HPV infection and TGF-β: Translating the science into treatments for HPV-associated cancers

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What are the current unmet needs for patients with advanced HPV-associated cancers?

Dr Judith Michels

Medical Oncologist
Institut Gustave Roussy
Villejuif, France

Interview recorded 3 September 2021

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What is the incidence of HPV-associated cancers and how do they vary according to sex?

Number of new HPV-associated cancer cases each year[1,2]

Female[1]

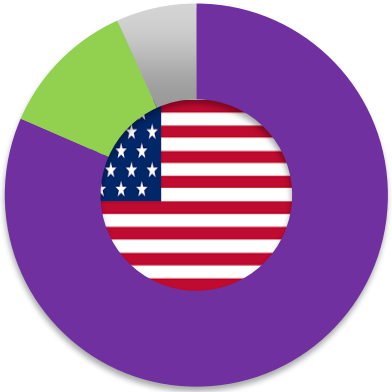
- Cervix 12,143
- Anus 4,751
- Vulva 4,114
- Oropharynx 3,530
- Vagina 867

Female[2]

- Cervix 58,000
- Vagina/vulva 5,100
- Anus 4,200
- Oropharynx 2,800

Male[1]

- Oropharynx 16,245
- Anus 2,332
- Penis 1,348



Male[2]

- Oropharynx 11,000
- Anus 2,700
- Penis 2,700

HPV, human papillomavirus.

1. Centers for Disease Control and Prevention. Cancers Associated with Human Papillomavirus, United States—2013–2017. Available at: www.cdc.gov/cancer/uscs/about/data-briefs/no18-hpv-assoc-cancers-UnitedStates-2013-2017.htm (accessed 15 September 2021); 2. de Martel C, et al. *Int J Cancer.* 2017;141:664–70.

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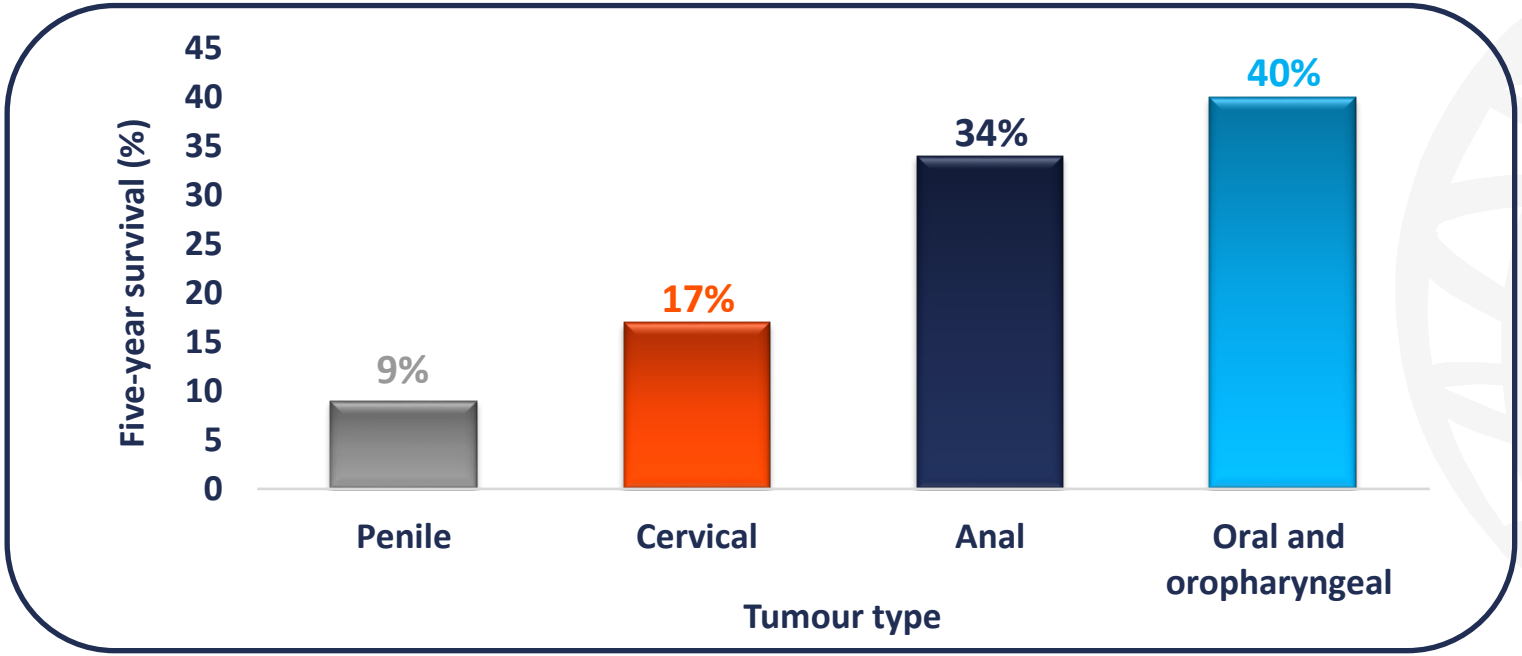
What is the survival rate of patients with advanced HPV-associated cancer?

Five-year relative survival for HPV-associated cancers with distant lesions[1–4]



HPV, human papillomavirus.

