#1070

Comprehensive Support Project For Oncological Research of Breast Cancer

Randomized, optimal dose finding, Phase II Study of tri-weekly nab-paclitaxel in patients with metastatic breast cancer（ABROAD）

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Background

- Although nab-paclitaxel (nab-PTX) has shown superior efficacy compared to conventional paclitaxel in metastatic breast cancer (MBC), chemotherapy induced peripheral neuropathy (CIPN) was more frequently observed in nab-PTX.
- In a single arm Phase 2 trail (CA002-0LD), low dose nab-PTX (175mg/m2) every 3 weeks (q3w) demonstrated a good objective response rate (39.5%) without grade 3 or higher CIPN.
- Herein, we conducted multicenter randomized controlled study to evaluate optimal dose of nab-PTX comparing lower dose (LD or MD) to standard dose (SD).

Study objectives

- To evaluate non-inferiority of low dose nab-PTX compared to current standard dose 260mg/m2 of nab-PTX in 1st or 2nd line chemotherapy for metastatic breast cancer.
- To compare adverse events including chemotherapy-induced peripheral neuropathy (CIPN), health-related QOL (HRQOL), and Patient Reported Outcomes (PROs) between the three different doses of nab-PTX.

Study design

Multicenter rP2 study

Patients with HER2-negative MBC in 1st or 2nd line Chemotherapy for MBC (N = 138)

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- **SD260 (standard dose) arm:** Nab-Paclitaxel: 260 mg/m^2, q3w IV
- **MD220 (Medium dose) arm** Nab-Paclitaxel: 220 mg/m^2, q3w IV
- **LD180 (Low dose) arm** Nab-Paclitaxel: 180 mg/m^2, q3w IV

Stratification factors
- Hormone receptor
- DFI
- Institution
- Prior chemotherapy
- Prior taxane

These treatments were repeated until PD or unacceptable toxicity

MBC: metastatic breast cancer, PD: progressive disease, DFI: Disease free interval

Primary endpoints

Progression-Free Survival (PFS), Incidence of Grade 3/4 peripheral neuropathy

Secondary endpoints

Time to Treatment Failure (TTF), Overall survival (OS), Overall response rate (ORR), Disease control rate (DCR), Adverse events (AEs), Health-Related Quality of Life (HR-QoLSNPs associated with CIPN (Translational research)

Key eligibility criteria

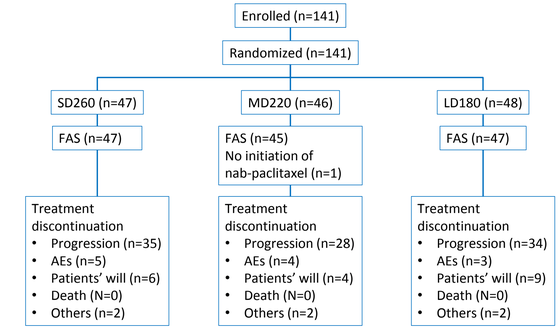
- Female and aged between 20 and 75 years,
- PS 0 or 1 (ECOG scale)
- Never received or 1 regimen of cytotoxic chemotherapy for MBC.
- Adequate organ function
- Peripheral neuropathy ≤ grade 1

Statistics

Optimal dose was selected by 2 step selection. At first, if hazard ratio (HR) for PFS was less than 0.75 or more than 1.33, the inferior dose was dropped. Then, if estimated incidence rate of grade 3/4 neurotoxicity exceed10% estimated by the logistic regression, that dose was also dropped.

The study was planned to ensure to select MD220 with a probability of 70%, when the one-year PFSs of the three doses are all 30% and the grade 3 neurotoxicity rates of SD260, MD220 and LD180 are 15%, 8% and 0.1%, respectively, which requires 40 patients per group with expected registration period of two years and mean follow-up period of two years, and finally 42 patients per group was chosen.

