대한항암요법연구회
KOREAN CANCER STUDY GROUP

Randomized Phase III trial of Irinotecan combined with capecitabine versus capecitabine in patients with metastatic breast cancer (MBC) previously treated with anthracycline and taxanes : PROCEED trial (KCSG BR11-01)

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Background

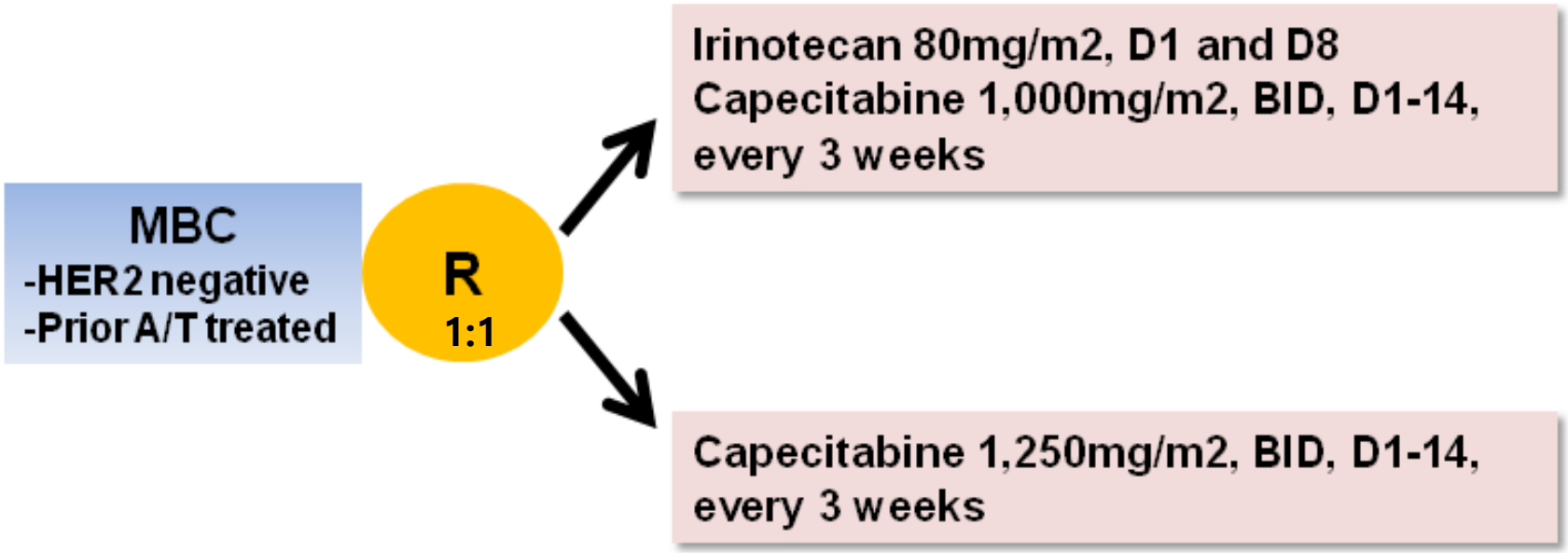
- Most patients with metastatic breast cancer (MBC) experience disease progression after being treated with an anthracycline or taxane.
- Irinotecan, a semisynthetic agent derived from the natural alkaloid camptothecin is metabolized to the active drug SN-38 which targets topoisomerase I leading to single and double strand DNA breaks.
- Irinotecan as a single agent demonstrated tumor activity with an objective response rate ranging from 5 to 23% in patients with MBC refractory to taxane and anthracycline.
- A phase II study that evaluated the efficacy and safety of irinotecan and capecitabine combination (IX) showed that the median progression free survival (PFS) was 7.6 months (95% CI, 5.0-10.2months), and the median OS was 22.6 months (95% CI, 15.4 – 29.8 months) with good tolerability in anthracycline and taxane pretreated MBC patients.
- We planned to conduct a multicenter, randomized phase III study which assesses the efficacy of irinotecan and capecitabine combination therapy compared with capecitabine alone in patients with anthracycline and taxane pretreated MBC.

