What is appropriate adjuvant therapy for gastric-type mucinous carcinoma of the uterine cervix?

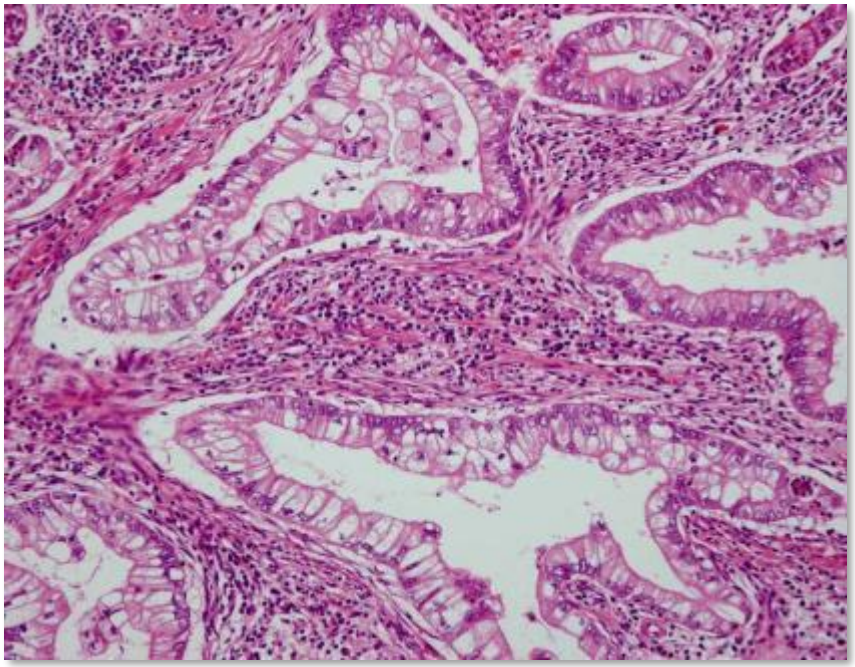
Shin Nishio

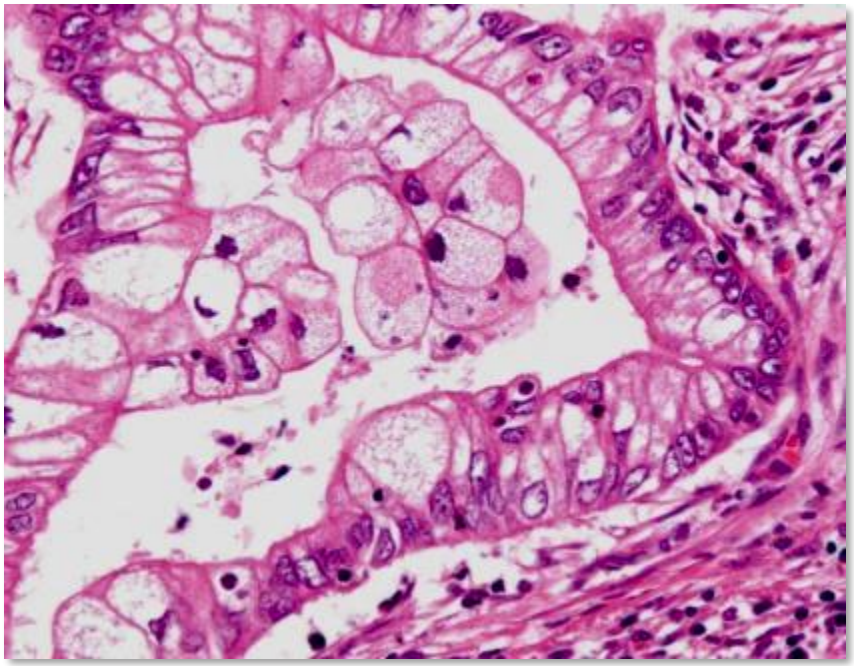
What is Gastric Adenocarcinoma of the Cervix (GAS)?

- The newly defined HPV-independent mucinous carcinoma of the cervix [1-4]
- Accounts for about 20-25% of all cervical adenocarcinomas [1-4]
- Prevalent in the 40s, 80% are well-differentiated [1-6]
- It is refractory to treatment and has a poor prognosis [5-6]

1. Kojima A, et al. Am J Surg Pathol 2007; 31: 664-72.
2. Kusanagi Y, et al. Am J Pathol 2010; 177: 2169-75.
3. Park KJ, et al. Am J Surg Pathol 2011; 35: 633-46
4. Houghton O, et al. Histopahology 2010; 57: 342-50
5. Kojima A, et al. Int J Gynecol Cancer 2018; 28: 99-106
6. Nishio S, et al. Gynecol Oncol 2019; 153:13-19

Histopathology of GAS





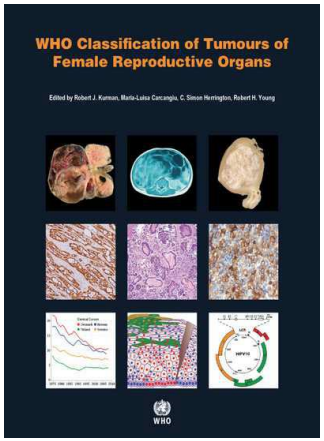
Morphologic Criteria

- Abundant cytoplasm
- Clear or pale eosinophilic
- Distinct cell borders

Kojima A, et al. Am J Surg Pathol 2007; 31: 664-672.

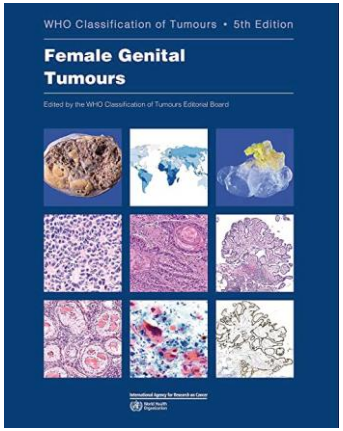
Adenocarcinoma of the Cervix WHO 2014

- **Usual-type adenocarcinoma (UEA)**
  - Villoglandular (pattern)
- Mucinous adenocarcinoma
  - **Gastric (includes Minimal Deviation Adenocarcinoma: MDA)**
  - Intestinal
  - Signet-ring cell
- Endometrioid adenocarcinoma
- Clear cell adenocarcinoma
- Serous adenocarcinoma
- Mesonephric adenocarcinoma



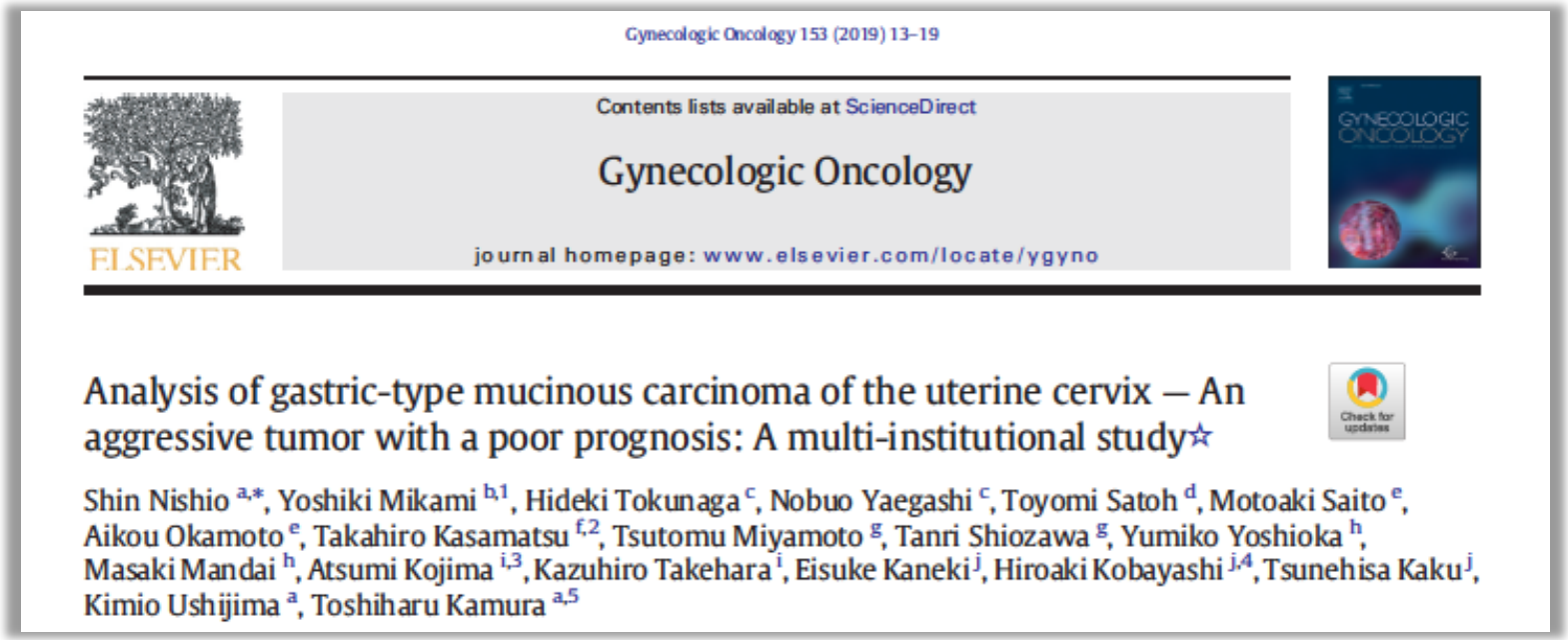
Adenocarcinoma of the Cervix WHO 2020

- Adenocarcinoma NOS
- Adenocarcinoma, HPV-associated
- **Adenocarcinoma, HPV-independent, gastric type**
- Adenocarcinoma, HPV-independent, clear cell type
- Adenocarcinoma, HPV-independent, mesonephric type
- Adenocarcinoma, HPV-independent, NOS
- Endometrioid adenocarcinoma NOS



