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HORMONAL THERAPY IN HIGH-GRADE SEROUS OVARIAN CARCINOMA: A REVIEW OF CURRENT EVIDENCE

Agnieszka Zaręba *(Corresponding Author, Email: zarebagnieszka@gmail.com)*
Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-9890-8310

Dawid Juszkiewicz
Medical University of Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0003-3392-8024

Krzysztof Kiełczewski
Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0009-6159-4598

Barbara Fetner
Medical University of Silesia, Faculty of Medical Sciences in Zabrze, Zabrze, Poland
ORCID ID: 0009-0006-9413-9901

Magdalena Dłużewska
Healthcare Center in Cieszyn, Cieszyn, Poland
ORCID ID: 0009-0006-5006-9112

Zuzanna Gebert
Międzyleski Specialist Hospital, Warsaw, Poland
ORCID ID: 0009-0000-6169-5799

Ivanna Ilkiv
Nowodworskie Medical Center, Nowy Dwór Mazowiecki, Poland
ORCID ID: 0009-0008-4223-3976

Agata Kucharska
Rey-Dent Holistic Dentistry Practice, Warsaw, Poland
ORCID ID: 0009-0009-9840-4911

Konrad Adler
Czerniakowski Hospital, Warsaw, Poland
ORCID ID: 0009-0006-9483-7072

Patrycja Stanowska
Silesian Academy, Faculty of Medical Sciences in Zabrze, Zabrze, Poland
ORCID ID: 0009-0003-9100-1948

ABSTRACT

Ovarian cancer remains one of the leading causes of cancer-related mortality among women worldwide. The most common histological subtype is high-grade serous ovarian carcinoma (HGSOC), which accounts for approximately 70-80% of epithelial cases and is characterized by profound genomic instability, nearly universal TP53 mutations, and a high propensity for recurrence. While the standard of care - comprising maximal cytoreductive surgery, platinum-based chemotherapy, and maintenance with poly (ADP-ribose) polymerase PARP inhibitors or anti-angiogenic agents- has improved outcomes, long-term prognosis for advanced disease remains poor. Hormonal therapy (HT) has emerged as a clinically relevant treatment option for selected patients with recurrent ovarian cancer, particularly in oestrogen receptor (ER)- positive tumours. Agents such as Tamoxifen and aromatase inhibitors (AIs), including Letrozole, Anastrozole, and Exemestane, demonstrate reproducible clinical benefit rates of 25-45%, primarily through disease stabilisation. Recent real-world cohort data (2025) and ongoing prospective trials- notably the phase III ENGOT-ov54/Swiss-GO-2/MATAO trial (NCT04111978) - represent critical steps towards establishing evidence-based endocrine therapy in HGSOC. This review evaluates the biological rationale for targeting the ER and progesterone receptor (PR) pathways, critically appraises current and emerging clinical evidence, discusses combination strategies with CDK4/6 inhibitors, PI3K/mTOR inhibitors, and PARP inhibitors, and highlights the unmet need for biomarker-driven patient selection.

KEYWORDS

High-Grade Serous Ovarian Carcinoma, Hormonal Therapy, Oestrogen Receptor, Aromatase Inhibitors, Tamoxifen, MATAO Trial, CDK4/6 Inhibitors, Letrazole

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1. Introduction

Ovarian cancer constitutes one of the most lethal gynaecological malignancies globally, ranking as the eighth most common cause of cancer-related death among women [1]. According to GLOBOCAN 2020, approximately 314,000 new cases and over 207,000 deaths were recorded worldwide [1]. The high case-fatality ratio reflects the overwhelmingly late-stage presentation at diagnosis, attributable to the non-specific nature of presenting symptoms and the current absence of validated population–level screening tools [2].

High-grade serous ovarian carcinoma (HGSOC) is the dominant histological subtype, comprising 70-80% of epithelial ovarian cancer (EOS) [3]. It is defined by near-universal somatic or germline TP53 mutations, frequent homologous recombination deficiency (HRD), high chromosomal instability, and a clinical pattern of initial platinum sensitivity followed by inevitable recurrence in the majority of patients [4]. Current first-line management centres on maximal cytoreductive surgery combined with platinum-taxane chemotherapy and, where appropriate, maintenance with PARP inhibitors (olaparib, niraparib) or bevacizumab [5,6]. A 2025 systematic reviev and meta-analysis published in JAMA Network Open cnfirmed that first-line PARP inhibitor maintenance improves progression-free survival across multiple HGSOC subgroups, but importantly identified no statistically significant overall survival benefit in any molecular subgroup and advocated for a precision-medicine approach to treatment selection [7].

