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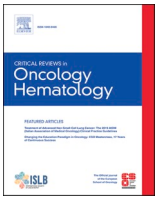

Towards less mutilating treatments in patients with advanced non-melanoma skin cancers by earlier use of immune checkpoint inhibitors

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ABSTRACT

Merkel cell carcinoma (MCC), advanced cutaneous squamous cell carcinoma (cSCC), and advanced basal cell carcinoma (BCC) are rare, and the often frail patients may require potentially mutilating local treatments. Immune checkpoint inhibitors (ICIs) are effective in melanoma and are moving towards the neoadjuvant setting. This systematic review explores data supporting the transition of ICIs from the metastatic to the (neo)adjuvant setting non-melanoma skin cancer (NMSC) and describes how knowledge from melanoma can be utilized. ICI response rates in advanced NMSC and melanoma are comparable. Five early phase studies show effectivity of neoadjuvant ICIs in melanoma and adjuvant treatment is standard-of-care. Eight adjuvant and 12 neoadjuvant ICI studies are ongoing for NMSC. Encouragingly, data from two small neoadjuvant ICI studies in NMSC, demonstrated complete responses in approximately half of patients. In conclusion, neoadjuvant ICI treatment has potential to avert mutilating treatments in NMSC. Progress can be accelerated by learning from melanoma.

1. Introduction

Merkel cell carcinoma (MCC), advanced cutaneous squamous cell carcinoma (cSCC), and advanced basal cell carcinoma (BCC) are rare (Table 1). These patients are frequently frail and elderly. The primary treatment consists of surgery and radiotherapy, in some cases resulting in functional and/or mutilating deficits, which can contribute to the patient's frailty (Moncrieff et al., 2009a, 2009b; Rong et al., 2015; Sobanko et al., 2015; Burdon-Jones et al., 2010).

Immune checkpoint inhibitors (ICIs) are approved monoclonal antibodies that target inhibitory immune checkpoints between immune- and tumor cells, including programmed cell death receptor 1 or its ligand (PD-(L)1) and cytotoxic T-lymphocyte-associated protein 4-pathway (CLTA-4). Interruption of the inhibitory signal can result in an anti-tumor immune response (Schadendorf et al., 2015; Hamid et al., 2019; Wolchok et al., 2022; Gutzmer et al., 2020). MCC, cSCC, and BCC are sensitive to ICIs (immunogenic) either due to viral antigen expression or to a high mutational burden caused by ultraviolet (UV)-radiation exposure (Kaufman et al., 2018; D'Angelo et al., 2021; Migden et al., 2020; Stratigos et al., 2021).

In other immunogenic cancer types, such as melanoma, ICI-treatment is expanding to the (neo)adjuvant setting (Eggermont et al., 2022, 2016; Ascierto et al., 2020; Luke et al., 2021; Rozeman et al., 2020, 2021; Amaria et al., 2018; Blank et al., 2020). Neoadjuvant ICI-treatments induce a robust immune response that is often broader than that achieved in the adjuvant setting and allow early evaluation of response (Rozeman et al., 2020, 2021; Amaria et al., 2018; Blank et al., 2020). Furthermore, neoadjuvant ICI treatment has the potential to reduce the use of mutilating localized treatments and may thereby improve the quality of life of frail patients confronted with advanced skin cancers.

The rarity of MCC, advanced cSCC, and BCC prevents the execution of adequately powered phase 3 clinical trials, as performed for melanoma. Patients with MCC, cSCC, and BCC may, however, benefit from the knowledge acquired during large, randomised ICI studies in melanoma. Therefore, this systematic review describes the development of ICI-treatment from the metastatic to the (neo)adjuvant setting in skin cancers. The epidemiology, etiology, and state of the art of ICI-treatment are discussed for melanoma, MCC, cSCC, and BCC. We discuss which lessons can be learned from melanoma to accelerate progress in NMSC

Abbreviations: ICIs, Immune checkpoint inhibitors; NMSC, Non-melanoma skin cancer; NAT, Neoadjuvant therapy.

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treatment aiming to decrease the need for mutilating localized treatments by use of immune checkpoint inhibitors as (neo)adjuvant treatment.

2. Methods

Firstly, all Food and Drug Administration (FDA) ICIs approvals for melanoma, MCC, cSCC, and BCC were retrieved. Between 2010 and 2020, most cancer therapies were approved by the FDA before they were approved by the European Medicines Agency (EMA), and therefore, we included ICIs that have received FDA-approval (Lythgoe et al., 2021). The registration trials were identified by their NCT number and published studies were retrieved from PubMed. Secondly, ongoing neoadjuvant ICI studies in melanoma and (neo)adjuvant ICI studies in MCC, cSCC, and BCC were identified via ClinicalTrials.gov, and published studies were retrieved from PubMed. PubMed search terms included: "neoadjuvant", "pre-operative", "adjuvant", or "postoperative" AND "immune checkpoint inhibitors" (including all registered anti-PD1, anti-PD-L1, anti-CTLA-4, and anti-LAG-3 monoclonal antibodies) AND "melanoma", "MCC", "cSCC", or "BCC". All searches were performed between Aug-18 and Dec-14 2021. To grade the benefit of these approved ICIs, the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores were retrieved from the ESMO website or, in cases where scores were unavailable, studies were scored using the standardized ESMO-MCBS forms (Cherny et al., 2015).

