Overview

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Title: Standard Versus Continuous Administration of Capecitabine in Metastatic Breast Cancer (GEICAM/2009-05): A Randomized, Noninferiority Phase II Trial With a Pharmacogenetic Analysis

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Author Summary: Abstract and Brief Discussion

Background

The approved capecitabine regimen as monotherapy in metastatic breast cancer (MBC) is 1,250 mg/m^2 twice daily for 2 weeks on and 1 week off (Cint). Dose modifications are often required because of severe hand-foot syndrome (HFS). We tested a continuous regimen with a lower daily dose but a similar cumulative dose in an attempt to reduce the severity of adverse events (AEs) while maintaining efficacy.

Methods

We randomized 195 patients with HER-2/neu-negative MBC to capecitabine 800 mg/m^2 twice daily throughout the 21-day cycle (Ccont) or to Cint to assess noninferiority in the percentage of patients free of progression at 1 year. Secondary

endpoints included efficacy and safety. Associations between polymorphisms in capecitabine metabolism-related genes and drug response were assessed.

Results

The percentage of patients free of progression at 1 year was 27.3% with Cint versus 25.3% with Ccont (difference of −2.0%; 95% confidence interval: −15.5% to 11.5%, exceeding the 15% deemed noninferior). Differences regarding other efficacy variables were also not found. Grade 3–4 HFS was the most frequent AE (41.1% in Cint vs. 42.3% in Ccont). Grade 3–4 neutropenia, thrombocytopenia, diarrhea, and stomatitis were more frequent with Cint. A 5′ untranslated region polymorphism in the carboxylesterase 2 gene was associated with HFS. One polymorphism in cytidine deaminase and two in thymidine phosphorylase were associated with survival.

Conclusion

Our study was unable to show noninferiority with the continuous capecitabine regimen (Ccont) compared with the approved intermittent regimen (Cint). Further investigation is required to improve HFS. Polymorphisms in several genes might contribute to interindividual differences in response to capecitabine.

Discussion

In this patient population (Table 1), continuous, lower daily doses of capecitabine were not shown to be noninferior in efficacy to the standard schedule despite maintaining the same cumulative dose and dose intensity (Fig. 1). The percentage of patients free of progression at 1 year were 27.3% with 1,250 mg/m^2 twice daily for 2 weeks on and 1 week off versus 25.3% with 800 mg/m^2 twice daily throughout the 21-day cycle (difference of −2.0%; 95% confidence interval: −15.5 to 11.5%), meaning that the margin deemed noninferior by the study design (15%) was exceeded. Median progression-free survival (PFS) and overall survival (OS) were numerically superior (although nonsignificant) with the approved intermittent administration schedule. Hand-foot syndrome (HFS) was not different between arms.

The greater incidence of severe adverse events (AEs) resulted in a larger percentage of patients requiring dose reductions with the approved intermittent regimen (67.4%) compared with the experimental continuous administration regimen (52.6%); however, patients in both arms received similar dose intensity. Stockler et al. [1] compared the classical cyclophosphamide, methotrexate, and fluorouracil (CMF) regimen with two different capecitabine schedules: an intermittent regimen with lower doses (1,000 mg/m^2 twice daily for 2 weeks on and 1 week off) and continuous administration of very low doses (650 mg/m^2 twice daily). Both capecitabine regimens showed similar PFS (6 months), response rates, and OS and achieved improved OS versus CMF. Despite the greater frequency of severe AEs, the rate of dose reduction and median duration of treatment were equivalent for the two arms. These data disagree with our study results, perhaps because of the use of a higher dose of capecitabine in our trial or the different criteria used to assess disease progression (strict Response Evaluation Criteria in Solid Tumors in ours vs. the need for palliative radiation or change in chemotherapy in the trial by Stockler et al. [1]). We found an association of HFS intensity and rs11075646 polymorphism in *CES2*. Ribelles et al. [2] previously described an association of the G allele of rs11075646 with capecitabine efficacy but not with HFS. We also found one polymorphism in *CDD* (rs2072671) and two in *TP* (rs11479, rs470119) associated with survival.

