Uncovering AR-v7 as a Common Early Event in Apocrine Breast Tumors: Rethinking Antiandrogen Therapy Strategies

Zoran Gatalica[1*], Julia Ye[2], Yunn-Yi Chen[2], Rick Baehner[2], Jeff Kimbrough[1], Inga Rose[1], Semir Beslija[3], Sarah Rapisardo[4], Semir Vranic[5]

[1] Reference Medicine, Phoenix, AZ; [2] Department of Pathology, University of California, San Francisco, San Francisco, CA; [3] Department of Oncology, Clinical Center, University of Sarajevo, Sarajevo, Bosnia and Herzegovina; [4] Duke University, Durham, NC; [5] College of Medicine, QU Health, Qatar University, Doha, Qatar

REFERENCE MEDICINE

Introduction

Androgen receptor (AR) signaling is essential for prostate cancer development and progression and has long been targeted by antiandrogen therapy. The development of resistance to antiandrogen therapy often involves the formation of constitutively active AR splice variant 7 (AR-v7) (**Figure 1**). AR signaling also plays a role in other cancers, notably apocrine breast carcinomas, which consistently overexpress AR, and it presents an opportunity for antiandrogen therapy. However, the role of AR-v7 in breast cancer, including apocrine carcinomas, remains largely unexplored.

