Expanding horizons in the treatment of endometrial cancer: How can data from ESGO 2023 guide clinical practice?

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Recorded following ESGO's 24th European Gynaecological Oncology Congress, 28 September–1 October 2023

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Agenda

- Molecular characterization of endometrial cancer: Latest developments
- Efficacy and safety data in advanced or recurrent endometrial cancer: New and emerging immunotherapies
- Efficacy and safety data in advanced or recurrent endometrial cancer: Other emerging agents

Molecular characterization of endometrial cancer: Latest developments

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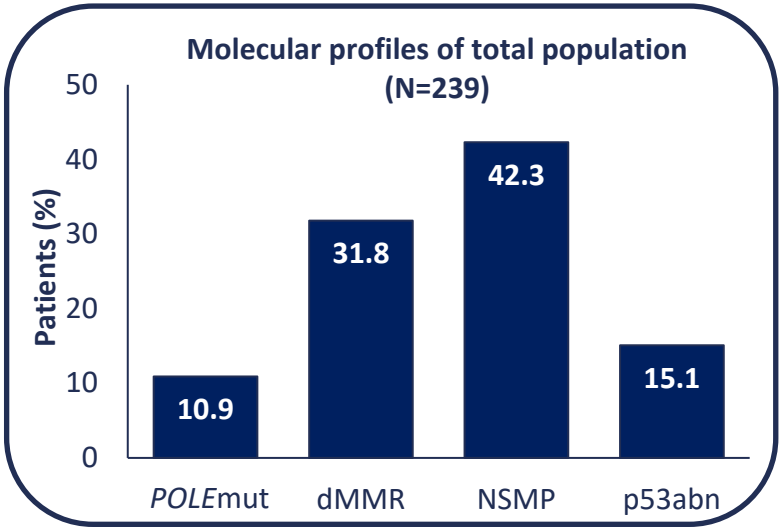
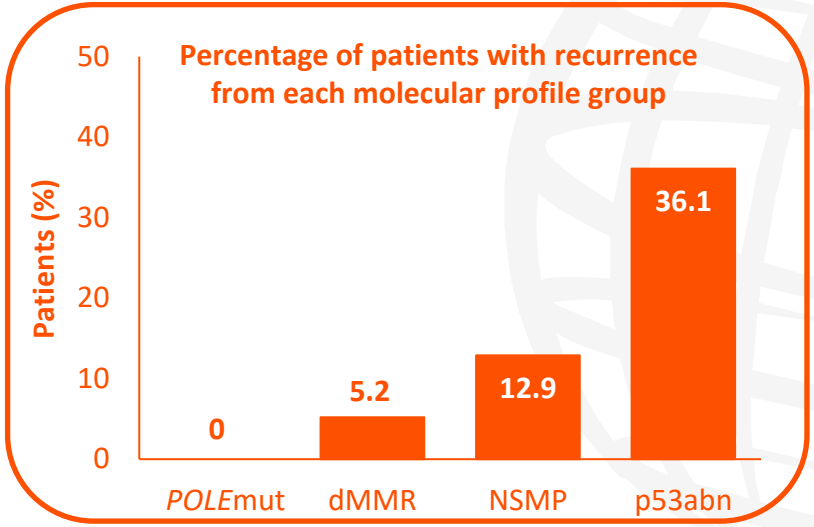
The impact of molecular classes on oncologic outcome of EC: A prospective analysis from a tertiary referral center

Xhindoli L, et al.

Prospective study comparing recurrence-free survival among four molecular classes of EC



Recurrence occurred in 12.1% of patients (n=29)



Molecular classification can help predict the risk of recurrence in EC:
*POLE*mut has a protective role and p53abn has a negative predictive value

dMMR, mismatch repair deficient; EC, endometrial cancer; NSMP, no specific molecular profile; p53abn, p53 abnormality; POLEmut, DNA polymerase epsilon mutation.

Xhindoli L, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 908.

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Integrating ESMO-ESGO-ESTRO guidelines with an immunological enhanced EC risk classification model

Bruno V, et al.

Study aiming to improve clinical risk prediction models by integrating existing guidelines with new '-omic' immunological predictive features extracted from the Cancer Genome Atlas Uterine Corpus Endometrial Carcinoma (TCGA-UCEC) dataset

- The relative abundances of five main immune populations in public data were estimated to generate a machine learning-based model for predicting disease-free survival probability prediction
- In an EC framework, this model can predict recurrence with a higher accuracy than guidelines parameters, expanding precision oncology approaches in terms of prognosis and decision making for treatment and follow-up

EC, endometrial cancer; ESGO, European Society of Gynaecological Oncology; ESMO, European Society for Medical Oncology; ESTRO, European Society of Therapeutic Radiation and Oncology.

Bruno V, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 225.