In conclusion, our study suggests that the schedule of capecitabine used in the treatment of MBC matters. The role of polymorphism in some genes involved in the metabolism of capecitabine should be further elucidated.

Trial Information

Disease	Breast cancer
Disease	Advanced cancer/Solid Tumor Only
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	2 prior regimens
Type of study - 1	Phase II
Type of study - 2	Randomized
PFS	*p*: .02913, HR: 1.2
TTP	*p*: .1445, HR: 1.3
Response Duration	*p*: .6479, HR: 1.1
Primary Endpoint	Time to Progression

Secondary Endpoint	Progression Free Survival
Secondary Endpoint	Overall Response Rate
Secondary Endpoint	Overall Survival
Secondary Endpoint	Safety
Additional Details of Endpoints or Study Design	Other secondary endpoints were duration of response (DOR) and clinical benefit rate (CBR). For safety, hematology, biochemistry and nonlaboratory AEs were recorded every cycle and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. A tertiary objective was to identify and validate polymorphisms associated with the metabolism of capecitabine that predict response and toxicity in these patients. On the Study design, see CONSORT Figure (Fig. 2)
Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information

Drug 1 **Generic/Working name**	Capecitabine
Trade name	Xeloda
Company name	F. Hoffmann-La Roche Ltd., Basel, Switzerland
Drug type	Small molecule
Drug class	Antimetabolite
Dose	800 mg (mg) per squared meter (m^2)
Route	Oral (po)
Schedule of Administration	Capecitabine dose in the control arm (Cint) was 1,250 mg/m^2 twice daily on days 1 to 14, every 21 days. Capecitabine dose in the experimental arm (Ccont) was 800 mg/m^2 twice daily without rest periods.

Patient Characteristics

Number of patients, male	0
Number of patients, female	195
Stage	Stage IV
Age	Median (range): 60 years (range 29–87)
Number of prior systemic therapies	Median (range): Patients previously received the following chemotherapies: anthracyclines (22.4%), taxanes (7.3%), both (53.1%) and other (19.8%). Patients could have received more than one of them.
Performance Status:	ECOG 0 —85 1 —48 2 —3 3 —0 Unknown —56
Other	35.9% of patients were premenopausal, 78.6% hormonal receptor positive, 78.1% had visceral disease and 50.1% had two or more metastatic sites (Table 1).
Cancer Types or Histologic Subtypes	

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened	98
Number of patients enrolled	98

Number of patients evaluable for toxicity	97
Number of patients evaluated for efficacy	97
Evaluation method	RECIST 1.0
Response assessment CR	0%
Response assessment PR	32%
Response assessment SD	39.2%
Response assessment PD	24.7%
Response assessment other	4.1%
(Median) duration assessments PFS	6.8 months, CI: 6.0-8.1
(Median) duration assessments TTP	6.8 months, CI: 6.0-8.1
(Median) duration assessments OS	23.3 months, CI: 18.2-33.7
(Median) duration assessments response duration	7.2 months
(Median) duration assessments duration of treatment	5.6 months

Control Arm: Total Patient Population

Number of patients screened	97
Number of patients enrolled	97
Number of patients evaluable for toxicity	95
Number of patients evaluated for efficacy	95
Evaluation method	RECIST 1.0
Response assessment CR	2.1%
Response assessment PR	29.5%
Response assessment SD	39.0%
Response assessment PD	20.0%
Response assessment other	9.5%
(Median) duration assessments PFS	8.5 months, CI: 5.7-10.2
(Median) duration assessments TTP	8.7 months, CI: 6.6-11.1
(Median) duration assessments OS	27.3 months, CI: 22.4-31.9
(Median) duration assessments response duration	10.1 months
(Median) duration assessments duration of treatment	5.3 months

Secondary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened	98
Number of patients enrolled	98
Number of patients evaluable for toxicity	92
Number of patients evaluated for efficacy	92
Evaluation method	RECIST 1.0
Response assessment CR	0%
Response assessment PR	31.5%
Response assessment SD	40.2%
Response assessment PD	23.9%
Response assessment other	4.4%
(Median) duration assessments PFS	6.8 months, CI: 6.0-8.1
(Median) duration assessments TTP	6.8 months, CI: 6.0-8.1
(Median) duration assessments OS	23.3 months, CI: 17.4-32.3
(Median) duration assessments response duration	7.0 months
(Median) duration assessments duration of treatment	5.9 months

