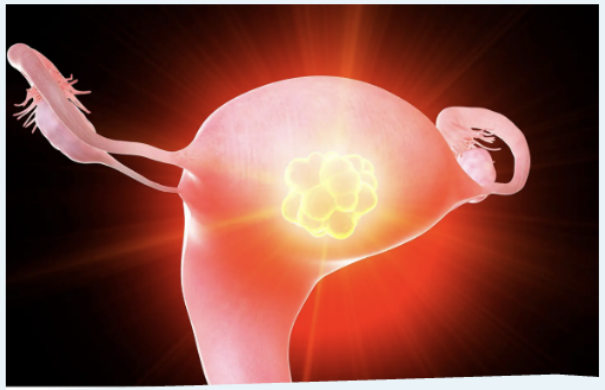
HER2-Directed Therapies in Endometrial & Other Cancers: Unanswered Questions

Amanda Fader, MD

Professor, Gynecologic Oncology

Johns Hopkins Hospital



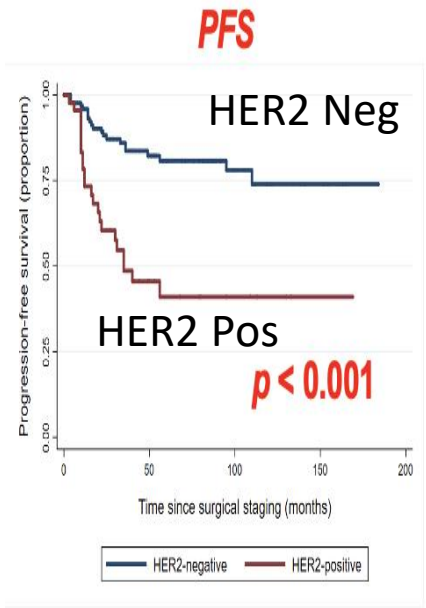
NSGO

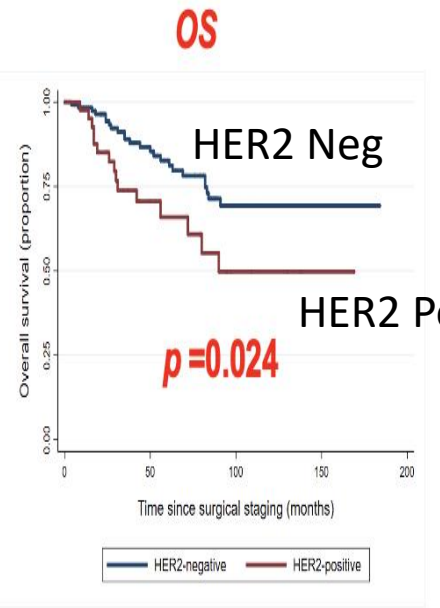
Disclosures

- I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:
- Grants: National Cancer Institute Cervical and Ovarian SPORE grants, NCI NRG Oncology: Co-PI of NRG-GY026
- Consulting/Ad Board: Eisai, Merck, Onconova

HER2

- Oncogenic potential of human epidermal growth factor receptor 2 (HER2) is widely recognized
- First identified as amplified in breast cancers in 1985
- Overexpression of this oncogene plays an important role in the development/progression of select aggressive types of breast, gastric, head and neck, and uterine cancers, as well as ovarian and cervical malignancies
- HER2 overexpression or amplification associated with metastatic disease and poor overall survival outcomes



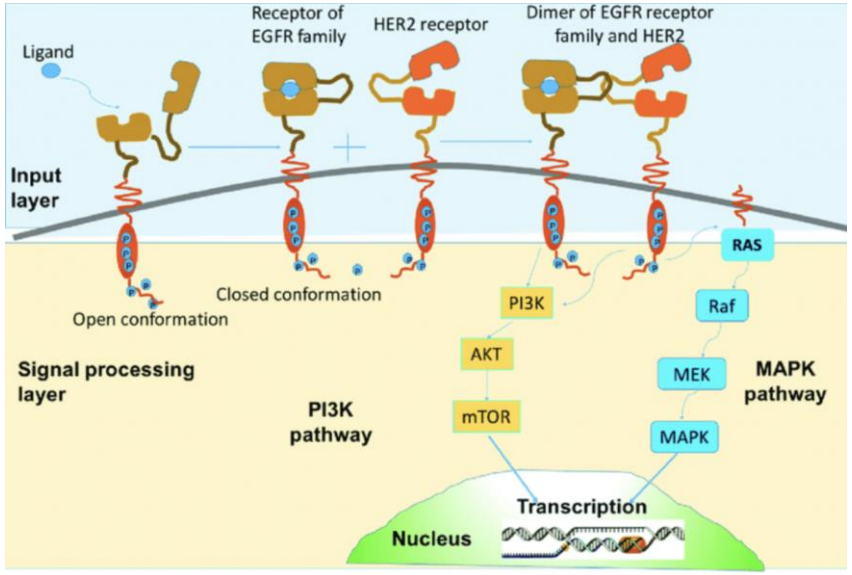


Erickson et al, Halle et al, Br J Cancer, 2018

NSGO

HER Family Members

- Receptor tyrosine kinase present on cell surface
- Activated by ligand-induced dimerization
- HER2 only member with no known ligand
- HER2 functions as a preferred partner for homo- or hetero-dimerization with any of the other EGF family members (HER1, HER3 and HER4) and responsible for regulating cell growth and differentiation

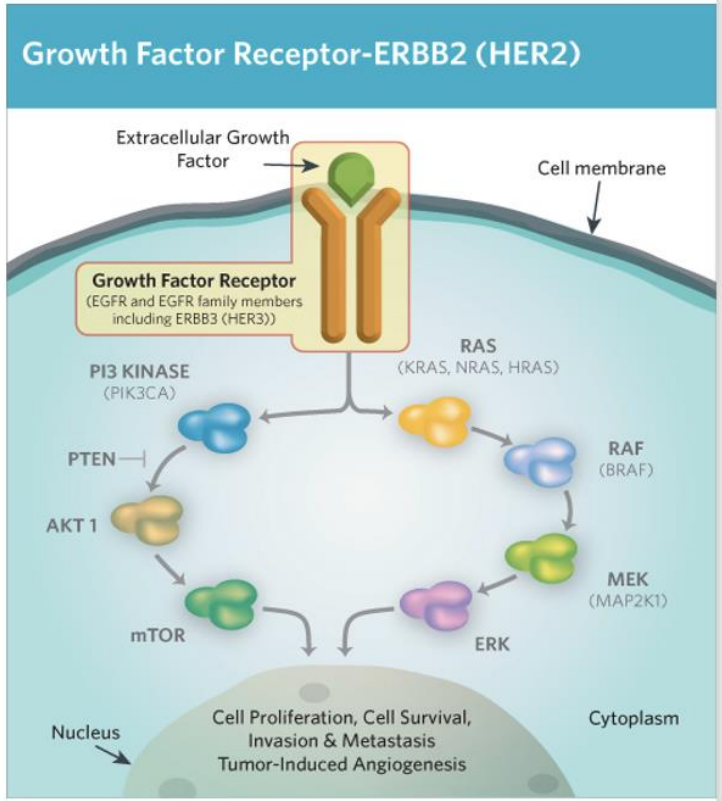


Nomenclature for the EGFR/ERBB family

Members of the EGFR/ERBB protein family	Other common names
HER1	EGFR, ERBB1
HER2	ERBB2, CD340, protooncogene neu
HER3	ERBB3
HER4	ERBB4

HER2: Human Epidermal Growth Factor Type II

- **Dimerizes with itself and other HER2 Receptors**
  - HER1, HER2, HER3, HER4
  - Activates PI3K/AKT, RAS/MAPK, JAK-STAT pathways
  - Responsible for proliferation, differentiation, apoptosis
- **HER2 amplification -> overexpression**
  - Constitutively activated
  - Breast, Gastroesophageal, H&N, GYN
- **ERBB2 Mutations**



NRG ONCOLOGY™

NSGO

Several Unanswered Questions

- What is the prevalence of HER2 overexpression/amplification in gynecologic cancers?
- What is the optimal HER2 testing platform?
- Is an endometrial/GYN cancer testing algorithm required?
- HER2 is what type of biomarker?
- What is the best upfront treatment for HER2 positive uterine serous carcinoma? Advanced Stage? Early-stage disease?
- For how long should maintenance treatment be continued?
- What can enhance trastuzumab response or overcome trastuzumab resistance?
- What is the best 1st line treatment for recurrence?
- What is best treatment for tumors with low HER2?
- Will ADCs be used in the front-line setting?

Unanswered Questions

- **What is the prevalence of HER2 overexpression/amplification in gynecologic cancers?**
- **What is the optimal HER2 testing platform?**
- **Is an endometrial/GYN cancer testing algorithm required?**
- **HER2 is what type of biomarker?**
- **What is the best upfront treatment for HER2 positive uterine serous carcinoma? Advanced Stage? Early-stage disease?**
- **For how long should maintenance treatment be continued?**
- **What can enhance trastuzumab response or overcome trastuzumab resistance?**
- **What is the best 1st line treatment for recurrence?**
- **Will ADCs be used in the front-line setting?**

HER2 Prevalence in Endometrial Cancer

Prevalence – Harder question to answer than it may seem

- **What type of test?**
- **Which guidelines?**
- **What part of the tumor?**

NRG ONCOLOGY™

HER2 Prevalence and Testing in USC

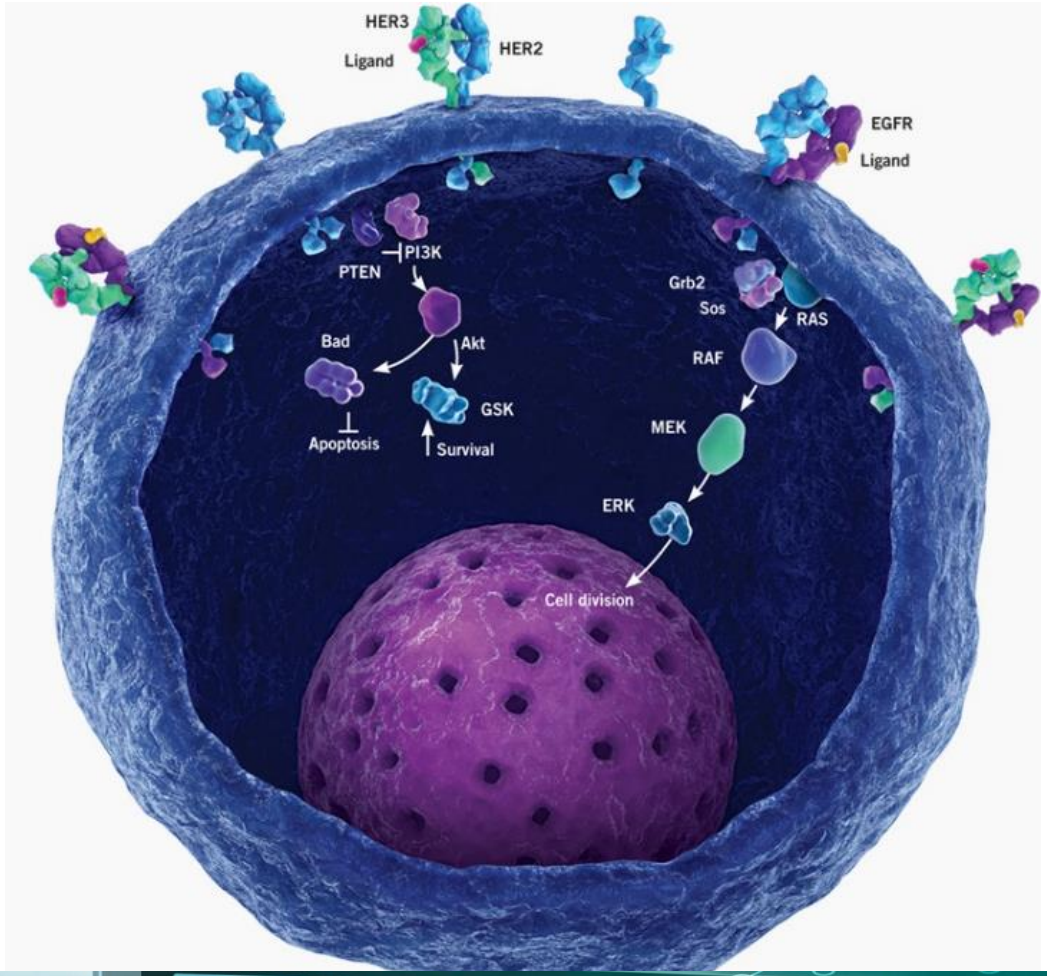
Study	Testing methods	Rate of HER2 positivity
Single institution reports (n<100)	IHC, ISH	18-42% IHC+ 16-47% ISH +
GOG 177 (n=38)	IHC, FISH	61% IHC+ 21% FISH+
TCGA (n=66)	IHC, FISH	27% IHC and FISH
GOG 210 (n=313)	IHC`	<5% IHC+

NRG ONCOLOGY™

NSGO

HER2 Expression in Several Cancers

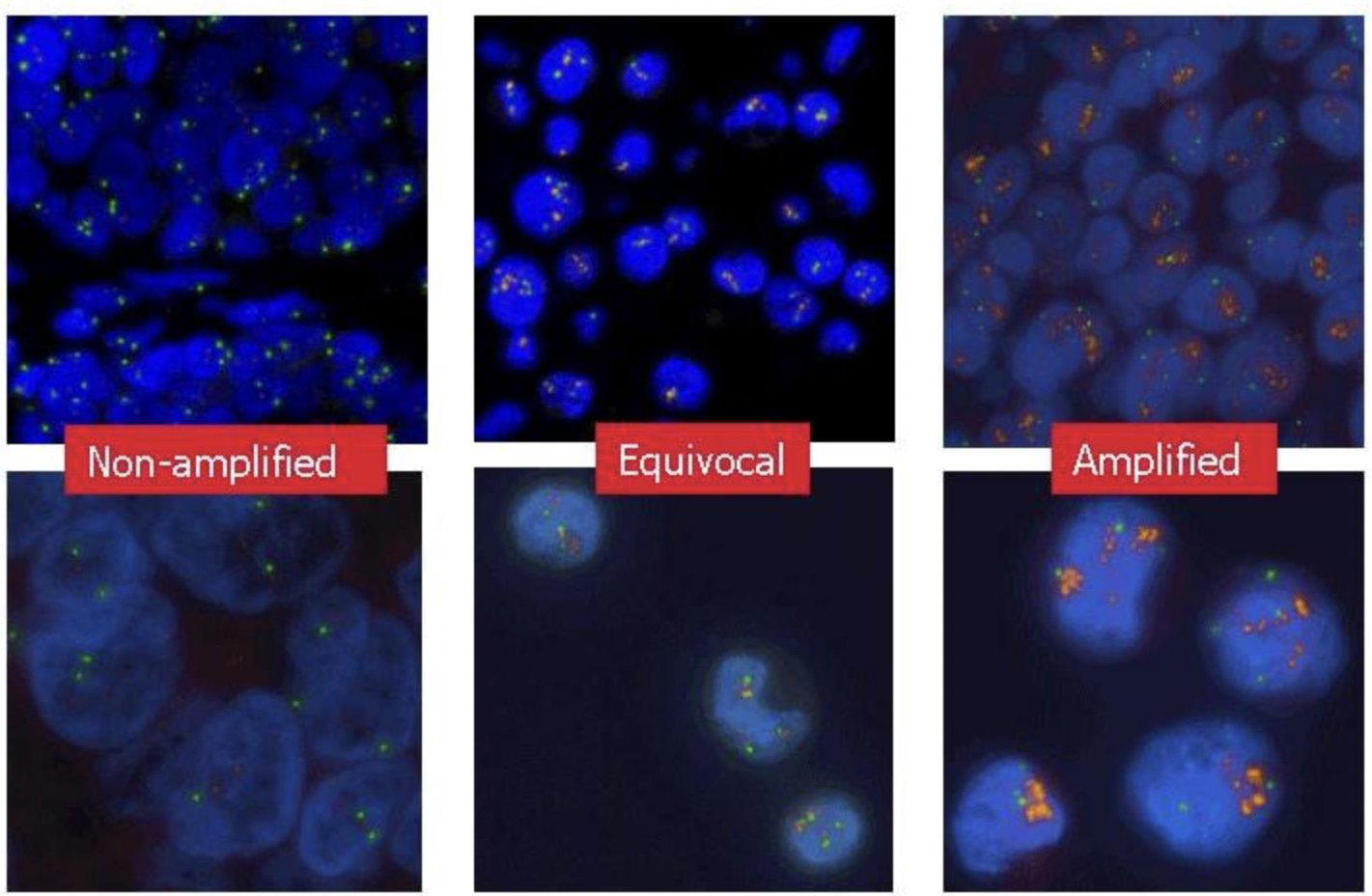
- **20-40% uterine serous carcinoma**
- **20-30% breast cancer**
- 10-25% of gastric/esophageal
- 15-20% uterine carcinosarcoma
- 15-20% uterine clear cell
- 1-20% cervical cancer
- 3-10% uterine endometrioid
- 5-10% ovarian epithelial carcinomas