A Cohort Study of Gastric-type Adenocarcinoma (GAS) of the Uterine Cervix

Multi-institutional Study by Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG)



Gynecologic Oncology 153 (2019) 13–19

Contents lists available at ScienceDirect

Gynecologic Oncology

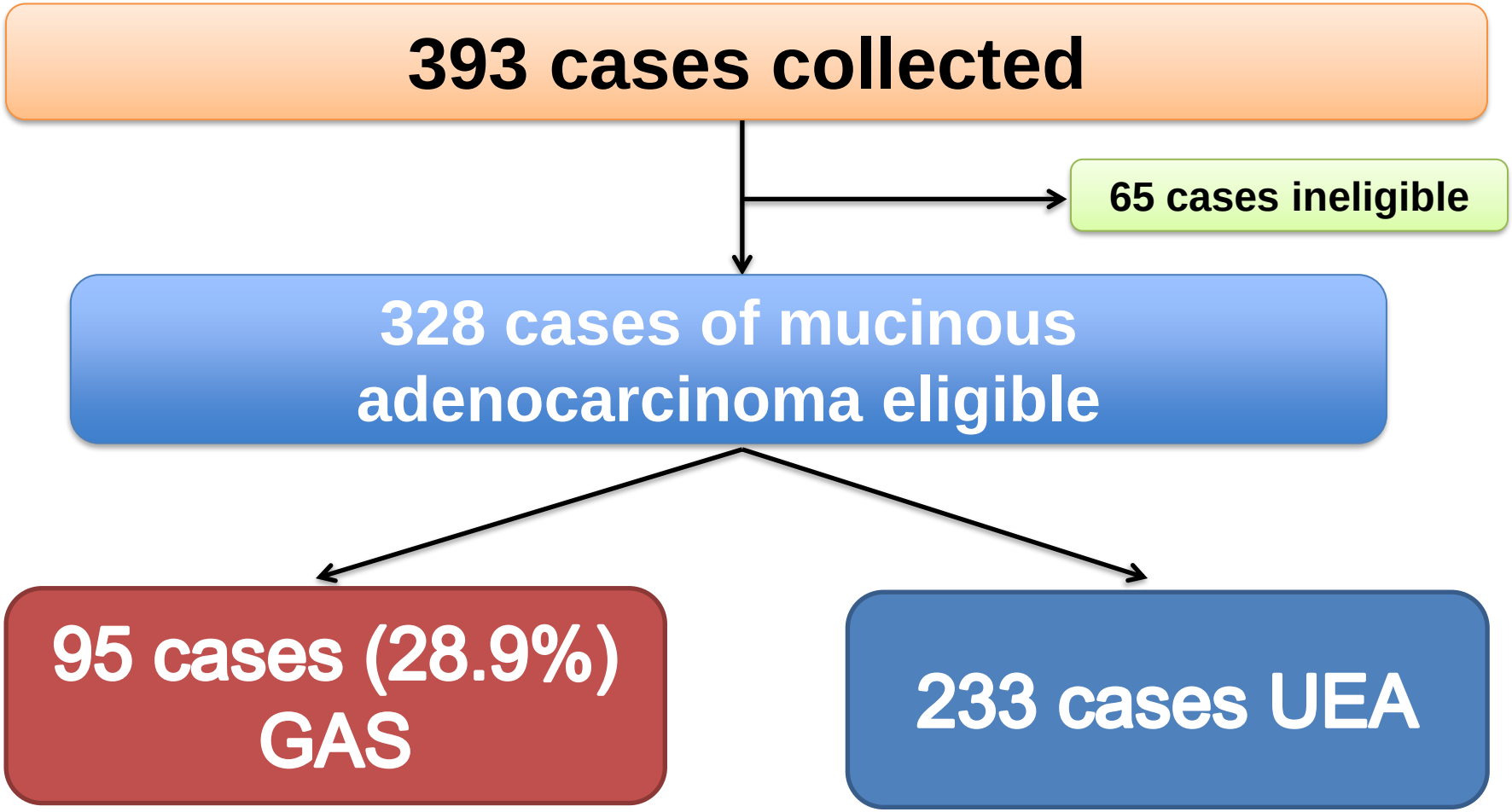
journal homepage: www.elsevier.com/locate/ygyno

Analysis of gastric-type mucinous carcinoma of the uterine cervix — An aggressive tumor with a poor prognosis: A multi-institutional study☆

Shin Nishio [a,*], Yoshiki Mikami [b,1], Hideki Tokunaga [c], Nobuo Yaegashi [c], Toyomi Satoh [d], Motoaki Saito [e], Aikou Okamoto [e], Takahiro Kasamatsu [f,2], Tsutomu Miyamoto [g], Tanri Shiozawa [g], Yumiko Yoshioka [h], Masaki Mandai [h], Atsumi Kojima [i,3], Kazuhiro Takehara [i], Eisuke Kaneki [j], Hiroaki Kobayashi [j,4], Tsunehisa Kaku [j], Kimio Ushijima [a], Toshiharu Kamura [a,5]

Nishio S, et al. Gynecol Oncol 2019; 153: 13-19

Study Schema 1



Nishio S, et al. Gynecol Oncol 2019; 153: 13-19

Comparison with GAS and UEA, clinicopathological factors

Factor	Histology		P-value
	GAS	UEA	
pT Stage			
IA	4	18	**P<0.0001**
IB1	33	165	
IB2	22	21	
IIA	12	10	
IIB	24	19	
Tumor diameter			
<40mm	50	189	**P<0.0001**
≥40	45	44	
Stromal invasion			
<2/3	38	183	**P<0.0001**
≥2/3	57	50	
LVSI			
Present	63	71	**P<0.0001**
Absent	32	162	

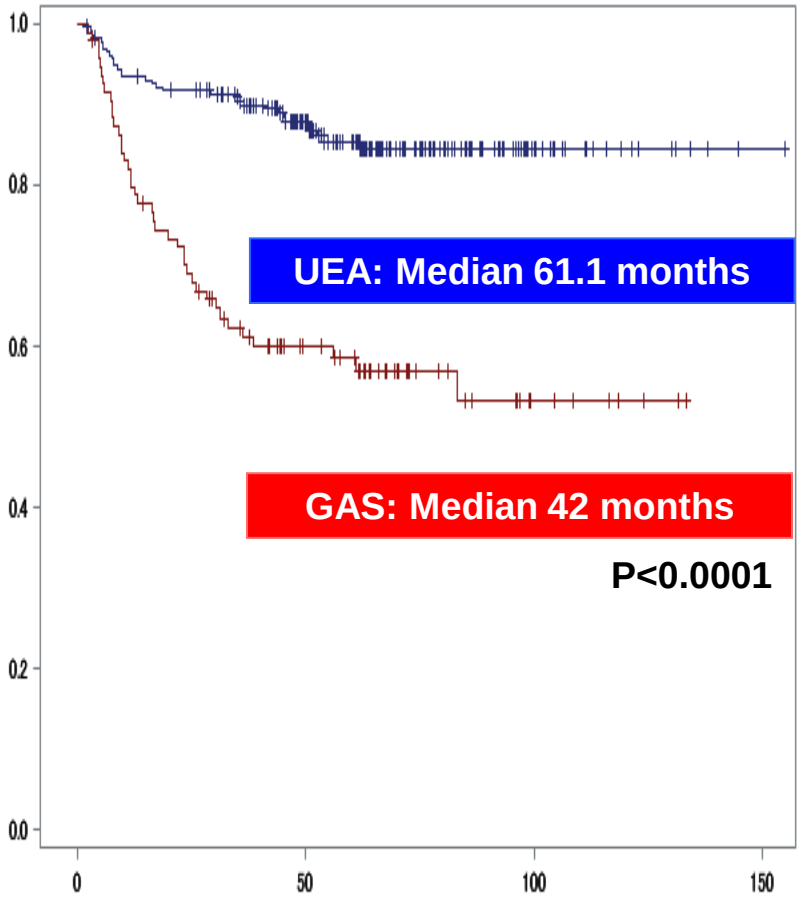
Comparison with GAS and UEA, clinicopathological factors (cont'd)

Factor	Histology		P-value
	GAS	UEA	
Parametrial invasion Present Absent	 25 70	 17 216	**P<0.0001**
Lymph node Mets* Present Absent	 33 57	 33 192	**P<0.0001**
Differentiation* Well Moderate, Poorly	 66 23	 167 42	P=0.2716
Ovary Mets Present Absent	 5 90	 3 230	**P=0.0481**
Ascites cytology* Positive Negative	 10 77	 8 197	**P=0.0136**

