

# Small Cell Neuroendocrine Carcinoma of the Breast in a Case Report

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## Case Report

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# Abstract

**Introduction:** Primary small cell neuroendocrine carcinoma (SCNEC) of the breast comprises less than 0.1% of all breast cancers. Optimal management remains undefined due to the absence of prospective data and therapeutic strategies.

**Case Presentation:** We present a 56-year-old woman diagnosed with poorly differentiated SCNEC of the breast Stage IIIA (cT2N1M0), triple negative. She progressed on neoadjuvant carboplatin and etoposide and developed new hepatic metastases. Liver biopsy confirmed **SCNEC** (ER 0%, PR 0%, HER2 IHC 0, Ki-67 99%, PD-L1 CPS 0, DLL3 IHC 90%). She was then treated with weekly paclitaxel but progressed within six weeks. Subsequently, she received tarlatamab, a DLL3-directed bispecific T-cell engager, but experienced hepatic progression after only three cycles. Genomic profiling identified high PRAME expression, and the patient was enrolled on a PRAME-directed T cell receptor (TCR)-engineered T cell therapy. Imaging showed favorable response on Day 42 post T-cell-infusion, however, day 60 scans revealed new liver lesions. She is currently enrolled in a clinical trial evaluating safety and tolerability of a DLL3 ADC, BL-M14D1 (NCT07080242, study registration date: 7/14/2025, <https://www.clinicaltrials.gov>).

**Conclusion:** This case illustrates and rapidly evolving landscape of targetable biology in SCNEC of the breast. It highlights the potential relevance of DLL3 expression as a biomarker across neuroendocrine histology and the emerging role of PRAME-directed therapies. Further research is needed for advancing the management of this rare breast cancer subtype.

## I. INTRODUCTION

Rare histologic subtypes of breast cancer represent the biologically heterogeneous group for which evidence-based management strategies remain limited. Poorly differentiated breast neuroendocrine carcinoma (Br-NEC) is an uncommon entity characterized by evolving diagnostic criteria, some overlapping morphologic features with conventional breast cancer and uncertainty regarding optimal therapeutic approaches[1–3]. Neuroendocrine neoplasms (NEN) of the breast, ranging from well-differentiated neuroendocrine tumors (NETs) to poorly differentiated NEC, are currently categorized as a distinct clinical entity from invasive breast cancers with neuroendocrine features or neuroendocrine differentiation. Although neuroendocrine differentiation may be observed in breast cancers, such as in NET of the breast, poorly differentiated neuroendocrine carcinoma, which includes small cell (SCNEC) or large cell (LCNEC) subtypes, represents a distinct clinical challenge with aggressive clinical course and limited effective therapeutic options[1, 3–5].

The incidence of NENs of the breast is estimated at 0.3–0.5% of all breast carcinomas, though reported prevalence varies considerably (0.1–5%) depending on the diagnostic criteria applied and the extent of immunohistochemical evaluation [5]. SCNEC is particularly rare, comprising less than 0.1% of all breast cancers and approximately 7% of all extrapulmonary small cell carcinomas [6]. Because neuroendocrine markers are not routinely employed in breast cancer diagnosis, many cases may go unrecognized, and true incidence is likely underestimated [7].

Given the scarcity of prospective data and standardized treatment algorithms, detailed clinical pathologic case analysis remains essential to inform multidisciplinary decision-making. Here we present a case of SCNEC of the breast and provide a focused review of contemporary literature to contextualize diagnostic considerations and therapeutic strategies within the broader landscape of rare breast cancer subtypes.

## II. PATIENT INFORMATION

### Patient Presentation and Initial Workup

A 56-year-old woman presented with a palpable left breast mass. Her past medical history is notable for hypothyroidism. She did not have a family history of cancer in first- or second-degree relatives. She is a nonsmoker and denies current alcohol use. Her genetic testing was negative for any clinically significant variants.

### Clinical Findings

Physical examination revealed a palpable mass in the left breast with clinically suspicious ipsilateral axillary lymphadenopathy. The cardiopulmonary exam was unremarkable.

### Diagnostic Assessment

Core needle biopsy of the left breast mass was performed. Histopathologic examination favored SCNEC. The tumor demonstrated high nuclear grade with characteristic features of small cell morphology, including hyperchromatic nuclei, nuclear molding, scant cytoplasm, and a high mitotic rate; Nottingham histologic grade 3.

Immunohistochemical profile revealed ER 0%, PR 20%, HER2 negative (IHC 0), Ki-67 proliferation index 90% (Table 1). Neuroendocrine marker positivity for synaptophysin and chromogranin was confirmed (Figure 1).

### Therapeutic Intervention

The case was reviewed at a multidisciplinary breast medical oncology tumor board, with additional input from thoracic medical oncology experts in the management of small cell carcinomas. A central deliberation was whether to treat this cancer as a breast carcinoma with a standard neoadjuvant breast cancer regimen or as a neuroendocrine carcinoma using regimens extrapolated from small cell lung cancer (SCLC).

