# Management of endometrial cancer in Latin America: raising the standard of care and optimizing outcomes

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## ABSTRACT

Molecular characterization of endometrial cancer is allowing for increased understanding of the natural history of tumors and paving a more solid pathway for novel therapies. It is becoming increasingly apparent that molecular classification is superior to histological classification in terms of reproducibility and prognostic discrimination. In particular, the Proactive Molecular Risk Classifier for Endometrial Cancer allows classification of endometrial cancer into groups very close to those determined by the Cancer Genome Atlas Research Network—that is, DNA polymerase epsilon-mutated, mismatch repair-deficient, p53 abnormal, and non-specific molecular profile tumors. The transition from the chemotherapy era to the age of targeted agents and immunotherapy, which started later in endometrial cancer than in many other tumor types, requires widespread availability of specialized pathology and access to novel agents. Likewise, surgical expertise and state-of-the-art radiotherapy modalities are required to ensure adequate care. Nevertheless, Latin American countries still face considerable barriers to implementation of international guidelines. As we witness the dawn of precision medicine as applied to endometrial cancer, we must make continued efforts towards improving the quality of care in this region. The current article discusses some of these challenges and possible solutions.

## INTRODUCTION

Although survival has improved since the mid-1970s for patients with the most common neoplasms, cancer of the uterine corpus—most of which is represented by endometrial cancer—is an exception, largely because of the lack of major therapeutic advances over recent decades.[1] However, this situation is likely to change in the near future, as molecular characterization of endometrial cancer becomes a standard step in the management of these patients and an increased understanding of the molecular landscape of these tumors paves a more solid pathway for novel therapies.[2–5] As a matter of fact, medical and surgical oncologists are already witnessing therapeutic improvements that result from the recent expansion of the knowledge base on endometrial cancer, particularly with regard to molecular tools that allow improved risk stratification and prediction of therapeutic effects.[2 6–8] Gains have become more evident both in first-line and second-line treatment and also in subsequent-line treatment of advanced disease, given recent clinical trials of agents with activity against specific molecular subgroups of endometrial cancer. The current article aims to provide an overview of the most salient issues regarding the management of women with endometrial cancer. This may inform decision-making in the Latin American setting, characterized in many countries by a dual healthcare system whereby state-of-the-art diagnostic and therapeutic interventions can be offered to just a fraction of the population through private insurance or government-funded treatment, whereas the majority rely on provision of care by systems—which are often publicly funded—affected by considerable resource limitation.[9 10]

## EPIDEMIOLOGY OF ENDOMETRIAL CANCER

Cancer of the uterine corpus, the sixth most commonly diagnosed neoplasm in women worldwide, is largely represented by endometrial cancer; uterine sarcomas account for only approximately 3–7% of cases.[1] Endometrial cancer largely affects elderly women, with a median age at diagnosis of 63 years.[3] Incidence rates for uterine cancer as a whole vary by up to 10-fold across countries, and the highest rates are found in North America and in Northern and Eastern Europe[1]; for example, uterine cancer is the most common gynecological malignancy in the United States.[11] Nevertheless, incidence rates for uterine cancer have been rising worldwide, and countries with historically lower rates have had the largest proportional increase in incidence.[1 12] For example, Brazil had the third largest average annual percent increase in incidence (nearly 5%) of endometrial cancer in a worldwide survey covering a recent 10-year period.[1]

Detailed epidemiological data on endometrial cancer in Latin America are scant, but GLOBOCAN provides estimates for the incidence of uterine cancer within countries globally. Here, the estimated number of new cases in 2022 was 12 616 in Brazil, 5347 in Mexico, 3045 in Colombia, and 4696 in Argentina.[13] Importantly, it is estimated that the total number of

new cases of uterine cancer in Latin America and the Caribbean will rise from approximately 33 000 in 2020 to an estimated 51 000 in 2040.[14] Reasons for the rising incidence of endometrial cancer are not fully understood, but an aging population, declining fertility rates, anovulation, nulliparity, early-onset menarche, late-onset menopause, and the increasing prevalence of obesity are among the factors thought to play a major role.[2 15] Similarly, there is a strong correlation between endometrial cancer and polycystic ovary syndrome, with women diagnosed with polycystic ovary syndrome being approximately three times more likely to develop endometrial cancer than those without the syndrome.[16] Of note, the association between obesity and endometrial cancer is stronger than for any other common malignancy, and an estimated 57% of all uterine cancers in the United States are related to obesity.[3 15] The uses of unopposed estrogen and tamoxifen are also recognized risk factors for endometrial cancer.[2 3] Importantly, Latin American countries are among those for which there is a high ratio between mortality and incidence rate for endometrial cancer.[12] Although there are several potential reasons for this high ratio, insufficient access to state-of-the-art molecular diagnosis and treatment probably plays an important role.[9]

