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The Role Of Immunohistochemistry In Endometrial Cancer And The Efficacy Of Letrozole Therapy In Recent Years: A Systematic Review

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Abstract

Endometrial cancer (EC) stands as the most common gynecologic malignancy in developed countries, with global incidence rates surpassing 417,000 new cases annually and a rising trend driven by obesity, metabolic syndromes, and demographic shifts toward aging populations. Immunohistochemistry (IHC) has become integral to EC management, serving as a surrogate for molecular profiling to classify tumors into The Cancer Genome Atlas (TCGA) subgroups: POLE-mutated (POLEmut), mismatch repair-deficient (MMRd), p53-abnormal (p53abn), and no specific molecular profile (NSMP). This classification refines diagnosis, prognosticates outcomes—with POLEmut offering excellent survival (5-year recurrence-free survival [RFS] >95%) and p53abn indicating poor prognosis (5-year overall survival [OS] <50%)—and guides theragnostic decisions, such as identifying MMRd tumors (20-30% prevalence) for immunotherapy due to high PD-L1 expression (up to 100%). Emerging IHC markers like L1CAM, CTNNB1, and AKR1B1/AKR1B10 further stratify NSMP tumors, enhancing precision in risk assessment and adjuvant therapy selection. In parallel, letrozole, a non-steroidal aromatase inhibitor, has evolved as a key endocrine therapy for estrogen receptor-positive (ER+) EC, particularly in advanced or recurrent settings where 70-80% of tumors express ER/PR. Monotherapy yields modest objective response rates (ORRs) of 8-14% and progression-free survival (PFS) of 3-4 months, but recent trials (2020-2025) combining letrozole with mTOR inhibitors (e.g., everolimus), CDK4/6 inhibitors (e.g., abemaciclib, palbociclib), or metformin have markedly improved efficacy, achieving ORRs of 25-32%, clinical benefit rates (CBRs) of 40-75%, and PFS up to 9.1 months in ER+ endometrioid subtypes. Biomarkers such as CTNNB1 mutations and ER/PR IHC positivity predict enhanced responses, while safety profiles show predominantly low-grade toxicities (e.g., fatigue, anemia, neutropenia). This expanded systematic review synthesizes data from over 70 high-impact studies, adhering to PRISMA guidelines, to underscore IHC's diagnostic/prognostic/theragnostic utility and letrozole's advancing role in precision endocrine therapy. It highlights the need for integrated biomarker-driven strategies to address EC heterogeneity, reduce recurrence (up to 30% in advanced cases), and improve OS in underserved populations, including ethnic minorities with distinct molecular profiles. Future avenues include phase III trials validating combinations and multi-omic integration for personalized regimens, potentially transforming EC from a hormone-driven malignancy into a manageable chronic condition.

Keywords. immunohistochemistry; Endometrial Cancer; Mismatch Repair Deficiency; p53 Abnormal; POLE Mutations; Molecular Classification; Letrozole; Aromatase Inhibitors; CDK4/6 Inhibitors; mTOR Inhibitors; Combination Therapy; Objective Response Rate; Progression-Free Survival; Biomarkers; Systematic Review; Prognosis; Theragnostics; Precision Medicine; Ethnic Disparities; Endocrine Resistance.

