ONKOLOJİ PRATİĞİNDE MOLEKÜLER BELİRTEÇLERİN ÖNEMİ

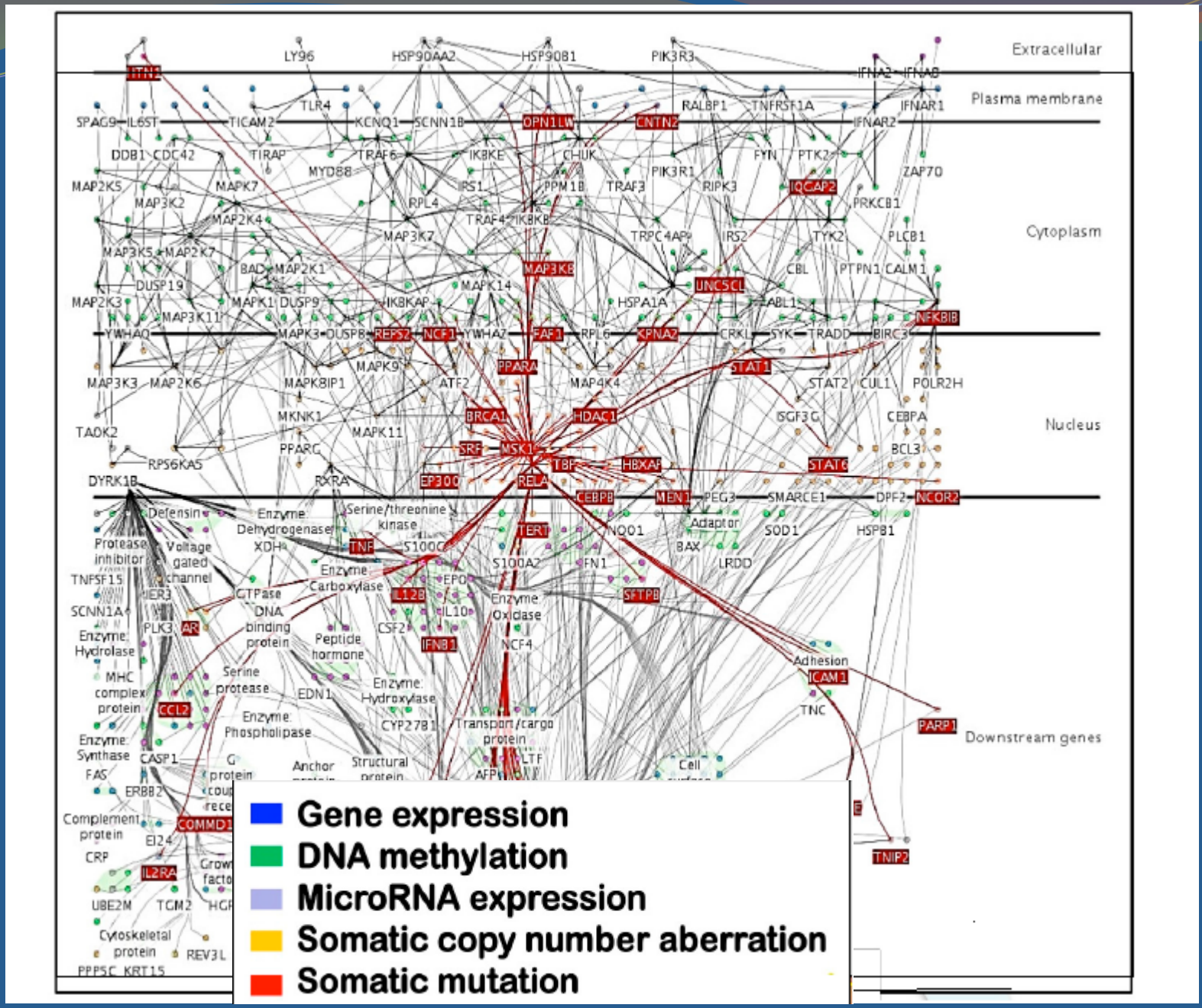
Dr. Öznur BAL
ANKARA NUMUNE EĞİTİM VE ARAŞTIRMA HASTANESİ, TIBBİ ONKOLOJİ KLİNİĞİ
30 Nisan 2016

ÇEVRESEL FAKTÖRLER

ÇOKLU GEN DEĞİŞİKLİKLERİ

BİYOLOJİK YOLAKLAR

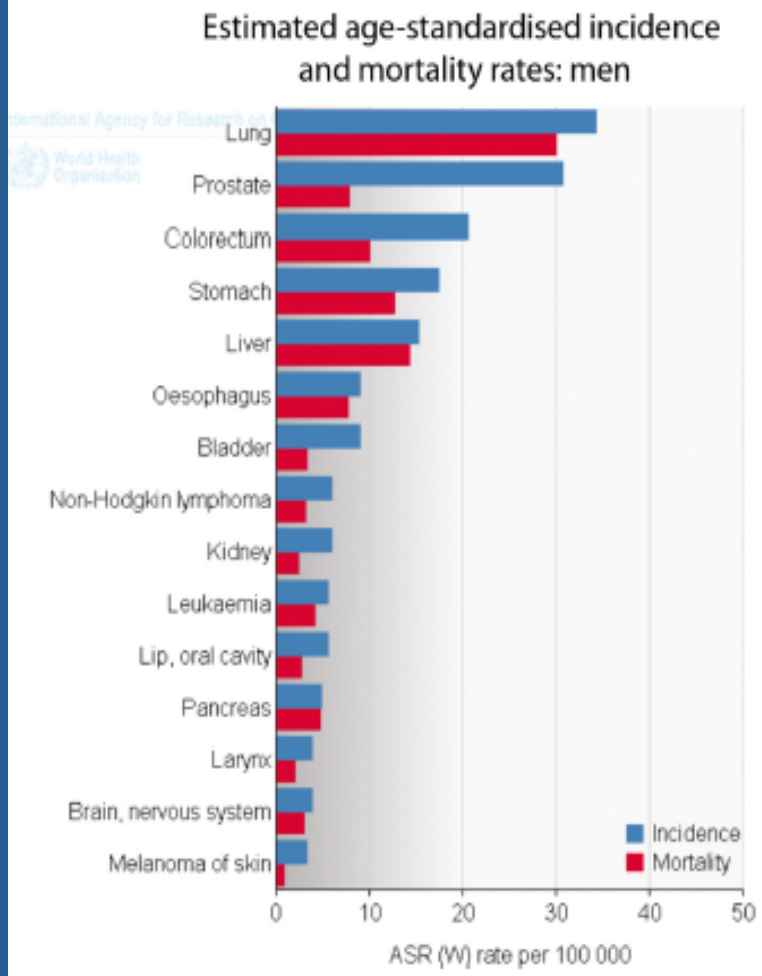
TÜMOROGENEZİS



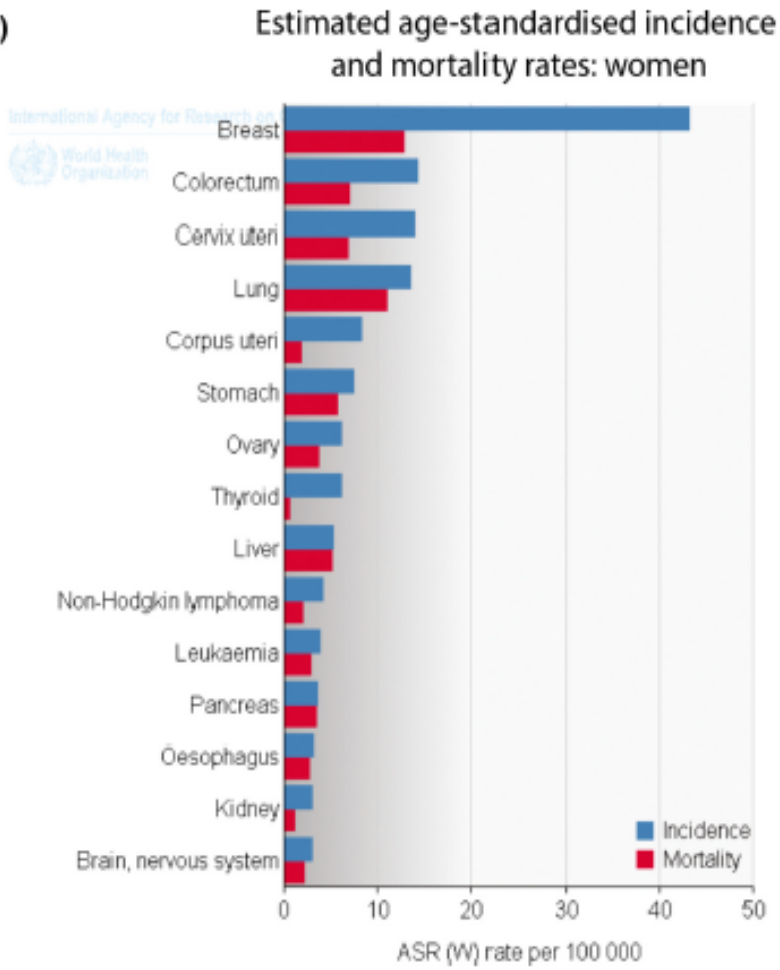
Int. J. Mol. Sci. **2015**, *16*(4), 8655-8675; doi:10.3390/ijms16048655

Neden Genetik ve Moleküler Belirteçlere İhtiyacımız Var?

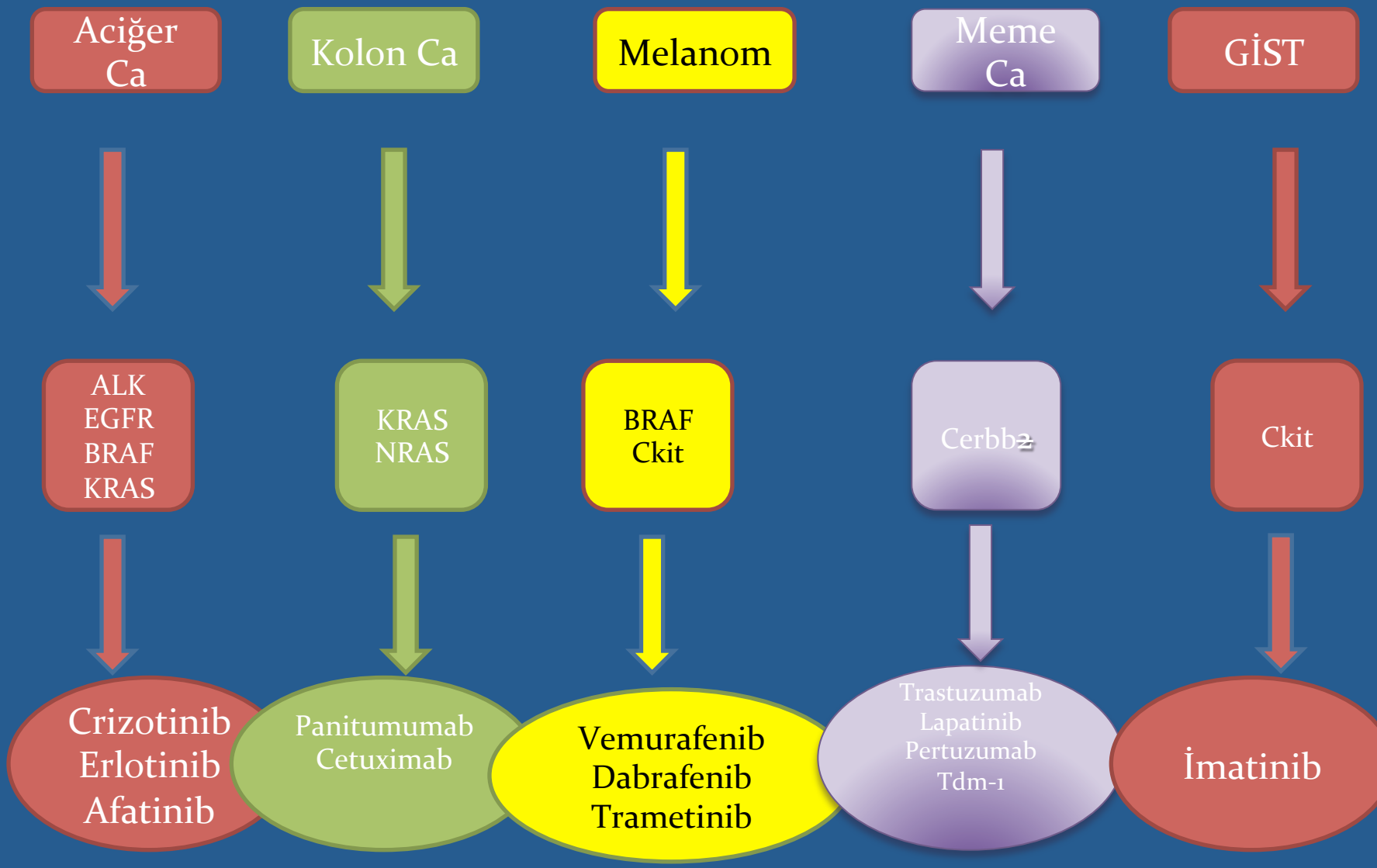
- Tanı
- Tedavi yanıtını ön görme (prediktif)
- Prognoz



(b)



NP, Foukakis T, De Petris L, Bergh J. J Intern Med. 2015 Dec;278(6):545-70. doi: 10.1111/joim.12429. Epub 2015 Sep 16. Review.The importance of moleculer markers for diagnosis and selection of targeted treatments in patients with cancer.


