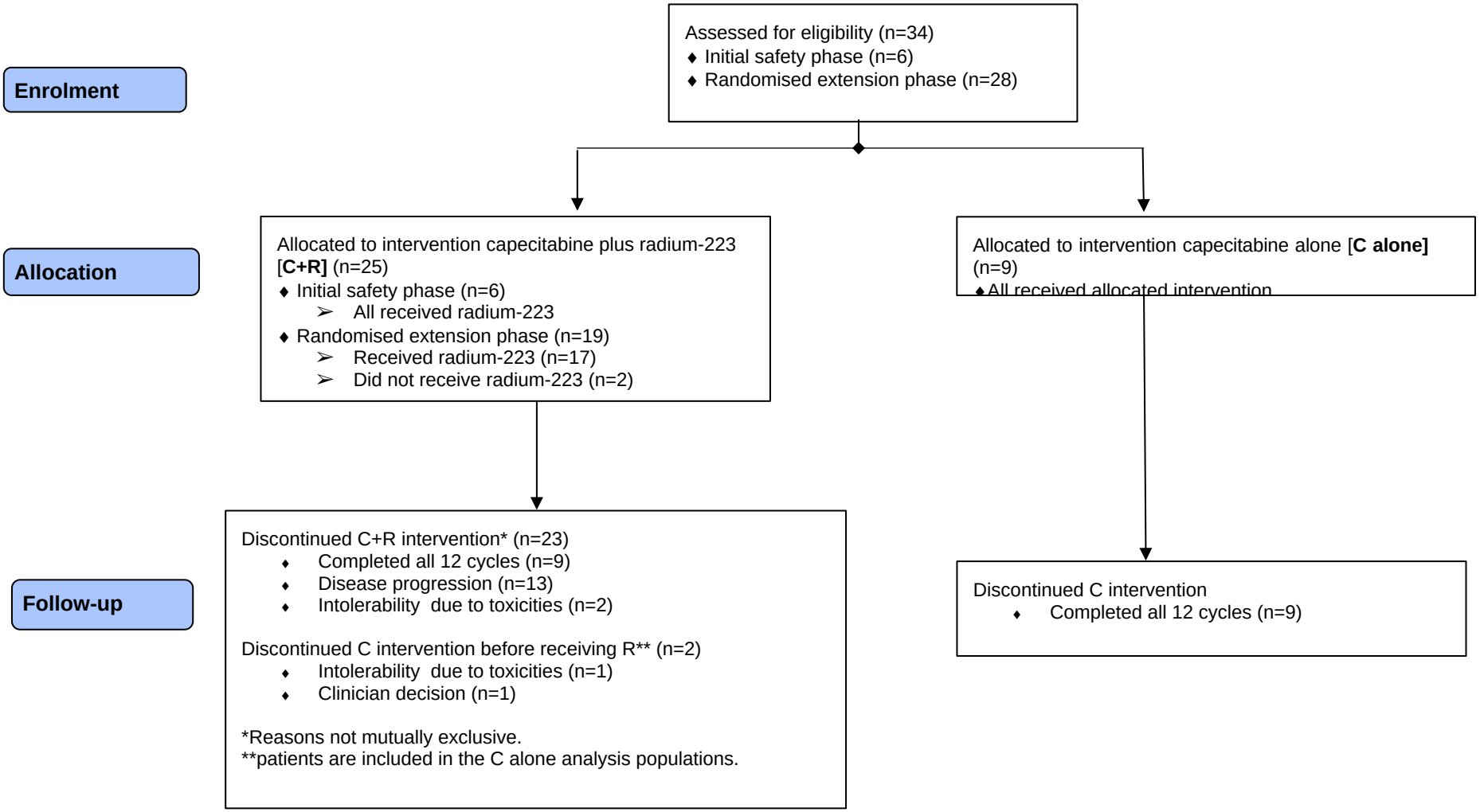
ISRCTN basic results report – CARBON ISRCTN92755158

CARBON closed to recruitment early during the randomised extension phase of the trial and results are reported below.

