Melanom Dışı Cilt Kanserleri
Tedavide Yenilikler

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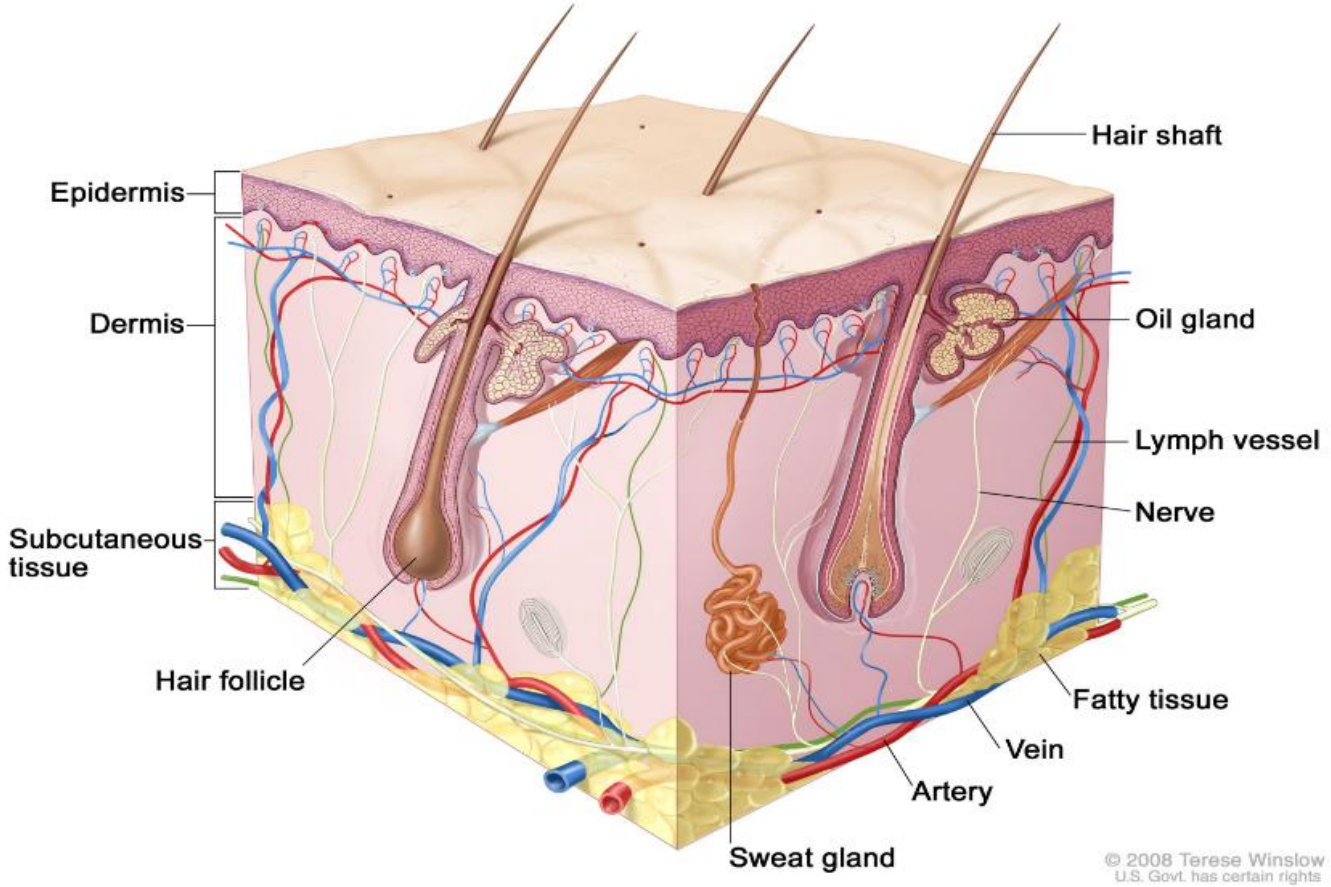
Tıbbi Onkoloji

Sunum İçeriği

- Cilt Tümörlerinin Sınıflandırılması
- Skuamöz Hücreli Cilt Tümörleri
- Bazal Hücreli Cilt Tümörleri

Cilt Tümörleri Sınıflandırma



Squamous cells: Thin, flat cells that form the top layer of the epidermis.
Basal cells: Round cells under the squamous cells.
Melanocytes: Cells that make melanin and are found in the lower part of the epidermis.

Cilt Tümörleri Sınıflandırma

Ming M, et al. J Invest Dermatol 2009;129:2109–12.

İnsidans ve Epidemiyoloji

- Melanom dışı cilt tümörleri(MDCT) en sık karşılaşılan kanserlerdir.
- US'de her yıl 3.5 milyon kişiye MDCT tanısı konur.
- Bu tümörlerin %80'i Bazal hücreli, %20'i SCC'dir.
- MDCK'i çoğunlukla erken evrede tanı konulur ve tedavi edilebilir.

Rogers HW, Arch Dermatol, 2010

İnsidans ve Epidemiyoloji

US'deki SCC insidans

- 186 157 – 419 543 arasında değişmektedir.
- Bunların 5604 ila 2572 de nodal metastaz gelişir.
- 3932 ila 8791 hastalık nedeniyle hayatını kaybetmektedir.

Karia PS, *J Am Acad Dermatol.* 2013

İnsidans ve Epidemiyoloji

- SCC da uzak metastazlara nadiren rastlanır.
- BHK ile karşılaştırıldığında çok daha sık görülür.
- SCC için metastaz riski %3.7, hastalığa spesifik ölüm riski %2.1 bulunmuş.
- Bazal Hücreli kanserde metastaz oranı < % 0.1 olarak saptanmış

Cranmer LD, Oncologist,2010, Nguven-Nielsen M, Eur J Dermatol 2015

Cilt Tümörleri Risk Faktörleri

- SCC nin patogenezi:

  UV radyasyonla başlayan bir takım edinsel genetik olaylar sonucu geliştiği düşünülmektedir.

- SCC'de UV radyasyon en önemli teratojendir.

- Direk olarak DNA tarafından absorbe edilir ve malign dönüşümü başlatacak genetik hasara yol açabilir.

- Sarışın kişiler, albinizm, radyasyona maruziyet xeroderma pigmentosum diğer nedenlerdir.

Cilt Tümörleri Risk Faktörleri

- **TP53** süpresör geninin mutasyonları UVB tarafından başlatılabilir.
- Bu mutasyon SCC li hastaların %45-60 ında tesbit edilmiştir.
- ***TP53*** *mutasyonu* kanser oluşumunda erken bir dönem olduğu düşünülmektedir.
- SCC gelişiminde diğer genetik değişiklikler **CDKA2A** ve **RAS** genlerinde olmaktadır.
- **CDKN2A** da mutasyon veya hipermetilasyon suretiyle inaktivasyon oluşması sık karşılaşılan bir durumdur.
- ***RAS*** *mutasyonları da aktinik keratozda ve SCC de %3-30 oranında belirlenmiştir.*
- *Sporadik SCC de ise %8 oranında karşılaşılmıştır.*

Benjamin CL, Adv Exp Med Biol, 2008

Cilt Tümörleri Risk Faktörleri

- Melanom tedavisinde kulanılan BRAF inhibitörlerinde(Vemurafenib, dabrafenib)
- SCC insidensinin %4-31 oranında arttığı ortaya konmuştur.
- BRAF inhibitörü alanlarda ortaya çıkan SCC de RAS mutasyonları sıktır.
- Moleküler mekanizması:
  MAPK yolağında paradoksal aktivasyon oluşmasıyla SCC gelişir.

Cilt Tümörleri Risk Faktörleri

TABLE 1

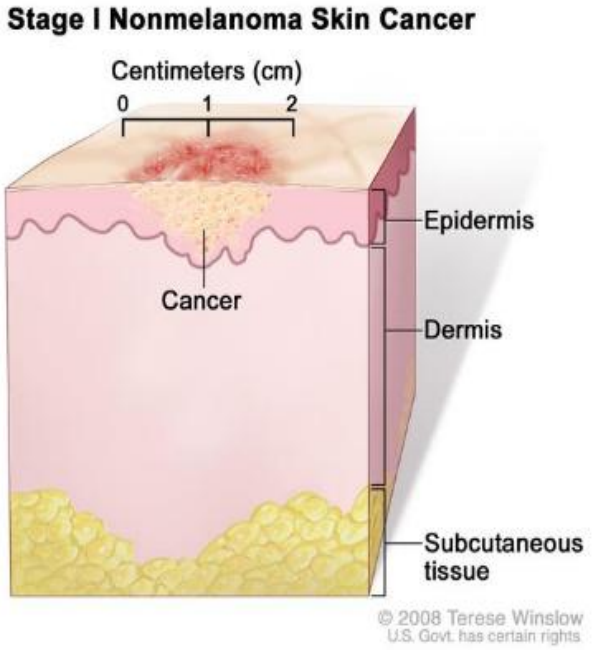
Risk factors for developing BCC (10–12)

Risk factor	Risk
Fair skin (skin types I and II)	OR 5.1 (95% CI: 1.4–11.3) in comparison to skin type IV
Intermittent UV exposure (sun burns)	OR 1.4 *(see Table 2)*
Personal history of BCC	3-year risk 44% (33–70%)
Prior treatment with ionizing radiation	RR 2.3 (95% CI: 1.7–3.1)
Genetic syndromes such as nevoid BCC syndrome; xeroderma pigmentosum	Development of multiple BCC in childhood possible
Chronic arsenic exposure	N.A.
Immunosuppression	N.A.

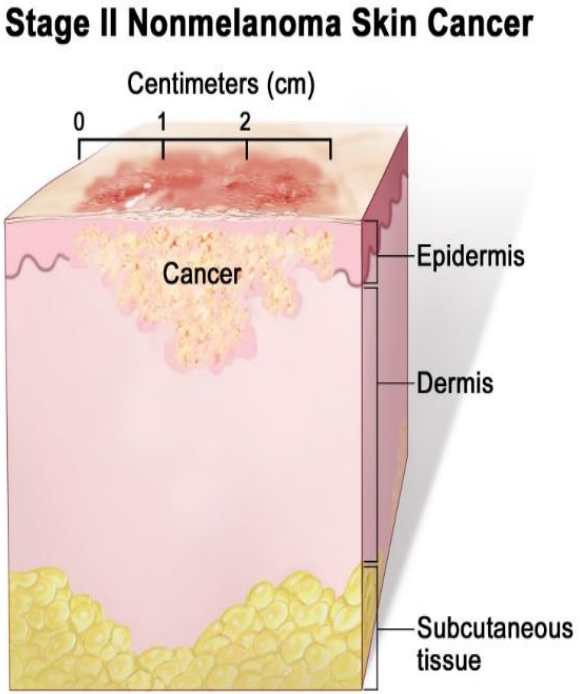
BCC, basal cell carcinoma; OR, odds ratio; CI, confidence interval; RR. relative risk; N.A., not available

Göppner D, J Skin Cancer, 2011

Cilt Tümörleri Evreleme



Stage I nonmelanoma skin cancer. The tumor is no more than 2 centimeters.