Against this background of therapeutic advancement, yet persistent, there has been renewed interest in endocrine strategies for HGSOC. Oestrogen receptor alpha (ERα) is expressed in 60-80% of ~HGSOC tumors [8,9], and progesterone receptor (PR) in approximately 30-40% [10]. Multiple phase II trials and retrospective real-world studies have confirmed reproducible clinical benefit rates (CBR) of 25-45% for tamoxifen and aromatase inhibitors (AIs) in recurrent HGSOC [11,12]. Critically, a 2025 real-world retrospective cohort study from the University Women's Hospital Basel which directly informed the onoing MATAO phase III trial, demonstrated that maintenance letrozole was associated wiyh a statistically significant improvement in overall

survival in the subgroup of HGSOC patients with no residual disease after primary surgery (median OS 114 months vs 49,9 months, p= 0, 006) [13]. These data represent the most contemporary and clinically compelling evidence to date for letrozole in the early maintenance setting of HGSOC.

This review critically evaluates the biological rationale for hormonal targeting in HGSOC, synthesises the current and most recent clinical evidence for individual agents, discusses predictive biomarkers, and outlines combination strategies and future trial priorities.

2. Biological Rationale for Hormonal Therapy in HGSOC

2.1. Oestrogen Signalling and Carcinogenesis

Oestrogen mediates its tumour-promoting effects primarily through oestrogen receptor alpha (ERα, encoded by ESR1), which drives transcriptional programmes governing cel cycle progression, anti-apoptotic signalling, and epithelial-mesenchymal transition (EMT) [14, 15]. In HGSOC, ERα overexpression activates downstream PI3K/AKT/mTOR and MAPK signalling cascades, promoting both proliferation and resistance to cytotoxic therapy [16, 17]. ERα positivity is detected in over 80% of HGSOC cases using immunohistochemistry (IHC), a prevalence comparable to that observed in breast cancer – a finding directly supported by TCGA PANCAN dataset analyses demonstrating similar ESR1 expression level across both tumour types [18,19].

ERβ (encoded by *ESR2*) generally exerts a tumour-suppressive role by antagonising ERα- mediated proliferation and has been associated with a more favourable prognosis in some ovarian cancer cohorts [20]. The G protein-coupled oestrogen receptor (GPER/GPR30) has emerged as an additional oestrogen-sensing mechanism in ovarian cancer cells, mediating both tumour-suppressive and tumour-promoting actions depending on cellular context, and representing a potential therapeutic target under active investigation [21].

Epidemiological evidence reinforce the biological link between oestrogen exposure and ovarian cancer risk. A 2024 multicenter real-world study confirmed that ERα expression is the defining molecular feature of endocrine-responsive hormone receptors [12]. Furthermore, hormone receptor co-expression profiling – incorporating androgen receptor (AR), ERα, and PR – has demonstrated improved predictive accuracy for survival and platinum sensitivity in HGSOC compared to any single receptor marker alone [22].

2.2. Progesterone Receptor Expression

Progesterone receptor (PR) expression confers antiproliferative and pro-apoptotic signalling in HGSOC, counterbalancing ERα- mediated miotogenic effects. A large consortium study examining over 2,900 patients demonstrated that high PR expression was independently associated with improved disease-specific survival in HGSOC ((HR 0.71; 95% CI 0.55–0.91; p = 0.008), while high ERα expression alone did not confer a survival benefit [10]. This prognostic asymmetry suggests that ER-toPR expression ratio, rather than individual receptor positivity, may be a more clinically informative biomarker for endocrine responsiveness.

A paired analysis of primary and recurrent HGSOC tissue demonstrated that while ERα expression remained stable between primary and relapsed disease, Pr expression was significantly lower in platinum-sensitive recurrent tumours, suggesting receptor-level plasticity during disease evolution that has important implications for serial biomarker assessment and the timing of endocrine therapy initiation [10].