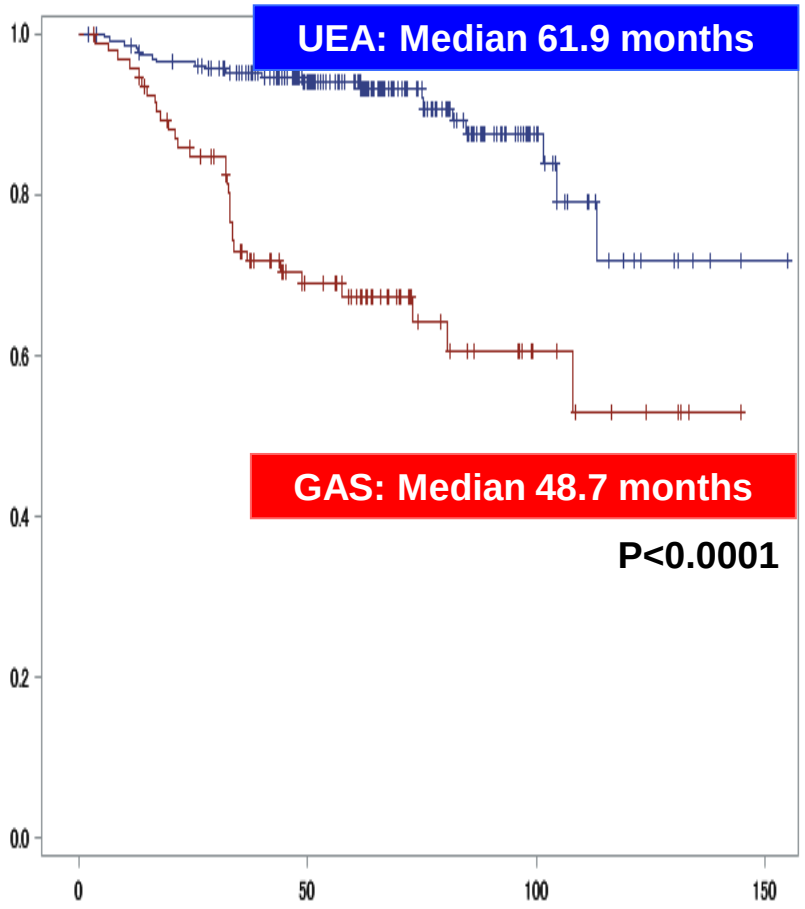
*including missing data

Kaplan-Meier Disease-free survival (DFS) and Overall survival (OS)

DFS



OS



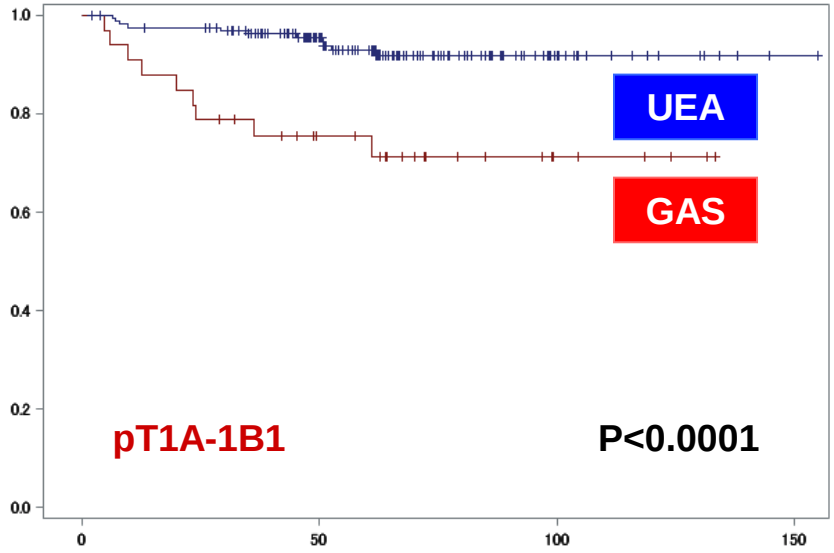
Nishio S, et al. Gynecol Oncol 2019; 153: 13-19

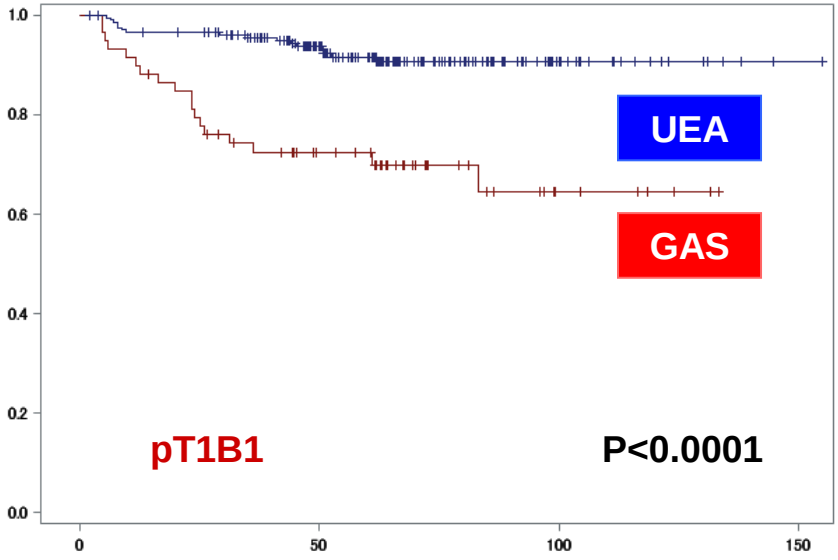
The effect on survival by multivariate analysis

Factor	P-value		Hazard Ratio		95%CI	
	PFS	OS	PFS	OS	PFS	OS
Tumor diameter	P=0.0001	P<0.0001	3.406	4.378	1.824-6.361	2.105-9.107
Parametrial invasion	P<0.0001	P=0.0035	3.461	2.885	1.864-6.428	1.416-5.879
Lymph node Mets	P=0.0064	P=0.0079	2.286	2.48	1.262-4.14	1.269-4.847
Differentiation	P=0.0003	P=0.0015	3.031	3.057	1.665-5.515	1.535-6.09
Ovary Mets	P<0.0001	P<0.0001	9.173	12.178	3.349-25.123	4.178-35.494
GAS	P=0.0032	P=0.001	2.361	3.034	1.333-4.182	1.566-5.877