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Immune checkpoint expression predicts clinical outcome in EC

Pan TL

Study evaluating RNA expression levels of PD-1, PDL-1 and IFNγ in 239 EC tissue samples

- Immune checkpoint molecule expression was significantly higher ($p<0.001$) in EC compared to control:

PD-1:	PD-L1:	IFNγ:
7-fold greater	3-fold greater	5-fold greater

- High expression of **PD-1, PD-L1** and **IFNγ** was associated with better clinical outcomes (RFS, DSS and OS)
- High expression of **PD-1** was predictive of **RFS** (HR 0.39, p=0.009)
- High expression of **PD-L1** was associated with better **OS** (HR 0.55, p=0.037)
- *POLE*mut and dMMR ('hot') tumours showed the highest expression of **PD-1** and **IFNγ**

Immune checkpoint molecule expression is strongly associated with clinical outcomes in patients with EC and their expression should guide therapeutic approaches

dMMR, mismatch repair deficient; DSS, disease-specific survival; EC, endometrial cancer; HR, hazard ratio; IFNγ, interferon gamma; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; POLE, DNA polymerase epsilon mutation; RFS, recurrence-free survival.

Pan TL. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 376.

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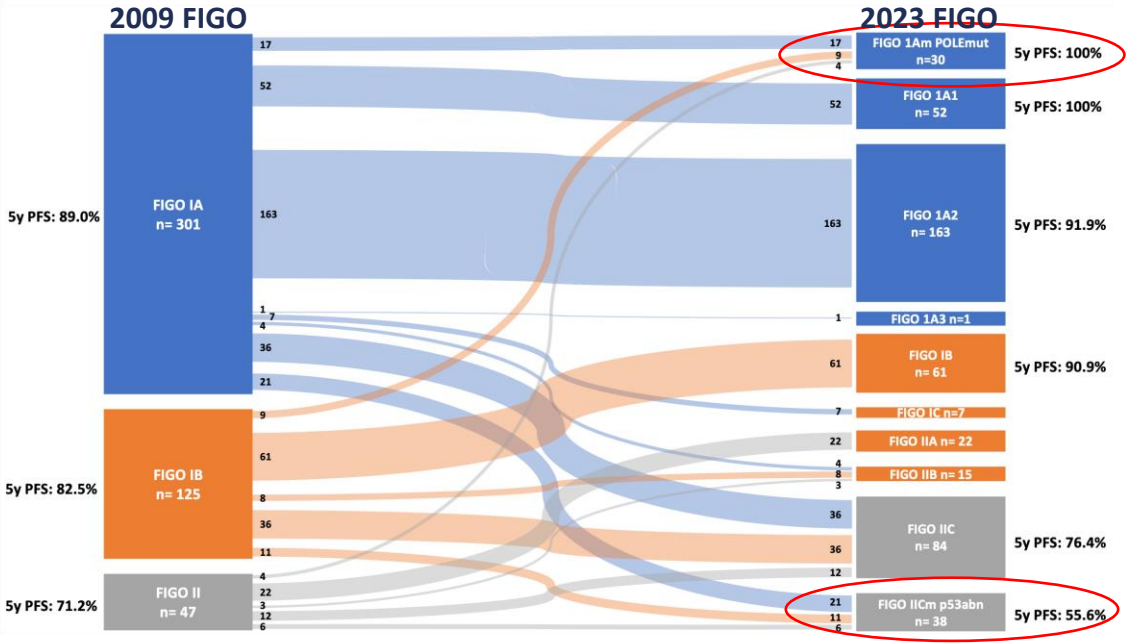
Verification of the prognostic precision of the new 2023 FIGO staging system in EC patients – An international pooled analysis of three ESGO accredited centers

Schwameis R, et al.

Retrospective study comparing the prognostic precision of the 2009 and 2023 FIGO staging systems

Stage shifts between 2009 and 2023 FIGO in **early-stage EC** (stages I/II n=473)



IAm *POLE*mut

IICm p53abn

EC, endometrial cancer; ESGO, European Society of Gynaecological Oncology; FIGO, International Federation of Gynecology and Obstetrics; m, molecular classification; p53abn, p53 abnormality; PFS, progression-free survival; POLEmut, DNA polymerase epsilon mutation; y, year.

Schwameis R, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 809. (Figure reproduced with permission).

