First FDA-approved PROTAC: Vepdegestrant moves targeted protein degradation into oncology practice

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On May 1, 2026, the US Food and Drug Administration approved VEPPANU (vepdegestrant; ARV-471), an oral PROTAC estrogen receptor (ER) degrader developed by Arvinas and Pfizer, for adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer after at least one line of endocrine therapy, as detected by an FDA-authorized test. The agency also approved Guardant360 CDx as a companion diagnostic, and the application was approved one month ahead of the FDA goal date. The decision is a regulatory milestone: for the first PROteolysis TArgeting Chimera (PROTAC) has moved from promise to approved medicine. Its boundaries are equally important. The label applies to selected patients with ESR1-mutated disease, not to all ER-positive, HER2-negative breast cancers.

ER-positive, HER2-negative disease is the dominant biological subtype of breast cancer, and endocrine therapy remains central in advanced disease. Yet therapeutic pressure can select ESR1 mutations that sustain ER signaling and reduce sensitivity to standard endocrine agents. In this population, the question is not whether ER remains relevant, but whether it can be suppressed more effectively after resistance emerges. Vepdegestrant was designed for that task to remove the receptor rather than merely compete with ligand binding or alter conformation.

MECHANISM BEYOND OCCUPANCY

PROTACs replace occupancy-driven pharmacology with event-driven degradation. A conventional inhibitor must remain bound to block activity; a heterobifunctional degrader instead brings a target protein and an E3 ubiquitin ligase into proximity, inducing ubiquitination and proteasomal destruction of the target.[1] This mechanism can, in principle, eliminate enzymatic and non-enzymatic functions, reduce reliance on continuous active-site blockade, and expand drug discovery toward targets that are difficult to inhibit directly.

