Review

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Advances in Endocrine Therapy for Endocrine-Related Cancers: Resistance, Treatment Failure, and Emerging Therapeutic Strategies

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Endocrine-related cancers comprise biologically diverse malignancies whose growth, functional activity, or therapeutic response depends on hormone production, receptor signaling, endocrine feedback, or related cellular functions. This review examines breast, prostate, thyroid, ovarian, endometrial, and adrenocortical cancers, together with neuroendocrine neoplasms, within a broader endocrine-directed therapeutic framework. Despite the availability of established endocrine-directed therapies, endocrine resistance and other forms of treatment failure remain major barriers to durable disease control. These failures encompass biologically distinct patterns, including biological endocrine resistance, loss of endocrine-associated function, pharmacokinetic treatment failure, and symptomatic or functional treatment failure. Shared adaptive features include remodeling of endocrine dependency and activation of compensatory phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) or mitogen-activated protein kinase signaling, whereas tumor-specific manifestations include estrogen receptor 1 (*ESR1*) gene alterations in breast cancer, androgen receptor reactivation or lineage plasticity in prostate cancer, impaired sodium/iodide symporter-dependent iodide handling in differentiated thyroid cancer, altered estrogen receptor/progesterone receptor dependence in ovarian and endometrial cancers, reduced or heterogeneous somatostatin receptor (SSTR) expression in neuroendocrine tumors, and inadequate mitotane exposure or hormonal control in adrenocortical carcinoma. The strength of clinical evidence also varies substantially across therapeutic strategies: cyclin-dependent kinase 4/6 inhibitor–endocrine combinations and selected PI3K/AKT/mTOR-targeted approaches are supported by randomized trials in hormone receptor-positive breast cancer, and peptide receptor radionuclide therapy has phase III support in selected SSTR-positive neuroendocrine tumors, whereas epigenetic, immune-based, and most G protein-coupled receptor–directed approaches remain investigational or preclinical. These findings support tumor-specific, biomarker-guided treatment selection based on the predominant mechanism of resistance or treatment failure and the strength of the available clinical evidence.

Keywords: endocrine therapy; endocrine resistance; treatment failure; endocrine-related cancers; targeted therapy

Introduction

Cancer is one of the leading causes of premature death worldwide, and the global cancer burden is expected to increase substantially in the coming decades. According to the GLOBOCAN 2022 estimates from the International Agency for Research on Cancer, approximately 20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide in 2022, indicating that cancer remains a major global health concern [1]. The development and progression of cancer are determined by interactions among various factors, including genetic alterations, environmental exposures, lifestyle, inflammatory responses, and immune status [2]. Among these factors, hormone signaling and endocrine regulation are particularly relevant to the biology and treatment of certain types of cancer. In this review, endocrine-related cancers are defined as malignancies in which tumor biology, functional activity, or therapeutic response is substantially influenced by hormone production, hormone receptor signaling, endocrine feedback regulation, or other endocrine-associated cellular functions (Fig. 1). Accordingly, this review considers conventional endocrine therapies targeting hormone synthesis or hormone receptor signaling together with broader endocrine-directed interventions that suppress or exploit tumor-specific endocrine axes within a common analytical framework. These approaches include estrogen receptor (ER)- and androgen receptor (AR)-targeted therapies in breast and prostate cancers [3,4], hormone receptor-directed approaches in selected ovarian and endometrial cancers [5,6], thyroid-stimulating hormone (TSH) suppression and sodium/iodide symporter (NIS)-dependent radioactive iodine (RAI) therapy in differentiated thyroid cancer [7,8], steroidogenesis-directed treatment in adreno-

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cortical carcinoma (ACC) [9], and somatostatin receptor (SSTR)-directed somatostatin analogs (SSAs) and peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors [10]. Although these modalities differ in their biological mechanisms and clinical roles, they share a common basis in targeting, suppressing, or exploiting endocrine dependency or endocrine-associated function. This framework allows the therapeutic pressure imposed by these treatments, the patterns of treatment failure that follow, and the corresponding therapeutic strategies to be compared across endocrine-related cancers.

Breast and prostate cancers are representative hormone-dependent malignancies in which estrogen–ER [3,11] and androgen–AR signaling [4,12], respectively, regulate transcriptional programs that promote tumor proliferation and progression (Fig. 2).

According to the GLOBOCAN 2022 statistics, female breast cancer (11.6%) and prostate cancer (7.3%) are among the most commonly diagnosed cancers worldwide [1]. Endocrine therapy is firmly established as a major component of the clinical management of these hormone-dependent cancers [3,4]. Selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), selective estrogen receptor degraders (SERDs), androgen deprivation therapy (ADT), and AR-targeted therapies have improved outcomes across treatment settings, including reduced recurrence with adjuvant therapy and prolonged survival in patients with advanced disease [13,14,15,16,17]. Despite these clinical successes, acquired or selected resistance during long-term treatment remains a major cause of treatment failure and recurrence, limiting the sustained efficacy of endocrine therapy through molecular processes that differ among tumor types [3,4]. However, treatment failure within a broader endocrine-directed framework should not be uniformly interpreted as biological endocrine resistance. Resistance to conventional endocrine therapy directed at the ER or AR signaling axis may reflect adaptive or acquired biological endocrine resistance, whereas failure of other endocrine-directed interventions may instead involve loss of endocrine-associated function, pharmacokinetic treatment failure, or symptomatic/functional treatment failure. Accordingly, these patterns should be differentiated according to the biological basis and clinical role of each therapeutic modality. Cross-tumor comparison can then distinguish shared mechanisms of biological endocrine resistance from tumor-specific patterns of endocrine-associated treatment failure and relate them to mechanism-based and biomarker-guided therapeutic strategies.

For this review, a narrative literature search was conducted in PubMed for studies published through September 2026. Search terms included combinations of cancer-specific terms, including breast cancer, prostate cancer, differentiated thyroid cancer, ovarian cancer, endometrial cancer, ACC, and neuroendocrine tumors, with terms related to endocrine therapy, endocrine resistance, treatment failure, hormone receptor signaling, radioactive iodine, mitotane, SSAs, PRRT, cyclin-dependent kinase 4/6 (CDK4/6), phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR), mitogen-activated protein kinase (MAPK), epigenetic regulation, immunotherapy, and G protein-coupled receptor (GPCR) signaling. Clinical guidelines, randomized clinical trials, prospective and retrospective clinical studies, translational studies, and mechanistic preclinical studies were considered where relevant to the topic being evaluated. Evidence was appraised along two axes: the strength of mechanistic and clinical support for a given pattern of treatment failure (Table 2), and the clinical maturity of a therapeutic strategy (Table 3). Both were assessed according to study design, consistency across studies, degree of clinical validation, and relevance to current clinical practice. For patterns of treatment failure, “substantial” was used for findings supported by multiple consistent mechanistic and/or clinical studies, and “limited” for sparse, inconsistent, indirect, or context-specific evidence. For therapeutic strategies, “established” denotes support from clinical guidelines or robust randomized clinical evidence; “early clinical” denotes evidence derived mainly from phase I/II or small prospective clinical studies; “investigational” denotes strategies under clinical evaluation without demonstrated clinical benefit; and “preclinical or exploratory” denotes strategies supported predominantly by experimental data or hypothesis-generating clinical observations without an established clinical target.

Endocrine Therapy: Resistance and Treatment Failure in Human Endocrine-Related Cancers

Endocrine-directed therapy may act by inhibiting or modulating hormone receptor function, suppressing hormonal stimulation, blocking hormone biosynthesis, destabilizing or degrading receptors, or exploiting endocrine-associated cellular functions, such as NIS-mediated iodide uptake and SSTR expression [3,5,7,8,10,13,18]. To facilitate cross-tumor comparison, this section examines endocrine-related cancers within a consistent framework, beginning with the disease-specific endocrine axis and representative therapeutic approaches, followed by the predominant patterns of treatment failure, their underlying mechanisms, and therapeutic implications (Table 1, Ref. [3,4,5,7,9,15,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81]). Within this framework, treatment failure is used as a broad clinical concept encompassing biologically distinct patterns across tumor types, including biological endocrine resistance, loss of endocrine-associated function, pharmacokinetic treatment failure, and symptomatic/functional treatment failure. These patterns are distinguished according to the predominant mechanism and clinical manifestation in each disease.

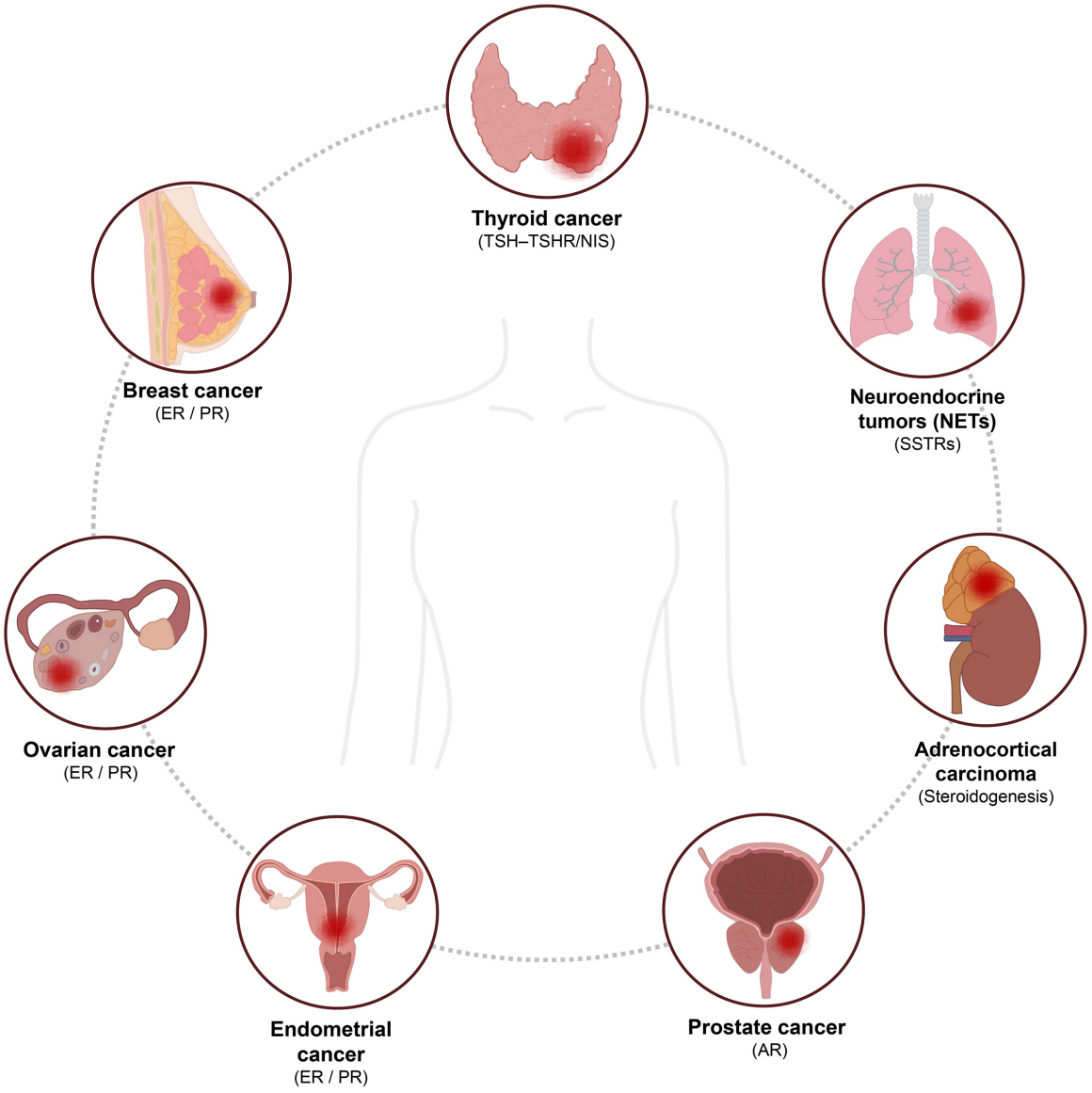


Fig. 1. Representative endocrine-related cancers and their major hormone–receptor signaling axes. This schematic illustrates representative cancers whose biological behavior or treatment is influenced by endocrine signaling. Major axes include ER/PR signaling in breast cancer and selected ovarian and endometrial cancers, AR signaling in prostate cancer, TSH–TSHR signaling and NIS-mediated iodide uptake in DTC, steroidogenesis involving cortisol and androgens in ACC, and SSTR expression in NETs arising from multiple organs. The degree of hormone dependence and receptor expression may vary according to histological subtype and differentiation status. This figure was created using Microsoft PowerPoint (Version 2609, Microsoft Corporation, Redmond, WA, USA), with Adobe Photoshop CC (Version 19.0, Adobe Inc., San Jose, CA, USA) used only for final image processing and resolution enhancement. ACC, adrenocortical carcinoma; AR, androgen receptor; DTC, differentiated thyroid cancer; ER, estrogen receptor; NETs, neuroendocrine tumors; NIS, sodium/iodide symporter; PR, progesterone receptor; SSTR, somatostatin receptor; TSH, thyroid-stimulating hormone; TSHR, thyroid-stimulating hormone receptor.