3. ICI-treatment in melanoma

Melanoma development is multifactorial, with genetic and environmental, e.g., UV exposure, factors contributing (Conforti and Zalaudek, 2021). Melanoma accounts for less than < 5% of all skin cancer diagnoses (Table 1). However, it is still the leading cause of skin cancer deaths but treatment for advanced disease has improved greatly with the introduction of ICIs and targeted agents Driver B-Raf proto-oncogene, serine/threonine kinase *(BRAF)*-mutations occur in ~50% of melanomas and make these patients amenable to targeted agents, i.e., BRAF/mitogen-activated protein kinase (MEK)-inhibitors, and currently these are mainly used when ICI treatment is not feasible or when patients have progressed on ICIs (da Silveira Nogueira Lima et al., 2017).

3.1. Unresectable or metastatic setting

Before the introduction of ICIs, patients with advanced (irresectable stage III/IV) melanoma had a 5-year overall survival (OS) of approximately 10% (Pavlík et al., 2014; Maio et al., 2015). The introduction of ICI-treatment remarkably improved OS (Hamid et al., 2019; Schadendorf et al., 2015; Wolchok et al., 2022). The ICIs ipilimumab (CTLA-4 antibody), pembrolizumab, nivolumab (both PD-1 antibodies), ipilimumab plus nivolumab, and atezolizumab (PD-L1 antibody, combined with BRAF/MEK-inhibitors) are FDA- and EMA- approved for the treatment of advanced melanoma (Fig. 1). The highest response rate, 61%, is observed in patients treated with ipilimumab plus nivolumab, resulting in a 6.5-year OS of 57% (Wolchok et al., 2022). Patients treated with single-agent pembrolizumab or nivolumab have lower survival rates at 5 years, but these drugs have a more tolerable toxicity profile compared to ipilimumab plus nivolumab.

3.2. Adjuvant setting

Ipilimumab, nivolumab, and pembrolizumab approvals in the adjuvant setting are based on three large randomised clinical trials (RCTs) performed in patients with completely resected stage III/IV melanoma. A phase 3 trial randomised 951 patients with resected stage III melanoma to adjuvant ipilimumab or placebo (Eggermont et al., 2016). At a median follow-up of 5.3 years, the 5-year disease-free survival (DFS) for ipilimumab was 41% versus 30% for placebo (hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.64–0.89, $p < 0.001$) and the 5-year OS was 65% versus 54% (HR 0.72, 95% CI 0.58–0.88, $p = 0.001$). In the ipilimumab cohort, grade 3–5 treatment-related adverse events (AEs) occurred in 43% of the patients, including five deaths, versus 3% in the placebo cohort. The EMA did not approve adjuvant ipilimumab for

Table 1
Epidemiology of melanoma, MCC, cSCC, and BCC.

	Melanoma	MCC	cSCC	BCC
Age at primary diagnosis				
Median age (years)	65	74	72	64
Incidence				
Primary tumors (per 100,000)	22.7	0.13 – 0.8	163 – 290	226 – 321
Presenting with locally advanced	7 – 10%	26 – 28%	4 – 5%	0.7 – 0.8%
Presenting with metastatic disease	1 – 3%	7 – 11%	2%	0.02 – 0.56%
Risk factors				
Demographic factors	increasing age male sex (at an older age)	increasing age male sex	increasing age male sex	increasing age male sex
Genetic and phenotypic factors	light skin type multiple nevi (> 20) atypical nevi family history familial atypical mole and melanoma syndrome dysplastic nevus syndrome xeroderma pigmentosum	light skin type	light skin type xeroderma pigmentosum epidermolysis bullosa oculocutaneous albinism epidermodysplasia verruciformis Fanconi anemia Ferguson-Smith syndrome dyskeratosis congenita Huriez syndrome Rothmund-Thomson syndrome Bloom syndrome Werner syndrome	light skin type basal cell nevus syndrome xeroderma pigmentosum Bazex-Dupré -Christol syndrome oculocutaneous albinism
Environmental factors	UV-radiation immunosuppression	UV-radiation Merkel cell polyomavirus immunosuppression	UV-radiation immunosuppression smoking	UV-radiation immunosuppression

Abbreviations: UV ultraviolet.

