

# The Shifting Landscape of p53abn Endometrial Cancers: A Review of the Prognostic and Predictive Impact and Current Therapeutic Directions

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## Abstract

The major stepping stone laid towards the identification of high-risk endometrial cancers was made by the Cancer Genome Atlas in 2013 when the four distinct molecular subtypes were initially described. This improved risk stratification for women with endometrial cancer and ignited a major interest which led to further research on the prognostic and predictive value of molecular subtyping. Through the elaboration of ProMisE, molecular risk assignment using surrogate markers became practical and accessible to most pathology laboratories. The p53abn molecular subtype of endometrial cancer is responsible for the worst outcomes. This review aims to provide an in-depth understanding of the characteristics of these aggressive ECs, summarizing up-to-date literature regarding the prognostic and predictive implications, as well as present and future treatment directions.

**Keywords:** *endometrial cancer; molecular classification; p53abn; adjuvant therapy; targeted therapy*

## 1. Introduction

With over 417,000 newly diagnosed cases globally in 2020, of which over 130,000 are in Europe and a reported increase in incidence rates (1), endometrial cancer (EC) is becoming a frequent cause of death by cancer in women. Going by the almost 100,000 yearly reported deaths attributed to EC (1), this type of malignancy is still facing management challenges which should not be overlooked.

Although the vast majority of ECs have a long-term favorable outcome due to early detection (80%), with 5-year survival rates as high as 95% for stage I disease (2), a major

challenge in the management of early-stage EC is delineating the patients presenting with a higher risk of recurrence and in need of a more intensified therapeutic approach. Solely basing treatment recommendations on traditional clinico-pathological factors minimalizes the heterogeneity of the tumoral biology and has already proven to be responsible for the frequent overtreatment or undertreatment of EC patients (3).

Paradoxically, the aggressive pathological features of a tumor can be insufficient in depicting the poorer long-term outcome for the patient with EC, as molecular characteristics have shown to be of more reliable prognosti-

cation value. Thus, integrating high risk pathological features such as the presence of myometrial or lymphovascular invasion and a higher tumor grade can lead to a more intensified treatment approach in cases with independently excellent outcomes, such as the *POLE* mutant tumors (4). On the opposite side of the spectrum, interpreting lower-grade endometrioid histotypes and early-stage diseases potentially harboring an aggressive molecular profile, such as the *TP53* mutant subtype, can lead to insufficient adjuvant treatment (3) and higher recurrence rates later on (5).

In this review, we have summarized the current literature about the importance of p53abn diagnosis as well as the prognostic and predictive implications of this aggressive subtype.

## **2. TCGA molecular classification and the development of ProMisE**

Through an extensive and complex genome-wide investigation performed using sequencing and array testing on 373 ECs, the cancer genome atlas (TCGA) elaborated the first molecular-based stratification system of ECs (6), showing 4 subtypes, each revealing distinct prognostic and predictive clinical value: Polymerase Epsilon ultra-mutated (*POLE* ultra-mutated), microsatellite instability hypermutated (MSI hypermutated), copy number low and copy number high. While *POLE*mut ECs exhibit a highly favorable outcome, independent of other clinicopathological variables (4) and do not benefit from adjuvant therapy (7), p53abn ECs are usually associated with higher-risk histotypes such as serous, clear cell, high-grade endometrioid or even carcinosarcomas (8), have a poor clinical outcome with the highest death rate documented among all molecular subtypes (5) and benefit the most from the addition of adjuvant chemotherapy.

