Immunotherapy and evolving approaches for basal cell carcinoma

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Management of advanced BCC: Can we do more?

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Boston, MA, USA

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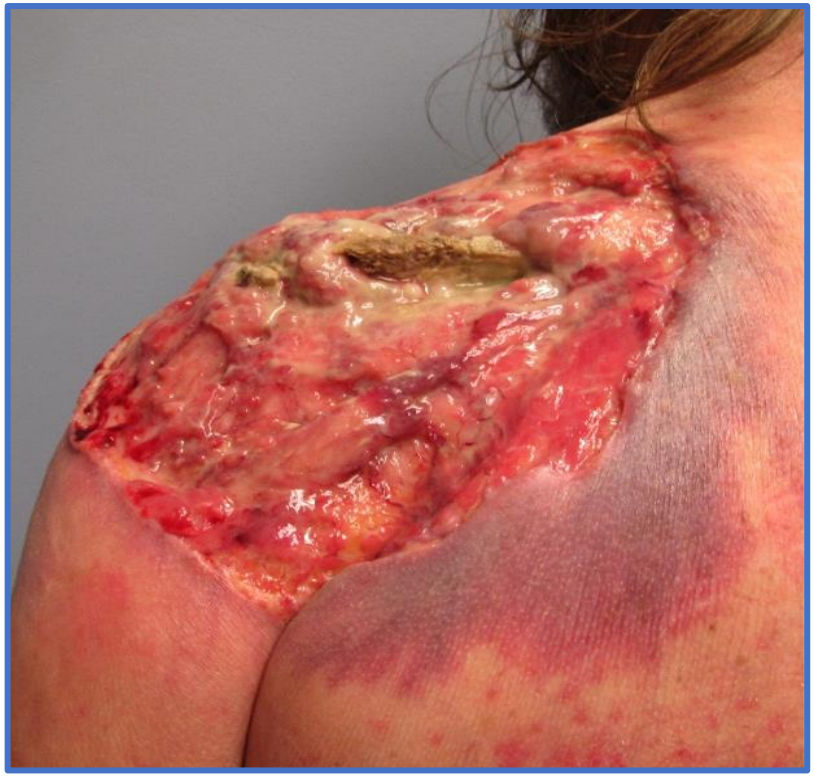
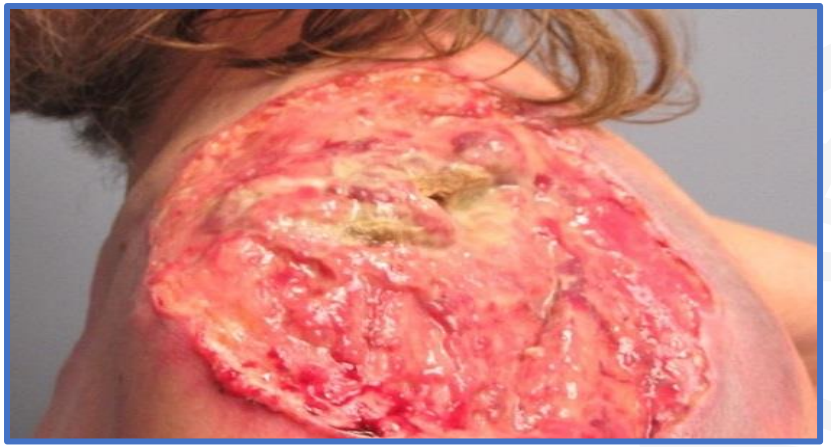
How significant is progressive disease in patients with basal cell carcinoma and what is the current standard of care?

Case study: Locally aggressive and metastatic BCC





Patient history

- 60-year old man: healthy except for ethyl alcohol abuse, sometimes undomiciled
- Diagnosis July 2017: infiltrating BCC
- PET-CT: avid tumour, avid left axillary, pectoral and supraclavicular lymph nodes
- MRI: tumour encasing multiple nerves

BCC, basal cell carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.
Images courtesy of Dr Ruiz.

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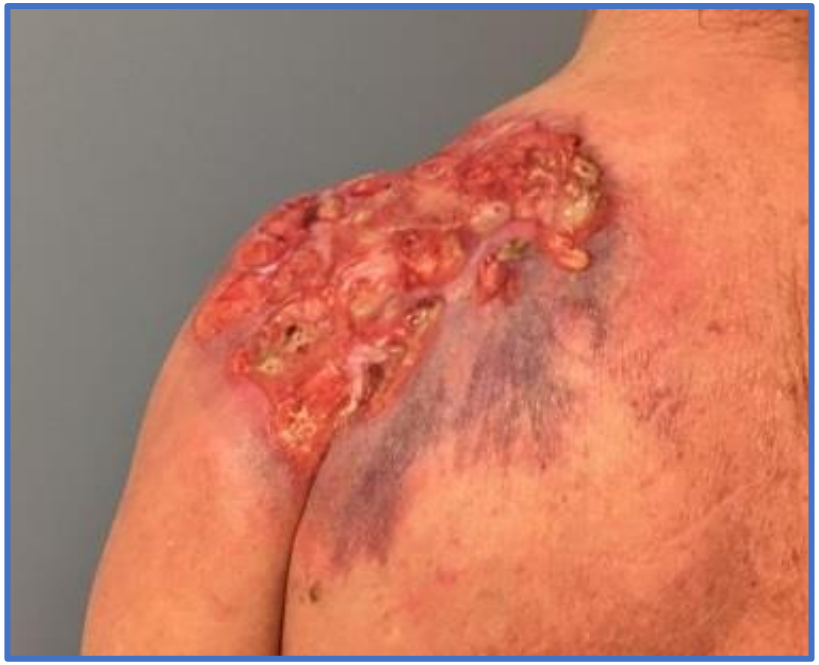
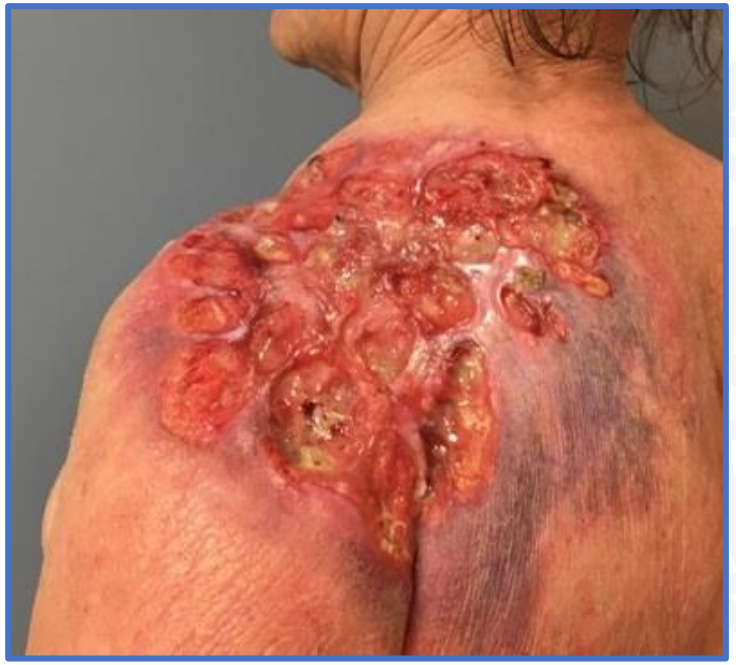
Clinical response to vismodegib (July 2017–May 2018)