Aciğer Ca
Kolon Ca
Melanom
Meme Ca
GİST
ALK
EGFR
BRAF
KRAS
KRAS
NRAS
BRAF
Ckit
Cerbb2
Ckit
Crizotinib
Erlotinib
Afatinib
Panitumumab
Cetuximab
Vemurafenib
Dabrafenib
Trametinib
Trastuzumab
Lapatinib
Pertuzumab
Tdm-1
İmatinib

Meme Kanseri

- Erken evre; adjuvan tedavi

Neye göre tedavi ?

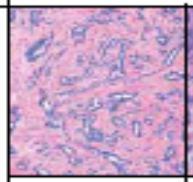
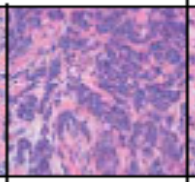
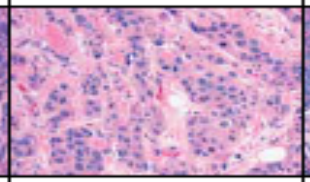
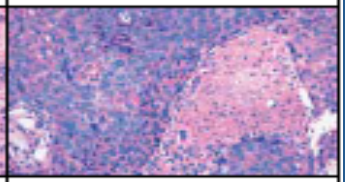
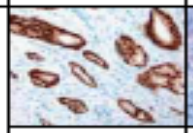
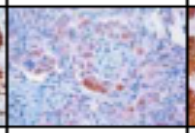
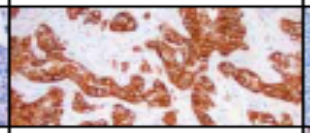
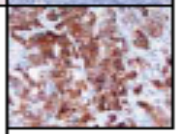
-Hasta özellikleri (yaş ,menopozal durum)

-Patolojik özellikler (evre, grade, tm çapı, ln , tümör morfolojisi

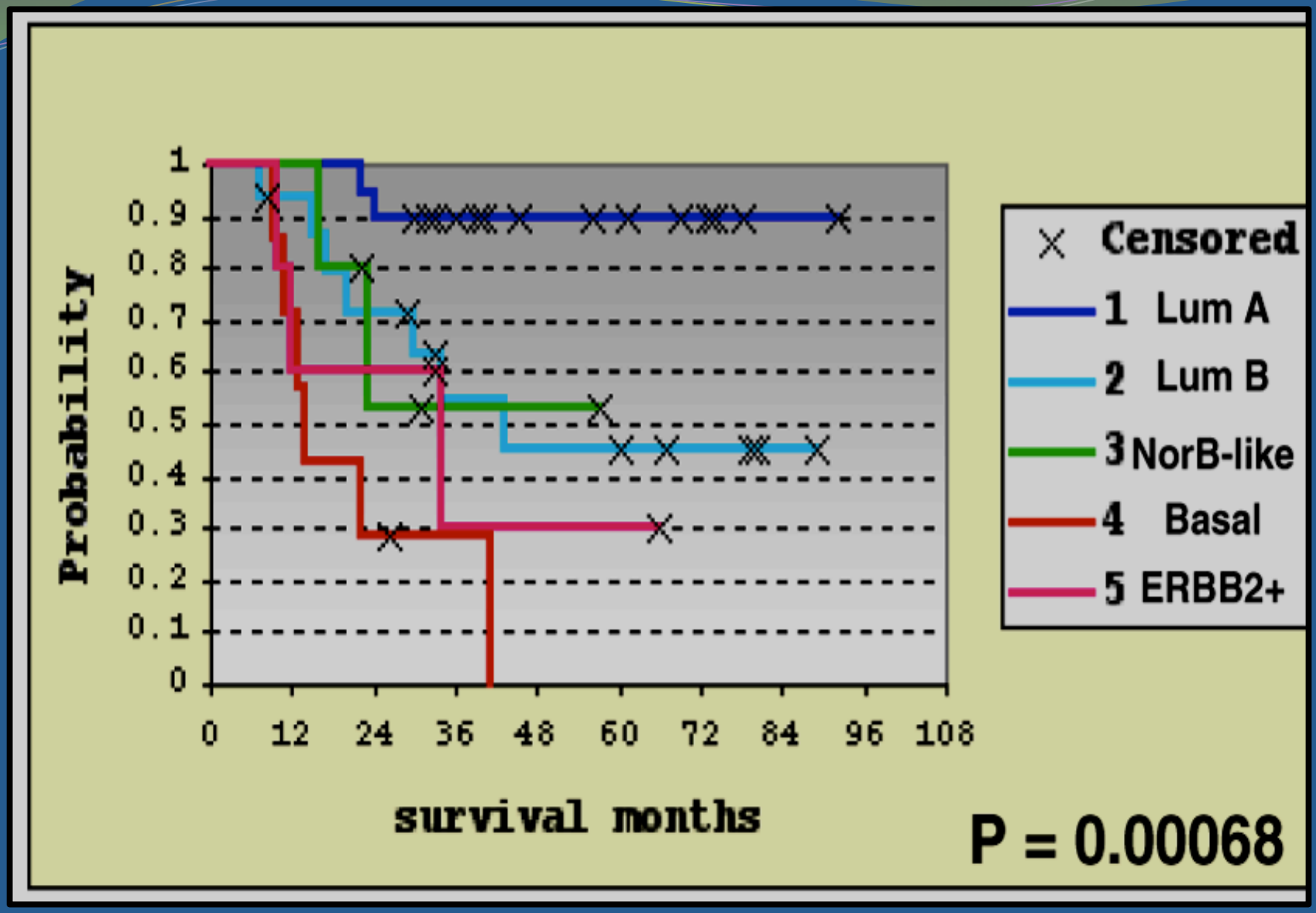
-Doku belirteçleri(ER,PR,HER2)

-Genomik profil(luminal A-B, HER2 zengin tip, Bazal benzeri)

-proliferasyon belirteçleri(ki 67, p53,uPA sistem, hc dışı HER2 bölgesi vs)

Molecular Subtype	Luminal (A and B)		HER2	Basal	
Genetic profile	↑ Luminal CKs and ER-related genes (A>B) B↑ in proliferation-related genes		↑ HER2-related genes	↑ Basal CKs	
Histologic correlates					
	A Lower-grade ER+	B Higher-grade ER+	High-grade, +/– apocrine features	High-grade, sheet-like, necrosis, inflammation *See exceptions	
Surrogate markers					ER/PR– HER2–
	A Strong ER+, PR+/–, HER2–, low Ki67	B Weaker ER+, PR+/–, HER2+/–, ↑ Ki67	HER2+, +/– ER/PR		CK5/6+/– EGFR+/–
Prognosis	Good	Intermediate	Worse	Worse	
Response to chemotherapy	Lower	Intermediate	Higher	Higher	

Molecular Pathology of Breast CancerWhat a Pathologist Needs to Know Kimberly H. Allison, Am J Clin Pathol. 2012 Dec;138(6):770-80



Sorlie T et al, PNAS 2001

Tedaviyi predikte eden faktörler

- ER ±PR ; hormonoterapi

- HER2; adjuvan trastuzumab

- Gen ekspresyon profilleri ; KT

*21 gen rekürrens skor (RS)
*endopredict
*breast cancer index (bcı)
*Amsterdam 70 gen profil

21 gen Rekürrens skor (RS)

- Meme kanseri için önemli olabilecek muhtemel 250 gen belirleyici
- Ekspresyon seviyelerinin belirlenmesi için RT-PCR

Paik S, Tang G, Shak S et al. J Clin Oncol. 2006 Aug 10;24(23):3726-34 PMID: **16720680**

RS < 18 ; düşük risk

RS 19-30 ; orta risk

>30 ;yüksek risk

Paik S, Tang G, Shak S, Kim C et al. NJ Clin Oncol. 2006;24(23):3726. PMID 16720680
Mamounas EP, Tang G, Fisher B, et al . J Clin Oncol. 2010;28(10):1677. PMID: 20065188

BRCA 1 ve BRCA 2

- Ailevi meme ca hastalarında görülen en sık germline mutasyonu
- Farklı klinik özellikleri+
- Bazal benzeri
- Platin analogları ile tedaviye daha iyi yanıt

*PARP inhb(olaparib) çalışma düzeyinde

Hemel D, Domchek SM. Hematol Oncol Clin North Am 2010; 24: 799–814.
Tutt A, Ellis P, Kilburn L et al. SABCS, 2014 [abstract S3-01].
Oza AM, Cibula D, Benzaquen AO et al. Lancet Oncol 2015; 16: 87–97.

BRCA 1 - BRCA 2

- ≤50 yaş meme ca tanısı
- Triple-negatif meme ca ≤60 yaş
- ≥2 primer meme ca
- Invasive over- fallop tup ca, or primer peritoneal ca
- Erkek meme ca

HER2

- Gen amplifikasyonu→ overekspreyonu ->%15
- Negatif prognostik
- Adjuvan –metastatik basamakta anti-HER2 tedaviye yanıtı predikte eder
- IHC/FISH

