COMPARISON OF RENAL TOXICITIES WITH LY231514 600MG/M²
VERSUS 500MG/M² IN THE TREATMENT OF STAGE III OR -IV
CERVICAL CANCER

A. Carstens (B.Pharm)

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Project Leader: Mrs Rina Meyer
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ABSTRACT

Cervical cancer is the most common cancer diagnosed in females in South Africa and constitutes 16.47% of all cancers registered. LY231514, a new multi-targeted antifolate, is a potent in vitro inhibitor of thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT). Anti-tumour activity has also been seen in vivo and preliminary results from Phase II clinical trials suggest that the drug has activity against a range of solid tumours. In this thesis, data from study H3E-MC-JMAM, sponsored by Eli Lilly & Company, was analysed and conclusions made upon results obtained. Twenty-four patients with advanced carcinoma of the cervix were treated with 600mg/m² LY231514, and eleven patients with 500mg/m². Patients who were entered into the study had advanced squamous cell carcinoma Stage III or -IV disease. The patients receiving 500mg/m² LY231514 were also given oral folic acid (5mg) supplementation for 2 days prior to treatment, on the day of treatment and also daily thereafter for 2 days. LY231514 was given as a 10-minute infusion every 21 days. A patient's treatment could be delayed or reduced according to the Common Toxicity Criteria results from the previous cycle. Twelve patients (50%) on the 600mg/m² regime were withdrawn from the study due to decreased creatinine clearance thus preventing further administration of the drug. In an attempt to reduce the incidence of renal toxicity, but without compromising response, the dosage of LY231514 was reduced to 500mg/m². On this new regime, only one patient out of 11 (9%) had to be discontinued from study due to a decreased creatinine clearance.

The initiative to do an analysis between the two specific patient treatment groups came to me as a result of my involvement as clinical research associate in study H3E-MC-JMAM sponsored by Eli Lilly & Company. This study was conducted to evaluate difference in response between the two treatment groups, as well as to establish a safe dosage regime. During this study I made the observation that certain patients developed a decrease in their creatinine clearance mostly during the second and third treatment cycle. I came to the conclusion that LY231514 had an influence on the renal function of the patient as observed by an extended increase in their creatinine clearance and subsequent removal from study as study drug had to be withheld for an extended period of time. Patients thus could not receive optimal treatment for their disease as 90% of LY231514 is excreted via the kidneys and decreased renal function increased the risk of toxic accumulation of the drug. I decided to investigate the possible factors responsible for the decrease in renal function while placing special emphasis on the differences seen between the 500mg/m² and 600mg/m² treatment.
groups. Another motivational factor to do this analysis was the fact that this phenomenon were not seen in other studies conducted with LY231514, definitely not in such a way that patients had to be discontinued from study due to renal toxicity.

Patients enrolled into study H3E-MC-JMAM signed an Informed Consent Document (Attachment I) before any study procedures were carried out. Eli Lilly & Company gave permission (Attachment II) to use the patient data to perform the analysis for this thesis. The two investigator sites participating in this study included Groote Schuur Hospital in Cape Town and National Hospital in Bloemfontein.

At the time of submission, the study used for the data analysis in this thesis, study H3E-MC-JMAM sponsored by Eli Lilly and Company, had ongoing patients. Eli Lilly and Company will release their final study results after all patients have been discontinued and the final statistical analysis report has been generated.
OPSOMMING

Karsinoom van die serviks is die mees algemene karsinoom gediagnoseer in vroue in Suid-Afrika en dra by tot 16.47% van alle geregistreerde karsinome. LY231514 is ‘n nuwe meerdoelige anti-folaat wat in vitro inhiberende aktwiteit teenoor timidilaat sintetase (TS), dihidrofolaat reduktase (DHFR) en glisienamied ribonukleotied formiel transferase (GARFT) getoon het. Anti-tumor aktwiteit is ook in vitro waargeneem en resultate van Fase II studies het aangedui dat die middel ook aktief is teenoor ander soliede tumore. Vir die analyse in hierdie tesis is data van studie H3E-MC-JMAM, uitgevoer deur Eli Lilly & Company, gebruik. Vyf en dertig pasiënte met gevorderde serviks karsinoom is in die studie ingesluit, waarvan vier-en-twintig 600mg/m² LY231514 en elf met 500mg/m² LY231514 behandels is. Slegs pasiënte met Klas III of -IV gevorderde plaveiselsel serviks karsinoom kon tot die studie toegelaat word. Pasiënte wat 500mg/m² LY231514 ontvang het, het ook addisionele oral foliensuur (5mg) twee dae voor behandeling, op die dag van behandeling, asook vir twee dae na behandeling ontvang. LY231514 is elke 21 dae as ‘n 10 minute intravenuese infusie toegedién. Die pasiënt se behandeling kon uitgestel of die dosering verminder word, afhankende van die toksisiteit wat tydens die 21 dae siklus ondervind is. Twaalf pasiënte (50%) op die 600mg/m² dosering moes hul deelname aan die studie staak weens ‘n verlaging in hul kreatinienopruiming en die gevolglike weerhouding van studiemiddel. In ‘n poging om die voorkoms van niertoksisiteit te verminder sonder om respons te beïnvloed, is die dosering van LY231514 verminder na 500mg/m². Slegs een pasiënt van die elf op die nuwe dosering (9%) moes van die studie onttrek weens ‘n konstante verlaagde kreatinienopruiming.

Die inisiatief om die verskil tussen die twee doseringsgroepe te analiseer is gevorm tydens die studie by die H3E-MC-JMAM by Eli Lilly & Company. Hierdie studie se doelwitte was om die verskil in respons tussen die twee doseringsgroepe aan te toon, asook om ‘n veilige doseringsregiem vas te stel. Gedurende die studie het ek tot die gevolgtrekking gekom dat sekere pasiënte ‘n verlaagde kreatinienopruiming, veral tydens die tweede en derde behandelingssiklus, ondervind het. Deur na die verlaging in kreatinienopruiming en gevolglike uitstel van behandeling en ontrekking vanuit die studie te kyk, is die gevolgtrekking gemaak dat LY231514 ‘n invloed op die renale funksie van die pasiënt moet hê. Pasiënte kon dus nie optimaal behandel word nie aangesien 90% van die middel renaal uitgeskei word en ‘n verlaging in nierfunksie die akkumulasie van die middel in die liggaam en gevolglike toksisiteit kon verhoog.
Ek het besluit om die faktore wat moontlik vir die verlaging in renale funksie verantwoordelik kon wees te ondersoek, en veral te kyk na die verskille tussen die 500mg/m² en 600mg/m² doseringgroepe. "n Ander motiveringsfaktor was die feit dat ander Fase I studies met LY231514 nie 'n sodanige verlaging in nierfunksie kon aantoon nie.

Pasiënte wat tot studie H3E-MC-JMAM toegelaat is het 'n Ingeligte Toestemmingvorm (Aanhegsel I) geteken voordat enige studie prosedures uitgevoer is. Eli Lilly & Company het ook toestemming gegee (Aanhegsel II) dat ek die data van hierdie pasiënte kon gebruik vir die analise in hierdie tesis. Die twee hospitale wat aan die studie deelgeneem het is Groote Schuur Hospitaal in Kaapstad, en Nasional Hospitaal in Bloemfontein.

Teen die tyd van publikasie van hierdie tesis was daar steeds pasiënte op studie H3E-MC-JMAM. Eli Lilly & Company sal hul finale data bekend stel sodra alle pasiënte van studie af is en die finale statistiese analise gedoen en gepubliseer is.
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Attachment I: Letter of Consent by Eli Lilly & Company

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CHAPTER 1: LITERATURE SEARCH

1.1 INCIDENCE OF CERVICAL CANCER

Introduction

Cervical carcinoma features as the most common cancer amongst women in the world, accounting for 6% of all malignancies in females (National Cancer Institute, 1998). The prognosis of this disease is markedly affected by the extent of the disease at the time of diagnosis.

1.1.2 Ethiology

Sitas et al. (1997: 621) reported that the annual incidence rate for cancer of the cervix in 1990-1991 was 26/100,000 overall and 28/100,000 for black women. The Central Statistical Services of South Africa (1991) reported 1500 deaths due to cervical cancer for 1989. In South Africa, cervical carcinoma is also the most common cancer in women with an incidence of 16.47% (Sitas et al., 1994:346). Cancer of the cervix accounts for 2.65% of all cancers in white females (Sitas et al., 1994:346) and 37.8% in black females (Michelow et al., 1999:36). One in every 21.25 black females will develop cancer of the cervix in their lifetime (0-74 years), if the current pattern were to continue (Sitas et al., 1994:346).

Table 1.1.2 Summary statistics for cancer of the cervix. National Cancer Registry, 1990-1991

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Crude</th>
<th>ASIR</th>
<th>Cumrate</th>
<th>Risk</th>
<th>Rank</th>
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<td>43.3</td>
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N = average number of cases for 1990 and 1991; % = percent of all cancers; Crude = crude incidence, per 100,000 population; ASIR = age-standardised incidence rate, per 100,000 population (world standard); Cumrate = cumulative incidence rate 0-74 years, percent; Risk = lifetime risk 0-74 years, one in x; Rank = ranking of cervical cancer, excluding basal and squamous cell skin cancers, and cancers of unknown origin.

(Sitas et al., 1997:621)

1.
During a study in an academic hospital at the University of the Orange Free State, Nel et al. (1994:18) found a statistically significant difference between black and white patients in South Africa with regard to the relative incidence of cervical intra-epithelial neoplasia (CIN), and invasive cervical cancer. They found a higher incidence of invasive cervical cancer than Stage III CIN (CIN III) in black patients, and a higher incidence of CIN III than invasive cervical cancer in white patients.

1.1.3 Age distribution
The age distribution for the incidence of cervical carcinoma is fairly similar throughout the world, with the incidence among women in their 20’s about one tenth of the incidence in women in their 30’s (Bailie, 1995). The disease generally appears in the early 20’s, with a sharp rise in incidence in the 30-40 years of age group, decreasing to a plateau at 40-60 years, followed by a decline (Bailie, 1995). Shingleton et al. (1995) found in their study that 27.4% of the patients diagnosed with squamous carcinoma of the cervix were younger than 40 years, 37.3% between 40-59 years, 29.7% between 60-79 years and 5.6% older than 79 years.

1.2 RISK FACTORS IN CERVICAL CANCER

1.2.1 General
Cervical carcinoma and the precancerous changes of the cervix are now viewed as a spectrum of sexually transmitted diseases, with the presence of the venereally transmitted Human Papilloma Virus (HPV) identified in over 90% of cases worldwide (O’Hanlan, 1997). Poor nutrition and low intake of anti-oxidant fruits and vegetables have been associated with a higher risk for developing cervical dysplasia and carcinoma. Vitamin A and folic acid levels were found to be higher in healthy controls than cervical cancer patients (O’Hanlan, 1998). Folic acid supplementation for patients on this trial will be discussed in a later section. The M.D. Anderson Cancer Center (1997) also identified other risk factors including; early age at first intercourse, multiple sexual partners, multiparity, infection with HPV, non-barrier methods of birth control, sexual contact with high risk males and smoking. In a study performed by Walker et al. (1985) in 1981 & 1982 in Soweto, Johannesburg, fifty percent of patients with cervical carcinoma died within 1.6 years of diagnosis.
This was far shorter than other periods reported such as 4.8 years in Melbourne, Australia, 4.5 years in Villejuif, France, and 5.1 years in Israel. They also found that the cervical cancer patients had their first child at an earlier age (20 years), compared to those in the control group (38.1 years). Nulliparity in the white population is reported to be protective and high parity a risk factor (Walker et al., 1985).

1.2.2 Human Papilloma Virus and cervical cancer

O'Hanlan (1997) documented that the precancerous changes of the cervix can be largely attributed to the venereally transmitted Human Papilloma Virus (HPV), identified in over 90% of cases worldwide. While the Papanicolaou Test has been confirmed as a cost-effective screening device, it is still under-utilised in most countries, including South Africa. The major risk for development of pre-invasive or invasive carcinoma of the cervix is HPV infection, which far outweighs other known risk factors such as high parity, increasing number of sexual partners, young age at first intercourse, low socio-economic status and a positive smoking history (Schiffman et al., 1993). At the moment studies are conducted to determine how HPV typing can be used to stratify women into follow-up and treatment groups.

1.3 PATHOLOGY OF CERVICAL CANCER

Squamous cell carcinomas are responsible for the majority of cases (85%), adenocarcinomas constitute 10-15%, and the rarer tumours such as small cell carcinomas, sarcomas, lymphomas and melanomas make up the rest (M.D. Anderson Cancer Center, 1997).