2.3. Intratumoral Aromatase Activity

Aromatase (CYP19A1) expression within ovarian cancer tissue and the surrounding tumour-associated stroma enables local oestrogen biosynthesis independent of circulating ovarian or adrenal oestrogen [23]. In postmenopausal women – who constitute the majority of HGSOC patients – peripheral aromatisation in adipose, skin, liver, and cardiac tissue sustains tissue-level oestrogenic stimulation despite cessation of ovarian function [13]. Elevated intratumoral aromatase activity sustains oestrogenic receptor occupancy and downstream signalling, providing a robus mechanistic basis for aromatase inhibitor therapy in HGSOC regardless of menopausal status.

A 2025 preclinical and translational study characterising local androgen and 11-oxyandrogen metabolism in HGSOC identified intratumoral steroidogenesis as a novel prognostic and therapeutic axis, highlighting that the complexity of intratumoral sex steroid metabolism in a HGSOC extends beyond classical oestrogen pathways and may include androgenic contributions through CYP11B1 and HSD11B1 enzymatic activity [24]. These findings raise the possibility that targeting multiple steroidogenic enzymes simultaneously may be required for effective endocrine blockade in certain HGSOC subtypes.

2.4. Androgen Receptor Signalling

The androgen receptor (AR) is expressed in up to 80% of HGSOC tumours and represents an increasingly recognised hormonal target [22]. AR expression has been positively correlated with improved progression-free survival, overall survival, and platinum sensitivity in independent HGSOC cohorts [22]. The functional interplay between AR, ERα, and PR within HGSOC cells – where AR activation may counteract ERα-mediated proliferation – adds complexity to the biology and therapeutic targeting of the hormonal axis in this disease.

A published case report of AR inhibition with bicalutamide in multiply relapsed HGSOC demonstrated prolonged disease control in an AR-positive, ER-positove tumor, providing preliminary proof-of-concept for AR-directed endocrine therapy as a subsequent line strategy preliminary proof-of-concept for AR-directed endocrine therapy as a subsequent line strategy in selected patients [25]. The 2025 study by Marolt et al. Further characterised the roles of 11-oxygenated androgens as active intratumoral androgens in HGSOC, identifying specific steroid-metabolising enzymes as potential therapeutic targets [24].

3. Hormonal Agents: Mechanisms of Action

3.1. Tamoxifen

Tamoxifen is a selective oestrogen receptor modulator (SERM) that competitively inhibits ERα, blocking oestrogen-stimulated transcription of target genes, including cyclin D1, thereby inducing G1 cell cycle arrest [26]. In HGSOC models, tamoxifen downregulates ERα-mediated transcriptional programmes, reduces VEGF secretion, and exhibits autophagy-inducing properties through mechanisms partially independent of ER – properties that may sensitise HGSOC cells to platinum-based chemotherapy [27]. Tamoxifen also demonstrates partial agonist activity in the uterus and bone, determined by the tissue-specific co-regulatory milieu, conferring a complex safety profile that requires monitoring with long-term use.

Mechanistically, tamoxifen-mediated reduction in BRCA1 expression and homologous recombination (HR) repair capacity provides preclinical support for contextual synthetic lethality when combined with PARP inhibitors in BRCA-wildtype HGSOC – a strategy currently being explored in ongoing clinical trials [28].

3.2. Aromatase Inhibitors

Third-generation aromatase inhibitors – the non-steroidal agents letrozole and anastrozole, and the steroidal inactivator exemestane – suppress oestrogen biosynthesis by inhibiting CYP19A1 with high potency. In postmenopausal patients, letrozole at 2,5mg daily reduces circulating oestradiol levels by up to 95%, effectively depending both systemic and – through inhibition of intratumoral aromatase – local oestrogenic stimulation of HGSOC cells [18, 29]. Letrozole and anastrozole act as reversible competitive inhibitors, while exemestane causes irreversible inactivation through pseudosubstrate binding, conferring non-cross-resistance between subclasses and supporting sequential use analogous to established breast cancer strategies.

At the cellular level, AI treatment reduces proliferative indices in HGSOC cell lines and attenuates activation of the downstream MAPK and PI3K/AKT signalling cascades. ESR1 gene expression in HGSOC is comparable to that in breast cancer, providing molecular-level justification of transposing the AI maintenance strategy – well-established in breast oncology – to the HGSOC setting [13,18].

3.3. Fulvestrant and Other Agents

Fulvestrant, a selective oestrogen receptor degrader (SERD), is a pure ERα antagonist that lacks the partial agonist activity of tamoxifen and causes proteasomal degradation of the receptor, leading to complete ERα expression, and has been associated with response in case reports involving TFF1-positive tumours [21, 30]. Clinical data for fulvestrant specifically in HGSOC remain limited, but its mechanism – particularly its lack of agonist activity at the endometrium – may confer advantages over tamoxifen in long-term maintenance contexts.

