Cervical Cancer Highlights and Emerging Treatment Strategies

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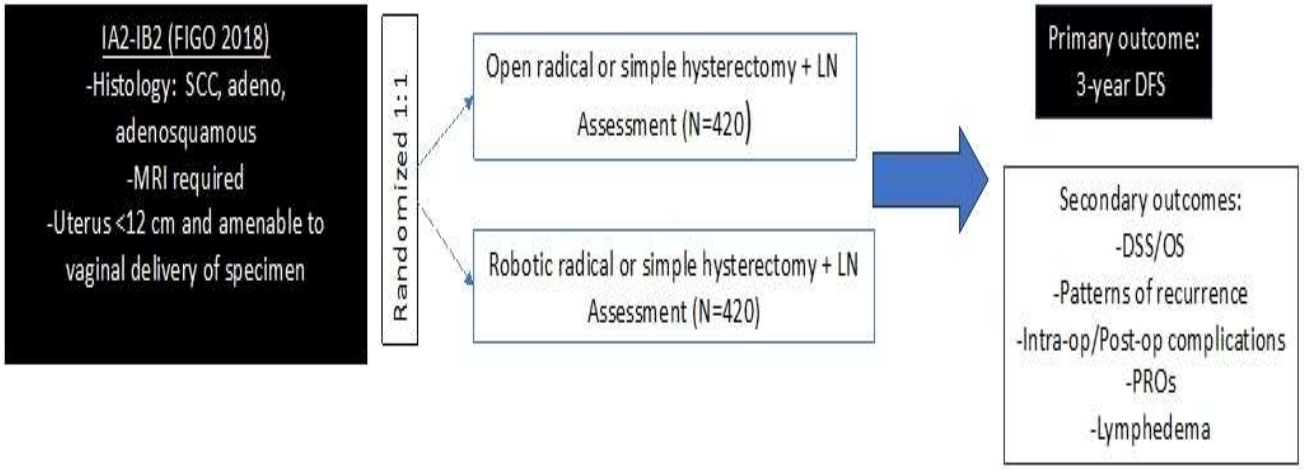
GOG-3043/ROCC

A Randomized Controlled Trial of Robotic versus Open Radical Hysterectomy for Early-Stage Cervical Cancer

PI: Kristin Bixel, MD | Co-PI: Mario Leitao, MD | DEI Chair: Colleen McCormick,



Surgical Requirements

- No transcervical/intrauterine manipulators permitted
- Tumor containment prior to colpotomy required

Key Inclusion

- Stage IA2-IB2 (FIGO 2018)
- Squamous, adenocarcinoma, adenosquamous histology
- Pelvic MRI required to verify tumor size
- Simple hysterectomy will be allowed in patients who meet the following criteria:
  - a) pelvic MRI must demonstrate a maximal tumor size of 2cm or less AND
  - b) less than 50% stromal invasion on MRI if tumor present or less than 10 mm of stromal invasion if an excisional (cold knife or LEEP) has been performed.

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KEYNOTE-A18/GOG-3047: OS results-ESMO 2024

Schema

Key Eligibility Criteria

- FIGO 2014 stage IB2-IIB (node-positive disease) or FIGO 2014 stage III-IVA (either node-positive or node-negative disease)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naïve

Stratification Factors

- Planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (stage IB2-IIB vs III-IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

R 1:1

- Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy + Pembrolizumab 200 mg Q3W for 5 cycles
- Pembrolizumab 400 mg Q6W for 15 cycles
- Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy + Placebo Q3W for 5 cycles
- Placebo Q6W for 15 cycles

End Points

- Primary: PFS (per RECIST v1.1) by investigator or histopathologic confirmation and OS
- Key secondary: 24-month PFS, ORR, PROs, and safety

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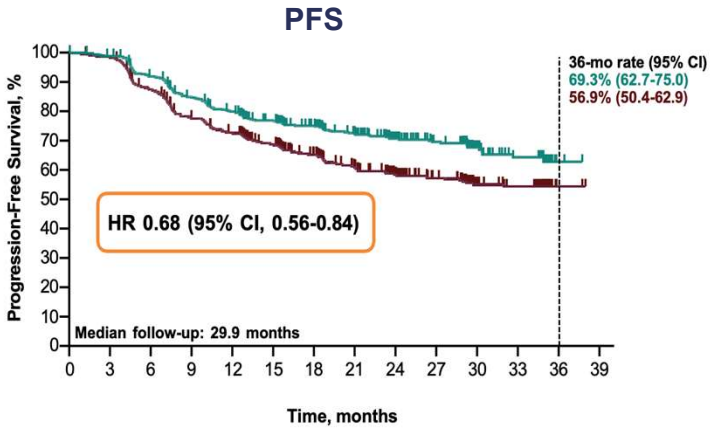