1.4 ROUTES OF SPREAD

Three main routes of spread have been identified for cervical cancer:
* Direct invasion of the tumour into the surrounding structures (parametrium, corpus and vagina).
* Lymphatic metastasis which are usually orderly and predictable with the parametrial-, pelvic-, common iliac- and para-aortic nodes.
1.5 PROGNOSIS OF CERVICAL CANCER

1.5.1 Influence of age
During a study conducted by Jennings et al. (1992), analysis of disease by stage revealed a significantly greater incidence of early stage disease in women younger than 35 years of age. The survival rate appeared to be lower in older patients (>35 years), however the stage of the disease had a marked effect on survival. Their study showed no significant difference between the survival rates of younger and older patients, which has also been reported by other literature such as that by Meanwell et al. (1988). A study conducted by Walker et al. (1985) established a mean age of 49.8 years for black women with invasive cancer in South Africa. This was much lower than the age reported for white patients (55 years). The highest age-specific survival rate in South Africa for all race and age groups occurs amongst the black population (65-69 years), which calculates a survival rate of 130 per 100 000 (Sitas et al., 1994). In South Africa the age standardised mortality rate for cervical cancer has been estimated to range from 3.6 of 100 000 in metropolitan Whites, to 30.2 for non-metropolitan Coloureds, and 25.7 for metropolitan Blacks. Poor data quality precluded an estimation for non-metropolitan Blacks, among which the rate would be expected to be even higher (Balie et al., 1996). It is thus clear that Coloureds and Blacks in South Africa have a high mortality associated with cervical cancer.

1.5.2 Influence of stage and metastasis
Lanciano et al. (1992), found no statistical difference between the survival of patients with Stage IA versus IB, Stage IIA versus IIB, Stage IIIA versus IIIB, and non-bulky versus bulky cervical disease. Regarding pelvic failure for Stage I, they found a difference between non-bulky and bulky cervical disease (94% versus 82% at 4 years). Regarding survival of patients with Stage IIB, the study of Lanciano et al. (1992) found a significant difference between unilateral versus bilateral parametrial involvement (70% versus 52% at 4 years). This was also seen in Stage IIIB patients with unilateral (43% at 4 years) and bilateral (27% at 4 years) sidewall involvement. For Stage I patients, the outcome is predicted by the bulk of invasive cervical disease, with which the incidence
of positive pelvic lymph nodes increases dramatically with increasing tumour bulk. For Stage IIIA and IIIB disease, the extent of pelvic disease had a significant prognostic value with respect to survival. Lower-third vaginal involvement is the least favourable pelvic extension and usually signifies high bulk disease.

Bilateral sidewall involvement is intermediate in prognosis and unilateral sidewall involvement the most favourable (Lanciano et al., 1992: 486).

O'Hanlan (1997) found that about 50% of patients with cervical cancer are cured. The following 5-year survival rates were published by the same author for the different stages of cervical disease: early small lesions are approximately 90%; Stage I patients are 75% (some Stage I cancers are large or have nodal metastasis); Stage II tumours invading the parametrium or upper vagina are 55%; tumours that have spread outward to the sidewall or ureter or down the vagina (Stage III) are 35%, and a smaller than 5% cure rate for disease that invades the bladder or rectum, or with distant spread (Stage IV).

1.6 PHARMACOLOGY OF LY231514

1.6.1 Antitumour activity and mechanism of action
LY231514 act as an antimetabolite which interferes with the manufacturing of DNA. Antimetabolites are structural analogues of normal metabolites that are required for cell function and replication.

Antimetabolites interact with cellular enzymes, stopping the cell from making the extra DNA necessary for replication. There are three ways in which antimetabolites interact with enzymes (National Cancer Institute, 1998);

- By substituting for a metabolite that is normally incorporated into a key molecule, making the key molecule function abnormally.
- By competing successfully with a normal metabolite for the occupation of the catalytic site of a key enzyme.
- By competing with a normal metabolite that acts at an enzyme regulatory site.
LY231514 is a novel pyrrolo[2,3-d] pyrimidine based antifolate currently undergoing extensive Phase II trials, of which H3E-MC-JMAM forms part. It is a new generation antifolate anti-metabolite deriving its antitumour activity from simultaneous and multiple inhibition of several key folate-requiring enzymes via its polyglutamated metabolites (Eli Lilly & Company, 1997).

As documented by Shih et al. (1997), LY231514 is one of the best-known substrates for the enzyme folylpolyglutamate synthetase. Studies have shown that the polyglutamates of LY231514 inhibit several key folate-requiring enzymes of folate metabolism, including thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycaminamide ribonucleotide formyltransferase (GARFT).

LY231514 is transported into the cells via the reduced folate carrier (RFC) and demonstrates a low affinity toward the "folate receptor" transport systems. It was discovered that the cytotoxicity of LY231514 can only be partially reversed by the addition of exogenous thymidine (5μM), and the cells can only be completely protected from the potent cytotoxic effect by the simultaneous addition of thymidine (5μM) and hypoxanthine (100μM). The combined effects of the multiple enzyme inhibition exerted by LY231514 at each target gives rise to an unusual end product reversal pattern and signature on metabolic folate and nucleotide pools, which are different from any other antifolates that have been studied so far (Eli Lilly & Company, 1997).

1.6.2 Pharmacokinetics of LY231514

A Phase I study (H3E-MC-JMAA), conducted by Eli Lilly and Company, has established a regime of 600mg/m² intravenous over 10 minutes every 21 days to be safe and effective. The Maximum Tolerated Dose (MTD) for LY231514 was established to be 600mg/m² (Eli Lilly & Company, 1997).

The pharmacokinetics of LY231514 were characterised by the weekly and every three week schedules (Eli Lilly & Company, 1997). These three Phase I studies, H3E-BP-001, H3E-MC-JMAB and H3E-MC-JMAA, were conducted for Eli Lilly & Company at the University of Texas Health Sciences Centre and associated institutions in San Antonio. The different administration schedules for the three studies were as follow: In study H3E-MC-JMAB it was weekly times 4 every 6 weeks with LY231514 administered as a 10-minute infusion with doses ranging from 10mg/m²/week to 40mg/m²/week; in study H3E-MC-JMAA, LY231514 was administered as a 10-minute infusion.
every three weeks on a schedule of 40mg/m²/week; and in study H3E-BP-001 it was daily times 5 every 3 weeks also as a 10-minute infusion.

The Cmax and AUC of LY231514 appeared to be linear from 10mg/m² to 700mg/m². Clearance of LY231514 appeared to decrease with a decrease in creatinine clearance and/or an increase in age (Eli Lilly & Company, 1997).

One patient was taking aspirin for other conditions at time of enrolment. Thereafter the patient received two cycles of treatment, one with and one without the co-administration of aspirin, while blood samples for pharmacokinetic measurements were taken. The serum concentration versus time curves for this patient suggested that the presence of aspirin could also cause a decrease in the clearance of LY231514 (Eli Lilly & Company, 1997).

Peak-plasma levels of LY231514 were reached within 30 minutes in most patients with a distribution half-life of 4-5 hours at the recommended dose for Phase II trials (600mg/m²). LY231514 reflected a small volume of distribution, reflecting the polar nature of the compound. Urine collections made in study H3E-MC-JMAA showed that up to 90% of the drug could be recovered in urine unchanged within 24 hours after administration (Eli Lilly & Company, 1997). The clearance of LY232514 is dependent upon the renal function, as assessed by measuring the creatinine clearance of each patient. This method was used as patients attended the clinic every 7 days for blood samples and serum creatinine levels were obtained and compared weekly to assess the renal function of the patient.

1.6.3 Previous toxicities documented for LY231514
In study H3E-MC-JMAA (Eli Lilly & Company, 1997), LY231514 was administered as a 10-minute infusion once every three weeks. Thirty-seven patients were entered into this study with doses ranging from 50mg/m² to 700mg/m². The Dose Limiting Toxicity (DLT) on this schedule was neutropenia with 3 out of 6 patients at 700mg/m² experiencing Common Toxicity Criteria (CTC) Grade 4 neutropenia during the first course of treatment. In addition, one patient developed CTC Grade 4 thrombocytopenia, and 3 patients had CTC Grade 3 thrombocytopenia. Twenty patients were treated with LY231514 600mg/m², including 3 patients with no prior chemotherapy for 7.
metastatic disease. CTC Grade 4 neutropenia and thrombocytopenia occurred in 5 and 1 patients respectively during the first course of treatment. Of the 3 patients with no prior chemotherapy, 1 patient developed CTC Grade 4 neutropenia during the first course of treatment. In a Phase I study conducted by McDonald et al. (1998), reversible disturbances of liver biochemistry were also observed.

Other non-haematological toxicities in study JMAA included rash, mucositis, nausea, vomiting, fatigue, anorexia, and elevations of liver transaminases. In patients who developed a rash, treatment with 4mg dexamethasone twice daily for 3 days, starting 1 day prior to treatment with LY231514, appeared to ameliorate or, in some cases, prevent the rash on subsequent cycles of therapy.

A common adverse event reported on patients who received LY231514 included reduced bone marrow function (Eli Lilly & Company, 1997). A decrease in the white blood cells increases the risk of developing an infection, a decrease in red blood cells may cause anaemia and a decrease in the platelet count may increase the risk of bruising and bleeding.

Less common adverse events reported by those receiving LY231514 included hair loss, shortness of breath, conjunctivitis (excessive watering of the eyes), and dizziness. Rare, but serious adverse events included neutropenic fever or sepsis due to low white blood cells, congestive heart failure, deterioration of kidney function or kidney failure, and possible death (Eli Lilly & Company, 1997).

### 1.6.4 Influence of folate status on incidence of toxicity with LY231514

Supplemental folic acid is clinically used to ameliorate the toxicities of antifolate agents including inhibitors of dihydrofolate reductase, glycinamide ribonucleotide formyltransferase and thymidylate synthase. The polyglutamylated forms of LY231413 are potent inhibitors of these three enzymes. LY231514 is transported into the cells mainly through the reduced folate carrier system and extensively metabolized to polyglutamated forms (Shih et al., 1997).

In a study performed by Worzalla et al. (1998), it was found that folic acid was 100- to 1000-fold less active than folinic acid at protecting cells from LY231514-induced toxicity. They demonstrated that folic acid supplementation was able to preserve the antitumour activity of LY231514 while reducing toxicity. In this study on mice, good antitumour activity was seen on both high and very 8.
low doses of folic acid in the diet. The mice were able to tolerate much higher doses of LY231514 when they were receiving higher levels of folic acid, but higher levels of LY231514 were required to produce good antitumour activity.

1.7 OTHER TREATMENTS CURRENTLY USED FOR STAGE III AND -IV CERVICAL CANCER

Antifolates in clinical use as single agents or in combination therapy in South Africa include 5-Fluorouracil (5-FU), ZD1694 (Tomudex ®) and methotrexate. 5-FU inhibits Thymidylate Synthetase (TS) and is used extensively in the treatment of gastrointestinal malignancies, colorectal-pancreatic- and gastric cancers, breast cancer and squamous carcinoma of the head and neck. Tomudex® is registered for colorectal cancer. Methotrexate, which inhibits Dihydrofolate Reductase (DHFR), is used in breast-, bladder-, head- and neck tumours, as well as childhood acute lymphoblastic leukaemia.

Stage III
Radiation: Coia et al. (1990) reported the treatment of choice to be external-beam therapy with two or more intracavitary applications. Patients with small volume para-aortic nodal disease and controllable pelvic disease may be cured with pelvic and para-aortic irradiation (National Cancer Institute, 1998). The use of high-dose-rate brachytherapy for the intracavitary portion of treatment is under clinical evaluation.

Clinical Trials: Combining radiation therapy and chemotherapy, neoadjuvant chemotherapy, altered radiation fractionation, high-dose-rate brachytherapy and template brachytherapy are ongoing.

Stage IV
Radiation: Alone or in combination with chemotherapy for palliative treatment, or treatment of distant metastases. Cisplatinum and 5-Fluorouracil have been added to radiation treatments both as sensitizers, but also to have a cytotoxic effect on distant disease. Preliminary analyses suggest that these drugs offer about a 10% improvement in survival probability (O’Hanlan, 1997). Hydroxyurea also has a proven advantage as a radiosensitizer in therapy for advanced disease (O’Hanlan, 1997).
Chemotherapy: Primary treatment for Stage IVb

- Cisplatinum - 15-25% response rate (Alberts et al., 1987; Thigpen et al., 1989)
- Ifosfamide - 31% response rate (Coleman et al., 1986)
- Paclitaxel - 17% response rate (Kudelka et al., 1996; Thigpen et al., 1995; McGuire et al., 1996)
- Irinotecan - 21% response rate for patients previously treated with chemotherapy (Verschraegen et al., 1997)
- Some trials using Navelbine® have also demonstrated some activity

Recurrent Cervical Cancer

No standard treatment is available for recurrent cervical disease that has spread beyond the confines of a radiation or surgical field. All such patients are appropriate candidates for clinical trials testing drug combinations or new anticancer agents. For locally recurrent disease, pelvic exenteration can lead to a 5-year survival rate of 32-62% in selected patients (Alberts et al., 1987).

- Recurrence in the pelvis only: Post-radical surgery and radiation in combination with chemotherapy may cure 40-50% of patients (Thomas et al., 1987).
- Chemotherapy for palliative treatment:
  
  Ifosfamide - 15-30% response rate (Coleman et al., 1986; Sutton et al., 1993)
  Paclitaxel - 17% response rate (McGuire et al., 1996).
CHAPTER 2: PROBLEM STATEMENT & OBJECTIVES

2.1 PROBLEM STATEMENT

Patients with confirmed Stage III or -IV cervical cancer who met all the entry criteria were enrolled into study H4E-MC-JMAM, sponsored by Eli Lilly and Company. In this trial, LY231514 was administered as a 10-minute intravenous infusion at a dosage of 600mg/m².