Gonadotropin-releasing hormone (GnRH) analogues have also been investigated based on evidence of GnRH receptors expression in a subset of EOCs, though their role in HGSOC specifically remains limited by sparse clinical evidence. Progestins, including megestrol acetate and medroxyprogesterone acetate, have demonstrable PR-mediated antiproliferative effects, but their tolerability profile has limited clinical uptake in the modern era [31, 32].

4. Clinical Evidence for Hormonal Therapy in Recurrent HGSOC

4.1. Tamoxifen

Tamoxifen remains the most extensively studied hormonal agent in recurrent ovarian cancer. The seminal Gynecologic Oncology Group (GOG) phase II trial (GOG 0198), enrolling 105 patients with measurable recurrent EOC, reported an overall response rate (ORR) of 18% (10% CR, 8% PR) with an additional 38% achieving disease stabilisation. A subsequent ancillary analysis of the same cohort focusing on platinum-refractory patients (n = 102) demonstrated an ORR of 13% with a median response duration of 4.4 months [33]. Progesterone receptor-positive tumours appeared to show numerically greater benefit, though formal biomarker analyses were not pre-specified.

A retrospective series from the Royal Marsden Hospital examining 97 patients treated with tamoxifen (n=43) or letrozole (n=54) for relapsed HGSOC (91% high-grade serous histology) demonstrated an overall CBR of approximately 60% - 65% for tamoxifen and 56% for letrozole - in a heavily pre-treated population (median 3 prior lines, 60% platinum-resistant) [11]. Notably, letrozole-treated patients had a significantly longer duration of response, which the authors attributed to its mechanism of consistent oestrogen suppression versus tamoxifen's partial agonist activity. The Edinburgh Cancer Centre cohort, analysing 269 eligible HGSOC patients over a 25-year period, confirmed comparable response rates for letrozole (8% ORR, 41% CBR) and tamoxifen (11% ORR, 33% CBR), with high ER histoscore and longer treatment-free interval identified as significant predictors of benefit [34].

From a clinical practice standpoint, a 2024 multicenter French real-world study identified 19/81 patients (23,5%) as "long responders" to endocrine therapy (disease stable >6 months), with 84,2% of this subgroup having high-grade serous histology and 63,2% having received endocrine therapy in a maintenance setting [12]. These real-world data corroborate the phase II evidence and highlight that endocrine-sensitive HGSOC represents a biologically distinct indolent subgroup, even within the high-grade category.

4.2. Letrozole

A single-centre Greek phase II trial of letrozole 2,5mg daily in 27 ER-positive recurrent EOC patients reported an ORR of 15% and a CBR of 33% with a median time to progression of 5.6months [35]. The Edinburgh series confirmed letrozole as the most commonly used endocrine agent in HGSOC clinical practice (77% of 269 patients), with 32,7% of patients remaining on therapy for ≥180 days and 14.1% for ≥365 days [34], underscoring its tolerability and utility as a long-term disease-control strategy.

The most contemporary and clinically impactful letrozole data derive from the 2025 real-world retrospective cohort study by Zwimpfer et al., involving 102 patients with newly diagnosed ER-positive HGSC receiving maintenance letrozole (n=64) or no letrozole (n=38) after primary surgery and chemotherapy at the University Women's Hospital Basel [13]. Whilst no significant overall PFS improvement was demonstrated in the whole cohort (median 20.56 months vs 29.34 months, $p = 0,53$), a statistically significant OS advantage was demonstrated in the no-residual-disease subgroup (median 114 months vs 46.9 months, $p = 0,006$). These these findings are instrumental in informing the design of the ongoing ENGOT-ov54/Swiss-GO-2/MATAO phase III randomised controlled trial (NCT04111978), which will prospectively evaluate letrozole maintenance versus placebo in 528 patients with ER-positive FIGO stage II-IV epithelial ovarian cancer [36].

An earlier proof-of-concept study by Heinzelmann-Schwarz et al. demonstrated that ESR1 expression in HGSOC was similarly high to that in breast cancer, and that letrozole maintenance was associated with a significantly prolonged recurrence-free interval at 24 months (60% vs 38.5%, p = 0,035), providing the mechanistic and empirical foundation for the MATAO trial. [30].

