

HER2 Immunostaining and FISH in Endometrial Serous Carcinoma

PRESENTED BY

Natalia Buza, Yale School of Medicine

Important Information Regarding CME/SAMs

The **Online CME/Evaluations/SAMs claim** process will only be available on the USCAP website until **September 30, 2020**

No claims can be processed after that date!

After **September 30, 2020** you will NOT be able to obtain any CME or SAMs credits for attending this meeting.



#IAMUSCAP
#USCAP2020

Disclosure of Relevant Financial Relationships

The faculty, committee members, and staff who are in position to control the content of this activity are required to disclose to USCAP and to learners any relevant financial relationship(s) of the individual or spouse/partner that have occurred within the last 12 months with any commercial interest(s) whose products or services are related to the CME content. USCAP has reviewed all disclosures and resolved or managed all identified conflicts of interest, as applicable.

Natalia Buza reported no relevant financial relationships



**PLEASE TURN OFF
YOUR CELL PHONES**



#IAMUSCAP
#USCAP2020

NCCN Guidelines 2019



Preferred chemotherapy regimen for Her2-positive advanced stage (st III/IV) or recurrent endometrial serous carcinoma:

carboplatin/paclitaxel/trastuzumab

Endometrial Serous Carcinoma

~10% of endometrial cancer

Postmenopausal women, no association with hormones, obesity or hyperplasia

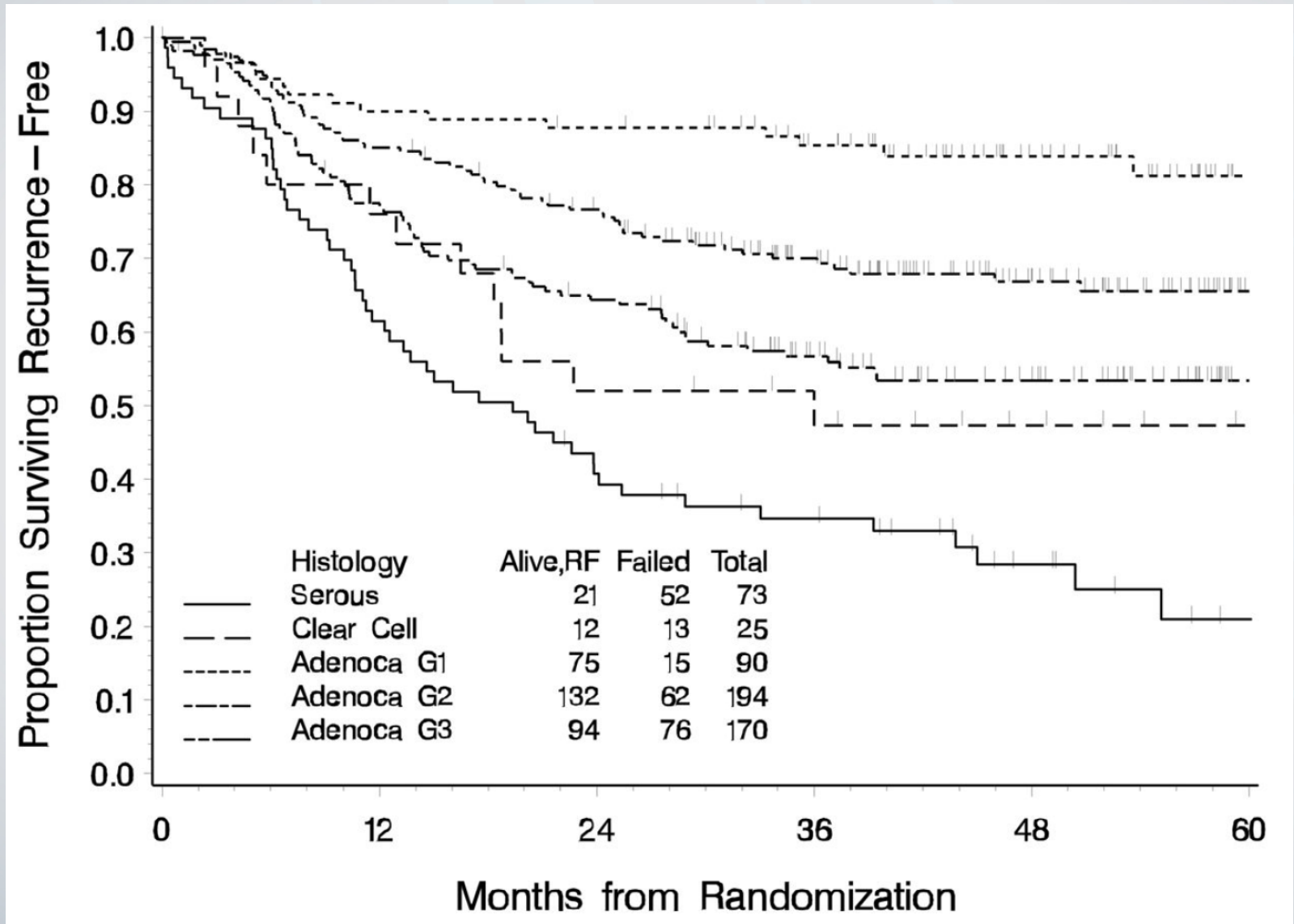
High histologic grade

Poor response to traditional chemotherapy

High rate of recurrence and mortality

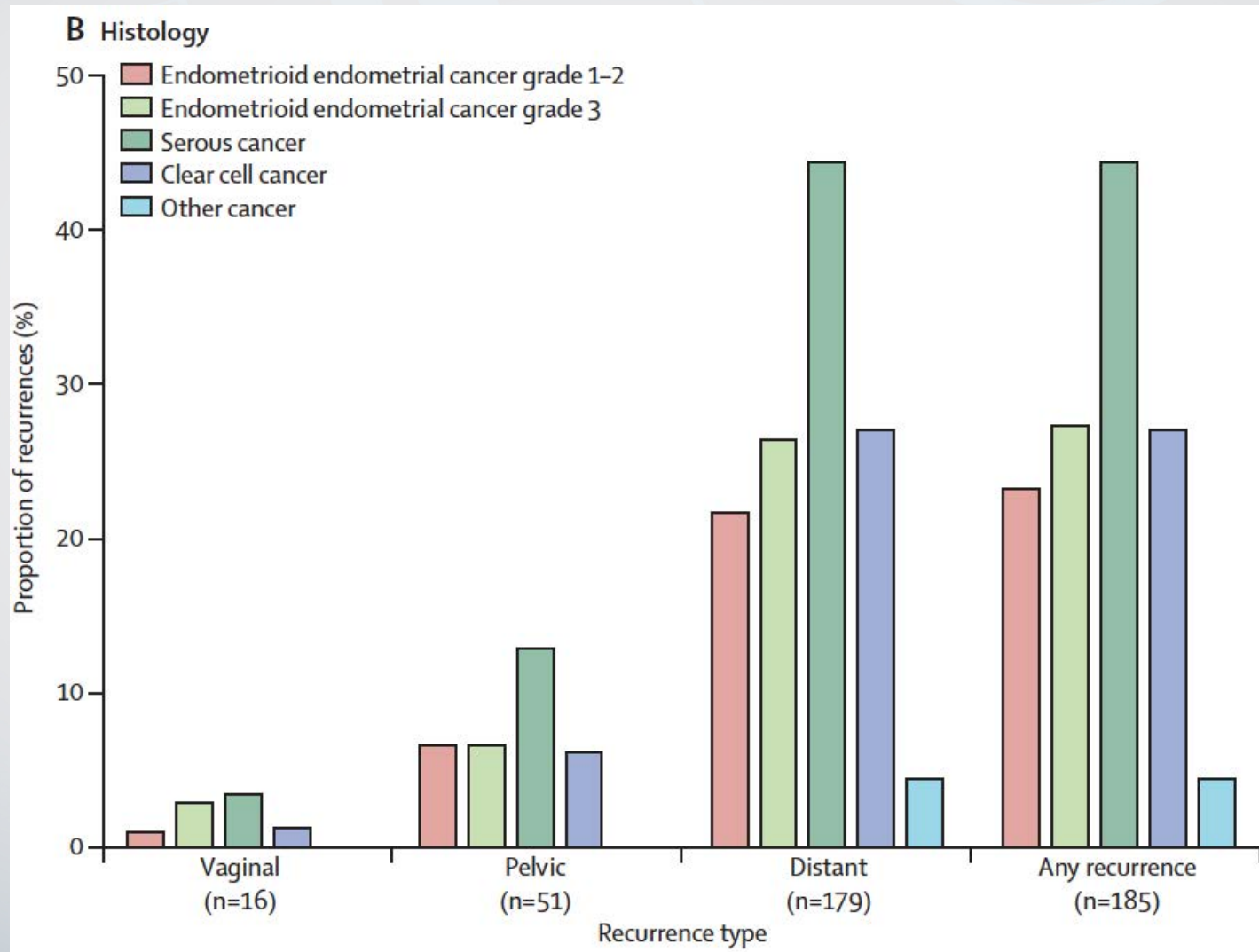
~40% of endometrial cancer deaths

Prognosis



Homesley et al.,
Gynecol Oncol 2009

Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial



Need for New Targeted Therapies

Interest in Her2 in Endometrial Cancer is not new...

1990s - 2010:

Her2 overexpression 14-80%

Her2 amplification 21-47%

Variation in testing and scoring methods and case inclusion criteria

Case reports of successful Her2-based therapies

GOG 181B clinical trial

GOG 181B

Gynecologic Oncology 116 (2010) 15–20



Contents lists available at ScienceDirect

Gynecologic Oncology

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



Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: A Gynecologic Oncology Group study ☆☆☆, ★, ★★

Gini F. Fleming^{a,*}, Michael W. Sill^{b,c}, Kathleen M. Darcy^b, D. Scott McMeekin^d, J. Tate Thigpen^e,
Lisa M. Adler^f, Jonathan S. Berek^{g,1}, Julia A. Chapman^{h,2}, Paul A. DiSilvestro^{i,3},
Ira R. Horowitz^j, James V. Fiorica^{k,4}

GOG 181B

Single agent trastuzumab for advanced or recurrent Her2 positive endometrial cancer

33 patients with Her2 positive tumors: 11 serous, 13 endometrioid, 3 clear cell, 5 mixed, 1 NOS

FDA scoring criteria for breast cancer

IHC scores 2+ and 3+, or FISH ratio >2.0

No clinical activity; trial closed early due to poor accrual

VOLUME 36 · NUMBER 20 · JULY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin

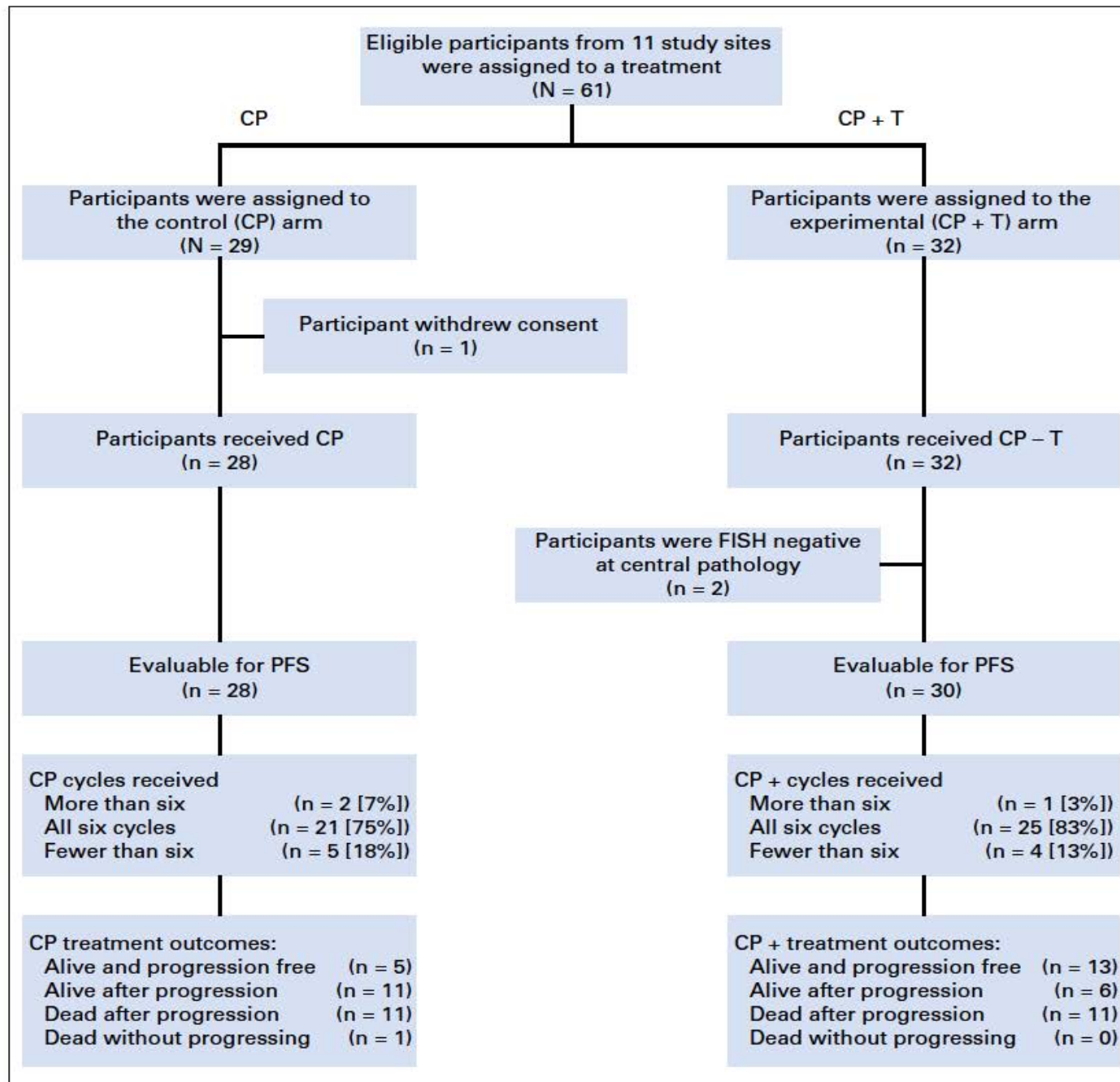
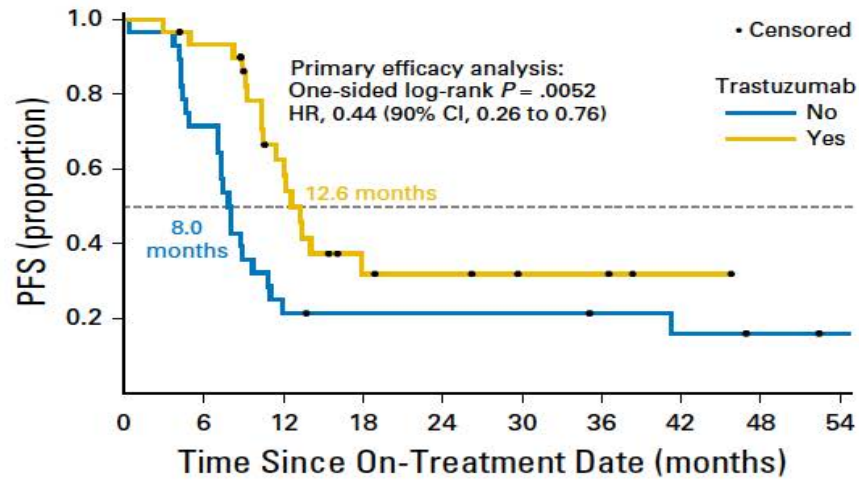
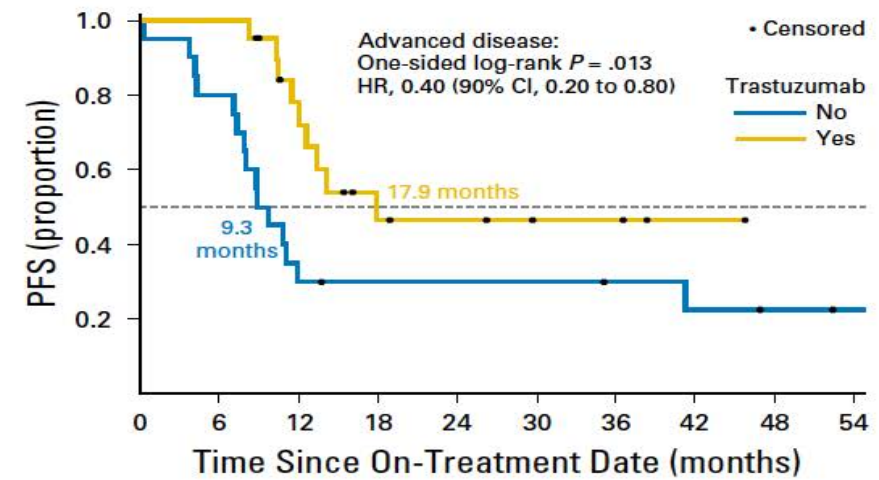