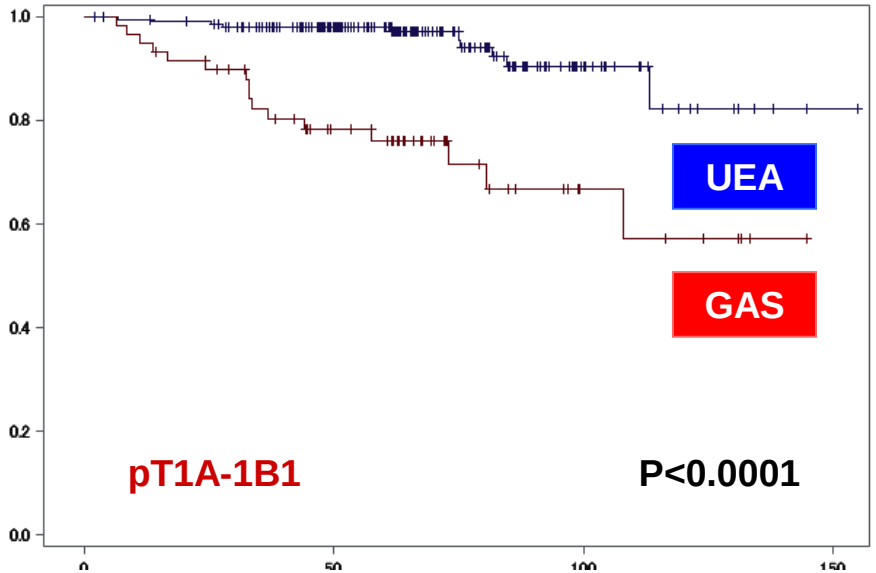
Survival curve of pT1A-1B1 and pT1B1

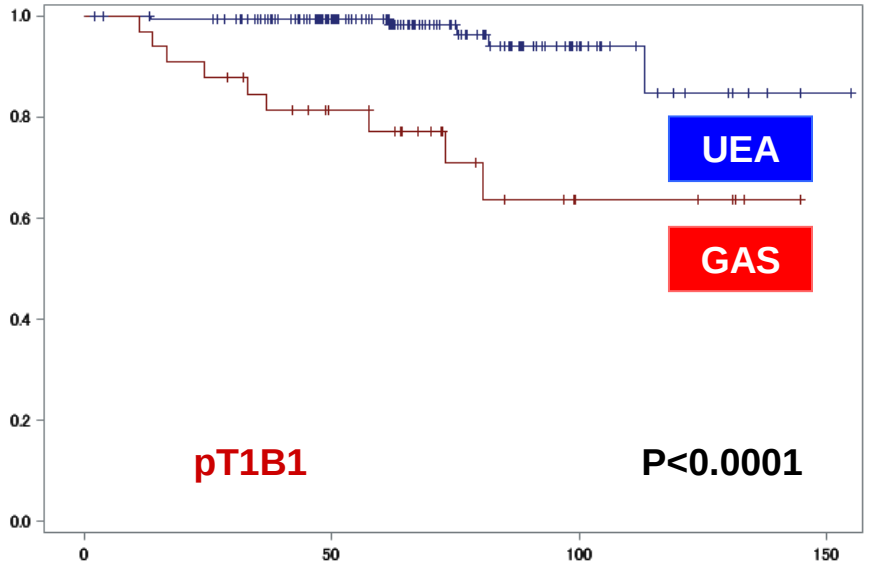
DFS





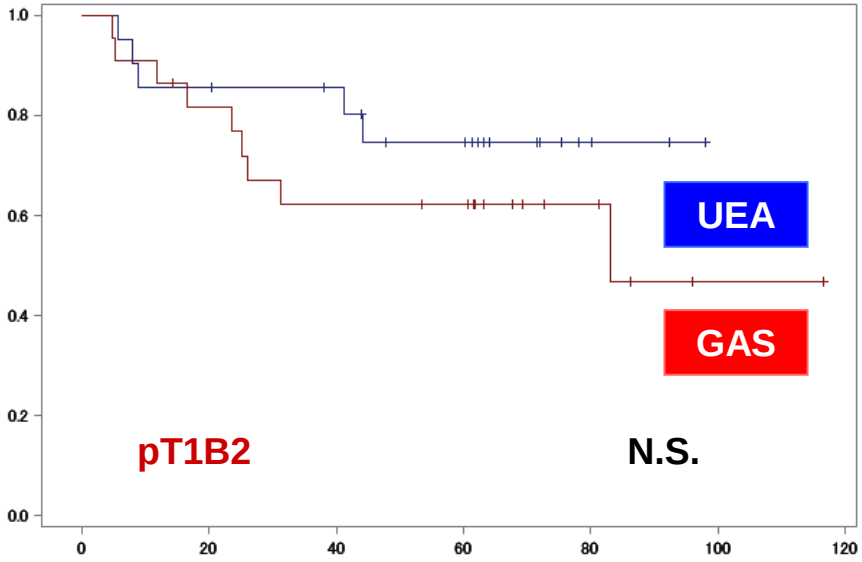
OS



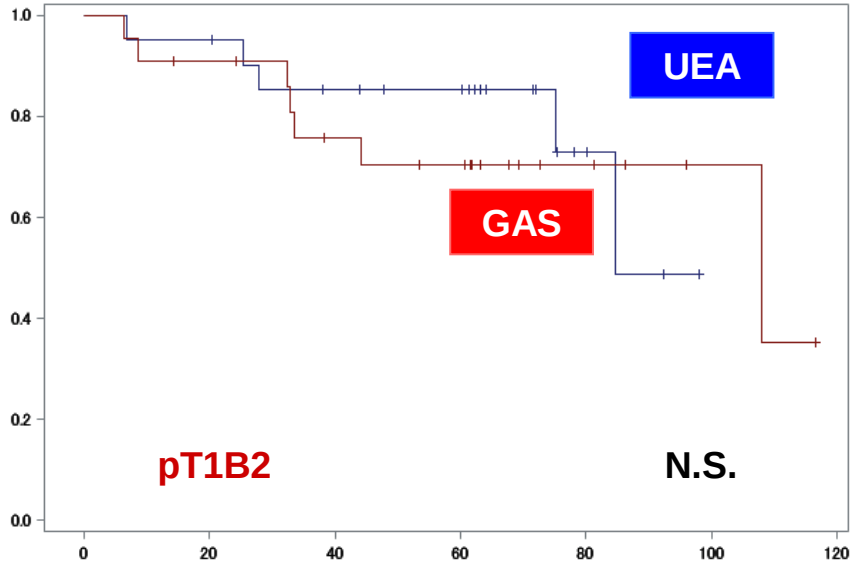


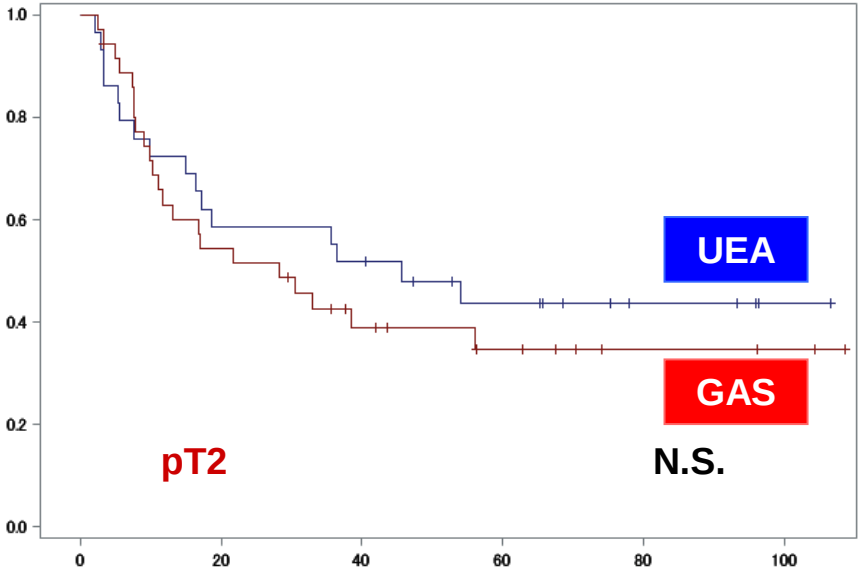
Survival curve of pT1B2 and pT2

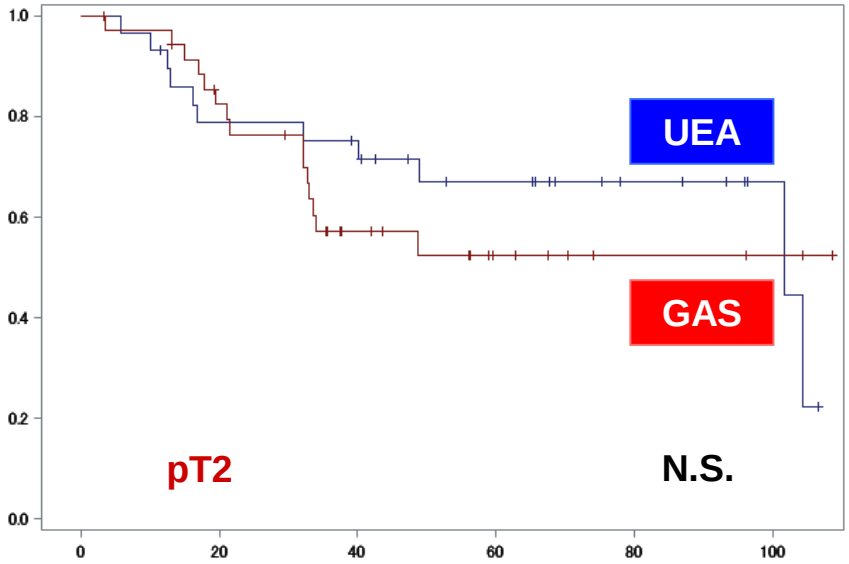
DFS



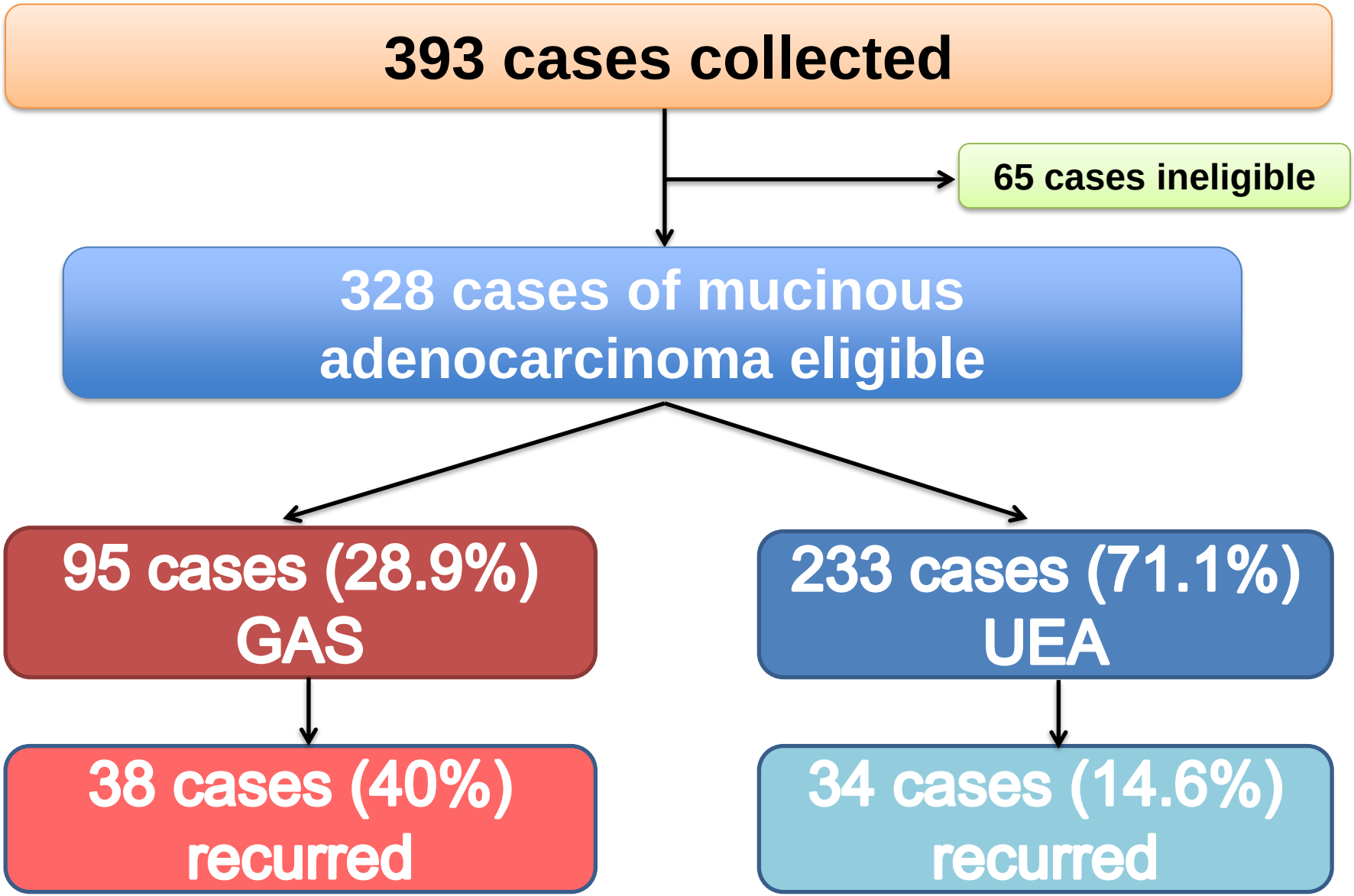
OS







Study Schema 2



Site of Recurrence*

Site	GAS	UEA
Brain	1	0
Lung	10	9
Liver	2	3
Peritoneum	3	1
Bone	2	0
Abdominal LYN	6	9
Pelvic LYN	6	7
Pelvis	8	5
Vaginal cuff	10	9

*Duplicated cases included

Site	GAS	UEA
Local site (L)	15	11
Distant site (D)	15	19
L+D	8	4

No significant difference between the groups

Response Rates for Chemotherapy by Histologic Type

Subtype	Response to CT（RECIST Criteria)					
	CR	PR	SD	PD	Response rate	
GAS (n=19)	2	5	3	9	36.8%	*
UEA (n=25)	3	5	5	12	32.0%	

*P=N.S.

