Thieme

Statement of the Uterus Commission of the Gynecological Oncology Working Group (AGO) on the Use of Primary Chemoimmunotherapy to Treat Patients with Locally Advanced or Recurrent Endometrial Cancer

Stellungnahme der Kommission Uterus der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) zur primären Chemo-Immuntherapie bei Patientinnen mit lokal fortgeschrittenem oder rezidiviertem Endometriumkarzinom

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ABSTRACT

The publication of two large randomized studies – the ENGOT-EN-6-NSGO/GOG-3031/RUBY trial and the NRG-GY018 trial – which investigated combining chemotherapy with immunotherapy to treat patients with primary advanced or recurrent endometrial cancer (EC) has transformed the clinical study landscape in terms of first-line therapy for affected patients and has set a new standard of therapy. In the ENGOT-EN-6-NSGO/GOG-3031/RUBY trial, the addition of dostarlimab to standard chemotherapy with carboplatin and paclitaxel resulted in

1. a significant and clinically relevant improvement of progression-free survival and overall survival in the overall population,
2. a significant and clinically relevant improvement of progression-free survival and overall survival in the subgroup with dMMR/MSI-high tumors, and
3. a significant and clinically relevant improvement of progression-free survival in the subgroup with pMMR/MSI-low tumors.

In the NRG-GY018 trial, the addition of pembrolizumab to standard chemotherapy with carboplatin and paclitaxel resulted in

1. a significant and clinically relevant improvement of progression-free survival in the group with dMMR tumors, and
2. a significant and clinically relevant improvement of progression-free survival in the group with pMMR tumors.

As expected, the effect in both trials was much more pronounced in the group of patients with dMMR/MSI-high tumors. According to the assessment of the Uterus Organ Commission of the AGO, all patients with dMMR/MSI-high tumors should receive chemoimmunotherapy and all patients with pMMR/MSI-low tumors who meet the inclusion criteria of the two trials discussed here may have chemoimmunotherapy. For dostarlimab this means:

1. patients with EC recurrence who will not undergo surgery or radiotherapy,
2. patients with stage IIIA, IIIB or IIIC1 disease and a measurable lesion postoperatively,
3. patients with stage IIIA, IIIB or IIIC1 disease with histological findings of serous EC, clear-cell EC or carcinosarcoma with or without a measurable lesion postoperatively, and
4. patients with stage IIIC2 or IV disease with or without a measurable lesion postoperatively.

For pembrolizumab this means:

1. patients with EC recurrence (except carcinosarcoma) who will not undergo surgery or radiotherapy, and
2. patients with stage III or IVA disease (except carcinosarcoma) and a measurable lesion postoperatively or with stage IVB disease with or without a measurable lesion.

ZUSAMMENFASSUNG

Die Publikation von 2 großen randomisierten Studien, ENGOT-EN-6-NSGO/GOG-3031/RUBY und NRG-GY018, zur kombinierten Chemo-Immuntherapie bei Patientinnen mit primär fortgeschrittenem oder rezidiviertem Endometriumkarzinom (EC) hat die Studienlandschaft zum Thema der Erstlinientherapie betroffener Patientinnen verändert und etabliert einen neuen Therapiestandard. In der ENGOT-EN-6-NSGO/GOG-3031/RUBY-Studie führte die Hinzunahme von Dostarlimab zur Standard-Chemotherapie mit Carboplatin und Paclitaxel zu einer

1. signifikanten und klinisch relevanten Verbesserung des progressionsfreien Überlebens und des Gesamtüberlebens in der Gesamtpopulation,
2. signifikanten und klinisch relevanten Verbesserung des progressionsfreien Überlebens und des Gesamtüberlebens in der Subgruppe der dMMR/MSI-high-Tumoren und einer
3. signifikanten und klinisch relevanten Verbesserung des progressionsfreien Überlebens in der Subgruppe mit pMMR/MSI-low-Tumoren.