1. ASCO Cancer.Net. Penile cancer: Statistics. Available at: www.cancer.net/cancer-types/penile-cancer/statistics (accessed 15 September 2021);
2. ASCO Cancer.Net. Cervical cancer: Statistics. Available at: www.cancer.net/cancer-types/cervical-cancer/statistics (accessed 15 September 2021);
3. ASCO Cancer.Net. Anal cancer: Statistics. Available at: www.cancer.net/cancer-types/anal-cancer/statistics (accessed 15 September 2021);
4. ASCO Cancer.Net. Oral and oropharyngeal cancer: Statistics. Available at: www.cancer.net/cancer-types/oral-and-oropharyngeal-cancer/statistics (accessed 15 September 2021).

What are the primary treatment options for advanced HPV-associated cancers?

Guideline recommendations for the three most common advanced/metastatic HPV-associated cancers

	Tumour type	ESMO	NCCN
Preferred first-line therapy	**Cervical**[1,2]	Cisplatin + paclitaxel + bevacizumab No recommendation given due to low response rates and short duration of response with different cytostatic agents	Combination: carboplatin/cisplatin + paclitaxel + bevacizumab Pembrolizumab for PD-L1-positive or MSI-H/dMMR tumours
Preferred first-line therapy	**Anal**[3,4]	Carboplatin + paclitaxel Cisplatin + 5-FU, carboplatin, doxorubicin, taxane, irinotecan ± cetuximab or combinations. PD-L1 inhibitors where possible in clinical trials	Carboplatin + paclitaxel Nivolumab or pembrolizumab (if not previously received)
Preferred second-line therapy	**Squamous cell carcinoma of the head and neck**[5,6]	Pembrolizumab + platinum-based chemotherapy + 5-FU or pembrolizumab monotherapy (CPS ≥1). Platinum + 5-FU + cetuximab if PD-L1 negative Nivolumab or pembrolizumab (if not previously received)	Pembrolizumab + platinum-based chemotherapy + 5-FU or pembrolizumab monotherapy if PD-L1-positive (CPS ≥1) Nivolumab or pembrolizumab (if not previously received)

5-FU, fluorouracil; CPS, combined positive score; dMMR, deficient mismatch repair; ESMO, European Society of Medical Oncology; HPV, human papilloma virus; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; PD-L1, programmed death-ligand 1.

1. Marth C, et al. *Ann Oncol.* 2017; 28: iv72–iv83; 2. NCCN. Cervical cancer 2020. Available at: www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (accessed 15 September 2021); 3. Rao S, et al. *Ann Oncol*. 2021;32:1087–100; 4. NCCN. Anal cancer. 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/anal.pdf (accessed 15 September 2021); 5. Machiels JP, et al. *Ann Oncol.* 2020;31:1462–75; 6. NCCN. Head and neck cancer. 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (accessed 15 September 2021).

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What are the associated outcomes of the available treatment options for advanced HPV-associated cancers?

Outcomes of clinical trials investigating therapies for the three most common HPV-associated cancers: Cervical

First line[1]

- GOG 240 phase III trial
- **Cisplatin + paclitaxel or paclitaxel + topotecan both ± bevacizumab**
- Patients with metastatic, persistent or recurrent cervical carcinoma
- mOS was significantly prolonged by the addition of bevacizumab (16.8 vs 13.3 months; HR, 0.77; 95% CI, 0.62–0.95; p=0.0068)

Second line[2,3]

- KEYNOTE-158 phase II trial
- **Pembrolizumab**
- Patients with PD-L1-positive tumours
  - mOS was 11 months (95% CI, 9.1–14.1 months)
- Patients with MSI-H/dMMR advanced noncolorectal cancer and failed prior therapy
  - mOS was 23.5 months (95% CI, 13.5 months to not reached)

CI, confidence interval; dMMR, deficient mismatch repair; HPV, human papillomavirus; HR, hazard ratio; mOS, median overall survival; MSI-H, microsatellite instability-high; PD-L1, programmed death-ligand 1.

1. Tewari KS, et al. *Lancet*. 2017;390:1654–63; 2. Chung HC, et al. *J Clin Oncol.* 2019;37:1470–8; 3.Marabelle A, et al. *J Clin Oncol.* 2020;38:1–10.

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Outcomes of clinical trials investigating therapies for the three most common HPV-associated cancers: Anal

First line[1]

- Phase II trial
- **Carboplatin + paclitaxel vs cisplatin + 5-FU**
- Patients with locally recurrent inoperable or metastatic disease
- mOS was 12.3 vs 20 months for cisplatin/5-FU vs carboplatin/paclitaxel, respectively (HR, 2.00; 95% CI, 1.15–3.47; p=0.014)

Second line

- **Nivolumab:** single-arm phase II trial[2]
- Patients with treatment-refractory metastatic squamous cell carcinoma of the anal canal previously treated for advanced disease
- Response according to RECIST was 24% (95% CI, 15–33)

- **Pembrolizumab:** KEYNOTE-028 phase Ib trial[3]
- Patients with PD-L1 positive (≥1%) recurrent carcinoma of the anal canal
- 17% overall response rate (95% CI, 5–37)

5-FU, fluorouracil; CI, confidence interval; dMMR, deficient mismatch repair; HPV, human papillomavirus; HR, hazard ratio; mOS, median overall survival; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Rao S, et al. *J Clin Oncol.* 2020;38:2510–8; 2. Morris VK, et al. *Lancet Oncol.* 2017;18:446–53; 3. Ott PA, et al. *Ann Oncol.* 2017;28:1036–41.

