ESGO-ESTRO-ESP Guidelines

for the Management of patients with Endometrial Carcinoma Update 2025[1]

Auszug mit Empfehlungen zur Immuntherapie

1. Nicole Concin, Xavier Matias-Guiu, David Cibula, Nicoletta Colombo, Carien L Creutzberg, Jonathan Ledermann, Mansoor Raza Mirza, Ignace Vergote, Nadeem R Abu-Rustum, Tjalling Bosse, Cyrus Chargari, Sophie Espenel, Anna Fagotti, Christina Fotopoulou, Sonia Gatius, Antonio González-Martin, Sigurd Lax, Bar Levy, Domenica Lorusso, Gabriella Macchia, Christian Marth, Philippe Morice, Ana Oaknin, Maria Rosaria Raspollini, Richard Schwameis, Jalid Sehouli, Alina Sturdza, Alexandra Taylor, Anneke Westermann, Pauline Wimberger, François Planchamp, Remi A Nout. ESGO-ESTRO-ESP guidelines for the management of patients with endometrial carcinoma: update 2025. Lancet Oncol. 2025 Aug;26(8):e423-e435.

Vorstand der AGO

Sehr geehrte Kolleginnen und Kollegen,

die Vielzahl neuer wissenschaflicher Erkenntnisse zum Endometriumkarzinom stellt eine Chance für unsere Patientinnen dar und stellt uns als betreuende Ärzt:innen vor die Herausforderung der stetigen Integration dieses neuen Wissens.

Die 2025 aktualisierte Triple-Europäische Guideline von ESGO, ESTRO und ESP bietet einen evidenzbasierten Rahmen für Diagnose, Behandlung und Nachsorge von Patientinnen mit einem Endometriumkarzinom.

Dieses Booklet fasst die wichtigsten Empfehlungen zusammen, unterstützt mit anschaulichen Grafiken und erleichtert die Auswahl optimaler Therapieoptionen.