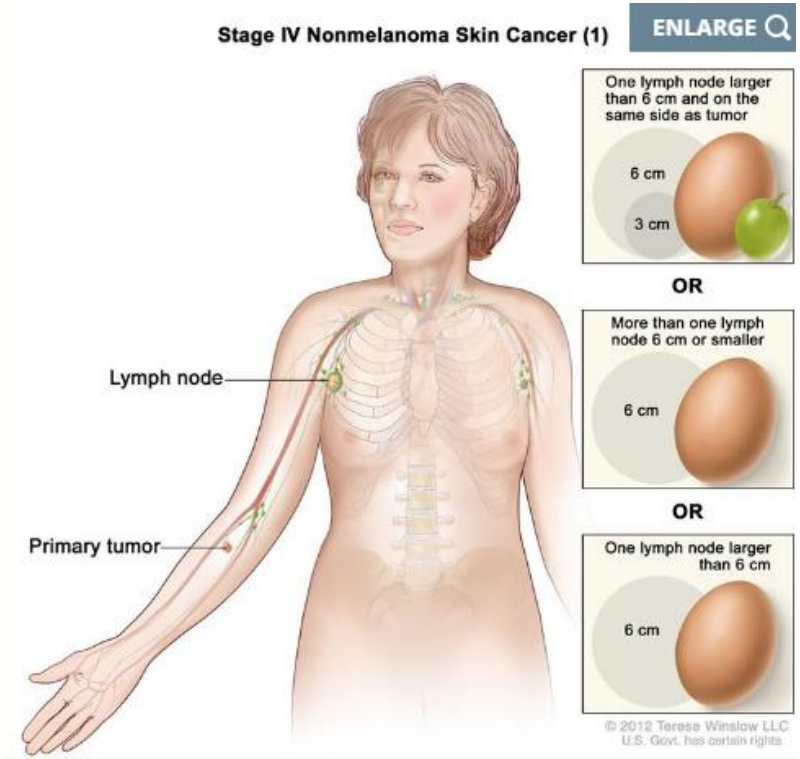
In stage II, the tumor is either:
larger than 2 centimeters at its widest point; or
any size and has two or more high-risk features.

Cilt Tümörleri Evreleme

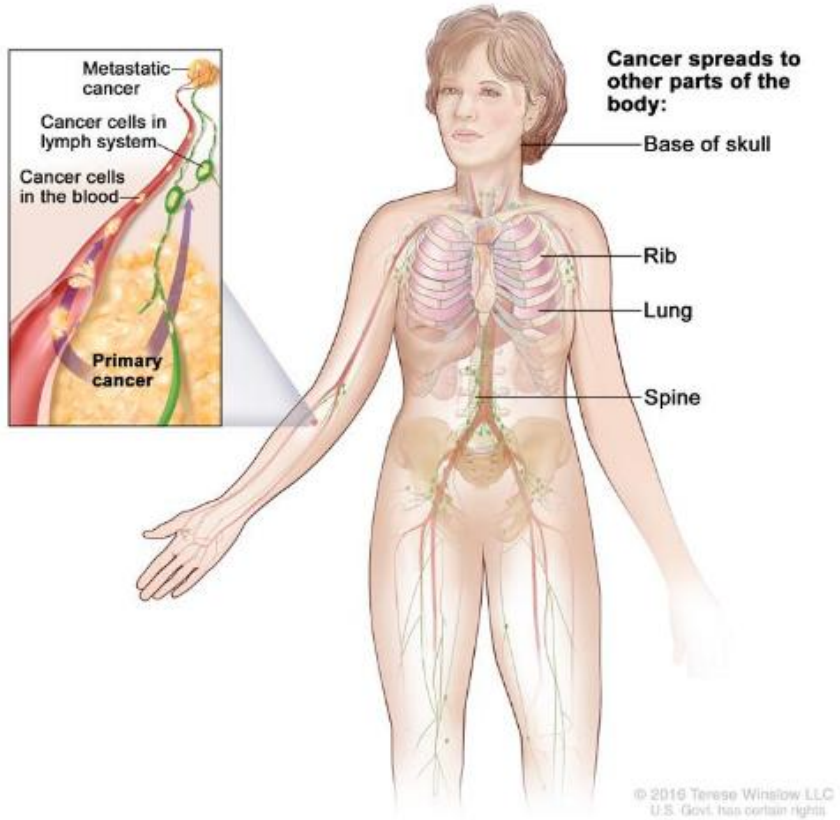
BEŞ YÜKSEK RİSK ÖZELİĞİ VAR

- (1) the tumor is thicker than 2 millimeters;
- (2) the tumor has spread into the lower layer of the skin or into the layer of fat below the skin;
- (3) the tumor has grown and spread along nerve pathways;
- (4) the tumor began on an ear or on a lip that has hair on it
- (5) the tumor has cells that look very different from normal cells under a microscope.

Cilt Tümörleri Evreleme



Stage IV nonmelanoma skin cancer (1). The tumor is any size. Cancer has spread to one lymph node that is larger than 3 centimeters but not larger than 6 centimeters and is on the same side of the body as the tumor; OR to more than one lymph node 6 centimeters or smaller on one or both sides of the body; OR to one lymph node that is larger than 6 centimeters.



Stage IV nonmelanoma skin cancer (2). The tumor is any size and has spread to the base of the skull, spine, ribs, lung, or other parts of the body.

Cilt Tümörleri Evreleme

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Staging

Table 1

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for Cutaneous Squamous Cell Carcinoma (cSCC)

(7th ed., 2010)

Primary Tumor (T)*

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor 2 cm or less in greatest dimension with less than two high-risk features**

T2 Tumor greater than 2 cm in greatest dimension
or
Tumor any size with two or more high-risk feature

T3 Tumor with invasion of maxilla, mandible, orbit, or temporal bone

T4 Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

*Excludes cSCC of the eyelid

**High-risk features for the primary tumor (T) staging

Depth/invasion	> 2 mm thickness
	Clark level ≥ IV
	Perineural invasion
Anatomic location	Primary site ear
	Primary site non-hair-bearing lip
Differentiation	Poorly differentiated or undifferentiated

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (M)

M0 No distant metastases

M1 Distant metastases

Continue

Cilt Tümörleri Evreleme

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Table 1 Continued

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for Cutaneous Squamous Cell Carcinoma (cSCC) (7th ed., 2010)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T Any	N3	M0
	T4	N Any	M0
	T Any	N Any	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Skuamöz Hücreli Karsinom Tedavi

- Simple excision.
- Mohs micrographic surgery.
- Radiation therapy.
- Electrodesiccation and curettage.
- Cryosurgery.

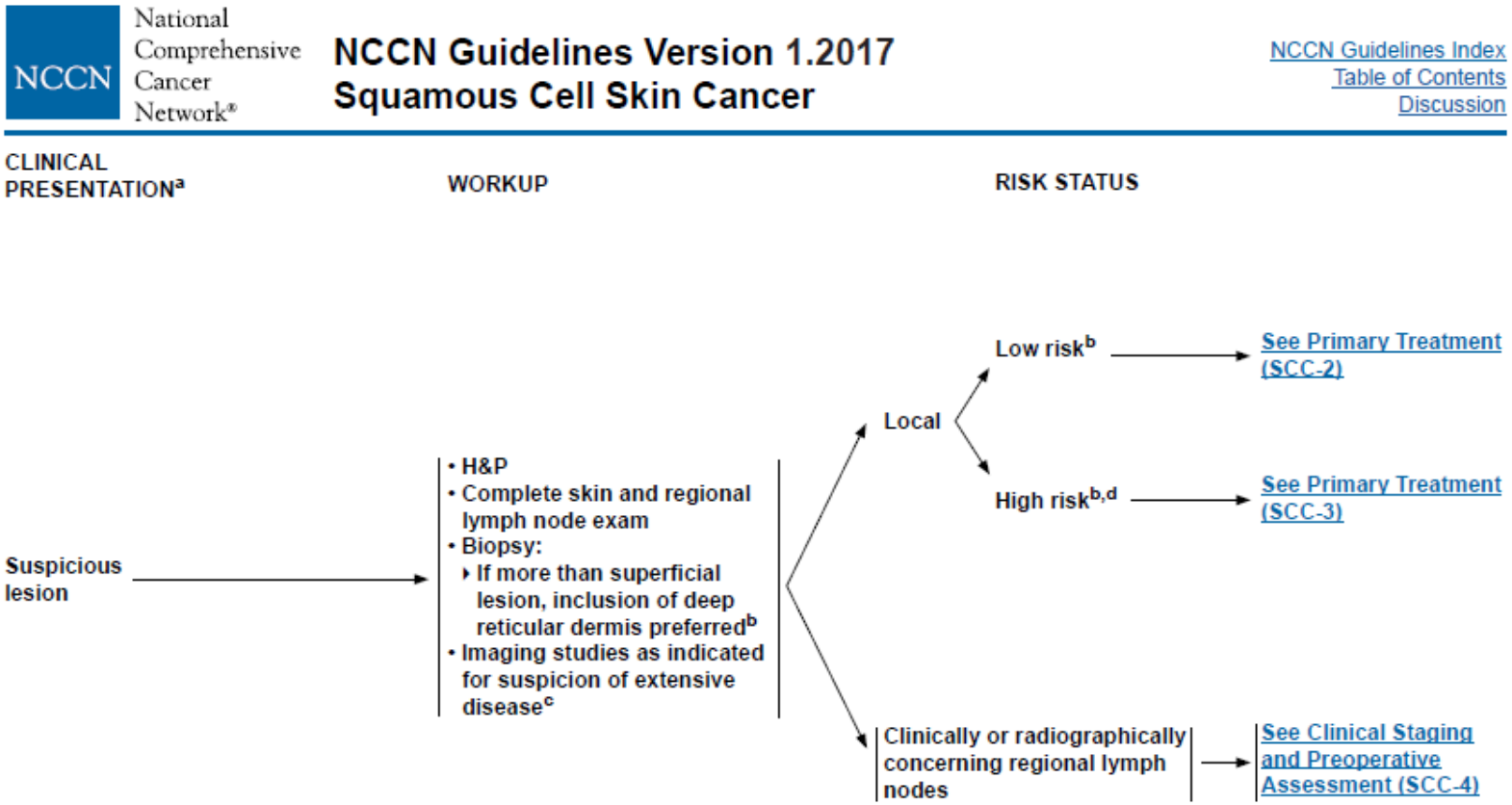
Treatment of recurrent squamous cell carcinoma may include the following:

- Simple excision.
- Mohs micrographic surgery.
- Radiation therapy.

Treatment of squamous cell carcinoma that is metastatic or cannot be treated with local therapy may include the following:

- Chemotherapy.
- Retinoid therapy and biologic therapy with interferon.
- A clinical trial of a new treatment.

Skuamöz Hücreli Karsinom Tedavi



[a]Including squamous cell skin cancer in situ (showing full-thickness epidermal atypia, excluding actinic keratoses).
[b]See Risk Factors for Local Recurrence or Metastases (SCC-A) and Identification and Management of High-Risk Patients (SCC-D).
[c]Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease or deep soft tissue involvement is suspected, MRI with contrast is preferred. If bone disease is suspected, CT with contrast is preferred.
[d]Any high-risk factor places the patient in the high-risk category.

