PATOLOJİ / MOLEKÜLER GENETİK RAPORUNDA NELER OLMALI ?

Mide Kanseri

Prof. Dr. Çiğdem (Ataizi) ÇELİKEL
MÜTF Patoloji ABD

5. Türk Tıbbi Onkoloji Kongresi, 21 Mart 2014, Antalya

Mide Kanseri

- *en sık 4. kanser (%7.8)*
- *kanser ölümlerinin 2. en sık nedeni (%9.7)*

Genetik Çevresel

- Tümör supressör gen

  p53, p16, APC, Rb, DCC
- "mismatch" tamir genleri
- Onkojenler

  siklin D1
- Büyüme faktör ve reseptörleri

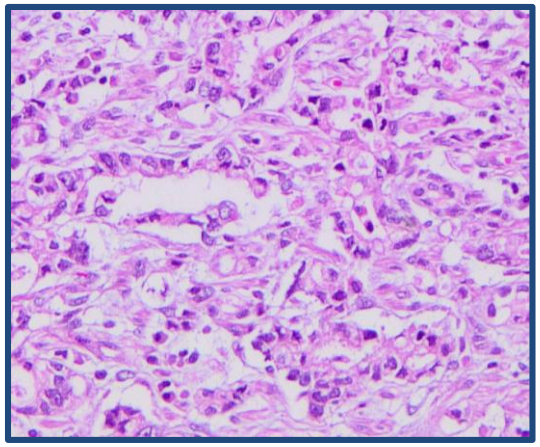
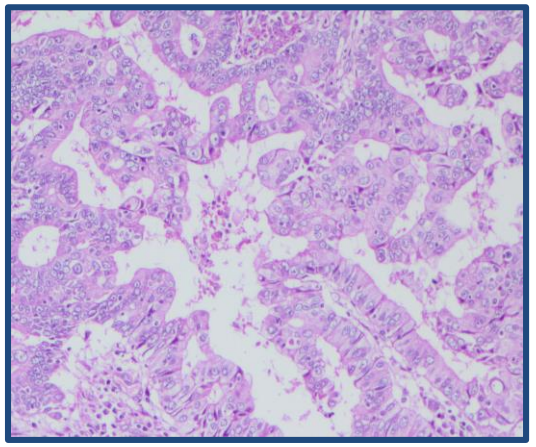
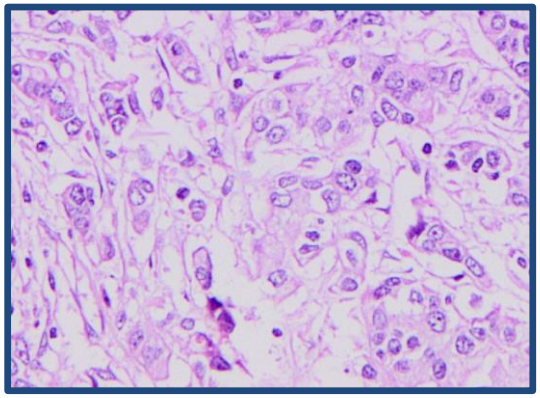
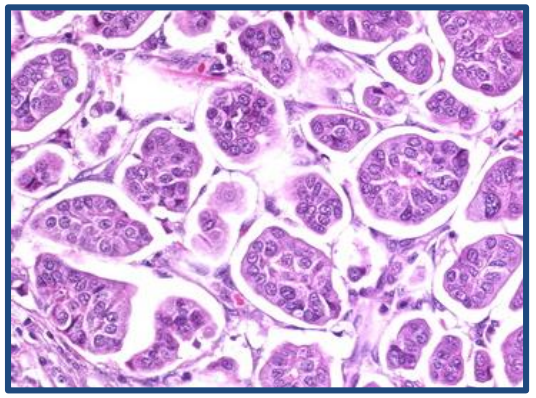
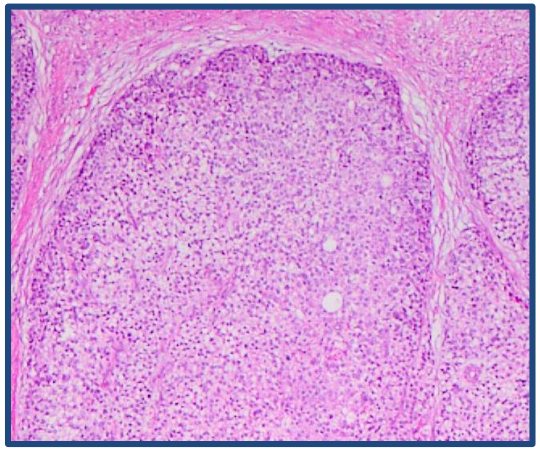
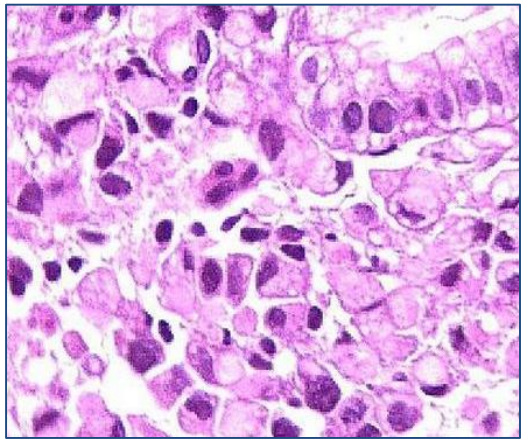
  EGFR, TGF-α, c-erbB2, c-met
- Hücre adhezyon molekülleri

  E-cadherin, α- /β-catenin

- Mutasyon
- Kromozomal kayıp
- Amplifikasyon
- Mikrosatellit instabilite
- Genetik polimorfizm
- Telomeraz aktivasyon

Mide Kanseri Histolojik Tip

fenotipik / genotipik olarak HETEROJEN

DSÖ Sınıflaması

ADENOKARSİNOM

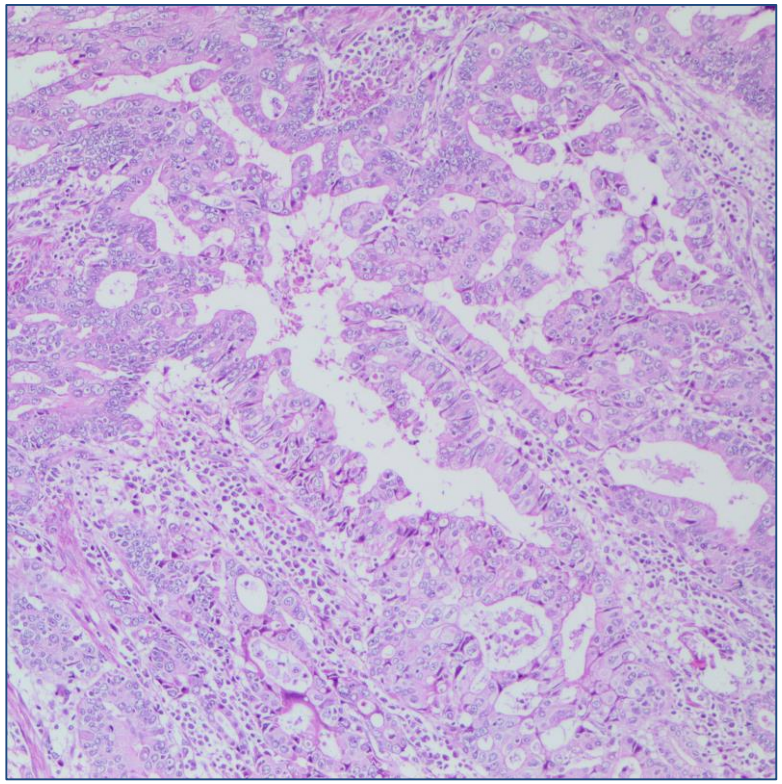
- Tubuler (intestinal)
- Papiller
- Zayıf Koheziv (taşlı yüzük komponenti -/+)
- Diffüz (nonkoheziv)
- Müsinöz
- Mikst

DİĞER

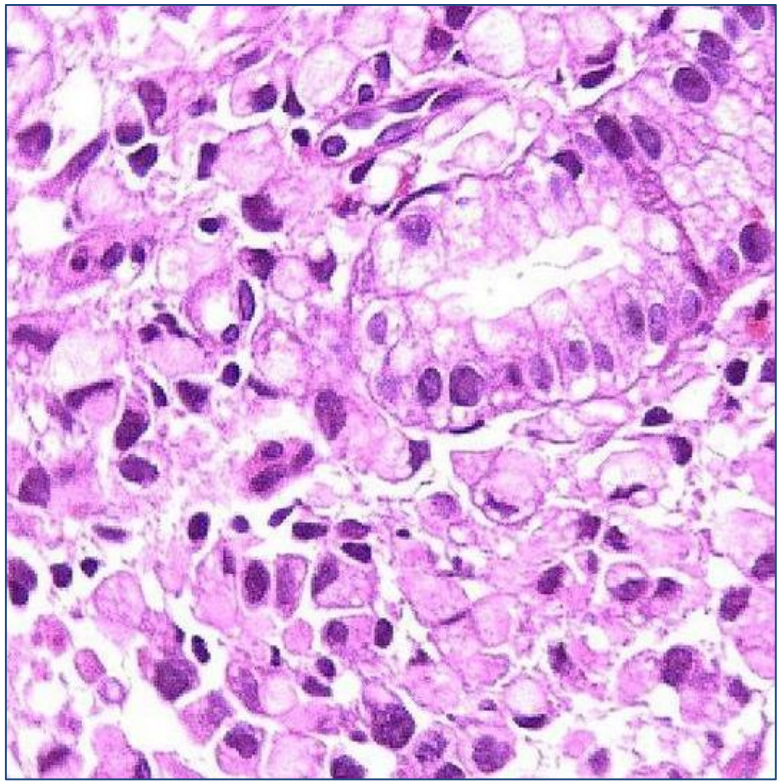
- Hepatoid Adenokarsinom
- Medüller Karsinom
- İndifferansiye Karsinom
- Skuamöz Hücreli Karsinom
- Adenoskuamöz Karsinom
- Nöroendokrin Karsinom

Lauren Sınıflaması

Intestinal Tip

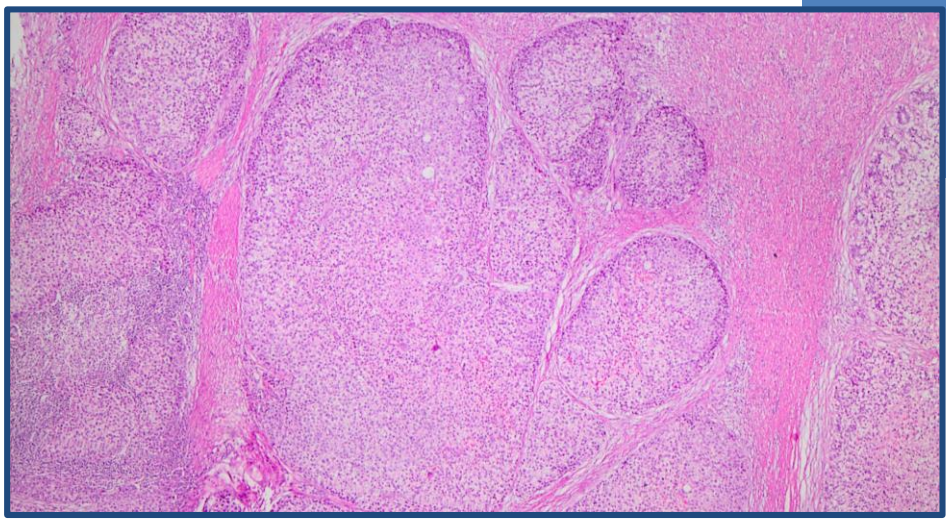


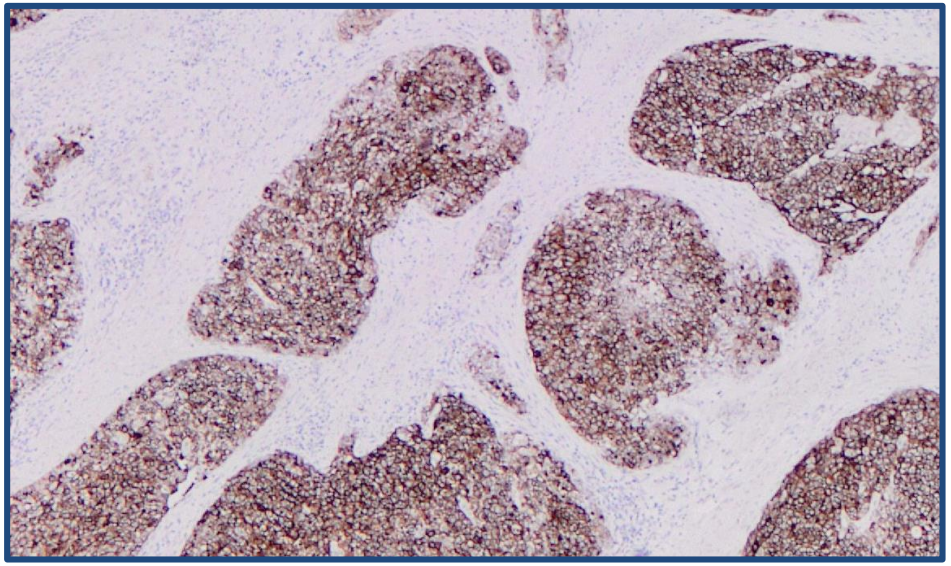
Diffüz Tip



MİDE KANSERİ
Sınıflama

- *MORFOLOJİK*
- *HİSTOKİMYASAL*
- *MOLEKÜLER*





Mide Kanseri

- Tümör supressör gen

  p53, p16, APC, Rb, DCC
- “mismatch” tamir genleri
- Onkojenler

  siklin D1
- Büyüme faktör ve reseptörleri

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- Kromozomal kayıp
- Amplifikasyon
- Mikrosatellit instabilite
- Genetik polimorfizm
- Telomeraz aktivasyon

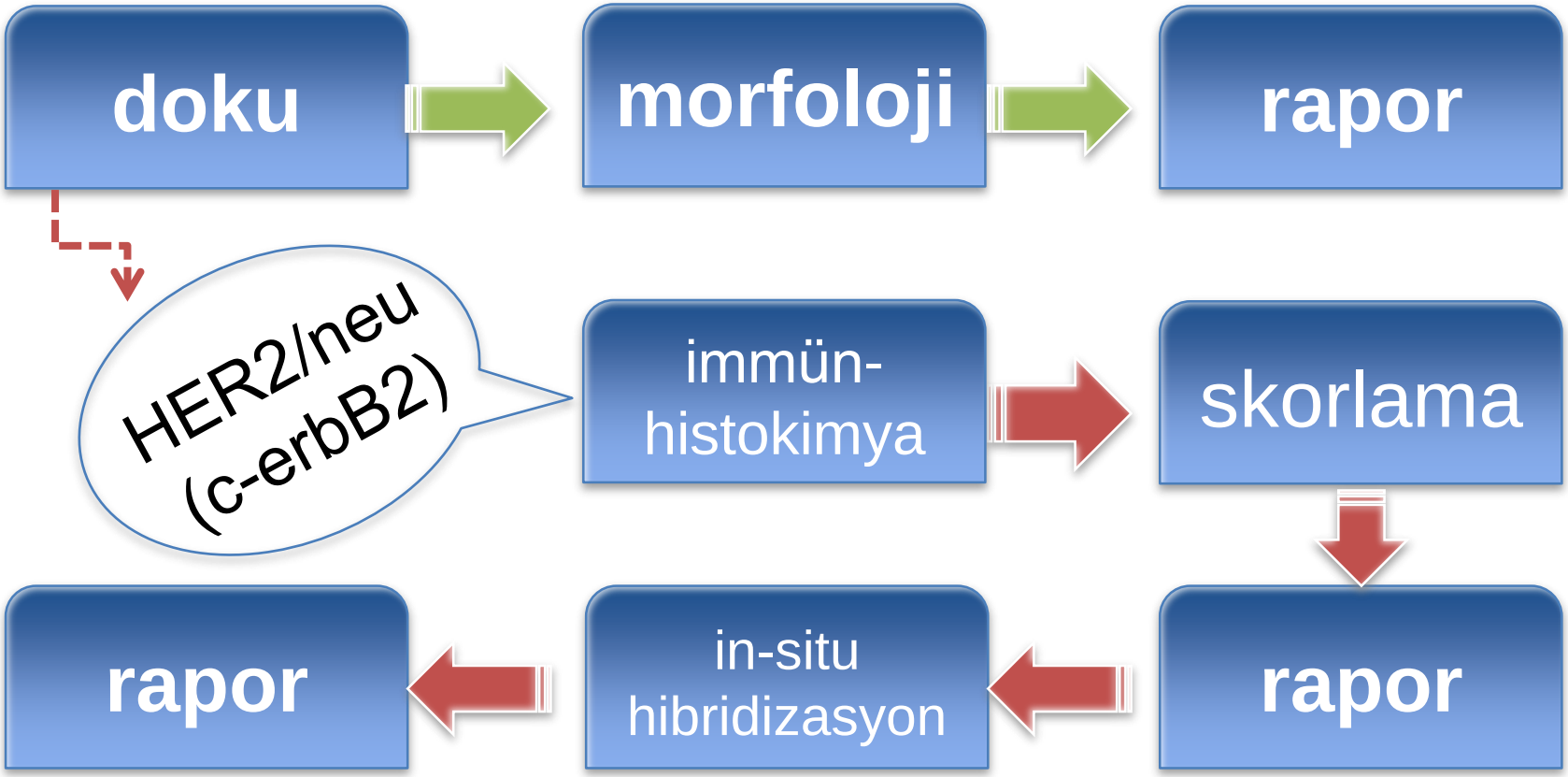
Hedefe Yönelik Tedavi

	Hedef	Endikasyon
monoklonal antikor	VEGF HER2 EGFR	metastatik(kolon, böbrek, meme), NSCLC meme kanseri, metastatik mide kanseri metastatik (kolon), baş-boyun/SCC
tirozin kinaz inhibitörleri	tirozin kinazlar	akciğer (NSCLC), pankreas kanseri hepatosellüler ve renal hücreli karsinom gastrointestinal stromal tümör
ER blokerleri	östrojen reseptör	meme kanseri

- **AMAÇ :** *uygulanması planlanan tedaviye yanıtı belirleyebilecek hedef belirteçlerin saptanması*

Mide Kanseri

PATOLOJİ / MOLEKÜLER GENETİK RAPORUNDA NELER OLMALI ?

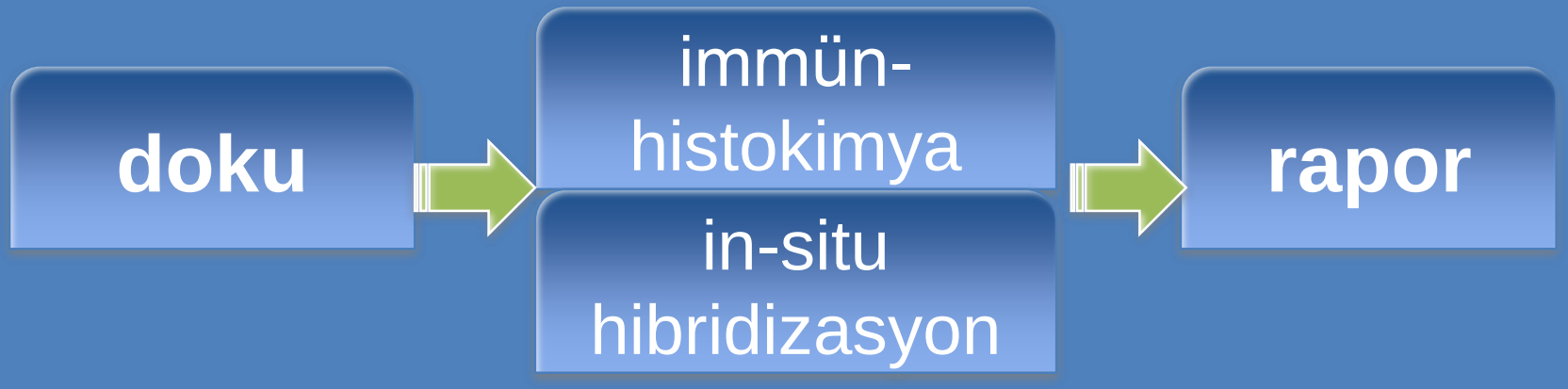


DOKU

Biyopsi

Cerrahi Spesmen

- uygun fiksatif
- yeterli fiksasyon süresi
- spesmen yeterliliği
  - biyopsi sayısı (6-8)
  - tümörü temsil eden



- **Moleküler Genetik Değerlendirme**

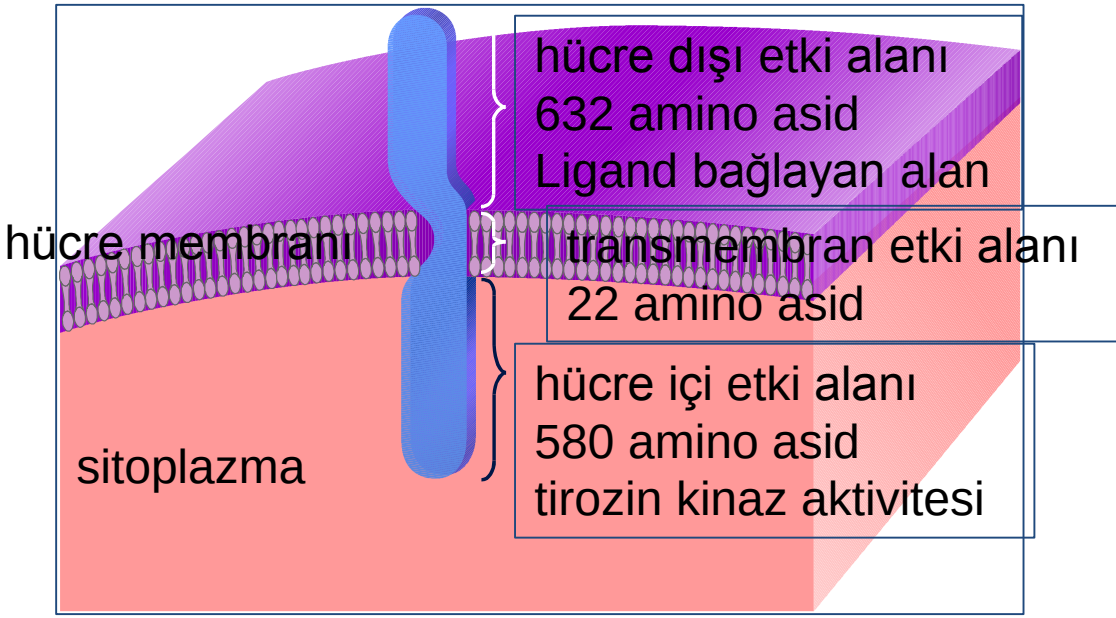
  ve

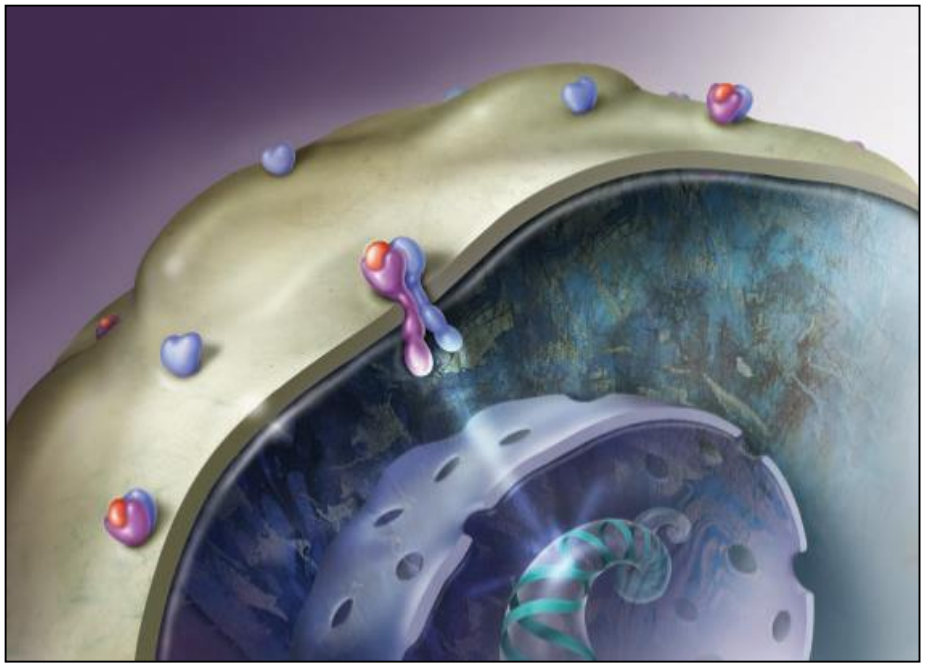
  RAPORLAMA

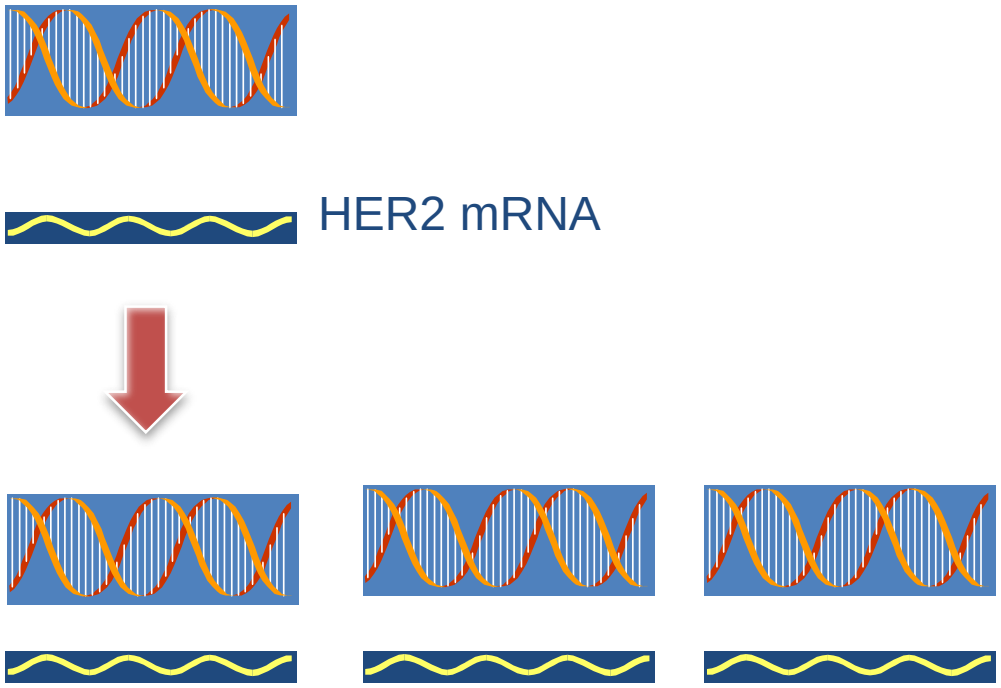
HER2 (c-erbB2/neu)

