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Profiling of metastatic cancers to the breast for the biomarkers of immuno-oncology therapy

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ABSTRACT

Female or male breast is a rare organ for non-mammary cancers to metastasize to, and molecular characteristics of these metastases have not been yet studied. We investigated molecular and immune characteristics of diverse types of metastases to the breast, in order to gain knowledge of potential therapy options.

We identified 64 patients with metastatic cancers to the breast: 51 carcinomas and 13 melanomas. PD-L1 expression was evaluated using SP142 (Ventana) (n=41), 22c3 (DAKO) (n=10) and 28-8 (DAKO) (n=13) antibodies. Gene sequencing was done using two different panels: 592-gene [n=19]; and 44-gene [n=41]). Copy number alterations (n=17), microsatellite instability (MSI) and tumor mutational burden (TMB) (n=19) were performed using next generation sequencing platforms (Illumina).

Three most common primary sites for metastatic carcinomas to the breasts were lung (37%), ovary (29%) and fallopian tubes/peritoneum (14%). Carcinomas of an unknown primary site (CUP) were rare (n=2) while melanomas of unknown primary (MUP) were common (n=10/13). Mutations in *TP53* gene were commonly (50%) observed among the carcinoma cases, while other mutated genes were characteristic for the primary tumor type (e.g. *VHL* in renal clear cell carcinomas, *BRCA1* in fallopian tube carcinoma, *SMARCB1* in renal medullary carcinoma and *BRAF* in melanomas). High TMB (≥10 mutations/Mb) was detected in five of 14 analyzed carcinomas (the highest TMB was 29/mb and was detected in a CUP case) and in three of seven analyzed melanomas, (two were MUP). No case exhibited MSI. Tumor cells (TC) PD-L1 expression was detected in six carcinomas but not in any of the melanoma, while immune cells (IC) expression of PD-L1 was seen in 17 carcinomas and 6 melanomas.

Metastases to the breast proved to be heterogeneous and biomarkers of potential benefit to approved immune-oncology therapy were limited to PD-L1 positive NSCLC, while targeted therapy biomarkers followed the pattern commonly seen in primary tumors.

METHODS

Assay	Number of tested cases
Copy number alterations (CNA)	17
Microsatellite instability (MSI)	19
Tumor mutational burden (TMB)	19
44-gene panel (TruSeq Amplicon panel)	41
592-gene panel (NGS)	19
Immunohistochemistry	
PD-L1	64
SP142 clone	41
28-8 clone (melanoma)	13
22c3 clone (NSCLC)	10

Table 1. Molecular assays used in the study and number of tested cases

OBJECTIVES

In the present study, we reviewed a large cohort (n=64) of cancers metastatic to breast profiled at a single reference center (Caris Life Sciences, Phoenix, AZ) for detected biomarkers of targeted and immuno-oncologic therapies.

RESULTS

Histotype	Mutations (n)
Carcinomas	
Lung cancer NSCLC	*TP53* (9), *KRAS* (3), *PTEN* (3), *RB1* (2), *AKT* (1), *FANCC* (1), *HRAS* (1), *ARID1A* (1), *ARID2* (1), *EGFR* (1)
SCLC	*TP53* (2), *RB1* (2), *FBXW7* (1)
Ovarian cancer	*TP53* (7), *BRAF* (2), *NRAS* (1)
Fallopian tube/peritoneum	*TP53* (3), *BRCA1* (1)
Kidney cancer	*VHL* (2), *SMARCB1* (1), *PIK3CA* (1)
Bladder cancer	*TP53* (2), *PIK3CA* (1)
Duodenum	none
Colon cancer	*TP53* (1), *NRAS* (1)
CUP	*KRAS* (1), *TP53* (1), *KDM6A* (1), *TSC2* (1), *STK1* (1)
Melanomas	
Total	*BRAF* (8), *APC* (1), *CHEK1* (1), *CTTNB1* (1), *GNA11* (1), *NRAS* (1), *PIK3CA* (1), *SF3B1* (1), *TP53* (1)
Melanoma of unknown primary	*BRAF* (6), *APC* (1), *NRAS* (1), *PIK3CA* (1), *TP53* (1)

Table 2. Mutational profile of metastatic cancers to the breast

Histotype	PD-L1 (TC)	PD-L1 (IC)	High TMB	H-MSI
Carcinomas	**6/51 (12%)**	**17/51 (33%)**	**5/14 (36%)**	**0/14** (0%)
- **Lung carcinoma**	**4/19 (21%)**	**7/19 (37%)**	**3/7 (43%)**	0/7 (0%)
a) NSCLC	**4/10 (40%)**	**4/10 (40%)**	**2/4 (50%)**	0/4 (0%)
b) SCLC	0/9 (0%)	**3/9 (33%)**	**1/3 (33%)**	0/3 (0%)
- **Ovarian carcinoma**	0/15 (0%)	**2/15 (13%)**	**1/4 (25%)**	0/4 (0%)
- **Fallopian tube/peritoneum**	0/7 (0%)	**5/7 (71%)**	0/1 (0%)	0/1 (0%)
- **Kidney carcinoma**	0/4 (0%)	0/4 (0%)	NA	N/A
a) Renal cell ca	0/3 (0%)	0/3 (0%)	NA	N/A
b) Medullary ca	0/1 (0%)	0/1 (0%)	NA	N/A
- **Bladder ca**	**1/2 (50%)**	**2/2 (100%)**	NA	N/A
- **Duodenal NEC**	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
- **Colorectal ca**	0/1 (0%)	**1/1 (100%)**	NA	N/A
- **CUP**	**1/2 (50%)**	0/2 (0%)	**1/1 (100%)**	0/1 (0%)
Melanomas	0/13 (0%)	**6/12 (50%)**	**3/7 (43%)**	0/5 (0%)
a) Of unknown primary	0/9 (0%)	**5/9 (55%)**	**2/4 (50%)**	0/2 (0%)
b) Skin melanoma	0/4 (0%)	**1/3 (33%)**	**1/3 (33%)**	0/3 (0%)

Table 3. The status of biomarkers of I-O therapy

CONCLUSIONS

- We confirm the rarity of secondary cancers to the breast (1.4% of all breast biopsies with a malignancy).
- The study also showed heterogeneity in terms of biomarkers of potential benefit to I-O and targeted therapies, necessitating individual patient profiling.