Outcomes of clinical trials investigating therapies for the three most common HPV-associated cancers: Head and neck

First line[1]

- **Pembrolizumab vs pembrolizumab + chemotherapy vs cetuximab + chemotherapy:** KEYNOTE-048 phase III trial
- Untreated locally incurable recurrent or metastatic HNSCC
- Pembrolizumab + chemotherapy significantly improved OS vs cetuximab + chemotherapy in high (HR, 0.60; 95% CI, 0.45–0.82; p=0.0004) and low (HR, 0.65; 95% CI, 0.53–0.80; p<0.0001) PD-L1 expressing populations

Second line

- **Nivolumab vs standard single-agent therapy:** phase III trial[2]
- Recurrent HNSCC with progression after platinum-based chemotherapy
- mOS was 7.5 months (95% CI, 5.5–9.1) vs 5.1 months (95% CI, 4.0–6.0) for nivolumab vs standard therapy, respectively (HR, 0.70; 97.73% CI, 0.51–0.96; p=0.01)

- **Pembrolizumab vs standard of care therapy:** phase III trial KEYNOTE-040 trial[3]
- Recurrent/metastatic HNSCC with progression during or after platinum-based chemotherapy
- mOS was 8.4 months (95% CI, 6.4–9.4) vs 6.9 months (95% CI, 5.9–8.0) for pembrolizumab vs standard therapy, respectively (HR, 0.80; 95% CI, 0.65–0.98; p=0.0161)

CI, confidence interval; HNSCC, head and neck squamous cell carcinomas; HPV, human papillomavirus; HR, hazard ratio; mOS, median overall survival; OS, overall survival; PD-L1, programmed death-ligand 1.

1. Burtness B, et al. *Lancet*. 2019.;394:1915–28; 2. Ferris RL, et al. *N Engl J Med*. 2016;375:1856–67; 3. Cohen EEW, et al. *Lancet.* 2019;393:156–67.

How can we improve outcomes for patients with HPV-associated cancers in the future?

HPV vaccine coverage by country

Country	Female	Male
Belgium	90% (in the Flemish community)	
UK	84% (three doses; 2017–2018)	
Australia	80%	76%
Austria	60–65%	
USA	43%	31%
Germany	43% (2017)	
Denmark	36% (two doses; 2017)	
France	28%	

HPV, human papillomavirus.

Institute National du Cancer. Available at: www.e-cancer.fr/Expertises-et-publications/Le-point-sur/10-arguments-sur-la-vaccination-contre-les-HPV (accessed 15 September 2021).

Future directions to improve outcomes

Increased uptake of prophylactic vaccines[1]

High HPV vaccine coverage has a substantial impact on reduced HPV infections, anogenital warts and preinvasive cervical lesions

Improved methods for early diagnosis[2]

Improved immunodiagnostic methods to detect the antigen in tumours or cells *in situ,* or to detect antibodies in sera or exocrine samples

Ongoing clinical research into new therapies[3]

- Therapeutic vaccines
- Immuno-oncology
- T-cell-based therapy
- Anti-TGF-β agents
- Combination approaches

More effective treatments in later stage metastatic cancers[4]

Patients with cervical cancer with distant metastases, either at initial presentation or at relapse, are rarely curable

HPV, human papillomavirus; TGF-β, transforming growth factor beta.

1. Garland SM, et al. *Clin Infect Dis*. 2016;63:519–27; 2. Dong Z, et al. *Front Immunol*. 2021;11:586796; 3. Fakhr E, et al. *Immunology*. 2021;163:33–45;
4. NCCN. Cervical cancer. 2020. Available at: www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (accessed 15 September 2021).

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What is the link between HPV and TGF-β in HPV-associated cancers?

Dr Andrew Sikora

Professor of Head and Neck Surgery
Director of Research
Department of Head and Neck Surgery
MD Anderson Cancer Center
Houston, TX, USA

Interview recorded 9 September 2021

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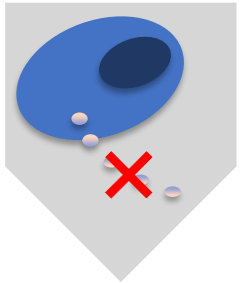
What are the immune evasion strategies by which HPV establishes persistent infection?

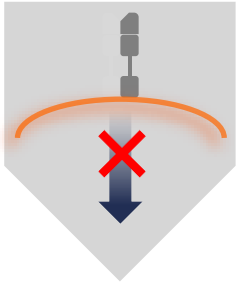
Intrinsic immune evasion mechanisms exploited by HPV oncoproteins

Suppress innate immune sensing and cytokine production



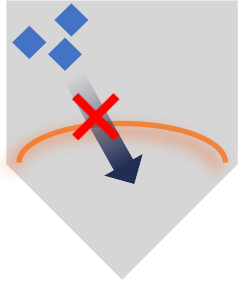
- Suppress TLR9 and CXCL14 transcription
- Downregulation of cGAS–STING cytosolic DNA-sensing system
- Degradation of pro-IL-1b

Suppress PRR-induced signal transduction and type I IFN signalling



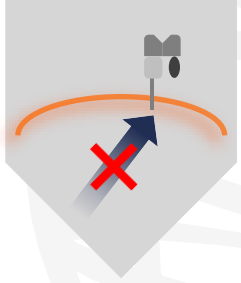
- Inhibit TRAF3 activation
- Prevent IRF transcriptional activity in the nucleus
- Decrease phosphorylation of STAT1 and STAT2

