THE LANCET Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; published online April 15. http://dx.doi.org/10.1016/S1470-2045(13)70096-2.

Web Appendix 1: Details of Translational Analyses

Tumour content in all samples was assessed by the study pathologist (AW). Immunohistochemical tests (HER-2 and PTEN) were performed on 3µm full sections. HER2 expression was detected using the PATHWAY anti-HER2/neu (4B5) antibody on an automated immuno-stainer (Benchmark® XT Ventana, Medical Systems Inc., Tucson, AZ), according to manufacturer's instructions. A minimum of five cells showing strong reactivity were required to score IHC3+. HER2 negative was defined as 0-1+, 2+ was graded as equivocal and HER2 positive as 3+. The BenchMark® XT automated slide processing system (Ventana Medical Systems, Inc., Tucson, Arizona) was used for the BDISH assay for HER2 and centromere probe on chromosome 17 (CEP 17) DNA targets. The 20 cohesive tumour cells showing the highest gene count on each section were counted initially. A ratio of <1.8 was considered negative and >2.2 was positive. For ratios 1.8–2.2, a further 20 cells were counted, and the ratio re-calculated for 40 cells. Samples with a HER2:CEP17 ratio ≥2.0 in 40 cells were then considered positive.

PTEN expression was detected using anti-human PTEN monoclonal antibody clone 6H2.1 (Cascade Bioscience, Winchester, MA). Staining was performed according to manufacturer's instructions. Expression was semi-quantitatively scored by one pathologist blinded to the treatment arm using light microscopy. PTEN expression was classified as positive (1+, 2+ or 3+ intensity), or null (no staining) and stromal cells were used as internal positive (3+) controls. For a tumour sample to be classified as PTEN null, adjacent 3+ stained stromal cells were required. Cases where no stromal expression was detected were considered uninterpretable. Where heterogenous expression was detected, the lowest score was recorded to detect PTEN null clones.

Mutational analyses were undertaken on DNA extracted from five 10µm-thick representative sections from each biopsy specimen. Macrodissection was used to maximise tumour content if an area of higher tumour concentration was identified. Tissue was proteinase K-digested and genomic DNA column-purified using a commercially available kit (QIAamp DNA FFPE Tissue Kit, QIAGEN, Crawley, UK). After purification, DNA concentration was measured by spectrophotometry using a NanoDrop6000. DNA samples were RQ-PCR amplified using primers/probes for exon four of KRAS.

Details of the primers used for BRAF, KRAS and PIK3CA are displayed in table 1 below. Analysis of the seven most commonly found mutations in codons 12 and 13 of the KRAS gene was performed using genomic DNA in a real time PCR assay from a commercially available kit (Therascreen K-RAS kit, QIAGEN). The limit of sensitivity for the Therascreen KRAS kit is 1% tumour content. Rare codon 12 and 13 mutations and codon 61 mutations are not detected. Analysis of mutations in exon 15 of BRAF was performed by PCR amplification followed by capillary electrophoresis-single strand conformation analysis (CE-SSCA). This method detects V600E, D, K, R, M and E2, as well as mutations in codons 599 and 601. Analysis for mutations in exons 9 and 20 of PIK3CA was conducted using CE-SSCA followed by direct sequencing of the mutated PCR products.

PRIMER NAME	PRIMER SEQUENCE
KRAS c12/13-Fw	GTTGTAAAACGACGGCCAGTGACTGAATATAAACTTGTGG
KRAS c12/13-Rv	CACAGGAAACAGCTATGACCCTATTGTTGGATCATATTCG
KRAS c61-Fw	GTTGTAAAACGACGGCCAGTAATTGATGGAGAAACCTGTCTCTT
KRAS c61-Rv	CACAGGAAACAGCTATGACCTCCTCATGTACTGGTCCCTCATT
PIK3CA x9-Fw	GTTGTAAAACGACGGCCAGTACAGCTCAAAGCAATTTCTACACG
PIK3CA x9-Rv	CACAGGAAACAGCTATGACCACCTGTGACTCCATAGAAAATCTTT
PIK3CA x20-Fw	GTTGTAAAACGACGGCCAGTCAAGAGGCTTTGGAGTATTTCA
PIK3CA x20-Rv	CACAGGAAACAGCTATGACCCAATCCATTTTTGTTGTCCA
BRAF-Fw	CTACTGTTTTCCTTTACTTACTACACCTCAGA
BRAF-Rv	ATCCAGACAACTGTTCAAACTGATG

Supplementary table 1 – Primers used to sequence for mutations in KRAS, BRAF and PIK3CA genes.