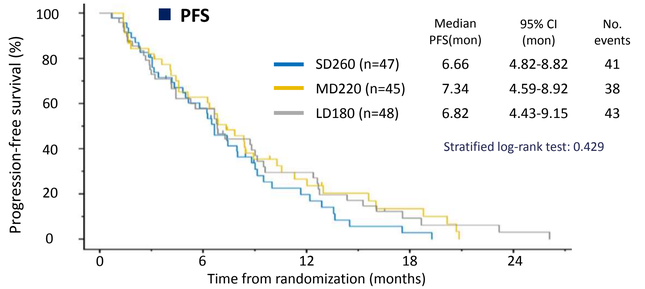
CONSORT diagram

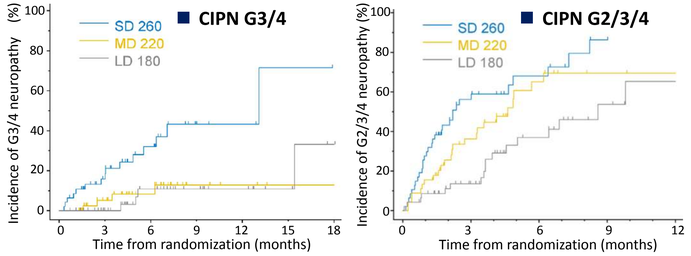


Patients characteristics

	SD260 (n=47)	MD220 (n=45)	LD180 (n=48)	P-value
Median age, yrs (range)	59.0 (36–75)	61.0 (34–74)	58.5 (35–74)	0.82
PS (ECOG)				0.22
0	38 (80.9%)	34 (75.6%)	31 (64.6%)	
1	9 (19.1%)	10 (22.2%)	17 (35.4%)	
ER-positive	38 (80.9%)	34 (75.6%)	37 (77.1%)	0.88
PgR-positive	29 (61.7%)	22 (48.9%)	27 (56.3%)	0.53
Disease-free interval				0.93
De novo	13 (27.7%)	12 (26.7%)	11 (22.9%)	
≥ 2 years	27 (57.4%)	24 (53.3%)	27 (56.3%)	
< 2 years	13 (27.7%)	9 (20.0%)	10 (20.8%)	
Chemotherapy for MBC				0.96
Yes	12 (25.5%)	11 (24.4%)	13 (27.1%)	
No	35 (74.5%)	34 (75.6%)	35 (72.9%)	
Prior taxane therapy				0.88
Yes	19 (40.4%)	17 (37.8%)	17 (35.4%)	
No	28 (59.6%)	28 (62.2%)	31 (64.6%)	

Results





First selection (equivalence)

Cox regression	Hazard ratio (HR)		Selection[1)]
	Estimate	95% CI	
MD220 vs SD260	0.73	(0.42, 1.28)	Drop SD260 due to HR<0.75
LD180 vs SD260	0.77	(0.42, 1.28)	Equivalent
LD180 vs MD220	0.96	(0.42, 1.28)	Equivalent

1) If HR <0.75 or >1.33, the inferior one will be dropped.

Second selection (peripheral sensory neuropathy)

Logistic regression	Incidence (%)		Selection[2)]
	Estimate	95% CI	
SD260	29.5	(18.7, 43.2)	Not candidate for 2nd selection
MD220	14.0	(8.8, 21.6)	Drop MD220 due to estimated incidence rate exceeding 10%
LD180	5.9	(2.3, 14.6)	Retain LD180

2) The dose with its estimated incidence rate exceeding 10% will be dropped.

Finally selected dose **LD180**

Overall response rate

	Treatment Arm								
	SD260			MD220			LD180		
Measurable	n	%	95% CI	n	%	95% CI	n	%	95% CI
No. Pts	39			34			37		
Response	19	48.7	(32.4, 65.2)	15	44.1	(27.2, 62.1)	14	37.8	(22.5, 55.2)

Dose reduction

	Treatment Arm								
	SD260 (n=47)			MD220 (n=45)			LD180 (n=48)		
Dose reduction	n	%	95% CI	n	%	95% CI	n	%	95% CI
Yes	19	40.4	(26.4, 55.7)	11	24.4	(12.9, 39.5)	7	14.6	(6.1, 27.8)
No. of dose reduction									
1	14	29.8	(17.3, 44.9)	8	17.8	(8, 32.1)	6	12.5	(4.7, 25.2)
2	5	10.6	(3.5, 23.1)	3	6.7	(1.4, 18.3)	1	2.1	(0.1, 11.1)
By treatment course									
By 1st course	0	0.0	(0, 7.5)	0	0.0	(0, 7.9)	0	0.0	(0, 7.4)
By 2nd course	3	6.4	(1.3, 17.5)	1	2.2	(0.1, 11.8)	0	0.0	(0, 7.4)
By 3rd course	5	8.5	(2.4, 20.4)	2	4.4	(0.5, 15.1)	0	0.0	(0, 7.4)

Adverse events

Events	SD260: n, (%)		MD220: n, (%)		LD180: n, (%)	
	Any	Grade≥3	Any	Grade≥3	Any	Grade≥3
No. of pts	n =47		n =45		n =48	
Leukopenia	31 (66.0)	9 (19.1)	35 (77.8)	12 (26.6)	29 (60.4)	7 (14.6)
Neutropenia	27 (57.4)	12 (25.4)	33 (73.3)	17 (37.7)	24 (50.0)	7 (14.6)
Hemoglobin	27 (57.4)	1 (2.1)	22 (48.9)	1 (2.2)	28 (58.3)	2 (4.2)
ALT elevation	26 (55.3)	1 (2.1)	20 (44.4)	2 (4.4)	18 (37.5)	0 (0.0)
Fatigue	38 (80.9)	1 (2.1)	35 (77.8)	0 (0.0)	34 (70.8)	0 (0.0)
Sensory neuropathy	43 (91.5)	15 (31.9)	38 (84.4)	4 (8.9)	39 (81.3)	4 (8.3)
Arthralgia	35 (74.5)	4 (8.5)	30 (66.7)	5 (11.1)	27 (56.3)	0 (0.0)
Myalgia	34 (72.3)	6 (12.8)	26 (57.8)	3 (6.7)	19 (39.6)	0 (0.0)
Rash	16 (34.1)	0 (0.0)	14 (31.1)	0 (0.0)	12 (25.0)	0 (0.0)
Anorexia	24 (51.1)	1 (2.1)	23 (51.1)	0 (0.0)	20 (41.7)	1 (2.1)

Conclusions

- Low dose nab-PTX at 180 mg/m2/3 weeks could be an optimal dose with good clinical efficacy and tolerability for patients with MBC.

Acknowledgement

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