Breast Cancer

ER Signaling and Endocrine-Directed Therapies

Breast cancer is the most commonly diagnosed cancer among women [1,82]. At the molecular level, breast cancer is classified according to the expression status of ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), which provides an important basis for treatment selection [83,84]. More than 70% of breast cancers are ER-positive, with estrogen-activated ER signaling promoting transcriptional programs involved in cell proliferation and survival, including those involving cyclin D1, *MYC*, and *BCL2* [11,84]. In addition to canonical genomic ER signaling, non-genomic ER signal-

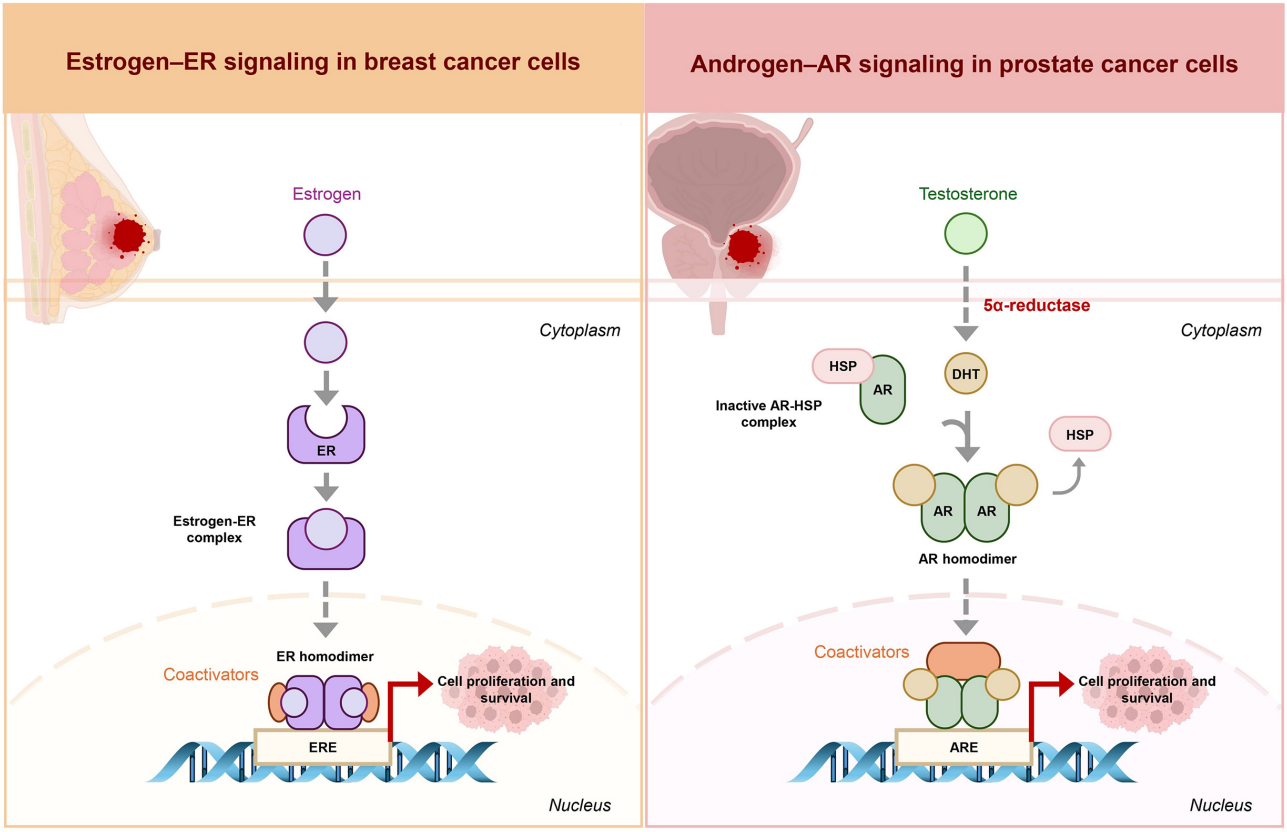


Fig. 2. Canonical activation of ER and AR signaling in breast and prostate cancer cells. Estrogen binding promotes the formation of an estrogen–ER complex, ER homodimerization, ERE binding, and coactivator recruitment. In prostate cancer cells, testosterone is converted to DHT by 5α-reductase. DHT binding to AR promotes HSP dissociation, AR homodimerization, ARE binding, and coactivator recruitment, thereby regulating transcriptional programs involved in tumor cell proliferation and survival. This figure was created using Microsoft PowerPoint (Version 2609, Microsoft Corporation, Redmond, WA, USA), with Adobe Photoshop CC (Version 19.0, Adobe Inc., San Jose, CA, USA) used only for final image processing and resolution enhancement. AR, androgen receptor; ARE, androgen response element; DHT, dihydrotestosterone; ER, estrogen receptor; ERE, estrogen response element; HSP, heat shock protein.

ing and crosstalk with the PI3K/AKT/mTOR and MAPK pathways contribute to tumor growth and endocrine resistance [84,85]. Accordingly, endocrine therapies targeting estrogen-dependent signaling are classified into three major groups according to their mechanisms of action [84].

Receptor Function Modulators: SERMs. Tamoxifen is a representative SERM used for ER-positive breast cancer and is a cornerstone of standard adjuvant endocrine therapy, particularly in premenopausal patients, with ovarian function suppression (OFS) added when indicated [16,86]. Mechanistically, tamoxifen competes with estrogen for binding to the ligand-binding domain (LBD) of ER, thereby inducing an anti-estrogenic receptor conformation. Consequently, coactivator binding is restricted, whereas corepressor recruitment is relatively enhanced, leading to the suppression of ER-dependent transcriptional programs involved in cell proliferation and survival [87,88]. Pharmacologically, tamoxifen is metabolized *in vivo* into active metabolites, including 4-hydroxytamoxifen and endoxifen, which bind to the ER with higher affinity than the parent compound and exert anti-estrogenic effects. Accordingly, genetic variation in drug-metabolizing enzymes, including CYP2D6, may alter exposure to active metabolites and potentially contribute to interindividual variability in treatment response [89,90]. Clinically, tamoxifen remains a standard adjuvant endocrine therapy for premenopausal patients with ER-positive breast cancer and has been shown to reduce long-term recurrence and breast cancer mortality [88,90].

Estrogen Biosynthesis Inhibitors: AIs. AIs inhibit the activity of aromatase (CYP19A1), a member of the cytochrome P450 (CYP) enzyme family, thereby blocking the conversion of androgen precursors into estrogens and effectively reducing systemic estrogen concentrations [91,92]. Based on this mechanism, AIs have become a central therapeutic strategy for highly estrogen-dependent breast cancer in postmenopausal women. Third-generation AIs used in clinical practice (letrozole, anastrozole, and exemestane)

Table 1. Endocrine therapeutic approaches, mechanisms of treatment failure, and therapeutic implications across endocrine-related cancers.

Cancer type	Dominant hormonal axis	Predominant pattern of treatment failure	Endocrine therapy profiles			References
			Representative endocrine therapies	Major mechanisms of treatment failure	Therapeutic implications	
Breast cancer (ER^+)	Estrogen–ER	Biological endocrine resistance	SERMs (tamoxifen); AIs (letrozole, anastrozole, exemestane); SERDs (fulvestrant and oral SERDs)	*ESR1* mutations; altered ER expression or coregulation; PI3K/AKT/mTOR, MAPK, or HER2/EGFR bypass signaling; tumor microenvironment remodeling; epigenetic reprogramming	Biomarker-guided treatment sequencing; oral SERDs for *ESR1*-mutant disease; CDK4/6- and PI3K/AKT/mTOR-directed combinations in selected patients	[3,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36]
Prostate cancer	Androgen–AR	Biological endocrine resistance	ADT; AR pathway inhibitors (enzalutamide, apalutamide, darolutamide); CYP17A1 inhibition (abiraterone)	AR amplification or mutation; AR-V7; intratumoral androgen synthesis; PI3K/AKT/mTOR, MAPK, or Wnt bypass signaling; lineage plasticity toward AR-independent or NEPC phenotypes	Molecular reassessment of AR dependence; sequencing of AR-directed therapies; consideration of non-AR-directed strategies when AR-independent lineage plasticity emerges	[4,15,37,38,39,40,41,42,43,44,45,46]
DTC	TSH–TSHR and iodide-handling machinery (NIS)	Loss of endocrine-associated function	TSH suppression with levothyroxine; RAI	Reduced NIS expression or membrane localization; persistent MAPK or PI3K/AKT signaling; dedifferentiation; epigenetic silencing of thyroid differentiation programs	Individualized TSH suppression based on treatment response and clinical risk; reassessment of RAI avidity; consideration of MAPK-directed redifferentiation in selected RAI-refractory disease	[7,47,48,49,50,51,52,53,54]
Ovarian and endometrial cancers	Estrogen–ER and progesterone–PR	Biological endocrine resistance	Progestins (MPA and MA; mainly for endometrial cancer); SERMs; AIs	Altered ER/PR expression or function; PI3K/AKT/mTOR or MAPK activation; intratumoral heterogeneity; epigenetic alterations affecting hormone receptor responsiveness	Selection by tumor type, histological subtype/grade, and ER/PR context; histological monitoring during fertility-sparing therapy; consideration of targeted combinations in selected recurrent endometrial cancer and MAPK-directed therapy in recurrent LGSOC	[5,55,56,57,58,59,60,61,62]
ACC	Autonomous adrenal steroidogenesis, frequently ACTH-independent	Pharmacokinetic and symptomatic/functional treatment failure	Mitotane; steroidogenesis inhibitors; GR and MR antagonists for control of hormone excess	Inadequate or variable mitotane exposure; drug interactions; incomplete hormone suppression; assay-related apparent resistance	TDM-guided mitotane dosing; rapid control of severe hormone excess; distinction between true and apparent treatment failure; adjunctive GR/MR blockade when clinically indicated	[9,18,63,64,65,66,67,68,69,70]
NETs	SSTR-mediated signaling and hormone secretion	Loss of endocrine-associated function; symptomatic/functional treatment failure	SSAs (octreotide and lanreotide); telotristat for carcinoid syndrome; selected use of pasireotide or interferon-α; SSTR-targeted PRRT	Reduced or heterogeneous SSTR expression; receptor internalization or desensitization; potential PI3K/AKT/mTOR or MAPK bypass signaling; higher Ki-67 and loss of differentiation associated with reduced SSA responsiveness	Reassessment of tumor grade and SSTR status; SSA dose escalation or interval shortening for persistent symptoms in selected cases; PRRT or other systemic antitumor therapy for radiological progression	[71,72,73,74,75,76,77,78,79,80,81]

