AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: TOMUDEX
ACTIVE INGREDIENT: RALTITREXED

Study No: 1694 TR/01
A Phase-II Study of TOMUDEX Plus Radiotherapy in Subjects With Inoperable or Recurrent Rectal Cancer (TOMUDEX)

Developmental phase: Phase II
Study Completion Date: 05 April 2006
Date of Report: 03 July 2006

OBJECTIVES:

This pilot study is designed to investigate the value of Neo-adjuvant Tomudex in combination with radiotherapy in patients with inoperable or recurrent rectal cancer in terms of response rate and increasing the resectability of initially inoperable rectal cancer.

This study aimed to evaluate the value of Neo-adjuvant TOMUDEX in combination with pelvic radiotherapy in patients with inoperable/recurrent rectal cancer in terms of response rate and increase the resectability rate. For the patients with inoperable/recurrent rectum carcinoma, the standard therapy is fractionated radiotherapy and also radiotherapy increases the resectibility of locally advanced tumor potentially. Chemotherapy may also be used to improve survival by preventing/treating distant metastases. Both in vivo and in vitro, some chemotherapeutic agents have been shown to act as radiosensitizer and have synergistic effects with radiotherapy. The radiosensitizing effect of TS inhibitors may be due to the impairment of repair of radiation induced DNA damage.

The combination of chemotherapy and radiotherapy in the treatment of inoperable/recurrent rectum carcinoma is still being evaluated and its exact efficacy value has not yet been established. Downstaging of locally advanced tumors can improve resectability and better local control of the disease may reduce local complications and severity of the disease in the rectum. However, this treatment approach can increase the pelvic toxicity of the radiotherapy in terms of diarrhea or skin toxicity. In order to combine two therapies, a dose reduction in chemotherapy is required compared to the dose of chemotherapy administrated alone, during the pelvic radiotherapy, Current chemotherapy doses used in 5FU-based radio-chemotherapy are approximately 80% of the standard dose of chemotherapy, when administrated alone.

Recently, it has been shown that Tomudex is, as effective as 5-FU as a radiosensitiser in both in vitro and in vivo models (Recht et al ASCO 1998 abstract nr 800). Studies on the combination of Tomudex and radiotherapy both as pre-operative treatment of inoperable/recurrent rectal carcinoma and postoperative treatment of radical resected Dukes' B or C rectal cancer have recently been reported. The recommended dosing regimen of Tomudex combined with radiotherapy, for the Phase II studies, is 2.6 mg/m^2 on the days of 1 and 22. 50 Gy is applied in 25 fractions of 2 Gy daily 5 times over 5 weeks and 50.4 Gy in 28 fractions of 1.8 Gy daily 5 times over 5-6 weeks in this radiotherapy treatment. Toxicity of this dosing regimen are tolerable diarrhea and bone marrow suppression (leucopenia). Dose reduction of Tomudex compared to the recommended dose of Tomudex used as a single treatment approach, is of the same magnitude as the reduction needed when 5-FU is combined with radiotherapy in the same indication.
The use of Tomudex in chemoradiotherapy regimens has potential advantages over 5-FU because it is as least as effective as a radiosensitiser and it's toxicity and dosing regimen makes Tomudex more preferable.
This pilot study is designed to investigate the value of Neo-adjuvant Tomudex in combination with radiotherapy in patients with inoperable or recurrent rectal cancer in terms of response rate and increasing the resectability of initially inoperable rectal cancer.

Primary Objective of the Study:
Response rate to the treatment (for all patients)
Rate of resectability (Primarily for the patients who cannot be operated)

Secondary Objective of the Study:
Revision and collection of radiotherapy related toxicity.
Revision and collection of chemotherapy related toxicity.
Period of progression.
Survival.