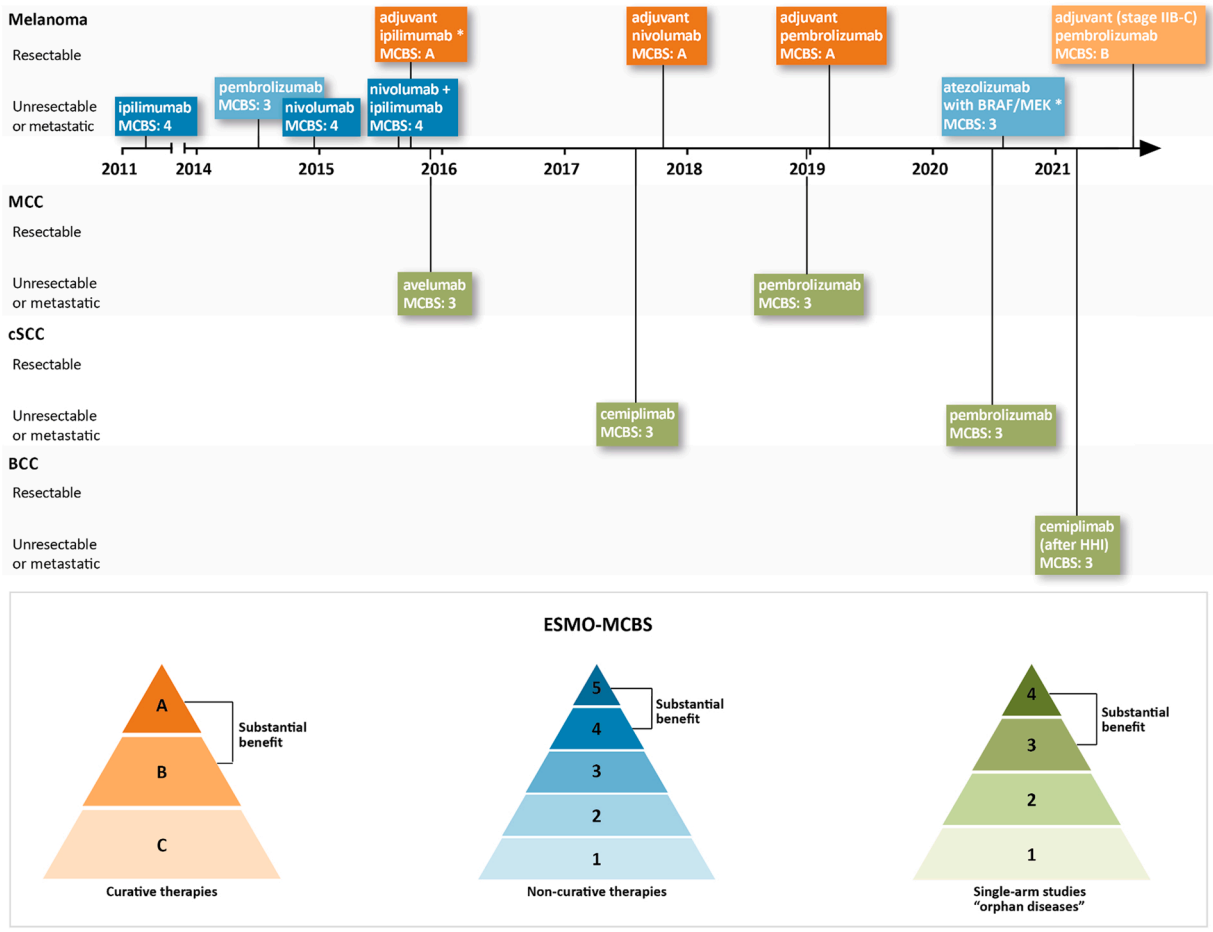

Fig. 1. First FDA-approved immune checkpoint inhibitor indications for melanoma, MCC, cSCC, BCC in time categorized by resectability of the tumor and ESMO-MCBS. * = vemurafenib plus cobimetinib. Abbreviations: MCC Merkel cell carcinoma, cSCC cutaneous squamous cell carcinoma, BCC basal cell carcinoma, ESMO-MCBS ESMO-magnitude of clinical benefit scale, HHI hedgehog pathway inhibitor.

resected stage III/IV. In the CheckMate 238 study, 906 patients with completely resected stage IIIB-IV melanoma were randomised between nivolumab and ipilimumab (Weber et al., 2017). After 4 years, DFS was 52% for nivolumab versus 41% for ipilimumab (HR 0.71, 95% CI 0.60–0.86, $p < 0.001$) and the 4-year OS was 78% versus 77% (HR 0.87, 95% CI 0.66–1.14, $p = 0.31$) (Ascierto et al., 2020). Grade 3–5 AEs occurred in 15% of the patients treated with nivolumab and in 46% for ipilimumab, including two deaths (Weber et al., 2017). In the EORTC 1325-MG/KEYNOTE-054, 1019 patients with resected stage III melanoma received 1 year of adjuvant pembrolizumab or placebo. At a median follow-up of 4.9 years, the DFS was 55% for pembrolizumab and 38% for placebo (HR 0.61, 95% CI 0.51–0.72). Most grade 3–5 AEs occurred with pembrolizumab, namely 15%, including one death, versus 3% with placebo. OS data of the EORTC 1325-MG/KEYNOTE-054 has not yet been reported (Eggermont et al., 2022). Adjuvant pembrolizumab is FDA- and EMA-approved for completely resected stage IIB-C melanoma. The KEYNOTE-716 trial randomised adjuvant pembrolizumab or placebo for 1 year in 976 high risk stage II patients. At a median follow-up of 14.4 months, DFS was 89% with pembrolizumab and 83% with placebo (HR 0.65, 95% CI 0.46–0.92, $p = 0.007$). The number of patients developing distant recurrences almost halved with 23 versus 38 events (Luke et al., 2021). Despite the improvements in DFS, so far, none of the adjuvant ICI studies in melanoma has resulted in an improved OS.

