5 Things You Need to Know in Cervical Cancer Treatment

New and Emerging Agents

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Global Burden of Cervical Cancer

- Half million cases diagnosed each year
- Most cases occur in developing nations
  - Many cases linked to lack of HPV vaccination
- 250,000 deaths annually
- Achieving disease prevention and curative outcomes represents one of the highest unmet needs in medicine

Global Burden of Cervical Cancer (cont'd)

- Affected population relatively homogeneous
  - Poor access to care
  - Marginalized populations
  - Did not receive HPV vaccine
- Rare disease in US
  - ~12,000 cases/year, most low-stage disease
  - ~3,000-4,000 locally advanced/metastatic disease requiring high-quality chemotherapy and radiation

Cervical Cancer: *Frontline Failure*

- Many factors to consider in choosing therapy following frontline failure
  - Patient health and performance status
  - Personal preferences
  - Progression/location of recurrence
  - Prior therapy, *for example*
    - > Surgery without radiation, consider chemoradiation
    - > Optimal frontline therapy, consider combination chemotherapy
    - > Use of bevacizumab or pembrolizumab regimens
    - > Antibody-drug conjugate: tisotumab vedotin-tftv

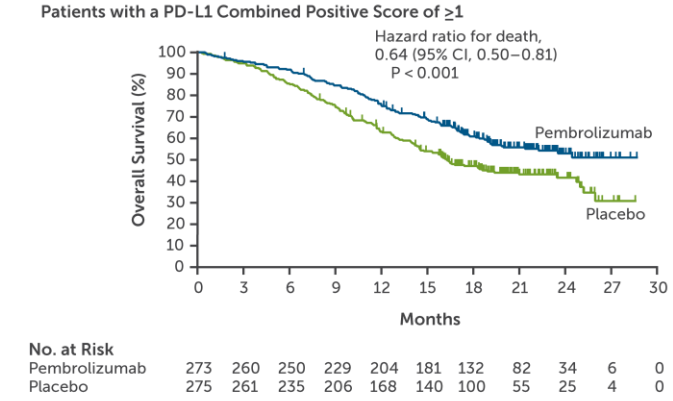
Emerging Approaches in Second-Line and Later Cervical Cancer: *Pembrolizumab*

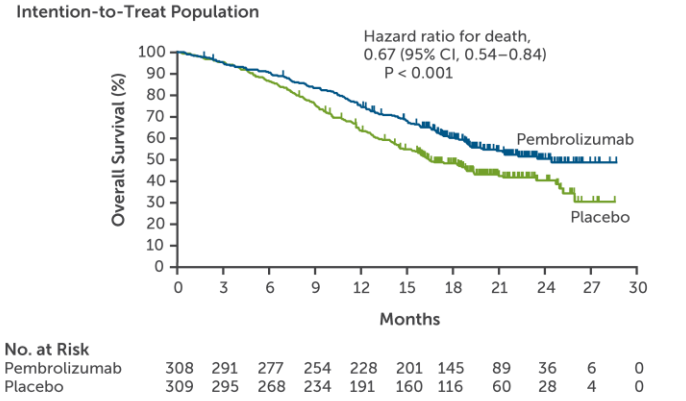
- KEYNOTE-826 evaluated pembrolizumab + chemotherapy +/- bevacizumab q3w for patients with persistent, recurrent, or metastatic cervical cancer
  - Eligible patients were unable to receive curative treatment and had received no prior systemic chemotherapy
  - Patients receiving placebo received chemotherapy +/- bevacizumab
  - Patients were also stratified by PD-L1 positive score (CPS; <1 vs 1 to <10 vs ≥10) and bevacizumab (yes/no)

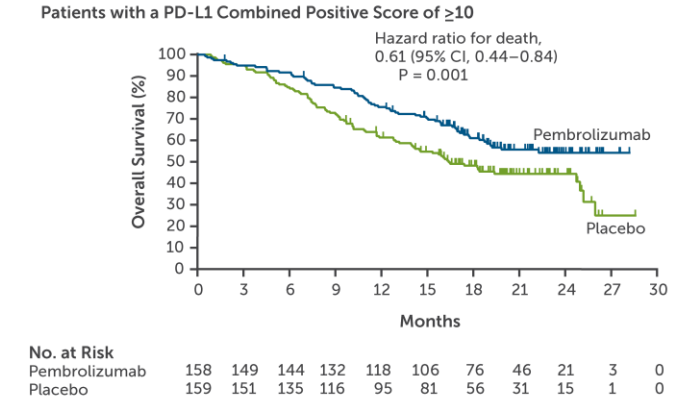
Colombo N, et al. *N Engl J Med*. 2021;385(20):1856-1867.

