Dostarlimab (Jemperli®) with carboplatin and paclitaxel for the treatment of mismatch repair deficient (dMMR)/ microsatellite instability high (MSI-H) primary advanced or recurrent endometrial cancer (EC)

General information

Drug description [1]

Dostarlimab (Jemperli®, TSR-042) is a humanised monoclonal antibody of the IgG4 isotype that binds to PD-1 receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway-mediated immune response results in inhibition of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti-tumour immuno responses through the blockade of PD-1 binding to PD-L1 and PD-L2.

Indication [2]

Dostarlimab (Jemperli®) in combination with carboplatin and paclitaxel is indicated for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent EC and who are candidates for systemic therapy.

Incidence [3]

In Austria, in 2020, a total of 903 women were newly diagnosed with EC. The age-standardised[1] incidence rate was 18.4 per 100,000 women.

Current treatment

For recurrent or metastatic disease, the ESMO[2] recommends the following [4]:

- For patients with locoregional recurrence following primary surgery alone, the preferred primary therapy should be RT with VBT.
- Adding systemic therapy to salvage RT could be considered.
- For patients with recurrent disease following RT, surgery should be considered only if a complete debulking with acceptable morbidity is anticipated.
- Complementary systemic therapy after surgery could be considered.
- The first-line standard chemotherapy treatment is carboplatin AUC5-6 plus paclitaxel 175 mg/m^2 every 21 days for 6 cycles.
- Hormone therapy could be considered as front-line systemic therapy for patients with low-grade carcinomas endometrioid histology.
- Progestins (medroxyprogesterone acetate 200 mg and megestrol acetate 160 mg) are the recommended agents.
- Other options for hormonal therapies include AIs, tamoxifen and fulvestrant.
- There is no standard of care for second-line chemotherapy.
- Doxorubicin and weekly paclitaxel are considered the most active therapies.
- ICB monotherapy could be considered after platinum-based therapy failure in patients with MSI-H/dMMR EC.
- Dostarlimab has recently been approved by both the EMA and the FDA for this indication (ESMO-MCBS v1.1 score: 3).
- Pembrolizumab is FDA approved for the treatment of TMB-H solid tumours (as determined by the FoundationOne CDx assay) that have progressed following prior therapy for EC (ESMO-MCBS v1.1 score: 3; not EMA approved).
- Pembrolizumab-lenvatinib is approved by the EMA for EC patients who have failed a previous platinum-based chemotherapy, and who are not candidates for curative surgery or RT. FDA approval is for EC patients whose tumours are not dMMR/MSI-H (ESMO-MCBS v1.1 score: 4).

Regulatory status

EMA [2]	FDA [5, 6]

[1] European Standard Population 2013.
[2] Currently, there is no Onkopedia guideline for EC available.

Approval status for this indication: On 12 October 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Jemperli®. The CHMP adopted a new indication as follows: ❖ Jemperli® is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent EC and who are candidates for systemic therapy. **Other indications**: ❖ Jemperli® is indicated as monotherapy for the treatment of adult patients with dMMR/MSI H recurrent or advanced EC that has progressed on or following prior treatment with a platinum containing regimen. ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[3]	**Approval status for this indication**: On 31 July 2023, the FDA approved dostarlimab-gxly (Jemperli®) with carboplatin and paclitaxel, followed by single-agent dostarlimab-gxly, for primary advanced or recurrent EC that is dMMR, as determined by an FDA-approved test, or MSI-H. **Other indications**: Jemperli® is indicated: ❖ as a single agent for the treatment of adult patients with dMMR recurrent or EC, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and is not candidates for curative surgery or radiation. ❖ as a single agent for the treatment of adult patients with dMMR recurrent or advanced solid tumours, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment option. This indication is approved under accelerated approval based on tumour response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Manufacturer

Jemperli® Is manufactured by GlaxoSmithKline.

Costs

Jemperli® concentrate for solution for infusion 500 mg/10 ml = € 6,950.00 (ex-factory price) [7]

Warnings and precautions [5]

- **Immune-mediated adverse reactions**
  - Immune-mediated adverse reactions which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for signs and symptoms of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver enzymes, creatinine, and thyroid function, at baseline and periodically during treatment.
  - Withhold or permanently discontinue Jemperli® and administer corticosteroids based on the severity of the reaction.
- **Infusion-related reactions**
  - Interrupt, slow the rate of infusion, or as a single agent for the treatment of adult patients with primary advanced permanently discontinue Jemperli® based on the severity of the reaction.
- **Complications of allogeneic HSCT**
  - Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1–blocking antibody.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception.