*Trastuzumab

*Lapatinib

*Pertuzumab

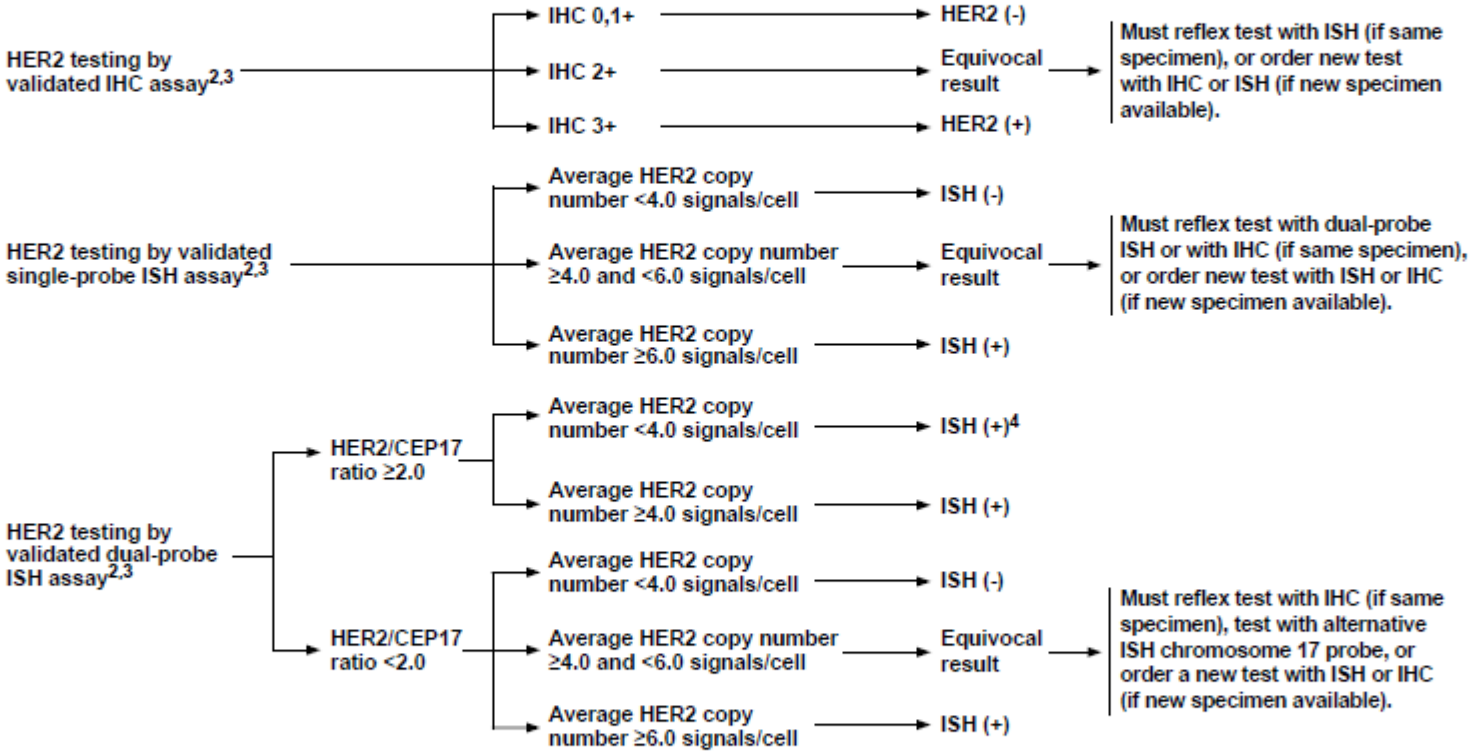
*T-DM1

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

PRINCIPLES OF HER2 TESTING[1,2]



[1]NCCN Endorses the ASCO/CAP HER2 testing guideline. "Principles of HER2 Testing" modified with permission from Wolff AC, Hammond EH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol 2013;31:3997-4013.For additional information, see http://bit.ly/ASCO-HER2GuidelineResources.

[2]Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Health care systems and providers must cooperate to ensure the highest quality testing.

[3]Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy.

[4]See ASCO/CAP HER2 Guideline Data Supplement 2E (available at http://www.asco.org/sites/www.asco.org/files/final_her2_testing_ds_10-3-13.pdf) for more information on these rare scenarios.

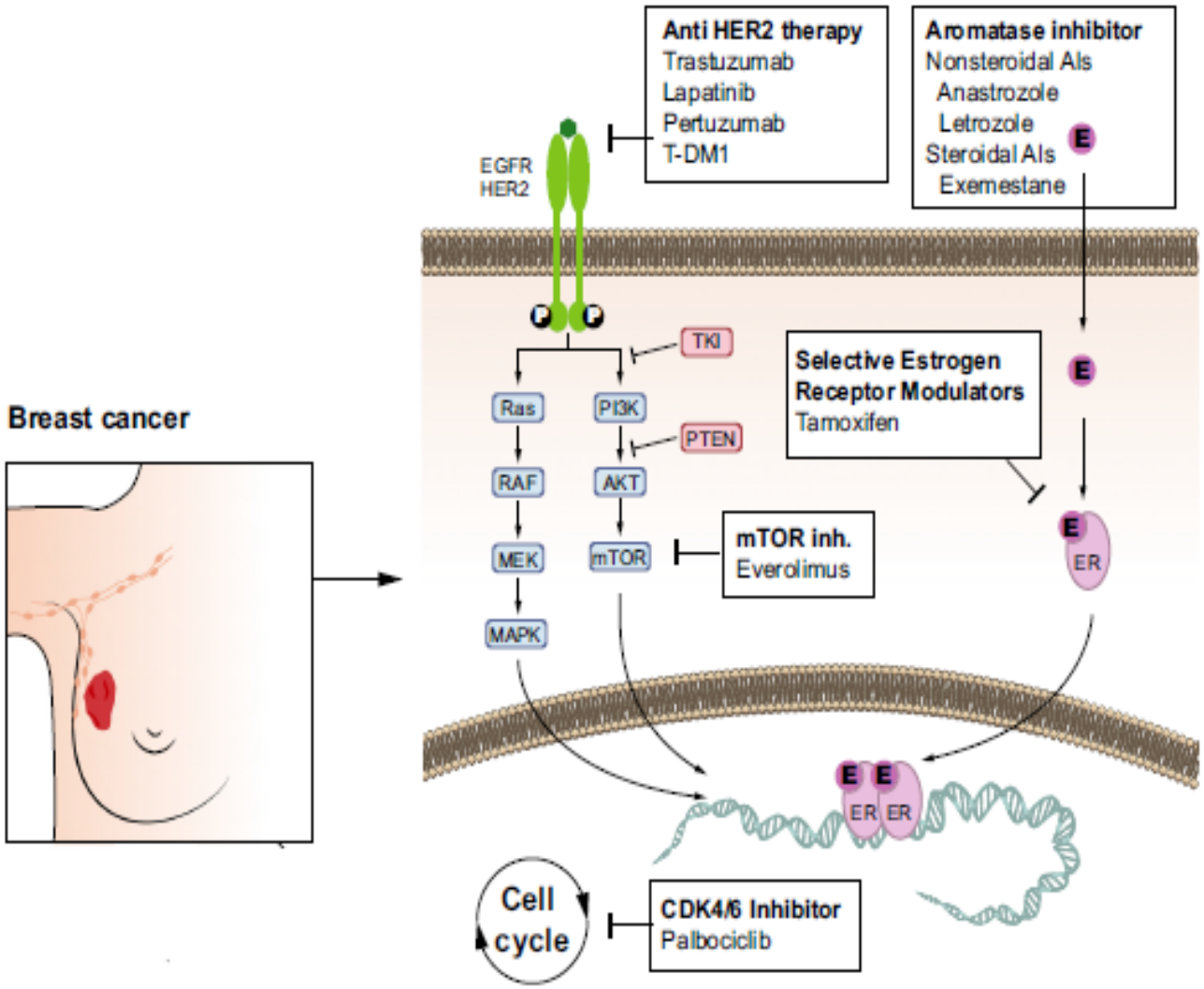
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PI3K-mTOR

- PI3K ; meme ca da en sık mutant gen
- Özellikle luminal tipler
- PI3K-mTOR yolağının mutasyon sonucu aktivasyonu ile HT ve antiHER2 tedaviye direnç

*Everolimus

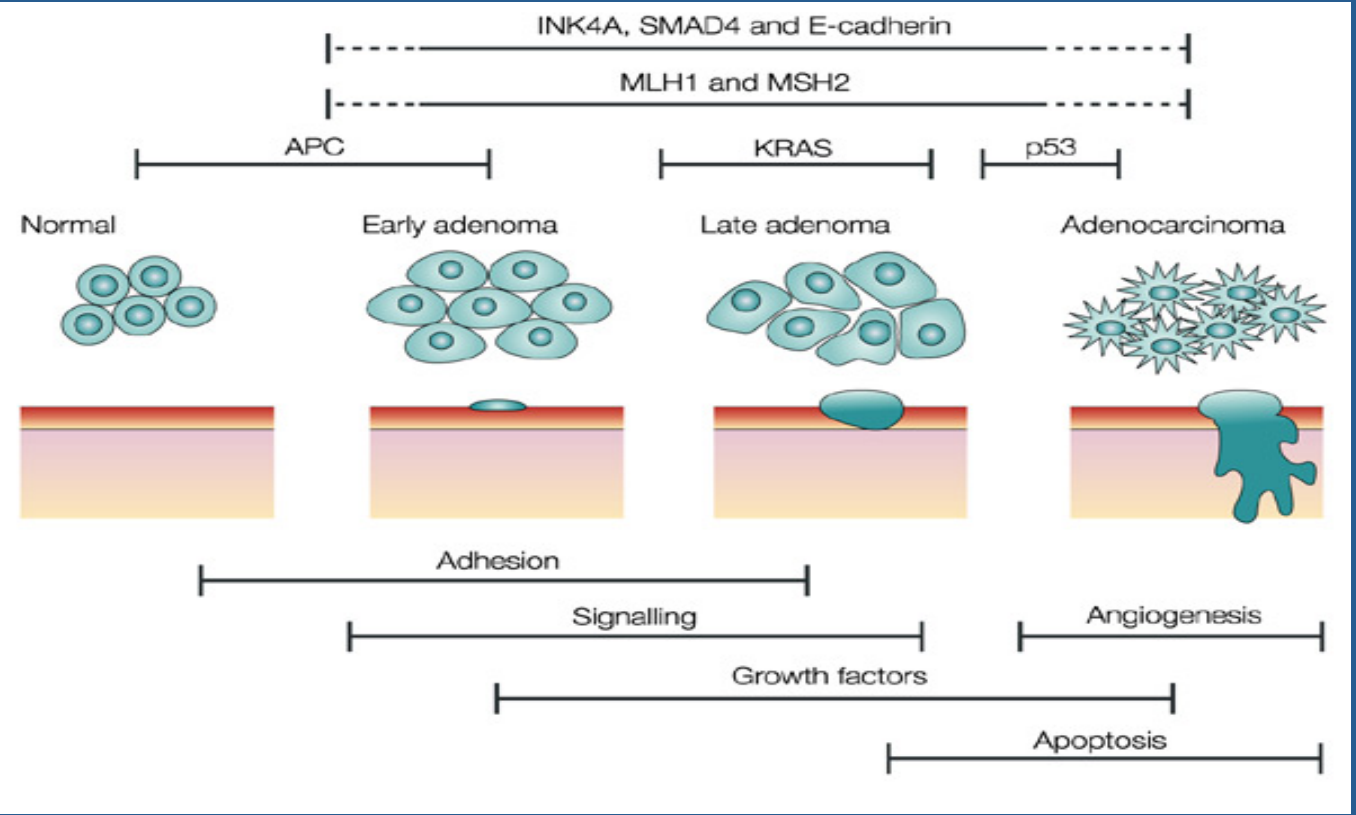
Cell. 2015 Jun 18;161(7):1681-96. PMID: 26091043
Baselga J, Campone M, Piccart M et al N Engl J Med. 2012 Feb 9;366(6):520 PMID: **22149876**