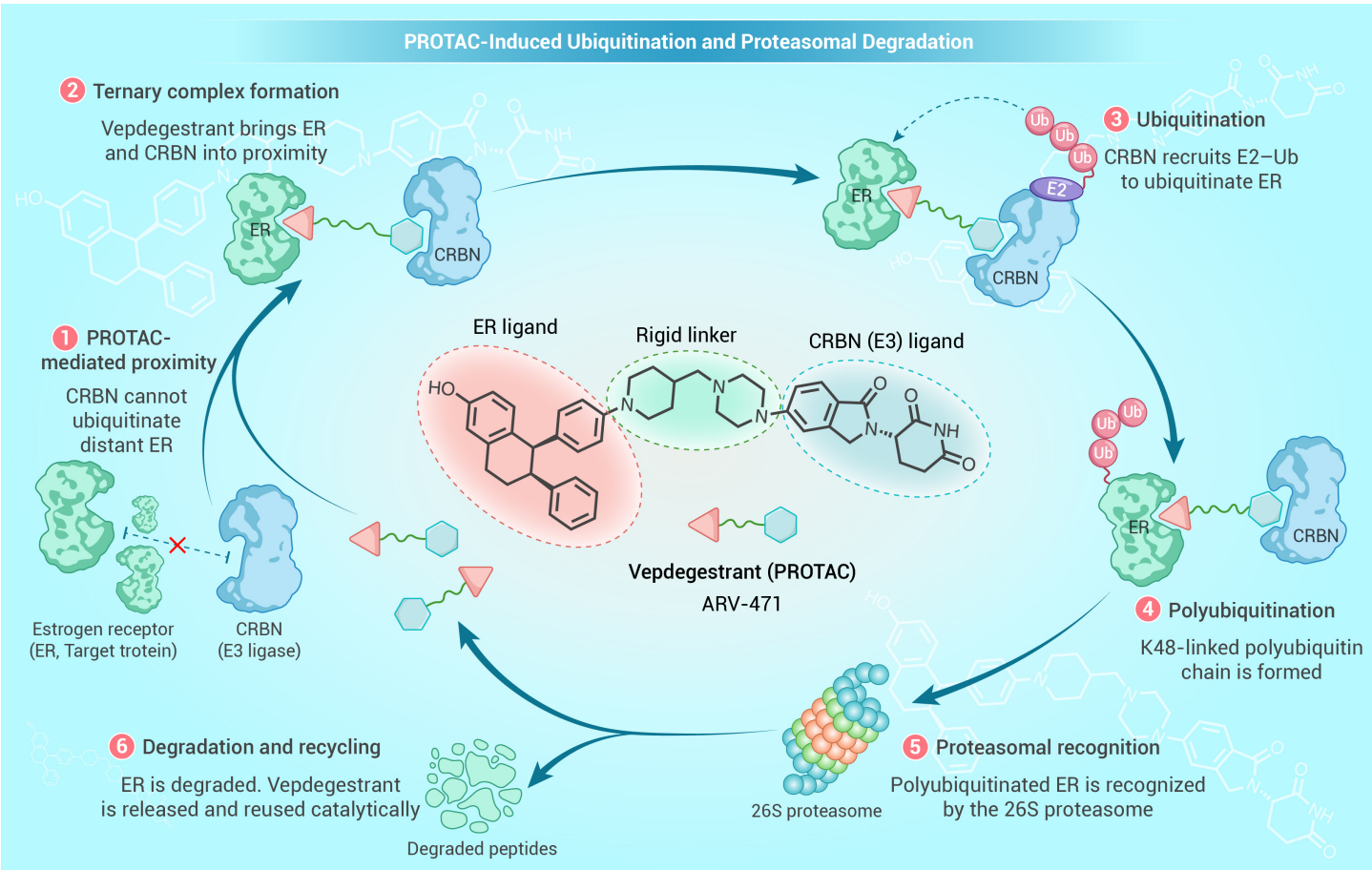

Figure 1. The approval of VEPPANU (vepdegestrant), an oral estrogen receptor degrader jointly developed by Arvinas and Pfizer, marks the first FDA-approved PROTAC therapy The schematic summarizes the induced-proximity mechanism by which a heterobifunctional degrader recruits ER and an E3 ubiquitin ligase into a ternary complex, leading to ubiquitination and proteasomal degradation of ER.

Vepdegestrant applies this logic to a validated oncology pathway. As an ER-directed PROTAC, it recruits ER to the ubiquitin-proteasome system and reduces receptor abundance in tumor cells. This matters in ESR1-mutated disease, where ligand-independent signaling can compromise classical endocrine therapies. Fulvestrant, the active comparator in the pivotal trial, is also an ER degrader, but it requires intramuscular administration and has

pharmacologic constraints. An oral degrader therefore offered a plausible route to improve convenience and test whether deeper or more consistent ER removal could translate into clinical benefit.

It does not show that every PROTAC will outperform every inhibitor, nor that degradation is a universal answer to resistance. It shows something more specific for drug discovery: a large, orally delivered, heterobifunctional molecule can be optimized, manufactured, dosed chronically, paired with a companion diagnostic, and reviewed under ordinary regulatory standards.

CLINICAL EVIDENCE: PRECISE BUT NUANCED

The regulatory case was built primarily on VERITAC-2, a global, randomized, open-label, active-controlled phase 3 trial comparing vepdegestrant with fulvestrant after prior endocrine-based therapy. A total of 624 patients underwent randomization, including 270 with ESR1-mutated tumors.[2] In this subgroup, vepdegestrant prolonged median progression-free survival to 5.0 months, compared with 2.1 months for fulvestrant, with a hazard ratio of 0.57. Objective response rates were also higher with vepdegestrant.

The broader result was more restrained. In the full randomized population, median progression-free survival was 3.8 months with vepdegestrant and 3.6 months with fulvestrant, and the difference was not statistically significant. The first approved PROTAC therefore did not demonstrate a universal advantage across all ER-positive, HER2-negative advanced breast cancers. Rather, it provided a biomarker-selected PFS benefit in ESR1-mutated disease, and the approval appropriately follows that biology.