The first 24 patients that were enrolled received 600mg/m² of LY231514. They underwent measurement of their serum creatinine on Day 8 and Day 22 of the treatment cycle to detect any renal toxicity. LY231514 was administered on Day 1 of each cycle. Day 1 of the next cycle usually coincided with Day 22 of the preceding cycle, depending on whether the next treatment cycle was delayed due to toxicity or other reasons (Refer to Schedule of Events, section 3.2). If the creatinine clearance of the patient was less than 45mL/min on Day 22, or prior to the start of the next cycle, the next treatment cycle was delayed until the creatinine clearance returned to a level of at least 45mL/min, whereafter the next treatment cycle was begun. If the patient did not receive treatment for more than 42 days, she was taken off study according to the protocol guidelines. Other haematological and non-haematological values were also taken into consideration for cycle delay and ending patient participation, but in this study creatinine clearance played a major role.

Of the 24 patients enrolled on the 600mg/m² dosage regime, 6 achieved a confirmed Partial Response (PR) and 14 patients had a best response of Stable Disease (SD). Of these SD's, two (14.3%) patients who had an initial response of PR could not be confirmed as their treatment cycles had to be delayed due to a decreased creatinine clearance. According to the protocol, a PR has to be confirmed with a MRI-scan within 4-6 weeks after the first MRI showed a PR. For these unconfirmed PR's, by the time the confirmation MRI was performed, it was already more than 8 weeks since the patient had her last treatment and the confirmation MRI showed progression of disease. If it was not for the renal toxicities experienced, these patients could have had another cycle of LY231514 and the possibility of a best response of PR would have been much higher.

Apart from the influence on the response rate of the patients, the renal toxicities experienced also
caused 12 patients to be taken off study as their treatment cycles were delayed for more than 42 days, whereafter they had to be taken off study according to the protocol guidelines.

After 24 patients received 600mg/m² of LY231514 every 21 days, it was decided to amend the protocol and reduce the dosage to 500mg/m² every 21 days to try and decrease the incidence and severity of renal toxicity, and also try to establish a better response rate. Eleven patients were enrolled onto this lower dosage and their safety data was collected in the same way as for those on the 600mg/m² regime. Serum creatinine values were measured and then used to calculate the creatinine clearance according to the Modified Cockcroft and Gault Method (Section 3.11.2).

In this study, a comparison between the two dosage regimes was made, with special emphasis on renal toxicity and the influence thereof on the response rate and the wellbeing of the patient.

2.2 OBJECTIVES

2.2.1 Objectives of clinical trial H3E-MC-JMAM

Primary Objective

The primary objective of this study was to determine the response rate for patients with inoperable, locally advanced, recurrent, or metastatic cervical cancer who had been treated with LY231514.

Secondary Objectives

The secondary objectives of this study were:

- To characterise the nature of toxicity of LY231514 in this patient group.
- To assess pharmacodynamics and population pharmacokinetics of all patients treated with LY231514.
- To assess the influence of folate status on toxicity of LY231514 by measuring appropriate vitamin metabolites.
- To measure the time to event efficacy variables including:
  - survival time
  - time to progressive disease
- time to treatment failure
- duration of response for responding patients

2.2.2 Objectives of this thesis

Primary Objective
The primary objective of this thesis is to determine the frequency and duration of episodes of decreased creatinine clearance, and the influence thereof on the response rate and lives of patients with inoperable, recurrent, or metastatic cervical cancer treated with 600mg/m² versus 500mg/m² of LY231514.

Secondary Objectives
- To assess the incidence of baseline hydronephrosis in patients who received either 600mg/m² or 500mg/m² of LY231514.
- To assess the correlation between hydronephrosis and renal toxicities found with LY231514.
- To measure and compare the data found on both treatment arms regarding the time from drug administration to the first episode of renal toxicity that resulted in treatment delay.
- To measure the period of recuperation after an episode of decreased creatinine clearance, and also compare the data between the two treatment regimes.
- To determine and compare data between the two treatment regimes regarding the percentage of patients who had to be taken off study due to prolonged decreased creatinine clearance.
- To evaluate if the protocol amendment from 600mg/m² to 500mg/m² LY231514 decreased the percentage of patients who had to discontinue from study, and hence try and achieve a better overall response rate.
- To compare survival and time to treatment failure between the two treatment regimes.
CHAPTER 3: METHODOLOGY

3.1 SUMMARY OF STUDY DESIGN

Study H3E-MC-JMAM was a nonrandomized study of LY231514 in patients with inoperable, locally advanced, recurrent, or metastatic cervical cancer who had received no prior chemotherapy. LY231514 was administered as an intravenous 10-minute infusion on Day 1 of a 21-day cycle. Thirty-five patients were enrolled into this two-stage study. The study was not terminated prematurely due to a lack of efficacy or unacceptable toxicity. Subject to continual approval from Eli Lilly and Company, patients were allowed to remain on study until disease progression was noted, unacceptable toxicity occurred, the patient received a maximum of 12 cycles of therapy or the investigator or patient decided it was in their best interest to discontinue participation.

3.2 SCHEDULE OF EVENTS

Table 3.2 Schedule of Events

<table>
<thead>
<tr>
<th>Cycle</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3(etc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Day within a cycle</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Visit</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3(etc)</td>
</tr>
<tr>
<td>Relative Day</td>
<td>Baseline</td>
<td>1</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Informed consent signed</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY232514 therapy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Folic acid supplementation*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Habits</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour measurement (visual or palpable)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest x-ray*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate radiological tests (CT, MRI, etc.)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cycle</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3(etc)</td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>-------</td>
</tr>
<tr>
<td>Electrocardiogram&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X&lt;sub&gt;eff&lt;/sub&gt;</td>
<td>X</td>
</tr>
<tr>
<td>Haematology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PT/aPTT</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Pregnancy Test&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Calculated creatinine clearance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vitamin metabolites assay</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CTC grading</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetic sampling</td>
<td>X</td>
<td></td>
<td>X&lt;sub&gt;eff&lt;/sub&gt;</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: CTC-Common Toxicity Criteria

a – Prior to receiving LY231514
b – Repeat as clinically indicated
c – In patients of childbearing potential
d – Pre-dose PK sampling
e – May be drawn up to 72 hours prior to the next scheduled dose.
f – If the site plans to use the local serum creatinine to calculate creatinine clearance for dose adjustments, then a sample must be drawn at baseline and prior to each cycle.
g – Folic acid supplementation will occur on the 2 days prior to, the day of, and 2 days following administration of LY231514. On the day of LY231514 administration, folic acid should not be taken until after blood has been drawn for the vitamin metabolite assay.

→ Monitor for toxicity using CTC from the time LY231514 infusion begins until next infusion starts. Repeat Cycles 2 and 3, respectively for Cycles 4 – 12 (Note: pk sampling will be drawn in Cycles 1 and 3 only. Tumour measurement is repeated every other cycle.)

### 3.3 CRITERIA FOR ENROLMENT

#### 3.3.1 Inclusion criteria

Patients were included in the study if they met all the following criteria:

[1] Histological or cytological diagnoses of squamous cell carcinoma of the cervix with Stage III or -IV disease. Lesions could not be amendable to surgery or radiation of a curative intent.

No prior radiation therapy. (Exception: Patients with Stage IV disease and pelvic radiotherapy with measurable lesions outside the pelvis may have had prior radiotherapy if it was completed at least 6 weeks prior to study enrolment.)

Performance status of 0 to 2 on the World Health Organisation (WHO) scale.

Disease status had to be that of measurable disease defined as:
Bidimensionally-measurable lesions with clearly defined margins by any of the following:
- medical photograph (skin or oral lesions), or plain x-ray, with at least one diameter 0.5cm or greater (bone lesions not included)
- CT, MRI, or other imaging scan, with both diameters greater than the distance between cuts of the imaging study
- palpation, with both diameters 2 cm or greater.

Estimated life expectancy of at least 12 weeks.

Patient compliance and geographic proximity that allowed adequate follow-up.

Adequate bone marrow reserve: white blood cell (WBC) count ≥3.5 x 10⁹/L, platelets ≥100 x 10⁹/L, haemoglobin ≥9 g/dL, absolute granulocyte count (AGC) >2.0 x 10⁹/L.

Written informed consent from the patient.

Patients at least 18 years of age.

Women of childbearing potential had to take medically approved contraceptive precautions during the trial and for 3 months afterwards.

### Exclusion criteria

Patients were excluded from the study for any of the following reasons:

- Active infection.
- Any CNS metastasis requiring steroid therapy excluded the patient.
- Inadequate liver function (bilirubin >1.5 times above normal range); abnormal prothrombin time (PT) or activated partial thromboplastin time (aPTT) greater than 1.5 times control; alanine transaminase (ALT) or aspartate transaminase (AST) greater than 3 times normal (ALT and AST could be elevated to 5 times normal in patients with known metastatic disease in the liver).
- Calculated creatinine clearance <45 ml/min calculated by the central laboratory.
Presence of clinically detectable third space fluid collections, for example ascites or effusions.

Pregnancy

Breast-feeding

Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator).

Second primary malignancy (except adequately treated basal cell carcinoma of the skin or other malignancy treated at least 5 years previously with no evidence of recurrence).

Use of any investigational agent 30 days before enrolment into the study.

3.3.3 WHO performance status

Only patients with a Performance Status of 0 to 2 on the WHO scale could be enrolled into study H3E-MC-JMAM.

Table 3.3.3 World Health Organisation (WHO) Performance Scale

<table>
<thead>
<tr>
<th>Activity Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic, fully active, and able to carry on all predisease performance without restrictions</td>
</tr>
<tr>
<td>1</td>
<td>Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, eg. light housework, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of the day.</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bedridden.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally bedridden.</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
3.4 DISEASE DIAGNOSTIC PROCEDURES

Patients had to have a histological or cytological diagnosis of Stage III or -IV cervical cancer, as staged by the American Joint Committee on Cancer Staging Criteria for Cervical Cancer.

3.4.1 Staging of cervical cancer

*American Joint Committee Cancer Staging Criteria*

Cervical Carcinoma has its origin at the squamous-columnar junction, whether in the endocervical canal or on the portio of the cervix. The precursor lesion is dysplasia or carcinoma in-situ (cervical intraepithelial neoplasia [CIN]), which can subsequently become invasive cancer. This process can be very slow. Longitudinal studies have shown that in untreated patients with in-situ cervical cancer, 30%-70% will develop invasive carcinoma over a period of 10-12 years (National Cancer Institute, 1998). Despite this, in about 10% of patients, the in-situ cancer can become invasive in less than one year (National Cancer Institute, 1998). Moving from in-situ to invasive, the cancer now invades the cervical stroma, resulting in ulceration, exophytic tumour or extensive infiltration of underlying tissue including bladder or rectum. In addition to local invasion cervical cancer can also spread via the regional lymphatics or bloodstream. In study H3E-MC-JMAM, cervical cancer staging was performed using the American Joint Committee on Cancer Staging Criteria. They use the TNM Staging Classification.

Patients were assessed using MRI prior to enrolment into the study, but previous staging as well as palpable lesions were also included in the staging process.

*Table 3.4.1 TNM Staging Classification*

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>
**Primary Tumour (T)**

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in-situ

T1 Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)
   - T1a Pre-clinical invasive carcinoma, diagnosed by microscopy only
   - T1a1 Minimal microscopic stromal invasion
   - T1a2 Tumour with an invasive component 5 mm or less in depth taken from the base of the epithelium and 7 mm or less in horizontal spread
   - T1b Tumour larger than T1a2

T2 Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
   - T2a Tumour without parametrial invasion
   - T2b Tumour with parametrial invasion

T3 Cervical carcinoma extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney
   - T3a Tumour involves the lower third of the vagina, with no extension to the pelvic wall
   - T3b Tumour extends to the pelvic wall and/or causes hydronephrosis or a malfunctioning kidney

T4* Tumour invades the mucosa of the bladder or rectum and/or extends beyond the true pelvis

* Presence of bullous oedema is not sufficient evidence to classify a tumour as T4.

<table>
<thead>
<tr>
<th>Stage IIIIB</th>
<th>T1</th>
<th>N1</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Any N</td>
<td>M0</td>
<td></td>
</tr>
</tbody>
</table>

| Stage IVA  | T4   | Any N| M0   |

| Stage IVB  | Any T| Any N| M1   |
**Regional Lymph Node (N)**

NX  Regional lymph node cannot be assessed  
N0  No regional lymph node metastasis  
N1  Regional lymph node metastasis

**Distant Metastasis (M)**

MX  Presence of distant metastasis cannot be assessed  
M0  No distant metastasis  
M1  Distant metastasis

Using the inclusion criteria, only patients with histological or cytological diagnosis of squamous cell carcinoma of the cervix with Stage III or -IV disease could be included in the study.