Suppress NF-κB signalling pathway



- Prevent the nuclear translocation of NF-κB
- Downregulate the NF-κB signalling pathway

Suppress antigen presentation by MHC I and CD1d



- Block transport of MHC I and CD1d proteins to the cell surface
- Genetic repression of MHC I, LMP2 and TAP1

CD1d, cluster of differentiation 1d; cGAS–STING, cyclic GMP–AMP synthase–stimulator of interferon genes; CXCL14, C-X-C motif chemokine ligand 14; HPV, human papillomavirus; IFN, interferon; IL, interleukin; IRF, interferon regulatory transcription factor; LPM2, latent membrane protein 2; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PRR, pathogen recognition receptor; STAT, signal transducer and activator of transcription; TAP1, transporter associated with antigen processing 1; TLR9, toll-like receptor 9; TRAF3, tumour necrosis factor receptor associated factor 3.

Zhou C, et al. *Front Oncol*. 2019;9:682.

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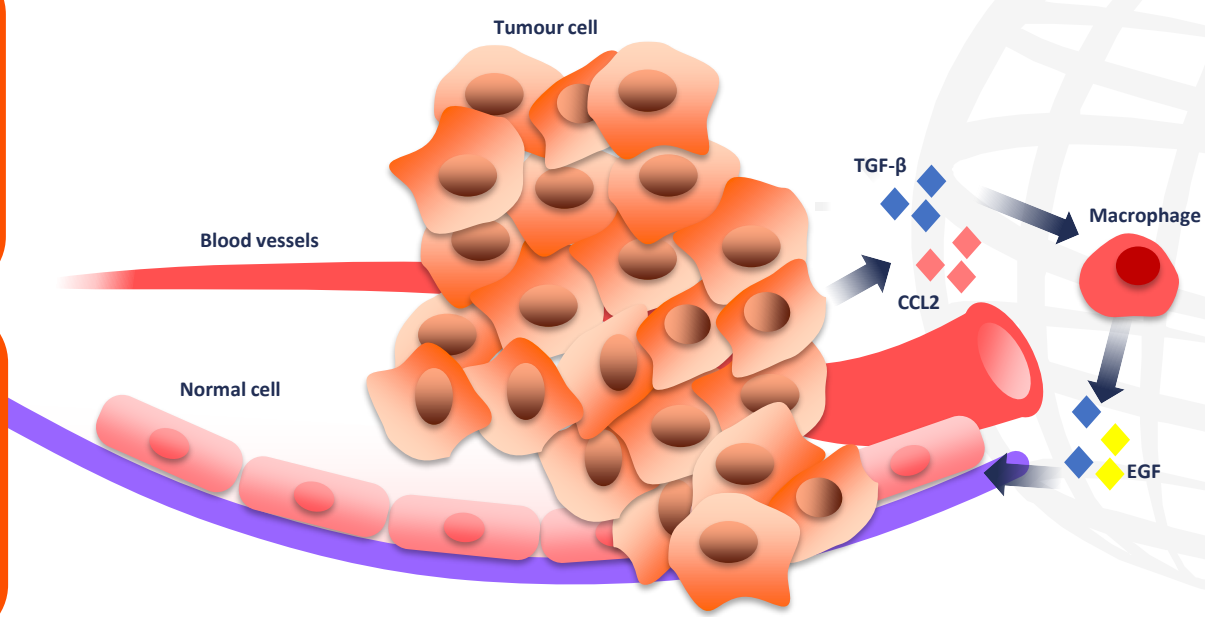
What are the primary features of the tumour microenvironment for HPV-positive tumours?

The tumour microenvironment of HPV-associated cancer is highly complex

The HPV-positive TME includes high levels of cytokines, chemokines and growth factors, including IL-10, CCL2, IL-6, TGF-β, TNF-α and EGF

The TME supports tumour progression through provision of intermediate metabolites, cytokines/chemokines and growth factors to promote tumour cell proliferation, invasion and metastasis



CCL2, C–C motif chemokine ligand 2; EGF, epidermal growth factor; HPV, human papillomavirus; IL, interleukin; TGF-β, transforming growth factor beta; TME, tumour microenvironment; TNF-α, tumour necrosis factor alpha.

Lechien JR, et al. *Cancers.* 2020;12:1060.

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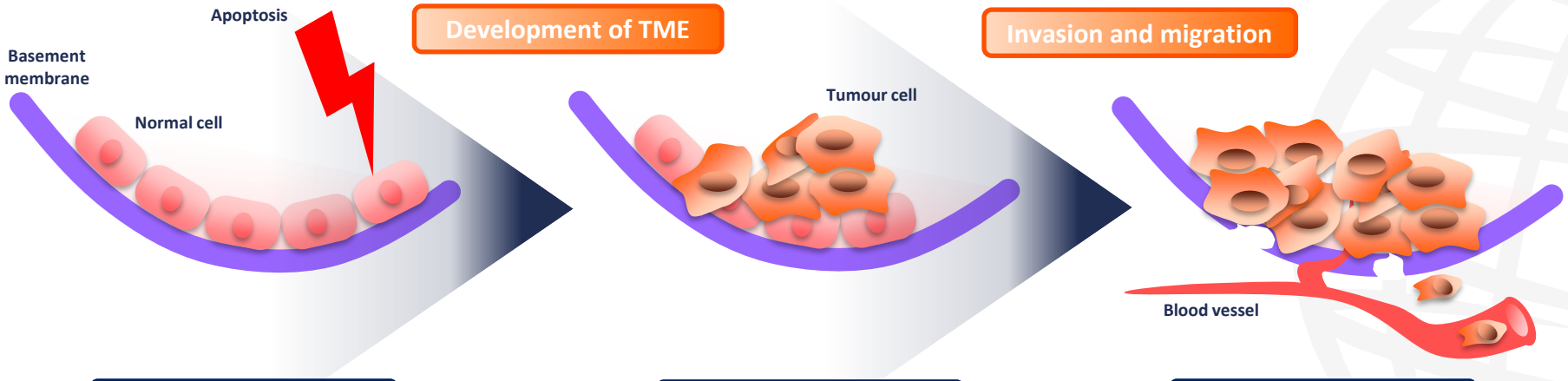
What is the dual role played by TGF-β in the tumour microenvironment?

