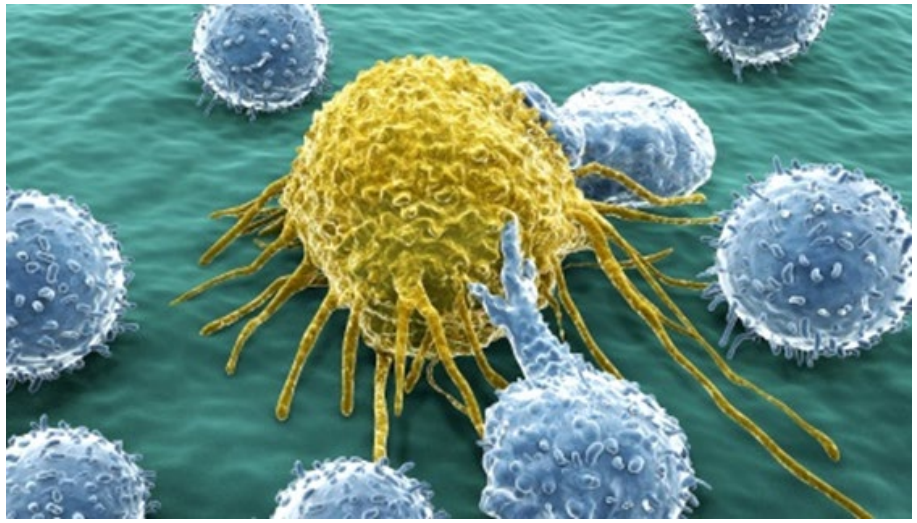
INSTITUT
JULES BORDET
INSTITUUT

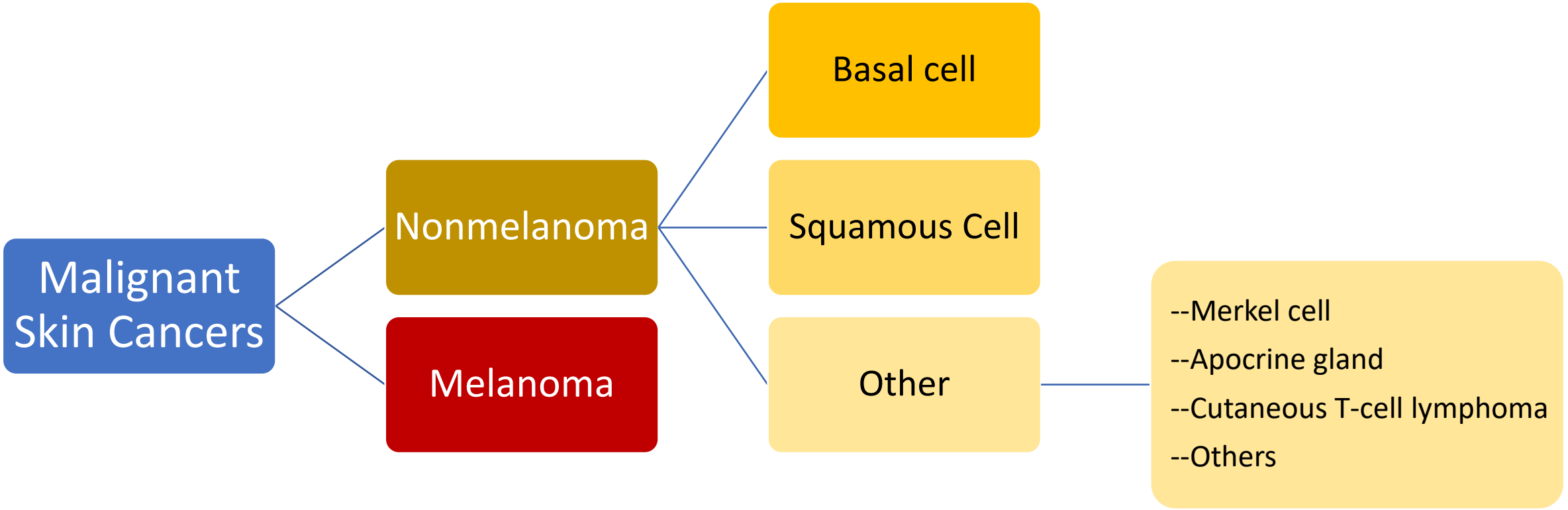


# *Traitements systémiques des carcinomes basocellulaires avancés ou métastatiques*

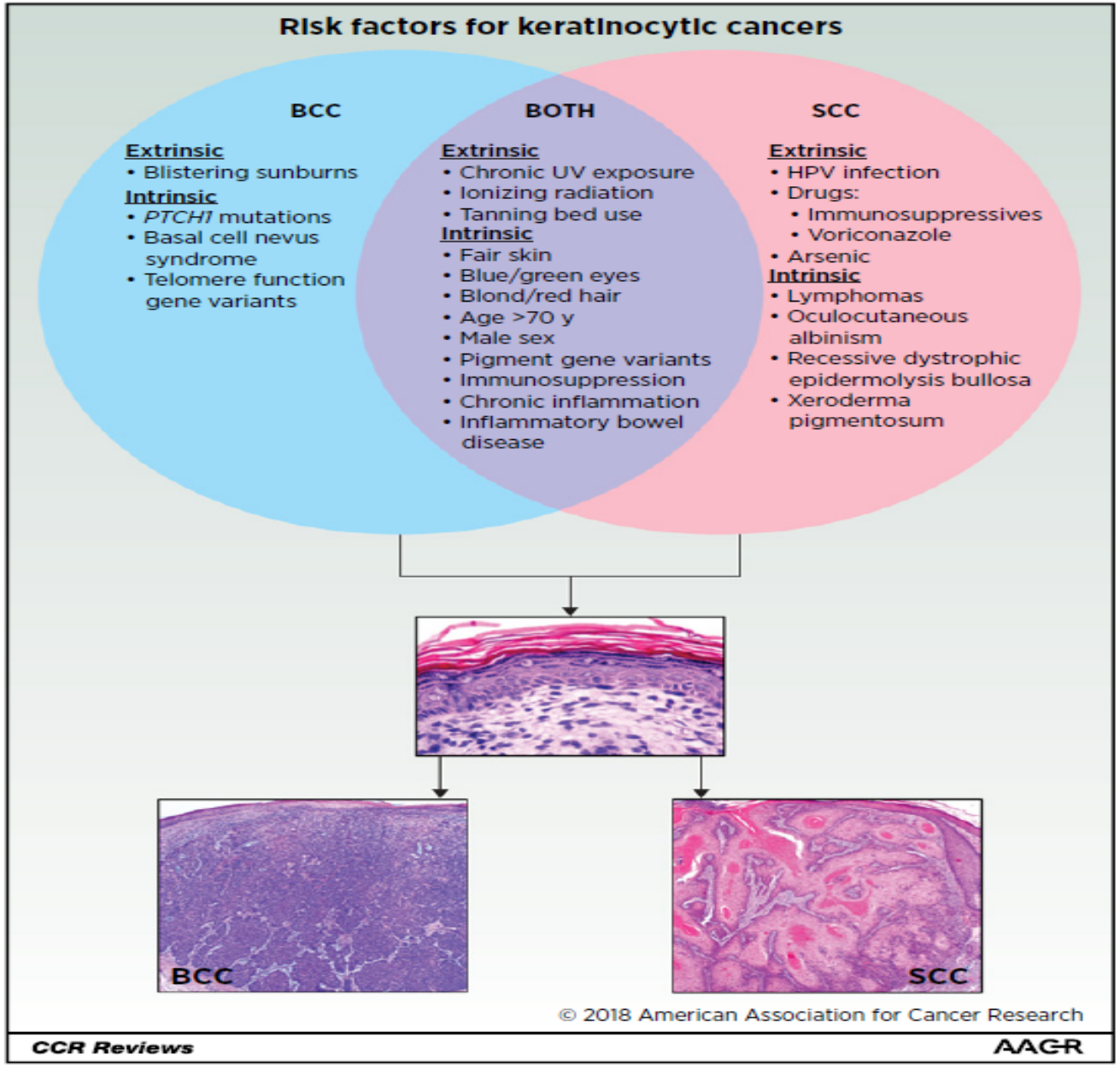
*joseph.kerger@hubruxelles.be*

ULB iris

# Types of skin cancer



# Non melanoma skin cancers (NMSC) - risk factors

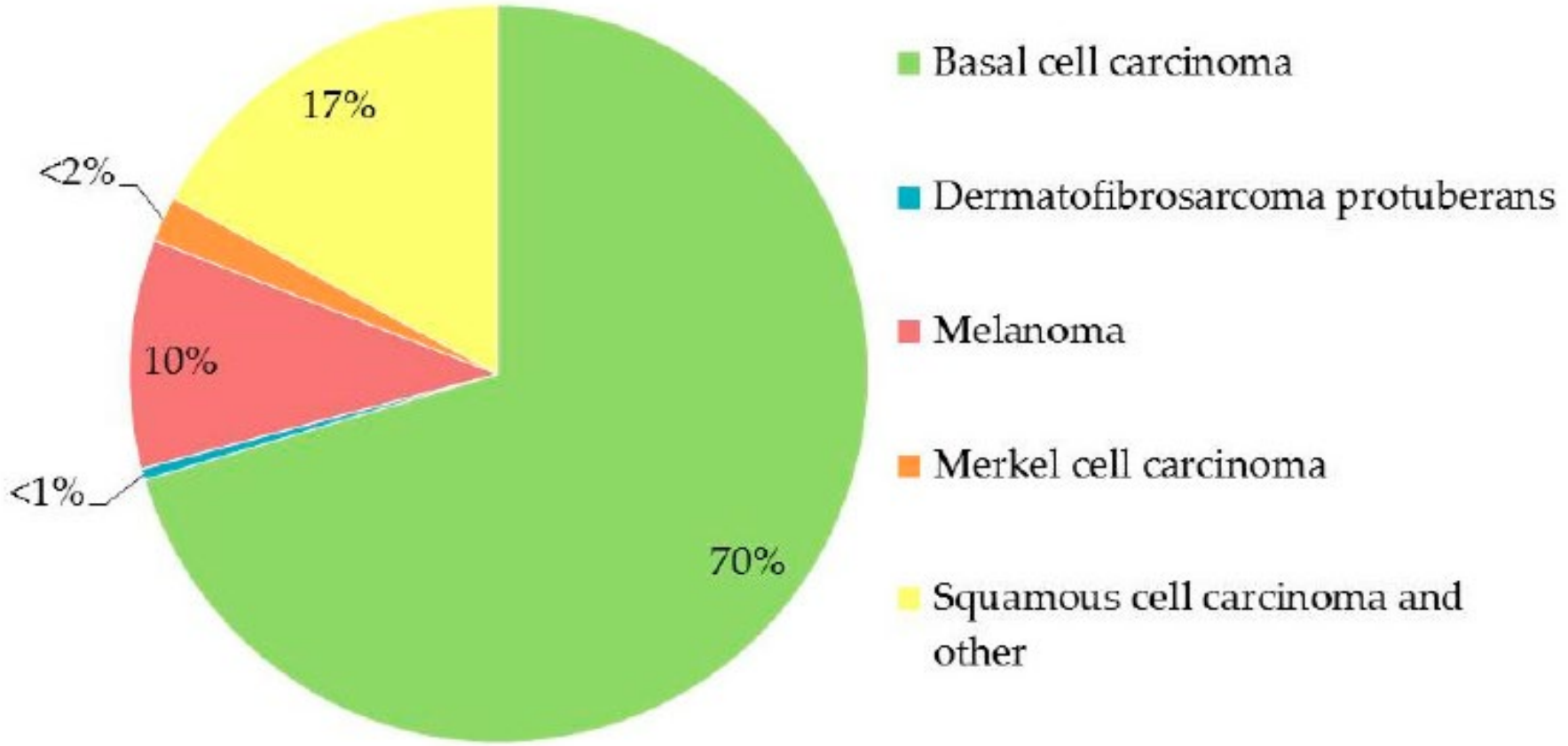


# Non melanoma skin cancers

- Basal cell carcinoma
  - Four times more common than squamous cell
  - Risk Factors
    - Same as melanoma
    - UVA/UVB exposure, higher risk in fair individuals
    - Radiation
    - **Gorlin syndrome** :
      autosomal dominant,
      multiple BCC,
      palmo-plantar pits,
      jaw cysts,
      frontal bossing,
      hypertelorism

- Squamous cell carcinoma
  - Risk Factors:
    - Sun exposure
    - Chemicals : arsenic, hydrocarbons (coal tars, soot, asphalt)
    - Tobacco
    - HPV
    - Radiation
    - Immunosuppression
      (organ transplant recipients, …)

# Incidence of the different skin cancers

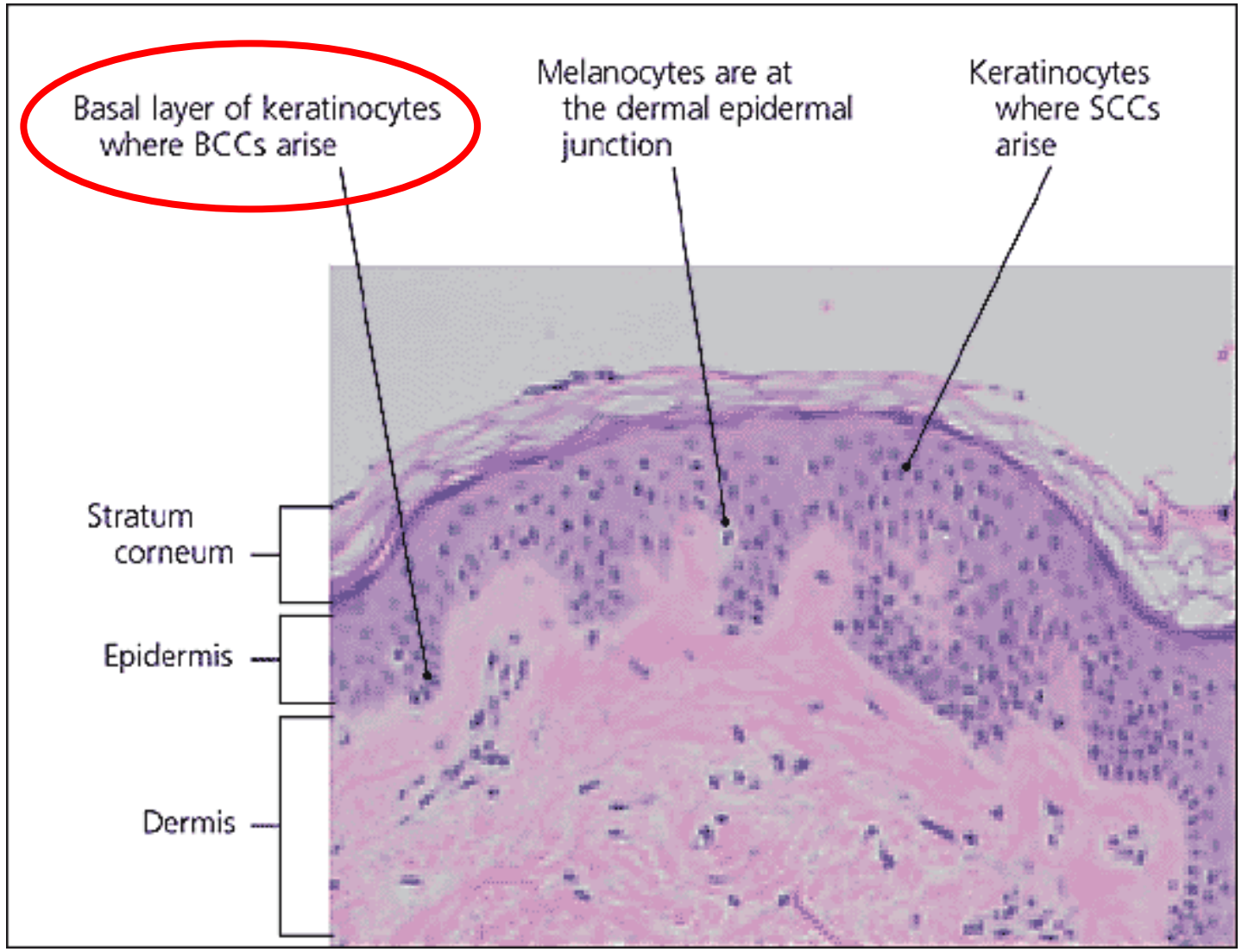



*KV Laikova et al.: Molecules 2019; 24: 1516*

# Skin cancers - Epidemiology in Europe and US

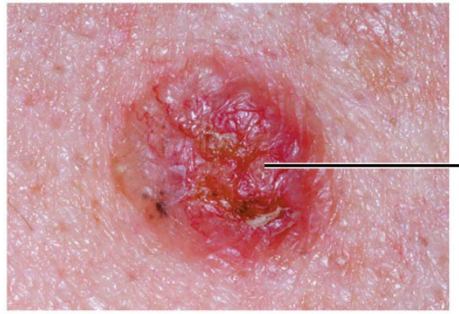
| Type of skin cancer | Incidence | Lifetime risk |
|---|---|---|
| Malignant melanoma (MM) | 20/100000 /yr | 1 : 70 |
| Basal cell carcinoma (BCC) | 120/100000 /yr | 1 : 7 |
| | | |
| Squamous cell carcinoma (SCC) | 30/100000 /yr | 1 : 20 |
| Actinic keratosis | 250/100000 /yr | 1 : 3 |