METHODS:

Study Design

Subject eligibility confirmed and subject entered into the study

Radiotherapy 5 times per week
For 5-6 weeks

1st dose TOMUDEX
Day 1

2nd dose TOMUDEX
Day 22

Subject is followed in accordance with the protocol
New adverse events are collected for 28 days following the last dose of TOMUDEX or Radiotherapy (whichever is the later).
All adverse events are followed for outcome.
All ongoing CTC Grade 3/4 hematology and biochemistry is followed until Grade 1/2 unless in the investigator's opinion they are never likely to improve.
Subjects are followed for signs of progression and survival

Subjects, who are considered to be eligible for pelvic radiotherapy, inoperable and have recurrent rectal cancer, have received 1.8 Gy daily for 5-6 weeks at 28 fractions to the pelvic area. (Total dose = 50.4 Gy) Subjects have retaken the dose of Day 1, 2.6 mg/m^2 TOMUDEX, on Day 22. The second dose administration of TOMUDEX may be reduced and/or postponed related to possible toxicity on Term 1.
In addition to 5-6 weeks of radiotherapy, subjects have also received 2 doses of TOMUDEX.

This is an open study of TOMUDEX in combination with radiotherapy. Up to 78 subjects was required to complete the study. It is recommended that TOMUDEX is given on the same day at least 1 hour before the radiotherapy. Subjects have received radiotherapy and TOMUDEX as follows:

a) Radiotherapy has been given by a ***planned volume (to be confirmed)*** to the pelvic area at 3 or 4 fields treating with 28 fractions at 1.8 Gy per fraction. Treatment has been daily on weekdays for a period of 5-6 weeks
b) TOMUDEX has been given on Day 1 and Day 22 where Day 1 is the first day that radiotherapy is given.

Doses must be based on surface area using actual weight and height.

TREATMENT PLAN

	Week1	Week2	Week3	Week4	Week5	Week6
Radiotherapy 1.8 Gy	✓✓✓✓✓	✓✓✓✓✓	✓✓✓✓✓	✓✓✓✓✓	✓✓✓	✓✓✓
TOMUDEX	Day1			Day22		

Radiotherapy should be stopped/changed by the decision of the radiotherapist. The second dose of TOMUDEX may be given at the investigators decision.
The study plan indicates the number and timing of the planned visits. The timing of subsequent visits should be planned to maintain the planned visit interval since the last visit. It is important to stick to the study plan as closely as possible. It is the responsibility of the investigator to ensure that the principal investigator will be informed if a patient is deviating from the pre-determined treatment plan.
N.B. It is important to maintain the visit schedule within a $\pm$ 3 day window.
Subjects have been recruited at MoH Okmeydanı Training and Research Hospital, Radiation Oncology Clinic.
It was estimated that up to 39 patients with locally advanced irresectable rectum carcinoma and up to 39 patients with recurrent rectum cancer would be required to complete this study.

Inclusion criteria
For inclusion, subjects must fulfill all of the following criteria:
1 Confirmed diagnosis of inoperable/recurrent rectal cancer.
2 Age $\geq$ 18 years.
3 At least 1 measurable lesion should be present
4 WHO performance status score $\leq$ 2.
5 Life expectancy of at least 12 weeks.
6 Subjects considered appropriate to receive systemic chemotherapy and pelvic radiotherapy.

7 Documented informed consent to participate in the study.

Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1 Previous systemic chemotherapy

2 Previous radiotherapy to the planned exposure area.

3 Subjects with distant metastases.

4 * (a) White blood cell (WBC) $< 4.0 \times 10^9$/L (unless absolute neutrophil count is $\geq 2.0 \times 10^9$/L),
or
(b) Platelet count $< 100 \times 10^9$/L.

5 * Serum creatine above the upper limit of the normal range.

6 * (a) Serum bilirubin > 1.25 times the upper limit of the normal range,
or
* (b) Asparate aminotransferase (AST) or Alanine aminotransferase (ALT) > 2.5 times the upper limit of the normal range.

7 Any severe concurrent medical condition which would make it undesirable, in the clinician's opinion, for the patient to participate in the study or which would affect compliance with the study protocol.

