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A Phase II trial of pan-HER inhibitor poziotinib, in patients with HER2-positive MBC who have received at least two prior HER2-directed regimens:

The Results of NOV120101-203 Trial

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Disclosure

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- YHP reports consultancy for Pfizer, Eisai, Spectrum Pharmaceuticals and research fund from AstraZeneca and Pfizer.
- SBK reports research fund from Novartis, Sanofi Aventis, Kyowa Kirin Inc, and Dongkook Pharma Co, Ltd
- JYK reports employment by NOV.
- JHK reports employment by Hanmi
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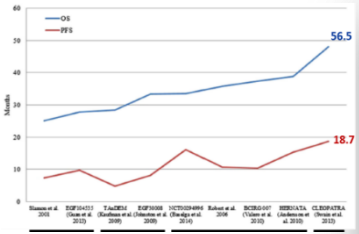
Targeting HER2+ Breast Cancer : major clinical advances

Phase II
Randomized trial
of T-DM1

Phase III
Pertuzumab



Need effective
HER2
blockade

1998 2007 2012 2013 2017

FDA
Approval

Trastuzumab — Lapatinib — Pertuzumab — T-DM1 — Neratinib
[HER2 + BC,
extended adj]

What's the
next?

Pivotal Trials: Targeting HER2

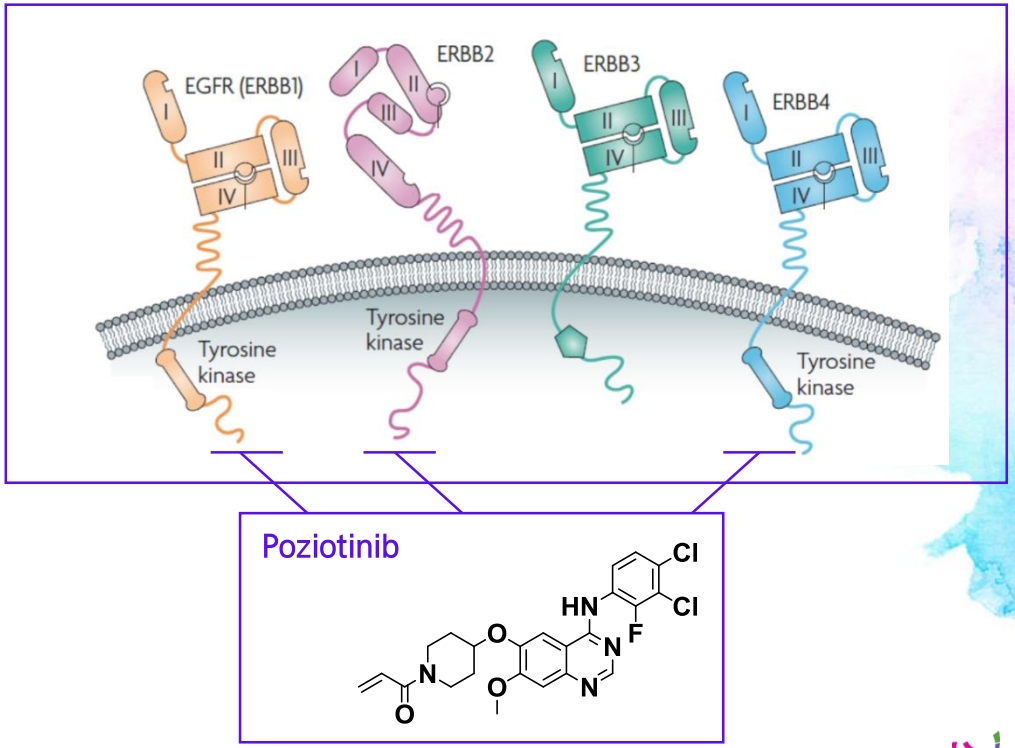
CLEOPATRA	EMILIA	TH3RESA
Trastuzumab-Pertuzumab dual inhibition HER2+, 1st line, MBC	T-DM1 vs. Lapatinib + Capecitabine HER2+, 2nd line, ABC	T-DM1 vs. TPC HER2+, 3rd line, MBC