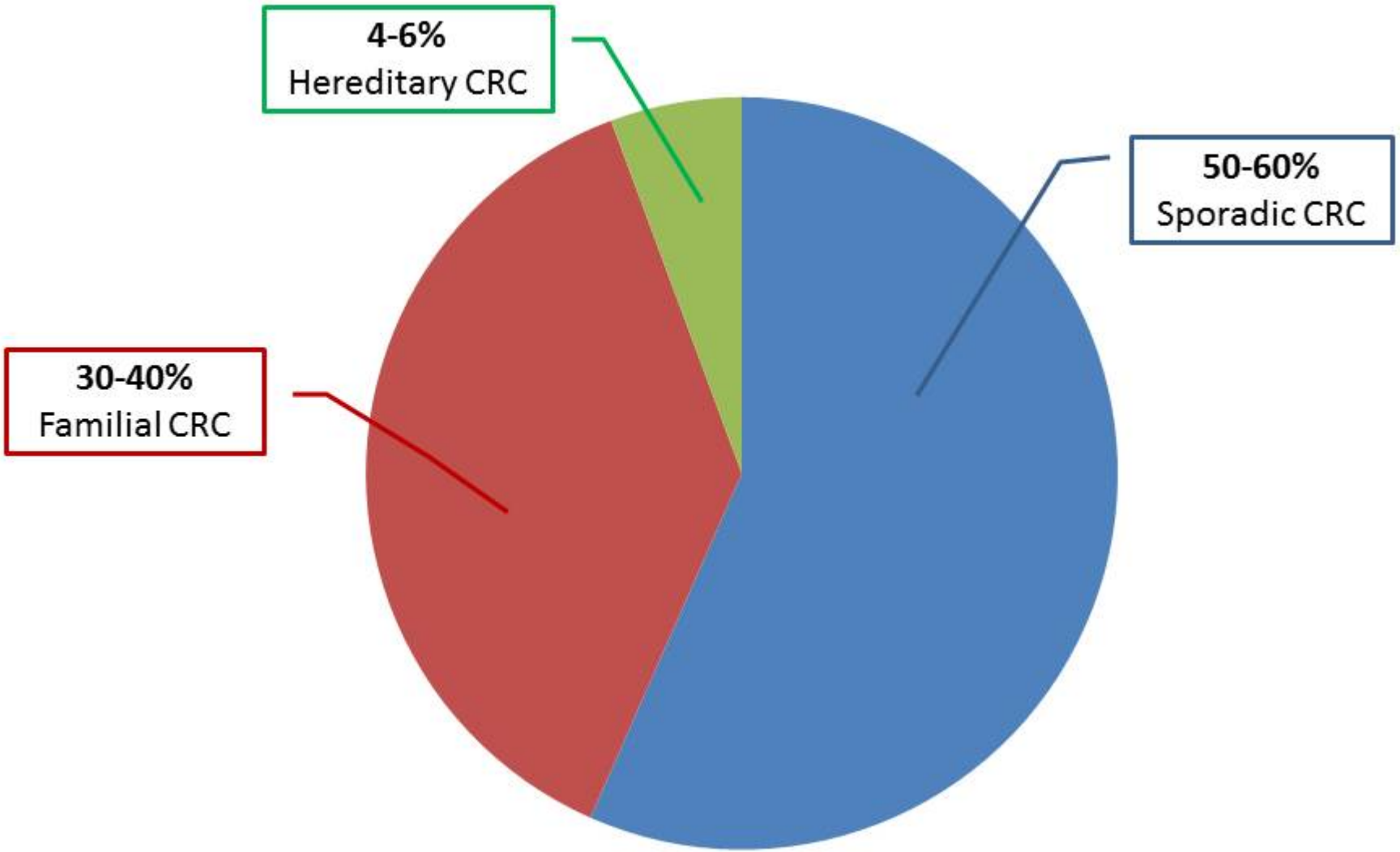
Tobin NP, Foukakis T, De Petris L, Bergh J. J Intern Med. 2015 Dec;278(6):545-70 PMID: 26373821

al

Kolon Kanseri



Kerr D. Nat Rev Cancer. 2003 Aug;3(8):615-22. Review. PMID: **12894249**



Genetics and Colorectal Cancer. *American Society of Colon & Rectal Surgeons*. Retrieved March 24, 2013

MSI

- Evre 2 kolon ca ***

*Risk stratifikasyonu

Klinikopatolojik özellikler

*t4

*ln <12

*obstrüksiyon , perforasyon

*tm grade

*lvi ,pni

*Cs

yüksek riskli

**KT

düşük riskli

**dMMR/MSI

MSI

MSS → KT

MSI- L → KT

MSI-H → İyi prognoz 5FU yararı yok

Sağkalım daha iyi

G, GafàR, Santini A, Maestri I, Guerzoni L, Cavazzini L J Clin Oncol. 2006;24(15):2359. PMID 16710035

Sinicrope FA, Mahoney MR, Smyrk TC et al J Clin Oncol. 2013 Oct;31(29):3664-72. PMID 24019539

KRAS

- Kirstein rat sarcoma
- RAS gen ailesi üyesi
- %37-40 mutant ve karsinogenezin çok erken dönemlerinde oluşur

- Ekzon 2(en sık) ; (Kodon 12-13),ekzon 3 ve 4
- mutant KRAS ; prognostik ?
  ; antiEGFR tedaviye yanıtsız(prediktif)

Arber, N., Shapira, I., Ratan, J., *et al.*Gastroenterology. 2000 Jun;118(6):1045-50.PMID: 10833479
Bos JL, Fearon ER, Hamilton SR *et al* Nature. 1987 May 28-Jun 3;327(6120):293-7.PMID: **3587348**

BRAF

- RAS-RAF-MAPK yolağı
- %5-10 mutant
- Çoğunlukla V600E mutasyonu
- Kötü prognostik (MSI-L ,MSS,metastatik)

Lochhead P, Kuchiba A, Imamura Y et al. J Natl Cancer Inst. 2013 Aug;105(15):1151-6. Epub 2013 Jul 22. PMID 23878352

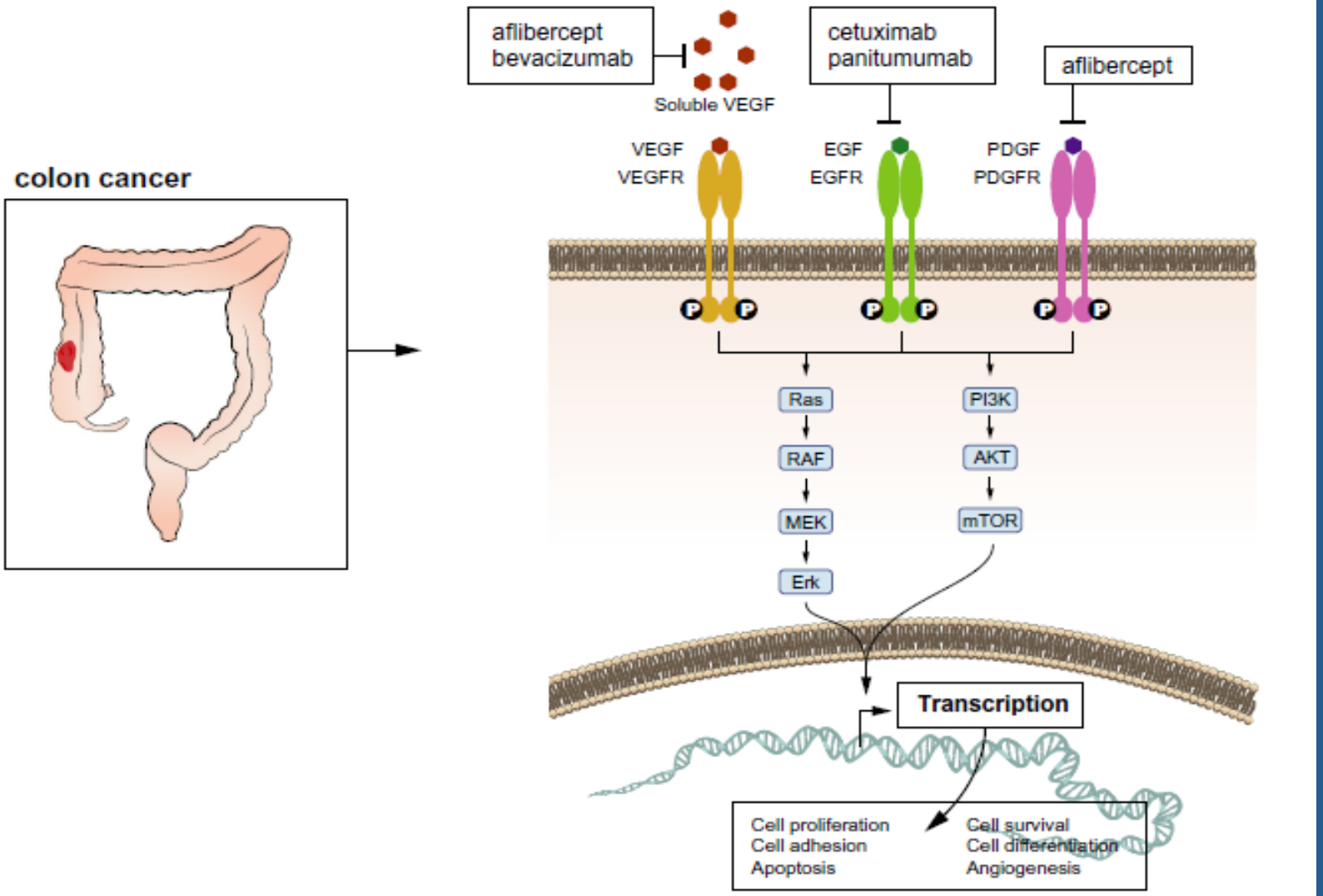
Van Cutsem E, Köhne CH, Láng I et al J Clin Oncol. 2011 May 20;29(15):2011-9. doi: 10.1200/JCO.2010.33.5091. PMID: 21502544

- Anti –EGFR tedaviler için prediktif değil

Bokemeyer C, Kohne C, Rougier P, et al. Cetuximab with chemotherapy as first-line treatment for metastatic colorectal cancer: Analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation status (abstract #3506). J Clin Oncol 2010; 28:262s.

Van Cutsem E, Köhne CH, Láng I et al . J Clin Oncol. 2011;29(15):2011. PMID 21502544

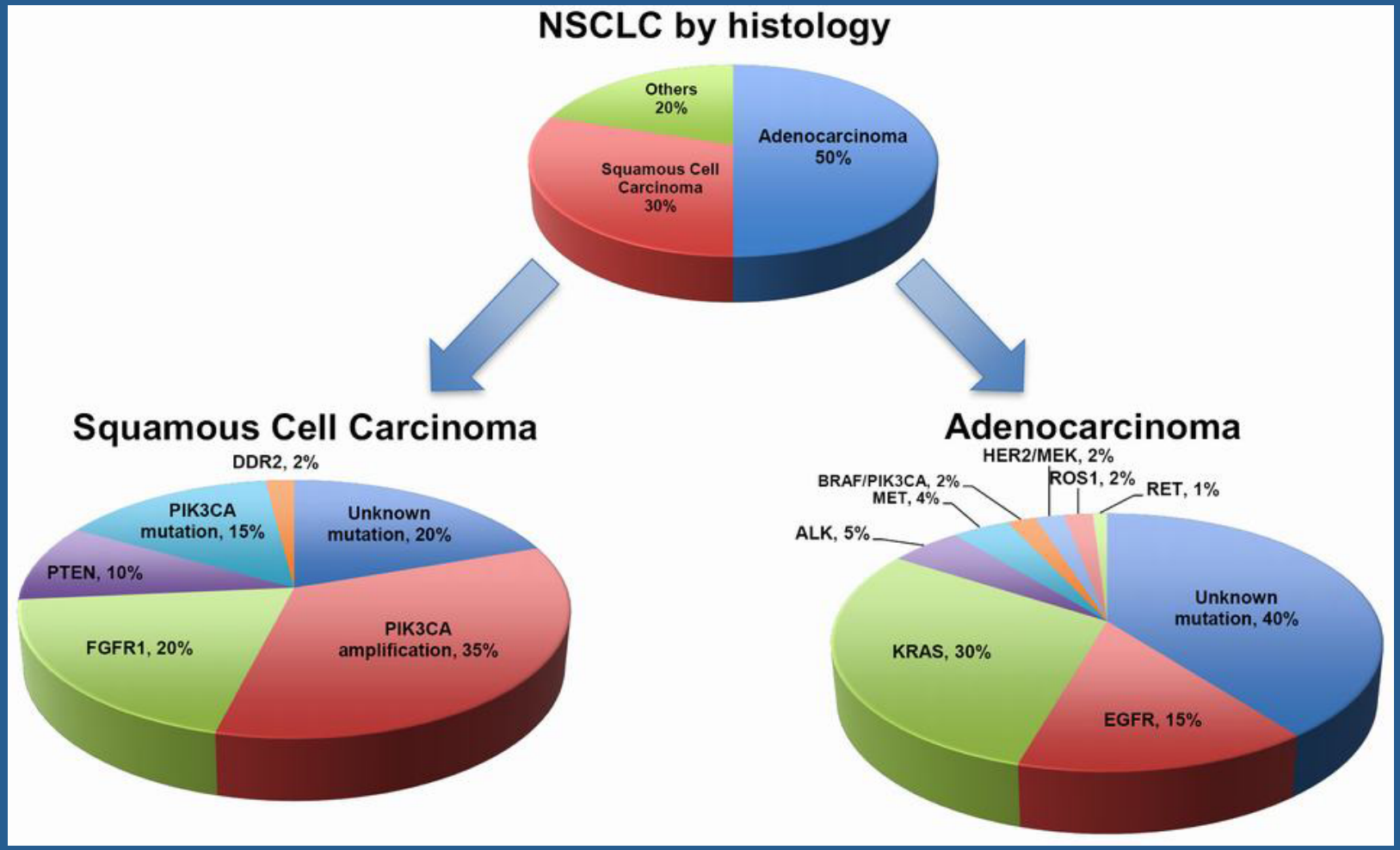
Ogino S, Shima K, Meyerhardt JA et al Clin Cancer Res. 2012;18(3):890. PMID 22147942