The KEYNOTE-522 regimen (carboplatin, paclitaxel, pembrolizumab followed by doxorubicin and cyclophosphamide with pembrolizumab) was considered, as it represents the standard-of-care neoadjuvant approach for early-stage high-risk triple-negative breast cancer [8]. However, several features of this tumor favored a neuroendocrine-directed approach: the clear small cell morphology with

diffuse neuroendocrine marker expression, the biologically aggressive phenotype, and the NCCN recommendation that extrapulmonary poorly differentiated neuroendocrine carcinomas follow SCLC treatment paradigms [9, 10]. The consensus recommendation was to initiate neoadjuvant 3-week carboplatin AUC 6 and etoposide 100 mg/m2 (EP) for a planned six cycles. She developed symptomatic anemia with hemoglobin 4.3 g/dL after cycle 2 of EP (baseline 13.0 g/dL and 9.3 g/dL prior to cycle 2). She also developed thrombocytopenia of platelets 15,000 K/uL after cycle 3 of EP, requiring platelet transfusion.

**Follow-Up and Outcomes**

Interval breast imaging after three cycles of EP revealed disease progression in the primary breast mass. PET CT showed new liver metastasis. Biopsy of the liver mass revealed SCNEC, ER negative (<1%), PR negative (<1%), HER2 negative (IHC 0), Ki-67 99%, PD-L1 CPS 0, DLL3 IHC 90% (Table 1).

| Marker      | Primary Breast (Baseline) | Liver Metastasis (Progression) |
|-------------|---------------------------|--------------------------------|
| ER          | 0%                        | Negative (<1%)                 |
| PR          | 20%                       | Negative (<1%)                 |
| HER2 (IHC)  | 0 (Negative)              | 0 (Negative)                   |
| Ki-67       | 90%                       | 99%                            |
| PD-L1 (CPS) | Not tested                | 0                              |
| DLL3 (IHC)  | Not tested                | 90%                            |

**Table 1.** Comparison of immunohistochemical profile between primary breast tumor and hepatic metastasis.

Several features of the metastatic biopsy were clinically significant. Persistent high Ki-67, PD-L1 negative, and strongly positive DLL3 (IHC 90%), identified a potentially actionable therapeutic target (Figure 2) [12-14].

**Subsequent Therapeutic Course**

**Subsequent therapy**

The patient was transitioned to weekly paclitaxel 80 mg/m2, due to its activity in both breast cancer and extrapulmonary neuroendocrine carcinomas and SCLC [9, 10]. Weekly dose #6 was reduced to 64 mg/m2 due to symptomatic anemia with fatigue and shortness of breath (hemoglobin 8.1 g/dL) and grade 2 neutropenia of 1.06 K/uL.

Unfortunately, after six weekly doses of paclitaxel, restaging imaging revealed disease progression with new hepatic metastases. Given the patient’s high Delta-like ligand 3 (DLL3) expression (90% by IHC), and

the established biological rationale for DLL3-targeted therapy across neuroendocrine tumors, the decision was made to treat with off-label tarlatamab[15]. DLL3 is an inhibitory ligand in the Notch signaling pathway that is aberrantly expressed on the surface of neuroendocrine tumor cells while largely absent from normal adult tissues, making it an attractive therapeutic target [12, 16].

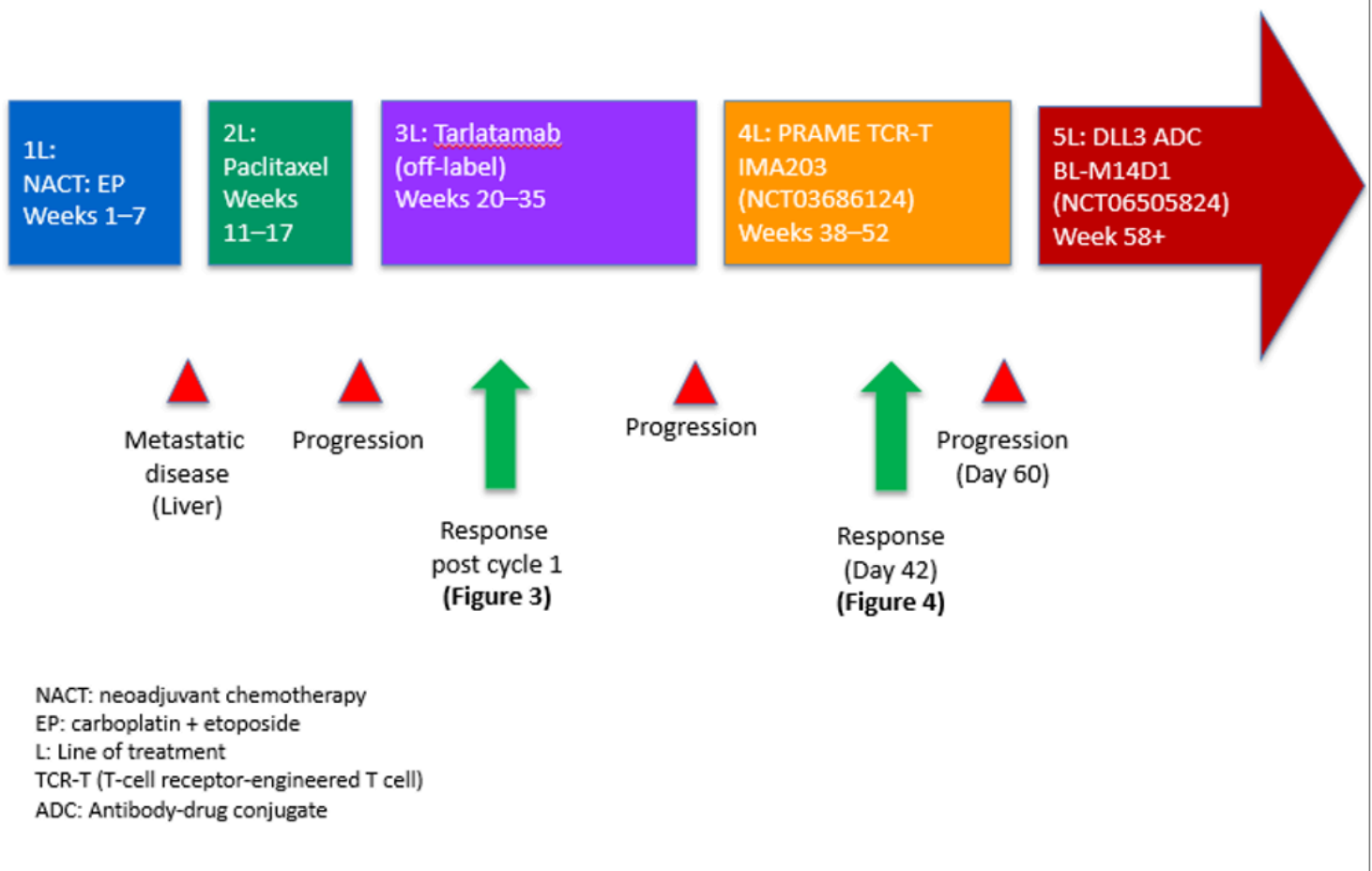
Tarlatamab was administered with an initial step-up dose of 1 mg on Cycle 1 Day 1, and then subsequent doses were 10 mg, with each cycle consisting of three-weeks-on, one-week-off schedule[17]. Cycle 1 was administered in the hospital per institutional policy to monitor closely for cytokine release syndrome (CRS). She tolerated a total of three cycles without any serious adverse events. She had decrease in size of the left breast biopsy proven mass measuring 2.1 x 2.8 cm compared to 3.2 x 2.6 cm previously with SUV max 4.8 compared to 13.7 previously (Figure 3). However, after three cycles of tarlatamab, restaging imaging demonstrated further disease progression.

