P5-10-15

FIRST SAFETY DATA FROM A RANDOMISED PHASE III (CIBOMA/2004-01/GEICAM 2003-11) TRIAL ASSESSING ADJUVANT CAPECITABINE MAINTENANCE THERAPY AFTER STANDARD CHEMOTHERAPY FOR TRIPLE-NEGATIVE EARLY BREAST CANCER

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BACKGROUND

- Patients with triple-negative breast cancer (TNBC) represent a difficult-to-treat population.
- Even after standard (neo)adjuvant treatment only 63% of patients are disease-free at 3 years, and 64% alive at 5 years.[1]
- Capecitabine has proven efficacy in metastatic breast cancer, both as monotherapy[2–6] and in combination with docetaxel,[7,8] trastuzumab[9,10] or bevacizumab.[11]
- In addition, capecitabine has a favourable safety profile characterised by minimal alopecia and myelosuppression.[12]
- A large adjuvant trial programme is exploring the role of capecitabine in early breast cancer (EBC).
- Preliminary data are promising, with interim efficacy data from the FinXX and ABCSG-24 studies showing significant improvements in recurrence-free survival and pathological complete response rate, respectively, when capecitabine is incorporated into standard (neo)adjuvant regimens.[13,14]
- Based on results of subset analyses of the FinXX and ABCSG-24 studies, in patients with TNBC,[15,16] there is a further supporting rationale for evaluating capecitabine in this patient population.
- A number of studies in the metastatic setting are attempting to improve outcomes for patients with TNBC. CIBOMA/2004-01/GEICAM 2003-11 is the first trial to specifically focus on this patient subgroup in the adjuvant setting.

OBJECTIVE

- We present interim safety data from CIBOMA/2004-01/GEICAM 2003-11, a multicentre, multinational, randomised, phase III trial that focuses on adjuvant capecitabine maintenance therapy after conventional induction chemotherapy in triple-negative EBC.

METHODS

Eligibility criteria

- Females aged ≥18 years.
- Operable node-positive (or node-negative with tumour diameter ≥1cm).
- Centrally confirmed hormone receptor-negative, HER2-negative EBC.
- No evidence of metastatic disease.
- Karnofsky performance status (KPS) ≥80.
- Received 6–8 cycles of standard anthracycline- and/or taxane-containing chemotherapy or 4 cycles of doxorubicin-cyclophosphamide (for node-negative disease) in the (neo)adjuvant setting.
- Adequate renal and hepatic function and haematology results.

Study treatment

- Patients are randomised to receive 8 cycles of capecitabine for 14 days followed by a 7-day rest period, or observation (Figure 1)
  - the time window allowed between the end of adjuvant therapy and study randomisation is <8 weeks for chemotherapy and 4 weeks for radiotherapy.

Study endpoints

- Primary endpoint: disease-free survival (DFS).
- Secondary endpoints: 5-year DFS; overall survival; safety; exploration of polymorphisms of thymidylate synthase and methylenetetrahydrofolate reduction in relation to the efficacy and safety of capecitabine.

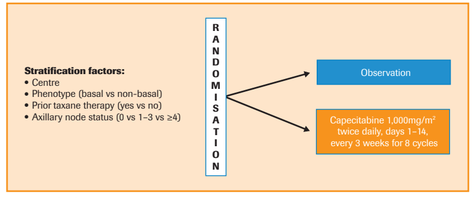

Figure 1. CIBOMA study design.

Statistical assumptions

- Assuming a 30% risk reduction in DFS rate at 5 years (from 64.7% to 73.7%, hazard ratio 0.70) with 80% power and a two-tailed log-rank test at 0.05, 834 evaluable patients will be required.
- With an expected drop-out rate of 5%, 876 patients will be enrolled.
- Recruitment should be completed by the end of 2010; efficacy analyses will be triggered after 255 events.

RESULTS

Patient disposition

- As of November 2010, 816 patients from eight countries (Brazil, Mexico, Chile, Peru, Ecuador, Colombia, Venezuela and Spain) have been randomised; here we report safety data for the first 400 patients (Figure 2).