**3.5 SAMPLE SIZE & PATIENT ASSIGNMENT**

Thirty-five patients were eligible for inclusion into the H3E-MC-JMAM study. Thirteen patients were to be enrolled into the first stage of the study, and if there were no responders, the study would have been stopped. This was not the case, and a further 22 patients were enrolled. If less than 7 patients exhibited a response to LY231514 therapy at the end of the second accrual stage, by which time 35 patients would have been enrolled into the study, the conclusion would be made that this regimen did not warrant any further study.

The procedure described above tests the null hypothesis (H₀) that the true response rate is ≤10%, versus the alternative hypothesis (Hₐ) that the true response rate is at least 25%. The significance level (i.e. the probability of rejecting the H₀ when it is true) is 0.06. The power (i.e. the probability of rejecting H₀ when the alternative hypothesis is true) is 80%. The average sample size for the test procedure described is 29 qualified patients whenever the true response rate is 10%, and is 30 qualified patients when the true response rate is 25%. All patients enrolled into this single-arm trial received LY231514.
3.6 DOSAGE AND ADMINISTRATION

3.6.1 LY231514

*Formulation:* LY231514 is supplied as a white or off-white lyophilised powder in 100mg vials. The product is stable if stored at room temperature. The vials were reconstituted with 2ml sterile Normal Saline to yield a solution of 50mg/ml. This solution was stable for 24 hours, either refrigerated or at room temperature.

*Administration:* LY231514 at a dose of 600mg/m² was administered intravenously over 10 minutes every 21 days. The total dose was calculated using the body surface area (BSA) of the patient. Patients with a BSA of >3m² could not receive more than 1800mg total dose.

3.6.2 Folic Acid

*Formulation:* Folic acid was supplied as 5mg tablets from a single commercial source.

*Administration:* Folic acid supplementation was given orally at a dose of 5mg daily for 2 days prior to the beginning of a cycle, as well as on Days 1, 2, and 3 of the cycle. On the day of LY231514 administration, folic acid was only administered after the blood for the vitamin metabolite assay has been drawn. The folic acid had to be taken at approximately the same time every day.

3.7 DOSAGE ADJUSTMENTS & DELAYS

3.7.1 Dose adjustments for subsequent doses

Dose adjustments for subsequent doses were calculated using the NADIR counts, or maximal non-haematological toxicities from the preceding cycle. Absolute granulocyte count (AGC) had to be ≥1.5 x 10⁹/L, and platelets ≥100 x 10⁹/L prior to the start of a cycle. Treatment could be delayed up to two weeks to allow sufficient time for recovery. Upon recovery, patients were treated using the guidelines in Table 3.7.1.1 and Table 3.7.1.2. If the AGC did not recover to ≥1.5 x 10⁹/L, or the platelets to ≥100 x 10⁹/L after two weeks, the patients were discontinued from the study.
Table 3.7.1.1 Dose adjustments based on NADIR haematology values of preceding cycles

<table>
<thead>
<tr>
<th>AGC ($\times 10^9/L$)</th>
<th>Platelets ($\times 10^9/L$) NADIR</th>
<th>Dose for Next Cycle ($mg/m^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 0.5$</td>
<td>And $\geq$</td>
<td>100% of previous dose</td>
</tr>
<tr>
<td>$&lt; 0.5$</td>
<td>And $\geq$</td>
<td>100% of previous dose</td>
</tr>
<tr>
<td>$&lt; 0.5 &gt; 5$ days</td>
<td>And $\geq$</td>
<td>85% of previous dose</td>
</tr>
<tr>
<td>$\geq 0.5$</td>
<td>And 25-49</td>
<td>85% of previous dose</td>
</tr>
<tr>
<td>$&lt; 0.5$</td>
<td>And 25-49</td>
<td>75% of previous dose</td>
</tr>
<tr>
<td>Any</td>
<td>And $&lt; 25$</td>
<td>50% of previous dose</td>
</tr>
<tr>
<td>A need for a third dose reduction</td>
<td>Discontinue patient from study</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.7.1.2 Mucositis

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Dose for Next Cycle ($mg/m^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>75% of previous dose</td>
</tr>
<tr>
<td>Grade 4</td>
<td>50% of previous dose</td>
</tr>
<tr>
<td>Recurrence of Grade 3-4 after treatment at 2 dose reductions</td>
<td>Discontinue patient from study</td>
</tr>
</tbody>
</table>

All patients had to have baseline local and central laboratory creatinine clearance test values. If results from the central laboratory were not available for treatment decisions, patients could be treated based on calculated creatinine clearance levels using local serum creatinine. Once a dose reduction had been made, the patient was not eligible for any dose escalations for the remainder of the protocol. A patient who could not receive treatment for 35 days from the time of last treatment, had to be discontinued from the study unless Eli Lilly and Company approved continuation.

For non-haematological effects greater than or equal to Grade 3, study drug had to be held until resolution to less than or equal to Grade 1 occurred. Treatment was restarted at a 25% dose reduction if deemed appropriate by the treating physician.
3.7.2 Cycle delay for subsequent doses

If a patient developed Common Toxicity Criteria (CTC) Grade 3 or 4 thrombocytopenia or neutropenia, or had a calculated creatinine clearance of <45mU/min, the next treatment cycle was delayed until the calculated creatinine clearance value returned to ≥45mU/min. If the patient's creatinine clearance did not resolve to ≥ 45mU/min within 5 weeks, the patient had to be discontinued from the study.

3.8 CONCOMITANT THERAPY

No other chemotherapy, radiotherapy, immunotherapy, hormonal therapy (excluding contraceptives and replacement steroids as outlined below), or experimental medications were permitted while the patient was on study. Corticosteroids were allowed for the treatment of rash. Disease progression requiring other forms of specific anti-tumour therapy called for the early discontinuation of the patient.

Patients could receive haematopoietic colony stimulating factors for prolonged myelosuppression. NSAID’s or salicylates were not permitted the day before, the day of, and the day after receiving LY231514. Long half-life NSAID’s (e.g. naproxen, piroxicam, diflunisal, or nabumetone) were not permitted 5 days before, the day of, and the day after receiving LY231514.

If a patient developed a CTC Grade 2 or greater rash following the administration of LY231514, they had to be pre-treated with dexamethasone 4mg twice daily on the day before, the day of, and the day after receiving LY231514.

Patients who developed CTC Grade 3 or greater mucositis had to be started on intravenous Leucovorin at a dose of 100mg/m² immediately. This was followed by a dose of 50mg/m² intravenously every 6 hours for 2 days, which was decreased to 40mg/m² intravenously every 6 hours for 6 additional days. Patients who developed Grade 4 myelosuppression for ≥7 days had to be started on the same dosage, beginning on the seventh day of the Grade 4 myelosuppression.
3.9 Efficacy and Safety Evaluations

3.9.1 Efficacy

3.9.1.1 Efficacy Measures

≤ 3 weeks before enrolment, one of the following radiological tests were performed to assess tumour measurement. The same method used at baseline was used consistently and repeated every 6 weeks.

- CT scan
- MRI
- Ultrasound
- X-ray

≤ 2 weeks before enrolment, the disease status of each patient was measured using the following procedures:

- Medical history, physical examination.
- Evaluation of performance status.
- Tumour measurement of palpable or visual lesions.
- Chest x-ray (repeated as clinically indicated).

Before each dose of LY231514:

- Weight measurement.
- Performance status evaluation.
- Medical history, physical examination and measurement of palpable lesions.

Before every other therapy cycle:

- Radiological imaging studies to demonstrate disease.

3.9.1.2 Efficacy Criteria

The revised Southwest Oncology Group (SWOG) solid tumour response definitions, as documented by Green and Weiss (1992), were used to evaluate patients throughout the study.
Disease Status

- **Measurable Disease:** Bidimensionally measurable lesions with clearly defined margins by
  1) medical photograph (skin or oral lesions) or plain x-ray with at least one diameter 0.5cm or
greater (bone lesions not included), or 2) CT, MRI, or other imaging scan, with both diameters
greater than the distance between cuts of the imaging study, or 3) palpation, with both diameters
2cm or greater.
- **Evaluable Disease:** Unidimensionally measurable lesions, masses with margins not clearly
defined, lesions with both diameters less than 0.5cm, lesions on scan with either diameter
smaller than the distance between cuts, palpable lesions with either diameter less than 2cm,
bone disease.
- **Nonevaluable Disease:** Pleural effusions, ascites, disease documented by indirect evidence only.

Objective Status

- **Complete Response (CR):** Complete disappearance of all measurable and evaluable disease. No
  new lesions. No disease-related symptoms. No evidence of nonevaluable disease.
- **Partial Response (PR):** Applied only to patients with at least one measurable lesion. Greater than
  or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of
  all measurable lesions. No progression of evaluable disease. No new lesions. Nonmeasurable
  lesions had to remain stable or regress for this category.
- **Stable Disease/No response:** Does not qualify for CR, PR, or progression.
- **Progression:** 50% increase, or an increase of 10cm² (whichever was smaller) in the sum of
  products of all measurable lesions over smallest sum observed; OR clear worsening of any
  evaluable disease; OR reappearance of any lesions which had disappeared; OR appearance of
  any new lesion; OR failure to return for evaluation due to death or deteriorating condition. For
  “scan-only” bone disease, increased uptake did not constitute clear worsening. Worsening of
  existing nonevaluable disease did not constitute progression.
- **Unknown:** Progression had not been documented, and one or more measurable or evaluable
  sites not been assessed.
**Best Response**

- **Disease assessment every 3-6 weeks:**
  Two objective status determinations of CR before progression were required for a best response of CR.
  Two determinations of PR or better before progression, but not qualifying for a CR, were required for a best response of PR.
  Two determinations of stable disease/no response or better before progression, but not qualifying as CR or PR, were required for a best response of stable disease/no response; if the first objective status was unknown, only one such determination was required.
  Patients with an objective status of progression on or before the second evaluation had a best response of increasing disease.
  Best response was unknown if the patient did not qualify for a best response of increasing disease and if all objective statuses after the first determination, and before progression were unknown.

- **Disease assessment at intervals of greater than 6 weeks:**
  Only one assessment of stable disease/no response or better before progression, but not qualifying for CR or PR, was required for a best response of stable disease/no response.
  For CR and PR, responses had to be confirmed 4 weeks after documentation of the response.
  Patients with an objective status of progression at the first evaluation had a best response of increasing disease.
  Best response was unknown if the patient did not qualify for a best response of increasing disease and all objective statuses before progression were unknown.

3.9.1.3 Definition of Efficacy Measures

A responder was defined as a patient who had a CR or PR. The duration of response was defined as the time from first objective status assessment of CR or PR, to the time of progression or death due to any cause. Time-to-treatment failure was defined as the time from study entry to the first observation of disease progression, death due to any cause, or early discontinuation of treatment. Survival was defined as the time from study entry to time of death due to any cause.
3.9.2 Safety

3.9.2.1 Clinical laboratory tests and procedures

≤ 2 weeks before enrolment, the disease status of each patient was assessed with the following tests:

- **Haematology**: Full blood count (FBC=haemoglobin, hematocrit, red blood cells, white blood count) and differential blood cell counts (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils), PT, aPTT, and platelets.
- **Blood chemistry**: bilirubin, alkaline phosphatase, ALT, AST, BUN, creatinine, uric acid, phosphorus, calcium, glucose, total protein, albumin, electrolytes (sodium, potassium, bicarbonate, and chloride).
- **Vitamin metabolite assay**.
- **Serum pregnancy test in patients of childbearing potential**.
- **Urinalysis**: colour, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, microscopic, and nitrate.
- **Calculated creatinine clearance**.
- **Electrocardiogram (ECG)**.
- **Vital signs** (blood pressure, pulse rate, and temperature).

During therapy:

- **Number of units required for transfusion at every cycle**.
- **FBC with differential and platelet counts at the start of every new cycle and weekly thereafter**.
- **Blood chemistry at the start of each new cycle, and one week after receiving LY231514**.
- **Urinalysis at the start of each new cycle**.
- **Calculated creatinine clearance at the start of each new cycle**.
- **Vitamin metabolite assay at the start of each new cycle**.
- **PT and aPTT as appropriate**.
- **Vital signs at the start of each new cycle**.
- **Toxicity rating using the CTC each cycle after receiving LY231514**.

A central laboratory was used to perform the blood chemistries, calculated creatinine clearance and urinalysis. The local laboratory was used to perform the haematology, coagulation studies and
serum pregnancy tests. Metabolite Laboratories Incorporated in the United States performed vitamin metabolite assays. Laboratory values that fell outside a clinically accepted reference range, or values that differed significantly from previous values, had to be evaluated and commented on by marking CS (clinically significant) or NCS (not clinically significant) next to each value.

3.10 PATIENT DISPOSITION CRITERIA

3.10.1 Discontinuations
A patient was discontinued from the study under the following circumstances:
- Evidence of progressive disease.
- Physician believed a change in therapy would be in the best interest of the patient.
- Patient requested discontinuation.
- The drug exhibited unacceptable toxicity.
- The patient became pregnant or failed to use adequate birth control.
- A maximum of 12 cycles LY231514 had been given.
- Eli Lilly and Company decided as sponsor to discontinue the patient.
- The patient missed treatment for 42 days (2 cycles).