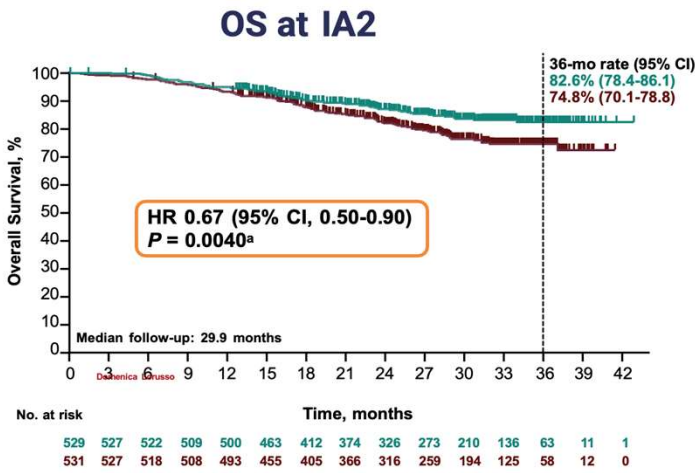

GOG Highlight Reel

Lorusso K et al ESMO 2024, Lancet. 2024 Apr 6;403(10434):1341-1350

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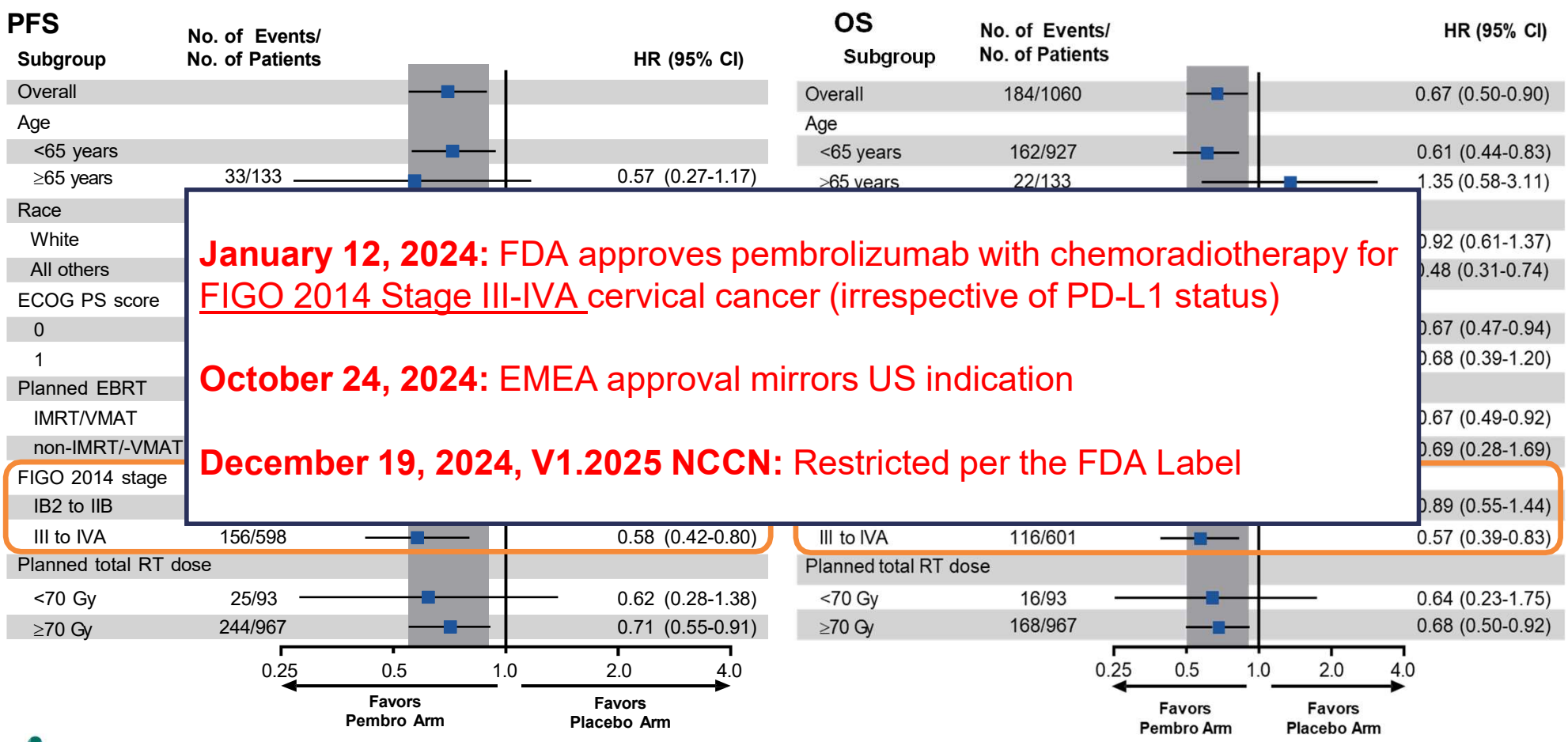
PFS/OS in Protocol-Specified Subgroups