In der NRG-GY018-Studie führte die Hinzunahme von Pembrolizumab zur Standard-Chemotherapie mit Carboplatin und Paclitaxel zu einer

1. signifikanten und klinisch relevanten Verbesserung des progressionsfreien Überlebens in der Gruppe der dMMR-Tumoren und einer
2. signifikanten und klinisch relevanten Verbesserung des progressionsfreien Überlebens in der Gruppe der pMMR-Tumoren.

In beiden Studien war der Effekt erwartungsgemäß in der Gruppe der Patientinnen mit dMMR/MSI-high-Tumoren deutlich ausgeprägter. Nach Einschätzung der Organkommission Uterus der AGO e. V. sollte somit eine Chemo-Immuntherapie bei allen Patientinnen mit dMMR/MSI-high-Tumoren bzw. kann eine Chemo-Immuntherapie bei allen Patientinnen mit pMMR/MSI-low-Tumoren erfolgen, die den Studieneinschlusskriterien der beiden diskutierten Studien entsprechen. Dies bedeutet für Dostarlimab:

1. Patientinnen mit EC-Rezidiv, bei denen keine Operation oder Strahlentherapie durchgeführt wird,
2. Patientinnen im Stadium IIIA, IIIB und IIIC1, wenn postoperativ eine messbare Läsion vorliegt,
3. Patientinnen im Stadium IIIA, IIIB und IIIC1 mit seröser, klarzelliger, oder Karzinosarkom-Histologie mit oder ohne messbare postoperative Läsion und
4. Patientinnen im Stadium IIIC2 und IV mit oder ohne postoperative messbare Läsion,

bzw. für Pembrolizumab:

1. Patientinnen mit EC-Rezidiv (außer Karzinosarkom), bei denen keine Operation oder Strahlentherapie durchgeführt wird und
2. Patientinnen im Stadium III und IVA (außer Karzinosarkom), wenn postoperativ eine messbare Läsion vorliegt und im Stadium IVB mit oder ohne messbare Läsion.

Introduction

The publication of two large randomized studies – the ENGOT-EN-6-NSGO/GOG-3031/RUBY trial and the NRG-GY018 trial – which investigated combining chemotherapy with immunotherapy to treat patients with primary advanced or recurrence endometrial cancer (EC) has transformed the study landscape in terms of first-line therapy for affected patients [1, 2]. The trials have convincingly shown for the first time that combining standard chemotherapy with carboplatin and paclitaxel with a checkpoint inhibitor, either the monoclonal PD-1 antibody pembrolizumab or the monoclonal PD-1 antibody dostarlimab, results in a significant and clinically relevant improvement in progression-free survival. As patients with primary advanced EC and patients with EC recur-

rence were included in both studies, the current recommendations on how to treat primary disease and recurrence have been summarized below. The results of the RUBY and NRG-GY018 trials are then presented and interpreted in this context.

Current Status of First-line Therapy for EC Recurrence

The current S3-guideline on the diagnosis and therapy of endometrial cancer recommends different strategies to treat patients with EC recurrence, ranging from surgery to radiotherapy to systemic chemotherapy [3]. Immunotherapy is currently not recommended as first-line therapy for EC recurrence.

Surgery for EC Recurrence

If EC recurrence is diagnosed, the first option is to evaluate whether surgical resection is feasible. The guideline specifically recommends: "Surgical therapy may be carried out to treat recurrence of endometrial cancer if complete resection of the recurrent tumor appears achievable and tomography has not found any signs of distant metastasis" [3]. Surgery may consist of local cytoreduction which aims to achieve completeness of cytoreduction (CCR) 0 resection (i.e., no macroscopic tumor rest) or systematic anterior, posterior, or complete exenteration, depending on the location of the recurrent tumor. Based on the data of Barlin et al., the guideline considers achieving CCR0 resection to be decisive [4]. Univariate analysis carried out in this retrospective examination of 14 cohort studies with a total of 672 patients with advanced or recurrent EC showed that progression-free survival and overall survival improved significantly if cytoreduction achieved complete removal of the tumor recurrence. A comparison of the investigated cohorts showed that every 10% increase in macroscopically tumor-free resection of tumor recurrence improved overall survival by 9.3 months. This needs to be qualified by pointing out that there are no randomized controlled data on cytoreduction/exenteration to treat recurrence of EC.

