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Adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for triple-negative breast cancer (cbcsg010): an open-label, randomised, multicentre, phase 3 trial

AHN Presenter: Diane BuchBarker, MD

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Backgound

- TNBC accounts for 12–17% of all breast cancers and is characterized by higher relapse rates and shorter overall survival
- Adjuvant anthracycline- and taxane-based therapy is the standard of care. ECOG1199 & SWOG S0221 reported AC-P resulted in substantial benefits in TNBC patients.
- EBCTCG analysis: dose intensity reduced 10-year risk of recurrence and death, especially in TNBC
- New adjuvant approaches are needed

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Backgound

- Capecitabine, an oral prodrug of fluorouracil, proved for the treatment of MBC, no cross resistant with anthracyclines and taxanes
- Early breast cancer:

Trial	Media-FU	Endpoint	HR(ALL)	HR(TN)
Concomitant use				
FinXX[1]	10.3y	RFS	0.88	0.53
USON01062[2]	5y	OS	0.68	0.62
Sequential monotherapy				
CREATE-X[3]	3.6y	DFS	0.70	0.58
CIBOMA[4]	7.3y	DFS	0.82	0.53(non-basal)

1.Joensuu H. *Lancet Oncol* 2009 2.O'Shaughnessy J. *Clin Cancer Res* 2015 3.Masuda N. *N Engl J Med* 2017 4.Martin M. SABCS 2018

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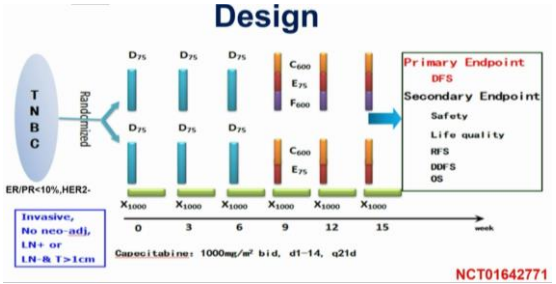
Design



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Statistical Plan

- Recruitment period of 2 years (Jun 4, 2012 and Dec 27, 2013)
- Adding capecitabine, 5-y DFS rate increase from 73% to 83% (HR, 0.59)
- 116 events needed, a two-sided type I error of 5% and a power of 80% to detect a significant difference
- Assuming 10% loss to follow-up
- 600 patients need to randomize in the study
- Events occurred slower than anticipated
- Data locked at 20.Mar.2019; Median FU is 67 months.

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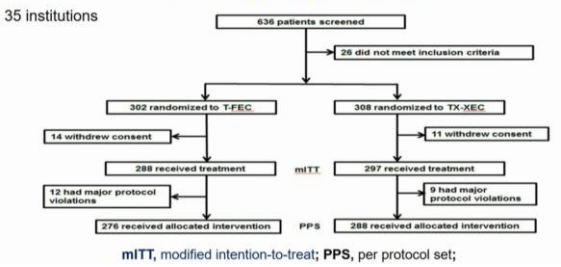
Patient Disposition



mITT, modified intention-to-treat; **PPS,** per protocol set;

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Baseline Patient Characteristics

	T-FEC (288)		XT-XEC (297)	
	n	%	n	%
Age (years), mean ± SD	48.3 ± 8.7		49.1 ± 10.4	
BSA (m^2), mean ± SD	1.6 ± 0.1		1.6 ± 0.1	
Menstruation				
Premenopausal	166	59.3	154	53.3
Postmenopausal	114	40.7	135	46.7
Family History	75	26.0	79	26.6
Operation Type				
Breast conserving	59	20.6	74	24.9
SLNB	75	26.1	75	25.3
Surgery-to-chemo time (days), mean ± SD	17.2 ± 7.9		18·0 ± 9.1	

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Baseline Patient Characteristics

	T-FEC (288)		XT-XEC (297)	
	n	%	n	%
Node Stage				
N0	185	64.9	196	66.9
N1	68	23.9	71	24.2
N2	20	7.0	12	4.1
N3	12	4.2	14	4.8
T Stage				
T1a,b	12	4.8	10	3.9
T1c	104	41.9	109	42.7
T2	120	48.4	132	51.8
T3	12	4.8	4	1.6
Histology				
IDC	255	89.2	265	89.5
Grade				
I	10	4.0	6	2.5
II	116	46.6	100	40.8
III	123	49.4	139	56.7
Ki67 ≥30%+	219	80.5	227	81.1
LVI +	40	14.1	29	9.8