January 12, 2024: FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer (irrespective of PD-L1 status)

October 24, 2024: EMEA approval mirrors US indication

December 19, 2024, V1.2025 NCCN: Restricted per the FDA Label

Lorusso K et al ESMO 2023, 2024; Lancet. 2024 Apr 6;403(10434):1341-1350

INTERLACE: Induction CT followed by CRT vs CRT alone as 1L treatment for Locally Advanced CC

Schema

Key eligibility criteria

- Newly diagnosed histologically confirmed FIGO (2008) stage IB1 node+,IB2 ,II,IIIB,IVa squamous, adeno, adenosquamous cervical cancer
- No nodes above aortic bifurcation
- Adequate renal/liver and bone marrow function
- Fit for chemotherapy & radical RT
- No prior pelvic RT

Randomised (n=500)

Induction chemotherapy (n=250)
Carboplatin (AUC2) & paclitaxel (80mg/m²) given weekly for **6 weeks**

Week 7

Standard CRT (n=250)
Chemotherapy: cisplatin (40mg/m²) weekly for 5 weeks
Radiotherapy: EBRT (40-50.4Gy in 20-28 fractions) & brachytherapy to give a minimum total EQD2 dose of 78Gy to point A,3D brachytherapy recommended
Overall treatment time </=50days
All centres underwent RTQA

Follow-up
3-monthly for 2 years then 6-monthly for 5 years

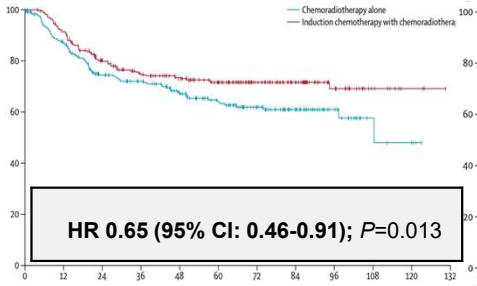
Stratified by

- Site
- Stage
- Nodal status
- 3D v IMRT EBRT
- 2D v 3D BT
- Tumour size
- SCC v other

Primary endpoints

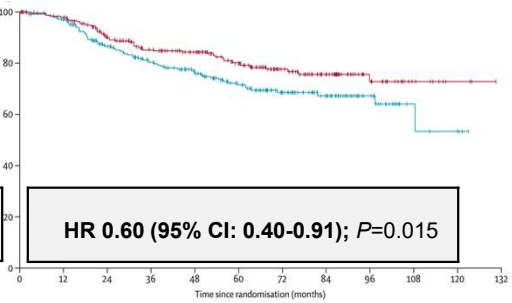
- PFS
- OS

PFS



HR 0.65 (95% CI: 0.46-0.91); *P*=0.013

OS



HR 0.60 (95% CI: 0.40-0.91); *P*=0.015

- 1st of several induction/NACT trials to be positive
- OUTBACK and GOG 724 negative
- Limited to pt with negative aortic nodes
- Lower rate of concurrent cis completion
- Lower rate of distant recurrence
- Short time to RT (within 7 wks) could be reason for success
- ?Effect of radiation technique evolution

NCT01566240

GOG Highlight Reel

McCormack The Lancet, v404, Issue 10462, 1525-35. Duska and Randall Lancet v404 Iss 10462, p.1494-6

GOG-3092: eVOLVE-Cervical PD1/CTLA4 bispecific

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of MEDI5752 as Sequential Therapy in Women with High Risk Locally Advanced Cervical Cancer Following Platinum-based, Concurrent Chemoradiation Therapy

Screening period	Randomization	Treatment period	Endpoints
FIGO 2018 IIIC-IVA cervical cancer (LN involvement)	Max **56** days after the end of CCRT	41/1000 randomized over 10 months	

Part I: Diagnosis/CRT

Patient consenting process step 1:

- Tumor sample submission and analysis
  - PD-L1 expression by VENTANA PD-L1 (SP263) Assay
- **Initial staging procedures** completed prior to any component of definitive treatment
  Increase specificity of nodal criteria

Part II: Post CRT

Patient consenting process step 2:

- After completion of SOC CCRT (≥4 cycles), CCRT dose requirement
- No progression after SOC CCRT, persistent disease must not be amenable to other available therapies with curative intent
- Grade > 1 toxicities resolved prior to randomization
- ECOG 0 or 1