## MOLECULAR PATHOLOGY AND BIOMARKERS

Historically, endometrial cancer has been broadly divided into endometrioid (nearly 80% of cases) and non-endometrioid tumors, each having somewhat distinct pathogeneses and associations with estrogen exposure.[3 4] Non-endometrioid tumors include endometrial serous carcinoma (the most common subtype), clear cell carcinoma, and carcinosarcoma (or malignant mixed Müllerian tumors).[3] Endometrial cancer is graded using the International Federation of Gynecology and Obstetrics (FIGO) system on a scale of 1 to 3; grade 1 and grade 2 tumors are associated with a good prognosis, whereas grade 3 tumors are associated with an intermediate or poor prognosis.[3 7]

Despite the usefulness of conventional pathology, it has become increasingly apparent that histological classification lacks reproducibility and is inadequate for reliable prognostic discrimination.[17] The Cancer Genome Atlas classification, based on a combination of somatic mutational burden and somatic copy number alterations, allowed the division of endometrial cancer into four molecular subtypes: DNA polymerase epsilon (*POLE*) ultramutated tumors, tumors with high microsatellite instability (MSI-H), copy-number-low tumors, and copy-number-high tumors.[5] More recently, the Proactive Molecular Risk Classifier for Endometrial Cancer initiative allowed a similar classification using surrogate testing with clinically available markers; endometrial cancer is thus classified as *POLE*-mutated, mismatch repair-deficient (MMRd), p53 abnormal (characterized by aberrant p53 immunohistochemical staining, corresponding to copy-number-high tumors), and non-specific molecular profile tumors (p53 wild type, corresponding to copy-number-low tumors).[18] This classification is shown in Table 1, which displays selected features of each of the four molecular subtypes of endometrial cancer.[4 7 18]

The molecular subtyping of endometrial cancer increasingly provides diagnostic and prognostic insights, and helps the clinician to make treatment decisions.[2 3 6] In both the early- and advanced-disease setting, molecular tumor features can already be used to guide therapy, particularly in MSI-H tumors.[3 19 20] Therefore, the Proactive Molecular Risk Classifier for Endometrial Cancer classification should be applied to all endometrial cancer specimens, regardless of histological type.[6 7 18] Moreover, molecular classification has predictive value, since MSI-H tumors are amenable to immunotherapy, as discussed later.[6] Furthermore, additional treatment-relevant molecular biomarkers, such as detection of human epidermal growth factor receptor 2 (HER2)-positive tumors, has implications, particularly for serous carcinoma, given the availability of anti-HER2 therapy.[21] MSI-H/MMRd testing also serves to screen for Lynch syndrome, which accounts for nearly 3% of all endometrial cancers and 9% of those in women aged <50 years.[3 7]

**Table 1** Selected typical features of the four molecular subtypes of endometrial cancer.

| Features | *POLE*-mutated | Mismatch repair-deficient | p53 abnormal | Non-specific molecular profile |
|---|---|---|---|---|
| Frequency, % of patients | 5–15 | 25–30 | 5–17 | 30–50 |
| Age <60 years, % of patients | ~60 | ~40 | ~5–10 | ~50 |
| Clinical features | Lower BMI<br>Early stage | Higher BMI<br>Lynch syndrome | Lower BMI<br>Advanced stage | Higher BMI |
| Histological features | Endometrioid<br>Often high grade<br>Prominent TILs | Endometrioid<br>Often high grade<br>Prominent TILs | Any histology<br>Often high grade<br>Low level of TILs | Endometrioid<br>Often low grade<br>Absence of TILs |
| Microsatellite status | Stable | Unstable | Stable | Stable |
| p53 abnormalities, % of patients | ~35 | ~5 | >90 | ~1 |
| Prognosis | Good | Intermediate | Poor | Intermediate |

Adapted from Morice et al 2016, Oaknin et al 2022, and Kommoss et al 2018.[4 7 18]
BMI, body mass index; *POLE*, DNA polymerase epsilon; TIL, tumor-infiltrating lymphocyte.