On-going clinical trials

Several ADCs pan-HER2 inhibitors HER3 targeting

Poziotinib

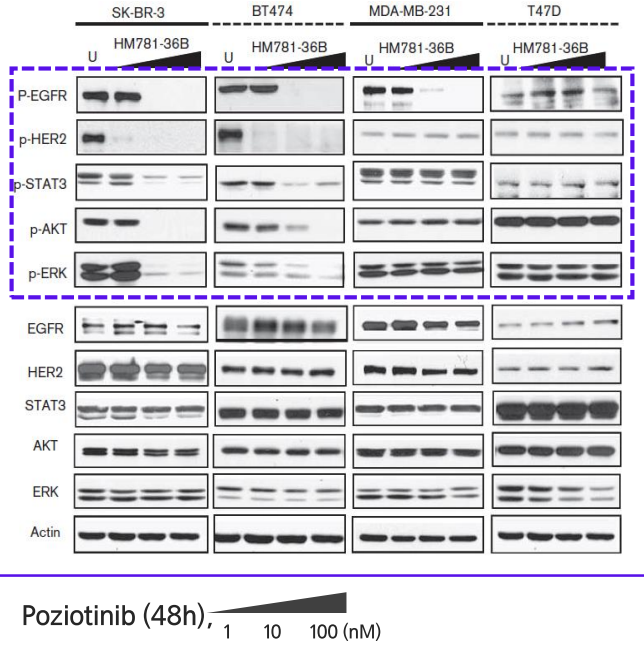
- A Novel, pan-HER inhibitor
- Orally available quinazoline compound class
- Irreversible inhibition of HER family tyrosine kinases



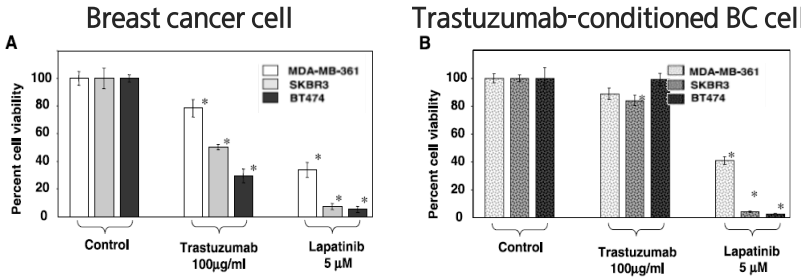
Cha MY, et al. Int J Cancer. 2012
Baselga J. Nat Rev Cancer 2009

Poziotinib Shows Strong Activity in HER2+ Breast Cancer Cells

Effect of Poziotinib on the HER2 signaling



Initially respond to trastuzumab, but begin to progress within one year



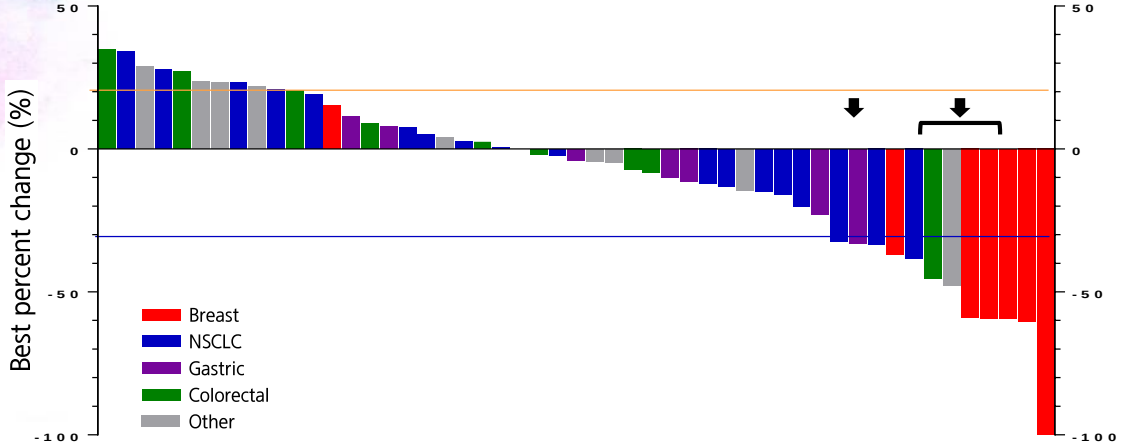
Trastuzumab *vs* Lapatinib *vs* Poziotinib (IC50 nmol/L)

