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HTA Strategy

Medical and Product Information

06 October 2006

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Dear Mr Feinmann

Re: **Gemcitabine/paclitaxel in the treatment of Metastatic Breast Cancer Single Technology Appraisal – Eli Lilly and Company Ltd Comments**

Thank you for forwarding the Appraisal Consultation Document (ACD) on the gemcitabine plus paclitaxel combination (GT) for metastatic breast cancer (MBC) and for the opportunity to comment on the Appraisal Committee's (AC) preliminary recommendation.

Having considered the content of the ACD and the Evidence Review Group Report (ERGR), Lilly have structured a response based on the key issues which appear to have driven the appraisal committee's recommendation with regards to GT and we would urge the AC to reconsider their recommendation in light of these comments.

A summary of the key points addressed by Lilly are as follows:

- Validity of the methods employed and results produced from the economic evaluation in the Lilly Submission – the evidence presented in this response will demonstrate that the methods employed by Lilly were both valid and completely justifiable given the lack of a common comparator. Without a common comparator, it is not possible to conduct adjusted indirect comparisons and therefore statistically test for heterogeneity within the phase III randomised clinical trials (RCTs) included in within this economic evaluation.

- Clinical equipoise and the need for choice for patients and physicians in metastatic breast cancer – GT is a combination that offers less toxicities compared to other taxane-based treatments and a different toxicity profile, when compared to other National Institute for Health and Clinical Excellence (NICE) recommended combination therapies. The toxicity associated with chemotherapy has a significant impact on the life of the patient and must be taken into consideration when choosing the most appropriate therapy for that individual.

- Paclitaxel post patent procurement price – The inclusion of paclitaxel at generic price was done to reflect the real decision problem facing the NHS. If the NICE decision is based on

branded paclitaxel price only, when NHS PASA (an executive agency of the Department of Health) has stated that generic paclitaxel it is available to the NHS with a minimum of 50% reduction of the BNF list price, is questionable how useful or valid the NICE decision will be to NHS decision makers.

Overall, the clinical efficacy of GT has been established in a large randomised phase III RCT, using a comparator (paclitaxel) which is licensed, NICE approved for use in MBC and is still used in clinical practice. GT has shown statistically significant improvements in overall survival, time to documented progression of disease, and overall response rates when compared to paclitaxel.

Lilly provided NICE with a high quality submission which met the requirements of the new Single Technology Appraisal process.

The aim of this response document is to address the concerns raised in the ERGR and NICE Pre-Meeting Briefing.

- Section 1.1 will focus on the decision by Lilly to perform an unadjusted indirect comparison of the evidence.
- Section 1.2 explains the adjustments made to account for heterogeneity relating to lines of treatment. The effect of the open-label design on biasing the way in which tumour response data were recorded in the JHQG trial is explored in
- Section 1.3. and Section 1.4 addresses the concerns about differences in patient characteristics contributing to the observed variation in haematological and non-haematological adverse events.
- Section 2 considers clinical equipoise and the need for choice for patients and physicians in the treatment of MBC.
- Section 3 provides supporting information regarding the post-patent expiration price reduction.
- Publication of the GT registration trial (JHQG) is considered in Section 4.

This response document will demonstrate that there remains no valid scientific (relating to methodology), clinical or economic grounds for a decision not to approve GT for the treatment of MBC patients.

1. Validity of the methods employed, and results produced from the economic evaluation in the Lilly submission

The Eli Lilly submission to NICE used phase III RCT evidence on efficacy obtained from a complete systematic review of the literature (further supported by data provided in confidence) and a review of published economic evaluations in MBC, to inform the design of its economic evaluation.

The pivotal phase III RCT (JHQG) provided an unbiased estimate of the treatment effect of GT compared to paclitaxel (T), finding that GT improved overall survival, tumour response and time to documented progression of disease, when compared to T monotherapy.

A multi-state transitory Markov model, based on a prior model used by NICE (Cooper et al., 2003), was developed to perform the economic evaluation of GT compared to relevant comparator therapies in the metastatic setting. This model was enhanced using systematic review of the literature and incorporated the effect of treatment on overall survival, time to disease progression and importantly, the effect of a wide range of adverse events using utility values obtained from the largest and most comprehensive study performed to date in MBC performed in accordance with the NICE reference case (Narewaska et al., 2005). The utility study has since been accepted for publication in a peer reviewed journal. This is also the first economic evaluation in MBC to incorporate the impact of adverse events into the utility estimates used.