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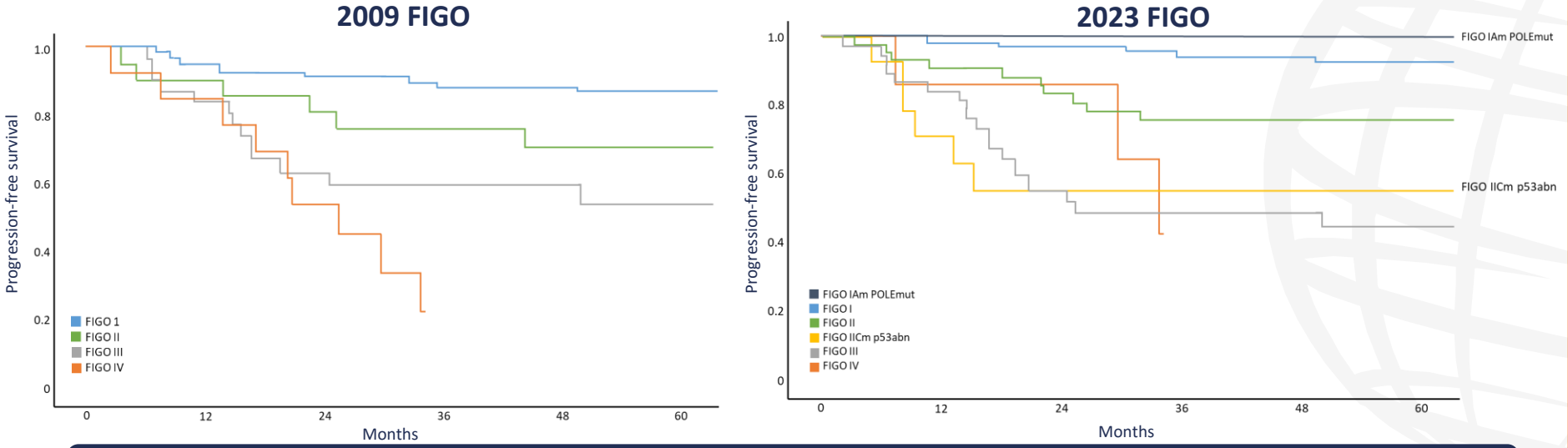
Verification of the prognostic precision of the new 2023 FIGO staging system in EC patients – An international pooled analysis of three ESGO accredited centers

Schwameis R, et al.

PFS in a study cohort of 232 patients with EC according to the FIGO staging system



The FIGO 2023 staging system has greater prognostic accuracy compared with the FIGO 2009 system

Figures adapted with permission from: Schwameis R, et al. *Eur J Cancer*. 2023. Available at: www.ejcancer.com/article/S0959-8049(23)00419-7/fulltext (accessed 3 October 2023).
EC, endometrial cancer; ESGO, European Society of Gynaecological Oncology; FIGO, International Federation of Gynecology and Obstetrics; m , molecular classification; p53abn, p53 abnormality; PFS, progression-free survival; POLEmut, DNA polymerase epsilon mutation.
Schwameis R, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 809.

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Conclusions

- It is important to perform molecular evaluation in all patients with EC to improve risk stratification and guide clinical decision making
- Immune checkpoint molecules may be associated with clinical outcomes in patients with EC and may be able guide therapeutic approaches
- The new 2023 FIGO staging system has increased prognostic precision compared with the 2009 FIGO staging system
- Machine learning and artificial intelligence are likely to play an increasingly important role in precision oncology in general, including contributions to improved prognostication and an influence on treatment decision making in EC

EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics.

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Efficacy and safety data in advanced or recurrent endometrial cancer: New and emerging immunotherapies

Prof. Nicole Concin
Innsbruck Medical University,
Innsbruck, Austria

Recorded following ESGO's 24th European Gynaecological Oncology Congress,
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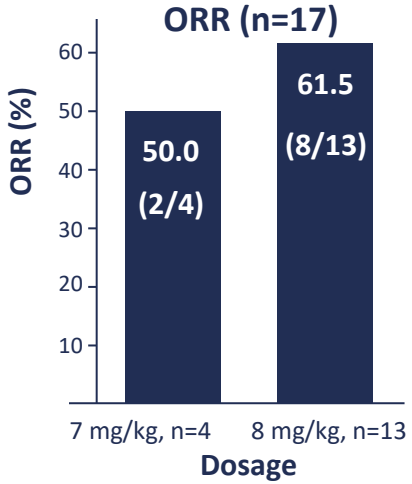
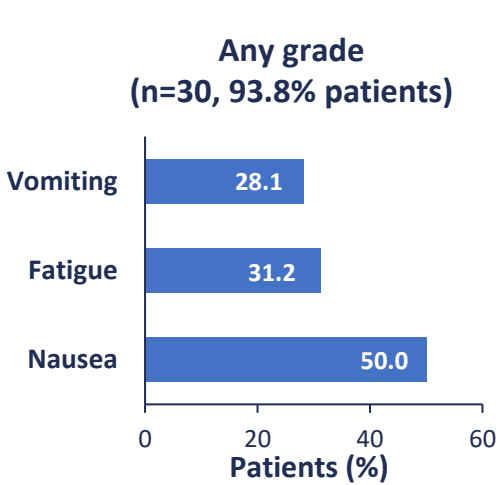
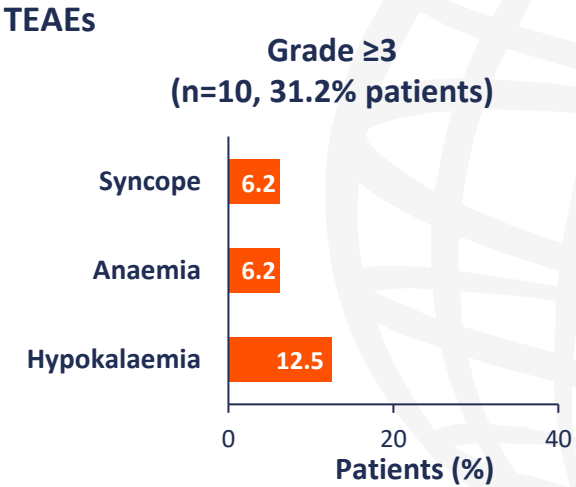
DB-1303,* a HER2-targeting ADC, for patients with advanced/metastatic EC: Preliminary efficacy and safety in ongoing phase I/IIa trial

