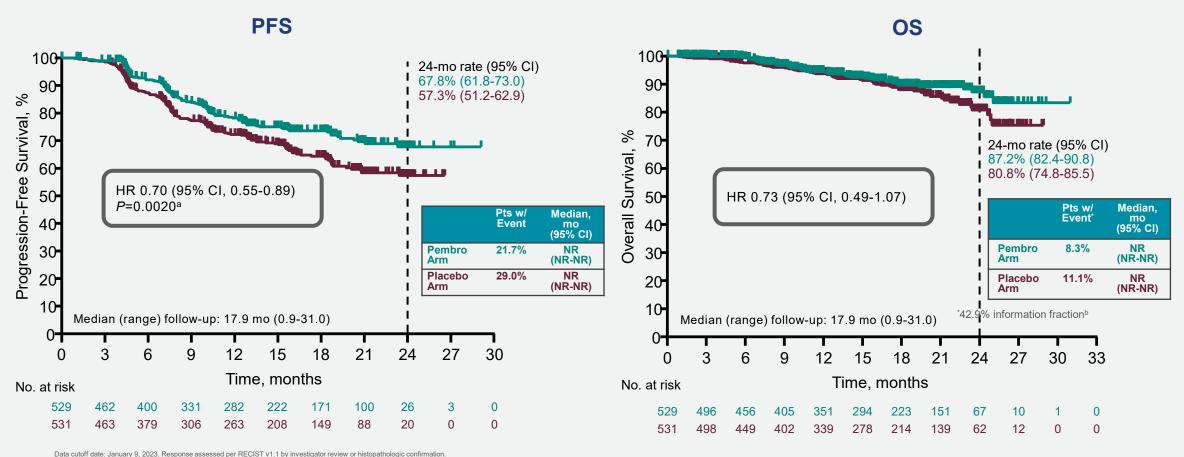
Cervical Cancer – New Data in CCRT, 1st Line, 2nd Line and How It Impacts Your Clinical Practice

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KEYNOTE-A18 (ENGOT-cx11/GOG-3047): Progression-Free Survival and Overall Survival



Data cutorit date: January 9, 2023. Response assessed per REUIST V1.1 by Investigator review of nistopathologic continuation.

"with 159 events (88.5% information fraction), the observed P = 0.0020 (1-sided) crossed the prespecified normal halpsis, "At this analysis, 103 of the 240 deaths expected at the final analysis had occurred.

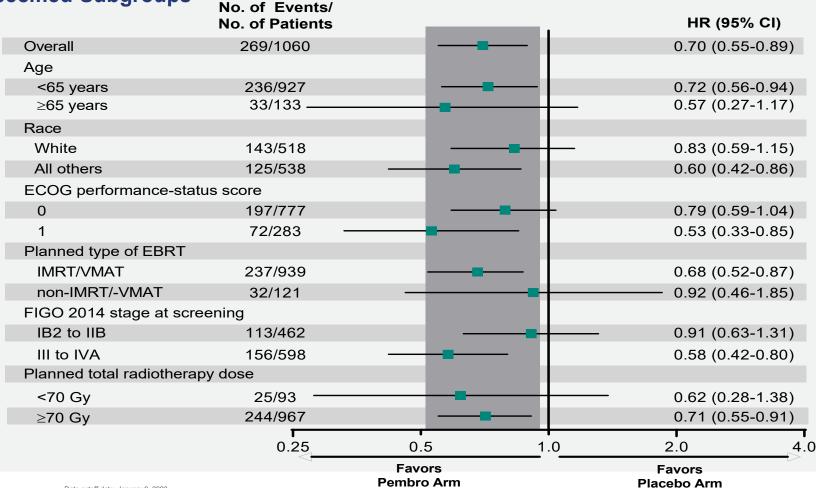
NR, not reached; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; pts, patients; RECIST, Response Evaluation Criteria in Solid Tumors