As the technologies used in the development of the TCGA molecular classification are less likely to be widely applicable in the clinical setting due to their complexity and cost-inefficiency, Talhouk et. al developed ProMisE (9), a substantially tested classifier using a combination of IHC and mutation analysis to assign patients with EC in one of the four redefined

molecular subtypes: *POLE*mut, mismatch-repair deficient (dMMR), no specific molecular profile (NSMP) and p53 abnormal (p53abn). This is more feasible and cost-effective, providing broader accessibility for most pathology labs. This classifier has proven to offer a consistent prognostic value for progression-free and disease-specific survival (10-11). In a further approach to validate the prognostic implications of the surrogate assignment, the TransPORTEC initiative analyzed 947 ECs of endometrioid histology deriving from the PORTEC-1 and PORTEC-2 trials (12) and confirmed how integrating clinicopathological factors such as age, tumor grade, depth of myometrial invasion and lymphovascular space invasion with molecular alterations can additionally refine the risk prognostication of ECs. Further studies have also proven a high concordance between pre-surgical endometrial biopsy specimens and definitive hysterectomy specimens regarding the molecular subtype assignment, as well as interlaboratory concordance (13-14).

## **3. P53abn diagnosis and interpretation**

The *TP53* mutational status, characteristic of the p53abn subtype, is most commonly determined through p53 IHC staining, which is used as a recognized surrogate for its reliable inter-laboratory reproducibility and high availability (15). This comes as a result of studies which have shown high concordance between p53abn IHC findings and *TP53* mutation obtained by NGS (16). In the analysis of the TransPORTEC cohort, the p53abn group and the presence of substantial LVSI have proven to be the strongest unfavorable indicators for locoregional and distant recurrence, as well as impaired overall survival, both being further designated as unfavorable risk factors (12). This comes as additional confirmation to another TransPORTEC study which evaluated the prognostic value of the molecular subtypes and described a lower 5-year recurrence-free survival interval (42%), a lower 5-year overall survival (40%) as well as a higher risk of developing distant metastasis in 5-years time (50%) for the p53abn subtype when compared to the other 3 molecular subtypes (17).

**Table 1.** p53abn important features (IHC – immunohistochemistry, NGS – next generation sequencing, RFS – recurrence free survival, EC – endometrial cancer, OS – overall survival)

**p53abn subtype**

<b>Diagnostic test</b>	p53 IHC („null” / overexpressed pattern) NGS for TP53
<b>Somatic copy number alterations</b>	Very high
<b>Defining mutation</b>	TP53 (92%)
<b>Clinical outcome</b>	Poor
<b>Prognostic value (%)</b>	Low 5-year RFS (42%) Low 5-year OS (40%) High risk of developing distant metastasis in 5 years (50%)
<b>Expression across EC histotypes (%)</b>	Serous carcinomas (93%) Carcinosarcomas (85%) Clear-cell carcinomas (35%) G3 Endometrioid EC (22%) G1/G2 Endometrioid EC (5%)
<b>Histological features</b>	Lymphovascular space invasion Myometrial invasion G3

The p53abn subtype is predominantly described as having the poorest clinical outcome. Although only accounting for about 15% of all ECs, it is consistently responsible for 50 to 70% of all EC deaths (18). In a multivariable analysis, the p53abn subtype has been shown to have a 1.8x higher risk of progression than the p53 wild-type, with patients of this group also having a 2 times higher risk of death (5). This subtype is typically defined by a very high number of somatic copy number alterations and the ubiquitous *TP53* mutation. The occurrence of the *TP53* mutation with a frequency of 92% in the copy number high TCGA subtype (6) is accountable for the gain and loss of the p53 function consecutive to a vast range of mutations. While the gain of function is associated with the accumulation of nuclear p53 in the cell nucleus and is responsible for a major overexpression identifiable by IHC, the loss of function interferes with accurate protein translation and leads to the so-called „null pattern” and much more rarely to the accumulation in

the cell cytoplasm (19). Singh et. al reported about a 5% prevalence of heterogenous expression patterns (15). These distinct patterns are defined by the overexpression, complete absence, cytoplasmic staining of p53 or any combination of these alternating with wild-type staining. An abnormal expression of at least 10% is required for it to be deemed as sub-clonal, although a more recent study proved that sub-clonality can appear as small multifocal areas in even less than 10% of the tumor volume (20). Literature suggests that the sub-clonal pattern might be discordant with the detection of a *TP53* mutation at times, this being dependent on the area of DNA extraction which will be later used in the sequencing process (21). A subsequent p53 expression analysis of 424 ECs included in the PORTEC-3 trial outlined a higher rate of 7% of subclonal staining, with all cases presenting as mutant overexpression and half of them presenting with an underlying *TP53* mutation (20). The subclonal *TP53* mutation is most frequently,

but not solely highlighted in *POLE* ultra-mutated or dMMR hypermutated ECs and is hypothesized as being acquired in a later stage of the tumor progression (20).