Primary Radiotherapy and Salvage Radiotherapy for EC Recurrence

The option to carry out radiotherapy should always be considered in cases with EC recurrence as it may be curative in cases with isolated vaginal stump recurrence, especially in radiotherapy-naive patients. The guideline specifically states: "Treatment for women with isolated vaginal or vaginal stump recurrence after endometrial cancer who did not previously receive radiotherapy during primary therapy should be radiotherapy with curative intent, consisting of external pelvic radiation and brachytherapy, with or without local tumor resection" [3]. The 5-year survival rate for these cases is more than 60%. In the PORTEC-1 trial, 30 radiotherapy-naive patients with isolated vaginal stump recurrence were treated with curative intent; 24 of them received radiotherapy alone, two had only surgery, three underwent surgery and radiotherapy and one patient received radiotherapy and hormone replacement therapy. The rate of complete remission after salvage radiotherapy and/or salvage tumor resection was 87% (26/30). The 5-year survival rate was 65% [5]. Other studies have reported 5-year survival rates of > 80%. In one study, 30 patients with isolated vaginal EC recurrence without previous adjuvant radiotherapy, who were treated with a combination of high-dose brachytherapy and teletherapy (mean EQD2 dose: 68.3 Gy), had a 5-year survival rate of 77% and a cancer-specific 5-year survival rate of 83% [6].

According to the guidelines, cases with EC recurrence who previously received adjuvant brachytherapy during primary treatment may also be treated with radiotherapy with curative intent with or without local tumor resection. Such cases should be assessed to determine whether repeat radiotherapy in the form of external radiation or brachytherapy with or without local tumor resection with curative intent is possible [3]. The prognosis for repeat radiotherapy in patients previously treated with radiotherapy is difficult and based on very limited data. Ng et al. reported complete remission in 6/6 patients with isolated vaginal stump recurrence treated with repeat radiotherapy (external, brachytherapy or a combination of the two) with or without tumor resection [7].

Systemic Chemotherapy for EC Recurrence

The current S3-guideline recommends systemic chemotherapy as the therapy of choice if radiation of the vagina or vaginal stump and/or surgery is not possible. The guideline specifically points out that the safety and efficacy of systemic chemotherapy to treat recurrence of EC is based on very good evidence. A Cochrane meta-analysis on this issue reviewed 14 randomized studies of women with primary advanced EC or recurrence of EC [8]. Eight of these randomized studies, which included data for a total of 1519 patients, compared combination chemotherapies (doublet and triplet combinations) with less intensive chemotherapy regimens. According to one meta-analysis, combination chemotherapy resulted in a significant increase in overall survival and a longer progression-free survival. Combination chemotherapy reduced the relative mortality risk by 14%. However, the difference in the mean duration of survival was only 1.5 months. Other randomized studies have compared different doublet chemotherapies or different regimens for individual substances. No significant differences were found and based on these studies, it is not possible to recommend an optimal chemotherapeutic substance or optimal chemotherapy combination. Active substances to treat EC recurrence include doxorubicin, cisplatin, carboplatin, cyclophosphamide, paclitaxel, docetaxel, methotrexate, vinblastine and ifosfamide. The guideline recommends using a combination of carboplatin and paclitaxel because it is well tolerated, there is extensive experience of this treatment combination, and it has been discussed in recently published studies. A prospective randomized phase III trial of 1381 patients with primary advanced or recurrent EC compared the use of carboplatin (AUC6)/paclitaxel (175 mg/m^2) q1, d21 × 7 with doxorubicin (45 mg/m^2; d1)/cisplatin (50 mg/m^2; d1)/paclitaxel (160 mg/m^2; d2) augmented by the addition of granulocyte colony-stimulating factor (GCSF) [9]. The carboplatin/paclitaxel regimen was found to be non-inferior with regards to overall survival and progression-free survival and was