Abbreviations: ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; ADT, androgen deprivation therapy; AIs, aromatase inhibitors; AKT, protein kinase B; AR, androgen receptor; AR-V7, androgen receptor splice variant 7; CDK4/6, cyclin-dependent kinases 4 and 6; DTC, differentiated thyroid cancer; EGFR, epidermal growth factor receptor; ER, estrogen receptor; GR, glucocorticoid receptor; HER2, human epidermal growth factor receptor 2; LGSOC, low-grade serous ovarian carcinoma; MA, megestrol acetate; MAPK, mitogen-activated protein kinase; MPA, medroxyprogesterone acetate; MR, mineralocorticoid receptor; mTOR, mechanistic target of rapamycin; NEPC, neuroendocrine prostate cancer; NETs, neuroendocrine tumors; NIS, sodium/iodide symporter; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; PRRT, peptide receptor radionuclide therapy; RAI, radioactive iodine; SERDs, selective estrogen receptor degraders; SERMs, selective estrogen receptor modulators; SSAs, somatostatin analogs; SSTR, somatostatin receptor; TDM, therapeutic drug monitoring; TSH, thyroid-stimulating hormone; TSHR, thyroid-stimulating hormone receptor; CYP17A1, Cytochrome P450 17A1; *ESR1*, estrogen receptor 1.

show high enzyme selectivity and potent inhibitory activity and are widely used in adjuvant and metastatic settings for postmenopausal patients. Letrozole and anastrozole are nonsteroidal agents that reversibly bind to CYP19A1, whereas exemestane has a steroid-like structure and induces irreversible, suicide-type inhibition of the enzyme [91,92]. In premenopausal women, negative feedback regulation through the hypothalamic–pituitary–ovarian axis remains intact. Therefore, AI monotherapy does not sufficiently suppress ovarian estrogen production. Accordingly, AIs should be administered in combination with OFS in this patient population [86,93,94].

Receptor Degradation-Based Inhibitors: SERDs. SERDs directly bind to the ER and induce conformational changes in the receptor, thereby impairing ER binding to chromatin, the assembly of transcriptional complexes, and the recruitment of coactivators. At the same time, SERDs promote the degradation of ER protein through the ubiquitin–proteasome pathway, resulting in the broad suppression of ER-dependent transcriptional programs [95]. Fulvestrant is the most widely used first-generation injectable SERD. It suppresses ER signaling that persists despite endocrine therapy by reducing cellular ER protein levels and has served as an important treatment option for metastatic or recurrent hormone receptor-positive breast cancer [3,95,96,97]. More recently, oral SERDs have been developed to address the formulation and pharmacokinetic limitations of fulvestrant and to target ER more effectively in resistant disease, including estrogen receptor 1 (*ESR1)*-mutated tumors [3,19]. Elacestrant demonstrated a progression-free survival (PFS) benefit in the phase III EMERALD trial and subsequently received Food and Drug Administration approval for ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer following progression on prior endocrine therapy [20,98]. Several other oral SERDs remain under clinical investigation [95,98,99,100].

Mechanisms of ER-Related Endocrine Resistance

In ER-positive breast cancer, endocrine resistance may occur as primary resistance, characterized by an inadequate response from the beginning of treatment, or as acquired resistance, which develops after an initial period of endocrine sensitivity under therapeutic selection pressure [3,21,22]. Multiple biological mechanisms contribute to these resistant states, including alterations in the ER itself, activation of alternative signaling pathways, changes in the tumor microenvironment, and epigenetic dysregulation [3,21,22]. A major molecular mechanism involves *ESR1* mutations (e.g., Y537S, D538G), which induce ligand-independent ER activity and result in resistance to AIs [23,24,25]. In addition, reduced ER expression, dysregulation of receptor coregulators, and abnormalities in RNA splicing may affect receptor function [19]. Cancer cells may also bypass ER inhibition by activating alternative growth and survival pathways, including the PI3K/AKT/mTOR, MAPK, and HER2/epidermal growth factor receptor (EGFR) pathways. Consistent with this mechanism, constitutive AKT activation has been shown to reduce responsiveness to anti-estrogen treatment in ER-positive breast cancer cells [101]. In particular, *PIK3CA* mutations are associated with resistance to endocrine therapy, and combination treatment strategies targeting this pathway have been developed [3,26,27]. The tumor microenvironment also contributes to the development of resistance. Changes involving cancer-associated fibroblasts, immunosuppressive cells, and angiogenesis may enhance local growth signals and reduce sensitivity to endocrine therapy [3,28]. Finally, abnormalities in epigenetic regulation, including DNA methylation and histone modifications, may suppress ER expression or limit therapeutic responses [21,29]. Thus, endocrine resistance in ER-positive breast cancer reflects multiple interacting mechanisms, and treatment selection should consider the predominant mechanism, including alterations in ER signaling and compensatory activation of survival pathways [3,26].

Prostate Cancer

AR Signaling and Endocrine-Directed Therapies

In the United States, prostate cancer is the most common cancer among men, excluding skin cancer, and is the second leading cause of cancer death among men [82]. Prostate cancer is an androgen-dependent malignancy in which the AR signaling axis plays a key role in tumor development and progression [102]. Testosterone can be converted by 5α-reductase into the more potent metabolite dihydrotestosterone (DHT), which activates AR-dependent transcription of target genes, including *KLK3* (encoding prostate-specific antigen), *TMPRSS2*, and *FKBP5*, thereby promoting cell growth and survival [12,15]. Accordingly, endocrine therapeutic strategies targeting the androgen–AR axis can be classified into three major approaches.

Androgen Biosynthesis Inhibition: ADT. ADT reduces circulating androgens (primarily testosterone) to castrate levels, thereby weakening AR signaling, and has been established as a central component of systemic treatment for hormone-sensitive prostate cancer [15,103]. Clinically, ADT is achieved through surgical castration (bilateral orchiectomy) or medical castration that suppresses the hypothalamic-pituitary-gonadal axis, with gonadotropin-releasing hormone (GnRH) agonists and antagonists being the main agents used for medical castration [103]. GnRH agonists (e.g., leuprolide and goserelin) may initially stimulate the pituitary gland, causing a transient increase in luteinizing hormone and testosterone; however, continuous administration induces receptor desensitization and ultimately suppresses testosterone to castrate levels [104]. In contrast, GnRH antagonists (e.g., degarelix and relugolix)

directly block GnRH receptors and have been reported to reduce testosterone levels more rapidly without an initial increase in testosterone. These pharmacological properties may therefore inform the selection of ADT according to the clinical situation [104].

Receptor Antagonists: AR Antagonists. First-generation nonsteroidal antiandrogens (bicalutamide, flutamide, and nilutamide) competitively block ligand binding to AR and inhibit AR-dependent transcription; however, their therapeutic effects may be limited by insufficient inhibitory potency and the development of resistance [15]. Second-generation AR signaling inhibitors (enzalutamide, apalutamide, and darolutamide) were developed to provide more potent AR blockade and more effectively suppress AR-mediated transcriptional programs that are maintained even in a castrate environment [15]. Clinically, second-generation AR-targeted therapies have demonstrated survival benefits in major phase III studies (e.g., PREVAIL [105,106], SPARTAN [17,107], ARAMIS [108,109]) and are now used across several disease stages, including non-metastatic and metastatic castration-resistant prostate cancer (CRPC) [37,110].

Androgen Biosynthetic Enzyme Inhibitors: CYP17A1 Inhibitors. CYP17A1 (17α-hydroxylase/17,20-lyase) is a key enzyme that directs steroid precursors into the androgen biosynthetic pathway. In prostate cancer, it may contribute to the maintenance of AR signaling through both testicular- and adrenal-derived androgens, as well as through the steroid metabolism and synthesis axis that remain active in a castrate environment [15,111,112,113]. Abiraterone acetate is converted *in vivo* into its active form, abiraterone, which inhibits the 17α-hydroxylase and 17,20-lyase activities of CYP17A1, thereby suppressing the production of androgen precursors and, ultimately, testosterone and DHT [111,114]. These agents are often administered with low-dose glucocorticoids to alleviate mineralocorticoid excess caused by CYP17A1 inhibition and have become an important component of ADT-based treatment for metastatic prostate cancer, supported by substantial clinical trial evidence [111,115,116,117].

AR Reactivation and Lineage Plasticity in Endocrine Resistance

Although ADT maintains serum testosterone at castrate levels, disease progression may still occur, marking the transition to CRPC [38,39]. Within this resistant state, disease progression under therapeutic pressure may remain AR-driven through reactivation of the AR signaling axis or, in some cases, shift toward an AR-independent phenotype [38,39]. A major mechanism involves quantitative and qualitative alterations in the AR itself [118]. AR gene amplification/overexpression and alterations in AR regulatory regions may maintain AR-dependent transcriptional programs even in low-ligand environments, whereas mutations in the AR LBD may alter drug sensitivity and reduce therapeutic efficacy [38,40]. In addition, AR splice variants, most notably AR-V7, lack the LBD and can maintain transcriptional activity in the absence of ligands, potentially contributing to resistance to AR-directed therapies, including enzalutamide and abiraterone [40,41,42]. Some CRPC tumors maintain a local androgen pool by utilizing adrenal-derived precursors or reactivating intratumoral steroid metabolism/synthesis pathways, with enzymes involved in steroid synthesis/conversion, including CYP17A1 and AKR1C3, reported to participate in this process [43,113]. In addition, the activation of alternative growth and survival signaling pathways, including PI3K/AKT/mTOR, MAPK, and Wnt, may provide bypass mechanisms that reduce the effects of AR inhibition [44]. In particular, reciprocal feedback and crosstalk between the PI3K/AKT/mTOR axis and AR provide a basis for understanding drug resistance and the rationale for combination therapies [45,46]. Finally, lineage plasticity under therapeutic pressure represents an important resistance mechanism that departs from AR-centered biology. This process has been associated with disruption of the *RB1*/*TP53* axis and epigenetic reprogramming and may result in a transition to an AR-independent phenotype, such as neuroendocrine prostate cancer [38]. Thus, CRPC may remain predominantly AR-driven or shift toward bypass signaling and AR-independent lineage plasticity. These distinctions are relevant to subsequent treatment selection [38,46].

Thyroid Cancer

TSH Signaling, Iodide Handling, and Endocrine-Directed Therapies

More than 90% of thyroid cancers are classified as differentiated thyroid cancers (DTCs), which primarily include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma [47]. These tumors retain TSH-dependent growth characteristics and often preserve some features of normal thyroid follicular cells, including TSH receptor (TSHR) expression and iodide metabolism-related genes such as NIS, thyroid peroxidase (TPO), and thyroglobulin (Tg) [119], which provide the biological basis for therapeutic strategies. TSH–TSHR binding activates the protein kinase A (PKA) pathway through Gs protein–adenylyl cyclase–cyclic adenosine monophosphate (cAMP) signaling and is linked to the regulation of genes associated with thyroid function, cell proliferation, and thyroid differentiation [47,119]. At the molecular level, PTC is commonly associated with alterations that activate the MAPK pathway (*BRAF* V600E mutations and *RET*/*NTRK* fusions), whereas RAS mutations and *PAX8*-*PPARG* rearrangements are more frequently observed in follicular-patterned tumors. *TERT* promoter mutations may cooperate with these driver alterations and are associated with more aggressive tumor behavior [120,121,122].