Accurately interpreting the p53 abnormal staining is detrimental in highlighting an underlying *TP53* mutation, with high pathological interobserver consistency being required. The three different staining patterns termed abnormal/mutation-type staining are: overexpression, complete absence, and cytoplasmic staining, with the latter being just recently included. In contrast, the wild-type pattern is rarely associated with the *TP53* mutation and only occurs due to less frequent truncating mutations (22). It is described as vague or diffuse staining across a variable percentage of the tumor cell nuclei in conformity with the cell's proliferative activity (22). A higher proliferation index can thus lead to more important staining and should therefore be discriminated from overexpression (22). The accumulation of p53 in the cell nucleus usually leads to visible staining in almost 100% of the cell nuclei while the complete absence of p53abn expression in the tumor cells is usually easy to recognize and shouldn't raise issues in the differential diagnosis with a p53 wild type pattern, both of them being highly indicative of the *TP53* mutant status (22). Characterized by clear cytoplasmic staining accompanied by variable nuclear staining, the cytoplasmic pattern is less commonly identified and was just recently included in the abnormal, mutated-type pattern (22). However, in the presence of strong nuclear overexpression, low-intensity cytoplasmic staining should be deemed as overexpression and not as cytoplasmic expression (22). The correct interpretation of p53abn presence via IHC optimization is majorly required to avoid underdiagnosis of ECs corresponding to a less favorable outcome.

An initially presumed impediment in the risk stratification and management of ECs based on their molecular classifier was acknowledged by the illustration of the so-called "multiple classifiers" (23). Based on their features, they can suggest divergent outcomes at a first glance, especially the co-occurrence of p53abn IHC in *POLE*mut or dMMR cases. The large molecular analysis of 3518

ECs done by León-Castillo et al. described their occurrence in 3% of the cases, with the most commonly recognized combinations being dMMR-p53abn (1,8%) and *POLE*mut-p53abn (0,9%), followed by the combination of these three (0,3%) (23). Although there are noticeable contrasting outcomes distinguished between multiple and single classifier ECs when comparing their 5-year recurrence-free survival rates (94,1% for *POLE*mut-p53abn and 92,2% for dMMR-p53abn respectively) as well as distinctive clinicopathological features between the *POLE*mut and dMMR phenotypes (21), both the *POLE*mut and dMMR signatures seem to prevail over the p53abn signature, suggesting the likelihood that *TP53* alterations in multiple classifiers occur as secondary passenger events and do not impair outcomes (23-24).

The proper risk assignment is highly important, especially in the earlier stages of the disease. Literature reviews described cases of lower-grade endometrioid histotypes and early-stage diseases harboring p53 abnormalities and suggested that these patients have lower recurrence-free survival and poorer overall outcomes (25-26), predicted to be 5-fold worse when compared to another stage I low-grade disease of a different molecular subtype (27). Other studies considered the potential of decreasing the recurrence rates through the optimization of adjuvant approaches in this subset of ECs (28). However, from a more clinical standpoint, the question is raised whether over 70% of stage I-II endometrial tumors, mostly endometrioid, should be analyzed for the p53abn status, as Imboden et al.'s study suggests (29) or should testing be potentially based on suggestive nuclear features, excluding unrequired testing in about half of the ECs? (30). Both these studies suggested that detection of the p53abn status was responsible only for a small percentage of patients (2,9% and 2,4% respectively) getting re-assigned to a different ESGO risk group and provided limited reasoning for systematical p53abn IHC testing of all samples. In another study, discordancy between traditional clinicopathologic and molecular risk stratification was noted in a meaningful 6,6% of cases, most of them (4,5%) needing an upshift in risk grouping due to the presence of the p53abn status (31).