Breast cancer cell line	BT-474	SK-Br3	MDA-MB-175	MDA-MB-453	MDA-MB-361
	Trastuzumab Sensitive HER2+ Cells			Trastuzumab **Resistant** Cells	
Trastuzumab	-	-	-	>10,000	>10,000
Lapatinib	36	80	70	3,900	989
Afatinib	9.5	16	34	1,500	726
Dacomitinib	18	34	5	2,000	300
Poziotinib	**1.2**	**1.0**	**0.1**	**5.4**	**44**

Rita Nahta, et al. Cancer Letters 2006, GE Konecny, et al. Cancer Res 2006, Kim HJ et al. Anti-cancer drugs .2012
Cha MY, et al. Int J Cancer. 2012, O Kalous, et al, Mol Cancer Ther. 2012, F O'Neill, et al. Molecular Cancer. 2013, Tanaka et al. Cancer science 105.8 2014

Phase1

Pooled Analysis: Efficacy Results



Best tumor response in target lesions
(n=51, treatment with 8 mg or more)

Objective Response Rate		Total	NSCLC	Gastric Cancer	Breast Cancer	Other Cancer
8-32mg (n=51)	Confirmed PR	12/51 (24%)	3/18 (17%)	1/7 (14%)	6/7 (86%)	2/19 (11%)

- MTD: 18 mg, 24 mg
- Recommended dose: 16 mg

Study Design

A Prospective, Open-label, Single-arm, Multicenter, Phase 2 Exploratory Trial to Evaluate the Efficacy and Safety of Poziotinib in Patients with HER2-overexpressed Recurrent, Stage IV Breast Cancer Who Have Received at Least Two Prior HER2-directed Regimens.

Patients with:

- HER2 overexpressed*
- Relapsed or initially stage IV breast cancer with metastatic lesions
- Previously received prior anticancer chemotherapy and at least two HER-2 directed** regimen including trastuzumab

(* lapatinib, T-DM1, pertuzumab, etc.)

Poziotinib 12 mg*,

2wks followed by 1 week of washout until disease progression or unacceptable toxicity

Primary: PFS
Secondary: ORR, OS, Safety

*ASCO guideline: IHC 3+ or FISH or SISH+
**Dose escalation up to 16mg was allowed
Dose reduction to 8~10mg were performed according to toxicities

Cut-off Date: 23 Feb 2017

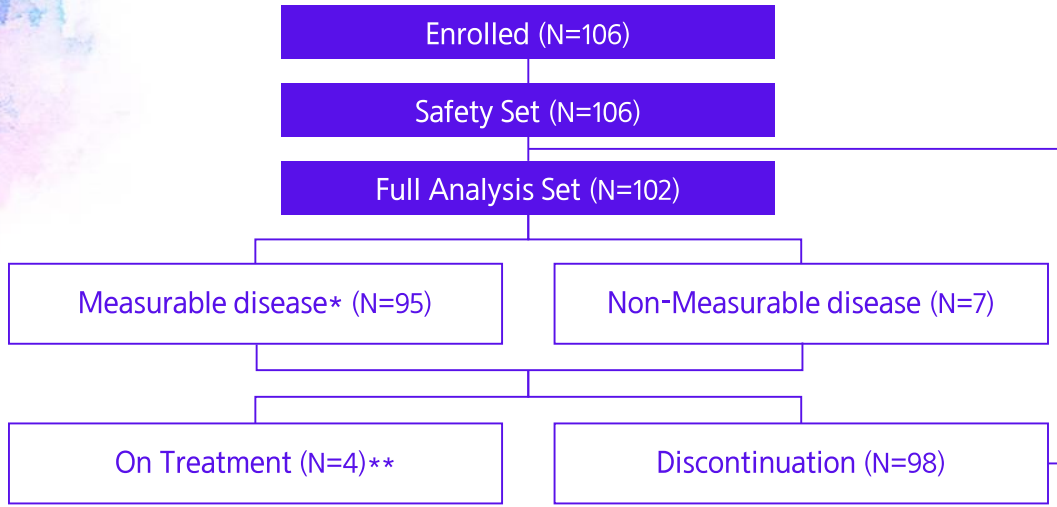
Major Inclusion Criteria

Inclusion Criteria	
Subjects had to meet all of the following inclusion criteria:	
1	Histopathologically confirmed recurrent or initially stage IV metastatic breast cancer.
2	Confirmed HER2 overexpression in the tumor samples (primary or metastatic) ([FISH] positive, [SISH] positive, or [IHC] 3+).
3	ECOG performance status 0-2.
4	Measurable or evaluable lesions as confirmed by RECIST ver1.1.
5	Having failed anticancer chemotherapy including taxane and at least two HER-2 directed* regimens including trastuzumab. *lapatinib, T-DM1 (trastuzumab emtansine), pertuzumab, afatinib