4.3. Anastrozole

Anastrazole has been evaluated in multiple smaller phase II studies. The PARAGON trial (ANZGOG-0903), a prospective phase II study of anastrozole in asymptomatic patients with ER/PR-positive recurrent aynaecological cancer and CA125 progression, demonstrated a disease control rate of 36% at 3 months and confirmed a stable patient-reported quality of life during treatment – data particularly relevant to the clinical scenario of biochemical-only recurrence in HGSOC [37]. A US phase II study demonstrated that 42% of patients with asymptomatic recurrent müllerian cancer had stable disease for >90 days, confirming tolerability. [38]. Anastrazole remains a reasonable AI option, particularly in patients intolerant to letrozole or in sequential endocrine therapy strategies.

4.4. Exemestane

Exemestane, the steroidal irreversible aromates inactivator, has the least extensive HGSOC-specific clinical dataset. A phase II study reported a CBR of 31% with a median PFS of 4.8 months in responders [39]. The theoretical rationale for its use following progression on non-steroidal AI (letrozole or anastrozole) – based on the principle of non-cross-resistance established in breast oncology – has not been prospectively validated in ovarian cancer but provides a pragmatic sequential endocrine strategy in clinical practice [40].

4.5. The Phase III Overesist Trial and Evolving Evidence

The Ovarian phase III trial randomised 283 patients with platinum-resistant ovarian cancer to chemotherapy (paclitaxel or pegylated liposomal doxorubicin) or tamoxifen endocrine therapy. The PFS was 12.7 weeks in the chemotherapy arm versus 8 weeks in the tamoxifen arm, confirming that endocrine therapy is inferior to chemotherapy as treatment for platinum-resistant disease in the unselected population and reinforcing the principle that biomarker-driven selection is essential [12]. However, as a subset of patients in the tamoxifen arm achieved durable disease stabilisation, the findings support continued investigation in ER-enriched populations.

Taken together, a meta-analysis of 53 trials encompassing 2,490 patients with all grades of epithelial ovarian carcinoma confirmed benefit for 41% of patients overall – 55% in platinum-sensitive versus 40% in platinum-resistant tumours – validating therapy as a reproducibly active, if modest, treatment modality in the recurrent setting [12].

5. Predictive Biomarkers and Patient Selection

The identification of reliable predictive biomarkers for hormonal therapy in HGSOC remains a major unmet need ERα) positivity (≥1% nuclear IHC staining) is the most commonly applied selection criterion, but (≥1% nuclear IHC staining) is the most commonly applied sslectione criterion, but ERα alone is not a validated predictive marker for response in HGSOC, unlike in breast cancer [13]. The 2022 paired analysis of primary and recurrent HGSOC by Schötzau et al. Highlighted that while ERα expression is stable across disease states and is present in the large majority of HGSOC, PR expression declines significantly in platinum-sensitive recurrent disease, suggesting that a composite ER/PR score – or dynamic assessment of PR across treatment lines – may be more informative than ERα status alone [10].

Hormone receptor co-expression profiling, incorporating AR, ERα, and PR, has demonstrated superior predictive performance compared to any individual receptor. In a validation cohort of 125 HGSOC patients, the AUC for combined AR/ ERα/PR co-expression in predicting platinum sensitivity was 0,945, substantially higher than for single-receptor IHC [22]. These findings support the development of a multi-receptor IHC panel as a clinical decision tool for patient selection in endocrine therapy trials.

The ER histoscore – a quantitative composite of staining intensity and proportion of positive nuclei – has been validated as a significant predictor of endocrine therapy benefit in the Edinburgh cohort, with patients in the highest ER histoscore quartile and the longest treatment-free interval showing the greatest clinical benefit rates [34]. Standardisation of ER histoscoring methodology across centres remains an important prerequisite for its implementation as a prospective stratification factor in clinical trials.

At the molecular level, TCGA-based molecular subtyping of HGSOC identifies four transcriptional subtypes (mesenchymal, immunoreactive, differentiated, and proliferative), with the „differentiated" subtype characterised by the highest ESR1 expression and potentially representing the most endocrine-sensitive subgroup [4]. Integration of molecular subtyping with receptor IHC may further refine patient selection and i san active area of translational research. Additionally, the 2025 study by Marolt et al. characterised the expression of androgen-metabolising enzymes as novel prognostic markers in HGSOC, identifying a potential role for steroidogenic enzyme profiling in endocrine therapy patient selection [24].