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

Skuamöz Hücreli Karsinom Tedavi

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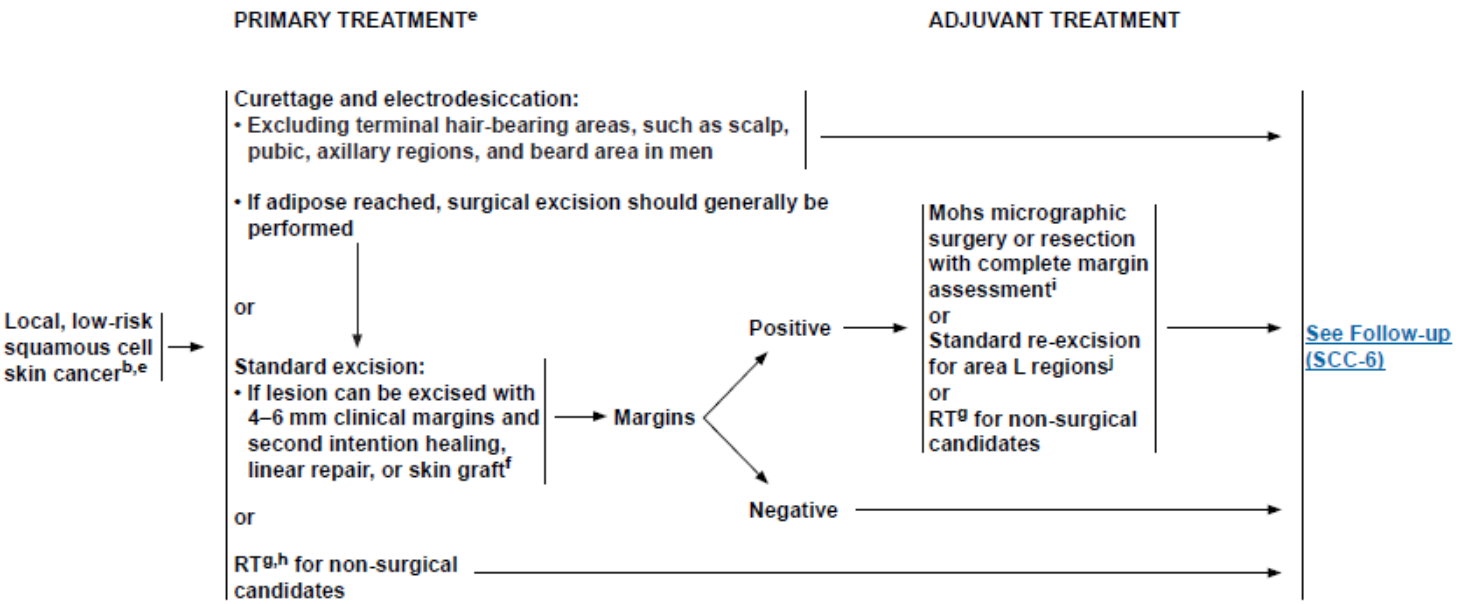

[b] See Risk Factors for Local Recurrence or Metastases (SCC-A) and Identification and Management of High-Risk Patients (SCC-D).
[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[f] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[g] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-C).
[h] RT is often reserved for patients over 60 years because of concerns about long-term sequelae.
[i] Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs micrographic surgery.
[j] Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See SCC-A)

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

Skuamöz Hücreli Karsinom Risk Sınıflandırması

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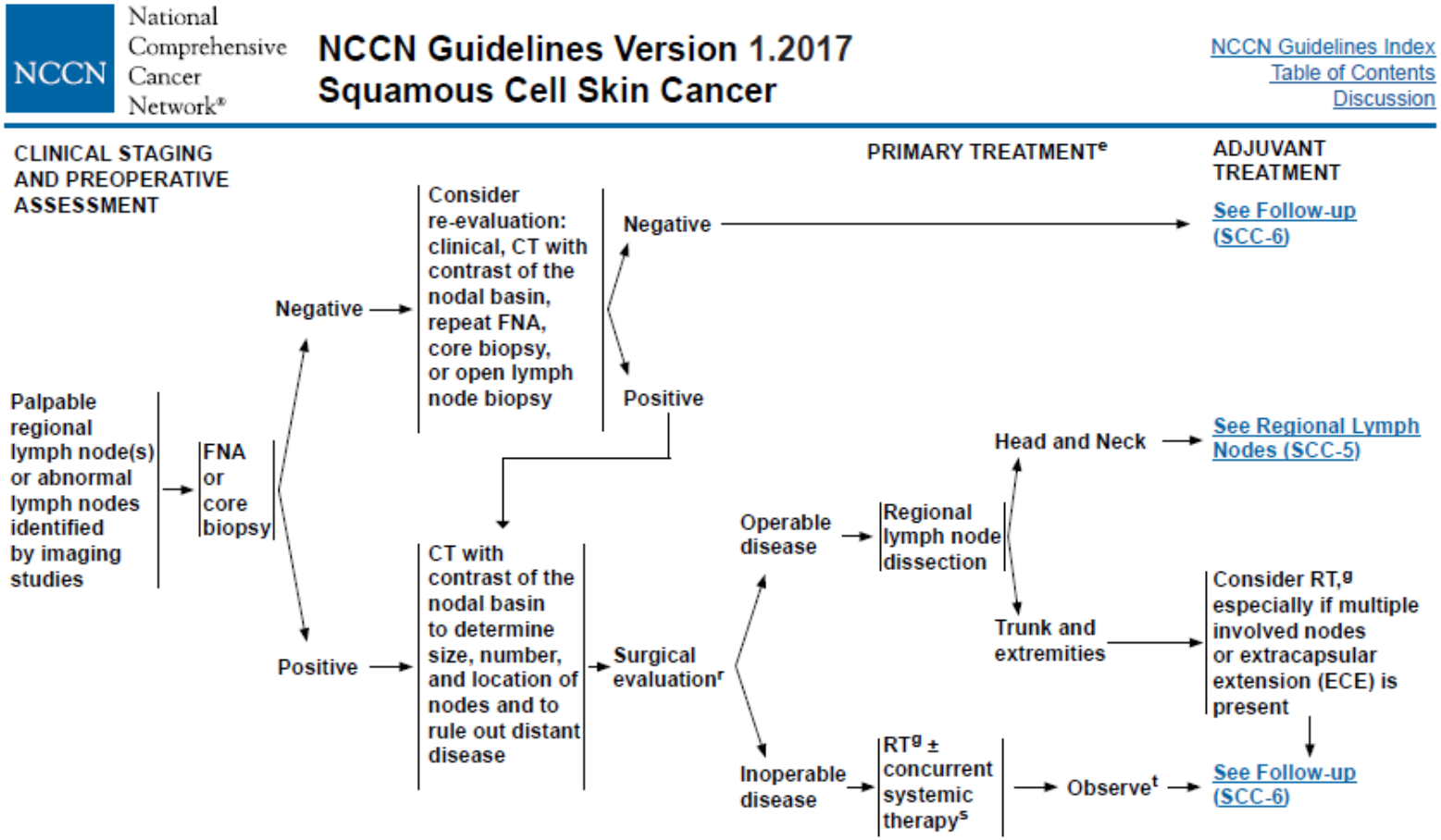
RISK FACTORS FOR LOCAL RECURRENCE OR METASTASES

H&P	Low Risk	High Risk
Location/size[1]	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm[4]	Area M ≥10 mm
		Area H[5]
Borders	Well-defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT or chronic inflammatory process	(-)	(+)
Rapidly growing tumor	(-)	(+)
Neurologic symptoms	(-)	(+)
Pathology		
Degree of differentiation	Well or moderately differentiated	Poorly differentiated
Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carcinosarcomatous) subtypes	(-)	(+)
Depth[2,3]: Thickness or Clark level	<2 mm or I, II, III	≥2 mm or IV, V
Perineural, lymphatic, or vascular involvement	(-)	(+)

[1]Must include peripheral rim of erythema.
[2]If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
[3]A modified Breslow measurement should exclude parakeratosis or scale crust, and should be made from base of ulcer if present.
[4]Location independent of size may constitute high risk.
[5]Area H constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs micrographic surgery is recommended for optimal tumor clearance and maximal tissue conservation. For tumors <6 mm in size, without other high risk features, other treatment modalities may be considered if at least 4-mm clinically tumor-free margins can be obtained without significant anatomic or functional distortions.

Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.
Area M = cheeks, forehead, scalp, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).

Skuamöz Hücreli Karsinom Tedavi



[e] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-B).
[g] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-C).
[r] Regional lymph node dissection is preferred unless the patient is not a surgical candidate.
[s] Multidisciplinary consultation is recommended. Consider systemic therapies recommended for use with radiation to treat head and neck squamous cell carcinomas. See NCCN Guidelines for Head and Neck Cancers.
[t] Re-evaluate surgical candidacy for post-radiation lymph node dissection as indicated. CT with contrast may be indicated to evaluate extent of residual disease.

Skuamöz Hücreli Karsinom Tedavi

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PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER

Primary Tumor		Dose Time Fractionation Schedule
Tumor Diameter	Margins[1]	Examples of Dose Fractionation and Treatment Duration[2]
<2 cm	1–1.5 cm	64 Gy in 32 fractions over 6–6.4 weeks 55 Gy in 20 fractions over 4 weeks 50 Gy in 15 fractions over 3 weeks 35 Gy in 5 fractions over 5 days
≥2 cm	1.5–2 cm	66 Gy in 33 fractions over 6–6.6 weeks 55 Gy in 20 fractions over 4 weeks
Postoperative adjuvant		50 Gy in 20 fractions over 4 weeks 60 Gy in 30 fractions over 6 weeks
Regional Disease: All doses at 2 Gy per fraction using shrinking field technique		
• After lymph node dissection		
‣ Head and neck; with ECE:		60–66 Gy over 6–6.6 weeks
‣ Head and neck; without ECE:		56 Gy over 5.6 weeks
‣ Axilla, groin; with ECE:		60 Gy over 6 weeks
‣ Axilla, groin; without ECE:		54 Gy over 5.4 weeks
• No lymph node dissection		
‣ Clinically (-) but at risk for subclinical disease:		50 Gy over 5 weeks
‣ Clinically evident adenopathy: head and neck:		66–70 Gy over 6.6–7 weeks
‣ Clinically evident adenopathy: axilla, groin:		66 Gy over 6.6 weeks

ECE= Extracapsular extension

- Protracted fractionation is associated with improved cosmetic results.
- Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, scleroderma).
- There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.

[1]When using electron beam, wider field margins are necessary than with orthovoltage x-rays due to the wider beam penumbra. Narrower field margins can be used with electron beam adjacent to critical structures (eg, the orbit) if lead skin collimation is used. Bolus is necessary when using electron beam to achieve adequate surface dose. An electron beam energy should be chosen that achieves adequate surface dose and encompasses the deep margin of the tumor by at least the distal 90% line. Appropriate medical physics support is essential.

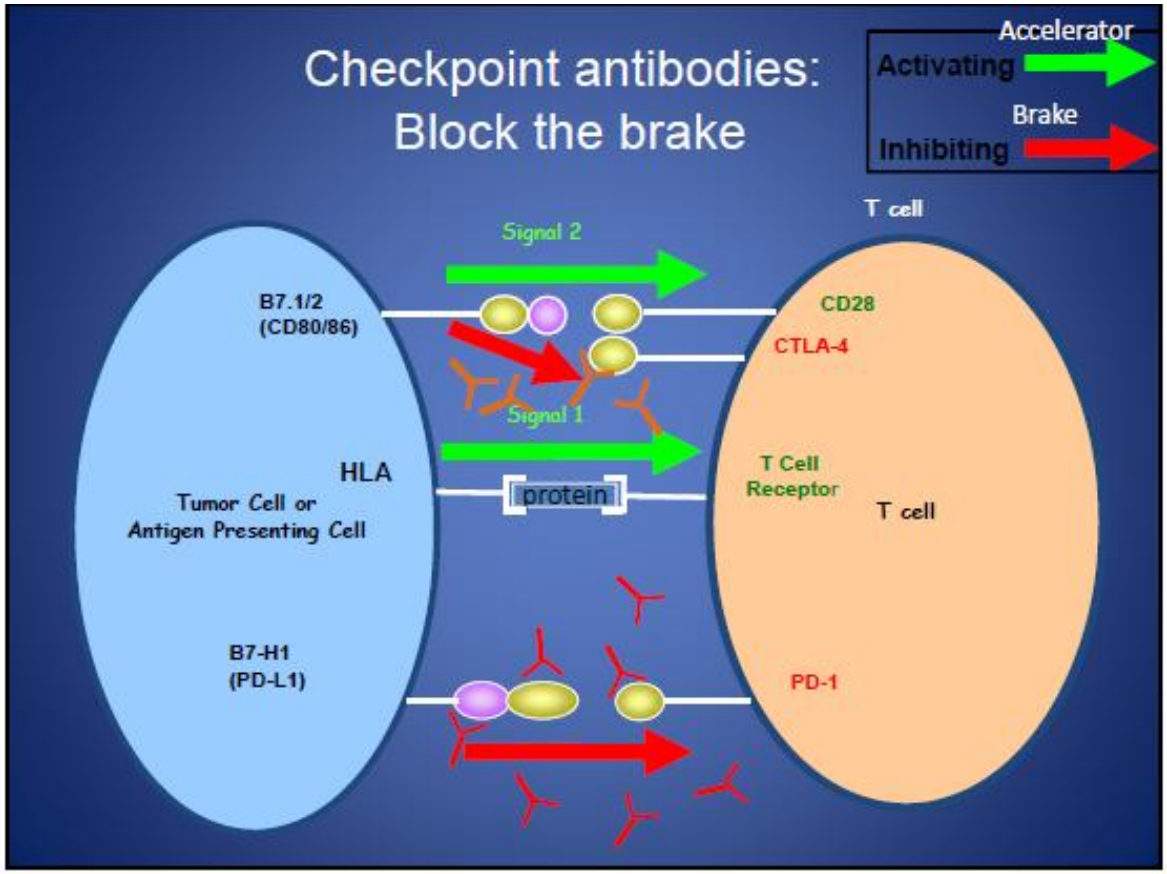
[2]Electron beam doses are specified at 90% of the maximal depth dose (Dmax). Orthovoltage x-ray doses are specified at Dmax (skin surface) to account for the relative biologic difference between the two modalities of radiation. If intensity-modulated radiation therapy is used to treat primary tumors, appropriate focus must be directed at assuring that there is adequate surface dose.