Objectives

- **Primary objectives** :- Progression free survival (PFS)

- **Secondary objectives** :
  - - Objective response rate
  - - Overall survival (OS)
  - **- Toxicity**
  - **- Quality of life (QoL)**
  - - Pharmacogenomic study of irinotecan and capecitabin

Study design



*stratification factors:

1. Visceral metastasis, negative vs. positive
2. Hormone receptor positive or negative
3. First line vs. 2nd and more than 2nd line

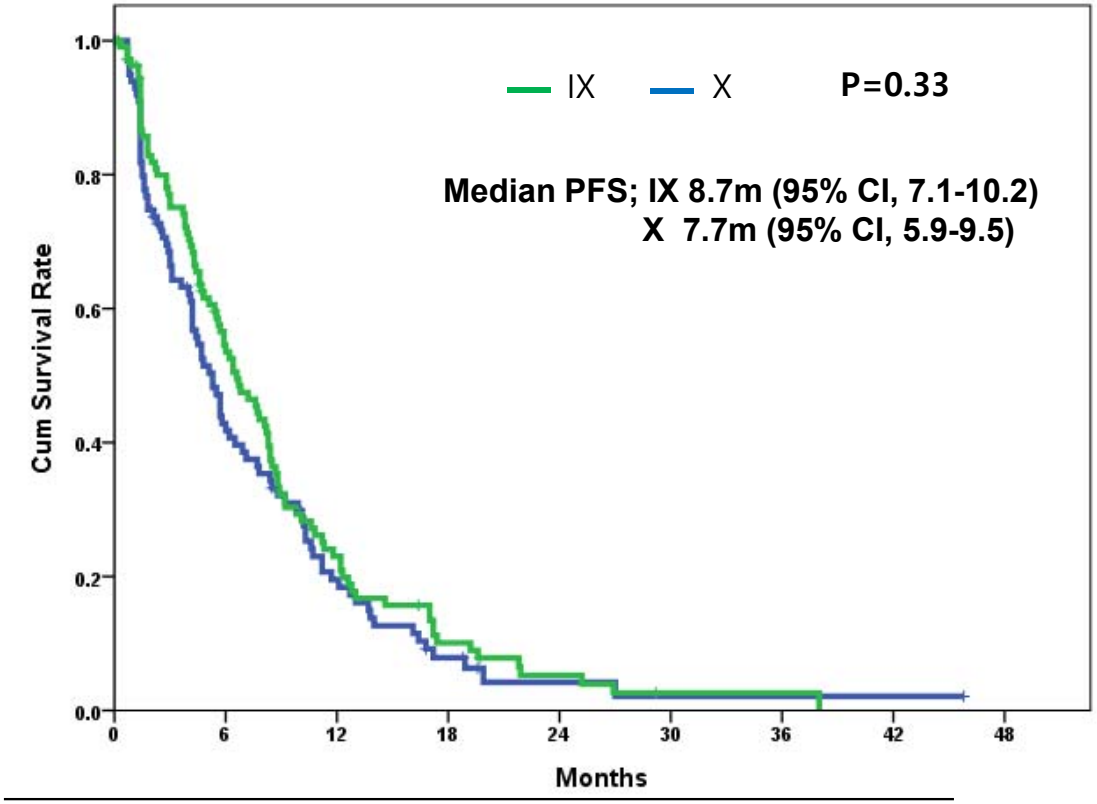
Patient characteristics

	IX (N=111)	X (N=100)	p-value
Age (yr, median, range)	50 (29-73)	49 (30-80)	0.47
ECOG			0.80
0	25 (22.5%)	22 (22%)	
1	85 (76.6%)	76 (76%)	
2	1 (0.9%)	2 (2%)	
Premenopausal	28 (25.2%)	29 (29%)	0.64