Control Arm: Total Patient Population

Number of patients screened	97
Number of patients enrolled	97
Number of patients evaluable for toxicity	90
Number of patients evaluated for efficacy	90
Evaluation method	RECIST 1.0
Response assessment CR	2.2%
Response assessment PR	31.1%
Response assessment SD	38.9%
Response assessment PD	18.9%
Response assessment other	9.5%
(Median) duration assessments PFS	8.6 months, CI: 5.9-10.3
(Median) duration assessments TTP	8.7 months, CI: 6.6-11.2
(Median) duration assessments OS	28.6 months, CI: 23.9-33.3
(Median) duration assessments response duration	10.1 months
(Median) duration assessments duration of treatment	5.4 months

Pharmacokinetics/Pharmacodynamics

N	111
Cmax	Not Collected
AUC	Not Collected
Half-life	Not Collected
Volume of distribution	Not Collected
Clearance	Not Collected
Notes	Sixteen polymorphisms in genes of the capecitabine metabolic pathway (*CES2, CDD, TP,* and *DPD*) and the 5-FU target gene (*TS*) were genotyped in 111 patients (50 in Cint and 61 in Ccont). These polymorphisms included: 4 promoter SNPs (rs532545, rs602950, rs603412, and rs3215400), and the coding SNP rs2072671 (Lys27Gln) in *CDD*; intronic SNP rs3918290 (IVS14+1G > A) in the splice donor site flanking exon 14 of *DPD*; intronic SNPs rs2241409, rs11568314, and rs11568311 and 5′UTR SNP rs11075646 (823C > G) in *CES2*; intronic SNP rs470119, and coding SNPs rs11479 (Ser471Leu), and rs131804 (Ala324Ala) in *TP*; and 3 polymorphisms located in the 5-FU of target gene *TS*, a 28-bp double- (TSER*2) or triple-tandem repeat (TSER*3), including a G > C mutation at the 12th nucleotide of the second repeat in the TS*3 alleles in the 5′ region and a 6-bp deletion in the 3′ region. All these polymorphisms had been previously studied in relation with 5-FU-based regimen response except SNPs in *TP* for which, tagSNPs were selected. The association between polymorphisms and severity of HFS (Grade 3-4 vs. the rest) was assessed in patients treated for at least 3 months ($n = 99$), using logistic regression. Polymorphisms were also correlated with PFS and OS using a Cox regression analysis ($n = 111$). Genetic main effects were modeled per copy of the minor allele; age, treatment arm, liver metastasis, treatment line, and ECOG PS were included as covariates. The minor allele of rs11075646 (5′UTR 823 C/G) in *CES2* was found to be associated with increased risk of grade 3-4 HFS (OR = 4.49; 95% CI, 1.43-14.14; p value = .01). A significant association with PFS was found for the promoter *CDD* variant rs602950 (HR per allele 1.44; 95% CI, 1.02−2.05; p value = .038) and for the missense *CDD* variant rs2072671 (HR= 1.77; 95% CI, 1.21−2.57; p value = .0031) being both variants in strong linkage disequilibrium (r2 = 0.790; D′=0.916). rs2072671 was also associated with OS (HR = 1.55; 95% CI, 1.04−2.33; p value = .032). In addition, both *TP* rs11479 and rs470119 polymorphisms were associated with OS (HR= 2.36; 95% CI, 1.23−4.52; p value = .010, and HR= 1.46; 95% CI, 1.03−2.07; p value =.034, respectively) but not with PFS. The unique patient carrying the

inactivating mutation IVS14+1G > A in *DPD* gene received only one cycle (total dose = 34,355.83 mg/m^2) before the treatment was interrupted due to severe toxicities (Grade 3 neutropenic fever, Grade 3 mucositis). None of the other markers were associated with the clinical outcomes considered (Table 2).