also tolerated better. Based on these data, the S3-guideline from September 2022 recommends that systemic chemotherapy "may" be used as first-line therapy for EC recurrence [3] if surgical resection cannot be carried out. The recommended first-choice chemotherapy regimen consists of carboplatin and paclitaxel. Specifically, the guidelines states: "There is currently no evidence that any specific chemotherapy regimen is superior when treating women with recurrence of endometrial cancer. The combinations carboplatin/paclitaxel and doxorubicin/cisplatin/paclitaxel have been found to be equi-effective chemotherapy substances to treat advanced or recurrence of endometrial cancer. Carboplatin (AUC6) and paclitaxel (175 mg/m^2) should be used because this combination is tolerated better" [3]. Immunotherapy is not currently recommended as first-line therapy.

Current Status of First-line Therapy for Primary Advanced EC

The current recommendations for the adjuvant therapy of locally advanced EC (FIGO 2023 stages III and IV [10]) include systemic chemotherapy alone or a combination of radiotherapy and chemotherapy [3]. Immunotherapy is currently not recommended as first-line therapy for locally advanced EC.

Chemotherapy for Primary Advanced EC

The current S3-guideline recommends both systemic chemotherapy and combined chemoradiotherapy as adjuvant first-choice therapies for patients with primary advanced EC. The guideline states: "Patients with primary stage pT3 and/or pN1 endometrial cancer must receive adjuvant chemotherapy or an adjuvant therapy based on the PORTEC-3 regimen" [3]. The guideline treats patients with serous EC as a separate group and recommends adjuvant chemotherapy to treat serous EC, irrespective of the stage of disease. Adjuvant chemotherapy with 6 cycles of carboplatin and paclitaxel may therefore be used to treat primary advanced-stage serous EC [3]. The addition of radiotherapy is not mandatory. This also applies to cases after successful surgery of pT4a or M1 EC. The guideline states: "Patients with stage pT4a or M1 endometrial cancer, who are macroscopically tumor-free after surgery or have postoperative residual tumor with a maximum diameter of less than 2 cm, should receive adjuvant chemotherapy, combined with radiotherapy if necessary" [3]. The adjuvant chemotherapy regimen of carboplatin/paclitaxel is recommended as the first-choice approach to treat primary advanced disease. "Adjuvant chemotherapy for endometrial cancer must be carried out with carboplatin AUC6 and paclitaxel 175 mg/m^2. The carboplatin dose after percutaneous radiotherapy should be AUC5" [3]. These recommendations are based primarily on data obtained from the GOG-259 [11] and GOG-249 trials [12].