#### **Fourth- and fifth Line Therapy: Clinical Trials**

Comprehensive genomic profiling through the Boston Gene platform revealed elevated PRAME (PReferentially expressed Antigen of MElanoma) expression. PRAME is a cancer-testis antigen expressed in a variety of malignancies but minimally expressed in normal tissues[18]. In breast cancer, PRAME expression has been associated with higher tumor grade, negative estrogen receptor status, increased rates of distant metastasis, and decreased overall survival [19]. Importantly, PRAME has emerged as a therapeutic target for T-cell receptor (TCR)-engineered T-cell therapies and other immune-based approaches[20, 21]. Therefore, the patient enrolled in clinical trial protocol: ACTengine® IMA203/IMA203CD8 as Monotherapy or in Combination with Nivolumab in Recurrent and/or Refractory Solid Tumors and she randomized to the genetically engineered autologous T-cell monotherapy arm (NCT03686124). Lymphodepletion regimen consisted of fludarabine 30 mg/m<sup>2</sup> IV and cyclophosphamide 500 mg/m<sup>2</sup> IV on Days -6 to -3; ACTengine T-cell product IV on Day 0; IL-2 SQ daily on Days 3 to 5, and IL-2 SQ BID on Days 6 to 10. Notable toxicity included grade 2 cytokine release syndrome (CRS) with fever and hypoxia requiring 2L supplemental oxygen by nasal cannula. CRS resolved after one dose of tocilizumab. Restaging CT of the chest abdomen and pelvis initially showed favorable response on day-42 post T-cell-infusion with decrease in the size of liver lesions (Figure 4); however, day-60 CT scan revealed disease progression with increase in size of the left breast mass and left axillary lymphadenopathy and new liver lesions.

DLL3-targeting ADCs have shown promising therapeutic efficacy in preclinical small cell lung cancer models [22]. Therefore, our patient is currently enrolled in a clinical trial evaluating safety and tolerability of a DLL3 antibody drug conjugate (ADC) BL-M14D1 (NCT06505824) [23].

### Treatment Timeline with Clinical Milestones



## III. DISCUSSION

### Classification and Diagnostic Considerations

The 5th Edition of the WHO Classification of Breast Tumors defines neuroendocrine carcinoma (NEC) as an invasive carcinoma characterized by high-grade neuroendocrine morphology (small cell or large cell), supported by the presence of neurosecretory granules and diffuse, uniform immunoreactivity for neuroendocrine markers [1]. The classification requires that the neuroendocrine component constitutes more than 90% of the tumor, and it specifically excludes solid papillary carcinoma and hypercellular mucinous carcinoma, which may exhibit neuroendocrine features but are considered distinct entities [24, 25]. Subtypes include SCNEC and LCNEC and these are newly included in breast classification to align with pulmonary and gastrointestinal nomenclature[1, 25].

Accurate diagnosis of breast NEC requires the integration of histomorphology, immunohistochemistry, clinical context, and, increasingly, genomic and transcriptomic profiling. Expression of traditional neuroendocrine markers such as synaptophysin, chromogranin A, and CD56 is essential but may overlap with breast adenocarcinomas exhibiting neuroendocrine differentiation. INSM1 has emerged as a more

specific and sensitive marker for neuroendocrine differentiation and may complement traditional markers[26] [27]. Reliance on morphology alone is insufficient, and systematic immunohistochemical evaluation is necessary to distinguish true primary NEC from conventional breast carcinoma with focal neuroendocrine features [5].