Postmenopausal	83 (74.8%)	71 (71%)	
ER/PgR			0.16
positive	60 (54.1%)	64 (64%)	
negative	51 (45.9%)	36 (36%)	
Adjuvant Chemotherapy	86 (77.5%)	72 (72%)	0.43
Adjuvant Endocrine	46 (41.4%)	39 (39%)	0.78
DFI (yr, median, range)			
Visceral meta			1
Yes	64 (57.7%)	58 (58%)	
No	47 (42.3%)	42 (42%)	
No. of previous Chemotherapy			0.40
0	12 (10.8%)	12 (12%)	
1	60 (54.1%)	46 (46%)	
≥2	39 (35.1%)	42 (42%)	

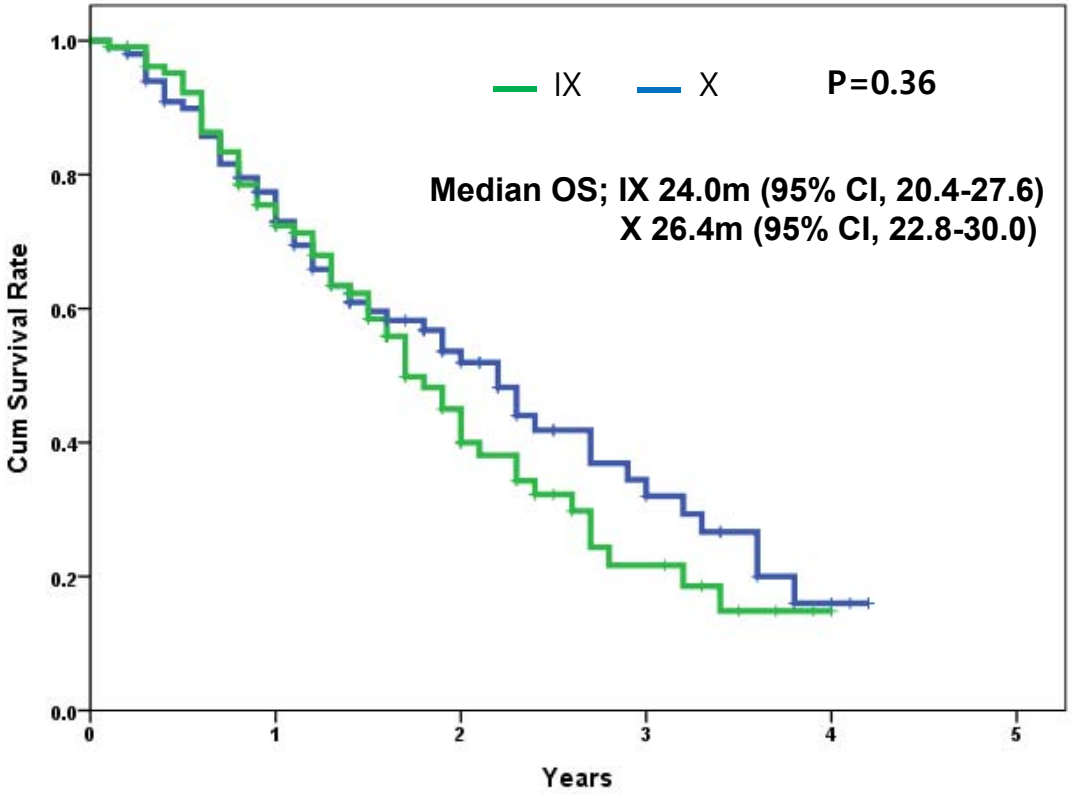
Clinical efficacy : response rate

	IX (N=111)	X (N=100)	
CR	4 (3.9%)	2 (2.0%)	
PR	39 (38.2%)	27 (27.0%)	
SD	39 (38.2%)	40 (40.0%)	
PD	18 (17.6%)	28 (28.0%)	
Not known	2 (2.0%)	1 (1.0%)	
ORR (CR+PR)	43 (42.7%)	29 (29.0%)	P=0.14