Halle et al, Br J Cancer, 2018;
Shao et al, Path Clin Res, 2020

HER2 Prevalence and Testing Platforms

- **HER2 protein expression- immunohistochemistry**
- **Gene amplification-in situ hybridization**
- **Gene amplification- NGS**
- **Gene mutations- NGS**



NSGO

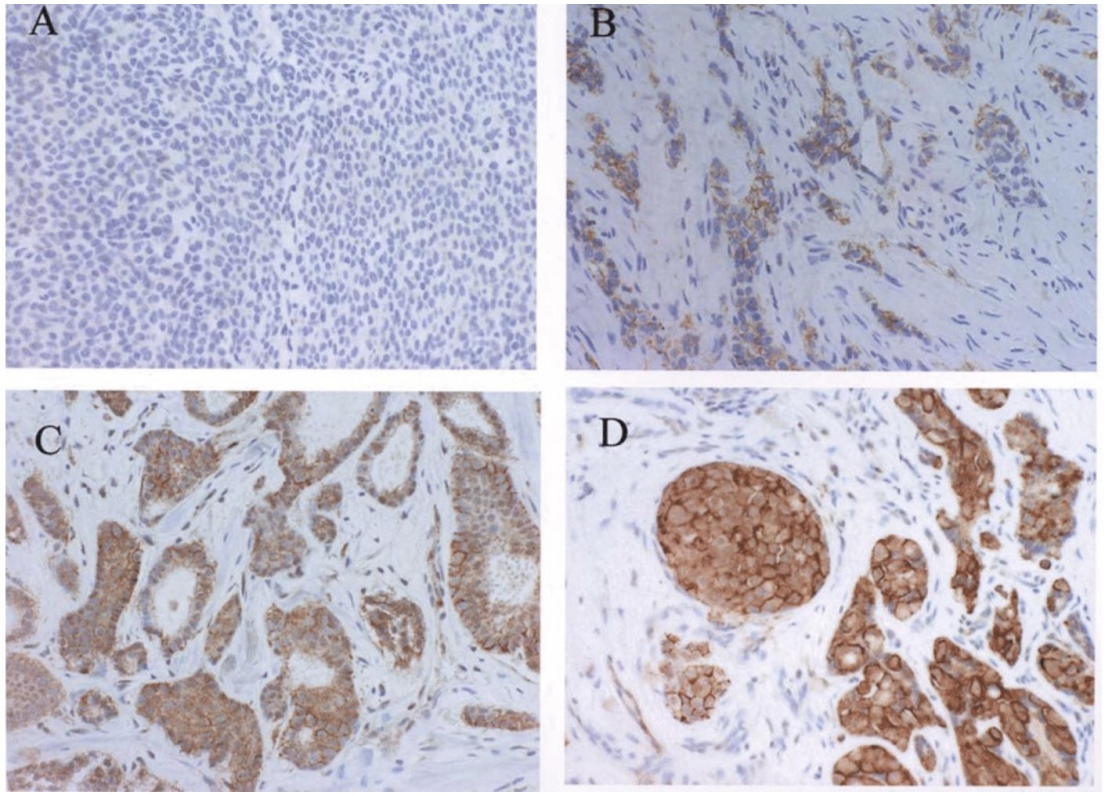
HER2 Prevalence and Testing

- **HER2 protein expression – Immunohistochemistry**

Breast Cancer 2018 ASCO/CAP guidelines:

- 0 : no staining or faint incomplete staining <10% **negative**
- 1+ : faint, incomplete membrane staining >10% **negative**
- 2+ : incomplete/weak circumferential membrane staining >10% **equivocal**
- 3+ : complete circumferential membrane staining >10% **positive**

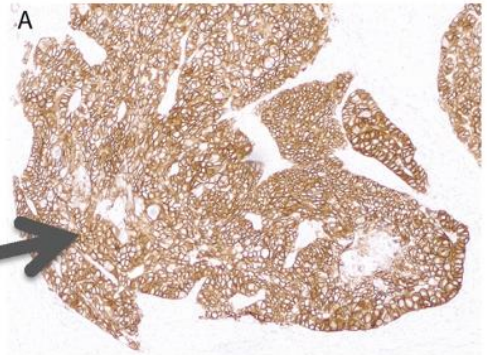
***Results are given based on a percentage of tumor cells that are positive for HER2 as well as the completeness of membrane staining**

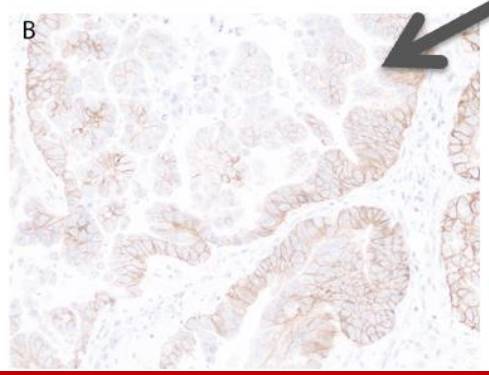


NSGO

HER2 Prevalence and Testing in USC

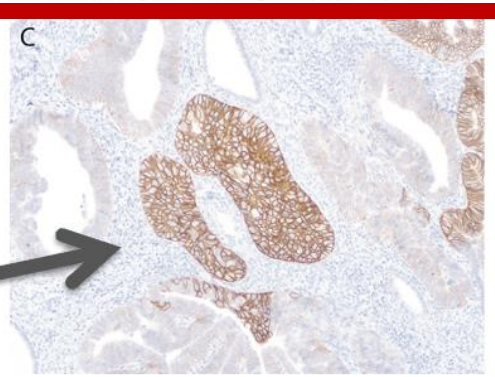
3+: strong complete membranous staining in >30%

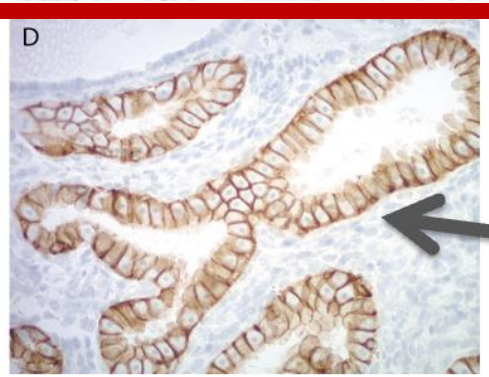




2+: weak to moderate membranous staining in a basolateral pattern in >10%

Heterogeneity of HER2 expression





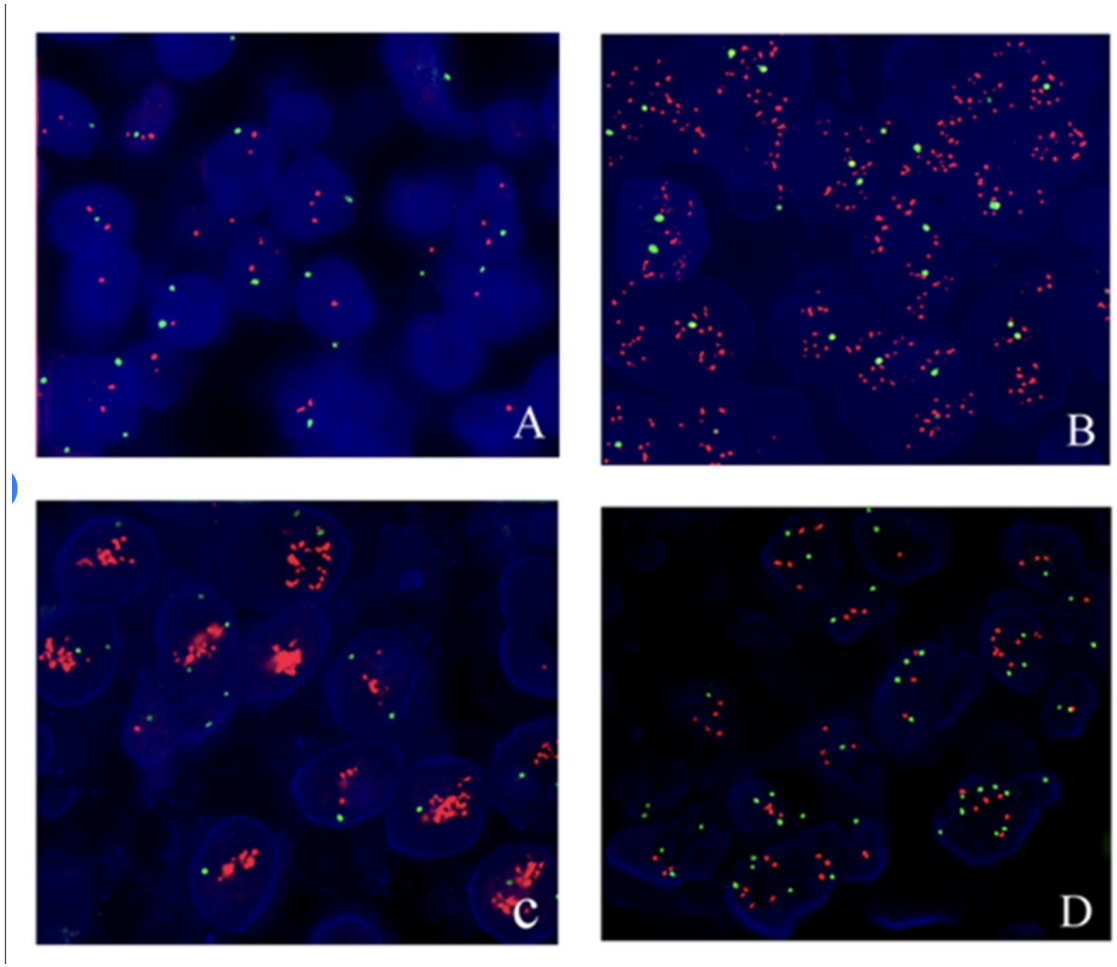
Lack of apical membrane staining

NRG ONCOLOGY™

Images from:
Buza, *Arch Pathol Lab Med 2021*

HER2 Prevalence and Testing

- HER2 protein expression – Immunohistochemistry
- **Gene amplification – in situ hybridization**
  - HER2/CEP17 ratio ≥ 2.0 AND HER2 copy number signals/cell ≥ 4 = **POSITIVE**
  - HER2/CEP17 ratio < 2.0 AND HER2 copy number signals/cell < 4 = **NEGATIVE**
  - Other scenarios require further workup



***HER2/CEP17 ratio by FISH quantifies the number of HER2 gene copies on chromosome 17 (ERBB2) in relation to the number of chromosome 17 centromere (CEP17) copies per nucleus**

HER2 Testing: How Aligned Are IHC and FISH/CISH?

Currently using ASCO/CAP 2018 Breast Cancer Criteria

13% of tumors classified at 0/1+ were FISH Pos!

Recommend consideration of both IHC and FISH in tumors, and repeating at recurrence

Banet, Fader et al, Am J Surg Path, 2020

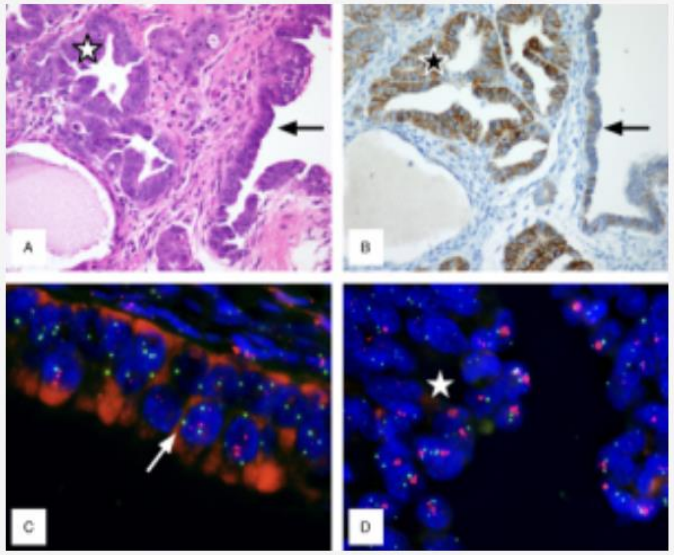


FIGURE 2
HER-2 status can vary between the SEIC component and the corresponding invasive USC component. A, SEIC (arrow) with corresponding underlying invasive serous carcinoma (star). In this case, the SEIC (arrow) was negative for HER-2 overexpression by IHC, while the underlying USC (star) was positive (B). The tumor was negative by FISH in both the SEIC component (arrow) (C) and in the invasive component (star) (D), with ***HER-2/CEP17*** ratios of 1.02 and 1.66, respectively.

SEIC and USC. In conclusion, USC displays HER-2 intratumoral heterogeneity, a high IHC/FISH discordance rate, and variation in HER-2 status between the SEIC and invasive components. Caution is required when evaluating HER-2 in small biopsies, which should be repeated on excisions. Both IHC and FISH should be performed on USC until clinical trials correlate HER-2 status with clinical response to HER-2-targeted therapy.