8 Pregnancy or breast feeding. Women of child-bearing age must use effective contraception method.

9 Previous or current malignancies at other sites, with the exception of adequately treated in-situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.

10 Patient participation in other studies.

* These assessments should be carried out within the 14-day period prior to study treatment.

The following restrictions should be applied to subjects in this study:

(1) Subjects who are blood donors should not donate blood during the study and for 3 months following their last dose of study treatment.

(2) Subjects must not receive folic acid (including any vitamin supplements which contain folic acid).

(3) Subjects must not receive any other concomitant systemic cancer therapy other than the study treatment.

It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- deliveries of such products from AstraZeneca Pharmaceuticals are received by a responsible person (e.g., a pharmacist)
- such deliveries are recorded
- study treatments are handled and stored safely and properly
- study treatments are only dispensed to study subjects in accordance with the protocol
- any unused products are returned to AstraZeneca Pharmaceuticals

At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist.

Formulation, presentation and storage
Formulation
TOMUDEX has been provided as a lyophile. Each vial contains 2 mg of TOMUDEX as the diacid buffered with 1.5 mg sodium phosphate, dibasic, heptahydrate, 203 mg mannitol and sodium hydroxide to adjust the pH to 7.4. The lyophile has an insert headspace of nitrogen (AstraZeneca formulation number F11354).

Presentation
TOMUDEX has been presented as a 2 mg white lyophile in sterile vials. The product is to be reconstituted with 4 ml of water for injections to produce an isotonic solution containing 0.5 mg/ml TOMUDEX. The vials are for single dose usage.

Storage
The vials must be stored at room temperature in a secure location away from the light. Do not freeze.
As there is no preservative or bacteriostatic agent in TOMUDEX, it is recommended that reconstituted TOMUDEX solution is used as soon as possible or stored in a refrigerator (2 to 8 ^{0}C) for up to 24 hours. Once prepared, the solution must be completely used or discarded within 24 hours.

Dosage and Administration
Concomitant Treatment
Standard cytotoxic handling procedures must be followed when preparing TOMUDEX for administration.
The contents of the reconstituted vials may be further diluted in either 5% dextrose or 0.9% saline. The concentration of the final solution must not be less than 0.002mg/ml or exceed 2 mg/ml. At these concentrations TOMUDEX is stable at 25°C exposed to ambient light for up to 24 hours. As there is no preservative or bacteriostatic agent in TOMUDEX, it is recommended that TOMUDEX be reconstituted and diluted under aseptic conditions and that reconstituted TOMUDEX solution is used as soon as possible or stored in a refrigerator (2 to 8 ^{0} C) for up to 24 hours.
Subjects have received a 15 minute IV infusion of the appropriate dose. Subjects have receive 2 doses of TOMUDEX separated by an interval of 3 weeks.

Dose Modification
It is intended that subjects should receive treatment as described above. However, the dose of TOMUDEX must be adjusted (delayed and/or reduced) in the presence of the toxicity development of renal failure.

Dose Delay

In the event of ongoing unacceptable or clinically relevant toxicity, dosing must be delayed, for a maximum of 14 days, until all signs of toxicity have resolved or are resolving. Diarrhea and mucositis must have resolved completely. All abnormal hematological and liver function test results must have returned to levels that meet the

study selection criteria. If after 14 days of delay these conditions are not met, the subject will receive no more doses of study therapy. For subjects with abnormal serum creatine at the time of intended retreatment, a creatine clearance should be performed or calculated. With a creatine clearance of 25 ml/min or less no further TOMUDEX treatment will be given. If the clearance is 25-65 ml/min the dose of TOMUDEX should be reduced by 50%. If the investigator assesses radiotherapy toxicity on day 21 prior to the second dose of TOMUDEX to be severe objectively:

- significant symptomatic moist skin desquamation;
- WHO grade 2 diarrhea with abdominal pain;

or subjectively feels that full treatment may not be completed due to toxicity then the second dose of TOMUDEX should be omitted.