Metastatik Skuamöz Hücreli Karsinom Tedavi

	Phase	Completion Date	Results
Chemotherapy Trials			
Prospective observational study of cisplatin, 5-fluorouracil, and bleomycin in pretreated SCCS (n = 14)[35]	II	1990	Four CR (30%), seven PR (54%). Local control after definitive XRT and/or surgery achieved in seven patients.
Prospective observational study of cisplatin and doxorubicin (n = 12)[35]	III	1990	Four CR (33%), three PR (25%), 42% with progressive disease at time of report, both treated and untreated patients included
13-*cis*-retinoic acid and IFN alpha-2a: effective combination therapy for advanced SCCS (n = 32)[34]	II	1992	28 evaluable; seven CR (25%), 12 PR (43%), 5-mo response duration
Oral 5-fluorouracil in SCCS (n = 14, pretreated patients)[35]	II	2000	Therapy-induced measurable improvement in nine patients (64.3%): two PR, three minimal remissions, and four arrests of disease with median duration of 30+ months
Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced SCCS[36]	II	2002	Six CR (17%), six PR (17%), median survival 14.6 mo, 67% RR in locally advanced and 17% RR in metastatic disease
Targeted Therapy Trials			
Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable SCCS[42] (n = 36)	II	2011	Disease control rate at 6 wk in 69% of pts (both locally advanced and metastatic). Best responses were eight partial responses and 2 CRs. No cetuximab-related deaths. Three related serious adverse events: two grade 4 infusion reactions and one grade 3 interstitial pneumopathy. Grades 1-2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS. EGFR expression required for study entry.
A phase II study of gefitinib for aggressive SCCS of the head and neck (n = 23)[45]	II	2011	Neoadjuvant approach followed by surgery or radiation; tolerable side effect profile; all patients received planned definitive treatment; 18% CR rate; Two-year OS 72.1%, PFS 63.6%. No EGFR mutations in 10 patients studied. Results led to a trial of erlotinib in this setting.
Phase 1 study of erlotinib plus radiation therapy in patients with advanced SCCS (n = 15)[33]	I	2012	Treatment was felt to be tolerable. Most common toxicity attributed to erlotinib was grades 2-3 dermatologic reaction in 100% of patients, followed by mucositis (87%), and diarrhea (20%). Two-year recurrence rate was 26.7%, and mean time to cancer recurrence was 10.5 mo. Two-year OS was 65%, and DFS was 60%.

Cisplatin+/-5-FU +/-Cetuximab

Metastatik Skuamöz Hücreli Karsinom Yeni Tedaviler



Skuamöz Hücreli Karsinom Tedavi

National Cancer Institute Clinical Trials Results

Cancer Type/Condition: Skin cancer, nonmelanomatous (squamous and basal cell)
Stage/Subtype: squamous cell carcinoma of the skin
Trial Type: Treatment

1. Docetaxel, Cisplatin, and Cetuximab in Treating Patients with Metastatic or Relapsed Head and Neck Cancer
Status: Active
Phase: Phase II
Type: Treatment
Age: 16 and over
Trial IDs: ENT0033, NCI-2011-03271, 22329, SU-08222011-8290, NCT01437449

2. Capecitabine or Fluorouracil with Pegylated Interferon Alpha-2b in Treating Patients with Unresectable or Metastatic Cutaneous Squamous Cell Carcinoma
Status: Active
Phase: Phase II
Type: Treatment
Age: 18 and over
Trial IDs: MCC 17759, NCI-2014-01864, 14.06.0011, NCT02218164

3. Stereotactic Radiosurgery in Treating Patients with Oligometastatic Disease
Status: Active
Phase: Phase II
Type: Treatment
Age: 18 and over
Trial IDs: 10-027, NCI-2014-01952, REN13120042, UPCI #10-027, NCT01345539

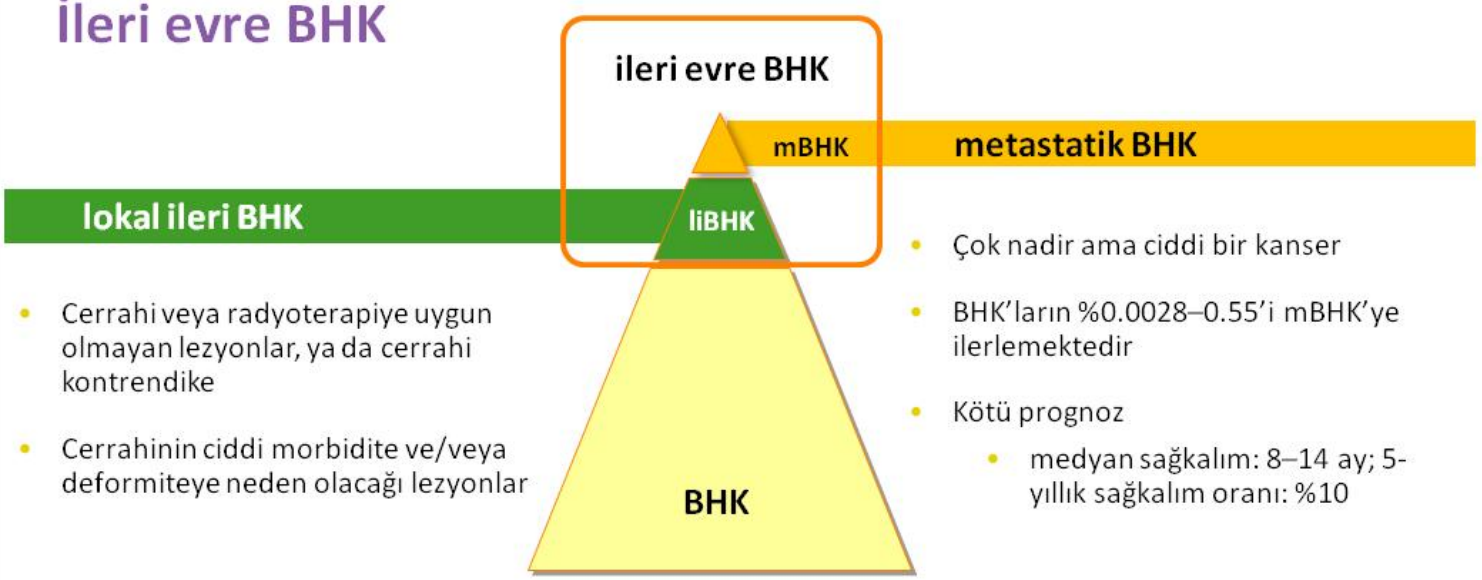
4. Stereotactic Radiosurgery in Treating Patients with Oligo-Recurrent Disease
Status: Active
Phase: Phase II
Type: Treatment
Age: 18 and over
Trial IDs: 10-028, NCI-2014-01953, REN13120040, UPCI# 10-028, NCT01345552

Skuamöz Hücreli Karsinom Yeni Tedaviler

5.Pembrolizumab in Treating Patients with Rare Tumors That Cannot Be Removed by Surgery or are Metastatic
Status: Active
Phase: Phase II
Type: Biomarker/Laboratory analysis, Treatment
Age: 18 and over
Trial IDs: 2015-0948, NCI-2016-00545, NCT02721732
6.Study of REGN2810 in Patients With Advanced Cutaneous Squamous Cell Carcinoma
Status: Active
Phase: Phase II
Type: Treatment
Age: 18 and over
Trial IDs: R2810-ONC-1540, NCI-2016-00692, NCT02760498
7.Pembrolizumab in Treating Patients with Locally Advanced or Metastatic Skin Cancer
Status: Active
Phase: Phase II
Type: Treatment
Age: 18 and over
Trial IDs: Winship3185-16, NCI-2016-00831, IRB00087412, NCT02964559
8.ALT-803 in Treating Patients with Advanced Cancer
Status: Active
Phase: Phase I
Type: Treatment
Age: Over 18
Trial IDs: CITN-06-ALT-803, NCI-2013-01999, CA-ALT-803-01-13, PCITN-06-ALT-803_A06PAMDREVW02, PCITN-06-ALT-803_A08PAMDREVW01, NCT01946789
9.Electronic Skin Surface Brachytherapy in Treating Older Patients with Newly Diagnosed Early Stage Basal Cell or Squamous Cell Skin Cancer
Status: Active
Phase: No phase specified
Type: Treatment
Age: 60 and over
Trial IDs: 14-001, NCI-2014-01090, NCT02131805
10.Cetuximab before Surgery in Treating Patients with Aggressive Locally Advanced Skin Cancer
Status: Active
Phase: No phase specified
Type: Biomarker/Laboratory analysis, Treatment
Age: 18 and over
Trial IDs: 091303, NCI-2014-02027, NCT02324608

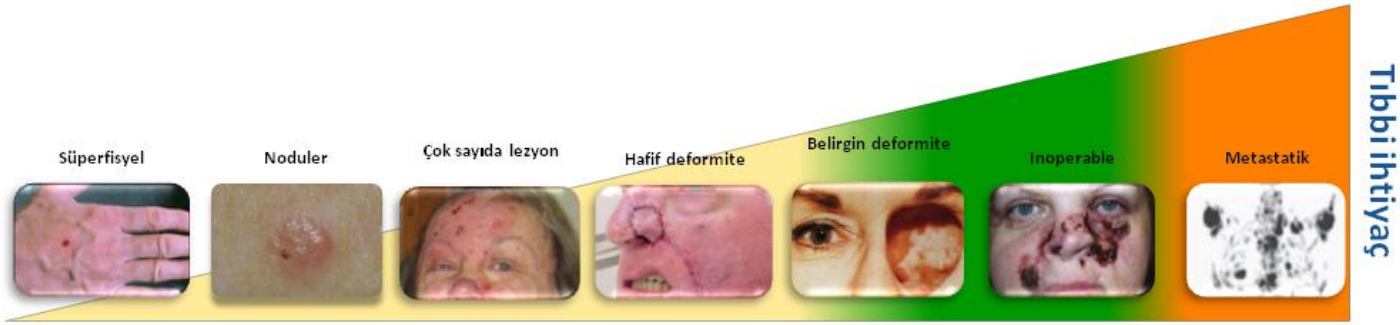
Bazal Hücreli Cilt Tümörlerinde Tedavi

İleri evre BHK



- Cerrahi veya radyoterapiye uygun olmayan lezyonlar, ya da cerrahi kontrendike
- Cerrahinin ciddi morbidite ve/veya deformiteye neden olacağı lezyonlar

- Çok nadir ama ciddi bir kanser
- BHK'ların %0.0028–0.55'i mBHK'ye ilerlemektedir
- Kötü prognoz
  - medyan sağkalım: 8–14 ay; 5-yıllık sağkalım oranı: %10



Sekulic A et al. New Engl J Med 2012;366:2171–9
Weiss GJ, Korn RL. Cancer 2012
Ting PT et al. J Cutan Med Surg 2005;9:10–15
von Domarus H, Stevens PJ. J Am Acad Dermatol 1984;10:1043–60
Lo JS et al. J Am Acad Dermatol 1991;24:715–19

Wong CSM et al. Br Med J 2003;327:794–8
Von Hoff DD et al. New Engl J Med 2009;361:1164–72
Ozbek N et al. N Z Med J 2004;117:U874
Goldberg LH et al. Arch Dermatol 2010;146:17–9
Image 3 reproduced from Goldberg et al (2010) and image 4 from Von Hoff et al (2009)