Nishio S, et al. Gynecol Oncol 2019; 153: 13-19

Response Rates for Radiotherapy by Histologic Type

Subtype	Response to RT（RECIST Criteria)					
	CR	PR	SD	PD	Response rate	
GAS (n=12)	1	5	0	6	50.0%	*
UEA (n=11)	4	5	1	1	81.8%	

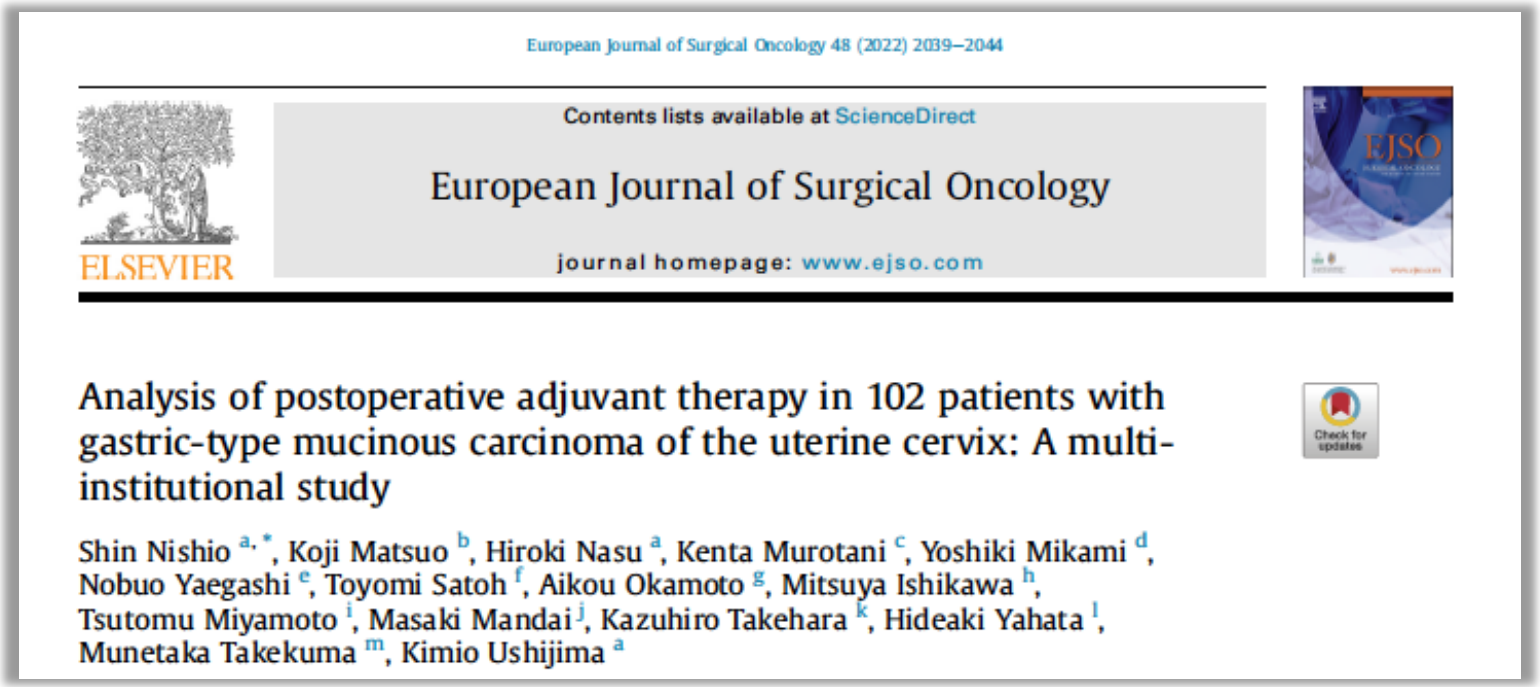
*P<0.001

Nishio S, et al. Gynecol Oncol 2019; 153: 13-19

Summary

- Among 328 endocervical adenocarcinomas, a total of 95 (28.9%) tumors were re-classified as GAS based on the novel criteria.
- As compared with UEA, GAS was significantly associated with a bulky mass, deep stromal invasion, lymph-vascular invasion, parametrial invasion, ovarian metastasis, positive ascitic cytology, pelvic lymph node metastasis, and pT factor, but was not correlated with tumor differentiation.
- DFS and OS were lower among patients with GAS compared to those with UEA.
- When stratified according to stage, patients with pTIA-IB1 adenocarcinoma had poorer outcomes, but the difference between groups with pTIB2 or more was not significant.

Analysis of postoperative adjuvant therapy in 102 patients with gastric-type mucinous carcinoma of the uterine cervix: a multi-institutional study



European Journal of Surgical Oncology 48 (2022) 2039–2044

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Analysis of postoperative adjuvant therapy in 102 patients with gastric-type mucinous carcinoma of the uterine cervix: A multi-institutional study

Shin Nishio [a,*], Koji Matsuo [b], Hiroki Nasu [a], Kenta Murotani [c], Yoshiki Mikami [d], Nobuo Yaegashi [e], Toyomi Satoh [f], Aikou Okamoto [g], Mitsuya Ishikawa [h], Tsutomu Miyamoto [i], Masaki Mandai [j], Kazuhiro Takehara [k], Hideaki Yahata [l], Munetaka Takekuma [m], Kimio Ushijima [a]

Nishio S, et al. Eur J Surg Oncol 2022; 48: 2039-44

Background

- The standard treatment for early-stage cervical cancer is radical hysterectomy or radiotherapy.
- In more than 80% of institutions in Japan, radical hysterectomy is the primary treatment for patients with stage IB1 and IIA1 cervical cancer[15].
- Adjuvant radiotherapy or concurrent chemoradiotherapy (CCRT) is recommended for patients with intermediate- or high-risk factors[16-19]. However, these strategies may not reduce distant metastasis and can cause severe gastrointestinal and urinary toxicity[20,21]. To avoid adverse events associated with adjuvant CCRT, many Japanese gynecologic oncologists administer chemotherapy[22].

To investigate the efficacy of adjuvant therapy for GAS

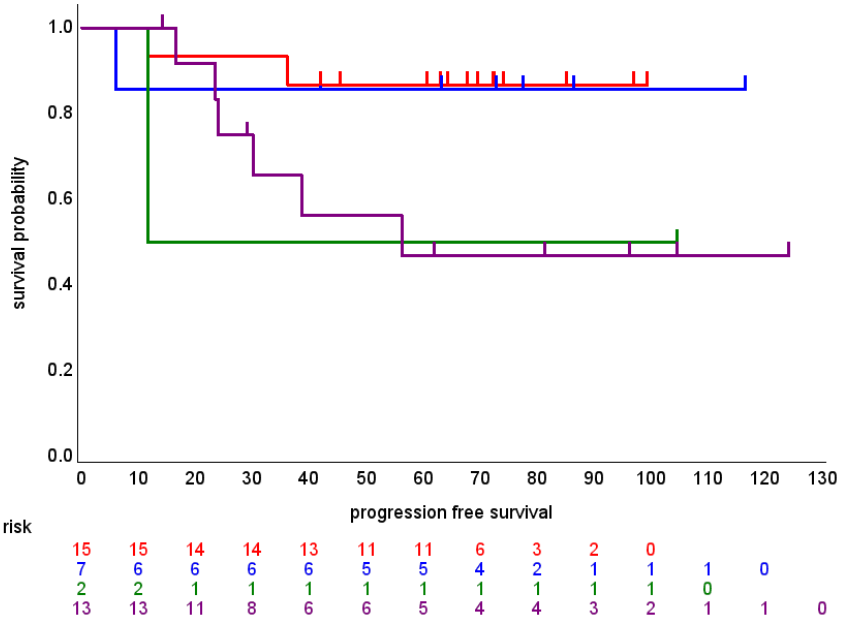
Risk classification for postoperative relapse of cervical cancer (JSGO)

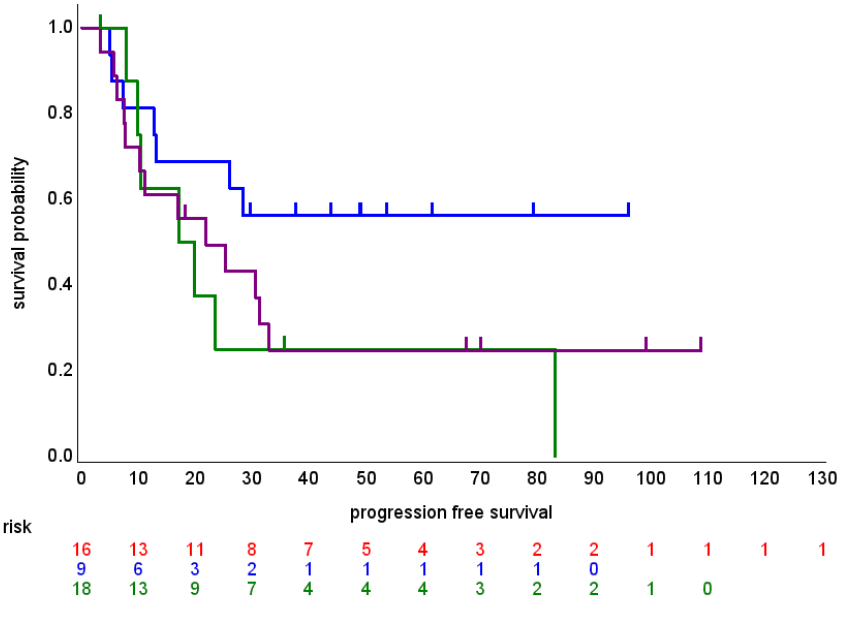
Low-risk group: Patients who satisfy all the following criteria:
1. Small cervical mass 2. Negative pelvic lymph node metastasis 3. Negative parametric invasion 4. Shallow cervical stroma invasion 5. Negative vascular invasion
Intermediate-risk group: Patients with negative pelvic lymph node metastasis and negative parametric invasion that satisfy any of the following criteria:
1. Large cervical mass 2. Deep cervical stromal invasion 3. Positive vascular invasion
High-risk group: Patients who satisfy either of the following items:
1. Positive pelvic lymph node metastasis 2. Positive parametric invasion

