Guideline-based treatment of recurrent/metastatic cervical cancer

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What do US guidelines recommend for the treatment of recurrent/metastatic cervical cancer?

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What do NCCN and ASCO guidelines recommend for the first-line treatment of recurrent/metastatic cervical cancer?

NCCN guidelines for R/M cervical cancer: First-line systemic therapy

Preferred regimens

- PD-L1–positive tumours:
  - Pembrolizumab + cisplatin/paclitaxel ± bevacizumab*
  - Pembrolizumab + carboplatin/paclitaxel ± bevacizumab*
- Cisplatin/paclitaxel/bevacizumab*
- Carboplatin/paclitaxel/bevacizumab*

Other recommended regimens

- Cisplatin/paclitaxel
- Carboplatin/paclitaxel
- Topotecan/paclitaxel/bevacizumab
- Topotecan/paclitaxel
- Cisplatin/topotecan
- Cisplatin
- Carboplatin

*An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; PD-L1, programmed death-ligand 1; R/M, recurrent/metastatic.

NCCN. Cervical cancer. V1.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (accessed 19 October 2023).

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ASCO treatment guidelines for R/M cervical cancer

The ASCO treatment guidelines are stratified by resource

Recommended systemic therapy includes:

- **2022 update:** Upfront pembrolizumab and chemotherapy with or without bevacizumab for eligible patients with persistent, recurrent or metastatic cervical carcinoma (± individualized radiation therapy and/or palliative care) in enhanced and maximal settings[1]

- **2016 guideline:** Chemotherapy ± bevacizumab ± individualized radiation therapy and/or palliative care[2]
  - Single-agent chemotherapy (carboplatin or cisplatin) is recommended in basic settings
  - Carboplatin recommended as first-line chemotherapeutic agent
  - Inclusion of bevacizumab with carboplatin or cisplatin and paclitaxel combination in maximal settings

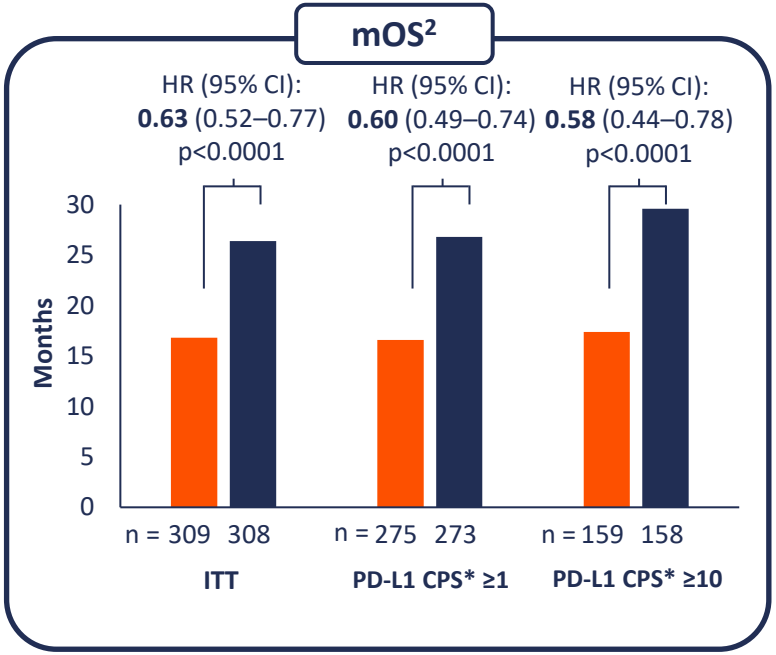
ASCO, American Society of Clinical Oncology; R/M, recurrent/metastatic.

1. Chuang LT, et al. *JCO Glob Oncol.* 2022;8:e2200027; 2. Chuang LT, et al. *J Glob Oncol.* 2016;2:311–40.

What are the latest clinical trial data that support the guideline-recommended preferred first-line treatments for recurrent/metastatic cervical cancer?

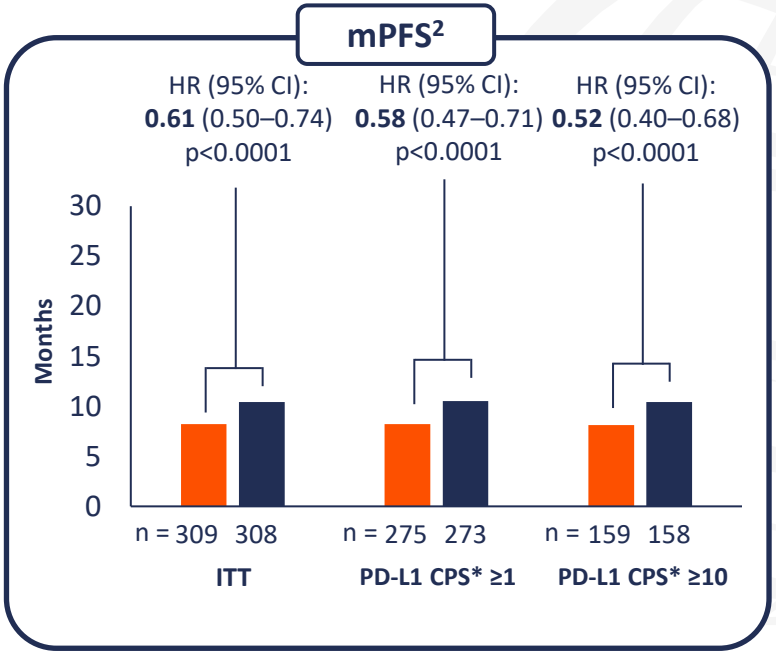
KEYNOTE-826: Pembrolizumab

Pembrolizumab or placebo, + chemotherapy + (per investigator discretion) bevacizumab for persistent, recurrent or metastatic cervical cancer: A multicentre, randomized, double-blind, phase III trial[1]



Placebo + chemotherapy ± bevacizumab group

Pembrolizumab + chemotherapy ± bevacizumab group



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CI, confidence interval; CPS, combined positive score; HR, hazard ratio; ITT, intention to treat; m, median; OS, overall survival;
PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Colombo N, et al. *N Engl J Med*. 2021;385:1856–67; 2. Monk B, et al. Presented at: 2023 ASCO Annual Meeting, Chicago, IL, USA. 2–6 June 2023. Abstr 5500.