Discordance Between HER2 Expression in Primary vs. Metastatic Endometrial Cancer Lesions

- 67 precursor lesions, 790 primary ECs and 383 metastatic lesions investigated for HER2 expression in relation to clinicopathologic features and outcome
  - 641 endometrioid, 72 serous and 30 clear cell carcinomas, 34 carcinosarcomas and 13 undifferentiated tumours.
- Protein levels assessed by IHC (using HercepTest and staining index (SI) criteria), mRNA levels by TMAs and amplification status by CISH
- A discordant HER2 expression pattern between paired primary and metastatic lesions was detected, revealing substantial reduction in HER2 expression from primary to metastatic disease
  - Within the HER2-high primary uterine tumours, 62% (21/34) had HER2-low corresponding metastatic lesions
  - Within the HER2-low primary tumours, 11% (12/108) had HER2-high corresponding metastases

Halle and Krakstad et al, B J Cancer, 2018;
Cardoso, ESMO Breast Guidelines, Annal Oncol, 2017

HER2 Prevalence and Testing

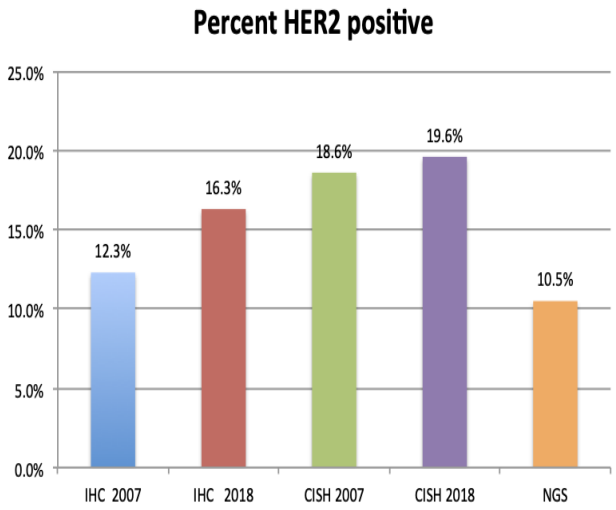
- HER2 protein expression – Immunohistochemistry
- Gene amplification – in situ hybridization
- **Gene amplification – NGS**
  - Not standardized
  - Typically HER2 positive if >6 copies

NSGO

HER2 Prevalence and Testing in USC

Klc et al, Gynecol Oncol 2022

- n=2,192 USC tumors from a commercial registry
- NGS, IHC, CISH
- HER2 positivity determined and compared among testing platforms



NRG ONCOLOGY™

HER2 Prevalence and Testing in USC

IHC vs CISH

	IHC+/CISH+ (n)	IHC-/CISH- (n)	IHC-/CISH+ (n)	IHC+/CISH- (n)	Concordance (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Testing via ASCO/ACP Breast Cancer 2018 Guidelines (n=1,423)	229	1178	11	5	98.9	97.9	99.1	95.4	99.6

CISH vs NGS

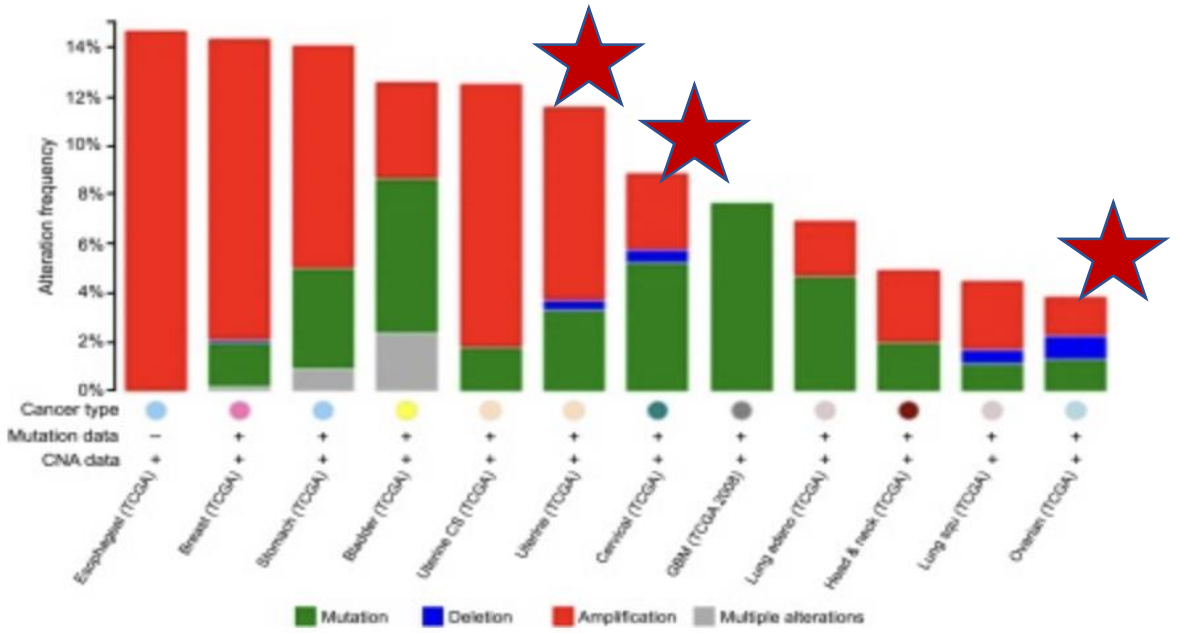
	CISH+/NGS+ (n)	CISH-/NGS- (n)	CISH-/NGS+ (n)	CISH+/NGS- (n)	Concordance (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
HER2 Testing via Breast Cancer 2018 Guidelines (n=1544)	191	1224	3	126	91.6	60.3	99.7	98.5	90.7

NRG ONCOLOGY™

*Ultimately NGS testing platforms need to be validated by response to targeted therapy.

The Cancer Genome Atlas of HER2 Mutation, Deletion and Amplification

Figure 1.



The Cancer Genome Atlas analysis of HER2 mutation, deletion, and amplification across the 12 most common disease sites. Breast, esophageal, stomach, and uterine carcinomas all present with similar rates of gene amplification, while mutation appears to be most common in glioblastoma, cervical, and lung adenocarcinoma. Therapeutic response to anti-HER2 therapies has been most closely associated with *HER2* gene amplification or protein overexpression, although understanding of HER2 mutations is expanding (http://www.cbioportal.org [33, 34]).

Unanswered Questions

- What is the prevalence of HER2 overexpression/amplification in gynecologic cancers?
- What is the optimal HER2 testing platform?
- Is an endometrial/GYN cancer testing algorithm required?
- HER2 is what type of biomarker?
- What is the best upfront treatment for HER2 positive uterine serous carcinoma? Advanced Stage? Early-stage disease?
- For how long should maintenance treatment be continued?
- What can enhance trastuzumab response or overcome trastuzumab resistance?
- What is the best 1st line treatment for recurrence?
- Will ADCs be used in the front line setting?

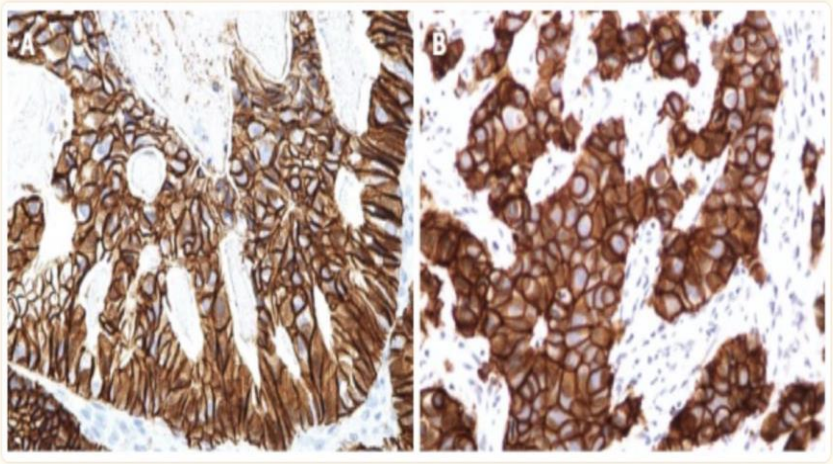


Figure 2

Human epidermal growth factor receptor 2 expression in gastric and breast tumors. A: A HER2-positive (3+) case of gastric adenocarcinoma; the cytoplasmic membranous immunostaining is incomplete and predominantly basolateral (× 400); B: A HER2-positive (3+) case of invasive ductal carcinoma of the breast; the cytoplasmic membranous staining is fully circumferential (× 400). HER2: Human epidermal growth factor receptor 2.

Key Differences Between HER2 IHC in Breast and Gastric-Esophageal Tumors

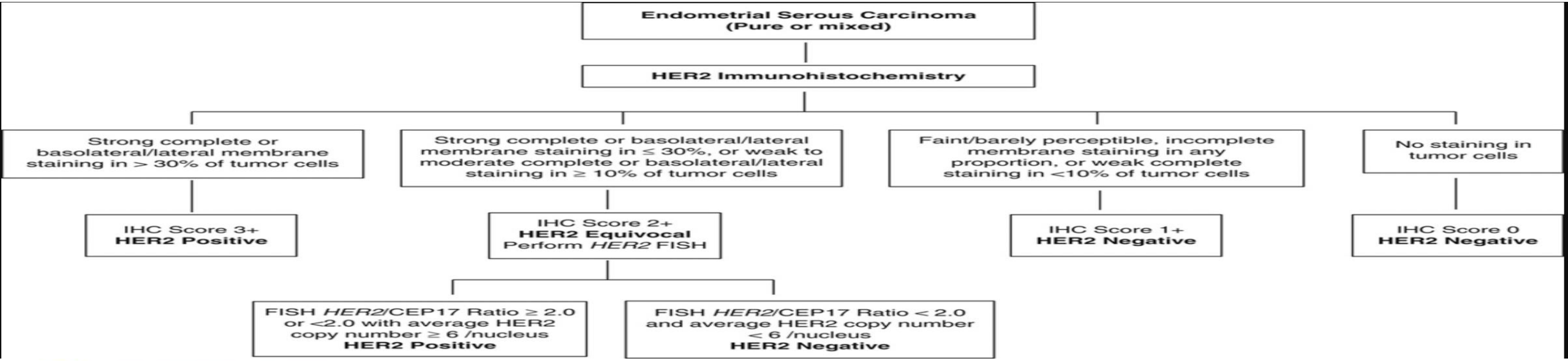
- Membranous distribution of the antibody in the neoplastic cells of breast cancer is predominantly circumferential, whereas in gastric cancer, it is generally incomplete, predominantly basolateral (“U”-shaped) or lateral (parallel lines)
    - Circularity of IHC staining is not a criterion for HER2 IHC scoring in gastric cancer
- Intratumoral heterogeneity, defined as the presence of areas with different HER2 scores within the same tumor, *i.e.*, focal or patchy positivity, is a common pattern encountered in gastric tumors but is only rarely seen in breast cancer

Argument for Endometrial HER2 Testing Guideline

TABLE 1 Criteria for HER2 positivity by immunohistochemistry and FISH in different tumor types

	Breast (ASCO/CAP 2007) 27	Breast (ASCO/CAP 2013) 28	Breast (ASCO/CAP 2018) 29	Gastric (ASCO/CAP 2016) 30	Colorectal (HERACLES trial) 31	Endometrial serous (Fader et al clinical trial) 24,25
HER2 IHC 3+	>30% strong, uniform, complete	>10% circumferential, strong, complete	>10% circumferential, strong, complete	≥10%, strong complete, or basolateral/lateral	≥50% strong complete, or basolateral/lateral	>30% strong complete, or basolateral/lateral
HER2 FISH amplification	HER2/CEP17 ratio >2.2 patients with HER2/CEP17 ratio between 2.0 and 2.2 also eligible for treatment)	HER2/CEP17 ratio ≥2.0 OR ratio < 2.0 and HER2 signal ≥6.0/nucleus	HER2/CEP17 ratio ≥2.0 and HER2 signal ≥4.0/nucleus OR ratio <2.0 and HER2 signal ≥6.0/nucleus (if IHC score 2+ or 3+)	HER2/CEP17 ratio ≥2.0 OR ratio <2.0 and HER2 signal >6.0 /nucleus	HER2/CEP17 ratio ≥2.0 in ≥50% of cells	HER2/CEP17 ratio ≥2.0

FISH indicates fluorescent in situ hybridization; IHC, immunohistochemistry.



Unanswered Questions

- What is the prevalence of HER2 overexpression/amplification in gynecologic cancers?
- What is the optimal HER2 testing platform?
- Is an endometrial/GYN cancer testing algorithm required?
- HER2 is what type of biomarker?
- What is the best upfront treatment for HER2 positive uterine serous carcinoma? Advanced Stage? Early-stage disease?
- For how long should maintenance treatment be continued?
- What can enhance trastuzumab response or overcome trastuzumab resistance?
- What is the best 1st line treatment for recurrence?
- Will ADCs be used in the front line setting?

HER2: What biomarker category?