Moore K, et al.

Dose-escalation/expansion study in patients that are HER2-positive (IHC 1/2/3+ or ISH+)







A DCR of 94.1% was achieved

- No occurrence of interstitial lung disease
- No drug discontinuation/death due to TEAEs

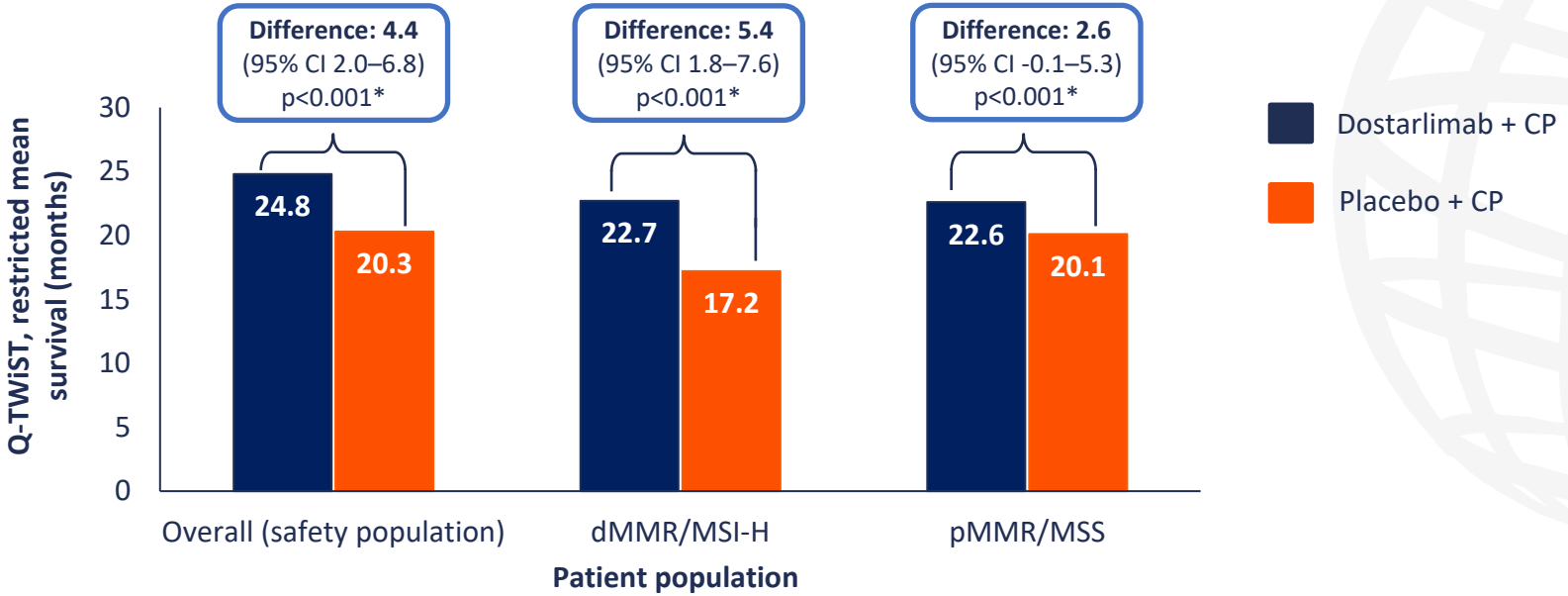
*DB-1303 is an ADC consisting of a humanized anti-HER2 IgG1 monoclonal antibody, covalently linked to a proprietary DNA topoisomerase I inhibitor (P1003) via a maleimide tetrapeptide-based cleavable linker. ADC, antibody–drug conjugate; DCR, disease control rate; EC, endometrial cancer; HER, human epidermal growth factor receptor 2; IgG, immunoglobulin G; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; TEAE, treatment-emergent adverse event.