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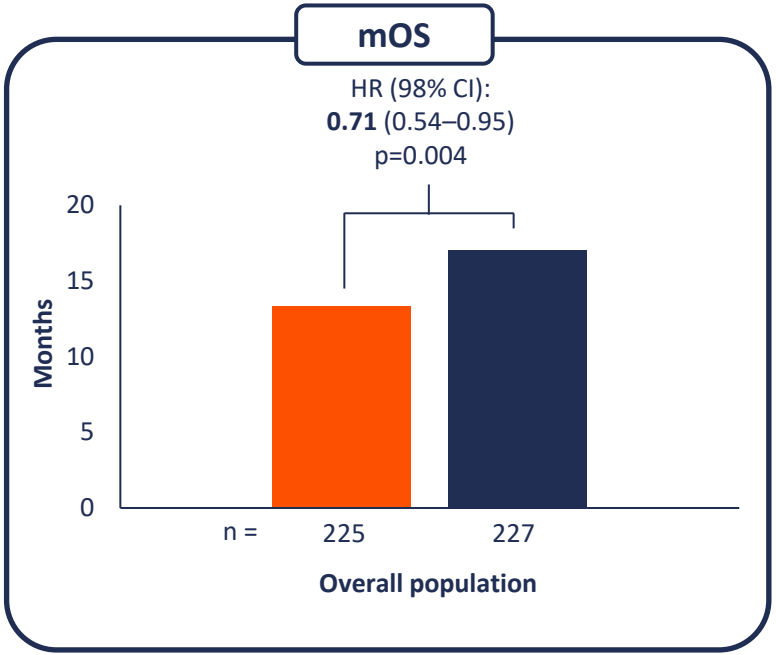
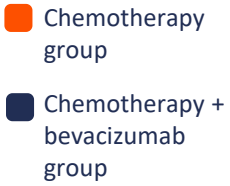
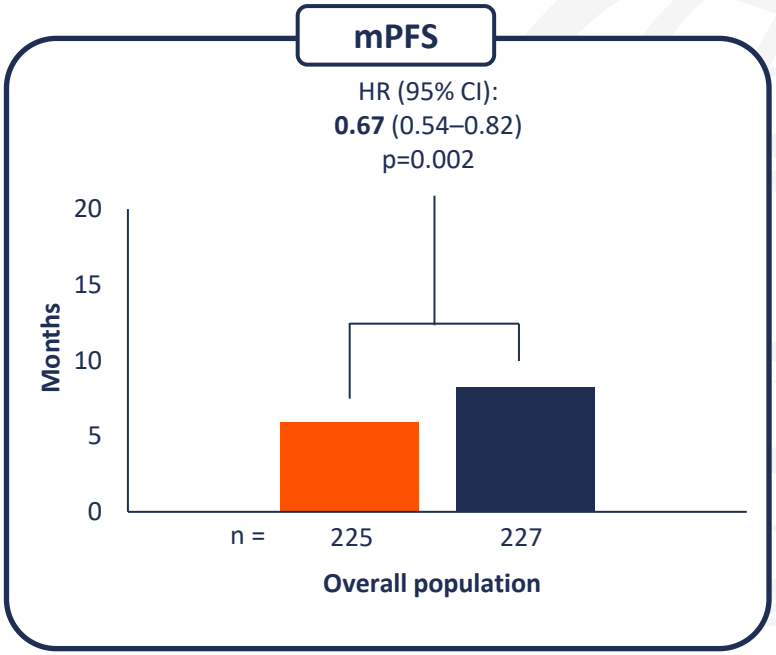
GOG-240 study: Bevacizumab

Chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer: A multicentre, randomized, phase III trial







CI, confidence interval; HR, hazard ratio; m, median; OS, overall survival; PFS, progression-free survival.
Tewari KS, et al. *N Engl J Med.* 2014;370:734–43.

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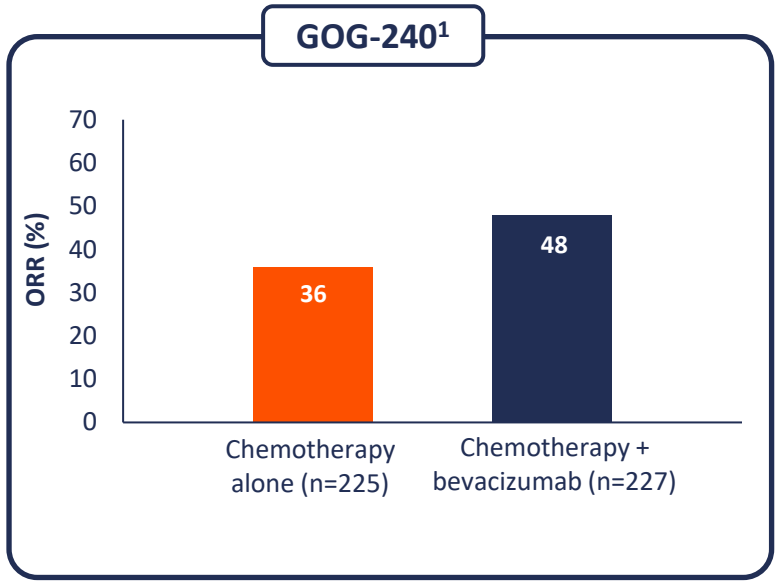
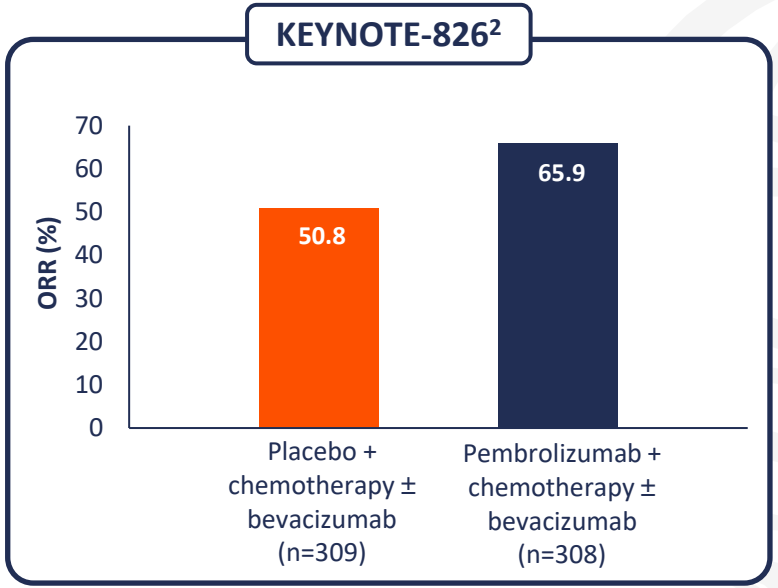
Response rates in GOG-240 and KEYNOTE-826





ORR, objective response rate.