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Safety: Adverse Events

	All grades (n,%)		Grade 3 or 4 (n,%)	
Event	T-FEC	XT-XEC	T-FEC	XT-XEC
All	282 (97.9)	289 (97.3)	238 (82.6)	241 (81.1)
Alopecia	253 (87.9)	254 (85.5)	205 (71.2)	206 (69.4)
Neutropenia	222 (77.1)	224 (75.4)	118 (41.0)	136 (45.8)
Febrile neutropenia	46 (16.0)	50 (16.8)	46 (16.0)	50 (16.8)
Thrombocytopenia	38 (13.2)	36 (12.1)	5 (1.7)	11 (3.7)
Increased ALT and/or AST	72 (25.0)	81 (27.3)	10 (3.5)	4 (1.4)
Stomatitis	113 (39.2)	110 (37.0)	3 (1.0)	15 (5.1)
Nausea	251 (87.2)	235 (79.1)	4 (1.4)	5 (1.7)
Vomiting	198 (68.8)	184 (62.0)	14 (4.9)	9 (3.0)
Diarrhea	52 (18.1)	46 (15.5)	3 (1.0)	3 (1.0)
Constipation	102 (35.4)	105 (35.4)	2 (0.7)	2 (0.7)
Peripheral neuropathy	106 (36.8)	121 (40.7)	1 (0.4)	1 (0.3)
Fatigue	227 (78.8)	237 (79.8)	2 (0.7)	5 (1.7)
Pain	122 (42.4)	112 (37.7)	3 (1.0)	9 (3.0)
Myalgia	134 (46.5)	130 (43.8)	5 (1.7)	5 (1.7)
Rash	40 (13.9)	49 (16.5)	4 (1.4)	1 (0.3)
Hand-foot syndrome	95 (33.0)	156 (52.5)	0 (0)	25 (8.4)

All grades AE ≥10% of patients, Grade 3 or 4 AE ≥1% of patients are listed

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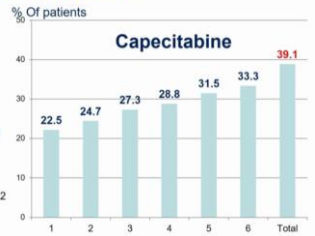
Dose Reduction

- **Completed all 6 cycles**
  XT-XEC, 252/297 (84.9%)
  T-FEC, 248/288 (86.1%)
- **Capecitabine Administration**
  39.1% had dose reductions
  7 patients: ≤750 mg/m²
  others: 900 mg/m² or 825 mg/m²



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Number of Events

Median follow-up 67 months

	T-FEC (n = 288)	XT-XEC (n = 297)
	n (%)	n (%)
Any event	57 (19.8)	41 (13.8)
Second primary	4	5
Contralateral breast	5	6
Local recurrence	18	7
Ipsilateral breast/chest	13	5
Regional lymph nodes	8	3
Distant recurrence	37	29
Liver	3	7
Lung	17	14
Bone	6	7
Other	27	14
Death*	26	19

* cumulative number

cut-off date: March 20, 2019

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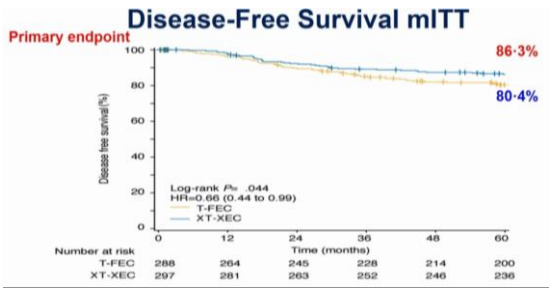

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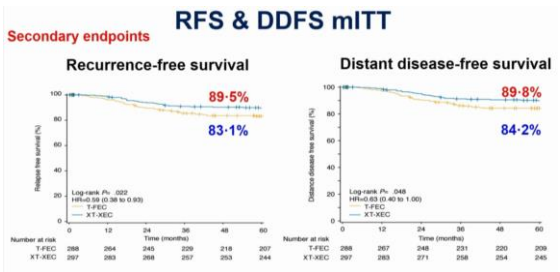

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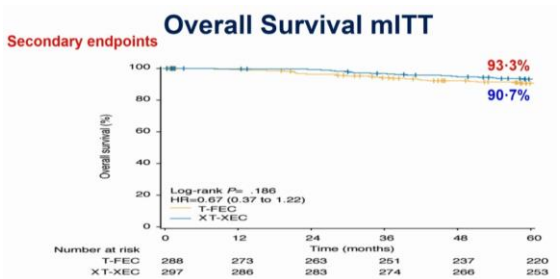

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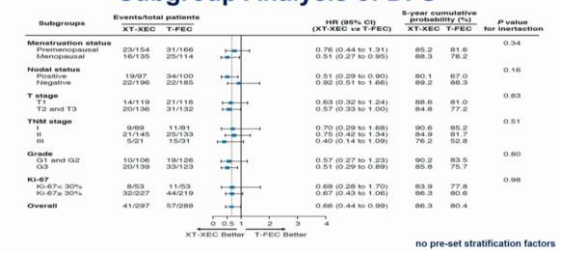
Subgroup Analysis of DFS



no pre-set stratification factors

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Limitation

- Definition of TNBC: ER/PR <10%
  - **10 patients in our study (five/group) had ER/PR 1–9% disease**
- Control group: T-FEC (Docetaxel & Epirubicin 75 mg/m2)
  - **Not recommended , DFS and RFS were comparable with published data**
- Limited to Chinese patients
  - **HFS rate & chemo completion rate were comparable with published data**
- TNBC is heterogeneous, not measured intrinsic subtype
  - **Cancer tissues retrospective collecting**

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Conclusion

- **Capecitabine, concomitantly administered with taxane/ anthracycline, significantly improved DFS rates in early TNBC**
  - **--5y DFS with capecitabine vs control 86·3% vs. 80·4% (HR 0·66, 95% CI 0·44–0·99)**
- **XT-XEC is an alternative adjuvant regimen for TNBC, with clinically meaningful improvement in survival and safety data in line with the known capecitabine safety profile.**
- **Further refinement of the current chemotherapy regimen with drugs targeted to specific tumour molecules in TNBC is warranted**

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