Role of the TGF-β signalling pathway in the pathogenesis of HPV-associated cancer



Normal epithelium

TGF-β signalling mediates cell cycle arrest and enhances apoptosis

Early-stage cancer

TGF-β signalling induces epithelial cell overproliferation and inhibits apoptosis

Advanced-stage cancer

TGF-β signalling induces epithelial-to-mesenchymal transition

HPV, human papillomavirus; TGF-β, transforming growth factor beta; TME, tumour microenvironment.

Xue VW, et al. *Cancers (Basel).* 2020;12:3099.

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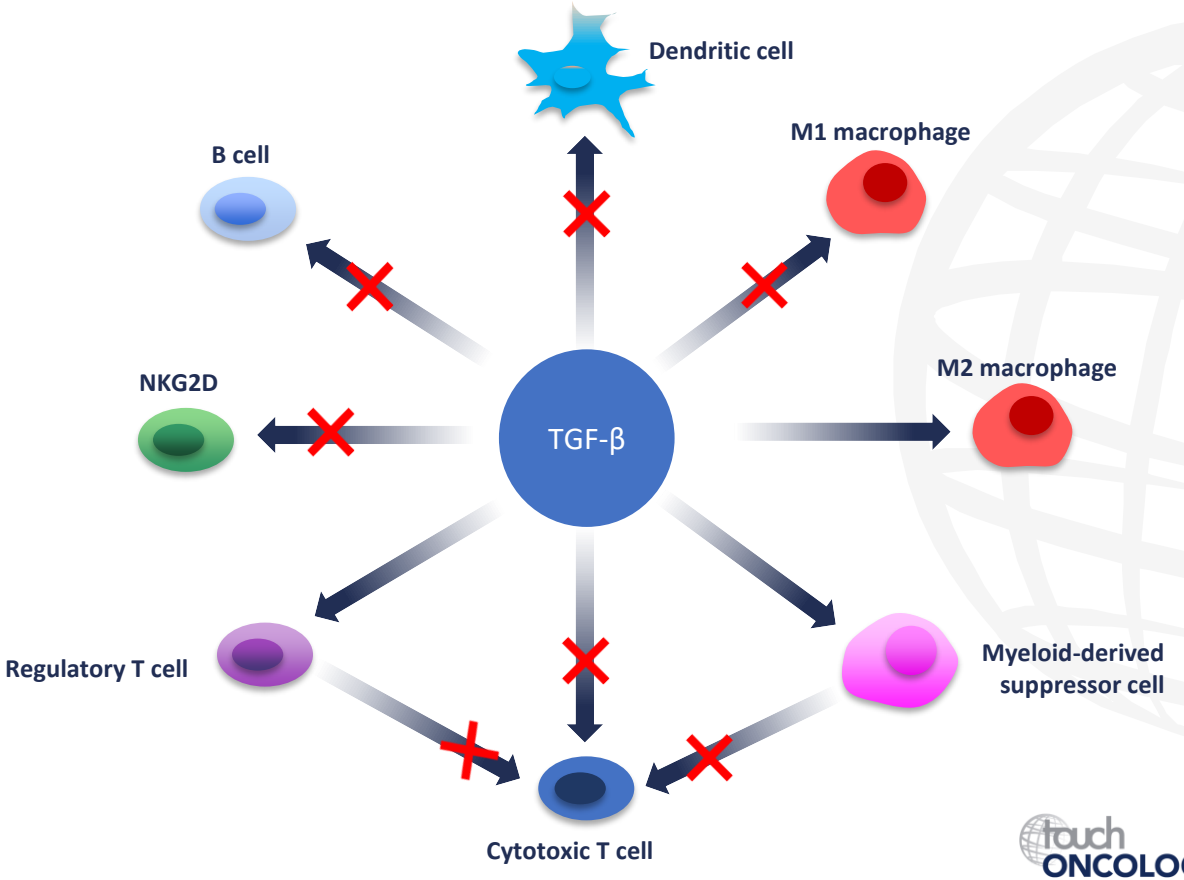
What is the impact of TGF-β on immune cells in HPV-associated cancer?

TGF-β regulation of the cells of the immune system

Impacts on:

- Immune surveillance
- Innate immune system
- Adaptive immune system



TGF-β, transforming growth factor beta.

Yang L, et al. *Trends Immunol.* 2010;31:220–7.