KEYNOTE-A18 (ENGOT-cx11/GOG-3047): **Treatment Exposure and Protocol-Specified Subgroups**

PFS^c: Protocol-Specified Subgroups







Key differences in CALLA and KEYNOTE A-18

	CALLA	A-18
Eligibility	Allows 1 pelvic node+	Must have 2 pelvic or aortic node + but allows PET SUV 2.5+
Target	PD-L1	PD1
Agent	Durvalumab	Pembrolizumab
Primary endpoint(s)	PFS	PFS/OS
Stratification factors	Stage Region of world	IMRT/VMAT vs non Total RT dose <70 vs ≥70 Gy Stage (1B2-IIB node + vs III/IVA node +/-)
Enrollment	45% Latin America 40% Asia 10% US/Europe	TBD but different





GCIG INTERLACE: Study Design

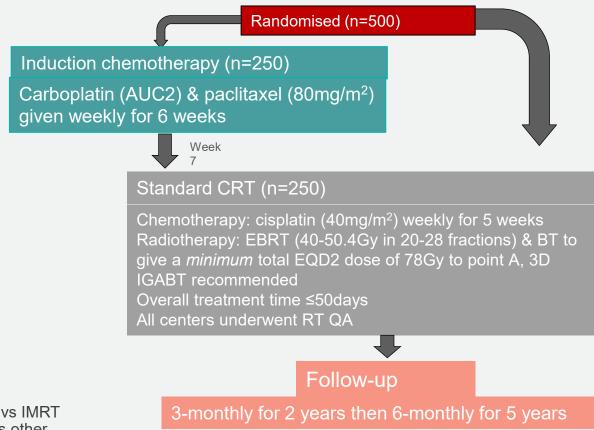
A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer

Key Eligibility Criteria:^{1,2}

- 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

Stratified by:

Site, stage, nodal status, 3D-conformal vs IMRT EBRT, 2D v 3D BT, tumour size, SCC vs other



- Primary endpoints: PFS
- OS

Secondary endpoints:

- Adverse events
- Pattern of relapse
- QOL
- Time to subsequent treatment

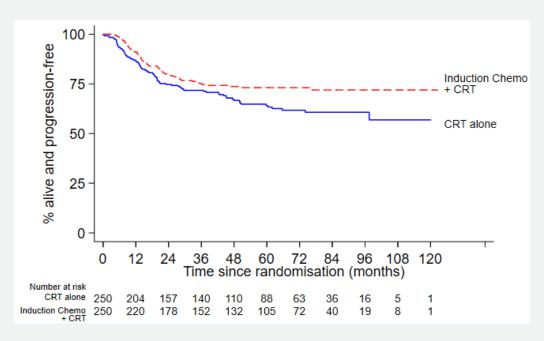




INTERLACE: Progression-Free Survival and Overall Survival

PFS (Median f/u: 64 months)

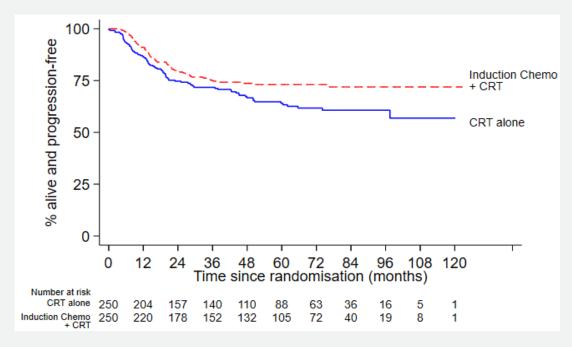
146 PFS events HR 0.65;95% CI:0.46 -0.91 *P*=0.013



	Induction Chemo+ CRT (n=250)	CRT alone (n=250)
3yr PFS	75%	72%
5yr PFS	73%	64%

OS (Median f/u: 64 months)