3.10.2 Qualification for analysis
All patients who received at least one dose of LY231514 were evaluated for safety. All enrolled patients meeting the following criteria were evaluated for efficacy:
- Histological or cytological diagnosis of cervical cancer.
- No prior chemotherapy.
- No concurrent systemic chemotherapy.
- Presence of bidimensionally measurable disease.
- Treatment with at least two doses of LY231514. A patient who discontinued from the study due to unacceptable drug toxicity prior to receiving two doses, was also included in the efficacy analysis.
3.11 COMPARISON OF RENAL TOXICITIES: 600MG/M² VERSUS 500MG/M² OF LY231514

3.11.1 Prior diagnosis of hydronephrosis
Obstruction of the urinary tract usually manifests as dilation of the urinary tract (hydronephrosis) proximal to the point of obstruction (Dept of Radiology at Indiana University, 1997). The degree to which function is reduced in the affected kidney depends on the severity and duration of the obstruction. All 35 patients were assessed during baseline using radiological imaging studies to establish tumour size and extend of disease.

The presence of hydronephrosis was documented as a pre-existing condition and used for the Cancer Staging of the patient using the American Joint Committee on Cancer Staging Criteria (See Section 2.2).

3.11.2 Baseline creatinine clearance
Of the 35 patients enrolled into the study, 24 patients received 600mg/m², and 11 patients 500mg/m² of LY231514. As per the schedule of events, the creatinine clearance of each patient was measured at baseline as well as prior to each cycle of LY231514. Using the local or central laboratory serum creatinine results, the Modified Cockroft and Gault Method was used to determine the calculated creatinine clearance.

*Modified Cockroft and Gault Method*

Weight in kg (W)
Height in cm (H)
Age in years (A)
Serum creatinine in mg/dL (C)

*Lean Body Weight (LBW) Females*

\[ 0.29569 \times (W) = \quad \text{_____} \]
\[ 0.41813 \times (H) = \pm \text{_____} \]
\[ -43.2933 \]
\[ = \text{LBW} \]

29.
Calculated creatinine clearance

\[
[140 - (A)] \times (LBW) = mL/min
71 \times (C)
\]

3.11.3 Common Toxicity Criteria (CTC) Results

Haematological and non-haematological toxicities related to study drug experienced by each patient was captured and graded using the Common Toxicity Criteria (Southwest Oncology Group Toxicity Criteria - SWOG). Abnormal laboratory values believed to be clinically significant and related to study drug, all other events graded as CTC Grade 1-4, as well as all other adverse events, related and also not related to study drug, were documented as Adverse Events. Dose adjustment and delays were performed using the CTC of the previous cycle (See section 3.7).

Table 3.11.3 Common Toxicity Criteria (CTC)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (x10^9/L)</td>
<td>≥4.0</td>
<td>3.0 – 3.9</td>
<td>2.0 – 2.9</td>
<td>1.0 – 1.9</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>PLT (x10^9/L)</td>
<td>WNL</td>
<td>75.0 – normal</td>
<td>50.0 – 74.9</td>
<td>25.0 – 49.9</td>
<td>&lt;25.0</td>
</tr>
<tr>
<td>Hg (g/dL)</td>
<td>WNL</td>
<td>10.0 – normal</td>
<td>8.0 – 10.0</td>
<td>6.5 – 7.9</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td>Granulocytes/ Bands (x10^9/L)</td>
<td>≥2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 – 1.4</td>
<td>0.5 – 0.9</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Lymphocytes (x10^9/L)</td>
<td>≥2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 – 1.4</td>
<td>0.5 – 0.9</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>WNL</td>
<td>--</td>
<td>&lt;1.5 x N</td>
<td>1.5 – 3.0 x N</td>
<td>&gt;3.0 x N</td>
</tr>
<tr>
<td>Transaminase (SGOT, SGPT)</td>
<td>WNL</td>
<td>≤2.5 x N</td>
<td>2.6 – 5.0 x N</td>
<td>5.1 – 20.0 x N</td>
<td>&gt;20.0 x N</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>WNL</td>
<td>≤2.5 x N</td>
<td>2.5 – 5.0 x N</td>
<td>5.1 – 20.0 x N</td>
<td>&gt;20.0 x N</td>
</tr>
<tr>
<td>Creatinine</td>
<td>WNL</td>
<td>&lt;1.5 x N</td>
<td>1.5 – 3.0 x N</td>
<td>3.1 – 6.0 x N</td>
<td>&gt;6.0 x N</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>No change</td>
<td>1+ or &lt;0.3 g% or</td>
<td>2 – 3+ or 0.3 – 1.0</td>
<td>4+ or &gt;1.0 g% or</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3 g/L</td>
<td>g% or 3 – 10 g/L</td>
<td>&gt;10 g/L</td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>Neg</td>
<td>Micro only</td>
<td>Gross, no clots</td>
<td>Gross + clots</td>
<td>Requires transfusion</td>
</tr>
<tr>
<td>Hyerglycaemia (mg/dL)</td>
<td>&lt;116</td>
<td>116 – 160</td>
<td>161 – 250</td>
<td>251 - 500</td>
<td>&gt;500 or ketoacidoses</td>
</tr>
</tbody>
</table>

30.
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia (mg/dL)</td>
<td>&gt;64</td>
<td>55 - 64</td>
<td>40 - 54</td>
<td>30 - 39</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Amylase</td>
<td>WNL</td>
<td>&lt;1.5 x N</td>
<td>1.5 - 2.0 x N</td>
<td>2.1 - 5.0 x N</td>
<td>&gt;5.1 x N</td>
</tr>
<tr>
<td>Hypercalcaemia (mg/dL)</td>
<td>&lt;10.6</td>
<td>10.6 - 11.5</td>
<td>11.6 - 12.5</td>
<td>12.6 - 13.5</td>
<td>≥13.5</td>
</tr>
<tr>
<td>Hypocalcaemia (mg/dL)</td>
<td>&gt;8.4</td>
<td>8.4 - 7.8</td>
<td>7.7 - 7.0</td>
<td>6.9 - 6.1</td>
<td>≤6.0</td>
</tr>
<tr>
<td>Hypomagnesemia (mg/dL)</td>
<td>&gt;1.4</td>
<td>1.4 - 1.2</td>
<td>1.1 - 0.9</td>
<td>0.8 - 0.6</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>None</td>
<td>Able to eat</td>
<td>Intake significantly decreased but can eat</td>
<td>No significant intake</td>
<td>--</td>
</tr>
<tr>
<td>Vomiting</td>
<td>None</td>
<td>1 episode in 24 hrs</td>
<td>2-5 episodes in 24 hrs</td>
<td>6-10 episodes in 24 hrs</td>
<td>&gt;10 episodes in 24 hrs, or requiring parenteral support</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>None</td>
<td>Increase of 2-3 stools/day over pre-Rx</td>
<td>Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping</td>
<td>Increase of 7-9 stools/day, or incontinence, or severe cramping</td>
<td>Increase of ≥10 stools/day, or grossly bloody diarrhoea, or need for parenteral support</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>None</td>
<td>Painless ulcers, erythema, or mild soreness</td>
<td>Painful erythema, oedema, or ulcers, but can eat</td>
<td>Painful erythema, oedema, or ulcers, and cannot eat</td>
<td>Requires parenteral or enteral support</td>
</tr>
<tr>
<td>Hypertension</td>
<td>None or no change</td>
<td>Asymptomatic, transient increase by greater than 20 mm Hg (D) or to 150/100 if previously WNL. No treatment required</td>
<td>Recurrent or persistent increase by greater than 20 mm Hg (D) or to 150/100 if previously WNL. No treatment required</td>
<td>Requires therapy</td>
<td>Hypertensive crisis</td>
</tr>
</tbody>
</table>

31.
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>None or no change</td>
<td>Changes requiring no therapy (including transient orthostatic hypotension)</td>
<td>Requires fluid replacement or other therapy but not hospitalisation</td>
<td>Requires therapy and hospitalisation; resolves within 48 hrs of stopping the agent</td>
<td>Requires therapy and hospitalisation for ≥48 hrs after stopping the agent</td>
</tr>
<tr>
<td>Neuro-sensory</td>
<td>None or no change</td>
<td>Mild paresthesias, loss of deep tendon reflexes</td>
<td>Mild or moderate objective sensory loss; moderate paresthesias</td>
<td>Severe objective sensory loss or paresthesias that interfere with function</td>
<td>--</td>
</tr>
<tr>
<td>Neuro-motor</td>
<td>None or no change</td>
<td>Subjective weakness; no objective findings</td>
<td>Objective weakness without significant impairment of function</td>
<td>Objective weakness with impairment of function</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Neuro-cortical</td>
<td>None</td>
<td>Mild somnolence or agitation</td>
<td>Moderate somnolence or agitation</td>
<td>Severe somnolence, agitation, confusion, disorientation, or hallucinations</td>
<td>Coma, seizures, toxic psychosis</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Slight incoordination, dysdiadokinesis</td>
<td>Intention Tremor, dysmetria, slurred speech, nystagmus</td>
<td>Severe somnolence, agitation, confusion, disorientation, or hallucinations</td>
<td>Coma, seizures, toxic psychosis</td>
</tr>
<tr>
<td>Neuro-mood</td>
<td>No change</td>
<td>Mild anxiety or depression</td>
<td>Moderate anxiety or depression</td>
<td>Severe anxiety or depression</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Neuro-headache</td>
<td>None</td>
<td>Mild</td>
<td>Moderate or severe but transient</td>
<td>Unrelenting and severe</td>
<td>--</td>
</tr>
<tr>
<td>Neuro-constipation</td>
<td>None or no change</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Ileus &gt;96 hours</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Grade 0</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neuro-hearing</td>
<td>None or no change</td>
<td>Asymptomatic, hearing loss on audiometry only</td>
<td>Tinnitus</td>
<td>Hearing loss interfering with function but correctable with hearing aid</td>
<td>Deafness not correctable</td>
</tr>
<tr>
<td>Neuro-vision</td>
<td>None or no change</td>
<td>--</td>
<td>--</td>
<td>Symptomatic subtotal loss of vision</td>
<td>Blindness</td>
</tr>
<tr>
<td>Haemorrhage (Clinical)</td>
<td>None</td>
<td>Mild, no transfusion</td>
<td>Gross, 1-2 units transfusion per episode</td>
<td>Gross, 3-4 units transfusion per episode</td>
<td>Massive, &gt;4 units transfusion per episode</td>
</tr>
<tr>
<td>Infection</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>Alopecia</td>
<td>No loss</td>
<td>Mild hair loss</td>
<td>Pronounced or total hair loss</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>None or no change</td>
<td>Asymptomatic, with abnormality in PFT’s</td>
<td>Dyspnoea on significant exertion</td>
<td>Dyspnoea at normal level of activity</td>
<td>Dyspnoea at rest</td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>&lt;5.0%</td>
<td>5.0 - 9.9%</td>
<td>10.0 - 19.9%</td>
<td>&gt;20.0%</td>
<td>--</td>
</tr>
<tr>
<td>Skin</td>
<td>None or no change</td>
<td>Scattered macular or papular eruption, or erythema that is asymptomatic</td>
<td>Scattered macular or papular eruption or erythema with pruritus or other associated eruption symptoms</td>
<td>Generalised symptomatic macular, papular, or vesicular</td>
<td>Exfoliative dermatitis or ulcerating dermatitis</td>
</tr>
<tr>
<td>Allergy</td>
<td>None</td>
<td>Transient rash, drug fever &lt;38 °C, 100.4 °F</td>
<td>Urticaria, drug fever = 38 °C, 100.4 °F, mild bronchospasm</td>
<td>Serum sickness, bronchospasm, requiring parenteral meds</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Fever in absence of infection</td>
<td>None</td>
<td>37.1 - 38.0 °C, 98.7 - 100.4 °F</td>
<td>38.1 - 40.0 °C, 100.5 - 104.0 °F</td>
<td>&gt;40.0 °C &gt;104.0 °F for less than 24 hrs</td>
<td>40.0 °C (104.0 °F) for more than 24 hrs or fever accompanied by hypotension</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Grade 0</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>---------</td>
<td>--------------------------------------------</td>
<td>----------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Local</td>
<td>None</td>
<td>Pain</td>
<td>Pain and swelling, with inflammation or phlebitis</td>
<td>Ulceration</td>
<td>Plastic surgery indicated</td>
</tr>
</tbody>
</table>

34.
CHAPTER 4: RESULTS

4.1 DATA ANALYSIS RESULTS

4.1.1 Patient characteristics

4.1.1.1 Demographics

Age

The age distribution for the 35 patients enrolled into the study was 26 to 76 years. All of the patients were either diagnosed with Stage IIIb or -IV cervical cancer. Twenty-five patients were Black and ten Coloured. The mean age for the Black patients was 52 years compared to 42.6 years for the Coloured group. Data from this study reflects a higher age of onset for Stage III or -IV disease in the Black population group if compared to data reported by Walker et al. (1985). He reported a mean age of 49.8 years for black patients with invasive cancer in his study. Unfortunately he reported no data for coloured patients. There were no white patients eligible for enrolment into this specific study.