6. Hormonal Therapy in Combination with Targeted Agents

6.1. Combination with CDK4/6 Inhibitors

The combination of CDK4/6 inhibitors with aromatase inhibitors has transformed HR-positive, HER2-negative metastatic breast cancer, and an analogous strategy is under active clinical investigation in ER-positive ovarian cancer. CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) prevent Rb phosphorylation and enforce G1 arrest, synergising with ER blockade to achieve dual inhibition of cell cycle entry.

A 2025 non-randomised open-label phase II study presented at the Society of Gynecologic Oncology (SGO) Annual Meeting evaluated abemaciclib plus hormonal therapy in 41 patients with recurrent low- or high-grade serous ovarian cancer or endometrioid endometrial cancer [41]. While the 24-week PFS rate in LGSOC was 72,3%, the corresponding rate in HGSOC was only 12,5% with minimal objective response. The investigator concluded that unselected HGSOC does not appear to derive meaningful benefit from this combination, reinforcing the hypothesis that molecular selection – potentially based on Rb expression status, CDK4/6 copy number, or HGSOC molecular subtype – will be essential for identifying the responsive HGSOC subpopulation.

The phase II GOG 3026 trial, evaluating letrozol plus ribociclib in recurrent low-grade serous carcinoma, reported a 24-week PFS rate of 63,3% in a TP53 wildtype cohort, validating the CDK4/6-endocrine combination in ER-enriched, low-grade disease, and establishing the proof-of-principle that informs analogous approaches in biomarker-selected HGSOC [42]. The ongoing phase II MITO-END-3 trial (NCT04527315) is evaluating letrozole plus ribociclib in ER-positive recurrent EOC, including both HGSOC and LGSOC, and results are awaited.

6.2. Combination with PI3K/AKT.mTOR Pathway Inhibitors

Cross-talk between ERα signalling and the PI3K/AKT/mTOR pathway is a well-established mechanism of acquired endocrine resistance. Ligand-independent ERα phosphorylation by activated AKT enables tumour proliferation despite oestrogen depletion or receptor blockade. Simultaneously, oestrogen signalling activates PI3K through genomic and non-genomic mechanisms, creating a self-reinforcing resistance loop [43].

The BOLERO-2 trial established the clinical benefit of everolimus (mTOR inhibitor) plus exemestane in AI-resistant breast cancer. Analogous preclinical data in HGSOC cell lines demonstrate synergistic growth suppression with dual mTOR and ERα inhibition, particularly in PIK3CA-mutant tumours [43]. Phase I/II studies combining AIs alpelisib (PI3Kα-selective inhibitor) or everolimus are ongoing in recurrent EOC, and a 2025 review of targeted therapy in HGSOC identified PI3K pathway inhibition as among the most promising combinatorial targets with endocrine therapy [44].

6.3. Combination with PARP Inhibitors

PARP inhibitors have established efficacy in HGSOC, particularly in BRCA-mutated and HRD tumors. The 2025 JAMA Network Open meta-analysis of seven RCTs involving first-line PARP inhibitor maintenance demonstrated consistently improved PFS but no OS benefit, and advocated for a „right-PARP-inhibitor-for-the-right-patient" paradigm, noting substantial variation in efficacy across molecular subgroups [7]. This underscores the need for combination strategies that can extend PARP inhibitor activity beyond the HRD population.

Tamoxifen has been shown to reduce BRCA1 expression and HR repair capacity in HGSOC cells, thereby potentially sensitising BRCA-wildtype tumours to PARP inhibitor-mediated synthetic lethality [28]. An ongoing clinical study of olaparib plus tamoxifen in recurrent BRCA-wildtype HGSOC (NCT04669587) seeks to validate this mechanistic hypothesis in patients who would not ordinarily be candidates for PARP inhibitor monotherapy.

A 2025 systematic review and meta-analysis in the Journal of Clinical Medicine evaluating the combination of PARO inhibitors with anti-angiogenic agents in recurrent ovarian cancer found no statistically significant PFS improvement for the combination versus PARP inhibitor monotherapy (HR 0,63, 95% CI 0,37-1,06) [45]. These findings contextualise the evolving combination landscape in HGSOC, highlighting that combining PARP inhibitors with endocrine agents – which target fundamentally distinct biological mechanisms – may offer complementary rather than additive resistance-overcoming potential.