109 deaths HR 0.61;95% CI: 0.40-0.91 *P*=0.04



	Induction Chemo + CRT (n=250)	CRT alone (n=250)	
3yr OS	86%	80%	
5yr OS	80%	72%	





GOG 3092: eVOLVE-Cervical

Screening period

FIGO 2018 IIIC-IVA cervical cancer (LN involvement)

Part I: Diagnosis (Day-154) to Day-1

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

Part II: Day -56 to -1

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

Randomization

Treatment period

period Endpoints

Max 56 days after the end of CCRT

Arm A

Volrustomig 750mg IV Q3W for 24 months

N=1000

Stratification factors

low/negative)

IIIC2 vs. IVA)

Asia)

PD-L1 expression (PD-L1 high expression vs.

FIGO stage (IIIC1 vs.

Region (Asia vs. non-

R 1:1

Arm B

Placebo IV Q3W for 24 months

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

Cervical Cancer 1st Line

Recurrent/Metastatic



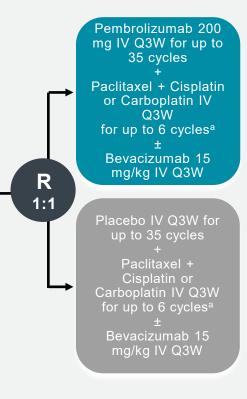


KEYNOTE-826: Study Design and Results

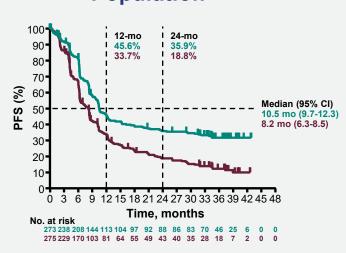
A phase 3 randomized, double-blind, placebo-controlled trial of pembrolizumab (MK-3475) plus chemotherapy vs chemotherapy plus placebo for the first-line treatment of persistent, recurrent, or metastatic cervical cancer

Key Eligibility Criteria: 1,2

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

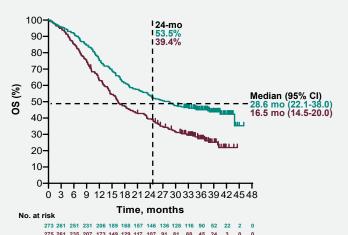


PFS: PD-L1 CPS ≥1 Population^{2,b}



	Pembro arm	Placebo arm		
n/N	171/273	220/275		
Events	62.6%	80.0%		
HR (95% CI)	0.58 (0.47-0.71)			

OS: PD-L1 CPS ≥1 Population²



	Pembro arm	Placebo arm	
n/N	153/273	201/275	
Events	56.0%	73.1%	
HR (95% CI)	0.60 (0.49-0.74)		

Columbo N et al NEJM 2021.

Primary Endpoints: PFS (per RECIST v1.1 by investigator),

OS

Secondary Endpoints: ORR, DOR, 12-mo PFS, safety





BEATcc (ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030): Study Design and Efficacy

A randomized phase III trial of first-line atezolizumab combined with a platinum doublet and bevacizumab for metastatic (stage IVB), persistent or recurrent cervical cancer

Key Eligibility Criteria:1,2

- Metastatic, persistent or recurrent cervical cancer not amenable to curative therapy
- GOG/ECOG PS
- No prior systemic anti-cancer therapy for R/M CC
- In patients with pelvic disease, no bladder or rectal mucosa involvement
- Available archival or fresh tumor sample for PD-L1 expression

Stratified by:

- Prior concurrent chemoradiation (Y/N)
- Histology (squamous cell carcinoma vs adenocarcinoma including Adenosquamous carcinoma)
- · Chemotherapy backbone

Atezolizumab 1200 mg + Bevacizumab 15 mg/kg + Paclitaxel+ cis/carboplatin^a all IV Q3W