3.3. Neoadjuvant setting

Data from five neoadjuvant ICI studies are available for melanoma (Table S2). The feasibility and potential efficacy of neoadjuvant ($n = 10$) versus adjuvant ($n = 10$) ipilimumab 3 mg/kg plus nivolumab 1 mg/kg in patients with high-risk stage IIIB melanoma was demonstrated in the phase 1b OpACIN study. Nine patients were evaluable for pathological response, seven achieved pathological responses, including three patients with pathological complete responses (pCR), three near-complete, and one partial response (Blank et al., 2018). Nine patients experienced grade 3–4 AEs. Therefore, the subsequent phase 2 trial OpACIN-neo randomised patients with resectable stage III melanoma with at least one measurable lymph node metastasis ($n = 89$) to one of three ipilimumab/nivolumab dosing regimens. The 2 cycles of 3-weekly ipilimumab/nivolumab (1+3 mg/kg, respectively) regimen resulted in a pCR rate of 57%, and was the most tolerable treatment regimen (Rozeman et al., 2020, 2021). In the extension cohort (PRADO), additional postsurgical adjuvant ICI-treatment was only administered to pathological non-responders (>50% viable tumor cells). Sixty of the 90 patients in the PRADO-study achieved major pathological responses in the largest lymph node metastasis, defined as 0–10% viable tumor cells (Blank et al., 2020). Subsequently, therapeutic lymph node dissection was omitted in the 58 patients (97%) with major pathological response. The short follow-up of the study precluded reporting median DFS. Another neoadjuvant phase 2 study evaluated 3 cycles ipilimumab/nivolumab (3+1 mg/kg, respectively) versus 4 cycles of nivolumab. This study was terminated prematurely since eight of 11 patients receiving

ipilimumab/nivolumab experienced grade 3 AEs, and two of 12 patients receiving nivolumab progressed early. Early progression also in these patients resulted in irresectability of the tumor (Amaria et al., 2018). Another trial evaluated one neoadjuvant pembrolizumab cycle for resectable stage III/IV melanoma, followed by resection at 3 weeks and 1 year adjuvant pembrolizumab. At resection, eight of 27 patients (30%) had pCR or major pathological response. None of these patients had recurred at a median follow-up of 25 months (Huang et al., 2019). Lastly, a study examining the safety of neoadjuvant combination therapy with ipilimumab combined with high dose interferon alfa-2b (HDI), randomised between 3 or 10 mg/kg ipilimumab. Using this approach, a pCR was induced in 9/28 evaluable patients. Most grade 3/4 AEs occurred in the highest ipilimumab dose arm (Tarhini et al., 2018).

Eighteen neoadjuvant ICI studies are ongoing in patients with melanoma (Supplement Table 2). The two largest are S1801 and NADINA RCTs. The S1801 (phase 2) evaluates neoadjuvant plus adjuvant pembrolizumab versus adjuvant pembrolizumab only. Intriguingly, the preliminary data of 313 randomised patients show a significantly higher event-free survival of neoadjuvant pembrolizumab compared to adjuvant pembrolizumab (HR 0.59, 95% CI 0.40–0.86, p = 0.0015) (Patel et al., 2022). Benefit of neoadjuvant therapy over adjuvant was consistent regarding age, sex, performance status, stage, LDH, ulceration, and BRAF-mutational status. In the neoadjuvant arm, 28 of the 131 (21%) patients with a submitted pathologic rapport had a pCR. The NADINA trial evaluates neoadjuvant ipilimumab/nivolumab versus adjuvant nivolumab. Only the patients without a pCR after neoadjuvant ICI receive adjuvant therapy. Other ongoing neoadjuvant ICIs studies are relatively small, often combined with other anti-cancer therapies, e.g., talimogene laherparepvec (T-VEC) and targeted therapies. Latest available results are from three small neoadjuvant combination therapy phase I/II studies which all showed the feasibility of the investigational neoadjuvant combinational treatments (Wei et al., 2022; Reijers et al., 2022; Long et al., 2022). One arm of the DONIMI study (2 cycles nivolumab plus ipilimumab and domatinostat once daily) was terminated early due to domatinostat related toxicity (Reijers et al., 2022).

4. ICI-treatments in non-melanoma skin cancer

4.1. MCC

MCC is a rare, rapidly-growing, potentially lethal skin tumor of which the incidence is rising worldwide (Table 1) (Fitzgerald et al., 2015; van der Zwan et al., 2013). For the pathogenesis of MCC two routes are recognized: UV-radiation exposure and Merkel cell polyomavirus (MCPyV) integration into the genome resulting in viral oncoprotein expression. Previously, patients with metastatic/irresectable MCC were treated with platinum-based chemotherapy with a 5-year OS of 14–18% (Kaufman et al., 2018; Harms et al., 2016; Lemos et al., 2010). This poor OS changed remarkably with the implementation of ICI's.