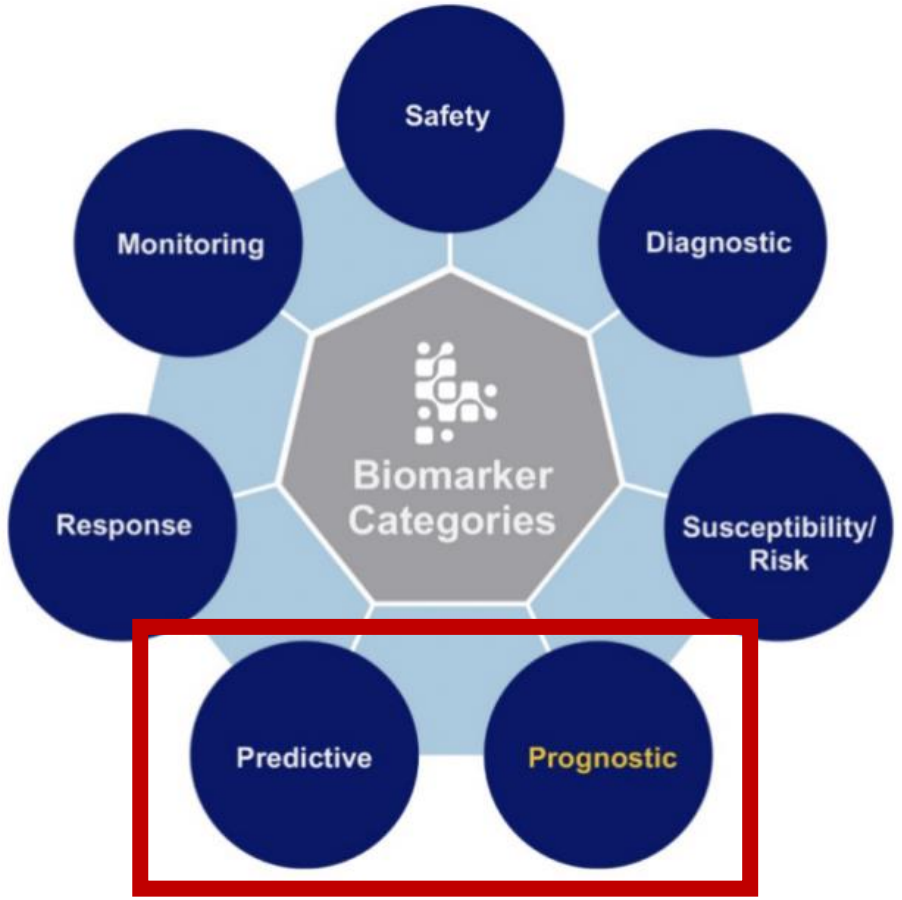


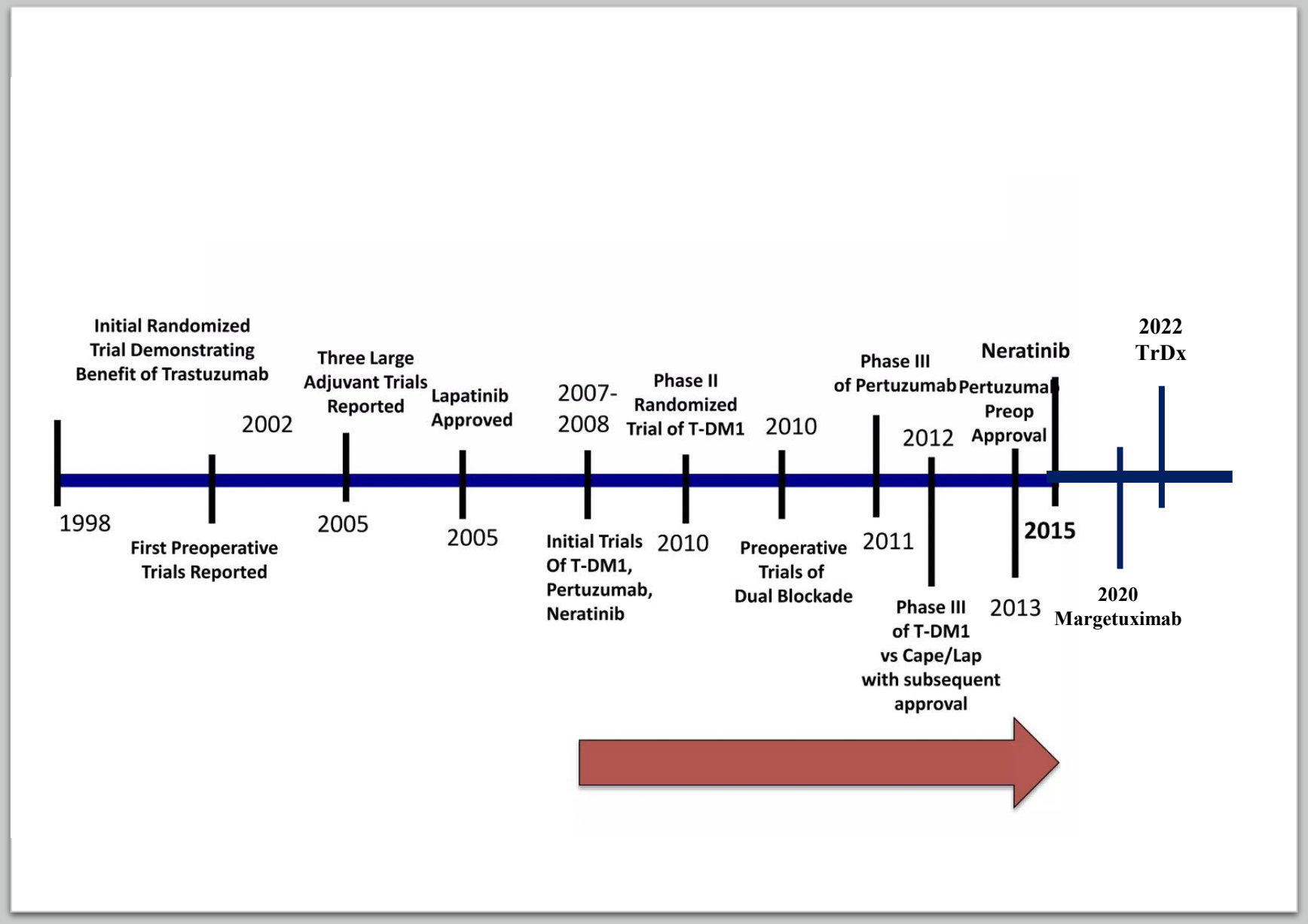
Image from FDA.gov: Biomarker Terminology: Speaking The Same Language

Halle et al, Br J Cancer, 2018

Unanswered questions

- What is the prevalence of HER2 overexpression/amplification in gynecologic cancers?
- What is the optimal HER2 testing platform?
- Is an endometrial/GYN cancer testing algorithm required?
- HER2 is what type of biomarker?
- What is the best upfront treatment for HER2 positive uterine serous carcinoma? Advanced Stage? Early-stage disease?
- For how long should maintenance treatment be continued?
- What can enhance trastuzumab response or overcome trastuzumab resistance?
- What is the best 1st line treatment for recurrence?
- Will ADCs be used in the front-line setting?

HER2+ Disease: Major Clinical Advances Over the Past 20 Years



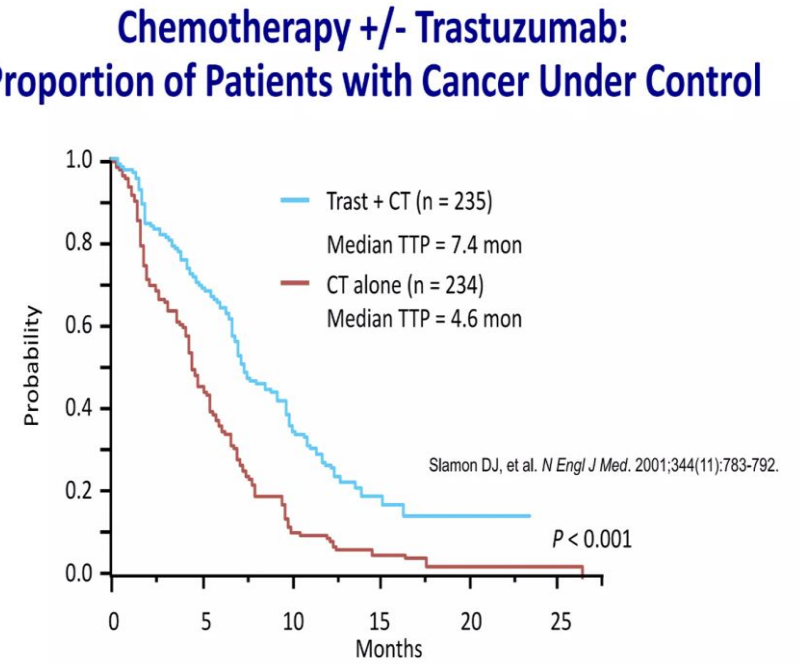
Anti-HER2 Therapies: Lessons From Breast Cancer

Drug	Class	Mechanism	FDA Approval
Trastuzumab	Monoclonal Antibody	Binds extracellular HER2 domain	HER2+ mBC, adjuvant for high risk BC, gastric cancer
Pertuzumab	Monoclonal antibody	Binds extracellular HER2 domain	HER2+ BC in combo with trastuzumab and chemo
Lapatinib	TKI	HER1/HER2 inhibitor	HER2+ mBC with chemo after trastuz, HER2+ HR+ mBC with letrozole
Neratinib	TKI	HER1/HER2/HER4 inhibitor	HER2+ high risk BC extended therapy after trastuzumab
Ado-trastuzumab Emtansine (T-DM1)	ADC	Trastuzumab + microtubule inhibitor	HER2+ BC residual dz after neoadj trastuzumab, mBC after trastuz +chemo
Trastuzumab deruxtecan (DS-8201a)	ADC	Trastuzumab + topo I inhibitor	3rd line HER2+ mBC, HER2 low mBC, HER2+ advanced gastric cancer, HER2+NSCLC
Margetuximab-cmkb	mAB, modified Fc region	Binds HER2,	3rd line HER2+ mBC

Background HER2

- **Trastuzumab**--humanized monoclonal antibody against Her2 approved by FDA in 1998 for the treatment of metastatic breast cancer overexpressing Her2 either in combination with paclitaxel or as a single agent in women who have received one or more chemotherapy regimens

- **Mechanisms of action** include:
  - Inhibition of tumor cell proliferation/induction of apoptosis (secondary to decreased HER2/neu receptor dimerization),
  - ADCC secondary to engagement of Fc receptors on effector cells (NK) (Dominant component of in vivo activity)



When trastuzumab was first approved based on the results above, few thought it would have such a profound effect on the course of HER2+ breast cancer

The HER2 Story in Endometrial Cancer

GOG HER2 Investigation in Uterine Cancer

GOG 181B: (Fleming et al, Gyn Onc 2010)

- Phase II GOG study of trastuzumab monotherapy in women with measurable Stage III, IV or recurrent EC
- Weekly trastuzumab
- 0% RR
- 33% USC
- Slow accrual, statistically underpowered (n=34)
- Most tumors were Type 1 (endometrioid) and fewer than half of tumors demonstrated HER2 amplification by ISH

GOG 229D: (Leslie et al, Gynecol Oncol 2012)

- Phase II GOG study of lapatinib monotherapy in women with measurable Stage III, IV or recurrent EC
- Daily Lapatinib
- 3% RR
- All comers, 8% HER2+, 71% EGFR+
- 23% USC

In Breast Cancer We Know…

- Trastuzumab monotherapy is not terribly efficacious
  - Early trials of single-agent trastuzumab in women with pretreated breast cancer demonstrated response rates of only 12%
  - Early HER2+ EC trials of trastuzumab did not show efficacy or clinical benefit

Diver et al, *Oncologist,* 2015

Minckwitz et al, *NEJM,* 2017

Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress Her2/neu (NCT01367002)

Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura 4 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

Yale University School of Medicine, New Haven, CT; John Hopkins School of Medicine, Baltimore, MD; University of Arkansas for Medical Sciences, Little Rock, AR; University of Arizona, Tucson, AZ; Duke University School of Medicine, Durham, NC; The Ohio State University School of Medicine, Columbus, OH; Montefiore Medical Center, Bronx, NY John Muir Medical Center, Brentwood, CA Penrose Cancer Center-St. Francis, Colorado Springs, CO, Walter Reed Medical Center, Bethesda, MD

Study Design

Eligible USC HER2+ Patients

Randomization 1:1

Paclitaxel 175 mg/m2 and carboplatin AUC 5 IV q 21 days x 6 cycles

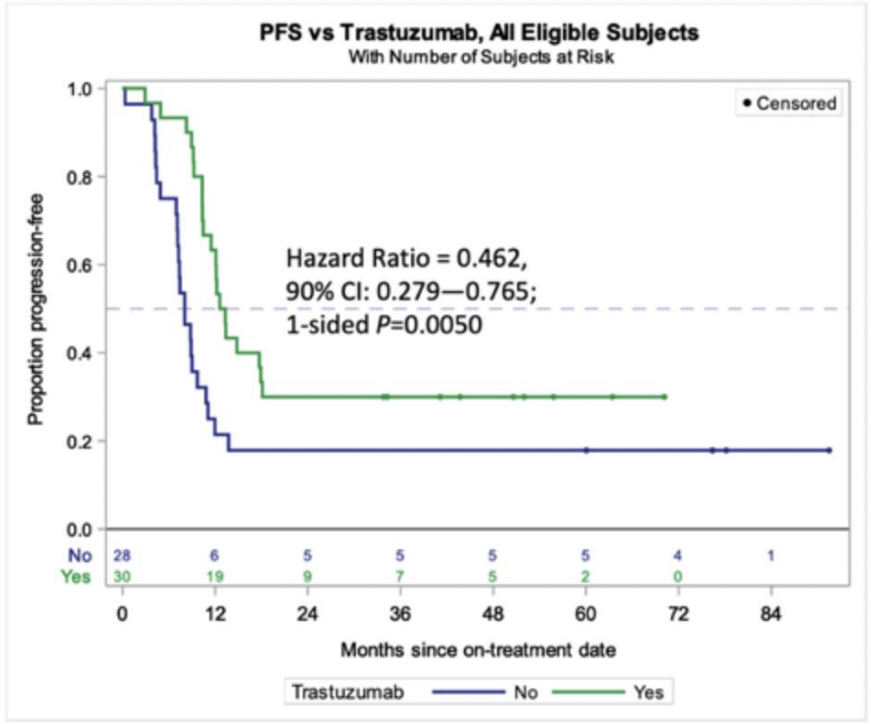
Paclitaxel 175 mg/m2 and carboplatin AUC 5 + Trastuzumab (at 8 mg/kg 1st dose & then 6 mg/kg in subsequent cycles) x 6 cycles f/b trastuzumab maintenance at 6 mg/kg until disease progression or prohibitive toxicity

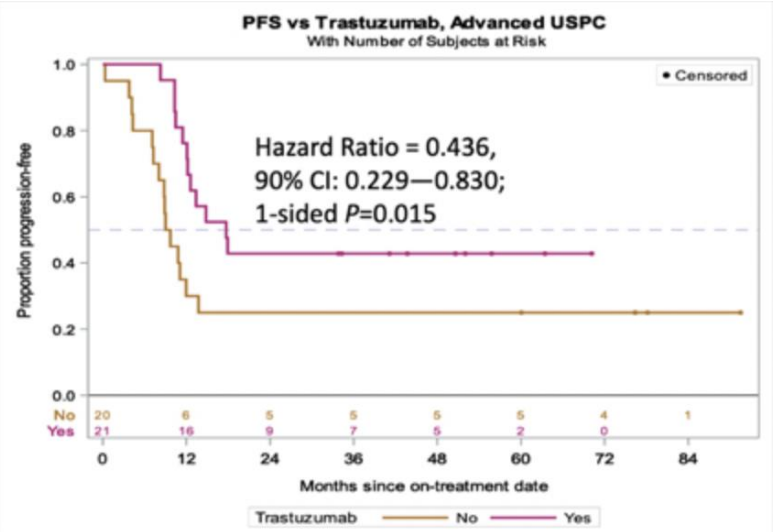
Improvement in PFS for Both Advanced-Stage and Recurrent Disease

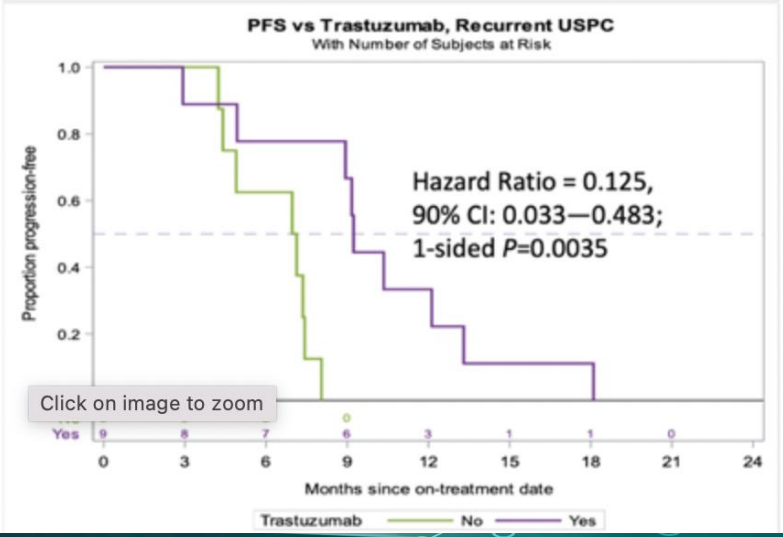
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

