Oesophago-gastric cancer
Assessment and management

NICE Guideline NG83
Appendix M
Network Meta-Analysis of Second Line Palliative Chemotherapy for Locally Advanced and Metastatic Disease
January 2018

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists
Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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## Contents

1 Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease ................................................................. 6  
   1.1 Introduction ........................................................................................................... 6  
   1.2 Methods ............................................................................................................... 6  
      1.2.1 Clinical data considered in the network meta-analyses .................................. 6  
      1.2.2 Review Strategy and Evidence Synthesis ...................................................... 7  
      1.2.3 Network meta-analysis model structure ....................................................... 12  
   1.3 Network meta-analysis results ........................................................................... 36  
      1.3.1 Inconsistency and heterogeneity ................................................................. 36  
      1.3.2 Estimated hazard ratios .............................................................................. 36
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

Review question: What is the optimal palliative second-line chemotherapy for locally advanced and metastatic oesophago-gastric cancer?

1.1 Introduction

Following first-line platinum/fluoropyrimidine based chemotherapy for advanced oesophago-gastric cancer, a proportion of patients may be suitable for and wish to be considered for second-line chemotherapy. Randomised trials have demonstrated a small but significant survival benefit for second-line chemotherapy as compared to best-supportive care. The modest survival benefit needs to be considered alongside potential treatment-related morbidity, impact of on quality of life and patients’ wishes for treatment.

This review aimed to investigate the optimal second-line palliative approaches for locally advanced and metastatic oesophago-gastric cancer. In addition we aimed to identify subgroups of patients most likely to benefit from second-line chemotherapy.

1.2 Methods

1.2.1 Clinical data considered in the network meta-analyses

The Network Meta-Analysis (NMA) considered the effectiveness of second line palliative chemotherapy for locally advanced and metastatic oesophago-gastric cancer. The NMA was populated with the results of the clinical evidence review conducted for this topic and includes randomised controlled trials in which the following second-line treatments were compared:

Monotherapy

- Irinotecan alone
- Taxane alone (paclitaxel or docetaxel)

Combination therapy

- Taxane combination
  - Docetaxel/Irinotecan +/- fluoropyrimidine (5FU/capecitabine)
- Irinotecan combination
  - FOLFIRI: Irinotecan, leucovorin (folinic acid), 5FU bolus and 5Fu infusion
  - IFL: irinotecan, fluorouracil bolus and leucovorin (folinic acid)
- Platinum combination
  - EOFp: Epirubicin, Platinum (Oxaliplatin or cisplatin), Fluoropyrimidine (5FU or Capecitabine)
- MMC/Capecitabine: Mitomycin C, Capecitabine ± platinum
Best supportive care (e.g. similar frequency of clinic follow-up as active treatment arm and symptomatic support as required)

All studies included people with locally advanced and metastatic oesophago-gastric cancer who have received one prior schedule of chemotherapy for locally advanced and metastatic disease.

Note that ramucirumab was excluded from the review protocol for this question as this intervention is covered by a NICE technology appraisal (TA378) and could not be considered by this guideline. However, for statistical validity, studies were included in which the interventions above are compared to interventions not in the list above (including ramucirumab). Such studies would only be considered if they provided indirect evidence to the network via a closed loop of treatment effects for included interventions. No such studies, however, were included in the final networks because none of the trials with excluded treatments closed a loop with included treatments.

Only studies published in the year 2000 or later were included in the NMA as it was considered evidence published prior to this date would not adequately represent current practice.

1.2.2 Review Strategy and Evidence Synthesis

The systematic review for this topic identified 16 studies appropriate for inclusion in the network meta-analysis. All of the studies were randomised controlled trials. The median follow-up (where reported) ranged from 6 to 59 months and the sample sizes ranged from 40 to 525 patients. See Table 1, Table 2 and Table 3.

Overall survival and progression free survival were entered into the NMA model in the form of hazard ratios comparing the intervention to the control. Where hazard ratios had not been reported in the original paper these were calculated using methods outlined in Parmar 2008.

Although treatment related morbidity outcomes were widely reported in the literature there was variation in the definitions used. It was also unclear when a study did not explicitly report an outcome (for example treatment related mortality) whether this meant there were no occurrences of this outcome. Therefore, the available data for the NMAs for these treatment related morbidity and mortality was much more limited and the results are likely to be less robust.

Table 1: Studies included in network meta-analyses of second line palliative chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bang 2015</td>
<td>6-10x4 week treatment cycle: Olaparib 100mg BD + paclitaxel 80mg/m2 IV days 1, 8, 15</td>
<td>Paclitaxel 80mg/m2 IV days 1, 8, 15</td>
</tr>
<tr>
<td></td>
<td>Maintenance: Olaparib 200mg BD</td>
<td>Placebo</td>
</tr>
<tr>
<td>Bang 2016</td>
<td>6-10x4 week treatment cycle: Olaparib 100mg BD + paclitaxel 80mg/m2 IV days 1, 8, 15</td>
<td>Paclitaxel 80mg/m2 IV days 1, 8, 15</td>
</tr>
<tr>
<td>Ford 2014</td>
<td>Docetaxel 75mg/m2 IV every 3 weeks x 6 cycles</td>
<td>BSC</td>
</tr>
</tbody>
</table>
### Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higuchi 2014</td>
<td>Irinotecan 60mg/m2 IV + cisplatin 30mg/m2 IV every 2 weeks</td>
<td>Irinotecan 150mg/m2 IV every 2 weeks</td>
</tr>
<tr>
<td>Hironaka 2013</td>
<td>Paclitaxel 80mg/m2 IV days 1, 8, 15 every 4 weeks</td>
<td>Irinotecan 150mg/m2 day 1 and 15 every 4 weeks</td>
</tr>
<tr>
<td>Kang 2012</td>
<td>Either docetaxel 60 mg/m2 every 3 weeks or irinotecan 150 mg/m2 every 2 weeks at the discretion of investigators</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>Kim B 20151</td>
<td>Docetaxel 75mg/m2 IV every 3 weeks</td>
<td>Arm 2: Docetaxel 60mg/m2 IV + Cisplatin 60mg/m2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 3: Docetaxel 60mg/m2 + S-1 30mg/m2 BD day 1-14</td>
</tr>
<tr>
<td>Kim JY 2015</td>
<td>Docetaxel 36mg/m2 IV day 1 and 8 every 3 weeks x 9 cycles</td>
<td>Docetaxel 80mg/m2 day every 3 weeks</td>
</tr>
<tr>
<td>Maruta 2007</td>
<td>Docetaxel 60 mg/m2 IV every 3 weeks x 2cycles</td>
<td>Docetaxel 60 mg/m2 IV every 3 weeks</td>
</tr>
<tr>
<td>Moehler 2013</td>
<td>6-week cycles: FOLFIRI two weekly followed by 4 weeks daily sunitinib 25mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>Nishikawa 2015</td>
<td>Irinotecan 60 mg/m2 + cisplatin 30mg/m2 every 2 weeks</td>
<td>Irinotecan 150 mg/m2 every 2 weeks</td>
</tr>
<tr>
<td>Nishina 2016</td>
<td>5FU 800mg/m2/day days 1-5 every 4 weeks</td>
<td>Paclitaxel 80mg/m2 IV days 1, 8, 15 every 4 weeks</td>
</tr>
<tr>
<td>Roy</td>
<td>Irinotecan 300mg/m2 every 3 weeks</td>
<td>Docetaxel 75mg/m2 every 3 weeks</td>
</tr>
<tr>
<td>Sym 2013</td>
<td>Irinotecan 150mg/m2 every 2 weeks x 12 cycles</td>
<td>Irinotecan 150mg + 5FU 1g/m2 + leucovorin 20mg/m2</td>
</tr>
<tr>
<td>Tanabe 2015</td>
<td>S-1 BD days 1-14 + Irinotecan 150mg/m2 every 21 days</td>
<td>Irinotecan 150mg/m2 every 2 weeks</td>
</tr>
<tr>
<td>Thuss-Patience2011</td>
<td>Irinotecan 250mg/m2 in cycle 1 then 350mg/m2 thereafter</td>
<td>BSC</td>
</tr>
</tbody>
</table>