Moore K, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 430.

Quality-adjusted time without symptoms of disease or toxicity in patients with primary advanced or recurrent EC treated with dostarlimab + CP vs CP: RUBY trial

Chase D, et al.

A post hoc survival analysis of Q-TWiST in the phase III RUBY trial (ENGOT-EN6-NSGO/GOG-3031)



*The p-values are nominal as results were not adjusted for multiple testing.

CI, confidence interval; CP, carboplatin-paclitaxel; dMMR/MSI-H, mismatch repair-deficient/microsatellite instability-high; EC, endometrial cancer; pMMR/MSS, mismatch repair-proficient/microsatellite-stable; Q-TWiST, quality-adjusted time without symptoms of disease or toxicity.

Chase D, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 267.

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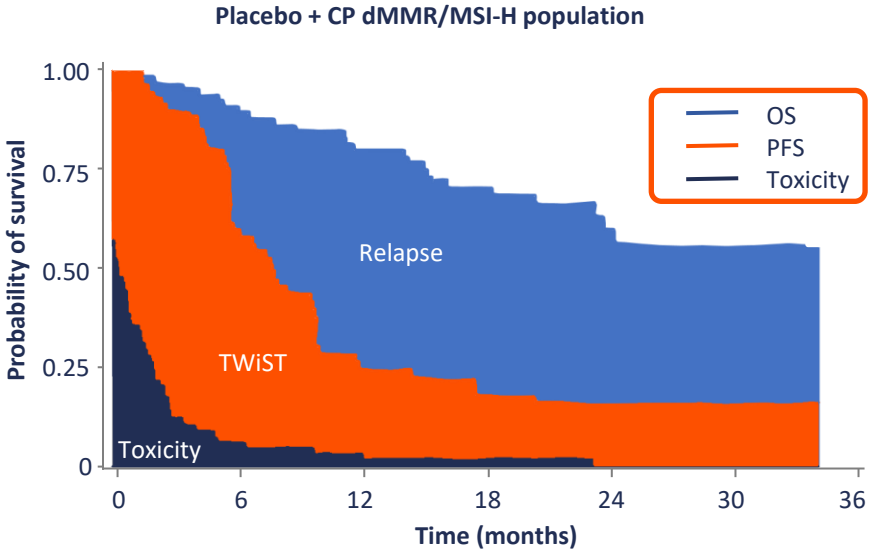
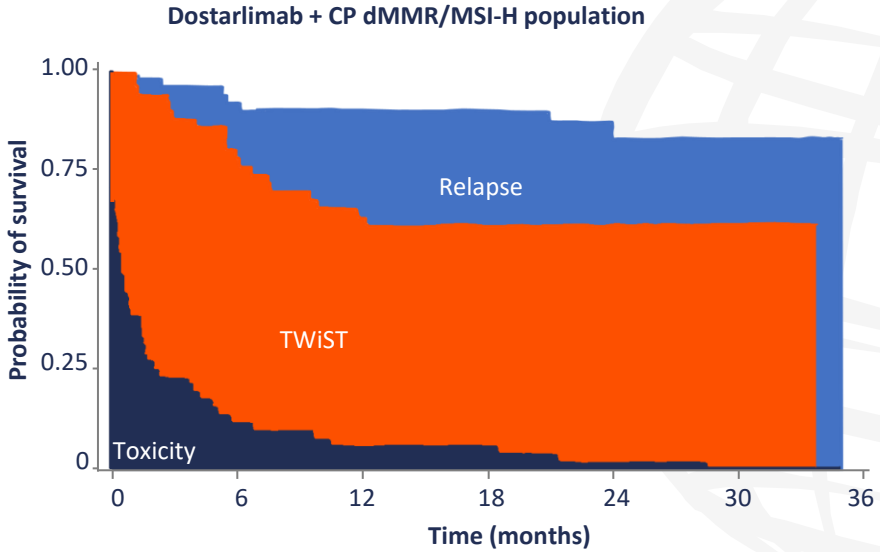
Quality-adjusted time without symptoms of disease or toxicity in patients with primary advanced or recurrent EC treated with dostarlimab + CP vs CP: RUBY trial

Chase D, et al.





Relative Q-TWiST gain of 21.99%* with dostarlimab + CP in the dMMR/MSI-H population

*Calculated as the absolute difference divided by restricted mean survival time of OS in the placebo arm (5.44/24.74 months).
CP, carboplatin-paclitaxel; dMMR/MSI-H, mismatch repair-deficient/microsatellite instability-high; EC, endometrial cancer; OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms of disease or toxicity.
Chase D, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 267. (Figures adapted with permission).