Participant flow diagram



Baseline Characteristics
All participants were female, due to this being a breast cancer study.

	C+R (n=23)	C alone (n=11)	Total (n=34)
Age (years)			
Mean (s.d.)	58.8 (12.2)	57.7 (12.0)	58.5 (11.9)
Median (range)	58.0 (34.0, 75.0)	55.0 (45.0, 85.0)	57.5 (34.0, 85.0)
Soft tissue metastases at other sites			
Yes	10 (43.5%)	2 (18.2%)	12 (35.3%)
No	13 (56.5%)	9 (81.8%)	22 (64.7%)
Visceral metastases at other sites			
Yes	13 (56.5%)	9 (81.8%)	22 (64.7%)
No	10 (43.5%)	2 (18.2%)	12 (35.3%)
Has the participant had any skeletal events?			
Yes	8 (34.8%)	4 (36.4%)	12 (35.3%)
No	15 (65.2%)	7 (63.6%)	22 (64.7%)
ECOG performance status			
0	12 (52.2%)	7 (63.6%)	19 (55.9%)
1	11 (47.8%)	4 (36.4%)	15 (44.1%)
Prior chemotherapy lines for metastatic breast cancer			
0	12 (52.2%)	9 (81.8%)	21 (61.8%)
1	10 (43.5%)	1 (9.1%)	11 (32.4%)
2	1 (4.3%)	1 (9.1%)	2 (5.9%)

Outcome Measures

Primary outcome in the initial safety phase=dose limiting toxicities (DLTs) within the first cycle of radium (i.e. cycle 2) up to the administration of cycle 3 day 1. Analysis population, n=6.

No DLTs were reported during the DLT reporting period.

Primary safety and toxicity outcome in the randomised extension phase=number and proportion of patients experiencing CTCAE ≥grade 3 toxicity within all cycles of treatment, with a focus on diarrhoea. Analysis population, n=34.

	C+R (n=23)	C alone (n=11)	Total (n=34)
Has patient experienced ≥grade 3 AE during treatment?			
Yes	11 (47.8%)	4 (36.4%)	15 (44.1%)
No	12 (52.2%)	7 (63.6%)	19 (55.9%)
Has patient experienced ≥grade 3 diarrhoea?			
Yes	0	0	0
No	23 (100.0%)	11 (100.0%)	34 (100.0%)
Maximum diarrhoea grade			
0 [did not experience diarrhoea]	7 (30.4%)	6 (54.5%)	13 (38.2%)
1	14 (60.9%)	4 (36.4%)	18 (52.9%)
2	2 (8.7%)	1 (9.1%)	3 (8.8%)

Primary efficacy outcome in the randomised extension phase=proportion of patients categorised as uNTX responders (≥30% reduction in uNTX level from baseline to end of cycle 5). For patients who progress or finish treatment prior to the end of cycle 5, the change in uNTX from baseline to their end of study treatment visit will be used). Analysis population, n=24.

uNTX responder at end of cycle 5?	C+R (n=16)	Proportion and 95% CI for C+R	C alone (n=8)	Proportion and 95% CI for C alone	Total (n=24)
Yes	3 (18.8%)	4.0-45.6%	2 (25.0%)	3.2-65.1%	5 (20.8%)
No	13 (81.3%)		6 (75.0%)		19 (79.2%)

Secondary outcome=treatment compliance (dose delays, omissions and reductions). Analysis population, n=34.

