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SPOTLIGHT

Who is the appropriate patient? Applying molecular testing for your patients with primary advanced / recurrent endometrial cancer through the MDT.

Professor Glenn McCluggage
Consultant Histopathologist, Department of Pathology, Belfast Heath and Social Care Trust

Dr Rupali Arora
Consultant Pathologist University College Hospital London

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GSK

Jemperli (dostarlimab) Injection 500 mg

PM-GB-DST-PPTX-250009 V2 | May 2025

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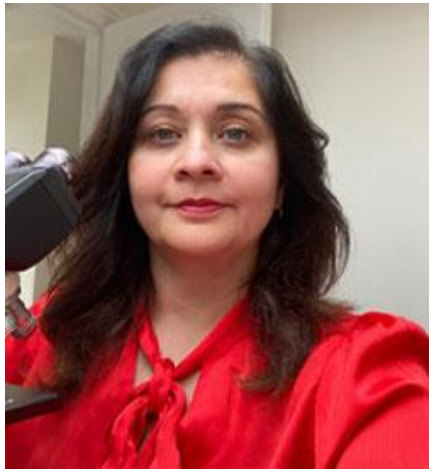
ABPI, Association of the British Pharmaceutical Industry.

Faculty



Prof. Glenn McCluggage, MD,FRCPath

Belfast Health and Social Care Trust



Dr Rupali Arora, MD FRCPath

University College London Hospital

Agenda

Timing	Session Title	Speaker
2 Minutes	Welcome and Introductions	Prof Glenn McCluggage
13 Minutes	Putting the RUBY trial into practice: ▼JEMPERLI (dostarlimab) with platinum-containing chemotherapy for primary advanced endometrial cancer.	Prof Glenn McCluggage & Dr Rupali Arora
13 Minutes	The Northern Ireland Experience of Integrating TGCA Classification Into Clinical Practice.	Prof Glenn McCluggage & Dr Rupali Arora
2 Minutes	Discussion & Close	Prof Glenn McCluggage

Putting the RUBY trial into practice: ▼JEMPERLI (dostarlimab) with platinum-containing chemotherapy for primary advanced endometrial cancer.

Dr Rupali Arora
Consultant Pathologist
University College Hospital London

SPOTLIGHT

Licensed Indications[1]

JEMPERLI is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite-instability high (MSI-H) recurrent or advanced EC that has progressed on or following treatment with a platinum containing regimen

1. JEMPERLI Summary of Product Characteristics

Speaker Disclosures
Dr Rupali Arora

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- Consultant Clinical Oncologist, University College Hospital London
- GSK
- Honoraria/meeting expenses: MSD
- Consultancy/Advisory Boards: GSK, Eisai, MSD

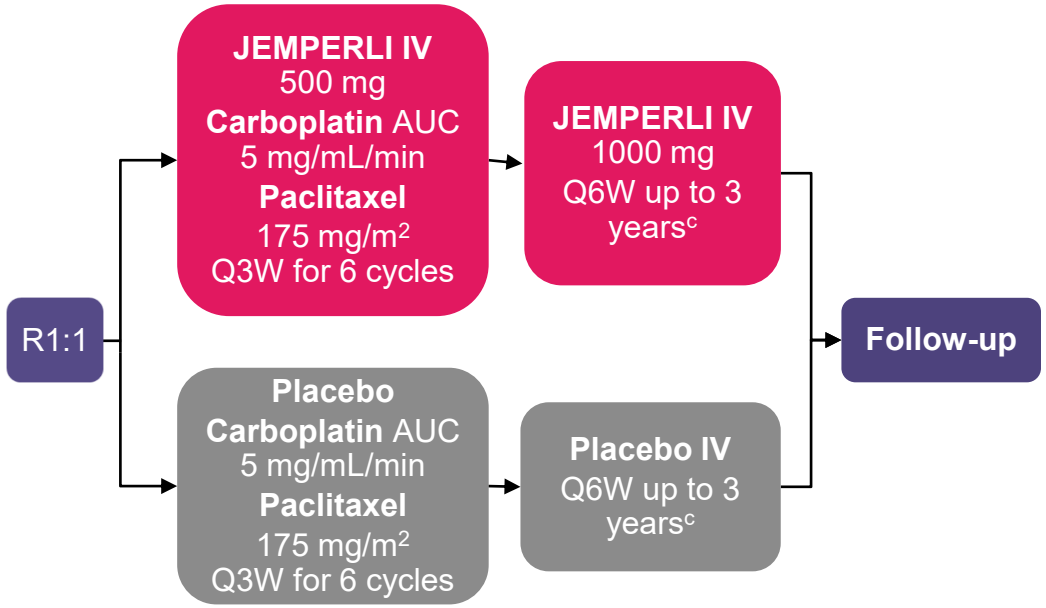
RUBY is a phase 3, multi-centre, double-blind, randomised, placebo-controlled trial investigating JEMPERLI + carboplatin/paclitaxel[1,2]

Eligible patients

- Women aged ≥18
- Histologically/cytologically proven primary advanced or recurrent endometrial cancer (EC)
- **Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination**
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted[a]
- Naïve to systemic therapy or has received prior neo-adjuvant or adjuvant systemic therapy and had recurrence or PD ≥ 6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification

- MMR/MSI status[b]
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- **OS** in overall population (IA2)
- **PFS** by INV in the overall population (IA1)
- **PFS** by INV in the dMMR/MSI-H population (IA1)

Pre-Specified subgroup analysis

- OS in dMMR/MSI-H population (IA2)
- OS in the MMRp/MSS population (IA2)
- PFS in the MMRp/MSS population (IA1)

Secondary endpoints

- PFS by BICR (IA1)
- PFS2 (IA2)
- ORR (IA1)
- DOR (IA1)
- DCR (IA1)
- HRQOL/PRO (IA1)
- Safety (IA2)

On-study imaging assessments are to be performed Q6W (±7 days) from the randomisation date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumour imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later, or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.
[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]patients were randomised based on either local or central MMR/MSI testing results. Central testing was used when local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, for up to 3 yras investigator's decision, or death, whichever occurs first.

AUC; area under the plasma or serum concentration-time curve**, BICR**; blinded independent central review, **DCR**; disease control rate, **dMMR/MSI-H;** mismatch repair deficient/microsatellite instability-high **DOR;** duration of response**, ECOG PS**; Eastern Cooperative Oncology Group Performance Status; **HRQoL**; Health Related Quality of Life, **IA**; Interim Analysis, **IV**; administered intravenously, **INV**; investigator assessment, **MMR/MSI**; mismatch repair/ microsatellite instability, **MMRp/MSS;** mismatch repair proficient/ microsatellite stability**, ORR**; overall response rate, **OS**; overall survival, **PD;** progressive disease, **PFS**; progression free survival, **PFS2;** time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy after study treatment or death by any cause, whichever is earlier, **PRO**; patient-reported outcome, **Q6W;** dose every 6 weeks

1. Mirza MR, et al. N Engl J Med. 2023;388(23):2145-2158.
2. Powell MA, et al. Ann Oncol 2024;35(8):728-738

RUBY Key Inclusion and Exclusion Criteria[1]

This is not an exhaustive list

Key inclusion criteria[1]:

- Has histologically or cytologically proven EC with recurrent or advanced disease
- Must have primary stage III or IV disease or first recurrent EC with a low potential for cure by radiation therapy or surgery alone or in combination and meet at least one of the following criteria:
  - Participant has primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v.1.1 based on Investigator's assessment; lesions that are equivocal or can be representative of post-operative change should be biopsied and confirmed for the presence of tumor
  - Participant has primary Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or histology) regardless of presence of evaluable or measurable disease on imaging
  - Participant has primary Stage IIIC2 or Stage IV disease regardless of the presence or evaluable or measurable disease
  - Participant has first recurrent disease and is naïve to systemic anticancer therapy
  - Participant has received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or progression of disease (PD) >=6 months after completing treatment (first recurrence only)
- Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Has adequate organ function

Key exclusion criteria[1]:

- Has received neoadjuvant or adjuvant systemic chemotherapy for primary stage III or IV disease and has not had a recurrence or progression of disease prior to entering the study,
- Has had a recurrence or progression of disease within 6 months of completing chemotherapy treatment prior to entering the study
- Has had >1 recurrence of EC
- Has received prior therapy with anti–PD-1, anti–PD-L1, or anti–PD-L2 agent
- Has received prior anticancer therapy (chemotherapy/targeted therapies/hormonal therapy/radiotherapy/immunotherapy) within 21 days or <5 times the half-life of the most recent therapy prior to study day 1
- Has a concomitant malignancy, or has a prior non-endometrial invasive malignancy and has been disease-free for <3 years or who received any active treatment in the last 3 years for that malignancy

AE = adverse event; CNS = central nervous system; EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IA = investigator assessment; MMR = mismatch repair; PD = progressive disease; PD-1 = programmed death-1; PD-L1/2 = programmed death ligand-1/2; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RT = radiation therapy.

Reference: 1.Mirza MR, et al. N Engl J Med 2023; DOI:10.1056/NEJMoa2216334.

The RUBY trial population was reflective of the UK patient population[1,2]

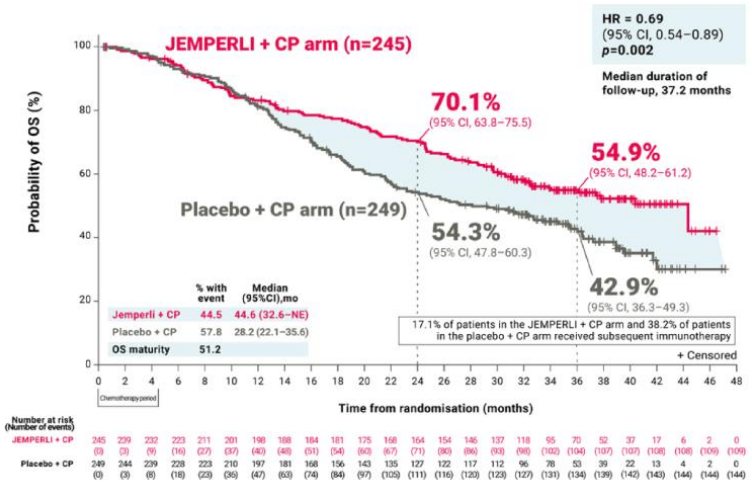
Variable, n (%)	dMMR/MSI-H population		Overall population	
	JEMPERLI + CP (N=53)	Placebo + CP (N=65)	JEMPERLI + CP (N=245)	Placebo + CP (N=249)
Prior external pelvic radiation				
Yes	8 (15)	13 (20)	41 (16.7)	45 (18.1)
No	45 (85)	52 (80)	204 (83.3)	204 (81.9)
Disease status				
Primary stage III	10 (19)	14 (22)	45 (18.4)	47 (18.9)
Primary stage IV	16 (30)	19 (29)	83 (33.9)	83 (33.3)
Recurrent	27 (51)	32 (49)	117 (47.8)	119 (47.8)
Histology Type				
Carcinosarcoma	**4 (8)**	**1 (2)**	**25 (10.2)**	19 (7.6)
Endometroid	44 (83)	56 (86)	134 (54.7)	136 (54.6)
Mixed carcinoma *(≥10% of carcinosarcoma, clear cell, or serous histology)*	2 (4)	4 (6)	10 (4.1)	9 (3.6)
Serous adenocarcinoma	1 (2)	1 (2)	50 (20.4)	52 (20.9)
Clear cell adenocarcinoma	0	0	8 (3.3)	9 (3.6)
Mucinous adenocarcinoma	0	0	0	1 (0.4)
Undifferentiated carcinoma	0	0	1 (0.4)	2 (0.8)
Other	2 (4)	3 (5)	17 (6.9)	21 (8.4)
MMR-MSI Status				
dMMR-MSI-H	53 (100)	65 (100)	53 (21.6)	65 (26.1)
pMMR-MSS	0	0	192 (78.4)	184 (73.9)

CP; carboplatin/paclitaxel, **dMMR**; mismatch repair deficient, **EC;** endometrial cancer, **MMR;** mismatch repair, **MSI;** microsatellite instability, **MSI-H**; microsatellite instability-high, **MSS;** microsatellite stable, **pMMR;** mismatch repair-proficient

1. Mirza MR, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med. 2023; 388 (2) 2145-2158
2. GSK; Data on File 2024

Dual Primary Endpoints

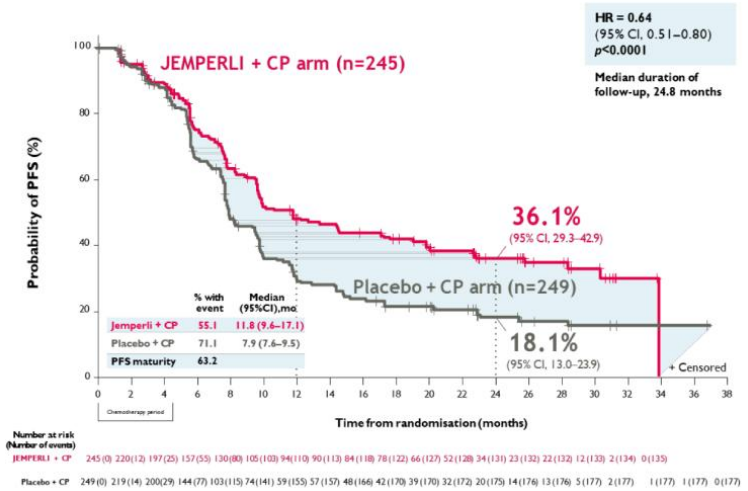
Overall survival in the overall population [1,2]



16.4-month improvement in median OS

with JEMPERLI + CP vs placebo + CP (median OS: 44.6 months [95% CI, 32.6–NE] vs 28.2 months [95% CI, 22.1–35.6], respectively)[1]

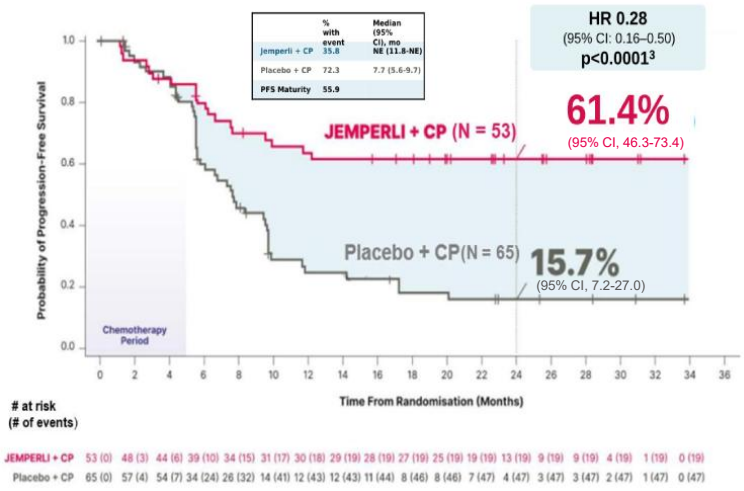
Progression free survival in the overall population [3-5]



3.9-month improvement in median PFS

with JEMPERLI + CP vs placebo + CP (median PFS: 11.8 months [95% CI, 9.6–17.1] vs 7.9 months [95% CI, 7.6–9.5])[5]

Progression free survival in the dMMR population [3-5]



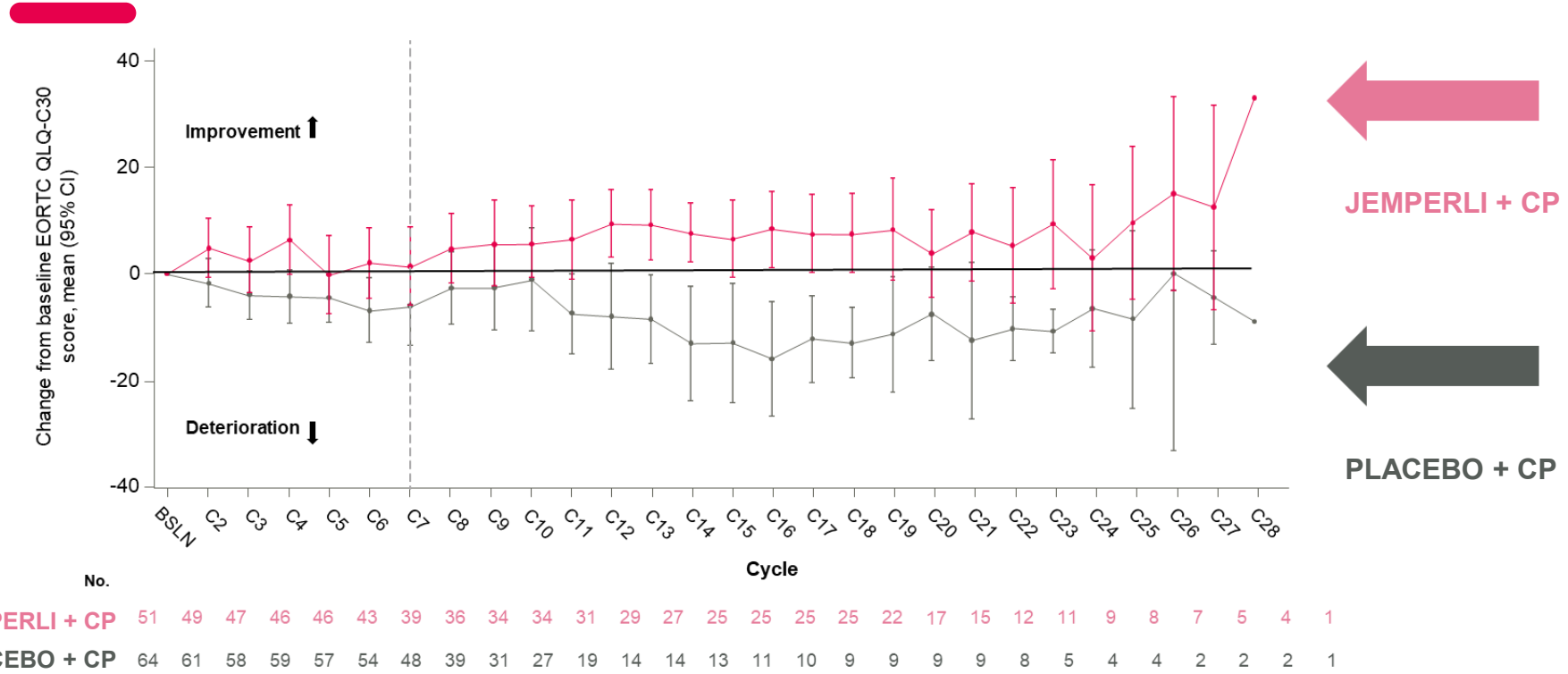
Median PFS was still not reached after 2 years

in the JEMPERLI + CP arm (95% CI, 11.8–NE) vs 7.7 months in the placebo + CP arm (95% CI, 5.6–9.7)

Adapted from Powell et al. 2024 & Mirza et al. 2023

1. Powell MA, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol. 2024;35(8):728-738.
2. Powell MA, et al. Overall survival in patients with primary advanced or recurrent endometrial cancer treated with dostarlimab plus chemotherapy in the ENGOT-EN6-NSGO-GOG-3031/RUBY trial. Presented at SGO. 16-18 March 2024; San Diego, USA
3. Mirza MR, et al. N Engl J Med. 2023;388(23):2145–2158.
4. Mirza MR, et al. Presented at ESMO Virtual Plenary. 14-15 September 2023.
5. JEMPERLI Summary of Product Characteristics

Secondary Endpoint (not statistically powered): HRQoL/PRO in dMMR/MSI-H population[1]



No.	BSLN	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28
JEMPERLI + CP	51	49	47	46	46	43	39	36	34	34	31	29	27	25	25	25	25	22	17	15	12	11	9	8	7	5	4	1
PLACEBO + CP	64	61	58	59	57	54	48	39	31	27	19	14	14	13	11	10	9	9	9	9	8	5	4	4	2	2	2	1

