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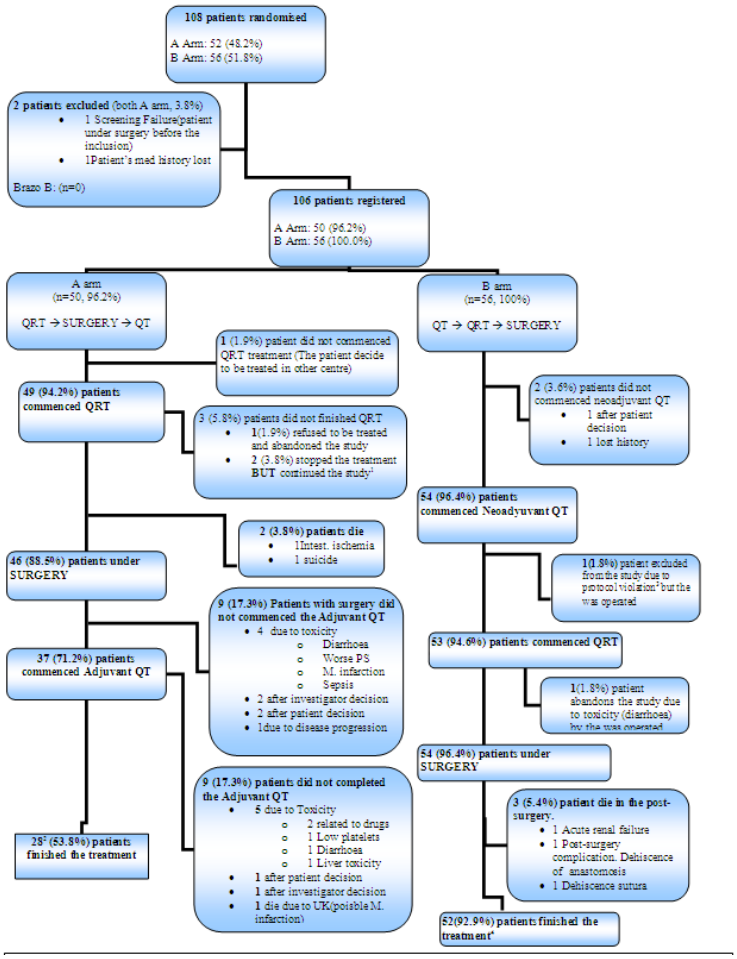
Sponsor / Company : sanofi-aventis **Drug Substance :** Oxaliplatin and Capecitabine	**Study Identifier** : NCT00421824 **Study Code** : PM_L_0098
Title of the study:	Phase II randomized trial of neoadjuvant chemotherapeutic treatment (CAPEOXA-XELOX) followed by chemoradiotherapy (CAPEOXA-XELOX/RT) and surgery versus chemoradiotherapy followed by surgery and chemotherapy in patients with high risk rectal cancer
Study center(s):	Complexe Sanitari Parc Taulí, Sabadell Instituto Valenciano de Oncología, Valencia Hospital Univ. La Fe, Valencia Hospital Univ. Arnau de Vilanova, Valencia Hospital Univ. General de Alicante, Alicante Hospital Univ. Miguel Servet, Zaragoza Hospital General de Valencia, Valencia Hospital de Navarra, Pamplona Hospital Clínico Univ. Lozano Blesa, Zaragoza Hospital Clínic, Barcelona Hospital de la Santa Creu i Sant Pau, Barcelona Hospital Univ. Dr. Peset, Valencia Hospital Son Dureta, Palma de Mallorca Hospital del Mar, Barcelona Hospital de Barbastro, Barbastro (Huesca) Hospital Univ. La Paz, Madrid
Study period: Date first **patient** enrolled: 09-MAY-2006 Date last **patient** completed: 30-NOV-2010	**Phase of development:** Phase II
Objectives:	**Primary objective**: Complete pathological (ypT0N0) response rate obtained with two different treatment strategies. **Secondary objectives:** • Safety • Assessment of downstaging rate of both strategies • Comparison of relative dose intensity of oxaliplatin and capecitabine of both strategies • Comparison of time to progression and overall survival of both strategies
Methodology:	Open-label, randomized, multicenter trial

Number of patients:	Planned : 108	Randomized : 108	Treated : 106
Evaluated:	Efficacy : 100	Safety : 103	



Note 1: Two patients did not finish the QRT treatment but continued in the study (Underwent surgery), and are included in the "SURGERY" group.

Note 2: Two patients received just 3 cycles of adjuvant chemotherapy, but were considered in the CRF as "finished treatment"

Note 3: This patient received radiotherapy before established.

Note 4: One patient had a "non resected tumor", but the investigator recorded it as" finished treatment".