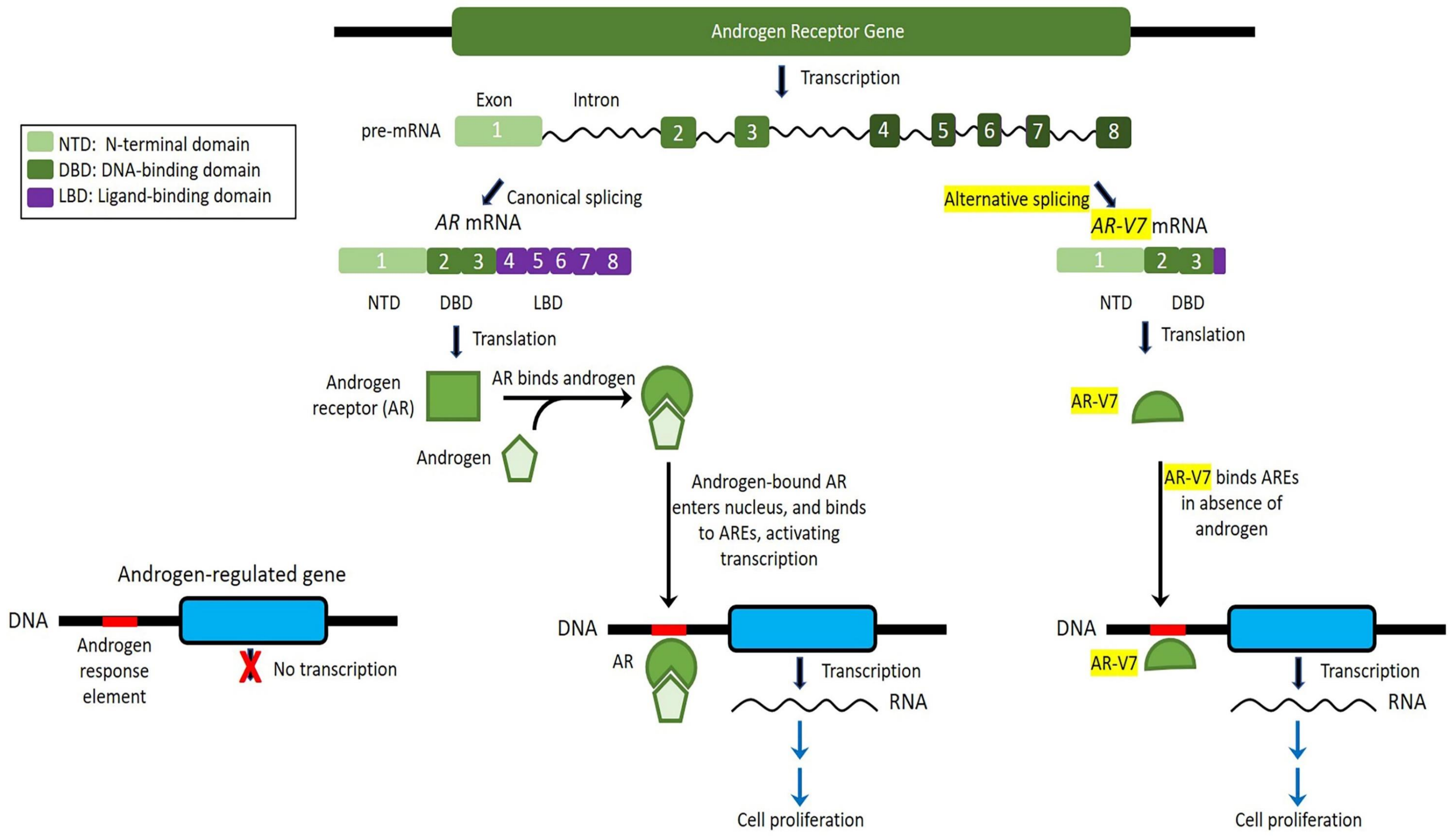

Figure 1. The structure and functions of the *AR* gene and its spliced variants, including *AR-V7*.

Design

Thirty-one in situ and invasive breast carcinomas were sequenced using the next-generation sequencing platform **TruSight Oncology 500**. Immunohistochemical stains detected estrogen receptor (ER), progesterone receptor (PR), AR, and HER2.

Results

All apocrine carcinomas (n=7) were ER-negative, PR-negative, AR-positive, and HER2-negative. The *AR-v7* variant appeared frequently among apocrine tumors, including two of three apocrine DCIS and two of four invasive apocrine carcinomas (**Table 1**). Remarkably, one stage IIIA apocrine carcinoma (ER-/PR-/HER2-, AR+) was successfully treated with antiandrogens and tested negative for *AR-v7* in both the primary tumor and lymph node metastasis (**Figure 2, Table 1**). In contrast, only 1 of 24 invasive breast carcinomas (ductal and lobular) harbored *AR-v7*, and that case also showed *TP53* and *DDX41* mutations. The spectrum of other genomic alterations detected in apocrine (*PIK3CA/PTEN, TP53*) (**Table 2**) and non-apocrine (*GATA3, PIK3CA, TP53, ERBB2, FGF19, CCND1, CDH1, ESR1*) breast cancers aligns with previous studies.