Adapted from Mirza et al. 2023 (Supplementary Appendix)[2]

Patients treated with JEMPERLI + CP saw

PFS and OS improvement

compared with placebo + CP

without compromising their quality of life[1-3]

JEMPERLI + CP **maintained HRQoL** in the dMMR/MSI-H population versus placebo + CP[1,2]

HRQoL PRO assessments were completed before treatment on day 1 of each treatment cycle, the end of treatment visit, and at safety and survival follow-up visits.
EORTC QLQ-C30: Functional scales: Physical, role, emotional, cognitive, social; Symptoms: Fatigue, nausea & vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties
EORTC QLQ-EN24: Functional scales: Sexual interest, sexual activity, sexual enjoyment ;Symptoms: lymphoedema, urological, gastrointestinal, poor body image, vaginal, pain in back and pelvis, tingling/numbness, muscular pain, hair loss, taste change.
BSLN; baseline, C; cycle, CI; confidence interval, CP; carboplatin + paclitaxel, dMMR; mismatch repair deficient, EORTC; European Organization for Research and Treatment of Cancer, HRQoL; health-related quality of life, MSI-H; microsatellite instability-high, PRO; patient-reported outcome, QLQ-C30; quality of life questionnaire – core 30, QLQ-EN24; quality of life questionnaire for endometrial cancer

1. Mirza MR, et al. N Engl J Med. 2023;388(23):2145–2158. 2. Mirza MR, et al. N Engl J Med. 2023;388(23):2145–2158. [Supplementary Appendix]. 3. Valabrega G, et al. Int J Gynecol Cancer 2024;0:1-11

Please consult the Jemperli SmPC for full safety profile and further information on the management of irAEs

JEMPERLI + CP offers a generally manageable safety profile, consistent with the known profiles of individual components, for up to 3 years of follow-up*[1,2]

	Jemperli + CP (N=241) n (%)	Placebo + CP (N=246) n (%)
Any TEAE	241 (100)	246 (100)
Any TRAE	236 (97.9)	243 (98.8)
Grade ≥3 TRAE	128 (53.1)	115 (46.7)
TEAE leading to discontinuation of Jemperli/placebo	46 (19.1)	20 (8.1)
TEAE leading to discontinuation of carboplatin	20 (8.3)	15 (6.1)
TEAE leading to discontinuation of paclitaxel	26 (10.8)	25 (10.2)
TEAE leading to death	5 (2.1)[a]	0
TRAE leading to death	2 (0.8)[b]	0
irAE related to Jemperli / placebo	98 (40.7)	40 (16.3)
Grade ≥3 irAE related to Jemperli/ placebo	32 (13.3)	8 (3.3)
IrAE leading to discontinuation of dostarlimab or placebo	21 (8.7)	8 (3.3)

Adapted from Powell *et al. 2024 and* Auranen *et al* 2024[1,2]

[a]Three deaths were not related to study treatment (opiate overdose, COVID-19, and general physical health deterioration). [b]One death was considered by the investigator as related to dostarlimab, carboplatin, and paclitaxel and occurred during the first 6 cycles (myelosuppression); one death was considered related to dostarlimab and occurred during the 90-day safety follow-up (hypovolemic shock).

*Median treatment duration of 43 weeks (range, 3.0;192.6) in the JEMPERLI + CP arm and 36 weeks (range, 2.1; 193.1) in the placebo + CP arm.

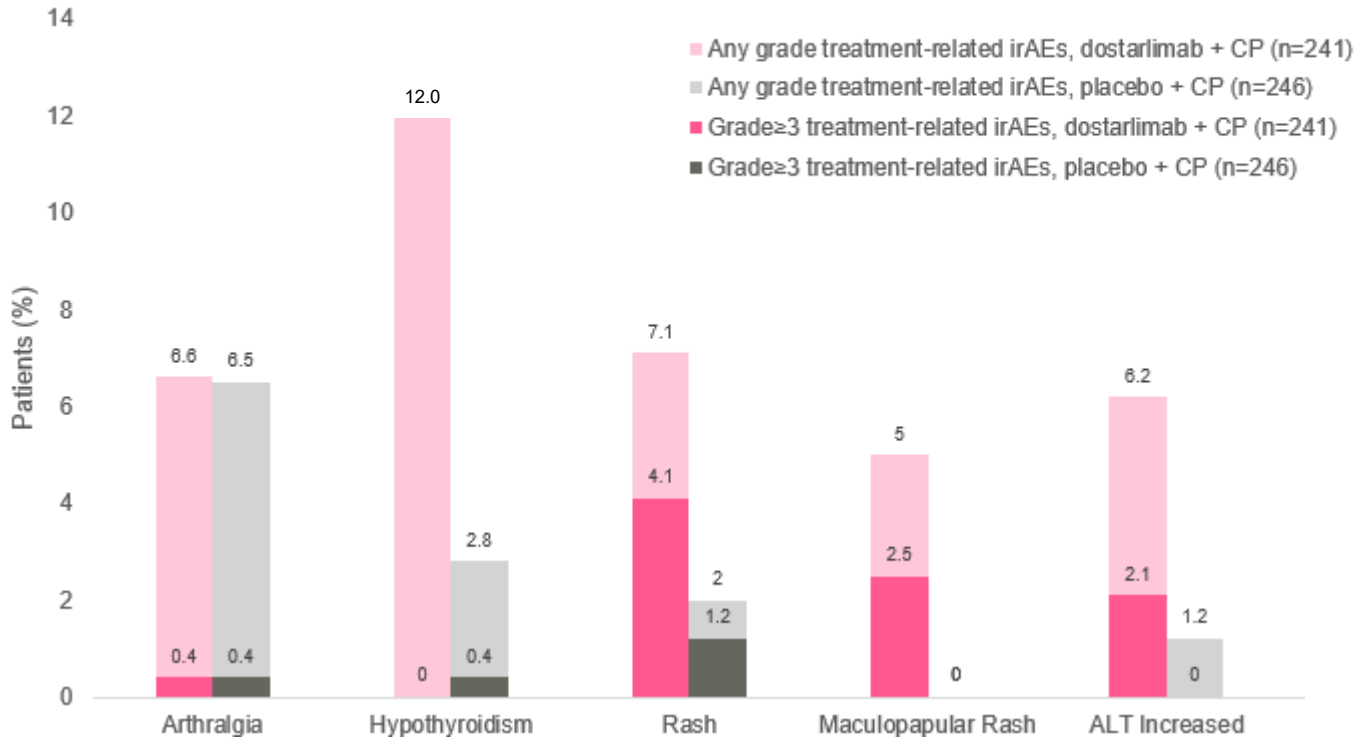
irAE is defined as Grade 2 or above from a pre-defined list of preferred terms.

CP; carboplatin-paclitaxel, irAE; Immune-related adverse event; TEAE; Treatment emergent adverse event, TRAE; Treatment related adverse event

1. Powell MA, et al. Ann Oncol. 2024; 35(8): 728–738. 2. Auranen et al., Therapeutic advances in medical oncology. 2024;16

Please consult the Jemperli SmPC for full safety profile and further information on the management of irAEs

The most common irAEs (≥5% of patients in either arm) related to JEMPERLI or placebo were hypothyroidism, rash, arthralgia, maculopapular rash and ALT increased[1]



Adapted from Auranen et al. 2024

Treatment-emergent irAEs led to a discontinuation of JEMPERLI /placebo in **8.7%** of patients in the **JEMPERLI + CP arm** and **3.3%** in the **placebo + CP arm** during the trial[1]

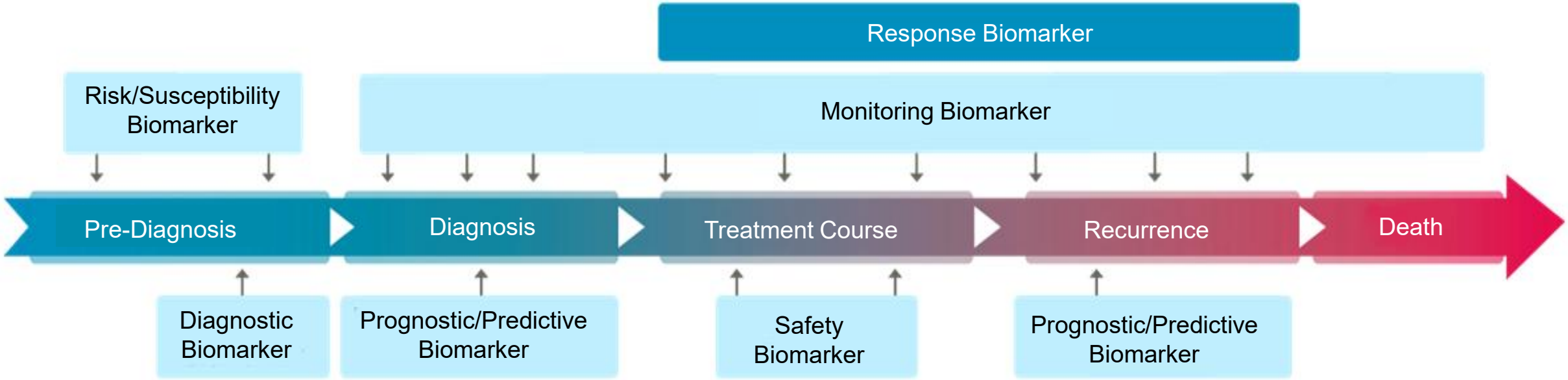
ALT; alanine aminotransferase, CP; carboplatin/paclitaxel irAE; immune-related adverse event

1. Auranen A, et al. Therapeutic Advances in Medical Oncology. 2024;16.

Biomarkers in the disease course

Biomarkers can be measured at any point in a patient's disease course, from before diagnosis (where they can be used to evaluate the risk of disease or to help with diagnosis) to after treatment in advanced disease (where they can be used to evaluate treatment efficacy and toxicity).[1]





Biomarkers along the clinical continuum[1,2]

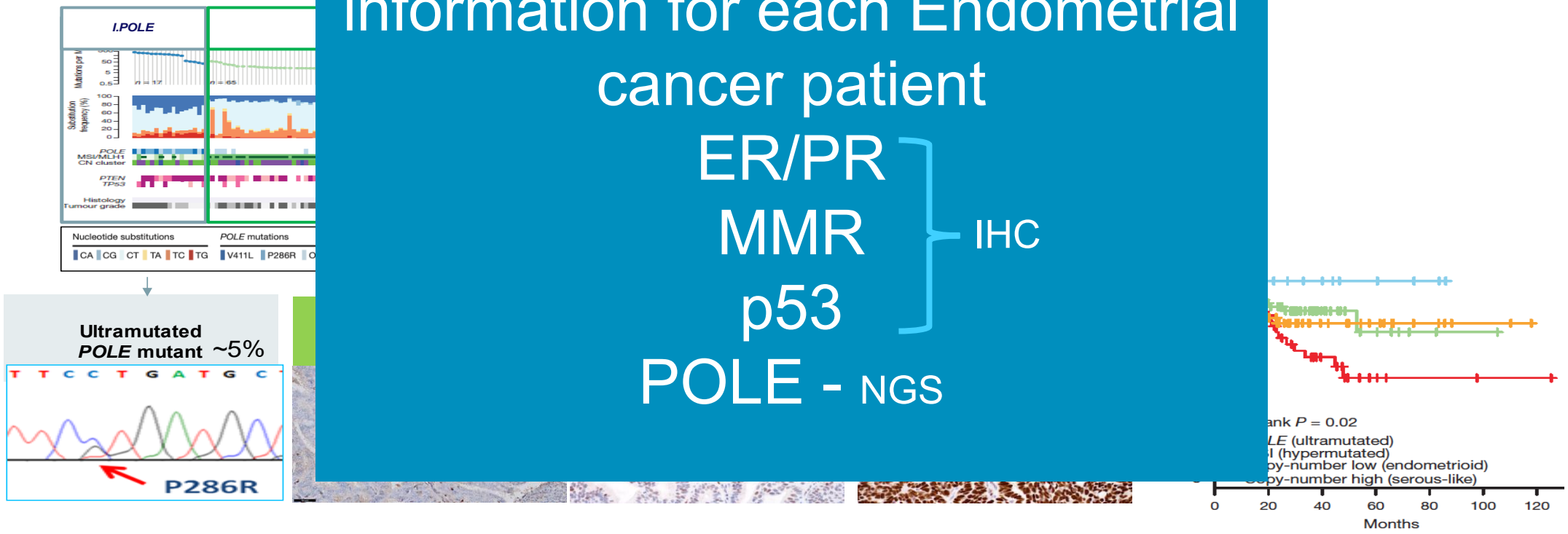
1. Cagney DN, et al. *Neuro-oncology*. 2018;20:1162-1172; 2. Colombo N, et al. *Int J Gynecol Cancer*. 2016;26:2-30.

Molecular classification & Endometrial cancer[1-3]

Must have the following information for each Endometrial cancer patient

ER/PR
MMR
p53
} IHC

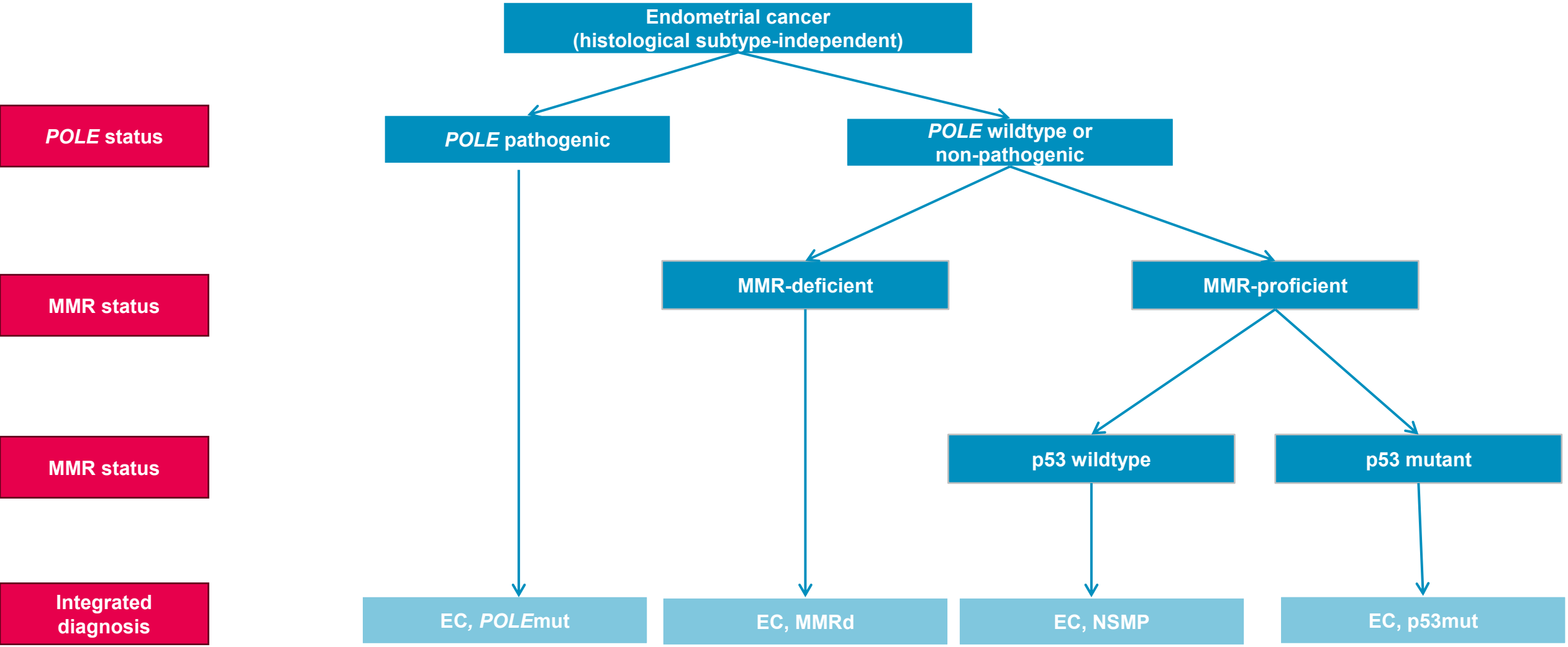
POLE - NGS



Images provided courtesy of speaker with relevant permissions obtained.

1. Billingsley CC, et al. Polymerase ε (POLE) mutations in endometrial cancer: clinical outcomes and implications for Lynch syndrome testing. Cancer. 2015 Feb 1;121(3):386-94. doi: 10.1002/cncr.29046. Epub 2014 Sep 15. PMID: 25224212; PMCID: PMC4304930 2. Vermij L,et al. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 2020 Jan;76(1):52-63. doi: 10.1111/his.14015. PMID: 31846532; PMCID: PMC6972558 3. Li HD, et al. PoleP286R mouse model of endometrial cancer recapitulates high mutational burden and immunotherapy response. JCI Insight. 2020 Jul 23;5(14):e138829. doi: 10.1172/jci.insight.138829. PMID: 32699191; PMCID: PMC7453891.

Integrated histomorphological classification



Based on speaker's experience

Implications for management of EC

Most molecular results done on the **initial hysteroscopy biopsy**

Test	Result	Outcome
POLE	Mutant / wild type	Treatment de-escalation in appropriate patients[1]
MMR	Proficient or deficient	Immunotherapy as option if dMMR and advanced EC. Lynch testing if dMMR & non-methylated
p53	Mutant / wild type	p53mut = Addition of chemotherapy in adjuvant setting for p53mut EC with myometrial invasion[1]
ER	Positive / negative (score out of 8)	Hormone manipulation in mEC an option if positive[1]
PR	Positive / negative (score out of 8)	Hormone manipulation in mEC an option if positive[1]

Information provided courtesy of speaker.

P53: Tumour Protein 53 ER: oestrogen receptor. PR: Progesterone receptor MMR: Mismatch repair POLE: DNA polymerase epsilon. dMMR: Mis Match repair deficient. mEC: metastatic endometrial cancer,

Reference: 1. Oaknin, A *et al.* Annals of oncology (2022),33 (9) available at: https://doi.org/10.1016/j.annonc.2022.05.009

MMR testing rates in EC vary by region and center

- Research suggests that **certain regions may not have fully incorporated MMR testing** into standard of care[1–4]
- **Continuing to educate and advocate** for MMR testing is important to enable optimal patient care[2]
- **MMR testing has evolved** beyond the testing for Lynch syndrome[2,4]

Testing rates are high, but data suggest some areas may benefit from increased understanding of the importance of MMR testing

EC, endometrial cancer; MMR, mismatch repair.

1. Zhang J, et al. Presented at AACR 2022. *Cancer Res.* 2022;82(12_Suppl):Abstract nr 6276; 2. Kelkar S, et al. *Gynecol Oncol Rep.* 2022;42:101026; 3. Ogando YM, et al. *Int J Gynecol Cancer.* 2022;32(Suppl 2):A105–106; 4. Huang M, et al. *Nature Sci Rep.* 2021;11(1):11712.

Who is a dMMR/MSI-H RUBY patient?

Example Checklist – presenter's own

This is not an exhaustive list. Other factors need to be considered. Please refer to the Summary of Product Characteristics before prescribing for any eligible patients

If a patient meets all three criteria below, they could benefit from receiving Jemperli in combination with platinum-containing chemotherapy.

1. **Pathology**
   - MMR deficient

2. **Stage**
   - First line recurrent* or advanced (stage 3C2/4)
   - Stage 3A/B with residual /measurable disease
   - Stage 3C1 with high risk histology or residual
   - Low chance of cure

3. **Patient**
   - Good PS/Fit for treatment
   - No contraindications to immunotherapy

✓ ✓ ✓

Patient eligible to receive **carboplatin paclitaxel + JEMPERLI**

*Naive to systemic therapy or prior neo-adjuvant/adjuvant systemic chemotherapy & had a recurrence or progressive disease ≥ 6 months after completing treatment
dMMR; mismatch repair deficient,MSI-H;microsatellite instability-high, MMR: mismatch repair, PS; performance status

This slide is developed by the speaker and reflects their own experience.