Combined Chemoradiotherapy for Primary Advanced EC

The PORTEC-3 trial has provided the most important data underpinning the recommendation of adjuvant combined chemoradiotherapy to treat primary advanced EC. The PORTEC-3 trial established pelvic radiation with 48.6 Gy (plus a brachytherapy boost for cases with cervical infiltration) combined with 2 cycles of cisplatin 50 mg/m^2 followed by 4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 as the new standard for high-risk EC [13]. A subsequent post-hoc analysis carried out in 2019 found that patients with FIGO 2019 stage III and/or serous EC benefited from combined chemoradiotherapy with regards to overall survival and recurrence-free survival [14]. The current S3-guideline therefore recommends combined chemoradiotherapy based on the PORTEC-3 regimen to treat these patients. The guideline states: "Patients with primary stage pT3 and/or pN1 endometrial cancer must receive adjuvant chemotherapy or an adjuvant therapy based on the PORTEC-3 regimen". For patients with serous EC, the guideline states: "Patients with serous endometrial cancer, FIGO stage I–III, should receive adjuvant therapy based on the PORTEC-III regimen (= radiochemotherapy followed by chemotherapy)" [3]. This needs to be qualified by noting that when molecular classifications were also included, probably only patients with abnormal p53 expression and p53 mutation status benefited from combined chemoradiotherapy based on the PORTEC-3 regimen. In a nested post-hoc analysis of the PORTEC trial (nested case control study), Leon-Castillo et al. investigated the predictive value of the 4 molecular subtypes (p53-abnormal, POLE-ultra-mutated, MMR-deficient and no specific molecular profile [NSMP]) in terms of the therapeutic success of combined chemoradiotherapy [15]. They found that only the group with p53-abnormal EC benefited in terms of longer overall survival and recurrence-free survival times while the POLE-ultra-mutated and MMR-deficient groups did not. Patients with the molecular subtype NSMP had longer recurrence-free survival times but no improvement of overall survival. These data therefore indicate that when treating patients with locally advanced EC, adjuvant chemoradiotherapy should only be carried out in cases with confirmed p53-abnormal subtype.

Chemoimmunotherapy: the ENGOT-EN-6-NSGO/GOG-3031/RUBY Trial

The RUBY trial, an international multicenter study carried out across 113 institutions in 19 countries, investigated patients with histologically or cytologically confirmed primary advanced EC (FIGO 2019 stages III and IV) or first recurrence of EC with no curative treatment option in the opinion of treating physicians [1]. Cases with stage IIIA, IIIB or IIIC1 disease must also have a measurable lesion postoperatively (except for cases with histological findings of serous or clear-cell EC or carcinosarcoma); cases with stage IIIC2 or IV disease do not need to have a measurable lesion. In cases with recurrence after neoadjuvant or adjuvant chemotherapy, there must be a minimum period of 6 months before recurrence is diagnosed. The study design was a placebo-controlled

▶ **Table 1** Study characteristics and results of the ENGOT-EN-6-NSGO/GOG-3031/RUBY and NRG-GY018 trials.

	ENGOT-EN-6-NSGO/GOG-3031/RUBY	NRG-GY018
Patients	n = 494	n = 816 (n = 591 [pMMR]; n = 225 [dMMR])
Inclusion criteria	EC FIGO stage III or IV or EC recurrence; for stage IIIA, IIIB, IIIC1 disease: measurable postoperative lesion required (exception: histological findings of serous EC, clear-cell EC or carcinosarcoma); EC stage IIIC2 or IV: no measurable lesion required; EC recurrence: minimum of 6 months after adjuvant CHXT	EC FIGO stage III or IV or first recurrence of EC; for stage III, IVA disease: measurable postoperative lesion required; all histological subtypes except carcinosarcoma; EC recurrence: minimum of 12 months after adjuvant CHXT
Therapy regimen	6 × C (AUC5) and P (175 mg/m^2) d1, q21 versus 6 × C (AUC5) and P (175 mg/m^2) d1, q21 and dostarlimab 500 mg IV d1, q21 during CHXT and 1000 mg IV d1, q42 for up to 3 years	6 × C (AUC5) and P (175 mg/m^2) d1, q21 versus 6 × C (AUC5) and P (175 mg/m^2) d1, q21 and pembrolizumab 200 mg IV d1, q21 during CHXT and 400 mg IV d1, q42 until death/progression/unacceptable toxicity or for up to 2 years
Toxicity	2 deaths possibly in connection with dostarlimab (2/241; 0.8 %); most common AEs: nausea (+ 8 % compared to placebo), alopecia (+ 3 %), fatigue (+ 3 %), skin rash (+ 9 %), hypothyroidism (+ 9 %), elevated liver function parameters (+ 5 %); discontinuation of therapy with dostarlimab: 17 %	1 death (1/112; 0.8 %) in the dMMR cohort and 6 deaths (6/295; 2 %) in the pMMR cohort; of these, 1 case with possible connection to pembrolizumab; grade 3 AEs > 1 %: infusion reactions (3.7 %), pneumonitis (1.8 %), renal insufficiency (1.8 %)
Progression-free survival	After 24 months: 36 % (dostarlimab) versus 18 % (standard arm); HR 0.64; 95 % CI: 0.51–0.80; p < 0.001 dMMR/MSI-high subgroup after 24 months: 61 % (dostarlimab) versus 15 % (standard arm); HR 0.28; 95 % CI: 0.16–0.50; p < 0.001	After 12 months in the dMMR cohort: risk of progression: 38 % (pembrolizumab) versus 74 % (standard arm); HR 0.30; 95 % CI: 0.19–0.48; p < 0.001 After 7.9 months in the pMMR cohort: mean duration of progression-free survival: 13.1 months (pembrolizumab) compared to 8.7 months (standard arm); HR 0.54; 95 % CI: 0.41–0.71; p < 0.001
Overall survival	After 24 months: 71 % (dostarlimab) versus 56 % (standard arm); HR 0.64; 95 % CI: 0.46–0.87; p = 0.0021 dMMR/MSI-high subgroup after 24 months: 83 % (dostarlimab) compared to 58 % (standard arm); HR 0.30; 95 % CI: 0.13–0.70	No data

