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Second- or Later-Line Treatments for Advanced and Metastatic Gastric Cancer: A Network Meta-Analysis Comparing Treatments to Paclitaxel

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INTRODUCTION

Globally, gastric cancer is the 5th most frequently diagnosed cancer.

In the second-line setting, the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) recommend ramucirumab in combination with (+) paclitaxel or (when combination therapy is not feasible) ramucirumab, docetaxel, paclitaxel, or irinotecan monotherapy. FOLFIRI is another second-line option. In the MSI-high or mismatch repair deficient setting, pembrolizumab or dostarlimab are recommended. Pembrolizumab is recommended when tumour mutational burden is ≥ 10/megabase.

In the third- and later-line settings, trifluridine/tipiracil or (when HER-2 positive) trastuzumab deruxtecan are recommend.

The relative efficacy and safety of many of these treatments have not been investigated.

AIMS

To investigate the relative efficacy and safety of treatments recommended by NCCN and ESMO for advanced and metastatic gastric cancers in the second- or later-line settings.

METHODS

- RCTs of relevant treatments (2009 - May 2024) were identified via a systemic search.
- Risk of bias assessments were conducted on identified studies using the Cochrane ROB-1 Tool.
- Bayesian Network Meta-Analyses (NMA) were conducted for: overall survival (OS); progression-free survival (PFS); objective response rate (ORR); and Grade ≥ 3 treatment-related adverse events (TRAEs).
- Eligibility for inclusion of RCTs in each network was assessed based on: line of treatment, outcomes reported, exchangeability and network connectivity.
- Paclitaxel was the pre-specified benchmark comparator given its widespread use.
- Forest plots of effect estimates versus paclitaxel, for all treatments, were presented.
- Analyses were conducted in R (v. 4.4.2) and JAGS (v. 4.3.1) using BUGSnet.

RESULTS

- 44 eligible RCTs were identified: 37 in the second-line setting, five in the second- and later-line setting and two in the third- and later-line setting.
- NMAs were feasible in the second-line setting only.
- The OS NMA included eight treatments, the PFS NMA included five treatments, the ORR NMA included six treatments and the Grade ≥ 3 TRAEs NMA included five treatments.
- There were no statistically significant differences in efficacy between any of the treatments versus paclitaxel. Certain numerical differences were noted in other comparisons.
- Pembrolizumab was associated with a significant decreased risk of Grade ≥ 3 TRAEs versus paclitaxel. Nominal differences were noted in other comparisons.

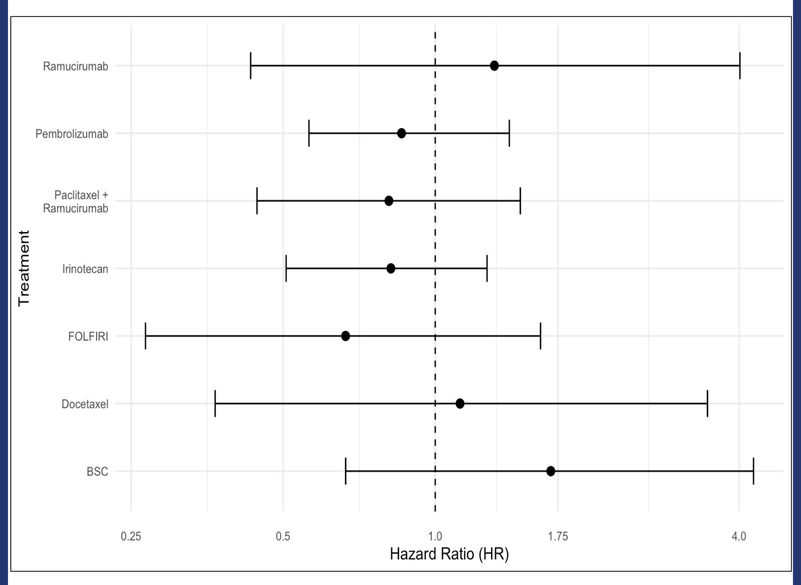

Fig 1: Forest Plot of Overall Survival
The vertical line, which corresponds to the value 1, is the line of 'no effect'. When the 95% CrI crosses here, the difference in outcome between the intervention and comparator is not statistically significant.