N=1000

R 1:1

Arm A

Volrustomig 750mg IV Q3W for 24 months

Arm B

Placebo IV Q3W for 24 months

Stratification factors

- PD-L1 expression (PD-L1 high expression vs. low/negative)
- FIGO stage (IIIC1 vs. IIIC2 vs. IVA)
- Region (Asia vs. non-Asia)

Primary Endpoint: PFS in PD-L1 high population (Inv)

Secondary Endpoint:

Key: PFS in ITT (Inv), OS in PD-L1 high population/ITT

Others: PFS (BICR), 12mons-PFS, 24mons-PFS, 36mons-OS, ORR, DOR, PFS2, TFST, incidence of local progression and distant disease progression, PK, ADAs, safety and tolerability, ePROs

Exploratory Endpoint: ctDNA, T cell proliferation/clonal expansion, baseline tumor immune and genomic profile, ePROs

NCT06079671

IGCS 2024 Annual Global Meeting DUBLIN

Cadonilimab plus Chemotherapy with or without Bevacizumab as First-line Treatment for Persistent, Recurrent, or Metastatic Cervical Cancer: A Randomized, Double-blind, Placebo-controlled Phase 3 Study (COMPASSION-16)

X.Wu[1], Y.Sun[2], H.Yang[3], J.Wang[4], H.Lou[5], D.Li[6], K.Wang[7], Z.Hu[8], T.Wu[9], Y.Li[10], C.Wang[11], G.Li[12], Y.Wang[13], D.Li[14], Y.Tang[15], M.Pan[16], H.Cai[17], T.Liu[18], Y.Xia[18]

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Key eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer
- Histologically types include squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma.
- No prior systemic therapy.
- ECOG PS 0-1.

R 1:1

Cadonilimab Group(n=222)
Cadonilimab 10mg/kg+Paclitaxel 175mg/m²+Cisplatin 50mg/m² or Carboplatin AUC4-5±Bevacizumab 15mg/kg, q3w×6

Maintenance therapy
Cadonilimab 10mg/kg ±Bevacizumab 15mg/kg, q3w

Placebo Group(n=223)
Placebo+Paclitaxel 175mg/m²+Cisplatin 50mg/m² or Carboplatin AUC4-5 ±Bevacizumab 15mg/kg, q3w×6

Maintenance therapy
Placebo±Bevacizumab 15mg/kg, q3w

✓ **Treatment continued until**
- disease progression
- unacceptable toxicity
- cadonilimab/placebo treatment for 2 years.

✓ Safety and survival follow-up are performed after the end of treatment.

Stratification factors:
- Use of Bevacizumab (Yes vs No)
- Prior CCRT(Yes vs No)