7. Safety and Tolerability

A defining advantage of hormonal therapy in recurrent HGSOC is its consistently favourable tolerability profile relative to cytotoxic chemotherapy and PARP inhibitors, which are associated with significant haematological toxicity (nausea, fatigue, anaemia and thrombocytopenia for PARP inhibitors; myelosuppression for chemotherapy). Aromatase inhibitors are associated with musculoskeletal adverse effects (arthralgia, myalgia), bone mineral density reduction, and vasomotor symptoms with prolonged use [46]. The 2025 Basel real-world cohort confirmed a low toxicity profile for letrozole maintenance in HGSOC, with no major adverse effects reported and a low treatment discontinuation rate, supporting its feasibility as a long-term maintenance strategy [13].

Tamoxifen carries a specific risk of endometrial pathology (hyperplasia, carcinoma) and venous thromboembolic events with long-term use, necessitating gynaecological surveillance in patients on extended therapy [47]. In the context of HGSOC – where the patient population is often elderly or medically frail and has accumulated therapy, it is a significant clinical asset that justifies its use even when objective response rates are modest.

Patient-reported quality of life (QoL) data from hormonal therapy trials in HGSOC-specific populations remain limited. The PARAGON trial demonstrated stable QoL during anastrozole therapy, and QoL assessments are embedded as secondary endpoints in the MATAO phase III trial [36, 37]. These prospective QoL data will be important for characterising the patient experience of long-term endocrine maintenance and informing shared decision-making in clinical practice.

8. Current Guidelines and Clinical Practice

Hormonal therapy is not endorsed as a standard first- or second-line treatment for HGSOC in major international clinical guidelines, reflecting the absence of level I evidence from randomised controlled trials. Both the NCCN (version 2.2026) and ESMO_ESGO (2019 consensus) acknowledge hormonal therapy as a reasonable option in selected clinical scenarios for recurrent EOC, particularly for patients who are not candidates for further cytotoxic therapy [5, 48].

In contemporary clinical practice, endocrine therapy is most commonly used in the following contexts: (1) maintenance therapy in patients achieving disease response or stabilisation to achieve a chemotherapy-free interval while preserving quality of life; (2) management of biochemical-only recurrence characterised by rising CA-125 in the absence of symptomatic or rapidly progressive disease; (3) patients with indolent disease biology and extemsive prior treatment history; and (4) elderly or frail patients for whom chemotherapy toxicity is prohibitive [12,13]. The 2024 multicenter real-world study from France observed that long-responders were more likely to have received endocrine therapy in a maintenance setting, had longer platinum sensitivity duration (median 40.5 months), and had received a median of three prior lines of chemotherapy, validating these clinical intuitions [12].

An important question for future guideline development concerns the optimal definitione of ER positivity as an eligibility criterion. Unlike breast cancer, where ASCO/CAP guidelines define ER positivity as ≥1% nuclear staining, ovarian cancer studies have applied varying thresholds (1%, 10%, 50%), contributing to heterogeneity in both patient selection and reported outcomes [13]. Standardisation of this threshold - will be a prerequisite for incorporating hormonal therapy into evidence-based HGSOC guidelines.

9. Future Directions

The most consequential near-term development in the field will be the results of the ENGOT-ov54/Swiss-GO-2/MATAO phase III randomised trial (NCT04111978), which is enrolling 528 patients with ER-positive FIGO stage II-IV epithelial ovarian cancer to receive letrozole 2,5mg daily or placebo as maintenance therapy for up to five years following primary treatment [36]. This is the first placebo-controlled phase III trial prospectively evaluating an aromatase inhibitor in the maintenance setting for HGSOC and represents a landmark study whose results have the potential to transform clinical practice if a PFS benefit is confirmed. In parallel, real-world data from the Basel cohort (Geissler et al., 2025) demonstrated an OS signal in the no-residual-disease subgroup, highlighting the clinical relevance of subset analyses in the ongoing MATAO trial. [13].

Second, the development of validated multi-receptor biomarker planes incorporating AR, ERα, and PR – with standardised IHC methodology and quantitative histoscoring systems – should be a research priority. The high predictive performance of combined receptor profiling (AUC 0,945 in the TJ-cohort validation study)

[22] suggests that multi-receptor panels could meaningfully improve patient selection beyond ERα alone, and should be embedded as prospective stratification factors in future endocrine therapy trials.