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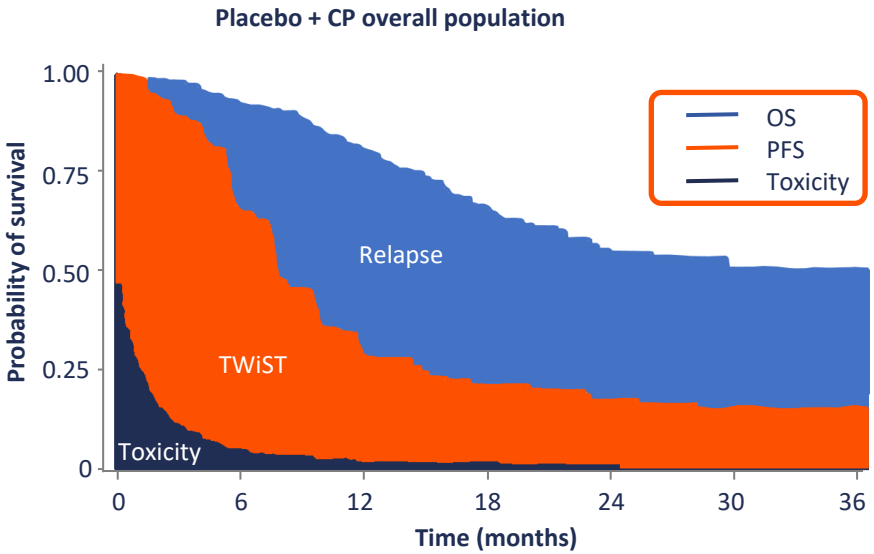
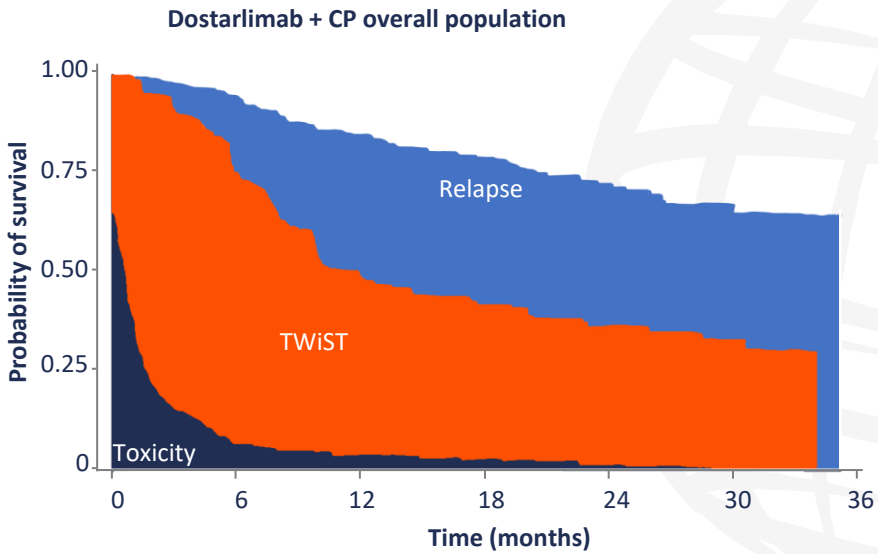
Quality-adjusted time without symptoms of disease or toxicity in patients with primary advanced or recurrent EC treated with dostarlimab + CP vs CP: RUBY trial

Chase D, et al.





Relative Q-TWiST gain of 17.65%* with dostarlimab + CP in the overall population

*Calculated as the absolute difference divided by restricted mean survival time of OS in the placebo arm (4.41/24.98 months).
CP, carboplatin-paclitaxel; EC, endometrial cancer; OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms of disease or toxicity.
Chase D, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 267. (Figures adapted with permission).