Fig 1. CONSORT diagram. CP, carboplatin-paclitaxel; CP + T, carboplatin-paclitaxel plus trastuzumab; FISH, fluorescence in situ hybridization; PFS, progression-free survival.

A

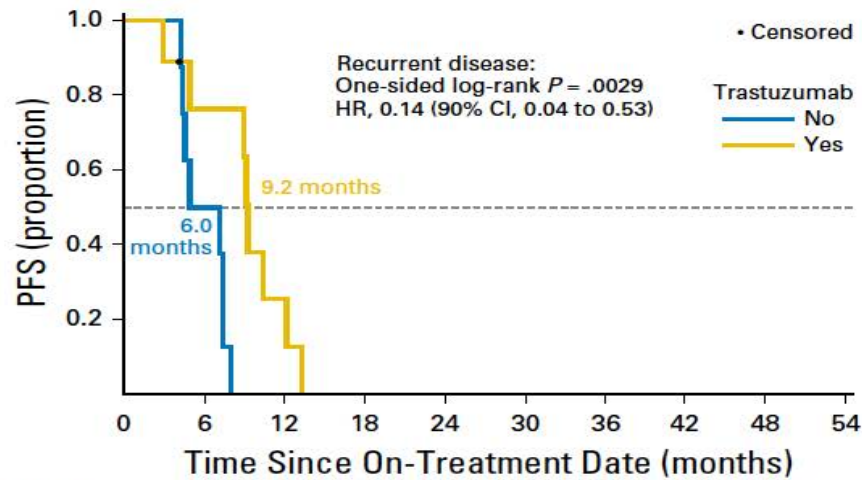
No. at risk

No	28	20	6	5	5	5	4	3	2	1
Yes	30	27	15	6	5	3	3	1	0	

B

No. at risk

No	20	16	6	5	5	5	4	3	2	1
Yes	21	21	13	6	5	3	3	1	0	

C

No. at risk

No	8	4	0	
Yes	9	6	2	0

NCCN Guidelines 2019



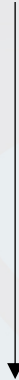
Preferred chemotherapy regimen for Her2-positive advanced stage (st III/IV) or recurrent endometrial serous carcinoma:

carboplatin/paclitaxel/**trastuzumab**

Trastuzumab approved for breast cancer



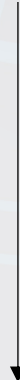
Lapatinib approved for breast cancer



Trastuzumab approved for gastric cancer



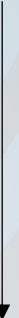
Pertuzumab approved for breast cancer



T-DM1 approved for breast cancer



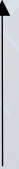
Trastuzumab biosimilars approved for breast and gastric cancer



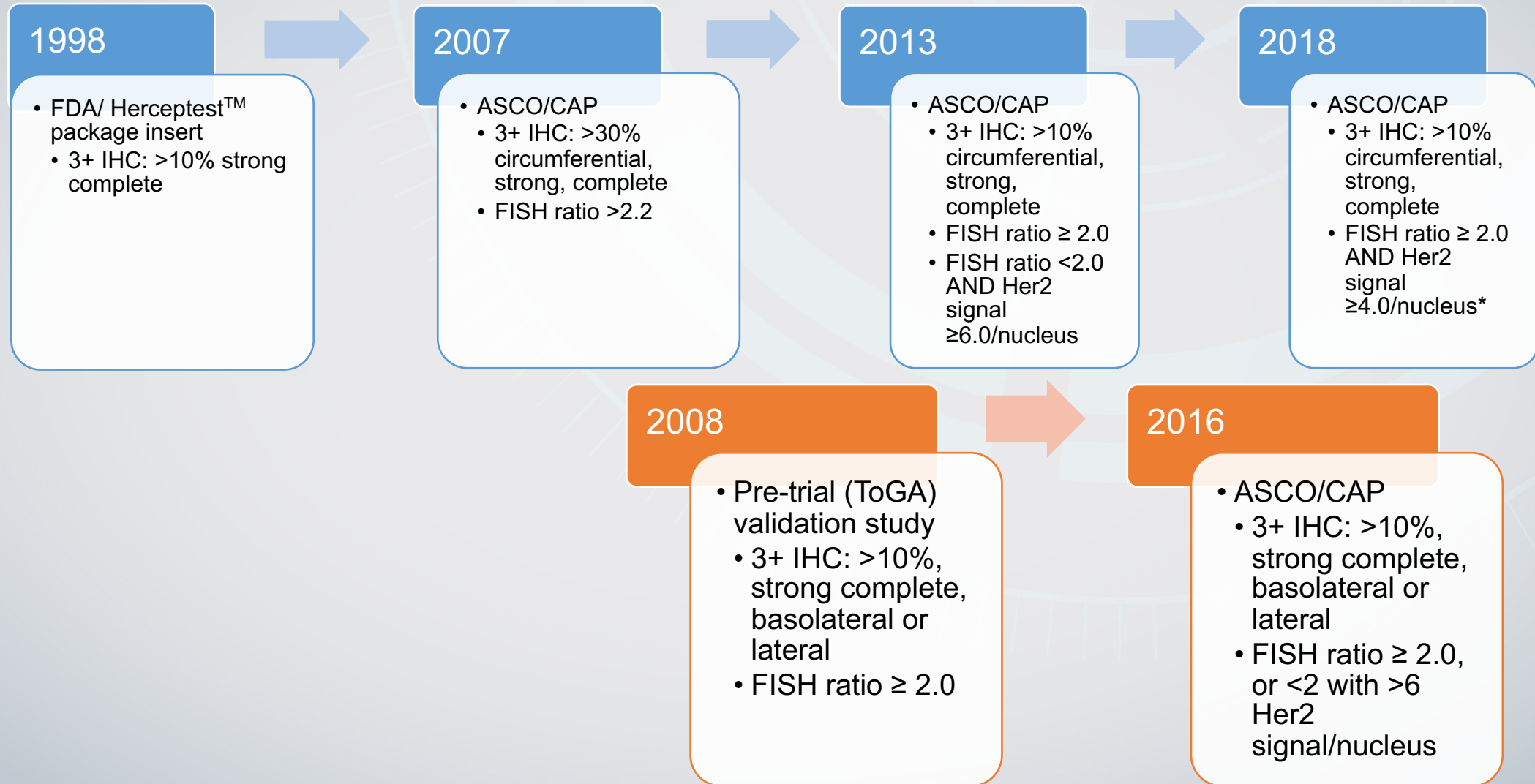
GOG 181B trial (single-agent trastuzumab in endometrial cancer)



Trastuzumab improves PFS and OS in endometrial serous carcinoma



Evolution of Her2 Guidelines in Breast and Gastric Cancer



Her2 in Breast and Gastric Cancer

	Breast	Gastric
Proportion Her2 positive	15-25%	22%
Heterogeneity IHC/FISH	Rare	Common, 50%
Basolateral/lateral IHC pattern	Rare, 2+	Common, 3+

Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice

Natalia Buza¹, Diana

¹*Department of Pathology
Obstetrics, Gynecology, a
CT, USA*

GENES, CHROMOSOMES & CANCER 52:1178–1186 (2013)

Marked Heterogeneity of *HER2/NEU* Gene Amplification in Endometrial Serous Carcinoma

Natalia Buza* and Pei Hui

Department of Pathology, Yale University School of Medicine, New Haven, CT, 06520-8023

108 cases (85 pure SC, 23 mixed SC)

Her2 IHC (DAKO Herceptest™)

Her2 FISH on all IHC 2+ cases, and in a smaller number of 0, 1+, and 3+ cases (PathVysion)

IHC scores per *FDA* and *2007 ASCO/CAP* breast criteria

Her2 amplification: Her2/CEP17 ratio ≥ 2.0

Her2 in Serous Carcinoma

FDA (breast) criteria:

38% Her2 + (by either
IHC/FISH)

ASCO/CAP 2007 (breast) criteria:

31% Her2 + (by either
IHC/FISH)

IHC-FISH Concordance

All IHC cases:

FDA: 75%

ASCO/CAP 2007: 81%

IHC 2+ excluded:

FDA: 78%

ASCO/CAP 2007: 86%

Her2 Immunohistochemistry

- 2007 ASCO/CAP breast guidelines:

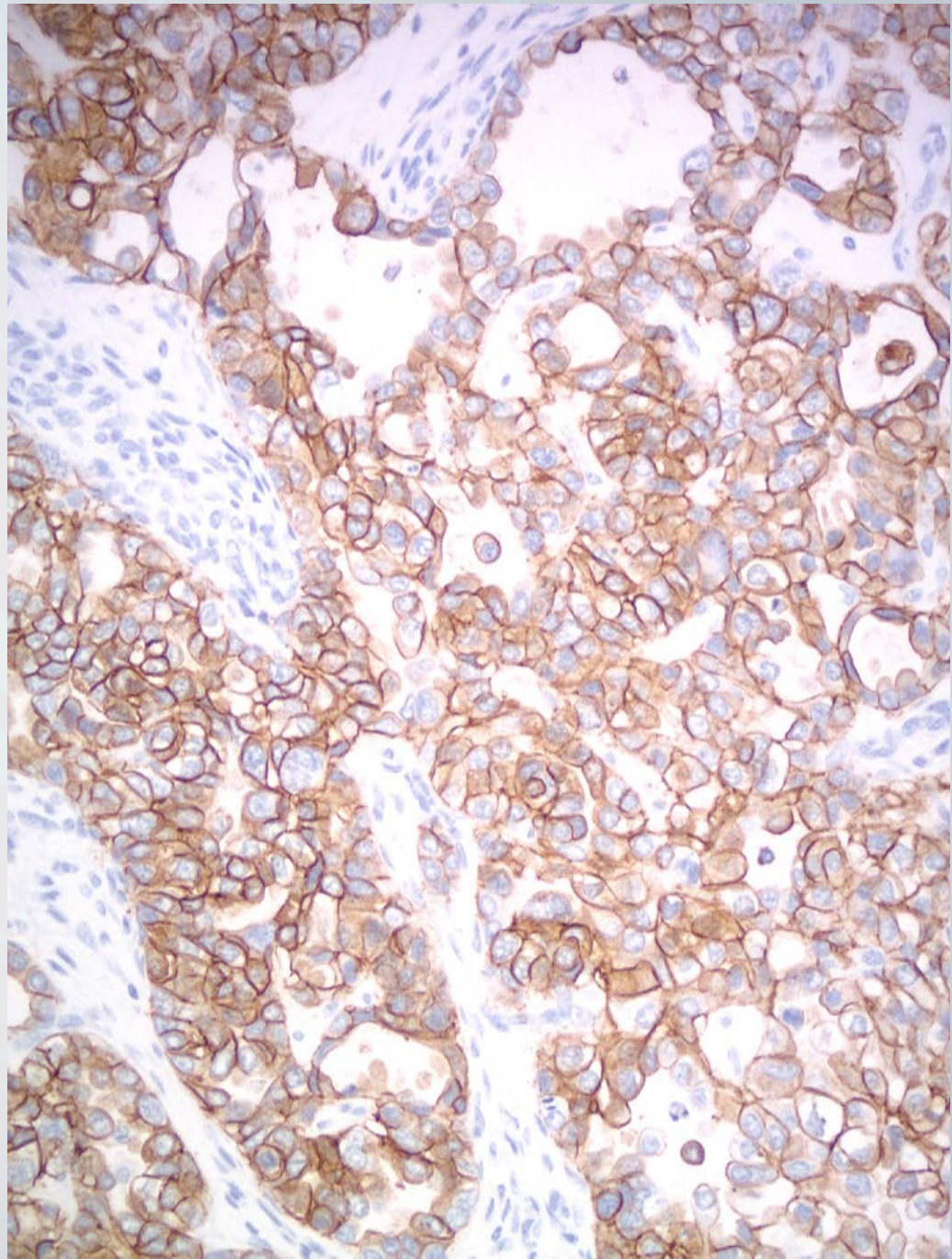
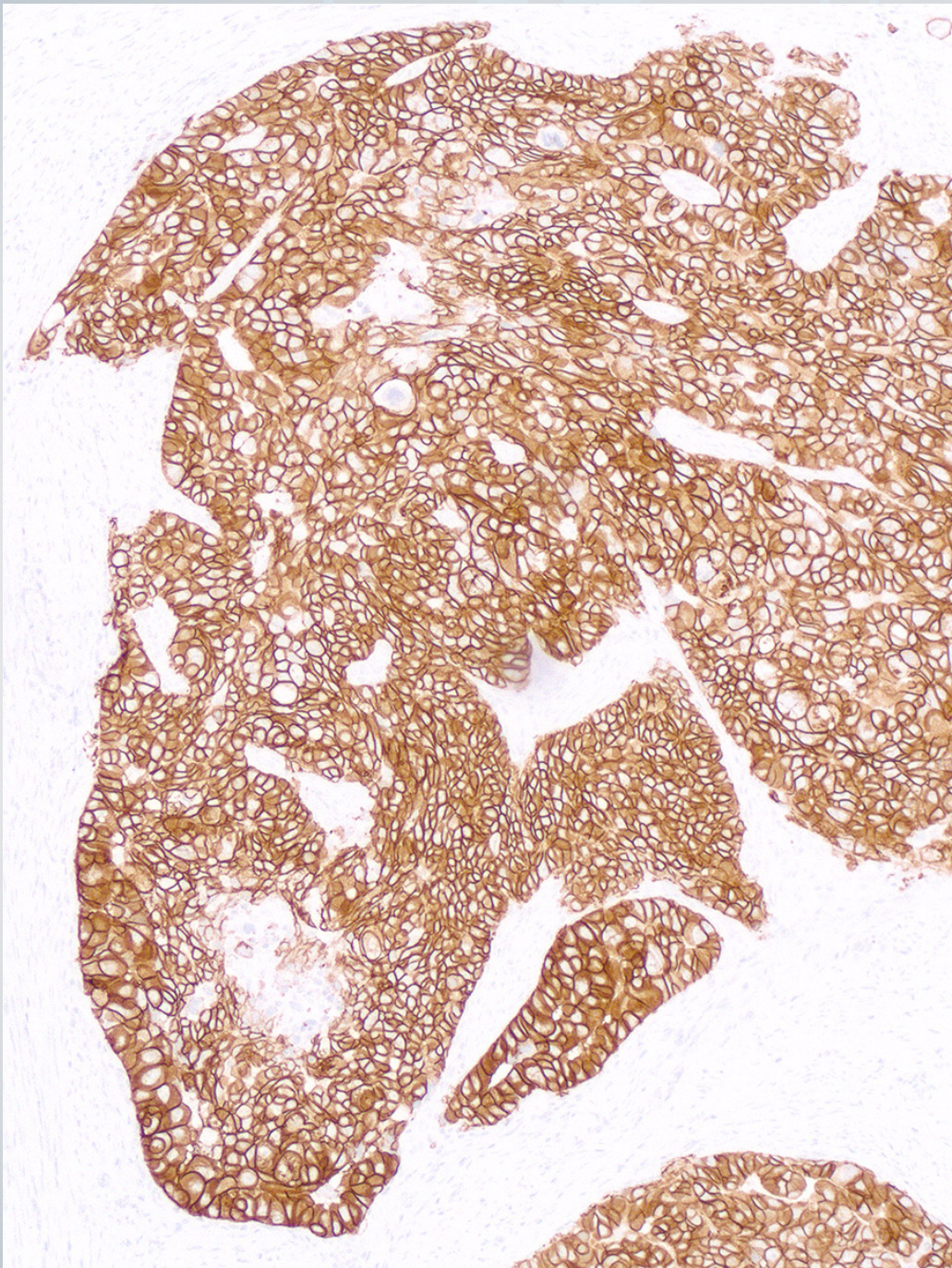
0 No staining in invasive tumor cells