Type of adjuvant therapy

	None	RT	CCRT	CT	Total
Low-risk	16	0	0	1	**17**
Intermediate-risk	17	7	2	11	**37**
High-risk	6	15	9	18	**48**

Progression-free survival in the intermediate-risk group and in the high-risk group

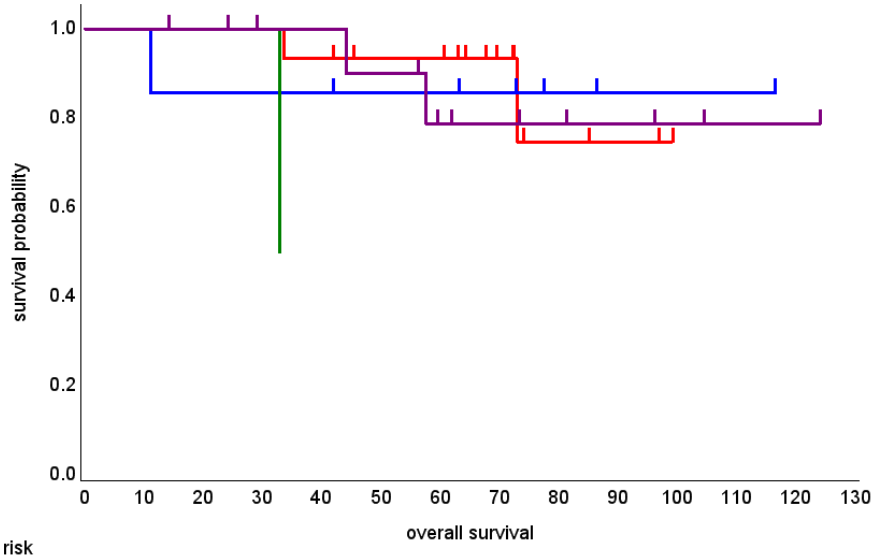


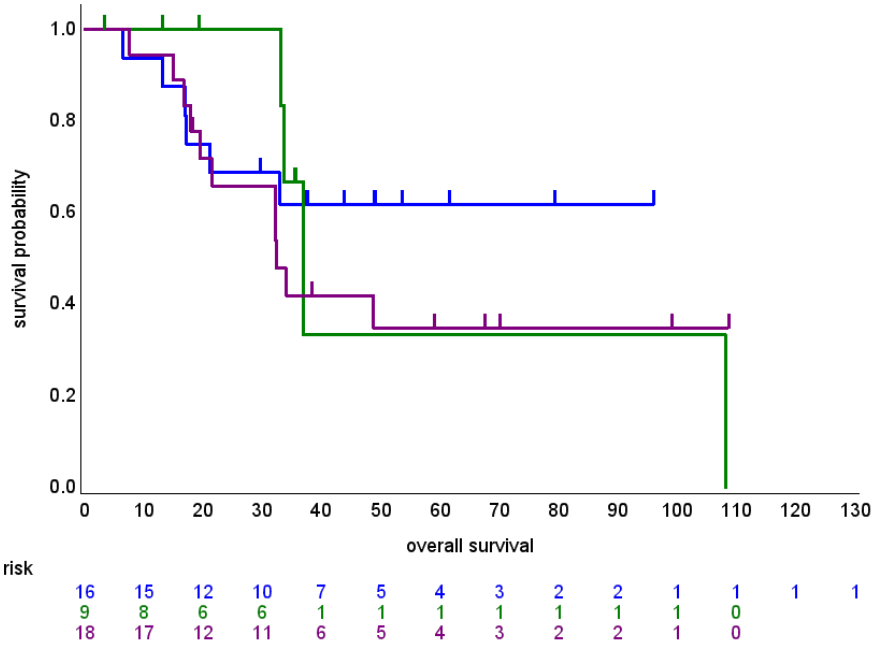


PFS in the intermediate-risk group and in the high-risk group (*P* = 0.141 and *P* = 0.169, respectively)

Nishio S, et al. Eur J Surg Oncol 2022; 48: 2039-44

Overall survival in the intermediate-risk group and in the high-risk group

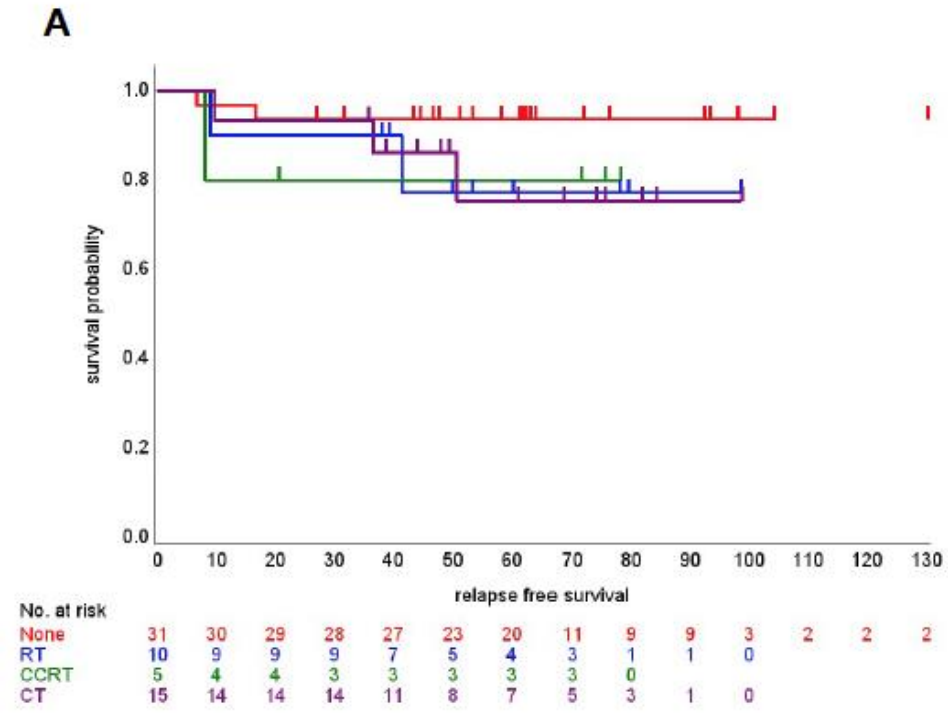


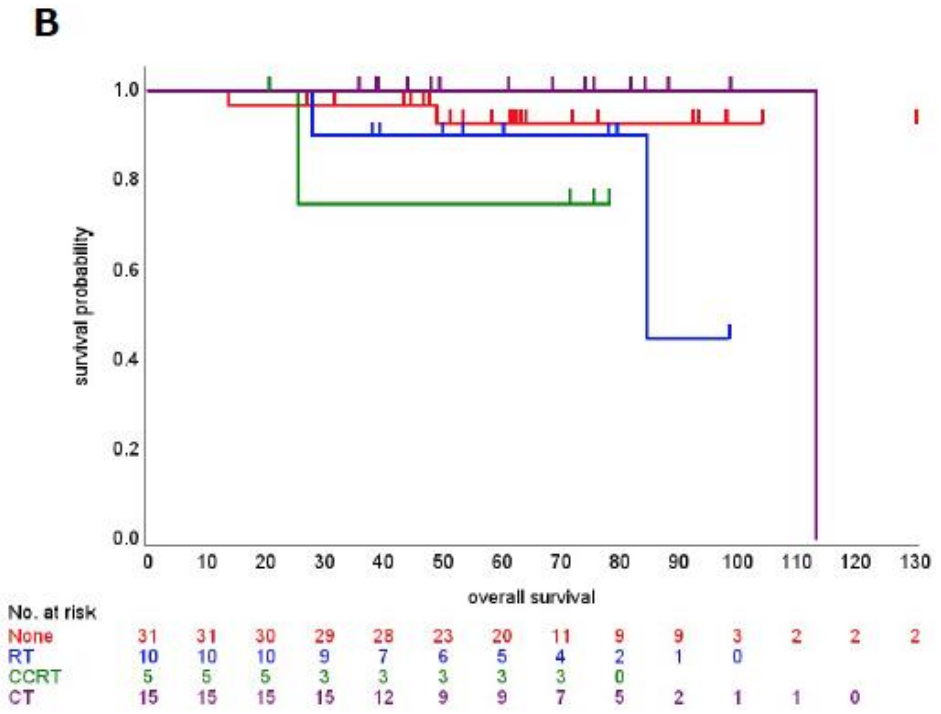


OS in the intermediate-risk group and in the high-risk group (*P* = 0.593 and *P* = 0.496, respectively)