4.1.1. Unresectable or metastatic setting

Avelumab and pembrolizumab are registered for metastatic/recurrent locally advanced MCC based on small, multicenter, prospective phase 2 studies (Fig. 1). Avelumab for metastatic MCC was studied in the JAVELIN Merkel 200 study that included 88 patients previously treated with chemotherapy and 116 patients who received avelumab as first-line treatment. After chemotherapy, the objective response rate (ORR) of avelumab was 33% (n = 29), and the median response duration was 40.5 months. Estimated progression-free survival (PFS) was 26% and 21% at 2- and 3-years, respectively. AEs grade $\geq$ 3 occurred in 10 patients (11%) (Kaufman et al., 2018; D'Angelo et al., 2020). First-line avelumab showed durable responses lasting $\geq$ 6 months in 35 patients (30%) (95% CI 22.0%−39.4%). At median follow-up of 21.2 months, the median OS was 20.3 months (95% CI 12.4-not-estimable). For 18% of the patients treated with avelumab in first line, grade 3–4 AEs were reported (D'Angelo et al., 2021). First-line pembrolizumab was evaluated in 50 patients in the KEYNOTE-017. Here a similar ORR of 58% (95% CI 43.2–71.8) was reported, and of these responses, 21 were ongoing at 3-years (Nghiem et al., 2021).

4.1.2. Adjuvant setting

Five trials are currently investigating adjuvant ICI-treatment in MCC (Table 2). The duration of adjuvant treatment in these studies varies from 6 months to 2 years. In the ADAM trial, patients receive avelumab or placebo for a maximum of 2 years until disease recurrence and/or unacceptable toxicity. Most other adjuvant studies have a 1-year treatment duration. In these studies, the control groups receive placebo or undergo observation only. An interim analysis of the ADMEC-O trial, where 179 patients with MCC were randomised between adjuvant nivolumab and observation, shows a DFS in favor of nivolumab of 87% versus 74% (HR 0.56, 95% CI 0.28–1.15) at a median follow up of 24.3 months. OS data is not yet available (Becker et al., 2022).

4.2. Neoadjuvant setting

The CheckMate 358 phase 1/2 study in patients with virus-associated cancer types included 39 patients with resectable MCC.

Table 2
Registered clinical studies with adjuvant immune checkpoint inhibitors in patients with MCC, cSCC, and BCC.

Skin tumor type	ClinicalTrails.gov Identifier	Study design	Study population	Local treatment	Adjuvant treatment	Treatment duration	Planned N	Primary outcome
MCC	NCT03271372	Phase III	Stage IIIA/B	Surgery or RT	avelumab	18 cycles	100	RFS
	NCT04291885	Phase II	Stage I-III	Surgery	avelumab	13 cycles	132	RFS
	NCT03712605	Phase III	Stage I-IIIAB	Surgery	pembrolizumab	17 cycles	280	RFS
	NCT02196961 Becker et al. (2022)	Phase II	Resected MCC (stage not reported)	Surgery	nivolumab	13 cycles	180	DFS
	NCT03798639	Phase I	Stage IIIA/B	Surgery (and RT in arm A)	Arm A: nivolumab Arm B: nivolumab + ipilimumab	Arm A: 13 cycles + 5x/ week RT for 6 weeks Arm B: 13 cycles	7	Tolerability
cSCC	NCT03969004	Phase III	High-risk cSCC	Surgery and RT	cemiplimab	Not reported	412	DFS
	NCT03833167	Phase III	high-risk LA cSCC	Surgery and RT	pembrolizumab	9 cycles + 18 additional cycles*	570	RFS
	NCT03057613	Phase II	cSCC of the head and neck	Surgery and RT	pembrolizumab	5 cycles	18	PFS
BCC	N/A							

Abbreviations: MCC Merkel cell carcinoma, RT radiotherapy, RFS recurrence-free survival, cSCC cutaneous squamous cell carcinoma, DFS disease-free survival, PFS progression-free survival, N/A not applicable, LA cSCC locally advanced cutaneous squamous cell carcinoma.
* = eligible for additional cycles in case of recurrent disease.

Thirty-six patients received 2 neoadjuvant cycles of nivolumab and subsequently underwent surgery. Forty-seven percent obtained a pCR, and none of the patients with a pCR recurred during the median follow-up of 20.3 months. DFS at 2-years was 69%. At 12- and 24-months, the OS rates were 93% and 79%, respectively (Topalian et al., 2020). Next to this relatively small study, three other small neoadjuvant ICI studies are ongoing (Table 3).

4.2.1. cSCC

cSCC is the second most common skin cancer. Patients with cSCCs rarely develop metastases (2%) (Table 1) (Thompson et al., 2016). Prior to ICI-introduction, platinum-based chemotherapy for metastatic cSCC was sometimes considered, although no standard regimen was defined (Trodello et al., 2017). These schedules had limited efficacy and were often poorly tolerated in older and frail patients confronted with advanced cSCC (Claveau et al., 2020).

4.2.2. Unresectable or metastatic setting

Cemiplimab, and pembrolizumab, are registered for patients with metastatic/recurrent and locally advanced cSCC (lacSCC) who are ineligible for curative surgery or radiation (Fig. 1). Cemiplimab registration was based on two phase 1/2 studies. The ORR was 44% in patients with irresectable lacSCC (n = 78) and 47% in metastatic cSCC (n = 59, both phase 2 part) (Migden et al., 2020; Rischin et al., 2021). The 2-year PFS, including both lacSCC and metastatic cSCC, was 44%. Grade 3–5 AEs were seen in 44% of patients with lacSCC and 51% with

Table 3
Ongoing or planned, registered clinical studies with neoadjuvant immune checkpoint inhibitors in patients with MCC, cSCC, and BCC.