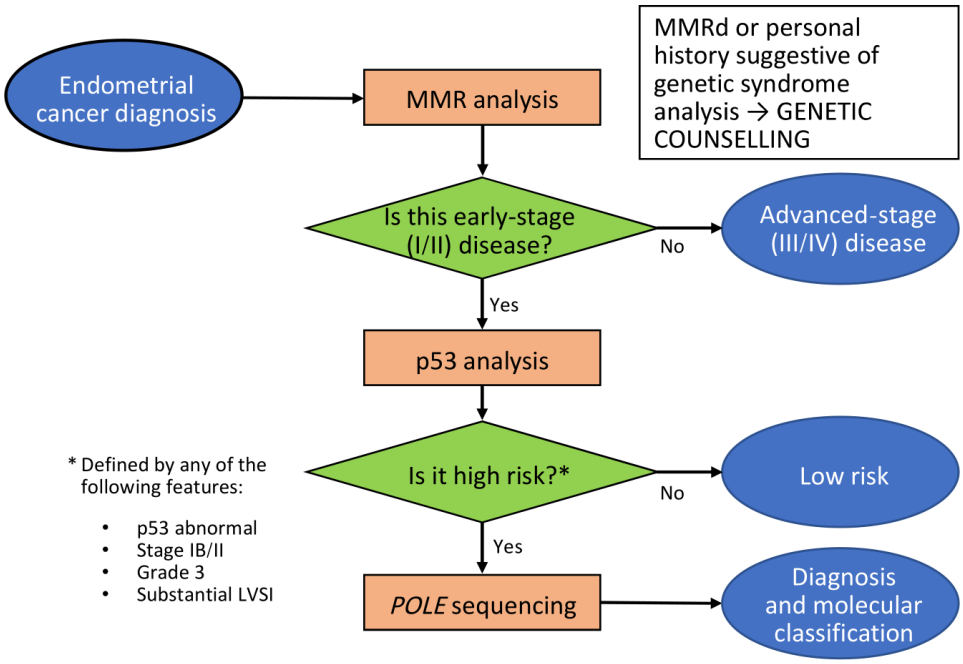


**Figure 1** Algorithm for treatment decisions in endometrial cancer using molecular classification and selected clinical features (adapted from Betella et al. 2022[22]). LVSI, lymphovascular space invasion; MMR, mismatch repair; MMRd, mismatch repair-deficient; *POLE*, DNA polymerase epsilon.

Figure 1 displays an algorithm that might lead to a reduction in the number of required tests without affecting risk classification.[22] Although the international literature suggests that Proactive Molecular Risk Classifier for Endometrial Cancer biomarkers can be assessed in routine surgical pathology without the need for extensive sequencing,[7] wide availability of such testing remains challenging in Latin America.[9]

In particular, *POLE* sequencing and the assessment of the tumor mutational burden remain problematic, since they are available in only a few centers in Latin America,[9] where efforts are needed to ensure wider availability and to streamline diagnostic capabilities within the region; without this, the full benefit offered by precision medicine cannot be achieved. The use of a small number of well-established immunohistochemical markers and selected clinical features, with *POLE* sequencing in a small number of cases not already classified by the other markers, is a potential approach for implementing molecular pathology in clinical practice.[7 22] *POLE* testing, where the minimal requirement is the adequate assessment of the five most frequent *POLE* hotspot variants, should be carried out in specialist centers; not all *POLE*-mutated tumors are pathogenic.[7 23]

## EVOLVING THERAPEUTIC LANDSCAPE IN ENDOMETRIAL CANCER

The transition from the chemotherapy era to the age of targeted agents and immunotherapy started later in endometrial cancer than in many other tumor types[24]; nevertheless, we are witnessing the dawn of precision medicine as applied to this disease, and the therapeutic landscape is rapidly changing.[7 8] The prognostic outcomes of the molecular subtypes of endometrial cancer can vary (Table 1): the presence of *POLE*-mutated subtype being an indicator for excellent prognosis, regardless of the type of adjuvant treatment; p53 abnormal subtype, an indicator for the poorest prognosis, with significant benefit from adjuvant chemotherapy; MMRd subtype, with intermediate prognosis and unclear benefit from adjuvant chemotherapy alone; non-specific molecular profile subtype, with intermediate prognosis and some benefit from adjuvant chemotherapy.[7 23] As we improve our understanding of molecular classification and of the role of targeted therapy and immunotherapy in the refractory setting, the use of precision medicine in the first line is shifting the treatment paradigm in endometrial cancer. Targeting different pathways, based on early molecular profiling of individual patients, offers a promising strategy to enhance anti-tumor activity.

Some of the most influential phase III trials in advanced/metastatic endometrial cancer provide a benchmark for comparison when considering the role of novel agents, such as targeted therapy and immunotherapy.[25–30] Table 2 summarizes the key features and results of these trials, which allowed the establishment of the current standard of carboplatin plus paclitaxel as the preferred first-line regimen for patients with metastatic disease[6 7 30]; moreover, Table 2 displays the results of recent phase III trials of immunotherapy.

