CME Part I: Immune checkpoint inhibitors to treat cutaneous malignancies

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ABSTRACT

As the incidence of cutaneous malignancies continue to rise and their treatment with immunotherapy expands, dermatologists and their patients are more likely to encounter these agents. While blockade of immune checkpoint target proteins (CTLA-4, PD-1, PD-L1) generates an anti-tumor response in a substantial fraction of patients, there is a critical need for reliable predictive biomarkers, as well as approaches to address refractory disease. This article reviews the indications, efficacy, safety profile and evidence supporting checkpoint inhibition as therapeutics for metastatic melanoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma. Pivotal studies resulting in the approval of ipilimumab, pembrolizumab, nivolumab, cemiplimab and avelumab by regulatory agencies for various cutaneous malignancies, as well as ongoing clinical research trials, are discussed.

ABBREVIATIONS USED:

AE: adverse event

BCC: basal cell carcinoma

CPI: checkpoint inhibitor

CR: Complete response

cSCC: cutaneous squamous cell carcinoma

CTLA-4: cytotoxic T-lymphocyte-associated protein-4

FDA: Food and Drug Administration

irAE: immune-related adverse event

MCC: Merkel cell carcinoma

ORR: Objective response rate

PD: Progressive disease

PD-1: programmed cell death-1

PD-L1: programmed cell death ligand-1

PFS: Progression-free survival

PR: Partial response

RR: Response rate

QoL: Quality of Life

SD: Stable disease

TRAE: treatment-related adverse event

INTRODUCTION

Immunotherapy has become a cornerstone of advanced tumor management. Via inhibition of the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1), tumor cells are targeted and indirectly destroyed by activated T cells that infiltrate the tumor microenvironment. The first of the immune checkpoint inhibitors (CPIs) approved was ipilimumab [Yervoy®]; an additional four (nivolumab [Opdivo®], pembrolizumab [Keytruda®], cemiplimab [Libtayo®], and avelumab [Bavencio®] are approved by regulatory agencies for cutaneous malignancies. In addition to melanoma, CPIs are indicated for cutaneous squamous cell carcinoma (cSCC) and Merkel cell carcinoma (MCC). There are currently no CPIs approved for basal cell carcinoma (BCC), cutaneous lymphomas, cutaneous sarcomas, or cutaneous adnexal carcinomas (CACs).

Mechanism of action of immune checkpoint inhibitors

Ipilimumab works by blocking the negative regulator CTLA-4, resulting in increased T helper cells and decreased regulatory T cell (Treg) immunosuppressive activity.[1] Pembrolizumab and nivolumab selectively block PD-1 receptors and suppress its expression by activated T cells, B cells, monocytes, and natural killer cells.[2] Atezolizumab, avelumab, and durvalumab inhibit binding of PD-L1 to PD-1 receptors on T cells, thereby resulting in downregulation of T cell quiescence and reinvigoration of the antitumor immune response[3] (Fig. 1).

Predictive biomarkers of response to immunotherapy

Markers of tumor response to immunotherapy have been investigated;[4] and while some have been associated with increased overall survival (OS) in patients with melanoma, none have been validated. In accordance with the National Comprehensive Cancer Network (NCCN)

Guidelines®, PD-L1 has potential utility in identifying melanoma patients who are more likely to respond to CPIs;[5,6] however, the routine use of PD-L1 expression is not recommended for treatment decisions.[5,7] Several additional immunotherapy biomarkers are under development for melanoma, including relative eosinophils and basophils count, low absolute monocytes, lactate dehydrogenase and neutrophil-to-lymphocyte ratio.[8-10] The occurrence of immune-related adverse events (irAEs) has also been implicated as potentially useful in tumor response to CPIs.[11] In addition, a decrease in regulatory T-cells and an increase in activated CD8 positive cells have been cited.[12-14] In advanced cSCC, although PD-L1 appears to be increased in high risk cSCC compared to normal skin specimens, its levels do not appear to correlate with the antitumor activity of PD-1 blockade.[15-17] However, a higher tumor mutational burden is more commonly observed in immunocompromised cSCC patients.[18-20] No predictors of response of MCC to CPIs are available yet.