Skin tumor type	ClinicalTrails.gov Identifier	Study design	Study population	Local treatment	Systemic treatment	Treatment duration	Planned N	Primary outcome
MCC	NCT04975152	Phase I	Stage I and II	Surgery	*Neoadjuvant* cemiplimab *Adjuvant* cemiplimab	1 cycle + 8 cycles	30	Number of patients with AEs, DFS, and OS
	NCT04869137	Phase II	Resectable disease	Surgery	*Neoadjuvant* lenvatinib + pembrolizumab *Adjuvant* pembrolizumab	2 cycles + 15 cycles	26	pathological complete response, PFS, and percentage of patients able to complete both neoadjuvant cycles of trial therapy and able to complete planned surgical resection
	NCT04428671	Phase I	High-risk	RT or Surgery	*Neoadjuvant* cemiplimab *Adjuvant* cemiplimab	2 cycles + 18 cycles	20	Pathological response rate
cSCC	NCT04154943 Gross et al., (2022)	Phase II	Stage II to IV	Surgery	*Neoadjuvant* cemiplimab	4 cycles	76	Pathological complete response
	NCT03565783 (Ferrarotto et al., 2021)	Phase II	Recurrent and Resectable Stage II-IV Head and Neck Cutaneous Squamous Cell Cancer	Surgery + /- RT	*Neoadjuvant* cemiplimab	2 cycles	40	ORR
	NCT04620200	Phase II	Resectable, stage III to IVA	Surgery + /- RT	*Neoadjuvant* Arm A: nivolumab Arm B: nivolumab followed by ipilimumab	Arm A: 2 cycles Arm B: 3 cycles	40	Histopathological response rate
	NCT04632433	Phase II	Resectable, high-risk, stage III	Surgery	*Neoadjuvant* cemiplimab *Adjuvant* cemiplimab	2 cycles + 17 cycles	25	MPR rate
	NCT04808999	Phase II	Resectable, high-risk, and treatment naïve disease	Surgery	*Neoadjuvant* pembrolizumab *Adjuvant* pembrolizumab	2 cycles + 15 cycles	30	Pathological complete response rate
	NCT04710498	Phase II	Resectable, advanced disease	Surgery	*Neoadjuvant* atezolizumab	3 cycles	20	Percentage of patients who complete neoadjuvant therapy and surgical resection
	NCT05025813	Phase II	Resectable stage II to IV	Surgery (and RT if >10% viable tumor cells at resection)	*Neoadjuvant* pembrolizumab *Adjuvant (if restaging imaging positive)* pembrolizumab	4 cycles + 17 cycles	27	Pathological response
	NCT05110781	Phase II	Resectable stage III to IV cSCC of the head and neck	Surgery (and RT in case of residual disease)	*Neoadjuvant* atezolizumab *Adjuvant (in case of residual disease)* atezolizumab	2 cycles + 13 cycles	18	Pathological complete response
BCC	NCT04323202	Phase IB	Resectable, advanced BCC of the head and neck	Surgery	*Neoadjuvant* pembrolizumab *Adjuvant* pembrolizumab	2 cycles + 13 cycles	15	Pathological response

Abbreviations: MCC Merkel cell carcinoma, AE adverse events, DFS disease-free survival, OS overall survival, PFS progression-free survival, RT radiotherapy, cSCC cutaneous squamous cell carcinoma, BCC basal cell carcinoma.

metastatic disease.

Pembrolizumab was FDA-approved based on the KEYNOTE-629. This study evaluated pembrolizumab in patients with lacSCC (n = 54) and metastatic/recurrent cSCC (n = 105). In patients with lacSCC, the 1-year ORR and PFS were 50% and 84%, respectively. In the metastatic/recurrent cohort, the ORR was 35% and PFS at 1 year was 78% (Hughes et al., 2021). Grade 3–5 AEs were experienced by 12% of patients, including two treatment-related deaths. The CARSKIN trial also evaluated pembrolizumab in patients with unresectable or metastatic cSCC (n = 57) (Maubec et al., 2020). In contrast to the KEYNOTE-629 trial, the CARSKIN also included patients still eligible for surgery or radiotherapy, raising interest in ICI-implementation in patients still eligible for local treatments.

4.2.3. Adjuvant setting

Similar to MCC, no (neo)adjuvant ICIs are registered for cSCC. There are three ongoing clinical trials in the adjuvant setting (Table 2). Two are large double-blind RCTs assessing cemiplimab and pembrolizumab in patients with high-risk resected cSCC. Furthermore, a phase 2 study in patients with resected cSCC of the head and neck is investigating adjuvant radiotherapy plus pembrolizumab.

4.3. Neoadjuvant setting

In the neoadjuvant setting, eight studies are evaluating ICIs for use in the treatment of resectable cSCC (Table 3). These relatively small studies administer 2–4 ICI cycles prior to surgery. Treatment after surgery varies from standard of care, including radiotherapy or follow-up, to adjuvant ICI treatment. A recent study investigating neoadjuvant cemiplimab showed 40 pCRs (51%) and 10 major pathological responses (13%) in 79 patients with stage III-IVA cSCC (Gross et al., 2022). Grade 3 or higher AEs were observed in 14 patients (18%). The second part of this study also evaluated optional adjuvant cemiplimab treatment, adjuvant radiation therapy or observation only and the approach was determined by the investigator discretion. Another pilot phase II study demonstrated that 11 out of 20 patients with stage III-IVA cSCC who received neoadjuvant cemiplimab had a pCR (Ferrarotto et al., 2021). In the 11 patients with pCR, the planned adjuvant radiotherapy was omitted. One patient with an unreported treatment response also declined adjuvant radiotherapy. None of these non-irradiated 12 patients recurred at a median follow-up of 22.6 months (range: 21.7–26.1.2).