1. Tewari KS, et al. *N Engl J Med.* 2014;370:734–43; 2. Colombo N, et al. *N Engl J Med*. 2021;385:1856–67.

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What do NCCN guidelines recommend for the preferred second-line treatment of recurrent/metastatic cervical cancer?

NCCN guidelines for R/M cervical cancer: Second-line or subsequent systemic therapy

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Pembrolizumab for TMB-H, MSI-H/dMMR or PD-L1–positive tumours • Cemiplimab* • Tisotumab vedotin	• Bevacizumab† • Paclitaxel • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan	• PD-L1–positive tumours: Nivolumab • HER2-positive tumours (IHC 3+ or 2+): Trastuzumab deruxtecan • *RET* gene fusion-positive tumours: Selpercatinib • *NTRK* gene fusion-positive tumours: Larotrectinib, entrectinib

*Cemiplimab is not currently approved by the FDA for cervical cancer. †An FDA-approved biosimilar is an appropriate substitute for bevacizumab
dMMR, mismatch repair deficient; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed death-ligand 1; R/M, recurrent/metastatic; TMB-H, tumour mutational burden-high.

NCCN. Cervical cancer. V1.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (accessed 19 October 2023).

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What are the latest clinical trial data that support the guideline-recommended second-line treatments for recurrent/metastatic cervical cancer?

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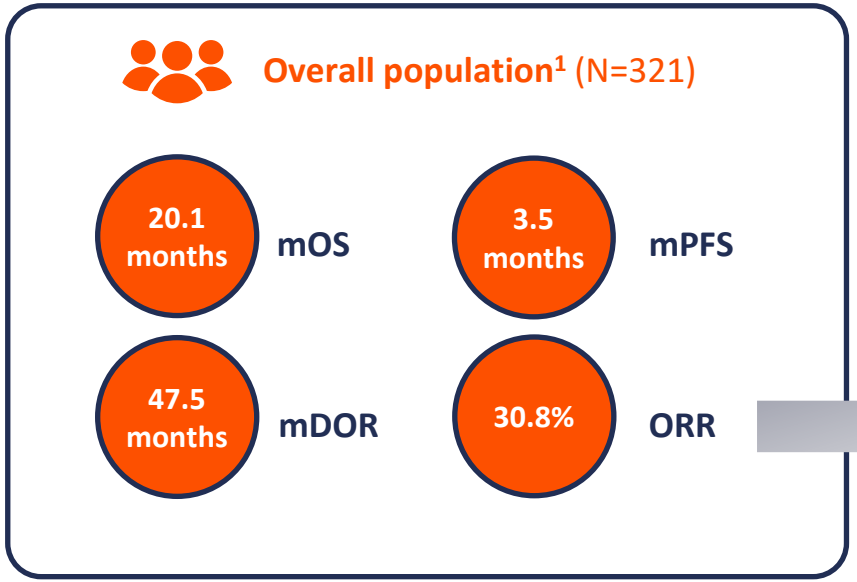
Pembrolizumab: KEYNOTE-158 study

Pembrolizumab in patients with advanced MSI-H/dMMR non-colorectal cancers: A multicohort phase II trial



14.6% ORR in patients with PD-L1– positive advanced cervical cancer (n=82)[2]

dMMR, mismatch repair deficient; DOR, duration of response; m, median; MSI-H, microsatellite instability-high; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Maio M, et al. *Ann Oncol.* 2022;33:929–38; 2. Chung HC, et al. *J Clin Oncol.* 2019;37:1470–8.

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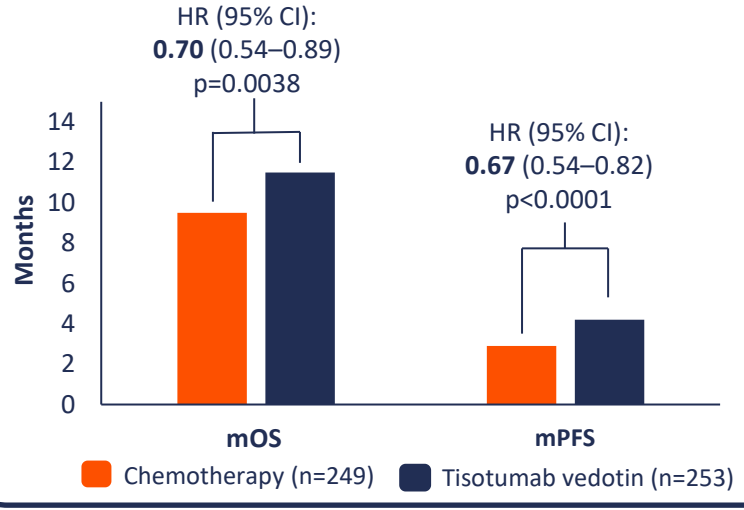
Tisotumab vedotin

Tisotumab vedotin vs chemotherapy* in 2L/3L setting for recurrent or metastatic cervical cancer: A randomized, open-label, phase III trial[1]

innovaTV 301/ENGOT-cx12/GOG-3057 data presented at ESMO 2023:[2]



Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer: A multicentre, open-label, single-arm phase II trial[2]

innovaTV 204/GOG-3023/ENGOT-cx6

Study population (N=101)

12.1 months	mOS
4.2 months	mPFS
8.3 months	mDOR
24%	ORR

*Investigator's choice of topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed.