Percentages are referred to number of randomised patients per arm.
QRT: Chemoradiotherapy
QT Chemotherapy

Diagnosis and criteria for inclusion:	Inclusion Criteria: • Patients with rectal adenocarcinoma • Operable tumour, confirmed by magnetic resonance of high resolution and / or endorectal echography, or, • Rectal tumour at distal third, or • Tumours spread more than 5 mm in perirectal fat • Functional state ECOG ≤ 2 • Good hematological, hepatic and renal function Exclusion Criteria: • Previous pelvis radiotherapy • Previous antitumoural chemotherapy • Pregnant or breastfeeding women • Childbearing women with a positive pregnancy test result at baseline. Menopausal women should not have the period for the last 12 months. • History of any other neoplasic illness within the last 5 years, except for already resolved small cell skin cancer or cervix cancer. • Clinically significant cardiovascular disease • Confirmed peripheral neuropathy • Gastrointestinal disorders or bad absorption syndrome or non-capable to take oral medication • Blood disorders • Intercurrent non-controlled or severe infections • Patients who have undergone major surgery, open biopsies or with significant trauma lesions within the previous 28 days
Investigational product: Dose: Administration:	Oxaliplatin and capecitabine Arm A: OXA 130 D1 + Capecitabine 2000 / day D1-D14 for 4 cycles. After 10 weeks of rest, XELOX-RT regimen x 5 weeks followed by surgery Arm B: XELOX-RT x 5 weeks followed by surgery and 4 cycles of adjuvant XELOX with the same scheme as arm A RT: Radiotherapy was delivered by a linear accelerator with a minimum of 6 MV by using a three- or four-field technique. The treatment volume included the primary tumor and the mesorectal, presacral, and internal iliac lymphnodes up to the level of the bottom part of the fifth lumbar vertebra. All patients received a total dose of 50.4 Gy, and daily fractions of 1.8 Gy were received 5 days per week. IV (Intravenous)
Duration of treatment: 4 cycles (one cycle=3 weeks) or until disease progression	**Duration of observation:** Up to 36 months
Criteria for evaluation:	
Efficacy:	Complete pathological (ypT0N0) response rate

Safety:	NCI-CTCAE v3.0 Criteria (Nationcal Cancer Institute-Common Terminology Criteria for Adverse Events)
Statistical methods:	Quality control prior to statistical analysis will be done once data are tabulated. Initial analysis of results will be done when all patients have been followed up for at least 3 months after surgery. Firstly, a description of baseline characteristics of patients included in the study by percentages and confidence intervals for categorical variables and measures of central tendency for quantitative variables (mean, median, standard deviation and range) will be done. The following variables will be described, among others: • Breakdown of patients excluded from the analysis, indicating the reason for exclusion. • Distribution of prognostic variables. • Distribution of toxicity. • Chemotherapy and radiotherapy administered dose, cycles and dose modifications, either delays or reductions, stating the reason and the intensity of drug relative doses. • Variables of efficacy observed: CPR (Complete Pathological Response) and downstaging rate. Final analysis will be performed when all patients have been followed up at least 1 year after surgery and will include: • Patterns of recurrence (local and systemic). • Recurrence-free survival. • Overall survival. • Toxicity deferred. Unless otherwise specified, a bilateral significance level of 5% in all tests will be used. The endpoint time to event onset is described using Kaplan-Meier curves and life tables. The confidence interval for median times will be calculated using nonparametric methods. The groups will be compared using tests of "logrank". Chi-square tests will be used to compare categorical variables in both groups, unless the expected frequency in any cell is <5 in which case using the Fisher exact test. The confidence intervals will be calculated through binary event rates. Continuous variables with normal distribution will be compared using the nonparametric test of Wilcoxon. The description of patients will include: • Breakdown of patients excluded from the analysis, indicating the reason for exclusion. • General description of the patients under study. For statistical analysis, the study used the SAS package.

Summary:	**Baseline Demographic and Clinical Characteristics for the Total Patient Group**
Efficacy results:	

Characteristic	Arm A: Post-operative Adjuvant CT (n = 52) No.	%	Arm B: Induction CT (n = 56) No.	%
Age, years				
Median	62		60	
Range	42-75		38-76	
Sex				
Male	34	65	39	70
Female	18	35	17	30
ECOG status				
0	36	69	33	59
1	15	29	22	39
2	—		1	2
Unknown	1	2	—	
Locally advanced rectal cancer definition by MRI ± US				
cT4 resectable	3	6	7	13
cT3 lower third (≤ 6 cm from anal verge) tumors	12	23	18	32
CRM threatened or involved, mid-rectal cancer	5	10	—	
Any cT3N+	31	59	31	55
Missing	1	2	—	
Pathologic grade				
Not otherwise specified	12	23	11	20
1: well differentiated	12	23	11	20
2: moderately differentiated	27	52	28	50
3: poorly differentiated	1	2	6	11

Abbreviations: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imagine; US, ultrasound; CRM, circumferential resection margin.