Expert clinical opinion was sought throughout the evaluation to guide the design of the model, the underlying structural assumptions and the configuration of treatment algorithms used for both the administration of chemotherapy and treatment of serious adverse events. The model reflected all relevant costs and clinically meaningful outcomes associated with the disease and its treatment. As such, it scored very highly against common check-lists for economic evaluation methods and adhered to the framework for good practice in modelling proposed by Philips et al., (2004).

1.1 Unadjusted vs. Adjusted Indirect Comparison Methods

1.1.1 There are many areas of health care where available clinical trials have not directly compared the specific treatments or regimens of interest. The submission to NICE on the use of GT for MBC is one such example. Here, the relative effectiveness of alternative interventions is compared using results from sets of studies making different treatment comparisons. However, it is not unusual that conclusions on relative efficacy end up based on indirect evidence (Glenny et al., 2005).

1.1.2 Prior to conducting the economic evaluation on the use of GT described in our submission, we consulted the recently published Health Technology Assessment (HTA) Report entitled '*Indirect comparisons of competing interventions*' (Glenny et al., 2005) for guidance on the most appropriate methodological approaches available to deal with the problem faced by Lilly of having no single common treatment linking one phase III RCT to another. Throughout the ERGR Glenny et al (2005) is the document that is referred to. The decision to perform an unadjusted indirect comparison of gemcitabine plus paclitaxel with

the relevant comparator therapies was considered appropriate and completely justifiable by Lilly. What follows is a detailed explanation as to the grounds for conducting the unadjusted indirect comparison performed.

1.1.3 In an **adjusted indirect comparison**, the comparison of the interventions of interest is adjusted by the results of their direct comparison with a common control group, partially using the strength of the RCT. Adjusted indirect comparisons can only be performed where there is a common treatment that links one clinical trial to another, such as a placebo. Glenny et al., (2005) define an **unadjusted indirect comparison** as a "naïve comparison", which is the term given to an analysis where data are pooled across treatment arms. Our submission employs this latter form of indirect comparison by using the absolute values reported for both the single trial of gemcitabine / paclitaxel treatments and the identified RCTs reporting data for the comparators, because there is no common treatment that links one RCT to another to perform an adjusted indirect comparison. *Use of* "naïve comparisons" is described as 'naïve' in the ERGR report, which is, when presented with the formal definitions used by Glenny et al., (2005), an erroneous misuse of terminology. The erroneous use of this descriptor in the ACD creates a poor impression of the economic analysis provided by Lilly and we request this statement be placed in context or removed completely.

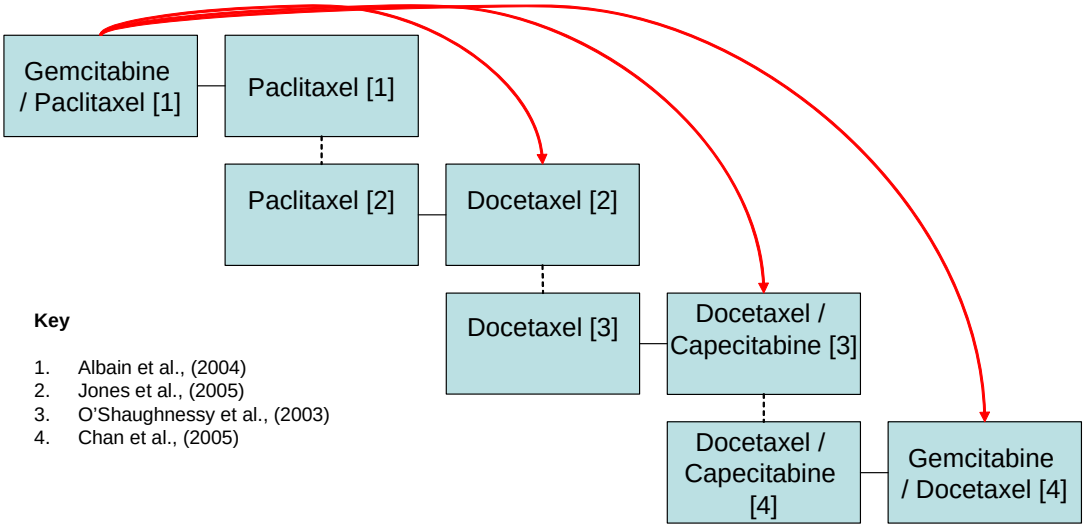
1.1.4 An unadjusted indirect comparison treats data as if they have come from a single trial and ignores the between-trial variance. To take the simplest case with no excess heterogeneity, SE^2 (θ) for a single trial of size n is σ^2. An unadjusted indirect comparison between k arms of treatment A and k arms of treatment B is equivalent to a single trial of size kn, so that SE^2 (θ) would be estimated as σ^2/k, which is half of the variance from the adjusted indirect comparisons by the method of Bucher et al., (1997).