The age distribution for the 24 patients receiving 600mg/m² was 26 to 76 years, with a mean age of 50, compared to an age distribution of 28 to 70 years, with a mean age of 47 for the 11 patients in the 500mg/m² group. This difference in mean age was not clinically significant (p>0.05, Pearson’s Chi Square Test)

![Chart 4.1.1(a) Comparison of mean age between 600mg/m² versus 500mg/m² LY231514 treatment groups](image)

Taking all 35 enrolled patients into consideration, 14.3% of them were ≤35 years old and 85.7% 36 years and older. Using a 12 month survival period, the survival rate for the ≤35 years age group was 40%, compared to 70% for patients 36 years and older.
This is significantly different to data from a study by Jennings et al. (1992), who found no significant difference in survival between younger and older patients with invasive carcinoma of the cervix. A factor that could have influenced this difference is the fact that the patients ≤35 years only represented 14% of the study population in this study and further investigation would be needed to validate a statistically significant difference.

![Chart 4.1.1(b) Comparison of 12 months survival rates between patients <35 years, and >35 years of age with Stage IIIb and Stage IV cervical cancer](chart.png)

**Stage**

During baseline, all patients were staged using radiological measures to classify them as having Stage IIIa, - IIIb or - IV cervical cancer. No patients in this trial were categorised as Stage IIIa, 22 patients were evaluated as being Stage IIIb, and 13 patients as having Stage IV cervical cancer.

**Total tumour sites**

Patients with Stage IV disease with measurable lesions outside the pelvis may have had prior radiotherapy if it was completed at least 6 weeks prior to study enrolment. The pelvic lesions of these patients were not documented as lesions as a true measurement of the pelvic tumour could not be made. Fibrosis caused by radiotherapy also reflected on the radiological image. In this study, 3 patients had prior radiotherapy and the measurement of their primary tumour sites was not taken into consideration.

The average amount of tumour sites for all 35 patients were 2, with 23 patients having one tumour site, 4 patients with two, and 8 patients with three or more lesions. The twelve months survival status for the different groups were as follow: of the patients with one lesion = 52%, patients with two lesions = 25%, and patients with three or more lesions = 50%.
From this data, the conclusion was made that the number of tumour sites does not have a negative influence on survival. The size and position of the lesions could have an influence on survival, but this data was not taken into consideration in this study and needs to be investigated further for specific analysis and conclusions.

4.1.1.2 Pre-existing conditions

**Diagnosis of hydronephrosis**

Hydronephrosis was diagnosed in 3 patients with Stage IIIb, and in 5 patients with Stage IV cervical cancer. As discussed in Section 3.11.1, the degree of impaired kidney function caused by the presence of hydronephrosis depended on the severity and duration of obstruction. Of the total of 8 patients with baseline diagnosis of hydronephrosis, 7 patients received 600mg/m², and 1 patient 500mg/m² LY231514.

**Baseline creatinine clearance**

Before enrolment (baseline), either the local or central laboratory measured the serum creatinine of each patient. Treatment delays, dose adjustments and CTC gradings were done using the results from the central laboratory (Covance in Cape Town).

The baseline creatinine clearance of each patient had to be ≥ 45 ml/min in order to meet the enrolment criteria. Of the 35 patients enrolled into the study, 17.1% had baseline creatinine clearance values of 45-50 ml/min, 14.3% of 51-60ml/min, and 68.6% of >60ml/min. Of the 8 patients diagnosed with hydronephrosis (7 on the 600mg/m² arm, and 1 on the 500mg/m² arm), 2 (25%) had a baseline creatinine clearance of 45-50ml/min, 1 (12.5%) of 51-60ml/min, and 5 (62.5%) of >60ml/min. This data show no significant difference in baseline creatinine clearance between patients with hydronephrosis and those without.

During baseline, 11 of the patients on the 600mg/m² regime had a baseline creatinine clearance of <60ml/min, compared to none on the 500mg/m² regime. Later on, eight of the 11 patients experienced events of decreased creatinine clearance resulting in cycle delay. The clinical data thus suggests that the patients with a low creatinine clearance (<60ml/min) had a greater change of developing expressed renal toxicity due to decreased renal function.
4.1.2 Efficacy analysis

4.1.2.1 Tumour response rate

Within the group of patients with either Stage IIIb or Stage IV disease, 4 (17.4%) of the 23 patients with Stage IIIb cervical cancer achieved a best response of Partial Response (PR), and 15 (65.2%) a best response of Stable Disease (SD). Of the 12 patients categorised as Stage IV cervical cancer patients, 4 (33.3%) achieved a best response of Partial Response (PR), and 7 (58.3%) a best response of Stable Disease (SD).

<table>
<thead>
<tr>
<th>Response Group</th>
<th>Response Rate</th>
<th>Stage IIIb</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>4/23 (17.4%)</td>
<td>4/12 (33.3%)</td>
<td>(-0.46; 0.14)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>15/23 (65.2%)</td>
<td>7/12 (58.3%)</td>
<td>(-0.28; 0.41)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>4/23 (17.4%)</td>
<td>1/12 (0.08%)</td>
<td>(-0.15; 0.32)</td>
</tr>
</tbody>
</table>

The distribution of response rate does not differ significantly between the two Disease Stages (p = 0.587; Fisher Exact Test). This contradicts the expectation that Stage IIIb patients would have had a better response due to their lesser extent of disease.
Table 4.1.2.1(b)  Comparison of response rates for patients who received 600mg/m² versus 500mg/m² LY231514

<table>
<thead>
<tr>
<th>Response Group</th>
<th>Response Rate 600mg/m²</th>
<th>Response Rate 500mg/m²</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>6/24 (25.0%)</td>
<td>2/11 (18.2%)</td>
<td>(-0.23 ; 0.37)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>14/24 (58.3%)</td>
<td>8/11 (72.7%)</td>
<td>(-0.49 ; 0.20)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>4/24 (16.7%)</td>
<td>1/11 (9.1%)</td>
<td>(-0.27 ; 0.42)</td>
</tr>
<tr>
<td>Total Patients</td>
<td>24</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

The distribution of response rate does not differ significantly between the two dosages ($p = 0.771$; Fisher Exact Test).

Comparing the tumour response rate of patients on different dosage regimes (600mg/m² versus 500mg/m²), 6 (25%) of the 24 patients receiving 600mg/m² LY231514 achieved a best response of Partial Response (PR), while 14 (58.3%) had a best response of Stable Disease (SD). On the 500mg/m² regime, 2 (18.2%) of the 11 patients had best response of PR, compared to 8 (72.7%) achieving a best response of SD.

Although not statistically significant, the difference in response rate between the two dosages is still clinically significant, with the 600mg/m² treatment arm showing a better response rate (25% versus 18.2%).

Despite the amendment’s aim not to decrease response rate by decreasing the dosage from 600mg/m² to 500mg/m², the patients on the lower dosage showed a clinically significant lower response rate than those receiving 600mg/m².

4.1.2.2 Overall Survival

Using a 12 months survival period, the average survival rate for the Stage IIIb patients were 72.7%, as compared to 38.5% for patients diagnosed as having Stage IV disease.

From this data the conclusion can be made that the patients diagnosed with Stage IV cervical cancer had a lower 12 month survival rate, compared to those with Stage IIIb disease. Although the patients with Stage IV disease showed a better response rate versus patients classified as Stage IIIb.
(33.3% versus 17.4%), Stage IIIb patients showed a significantly higher 12 months survival rate. For the 35 patients enrolled into the study, survival was between 3 and 30 months, with 18 patients still alive at present.

The survival interval for patients receiving 600mg/m² LY231514 was 3 to 30 months, with 7 patients still alive at present, compared to 3 to 16 months for patients receiving 500mg/m², with all patients still alive in this treatment group.

Figure 4.1.2.2 Kaplan-Meier Survival Curve (adjusted for age) for 600mg/m² versus 500mg/m² LY231514 (Group 0 = 600mg/m²; Group 1 = 500mg/m²). Survival was measured in months.

The survival probability for the two treatment groups has been displayed in Figure 4.1.2.2 using a Kaplan-Meier Survival Curve. These two curves were found to be of significant difference (P=0.0871), using the Log Rank Test.
4.1.2.3 Time to treatment failure

Time to treatment failure was defined as the time from study entry to the first observation of disease progression, death due to any cause, or early discontinuation of treatment. For the 35 patients enrolled, the average time from receiving their first dosage of LY231514 until the first progression of disease was 3 months, with a range from 3 to 30 months. A distinction between Stage IIIb and -IV patients was made, with the average time to treatment failure for Stage IIIb patients being 12.1 months, with a range from 3 to 30 months, compared to an average of 8.6 months, and a range of 2 to 21 months for Stage IV patients. Stage IIIb patients showed a longer time to treatment failure rate than Stage IV patients in this study.

The average time to treatment failure for the 600mg/m² regime was 11.9 months, with a range of 3 to 30 months, compared to an average of 7.4 months with a range of 3 to 16 months for those patients who received 500mg/m². As the patients on the 600mg/m² were enrolled before treatment on 500mg/m² treatment arm was started, all the patients on the 500mg/m² treatment regime were still alive at the time this analysis was made.

Figure 4.1.2.3 Kaplan-Meier Survival Curve (adjusted for age) for the Time to Treatment Failure (months) of 600mg/m² versus 500mg/m² LY231514 (600mg/m² = 0; 500mg/m² = 1)
Time to Treatment Failure for the two treatment groups are displayed in Figure 4.1.2.3 using a Kaplan-Meier Survival Curve. These two curves were found to be of significant difference using the Log Rank Test ($p = 0.0884$).

4.1.2.4 Duration of response

For this analysis, the duration of response was defined as the number of weeks from achieving a PR or CR, until progression of disease was noted and the patient no longer qualified for a best response of PR or CR. The average duration of response for the 8 patients who had a best response of PR was 9.4 weeks. If broken down into the two treatment regimes, 6 of these patients received 600mg/m$^2$ of LY231514 and achieved an average duration of response of 10.8 weeks, with an interval of 7 to 24 weeks. For the 2 patients who received 500mg/m$^2$, the average duration of response was 5 weeks, with an interval of 4 to 6 weeks. Clinically this shows a decrease in duration of response in the 500mg/m$^2$ treatment arm, but this needs to be further investigated as in this study the patient population was too small to draw any statistical conclusions.

The rationale for the amendment from 600mg/m$^2$ to 500mg/m$^2$ of LY231514 was to minimise toxicity, but not to compromise response. In the sections to follow, it will be seen that although toxicity, especially renal toxicity, was less common and severe, the response rate as well as the duration of response was compromised for the 500mg/m$^2$ treatment group.

4.1.3 Safety analysis

4.1.3.1 Incidence and comparison of Grade 3-4 CTC toxicities: 600mg/m$^2$ versus 500mg/m$^2$ LY231514

Laboratory parameters

The following laboratory parameters of each enrolled patient were measured to calculate the Common Toxicity for the specific treatment cycle:

Day 8, -15 and -22 of the treatment cycle-
Haematology: white blood count (WBC), platelets, haemoglobin (Hgb), granulocytes/bands and lymphocytes
Day 8 and -22 of the treatment cycle-
Chemistry: bilirubin, transaminase, and alkaline phosphatase

Day 22 of the treatment cycle-
Calculated creatinine clearance and urinalysis (proteinuria and haematuria)
(Refer to section 3.2 and 3.11.3)

The following Grade 3 or 4 CTC toxicities were observed:
- Overall data for all 35 patients enrolled

The incidences were as follow: leukopenia = 57.1%; thrombocytopenia = 5.7%; anaemia = 31.4%; neutropenia = 71.4%; decreased lymphocytes = 60%, and elevated transaminase levels = 48.6%.

Table 4.1.3.1(a) Comparison of haematological toxicity rates for patients who received 600mg/m² versus 500mg/m² LY231514

<table>
<thead>
<tr>
<th>Haematological Toxicity</th>
<th>Neutropenia</th>
<th>Leukopenia</th>
<th>Anaemia</th>
<th>Thrombocytopenia</th>
<th>Lymphocytes</th>
<th>Transaminases</th>
</tr>
</thead>
<tbody>
<tr>
<td>600mg/m²</td>
<td>9/24 (37.5%)</td>
<td>15/24 (62.5%)</td>
<td>9/24 (37.5%)</td>
<td>2/24 (8.3%)</td>
<td>16/24 (66.7%)</td>
<td>13/24 (54.2%)</td>
</tr>
<tr>
<td>500mg/m²</td>
<td>6/11 (54.5%)</td>
<td>5/11 (45.4%)</td>
<td>2/11 (18.2%)</td>
<td>0/11 (0%)</td>
<td>5/11 (45.4%)</td>
<td>4/11 (36.4%)</td>
</tr>
</tbody>
</table>

* p-Value associated with Pearson’s Chi Square Test or Fisher’s Exact Test (FE)

With the statistical analysis, none of the haematology tests results differed significantly between the two treatment groups (p>0.05 for all tests).

- Data for patients who received 600mg/m² LY231514 (n=24)

Grade 3 or 4 CTC toxicities which occurred were as follow: leukopenia = 62.5%; thrombocytopenia = 8.3%; anaemia = 37.5%; neutropenia = 37.5%; decreased lymphocytes = 66.7%; and elevated transaminase levels = 48.6%.
transaminase levels = 54.2%.