MELANOMA

Key points

- Ipilimumab, pembrolizumab, and nivolumab are approved for advanced melanoma.
- In melanoma, combination therapy with nivolumab and ipilimumab results in higher overall survival compared to ipilimumab alone.
- Nivolumab and pembrolizumab have each shown superior overall survival, with a better safety profile than ipilimumab.

Melanoma of the skin, despite its rising incidence and lower prevalence compared to other cutaneous malignances, is one of the most aggressive forms of cancer. Non-invasive melanoma (melanoma in situ) has a good surgical prognosis; however, advanced melanoma lacks curative treatment options. Three CPIs are currently available to treat advanced melanoma: ipilimumab, nivolumab, and pembrolizumab.

Ipilimumab: anti-CTLA-4 therapy for advanced melanoma

Based on the improved overall survival (OS) results of the MDX010-20 phase 3 trial (Table I), ipilimumab (anti-CTLA-4) was approved in 2011, becoming the first CPI to be indicated for the treatment of nonresectable or metastatic melanoma (Fig. 2).[21] Ipilimumab was found to elicit a dose-dependent effect on efficacy and safety measures, lending support to further studies at a dose of 10 mg/kg.[22] However, while the 10 mg/kg dosing regimen of ipilimumab does result in significantly longer OS than does ipilimumab 3 mg/kg, it also leads to an increased frequency of treatment-related adverse events (TRAEs).[23] In 2015, as significantly improved recurrence-free survival (RFS) for patients with completely resected high-risk stage III melanoma was observed in the EORTC 18071 phase 3 trial, ipilimumab was approved for this

indication (Fig. 2). Significantly higher rates of RFS, OS, and distant metastasis-free survival (DMFS) compared to placebo were observed; [24-26] and the frequency of irAEs (Table 1) was consistent with that observed in advanced melanoma.[21,26] However, the adverse event profile was worse in the EORTC trial than in the MDX010-20 trial, in particular for endocrinopathies.

Pembrolizumab: anti-PD-1 therapy for advanced melanoma

In September 2014, pembrolizumab was the first PD-1 inhibitor approved for patients with unresectable or ipilimumab-refractory advanced melanoma following treatment with a BRAF inhibitor if positive for the BRAF V600 mutation (Fig.).[27] The phase 1 trial demonstrated that pembrolizumab was safe and efficacious at both doses of 2 mg/kg and 10 mg/kg every 3 weeks (Table II).[28] In December 2015, based on the results of the phase 3 KEYNOTE-006 trial, which showed a substantial prolonged OS, PFS, and less high-grade toxicity than did ipilimumab (Table II),[29] the United States Food and Drug Administration (FDA) expanded the approval to include frontline treatment of patients with advanced melanoma with pembrolizumab regardless of *BRAF* status (Fig. 2). In February 2019, as per impactful results from the EORTC1325 / KEYNOTE-054 phase 3 trial showing improved RFS of pembrolizumab over placebo (Table II),[30] pembrolizumab was approved for the adjuvant treatment of high-risk stage III melanoma patients with resected lymph nodes (Fig. 2).

Nivolumab: anti-PD-1 therapy for advanced melanoma

Following the results of the CHECKMATE-037 phase 3 trial[31] (Table III), in which nivolumab led to a greater proportion of confirmed objective responses and fewer toxic effects compared to chemotherapy in patients with ipilimumab- and BRAF inhibitor-refractory melanoma, the FDA granted accelerated approval in December 2014[32] (Fig. 2). The following

year, after a favorable benefit-risk profile associated with significant improvements in OS and PFS (as compared with dacarbazine) was demonstrated by the phase 3 trial[33] (Table III), nivolumab received additional FDA approval as first-line single agent treatment of patients with BRAF(V600) wild-type, unresectable or metastatic melanoma[34] (Fig. 2).