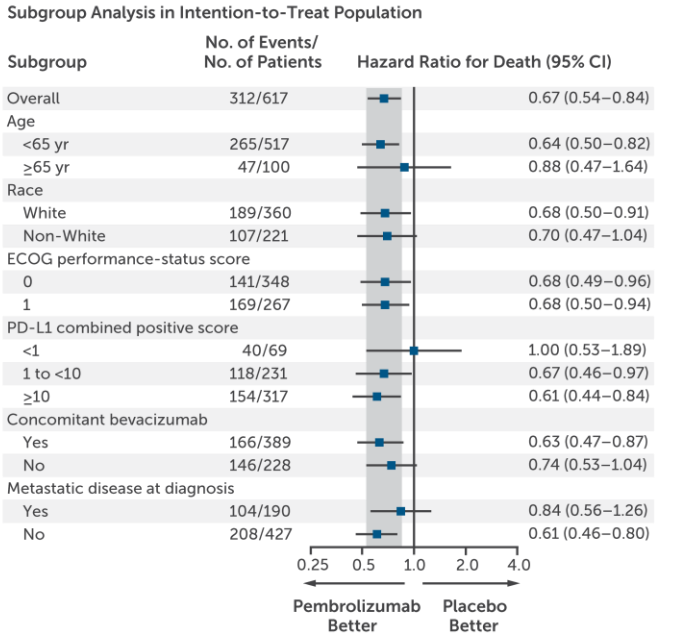
Emerging Approaches in Second-Line and Later Cervical Cancer: ***Pembrolizumab*** (cont'd)

KEYNOTE-826









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Emerging Approaches in Second-Line and Later Cervical Cancer: ***Pembrolizumab*** (cont'd)

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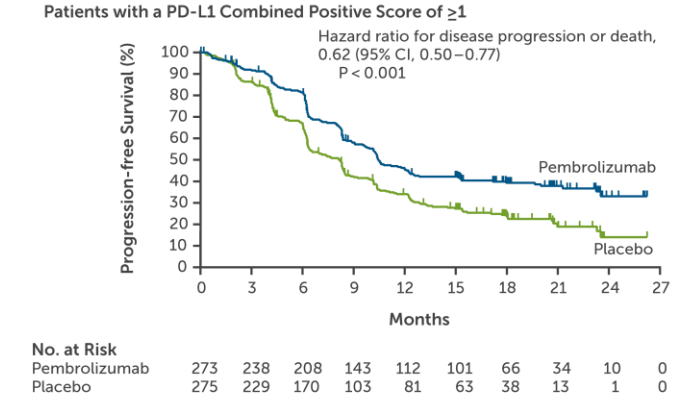
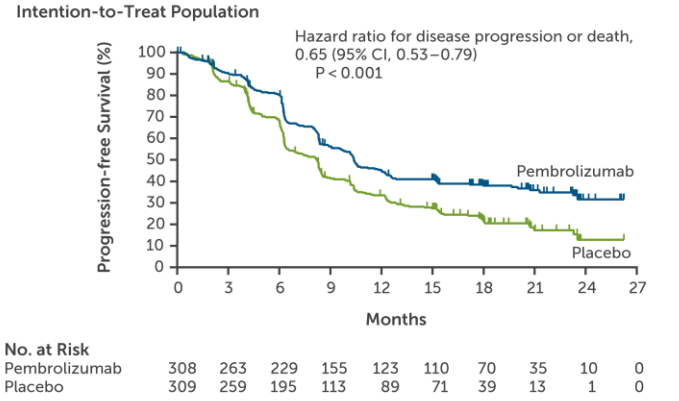
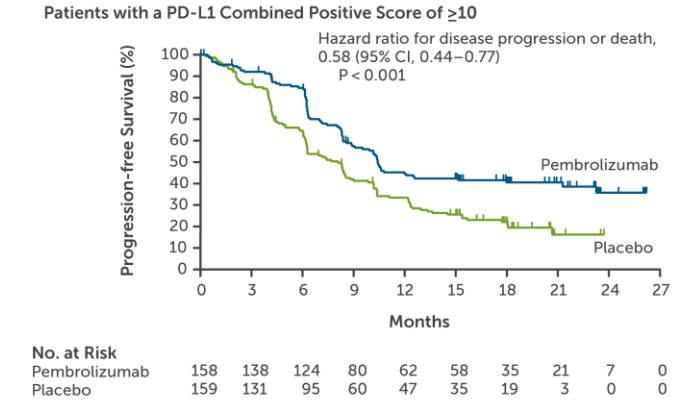
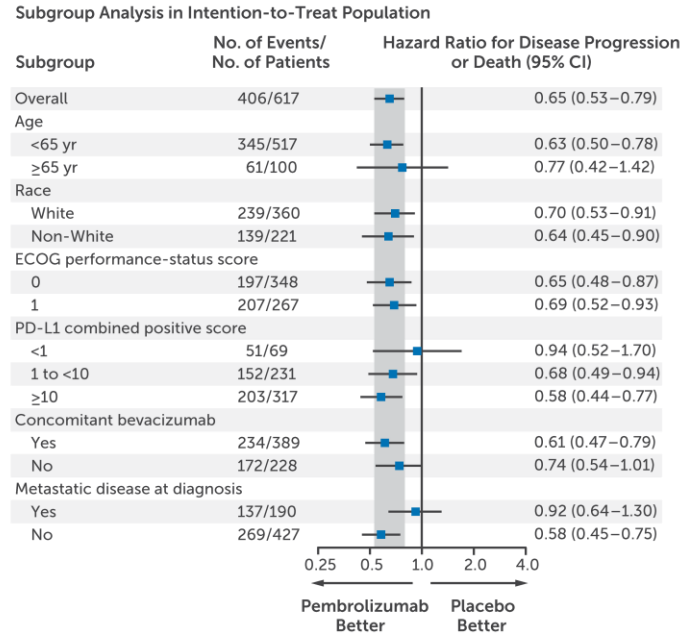








