Redefining the Position of Hormonal Therapy in Endometrial Cancer in the Era of Molecular Classification

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Introduction

Endometrial cancer (EC) is currently the sixth most common malignancy in women worldwide, accounting for approximately 97,000 deaths per year and with rapidly increasing incidence.[1] EC can be characterized based on molecular signatures into four prognostically distinct subgroups[2-4]: (1) ultramutated tumors characterized by *POLE* hotspot mutations with excellent prognosis; (2) hypermutated tumors characterized by mismatch repair deficiency (MMRd) resulting in microsatellite instability (MSI) with intermediate prognosis; (3) tumors with no specific molecular profile (NSMP) or copy-number low (p53 wild-type) with intermediate prognosis; and (4) copy-number high (CNH) tumors, characterized by *TP53* mutations (p53abn) and poor prognosis.

This molecular classification only partly overlaps with the classical histologic classification in which EC was subdivided into estrogen-related type 1 tumors (endometrioid EC, generally with good prognosis) and unrelated to estrogen type 2 tumors (nonendometrioid EC with poor outcome). As shown in Figure 1, all four molecular subgroups are present across type 1 and 2 tumors. However, type 1 tumors are mainly represented by the NSMP group (90% grade 1-2; 85% International Federation of Gynecology and Obstetrics staging system [FIGO] I), whereas type 2 tumors by the *TP53*-mutant group (91% grade 3; 45% FIGO I).[5-7]

There are emerging data available on the potential clinical utility of tumor molecular features for early detection and risk stratification, but also for selection of patients who could benefit from targeted therapies, as for instance, patients with *POLE* ultramutated and MMRd/MSI tumors, which are likely to respond to immune therapies.[8,9]

Hormonal therapy (HT) can be considered the first available targeted treatment option for EC and can be effective in early-stage disease and advanced-stage disease.[10,11] Historically, hormonal drugs have been used since the 1950s, after it became clear that progesterone could induce complete regression of endometrial hyperplasia and carcinoma. This resulted in widespread application of progestin-based therapy,[12-14] and initial reports showed response rates as high as 56% in patients with advanced and recurrent EC.[15,16] However, subsequent and better-designed trials with clear end points for response assessment scaled back these initial evidences and reported response rates of 11%-24% to progestin,[14,17,18] and even lower response rates for other hormonal drugs such as tamoxifen and aromatase inhibitors.[19,20] On the basis of these evidences and the outcomes of initial studies using chemotherapy, where response rates of 30%-45% were achieved,[21,22] the application of chemotherapy increased during the past decades, while the use of HT decreased.[23,24] HT is now mainly restricted to specific patient subgroups, that is, young patients with FIGO stage I disease wishing to preserve fertility, older patients who are medically unfit for primary surgical or chemo/radiotherapeutic treatment, and as palliative treatment in advanced and recurrent disease.[25,26]

