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Genomic profile and response prediction of eribulin mesylate based neoadjuvant chemotherapy in triple negative breast cancer patients

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Background

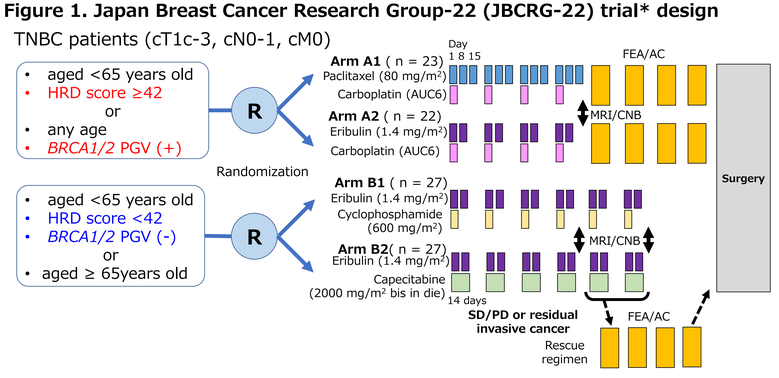
- Triple-negative breast cancer (TNBC) is an aggressive subtype of primary breast cancer that has heterogenous subgroups.
- The sensitivity to chemotherapy differs among TNBC patients, thus predicting a response remains a big issue to explore in breast cancer research and treatment.
- Still little is known about the predictive factors for eribulin mesylate (eribulin) based chemotherapy among the TNBC patients.

Purpose

- In this translational research of a randomised neoadjuvant phase II study, we aimed to explore predictive factors for eribulin based neoadjuvant chemotherapy in triple negative breast cancer (TNBC) using tumour genomic profiling.

Methods

Figure 1. Japan Breast Cancer Research Group-22 (JBCRG-22) trial* design



*JBCRG-22 trial; A multicenter randomized phase Ⅱ clinical trial with neo -adjuvant chemotherapy containing eribulin mesylate for triple negative primary breast cancer patients (Neo-Entrance study) [1)]

PGV; pathogenic germline variant (= "Deleterious" or "Suspected Deleterious" by Myriad test)
MRI; magnetic resonance imaging
CNB; core needle biopsy
SD; stable disease
PD; progressive disease
FEC; 5-fluorouracil–epirubicin–cyclophosphamide regimen
AC; doxorubicin–cyclophosphamide regimen

- Tumour DNA extracted from formalin-fixed paraffin-embedded (FFPE) specimens of biopsy material before treatment was evaluated for HRD (Homologous Recombination Deficiency) score and *BRCA1/2* alterations by the Myriad Genetics (Salt Lake City, USA).
- Tumour DNA extracted from biopsy material before or during chemotherapy, or surgical specimen, was also analysed by targeted-capture sequencing of 189 genes associated with breast cancer using Genomon2 pipeline [2)] .

References

1)Breast Cancer Res Treat. 2021 Jul;188(1):117-131.
2)http://genomon.readthedocs.io/ja/latest/index.html

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COI Disclosure Information

I have no financial relationships to disclose.

Results

Table 1. Patient characteristics

Characteristic	*BRCA1/2* status analyzed cases				Targeted sequencing cases
	A1 (N = 23)	A2 (N = 22)	B1 (N = 20)	B2 (N = 21)	(N=50)
Age					
median (minimum - maximum)	44.0 (28-64)	47.5 (26-63)	57.0 (35-70)	55.8 (37-70)	54.6 (26-70)
< 50	14	13	3	3	17
>= 50	9	9	17	18	33
< 65	23	22	17	16	42
>= 65	0	0	3	5	8
TNM classification: T					
T1c	10	6	1	5	8
T2	12	14	17	14	36
T3	1	2	2	2	6
TNM classifcation: N					
N0	15	14	10	14	27
N1	8	8	10	7	23
Histological grade (B&R)					
1	1	0	0	1	1
2	3	4	6	7	12
3	16	17	13	9	32
unknown	3	1	1	4	5
Ki67 index, %					
Median (minimum- maximum)	58.0 (20.2 - 92.4)	66.2 (36.4 -89.6)	51.0 (20.0 –90.4)	51.6 (16.2 - 82)	57.3 (16.2 - 90.4)
< 30	3	0	3	5	10
>= 30	20	22	17	16	40
HRD score					
< 42	0	0	14	15	18
>= 42	23	22	0	0	21
NA	0	0	6	6	11
BRCA1/2* status					
BRCA1 positive	6	5	0	0	4
BRCA2 positive	3	3	0	0	3
negative	14	14	20	21	43
Anthracycline treatment					
Yes	22	21	7	8	30
No	1	1	13	13	20
pCR rate, %	65.2	45.5	10.0	23.8	-
Yes (n)	15	10	2	5	11
No (n)	8	12	18	16	39
Treatment arm					
A1	23	-	-	-	8
A2	-	22	-	-	13
B1	-	-	20	-	15
B2	-	-	-	21	14