Inhibition of Hormonal Stimulation: TSH Suppression Therapy. In postoperative patients with DTC, TSH suppression using levothyroxine has traditionally been used to reduce TSH-mediated growth stimulation of residual tumors, with the degree of suppression determined according to recurrence risk and treatment response [123]. Earlier guidelines recommended risk-stratified numerical TSH targets, with more intensive suppression for patients at higher risk of recurrence. However, more recent guidelines have shifted away from fixed numerical targets based solely on the initial recurrence-risk category. Instead, they emphasize an individualized approach based on the response to therapy and the balance between potential therapeutic benefits and adverse effects [48,123]. TSH levels are generally maintained within the normal reference range in patients with an excellent or indeterminate response, whereas suppression below the normal reference range may be considered in patients with a biochemical or structural incomplete response [48]. Accordingly, the risks and benefits of continued TSH suppression should be reassessed over time, particularly in patients at risk of cardiovascular or skeletal complications [48].

Selective Cancer Cell Elimination Strategy: RAI. DTC retains some characteristics of normal thyroid follicular cells and selectively takes up iodide through NIS. In particular, NIS is a key molecule that actively transports iodide into the cells and provides the biological basis for the use of RAI in DTC. Clinically, RAI is an established therapeutic modality for appropriately selected patients with DTC, and its use is determined according to recurrence risk and disease characteristics [48]. Following NIS-mediated uptake at the basolateral membrane, iodide is transported toward the apical membrane, oxidized by TPO, and incorporated into Tg. Preservation of this iodide-handling machinery contributes to the retention and therapeutic efficacy of ^{131}I in differentiated tumor cells [47,124]. RAI uses the radioactive isotope of iodine, ^{131}I (iodine-131), which emits β-particles and selectively destroys tumor cells by inducing localized radiation damage at the cellular level [124,125]. To maximize therapeutic efficacy, TSH levels are temporarily increased before RAI through thyroid hormone withdrawal or administration of recombinant human TSH [48,126,127].

Loss of Thyroid Differentiation and Radioiodine Refractoriness

In DTC, treatment failure with endocrine-directed therapy may arise from the loss of the endocrine-associated functions that support TSH responsiveness and NIS-mediated iodide uptake. Progression to an RAI-refractory phenotype therefore represents a tumor-specific form of treatment failure that may involve impaired iodide handling, oncogenic signaling, reduced cellular differentiation, and epigenetic reprogramming rather than a single mechanism [47,48,49]. Clinically, RAI refractoriness is increasingly regarded as a spectrum of reduced responsiveness rather than being defined solely by the complete absence of iodide uptake. Strong criteria suggesting RAI-refractory DTC include either the absence of ^{131}I uptake on post-therapy imaging despite disease detectable by structural imaging or ^{18}F-fluorodeoxyglucose positron emission tomography (PET), or disease progression within 6 months after an appropriately administered therapeutic dose of RAI despite demonstrated uptake. The absence of uptake on diagnostic RAI imaging and heterogeneous uptake among tumor lesions may additionally indicate reduced RAI sensitivity [47,48,50]. Impaired iodide uptake is a major mechanism underlying RAI refractoriness. In RAI-refractory DTC, NIS (*SLC5A5*) expression, which serves as a gateway for RAI treatment, may be reduced, or its transport and retention at the plasma membrane (trafficking) may be impaired, thereby limiting the accumulation of radiation within the tumor. Consequently, the tumor gradually acquires a non-iodide-avid phenotype, markedly limiting the therapeutic efficacy of RAI [49]. These alterations are associated with persistent activation of the MAPK or PI3K/AKT signaling pathways. In particular, the *BRAF* V600E mutation has repeatedly been associated with RAI resistance in the context of the suppression of thyroid differentiation programs and iodide metabolism-related gene expression. Persistent activation of the MAPK pathway can suppress NIS transcription and interfere with its localization to the plasma membrane, thereby linking oncogenic signaling to impaired iodide uptake and reduced RAI sensitivity [47,124]. Another important mechanism is tumor cell dedifferentiation. During the progression of DTC to poorly differentiated or anaplastic thyroid cancer, the expression of thyroid differentiation marker genes, including TSHR, Tg, and TPO, decreases. Accordingly, reduced TSHR expression may diminish dependence on TSH-regulated signaling. In this setting, the relative antitumor effect of TSH suppression may become more limited as dedifferentiation progresses [47,49]. More recently, dysregulation of epigenetic mechanisms has been investigated as a potential contributor to treatment failure in DTC. Alterations in DNA methylation, histone modifications, and non-coding RNA regulation may contribute to reduced expression of differentiation and iodide metabolism-related genes, including NIS, TSHR, and TPO, thereby potentially promoting the loss of iodide uptake and tumor dedifferentiation. These mechanisms provide a theoretical basis for redifferentiation strategies using epigenetic-targeted agents, such as histone deacetylase (HDAC) inhibitors or DNA methylation inhibitors [49,52]. However, the clinical evidence supporting the use of epigenetic agents for redifferentiation therapy remains limited. In contrast, early clinical evidence supports MAPK pathway-directed redifferentiation in RAI-refractory DTC [47,51,53,54]. Therefore, these mechanisms interact rather than acting in isolation, supporting further evaluation of molecular mechanism-based targeted

treatments and combination strategies for selected patients with treatment-refractory DTC [47,49].

Ovarian and Endometrial Cancers

Hormone Receptor Dependence and Endocrine-Directed Therapies

Ovarian and endometrial cancers are major malignancies arising in the female reproductive tract. Endometrial cancer has a high incidence, whereas ovarian cancer accounts for a substantial proportion of deaths from gynecologic malignancies [1]. Selected ovarian and endometrial cancer subtypes retain ER and/or PR expression and may exhibit hormone-responsive tumor biology [5,6,55,128]. In particular, ER and PR expression patterns have been associated with clinically relevant tumor characteristics and outcomes in low-grade serous ovarian carcinoma (LGSOC) and endometrioid ovarian carcinoma [55,129]. In the endometrium, particularly in type I endometrial cancer, estrogen–ER signaling is associated with proliferative programs, whereas progesterone–PR signaling induces differentiation and antiproliferative pathways, thereby exerting mutually antagonistic effects [130]. Therefore, hormone receptor expression (particularly ER/PR status) may serve as an indicator for assessing the potential applicability of endocrine therapy, and associations with prognosis have also been reported in some cohorts. However, the predictive and prognostic value of hormone receptor status may vary according to tumor type and clinical context [5,6,55,129]. The current molecular classification divides endometrial cancer into *POLE*-mutated, mismatch repair-deficient, no specific molecular profile (NSMP), and p53-abnormal subgroups. Hormone receptor expression is more commonly retained in low-grade endometrioid and NSMP tumors, suggesting that integrating molecular classification with ER/PR status may improve patient selection for endocrine therapy [128]. LGSOC is characterized by frequent ER expression and recurrent alterations in the MAPK pathway genes (e.g., *KRAS*, *BRAF*, and *NRAS*), whereas PR expression is more variable. These molecular features provide the biological basis for endocrine therapy and MAPK-directed treatment strategies [55,56,131,132]. Accordingly, the clinical role of endocrine therapy differs between these tumor types and depends on hormone receptor status and disease context. In selected hormone receptor-positive ovarian cancers, particularly LGSOC, endocrine therapy may be used for long-term disease control or maintenance [56,131,132,133], whereas progestin-based fertility-sparing treatment is used in carefully selected patients with early-stage, low-grade endometrioid endometrial cancer [57].

Progestins. Medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are representative progestins [134]. Through the activation of PR signaling, these agents suppress estrogen-dependent proliferation and induce differentiation in the endometrium, thereby exerting antitumor effects [134,135,136]. Clinically, progestin-based therapy is a guideline-supported fertility-sparing option for carefully selected patients with early-stage, low-grade endometrioid endometrial cancer or atypical endometrial hyperplasia [57,58,136]. However, the supporting evidence is derived largely from nonrandomized studies rather than from randomized comparative trials [57]. Recommended oral regimens include MPA at 400–600 mg/day or MA at 160–320 mg/day [57]. Fertility-sparing treatment is generally restricted to carefully selected patients with grade 1 endometrioid carcinoma confined to the endometrium and requires the exclusion of myometrial invasion and extrauterine disease. A levonorgestrel-releasing intrauterine device may be used alone or in combination with oral progestins, with repeated histological assessments required to evaluate the treatment response [57]. In ovarian cancer, the evidence for endocrine therapy is more focused on anti-estrogen agents and AIs. Progestins have only limited supporting evidence in ER/PR-positive subtypes (e.g., LGSOC) and should therefore be described as an option considered only in selected clinical situations [5,137,138].

SERMs. Tamoxifen may be considered a relatively low-toxicity endocrine treatment option in some patients with recurrent or metastatic endometrial cancer (particularly those with low-grade, hormone receptor-positive tumors) [139,140,141] and in selected patients with epithelial ovarian cancer, particularly LGSOC [5,133]. However, the available evidence is mainly based on retrospective analyses or small studies, and the strength of clinical evidence should therefore be considered limited [5,133,139,140]. In advanced endometrial cancer, alternating treatment with MA and tamoxifen has demonstrated clinical activity in a phase II study, based on the rationale that tamoxifen may increase PR expression and thereby restore or enhance sensitivity to progestins. However, this approach is not suitable for all patients because treatment benefits are variable and thromboembolic toxicity must be considered [142].

AIs. AIs, including letrozole, anastrozole, and exemestane, represent another low-toxicity endocrine treatment option for selected patients with hormone receptor-positive ovarian or endometrial cancers, particularly those with recurrent disease [139,141,143]. In LGSOC, AIs are considered relatively well-tolerated long-term treatment options for disease control, including maintenance therapy after first-line treatment [56,131,132,133]. Retrospective data have shown that hormonal maintenance therapy after primary surgery and chemotherapy is associated with longer PFS than surveillance alone, although prospective confirmation and more precise predictive biomarkers remain necessary [133]. In endometrial cancer, AIs may also be considered alternative endocrine treatment options when progestin-based treatment is difficult to administer [139,144].

