National Institute for Health and Care Excellence

Version 1.0 Pre-consultation

Oesophago-gastric cancer

Assessment and management

Appendix M

Network Meta-Analysis of Second Line Palliative Chemotherapy for Locally Advanced and Metastatic Disease

15 June 2017

Draft for Consultation

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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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 explicity 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 mortbidity 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

Study	Intervention	Comparator
Bang 2015	6-10x4 week treatment cycle: Olaparib 100mg BD + paclitaxel 80mg/m2 IV days 1, 8, 15	Paclitaxel 80mg/m2 IV days 1, 8, 15
	Maintenance: Olaparib 200mg BD	Placebo
Bang 2016	6-10x4 week treatment cycle: Olaparib 100mg BD + paclitaxel 80mg/m2 IV days 1, 8, 15	Paclitaxel 80mg/m2 IV days 1, 8, 15
Ford 2014	Docetaxel 75mg/m2 IV every 3 weeks x 6 cycles	BSC

Study	Intervention	Comparator
Higuchi 2014	Irinotecan 60mg/m2 IV + cisplatin 30mg/m2 IV every 2 weeks	Irinotecan 150mg/m2 IV every 2 weeks
Hironaka 2013	Paclitaxel 80mg/m2 IV days 1, 8, 15 every 4 weeks	Irinotecan 150mg/m2 day 1 and 15 every 4 weeks
Kang 2012	Either docetaxel 60 mg/m2 every 3 weeks or irinotecan 150 mg/m2 every 2 weeks at the discretion of investigators	Best supportive care
Kim B 2015[1]	Docetaxel 75mg/m2 IV every 3 weeks	Arm 2: Docetaxel 60mg/m2 IV + Cisplatin 60mg/m2 Arm 3: Docetaxel 60mg/m2 + S-1 30mg/m2 BD day 1-14
Kim JY 2015	Docetaxel 36mg/m2 IV day 1 and 8 every 3 weeks x 9 cycles	Docetaxel 80mg/m2 day every 3 weeks
Maruta 2007	Docetaxel 60 mg/m2 IV every 3 weeks x 2cycles	Docetaxel 60 mg/m2 IV every 3 weeks
Moehler 2013	6-week cycles: FOLFIRI two weekly followed by 4 weeks daily sunitinib 25mg	Placebo
Nishikawa 2015	Irinotecan 60 mg/m2 + cisplatin 30 mg/m2 every 2 weeks	Irinotecan 150 mg/m2 every 2 weeks
Nishina 2016	5FU 800mg/m2/day days 1-5 every 4 weeks	Paclitaxel 80mg/m2 IV days 1, 8, 15 every 4 weeks
Roy	Irinotecan 300mg/m2 every 3 weeks	Docetaxel 75mg/m2 every 3 weeks
Sym 2013	Irinotecan 150mg/m2 every 2 weeks x 12 cycles	Irinotecan 150mg + 5FU 1g/m2 + leucovorin 20mg/m2
Tanabe 2015	S-1 BD days 1-14 + Irinotecan 150mg/m2 every 21 days	Irinotecan 150mg/m2 every 2 weeks
Thuss-Patience 2011	Irinotecan 250mg/m2 in cycle 1 then 350mg/m2 thereafter	BSC

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

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

Study	Intervention (arm1)	Comparison (arm 2)	N1	N2	Median follow-up (months)	Location	Overall Survival (HR 95% CI)	Progression free survival (HR 95% CI)
Thuss-Patience 2011	irinotecan	BSC	21	19	NR	Europe	0.48 (0.25 to 0.92)	NR
Kang 2012	docetaxel / irinotecan	BSC	126	62	NR	Asia	0.711 (0.536 to 0.974)	NR
Bang 2016	olaparib+paclitaxel	placebo + paclitaxel	263	262	NR	Asia	0.79 (0.63 to 1)	0.84 (0.67 to 1.04)

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

Study	Nausea arm 1	Nausea arm 2	neutropaenic sepsis arm1	neutropaenic sepsis arm 2	neutropaenia arm1	neutropaenia arm2	diarrhoea arm1	diarrhoea arm2	treatment related death arm1	treatment related death arm2
Bang 2015	0	0	1	0	35	24	2	6	0	0
Ford 2014	NR	NR	6	0	18	0	NR	NR	0	0
Higuchi 2014	3	3	0	3	25	24	1	4	0	0
Hironaka 2013	2	5	3	10	31	43	1	1	0	2
Kim B 2015 (arm 1 vs arm 2)	NR	NR	2	3	5	6	NR	NR	NR	NR
Kim B 2015 (arm 2 v arm 3)	NR	NR	3	1	6	3	NR	NR	NR	NR
Kim B 2015 (arm 1 v arm 3)	NR	NR	2	1	5	3	NR	NR	NR	NR
Kim JY 2015	0	1	0	5	0	8	0	1	0	0
Maruta 2007	1	0	NR	NR	4	4	0	0	NR	NR
Moehler 2013	3	3	NR	NR	25	9	1	6	NR	NR

Study	Nausea arm 1	Nausea arm 2	neutropaenic sepsis arm1	neutropaenic sepsis arm 2	neutropaenia arm1	neutropaenia arm2	diarrhoea arm1	diarrhoea arm2	treatment related death arm1	treatment related death arm2
Nishikawa 2015	4	5	NR	NR	35	28	0	3	0	0
Nishina 2016	3	0	2	0	14	6	5	0	1	0
Roy 2013	0	2	2	5	7	2	1	8	0	0
Sym 2013	0	0	0	0	8	11	1	2	1	0
Tanabe 2015	7	12	12	1	57	39	7	10	0	2
Thuss-Patience 2011	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kang 2012	19	20	6	0	76	8	18	11	NR	NR
Bang 2016	NR	NR	NR	NR	79	60	NR	NR	NR	NR

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 comarisons between those nodes.