Web Appendix 2: Advice Regarding Dose Modifications (Adapted from the REAL-3 Trial Protocol)

Panitumumab Dosage Adjustments
For patients who experience toxicities while on study, one or more doses of panitumumab may need to be withheld, reduced, or delayed (administered at > 21 day intervals). On resolution of toxicity, a limited number of attempts to re-escalate reduced panitumumab doses will be allowed (outlined in Figure 1). Dose escalations above 9.0 mg/kg starting dose are not allowed. Panitumumab dose reductions are listed in **Table 1**.

Table 1: Panitumumab Dose Reductions			
	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg (dose levels -1, 0, 1, 2)	9	7.2	5.4

Criteria for Withholding a Dose of Panitumumab
Skin- or nail-related toxicities:

- Symptomatic skin- or nail-related toxicity requiring narcotics, systemic steroids, or felt to be intolerable by the subject.
- Skin or nail infection requiring IV antibiotic or IV antifungal treatment.
- Need for surgical debridement.
- Any skin- or nail-related serious adverse event.

Non-skin- or nail-related toxicities:

- Treatment should be interrupted for any grade 3 or 4 toxicity present on the day of treatment and the algorithm in figure 1. should be followed, unless it can be corrected:
- Patients that experience grade 3 diarrhoea should have the next dose of panitumumab omitted unless the diarrhoea has settled to ≤ Grade 1 or returned to baseline. If no diarrhoea is present on day 1 of the next cycle, panitumumab may be administered with a 20% dose reduction.
- Grade 4 or recurrent grade 3 diarrhoea should be discussed with the Chief Investigator (CI)

Potentially correctable toxicities:

- Panitumumab will be withheld only for symptomatic hypomagnesaemia and/or hypocalcaemia that persists despite aggressive magnesium and/or calcium replacement.
- Panitumumab will be withheld for grade ≥ 3 anaemia only if it cannot be managed by treatment delay for transfusion(s) or cytokine therapy.
- If the above abnormalities can be fully corrected on the day that treatment is due, it may still be given, rather than omitting the dose.

Criteria for Re-treatment with Panitumumab
Skin- or nail-related toxicities:
Panitumumab administration may be restarted once:

- The adverse event has improved to ≤ Grade 2 or returned to baseline, or;
- The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or,
- Systemic steroids are no longer required, or
- IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:
Panitumumab administration may be restarted once the adverse event has improved to ≤ Grade 1 or returned to baseline. After grade 3 diarrhoea, panitumumab may be restarted with a 20% dose reduction once the diarrhoea has resolved to ≤ Grade 1 or returned to baseline. Recurrent grade 3 or grade 4 diarrhoea should be discussed with the CI.

Dose Modification Schedule
Patients should be assessed for toxicity before each treatment cycle. For patients randomised to receive panitumumab, dose modification should be performed according to the schedule described below and outlined in Figure 1.

Patients who develop a toxicity that does not meet the criteria for withholding a dose of panitumumab should continue to receive panitumumab and their symptoms should be treated.
Panitumumab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with panitumumab.

For patients who experience a toxicity that meets the criteria for withholding a dose of panitumumab:

- Patients receiving either 100% or 80% of the starting dose of panitumumab are allowed to have up to 2 subsequent doses withheld for toxicity. However a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.
- Patients treated at the 100% dose level, whose toxicity resolves after 1 dose of panitumumab is withheld, should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).
- If toxicity recurs, patients treated at the 100% dose or 80% dose should be restarted at the 80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of panitumumab.
- Patients treated at the 100% dose level whose toxicity resolves only after 2 subsequent doses of panitumumab are withheld should be re-started at the 80% dose level.
- Patients treated at the 80% dose level whose toxicity resolves after withholding 1 or 2 doses of panitumumab should be re-started at the 60% dose level.
- Patients who experience toxicity at the 60% dose level will not be re-treated with panitumumab.