Clinical efficacy : PFS & OS

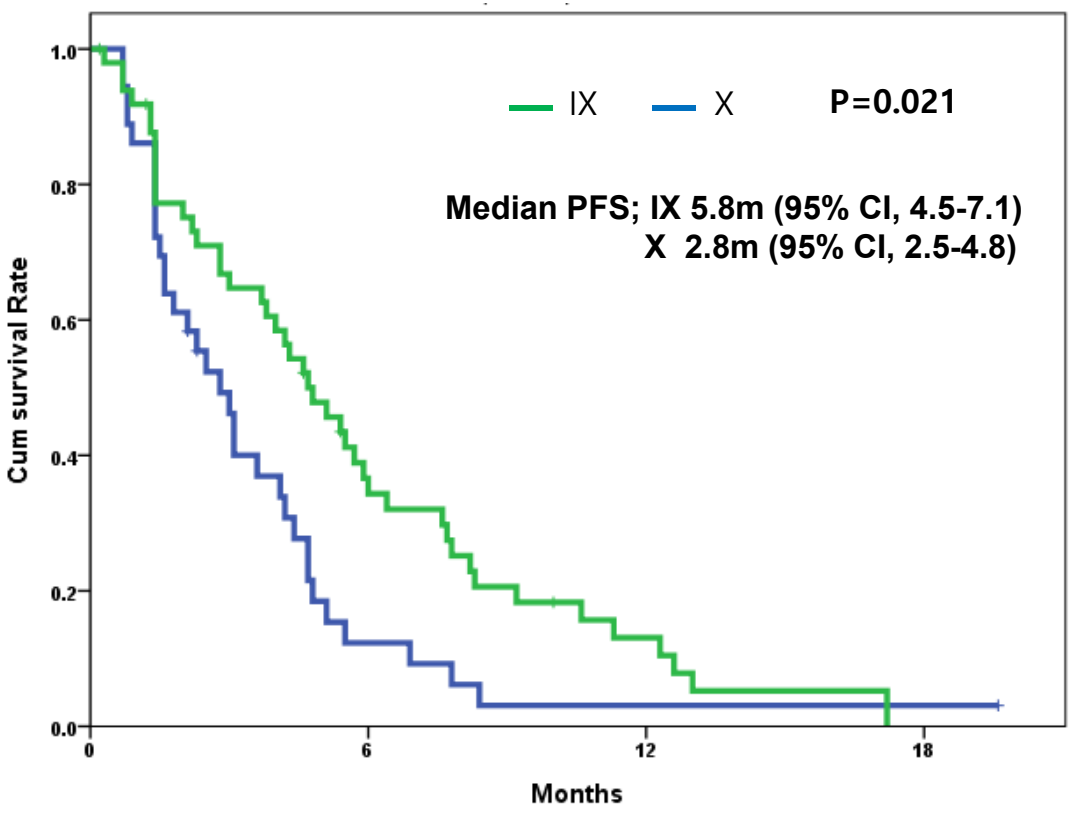


