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Dr. Sauder is currently an assistant professor in the division of dermatology at the University of Toronto. He is an onco- dermatologist at Princess Margaret Cancer Centre as well as the research director at Toronto Research Centre. He earned his Doctor of Medicine degree at McMaster University, completed a residency in dermatology at The University of Ottawa and completed fellowship training in cutaneous oncology at Harvard Medical School.

# Systemic treatments for non-melanoma skin cancers

One in every 3 cancers diagnosed, including both melanoma and non-melanoma, is a skin cancer.[1] Non-melanoma skin cancer (NMSC) which includes basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and, among others, other rarer NMSC such as Merkel cell carcinoma (MCC), represents the majority of skin cancers diagnosed in Canada and globally. NMSC is not included in most provincial and territorial cancer registries making it difficult to characterize the incidence and outcomes. Dermatologists across Canada manage NMSC daily with topical and surgical treatments. However, in rare cases these tumours can progress to become unresectable, locally destructive, metastasize and even cause death. For NMSC that progresses, there are systemic treatment options to help manage these malignancies. The aim of this article is to review the common systemic treatments for management of locally advanced, unresectable and/or metastatic NMSCs.

### Basal Cell Carcinoma (BCC)

BCCs are estimated to be the most common form of NMSC by incidence; however, some studies show that the incidence of SCC may be equal to BCC.[2,3] It is estimated that between 0.0028% to 1% of BCCs will become locally advanced or metastasize.[4,5] Locally advanced is defined as tumours that have invaded underlying tissues, nerves, muscles, bone or into surrounding organs such as the eyes, the ears or the nose. In Canada, there are 2 approved systemic treatments for locally advanced or metastatic BCC: vismodegib and cemiplimab.

Mutations in the hedgehog (Hh) signaling pathway , including *PTCH1, PTCH2, SMO* or *SUFU* genes, that lead to constitutive activation are responsible for ~90% of the cases of both sporadic and familial BCC.[6] Vismodegib is an oral small molecule that blocks activation of Hh by binding to SMO leading to downstream inactivation (**Figure 1**). Vismodegib was approved in Canada in 2013 for adult patients with metastatic BCC or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.[7] Approval was based on ERIVANCE BCC pivotal trial that demonstrated vismodegib shrank locally advanced tumours by 43% and metastatic lesions by 30% with a median duration of response of 7.6 months (**Figure 2**).[8] The approved dose of vismodegib is 150 mg orally once daily. The most common side effects (≥ 20%) are muscle spasms, alopecia, dysgeusia, weight decrease, fatigue, nausea, decreased appetite and diarrhea (**Table 1**).[8] These adverse effects often limit the duration of treatment and/or require drug holidays for their management. Patients only derive benefit of vismodegib while on medication versus immunotherapy that can have a durable effect long after discontinuation.

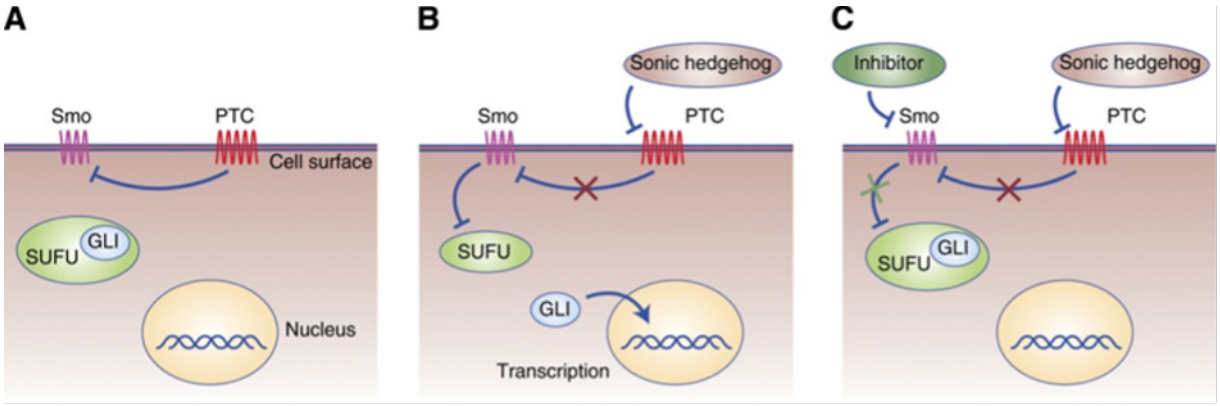


***Figure 1.*** *The hedgehog inhibitor pathway. (A) In the absence of the sonic hedgehog ligand, the patched receptor (PTCH) inhibits the activity of smoothened (Smo), allowing suppressor of fused (SUFU) to bind to and inactivate GLI transcription factors. (B) Binding of the sonic hedgehog ligand to PTCH allows activation of Smo, inhibiting the binding of SUFU to GLI. The GLI transcription factors are then able to enter the nucleus and modulate transcription of hedgehog pathway-associated genes. (C) Vismodegib and LDE225 inhibit Smo activation, preventing inhibition of SUFU binding and subsequent changes in hedgehog pathway-associated gene transcription; adapted from JT Lear, 2014*