#### 4. Conventional therapy for p53abn EC

According to the 2020 ESGO/ESTRO/ESP and the 2022 ESMO risk stratification system for EC, every p53abn EC with myometrial invasion should be considered high risk, independently of its histology, grade, or stage, and should therefore receive adjuvant therapy (32). p53abn expression was found to be variable across multiple histologic types of ECs, with the highest prevalence being observed in more aggressive histotypes such as serous ECs (93%), carcinosarcomas (85%), clear cell ECs (38%) and a lower prevalence in more favorable histologies (22% in grade 3 EECs and only 5% in grade 1 and 2 EECs) (8). Nevertheless, independently of the favorable or unfavorable histologic type of the tumor, the expression was associated with a worse prognosis (18), while the use of adjuvant chemotherapy showed invariable benefits among histotypes (33). As every stage I low-grade (G1/G2) endometrioid EC was considered low-risk in previous stratification systems, even in the unknown unfortunate scenario of harboring the p53abn subtype, (9.7%, according to a recent analysis) (34), patients were at risk of being treated with surgery alone.

The PORTEC-3 trial is a landmark study for the current management of ECs which

demonstrated the benefit of adding chemotherapy to adjuvant radiotherapy in high-risk ECs (34), but it was the publication of its retrospective molecular analysis that refined the risk groups and therapeutic strategy, as its results underlined the significant impact of combined chemoradiotherapy on 5-year RFS (58.6%) and overall survival (64.9%) in comparison with RT alone (RFS of 36.2% and OS of 41.8% respectively) in p53abn patients (35). In consonance with this study, a more recent, pan-Canadian, molecular analysis of 2472 real-world treated ECs additionally emphasized the benefit of adjuvant chemotherapy in addition to radiotherapy versus radiotherapy alone in the p53abn group, while also revealing that as much as 47% of the patients retrospectively recognized as harboring the p53abn subtype were undertreated if current guidelines were to be applied (36). Although clinicians are still reserved to use adjuvant chemotherapy for stage I ECs, both these studies also confirmed that its addition was associated with improved outcomes even for the early-stage cases bearing the p53abn subtype (35-36). In addition to their potential impact on clinical practice, these findings also serve as a considerable starting point for the development of future trials.

**Table 2.** Ongoing clinical trials using conventional therapies

Trial name	Start date	Estimated completion date	Phase	Inclusion criteria	Treatment plan	Primary endpoint
<b>PORTEC 4-a NCT03469674</b>	June 2016	Dec 2025	III	Intermediate/ High-risk	(I) Vaginal brachytherapy (II) Observation, EBRT, Brachytherapy	Vaginal recurrence at 5 years
<b>RAINBO-RED</b>	Nov 2021	Jan 2030	III	p53abn	p53abn-RED trial: chemoradiotherapy versus chemoradiotherapy followed by PARPi	RFS

<b>CAN-STAMP NCT04159155</b>	Nov 2020	Sept 2025	II/III	Early/advanced stage	Early stage: Arm A: chemotherapy Arm B1: chemoradiotherapy + chemotherapy  Advanced stage: Arm C: chemotherapy Arm D1: chemotherapy + Niraparib (maintenance)	DFS at 3 years
<b>NCT05489848</b>	Aug 2022	Aug 2028	II/III	Post-operative stage I-IVA p53abn	(I) Radiotherapy + chemotherapy (II) Chemotherapy	2-year PFS
<b>PROBEAT NCT05179447</b>	Jan 2022	Dec 2023	III	p53abn	(I) Radiotherapy (II) Chemoradiotherapy	Total (vaginal, pelvic or distant) recurrence at 3 years

