Case Report
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Response to Checkpoint Blockade in a Patient with Metastatic HER2-positive Breast Cancer

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Abstract

The success of immunotherapy in breast cancer care is limited to the triple negative subtype. There are no current recommendations for the use of checkpoint inhibitors in HER2 positive disease; although the tumor biology in HER2-positive breast cancer demonstrates that the immune system has a potentially substantial contribution to the therapeutic effects of trastuzumab. Our group is currently conducting an investigator initiated clinical trial of safety and clinical activity for atezolizumab (a PDL-1 inhibitor) added to standard of care paclitaxel, trastuzumab and pertuzumab for first line treatment of patients with metastatic HER2-positive breast cancer (NCT03125928, PI: LJ Goldstein, co-PI: E Obeid). Our case report demonstrates the successful use of immunotherapy (in this case, pembrolizumab) and trastuzumab in a patient with metastatic HER2-positive breast cancer with low PD-L1 positivity and a high tumor mutational burden seen on Caris testing. This case demonstrates clinical support for the use of this combination and illustrates the importance of continued research to better identify the role of immunotherapy in HER2-positive patients. We believe this report adds significant information to previously published data and alerts treating breast oncologists to such therapies, as the field awaits our and other clinical trials of immunotherapy in metastatic HER2-positive breast cancer.

Keywords: Immunotherapy • Breast cancer • HER2-positive

Introduction

The treatment of patients with HER2-positive breast cancer has improved significantly. One can argue that the understanding of the tumor biology in HER2-positive breast cancer has been amongst the most important breakthroughs in breast cancer treatment in the past two decades [1,2]. In metastatic HER2-positive breast cancer, the reported median survival time using modern combination therapies targeting the HER2 pathway is now approximately 5 years. The therapeutic advances in targeted therapy in HER2-positive breast cancer includes direct oral tyrosine kinase inhibitors (TKI) such as lapatinib, neratinib and tucatinib [3-5]. Additionally, antibody-drug conjugates have made significant advances in the treatment including trastuzumab-emtansine (T-DM1) [6] and trastuzumab-deruxtecan (Enhertu) [7]. Despite the improvement in survival seen with these new anti-HER2 therapies, patients with metastatic HER2-positive breast cancer ultimately develop resistance to therapy.

Checkpoint inhibitors have revolutionized the way cancer is treated with approval in several different tumor types. While there has been some benefit seen in metastatic breast cancer (MBC), this has largely been seen in the triple negative subtype [8]. Overall, the success of immunotherapy in breast cancer care remains less impressive. The tumor biology in HER2-positive breast cancer demonstrates that the immune system has a potentially substantial contribution to the therapeutic effects of trastuzumab [9,10]. Increased clinical activity may follow the activation of the immune system in HER2-positive breast cancers. In a phase I clinical trial of 26 PD-L1-unselected, HER2-positive MBC patients, single agent avelumab resulted in no objective responses [11]. Another phase Ib/II trial of patients with HER2-positive MBC who had progressed on previous trastuzumab-containing regimens, were treated with pembrolizumab and trastuzumab and showed 15% objective responses in PD-L1-positive tumors [12]. While this is less impressive, it was the first direct clinical evidence for a possible role of checkpoint inhibition with HER2-blockade therapy in this disease. Herein, we report a case of a woman with ER negative, HER2-positive MBC treated with pembrolizumab. This patient provided consent to publish her information and images.