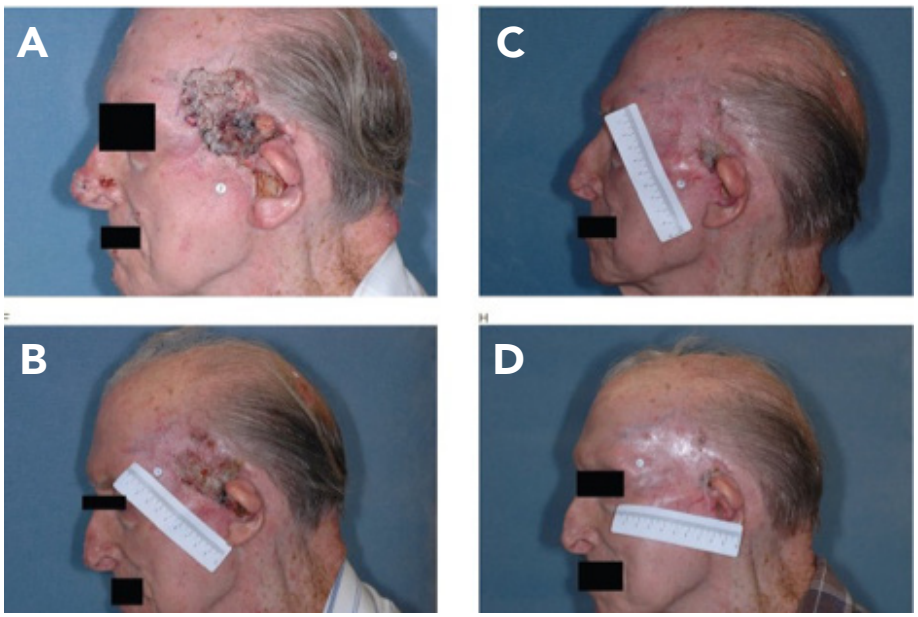


***Figure 2.*** *Representative examples of individual patient responses. Target lesion on the left temple in an 82-year-old man at screening A. 8 weeks B. 16 weeks C. and 24 weeks D; from Chang et al, 2016*

| Event | Any Grade | Grade 1 | Grade 2 | Grade 3 or 4 |
|---|---|---|---|---|
| | *percentage of patients* | | | |
| Muscle spasms | 68 | 48 | 16 | 4 |
| Alopecia | 63 | 49 | 14 | 0 |
| Dysgeusia | 51 | 28 | 23 | 0 |
| Decrease in weight | 46 | 27 | 14 | 5 |
| Fatigue | 36 | 27 | 5 | 4 |
| Nausea | 29 | 21 | 7 | 1 |
| Decrease in appetite | 23 | 14 | 6 | 3 |
| Diarrhea | 22 | 16 | 5 | 1 |

***Table 1.*** *Commonly reported adverse events, according to grade; adapted from Sekulic et al, 2012*

In 2021, cemiplimab was approved for locally advanced BCCs previously treated with a hedgehog pathway inhibitor. Cemiplimab is a monoclonal antibody that inhibits PD1 on T-cells. The approved dose of cemiplimab is 350 mg via intravenous infusion given over 30 minutes every 3 weeks. Tumour mutational burden (TMB) is a predictor of response to immunotherapy.[9] Among skin cancers, melanoma, SCC and virus negative MCC have the highest TMB.[10] Thus, while BCCs can respond to immunotherapy, the response rate is lower than other skin cancers. As such, cemiplimab may be used as a second line therapy for locally advanced or metastatic BCC.

**Squamous cell carcinoma and Merkel Cell Carcinoma**

Immunotherapy has created a paradigm shift in how cancers are managed. Rather than therapies targeting tumours such as traditional chemotherapies or targeted therapies, immunotherapies activate the body's immune system that had previously been unable to respond to the tumour. There are a growing number of approved immunotherapy targets and an ever-growing list of indications. Within skin cancers, approved immune checkpoint targets include: CTLA4, PD-1 and PDL-1 (**Figure 3**).