Histologically, SCNEC is characterized by densely packed, uniform small dark hyperchromatic cells that have high nuclear to cytoplasm ratio, scant cytoplasm and inconspicuous nucleoli. Nuclear molding and tumor necrosis are often present. Small cell carcinoma of the breast is histologically and immunohistochemically indistinguishable from its counterparts in lung, gastrointestinal tracts or other sites. Significant numbers of small cell carcinoma from any organs express TTF-1 including breast. PR positivity can also be seen in small cell carcinoma from organs other than breast. The absence of a primary small cell carcinoma elsewhere and the presence of in situ component or conventional-type mammary carcinoma support a primary breast origin [28, 29].

### **Therapeutic Uncertainty and the Treatment Paradigm Dilemma**

The management of breast NEC presents a fundamental therapeutic dilemma: should these tumors be treated as breast carcinomas guided by hormone receptor and HER2 status, or as NET using regimens extrapolated from SCLC and extrapulmonary NET. Currently, there is no randomized data to inform this decision, and management is entirely based on case reports, small retrospective series, expert consensus, and extrapolation from other disease sites [6].

The NCCN Guidelines for Neuroendocrine and Adrenal Tumors recommend that extrapulmonary poorly differentiated NECs follow treatment paradigms used for SCLC, given shared morphologic, biologic, and clinical characteristics [9, 10]. First-line platinum-etoposide (EP) chemotherapy is the backbone of this approach, with alternative platinum doublets (e.g., irinotecan-cisplatin) also utilized. However, the response rates and durability of EP in extrapulmonary NEC are generally inferior to those observed in SCLC, with median progression-free survival of approximately 4–6 months [6, 30, 31]

Conversely, for breast NECs with hormone receptor positivity and lower proliferative indices, treatment following standard breast cancer paradigms (including endocrine therapy, CDK4/6 inhibitors, and standard breast chemotherapy regimens) may be appropriate. Case reports have described dramatic responses to palbociclib in combination with endocrine therapy in hormone receptor-positive breast NEC [32]. However, for SCNEC of the breast — particularly with the biological profile seen in our patient (ER 0%, Ki-67 90–99%) — the neuroendocrine-directed approach is generally favored [10].

In our patient, the multidisciplinary consensus to treat with neoadjuvant EP was based on the clearly small cell morphology, extremely high proliferative index, and guidance from thoracic oncology colleagues. The rapid progression on EP after three cycles established primary platinum-refractory disease, a particularly adverse prognostic indicator that carries a median overall survival of 6–9 months in extrapulmonary NEC [33].

After platinum failure, treatment decisions in our patient were guided by an iterative biomarker-driven approach, integrating hormone receptor status, proliferation index, disease burden, DLL3 expression, PD-L1 status, and PRAME expression. This sequential molecular profiling strategy is increasingly recognized as essential in rare cancers where empiric therapy options are limited and where emerging basket trial and histology-agnostic approaches may offer therapeutic opportunities [34].

The transition to weekly paclitaxel after platinum failure reflected the dual consideration of this tumor as both a breast carcinoma and a neuroendocrine carcinoma. Taxanes have established activity in breast cancer and have been used in second-line settings for both SCLC and extrapulmonary NEC, though response rates are modest (10–20%)[9, 33].

### **DLL3 as a Therapeutic Target in Neuroendocrine Malignancies**

Delta-like Ligand 3 (DLL3) is a member of the Delta/Serrate/Lag-2 (DSL) family of Notch ligands. Unlike other Notch ligands, DLL3 functions as an inhibitory ligand, primarily localized to the Golgi apparatus under normal conditions, but aberrantly expressed on the cell surface in neuroendocrine tumors. DLL3 surface expression is enriched in SCLC, LCNEC, and high-grade extrapulmonary NEC while being largely absent from normal adult tissues, establishing a favorable therapeutic window [14, 16]

While DLL3-directed therapy has shown transformative activity in SCLC, its efficacy in extrapulmonary neuroendocrine carcinomas, including breast NEC, remains to be defined. The decision to pursue off label tarlatamab was driven by the DLL3 IHC result of 90%, which placed this tumor within the range of expression seen in SCLC where tarlatamab has demonstrated significant clinical activity. While the DeLLphi-301 trial led to FDA approval specifically in SCLC, the biological rationale for DLL3-targeted therapy extends across neuroendocrine histologies. Recent analyses have demonstrated DLL3 positivity in approximately one-third of extrapulmonary NENs, with enrichment in high-grade, poorly differentiated tumors [15, 35]. Multiple ongoing trials are now evaluating tarlatamab in extrapulmonary NEC (NCT06788938, NCT06816394), and early real-world data suggest that some patients with extrapulmonary small cell carcinoma do respond to tarlatamab [36, 37]

The failure of tarlatamab in this patient after three cycles raises important questions about the biology of DLL3-expressing non-pulmonary neuroendocrine tumors. Potential mechanisms of resistance include inadequate T-cell infiltration or activation in the tumor microenvironment, DLL3 expression heterogeneity not captured by bulk IHC, T-cell exhaustion, and tumor-intrinsic immune evasion mechanisms (e.g., MHC downregulation, immunosuppressive cytokine milieu). The PD-L1 CPS of 0 in this patient is consistent with a generally immunologically cold microenvironment, which may limit the efficacy of T-cell-engaging therapies [11].