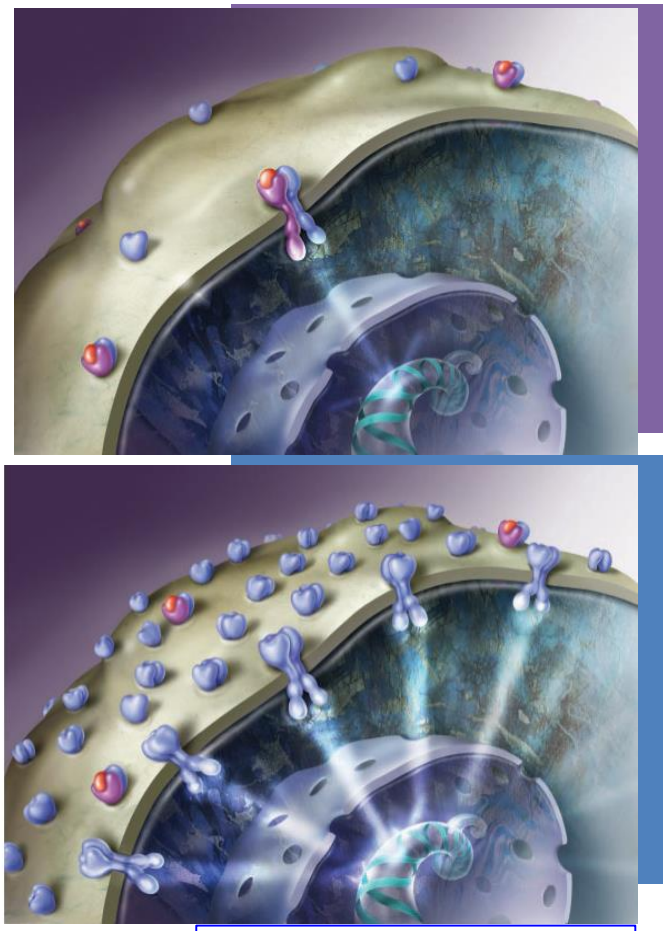
human epidermal growth factor receptor 2

- EGFR ailesinden bir transmembran tirozin kinaz reseptörü
- Bilinen spesifik bir ligandı yok







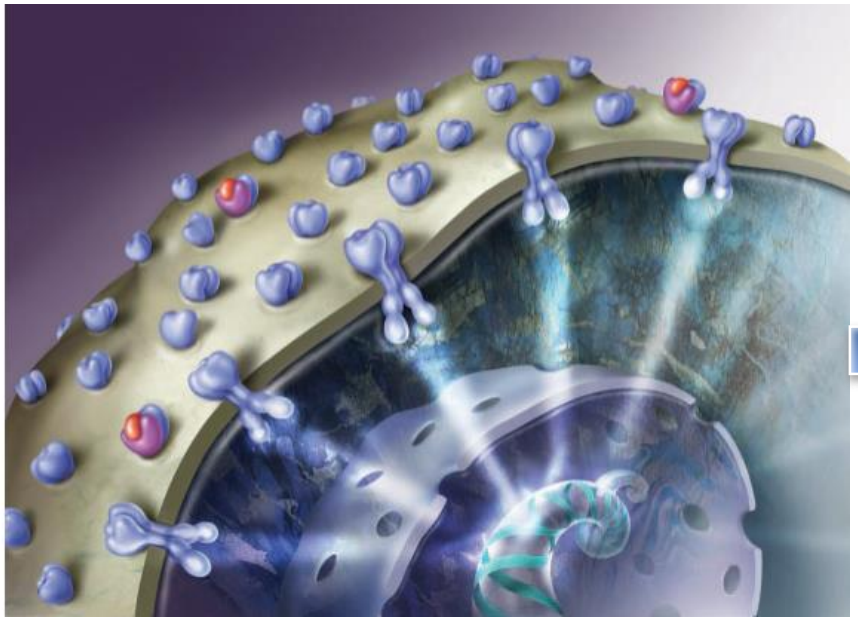


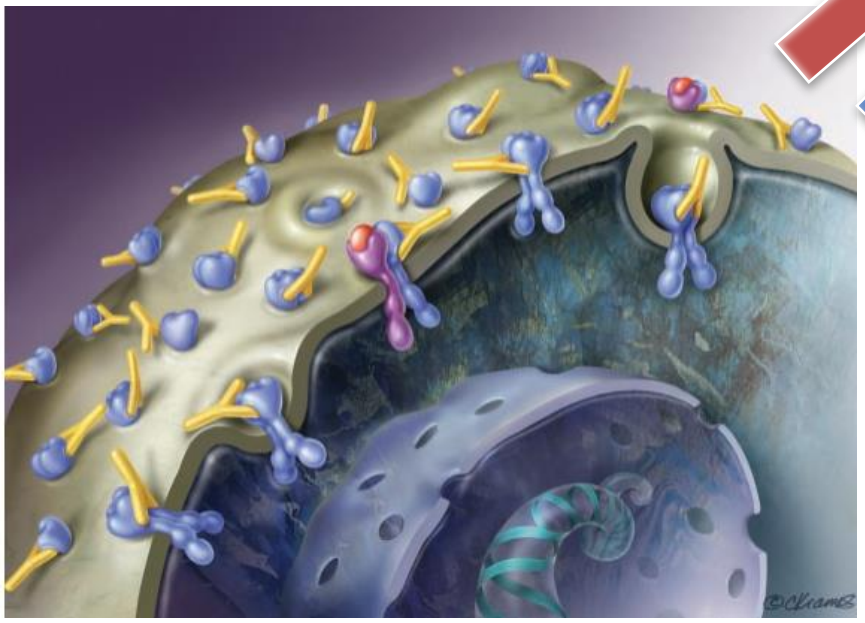
artmış HER2 protein sayısı

HER2/neu (ERBB2) Gen Amplifikasyonu

17q21'de lokalize

epidermal büyüme faktör reseptör-2 geni





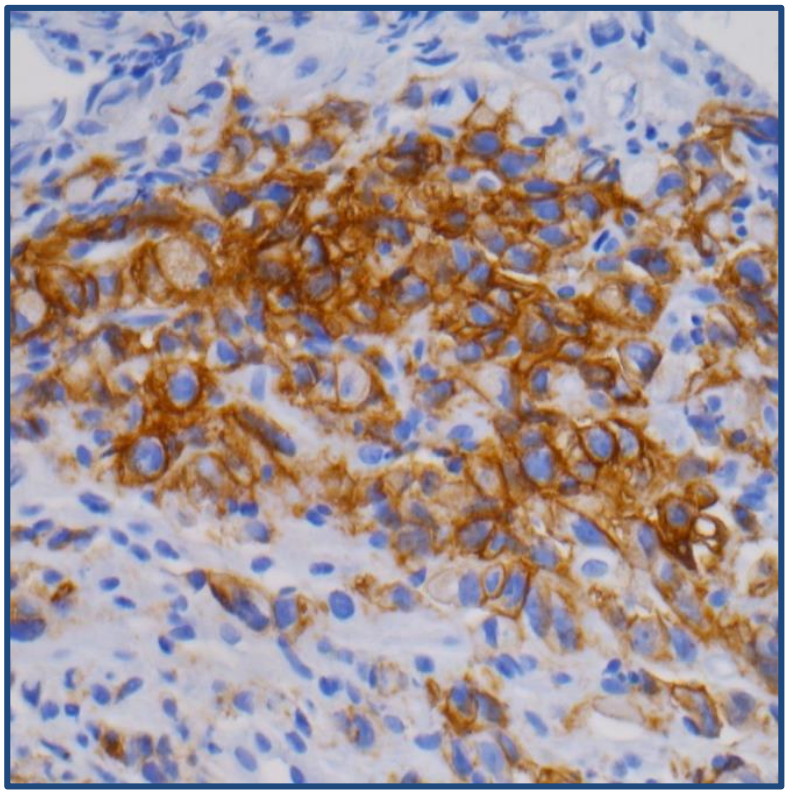
+ trastuzumab

neoplastik hücrelerde

- antikor bağımlı sitotoksisite
- HER2 bağımlı hücre içi sinyal iletiminin ortadan kaldırılması
- HER2 reseptörünün hücre dışı etki alanı yarılmasının önlenmesi

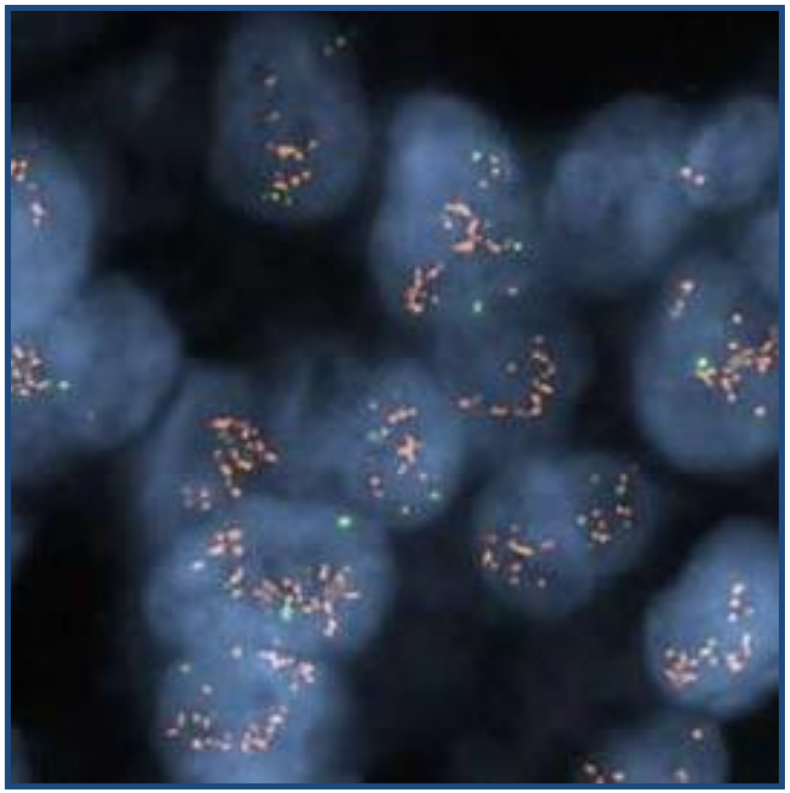
HER2 (c-erbB2/neu)

İMMÜNHİSTOKİMYA

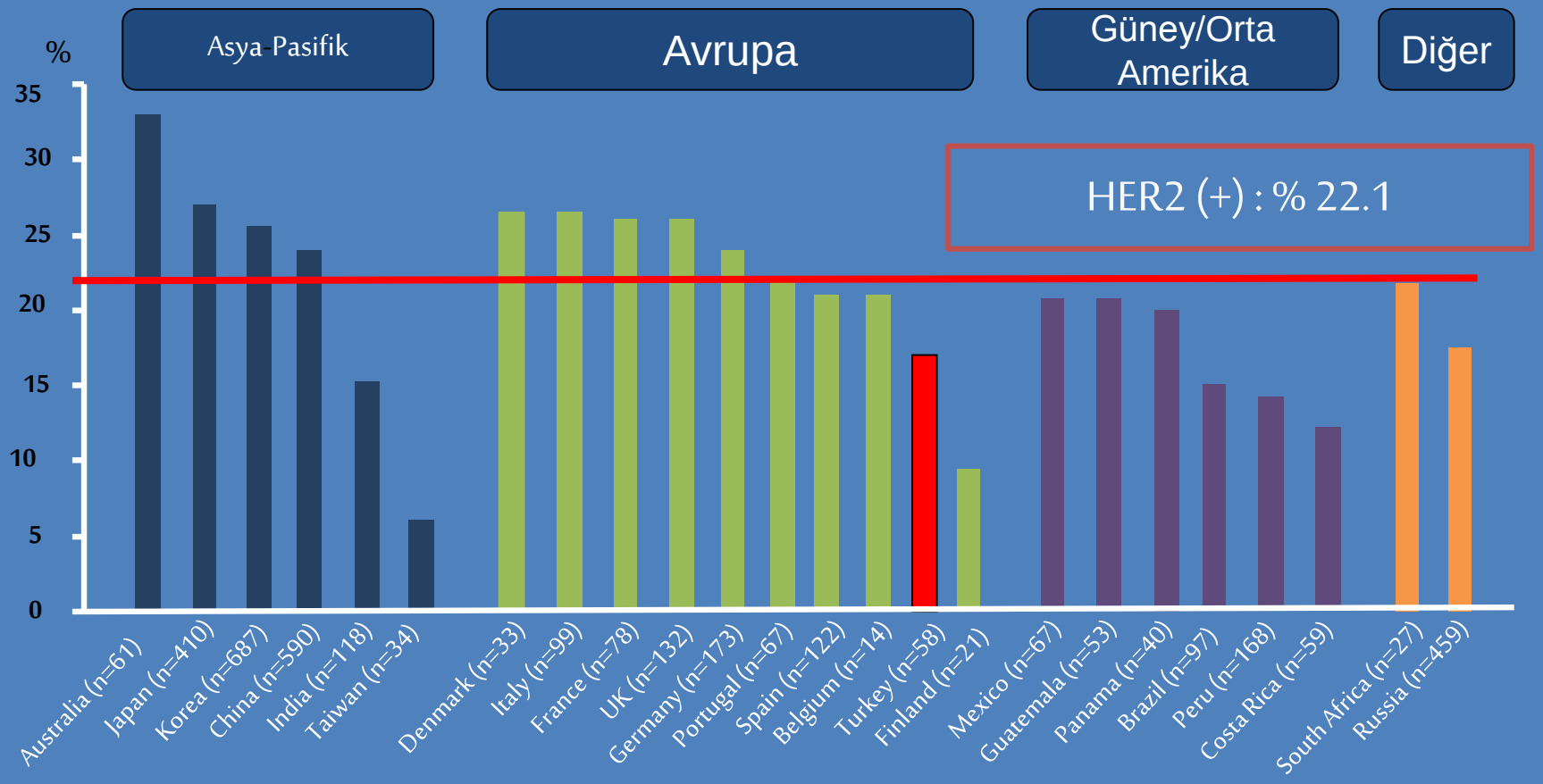


HER2 hücre yüzey reseptörü

İN-SİTU HİBRİDİZASYON



HER2 gen/17. kromozom



Mide Kanseri HER2-pozitiflik oranı (ToGA)

HER2-amplifikasyonu sağ kalım

VOLUME 29 · NUMBER 22 · AUGUST 1 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic Implications of Altered Human Epidermal Growth Factor Receptors (HERs) in Gastric Carcinomas: HER2 and HER3 Are Predictors of Poor Outcome

Maria D. Begnami, Emy Fukuda, José H.T.G. Fregnani, Suely Nonogaki, André L. Montagnini, Wilson L. da Costa Jr, and Fernando A. Soares

Maria D. Begnami, Emy Fukuda, Suely Nonogaki, André L. Montagnini, Wilson L. da Costa Jr, and Fernando A. Soares, Hospital A.C. Camargo; Suely Nonogaki, Institute Adolpho Lutz, São Paulo; and José H.T.G. Fregnani, Hospital do Câncer de Barretos, Barretos, Brazil.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2922-3030/$20.00

DOI: 10.1200/JCO.2010.33.6313

A B S T R A C T

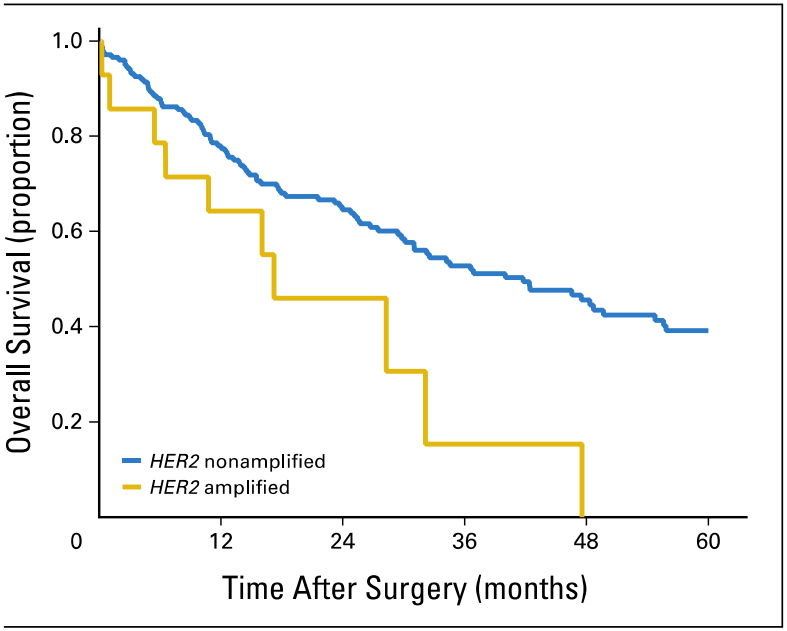
Purpose
The human epidermal growth factor receptor (HER) family consists of four members: ErbB-1 (HER1), ErbB-2 (HER2), ErbB-3 (HER3), and ErbB-4 (HER4). These receptors activate numerous downstream pathways in response to extracellular ligands, regulating diverse processes that include differentiation, migration, proliferation, and survival. Alterations in these genes play a role in the development and progression of many human cancers. In gastric carcinomas (GCs), expression of HER1 and HER2 is thought to be a prognostic factor and target of novel biologic agents. The effect of HER3 or HER4 expression in GC has not been sufficiently studied. In this study, we explored the gene and protein expression of the HER family in GC to establish new potential prognostic factors.

Patients and Methods
Immunohistochemistry and fluorescence in situ hybridization were performed in 221 patients with GC using tissue microarray. Correlation between the expression or amplification of *HER* genes and the clinicopathologic parameters was statistically analyzed.

Results
Alterations of members of the HER family were significantly associated with the parameters involved in tumor progression, including depth of tumor invasion, involved lymph nodes, and tumor stage. In addition, *HER2* amplification and HER3 expression were significantly related to worse survival.

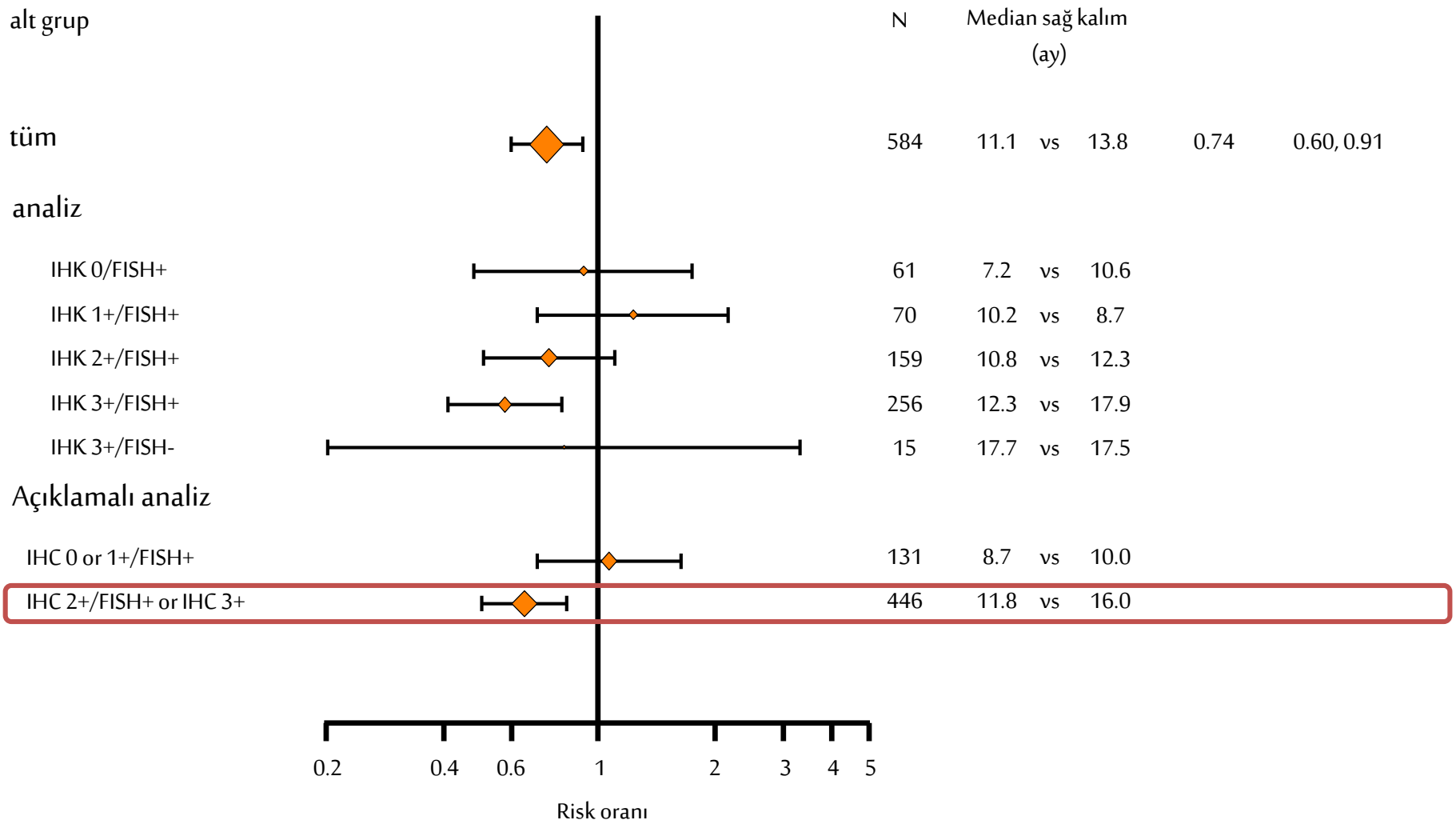
Conclusion
These results reveal that all members of the HER family are expressed in GC. Furthermore, expression of HER2 and HER3 is a significant predictor of poor survival in GC. Therefore, the development of HER-targeted agents and agents targeting downstream signaling pathways provides new possibilities in the treatment of GC.

J Clin Oncol 29:3030-3036. © 2011 by American Society of Clinical Oncology



ig 1. Kaplan-Meier curve for the overall survival of patients with amplification *HER2* (n = 188). Median survival time was 17 months for patients with gastric cinoma with amplification of *HER2* (n = 11) compared with 40 months for ients with nonamplification of *HER2* (n = 177). The difference was significant the log-rank test (*P* = .023).