1+ Weak, incomplete membrane staining in any proportion or weak, complete membrane staining in <10% of tumor cells

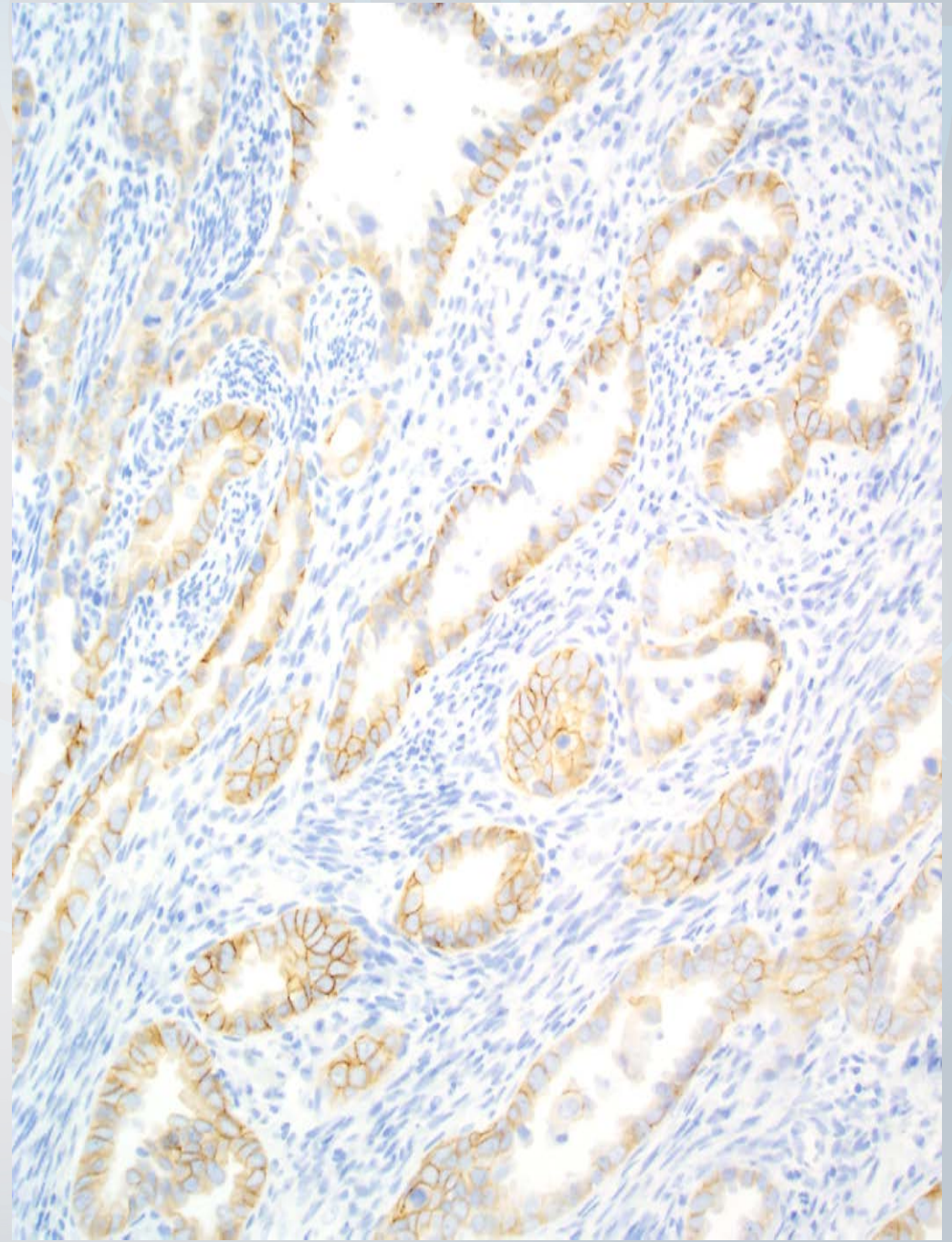
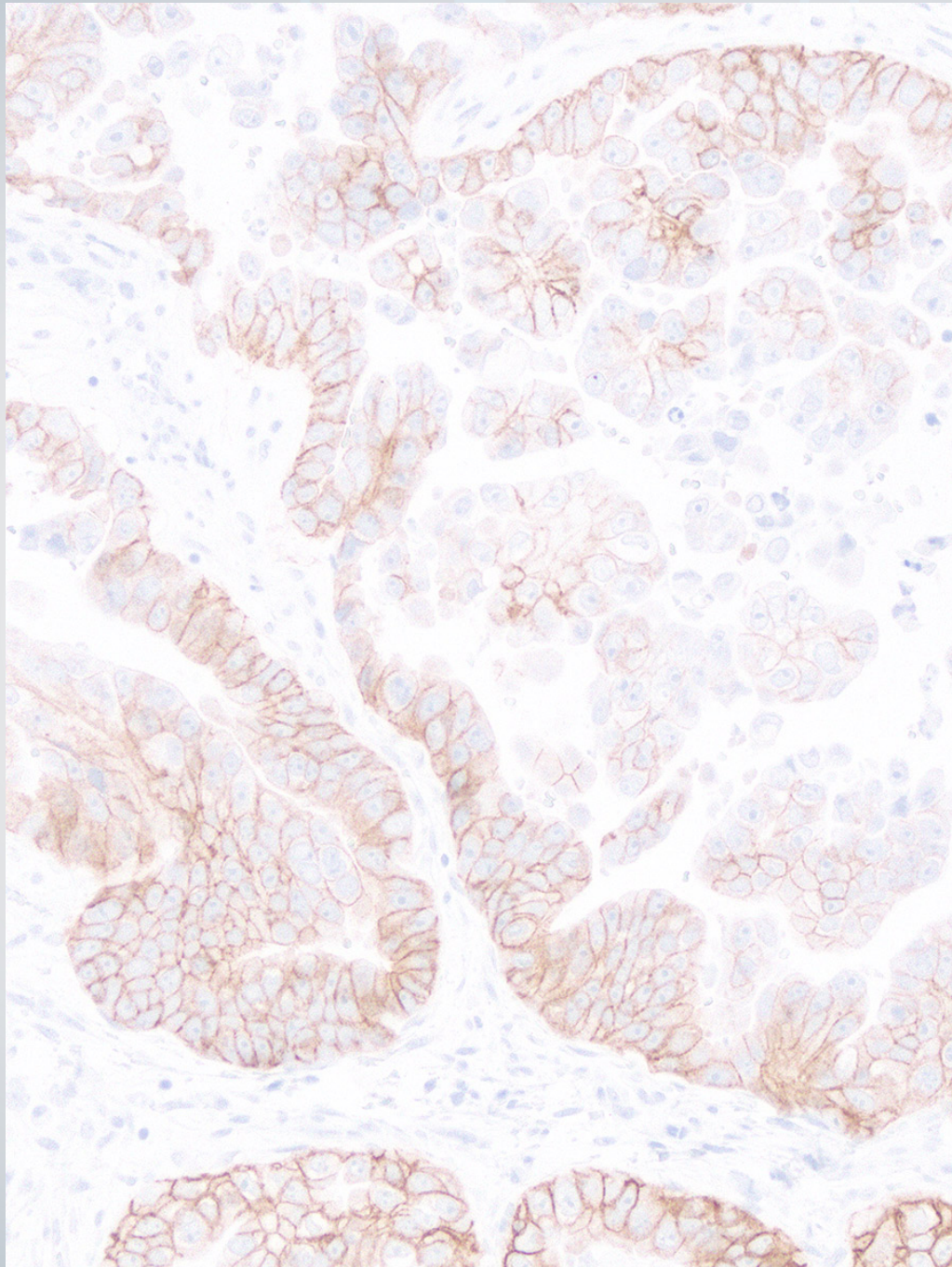
2+ Complete membrane staining that is nonuniform or weak but with obvious circumferential distribution in at least 10% of cells or intense complete membrane staining in $\leq 30\%$ of tumor cells