Tobin NP, Foukakis T, De Petris L, Bergh J. J Intern Med. 2015 Dec;278(6):545-70 PMID: 26373821

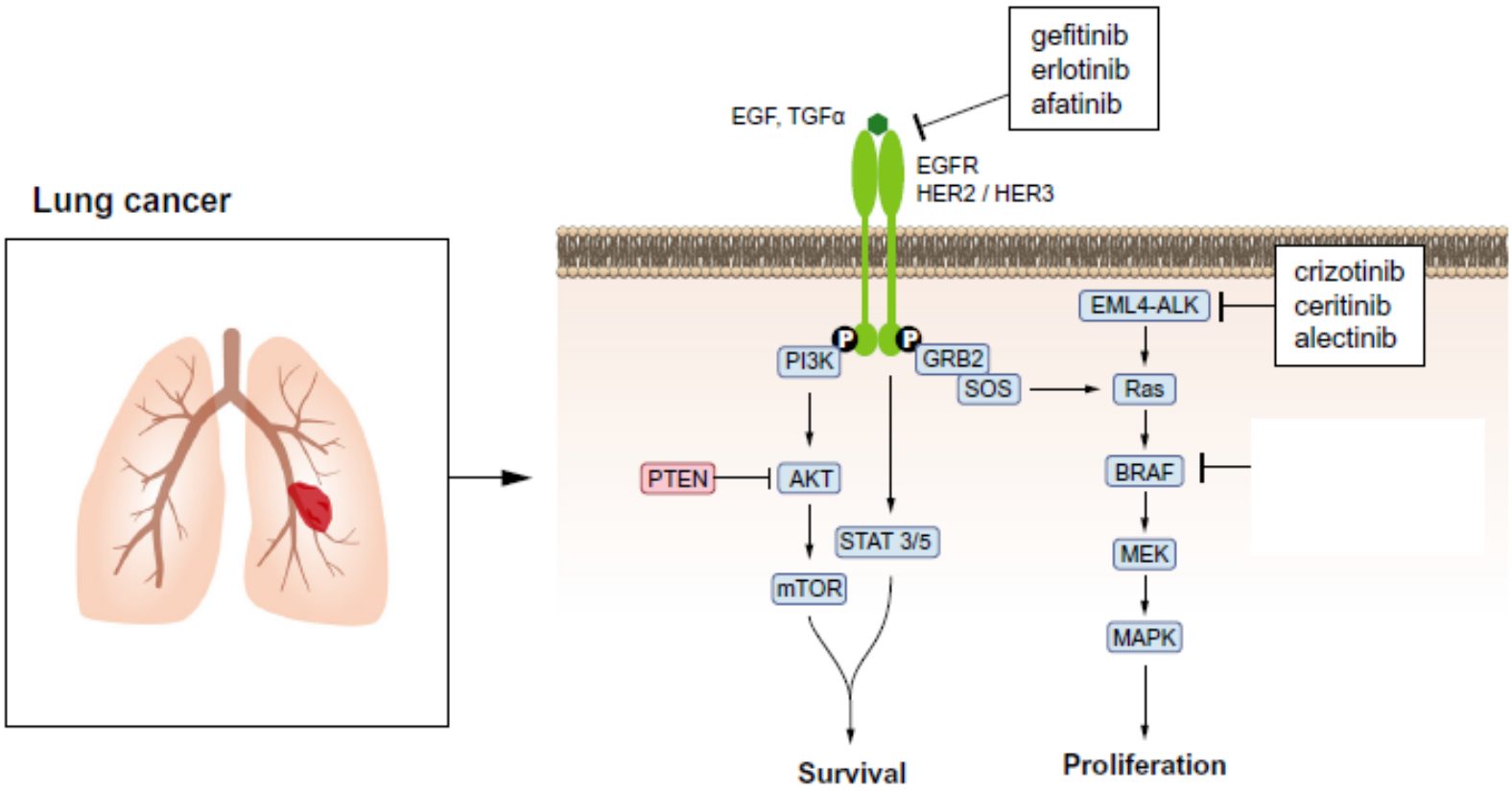
al

Akciğer kanseri



Chan BA, Hughes BG.Transl **Lung Cancer** Res. 2015 Feb;4(1):36-54. doi: 10.3978/j.issn.2218-6751.2014.05.01. Review.PMID: 25806345

Gen	Insidans
KRAS	15% - 25%
EGFR	**10% - 35%**
ALK	**3% - 7%**
MET	2% - 4%
HER2	2% - 4%
BRAF	1% - 3%
PIK3CA	1% - 3%
AKT1	1%
MAP2K1	1%
NRAS	1%
ROS1	1%
RET	1%



Tobin NP, Foukakis T, De Petris L, Bergh J. J Intern Med. 2015 Dec;278(6):545-70 PMID: 26373821

al

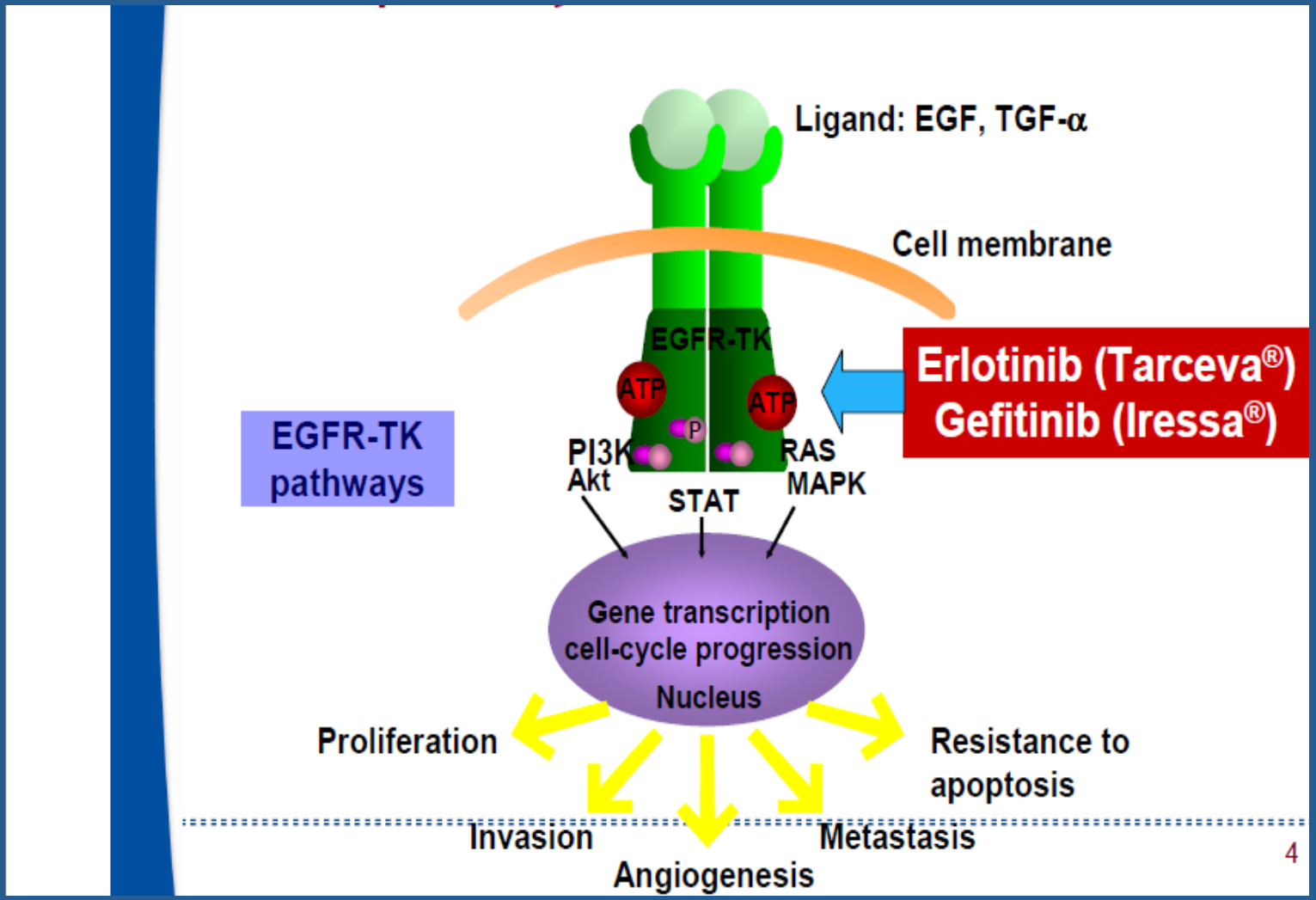
EGFR

- Ekstra ve intraselüler bölgeye sahip bir transmemran trozinkinaz
- Mutasyon sonrası tirozin kinaz aktivitesinde artış sonucu onkojenik transformasyon
- %10-15 mutant

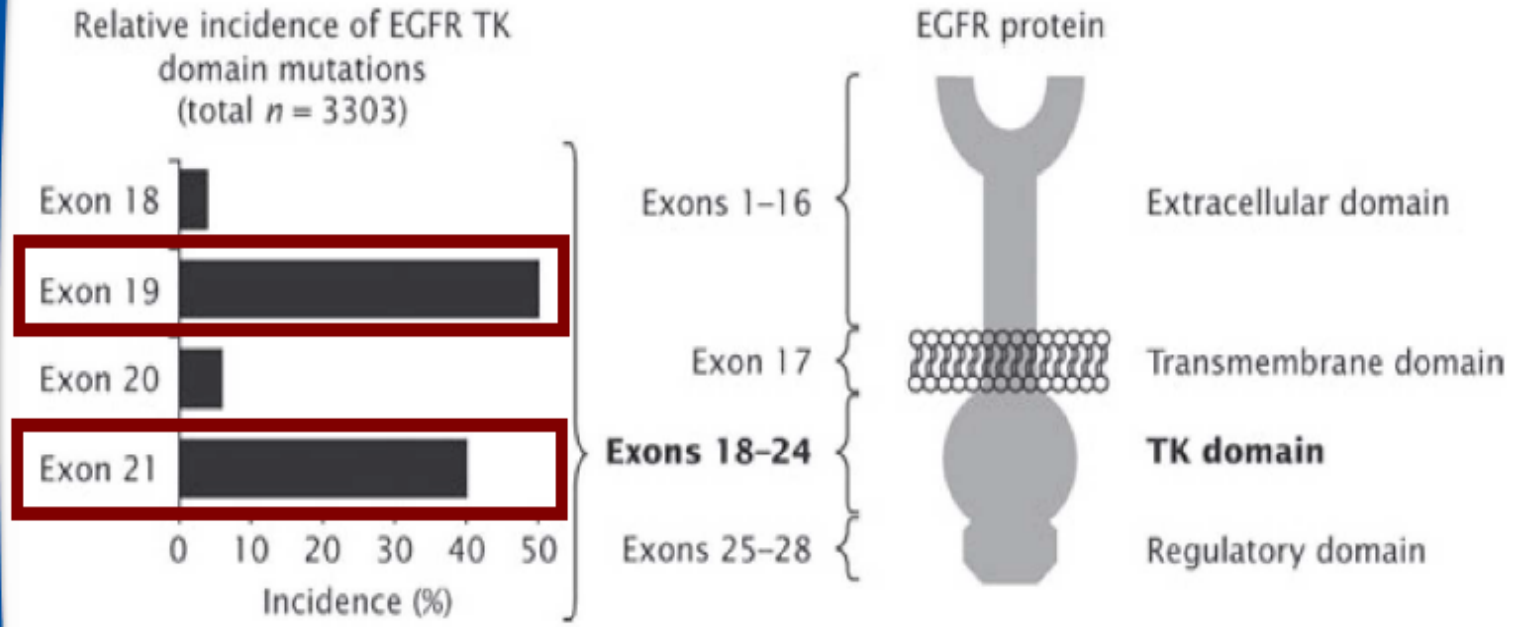
- Daha iyi prognoz
- EGFR TKI tedaviye yanıt