It is recommended that panitumumab doses will be escalated in patients whose toxicity resolves to the degree that meets the criteria for re-starting a dose of panitumumab. Dose escalations are recommended but not required. Dose escalations should occur in the following manner:

- Patients treated at the 80% dose level whose toxicity does not recur should receive the 100% dose level at the next cycle unless a previous attempt to re-escalate to the 100% dose level was not tolerated (re-initiation of the 80% dose is allowed as an alternative to dose escalation).
- Patients treated at the 60% dose level whose toxicity does not recur should receive the 80% dose at the next cycle unless a previous attempt to re-escalate to the 80% dose level was not tolerated (re-initiation of the 60% dose is allowed as an alternative to dose escalation).

Patients, who must have a delay of panitumumab administration beyond 9 weeks from the previous dose of panitumumab (i.e., 3 or more consecutively missed doses) due to toxicity, will be considered unable to tolerate panitumumab and will not be retreated with panitumumab.

If a subject demonstrates a clinical benefit with a documented response of stable disease, partial response or complete response and there are reasons that the above dose modification rules can not be implemented, the investigator should contact and discuss these reasons with the chief investigator. The investigator must obtain written agreement from chief investigator before any changes in the dose modification rules can be implemented.

Panitumumab Delayed- or Missed-Doses
Panitumumab should be given on the first day of each chemotherapy cycle. If a cycle of chemotherapy is delayed, panitumumab administration should also be delayed. If the subsequent cycle of chemotherapy is also delayed, with greater than 9 weeks from the previous dose of chemotherapy, and the subject has not had disease progression, panitumumab monotherapy should be administered as soon as possible. Delays of panitumumab administration greater than 9 weeks from the previous dose of panitumumab for reasons other than panitumumab toxicity are not allowed.
Reasons to withhold a dose of panitumumab are described above. If a subject is able to receive a cycle of EOX but panitumumab must be withheld due to toxicity, EOX should be administered, and this dose of panitumumab will be considered missed. For all patients, delays of panitumumab administration beyond 9 weeks from the previous dose of panitumumab (i.e., 3 or more consecutively missed doses) are not allowed and panitumumab therapy will be permanently discontinued. Missed panitumumab doses will not be made up.

Electrolyte management
As panitumumab has been associated with hypomagnesaemia, it is important to monitor serum biochemistry during study treatment, especially serum magnesium and calcium levels. Serum biochemistry assessments should be performed at the start of each cycle of study treatment and should also be performed if clinical symptoms suggestive of electrolyte abnormalities occur (such as seizures or clinically significant lethargy). Hypomagnesaemia or other electrolyte abnormalities should be

managed according to institutional practice either by oral and/or parenteral replacement. Serum potassium and calcium levels should be monitored carefully in patients who are hypomagnesaemic. It is recommended that serum magnesium, calcium and potassium levels are maintained within normal ranges during study treatment.