 Continued until disease progression/unacceptable toxicity

N = 410

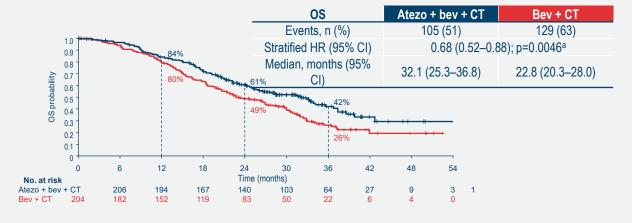
R

1:1

Bevacizumab 15 mg/kg + Paclitaxel + cis/carboplatin^a all IV Q3W **Dual primary endpoint: PFS**



Dual primary endpoint: OSc



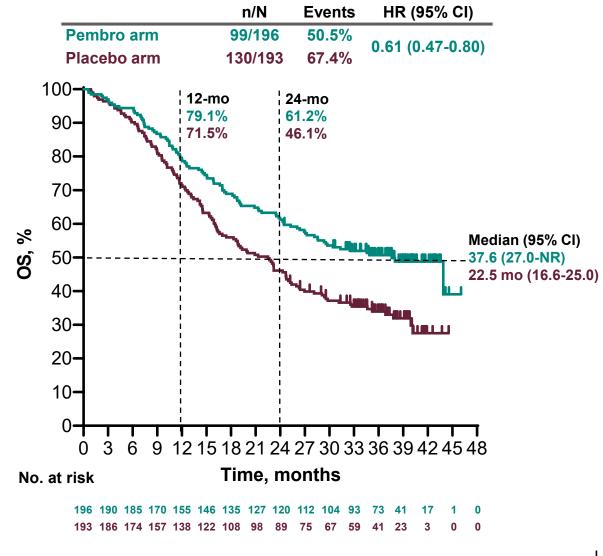
Oaknin A et al ESMO virtual 2023.