- Data for patients who received 500mg/m² LY231514 (n=11)
  Leukopenia = 45.4%; thrombocytopenia = 0%; anaemia = 18.2%; neutropenia = 54.5%; decreased lymphocytes = 45.4%; and elevated transaminase levels = 36.4%.

With the exception of neutropenia and leukopenia, there was clinically a higher rate of haematological toxicities seen in the 600mg/m² treatment regime compared to data for 500mg/m².

**Non-laboratory parameters**

Taking all 35 enrolled patients into consideration, the following Grade 3-4 CTC non-laboratory toxicities occurred: nausea (17.1%); vomiting (5.7%); diarrhoea (5.7%); stomatitis (11.4%); and skin abnormalities (8.6%).
Table 4.1.3.1 (b) Comparison of non-haematological toxicity rates for patients who received 600mg/m² versus 500mg/m² LY231514

<table>
<thead>
<tr>
<th>Non-Haematological Toxicity</th>
<th>600mg/m²</th>
<th>500mg/m²</th>
<th>95% Confidence Interval</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3/24 (12.5%)</td>
<td>3/11 (27.3%)</td>
<td>0.2817 (-0.42 ; 0.12)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2/24 (8.3%)</td>
<td>0/11 (0%)</td>
<td>0.5563 (FE)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2/24 (8.3%)</td>
<td>0/11 (0%)</td>
<td>0.5563 (FE) (-0.08 ; 0.25)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4/24 (16.7%)</td>
<td>0/11 (0%)</td>
<td>0.2849 (FE)</td>
<td></td>
</tr>
<tr>
<td>Skin erythema</td>
<td>3/24 (12.5%)</td>
<td>0/11 (0%)</td>
<td>0.5361 (FE)</td>
<td></td>
</tr>
</tbody>
</table>

* p-Value associated with Pearson’s Chi Square Test or Fisher’s Exact Test (FE)

In Figure 1.4.3.1(b), the two different dosage groups were divided and analysed separately, and the following Grade 3-4 non-laboratory toxicities documented for the 600mg/m² group: nausea (12.5%), vomiting (8.3%), diarrhoea (8.3%), stomatitis (16.7%), and skin abnormalities (12.5%).

Data for the 500mg/m² dosage group showed the following: nausea (27.3%), vomiting (0%), diarrhoea (0%), stomatitis (0%), and skin abnormalities (0%).

No statistically significant difference was seen between the two groups, but a clinical difference was noted between the groups as there were no vomiting, diarrhoea, stomatitis or skin erythema reported for the 500mg/m² treatment group. These adverse events were documented for the 600mg/m² group with incidences as recorded in Table 4.1.3.1 (b).

4.1.3.2 Comparison of renal toxicities: 600mg/m² versus 500mg/m² LY231514

*Influence of prior diagnosis of hydronephrosis*

Four out of the eight patients with prior diagnosed hydronephrosis had to be discontinued from the study due to decreased creatinine clearance, prohibiting them from receiving therapy for more than 42 days. All four patients received 600mg/m² LY231514. None of the four patients with prior
Hydronephrosis on the 500mg/m² treatment regime had to be discontinued from study due to prolonged decreased creatinine clearance, showing another significant difference in renal toxicity between the two treatment groups.

**Influence of creatinine clearance**

The serum creatinine clearance of each patient was measured at baseline, as well as prior to each cycle of LY231514 (See section 3.11.2). The creatinine clearance was then calculated using the Modified Cockroft and Gault Method (Section 3.11.2).

The 24 patients in the 600mg/m² treatment group experienced a 22.6% incidence of decreased creatinine clearance. This was calculated using the total number of cycles in which decreased creatinine clearance caused a cycle delay or end of study participation (19), divided by the total amount of treatment cycles (84). The percentage decreased creatinine clearance events for patients that received 500mg/m² was 5%, calculated by dividing the amount of cycles in which renal toxicity occurred (2), by the total amount of treatment cycles received (43). This data shows a significant difference for the renal toxicity experienced by the 600mg/m² treatment group, compared to that of the 500mg/m² treatment group (T-test odds ratio = 0.17). The 600mg/m² treatment group experienced a much higher incidence of renal toxicity than the 500mg/m² group.

Of the 24 patients enrolled on the 600mg/m² treatment regime, 12 (50%) had to be discontinued from the study due to a decreased creatinine clearance, prohibiting the administration of drug for > 42 days. For the 11 patients who received 500mg/m² of LY231514, only one (1%) had to be discontinued from the study due to a decreased creatinine clearance which prohibited study drug administration for > 42 days.

**Table 4.1.3.2(a) Comparison of renal toxicity rates for patients who received 600mg/m² versus 500mg/m² LY231514**

<table>
<thead>
<tr>
<th>Renal Toxicity Rate</th>
<th>p-Value*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>600mg/m²</td>
<td>500mg/m²</td>
<td></td>
</tr>
<tr>
<td>13/24 (54.2%)</td>
<td>2/11 (18.2%)</td>
<td>0.0458</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.007; 0.713)</td>
</tr>
</tbody>
</table>

* p-Value associated with Pearson’s Chi Square Test

46.
The incidence of renal toxicity between the two dosage regimes differ significantly ($p = 0.0458$; Pearson’s Chi Square Test). Thirteen out of the 24 (54.2%) patients on the 600mg/m² regime experienced renal toxicity during their treatment cycles, compared to only 2 out of 11 (18.2%) on the 500mg/m² regime.

By categorising the patients as either Stage IIIb or -IV, it was found that there was not a statistical significant difference between the two groups with regard to renal toxicity ($p = 0.1763$; Fisher Exact Test).

Although the difference is not statistically significant for the Stage IIIb patients, it is still of clinical importance to note that nearly half the patients on the 600mg/m² regime experienced renal toxicity, compared to only 12.5% of the 500mg/m² regime. The patient population was too small to show a statistical difference.

Table 4.1.3.2(b)  Comparison of renal toxicity rates for Stage IIIb cervical cancer patients who received 600mg/m² versus 500mg/m² LY231514

<table>
<thead>
<tr>
<th>Renal Toxicity Rate</th>
<th>p-Value* 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>600mg/m²</td>
<td>500mg/m²</td>
</tr>
<tr>
<td>7/15 (46.7%)</td>
<td>1/8 (12.5%)</td>
</tr>
</tbody>
</table>

*p-Value associated with Fisher’s Exact Test (FE)

Data for the patients diagnosed with Stage IV cervical cancer also showed no statistically significant difference between the two dosage groups with regard to renal toxicity. Once again, although not statistically different, 66.7% on the 600mg/m² regime versus 33.3% on the 500mg/m² regime constitutes to a clinically significant difference between the two treatment groups.

Table 4.1.3.2(c)  Comparison of renal toxicity rates for Stage IV cervical cancer patients who received 600mg/m² versus 500mg/m² LY231514

<table>
<thead>
<tr>
<th>Renal Toxicity Rate</th>
<th>p-Value* 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>600mg/m²</td>
<td>500mg/m²</td>
</tr>
<tr>
<td>6/9 (66.7%)</td>
<td>1/3 (33.3%)</td>
</tr>
</tbody>
</table>

*p-Value associated with Fisher Exact Test (FE)
CHAPTER 5: CONCLUSION

5.1 EFFICACY MEASURES

5.1.1 Tumour response rate
On this study 8 patients achieved a best response of Partial Response divided between the 600mg/m² and 500mg/m² treatment groups. Six patients received 600mg/m², and two 500mg/m². This constituted to a 25% (6/24) versus an 18% (2/11) response rate. Statistical analysis showed no significant difference between the two groups (p=0.771; Fisher Exact Test), but the difference is of clinical value. Four of the 8 patients were diagnosed as having Stage IIIb-, and 4 as having Stage IV cervical cancer. There was no statistical significant difference found between the response rates for the two categories (p = 0.587; Fisher Exact Test), but a response of 17.4% for the Stage IIIb patients versus 33.3% for the Stage IV patients is also of clinical importance.

5.1.2 Time to treatment failure
The average time to treatment failure for all patients enrolled was 3 months, with a range of 3 to 30 months. Stage IIIb patients had an average of 12.1 months before progression of disease, compared to 8.6 months for Stage IV patients. Although the Stage IV patients showed a better response rate, the Stage IIIb patients had a longer response period with a difference of +/-4 months.

Patients who received 600mg/m² had an 11.9 months time to treatment failure period, compared to 7.4 months for the 500mg/m² treatment group. A Kaplan-Meier graph was used to depict the difference in time to treatment failure between the two groups. The difference was found to be significant, with a p-Value of 0.0884 using the Log Rank Test.

5.1.3 Survival
A 12 months survival period was used to compare Stage IIIb with Stage IV patients. Stage IIIb patients showed a 72.7% survival, compared to 38.5% of patients with Stage IV disease surviving 12 months or longer. Once again, despite showing a better response rate, the Stage IV patients showed a much lower 12 month survival than those diagnosed with Stage IIIb disease.

The 600mg/m² group showed a survival range of 3 to 30 months, with 7 patients of the 24 still alive.
at present, compared to the 500mg/m² group which had a range of 3 to 16 months, with all of the 11 patients still alive at present. The difference between the two groups was found to be significant as illustrated by a Kaplan-Meier graph and the Log Rank Test (p = 0.0871).

5.1.4 Duration of response
The duration of response was defined as the time from first objective status assessment of PR/CRI to the time of progression or death due to any cause. For the 8 patients who achieved a best response of PR in this study, this period was 9.4 weeks. The 6 patients who received 600mg/m² had a duration of response of 10.8 weeks compared to 5 weeks for the 500mg/m² group. Although the data is clinically significantly different, the patient population was too small to come to any definite statistical conclusions. Despite the aim of the amendment not to compromise response while reducing the incidence and severity of renal toxicity, from the data it can be seen that response rate as well as duration of response was compromised for the 500mg/m² treatment group.

5.2 SAFETY MEASURES

5.2.1 Comparison of Grade 3-4 CTC toxicities: 600mg/m² versus 500mg/m² LY231514

Laboratory Parameters
Except for neutropenia and leukopenia, there were clinical differences seen between the toxicities experienced by the two groups. There was a lower incidence of thrombocytopenia, anaemia, decreased lymphocytes, as well as raised serum transaminases in the 500mg/m² group. Although not statistically significant (p>0.05 for all tests), the difference is of clinical value by pointing out that the 600mg/m² group had a higher incidence of these toxicities.

Non-laboratory Parameters
Once again, the 600mg/m² group had a higher incidence of Grade 3-4 CTC toxicities. Nausea, vomiting, diarrhoea, stomatitis and skin erythema was reported for this group, while only nausea occurred in the 500mg/m² treatment group. The statistical analysis showed no significant difference between the two groups (p>0.05 for all tests), but the difference is of clinical value pointing out a much lower rate of those toxicities that influence patient compliance.
5.2.2 Comparison of renal toxicities: 600mg/m² versus 500mg/m² LY231514

The elimination of this compound relies greatly on the kidney function of the patient as 90% of LY231514 is excreted in the urine (See section 1.6.2). The presence of hydronephrosis compromises renal function, leading to a presumed decreased elimination of LY231514 and a higher incidence of renal toxicity in patients. There was an even distribution of patients with hydronephrosis between the two dosage groups (4 in each), eliminating any bias in the treatment arms with regards to renal toxicity.

Four of the patients on the 600mg/m² regime with prior diagnoses of hydronephrosis had to be discontinued from study due to prolonged decreased creatinine clearance (>42 days). None of the patients on the 500mg/m² regime with prior diagnoses of hydronephrosis had to be discontinued from study. This difference seen between the two dosage groups indicated that patients with prior diagnosed hydronephrosis receiving 600mg/m² had a much higher chance of developing renal dysfunction as measured by a decrease in their creatinine clearance. If only the safety aspects were considered, 500mg/m² would be the dosage of choice for patients with prior diagnosed hydronephrosis. As discussed in Section 5.1.1, the response rate for the 600mg/m² group was 25% compared to 18% of the 500mg/m² treatment group.

Taking all 35 enrolled patients into consideration and looking at the amount of patients who had to be discontinued from study due to a decreased creatinine clearance, the incidence was fifty percent (12/24) of the patient on the 600mg/m² regime compared to 9% (1/11) on 500mg/m² regime. This again highlighted that the 500mg/m² caused less severe renal impairment of the patient and should be considered despite the difference in response rate. The incidence of decreased creatinine clearance was documented as follows: 22.6% of patients on the 600mg/m² regime experienced renal toxicity, compared to 5% on the 500mg/m² regime. This difference was found to be significant with a T-test Odds Ratio of 0.17. Fifty percent (12/24) of the patients on the 600mg/m² regime had to be discontinued from study due to prolonged decreased creatinine clearance. This incidence is approximately forty percent higher than that experienced by the 500mg/m² group, where only one patient (9%) had to be discontinued for the same reason.
By looking at the overall incidence of decreased creatinine clearance (including all patients irrespective if they had hydronephrosis or were discontinued from study), patients on the 600mg/m² regime experienced a much higher incidence of renal toxicity as compared to the 500mg/m² group. Thirteen out of the 24 patients (54%) on the 600mg/m² regime experienced renal toxicity, compared to only 2 out of the 11 patients (18%) on the 500mg/m² regime. This difference in the incidence of renal toxicity was found to be statistically significant (p = 0.0458; Pearson’s Chi Square Test).