Figure 1: Network for overall survival

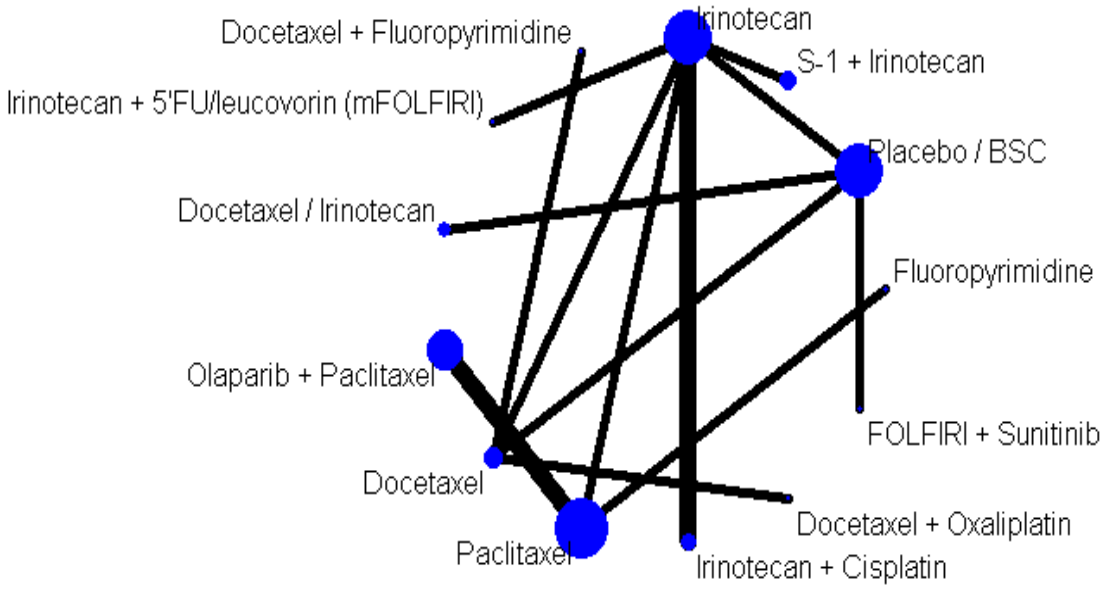


Figure 2: Network for progression free survival

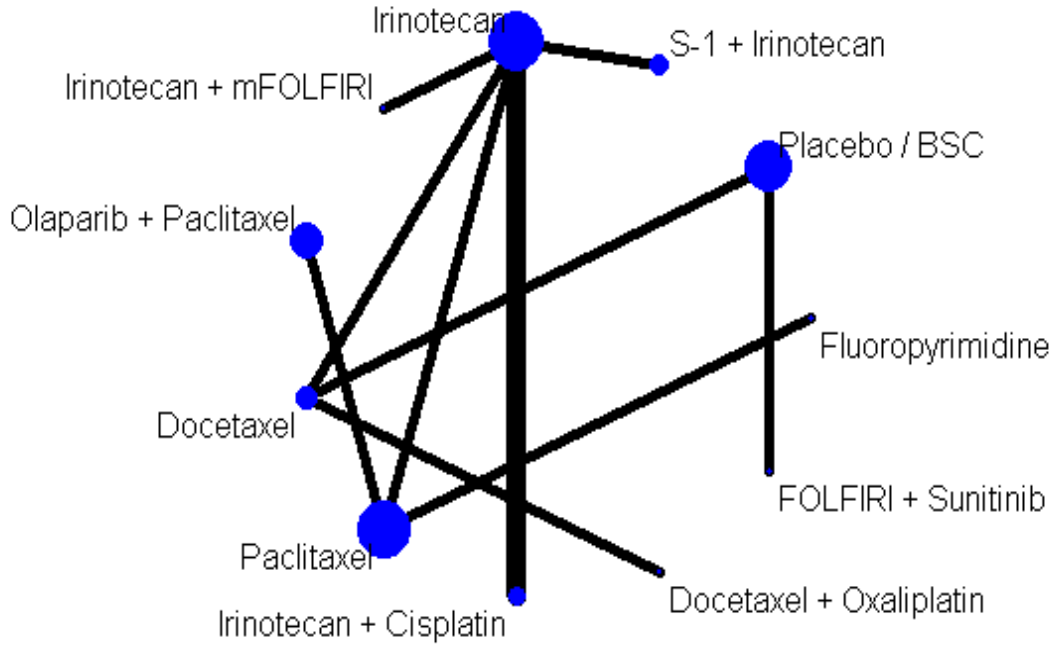


Figure 3: Network for treatment related morbidity - nausea

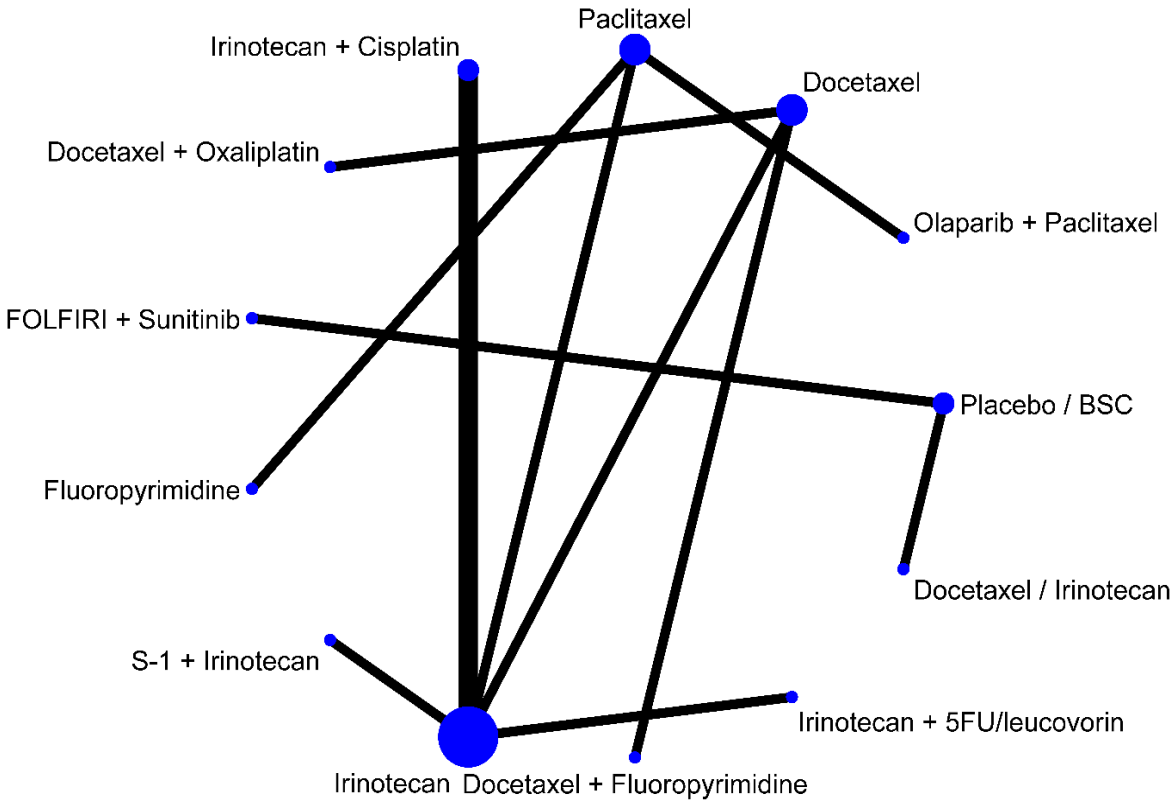


Figure 4: Network for treatment related morbidity – neutropenic sepsis

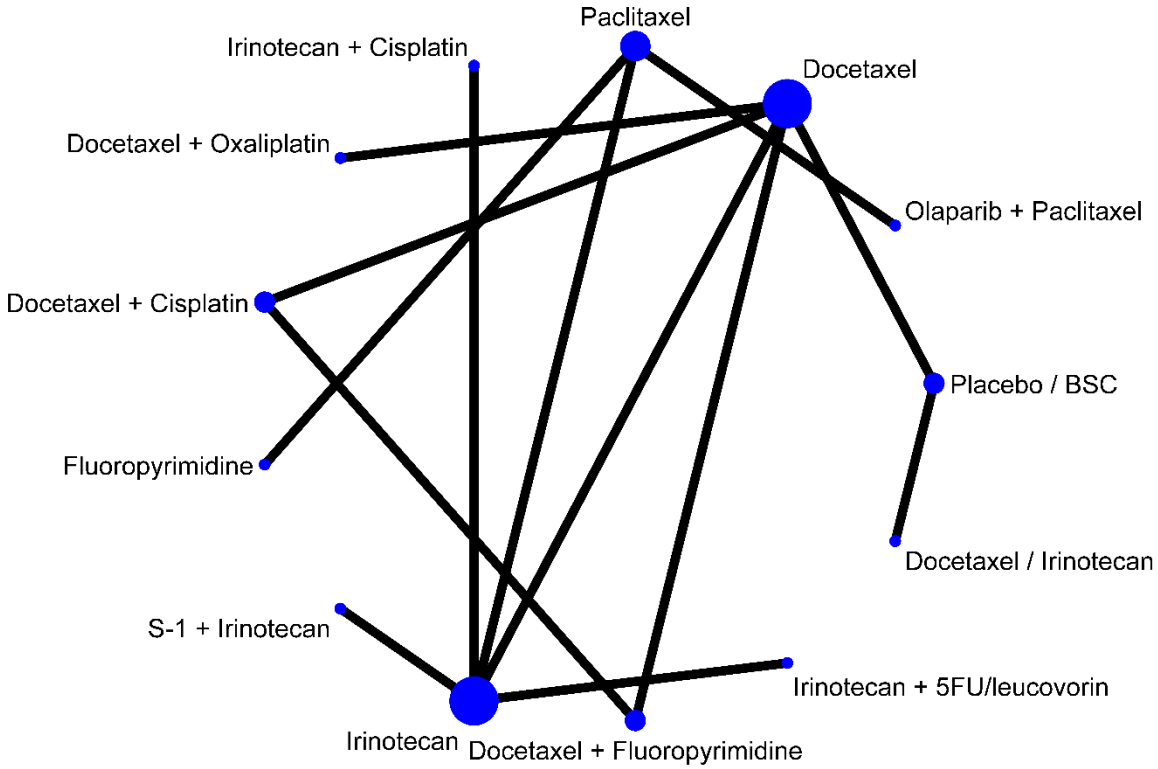


Figure 5: Treatment related morbidity - neutropenia

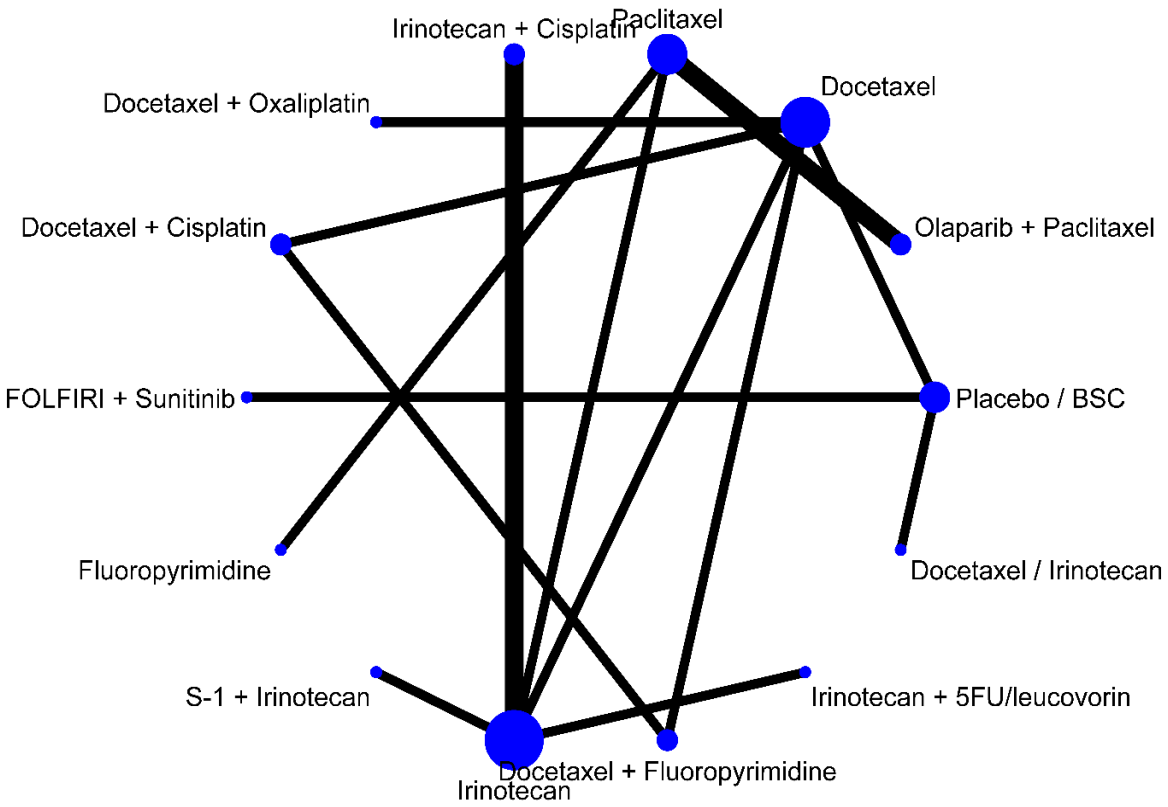


Figure 6: Treatment related morbidity – diarrhoea

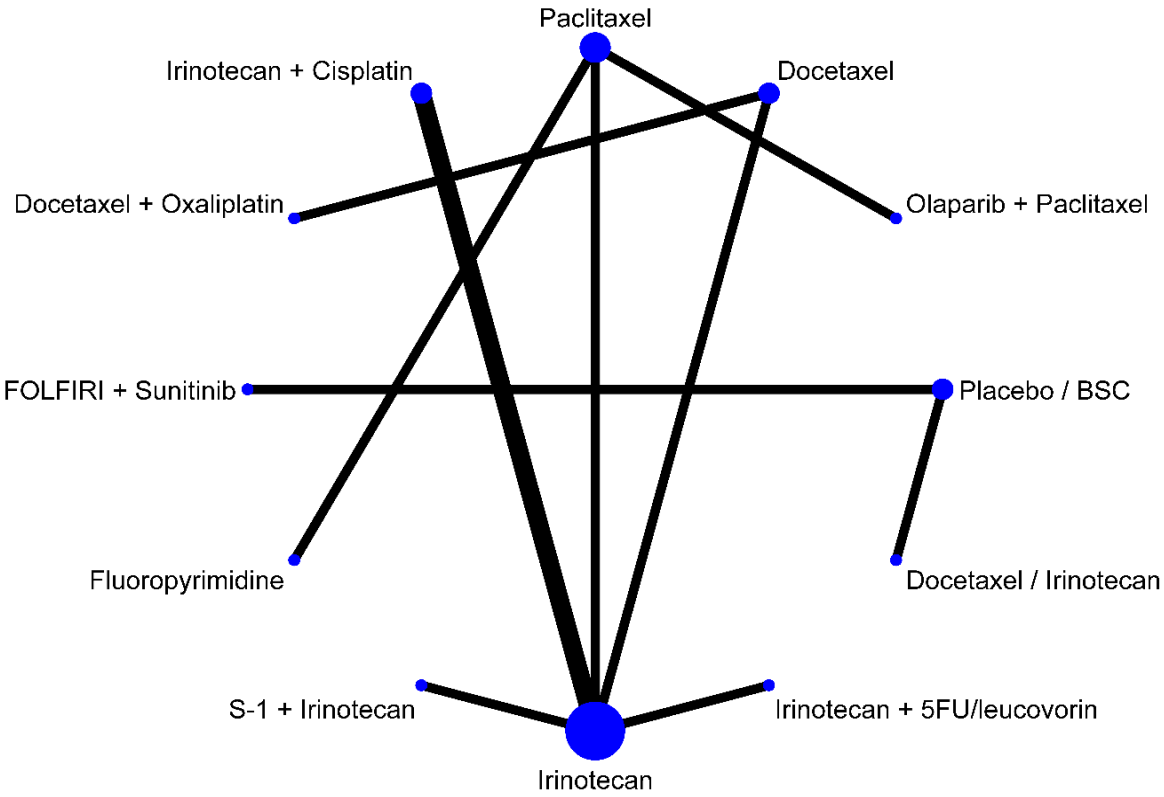
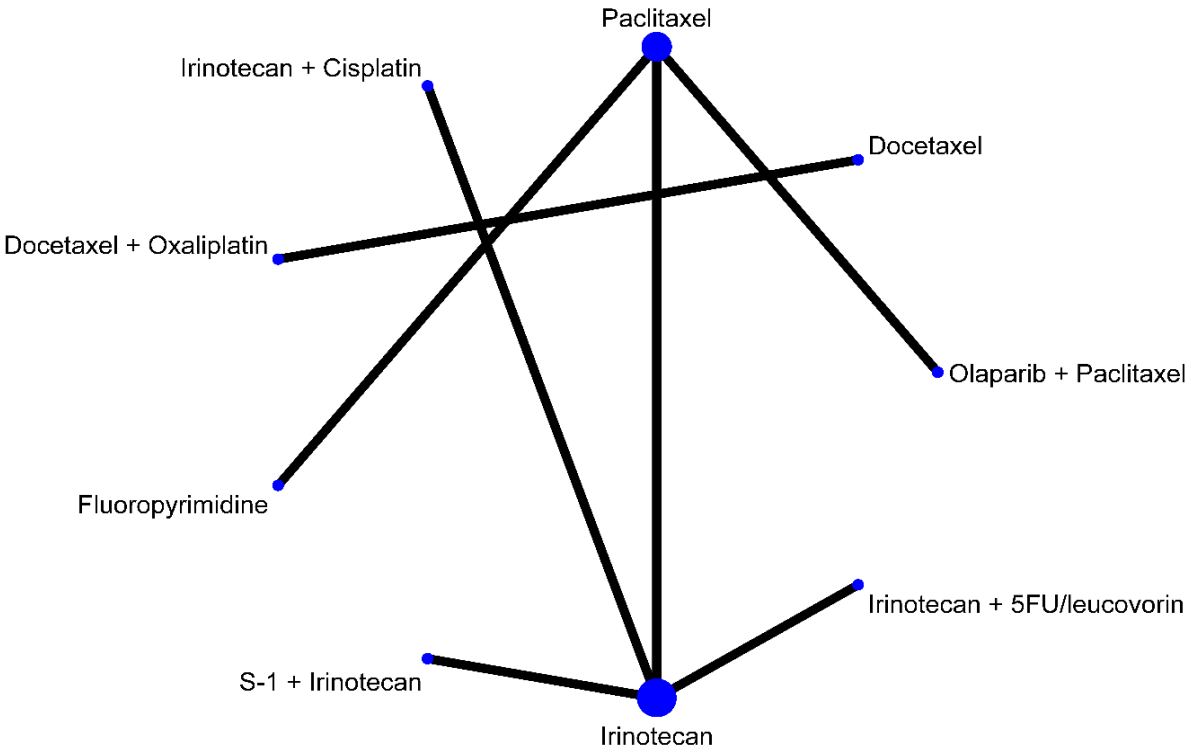


Figure 7: Treatment related mortality



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

```
* Change network directory to your working directory
cd "<FILE PATH TO YOUR WORKING DIRECTORY>"

* Imports Excel file (remember to update if you save excel file as new version
//and don't include spaces in name)
import excel using NMA_data_v4, sheet("NMA_data_v3") firstrow clear

* Drops observations that aren't your actual dataset (i.e. the list of treatment
codes)
drop if Author==""

* Gives STARID value to study with missing STARID
replace STARID=1 if Author=="Ohtsu" & Date==2013

drop Arm1code Arm2code Arm3code
destring Armcode1, replace
destring Armcode2, replace
destring Armcode3, replace
drop if Armcode1 == 0
drop if Armcode2 == 0

* Rename variables to give them shorter names (easier to refer to them in code)
```

```
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 Studylocation1western2eas s_loc
rename ECOGScore0arm1 ecog0_1
rename ECOGscore1arm1 ecog1_1
rename ECOGscore2arm1 ecog2_1
rename ECOGscore0arm2 ecog0_2
rename ECOGscore1arm2 ecog1_2
rename ECOGscore2arm2 ecog2_2
rename ECOGscore2arm3 ecog2_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 locallyadvancearm3 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"
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 ecog1_2 = "" if ecog1_2=="NR"
destring (ecog1_2), replace
replace ecog2_2 = "" if ecog2_2=="NR"
destring (ecog2_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