HER2 durumu : tedavi / genel sağ kalım

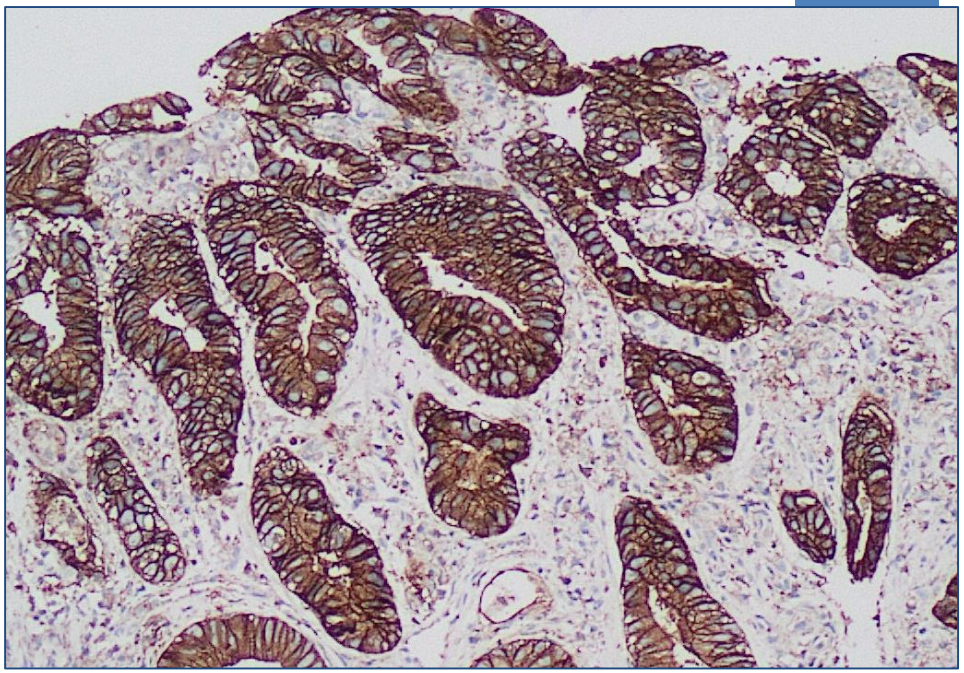


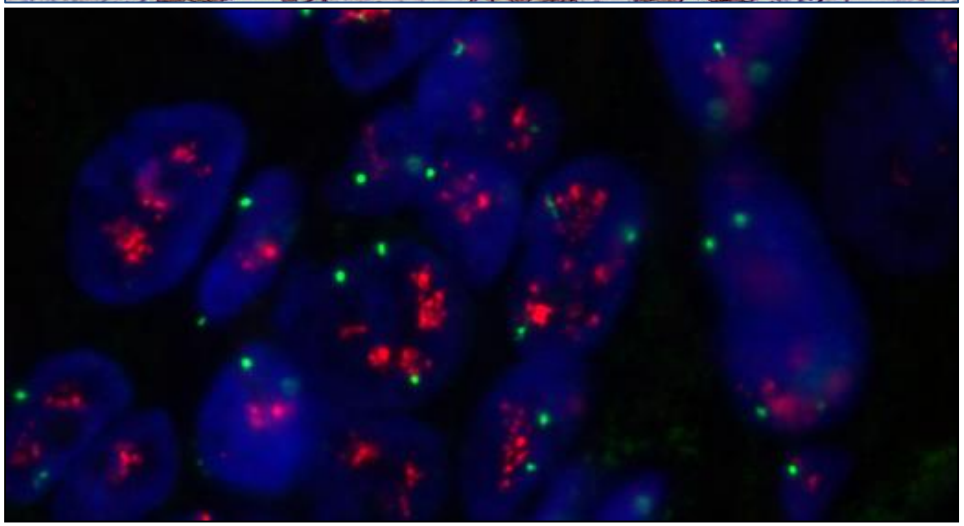
Van Cutsem E, *et al J Clin Oncol* 2009; **27**:Abstract 4509.

Mide Kanseri HER-2

Mide ve GEJ Kanserleri HER2 açısından değerlendirilmeli

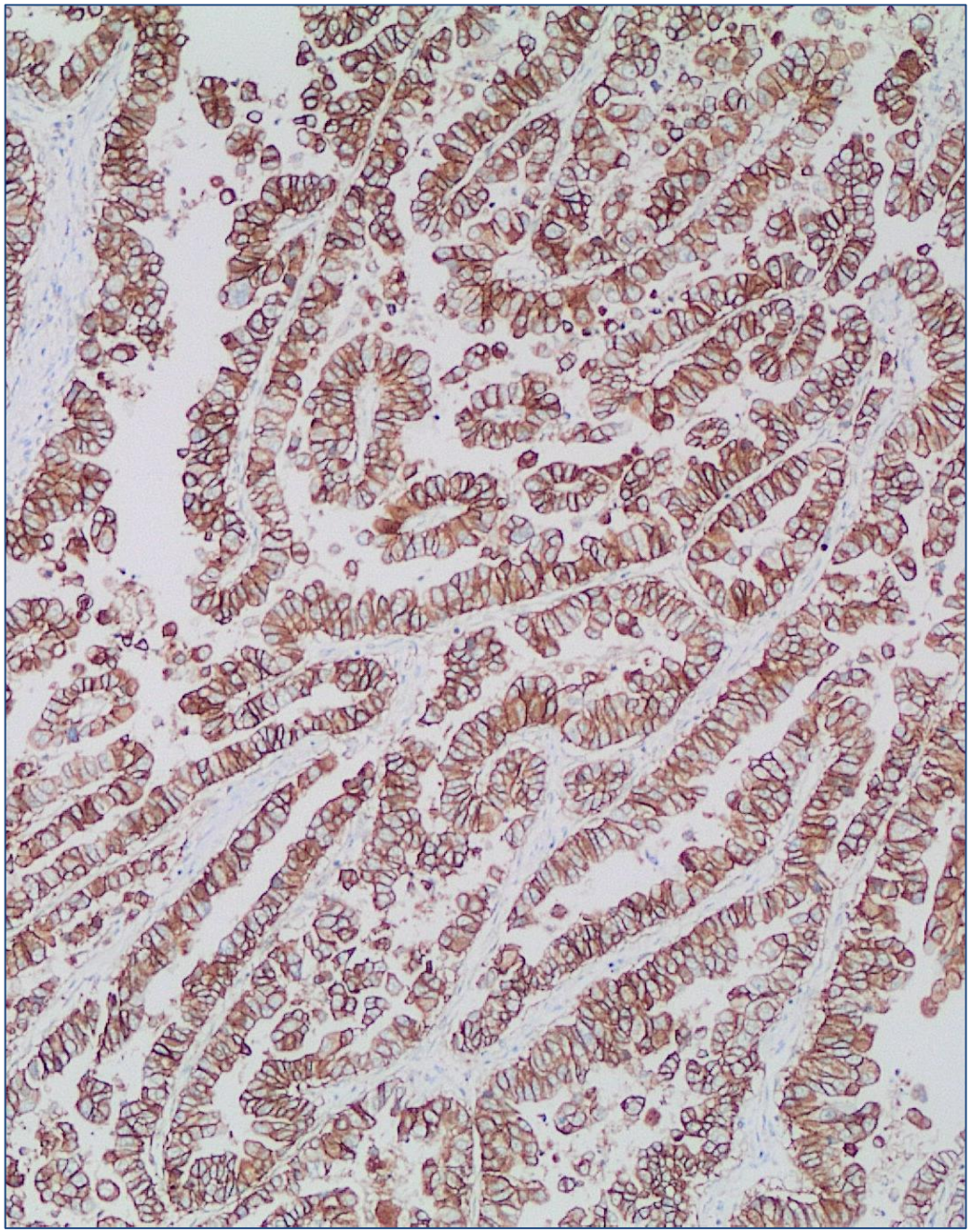
- Immünhistokimya
- In-situu hibridizasyon

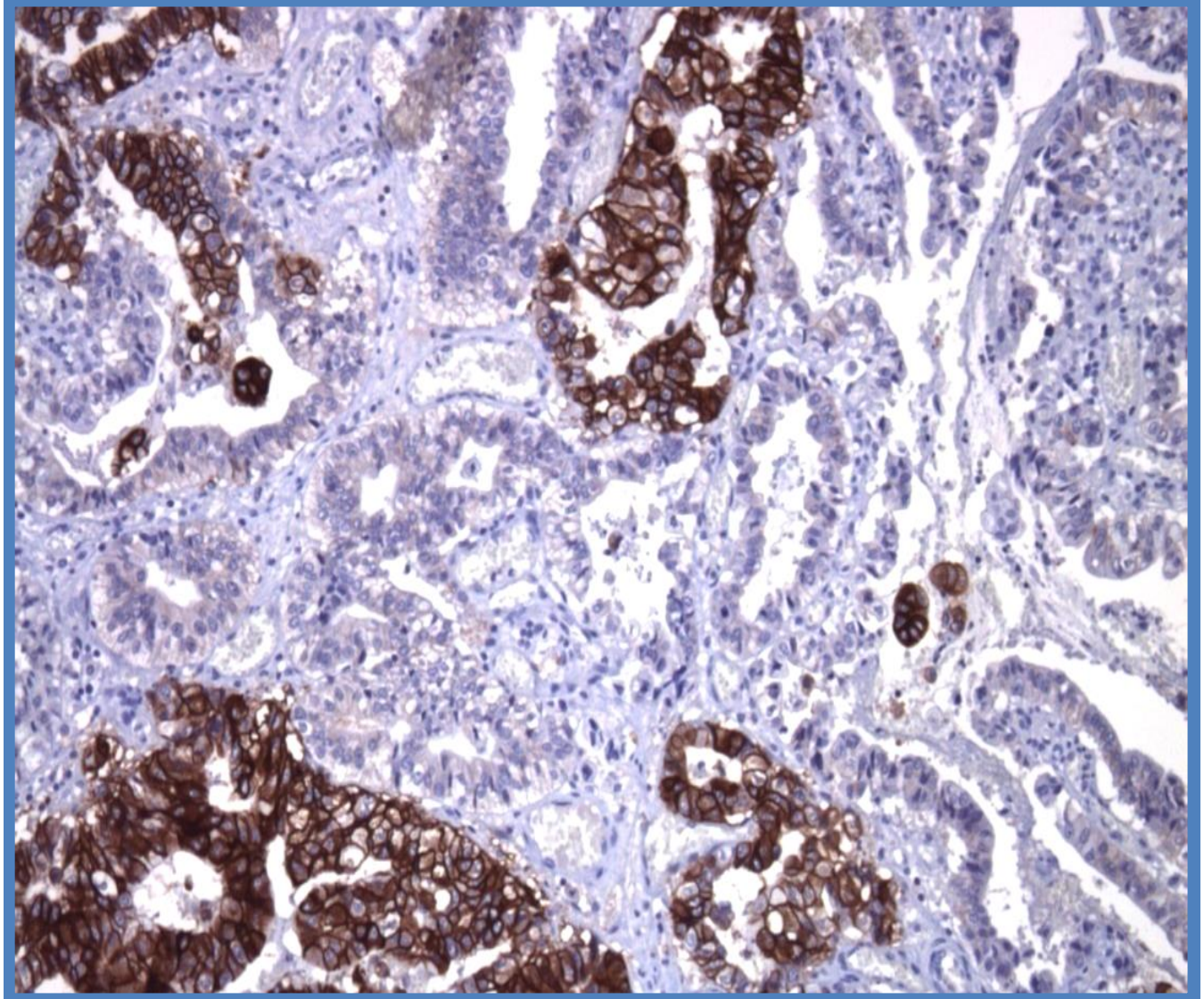




HER2/neu
(c-erbB2)

İMMÜN-
HİSTOKİMYA



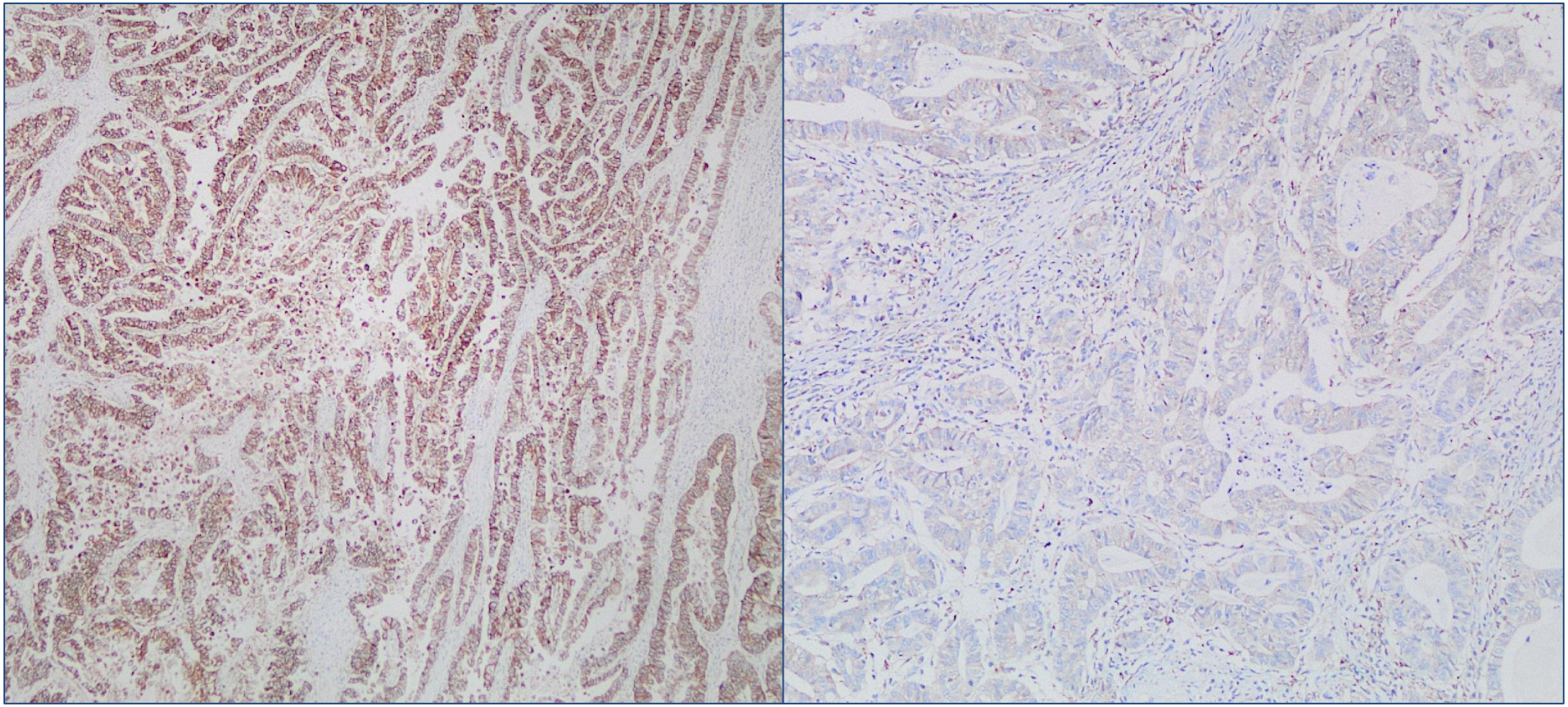


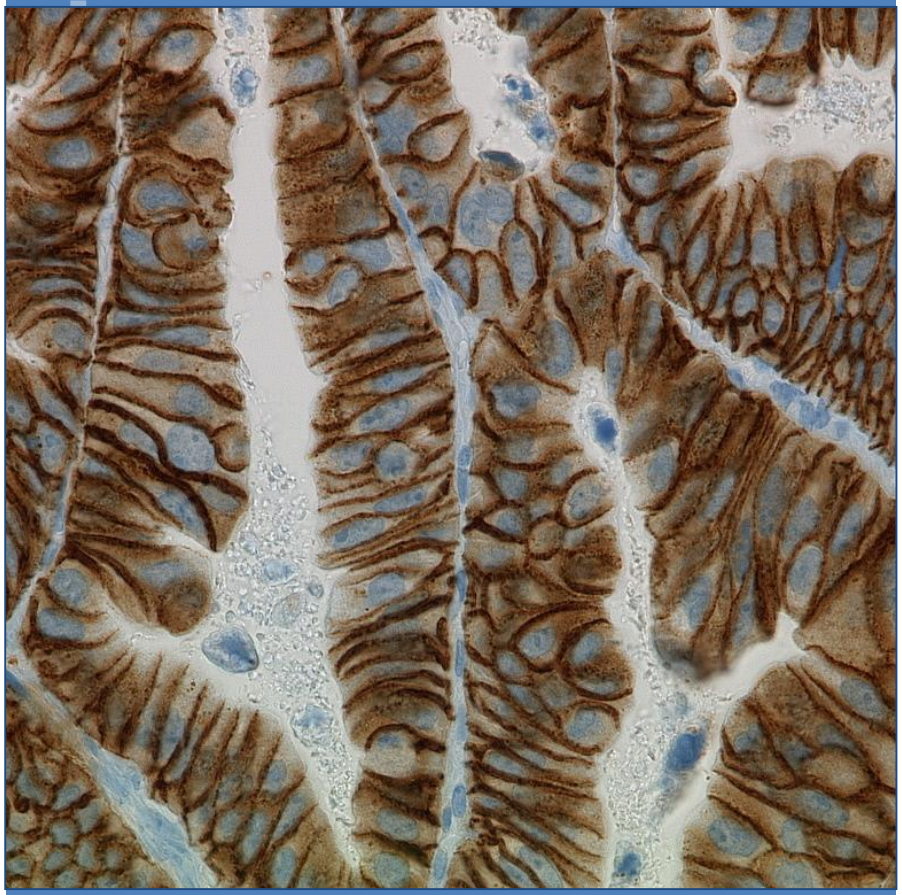
HER2/neu IHK

Gastrik Karsinom

heterojen boyanma

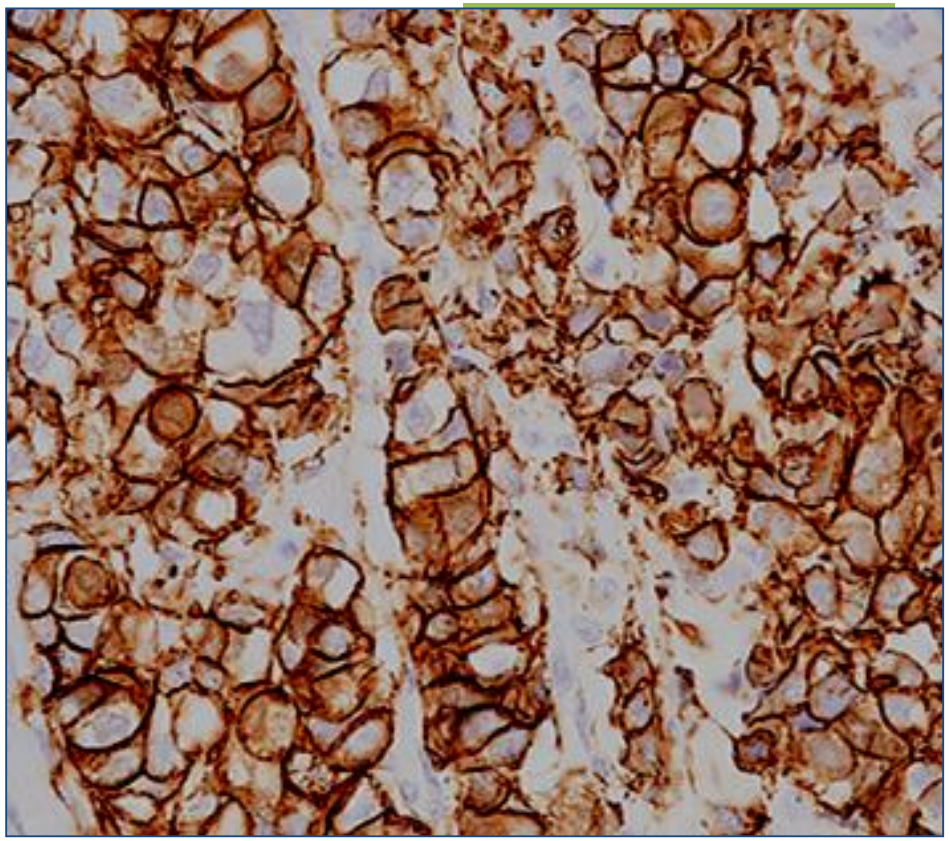
Mide Kanseri
Tümör Heterojenitesi





- lateral
- bazolateral
- komplet

HER2/neu IHK

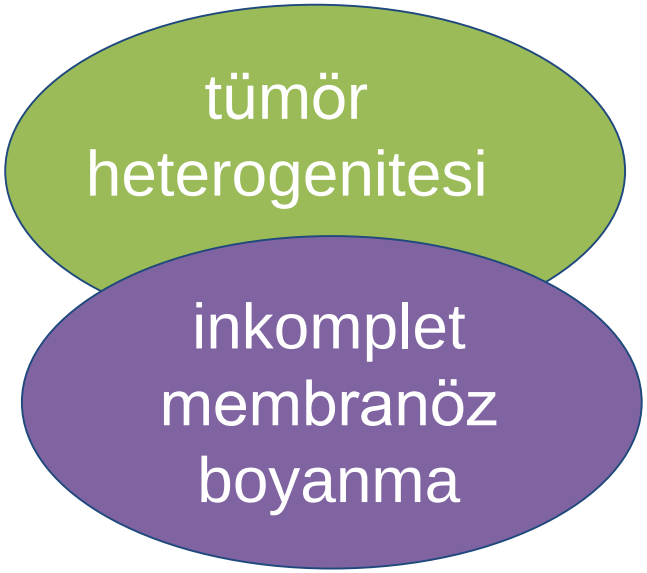


Gastrik Karsinom

boyanma patterni

HER2 (IHK)

- Gastrik karsinom için skorlama sistemi



İMMUNEKSPRESYON

- ✓ Şiddeti
- ✓ IHK (+) tümör hücre oranı / sayısı

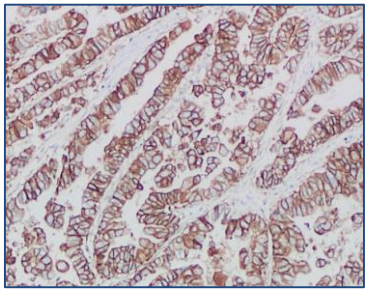
Hofmann M, et al. Histopathology 2008; 52: 797-805.

HER2/neu (IHK) - boyanma şiddeti

IHK 3+

5x

Membranöz Boyanma



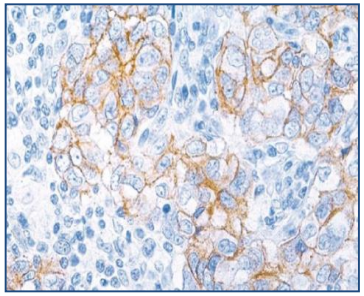
5x

IHK 2+

10x

20x

Membranöz Boyanma

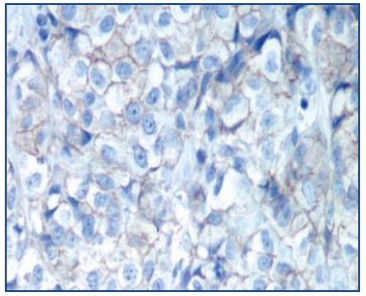


20x

IHK 1+

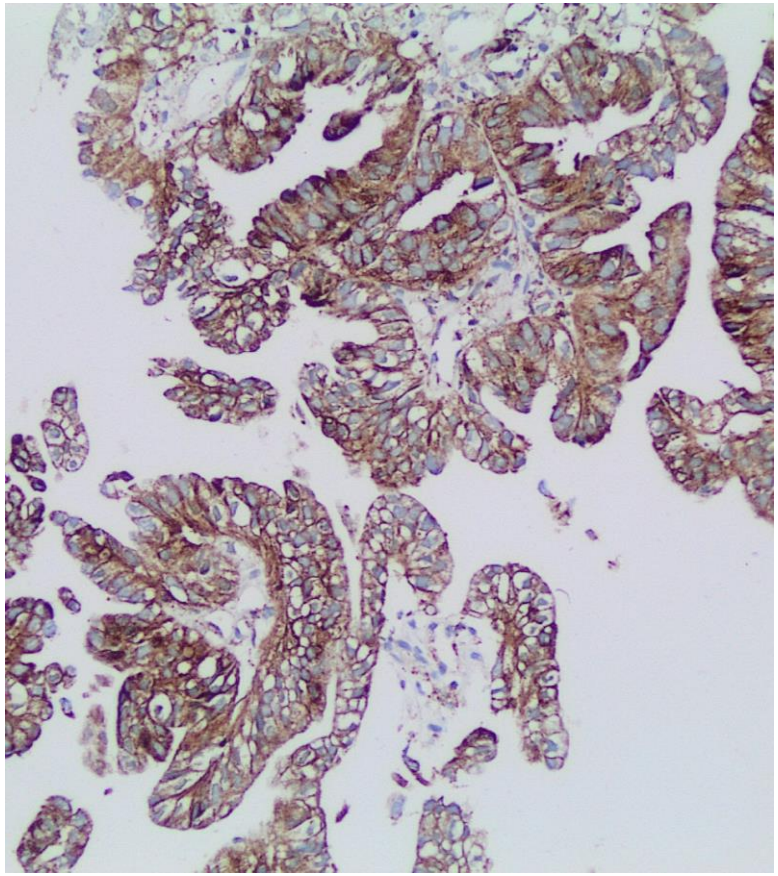
40x

Membranöz Boyanma

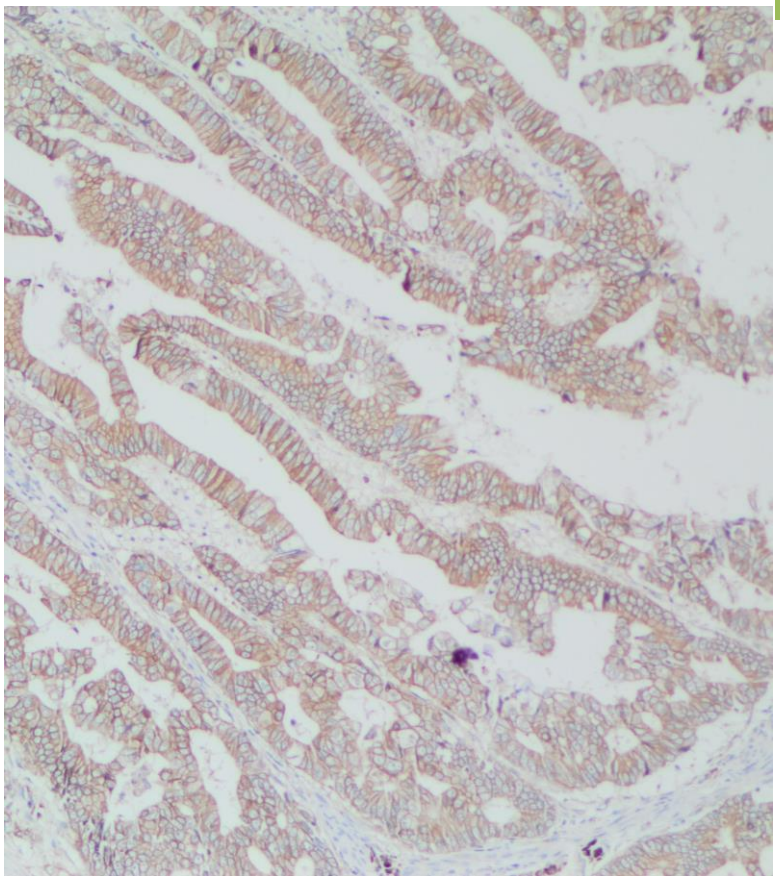


40x

HER2/neu (IHK) – boyanan tümör hücre sayısı/oranı

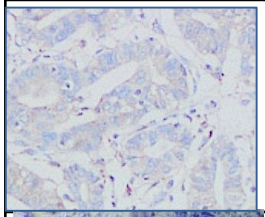
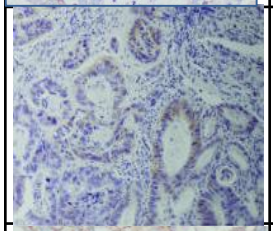
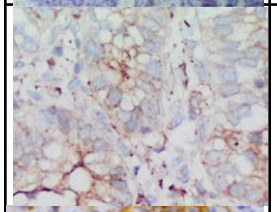
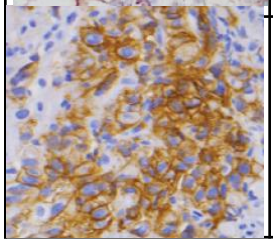


