relationship.

Results

- In total there were 63 trials, 96 trial-subgroups identified for the analysis.
- The surrogate relationship between treatment effects on PFS and OS including all RCTs, shown in Figure 3 was strong.
- Seven different treatment combinations were classified and the results are shown in Figure 4;
- For treatment classes with eight or more trials, PFS as a surrogate for OS appeared to have a stronger surrogate relationship than for all data combined.
- Hierarchical model produces estimates with reduced uncertainty for all treatment classes.

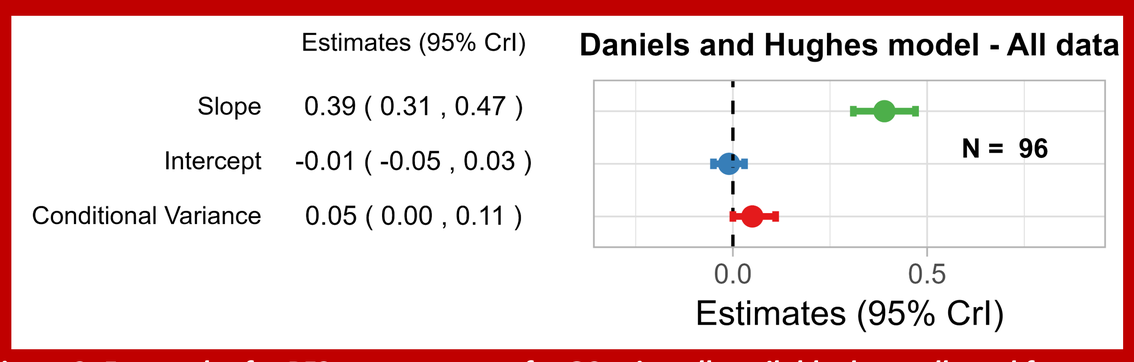

Figure 3: Forest plot for PFS as a surrogate for OS using all available data collected from systematic review.

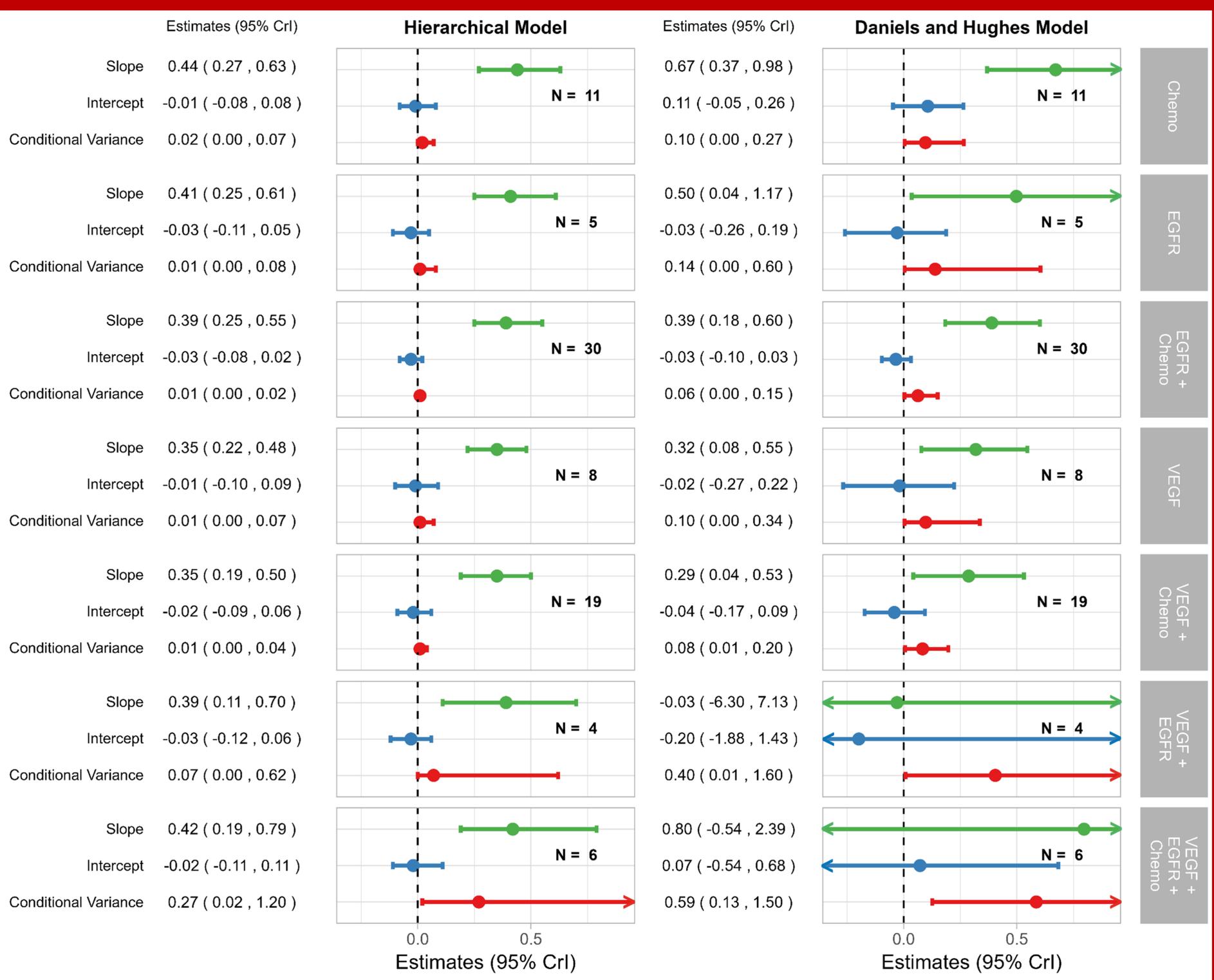

Figure 4: Forest plots assessing PFS as a surrogate for OS using the hierarchical model and the Daniels and Hughes model

Results continued..

- The surrogate relationship between the treatment effects on PFS and OS was strongest for the EGFR + Chemotherapy group.
- For treatment classes with eight or more trials, PFS as a surrogate for OS appeared to have a stronger surrogate relationship than for all data combined.

Conclusions

There may be some impact of the mechanism of action on the surrogacy patterns in mCRC for PFS as a surrogate for OS.

References:

[1] - Daniels, Michael J, and Michael D Hughes. 'Meta-analysis for the Evaluation of Potential Surrogate Markers'. STATISTICS IN MEDICINE, VOL. 16, 1965–1982 (1997)

[2] - Bujkiewicz, S., Achana, F., Papanikos, T., Riley, R.D., Abrams, K.R. NICE DSU Technical Support Document 20: Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints. 2019; available from http://www.nicedsu.org.uk

[3] - Papanikos T, Thompson JR, Abrams KR, Städler N, Ciani O, Taylor R, et al. Bayesian hierarchical meta-analytic methods for modeling surrogate relationships that vary across treatment classes using aggregate data. Statistics in Medicine. 2020;39(8):1103–24.

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