Several ongoing trials are investigating tarlatamab and other DLL3-targeting agents (including obixtamig/BI 764532, a DLL3/CD3 IgG-like T-cell engager) in extrapulmonary NEC, with promising early signals in this space[38]. Obixtamig has received FDA fast track designation for SCLC and extrapulmonary NEC, and is being evaluated in the phase 2 DAREON-5 trial [39]. Phase 1 data

demonstrated a confirmed ORR of 18% across DLL3-positive tumors, including NECs of extrapulmonary origin[38]. DLL3-targeted antibody-drug conjugates (ADCs) and chimeric antigen receptor (CAR) T-cell therapies directed against DLL3 are also in development, expanding the modalities through which this target can be exploited (NCT06505824 – BL-M14D1 study).

The heterogeneity of DLL3 expression across neuroendocrine tumor types and the lack of standardized DLL3 IHC assays and positivity cutoffs for non-SCLC indications represent ongoing challenges. The FDA approval of tarlatamab in SCLC was not contingent on DLL3 expression level, but emerging extrapulmonary trials (e.g., NCT06788938) require DLL3 positivity ( $\geq 25\%$  for stage 1 enrollment,  $\geq 1\%$  for stage 2), reflecting the need for biomarker-driven patient selection in less common NEC subtypes [40].

### **PRAME as an Emerging Therapeutic Target**

PRAME (PReferentially expressed Antigen of MElanoma) is a cancer-testis antigen that functions as a transcriptional repressor of the retinoic acid signaling pathway. It is expressed in a variety of malignancies including melanoma, sarcoma, lung cancer, and breast cancer, while showing minimal expression in normal tissues outside the testis. In breast cancer, PRAME expression has been associated with higher tumor grade, ER-negative status, increased distant metastasis, and decreased overall survival, making it both a prognostic marker and a potential therapeutic target[19].

The identification of PRAME as a targetable antigen in this patient illustrates the value of comprehensive molecular profiling beyond standard biomarkers in rare and refractory cancers. Early-phase data from the IMA203 trial, a first-in-human study of autologous PRAME-directed TCR T-cell therapy in HLA-A\*02-positive patients with PRAME-positive advanced solid tumors, has demonstrated durable responses in melanoma and synovial sarcoma, supporting further investigation across PRAME-expressing malignancies [20].

PRAME-directed therapeutic strategies include TCR-engineered T-cell therapies, ADCs, and bispecific antibodies. IMA203, an autologous PRAME-directed TCR T-cell therapy, demonstrated safety and durable responses in a first-in-human phase 1 trial in HLA-A\*02-positive patients with PRAME-positive advanced solid tumors, including melanoma and synovial sarcoma [20]. The extension of PRAME-directed therapy to breast NEC, as in our patient, represents a novel application enabled by comprehensive genomic profiling and reflects the broader trend toward antigen-driven, histology-agnostic therapeutic approaches.

### **SEZ6 as a Potential Additional Target**

Seizure-related homolog protein 6 (SEZ6), a membrane-associated protein, has also been identified in neuroendocrine neoplasms and both DLL3 and SEZ6 are targets of novel ADCs [41]. Early studies have shown promising antitumor activity, suggesting the potential for SEZ6 to be another druggable target [42].

## ***Lessons from This Case in the Context of Rare Breast Cancer***

This case highlights several broader themes relevant to the management of rare breast cancer subtypes. The distinction between invasive breast carcinoma with neuroendocrine features and true primary NEC of the breast has direct therapeutic implications. The 2019 WHO classification provides a more rigorous framework, but diagnostic reproducibility remains a challenge. Comprehensive immunohistochemical panels, including newer markers such as INSM1, SEZ6 and DLL3, molecular profiling, and pathologic expertise in neuroendocrine tumors are essential [31, 41].

The absence of prospective clinical trials in breast NEC means that treatment decisions require extrapolation from either breast cancer or NEC paradigms and are ultimately individualized. In our patient, sequential treatment incorporated both breast cancer agents (paclitaxel) and neuroendocrine-directed therapies (etoposide, carboplatin, tarlatamab), reflecting the hybrid biology of this tumor.

The involvement of breast medical oncology, thoracic medical oncology, pathology, radiology, and clinical trial teams was essential at every decision point in this case. Rare tumor boards and institutional expertise in neuroendocrine malignancies significantly impact management quality.

### **Comprehensive molecular profiling enables novel therapeutic strategies.**

The results of comprehensive molecular profiling identified DLL3 and PRAME as actionable targets. This led to our patient receiving targeted therapy and participating in clinical trials. For rare, treatment-refractory cancers, comprehensive profiling should be considered early in the disease course to maximize therapeutic options.

The rarity of breast NEC precludes traditional randomized controlled trials. Multi-institutional registries, basket trials incorporating neuroendocrine histologies regardless of primary site, and histology-agnostic trials targeting molecular features (DLL3, PRAME, and others) represent the most viable paths to generating evidence in this disease [13, 37]

## **IV. CONCLUSION**

SCNEC of the breast, remains a diagnostic and therapeutic entity within the spectrum of rare breast cancers. This case underscores the importance of individualized treatment strategies, multidisciplinary evaluation, comprehensive molecular profiling, and continued investigation into the biology and optimal management of neuroendocrine breast carcinomas within the broader category of neuroendocrine neoplasms. The emerging landscape of DLL3-directed and PRAME-directed therapies offers cautious optimism, but the clinical development of these approaches in extrapulmonary NEC, including breast NEC, requires dedicated prospective evaluation. Collaborative, multi-institutional efforts and enrollment in basket and histology-agnostic trials are essential to advance the care of patients with this rare and aggressive disease.