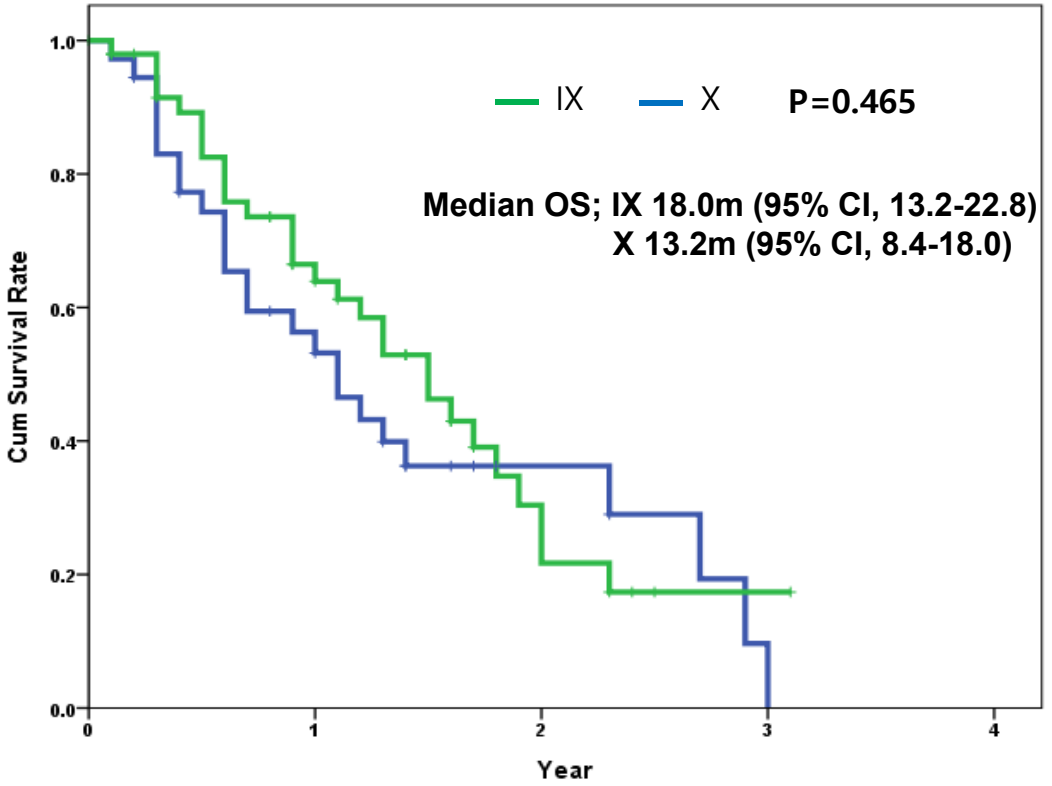
IX (N=111)	63	33	21	17	15	15	14
X (N=100)	44	24	14	12	11	11	11