3+ Uniform intense membrane staining in > 30% of tumor cells

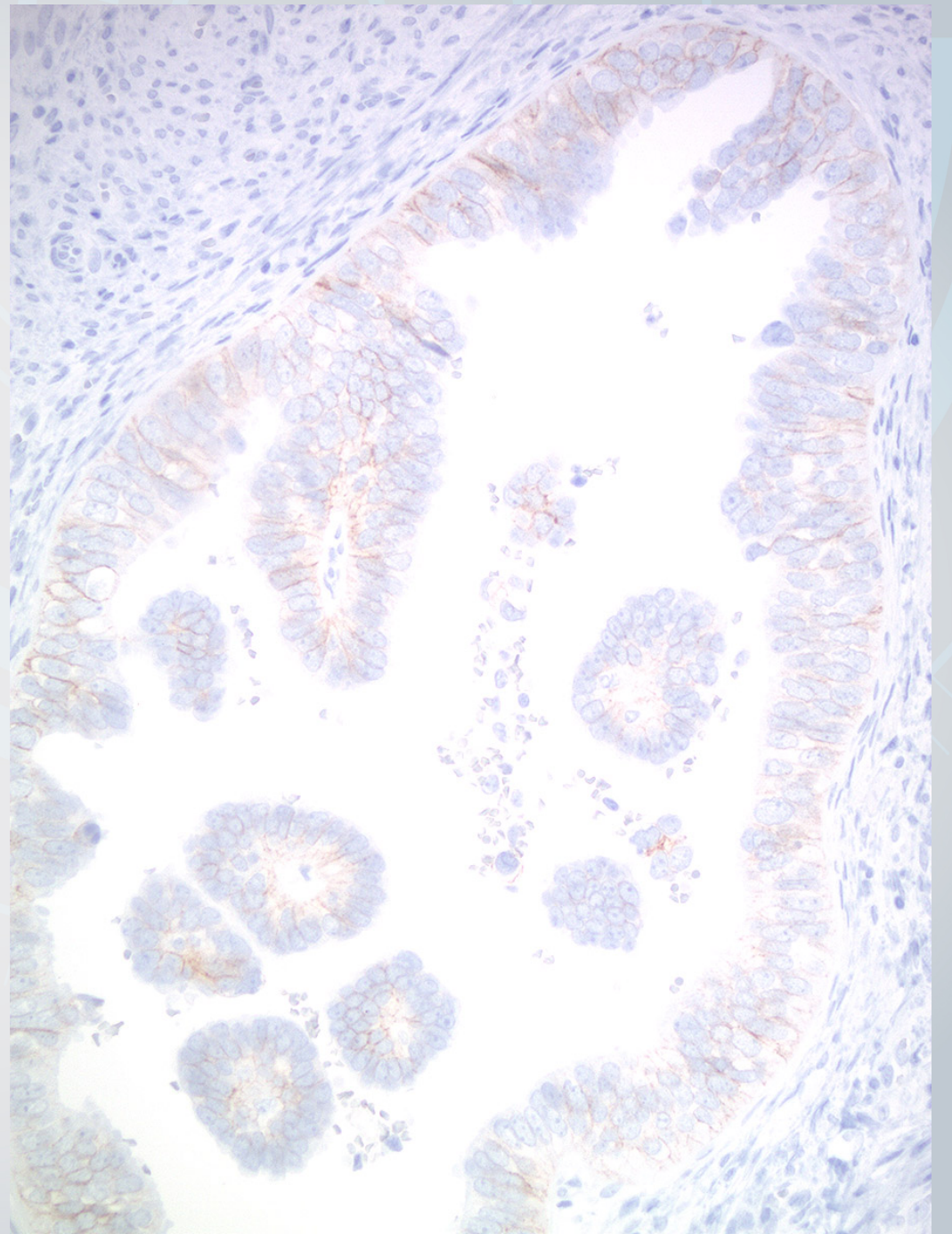
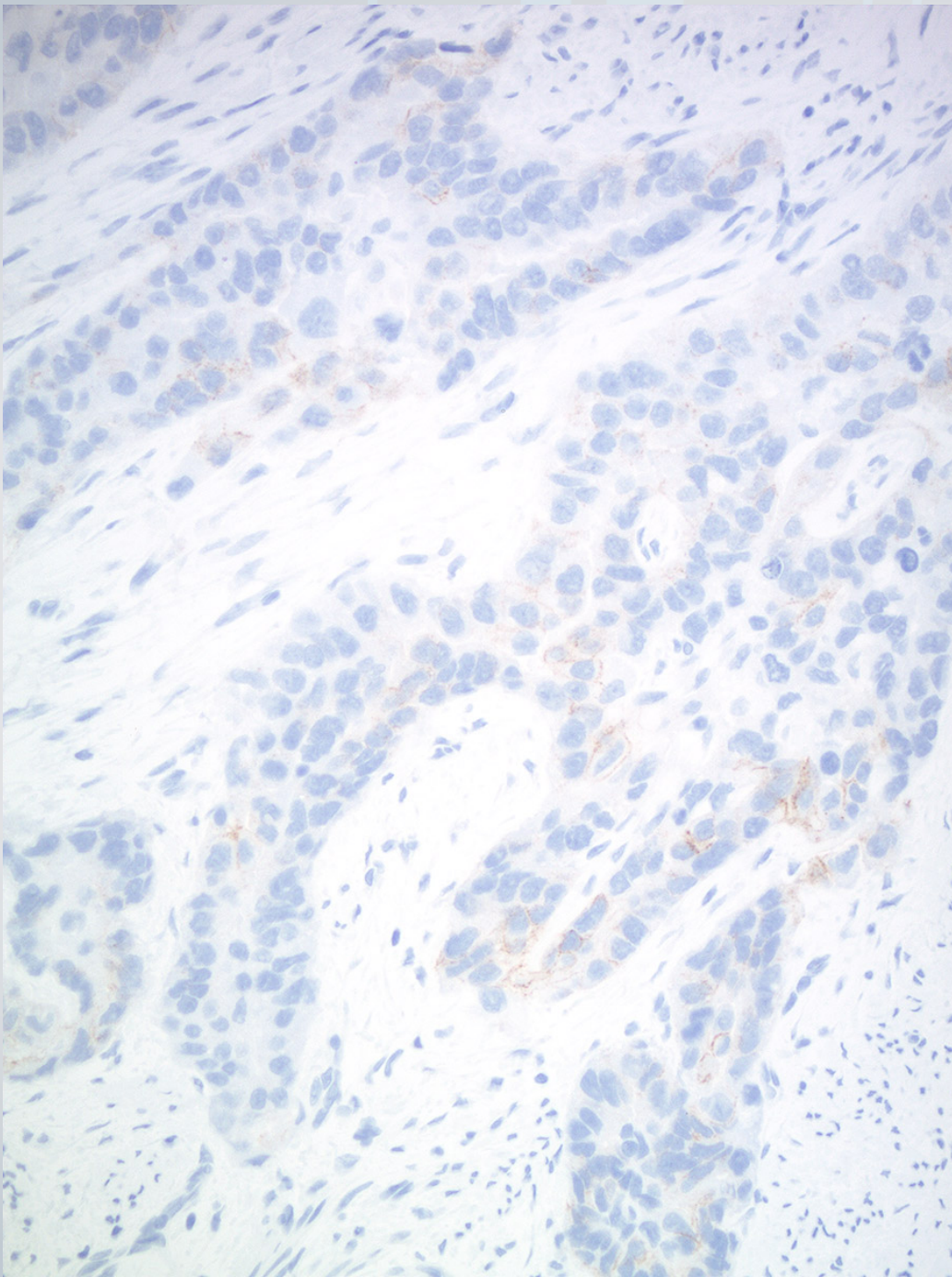
3+



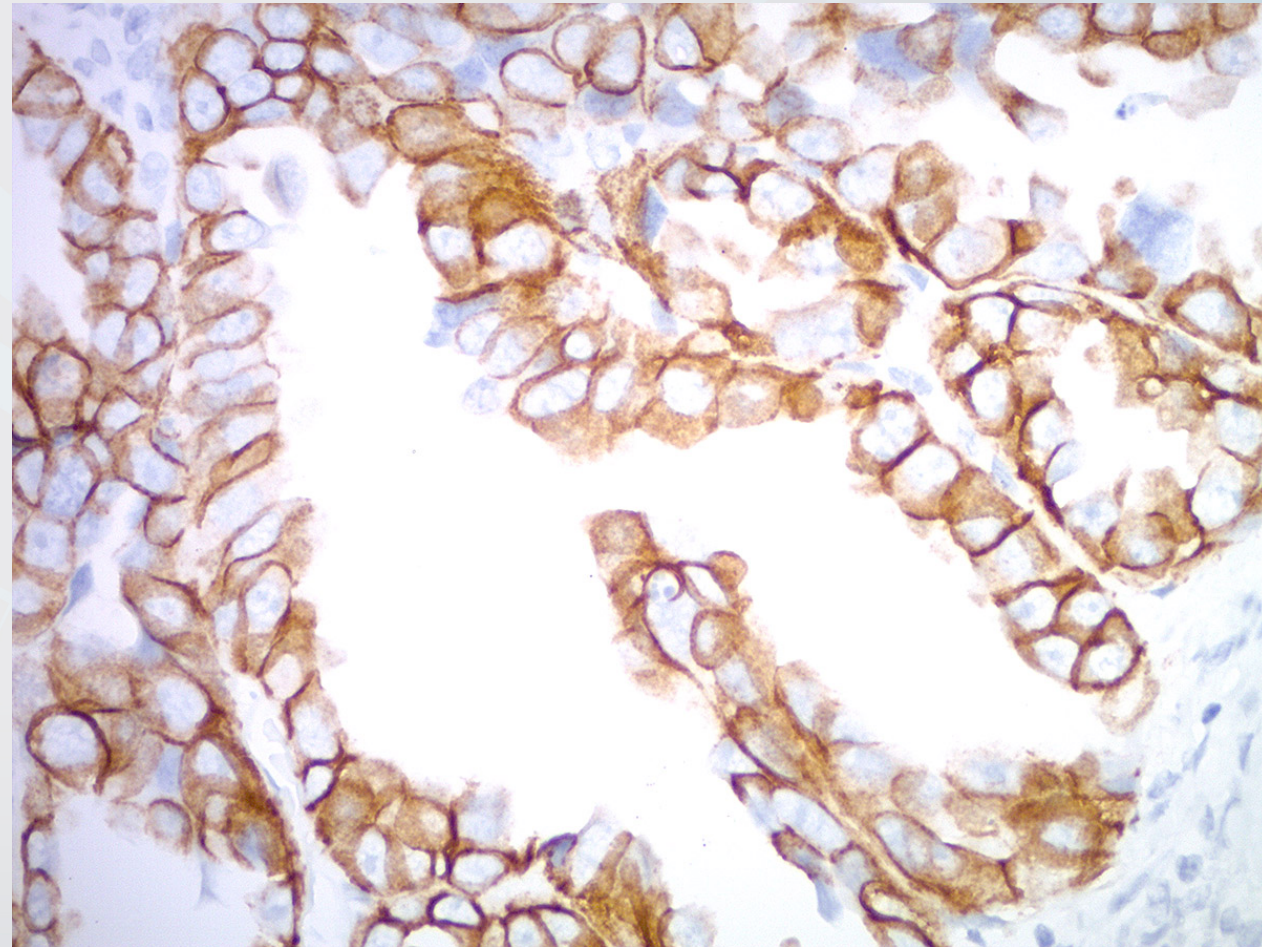
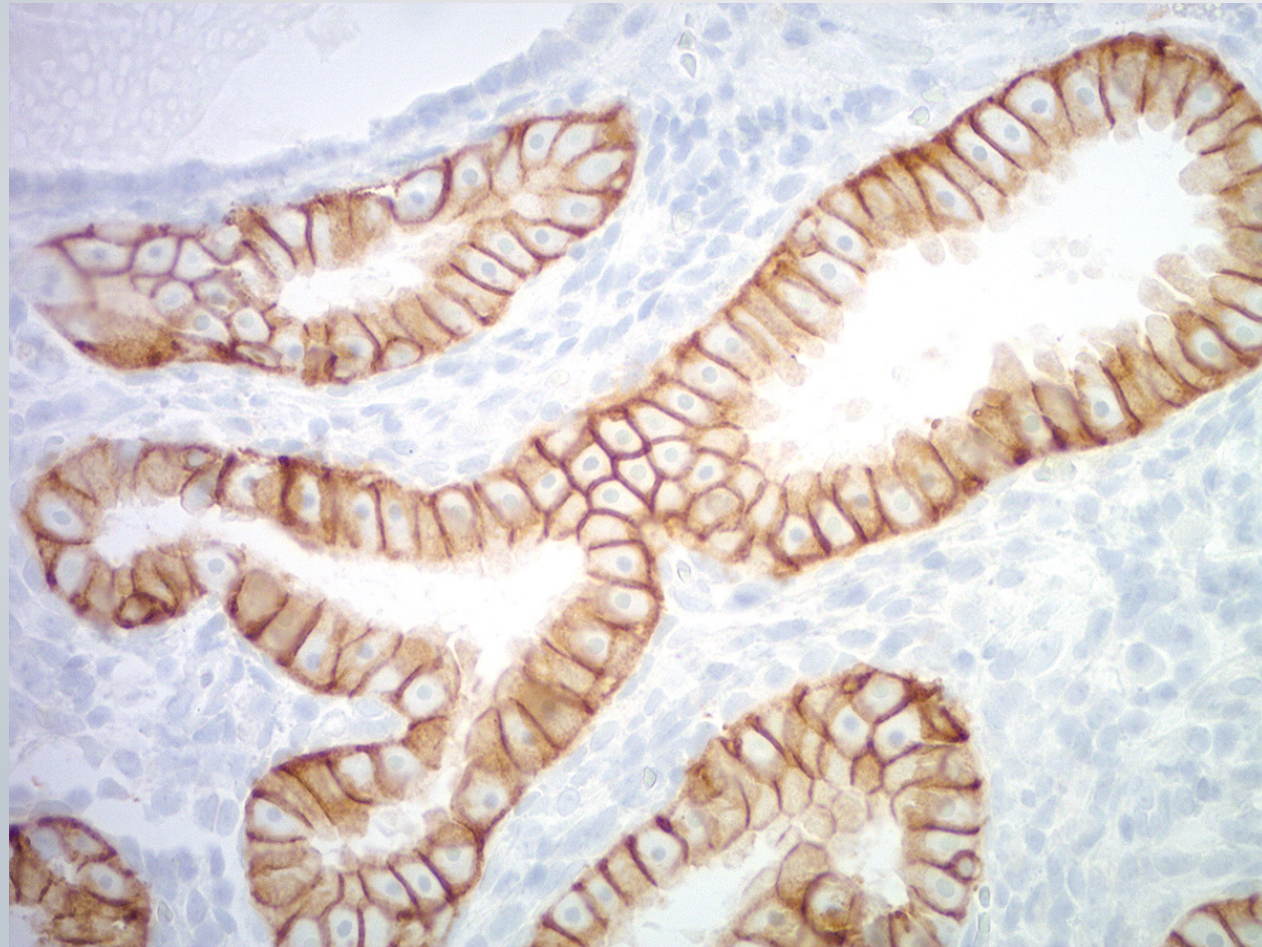
2+