# Declarations

## PATIENT PERSPECTIVE

Our patient was unable to provide a patient perspective, but she was in full support of her case presentation and this manuscript. She provided written informed consent for participation in and publication of this case report. The consent can be provided upon request.

## ETHICS STATEMENT

This retrospective study was reviewed and approved by the UT MD Anderson Institutional Review Board (IRB protocol #2025-1047. All procedures were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki.

## AUTHORS CONTRIBUTION STATEMENT

A.B. and B.L. wrote the main manuscript text, B.L. prepared Table 1 and A.B. prepared the Timeline and Figure 4. Y.W. prepared Figures 1 and 2 and contributed to pathology description and discussion. E.L. provided institutional perspective based on her review of our institutional management of patients with breast small cell neuroendocrine carcinomas; she also prepared Figure 3. V.V. and S.G. provided leadership and expert guidance for patient's treatment navigation on off-label and investigational treatments. All authors reviewed the manuscript.

## DATA AVAILABILITY

The datasets generated and/or analyzed during this case report are not publicly available due to this being a case report and the genomic data being limited to one patient case but are available from the corresponding authors (AB and BL) on reasonable request.

## DISCLOSURE OF POTENTIAL CONFLICT OF INTEREST

AB served consultancy/advisory role for Daichi-Sankyo, Novartis, AstraZeneca, Gilead, Biotheranostics, Curio Science, and received research funding from Radionetics Oncology.

BL served consultancy/advisory role for Celcuity, Natera, Daichi-Sankyo, Novartis, Pfizer, AstraZeneca, and received honoraria from Puma Biotechnology, Novartis, Pfizer, received grant/research funding from Genentech, Takeda, Merck, Celcuity, Eli Lilly, Puma biotechnology, Calithera therapeutics, and fundings from NCI, DOD, CPRIT, Hope foundation, Adopt-a-scientist.

VV served consultancy/advisory role for Genomic Health.

EL, YW, and SG report no conflict of interest.