MLH1 promotor hypermethylation and Lynch syndrome testing[1]

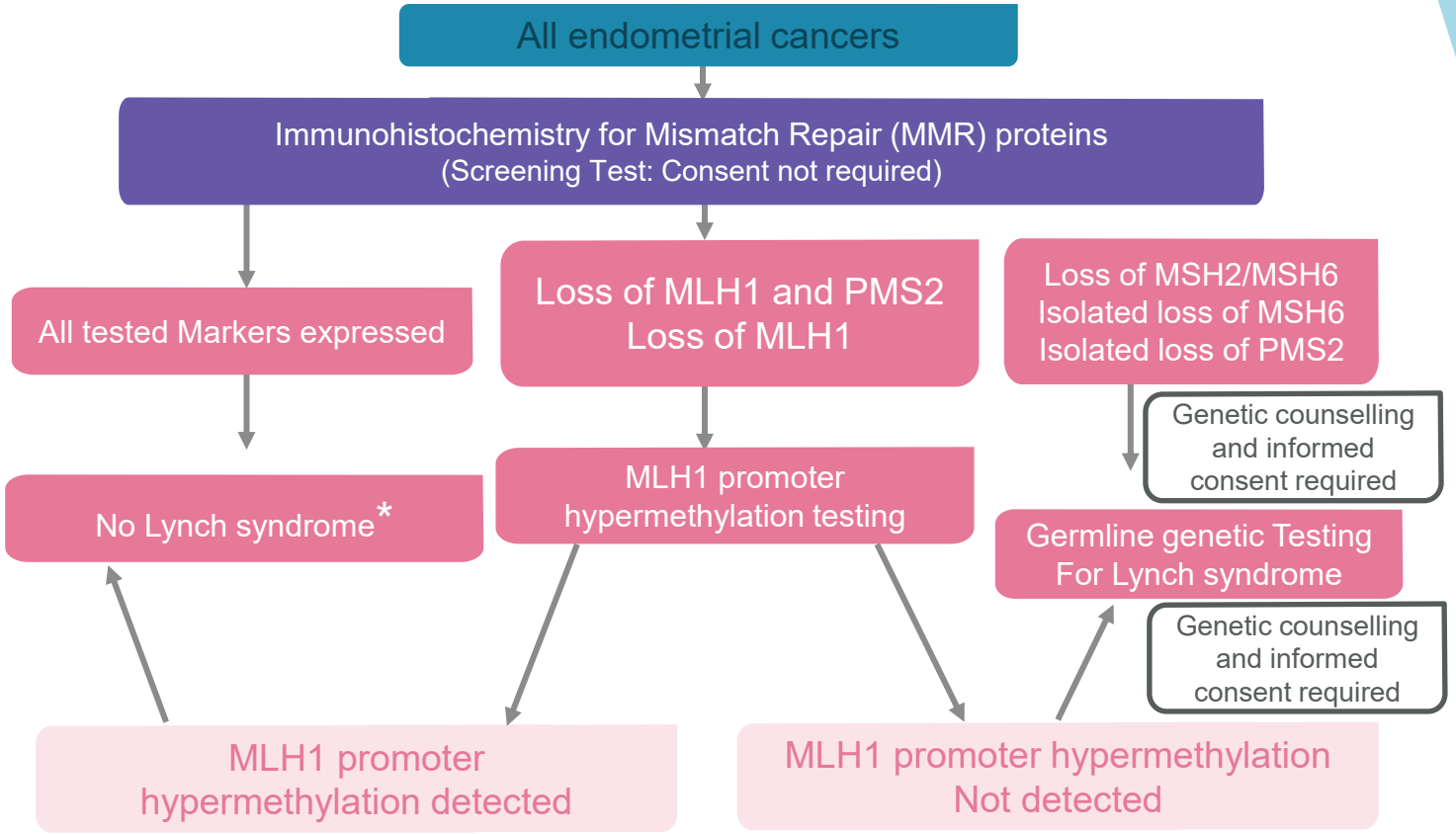
If loss of MMR proteins:[2,3]

- MLH1 loss - Perform hypermethylation testing
  - Hypermethylation detected – acquired mutation therefore no genetic testing needed
  - No hypermethylation detected – refer for genetic screening
- Loss of MSH2, MSH6 or PMS6 without MLH1 – refer for genetic screening

Therefore, this patient was sent for genetic screening without hypermethylation testing

*Despite this result, if there is a strong family/clinical history suggestive of Lynch and related syndromes; referral to Clinical Genetics services should be considered.[2]

NICE diagnostics guidance DG42: Testing strategies for Lynch syndrome in people with endometrial cancer[2,3]



Adapted from British Gynaecological Cancer Society 2020[2]

MLH=MutL Homolog 1; MSH2=MutS homolog 2; MSH6=MutS homolog 6; PMS2=postmeiotic segregation increased 2.

1. Morrison J, et al. Eur J *Obstet Gynecol Reprod Biol.* 2022; 270: 50–89. 2. British Gynaecological Cancer Society. The British Association of Gynaecological Pathologists. The Royal College of Pathologists. NICE diagnostics guidance DG42: Testing strategies for Lynch syndrome in people with endometrial cancer. Available from: https://www.bgcs.org.uk/wp-content/uploads/2020/11/BAGP-BGCS-NICE-MMR-pathway.pdf (Accessed January 2025); 3. NICE diagnostics guidance DG42: Testing strategies for Lynch syndrome in people with endometrial cancer. Available from: https://www.nice.org.uk/guidance/dg42 (Accessed January 2025).

Alternative two-antibody IHC testing pathway for MMR

This method involves staining for PMS2 and MSH6, as loss of function in either of these proteins can result in a loss of expression in both members of the heterodimer complex they form.

This approach is often used as a screening test for MMR deficiency.

It can be a cost-effective alternative to testing all four MMR proteins (MLH1, MSH2, MSH6, PMS2).

Patient Case Study.

Patient Case 1

Patient presentation

- 45 years old
- Irregular vaginal bleeding
- No significant PMH / No significant FH
- No medications

Surgery – December 2023

- Midline laparotomy, total abdominal hysterectomy
- BSO
- Bilateral SLN excision
- Supracolic omentectomy

BSO=bilateral salpino-oophorectomy; ER=oestrogen receptor; FH=family history; FIGO=International Federation of Gynaecology and Obstetrics; IHC=immunohistochemistry; LVSI=lymph-vascular space invasion; MSH2=MutS homolog 2; MSH6=MutS homolog 6; P53wt=tumour protein P53 wild type; POLEwt=deoxyribonucleic acid polymerase epsilon wild type; PMH=previous medical history; PR= progesterone receptor; SLN=sentinel lymph node.

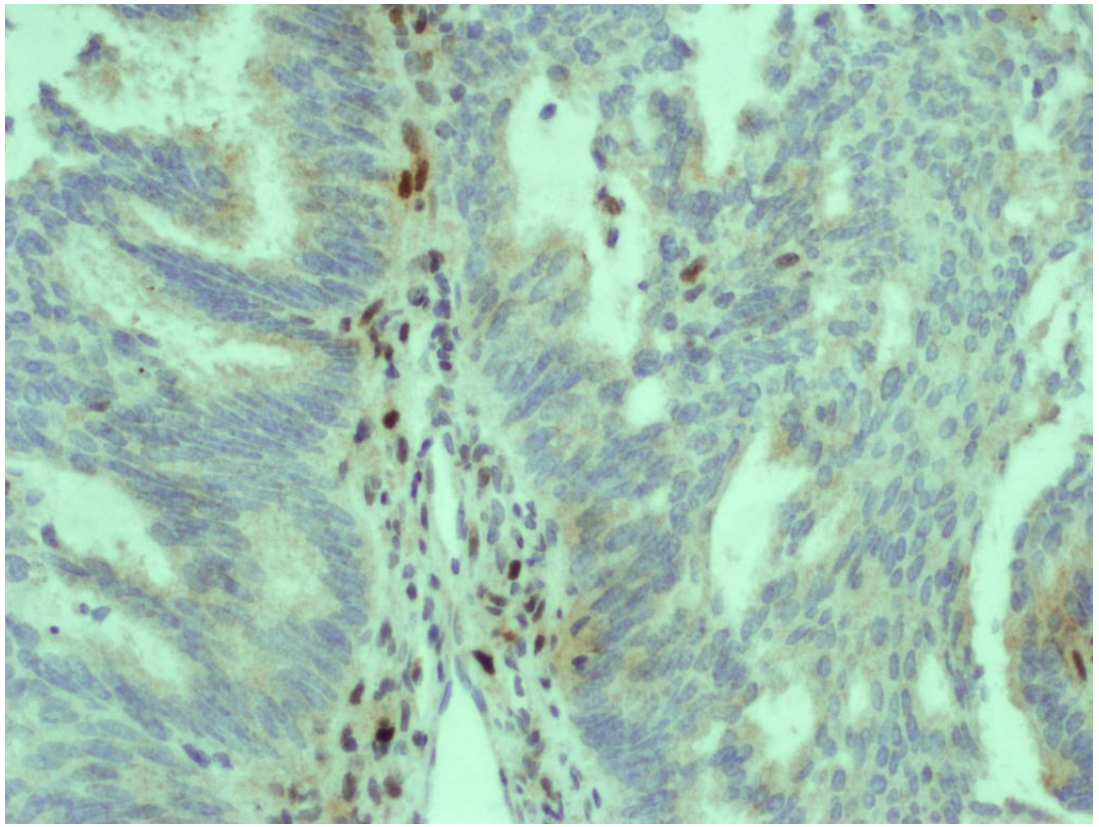
Patient case study provided courtesy of speaker with permissions obtained

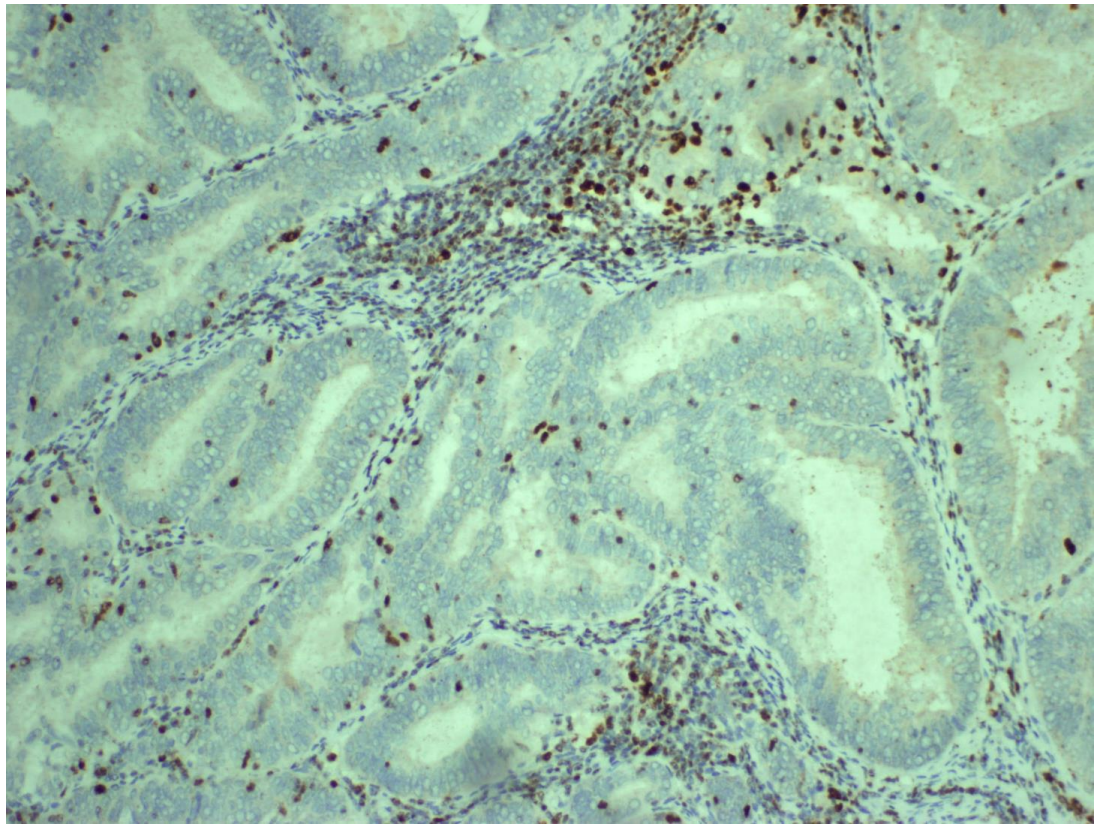
Stage 1A endometrial carcinoma



Patient case study provided courtesy of speaker with permissions obtained

Loss of MSH2 and MSH6





MSH2=MutS homolog 2; MSH6=MutS homolog 6.

Patient case study provided courtesy of speaker with permissions obtained

Abnormal, MSH2 and MSH6 loss : report

On immunohistochemistry, the tumour cells show loss of expression of the mismatch repair proteins MSH2 and MSH6 (with normal nuclear staining for MLH1 and PMS2).

Conclusion: This mismatch repair deficiency is associated with Lynch and related syndromes.

NICE guideline-based action: Clinical referral for germline genetic testing required for Lynch syndrome.

Patient case 1

Patient presentation

- 45 years old
- Irregular vaginal bleeding
- No significant PMH / No significant FH
- No medications

Surgery – December 2023

- Midline laparotomy, total abdominal hysterectomy
- BSO
- Bilateral SLN excision
- Supracolic omentectomy

Pathology

- **FIGO 1A** grade 2 endometrioid adenocarcinoma of the endometrium
- No myoinvasion, 20mm max dimension
- No LVSI
- **POLEwt, p53wt, loss of MSH2 and MSH6, ER/PR 6/8**
- **IHC pending on peritoneal nodule**

BSO=bilateral salpino-oophorectomy; ER=oestrogen receptor; FH=family history; FIGO=International Federation of Gynaecology and Obstetrics; IHC=immunohistochemistry; LVSI=lymph-vascular space invasion; MSH2=MutS homolog 2; MSH6=MutS homolog 6; P53wt=tumour protein P53 wild type; POLEwt=deoxyribonucleic acid polymerase epsilon wild type; PMH=previous medical history; PR= progesterone receptor; SLN=sentinel lymph node.

Patient case study provided courtesy of speaker with permissions obtained

Patient Case 1

- FIGO IA grade 2 endometrioid adenocarcinoma of the endometrium, no myoinvasion, 20mm max dimension, No LVSI
- Low risk
- POLEwt, p53wt, Loss of MSH2 and MSH6, ER/PR 6/8
- IHC pending on peritoneal nodule

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Risk group	Molecular classification unknown	Molecular classification known
Low	• Stage IA endometrioid + low-grade + LVSI negative or focal	• Stage I-II **POLEmut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade + LVSI negative or focal
Intermediate	• Stage IB endometrioid + low-grade + LVSI negative or focal • Stage IA endometrioid + high-grade + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion • Stage IB endometrioid high-grade regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with no residual disease	• Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I-IVA **MMRd/NSMP** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA **MMRd/NSMP** with residual disease of any molecular type • Stage IVB of any molecular type

FIGO=International Federation of Gynaecology and Obstetrics; LVSI=lymph-vascular space invasion; MLH=MutL Homolog; MMRd=mismatch repair deficient; MSH2=MutS homolog 2; MSH6=MutS homolog 2; P53wt=tumour protein P53 wild type; POLEwt=deoxyribonucleic acid polymerase epsilon wild type, IHC -=immunohistochemistry

Table adapted from Concin N, et al, 2021

Patient case study provided courtesy of speaker with permissions obtained

1. Concin N, et al. *Int J Gynecol Cancer*. 2021. 31(1):12–39.

Lynch syndrome report

Technical Information

Variant details

Gene	Zygosity	Inheritance	HGVS description	Transcript	Classification
MSH2	Heterozygous	AD	c.2396del p.(Asn799IlefsTer13)	NM_000251.3	Pathogenic

Evidence for classification:

- Predicted null variant where loss of function is known disease mechanism (PVS1-very strong)
- This variant is absent from the gnomAD population database (PM2-moderate)
- Patient's phenotype or family history is highly specific for gene (PP4-supporting)

Variants reported have been confirmed by Sanger sequencing or MLPA unless otherwise specified. Only variants that are considered likely to be relevant to this patient's clinical phenotype are reported. Variants classified as benign, likely benign or uncertain significance, where further testing would not alter classification are not reported.

Panel Details:

Inherited MMR deficiency_R210
Genes tested: ***MLH1, MSH2, MSH6, PMS2*, EPCAM*** (copy number analysis for 3' end of gene only)
Coverage: 100% of the coding region and intron/exon splice boundaries (+/- 20bp) for the specified genes have been sequenced to the minimum 30x read depth. *100% of *PMS2* exons 1-10 has been sequenced to the required read depth, however due to the presence of closely related pseudogenes, test sensitivity for *PMS2* exons 11-15 may be reduced as this region may not have been uniquely captured by this method. Copy number analysis using the SavvyCNV and DeCon tools is not undertaken for *PMS2* exons 11-15.

AD=autosomal dominant; CNV=copy number variant; EpCAM=Epithelial cell adhesion molecule; DeCon=Detection of Exon Copy Number; gnomAD=The Genome Aggregation Database; MLH1=MutL Homolog 1; MSH2=MutS homolog 2; MSH6=MutS homolog 6; MLPA=multiplex ligation-dependent probe amplification; MMR=mismatch repair; PMS2=postmeiotic segregation increased 2; PP4=protein phosphatase 4.