4.3.1. BCC

BCC accounts for approximately 75% of all skin cancers. However, BCCs are not always included in cancer registries, and therefore, incidences are imprecise and possibly underestimated. Approximately 0.8% of the patients with BCC will develop locally advanced disease, and less than 0.6% eventually develop metastatic disease (Table 1) (Goldenberg et al., 2016; Lo et al., 1991). Until recently, systemic treatments for advanced BCC were limited to the hedgehog pathway inhibitors (HHIs); vismodegib and sonidegib. These treatments resulted in response rates and median PFS of $\leq$ 69% and 24.9 months for locally advanced BCC and 39% and 13.1 months for patients with metastatic BCC (Basset-Seguin et al., 2015; Migden et al., 2015; Sekulic et al., 2017; Dummer et al., 2020).

4.3.2. Unresectable or metastatic setting

Cemiplimab is FDA-approved for patients with advanced BCC after HHIs based on a phase 2 trial (Stratigos et al., 2021). The study included patients with locally advanced and metastatic BCC ineligible for further HHIs due to progressive disease or intolerance. In the 84 patients with locally advanced BCC, the ORR was 31% with a median time to response of 4.3 months. The estimated duration of response at 12 months was 85%, with a median follow-up of 15 months. Almost half of the patients experienced grade 3–4 AEs. The interim analysis of the metastatic BCC cohort (n = 28) demonstrated an ORR of 21% with a median time to response of 3.2 months (Lewis et al., 2021).

4.3.3. (Neo)adjuvant setting

No published (neo)adjuvant or ongoing adjuvant ICI studies were identified for BCC (Table 2). One small phase 1 study with neoadjuvant pembrolizumab treatment in patients with resectable BCC of the head and neck is ongoing (Table 3). The primary outcome is the pathological response rate after 4 cycles of treatment followed by surgery. Despite the small size, this study will be the first to indicate potential neoadjuvant ICI efficacy in patients with locally advanced BCC.

5. Discussion and future perspective

In melanoma, the striking efficacy of ICIs is obvious in the metastatic setting, and these drugs are very promising in the neoadjuvant setting (Hamid et al., 2019; Wolchok et al., 2022; Rozeman et al., 2021; Blank et al., 2018). ICI-response rates are at least as high in metastatic/recurrent non-melanoma skin cancers also making neoadjuvant ICI-treatment of great interest in these cancers (Kaufman et al., 2018; D'Angelo et al., 2021; Migden et al., 2020; Stratigos et al., 2021).

Compared to melanoma, cSCC and BCC are associated with an infiltrative rather than invasive growth pattern and this, in combination with the rates of distant metastases make neoadjuvant strategies logical. This is reflected by the number of neoadjuvant studies performed compared to adjuvant studies. In MCC, which does frequently metastasizes, neoadjuvant ICI interest has been fueled by the encouraging outcomes observed with neoadjuvant ICI in melanoma. In addition, neoadjuvant studies are of special interest due to the potential for translational research helping us understand mechanisms of sensitivity and resistance. Moreover, to date, none of the adjuvant ICI-treatments in melanoma or MCC have resulted in improved OS.

The International Neoadjuvant Melanoma Consortium recommends neoadjuvant systemic treatment durations of 6–8 weeks (Amaria et al., 2019). The median time to response in the advanced setting is generally shorter in patients with non-melanoma skin cancers (1.4–3.2 months) than in those with advanced melanoma (2.1–3.3 months). There is, therefore, no rationale for longer treatment schedules in non-melanoma skin cancer, especially considering that prolonged neoadjuvant treatment increases the risk of irresectability in non-responders. Immuno--PET is a non-invasive tool that has the potential to predict and monitor therapy response and may, in the future, help identify neoadjuvantly treated patients who no longer require mutilating surgery, potentially reducing morbidity in this vulnerable patient population (Menzies and Lastoria, 2022). Additionally, biomarkers with the most predictive potential in neoadjuvant melanoma studies, like interferon gamma gene expression signature, should be considered in the non-melanoma skin cancer studies (Rozeman et al., 2021; Amaria et al., 2018).

With ICI-treatment transitioning from the metastatic to the (neo) adjuvant setting, treatment toxicity, possible resistance mechanisms, and associated costs should be taken into account. Toxicity associated with ICIs is often acute and reversible with adequate immunosuppressive treatment. However, for example, endocrine and rheumatic toxicities can persist and require lifelong treatment (Johnson et al., 2022; Rogiers et al., 2019). Chronic immune-related AEs, after ICI cessation, are present in up to 46% of advanced cancer survivors (Patrinely et al., 2020, 2021). Data on long-term toxicity after (neo)adjuvant treatment is still lacking, it may be lower due to shorter treatment duration but warrants further study considering the favorable prognosis of these patients. For the frail, elderly non-melanoma skin cancer patients, functional deficits induced by local treatments may have a larger impact on overall quality of life than long-term immune-related AEs (Fig. 2).