1 Kim B 2015 was a three arm trial and was included in the network as three pairs of comparisons, weighted accordingly.
Table 2: Details of studies included in overall survival and progression free survival network meta-analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention (arm1)</th>
<th>Comparison (arm 2)</th>
<th>N1</th>
<th>N2</th>
<th>Median follow-up (months)</th>
<th>Location</th>
<th>Overall Survival (HR 95% CI)</th>
<th>Progression free survival (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bang 2015</td>
<td>olaparib+paclitaxel</td>
<td>placebo + paclitaxel</td>
<td>61</td>
<td>62</td>
<td>8.4</td>
<td>Asia</td>
<td>0.56 (0.35 to 0.87)</td>
<td>0.8 (0.62 to 1.03)</td>
</tr>
<tr>
<td>Ford 2014</td>
<td>docetaxel</td>
<td>BSC</td>
<td>84</td>
<td>84</td>
<td>6</td>
<td>Europe</td>
<td>0.67 (0.49 to 0.92)</td>
<td>0.67 (0.48 to 0.92)</td>
</tr>
<tr>
<td>Higuchi 2014</td>
<td>irinotecan + cisplatin</td>
<td>irinotecan</td>
<td>64</td>
<td>66</td>
<td>NR</td>
<td>Asia</td>
<td>1 (0.69 to 1.44)</td>
<td>0.68 (0.47 to 0.98)</td>
</tr>
<tr>
<td>Hironaka 2013</td>
<td>paclitaxel</td>
<td>irinotecan</td>
<td>111</td>
<td>112</td>
<td>17.6</td>
<td>Asia</td>
<td>1.13 (0.86 to 1.49)</td>
<td>1.14 (0.88 to 1.49)</td>
</tr>
<tr>
<td>Kim B 2015 (arm 1 vs arm 2)</td>
<td>docetaxel</td>
<td>docetaxel + cisplatin</td>
<td>23</td>
<td>24</td>
<td>NR</td>
<td>Asia</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kim B 2015 (arm 2 v arm 3)</td>
<td>docetaxel + cisplatin</td>
<td>docetaxel + S-1</td>
<td>24</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kim B 2015 (arm 1 v arm 3)</td>
<td>docetaxel</td>
<td>docetaxel + S-1</td>
<td>23</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kim JY 2015</td>
<td>docetaxel</td>
<td>docetaxel + oxaliplatin</td>
<td>27</td>
<td>25</td>
<td>NR</td>
<td>Asia</td>
<td>1.17 (0.67 to 2.04)</td>
<td>0.5 (0.27 to 0.91)</td>
</tr>
<tr>
<td>Maruta 2007</td>
<td>docetaxel</td>
<td>docetaxel + 5'DFUR</td>
<td>12</td>
<td>12</td>
<td>NR</td>
<td>Asia</td>
<td>3.11 (1.22 to 7.97)</td>
<td>NR</td>
</tr>
<tr>
<td>Moehler 2013</td>
<td>FOLFIRI + sunitinib</td>
<td>placebo</td>
<td>45</td>
<td>46</td>
<td>NR</td>
<td>Europe</td>
<td>0.816 (0.5 to 1.34)</td>
<td>1.11 (0.7 to 1.74)</td>
</tr>
<tr>
<td>Nishikawa 2015</td>
<td>irinotecan + cisplatin</td>
<td>irinotecan</td>
<td>84</td>
<td>84</td>
<td>59</td>
<td>Asia</td>
<td>0.834 (0.596 to 1.167)</td>
<td>0.86 (0.615 to 1.203)</td>
</tr>
<tr>
<td>Nishina 2016</td>
<td>5-fluouracil (5-FU)</td>
<td>paclitaxel</td>
<td>49</td>
<td>51</td>
<td>NR</td>
<td>Asia</td>
<td>0.887 (0.571 to 1.377)</td>
<td>0.58 (0.383 to 0.88)</td>
</tr>
<tr>
<td>Roy 2013</td>
<td>docetaxel</td>
<td>Irinotecan</td>
<td>44</td>
<td>44</td>
<td>NR</td>
<td>Asia</td>
<td>1.064 (1.639 to 0.6993)</td>
<td>0.8403 (1.282 to 0.546)</td>
</tr>
<tr>
<td>Sym 2013</td>
<td>irinotecan</td>
<td>irinotecan + 5'FU/leucovorin (mFOLFIRI)</td>
<td>29</td>
<td>30</td>
<td>NR</td>
<td>Asia</td>
<td>1.04 (0.62 to 1.75)</td>
<td>1.13 (0.68 to 1.89)</td>
</tr>
<tr>
<td>Tanabe 2015</td>
<td>S-1+ Irinotecan</td>
<td>irinotecan</td>
<td>153</td>
<td>151</td>
<td>NR</td>
<td>Asia</td>
<td>0.99 (0.78 to 1.25)</td>
<td>0.85 (0.67 to 1.07)</td>
</tr>
</tbody>
</table>
## Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention (arm 1)</th>
<th>Comparison (arm 2)</th>
<th>N1</th>
<th>N2</th>
<th>Median follow-up (months)</th>
<th>Location</th>
<th>Overall Survival (HR 95% CI)</th>
<th>Progression free survival (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thuss-Patience 2011</td>
<td>irinotecan</td>
<td>BSC</td>
<td>21</td>
<td>19</td>
<td>NR</td>
<td>Europe</td>
<td>0.48 (0.25 to 0.92)</td>
<td>NR</td>
</tr>
<tr>
<td>Kang 2012</td>
<td>docetaxel / irinotecan</td>
<td>BSC</td>
<td>126</td>
<td>62</td>
<td>NR</td>
<td>Asia</td>
<td>0.711 (0.536 to 0.974)</td>
<td>NR</td>
</tr>
<tr>
<td>Bang 2016</td>
<td>olaparib+paclitaxel</td>
<td>placebo + paclitaxel</td>
<td>263</td>
<td>262</td>
<td>NR</td>
<td>Asia</td>
<td>0.79 (0.63 to 1)</td>
<td>0.84 (0.67 to 1.04)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; HR, hazard ratio; N1, N2 – number of patients in arms 1 and 2 respectively; NR, not reported.*

### Table 3: Details of studies included in and treatment related morbidity and mortality NMAs

<table>
<thead>
<tr>
<th>Study</th>
<th>Nausea arm 1</th>
<th>Nausea arm 2</th>
<th>Neutropenic sepsis arm1</th>
<th>Neutropenic sepsis arm 2</th>
<th>Neutropenia arm 1</th>
<th>Neutropenia arm 2</th>
<th>Diarrhoea arm 1</th>
<th>Diarrhoea arm 2</th>
<th>Treatment related death arm 1</th>
<th>Treatment related death arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bang 2015</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>35</td>
<td>24</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ford 2014</td>
<td>NR</td>
<td>NR</td>
<td>6</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Higuchi 2014</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>25</td>
<td>24</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hironaka 2013</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>10</td>
<td>31</td>
<td>43</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Kim B 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(arm 1 vs arm 2)</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kim B 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(arm 2 vs arm 3)</td>
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<td>NR</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kim B 2015</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(arm 1 vs arm 3)</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kim JY 2015</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maruta 2007</td>
<td>1</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Moehler 2013</td>
<td>3</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>25</td>
<td>9</td>
<td>1</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Appendix M

Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Nausea arm 1</th>
<th>Nausea arm 2</th>
<th>Neutropaenic sepsis arm 1</th>
<th>Neutropaenic sepsis arm 2</th>
<th>Neutropaenia arm 1</th>
<th>Neutropaenia arm 2</th>
<th>Diarrhoea arm 1</th>
<th>Diarrhoea arm 2</th>
<th>Treatment related death arm 1</th>
<th>Treatment related death arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishikawa 2015</td>
<td>4</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>35</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nishina 2016</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>14</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Roy 2013</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sym 2013</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tanabe 2015</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>1</td>
<td>57</td>
<td>39</td>
<td>7</td>
<td>10</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thuss-Patience 2011</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Kang 2012</td>
<td>19</td>
<td>20</td>
<td>6</td>
<td>0</td>
<td>76</td>
<td>8</td>
<td>18</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bang 2016</td>
<td>NR</td>
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<td>79</td>
<td>60</td>
<td>NR</td>
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<td>NR</td>
</tr>
</tbody>
</table>

**Abbreviations:** NR, not reported
1.2.3 Network meta-analysis model structure

The networks for each of the NMAs (per outcome) are shown in Figure 1 to Figure 7. Note that the area of the nodes are in proportion with the number of patients receiving that treatment and the thickness of the lines connecting the nodes is proportional to the number of direct comparisons between those nodes.

Figure 1: Network for overall survival
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

Figure 2: Network for progression free survival

Figure 3: Network for treatment related morbidity - nausea
Figure 4: Network for treatment related morbidity – neutropenic sepsis
Figure 5: Treatment related morbidity - neutropenia

[Diagram showing various chemotherapy combinations and their relationships with neutropenia.]
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

Figure 6: Treatment related morbidity – diarrhoea
A general model for treatment contrasts (Salanti et al. 2008; as implemented in the STATA network suite by White, 2015a) was used to estimate the hazard ratios for OS and PFS and the risk ratios for treatment related morbidities and mortality compared to the reference treatments:

**Table 4: STATA code used to estimate hazard ratios for survival outcomes and risk ratios for treatment related morbidities for all treatment options**

<table>
<thead>
<tr>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Change network directory to your working directory</td>
</tr>
<tr>
<td>cd &quot;&lt;FILE_PATH_TO_YOUR_WORKING_DIRECTORY&gt;&quot;</td>
</tr>
<tr>
<td>* Imports Excel file (remember to update if you save excel file as new version //and don’t include spaces in name)</td>
</tr>
<tr>
<td>import excel using NMA_data_v4, sheet(&quot;NMA_data_v3&quot;) firstrow clear</td>
</tr>
<tr>
<td>* Drops observations that aren’t your actual dataset (i.e. the list of treatment codes)</td>
</tr>
<tr>
<td>drop if Author==&quot;&quot;</td>
</tr>
<tr>
<td>* Gives STARID value to study with missing STARID</td>
</tr>
<tr>
<td>replace STARID=1 if Author==&quot;Ohtsu&quot; &amp; Date==2013</td>
</tr>
<tr>
<td>drop Armcode Arm2code Arm3code</td>
</tr>
<tr>
<td>destring Armcode1, replace</td>
</tr>
<tr>
<td>destring Armcode2, replace</td>
</tr>
<tr>
<td>destring Armcode3, replace</td>
</tr>
<tr>
<td>drop if Armcode1 == 0</td>
</tr>
<tr>
<td>drop if Armcode2 == 0</td>
</tr>
<tr>
<td>* Rename variables to give them shorter names (easier to refer to them in code)</td>
</tr>
</tbody>
</table>

---

* Figure 7: Treatment related mortality

---
rename Firstlinechemotherapycode firstline
rename FirstLineTimemonths first_t
rename Overallsurv OSHR
rename OverallsurvivalCIupper OSUCI
rename overallsurvivalCIlower OSLCI
rename ProgFreesurv PFSHR
rename ProgFreesurvupper95CI PFSUCI
rename ProgFreesurv95CIlower PFSLCI
rename Nauseaarm1 nausea1
rename Nauseaarm2 nausea2
rename Nauseaarm3 nausea3
rename NeutropaenicfeversepsisArm1 ns1
rename neutropaenicfeverarm2 ns2
rename neutropaenicsepsisarm3 ns3
rename neutropaeniaarm1 np1
rename neutropaeniaarm2 np2
rename neutropaeniaarm3 np3
rename Peripheralneuropathyarm1 pn1
rename peripheralneuropathyarm2 pn2
rename peripheralneuropathyarm3 pn3
rename Thrombocytopaeniaarm1 tp1
rename Thrombocytopaeniaarm2 tp2
rename thrombocytopaeniaarm3 tp3
rename Diarrhoeaarm1 dr1
rename diarrhoeaarm2 dr2
rename diarrhoeaarm3 dr3
rename Treatmentrelateddeatharm1 dt1
rename treatmentrelateddeatharm2 dt2
rename Medianfollowupmonths fu
rename Studylocation1western2east s_loc
rename ECOGScore0arm1 ecog0_1
rename ECOGscore0arm1 ecog0_1
rename ECOGscore0arm1 ecog0_1
rename ECOGscore0arm2 ecog0_2
rename ECOGscore0arm2 ecog0_2
rename ECOGscore0arm2 ecog0_2
rename ECOGscore0arm3 ecog0_3
rename MedianAgearm1 age1
rename medianagearm2 age2
rename medianagearm3 age3
rename Femalegenderarm1 f1
rename femalegenderarm2 f2
rename femalearm3 f3
rename locallyadvancedarm1 la1
rename metastaticarm1 m1
rename locallyadvancedarm2 la2
rename metastaticarm2 m2
rename locallyadvancedarm3 la3
rename metastaticarm3 m3