Major Exclusion Criteria

Exclusion Criteria	
Subjects who fell under any of the following exclusion criteria were excluded from the trial:	
1	History of primary malignancies except for breast cancer.
2	Central nervous system (CNS) metastases, except for the followings. a. Radiologically stable for at least 4 weeks as confirmed by CT or MRI and treatment with corticosteroids at a stable dose for at least 4 weeks. b. Evidence of leptomeningeal or parenchymal metastases that have been appropriately treated and have no symptoms and no previous treatment with anticonvulsants or steroids for the control of intracranial pressure within 4 weeks prior to study participation.
3	Treatment with other investigational product or investigational medical device within 4 weeks before the administration of the investigational product.

Consort Diagram



No tumor assessment (N=4)

Study Complete (N=102)
Reason for Discontinuation

Withdrawal by subject (N=6)
Progressive Disease (N=88)
Adverse event (N=6)
Other (N=2)

* Measurable disease : subject with target lesion at screening

**#1. 14.6 months+
**#2. 19.6 months+
**#3. 13.2 months+
**#4. 12.3 months+

Demographics and Disease Characteristics

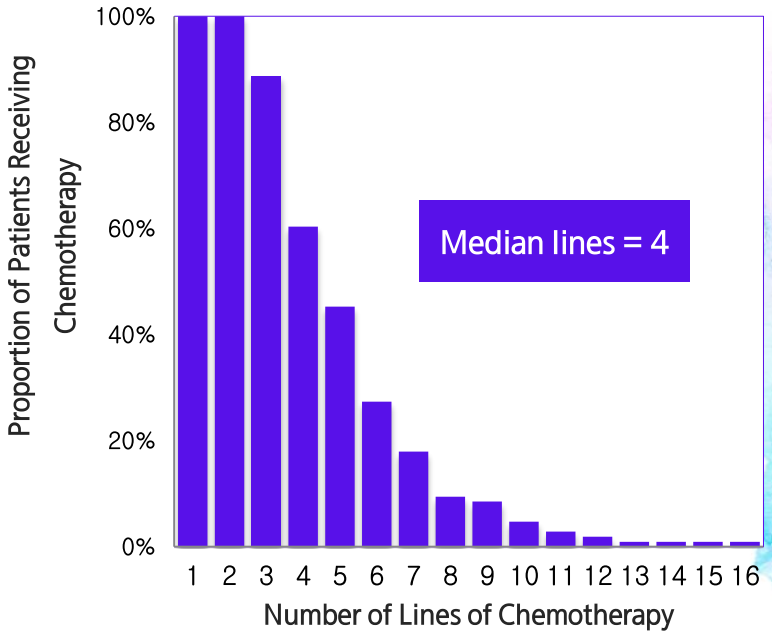
Category	Safety Set (N=106)
Age(years)*	
Median (Min, Max)	51.0 (30, 76)
Age group, N(%)	
< 45 years	23 (21.7%)
45 ~ 64 years	70 (66.0%)
≥ 65 years	13 (12.3%)
Gender, N(%)	
Female	106 (100.0%)
BMI(kg/m^2)	
Mean (SD)	22.4 (3.4)
Hormone receptor status, N(%)**	
ER positive and/or PR positive	51 (48.1%)
ER negative and PR negative	54 (51.9%)
IHC status, N(%)	
2+	15(14.2%)
3+	91(85.8%)

Category	Safety Set (N=106)
ECOG, N(%)	
0	40 (37.7%)
1	63 (59.4%)
2	3 (2.8%)
Menopause Status, N(%)	
Postmenopausal	55 (51.9%)
Premenopausal	51 (48.1%)
Visceral disease#, N(%)	
Yes	81 (76.4%)
No	25 (23.6%)
Distant metastatic, N (%)	
Brain	6 (5.7%)
Bone	38 (35.9%)
Skin	11 (10.4%)
Liver	41 (38.7%)
Lung	58 (54.7%)

*Age : Age on the date of informed consent | ** 1 subject : ER, PR status not done
Visceral : Liver or lung or Brain metastasis at screening