Colombo N, et al. *N Engl J Med*. 2021;385(20):1856-1867.

Emerging Approaches in Second-Line and Later Cervical Cancer: *Durvalumab + CRT + Image-Guided Brachytherapy*

- CALLA phase 3 trial tested a novel immunotherapy approach in persistent/recurrent/metastatic cervical cancer
- Adjuvant durvalumab + chemoradiotherapy (CRT) + image-guided brachytherapy vs CRT + image-guided brachytherapy
- 2022 update
  - Durvalumab + chemoradiotherapy + image-guided brachytherapy did not achieve statistical significance for the primary endpoint (PFS) vs CRT + image–guided brachytherapy

Mayadev, J, et al. *Int J Gynecol Cancer*. 2020;30(7):1065-1070; Update on CALLA phase 3 trial: https://www.astrazeneca.com/media-centre/press-releases/2022/update-on-calla-phase-iii-trial-for-imfinzi.html

Emerging Approaches in Second-Line and Later Cervical Cancer: *Pembrolizumab*

- KEYNOTE-028 assessed patients with locally advanced or metastatic PD-L1+ cervical cancer who failed prior standard therapy or those for which no suitable prior therapy existed
- Patients received 10 mg/kg pembrolizumab q2w for 24 months, and assessed q8w for 6 months, q12w thereafter
- Primary endpoint was overall response rate (ORR)

Frenel, JS, et al. *J Clin Oncol*. 2017;35(36):4035-4041.

Emerging Approaches in Second-Line and Later Cervical Cancer: *Pembrolizumab** (cont'd)