* Remove "not reported" cells to allow variable to be made from string to numerical (for analysis)
destring(N3), replace
replace firstline = "" if firstline=="NR"
destring(firstline), replace
replace first_t = "" if first_t=="NR"
destring (first_t), replace
replace OSHR = "" if OSHR=="NR"
destring (OSHR), replace
replace OSUCI = "" if OSUCI=="NR"
destring (OSUCI), replace
replace OSLCI = "" if OSLCI=="NR"
destring (OSLCI), replace
replace PFSHR = "" if PFSHR=="NR"
destring (PFSHR), replace
replace PFSUCI = "" if PFSUCI=="NR"
destring (PFSUCI), replace
replace PFSLCI = "" if PFSLCI=="NR"
destring (PFSLCI), replace
replace nausea1 = "" if nausea1=="NR"
destring (nausea1), replace
replace nausea2 = "" if nausea2=="NR"
destring (nausea2), replace
replace nausea3 = "" if nausea3=="NR"
destring (nausea3), replace
replace ns1 = "" if ns1=="NR"
destring (ns1), replace
replace ns2 = "" if ns2=="NR"
destring (ns2), replace
replace ns3 = "" if ns3=="NR"
destring (ns3), replace
replace np1 = "" if np1=="NR"
destring (np1), replace
replace np2 = "" if np2=="NR"
destring (np2), replace
replace np3 = "" if np3=="NR"
destring (np3), replace
replace pn1 = "" if pn1=="NR"
destring (pn1), replace
replace pn2 = "" if pn2=="NR"
destring (pn2), replace
replace pn3 = "" if pn3=="NR"
destring (pn3), replace
replace tp1 = "" if tp1=="NR"
destring (tp1), replace
replace tp2 = "" if tp2=="NR"
destring (tp2), replace
replace tp3 = "" if tp3=="NR"
destring (tp3), replace
replace dr1 = "" if dr1=="NR"
destring (dr1), replace
replace dr2 = "" if dr2=="NR"
destring (dr2), replace
replace dr3 = "" if dr3=="NR"
destring (dr3), replace
replace dt1 = "" if dt1=="NR"
destring (dt1), replace
replace dt2 = "" if dt2=="NR"
destring (dt2), replace
replace fu = "" if fu=="NR"
destring (fu), replace
replace s_loc = "" if s_loc=="NR"
destring (s_loc), replace
replace s_loc = "3" if s_loc=="both/all" //3 denotes study location in both western and eastern locations
replace s_loc = "3" if s_loc=="both"
destring (s_loc), replace
replace ecog0_1 = "" if ecog0_1=="NR"
destring (ecog0_1), replace
replace ecog1_1 = "" if ecog1_1=="NR"
destring (ecog1_1), replace
replace ecog2_1 = "" if ecog2_1=="NR"
destring (ecog2_1), replace
replace ecog0_2 = "" if ecog0_2=="NR"
destring (ecog0_2), replace
replace ecog0_2 = "" if ecog1_2=="NR"
destring (ecog1_2), replace
replace ecog1_2 = "" if ecog2_2=="NR"
destring (ecog2_2), replace
replace ecog2_2 = "" if ecog3_2=="NR"
destring (ecog3_2), replace
replace ecog2_3 = "" if ecog2_3=="NR"
destring (ecog2_3), replace
replace age1 = "" if age1=="NR"
destring (age1), replace
replace age2 = "" if age2=="NR"
destring (age2), replace
replace age3 = "" if age3=="NR"
destring (age3), replace
replace f1 = "" if f1=="NR"
destring (f1), replace
replace f2 = "" if f2=="NR"
destring (f2), replace
replace f3 = "" if f3=="NR"
destring (f3), replace
replace la1 = "" if la1=="NR"
destring (la1), replace
replace m1 = "" if m1=="NR"
destring (m1), replace
replace la2 = "" if la2=="NR"
replace la2 = "" if la2=="NR"
destring (la2), replace
replace m2 = "" if m2=="NR"
destring (m2), replace
replace la3 = "" if la3=="NR"
destring (la3), replace
replace m3 = "" if m3=="NR"
destring (m3), replace
replace Oarm1 = "" if Oarm1=="NR"
destring (Oarm1), replace
replace GEJarm1 = "" if GEJarm1=="NR"
destring (GEJarm1), replace
replace Garm1 = "" if Garm1=="NR"
destring (Garm1), replace
replace Oarm2 = "" if Oarm2=="NR"
destring (Oarm2), replace
replace GEJarm2 = "" if GEJarm2=="NR"
destring (GEJarm2), replace
replace Garm2 = "" if Garm2=="NR"
destring (Garm2), replace
replace Oarm3 = "" if Oarm3=="NR"
destring (Oarm3), replace
replace GEJarm3 = "" if GEJarm3=="NR"
destring (GEJarm3), replace
replace Garm3 = "" if Garm3=="NR"
destring (Garm3), replace

gen logOSHR=ln(OSHR)
gen logOSLCI=ln(OSLCI)
gen logPFSHR=ln(PFSHR)
gen logPFSLCI=ln(PFSLCI)
gen logOSSE = (logOSHR-logOSLCI)/1.96
gen logPFSSE = (logPFSHR-logPFSLCI)/1.96

/* Assign new label to specific treatment variables*/
label values Arm1code treatlabels
label values Arm2code treatlabels
label values Arm3code treatlabels
label values firstline treatlabels */

* Give labels to treatment codes
#delimit ; // Changes the end of a command to be defined by ";" (so that you //can write a command over multiple lines)
label define treatlabels
1 "Placebo / BSC"
2 "Olaparib + Paclitaxel"
3 "Docetaxel"
4 "Paclitaxel"
5 "Irinotecan + Cisplatin"
6 "Docetaxel + Oxaliplatin"
7 "Docetaxel + Cisplatin"
8 "FOLFIRI + Sunitinib"
9 "Fluoropyrimidine"
10 "S-1 + Irinotecan"
11 "Irinotecan"
12 "Docetaxel + Fluoropyrimidine"
13 "Irinotecan + 5FU/leucovorin"
14 "Docetaxel / Irinotecan"
, replace
; // ends command
#delimit cr // changes the end of a command to be defined by a new line in the do file

* Same command as above can also be achieved by using a for loop
foreach X of varlist Armcode1 Armcode2 Armcode3 firstline {
    label values `X' treatlabels
}

* Assigning new labels to specific treatment variables
*label values STARID study
#delimit ; // Changes the end of a command to be defined by ";" (so that you //can write a command over multiple lines)
label define study
1 "Ohtsu 2013"
454645 "Bang 2015"
454689 "Dutton 2014"
454700 "Ford 2014"
454708 "Fuchs 2014"
454730 "Higuchi 2014"
454734 "Hironaka 2013"
454764 "Kim B 2015"
4547642 "Kim B arm2v3 2015"
4547643 "Kim B arm1v3 2015"
454770 "Kim JY 2015"
454813 "Maruta 2007"
454824 "Moehler 2013"
454832 "Nishikawa 2015"
454834 "Nishina 2016"
454875 "Roy 2013"
454882 "Satoh 2015"
454902 "Sym 2013"
454911 "Tanabe 2015"
454919 "Thuss-Patience 2011"
454944 "Wilke 2014"
; // ends command
#delimit cr
*Same command as above can also be achieved by using a for loop
foreach X of varlist STARID {
    label values `X' study
}

label variable STARID "Study ID"

/************** Direct estimates **************/

****** Overall Survival ******
replace OSUCI = 0.6993 if OSUCI==1.639 & OSLCI==0.6993
replace OSLCI = 1.639 if OSUCI==0.6993 & OSLCI==0.6993
gen 1OS = ln(OSHR)
gen 1OS195 = ln(OSUCI)
gen 1OSu95 = ln(OSLCI)
egen comp = concat (Armcode1 Armcode2), punct("v")
egen complab = concat(Armcode1 Armcode2), decode p(" v ")
egen invcomplab = concat(Armcode1 Armcode2), decode p(" v ")
gen invOS = -1OS
gen invOSu95 = -1OS195
gen invOS195 = -1OSu95

#delimit ;
metan lOS lOSl95 lOSu95, eform fixed
by(complab)
noverall
lcols(STARID)
graphregion(fcolor(white))
classic
boxsca(60)
effect("HR")
nowt
texts(130)
xtick(0.2,0.5,1,5,8)
xlab(0.2,0.5,1,5,8)
;
#delimit cr
graph export OS_Forest.png, replace width(10000)

#delimit;
metan invOS invOS195 invOSu95, eform fixed
by(invcomplab)
noverall
lcols(STARID)
graphregion(fcolor(white))
classic
boxsca(60)
effect("HR")
nowt
texts(150)
xtick(0.2,0.5,1,5,8)
xlab(0.2,0.5,1,5,8)
;
#delimit cr
graph export OS_ForestInv.png, replace width(3000)
*/

/************** ProgFree Survival **************/
replace PFSUCI = 0.546 if PFSUCI==1.282 & PFSLCI==0.546
replace PFSLCI = 1.282 if PFSUCI==0.546 & PFSLCI==0.546
gen 1PFS = ln(PFSHR)
gen 1PFS195 = ln(PFSUCI)
gen lPFSu95 = ln(PFSLCI)
egen comp = concat (Armcode1 Armcode2), punct("v")
egen complab = concat(Armcode1 Armcode2), decode p(" v ")
egen invcomplab = concat(Armcode2 Armcode1), decode p(" v ")

drop if lPFS==. | lPFS195==.
gen invPFS = -lPFS
gen invPFSu95 = -lPFS195
gen invPFS195 = -lPFSu95

#delimit ;
metan lPFS lPFS195 lPFSu95
eform fixed
by(complab)
noverall
lcols(STARID)
graphregion(fcolor(white))
classic
boxsca(60)
effect("HR")
nowt
texts(130)
xtick(0.2,0.5,1,5,8)
xlab(0.2,0.5,1,5,8)
;
#delimit cr
graph export PFS_Forest.png, replace width(10000)

#delimit;
metan invPFS invPFS195 invPFSu95, eform fixed
by(invcomplab)
noverall
lcols(STARID)
graphregion(fcolor(white))
classic
boxsca(60)
effect("HR")
nowt
texts(130)
xtick(0.2,0.5,1,5,8)
xlab(0.2,0.5,1,5,8)
;
#delimit cr
graph export PFS_ForestInv.png, replace width(3000)

/***** Nausea ********
gen nonausea1=N1-nausea1
gen nonausea2=N2-nausea2
egen comparison = concat (Arm1code Arm2code), punct(" v") decode

#delimit ;
metan nause2 nonause2 nause1 nonause1,
by(comp)
label(namevar=STARID)
rr
noverall
classic
graphregion(color(white))
effect("RR")
;
#delimit cr
graph export Nausea_Forest.png, replace width(3000)

  sum N1 if nausea1!=. 
di r(sum)
  sum N2 if nausea2!=. 
di r(sum)

  /*
  /***/ neutropaenic sepsis *************
  gen nons1=N1-ns1
  gen nons2=N2-ns2
  *gen nons3=N3-ns3 //no longer needed now data is entered as 2-arm studies
  egen comp = concat (Armcode1 Armcode2), punct(" v ") decode

  #delimit ;
  metan ns2 nons2 ns1 nons1, 
  by(comp)
  label(namevar=STARID)
  rr
  nooverall
  classic
  graphregion(color(white))
  effect("RR")
  ;
  #delimit cr
  graph export NS_Forest.png, replace width(3000)

  sum N1 if ns1!=. 
di r(sum)
  sum N2 if ns2!=. 
di r(sum)