Hormone Receptor Alterations and Bypass Signaling in Endocrine Resistance

In ovarian and endometrial cancers, endocrine therapy is used mainly in selected hormone-responsive or hormone receptor-expressing subtypes; however, the clinical manifestations of resistance differ according to tumor type and treatment setting. In endometrial cancer, resistance may manifest as failure to achieve or maintain a response to progestin-based conservative therapy or as disease progression during endocrine treatment of recurrent or advanced disease. In ovarian cancer, particularly LGSOC, resistance more commonly manifests as disease progression or loss of disease control during endocrine therapy [56,59,139]. This resistance arises through complex mechanisms, including altered receptor expression, reorganization of downstream signaling pathways, and increased molecular heterogeneity of the tumor [59,139]. Alterations in ER/PR expression or receptor function represent important mechanisms associated with reduced responsiveness to progestin- and anti-estrogen-based therapies [59,139]. In endometrial cancer, lower PR expression has also been associated with a reduced likelihood of response to conservative progestin therapy, although receptor status alone does not fully predict treatment outcomes [58,59]. Differences in receptor expression intensity, intratumoral heterogeneity, receptor functionality, and the activity of downstream signaling pathways may explain why tumors with apparently similar ER/PR expression show different responses to endocrine therapy [5,59,128,139]. At the same time, tumors may bypass ER/PR inhibition by enhancing growth and survival signaling through pathways such as PI3K/AKT/mTOR and MAPK, particularly in the context of frequent alterations in the *PTEN*/*PIK3CA* axis in endometrial cancer [59,139]. These findings provide a biological rationale for combined targeting of endocrine signaling and the PI3K/AKT/mTOR pathway, although clinical evidence remains limited and predictive biomarkers are not yet well established [59,60,61,139]. In ovarian cancer, particularly LGSOC, alterations in the MAPK pathway are frequently observed despite the retention of ER expression. Nevertheless, responses to AIs or SERMs may vary and may not provide durable disease control in all patients [56,131,132]. The clinical relevance of targeting the MAPK pathway is supported by randomized evidence for mitogen-activated protein kinase kinase (MEK) inhibition in recurrent disease [62]. In endometrial cancer, epigenetic regulation of PR has also been implicated in progestin resistance. Aberrant methylation of the PR promoter can reduce PR expression and progestin sensitivity, whereas experimental inhibition of DNA methylation or histone deacetylation has been shown to restore PR expression in endometrial cancer cell models [59]. However, these findings are derived largely from mechanistic and preclinical studies, and epigenetic modulation has not yet been clinically validated as a strategy to overcome progestin resistance [59]. Taken together, subsequent therapeutic strategies should consider tumor type, retained ER/PR dependence, and molecular pathways contributing to resistance. Combination therapies incorporating targeted agents may be appropriate in selected molecular and clinical contexts; however, further validation of treatment sequencing and predictive biomarkers remains necessary [56,59,60,61,139,141].

Adrenocortical Carcinoma

Steroidogenesis and Endocrine-Directed Therapies

ACC is a rare and aggressive endocrine malignancy, with an estimated annual incidence of approximately 0.7–2 cases per million, a high risk of recurrence, and a poor prognosis [18,145,146]. Approximately 40–60% of patients present with excessive secretion of steroid hormones, including cortisol, androgens, and aldosterone, and such hormone excess can contribute substantially to systemic metabolic and clinical morbidity [9,145,146]. In the normal adrenal cortex, steroidogenesis depends on enzymes including CYP11A1, CYP17A1, CYP21A2, and CYP11B1, with adrenocorticotropic hormone (ACTH)–cAMP–PKA signaling playing a central regulatory role, particularly in glucocorticoid and adrenal androgen production [63]. However, in ACC, dysregulated steroidogenic programs may permit autonomous hormone production. Overexpression of steroidogenic factor 1, together with altered expression of steroidogenic CYP enzymes, may contribute to the maintenance of this ACTH-independent steroidogenic phenotype [63]. Molecular alterations including *IGF2* overexpression, Wnt/β-catenin activation, and *TP53* mutations further enhance tumor growth and survival [147], and genomic analyses have demonstrated additional heterogeneity involving cell-cycle regulation, telomere maintenance, chromatin remodeling, and steroidogenic programs [148]. Based on this pathophysiology, endocrine-directed management of ACC includes both tumor-directed mitotane therapy and control of hormone excess through inhibition of steroidogenesis or blockade of hormone action.

Adrenal-Selective Adrenolytic Agent: Mitotane. Mitotane is a representative agent in ACC that exerts both selective cytotoxic effects on adrenocortical cells and inhibitory effects on steroidogenesis, thereby suppressing tumor growth and controlling hormone excess [63,149]. Mechanistically, mitotane disrupts mitochondrial membrane integrity, steroidogenic CYP enzyme systems, and intracellular cholesterol handling, thereby reducing steroidogenic capacity and promoting cell death [63,149,150]. However, no single pathway fully accounts for its activity. Clinically, mitotane is a guideline-supported adjuvant treatment administered after complete resection in patients with a high risk of recurrence, although the supporting evidence is based largely on nonrandomized data [64]. In advanced ACC that is not amenable to complete local treatment, treatment with mitotane monotherapy or etoposide,

doxorubicin, and cisplatin plus mitotane (EDP-M) is guided by prognostic factors, with EDP-M supported by randomized clinical trial evidence [64,151]. From the perspective of therapeutic response and toxicity management, plasma concentration-based therapeutic drug monitoring (TDM) has been repeatedly emphasized. Plasma concentrations of approximately 14–20 mg/L are commonly used as a therapeutic target range. As this range is derived largely from observational evidence, it may be more appropriately interpreted as a reference range rather than an absolute threshold, and mitotane concentrations should be considered together with clinical response, toxicity, and individual patient characteristics [18,65,152]. Mitotane can also accelerate glucocorticoid metabolism by inducing CYP3A4 expression [66]. Therefore, particularly when a block-and-replace strategy is applied, symptoms of adrenal insufficiency and the need for adjustment of glucocorticoid replacement doses should be closely monitored [66,152].

Steroidogenesis Inhibitors. Mitotane alone exerts both antitumor and steroidogenesis-inhibitory effects. However, because of its considerable pharmacokinetic variability, time may be required to achieve effective drug exposure. In particular, when severe hypercortisolism is present in functional ACC, systemic complications, including infection, thrombosis, and metabolic abnormalities, may determine the clinical course. Therefore, the use of steroidogenesis inhibitors to reduce cortisol levels more rapidly is considered a guideline-supported strategy during the initial treatment phase or at the time of symptom exacerbation, particularly in cases of severe hypercortisolism [64,67]. However, the available evidence for steroidogenesis inhibitors in ACC is based largely on clinical experience and observational data rather than ACC-specific randomized trials [64]. Mechanistically, these agents target different enzymatic steps and may be used alone or in combination according to the clinical situation, following a block-and-replace strategy when necessary. For example, ketoconazole broadly inhibits several CYP enzymes, particularly those involved in key steps of the steroidogenic pathway, and is used to reduce cortisol/androgen synthesis. Metyrapone mainly reduces cortisol production through CYP11B1 inhibition, although the possibility of worsening mineralocorticoid-like effects on blood pressure and potassium levels caused by precursor accumulation should be considered [67]. In severe hypercortisolism requiring immediate suppression or when oral treatment is not feasible, intravenous etomidate may be considered for enzymatic inhibition at subsedative doses in an intensive care setting, with close monitoring of the level of consciousness, electrolytes, and hemodynamic status [9,153,154].

Steroid Hormone Receptor Antagonists. Lowering hormone levels through steroidogenesis inhibition alone may not control clinical symptoms of hypercortisolism sufficiently rapidly, particularly its metabolic, cardiovascular, and immune effects. In addition, it may be difficult to administer adequate doses of enzyme inhibitors because of hepatotoxicity and drug interactions. Therefore, a strategy that blocks hormone action at the receptor level has been considered. Mifepristone may be considered in selected patients to reduce the clinical burden of hypercortisolism by blocking glucocorticoid receptor (GR) signaling. Because circulating cortisol levels may remain elevated or increase during GR antagonism, cortisol concentrations should not be used as a direct marker of treatment response; instead, monitoring should rely primarily on clinical findings, blood pressure, blood glucose, and electrolytes, particularly K^+ [68]. Meanwhile, under hypercortisolemic conditions, cortisol may activate the mineralocorticoid receptor (MR) through mechanisms such as saturation of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), thereby aggravating hypertension and hypokalemia. Accordingly, the concomitant use of an MR antagonist, such as spironolactone or eplerenone, may be considered to reduce the electrolyte and blood pressure burden [9,67,68]. Thus, GR and MR antagonists should be regarded primarily as adjunctive therapies for controlling the clinical consequences of hormone excess rather than as established tumor-directed treatments for ACC [64,68].

Mitotane Treatment Failure and Inadequate Hormonal Control

In this review, endocrine treatment failure in ACC is considered along two clinically distinct axes: tumor recurrence or progression despite mitotane-based treatment and inadequate control of hormone excess despite pharmacological treatment [9,64,69]. Substantial interindividual pharmacokinetic variability may lead to inadequate mitotane exposure and limit its antitumor efficacy; therefore, TDM remains important when evaluating treatment failure [69]. Since no validated molecular biomarker can yet reliably predict mitotane sensitivity in individual patients, TDM should be interpreted together with radiological response, hormonal control, treatment adherence, toxicity, and possible drug interactions [64,70]. In functional ACC, particularly when Cushing syndrome is present, rapid control of hormone excess is an important therapeutic goal because uncontrolled hypercortisolism contributes substantially to morbidity and mortality [64,67]. In functional ACC, treatment failure may present as persistent or recurrent hormone excess despite steroidogenesis inhibition. When mitotane is administered concomitantly, increased cortisol-binding globulin concentrations and altered steroid metabolism may complicate the interpretation of total cortisol measurements [69,70]. In addition, steroidogenesis inhibitors such as metyrapone can increase steroid precursors, including 11-deoxycortisol, which may cross-react in some cortisol immunoassays [67]. Therefore, true treatment failure should be distinguished from apparent resistance caused by pharmacokinetic or measurement-related

limitations [67,68,69,70]. Management of endocrine treatment failure in ACC requires distinguishing among inadequate drug exposure, true tumor progression, insufficient hormonal control, and apparent resistance before modifying the treatment strategy.

Neuroendocrine Tumors

Hormone Secretion and Endocrine-Directed Therapies

Although Neuroendocrine neoplasms (NENs) are relatively rare neoplasms, their incidence and prevalence have increased over time [155]. They comprise a clinically and pathologically heterogeneous group arising in various organs, including the gastroenteropancreatic (GEP) tract and lungs [71,156,157]. Reflecting this heterogeneity, NENs are pathologically classified into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs), with GEP NETs further graded as G1–G3 based on the Ki-67 proliferation index and mitotic rate [158,159]. Distinguishing well-differentiated NET G3 from poorly differentiated NEC is clinically important because these entities differ in molecular characteristics, biological behavior, and treatment response; because SSTR-directed approaches are primarily relevant to well-differentiated NETs, this section focuses on NETs rather than NECs [71,159,160]. Clinically, NETs are divided into functional and non-functional tumors according to whether the bioactive amines and peptides secreted by tumor cells cause an overt clinical syndrome [161]. Functional NETs may present with various hormone hypersecretion syndromes, including carcinoid syndrome, in which serotonin is a major hormonal mediator [162], as well as syndromes associated with insulinoma, gastrinoma, glucagonoma, and vasoactive intestinal peptide-secreting tumors. These syndromes can contribute substantially to disease burden [71,157]. NETs share neuroendocrine differentiation programs, but cell-cycle regulation, protein translation, chromatin remodeling, growth factor–receptor signaling, and differentiation state are rewired differently according to organ of origin and grade [157,163]. Genomic analyses of pancreatic neuroendocrine tumors (pNETs), for example, show recurrent alterations involving *MEN1*, *DAXX*/*ATRX*, DNA damage repair, telomere maintenance, and mTOR signaling, indicating that NETs arising in different organs do not share a uniform molecular background [163]. Among these features, SSTR2 expression in well-differentiated GEP-NETs, including many pNETs, is particularly relevant to endocrine therapy [71,72,156,157,160]. SSTR expression underlies the suppression of hormone secretion and the antiproliferative effects through SSAs, while SSTR PET enables whole-body assessment of receptor expression, and PRRT provides targeted radionuclide treatment. Because SSTR expression and function vary according to tumor subtype and degree of differentiation, treatment should be stratified accordingly rather than applied uniformly across NETs [71,72,73].