MRI: progression of lymph node metastasis

MRI, magnetic resonance imaging.

Images courtesy of Dr Ruiz.

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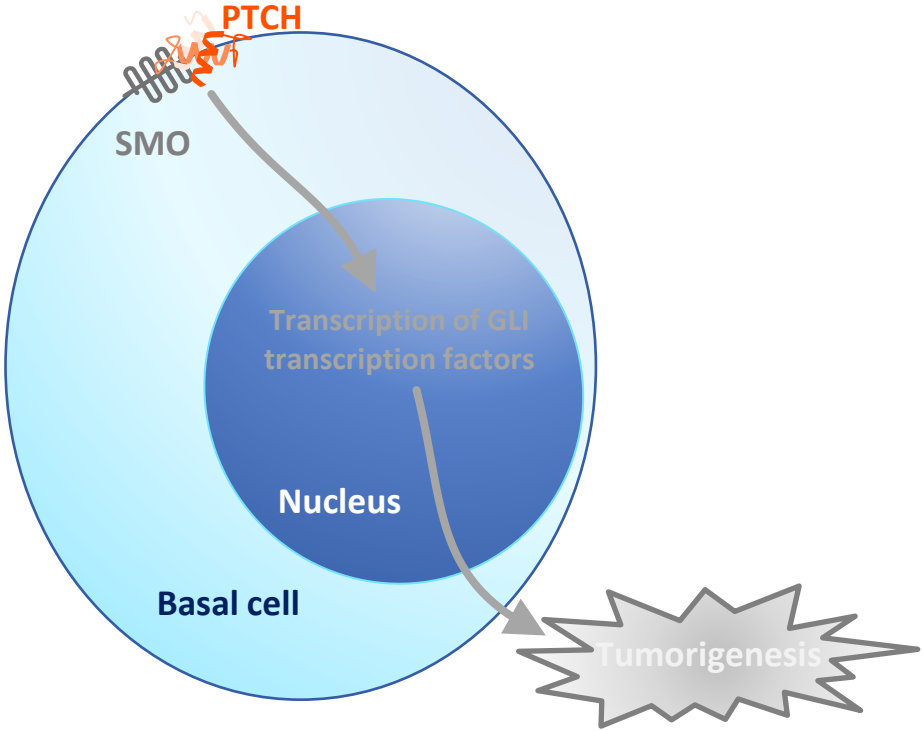
How has the introduction of hedgehog pathway inhibitors altered the management of basal cell carcinoma?

Role of hedgehog pathway signalling in BCC



- 95% of sporadic BCCs have abnormal hedgehog pathway signalling[1]
- 67% of BCC are PTCH deficient, and 10% have activating *SMO* mutations[1]
- Hedgehog inhibitors downregulate SMO signalling and impede BCC tumorigenesis[2]

Meta-analysis of hedgehog inhibitor data:[2]

Endpoint	Vismodegib	Sonidegib
ORR (laBCC)	69%	57%
CR rate (laBCC)	31%	3%
ORR (mBCC)	39%	15%

CR, complete response; GLI, glioma-associated oncogene; la/mBCC, locally advanced/metastatic basal cell carcinoma; ORR, overall response rate; PTCH, protein patched homolog 1; SMO, smoothened transmembrane protein.

1. Tay EY-X, et al. *Dermatol Ther (Heidelb).* 2019;9:33–49; 2. Xie P, Lefrançois P. *J Am Acad Dermatol.* 2018;79:1089–100.

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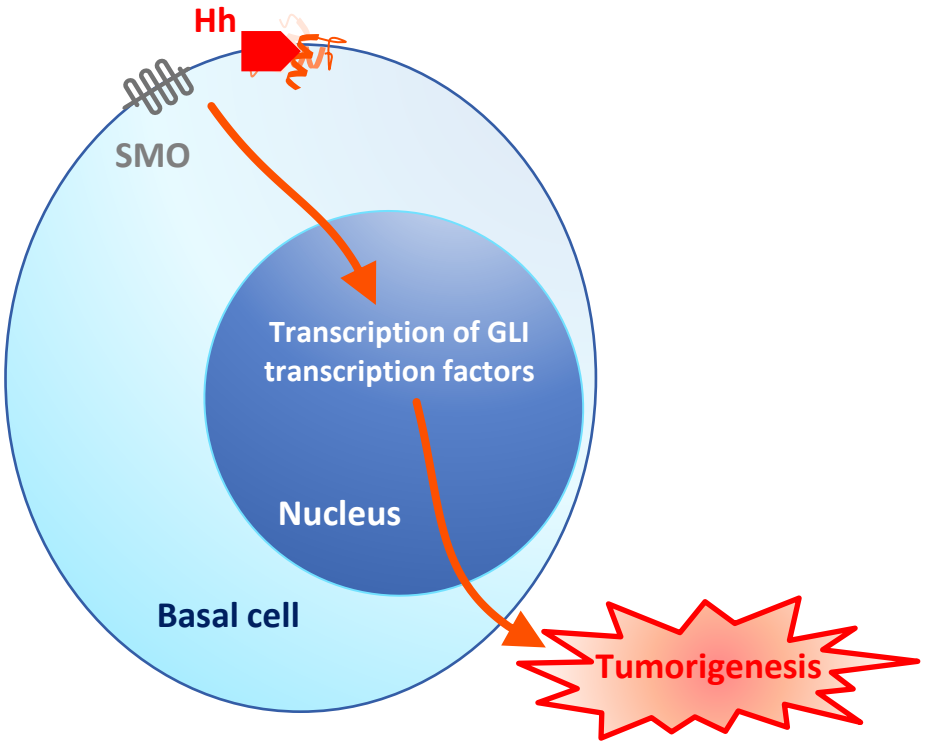
Role of hedgehog pathway signalling in BCC