/* Assing 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
       }

* Assing new label 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 lOS = ln(OSHR)
gen lOSl95 = ln(OSUCI)
gen lOSu95 = 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 = -lOS
gen invOSu95 = -lOSl95
gen invOSl95 = -lOSu95

#delimit ;
metan lOS lOSl95 lOSu95, eform fixed
by(complab)
nooverall
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 invOSl95 invOSu95, eform fixed
by(invcomplab)
nooverall
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 lPFS = ln(PFSHR)
gen lPFSl95 = 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==. | lPFSl95==.

gen invPFS = -lPFS
gen invPFSu95 = -lPFSl95
gen invPFSl95 = -lPFSu95

#delimit ;
metan lPFS lPFSl95 lPFSu95
, eform fixed
by(complab)
nooverall
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 invPFSl95 invPFSu95, eform fixed
by(invcomplab)
nooverall
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 nausea2 nonausea2 nausea1 nonausea1,
by(comp)
label(namevar=STARID)
rr
nooverall
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
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 (Arm1code Arm2code), 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)
*/


/***** Thrombocytopaenia ******
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
```

```
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
        Coef.      Std. Err.  Coef.      Std. Err.  Coef.      Std. Err.  P>|z|
B E             .          .          .          .          .          .      .
```

```
B H *    1.609438   1.534782   .0778039    60.9027   1.531634   60.92203  0.980
B I *        -1.5   1.732051         -1   9.49e+07        -.5   9.49e+07  1.000
A C *   -.0160003   1.991983   1.402118   704.2841  -1.418118   704.2869  0.998
C F *    1.985131   1.498827  -2.228963   313.0725   4.214094   313.0816  0.989
C H *    .9073207   .8258703   2.874379    132.489  -1.967058   132.4912  0.988
D H *    .1212528   .5051428   3.217788   195.2133  -3.096536   195.2139  0.987
G H *    .5521546   .4615539   3.289085   244.9686   -2.73693   244.9688  0.991
H J *   -.0327898   1.983534  -3.216788   489.9116   3.183998   489.9156  0.995