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Correlative Endpoints Met
Investigator's Assessment	Inactive because results did not meet primary endpoint

Discussion

In this patient population (Table 1), continuous, lower daily doses of capecitabine were not shown to be noninferior in efficacy to the standard intermittent schedule (2 weeks on, 1 week off) despite maintaining the same cumulative dose and dose intensity of the drug (Fig. 1). The percentage of patients free of progression at 1 year were 27.3% with 1,250 mg/m^2 twice daily for 2 weeks on and 1 week off versus 25.3% with capecitabine 800 mg/m^2 twice daily throughout the 21-day cycle (difference of −2.0%; 95% confidence interval [CI]: −15.5 to 11.5% in the intent-to-treat population), meaning that the margin deemed noninferior by the study design (15%) was exceeded (Fig. 3). Both median progression-free survival (PFS) and overall survival (OS) were numerically superior with the approved intermittent administration schedule, although the differences were nonsignificant (Table 3). The most clinically relevant toxicity, hand-foot syndrome (HFS), was not different between arms (Table 4). The greater incidence of severe adverse events (AEs) resulted in a larger percentage of patients requiring dose reductions with the intermittent regimen (67.4%) compared with the continuous regimen (52.6%); however, patients in both arms received similar dose intensity (Table 5).

Although no prospective randomized trials have been performed yet [3], at least four phase II studies in metastatic breast cancer (MBC) have suggested that a lower initial dose of capecitabine (1,000 mg/m^2 for 2 weeks on and 1 week off) could be better tolerated with similar efficacy than the approved regimen (1,250 mg/m^2) [1, 4–6]. Bajetta et al. [4] focused on a population of elderly women (median age: 73 years) with MBC in which 95% of patients in the low-dose group did not require dose reductions, whereas 30% of patients receiving the approved dose did. Although not statistically significant, the response rate was slightly higher with the standard regimen (36.7%; 95% CI: 19.9%–56.1%) than in the lower dose group (34.9%; 95% CI: 21.0%–50.9%). The authors suggested that a capecitabine dose of 1,000 mg/m^2 should be considered standard for elderly patients without severe renal impairment. Similarly, Rossi et al. [5] confirmed the activity and safety of a lower capecitabine dose (1,000 mg/m^2) in both chemotherapy-naive and pretreated patients, allowing longer treatments and reducing side effects, such as diarrhea, stomatitis, and vomiting. The Mono Efficacy of Capecitabine (MONICA) trial [6] evaluated the activity and safety of capecitabine monotherapy at a dose of 1,000 mg/m^2 twice daily as first-line treatment in MBC patients. Median time to progression and OS were 7.3 months (95% CI: 6.2–8.4) and 17.1 months (95% CI: 14.0–20.3), respectively. Overall response rate was 26.1%. These results also confirmed the efficacy and safety of capecitabine 1,000 mg/m^2 twice daily as first-line therapy. Stockler et al. [1] compared the classical cyclophosphamide, methotrexate, and fluorouracil (CMF) regimen with two different capecitabine schedules: an intermittent regimen with lower doses (1,000 mg/m^2 twice daily on days 1 to 14 every 21 days) and continuous administration of very low doses (650 mg/m^2 twice daily without rest periods). Both capecitabine regimens were similarly effective in terms of PFS (6 months), response rate, and OS and improved OS with respect to classical CMF. Despite the greater frequency of severe AEs, the rate of dose reduction and the median duration of treatment were equivalent for the two arms.

These data disagree with our study results, perhaps because of the use of a higher dose of capecitabine in our trial. In addition, our trial was specifically designed to look at noninferiority, whereas for Stockler et al. [1], trial noninferiority was not the focus. In addition, the authors stated that the need for palliative radiation or change in chemotherapy was considered an indication of disease progression, regardless of Response Evaluation Criteria in Solid Tumors (RECIST) measurements; however, in our study, strict RECIST criteria for progression were required to establish disease progression. Finally, Stockler et al. [1] enrolled a particular population, "patients where chemotherapy for advanced disease was being considered for the first time, and where more intensive chemotherapy was not considered appropriate."

A trial testing the administration of dose-dense regimens of capecitabine has been recently reported. The 7/7 regimen, a schedule based on a mathematical method for the optimization of anticancer drug scheduling, administers high doses of

capecitabine (up to 2,000 mg twice a day) over 7 days with 7 days rest [7]. Although efficacy and toxicity results are promising, randomized prospective trials are necessary to ascertain the real interest of this approach.