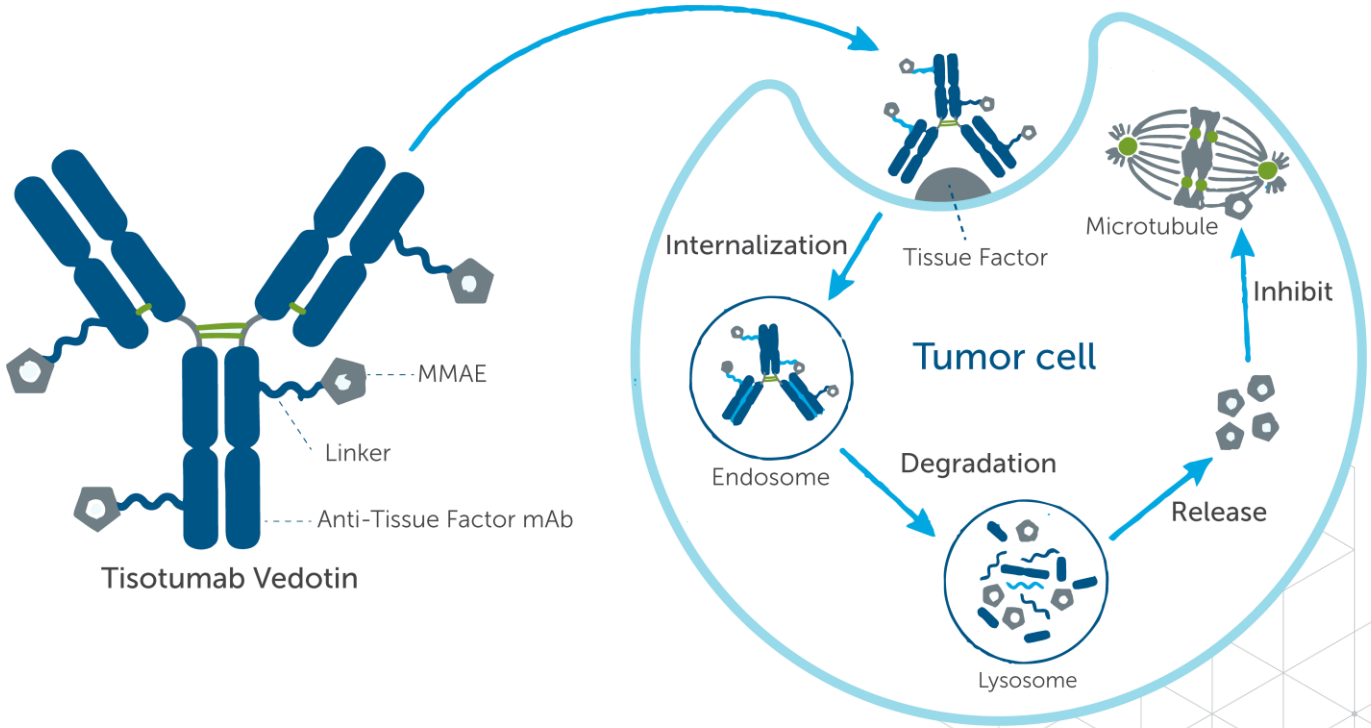
Best Overall Response	No. Patients	% (95% CI)
Partial Response	**4**	**17 (5 to 37)**
Stable Disease	3	13 (3 to 32)
Progressive Disease	16	67 (45 to 84)
No Assessment	1	4 (<1 to 21)

*KEYNOTE-028; 10 mg/kg q2w for 24 months/assessed q8w for 6 months, q12w thereafter.

Frenel, JS, et al. *J Clin Oncol*. 2017;35(36):4035-4041.

Second-Line and Later Cervical Cancer: *Tisotumab Vedotin-tftv*

- Tisotumab vedotin-tftv (TV) is a monoclonal antibody-drug conjugate (ADC) that consists of a degradable linker to monomethyl auristatin E (MMAE), the cytotoxic component of the drug
- TV binds to tissue factor expressed on cervical tumors and releases MMAE upon cell entry to mediate its cytotoxic activity on microtubules
- On September 20, 2021, *based on findings from the innovaTV 204 trial*, FDA granted TV accelerated approval for adult patients with recurrent of metastatic cervical cancer with disease progression on/after chemotherapy



https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer

Second-Line and Later Cervical Cancer: *Tisotumab Vedotin-tftv* (cont'd)

- Patients:
  - Recurrent or metastatic squamous cell, adenocarcinoma, or adenosquamous cervical cancer
  - Disease progression on/after doublet chemotherapy with bevacizumab; patients who had received 2 or fewer previous systemic regimens for recurrent or metastatic disease and had measurable disease based on RECIST, version 1.1
- 101 patients received at least 1 dose of TV
  - No biomarker requirements
  - Patients received 2.0 mg/kg (up to a maximum of 200 mg) TV IV q3w until disease progression
  - Median follow-up at the time of analysis was 10 months

Coleman RL, et al. *Lancet Oncol.* 2021;22(5):609-619.