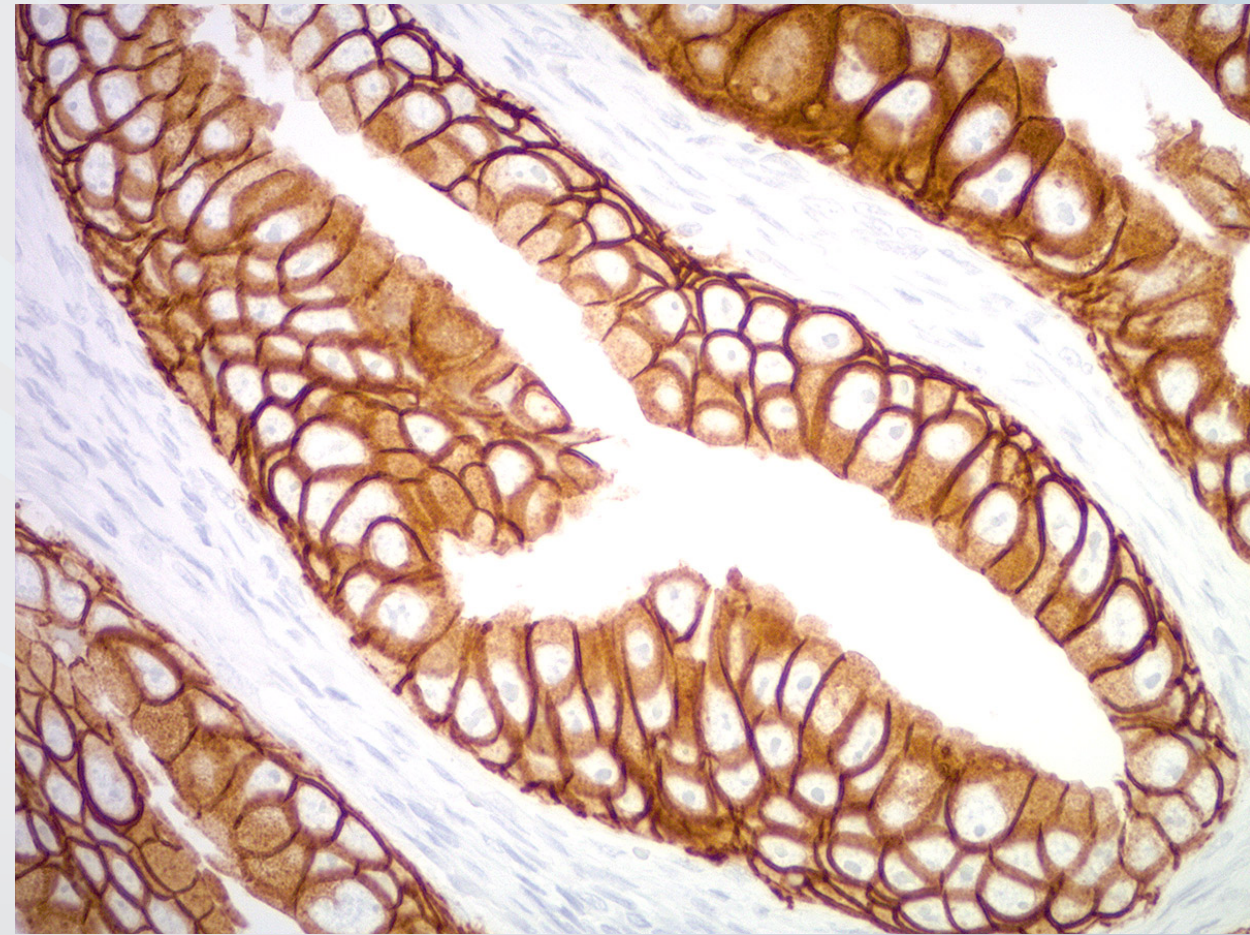
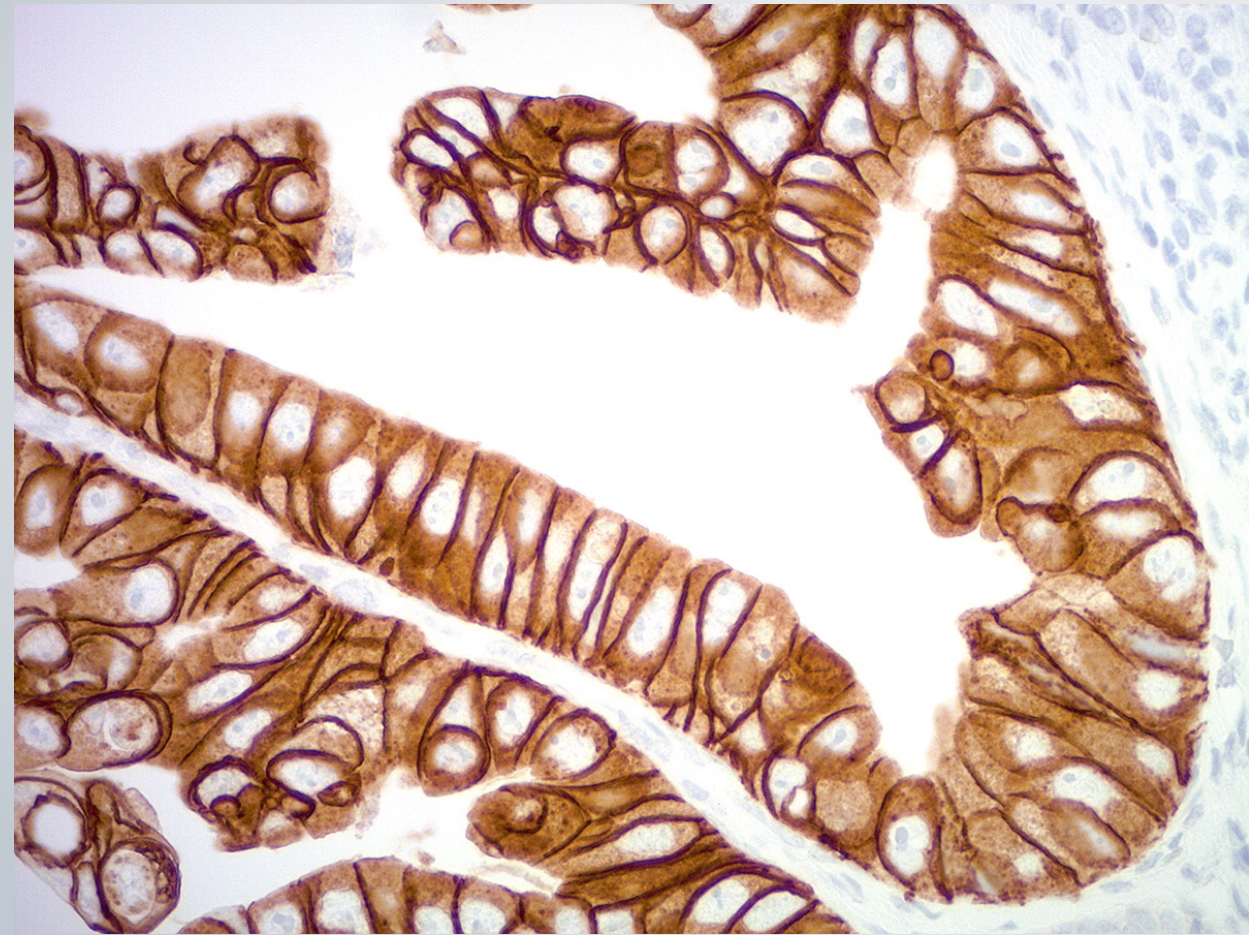
1+



Lack of Apical Her2 Staining



Lack of Apical Her2 Staining

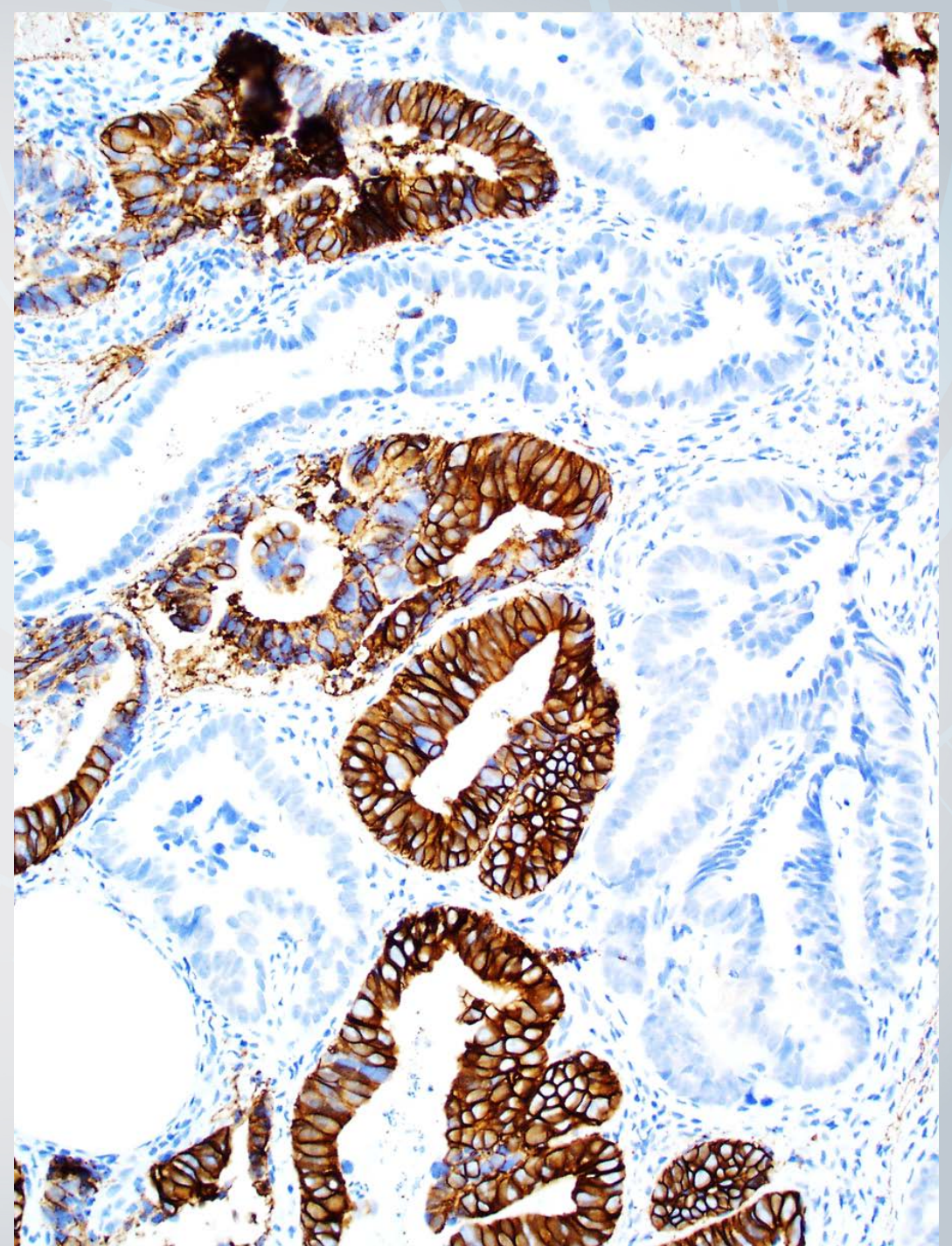
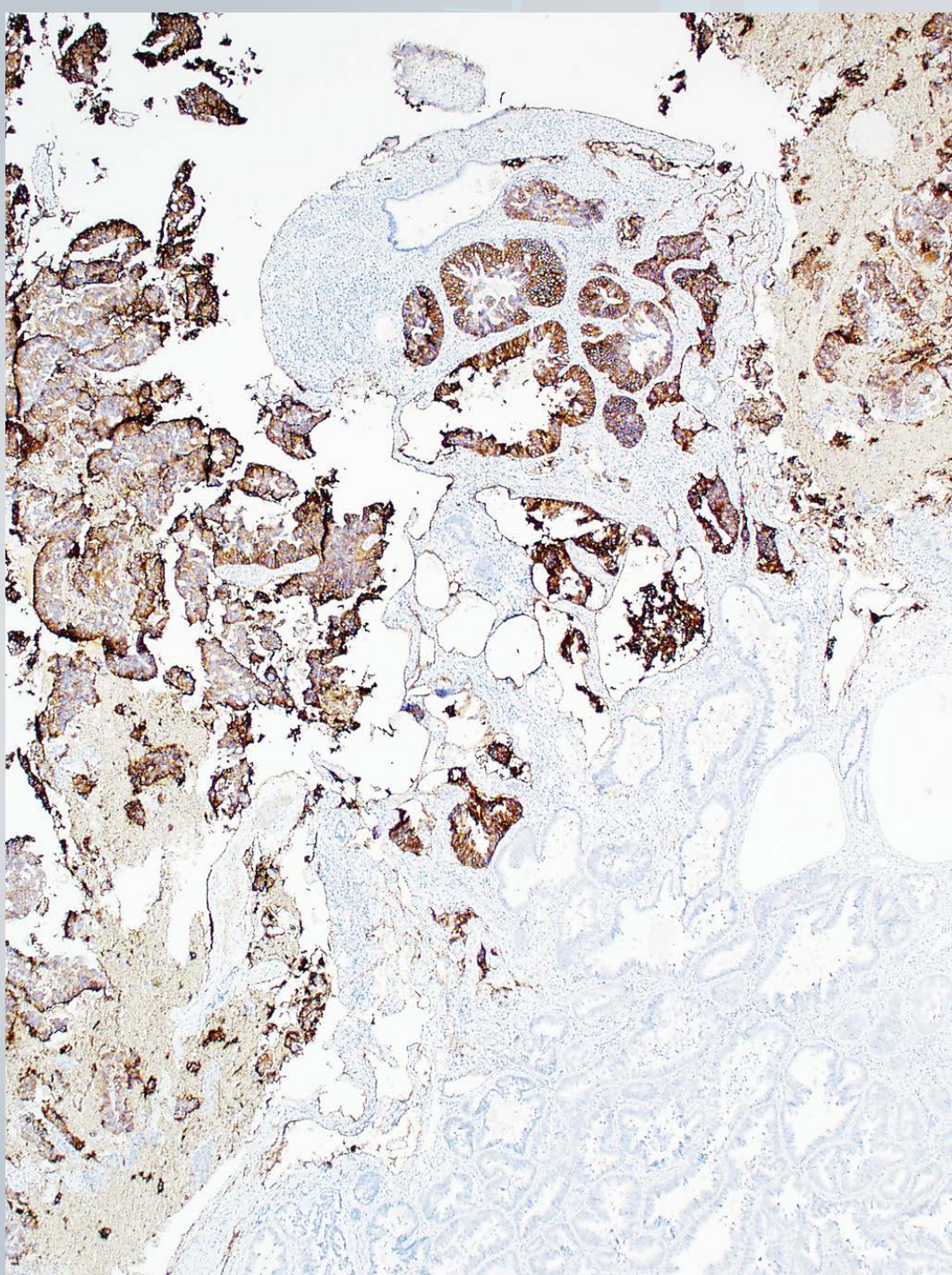