2L/3L, second or third line; CI, confidence interval; DOR, duration of response; ESMO, European Society for Medical Oncology; HR, hazard ratio; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

1. Vergote IB, et al. *Ann Oncol*. 2023;34, S1276–S1277; 2. Coleman RL, et al. *Lancet Oncol.* 2021;22:609–19.

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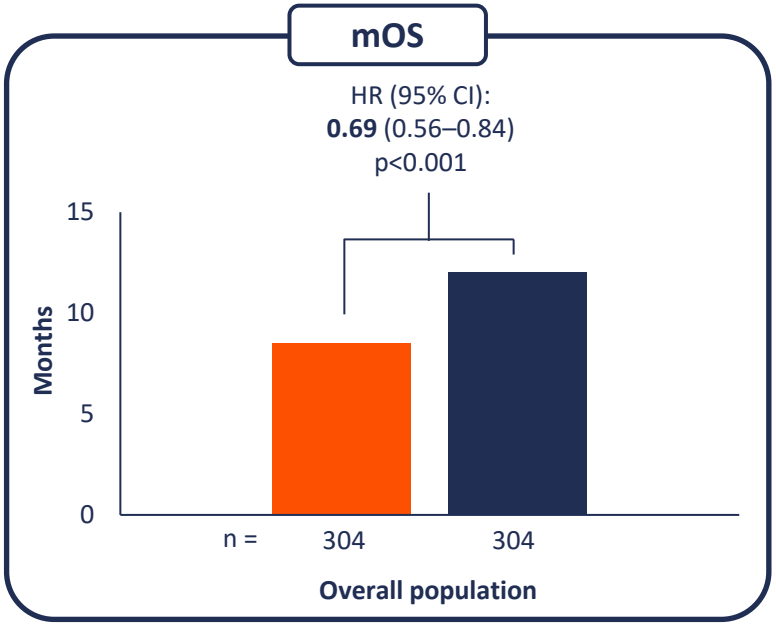
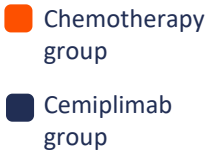
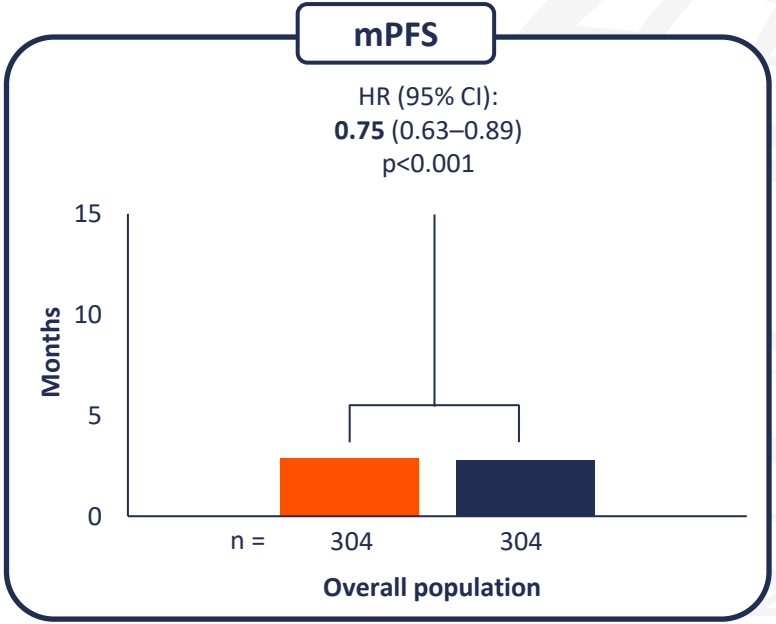
Cemiplimab: EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9

Cemiplimab or single-agent chemotherapy in patients with recurrent or metastatic cervical carcinoma: An open-label, multicentre, randomized, phase III trial







CI, confidence interval; HR, hazard ratio; m, median; OS, overall survival; PFS, progression-free survival.
Tewari KS, et al. *N Engl J Med.* 2022;386:544–53.

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What is your approach to determining the most appropriate guideline-based treatment for each patient?

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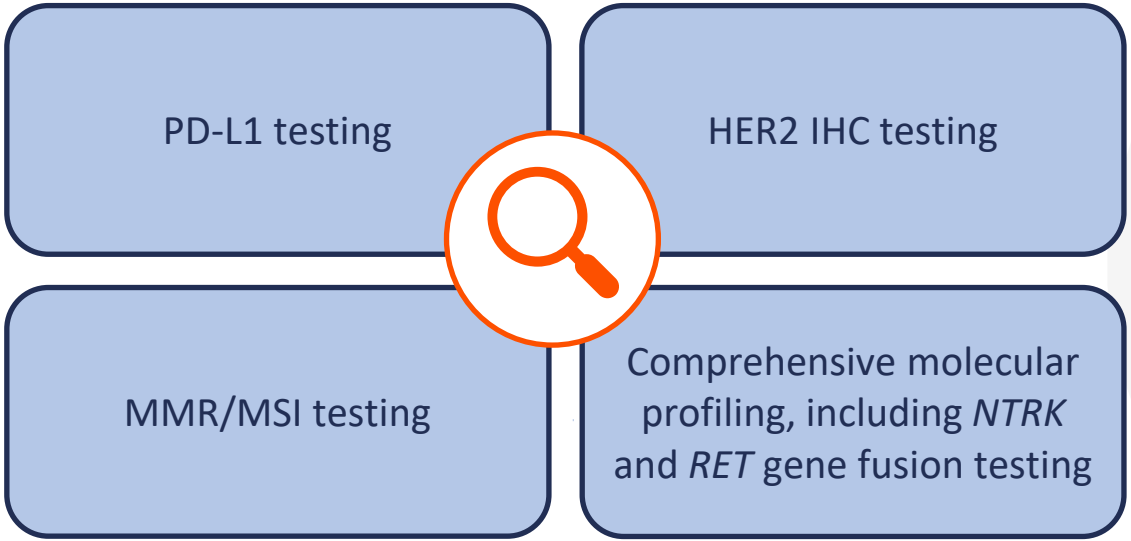
NCCN guidelines for biomarker testing



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed death-ligand 1.

NCCN. Cervical cancer. V1.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (accessed 19 October 2023).

What do European guidelines recommend for the treatment of recurrent/metastatic cervical cancer?

Dr Domenica Lorusso
Gynaecological Oncologist,
La Fondazione Policlinico
Universitario Agostino Gemelli,
Rome, Italy

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What do the current European guidelines recommend for the treatment of recurrent/metastatic cervical cancer?