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)

[3] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

RUBY ENGOT-EN-6-NSGO/ GOG-3031 NCT03981796	494[4] (1:1)	**dostarlimab 500 mg IV** + **carboplatin** (AUC, 5 mg/ml/min) and **paclitaxel** (175 mg/m^2 of BSA) every 3 weeks (6 cycles), **followed by dostarlimab** 1000 mg IV every 6 weeks for up to 3 years[5]	**placebo IV** + **carboplatin** (AUC, 5 mg/ml/min) and **paclitaxel** (175 mg/m^2 of BSA) every 3 weeks (6 cycles), **followed by placebo** IV every 6 weeks for up to 3 years[6]	PFS by the investigator according to (RECIST v1.1.) + OS	**24.8** months in the **dMMR–MSI-H** population and **25.4** months in the **overall population**	**ongoing**[7], global, double-blind, randomized, placebo-controlled phase 3 trial	PD-1	GlaxoSmithKline	RUBY trial [10]

Inclusion criteria[8]	Exclusion criteria	Patient characteristics at baseline: dMMR/MSI-H population (I vs. C, n=53 vs. n=65)
❖ Females ≥18 years of age; written informed consent. ❖ Subject has histologically or cytologically proven EC with recurrent or advanced disease. ❖ Subject must provide adequate tumour tissue sample at Screening for MSI status testing. ❖ Subject must have primary Stage III or Stage 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: • Primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per RECIST v.1.1 based on Investigator's assessment. • Primary Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology regardless of presence of evaluable or measurable disease on imaging. • Primary Stage IIIC2 or Stage IV disease. • First recurrent disease and is chemotherapy naïve. • Prior neo-adjuvant/adjuvant systemic chemotherapy and had a recurrence or PD ≥ 6 months after completing treatment (first recurrence). ❖ ECOG performance status of 0 or 1. ❖ Subject has adequate organ function, defined as follows:	❖ Subject has received neo-adjuvant/adjuvant systemic chemotherapy for primary Stage III or IV disease and: • has not had a recurrence or PD prior to entering the study OR • has had a recurrence or PD within 6 months of completing chemotherapy treatment prior to entering the study. ❖ > 1 recurrence of EC. ❖ Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. ❖ Prior anticancer therapy within 21 days or < 5 times the half-life of the most recent therapy prior to Study Day 1, whichever is shorter. ❖ Concomitant malignancy, or subject has a prior non-endometrial invasive malignancy who has been disease-free for < 3 years or who received any active treatment in the last 3 years for that malignancy. Non-melanoma skin cancer is allowed. ❖ Known uncontrolled CNS metastases, carcinomatosis meningitis, or both. ❖ Known history of HIV; HIV 1/2 antibodies. ❖ Known active hepatitis B or hepatitis C.	❖ Median: 61 years (range, 45–81) vs. 66 (range, 39–85) ❖ ≥65 years: 43% vs. 54% ❖ Race or ethnic group: • White: 83% vs. 86% • Black: 8% vs. 9% • Asian: 4% vs. 0% • American Indian or Alaska Native: 2% vs. 0% • Native Hawaiian or other Pacific Islander: 2% vs. 0 • Unknown or not reported: 4% vs. 3% ❖ ECOG PS: • 0: 54% vs. 60% • 1: 46% vs. 40% ❖ FIGO stage at diagnosis: • I: 34% vs. 34% • II: 6% vs. 8% • III: 26% vs. 31% • IV: 26% vs. 23% • Unknown: 8% vs. 5% ❖ Disease status • Primary stage III: 19% vs. 22% • Primary stage IV: 30% vs. 29% • Recurrent: 51% vs. 49% ❖ Median BMI: 30.6 (range, 20.1–54.4) ❖ Histologic type:

[4] Of the 494 patients who underwent randomization, 118 (23.9%) had dMMR/MSI-H tumours.
[5] Treatment ends after 3 years, progression of disease, toxicity, withdrawal of consent, Investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator.
[6] Treatment ends after 3 years, progression of disease, toxicity, withdrawal of consent, Investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator.
[7] The RUBY trial is currently ongoing; estimated study completion date is 11/2026.
[8] For detailed in- and exclusion criteria, please see trial protocol.