Prior Number of Chemotherapeutic Regimens

Category	Safety Set (N=106)
Number of regimens in advance disease	
Median (Min, Max)	4 (2, 16)
2	12 (11.3%)
3	30 (28.3%)
4	16 (15.1%)
≥5	48 (45.3%)
Prior HER2-directed therapy	102 (100)
Lapatinib	96 (94.1)
Trastuzumab	92 (90.2)
T-DM1	19 (18.6)
Trastuzumab + Pertuzumab	9 (8.8)
Afatinib	1 (1.0)

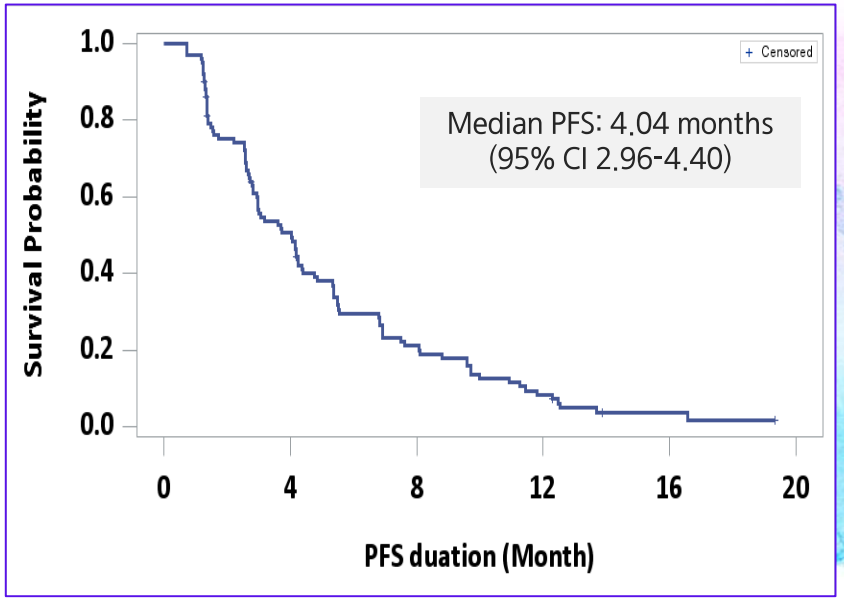


Progression Free Survival

Progression Free Survival	N= 102
Number of subjects with an event	94 (92.16)
Earliest contributing event, n(%)	
Progressive disease	93 (91.18)
Death	1 (0.98)
Progression free survival (Month)	
Median (95% CI)	4.04 (2.96, 4.40)

PFS(Month)=(date of PD confirmation or death, whichever occurs first- date of first study drug administration+1)/(365.25/12)
Subjects with no event was censored at last available tumor assessment date

Cut-off date: 2017-02-23



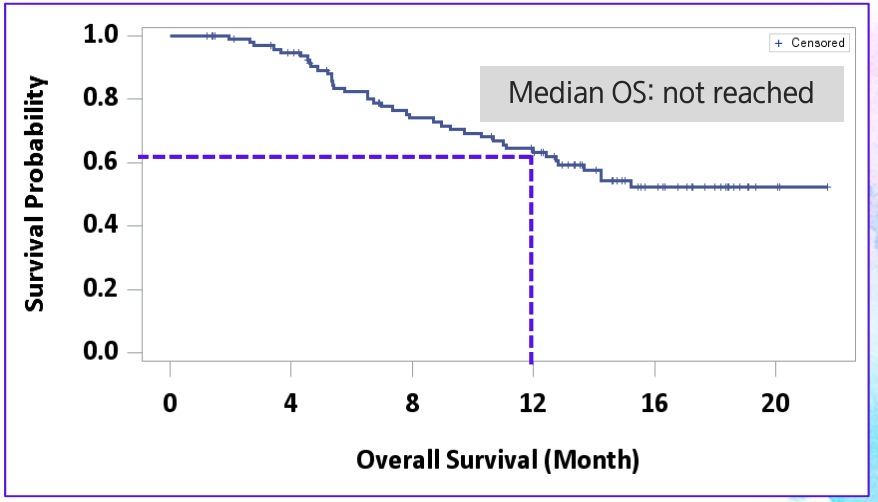
Overall Survival

Overall Survival	N= 102
Number of subjects with an event	39 (38.24)
Earliest contributing event, n(%)	
Death	39 (38.24)
Overall Survival (Month)	
Median (95% CI for Median)	NA (12.75, NA)

Overall survival = The interval from first study drug administration date to death from any cause.