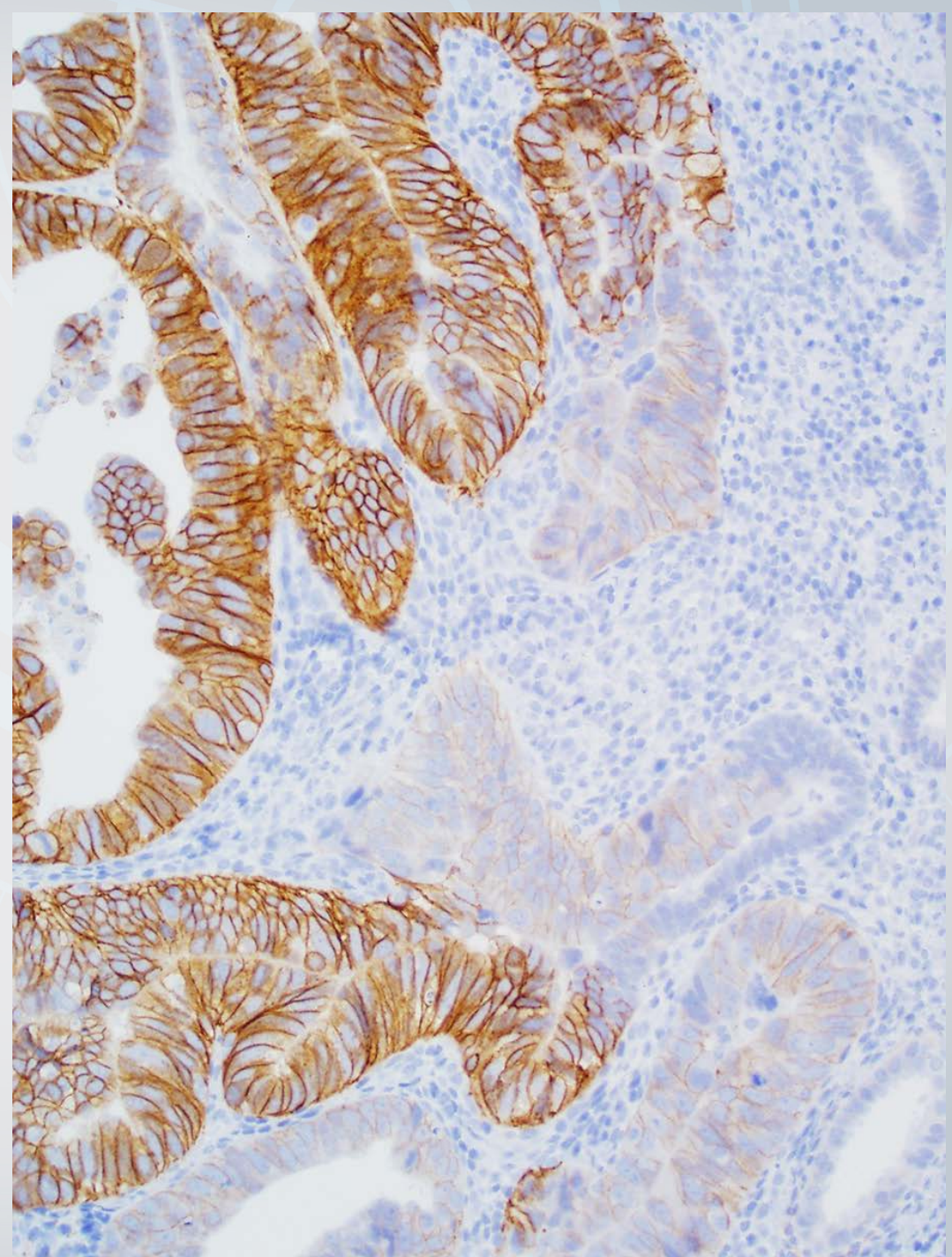
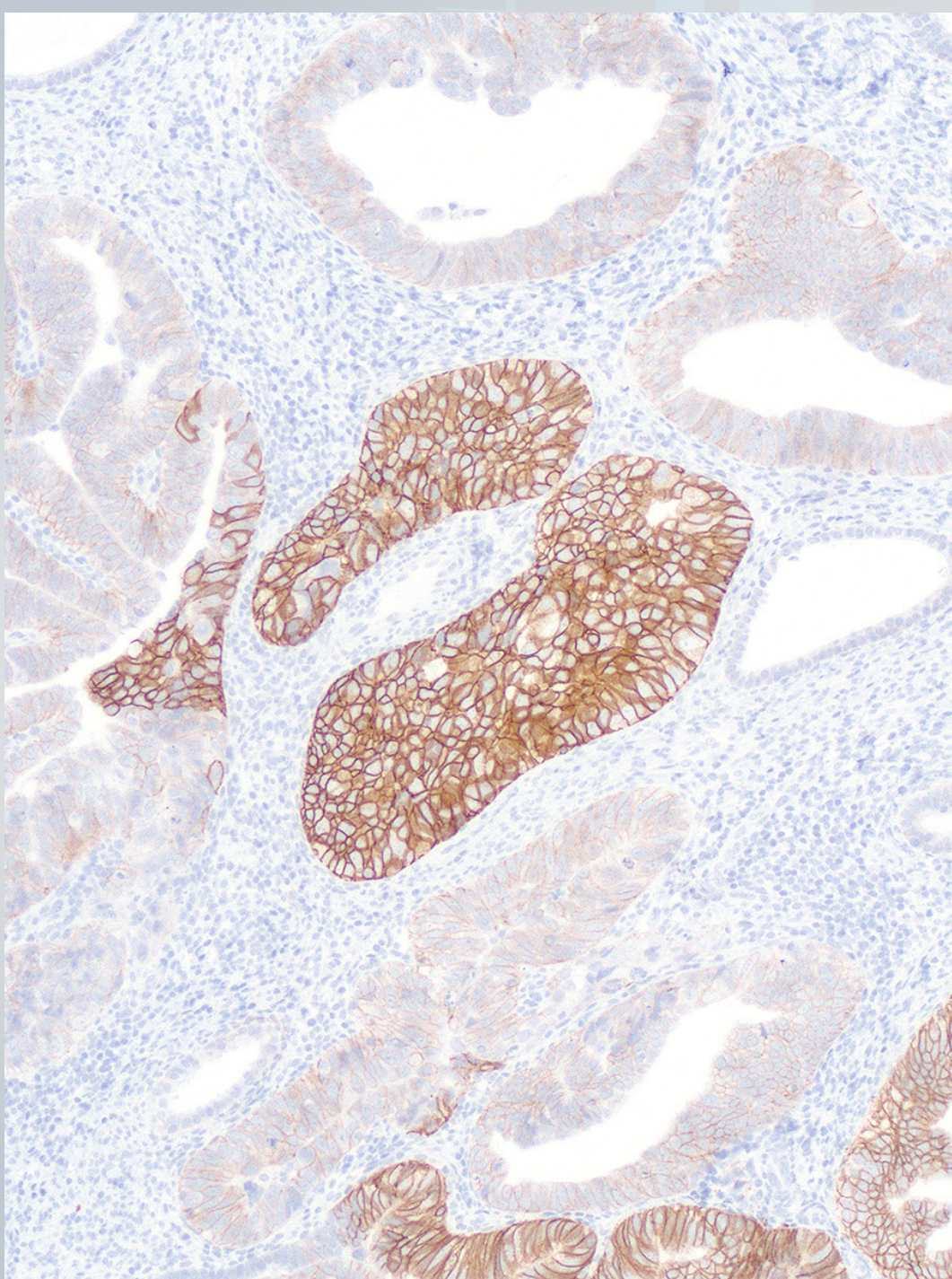
Marked Heterogeneity of Her2 Expression by IHC

31% of all serous carcinomas (33/108)

53% of Her2 positive tumors (20/38)

19% of Her2 negative tumors (13/70)





Her2 FISH

2007 ASCO/CAP breast guidelines:

Positive: Her2/CEP17 ratio >2.2

Equivocal: Her2/CEP17 ratio 1.8 – 2.2

Patients with ratio ≥ 2.0 eligible for trastuzumab therapy

Her2 FISH

Heterogeneity of Her2 gene amplification

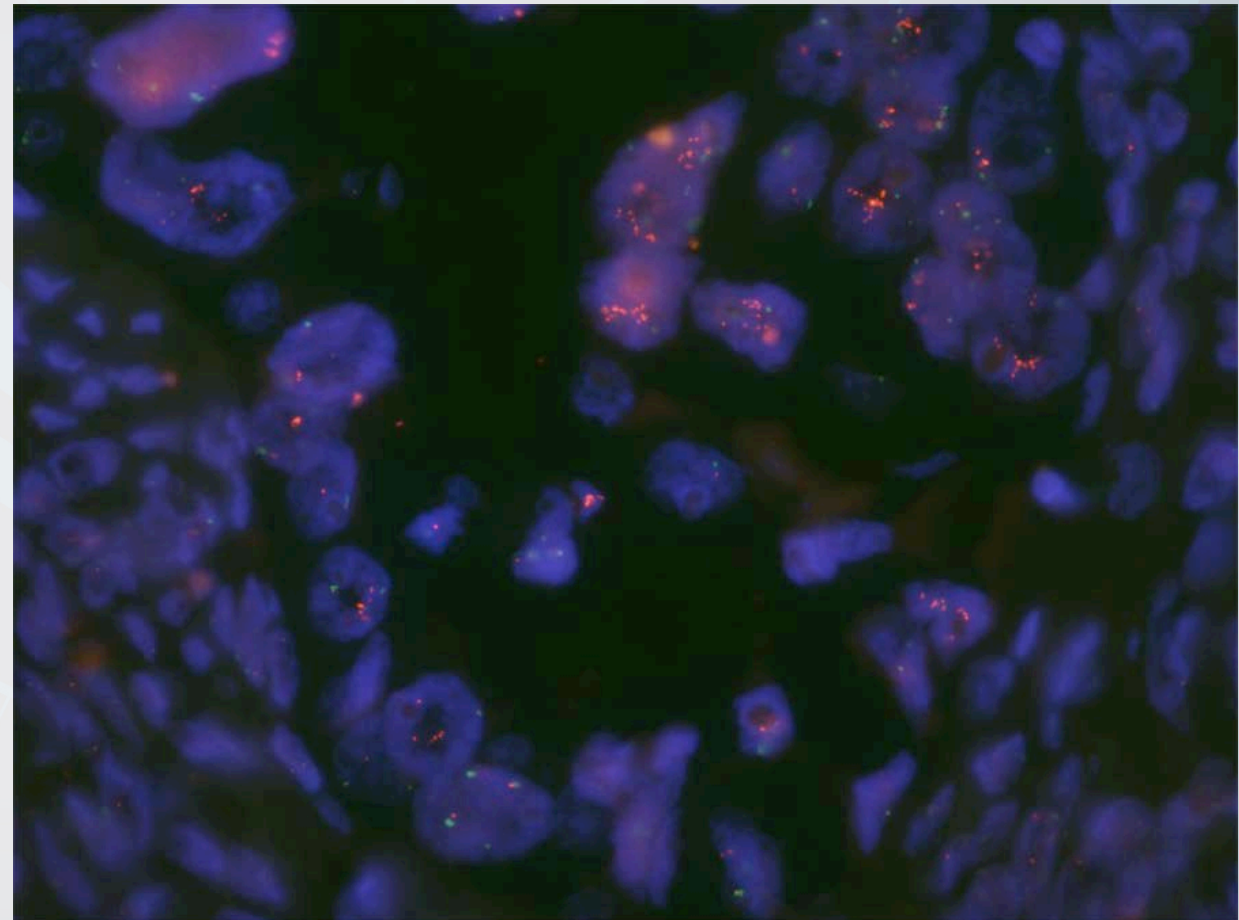
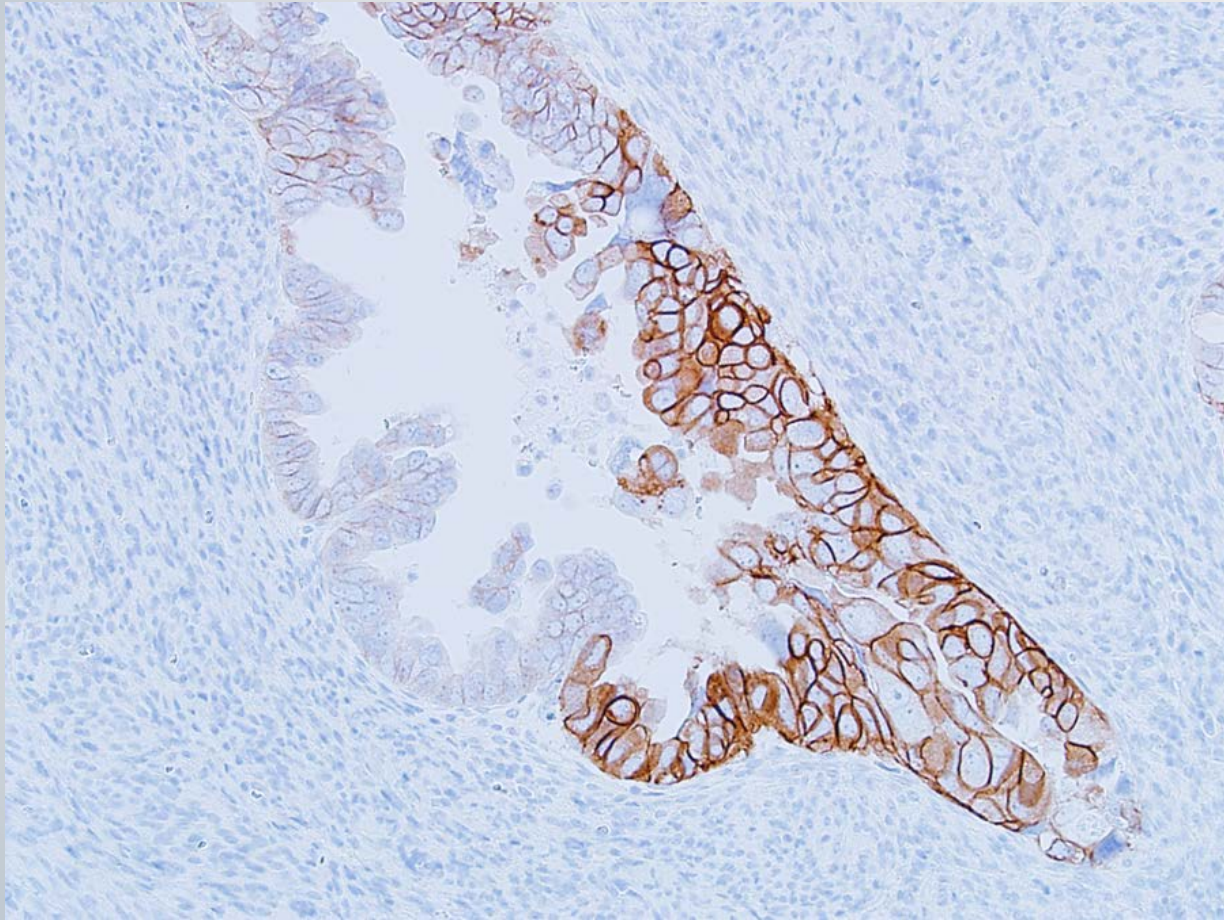
Cluster amplification in most cases with heterogeneous IHC