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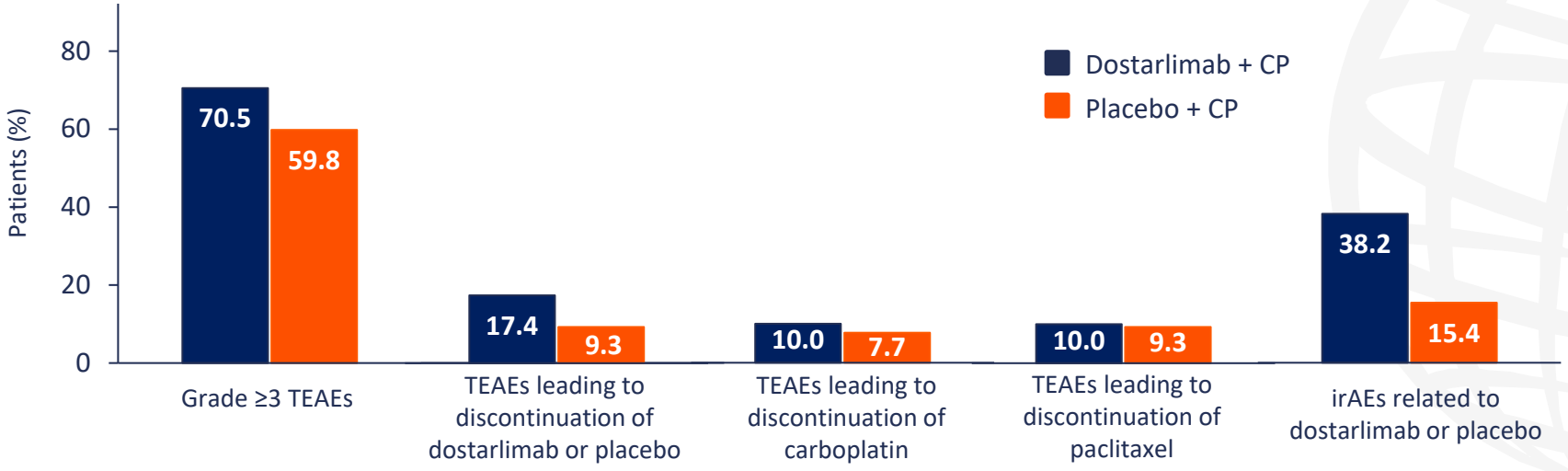
Safety of dostarlimab + CP in patients with primary advanced or recurrent EC in the RUBY trial (ENGOT-EN6-NSGO/GOG-3031)

Auranen A, et al.

An evaluation of the safety data from the phase III RUBY trial (ENGOT-EN6-NSGO/GOG-3031)



Median time to TEAE was 2.0 days in the dostarlimab + CP arm and 2.5 days in the placebo + CP arm

AE, adverse event; CP, carboplatin-paclitaxel; EC, endometrial cancer; irAE, immune-related AE; TEAE, treatment-emergent AE.

Auranen A, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 540.

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Safety of dostarlimab + CP in patients with primary advanced or recurrent EC in the RUBY trial (ENGOT-EN6-NSGO/GOG-3031)

Auranen A, et al.

	Patients with adverse events (%)	
	Dostarlimab + CP (n=241)	Placebo + CP (n=246)
• **TEAEs in ≥50% of either arm:**		
○ Fatigue	51.9	54.5
○ Alopecia	53.5	50.0
○ Nausea	53.9	45.9
• **Grade ≥3 TEAEs in ≥10% of either arm:**		
○ Anaemia	14.9	16.3
○ Neutrophil count reduced	8.3	13.8
• **TEAEs leading to death**	2.1*	0

*Five deaths were reported in the dostarlimab arm; two were related to dostarlimab and three were not related to study treatment.
CP, carboplatin-paclitaxel; EC, endometrial cancer; TEAE, treatment-emergent adverse event.
Auranen A, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 540.

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Conclusions

- DB-1303, a HER2-targeting ADC, showed promising anti-tumour activity and has a manageable safety profile in an ongoing phase I/II trial
- In the phase III RUBY trial (ENGOT-EN6-NSGO/GOG-3031):
  - Dostarlimab + CP led to significantly longer quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) than CP alone
  - The safety profile of dostarlimab + CP was consistent with that of the individual components
  - The most common TEAEs occurred more frequently during the chemotherapy period
  - Addition of dostarlimab did not compromise the chemotherapy completion rate

ADC, antibody–drug conjugate; CP, carboplatin-paclitaxel; HER2, human epidermal growth factor receptor 2.

Efficacy and safety data in advanced or recurrent endometrial cancer: Other emerging agents

Prof. Nicole Concin
Innsbruck Medical University,
Innsbruck, Austria

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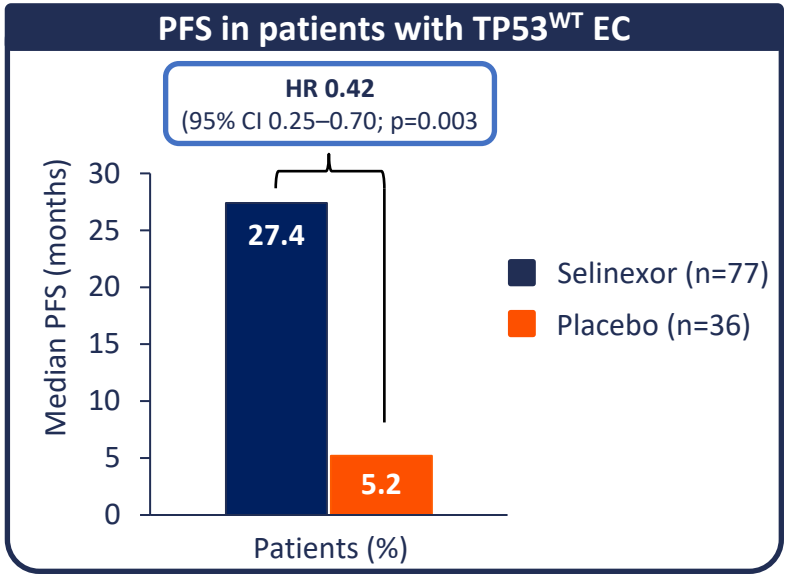
Long-term follow up of selinexor maintenance for patients with TP53^{WT} advanced or recurrent EC: A pre-specified subgroup analysis from the phase III SIENDO study (ENGOT-EN5/GOG-3055)