Primary Endpoints：
- PFS assessed by BICR according to RECIST v1.1
- OS

Second Endpoints：
PFS assessed by INV, ORR, DoR, DCR, TTR, Safety

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GOG Highlight Reel

Wu X et al. LBA. IGCS 2024

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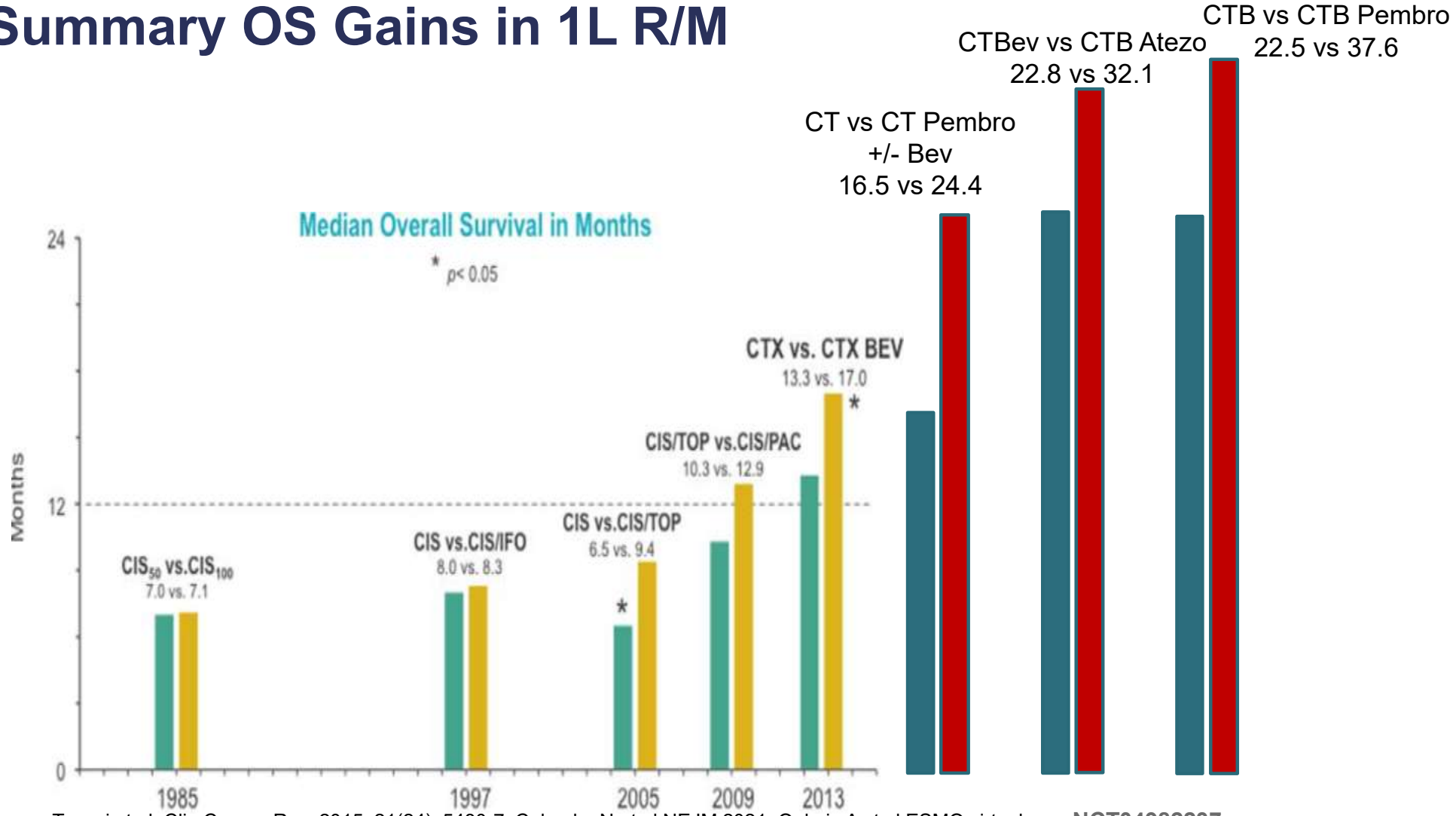
Summary OS Gains in 1L R/M



Tewari et al. Clin Cancer Res. 2015; 21(24): 5480-7. Columbo N et al NEJM 2021. Oaknin A et al ESMO virtual 2023. Lorusso K et al. ESGO 2023.

NCT04982237

Progress in 1L Disease Status at Enrollment 1L Metastatic, Recurrent, Persistent Trials

Trial	n	$mPFS_{exp}$ (mos)	HR PFS	mOS_{exp}	HR OS
GOG 204[1]	503			12.9	
GOG 240[2]	452	8.2	0.71	17.0	0.67
KN 826 ± bev[3]	617	10.4	0.65	24.4	0.67
KN 826 + bev[4]		15.2	0.57	37.6	0.61
BEATcc[5]	410	13.7	0.62	32.1	0.68
COMPASSION ± bev[6]	445	13.3	0.62	NR* (27.0, NR)	0.64

1. Monk BJ et al. JCO 2009;27(28):4649-4655 2. Tewari KS et al. NEJM 2014;370(8):734-743. 3.Columbo N et al. NEJM 4.Monk BJ et al. ASCO 2024 5. Oaknin A et al. ESMO Virtual 2023 6. Wu X et al IGCS 2024

Summary of Safety

TEAE	Cadonilimab (N = 226)*	Placebo (N = 219)
Any Grade, n(%)	225 (99.6)	219 (100)
≥Grade 3, n (%)	193 (85.4)	176 (80.4)
SAE, n (%)	126 (55.8)	74 (33.8)
Led to discontinuation of any trial agent, n (%)	63 (27.9)	23 (10.5)
Led to Death, n (%)	12 (5.3)	7 (3.2)
irAE	103 (45.6)	15 (6.8)
≥Grade 3 irAE, n (%)	22 (9.7)	2 (0.9)

37.5%
KN826

Drug Exposure Cycle(median): Cadonilimab vs Placebo

- Cadonilimab/Placebo: 15.02 vs 12.33
  - Carboplatin: 6.26 vs 6.14
  - Cisplatin: 6.14 vs 6.10
  - Paclitaxel: 6.19 vs 6.10
- Bevacizumab: 17.29 vs 14.38

*Due to protocol deviations, 4 patients in the control group were administered cadonilimab and were classified into the cadonilimab group during the safety analysis.