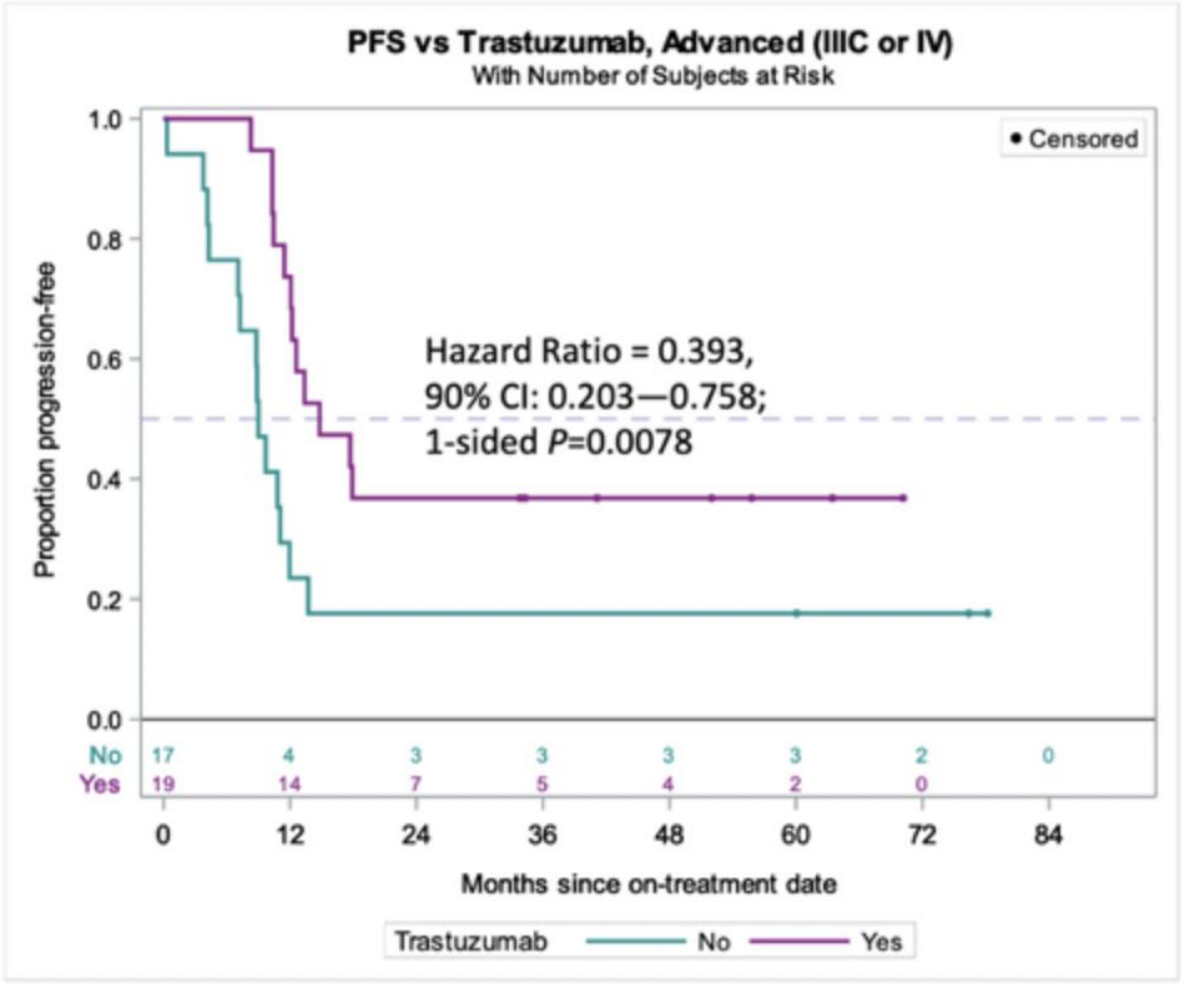


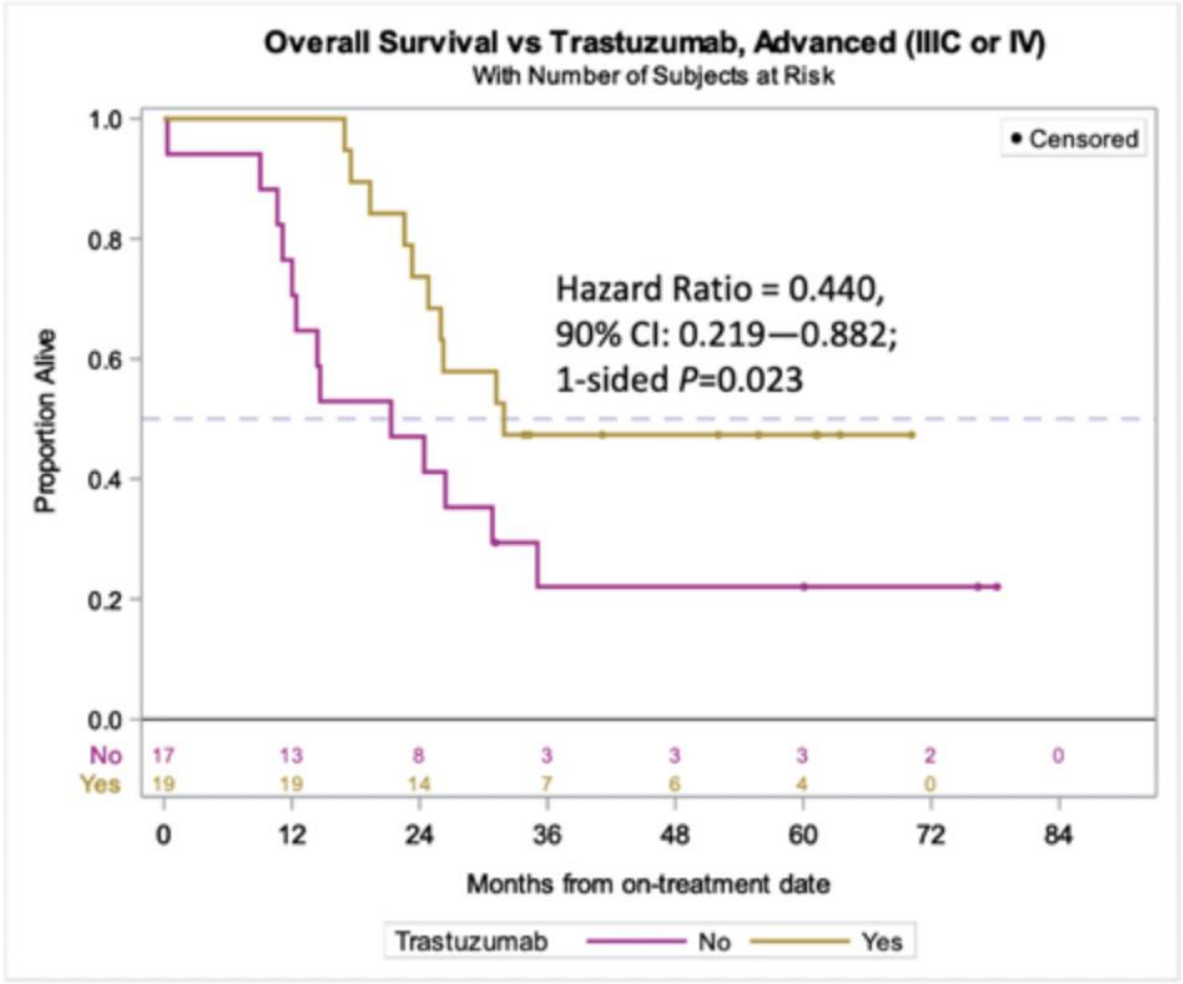




Fader AN, J Clin Oncol, 2018

Improvement in PFS and OS for Advanced-Stage Disease

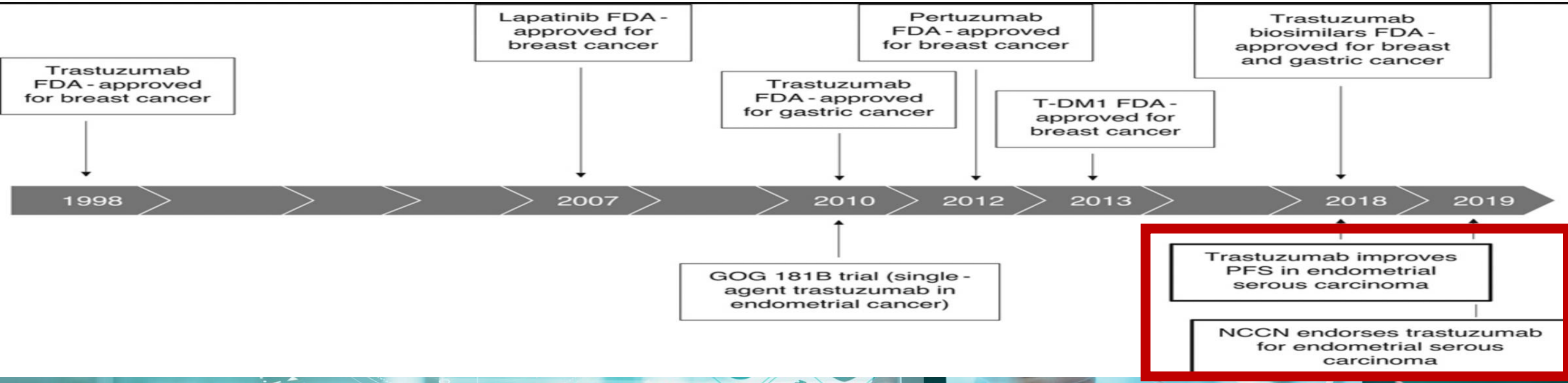




Fader AN, Clin Cancer Res, 2020

NCCN Guideline Change: 2019

Addition of trastuzumab to C/T is a 2A category recommendation) as the **preferred regimen** for women with HER2+, advanced or recurrent USC (http://www.jnccn.org).



What About in Early-stage Disease?

Gynecol Oncol. 2020 Oct; 159(1): 17–22.
PMID: 32709539
Published online 2020 Jul 21. doi: 10.1016/j.ygyno.2020.07.016

Human Epidermal Growth Factor 2 (HER2) in Early Stage Uterine Serous Carcinoma: A Multi-Institutional Cohort Study

Britt K. Erickson,[a,1] Omar Najjar,[b,1] Shari Damast,[c] Adriana Blakaj,[c] Joan Tymon-Rosario,[d] Maryam Shahi,[e] Alessandro Santin,[d] Molly Klein,[f] Michelle Dolan,[f] Ashley Cimino-Mathews,[e] Natalia Buza,[g] J. Stuart Ferriss,[b] Rebecca L. Stone,[b] Mahmoud Khalifa,[f] and Amanda N. Fader[b]

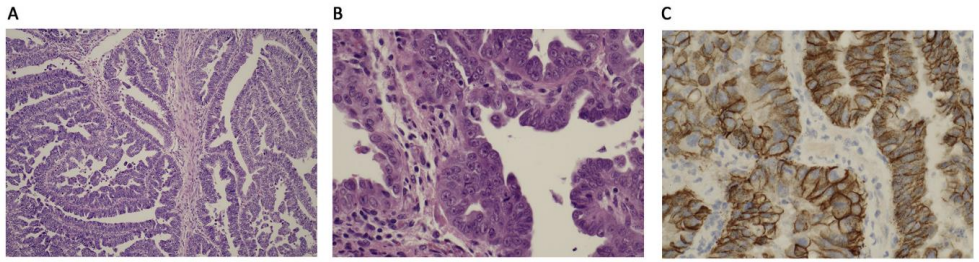


Figure 1:
Uterine serous carcinoma. a. papillary growth pattern b. malignant cells with prominent nucleoli and brisk mitotic activity c. HER2 immunohistochemical staining with 3+ staining pattern.

Highlights

- Twenty six percent of stage I uterine serous carcinoma tumors were HER2 positive
- HER2 positivity was associated with a 3 fold greater risk of disease recurrence
- HER2 is a potential prognostic biomarker for women with early stage disease

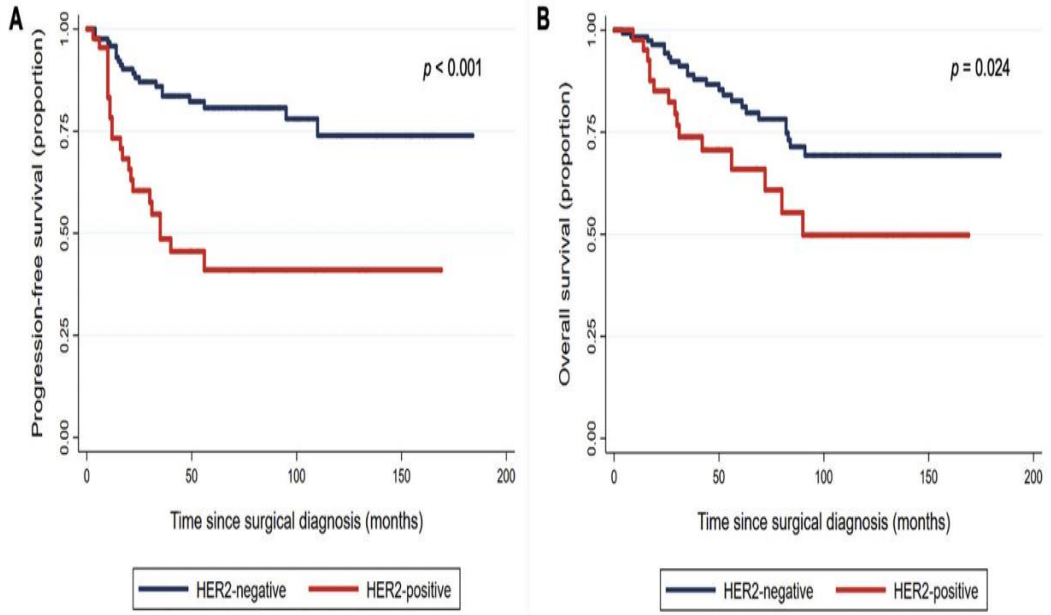
Results

Table 2:

Comparison of rates of disease recurrence and death according to HER2 status

	HER2-negative n = 125	HER2-positive n = 44	p-value
Recurrence	21 (16.8 %)	22 (50.0 %)	< 0.001
Death *	24 (19.2 %)	15 (34.1 %)	**0.044**

* Deaths due to all causes. Nine patients died of non-uterine cancer causes including 8 in the HER2- negative cohort and 1 in the HER2-positive cohort.



Erickson, Fader et al Gynecol Oncol, 2020

Figure 2:
Kaplan-Meier curves demonstrating (A) progression-free and (B) overall survival in women with stage I uterine serous carcinoma, stratified by HER2 status

Unanswered Questions

- What is the prevalence of HER2 overexpression/amplification in gynecologic cancers?
- What is the optimal HER2 testing platform?
- Is an endometrial/GYN cancer testing algorithm required?
- HER2 is what type of biomarker?
- What is the best upfront treatment for HER2 positive uterine serous carcinoma? Advanced Stage? Early-stage disease?
- For how long should maintenance treatment be continued?
- What can enhance trastuzumab response or overcome trastuzumab resistance?
- What is the best 1st line treatment for recurrence?
- Will ADCs be used in the front-line setting?