# Origin of BCC and SCC



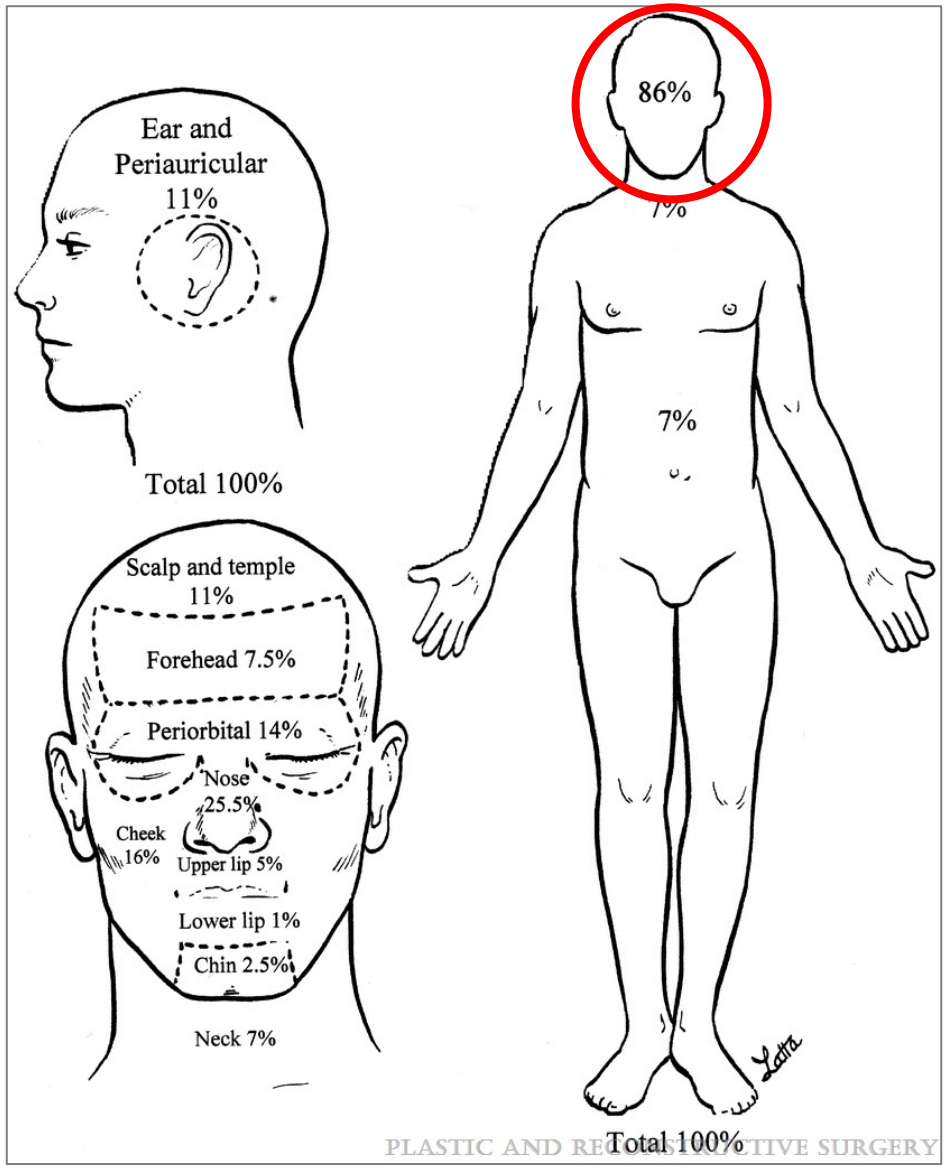
# Basal cell carcinoma

- **Basal cell carcinoma**
  - most *common* of all cancers, including skin cancer
  - arises from keratinocytes in stratum basale of epidermis
  - typically found on skin that is *regularly exposed* to UV radiation
  - generally forms a *nodule* with a *central crater that ulcerates*
  - generally does not metastasize
  - *Surgical removal usually resolves it completely*




**(a) Basal cell carcinoma:** cancer of keratinocytes in stratum basale; generally forms a nodule with a "cratered" center

# Distribution of basal cell carcinomas across the human body




*Shanoff LB, Plast. Reconstr. Surg. 1967; 39: 619. Netscher DT, Plastic and Reconstructive Surgery 2004; 113: 74e-94e.*

# BCC – Basal cell nevus or Gorlin syndrome

Robert Gorlin (dentist) identified a syndrome in which multiple abnormalities occur[1]
Autosomic dominant
Prevalence varies from 1/57,000 to 1/256,000
Patients can develop hundreds of BCCs - usually starting by age 35
Histological appearance does not differ from sporadic BCCs

- Major Criteria
  - Multiple BCCs or one under 20 yrs
  - Odontogenic keratocysts
  - Palmar/plantar pits
  - Bilamellar calcification of the flax cerebri
  - Bifid, fused or splayed ribs
  - Affected 1st degree relatives

- Minor Criteria
  - Macrocephaly
  - Congenital malformations (e.g. cleft lip)
  - Ovarian fibroma
  - Skeletal abnormalities
  - Medulloblastoma

1. *Gorlin RJ. Nevoid basal-cell carcinoma syndrome. Medicine 1987;66:98-113.*

# Most frequent genodermatoses with the occurrence of BCC

Most frequent genodermatoses with the occurrence of BCC.

| Genodermatosis | Affected gene | Transmission mode | Main characteristics |
|---|---|---|---|
| *Xeroderma pigmentosum* | DNA repair genes | Recessive | Multiple skin tumours (BCC, cSCC, melanoma, others); precancerous lesions; freckles and hypopigmented macules on sun-exposed areas; neurological defects |
| Gorlin syndrome | *PTCH, SMO, SUFU* | Dominant | Multiple BCCs; odontogenic keratocysts; palmo-plantar pits; skeletal abnormalities; other developmental defects |
| Bazex–Dupré–Christol syndrome | X-linked dysregulation of *ARHGAP36* | Dominant | Multiple BCCs; follicular atrophoderma; congenital hypotrichosis; hypohidrosis; facial milia |
| Oculocutaneous albinism | *TYR, OCA2* | Recessive | Multiple skin tumours including BCC; albinism; nystagmus; strabismus; diminished visual acuity. |
| Muir–Torre syndrome | Mismatch repair genes (*MLH1, MSH2, MSH6*) | Dominant | Sebaceous gland neoplasms; keratoacanthomas; cSCC and BCC; one or more visceral malignancies, particularly gastrointestinal or genito-urinary. |

# BCC - Local therapy modalities

- Overwhelming majority cured with local ablation
  - surgery
  - Mohs micrographic surgery
  - cryotherapy
  - radiation therapy
  - photodynamic therapy
  - topical : iniquimod (Aldara®), 5FU (Efudix®)

- BCC with more significant or complex problem
  - advanced: ↑ risk local/recurrent/spread
  - neglected lesions : major surgery and reconstruction
  - multiple lesions : complex sequencing of surgery
  - elderly/comorbidities :
    recurrence after limited surgery or radiation therapy
  - rarely: Gorlin syndrome

# Basal cell carcinoma (BCC)

- 70% NMSC = BCC !
- ↑ incidence rate

| | 1999 | 2012 |
|---|---|---|
| Men | 125/100000 | 160/100000 |
| Women | 90/100000 | 125/100000 |

*Leiter U, J Investig Dermatol 2017, 137, 1860-1867*

- Frequency of difficult to treat (DTT) BCC ?
  - Uncomplicated cases: N = 8954/9652
  - Complicated cases : N = 698/9652 (7,2 %)
    → might benefit from new medical treatment options
  - Cases with complications: N = 58/9652 (0,6%)
    → benefit from a well tolerated systemic therapy

*Dreier J, Br J Dermatol 2014, 17, 1066*

# Advanced NMSC (include BCC, SCC, MCC)

**Two different groups of patients**
with different features and response criteria

**Locally advanced disease :**
(typically one very large or multiple primary tumors)

**Metastatic disease :**
regional or distant

**Risk factors in complex cases :**
comorbidities, neglection, immune suppression
(i.e. CLL patients, organ transplant recipients,…)

## BASAL CELL CARCINOMA: HIGHER RISK FACTORS FOR SUBCLINICAL INVASION AND RECURRENCE

- Recurrent tumor
- Anatomic location

  *High risk:* Central face, eyelid, eyebrow, periorbital, nose, lip, chin, mandible, temple, ear, in front or behind the ear, genitalia, hand and foot

  *Medium risk:* Cheeks, forehead, scalp, and neck

  *Low risk:* Trunk, extremity (excluding hand/foot)
- Size

  Lesions ≥6 mm on high-risk area

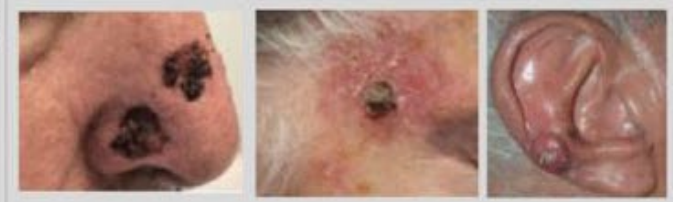
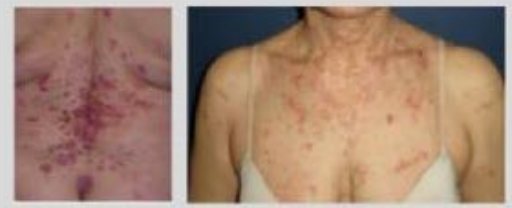
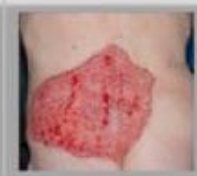
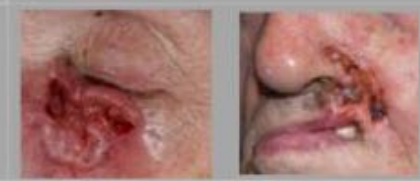
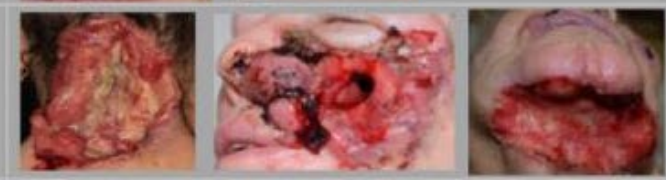
  Lesions ≥10 mm on medium-risk area

  Lesions ≥20 mm on low-risk area
- Histologic subtype pattern

  Aggressive growth (morpheaform, fibrosing, sclerosing, infiltrating)

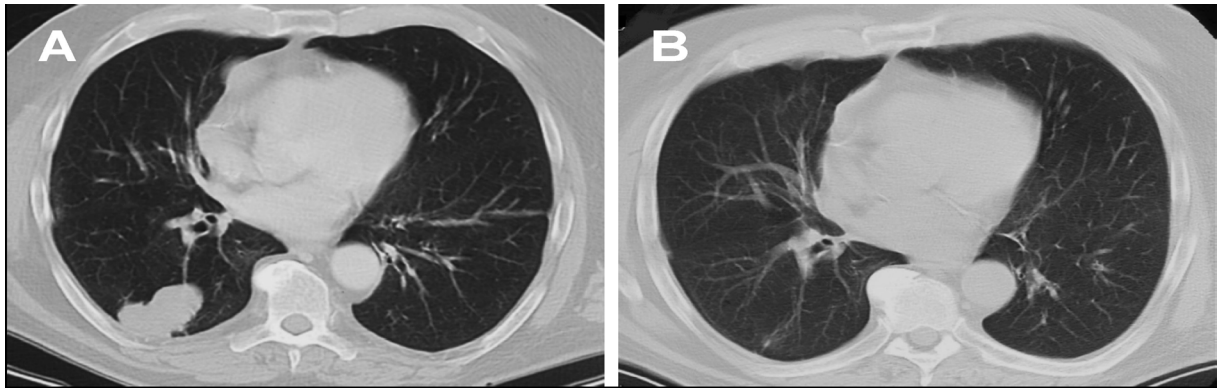
  Micronodular
- Ill-defined clinical borders
- Perineural invasion
- Development in sites of prior radiation
- Immunosuppression

From Sondak VK, Sabel MS, Mulé JJ. Allogeneic and autologous melanoma vaccines: where have we been and where are we going? *Clin Cancer Res* 2006;12:2337s–2341s.

| Risk | Stage | | Characteristics | | Illustrative pictures | DTT-BCC Group (part 1) |
|---|---|---|---|---|---|---|
| Easy To Treat and low risk of recurrence | Common BCC | I | Low-risk common BCC | **None of the other stages characteristics.**<br>*Recurrences only come from blind treatments, or insufficient surgical margins.* | | *Not included* |
| <= Increasingly Difficult To Treat and increasing risk of recurrence | Common BCC | IIA | Common BCC but somewhat DTT | Common BCC but management is more complex than usual for any reason linked to the tumor (location requiring technical skill, poorly defined tumor borders, prior recurrence) and/or to the patient (poor general status, comorbidities, or unwillingness to cooperate ...).<br>*Good results and low rate of recurrence expected with surgery even if technically complicate, when the patient cooperates.* |  | *1* |
| | Common BCC | IIB | DTT-BCC mainly due to multiplicity of common BCC | Very high number of common BCC (>10) or multiple complex BCC (> 5) in the setting of apparently sporadic cases or in Gorlin syndrome*.<br>*When at least 1 of the multiple BCC can be classified III or IV, the patient will be classified accordingly, and not IIB |  | *2* |
| | Advanced BCC | IIIA | Locally advanced DTT-BCC out of critical areas | Large and/or destructive tumors in non-critical or functionally significant areas.<br>*Deemed curable without expected functional mutilations.* |  | *3* |
| | Advanced BCC | IIIB | Locally advanced DTT-BCC in critical areas | Large and/or or destructive tumors in critical or functionally important areas (periorificial, nose, ...).<br>*Deemed curable by surgery, but functional impairment and/or mutilation are inevitable.* |  | *4* |
| | Advanced BCC | IIIC | Extremely advanced DTT- BCC | Giant and/or deeply invasive tumors involving extracutaneous tissue (bone, muscles, vital or sensorial structures) responsible for an extreme clinical situation.<br>*Cure cannot be expected by surgery whatever its extent.* |  | *5* |
| | Metastatic BCC | IV | | Distant metastases*.<br>*Whatever the initial BCC staging, patient must be classified IV when metastatic. | | *Not included* |