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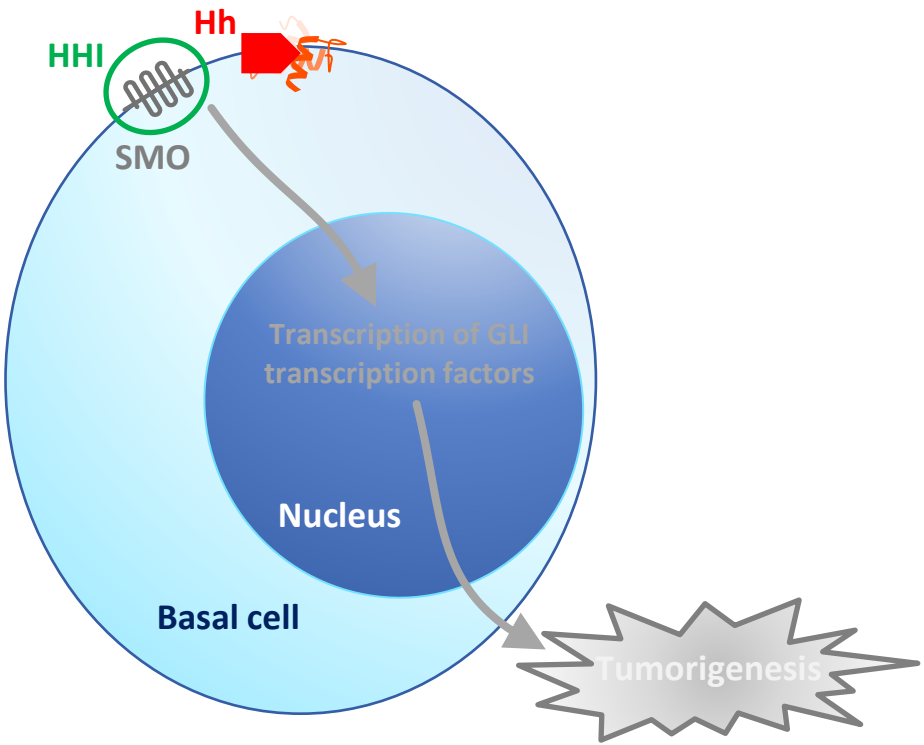
Role of hedgehog pathway signalling in BCC



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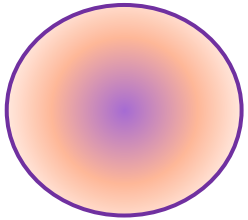
How might hedgehog inhibitors be used in the neoadjuvant setting in patients with locally advanced disease?

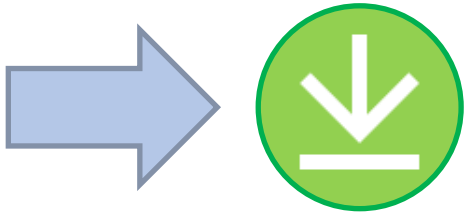
Neoadjuvant hedgehog inhibitor therapy in locally advanced BCC

VISMONEO phase II study (NCT02667574)

- 55 patients (median age 73 years) with locally advanced facial BCCs received neoadjuvant vismodegib for 4–10 months before planned surgery



Mean target lesion size: **47.3 mm**
Mean treatment duration: **6 months**



- **44 patients** (80%) downstaged after treatment
- Mean target lesion size: **15.2 mm**

ORR 71% by RECIST v1.1: **27 patients** (49%) had a complete clinical response

- At 3 years' follow-up:
  - 10/44 downstaged patients had no recurrence
  - 16/44 downstaged patients had recurrent disease (two patients had died)

BCC, basal cell carcinoma; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.
Bertrand N, et al. *EClinicalMedicine*. 2021;35:100844.

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What clinical challenges remain with hedgehog inhibitor-based treatment strategies in basal cell carcinoma?

Ongoing challenges with hedgehog inhibitors for BCC

Adverse events[1,2]

- Dysgeusia
- Anorexia
- Alopecia
- Muscle spasms

Discontinuation due to AEs

Acquired resistance (*SMO* mutations)[1]

Poor and partial response to HHIs

Patient eligibility[3,4]

Recurrent disease or not eligible for surgery or radiotherapy

AE, adverse event; BCC, basal cell carcinoma; HHI, hedgehog inhibitor; SMO, smoothened transmembrane protein.

1. Tay EY-X, et al. *Dermatol Ther (Heidelb).* 2019;9:33–49; 2. Lacouture ME, et al. *Oncologist*. 2016;21:1218–29. 3. Vismodegib prescribing information 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/203388s016lbl.pdf (Accessed August 2021); 4. Sonidegib prescribing information 2019. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2019/205266s006lbl.pdf (Accessed August 2021).