Trastuzumab Dosing, Safety Profile & Duration of Maintenance Therapy

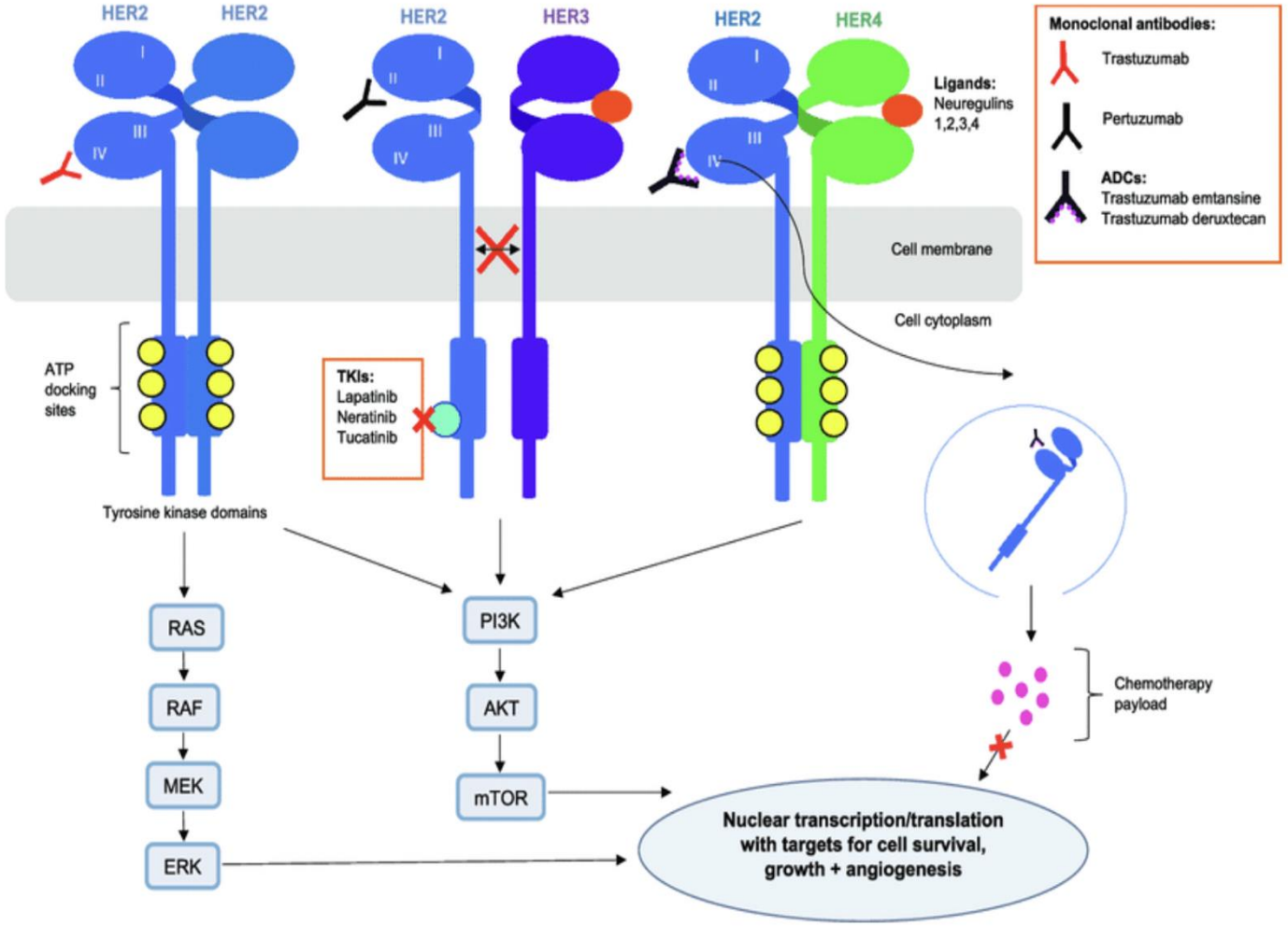
- Dosing strategy: IV Carboplatin AUC 5 and Paclitaxel 175 mg/m^2 q 21 days with or without IV trastuzumab at 8mg/kg for the first dose and 6 mg/kg in subsequent cycles

- Excellent safety profile with no significantly increased toxicities in HER2 study arm
  - Check interval echocardiograms, risk of cardiac toxicity is low (<2%)

- Tolerated well as maintenance therapy on a long-term basis
- Can be used in conjunction with EBRT (N=2 Fader et al, GORS, 2023 unpublished)

Other Potential Treatment Targets

- Trastuzumab/ Pertuzumab: humanized monoclonal antibodies against HER2/neu
- Pertuzumab--humanized monoclonal antibody against HER2/neu,
- In vitro studies by Santin et al demonstrate pertuzumab and trastuzumab induce equally strong antibody dependent cell cytotoxicity (ADCC) and CDC in six FISH-positive USC cell lines



The HER2 receptor and its drug targets. Abbreviations: ADCs, antibody-drug conjugates; TKIs, tyrosine kinase inhibitors; ATP, adenosine triphosphate.

In Breast Cancer…

- Pertuzumab/trastuzumab has greater efficacy than trastuzumab alone when combined with chemotherapy
- Pertuzumab/trastuzumab is most efficacious when used in combination with cytotoxic chemotherapy AND in the upfront setting

Swain et al, Lancet Oncol, 2020

APHINITY Trial Supports Adjuvant Pertuzumab and Trastuzumab + Chemotherapy

PrimO Practical Recommendations in Immuno & Molecular Oncology ADC Summit

APHINITY: Phase 3 Trial of Adjuvant Pertuzumab and Trastuzumab + Chemotherapy

- Randomized, double-blind, placebo-controlled trial

- Primary endpoints: IDFS duration, percentage of patients with both HF (NYHA Class III or IV), and drop in LVEF of ≥ 10 points from baseline and to below 50%

Clinicaltrials.gov. NCT01358877.

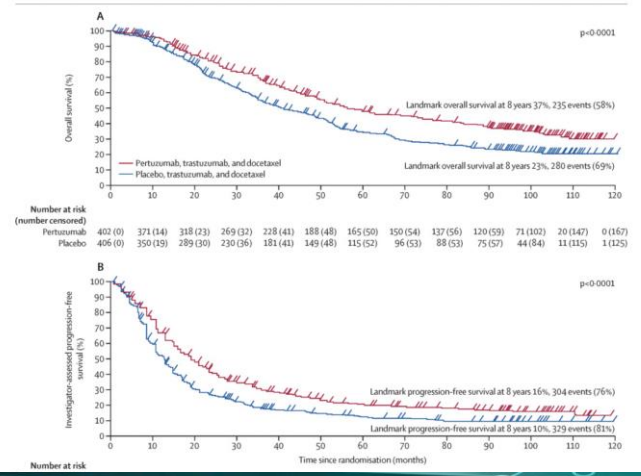
- Randomized, double-blind, placebo-controlled phase 3 trial assessing the safety and efficacy of pertuzumab in addition to chemotherapy plus trastuzumab as adjuvant therapy in participants with operable HER2-positive primary BC
- 171 patients (7.1%) in the pertuzumab group and 210 patients (8.7%) in the placebo group had disease recurrence (HR, 0.81; 95% CI, 0.66-1.00; $P = 0.045$)
- Estimates of the 3-year rates of iDFS were 94.1% in the pertuzumab group and 93.2% in the placebo group
- Diarrhea of grade 3 or higher occurred almost exclusively during chemotherapy, more frequently with pertuzumab than with placebo

When added to chemotherapy and trastuzumab, pertuzumab significantly improved the rates of iDFS among patients with HER2-positive early breast cancer (APHINITY)

l, confidence interval; HR, hazard ratio.

n Minckwitz G, Procter M, de Azambuja, E. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017;377:122-31. DOI: 10.1056/NEJMoa1703643.

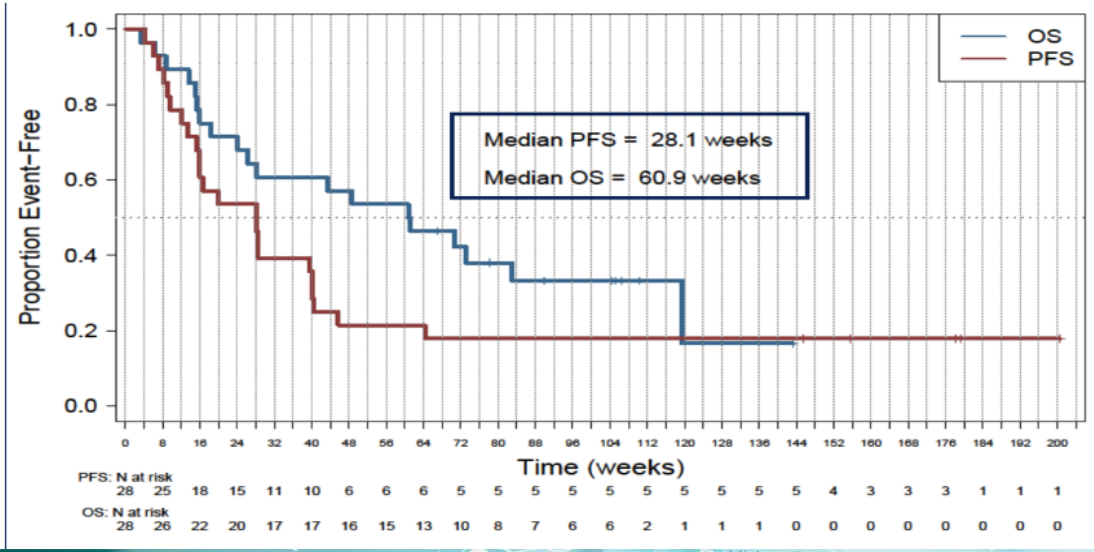
Cleopatra Trial: Long-term Survival Data



Pertuzumab plus trastuzumab in patients with uterine cancer with *ERBB2 or ERBB3* amplification, overexpression or mutation: Phase II TAPUR Study

- **Most tumors (75%) were ERBB2 (HER2) amplified by FISH**

- **Heavily pre-treated patients: 57% had >/=3 prior lines of treatment**



ASCO TAPUR™
Targeted Agent and Profiling Utilization Registry Study

Median age, yrs (range)		69 (44, 90+)
ECOG PS, %	0	32
	1	57
	2	11
Prior systemic regimens, %	1-2	43
	≥3	57
ORR rate, % (95% CI)		**7.1 (0.8, 24)**
DC rate, % (OR or SD16+) (95% CI)		**37 (21, 50)**

Courtesy of Houssein Ali-Ahmad

NRG GY-026

PI: Britt Erickson
Co-PI: Amanda Fader
Intl Co-PI: Clare Scott
Translx PI: Alessandro Santin

Newly Diagnosed, Stage I-IVB, HER2 positive uterine serous or carcinosarcoma

Randomize 1:1:1

Arm 1:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles (may continue to 10 cycles if measurable disease and SD or PR)

Arm 2:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + trastuzumab 8 mg/kg IV loading dose f/b 6 mg/kg IV q 21 days

Maintenance trastuzumab 6mg/kg IV every 21 days x 1 year (or progression/ prohibitive toxicity)

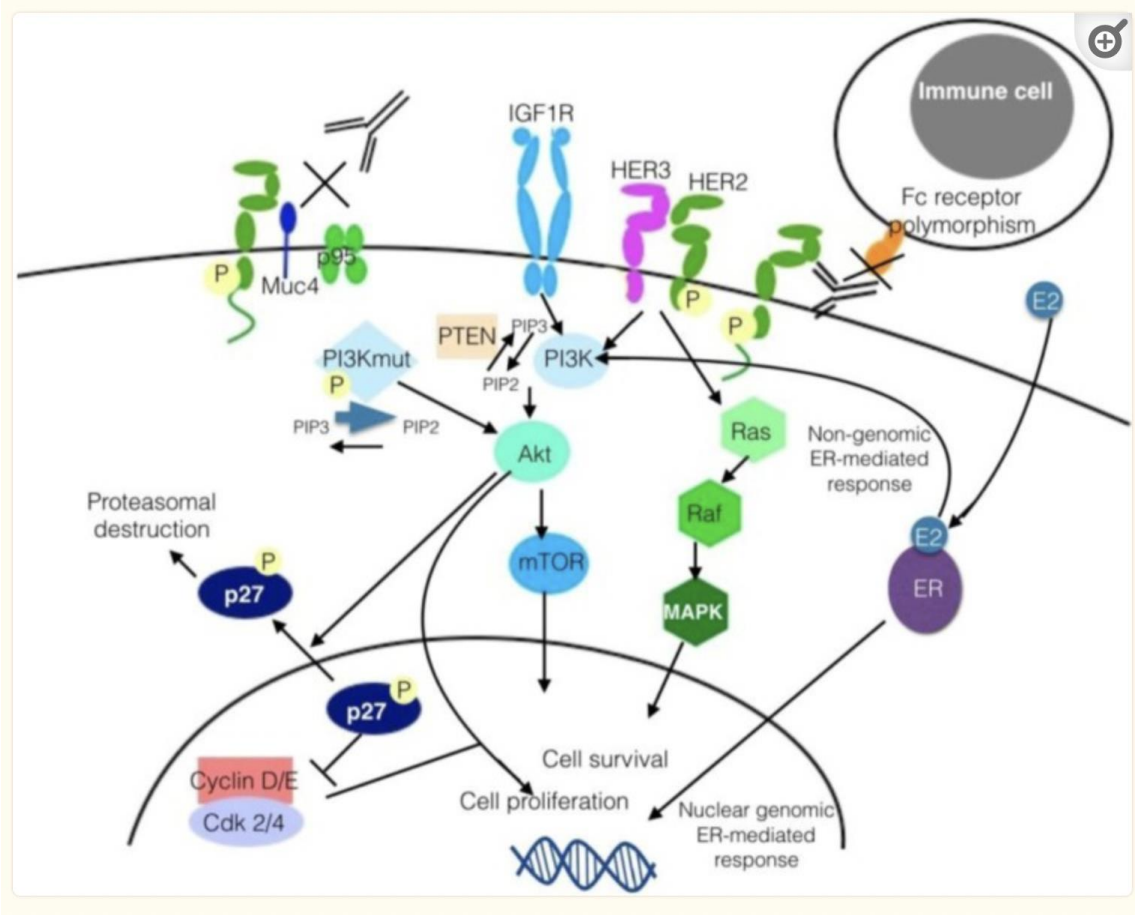
Safety Lead-In (n=45)

Arm 3:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ (with initial 1200 mg SQ pertuzumab loading dose w 1st cycle)

Maintenance fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ q 21 days for 1 year (or until disease progression or prohibitive toxicity)

Strata:
- **Stage (I-II vs III-IV)**
- **Measurable vs. non-measurable dz**
- **Histology (serous vs carcinosarcoma)**

Mechanisms of Trastuzumab Resistance



- MUC4 through the NF-κB pathway to reduce the effectiveness of antibody dependent cellular toxicity (ADCC)
- PI3K/MTOR pathway, cross-talk with estrogen receptors, immune response, cell cycle control mechanisms, and other TKRs

Luque-Cabal, Clin Med Insights Oncol, 2016

PIK3CA Mutations

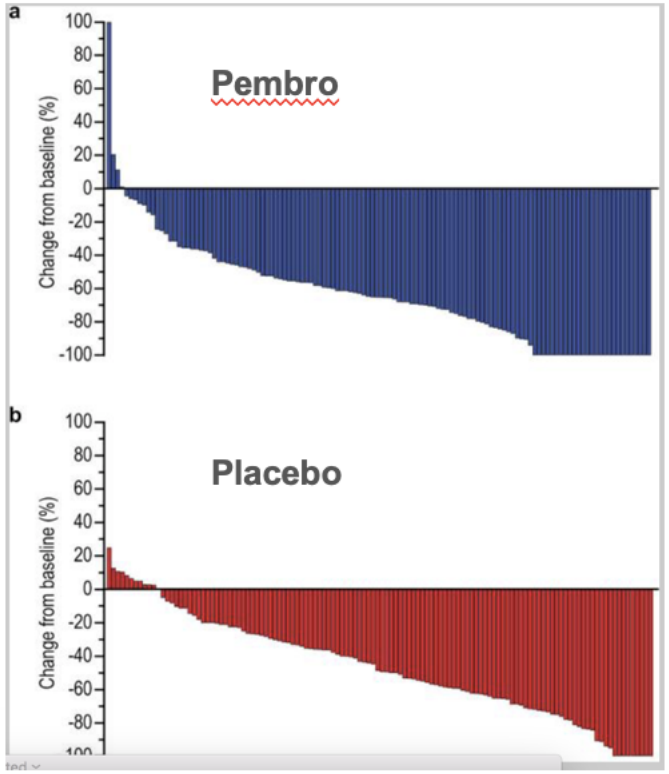
- May be present in up to 60% of HER2/neu amplified USC--demonstrated to represent

- Consideration for PIK3CA pathway inhibitors
  - PI3K/AKT/mTOR inhibitors tested against primary USC cell lines and xenografts -- Preclinical studies of AZD8055 (*mTORC* 1/2 inhibitor), GDC-0980 (inhibitor of class one *PI3K* and *mTORC 1/2*), and GDC-0032 (taselisib, *PIK3CA* inhibitor) show promising results
  - Preclinical data combining the *PIK3CA* inhibitor taselisib and the pan-Her inhibitor neratinib, found the combination to be highly synergistic and well-tolerated in vivo
  - Combo prevented development of resistance in preclinical USC models, and led to substantial tumor regression in large USC xenografts that were previously resistant to single-agent *PIK3CA* or pan-*Her* inhibition

Black et al. Brit J. Cancer, 2015
Bonnazzol, Santin et al, Gynecol Oncol, 2019.