Dose Reduction

Dose reduction has applied to TOMUDEX only. The second dose of TOMUDEX has been based upon the worst WHO grade of selected hematological and non hematological toxic effects observed after the first dose. The hematological variables considered have been the leukocyte, neutrophil and platelet counts. The non-hematological effects considered have been diarrhea. In addition, creatine clearance has been considered in those subjects with abnormal serum creatine values.

Patient Entry

The eligibility of each subject has been established before allocation to treatment.
Inclusion/exclusion criteria must be strictly obeyed. Subject numbers have been allocated strictly sequentially as subjects enter the study. Once a number has been assigned, no attempt has been made to use that number again if, for example, a subject drops out or withdraws. No subject has entered twice into the study.

Drug or Study Treatment Monitoring

The study treatment must be used only as directed in the protocol. Records of overall dispensing and returns have been maintained by each centre, separately from the case report forms (CRFs) as the record of the drug dispensed to individual subjects.
The investigator must retain all unused medication and empty containers until they are collected by AstraZeneca Pharmaceuticals authorized personnel, along with any study treatments not dispensed.
It is essential that all medication and other treatments are accounted for by the investigator or institution, and that any discrepancies are explained and documented.

Assignment to Treatment

The eligibility of each subject has been established before allocation to treatment. Subject numbers have been allocated strictly sequentially as subjects enter the study. Once a number has been assigned, no attempt has been made to use that number again if, for example, a subject is withdrawn from the study. No subjects have entered into the study more than once.
Subjects must not receive any other systemic anticancer therapy with the study treatment. They should also not take vitamin supplements containing folic acid.

Though $5HT_3$ antagonist are generally not required, subject may use antiemetic for prophylaxis.
It is essential that subjects experiencing WHO grade 3 or 4 toxicity have appropriate dose reduction or are withdrawn from treatment.
In the event of severe toxicity, the patient should receive full supportive care. It is recommended that patients with grade 3 or 4 diarrhea should be admitted to hospital and treated with intravenous fluids and antibiotics, especially when there is concomitant leucopenia. If anti-proliferative toxicities are not settling within 4 to 5 days folinic acid should be used ($25mg/m^2$ intravenously every 4 to 6 hours). In the presence of rapidly decreasing serum albumin, total parenteral nutrition should be added. If leucopenia is protracted, in addition to folinic acid, G-CSF may be added, according to local practice.
All concurrent therapies should be reported on the appropriate section of the CRF's.

Clinical and Laboratory Evaluation
Primary Endpoints

The following parameters have been assessed:
Clinical staging pre and post chemoradiotherapy; Measurement of marker lesion dimensions; Clinical resectability after chemo-radiotherapy; pathological staging after resection.

Secondary Endpoints

Time to progression
Survival
Collection and review of radiotherapy toxicity: (adverse events, treatment breaks, radiotherapy dose reductions and withdrawals).
Collection and review of chemotherapy toxicity: (adverse events, dosing delays and reductions and withdrawals).

Safety Evaluations
Hematology and Biochemistry

Laboratory parameters have been assessed during the treatment period and in the follow-up period defined below.
Hematology and biochemistry evaluations have been performed at the local laboratory for the study centre before each treatment course. For the first treatment course, these assessments must be carried out within the 14-day period prior to treatment. For the second TOMUDEX dose, hematology must be assessed no more than 3 days and biochemistry no more than 7 days prior to the second dose.
Hematology evaluations have been performed weekly from the 1st dose of TOMUDEX until 3 weeks after the second TOMUDEX dose and a further biochemistry evaluation has been performed 3 weeks after the second TOMUDEX dose.

Subjects who experience diarrhea WHO grade 2 or more in severity should have a blood count (for leucocytes, neutrophilis and platelets) performed immediately. Subjects receiving TOMUDEX who develop abnormal serum creatine values should have a creatine clearance performed or calculated. This can be calculated as follows using the Cockcroft Formula.