BİYOPSİ
> 5 tümör hücresi



REZEKSİYON SPESMENİ

Mide Kanseri - HER2
IHK skorlama kriteri

	SKOR	cerrahi spesmen boyanma patterni	biyopsi spesmeni boyanma patterni	**HER2** değerlandirme
	0	Boyanma yok ▪ < %10 hücrede membranöz	Boyanma yok ▪ 5'den az hücrede membranöz boyanma	Negatif
	1+	▪ > %10 hücrede ▪ membranöz, zayıf ▪ parsiyel	▪ > 5 hücrede (küme) ▪ membranöz, zayıf ▪ parsiyel	Negatif
	2+	▪ > %10 hücrede ▪ membranöz, orta, ▪ bazolateral /lateral	▪ > % 5 hücrede (küme) ▪ membranöz, orta, ▪ bazolateral /lateral	Belirsiz
	3+	▪ > %10 hücrede ▪ membranöz, kuvvetli, ▪ bazolateral /lateral	▪ > % 5 hücrede (küme) ▪ membranöz, kuvvetli, ▪ bazolateral /lateral	Pozitif

IHK Raporu

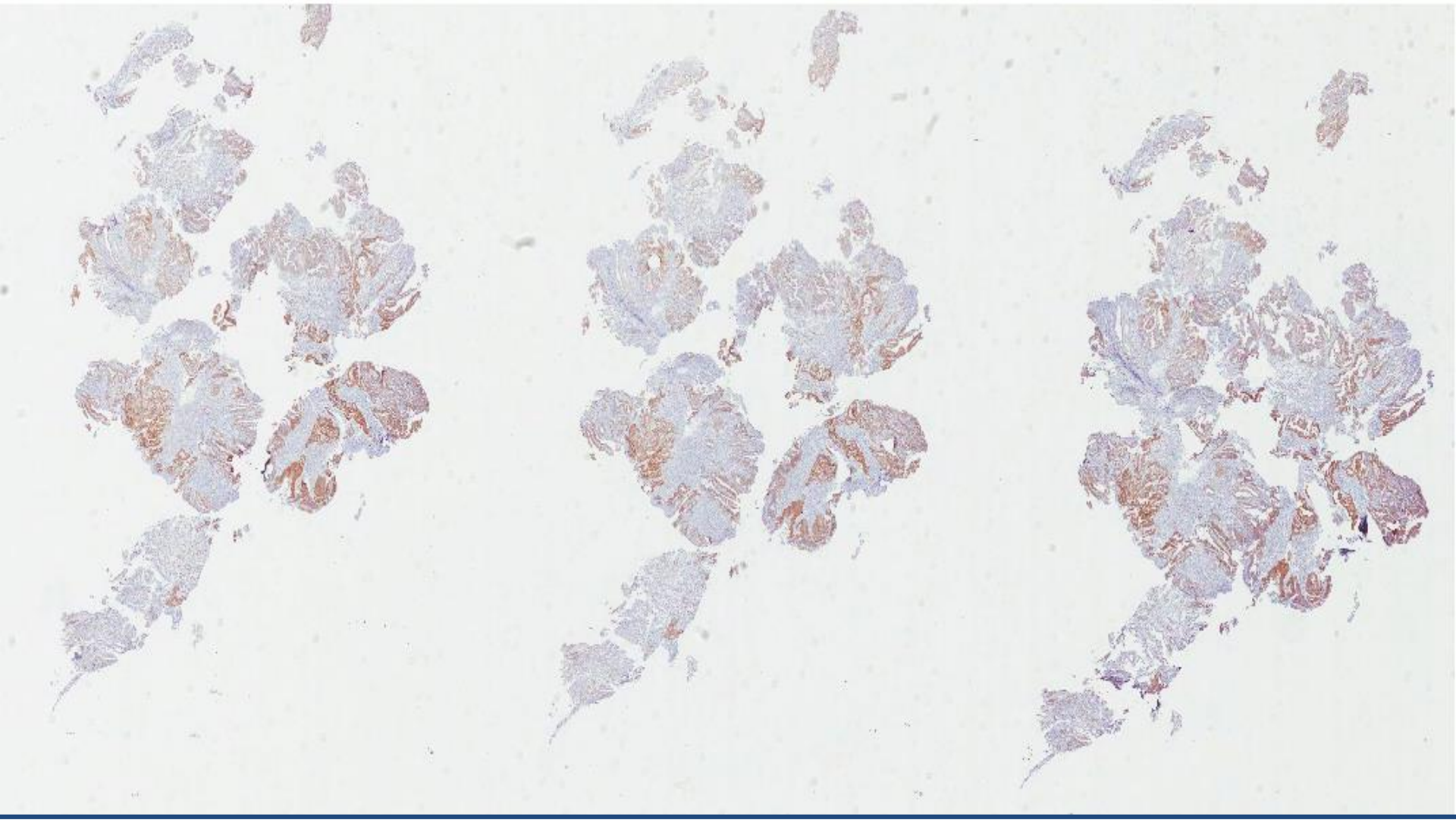
- *UYGULANAN YÖNTEM :* IHK
  Kullanılan Primer Antikor :
  4B5, Hercept Test, A0485, SP3, CB11

- İMMÜNEKSPRESYON :
  Negatif (skor 0)
  Negatif (skor 1+)
  Şüpheli pozitif (2+)
  Pozitif (skor 3+)
  Belirlenemez (tanımla)

+

- boyanan neoplastik hücre sayısı (biyopsi)
- boyanan neoplastik hücre oranı (rezeksiyon)

YORUM : Doku değerlendirme açısından yeterli /yetersiz



HER2/neu (c-erbB2)

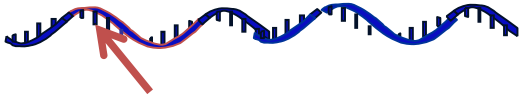
İN-SİTU HİBRİDİZASYON

In-Situ Hibridizasyon (ISH)

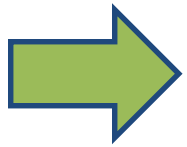
2-3 (4) µm kesit
formalin fikse, parafinde gömülü doku blokları
uygun fiksasyon süresi : 12-24 saat

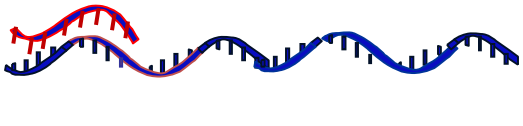
“fluorescent/chromogene“
işaretli probe (direkt / indirekt)

işaretli probun spesifik
gen alanına hibridizasyonu



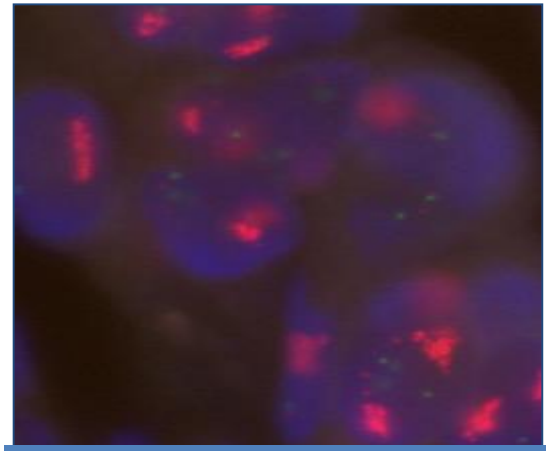
17. kromozom yüzeyindeki
Her2/neu alanı



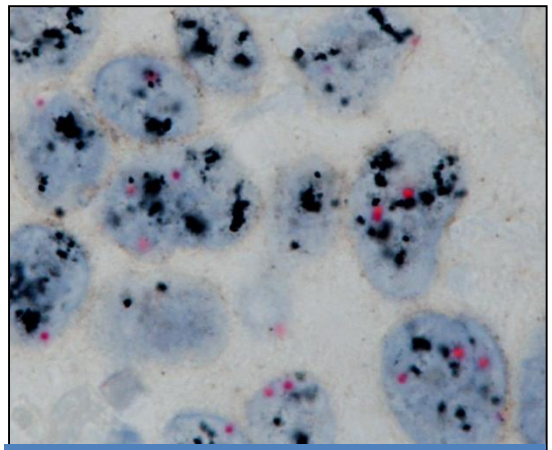


Sinyal Analizi

FISH



floresan mikroskopu

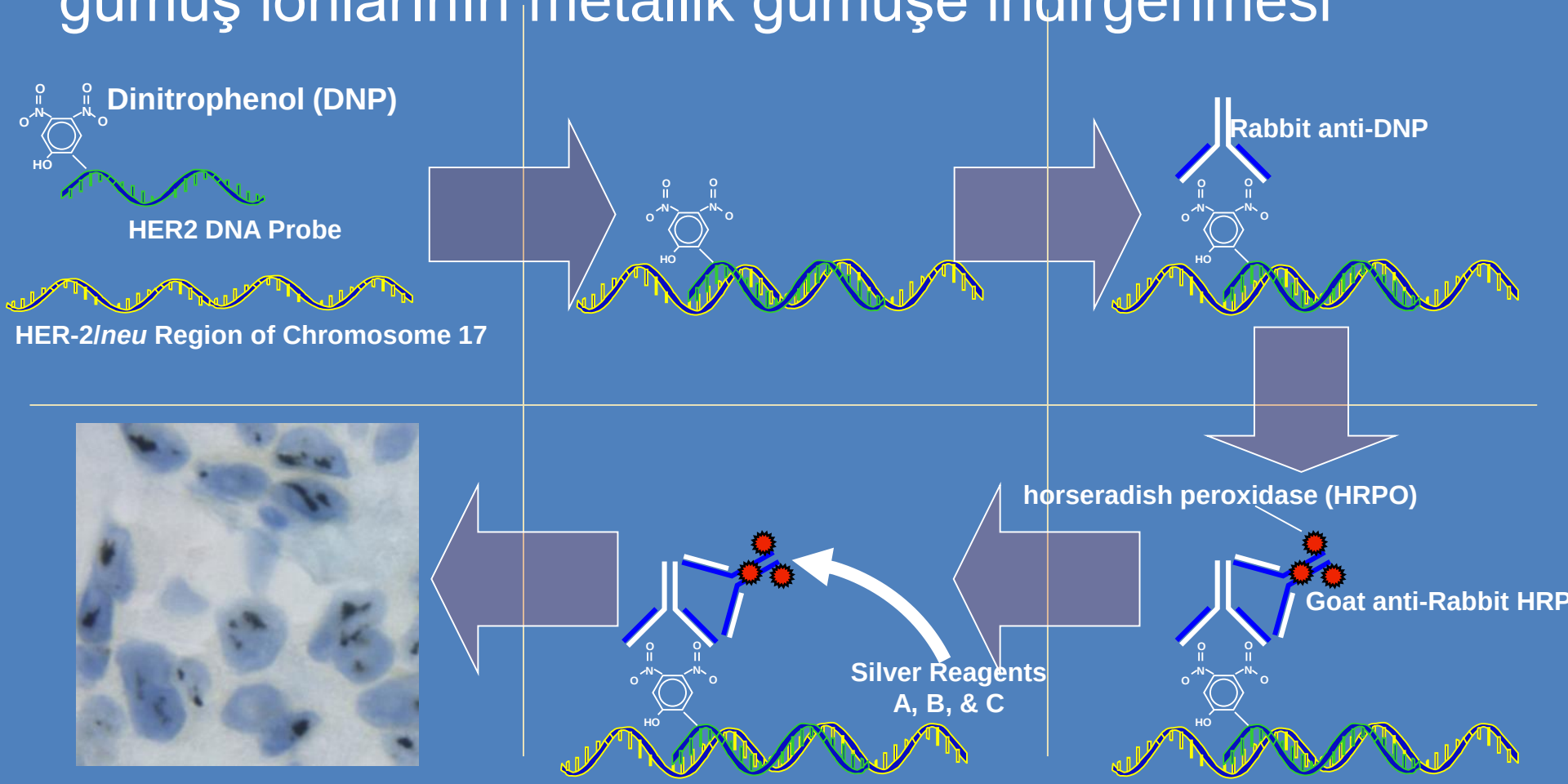


ışık mikroskopu

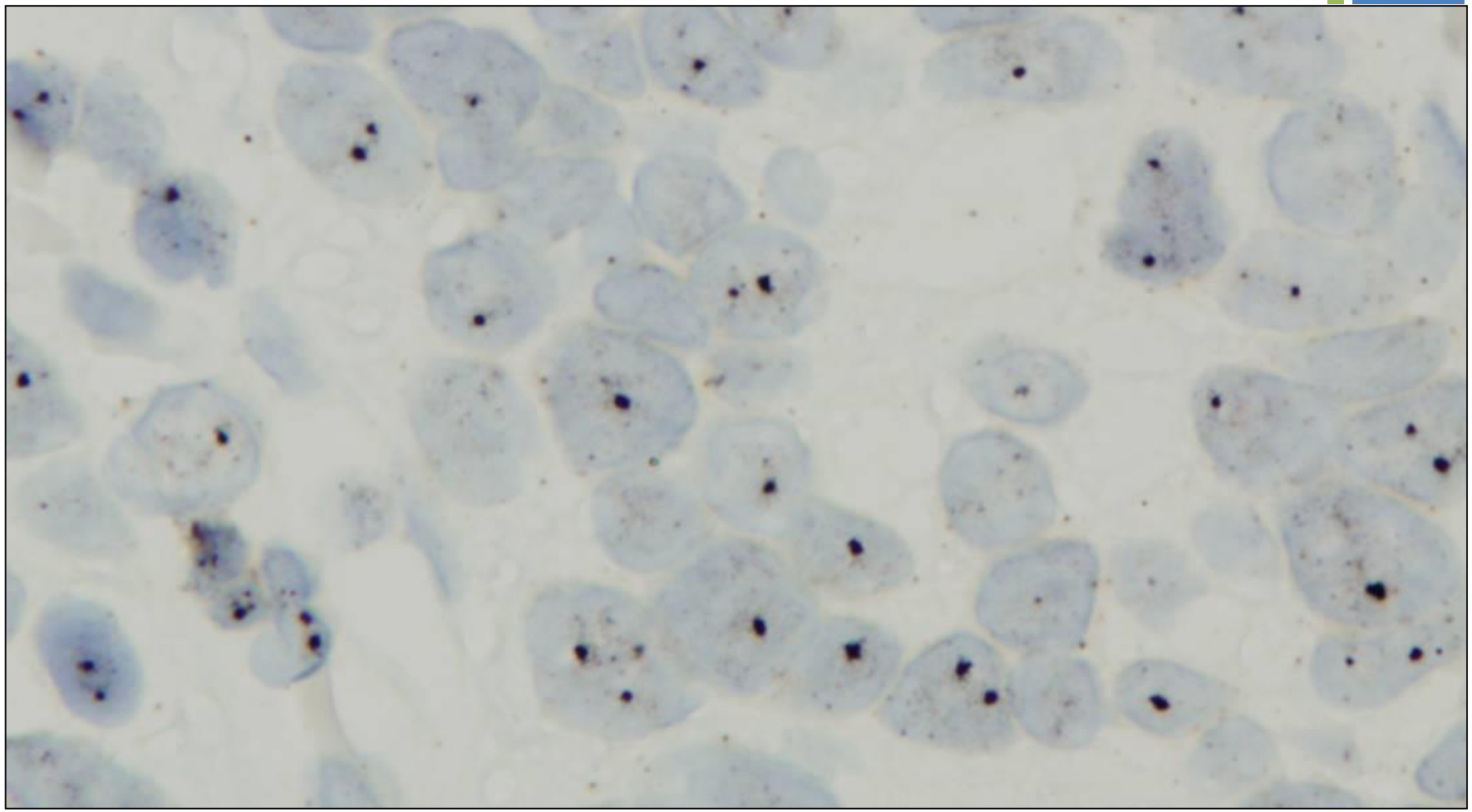
CISH

SISH

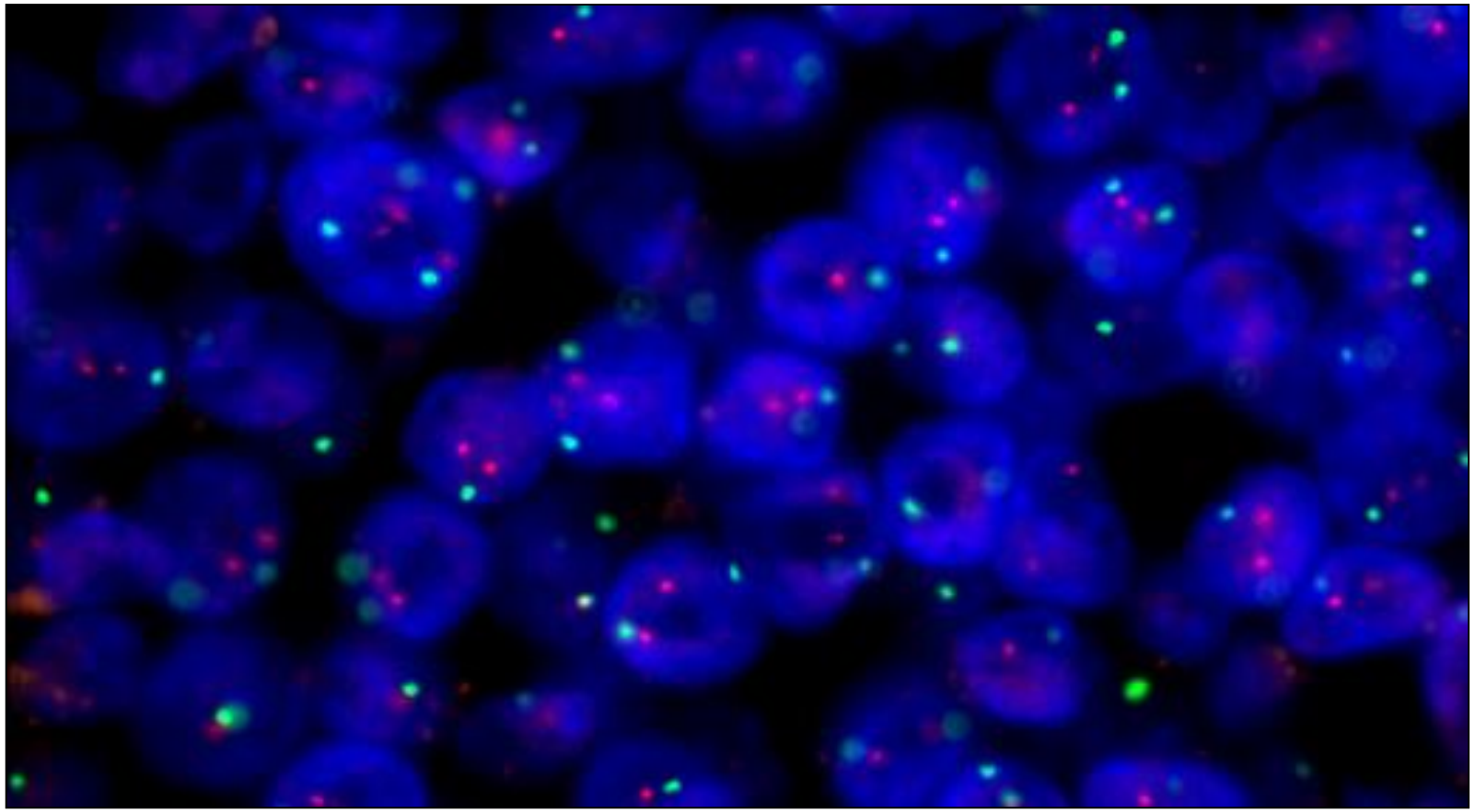
Enzim (HRP) katalizsyonu –
gümüş ionlarının metallik gümüşe indirgenmesi

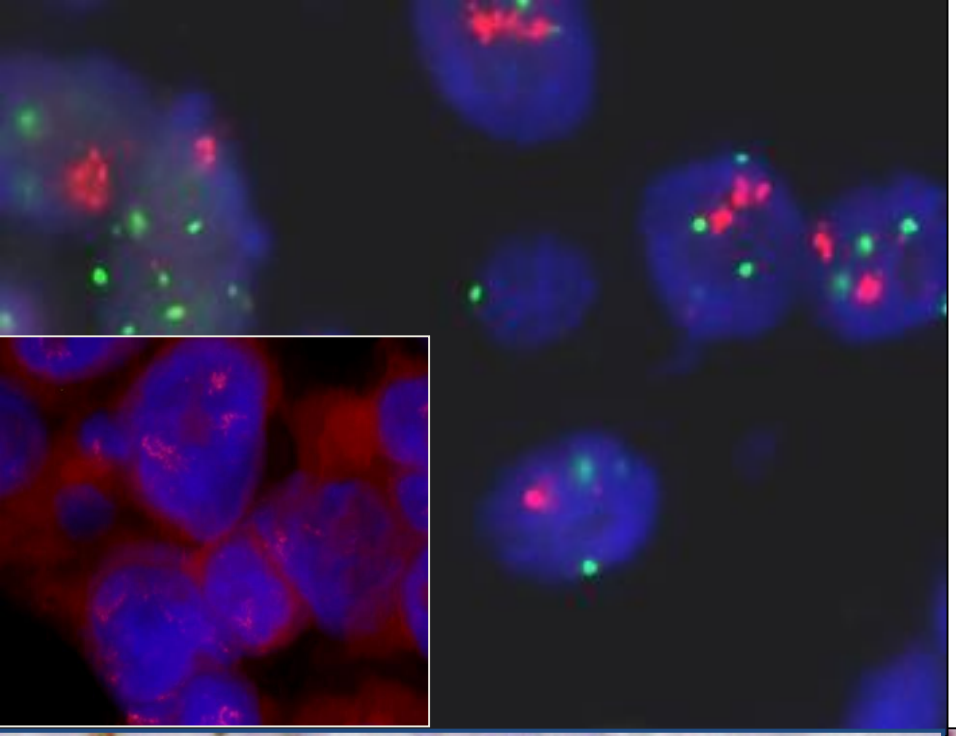


TEK “probe” – HER2 gen alanı



ÇİFT "probe" - HER2 gen alanı (+) 17. kromozom sentromeri (CEP17)



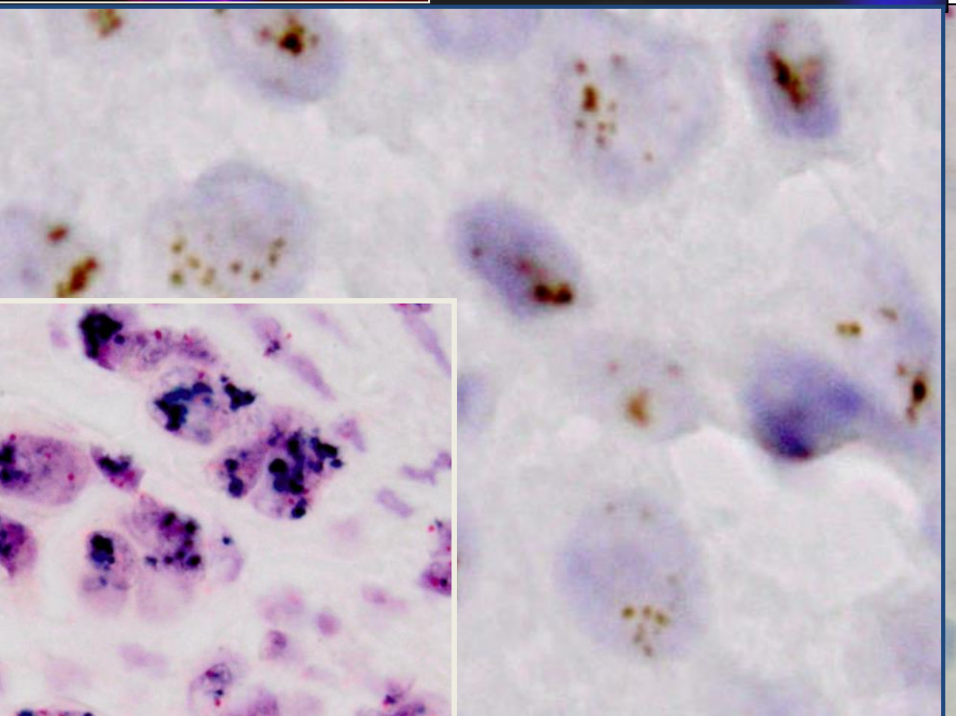


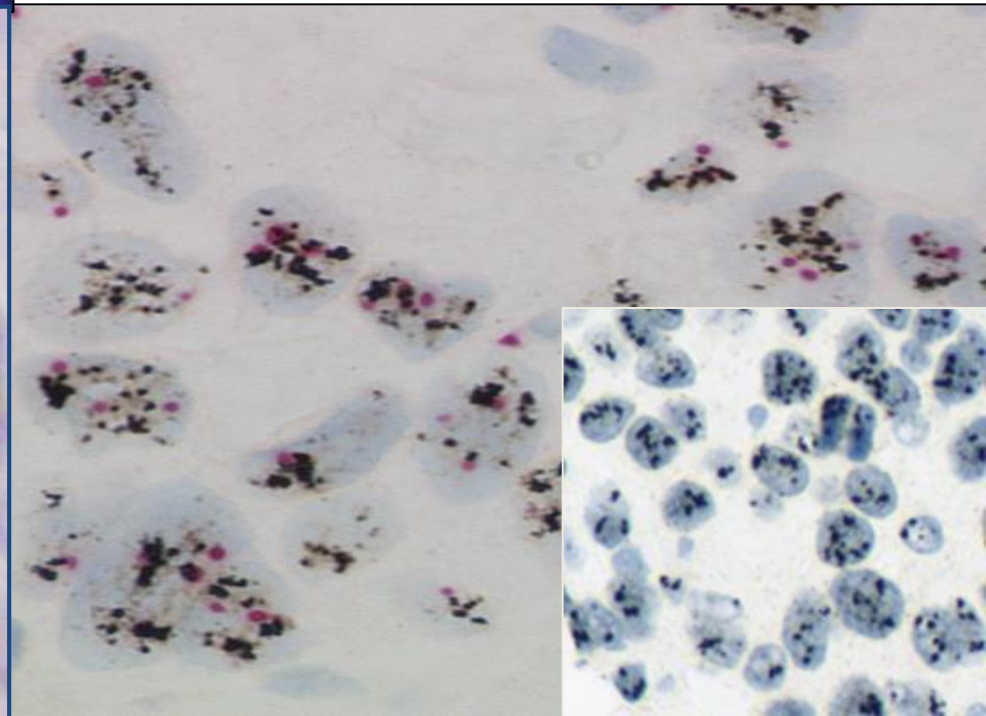
ISH

- FISH / CISH / SISH

(fluorescence/chromogene/silver)

- Her2 geni → Tek “Probe”
- Her2 geni (+) CEP17(sentromer) → ÇİFT “Probe”





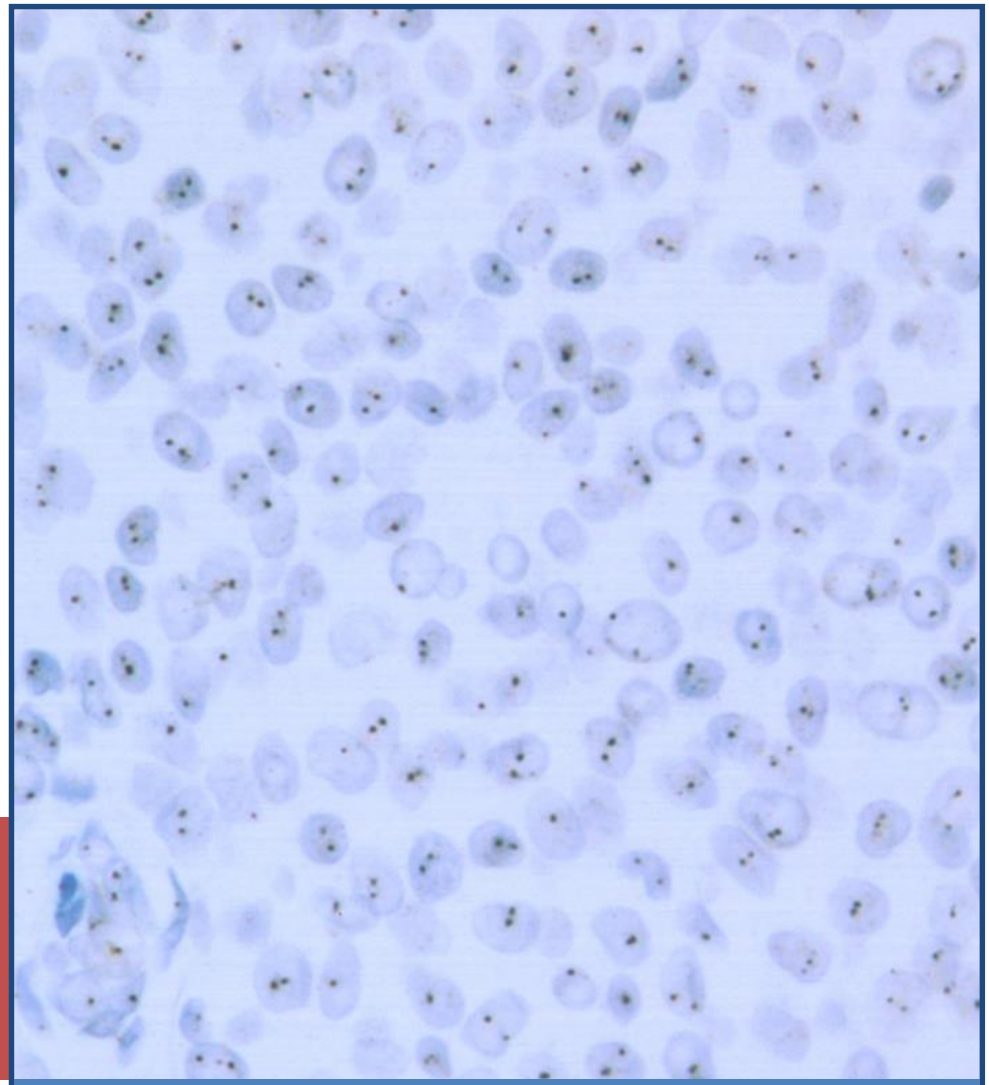
+

FISH/CISH/SISH
Tek “probe”

17. kromozomda HER2 gen alanı

AMPLİFİKASYON YOK

< 6 HER2



- En az 20 neoplastik hücre
- toplam HER2 sinyal sayısı / sayılan tümör hücre sayısı

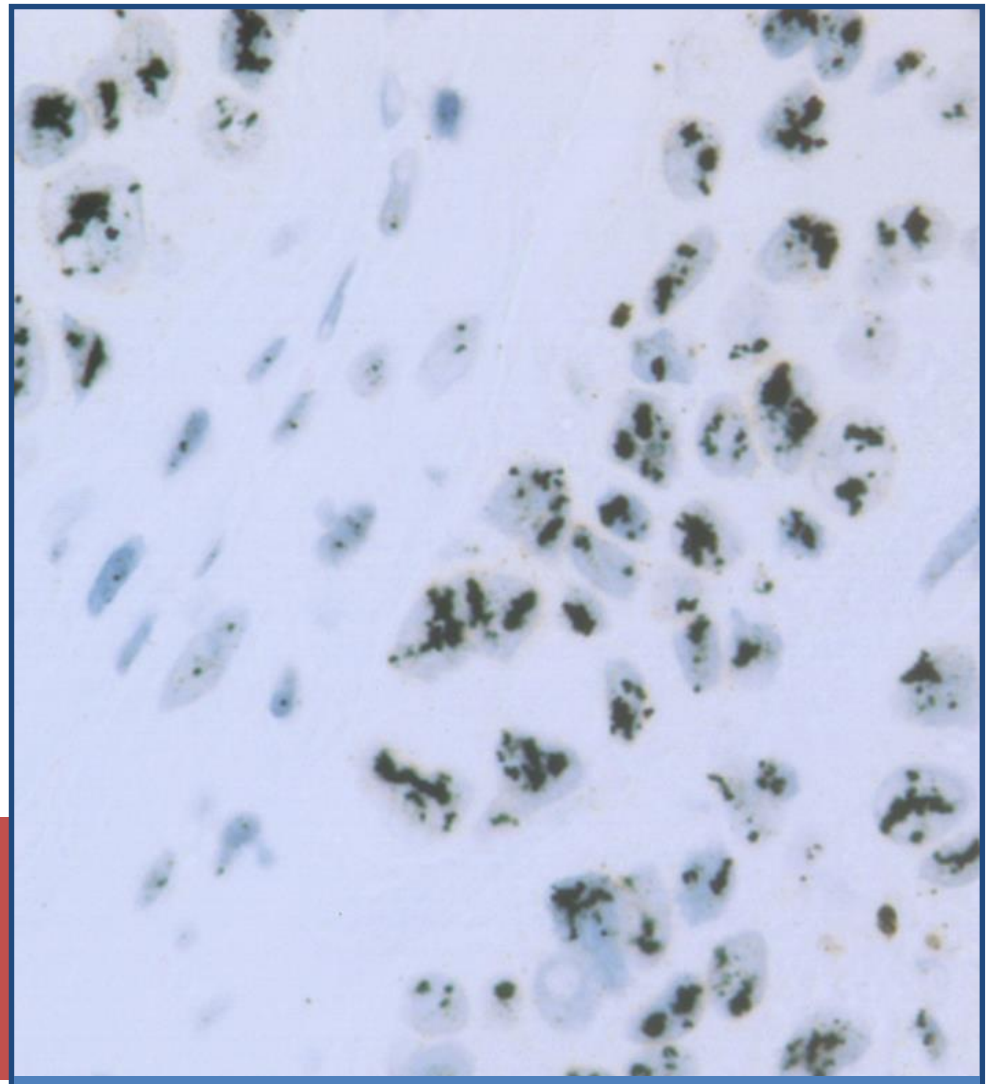
+

FISH/CISH/SISH
Tek “probe”

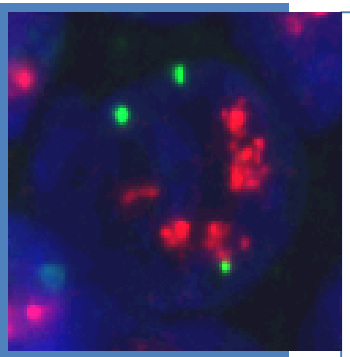
17. kromozomda
HER2 gen alanı

AMPLİFİKASYON
VAR

≥ 6 HER2



- En az 20 neoplastik hücre
- toplam HER2 sinyal sayısı / sayılan tümör hücre sayısı



FISH/CISH/SISH

Çift "probe"

17. kromozomda HER2 gen alanı (+)

17. kromozom sentromer (CEP 17)

- 20 neoplastik hücre
  - HER2 sinyali (turuncu)
  - CEP 17 sinyali (yeşil)
- HER2 sinyal toplamı / CEP 17 sinyal toplamı (HER2/CEP 17)
  - **< 1.8** → amplifikasyon (-)
  - **1.8 – 2.2** → belirsiz
  - **> 2.2** → amplifikasyon (+)
- HER2/CEP17=1.8 – 2.2 ise 40 hücre daha sayılmalı
  - **≥ 2.0** → amplifikasyon (+)

+

FISH/CISH/SISH

Çift "probe"

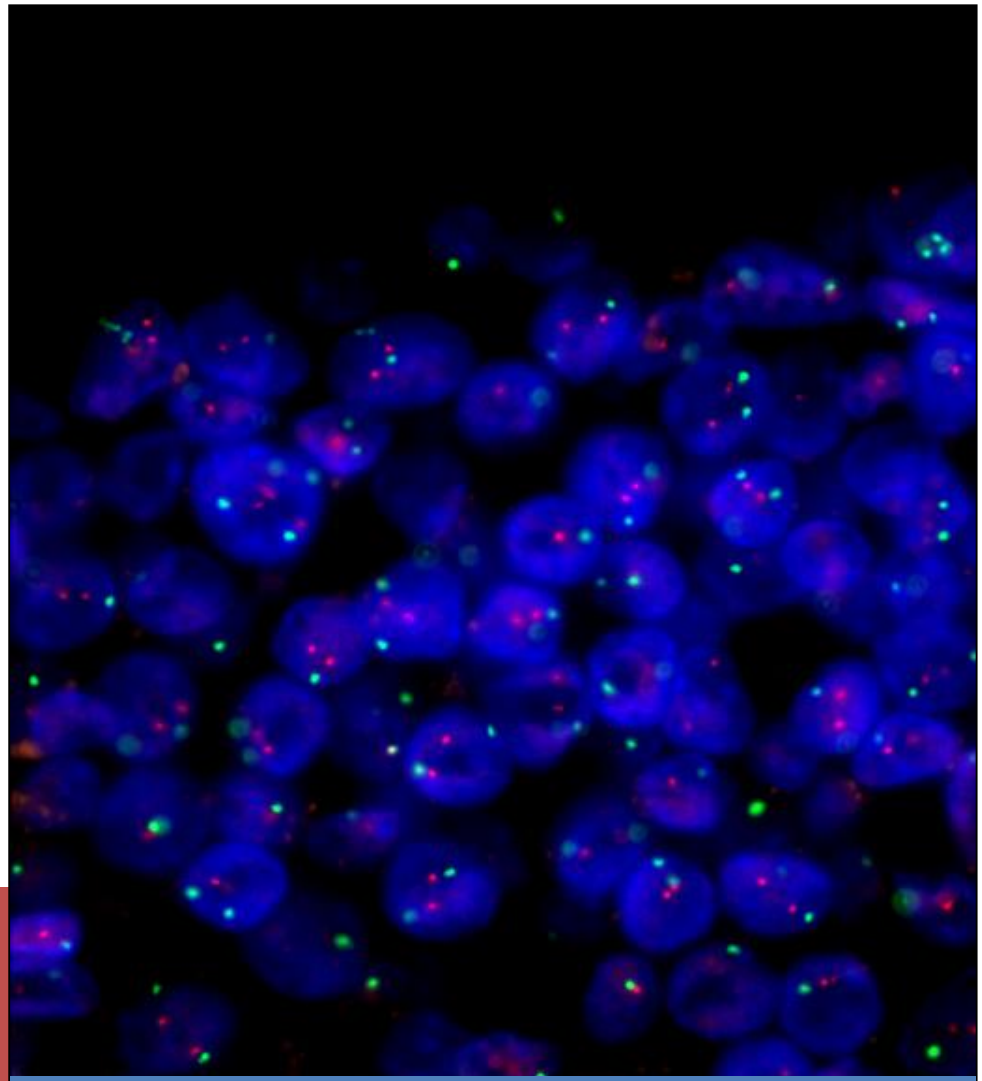
17. kromozomda HER2 gen alanı

(+)

17. kromozom sentromeri

AMPLİFİKASYON ➔ YOK

HER2 / CEP 17 oranı < 1.8



20 neoplastik hücre sayılmalı

- HER2 sinyali (turuncu)
- CEP sinyali (yeşil)

+

FISH/CISH/SISH

Çift "probe"

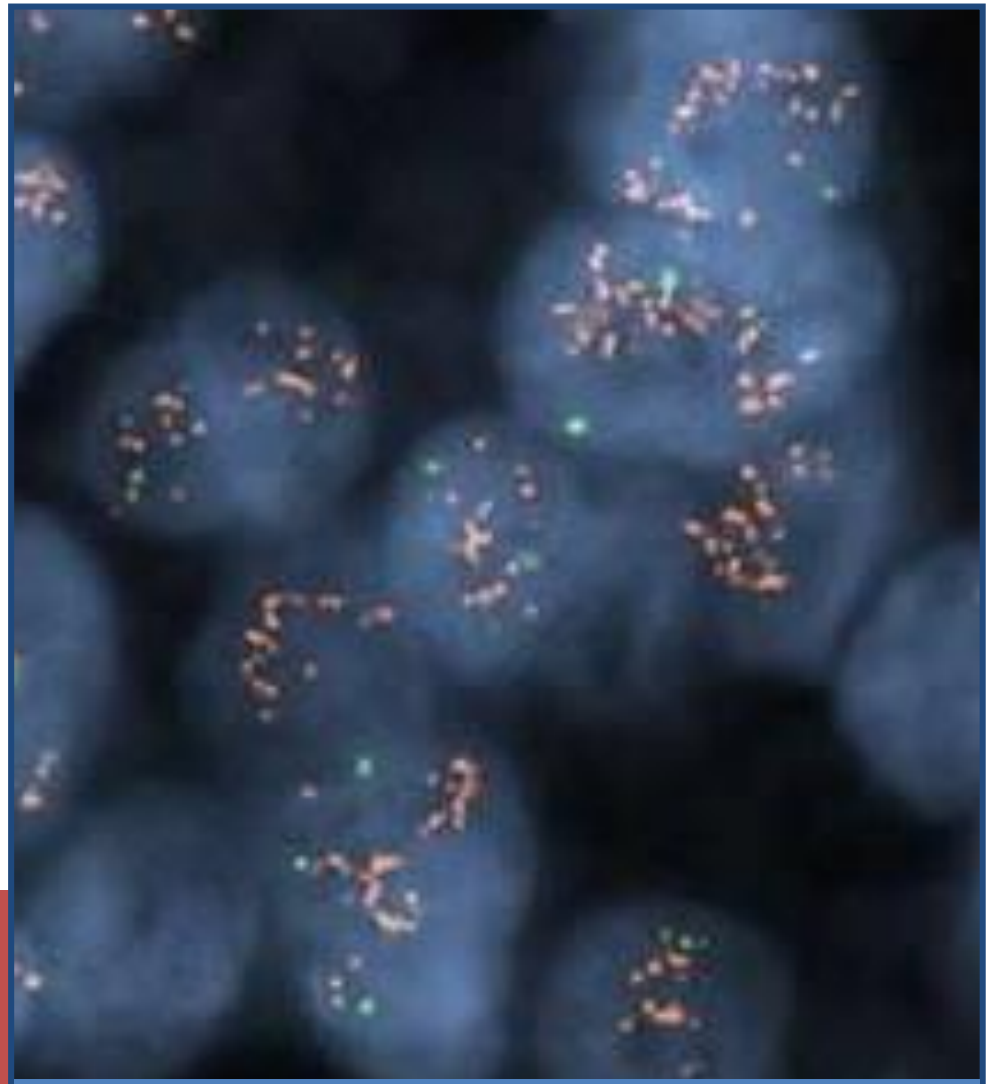
17. kromozomda HER2 gen alanı

(+)

17. kromozom sentromeri

AMPLİFİKASYON ➔ VAR

HER2 / CEP 17 oranı ≥ 2.0



20 neoplastik hücre sayılmalı

- HER2 sinyali (turuncu)
- CEP sinyali (yeşil)

FISH / CISH / SISH

	FISH Amplifikasyon (+)	FISH Amplifikasyon (+)
CISH Amplifikasyon (+)	15	0
CISH Amplifikasyon (+)	0	104

Yan B, *et al.* J Clin Pathol 2011;65:880-883.

	N	(%) uyum (95% CI)
SISH & FISH	241/253	95.3 (91.9 – 97.3)
FISH	84/88	95.5 (88.9 – 98.2)
SISH	157/165	95.2 (90.7 – 97.5)

Powell WC, *et al.* ASCO 2010 Gastrointestinal Cancers Symposium, Orlando; Abstract 17.

Değerlendiren Kişi Sayısı :

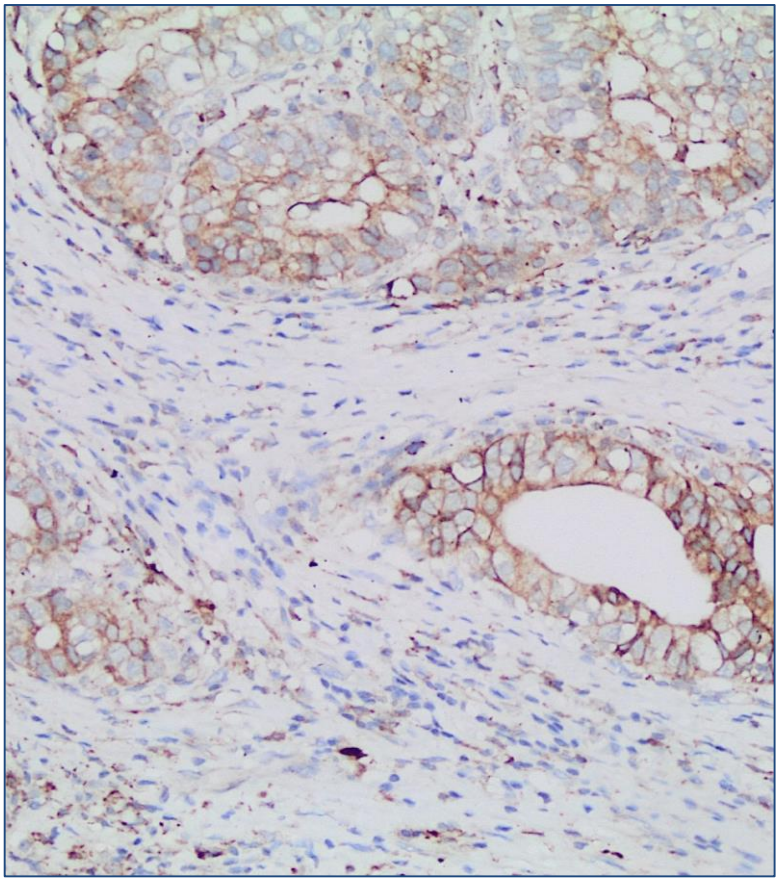
UYGULANAN YÖNTEM : FISH / SISH / CISH
MONO / DUAL işaretleme

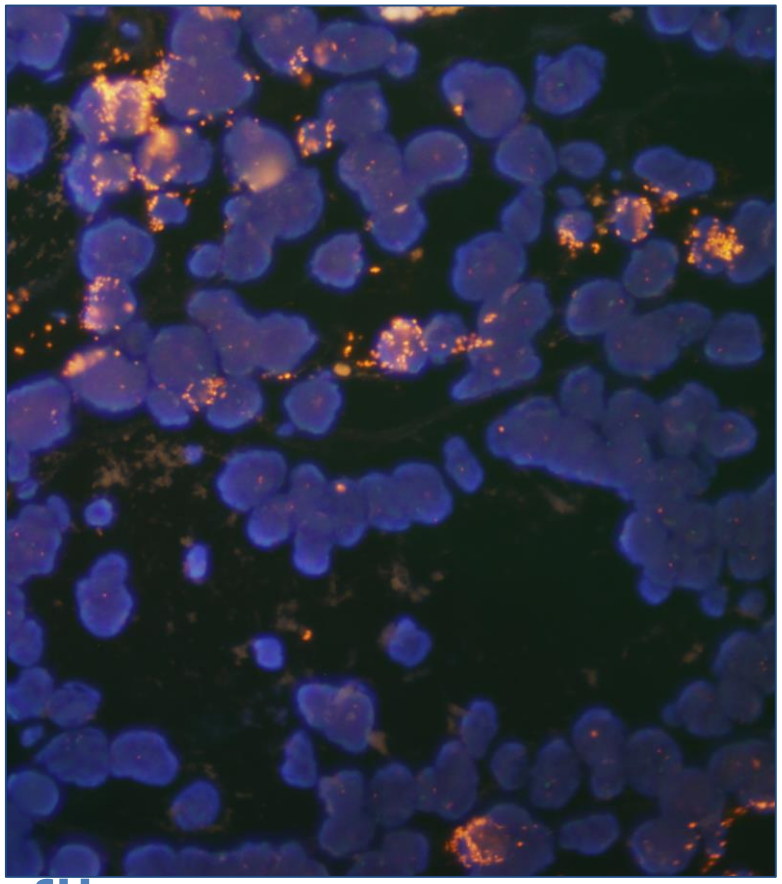
MONO (HER2) İşaretli
Sayılan Neoplastik Hücre Sayısı
Toplam HER2 sinyali
→ HER2 sinyali/hücre sayısı

DUAL (HER2/CEP17)İşaretli
Sayılan Neoplastik Hücre Sayısı
Toplam HER2 sinyali
Toplam CEP17 sinyali
\+ HER2 sinyali/hücre sayısı
CEP17 sinyali / hücre sayısı
→ HER2 / CEP17 sinyal oranı

ISH

YORUM : Amplifikasyon VAR / YOK
EPİKRİZ : Doku değerlendirme açısından yeterli /yetersiz





fiksasyon

Mide Kanseri HER-2

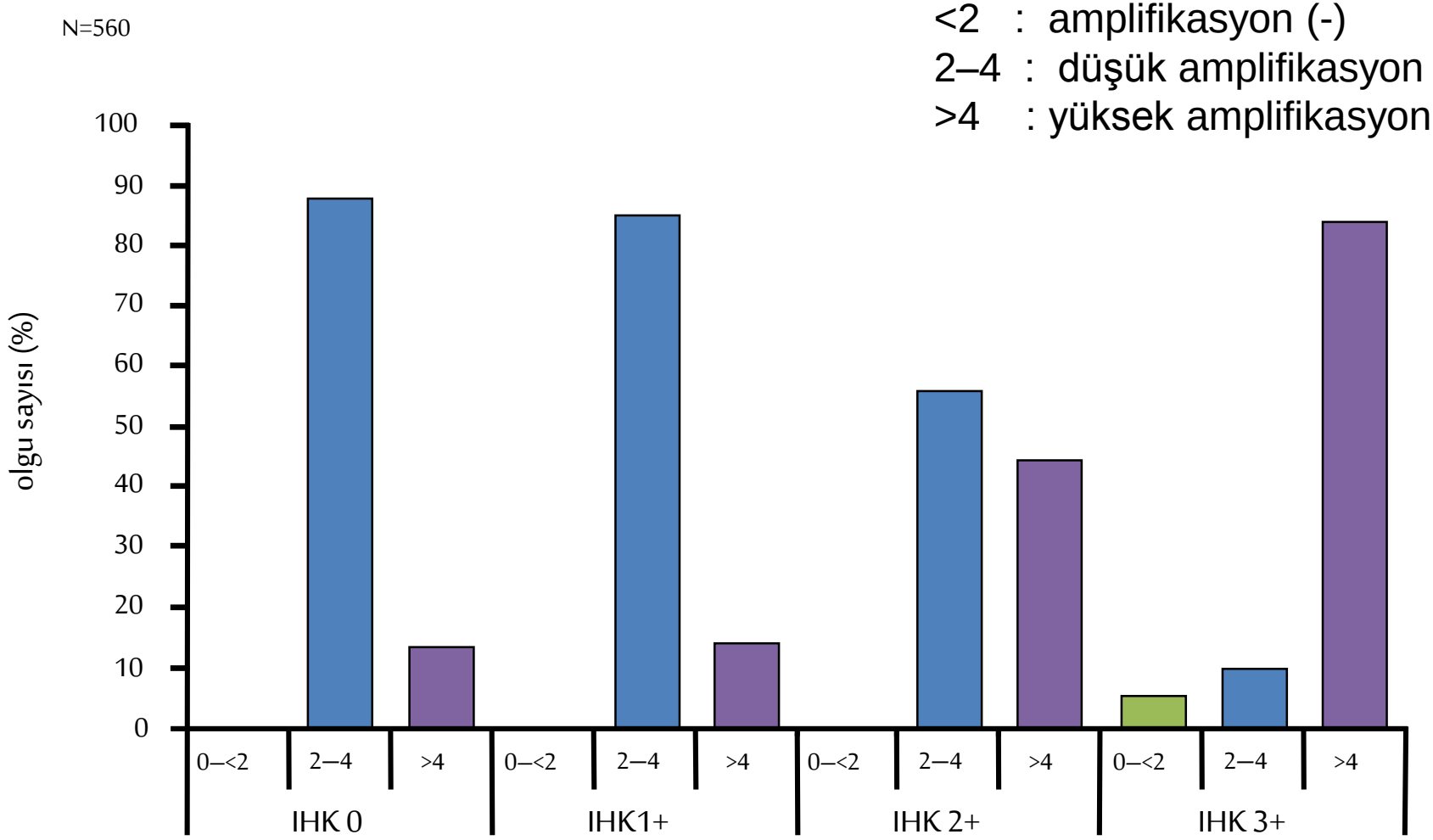
Mide ve GEJ Kanserleri HER2 açısından değerlendirilmeli

ÖNCELİK ?

- İMMUNHİSTOKİMYA
- İN-SİTU HİBRİDİZASYON

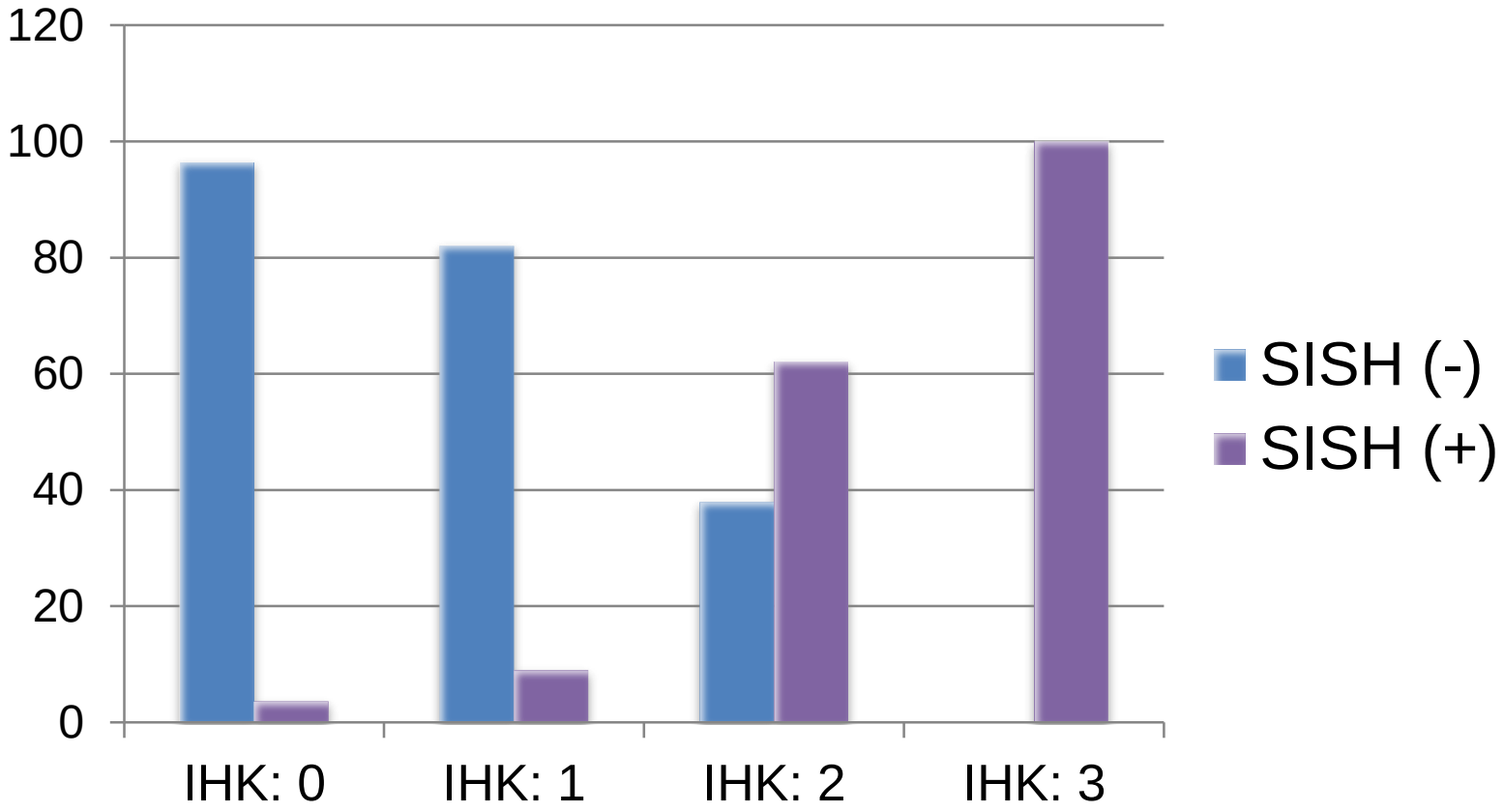
HER2
FISH / immünhistokimya

FISH ORANI
<2 : amplifikasyon (-)
2–4 : düşük amplifikasyon
>4 : yüksek amplifikasyon.



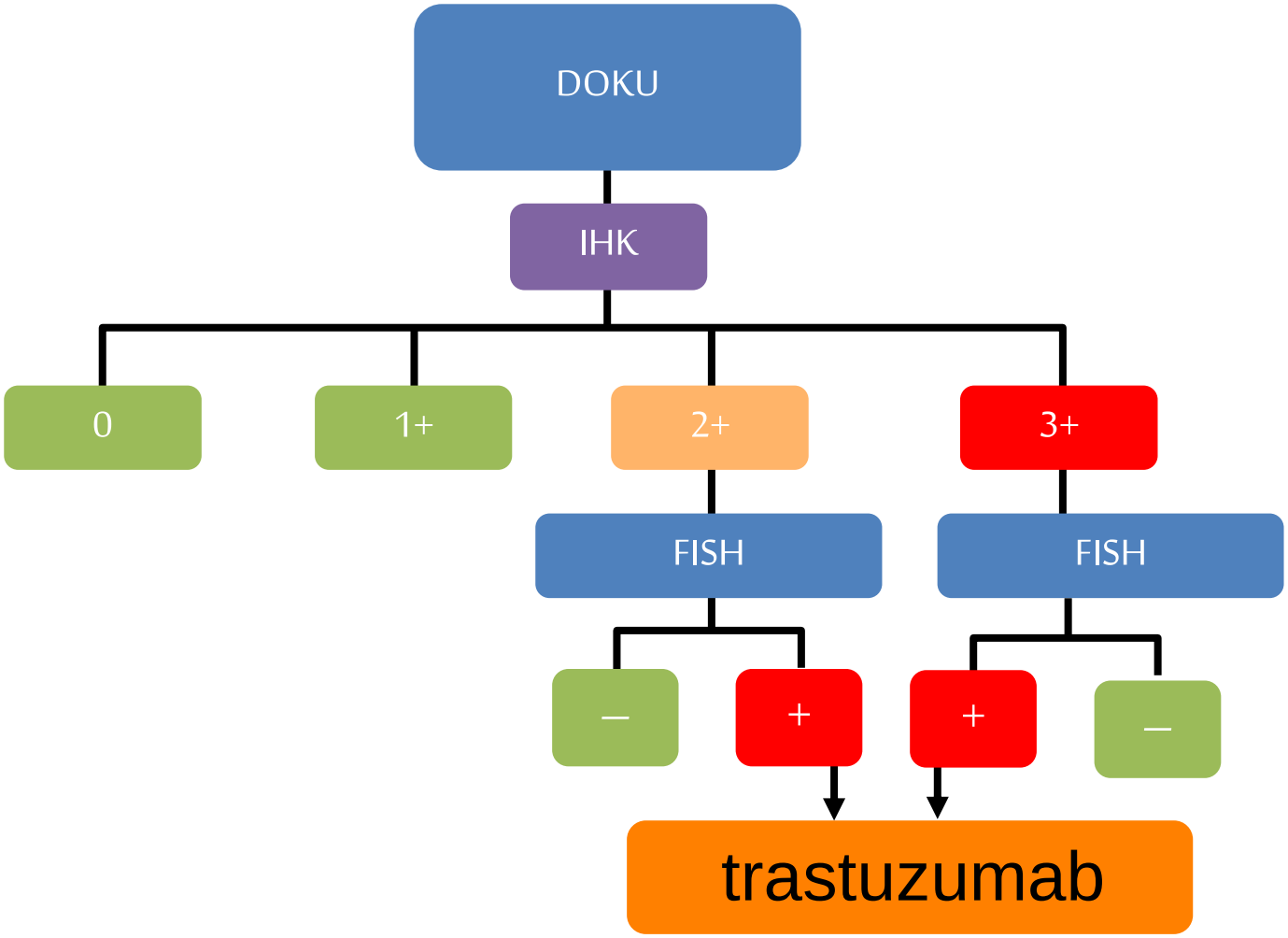
Van Cutsem E, *et al.* ECCO 15/ESMO 34 - Berlin 20-24 September 2009;Abstract 7BA.

HER2
SISH / immünhistokimya

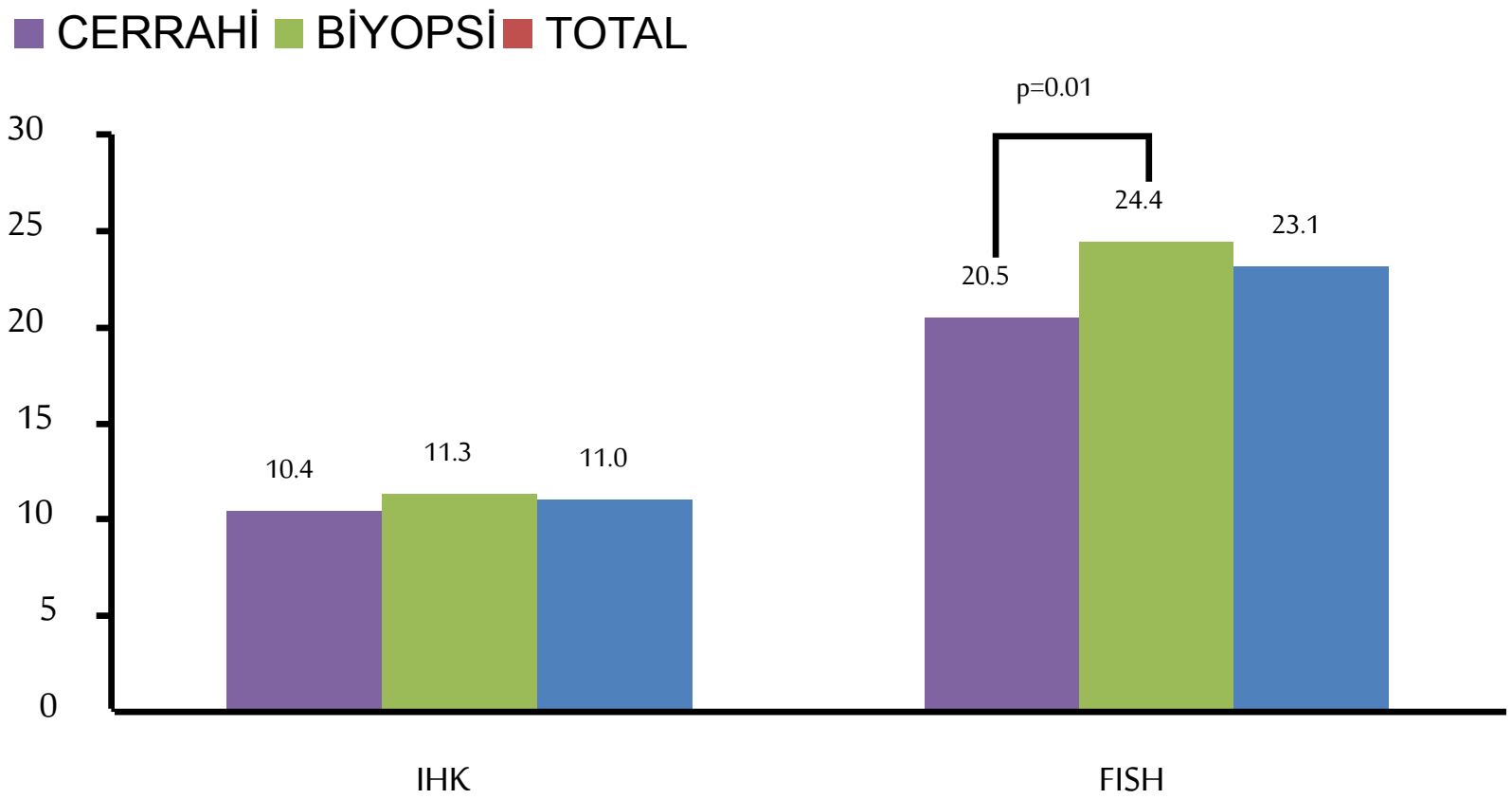


Park YS, *et al*. Human Pathology 2012;43:413-422..

HER2
FISH / immünhistokimya



HER2-positiflik oranları



Bang YJ, *et al. J Clin Oncol* 2009; **27**:Abstract 4556.

IHK / ISH

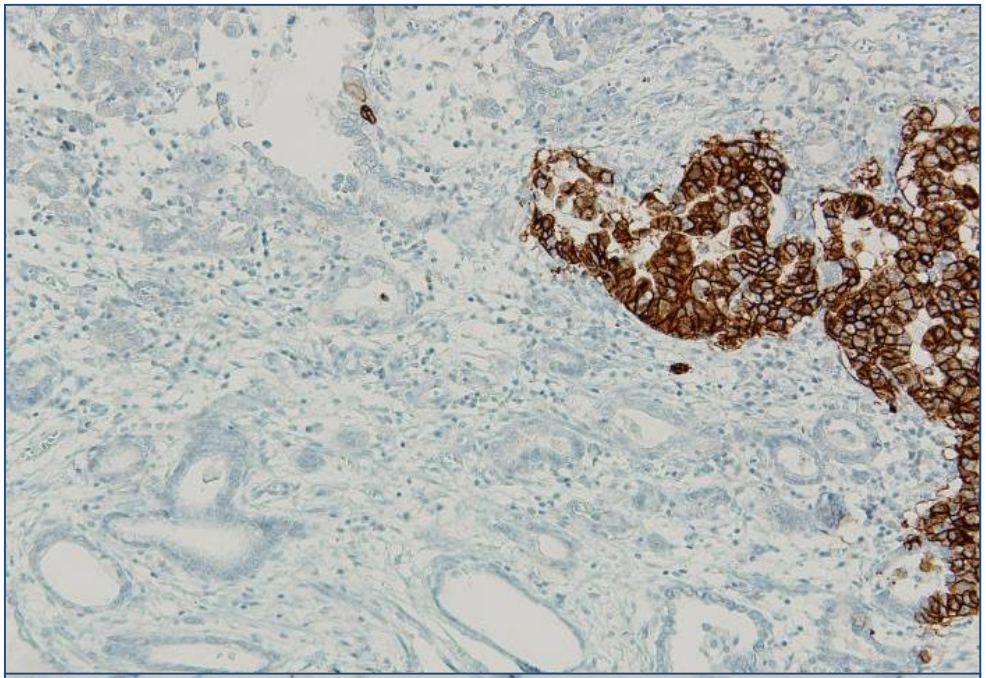
BİYOPSİ

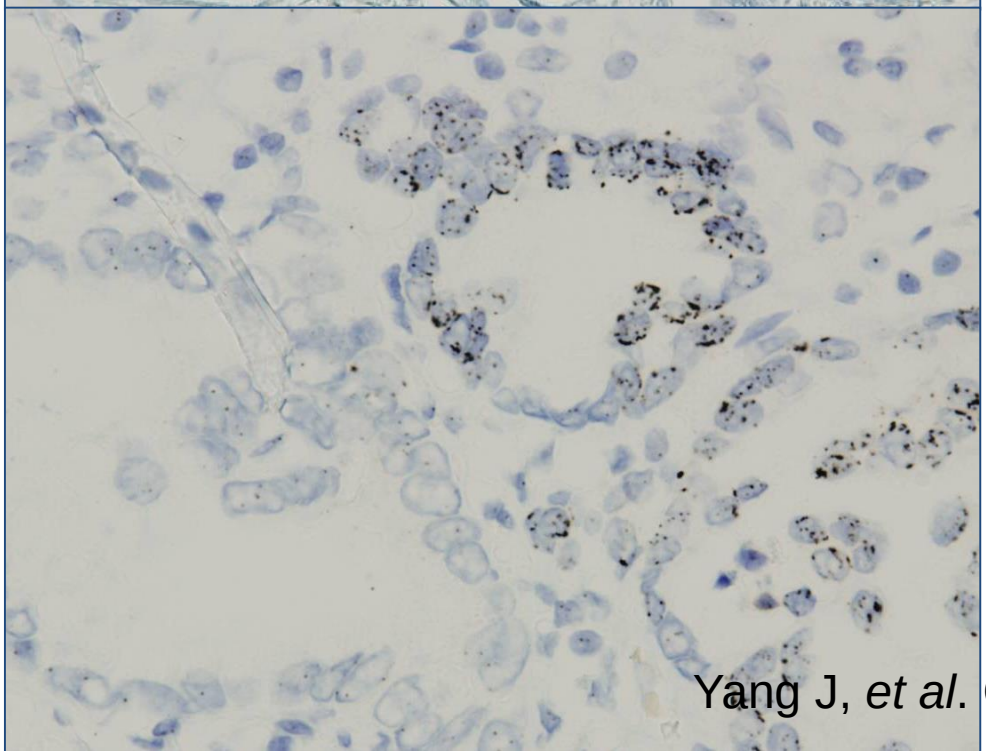
IHK skoru	FISH (+)	FISH (-)	Diskordans
0 / 1 (+) (n=125)	2	123	% 1.6
2 (+) (n=7)	2	5	% 71.4
3 (+) (n=16)	14	2	% 12.5
Total (n=148)	18	16	% 6.1

CERRAHİ SPESMEN

IHK skoru	FISH (+)	FISH (-)	Diskordans
0 / 1 (+) (n=93)	1	5	% 1.1
2 (+) (n=5)	3	2	% 40
3 (+) (n=19)	18	1	% 5.3
Total (n=117)	22	8	% 3.4

Yang J, *et al*. Cell Biochem Biophys 2012;62:221-228.





Mide Kanseri Heterojenite

DİSKORDANS NEDENİ

- Endoskopik bx

IHK / ISH - % 75

- Bx/Cerrahi - %75

HER2 (+)
Cerrahi Spesmenin bx'de saptanabilmesi

- Yalnız IHK - % 45.5
- IHK (+) ISH - % 81.8

Yang J, *et al*. Cell Biochem Biophys 2012;62:221-228.

Annals of Oncology 24: 725–733, 2013
doi:10.1093/annonc/mds528
Published online 8 November 2012

Her2/neu testing in gastric cancer: evaluating the risk of sampling errors

V. S. Warneke[1,†], H.-M. Behrens[1,2,†], C. Böger[1], T. Becker[3], F. Lordick[4], M. P. A. Ebert[5] & C. Röcken[1*]

[1]*Department of Pathology, Christian-Albrechts University, Kiel;* [2]*Department of Pathology, Charité University Hospital, Berlin;* [3]*Department of General Surgery and Thoracic Surgery, Christian-Albrechts University, Kiel;* [4]*University Cancer Centre Leipzig, University of Leipzig, Leipzig;* [5]*Department of Medicine II, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Mannheim, Germany*

Subject	Comparing	Contingency table	p-value of Fisher's exact test	Kappa	p-value of Kappa
Her2/neu-status of whole section	Observer 1 versus Observer 2	Whole Section Her2 status / Observer 2: negative / positive / Total Observer 1 negative: 416 / 1 / 417 Observer 1 positive: 0 / 37 / 37 Total: 416 / 38 / 454	<0.001	98.5%	<0.001
Her2/neu-status of TMA	Observer 1 versus Observer 2	TMA Her2 status / Observer 2: negative / positive / Total Observer 1 negative: 417 / 1 / 418 Observer 1 positive: 1 / 27 / 28 Total: 418 / 28 / 446	<0.001	96.2%	<0.001
Her2/neu-status of Observer 1	Whole section versus TMA	Observer 1 / TMA Her2 status: negative / positive / Total Whole Section Her2 status negative: 409 / 3 / 412 Whole Section Her2 status positive: 9 / 25 / 34 Total: 418 / 28 / 446	<0.001	79.2%	<0.001
Her2/neu-status of Observer 2	Whole section versus TMA	Observer 2 / TMA Her2 status: negative / positive / Total Whole Section Her2 status negative: 409 / 2 / 411 Whole Section Her2 status positive: 9 / 26 / 35 Total: 418 / 28 / 446	<0.001	81.2%	<0.001
Her2/neu-IHC score of Observer 1	Whole section versus TMA	Observer 1 / TMA IHC score: 0 / 1+ / 2+ / 3+ / Total Whole section IHC score 0: 363 / 15 / 4 / 0 / 382 1+: 16 / 5 / 0 / 0 / 21 2+: 6 / 5 / 3 / 0 / 14 3+: 4 / 1 / 7 / 17 / 29 Total: 389 / 26 / 14 / 17 / 446	X^2: <0.001	47.3 %	<0.001
Her2/neu-IHC score of Observer 2	Whole section versus TMA	Observer 2 / TMA IHC score: 0 / 1+ / 2+ / 3+ / Total Whole section IHC score 0: 352 / 17 / 1 / 2 / 372 1+: 23 / 6 / 0 / 0 / 29 2+: 6 / 6 / 5 / 2 / 19 3+: 4 / 1 / 5 / 16 / 26 Total: 385 / 30 / 11 / 20 / 446	X^2: <0.001	44.8 %	<0.001