\* (EBRT – External beam radiotherapy, PARPi – PARP inhibitor, RFS – Recurrence free survival, DFS – Disease free survival, PFS – Progression free survival)

Several clinical trials are currently recruiting or close to publishing results which could potentially define what's the optimal post-surgical approach for p53abn patients, furthermore refining EC treatment guidelines. The PORTEC-4a trial, which is set to publish its first results shortly, was the first to use the molecular risk profile in determining adjuvant treatment recommendations (37). Patients were randomized for observation or to receive adjuvant radiation (VBT or EBRT) based on their integrated molecular risk and compared to a standard arm receiving conventional VBT. Targeting high-risk ECs such as serous and p53abn, the randomized, phase III, CANSTAMP study is looking to evaluate the right treatment option through DFS for early-stage disease and will randomize patients to receive chemotherapy alone or a combination of CHT and EBRT, while advanced ECs are set to receive adjuvant chemotherapy alone or chemotherapy followed by PARPi maintenance (38). Additional studies are looking to assess if there are any statistical DFS differences between chemotherapy alone versus combined chemotherapy and EBRT in an at-

tempt to avoid supplementary radiation-related toxicities and the impact of adjuvant EBRT on the time of locoregional recurrence in high-risk ECs (39-40).

### 5. Targeted therapy for p53abn EC

Treatment advances in p53abn ECs can also be achieved by targeting molecular alterations, with ongoing studies looking to broaden the therapeutic landscape this way in the metastatic/recurrent setting. Vast research on the complexity and aggressiveness of this subtype led to the discovery of its molecular similarities with high-grade serous ovarian (HGSOC) and basal-like breast carcinoma (BLBC) (18,41). Some of the observed resemblances with these histotypes include defects in the homologous recombination repair pathway (HRD). Studies have shown that about half of HGSOC and BLBC cases are HRD carriers (42-43). In ECs, HRD was observed in about 24% of cases, all of which were restricted to non-endometrioid histologies, while an even higher prevalence of 46% was observed in the *TP53* mutated subgroup, accord-

ing to a small study (44). A more recent analysis that aimed to outline the HRD prevalence in serous ECs evaluated 19 tumors and showcased that 53% of them (10 out of 19) had an HRD score over 42, which is indicative of an HRD phenotype (45). HRD is already known to be a valuable biomarker in predicting response to platinum-based regimens in other malignancies (46-47), but not much is yet known about the benefit extent of using platinum-based chemotherapy in women with EC in the context of HRD. A recent study suggested the possibility that patients with a high HRD score could benefit from both platinum chemotherapy and the use of poly (ADP-ribose) polymerase inhibitors (PARPi) based on how tumor specimens have shown in vivo sensitivity to such therapies. On another end, the same study proved the clinical utility of the HRD score testing in predicting DFS in patients with EC, with a higher HRD score ( $\geq 4$ ) being related to a worse survival compared to an HRD score  $<4$  in the two included EC cohorts (48). With the vast majority of serous ECs expressing the unfavorable *TP53* mutation and having a clinical outcome and mutational profile rather similar to that of HGSOE, it is likely that these patients could represent an ideal candidate for further trials evaluating the use of PARPi. The rationale of using PARPi is also supported by the likelihood that a major number of p53abn ECs are harboring an HR deficiency which led to the development of multiple ongoing trials aiming to assess the effects of mono or combined PARPi therapy. The phase I/II ENDOLA trial enrolled 35 patients with recurrent/metastatic ECs and aimed to assess the safety and benefit of combining Olaparib with metronomic Cyclophosphamide and Metformin. The rationale of this combination resides in the potential of metronomic Cyclophosphamide to increase the activity of PARPi through the alkylating of DNA and the inhibition of the frequently mutated PI3K-AKT-mTOR pathway with Metformin. Results have shown a mPFS of 5.1 months (7.5 months for endometrioid ECs and 4.3 months for serous ECs) and an acceptable safety profile (49). PARPi maintenance therapy with Olaparib (UTOLA phase IIB trial with 53% of the patients included bearing the *TP53* muta-