The clinical experience with capecitabine in MBC shows significant interpatient variability in response and toxicity. Largillier et al. [8] reported a strong tendency toward a higher frequency of grade 3–4 toxicities with capecitabine in patients homozygous for the *TS* 3RG allele. We observed no associations between any of the polymorphisms studied in this gene and HFS grade. In contrast, we found an association of HFS intensity and rs11075646 in *CES2*. Ribelles et al. [2] showed that the G allele of rs11075646 was associated with better response to capecitabine and longer time to disease progression but not with HFS. The *CES2* gene encodes the enzyme carboxylesterase 2, which metabolizes capecitabine in the liver to 5′-deoxy-5-fluorocytidine. This is then converted to 5′-deoxy-5-fluorouridine by the enzyme cytidine deaminase (encoded by the *CDD* gene) and activates 5-fluorouracil (5-FU) by the enzyme thymidine phosphorylase (encoded by the *TP* gene). Mutations in the regulatory elements of *CES2*, such the 5′ untranslated region variant rs11075646, could alter the concentration of active 5-FU in both tumor and normal cells, causing higher cytotoxicity and thus greater efficacy in eliminating tumor cells but also higher toxicity in normal cells, explaining the observed associations with both response and toxicity. This model might also explain the observed association between survival and the *CDD* variant that was previously reported to be associated with toxicities in capecitabine-treated patients [2, 8–17]. In addition, we identified, for the first time, the association of two single nucleotide polymorphisms in the *TP* gene (rs11479, rs470119) with OS in capecitabine-treated patients (Table 2). Although these results provide preliminary evidence of the role of these genes in capecitabine response, the real predictive interest of these polymorphisms should be established in larger, prospective studies.

In conclusion, our study suggests that the schedule of capecitabine used in the treatment of metastatic breast cancer matters. The role of polymorphisms in some genes involved in the metabolism of capecitabine should be further elucidated.

Acknowledgments

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Figures and Tables

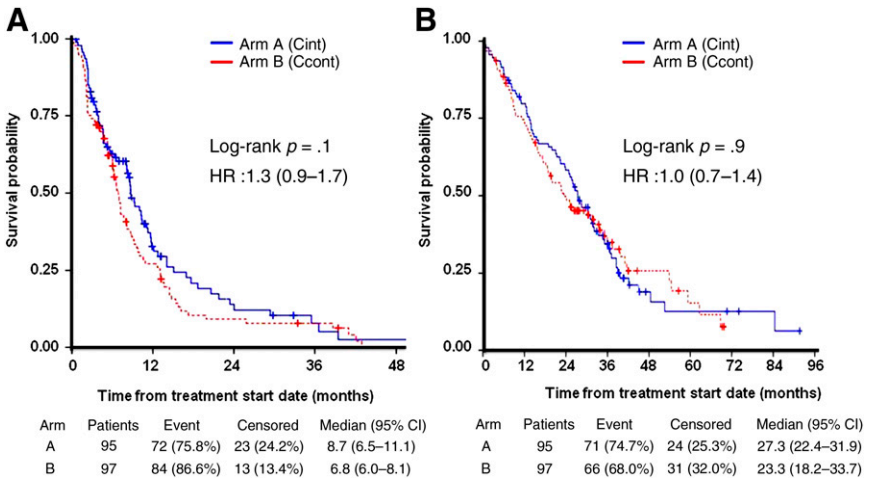

Figure 1. Kaplan-Meier analysis of time to progression **(A)** and overall survival **(B)** in the intention-to-treat population.
Abbreviations: Ccont, capecitabine continuous doses; CI, confidence interval; Cint, capecitabine intermittent doses; HR, hazard ratio.