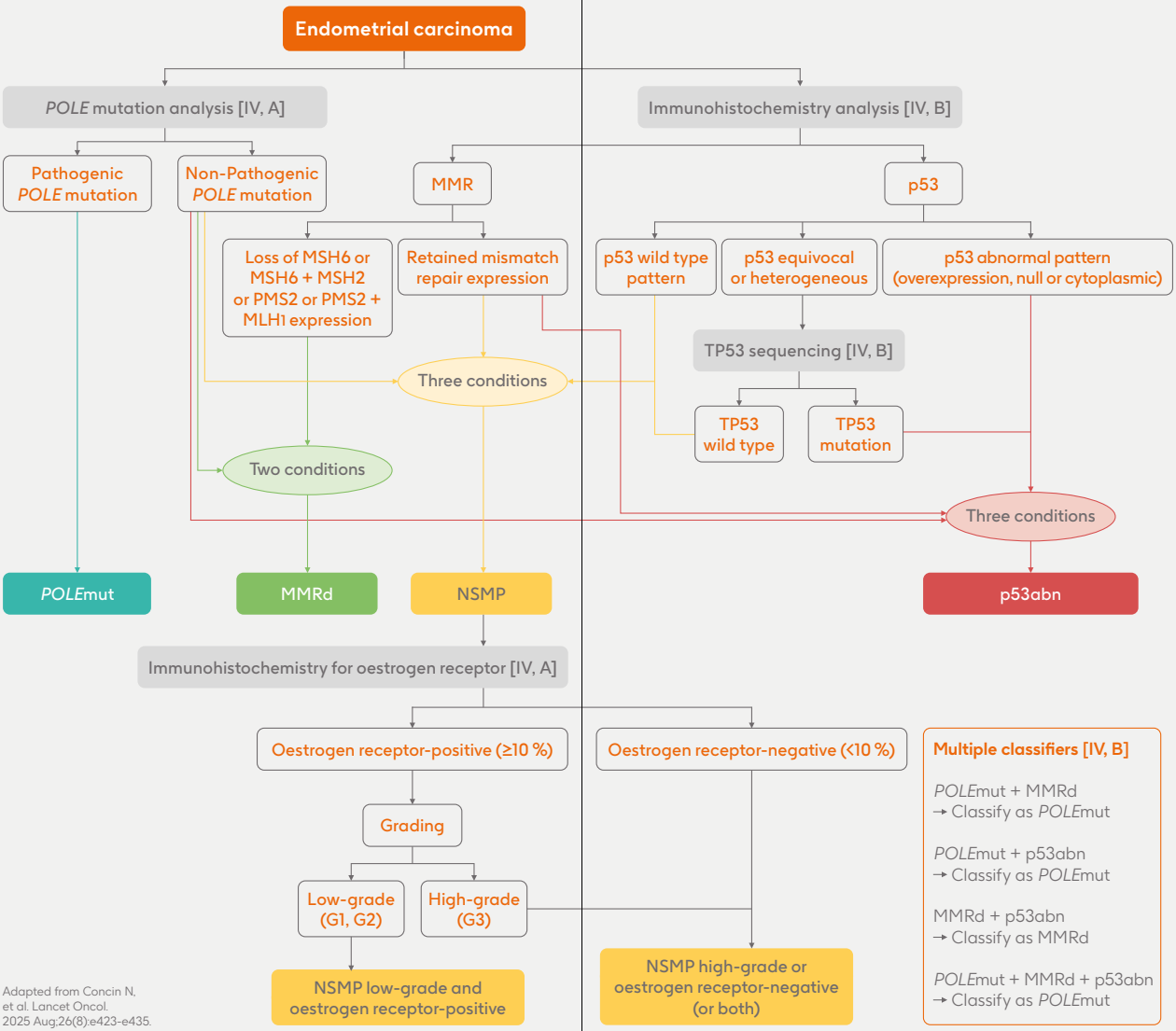
Viel Erfolg bei der Umsetzung der Leitlinien in Ihrer klinischen Praxis.

Mit kollegialen Grüßen

Nicole Concin,
AGO Präsidentin, im Namen des AGO Vorstands

Dieses Booklet wurde von der AGO Österreich reviewed und verifiziert.

Integration of Molecular Classification and other Biomarkers



Adapted from Concin N, et al. Lancet Oncol. 2025 Aug;26(8):e423-e435.

EC, endometrial carcinoma; **ER**, oestrogen receptor; neg, negative; pos, positive; **HER2**, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **MMR**, mismatch repair; **MMRd**, mismatch repair deficient; **NSMP**, non-specific molecular profile; **POLE**, polymerase epsilon; **WHO**, World Health Organisation; **p53abn**, p53 abnormal.

Integration of Molecular Classification and other Biomarkers

- Molecular classification [*POLE*mut, MMRd, non-specific molecular profile (NSMP), p53abn] should be done for all types of ECs and requires three basic analyses to determine the *POLE* mutational, MMR and p53 status (2020 WHO tumour classification) [IV, A].
- It is recommended to perform oestrogen receptor (ER) status by IHC in all ECs as it can facilitate diagnosis, is prognostic in the NSMP group, and predictive for response to endocrine therapy in advanced/recurrent disease [IV, A].
- All advanced/recurrent p53abn ECs and all serous carcinomas/carcinosarcomas may be tested for HER2 overexpression by IHC and in case of immunoreactive score 2+ by in situ hybridization using standardised criteria [IV, C].
- EC with multiple classifier features should be classified according to their genomic driver such as *POLE*mut (combination of pathogenic *POLE*mut with p53abn and/or MMRd) or MMRd (combination of MMRd with p53abn) [IV, B].
- The molecular subgroup NSMP high-grade or oestrogen receptor-negative (or both) consists of either high-grade NSMP endometrial carcinoma, or oestrogen receptor-negative NSMP endometrial carcinoma, or of NSMP endometrial carcinomas with a combination of both high-grade and oestrogen-receptor negativity.
- In general, estimated less than 5 % of EC (depending on cohort) shows more than one molecular feature, which is sometimes referred to as “multiple classifiers”. Carcinomas that are *POLE*mut + MMRd or *POLE*mut + p53abn or *POLE*mut + MMRd + p53abn behave clinically similarly to pure *POLE*mut carcinomas and therefore should be categorised as *POLE*mut. In combination with MMR deficiency and/or mutant-type p53 staining, the pathogenic *POLE* mutations are considered the genomic driver. Similarly, in case of double classifiers of MMRd and mutant-type p53 staining the carcinoma should be categorised as MMRd.