tion) (50), Rucaparib versus Placebo estimated to finish this year (51), and Niraparib (for stage III/IV serous ECs)(52) after completion of chemotherapy are also being assessed in patients with advanced or metastatic ECs sensitive to platinum regimens. In the context of recent study results suggesting a potential combined benefit of chemotherapy and PARPi in p53abn cases, the transPORTEC RAINBO trial includes a red cohort of stage I-IV p53abn ECs randomized into two arms: one receiving combined chemoradiotherapy and one receiving combined chemoradiotherapy followed by Olaparib maintenance (8).

Known to have a remarkably low abundance of TILs and a lack of TLS (53) responsible for a non-immunogenic tumor microenvironment, the p53abn subtype is a less favorable candidate for immune checkpoint inhibitor (ICI) therapy (54). Current directions are attempting to explore immune priming through the upregulation of PD-1 and PD-L1 expression by inducing DNA damage with PARPi (55), making the combination of PARPi with ICI a strategically new therapeutic option. The results of the phase II DOME trial which evaluated the combination of Olaparib and Durvalumab in 55 metastatic/recurrent ECs have shown an ORR of 16%, a mPFS of 3.4 months, and a mOS of 8.0 months. However, the 6-month PFS rate fell short at only 34% and did not reach the prespecified 50% (56). Another phase II trial also evaluated the combination of Pembrolizumab and Doxorubicin in patients with metastatic/ recurrent EC who received prior first-line chemotherapy and showed a mPFS of 6.4 months and mOS of 14.8 months for the p53abn subgroup (57), clearly underlining the benefit of a cytotoxic-based regimen.

The use of Cediranib, an anti-VEGF antibody, is being tested in two different trials: the three-arm, phase II, COPELIA trial and the phase II NRG-GY012 study with 6 arms in which different Cediranib-based combinations are being tested in advanced ECs (58-59). Preliminary results of the later study have shown a modest efficacy in the Cediranib plus Olaparib arm (mPFS of 5.5 months) and no major differences compared to the Cediranib monotherapy arm (mPFS of 3.8 months),

while the Olaparib monotherapy arm severely underperformed with a mPFS of just 2.0 months (59).

Other trials, some still ongoing, including the combination of Olaparib and Lurbinectedin (the POLA Study which enrolled 26 EC patients and showed a 15,4% ORR, much higher than the 6,6% observed in ovarian cancer, majorly influenced by the number of previous

lines and a mOS of 4.8 months) (60), Rucaparib and Nivolumab (61) and the combination of Rucaparib and Bevacizumab in a phase II trial which has shown a modest 17% response rate for ECs but has failed to show any significant anti-tumor activity except for the patients presenting with the ARID1A mutation which showcased a higher response rate (62).

**Table 3.** Ongoing clinical trials using targeted therapies and immunotherapy

<b>Trial name</b>	<b>Start Date</b>	<b>Estimated completion date</b>	<b>Phase</b>	<b>Inclusion criteria</b>	<b>Treatment plan</b>	<b>Primary endpoint</b>
<b>UTOLA Study NCT03745950</b>	Feb 2019	Mar 2023	II	Advanced/ Metastatic EC	(I) Placebo (II) Olaparib	PFS1
<b>Rucaparib vs Placebo NCT03617679</b>	Mar 2019	May 2024	II	Metastatic/ Recurrent EC	(I) Placebo (II) Rucaparib	PFS
<b>NCT04080284</b>	Dec 2019	July 2024	II	Stage III/IV and platinum-sensitive recurrent USC	Niraparib	PFS at 1 year
<b>DUO-E Study NCT04269200</b>	May 2020	Sept 2023	III	Advanced/ Recurrent EC	(A) Chemotherapy + Placebo, followed by Placebo (B) Chemotherapy + Durvalumab, followed by Durvalumab (C) Chemotherapy + Durvalumab, followed by Durvalumab + Olaparib	PFS
<b>NCT03660826</b>	Sept 2018	April 2024	II	static/ Recurrent EC	(I) Cediranib (II) Olaparib (III) Cediranib + Olaparib (IV) Olaparib + Capivasertib (V) Olaparib + Durvalumab (VI) Cediranib + Durvalumab	PFS