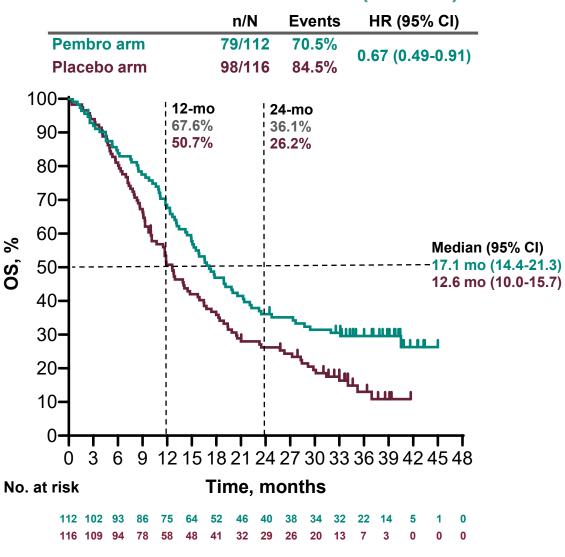


OS by Bevacizumab Use, All-Comer Population

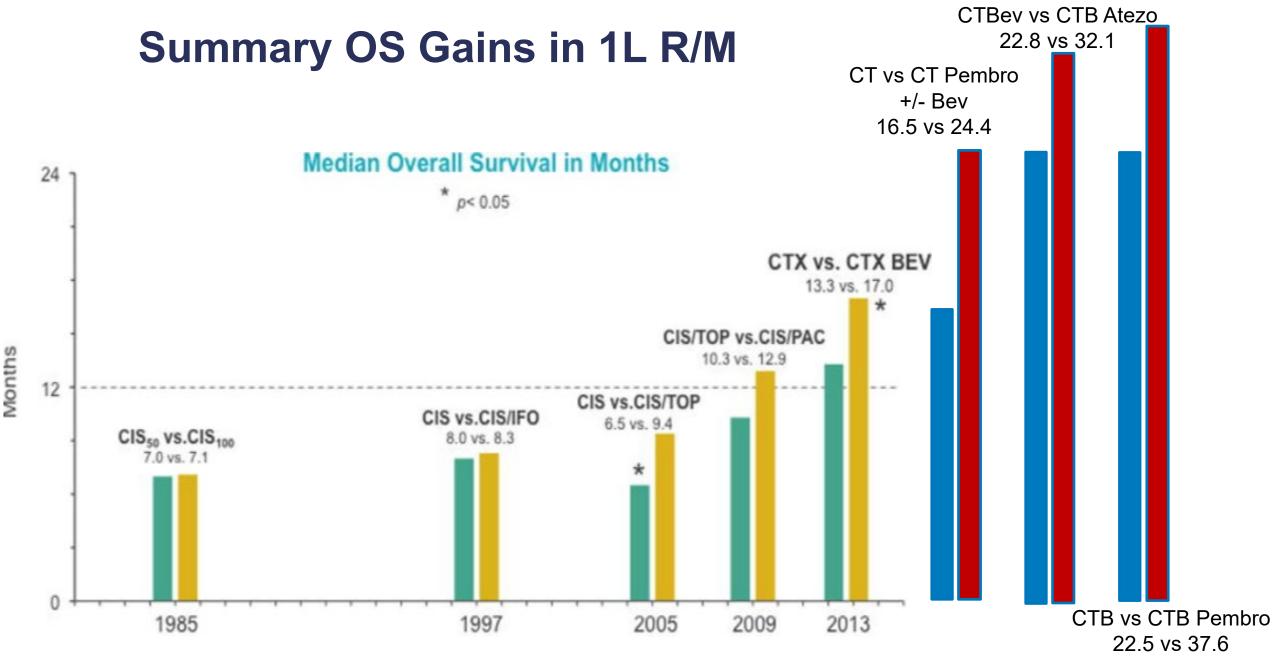
With Bevacizumab (N=389)



Without Bevacizumab (N=228)



Lorusso K et al. ESGO 2023.



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.

Table 1. Selected Adverse Events among the Study Patients, According to Treatment Group.*					
Event	Chemotherapy Alone (N = 219)	Chemotherapy plus Bevacizumab (N=220)	Odds Ratio (95% CI)	P Value	
	no. of p	patients (%)			
Gastrointestinal events, excluding fistulas (grade ≥2)	96 (44)	114 (52)	1.38 (0.93–2.04)	0.10	
Fistula (grade ≥3)					
Gastrointestinal	0	7 (3)	NA (1.90–∞)	0.02	
Genitourinary	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12	
Total†	1 (<1)	13 (6)	13.69 (2.01–584.00)	0.002	
Hypertension (grade ≥2)‡	4 (2)	54 (25)	17.50 (6.23–67.50)	<0.001	
Proteinuria (grade ≥3)	0	4 (2)	NA (0.90–∞)	0.12	
Pain (grade ≥2)	62 (28)	71 (32)	1.21 (0.79–1.85)	0.41	
Neutropenia (grade ≥4)	57 (26)	78 (35)	1.56 (1.02–2.40)	0.04	
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)	1.00 (0.40–2.48)	1.00	
Thromboembolism (grade ≥3)	3 (1)	18 (8)	6.42 (1.83–34.4)	0.001	
CNS bleeding (grade ≥3)	0	0	NA		
Gastrointestinal bleeding (grade ≥3)∫	1 (<1)	4 (2)	4.04 (0.39–200.00)	0.37	
Genitourinary bleeding (grade ≥3)∫	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12	





Grades 3-5 Treatment-Related Adverse Events of Interest

	Pembro Arm ^a (N=308)		Placebo Arm ^a (N=309)	
	Bev Yes (N=196)	Bev No (N=111)	Bev Yes (N=193)	Bev No (N=116)
Hypertension	11.7%	0	13%	0.9%
Perforation	2.5%	0	1.5%	0
Pelvic fistula ^b	2.5%	1.8%	4.7%	0
Other fistula ^c	0.5%	0	1.5%	0
Embolism	0.5%	0	1.0%	1.7%