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ESGO/ESTRO/ESP guidelines for R/M cervical cancer: Systemic therapy

First-line therapy

- Platinum-based chemotherapy ± bevacizumab is recommended for chemotherapy-naive, medically fit patients with R/M disease
  - Carboplatin/paclitaxel and cisplatin/paclitaxel are the preferred regimens
  - Addition of bevacizumab to platinum-based chemotherapy is recommended when the risk of significant GI/GU toxicities has been carefully assessed and discussed with the patient
- PD-L1–positive tumours (CPS ≥1): Addition of pembrolizumab to platinum-based chemotherapy ± bevacizumab is recommended

Second-line therapy

- If patients have not previously received immunotherapy and regardless of PD-L1 tumour status, patients should be offered cemiplimab, an anti-PD-1 agent
- If patients have previously received immunotherapy, chemotherapy is recommended if ECOG PS ≤2 and best supportive care is recommended if ECOG PS >2

Inclusion of patients with R/M disease in clinical trials is strongly recommended

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; ESGO, European Society of Gynaecological Oncology; ESP, European Society of Pathology; ESTRO, European Society for Radiotherapy and Oncology; GI, gastrointestinal; GU, genitourinary; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; R/M, recurrent/metastatic.

Cibula D, et al. *Int J of Gynecol Cancer* 2023;33:649–66.

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ESMO guidelines for R/M cervical cancer: Systemic therapy

Guidelines published in 2017

First-line therapy

- Paclitaxel + cisplatin combined with bevacizumab
- Paclitaxel + carboplatin is an alternative if cisplatin is not suitable

Second-line therapy

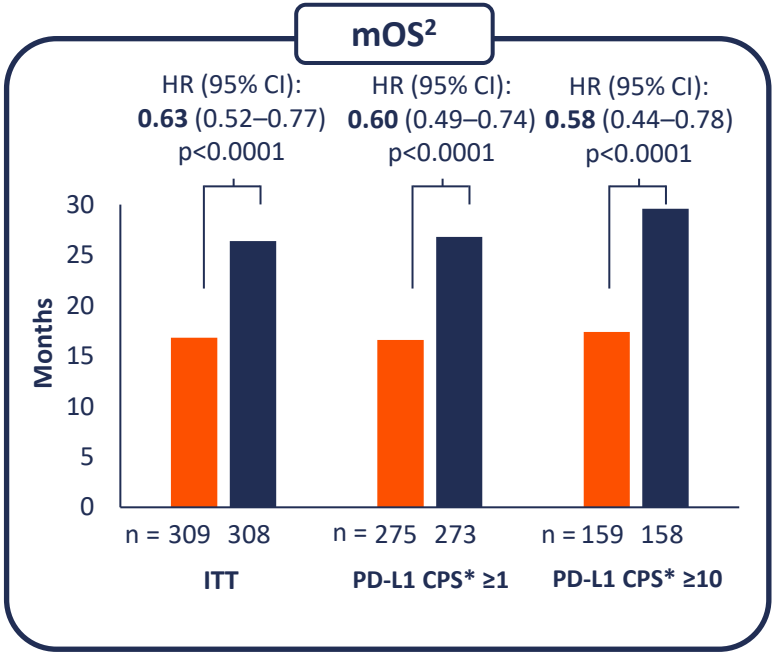
- No recommendation is given about the most effective second-line treatment

ESMO, European Society of Medical Oncology; R/M, recurrent/metastatic.
Marth C, et al. *Ann Oncol.* 2017;28(Suppl. 4):iv72–83

What are the latest clinical trial data that support the European guidelines?

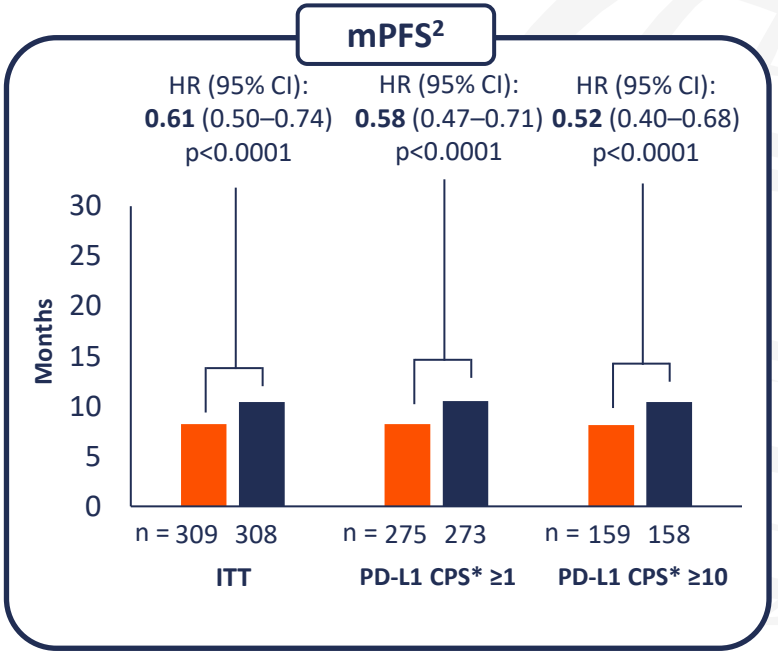
Pembrolizumab: KEYNOTE-826

Pembrolizumab or placebo, + chemotherapy + (per investigator discretion) bevacizumab for persistent, recurrent or metastatic cervical cancer: A multicentre, randomized, double-blind, phase III trial[1]