<b>NCT05256225</b>	Nov 2022	Oct 2027	II/III	Stage I-IV HER2 positive Endometrial Serous Carcinoma / Carcinosarcoma	(I) Chemotherapy + Herceptin (II) Chemotherapy + Hylecta (III) Chemotherapy + Phesgo	PFS OS
<b>DESTINY PanTumor02</b>	Aug 2020	June 2023	II	Cohort 4: HER2 positive Endometrial Cancer	Trastuzumab deruxtecan	ORR
<b>NCT05150691</b>	Jan 2022	June 2025	I/II	HER2 positive Endometrial Cancer	DB-1303	ORR
<b>NCT05156268</b>	Jan 2022	Jan 2024	II	Persistent / Recurrent EC	Pembrolizumab + Olaparib	ORR
<b>RUBY TRIAL NCT03981796</b>	July 2019	Nov 2026	III	Advanced (Stage 3/4) / Recurrent EC	(I) Dostarlimab + chemotherapy, followed by Dostarlimab (II) Placebo + chemotherapy, followed by Placebo (III) Dostarlimab + chemotherapy, followed by Dostarlimab + Niraparib (IV) Placebo + chemotherapy, followed by Placebo	PFS OS
<b>AtTEND NCT03603184</b>	Oct 2018	Nov 2023	III	Advanced / Recurrent EC	Atezolizumab + Chemotherapy Placebo + Chemotherapy	PFS OS
<b>NCT03526432</b>	Aug 2018	Aug 2023	II	Advanced / Persistent / Recurrent EC	Bevacizumab + Atezolizumab	CR PR
<b>NCT03367741</b>	April 2018	Oct 2023	II	Advanced / Recurrent / Metastatic EC	(A) Nivolumab + Cabozantinib (B) Nivolumab	PFS

\* PFS – Progression free survival, EC – endometrial cancer, USC – uterine serous carcinoma, OS – overall survival, HER2 - human epidermal growth factor receptor 2, ORR – overall response rate, CR – complete response, PR – partial response

Another common genetic abnormality identified in p53abn ECs is HER2 overexpression and/or amplification (20). In serous ECs,

HER2 overexpression was reported to largely vary between 14% and 80%, while HER2 amplification was reported between 21% and

47% respectively. On the other hand, HER2 overexpression and amplification rates reported in endometrioid carcinomas seem to be much lower (63). The GOG-177 study found that HER2 amplification was more commonly seen in higher-grade and serous tumors (64). Studies reporting on survival analysis of EC patients expressing HER2 amplification and/or overexpression found them to be linked to significantly shorter survivals (median of 5.2 years in HER2 overexpression and 3.5 years in HER2 amplification in all histological types) when compared to absent amplification and/or overexpression (median survival of all cases: 13 years) (65-67). When the HER2 status was retrospectively investigated in the PORTEC-3 cohort, results have shown a distinct association between HER2 positivity and the p53abn subtype, with all but one of the HER2 positive cases being classified as p53abn (95,8%). HER2 positivity was identified in 25% of all p53abn ECs, while no other subtype expressed a positive HER2 status (68). Important to note is that this analysis was not able to confirm the independent prognostic value of HER2 positivity in the multivariable analysis, but proved the relation between the positive status and a significantly worse relapse-free survival in the univariable evaluation (68). Although the initial phase II GOG study assessing the use of Trastuzumab (anti-HER2 antibody) monotherapy in HER2-positive patients with EC did not demonstrate anti-tumoral activity in either overexpressed or amplified cases (69), the updated OS analysis of a more recent phase II study which combined Trastuzumab with chemotherapy and compared it to chemotherapy alone in HER2 positive stage III/IV recurrent serous ECs concluded more favorable results in the experimental arm, both in terms of mPFS (17.7 months versus 9.3 months in the 1st line setting and 9.2 months versus 7.0 months in patients with recurrent disease) and mOS (29.6 months versus 24.4 months) (70).