For Male patients creatine clearance is equal to:

$$\frac{88.4 \times (140 - \text{Age}) \times \text{Weight}}{72 \times \text{serum creatine}}$$

For Female patients creatine clearance is equal to:

$$\frac{75.23 \times (140 - \text{Age}) \times \text{Weight}}{72 \times \text{serum creatine}}$$

where the units are

Creatine clearance - mL/min
Age - years
Weight - Kg
Serum creatine - μmol/L

Dose modification for the second dose should be calculated based on the worst grade of diarrhea and hematological suppression (leucopenia, neutropenia and/or thrombocytopenia) after the first dose and creatine clearance during the treatment.

Laboratory assessments are as follows :
Hematology:
Hemoglobin
Platelet count
White blood cell count (Total)
Neutrophils

Serum biochemistry :
Total protein
Albumin
Total bilirubin
Alkaline phosphatase
Aspartase aminotransferase (AST)
Alanine aminotransferase (ALT)
Sodium
Potassium
Creatine

Hematology assessments must continue weekly until 3 weeks after the last dose of TOMUDEX. Biochemistry assessment must be carried out until 3 weeks after the last dose of TOMUDEX.
Analyses of the blood samples have been carried out at the local hospital laboratory.
In order to allow more accurate evaluation of safety, all subjects who have WHO grade 3 or 4 laboratory values at the end of the treatment period should be followed until they

have returned to grade 1 or 2. Unless, in the investigator's decision, these are never likely to improve due to the underlying disease.

Clinical Evaluations

A medical history including demographic information (date of birth, race and height) have been obtained and recorded within 21 days prior to study treatment.
A full physical examination has been performed at baseline.

RESULTS:

Considering demographic features, a total of 49 patients (mean age: 58.55 ± 12.91 years, males: 71.4%) were enrolled in the study. Population was shown to be homogenous in terms of age and gender. The majority of the patients (57.1%) were between 50-70 years of age. Mean values for height and weight were 167.36 ± 11.14 cm and 69.03 ± 9.38 kg, respectively. The study population was found to be normal in physical examination. Gastrointestinal symptoms (i.e. abdominal pain, flactulance, rectal bleeding, constipation and diarrhea were the most frequent complaints when compared to other systems (75.5%).
A total of 43 patients (87.8%) were diagnosed with a locally advanced rectal cancer. Raltitrexed was applied accordingly without any dose reductions, thus, the doses of the drug did not show a significant difference in two consecutive treatment cycles. 24.5% of the patients stated that they were previously treated for a malignancy. In 85.7% (n=42) of the patients, there was a single concurrent medical illness in the medical history. But only 5 (10.2%) of them was found to have active illness. A second accompanying disorder was present in 79.6% (n=39) of the patients. Among them only 24.5% (n=12) reported an ongoing clinical disorder. A third accompanying medical disorder was present in 57.1% (n=28) of the patients of which only 24.5% (n=12) reported current disorder-related complaints.
The number of patients showed a decline at each visit during the course of the study. Overall, the mean of the patients remained in the study was 33.27 ± 16.37.

Performance status of the patients

According to the performance scores, 57.1% of the patients were completely active in both initial screening and 1st cycle. Another 53.1% was completely active in the 2nd cycle of the treatment. There was no statistically significant difference between patients of screening and treatment cycles regarding the performance status (p=1.183).

Hematological and biochemical *parameters*

Hemoglobin, leukocyte and platelet counts were found to be decreased significantly at the end of the treatment period when compared to baseline levels.
Considering the biochemical profile, serum total protein (6.95 ± 0.72 g/L vs 6.73 ± 0.6 g/L; $p<0.01$), albumin (3.83 ± 0.57 g/L vs 3.60 ± 0.72 g/L; $p<0.001$) and ALP (137.45 ± 88.6 IU/L vs 106.56 ± 74.86 IU/L; $p<0.05$) levels were decreased while AST (19.38 ± 8.53 IU/L vs 39.18 ± 26.29 IU/L; $p<0.001$), and ALT (17.02 ± 10.9 IU/L vs 50.06 ± 58.8 IU/L; $p<0.01$) levels were found to be increased at the 2nd cycle of the treatment (day 22) compared to baseline values.