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irAE in Cadonilimab group

	Cadonilimab Group(N=226)		Placebo Group(N=219)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
All events	103 (45.6)	22 (9.7)	15 (6.8)	2 (0.9)
Hypothyroidism	61 (27.0)	1 (0.4)	5 (2.3)	0
Hyperthyroidism	33 (14.6)	1 (0.4)	0	0
Thyroiditis	8 (3.5)	0	2 (0.9)	0
Rash	6 (2.7)	1 (0.4)	1 (0.5)	0
Immune-mediated thyroiditis	5 (2.2)	1 (0.4)	0	0
Adrenal insufficiency	5 (2.2)	0	0	0
Hypopituitarism	3 (1.3)	2 (0.9)	1 (0.5)	0
Hyperglycemia	3 (1.3)	1 (0.4)	0	0
Drug eruption	3 (1.3)	1 (0.4)	0	0
Blood thyroid stimulating hormone increased	3 (1.3)	0	2 (0.9)	0
Secondary hyperthyroidism	3 (1.3)	0	1 (0.5)	0

33.9% KN826

11.4% KN826

irAE: Immune-related Adverse Event

* All irAEs have undergone a secondary adjudication process by the sponsor.

BARCELONA 2024 ESMO congress

Efficacy and Safety of Sacituzumab Tirumotecan (sac-TMT) Plus Pembrolizumab in Patients with Recurrent or Metastatic Cervical Cancer

Xiaohua Wu[1], Jing Wang[2], Ruifang An[3], Yi Huang[4], Jieqing Zhang[5], Jeffrey C. Goh[6], Kui Jiang[7], Guohua Yu[8], Liang Chen[9], Diane Provencher[10], Ying Tang[11], Guiling Li[12], Hui Qiu[13], Omobolaji·O. Akala[14], Elliot Chartash[14], Yiting Zhou[15], Xiaoping Jin[15], Junyou Ge[15]

Cohort A: 2L or 3L recurrent or metastatic CC (N=40)

Key inclusion criteria

- Received 1 or 2 prior systemic regimens (prior anti-PD-1/L1 allowed) for recurrent or metastatic CC
- Progressed on or after platinum-doublet chemotherapy
- ECOG PS 0 or 1

Safety run-in

Sac-TMT 3 or 5 mg/kg Q2W + pembrolizumab 400 mg Q6W

Expansion

Sac-TMT 5 mg/kg Q2W + pembrolizumab 400 mg Q6W

Treatment continues until

- Disease progression
- Unacceptable toxicity

Primary endpoints

- Safety (DLT, AEs)
- ORR per RECIST v1.1

Secondary endpoints

- DCR, DoR, PFS, OS
- PK, immunogenicity

Tumor assessment:

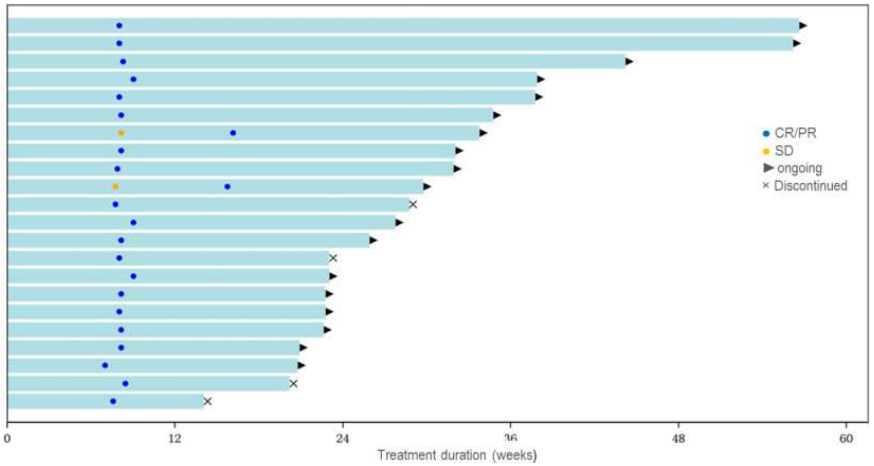
- Every 8 weeks for the first 12 months, and every 12 weeks thereafter