Complete pathological response (evaluable population)

Complete pathological response was present in 15 (15.00%) out of the 100 patients evaluated for response: of the 46 evaluable patients in arm A, 7 had complete pathological response (15.22% CI [6.34% -28.87%]); in arm B: 8 (14.81% CI [6.62% -27.12%]) out of the 54 evaluable patients had a complete pathological response. Two patients in arm B have not been evaluated because they presented unresectable tumours. No statistical differences were found between groups.

	Complete pathological response (ITT Population) Complete pathological response was present in 15 (13.89%) out of the 108 randomized patients. Of the 52 patients randomized to arm A, 7 had complete pathologic response (13.46% [5.59% -25.79%]); in arm B: 8 (14.29% [6.38% - 26.22%]) out of the 56 randomized patients had a complete pathological response. Two patients in arm B have not been evaluated because they presented unresectable tumours. No statistical differences were found between groups. **Curative resection (evaluable population)** Of the100 patients with surgery, resection was curative in 93 (93.00%). Of the 46 evaluable patients in arm A, 45 (97.83%, CI [88.47% -99.94%]) were R0 versus 48 of the 54 evaluated patients in arm B (88.89%, CI [77.37% - 95.81%]). No statistical differences were found between groups. **Curative resection (ITT population)** Of the108 randomized patients with surgery, resection was curative in 93 (86.11%). Of the 52 patients randomized to arm A, 45 (86.54%, CI [74.21% - 94.41%]) were R0 versus 48 of the 56 randomized to arm B (85.71%, CI [73.78% - 93.62%]). No statistical differences were found between groups. **Downstaging (evaluable population)** Of the 100 patients evaluable, 54 (54.00%) were downstaged. Rate was 30 out of 46 (65.22%, CI [49.75% -78.65%]) in arm A; and 24 out of 54 (44.44%, CI [30.92% -58.60%]) in arm B.Two patients in arm B were treated as missing, due to presence of unresectable tumor. **Downstaging (ITT population)** 54 of the 108 randomized patients (50.00%) were downstaged. Rate was 30 out of 52 (57.69%, CI [43.20% -71.27%]) in arm A; and 24 out of 54 (42.86%, CI [29.71% -58.78%]) in arm B. Two patients in arm B were considered missing, due to presence of unresectable tumor. **Dose Intensity** In the TCP phase, both for the treatment with capecitabine and with oxaliplatin, significant differences in mean dose intensity were detected. In the adjuvant / neoadjuvant chemotherapy phase, there has been an average oxaliplatin relative intensity dose of 0.97 in arm B, and 0.60 in arm A (p-value <0.001). For capecitabine, the average intensity dose is 0.94 in arm B, compared to an average of 0.58 (p-value <0.001) in arm A. The overall intensity dose of each drug throughout the study (TCP + QT) was also analyzed. A mean intensity dose of oxaliplatin of 0.73 in arm A, and 0.94 in the arm B (p-value <0.001) was obtained. For capecitabine, the average is 0.67 in arm A, and 0.91 (p-value <0.001) in arm B.

Safety results:

Patients evaluable for safety are those who have received any dose of treatment. There are 49 patients at arm A and 54 patients at arm B.

Adverse events were reported in 49/49 patients (100.0%) in arm A and 53/54 (98.15%) at arm B. For grade 3-4 adverse events, rates were 26/49 (53.06%) in arm A and 19/54 (35.19%) in arm B (no significant difference).

Statistically significant differences were found in the rate of patients with grade 3-4 adverse events in the chemotherapy phase. In arm A, 54.05% of the patients suffered from adverse events grade 3-4, compared to 18.52% of arm B (p-value = 0.0004).

The most common adverse events throughout the study were:

Arm A		Arm B	
Diarrhea	34(69.39%)	Neurology-Other	39 (72.22%)
Fatigue	29 (59.18%)	Diarrhea	33 (61.11%)
Neurology-Other	25 (51.02%)	Fatigue	32 (59.26%)
Pain	21 (42.86%)	Platelets	30 (55.56%)

Grade 3-4 adverse events more common in the study were

Arm A		Arm B	
Diarrhea	11(22.45%)	Diarrhea	5 (9.26%)
Fatigue	6 (12.24%)	Fatigue	5 (9.26%)
Neutrophils	4 (8.16%)	Hand –Foot	2 (3.70%)
Pain	3 (6.12%)	Allergic reaction/hypersensivity	2 (3.70%)
Nausea	3 (6.12%)	Pain	2 (3.70%)
Hemarrohage	2 (4.08%)	Anorexia	2 (3.70%)

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