Evaluation of the tumor

In 87.8% (n=43) of the study population had an inoperable disease. The most frequent tumor grades among the study population were t3NxM0 (n=18; 36.7%) and t3NxM (n=9; 18.4%). The tumor region in the patients were rectum (n=32; 65.3%) and pelvis (n=1; 2%). In 16 patients, the tumor region was immeasurable. Tumor size was found to be 2.38 ± 2.46 cm and 3.26 ± 3.30 cm at two subsequent measurements in 29 patients.

Response to treatment

At the 1st follow-up visit, the complete and partial clinical response rates were 14.3% (n=7) and 28.6% (n=14), respectively. In 16.3% (n=8) of the patients, no clinically significant improvement was observed. Disease progression was 6.1% (n=3). At the 1st visit, it was observed that in 33 patients (67.3%) the tumor was resected. Four patients were not operated and 12 patients were lost to follow-up. In the tumor-resected patients, the most frequent tumor grades were as follows: T3N2M0 (n=8; 16.3%), T3N0M0 (n=5; 10.2%), T2N0M0 (n=3, 6.1%) and T2N1M0 (n=3; 6.1%) and T2N2M0 (n=2; 4.1%). At the 2nd follow-up visit, the complete and partial clinical response rates were 6.1% (n=3) and 2.0% (n=1), respectively. In 2.0% (n=1) of the patients, the treatment regimen did not seem to promote a clinical improvement. Disease progression was observed in 6.1% (n=3) of the patients. At the 3rd follow-up visit, the complete response rate was 2.0% (n=1) and disease progression was 4.1% (n=2). At the 4th follow-up visit, disease progression rate was observed in 5 patients. At the 5th follow-up visit, the treatment regimen did not seem to alter the clinical course in 1 patient (2.0%). Disease progression was detected in 3 patients (6.1%).

Adverse events

A total of 37 patients experienced adverse events such as diarrhea, nausea, abdominal pain, polyuria, leukopenia, anemia, tachycardia which prolonged the duration of hospitalization. None of these adverse effects caused permanent disability or were life-threatening. Most frequently observed event was grade III diarrhea (17.5%). Grade II nausea was reported as the second most commonly experienced adverse event (15.5%). Of the 97 events, 43 were mild (44.3%), 43 were moderate (44.3%) and the remaining 10 were severe (10.3%). Raltitrexed was found to be related with 51 (52.6%) of the total adverse events whereas radiotherapy was associated with 67 (69.1%) of the total events.
Severe adverse event (SAE) was observed in 14.3% (n=7; 4 males and 3 females) of the patients. The major outcomes of the SEAs were death in 3 patients (6.1%), life-threatening event in 1 patient (2%) and hospitalization or prolongation of hospitalization period in 3 patients (6.1%). Among patients with SAEs, 6 (12.2%) were under treatment with raltitrexed.
A total of 57.1% of the study population completed the study.

Survival rate and time *to progression*

According to Kaplan-Meier survival analysis, the median survival rate of the study population was 23.69 months. In the total of 49 patients, 4 of them died (survival rates: 0.98 ± 0.02; 0.95 ± 0.03; 0.92 ± 0.04 and 0.46 ± 0.33). Cox regression analysis demonstrated no significant relationship between tumor resectability and the mortality rate of the patients ($p>0.05$).

Inventory of Distribution and Usage of the Investigational Product

The study drugs were provided by AstraZeneca Corp. The study drugs were prepared to be given to the patients via 3 boxes per visit. (TOMUDEX, 2 mg was delivered to subjects as white lyophile in sterile vials)

**It is required in all multicentral studies that, the outcome reports, which are conducted by each site, must be delivered to the Ministry with the approval of only the co-coordinator centre and the whole data processed.*