Cemiplimab, a fully human monoclonal anti-PD-1 antibody, was approved in 2019 for patients with metastatic or locally advanced cutaneous SCC who are not candidates for curative surgery or curative radiation.[11] The approved dose is the same as for BCC. The EMPOWER-CSCC-1 (Study 1540) and two advanced CSCC expansion cohorts from a multi-center, open-label, non-randomized Phase 1 trial (Study 1423) demonstrated response with cemiplimab in approximately half the patients.[12] Adverse events are similar to other immune checkpoint inhibitors including dermatitis/rash, pneumonitis, colitis, hepatitis and thyroiditis leading to hypothyroidism. Recently, long-term data from the original pivotal trials were published with a median duration of follow-up of 15.7 months that demonstrated overall survival (OS) of 73% (95% CI: 66.1% to 79.2%) at 24 months, with median OS not reached.[13] Cemiplimab is a first-line therapy for metastatic or locally advanced cutaneous SCC (**Figure 4**).

Avelumab, a fully human monoclonal anti-PD-L1 antibody, was approved in 2018 for patients with metastatic MCC in previously treated adults (second line therapy). The approved dose of avelumab is 10 mg/kg body weight intravenous over 60 minutes every 2 weeks. Approval of the medication was based on JAVELIN Merkel 200 trial, an open-label, single-arm, multi-centre phase II study in patients with metastatic MCC whose disease had progressed after at least one chemotherapy treatment for distant metastatic disease. The most recent data of this cohort had a median follow-up of 65.1 months the median OS was 12.6 months [95% confidence interval (CI) 7.5-17.1 months], with a 5-year OS rate of 26% (95% CI 17% to 36%)[i]. The side effect profile is similar to that seen with cemiplimab and other immune checkpoint inhibitors; however, since it is the ligand, the incidence of adverse events are lower although direct comparisons cannot be made.

**Conclusion**

Melanoma management in Canada has a clearly established pathway with a multitude of systemic treatments for stages IIB to IV. While it is rare for NMSC to become locally advanced or metastatic, there are effective first and second-line systemic treatments for these malignancies. When faced with patients whose NMSC has progressed beyond surgery or radiation, it is recommended to refer to a regional cancer centre for consideration of one of these systemic therapies.

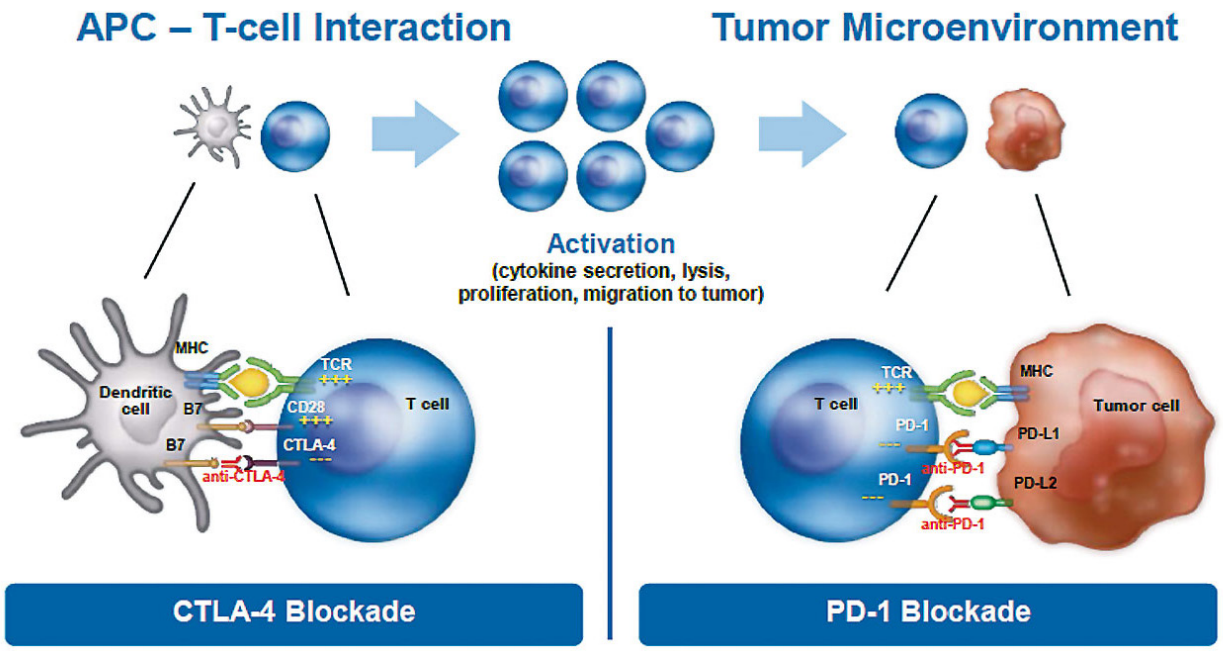


***Figure 3.*** *Blockade of PD-1 or CTLA-4; adapted from Cancerworld, The role of immunotherapy in treating solid cancers, Jan/Feb 2017*