Skin toxicity management

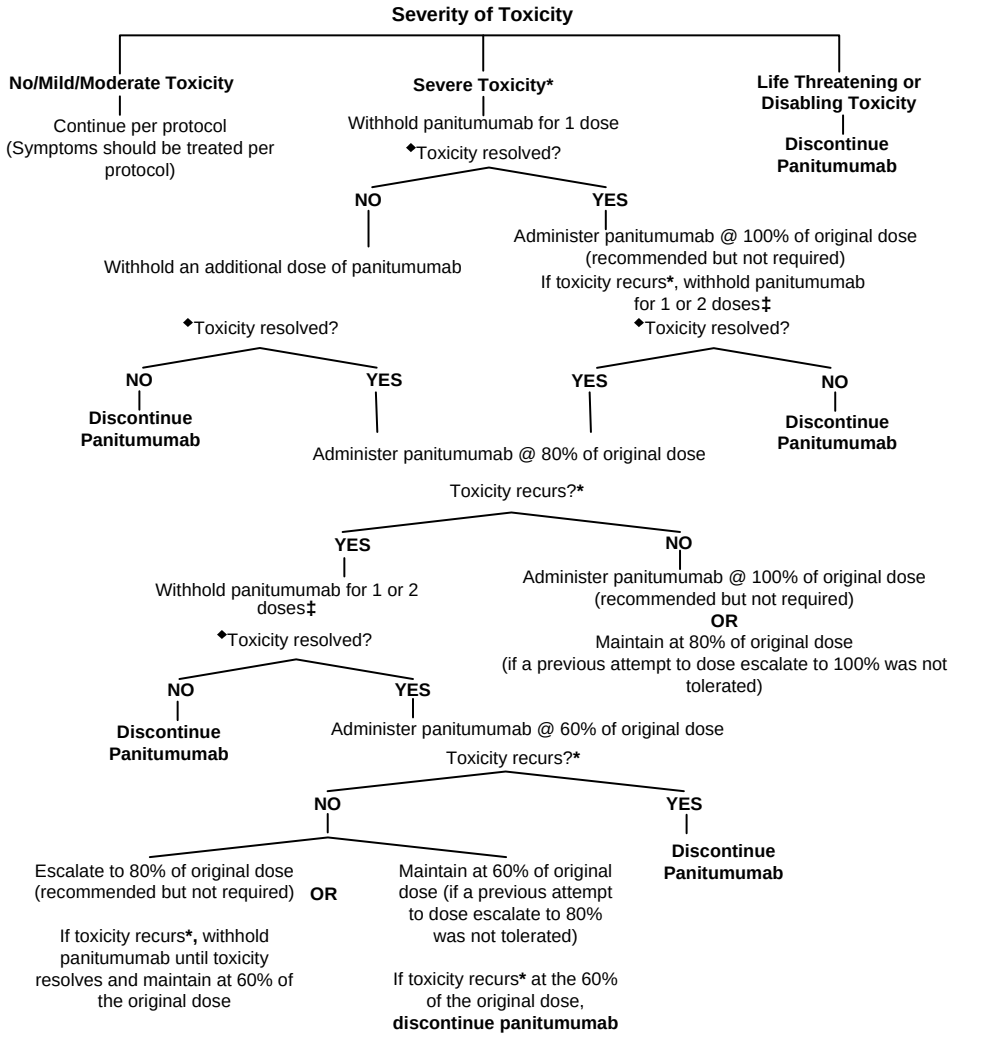
All patients should use topical emollients at least daily. Skin toxicity may be managed according to usual local practice, including the use of topical steroids, topical and systemic antibiotics as clinically indicated.

Oral and topical antibiotics (e.g lymecycline 408mg od or doxycyline 100mg bd plus clindamycin 1% lotion bd) are recommended for all patients with grade 2-3 rash.

In patients developing grade 2-3 rash who are already receiving prophylactic oral antibiotics, the dose should be increased (e.g lymecycline 408mg increased to bd, doxycline increased to 200mg bd).

Patients with grade 4 (or persistent grade 3) rash should be reviewed by a dermatologist.

Figure 1. Panitumumab Dose Modification Algorithm for Toxicity.



***** Assess toxicity before each cycle. Toxicity recurs = meets the criteria for withholding a dose of panitumumab at any time during the study (See Section 6.0.6.1).

◆ Assess toxicity before each cycle. Toxicity resolved = meets the criteria for restarting panitumumab (see section 6.0.6.2). Subjects from whom > 2 subsequent cycles of panitumumab are required to be withheld should not be re-treated with panitumumab.

‡ Up to 2 subsequent doses of panitumumab may be withheld but panitumumab may not be withheld longer than 9 weeks from the previous dose. The second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.