# BCC – Systemic cytotoxic chemotherapy

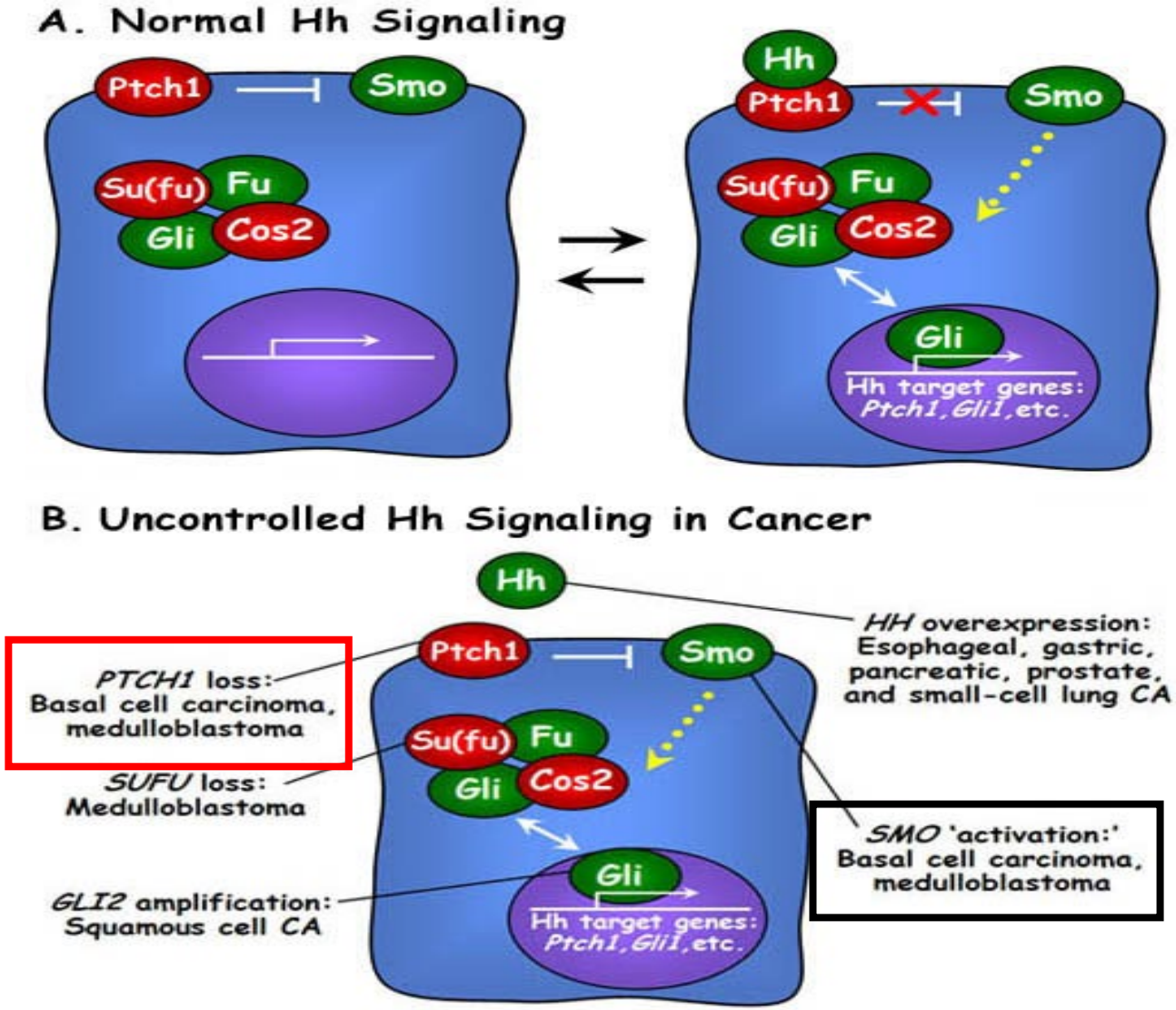
- Metastatic
  - Numerous agents on case-report basis :
    - Cyclophosphamide, Etoposide, 5-FU, MTX, Bleomycin, Doxorubicin, Cisplatin, Carboplatin, Paclitaxel
  - Cisplatin (alone or combination) likely most effective:
    - 12 patients treated with platinum containing regimen[1]:
      - 5 CR (3 to 18 months)
      - 4 PR
      - 3 SD




1. *Carneiro BA et al Cancer Invest, 2006*

# Hedgehog Signaling Pathway

The hedgehog pathway is active during embryonic development but dormant after birth




**Basal cell nevus syndrome**: Germline mutation in PTCH gene

# Basal cell nevus syndrome

Positional cloning and subsequent screening identified a spectrum of PTCH mutations in BCNS patients

BCCs develop secondary to activation of target genes of Hh pathway in cells that have lost both normal copies of PTCH

# Sporadic BCC

Majority show allelic loss for chromosome 9q22 and inactivating mutations of PTCH

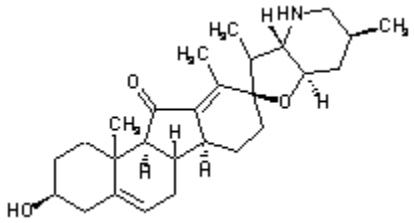
Activating mutations of SMO in 10-20% sporadic BCCs

Suggests abnormal Hh signaling involved in most (all?) BCCs - high levels of Hh target genes such as GLI1

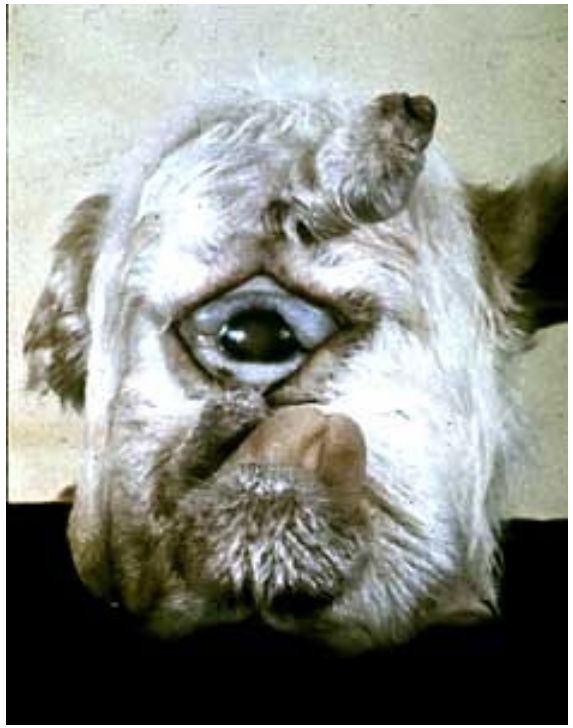
# Anomalous development due to disruption of Hedgehog signaling

Enabled by the ingenuity of Lynn James, from the US Department of Agriculture, in investigating the curious case of an epidemic of cyclopic lambs in Idaho, 1957

*Veratrum Californicum*

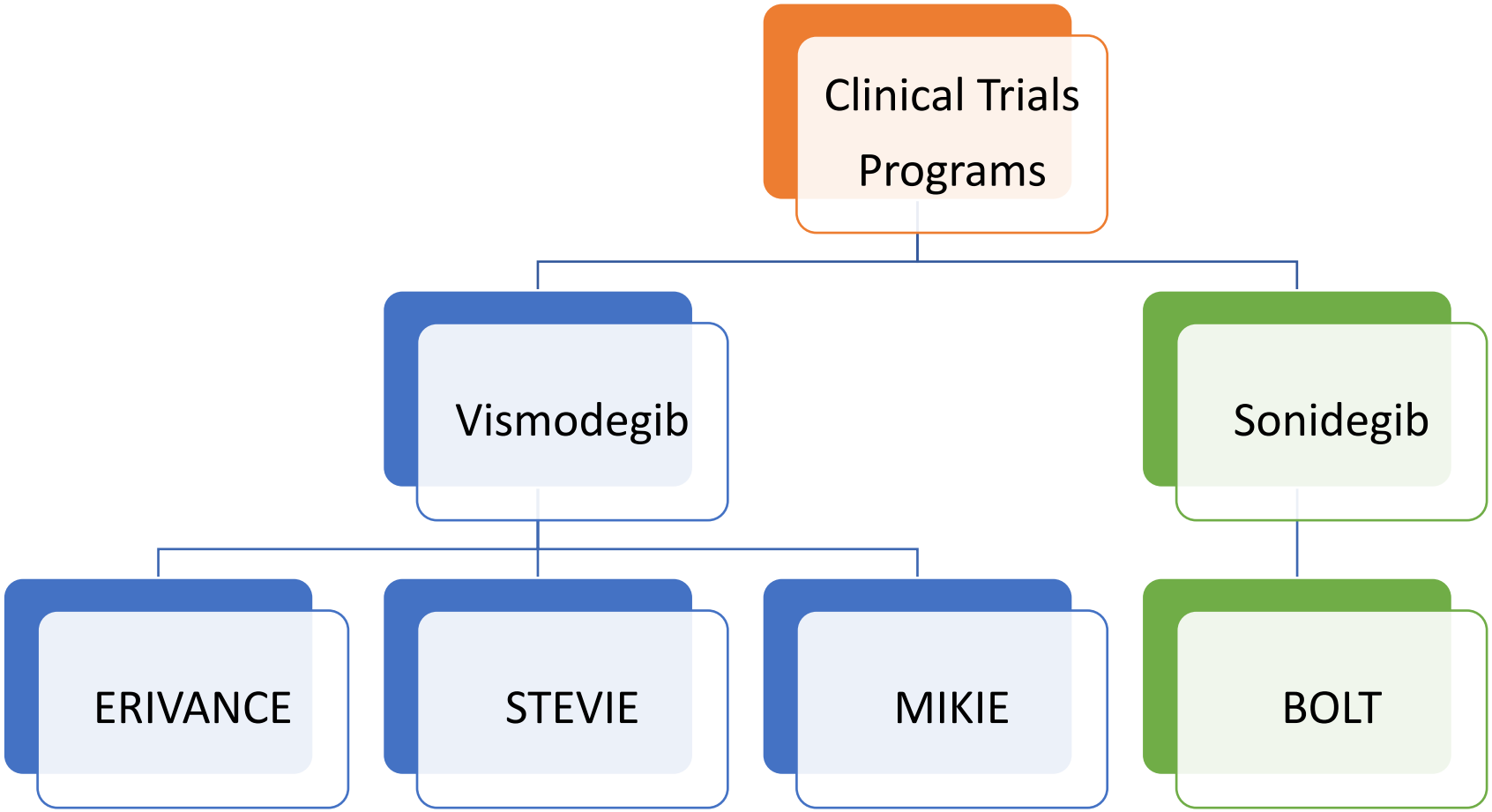


Cyclopamine



Cyclopic lamb

# Clinical trials programs of Hedgehog inhibitors for advanced BCC



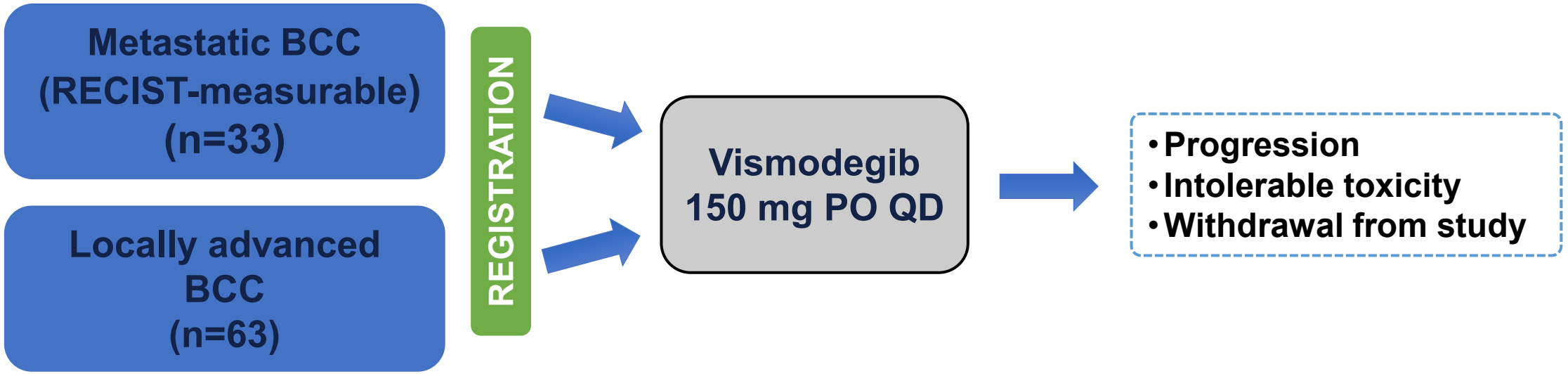
# Two Hedgehog inhibitors currently approved for advanced BCC by FDA / EMA

| Hedgehog Inhibitor | Indication | Dosage & Administration |
|---|---|---|
| Sonidegib (Odomzo)[1] | Adult with laBCC that has recurred following surgery or RT, or those who are not candidates for surgery or RT | 200 mg PO QD on an empty stomach |
| Vismodegib (Erivedge)[2] | Adults with laBCC that has recurred following surgery or those who are not candidates for surgery and who are not candidates for RT | 150 mg PO QD |

BCC, basal cell carcinoma; laBCC, locally advanced basal cell carcinoma; RT, radiation therapy

1. Odomzo [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; July 2020.
2. Erivedge [package insert]. South San Francisco, CA: Genentech USA, Inc.; August 2020.

# ERIVANCE: Phase 2 Study of Vismodegib in Advanced BCC




- Locally advanced BCC:
  - Inoperable
  - Surgery inappropriate
    - ≥1 cm
    - ≥2 recurrences after surgery and curative resection unlikely and/or anticipated substantial morbidity and/or deformity from surgery

RECIST, Response Evaluation Criteria In Solid Tumors

Sekulic A, et al. *N Engl J Med*. 2012;366(23):2171-2179.

# ERIVANCE: Efficacy* at 39 months

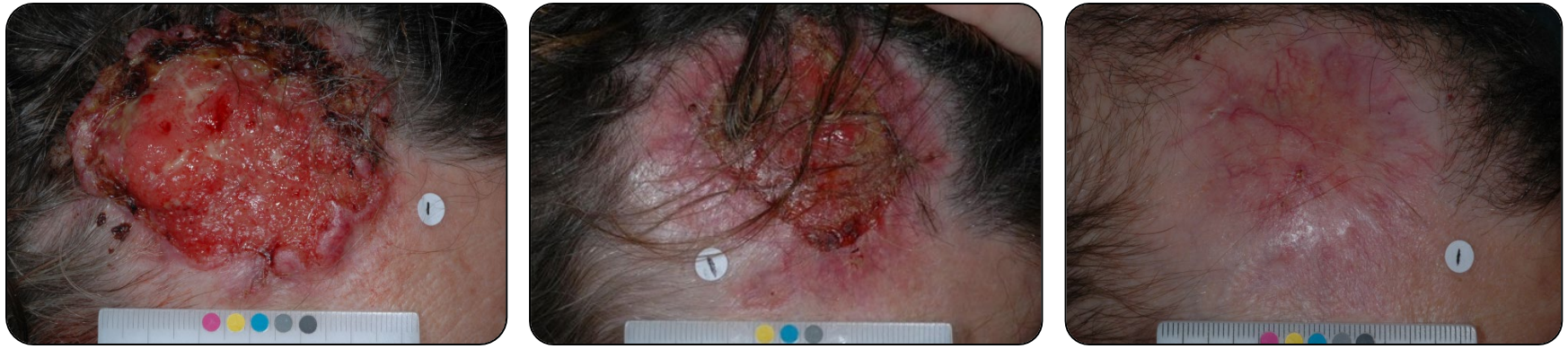
| Outcome | mBCC (n=33) | laBCC (n=63) |
|---|---|---|
| Objective response, %<br>Complete response<br>Partial response<br>Stable disease<br>Progressive disease | 48.5%<br>0%<br>48.5%<br>42.4%<br>6.1% | 60.3%<br>31.7%<br>28.6%<br>23.8%<br>9.5% |
| Median duration of response | 14.8 mos | 26.2 mos |
| Median progression-free survival | 9.3 mos | 12.9 mos |
| Median overall survival | 33.4 mos | NE |
| 2-y survival rate | 62.3% | 85.5% |

NE, not estimable

*Investigator assessed

Sekulic A, et al. *BMC Cancer*. 2017;17:332.