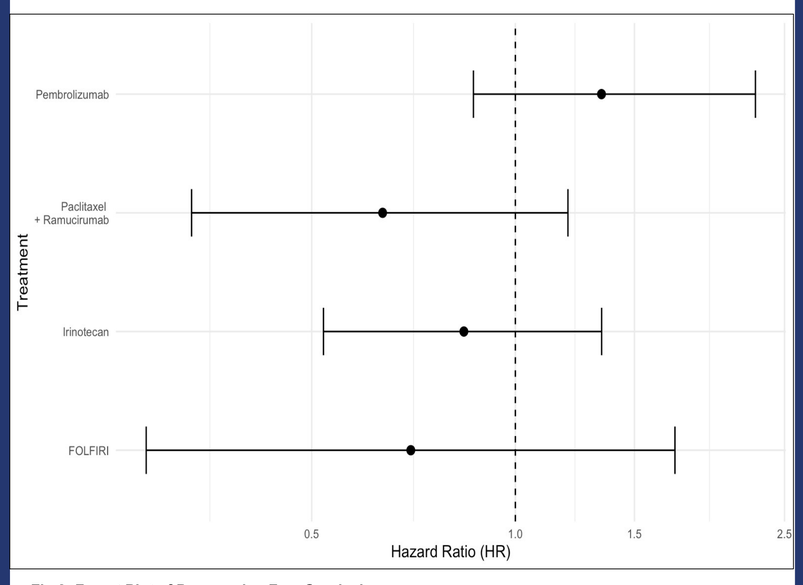

Fig 2: Forest Plot of Progression Free Survival
The vertical line, which corresponds to the value 1, is the line of 'no effect'. When the 95% CrI crosses here, the difference in outcome between the intervention and comparator is not statistically significant.

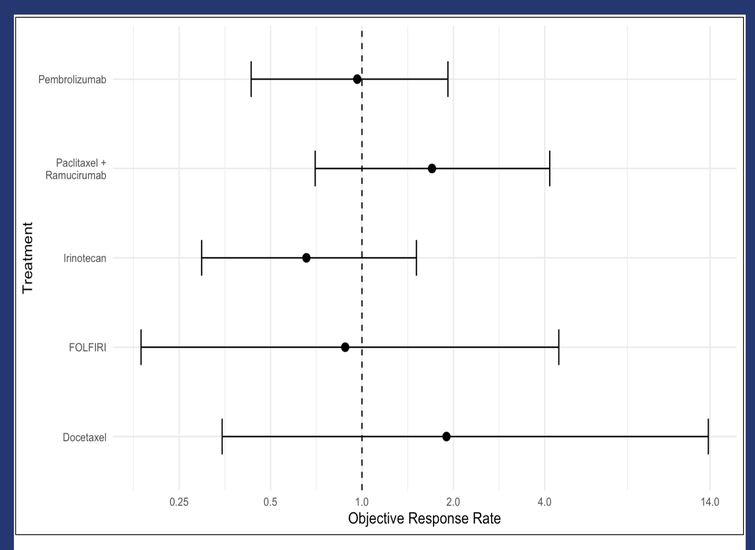

Fig 3: Forest Plot of Objective Response Rate
The vertical line, which corresponds to the value 1, is the line of 'no effect'. When the 95% CrI crosses here, the difference in outcome between the intervention and comparator is not statistically significant.

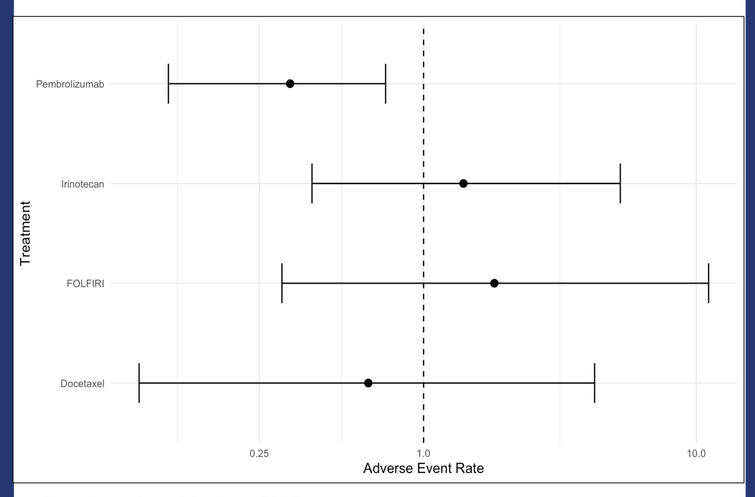

Fig 4: Forest Plot of Grade ≥ 3 TRAEs
The vertical line, which corresponds to the value 1, is the line of 'no effect'. When the 95% CrI crosses here, the difference in outcome between the intervention and comparator is not statistically significant.

DISCUSSION

- NMAs were feasible in the second-line setting only.
- Pembrolizumab was associated with a significant decreased risk of Grade ≥ 3 TRAEs versus paclitaxel. There were no other statistically significant findings, although certain trends were observed.
- Low event rates and small sample sizes were associated with reduced statistical power which was evidenced by wide credible intervals and non-significant results.
- Larger, well powered RCTs are needed to improve precision and strengthen conclusions on comparative treatment outcomes.

CONCLUSION

- The treatment landscape, in this setting, is rapidly evolving.
- Our work indicates that there remains a need for novel treatments that will be associated with significant benefits in relative efficacy and safety.

Contact Information

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