Patient case study provided courtesy of speaker with permissions obtained

Patient presentation

- 45 years old
- Irregular vaginal bleeding
- No significant PMH / No significant FH
- No medications

Surgery – December 2023

- Midline laparotomy, total abdominal hysterectomy
- BSO
- Bilateral SLN excision
- Supracolic omentectomy

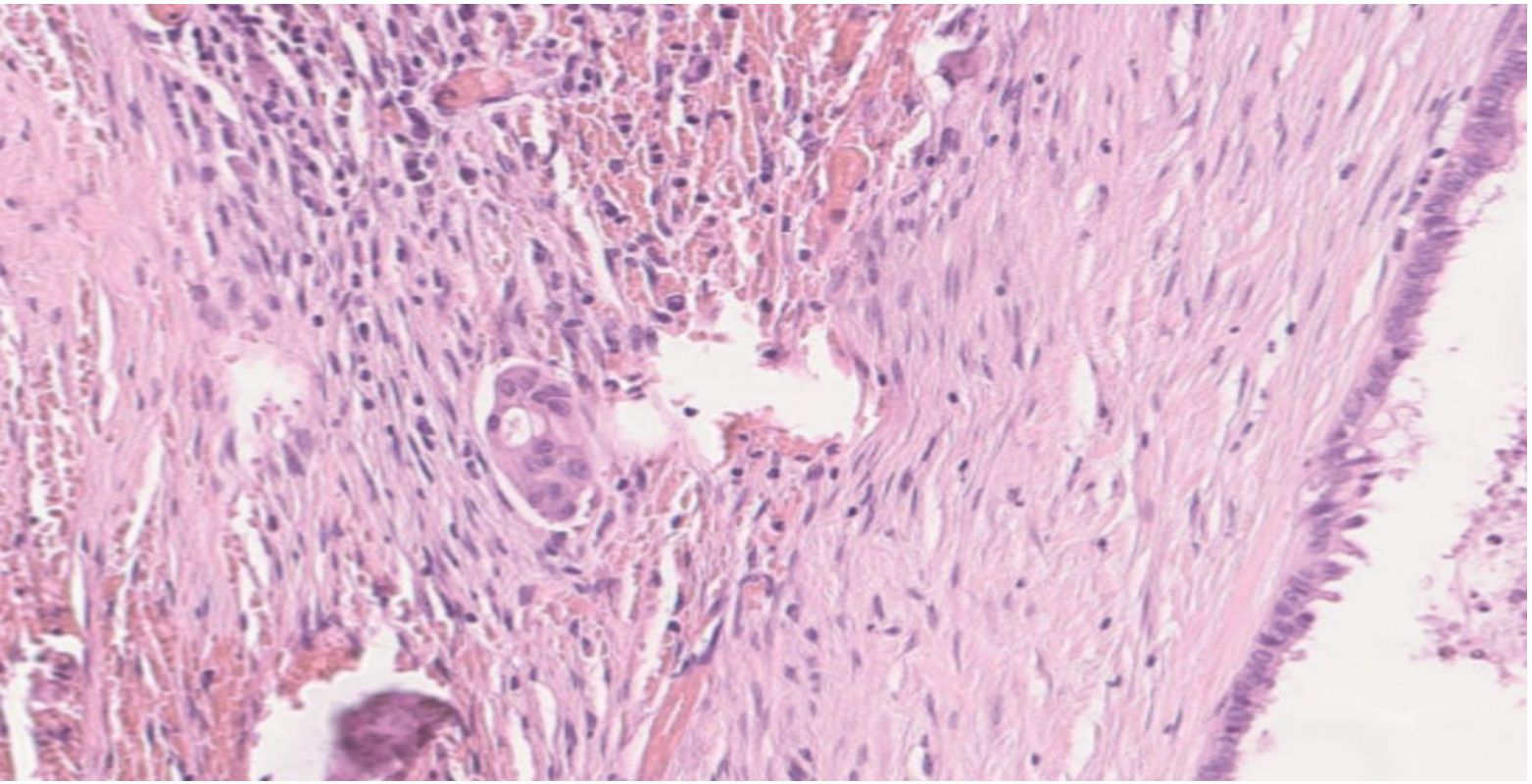
Pathology

- **FIGO IA** grade 2 endometrioid adenocarcinoma of the endometrium
- No myoinvasion, 20mm max dimension
- No LVSI
- **POLEwt, p53wt, Loss of MSH2 and MSH6, ER/PR 6/8**
- **Lynch syndrome confirmed**

BSO=bilateral salpino-oophorectomy; FIGO=International Federation of Gynaecology and Obstetrics; IHC=immunohistochemistry; LVSI=lymph-vascular space invasion; MSH2=MutS homolog 2; MSH6=MutS homolog 6; P53wt=tumour protein P53 wild type; POLEwt=deoxyribonucleic acid polymerase epsilon wild type; SLN=sentinel lymph node.

Patient case study provided courtesy of speaker with permissions obtained

Peritoneal nodule



IHC=immunohistochemistry.

Patient case study provided courtesy of speaker with permissions obtained

ESGO/ESP/ESTRO guidance

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Risk group	Molecular classification unknown	Molecular classification known
Low	• Stage IA endometrioid + low-grade + LVSI negative or focal	• Stage I-II **POLEmut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade + LVSI negative or focal
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High-intermediate	• Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion • Stage IB endometrioid high-grade‡regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with no residual disease	• Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I-IVA **MMRd/NSMP** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA **MMRd/NSMP** with residual disease of any molecular type • Stage IVB of any molecular type

Advanced metastatic

- FIGO 4B grade 2
- No LVSI
- POLEwt
- P53wt
- ER/PR 6/8
- MMRd (loss of MSH2 and MSH6)
- Lynch syndrome

Table adapted from Concin et al. 2021[1]

FIGO=International Federation of Gynaecology and Obstetrics; LVSI=lymph-vascular space invasion; MLH=MutL Homolog; MMRd=mismatch repair deficient; MSH2=MutS homolog 2; MSH6=MutS homolog 2; P53wt=tumour protein P53 wild type; POLEwt=deoxyribonucleic acid polymerase epsilon wild type.

Patient case study provided courtesy of speaker with permissions obtained

1. Concin N, et al. *Int J Gynecol Cancer*. 2021. 31(1):12–39.

Who is a dMMR/MSI-H RUBY patient?

Example Checklist – presenter's own

This is not an exhaustive list. Other factors need to be considered. Please refer to the Summary of Product Characteristics before prescribing for any eligible patients

If a patient meets all three criteria below, they could benefit from receiving Jemperli in combination with platinum-containing chemotherapy.

1. **Pathology**
   - MMR deficient – **loss of MSH2 and MSH6**
   - Needs genetic testing

2. **Stage**
   - FIGO 4B
   - High chance of other micrometastatic disease
   - Low chance of cure

3. **Patient**
   - Good PS- 0
   - Fit for treatment
   - No contraindications to immunotherapy
   - Keen for full active management

Patient eligible to receive **carboplatin paclitaxel + JEMPERLI**

*Naive to systemic therapy or prior neo-adjuvant/adjuvant systemic chemotherapy & had a recurrence or progressive disease ≥ 6 months after completing treatment
dMMR; mismatch repair deficient,MSI-H;microsatellite instability-high, MMR: mismatch repair, PS; performance status

This slide is developed by the speaker and reflects their own experience.

Patient case study provided courtesy of speaker with permissions obtained
Treatment is still ongoing at the time of presentation

Surgery – December 2023

- Midline laparotomy, total abdominal hysterectomy
- BSO
- Bilateral SLN excision
- Supracolic omentectomy

Pathology

- FIGO IA grade 2 endometrioid adenocarcinoma of the endometrium
- No myoinvasion, 20mm max dimension
- No LVSI
- **POLEwt, p53wt, loss of MSH2 and MSH6, ER/PR 6/8**
- **Lynch syndrome confirmed**

Pathology
FIGO 4B (peritoneal nodule of <100 tumour cells, 1mm size) grade 2 endometrioid adenocarcinoma of the endometrium

- No myoinvasion, 20mm max dimension
- No LVSI
- **POLEwt, p53wt, Loss of MSH2 and MSH6 (Lynch confirmed)**

Subsequent treatment

- JEMPERLI + CP

JEMPERLI as combination therapy is 500 mg dostarlimab Q3W for 6 cycles followed by 1000 mg Q6W for all cycles thereafter until disease progression or unacceptable toxicity, or for a duration of up to 3 years.[1]

BSO=bilateral salpingo-oophorectomy; CP=carboplatin + paclitaxel; ER= oestrogen receptor; FIGO=International Federation of Gynaecology and Obstetrics; IHC=immunohistochemistry; LVSI=lymph-vascular space invasion; MLH=MutL Homolog; MSH2=MutS homolog 2; MSH6=MutS homolog 6; P53wt=tumour protein P53 wild type; POLEwt=deoxyribonucleic acid polymerase epsilon wild type; PR=progesterone receptor; Q3W=every 3 weeks; Q6W=every 6 weeks; SLN=sentinel lymph node.1. Jemperli (dostarlimab) Summary of Product Characteristics UK

Thank you

This meeting has been organised and funded by GSK for UK Healthcare professionals only.
Prescribing information can be found at the end of this presentation and at the GSK stand.

SPOTLIGHT

The Northern Ireland experience of integrating TGCA endometrial carcinoma classification into clinical practice

Professor Glenn McCluggage
Consultant Histopathologist, Department of Pathology, Belfast Heath and Social Care Trust

Adverse events should be reported. Reporting forms and information can be found at: https://yellowcard.mhra.gov.uk (UK) or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to GSK on 0800 221 441 or by email at uksafety@gsk.com

GSK

Jemperli (dostarlimab) Injection 500 mg

Speaker Disclosures
Prof. Glenn McCluggage

I am presenting at this symposium on behalf of GSK, the sponsor of this meeting, and I am contracted with GSK for this service. The information being presented is consistent with the ABPI Code of Practice guidelines.

- Consultant Histopathologist, Department of Pathology, Belfast Heath and Social Care Trust
- Speaker: GSK
- Honoraria/meeting expenses: GSK

WHO classification of endometrial carcinomas[1,2]

- Endometrioid adenocarcinoma
- Serous carcinoma
- Clear cell carcinoma
- Undifferentiated and dedifferentiated carcinoma
- Mixed carcinoma
- Mesonephric adenocarcinoma
- Squamous cell carcinoma
- Mucinous carcinoma, intestinal type
- Mesonephric-like adenocarcinoma
- Carcinosarcoma

This is predominantly a morphological classification, supplemented by immunohistochemistry[3]

WHO, World Health Organization.

1. WHO Classification of Tumours Editorial Board ed. World Health Organization classification of tumours. 5th ed. (2020) Female genital tumours. Lyon: IARC Press; 2. McCluggage WG, et al. Histopathology. 2022;80(5):762-778. 3. Wang M, Hui P.. Arch Pathol Lab Med. 2021 ;145(11):1367-1378.

Significant interobserver variability in reporting of endometrial carcinoma (EC), especially of high-grade EC

Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma

Am J Surg Pathol. 2013 Jun;37(6):874-81

Gilks CB, Oliva E, Soslow RA.

EC, endometrial cancer.

Gilks CB, et al. Am J Surg Pathol. 2013 Jun;37(6):874-81

Integrated genomic characterization of endometrial carcinoma

Nature. 2013 May 2;497(7447):67-73

The Cancer Genome Atlas Research Network

- An integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas
- Endometrial carcinomas can be divided into 4 groups (POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high)

POLE, DNA polymerase epsilon.

Cancer Genome Atlas Research Network; Kandoth C, et al. Nature. 2013 May 2;497(7447):67-73. Erratum in: Nature. 2013 Aug 8;500(7461):242.

Endometrial cancer: TCGA molecular groups[1]

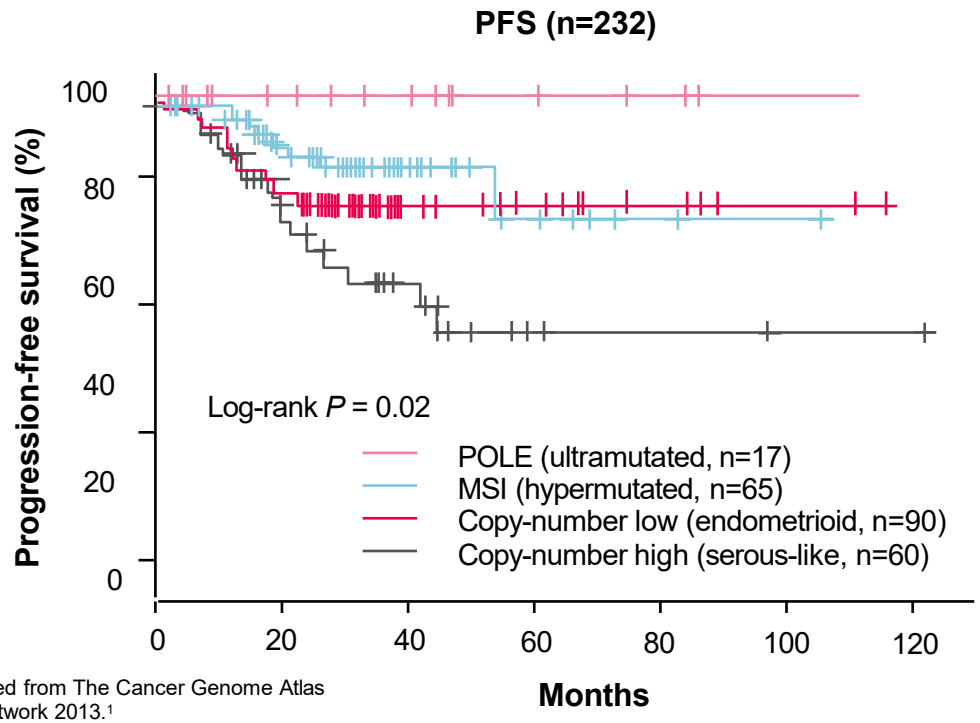


Figure adapted from The Cancer Genome Atlas Research Network 2013.[1]

- 4 distinct groups:
  - ***POLE***
  - **MSI**
  - **Copy-number low**
  - **Copy-number high**

EC, endometrial cancer; MSI, microsatellite instability; PFS, progression-free survival; POLE, DNA polymerase epsilon.

1. The Cancer Genome Atlas Research Network. Nature. 2013;497:67–73.

Different names for molecular classification

- ***POLE*** / ultramutated (exceptionally high mutational burden; >100 mutations/Mb)
- MSI / MMR deficient **MMRd** / hypermutated (high mutational burden; 10-100 mutations/Mb)
- Copy-number high / serous-like / p53 mutated / p53 abnormal **p53abn**
- Copy-number low **/ no specific molecular profile (NSMP)**
- These are biologically and clinically distinct tumours ; this is an objectively and largely non overlapping classification.

POLE, DNA polymerase epsilon; MMR, mismatch repair; MSI, microsatellite instability; p53, tumour suppressor p53.
Information provided courtesy of speaker and reflects speaker's own views and experience.

ORIGINAL TCGA PERCENTAGES: VARY BETWEEN DIFFERENT COHORTS

- % *POLE* mutated (7%)[1,2]
- % NSMP (38.8%)[3]
- % MMR deficient (28%)[1]
- % p53 abnormal (25.9%)[4]

REMEMBER THIS WAS A SELECTION OF CASES OF ENDOMETRIOID AND SEROUS CARCINOMAS FROM VARIOUS INSTITUTIONS (NOT POPULATION-BASED)

POLE: DNA polymerase epsilon, NSMP: no specific molecular profile, MMR: Mis Match Repair, p53: Tumour protein 53.

1. Zannoni GF, *et al. Front Oncol* 2022; 12, 805613 2:Vermij L, et al. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 2020 Jan;76(1):52-63. doi: 10.1111/his.14015. PMID: 31846532; PMCID: PMC6972558 805613. 3. Jamieson A, *et al. Mod Pathol* 2023; 36: 100085. 4. Yano M, *et al. Mod Pathol* 2019; 32: 1023–1031.

Personalised treatment of endometrial carcinomas

- Age important
- Traditional pathological factors important: tumour grade, tumour stage, LVSI
- **Potential de-escalation of treatment in *POLE***
- **Chemotherapy in p53abn (also interest in PARP/ HRD, HER2)**
- **Immune checkpoint inhibitors in MMRd**
- **NSMP (variety of different tumours which needs to be more explored)**

Slide based on speaker's experience

Surrogate TCGA endometrial carcinoma molecular classification

Diagnosis requires 3 tests (ProMisE classifier):

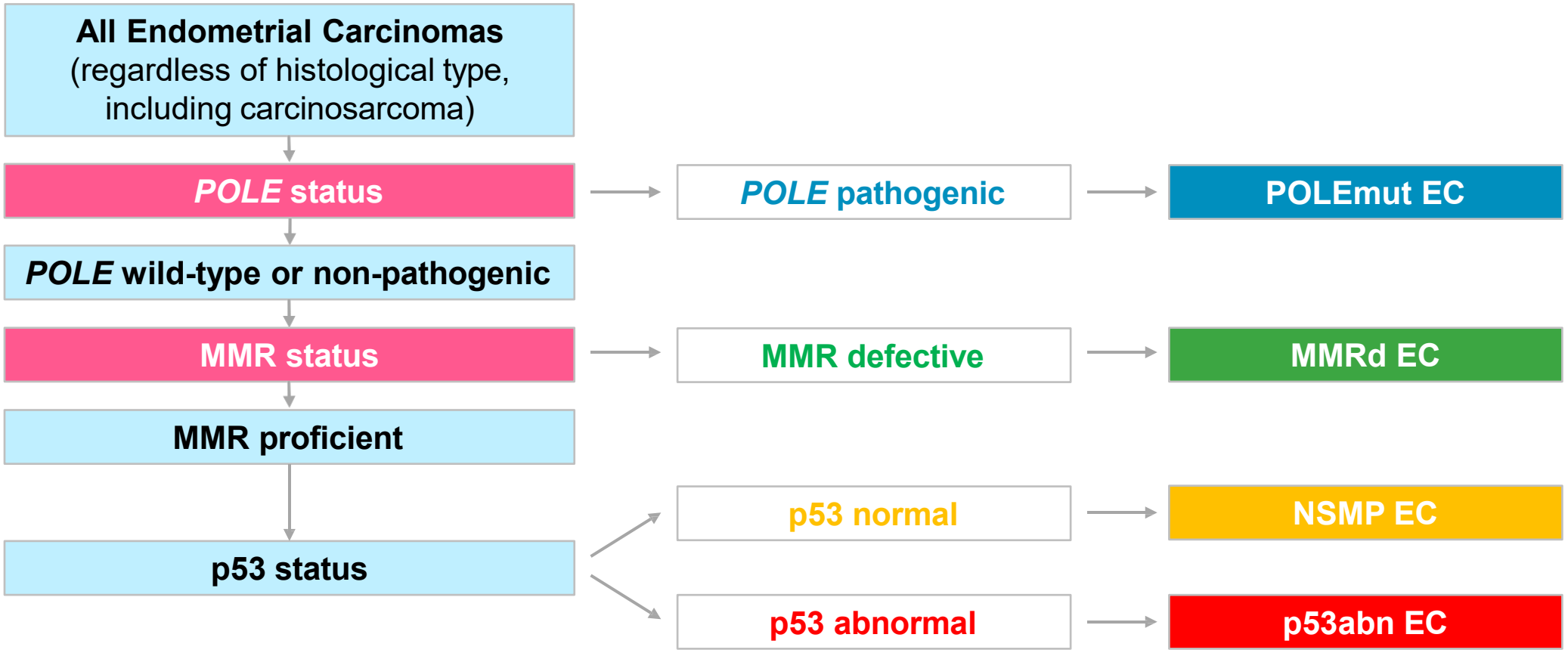
- MMR immunohistochemistry (**AVAILABLE** IN ALMOST ALL PATHOLOGY LABS)
- p53 immunohistochemistry (**AVAILABLE** IN ALMOST ALL PATHOLOGY LABS)
- *POLE* mutation testing (**NOT** AVAILABLE IN MANY PATHOLOGY LABS)

THIS IS NOT PURE MOLECULAR TESTING BUT LARGELY A SURROGATE (CAN DO ALL BY NGS - PURE MOLECULAR TESTING)

MMR, mismatch repair; p53, tumour suppressor p53; NGS, next generation sequencing; POLE, DNA polymerase epsilon; ProMisE, Proactive Molecular Risk Classifier for Endometrial Cancer.

1. Talhouk A, et al. Br J Cancer. 2015;113:299–310.

PROMISE Algorithm for molecular classification in clinical practice



abn, abnormal; EC, endometrial cancer; MMR, mismatch repair; MMRd, mismatch repair deficient; mut, mutated; NSPM, no specific mutational subtype; p53, tumour protein 53; POLE, DNA polymerase epsilon.

Content provided courtesy of speaker and relects speaker's own views and experience. ADAPTED FROM GYNECOLOGICAL TUMORSVOLUME 29, ISSUE 5P1180-1188MAY 2018

Minimum immunohistochemistry to be performed on biopsy specimens of all endometrial carcinomas

- BAGP recommendations for several years now; ER, MMR (2 or 4 markers), p53
- Best done on biopsies since best to have information upfront (in case influences management) and fixation issues so often better on biopsies.
- Other markers can be performed depending on differential diagnosis

ER, Oestrogen Receptor, MMR, Mis Match Repair, p53, tumour protein 53

Content provided courtesy of speaker and reflects speaker's own views and experience.

Why test for ER IHC on all endometrial biopsies?