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 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'
}

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
network sidesplit all, fixed




netleague, eform
drop in l
network rank min, reps(2000) line meanrank

*/
```

```
/* Naeutropaenia

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


#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'
}


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)


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

network sidesplit all, fixed



netleague, eform
network rank min, reps(2000) line meanrank

*/



/* Diarrhoea

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


#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 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


Side    Direct                Indirect              Difference
        Coef.      Std. Err.  Coef.      Std. Err.  Coef.      Std. Err.  P>|z|
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   239.8184  0.989
C F *    2.437116   1.463758  -5.360514   253.0106    7.79763   253.0221  0.975
C H *   -.0089687   1.407857   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    259.873   -3.81932   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
*/
```

```
/* Treatment-related adverse events

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


#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 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


Side    Direct                Indirect              Difference
        Coef.      Std. Err.  Coef.      Std. Err.  Coef.      Std. Err.  P>|z|
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   239.8184  0.989
C F *    2.437116   1.463758  -5.360514   253.0106    7.79763   253.0221  0.975
C H *   -.0089687   1.407857   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    259.873   -3.81932   259.8732  0.988
H I *    .6592456   1.196739  -4.275096   273.2625   4.934341    273.267  0.986
```

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



/* THrombocytopaenia

drop if tp1 == tp2 & N1==N2
drop if tp1==.