TMA denotes tissue micro array and IHC immunohistochemistry

ISH

IHK

Cerrahi Spesmen / Biyopsi

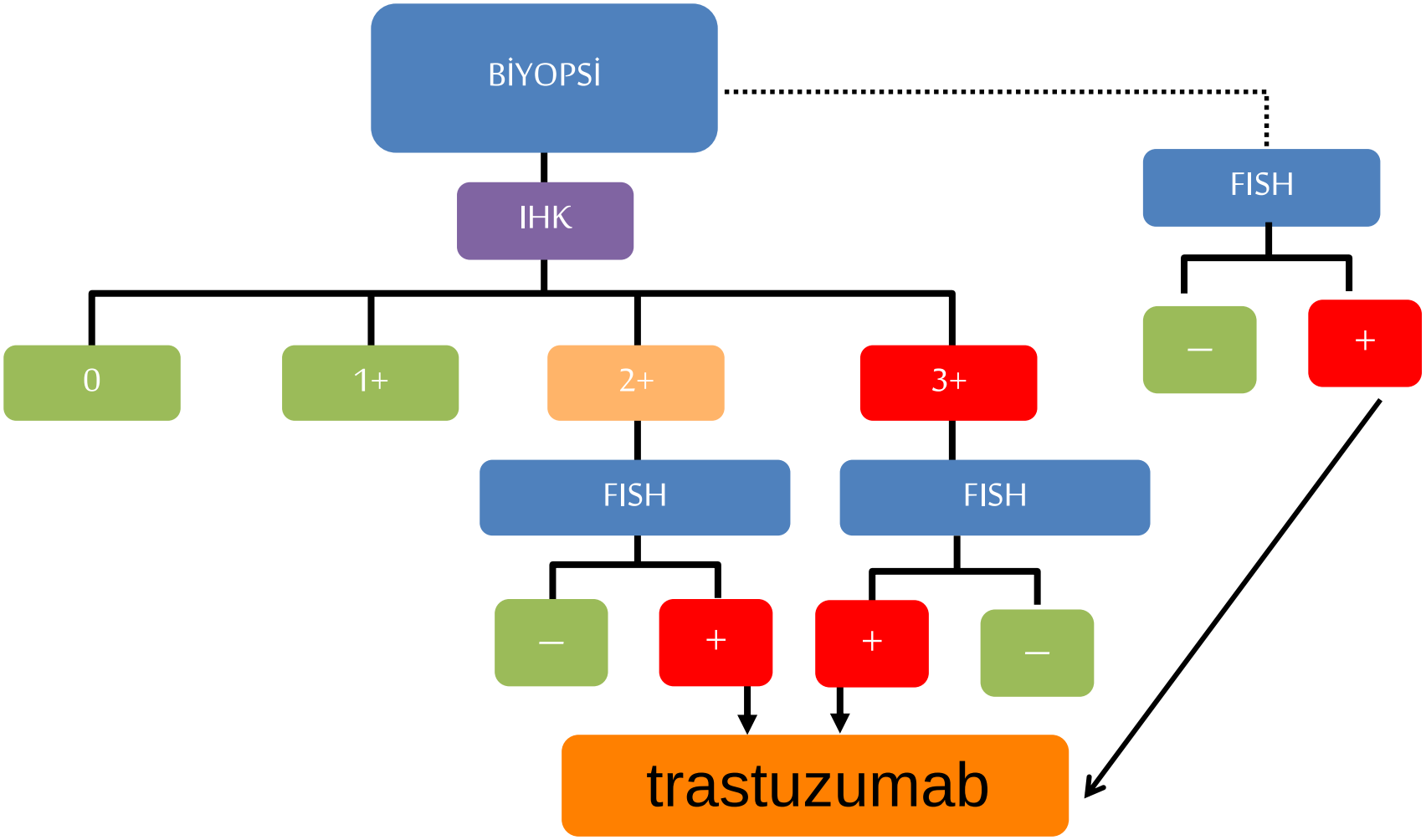
- Gözlemciler arası uyum yüksek
- Biyopsi / cerrahi spesmen uyumu düşük

Biyopsi ile;

yanlış (+) oranı : %3

yanlış (-)oranı : % 24

HER2
FISH / immünhistokimya

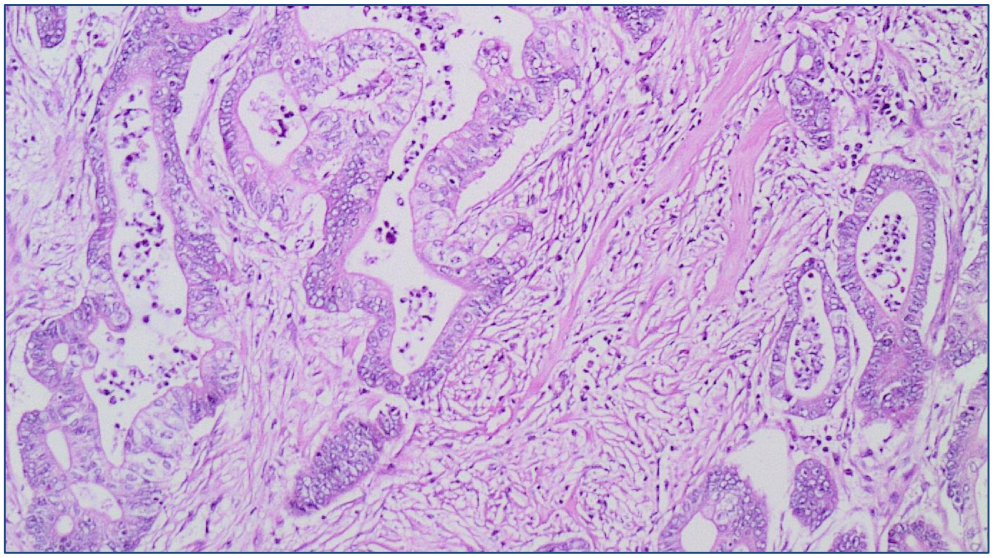


HER2 /neu

Prognostik Faktör

- Histolojik Alt Tip (intestinal > diffüz)
- Yüksek Grade
- Lenfovasküler İnvazyon
- Lenf Nodu Metastazı

Kim KC,. Ann Surg Oncol 2011;18:2833-40.



Annals of Oncology 24: 693–701, 2013
doi:10.1093/annonc/mds506
Published online 6 November 2012

A clinical–biological risk stratification model for resected gastric cancer: prognostic impact of Her2, Fhit, and APC expression status

E. Bria[1,2], G. De Manzoni[3], S. Beghelli[1], A. Tomezzoli[4], S. Barbi[4], C. Di Gregorio[5], M. Scardoni[1,4], E. Amato[1], M. Frizziero[2], I. Sperduti[6], V. Corbo[1], M. Brunelli[4], S. Bersani[1,4], G. Tortora[2,†] & A. Scarpa[1,4*,†]

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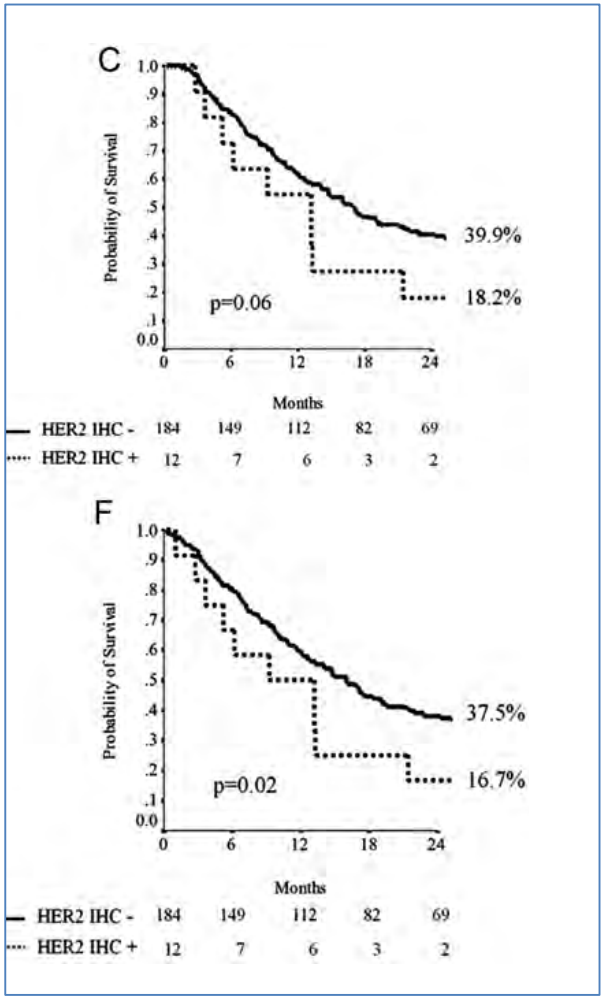
cancer spesific survival



overall survival

HER2 immüneksprесyonu (% 5.8)

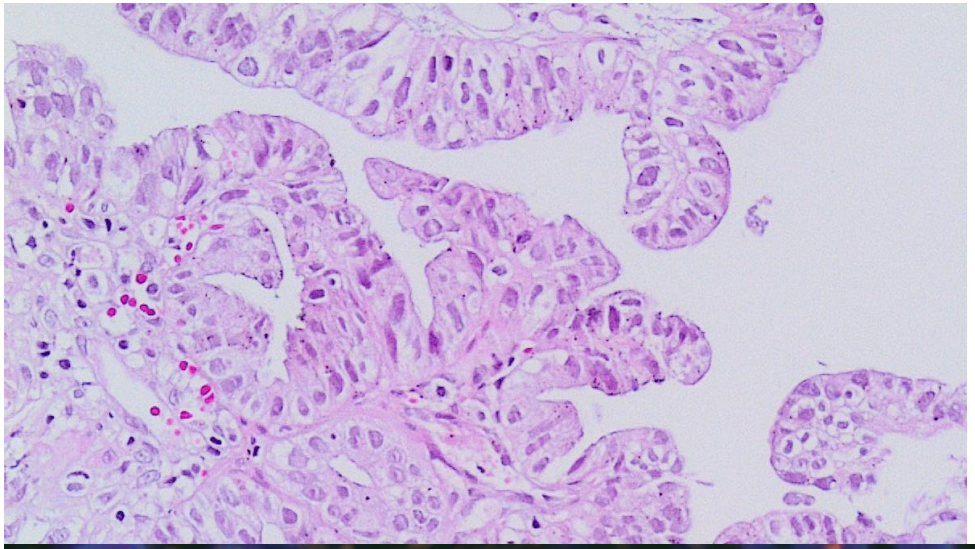
BAĞIMSIZ PROGNOSTİK FAKTÖR

HER2 gen amplifikasyonu (% 7.7)

PROGNOZLA İLİŞKİSİZ

Mide Kanseri HER2/neu (cerbB2)

MÜTF

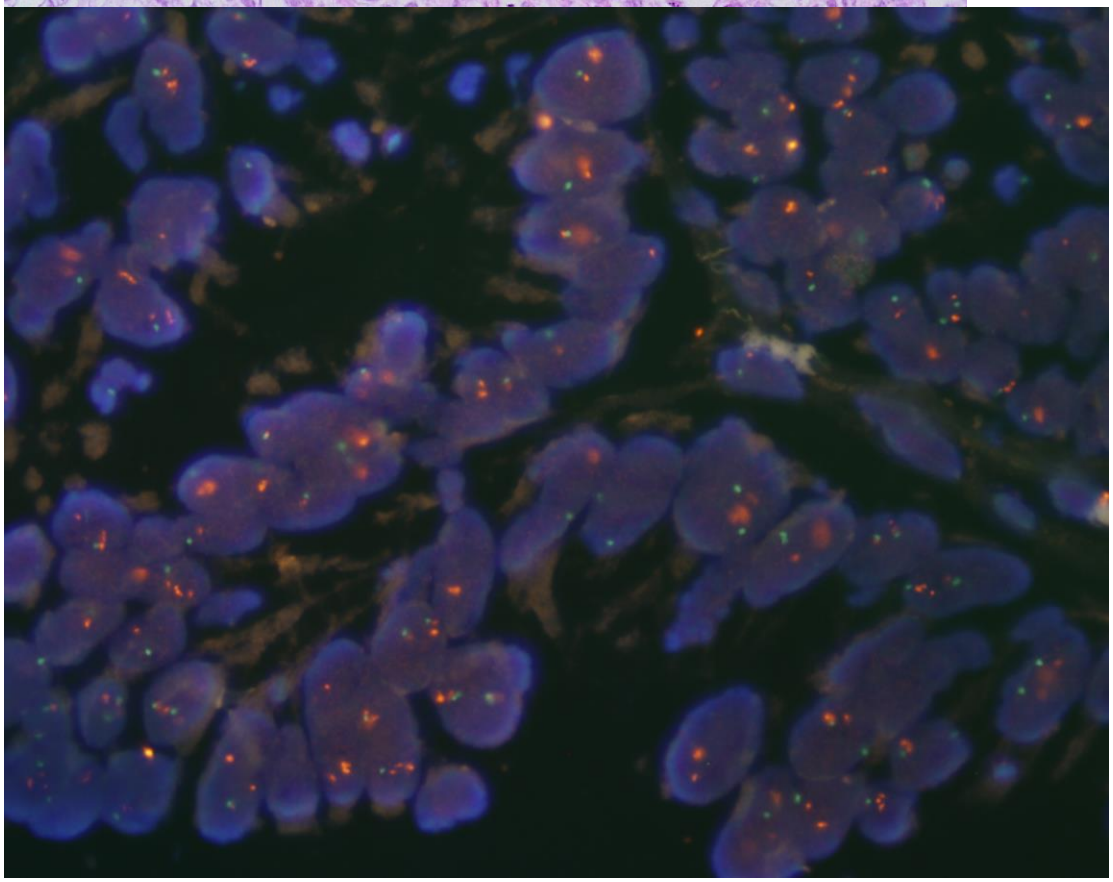


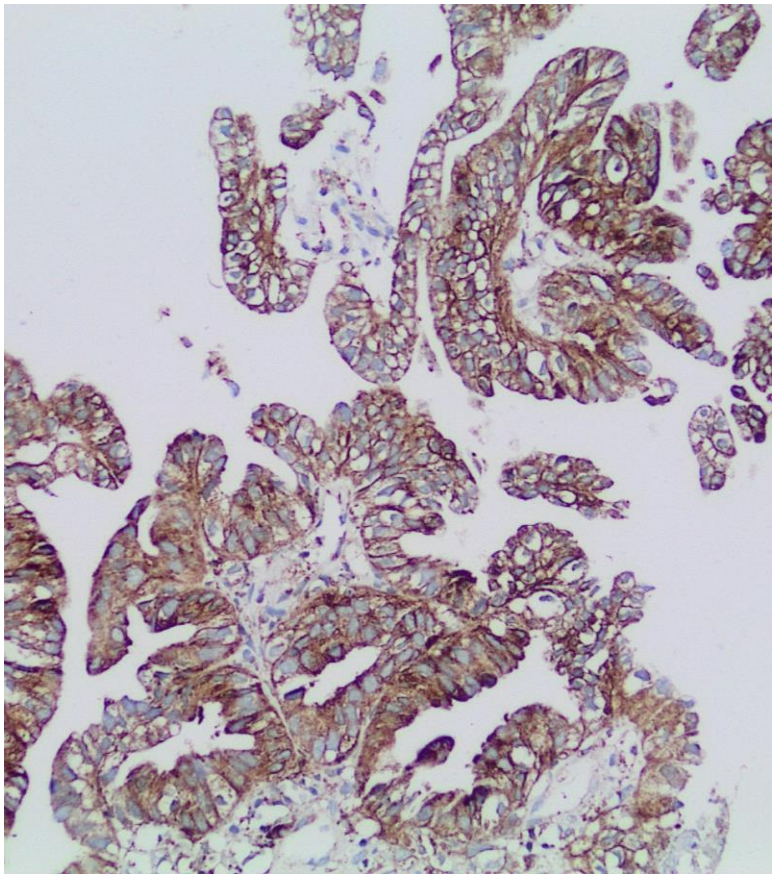
47 biyopsi

% 8.6 IHK (+)

IHK (+) tüm biyopsiler

FISH (+)

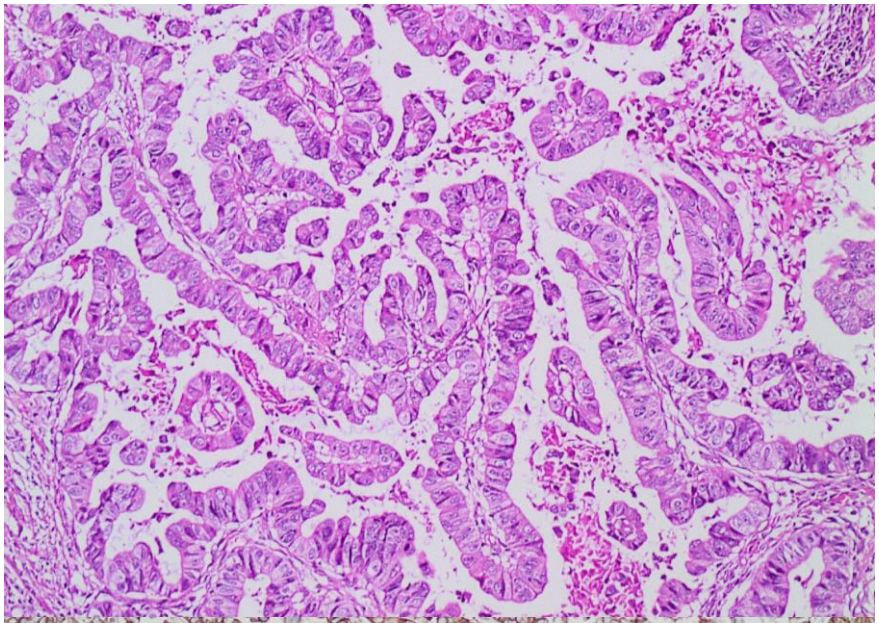


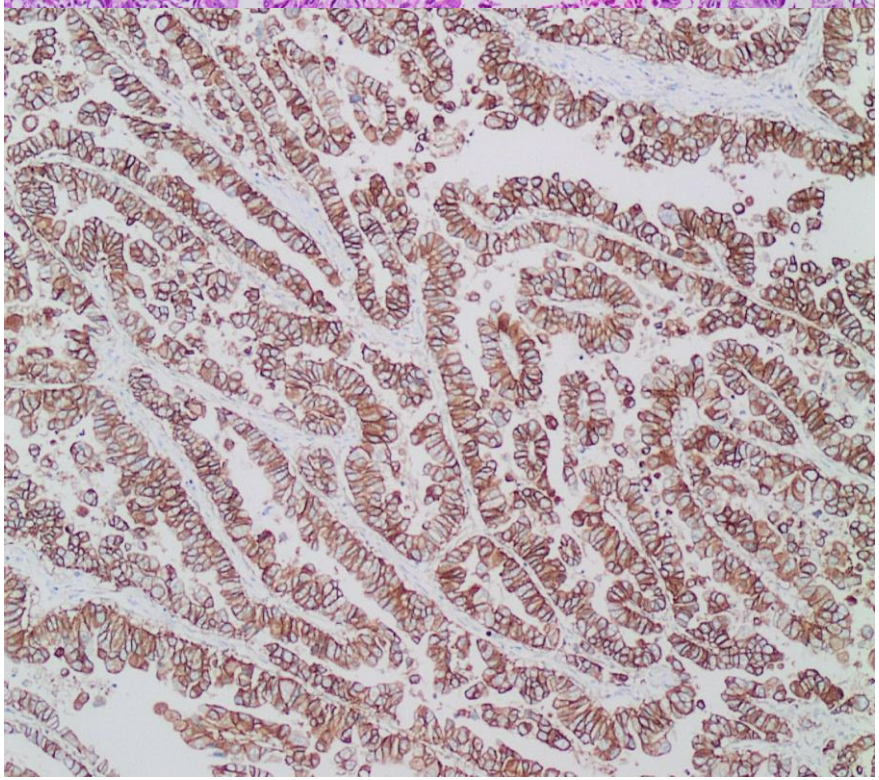


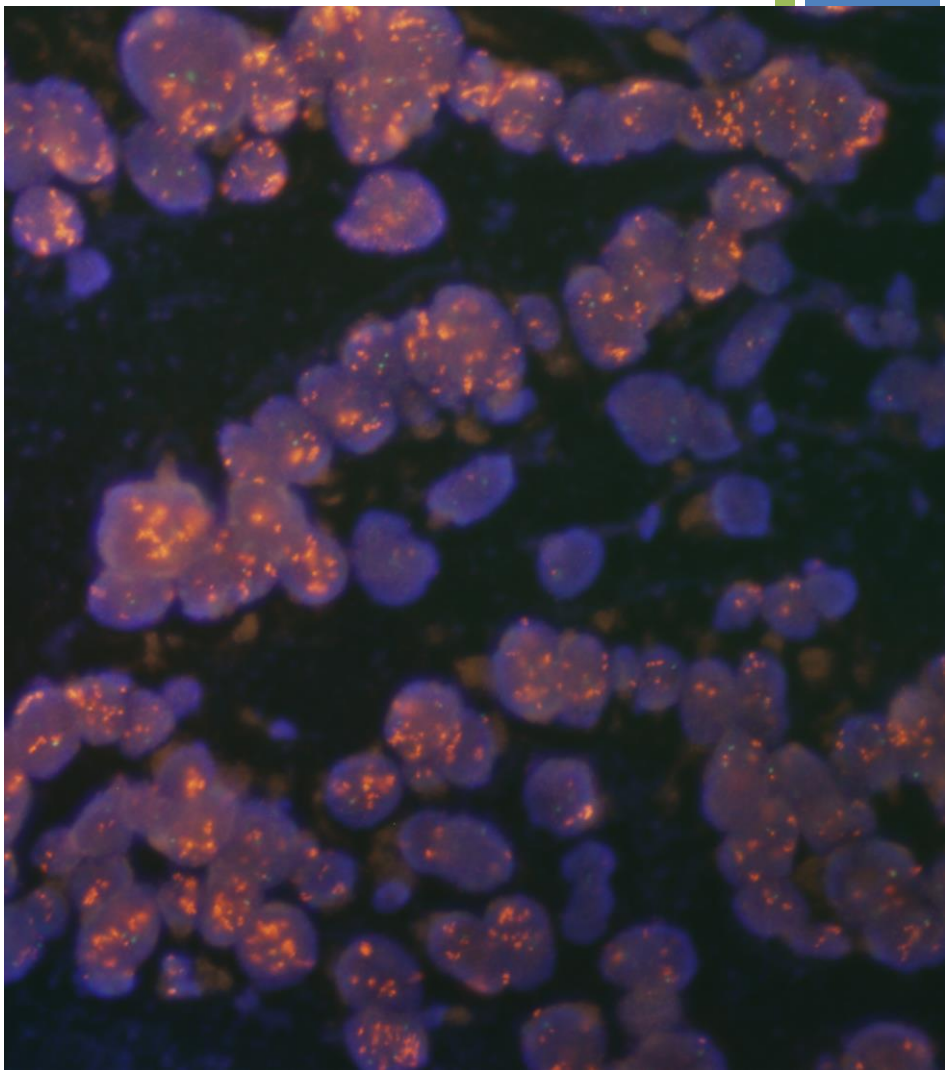
160 rezeksiyon spesmeni

% 11.2 IHK (+)

IHK (+) 1 olguda FISH (-)





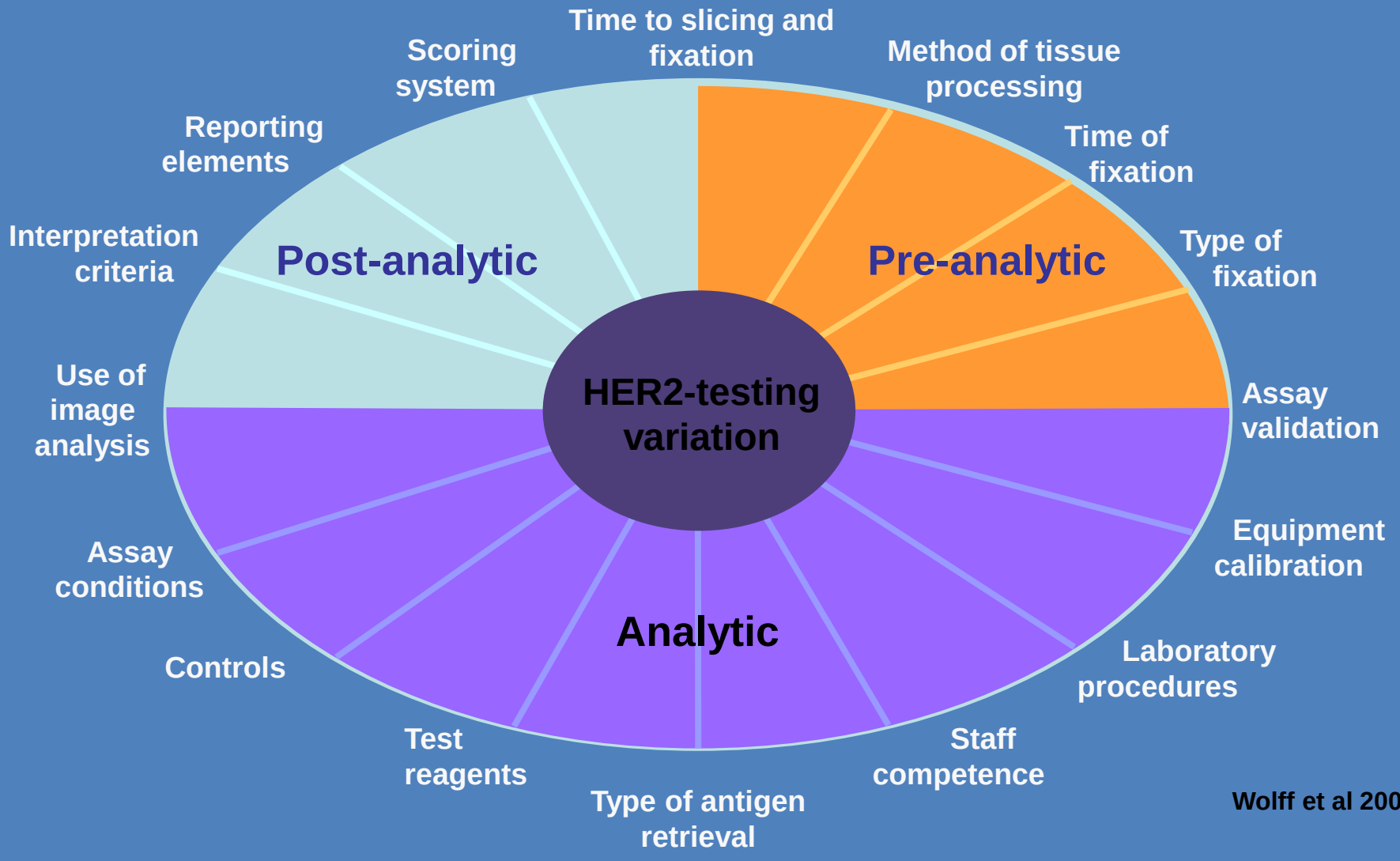


Mide Kanseri

Moleküler Genetik değerlendirme ve RAPORLAMA

- HER2/neu (cerbB2)