NCT05351788

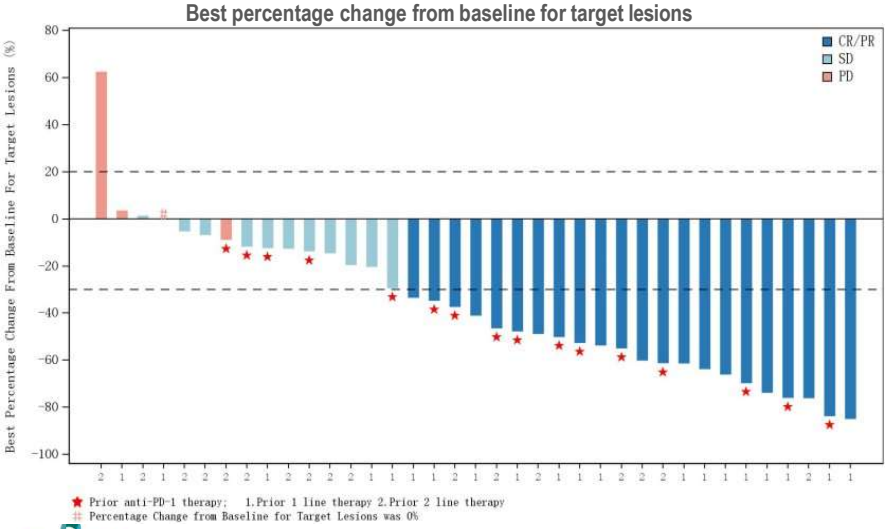
1. Fang W et al. *J Clin Oncol* 2024;42:Abstr 8502.

2L, second-line; 3L, third-line; ADC, antibody-drug conjugate; AE, adverse event; CC, cervical cancer; DAR, drug-to-antibody ratio; DCR, disease control rate; DLT, dose limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1;PFS, progression-free survival; Q2W, every 2 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TROP2, trophoblast cell-surface antigen 2.

Time to response and duration of treatment for responders



Best percentage change from baseline for target lesions



Subgroup		N	ORR, n (%)[a]	6-month PFS rate, % (95% CI)
CPS status	CPS ≥ 1	14	7 (50.0)	68.8 (35.7, 87.3)
	CPS < 1	15	9 (60.0)	74.9 (39.1, 91.5)
	Unknown	9	6 (66.7)	43.8 (10.1, 74.2)
Prior anti-PD-1 based therapy	Yes	16	11 (68.8)	78.6 (47.2, 92.5)
	No	22	11 (50.0)	58.0 (32.4, 76.8)
Prior bevacizumab	Yes	20	12 (60.0)	67.1 (40.9, 83.7)
	No	18	10 (55.6)	67.5 (38.2, 85.2)
No. of prior systemic therapy	1	20	15 (75.0)	73.1 (46.7, 87.9)
	2	18	7 (38.9)	54.3 (21.8, 78.3)

Wu X et al. Abstract 716MO. ESMO 2024

NCT05351788

GOG-3101/TroFuse-020/ENGOT-cx20

A Phase 3 Randomized, Active-controlled, Open-label, Multicenter Study to Compare the Efficacy and Safety of MK-2870 Monotherapy Versus Treatment of Physician's Choice as Second-line Treatment for Participants with Recurrent or Metastatic Cervical Cancer

PI: Ritu Salani, MD

Eligibility

- Squamous, adenosquamous, adenocarcinoma cervical cancer
- Recurrent or metastatic:
  - Progressed on or after treatment with 1 prior line of systemic platinum doublet chemotherapy (with or without bevacizumab) NOTE: may have also received prior chemoradiotherapy in the LACC setting

  AND
  - Received anti-PD-1/anti-PD-L1 therapy as part of prior cervical cancer regimens
- Measurable disease per RECIST 1.1
- ECOG PS 0-1
- <Grade 2 PN

Safety run-in

Sacituzumab tirumotecan (sac-TMT) 4 mg/kg IV q2 wk

ORR
Safety/Tolerability

R
1:1

sac-TMT 4 mg/kg IV q2 wk

Treatment of Physician's Choice (TPC)
Tisotumab vedotin, pemetrexed, topotecan, vinorelbine, gemcitabine, or irinotecan

Primary Endpoint

- OS

Secondary Endpoints

- PFS
- ORR
- DOR
- Safety/Tolerability
- PROs
  - Time to first deterioration EORTC-QLQ-C30
  - Change baseline C30
    - Health status
    - QOL
    - Physical functioning
    - Role functioning