Has the patient…	C+R (n=23)	C alone (n=11)	Total (n=34)
Had a cycle delayed?			
Yes	14 (60.9%)	5 (45.5%)	19 (55.9%)
No	9 (39.1%)	6 (54.5%)	15 (44.1%)

Has the patient…	C+R (n=23)	C alone (n=11)	Total (n=34)
Had a permanent capecitabine reduction?			
Yes	11 (47.8%)	6 (54.5%)	17 (50.0%)
No	12 (52.2%)	5 (45.5%)	17 (50.0%)
Taken a different capecitabine dose to prescribed?			
Yes	12 (52.2%)	3 (27.3%)	15 (44.1%)
No	11 (47.8%)	8 (72.7%)	19 (55.9%)
Omitted a capecitabine dose?			
Yes	10 (43.5%)	3 (27.3%)	13 (38.2%)
No	13 (56.5%)	8 (72.7%)	21 (61.8%)

Secondary outcome=time to first symptomatic skeletal event (SSE) calculated from date of registration/randomisation to first SSE during the study. Analysis population, n=34.

Due to the small number of SSEs reported during the study, median time to first SSE could not be calculated.

Has the patient experienced an SSE?	C+R (n=23)	C alone (n=11)	Total (n=34)
Yes	3 (13.0%)	1 (9.1%)	4 (11.8%)
No	20 (87.0%)	10 (90.9%)	30 (88.2%)

Secondary outcome=time to progression of bone disease calculated from date of registration/randomisation to progression in bone. Analysis population, n=34.

Due to the small number of bone disease progressions reported during the study, median time to first time to bone disease progression could not be calculated.

Has the patient experienced bone disease progression?	C+R (n=23)	C alone (n=11)	Total (n=34)
Yes	2 (8.7%)	1 (9.1%)	3 (8.8%)
No	21 (91.3%)	10 (90.9%)	31 (91.2%)

Secondary outcome=time to progression of extraskeletal disease calculated from date of registration/randomisation to first document evidence of extraskeletal disease progression. Analysis population, n=34.

	C+R (n=23)	C alone (n=11)
Progression event	18 (78.3%)	7 (63.6%)
No event	5 (21.7%)	4 (36.4%)
Median extraskeletal PFS estimate in months (95% confidence intervals)	8.0 (5.5-12.4)	13.7 (11.9-15.6)

Secondary outcome=percentage changes from baseline in serum bone turnover markers (BALP, PINP and CTX). Analysis population, n=34.

	CTX		PINP		BALP	
	C+R	**C alone**	**C+R**	**C alone**	**C+R**	**C alone**
End of cycle 5						
Mean (s.d.)	34.37 (135.98)	-3.12 (18.26)	-12.98 (54.83)	-4.45 (86.57)	-3.16 (47.37)	-0.70 (49.68)
Median (range)	-2.47 (-26.57, 521.78)	-7.29 (-38.76, 19.77)	-9.04 (-92.96, 118.20)	-39.23 (-74.51, 171.03)	-4.96 (-72.28, 107.62)	5.00 (-67.73, 77.55)
Missing	8	2	8	2	8	5
N	15	9	15	9	15	6
End of study treatment visit						
Mean (s.d.)	48.79 (151.48)	27.24 (41.80)	-2.48 (58.79)	4.99 (76.10)	-21.33 (39.04)	7.01 (54.33)
Median (range)	1.16 (-51.72, 529.70)	19.28 (-16.59, 97.67)	14.38 (-77.48, 80.69)	-37.64 (-72.12, 136.51)	-23.76 (-71.88, 97.58)	12.75 (-67.92, 66.05)
Missing	6	3	6	3	7	4
N	17	8	17	8	16	7

Secondary outcome=quality of life (QOL) using EORTC QLQ-C30 and QLQ-BM22, and pain scores using the Brief Pain Inventory (BPI). Analysis population, n=34.