EC = endometrial cancer; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; CHXT = chemotherapy; AUC = area under the curve; C = carboplatin; P = paclitaxel; AE = adverse event; HR = hazard ratio; CI = confidence interval; dMMR = mismatch repair deficiency; MSI = microsatellite instability; pMMR = MMR proficiency

study with 1 : 1 randomization. Test subjects received 6 cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2) every 3 weeks (standard arm) or 6 cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2) every 3 weeks and dostarlimab 500 mg IV every 3 weeks during chemotherapy and 1000 mg IV every 6 weeks for up to 3 years (experimental arm) (▶ **Table 1**). Randomization was stratified based on the criteria "MMR/MSI status", "prior pelvic radiation therapy", and "disease status" (recurrence vs. stage III vs. stage IV). Primary endpoint of the study was progression-free survival. The study hypothesis was that the addition of dostarlimab would result in a hazard ratio (HR) of at least 0.5 with regards to the risk of progression. A total of 494 patients were randomized (245 into the dostarlimab arm vs. 249 into the standard arm).

Results of the ENGOT-EN-6-NSGO/GOG-3031/RUBY Trial

The results of the RUBY trial are impressive. The addition of dostarlimab to standard chemotherapy resulted in

1. **a significant and clinically relevant improvement of progression-free survival and overall survival in the overall population,**
2. **a significant and clinically relevant improvement of progression-free survival and overall survival in the subgroup with dMMR/MSI-high tumors, and**
3. **a significant and clinically relevant improvement of progression-free survival in the subgroup with pMMR/MSI-low tumors.**

The primary endpoint (progression/death) was reached in September 2022 (data cut-off) for 177 patients in the standard arm and 135 patients in the dostarlimab arm; the mean observation period was 25.4 months. The intention-to-treat analysis of the total population calculated the probability of progression-free survival after 24 months as 36 % for the dostarlimab arm compared to 18 % for the standard arm (HR 0.64; 95 % confidence interval [CI]: 0.51–0.80; p < 0.001). The probability of survival after 24 months was 71 % (dostarlimab arm) compared to 56 % (standard arm) (HR 0.64; 95 % CI: 0.46–0.87; p = 0.0021).