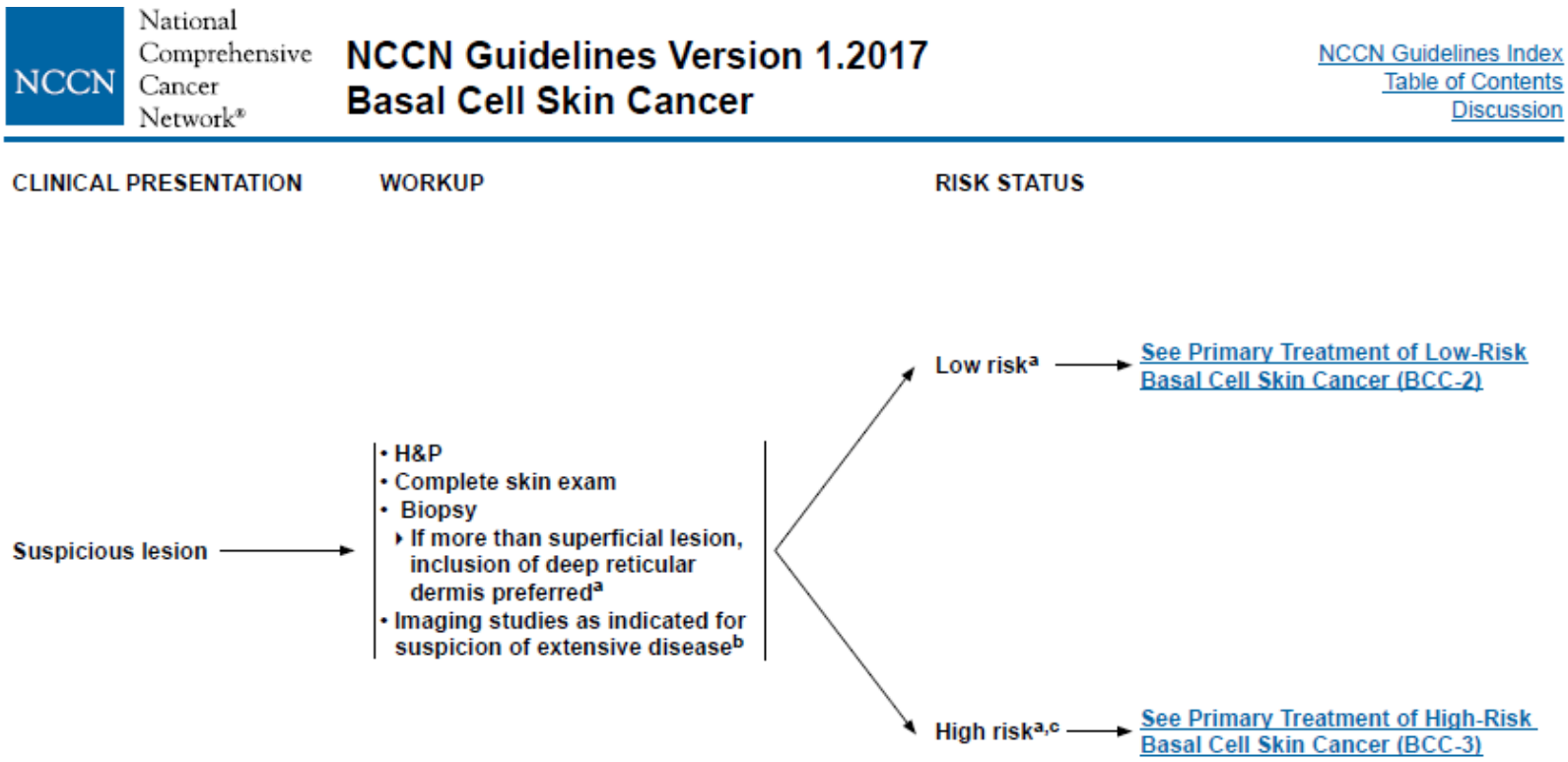
Bazal Hücreli Cilt Tümörlerinde Tedavi

- Simple excision.
- Mohs micrographic surgery.
- Radiation therapy.
- Electrodesiccation and curettage.
- Cryosurgery.
- Photodynamic therapy.
- Topical chemotherapy.
- Topical biologic therapy with imiquimod.
- Laser surgery.

Treatment of basal cell carcinoma that is metastatic or cannot be treated with local therapymay include the following:

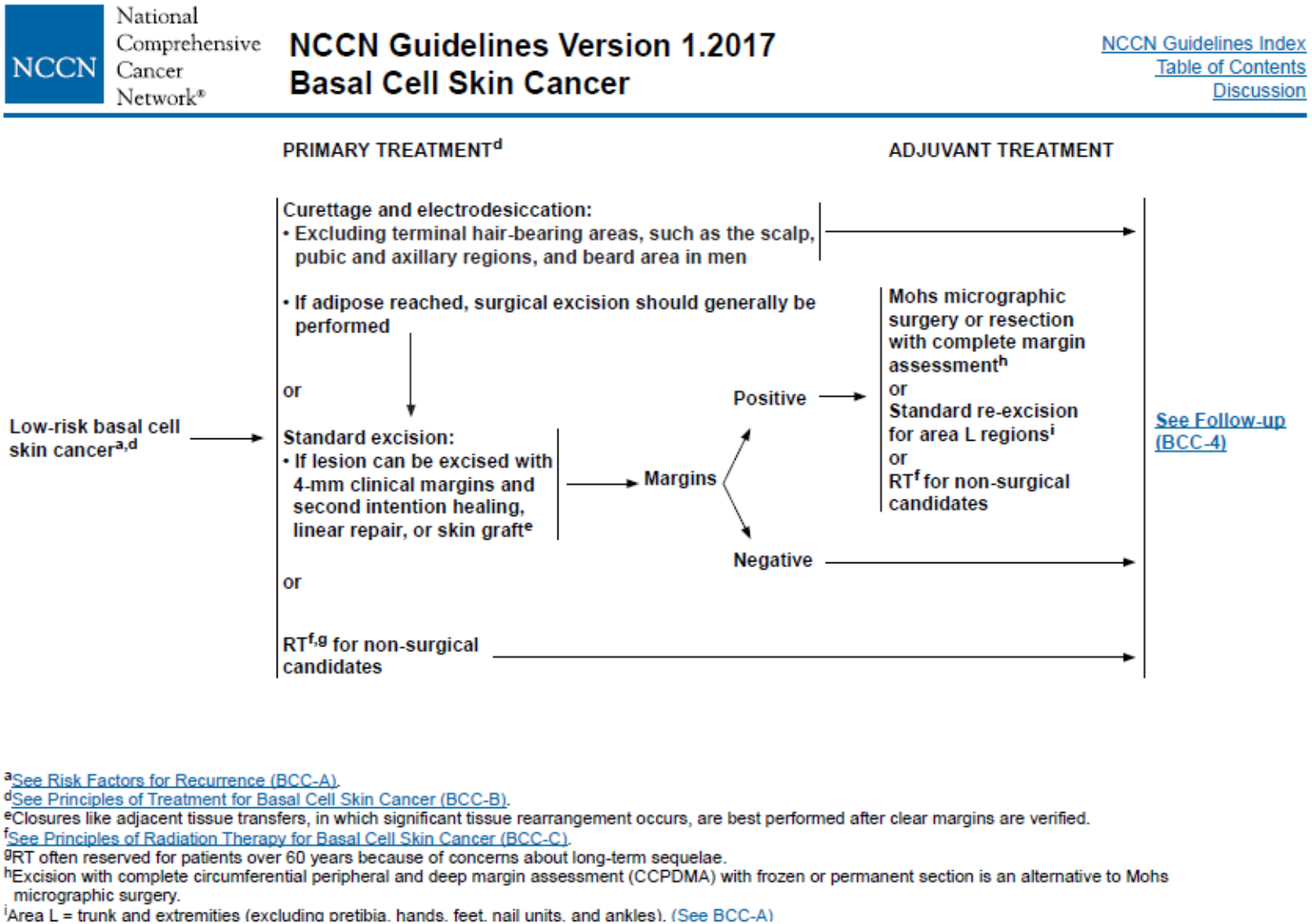
- Targeted therapy with a signal transduction inhibitor.
- Chemotherapy.
- A clinical trial of a new treatment

Bazal Hücreli Cilt Tümörlerinde Tedavi



[a] See Risk Factors for Recurrence (BCC-A).
[b] Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI with contrast is preferred. If bone disease is suspected, CT with contrast is preferred.
[c] Any high-risk factor places the patient in the high-risk category.

Bazal Hücreli Cilt Tümörlerinde Tedavi



[a] See Risk Factors for Recurrence (BCC-A).
[d] See Principles of Treatment for Basal Cell Skin Cancer (BCC-B).
[e] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[f] See Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-C).
[g] RT often reserved for patients over 60 years because of concerns about long-term sequelae.
[h] Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs micrographic surgery.
[i] Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See BCC-A)

Bazal Hücreli Cilt Tümörlerinde Tedavi

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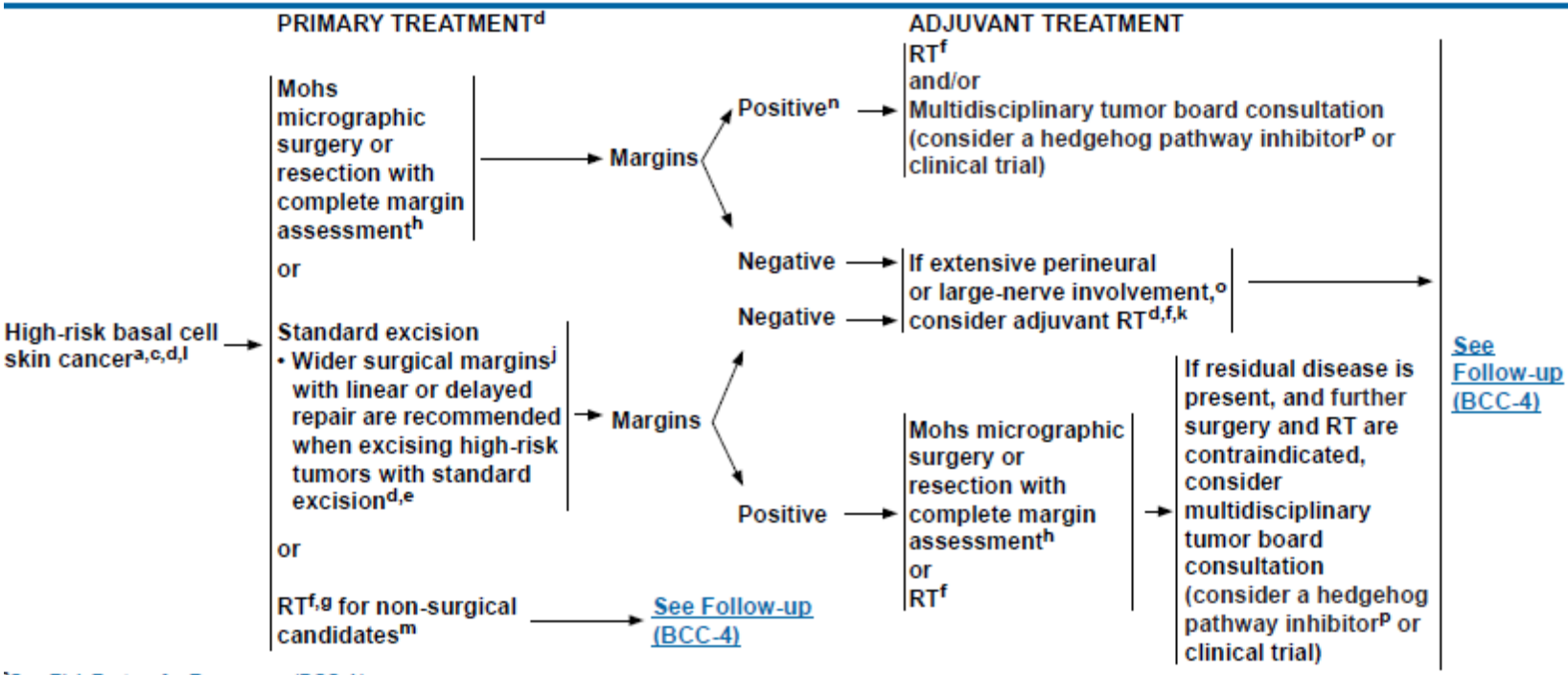

[a] See Risk Factors for Recurrence (BCC-A).
[c] Any high-risk factor places the patient in the high-risk category.
[d] See Principles of Treatment for Basal Cell Skin Cancer (BCC-B).
[e] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[f] See Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-C).
[g] RT is often reserved for patients over 60 years because of concerns about long-term sequellae.
[h] Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs micrographic surgery.
Due to the wide variability of clinical characteristics that may define a high-risk tumor, it is not feasible to recommend a defined margin for standard excision of high-risk BCC. Keen awareness of the subclinical extension of BCC is advised when selecting a treatment modality without complete margin assessment for a high-risk tumor. These margins may need to be modified based on tumor- or patient-specific factors.

