

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Tomudex

ACTIVE INGREDIENT: Raltitrexed

Trial title: Pan-European Trials in Adjuvant Colon Cancer (PETACC-1) Randomized Phase III trial of Tomudex (Raltitrexed) vs. Standard Leucovorin modulated bolus 5-FU in patients with Dukes' stage C colon cancer.

Developmental phase: III

First subject recruited: 27 February 1998

Data cut-off date: 17 July 2003

Approval date: 06 November 2007

OBJECTIVES

Primary Objective

The primary endpoints are RFS (recurrence-free survival) and duration of survival. The primary objective of the trial is to investigate whether Tomudex is equivalent to bolus 5-FU+LV with respect to recurrence-free survival (RFS) and duration of survival, in patients with Dukes' Stage C colon cancer, who have had a curative resection within the last 56 days.

Secondary Objectives

The secondary objective of the trial is to compare the safety profiles of Tomudex and 5-FU + LV and to explore the effect of different doses of 5-FU on toxicity.

However, because the trial was terminated prematurely, the effect of dosing of 5-FU in relation to treatment toxicity was not analyzed and this secondary objective is thus not presented in the present report.

METHODS

Study Design

This trial is a randomized parallel group multicentre international intergroup phase III trial.

Treatment regimen

Patients will be randomized between either of:

Standard arm:

Leucovorin 20 mg/m² i.v. bolus, followed by 5-fluorouracil 425 (or 370) mg/m² i.v. bolus Both drugs given on days 1 to 5, repeated on day 29 to 33 and so on for 6 cycles (24 weeks). Day 1 to day 28 is one cycle.

Experimental arm:

Tomudex 3.0 mg/m² 15 minutes i.v. infusion given on day 1, repeated on day 22 for 8 cycles (24 weeks). Day 1 to 21 is one cycle.

Stratification for: Institution

Primary endpoints: RFS and duration of survival

Secondary endpoints: Safety

Sample Size

Both primary endpoints have been used for the calculation of sample size. Assuming the 5-year survival for Dukes' C patients in the control arm (5-FU + LV arm) to be 67% (Wolmark et al., 1993), Tomudex will be judged to be equivalent (not inferior) if the relative risk of death for patients on Tomudex was significantly less than 1.25 using a one-sided hypothesis test at the 0.05 level of significance (i.e. the upper one-sided 95% confidence limit for the hazard ratio must be less than 1.25). This corresponds to a 5-year survival for the Tomudex arm significantly greater than 60.62%. Based on a one-sided power of 90%, a total of 703 deaths are needed before performing the final analysis. If we further assume 2 years of recruitment and 3 more years of follow-up, a total of 2514 patients should be randomized between the 2 arms. This number will be further increased by 10% for any possible loss to follow-up. This adds up to a total of 2765 Dukes' C patients to be randomized. For RFS, the same number of events, that is, 703 recurrences or deaths whichever occurs first, will be sufficient to test the equivalence (non-inferiority) of Tomudex to bolus LV-modulated 5-FU with respect to RFS. The same definition of equivalence will be used, that is, a hazard ratio significantly less than 1.25 using a one-sided hypothesis test at the 0.05 level of significance and a power of 90%. This analysis will be performed when these 703 events are reported. Assuming the 3-year RFS estimates in the control arm to be 67% (Wolmark et al., 1993), these 703 events are expected to be observed approximately one and half years after closing the trial to patient entry, assuming a 2-year recruitment period.

Target patient population

All randomized patients will be analyzed in the arm to which they were allocated by randomization. All patients who are eligible, randomized before or on January 15, 1999 and have started the allocated treatment (at least one dose of study drug) are included in the primary analysis of the study (RFS and duration of survival). The patients who joined the trial after January 15, 1999 are excluded from this population to guarantee that all patients included had completed treatment by July 16, 1999, when the trial was prematurely closed.

A patient will be considered *Eligible* if he/she did not have any major deviation from the study selection criteria as listed in the protocol chapter 3.

Among the eligibility criteria, the patients are required to have a Dukes' Stage C colon cancer with a curative resection within the last 56 days.

	Treatment allocated		
	LV-modul bolus 5-FU (N=969) N (%)	Tomudex (N=952) N (%)	Total (N=1921) N (%)
Eligible			
Yes	953 (98.3)	934 (98.1)	1887 (98.2)
No	16 (1.7)	18 (1.9)	34 (1.8)
Reason for ineligibility			
Not Duke's C colon cancer	9	11	20
Curative radical resection more than 56 days before start of trial	1	2	3
Serum creatinine > 1.5 UNL value	0	1	1
Abnormal liver function	3	2	5
Previous malignancy during the last ten years	2	2	4
Curative radical resection more than 56 days before start of trial AND Serum creatinine > 1.5 UNL value	1	0	1

Duration of treatment

Treatment given	Treatment allocated		
	LV-modul bolus 5-FU (N=969)	Tomudex (N=952)	Total (N=1921)
	N (%)	N (%)	N (%)
LV-modul bolus + 5-FU	937 (96.7)	1 (0.1)	938 (48.8)
Tomudex	0 (0.0)	918 (96.4)	918 (47.8)
Non protocol treatment or no treatment	32 (3.3)	33 (3.5)	65 (3.4)