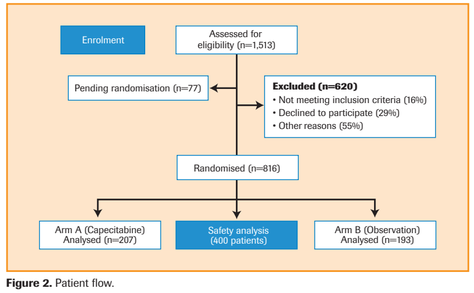

Figure 2. Patient flow.

- Patient baseline demographics are well balanced between the capecitabine and observation groups (Table 1)
  - median patient age is 51 years (range 26–82)
  - approximately two-thirds of patients are Caucasian (63.9%) and postmenopausal (68.2%)
  - the majority of patients (84.6%) have a KPS score of 100.
- Baseline disease characteristics are also well balanced between the two treatment groups (Table 2)
  - the majority of patients have a basal phenotype (82.0%) and invasive ductal histology (88.5%)
  - more than half of the patients have received previous adjuvant treatment with an anthracycline and a taxane (54.7%).

Table 1. Baseline demographics.

	Capecitabine (n=207)	Observation (n=193)
Median age, years (range)	52 (27–79)	49 (26–82)
Race, n (%)		
Caucasian	131 (63.3)	125 (64.8)
Black	12 (5.8)	5 (2.6)
Hispanic	61 (29.5)	56 (29.0)
Other	3 (1.4)	7 (3.6)
KPS, n (%)		
80	3 (1.4)	6 (3.1)
90	29 (14.0)	23 (11.9)
100	175 (84.6)	164 (85.0)
Postmenopausal, n (%)	144 (69.6)	129 (66.8)

Table 2. Baseline disease characteristics.

	Capecitabine (n=207)	Observation (n=193)
Node axillary dissection, n (%)		
Lymphadenectomy (L)	169 (81.6)	138 (71.5)
Sentinel node biopsy (SNL)	32 (15.5)	42 (21.8)
L + SNL	6 (2.9)	13 (6.7)
Histological type, n (%)		
Invasive ductal	181 (87.5)	173 (89.6)
Invasive lobular	3 (1.4)	3 (1.6)
Other	23 (11.1)	17 (8.8)
Grade, n (%)		
GX	9 (4.3)	13 (6.7)
G1	10 (4.8)	5 (2.6)
G2	43 (20.8)	38 (19.7)
G3	145 (70.1)	137 (71.0)
Triple-negative phenotype, n (%)		
Basal*	168 (81.2)	160 (82.9)
Non-basal	39 (18.8)	33 (17.1)
Chemotherapy received, n (%)		
Adjuvant only	179 (86.4)	170 (88.1)
Neoadjuvant only	20 (9.7)	19 (9.8)
Adjuvant and neoadjuvant	8 (3.9)	4 (2.1)
Prior chemotherapy, n (%)		
Anthracyclines without taxanes	95 (45.9)	86 (44.6)
Anthracyclines with taxanes	112 (54.1)	107 (55.4)

*Cytokeratins 5/6 positive and/or epidermal growth factor receptor (EGFR) positive

Delivered dose

- The planned dose of capecitabine was 1,000mg/m² twice daily for 14 days, every 3 weeks, for 8 cycles.
- In total, 1,440 cycles of capecitabine were administered (median 8.0, range 0–8).
- All 8 cycles were completed by 77.3% of patients (Table 3).

Table 3. Delivered dose of capecitabine.

Received treatment cycle, n (%)	Capecitabine (n=207)
0	6 (2.9)
1	4 (1.9)
2	10 (4.8)
3	3 (1.4)
4	7 (3.4)
5	7 (3.4)
6	6 (2.9)
7	4 (1.9)
8	160 (77.3)
Median relative dose intensity (RDI) %, (range)	90.0 (4.11–127.02)

- Median RDI of capecitabine was 90.0%.
- Overall, 105 patients had abnormal capecitabine RDI, with values ranging from <60% to 127%; toxicity was the main reason for dose modification (Figure 3).