Second-Line and Later Cervical Cancer: *Tisotumab Vedotin-tftv* (cont'd)

- Findings:
  - The confirmed objective response rate was 24% (95% CI 16–33), with 7 (7%) complete responses and 17 (17%) partial responses
- Study conclusions:
  - TV showed clinically meaningful and durable antitumor activity with a manageable and tolerable safety profile in patients with previously treated recurrent or metastatic cervical cancer
  - Considering the poor prognosis for these patients and low activity of current therapies in this setting, the 2021 approval of TV represents a new treatment option for patients with recurrent or metastatic cervical cancer

Coleman RL, et al. *Lancet Oncol.* 2021;22(5):609-619.

Tisotumab Vedotin-tftv: NCCN and First-Line Potential

- TV has been added to NCCN Guidelines for second-line and subsequent systemic therapy for cervical cancer with a category 2A recommendation
- innovaTV 205 trial (ASCO 2022)*
  - TV + pembrolizumab as first-line therapy for recurrent/metastatic cervical cancer (interim safety and efficacy report)
  - 33 patients (prior chemoradiation eligible) received TV + 200 mg IV pembrolizumab q3w
  - Median follow-up 12.2 months

Lorusso D, et al. *J Clin Oncol*. 2022;40(16_suppl):5507. *https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.5507

Tisotumab Vedotin-tftv: NCCN and First-Line Potential (cont'd)

- Confirmed ORR = 41% (32 patients evaluated)
- 3 (9%) complete responses; 10 (31%) partial responses
  - > Median duration of response, not reached
  - > Response ongoing in 7/13 patients
- Median PFS = 5.3 months (95% CI 4.0-12.2)
- Acceptable safety profile

- Interim study conclusion:
  - TV + pembrolizumab demonstrated durable antitumor activity with manageable adverse events as first-line regimen for patients with recurrent/metastatic cervical cancer

*https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.5507

Managing Ocular Toxicity to Optimize Exposure: *Tisotumab Vedotin-tftv*

- Ocular AEs occurred in 60% of cervical cancer patients treated with TV across clinical trials
  - Primarily conjunctival (40%), dry eye (29%), corneal (21%), and blepharitis (8%); grade 3 AEs occurred in ~4% of patients, including severe ulcerative keratitis
- Dosage modifications and an eye care protocol are provided to prevent/limit ocular AEs, including routine ophthalmic exams and use of vasoconstrictor, corticoid, and lubricating eyedrops
- At last clinical follow-up, 85% of ocular AEs had resolved
  - 55% full resolution; 30% partial resolution

https://www.tivdakhcp.com/eye-care/

Emerging Approaches in Second-Line and Later Cervical Cancer: *Ipilimumab + Nivolumab*

- CheckMate 358 assessed nivolumab-containing regimens in patients with recurrent cervical, vaginal, or vulvar carcinoma
- 79% (15/19) of patients had received prior systemic therapy
- Phase 1/2 study
  - Eligible patients had HPV+ disease
  - Demonstrated ORR 26.3% and median OS of 21.9 months for patients with recurrent cervical cancer

Naumann RW, et al. *J Clin Oncol*. 2019;37(31):2825-2834.

Emerging Approaches in Second-Line and Later Cervical Cancer: *Ipilimumab + Nivolumab* (cont'd)

- CheckMate 358 also evaluated combination ipilimumab (ipi) and nivolumab (nivo) in patients with recurrent/metastatic cervical cancer
- ESMO 2019
  - Eligible patients (N = 91) had been treated with 0-2 prior systemic therapies
  - Randomized to nivo 3 mg/kg q2w + ipi 1 mg/kg q6w (Combo A), or nivo 1 mg/kg + ipi 3 mg/kg q3w for 4 doses, followed by nivo 240 mg q2w (Combo B), for ≤24 mo until progression or unacceptable toxicity
  - Primary endpoint: investigator-assessed ORR by RECIST 1.1
  - Secondary endpoints: OS, PFS, and DOR

Naumann RW. Presented at ESMO 2019 Congress; September 27-October 2, 2019; Barcelona, Spain. Abstract LBA62.