Third, the 2025 SGO data abemaciclib plus hormonal therapy demonstrate that unselected HGSOC does not respond to CDK4/6-endocrine combinations to the same degree as LGSOC [42], reinforcing that molecular preselection strategies are essential. Future trials should stratify HGSOC patients by Rb expression, CDK4/6 amplification status, and HGSOC molecular subtype (TCGA classification) to identify the CDK4/6-inhibitor responsive HGSOC subset.

Fourth, the potential of the ER-immune axis deserves systematic investigation. Preclinical data demonstrate that tumour cell-independent oestrogen signalling drives disease progression through mobilization of myeloid-derived suppressor cells and suppression of T-cell-dependent anti-tumour immunity, and that ER blockade may reverse this immunosuppressive phenotype and potentially synergize with immunotherapy [49]. Combining hormonal therapy with immune checkpoint inhibitors is biologically rational and should be explored in phase I/II combination studies in ER-positive HGSOC.

Fifth, the role of novel SERDs – including oral SERDs such as elacestrant, which have demonstrated clinical benefit in ESR1-mutant breast cancer [50] - warrants investigation in HGSOC with documented ESR1 mutations. Although ESR1 mutations are rare in HGSOC (0.07–0.3%), they are enriched in patients previously treated with aromatase inhibitors (1.26%), suggesting acquired endocrine resistance as a potential mechanism [51, 52]. The subset of recurrent HGSOC patients with acquired ESR1 mutations may represent a distinct population potentially responsive to SERD-based therapy, as clinical benefit from ER-targeted therapy has been documented in gynecologic malignancies harboring these mutations [51].

Finally, the intratumoral steroidogenesis axis characterised in 2025 – including the contributions of 11-oxygenated androgens and their metabolising enzymes – opens new therapeutic avenues through enzyme-directed endocrine blockade that may supplement or replace current systemic hormonal approaches in selected HGSOC subtypes [24].

10. Conclusions

Hormonal therapy occupies a well-defined and clinically valuable niche in the management of recurrent HGSOC. The biological rationale is compelling: ERα is expressed in over 80% of HGSOC tumours, intratumoral aromatase sustains oestrogenic signalling independent of systemic levels, and the AR/ ERα/Pr co-expression profile predicts both endocrine sensitivity and platinum responsiveness. Clinical evidence from multiple phase II trials, large retrospective cohorts, and a 2024 real-world multicenter study consistently demonstrates CNRs of 25-55% for tamoxifen and aromatase inhibitors, primarily through disease stabilisation rather than objective tumor regression.

The most important recent development is the 2025 real-world cohort data from Basel demonstrating a statistically significant OS improvement with maintenance letrozole in the no-residual-disease HGSOC subgroup, directly informing the ongoing MATAO phase III trial [13]. The 2025 SGO data on abemaciclib plus hormonal therapy clarify that CDK4/6-endocrine combinations have limited activity in unselected HGSOC, while the 2025 JAMA Network Open PARP inhibitor meta-analysis advocates for a precision medicine approach that naturally complements endocrine therapy as a distinct and well-tolerated maintenance strategy [7, 41].

Progress in this field will require the prospective validation of multi-receptor biomarker panels for patient selection, mature results from the MATAO phase III trial, and the development of rational combination strategies targeting complementary resistance mechanisms. WITH these advances, hormonal therapy is well-positioned to evolve from a pragmatic palliative option into a cornerstone of precision endocrine oncology for ER-positive HGSOC.

Author Contributions

Conceptualization: Agnieszka Zaręba
Methodology: Agnieszka Zaręba, Dawid Juszkiewicz
Literature review: Krzysztof Kiełczewski, Barbara Fetner, Magdalena Dłużewska
Data analysis and interpretation: Zuzanna Gebert, Ivanna Ilkiv, Agata Kucharska
Writing - original draft: Agnieszka Zaręba, Dawid Juszkiewicz, Krzysztof Kiełczewski, Barbara Fetner, Magdalena Dłużewska, Zuzanna Gebert, Ivanna Ilkiv, Agata Kucharska, Patrycja Stankowska, Konrad Adler
Writing - review & editing: Agnieszka Zaręba, Patrycja Stankowska, Konrad Adler
Supervision: Agnieszka Zaręba
Final approval: All authors

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