[k] There are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs micrographic surgery.
[l] For complicated cases, consider multidisciplinary tumor board consultation.
[m] If surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.
[n] Negative margins unachievable by Mohs micrographic surgery or more extensive surgical procedures.
[o] If large nerve involvement is suspected, consider MRI with contrast to evaluate extent and rule out base of skull involvement or intracranial extension in head and neck tumors.
[p] Current FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.

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RISK FACTORS FOR RECURRENCE

H&P	Low Risk	High Risk
Location/size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm[1]	Area M ≥10 mm
		Area H[3]
Borders	Well defined	Poorly defined
Primary vs. Recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology		
Subtype	Nodular, superficial[2]	Aggressive growth pattern[4]
Perineural involvement	(-)	(+)

Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.
Area M = cheeks, forehead, scalp, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).

[1]Location independent of size may constitute high risk.
[2]Low-risk histologic subtypes include nodular, superficial, and other non-agressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
[3]Area H constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs micrographic surgery is recommended for optimal tumor clearance and maximal tissue conservation. For tumors <6 mm in size, without other high-risk features, other treatment modalities may be considered if at least 4-mm clinically tumor-free margins can be obtained without significant anatomic or functional distortions.
[4]Having morpheaform, basosquamous (metatypical), sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor. In some cases basosquamous (metatypical) tumors may be prognostically similar to SCC. Clinicopathologic consultation is recommended.

Bazal Hücreli Cilt Tümörlerinde Tedavi

Drugs Approved for Basal Cell Carcinoma

- Aldara (Imiquimod)
- Efudex (Fluorouracil--Topical)
- Fluorouracil—Topical
- Imiquimod
- Sonidegib
- Vismodegib

Cerrahiye uygun olmayan, yüzeyel, düşük risk grubu tümörler

Lokal İleri ve Metastatik hasta grubunda

Bazal Hücreli Cilt Tümörlerinde Tedavi

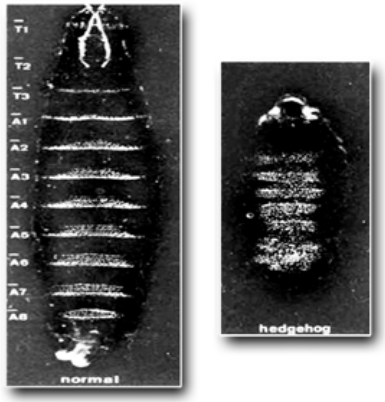
Table 1. Studies Comparing Superficial Therapies in Patients with Superficial BCC

Study	Histologic Subtype	Treatments (n)	Efficacy			Cosmetic Outcome			
Phase III randomized trial Wang 2001[196]	Superficial and nodular	Cryosurgery (39) ALA-PDT (44)	1-year recurrence:	15% 25%	} NS	Excellent:	8% 50%	} *P*<.001	
Randomized trial Basset-Seguin 2008[197]	Superficial	Cryotherapy (58) MAL-PDT (60)	5-year recurrence:	20% 22%	} NS	Excellent:	16% 60%	} *P*=.00078	
Meta-analysis[a] Roozeboom 2012[213]	Superficial	Imiquimod (1088) PDT (934)	1-year tumor-free survival:	87% 84%	} NS	NR			
Randomized, single-blind, non-inferiority ISRCTN 79701845 Arits 2013[193]	Superficial	MAL-PDT (202) Imiquimod cream (198) Fluorouracil cream (201)	Treatment success[b]:	73% 83% 80%	} *P*=.021 } NS } NS	Good/ excellent:	62% 61% 58%	All comparisons NS	

MAL, methyl aminolevulinate; NR, not reported; NS, no statistically significant difference; PDT, photodynamic therapy.
[a]Meta-analysis of 23 randomized and non-randomized studies.
[b]Treatment success was defined as the product of the percent of patients with clearance at 3 months by the percentage with sustained clearance during the next 9 months.

Bazal Hücreli Cilt Tümörlerinde Patogenez

Hedgehog Sinyal Yolağı



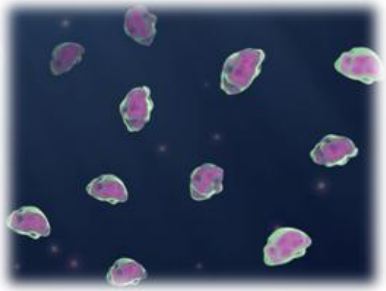
- Hedgehog sinyal yolağı, normal embriyonik gelişmede temel bir rol oynar.
  - Embriyonik gelişme döneminde organ oluşumunun kontrolü için hücre büyümesi ve farklılaşmasında rol oynar.
- Yetişkinlerde Hedgehog yolağı dokunun korunması ve onarımındaki rolleri hariç **normalde inaktiftir**.

Donnai D, Read AP. Lancet 2003;362:477–84
Caro I, Low JA. Clin Cancer Res 2010;16:3335–9
Briscoe J, Therond PP Nat Rev Mol Cell Biol 2013;14:416–29

Bazal Hücreli Cilt Tümörlerinde Patogenez

Hedgehog Sinyal Yolağı ve BHK

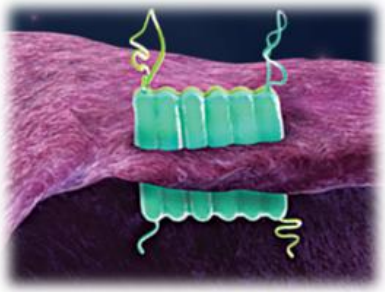
- BHK'nin moleküler temelinde **anormal Hedgehog sinyalizasyonu** vardır
  - BHK'larının **%90'ından fazlasında** Hedgehog yolağı aşırı aktiftir
- Hedgehog yolağının komponentleri;
  - Hedgehog ligandları
  - İnhibitör reseptör: Patched (PTCH)
  - Sinyal reseptörü: Smoothened (SMO)



Hedgehog ligand

Sinyal iletimini başlatır

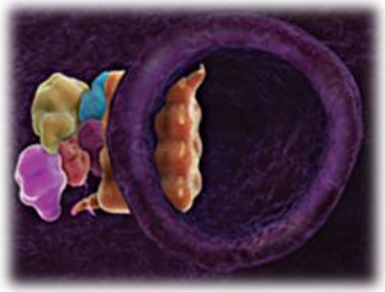
Scales SJ, de Sauvage FJ. Trends Pharmacol Sci 2009;30:303–12
Bale AE, Yu KP Hum Mol Genet 2001; 10: 757-62
Hutchin ME, et al. Genes Dev 2005; 19; 214-23



PTCH

SMO'yu baskılar

Epstein EH. Nat Rev Cancer 2008;8:743–54
Teh MT, et al. Cancer Res 2005; 65: 8597-603
Kallassy M, et al. Cancer Res 1997; 57: 4731-5