  */
  /***/ neutropaenia *************
  gen nonp1=N1-np1
  gen nonp2=N2-np2
  *gen nonp3=N3-np3 //no longer needed now data is entered as 2-arm studies
  egen comparison = concat (Armcode1 Armcode2), punct(" v ") decode

  #delimit ;
  metan np2 nonp2 np1 nonp1, 
  by(comp)
  label(namevar=STARID)
  rr
  nooverall
  boxsca(50)
  classic
  graphregion(color(white))
  effect("RR")
  ;
  #delimit cr
  graph export Np_Forest.png, replace width(3000)

  sum N1 if np1!=. 
di r(sum)
  sum N2 if np2!=. 
di r(sum)

  */
  /***/ diarrhoea *************
  gen nodr1=N1-dr1
  gen nodr2=N2-dr2
*egen comparison = concat (Arm1code Arm2code), punct(" v ") decode

#delimit ;
metan dr2 nodr2 dr1 nodr1,
by(comp)
label(namevar=STARID)
rr
nooverall
classic
graphregion(color(white))
effect("RR")
;
#delimit cr
graph export Dr_Forest.png, replace width(3000)

sum N1 if dr1!=.
di r(sum)
sum N2 if dr2!=.
di r(sum)

***** treatment related death *****
gen nodt1=N1-dt1
gen nodt2=N2-dt2
*egen comparison = concat (Armcode1 Armcode2), punct(" v ") decode

#delimit ;
metan dt2 nodt2 dt1 nodt1,
by(comp)
label(namevar=STARID)
rr
nooverall
classic
graphregion(color(white))
effect("RR")
;
#delimit cr
graph export Dt_Forest.png, replace width(3000)

sum N1 if dt1!=.
di r(sum)
sum N2 if dt2!=.
di r(sum)
*/

/***** Thrombocytopenia *****
gen notp1=N1-tp1
gen notp2=N2-tp2
egen comparison = concat (Armcode1 Armcode2), punct(" v ") decode

#delimit ;
metan tp2 notp2 tp1 notp1,
by(comp)
label(namevar=STARID)
rr
nooverall
classic
graphregion(color(white))
effect("RR")
;
#delimit cr
network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

```stata
graph export Tp_Forest.png, replace width(3000)
sum N1 if dt1!=.
di r(sum)
sum N2 if dt2!=.
di r(sum)
*/
/***************  NMA  ******************

* Nausea
drop if nausea1 == nausea2 & N1==N2
drop if nausea1==.

#delimit ;
reshape long nausea Arm Armcode N NT ns np pn tp dr dt age ecog0_ ecog_1 ecog_2 f la m Oarm GEJarm Garm ,
i(STARID)
j(armnum)
;
#delimit cr
drop if Armcode==.
drop if STARID==4547642
drop if STARID==4547643
/*

network setup nausea N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map
graph export Nausea_Network.png, replace width(10000)
*/
drop if Armcode==1 | Armcode==8 | Armcode==14
sum(N)
di r(sum)
foreach X of numlist 1(1)14 {
            sum(N) if Armcode==`X'
            local i = r(sum)
            di `X'
            di `i'
}

network setup nausea N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map
network meta consistency, showall eform
network meta consistency, showall eform fixed
netleague, eform
network sidesplit all, fixed

Side  Direct            Indirect          Difference
B E               .           .        .           .        .           .
```

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network rank min, reps(1000) line meanrank
*/

/* Naeutropaenic Sepsis

drop if ns1 == ns2 & N1==N2
drop if ns1==.

#delimit ;
reshape long
nausea Arm Armcode N NT ns np tp dr dt age ecog0_ ecog_1 ecog_2 f la m Oarm
GEJarm Garm
, i(STARID)
j(armnum)
;#delimit cr

drop if Armcode==.
drop if STARID==4547642
drop if STARID==4547643

sum(N)
di r(sum)

di r(sum)

foreach X of numlist 1(1)14 {
   sum(N) if Armcode==`X'
   local i = r(sum)
   di `X'
   di `i'
}

network setup ns N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map
graph export ns_Network.png, replace width(10000)
network meta consistency, showall eform fixed
netleague, eform
drop in l
network rank min, reps(2000) line meanrank
*/
/* Naeutropaenia

```stata
drop if np1 == np2 & N1==N2
drop if np1==.
```

```stata
#delimit ;
reshape long
nausea Arm Armcode N NT ns np pn tp dr dt age ecog0_ ecog_1 ecog_2 f la m Oarm
GEJarm Garm
,i(STARID)
j(armnum)
;
#delimit cr
drop if Armcode==.
drop if STARID==4547642
drop if STARID==4547643
sum(N)
di r(sum)
foreach X of numlist 1(1)14 {
    sum(N) if Armcode==`X'
    local i = r(sum)
    di `X'
    di `i'
}
```

```stata
network setup np N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map
graph export np_Network.png, replace width(10000)
```

```stata
network meta consistency, showall eform fixed
est store B
network meta consistency, showall eform
est store A
lrtest B A
```

```stata
network sidesplit all, fixed
```

```stata
netleague, eform
network rank min, reps(2000) line meanrank
*/
```

/* Diarrhoea

```stata
drop if dr1 == dr2 & N1==N2
drop if dr1==.
```

```stata
#delimit ;
reshape long
```
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

```
nausea Arm Armcode N NT ns np tp dr dt age ecog0_ ecog_1 ecog_2 f la m Oarm GEJarm Garm
  i(STARID)
  j(armnum)
  ;
  #delimit cr
  drop if Armcode==.
  drop if STARID==4547642
  drop if STARID==4547643
  /*
  network setup dr N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
  format(augment) armvars(keep nausea)
  network map
  graph export dr_Network.png, replace width(10000)
  */
  drop if Armcode==1 | Armcode==8 | Armcode==14
  sum(N)
  di r(sum)
  foreach X of numlist 1(1)14 {
    sum(N) if Armcode==`X'
    local i = r(sum)
    di `X'
    di `i'
  }
  network setup dr N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
  format(augment) armvars(keep nausea)
  network map
  network meta consistency, showall eform fixed
  est store B
  network meta consistency, showall eform
  est store A
  lrtest B A
  network sidesplit all, fixed

  B E      .          .          .          .          .          .          .          .          .
  B H *    2.079442   1.039012   -.2056275   56.08011   2.285069   56.08974   0.968
  A C *    1.082352   .7963317   4.462119   239.8184   -3.379767   239.8148   0.989
  C F *    2.437116   1.463758   5.360514   253.0106   7.79763   253.0221   0.974
  C H *    -.0089687   1.407358   2.750938   86.29061   2.759907   86.30209   0.974
  D H *    1.562282   .8900783   4.716708   249.8222   -3.154426   249.8216   0.990
  G H *    .369833   .4792689   4.189153   259.8732   4.934341   259.8732   0.988
  H I *    .6592456   1.196739   -4.275096   273.2625   4.934341   273.267   0.986

  netleague, eform
  network rank min, reps(2000) line meanrank
  */```
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

/* Treatment-related adverse events

drop if dt1 == dt2 & N1==N2
drop if dt1==.

#delimit ;
reshape long
nausea Arm Armcode N NT ns np tp dr dt age ecog0_ ecog_1 ecog_2 f la m Oarm
GEJarm Garm
i(STARID)
j(armnum)
;
#delimit cr

drop if Armcode==.
drop if STARID==4547642
drop if STARID==4547643

/*
network setup dt N, studyvar(STARID) ref("Paclitaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map
graph export dt_Network.png, replace width(10000)
*/

drop if Armcode==3 | Armcode==6
sum(N)
di r(sum)

foreach X of numlist 1(1)14 {
    sum(N) if Armcode==`X'
    local i = r(sum)
    di `X'
    di `i'
}

network setup dt N, studyvar(STARID) ref("Paclitaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map

network meta consistency, showall eform fixed

network sidesplit all, fixed

<table>
<thead>
<tr>
<th>Side</th>
<th>Direct</th>
<th>Indirect</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B E</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>B H *</td>
<td>2.079442</td>
<td>1.039012</td>
<td>-.2056275</td>
</tr>
<tr>
<td>A C *</td>
<td>1.082352</td>
<td>.7963317</td>
<td>4.462119</td>
</tr>
<tr>
<td>C F *</td>
<td>2.437116</td>
<td>1.463758</td>
<td>5.360514</td>
</tr>
<tr>
<td>C H *</td>
<td>-.0089678</td>
<td>1.407857</td>
<td>2.750938</td>
</tr>
<tr>
<td>D H *</td>
<td>1.562282</td>
<td>.9000783</td>
<td>4.716708</td>
</tr>
<tr>
<td>G H *</td>
<td>.369833</td>
<td>.4792689</td>
<td>4.189153</td>
</tr>
<tr>
<td>H I *</td>
<td>.6592456</td>
<td>1.196739</td>
<td>4.275096</td>
</tr>
</tbody>
</table>
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

```plaintext
netleague, eform
drop in 1
network rank min, reps(2000) line meanrank
*/

/* THrombocytopaenia
drop if t1 == t2 & N1==N2
drop if t1==.
#delimit ;
reshape long
nausea Arm Armcode N NT ns np pn tp dr dt age ecog0_ ecog_1 ecog_2 f la m Oarm
GEJarm Garm
' i(STARID)
j(armnum)
;
#delimit cr
drop if Armcode==.
drop if STARID==4547642
drop if STARID==4547643
/*
network setup tp N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map
graph export tp_Network.png, replace width(10000)
*/
drop if Armcode==1 | Armcode==14 | Armcode==13
sum(N)
di r(sum)
network setup tp N, studyvar(STARID) ref("Docetaxel") rr trtvar(Armcode)
format(augment) armvars(keep nausea)
network map