	Baseline		Cycle 6		End of study treatment visit (EOS)	
	C+R	**C alone**	**C+R**	**C alone**	**C+R**	**C alone**
Questionnaire compliance						
Completed	23 (100.0%)*	11 (100.0%)	17 (73.9%)	7 (63.6%)	18** (78.3%)	8 (72.7%)

	Baseline		Cycle 6		End of study treatment visit (EOS)	
	C+R	**C alone**	**C+R**	**C alone**	**C+R**	**C alone**
Not completed	0	0	0	2 (18.2%)	5 (21.7%)	3 (27.3%)
Did not start cycle	N/A	N/A	6 (26.1%)	2 (18.2%)	N/A	N/A
QLQ-C30						
Global health status: mean [95% CI]	66.7 [58.8-74.5]	68.9 [53.3-84.6]	67.6 [55.6-79.7]	82.1 [79.2-85.1]	67.2 [55.5-78.8]	60.4 [39.8-81.1]
QLQ-BM22: mean [95% CI]						
Painful sites	26.4 [19.3-33.4]	23.0 [5.5-40.5]	18.8 [11.7-25.9]	2.9 [-2.0-7.7]	24.6 [14.1-35.1]	6.7 [-2.8-16.1]
Pain characteristics	29.8 [20.0-39.6]	15.2 [1.7-28.6]	21.6 [12.2-31.0]	1.6 [-2.3-5.5]	23.9 [12.9-34.8]	6.9 [-1.6-15.5]
Functional interference	36.6 [26.5-46.6]	18.6 [1.6-35.6]	23.7 [15.7-31.7]	6.5 [-0.1-13.2]	26.5 [16.1-37.0]	9.4 [-0.1-18.8]
Psychosocial aspects	40.2 [32.0-48.3]	36.5 [17.8-55.1]	35.3 [25.9-44.7]	32.5 [13.7-51.4]	36.3 [24.4-48.1]	35.6 [19.3-51.8]

*1 C+R patient did not complete any of the baseline QLQ-BM22 questions. **1 C+R patient did not complete the EOS QLQ-C30 or QLQ-BM22.

Adverse Events Analysis population, n=34

Serious adverse events (SAEs) – summary statistics

	C+R	C alone	Total
Number of patients with one or more SAE	8	2	10
Number of serious adverse reactions (SARs)	0	1	1
Number of suspected unexpected serious adverse reactions (SUSARs)	0	0	0
Number of SAEs (including SARs and SUSARs) reported	11	7	18
Number of SAEs per patient			
Mean (Standard Deviation)	1.4 (0.52)	3.5 (3.54)	1.8 (1.55)
Median (Interquartile Range)	1.0 (1, 2)	3.5 (1, 6)	1.0 (1, 2)
Range	(1, 2)	(1, 6)	(1, 6)

SAEs – number of events by MedDRA code (not mutually exclusive)

MedDRA System Organ Class	C+R N (%)	C alone N (%)	Total N (%)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (14.3)	1 (5.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (36.4)	4 (57.1)	8 (44.4)
Nervous system disorders	2 (18.2)	0 (0.0)	2 (11.1)
Gastrointestinal disorders	0 (0.0)	1 (14.3)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	1 (9.1)	0 (0.0)	1 (5.6)
Infections and infestations	4 (36.4)	1* (14.3)	5 (27.8)
Vascular disorders	1 (9.1)	0 (0.0)	1 (5.6)
Total	**11 (100.0)**	**7 (100.0)**	**18 (100.0)**

*1 capecitabine related SAR=Infections and infestations

Adverse events – maximum CTCAE grade experienced for events occurring in more than 15% of patients. Grade 0 denotes patient not experiencing event.