IO Plus HER2 Blockade?

KEYNOTE 811: PD-1 and HER2 blockade in HER2+ gastric cancer



	Pembro Group n=133	Placebo n=131
Objective Response	74.4%	51.9%
Disease Control	96.2%	89.3%

Janjigian et al, Nature 2021

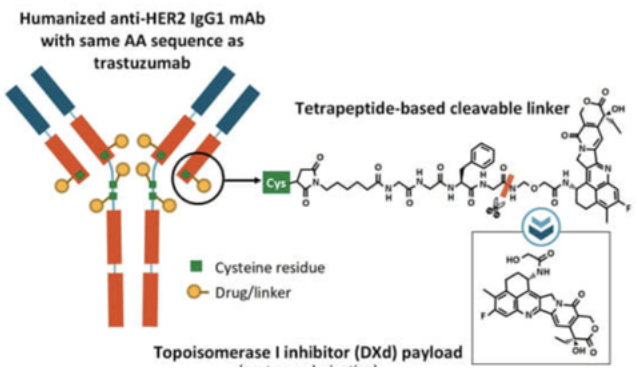
Targeting HER2: Lessons from Breast Cancer

Antibody Drug Conjugates: Antibody + peptide linker + payload

Examples:

- T-DMI (trastuzumab emtansine) – microtubule inhibitor payload
- T-DXd, DS8201a (trastuzumab deruxtecan) – topo I inhibitor payload
- SYD985 (trastuzumab duocarmazine) – alkylating payload
- ARX788 – tubulin inhibitor payload
- DB-1303 – topo I inhibitor payload

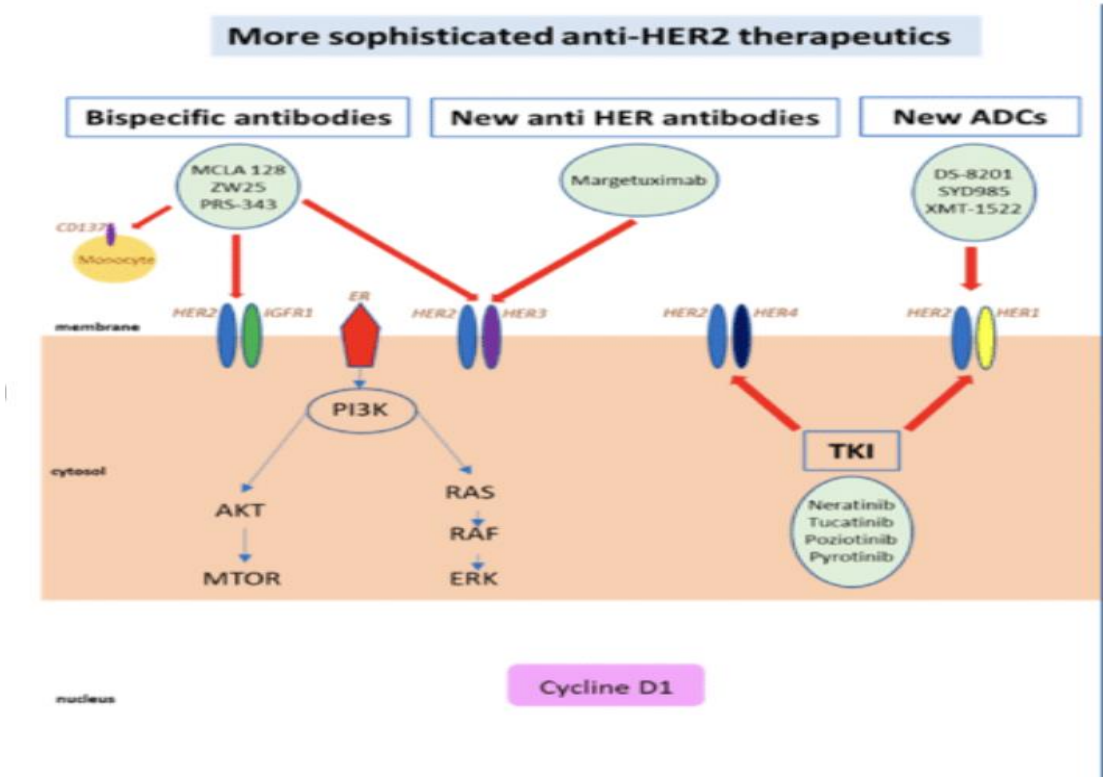
HER2-Targeted ADC: Trastuzumab Deruxtecan



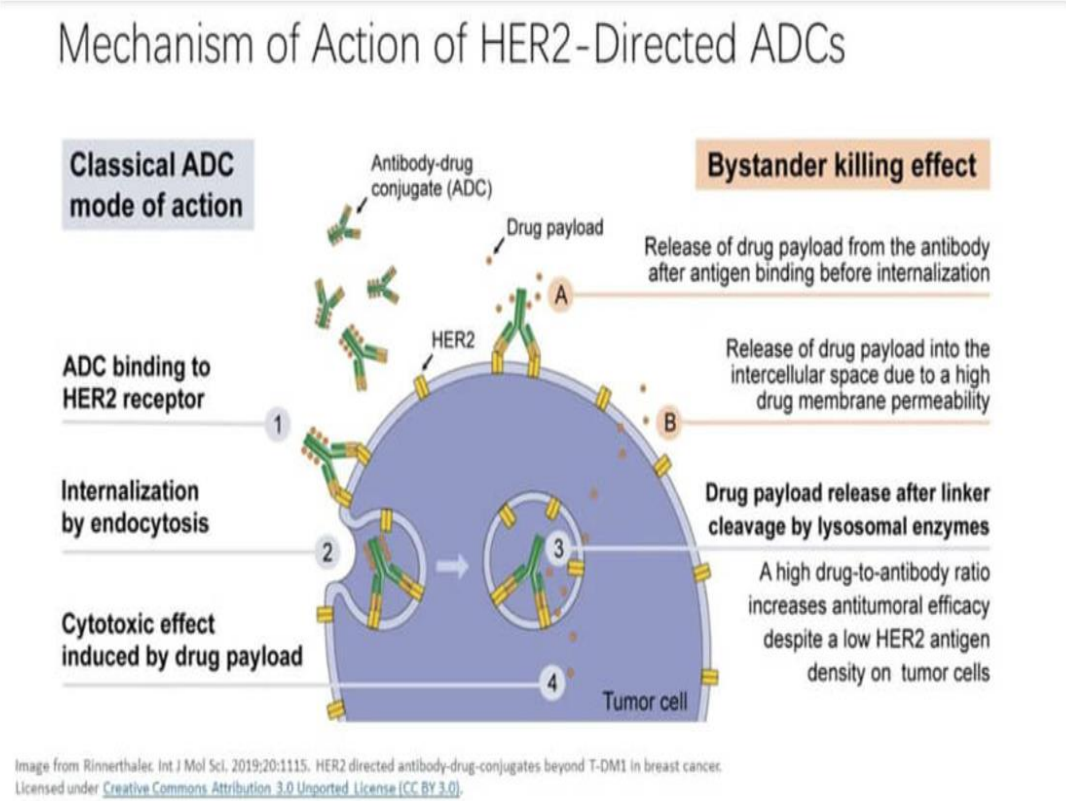
- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

HER2-LOW Gynecologic Cancers

- Unmet clinical need
- Limited benefit to conventional anti-HER2 blockade in this population



Targeting HER2: Lessons from Breast Cancer

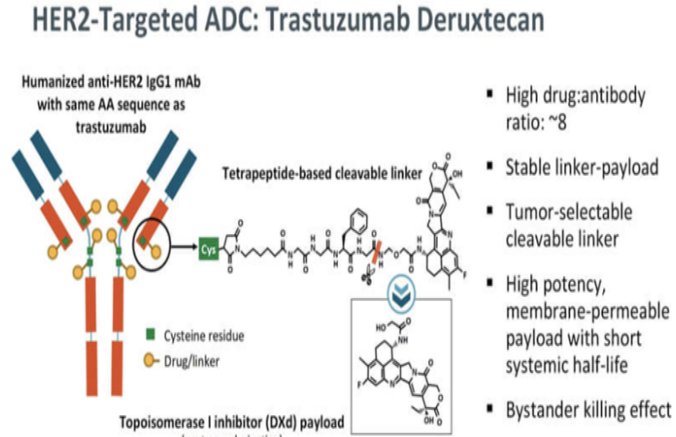


Targeting HER2: Lessons from Breast Cancer

Antibody Drug Conjugates: Antibody + peptide linker + payload

Examples:

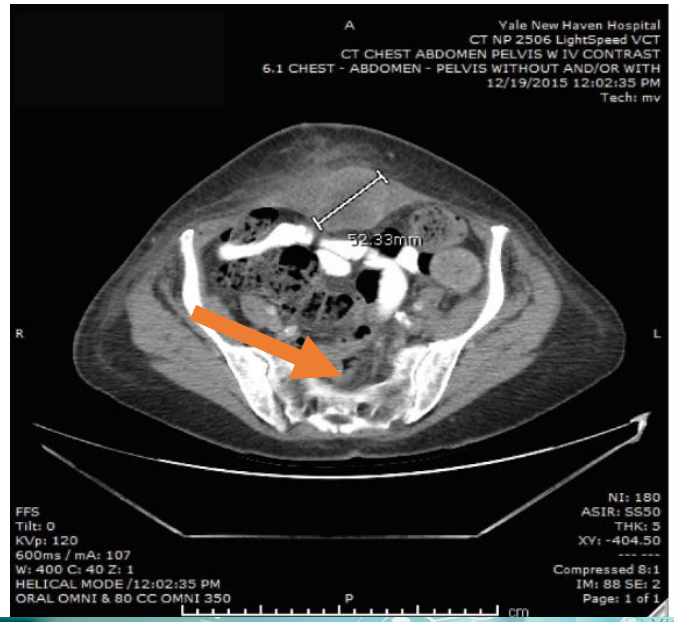
- T-DMI (trastuzumab emtansine) – microtubule inhibitor payload
- T-DXd, DS8201a (trastuzumab deruxtecan) – topo I inhibitor payload
- SYD985 (trastuzumab duocarmazine) – alkylating payload
- ARX788 – tubulin inhibitor payload
- DB-1303 – topo I inhibitor payload