As up to 30% of patients with advanced endometrial cancer have MSI-H/MMRd tumors, which is often associated with a relatively high level of neoantigens and tumor-infiltrating lymphocytes,[7 31] there is sufficient evidence to recommend the use of immunotherapy in patients with advanced or recurrent endometrial cancer whose cancer has progressed following prior therapy.[3 7] Such evidence stems from phase I–III trials of a variety of agents, including atezolizumab, dostarlimab, durvalumab, pembrolizumab (with or without lenvatinib), and tremelimumab.[7 19 20 31–33] Currently approved among these agents in patients with advanced or recurrent endometrial cancer are pembrolizumab, following prior treatment for endometrial cancer, and dostarlimab, following prior platinum-based treatment for endometrial cancer for MMRd tumors; pembrolizumab for tumors with high tumor mutational

**Table 2** Selected phase III trials in advanced/metastatic endometrial cancer.

| Trial overview and outcomes | GOG[25] | EORTC55872[26]* | GOG107[27] | GOG[28] | GOG[29] | GOG0209[30] | RUBY[41] | NRG-GY018[40] | AtTEnd[33 38] | DUO-E[39] | LEAP-001[43] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Key question | Role of chemotherapy | Single agent vs doublet | Single agent vs doublet | Doublet vs doublet | Doublet vs triplet | Doublet vs triplet | Role of dostarlimab | Role of pembrolizumab | Role of atezolizumab | Role of durvalumab + olaparib | Role of pembrolizumab + lenvatinib |
| Population | Stage III/IV | Stage III/IV and relapsed | Stage III/IV and relapsed | Stage III/IV and relapsed | Stage III/IV and relapsed | Stage III/IV | Stage III/IV (23.9% MSI-H/MMRd) | Stage III/IV (27.6% MMRd) | Stage III/IV (22.8% MMRd) | Stage III/IV (19.9% MMRd) | Stage III/IV |
| N | 396 | 177 | 299 | 317 | 273 | 1381 | 494 | 816 | 549 | 718 | 842 (estimated) |
| Comparison | Whole-abdominal irradiation vs Dox + CDDP | Dox vs Dox + CDDP | Dox vs Dox + CDDP | Dox + CDDP vs Dox + P | Dox + CDDP vs Dox + CDDP + P | Carbo + P vs Dox + CDDP + P | Carbo + P ± dostarlimab | Carbo + P ± pembrolizumab | Carbo + P ± atezolizumab | Carbo + P vs Carbo + P + durvalumab vs Carbo + P + durvalumab + olaparib | Carbo + P vs pembrolizumab + lenvatinib |
| PFS | Significant HR=0.71 | NS | Significant HR=0.73 | NS | Significant p<0.01 | Non-inferior | Significant HR=0.28 in MSI-H/MMRd and 0.64 overall | Significant HR=0.30 in MMRd and 0.54 in MMRp | Significant HR=0.36 in MMRd | Significant HR=0.71 in durvalumab arm and 0.55 in durvalumab + olaparib arm | PEP not met |
| OS | Significant HR=0.68 | NS | NS | NS | Significant p<0.037 | Non-inferior | Significant HR=0.64 overall | Not available | Interim data: Significant HR=0.82 overall | Interim data: HR=0.77 in durvalumab arm and 0.59 in durvalumab + olaparib arm | PEP not met |

*A phase II/III trial.
Carbo, carboplatin; CDDP, cisplatin; Dox, doxorubicin; EORTC, European Organisation for Research and Treatment of Cancer; GOG, Gynecological Oncology Group; HR, hazard ratio; MMRd, mismatch repair-deficient; MMRp, mismatch repair-proficient; MSI-H, microsatellite instability-high; NS, not significant; OS, overall survival; P, paclitaxel; PEP, primary endpoint; PFS, progression-free survival.

burden following prior treatment; and pembrolizumab plus lenvatinib in the United States, following prior systemic treatment for endometrial cancer for those with neither MSI-H/MMRd, and in Europe, following prior platinum-based treatment for endometrial cancer for those regardless of mismatch repair status and who are not candidates for curative surgery or radiotherapy.[34–37]

Moreover, several phase III trials in the front-line primary advanced or recurrent setting have reported positive results or are currently ongoing to test immunotherapy alone or combined with chemotherapy or other agents. For example, data from the phase III AtTEnd trial, in which 549 patients (22.8% with MMRd tumors) with advanced or recurrent endometrial cancer (stage III/IV, newly diagnosed or recurrent disease with no prior systemic chemotherapy for recurrence) were randomized to receive either carboplatin plus paclitaxel combined with atezolizumab (a programmed cell death ligand 1 (PD-L1) inhibitor) or placebo, followed by atezolizumab monotherapy or placebo until disease progression, were encouraging.[33] In the MMRd subgroup, patients treated with atezolizumab demonstrated significant improvements in progression-free survival relative to those in the control arm (HR=0.36; 95% CI 0.23 to 0.57; p=0.0005).[33] In addition, interim analysis of overall survival indicated a positive trend for atezolizumab in the MMRd population.[33 38] The safety profile was consistent with expected toxicities.[33 38] In the phase III DUO-E trial, which also included patients with advanced or recurrent endometrial cancer, the combination of carboplatin plus paclitaxel with durvalumab (a PD-L1 inhibitor), followed by ongoing treatment with durvalumab with or without olaparib, showed a statistically significant and clinically meaningful progression-free survival benefit in the overall population: HR=0.71 (95% CI 0.57 to 0.89; p=0.003) and 0.55 (95% CI 0.43 to 0.69; p<0.0001) for the durvalumab and durvalumab plus olaparib arms, respectively.[39] The progression-free survival pre-specified subgroup analysis showed benefit in both MMRd and in the mismatch repair-proficient (MMRp) populations, with a consistent safety profile with the known toxicities of the agents observed across treatment arms.[39]