- Important prognostic indicator in NSMP endometrial carcinomas (optimal cut-off not determined; cut-offs of 1% and 10% have been suggested)
- May help to pick up ER-negative tumours (mesonephric-like, gastric/gastrointestinal type/ clear cell) which may be missed
- Clinicians may ask for this sometime later when considering hormone therapies after tumour recurrence, so easier to have done upfront

ER, Oestrogen Receptor, NSMP, No specific molecular profile

Content provided courtesy of speaker and reflects speaker's own views and experience.

Why test for p53 on all endometrial biopsies?

- Needed for TCGA molecular classification
- p53-abnormal tumours have worse prognosis[1]
- p53-abnormal tumours may benefit from chemotherapy treatment[1]
- May help to pick up subtle p53-abnormal tumours such as glandular variant of serous carcinoma, intestinal-type adenocarcinomas or distinguish between serous and grade 3 endometrioid carcinoma[1]
- p53-abnormal low-grade endometrioid carcinomas (a small percentage) have worse outcome than p53-wild-type even when Stage I[2]
- p53-abnormal tumours may be HER2 amplified and HRD: ongoing investigation of possibility of specific targeted therapies

TCGA, The Cancer Genome Atlas, p53, tumour protein 53, HER2, Human epidermal growth factor receptor 2, HRD, homologous recombination deficient.

Content provided courtesy of speaker and reflects speaker's own views and experience.

1. Oaknin, A et al. Annals of oncology (2022),33 (9) available at: https://doi.org/10.1016/j.annonc.2022.05.009, 2. Jamieson A, Vermij L, Kramer CJH, et al. Clinical Behavior and Molecular Landscape of Stage I p53-Abnormal Low-Grade Endometrioid Endometrial Carcinomas. *Clin Cancer Res*. 2023;29(23):4949-4957. doi:10.1158/1078-0432.CCR-23-1397

Interpretation of P53 Immunohistochemistry in Endometrial Carcinomas: Toward Increased Reproducibility

Martin Köbel, Brigitte M. Ronnett, Naveena Singh, Robert A. Soslow, C. Blake Gilks, W. Glenn McCluggage

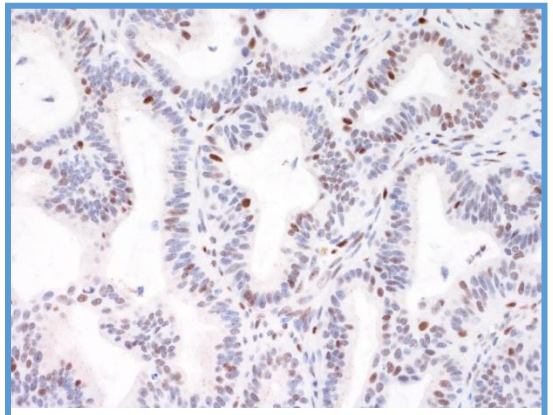
P53, Tumour Protein 53

Köbel M, Ronnett BM, Singh N, Soslow RA, Gilks CB, McCluggage WG. Interpretation of P53 Immunohistochemistry in Endometrial Carcinomas: Toward Increased Reproducibility. *Int J Gynecol Pathol*. 2019 Jan;38 Suppl 1(Iss 1 Suppl 1):S123-S131. doi: 10.1097/PGP.0000000000000488.

Interpretation of p53 Immunohistochemistry

p53 normal/wild-type

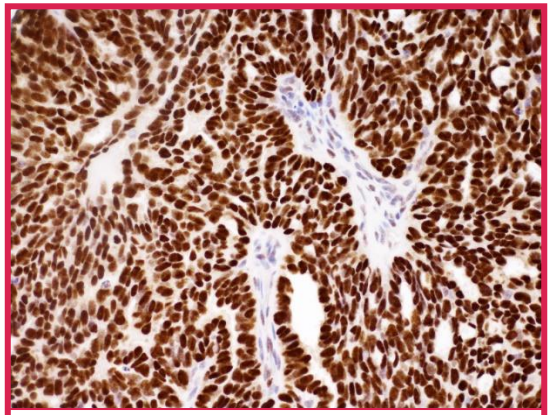
No *TP53* mutation



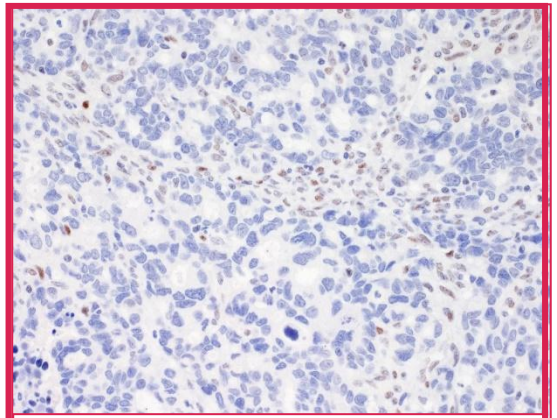
Wild-type pattern

p53 abnormal/ mutation-type

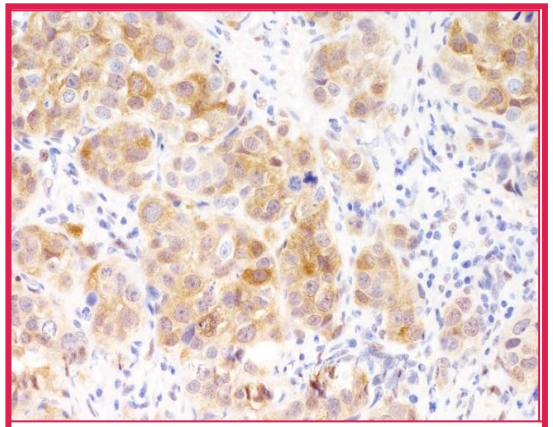
***TP53* mutation**



p53 overexpression



p53 complete absence



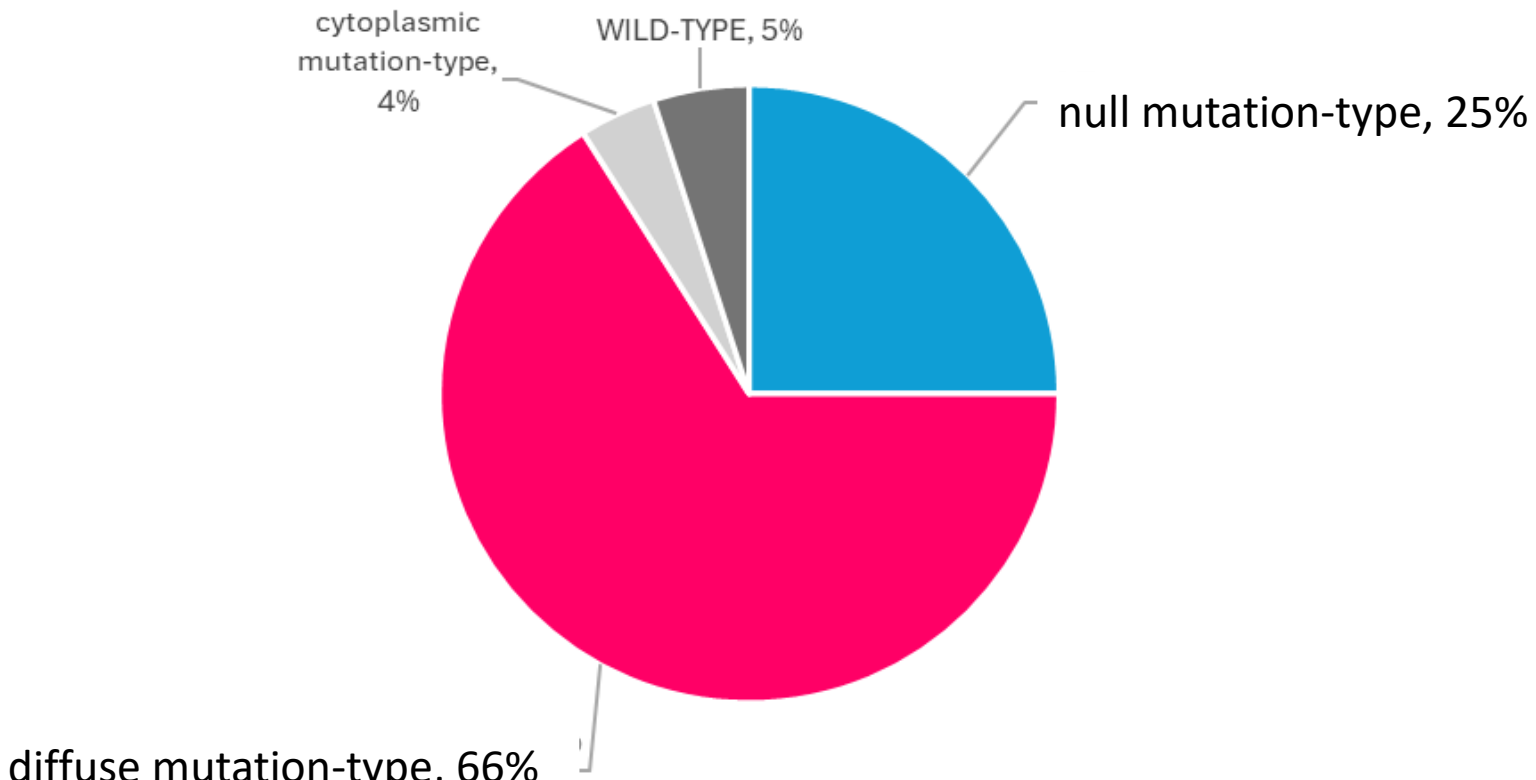
p53 cytoplasmic

P53, Tumour Protein 53

Köbel M, Ronnett BM, Singh N, Soslow RA, Gilks CB, McCluggage WG. Interpretation of P53 Immunohistochemistry in Endometrial Carcinomas: Toward Increased Reproducibility. *Int J Gynecol Pathol*. 2019 Jan;38 Suppl 1(Iss 1 Suppl 1):S123-S131. doi: 10.1097/PGP.0000000000000488.

Images provided by speaker

Types of p53 expression in a series of tubo-ovarian HGSC with proven TP53 mutations



PMID 27840695

MMR immunohistochemistry

- MMR IHC is a good surrogate for MSI testing (molecular test)
  - In many ways, superior to MSI testing (quicker, suggests which gene involved, pathologists can interpret and diagnose, MSH6 deficient tumours may be MSS rather than MSI-H); however, IHC is more prone to fixation issues; NICE recommends MMR IHC (not MSI testing[1])
- Value of “upfront” MMR IHC:
  - Lynch syndrome identification
  - Diagnosis (endometrial vs cervical adenocarcinoma/ endometrioid versus serous)
  - **Predictive of response to immune checkpoint inhibitors**
  - Molecular classification
  - Provides prognostic and predictive information
  - If results are available upfront, do not generally need to go back and repeat on old cases

  ► PATHOLOGISTS MUST KNOW HOW TO INTERPRET RESULTS
- Can also use molecular testing (NGS) for MMR genes

IHC, immunohistochemistry; MMR mismatch repair; MSI, microsatellite instability high; NGS, next generation sequencing; NICE, National Institute for Health and Care Excellence; PCR, polymerase chain reaction.

Content provided courtesy of speaker and reflects speaker’s own views and experience. 1. NICE diagnostics guidance DG42. (2020) Accessed May 2025 from https://www.nice.org.uk/guidance/dg42.

The medical teams supporting the patient journey

Testing for Lynch syndrome using IHC

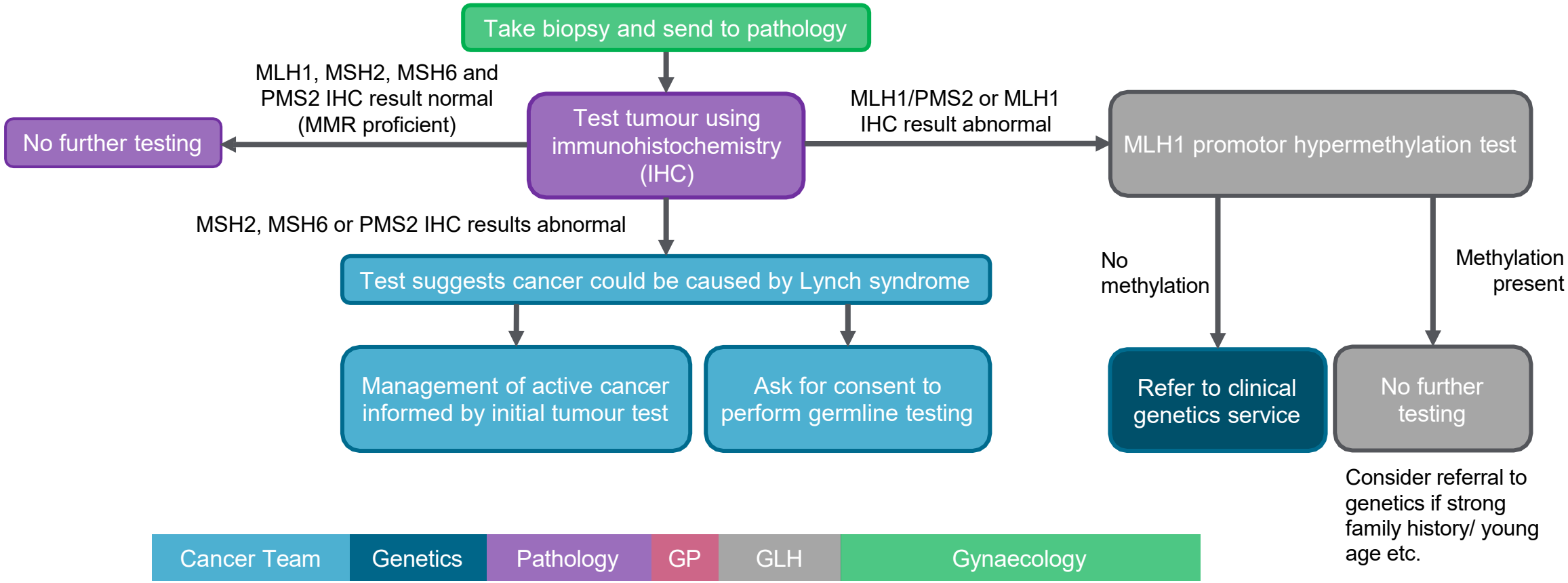


Figure adapted from NHS England[1] as advised by speaker.
GLH, genomics laboratory hub; GP, general practitioner; IHC, immunohistochemistry; MMR, mismatch repair.

1. NHS England. Implementing Lynch syndrome testing and surveillance pathways. Accessed May 2025 from https://www.england.nhs.uk/wp-content/uploads/2021/07/B0622-implementing-lynch-syndrome-testing-and-surveillance-pathways.pdf

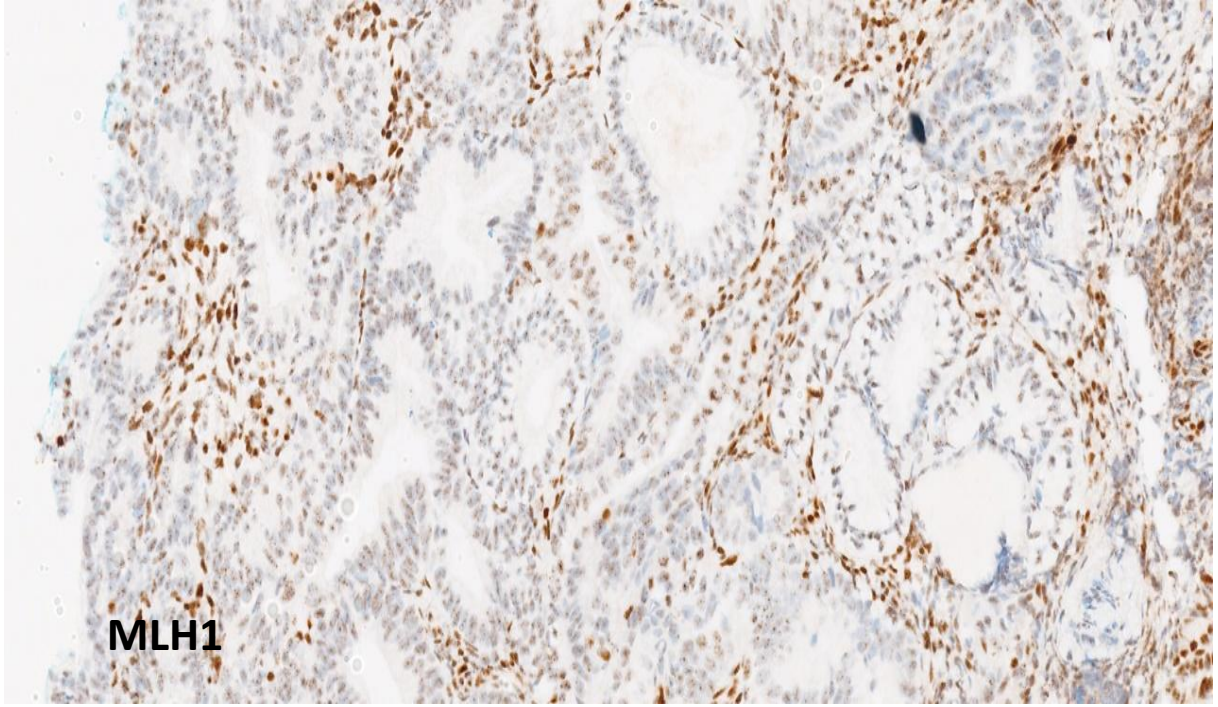
The British Association of Gynaecological Pathologists

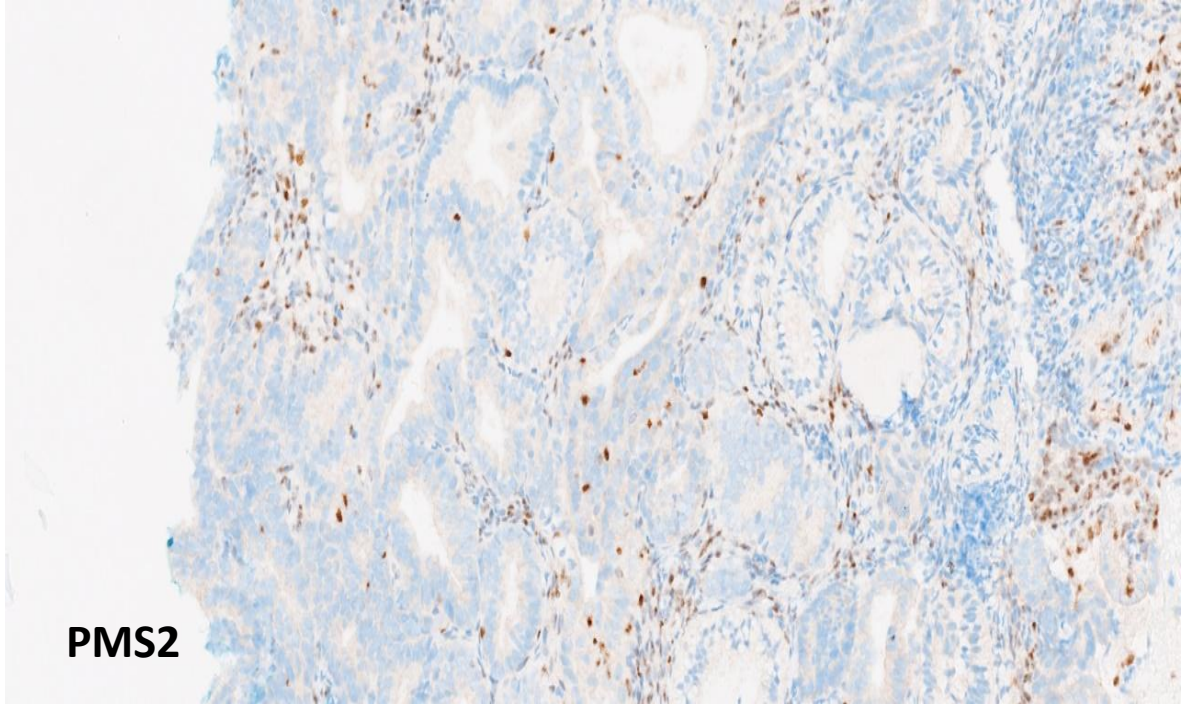
Interpretation and Reporting Terminology for Mismatch Repair Protein Immunohistochemistry in Endometrial Cancer[1]