In the setting of advanced and recurrent EC, recent reviews and meta-analyses confirmed a response to progestin treatment of 30% in unselected patients.[23,27,28] However, these studies also emphasized that the efficacy of HT is higher in selected subgroups of patients with hormone receptor–positive tumors. In these patient groups, HT can be as effective as chemotherapy, which is especially relevant in patients with advanced and recurrent EC who often
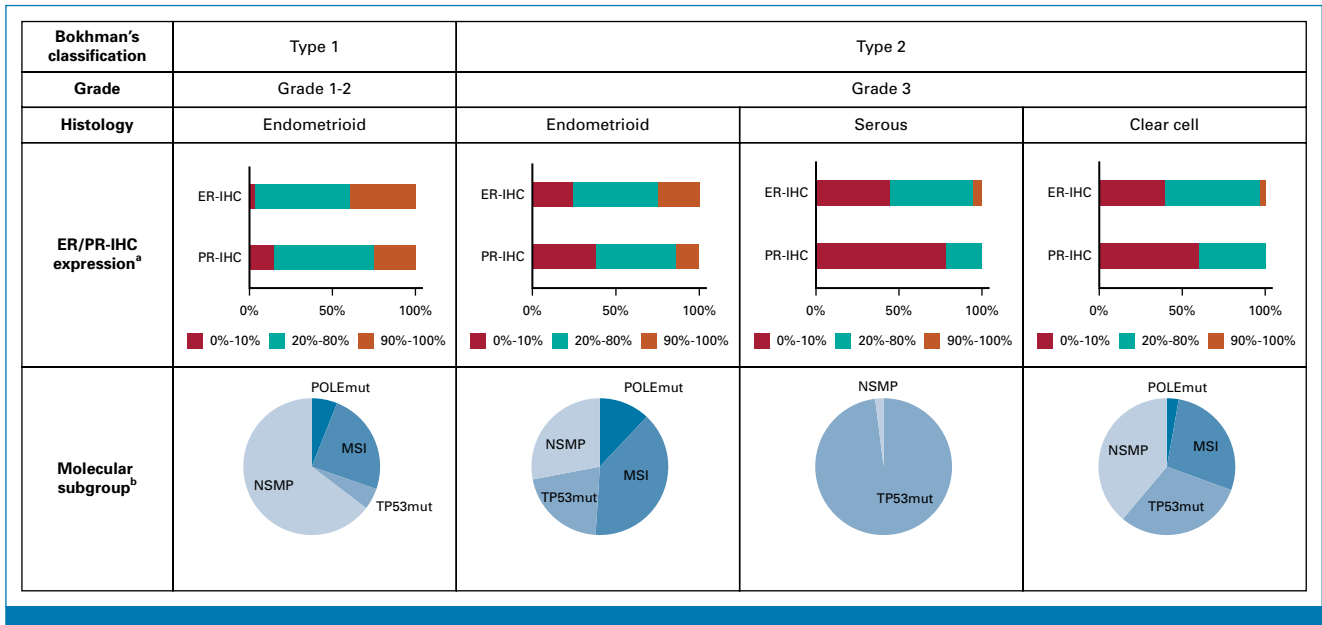
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FIG 1. Relation between type 1 and type 2 endometrial cancers, immunohistochemical expression of ER-IHC/PR-IHC in relation to tumor grade, and molecular classification. [a]On the basis of data from van Weelden et al. [b]Data from Travaglino et al,[6] Urick et al,[9] and Reijnen et al.[7] ER, estrogen receptor; IHC, immunohistochemistry; MSI, microsatellite instability; NSMP, no specific molecular profile[5-7]; POLEmut, polymerase epsilon–mutated; PR, progesterone receptor; TP53mut, tumor protein p53-mutated.

have multiple comorbidities, precluding the use of targeted treatment or chemotherapy. In fact, HT has a good safety profile, whereas chemotherapy is associated with grade 3 treatment-related toxicity in 35% of the patients, compared with only 6.5% with progestin therapy.[29-31]

On the basis of these facts, we strongly believe that the position of hormonal drugs for preselected groups of patients with EC should be redefined in the context of the molecular classification. To this end, there are a number of considerations and remaining challenges with current data that should be addressed, as discussed in the following part.

Lack of High-Quality Data

In a Cochrane review from 2010, six studies with a total of 542 patients were included.[32] However, these studies were characterized by large heterogeneity in populations, type of hormonal drug, and dosage. After publication of this review, only one randomized controlled trial on hormonal monotherapy was published. In this study, a novel drug blocking the steroid sulfatase (Irosustat) was compared with progestin megestrol acetate. Although Irosustat resulted inferior to progestin and the study was prematurely terminated, among the 35 women treated with progestin, 54.1% had not progressed or died after 6 months.[33] A more recent review providing an up-to-date summary of available evidence on the use of progestin as monotherapy included 26 studies (n = 1,639 patients) and showed an overall response rate of 30% in unselected patients.[28] Also, in this review, the quality of the available studies was reported as low, with

heterogeneous study populations and different progestin drugs and dosages. Importantly, studies on HT most often have response rate as the main outcome measure, instead of more robust outcome measures such as progression-free survival or EC-specific survival. This might have negatively affected the clinical application of HT for EC over the past years.