• Absolute neutrophil count ≥ 1,500 cells/µL • Platelets ≥ 100,000 cells/µL • Haemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L • Serum creatinine ≤ 1.5× upper limit of normal (ULN) or calculated creatinine • clearance ≥ 50 mL/min using the Cockcroft-Gault equation for subjects with • creatinine levels > 1.5 × institutional ULN • Total bilirubin ≤ 1.5× ULN and direct bilirubin ≤ 1× ULN • Aspartate aminotransferase and alanine aminotransferase ≤ 2.5× ULN unless liver metastases are present, in which case they must be ≤ 5× ULN • International normalized ratio or prothrombin time ≤ 1.5× ULN and activated partial thromboplastin time ≤ 1.5× ULN. ❖ Subject must have a negative serum pregnancy test within 72 hours of the first dose of study medication, unless they are of nonchildbearing potential. ❖ Subjects of childbearing potential must agree to use 2 adequate methods of contraception with their partners starting with the screening visit through 180 days after the last dose of study treatment.	❖ Active autoimmune disease that has required systemic treatment in the past 2 years. ❖ Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of systemic immunosuppressive therapy within 7 days prior to the first dose of study treatment. ❖ Subject has not recovered from cytotoxic therapy-induced AEs. ❖ Subject has not recovered adequately from AEs or complications from any major surgery prior to starting therapy. ❖ Known hypersensitivity to carboplatin, paclitaxel, or dostarlimab components or excipients. ❖ Subject is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring systemic therapy. ❖ Subject is pregnant or breastfeeding or is expecting to conceive children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study treatment.	• Carcinosarcoma: 8% vs. 2% • Endometrioid: 83% vs. 86% • Mixed carcinoma ≥10% of carcinosarcoma, clear-cell, or serous histologic type: 4% vs. 6% • Serous adenocarcinoma: 2% vs. 2% • Clear-cell adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma: 0% vs. 0% • Other: 4% vs. 5% ❖ MMR–MSI status: • dMMR–MSI-H: 100% vs. 100% • pMMR–MSS: 0% vs. 0% ❖ Previous external pelvic radiotherapy • Yes: 15% vs. 20% • No: 85% vs. 80%

Efficacy (I vs. C):	**Safety** (I vs. C), **overall population (n=241 vs. n=246)**
<u>Data-cutoff date 8 September 2022:</u> **DMMR/MSI-H population (n=53 vs. n=65):** Patients who had died or had disease progression as of the data cutoff date: 36% vs. 72% Estimated Kaplan–Meier probability of PFS at 24 months: 61.4% (95% CI, 46.3-73.4) vs. 15.7% (95% CI, 7.2-27.0); HR 0.28 (95% CI, 0.16-0.50; p<0.001) Kaplan–Meier estimates of OS at 24 months: 83.3% (95% CI, 66.8-92.0) vs. 58.7% (95% CI, 43.4-71.2); HR 0.30 (95% CI, 0.13-0.70) **Overall population (n=241 vs. n=246):** Patients who had died or had disease progression as of the data cutoff date: 55.1% vs. 71.1% PFS at 24 months: 36.1% (95% CI, 29.3-42.9) vs. 18.1% (95% CI, 13.0-23.9); HR for progression or death, 0.64 (95% CI, 0.51-0.80; p<0.001) The Kaplan–Meier probability of survival at 24 months: 71.3% (95% CI, 64.5-77.1) vs. 56.0% (95% CI, 48.9-62.5); HR for death 0.64 (95% CI, 0.46-0.87; p=0.0021)	**AEs:** 70.5% vs. 59.8% **sAEs:** 37.8% vs. 27.6% **Any irAEa:** 56.8% vs. 35.8% **Any irAE grade ≥3:** 16.6% vs. 6.1% **Discontinuation due to AEs:** 17.4% vs. 9.3% **Deaths due to AEs:** n=2.1%[9] vs. n=0

[9] One death that was reported by the investigator as related to the dostarlimab regimen occurred during the first 6 cycles (myelosuppression), one death was related to dostarlimab and occurred during the 90-day safety follow-up (hypovolemic shock), and three were judged not to be related to the dostarlimab regimen (opiate overdose, coronavirus disease 2019, and general deterioration of physical health).

pMMR–MSS population

PFS at 24 months: 28.4% (95% CI, 21.2-36.0) vs. 18.8% (95% CI, 12.8-25.7); HR for disease progression or death 0.76 (95% CI, 0.59-0.98)

Kaplan–Meier estimates of OS at 24 months: 67.7% (95% CI, 59.8-74.4) vs. 55.1% (95% CI, 46.8 to 62.5), HR for death 0.73 (95% CI, 0.52-1.02).