# Vismodegib in locally advanced BCC



**Week 16: no BCC on biopsy**

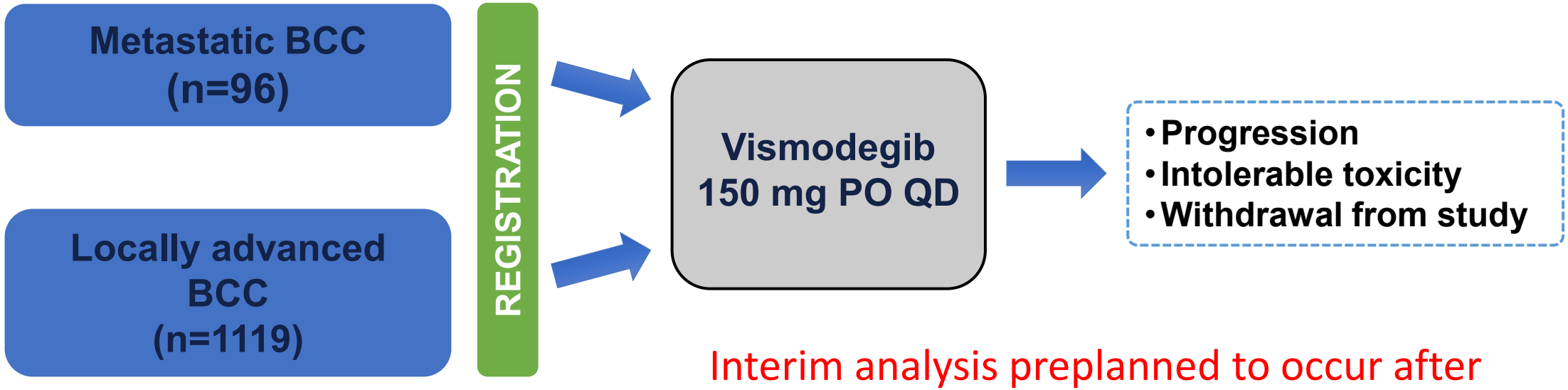
Sekulic A et al. *N Engl J Med*. 2012;366:2171-2179.

# ERIVANCE: Safety

| Treatment-emergent adverse event | Exposure <12 mos (n=48) | | Exposure ≥12 mos (n=56) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any adverse event | 100.0% | 56.3% | 100.0% | 55.4% |
| Muscle spasms | 52.1% | 4.2% | 87.5% | 7.1% |
| Alopecia | 50.0% | NA | 80.4% | NA |
| Dysgeusia | 41.7% | NA | 67.9% | NA |
| Weight decreased | 37.5% | 0% | 64.3% | 16.1% |
| Fatigue | 35.4% | 8.3% | 50.0% | 1.8% |
| Nausea | 22.9% | 0% | 41.1% | 0% |
| Decreased appetite | 31.3% | 4.2% | 25.0% | 1.8% |
| Diarrhea | 20.8% | 0% | 32.1% | 5.4% |
| Constipation | 20.8% | 0% | 17.9% | 0% |

Sekulic A, et al. *BMC Cancer*. 2017;17:332.

# STEVIE: Open-Label Study of Vismodegib in Advanced BCC




- Locally advanced BCC not eligible for surgery

Interim analysis preplanned to occur after 500 patients achieved 1 y of follow-up

N= 499 patients (median exposure 36.4wks)

- 400 (80%) discontinued treatment
  - 36% due to AE
  - 14% due to progressive disease
  - 10% due to patient request
- Serious AE in 22%
- AE causing death in 4.2%

Basset-Seguin N, et al. *Lancet Oncol*. 2015;16(6):729-736.

# STEVIE: Primary Analysis – Efficacy* at median 8.6 months

| Outcome | mBCC (n=84) | laBCC (n=1077) |
|---|---|---|
| Overall response, %<br>Complete response<br>Partial response<br>Stable disease<br>Progressive disease | 36.9%<br>4.8%<br>32.1%<br>46.4%<br>10.7% | 68.5%<br>33.4%<br>35.1%<br>25.1%<br>1.9% |
| Median duration of response | 13.9 mos | 23.0 mos |
| Median progression-free survival | 13.1 mos | 23.2 mos |

*Investigator assessed

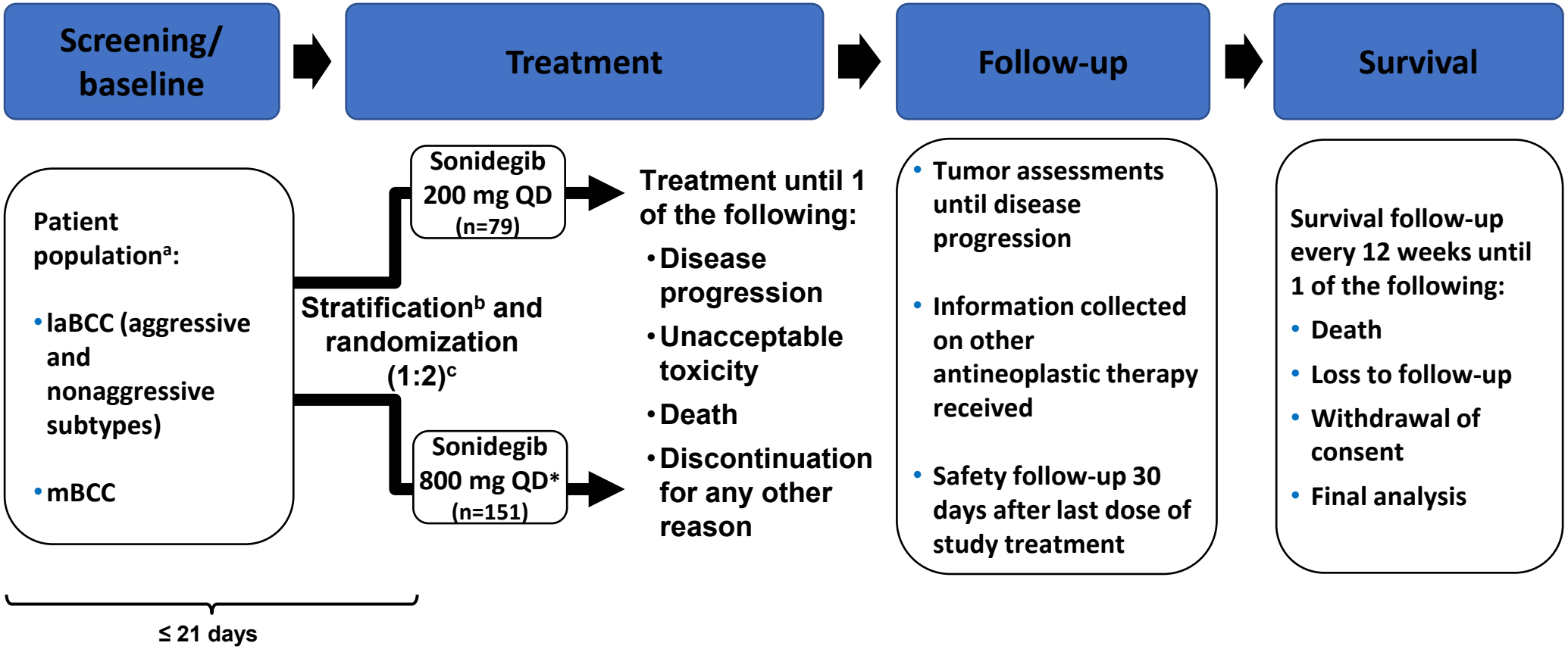
Basset-Seguin N, et al. *Eur J Cancer*. 2017;86:334-348.

# STEVIE: Primary Analysis – Safety at median 8.6 months

| Most common TEAE | |
|---|---|
| Any AE | 98% |
| Muscle spasm | 66% |
| Alopecia | 62% |
| Dysgeusia | 55% |
| Weight decreased | 41% |
| Decreased appetite | 25% |
| Asthenia | 24% |

Basset-Seguin N, et al. *Eur J Cancer*. 2017;86:334-348.

# BOLT: Phase 2 Study of Sonidegib in Advanced BCC




[a] Patients previously treated with sonidegib or other Hh pathway inhibitors were excluded. [b] Patients were stratified based on stage, disease histology for laBCC (nonaggressive vs aggressive), and geographic region. [c] Patients were randomized to receive sonidegib 200 mg QD (lowest dose level tested that showed antitumor activity) and 800 mg QD (highest well-tolerated, biologically active dose) based on the phase 1 study.[8]
*Dosing regimen not approved by US FDA

Migden M, et al. *Lancet Oncol*. 2015;16(6):716-728.

# BCC – Sonidegib BOLT trial

| Sonidegib dose | 200 mg | | 800 mg | |
|---|---|---|---|---|
| **Disease extent** | **Locally advanced** | **Metastatic** | **Locally advanced** | **Metastatic** |
| N pts | 66 | 13 | 128 | 23 |
| ORR | 47 % | 15 % | 35 % | 17 % |
| CR | 3 % | 0 | 0 | 0 |
| DCR | 89 % | 85 % | 86 % | 83 % |
| mDOR (mos) | 26.1 | 24.0 | 23.3 | ? |
| mPFS (mos) | 22.1 | 13.1 | 24.9 | 11.1 |

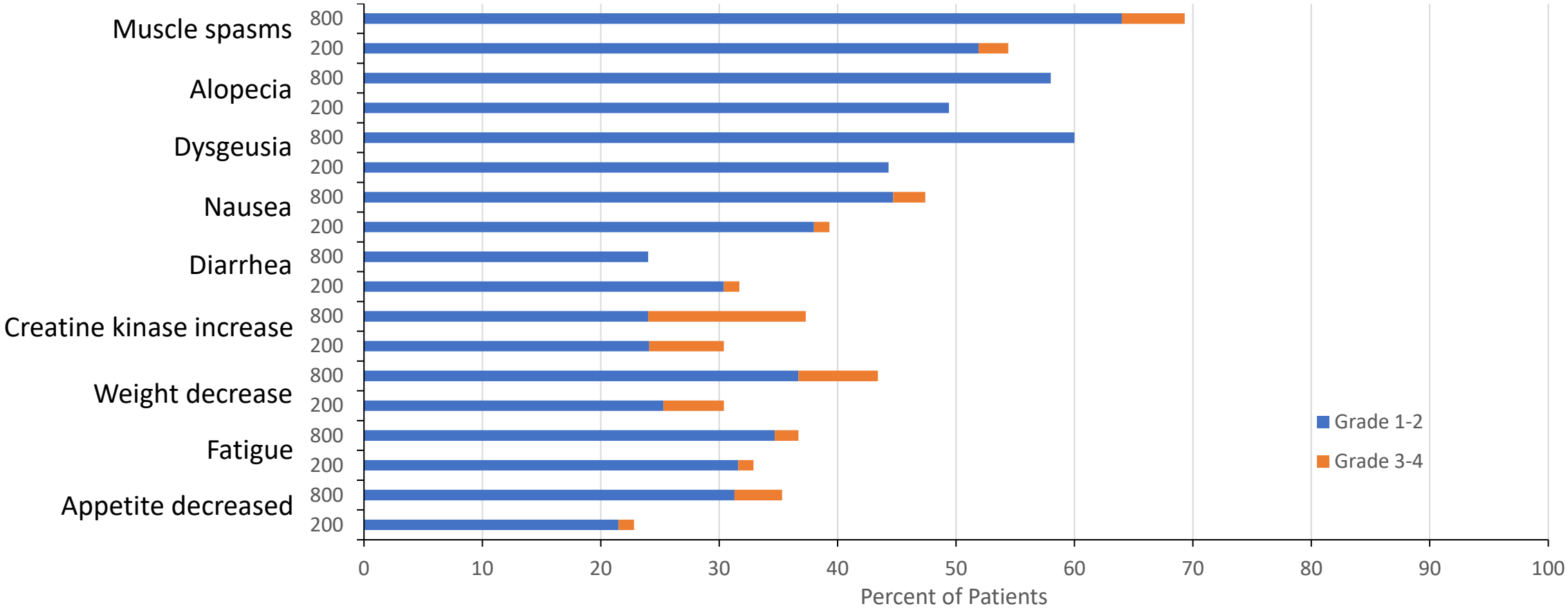
*Migden M, et al. Lancet Oncol. 2015;16(6):716-728*

# BCC – Sonidegib toxicities

| | 200 mg od | | 800 mg od | |
|---|---|---|---|---|
| **Type (%)** | **G1-2** | **G3-4** | **G1-2** | **G3-4** |
| **Muscle spasms** | 51.9 | 2.5 | 64.0 | 5.3 |
| **Alopecia** | 49.4 | | 58.0 | |
| **Dysgueusia** | 44.3 | | 60.0 | |
| **Nausea** | 38.0 | 1.3 | 44.7 | 2.7 |
| **Diarrhea** | 30.4 | 1.3 | 24.0 | |
| **↑ CPK (DLT)** | 24.1 | 8.3 | 24.0 | 13.3 |
| **Weight loss** | 25.3 | 5.1 | 36.7 | 6.7 |
| **Fatigue** | 31.6 | 1.3 | 34.7 | 2.0 |

*Dummer R, Br J Dermatol 2019*

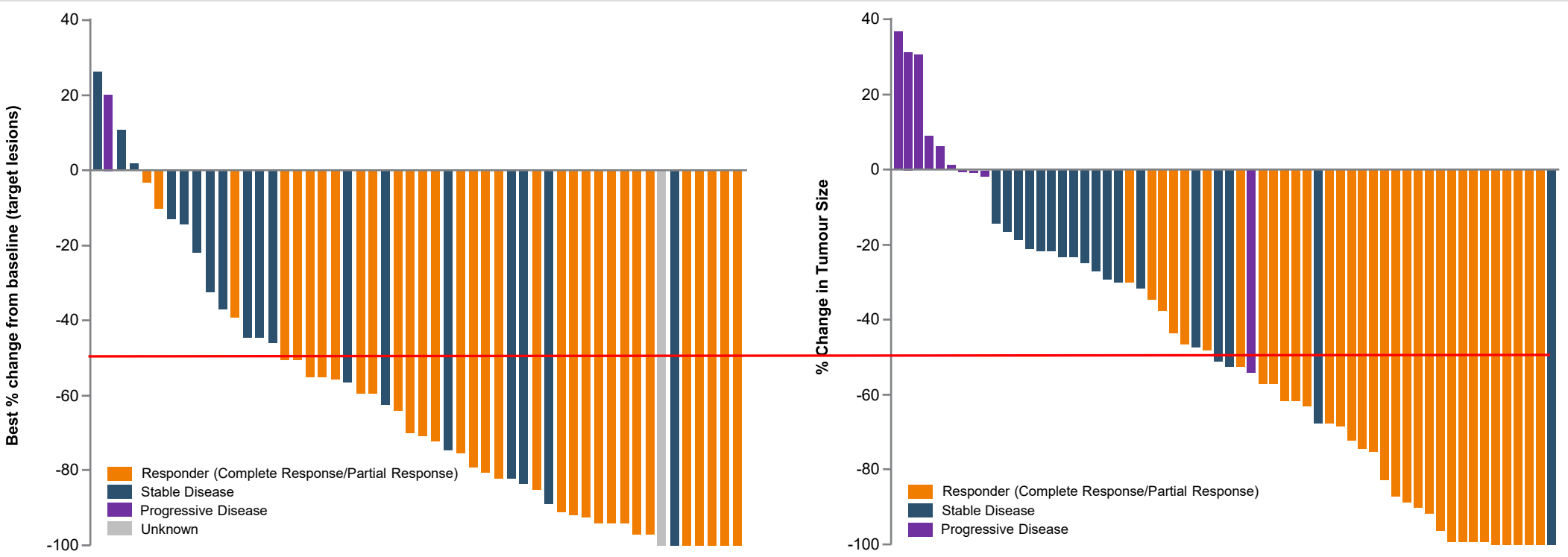
# BOLT: Safety over 42 months




Dummer R, et al. *Br J Dermatol*. 2020;182:1369-1378.

# HHIs ARE VERY EFFECTIVE BECAUSE THEY TARGET THERE WERE THE MUTATIONS ARE IN THE HEDGEHOG-SIGNALING PATHWAY

## Individual Shrinkage of tumor size in pivotal studies (central review)




Sonidegib 200 mg/d[1]
N=52

Vismodegib 150 mg/d[2]
N=60

**1.** SmPC Odomzo. **2.** SmPC Erivedge.

# Common AEs of HHIs

## Sonidegib (Incidence of ≥ 10%)[a]

- Muscle spasms
- Alopecia
- Dysgeusia
- Fatigue
- Nausea
- Musculoskeletal pain
- Diarrhea
- Decreased weight
- Decreased appetite
- Myalgia
- Abdominal pain
- Headache
- Pain
- Vomiting
- Pruritus

## Vismodegib (incidence of ≥ 10%)[b]

- Muscle spasms
- Alopecia
- Dysgeusia
- Weight loss
- Fatigue
- Nausea
- Diarrhea
- Decreased appetite
- Constipation
- Arthralgias
- Vomiting
- Ageusia

a. Sonidegib [PI]. Approved 2015. Revised May 2019; b. Vismodegib [PI]. Approved 2012. Revised July 2020.