EOX chemotherapy dosage adjustments
Please note that if the dose of capecitabine is stopped for any reason, the doses are omitted, not delayed. Capecitabine treatment should stop at day 21 of each cycle rather than continuing until all tablets have been taken.

Dihydropyrimidine dehydrogenase deficiency
With any 5FU regimen, the occasional patient is encountered (approximately 1-3%) who has markedly exaggerated toxicity due to reduced 5FU catabolism. If this occurs, await full recovery and then re-start capecitabine at a 50% reduction.

Neutropenia with infection/fever
If at any time during the previous cycle, infection/fever associated with neutropenia has occurred e.g.:

- CTC AE grade 3 (neutrophil count $<1.0x10^9/l$), delay all chemotherapy until neutrophil count recovers to $\geq 1.0x10^9/l$, then dose reduce epirubicin by 25%. Oxaliplatin should also be reduced to $100mg/m^2$ on subsequent cycles (Arm A) or to $80mg/m^2$ for patients starting on a dose of $100mg/m^2$ (Arm B). Capecitabine can be restarted at full dose following resolution of the episode.
- CTC AE grade 4, (neutrophil count $<0.5x10^9/l$), delay all chemotherapy until neutrophil count recovers then dose reduce epirubicin by 50%. Oxaliplatin should also be reduced to $100mg/m^2$ (Arm A) or to $80mg/m^2$ (Arm B) on subsequent cycles. Capecitabine can be restarted at full dose following resolution of the episode.
- Dose reductions for epirubicin relate to percentage reductions of the initial dose from the dose of the previous cycle (ie. first dose reduction: administer 75% of initial dose; second dose reduction: administer 50% of initial dose; third dose reduction: administer 25% of initial dose) and should be maintained in subsequent cycles.
- Growth factors such as G-CSF may be used as per local practice for treatment or secondary prevention of myelosupression.

Haematological toxicity without infection/fever
Check FBC on day 1 of (or up to 3 days before) each cycle.
If neutropenia or thrombocytopenia or both (in the absence of infection/fever) is present on the day treatment is due, delay treatment until neutrophil count recovers to $\geq 1.0 \times 10^9/l$ and platelet count recovers to $\geq 75 \times 10^9/l$, then dose reduce as indicated in **tables 2 and 3**. Dose reductions related to epirubicin refer to percentage reductions of the initial dose from the dose of the previous cycle (ie. first dose reduction: administer 75% of initial dose; second dose reduction: administer 50% of initial dose; third dose reduction: administer 25% of initial dose) and should apply to all subsequent cycles. Please note that the greatest reduction for toxicity should be followed.
If anaemia ≥ Grade 3 is present on the day that treatment is due, the patient should receive a blood transfusion and/or cytokines and all treatment should be withheld (for a maximum of 1 week), until anaemia is corrected to ≤ Grade 2. Anaemia < Grade 3 on the day of treatment may be corrected by transfusion or cytokines after the administration of treatment, at the investigator's discretion. No dose reduction is necessary.
Significant or persistent anaemia that is not consistent with chemotherapy-induced myelosuppression should be investigated appropriately.

Table 2: Dose modifications for EOX based on neutrophil count (on day of treatment)

Neutrophil count ($x10^9/l$)	CTC AE grade	Action
≥1.0	0-2	Full dose of all drugs
≥0.5-<1.0	3	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Reduce epirubicin by 25%. Reduce oxaliplatin to $100mg/m^2$ (Arm A) or to $80mg/m^2$ (Arm B).
<0.5	4	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose.

		Reduce epirubicin by 50%. Reduce oxaliplatin to 100mg/m^2 (Arm A) or to 80mg/m^2 (Arm B). .

Table 3: Dose modifications for EOX based on platelet count (on day of treatment)

Platelet count (x10^9/l)	CTC AE grade	Action
≥75	0-1	Full dose of all drugs
50-74	2	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Reduce epirubicin by 25%. Reduce oxaliplatin to 100mg/m^2. (Arm A) or to 80mg/m^2 (Arm B).
25-49	3	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Reduce epirubicin by 50%. Reduce oxaliplatin to 100mg/m^2 (Arm A) or to 80mg/m^2 (Arm B).
<25	4	Stop capecitabine and delay oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Cease epirubicin. Reduce oxaliplatin to100mg/m^2 (Arm A) or to 80mg/m^2 (Arm B).

