PROTACs as Next Generation Degraders: The Development of ARV – 471 in ER+ Breast Cancer

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Introduction

Breast cancer is one of the most common cancers among women with 80% being estrogen receptor (ER)- positive breast cancer.[1] For ER+ breast cancers, the estrogen receptor (ER) drives tumor growth, making it a primary target for therapeutic intervention. Standard therapies include selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs); however, these treatments often encounter limitations due to acquired resistance, especially in cases with ESR1 mutations (e.g., Y537S, D538G). These mutations allow ER signaling to persist despite therapy, necessitating the need to develop novel approaches that can degrade both wild-type and mutant ER forms to overcome resistance effectively.[2,3]

PROTACs as a New Therapeutic Approach

PROTACs (Proteolysis-Targeting Chimeras) represent an emerging technology designed to achieve selective protein degradation. Unlike inhibitors that block protein function, PROTACs recruit the target protein to an E3 ubiquitin ligase, forming a ternary complex (**Figure 1**) that tags the protein for degradation by the ubiquitin-proteasome system. This catalytic degradation mechanism allows PROTACs to reduce protein levels continuously, making them highly effective in reducing target-driven cancer growth. For breast cancer, this technology has shown promise in potentially overcoming limitations associated with traditional therapies by directly targeting and degrading both the wild-type and the resistant variant ER proteins.[4,5]

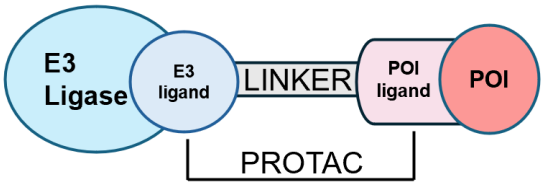

Figure 1: Formation of ternary complex

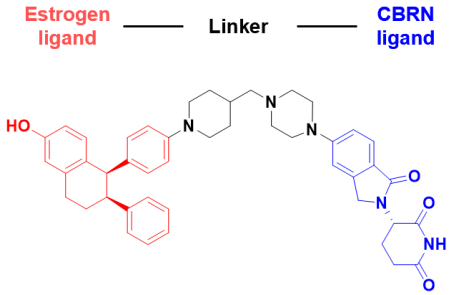

Figure 2: Chemical Structure of ARV – 471 that captures the three different parts of the PROTAC.

Mechanism of PROTACs – ARV-471

A PROTAC, and specifically ARV – 471, (**Figure 2**), is a bifunctional molecule containing an estrogen ligand known as warhead, a cereblon (CRBN, E3 ligase) ligand and a linker connecting these two moieties in proximity. ARV – 471 degrades the ER by recruiting E3 ubiquitin ligase CRBN and inducing ubiquitination of ER, leading to its degradation via the proteasome. This efficient degradation of ER reduces the activation of the signaling pathways of ER associated with the growth and survival of breast cancer cells. The selectivity and efficiency of ARV – 471 makes it a promising therapeutic candidate over existing non PROTAC-based degraders like SERDs.[5] ARV-471 has also been demonstrated to selectively degrade both the wild-type and the mutant ER forms, which are often resistant to SERMs and SERDs. Preclinical data indicate ARV-471 has a potent EC50 in the low nanomolar range(~2.2nM), achieving significant ER degradation in ER+ cell lines and similar binding affinity to the ER in comparison to estrogen (Ki of estrogen = 0.24nM, Ki of ARV- 471= 0.28nM).[6]

Clinical Trials and Findings

In Phase II clinical trials, ARV-471 as a monotherapy demonstrated encouraging results, with a clinical benefit rate (CBR) of 37.1% and a progression-free survival (PFS) of 3.5 months at a 200 mg dose. In patients with ESR1-mutant tumors, the CBR reached 47.4%, with a PFS of 5.5 months. ARV-471 was well-tolerated, with most adverse events being mild to moderate. These results underscore ARV-471's potential in treating advanced ER+ HER2- breast cancer, particularly in patients who have developed resistance to standard endocrine therapies.[6,7,8] Also, ARV-471 was combined with the CDK4/6 inhibitor palbociclib in clinical trials (Phase 1b) showed promising antitumor activity, achieving a clinical benefit rate (CBR) of 63%, with an even higher rate of 72.4% in ESR1-mutant patients. The combination therapy provided a progression-free survival (PFS) of 11.2 months and was well-tolerated with no dose-limiting toxicities. These results suggest ARV-471 and palbociclib as a potent treatment option for ER+ breast cancer, particularly for patients resistant to standard therapies.[9]

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