# Methods to prevent discontinuation and prolonging HHI therapy

1. Every-other-day-dosing*
2. Treatment interruption (on-off-treatment)
3. Rechallenge with HHI after treatment discontinuation
4. Active treatments of side effects

* Alternate day dose in label treatment for sonidegib

# 1. Dose-reduction *(every-other-day-dosing)**

Retrospective case series of 20 laBCC patients

- 12 (60%) patients were considered with CR, 6 (30%) with PR, 2 (10%) with SD. None presented PD.
- Patients receiving alternate day dose (9/20) showed comparable clinical responses, with milder AEs compared with patients receiving daily dosing regimen
  - In the dose adjustment group, 66.7% (6/9) patients and 33.3% (3/9) presented CR and PR, respectively.
  - All of the 9 patients experienced mild (grade 1-2) AEs

Table 1. Characteristics of the 9 patients treated with dose adjustment

| Patient/ (sex; age) | Localization | Dose reduction scheme | Response at treatment end | Adverse effects | Degree of adverse effects | Observation period (months) |
|---|---|---|---|---|---|---|
| 1/ M; 80y | left leg | 16 wk 1/1; 16 wk 1/2 | CR | dysgeusia, muscle spasms | 1-2 | 8 months |
| 2/ M; 67y | periauricular region | 12 wk 1/1; 16 wk 1/2 | CR | muscle spasms | 1-2 | 7 months |
| 3/ M; 68y | central face | 16 wk 1/1; 12 wk 1/2 | PR | fatigue, muscle spasms, dysgeusia | 1-2 | 7 months |
| 4/ M; 96y | central face | 20 wk 1/1; 8 wk 1/2 | CR | muscle spasms, fatigue, alopecia | 1-2 | 7 months |
| 5/ M; 84y | ocular region | 24 wk 1/1; 8 wk 1/2 | PR | diarrhea, dysgeusia, muscle spasms | 1-2 | 8 months |
| 6/ M; 96y | multiple BCCs central face | 12 wk 1/1; 12 wk 1/2 | CR | dysgeusia | 1 | 6 months |
| 7/ F; 82y | Nose | 16 wk 1/1; 16 wk 1/2 | CR | muscle spasms,dysgeusia | 1-2 | 8 months |
| 8/ M; 82y | multiple BCCs central face | 12 wk 1/1; 16 wk 1/2 | PR | muscle spasms, fatigue, alopecia | 1-2 | 7 months |
| 9/ M; 85y | Forehead | 16 wk 1/1; 12 wk 1/2 | CR | muscle spasms, dysgeusia | 1-2 | 7 months |

wk: week of treatment; 1/1 once daily; ½ once every second day

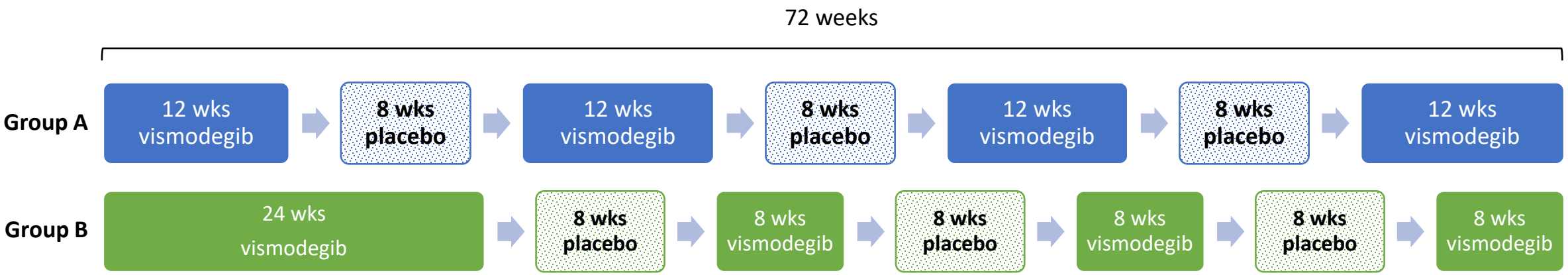
** Alternate day dose in label treatment for sonidegib*

*Villani A et al. J Am Acad Dermatol. 2020 Dec 7;S0190-9622(20)33150-9..*

# 2. Intermittent dosing/therapy

## MIKIE: intermittent dosing regimens with Vismodegib

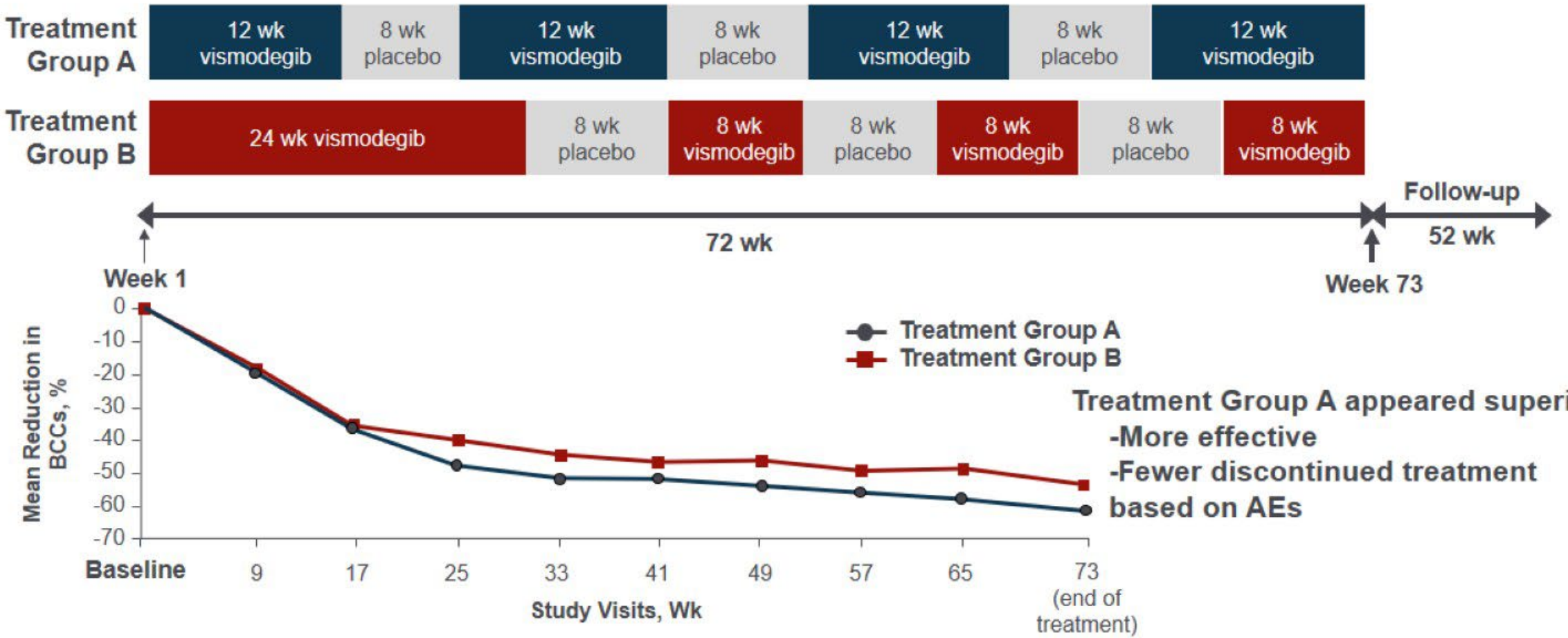
- Goal: Assess safety and efficacy of long-term intermittent dosing of vismodegib in patients with multiple basal cell carcinomas
  - ≥1 histologically confirmed and ≥6 clinically evident
- All patients received vismodegib 150 mg/d
- Primary endpoint: % reduction in number of clinically-evident BCCs at wk 73




Dreno B, et al. *Lancet Oncol*. 2017;18(3):404-412.

# Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial

*Brigitte Dréno, Rainer Kunstfeld, Axel Hauschild, Scott Fosko, David Zloty, Bruno Labeille, Jean-Jacques Grob, Susana Puig, Frank Gilberg, Daniel Bergström, Damian R Page, Gary Rogers, Dirk Schadendorf*




Dréno B, et al. Lancet Oncol. 2017;18:404-412.

# MIKIE: intermittent dosing regimens with Vismodegib – Safety

| Safety Outcome | Group A | Group B |
|---|---|---|
| TEAE | 99% | 97% |
| Grade ≥3 treatment-related muscle spasms | 4% | 11% |
| Grade ≥3 treatment-related increased creatine kinase | 1% | 4% |
| Grade ≥3 treatment-related hypophosphatemia | 0% | 3% |
| Serious TEAE | 19% | 17% |
| Discontinued treatment due to AE | 20% | 27% |

Conclusion:
Both intermittent dosing regimens provided good efficacy with similar/better safety profile than in STEVIE

Dreno B, et al. *Lancet Oncol*. 2017;18(3):404-412.

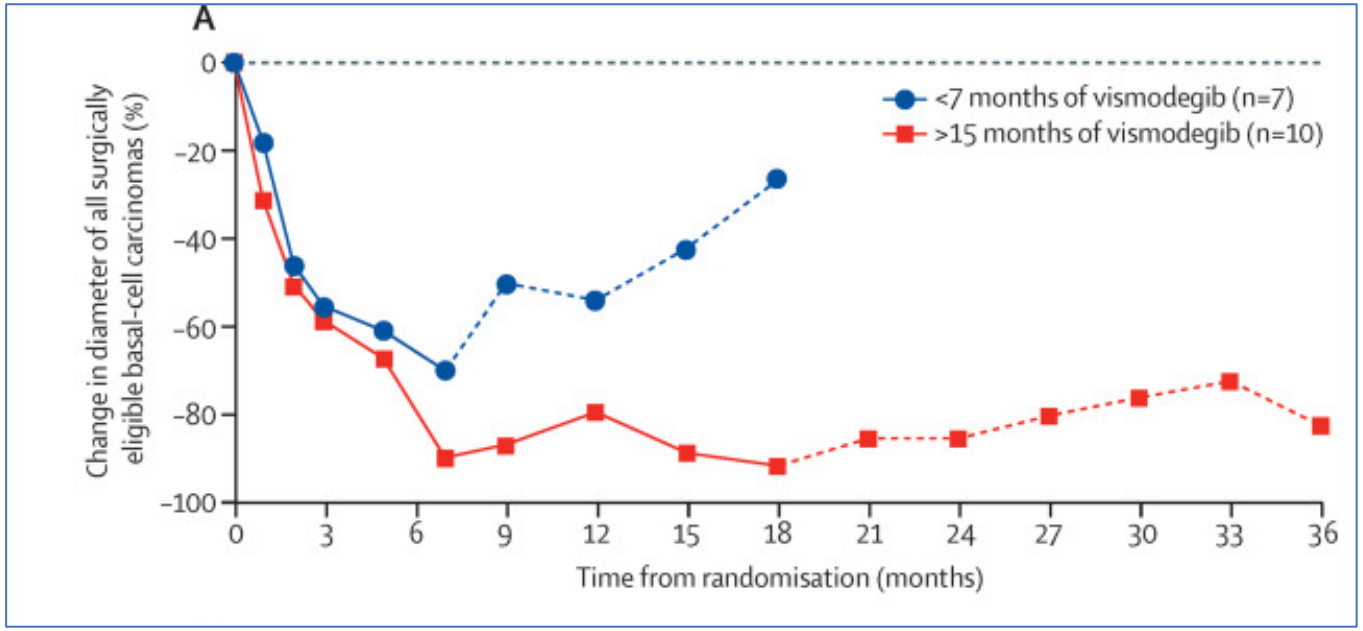
# After longer periods of treatment, longer duration of benefit after stopping the HHI

THE LANCET
Oncology
Volume 17, Issue 12, December 2016, Pages 1720-1731

Articles

## Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

Jean Y Tang MD [a, b, †], Mina S Ally MD [a, b, †], Anita M Chanana BS [a], Julian M Mackay-Wiggan MD [c], Michelle Aszterbaum MD [d], Joselyn A Lindgren MS [a], Grace Ulerio BA [c], Melika R Rezaee BA [a], Ginny Gildengorin PhD [a], Jackleen Marji MD [c], Charlotte Clark MD [c], Prof David R Bickers MD [c], Dr Ervin H Epstein Jr MD [a]



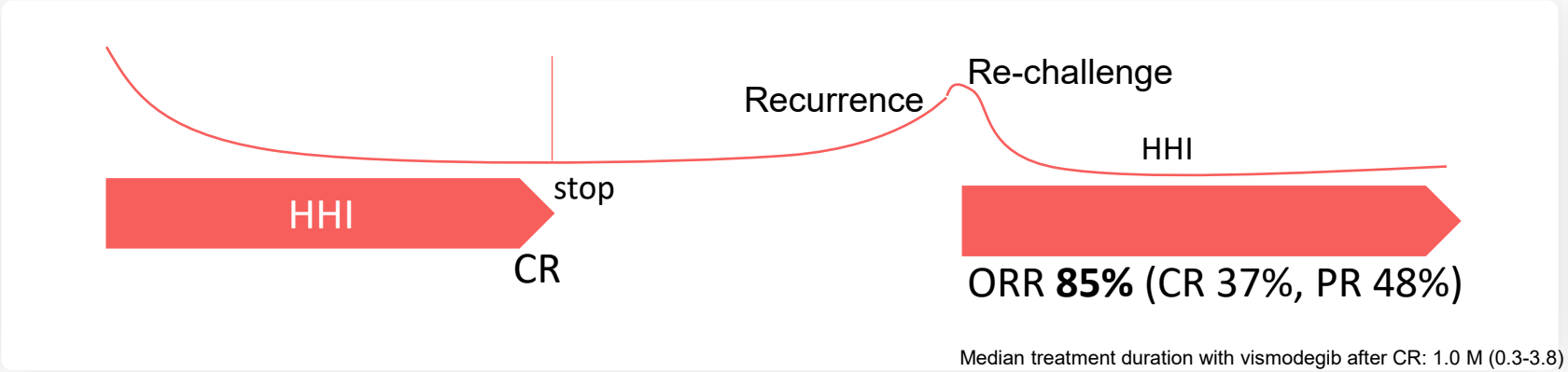

In patients who took vismodegib continuously for at least 15 months (n=10), the anti-basal-cell carcinoma effect was maintained (ie, there was no return to baseline tumour burden) for 18 months after discontinuing the drug

# 3. Rechallenge with HHI after treatment discontinuation (= interruption of treatment)

**Follow-Up of Patients With Complete Remission of Locally Advanced Basal Cell Carcinoma After Vismodegib Discontinuation: A Multicenter French Study of 116 Patients**

Florian Herms, MD[1,2]; Jerome Lambert, MD[1,2]; Jean-Jacques Grob, MD, PhD[3]; Luc Haudebourg, MD[1,2]; Martine Bagot, MD, PhD[1,2]; Sophie Dalac, MD[4]; Caroline Dutriaux, MD[5,6]; Bernard Guillot, MD, PhD[7]; Geraldine Jeudy, MD[4]; Christine Mateus, MD[8]; Sandrine Monestier, MD[3]; Laurent Mortier, MD, PhD[9]; Nicolas Poulalhon, MD[10]; Sorilla Prey, MD, PhD[5,6]; Caroline Robert, MD, PhD[8]; Pierre Vabres, MD, PhD[4]; Celeste Lebbe, MD, PhD[1,2]; Nicolas Meyer, MD, PhD[11]; and Nicole Basset-Seguin, MD, PhD[1,2]

- 54 patients who experienced relapse during follow-up, 27 (50%) were retreated with vismodegib.
- Among them, 23 (85%) had an objective response again.
- 24 patients (42%) were eligible for surgery




Discontinuation = temporary interruption of treatment

mRFS 18.4 months after discontinuation for the whole group

*Herms F et al. J Clin Oncol. 2019 Dec; 37(34):3275-3282*

# Sonidegib in advanced BCC resistant to Vismodegib

- 9 patients with aBCC previously resistant to vismodegib
  - 3 primary resistance
  - 6 secondary resistance
- treated with sonidegib 800 mg QD*
- Median treatment: 6 wks
- 5 progressive disease, 3 stable disease, 1 not evaluable (due to Gr3 AE)
- SMO mutations with previously reported functional resistance in vitro were identified in 5/8 available baseline tumor samples

Conclusion:
Sonidegib after Vismodegib failure is not likely to improve response

*Dosing regimen not approved by US FDA

Danial C, et al. *Clin Cancer Res*. 2016;22(6):1325-1329.