1.1.5 There is no discussion within the ERGR of circumstances where the use of unadjusted indirect comparisons is appropriate. The HTA Report by Glenny et al., (2005) makes reference to at least eight published studies where similar problems have existed (i.e. the absence of a single common treatment that links one trial to another) yet have been successfully resolved using the same unadjusted indirect comparison performed by Lilly. These are referenced as follows: drugs used to treat menorrhagia [Coulter et al., 1997], second-line drugs in rheumatoid arthritis (Felson et al., 1990), efficacy of thromboprophylaxis following total hip replacement (Imperiale & Speroff, 1994), efficacy of therapeutic agents used in the treatment of lupus nephritis using outcomes of end-stage renal disease and total mortality (Bansal & Beto, 1997), antihypertensive agents to reduce left ventricular hypertrophy (Schmieder et al., 1996), anti-*Helicobacter pylori* regimens (Unge & Berstad, 1996), a meta analysis to evaluate the speed of healing and symptom relief in grade II-IV gastroesophageal reflux disease (Chiba et al., 1997) and finally, a review comparing the antihypertensive efficacy of available drugs in the angiotensin II antagonist (AIIA) class (Conlin et al., 2000).

1.1.6 We accept that it is not appropriate or advisable to perform an unadjusted indirect comparison where the opportunity exists to link trials via a single common comparator. Given the absence of such opportunity, every effort was made to explore alternative

approaches. Prior to performing the unadjusted indirect comparison, the feasibility of undertaking an adjusted indirect comparison was considered. Figure 1 illustrates the treatment options under consideration in our submission and how through a chain they inter-relate to one another.

Figure 1: Schematic overview of the different linkages between the direct trials



1.1.7 As is evident from Figure 1, there is not a single common treatment that links one trial to another, but instead 4 phase III RCTs that can be linked via a chain. Performing an adjusted indirect comparison in this way biases the results, as trials are selected solely on the basis that they provide linkages to the chain, irrespective of any formal inclusion criteria or relevant baseline characteristics. Adjusted indirect comparisons work on the premise that included RCTs are demonstrably homogeneous. According to Naylor (1989) and modified by Sutton et al., (1998), specific factors that may cause heterogeneity are:

1.1.7.1) Differences in inclusion and exclusion criteria;

1.1.7.2) Variability in control or treatment interventions (e.g. doses, timing, and brand);

1.1.7.3) Broader variability in management (e.g. pharmacological co-interventions, responses to intermediate outcomes including crossovers and different settings for patient care);

1.1.7.4) Differences in outcome measures, such as follow-up times, use of cause-specific mortality, etc;

1.1.7.5) Variation in analysis, especially in handling withdrawals, drop-outs, and crossovers; and

1.1.7.6) Other pertinent differences in baseline states of available patients despite identical selection criteria.

1.1.8 Points 1.1.7.2 to 1.1.7.5 were not considered cause for any concern since the descriptive data extracted on each of the included trials confirms that they are sufficiently comparable. Section 2 covers the rationale for including studies of anthracycline-naïve patients so addresses point 1.1.7.1. Given the absence of individual patient data for two of the key phase III RCTs (Jones et al., 2005; O'Shaughnessy et al., 2003) that form an integral part of this chain in Figure 1 to perform an adjusted indirect comparison, it was not possible to perform a meta-regression to investigate the extent of the heterogeneity between these two trials as far as point 1.1.7.6 is concerned (i.e. selection bias). Drs. Makris and Verill in their personal statements provided to NICE both make reference to the complexity of the disease in relation to evaluations of treatment. Even if selection bias was found not to exist between the trials included in the economic evaluation, there would still be a debate surrounding whether the trial populations reflect the heterogeneous MBC patient population.

1.1.9 In recognition of the absence of 1) a single common treatment comparator to link the trials; 2) the problem of heterogeneity with the disease *per se* (that is also reflected in the case-mix of patients included in RCTs of any treatments for MBC); 3) trials where patients receiving clearly delineated but different lines of therapy were included but where data for each were not reported separately, and 4) the inability to statistically test for heterogeneity because of both reason 1 and no access to patient-level data to undertake regression analyses, a decision was made to perform an unadjusted indirect comparison that allowed the inclusion of data from additional phase III RCTs that otherwise would have been excluded.