Despite the lack of rigorous studies in the past, a number of good-quality and promising studies on the use of HT in EC have been recently conducted or are ongoing (see also next section). HT has been investigated in combination with other targeted therapies. This can be an attractive option, as combined therapy can interfere with tumor development and progression through multiple mechanisms. For example, the combination of hormonal drugs with mammalian target of rapamycin (mTOR) inhibitors has been tested extensively. Although combined progestins with the mTOR inhibitor temsirolimus resulted in excessive thrombotic complications, thus hampering any clinical use, the aromatase inhibitor letrozole combined with the mTOR inhibitor everolimus was tested in 38 patients and showed a response rate of 32%.[34] Everolimus/letrozole can therefore be an alternative to progestin therapy in advanced and recurrent EC.[35] Advances in our knowledge of the molecular mechanisms underlying tumor growth and the interplay between hormone with other intracellular signaling pathways have also increased the interest into the combination of HT with other targeted treatments including AKT inhibitors, PI3K pathway inhibitors, and CDK inhibitors (Appendix Table A1, online only). Overall, however, the use of HT for EC is

understudied. In the Clinical Trials database, for instance, of 94 studies on advanced-stage/recurrent EC and targeted treatment, only 17 included a hormonal drug (Clinical-Trials.gov, accessed June 2023; Appendix Table A1).

Limited Available Predictive Biomarkers

Immunohistochemical expression of estrogen receptor (ER) and progesterone receptor (PR) in tumor tissue are the most commonly used predictive biomarkers for efficacy of HT. Mechanistically, progestin therapy inhibits estrogen-driven tumor growth by binding to progesterone receptor. The resultant progestin-PR complex moves intracellularly where it serves as a strong inhibitor of estrogenic actions. Thus, the mechanistic rationale for using ER and PR as predictive biomarkers is quite strong. Available studies include a randomized controlled trial in which different doses of progestin therapy were compared. In a subgroup analysis of all included patients stratified by PR status, response was 37.0% in PR-positive compared with 8.1% in PR-negative cases.[17] In the control arm of another randomized study, response at 6 months after start of progestin treatment was 35.3% in an ER-positive population.[33] Finally, a study evaluating the combination of everolimus (PI3K inhibitor), letrozole (aromatase inhibitor), and metformin demonstrated a response of 45% in PR-positive versus 9% in PR-negative advanced and recurrent EC.[36] A recent review on progestin monotherapy endorsed these findings, observing a significant difference in response of 55.4% in PR-positive versus 12.2% in PR-negative disease.[28]

In conclusion, there are robust data on the predictive value of ER and PR positivity for response rate in EC. However, there are several challenges that hamper routine use in clinical practice. First, the currently used cutoff values for ER/PR positivity by immunohistochemistry are adopted from breast cancer, and have not been validated for EC. We recently demonstrated in a multicenter study that a three-tiered cutoff for ER/PR expression resulted in improved prognostication: 0%-10% with worst outcome, 20%-80% with an intermediate outcome, and 90%-100% with the best outcome, supported by the group of Weinberger et al.[5,37] For the prediction of response to HT, a cutoff of 1% or 10% is used for breast cancer.[38] However, in a recent retrospective multicenter study on pretreatment tumor biopsies (n = 81), none of the cases with ER/PR expression below 50% showed response to HT, whereas patients with >50% PR expression had a response rate of 50%.[29] Awaiting prospective validation, the currently used cutoff for hormone receptor positivity might need to be adjusted (ClinicalTrials.gov identifier: NCT03621904). Second, during EC progression and recurrence, PR expression is frequently lost, which may result in reduced sensitivity to progestins, underlining the relevance of recent (pretreatment) biopsy when HT is considered in recurrent EC.[39,40] For example, in the study on combination treatment of everolimus, letrozole, and metformin, PR status was available in 12 primary tumors and metastases of the same patients and matched in 75% of cases. In a larger

study of primary tumors and subsequent metastases, loss of PR increased with disease progression, with 23% of primary tumors and 76% of metastases demonstrating PR loss.[39] Finally, tumor heterogeneity is a common challenge in targeting cancer treatment. Determination of the percentage of ER/PR positivity within the tumor biopsy might be a first step toward understanding whether the tumor is heterogeneous for ER/PR expression. Yet, as sampling errors are inherent to patients with multiple tumor localizations, this will remain difficult to tackle. The recent innovations of using an ER tracer in positron emission tomography (PET) scan imaging might help to determine the ER positivity in relation to all tumor localization (ratio fluoroestradiol F18-positron emission tomography–PET/PET scan).[41] So far, PR tracers are not yet available in the clinic, but might be even more important in the future of HT.

Integration of Molecular Subgroups With Predictive Biomarkers

Now that the development and validation of the molecular classification in EC is completed, it is ready for integration with existing predictive biomarkers. The prognostic value of ER expression has been investigated in recent studies within The Cancer Genome Atlas groups, and remains clinically relevant.[30,31,42] The prognostic value of ER expression appears most relevant in the NSMP group. In the adjuvant treatment setting, a first randomized study is planned to investigate efficacy of adjuvant HT in the NSMP group with advanced EC (ClinicalTrials.gov identifier: NCT05255653). However, ER-/PR-positive tumors are seen throughout all four molecular subgroups. Application of the three-tiered classification for ER/PR expression according to molecular subgroup was investigated in a cohort of 739 ECs. ER and PR expression >90% was found in 25.4% of NSMP tumors, 14.2% of MSI, and still 6.5% of p53-mutant tumors.[43] In this study, ER/PR IHC expression remained prognostically relevant in the entire cohort and within all four molecular subgroups, suggesting that HT could be applied in tumors across the four molecular subgroups. There is a clear need to investigate the efficacy of HT in the adjuvant setting, considering benefits to patients in terms of toxicity and patient convenience compared with chemotherapy or immunotherapy.

Molecular biomarkers such as *POLE*, MSI, and p53 could also have predictive value in relation to HT. This has been investigated in a fertility preservation population with 57 cases with low-grade, stage I EC. MSI-high cases had 11% complete response at 6 months, compared with 53.3% for MSI-low cases, which was significantly different. Importantly, the PR expression also had significant impact on response to HT.[44] Therefore, questions remain regarding applicability of these results in the advanced and recurrent EC setting and if predictive value of MSI status is still relevant if analyzed in conjunction with PR expression.

Finally, to define the position of HT in EC, we also need to better understand the biology of hormone signaling and

identify biomarkers that better predict response. To this end, proper selection of patients by using recent *pretreatment* biopsies assessing ER/PR IHC with validated cutoff values and ER/PR pathway activity tests are necessary. In this context, it is encouraging that novel powerful mRNA–based tools measuring the activation of the downstream hormone signaling cascade have been developed and show promising prediction of hormone responsiveness in breast cancer.[45] Similar tools measuring the activation of PI3K, MAPK, and other pathways are also available, making it feasible to predict patient responsiveness to multiple drug regimens.

In conclusion, hormonal drugs represent valuable therapeutic agents in the treatment of EC, both in the early–stage and as palliative treatment. Application of HT in patients with EC should be based on ER/PR expression. Preliminary data support the integration of hormone signaling biomarkers that better reflect hormone signaling activation to facilitate clinical use of HT. Results from active trials are awaited to better understand how and to whom hormonal drugs should be indicated. Finally, yet importantly, HT is cost–effective and can be administered orally, allowing application in regions with impaired accessibility to specialized infrastructures and low resources.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No potential conflicts of interest were reported.

APPENDIX

TABLE A1. Clinical Trials on Advanced-Stage, Recurrent, Metastatic, or Persistent Endometrial Cancer Registered at the Database Clinical Trails