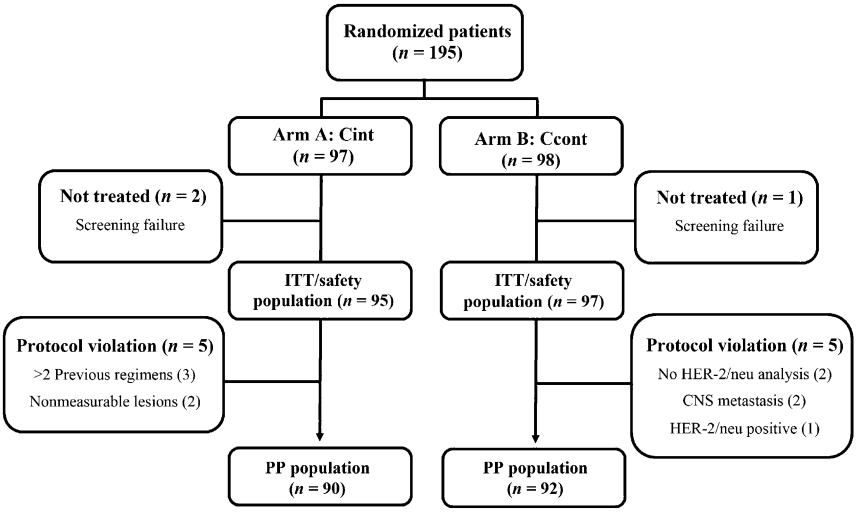

Figure 2. Patient disposition.
Abbreviations: Ccont, capecitabine continuous doses; Cint, capecitabine intermittent doses; CNS, central nervous system; ITT, intention to treat; PP, per protocol.

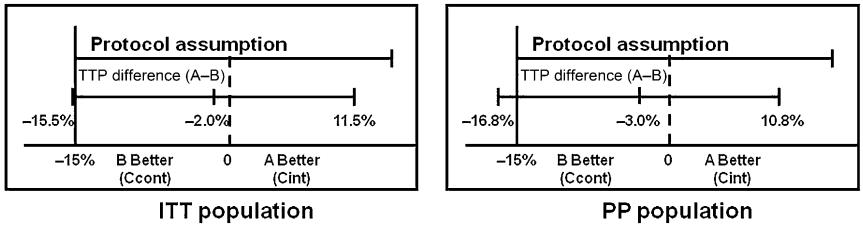

Figure 3. Analysis of noninferiority in the time to progression at 1 year of Ccont versus Cint.

Abbreviations: Ccont, capecitabine continuous doses; Cint, capecitabine intermittent doses; ITT, intention to treat; PP, per protocol; TTP, time to progression.

Table 1. Baseline patient and tumor characteristics

Characteristic	Arm A, Cint ($n = 95$)	Arm B, Ccont ($n = 97$)
Age, years, median (range)	61 (34–87)	59 (29–81)
Menopausal status, *n* (%)		
Premenopausal	32 (33.7)	37 (38.1)
Postmenopausal	62 (65.3)	60 (61.9)
ECOG PS, *n* (%)		
0	41 (43.2)	44 (45.4)
1	21 (22.1)	27 (27.8)
2	3 (3.2)	0
Hormone receptor status, *n* (%)		
Positive	75 (79.0)	76 (78.4)
Negative	18 (19.0)	16 (16.5)
Unknown	2 (2.1)	5 (5.2)
Type of metastases, *n* (%)		
Visceral	72 (75.8)	78 (80.4)
Nonvisceral	23 (24.2)	19 (19.6)
Metastatic sites, *n* (%)		
1	41 (43.2)	50 (51.6)
2	27 (28.4)	25 (25.8)
$\geq$3	26 (27.4)	22 (22.7)
Prior chemotherapy exposure, *n* (%)		
Anthracyclines	23 (24.2)	20 (20.6)
Taxanes	8 (8.4)	6 (6.2)
Anthracyclines and taxanes	48 (50.5)	54 (55.7)
Prior treatment for metastases, *n* (%)		
Chemotherapy	59 (62.1)	55 (56.7)
Hormone therapy	62 (65.3)	58 (59.8)

Abbreviations: Ccont, capecitabine continuous regimen; Cint, capecitabine intermittent regimen; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Genetic markers for which associations with progression-free survival, overall survival, and hand-foot syndrome were assessed