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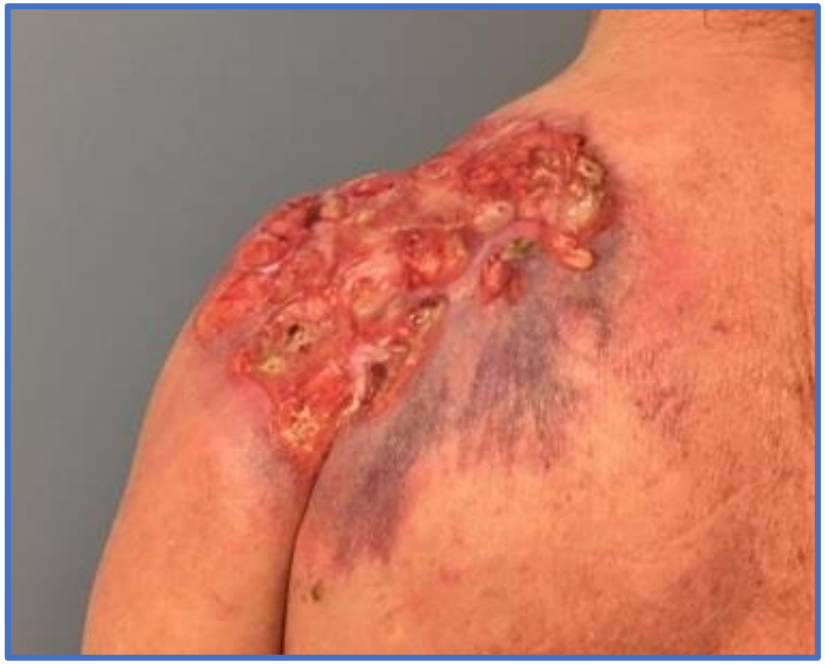
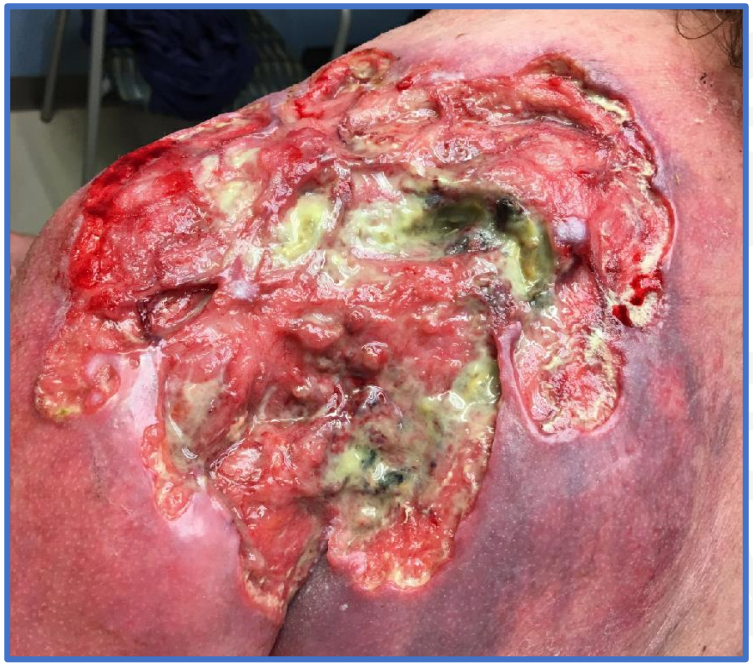
How might the approval of immune checkpoint inhibitor therapy as a second-line therapy address current unmet needs in basal cell carcinoma?

Case study: July 2018, patient switched to immunotherapy



Received two infusions of cemiplimab



Significant disease progression

Images courtesy of Dr Ruiz.

Clinical response to further treatment

Third and subsequent lines of treatment

- Restarted on vismodegib, September 2018
  - no response
- Switched to sonidegib, December 2019
  - no response
- Switched to ipilimumab/nivolimab, March 2019
  - no response
- Intratumoural flu vaccine, June 2019 (one injection)
  - no response
- Died July 2019
  - tumour-related sepsis

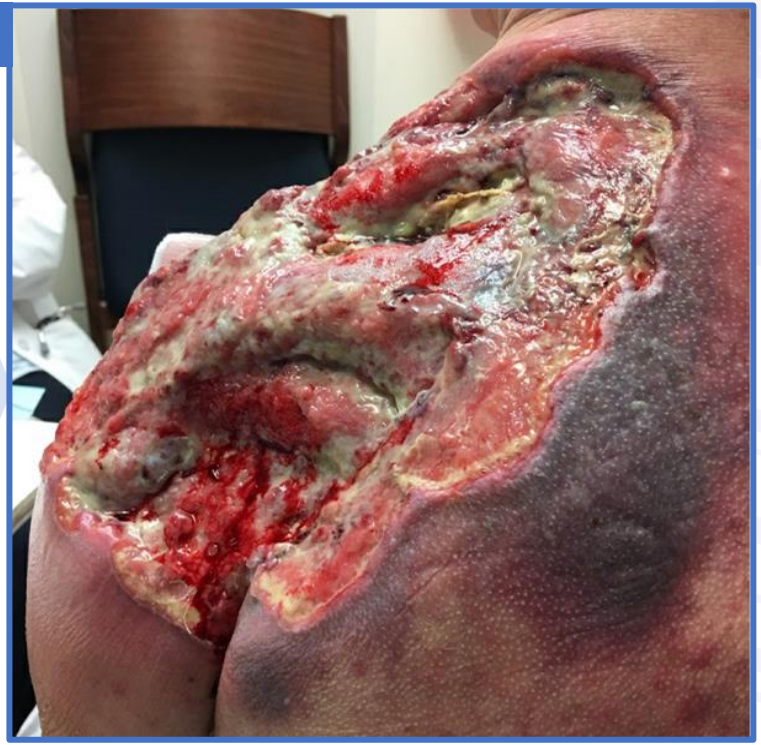


Image courtesy of Dr Ruiz.