Levels of Evidence and Grades of Recommendations

Levels of Evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
Grades of Recommendations	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Reference:
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Definition of Risk Groups – Based on 2023 FIGO staging and molecular classification

2023 FIGO staging[π]			Molecular classification				
			*POLE*mut	MMRd	NSMP Low-grade+ ER-pos	NSMP high-grade/ ER-neg*	p53abn
I		**Confined to the uterine corpus**					
IA	IA1	Low-grade endometrioid, confined to polyp or endometrium (no myoinvasion)	IAm*POLE*mut			*	
	IA2	Low-grade endometrioid, myoinvasion < 50 %, no/focal LVSI	IAm*POLE*mut			*	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#				*	
IB		Low-grade endometrioid, myoinvasion ≥ 50 %, no/focal LVSI	IAm*POLE*mut			*	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium	IAm*POLE*mut		n.a.		
II		**Confined to the uterus**					
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm*POLE*mut			*	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI**	IAm*POLE*mut			*	IICm p53abn
IIC		High-grade histologies^, myoinvasion	IAm*POLE*mut	Myoinvasion < 50 %, no/focal LVSI	n.a.		IICm p53abn
			IAm*POLE*mut	Myoinvasion ≥ 50 %, no/focal LVSI			
			IAm*POLE*mut	Cervical stromal invasion, no/focal LVSI			
			IAm*POLE*mut	Substantial LVSI**			
III		**Local spread, regional spread, or both**					
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage 1A3 criteria)					
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa					
IIIB	IIIB1	Metastasis or direct spread to the vagina, parametria, or both					
	IIIB2	Metastasis to the pelvic peritoneum					
IIIC	IIIC1	Pelvic lymph node metastasis					
	IIIC1i	Micrometastasis					
	IIIC1ii	Macrometastasis					
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIIC2i	Micrometastasis					
	IIIC2ii	Macrometastasis					
IV		**Locally advanced disease, metastatic disease, or both**					
IVA		Invasion of bladder mucosa or intestinal mucosa, or both					
		Metastatic disease or residual disease after surgery					
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

π 2023 FIGO staging when molecular classification is known, the FIGO stage should be reported with an annotation of m (for molecular) followed by the specific molecular subtype. There are two specific molecularly defined FIGO stages, namely stage IAm *POLE*mut (stages I and II disease with a pathogenic *POLE* mutation) and stage IICm p53abn (stages I and II disease with a p53 abnormality and myometrial invasion). (these two molecularly defined FIGO stages are indicated in the table's cells)

* The molecular subgroup NSMP high-grade/ER-neg consists of either high-grade NSMP cases or ER-neg NSMP cases. Thus, in FIGO stages referring to low-grade endometrioid carcinomas (i.e. IA1, IA2, IA3, IB, IIA and IIB) only to the ER-neg cases of the molecular subgroup NSMP high-grade/ER-neg apply.

** Substantial LVSI is defined according to WHO criteria by ≥ 4 vessels in at least one H&E slide.

\# Myoinvasion < 50 % + no/focal LVSI + ovarian tumour pT1a.

^ High-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3), serous, clear cell carcinomas, carcinosarcomas, undifferentiated, mixed, mesonephric-like, and gastrointestinal mucinous type carcinoma.