In the randomized MITO END-2 trial, Bevacizumab combined with Carboplatin and Paclitaxel failed to demonstrate a noteworthy benefit in terms of PFS when compared to chemotherapy alone, but patients in the experimental arm experienced a significant increase

in 6-month disease control rate (70.4% versus 90.7%) (71). Further analysis of the *TP53* mutational status in the GOG-86P study which combined targeted agents (Bevacizumab or Temsirolimus) with standard platinum-based chemotherapy has shown an improvement of PFS and OS in *TP53* mutant / p53abn patients that received Bevacizumab and not Temsirolimus (72), proving that the addition of Bevacizumab could be potentially beneficial in improving outcomes of p53abn ECs and establishing in it a potential biomarker value for future guidance of clinical trials (73).

The presence of the *TP53* mutation frequently leads to cell-cycle dysregulation. The tumor cell thus becomes more dependent on WEE1-mediated regulation and potentially more sensitive to the effects of WEE1 inhibition. The clinical activity of Adavosertib, a WEE1 inhibitor, was investigated in the phase IIB ADAGIO trial in 34 women with persistent or recurrent serous ECs and results have noted an ORR of 29,4%, a mPFS of 6.1 months (with 16 patients progression-free at 6 months), and a mDOR of 9.0 months (74).

In conclusion, we're currently facing a transition phase in which incorporating precise biomarkers with validated prognostic and predictive value can re-define the traditional concepts of EC management. The molecular-based risk assesment of ECs is of substantially predictive value. Therefore, applying the ProMisE classifier and further guiding treatment decissions upon results should be strongly advised for all laboratories where molecular classification using the surrogate markers is attainable. If the testing resources are limited, high-grade and high-stage cases that need adjuvant therapy should be prioritised, as this could have a great consequence on their treatment recommendations. In this day, identifying the patients most likely to have their treatment plan impacted by molecular risk-based reassigment and optimizing IHC diagnosis through consistent pathological interpretation while also avoiding unnecessary testing are some current challenges we need to overcome. Through these, we have the ability to improve outcomes where it is much needed, such as in the highly unfavourable p53abn subtype.

## **Abbreviations:**

EC – endometrial cancer  
POLE – polymerase-epsilon  
TCGA – The Cancer Genome Atlas  
MSI – microsatellite instability  
IHC – immunohistochemistry  
dMMR – deficient mismatch repair  
NSMP – no specific molecular profile  
NGS – next-generation sequencing  
LVSI – lymphovascular space invasion  
ESGO – European Society of Gynaecological Oncology  
ESTRO – European Society for Radiotherapy & Oncology  
ESP – European Society of Pathology  
ESMO – European Society for Medical Oncology  
EEC – endometrioid endometrial cancer  
RFS – recurrence free survival  
RT – radiotherapy  
OS – overall survival  
VBT – vaginal brachytherapy  
EBRT – external beam radiotherapy  
DFS – disease-free survival  
CHT – chemotherapy  
PARPi – poly (ADP-ribose) polymerase inhibitor  
HGSOC – high-grade serous ovarian cancer  
BLBC – basal-like breast carcinoma  
HRD – homologous recombination repair pathway  
mPFS – median progression-free survival  
TILs – tumor infiltrating lymphocytes  
TLS – tertiary lymphoid structures  
ICI – immune checkpoint inhibitor  
PD-1 – programmed death protein ligand 1  
PD1 – programmed cell death protein 1  
ORR – objective response rate  
VEGF – vascular endothelial growth factor  
HER2 – human epidermal growth factor receptor 2  
mDOR – median duration of response

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