Ji H, Li D, Chen L, Shimamura T et al **Cancer** Cell. 2006 Jun;9(6):485-95. PMID: 16730237
Yip PY, Yu B, Cooper WA et al J Thorac Oncol. 2013 Apr;8(4):408-14.PMID: 23392229

EGFR


Ligand: EGF, TGF-α
Cell membrane
EGFR-TK
ATP
ATP
P
Erlotinib (Tarceva®)
Gefitinib (Iressa®)
EGFR-TK pathways
PI3K
Akt
STAT
RAS
MAPK
Gene transcription
cell-cycle progression
Nucleus
Proliferation
Resistance to apoptosis
Invasion
Metastasis
Angiogenesis

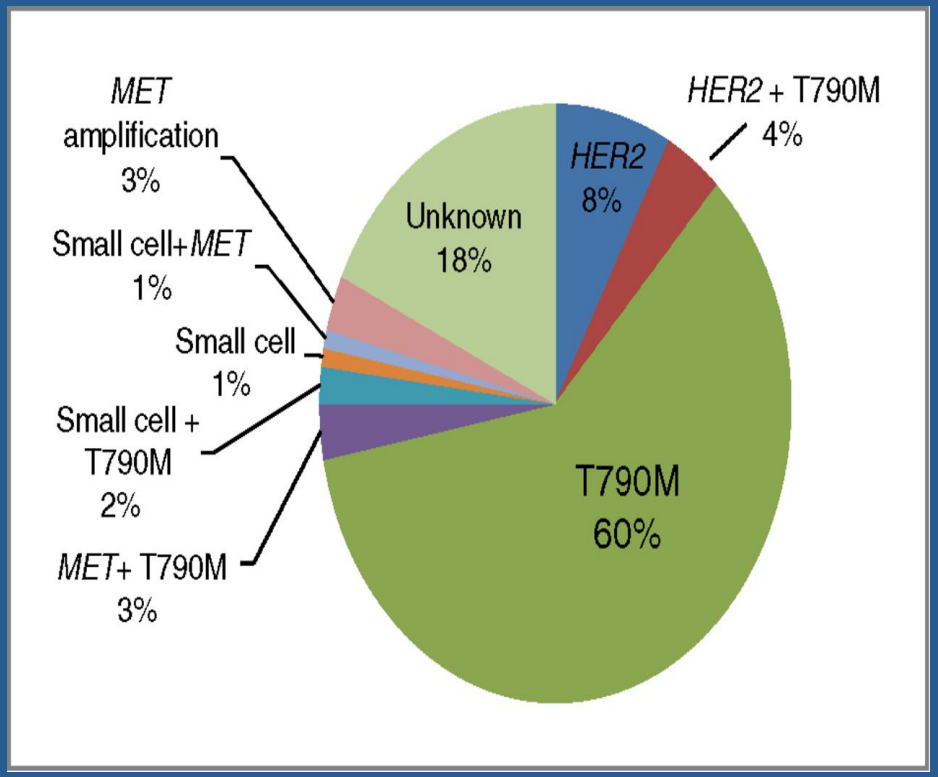
EGFR



Classical activating mutations

Paz-Ares J Cell Mod Med 2010

EGFR TKI direnci



- EGFR ikinci mutasyon

*methionine - threonine 790 .poziyon

- MET amplifikasyonu

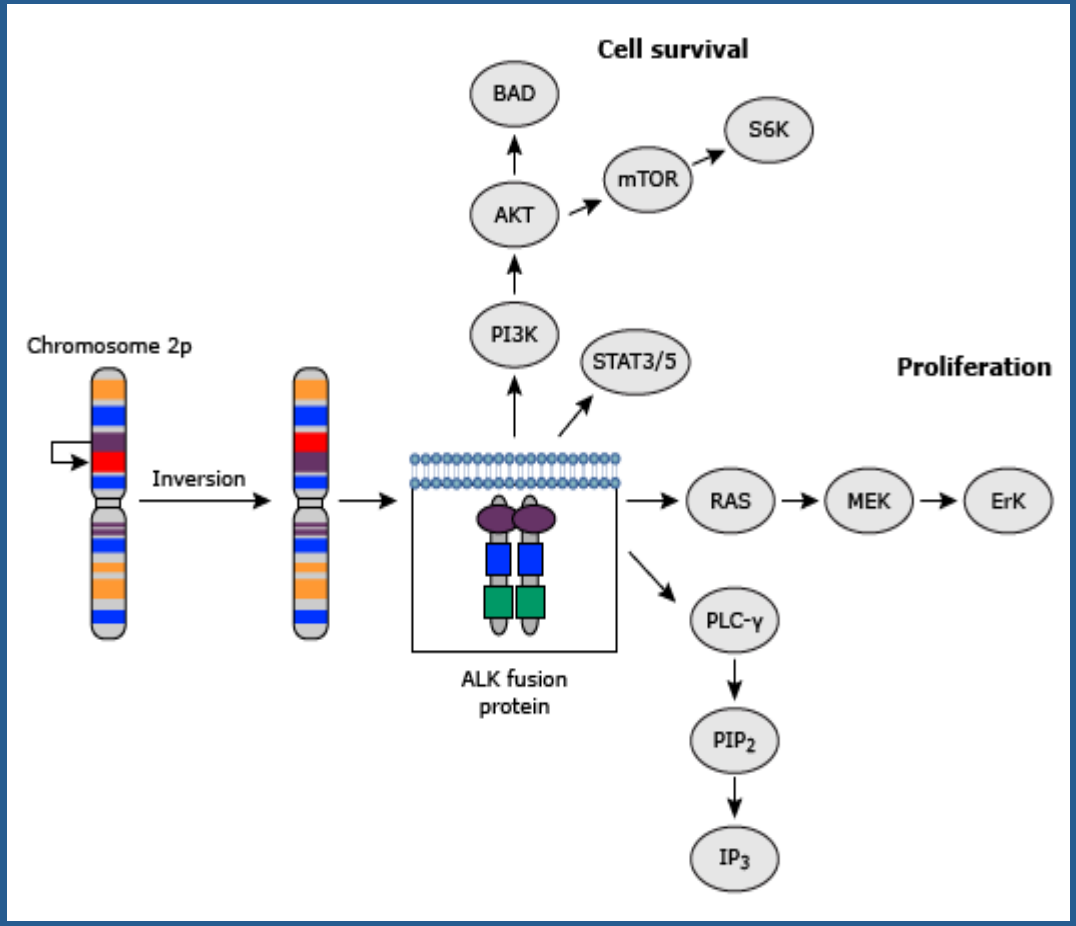
*%5-20

*EGFR direnci olmadan primer dokuda bulunması kötü prognostik

***afatinib, osimertinib

Blakely CM, Bivona TG. Cancer Discov. 2012;2:872-875.
Cappuzzo F, Marchetti A, Skokan M, J Clin Oncol. 2009;27(10):1667.

ALK



- anaplastic lymphoma kinase-echinoderm microtubule-associated protein-like 4
- Translokasyon varlığı ALK TKI yanıtını predikte eder

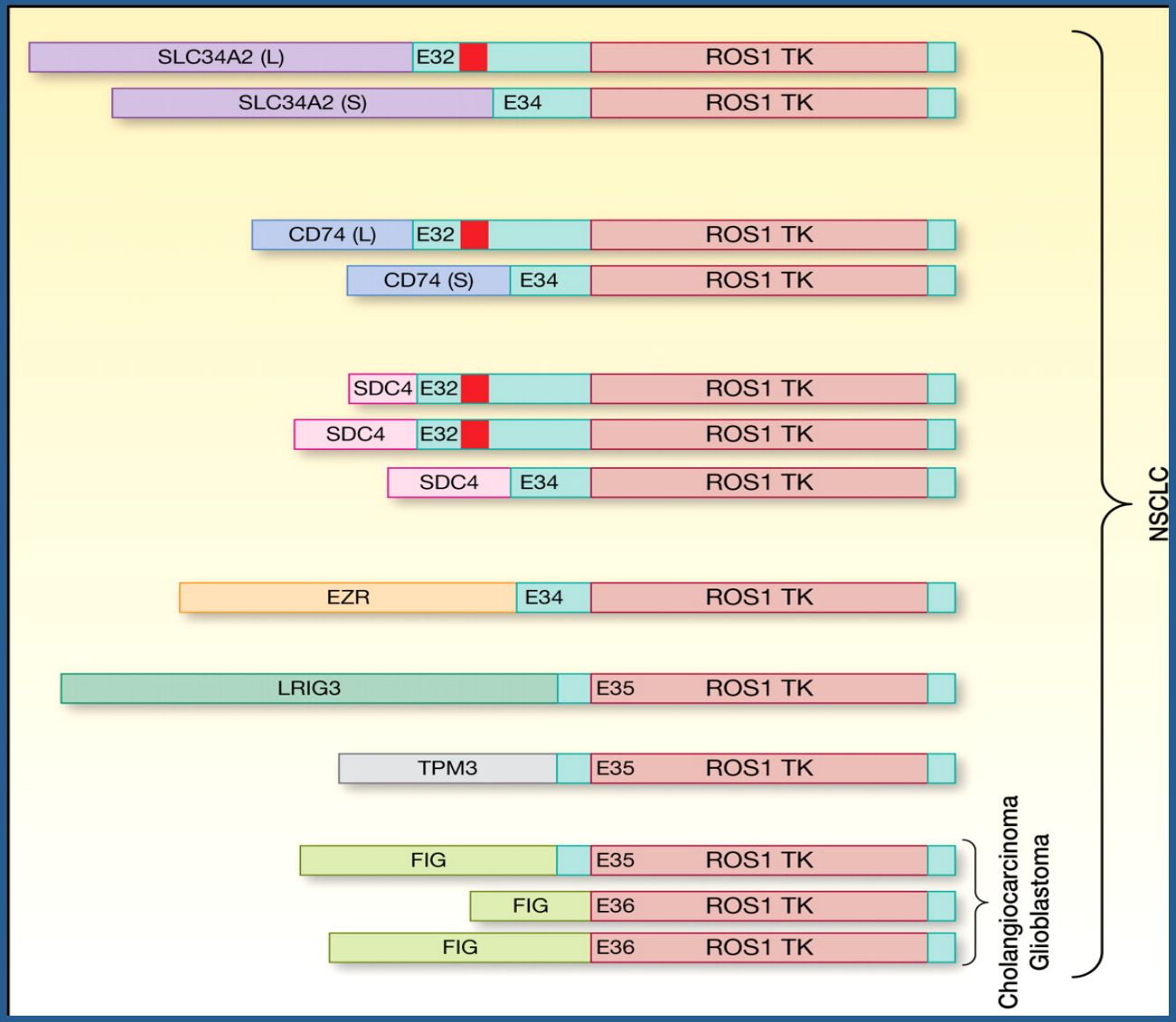
**crizotinib ,ceritinib

Reproduced with permission from: Shaw AT, Solomon B. Targeting Anaplastic Lymphoma Kinase in Lung Cancer. Clin Cancer Res 2011; 17: 2081