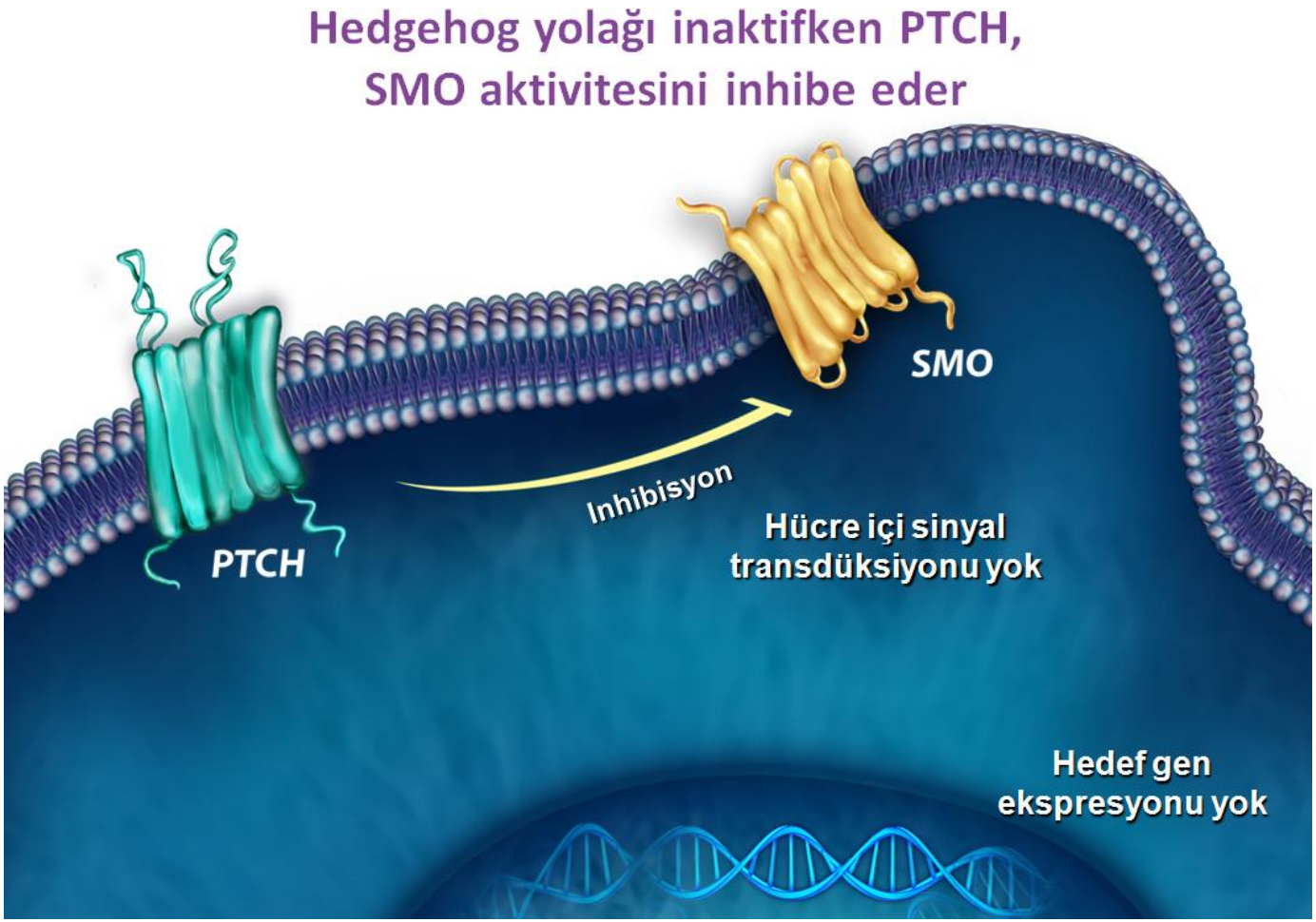


SMO

Transkripsiyon faktörlerini aktive eder

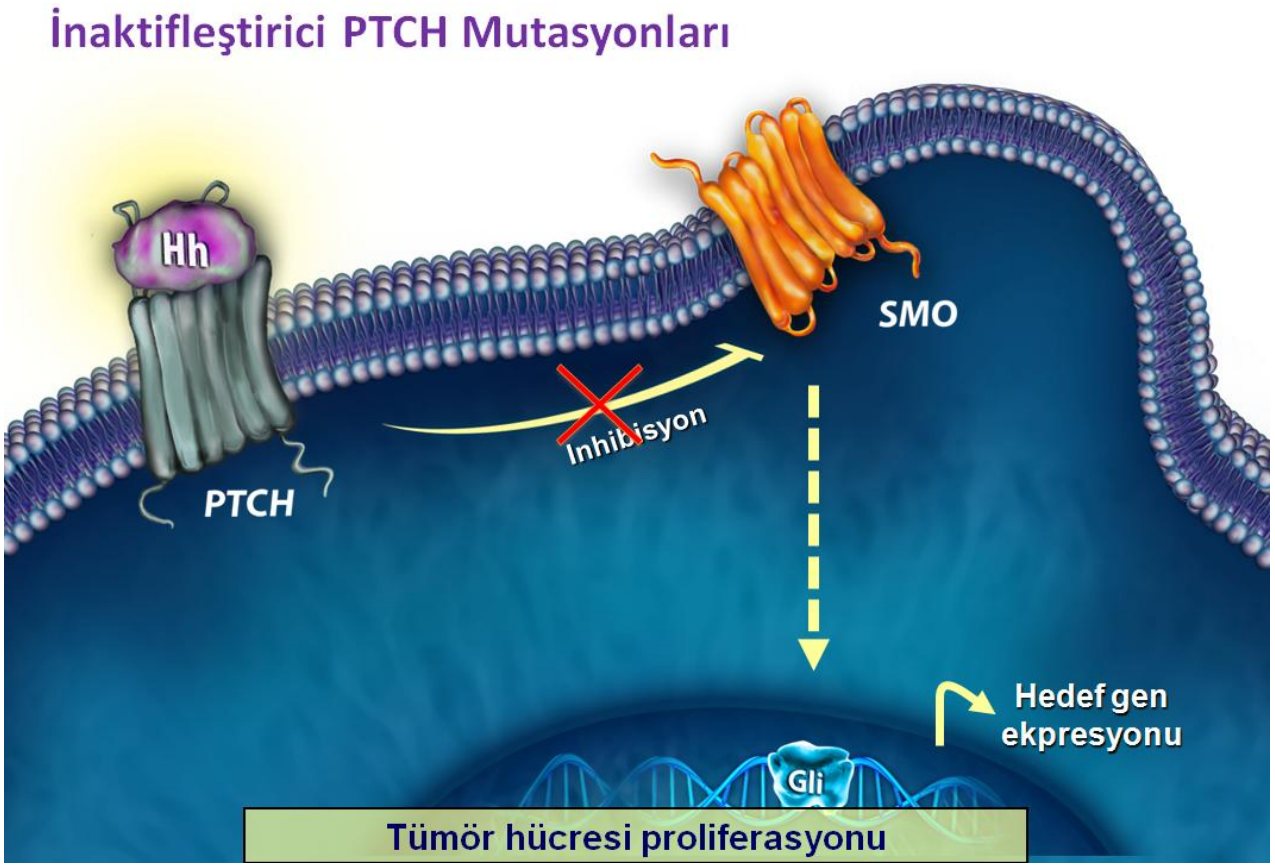
Unden AB, et al. Cancer Res 1997; 57: 2336-40
Carol, Low JA. Clin Cancer Res 2010;16:3335–9
Rudin CM. Cancer Prev Res 2010;3:1–3
Scales SJ. Trends Pharmacol Sci 2009;30:303–12

Bazal Hücreli Cilt Tümörlerinde Tedavi



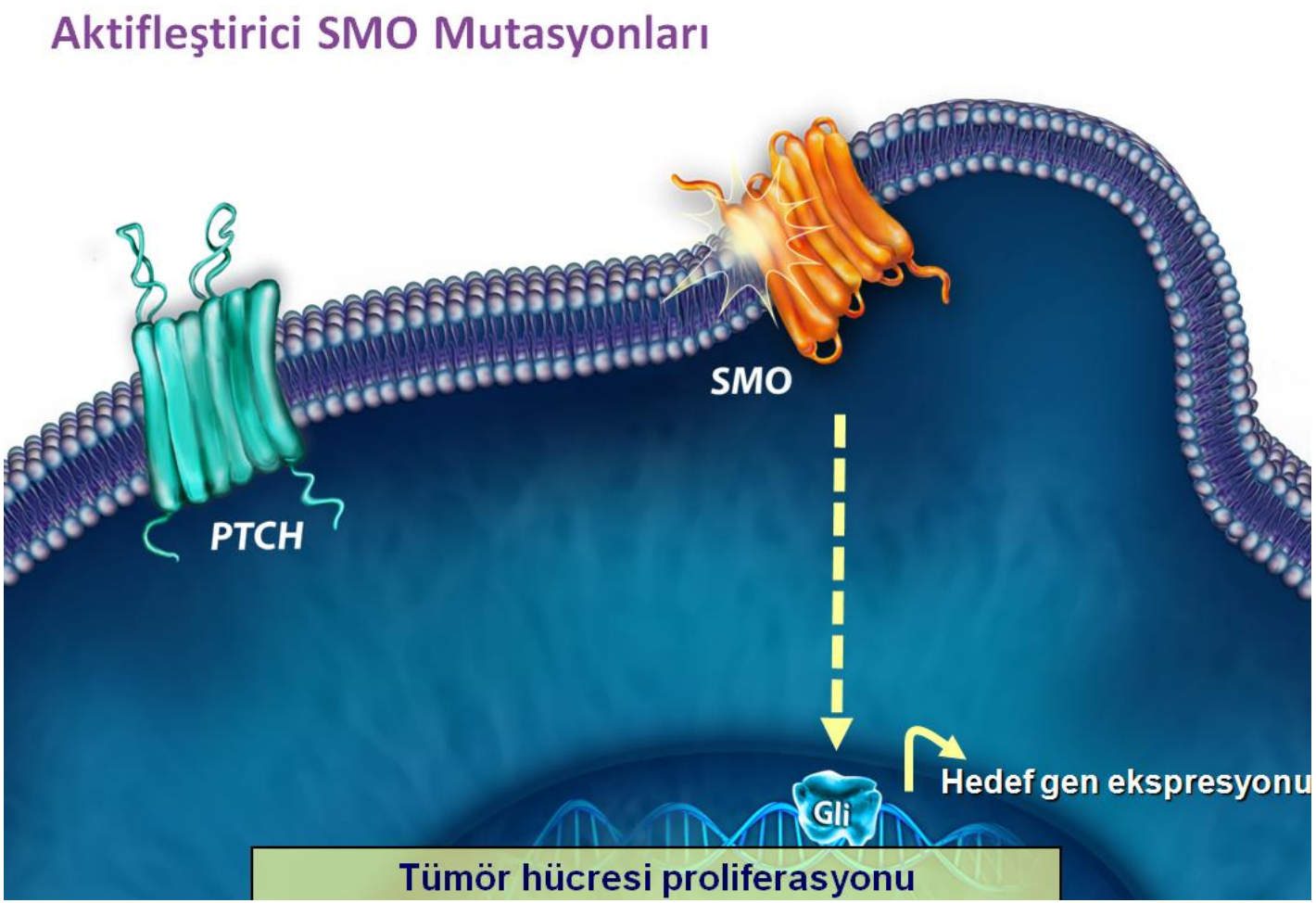
Normal bir erişkin dokusunda patched komponenti smoothenedı inhibe eder ve bu sayede sinyal transdüksiyonu baskılanmış halde durur.

Bazal Hücreli Cilt Tümörlerinde Tedavi



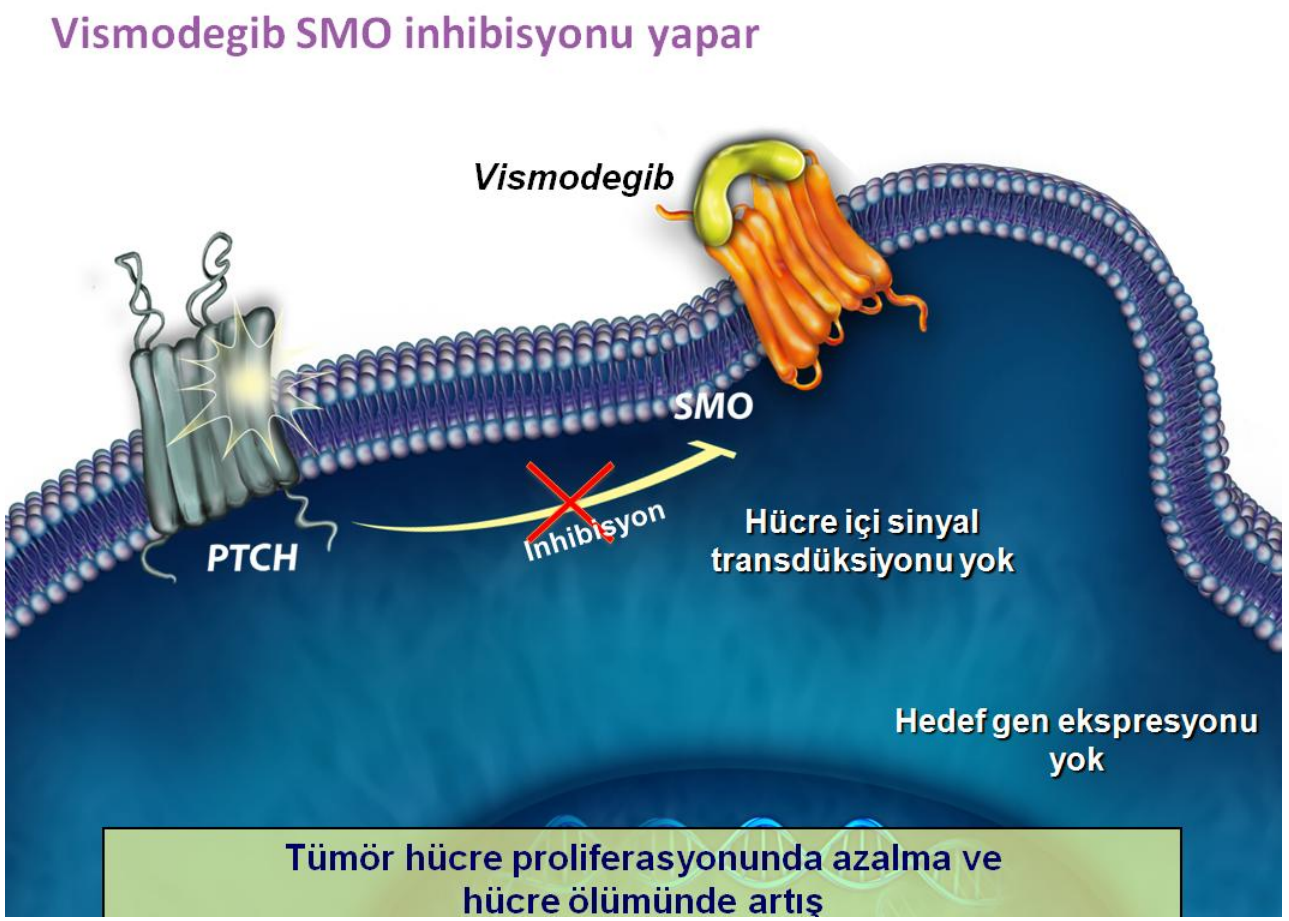
- Yara iyileşmesi gibi fizyolojik bir gereksinim durumunda hedgehog ligandı PTCH'e bağlanır inhibisyon ortadan kalkar. Bu nedenle SMO aktive olur , hedgehog gen ekspresyonu ile hücre proliferasyonu gerçekleşir ve yara iyileşir.
- PTCH'de oluşan bir mutsayon da benzer etkiyle SMO üzerindeki baskıyı kaldırır ve hücreler kontrolsüz olarak çoğalır; tümör hücreleri prolifere olur.

Bazal Hücreli Cilt Tümörlerinde Tedavi



- Mutasyon SMO'da olursa yine PTCH inhibitör etkisi yok olur ve tümör hücreleri prolifere olur.