Cardiac toxicity

- Cardiac failure: Any patient who develops cardiac failure while on treatment should permanently discontinue epirubicin.
- Fluoropyrimidine-related chest pain: Fluoropyrimidines (e.g. capecitabine) are known to rarely cause a syndrome of angina like chest pain, which is thought to relate to coronary artery spasm.
- If patients develop angina like pain whilst receiving capecitabine, then treatment should be discontinued immediately pending further clinical assessment.
- If chest pain is deemed to be capecitabine related, patients should not recommence treatment with capecitabine. The Chief Investigator or study clinical co-coordinator should be contacted via the trials unit to discuss suitable alternatives.

Liver Toxicity

- Bilirubin: If bilirubin increases to >1.5xULN (upper limit of normal range), epirubicin should be omitted until bilirubin returns to acceptable levels i.e. ≤1.5xULN.
- Raised transaminases: Capecitabine undergoes hepatic metabolism. Patients on capecitabine may have temporary treatment-related elevation of transaminases. An isolated rise in transaminase above 5xULN during treatment is likely to be treatment-related, and capecitabine should be interrupted until recovery i.e. ≤2.5xULN.

Renal Toxicity

- Creatinine clearance should be calculated or measured at baseline and prior to each cycle of chemotherapy. Calculations can be made according to local practice. If the serum creatinine is above normal, or if the calculated creatinine clearance is borderline abnormal, then creatinine clearance should be measured by 24 hour urine collection or as per local procedure. If creatinine clearance falls to less than 50mls/min during treatment then the dose of capecitabine should be reduced according to **table 4**. Epirubicin and oxaliplatin can be safely continued unless creatinine clearance falls below 30mls/minute; in which case they should be omitted until renal function recovers. Capecitabine can resume at normal dose upon recovery of renal function.

Table 4: Capecitabine dose modifications for EOX

Creatinine Clearance (mls/min)	Capecitabine dose
≥50	100%
30-49	75%
<30	Omit capecitabine

Neurotoxicity

Guidance for dose reductions of oxaliplatin for neurotoxicity are displayed in **table 5**. If oxaliplatin is ceased due to neurotoxicity, carboplatin at a dose of AUC5, based on calculated or measured GFR, may be substituted at the discretion of the investigator. If carboplatin is substituted for oxaliplatin, epirubicin should be omitted (to avoid undue myelosuppression), so that patients only receive carboplatin and capecitabine (Carbo-X). Carboplatin may be administered as per usual local procedure.

Table 5: Oxaliplatin dose modifications for neurotoxicity

Toxicity	Duration of toxicity 1-7 days	Duration of toxicity >7days	Persistent between cycles
Cold-related dysaesthesia	No reduction.	No reduction.	Withhold oxaliplatin until recovery then restart at 100mg/m^2 (Arm A) or to 80mg/m^2 (Arm B). Omit oxaliplatin if recurs.
Paraesthesia without pain	No reduction.	No reduction.	Withhold oxaliplatin until recovery then restart at 100mg/m^2 (Arm A) or to 80mg/m^2 (Arm B). Omit oxaliplatin if recurs.
Paraesthesia with pain	No reduction.	Reduce to 100mg/m^2 (Arm A) or to 80mg/m^2 (Arm B). Omit oxaliplatin if recurs.	Omit oxaliplatin.
Paraesthesia with functional impairment	No reduction.	Reduce to 100mg/m^2 (Arm A) or to 80mg/m^2 (Arm B). Omit oxaliplatin if recurs.	Omit oxaliplatin.