Case

Our patient was diagnosed in 2015, at age 45, after self-palpating a right breast mass. Biopsy revealed an infiltrating ductal carcinoma, grade III, estrogen receptor (ER) 0% negative, progesterone receptor (PR) 0% negative and HER-2/neu 3+ positive. A staging positron emission technology (PET) scan showed extensive adenopathy in the bilateral neck, left supraclavicular region, bilateral axilla, retropectoral muscle and mediastinum. Brain MRI was negative. A left axillary biopsy was negative. She was at least a clinical stage IIIB (cT2,cN3,cM0) and despite the likelihood of metastatic disease, her young age prompted the decision to proceed with curative intent therapy. She completed 6 cycles of TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab). Follow up PET scan showed a near complete metabolic response. She declined any surgical intervention and opted for maintenance HP. She developed shortness of breath 8 months after completion of chemotherapy and workup revealed new mediastinal and paratracheal adenopathy. Paratracheal node biopsy on 6/23/16 revealed HER2+ MBC. Given her previous response to taxane-based therapy, she received THP (paclitaxel, trastuzumab, pertuzumab) and achieved a partial response. Ultimately paclitaxel was discontinued for progressive neuropathy. She switched to trastuzumab, pertuzumab and vinorelbine on 3/20/17 but progressed after 10 months of therapy. She then received T-DM1 for 5 months prior to progression from enlarging left chest/axillary cutaneous masses and hilar adenopathy. She was started on 4th line therapy with Lapatinib and capecitabine on 11/3/18 with a short-lived response before progressing in the left chest wall mass. Her quality of life was considerably affected by chemotherapy side effects and severe pain from the enlarging left chest wall mass with an open wound (Figure 1). She received palliative radiation to the left axilla in March 2019. Three weeks later, the mass became significantly enlarged and radiation did not give the anticipated effect. She previously had next generation sequencing completed on her tumor biopsy from the chest wall lesion using Caris Molecular Intelligence Profile.

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Her Caris profile reported the tumor to be positive for PD-L1 receptor at 2+ (5%) by the SP142 antibody and had a high tumor mutational burden (TMB) of 20 Mutations/Mb (Figure 2). We decided to attempt immunotherapy with pembrolizumab. Her first dose was given April 15, 2019. Her subsequent visit on May 10, 2019 revealed an early decrease in the size of her open chest wall mass and near complete resolution of her multiple subcutaneous nodules. We decided to re-start trastuzumab with her second dose of pembrolizumab as per the PANACEA trial [12]. She had a significant clinical response (Figure 1). Restaging CT scans were completed after 4 doses of pembrolizumab and showed a near complete resolution of the infiltrative disease in the left breast/axilla and pulmonary nodules (Figure 3). She received 7 cycles of pembrolizumab and on 8/23/19, the day of her 7th dose, she had a new seizure with the subsequent diagnosis of a left frontal mass measuring 5 mm with surrounding vasogenic edema.

In October 2019, she was restarted on trastuzumab. Her pembrolizumab had been held since her CNS diagnosis in anticipation of biopsy/resection of her left frontal mass, except for one dose in early November 2019. However, she ultimately decided against having the CNS lesion biopsied or removed. In January 2020, she showed progression in her lung lesions, mediastinal nodes and chest wall mass. Therefore, her pembrolizumab was restarted on January 23, 2020. Repeat brain MRI in March 2020 showed the mass to be stable. By the time of writing this report in January 2022, she remains with continued response (intracranial and extracranial) and no evidence of new disease.

Discussion

We reported here a patient with heavily pretreated metastatic HER2-positive breast cancer who was successfully treated with combination immunotherapy and HER2 directed therapy. Her chest wall tumor was enlarging at a significant pace while on chemotherapy and undeterred by additional lines of HER2 based therapy or radiation. Her subcutaneous nodules and left chest wall mass responded to single agent pembrolizumab and continued to respond with the addition of trastuzumab without the use of additional chemotherapy. The novel HER2 therapies trastuzumab deruxtecan and tucatanib, were unavailable at the time of this patient's rapid progression and this case highlights the importance of tumor profiling to help uncover additional potential targeted therapy. All patients with MBC should undergo tumor profiling and if any biomarker of immune response is identified, checkpoint inhibition should be considered for treatment. In our patient, we do not know which biomarker was more indicative of her complete response: PD-L1 5% positivity by SP142 or the high TMB of 20 mutations/Mb.