Patient-reported outcomes [10, 12]

- EORTC QLQ-C30 and EN24 were prespecified secondary endpoints.
- PROs were administered on Day 1 of each treatment cycle, end of treatment, and at safety and survival follow-ups.
- PRO outcomes were similar for I and C through the chemo period (C7, end of chemotherapy).
- Further, no differences across the 3-year period between the 2 arms were reported; LSM (standard error) for global QoL was 0.5 (1.42; p=0.72), PF was 20.7 (1.39; p=0.63), fatigue was 0.2 (1.75; p=0.91) and pain was 21.0 (1.99; p=0.62).
- Mean change from baseline to end of chemotherapy showed improvement in back/pelvic pain for I and deterioration in global QoL/GHS, social functioning, body image, and change in taste for patients in placebo group.
- During the chemotherapy period, the mean change from baseline in EORTC-QLQ-C30 GHS and QoL scores indicated no differences between groups. Results were similar in both the overall population and the dMMR–MSI-H population.

ESMO-MCBS version 1.1 [13]

Scale	Int.	Form	MG ST	MG (based on [14])	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	>6 months	PFS: 25 months (Calculated estimate of gain based on PE HR 0.28)	0.28 (0.16-0.50)	HR ≤0.65 AND gain ≥3 months	3	-	-	+1[10]	4
Adapted	NC	2B	>6 months	PFS: 25 months (Calculated estimate of gain based on PE HR 0.28)	0.28 (0.16-0.50)	HR ≤0.65 AND gain ≥3 months	3	+10.2% sAEs	-	+1/-1[11]	3

Risk of bias (RCT) [15]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes low risk	unclear[12] unclear risk	yes[13] high risk	Unclear risk

Ongoing trials [16]

NCT number/trial name	Description	Estimated study completion date
NCT03981796/ RUBY	Please see above.	11/2026
NCT05201547/ DOMENICA	Randomized phase III trial in MMR deficient EC patients comparing chemotherapy alone vs. dostarlimab in first-line advanced/metastatic setting.	10/2029
NCT04774419	Adjuvant checkpoint blockade plus radiation in locally advanced, MMR-D/MSI-H EC, a phase 2 trial.	02/2024
NCT03016338	A phase II, open-label study of the poly(ADP-ribose) polymerase inhibitor niraparib in monotherapy or combination with anti-PD1 inhibitor TSR-042 in recurrent EC.	12/2025
NCT05559879	A phase Ib/II single-arm study of cabozantinib plus dostarlimab in women with recurrent gynaecologic carcinosarcoma.	12/2025

Available assessments

[10] Upgrade 1 level due to long-term plateau in the PFS curve.

[11] Upgrade 1 level due to long-term plateau in the PFS curve. Downgrade 1 level due to ≥10% more sAEs in the dostarlimab group.

[12] The RUBY trial is ongoing; currently, only interim analysis data is available.

[13] The trial was designed by the sponsor in collaboration with the authors and academic groups under the European Network of Gynaecological Oncological Trial (ENGOT) groups and the GOG Foundation. The sponsor was responsible for overseeing the collection, analysis, and interpretation of data. Medical writing assistance with the submitted manuscript was funded by the sponsor.

- In March 2022, NICE published a Technology appraisal guidance "Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency" [17].
- NIHR published a Health Technology Briefing in May 2021: "Dostarlimab in addition to carboplatin and paclitaxel for recurrent or primary advanced endometrial cancer" [18].
- CADTH´s reimbursement review for dostarlimab in patients with EC is currently ongoing [19].
- No further assessments were identified via ICER and G-BA.