Immunotherapy and emerging options in BCC: Key data and insights

Prof. Ketty Peris

Department of Medicine and
Translational Surgery
Catholic University of Rome
Rome, Italy

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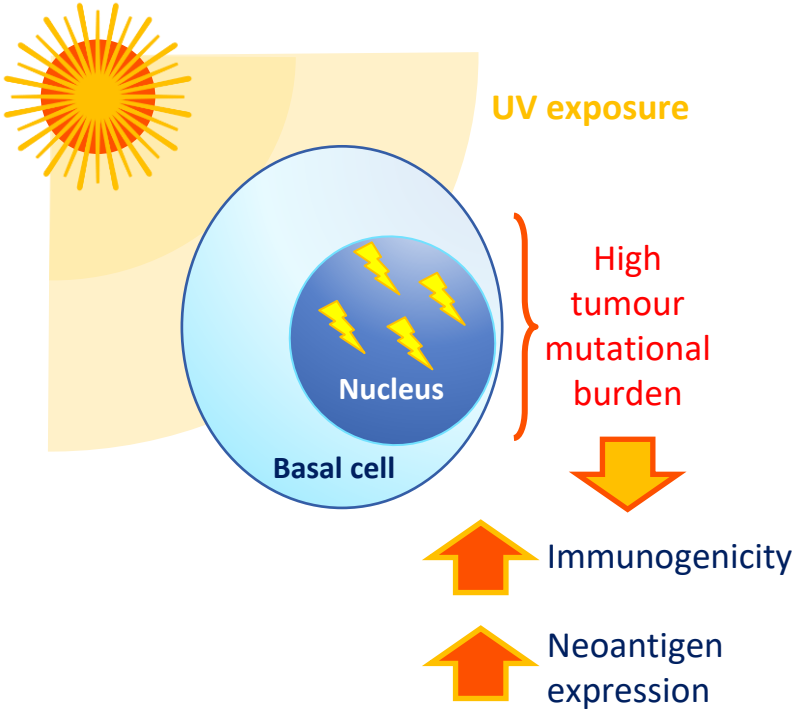
What is the rationale for the use of immunotherapy in basal cell carcinoma?

Rationale for immunotherapy in BCC[1] and clinical study landscape



Advanced/refractory or metastatic BCC

- **Pembrolizumab ± vismodegib** (NCT02690948)
- **PD-L1 vaccine**[2] (NCT03714529)
- **Cemiplimab after progression on HHI** (NCT03132636)
- **Cemiplimab + pulsed HHI** (NCT04679480)
- **Nivolumab ± relatlimab or ipilimumab** (NCT03521830)
- **Laser therapy ± topical nivolumab** (NCT04570683)
- **Neoadjuvant-adjuvant pembrolizumab** (NCT04323202)

Rare or solid tumours including BCC

- **Nivolumab + ipilimumab** (NCT02834013)
- **TVEC + nivolumab** (NCT02978625)
- **Bispecific PD-1 x CTLA-4 antibody** (NCT03517488)

completed | ongoing | recruiting

BCC, basal cell carcinoma; CTLA-4, cluster of differentiation 152; HHI, hedgehog inhibitor; PD-L1, programmed death–ligand 1; TVEC, talimogene laherparepvec; UV, ultraviolet.

1. Hall ET, et al. *Am Soc Clin Oncol Educ Book*. 2020;40:1–10; 2. Jørgensen NG, et al. *Cancers.* 2021;13:911. All NCT records: www.clinicaltrials.gov (accessed August 2021).

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What is the evidence base for the approval of cemiplimab for the treatment of locally advanced or metastatic basal cell carcinoma?

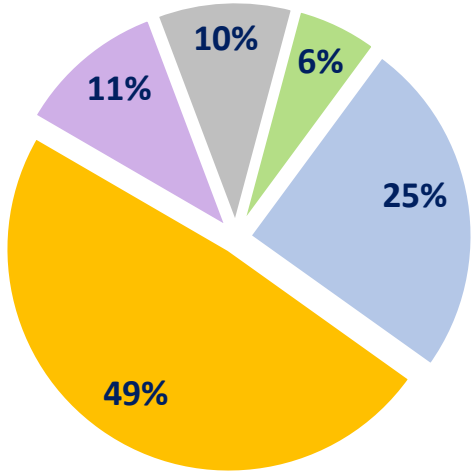
Cemiplimab following hedgehog inhibitor treatment for metastatic or locally advanced BCC

Single-arm phase II trial (NCT03132636)

Cemiplimab 350 mg IV every 3 weeks up to 93 weeks

84 patients
- Median 70 years old
- Progression on or intolerance to HHI
- Prior vismodegib (94%)
  sonidegib (17%)
  combined (11%)
- Prior radiotherapy (50%)

ORR 31% (95% CI 21–42)



- Median time to response 4.3 months
- Median duration of response not reached (range 2–21 months)
  79% with ≥6 months; 46% with ≥12 months

BCC, basal cell carcinoma; CI, confidence interval; HHI, hedgehog inhibitor; IV, intravenous; ORR, objective response rate.

Stratigos AJ, et al. *Lancet Oncol.* 2021;22:848–57.

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What are the key safety considerations surrounding the use of immunotherapy in patients with basal cell carcinoma?

Adverse events with cemiplimab following hedgehog inhibitor treatment for BCC

Adverse event >10% (any attribution)	Grade 1–2 (N=84)
Fatigue	26%
Diarrhoea	24%
Pruritis	21%
Asthenia	19%
Anaemia	14%
Decreased appetite	14%
Arthralgia	13%
Headache	13%
Nausea	13%
Dyspnoea	12%
UTI	11%

Adverse event >2% (any attribution)	Grade 3 (N=84)
Colitis	5%
Hypertension	5%
Fatigue	4%
UTI	4%

Adverse event (any attribution)	Grade 4 (N=84)
Visual impairment	1%
Myocardial infarction	1%

No treatment-related deaths

Immune-related adverse events

25% of patients
- Hypothyroidism (10%)
- Immune-related colitis (4%)

Grade 3 events in eight patients
- Immune-related colitis (n=3)
- Adrenal insufficiency (n=2)
- No other grade 3 events in >1 patient

No grade 4 or 5 immune-related events

BCC, basal cell carcinoma; UTI, urinary tract infection.
Stratigos AJ, et al. *Lancet Oncol.* 2021;22:848–57.