1.1.10 The benefits of randomisation do not hold as greatly with this approach. However, contrary to suggestions made in the ERGR, it is not appropriate to use data from observational studies in the model. Moher et al., (1996) suggest the design features of trials which affect a trial's quality and can be assessed, can be split into four areas, namely assignment, masking, patient follow-up and statistical analysis. Assignment is the single most important design feature which is why the RCT methodology is considered the most reliable method on which to assess the efficacy of treatment (Cook et al., 1992). Sutton et al., (1998) in their HTA Review entitled '*Systematic review of trials and other studies*' advise that 'it is not helpful to include evidence where the risk of bias is high, even if there is no better evidence' (page 8). Observational studies have a greater susceptibility to bias than clinical trials since treatment allocation is left to a haphazard mixture. Similarly, ascertaining that differences observed between groups of patients (in observational studies) are due to the interventions is a far harder exercise than it is in experimental studies. For this reason, we stand by our decision to use the highest quality source of evidence from randomised controlled phase III clinical trials to inform their economic evaluation.

1.1.11 Under section 4.6 of the ACD, Lilly note that the AC considered that the manufacturer's indirect estimates were inconsistent with published data (Jones et al., 2005). However, this clinical trial (also named TAX311) which started in 1994 is the only phase III open label study which directly compared docetaxel to paclitaxel within their licensed doses and represents only one trial arm of docetaxel in a pooled analysis of 8 robust phase III RCTs

and therefore cannot be considered representative of docetaxel effectiveness on its own. The sample size of this study was powered for its primary endpoint, overall tumour response. However the results of TAX311 trial did not demonstrate a statistical difference for overall tumour response, therefore the trial failed to meet its primary endpoint. Secondary endpoints included overall survival and time to disease progression which were reported as being statistically different.

1.2. Adjustments made to account for heterogeneity relating to lines of treatment

1.2.1 As explained in our submission (Page 56), the likely effect of RCTs not clearly delineating their results by line of treatment is that the median overall survival achieved by patients receiving first line metastatic treatment would be higher than for those patients receiving second-line metastatic treatment, yet data by line of treatment were combined in some trials. Therefore, an important distinction was made between those trials that included patients who were first-line following a prior anthracycline therapy (as in JHQG and current UK treatment) and those who received the therapy and had not been exposed to an anthracycline in an attempt to correct for this problem. These latter trials (Chan et al., 1999, Winer et al., 2004, Sledge et al., 2003, Extra et al., 2005) essentially reflected expected first-line metastatic survival for the therapy but are not reflective of patient population being addressed in this submission (i.e. anthracycline pre-treated, first-line metastatic breast cancer patients) or current UK practice (i.e. prior anthracycline used in the adjuvant setting). They were included to increase the survival estimates of docetaxel and paclitaxel as, in both of these therapies, RCT had been based upon mixed lines of therapy due to the fact that when the trials were conducted it was still standard UK clinical practice to give anthracyclines in the metastatic setting. The base case of the model included both types of patients and the effect of removing the studies where patients had not received anthracycline-based therapy was explored in the sensitivity analyses.

1.3. Concerns regarding Tumour Responses in JHQG

1.3.1 The open-label nature of the clinical trial is most unlikely to have biased the data reported on tumour response. The way in which tumour response was determined in the JHQG trial was by **independent assessment** which was defined as:

For measurable parameters e.g. CT/MRI Scans that have been assessed by same imaging test originally used to document disease and confirmed by repeat procedure not less than 4 weeks after response first seen.

1.3.2 Independent assessments were made by investigators blinded to treatment and the state of the patient, making this type of assessment very robust and not subject to the level of bias that might be observed with **investigator-assessed** response rates (where response can only be estimated). Typically, independent-assessment results in lower response rates being reported because this is a more accurate method of assessment, which is the main reason why most phase III clinical trials report investigator-assessed response rates. An independent assessment of time to progressive disease, progression-free survival and

overall response rate further demonstrated that there were minimal investigator biases and that the results are valid. The use of the more robust parameters in JHQG is part of the commitment of Lilly to the highest standards in clinical trials methodology.

1.4. Concerns regarding Comparative Safety Data on Haematological and Non-Haematological Events

1.4.1 The ERGR raised concerns about the way in which the incidence of adverse events varied between the trials and attributed this observation to differences in baseline characteristics that they believe will have skewed the results.