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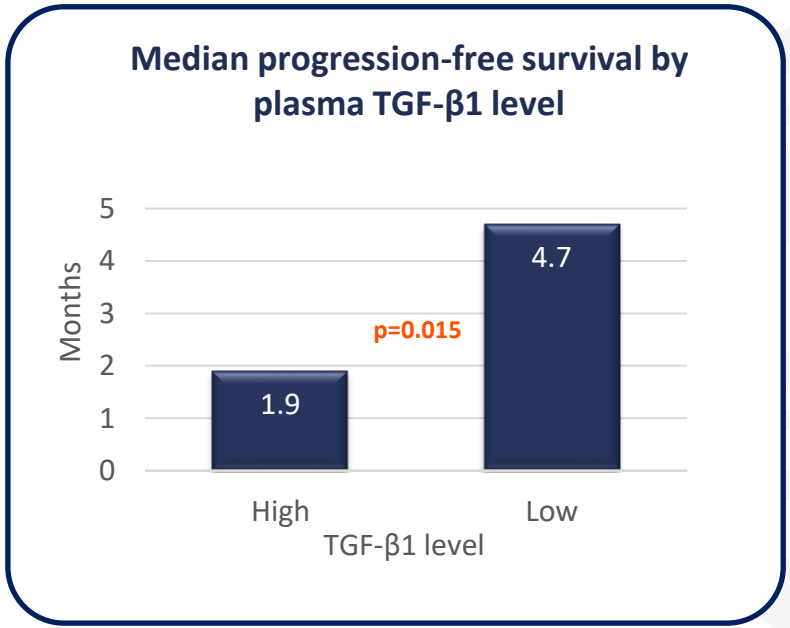
How could TGF-β expression affect outcomes in patients with SCCHN?

The link between patient outcomes and TGF-β in SCCHN

Phase II trial of patients with recurrent and/or metastatic SCCHN who received cetuximab-based therapy

Arm A: cetuximab 400 mg/m2 IV on day one followed by 250 mg/m2 IV weekly
Arm B: same dose/schedule + 400 mg sorafenib PO twice a day



IV, intravenous; PO, oral; SCCHN, squamous cell carcinoma of the head and neck; RFS, recurrence free survival; TGF-β, transforming growth factor beta.
Gilbert J, et al. *Oral Oncol*. 2015;51:376–82.

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What therapeutic approaches targeting HPV and TGF-β are being investigated for HPV-associated cancer?

Dr Krishnansu Tewari

Professor and Division Director
Division of Gynecologic Oncology
University of California
Irvine, CA, USA

Interview recorded 7 September 2021

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How are immuno-oncology therapies contributing to the treatment of HPV-associated cancers?

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Role of immunotherapy in HPV-associated cancer

Current NCCN guidelines

- **Cervical cancer**[1]
  - Second-line pembrolizumab for PD-L1-positive or MSI-H/dMMR tumours
- **Anal cancer**[2]
  - Second-line nivolumab or pembrolizumab (if not previously received)
- **Squamous cell carcinoma of the head and neck**[3]
  - First-line pembrolizumab + platinum-based chemotherapy + 5-FU or pembrolizumab monotherapy if PD-L1-positive (CPS ≥1)
  - Second-line nivolumab or pembrolizumab (if not previously received)

Limited overall response rate to immunotherapy and increasing interest in identifying predictive biomarkers and alternative treatment options[4]

5-FU, fluorouracil; CPS, combined positive score; dMMR, deficient mismatch repair; HPV, human papillomavirus; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; PD-L1, programmed death-ligand 1.

1. NCCN. Cervical cancer. 2020. Available at: www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (accessed 15 September 2021);
2. NCCN. Anal cancer. 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/anal.pdf (accessed 15 September 2021);
3. NCCN. Head and neck cancer. 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (accessed 15 September 2021);
4. Wang HC, et al. *Int J Mol Sci.* 2020;21:7621.

Immunotherapy in cervical cancer: Future directions

- **Cemiplimab**[1]
  - Phase III trial of cemiplimab vs single-agent chemotherapy following progression on first-line platinum-based chemotherapy ± bevacizumab
  - Patients with squamous cell histology had a median OS of 11.1 months with cemiplimab vs 8.8 months with chemotherapy (HR, 0.73; p=0.003)
- **Balstilimab**[2]
  - Phase II clinical trial of balstilimab in patients with previously-treated, recurrent/metastatic cervical cancer
  - ORR was 15% (95% CI, 10.0–21.8%)
  - Phase II trial of balstilimab, alone and in combination with zalifrelimab, in patients with recurrent/metastatic cervical cancer who progressed after prior platinum-based chemotherapy, currently underway (NCT03495882)
- **Pembrolizumab (first line)**
  - Phase III trial of pembrolizumab plus chemotherapy (paclitaxel plus cisplatin or paclitaxel plus carboplatin) administered with or without bevacizumab as a first-line treatment for persistent, recurrent or metastatic cervical cancer[3]
  - Interim analysis reported that pembrolizumab plus platinum-based chemotherapy ± bevacizumab demonstrated statistically significant improvements in OS and PFS compared to the same platinum-based chemotherapy regimens with or without bevacizumab alone, regardless of PD-L1 status[4]

CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Tewari KS, et al. ESMO Congress 2021. Abstract VP4-2021. Presented 12 May 2021; 2. O'Malley DM, et al. *Gynecol Oncol*. 2021:S0090-8258(21)01316-0; 3. Fujiwara K, et al. *Ann Oncol.* 2019;30:IX89–90; 4. Merck. Press release. 22 June 2021. Available at: https://bit.ly/3BMwsMG (accessed 15 September 2021).