The phase III NRG-GY018 trial assessed paclitaxel plus carboplatin combined with pembrolizumab or placebo in 816 patients with endometrial cancer (newly diagnosed stage III/IV or with first recurrence), 27.6% of whom had MMRd tumors.[40] The addition of pembrolizumab significantly increased progression-free survival, the primary endpoint in this trial. The HR was 0.30 (95% CI 0.19 to 0.48; p<0.001) in the MMRd population, and 0.54 (95% CI 0.41 to 0.71; p<0.001) in the MMRp population.[40] In the recent phase III RUBY trial, 494 patients (23.9% with MSI-H/MMRd tumors) with advanced endometrial cancer (newly diagnosed stage III/IV or with a first recurrence) were randomized to receive carboplatin plus paclitaxel combined with dostarlimab or placebo (every 3 weeks for six cycles), followed by dostarlimab or placebo (every 6 weeks for up to 3 years), with progression-free survival and overall survival as dual primary endpoints.[41] The addition of dostarlimab significantly increased progression-free survival, with a HR of 0.28 (95% CI 0.16 to 0.50; p<0.001) in the MSI-H/MMRd population and 0.64 (95% CI 0.51 to 0.80; p<0.001) in the overall population. The HR for overall survival at the first interim analysis was 0.64 (95% CI 0.46 to 0.87) in the overall population; however, overall survival results were not yet mature at this time.[41] In a recent update, statistically significant overall survival benefits in the overall population were announced for the RUBY trial, which makes dostarlimab plus chemotherapy the first immuno-oncology combination regimen to show an overall survival benefit in this patient population.[42] In both trials, the profile of adverse events was expected for these agents.[40 41] Of note, the most recent recommendations by the National Comprehensive Cancer Network (NCCN) already include dostarlimab and pembrolizumab (category 1) on the basis of these trials and according to their respective populations.[8]

More recently, in the phase III LEAP-001 trial, pembrolizumab plus lenvatinib treatment did not meet its dual primary endpoints of progression-free survival and overall survival for the first-line treatment of patients with advanced or recurrent endometrial cancer whose disease was MMRp/not MSI-H or MMRd/MSI-H.[43] Based on these results, pembrolizumab plus lenvatinib is not likely to be an approved approach in the first-line setting, although continues to be a treatment option for those previously treated for endometrial cancer as described in the aforementioned approvals in this setting.[34 36 44]

The positive results from the immuno-oncology trials have begun to affect the approved treatment options for primary advanced or recurrent endometrial cancer,[7 8] with the first indications aligned to the RUBY trial.[41] In the United States (US Food and Drug Administration), dostarlimab was approved in combination with carboplatin and paclitaxel, followed by single-agent dostarlimab, for advanced or recurrent endometrial cancer that is MMRd or MSI-H.[37 42 44] Dostarlimab plus chemotherapy gained approval as the first front-line immuno-oncology treatment in Europe (European Medicines Agency) for patients with advanced or recurrent MMRd/MSI-H endometrial cancer.[35 45 46] In other regions, dostarlimab has been approved for the treatment of patients with advanced or recurrent MMRd/MSI-H endometrial cancer as first-line treatment in Canada and the United Kingdom, and as second-line treatment in Argentina and Brazil.[42 47–49]

Subsequent exploratory analysis from the RUBY trial by molecular classification was associated with improved progression-free survival and overall survival outcomes in the dostarlimab plus carboplatin–paclitaxel arm, thereby potentially enabling the use of additional predictive markers for response to immunotherapy in patients with advanced or recurrent endometrial cancer.[50] In the 400 patients with whole exome sequencing results available (400/494 subjects), progression-free survival according to molecular subgroup were reported as follows: HR=0.31 (95% CI 0.17 to 0.56), 0.55 (95% CI 0.3 to 0.99), and 0.77 (95% CI 0.55 to 1.07) in the MMRd/MSI-H, p53 abnormal, and non-specific molecular profile subgroups, respectively. Likewise, overall survival according to molecular subgroup were reported as follows: HR=0.4 (95% CI 0.17 to 0.95), 0.41 (95% CI 0.2 to 0.82), and 0.87 (95% CI 0.56 to 1.36) in the MMRd/MSI-H, p53 abnormal, and non-specific molecular profile subgroups, respectively.[50] These exploratory results further demonstrate the importance of molecular characterization, and highlight the heterogeneity within the MMRp population.