Mosaic amplification

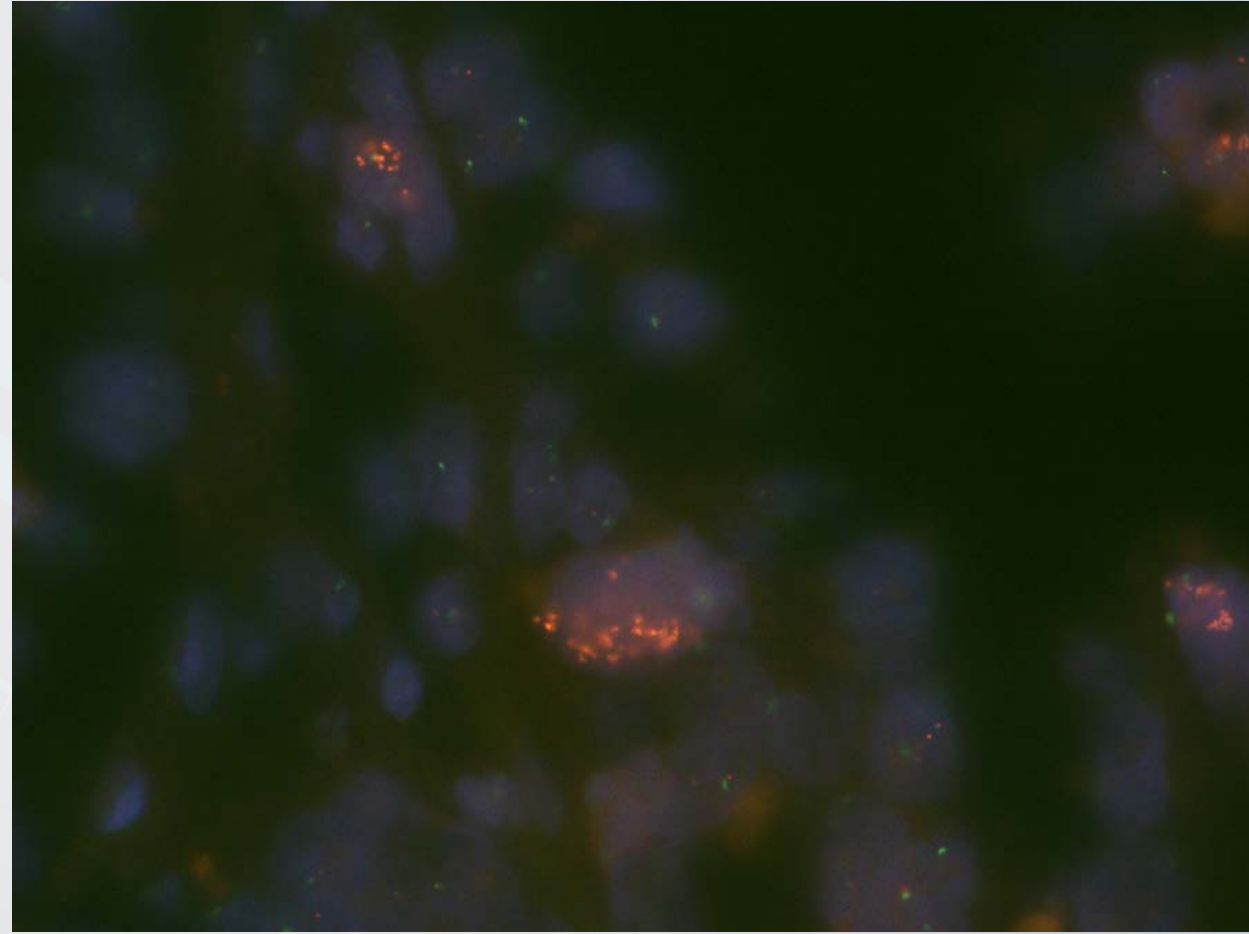
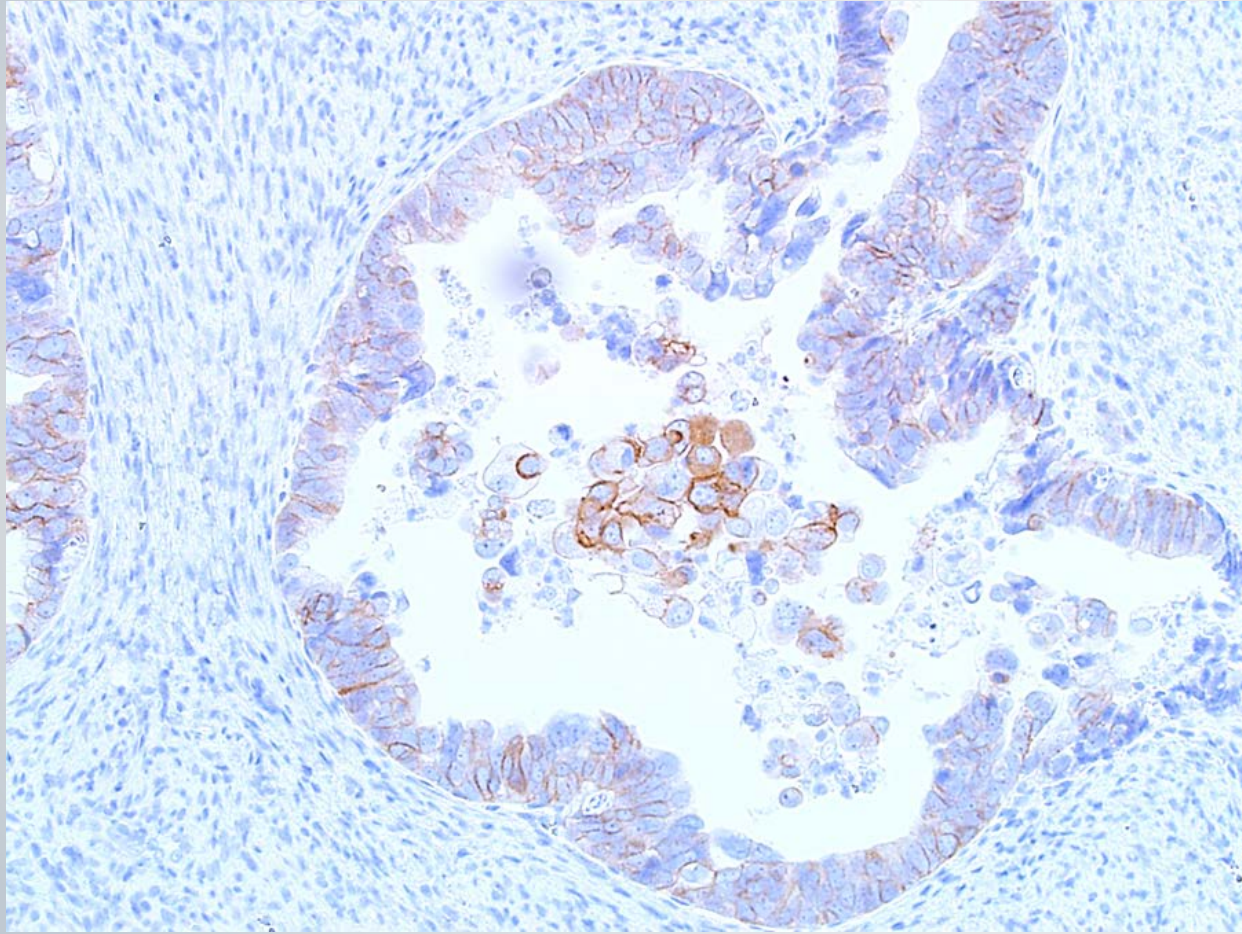
Her2 protein expression by IHC closely correlates at the cellular level with Her2 gene amplification

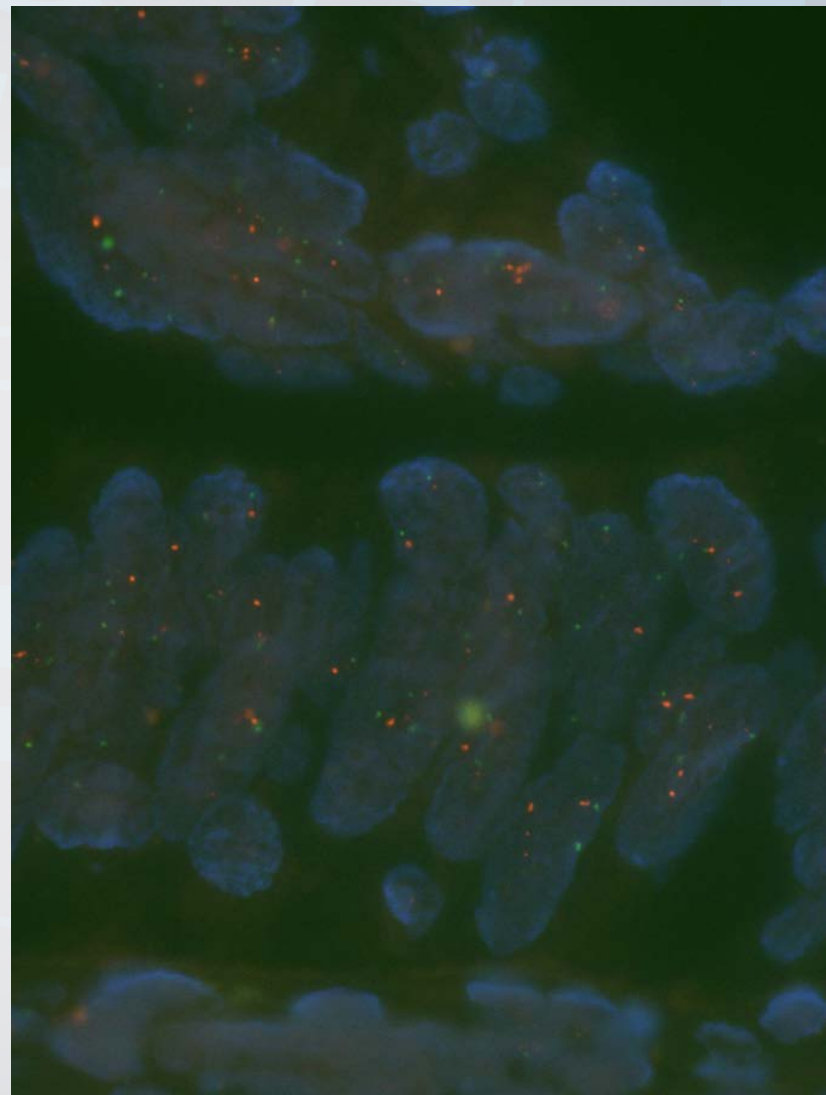
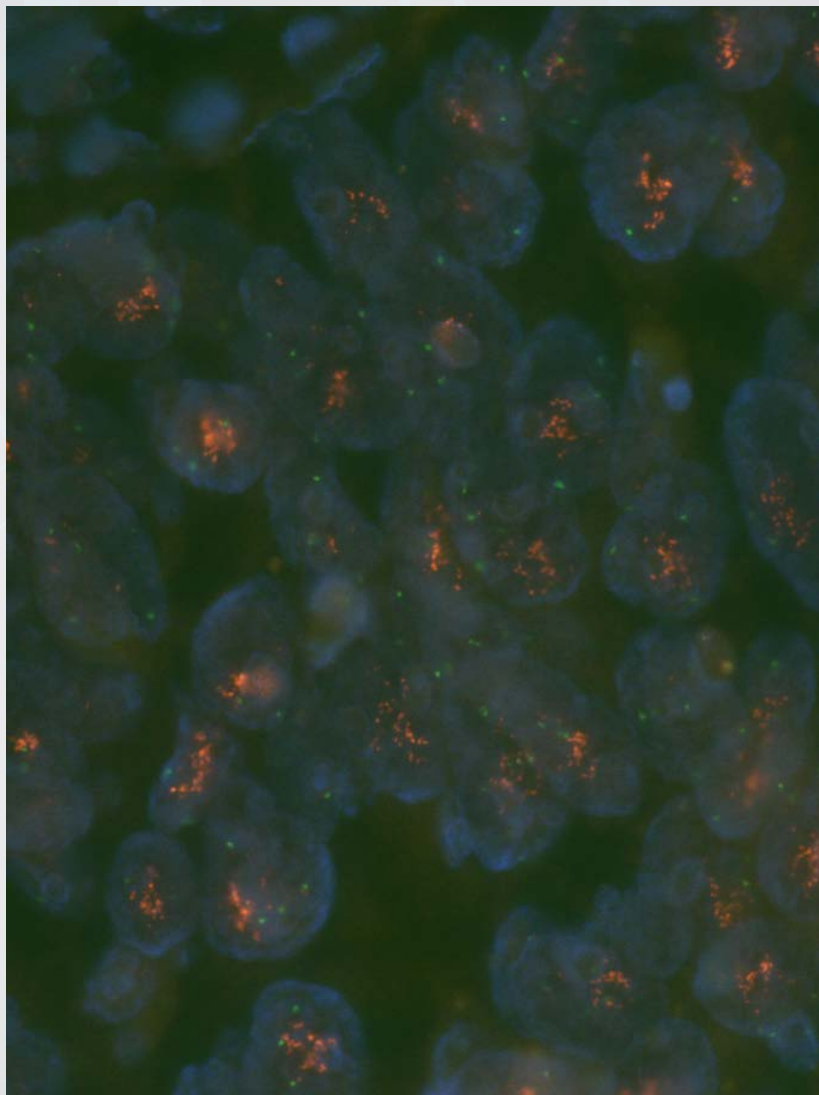
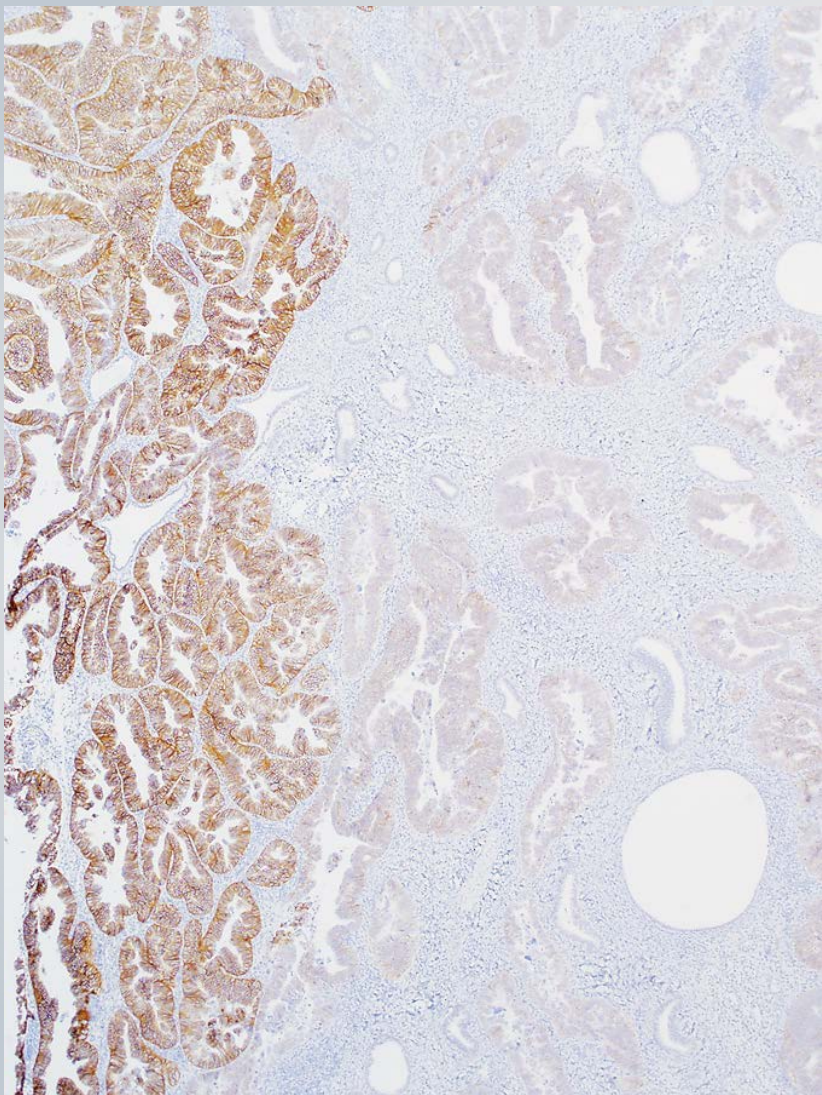
Chr 17 polysomy is rare

Cluster Amplification



Mosaic Amplification





Criteria Used in Recent Clinical Trial

2007 ASCO/CAP breast with specific modifications:

Complete circumferential staining not required, basolateral/lateral pattern also accepted

Large tumor section(s) selected for IHC (on hysterectomy)