Adverse event	C+R (n=23)	C alone (n=11)	Total (n=34)
Abdominal pain			
0	19 (82.6%)	10 (90.9%)	29 (85.3%)
1	2 (8.7%)	1 (9.1%)	3 (8.8%)
2	2 (8.7%)	0	2 (5.9%)
Alopecia			
0	20 (87.0%)	8 (72.7%)	28 (82.4%)
1	2 (8.7%)	3 (27.3%)	5 (14.7%)
2	1 (4.3%)	0	1 (2.9%)
Anemia			
0	21 (91.3%)	8 (72.7%)	29 (85.3%)
1	2 (8.7%)	1 (9.1%)	3 (8.8%)
2	0	2 (18.2%)	2 (5.9%)
Anorexia			
0	13 (56.5%)	8 (72.7%)	21 (61.8%)
1	6 (26.1%)	2 (18.2%)	8 (23.5%)
2	4 (17.4%)	1 (9.1%)	5 (14.7%)
Back pain			
0	21 (91.3%)	7 (63.6%)	28 (82.4%)
1	2 (8.7%)	3 (27.3%)	5 (14.7%)
2	0	1 (9.1%)	1 (2.9%)
Bone pain			
0	18 (78.3%)	9 (81.8%)	27 (79.4%)
1	3 (13.0%)	1 (9.1%)	4 (11.8%)
2	1 (4.3%)	1 (9.1%)	2 (5.9%)
3	1 (4.3%)	0	1 (2.9%)
Constipation			
0	20 (87.0%)	8 (72.7%)	28 (82.4%)
1	1 (4.3%)	2 (18.2%)	3 (8.8%)
2	2 (8.7%)	1 (9.1%)	3 (8.8%)
Diarrhea			
0	7 (30.4%)	6 (54.5%)	13 (38.2%)

Adverse event	C+R (n=23)	C alone (n=11)	Total (n=34)
1	14 (60.9%)	4 (36.4%)	18 (52.9%)
2	2 (8.7%)	1 (9.1%)	3 (8.8%)
Dysgeusia			
0	17 (73.9%)	8 (72.7%)	25 (73.5%)
1	4 (17.4%)	3 (27.3%)	7 (20.6%)
2	2 (8.7%)	0	2 (5.9%)
Dyspnea			
0	20 (87.0%)	9 (81.8%)	29 (85.3%)
1	1 (4.3%)	2 (18.2%)	3 (8.8%)
2	2 (8.7%)	0	2 (5.9%)
Fatigue			
0	9 (39.1%)	3 (27.3%)	12 (35.3%)
1	9 (39.1%)	6 (54.5%)	15 (44.1%)
2	5 (21.7%)	2 (18.2%)	7 (20.6%)
Mucositis oral			
0	13 (56.5%)	8 (72.7%)	21 (61.8%)
1	8 (34.8%)	2 (18.2%)	10 (29.4%)
2	2 (8.7%)	1 (9.1%)	3 (8.8%)
Nausea			
0	9 (39.1%)	6 (54.5%)	15 (44.1%)
1	10 (43.5%)	5 (45.5%)	15 (44.1%)
2	4 (17.4%)	0	4 (11.8%)
Neutrophil count decreased			
0	18 (78.3%)	10 (90.9%)	28 (82.4%)
2	2 (8.7%)	1 (9.1%)	3 (8.8%)
3	3 (13.0%)	0	3 (8.8%)
Pain in extremity			
0	18 (78.3%)	10 (90.9%)	28 (82.4%)
1	3 (13.0%)	1 (9.1%)	4 (11.8%)
2	2 (8.7%)	0	2 (5.9%)
Palmar-plantar erythrodysesthesia syndrome			
0	8 (34.8%)	3 (27.3%)	11 (32.4%)

Adverse event	C+R (n=23)	C alone (n=11)	Total (n=34)
1	6 (26.1%)	4 (36.4%)	10 (29.4%)
2	8 (34.8%)	4 (36.4%)	12 (35.3%)
3	1 (4.3%)	0	1 (2.9%)
Paresthesia			
0	19 (82.6%)	10 (90.9%)	29 (85.3%)
1	3 (13.0%)	1 (9.1%)	4 (11.8%)
3	1 (4.3%)	0	1 (2.9%)
Vomiting			
0	17 (73.9%)	7 (63.6%)	24 (70.6%)
1	4 (17.4%)	0	4 (11.8%)
2	2 (8.7%)	3 (27.3%)	5 (14.7%)
3	0	1 (9.1%)	1 (2.9%)