				PFS			*OS*			*HFS*		
Marker	**Gene**	**MAF**	**pHWE**	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
rs2241409	*CES2*	0.20	0.37	0.88	0.59–1.30	.51	0.73	0.48–1.13	.16	1.83	0.88–3.77	.10
rs11568314	*CES2*	0.05	1.00	1.20	0.62–2.30	.59	1.16	0.51–2.61	.73	1.65	0.44–6.19	.46
rs11075646	*CES2*	0.10	0.59	1.23	0.72–2.12	.45	0.75	0.40–1.40	.36	4.49	1.43–14.14	**.01**
rs2072671	*CDD*	0.35	0.15	1.77	1.21–2.57	**.0031**	1.55	1.04–2.33	**.032**	1.23	0.62–2.42	.56
rs532545	*CDD*	0.36	0.40	1.31	0.92–1.85	.13	1.36	0.91–2.02	.13	1.21	0.62–2.35	.58
rs602950	*CDD*	0.36	0.40	1.44	1.02–2.05	**.038**	1.39	0.93–2.08	.10	1.50	0.75–3.00	.26
rs603412	*CDD*	0.42	1.00	1.23	0.90–1.69	.19	1.24	0.87–1.78	.24	1.08	0.59–1.97	.81
rs3215400	*CDD*	0.42	0.70	0.80	0.58–1.09	.16	0.73	0.51–1.04	.08	1.09	0.60–1.98	.78
rs3918290	*DPD*	0.00	1.00	4.78	0.60–37.85	.14	0.36	0.04–3.10	.36	1.00	1.00–1.00	
rs470119	*TP*	0.31	0.82	1.10	0.78–1.54	.60	1.46	1.03–2.07	**.034**	0.80	0.43–1.48	.47
rs131804	*TP*	0.32	0.36	0.95	0.65–1.38	.77	1.34	0.90–1.99	.15	1.12	0.56–2.22	.75
rs11479	*TP*	0.07	1.00	1.13	0.58–2.20	.73	2.36	1.23–4.52	**.010**	0.42	0.12–1.53	.19
TS-3′-UTR	*TS*	0.38	0.83	0.97	0.72–1.31	.84	0.86	0.61–1.21	.38	0.72	0.39–1.32	.28
TS-5′-UTR[a]	*TS*	0.25	0.80	0.99	0.70–1.39	.95	0.96	0.66–1.38	.81	1.24	0.63–2.45	.54
TS-5′-UTR[b]	*TS*	0.54	1.00	0.79	0.59–1.05	.11	0.89	0.65–1.23	.49	0.98	0.55–1.76	.96

Statistical significant *p* values are shown in bolded text. Multivariable analyses using age, treatment arm, liver metastasis, treatment line, and Eastern Cooperative Oncology Group performance status as covariates in all analyses.

[a]Analysis was performed considering exclusively the number of repeats of a 28-bp sequence: two repeat (2R) or three repeat (3R). Genotype possibilities are 2R/2R, 2R/3R, and 3R/3R.

[b]Analysis was performed considering exclusively the number of repeats of a 28-bp sequence and a G>C single nucleotide polymorphism in the second repeat of the 3R allele (TSER*3 G>C). Genotype possibilities are grouped by the functional E-box binding sites (2RC/2RC, 2RC/3RC, 3RC/3RC vs. 2RC/3RG, 3RC/3RG vs. 3RG/3RG; TS 5′ class 2 vs. TS 5′ class 3 vs. TS 5′ class 4, respectively).

Abbreviations: CI, confidence interval; HFS, hand-foot syndrome; HR, hazard ratio; MAF, minor allele frequency; OR, odds ratio; OS, overall survival; PFS, progression-free survival; pHWE, Hardy-Weinberg equilibrium; UTR, untranslated region.