Nishio S, et al. Eur J Surg Oncol 2022; 48: 2039-44

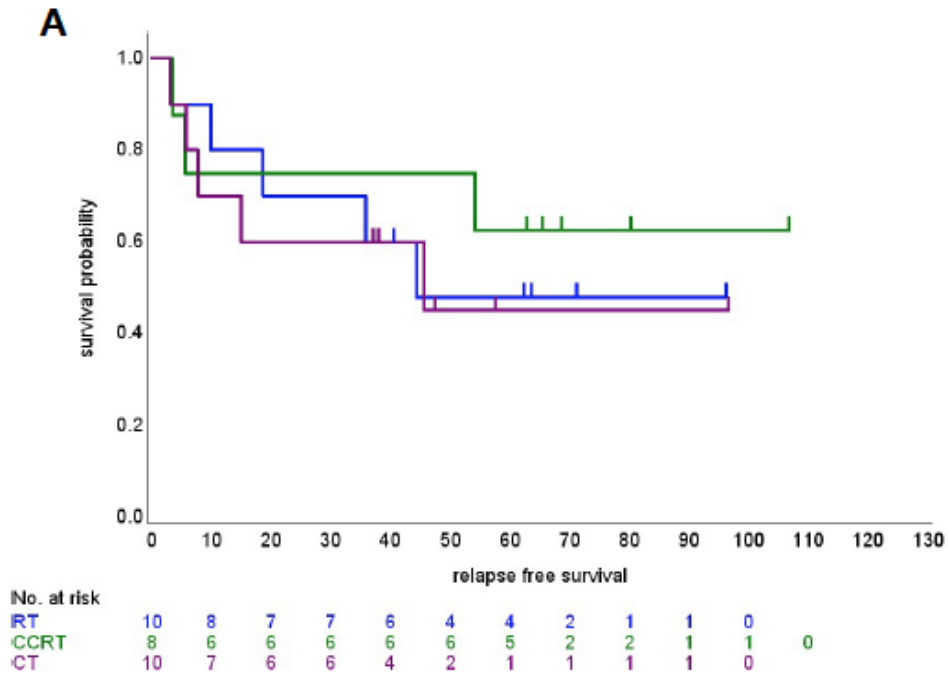
PFS and OS in the intermediate-risk group with UEA

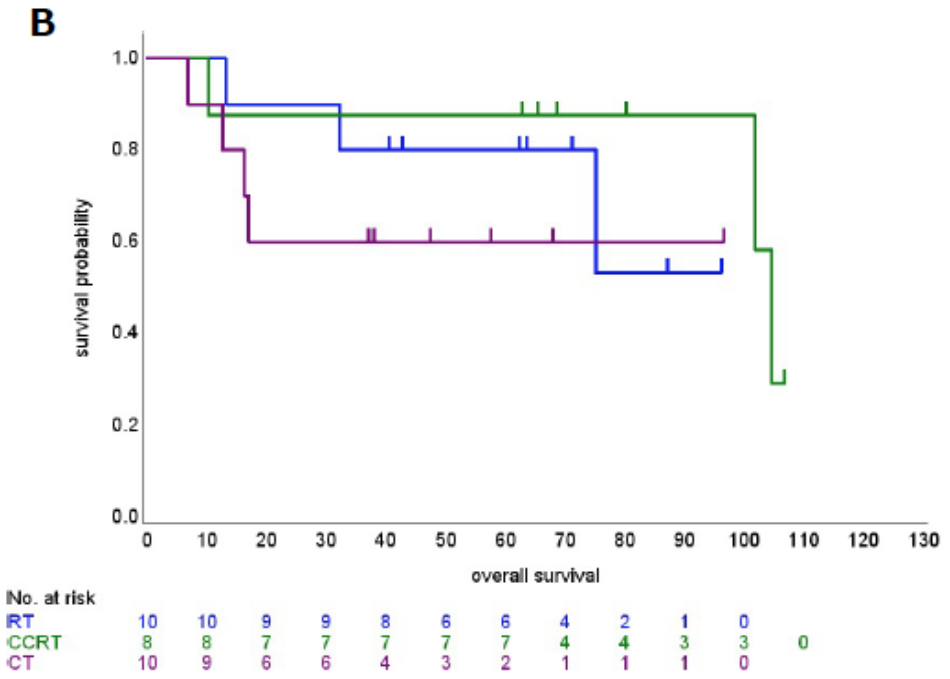




Nishio S, et al. Eur J Surg Oncol 2022; 48: 2039-44

PFS and OS in the high-risk group with UEA





Nishio S, et al. Eur J Surg Oncol 2022; 48: 2039-44

Summary of genomic profiling in GAS

Gene	%
TP53	32–74
CDKN2A	18-67
KRAS	17-36
SLX4	10-36
STK11	10-33
ARID1A	20-29
BRCA2	10-21
PTEN	20
PIK3CA	7-18
ELF	7-18
ERBB2	6-15
ERBB3	9–15
SMAD4	9–15
FGFR4	14
GNAS	9-11

Summary

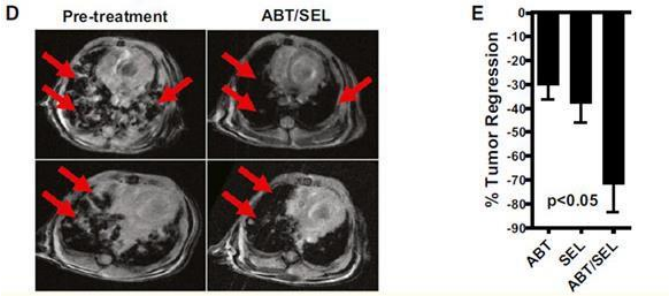
- In conclusion, the prognosis of GAS was again confirmed to be poor, even in cases of early-stage cancer and following surgical resection.
- Notably, postoperative **adjuvant chemotherapy** is associated with a **poor prognosis.**
- In the future, the use of targeted molecular therapies that take genetic background into account may help to achieve better clinical outcomes among patients with cervical carcinomas.

Target therapy for RAS

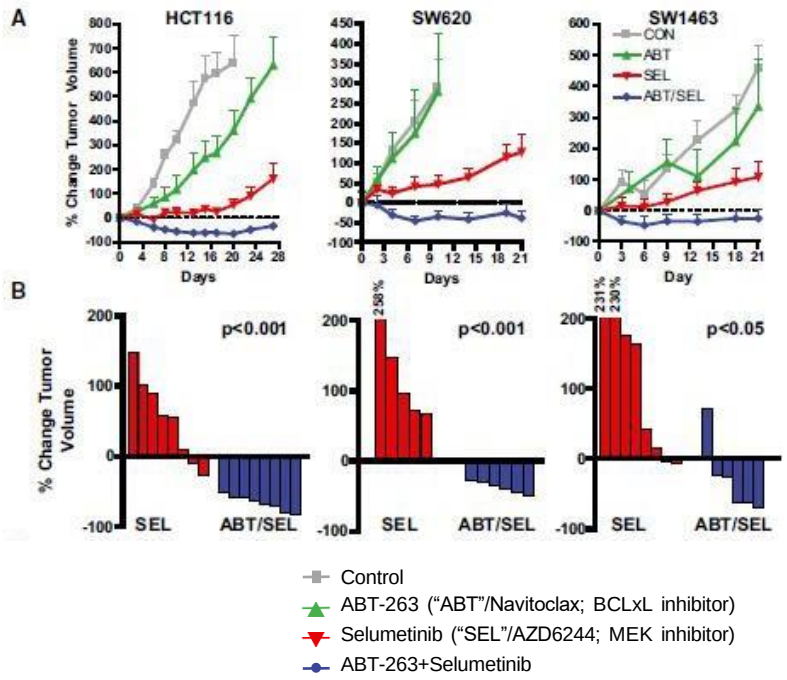
Activity of combination trametinib/navitoclax in patients with *RAS*-mutated gynecologic (GYN) cancers in a Phase 1/2 study

Preclinical data support synergistic activity between concurrent MEK and BCLxL inhibition

- BCLxLi + MEKi combination reduced tumor burden in 3 xenograft models of *KRAS* mutant colon cancer compared to either agent alone
- Similar efficacy in a syngeneic *KRAS* mutant lung cancer model
- Remissions were highly durable in many mice