network meta consistency, showall eform fixed
netleague, eform

network sidesplit all, fixed

network rank min, reps(2000) line meanrank
*/

/*/ ------------------------N.Pillai additional code------------------------

* Draw forest plot to examine results in more detail
network forest, eform list
network forest, ytitle (Study ID) xline(0) xtitle(Log risk ratio and 95% CI)
title(Neutropaenic sepsis Network)
```
* Consistency model
* regression analysis for a baseline characteristic: network meta consistency,
  showall regress(Age)
network meta consistency, showall eform
est store A
network meta inconsistency, showall eform //force
est ic
est store B
lrtest B A
*lincom [y_C]_cons - [y_E]_cons, eform

* Create league table of indirect estimates for each comparison in network
network meta c, fixed
netleague, eform
*lab("olaparib+paclitaxel" "gefitinib" "taxane" "ramucirumab" "irinotecan +
platinum" "taxane+platinum" "FOLFIRI + sunitinib" "fluoropyrimidine" "everolimus"
"nimotuzumab + irinotecan" "S-1 + irinotecan" "irinotecan + paclitaxel" "docetaxel +
fluoropyrimidine" "irinotecan + 5FU/leucovorin") sort
(*olaparib+paclitaxel* "gefitinib" "taxane" "ramucirumab" "irinotecan +
platinum" "taxane+platinum" "FOLFIRI + sunitinib" "fluoropyrimidine" "everolimus"
"nimotuzumab + irinotecan" "S-1 + irinotecan" "irinotecan + paclitaxel" "docetaxel +
fluoropyrimidine" "irinotecan + 5FU/leucovorin")

network meta c
est store A
network meta c, fixed
est store B
lrtest B A

* Rankings
network rank min, reps(1000) line
network sidesplit all, fixed

***** NMA for overall survival **************
*netleague logOSHR logOSSE Arm1code Arm2code, nomv eform
export("/Users/natashapillai/Desktop/NMA RCOG work/networktest.xlsx") nokeep
drop if STARID==454764 //because this study has missing survival data

network import, studyvar(STARID) treat(Arm1code Arm2code) effect(logOSHR)
stderr(logOSSE)
*network import, studyvar(STARID) ref("placebo or BSC") treat(Arm1code Arm2code)
effect(logPFSHR) stderr(logPFSSE)

network convert augmented
*draw network plot

network map

* Draw forest plot to examine results in more detail
network forest, eform
network forest, ytitle (Study ID) xtitle(Log hazard ratio and 95% CI)
title(Overall Survival Network)

* Consistency model
network meta c, fixed
netleague, eform
* Rankings
network rank min, reps(1000) line

* Inconsistency model - cannot do inconsistency because there is no closed loop
*network meta inconsistency eform

*/
*********** NMA Plots for OS and PFS vs placebo ***************
cd "<FILE PATH TO YOUR WORKING DIRECTORY>"
import excel using PFS_OS_vsPlacebo_v2, firstrow clear
gen lhr = ln(HR)
replace 195 = ln(195)
replace u95 = ln(u95)

label variable Out "Outcome"
#delimit ;
mstopi lhr 195 u95, eform
by(Treat)
nobox
lcols(Out)
nosubgroup nooverall
classic
graphregion(color(white))
texts(250)
xlab(0.1, 0.5, 1, 5)
effect("HR")

#delimit cr
graph export PFS_OS_vsPlacebo.png, replace width(16000)

*/
********** NMA Plots for Adverse Events vs placebo ***************
import excel using AEs_vsPlacebo, firstrow clear
rename NMAvPaclitaxel nma
drop if nma=="ref"
egen rr = ends(nma), punct("(") trim head
replace rr = "0.005" if rr=="0.00"
destring rr, replace
egen interu95 = ends(nma), punct(")") trim tail
egen u95 = ends(interu95), punct("") trim head
replace u95 = "1000" if u95==">999"
destring u95, replace
replace u95 = 1000 if u95>1000
egen interl95 = ends(nma), punct(",")) trim head
egen l95 = ends(interl95), punct("")) trim tail
replace l95 = "0.004" if 195=="<0.01"
destring l95, replace
replace l95 = "0.004" if 195=="<0.00"
destring 195, replace

gen lor = ln(rr)
replace 195 = ln(195)
replace u95 = ln(u95)

replace lor = -lor if direction==2
replace 195 = -195 if direction==2
replace u95 = -u95 if direction==2

gen temp195 = 195
replace temp195 = u95 if direction==2

gen tempu95 = u95
replace tempu95 = l95 if direction==2

replace 195 = temp195
replace u95 = tempu95


gen invlor = -lor

gen invl95 = -u95

gen invu95 = -l95

label variable out "Outcome"

replace out="Nausea" if out=="nausea"
replace out="Neutropaenic fever/sepsis" if out=="ns"
replace out="Neutropaenia" if out=="np"
replace out="Diarrhoea" if out=="dr"
replace out="Treatment-related death" if out=="dt"

replace treat = "{bf:Docetaxel}" if treat== "Docetaxel"
replace treat = "{bf:Irinotecan + mFOLFIRI}" if treat== "Irinotecan + 5'FU/leucovorin (mFOLFIRI)"
replace treat = "{bf:Docetaxel + Fluoropyrimidine}" if treat== "Docetaxel + Fluoropyrimidine"
replace treat = "{bf:Irinotecan}" if treat== "Irinotecan"
replace treat = "{bf:S-1+ Irinotecan}" if treat== "S-1+ Irinotecan"
replace treat = "{bf:Fluoropyrimidine}" if treat== "Fluoropyrimidine"
replace treat = "{bf:Docetaxel + Oxaliplatin}" if treat== "Docetaxel + Oxaliplatin"
replace treat = "{bf:Irinotecan + Cisplatin}" if treat== "Irinotecan + Cisplatin"
replace treat = "{bf:Olaparib + Paclitaxel}" if treat== "Olaparib + Paclitaxel"
replace treat = "{bf:Docetaxel / Irinotecan}" if treat== "Docetaxel / Irinotecan"
replace treat = "{bf:Docetaxel + Cisplatin}" if treat== "Docetaxel + Cisplatin"
replace treat = "{bf:Placebo / BSC}" if treat== "Placebo / BSC"
replace treat = "{bf:FOLFIRI + Sunitinib}" if treat== "FOLFIRI + Sunitinib"

drop if lor==.

#delimit ;

temetan inv lor invl95 invu95, eform
by(treat)
nobox
lcols(out)
nosubgroup nooverall
classic
graphregion(color(white))
texts(200)
xlab(0.1, 0.5, 1, 5,10,100)
xtick(0.1, 0.5, 1, 5,10,100)
effect("RR")
;
#delimit cr
graph export AEs_vsPlacebo.png, replace width(16000)
*/
1.3 Network meta-analysis results

1.3.1 Inconsistency and heterogeneity

Table 5: Inconsistency and heterogeneity

<table>
<thead>
<tr>
<th>Network</th>
<th>N treatments</th>
<th>N comparisons</th>
<th>N patients</th>
<th>Incoherence</th>
<th>tau – between studies heterogeneity (SD)</th>
<th>Test of heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>13</td>
<td>15</td>
<td>2442</td>
<td>No closed loops</td>
<td>≈ 0 (but only 2 comparisons with multiple studies)</td>
<td>P=0.460</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>11</td>
<td>11</td>
<td>2131</td>
<td>No closed loops</td>
<td>≈ 0 (but only 1 comparison with multiple studies)</td>
<td>P=0.356</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>10</td>
<td>1271</td>
<td>No closed loops</td>
<td>≈ 0 (but only 1 comparison with multiple studies)</td>
<td>P not calculable</td>
</tr>
<tr>
<td>Neutropaenic sepsis</td>
<td>14</td>
<td>12</td>
<td>1505</td>
<td>No closed loops</td>
<td>no comparisons with multiple studies</td>
<td>not applicable</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>14</td>
<td>18</td>
<td>2289</td>
<td>No closed loops</td>
<td>≈ 0 (but only 2 comparisons with multiple studies)</td>
<td>P &gt; 0.50</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9</td>
<td>9</td>
<td>1247</td>
<td>No closed loops</td>
<td>≈ 0 (but only 1 comparison with multiple studies)</td>
<td>P &gt; 0.50</td>
</tr>
<tr>
<td>Treatment related mortality</td>
<td>10</td>
<td>6</td>
<td>1271</td>
<td>No closed loops</td>
<td>no comparisons with multiple studies</td>
<td>not applicable</td>
</tr>
</tbody>
</table>

1.3.2 Estimated hazard ratios

Table 6: Indirect and direct comparisons for overall survival

| Placebo / BSC                  | 0.57         | 0.71         | 0.65         | 0.82         |        |
|                                | (0.38, 0.85) | (0.54, 0.94) | (0.48, 0.86) | (0.5, 1.33) |        |
## Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th></th>
<th>5-FU + Irinotecan</th>
<th>Irinotecan</th>
<th>Docetaxel + Fluoro</th>
<th>Irinotecan + mFOLFIRI</th>
<th>Docetaxel</th>
<th>Olaparib + Paclitaxel</th>
<th>Docetaxel + Irinotecan</th>
<th>Paclitaxel</th>
<th>Irinotecan + Cisplatin</th>
<th>Irinotecan + Oxaliplat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-FU</strong></td>
<td>0.56</td>
<td>1.01</td>
<td>0.96</td>
<td>0.71</td>
<td>1.14</td>
<td>0.2</td>
<td>3.11</td>
<td>1.35</td>
<td>0.55</td>
<td>0.85</td>
</tr>
<tr>
<td>(0.35, 0.9)</td>
<td>(0.8, 1.28)</td>
<td>(0.57, 1.61)</td>
<td>(0.79, 1.64)</td>
<td>(0.71, 1.16)</td>
<td>(0.49, 1.49)</td>
<td></td>
<td>(1.22, 7.93)</td>
<td>(1.1, 1.66)</td>
<td>(0.57, 1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Irino</strong></td>
<td>0.57</td>
<td>0.97</td>
<td>0.96</td>
<td>2.62</td>
<td>1.14</td>
<td>0.97</td>
<td>3.11</td>
<td>1.35</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>(0.38, 0.85)</td>
<td>(0.55, 1.72)</td>
<td>(0.57, 1.61)</td>
<td>(0.85, 8.12)</td>
<td>(0.71, 1.16)</td>
<td>(0.49, 1.49)</td>
<td></td>
<td>(1.22, 7.93)</td>
<td>(1.1, 1.66)</td>
<td>(0.57, 1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Doceta</strong></td>
<td>0.21</td>
<td>0.37</td>
<td>0.37</td>
<td>3.43</td>
<td>3.11</td>
<td>0.67</td>
<td>1.35</td>
<td>1.35</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>(0.08, 0.55)</td>
<td>(0.13, 1.04)</td>
<td>(0.13, 1.00)</td>
<td>(1.24, 9.5)</td>
<td>(0.64, 2.68)</td>
<td>(1.1, 1.66)</td>
<td></td>
<td>(1.22, 7.93)</td>
<td>(1.1, 1.66)</td>
<td>(0.57, 1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Olapari</strong></td>
<td>0.47</td>
<td>0.85</td>
<td>0.84</td>
<td>2.28</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>(0.28, 0.81)</td>
<td>(0.56, 1.28)</td>
<td>(0.6, 1.18)</td>
<td>(0.79, 6.59)</td>
<td>(0.47, 1.62)</td>
<td>(0.49, 1.49)</td>
<td></td>
<td>(0.49, 1.49)</td>
<td>(0.49, 1.49)</td>
<td>(0.57, 1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Doceta</strong></td>
<td>0.65</td>
<td>1.15</td>
<td>1.14</td>
<td>3.11</td>
<td>1.18</td>
<td>0.87</td>
<td>1.35</td>
<td>1.35</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>(0.48, 0.86)</td>
<td>(0.75, 1.78)</td>
<td>(0.79, 1.64)</td>
<td>(1.22, 7.93)</td>
<td>(0.63, 2.23)</td>
<td>(0.63, 1.36)</td>
<td></td>
<td>(0.63, 1.56)</td>
<td>(0.63, 1.56)</td>
<td>(0.57, 1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>0.64</strong></td>
<td>1.14</td>
<td>1.13</td>
<td>3.08</td>
<td>1.18</td>
<td>0.85</td>
<td>0.72</td>
<td>0.85</td>
<td>0.85</td>
<td>1.08</td>
<td>1.08</td>
</tr>
<tr>
<td>(0.39, 1.05)</td>
<td>(0.79, 1.64)</td>
<td>(0.86, 1.48)</td>
<td>(1.09, 8.73)</td>
<td>(0.65, 2.11)</td>
<td>(0.71, 1.65)</td>
<td></td>
<td>(0.42, 1.77)</td>
<td>(0.42, 1.77)</td>
<td>(0.53, 2.19)</td>
<td></td>
</tr>
<tr>
<td><strong>0.51</strong></td>
<td>0.91</td>
<td>0.91</td>
<td>2.47</td>
<td>0.94</td>
<td>0.72</td>
<td>0.79</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>1.08</td>
</tr>
<tr>
<td>(0.32, 0.83)</td>
<td>(0.65, 1.29)</td>
<td>(0.71, 1.16)</td>
<td>(0.88, 6.95)</td>
<td>(0.53, 1.67)</td>
<td>(0.41, 1.26)</td>
<td></td>
<td>(0.49, 1.49)</td>
<td>(0.49, 1.49)</td>
<td>(0.53, 2.19)</td>
<td></td>
</tr>
<tr>
<td><strong>0.55</strong></td>
<td>0.98</td>
<td>0.97</td>
<td>2.66</td>
<td>1.01</td>
<td>0.78</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>1.08</td>
</tr>
<tr>
<td>(0.29, 1.03)</td>
<td>(0.49, 1.99)</td>
<td>(0.5, 1.89)</td>
<td>(0.89, 7.9)</td>
<td>(0.44, 2.35)</td>
<td>(0.39, 1.54)</td>
<td></td>
<td>(0.42, 1.77)</td>
<td>(0.42, 1.77)</td>
<td>(0.53, 2.19)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI + Sunitinib</th>
<th>Fluoropyrimidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.82 (0.5, 1.33)</td>
<td>1.46 (0.74, 2.88)</td>
<td>1.5 (1.32, 11.8)</td>
</tr>
<tr>
<td>1.44 (0.76, 2.73)</td>
<td>1.15 (0.66, 2.02)</td>
<td>1.72 (0.84, 3.55)</td>
</tr>
<tr>
<td>3.93 (1.32, 11.8)</td>
<td>1.27 (0.72, 2.24)</td>
<td>1.28 (0.64, 2.55)</td>
</tr>
<tr>
<td>1.44 (0.76, 2.73)</td>
<td>1.59 (0.8, 3.16)</td>
<td>1.48 (0.67, 3.28)</td>
</tr>
<tr>
<td>0.57 (0.29, 1.1)</td>
<td>1.01 (0.57, 1.79)</td>
<td>1 (0.6, 1.68)</td>
</tr>
<tr>
<td>2.74 (0.88, 8.47)</td>
<td>1.04 (0.5, 2.17)</td>
<td>0.8 (0.39, 1.64)</td>
</tr>
<tr>
<td>1.2 (0.74, 1.95)</td>
<td>1.2 (0.74, 1.95)</td>
<td>0.88 (0.47, 1.66)</td>
</tr>
<tr>
<td>0.89 (0.57, 1.38)</td>
<td>1.11 (0.62, 1.97)</td>
<td>1.03 (0.44, 2.39)</td>
</tr>
<tr>
<td>1.15 (0.65, 2.02)</td>
<td>1.27 (0.72, 2.24)</td>
<td>0.88 (0.47, 1.66)</td>
</tr>
<tr>
<td>1.2 (0.74, 1.95)</td>
<td>1.2 (0.74, 1.95)</td>
<td>0.89 (0.57, 1.38)</td>
</tr>
<tr>
<td>1.11 (0.62, 1.97)</td>
<td>1.03 (0.44, 2.39)</td>
<td>0.7 (0.31, 1.58)</td>
</tr>
</tbody>
</table>

Lower half displays indirect NMA results. Upper half displays direct results from included studies.

Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.

Boxes shaded orange show results where the 95% confidence intervals do not pass 1.
## Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>k</th>
<th>SUCRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + Fluoropyrimidine</td>
<td>12</td>
<td>1</td>
<td>97</td>
</tr>
<tr>
<td>Olaparib + Paclitaxel</td>
<td>324</td>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>Irinotecan + Cisplatin</td>
<td>148</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>Irinotecan + mFOLFIRI</td>
<td>30</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>Docetaxel + Oxaliplatin</td>
<td>25</td>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>S-1 + Irinotecan</td>
<td>153</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>441</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>Fluoropyrimidine</td>
<td>49</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>167</td>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>486</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Docetaxel / Irinotecan</td>
<td>126</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>FOLFIRI + Sunitinib</td>
<td>45</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Placebo / BSC</td>
<td>436</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease
### Table 7: Indirect and direct comparisons for progression free survival

<table>
<thead>
<tr>
<th>Placebo / BSC</th>
<th>S-1 + Irinotecan</th>
<th>Irinotecan</th>
<th>Irinotecan + mFOLFIRI</th>
<th>Olaparib + Paclitaxel</th>
<th>Docetaxel</th>
<th>Paclitaxel</th>
<th>Irinotecan + Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.68 (0.37, 1.23)</td>
<td>1.18 (0.93, 1.49)</td>
<td>0.88 (0.53, 1.47)</td>
<td>1.19 (0.95, 1.49)</td>
<td>0.67 (0.48, 0.94)</td>
<td>1.11 (0.7, 1.76)</td>
<td>0.62 (0.34, 1.12)</td>
<td>0.77 (0.6, 0.99)</td>
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<tr>
<td>0.8 (0.46, 1.38)</td>
<td>1.18 (0.93, 1.49)</td>
<td>0.84 (0.55, 1.29)</td>
<td>1.14 (0.88, 1.48)</td>
<td>0.77 (0.6, 0.99)</td>
<td>0.76 (0.4, 1.45)</td>
<td>1.13 (0.74, 1.71)</td>
<td>0.99 (0.6, 1.62)</td>
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<td>0.76 (0.4, 1.45)</td>
<td>0.96 (0.68, 1.35)</td>
<td>1.08 (0.59, 2)</td>
<td>1.14 (0.88, 1.48)</td>
<td>0.67 (0.48, 0.94)</td>
<td>0.91 (0.5, 1.66)</td>
<td>1.34 (0.94, 1.91)</td>
<td>0.91 (0.65, 1.28)</td>
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<tr>
<td>0.67 (0.48, 0.94)</td>
<td>0.84 (0.55, 1.29)</td>
<td>0.95 (0.49, 1.85)</td>
<td>1.19 (0.51, 1.52)</td>
<td>1.36 (0.82, 2.24)</td>
<td>1.08 (0.59, 2)</td>
<td>0.95 (0.49, 1.85)</td>
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</tr>
<tr>
<td>0.71 (0.33, 1.49)</td>
<td>1.04 (0.59, 1.82)</td>
<td>0.88 (0.53, 1.47)</td>
<td>1.14 (0.88, 1.48)</td>
<td>0.67 (0.48, 0.94)</td>
<td>0.84 (0.55, 1.29)</td>
<td>0.91 (0.5, 1.66)</td>
<td>0.91 (0.65, 1.28)</td>
</tr>
<tr>
<td>0.7 (0.33, 1.49)</td>
<td>1.04 (0.59, 1.82)</td>
<td>0.88 (0.53, 1.47)</td>
<td>1.14 (0.88, 1.48)</td>
<td>0.67 (0.48, 0.94)</td>
<td>0.84 (0.55, 1.29)</td>
<td>0.91 (0.5, 1.66)</td>
<td>0.91 (0.65, 1.28)</td>
</tr>
</tbody>
</table>
### Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

Lower half displays indirect NMA results. Upper half displays direct results from included studies.

Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results.

Boxes shaded orange show results where the 95% confidence intervals do not pass 1.

<table>
<thead>
<tr>
<th>Docetaxel + Oxaliplat</th>
<th>FOLFIRI + Sunitinib</th>
<th>Fluoropyrimidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.34 (0.67, 2.7)</td>
<td>1.11 (0.7, 1.76)</td>
<td>0.53 (0.25, 1.1)</td>
</tr>
<tr>
<td>1.9 (0.79, 3.57)</td>
<td>1.64 (0.77, 3.48)</td>
<td>0.78 (0.45, 1.34)</td>
</tr>
<tr>
<td>1.76 (0.77, 4.01)</td>
<td>1.39 (0.68, 2.84)</td>
<td>0.66 (0.41, 1.08)</td>
</tr>
<tr>
<td>2 (1.08, 3.7)</td>
<td>1.57 (0.66, 3.78)</td>
<td>0.75 (0.37, 1.51)</td>
</tr>
<tr>
<td>1.68 (0.77, 4.71)</td>
<td>1.45 (0.66, 3.21)</td>
<td>0.69 (0.43, 1.11)</td>
</tr>
<tr>
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<td>1.66 (0.94, 2.93)</td>
<td>0.79 (0.41, 1.51)</td>
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<tr>
<td>2.17 (0.98, 4.8)</td>
<td>1.22 (0.57, 2.61)</td>
<td>0.58 (0.38, 0.88)</td>
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</table>

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### Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
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<th>SUCRA</th>
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</thead>
<tbody>
<tr>
<td>Fluoropyrimidine</td>
<td>49</td>
<td>1</td>
<td>89</td>
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<tr>
<td>Irinotecan + Cisplatin</td>
<td>148</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>167</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>S-1 + Irinotecan</td>
<td>153</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>Irinotecan + mFOLFIRI</td>
<td>30</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>Olaparib + Paclitaxel</td>
<td>263</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>441</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>Paclitaxel</td>
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<td>3</td>
<td>28</td>
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<tr>
<td>Placebo / BSC</td>
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<td>26</td>
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<tr>
<td>FOLFIRI + Sunitinib</td>
<td>45</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Docetaxel + Oxaliplat</td>
<td>25</td>
<td>1</td>
<td>11</td>
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Figure 8: NMA results for overall and progression free survival outcomes in comparison to placebo or best supportive care

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-1 + Irinotecan</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.56 (0.35, 0.90)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.68 (0.37, 1.23)</td>
</tr>
<tr>
<td>Irinotecan</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.57 (0.38, 0.85)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.80 (0.46, 1.38)</td>
</tr>
<tr>
<td>Docetaxel + Fluoropyrimidine</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.21 (0.08, 0.55)</td>
</tr>
<tr>
<td>Irinotecan + mFOLFIRI</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.54 (0.28, 1.05)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.71 (0.33, 1.49)</td>
</tr>
<tr>
<td>Docetaxel / Irinotecan</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.71 (0.54, 0.94)</td>
</tr>
<tr>
<td>Olaparib + Paclitaxel</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.47 (0.28, 0.81)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.76 (0.40, 1.45)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.65 (0.48, 0.86)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.67 (0.48, 0.94)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.64 (0.39, 1.05)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.91 (0.50, 1.66)</td>
</tr>
<tr>
<td>Irinotecan + Cisplatin</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.51 (0.32, 0.83)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.62 (0.34, 1.12)</td>
</tr>
<tr>
<td>Docetaxel + Oxaliplatin</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.55 (0.29, 1.03)</td>
</tr>
<tr>
<td>PFS</td>
<td>1.34 (0.67, 2.70)</td>
</tr>
<tr>
<td>FOLFIRI + Sunitinib</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.82 (0.50, 1.33)</td>
</tr>
<tr>
<td>PFS</td>
<td>1.11 (0.70, 1.76)</td>
</tr>
<tr>
<td>Fluoropyrimidine</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.57 (0.29, 1.11)</td>
</tr>
<tr>
<td>PFS</td>
<td>0.53 (0.25, 1.10)</td>
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</table>
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease
Table 8: Indirect and direct comparisons for treatment related morbidity - nausea

<table>
<thead>
<tr>
<th>Docetaxel</th>
<th>0.33 (0.01,7.45)</th>
<th>5.00 (0.25,101)</th>
<th>3.23 (0.14,75.83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.83 (0.04,659)</td>
<td>Irinotecan + mFOLFIRI</td>
<td>1.03 (0.02,50.42)</td>
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</tr>
<tr>
<td>0.33 (0.01,7.45)</td>
<td>0.07 (&lt;0.01,23.1)</td>
<td>Docetaxel + Fluoro</td>
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</tr>
<tr>
<td>5.00 (0.25,101)</td>
<td>1.03 (0.02,50.4)</td>
<td>14.99 (0.20,&gt;999)</td>
<td></td>
</tr>
<tr>
<td>2.88 (0.12,66.5)</td>
<td>0.59 (0.01,32.2)</td>
<td>8.63 (0.10,715)</td>
<td>0.58 (0.23,1.42)</td>
</tr>
<tr>
<td>14.67 (0.16,&gt;999)</td>
<td>3.04 (0.02,515)</td>
<td>44.02 (0.19,&gt;999)</td>
<td>2.94 (0.10,84.06)</td>
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<tr>
<td>3.23 (0.14,75.8)</td>
<td>0.67 (&lt;0.01,230)</td>
<td>9.69 (0.12,812)</td>
<td>0.65 (0.01,50.57)</td>
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<tr>
<td>4.42 (0.19,105)</td>
<td>0.92 (0.02,50.6)</td>
<td>13.72 (0.16,&gt;999)</td>
<td>0.89 (0.33,2.38)</td>
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<tr>
<td>2.02 (0.07,61.3)</td>
<td>0.42 (0.01,28.1)</td>
<td>6.05 (0.06,612)</td>
<td>0.40 (0.08,2.04)</td>
</tr>
<tr>
<td>2.05 (0.01,367)</td>
<td>0.42 (&lt;0.01,132)</td>
<td>6.15 (0.01,&gt;999)</td>
<td>0.41 (0.01,28.08)</td>
</tr>
</tbody>
</table>

Lower half displays indirect NMA results. Upper half displays direct results from included studies.
Results, read horizontally, show the risk ratios for experimental vs control for indirect results and control vs experimental for direct results.
Boxes shaded orange show results where the 95% confidence intervals do not pass 1.
### Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Class</th>
<th>N</th>
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<th>SUCRA</th>
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<tbody>
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<td>80</td>
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<tr>
<td>Docetaxel</td>
<td>83</td>
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<td>70</td>
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<tr>
<td>Olaparib + Paclitaxel</td>
<td>61</td>
<td>1</td>
<td>60</td>
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<tr>
<td>Paclitaxel</td>
<td>224</td>
<td>3</td>
<td>60</td>
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<tr>
<td>Docetaxel + Oxaliplatin</td>
<td>25</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>S-1+ Irinotecan</td>
<td>153</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Irinotecan + Cisplatin</td>
<td>148</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Irinotecan + mFOLFIRI</td>
<td>30</td>
<td>1</td>
<td>40</td>
</tr>
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<td>Irinotecan</td>
<td>486</td>
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<td>30</td>
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<tr>
<td>Fluoropyrimidine</td>
<td>49</td>
<td>1</td>
<td>20</td>
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Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease
### Table 9: Indirect and direct comparisons for treatment related morbidity – neutropenic sepsis

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel</th>
<th>0.50 (0.05,5.14)</th>
<th>2.50 (0.51,12.20)</th>
<th>1.44 (0.26,7.83)</th>
<th>11.85 (0.69,204)</th>
<th>0.08 (&lt;0.01,1.34)</th>
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<tr>
<td>0.50 (0.01,28.3)</td>
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<tr>
<td>2.42 (0.04,161)</td>
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<tr>
<td>2.50 (0.51,12.2)</td>
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<tr>
<td>29.60 (2.26,388)</td>
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<tr>
<td>3.93 (0.10,148)</td>
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<tr>
<td>1.44 (0.26,7.83)</td>
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</tbody>
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<table>
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<tr>
<th></th>
<th>Docetaxel</th>
<th>0.50 (0.05,5.14)</th>
<th>2.50 (0.51,12.20)</th>
<th>1.44 (0.26,7.83)</th>
<th>11.85 (0.69,204)</th>
<th>0.08 (&lt;0.01,1.34)</th>
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<tr>
<td>0.50 (0.01,28.3)</td>
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<td>2.42 (0.04,161)</td>
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<tr>
<td>2.50 (0.51,12.2)</td>
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<tr>
<td>29.60 (2.26,388)</td>
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<tr>
<td>3.93 (0.10,148)</td>
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</tr>
<tr>
<td>1.44 (0.26,7.83)</td>
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</table>
Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel + Oxaliplat</th>
<th>Irinotecan + Cisplatin</th>
<th>Paclitaxel</th>
<th>Placebo / BSC</th>
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<tbody>
<tr>
<td><strong>Risk Ratio</strong></td>
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<td><strong>95% CI</strong></td>
<td><strong>95% CI</strong></td>
<td><strong>95% CI</strong></td>
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<td>Docetaxel + Oxaliplat</td>
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<td>0.09 (&lt;0.01, 7.59)</td>
<td>0.01 (&lt;0.01, 3.7)</td>
</tr>
<tr>
<td>Irinotecan + Cisplatin</td>
<td>0.01 (&lt;0.01, 0.4)</td>
<td>0.03 (&lt;0.01, 2.5)</td>
<td>0.19 (0.01, 3.91)</td>
<td>0.01 (&lt;0.01, 0.3)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.15 (0.01, 6.1)</td>
<td>0.19 (&lt;0.01, 5.1)</td>
<td>0.19 (0.01, 22.0)</td>
<td>0.01 (&lt;0.01, 3.7)</td>
</tr>
<tr>
<td>Placebo / BSC</td>
<td>0.08 (&lt;0.01, 1.3)</td>
<td>0.05 (&lt;0.01, 1.4)</td>
<td>0.01 (&lt;0.01, 0.3)</td>
<td>0.01 (&lt;0.01, 3.7)</td>
</tr>
</tbody>
</table>

Lower half displays indirect NMA results. Upper half displays direct results from included studies. Results, read horizontally, show the risk ratios for experimental vs control for indirect results and control vs experimental for direct results. Boxes shaded orange show results where the 95% confidence intervals do not pass 1.
<table>
<thead>
<tr>
<th>Class</th>
<th>N</th>
<th>k</th>
<th>SUCRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo / BSC</td>
<td>146</td>
<td>2</td>
<td>90</td>
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<td>Irinotecan + Cisplatin</td>
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<td>Docetaxel + Fluoropyrimidine</td>
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<td>Docetaxel</td>
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<td>60</td>
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<td>Paclitaxel</td>
<td>224</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>Docetaxel / Irinotecan</td>
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<td>1</td>
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<tr>
<td>Docetaxel + Cisplatin</td>
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<td>2</td>
<td>50</td>
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<tr>
<td>Olaparib + Paclitaxel</td>
<td>61</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Irinotecan + 5'FU/leucovorin (mFOLFIRI)</td>
<td>126</td>
<td>1</td>
<td>40</td>
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<tr>
<td>Irinotecan</td>
<td>402</td>
<td>5</td>
<td>40</td>
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<tr>
<td>Fluoropyrimidine</td>
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<td>30</td>
</tr>
<tr>
<td>Docetaxel + Oxaliplatin</td>
<td>25</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>S-1+ Irinotecan</td>
<td>153</td>
<td>1</td>
<td>10</td>
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Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease
### Table 10: Indirect and direct comparisons for treatment related morbidity – neutropenia

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>Group 9</th>
<th>Group 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Docetaxel/Irinotecan</td>
<td>Fluorouracil</td>
<td>Fluorouracil/Irinotecan</td>
<td>Docetaxel/Irinotecan</td>
<td>Docetaxel/Irinotecan</td>
<td>Docetaxel/Irinotecan</td>
<td>Docetaxel/Irinotecan</td>
<td>Docetaxel/Irinotecan</td>
<td>Docetaxel/Irinotecan</td>
</tr>
<tr>
<td>0.13 (0.01,2.24)</td>
<td>0.38 (0.07,2.07)</td>
<td>0.60 (0.16,2.22)</td>
<td>0.29 (0.06,1.30)</td>
<td>1.15 (0.41,3.25)</td>
<td>18.31 (1.11,302)</td>
<td>0.03 (&lt;0.01,0.44)</td>
<td>0.21 (0.11,0.41)</td>
<td>0.03 (&lt;0.01,0.44)</td>
<td>0.21 (0.11,0.41)</td>
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<tr>
<td>Docetaxel/Irinotecan</td>
<td>0.60 (0.16,2.22)</td>
<td>4.71 (0.20,110)</td>
<td>0.75 (0.35,1.60)</td>
<td>1.92 (0.54,6.77)</td>
<td>0.29 (0.06,1.30)</td>
<td>0.13 (0.01,2.24)</td>
<td>0.38 (0.07,2.07)</td>
<td>0.60 (0.16,2.22)</td>
<td>0.29 (0.06,1.30)</td>
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<tr>
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<td>0.75 (0.35,1.60)</td>
<td>0.48 (0.06,3.53)</td>
<td>1.44 (1.03,2.03)</td>
<td>1.17 (0.87,1.57)</td>
<td>0.73 (0.50,1.06)</td>
<td>0.41 (0.09,1.95)</td>
<td>0.08 (&lt;0.01,1.35)</td>
<td>0.61 (0.24,1.53)</td>
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<td>0.41 (0.09,1.95)</td>
<td>3.25 (0.12,84.5)</td>
<td>1.09 (0.47,2.48)</td>
<td>0.69 (0.09,5.24)</td>
<td>1.44 (1.03,2.03)</td>
<td>1.17 (0.87,1.57)</td>
<td>0.73 (0.50,1.06)</td>
<td>0.41 (0.09,1.95)</td>
<td>0.08 (&lt;0.01,1.35)</td>
<td>0.61 (0.24,1.53)</td>
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<td>0.51 (0.08,3.02)</td>
<td>3.98 (0.14,116)</td>
<td>1.33 (0.39,4.48)</td>
<td>0.84 (0.09,7.74)</td>
<td>1.77 (0.68,4.58)</td>
<td>1.22 (0.45,3.36)</td>
<td>0.41 (0.17,0.99)</td>
<td>0.35 (0.19,0.67)</td>
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<td>0.08 (&lt;0.01,1.35)</td>
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<td>0.20 (0.01,5.64)</td>
<td>0.13 (0.01,3.00)</td>
<td>0.27 (0.01,6.87)</td>
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<td>0.61 (0.24,1.53)</td>
<td>0.20 (0.01,5.64)</td>