NCT06459180

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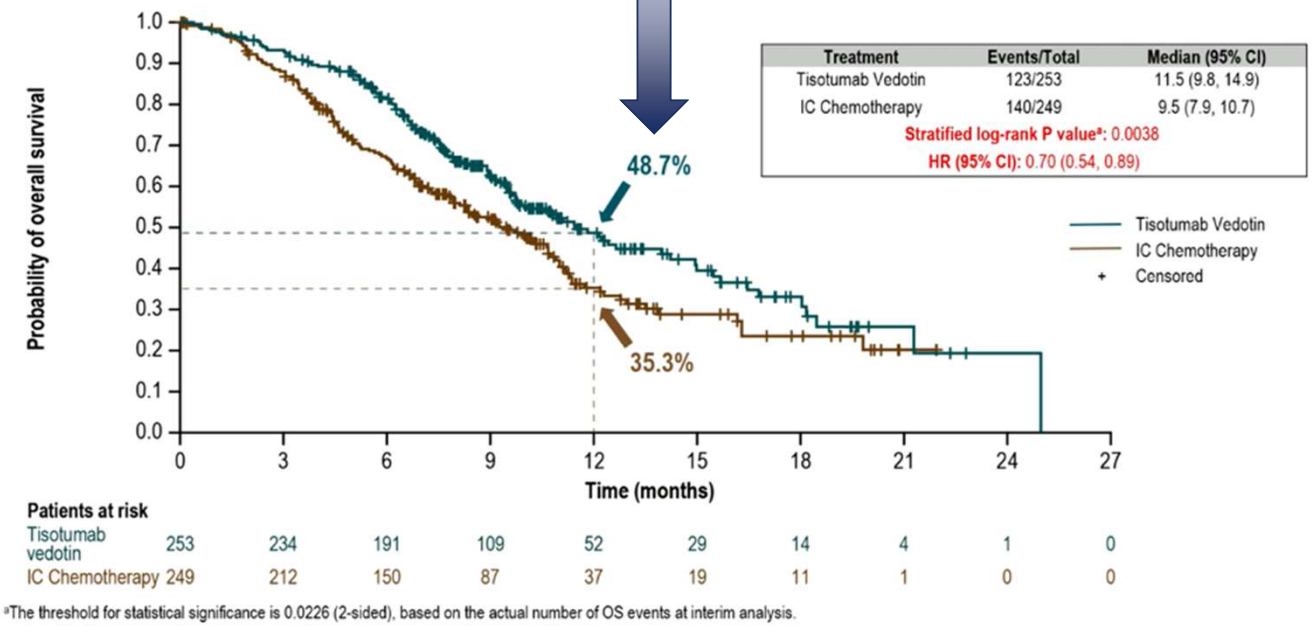
Tisotumab – while not studied specifically in a “post CPI” setting has become a preferred SOC based on modest improvements in OS

	Tisotumab Vedotin (N=253)	IC Chemotherapy (N=249)
ORR, % (95% CI)	17.8 (13.3-23.1)	5.2 (2.8-8.8)
Odds ratio (95% CI)	4.0 (2.1-7.6)	
P value	p<0.0001	
Best Overall Response, n (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
Not evaluable/Not available	15 (5.9)	30 (12.0)
DCR[a], % (95% CI)	75.9 (70.1-81.0)	58.2 (51.8-64.4)
Median DOR (95% CI)	5.3 (4.2-8.3)	5.7 (2.8-NR)

We can agree here that IC chemotherapy is just insufficient for our patients

innovaTV 301
ORR 17.8 vs.5.2%
mOS 11.5 vs. 9.5 months



[a]The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

Vergote et al. 2024

Tisotumab – Now NCCN Category 1!

Second-line or Subsequent Therapy[g,j]

Preferred Regimens
- Pembrolizumab for TMB-H tumors[f,k] or PD-L1–positive[h] or MSI-H/dMMR tumors[f,16]
- Tisotumab vedotin-tftv (category 1)[17,18]

Other Recommended Regimens
- Bevacizumab
- Paclitaxel[15,19]
- Albumin-bound paclitaxel
- Docetaxel
- Fluorouracil
- Gemcitabine
- Pemetrexed
- Topotecan
- Vinorelbine
- Irinotecan
- Cemiplimab[f,20]

Useful in Certain Circumstances
- PD-L1–positive tumors
  - Nivolumab[f,h,21]
  - Tisotumab vedotin-tftv + pembrolizumab[h,l,22]
- HER2-positive tumors (IHC 3+ or 2+)
  - Fam-trastuzumab deruxtecan-nxki[23]
- HER2-mutant
  - Neratinib[24]
- *RET* gene fusion-positive tumors
  - Selpercatinib
- *NTRK* gene fusion-positive tumors
  - Larotrectinib
  - Entrectinib
  - Repotrectinib[m,25]

Vergote et al. 2

Tisotumab Vedotin as Second- or Third-Line Therap...
www.nejm.org

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ORIGINAL ARTICLE

Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer

Authors: Ignace Vergote, M.D., Ph.D., Antonio González-Martín, M.D., Ph.D., Keiichi Fujiwara, M.D., Ph.D., Elsa Kalbacher, M.D., Andrea Bagaméri, M.D., Sharad Ghamande, M.D., Jung-Yun Lee, M.D., Ph.D., +24, for the innovaTV 301/ENGOT-cx12/GOG-3057 Collaborators* Author Info & Affiliations