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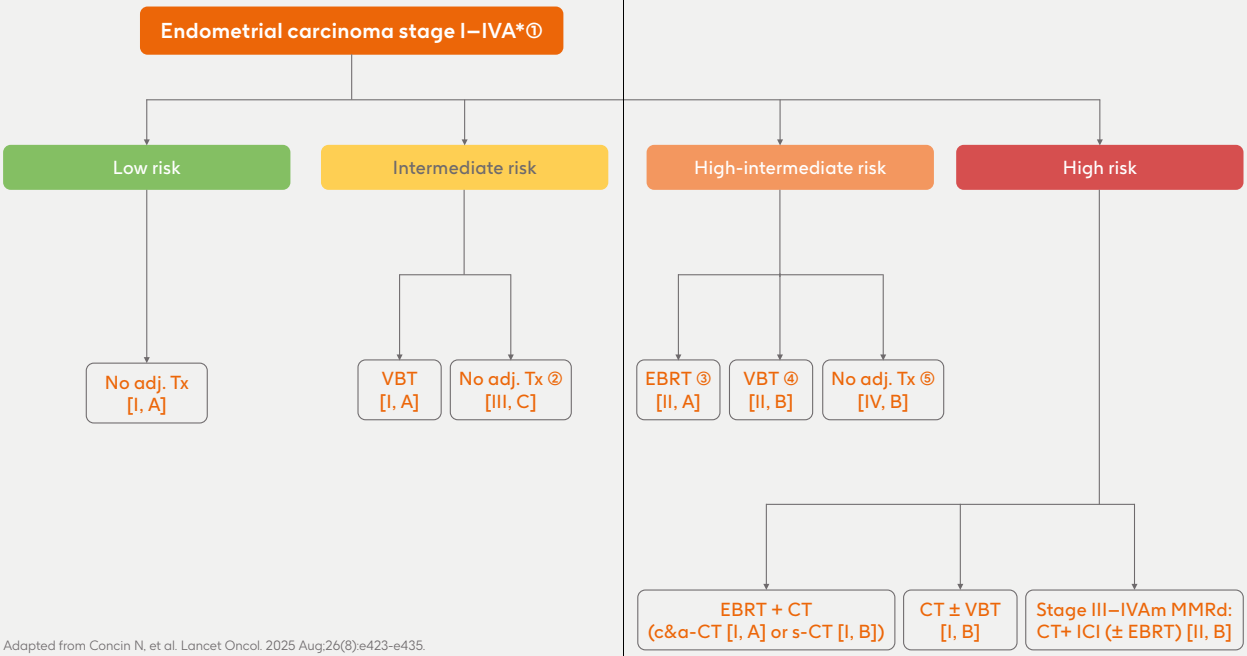
Prognostic risks in the respective groups are defined as estimated overall 5-year risk of recurrence:

- **Low risk group:** risk less than 8 %
- **Intermediate risk group:** risk between 8 and 15 %
- **High-intermediate risk group:** risk between 15 and 25 %
- **High risk group:** risk higher than 25 %

ER, oestrogen receptor; **FIGO**, International Federation of Gynaecology and Obstetrics; **H&E**, haematoxylin and eosin; **LVSI**, lymphovascular space invasion; **MMRd**, mismatch repair deficient; mut, mutation; neg, negative; **NSMP**, non-specific molecular profile; **POLE**, polymerase epsilon; pos, positive; **WHO**, World Health Organisation.

Adjuvant Therapy



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① The group of patients with uncertain risk is not depicted in the algorithm. Recommendations for these patients are provided in the text below.
② Especially for patients under 60 years of age and/or low-grade EC [II, A].
③ EBRT is recommended for optimal pelvic control.
④ VBT is an alternative option, especially for patients who underwent lymph node staging and are pN0.
⑤ No adjuvant therapy can be considered, especially for patients who underwent lymph node staging and are pN0, without substantial LVSI and low-grade.