Cervical Cancer 2nd Line

+ Recurrent/Metastatic





Current NCCN Guidelines

Released September 2023



NCCN Guidelines Version 1.2024 Cervical Cancer

NCCN Guidelines Index Table of Contents Discussion

SYSTEMIC THERAPY FOR CERVICAL CANCER^a

	Squamous Cell Carcinoma, Adenocarcinoma	a, or Adenosquamous Carcinoma		
Chemoradiation ^b	on ^b Recurrent or Metastatic Disease			
	First-line Therapy ^{b,d} Second-line or Subsequent Therapy ⁱ			
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant Other Recommended Regimens ^c (if cisplatin and carboplatin are unavailable) • Capecitabine/ mitomycin ¹ • Gemcitabine ² • Paclitaxel ^{3,4}	Preferred Regimens • PD-L1-positive tumors • Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)e.f.g.h.5 • Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)e.f.g.h.5 • Cisplatin/paclitaxel/bevacizumabe.h.6 (category 1) • Carboplatin/paclitaxel/bevacizumabe.h Other Recommended Regimens • Cisplatin/paclitaxel (category 1) ^{7,8} • Carboplatin/paclitaxel (category 1) ^{7,8} • Carboplatin/paclitaxel/bevacizumabe.h Other Recommended Regimens • Cisplatin/paclitaxel (category 1) ^{7,8} • Carboplatin/paclitaxel/bevacizumabe.h.6,11 (category 1) • Topotecan/paclitaxel/bevacizumabe.h.6,11 • Cisplatin/topotecan ¹¹ • Cisplatin/topotecan ¹¹ • Cisplatin ^{12,13}	Preferred Regimens Pembrolizumab for TMB-H tumors ^{f,j} or PD-L1-positive ^g or MSI-H/dMMR tumors ^{f,14} Tisotumab vedotin-tftv ¹⁵ Cemiplimab ^{f,16} Other Recommended Regimens Bevacizumab ^e Paclitaxel ^{13,17} Albumin-bound paclitaxel Docetaxel Fluorouracil Gemcitabine Pemetrexed Topotecan Vinorelbine Irinotecan Useful in Certain Circumstances PD-L1-positive tumors Nivolumoli,0.18 HER2-positive tumors (IHC 3+ or 2+) Fam-trastuzumab deruxtecan-nxki ¹⁹ KET gene rasion-positive tumors Selpercatinib		
		NTRK gene fusion-positive tumors Larotrectinib Entrectinib		

In the post immunotherapy patient:

The opportunities are:

For all: Tisotumab vedotin

For her2 high: Trastuzumab deruxtecan

Antibody-drug conjugates





InnovaTV 301 (ENGOT cx-12/GOG 3057): Study Design

A randomized, open-label, phase 3 confirmatory trial of tisotumab vedotin vs investigator's choice chemotherapy in 2L/3L recurrent or metastatic cervical cancer¹

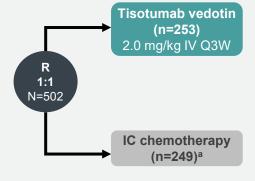
Key Eligibility Criteria²

- Recurrent or metastatic cervical cancer
- Disease progression on or after chemotherapy doublet ± bevacizumab and an anti-PD-(L)1 agent, if eligible and available
- ≤2 prior lines
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

Stratification Factors

- ECOG PS (0 vs 1)
- Prior bevacizumab (yes vs no)
- Prior anti-PD-(L)1 therapy (yes vs no)
- Geographic region (US, Europe, Other)