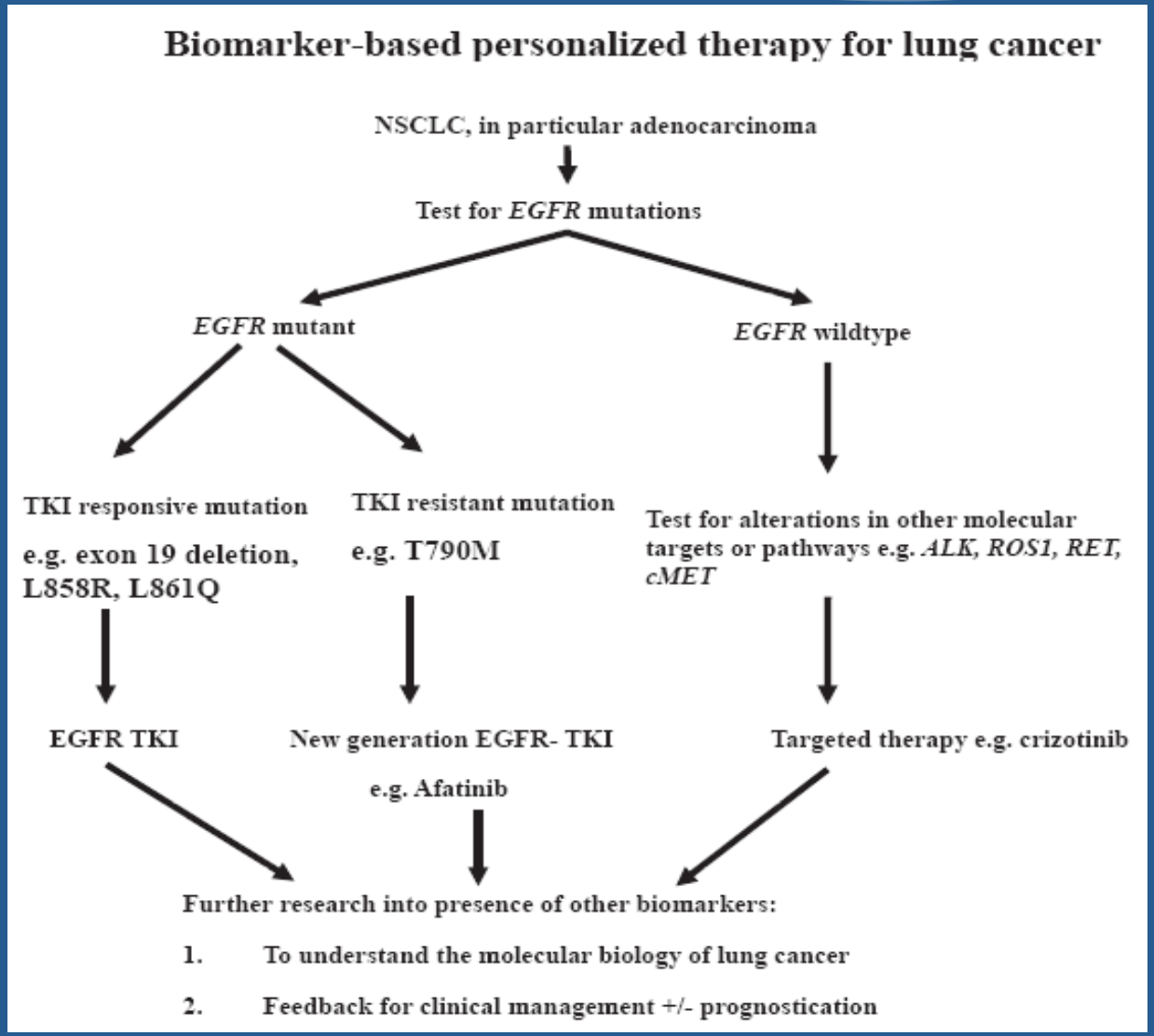
ROS-1

- İnsülin reseptör ailesine ait rtk
- %1-2 driver onkogen
- Diğer genler- tanslokasyon –ROS1 –CD74 en sık
- FISH break-apart assay
- ROS 1 translokasyonu + ; crizotinib

Bergethon K, Shaw AT, Ou SH et al .J Clin Oncol. 2012 Mar;30(8):863-70. Epub 2012 Jan 3.PMID22215748
Shaw AT, Ou SH, Bang YJ et al. N Engl J Med. 2014;371(21):1963.PMID 25264305



Stumpfova M, Jänne PA.Clin **Cancer** Res. 2012 Aug 15;18(16):4222-4. PMID: 22859716

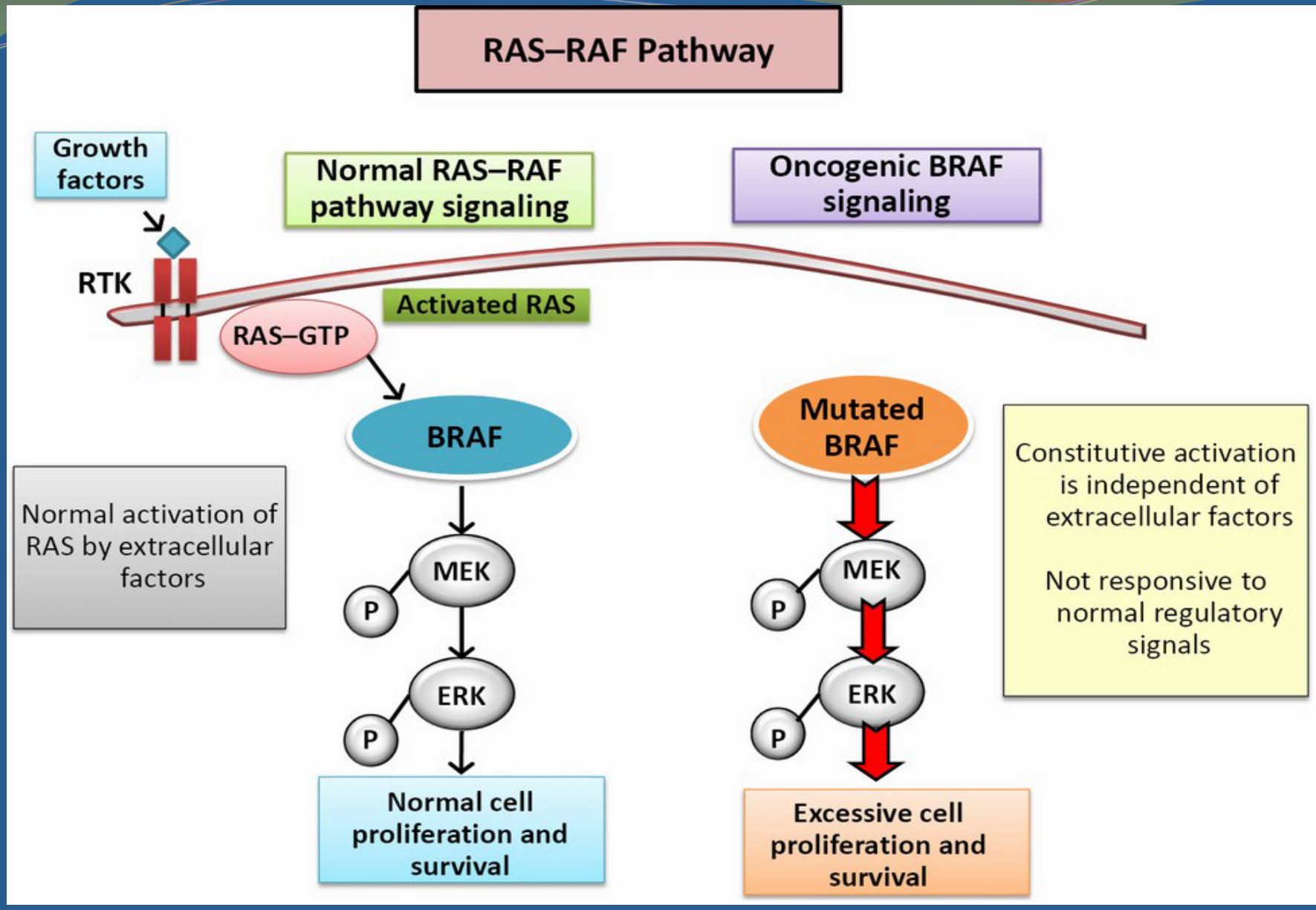


Cooper WA, Lam DC, O'Toole SA, Minna JD.J Thorac Dis. 2013 Oct;5 Suppl 5:S479-90. doi: 10.3978/j.issn.2072-1439.2013.08.03. Review. PMID: 24163741

Malign Melanom

- BRAF ;%42-55;
- NRAS; %15-20 ; kötü prognostik
- Ckit ;%10(akral,mukozal; kötü prognostik)

Glitza IC, Davies MA.Chin Clin Oncol. 2014 Sep;3(3):27.
PMID: 25632386
Devitt B, Liu W, Salemi R et al.Pigment Cell **Melanoma** Res. 2011 Aug;24(4):666-72..x. Epub 2011 Jun 22.PMID: 21615881



Muñoz-Couselo E, García JS, Ann Transl Med. 2015 Sep;3(15):207. PMID: 26488003

BRAF

- Kötü prognoz
- V600E en yaygın
- PCR

** vemurafenib
dabrafenib

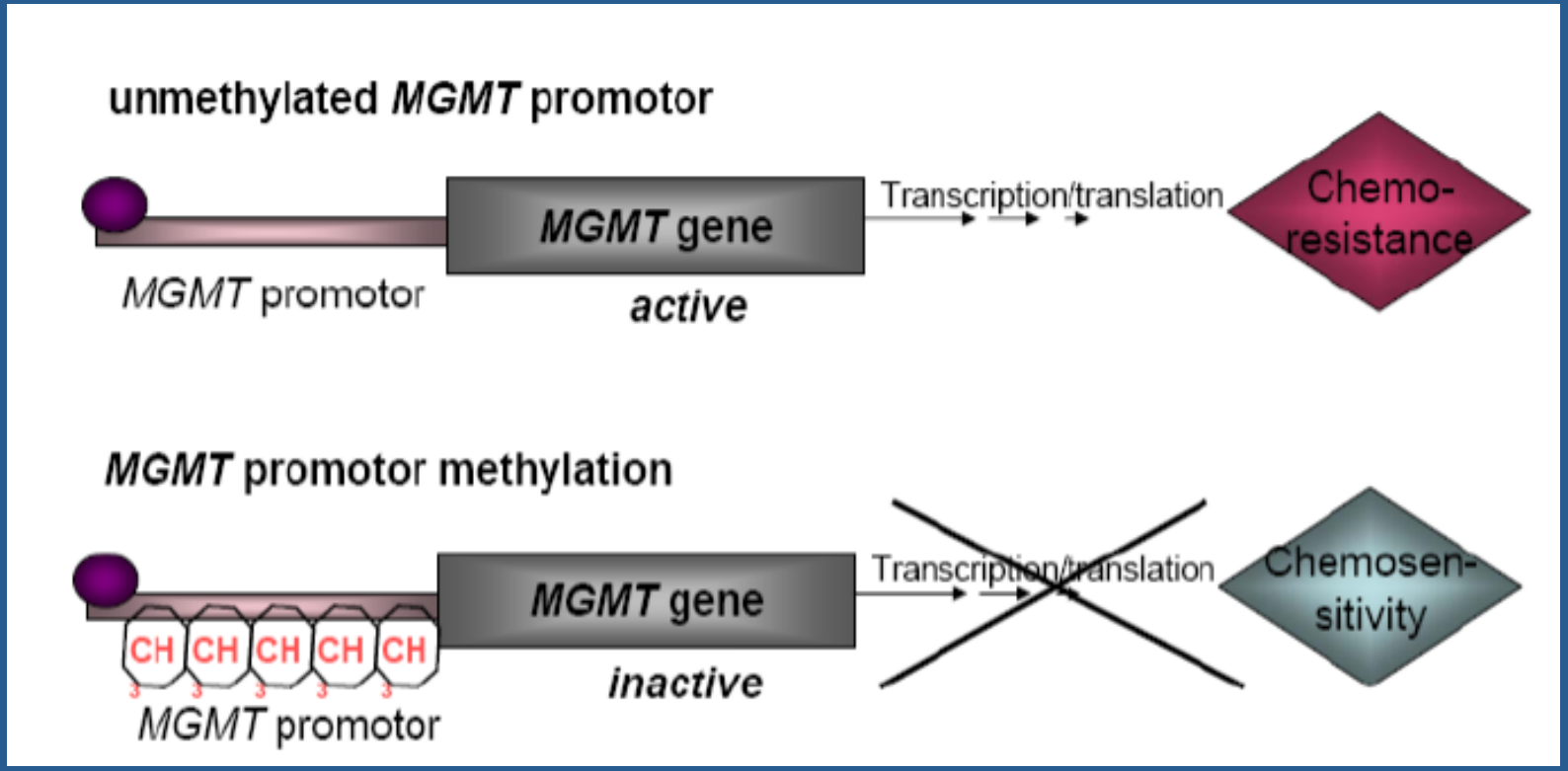
**MEK inhb (trametinib ,Cobimetinib)

Halaban R, Zhang W, Bacchiocchi A et al Pigment Cell **Melanoma** Res. Pigment Cell **Melanoma** Res. 2012 May;25(3):402.PMID: 20149136
Grob JJ, Amonkar MM, Martin-Algarra S et al. Ann Oncol. 2014 Jul;25(7):1428-36. PMID: 24769640
Collisson EA, De A, Suzuki H, Gambhir SS, Kolodney MS.Cancer Res. 2003 Sep 15;63(18):5669-73. PMID: 14522881

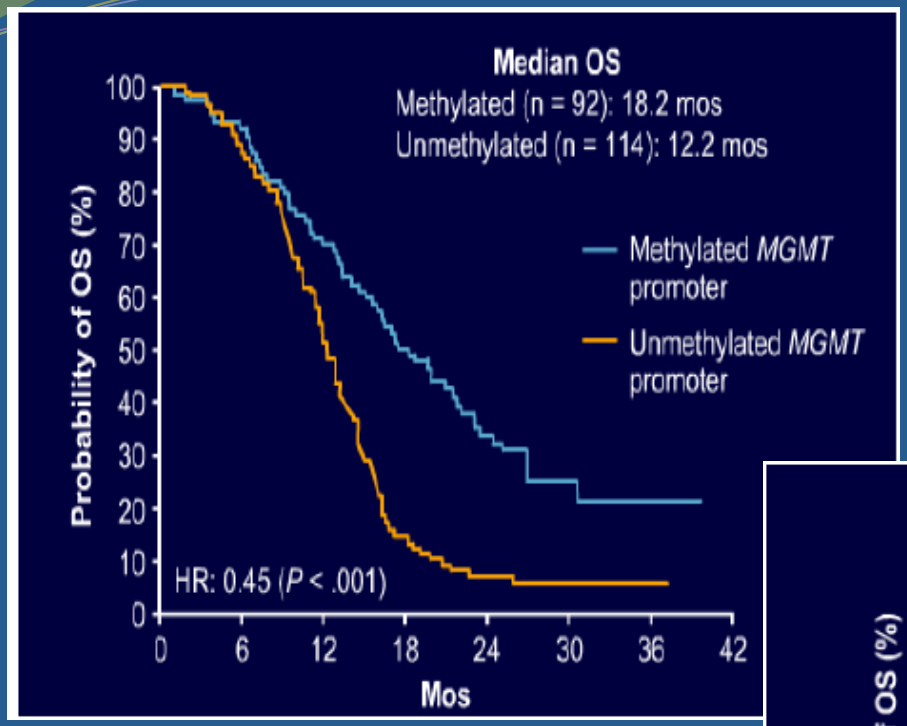
GBM

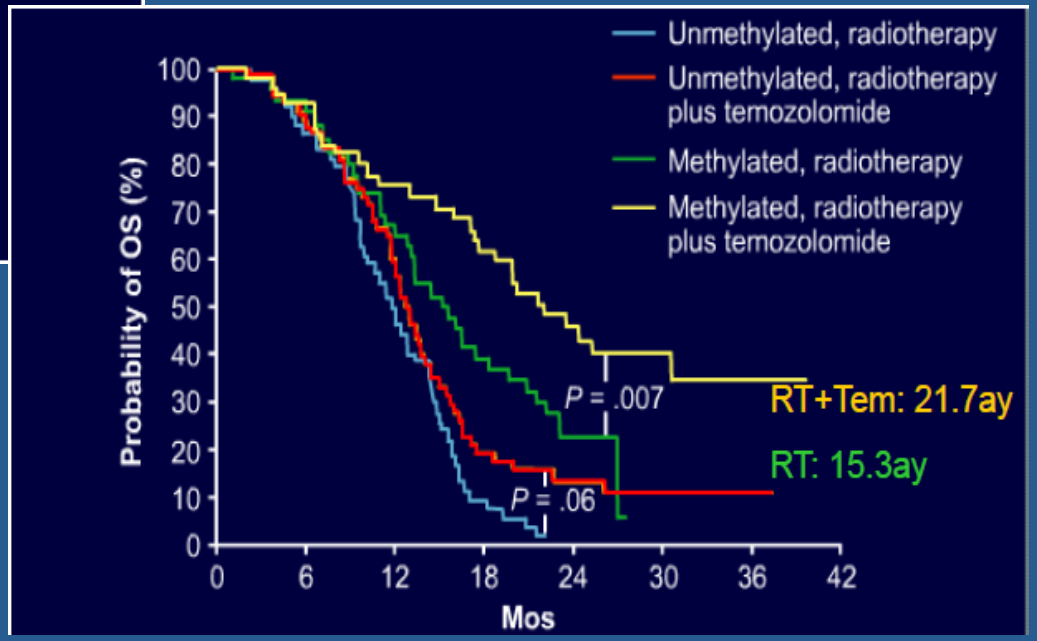
- O6-Metilguanin-DNA metiltransferaz (MGMT)
- 1p19q kodelesyonu
- İzositrat Dehidrogenaz (IDH)mutasyonu

MGMT



Weller et al. Nat Rev Neurol 2010





Heigi M et al. NEJM 2005

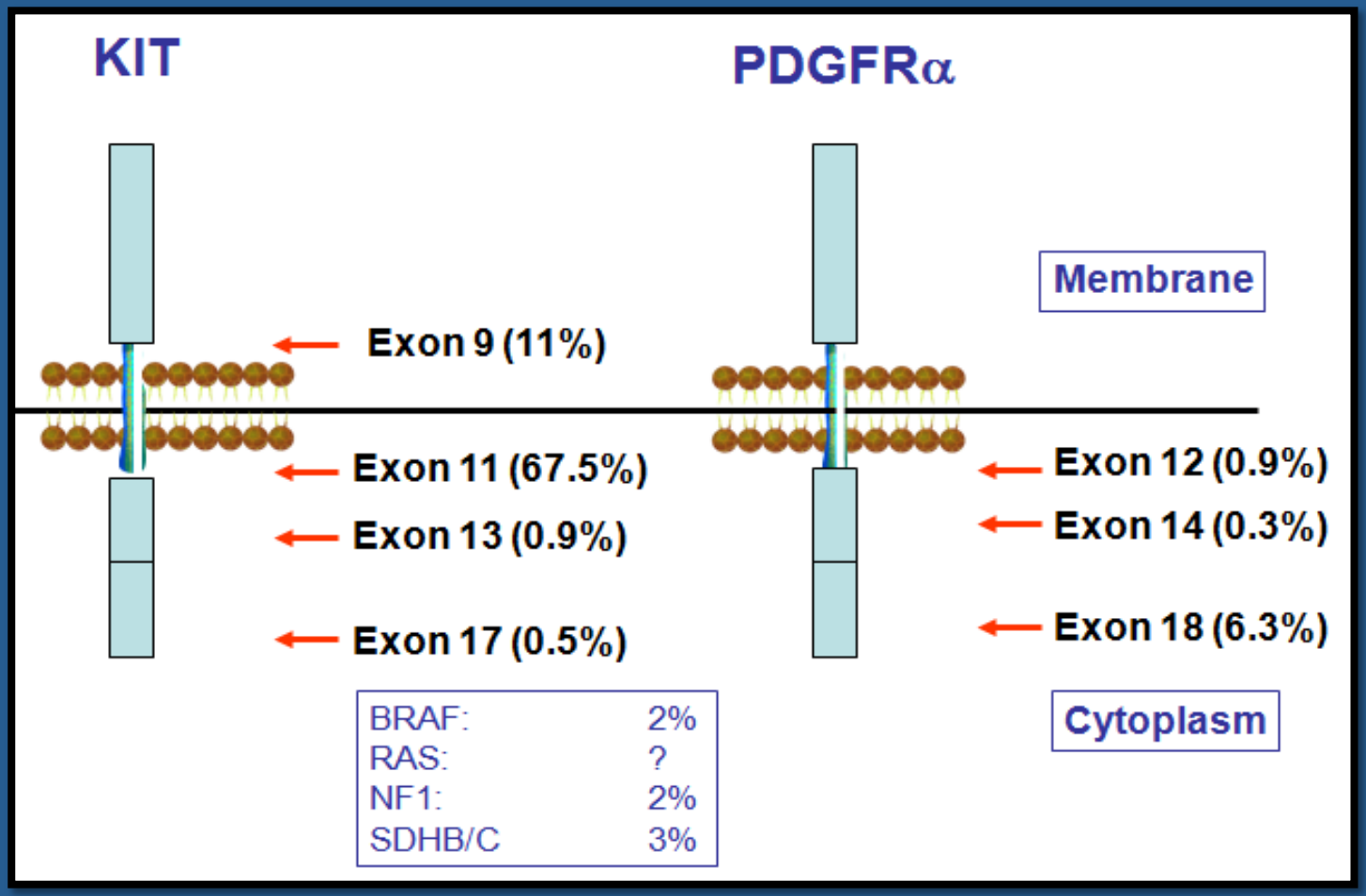
GIST

- KIT gen mutasyonu %80
- CD117%95 + (KIT rtk üzerinde epitop)
- PDGFRa mutasyonu %6-10

D842v /exon 18 mutayonu

- %10-15 KIT ve PDGFRa mutasyonu yok

Miettinen M, Lasota JVirchows Arch. 2001;438(1):1.PMID 11213830
Miettinen M, Lasota J, Sobin LH.Am J Surg Pathol. 2005;29(10):1373.PMID 16160481



Blay JY, Le Cesne A, Cassier PA, Ray-Coquard IL.Discov Med. 2012 May;13(72):357-67. Review. PMID: 22642917

	Adjuvant Phase	Metastatic Phase
KIT Exon 11	Imatinib 400mg/d	Imatinib 400mg/d
KIT Exon 9	Imatinib 400mg/d	Imatinib 800mg/d
KIT other sites	Imatinib 400mg/d	Imatinib 400mg/d*
PDGFRA D842V	No imatinib	No imatinib
PDGFRA non D842V	Imatinib 400mg/d	Imatinib 400mg/d
NF1	No concensus*	Imatinib 400mg/d**
BRAF	No concensus*	Imatinib 400mg/d**
K-Ras/N-Ras	No concensus*	Imatinib 400mg/d**
SDHB or C	No concensus*	Imatinib 400mg/d**
IGF1R overexpression	No concensus*	Imatinib 400mg/d**

Blay JY, Le Cesne A, Cassier PA, Ray-Coquard IL.Discov Med. 2012 May;13(72):357-67. Review. PMID: 22642917

Sonuç olarak…

- Maksimum sağkalım /tümör yanıtı
- Minimal yan etki
- Tedaviden en çok fayda görebilecek hasta grubu
- Tedaviye yanıtı predikte edebilecek belirteçler
- Prognoz
- Hedef tedaviler

IHC / morfoloji
DNA /RNA bazlı genetik yöntemler
DNA /ekzom sekanslama yöntemleri