	Treatment allocated		
	LV-modul bolus 5-FU (N=969)	Tomudex (N=952)	Total (N=1921)
	N (%)	N (%)	N (%)
Intent to treat population	969 (100.0)	952 (100.0)	1921 (100.0)
Per protocol population*	489 (50.5)	504 (52.9)	993 (51.7)
Safety population	937 (96.7)	918 (96.4)	1855 (96.5)

*Per protocol population: all patients who are eligible, randomized before or on January 15, 1999 and have started the allocated treatment (at least one dose of study drug)

NB: Patient entered before and up to cut-off date January 15, 1999, included: LV-5FU: 508 (52.4%), TOMUDEX: 528 (55.5%), TOTAL: 1036 (53.6%)

Criteria for evaluation

Efficacy Endpoints

Recurrence-free survival is the time from randomization to recurrence or death, whichever occurs first. Patients without the event of interest are censored at the time of most recent follow-up visit.

Recurrence-free survival duration is therefore the number of days elapsed between the day of randomization and the minimum of the date of recurrence, the date of death or most recent follow-up visit.

Duration of survival is the time from randomization to death. Patients without the event of interest are censored at the time of most recent follow-up visit. Overall survival duration is therefore the number of days elapsed between the day of randomization and the minimum of the date of death or most recent follow-up visit.

Safety

All patients that received at least one dose of assigned chemotherapy will be evaluable for safety of the treatment, irrespective of eligibility. Patients who received CTs that differed from those assigned according to randomization schedule will be excluded from entire safety analyses with explanations. They will be described separately.

Patient population

Recruitment				
Group	Recruitment Period			
	≤6 months (N=366)	6-12 months (N=869)	12-18 months (N=686)	Total (N=1921)
	N (%)	N (%)	N (%)	N (%)
APIO	0 (0.0)	7 (0.8)	4 (0.6)	11 (0.6)
CGCRC	38 (10.4)	109 (12.5)	110 (16.0)	257 (13.4)
ECS	32 (8.7)	17 (2.0)	7 (1.0)	56 (2.9)
EORTC	74 (20.2)	232 (26.7)	164 (23.9)	470 (24.5)
FFCD	3 (0.8)	18 (2.1)	21 (3.1)	42 (2.2)
GG2	43 (11.7)	85 (9.8)	66 (9.6)	194 (10.1)
GOCCI	3 (0.8)	15 (1.7)	16 (2.3)	34 (1.8)
ICMTC	4 (1.1)	33 (3.8)	41 (6.0)	78 (4.1)
INTACC	58 (15.8)	102 (11.7)	97 (14.1)	257 (13.4)
QUASAR	32 (8.7)	128 (14.7)	75 (10.9)	235 (12.2)
TTD	79 (21.6)	123 (14.2)	85 (12.4)	287 (14.9)

Recruitment			
Group	Treatment allocated		
	LV-modul bolus 5-FU (N=969)	Tomudex (N=952)	Total (N=1921)
	N (%)	N (%)	N (%)
APIO (Associação Portuguesa da Investigação Oncológica) Dr. Evaristo Sanches	7 (0.7)	4 (0.4)	11 (0.6)
CGCRC (Canadian Group for Colorectal Cancer) Dr. Mark Vincent	131 (13.5)	126 (13.2)	257 (13.4)
ECS (Egyptian Cancer Society) Pr. Mostafa El-Serafi	31 (3.2)	25 (2.6)	56 (2.9)
EORTC (European Organization for Research and Treatment of Cancer) Prof. J. Wils	236 (24.4)	234 (24.6)	470 (24.5)
FFCD (Fondation française de Cancérologie digestive) Pr. Laurent Bedenne	24 (2.5)	18 (1.9)	42 (2.2)
GG2 (Gruppo Interdisciplinare Valutazione Interventi in Oncologia, Gruppo Italiano Studio Carcinomi apparato Digerente) Pr. Roberto Labianca	94 (9.7)	100 (10.5)	194 (10.1)
GOCCI (Gruppo Oncologico Chirurgico Cooperativo Italiano) Dr. Enrico Mini	15 (1.5)	19 (2.0)	34 (1.8)
ICMTC (Intergruppo Centro-Meridionale Tumori Colon-retto) Pr. Raffaele Bianco	40 (4.1)	38 (4.0)	78 (4.1)
INTACC (Intergruppo Nazionale Terapia Adjuvante Carcinoma Colon) Pr. Francesco Di Costanzo	125 (12.9)	132 (13.9)	257 (13.4)
QUASAR (Clinical Trials Unit) Pr. David Kerr	121 (12.5)	114 (12.0)	235 (12.2)
TTD (Grupo Espanol para el Tratamiento de Tumores Digestivos) Pr. Alfredo Carrato Mena	145 (15.0)	142 (14.9)	287 (14.9)
Year of recruitment			
1998	465 (48.0)	495 (52.0)	960 (50.0)
1999	504 (52.0)	457 (48.0)	961 (50.0)