Placebo + chemotherapy ± bevacizumab group

Pembrolizumab + chemotherapy ± bevacizumab group



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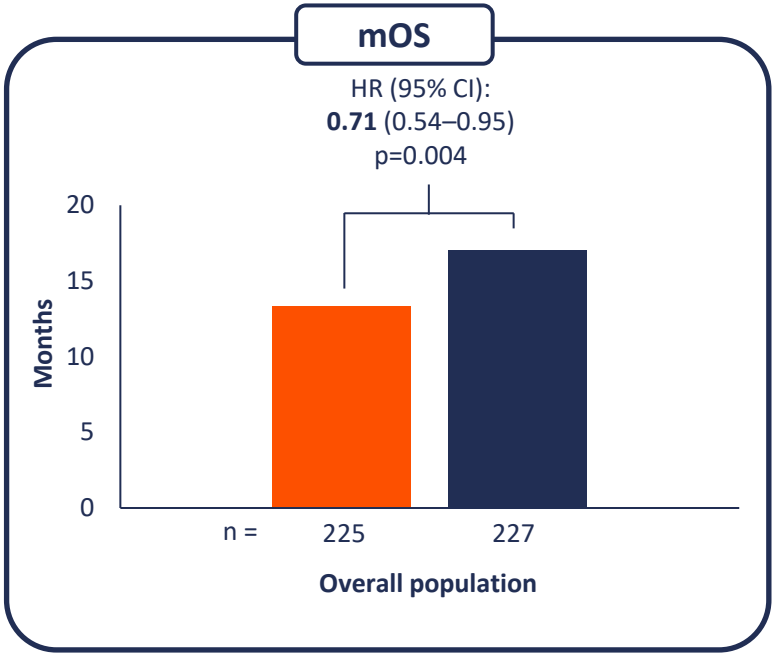
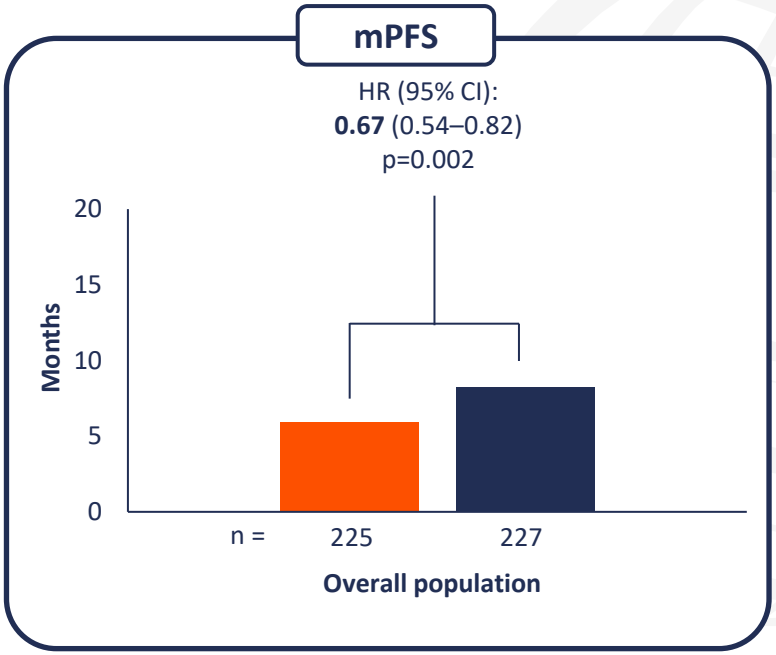


Chemotherapy group

Chemotherapy + bevacizumab group



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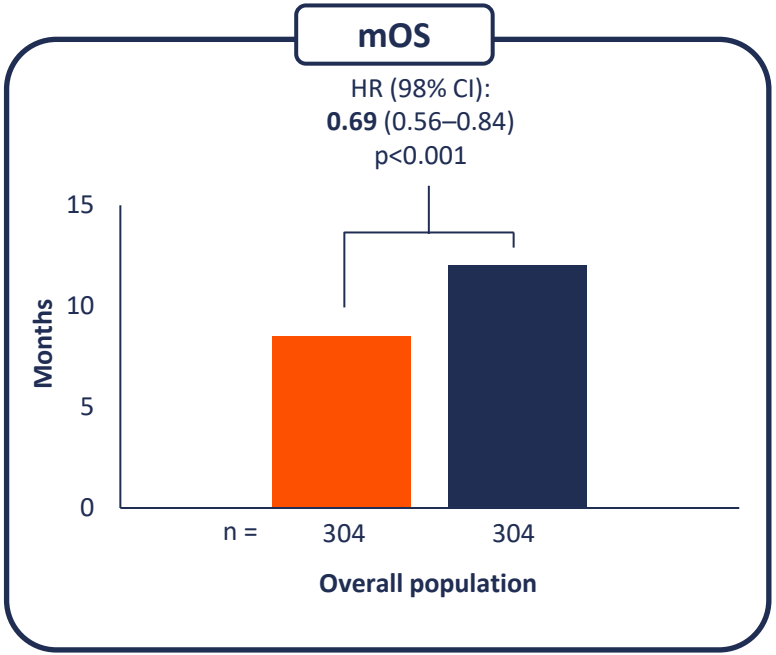

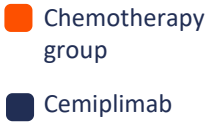

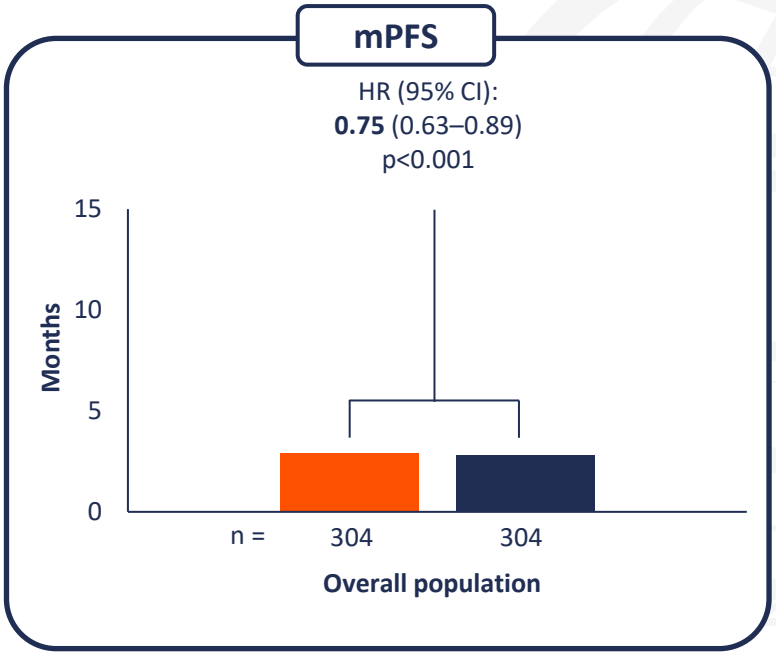

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What is your approach to determining the most appropriate guideline-based treatment for each patient?