Safety data support the same balanced interpretation. In VERITAC-2, grade 3 or higher adverse events occurred in 23.4% of patients receiving vepdegestrant and 17.6% receiving fulvestrant; adverse events leading to treatment discontinuation occurred in 2.9% and 0.7%, respectively. Most adverse events with vepdegestrant were low grade, but the FDA label includes warnings for QTc interval prolongation and embryo-fetal toxicity. The recommended dose is 200 mg orally once daily with food until disease progression or unacceptable toxicity. Thus, the approval reflects a favorable benefit-risk profile in the selected population, not the absence of safety questions.

WHY THIS FIRST SUCCESS MATTERS

That the first approved PROTAC emerged in ER-positive breast cancer is not accidental. First-in-modality success rarely starts with the most exotic target; it more often aligns a new modality with mature biology, robust biomarkers, an accepted endpoint, and a tractable comparator. ER is one of oncology's best understood drivers, ESR1 mutation testing defines a mechanistically plausible population, and fulvestrant provides a meaningful benchmark. Vepdegestrant is therefore both a drug approval and a case study in clinical de-risking.

The comparison with existing options remains important. Elacestrant is already approved for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer after endocrine therapy, and capivasertib plus fulvestrant is approved for HR-positive, HER2-negative disease with qualifying PIK3CA, AKT1, or PTEN alterations. Vepdegestrant should therefore be viewed as a mechanistic and regulatory advance for PROTAC discovery and as an additional biomarker-directed endocrine option, not as proof of broad superiority over all second-line strategies.

PROTACs have long promised to redirect the cell's protein-disposal machinery, but practical concerns persisted: large and flexible molecular architectures, challenging permeability, complex pharmacokinetic and pharmacodynamic relationships, tissue distribution constraints, and dependence on both target and E3 ligase expression. Vepdegestrant does not remove these barriers, but it shows they can be solved well enough to support an approved oral drug.

The approval may also reshape development strategy. Early narratives emphasized drugging the 'undruggable.' That ambition remains important, but vepdegestrant points to a disciplined path: select a target for which degradation is biologically preferable to inhibition, identify a population in which the target remains a driver, and design a trial that tests the mechanism rather than the platform slogan.

Industry enthusiasm should be tempered by translational discipline. The first approval will likely energize work on new E3 ligase recruiters, tissue-selective degraders, molecular glues, and induced-proximity chemistries.[3] The next decisive advances, however, will come from showing where degradation creates a therapeutic index that inhibition, antagonism, or antibody-based approaches cannot achieve.

OPEN QUESTIONS AFTER APPROVAL

Several questions remain. Real-world uptake will depend on timely ESR1 testing, clinician confidence in sequencing after endocrine therapy and CDK4/6 inhibition, adherence to oral therapy, and management of adverse events. Whether vepdegestrant can move into earlier lines, combinations, or additional biomarker-defined settings will require further validation.

Resistance also deserves attention. Long-term pressure from an ER-directed degrader could select changes that reduce target engagement, alter ER dependence, affect ubiquitin-proteasome pathway components, or change E3 ligase availability. These possibilities remain to be defined clinically, but they reinforce the need for longitudinal biomarker studies and rational sequencing.

At the platform level, one successful ER degrader does not make targeted degradation automatically generalizable. Different targets will impose different structural, cellular, and tissue-distribution barriers, and E3 ligase availability varies by cell type and disease state. Selectivity must also be monitored to avoid unintended proteome remodeling. Next-generation degraders, molecular glues, tissue-selective E3 ligase recruiters, and combinations must produce reproducible clinical advantages over existing therapies.

OUTLOOK

Vepdegestrant's approval changes the central question for PROTAC therapeutics but does not settle the field's clinical value. The field no longer needs to ask whether a heterobifunctional degrader can become an approved drug; that threshold has been crossed. The more important question is how broadly, predictably, and safely the approach can be repeated across targets and diseases. If the next wave combines rigorous target selection, biomarker-guided development, and clinically meaningful outcomes, VEPPANU will be remembered not only as a breast cancer drug, but also as an early proof point for targeted protein degradation as a clinically validated drug-discovery modality.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.