#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
estat 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" "ramicurimab" "irinotecan +
platinum" "taxane+platinum" "FOLFIRI + sunitinib" "fluoropyrimidine" "everolimus"
"nimotuzumab + irinotecan" "S-1+ irinotecan" "irinotecan" "ramucirumab +
paclitaxel" "docetaxel + fluoropyrimidine" "irinotecan + 5FU/leucovorin") sort
("olaparib+paclitaxel" "gefitinib" "taxane" "ramicurimab" "irinotecan + platinum"
"taxane+platinum" "FOLFIRI + sunitinib" "fluoropyrimidine" "everolimus"
"nimotuzumab + irinotecan" "S-1+ irinotecan" "irinotecan" "ramucirumab +
paclitaxel" "docetaxel + fluoropyrimidine" "irinotecan + 5FU/leucovorin")

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

* 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 l95 = ln(l95)
replace u95 = ln(u95)

label variable Out "Outcome"

#delimit ;
metan lhr l95 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 l95=="<0.01"
replace l95 = "0.004" if l95=="0.00"
```

```
destring l95, replace


gen lor = ln(rr)
replace l95 = ln(l95)
replace u95 = ln(u95)

replace lor = -lor if direction==2
replace l95 = -l95 if direction==2
replace u95 = -u95 if direction==2
gen templ95 = l95
replace templ95 = u95 if direction==2
gen tempu95 = u95
replace tempu95 = l95 if direction==2
replace l95 = templ95
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 ;
metan invlor 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

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

1.3.2 Estimated hazard ratios

Table 6: Indirect and direct comparisons for overall survival

Placebo / BSC		0.57 (0.38, 0.85)			0.71 (0.54, 0.94)		0.65 (0.48, 0.86)				0.82 (0.5, 1.33)	

0.56 (0.35, 0.9)	S-1 + Irinotecan	1.01 (0.8, 1.28)										
0.57 (0.38,0.85)	1.01 (0.8, 1.28)	Irinotecan		0.96 (0.57, 1.61)			1.14 (0.79, 1.64)	1.13 (0.86, 1.48)	0.91 (0.71, 1.16)			
0.21 (0.08, 0.55)	0.37 (0.13, 1.04)	0.37 (0.13, 1.00)	Docetaxel + Fluoro				3.11 (1.22, 7.93)					
0.54 (0.28, 1.05)	0.97 (0.55, 1.72)	0.96 (0.57, 1.61)	2.62 (0.85, 8.12)	Irinotecan +mFOLFIRI								
0.71 (0.54, 0.94)	1.27 (0.73, 2.2)	1.26 (0.76, 2.06)	3.43 (1.24, 9.5)	1.31 (0.64, 2.68)	Docetaxel/ Irinotecan							
0.47 (0.28, 0.81)	0.85 (0.56, 1.28)	0.84 (0.6, 1.18)	2.28 (0.79, 6.59)	0.87 (0.47, 1.62)	0.67 (0.36, 1.22)	Olaparib + Paclitaxel		1.35 (1.1, 1.66)				
0.65 (0.48, 0.86)	1.15 (0.75, 1.78)	1.14 (0.79, 1.64)	3.11 (1.22, 7.93)	1.18 (0.63, 2.23)	0.91 (0.61, 1.36)	1.36 (0.83, 2.24)	Docetaxel			0.85 (0.49, 1.49)		
0.64 (0.39, 1.05)	1.14 (0.79, 1.64)	1.13 (0.86, 1.48)	3.08 (1.09, 8.73)	1.18 (0.65, 2.11)	0.9 (0.51, 1.59)	1.35 (1.1, 1.66)	0.99 (0.63, 1.56)	Paclitaxel				0.89 (0.57, 1.38)
0.51 (0.32, 0.83)	0.91 (0.65, 1.29)	0.91 (0.71, 1.16)	2.47 (0.88, 6.95)	0.94 (0.53, 1.67)	0.72 (0.41, 1.26)	1.08 (0.71, 1.65)	0.79 (0.51, 1.23)	0.8 (0.55, 1.16)	Irinotecan +Cisplatin			
0.55 (0.29, 1.03)	0.98 (0.49, 1.99)	0.97 (0.5, 1.89)	2.66 (0.89, 7.9)	1.01 (0.44, 2.35)	0.78 (0.39, 1.54)	1.16 (0.55, 2.46)	0.85 (0.49, 1.49)	0.86 (0.42, 1.77)	1.08 (0.53, 2.19)	Docetaxel +Oxaliplat		

0.82 (0.5, 1.33)	**1.46 (0.74, 2.88)**	**1.44 (0.76, 2.73)**	**3.93 (1.32, 11.8)**	**1.5 (0.66, 3.41)**	**1.15 (0.65, 2.02)**	**1.72 (0.84, 3.55)**	**1.27 (0.72, 2.24)**	**1.28 (0.64, 2.55)**	**1.59 (0.8, 3.16)**	**1.48 (0.67, 3.28)**	**FOLFIRI + Sunitinib**	
0.57 (0.29, 1.1)	**1.01 (0.57, 1.79)**	**1 (0.6, 1.68)**	**2.74 (0.88, 8.47)**	**1.04 (0.5, 2.17)**	**0.8 (0.39, 1.64)**	**1.2 (0.74, 1.95)**	**0.88 (0.47, 1.66)**	**0.89 (0.57, 1.38)**	**1.11 (0.62, 1.97)**	**1.03 (0.44, 2.39)**	**0.7 (0.31, 1.58)**	**Fluoropyrimidine**

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.

Treatment	N	k	SUCRA
Docetaxel + Fluoropyrimidine	12	1	97
Olaparib + Paclitaxel	324	2	76
Irinotecan + Cisplatin	148	2	68
Irinotecan + mFOLFIRI	30	1	58
Docetaxel + Oxaliplatin	25	1	57
S-1 + Irinotecan	153	1	56
Irinotecan	441	7	54
Fluoropyrimidine	49	1	53
Docetaxel	167	4	39
Paclitaxel	486	4	36
Docetaxel / Irinotecan	126	1	31
FOLFIRI + Sunitinib	45	1	21
Placebo / BSC	436	4	3

Table 7: Indirect and direct comparisons for progression free survival

Placebo / BSC					**0.67 (0.48, 0.94)**				1.11 (0.7, 1.76)	
0.68 (0.37, 1.23)	**S-1 + Irinotecan**	1.18 (0.93, 1.49)								
0.8 (0.46, 1.38)	1.18 (0.93, 1.49)	**Irinotecan**	0.88 (0.53, 1.47)		0.84 (0.55, 1.29)	1.14 (0.88, 1.48)	**0.77 (0.6, 0.99)**			
0.71 (0.33, 1.49)	1.04 (0.59, 1.82)	0.88 (0.53, 1.47)	**Irinotecan +mFOLFIRI**							
0.76 (0.4, 1.45)	1.13 (0.74, 1.71)	0.96 (0.68, 1.35)	1.08 (0.59, 2)	**Olaparib + Paclitaxel**		1.19 (0.95, 1.49)				
0.67 (0.48, 0.94)	0.99 (0.6, 1.62)	0.84 (0.55, 1.29)	0.95 (0.49, 1.85)	0.88 (0.51, 1.52)	**Docetaxel**			**2 (1.08, 3.7)**		
0.91 (0.5, 1.66)	1.34 (0.94, 1.91)	1.14 (0.88, 1.48)	1.29 (0.73, 2.28)	1.19 (0.95, 1.49)	1.36 (0.82, 2.24)	**Paclitaxel**				**0.58 (0.38, 0.88)**
0.62 (0.34, 1.12)	0.91 (0.65, 1.28)	**0.77 (0.6, 0.99)**	0.87 (0.5, 1.54)	0.81 (0.53, 1.23)	0.92 (0.56, 1.51)	**0.68 (0.47, 0.97)**	**Irinotecan +Cisplatin**			

1.34 (0.67, 2.7)	1.98 (0.9, 4.35)	1.68 (0.79, 3.57)	1.9 (0.77, 4.71)	1.76 (0.77, 4.01)	**2 (1.08, 3.7)**	1.47 (0.67, 3.27)	2.17 (0.98, 4.8)	**Docetaxel +Oxaliplat**		
1.11 (0.7, 1.76)	1.64 (0.77, 3.48)	1.39 (0.68, 2.84)	1.57 (0.66, 3.78)	1.45 (0.66, 3.21)	1.66 (0.94, 2.93)	1.22 (0.57, 2.61)	1.8 (0.85, 3.83)	0.83 (0.36, 1.92)	**FOLFIRI + Sunitinib**	
0.53 (0.25, 1.1)	0.78 (0.45, 1.34)	0.66 (0.41, 1.08)	0.75 (0.37, 1.51)	0.69 (0.43, 1.11)	0.79 (0.41, 1.51)	**0.58 (0.38, 0.88)**	0.85 (0.49, 1.48)	**0.39 (0.16, 0.96)**	0.47 (0.2, 1.13)	**Fluoropyrimidine**

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.

Treatment	N	k	SUCRA
Fluoropyrimidine	49	1	89
Irinotecan + Cisplatin	148	2	80
Docetaxel	167	3	70
S-1 + Irinotecan	153	1	68
Irinotecan + mFOLFIRI	30	1	61
Olaparib + Paclitaxel	263	1	53
Irinotecan	441	6	45
Paclitaxel	424	3	28
Placebo / BSC	374	2	26
FOLFIRI + Sunitinib	45	1	21
Docetaxel + Oxaliplat	25	1	11

Figure 8: NMA results for overall and progression free survival outcomes in comparison to placebo or best supportive care

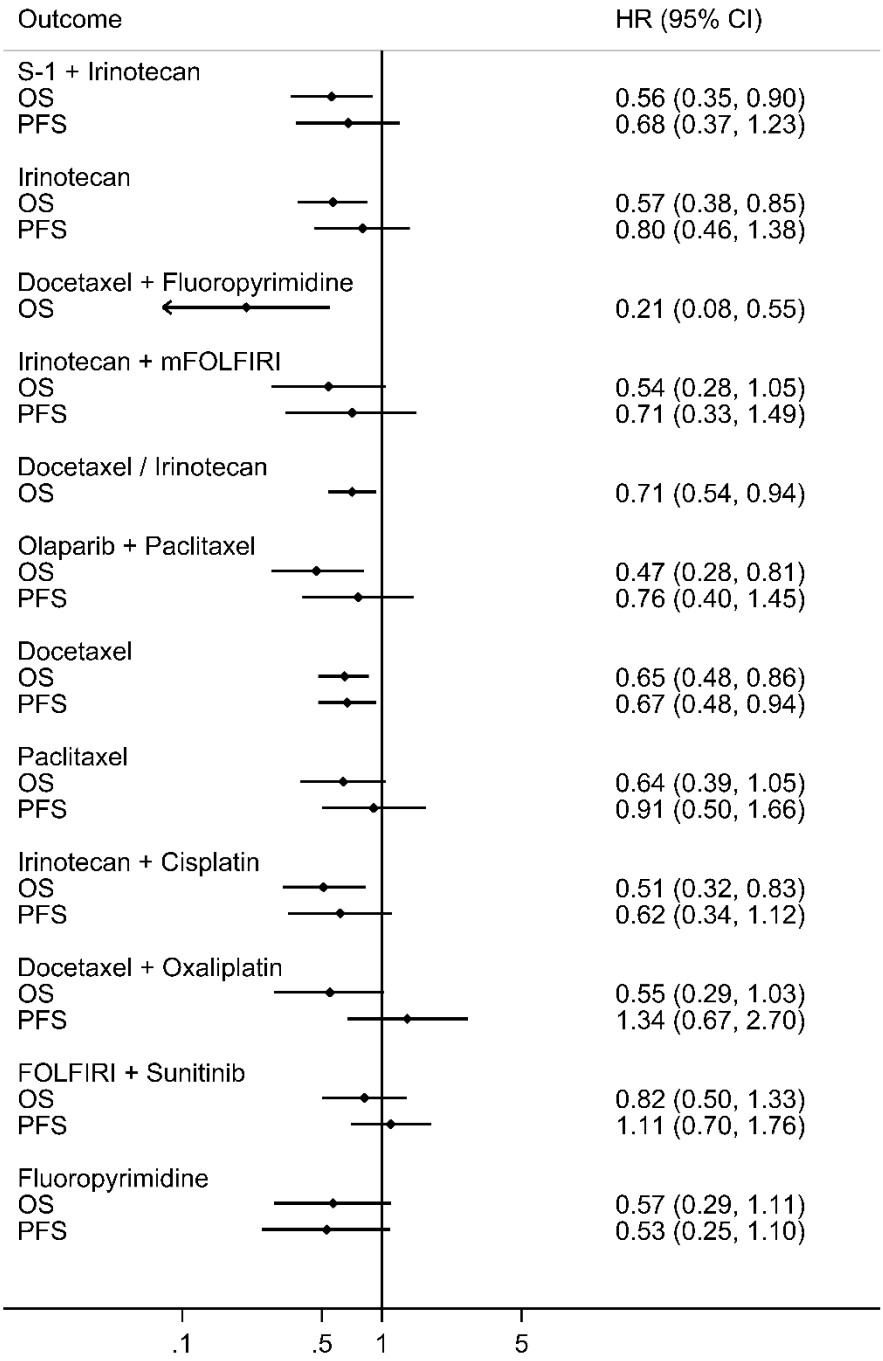


Table 8: Indirect and direct comparisons for treatment related morbidity - nausea

Docetaxel		0.33 (0.01,7.45)	5.00 (0.25,101)			3.23 (0.14,75.83)			
4.83 (0.04,659)	**Irinotecan + mFOLFIRI**		1.03 (0.02,50.42)						
0.33 (0.01,7.45)	0.07 (<0.01,23.1)	**Docetaxel + Fluoro**							
5.00 (0.25,101)	1.03 (0.02,50.4)	14.99 (0.20,>999)	**Irinotecan**	0.58 (0.23,1.42)			0.89 (0.33,2.38)	0.40 (0.08,2.04)	
2.88 (0.12,66.5)	0.59 (0.01,32.2)	8.63 (0.10,715)	0.58 (0.23,1.42)	**S-1+ Irinotecan**					
14.67 (0.16,>999)	3.04 (0.02,515)	44.02 (0.19, >999)	2.94 (0.10,84.06)	5.10 (0.16,165)	**Fluoropyrimidine**			0.14 (0.01,2.59)	
3.23 (0.14,75.8)	0.67 (<0.01,230)	9.69 (0.12,812)	0.65 (0.01,50.57)	1.12 (0.01,96.39)	0.22 (<0.01,53.9)	**Docetaxel + Oxaliplat**			
4.42 (0.19,105)	0.92 (0.02,50.6)	13.27 (0.16, >999)	0.89 (0.33,2.38)	1.54 (0.40,5.88)	0.30 (0.01,9.96)	1.37 (0.02,120)	**Irinotecan + Cisplatin**		
2.02 (0.07,61.3)	0.42 (0.01,28.1)	6.05 (0.06,612)	0.40 (0.08,2.04)	0.70 (0.11,4.48)	0.14 (0.01,2.59)	0.62 (0.01,65.25)	0.46 (0.07,3.04)	**Paclitaxel**	1.02 (0.02,50.41)
2.05 (0.01,367)	0.42 (<0.01,132)	6.15 (0.01, >999)	0.41 (0.01,28.08)	0.71 (0.01,53.67)	0.14 (<0.01,18.5)	0.63 (<0.01,275)	0.46 (0.01,35.54)	1.02 (0.02,50.41)	**Olaparib + Paclitaxel**

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.

Class	N	k	SUCRA
Docetaxel + Fluoropyrimidine	12	1	80
Docetaxel	83	3	70
Olaparib + Paclitaxel	61	1	60
Paclitaxel	224	3	60
Docetaxel + Oxaliplatin	25	1	50
S-1+ Irinotecan	153	1	50
Irinotecan + Cisplatin	148	2	40
Irinotecan + mFOLFIRI	30	1	40
Irinotecan	486	6	30
Fluoropyrimidine	49	1	20

Table 9: Indirect and direct comparisons for treatment related morbidity – neutropenic sepsis

Docetaxel			0.50 (0.05,5.14)	2.50 (0.51,12.20)			1.44 (0.26,7.83)	11.85 (0.69,204)				0.08 (<0.01,1.34)
0.50 (0.01,28.3)	Docetaxel /Irinotecan											0.16 (0.01,2.71)
2.42 (0.04,161)	4.88 (0.01,>999)	Irinotecan +mFOLFIRI		1.03 (0.02,50.42)								
0.50 (0.05,5.14)	1.01 (0.01,107)	0.21 (<0.01,25.2)	Docetaxel +Fluoro				2.88 (0.32,25.68)					
2.50 (0.51,12.2)	5.04 (0.07,388)	1.03 (0.02,50.4)	5.00 (0.30,83.7)	Irinotecan	**11.84 (1.56,89.94)**				0.15 (0.01,2.80)	0.30 (0.09,1.07)		
29.60 (2.26,388)	59.7 (0.49,>999)	12.24 (0.15,981)	**59.20 (1.84,>999)**	**11.84 (1.56,89.9)**	S-1+ Irinotecan							
3.93 (0.10,148)	7.93 (0.03,>999)	1.63 (0.01,261)	7.87 (0.11,588)	1.57 (0.06,41.23)	0.13 (<0.01,6.21)	Fluoropyrimidine				0.19 (0.01,3.91)		
1.44 (0.26,7.83)	2.90 (0.04,232)	0.59 (0.01,55.0)	2.88 (0.32,25.68)	0.58 (0.06,5.86)	0.05 (<0.01,1.06)	0.37 (0.01,20.08)	Docetaxel + Cisplatin					

11.85 (0.69,204)	23.88 (0.17,>999)	4.90 (0.03,781)	23.69 (0.60,937)	4.74 (0.18,123)	0.40 (0.01,18.56)	3.01 (0.03,303)	8.24 (0.30,226)	Docetaxel +Oxaliplat				
0.37 (0.01,10.4)	0.74 (<0.01,141)	0.15 (<0.01,20.0)	0.74 (0.01,43.33)	0.15 (0.01,2.80)	**0.01 (<0.01,0.44)**	0.09 (<0.01,7.59)	0.26 (0.01,10.87)	0.03 (<0.01,2.51)	Irinotecan + Cisplatin			
0.76 (0.10,5.75)	1.53 (0.02,140)	0.31 (0.01,18.64)	1.51 (0.07,33.20)	0.30 (0.09,1.07)	**0.03 (<0.01,0.28)**	0.19 (0.01,3.91)	0.53 (0.04,7.40)	0.06 (<0.01,2.10)	2.06 (0.08,50.59)	Paclitaxel	3.05 (0.13,73.40)	
2.31 (0.05,100)	4.65 (0.02,>999)	0.95 (0.01,169)	4.61 (0.05,389)	0.92 (0.03,28.29)	0.08 (<0.01,4.16)	0.59 (0.01,46.83)	1.60 (0.03,100)	0.19 (<0.01,22.0)	6.27 (0.07,572)	3.05 (0.13,73.40)	Olaparib + Paclitaxel	
0.08 (<0.01,1.34)	0.16 (0.01,2.71)	0.03 (<0.01,5.12)	0.15 (<0.01,6.16)	**0.03 (<0.01,0.81)**	**<0.01 (<0.01,0.12)**	0.02 (<0.01,1.99)	0.05 (<0.01,1.49)	0.01 (<0.01,0.37)	0.21 (<0.01,17.0)	0.10 (<0.01,3.39)	0.03 (<0.01,3.79)	Placebo / BSC

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.

Class	N	k	SUCRA
Placebo / BSC	146	2	90
Irinotecan + Cisplatin	64	1	70
Docetaxel + Fluoropyrimidine	23	2	70
Docetaxel	178	5	60
Paclitaxel	224	3	60
Docetaxel / Irinotecan	30	1	60
Docetaxel + Cisplatin	24	2	50
Olaparib + Paclitaxel	61	1	40
Irinotecan + 5'FU/leucovorin (mFOLFIRI)	126	1	40
Irinotecan	402	5	40
Fluoropyrimidine	49	1	30
Docetaxel + Oxaliplatin	25	1	20
S-1+ Irinotecan	153	1	10

Table 10: Indirect and direct comparisons for treatment related morbidity – neutropenia

Docetaxel			0.60 (0.16,2.22)	0.29 (0.06,1.30)				1.15 (0.41,3.25)	**18.31 (1.11,302)**				**0.03 (<0.01,0.44)**
0.13 (0.01,2.24)	Docetaxel /Irinotec												**0.21 (0.11,0.41)**
0.38 (0.07,2.07)	2.99 (0.11,83.4)	Irinotecan +mFOLFIRI		0.75 (0.35,1.60)									
0.60 (0.16,2.22)	4.71 (0.20,110)	1.57 (0.19,13.4)	Docetaxel + Fluoro					1.92 (0.54,6.77)					
0.29 (0.06,1.30)	2.25 (0.09,57.5)	0.75 (0.35,1.60)	0.48 (0.06,3.53)	Irinotecan	**1.44 (1.03,2.03)**					1.17 (0.87,1.57)	0.73 (0.50,1.06)		
0.41 (0.09,1.95)	3.25 (0.12,84.5)	1.09 (0.47,2.48)	0.69 (0.09,5.24)	**1.44 (1.03,2.03)**	S-1+ Irinotecan								
0.51 (0.08,3.02)	3.98 (0.14,116)	1.33 (0.39,4.48)	0.84 (0.09,7.74)	1.77 (0.68,4.58)	1.22 (0.45,3.36)	Fluoropyrimidine					**0.41 (0.17,0.99)**		
0.08 (<0.01,1.35)	0.61 (0.24,1.53)	0.20 (0.01,5.64)	0.13 (0.01,3.00)	0.27 (0.01,6.87)	0.19 (0.01,4.85)	0.15 (0.01,4.46)	FOLFIRI + Sunitinib						**0.35 (0.19,0.67)**