FAS set-Subjects who have had at least one dose of IP administration and have at least one post-baseline tumor assessment

Cut-off date: 2017-02-23

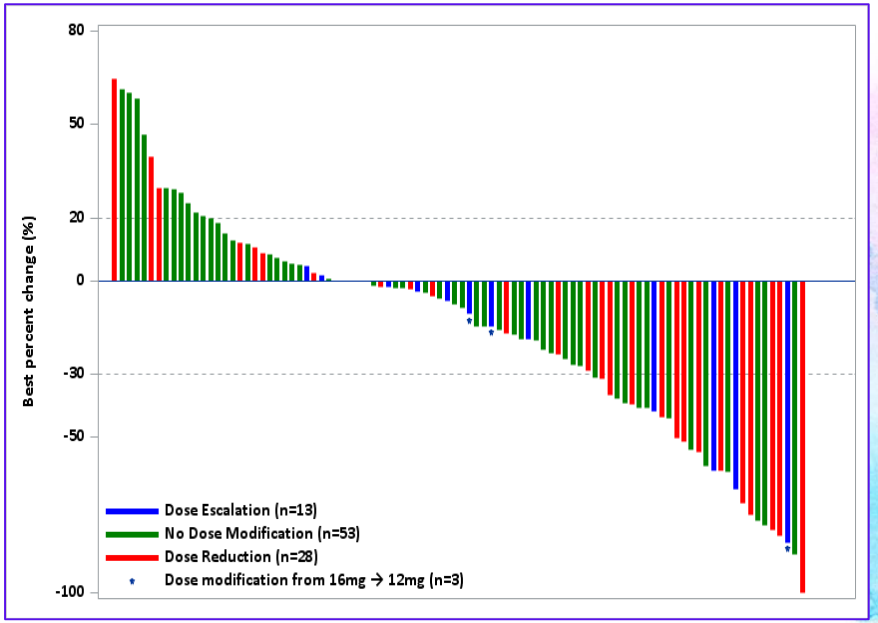


- 1 Year Overall survival rate = 63%
- Median F/U Duration = 12.2 month

Overall Response

Overall Response	Measurable Disease (N= 95)
Overall response rate, n(%)	26 (27.4)
95% Confidence Interval	(18.7 - 37.5)
Overall response rate (Confirmed), n(%)	20 (21.1)
95% Confidence Interval	(13.3 - 30.7)
Disease Control Rate, n(%)	71 (74.7)
95% Confidence Interval	(64.8 - 83.1)
Disease Control Rate (Confirmed), n(%)	71 (74.7)
95% Confidence Interval	(64.8 - 83.1)
Best Overall Response (Confirmed), n(%)	
CR	0
PR	20 (21.1)
SD	51 (53.7)
PD	24 (25.3)
NE	0

≥ SD for ≥ 12 weeks: 73% (52/71)
Median duration of response was 5.6 months.

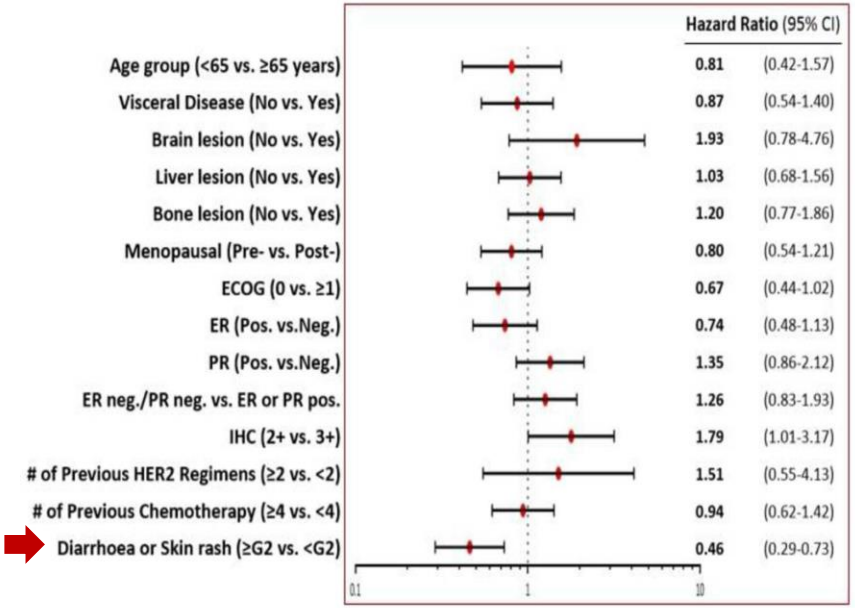


Best percent change in target lesions (%) = (the smallest post-treatment tumor diameter - baseline tumor diameter) / baseline tumor diameter *100