What are the current data supporting the targeting of TGF-β for the treatment of HPV-associated cancers?

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Trials targeting TGF-β in treating HPV-associated cancers

Cervical cancer

- **Phase I and II studies in patients with immune checkpoint inhibitor-naive, recurrent or metastatic cervical cancer treated with bintrafusp alfa monotherapy[1]**
  - At time of analysis, 39 patients had received bintrafusp alfa for a median duration of 2.8 months (range, 0.5–19.3)
  - In patients who received at least one line of prior platinum doublet therapy, ORR was 26.5% and DCR was 32.4%
  - Grade ≥3 TRAEs occurred in eight (20.5%) patients (anaemia, colitis, gastroparesis, upper gastrointestinal haemorrhage, keratoacanthoma, cystitis noninfective, haematuria, pneumonitis, rash macular [n=1 each])

Multiple tumour types

- **Phase I and II trials of patients with advanced, pre-treated, checkpoint inhibitor-naïve HPV-associated cancers (cervical, anal, vaginal, rectal and head and neck SCC)[2]**
  - ORR in the checkpoint inhibitor-naive, full-analysis population was 30.5% (95% CI, 19.2–43.9%)
  - Grade 3/4 adverse events were reported in 27.1% of patients

Head and neck cancer

- **Phase I trial of patients with pre-treated oesophageal SCC[3]**
  - ORR was 10.0% (95% CI, 2.1–26.5)
  - Grade 3/4 adverse events were reported in 23.3% of patients
- **Phase I trial of patients with previously treated head and neck SCC[4]**
  - ORR was 13% (95% CI, 4–29%)
  - Grade 3 TRAEs were reported in 11 patients (34%), with no grade 4 TRAEs

CI, confidence interval; DCR, disease control rate; HPV, human papillomavirus; ORR, overall response rate; SCC, squamous cell carcinoma; TGF-β, transforming growth factor beta; TRAE, treatment-related adverse event.

1. Strauss J, et al. 2021 ASCO Annual Meeting. Abstract 5509; 2. Strauss J, et al. *J Immunother Cancer*. 2020;8:e001395; 3. Lin CC, et al. *Target Oncol.* 2021;16:447–59; 4. Cho BC, et al. *J Immunother Cancer*. 2020;8:e000664.

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What are the ongoing investigations regarding therapeutic vaccines either alone or in combination with other immunotherapeutic agents for treating HPV-associated cancers?

Therapeutic vaccines in combination with checkpoint inhibitors

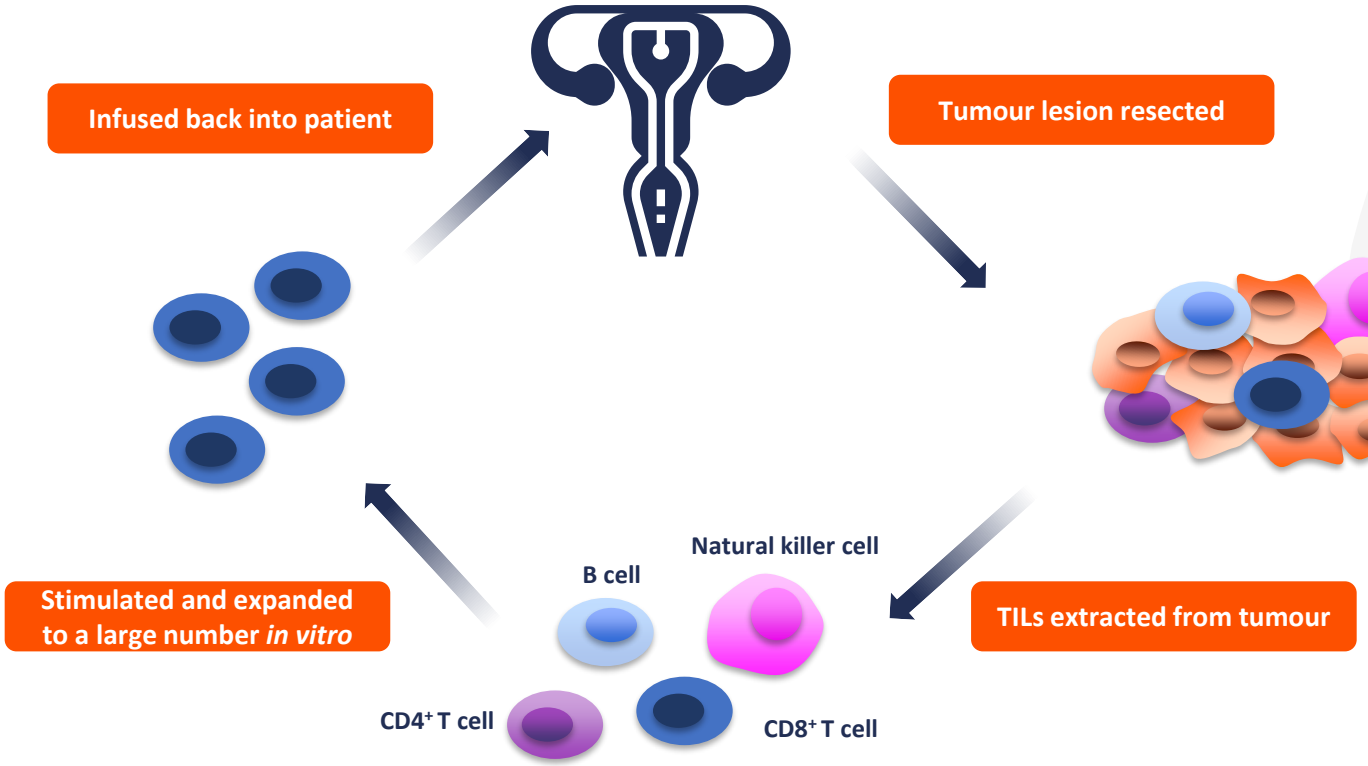
NCT #[1]	Phase	Combination	Tumour type	Status
NCT04287868[2]	II	PDS0101 + bintrafusp alfa and NHS-IL12	Locally advanced or metastatic HPV-associated malignancies	Completion Jan 2022
NCT03439085[2]	II	MEDI0457 + durvalumab	Cervical, anal, penile, vulvar or vaginal cancer positive for HPV16 and/or HPV18	Completion Dec 2021
NCT02426892[2]	II	ISA101 + nivolumab	Incurable HPV16-positive solid tumours including OPSCC, cervical, vulvar, vaginal, anal and penile cancer	Completed
NCT03946358[2]	II	UCPVax + atezolizumab	Locally advanced or metastatic HPV-positive cancers, anal cancer, head and neck carcinoma, cervical and vulvar carcinoma	Completion Sep 2022
NCT04260126[2]	II	PDS0101 + pembrolizumab	Recurrent, metastatic or persistent HNSCC; confirmed HPV16 infection; confirmed tumour PD-L1 expression	Completion Mar 2024
NTC03669718[2]	II	ISA101b + cemiplimab	HPV16-positive OPSCC	Completion Nov 2022
NCT04369937[2]	II	ISA101b + pembrolizumab + radiation + cisplatin	HPV-associated HNSCC	Completion Jun 2022
NCT04432597[3]	I/II	PRGN-2009 ± bintrafusp alfa	HPV-positive vulvar, vaginal, penile, rectal, anal, oropharyngeal and cervical cancer	Completion Oct 2023

HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma; PD-L1, programmed death-ligand 1.

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ (accessed 15 September 2021); 2. Rumfield CS, et al. *J Clin Cell Immunol.* 2021;12:608;
3. Floudas CS, et al. *J Clin Oncol*. 2021;39:TPS6092.

What is the potential role of T-cell-based therapies against HPV onco-antigens for the treatment of HPV-induced cancers?

The principles of TIL-based therapy



TIL, tumour-infiltrating lymphocyte.
Wang S, et al. *BMC Medicine.* 2021;19:140.

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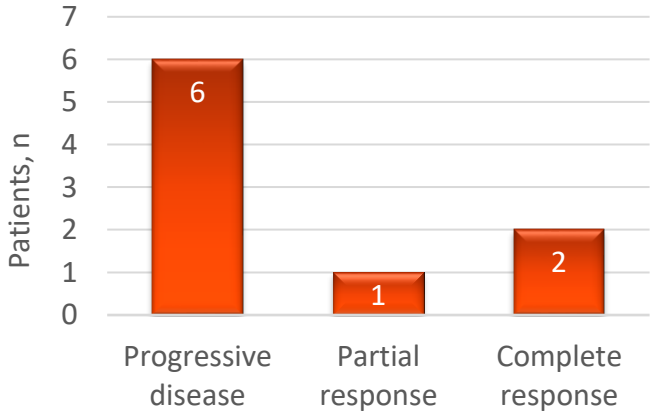
The role of TIL-based therapies in HPV-associated cancers

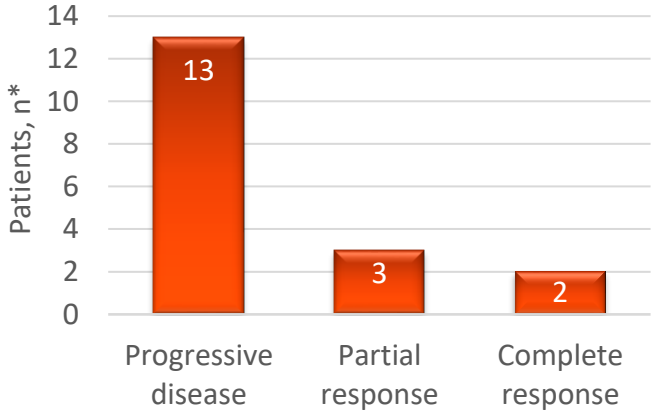
Trial of nine patients with metastatic or locally advanced refractory or recurrent cervical cancer following previous treatment[1]

Patients were treated with a single infusion of tumour-infiltrating T cells selected, when possible, for HPV E6 and E7 reactivity



Phase II trial of 29 patients with metastatic HPV-associated cancer; cervical cancer and non-cervical cancer cohorts[2]

TIL infusion was preceded by a lymphocyte-depleting conditioning regimen and followed by systemic high-dose aldesleukin



*Cervical cancer cohort.
HPV, human papillomavirus; TIL, tumour-infiltrating lymphocyte.
1. Stevanović S, et al. *J Clin Oncol.* 2015;33:1543–50; 2. Stevanović S, et al. *Clin Cancer Res*. 2019;25:1486–93.

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What does the future look like for the combination of therapies for the treatment of HPV-associated cancers?