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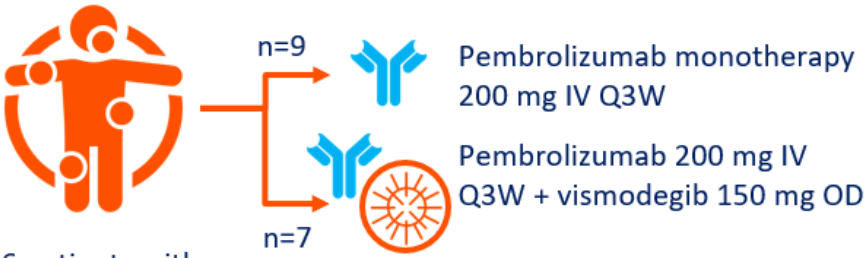
What other efficacy outcomes from clinical trials using anti-PD-1 therapies have been reported in advanced basal cell carcinoma?

Anti-PD-1 therapy in BCC: Proof of concept

Pembrolizumab[1]

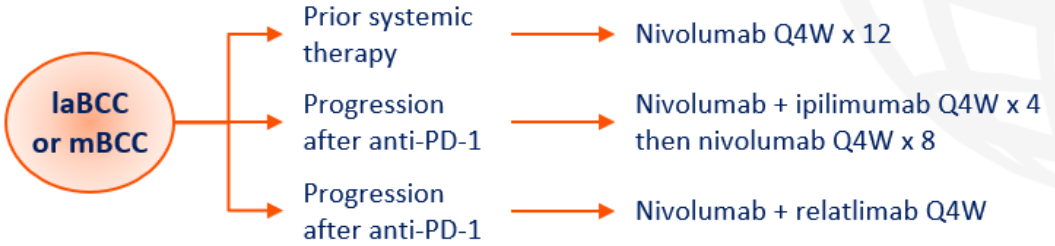
Phase II study (NCT02690948)



	ORR at 18 weeks	Median time to response	Median duration of response	1-year PFS probability	1-year OS probability
	44%	12.4 weeks	67.6 weeks	62%	89%
	29%	10.3 weeks	52.8 weeks	83%	100%
Overall	**38%**	**10.4 weeks**	**67.3 weeks**	**70%**	**94%**

Nivolumab ± ipilimumab or relatlimab (anti-LAG-3 antibody)

Phase II study (NCT03521830)



IV, intravenous; la/mBCC, locally advanced/metastatic basal cell carcinoma; LAG lymphocyte-activation gene; OD, once daily; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; Q3/4W; every 3/4 weeks.

1. Chang ALS, et al. *J Am Acad Dermatol.* 2019;8:564–6. All NCT records: www.clinicaltrials.gov (accessed August 2021).

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How might ongoing research result in further treatment options being available?

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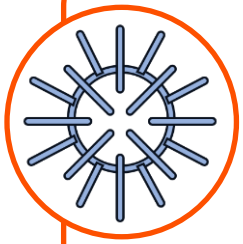
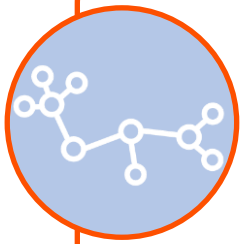
Emerging approaches in BCC



Second-generation HHIs (phase I)[1]

- Patidegib (NCT01609179)
- Taladegib (NCT01226485)
- LEQ-506 (NCT01106508)
- BMS-833923 (NCT00670189)
- TAK-441 (NCT01204073)
- ZSP1602 (NCT03734913)

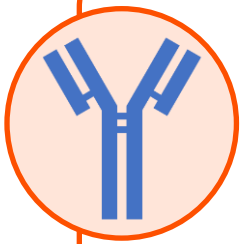


Itraconazole as an SMO inhibitor

- Anti-BCC activity between biopsy and resection in a small phase 2 biomarker study (NCT01108094)[2]
- Combination study with arsenic trioxide underway (NCT02699723)[1]

Radiotherapy combinations

- Radiotherapy with concurrent vismodegib feasible and active in case studies[3,4]
- Phase II study completed (NCT01835626)



Neoadjuvant immunotherapy

- Pembrolizumab under investigation in resectable advanced BCC of the head and neck (NCT04323202)

BCC, basal cell carcinoma; HHI, hedgehog inhibitor; SMO, smoothened transmembrane protein.

1. Niebel D, et al. *Dermatol Ther (Heidelb).* 2020;10:835–46; 2. Kim DJ, et al. *J Clin Oncol.* 2014;32:745–51; 3. Pollom EL, et al. *JAMA Dermatol.* 2015;151:998-1001; 4. Amini A, et al. *Mol Clin Oncol*. 2021;14:46. All NCT records: www.clinicaltrials.gov (accessed August 2021).

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Transforming BCC treatment: What does the future hold?

Prof. Axel Hauschild

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University Hospital Schleswig-Holstein
Kiel, Germany

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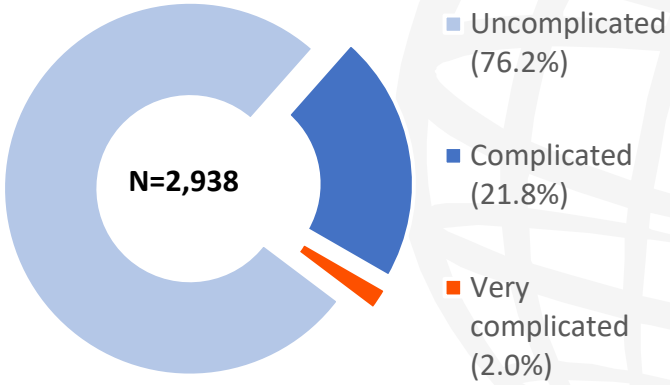
What is the role of the multidisciplinary tumour board in the modern management of basal cell carcinoma?

Key members of the MDT in BCC

Severity estimation of BCC cases at a tertiary referral centre[1]



Treatment choice for advanced BCC should be discussed by an MDT[2]

Figure courtesy of Prof. A Hauschild. BCC, basal cell carcinoma, MDT, multidisciplinary tumour board.