The therapeutic effect of dostarlimab was even more impressive for a predefined subpopulation with dMMR/MSI-high tumors. Progression-free survival after 24 months was 61% in the dostarlimab arm compared to just 15% in the standard arm (HR 0.28; 95% CI: 0.16–0.50; p < 0.001). The overall survival after 24 months was 83% in the dostarlimab arm compared to 58% in the standard arm (HR 0.30; 95% CI: 0.13–0.70).

The results for the subpopulation with pMMR/MSI-low tumors were also remarkable, especially as it was expected that the effect would be significantly lower or even nonexistent. A significant and clinically relevant effect was also apparent in this group. The progression-free probability of survival after 24 months was 28% for the dostarlimab arm compared to just 18% for the standard arm (HR 0.76; 95% CI: 0.59–0.98). Overall survival was also higher in the dostarlimab group (67% vs. 55%) but just missed statistical significance (HR 0.73; 95% CI: 0.52–1.02).

The toxicity of dostarlimab was within the expected range. There were 5 deaths in the dostarlimab group, 2 of which were possibly connected to dostarlimab (myelosuppression and hypovolemic shock; 2/241; 0.8%). Grade 3 adverse events occurred around 10% more often with dostarlimab compared to placebo. The most common adverse events with dostarlimab were nausea (+ 8% compared to placebo), alopecia (+ 3%), fatigue (+ 3%), skin rash (+ 9%), hypothyroidism (+ 9%) and elevated liver function parameters (+ 5%). 17% of test subjects in the dostarlimab arm discontinued therapy compared to just 9% in the standard arm.

Chemoimmunotherapy: NRG-GY018

The second trial, NRG-GY018 – an international multicenter study carried out across 395 institutions in 4 countries – investigated 816 patients with primary advanced EC (FIGO 2019 stage III or IV A/B) or primary recurrence of EC [1]. All histological subtypes except for carcinosarcoma were included. Women with EC recurrence who had previously had chemotherapy were included if a minimum of 12 months had passed since they had previously received chemotherapy. In a placebo-controlled study design with 3 : 1 stratification (n = 591 [pMMR] vs. n = 225 [dMMR]) and subsequent 1 : 1 randomization, test subjects received either 6 cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2) every 3 weeks (standard arm) or 6 cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2) every 3 weeks and pembrolizumab 200 mg IV every 3 weeks during chemotherapy and 400 mg IV every 6 weeks until progression/death/intolerable toxicity (experimental arm) (▶ **Table 1**). If patients responded to chemotherapy (carboplatin/paclitaxel), it could be increased to a maximum of 10 cycles. Randomization was stratified according to the criteria “MMR status”, “prior chemotherapy” and “general condition based on Eastern Cooperative Oncology Group (ECOG) criteria (0 vs. 1 vs. 2)”. Primary endpoint of the study was progression-free survival. The study hypothesis was that the addition of pembrolizumab would lead to a relative reduction in the risk of progression of at least 40%. A total of 816 patients (225 with dMMR tumors and 591 with pMMR tumors) were included in the study and randomized (112 dMMR + 295 pMMR in the pembrolizumab arm vs. 113 dMMR + 296 pMMR in the standard arm).

Results of the NRG-GY018 Trial

The results of the NRG-GY018 trial were as remarkable as the results of the RUBY trial. The addition of pembrolizumab to standard chemotherapy led to

1. **a significant and clinically relevant improvement of progression-free survival in the group with dMMR tumors, and**
2. **a significant and clinically relevant improvement of progression-free survival in the group with pMMR tumors.**

The mean observation time until December 2022 (data cut-off) was 12 months (dMMR group) and 7.9 months (pMMR group), respectively. In the intention-to-treat analysis of the dMMR population, the addition of pembrolizumab increased the probability of progression-free survival after 12 months by 70%. Progression-free survival in the pembrolizumab arm was 74% compared to 38% in the standard arm (HR 0.30; 95% CI: 0.19–0.48). The addition of pembrolizumab also increased the probability of progression-free survival after 7.9 months in the pMMR population. The mean duration of progression-free survival in the pembrolizumab arm was 13.1 months compared to 8.7 months in the standard arm (HR 0.54; 95% CI: 0.41–0.71; p < 0.001).