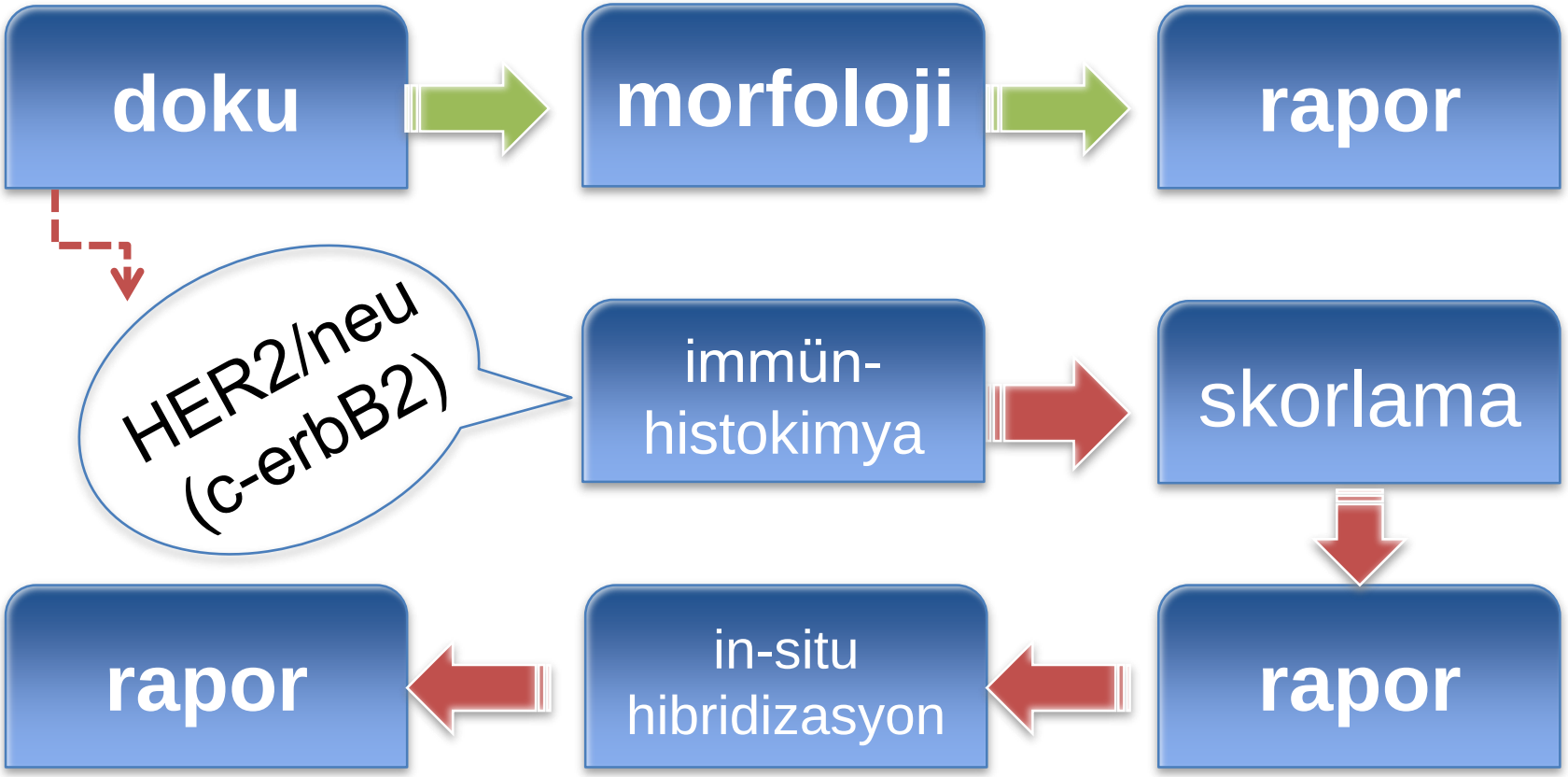
HER2



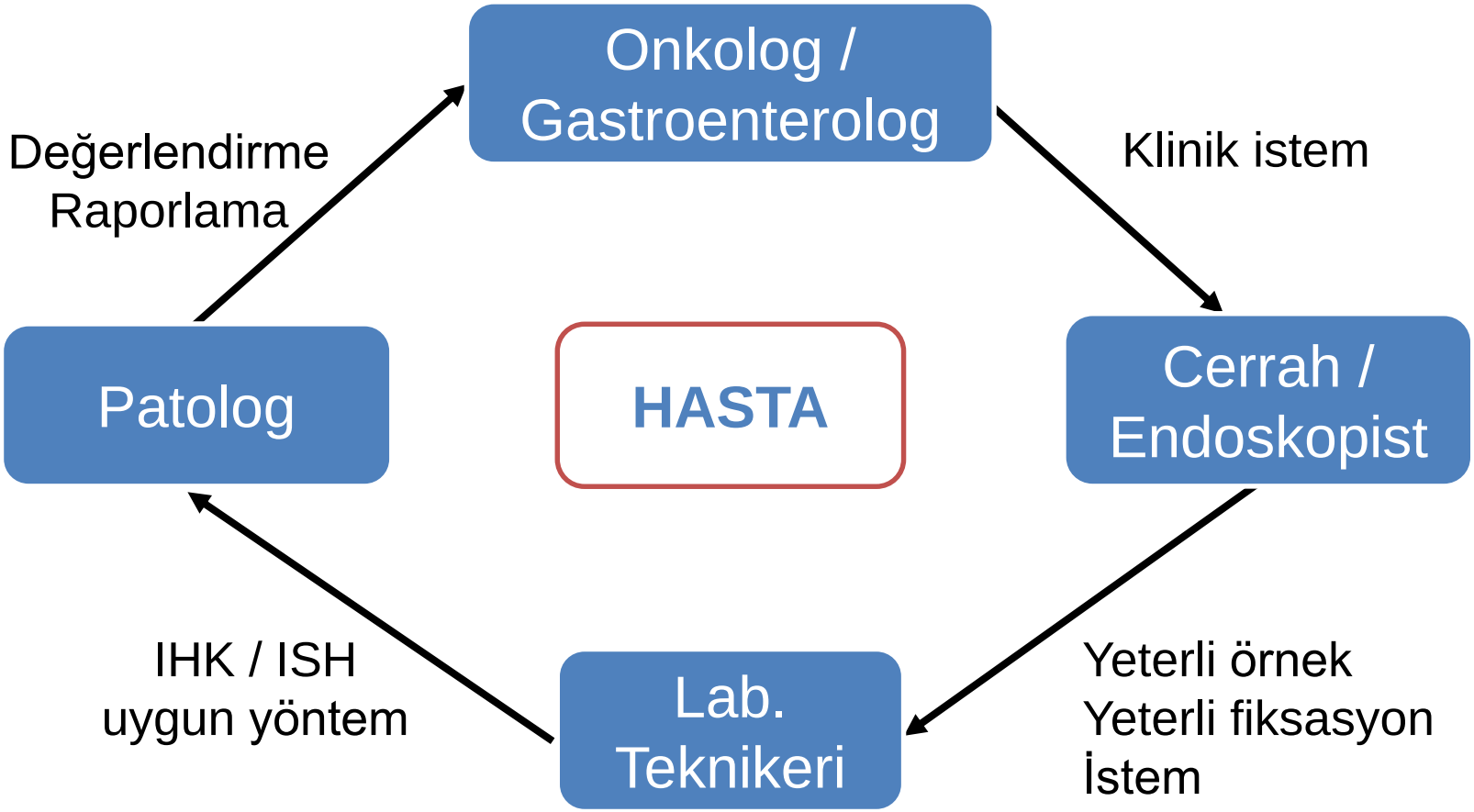
Wolff et al 2007

patoloji/ moleküler genetik raporu

5 İŞ GÜNÜ



MULTİDİSİPLİNER YAKLAŞIM



Mide Kanseri

Moleküler Genetik değerlendirme ve RAPORLAMA

- HER2/neu (cerbB2)
- Herediter Diffüz Gastrik Karsinom

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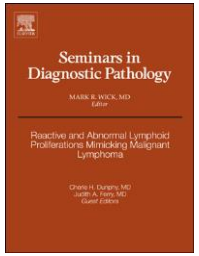

Contributions of molecular analysis to the diagnosis and treatment of gastrointestinal neoplasms

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ARTICLE INFO

Keywords:
Gastrointestinal neoplasia
Molecular diagnostics
Hereditary cancer predisposition syndrome
Predictive testing
HER2
KRAS

ABSTRACT

This review discusses the role of molecular analysis in the diagnosis and treatment of gastrointestinal (GI) neoplasms. It is divided into 3 sections. The first section describes clinical applications of 11 immunohistochemical stains (p53, HER2, KIT, SDHB, SMAD4, beta-catenin, L-FABP, MLH1, PMS2, MSH2, and MSH6), the results of which directly reflect underlying genetic or epigenetic events. These applications are mainly diagnostic but in a few instances are predictive. Germline mutation testing is a diagnostic cornerstone in the hereditary cancer predisposition syndromes (HCPSs). Section two will describe the genotype and phenotype of 8 HCPSs presenting in the GI tract. Where available, guidelines based on evidence and/or expert opinion as to whom to test are presented. With our ever-expanding knowledge of the molecular genetic basis of cancer and an increasingly "biologic-oriented" therapeutic armamentarium, pathologists play a vital role in directing molecular-based predictive testing. The final section will discuss the 4 most mature examples in the GI tract: (1) HER2 testing to select patients with advanced gastroesophageal adenocarcinoma for anti-HER2 therapy, (2) *KIT* and *PDGFRA* mutation analysis to direct tyrosine kinase inhibitor therapy in gastrointestinal stromal tumor, (3) DNA mismatch repair function testing to determine the applicability of adjuvant chemotherapy in patients with stage II colorectal cancer (CRC), and (4) *KRAS* mutation analysis and related testing to determine the appropriateness of anti-EGFR monoclonal antibody therapy in patients with metastatic CRC.

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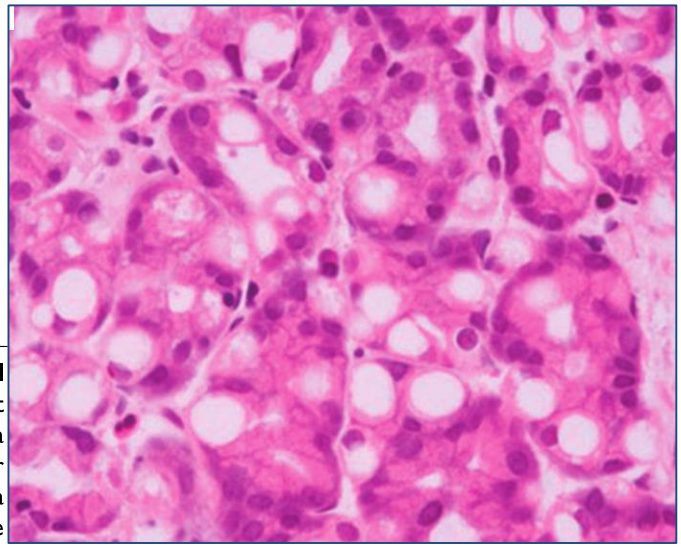
Case Report

Hereditary Diffuse Gastric Cancer: A Family Diagnosis and Treatment

Adedayo A. Onitilo, MD, MSCR, FACP; Govinda Aryal, MD; and Jessica M. Engel, MS, RN



Hereditary diffuse gastric cancer (HDGC) is a rare cancer representing approximately 2% of all gastric cancers. It is caused by CDH1 gene mutations, inherited in an autosomal dominant fashion, that affect the function of E-cadherin. Approximately 38% of HDGC families have a CDH1 gene mutation. With an estimated 75% penetrance rate, carriers are at high risk for HDGC. We describe the case of a Caucasian male of German-Russian ancestry, carrying a CDH1 gene mutation, who survived for 18 months after being diagnosed with HDGC. The results of genetic testing undergone by his family members are also reported, along with a review of the current literature. Since surveillance methods for HDGC are ineffective and unreliable, total prophylactic gastrectomy is advised for individuals with the gene mutation. Additionally, a diagnosis of HDGC should lead to genetic evaluation of family members followed by preventative measures.

Keywords: CDH1 gene mutation; E-cadherin; Genetic testing; High disease expression; Prophylactic gastrectomy

- CDH1 germline mutasyon ➔ **E-Cadherin**
- Otozomal Dominant
- Mide Taşlı Yüzük Hücreli Karsinom
- Meme Lobüler Karsinom

} Risk ↑

GELECEK …

moleküler genetik

- Tümör supressör gen

  p53, p16, APC, Rb, DCC
- “mismatch” tamir genleri
- Onkojenler

  siklin D1
- Büyüme faktör ve reseptörleri

  EGFR, TGF-α, c-erbB2, c-met
- Hücre adhezyon molekülleri

  E-cadherin, α- /β-catenin

Amplifikasyon

HER2, FGFR2, EGFR, c-MET

Mutasyon

HER2, KRAS, PIK3, BRAF

Gen Rearanjmanı

SLC34-*ROS1* (%0.5-1)
(ALK ile homolog)
AGTRAP-*BRAF*
SND1-*BRAF*
CDK12-*ERBB2*
NECROD2-*ERBB2*

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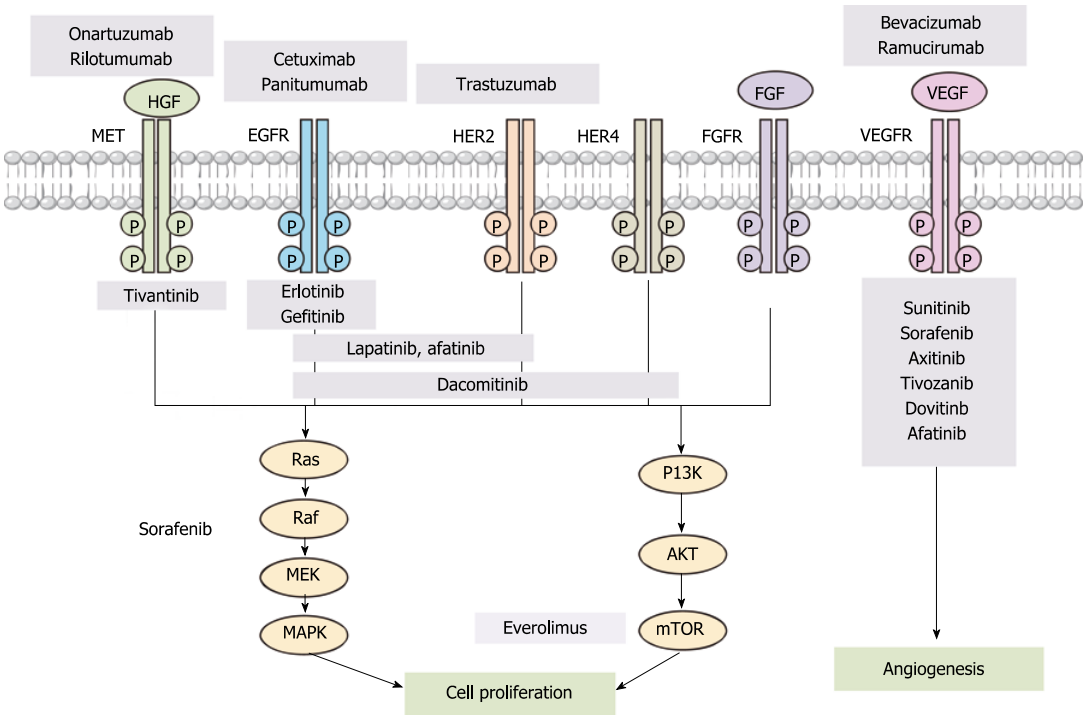
Targeted therapy in gastric cancer: Personalizing cancer treatment based on patient genome

Sun Min Lim, Jae Yun Lim, Jae Yong Cho



HÜCRE RESEPTÖRLERİ
HER2 mutasyonu (% 5)
EGFR
VEGFR

HÜCRE İÇİ SİNYAL İLETİ
Fosfoinositid- kinaz (%5-7)
mTOR
HER4 kinaz (%1.7)
KRAS (%4.1)
BRAF (% 1.6)- $V600^{M}$

ANGİOGENEZ
VEGFR-1
VEGFR-2

microRNA

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The role of microRNAs in cancers of the upper gastrointestinal tract

Shumei Song and **Jaffer A. Ajani**
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Interrelationship between microsatellite instability and microRNA in gastrointestinal cancer

Hiroyuki Yamamoto, Yasushi Adachi, Hiroaki Taniguchi, Hiroaki Kunimoto, Katsuhiko Nosho, Hiromu Suzuki, Yasuhisa Shinomura

Kanser Kök Hücre

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PLOS ONE

Prognostic Value of CD166 Expression in Cancers of the Digestive System: A Systematic Review and Meta-Analysis

Chao Ni[1☯], Zhigang Zhang[1☯], Xiaotao Zhu[1], Yang Liu[1], Dihong Qu[1], Ping Wu[1], Jian Huang[1,2*], A-xiang Xu[3*]

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PLOS ONE

Prognostic Value of Cancer Stem Cell Marker CD133 Expression in Gastric Cancer: A Systematic Review

Lei Wen, Xin-Zu Chen, Kun Yang, Zhi-Xin Chen, Bo Zhang, Jia-Ping Chen, Zong-Guang Zhou, Xian-Ming Mo, Jian-Kun Hu*

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Kök Hücre

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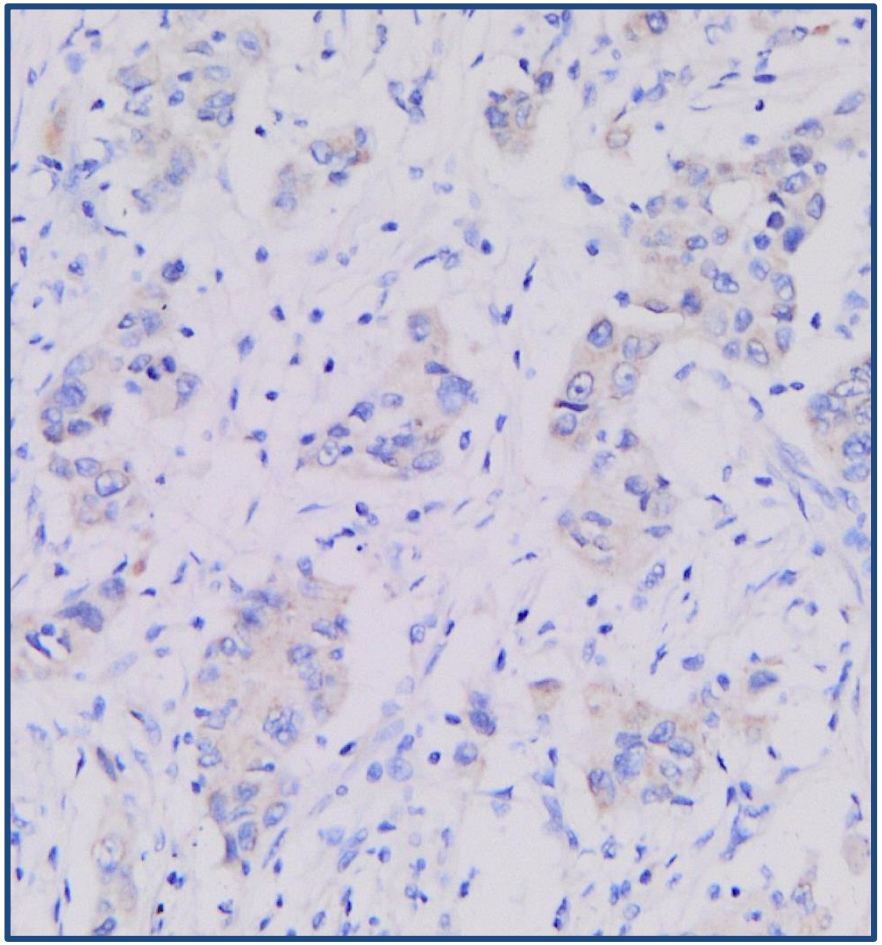
BRIEF ARTICLE

Intestinal stem cell marker LGR5 expression during gastric carcinogenesis

Zhi-Xue Zheng, Yu Sun, Zhao-De Bu, Lian-Hai Zhang, Zi-Yu Li, Ai-Wen Wu, Xiao-Jiang Wu, Xiao-Hong Wang, Xiao-Jing Cheng, Xiao-Fang Xing, Hong Du, Jia-Fu Ji

Table 3 LGR5 expression in gastric cancer tissues of various differentiation *n* (%)

Tissue	LGR5 expression		*P* value
	Negative	Positive	
Intestinal metaplasia	25 (27.8)	65 (72.2)	0.000
Normal tissue	106 (73.1)	39 (26.9)	
Dysplasia with IM			0.004
Yes	3 (18.8)	13 (81.2)	
No	23 (62.2)	14 (37.8)	
Lauren type			0.035
Intestinal	48 (41.4)	68 (58.6)	
Diffuse/other	37 (57.8)	28 (42.2)	
Intestinal type GC			0.019
Metastasis or recurrence	6 (12.5)	21 (31.3)	
No metastasis or recurrence	42 (87.5)	46 (68.7)	



jgc
J Gastric Cancer 2013;13(3):129-135 • http://dx.doi.org/10.5230/jgc.2013.13.3.129 Review Article

Molecular Diagnosis for Personalized Target Therapy in Gastric Cancer

Jae Yong Cho

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Gastric cancer is the second leading cause of cancer-related deaths worldwide. In advanced and metastatic gastric cancer, the conventional chemotherapy with limited efficacy shows an overall survival period of about 10 months. Patient specific and effective treatments known as personalized cancer therapy is of significant importance. Advances in high-throughput technologies such as microarray and next generation sequencing for genes, protein expression profiles and oncogenic signaling pathways have reinforced the discovery of treatment targets and personalized treatments. However, there are numerous challenges from cancer target discoveries to practical clinical benefits. Although there is a flood of biomarkers and target agents, only a minority of patients are tested and treated accordingly. Numerous molecular target agents have been under investigation for gastric cancer. Currently, targets for gastric cancer include the epidermal growth factor receptor family, mesenchymal-epithelial transition factor axis, and the phosphatidylinositol 3-kinase–AKT–mammalian target of rapamycin pathways. Deeper insights of molecular characteristics for gastric cancer has enabled the molecular classification of gastric cancer, the diagnosis of gastric cancer, the prediction of prognosis, the recognition of gastric cancer driver genes, and the discovery of potential therapeutic targets. Not only have we deeper insights for the molecular diversity of gastric cancer, but we have also prospected both affirmative potentials and hurdles to molecular diagnostics. New paradigm of transdisciplinary team science, which is composed of innovative explorations and clinical investigations of oncologists, geneticists, pathologists, biologists, and bio-informaticians, is mandatory to recognize personalized target therapy.

Key Words: Stomach neoplasms; Therapeutics; Biological markers; Gene expression; Sequence analysis

Introduction

The personalized cancer therapy target aberrations that drive tumor growth and survival, by administering the right drug combination for the right person. Advances in high-throughput technologies such as microarray and next generation sequencing for gene or protein expression profiles and oncogenic signaling pathways have reinforced the discovery of treatment targets and predictive biomarkers. Because of the dramatic advances in genome-scale technologies and analytical tools, the personalized cancer therapy has been attracted oncologists' attention since the 2000s. To exploit informative biomarker is also obligatory to develop target treatment.[1] The DNA-based markers include mutations, single nucleotide polymorphisms (SNPs), chromosomal aberrations, changes in DNA copy number, differential methylation. The RNA-based biomarkers include overexpressed or underexpressed transcripts and microRNAs. The protein markers include growth factors, cell surface receptors, phosphorylation states, and peptides released by tumors into serum. In 1990s, the Human Genome Project that firstly sequenced a human genome, consumed $2,700,000,000 and was completed after 15 years,[2] however, only $1,000 whole genome sequencing is currently available. The era of personal genome sequencing has accelerated personalized target treatment (Fig. 1).

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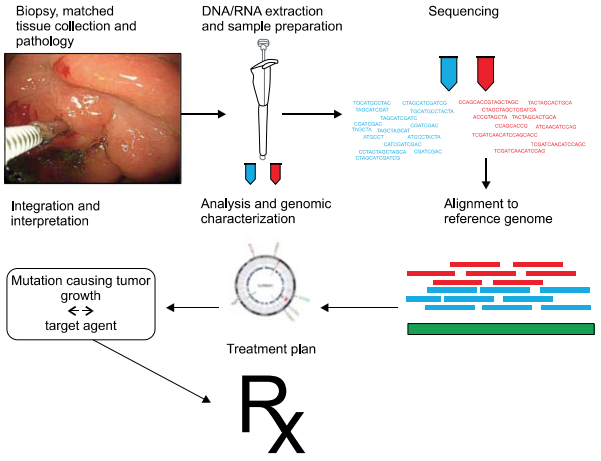

Fig. 1. Fitting the cancer tre
different patients genome.

Paradigma Değişikliği

Mide Kanseri

Kişileştirilmiş Tedavi

Morfolojik/genetik değerlendirmenin sınırlılıkları algılanmalı

GÜZEL BİR GELECEK…