Plantar-Palmar erythema (PPE)

- On development of CTC AE grade 1 PPE, continue capecitabine but commence pyridoxine 50mg TDS.
- For CTC AE grade 2, stop capecitabine and commence pyridoxine 50mg TDS. On resolution of toxicity to ≤ grade 1, restart capecitabine with 15% dose reduction.
- For CTC AE grade 3, stop capecitabine and commence pyridoxine 50mg TDS. On resolution of toxicity to ≤ grade 1, restart capecitabine with 25% dose reduction.
- For recurrent CTC AE grade 3, stop capecitabine. On resolution of toxicity to ≤ grade 1, restart capecitabine with 50% dose reduction.

When capecitabine is stopped for toxicity the doses are omitted, not delayed.

Stomatitis, Diarrhoea, Nausea and Vomiting

For CTC AE grade 2-3 toxicity, stop capecitabine and administer appropriate symptomatic management (e.g. sucralfate for stomatitis, codeine phosphate for diarrhoea). If toxicity is adequately controlled with symptomatic measures alone within 2 days, then capecitabine may be restarted at 100% full dose. If toxicity persists, dose reductions as indicated in **table 6** should be made. Doses of capecitabine should be rounded to the nearest 150mg tablets. In the case of diarrhoea, if the patient is in arm B and receiving panitumumab, then **figure 1** should also be consulted for dose modifications for panitumumab.

When capecitabine is stopped for toxicity the doses are omitted, not delayed.

Additional guidance to the management of diarrhoea:

- **Grade 1-2 *without* associated complications:** Start loperamide 4mg followed by 2mg every 4 hours or after each unformed stool (max 16mg/24hours). If diarrhoea persists on loperamide for >24 hours, the patient should be reviewed by the study team and oral ciprofloxacin should be commenced (for 1 week). If diarrhoea worsens to grade 3-4 after 24 hours or persists on loperamide for >48 hours, stop loperamide and the patient should be admitted for investigation, iv fluids and consideration of sc octreotide. Prophylactic low molecular weight heparin should be considered for patients according to usual local practice, unless contraindicated,
- **Grade 3-4 diarrhoea or grade 1-2 diarrhoea *with* complications (moderate or severe abdominal pain, ≥grade 2 nausea or vomiting, decreased performance status, fever, sepsis, neutropenia, dehydration or frank bleeding):** Admit patient for investigation, iv fluids, antibiotics (such as oral ciprofloxacin), consideration of sc octreotide and prophylactic low molecular weight heparin, according to usual local practice. Co-existing febrile neutropaenia should be managed with iv antibiotics, G-CSF and prophylactic low molecular weight heparin (unless contraindicated) as per the usual local practice.

Table 6: Management of stomatitis, diarrhoea, nausea and vomiting

Incidence	CTC AE Grade 2	CTC AE Grade 3	CTC AE Grade 4
1st appearance	Interrupt treatment until resolved to grade 0-1, then continue capecitabine at same dose.	Interrupt treatment until resolved to grade 0-1, then continue capecitabine at 75% of original dose with prophylaxis where possible (Arm B; continue panitumumab at 80% of original dose for grade 3 diarrhoea only once resolved to grade ≤1)	Discontinue treatment unless Investigator considers it to be in the best interest of the patient to continue capecitabine at 50% of original dose, once toxicity has resolved to grade 0-1 (after discussion with the study Chief Investigator). (Arm B; for grade 4 diarrhoea, discuss case with CI)
2nd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1, then continue capecitabine at 75% of original dose.	Interrupt treatment until resolved to grade 0-1, then continue capecitabine at 50% of original dose. (Arm B; for recurrent grade 3 diarrhoea, discuss case with CI)	Discontinue capecitabine
3rd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1, then continue capecitabine at 50% of original dose.	Discontinue capecitabine	N/A
4th appearance of same toxicity	Discontinue treatment	N/A	N/A

Allergic Reactions
Grade 4 allergic reactions (anaphylaxis) occurring during administration of oxaliplatin should be treated according to usual local practice. Patients should not be re-challenged with oxaliplatin following a grade 4 allergic reaction.

Fatigue
Dose reductions should not usually be made for grade 3 fatigue. However, patients with persistent grade 3 fatigue, in whom disease progression has been excluded, should be discussed with the Chief Investigator.