Other aspects and conclusions

- In October 2023, the **CHMP adopted a new indication** for Jemperli®, indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent EC and who are candidates for systemic therapy. In July 2023, the **FDA approved** Jemperli® with carboplatin and paclitaxel, followed by single-agent Jemperli®, for primary advanced or recurrent EC that is dMMR, as determined by an FDA-approved test, or MSI-H.
- The **ongoing, phase 3**, global, double-blind, randomized, placebo-controlled **RUBY trial (NCT03981796)**, evaluates the efficacy and safety of dostarlimab in combination with carboplatin and paclitaxel as compared with placebo plus carboplatin and paclitaxel in patients with primary advanced or recurrent EC. Eligible patients are ≥18 years old and have histologically or cytologically confirmed primary advanced or recurrent (FIGO stage III or IV) EC that is not amenable to curative therapy. Patients with primary advanced stage IIIA, IIIB, or IIIC1 disease, primary advanced stage IIIC1 disease with carcinosarcoma, clear-cell, serous, or mixed histologic characteristics; primary advanced stage IIIC2 or stage IV disease, or disease that either was in its first recurrence and had not been treated with systemic therapy or had been treated with neoadjuvant or adjuvant systemic therapy and had recurred or progressed at least 6 months after completion of treatment, were included. Patients who have received neo-adjuvant/adjuvant systemic chemotherapy for primary Stage III or IV disease, have > 1 recurrence of EC, have received prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent, or who received prior anticancer therapy, were excluded. 23.9% of randomized patients had dMMR/MSI-H tumours.
- **Primary endpoints** were **PFS** as assessed by the investigator according to RECIST, version 1.1, and **OS**. In the dMMR–MSI-H population, estimated PFS at 24 months was 61.4% (95% CI, 46.3-73.4) vs. 15.7% (95% CI, 7.2-27.0); HR for progression or death, 0.28; 95% CI, 0.16-0.50; p<0.001. Kaplan–Meier estimates of OS at 24 months were 83.3% (95% CI, 66.8-92.0) vs. 58.7% (95% CI, 43.4-71.2); HR 0.30; 95% CI, 0.13-0.70.
- Assessment of **PROs** showed that during the chemotherapy period, the mean change from baseline in EORTC-QLQ-C30 GHS and QoL scores indicated **no differences** between groups. Results were similar in both the overall population and the dMMR–MSI-H population.
- The **original and adapted ESMO-MCBS** were applied, resulting in a **final adjusted magnitude of clinical benefit grade of 4 and 3**, respectively.
- Due to the ongoing status of the RUBY trial, the **risk of bias** was considered **unclear**. However, it is **increased** by the involvement of the sponsor in the collection, analysis, and interpretation of data.
- Besides the ongoing RUBY trial, one further randomized phase III trial (NCT05201547/ DOMENICA) in MMR deficient EC patients comparing chemotherapy alone vs. dostarlimab in first-line advanced/metastatic setting, was identified.
- Considering that only 118 patients (23.9%) participating in RUBY trial had dMMR/MSI-H tumours, more robust phase 3 data is required to assess the efficacy and safety of dostarlimab in this patient population.

First published: 11/2023

Abbreviations: AE=adverse event, AJ=adjustment, AUC=area under the concentration–time curve, BMI=body mass index BSA=body surface area, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, dMMR=mismatch repair deficient, ECOG=Eastern Cooperative Oncology Group, EMA=European Medicines Agency, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer QLQ-C30 Quality of Life Questionnaire C30 (Core), ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FIGO=International Federation of Gynecology and Obstetrics, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GHS=global health score, HIV=human immunodeficiency virus, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, ir=immune-related, IV=intravenous, LSM=least-squares means, MG=median gain, MSI-H=microsatellite instability high, n=number of patients, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health Research, OS=overall survival, PD=progression of disease, PD-1=programmed cell death-1, PD-L1=programmed cell death-ligand 1, PD-L2=programmed cell death-ligand 2, PE=primary endpoint, PF=physical function, PFS=progression-free survival, PM=preliminary grade, PRO=patient-reported outcome, QoL=quality of life, QLQ-EN24=Endometrial Cancer Module, RECIST=Response Evaluation Criteria in Solid Tumors, RT=radiotherapy, SAE=serious adverse event, ST=standard treatment, TMB-H=tumour mutational burden high, ULN=upper limit of normal, VBT=vaginal brachytherapy,

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