NCT No. (acronym) Reference	Start End	Conditions Relative to EC	No.	Study Design	Drug	Phase	Therapeutic Outcome Measures	Study Results
Studies exploring the efficacy of HT in combination with other targeted drugs								
NCT00729586	2008 2017	Rec, Adv, Per	73	RCT	mTOR-I (TEM) v mTOR-I + HT (MA + Tam)	II	RECIST response, TTP, OS, PFS	RR: 22% v 14%; PFS: 5.6 (95% CI, 4.0 to 8.2) v 4.2 (95% CI, 1.5-6.2)
NCT01068249[34]	2010 2021	Rec, Adv	42	Single group	AI (LET) + mTOR-I (EVE)	II	RECIST response	CBR: 40%; RR: 32%
NCT01797523[36]	2013 2020	Rec, Adv	62	Single group	AI (LET) + mTOR-I (EVE) + MET	II	RECIST response, PFS	Partial response: 28%; SD: 22%; PFS: 5.7 (95% CI, 3.0 to 8.1); OS 19.6 (95% CI, 14.2 to 26.3)
NCT02476955	2015 2021	Adv, Met[a]; ER+ Known status of AKT1, PIK3CA, PIK3R1, PTEN	40	Single group	AKT-I (ARQ092) +AI (ANA)	I-II	RECIST response	Not available yet
NCT02228681	2014 2018	Rec, Adv, Per	74	RCT	AI (EVE) + mTOR-I (LET) v HT (TAM + MPA, alternating)	II	RECIST response, PFS	RR: 24% v 22%; PFS: 6.4 (95% CI, 3.8 to 17.7) v 3.7 (95% CI, 2.5 to 8.9)
NCT02188550	2014 2016	Adv, Per[a]	20	Single group	AI (LET) + mTOR-I (EVE)	II	RECIST response, OS	Not available
NCT02730429	2016 2022	Met; ER+	78	RCT	AI (LET) v AI + CDK-I (PAL)	II	RECIST response, PFS	Not available yet
NCT02657928[46]	2016 2021	Rec[a]; ER+	40	Single group	AI (LET) + CDK-I (RIB)	II	RECIST response, PFS, OS	PFS at 12 months: 55% PFS at 24 months: 35%
NCT02730923 (VICTORIA)[47]	2016 2020	Rec, Adv; HR+	75	RCT	AI (ANA) v AI + mTOR-I (AZD2014)	I-II	RECIST response, PFS, OS	PFS at 8 weeks: 67% v 39%; ORR: 7.4% (95% CI, 5.0 to 39) v 24% (95% CI, 13 to 39) PFS: 1.9 (95% CI, 1.6 to 8.9) v 5.2 (3.4 to 8.9)
NCT03008408	2017 2022	Rec, Adv	76	Single group	AI (LET) + mTOR-I (EVE) + CDK-I (RIB)	II	RECIST response, PFS, OS	Not available yet
NCT03643510	2018 2021	Rec; HR+	25	Single group	FUL + CDK-I (ABE)	II	RECIST response	Not available yet
NCT04049227	2019 2023	All	27	Single group	AI (LET) + CDK-I (ABE)	I	Pathologic Response (Ki67)	Not available yet
NCT03675893[48]	2018 2023	Rec, Met; ER+	40	Single group	AI (LET) + CDK-I (ABE)	II	RECIST response	PFS at 6 months: 55.6% (95% CI, 35 to 72); RR: 30% (95% CI, 15 to 50); PFS: 9.1 Median duration of response: 7.4 months
NCT04393285	2020 2023	Adv, Per, Rec	50	Single group	CDK-I (ABE) + AI (LET)	II	RECIST response, PFS, RR	Not available yet
NCT05082025	2022 2026	Adv, Met[a]; HR+ PI3K and/or PTEN alterations[b]	78	Single group	PI3K-I (COP) + FUL	II	Safety, tolerability, toxicity, ORR, PFS, OS	Not available yet
NCT05154487	2023 2025	Adv, Per, Rec; likely incurable	51	Single group	PI3K-I (ALP) + FUL	II	RECIST response, RR, ORR	Not available yet
NCT05538897	2023 2027	Endometrioid EC (grade 1, 2, Met)	96	RCT	AKT-I (IPA) + MA v MA	I-II	1: toxicity, dose for phase II; 2: PFS, ORR, RECIST response	Not available yet
Studies exploring the efficacy of HT in combination with other agents								
NCT03671811	2018 2020	All	36	RCT	MA v MA + pterostilbene	II	Pathologic response (Ki67)	Not available yet
NCT02064725	2014 2018	Rec, Per; PR−	8	Single group	Sodium cridanimod + MA or MPA	II	RECIST response, PFS, OS	Not available yet
NCT03077698	2017 2021	Rec, Per; PR+	72	Single group	Sodium cridanimod + MA	II	RECIST response, PFS, OS	Not available yet

(continued on following page)

TABLE A1. Clinical Trials on Advanced-Stage, Recurrent, Metastatic, or Persistent Endometrial Cancer Registered at the Database Clinical Trails (continued)