Previous anti-PD-1 or anti-PD-L1 therapy was permitted



IC Chemotherapy

- Topotecan
- Vinorelbine
- Gemcitabine
- Irinotecan
- Pemetrexed

Primary endpoint: OSb

Secondary endpoints: PFS°, ORR°, Safety

Baseline Patient and Disease Characteristics

	Tisotumab Vedotin (N=253)	IC Chemotherapy (N=249)
Number of prior r/m systemic regimens, n(%) 1 2 Unknown	159 (62.8) 93 (36.8) 1 (0.4)	149 (59.8) 100 (40.2) 0
Prior bevacizumab, n (%)	164 (64.8)	157 (63.1)
Prior anti-PD-(L)1 therapy, n (%)	71 (28.1)	67 (26.9)
Prior radiation therapy for cervical cancer, n (%)	205 (81.0)	203 (81.5)

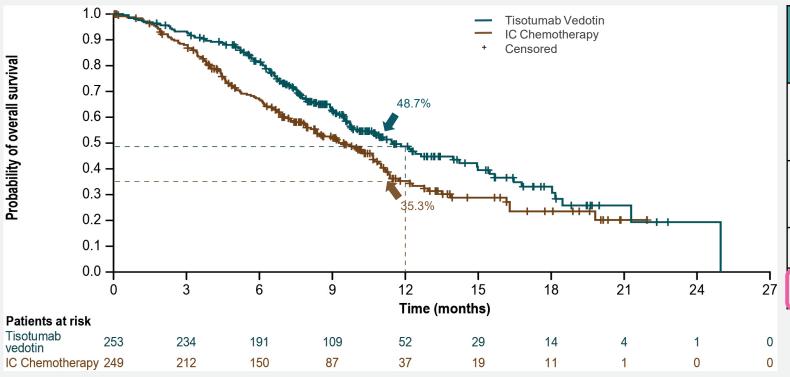
Baseline patient demographics were balanced across both arms





InnovaTV 301 (ENGOT cx-12/GOG 3057): Overall Survival

Overall Survival (Primary endpoint)



Treatment Events/Total	Median (95% CI)	
Tisotumab Vedotin 123/253 11.	5 (9.8, 14.9)	
IC Chemotherapy 140/249 9.5	5 (7.9, 10.7)	

Stratified log-rank P value^a: 0.0038

HR (95% CI): 0.70 (0.54, 0.89)





DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

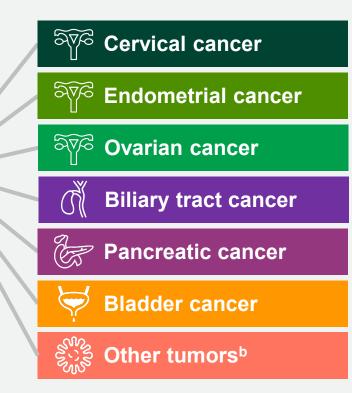
An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
 - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines¹)^a
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd 5.4 mg/kg q3w

> n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)



Primary endpoint

 Confirmed ORR (investigator)^c

Secondary endpoints

- DOR^c
- DCR°
- PFS^c
- OS
- Safety

Data cut-off for analysis:

Nov 16, 2022

IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization. 1. Hofmann M, et al. *Histopathology* 2008;52(7):797–805.

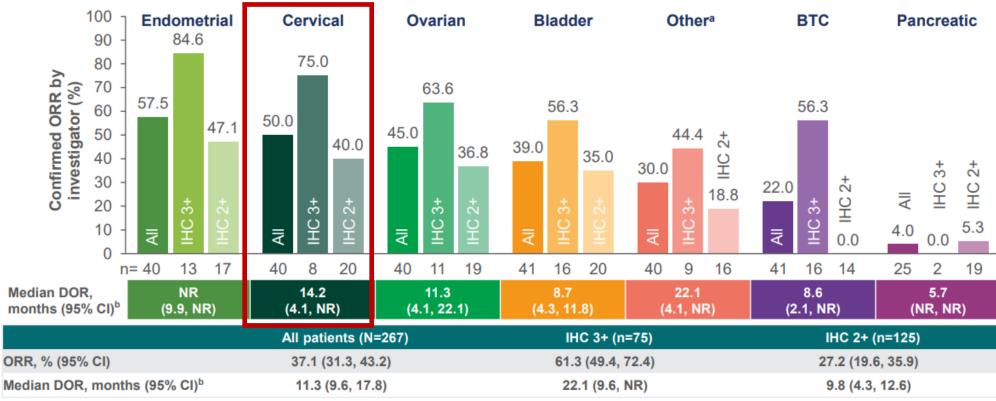




^aPatients were eligible for either test. All patients were centrally confirmed. ^bPatients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. ^cInvestigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