IX (N=111)	83	59	51	49
X (N=100)	74	58	49	44

Clinical efficacy : PFS & OS in metastatic TNBC





IX (N=51)	20	11	6		IX (N=51)	38	26	14	2
X (N=36)	6	3	3		X (N=36)	24	12	0	0

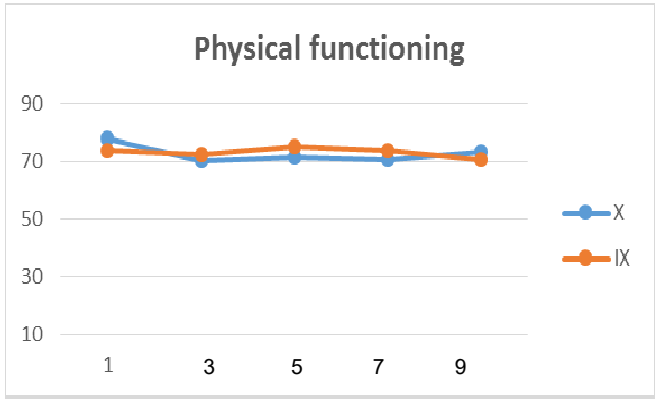
Safety: NCI-CTCAE v 4.0

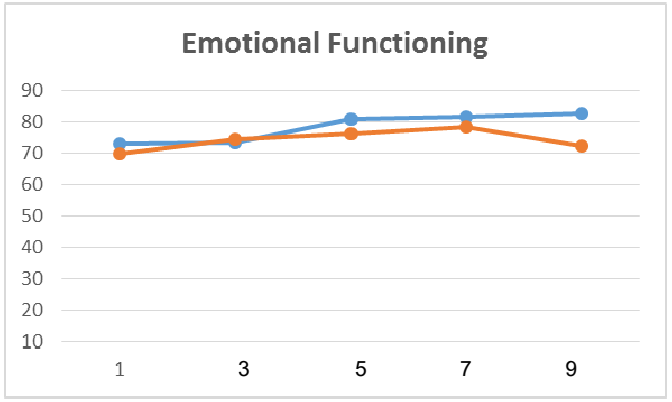
	IX (N=111)		X (N=100)		P-value
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	
Hematologic AE					
Neutropenia	26 (23.4%)	44 (**39.6**%)	7 (7.0%)	9 (**9.0**%)	<0.001
Anemia	3 (2.7%)	16 (14.4%)	10 (10.0%)	1 (1.0%)	<0.001
Thrombocytopenia	7 (6.3%)	0	4 (4.0%)	0	0.45
Non-hematologic AE					
Hand-foot syndrome	33 (29.7%)	2 (1.8%)	49 (49.0%)	4 (4.0%)	0.007
Diarrhea	46 (41.4%)	3 (2.7%)	29 (29.0%)	1 (1.0%)	0.012
Nausea/vomiting	61 (54.9%)	0	36 (36.0%)	2 (2.0%)	0.03
Liver function abnormality	2 (1.8%)	0	7 (7.0%)	1 (1.0%)	0.098
Paronychia	2 (1.8%)	0	4 (4.0%)	1 (1.0%)	0.36
Edema	9 (8.1%)	0	5 (5.0%)	0	0.37
Asthenia	3 (2.7%)	0	5 (5.0%)	0	0.38
Insomnia	15 (13.5%)	0	7 (7.0%)	0	0.12

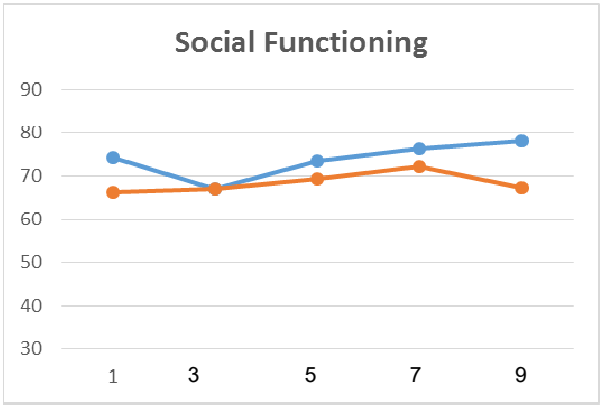
Treatment administration

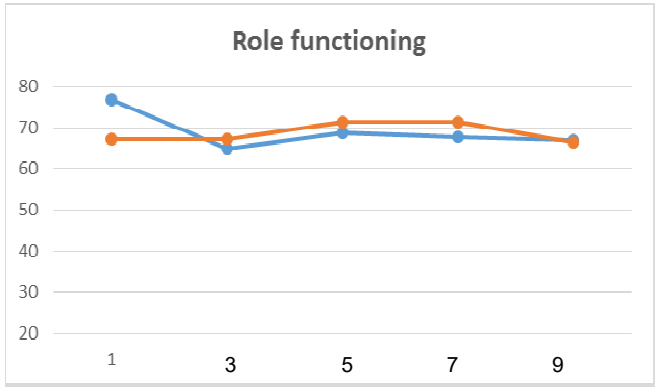
	IX (N=111)	X (N=100)
Dose reduction, N (%)	61 (54.9%)	34 (34.0%)
- Hematologic AE	52 (85.2%)	9 (26.5%)
- HFS	12 (23.1%)	17 (50.0%)
- Diarrhea	4 (6.6%)	0
Dose interruption, N (%)	38 (34.2%)	25 (25.0%)
- Hematologic AE	27 (71.1%)	14 (56.0%)
- HFS	5 (13.2%)	7 (28.0%)
- Neutropenic fever	1 (2.6%)	1 (4.0%)
- Diarrhea	1 (2.6%)	1 (4.0%)
Treatment discontinuation, N(%)	1 (0.9%) (arrhythmia)	3 (3.0%) (1=infection, 2=hematologic AE)