# 4. Active treatments of side effects

- **Muscle spasms**
  - Reduction in frequency of muscle cramps and number of affected body locations by using L-Carnitine.[1]
  - Reduction in frequency of muscle cramps by using Amlodipine.[2]

- **Dysgeusia**
  - Improvement of gustatory function and reduction of the severity of dysgeusia by using zinc gluconate.[3]

- **Weight loss**
  - Reduction of the probability of experiencing a weight loss >5% by nutritional management.[4]
    - Counseling on dietary meal enrichment
    - Weight loss >5%. Oral nutritional supplements (high protein and high-calorie supplements between meals)
    - Weight loss >10%. Enteral nutrition support

**1.** Cannon JGD *et al. JEADV* 2018;32(7):e298-e299. **2.** Ally MS *et al. JAMA Dermatol*. 2015;151(10):1132-1134. **3.** Heckmann SM *et al. J Dent Res*. 2005;84(1): 35-8. **4.** Le Moigne M *et al. Support Care Cancer* 2016;24:1689-1695.

# 4. Active treatments of side effects

DERMATOLOGIC THERAPY

LETTER | Open Access

Sonidegib-induced muscle spasms in the treatment of basal cell carcinoma: Strategies to adopt

Alessia Villani, Gabriella Fabbrocini, Massimiliano Scalvenzi

First published: 21 April 2022 | https://doi.org/10.1111/dth.15531

Several strategies were adopted during treatment to manage muscle spasms:

- 21 out of 49 patients (43%) were prescribed magnesium supplementation
- 16 patients (33%) received the alternate dosing regimen (200 mg sonidegib every other day)
- 12 patients were prescribed gabapentin (100 mg or 200 mg daily according to the grade of severity)

Cancers (Basel). 2022 May 19;14(10):2496. doi: 10.3390/cancers14102496.

Eight Years of Real-Life Experience with Smoothened Inhibitors in a Swiss Tertiary Skin Referral Center

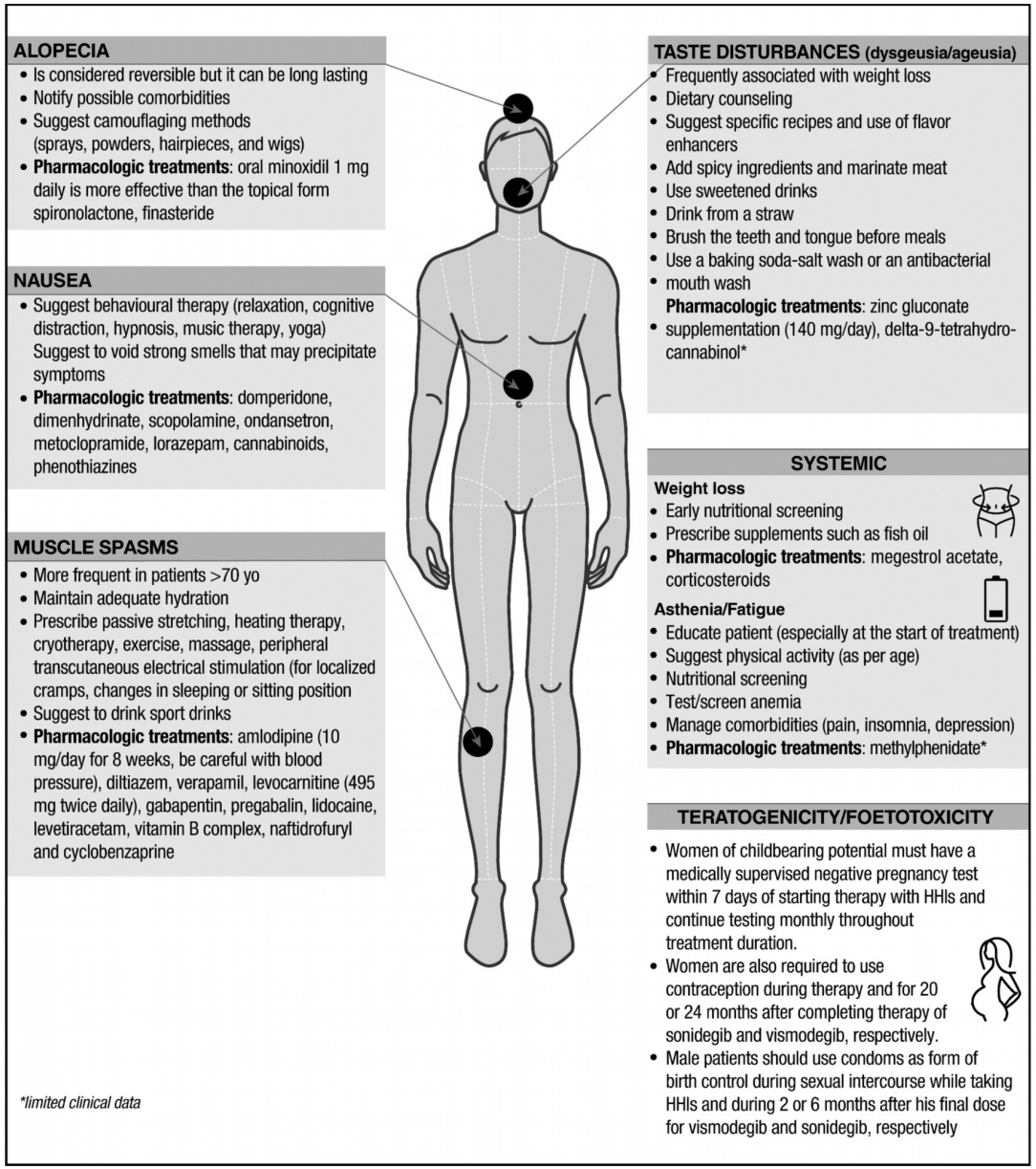
Lara E Grossmann [1], Egle Ramelyte [1], Mirjam C Nägeli [1], Reinhard Dummer [1]

Affiliations + expand

PMID: 35626100 PMCID: PMC9139771 DOI: 10.3390/cancers14102496

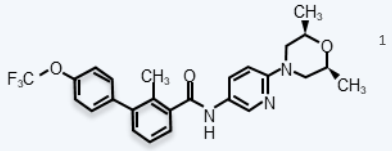
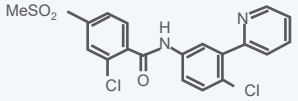
- Muscle spasms could be subjectively reduced with quinine sulfate (200–250 mg twice a day). Some patients also benefited from peroral magnesium or muscle relaxants such as tizanidine.
- With a 2 months on/2 months off intermittent treatment we were able to avoid total alopecia, which was an important prerequisite for starting therapy, especially for women.

# Management of adverse events




Bossi et al. Long-term strategies for management of advanced basal cell carcinoma with hedgehog inhibitors. Crit Rev Oncol Hematol. 2023 Jul 11;189:104066

# Hedgehog Pathway Inhibitors in Advanced BCC: Two Different Molecules

| | | Sonidegib | Vismodegib |
|---|---|---|---|
| | **Molecular structure** |  [1] |  [3] |
| | **Dosing** | 200 mg orally once daily (empty stomach)*[2] | 150 mg orally once daily [4] |
| | **Approved dose modifications** | Alternate day dosing [2] | None |
| At steady state | **Half-life (T ½)** | ~28 days [2] | ~4 days [4] |
| At steady state | **Plasma peak concentration (Cmax)** | 1030 ng/ml [1] | 11449 ng/ml [5] |
| At steady state | **Lowest plasma concentration (Cmin)** | 890 ng/ml [1] | 10493 ng/ml [5] |
| At steady state | **Skin concentration** | 6-fold higher in skin than in plasma [2] | Not measured |
| At steady state | **Apparent volume of distribution (Vss/F)** | 9170 litres [2] | 16.4-26.6 litres [4] |

* ≥2 hours after a meal and ≥1 hour before the following meal

1. Odomzo® US prescribing information 2019. 2. Odomzo® summary of product characteristics 2019. 3. Erivedge® US prescribing information 2019. 4. Erivedge® summary of product characteristics 2019. 5. Sharma MR, Clin Cancer Res. 2013 Jun 1;19(11):3059-67.

# Sonidegib and Vismodegib
# Different pharmacocinetic profiles

Retrospective single-center analysis N=33: vismodegib n=30, sonidegib n=12 (3 as first-line and 9 after vismodegib)

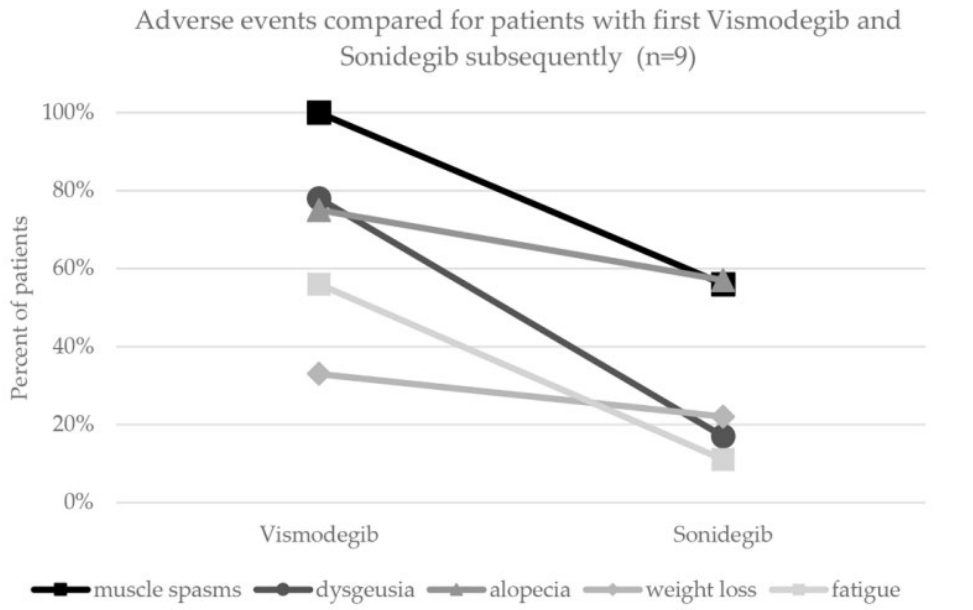



**Figure 2.** Comparison of adverse events for vismodegib versus sonidegib in 9 patients with both treatments subsequently.

Vismodegib has a volume of distribution of 16–27 liters, suggesting that it is largely confined to the plasma and has limited tissue penetration.

In contrast, Sonidegib seems to be more lipophilic than Vismodegib and has a volume of distribution of >9.000 liters, indicating extensive distribution in the tissues.

Consequently, the concentration of Sonidegib is six-times higher in skin than in plasma.

***"In theory, these evidences suggest that Sonidegib is more extensively distributed in the skin compared with Vismodegib, which may explain potential differences in toxicity between them."***

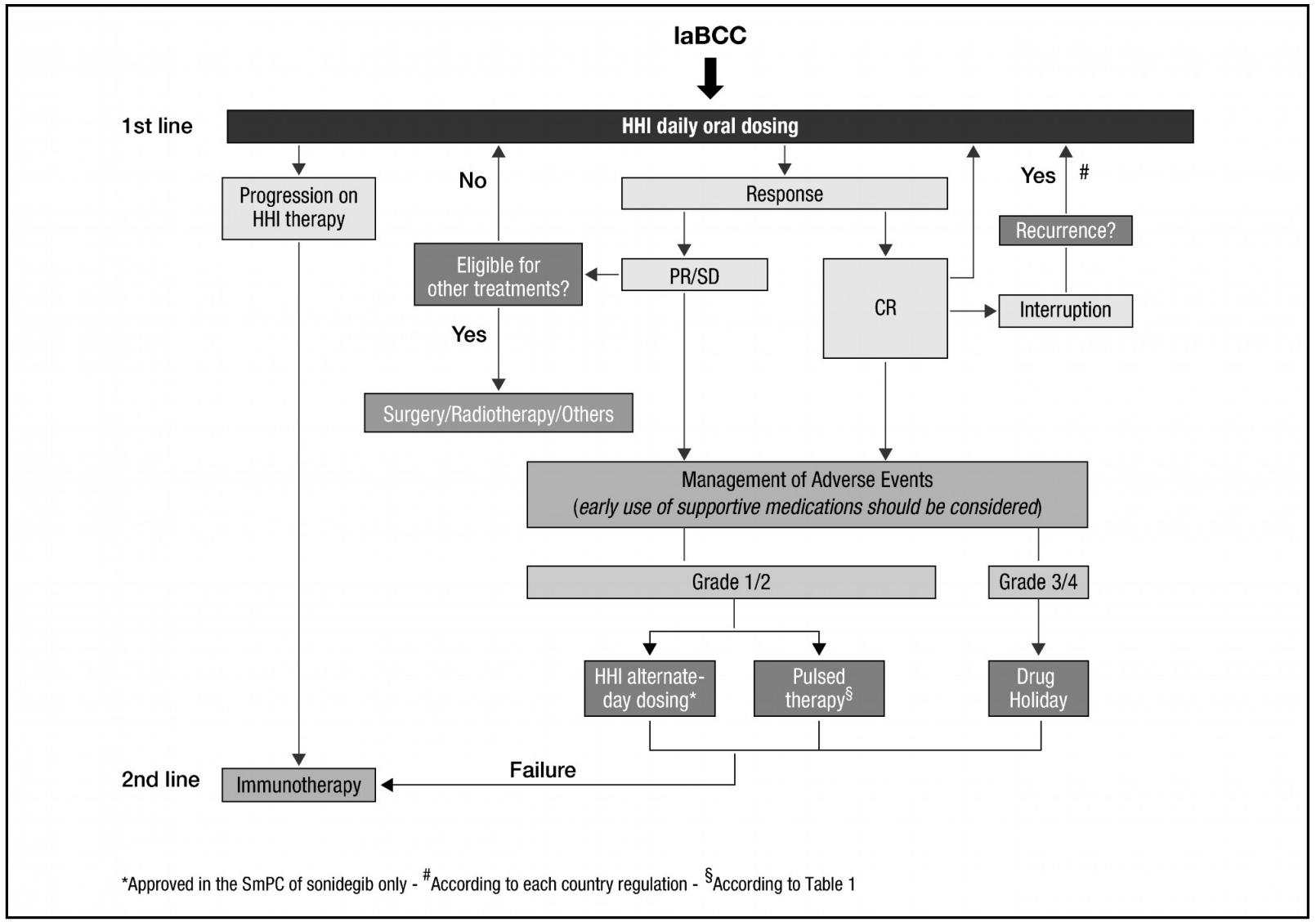
*"Our data seem to suggest that **sonidegib has less adverse events compared to vismodegib**, which was especially observed in patients who were treated with both sonidegib and vismodegib sequentially."*

*"Pharmacokinetic profiles of **sonidegib have shown better tissue penetration and thus higher concentration of sonidegib in skin compared to vismodegib**".*

*Grossmann L, Dummer R:Cancers (Basel). 2022 May 19;14(10):2496.*

*Dummer R et al. J Eur Acad Dermatol Venereol. 2020 Jan 28*

# THERAPEUTIC ALGORITHM FOR ADVANCED BCC: 1ST AND 2ND TREATMENT OPTIONS




*Bossi et al. Long-term strategies for management of advanced basal cell carcinoma with hedgehog inhibitors. Crit Rev Oncol Hematol. 2023 Jul 11;189:104066*