1. Dreier J, et al. *Br J Dermatol.* 2014;171:1066–72; 2. Peris K, et al. *Eur J Cancer*. 2019;118:10–34.

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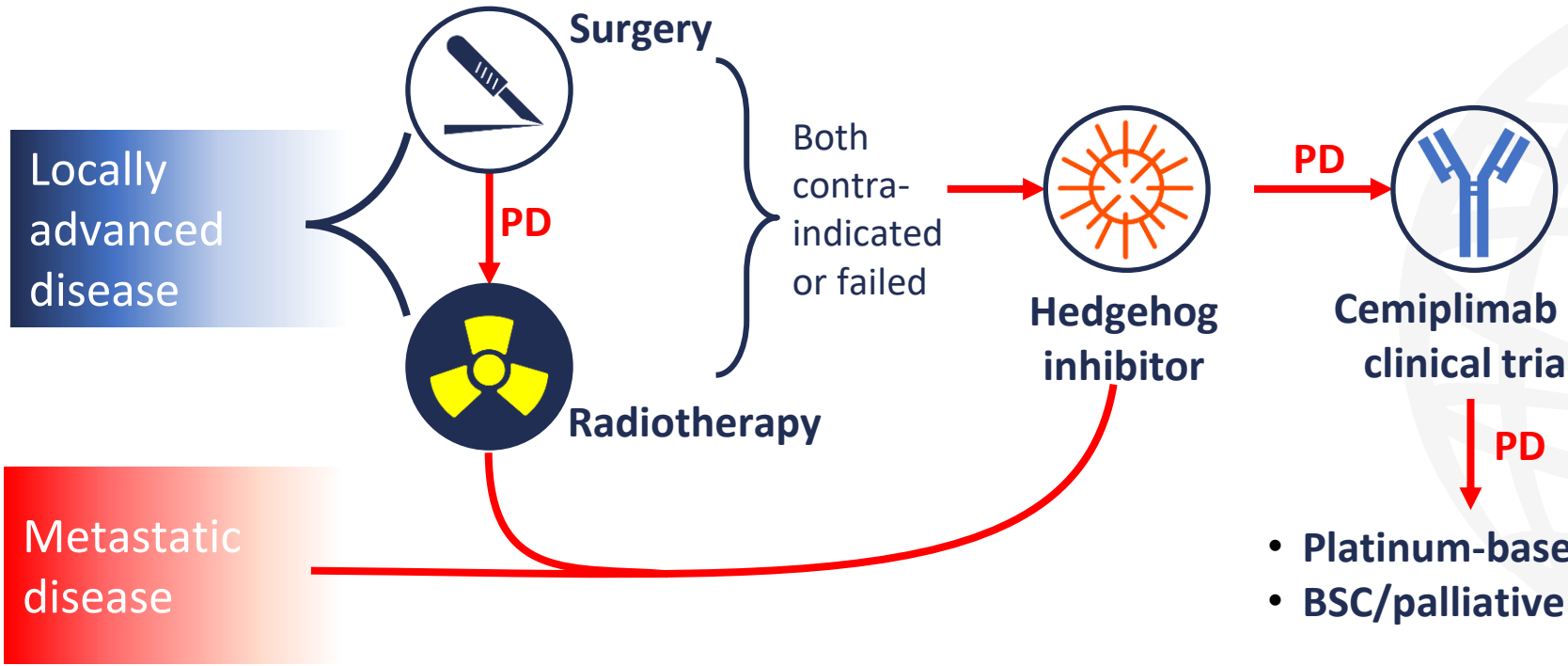
How might immunotherapy-based treatment strategies impact the current treatment paradigm for patients with advanced basal cell carcinoma?

Treatment algorithm for advanced BCC[1–4]



BCC, basal cell carcinoma; BSC, best supportive care; CT, chemotherapy; PD, progressive disease.

1. Mohan SV, Chang ALS. *Curr Derm Rep.* 2014;3:40–5; 2. Bichakjian C, et al. *J Am Acad Dermatol.* 2018;78:540–9; 3. Peris K, et al. *Eur J Cancer*. 2019;118:10–34; 4. Basal cell skin cancer. NCCN Clinical Guidelines v2.2021. www.nccn.org/guidelines/guidelines-detail?category=1&id=1416 (accessed August 2021).

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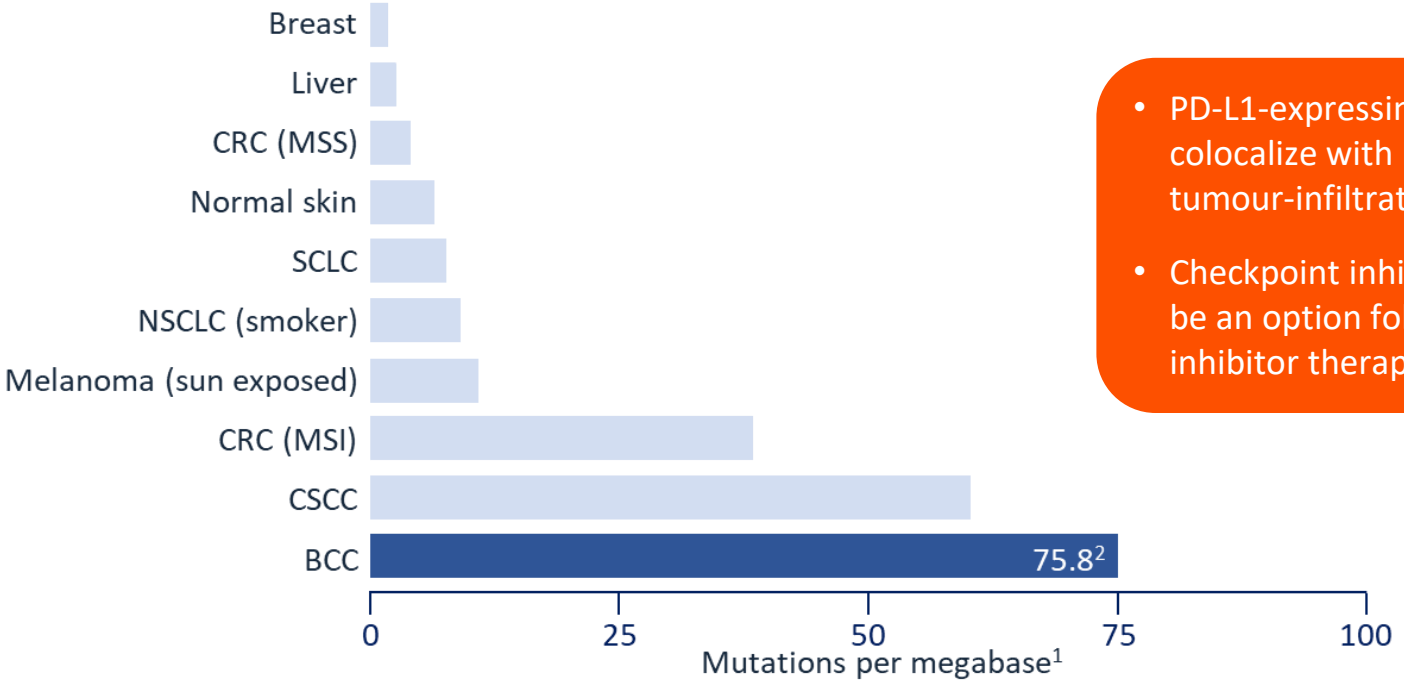
Is there a rationale for biomarker testing to optimize use of immunotherapy in basal cell carcinoma?