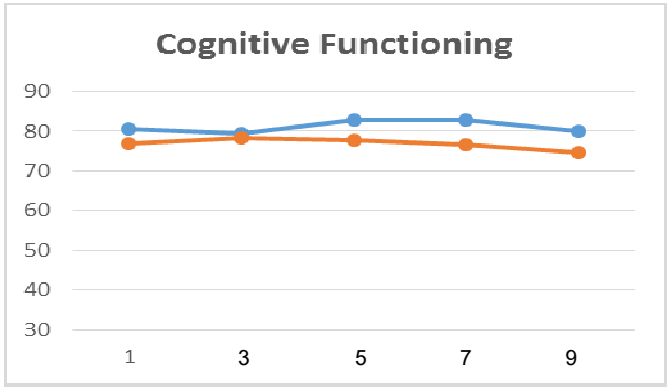
QoL: EORTC - QLQ - C30; Functional scales

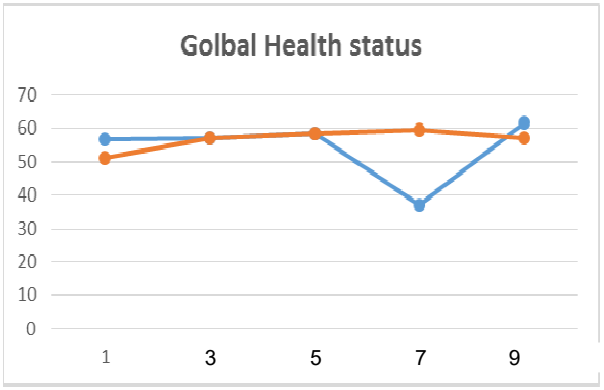




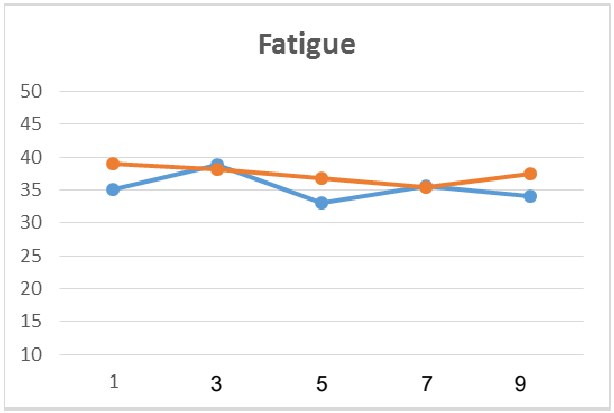


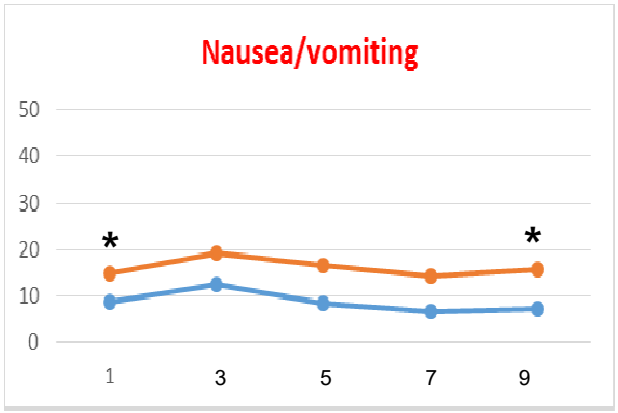


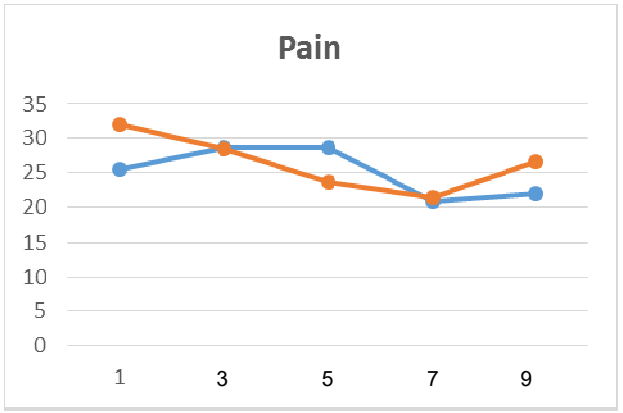


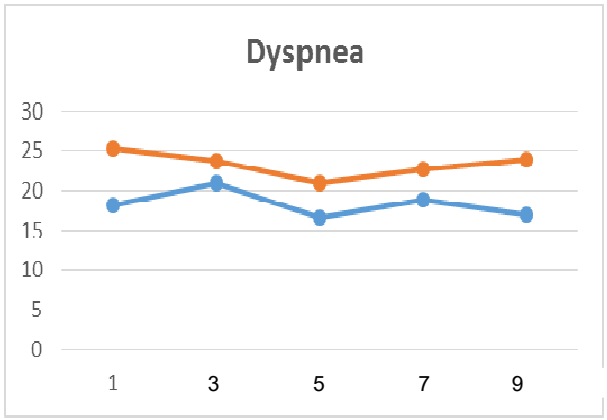


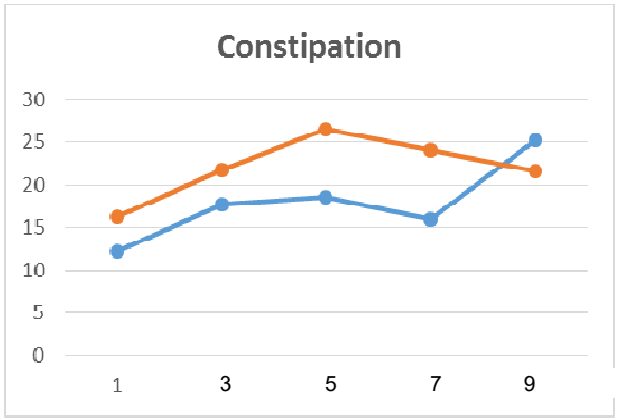
QoL: EORTC - QLQ - C30; Symptom scales

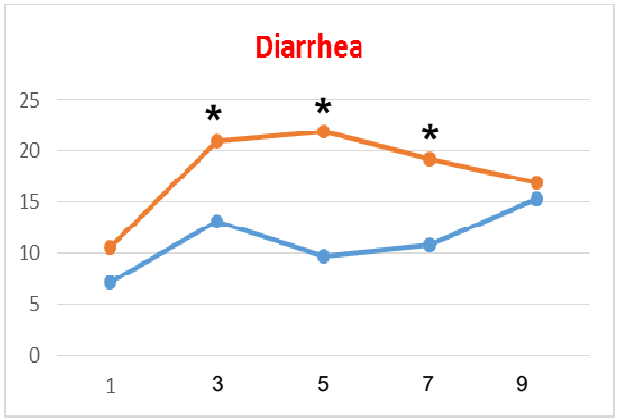












*, $p<0.05$

Conclusions

- Irinotecan plus capecitabine did not demonstrate superior clinical activity in heavily treated HER2 negative MBC patients.
- Neutropenia was more common in IX arm, which caused frequent dose modification. However, permanent drug discontinuation was rarely required.
- Most of non-hematologic AEs were of low severity with grade 1 or 2 and manageable with supportive care.
- QoL data showed similar global health status in both arms, while several symptom scales were much worse in the combination arm.
- However, PFS benefit was observed in triple negative MBC subset by addition of irinotecan. The role of irinotecan in triple negative breast cancer needs to be elucidated in further study.

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