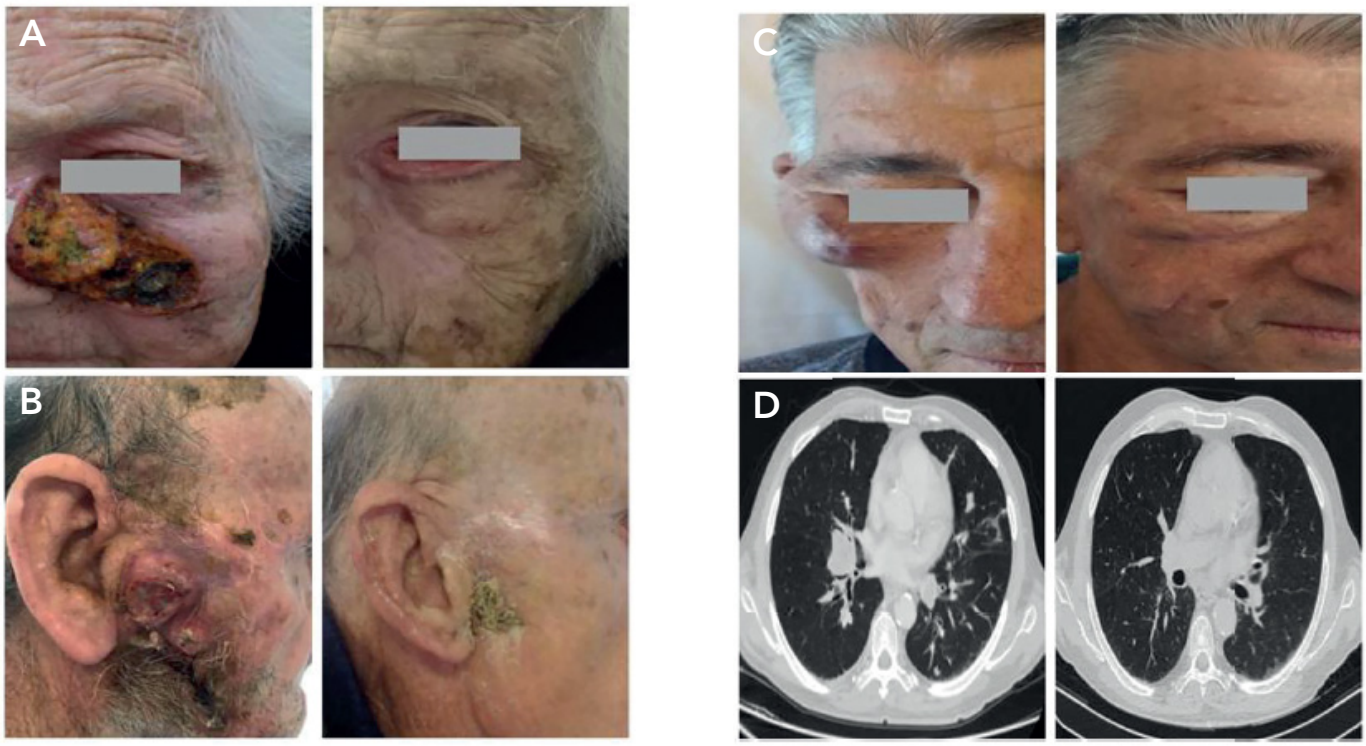


***Figure 4.*** *Representative cases of patients obtaining a major response to cemiplimab. (A) An 88-year-old female with a large locally advanced cutaneous squamous cell carcinoma (laCSCC) of the left nasal-infraorbital region achieving a complete response. Neither had she received prior radiotherapy nor anticancer systemic therapy. (B) An 89-year-old man with a large laCSCC tumor of the right parotid region obtaining a complete response after 6 cycles of cemiplimab and concurrent radiotherapy. (C, D) A 67-year-old man with metastatic cutaneous squamous cell carcinoma in immunosuppressive therapy due to a previous kidney transplantation. The patient achieved a near-complete response both at the right zygomatic area and the metastatic lung lesions; available from Strippoli, Sabino, et al., 2021.*

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