In patients with non-melanoma skin cancers, 41% will develop a second skin cancer within 5 years (Wehner et al., 2015). Patients with hereditary skin cancer syndromes and those receiving immunosuppressive medication are even at higher risk of developing multiple primary skin cancers. Examples of hereditary skin cancer syndromes are

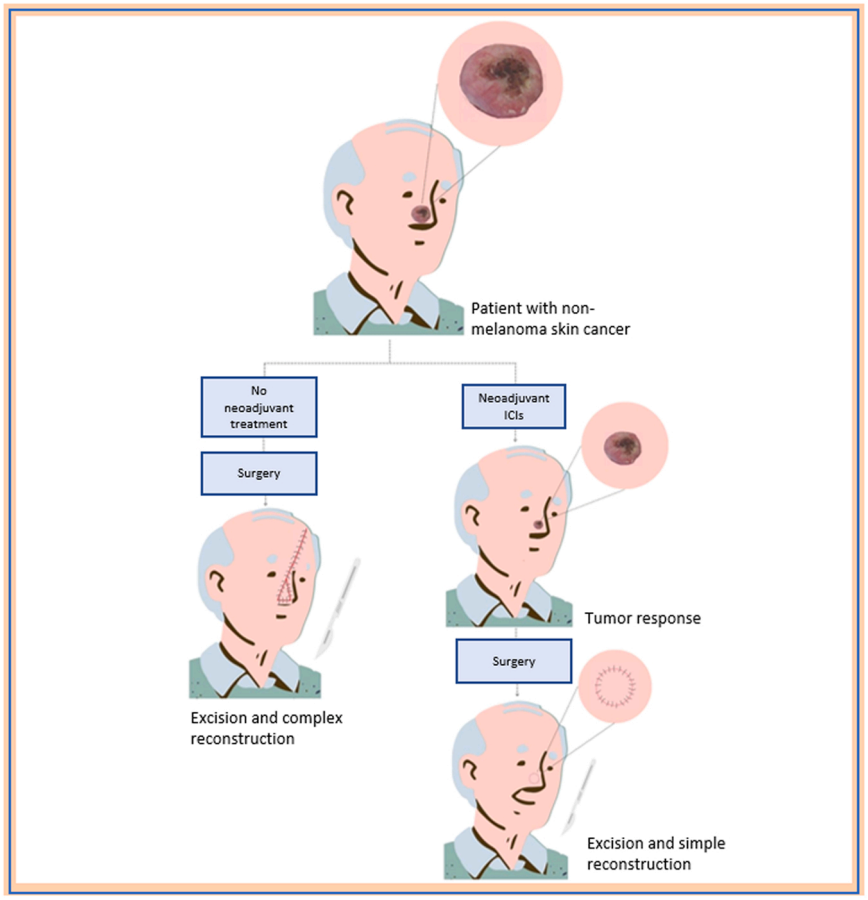

Fig. 2. . The potential of early administration of neoadjuvant immune checkpoint inhibitors in patients with non-melanoma skin cancer.

xeroderma pigmentosum (XP), basal cell nevus syndrome (BCNS), and epidermolysis bullosa (EB) (Jaju et al., 2016). A median of 160 BCCs (range: 0–2200) are diagnosed in the lifetime of a patient with BCNS (Solis et al., 2017). For patients with XP, the risks of developing non-melanoma and melanoma skin cancers are, respectively, 10,000 and 2,000-fold higher than for the general population (Kraemer and DiGiovanna, 2015). ICIs may, in the future, contribute to decreased lifetime skin cancer incidence in these high-risk patients. Three patients with XP had decreased cSCC incidence after ICI-treatment suggesting potential effectiveness for cSCC prevention (Ameri et al., 2019). Case reports of ICI tumor responses in patients with EB have also been reported (Duong et al., 2021; Khaddour et al., 2020). Additional studies are needed to confirm the safety and efficacy of skin tumor prevention with ICIs in patients with hereditary skin cancer syndromes.

Transplant recipients are also at high risk of developing skin cancers due to long-term use of immunosuppressive medication (Pennington and Stasko, 2004). A pooled incidence of non-melanoma skin cancers of 13% has been reported in patients with a renal transplant (Matinfar et al., 2018). In these patients, ICI-treatment can lead to allograft rejection. In a systematic review, allograft rejection occurred in 40% of 83 patients treated with ICIs, with variation in continuation of immunosuppressive medication (d'Izarny-Gargas et al., 2020). An ongoing study (NCT03816332) in 16 kidney transplant recipients with unresectable or metastatic cancer is examining nivolumab combined with tacrolimus and prednisone for immune suppression. Patients who experience cancer progression or allograft loss will receive ipilimumab and nivolumab treatment. This study will provide additional knowledge on the use of ICIs in transplant recipients.

ICI-treatment for skin cancers is moving towards earlier treatment settings. Studies in patients with MCC, cSCC, and BCC need to confirm effectivity of neoadjuvant ICI treatment to determine the real potential to reduce mutilating local treatments and improve survival while maintaining quality of life.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2022.103855.

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