1.15 (0.41,3.25)	9.03 (0.43,191)	3.02 (0.41,22.0)	1.92 (0.54,6.77)	4.01 (0.64,25.2)	2.78 (0.43,18.0)	2.27 (0.29,18.0)	14.87 (0.71,312)	Docetaxel + Cisplatin					
18.31 (1.11,302)	144 (2.61,>999)	48.06 (1.82,>999)	30.51 (1.38,672)	**63.88 (2.65,>999)**	**44.29 (1.80,>999)**	36.15 (1.30,>999)	**236 (4.32,>999)**	15.92 (0.80,316)	Docetaxel + Oxaliplatin				
0.33 (0.07,1.56)	2.63 (0.10,68.2)	0.88 (0.39,1.98)	0.56 (0.07,4.22)	1.17 (0.87,1.57)	0.81 (0.52,1.27)	0.66 (0.24,1.79)	4.33 (0.17,112)	0.29 (0.05,1.87)	**0.02 (<0.01,0.45)**	Irinotecan + Cisplatin			
0.21 (0.04,0.99)	1.64 (0.06,42.8)	0.55 (0.24,1.27)	0.35 (0.05,2.66)	0.73 (0.50,1.06)	**0.50 (0.30,0.84)**	**0.41 (0.17,0.99)**	2.70 (0.10,70.2)	0.18 (0.03,1.18)	**0.01 (<0.01,0.28)**	0.62 (0.38,1.01)	Paclitaxel	1.37 (1.09,1.73)	
0.29 (0.06,1.38)	2.25 (0.09,59.2)	0.75 (0.31,1.80)	0.48 (0.06,3.70)	1.00 (0.64,1.56)	0.69 (0.40,1.21)	0.56 (0.23,1.39)	3.70 (0.14,97.0)	0.25 (0.04,1.64)	**0.02 (<0.01,0.39)**	0.85 (0.50,1.45)	**1.37 (1.09,1.73)**	Olaparib + Paclitaxel	
0.03 (<0.01,0.44)	0.21 (0.11,0.41)	0.07 (<0.01,1.86)	0.05 (<0.01,0.99)	0.10 (<0.01,2.27)	0.07 (<0.01,1.60)	0.05 (<0.01,1.48)	0.35 (0.19,0.67)	**0.02 (<0.01,0.46)**	**<0.01 (<0.01,0.08)**	0.08 (<0.01,1.97)	0.13 (0.01,3.19)	0.10 (<0.01,2.34)	Placebo / BSC

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.

Class	N	k	SUCRA
Placebo / BSC	192	3	100
Paclitaxel	486	4	80
FOLFIRI + Sunitinib	45	1	80
Docetaxel / Irinotecan	126	1	70
Olaparib + Paclitaxel	324	2	60
Irinotecan	486	6	60
Irinotecan + Cisplatin	148	2	50
Irinotecan + mFOLFIRI	30	1	50
S-1+ Irinotecan	153	1	40
Fluoropyrimidine	49	1	40
Docetaxel + Fluoropyrimidine	23	2	40
Docetaxel	178	5	20
Docetaxel + Cisplatin	24	2	20
Docetaxel + Oxaliplatin	25	1	0

Table 11: Indirect and direct comparisons for treatment related morbidity – diarrhoea

Docetaxel		**7.99 (1.04,61.24)**			0.31 (0.01,7.26)			
15.45 (0.69,345)	**Irinotecan +mFOLFIRI**	0.52 (0.05,5.40)						
7.99 (1.04,61.24)	0.52 (0.05,5.40)	**Irinotecan**	0.69 (0.27,1.77)			0.21 (0.04,1.20)	1.01 (0.06,15.91)	
5.52 (0.59,51.99)	0.36 (0.03,4.47)	0.69 (0.27,1.77)	**S-1+ Irinotecan**					
92.16 (1.05,>999)	5.96 (0.06,605)	11.53 (0.22,617)	16.69 (0.28,996)	**Fluoropyrimidine**			0.09 (<0.01,1.54)	
3.23 (0.14,75.83)	0.21 (<0.01,17.5)	0.40 (0.01,17.28)	0.59 (0.01,28.08)	0.04 (<0.01,8.34)	**Docetaxel +Oxaliplat**			
1.68 (0.11,24.47)	0.11 (0.01,2.02)	0.21 (0.04,1.20)	0.30 (0.04,2.20)	0.02 (<0.01,1.40)	0.52 (0.01,32.61)	**Irinotecan + Cisplatin**		
8.06 (0.26,249)	0.52 (0.01,19.50)	1.01 (0.06,15.91)	1.46 (0.08,26.91)	0.09 (<0.01,1.54)	2.49 (0.02,264)	4.81 (0.18,126)	**Paclitaxel**	0.34 (0.07,1.61)
2.73 (0.06,118)	0.18 (<0.01,9.12)	0.34 (0.01,8.13)	0.49 (0.02,13.49)	**0.03 (<0.01,0.78)**	0.85 (0.01,115)	1.63 (0.04,60.72)	0.34 (0.07,1.61)	**Olaparib + Paclitaxel**

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.

Class	N	k	SUCRA
Docetaxel	71	2	90
Irinotecan + Cisplatin	148	2	80
Olaparib + Paclitaxel	61	1	70
Docetaxel + Oxaliplatin	25	1	60
S-1+ Irinotecan	153	1	50
Paclitaxel	224	3	40
Irinotecan	486	6	40
Irinotecan + mFOLFIRI	30	1	30
Fluoropyrimidine	49	1	10

Table 12: Indirect and direct comparisons for treatment related morbidity – treatment related mortality

Paclitaxel		4.96 (0.24,102)		3.12 (0.13,74.80)		1.02 (0.02,50.41)
1.60 (0.02,127)	**Irinotecan +mFOLFIRI**	3.10 (0.13,73.14)	0.61 (0.01,48.73)			
4.96 (0.24,102)	3.10 (0.13,73.14)	**Irinotecan**			1.03 (0.02,51.18)	
0.98 (0.01,70.67)	0.61 (0.01,48.73)	0.20 (0.01,4.08)	**S-1+ Irinotecan**			
3.12 (0.13,74.80)	1.95 (0.01,435)	0.63 (0.01,50.61)	3.19 (0.02,659)	**Fluoropyrimidine**		
5.11 (0.04,714)	3.20 (0.02,486)	1.03 (0.02,51.18)	5.22 (0.04,731)	1.64 (<0.01,582)	**Irinotecan + Cisplatin**	
1.02 (0.02,50.41)	0.64 (<0.01,224)	0.21 (<0.01,28.6)	1.04 (<0.01,341)	0.33 (<0.01,50.0)	0.20 (<0.01,108)	**Olaparib + Paclitaxel**

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.

Class	N	k	SUCRA
Paclitaxel	224	3	70
Olaparib + Paclitaxel	61	1	60
S-1+ Irinotecan	153	1	60
Irinotecan + mFOLFIRI	30	1	50
Fluoropyrimidine	49	1	40
Irinotecan + Cisplatin	64	1	30
Irinotecan	358	2	30

Figure 9: NMA results for treatment related morbidity and mortality outcomes in comparison to paclitaxel