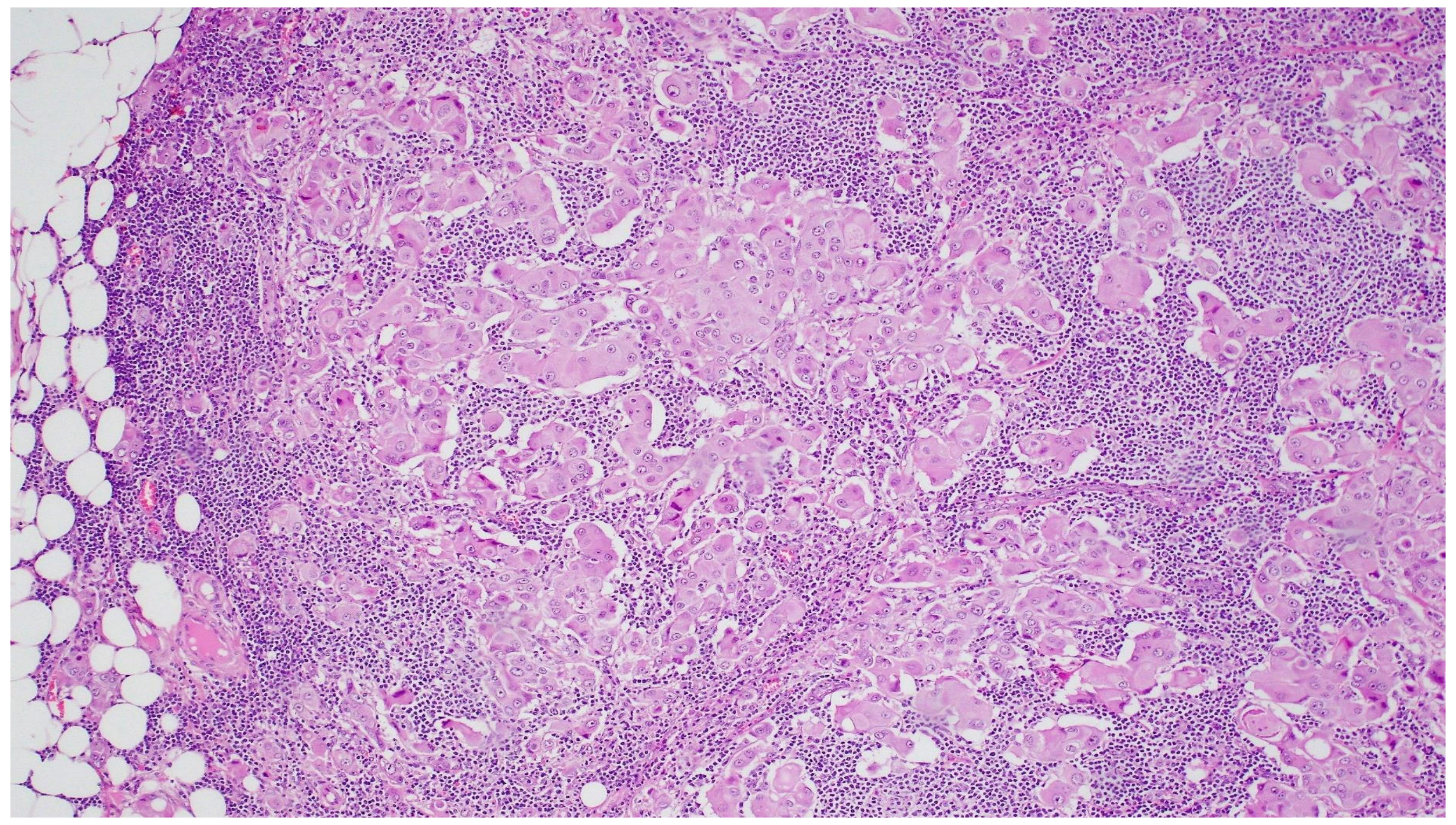

Figure 2. Metastatic (axillary lymph node) triple-negative apocrine carcinoma (AR+) without *AR-V7,* successfully treated with antiandrogen therapy (case#7, Table 1).

Case	Diagnosis	Mutational profile	TMB status**	MSI status	Add. genomic alterations
#1	Apocrine DCIS	PTEN	6.3 mut/Mb	Stable	AR-v7
#2	Apocrine DCIS	PIK3CB	0.8 mut/Mb	Stable	ESR1 loss
#3	Apocrine DCIS	PIK3CA, SMARCD1	2.3 mut/Mb	Stable	AR-v7
#4	Invasive apocrine carcinoma	NF1	1.6 mut/Mb	Stable	AR-v7
#5	Invasive apocrine carcinoma	CDKN2A, PTEN, TP53	n/a	n/a	AR-v7
#6	Invasive apocrine carcinoma	PIK3CA, TP53, ARID1A, MALT1, EZH2	7.0 mut/Mb	Stable	EGFR-AS1
#7	Invasive apocrine carcinoma*	TP53*	n/a	n/a	none

Table 1. Overview of the clinical and molecular features of seven apocrine carcinomas.

*Both primary and metastatic tumors (axillary lymph node) were sequenced.

**TMB-high is >30 mutations/Mb

Gene	Alteration	Drug class matched	ESCAT score*
PIK3CA	Mutations	α-specific PI3K inhibitors	IA (ER+. HER2-)
PTEN	Mutations/ Deletions	Akt inhibitors	I/II

Table 2. NGS also revealed clinically actionable genomic alterations in apocrine carcinomas.

*ESMO, https://doi.org/10.1016/j.annonc.2024.04.005

Key Takeaways

- *AR-v7* is a frequent early genomic change in apocrine breast tumors, including preinvasive lesions.
- Testing for *AR-v7* should be considered for all apocrine carcinomas potentially amenable to antiandrogen therapy.
- NGS also revealed potentially targetable genomic alterations in apocrine carcinoma of the breast.

ID# 35

Disclosures: All authors declare no conflict of interest.

***Presenting author:**
zoran@referencemedicine.com