Recommendations for patients with uncertain risk:

In early-stage disease, uncertain risk categories consist of first, stage IA1m NSMP high-grade/ER-neg or IA1m p53abn endometrial carcinoma, and second, stage ICm NSMP high-grade/ER-neg or ICm p53abn endometrial carcinoma. For these cases, there are scarce data suggesting that the risk of recurrence is somewhat higher than for low-risk carcinoma. However, adjuvant therapy is generally not recommended (IV, C).

In advanced stage disease, uncertain risk categories consist of stage IIIm *POLE*mut and IVAm *POLE*mut endometrial carcinoma. For patients with stage IIIm *POLE*mut and IVAm *POLE*mut endometrial carcinoma, due to scarce data, no firm treatment guidelines can be given. However, following a case-by-case multidisciplinary team discussion, de-escalation from high-risk treatment can be considered (IV, B).

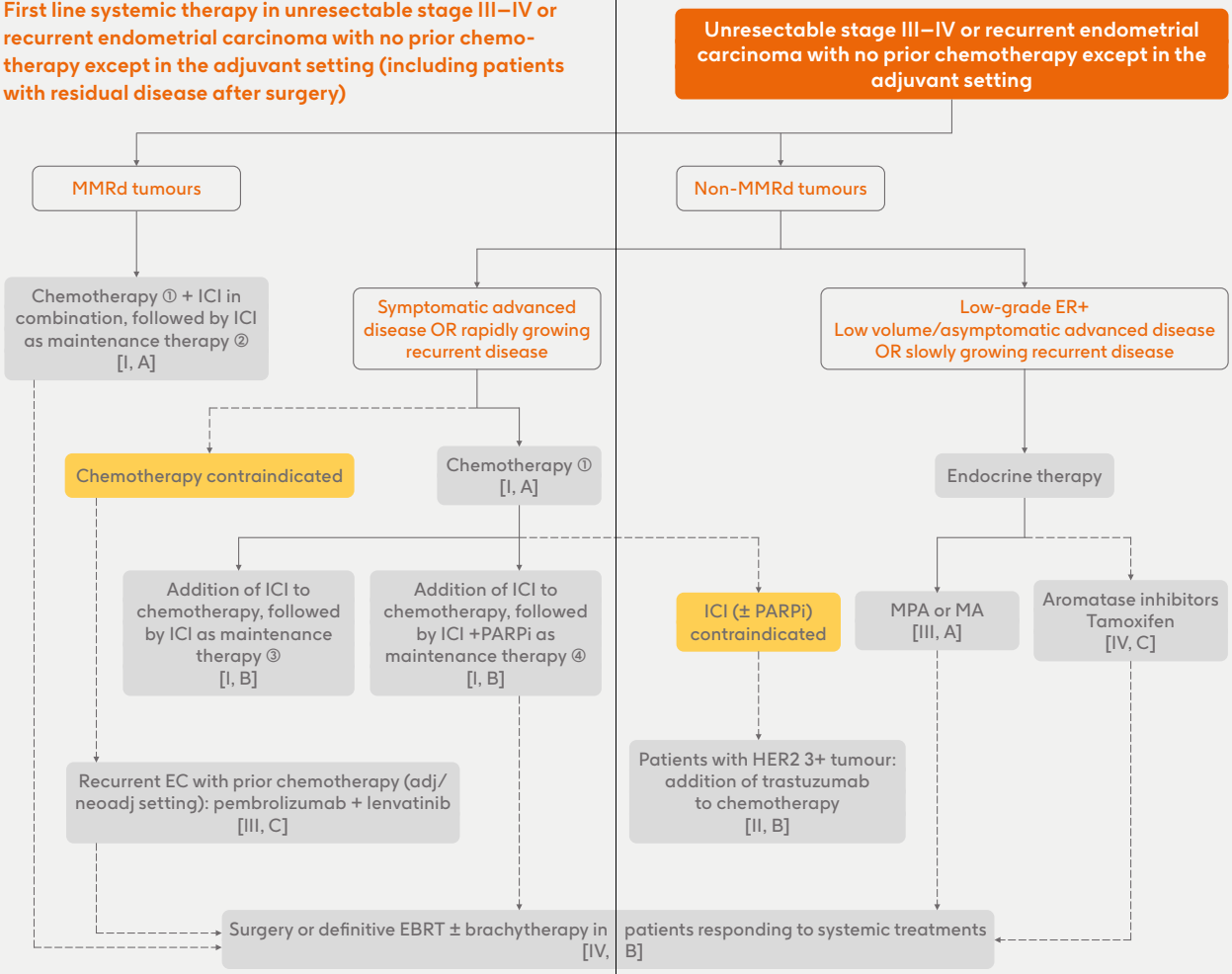
Adjuvant therapy for high risk group:

- EBRT with concurrent and adjuvant chemotherapy [I, A].
- Alternatively sequential chemotherapy and radiotherapy are recommended [I, B].
- Chemotherapy ± brachytherapy is an alternative option [I, B].
- For patients with FIGO 2023 stage IIIm-IVAm MMRd EC, adjuvant chemotherapy combined with an ICI (± EBRT) should be considered [II, B].

Adj. Tx, adjuvant therapy; **c&a-CT**, concurrent and adjuvant chemotherapy; **CT,** chemotherapy; **EBRT**, external beam radiotherapy; **EC**, endometrial carcinoma; **FIGO**, International Federation of Gynaecology and Obstetrics; **ICI**, immune checkpoint inhibitor; **MMRd**, mismatch repair deficient; mut, mutation; **POLE**, polymerase epsilon; **s-CT**, sequential chemotherapy; **VBT**, vaginal brachytherapy.

Systemic Therapy – First Line

First line systemic therapy in unresectable stage III–IV or recurrent endometrial carcinoma with no prior chemo-therapy except in the adjuvant setting (including patients with residual disease after surgery)

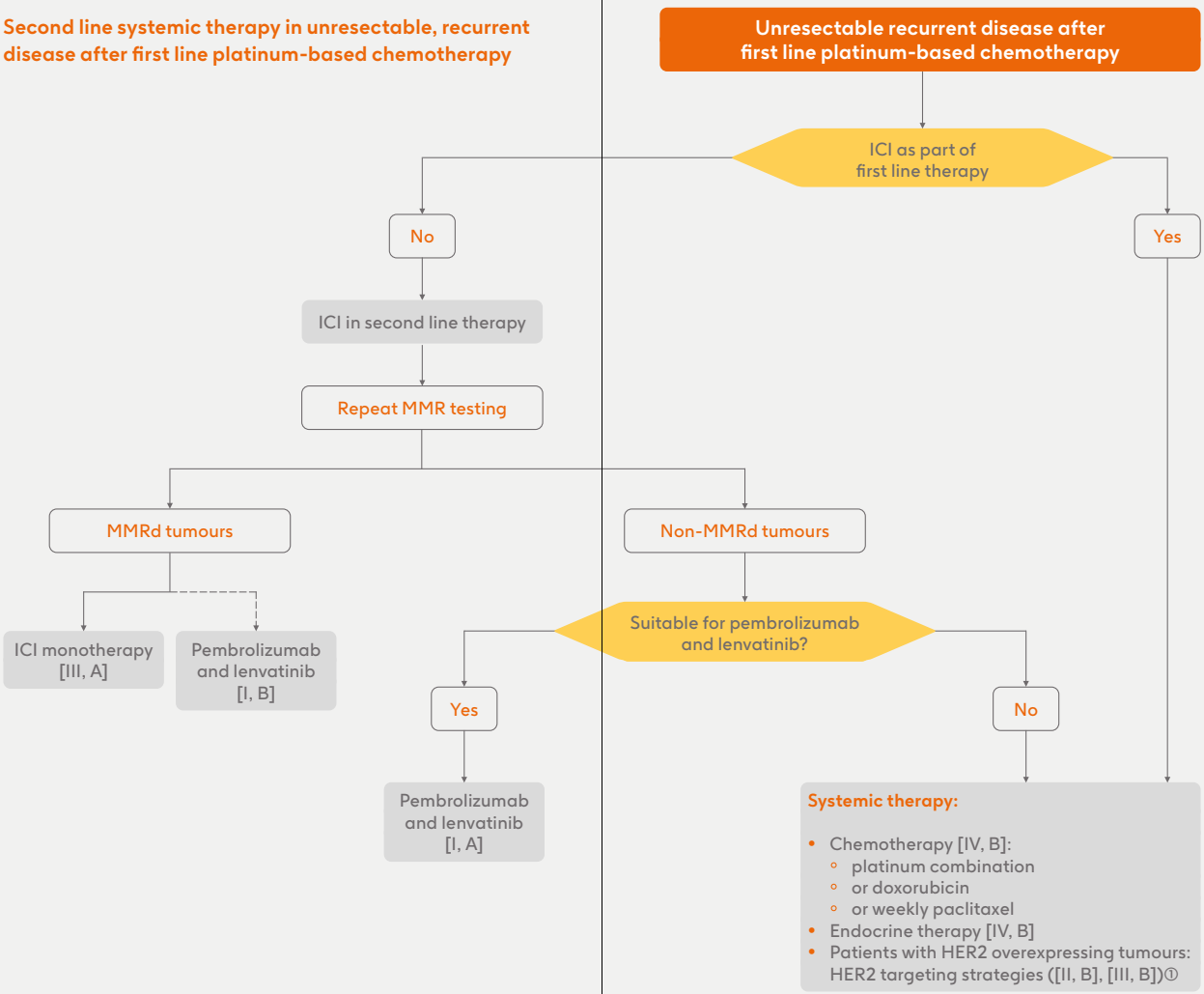


① The standard chemotherapy regimen is carboplatin + paclitaxel.
② Immune checkpoint inhibitor (ICI): dostarlimab or durvalumab or pembrolizumab (drugs in alphabetical order).
③ ICI: dostarlimab or pembrolizumab.
④ ICI + poly(ADP-ribose) polymerase inhibitor (PARPi): durvalumab + olaparib.