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## Figures

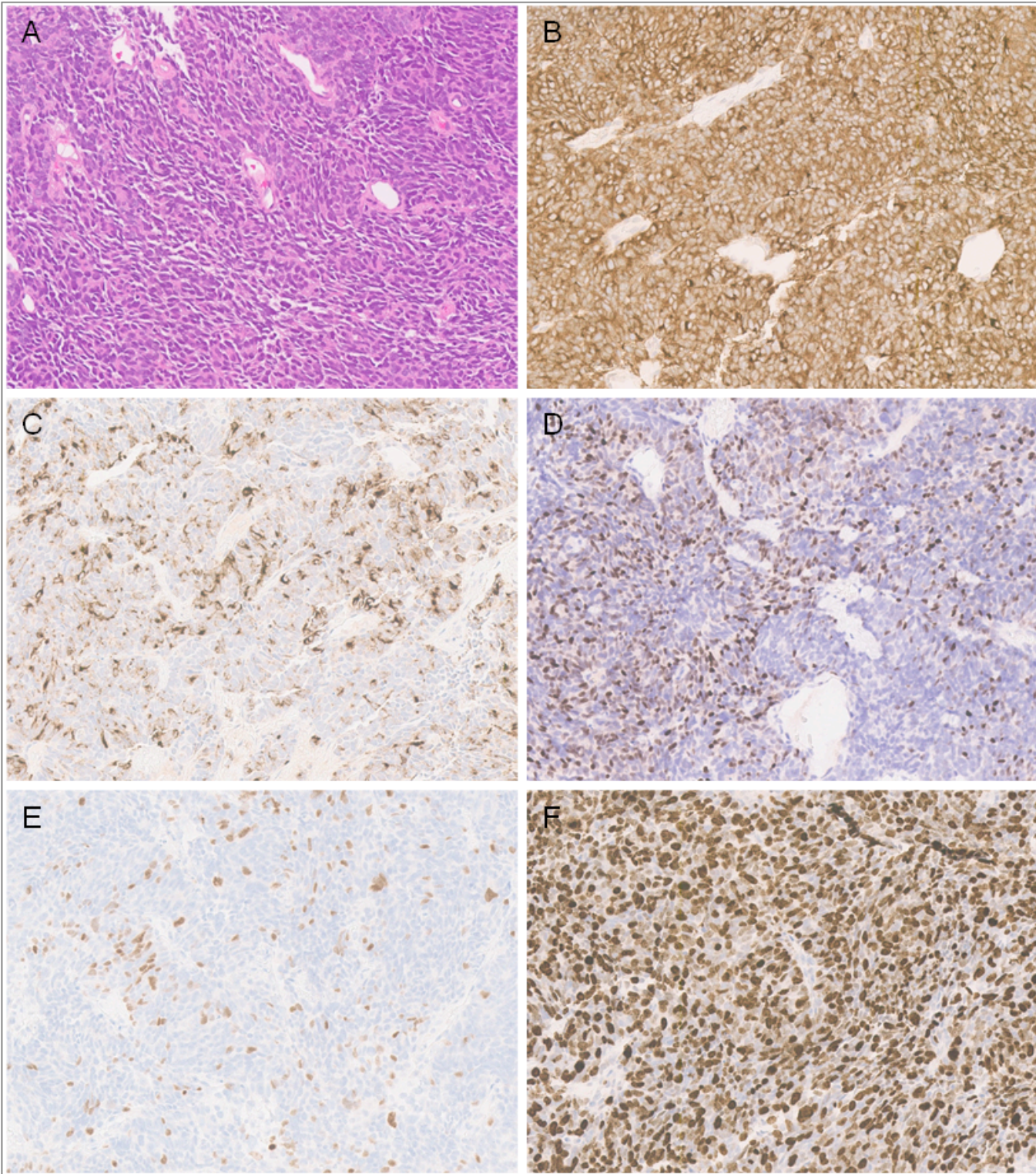


**Figure 1**

A. Breast core needle biopsy demonstrates solid nests of uniform tumor cells with hyperchromatic nuclei, high N:C ratio, scant cytoplasm, and prominent nuclear molding. Histologic features support the diagnosis of small cell carcinoma. B. Tumor cells are diffusely positive for neuroendocrine marker synaptophysin. C. positive for chromogranin. D. Focally positive for progesterone receptor (20%, moderate intensity). E. Focally positive for GATA3, supporting the breast origin. F. Mib-1 stain

demonstrates high Ki67 proliferation rate (up to 90%). Tumor cells are also negative for estrogen receptor and HER/neu (data not shown). TNM staging at presentation was stage IIIA: cT2 cN1 cM0.

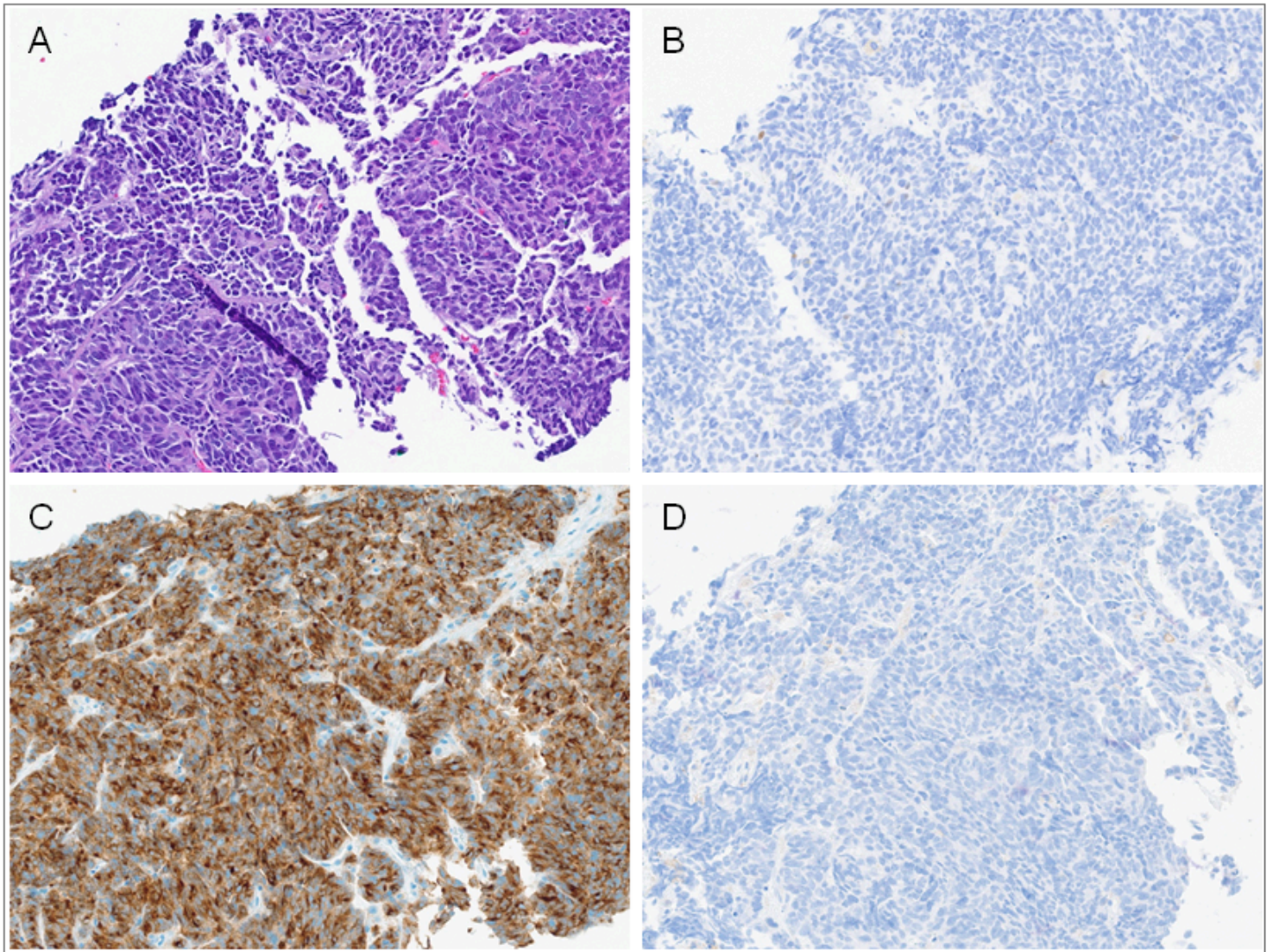


**Figure 2**

A. CT-guided core biopsy of the liver demonstrates metastatic small cell carcinoma with identical histologic features shown in the breast. B. The tumor cells are negative for progesterone receptor. C. Diffusely positive for DLL-3. D. Negative for PD-L1. Tumor cells are also negative for estrogen receptor and HER/neu (data not shown).