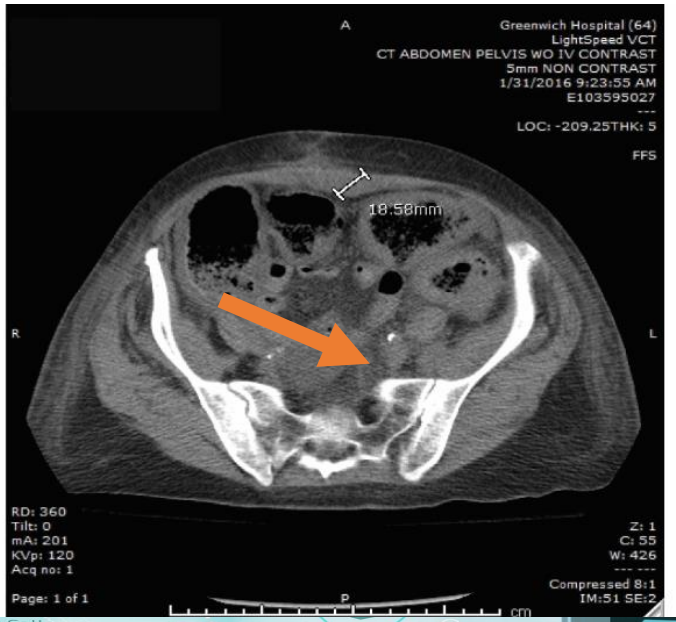


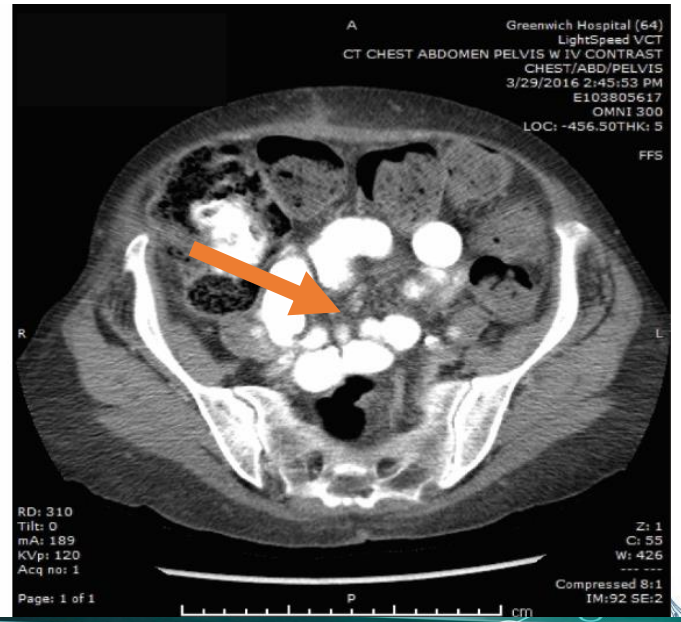
NRG ONCOLOGY™

Other Potential Targets

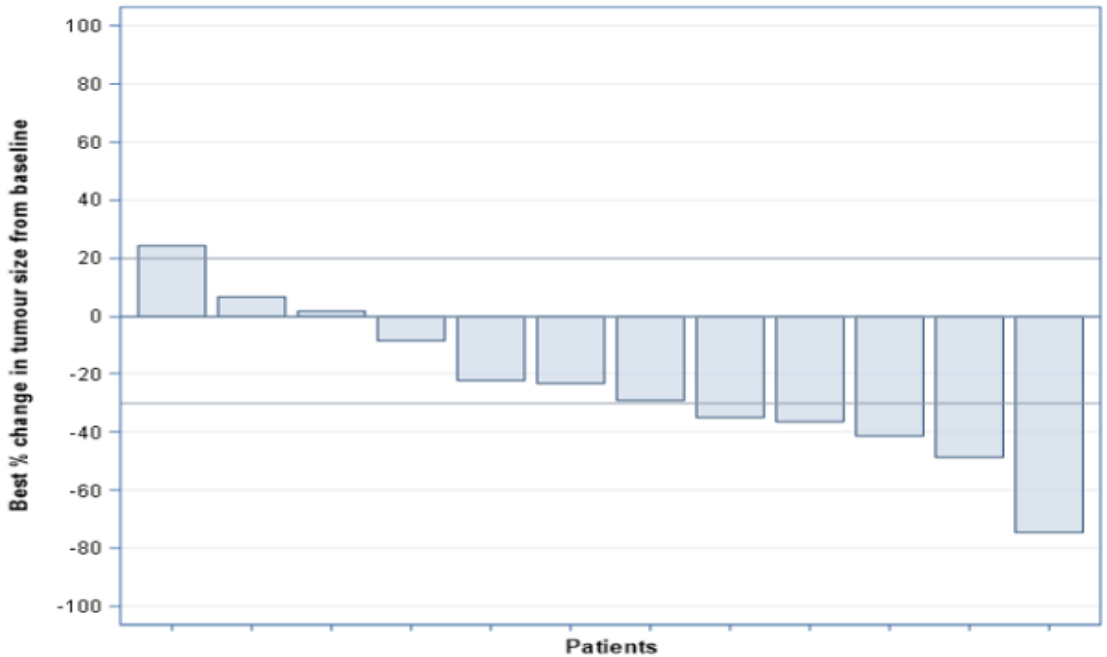
- TDM-1: (i.e., Trastuzumab-emtansine, a novel antibody-drug conjugate)
  - Improves DFS in early and advanced/recurrent HER2+ breast CA
  - Santin et al, Gynecol Oncol Reports, 2016: Case report in USC—heavily pretreated recurrent, HER2+-complete resolution of dz and long disease control







SYD985 (Trastuzumab duocarmazine) endometrial expansion cohort.



Banerji et al, Lancet Oncol 2019

Duality: DB-1303: FDA Fast Track Designation

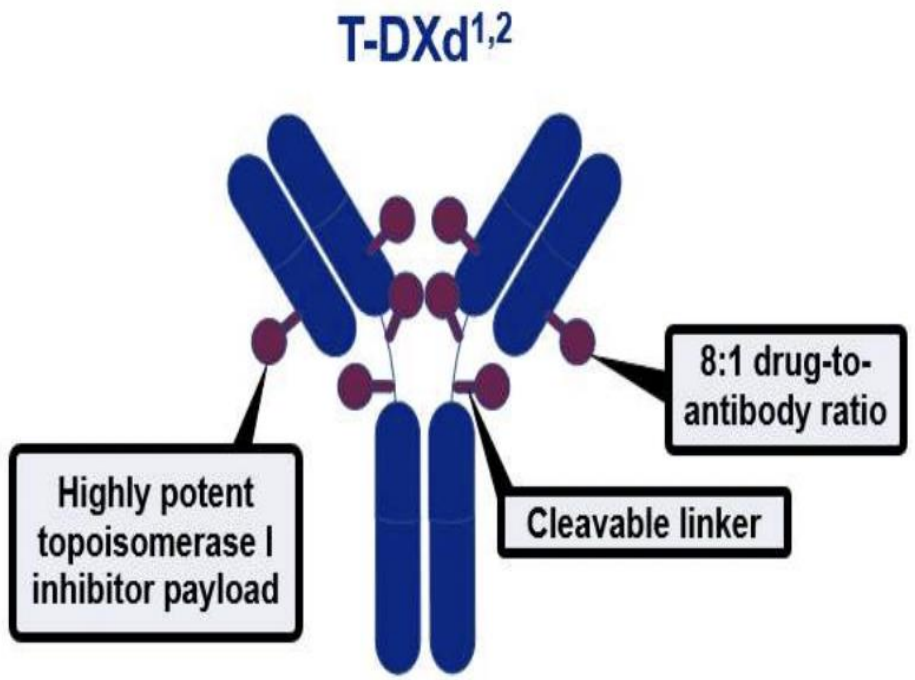
- **Third generation HER2 ADC, FIH agent**
- **Anti-HER2 monoclonal antibody, an enzymatically cleavable peptide linker, and proprietary topoisomerase I inhibitor P1003.**
- Multicenter, non-randomized, open-label study administered DB-1303 intravenously on day 1 of each cycle once every 3 weeks at various dose levels in patients with HER2-positive advanced solid tumors.
- Primary end points for the phase 2a portion of the trial included treatment-emergent adverse effects (TEAEs), serious AEs, and ORR
- Thirteen HER2+ breast cancer (BC) (50.0%, 13/26, including 5 pts with brain metastases [55.6%, 5/9]), 5 HER2 low BC (38.5%, 5/13), 2 colorectal cancer (66.7%, 2/3), 1 endometrial carcinoma (33.3%, 1/3), 1 esophageal cancer (50.0%, 1/2), and 1 ovarian cancer (50.0%, 1/2).
- Among all the pts, the **DCR was 88.5% (46/52)**; for pts with HER2+ BC and HER2-low BC, the DCRs were 96.2% (25/26) and 84.6% (11/13), respectively.
- Well tolerated

News release. Duality Biologics. January 20, 2023. Accessed January 23, 2023. prn.to/3JdgP82; Moore et al, ASCO 2023

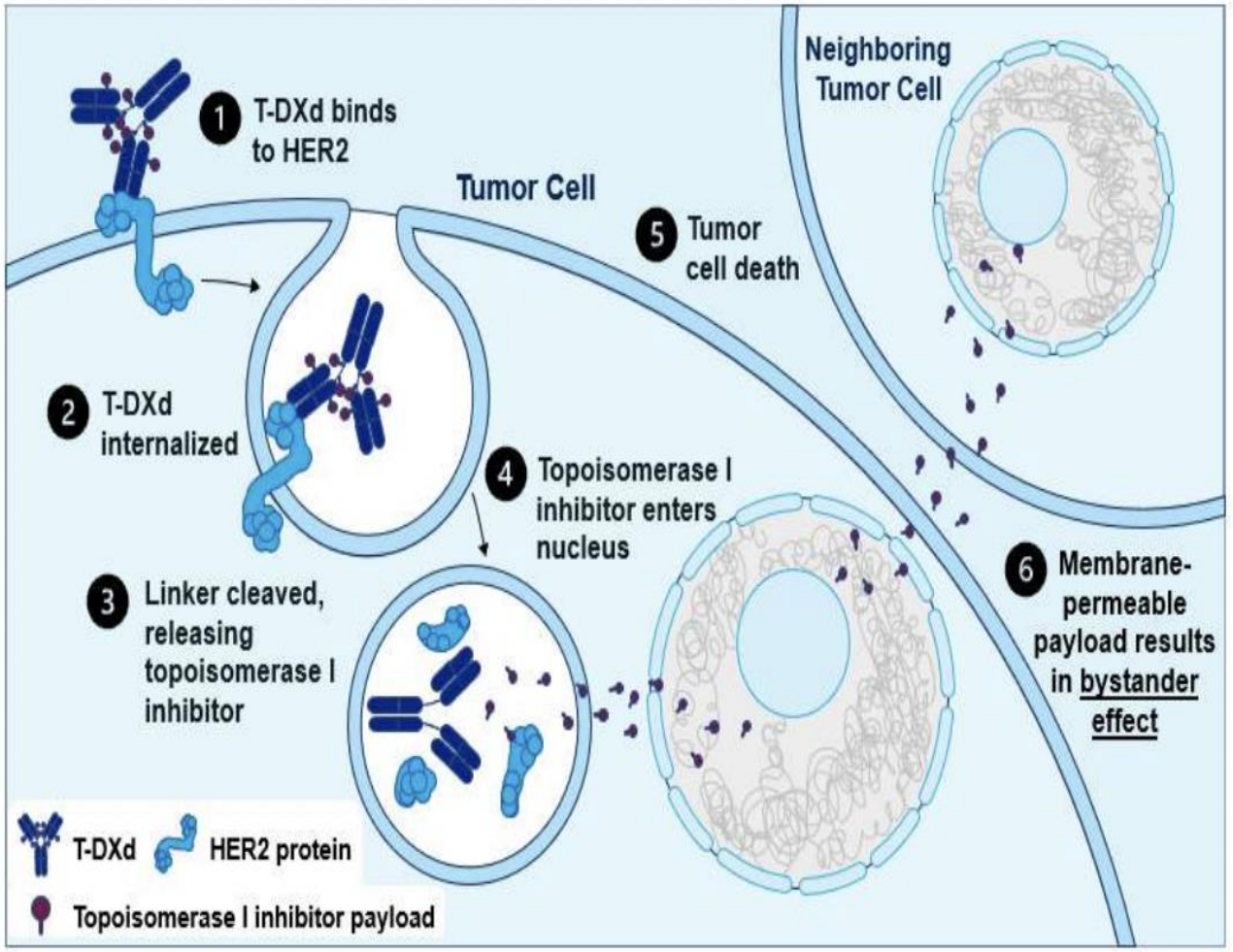
T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC

DESTINY-Breast04

Daiichi-Sankyo



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

2023 ASCO ANNUAL MEETING

DESTINY-PanTumor02

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

Funda Meric-Bernstam

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 5, 2023

Additional authors: Vicky Makker, Ana Oaknin, Do-Youn Oh, Susana Banerjee, Antonio González-Martí Kyung Hae Jung, Iwona Ługowska, Luis Manso, Aránzazu Manzano, Bohuslav Melichar, Salvatore Sie Daniil Stroyakovskiy, Chiedozie Anoka, Yan Ma, Soham Puvvada, Jung-Yun Lee

On behalf of the DESTINY-PanTumor02 investigators

DESTI

Email Paolo

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 guidelines[1])[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)

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients 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.
[c]Investigator-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; 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.

ANNUAL MEETING ON WOMENS' CANCER®
BUILDING BRIDGES // BREAKING BARRIERS
SGO // PHOENIX, ARIZONA // MARCH 18 – 21, 2022

ic Oncology

Efficacy endpoints: ORR, DCR and DOR

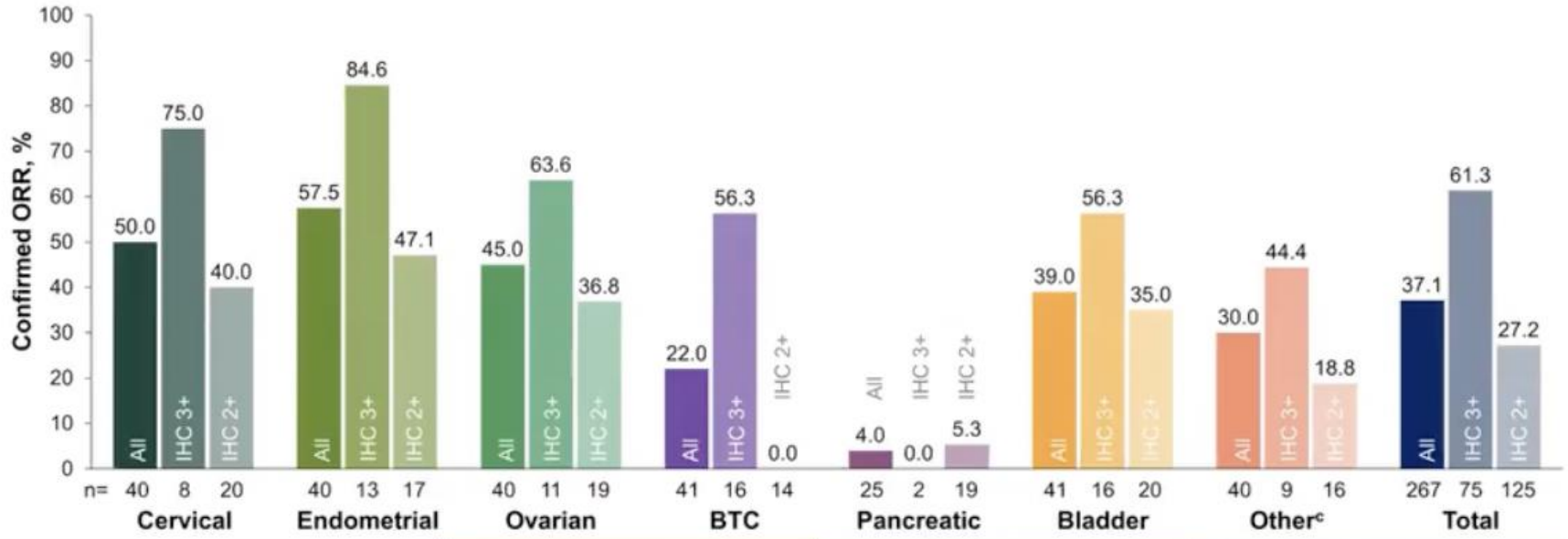
		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease.

ORR T-DXd Trial

DESTINY-PanTumor02

Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR 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. [c]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

ADCs in Endometrial Cancer, Trials in Progress

Clinical Trial #	Agent	Trial
NCT05150691	DB-1303	Phase 1/2A first in human study of DB-1303 in patients with advanced metastatic solid tumors that express HER2
NCT04486352	Cohort 4: T-DM1 (trastuz emtansine)	EndoMAP – A Phase IB/II Multi-cohort study of targeted agents with Atezolizumab for patient with recurrent or persistent endometrial cancer (AFT50)
NCT04482309	TDXd/DS-8201a (trastuz deruxtecan)	Phase II study of trastuzumab deruxtecan in patient with HER2 expressing tumors, dedicated endometrial cohort
NCT04585958	TDXd/DS-8201a (trastuz deruxtecan) + olaparib	Testing the combination of DS-8201 and olaparib in HER2 expressing cancer – Endometrial expansion cohort
NCT04205630	SYD985 (trastuz duocarmazine)	SYD985 in patients with HER2 expressing recurrent, advanced or metastatic endometrial cancer
NCT02491099	Afatinib	A phase II evaluation of afatinib in patient with persistent or recurrent HER2 positive uterine serous carcinoma

Study	Drug	N (endometrial)	Response Rate
NCI-MATCH (Protocol Q)	T-DM1	14 GYN, 3 endometrial	0%
Li et al, Basket Trial	T-DM1 (trastuz emtansine	18	22%
Banerji et al, Basket Trial	SYD985 (trastuz duocarmazine)	13	39%

Jhaveri KL et al. *Ann Oncol.* 2019
Li et al. ASCO 2018 Abstract #2502
Banerji et al, Lancet Oncol 2019

NRG ONCOLOGY™

NRG ONCOLOGY™

Society of Gynecologic Oncology

Thank you!

- Professor Mansoor Mirza
- NSGO

- afader1@jhmi.edu