NA; Not Analyzed pCR; ypT0+ypN0
* *BRCA1/2* status;
positive = deleterious BRCA1/2 alterations were detected by Myriad test and/or targeted sequencing

Figure 2. Correlation between *BRCA1/2* status and PCR rate in Arm A1 & A2 (HRD positive group)

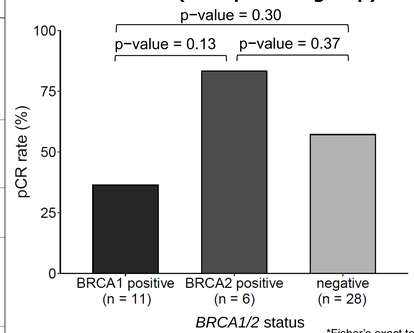


Figure 3. Correlation between HRD score and pCR rate

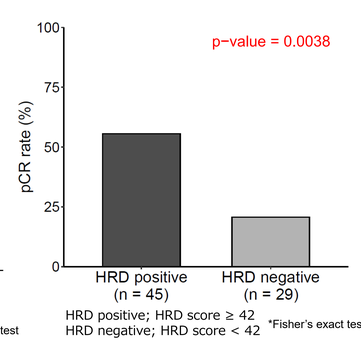
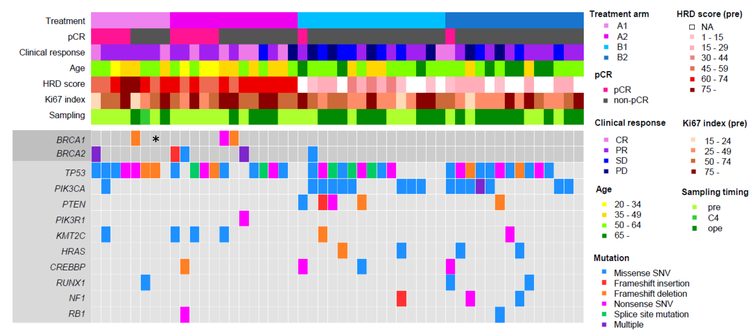


Figure 4. Mutational landscape (Targeted sequencing data)



CR; complete response PR; partial response SD; stable disease PD; progressive disease
pre; biopsy samples before chemotherapy C4; biopsy samples post 4 cycles of chemotherapy
ope; surgical samples post chemotherapy
SNV; single nucleotide variant.
＊ ; deleterious rearrangement was detected by Myriad test

- pCR rates of tumours with deleterious *BRCA2* alterations were higher than those with *BRCA1* alterations.
- HRD-positive tumours (Arm A1 & A2) showed higher pathological complete response (pCR) rates as compared with HRD-negative tumours (Arm B1 & B2).
- HRD-negative tumours had mutations in *PIK3CA* and *PTEN* frequently (61%, 22%, respectively). Contrary, these abnormalities are rare in HRD-positive tumours (5%, 0%, respectively).

Conclusion and Discussion

- *BRCA1/2* status may have a different role in predicting pCR in TNBC patients receiving neoadjuvant chemotherapy.
- HRD score might be a good predictor in assessing sensitivity of eribulin based chemotherapy regardless of *BRCA1/2* status.
- Further validation studies are warranted to conduct for clarifying the relationship between *BRCA1/2* variants and sensitivity to the eribulin-based chemotherapy.