The mechanisms of action for the HER2-targeted antibody, trastuzumab, in combination with chemotherapy are complex, but literature indicates an important component of the activity is mediated through the adaptive immune system by antibody-dependent cell-mediated cytotoxicity (ADCC) [9]. Most patients eventually develop resistance to trastuzumab. The impact of T-cell activation may be abolished by upregulation and interaction of normal checkpoint inhibitors such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1). In fact, efforts to enhance the immune-based components of trastuzumab therapy with check-point blockers (anti-PD-1 or anti-PD-L1) may be more productive than efforts to address the resistance mechanisms. Immune checkpoint blockade co-administered with HER2-targeted antibody can improve the long-term efficacy of the therapy, as seen in our patient. The activity of HER2-specific cytotoxic T cells might be inhibited by the expression of PD-L1 on the surface of HER2-positive cells that were not eliminated by inhibition of oncogenic signaling or ADCC. This immune tolerance

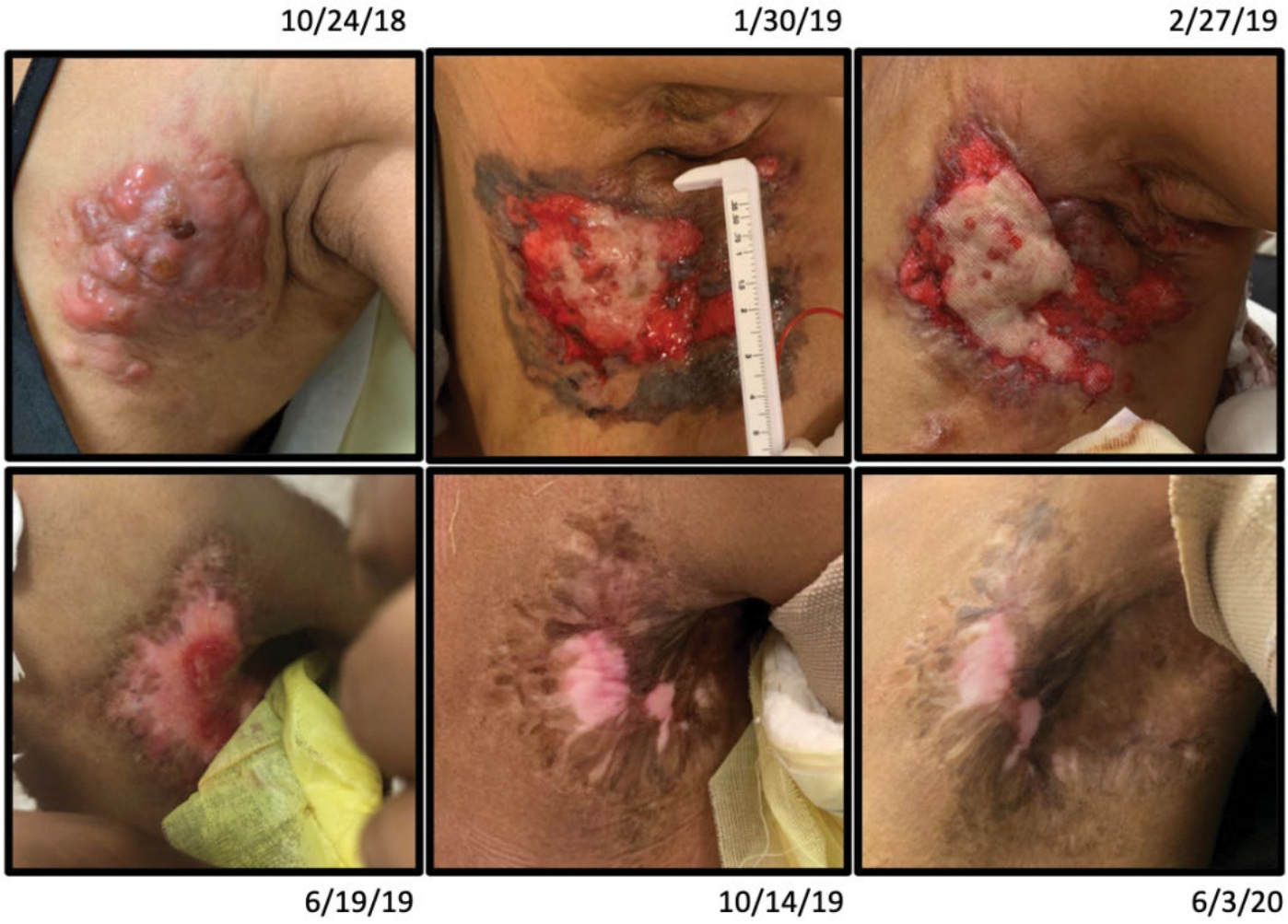
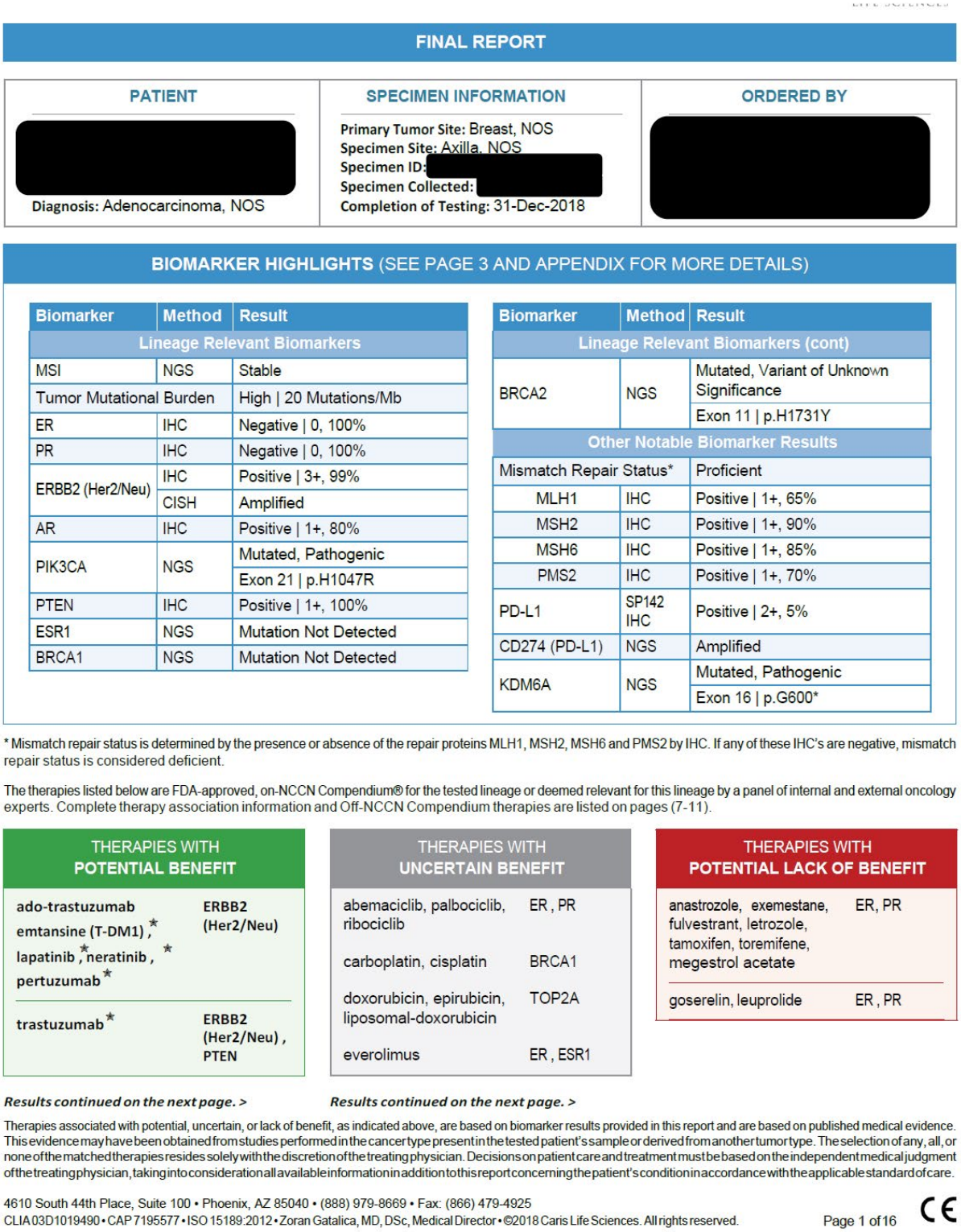