ABT:	ABT-263/Navitoclax; BCLxL inhibitor
SEL:	Selumetinib; MEK inhibitor

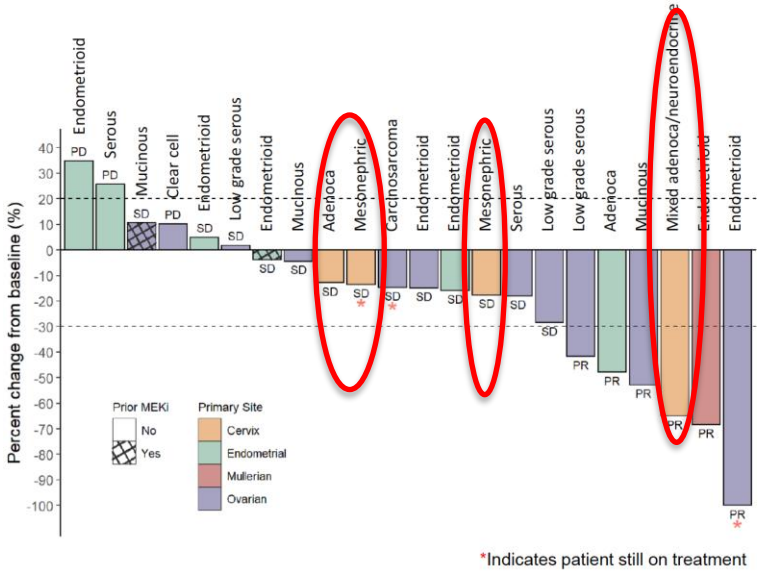


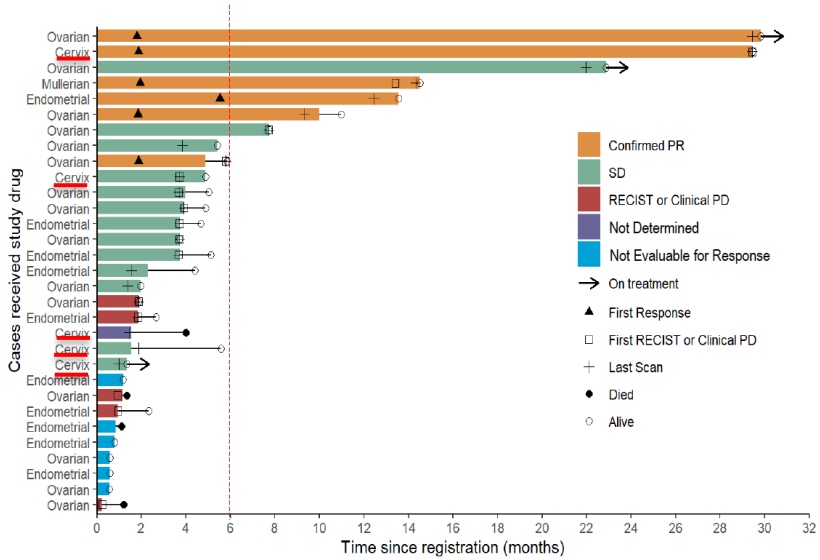
Corcoran et al., *Cancer Cell* 2013

Clinical Activity

	Part 1/Phase Ib Dose Escalation	Part 2/Phase II Expansion	Overall
	(N=7)	(N=24)	(N=31)
Best Overall Response			
Confirmed PR	1 (14.3%)	5 (20.8%)	6 (19.4%)
SD	4 (57.1%)	9 (37.5%)	13 (41.9%)
PD	0 (0%)	4 (16.7%)	4 (12.9%)
Not Determined*	0 (0%)	1* (4.2%)	1 (3.2%)
Not Evaluable	2 (28.6%)	5 (20.8%)	7 (22.6%)

*Patient's restaging imaging was performed without contrast and was deemed non-evaluable by RECIST criteria





Median PFS: 3.9 months (95% CI 3.7-13.4) PFS at 6 mos: 36.4% (95% CI 16.9-56.2%)

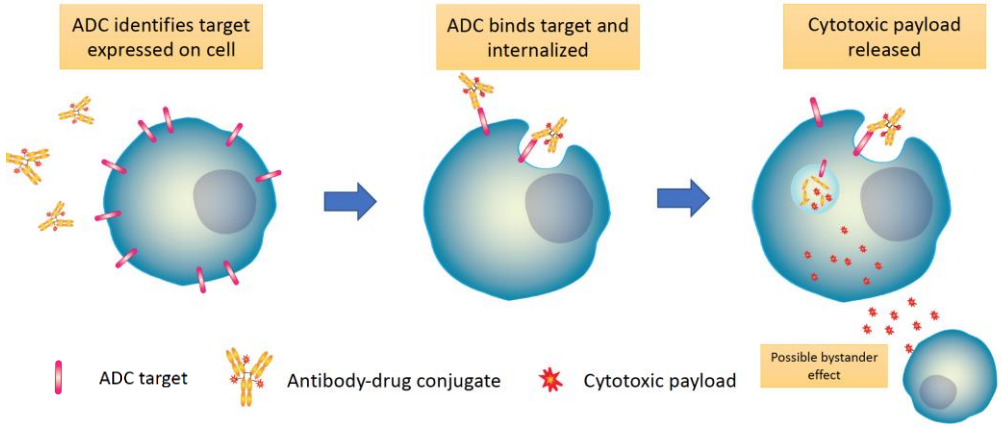
Median DOR (in responders): 9.5 months (range 3.9-27.6)

Liu J, et al. SGO 2022

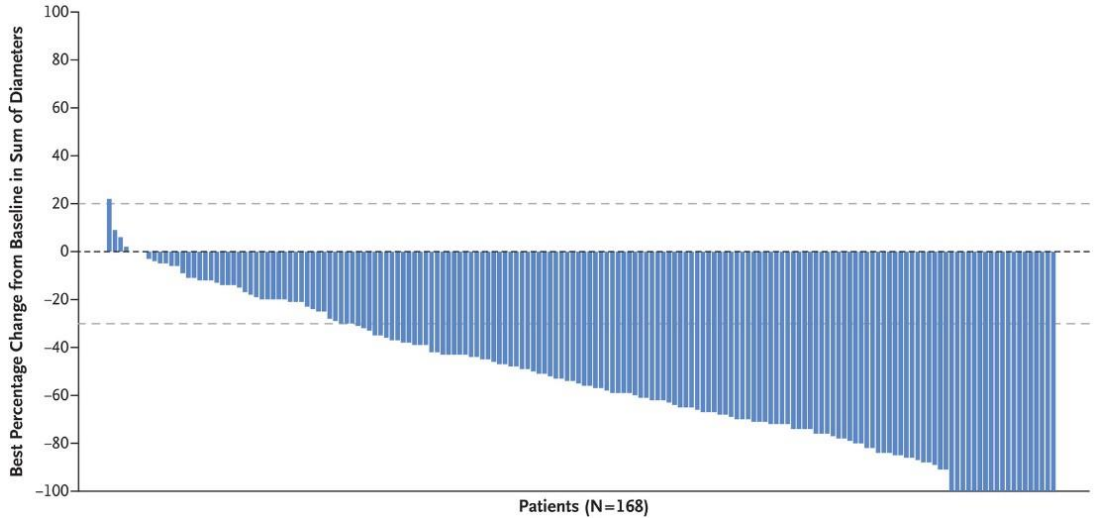
Target therapy for HER2

Trastuzumab deruxtecan (T-DXd)

- Target: HER2
  - Ovarian cancer: 11-66%[1]
  - Uterine cancer: 17-30% (amp); up to 61-80% with expression[2]
  - **<u>Cervical cancer: 1-12%[3]</u>**
- Payload: exatecan derivative (novel topo I inhibitor)
- Linker: Cleavable tetrapeptide linker



DESTINY-Breast01
T-DXd in Her2-treated breast cancer

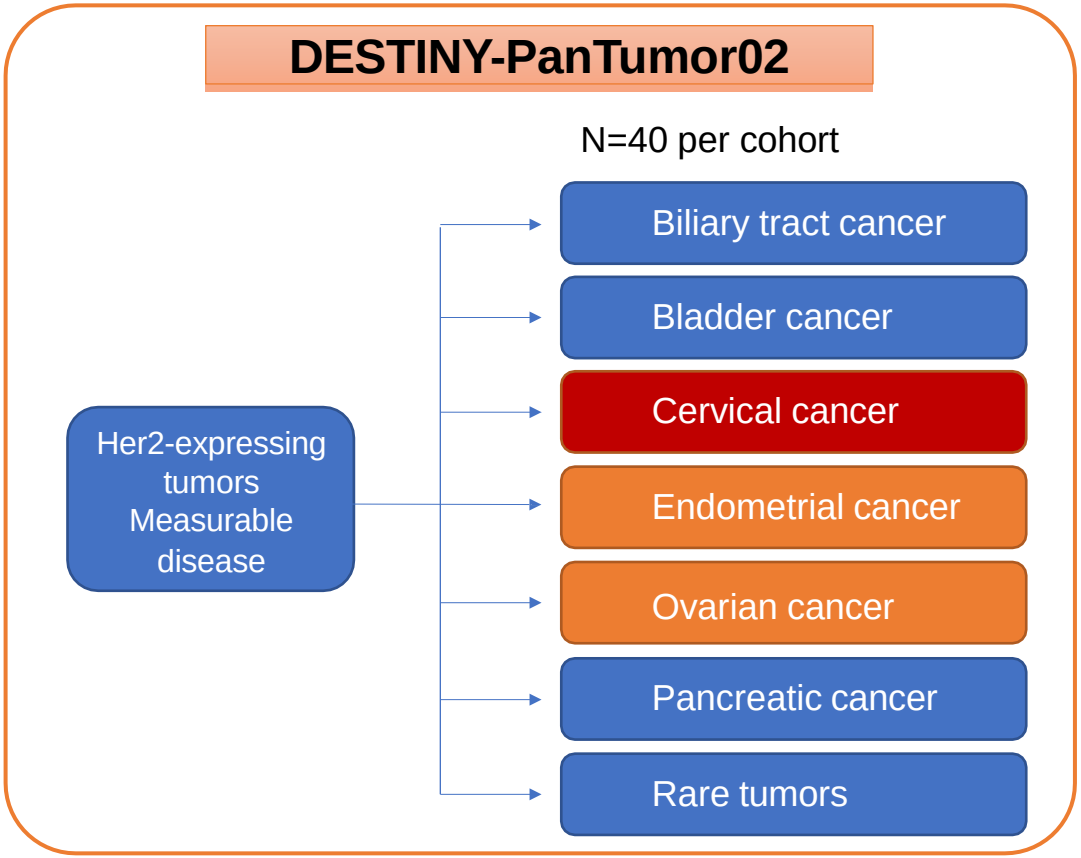


[1]Luo et al., *PLoS One* 2018
[2]Diver et al., *Oncologist* 2015
[3]Oh et al., *Oncotarget* 2015

Modi et al., N Engl J Med 2020

Ongoing trials of T-DXd in gynecologic malignancies

- **DESTINY-PanTumor02**
  - Phase 2, open-label trial of T-DXd for selected Her2- expressing tumors
- **ETCTN 10355**
  - Phase I study of DS-8201a in combination with olaparib in Her2-expressing malignancies
  - Expansion cohorts in gyn malignancies



Meric-Bernstam et al., ASCO 2021