Regardless, the notable benefit in overall survival rates observed in the RUBY trial, coupled with the approval of dostarlimab by major regulatory agencies, has the potential to establish a new treatment standard for patients with advanced or recurrent endometrial cancer.[45] Unlike many phase III trials, including NRG-GY018, the RUBY trial included patients with carcinosarcoma (approximately 10%), an aggressive histology, and as such dostarlimab is

currently the only immuno-oncology therapy recommended in this subtype.[35 37 40 42]

A low-hanging fruit in the attempt to choose treatment for patients with recurrent endometrial cancer based on molecular features is represented by HER2-positive disease, present in up to one-third of women with endometrial serous carcinomas.[6 7] The addition of trastuzumab to the backbone of carboplatin plus paclitaxel improves progression-free survival and overall survival in these women and is considered the preferred option in HER2-positive serous carcinomas.[8 21 51] In a non-randomized phase II study in patients with recurrent MMRp endometrial cancer, the use of avelumab in combination with talazoparib (polyadenosine diphosphate-ribose polymerase inhibitor) showed clinical benefit (objective response rate 11.4%, and progression-free survival rate at 6 months 22.9%) and a favorable toxic effects profile in a subset of patients with homologous recombination repair alterations and/or a platinum-free interval of ≥6 months, warranting further investigation.[52]

In the second-line treatment, a large number of trials have tested a variety of single agents. Of note, treatment with monotherapy with immune checkpoint inhibitors pembrolizumab and dostarlimab has proved effective as a second-line therapy in patients with previously treated, MMRd/MSI-H endometrial cancer, as demonstrated by the KEYNOTE-158 and GARNET studies.[19 20] In the phase II non-randomized KEYNOTE-158 study, patients demonstrated a robust and durable antitumor activity with an objective response rate of 48% (95% CI 37 to 60), the primary endpoint in this trial.[19] Dostarlimab was granted approval as a result of positive findings from the ongoing phase I GARNET study, which reported an objective response rate of 45.5% (95% CI 37.1 to 54.0) and 15.4% (95% CI 10.1 to 22.0) for patients with MMRd/MSI-H and MMRp/microsatellite stable endometrial cancer, respectively.[35 37] In addition, a phase II non-randomized study (PHAsE II trial of DuRvalumab in Advanced Endometrial Cancer (PHAEDRA)) in patients with advanced endometrial cancer found treatment with durvalumab might benefit those with MMRd tumors irrespective of prior lines of chemotherapy, whereas evidence of activity in those with MMRp tumors was limited.[53]

Other phase II trials in the second line tested single agents, with response rates averaging 15%, with short durations of response and progression-free survival.[54–56] More recently, however, notable improvements relative to chemotherapy have been demonstrated in trials evaluating newer modalities in the second line, which have led to the development of additional phase III trials in the primary treatment setting.[39 40] For example, hormone therapy remains an option for women with hormone-receptor-positive, advanced or recurrent endometrioid tumors that are grade 1 or 2; unfortunately, no phase III trials have compared chemotherapy with hormonal therapy as first-line treatment.[3 6 7] However, a recent randomized phase II trial has shown improvements in disease-control rate and progression-free survival for letrozole plus palbociclib, compared with letrozole plus placebo,[57] leading to the design of an ongoing phase III trial testing a similar strategy in the first line (European Network for Gynecological Oncological Trials (ENGOT)-en17/GINECO/EQ132-303).[58]

The identification of other molecular alterations is progressively allowing the exploration of approaches to precision medicine for the management of patients with endometrial cancer. For instance, the mammalian target of rapamycin pathway is dysregulated in endometrial cancer, and inhibition of this pathway shows clinical activity that is potentially superior to that of single-agent endocrine or chemotherapy in recurrent disease, despite increased toxicity.[59] Likewise, phosphoinositide 3-kinase (PI3K) and fibroblast growth factor receptor alterations in endometrial cancer provide a basis for testing agents such as alpelisib (a PI3K inhibitor) and infigratinib (a fibroblast growth factor receptor 2 inhibitor), among others.[60] Given the relevance of the PI3K pathway in endocrine-sensitive tumors, an ongoing randomized phase II trial (ENGOT-en19/NSGO-CTU/ALPACA) is testing the addition of PI3K inhibitor alpelisib to letrozole among patients with estrogen-receptor-positive, advanced endometrioid tumors.[61] Finally, the exportin-1 inhibitor selinexor has shown promising results in early trials and has improved progression-free survival in comparison with placebo when used as maintenance therapy, particularly in p53-wild type and MMRp tumors.[62] A phase III trial of selinexor (ENGOT-EN5/GOG-3055/SIENDO) is ongoing in patients with p53-wild type tumors.[62]

Finally, based on the ever-growing understanding of disease biology and biomarkers in endometrial cancer, ongoing randomized trials such as Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) 4a and the Refining Adjuvant treatment IN endometrial cancer Based On molecular features (RAINBO) program aim to validate adjuvant treatment decisions for all histological subtypes, across four molecular class-directed adjuvant treatment strategies following surgical resection.[63–65] These trials may enable more refined treatment selection, including the potential to de-escalate treatment in select situations.