Figure 1. Enlarged left chest wall mass with an open wound.



FINAL REPORT

PATIENT

[redacted]

Diagnosis: Adenocarcinoma, NOS

SPECIMEN INFORMATION

Primary Tumor Site: Breast, NOS
Specimen Site: Axilla, NOS
Specimen ID: [redacted]
Specimen Collected:
Completion of Testing: 31-Dec-2018

ORDERED BY

[redacted]

BIOMARKER HIGHLIGHTS (SEE PAGE 3 AND APPENDIX FOR MORE DETAILS)

Biomarker	Method	Result
Lineage Relevant Biomarkers		
MSI	NGS	Stable
Tumor Mutational Burden		High | 20 Mutations/Mb
ER	IHC	Negative | 0, 100%
PR	IHC	Negative | 0, 100%
ERBB2 (Her2/Neu)	IHC	Positive | 3+, 99%
	CISH	Amplified
AR	IHC	Positive | 1+, 80%
PIK3CA	NGS	Mutated, Pathogenic
		Exon 21 | p.H1047R
PTEN	IHC	Positive | 1+, 100%
ESR1	NGS	Mutation Not Detected
BRCA1	NGS	Mutation Not Detected

Biomarker	Method	Result
Lineage Relevant Biomarkers (cont)		
BRCA2	NGS	Mutated, Variant of Unknown Significance
		Exon 11 | p.H1731Y
Other Notable Biomarker Results		
Mismatch Repair Status*		Proficient
MLH1	IHC	Positive | 1+, 65%
MSH2	IHC	Positive | 1+, 90%
MSH6	IHC	Positive | 1+, 85%
PMS2	IHC	Positive | 1+, 70%
PD-L1	SP142 IHC	Positive | 2+, 5%
CD274 (PD-L1)	NGS	Amplified
KDM6A	NGS	Mutated, Pathogenic
		Exon 16 | p.G600*

* Mismatch repair status is determined by the presence or absence of the repair proteins MLH1, MSH2, MSH6 and PMS2 by IHC. If any of these IHC's are negative, mismatch repair status is considered deficient.

The therapies listed below are FDA-approved, on-NCCN Compendium® for the tested lineage or deemed relevant for this lineage by a panel of internal and external oncology experts. Complete therapy association information and Off-NCCN Compendium therapies are listed on pages (7-11).

THERAPIES WITH POTENTIAL BENEFIT	
ado-trastuzumab emtansine (T-DM1)*, lapatinib*, neratinib*, pertuzumab*	ERBB2 (Her2/Neu)
trastuzumab*	ERBB2 (Her2/Neu), PTEN

THERAPIES WITH UNCERTAIN BENEFIT	
abemaciclib, palbociclib, ribociclib	ER, PR
carboplatin, cisplatin	BRCA1
doxorubicin, epirubicin, liposomal-doxorubicin	TOP2A
everolimus	ER, ESR1

THERAPIES WITH POTENTIAL LACK OF BENEFIT	
anastrozole, exemestane, fulvestrant, letrozole, tamoxifen, toremifene, megestrol acetate	ER, PR
goserelin, leuprolide	ER, PR

Results continued on the next page. > *Results continued on the next page. >*

Therapies associated with potential, uncertain, or lack of benefit, as indicated above, are based on biomarker results provided in this report and are based on published medical evidence. This evidence may have been obtained from studies performed in the cancer type present in the tested patient's sample or derived from another tumor type. The selection of any, all, or none of the matched therapies resides solely with the discretion of the treating physician. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information in addition to this report concerning the patient's condition in accordance with the applicable standard of care.