**Figure 3. CT imaging of DLL3-positive Br-NEC response to off-label Tarlatamab**

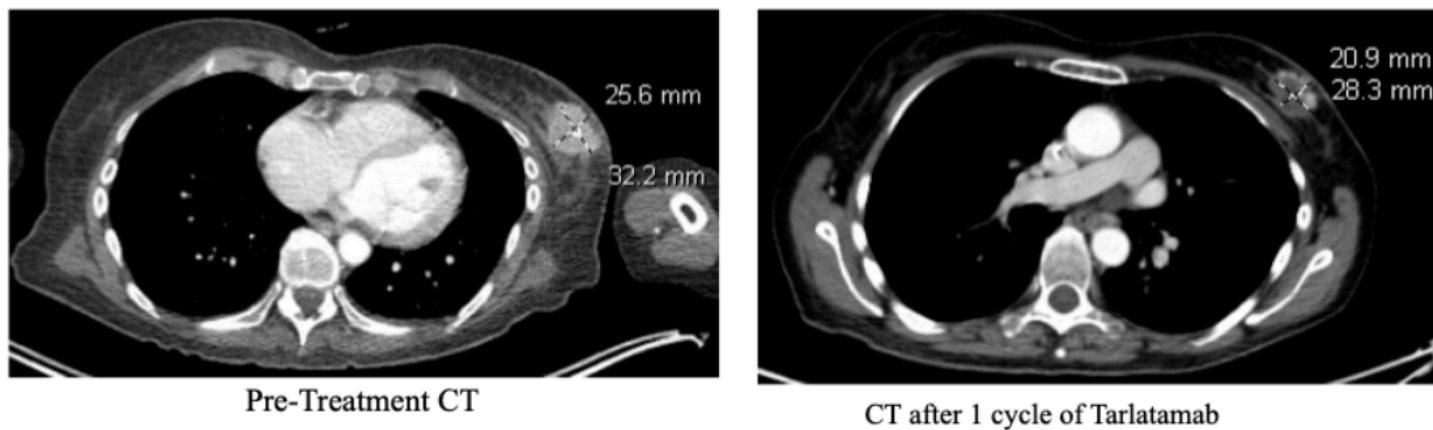


**Figure 3**

Decrease in size of the left breast biopsy proven mass measuring 2.1 x 2.8 cm, compared to 3.2 x 2.6 cm previously, after 1 cycle of tarlatamab.

**Figure 4. CT imaging of PRAME-directed T-Cell therapy, pre-infusion and on Day-42 post T-cell infusion**

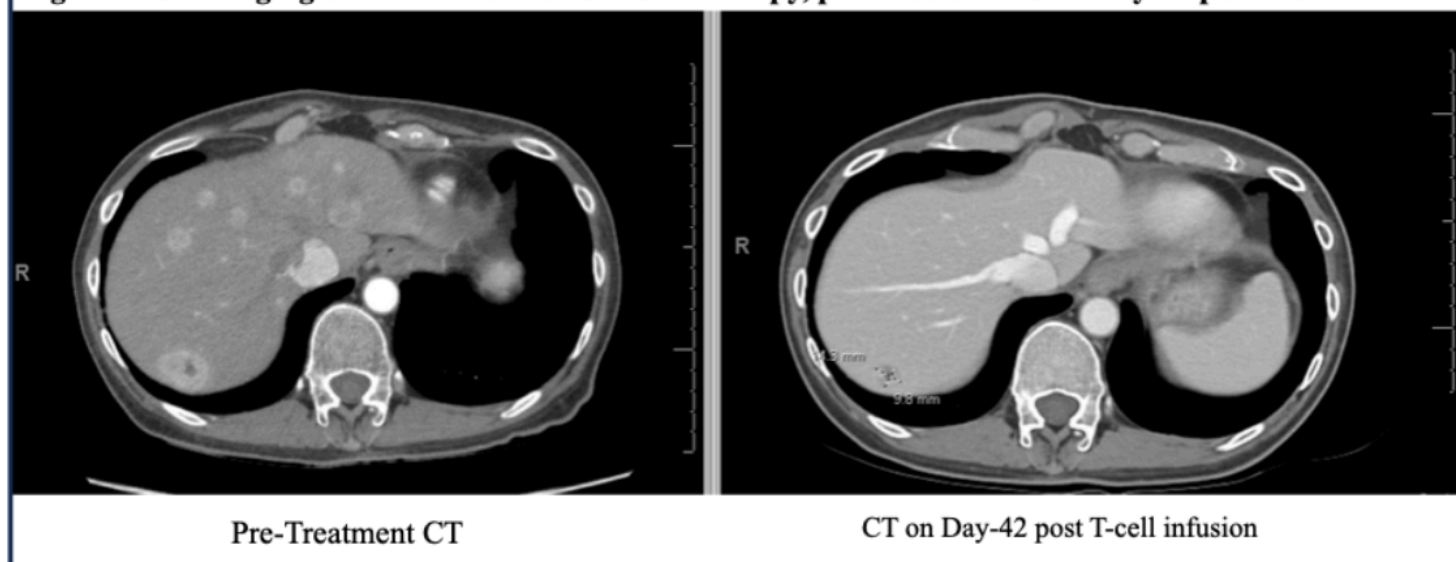


**Figure 4**

Favorable response on day-42 post PRAME-directed T-cell-infusion with decrease in size and number of liver lesions.