SSAs. Octreotide and lanreotide bind preferentially to SSTR2, with additional affinity for SSTR5, and suppress hormone secretion. Their antiproliferative effects have been associated with the modulation of downstream signaling pathways, including MAPK and PI3K/AKT/mTOR signaling, although much of the mechanistic evidence derives from preclinical studies [73,74]. The clinical role of SSAs extends beyond the control of hormone-related symptoms, as randomized trials have also shown delayed tumor progression in selected well-differentiated NETs. In the PROMID trial, long-acting octreotide delayed tumor progression in metastatic midgut NETs, whereas the CLARINET trial showed PFS with lanreotide in advanced non-functioning enteropancreatic NETs [156,157]. Together, these findings support the current use of SSAs as standard, guideline-supported treatment options for appropriately selected patients with SSTR-positive, well-differentiated NETs [71,73]. The antiproliferative effect of SSAs is generally greater in well-differentiated, slowly progressive, and SSTR-positive tumors, whereas objective tumor shrinkage is relatively uncommon. Therefore, SSAs are used primarily to achieve hormonal control and disease stabilization rather than rapid tumor reduction [71,73,157].

Interferon-α and Exploratory Dopamine Receptor-Targeted Approaches. Interferon-α may provide hormonal and antiproliferative activity in selected patients with NETs, particularly when symptom control with SSAs alone is inadequate. However, its current clinical use is limited by treatment-related toxicity and the availability of alternative systemic therapies [71,75]. In contrast, dopamine receptor-targeted approaches, including somatostatin–dopamine chimeric compounds, have shown antisecretory activity in experimental NET models, but their clinical role in GEP-NETs has not been established and the available evidence remains largely preclinical [164].

Other Agents: Telotristat and Pasireotide. Telotristat ethyl inhibits tryptophan hydroxylase 1, a key enzyme in serotonin biosynthesis, and is used to control diarrhea associated with carcinoid syndrome. Its use in patients whose diarrhea remains inadequately controlled by SSAs is supported by phase III clinical evidence [76]. Pasireotide is a second-generation SSA capable of binding to multiple SSTR subtypes (SSTR1–5) and has been evaluated in patients with persistent carcinoid symptoms despite conventional SSA therapy. However, a randomized phase III study did not show superior symptom control compared with high-dose octreotide; therefore, its clinical role in this setting remains less well established [77,78].

Persistent Hormonal Symptoms and Tumor Progression During SSA Therapy

In this review, endocrine treatment failure in NETs is considered in two clinically distinct forms: persistent

Table 2. Cross-tumor comparison of endocrine-associated treatment failure: shared patterns, tumor-specific manifestations, and evidence strength.

Treatment-failure theme	Shared cross-tumor pattern	Tumor-specific manifestations	Representative cancer contexts	Evidence strength and key limitations	References
Remodeling or loss of endocrine dependency	Alteration or loss of the endocrine-associated axis or cellular function required for therapeutic response	Breast: *ESR1* mutations, reduced ER expression or altered receptor regulation; Prostate: AR amplification/mutation and AR-V7; DTC: reduced or mislocalized NIS; Ovarian/endometrial: altered ER/PR expression, function, or dependence; NETs: reduced or heterogeneous SSTR expression and receptor desensitization	Breast cancer; prostate cancer; DTC; ovarian/endometrial cancers; NETs	Substantial mechanistic and clinical evidence, particularly for *ESR1* alterations in breast cancer, AR remodeling in prostate cancer, and NIS loss in DTC; less uniform evidence across ovarian/endometrial cancers and NETs	[19,23,24,25,40,41,42,43,47,49,55,59,73,74,139]
Compensatory bypass signaling	Activation of alternative survival pathways and reduced dependence on the primary endocrine axis	Breast: PI3K/AKT/mTOR, MAPK, and HER2/EGFR signaling; **Prostate:** PI3K/AKT/mTOR, MAPK, and Wnt signaling; DTC: persistent MAPK or PI3K/AKT signaling; Ovarian/endometrial: PI3K/AKT/mTOR or MAPK activation; NETs: potential PI3K/AKT/mTOR or MAPK bypass signaling	Breast cancer; prostate cancer; DTC; ovarian/endometrial cancers; NETs	Substantial mechanistic evidence across multiple tumor types; clinical validation of pathway-directed treatment in selected breast and gynecologic cancer contexts; context-dependent direct evidence for bypass signaling as a clinically actionable resistance mechanism	[3,26,27,34,35,36,44,45,46,47,59,60,61,62,73,74,79,124,132,139]
Changes in differentiation state and lineage plasticity	Reduced dependence on the differentiated endocrine-responsive phenotype targeted by treatment	Prostate: lineage plasticity and transition toward AR-independent NEPC; DTC: dedifferentiation with loss of thyroid differentiation programs; NETs: higher Ki-67 and loss of differentiation associated with reduced or less durable SSA responsiveness	Prostate cancer; DTC; NETs	Substantial mechanistic and clinical evidence in prostate cancer and DTC; comparatively limited evidence in NETs, based mainly on clinicopathological associations and mechanistic studies	[38,47,49,71,73,159]
Epigenetic reprogramming	Epigenetic stabilization of resistant transcriptional states and loss of endocrine responsiveness	Breast: DNA methylation and histone alterations affecting ER-associated programs; Prostate: epigenetic reprogramming accompanying lineage plasticity; DTC: silencing of NIS and other thyroid differentiation genes; Endometrial: epigenetic alterations associated with loss of hormone receptor responsiveness	Breast cancer; prostate cancer; DTC; endometrial cancers	Substantial mechanistic and preclinical evidence; limited clinical validation of causal and therapeutically reversible epigenetic drivers; inconsistent clinical results from epigenetic intervention studies	[21,29,38,49,52,59,165,166]
Pharmacokinetic and functional treatment failure	Pharmacokinetic, hormonal-control, and monitoring-related treatment failure distinct from receptor remodeling or bypass signaling	ACC: inadequate or variable mitotane exposure, clinically relevant drug interactions, incomplete control of hormone excess, and limitations in treatment monitoring	ACC	Substantial clinical and pharmacokinetic evidence in ACC; limited validated molecular biomarkers for predicting mitotane sensitivity or treatment failure	[64,65,66,67,68,69,70]

Abbreviations: ACC, adrenocortical carcinoma; AKT, protein kinase B; AR, androgen receptor; AR-V7, androgen receptor splice variant 7; DTC, differentiated thyroid cancer; EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NEPC, neuroendocrine prostate cancer; NETs, neuroendocrine tumors; NIS, sodium/iodide symporter; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; SSA, somatostatin analog; SSTR, somatostatin receptor.

DISCOVERY MEDICINE 2001 DM

hormone-related symptoms despite SSA therapy and radiological disease progression during treatment [71]. These patterns of treatment failure may reflect both tumor heterogeneity and adaptive changes during therapy rather than a single uniform mechanism [73,74]. Reduced or heterogeneous SSTR expression, particularly SSTR2 expression, together with receptor internalization or desensitization, has been implicated in reduced responsiveness to SSAs [74,78]. These changes may diminish both the hormone-suppressive and antiproliferative effects of SSA therapy. In addition, persistent activation of the PI3K/AKT/mTOR or MAPK pathways has been proposed as a potential bypass mechanism that may sustain tumor growth despite SSA therapy [74,79]. However, much of the supporting evidence remains mechanistic or preclinical. Tumor grade, differentiation status, and the Ki-67 proliferation index are also clinically relevant to SSA responsiveness. Higher Ki-67 and loss of differentiation are associated with more aggressive tumor biology and may be accompanied by reduced or less durable responsiveness to SSA therapy [71,73,159]. Clinically, subsequent management should be guided by the pattern of treatment failure. When hormone-related symptoms persist despite standard-dose SSA therapy, dose escalation or shortening of the administration interval may be considered, although the supporting evidence remains limited and heterogeneous [71,80]. In contrast, radiological disease progression generally requires reassessment of tumor grade, SSTR expression, tumor burden, and the overall pattern of progression, with consideration of antitumor strategies such as PRRT or molecularly targeted therapy [71,75,81]. In patients with progressive SSTR-positive midgut NETs, the phase III NETTER-1 trial demonstrated that PRRT with ^{177}Lu-DOTATATE significantly prolonged PFS compared with high-dose long-acting octreotide, providing randomized clinical trial support for PRRT in this setting [81]. Pasireotide has also been evaluated in patients with inadequate symptom control, although its role in this setting remains less well established [77,78]. Thus, these strategies should not be considered universally interchangeable, and treatment selection should remain individualized according to the biological and clinical characteristics of the tumor [71,75]. Accordingly, endocrine treatment failure should be viewed as a decision point for reassessment and modification of the therapeutic strategy rather than as an automatic indication for treatment discontinuation.

Although the specific manifestations of endocrine resistance and other forms of treatment failure differ across cancer types, cross-tumor comparison reveals several recurrent patterns of adaptation to endocrine-directed therapeutic pressure. Across endocrine-related cancers, treatment failure may arise through remodeling or loss of the endocrine-associated function on which treatment depends, or through compensatory activation of alternative survival signaling pathways. These changes manifest differently according to tumor context, including alterations in ER signaling in breast cancer, AR reactivation or lineage plasticity in prostate cancer, loss of NIS-dependent iodide handling and dedifferentiation in DTC, altered ER/PR dependence in selected ovarian and endometrial cancers, and reduced or heterogeneous SSTR expression in NETs. Across several of these cancers, PI3K/AKT/mTOR and MAPK signaling recur as bypass pathways, whereas changes in differentiation state and epigenetic regulation can further stabilize reduced therapeutic responsiveness. ACC represents a distinct pattern in which treatment failure may additionally reflect inadequate mitotane exposure, incomplete control of hormone excess, drug interactions, or assay-related apparent resistance. Thus, the commonality across endocrine-related cancers lies less in a single universal molecular alteration than in recurrent adaptive routes through which tumors escape endocrine-directed therapeutic pressure. At the same time, the molecular determinants, clinically informative biomarkers, and appropriate therapeutic interventions remain strongly tumor specific. Both the shared adaptive themes and their tumor-specific manifestations are summarized for each cancer type (Table 2, Ref. [3,19,21,23,24,25,26,27,29,34,35,36,38,40,41,42,43,44,45,46,47,49,52,55,59,60,61,62,64,65,66,67,68,69,70,71,73,74,79,124,132,139,159,165,166]). These patterns can be further conceptualized as an iterative process in which endocrine-directed treatment generates therapeutic pressure, followed by an adaptive response that necessitates reassessment before subsequent treatment selection (Fig. 3).

Strategies to Overcome Endocrine Resistance and Treatment Failure in Human Endocrine-Related Cancers

This section examines mechanism-based and biomarker-guided strategies directed at endocrine resistance and other forms of treatment failure, classified according to their mechanisms of action (Table 3, Ref. [29,30,31,32,33,34,35,36,51,53,54,60,61,62,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186]). Specifically, the available evidence and its limitations are discussed, with a focus on cell-cycle pathway targeting, PI3K/AKT/mTOR pathway targeting, MAPK pathway targeting and redifferentiation, epigenetic modulation, immunotherapy, and aberrant GPCR targeting. Within this framework, however, no single strategy applies uniformly across endocrine-related cancers; therefore, each strategy is considered in relation to the tumor types in which it has been evaluated and the strength of the available evidence.

Cell-Cycle Pathway Targeting

Continued proliferation during endocrine treatment may reflect escape from cell-cycle control. Therefore, tar-

Table 3. Mechanism-based strategies to address endocrine resistance and treatment failure.

Strategy	Treatment-failure axis	Representative approach	Main context	Clinical positioning/ evidence level	Key evidence and limitations	References
Cell-cycle pathway targeting	Cell-cycle escape and compensatory survival signaling	CDK4/6i + ET	HR-positive/HER2-negative breast cancer; metastatic CRPC	Established in HR-positive breast cancer with randomized phase III evidence; not established in prostate cancer	Subsequent resistance through *RB1* loss, cyclin E–CDK2 activation, or compensatory signaling; no benefit demonstrated in metastatic CRPC	[30,31,32,33,167,168]
PI3K/AKT/mTOR pathway targeting	PI3K/AKT/mTOR-mediated bypass survival signaling	Alpelisib + fulvestrant; capivasertib + fulvestrant; ipatasertib + abiraterone; everolimus ± ET	HR-positive/HER2-negative breast cancer; *PTEN*-loss metastatic CRPC; recurrent endometrial cancer; NETs	Established in selected breast cancer settings, including biomarker-defined populations; randomized phase III evidence restricted to a biomarker-defined subgroup in prostate cancer; phase II clinical evidence in recurrent endometrial cancer; randomized phase III evidence in NETs	Benefit depends on molecular and tumor context; predictive biomarkers and treatment-related toxicity remain relevant limitations; in NETs, everolimus activity reflects antitumor effect rather than reversal of endocrine resistance	[34,35,36,60,61,169,170]
MAPK pathway targeting and redifferentiation	MAPK-driven bypass signaling and loss of differentiation	MEK or *BRAF* inhibition for redifferentiation; trametinib	RAI-refractory DTC; recurrent LGSOC	Early clinical evidence in selected RAI-refractory DTC; randomized phase II/III evidence for trametinib in recurrent LGSOC	Variable restoration and durability of RAI uptake in DTC; trametinib evidence does not establish an endocrine–MAPK combination in LGSOC	[51,53,54,62]

Table 3. Continued.

Strategy	Treatment-failure axis	Representative approach	Main context	Clinical positioning/ evidence level	Key evidence and limitations	References
Epigenetic modulation	DNA methylation; histone/ chromatin remodeling; polycomb-mediated lineage plasticity	DNMTi + HDACi; HDACi + ET; EZH2i + AR pathway inhibitor	HR-positive breast cancer; metastatic CRPC	Investigational; phase III benefit not demonstrated in breast cancer; phase III evaluation ongoing in prostate cancer	Limited and inconsistent clinical efficacy in breast cancer despite mechanistic rationale; prostate cancer data remain early phase pending randomized confirmation	[29,165,166,171,172]
Immunotherapy	Immune evasion; suppressive TME	PD-1i + ET; PD-1i ± CTLA-4i or antiangiogenic therapy	HR-positive breast cancer; metastatic CRPC; ACC	Investigational; phase II and small phase Ib/II evidence in breast cancer; negative phase III result in prostate cancer; single-arm phase II activity in ACC	Modest activity in breast cancer; no benefit when added to AR pathway inhibition; higher response rates in ACC with combination regimens, but no validated predictive biomarker	[173,174,175,176,177,178,179]
Aberrant GPCR targeting	GPER signaling; dysregulated GIPR/AVPR1A	GPER antagonists/ inverse agonists; GIPR radioligands	Breast cancer (GPER); NETs and other endocrine tumors (GIPR, AVPR1A)	Preclinical or exploratory in all tumor types; no clinically established target	Direct experimental evidence is strongest for GPER in breast cancer; GIPR and AVPR1A are not established targets of endocrine resistance	[180,181,182,183,184,185,186]

Abbreviations: ACC, adrenocortical carcinoma; AKT, protein kinase B; AR, androgen receptor; AVPR1A, arginine vasopressin receptor 1A; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CDK2, cyclin-dependent kinase 2; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CRPC, castration-resistant prostate cancer; CTLA-4i, cytotoxic T-lymphocyte-associated protein 4 inhibitor; DNMTi, DNA methyltransferase inhibitor; DTC, differentiated thyroid cancer; ET, endocrine therapy; EZH2i, enhancer of zeste homolog 2 inhibitor; GIPR, glucose-dependent insulinotropic polypeptide receptor; GPCR, G protein-coupled receptor; GPER, G protein-coupled estrogen receptor; HDACi, histone deacetylase inhibitor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LGSOC, low-grade serous ovarian carcinoma; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; NETs, neuroendocrine tumors; PD-1i, programmed cell death protein 1 inhibitor; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RAI, radioactive iodine; RB1, RB transcriptional corepressor 1; TME, tumor microenvironment.

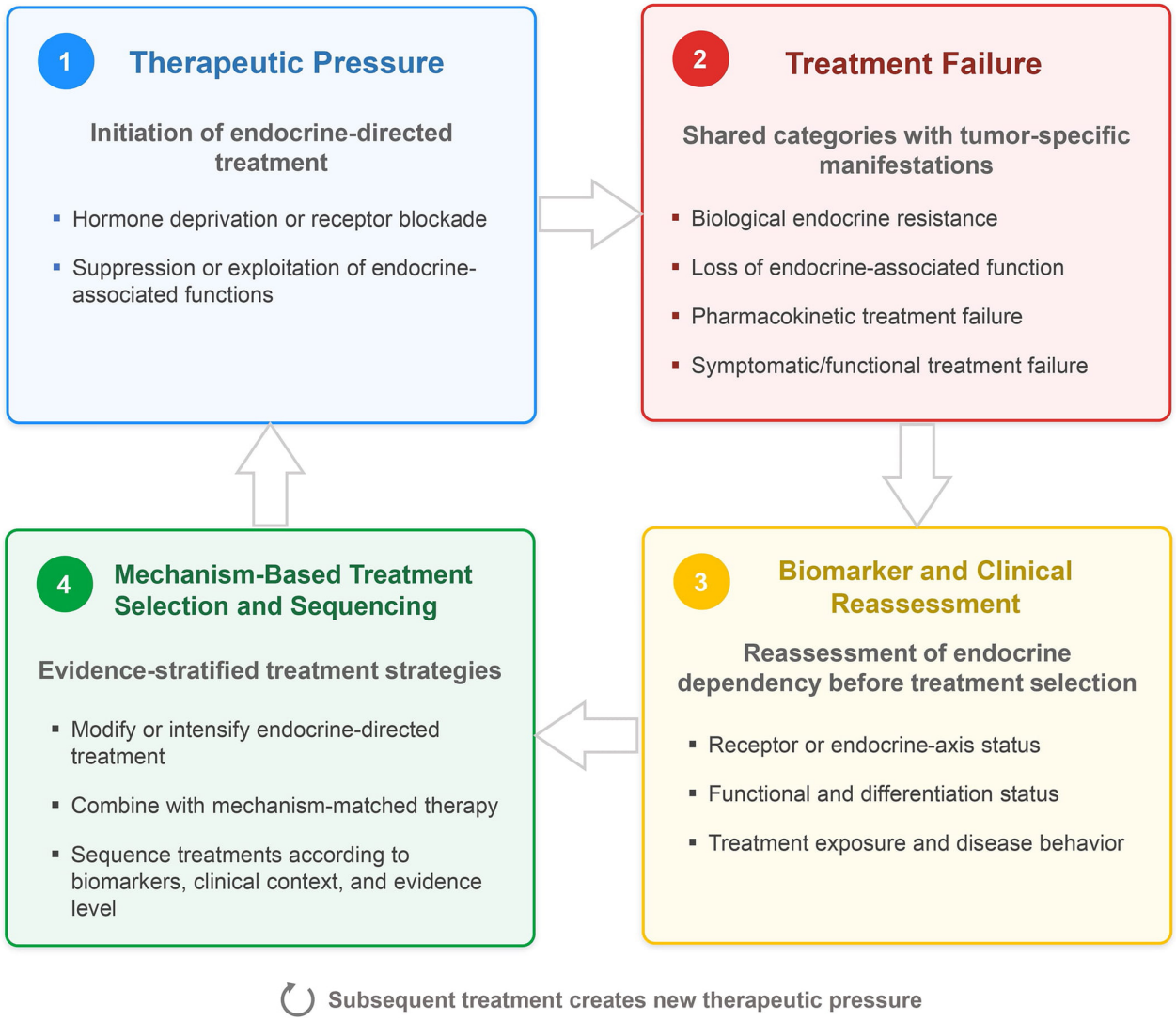


Fig. 3. Iterative framework of endocrine treatment failure and mechanism-based treatment selection. Endocrine-directed treatment imposes therapeutic pressure by suppressing hormone-dependent signaling or exploiting endocrine-associated tumor functions. Treatment failure may subsequently manifest as biological endocrine resistance, loss of endocrine-associated function, pharmacokinetic treatment failure, or symptomatic/functional treatment failure, depending on the tumor type and therapeutic context. When treatment failure is recognized, receptor or endocrine-axis status, functional and differentiation state, treatment exposure, and disease behavior should be reassessed. Subsequent treatment can then be selected and sequenced according to the dominant underlying mechanism, relevant biomarkers, clinical context, and the strength of available evidence. Because each subsequent treatment generates new therapeutic pressure, this process may recur during disease progression. This figure was created by the authors using Microsoft PowerPoint (Version 2609, Microsoft Corporation, Redmond, WA, USA), with Adobe Photoshop CC (Version 19.0, Adobe Inc., San Jose, CA, USA) used only for final image processing and resolution enhancement.

geting the cyclin D–CDK4/6–retinoblastoma protein (RB) axis alongside endocrine signaling can restore cell-cycle arrest in tumors that remain endocrine-dependent. In hormone receptor (HR)-positive/HER2-negative advanced breast cancer, the addition of CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) to endocrine therapy has consistently improved PFS and, with an overall survival (OS) benefit demonstrated in several clinical settings, providing

substantial clinical evidence for this combination strategy [30,31,32,167]. CDK4/6 inhibitors prevent RB phosphorylation and E2F-mediated cell-cycle progression, thereby maintaining cancer cells in the G1 phase and enhancing the antiproliferative effects of endocrine therapy. However, resistance may subsequently develop through mechanisms including *RB1* loss, activation of the cyclin E–CDK2 axis, and compensatory activation of growth factor signaling pathways [33]. A comparable strategy has also been examined in prostate cancer. In the randomized phase III CYCLONE 2 trial, the addition of abemaciclib to abiraterone in metastatic CRPC did not improve radiographic PFS (hazard ratio 0.83; 95% confidence interval 0.62–1.11) [168]. This contrast indicates that cell-cycle dependency during endocrine-directed treatment is not uniform across endocrine-related cancers, and that the benefit of CDK4/6 inhibition remains confined to settings in which such dependency has been demonstrated.

PI3K/AKT/mTOR Pathway Targeting

Endocrine resistance is frequently associated with the activation of the PI3K/AKT/mTOR signaling pathway, providing a rationale for pathway-directed treatment in resistant disease. In HR-positive/HER2-negative advanced breast cancer, several strategies targeting different components of this pathway are supported by randomized phase III clinical trials. The PI3K inhibitor alpelisib combined with fulvestrant prolonged PFS in patients with *PIK3CA*-mutated disease [34]. Similarly, the AKT inhibitor capivasertib combined with fulvestrant prolonged PFS after progression on previous endocrine therapy, with a pronounced benefit in tumors harboring alterations in *PIK3CA*, *AKT1*, or *PTEN* [35]. Everolimus, an allosteric mTOR complex 1 inhibitor, combined with exemestane also improved PFS after progression during or following previous endocrine therapy, although a significant OS benefit was not demonstrated in the final analysis [36]. The same pathway has been targeted in prostate cancer, where *PTEN* loss and consequent AKT activation can sustain tumor growth during androgen receptor–directed treatment. In the phase III IPATential150 trial, the AKT inhibitor ipatasertib combined with abiraterone improved radiographic PFS in patients with *PTEN*-loss metastatic CRPC. However, in the final analysis, no OS benefit was observed in either the immunohistochemistry-defined *PTEN*-loss population or the intention-to-treat population. Exploratory next-generation sequencing analyses identified a potential benefit in tumors harboring alterations in *PIK3CA*, *AKT1*, or *PTEN*, with a median OS of 37.1 versus 29.2 months, although this finding requires prospective validation [169]. A similar pathway-directed approach has also been examined in recurrent endometrial cancer. Phase II studies of everolimus combined with letrozole have shown antitumor activity, although the available clinical evidence remains more limited than the evidence for breast cancer [60,61]. In NETs, everolimus prolonged PFS in patients with advanced, progressive, and well-differentiated non-functional tumors [170]. However, this finding reflects the antitumor activity of mTOR inhibition and does not demonstrate that everolimus directly reverses resistance to endocrine therapy. Overall, the clinical relevance of PI3K/AKT/mTOR pathway inhibition varies according to tumor type, prior treatment, and molecular context, including alterations in *PIK3CA*, *AKT1*, and *PTEN* [34,35,169]. Treatment-related toxicities, including hyperglycemia, rash, and stomatitis, should also be considered with the use of these agents [34,35,36].