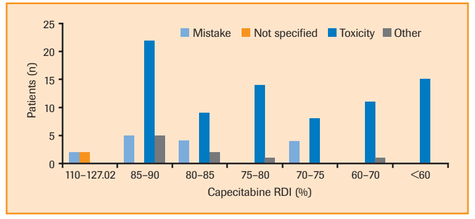

Figure 3. Patients with abnormal capecitabine RDI (100±10%).

Dose modification

- Toxicity (driven primarily by hand-foot syndrome) was the most common reason for dose modification (omissions, reductions or delays) in 12.2% of cycles (Table 4).

Table 4. Proportion of cycles with dose modification.

Cycles, n (%)	N=1,440
Toxicity	175 (12.2)
Hand-foot syndrome	107 (7.4)
Neutrophils/granulocytes	17 (1.2)
Diarrhoea	16 (1.1)
Mucositis/stomatitis	7 (0.5)
Leucocytes	6 (0.4)
Fatigue	5 (0.3)
Ocular surface disease	4 (0.3)
Pain: gastrointestinal	4 (0.3)
Other	59 (4.1)
Mistake	96 (6.7)
Other	41 (2.8)

Safety

- The most frequent grade 3/4 capecitabine-related clinical adverse events were hand-foot syndrome (grade 3 only, 17.4%), diarrhoea (2.9%), and fatigue (1.9%) (Table 5).

Table 5. Grade 3/4 adverse events (NCI-CTCAE version 3.0) occurring in ≥2 patients in either treatment arm.

	Treatment related	Unrelated	
Patients, n (%)	Capecitabine (n=207)	Capecitabine (n=207)	Observation (n=193)
Hand-foot syndrome*	36 (17.4)	-	-
Diarrhoea	6 (2.9)	-	-
Fatigue	4 (1.9)	-	-
Vomiting	2 (1.0)	-	-
Nail changes	2 (1.0)	-	-
Bilirubin elevated	2 (1.0)	-	-
Irregular menses	1 (0.5)	19 (9.2)	15 (7.8)
Lymphopenia	-	2 (1.0)	-
Syncope	-	3 (1.4)	-

*Grade 3 only; NCI-CTCAE = National Cancer Institute–Common Terminology Criteria for Adverse Events

- Patient withdrawal request (7.8%), and unacceptable toxicity (7.2%), were the most common reasons for discontinuation in the capecitabine arm (Table 6).
- Five deaths occurred during the study: three in the capecitabine arm and two in the observation arm
  - reasons for death in the capecitabine arm were brain haemorrhage (unrelated), cerebrovascular ischaemia (unrelated) and septic shock (related to treatment).

Table 6. Reasons for discontinuation.

Patients, n (%)	Capecitabine (n=207)	Observation (n=193)
Withdrawal request by the patient	16 (7.8)	2 (1.0)
Unacceptable toxicity	15 (7.2)	1 (0.5)
Disease relapse	5 (2.4)	7 (3.7)
Treatment interruption >3 weeks	4 (1.9)	-
Death	3 (1.4)	2 (1.0)
Protocol deviation	2 (1.0)	1 (0.5)
Lost to follow-up	1 (0.5)	1 (0.5)
Other causes	-	3 (1.5)
Not specified	3 (1.4)	8 (4.2)

CONCLUSIONS

- CIBOMA/2004-01/GEICAM 2003-11 is the first prospective, adjuvant study to specifically target patients with TNBC and is the first study of capecitabine to target a specific molecular subtype.
- The rationale for evaluating capecitabine in this patient population is supported by results of subset analyses of the FinXX and ABCSG-24 studies, in patients with TNBC.[15,16]
- Recruitment to the study is currently ongoing with accrual of 876 patients planned.
- The safety profile of adjuvant capecitabine as maintenance therapy is consistent with its known toxicity profile
  - more than 75% of patients are able to finish their treatment as planned, with around 15% of patients discontinuing due to toxicity or patient withdrawal
  - most common adverse events are hand-foot syndrome and diarrhoea.

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