The toxicity of pembrolizumab was within the expected range. One death occurred in the dMMR cohort (1/112; 0.8%) and 6 deaths in the pMMR cohort (6/295; 2%), although only 1 case was possibly connected to pembrolizumab. Grade 3 events which occurred with a frequency of > 1% included infusion reactions (3.7%), pneumonitis (1.8%) and renal insufficiency (1.8%).

The data on overall survival are not yet available in the full paper but can be found in the publication’s supplementary files. They include a preliminary evaluation of the dMMR and pMMR populations, although the 95% confidence intervals of the survival curves overlap and no statistically significant effect with regards to overall survival is currently visible. For a final assessment, we will have to wait until further study evaluations after longer follow-up periods will be available.

Summary and Treatment Recommendation

The publication of two large randomized studies, the ENGOT-EN-6-NSGO/GOG-3031/RUBY trial and the NRG-GY018 trial, on the impact of combined chemoimmunotherapy in patients with primary advanced EC (FIGO 2019 stage III/IV) or EC recurrence has transformed the study landscape with regards to first-line therapy of affected patients and set a new therapy standard. Patients with MMR-deficient, primary advanced or recurrent EC who meet the inclusion criteria should therefore receive combined chemoimmunotherapy with dostarlimab or pembrolizumab. As expected, the therapeutic effect of chemoimmunotherapy was less pronounced in patients with MMR-proficient, primary advanced or recurrent EC. The use of chemoimmunotherapy in these patients should therefore be discussed on an individual basis; the data are still too immature to make a final assessment. The approval status of both medications also remains to be seen. It is possible that dostarlimab and pembrolizumab will only be approved for the first-line therapy of primary advanced or recurrent EC in patients with dMMR/MSI-high tumors. However in this case, it will be pos-

sible to make a case for their off-label use to treat pMMR/MSI-low tumors based on the already existing data. It is not possible to provide specific recommendations for either of the two immunotherapies. The currently available trial results for dostarlimab are more mature, and data on the overall survival rates with dostarlimab are already available. Whether chemoimmunotherapy could also be used as adjuvant therapy to treat patient with uterine node-positive EC is still disputed. In the RUBY trial, 18% of test subjects had FIGO 2019 stage III disease (55/298). The study did not differentiate between purely node-positive cases (stage IIIC1 pelvic; IIIC2 paraaortic; stage IIIC1i or IIIC2i with micrometastasis; stage IIIC1ii or IIIC1ii with macrometastasis; sentinel-positive patients) and patients with tumor spread to the serosa or adnexa (stage IIIA), the lesser pelvis (stage IIIB) or abdomen (stage IVB). In the opinion of the Uterus Organ Commission of the AGO, all patients with dMMR/MSI-high tumors should receive chemoimmunotherapy and all patients with pMMR/MSI-low tumors who meet the inclusion criteria of the two studies may receive chemoimmunotherapy.

For dostarlimab this means:

1. **patients with EC recurrence who will not undergo surgery or radiotherapy,**
2. **patients with stage IIIA, IIIB or IIIC1 disease with a measurable lesion postoperatively,**
3. **patients with stage IIIA, IIIB or IIIC1 disease with histological findings of serous or clear-cell EC or carcinosarcoma with or without a measurable postoperative lesion, and**
4. **patients with stage IIIC2 or IV disease with or without a measurable lesion postoperatively.**

For pembrolizumab this means:

1. **patients with EC recurrence (except carcinosarcoma) who will not undergo surgery or radiotherapy, and**
2. **patients with stage III or IVA disease (carcinosarcoma) with a measurable lesion postoperatively or stage IVB disease with or without a measurable lesion.**

Conflict of Interest

The authors state that they have no conflict of interests.

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