Table 3. Other efficacy variables: response rate, clinical benefit rate, duration of response, progression-free survival, and time to treatment failure

	ITT population		**PP population**	
Variable	**Arm A Cint (*n* = 95)**	**Arm B Ccont (*n* = 97)**	**Arm A Cint (*n* = 90)**	**Arm B Ccont (*n* = 92)**
CR, *n* (%)	2 (2.1)	0 (0.0)	2 (2.2)	0 (0.0)
PR, *n* (%)	28 (29.5)	31 (32.0)	28 (31.1)	29 (31.5)
SD, *n* (%)	37 (39.0)	38 (39.2)	35 (38.9)	37 (40.2)
PD, *n* (%)	19 (20.0)	24 (24.7)	17 (18.9)	22 (23.9)
Unknown, *n* (%)	9 (9.5)	4 (4.1)	8 (8.9)	4 (4.4)
ORR, n (%)	30 (31.6)	31 (32.0)	30 (33.3)	29 (31.5)
Clinical benefit rate, *n* (%)	56 (59.0)	56 (57.7)	54 (60.0)	54 (58.7)
Response duration, months, median (95% CI)	10.1 (8.0–16.7)	7.2 (4.1–12.7)	10.1 (8.0–16.7)	7.0 (4.1–12.4)
TTP, months, median (95% CI)	8.7 (6.6–11.1)	6.8 (6.0–8.1)	8.7 (6.6–11.2)	6.8 (6.0–8.1)
PFS, months, median (95% CI)	8.5 (5.7–10.2)	6.8 (6.0–8.1)	8.6 (5.9–10.3)	6.8 (6.0–8.1)

Time to treatment failure, months, median (95% CI)	5.3 (4.3–7.4)	5.6 (2.9–6.8)	5.4 (4.3–8.0)	5.9 (3.6–7.1)
OS, months, median (95% CI)	27.3 (22.4–31.9)	23.3 (18.2–33.7)	28.6 (23.9–33.3)	23.3 (17.4–32.3)

Abbreviations: Ccont, capecitabine continuous regimen; CI, confidence interval; Cint, capecitabine intermittent regimen; CR, complete response; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PP, per protocol; PR, partial response; SD, stable disease; TTP, time to progression.

Table 4. Adverse events

Adverse event	**Arm A, Cint ($n = 95$), *n* (%)**		**Arm B, Ccont ($n = 97$), *n* (%)**	
Grade	**1–2**	**3–4**	**1–2**	**3–4**
Hematologic				
Anemia	35 (36.8)	1 (1.1)	23 (23.7)	2 (2.1)
Neutropenia	18 (19.0)	9 (9.5)	9 (9.3)	2 (2.1)
Thrombocytopenia	9 (9.5)	3 (3.2)	4 (4.1)	0 (0.0)
Diarrhea	29 (30.5)	19 (20.0)	25 (25.8)	6 (6.2)
Dyspnea	8 (8.4)	2 (2.1)	10 (10.3)	5 (5.2)
Fatigue	45 (47.4)	14 (14.7)	42 (43.3)	7 (7.2)
Hand-foot syndrome	35 (36.8)	39 (41.1)	38 (39.2)	41 (42.3)
Infection	28 (29.5)	6 (6.3)	23 (23.7)	4 (4.1)
Pain	36 (37.9)	5 (5.3)	26 (26.8)	7 (7.2)
Stomatitis	27 (28.4)	11 (11.6)	26 (26.8)	2 (2.1)

National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0 was used (grades 3–4 reported in >3% of patients in the safety population).
Abbreviations: Ccont, capecitabine continuous regimen; Cint, capecitabine intermittent regimen.

Table 5. Capecitabine dosing exposure

Variable	**Arm A, Cint ($n = 95$)**	**Arm B, Ccont ($n = 97$)**
Number of cycles, median (range)	7.0 (1.0–99.0)	7.0 (1.0–60.0)
Duration of therapy, weeks, median (range)	24.0 (3.0–322.4)	26.0 (3.0–187.0)
Dose intensity, mg/m_2/week, median (range)	9210.5 (803.2–12121.2)	9087.8 (4469.2–13750.0)
Relative dose intensity, median (range)	0.8 (0.1–1.0)	0.8 (0.4–1.2)
Dose delays, *n* (%)		
Patients	64 (67.4)	54 (55.7)
Cycles	151.0 (13.0)	140.0 (13.6)
Patients with dose reductions, *n* (%)	64 (67.4)	51 (52.6)

Abbreviations: Ccont, capecitabine continuous regimen; Cint, capecitabine intermittent regimen.