MAPK Pathway Targeting and Redifferentiation

Inhibition of the MAPK pathway serves different therapeutic purposes in selected endocrine-related cancers. In RAI-refractory DTC, short-term inhibition of MEK with selumetinib or of mutant *BRAF* with vemurafenib has restored RAI uptake in selected patients, providing a basis for MAPK-directed redifferentiation. However, the degree and durability of restored RAI uptake vary among patients and according to the underlying molecular alterations [51,53,54]. MAPK-directed treatment has also been evaluated in recurrent LGSOC. In the randomized phase II/III GOG 281/LOGS trial, trametinib improved PFS compared with standard-of-care treatment [62]. This result supports MAPK inhibition as an antitumor strategy for recurrent LGSOC; however, it does not establish a combined endocrine–MAPK approach. Thus, MAPK-directed treatment remains a context-dependent strategy whose clinical value differs according to tumor type and therapeutic purpose.

Epigenetic Modulation

Epigenetic remodeling can support endocrine resistance by stabilizing transcriptional states that no longer depend on normal hormone receptor signaling. DNA methylation, altered histone acetylation, and changes in chromatin accessibility can suppress receptor-associated genes or redirect transcription toward survival pathways. In ER-positive breast cancer, these changes have been associated with disruption of *ESR1*-centered transcription, as well as broader reorganization of enhancer activity and cell-state identity [29]. This biological plasticity provides a rationale for testing DNA methyltransferase and HDAC inhibitors as agents that may restore endocrine sensitivity. Despite this rationale, their clinical performance has been inconsistent. A phase II study of 5-azacitidine plus entinostat showed that combined epigenetic treatment was feasible but produced limited antitumor activity in advanced breast cancer [165]. In the subsequent phase III E2112 trial, the addition of entinostat to exemestane did not significantly improve PFS or OS in patients with HR-positive advanced breast cancer [166]. A distinct epigenetic strategy has been examined in prostate cancer, where enhancer of zeste homolog 2

(EZH2)-mediated polycomb repression contributes to lineage plasticity and loss of androgen receptor dependence [172]. The EZH2 inhibitor mevrometostat, combined with enzalutamide, is currently being evaluated against enzalutamide alone in two phase III trials in metastatic CRPC [171]. Taken together, these findings indicate that epigenetic modulation remains an investigational strategy rather than an established treatment for endocrine resistance in both settings. Its future clinical value will likely depend on identifying tumors in which a specific, reversible epigenetic state is directly responsible for the loss of endocrine responsiveness.

Immunotherapy

Endocrine resistance and other forms of treatment failure may also develop within an immunosuppressive tumor microenvironment. Hormone receptor signaling can influence cytokine production, immune-cell recruitment, antigen presentation, and immune checkpoint expression, and these interactions may contribute to immune evasion in endocrine-resistant tumors [173]. This interaction provides a biological rationale for combining endocrine therapy with programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitor therapy. However, clinical evidence does not yet support a broad claim of synergy. In a phase II study of pembrolizumab combined with an AI in metastatic HR-positive breast cancer, clinical activity was modest, and the regimen did not establish a new standard of care [174]. A later phase Ib/II study in premenopausal ER-positive/HER2-negative advanced breast cancer showed a signal of clinical activity with pembrolizumab, exemestane, and leuprolide; however, the study included only a small number of patients and requires confirmation in larger randomized trials [175]. A similar rationale has been examined in prostate cancer, where androgen deprivation can increase intratumoral immune infiltration [187]. In the randomized phase III KEYNOTE-641 trial, however, adding pembrolizumab to enzalutamide in chemotherapy-naive metastatic CRPC did not improve either radiographic PFS nor OS, and the trial was stopped for futility [176]. Immune checkpoint blockade has also been evaluated in ACC, independently of endocrine-directed treatment. In a phase II study, pembrolizumab monotherapy produced an objective response rate of 20%, although neither PD-L1 expression nor tumor-infiltrating lymphocyte score predicted the response [177]. Dual cytotoxic T-lymphocyte-associated protein 4 and PD-1 blockade with ipilimumab and nivolumab produced a confirmed objective response rate of 14% (3/21) in the DART/SWOG S1609 ACC cohort, whereas immune-related assessment yielded an immune objective response rate of 19% (4/21) and an immune clinical benefit rate of 33% (7/21) [178]. A higher objective response rate of approximately 50%, with a median PFS of 13.3 months, was subsequently reported when the PD-1 inhibitor camrelizumab was combined with the antiangiogenic agent apatinib [179]. However, this result derives from a separate single-arm study and cannot be compared directly with the preceding trials. Accordingly, immune checkpoint blockade remains an investigational, context-dependent strategy rather than an established approach for overcoming endocrine resistance or other forms of treatment failure, either in combination with endocrine therapy or as an independent treatment. Potential determinants of response include immune-cell infiltration, tumor mutational features, prior treatment, and the extent of continued hormone receptor dependence, although no biomarker has yet been validated for this purpose [173,174,175,176,177,178,179].

Aberrant GPCR Targeting

Aberrant GPCR signaling may provide an alternative route through which tumor cells bypass conventional nuclear hormone receptor blockade. Notably, the GnRH receptor, the most clinically established GPCR target in this field, functions as a component of primary endocrine therapy in prostate cancer rather than as a means of overcoming treatment failure [103,104]. The receptors considered here are therefore those implicated specifically as candidate routes of escape from endocrine-directed treatment. Among the GPCRs examined in endocrine-related cancers, the G protein-coupled estrogen receptor (GPER) has the most direct mechanistic connection to endocrine resistance. GPER can activate EGFR/extracellular signal-regulated kinase (ERK), PI3K/AKT, and stromal signaling and has been implicated in tamoxifen resistance and epithelial–mesenchymal transition in breast cancer models [180,181,182]. Continuous exposure of breast cancer cells to tamoxifen has also been shown to increase GPER expression and GPER-dependent proliferative signaling, providing additional experimental support for its involvement in acquired endocrine resistance [183]. By contrast, arginine vasopressin receptor 1A (AVPR1A) has emerged as a candidate target based on receptor-expression profiling and bioinformatic analyses of endocrine tumors [184]. Abnormal expression alone does not establish a direct causal role for AVPR1A in endocrine resistance. In the case of the glucose-dependent insulinotropic polypeptide receptor (GIPR), receptor-targeting studies in NETs have largely focused on molecular imaging and theranostic development rather than on reversing endocrine resistance [185]. Therefore, GIPR and AVPR1A remain exploratory candidates rather than validated therapeutic targets for overcoming endocrine resistance. Compared with these receptors, GPER has more direct experimental support for a role in endocrine resistance, particularly in breast cancer models [181,183]. Experimental studies of GPER-selective antagonists and inverse agonists have suggested potential antiproliferative effects; however, these approaches remain at an early preclinical stage and have not yet translated into clinically established therapies [182,186].

Overall, the strategies discussed in this section vary substantially in their degree of clinical validation across mechanisms and tumor types. Cell-cycle and pathway-directed approaches have the strongest clinical support in selected breast cancer settings [30,31,34,35,36,167], whereas the same mechanisms have yielded negative or biomarker-restricted results in prostate cancer [168,169]. Epigenetic and immune-based strategies remain under investigation across tumor types [165,166,171,174,175,176,177,178,179], whereas GPCR-directed approaches are supported primarily by preclinical or exploratory evidence [180,181,182,183,184,185,186]. These differences emphasize the need to select and sequence therapies according to the dominant underlying mechanism, molecular context, and available biomarkers rather than applying a uniform strategy across endocrine-related cancers.

Discussion

Endocrine-directed therapies are clinically important across endocrine-related cancers, but the biological basis of therapeutic response and treatment failure differs substantially among tumor types. Nevertheless, cross-tumor comparison reveals several shared adaptive patterns, although their underlying mechanisms and clinical relevance remain tumor-specific. Accordingly, biological endocrine resistance should be distinguished from loss of endocrine-associated function, pharmacokinetic treatment failure, and symptomatic/functional treatment failure when interpreting therapeutic response and selecting subsequent treatments. A second major issue is that a strong biological rationale does not necessarily indicate clinical readiness. Randomized clinical evidence supports several resistance-directed approaches in selected HR-positive breast cancer settings, including CDK4/6 inhibitor–endocrine combinations and therapies targeting the PI3K/AKT/mTOR pathway [30,31,34,35,36,167]. However, these findings have not been consistently reproduced in other hormone-dependent settings: cell-cycle inhibition did not improve outcomes in metastatic castration-resistant prostate cancer, and AKT inhibition benefited only a biomarker-defined subgroup [168,169]. Randomized phase III trials also support the use of PRRT in appropriately selected patients with progressive SSTR-positive NETs [81]. By contrast, MAPK-directed redifferentiation in RAI-refractory DTC remains dependent on molecular context, with variable restoration of RAI uptake [51,53,54], whereas endocrine-targeted combinations in gynecologic cancers remain supported mainly by phase II or context-specific evidence [60,61]. Epigenetic and immune-based approaches have not yet established consistent clinical benefit in endocrine-resistant disease [165,166,174,175], although both have entered randomized or single-arm evaluations beyond breast cancer [171,176,177,178,179], and most GPCR-directed strategies remain primarily preclinical or exploratory [180,181,182,183,184,185,186]. This uneven evidence base limits the extent to which mechanistically attractive strategies can be generalized across endocrine-related cancers. Clinical translation is further complicated by molecular and functional heterogeneity. A single biomarker measured at a single time point may not fully represent the dominant mechanism of resistance or treatment failure, particularly when tumors retain partial endocrine dependence while simultaneously activating bypass signaling or undergoing changes in differentiation. The predictive value of receptor expression also varies according to the tumor context [55,58,71,73,128,129]. Validated biomarkers remain limited in several clinically important settings, including mitotane sensitivity in ACC [69,70] and the selection of alternative strategies after SSA failure in NETs [71,75]. Treatment-related toxicity, pharmacokinetic variability, and uncertainty regarding the optimal sequence of endocrine and targeted therapies pose additional barriers to long-term implementation [34,35,36,60,61,69,70,75].

Conclusion

Collectively, these findings argue against a uniform approach to endocrine resistance and other forms of treatment failure. A more useful framework would be to determine which endocrine dependency remains biologically relevant, identify the dominant mechanism through which the tumor escapes therapeutic pressure, and then select a treatment whose level of clinical evidence is appropriate for the molecular and clinical context. Future studies should prioritize biomarker-guided, longitudinal reassessment of resistance and treatment failure, together with prospective evaluation of treatment sequencing and combination strategies. Such an approach may allow endocrine resistance and treatment failure to be viewed not as fixed endpoints but as evolving states that can inform subsequent treatment selection.

Availability of Data and Materials

Not applicable.

Author Contributions

SP: Writing-original draft, literature search, data collection, investigation, visualization. JHO: Conceptualization, writing-review and editing, supervision, funding acquisition, project administration. Both authors gave final approval of the version to be published. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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