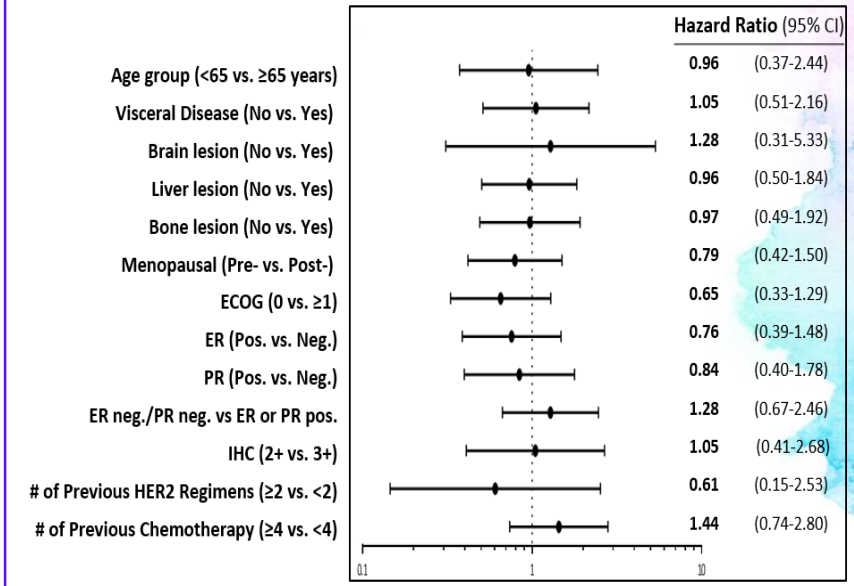
* 8 subjects are not included in the above results (7 subjects: non-target lesion, 1 subject: no assessable target lesion at post-baseline).

Subgroup Analysis for PFS and OS

Progression-Free Survival



Overall Survival



Safety analysis : Adverse Events (All Grades>=10%)

Preferred Term	Safety (N=106)	
	All n(%)	>=Grade 3 n(%)
Subjects with any AEs	106 (100.0)	40 (37.7)
Diarrhoea	102 (96.2)	15 (14.2)
Stomatitis	98 (92.5)	13 (12.3)
Pruritus	67 (63.2)	0
Rash	67 (63.2)	4 (3.8)
Dry skin	41 (38.7)	0
Dermatitis acneiform	34 (32.1)	4 (3.8)
Decreased appetite	32 (30.2)	0
Alopecia	26 (24.5)	0
Nausea	22 (20.8)	0
Mucosal inflammation	21 (19.8)	0

Preferred Term	Safety (N=106)	
	All n(%)	>=Grade 3 n(%)
Dyspepsia	16 (15.1)	0
Cough	16 (15.1)	0
Dyspnoea	14 (13.2)	2 (1.9)
Vomiting	14 (13.2)	0
Constipation	13 (12.3)	0
Rhinorrhoea	13 (12.3)	0
Myalgia	13 (12.3)	0
Fatigue	12 (11.3)	2 (1.9)
Upper respiratory tract infection	12 (11.3)	0
Palmar-plantar erythrodysaesthesia syndrome	11 (10.4)	0
Abdominal pain	11 (10.4)	0