²L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2:

Objective response and duration of response



Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. aResponses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer; bincludes patients with a confirmed objective response only

BTC, billiary tract cancer; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

Additional information available https://bit.ly/3rydQjX

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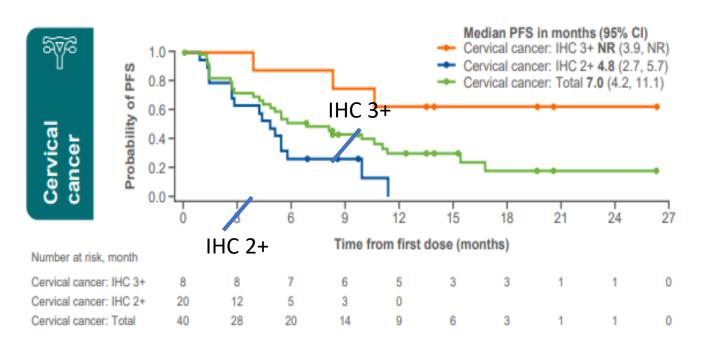


Funda Meric-Bernstam





PFS by her2 1 vs 2 vs 3+



Circle indicates a censored observation

CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; F



Funda Meric-Bernstam

- Still small numbers
 - N=40
 - 3+ n=8
 - •2+ n=20
- Benefit appears to be in 3+?





Assessment of her2 expression

Fig.1 Comparison of breast and gastric cancer HER2 interpretive guidelines				
IHC score	Breast (biopsy or resection)	Gastric resection	Gastric biopsy	
0	No staining; incomplete or faint/ barely perceptible staining in ≤10% of invasive tumor cells	No staining; non- membranous staining; staining in <10% of cells	No staining; non- membranous staining; staining in <10% of cells	
1+	Incomplete or faint/barely perceptible in >10% of invasive tumor cells	Complete/basolateral/ lateral staining in ≥10% of cells evident only at 40x	Complete/basolateral/ lateral staining in ≥10% of cells evident only at 40x	
2+	Incomplete or weak/moderate circumferential membranous staining in >10% of invasive tumor cells, or complete intense circumferential membranous staining in ≤10% of invasive tumor cells	Complete/basolateral/ lateral staining in ≥10% of cells evident at 10–20x	Complete/basolateral/ lateral staining in ≥10% of cells evident at 10–20x	
3+	Complete intense circumferential membranous staining in >10% of invasive tumor cells	Complete/basolateral/ lateral staining in ≥10% of cells evident at 4x	Cluster of at least 5 cells with complete/ basolateral/lateral staining evident at 4x	

https://www.captodayonline.com/second-act-for-her2-in-gastric-cancers. Accessed 11/1/2023. Adapted from Hofmann M, et al. *Histopathology*. 2008;52:797–805. Rüschoff J, et al. *Virchows Arch*. 2010;457:299–307. Wolff AC, et al. *Arch Pathol Lab Med*. 2014;138(2):241–256.

Gastric staining in DESTINY PanTumor02

Appears more predictive than breast but maybe just more active drug in T-DXd







ROCC GOG-3043 Recruitment Update

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

Region	Country	Sites Activated	# Patients Screened	# Patients SF	# Patients Randomized	# Patients Treated
NA	United States	60	111	6	105	94
NA	Canada	2	2	0	2	2
SA	Brazil	0	0	0	0	0
APAC	South Korea	0	0	0	0	0

20 Sites Pending Activation:

