Akciğer Kanserinde Hedefe Yönelik Tedaviler

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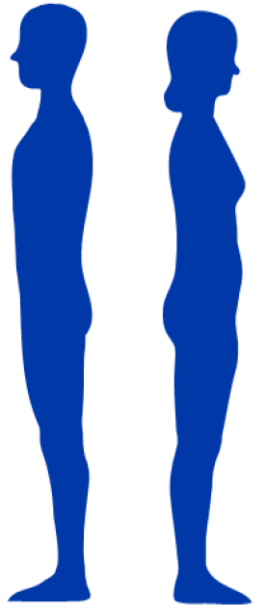
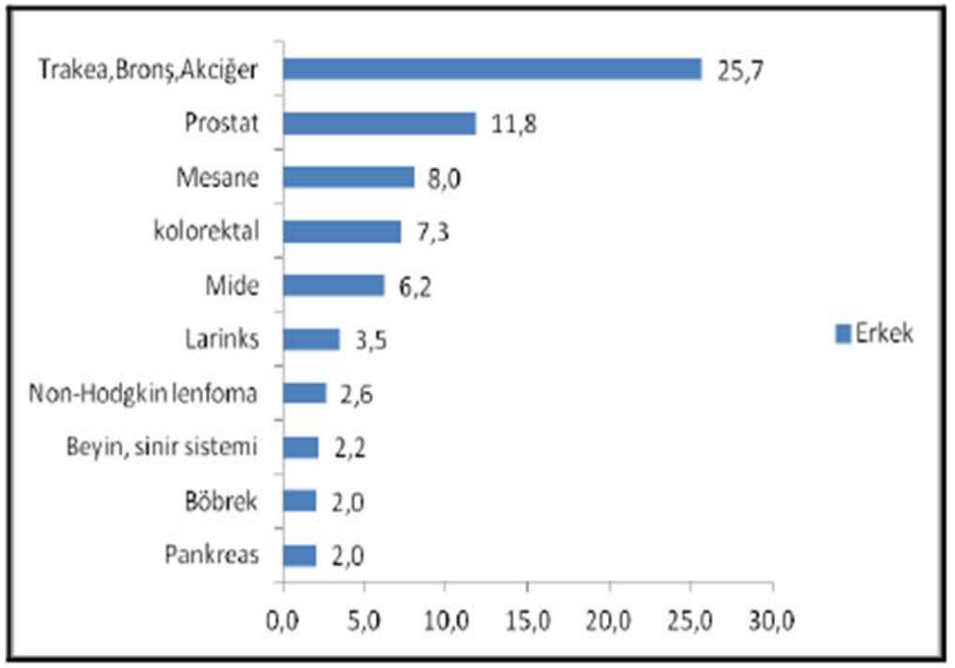
Kanser Sorunu

2012 Estimated US Cancer Deaths

Men 301,820		Women 275,370	
Lung & bronchus	29%	26%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	9%	9%	Colon & rectum
Pancreas	6%	7%	Pancreas
Liver & intrahepatic bile duct	5%	6%	Ovary
Leukemia	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Urinary bladder	3%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain/other nervous system
All other sites	25%	24%	All other sites



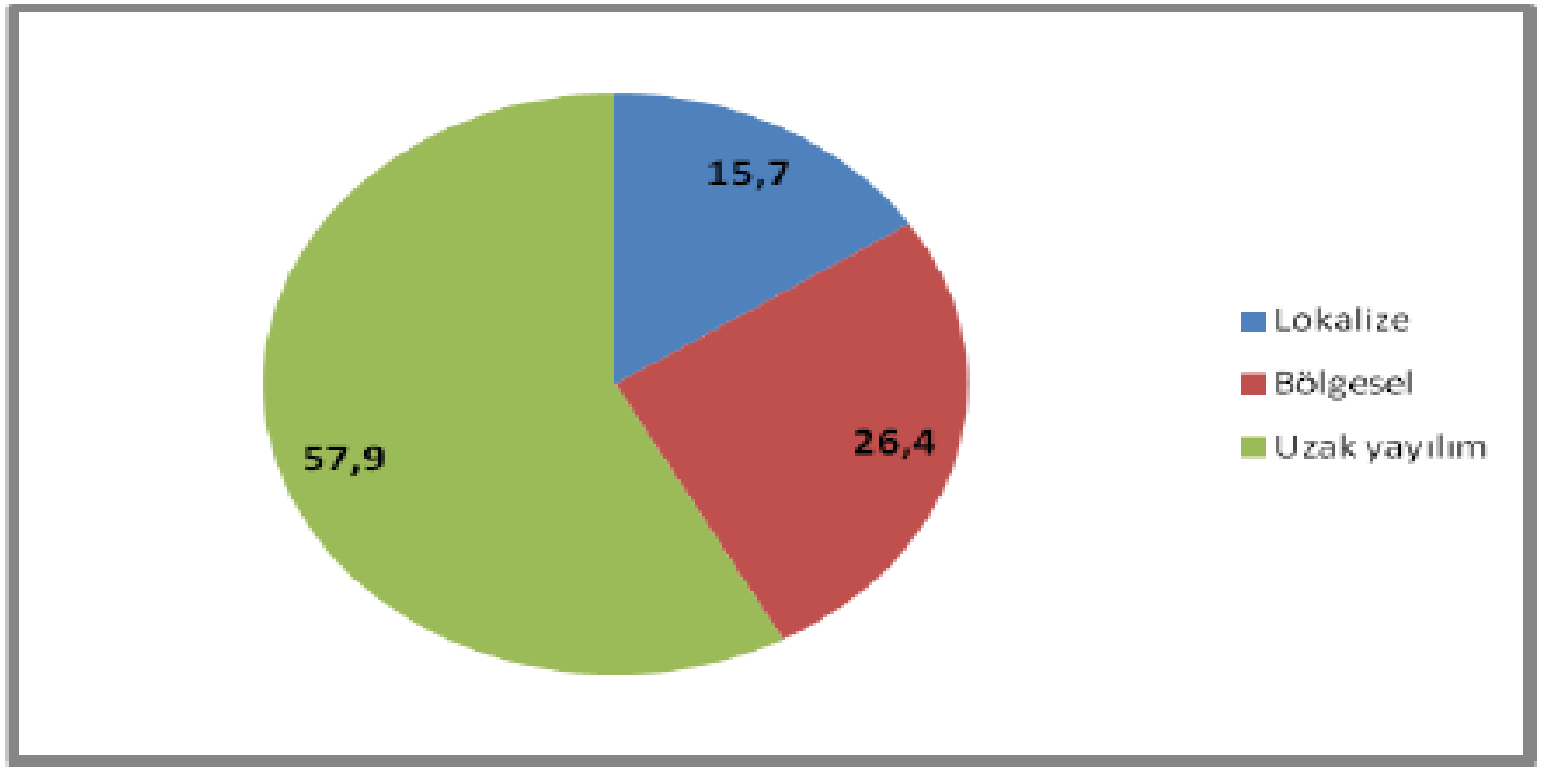
American Cancer Society, Cancer Facts and Figures 2012.



Şekil 8. Tüm Yaş Gruplarındaki Erkeklerde En Sık Görülen Bazı Kanserlerin Bu Grup İçindeki Yüzde Dağılımları (Birleşik Veri Tabanı, 2009)

Kanser Sorunu

2009 Bazı Kanserlerde Evreler



Şekil 23. Akciğer Kanseri Evrelerinin Yüzde Dağılımları (Birleşik Veri Tabanı, 2009)

Akciğer Kanseri Heterojen hastalık

Hasta alt grupları
Onkogenezde etkili mutasyonlar
Mutasyonları hedefleyen tedavi

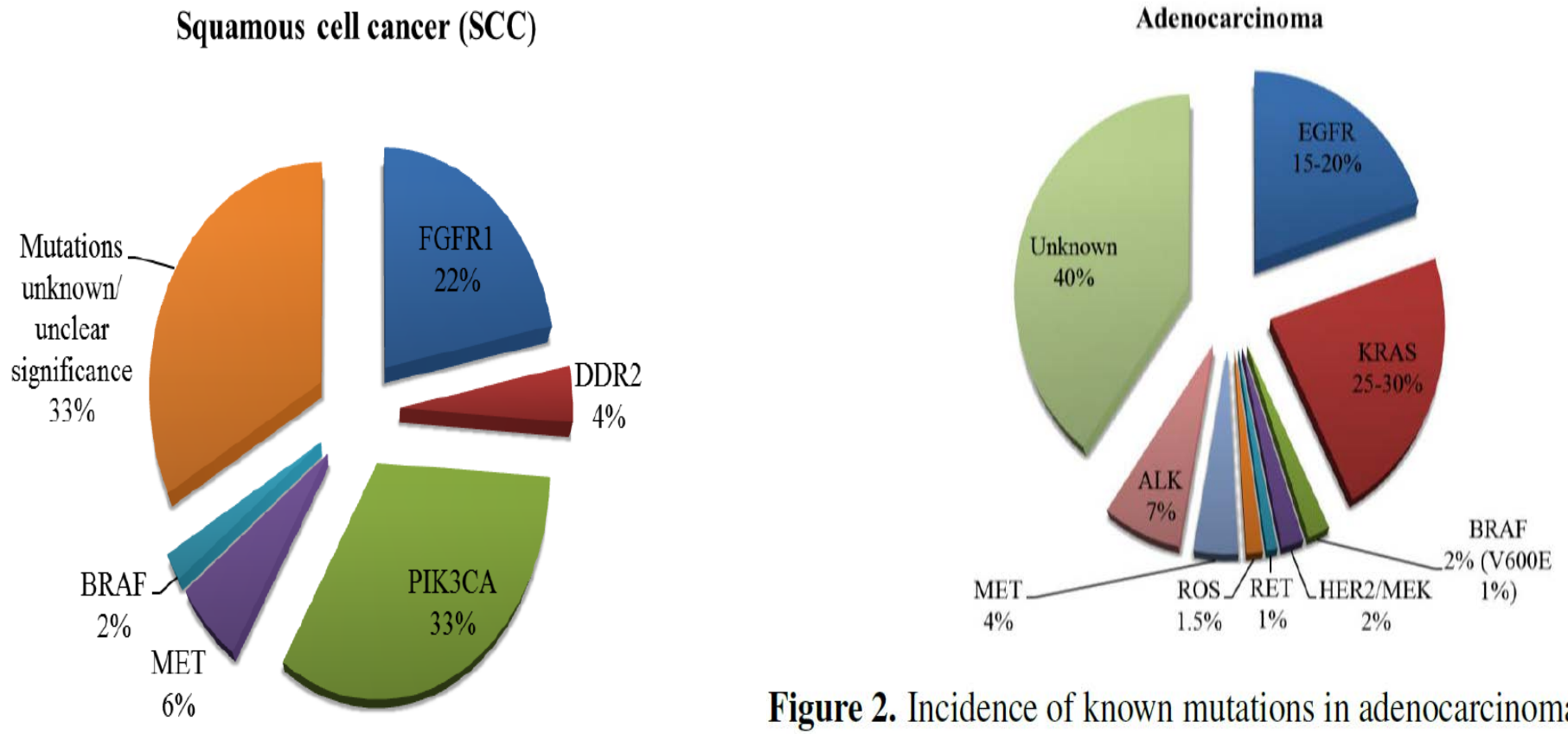
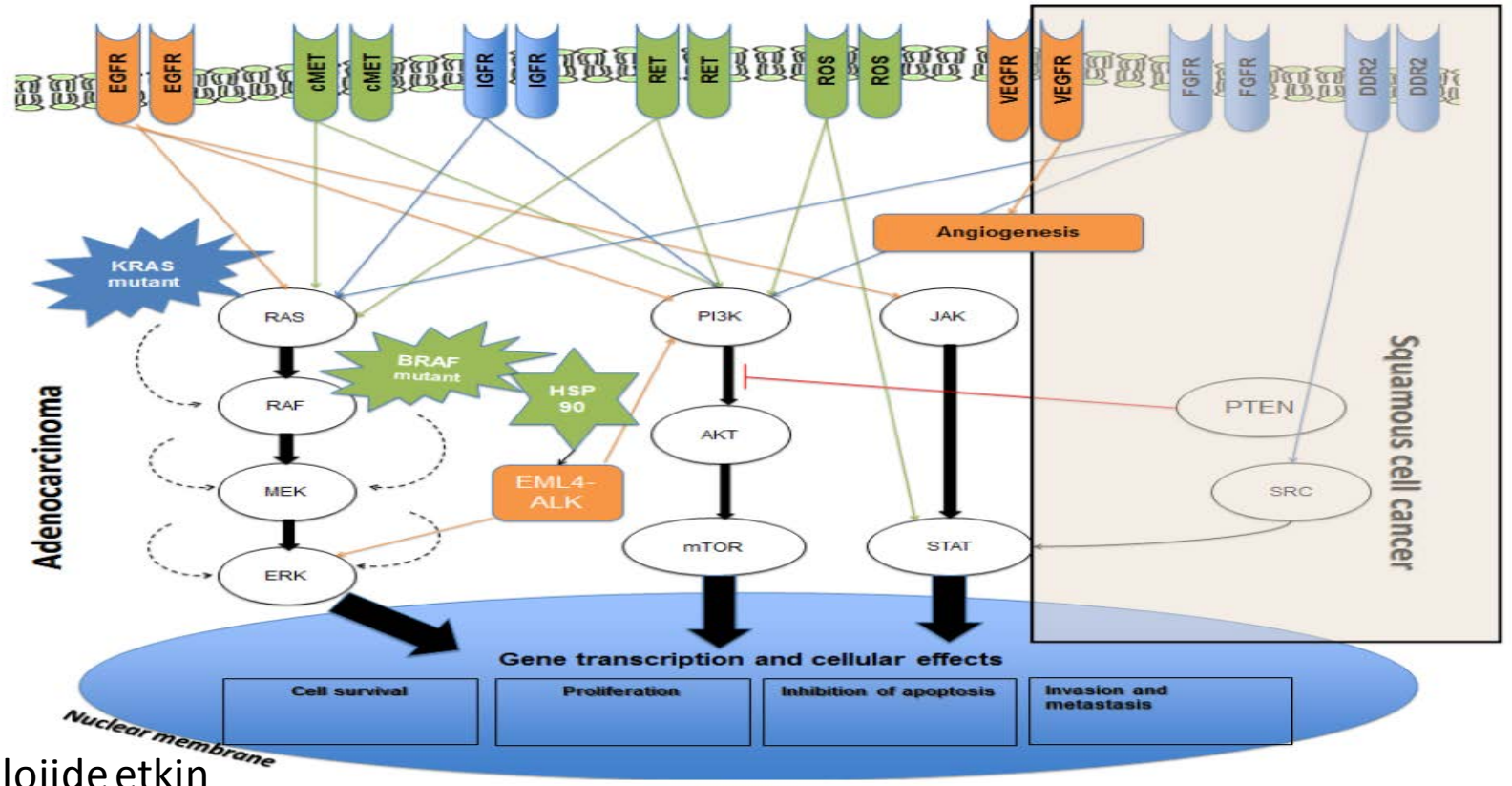


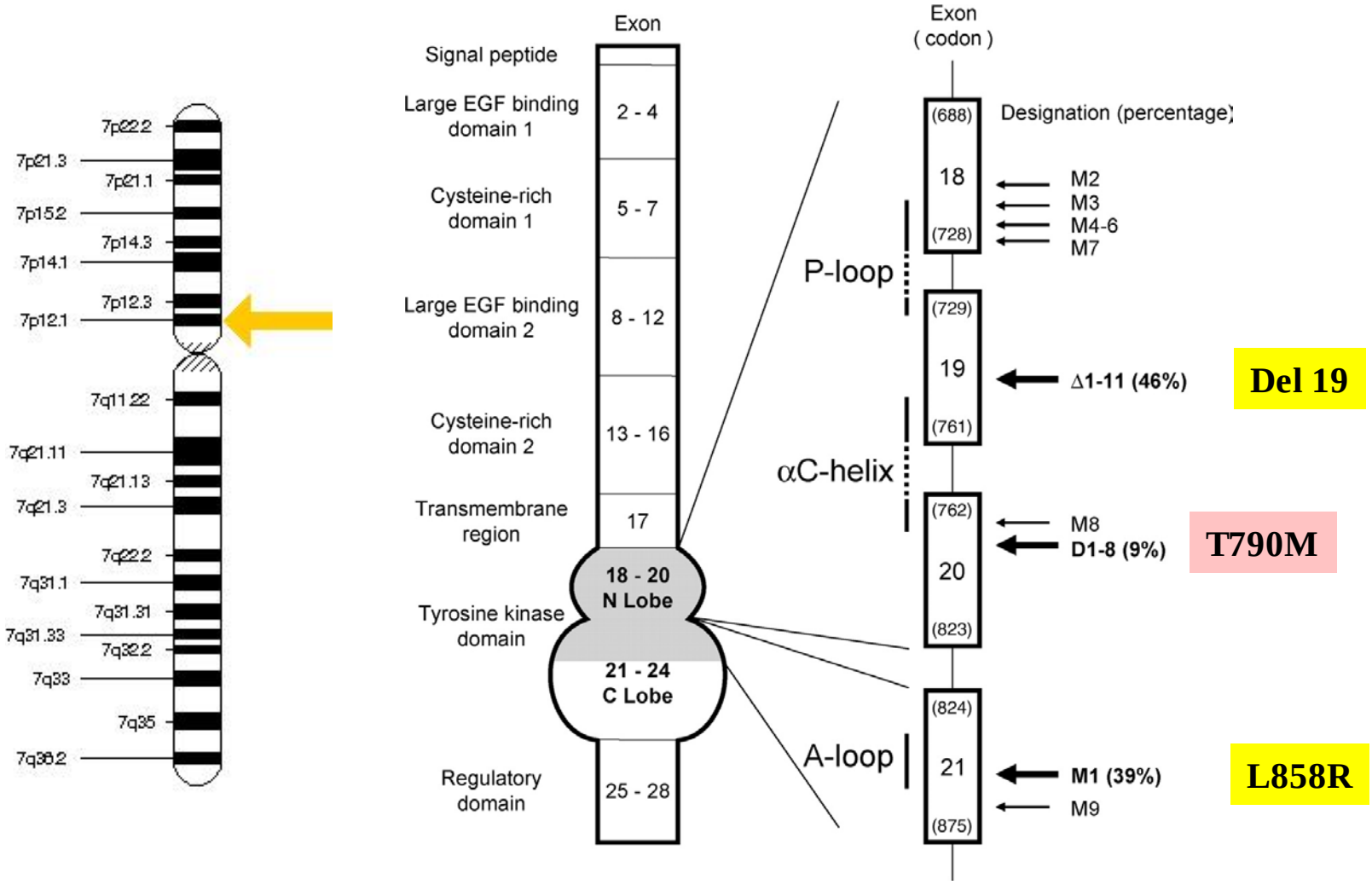
Figure 2. Incidence of known mutations in adenocarcinomas of the lung.

Akciğer kanseri - Mutasyonlar



Anjioenezis her iki histolojide etkin
Kahverengi: Hedefe yönelik tedavi seçeneği var
Yeşil: Hedefe yönelik tedavi seçeneği geliştiriliyor
Mavi: Hedefe yönelik tedavi seçeneği yok

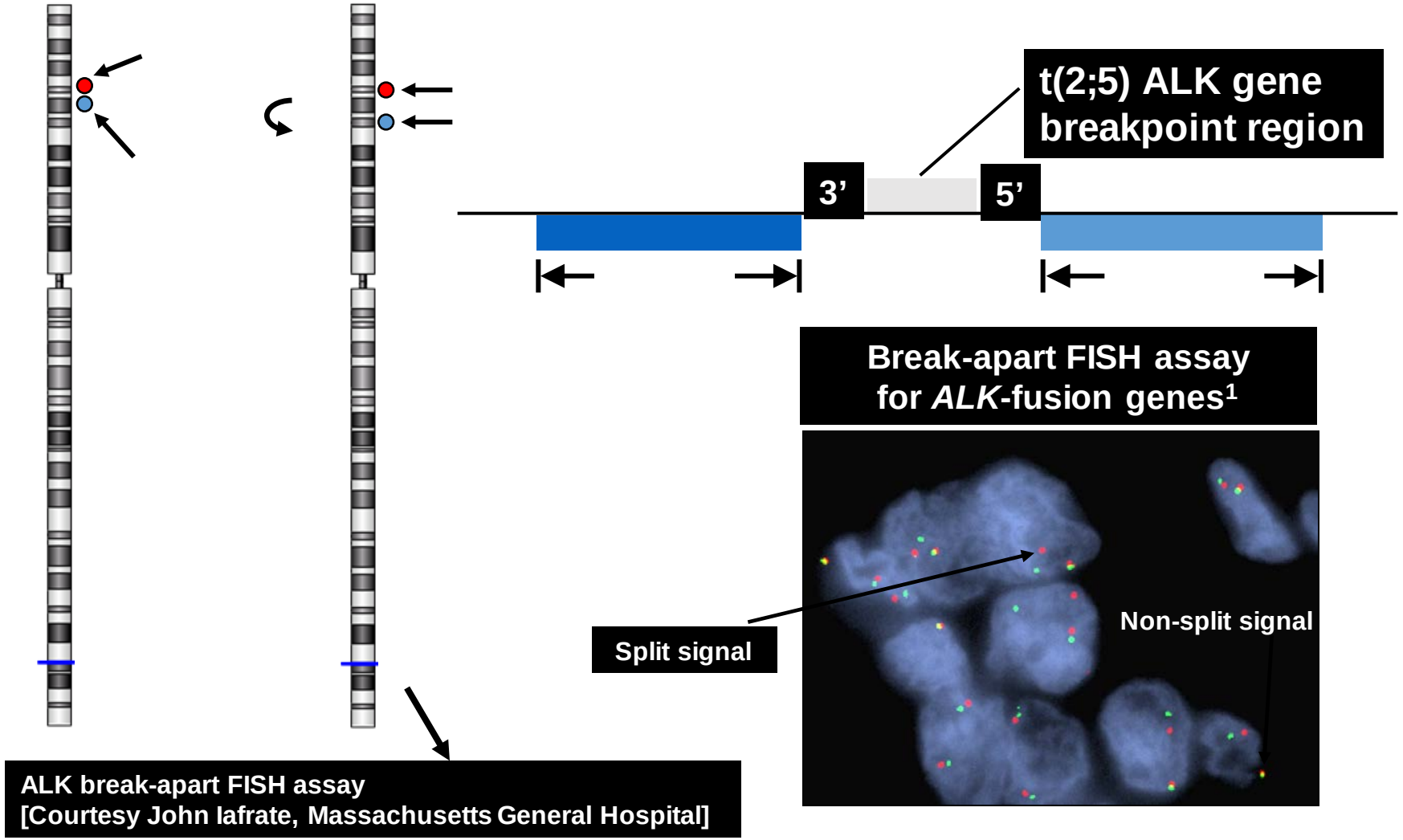
Locations and Types of the 134 EGFR Gene Mutations Detected in Lung Cancers



Shigematsu H et al. JNCI J Natl Cancer Inst 2005;97:339-346

JNCI

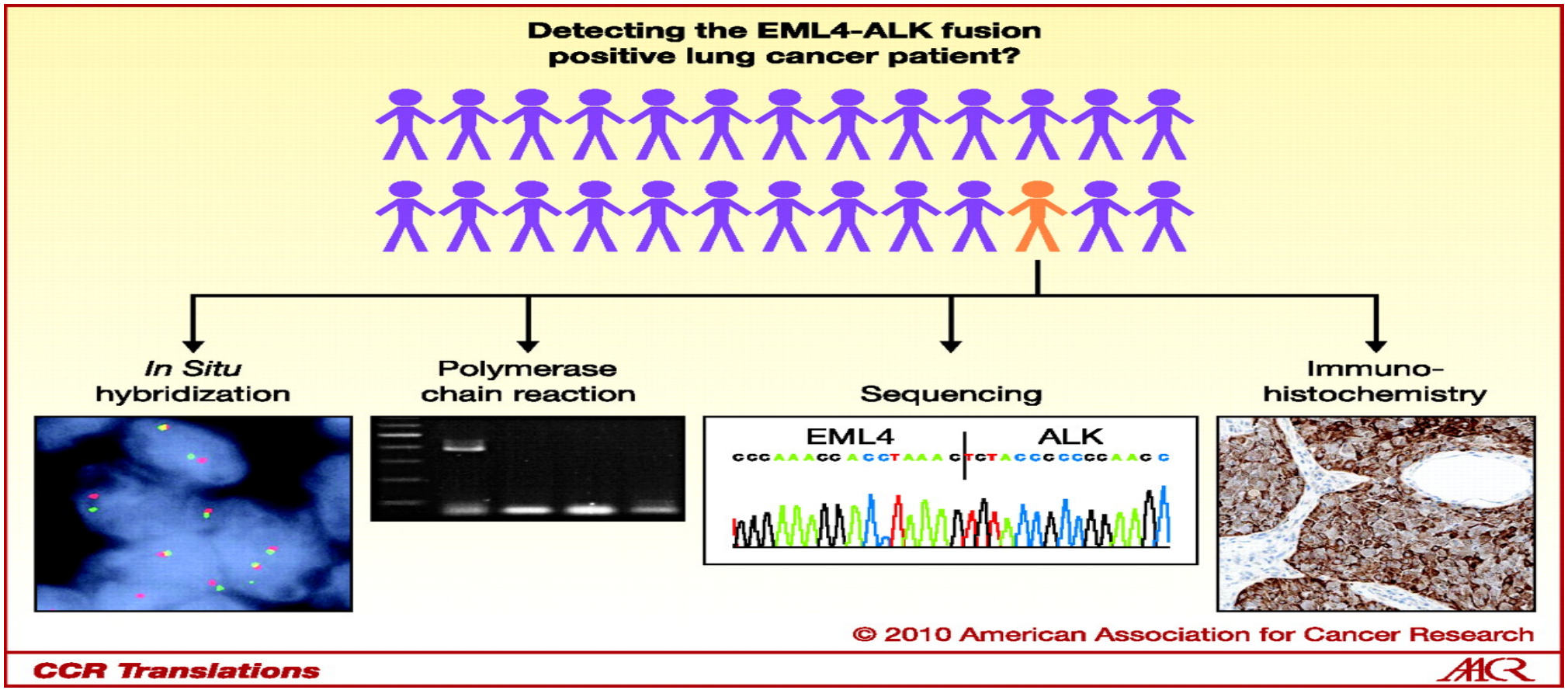
ALK Rearrangement



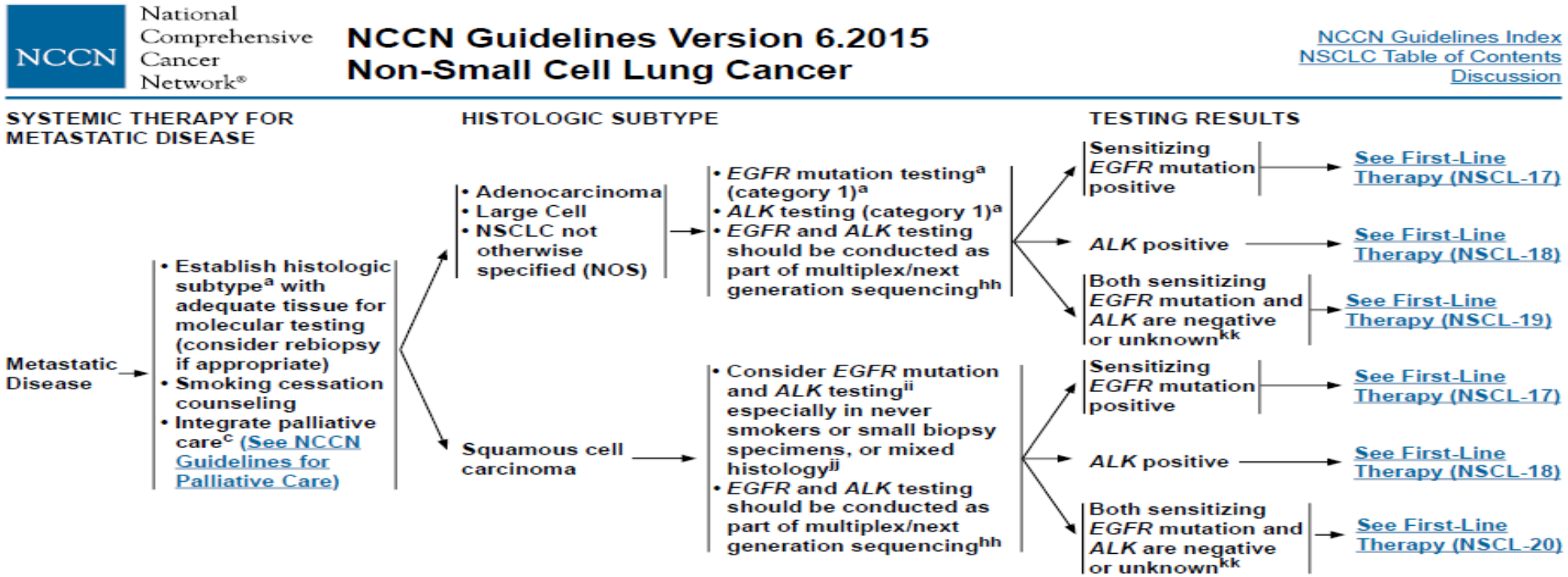
*Assay is positive if rearrangements can be detected in ≥15% of cells

[1]Shaw AT et al. J Clin Oncol 2009;27:4247–4253

Mutasyonların Tanınması



Kime Mutasyon Analizi Yapılmalı



[a] See Principles of Pathologic Review (NSCL-A).
[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
[hh] The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[ii] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[jj] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.
[kk] Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

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.

EGFR TKI'lar ile kişiselleştirilmiş tedavi tarihi

EGFR

- Adenokarsinoma %20 sinde
- Exon 19 (delesyon)
- Exon 21 (L825R) nokta mutasyon

  mutasyonların %85 i

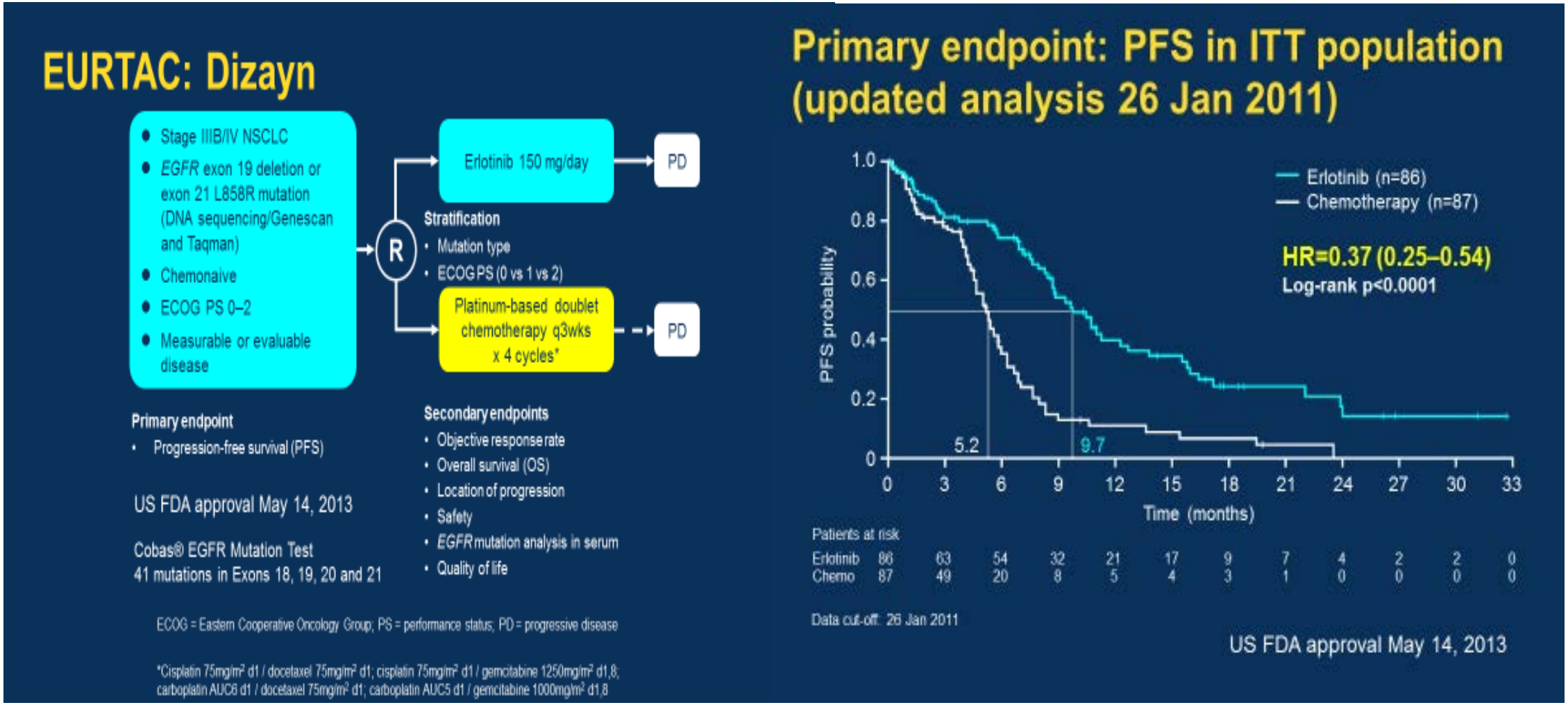
- Adeno
- Asyalı
- Kadın
- Sigara içmemiş

Direnç:

Exon 20 (insertion)

T790M

EGFR TKI İlk Seçim Tedavi



1 kuşak EGFR inhibitörü TKI

- Reversibl kompetitif inh.
- Kemoterapiden daha etkili
- Yan etki profili

  Diare

  acneiform döküntü

  pnomonitis

Table 1. Trials showing the efficacy of EGFR TKI in EGFR mutant advanced NSCLC.

First Generation EGFR TKI (Erlotinib, Gefitinib)-First-Line Studies						
Trial	Population	Number	Agent (A)	Comparator (C)	Median PFS A *vs.* C (Months)	HR
Mok *et al.* (2009) [40] Phase III	Adenocarcinoma, Asian, never or light smokers	1217	Gefitinib	Carboplatin, paclitaxel	9.8 *vs.* 6.4	0.48
Maemondo *et al.* (2010) [41] Phase III	EGFR mutant	230	Gefitinib	Carboplatin, paclitaxel	10.8 *vs.* 5.4	0.30
Mitsudomi *et al.* (2010) [42] Phase III	EGFR mutant	172	Gefitinib	Cisplatin, docetaxel	9.2 *vs.* 6.3	0.489
Han *et al.* (2012) [43] Phase III	Adenocarcinoma, Asian, never or light smokers	309 42 EGFR +ve	Gefitinib	Cisplatin, gemcitabine	5.8 *vs.* 6.4 8.0 *vs.* 6.3	1.198 0.544
Zhou *et al.* (2011) [44] Phase III	EGFR mutant	154	Erlotinib	Carboplatin, gemcitabine	13.1 *vs.* 4.6	0.16
Rosell *et al.* (2012) [45] Phase III	EGFR mutant	173	Erlotinib	Platinum doublet	9.7 *vs.* 5.2	0.37

2 Kuşak EGFR TKI

- Afatinib
- Pan Erb B
- EGFR,HER2,HER4 inh
- İrreversibl inh
- T790M mut etkili

Sequist *et al.* (2013) [52] Phase III	EGFR mutant- 1st line setting	345	Afatinib	Cisplatin, pemetrexed	11.1 vs. 6.9	0.58
Wu *et al.* (2014) [60] Phase III	EGFR mutant- 1st line setting	364	Afatinib	Cisplatin, gemcitabine	11.0 vs. 5.6	0.28
Yang *et al.* (2012) [53] Phase II	EGFR mutant- 2nd line with no prior EGFR TKI	129	Afatinib	Single arm	14.0	NA
Miller *et al.* (2012) [54] Phase IIb/III	EGFR mutant- after treatment with EGFR TKI	585	Afatinib	Placebo	3.3 vs. 1.1	0.38
Katakami *et al.* (2013) [55] Phase II	Clinical post 1st line EGFR TKI, 72.6% mutant	62	Afatinib	Single arm	4.4	NA

2 Kuşak EGFR TKI

- Dacomitinib
- Neratinib
- Yüksek toksisite profili
- Düşük etkinlik

3.Kuşak TKI

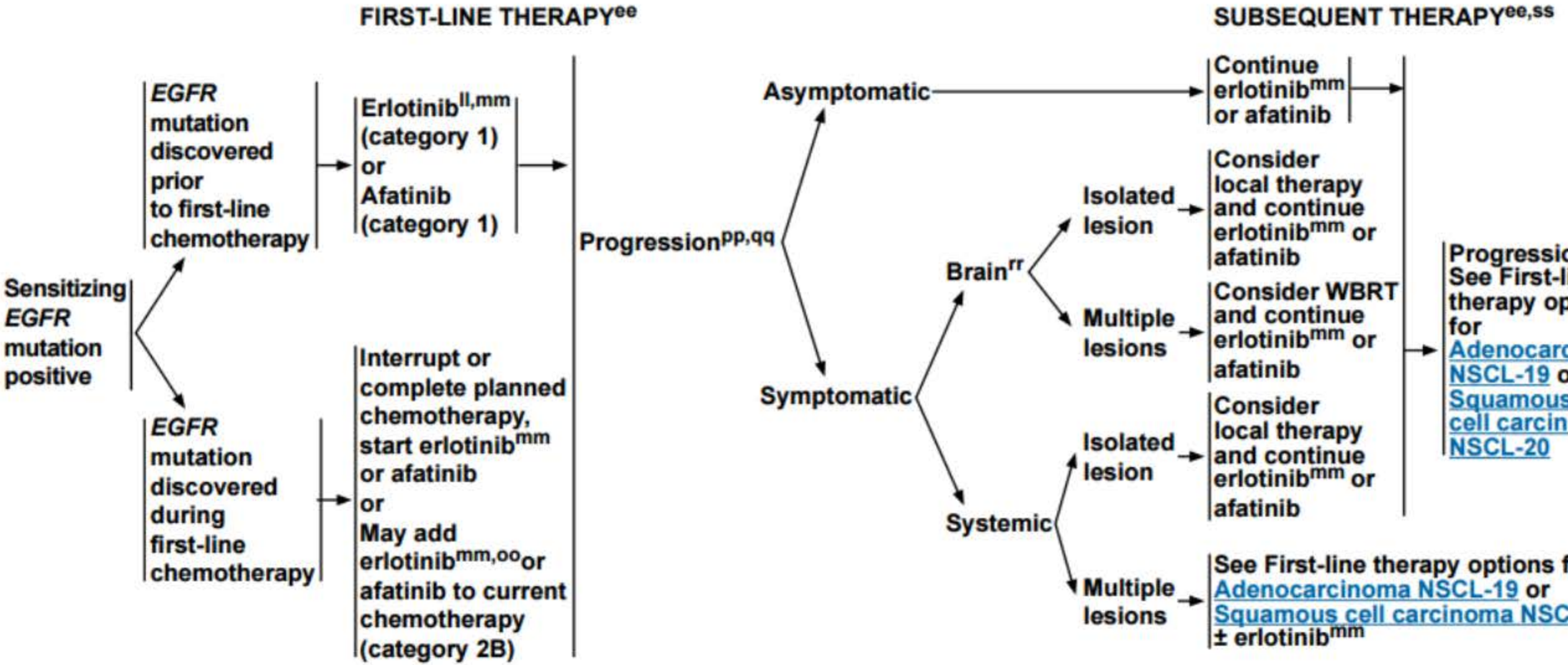
- İrreversibl EGFR ve minimal Erb
- Özellikle T790 M mut etkili
- Rociletinib

- Rociletinib: FazII: TKI sonrası

Cevap oranı :% 59 T790M +

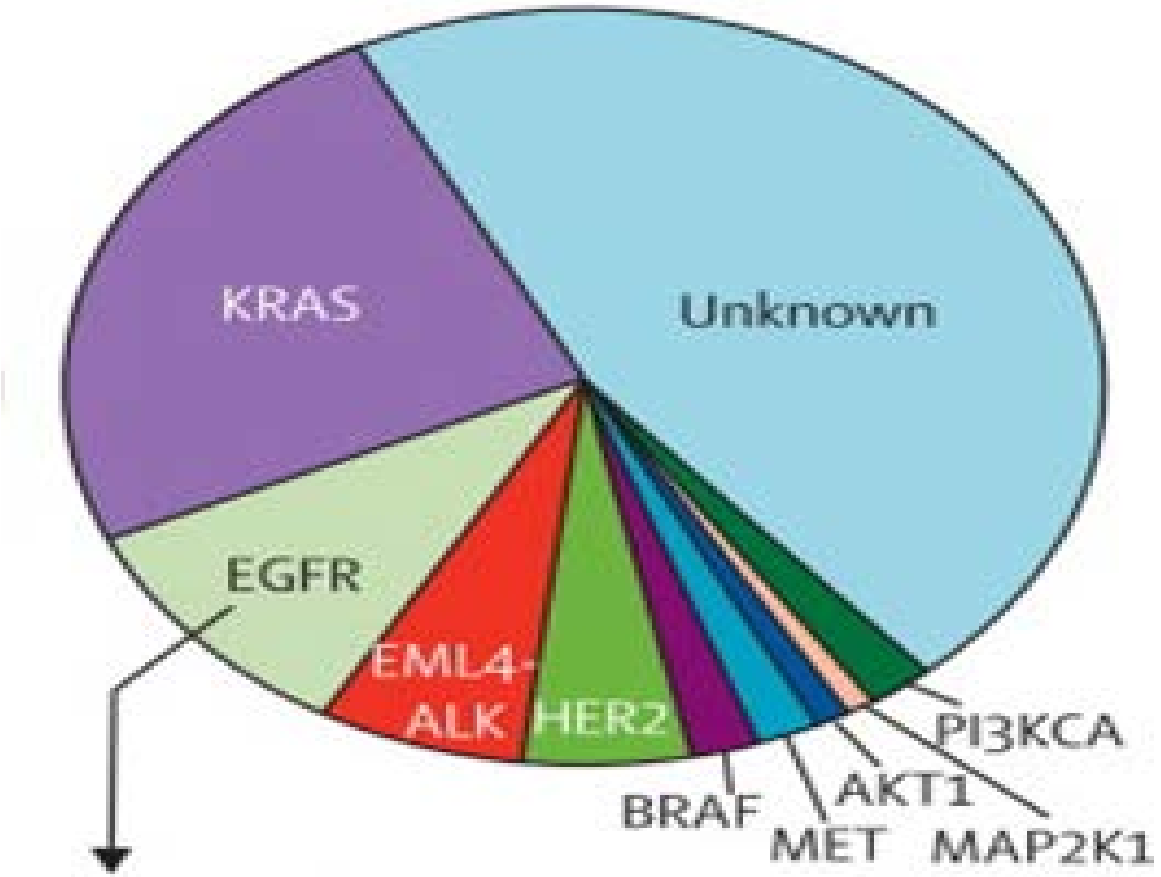
: %29 T790M -

SENSITIZING EGFR MUTATION POSITIVE[a]

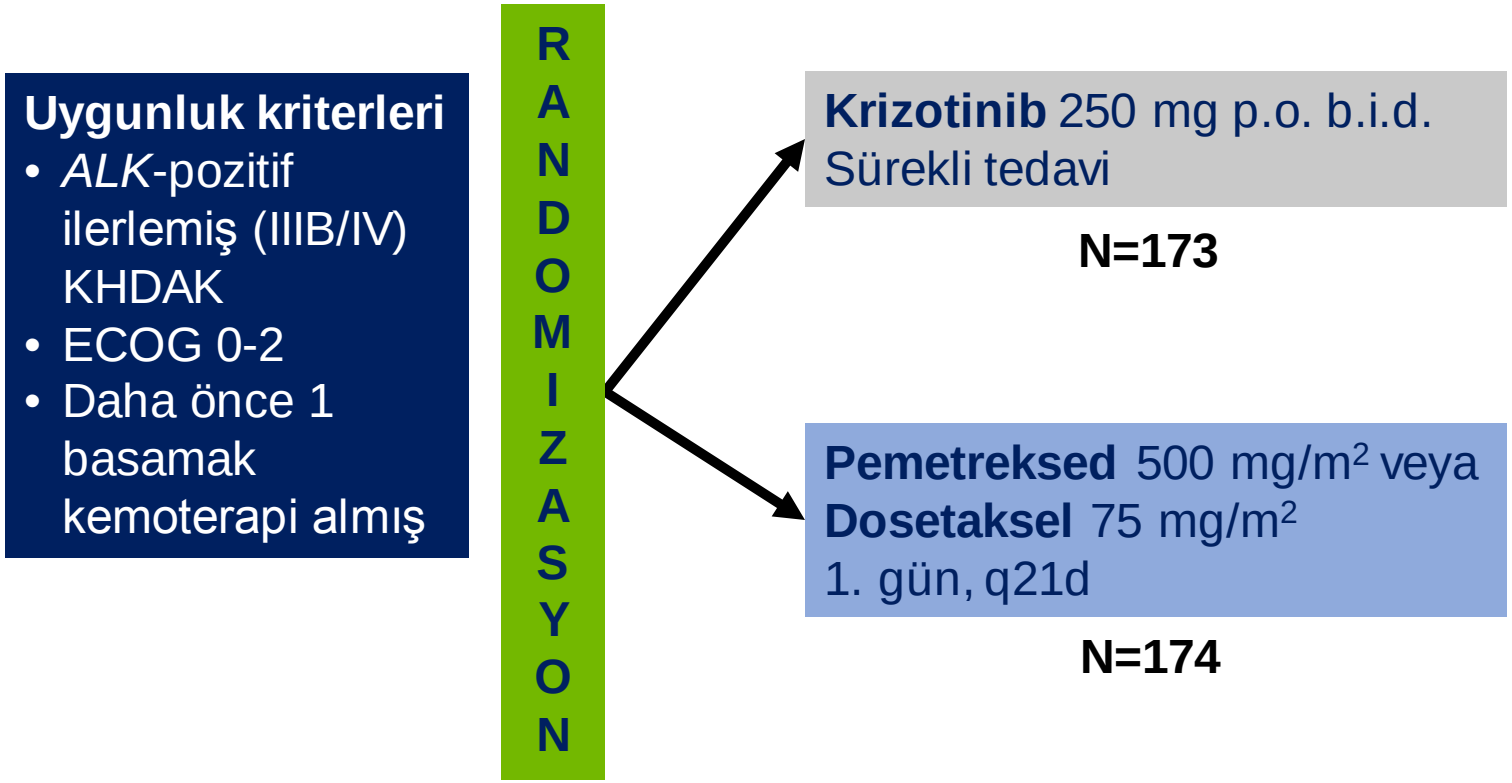


[a] See Principles of Pathologic Review (NSCL-A).
[ee] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ll] For performance status 0-4.
[mm] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[qq] Beware of flare phenomenon in subset of patients who discontinue EGFR disease flare occurs, restart EGFR TKI.
[rr] Consider pulse erlotinib for carcinomatosis meningitis.
[ss] Afatinib appears to have some efficacy in patients who progressed on EG therapy. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for pa

- ALK EML4 Füzyon Geni:
- Mutasyon oranı:%3-7



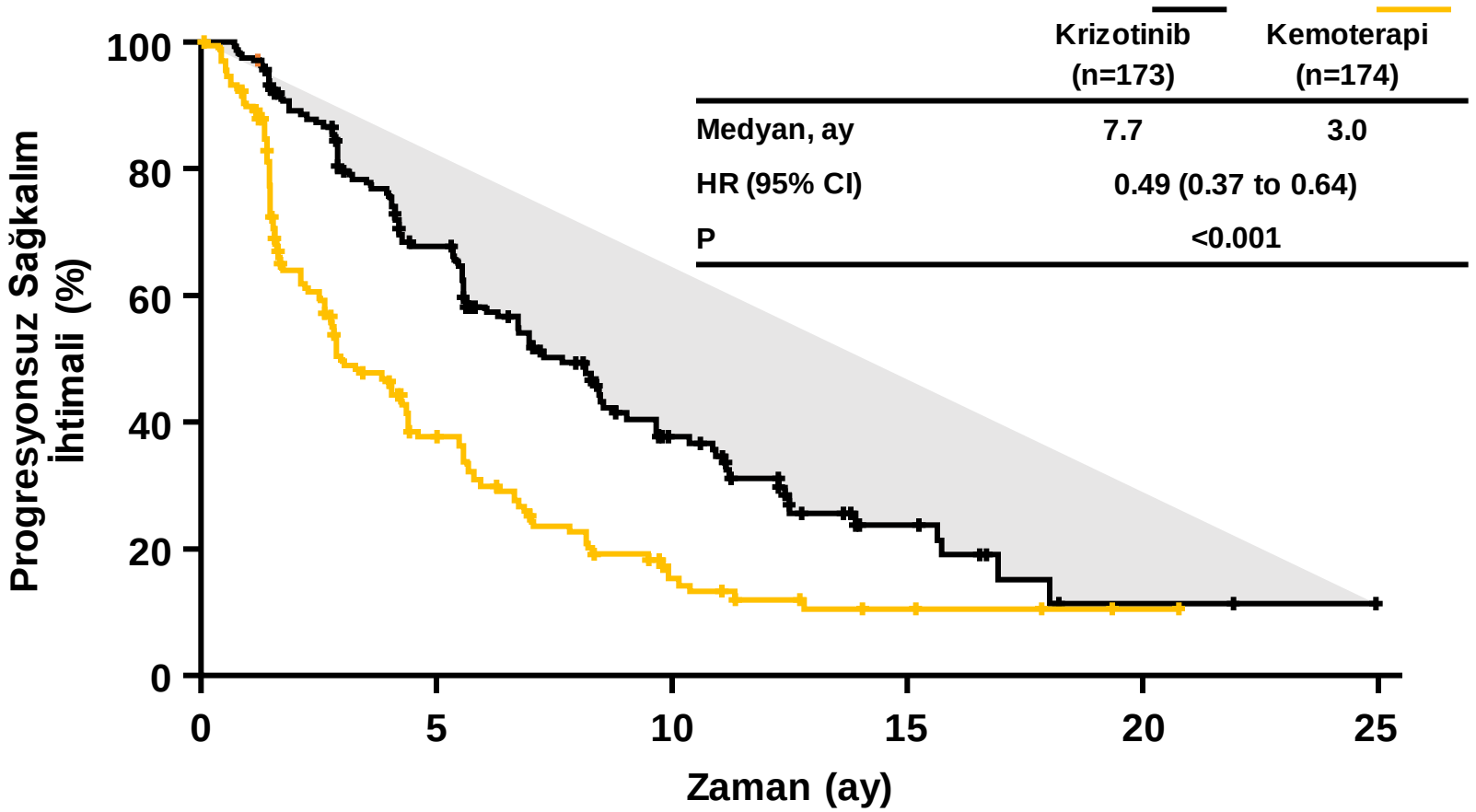
PROFILE 1007: Çalışma tasarımı



Primer sonlanım noktası: PFS*
Sekonder sonlanım noktaları: OS; ORR, DCR, DR, güvenlilik, QoL, PK

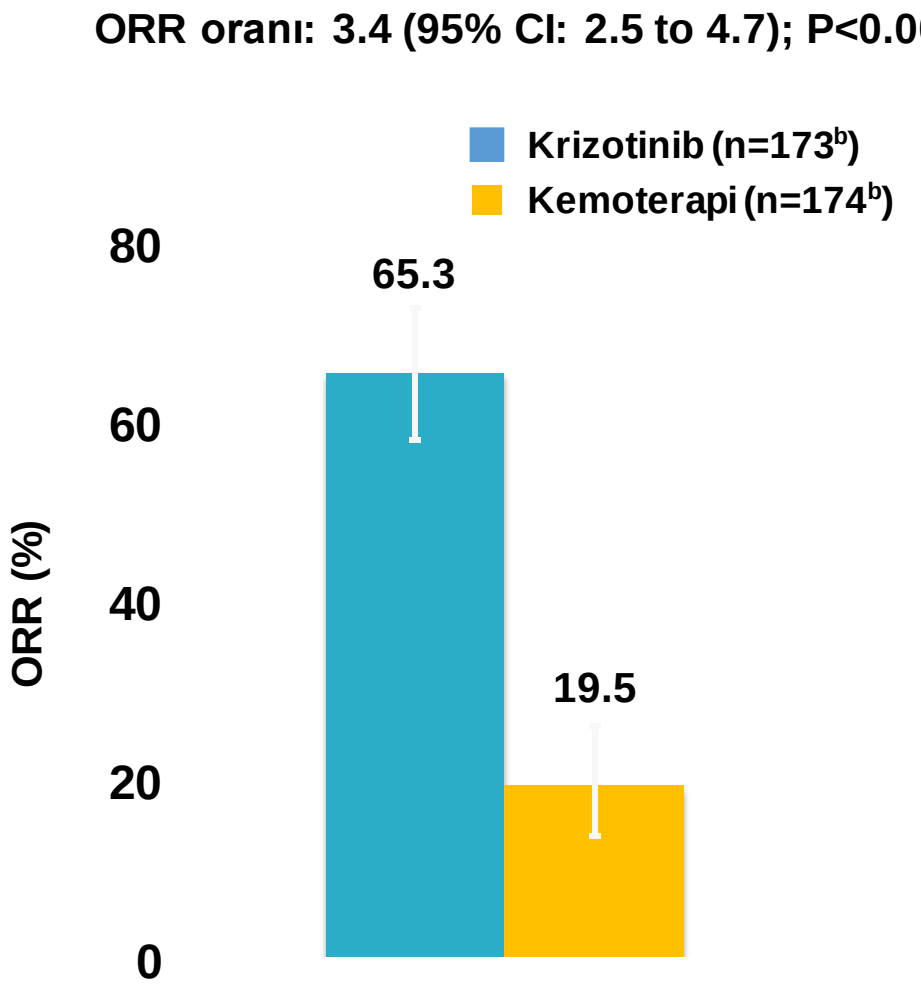
ClinicalTrials.gov ID: NCT00932893

PROFILE 1007 Primer sonlanım noktası: PFS



Riskteki hasta						
Krizotinib	173	93	38	11	2	0
Kemoterapi	174	49	15	4	1	0

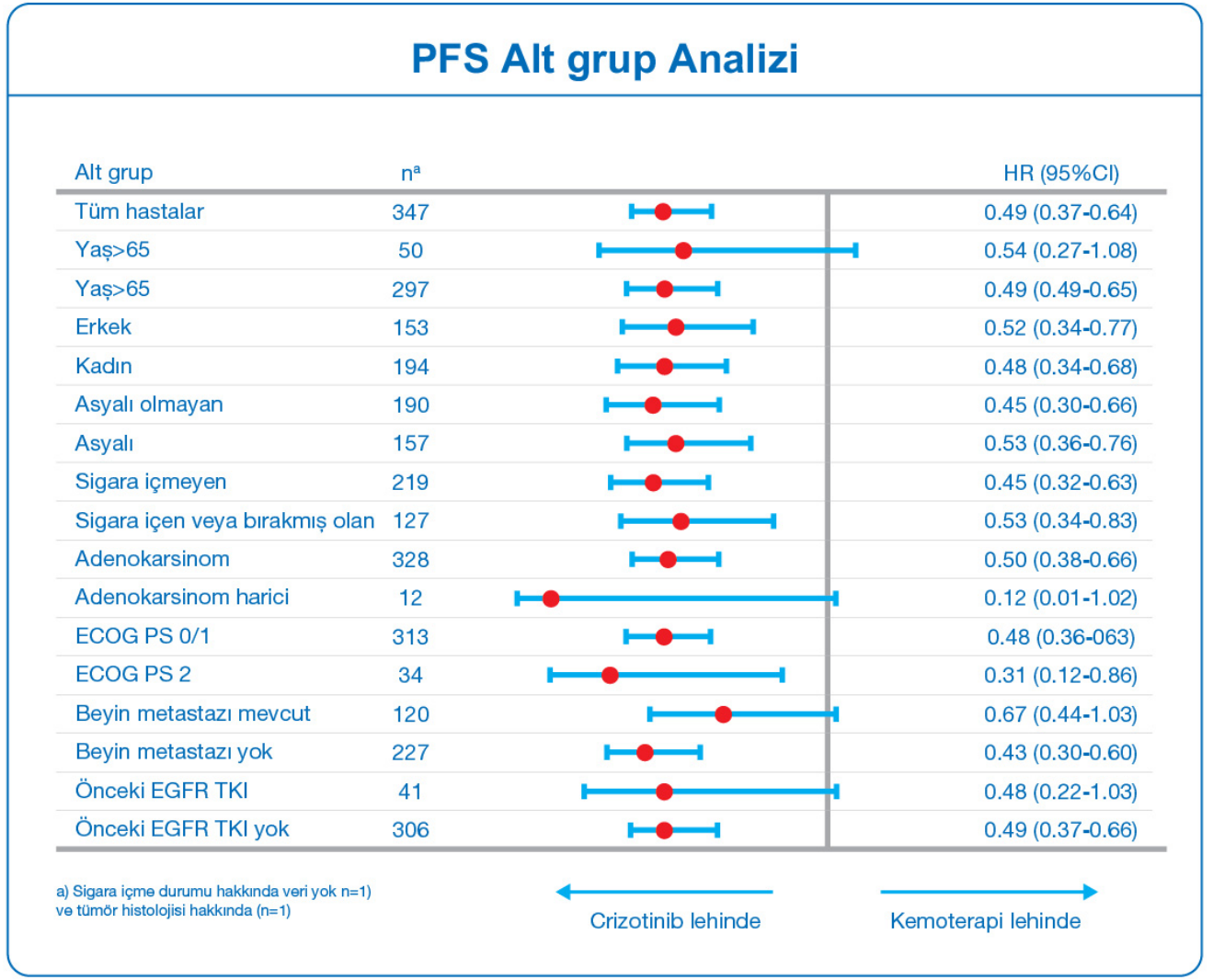
PROFILE 1007 Bağımsız Radyolojik Değerlendirmeye göre yanıt oranları



[a]RECIST v1.1; [b]ITT population; [c]as-treated population

Shaw AT, et al. N Engl J Med 2013;368:2385–94

PROFILE 1007 Alt gruplar



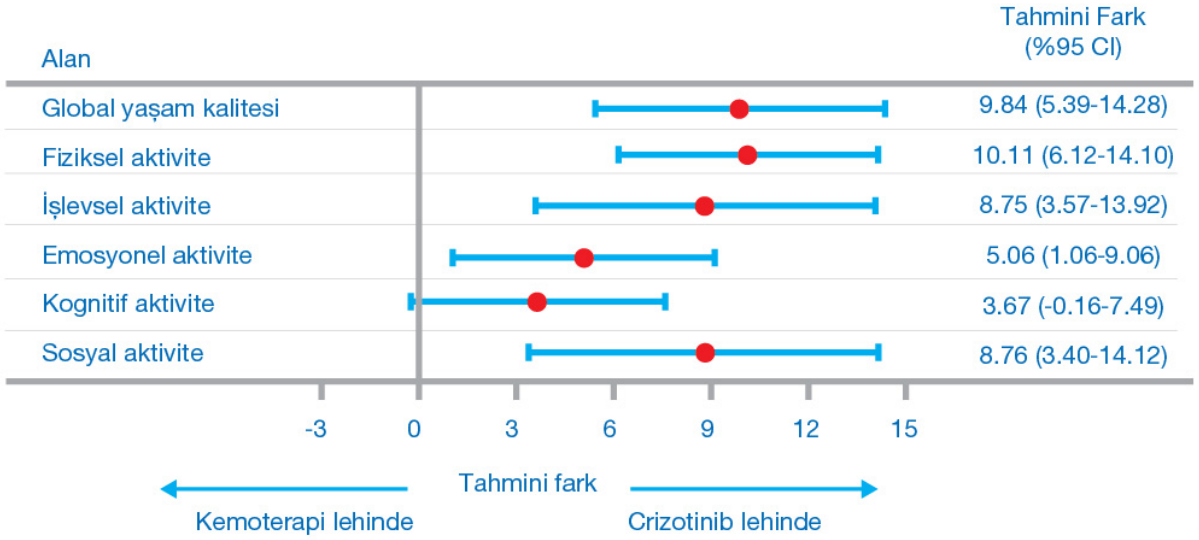
Shaw AT, et al. N Engl J Med 2013;368:2385–94

PROFILE 1007
Krizotinib tedavisi güvenlilik sonuçları

Hastaca Bildirilen Sonuçlar
Semptomlar ve Yaşam Kalitesi[a]

SEMPTOMLAR: Crizotinib ile öksürük, dispne, halsizlik, alopesi, uykusuzluk ve ağrıda başlangıca göre daha fazla iyileşme (istatistiksel olarak anlamlı: hepsinde P<0.0001)[b]

YAŞAM KALİTESİ: Crizotinib ile tedavi edilen hastalarda global yaşam kalitesinde başlangıca göre daha fazla iyileşme (istatistiksel olarak anlamlı: P<0.0001)[b]



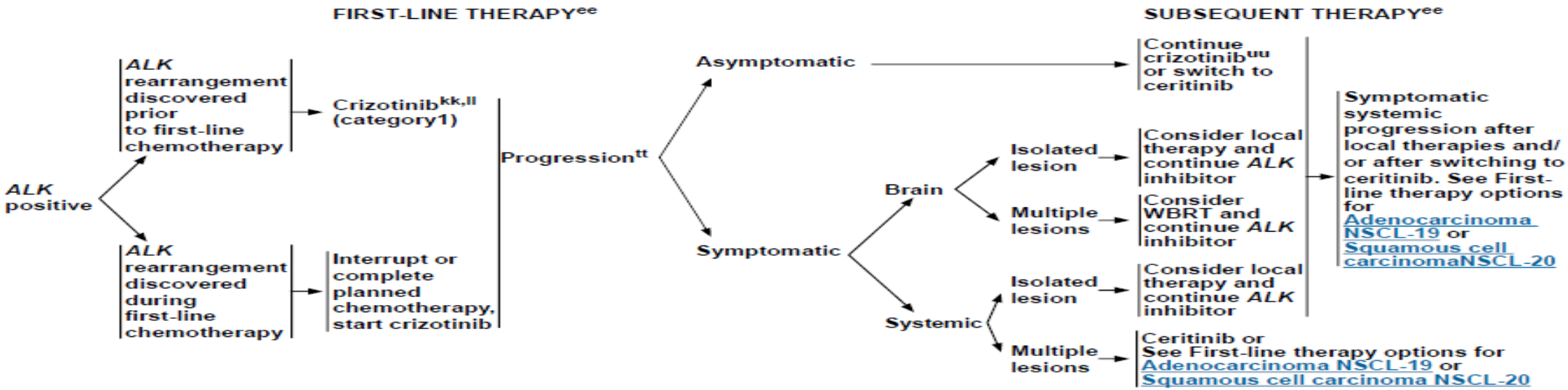
a) EORTC QLQ-C30 ve QLQ-LC13; b engelleme ile tekrarlayan ölçüler karışık-etki modeline dayanarak tedavi, süre etkileşimine göre tedavi ve alt ölçek başlangıç skoru; test çokluğuna göre ayarlama yapılmamış

İkinci Kuşak ALK TKI

Second Generation ALK TKI (Ceritinib, Alectinib)						
Shaw *et al.* (2014) [83] Phase I	ALK positive (68% progressed on Crizotinib)	130	Ceritinib	Single arm	7.0 overall, 10.4 for ALK inhibitor naïve, 6.9 in prev. treated	NA
Seto *et al.* (2013) [85,86] Phase I/II	ALK positive- 1st line setting	58	Alectinib	Single arm	Not yet reached >10.3	NA

- Alectinib: FazI-II RR %93
- Ceritinib: Crizotinib sonrası: RR%53 PFS:7 ay
- Crizotinib + Ceritinib: PFS:17 ay
- OS:49 ay

ALK POSITIVE[a]



[a] See Principles of Pathologic Review (NSCL-A).
[ee] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[kk] Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in *ROS1*-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.
[ll] For performance status 0-4.
[tt] Patients who are intolerant to crizotinib may be switched to ceritinib.
[uu] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

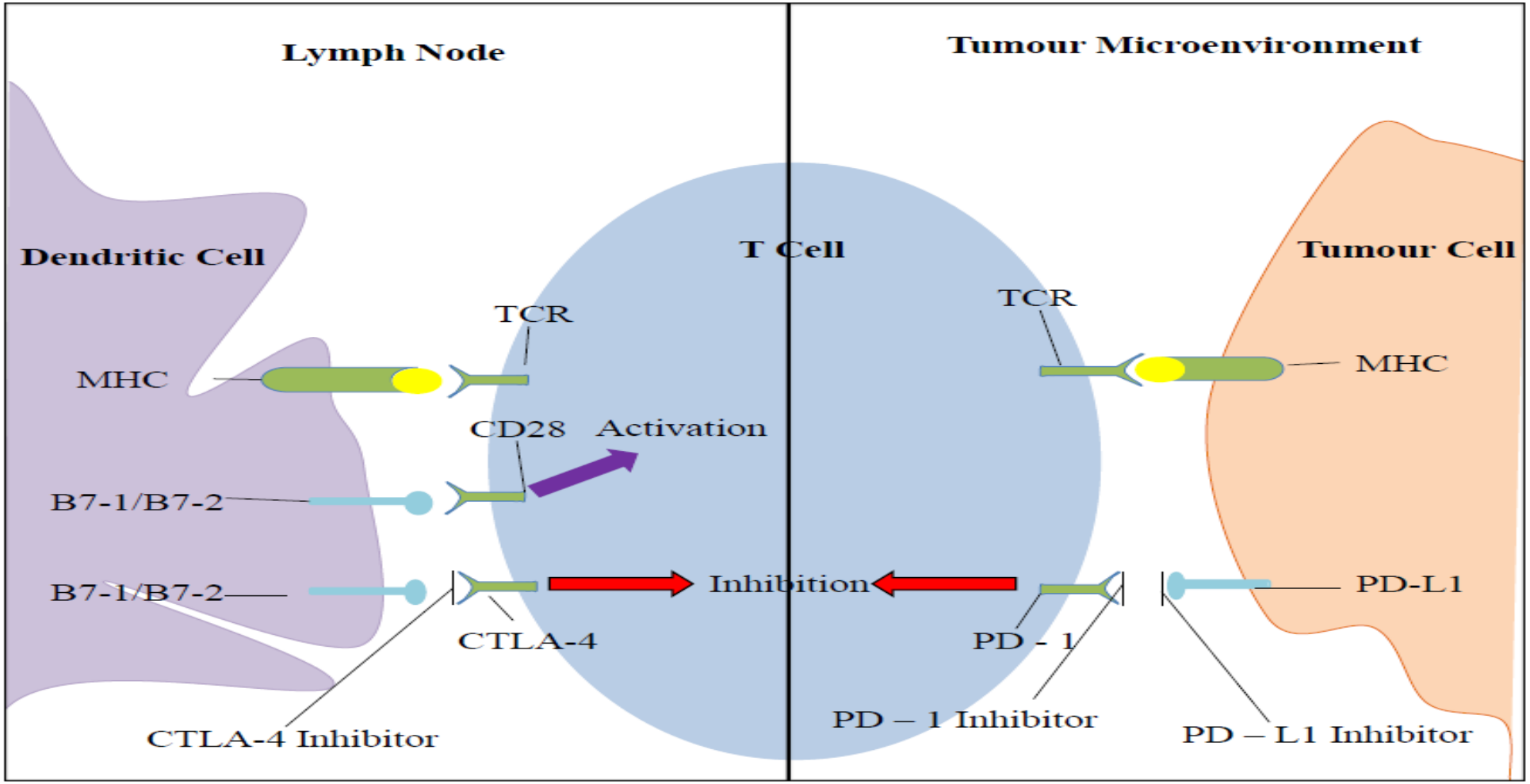
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Antianjiojenik Ajanlar

- Bevacizumab
- Aflibercept
- Nintedanib
- Ramucirumab

- Sağ kalım farkı yok
- Sağ kalım farkı yok
- İkinci seçim KT (Docetaxel) PFS
- İkinci seçim K de PFS OS farkı

İmmun Yanıtın Baskılanması



Güncel Akciğer Kanser Tedavisi

- Histolojik alt tip tedavi seçiminde önemlidir
- Genetik mutasyonlar hedefe yönelik tedaviyi belirler
- Tanı ve tedavi kararı için yeterli doku temini planlanmalıdır
- Uygun tedavi sağ kalımı ve yaşam kalitesini etkiler