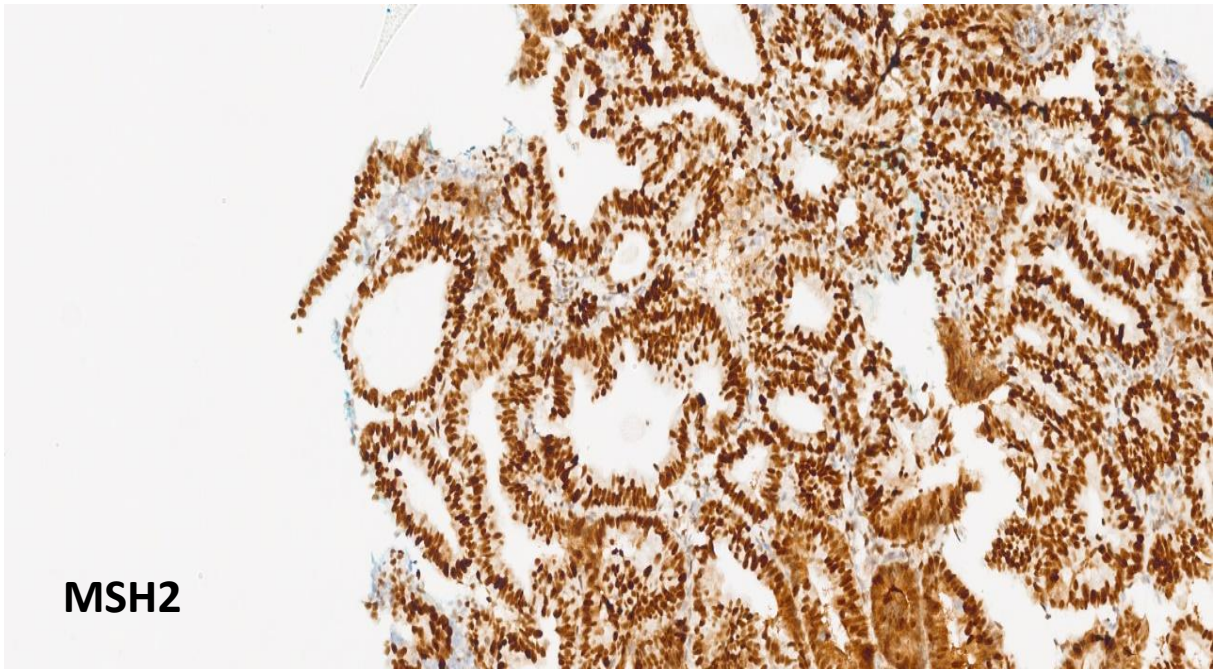
Int J Gynecol Pathol. 2019;38 Suppl 1(Iss 1 Suppl 1):S123-S131.

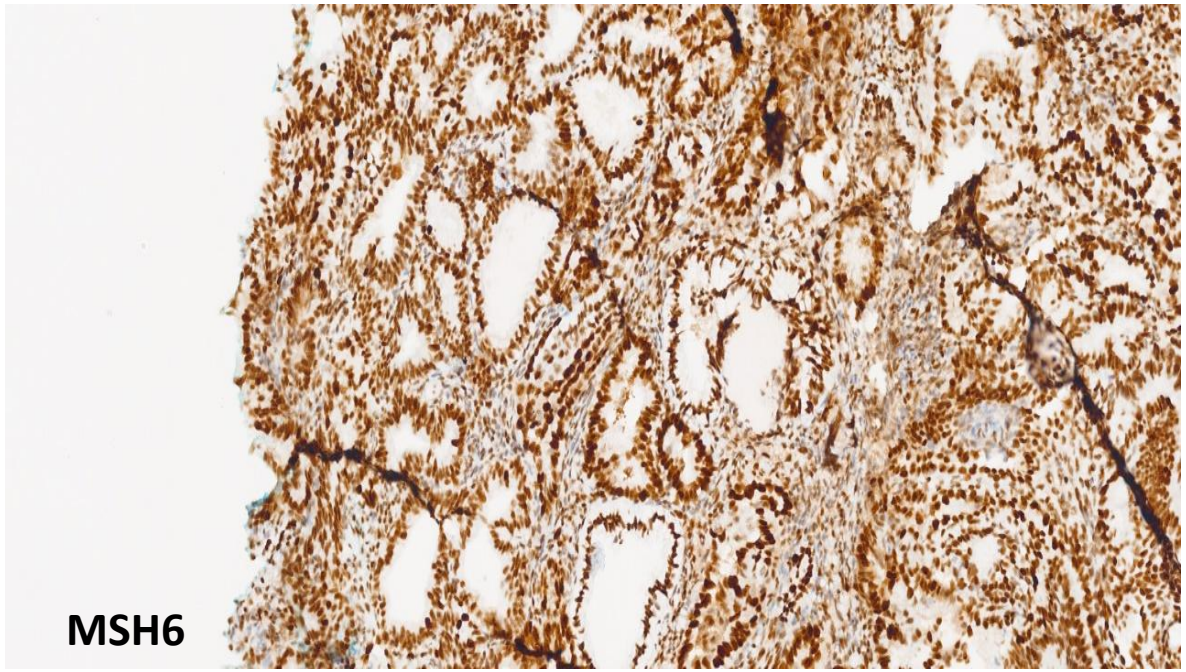
Naveena Singh, Richard Wong, Nairi Tchrakian, Shara-Gaye Allen, Blaise Clarke, C Blake Gilks.

1. Singh, et al., Int J Gynecol Pathol, 2019. 38 (Supp)



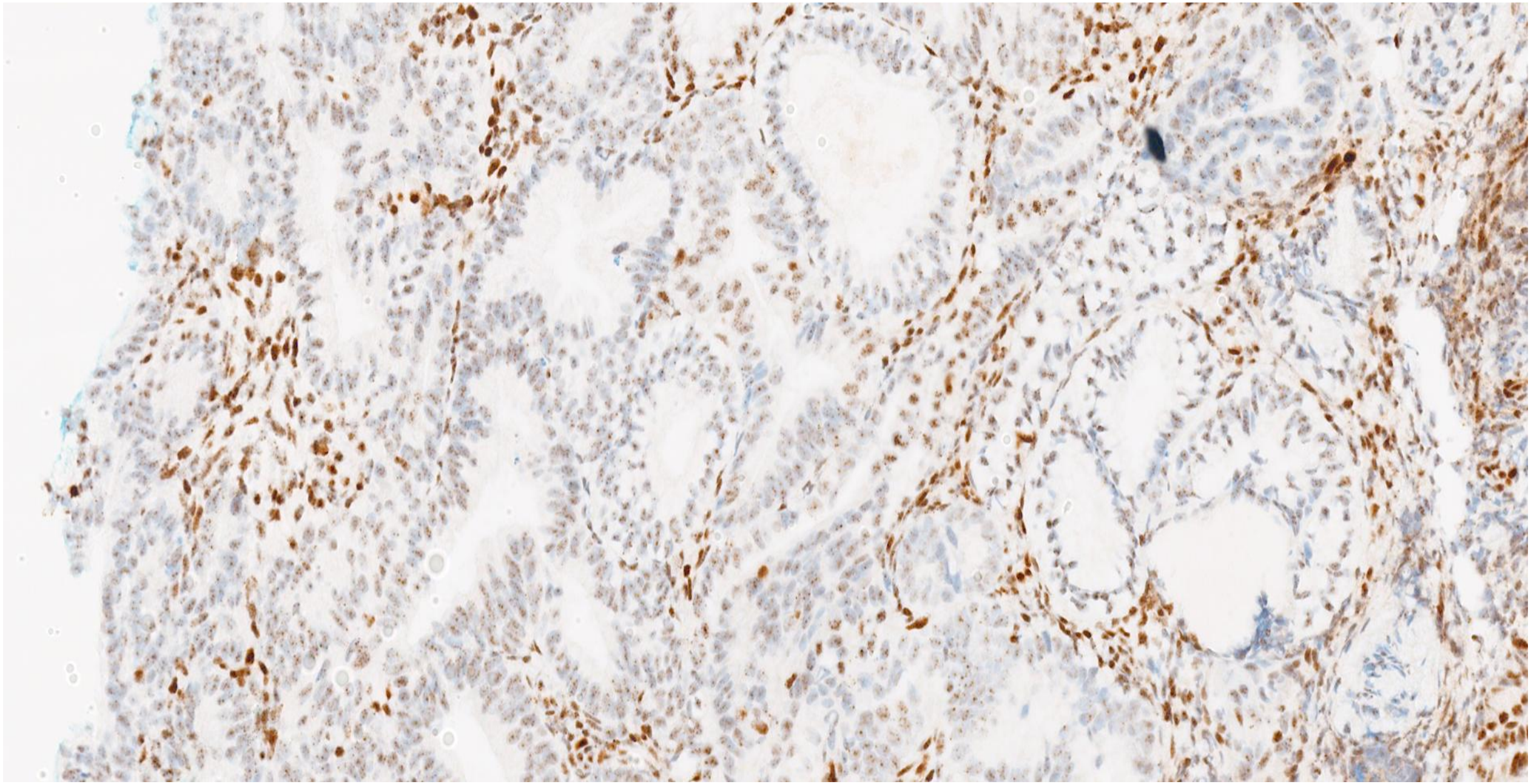






Images provided by speaker

Artefactual speckled MLH1



Images provided by speaker

MMR deficiency in Endometrial Carcinomas

Up to 30% of endometrial carcinomas are dMMR/MSI-H tumours[1]

These signatures mostly occur due to MLH1 promoter hypermethylation (sporadic) with loss of MLH1/ PMS2 [2]

Approximately 5% of endometrial carcinomas are attributed to an inherited predisposition to cancer. Lynch syndrome accounts for the majority of inherited endometrial carcinomas[3]

MSI-H, microsatellite instability-high.

1. Oaknin A, *et al. J Immunother Cancer* 2022; **10**: e003777. 2. Kaneko E, *et al. J Gynecol Oncol* 2021; **32**: e79.
3. Meyer A, *et al. Cancer Control* 2009; **16**: 14–22.

Should MMR immunohistochemistry be repeated on tumour recurrences?[1]

Limited literature is somewhat variable

Recurrent endometrial carcinomas are often inaccessible to biopsy

In most cases, no difference in MMR expression pattern between primary and recurrent tumour

It is uncommon (but occasionally occurs) for MMR-proficient tumours to become MMR deficient at recurrence so worth testing if previously MMR-proficient (PMID 39269025) [2]

1. Aird JJ, Steel MJ, Chow C, et al. *Histopathology*. 2020;76(4):521-530. doi:10.1111/his.14026, 2. Moreno-Moreno E et al. Am J Surg Pathol. 2024 Sep 13;48(12):1580–7
This slide reflect speaker experience

POLE TESTING

- Do not yet have an immunohistochemical marker as a surrogate of an underlying POLE mutation
- Must perform targeted sequencing of POLE exonuclease domain
- Can do as stand-alone test or part of NGS panel (some rapid and inexpensive “stand-alone” POLE tests now available)
- Currently testing not readily available in many/ most pathology labs, even in developed countries
- Even if testing available, report not always available in clinically relevant time

NGS, next generation sequencing; POLE, DNA polymerase epsilon.

1. BAGP POLE NGS testing guidance, 2022

MORPHOLOGY OF *POLE*-MUTATED ENDOMETRIAL CARCINOMAS

Often high-grade endometrioid (60%) or ambiguous morphology[1,2]

Sometimes markedly atypical giant cells[2]

Often have extensive LVSI

Often prominent tumour-infiltrating lymphocytes; tertiary lymphoid structures/ Crohn's-like infiltrates[3]

Often morphological overlap with MMR-deficient tumours[2]

This slide represents speaker experience

1. Hussien, et al., 2015. Modern Pathol.; 28:505 2. Joehlin-Price A, et al. Molecularly Classified Uterine FIGO Grade 3 Endometrioid Carcinomas Show Distinctive Clinical Outcomes But Overlapping Morphologic Features. Am J Surg Pathol. 2021 Mar 1;45(3):421-429. doi: 10.1097/PAS.0000000000001598. PMID: 33021522.3. Antonio Raffone et al. Tumor-infiltrating lymphocytes and POLE mutation in endometrial carcinoma, Gyne Oncol. 2021 Published:March 12, 2021DOI:https://doi.org/10.1016/j.ygyno.2021.02.030

POLE MUTATED ENDOMETRIAL CARCINOMA

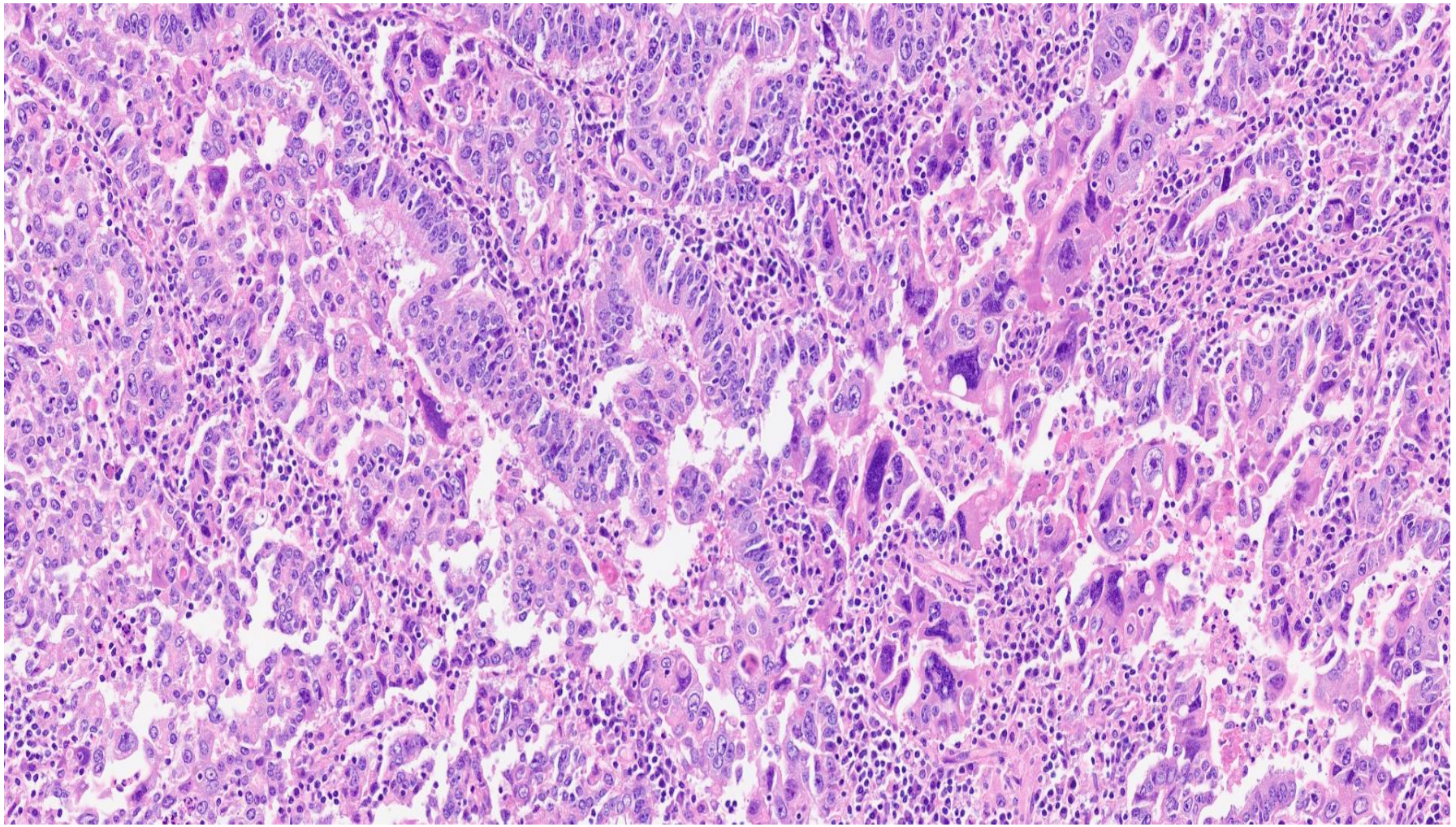
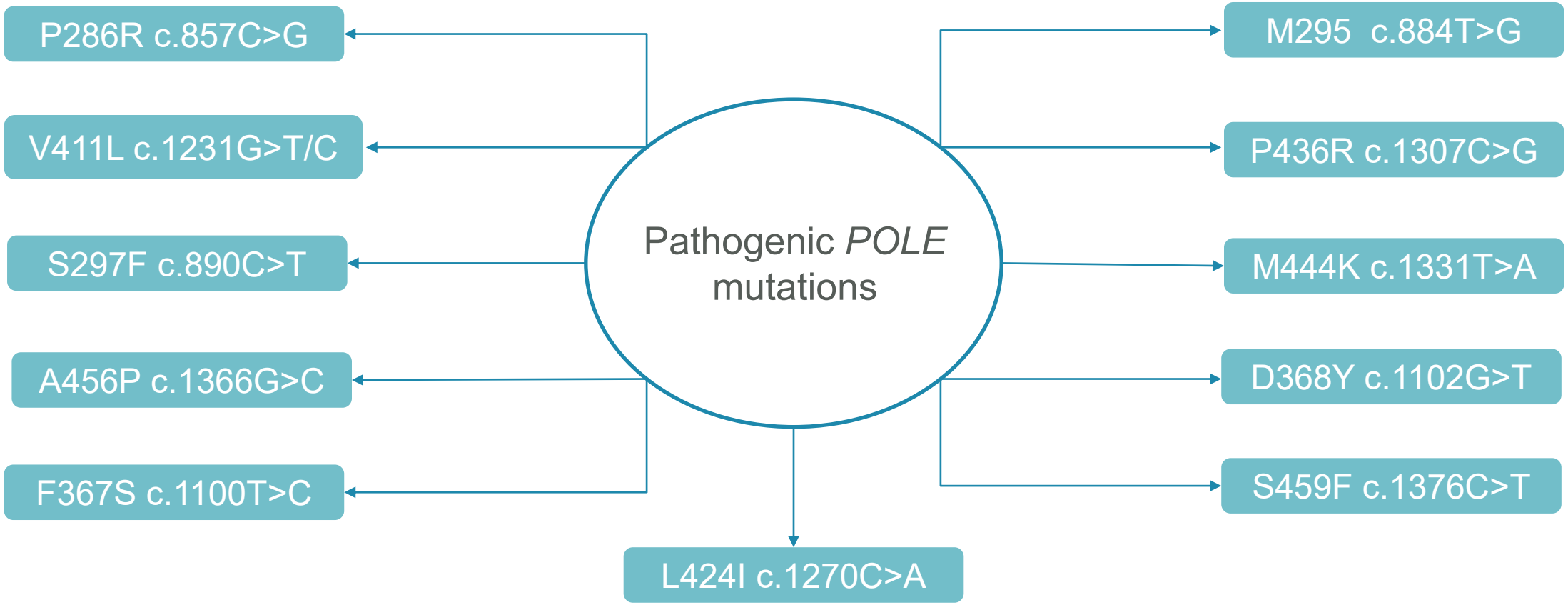


Image provided courtesy of speaker

Pathogenic *POLE* mutations

(Only 11 currently, but likely that more will be described)