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<td>Control Group</td>
<td>Risk Ratio (95% CI)</td>
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<tr>
<td>Docetaxel + Cisplatin</td>
<td>Docetaxel + Oxaliplatin</td>
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<td>Docetaxel + Cisplatin</td>
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<td></td>
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<td></td>
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<tr>
<td>Docetaxel + Oxaliplatin</td>
<td>Irinotecan + Cisplatin</td>
<td>0.31 (0.7, 1.5)</td>
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</tr>
<tr>
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<td>Paclitaxel</td>
<td>1.37 (1.09, 1.73)</td>
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<tr>
<td>Paclitaxel</td>
<td>Olaparib + Paclitaxel</td>
<td>&lt;0.01 (0.01, 0.45)</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Lower half displays indirect NMA results. Upper half displays direct results from included studies. Results, read horizontally, show the risk ratios for experimental vs control for indirect results and control vs experimental for direct results. Boxes shaded orange show results where the 95% confidence intervals do not pass 1.
## Appendix M

- Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Class</th>
<th>N</th>
<th>k</th>
<th>SUCRA</th>
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</thead>
<tbody>
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<td>3</td>
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<td>486</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>FOLFIRI + Sunitinib</td>
<td>45</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>Docetaxel / Irinotecan</td>
<td>126</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>Olaparib + Paclitaxel</td>
<td>324</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>486</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>Irinotecan + Cisplatin</td>
<td>148</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Irinotecan + mFOLFIRI</td>
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<td>50</td>
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<tr>
<td>S-1+ Irinotecan</td>
<td>153</td>
<td>1</td>
<td>40</td>
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<tr>
<td>Fluoropyrimidine</td>
<td>49</td>
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<td>Docetaxel + Fluoropyrimidine</td>
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<td>Docetaxel</td>
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<td>5</td>
<td>20</td>
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<td>20</td>
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<td>Docetaxel + Oxaliplatin</td>
<td>25</td>
<td>1</td>
<td>0</td>
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Appendix M – Network meta-analysis of second line palliative chemotherapy for locally advanced and metastatic disease
### Table 11: Indirect and direct comparisons for treatment related morbidity – diarrhoea

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<thead>
<tr>
<th></th>
<th>7.99 (1.04,61.24)</th>
<th>0.31 (0.01,7.26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.45 (0.69,345)</td>
<td>0.52 (0.05,5.40)</td>
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</tr>
<tr>
<td><strong>7.99 (1.04,61.24)</strong></td>
<td>0.69 (0.27,1.77)</td>
<td>0.21 (0.04,1.20)</td>
</tr>
<tr>
<td>5.52 (0.59,51.99)</td>
<td>0.36 (0.03,4.47)</td>
<td>0.69 (0.27,1.77)</td>
</tr>
<tr>
<td><strong>92.16 (1.05,&gt;999)</strong></td>
<td>5.96 (0.06,605)</td>
<td>11.53 (0.22,617)</td>
</tr>
<tr>
<td>3.23 (0.14,75.83)</td>
<td>0.40 (0.01,17.28)</td>
<td>0.59 (0.01,28.08)</td>
</tr>
<tr>
<td><strong>1.68 (0.11,24.47)</strong></td>
<td>0.21 (0.01,2.02)</td>
<td>0.30 (0.04,2.20)</td>
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<tr>
<td><strong>8.06 (0.26,249)</strong></td>
<td>1.01 (0.06,15.91)</td>
<td>1.46 (0.08,26.91)</td>
</tr>
<tr>
<td><strong>2.73 (0.06,118)</strong></td>
<td>0.34 (0.01,8.13)</td>
<td>0.49 (0.02,13.49)</td>
</tr>
</tbody>
</table>

Lower half displays indirect NMA results. Upper half displays direct results from included studies. Results, read horizontally, show the risk ratios for experimental vs control for indirect results and control vs experimental for direct results. Boxes shaded orange show results where the 95% confidence intervals do not pass 1.
### Table

<table>
<thead>
<tr>
<th>Class</th>
<th>N</th>
<th>k</th>
<th>SUCRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>71</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>Irinotecan + Cisplatin</td>
<td>148</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>Olaparib + Paclitaxel</td>
<td>61</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>Docetaxel + Oxaliplatin</td>
<td>25</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>S-1+ Irinotecan</td>
<td>153</td>
<td>1</td>
<td>50</td>
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<tr>
<td>Paclitaxel</td>
<td>224</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>486</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Irinotecan + mFOLFIRI</td>
<td>30</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Fluoropyrimidine</td>
<td>49</td>
<td>1</td>
<td>10</td>
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</table>
### Table 12: Indirect and direct comparisons for treatment related morbidity – treatment related mortality

<table>
<thead>
<tr>
<th>Paclitaxel</th>
<th>4.96 (0.24,102)</th>
<th>3.12 (0.13,74.80)</th>
<th>1.02 (0.02,50.41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.60 (0.02,127)</td>
<td>3.10 (0.13,73.14)</td>
<td>0.61 (0.01,48.73)</td>
<td></td>
</tr>
<tr>
<td>4.96 (0.24,102)</td>
<td>3.10 (0.13,73.14)</td>
<td>1.03 (0.02,51.18)</td>
<td></td>
</tr>
<tr>
<td>0.98 (0.01,70.67)</td>
<td>0.61 (0.01,48.73)</td>
<td>0.20 (0.01,4.08)</td>
<td></td>
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<tr>
<td>3.12 (0.13,74.80)</td>
<td>1.95 (0.01,435)</td>
<td>0.21 (&lt;0.01,122)</td>
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</tr>
<tr>
<td>5.11 (0.04,714)</td>
<td>3.20 (0.02,486)</td>
<td>1.04 (&lt;0.01,341)</td>
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<tr>
<td>1.02 (0.02,50.41)</td>
<td>0.64 (&lt;0.01,224)</td>
<td>0.33 (&lt;0.01,50.0)</td>
<td></td>
</tr>
</tbody>
</table>

Lower half displays indirect NMA results. Upper half displays direct results from included studies.

Results, read horizontally, show the risk ratios for experimental vs control for indirect results and control vs experimental for direct results.

Boxes shaded orange show results where the 95% confidence intervals do not pass 1.
<table>
<thead>
<tr>
<th>Class</th>
<th>N</th>
<th>k</th>
<th>SUCRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>224</td>
<td>3</td>
<td>70</td>
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<tr>
<td>Olaparib + Paclitaxel</td>
<td>61</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>S-1+ Irinotecan</td>
<td>153</td>
<td>1</td>
<td>60</td>
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<tr>
<td>Irinotecan + mFOLFIRI</td>
<td>30</td>
<td>1</td>
<td>50</td>
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<tr>
<td>Fluoropyrimidine</td>
<td>49</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Irinotecan + Cisplatin</td>
<td>64</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>358</td>
<td>2</td>
<td>30</td>
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Figure 9: NMA results for treatment related morbidity and mortality outcomes in comparison to paclitaxel

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<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Docetaxel</td>
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<tr>
<td>Neutropenia</td>
<td>2.02 (0.71, 6.32)</td>
</tr>
<tr>
<td>Neutropenia, febrile neutropenia</td>
<td>0.76 (0.10, 5.76)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.21 (0.04, 1.09)</td>
</tr>
<tr>
<td>Diarrhoea - related death</td>
<td>0.12 (0.00, 3.89)</td>
</tr>
<tr>
<td>Irinotecan + FOLFIRI</td>
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</tr>
<tr>
<td>Neutropenia</td>
<td>0.42 (0.01, 28.12)</td>
</tr>
<tr>
<td>Neutropenia, febrile neutropenia</td>
<td>0.21 (0.02, 18.34)</td>
</tr>
<tr>
<td>Neutropenia, febrile neutropenia</td>
<td>0.05 (0.04, 1.27)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.92 (0.05, 71.07)</td>
</tr>
<tr>
<td>Diarrhoea - related death</td>
<td>1.94 (0.03, 100.00)</td>
</tr>
<tr>
<td>Docetaxel + Fluoropyrimidines</td>
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<tr>
<td>Neutropenia</td>
<td>0.05 (0.05, 0.11)</td>
</tr>
<tr>
<td>Neutropenia, febrile neutropenia</td>
<td>1.51 (0.07, 33.33)</td>
</tr>
<tr>
<td>Neutropenia, febrile neutropenia</td>
<td>0.35 (0.05, 2.69)</td>
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<tr>
<td>Diarrhoea</td>
<td>0.40 (0.05, 3.04)</td>
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<tr>
<td>Diarrhoea, related death</td>
<td>0.30 (0.07, 1.27)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.73 (0.50, 1.06)</td>
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<tr>
<td>Neutropenia, related death</td>
<td>0.99 (0.00, 15.00)</td>
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<tr>
<td>Diarrhoea - related death</td>
<td>0.99 (0.00, 15.00)</td>
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<tr>
<td>5-FU + Irinotecan</td>
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<tr>
<td>Neutropenia</td>
<td>0.70 (0.11, 4.48)</td>
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<tr>
<td>Neutropenia, febrile neutropenia</td>
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</tr>
<tr>
<td>Neutropenia</td>
<td>0.00 (0.00, 0.84)</td>
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<td>Diarrhoea</td>
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<td>Neutropenia</td>
<td>1.14 (0.01, 12.58)</td>
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<td>Diarrhoea</td>
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<td>Diarrhoea</td>
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<td>Diarrhoea, related death</td>
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