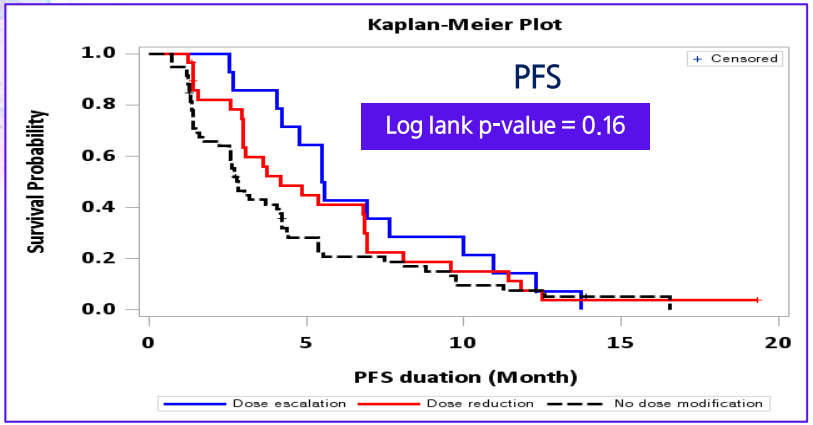
Safety analysis : SAE

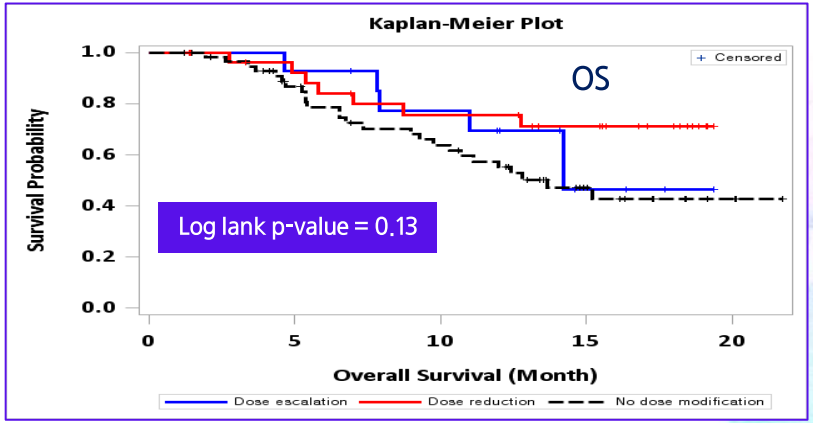
Preferred Term	Safety N=106 n(%)	Intensity
Subjects with any SAEs	9(8.5)	
Diarrhoea	2(1.9)	Grade 3
Pleural effusion	1(0.9)	Grade 3
Pneumothorax	1(0.9)	Grade 2
Catheter site pain	1(0.9)	Grade 3
Urosepsis	1(0.9)	Grade 4
Hydronephrosis	1(0.9)	Grade 3
Thrombosis	1(0.9)	Grade 2
Fracture	1(0.9)	Grade 2
Flank pain	1(0.9)	Grade 3

Dose Modification

Dose Modification Pattern*	Safety (N=106) n(%)
Dose Escalated to 16 mg	14 (13.2)
Dose reduced from 16 mg to 12 mg	3 (2.8)
No Dose modification	61 (57.6)
Dose Reduction	31 (29.3)
Dose reduction to 10 mg (1st)	23 (21.7)
Dose reduction to 8 mg (2nd)	8 (7.6)

PFS and OS according to Dose Modifications





	Dose escalation (N=14)	Dose reduction (N=29)	No dose modification (N=59)
No. of event	14	26	54
Median PFS (month)	5.52	4.17	2.83
95% CI	4.07, 9.99	2.99, 6.83	2.56, 4.17
HR(95% CI) vs No dose modification	0.58 (0.38, 0 .88)	0.73 (0.53, 1.01)	—
p-value	0.01	0.06	—

	Dose escalation (N=14)	Dose reduction (N=29)	No dose modification (N=59)
No. of event	6	7	26
Median OS (month)	14.23	—	13.67
95% CI	7.91, —	12.75, —	9.72, —
HR(95% CI) vs No dose modification	0.71 (0.38, 1.36)	0.44 (0.24, 0.80)	—
p-value	0.30	0.06	—

Conclusion

01 The patients who had received median 4 prior anticancer therapies including median 2 HER2 directed therapies in MBC were enrolled.

02 The median PFS was 4.04 months, (95% CI, 2.96-4.40 months) & median OS has not been reached.

03 The DCR was 74.7% (71/95) including 20 patients with confirmed PR (confirmed ORR: 21.1%, 20/95).

Conclusion

04 The most common treatment-related AEs (grade ≥3) were diarrhea (14.2%), stomatitis (12.3%), rash (3.8%), and dermatitis acneiform (3.8%).

05 Confirmation of the efficacy and safety in a larger number of subjects through a phase 3 study is deemed necessary.

06 Biomarker study being analyzed from pre- and on-treatment biopsies is warranted.

Acknowledgements

We thank the patients participating in this trial,
and the study investigators.

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I am especially grateful to Prof. Seock-Ah Im, co-PI.

Thank you for your attention!

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