Based on speaker's experience

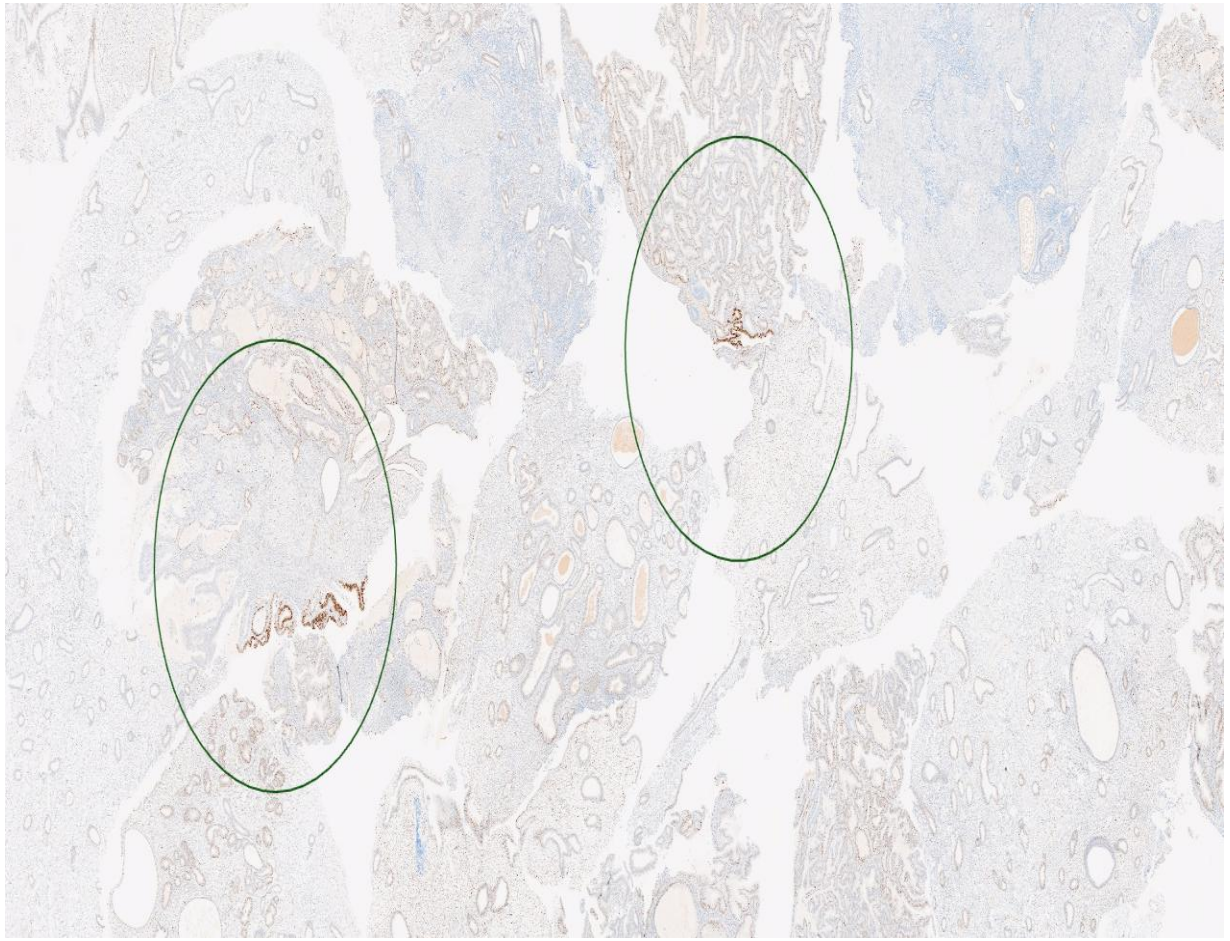
Multiple Classifiers

- ~3 - 5% of endometrial carcinomas harbour > 1 molecular classifying alteration and are referred to as multiple classifier[1]
- POLEmut and MMRd; high mutational burden with acquisition of secondary mutations, often TP53
- MMRd-p53abn > POLEmut-p53abn > POLEmut-MMRd > MMRd-POLEmut-p53abn*
- Outcome data show that in these cases the tumour biology is most in keeping with the molecular subgroup with the best prognosis[2]

* Of 167 EC tumours, 30 were classified as MMRd–POLEmut ECs and were reported seperately
Within the initial cohort of 3518 tumours, The most common combination of clas- sifiers was MMRd–p53abn (64; 1 .8 % of 3518), fol- lowed by POLEmut–p53abn (31; 0 .9 % of 3518) and MMRd–POLEmut–p53abn (12; 0 .3 % of 3518)

1. León-Castillo A, Gilvazquez E, et al. Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. J Pathol. 2020 Mar;250(3):312-322. doi: 10.1002/path.5373. Epub 2020 Jan 12. PMID: 31829447; PMCID: PMC7065184. 2. Leon Castillo et al, ESMO 2019 and speaker's own experience

DOUBLE CLASSIFIER: *POLE*mut with secondary *TP53* mutation- often subclonal p53 mutation-type staining



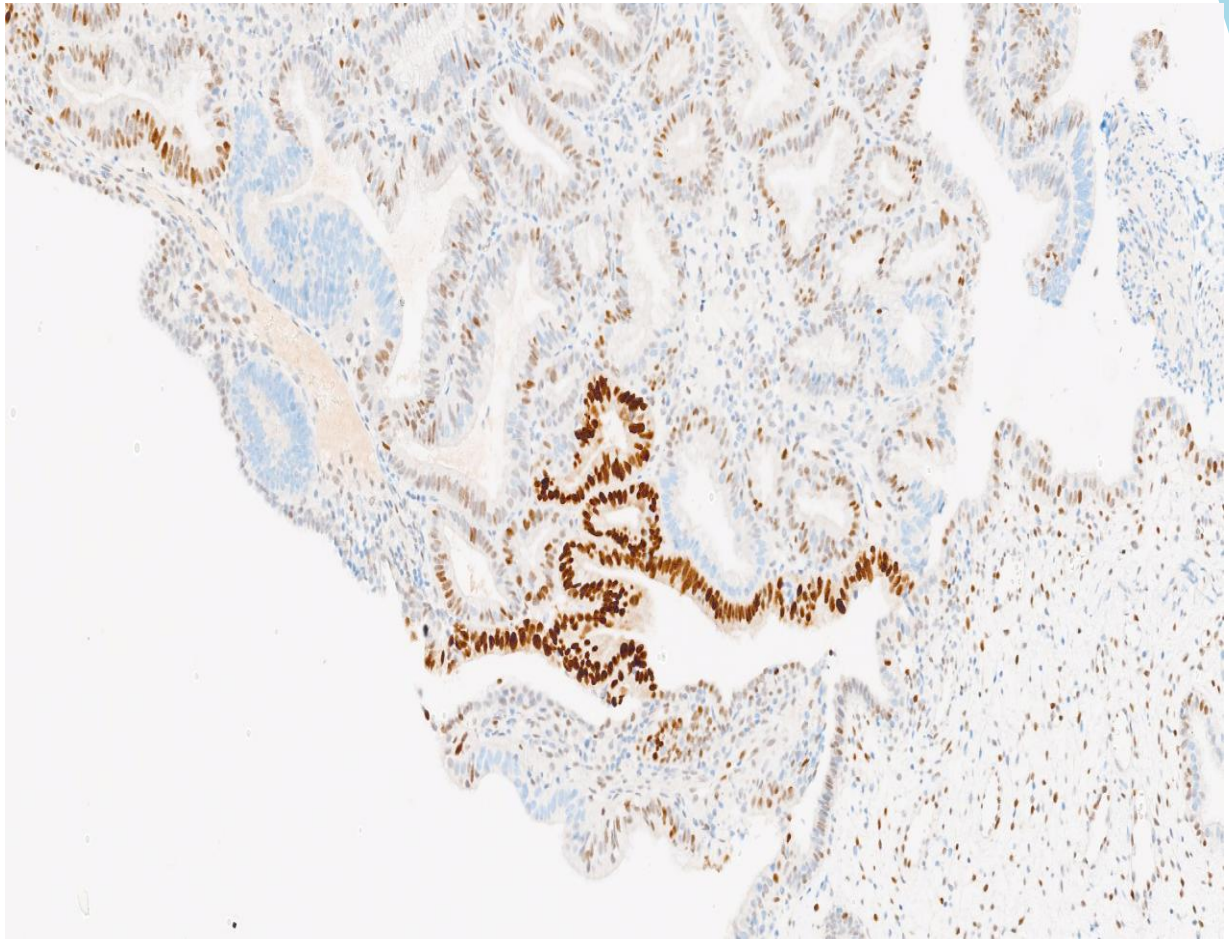
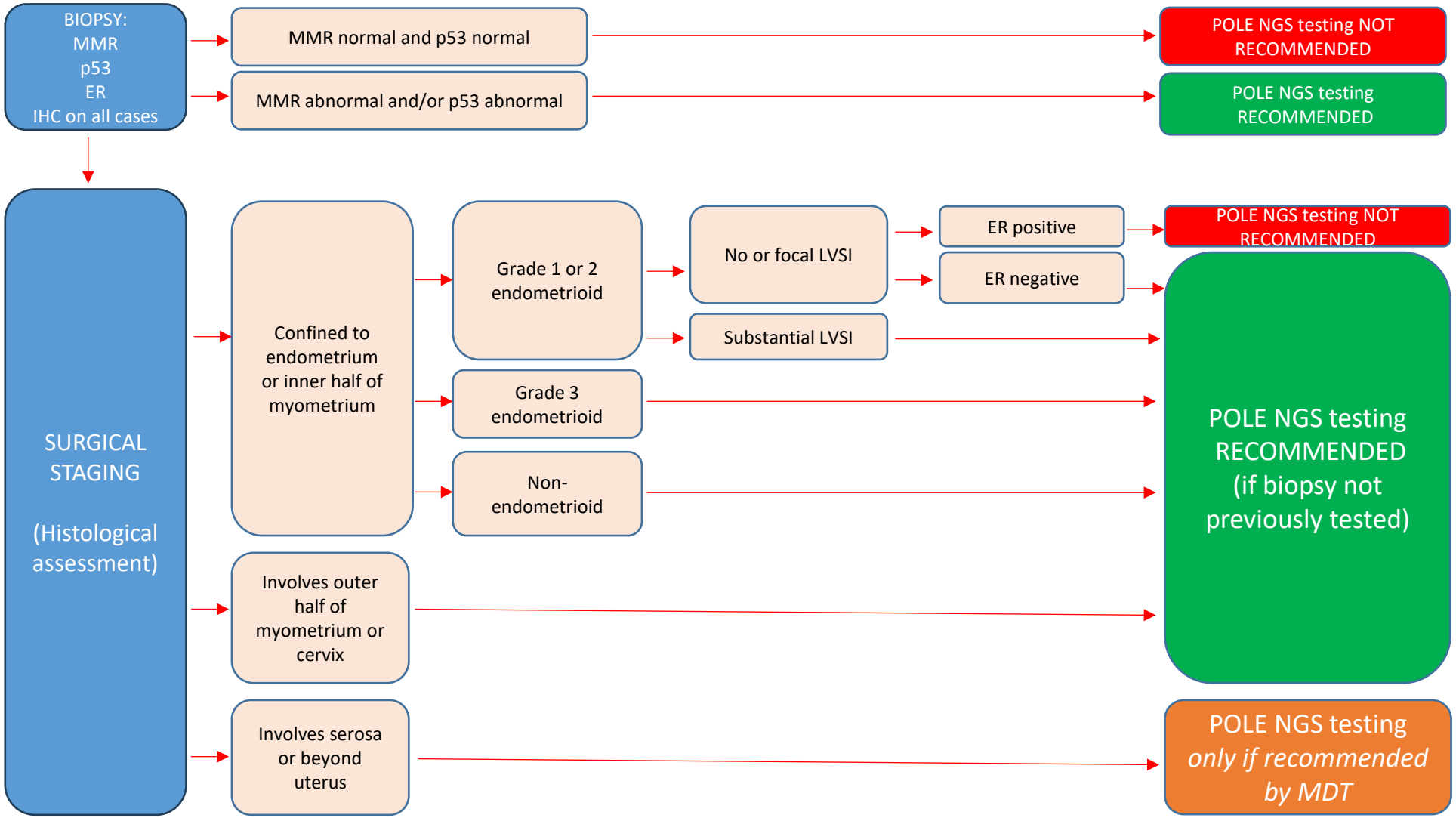


Image provided courtesy of speaker

BAGP/ BGSC POLE NGS Testing guidance

All endometrial carcinomas regardless of histological type



Images provided by speaker

1. BAGP POLE NGS testing guidance, v1.2, dated 26 July 2022 available at https://www.thebagp.org/wp-content/uploads/download-manager-files/BAGP-POLE-testing-in-Endometrial-cancer-v1.2-July-2022.pdf (last accessed May 2025)

Targeted molecular testing in endometrial carcinoma

p53 and MMR immunohistochemistry on all endometrial carcinomas in a population-based cohort

POLE testing restricted to those:

- With abnormal p53 and/or MMR immunohistochemistry – to identify those with secondary abnormalities in p53 and/or MMR
- And to those with high-grade or non-endometrioid histology or > stage IA or with LVSI – To avoid testing very low-risk tumours where knowledge of *POLE* would not impact patient care

Using this algorithm, POLE testing would not be needed in 55% of biopsies and in 38% of all endometrial cancers after resection

These very low-risk endometrioid carcinomas had excellent clinical outcomes

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626 and speaker's own experience

Initiation of molecular testing of endometrial carcinomas in a population-based setting: practical considerations and pitfalls

Histopathology

Machuca-Agudo J, Catherwood M, Houghton O, Taylor J, Shah R, Ben-Mussa A, Gonzalez D & McCluggage WG.

EC, endometrial cancer.

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626

The Belfast experience of integrating TCGA classification into clinical practice

- ER, MMR, p53 performed on all endometrial biopsies for several years (throughout Northern Ireland)

- All endometrial biopsies with diagnosis of carcinoma/ carcinosarcoma sent for molecular testing from Feb/ March 2023 (throughout Northern Ireland)
  - Testing comprises an NGS panel, including *POLE, TP53*, including MMR genes, MSI testing.

- Results usually back in 2 weeks after receipt in molecular pathology laboratory

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626 and speaker's own experience

Histopathology and gynaecological cancers in Northern Ireland

- Population of approximately 2 million
- Relatively static population
- Approximately 250-300 endometrial cancers per year
- All gynaecological cancers discussed at a central weekly MDT meeting
- 4 pathology laboratories (1 cancer centre - Belfast; 3 cancer units- Altnagelvin, Antrim, Craigavon)
- All 4 pathology laboratories use same digital reporting system where all reports and slides can be accessed by all pathologists
- All cases reviewed (to some extent) by gynaecological pathologists in Belfast

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626 and speaker's own experience

The Northern Ireland experience of integrating TCGA classification into clinical practice

- First year experience (267 endometrial carcinomas; 262 sufficient for NGS)
- All cases had ER, MMR, p53 immunohistochemistry on biopsy
- All cases had NGS (including *POLE, TP53*, MSI) on biopsy specimen
- First “true” population-based study (difficult/ impossible to replicate in other settings)
- MSI (NGS) or MMR loss on IHC put into MMRd group
- p53 mutation-type staining or *TP53* mutation on NGS put into p53abn group

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626 and speaker’s own experience

The Northern Ireland experience of integrating TCGA classification into clinical practice

- POLEmut (19; 7.3%); MMRd (63; 24%); p53abn (62; 23.7%); no specific molecular profile (NSMP) 118 (45%); REMARKABLY SIMILAR TO ORIGINAL TCGA FIGURES

- 17 (6.5%) were “multiple-classifiers”: 5 POLEmut-p53abn, 2 POLEmut-MMRd, 1 POLE-MMRd-p53abn (all included in the POLEmut TCGA group) and 9 MMRd-p53abn (included in the MMRd group)

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626 and speaker’s own experience

Decision to use biopsy samples for molecular testing

- IHC already performed on biopsy material
- Biopsies better fixed and often more pure tumour population providing higher quality material (for IHC and NGS)
- Surgical management can be tailored if TCGA group known before surgery
- All information can be integrated and recorded on final pathology report of hysterectomy

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626 and speaker's own experience

Integrated molecular and histopathology reports

- Molecular results back by time hysterectomy specimen is reported
- An integrated report can be generated including the molecular classification
- ? Should molecular classification be included in RCPath updated endometrial cancer dataset

This slide reflects speaker experience

SAMPLE MOLECULAR REPORT

TEST RESULTS

The macro-dissected area of this specimen contains approximately 70% neoplastic nuclei and is of intermediate cellularity. DNA sequencing has yielded 1530x mean unique coverage depth, making it suitable for analysis.

Sequence variants

Gene	Result*	VAF**	Comments
POLE	c.857C>G ; p.(Pro286Arg)	32%	
TP53	c.638G>A ; p.(Arg213Gln)	5%	

Structural variants

Gene	Result	Comments
NTRK†	No rearrangement detected	

Microsatellite instability testing (MSI)

Instability was observed in 0% of microsatellite regions analysed, consistent with a Microsatellite Stable (MSS) tumour.

CLINICAL REPORT

A known recurrent pathogenic variant associated with an 'ultra-mutated' phenotype was detected in POLE.

A subclonal TP53 variant was DETECTED, likely as a consequence of the abnormal POLE activity.
No microsatellite instability was detected above the limit of detection of the assay.

Jemperli is indicated in the United Kingdom[1]:

JEMPERLI is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

This slide reflects speaker experience with report provided curtesy of speaker 1. Jemperli Summary of Product Characteristics

MOLECULAR RESULT CAN BE INTEGRATED INTO FINAL PATHOLOGY REPORT

IMMUNOHISTOCHEMISTRY: Performed on preoperative endometrial biopsy ([redacted]). This showed focal nuclear staining with ER and wild-type immunoreactivity with p53. There was loss of nuclear immunoreactivity with the mismatch repair proteins MLH1 and PMS2 with retention of staining with MSH2 and MSH6.

PROVISIONAL FIGO STAGE: IA

BLOCK KEY: A1 and A5 - cervix, A2 and A4 - lower uterine segment, A3, A6 to A8 endometrium/myometrium, A9 and A10 - right parametrium, A11 and A12 - left parametrium, A13 - right ovary, A14 - right tube, A15 - left ovary, A16 - left tube.

MOST REPRESENTATIVE TUMOUR BLOCK: A6

FURTHER COMMENTS

The tumour comprises a grade II endometrioid adenocarcinoma with glandular and solid elements, areas of cytoplasmic clearing and areas of necrosis. The tumour has a polypoid appearance and projects into the cervical canal but there is no actua attachment of the tumour to the cervix to upstage the neoplasm.

A small fibroma is present within the right ovary.

The preoperative endometrial biopsy was sent for molecular testing (full report [redacted]). This showed an MSI high tumour with a TP53 mutation but no POLE mutation. In the molecular classification, this corresponds to a mismatch repair deficient endometrial carcinoma with a secondary TP53 mutation.

Jemperli is indicated in the United Kingdom[1]:

JEMPERLI is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

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This slide reflects speaker experience with report provided curtesy of speaker 1. Jemperli Summary of Product Characteristics

MOLECULAR RESULT CAN BE INTEGRATED INTO FINAL PATHOLOGY REPORT

IMMUNOHISTOCHEMISTRY: Performed on preoperative biopsy [redacted]. This showed diffuse mutation type staining with p53 and negative staining with ER. There was loss of immunohistochemical staining with the mismatch repair protein MSH6 but retention of staining with MLH1, PMS2 and MSH2.
PROVISIONAL FIGO STAGE: IA.

BLOCK KEY: A1 and A2. B1. C1 and C6 - cervix, C2 and C5 - lower uterine segment, C3, C4, C7 endometrium/myometrium, C8 - right ovary, C9 - right tube, C10 - left ovary, C11 - left tube.