1.4.2 A rapid review of the literature has retrieved no evidence to suggest that a relationship exists between the baseline characteristics of patients and the incidence of serious (grade 3 / 4) treatment-related adverse events in MBC. Although there is anecdotal evidence among clinicians that there is a link between baseline characteristics (such as performance status, organ function) and adverse events, clinical trial design will limit this risk by inclusion of patients with good organ function and good performance status. Therefore in comparing results of different clinical trials included in our submission, the extent to which baseline characteristics may have skewed the toxicity results is questionable, particularly as it was shown that these patient baseline characteristics were comparable across the clinical trials included in our submission. The lack of patient level data from key trials included in our submission also limits the ability to assess impact of baseline characteristics toxicity by line of therapy.

Whilst it is difficult to compare trials in regards to toxicity, there should be no mistaking the fact that treatment with GT offers patients with MBC a much improved toxicity profile to the alternative approved treatments, and therefore represents a much needed and welcome alternative option of care. (see Appendix 1 which highlights the toxicity benefits of GT)

2. Clinical equipoise and the need for Choice for patients and physicians in Metastatic Breast Cancer

2.1 Current best clinical practice in England and Wales is guided, in the most part, by NICE recommendation. One of the likely causes of clinical equipoise amongst clinicians in the treatment of MBC as alluded to by both Drs. Verrill and Makris, stem from the decision by NICE to approve the chemotherapy doublet, docetaxel /capecitabine (DC) for use in MBC patients, making DC the only chemotherapy doublet licensed and positively endorsed by NICE for use in patients with anthracycline pre-treated metastatic breast cancer. The Lilly economic evaluation included DC as a comparator treatment. However concerns have been raised by clinicians that the patient-felt toxicities of DC (e.g hand/foot syndrome which leads to some patients experiencing real difficulty with walking and everyday use of their hands; lethargy/malaise; severe diarrhoea and vomiting and febrile neutropenia), limits DC use despite the high response rates and longer survival.

2.2 Therefore Lilly would like to draw the Committee's attention to the cost-effectiveness estimates of GT vs DC shown in table 1. As can be seen the GT option represents a cost-effective option, regardless of the post patent expiration price reduction for paclitaxel,

when compared to the only other NICE endorsed chemotherapy doublet i.e. capecitabine/docetaxel (DC).

Table 1. Incremental Cost-Effectiveness Ratios of GT vs. DC

ICERs	GT	DC
Without paclitaxel post patent expiration price reduction		
Cost per QALY	£23,152	reference
Cost per LY	£14,484	reference
With paclitaxel post patent expiration price reduction		
Cost per QALY	£8,276	Reference
Cost per LY	£5,178	Reference

2.3 Although there is no direct comparison from GT to DC, the advantages of the GT combination is that it offers fewer toxicities compared to other taxane-based treatments, a different toxicity profile to DC (Appendix 1), and paclitaxel is available as a generic preparation so cost of paclitaxel will typically continue to decrease. This makes GT a cost-effective combination option.

2.4 The Committee heard from the clinical specialists that 'GT would be valued as an option in a group of patients who required higher efficacy than could be achieved with a single taxane agent (for example in patients with visceral metastasis) and who were also considered fit enough to receive combination therapy' and that GT 'would probably be used as an alternative option to the combination of docetaxel plus capecitabine because it is considered to be equally effective, but with less toxicity'. For those patients, who may still be leading a relatively active life, the clinician may wish to treat using a combination treatment that has less impact on the patient in terms of toxicity.

2.5 Appendix 1 provides a summary of the grade 3 and 4 adverse events (AEs) reported in the clinical trials for the comparators selected in the Lilly submission. It also provides a description of these AEs and the impact on the patient. Gemcitabine / paclitaxel offers patients an alternative treatment that produces similar efficacy benefits to docetaxel/capecitabine but with fewer toxicities and different toxicity profile, which meets the objectives of treatment for MBC, which are to delay disease progression and maintain an acceptable quality of life to patients.