Of the Stage IIIb patients, 46.7% of the patients that received 600mg/m² and 12.5% of the patients that received 500mg/m² experienced renal toxicity. The difference was not found to be statistically significant (p = 0.1763; Fisher Exact Test), but supports the difference found between 600mg/m² versus 500mg/m² LY231514 when comparing renal toxicity. The same tendency was seen for the Stage IV patients, where 66.7% on the 600mg/m² regime had renal toxicity, compared to 33.3% on the 500mg/m² regime.
5.3 RECOMMENDATIONS

Based on the results of this analysis, the following recommendations are made:

- Although the 500mg/m² regime showed much less renal toxicity, response as well as duration of response was compromised for this group. To eliminate this, the recommendation will be to keep the dosage at 600mg/m² to minimise loss of response, but to reduce the amount of cycles to two or three and follow up with other treatment eg. radiotherapy (see third recommendation).

- To try and reduce renal toxicity in the 600mg/m² group, the recommendation is to administer folic acid every day throughout the study, and not only for 2 days prior, the day of, and 2 days after administration of LY231514. Folic acid has been proved to minimise toxicities seen with LY231514.

- To try and optimise response as well as minimise toxicity, the recommendation is that LY231514 be administered for only 3 cycles, whereafter a full cycle of radiotherapy is begun. Renal toxicity usually sets in at/after Cycle 3 of treatment with LY231514, and the recommended administration procedure would minimise the amount of patients that would have to be discontinued from study due to prolonged decreased creatinine clearance. Most patients that achieved a best response of PR had their first response at the end of Cycle 2. This treatment regime will ensure that patients achieve a good response, without having exposure to extensive renal toxicity.

- It would also be of value to test the compound against earlier stages of cervical cancer, starting as early as Stage II.
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>Age in years</td>
</tr>
<tr>
<td>AGC</td>
<td>Absolute Granulocyte Count</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Transaminase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Transaminase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>C</td>
<td>Serum creatinine in mg/dL</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical Intra-epithelial Neoplasia</td>
</tr>
<tr>
<td>CR</td>
<td>Complete Response</td>
</tr>
<tr>
<td>CS</td>
<td>Clinically Significant</td>
</tr>
<tr>
<td>CTC</td>
<td>Common Toxicity Criteria</td>
</tr>
<tr>
<td>DHFR</td>
<td>Dihydrofolate Reductase</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose Limiting Toxicity</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
</tr>
<tr>
<td>5-FU</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>GARFT</td>
<td>Glycinamde Ribonucleotide Formyl Transferase</td>
</tr>
<tr>
<td>H</td>
<td>Height in cm</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papilloma Virus</td>
</tr>
<tr>
<td>LBW</td>
<td>Lean Body Weight</td>
</tr>
<tr>
<td>M</td>
<td>Metastasis</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum Tolerated Dose</td>
</tr>
<tr>
<td>N</td>
<td>Regional lymph node</td>
</tr>
<tr>
<td>NCS</td>
<td>Not Clinically Significant</td>
</tr>
<tr>
<td>NSAID's</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
</tr>
<tr>
<td>PR</td>
<td>Partial Response</td>
</tr>
<tr>
<td>aPTT</td>
<td>activated Partial Thromboplastin Time</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin Time</td>
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53.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>RFC</td>
<td>Reduced Folate Carrier</td>
</tr>
<tr>
<td>SD</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>SWOG</td>
<td>Southwest Oncology Group</td>
</tr>
<tr>
<td>T</td>
<td>Primary tumour</td>
</tr>
<tr>
<td>TS</td>
<td>Thymidylate Synthetase</td>
</tr>
<tr>
<td>W</td>
<td>Weight in kg</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Count</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<th>Description</th>
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Table 4.1.2.1(b)  Comparison of response rates for patients who received 600mg/m² versus 500mg/m² LY231514

Figure 4.1.2.2  Kaplan-Meier Survival Curve (adjusted for age) for 600mg/m² versus 500mg/m² LY231514 (Group 0=600mg/m²; Group 1 =500mg/m²). Survival was measured in months.

Figure 4.1.2.3  Kaplan-Meier Survival Curve (adjusted for age) for Time to Treatment Failure (months) of 600mg/m² versus 500mg/m² LY231514 (600mg/m²=0; 500mg/m²=1).

Table 4.1.3.1(a)  Comparison of haematological toxicity rates for patients who received 600mg/m² versus 500mg/m² LY231514

Graph 4.1.3.1  Comparison of Grade 3-4 CTC haematological toxicity rates between patients who received 600mg/m² versus 500mg/m² LY231514

Table 4.1.3.1(b)  Comparison of non-haematological toxicity rates for patients who received 600mg/m² versus 500mg/m² LY231514

Table 4.1.3.2(a)  Comparison of renal toxicity rates for patients who received 600mg/m² versus 500mg/m² LY231514

Table 4.1.3.2(b)  Comparison of renal toxicity rates for Stage IIIb cervical cancer patients who received 600mg/m² versus 500mg/m² LY231514

Table 4.1.3.2(c)  Comparison of renal toxicity rates for Stage IV cervical cancer patients who received 600mg/m² versus 500mg/m² LY231514

56.
REFERENCES


58.


59.


November 25, 1999

The Registrar
PU for CHE
POTCHEFSTROOM

To whom it may concern

COMPARISON OF RENAL TOXICITIES WITH LY231514
600MG/M² IN THE TREATMENT OF
STAGE IIIb OR IV CERVICAL CANCER

The abovementioned scription by Ms A Carstens, a Senior Clinical Research Associate
at Eli Lilly (SA) (Pty) Ltd, refers.

She has permission from the Company to use data collected under a research protocol
entitled "A PHASE II TRIAL OF LY231514 ADMINISTERED INTRAVENOUSLY EVERY
21 DAYS IN PATIENTS WITH CERVICAL CANCER", with a confidentiality proviso.

We respectfully request that this data will not be publicly available at your facility for
the next five years based on the following reasons:

- The Company has not completed its own analyses on this Phase II Trial
- Clearly this product is still in early development and data should thus not be shared
  with our competitors at this stage.
- Obviously this product has not been registered yet.

Should you have any questions, please do not hesitate to contact me on 011 928 8142.

Yours faithfully,

DR. A. D. DU PLESSIS
M.B.Ch.B., M.Med.Sc. (Pharmacology)
MEDICAL DIRECTOR
Protocol H3E-MC-JMAM
Cervical Cancer
15 November 1988, Page 1

Protocol H3E-MC-JMAM: LY231514 in Cervical Cancer

Informed Consent

I have been informed by my doctor that I have cancer of the cervix. Surgery, radiotherapy or conventional chemotherapy would not be appropriate treatment for my disease. Therefore I will have the option to be treated with a new drug called TSI (LY231514). LY231514 has shown encouraging results in early studies in patients with cancer. Approximately 95 patients worldwide have already received LY231514 and another 445 patients will receive the drug in studies similar to this.

The chemotherapy will be given in cycles. Each cycle will be 3 weeks long and will involve TSI being given to me as an injection once every 3 weeks. A maximum of 12 cycles will be given. On the day that I receive TSI it will be necessary for me to attend the hospital as an outpatient. The dose may be decreased depending on how it is affecting me.

PROCEDURES

Prior to being enrolled in this study, I will receive a physical examination, laboratory studies (blood and urine tests), a chest X-ray, ECG, and appropriate radiological tests (MRI), for evaluating internal organs.

In order to check that the drugs are not adversely affecting me, I will have blood tests performed every week during the course of my treatment. In addition, I will have extra blood drawn 4 times in 24 hours at the first and third cycle of treatment so that more may be learned about the way the drug acts within the body. It may be necessary for me to remain in hospital overnight when this particular testing is being done. A urine sample will also be taken for testing every three weeks, i.e.: once per cycle of treatment. All of these tests are essential to help to ensure my safety and it is therefore important that, while I am on this study, I attend the clinic at the scheduled visits.

I will also have check-ups, X-rays and scans in order to assess how well the drug is working. These will be planned at regular intervals during and after I have stopped my treatment.

RISKS

I understand that any new drug may have adverse side-effects which we presently are not aware of. However, I will be carefully monitored for these, and at all times my personal safety will be my doctor's prime concern.

The most frequently observed side-effects associated with TSI therapy include: decreased white blood cells which may result in a tendency to develop infection, decreased platelets, which may result in a tendency to bleed or prolonged bleeding, and anaemia. At times patients have experienced a rash, nausea and vomiting, mouth ulcers, extreme tiredness and lack of appetite. Interference with liver functions have also been noted, and occasionally patients have had a deterioration of their kidney function. Instances have been noted where patients have developed central nervous system symptoms, increased body temperature and swelling of the limbs. These symptoms may have been caused by TSI. The events described above do not comprise a complete list of all adverse events observed with TSI therapy as other events have been recorded that may not have been due to the use of this agent.
I understand that if I experience any injury or bad effect, I should contact my doctor immediately. My general practitioner (G.P.) will have been informed that I am participating in this study.

As with any new chemotherapy being tested, in the treatment of cancer, unexpected serious side effects may occur to me or to my unborn child should I be or become pregnant. If I plan to become pregnant or plan to father a child during this study or for three months afterwards, I should not enter this study.

**BENEFITS**

It is not possible to say whether I will benefit from being enrolled in this study, although it may help my disease and the knowledge gained may benefit others who have a similar disease in the future.

**VOLUNTARY PARTICIPATION**

I am under no obligation to enter this study and if I decide to withdraw, I may do so at any moment after informing my doctor of my decision. Such a decision will not adversely affect my treatment.

**STOPPING THE STUDY**

I understand that my doctor, Eli Lilly and Company, or the regulatory authorities, may stop my participation in this study at any time without my agreement.

**CONFIDENTIALITY**

All records from the study which identify me will be confidential except when they are requested for inspection by the sponsor (Lilly monitor and/or medical quality assurance), the local Medicines Control Council (MCC), and the US Food and Drug Administration (FDA) and will not otherwise be released unless requested by law. A copy of my signed consent will be kept in my file and I will receive a copy.

**COMPENSATION**

If during the course of and as a result of my participation in this research study, any physical injury shall occur to me which is caused by any substance ingested or administered as a result of treatment with TSI in this study, or as required by the protocol, Eli Lilly and Company agrees to pay all medical expenses necessary to treat such injury -

1. To the extent that I am not otherwise reimbursed by medical insurance, and
2. Provided that I have followed the directions of the doctors whose care I am under.

Eli Lilly and Company makes no commitment to provide compensation beyond that specified.
QUALIFICATIONS

My doctor has told me that I cannot be in this study if I am a woman who is pregnant, breast feeding a child or am not sterile by means of surgery, irradiation or menopause and not using adequate birth control methods. I also cannot be in this study if I have significant liver, kidney, or heart disease.

Applicable for women for childbearing potential:
I am a woman of childbearing potential and not pregnant at the present time. Because TSI has not been studied in pregnant women, there may be unforeseen risks to a pregnant woman or to an unborn child. Therefore, I agree that during the course of this study and for three months after treatment has been stopped, I will avoid getting pregnant. I will discuss the method of birth control with the doctor responsible for my care during the course of this study. I also confirm that I am not breast feeding at this time. If I become pregnant during this time, I will notify my doctor immediately, and will be discontinued from the study.

UNDERSTANDING

My doctor has explained this study and this consent form to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.
CONSENT

This study and the consent form have been explained to me. I have read all the pages of this consent form. I have had an opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study. I have received a copy of the agreement and understand that a signed copy will be kept in my file.

PATIENT NAME: .................................................................

PATIENT SIGNATURE: ...........................................................

DATE: ...........................................................................

PATIENT NUMBER: ...........................................................

WITNESS NAME: .................................................................

WITNESS SIGNATURE: ...........................................................

DATE: ...........................................................................

INVESTIGATOR NAME: ...........................................................

INVESTIGATOR SIGNATURE: ...........................................................

DATE: ...........................................................................

Disposition of this Document:
1. Give one copy to the patient.
2. Place the original in the patient's medical records, at the investigator's site.
STATEMENT OF INVESTIGATOR RESPONSIBILITY

I have explained the nature, purpose and procedures of the study and have fully answered related questions. I believe that the patient fully understands my explanation and has freely given informed consent.

INVESTIGATOR NAME:  .................................................................
INVESTIGATOR SIGNATURE:  ......................................................
DATE:  ........................................
WITNESS NAME:  .................................................................
WITNESS SIGNATURE:  ......................................................
DATE:  ........................................

INVESTIGATOR NUMBER:  .........................
PATIENT NUMBER:  .............................
PATIENT INITIALS:  ............................

Disposition of this Page:
1. Give one copy to the patient.
2. Forward one copy to Eli Lilly and Company with Baseline CRF Visit.