		Treatment allocated		
		LV-modul bolus 5-FU (N=969)	Tomudex (N=952)	Total (N=1921)
		N (%)	N (%)	N (%)
Gender				
	Female	460 (47.5)	434 (45.6)	894 (46.5)
	Male	509 (52.5)	518 (54.4)	1027 (53.5)
Race?				
	Caucasian	933 (96.3)	924 (97.1)	1857 (96.7)
	Other	30 (3.1)	26 (2.7)	56 (2.9)
	Unknown	6 (0.6)	2 (0.2)	8 (0.4)
Age (years)				
	Median	63.7	62.6	63.3
	Range	20.2 - 84.8	19.9 - 87.5	19.9 - 87.5
	Q1-Q3	55.5 - 69.8	54.2 - 69.3	54.6 - 69.6
	Mean (SD)	62.03 (10.74)	61.22 (10.72)	61.63 (10.74)
	N obs	968	952	1920
Histopathology grading				
	Well differentiated	127 (13.1)	126 (13.2)	253 (13.2)
	Moderately differentiated	627 (64.7)	615 (64.6)	1242 (64.7)
	Poorly differentiated	166 (17.1)	152 (16.0)	318 (16.6)
	Undifferentiated	3 (0.3)	3 (0.3)	6 (0.3)
	Unknown	44 (4.5)	50 (5.3)	94 (4.9)
	Missing	2 (0.2)	6 (0.6)	8 (0.4)
T classification (UICC 1997)				
	T1	14 (1.4)	10 (1.1)	24 (1.2)
	T2	76 (7.8)	81 (8.5)	157 (8.2)
	T3	741 (76.5)	723 (75.9)	1464 (76.2)
	T4	131 (13.5)	125 (13.1)	256 (13.3)
	Tis	1 (0.1)	0 (0.0)	1 (0.1)
	Unknown	6 (0.6)	13 (1.4)	19 (1.0)
N classification (UICC 1997)				
	N1	653 (67.4)	645 (67.8)	1298 (67.6)
	N2	310 (32.0)	297 (31.2)	607 (31.6)
	Unknown	6 (0.6)	10 (1.1)	16 (0.8)
M classification (UICC 1997)				
	M0	956 (98.7)	928 (97.5)	1884 (98.1)
	M1	1 (0.1)	7 (0.7)	8 (0.4)
	Unknown	12 (1.2)	16 (1.7)	28 (1.5)
	Missing	0 (0.0)	1 (0.1)	1 (0.1)
Lymphatic vessels invaded?				
	No	301 (31.1)	315 (33.1)	616 (32.1)
	Yes	186 (19.2)	196 (20.6)	382 (19.9)
	Unknown	481 (49.6)	437 (45.9)	918 (47.8)
	Missing	1 (0.1)	4 (0.4)	5 (0.3)

Results

The trial data provided a median follow-up of 4 years up to the cut-off date of July 16, 2003 on all patients in the intent-to-treat population.

The data analysis reflected the trial history, with a per protocol population that excluded the patients who may not have finished the complete treatment (lasting 6 months in theory) by the date when the trial was prematurely terminated.

The results indicated that there were differences in side effects between the two groups, but the toxicity observed is consistent with published results: the hematological and gastrointestinal toxicity was higher in the 5FU/LV arm whereas liver toxicity (transaminases) was higher in the Tomudex group. The number of fatal serious adverse events was also higher in the Tomudex arm (20 vs 8), but did not relate to significant survival deficit for the Tomudex arm. Indeed, with 5% risk of a false positive conclusion, the results are within the boundary of non inferiority for overall survival.

The efficacy results in the per protocol population however show that Tomudex is not equivalent to 5FU-LV as regards recurrence-free survival.

The possibility of cross-over to other drugs after trial closure, especially in the ITT population, may artificially inflate the risk of erroneously claiming non inferiority.

	Treatment allocated		
	LV-modul bolus 5-FU (N=909)	Tomudex (N=952)	Total (N=1921)
	N (%)	N (%)	N (%)
Overall Survival			
Alive	716 (73.9)	700 (73.5)	1416 (73.7)
Dead	253 (26.1)	252 (26.5)	505 (26.3)
Cause of death (% of dead patients)			
Cancer alone	141 (55.7)	140 (55.6)	281 (55.6)
Fatal SAE related to treatment	8 (3.2)	20 (7.9)	28 (5.5)
Other / missing/Unknown	104 (41.1)	92 (36.5)	206 (40.0)
Number of deaths within 6 weeks of entry in the trial	8	4	10
Number of events (deaths) after cut-off date 16JUL2003	3	6	9

In total, there were fatal SAEs related to treatment (reported as SAEs or in the death report form in 8 patients on 5FU/LV vs 20 patients on Tomudex (see listing), however, this did not lead to any significant survival difference between the two treatment groups.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Tomudex™ (Raltitrexed), Healthcare Professionals should [view their specific country information](#).