Fidalgo AP, et al.

Evaluation of selinexor vs placebo as maintenance in patients with advanced/recurrent EC

PFS in patients with TP53^{WT} EC



Patients with AEs (%)

	Selinexor	Placebo
Most common AEs (any grade):		
◦ Nausea	90.8	34.3
◦ Vomiting	60.5	11.4
◦ Diarrhoea	39.5	34.3
Most common grade ≥3AEs:		
◦ Neutropenia	18.4	0
◦ Nausea	11.8	0
◦ Thrombocytopenia	9.2	0

AE, adverse event; CI, confidence interval; EC, endometrial cancer; HR, hazard ratio; PFS, progression-free survival; TP53, tumour protein p53; WT, wild type.

Fidalgo AP, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 264.

ENGOT-EN20/GOG-3083/XPORT-EC-042 A phase III, randomized, placebo-controlled, double-blind, multicenter trial of selinexor in maintenance therapy for patients with p53 wild-type, advanced or recurrent endometrial carcinoma

Vergote I, et al.

Safety and efficacy study evaluating selinexor as maintenance therapy in patients with $TP53^{WT}$ primary stage IV/ recurrent EC following response to chemotherapy with/without immunotherapy

Ongoing enrolment

Patient characteristics

- N=220
- Adults with *TP53*^{WT} determined by NGS
- Primary stage IV or recurrent EC
- PR/CR per RECIST v1.1 after completing ≥12 weeks platinum combination chemotherapy ± immunotherapy

Phase II

Dosage
randomized 1:1

- **Selinexor 60 mg QW/cycle**
- **Placebo**

1 cycle = 28 days
until progressive disease or toxicity, or 3 years if in complete response

Primary endpoint
PFS based on RECIST v1.1

Secondary endpoints

- Overall survival
- Safety assessments
- PFS assessed by blinded independent central review

CR, complete response; EC, endometrial cancer; NGS, next-generation sequencing; PFS, progression-free survival; PR, partial response; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumours; TP53, tumour protein p53; WT, wild type.

Vergote I, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 265.

Trial in progress: A phase II/III study of navtemadlin as maintenance therapy in patients with advanced or recurrent endometrial cancer (EC) who responded to chemotherapy (ENGOT-EN21 and GOG-3089)

Concin N, et al.

Safety and efficacy study evaluating navtemadlin* as maintenance therapy in TP53^{WT} advanced/recurrent EC patients following response to chemotherapy

Enrolment

Patient characteristics

- Adults with *TP53*^{WT}
- Advanced/recurrent EC; ECOG PS 0 or 1
- Completed up to six cycles of chemotherapy excluding adjuvant/ neo-adjuvant therapy
- CR/PR after chemotherapy

Phase II

Navtemadlin dosage

- n=21 **Arm 1** 180 mg QD
- n=21 **Arm 2** 240 mg QD
- n=21 **Arm 3** control

Day 1–7/cycle (1 cycle = 28 days)

Primary endpoint is RP3D

Phase III*

Randomized 2:1
Day 1–7/cycle
Primary outcome: PFS

- **Arm A/B (n=150)** Phase III dose†
- **Arm C/D (n=75)** Placebo matching dose

*Continuous enrolment; †as determined by safety review committee.
CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PFS, progression-free survival; PR, partial response; QD, once daily; RP3D, recommended phase III dose; TP53, tumour protein p53; WT, wild type.
Concin N, et al. Presented at: ESGO 2023 Congress, Istanbul, Turkey. 28 September–1 October 2023. Abstr 84.

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Conclusions

- Selinexor maintenance in a subgroup of patients with TP53^{WT} EC showed durable PFS, offering the potential to prolong prior chemotherapy response
  - TP53 status is a prognostic biomarker for EC, and selinexor may benefit patients with TP53^{WT}
- Navtemadlin, a selective, potent, oral MDM2 inhibitor that restores p53-mediated apoptosis in TP53^{WT} tumours, is currently being investigated in a phase II/III study

EC, endometrial cancer; MDM2, murine double minute 2; PFS, progression-free survival; TP53, tumour protein p53; WT, wild type.