## SPECIFIC CHALLENGES AND SOLUTIONS IN LATIN AMERICA

Latin American countries face considerable constraints in healthcare that hamper implementation of the more costly state-of-the-art interventions recommended by international guidelines.[9 10 66] When it comes to the treatment of endometrial cancer, such constraints mainly affect the availability of specialized surgeons, contemporary radiotherapeutic modalities, imaging, and pathology expertise, including molecular methods, and novel agents, such as targeted therapy and immunotherapy.[9] Nevertheless, there is considerable heterogeneity in access to such interventions within the same country.[10] As a result, the following discussion considers that internationally recognized guidelines should be followed whenever possible, given local characteristics of healthcare; conversely, sensible alternatives are discussed for settings in which guideline implementation remains unrealistic.

### Early-Stage Disease

Timely evaluation of symptomatic patients, a key component in the management of early-stage disease, remains problematic in the typical healthcare setting in Latin America.[67] Experience from large institutions suggests that up to a third of patients present with advanced disease, with no apparent trend for improvement over the past two decades.[68 69] The ideal of clinical and gynecological examination, transvaginal ultrasound, blood workup, and MRI of the pelvis is often incompletely available in a timely manner.[7] As a result, the Brazilian Society of Surgical Oncology, for example, has recommended that MRI can be omitted in patients with apparent early-stage endometrial cancer by physical examination and

transvaginal ultrasound, with CT used to evaluate lymph nodes and lungs in cases of suspected locally advanced or extrauterine disease.[9]

Waiting times for surgery are also problematic in Latin America,[67] despite the adverse prognostic implications found in endometrial cancer.[70] For patients who can undergo surgery for early-stage (FIGO stages I and II) disease, minimally invasive surgery is considered the preferred approach in international guidelines, based on randomized trials demonstrating similar outcomes to those from laparotomy.[6–8] Likewise, sentinel lymph-node dissection plays a major role among patients with low and intermediate risks, affording reduced morbidity, increased sensitivity, and no impact on survival.[6–9] Owing to the often limited availability of surgical expertise and infrastructure for sentinel lymph node dissection and laparoscopy in resource-limited centers, the Brazilian Society of Surgical Oncology recommends the following: performing a complete lymphadenectomy for patients with micrometastases detected by ultrasound, and considering the addition of pelvic and systematic retroperitoneal lymphadenectomy if radiotherapy is unavailable.[9] In centers without access to radiotherapy, the Brazilian Society of Surgical Oncology recommends the surgeon to consider radical hysterectomy as a strategy to ensure free margins. Moreover, in the absence of brachytherapy, in patients with cervical invasion without parametrial invasion, radical hysterectomy is not recommended.[9]

### Adjuvant Therapy

Using conventional pathology, the surgical staging of endometrial cancer includes assessment of lymph nodes, and risk stratification also takes into account histological type, grade, the presence of lymphovascular space invasion, myometrial infiltration, and local/regional involvement.[6–8] As discussed, molecular features are increasingly being used to improve prognostic stratification. As a result, the current definition of prognostic risk groups recommended in the joint statement of the European Society of Gynaecological Oncology, European Society for Radiotherapy and Oncology, and European Society of Pathology is provided both for situations in which molecular classification is available and unavailable.[6]

Adjuvant treatment recommendations can then be tailored on the basis of prognostic risk groups.[6] The frequent unavailability of molecular testing in Latin American institutions limits the use of the molecular-based system. Moreover, given the scarcity of resources, radiotherapy and brachytherapy may represent a bottleneck for patients at intermediate, high–intermediate, and high risks; in Brazil, for example, it has been estimated that a deficit of 255 radiotherapy machines, 387 radiation oncologists, and 546 radiation physicists existed in 2015.[67] For high-risk patients, in whom combination chemotherapy has been associated with favorable long-term outcomes in some studies,[25 71] chemotherapy availability can also be problematic, considering patient distance from centers, drug shortages, pricing issues, and the infrastructure required to provide safe administration.[9 67] Likewise, continued effort is needed to implement state-of-the-art chemoradiation, especially in light of significant gains in both overall survival and failure-free survival, when compared with radiation alone, particularly among women with stage III endometrial cancer.[72] However, it should be noted that there is some evidence suggesting that the addition of radiotherapy to chemotherapy might not prolong disease-free survival or overall survival compared with chemotherapy alone; chemotherapy alone may thus be an option for high-risk patients at sites where radiotherapy is not available.[71]