# Skin cancers - Mutation rates

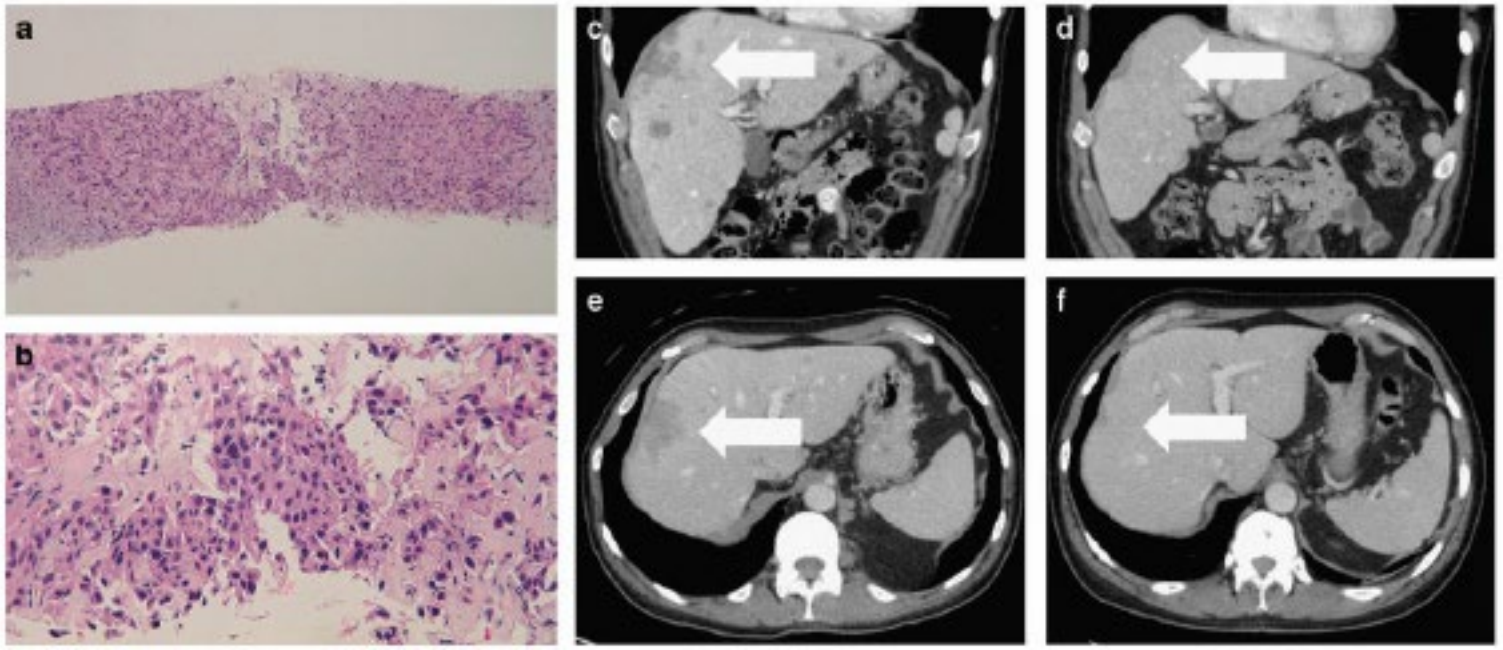
| Disease type | Specimen count | median mutation nb/MB | % > 20 |
|---|---|---|---|
| Basal cell carcinoma (BCC) | 92 | 47.3 | 70.7 |
| Squamous cell carcinoma (SCC) | 266 | 45.2 | 67.3 |
| Merkel cell carcinoma (MCC) | 206 | 4.3 | 37.9 |
| Malignant melanoma (MM) | 879 | 14.4 | 39.7 |

*Chalmeers, Genome Medicine 2017; 9: 34*

# Immunotherapy in resistant BCC

BCC resistant to hedgehog inhibitor treated with PD-1 antibody

Baseline 4 months




Ikeda S, et al. *NPJ Genom Med.* 2016;1:16037.

# Phase 2 Trial Led to Cemiplimab Approval in BCC

Open-label, multicenter, single-arm, phase 2 trial[a,b]

**Patients with**
**mBCC (group 1) or**
**laBCC (group 2)**
Age ≥ 18 y
ECOG PS 0 or 1

**Cemiplimab**
350 mg IV every
3 wk

*Patients enrolled were not candidates for further HHI therapy due to disease progression on or intolerance to prior HHI therapy*

**Endpoints**

**Primary:** ORR (central review)

**Secondary:** ORR (investigator review), DoR, PFS, OS, TTR, disease control, durable disease control, safety

## Clinical responses observed:

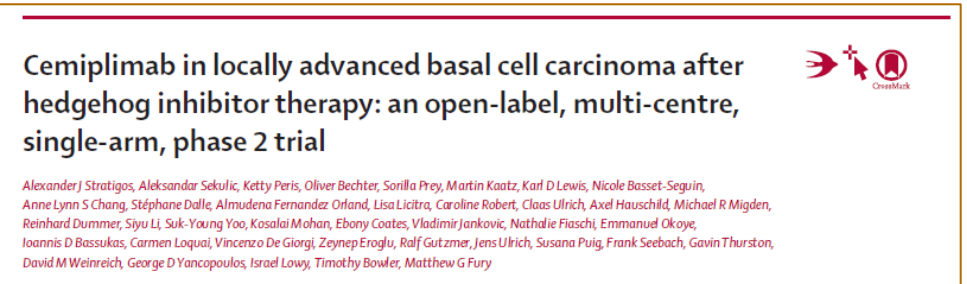
- **laBCC** ORR: 31% (95% CI: 21%, 42%)[a]
- **mBCC** ORR: 21.4% (95% CI: 8.3%, 41.0%)[b]

Median DoR was not reached in either group[a,b]

a. Stratigos AJ, et al. Lancet Oncol. 2021;22:848-857; b. Lewis KD, et al. J Immunother Cancer. 2020;8(Suppl 3):428.

# Phase 2 study of Cemiplimab for locally advanced BCC

- Median baseline tumor mutational burden
  - 58.2 mutations/Mb among responders
  - 23.5 mutations/Mb among nonresponders
- Among 84 patients:
  - ORR 31%
  - 5 CR, 21 PR
  - 85% of responses ongoing at 12 mos
- Not reached
  - Median DOR
  - Median PFS
  - OS
- Most common AEs
  - Fatigue (30%), diarrhea (24%), pruritus (21%)
- 17% discontinued treatment due to AEs



Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial

Alexander J Stratigos, Aleksandar Sekulic, Ketty Peris, Oliver Bechter, Sorilla Prey, Martin Kaatz, Karl D Lewis, Nicole Basset-Seguin, Anne Lynn S Chang, Stéphane Dalle, Almudena Fernandez Orland, Lisa Licitra, Caroline Robert, Claas Ulrich, Axel Hauschild, Michael R Migden, Reinhard Dummer, Siyu Li, Suk-Young Yoo, Kosalai Mohan, Ebony Coates, Vladimir Jankovic, Nathalie Fiaschi, Emmanuel Okoye, Ioannis D Bassukas, Carmen Loquai, Vincenzo De Giorgi, Zeynep Eroglu, Ralf Gutzmer, Jens Ulrich, Susana Puig, Frank Seebach, Gavin Thurston, David M Weinreich, George D Yancopoulos, Israel Lowy, Timothy Bowler, Matthew G Fury

Stratigos AJ, et al. *Ann Oncol*. 2020;31(suppl 4):S1142-S1215. Abstract LBA47.

# CEMIPLIMAB tolerability

- 99% of patients had AEs[1]
- 37% had serious AEs[1]
- 18% discontinued due to AE[1]

- Excessive immune activation may lead to multi- (any) organ immune-related AEs
  - 25% (21/84) patients had immune-related AEs, of which 38% (8/84) had grade 3 (no grade 4 or grade 5 immune-related AEs)[2].
  - Can be fatal and can occur also after discontinuation[3]
    - Patients should be closely monitored with clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment[3]

[1]Stratigos et al. Presented at EADO 2022. [2]Stratigos et al. Lancet Oncol. 202122(6):848-857

# PD-1-STUDY: CEMIPLIMAB in 2nd line LABCC

No clinically meaningful associations between objective response and TMB

Exploratory correlative biomarker analyses did not support the use of PD-L1 or TMB to predict response to or clinical benefit of cemiplimab in laBCC.

**Figure S6. Clinical activity of cemiplimab and TMB**

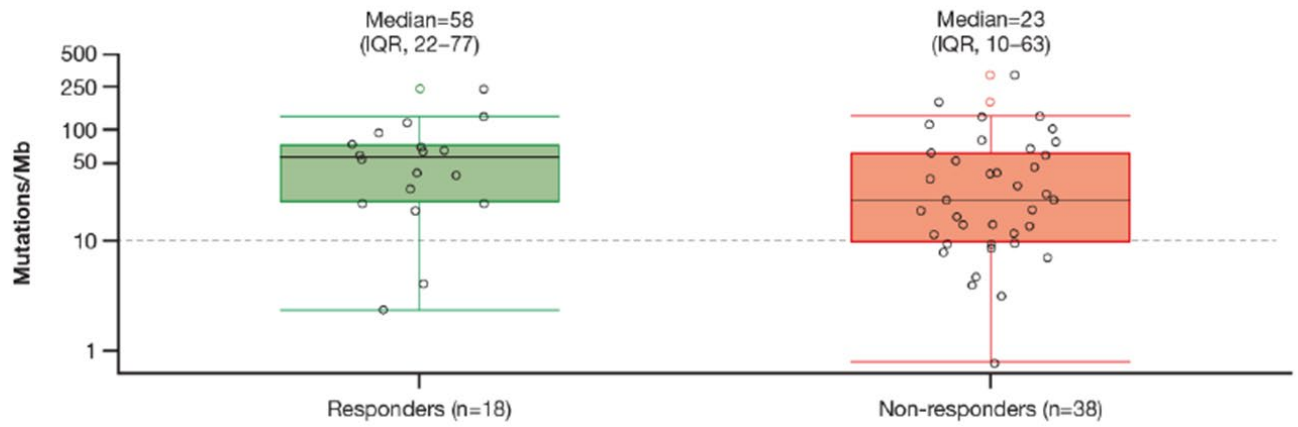



Figure shows TMB for responders (complete or partial response) versus non-responders (stable disease, progressive disease, or not evaluable) as per independent central review. Black lines in each box denote median; lower and upper boundaries of box denote lower quartile and upper quartile (IQR), respectively; and upper and lower whiskers indicate maximum (Q3 + 1.5*IQR) and minimum (Q1 – 1.5*IQR) values, respectively. Individual patients are indicated by open black circles. Open black circles beyond the whiskers are outliers. Open green circles and open red circles are duplicates of the outliers (the plots are overlap of boxplots and scatter plots). The dashed line marks the cut-off for high TMB of 10 mut/MB and above.

Q=quartile; TMB=tumour mutational burden.

Stratigos A *et al. Lancet Oncol* 2021; doi.org/10.1016/S1470-2045(21)00126-1

# Pembrolizumab KEYNOTE-158

- Prospectively planned retrospective analysis of 10 cohorts of patients with various previously treated unresectable or metastatic solid tumors with high TMB

| | TMB ≥ 10 mut/Mb (n = 102) | TMB ≥ 13 mut/Mb (n = 70) |
|---|---|---|
| **ORR, %** | 29 | 37 |
| **Probability** | | |
| **% with duration ≥ 12 mo** | 57 | 58 |

Marabelle A, et al. Lancet Oncol. 2020;21:1353-1365.

# Pembrolizumab ± Vismodegib for Advanced BCC

| | All Participants (N = 16) | Pembrolizumab* + Vismodegib (n = 7) | Pembrolizumab* (n = 9) |
|---|---|---|---|
| ORR, % | 38 | 29 | 44 |
| **Probability, %** | | | |
| 1-y PFS | 70 | 83 | 62 |
| 1-y OS | 94 | 100 | 89 |

- Combination did not appear more toxic
- No life-threatening AEs or deaths during study
- 3 grade 3 AEs occurred out of 98 AEs from 16 participants (1 case of TRAE hyponatremia)
- 23 immune-related AEs (grade 1/2 dermatitis and fatigue most common)

*Pembrolizumab is not currently FDA approved for BCC.

Chang AL, et al. J Am Acad Dermatol. 2019:80:564-566.

# Phase 2 Study of NIVO ± RELA or IPI for Patients With Advanced Treatment-Naive or -Refractory BCC

**Patient characteristics:**

- 19 evaluable patients
- Median (range) age = 68 (53-91) y
- Females = 7 (37%)
- 16 locally advanced, 3 mBCC
- Prior therapy for NIVO cohort: 9 treatment naive, 4 received prior HHI

- Adults with histologically confirmed BCC that is metastatic or considered by the investigator to be unresectable
- ECOG PS 0 or 1
- No concurrent systemic immune suppression therapy

**NIVO**
Treatment-naive or HHI-refractory aBCC

›

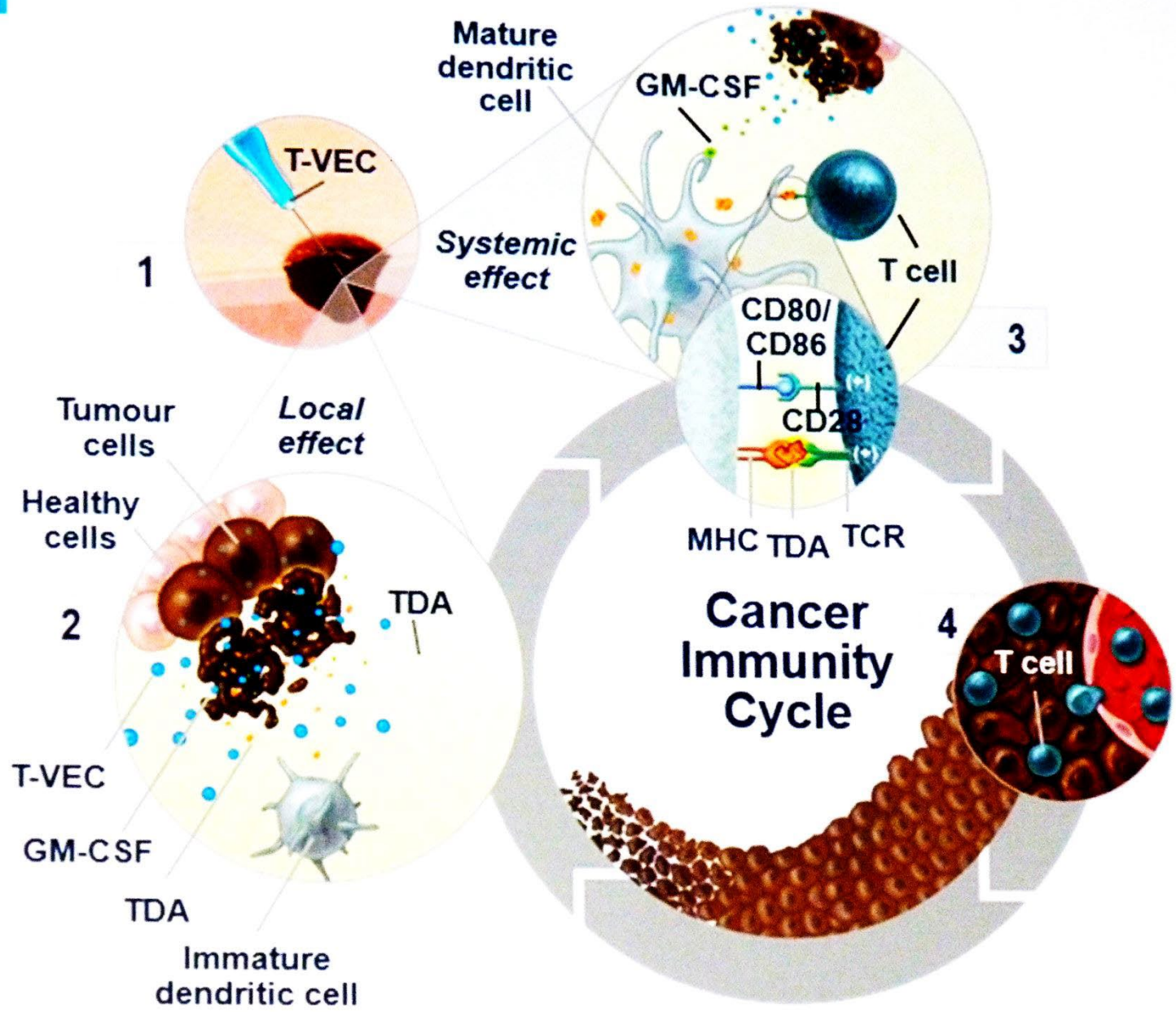
**NIVO + RELA**
aBCC refractory* to anti-PD-(L)1