BCC commonly expresses PD-L1 and has high TMB

Mutation burden in solid tumours[1,2]



- PD-L1-expressing BCC cells colocalize with PD-1-expressing tumour-infiltrating lymphocytes[3]
- Checkpoint inhibitor therapy may be an option following hedgehog inhibitor therapy failure[3,4]

BCC, basal cell carcinoma; CRC, colorectal carcinoma; CSCC, cutaneous squamous cell carcinoma; MSI, microsatellite instable; MSS, microsatellite stable; NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SCLC, small cell lung cancer; TMB, tumor mutational burden.

1. Karran P, Brem R. *DNA Repair*. 2016;44:178–85; 2. Jayaraman SS, et al. *J Invest Dermatol*. 2014;134:213–20; 3. Lipson EJ, et al. *J Immunother Cancer*. 2017;5:23; 4. Goodman AM, et al. *Oncoimmunology*. 2018;7:e1404217.

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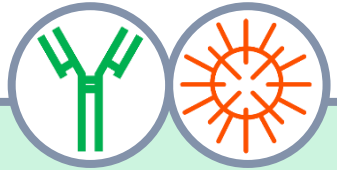
What approaches to safety management are needed for the integration of immunotherapy-based treatment regimens in basal cell carcinoma?

Adverse events associated with systemic immunotherapy regimens in BCC

Cemiplimab[1]

- N=84, after progression on HHI
  - Grade 1–2 (46% of patients): fatigue (26%), diarrhoea (24%), pruritis (21%), asthenia (19%)
  - Grade 3 or 4 (48% of patients): hypertension, colitis (5%); fatigue, UTI, visual impairment (4%)
  - Immune-related (25% of patients): hypothyroidism (10%), immune-related colitis (4%)



Pembrolizumab ± vismodegib[2]

- N=16
  - Three grade 3 AEs, one attributed to pembrolizumab (hyponatraemia)
  - 23 immune-related AEs, most commonly dermatitis and fatigue (all grade 1–2)

Immunotherapy-related AE types[3]

Most common
- Skin toxicities
- Gastrointestinal toxicities
- Thyroid & hepatic toxicity

Less common but serious
- Endocrine toxicities (pituitary/adrenal/diabetes)
- Pneumonitis

Commonly overlooked
- Arthralgia/arthritis
- Mucositis/xerostomia
- Neuropathy
- Nephritis

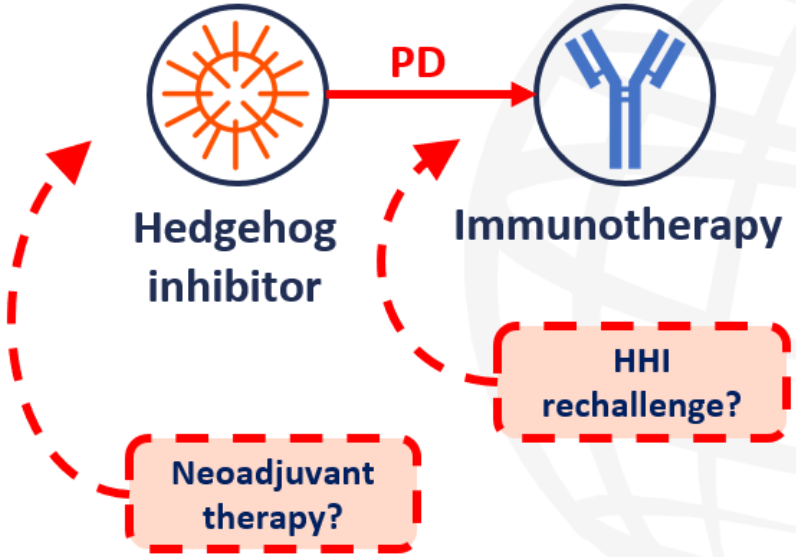
AE, adverse event; BCC, basal cell carcinoma; HHI, hedgehog inhibitor; UTI, urinary tract infection.

1. Stratigos AJ, et al. *Lancet Oncol.* 2021;22:848–57; 2. Chang ALS, et al. *J Am Acad Dermatol*. 2019;80:564–6; 3. Wood LS. *J Adv Pract Oncol.* 2019;10(suppl 1):47–62.

How might ongoing trials with hedgehog inhibitors impact the future treatment paradigm?

Evolving role of hedgehog inhibitors in BCC

Regimen	Phase	Expected primary completion date
Neoadjuvant vismodegib	Phase II NCT02667574	05/2021
Intralesional gusacitinib (SYK/JAK inhibitor) + vismodegib	Phase II NCT04416516	07/2022
Tailored sonidegib after CR (2 weeks on/2 weeks off and 1 week on/3 weeks off)	Phase II NCT04806646	01/2024
Cemiplimab + pulsed sonidegib (2 weeks on/2 weeks off)	Phase II NCT04679480	12/2024



CR, complete response; HHI, hedgehog inhibitor; SYK/JAK, spleen tyrosine kinase and janus kinase; PD, progressive disease.
Study status and descriptions avaialble at https://clinicaltrials.gov/ (accessed August 2021).

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