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Figure 2. Caris profile reported the tumor to be positive for PD-L1 receptor at 2+ (5%) by the SP142 antibody and had a high tumor mutational burden (TMB) of 20 Mutations/Mb.

could provide a survival mechanism that allows cells to acquire resistance to HER2-blockade. Recently, it was demonstrated in the NeoSphere trial that increased PD-L1 expression was associated with reduced pathologic complete response (pCR) [13]. Blocking of PD-L1 receptor along with anti-HER2 therapy in patients with HER2-positive breast cancer could be an option to improve outcomes and eliminate resistance to targeted HER2 therapy.

CNS metastases are associated with a poor prognosis without great systemic therapeutic options. Recently approved tucatinib and trastuzumab deruxtecan have both shown significant benefit in ORR in patients with HER2+ MBC [5,7]. Both studies included patients with brain metastases and tucatinib showed a significant improvement in PFS in this patient population. These drugs were not approved at the time our patient developed CNS disease. Historically, most clinical trials excluded patients with brain metastases. Pembrolizumab was evaluated in a clinical trial of patients with melanoma and NSCLC with brain metastases. The intracranial ORR was 26% and the intracranial disease control rate was 30%. All patients who had an intracranial response also had concordant extracranial responses which were maintained at 24 months with a 2-year OS of 48% [14]. This small study suggests that a subset of patients can achieve intracranial disease control while on checkpoint blockade. Our patient declined local therapy with radiation or surgical resection

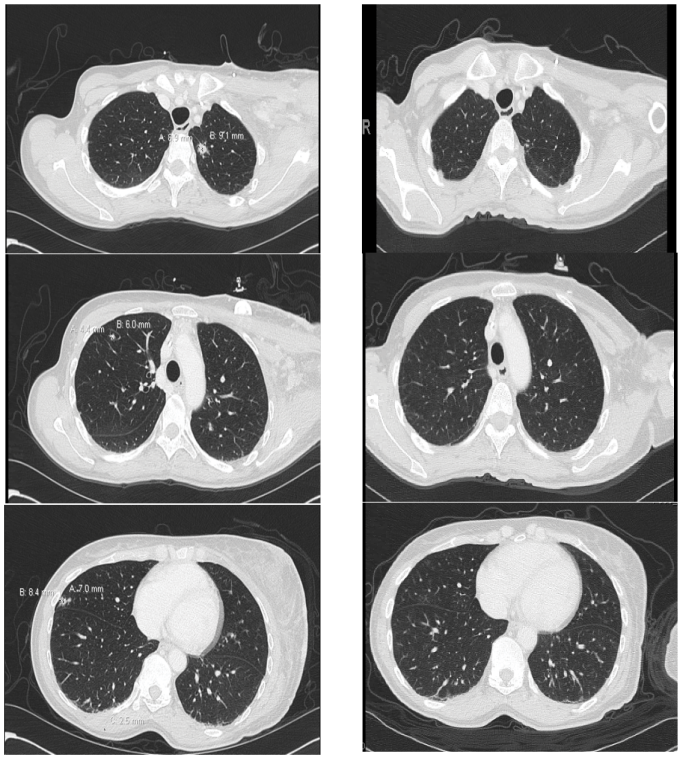

Figure 3. CT scans of the infiltrative disease in the left breast/axilla and pulmonary nodules.

and yet has had four stable brain MRIs from October 2019 through January 2022 without evidence of intracranial progression.

Conclusion

In conclusion, we have presented a case of a heavily pretreated patient with metastatic HER2+ breast cancer with PD-L1 positivity and high TMB who has had a remarkable response to immunotherapy in combination with trastuzumab. Our case illustrates the importance of continued research to better identify the role of immunotherapy in HER2-positive patients.

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