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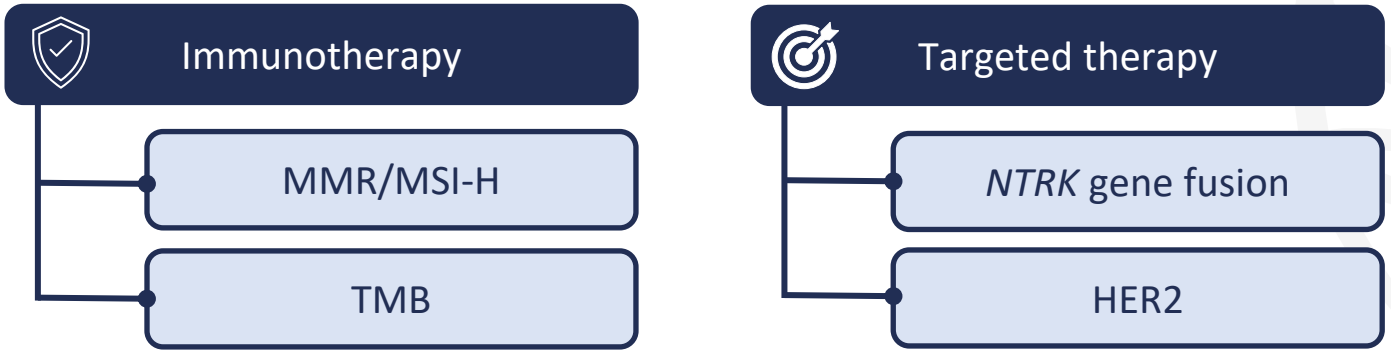
Future considerations for biomarker testing to guide therapy selection

Owing to the increased clinical use of molecular techniques such as NGS and IHC, molecular profiling may help in further personalizing therapy for cervical cancer[1,2]



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; TMB, tumour mutation burden.

1. Chen L, et al. *Front Oncol.* 2021;11:752453; 2. Kim YN, et al. *Front Oncol.* 2023;13:1156973.

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How can we safely use immunotherapies and targeted agents in patients with recurrent/metastatic cervical cancer?

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What are the key safety considerations with immunotherapies for the treatment of recurrent/metastatic cervical cancer?

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ICIs: Overview of common AEs

ICI use is associated with a spectrum of side effects related to the mechanism of action, which is different from other systemic therapies such as cytotoxic chemotherapy[1]

AEs may involve any organ or system of the body, with the following predominating:[1]

Gastrointestinal | **Dermatological** | **Hepatic** | **Endocrine** | **Pulmonary**

Product information for cemiplimab* and pembrolizumab† contains special warnings and precautions for use for various immune-related conditions, including:[2–4]

- Pneumonitis
- Colitis
- Endocrinopathies
- Nephritis
- Hepatitis
- Cutaneous reactions

*Not approved by the FDA for the treatment of cervical cancer. Other fatal and life-threatening immune-mediated adverse reactions have been observed in patients receiving cemiplimab, including paraneoplastic encephalomyelitis, meningitis, myositis, myocarditis and transplant-related adverse reactions. †The following additional clinically significant, immune-mediated adverse reactions have also been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain–Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis, cystitis non-infective, hypoparathyroidism and transplant-related adverse reactions.

AE, adverse event; ICI, immune checkpoint inhibitor; FDA, US Food and Drug Administration.

1. Schneider BJ, et al. *J Clin Oncol.* 2021;39:4073–126; 2. EMA. Cemiplimab SmpC. Available at: www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_en.pdf (accessed Nov 2023); 3. EMA. Pembrolizumab SmPC. Available at: www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf (accessed Nov 2023); 4. FDA. Pembrolizumab PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf (accessed Nov 2023).

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How should patients receiving an immunotherapy be monitored for possible side effects?

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ICIs: Identification of AEs

CBC with differential, CMP, TSH and fT4 should be performed prior to initiating ICI therapy, and intermittently throughout the course of treatment

Pneumonitis

- Symptoms include dyspnoea, persistent cough, chest pain, fever and hypoxia
- If pneumonitis is suspected, high-resolution chest CT should be performed; consider PFTs if CT scan is negative

Colitis

- Diarrhoea is a common symptom; alarm symptoms are pain and haematochezia
- For grade 1 diarrhoea/colitis symptoms, perform CBC, CMP and faecal lactoferrin
- For grade ≥2 symptoms, perform faecal calprotectin and stool infectious analysis

Nephritis

- Manifests as reduced renal function, including rising serum creatinine, low-grade proteinuria and sterile pyuria
- Urinalysis should be considered to evaluate for baseline kidney disease

AE, adverse event; CBC, complete blood count; CMP, comprehensive metabolic panel; CT, computerized tomography; fT4, free thyroxine; ICI, immune checkpoint inhibitor; PFT, pulmonary function test; TSH, thyroid-stimulating hormone.

Brahmer JR, et al. *J Immunother Cancer.* 2021;9:e002435.

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ICIs: Identification of AEs

Hepatitis

- Often asymptomatic; typically manifests as an elevation in alanine transaminase and/or aspartate transaminase serum levels
- LFTs should be checked prior to each ICI infusion, and rechecked weekly for patients experiencing grade 1 or 2 liver toxicities and every 1–2 days for patients with liver toxicities of grade ≥3

Cutaneous reactions

- Symptoms include rash, often accompanied by pruritus
- Monitor for pruritus, development of a rash; be aware of rash with blisters, mucosal involvement or bullous formation

Endocrinopathies

- Symptoms are often non-specific and difficult to diagnose without additional testing
- Thyroid-stimulating hormone and free thyroxine should be monitored prior to beginning ICI therapy and intermittently throughout the course of treatment

AE, adverse event; ICI, immune checkpoint inhibitor; LFT, liver function test.

Brahmer JR, et al. *J Immunother Cancer.* 2021;9:e002435.

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What management strategies can be used if side effects occur with immunotherapy treatment?

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ICIs: Management of AEs

There should be a high level of suspicion that new symptoms are treatment related

Grade 1

- ICI therapy should be continued with close monitoring except for some neurological, haematological and cardiac toxicities

Grade 2

- Consider holding ICIs and resume when symptoms and/or laboratory values revert to grade ≤1
- Corticosteroids (initial dose of 0.5–1 mg/kg/d of prednisone or equivalent) may be administered

Grade 3

- Hold ICIs and initiate high-dose corticosteroids (prednisone 1–2 mg/kg/d or equivalent)
  - Corticosteroids should be tapered, and infliximab may be an option for some toxicities if steroids do not improve symptoms
  - When AEs revert to grade ≤1, rechallenging with ICIs may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended

Grade 4

- Warrants permanent discontinuation of ICIs

AE, adverse event; ICI, immune checkpoint inhibitor; irAE, immune-related AE.