›

**NIVO + IPI**
aBCC refractory* to NIVO + RELA

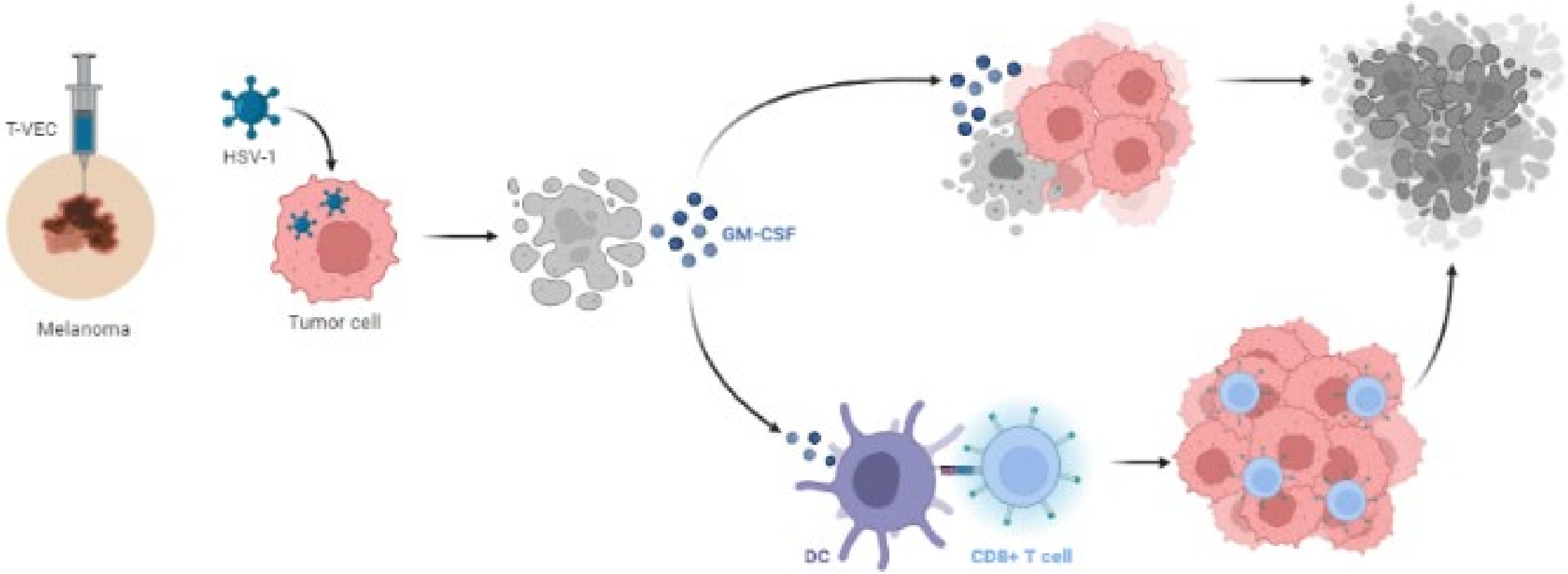
**Primary endpoint:**
ORR per RECIST 1.1

*Refractory: SD at 36 wk or PD during treatment or within 16 wk of treatment discontinuation.
aBCC, advanced basal cell carcinoma; IPI, ipilimumab; NIVO, nivolumab; RELA, relatlimab.
Schenk K, et al. Ann Oncol. 2022;33(suppl 1):820P.


Mature dendritic cell
GM-CSF
T-VEC
1
Systemic effect
T cell
CD80/ CD86
3
CD28
Tumour cells
Local effect
Healthy cells
MHC
TDA
TCR
2
TDA
Cancer Immunity Cycle
4
T cell
T-VEC
GM-CSF
TDA
Immature dendritic cell

# T-VEC Mode of Action

1. Injection of engineered T-VEC.
2. Selective uptake of T-VEC virus (HSV-1) by tumor cells.
3. Apoptotic tumour cells release GM-CSF.
4a. **Local effect:** Released GM-CSF causes apoptosis of surrounding tumor cells.
5. Tumor cell death and apoptosis.




4b. **Systemic effect**: GM-CSF activates dendritic cells (DC), activating CD8+ T cells.

# NIVO ± RELA or IPI for Patients With Advanced Treatment-Naive or -Refractory BCC: *Efficacy and Safety*

## Best Overall Response of Patients With aBCC to NIVO and NIVO + RELA

| Best Response per RECIST 1.1, No. (%) | NIVO | | NIVO + RELA (n = 5) |
|---|---|---|---|
| | All Evaluable (n = 13) | Treatment-Naive (n = 9) | |
| CR/PR | 6 (46) | 5 (56) | 1 (20)* |
| SD ≥ 9 mo | 3 (23) | 1 (11) | 3 (60) |
| PD/SD < 9 mo | 4 (31) | 3 (33) | 1 (20) |

- ORR among 9 patients with aBCC who received first-line NIVO was 56%
- Toxicities associated with each regimen were consistent with previous experience

*Patient who experienced PR to NIVO + RELA previously experienced SD on NIVO lasting > 48 wk.

Schenk K, et al. Ann Oncol. 2022;33(suppl 1):820P.

# NeoBCC

## *Phase 2 Trial of Neoadjuvant T-VEC in Difficult-to-Resect Primary BCC*

- Histologically confirmed BCC
- Difficult-to-resect* BCC

N = 18


**Primary objective:** to evaluate number of patients with BCC that becomes resectable after 6 cycles of T-VEC with primary wound closure without requiring skin flaps or skin grafts

| Baseline Patient Characteristics | Patients (N = 18) |
|---|---|
| Female, No. (%) | 11 (61.0) |
| Male, No. (%) | 7 (39.0) |
| Age, median (range), y | 74.50 (49-92) |
| Height, median (range), m | 1.68 (1.50-1.85) |
| Histopathological BCC subtype, No. (%) | |
| Nodular | 9 (50.0) |
| Infiltrative | 9 (50.0) |
| BCC localization, No. (%) | |
| Head and neck | 13 (72.0) |
| Lower extremities | 2 (11.0) |
| Trunk | 3 (17.0) |
| Largest tumor diameter, median (range), cm | 1.42 (0.70-13.70) |
| Serum HSV IgG, No. (%) | |
| Negative | 1 (6.0) |
| Positive | 17 (94.0) |

*Assessed by an expert panel to require either a skin flap or graft for wound closure. †Initial dose of 106 PFU/mL, 108 PFU/mL 3 wk later, remaining 4 doses of 108 PFU/mL given once every 2 wk (total treatment period: 13 wk).

HSV, herpes simplex virus; IgG, immunoglobulin G; PFU, plaque-forming unit; T-VEC, talimogene laherparepvec.

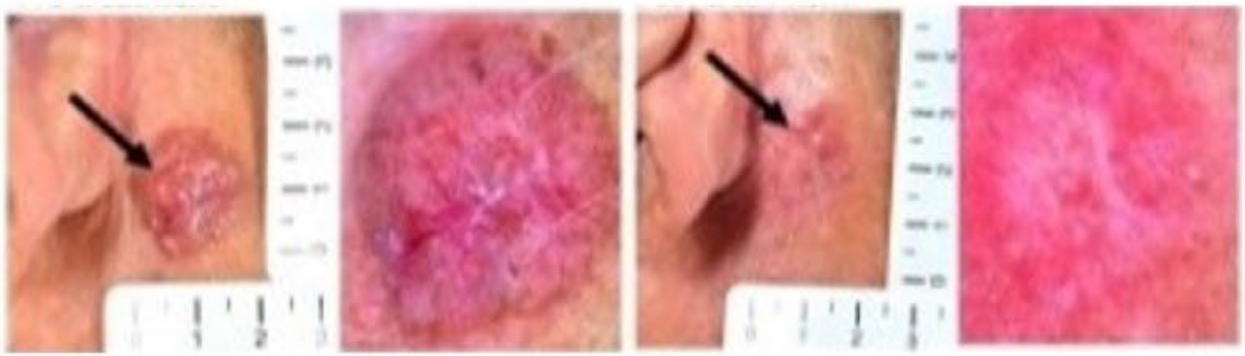
Ressler JM, et al. Ann Oncol. 2022;33(suppl 1):794P.

# NeoBCC
## *Response to Neoadjuvant T-VEC*

### Neoadjuvant T-VEC Showed High Activity in BCC

Pretreatment

Posttreatment



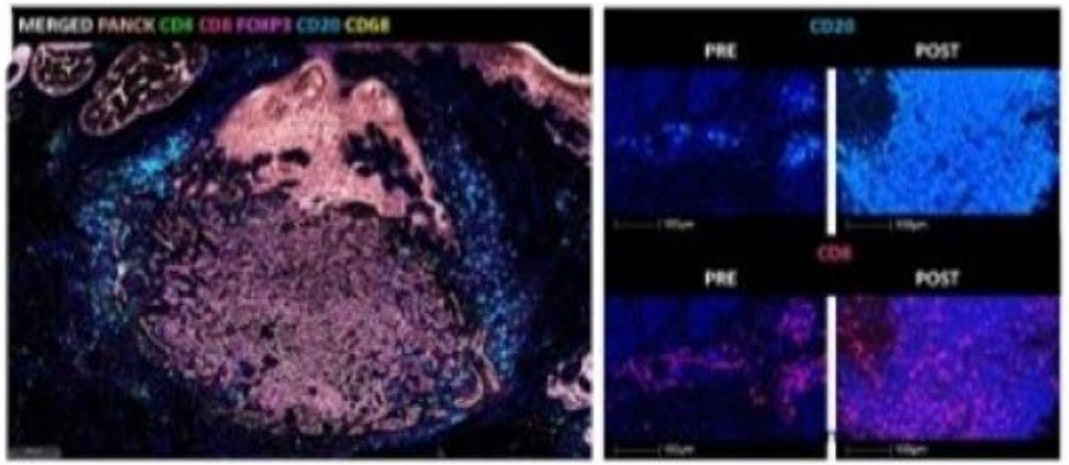
**Clinical Response**

| | |
|---|---|
| SD | 41.2% |
| PR | 23.5% |
| CR | 35.3% |

**Pathologic Response**

| | |
|---|---|
| Non-pCR | 64.71% |
| pCR | 35.29% |

### Significant Increase in CD8⁺ T Cells and CD20⁺ B Cells in Complete Responders Upon T-VEC Treatment



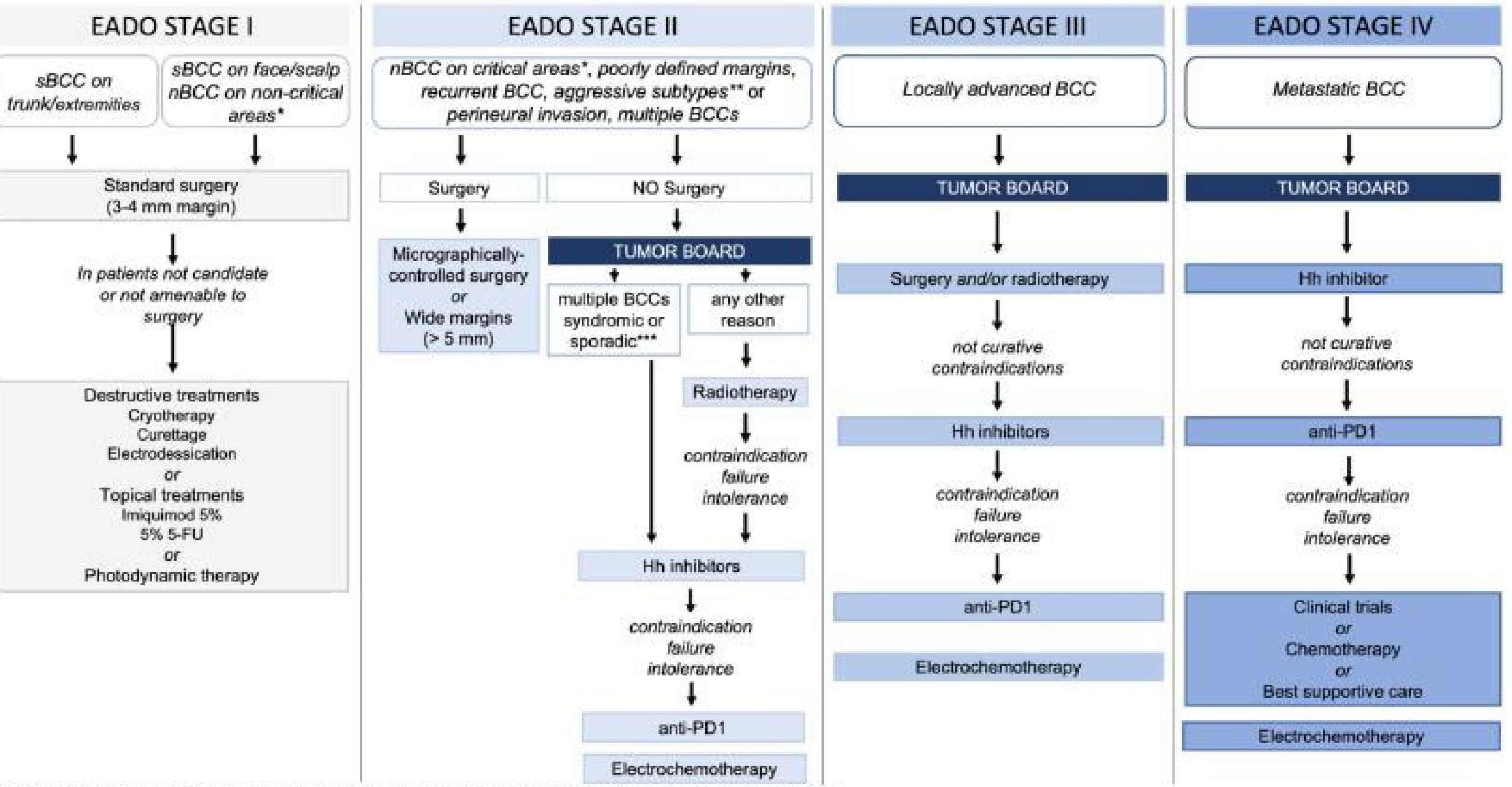

Ressler JM, et al. Ann Oncol. 2022;33(suppl 1):794P.

# Safety Profile of T-VEC

| AE | T-VEC Related, No. (%) | | | |
|---|---|---|---|---|
| | All Grades | Grade 1 | Grade 2 | Grade 3-4 |
| Injection-site reaction | 9 (21.95) | 5 (12.20) | 4 (9.76) | -- |
| Chills | 4 (9.76) | 3 (7.32) | 1 (2.44) | -- |
| Headache | 4 (9.76) | 3 (7.32) | 1 (2.44) | -- |
| Erythema | 1 (2.44) | -- | 1 (2.44) | -- |
| Swelling | 1 (2.44) | -- | 1 (2.44) | -- |
| Diarrhea | 1 (2.44) | -- | 1 (2.44) | -- |
| Nausea | 1 (2.44) | 1 (2.44) | -- | -- |

AE, adverse event.

Ressler JM, et al. Ann Oncol. 2022;33(suppl 1):794P.




critical areas: central face, eyelids, eyebrows, nose, lips, chin, ear, periauricular; **aggressive subtypes: micronodular, morpheaform, nfiltrative, metatypical (basosquamous carcinoma); ***in cases of multiple sporadic BCCs, radiotherapy might be used to treat one or ew large tumors

# CONCLUSION

- Focus on a **long-term** treatment strategy of laBCC ensuring patients **don't run out of options**

- Get the most out of the very effective therapy with **HHIs** (ORR: 47-60%, DCR 80-90%) with **proper side effect management:**
  - alternate day dose/ interruptions/ re-challenge/medical treatment side effects

- In case of **progression after discontinuation** of a HHI: **rechallenge** with a **HHI**

- **Immunotherapy** can be considered
  - if **proper side effect management** during HHI treatment did not improve tolerability, or
  - in case of resistance (progression during HHI treatment)

- **Immunotherapy** standard second line in progressive BCC
  may be considered earlier in case of contra-indication/intolerance to HHI