Adj/neoadj, adjuvant/neoadjuvant; **CT**, chemotherapy; **EBRT**, external beam radiotherapy; **EC**, endometrial carcinoma; **ER+**, oestrogen receptor-positive; **HER2**, human epidermal growth factor receptor 2; **ICI**, immune checkpoint inhibitor; **MA**, megestrol acetate; **MMR**, mismatch repair; **MMRd**, mismatch repair deficiency; **MPA**, medroxyprogesterone acetate; **non-MMRd**, non-mismatch repair deficiency; **NSMP**, non-specific molecular profile; **PARPi**, poly(ADP-ribose) polymerase inhibitor.

Systemic Therapy – Second Line

Second line systemic therapy in unresectable, recurrent disease after first line platinum-based chemotherapy



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① Carboplatin + paclitaxel + trastuzumab (in HER2 3+ tumours by immunohistochemistry) if chemotherapy re-challenge is an option [II, B]; Trastuzumab deruxtecan (in HER2 2/3+ tumours by immunohistochemistry) [III, B].

dMMR/MSI-H, mismatch repair deficiency/microsatellite instability-high; **HER2**, human epidermal growth factor receptor 2; **ICI**, immune checkpoint inhibitor; **MMR**, mismatch repair

Diese Information ist für Fachkreise und dient der Fortbildung und Beantwortung konkreter wissenschaftlicher Fragestellungen.

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GlaxoSmithKline Pharma GmbH
Wienerbergstraße 7, 5. Stock
1100 Wien

Handelsgericht Wien, FB-Nr.: FN 115955y