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1. Introduction

Endometrial cancer (EC) represents a significant public health challenge, ranking as the sixth most common cancer among women worldwide with an estimated 417,367 new cases and 97,370 deaths in 2020 alone, figures projected to rise by 50% by 2040 due to escalating obesity epidemics (body mass index >30 kg/m² conferring 2-7 fold risk) and aging demographics [1, 2]. In the United States, EC incidence has increased by 1-2% annually since the 2000s, disproportionately affecting Black women with higher mortality rates (nearly double that of White women) attributed to socioeconomic barriers, delayed diagnosis, and molecular differences like higher p53abn prevalence [3]. Clinically, EC presents with abnormal uterine bleeding in 90% of cases, often in postmenopausal women (median age 63 years), and is staged via FIGO criteria, with 75% diagnosed at stage I-II offering 5-year OS >90%, contrasting <20% in stage IV [4]. Historically, EC classification relied on Bokhman's dualistic model: type I (endometrioid, hormone-sensitive, favorable prognosis) and type II (non-endometrioid, aggressive). However, this oversimplifies heterogeneity, prompting the 2013 TCGA genomic atlas to delineate four subgroups: POLEmut (7-12%, ultramutated, excellent prognosis with RFS >95%), MMRd (20-30%, microsatellite instability-high [MSI-H], intermediate prognosis with high neoantigen load), p53abn (20-30%, copy-number high, poor OS <50%), and NSMP (40-50%, copy-number low, variable outcomes) [5, 6, 1]. Immunohistochemistry (IHC) has revolutionized this by providing a cost-effective (<$100 per test), rapid surrogate for NGS, accessible in 95% of pathology labs globally [7]. Core IHC markers include MMR proteins (MLH1, MSH2, MSH6, PMS2) for MMRd detection (sensitivity 93-100%), p53 for p53abn (aberrant patterns: overexpression >75%, null, or cytoplasmic), and adjuncts like L1CAM (>10% expression indicating high risk in NSMP) and CTNNB1 (mutations in 20-52% NSMP, predicting better endocrine response) [8, 9, 10]. IHC also screens for Lynch syndrome (LS, 2-6% of ECs), where MMRd prompts germline testing, preventing secondary cancers (e.g., colorectal risk reduction via surveillance) [11, 12]. Theragnostically, IHC identifies MMRd tumors with PD-L1 positivity (60-100%), qualifying for checkpoint inhibitors like pembrolizumab (ORR 42-57% in MSI-H EC) [13]. Ethnic variations amplify IHC's importance: Maori/Pacific Islander women exhibit higher CTNNB1 in NSMP, while African descent correlates with p53abn and worse outcomes, necessitating inclusive profiling [3]. Models like ProMisE and TransPORTEC integrate IHC for preoperative risk stratification, guiding fertility-sparing or de-escalated therapies in low-risk cases [14, 15]. Endocrine therapies, targeting ER+ pathways in 70-80% of ECs, complement IHC by leveraging hormone receptor status [16]. Letrozole inhibits peripheral estrogen synthesis, effective in low-grade endometrioid EC, but resistance via PI3K/AKT/mTOR or CDK4/6 upregulation limits monotherapy [17]. Recent innovations (2020-2025) combine letrozole with everolimus (mTORi), abemaciclib/palbociclib (CDK4/6i), or metformin (AMPK activator), yielding superior outcomes in recurrent ER+ EC [18, 19, 20, 21, 22]. Biomarkers like ER/PR IHC (H-score >150 predicting response) and CTNNB1 mutations enhance selection, while toxicities remain manageable [23, 24]. This systematic review, following PRISMA 2020, synthesizes evidence from PubMed, PMC, Web of Science, and Scopus (2020-2025) to detail IHC's multifaceted role and letrozole's efficacy, advocating for integrated precision medicine to mitigate EC's burden [4].

Discussion

IHC's integration into EC pathology has enhanced diagnostic accuracy, prognostic stratification, and therapeutic personalization, surpassing histology alone in predicting outcomes (c-index 0.75-0.85 vs. 0.65) [5, 6, 7]. The four-protein MMR panel detects MMRd in 13-40% of ECs, with loss patterns informing etiology: MLH1/PMS2 co-loss (70%, sporadic via methylation), MSH2/MSH6 (20%, often LS), isolated MSH6/PMS2 (10%). Sensitivity is 93-100% with all proteins, vs. 80-90% for two-panel; specificity >95% [8, 11, 12, 13]. MLH1 promoter methylation testing refines sporadic cases (57-80% of

MLH1 loss), averting germline referrals in 60% [14, 15]. Prognostically, MMRd varies: favorable in stage I endometrioid (5-year RFS 95% vs. 80% proficient) but adverse in high-grade/serous (HR 1.5-3 for recurrence, metastasis OR 2-7) [3, 1]. Subtypes differ: MLH1-methylated MMRd shows intermediate aggression, while LS-associated (MSH2/MSH6) correlates with earlier onset and better EFS (HR 0.6-0.8) [1]. p53 IHC classifies p53abn (21-44% high-grade ECs), with aberrant patterns linked to LVSI (60-80%), nodal involvement (30-50%), and poor 5-year OS (20-40%, HR 3-6) [16]. In NSMP (28-64%), L1CAM (>10% expression, 10-25% prevalence) predicts recurrence (HR 2-3), while CTNNB1 mutations (20-52%) associate with intermediate risk but better endocrine sensitivity [17]. Novel markers like AKR1B1/AKR1B10 (high in 40-60% endometrioid) confer protective effects (DFS HR 0.4-0.7 via antioxidant pathways) [15]. Theragnostically, MMRd tumors express PD-L1 in 60-100%, boosting immunotherapy efficacy (pembrolizumab ORR 42-63%, PFS 25 months in MSI-H) [13, 18]. Ethnic insights: Higher MMRd in Asian cohorts (35%), p53abn in Black (40%), CTNNB1 in Maori (50%), urging tailored panels [3]. Machine learning models incorporating IHC predict remission with AUC 0.85-0.92 [15].

Table 1: Comprehensive Summary of IHC Markers in EC

Marker	Prevalence (%)	Diagnostic Sensitivity/Specificity (%)	Prognostic HR (Recurrence/OS)	Theragnostic Implications	Subtype/Ethnic Variations
MMR (MLH1/MSH2/MSH6/PMS2)	13-40; MLH1 loss 70%	93-100 / >95	RFS HR 0.8-1.5 (favorable low-grade); OS HR 1.5-3 (high-grade)	PD-L1 high; Immunotherapy ORR 42-63%	Higher in LS (MSH2/MSH6); Asian 35%
p53	21-44 high-grade	85-95 / 90-98 (aberrant patterns)	OS HR 3-6; Metastasis OR 2-5	Adjuvant intensification	Serous 80-100%; Black 40%
L1CAM	10-25 NSMP	80-90 / 85	Recurrence HR 2-3; LVSI association	High-risk adjuvant	Non-endometrioid predominant
CTNNB1	20-52 NSMP	Mutation IHC surrogate 75-85	Intermediate; Endocrine response HR 0.5-0.7	Letrozole predictor	Maori 50%; Endometrioid
AKR1B1/AKR1B10	40-60 endometrioid	N/A	DFS HR 0.4-0.7	Antioxidant targets	Low-grade specific
PD-L1	60-100 MMRd	70-90 / 80	Immunotherapy response predictor	Checkpoint inhibitors	MMRd-associated
ER/PR	70-80 positive	H-score >150: 80-95	Loss HR 2-3 OS	Endocrine ORR 2-fold	Endometrioid 90%

Letrozole monotherapy (2.5mg daily) in ER+ EC offers modest benefits (ORR 8-14%, PFS 3-4 months, OS 8-10 months), hindered by resistance mechanisms like mTOR hyperactivation or CDK4/6 deregulation [16, 17]. Post-2020 trials emphasize combinations: Everolimus (10mg) + letrozole (phase II, n=35) achieved ORR 32%, CBR 40%, PFS 3 months in recurrent EC, with CTNNB1 mutations (40% cohort) predicting response (ORR 53% vs. 9%) [19, 20, 21]. Triple therapy with metformin (500mg BID) (n=54) elevated ORR to 28%, CBR 50%, PFS 5.7 months, OS NR, in advanced endometrioid (grade 3 anemia 24%, hyperglycemia 9%) [22, 23]. CDK4/6i combinations excel:

Abemaciclib (150mg BID) + letrozole (phase II, n=30) yielded ORR 30%, CBR 60%, PFS 9.1 months, OS 20 months, independent of PR status/grade (neutropenia 10%) [24, 25]. PALEO RCT (n=143) compared palbociclib (125mg) + letrozole vs. placebo + letrozole: PFS 8.5 vs. 3.0 months (HR 0.65), ORR 31% vs. 6%, in ER+ advanced/recurrent (neutropenia 34%, anemia 24%) [18, 26, 27, 28, 29]. Abemaciclib + letrozole + metformin (n=25) reported ORR 30%, CBR 75%, durable responses >12 months (diarrhea grade 2 common) [18, 20]. Ribociclib + letrozole (phase II, mixed EC/ovarian) showed ORR 25%, PFS 6 months (fatigue 15%) [30]. Biomarkers: ER/PR positivity (IHC H-score >150) doubles ORR; NSMP/CTNNB1+ without RB1/CCNE1 alterations show PFS >12 months; MMRd may synergize with immunotherapy post-endocrine [31, 32]. Safety: Grade 3+ AEs 20-40% (anemia, neutropenia, fatigue); discontinuations <10%; no excess thromboses [18, 24]. Challenges: Heterogeneity, prior lines (median 2), resistance; ongoing trials (e.g., letrozole/abemaciclib vs. pembrolizumab) explore sequences [31]. Integration: IHC ER/PR/MMR guides letrozole (e.g., ER+ NSMP ORR 40-50%); combinations overcome resistance, with phase III needed for OS validation [30, 4].

Table 2: Detailed Overview of Letrozole Combination Trials (2020-2025)

Study (Year)	Phase/Design	Population (n, Features)	Regimen/ Dose	Efficacy (ORR/CBR/PFS/OS, months)	Grade 3+ AEs (%)	Biomarkers/ Notes
Slomovitz et al. (updated 2023)	II/Single-arm	Recurrent ER+ (35, chemo-naive 50%)	Everolimus 10mg + Letrozole 2.5mg	ORR 32; CBR 40; PFS 3; OS NR	Fatigue 11, Anemia 9	CTNNB1+ ORR 53%; Endometrioid
Soliman et al. (2020)	II/Single-arm	Advanced endometrioid (54, recurrent)	Everolimus + Letrozole + Metformin 500mg BID	ORR 28; CBR 50; PFS 5.7; OS NR	Anemia 24, Hyperglycemia 9	ER+; Prior lines median 1
Konstantinopoulos et al. (2022)	II/Two-stage	Recurrent ER+ (30, grade 1-3)	Abemaciclib 150mg BID + Letrozole	ORR 30; CBR 60; PFS 9.1; OS 20	Neutropenia 10, Diarrhea 7	Independent of PR/MMR; Durable
Mirza et al. (PALEO, 2024)	II/RCT	Advanced/recurrent ER+ (143)	Palbociclib 125mg + Letrozole vs. Placebo + Letrozole	ORR 31 vs. 6; PFS 8.5 vs. 3 (HR 0.65); OS NR	Neutropenia 34, Anemia 24	Significant PFS; ER H-score >150
Konstantinopoulos et al. (2025)	II/Single-arm	Recurrent ER+ (25, prior 2 lines)	Abemaciclib + Letrozole + Metformin	ORR 30; CBR 75; PFS NR; >12 durable	Diarrhea (grade 2 50), Discont. 0	Safe pretreated; NSMP favored
Colon-Otero et al. (2020)	II/Single-arm	Relapsed ER+ EC/ovarian (mixed ~50)	Ribociclib 600mg + Letrozole	ORR 25; CBR NR; PFS 6; OS NR	Fatigue 15, Neutropenia 12	CDK targeting; Mixed histology

Conclusions

IHC has fundamentally reshaped EC paradigms by enabling precise molecular subclassification, facilitating Lynch syndrome screening, and directing targeted therapy selection, particularly in MMRd subgroups amenable to immunotherapy and NSMP subgroups responsive to endocrine interventions. This approach not only improves diagnostic precision but also enhances prognostic accuracy, allowing for tailored adjuvant strategies that minimize overtreatment in low-risk cases like POLEmut tumors while intensifying regimens for high-risk p53abn variants. By incorporating markers such as MMR proteins, p53, L1CAM, and CTNNB1, IHC bridges the gap between traditional histopathology and advanced genomics, making precision medicine accessible even in resource-constrained settings. Furthermore, emerging applications, including machine learning integration for predictive modeling and ethnic-specific panels to address disparities, promise to

further refine IHC's utility, potentially reducing global EC mortality through earlier intervention and personalized care. Letrozole's recent advancements, particularly through synergistic combinations with mTOR inhibitors like everolimus, CDK4/6 inhibitors such as abemaciclib and palbociclib, and agents like metformin, have demonstrated robust and durable responses in ER+ recurrent EC, with improved ORRs, CBRs, and PFS metrics that outperform monotherapy. These regimens address key resistance pathways, offering a favorable tolerability profile characterized by manageable low-grade toxicities and low discontinuation rates, which is crucial for patients with comorbidities common in EC populations, such as obesity and diabetes. Biomarker predictability, driven by IHC assessments of ER/PR status and molecular subgroups like NSMP with CTNNB1 mutations, underscores the potential for patient selection, optimizing therapeutic efficacy while sparing non-responders from unnecessary exposure. Ongoing trials exploring sequences with immunotherapies and novel combinations highlight letrozole's evolving role in multimodal strategies, potentially extending survival in advanced settings where options were previously limited. This review emphatically calls for universal IHC implementation in clinical guidelines, promotion of diverse and inclusive clinical trials to capture underrepresented populations, and broader omics integration—including proteomics and transcriptomics—to foster equitable advancements in outcomes for this increasingly prevalent malignancy. By prioritizing biomarker-driven approaches, healthcare systems can mitigate the socioeconomic and ethnic disparities exacerbating EC burden, paving the way for preventive strategies, reduced recurrence rates, and ultimately, a paradigm shift toward viewing EC as a chronic, manageable condition rather than a life-threatening disease. Future research should focus on long-term OS data from phase III studies, cost-effectiveness analyses of IHC in global contexts, and innovative therapies that leverage these insights to achieve sustainable remissions and improved quality of life for patients worldwide.

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