Emerging Approaches in Second-Line and Later Cervical Cancer: *Ipilimumab + Nivolumab* (cont'd)

- Findings:
  - Median follow-up was 10.7 mo (Combo A, n = 45) and 13.9 mo (Combo B, n = 46)
  - ORR was higher in Combo B vs Combo A without prior systemic therapy (46% vs 32%) and with prior systemic therapy (36% vs 23%)
  - Median PFS in Combo A was 13.8 mo in patients without prior systemic therapy and 3.6 mo in patients with prior systemic therapy
  - Median PFS in Combo B was 8.5 mo without prior systemic therapy and 5.8 mo with prior systemic therapy
  - Median OS in Combo A was Not Reached in patients without prior systemic therapy and 10.3 mo in patients with prior systemic therapy
  - Median OS in Combo B was Not Reached without prior systemic therapy and 25.4 mo with prior systemic therapy

Naumann RW. Presented at ESMO 2019 Congress; September 27-October 2, 2019; Barcelona, Spain. Abstract LBA62.

Emerging Approaches in Second-Line and Later Cervical Cancer: *Ipilimumab + Nivolumab* (cont'd)

- Overall conclusion from CheckMate 358:

"Clinical benefit from two regimens of Nivo + Ipi in patients with recurrent/metastatic cervical cancer was observed regardless of PD-L1 status."

"Combo B had notable efficacy in patients with prior systemic therapy."

(nivo 1 mg/kg + ipi 3 mg/kg q3w for 4 doses, followed by nivo 240 mg q2w)

Naumann RW. Presented at ESMO 2019 Congress; September 27-October 2, 2019; Barcelona, Spain. Abstract LBA62.

Emerging Approaches in Second-Line and Later Cervical Cancer: *GX-188E Vaccine + Pembrolizumab*

- Open-label, single-arm, phase 2 trial interim analysis
- Histologically confirmed recurrent/advanced HPV+ (HPV 16/18) inoperable cervical cancer; progression after standard of care therapy
- Patients received IM 2 mg GX-188E at weeks 1, 2, 4, 7, 13, and 19 (optional dose week 46); and pembrolizumab 200 mg q3w for up to 2 years/until disease progression
- Primary endpoint: ORR within 24 weeks (RECIST 1.1) in patients who received ≥45 days of treatment with ≥1 post-baseline tumor assessment

Youn JW, et al. *Lancet Oncol*. 2020;21(12):1653-1660.

Emerging Approaches in Second-Line and Later Cervical Cancer: *GX-188E Vaccine + Pembrolizumab*

- 26/36 patients evaluable, receiving ≥1 treatment dose; and with ≥1 post-baseline tumor assessment at week 10 (trial ongoing)
  - Median follow-up was 6.2 months
  - At 24 weeks, 11 (42%) of 26 patients achieved an overall response
  - 4 (15%) had a complete response and 7 (27%) had a partial response
- Conclusions:
  - Treatment with GX-188E therapeutic vaccine + pembrolizumab for patients with recurrent/advanced cervical cancer was safe; treatment-related adverse events were manageable
  - The combination showed preliminary antitumor activity, which could represent a new potential treatment option for these patients

Youn JW, et al. *Lancet Oncol*. 2020;21(12):1653-1660.

Emerging Approaches in Second-Line and Later Cervical Cancer: *TILs*

- TILs: tumor-infiltrating lymphocytes
- Moving into the frontline and post pembrolizumab failures
- Requires
  - Substantial tumor material to develop TILs
  - Substantial lead-in time needed to develop TILs
  - Not yet a widely available option

Emerging Approaches in Second-Line and Later Cervical Cancer: *TILs* (cont'd)

- Ongoing study, C-145-04, open-label phase 2
- Patients (N = 12): advanced cervical cancer failing ≥1 prior therapy; prior checkpoint inhibitor not eligible
- Primary endpoint: ORR per RECIST 1.1
- Secondary endpoints: DOR, disease control rate (DCR), and LN-154 (TILs) safety
- Findings warranting further evaluation:
  - ORR = 44% (1 complete, 9 partial, and 1 unconfirmed partial responses)
  - DCR = 89% at 3.5 months (11/12 maintained response)
  - AEs consistent with advanced disease and lymphodepletion and IL-2 regimens

Jazaeri AM, et al. *J Clin Oncol*. 2019;37(15_Suppl):2538.

5 Things You Need to Know in Cervical Cancer Treatment

1. Prevention makes more sense than treatment: Vaccinate!
2. New therapies are changing the outcome landscape in cervical cancer, but access disparities remain a challenge
3. Drug development efforts in cervical cancer are increasing and are increasingly successful
4. Efforts to identify biomarkers that help match therapy with patient must continue
5. Clinical trials are critical, so continue to enroll your patients

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