3. Paclitaxel post patent expiration price reduction

3.1 In section 4.7 of the ACD, the Committee has made the following comment regarding the price of paclitaxel:

'The duration of any procurement discounts is unknown and the Committee was not persuaded that negotiated procurement discounts would be universally available within the NHS in England and Wales'

3.2 Lilly provided a letter from NHS PASA (an executive agency of the Department of Health) that stated there is a procurement discount of "between 50% and 60% from the British National Formulary list price for all presentations of paclitaxel". It is surprising that NICE do not consider a DoH source to provide sufficient evidence regarding the price of generic paclitaxel. Paclitaxel at generic price was included in the model to reflect the real decision problem facing the NHS. If the NICE decision is based on branded paclitaxel price only, when the DoH agency has stated that it is available to the NHS at least 50% reduction of this price, it is questionable how useful or valid the NICE decision will be to NHS decision makers. At present NHS PASA has negotiated a new even lower price that will be available across NHS trusts in England from November 2006. Lilly would urge NICE to contact NHS PASA and Welsh Health Supplies to obtain further assurance regarding the cost of paclitaxel to the NHS.

3.3 In the ACD, generic paclitaxel is listed as being more expensive than branded paclitaxel (Taxol ®) i.e. The 25ml vial generic price at £561 vs the branded Taxol ® price for the same vial at £521. This is highly unlikely to reflect the reality in the NHS today as generic paclitaxel will be increasingly discounted, as stated by the NHS PASA reference letter provided in our submission.

4. Publication of GT registration trial (JHQG)

4.1 The manuscript of the GT registration trial (JHQG) will be submitted imminently to a clinical peer reviewed journal. Lilly are providing, with this response, an academic-in-confidence copy of the draft manuscript for the appraisal committee's information.

Conclusion

In conclusion, Lilly have set out to address the principal grounds for concern raised by the ERG on our submission, which appear to relate, in the most part, to our decision to employ an unadjusted indirect comparison of the available evidence and further concerns about the way in which tumour response was recorded in the JHQG trial and equipoise amongst clinicians surrounding current best practice.

Based on this response, we have demonstrated the following:

- The methodological approach used to assess the available evidence on taxane-based treatments in MBC is valid and justifiable. We would be interested to hear how ERG would propose to conduct an adjusted indirect comparison given the lack of a common comparator, inability to adjust or statistically test for heterogeneity without patient level data for key trials included in our submission.
- Patient and physician choice are important aspects which the appraisal committee should take into account, considering the significant impact chemotherapy-associated toxicity has on a patient's life, and the lack of choice for physicians with regards to NICE-recommended combination treatments for MBC. GT is a combination option which is considered equally effective but with fewer toxicities and different toxicity profile than the only other NICE recommended doublet.

- Paclitaxel at generic price was incorporated to reflect the real decision problem facing the NHS. If the NICE decision is based on branded paclitaxel price only, when a DoH agency has stated that it is available to the NHS with a minimum of 50% reduction of the BNF list price, it is questionable how useful or valid the NICE decision will be to NHS decision makers.

We trust that we have fully addressed all the concerns raised in the ERGR and the ACD. On this basis we believe there should be no scientific; clinical or economic grounds, for gemcitabine / paclitaxel in metastatic breast cancer, not to be approved by NICE.

Yours sincerely

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Table 1: Comparative Safety Data on Serious Adverse Events for the comparator clinical trials

Toxicity	Jones et al 2003		O'Shaughnessy et al 2002		Study JHQG	
	Docetaxel Monotherapy (n=222)	Paclitaxel Monotherapy (n=222)	Capecitabine + Docetaxel (n=251)	Docetaxel Monotherapy (n=255)	Gemcitabine + Paclitaxel (n=262)	Paclitaxel Monotherapy (n=259)
	Grades 3 & 4	Grades 3 & 4	Grades 3 & 4	Grades 3 & 4	Grades 3 & 4	Grades 3 & 4
Neutropenia	93%	55%	63.40%	72.20%	48.4%*	10.80%
Febrile Neutropenia	15%	2%	16%	21%	5%*	2%
Leukopenia	NR	NR	61%	75%	10.6%*	1.50%
Anemia	10%	7%	10%	5%	6.8%*	2.30%
Thrombocytopenia	5%	3%	2.80%	2.80%	5.7%*	0%
Nausea	5	3	6	2	1.10	1.50
Vomiting	3	0	5	2	1.90	1.90
Diarrhoea	5	1	14.40	5	3	1.90
Stomatitis/Mucositis	11	0	17.40	5	1.50	0.80
Hand Foot Syndrome	NR		21	1	0	0
Asthenia	21	5	4	6	0	0.4*
Infection	10	2	NR		0.80	0.80
Motor Neuropathy	5	2	NR		2.70	0.80
Sensory Neuropathy	7	4	NR		5.70	3.50
Peripheral Odema	7	1	NR		0.40	0
Dyspnoea	NR		NR		1.90	0
Fatigue	NR		4	6	6.5**	1.60