Schneider BJ, et al. *J Clin Oncol.* 2021;39:4073–126.

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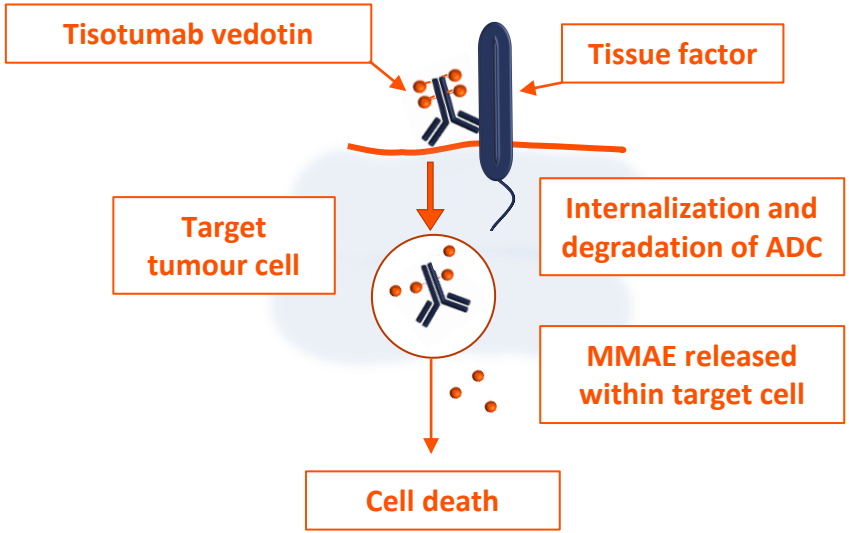
What are the key safety considerations with the antibody–drug conjugate tisotumab vedotin for the treatment of recurrent/metastatic cervical cancer?

Tisotumab vedotin: Mechanism of action

Antibody–drug conjugate



A fully human mAb specific for tissue factor conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable linker, which enables preferential release of MMAE within target cells and concomitant cell death

ADC, antibody–drug conjugate; mAb, monoclonal antibody; MMAE, monomethyl auristatin E.

Arn CR, et al. *J Adv Pract Oncol.* 2023;14:139–52.

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Tisotumab vedotin: Overview of AEs

Common (≥25%) AEs

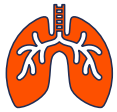
- Laboratory abnormalities*
- Fatigue
- Nausea
- Peripheral neuropathy
- Alopecia
- Epistaxis
- Conjunctival adverse reactions
- Haemorrhage
- Dry eye
- Diarrhoea
- Rash

AEs of special interest

Ocular toxicity
Conjunctival and corneal AEs, dry eye and blepharitis

Bleeding events

Pneumonitis



Peripheral neuropathy

*Decreased haemoglobin, lymphocytes and leukocytes; increased creatinine and PT; prolonged aPTT.
AE, adverse event; aPTT, activated partial thromboplastin time; PT, prothrombin time.
FDA. Tisotumab vedotin PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761208Orig1s000lbledt.pdf (accessed November 2023).

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How should patients receiving tisotumab vedotin be monitored for possible side effects?

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Tisotumab vedotin: Monitoring AEs of special interest

Ocular

- Refer patients to an eye care provider for an ophthalmic exam, including visual acuity and slit lamp exam at baseline, prior to each dose and as clinically indicated

Peripheral neuropathy

- Monitor patients for signs and symptoms of neuropathy, such as paraesthesia, tingling or a burning sensation, neuropathic pain, muscle weakness or dysesthesia

Haemorrhage

- Monitor patients for signs and symptoms of haemorrhage

Pneumonitis

- Monitor patients for pulmonary symptoms indicative of pneumonitis
- Symptoms may include hypoxia, cough, dyspnoea or interstitial infiltrates on radiological exam. Infectious, neoplastic and other causes for such symptoms should be excluded through appropriate investigations

AE, adverse event.

FDA. Tisotumab vedotin PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761208Orig1s000lbledt.pdf (accessed November 2023).

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What management strategies can be used if side effects occur with tisotumab vedotin treatment?

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Tisotumab vedotin: Management of ocular AEs

Reducing the risk of ocular adverse reactions

Adhere to the following recommendations to reduce the risk of ocular adverse reactions:

Ophthalmic exam at baseline, prior to each dose and as clinically indicated

Use cooling eye pads during the infusion

Advise patients to avoid wearing contact lenses for the entire duration of therapy

- Topical corticosteroid eye drops prior to each infusion and for 72 hours after infusion
- Topical lubricating eye drops for the duration of therapy and for 30 days after the last dose
- Topical ocular vasoconstrictor drops prior to each infusion

Management of ocular adverse reactions

- Dose modifications are recommended within the product information based on the adverse ocular reaction that occurs
- Withhold, reduce the dose or permanently discontinue based on the severity of the adverse reaction
- Promptly refer patients to an eye care provider for any new or worsening ocular signs and symptoms

AE, adverse event.

FDA. Tisotumab vedotin PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761208Orig1s000lbledt.pdf (accessed November 2023).

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Tisotumab vedotin: Management of other AEs of special interest

Management of peripheral neuropathy

- For patients experiencing new or worsening peripheral neuropathy, depending on the severity, either withhold dose, then resume at lower dose, or permanently discontinue

Management of haemorrhage

- Treatment should be permanently discontinued for patients experiencing any grade pulmonary or CNS haemorrhage, a second occurrence of a grade 3 haemorrhage in any other location, or a grade 4 haemorrhage in any other location
- For a grade 2 or first occurrence of a grade 3 haemorrhage in any other location, withhold until resolved and then resume treatment at same dose

Management of pneumonitis

- Withhold therapy for patients who develop persistent or recurrent grade 2 pneumonitis and consider dose reduction
- Permanently discontinue in all patients with grade 3 or 4 pneumonitis

AE, adverse event; CNS, central nervous system.

FDA. Tisotumab vedotin PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/761208Orig1s000lbledt.pdf (accessed November 2023).

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