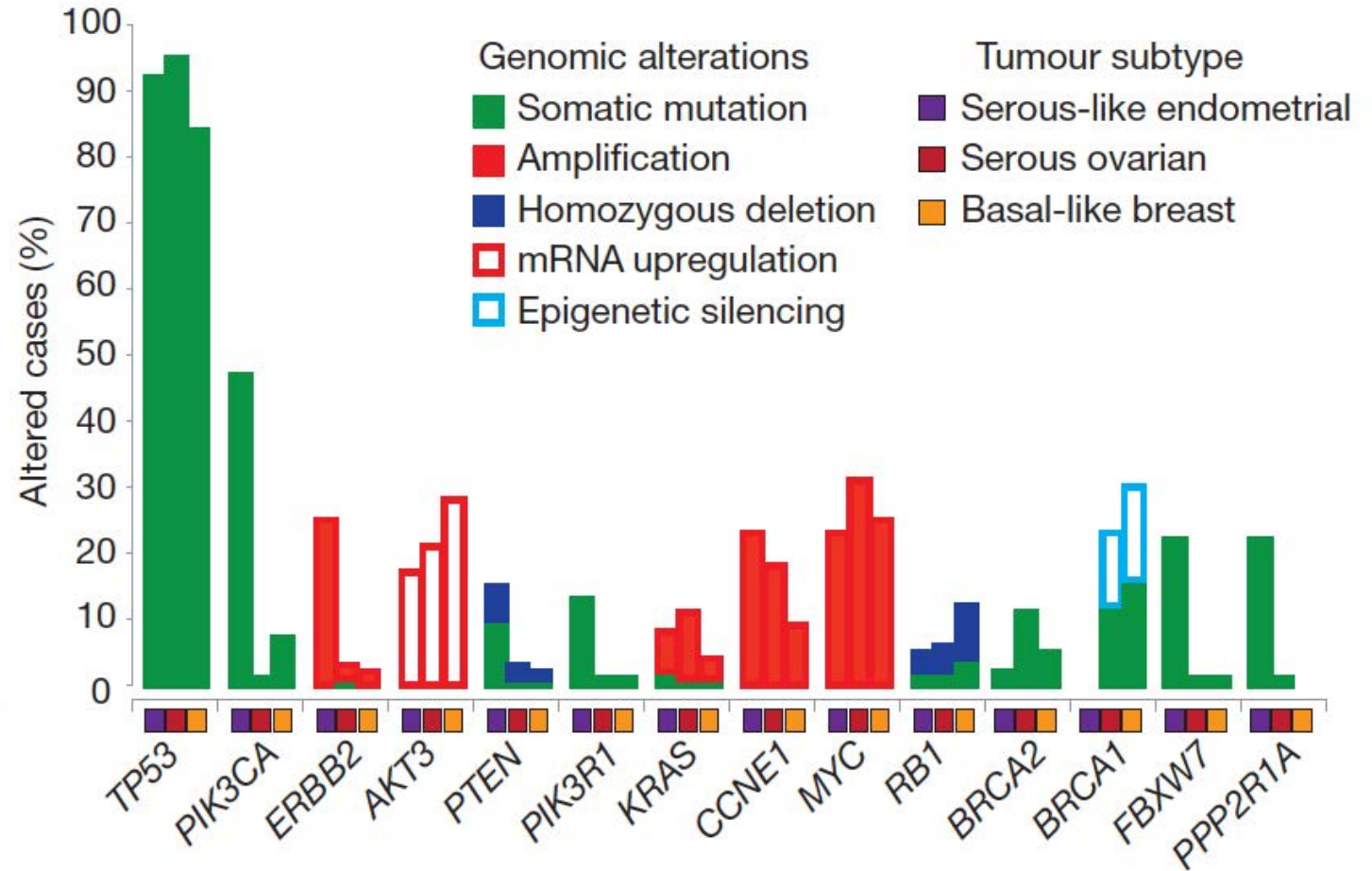
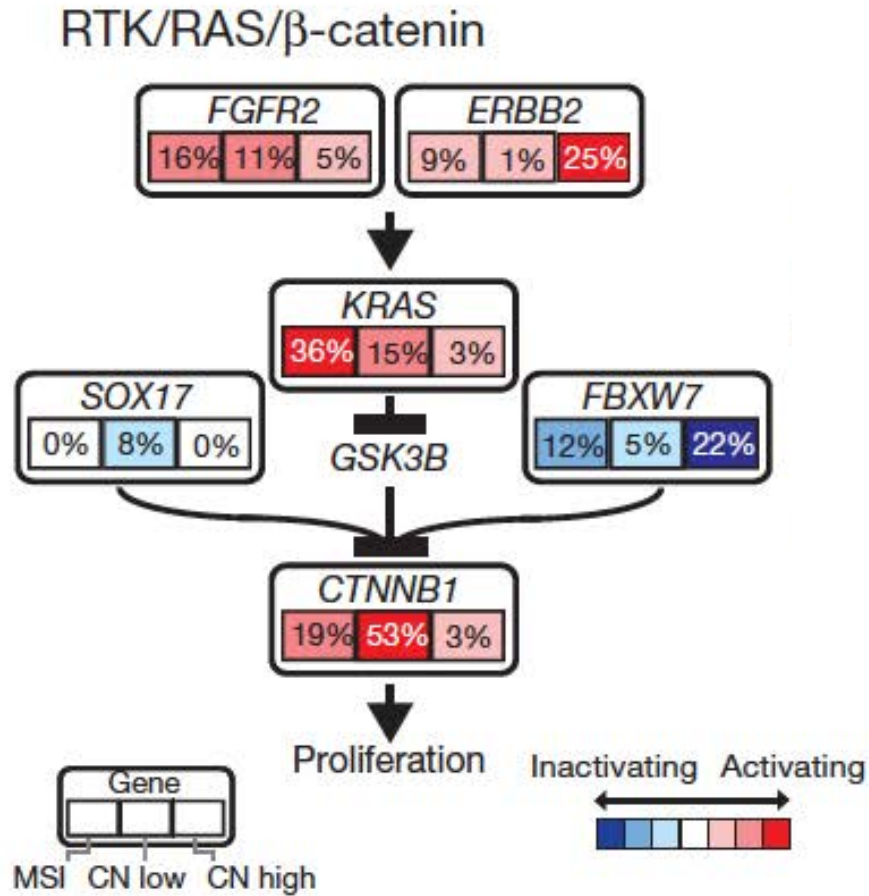
FISH on 2+ IHC only, in direct correlation with IHC

Larger tumor area selected for FISH ($\geq 1 \text{ cm}^2$)

Her2/CEP17 ratio ≥ 2.0

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*



HER2 Immunohistochemistry Significantly Overestimates HER2 Amplification in Uterine Papillary Serous Carcinomas

Mark J. Mentrikoski, MD and Mark H. Stoler, MD

TMA with 69 uterine serous carcinomas

Her2 overexpression by IHC: 20% (2007), 40% (2013)

Her2 amplification by CISH: 13%

IHC-CISH concordance (positive cases only):

ASCO/CAP 2007 64% (9/14)

ASCO/CAP 2013 32% (9/28)

Histopathology

Histopathology 2020 DOI: 10.1111/his.14001

Intratour heterogeneity in endo assessed by targeted sequencing a dependent probe amplification: a c

Dolors Cuevas,¹ Ana Velasco,¹ Marta Vaquero,¹ M
Núria Eritja,¹ Elena Estaran¹ & Xavier Matias-Guiu¹..
¹Hospital Universitari Arnau de Vilanova, Universitat de Lleida, IRI
de Bellvitge, Idibell, Barcelona, Spain

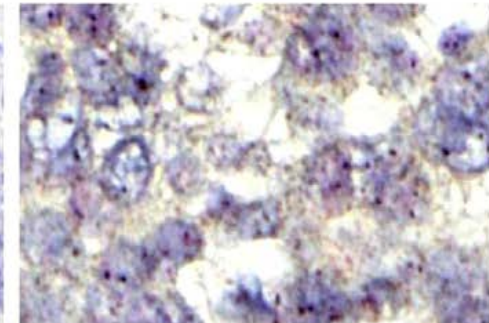
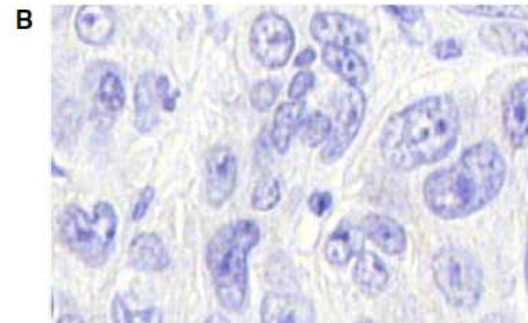
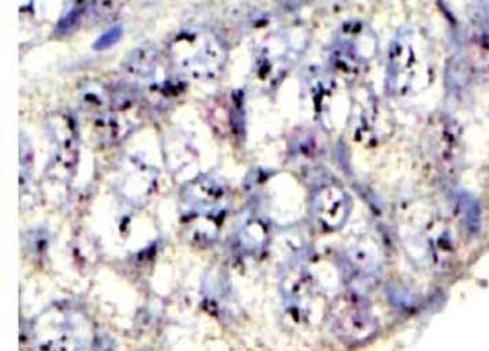
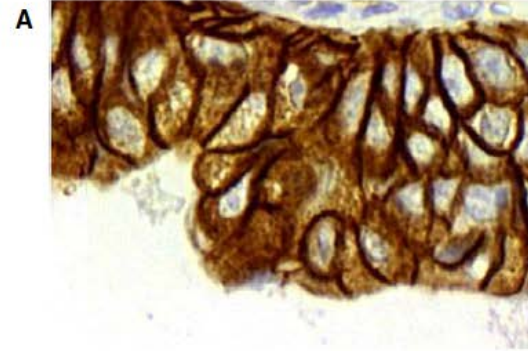
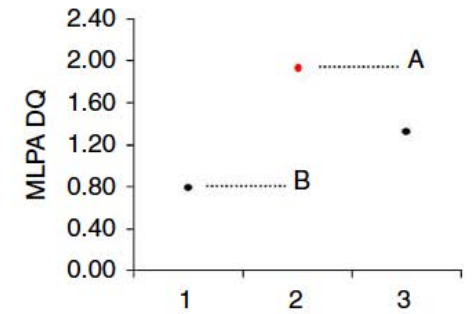
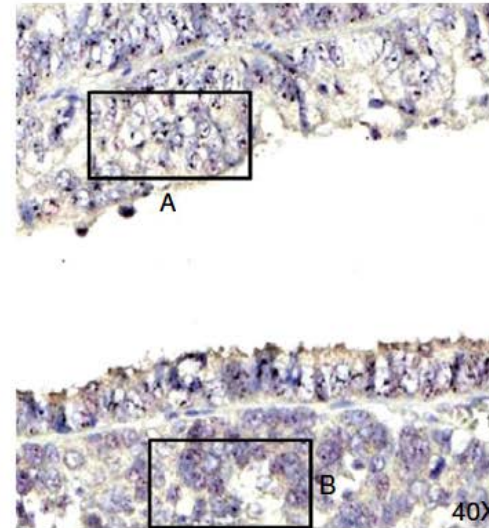
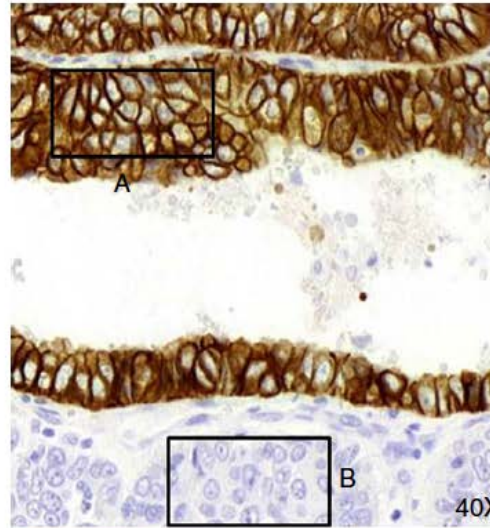
Intratoural
heterogeneity of
ERBB2 in 67%

Case 1

IHC

SISH

MLPA



GAIN
DQ = 1.93

NORMAL
DQ = 0.81

Her2 IHC and FISH Assays (for Breast Cancer)

IHC:

HercepTest (A085; DAKO)
Pathway anti-Her2 (4B5;
Ventana)
Bond Oracle (CB11; Leica)

FISH:

PathVysion (Abott)
HER2 FISH PharmDx (DAKO)

Dual ISH

Inform Her2 (Ventana)

LDTs

Remaining Practical Issues

Correlation with clinical response: IHC or FISH (or NGS) ?

Clinical impact of:

FDA vs ASCO/CAP 2007 vs 2013 vs 2018 guidelines

Her2 heterogeneity

Sample selection

Bx/curettage vs hysterectomy

Primary vs metastasis

Specimen handling/Fixation time

Sample Selection

“Does Specimen Type Have an Impact on Her2 Status in Endometrial Serous Carcinoma?” Rottmann, D. et al., abstract number #1083, poster #211

Stowell-Orbison Award Poster Session, Monday, March 2, 9:30 AM

95% concordance rate of HER2 status between biopsy and hysterectomy

Sample Selection

Primary vs metastasis:

23% of tumors with discordant Her2 expression on TMA

Potential Pitfalls

Heterogeneity:

Immunohistochemistry

FISH

Membrane staining pattern: complete vs. basolateral

Rare cases of co-amplification

Her2 testing of mixed carcinomas

Future Directions - Her2 in Carcinosarcomas

International Journal of Gynecological Pathology
31:211–221, Lippincott Williams & Wilkins, Baltimore
© 2012 International Society of Gynecological Pathologists

Original Article

HER2/neu as a Potential Target in Gynecologic Carcinosarcomas

Federica Guzzo, M.D., Stefania Bellone, Ph.D., Natalia
Luisa Carrara, M.D., Joyce Varughese, M.D., Emiliano
Paola Todeschini, M.S., Sara Gasparrini, M.S.,
Thomas J. Rutherford, M.D., Ph.D., Roberto Angioli,
and Alessandro D. Santin

Modern Pathology
<https://doi.org/10.1038/s41379-019-0358-x>



ARTICLE



HER2 testing of gynecologic carcinosarcomas: tumor stratification for potential targeted therapy

Douglas Rottmann¹ · Olivia L. Snir² · Xinyu Wu¹ · Serena Wong¹ · Pei Hui¹ · Alessandro D. Santin³ · Natalia Buza¹

Received: 22 June 2019 / Revised: 30 July 2019 / Accepted: 31 July 2019
© United States & Canadian Academy of Pathology 2019

Her2 positive (ASCO/CAP 2007): uterine 14%, tubo-ovarian 7%

All Her2 positive uterine tumors had serous or mixed ca component

Summary

~30% of endometrial serous carcinomas Her2 positive

Addition of trastuzumab to chemotherapy significantly improves progression-free survival

ASCO/CAP 2007 breast scoring criteria with modifications:

- Lack of apical membrane staining

- Heterogeneity

- FISH on 2+ cases

 - Large area in correlation with IHC

 - Ratio ≥ 2.0

THANK YOU!



#IAMUSCAP
#USCAP2020