Bazal Hücreli Cilt Tümörlerinde Tedavi



- Erivedge SMO bağlanarak etki gösterdiği için mutasyon PTCH ya da SMO hangisinde olursa olsun tümör hücre proliferasyonunu engeller.

ERIVANCE mBCC ve liBCC'de Araştırıcının değerlendirdiği etkinlik- 30 ay sonuçları

	30 aylık güncelleme (30 Mayıs 2013, Veri kesim tarihi)		
	mBCC (n=33)	liBCC (n=63)	Total (n=96)
Objektif yanıt, n (%) [95% CI]	16 **(48.5)** [30.8–66.2]	38 **(60.3)** [47.2–71.7]	54 (56.3) [45.7–66.4]
Tam yanıt Kısmi yanıt Stabil Hastalık Progresif Hastalık	0 16 14 2	20 18 15 6	20 34 29 8
Medyan yanıt süresi, ay (95% CI)	14.8 (5.6–17.0)	26.2 (9.0–37.6)	16.1 (9.5–26.2)

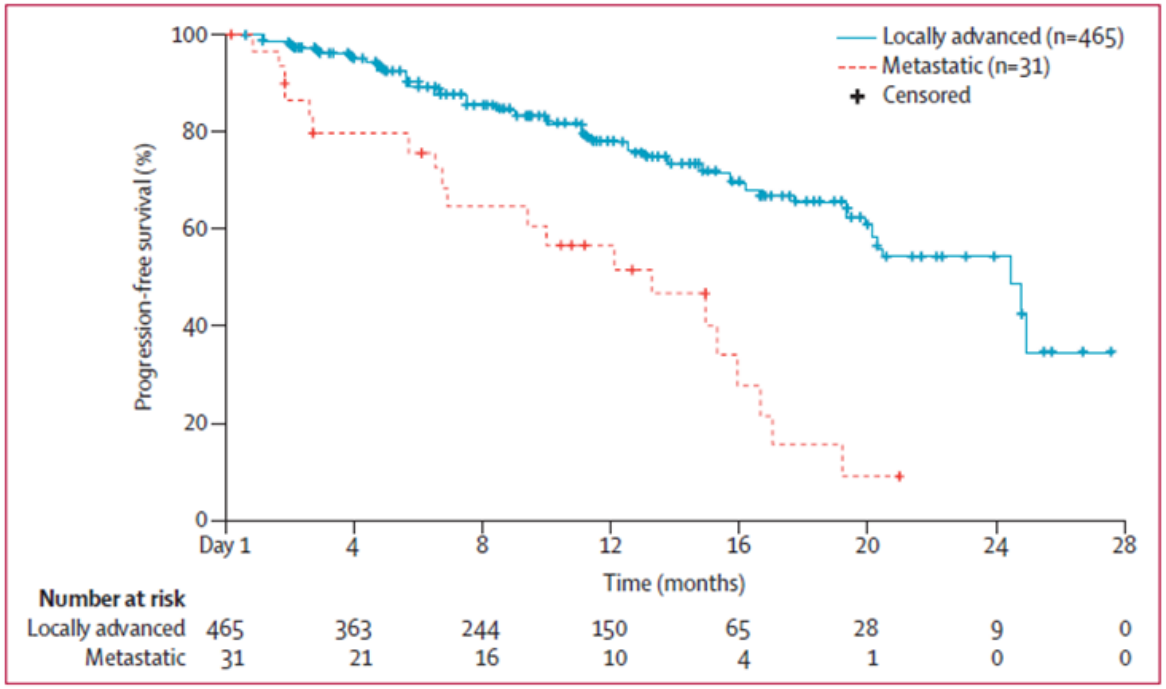
Sekulic A et al. Poster presentation at ASCO 2014

STEVIE ilk 500 hasta: RECIST kriterlerine göre yanıt (Araştırıcı değerlendirmesi)

	Tüm Hastalar N=482	liBCC n=453	Metastatik BCC n=29
Tam Yanıt	155 (32%)	153 (34%)	2 (7%)
Kısmi Yanıt	158 (33%)	149 (33%)	9 (31%)
Stabil Hastalık	128 (27%)	118 (26%)	10 (34%)
Progresif Hastalık	15 (3%)	11 (2%)	4 (14%)
Değerlendirilmedi	6 (5%)	22 (5%)	4 (14%)
Genel Yanıt Oranı (Tam + Kısmi Yanıt)	**%65**	**%67**	**%38**

Basset-Seguin N et al. Lancet Oncol 2015; 16: 729–36

STEVIE ilk 500 hasta: Progresyonsuz Sağkalım



	liBCC	Metastatik BCC	Tüm hastalar N=496
Medyan PFS	24.5 ay	13.1 ay	20.2 ay

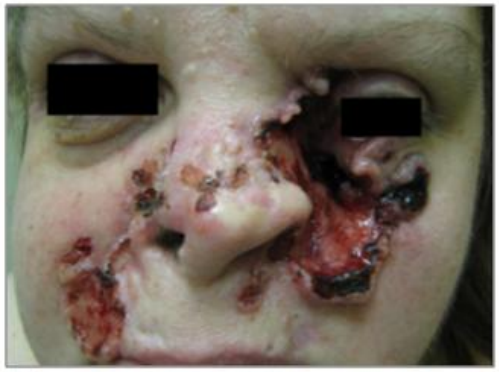
Basset-Seguin N et al. Lancet Oncol 2015; 16: 729–36

STEVIE ilk 500 hasta: Progresyonsuz Sağkalım

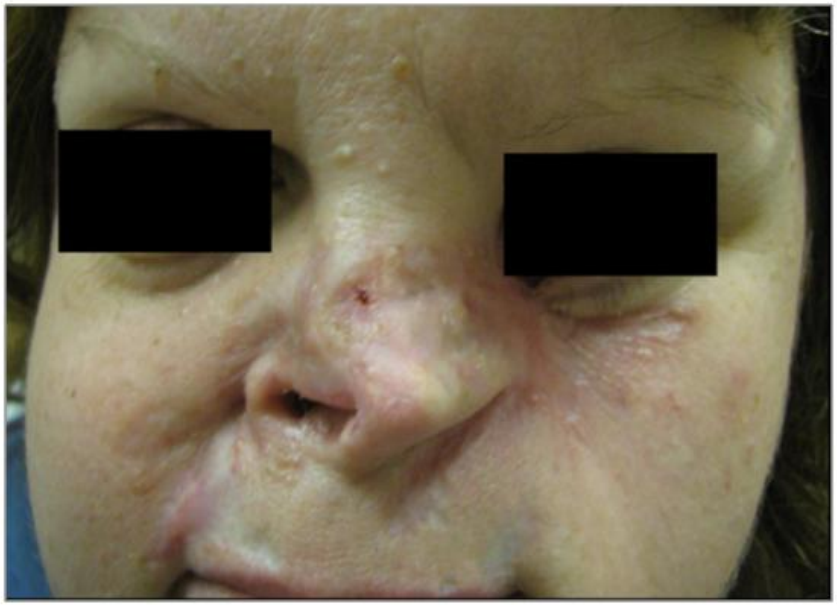
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Herhangi bir Advers Olay	85 (17%)	191 (38%)	170 (34%)	23 (5%)	21 (4%)
	165 (33%)	114 (23%)	38 (8%)	0	0
Alopesi	178 (36%)	127 (25%)	2 (<1%)	0	0
Disgüzi	156 (31%)	102 (20%)	11 (2%)	0	0
Asteni	76 (15%)	51 (10%)	12 (2%)	1 (<1%)	1 (<1%)
İştah azalması	76 (15%)	39 (8%)	11 (2%)	0	0
Kilo kaybı	72 (14%)	71 (14%)	17 (3%)	1 (<1%)	0
Diyare	64 (13%)	16 (3%)	3 (<1%)	0	0
Bulantı	59 (12%)	20 (4%)	1 (<1%)	0	0
Agüzi	55 (11%)	46 (9%)	10 (2%)	1 (<1%)	0
Halsizlik	50 (10%)	18 (4%)	11 (2%)	1 (<1%)	0

Basset-Seguin N et al. Lancet Oncol 2015; 16: 729–36

İleri Evre BCC Vaka Örnekleri



- Tedaviden 9 ay sonra
- Stabil Hastalık (görüntüleme ile değerlendirilmiş)



Von Hoff DD, et al. *N Engl J Med* 2009; 361: 1164-1172

Bazal Hücreli Cilt Tümörlerinde Yeni Tedavi

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Table 2. Hedgehog Pathway Inhibitors in Advanced BCC[a]

Study		Tx[b]	Patients, n		Follow-up Time, Minimum (median)[c]		Objective Response Rate[d]		Time to Response, Median[c]		Duration Response, Median[c]		Progression-free Survival, Median[c] (% progressed)	
Name and References	*Phase, Design*		*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*
ERIVANCE NCT00833417[e,221]	II OL	Vismo	71	33	≥21; (22.4)	≥21; (21.7)	48%	33%	NR	NR	9.5	7.6	9.5 (3%)	9.5 (13%)
NCT01160250[224]	II OL	Vismo	56	39	NR[f] (6.5)		46%	31%	2.6	2.6	NR	NR	NR (0%)	NR (8%)
STEVIE NCT01367665[225]	II OL	Vismo	453	29	≥12; (12.7)	≥12; (12.9)	67%	38%	2.6	2.8	22.7	10	24.5 (2%)	13.1 (14%)
RegiSONIC NCT01604252[233]	Obs	Vismo	66	-	(13.2)	-	68%	-	NR	-	5.95	-	NE	-
BOLT NCT01327053[226]	II RDB	Soni 200 mg	42	13	≥6 (13.9)		43%	15%	3.9	4.6	NE	NE	NE (12%)	13.1 (31%)
		Soni 800 mg	93	23			38%	17%	3.7	1.0	NE	NE	NE (9%)	7.6 (43%)

laBCC, locally advanced BCC; mBCC, metastatic BCC; NR, not reported; NE, not reached; Obs, prospective observational; OL, open-label; RDB, randomized double-blind; Soni, sonidegib; Tx, treatment; Vismo, vismodegib.

[a]Trials included patients with advanced BCC that was inappropriate for surgery or RT.

[b]Inhibitors were taken orally once daily. Vismodegib dose was 150 mg.

[c]Times are reported in months.

[d]Response criteria varied between studies.

[e]ERIVANCE data per independent review facility assessment.

[f]Trial was terminated early due to FDA approval of vismodegib.

Bazal Hücreli Cilt Tümörlerinde Yeni Tedaviler

Radiation Therapy and Vismodegib in Treating Patients With Locally Advanced Head and Neck Cancer
Status: Active
Age: 18 years and over
Gender: Male or Female
Location: 2 locations

Topical Itraconazole in Treating Patients with Basal Cell Cancer
Status: Active
Age: 18 years and over
Gender: Male or Female
Location: Stanford Cancer Institute, Palo Alto, California

Pembrolizumab with or without Vismodegib in Treating Skin Basal Cell Cancer That Is Metastatic or Cannot Be Removed by Surgery
Status: Active
Age: 18 years and over
Gender: Male or Female
Location: Stanford Cancer Institute, Palo Alto, California

Photodynamic Therapy and Vismodegib in Treating Patients with Multiple Basal Cell Cancers
Status: Active
Age: 18 years and over
Gender: Male or Female
Location: The University of Arizona Medical Center-University Campus, Tucson, Arizona

Bazal Hücreli Cilt Tümörlerinde Yeni Tedaviler

Sonidegib and Buparlisib in Treating Patients with Advanced or Metastatic Basal Cell Cancer
Status: Active
Age: 18 years and over
Gender: Male or Female
Location: Stanford Cancer Institute, Palo Alto, California

Itraconazole in Treating Patients with Basal Cell Carcinoma
Status: Active
Age: 19 years and over
Gender: Male or Female
Location: Johns Hopkins University / Sidney Kimmel Cancer Center, Baltimore, Maryland

Effectiveness of Narrow Margins in Patients with Low-Risk Basal Cell Carcinoma Undergoing Surgery
Status: Active
Age: Not specified
Gender: Male or Female
Location: See Clinical Trials.gov