FURTHER COMMENTS
No residual tumour is present in this specimen.

The prior biopsy [redacted] has been reviewed and the presence of a clear cell carcinoma confirmed. The preoperative biopsy was sent for molecular testing ([redacted]). This showed a TP53 mutation but no POLE mutation. The tumour was microsatellite stable (MSS). Given the MSH6 immunohistochemical deficiency, this is regarded as a mismatch repair deficient endometrial cancer with a secondary TP53 mutation. Sometimes MSH6 deficient tumours are microsatellite stable.

Jemperli is indicated in the United Kingdom[1]:

JEMPERLI is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

This slide reflects speaker experience with report provided curtesy of speaker 1. Jemperli Summary of Product Characteristics

Challenges in implementation/ points of improvement

- In cancer units, cases often reported by general pathologists; occasional cases not sent for molecular testing and had to be ordered later
- Some cases reported in private laboratories or outsourced to private laboratories; molecular testing usually arranged at a later date following referral to MDTM
- In cancer units, results of NGS were usually not included on final hysterectomy report; should have been communicated more widely beforehand
- In 1.9% (5/267) of cases, molecular analysis was not possible due to insufficient material and was not always repeated on hysterectomy specimens

Initiation of molecular testing of endometrial carcinomas in a population-based setting: practical considerations and Pitfalls Jesus Machuca-Aguado,1 Mark Catherwood,2 Oisin Houghton,3 Jennifer Taylor,3 Rajeev Shah,4 Ali Ben-Mussa,5 David Gonzalez6 & W Glenn McCluggage3 1Department of Pathology, Virgen Macarena University Hospital, Seville, Spain, 2Regional Molecular Diagnostics Service, 3Department of Pathology, Belfast Health and Social Care Trust, Belfast, 4Department of Pathology, Southern Health and Social Care Trust, Craigavon, 5Department of Pathology, Western Health and Social Care Trust, Londonderry, Northern Ireland and 6Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, UK Date of submission 15 July 2024 Accepted for publication 26 October 2024

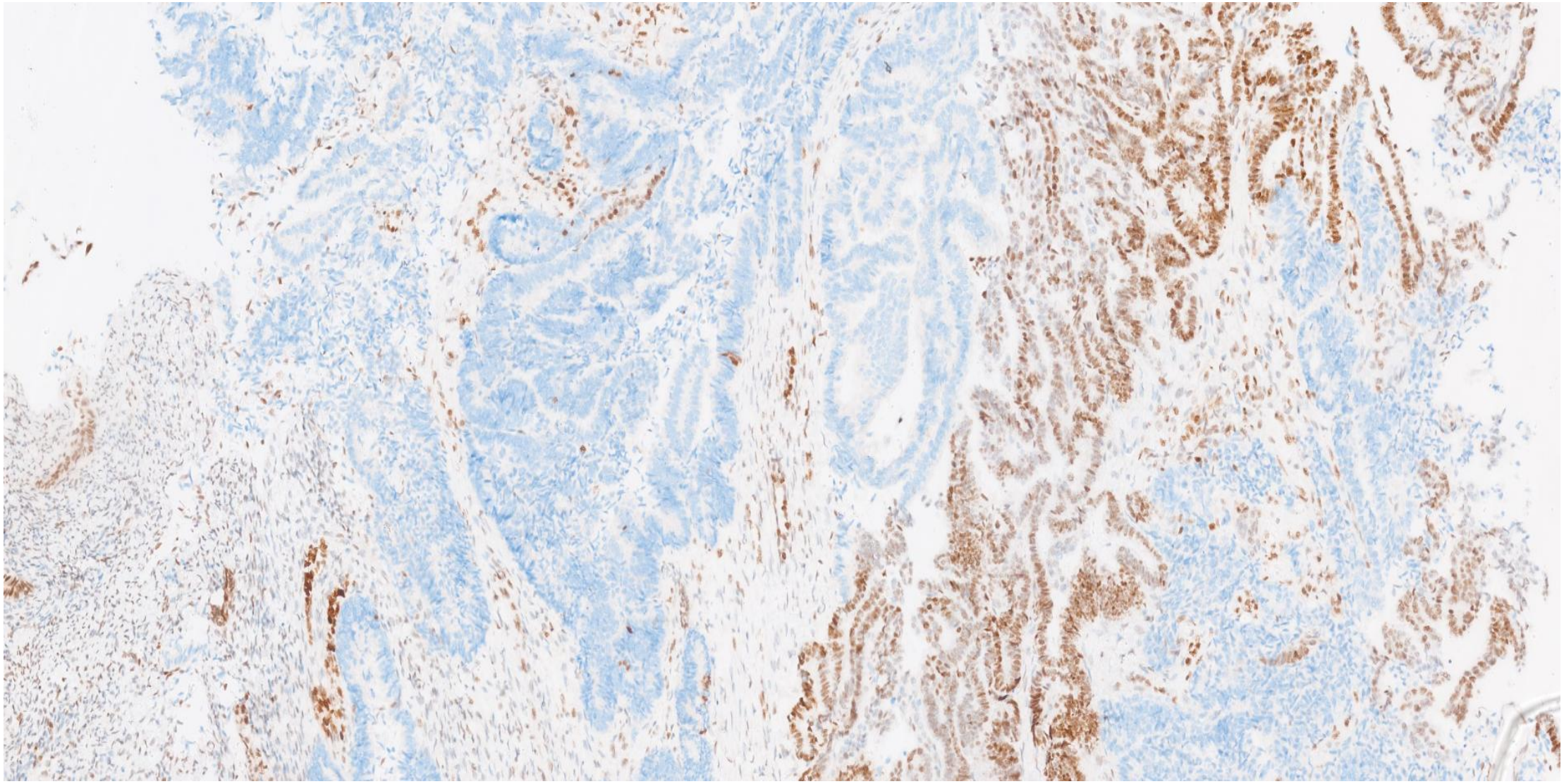
Detailed analysis of *POLE* cases

- 89.4% (17/19) of *POLE* mutations were known pathogenic mutations (P286R: 8; V411L: 7; S297F: 2)
- 2 additional mutations which have previously been reported identified (S461T and A465V); the tumours showed >50 mutations per Megabase of DNA on NGS (ultramutated); thus considered *POLE*mut tumours
- Almost all *POLE*mut were low-stage endometrioid carcinomas with 48.4% being high-grade (consistent with literature)

Correlation between MMR immunohistochemistry and MSI

- High concordance (95.2%) between immunohistochemistry and MSI testing
- MSI testing failed to identify 8 of 62 cases which were MMRd on immunohistochemistry; some, but not all, of these were MSH6 deficient tumours on immunohistochemistry (well known that may be MSS)
- 4 cases which were MSI-H with retention of staining with MMR proteins
- Consider MMR immunohistochemistry more sensitive and cost-effective than MSI, especially in resource-limited centres and in centres where molecular testing is not easily available
- Performing both MSI testing and immunohistochemistry is ideal since it increases diagnostic sensitivity by picking-up some cases not identified on immunohistochemistry
- Some cases with subclonal loss of MMR proteins (mainly *POLE*mut)

Subclonal loss of MSH6 in *POLE* mutated endometrial carcinoma



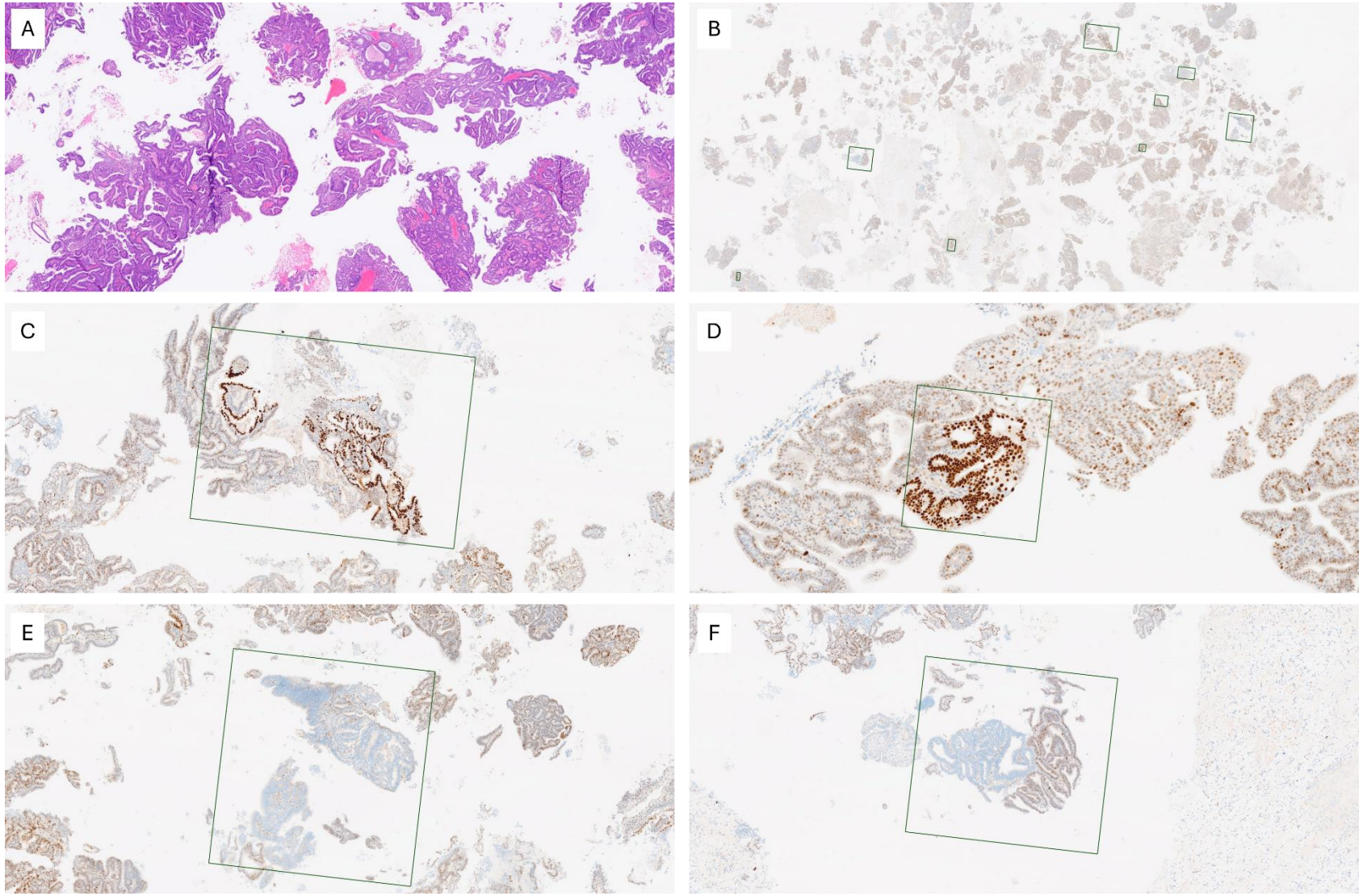
Images provided by speaker

Correlation between p53 Immunohistochemistry and *TP53* molecular testing: paper in preparation

- 386 endometrial carcinomas
- All had NGS and immunohistochemistry (IHC)
- Initial concordance between IHC and NGS was 88.6% (11.4% discordance) on review of reports; most discordant cases had wild-type IHC and *TP53* mutation on NGS
- Discordance reduced to 6.5% after review of p53 slides (some had subclonal mutation-type staining; some had what was interpreted as high wild-type but on review, likely diffuse mutation-type)
- Discordance reduced to 5.1% after excluding *POLE* and MMRd carcinomas
- Still cohort of 19 *POLE* wild-type/ MMR proficient carcinomas (8 low-grade endometrioid, 9 high-grade endometrioid, 2 carcinosarcomas), with wild-type p53 staining but with *TP53* mutations on NGS
- These cases (when low-grade endometrioid) represent a dilemma for pathologists (which TCGA group to put into) and clinicians (? To administer adjuvant treatment on basis of *TP53* mutation only with no other adverse features)
- If just relying on NGS, these cases could have been put into p53 abn group

Machuca-Agudo J, et al. Histopathology. 2025Mar;86(4):611-626 and speaker's own experience

Case with p53 IHC reported as wild-type but *TP53* mutation on NGS



Images provided by speaker

GYNAE MDT- TO BE FILLED IN FOR ALL ENDOMETRIAL CANCERS (USUALLY ON HYSTERECTOMY BUT ON BIOPSY SPECIMEN IF NO HYSTERECTOMY BEING PERFORMED)

- **ER**- negative; focal (<50%); diffuse (>50%), not done
- **MMR immunohistochemistry**- retained; diffuse loss (specify which proteins are lost); subclonal loss (specify which proteins are lost); not done
- **p53 immunohistochemistry** – wild-type; mutation-type throughout; subclonal mutation-type; not done
- **Molecular for MSI** - MSI-H; MSS; MSI-uncertain; not done
- **Molecular for TP53-** TP53 mutation absent; TP53 mutation present; not done
- **POLE mutation-** Yes; No; not done
- **TCGA molecular classification-** NSMP; p53 abnormal; MSI (MMRd); POLE; not evaluable

Thank you

Please visit the GSK stand for more information and a copy of today's slides !

▼JEMPERLI (dostarlimab) 500 mg concentrate for solution for infusion prescribing information – United Kingdom

Refer to the Summary of Product Characteristics (SmPC) before prescribing JEMPERLI.

Adverse events should be reported. Reporting forms and information can be found at: https://yellowcard.mhra.gov.uk/ (UK) or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to GSK: please call 0800 221 441 or email uksafety@gsk.com

Presentation: Concentrate for solution for infusion. Each vial contains 500mg dostarlimab in 10 mL concentrate (50mg/mL). Clear to slightly opalescent colourless to yellow solution, essentially free from visible particles.
Indication: JEMPERLI is indicated:

- In combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.
- As monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

Dosage and administration: *JEMPERLI in combination with chemotherapy:* Recommended dose is 500mg dostarlimab every 3 weeks for 6 cycles followed by 1000mg every 6 weeks thereafter (cycle 7 onwards) until disease progression or unacceptable toxicity, or for a duration of up to 3 years. Administer JEMPERLI prior to chemotherapy on the same day. For the dosage or recommended dose modifications of concomitantly used chemotherapeutic agents, refer to the product information for these medicinal products. *JEMPERLI monotherapy*: Recommended dose is 500 mg dostarlimab every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter (cycle 5 onwards), until disease progression or unacceptable toxicity.
Administer JEMPERLI by intravenous infusion using an infusion pump over 30 minutes. Do not administer JEMPERLI as an intravenous push or bolus injection. Do not co-administer other medicinal products through the same infusion line. A 0.2 or 0.22 micron in-line polyethersulfone (PES) filter must be used during administration of JEMPERLI.
Special populations: *Elderly*: No dose adjustment recommended in patients ≥65 years; limited data in patients ≥75 years. *Renal impairment*: No dose adjustment recommended in mild or moderate renal impairment; limited data in patients with severe impairment or end-stage renal disease undergoing dialysis. *Hepatic impairment*: No dose adjustment recommended in patients with mild hepatic impairment; limited data in moderate hepatic impairment and no data in severe hepatic impairment. *Paediatrics*: Safety and efficacy not established in patients <18 years.
Dose modifications: Dose reduction is not recommended. Permanently discontinue JEMPERLI for any grade confirmed exfoliative dermatologic conditions; grade ≥2 myocarditis, severe neurological toxicity, recurrence or worsening of hypophysitis or adrenal insufficiency while on adequate hormonal therapy; grade ≥3 hepatitis
, nephritis, pneumonitis (or if grade 2 recurs after resolution), recurrence of immune-related adverse reactions (irARs) after resolution to ≤ grade 1, and infusion-related reactions (or if grade 2 recurs with adequate premedication); grade 4 colitis, and other irARs. See SmPC for full details.
Contraindications: Hypersensitivity to the active substance or to any of the excipients. See SmPC for full details.

Warnings and precautions:

• irARs may be severe or fatal. These include pneumonitis, colitis, hepatitis, endocrinopathies including hypo- and hyper- thyroidism and adrenal insufficiency, nephritis, rash and exfoliative dermatologic conditions, arthralgia, myositis, myocarditis, encephalitis, demyelinating neuropathy (including Guillain Barré syndrome), sarcoidosis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, uveitis and solid organ transplant rejection. While irARs usually occur during treatment, symptoms can occur after discontinuation. IrARs may occur in any organ or tissue and may affect more than one body system simultaneously. Monitor for signs and symptoms of irARs. Evaluate haematological and clinical chemistries, including liver, kidney and thyroid function, at baseline and periodically during treatment. Based on the severity of the AR, withhold or permanently discontinue JEMPERLI and administer corticosteroids or other appropriate therapy. Upon improvement to grade ≤1, initiate corticosteroid taper and continue for at least 1 month.
• Infusion-related reactions can be severe or life threatening. For grade ≥3 reactions, or if grade 2 recurs with adequate premedication, stop infusion and permanently discontinue.
• Fatal and other serious complications can occur in allogeneic haematopoietic stem cell transplant patients before or after treatment with a PD-1/PD-L1–blocking antibody. Follow patients closely and intervene promptly. Consider benefit versus risks of treatment.
Interactions:
No interaction studies have been performed. Monoclonal antibodies such as JEMPERLI are not substrates for cytochrome P450 or active substance transporters. JEMPERLI is not a cytokine and is unlikely to be a cytokine modulator. Interaction with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies.
Fertility, pregnancy and lactation: *Fertility:* No clinical data on fertility. *Pregnancy:* No or limited clinical data on use in pregnant women. JEMPERLI can cause foetal harmful pharmacological effects when administered during pregnancy. Not recommended in pregnancy and in women of childbearing potential (WOCBP) not using effective contraception. WOCBP must use effective contraception during treatment and until 4 months after last dose. *Lactation:* Not recommended during breast-feeding. Avoid breast-feeding for at least 4 months after last dose. Refer to the SmPC for full details.
Undesirable effects: JEMPERLI in combination therapy: Very common (≥1/10): hypothyroidism, rash, dry skin, alanine aminotransferase increased, aspartate aminotransferase increased, pyrexia**; Common (≥1/100 to <1/10)**: hyperthyroidism, pneumonitis, colitis, pancreatitis; **Uncommon (≥1/1000 to <1/100):** thyroiditis, adrenal insufficiency, type 1 diabetes mellitus, myasthenic syndrome, uveitis, myocarditis, immune mediated gastritis, vasculitis gastrointestinal, immune-mediated arthritis, myositis, systemic inflammatory response syndrome**. JEMPERLI monotherapy: Very common (≥1/10)**: anaemia, hypothyroidism, diarrhoea, nausea, vomiting, rash, pruritus, arthralgia, pyrexia, transaminases increased; **Common (≥1/100 to <1/10)**: hyperthyroidism, adrenal insufficiency, pneumonitis, colitis, pancreatitis, gastritis, hepatitis, myalgia, chills, infusion-related reaction; **Uncommon (≥1/1000 to <1/100)**: thyroiditis, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, encephalitis, myasthenia gravis, uveitis, oesophagitis, immune-mediated arthritis, polymyalgia rheumatica, immune-mediated myositis, nephritis .
Immune checkpoint inhibitor class effects: cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors and might also occur with dostarlimab: coeliac disease; pancreatic exocrine insufficiency.
Refer to the SmPC for a full list of adverse events.
Overdose: Refer to SmPC
Legal Category: POM.
Pack size: 1 vial of 500mg/10mL £5887.33
MA Number: PLGB 19494/0297
MA Holder: GlaxoSmithKline UK Limited at 79 New Oxofrd Street, London, WC1A 1DG, United Kingdom.
Full SmPC available from GSK Limited or from www.medicines.org.uk
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Jemperli (dostarlimab) Injection 500 mg