### Recurrent and Metastatic Disease

The treatment of patients with recurrent/metastatic endometrial cancer is ideally provided using a multidisciplinary approach in specialized centers and should be guided by the patient's condition, extent of disease, prior treatment, and molecular profile, when feasible.[7] Unfortunately, tumor boards and other types of multidisciplinary interaction do not seem to be common in Latin American institutions. Nevertheless, this approach is feasible, but requires continual efforts and institutional support.[73] Similar efforts are needed to reduce disparities, improve access to diagnostic and therapeutic modalities, and increase access to clinical trials for Latin American patients. In the first line, the conventional regimen of carboplatin (area under the curve 5–6 mg/mL/min) and paclitaxel (175 mg/m$^2$ every 3 weeks) for six cycles is generally available, and trastuzumab can be added in HER2-positive disease, particularly for serous tumors.[6–8 21 30] Trastuzumab, although recommended by the NCCN for patients with advanced or recurrent HER2-positive serous carcinoma,[8] is not approved for endometrial cancer in Brazil and elsewhere, which may preclude reimbursement both in the public and private settings; however, the availability of trastuzumab biosimilars when approved is expected to facilitate treatment of HER2-positive disease.[7 8] For patients with low-grade tumors without rapidly progressive disease, medroxyprogesterone acetate (200–300 mg/day) or megestrol acetate (160 mg/day) can be tried before chemotherapy.[6]

Until very recently, there was no standard second-line therapy for patients with recurrent disease after carboplatin plus paclitaxel,[4 6–8] but there is increasing reason to choose second-line therapy based on molecular profile. Indeed, current NCCN guidelines recommend (category 1) dostarlimab or pembrolizumab for MMRd tumors and pembrolizumab–lenvatinib for MMRp tumors.[8] Moreover, the European Society for Medical Oncology provides recommendations for second-line therapy based on mismatch repair status, with dostarlimab and pembrolizumab–lenvatinib as options for MMRd tumors.[7] Pembrolizumab (200 mg every 3 weeks) plus lenvatinib (20 mg/day) is an attractive regimen for MMRp tumors because of its progression-free survival and overall survival superiority to single-agent chemotherapy, but doubts remain surrounding its toxicity profile, and the safety of reducing lenvatinib doses without loss of efficacy in clinical practice. The toxicity associated with this combination includes hypertension in relation to lenvatinib, hypothyroidism in relation to pembrolizumab, nausea/vomiting, diarrhea, fatigue, decreased appetite, weight loss, hand–foot syndrome, and proteinuria.[32 34 36] These adverse reactions must be managed with supportive care medications and judicious modifications of lenvatinib doses, reduced from the recommended dose of 20 mg/day as needed (14 mg/day, 10 mg/day, 8 mg/day, or 4 mg/day) to ensure safety and tolerability are prioritized.[32] Single-agent immunotherapy remains an option in patients with MMRp tumors when toxicity concerns

remain, in which case single-agent pembrolizumab or dostarlimab could be considered, respecting their corresponding and slightly different indications.[8 20] Once again, molecular profiling and access to these agents is a barrier to be overcome in Latin America in order to ensure widespread implementation of this strategy.

## CONCLUSION

Despite the lack of major therapeutic advances over recent decades, we are witnessing the dawn of precision medicine for understanding and management of endometrial cancer, and the therapeutic landscape is rapidly changing due to the introduction of molecular characterization and targeted treatment of this disease. Targeting different mechanistic pathways on the basis of molecular profiling offers a promising strategy to enhance anti-tumor activity, and recent phase III trials confirm the value of this approach.[40 41] Indeed, the first significant improvements in overall survival relative to chemotherapy alone have been demonstrated in the RUBY trial due to these advancements.[42]

Ongoing randomized trials aim to expand the role of such strategies with novel agents and in additional treatment settings. Although the heterogeneity of care in Latin America continues to be a reason for concern, efforts are being made at various levels to increase access to contemporary surgical, radiotherapeutic, imaging, and pathology expertise, as well as to novel systemic agents. Developing and implementing a reproducible and affordable system encounters significant cost barriers and resource limitations, exacerbating healthcare disparities and widespread accessibility.[9 10] The challenge lies in developing a sustainable model that addresses these issues, ensuring comprehensive care of all patients with endometrial cancer. It is hoped that an increasing number of patients in this world region will receive state-of-the-art management, including access to novel treatments, as recommended by international guidelines. Resource-stratified guidelines are welcome in low-income and middle-income areas.

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