NCT No. (acronym) Reference	Start End	Conditions Relative to EC	No.	Study Design	Drug	Phase	Therapeutic Outcome Measures	Study Results
NCT01686126 feMMe[49,50]	2012 2020	EH Early stage EC	165	RCT	LEV (reference) v LEV + MET v LEV + weight loss	II	Pathologic response (Ki67)	CR reference (n = 35): 61% (95% CI, 42 to 77) CR MET (n = 47): 57% (95% CI, 41 to 72) CR WL (n = 36): 67% (95% CI, 48 to 82)
NCT04576104	2020 2023	EH, EC	50	RCT	MA v MA + MET	II	Pathologic response (Ki67)	Not available yet
Studies exploring the efficacy of HT alone								
NCT03909152	2019 2021	All[a]; PR+	84	Single group	Anti-P (ONA)	II	RECIST response	Not available yet
NCT02052128[51]	2014 2015	All[a]; PR+	60	Single group	Anti-P (ONA)	I-II	RECIST response	RR: 17% for all cancer types CBR: 15% for EC (n = 13)
NCT03909152	2019 2024	Endometrioid EC[a]	43	Single group	Anti-P (ONA)	II	RECIST response	Not available yet
NCT04719273	2021 2024	Rec, Met; HR+	25	Singe group	Anti-P (ONA) + AI (ANA)	II	RECIST response, RR, PFS	Not available yet
NCT05454358	2022 2028	Primary EC; eligible for adjuvant treatment[c]	299	RCT	AI (LET) v no treatment; AI as adjuvant treatment	II-III	3-year PFS, OS 5-year PFS, OS QOL[d]	Not available yet
NCT03926936 (FUCHSia)	2019 2025	All[a]; ER+	200	Single group	FUL	II	RECIST response, PFS	Not available yet
NCT03621904 (PROMOTE)	2022 2026	Rec, Adv; with HT	150	Single group	HT (AI, TAM, MA, MPA)	II	RECIST response, PFS, QOL[e]	

NOTE. Studies on fertility preservation were excluded. In case of studies enrolling conditions other than EC, study design refers to the EC arm. Responses are given in months. RECIST response criteria 1.0 or 1.1 are used.

Abbreviations: ABE, abemaciclib; Adv, advanced; AI, aromatase inhibitor; AKT-I, Akt inhibitor; ALP, alpelisib; ANA, anastrozole; Anti-P, progesterone receptor antagonist/modulator; CBR, clinical benefit rate (CR + partial response + SD); CDK-I, cyclin-dependent kinase inhibitor; COP, copanlisib; CR, complete response; EC, endometrial cancer; EH, endometrial hyperplasia; ER, estrogen receptor; EVE, everolimus; FUL, fulvestrant; HR, hormone receptor; HT, hormonal treatment; IPA, ipatasertib; LET, letrozole; LEV, levogastrol; MA, megestrol acetate; Met, metastatic; MET, metformin; MPA, medroxyprogesterone acetate; mTOR-I, mammalian target of rapamycin inhibitor; NCT, National Clinical Trial; ONA, onapristone; ORR, objective response rate; OS, overall survival; Per, persistent; PFS, progression-free survival; PI3K-I, phosphoinositide 3-kinase inhibitor; PR, progesterone receptor; QOL, quality of life; RCT, randomized clinical trial; Rec, recurrent; RR, response rate (CR + partial response); SD, stable disease; TEM, temsirolimus.

[a]Subjects' other cancers than EC are also included.

[b]Alterations were detected in tumor tissues and were PIK3CA gain of function mutations, PIK3R1 loss of function mutations, PTEN loss of function mutations, and PTEN deletions.

[c]Those were EC subtypes NSMP with intermediate or higher prognostic risk and life expectancy of 2 or more years. Risk groups on the basis of postoperative clinical-pathologic assessment and molecular classification. All subjects underwent hysterectomy and bilateral salpingo-oophorectomy.

[d]Quality of life assessed with the EORTC QLQ-C30 V3.0-EN24 and MENQOL.

[e]Quality of life assessed with the EORTC-QLQ-C30 and EORTC-QLQ-EN24.