In December 2017, as further improvements in RFS and a lower rate of grade 3 or 4 adverse events were seen in the CHECKMATE-238 phase 3 trial of 906 patients with resectable high risk and advanced melanoma[35] (Table III), nivolumab was approved as adjuvant therapy (Fig. 2). Since then, long-term favorable efficacy and tolerability perseveres in patients with advanced or recurrent melanoma who were treated with nivolumab, irrespective of melanoma type,[36] with or without BRAF mutations.[37,38]

Nivolumab plus ipilimumab: combination therapy for advanced melanoma

In 2015, the results of the CheckMate-069 phase 2 trial[39] led to accelerated FDA approval of the first-ever immunotherapy combination of nivolumab plus ipilimumab for patients with BRAF V600 wild-type, unresectable or metastatic melanoma (Fig. 2). Among 109 patients, the combination had a response rate (RR) of 60% compared to 11% for ipilimumab alone, and an acceptable safety profile (Table IV).[39] Afterward, based on longer PFS rates observed with combination immunotherapy as opposed to ipilimumab alone on the CheckMate-067 phase 3 trial, ipilimumab plus nivolumab was granted accelerated approval in January 2016 for patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma (Fig. 2).[40]

Among patients with advanced melanoma, therapy with nivolumab plus ipilimumab or nivolumab alone results in longer progression-free and OS than with ipilimumab alone[6,41] (Fig.

4); and according to the most recently published data, a sunstained long-term OS rate has been observed at 5 years in the nivolumab-plus-ipilimumab (52%) versus nivolumab (44%) versus ipilimumab group (26%).[6] However, the nivolumab plus ipilimumab combination results in a high degree of side effects; and choosing which patients should receive combination immunotherapy and which patients should receive nivolumab or pembrolizumab alone is a major clinical challenge.

CUTANEOUS SQUAMOUS CELL CARCINOMA

Key points

- Cemiplimab is the only approved CPI for cSCC.
- Pembrolizumab demonstrated antitumor activity against cSCC in a phase 2 trial.
- Most patients with cSCC do not respond to immunotherapy.

cSCC is the second most common cutaneous malignancy.[42] Despite excellent prognosis, 4% of cSCC are unresectable and 1.5% of patients die from the disease.[43] Until recently, there was no accepted standard of care for advanced cSCC. The use of CPIs in cSCC attracts considerable interest as cSCC has high mutational burden and is more commonly observed in immunosuppressed patients.[18-20]

In 2018, based on the results of the EMPOWER-CSCC-1 and NCT02383212 trials (Table V), cemiplimab, an anti-PD-1 agent, became the first approved CPI for cSCC (Fig. 3). The most recent update of the EMPOWER-CSCC-1 phase 2 trial[44] reports a long-lasting antitumor effect and favorable safety profiles in patients with metastatic cSCC.[45] The NCT02383212 phase 1 trial has also demonstrated a positive risk/benefit ratio with durable antitumor response in advanced cSCC (Table V).[46]

Pembrolizumab is being evaluated as first-line therapy in patients with unresectable cSCC in the NCT02883556 trial.[17] Initial results showed a promising ORR of 38.5% at 15 weeks of with a median PFS of 8.4 months. AEs occurred in 67% of patients and caused discontinuation in 10% of patients. Eight percent of patients had severe AEs, including cholestasis and colitis. Retrospective studies and case reports of pembrolizumab for cSCC have shown varying responses.[15,47-52] The efficacy of CPIs in immunosuppressed patients is not well studied.[53]

Favorable responses to CPIs have been reported in transplant recipients either with or without graft rejection.[47,48] Optimal immunosuppressive regimens that promote graft preservation without dampening CPI antitumor activity would greatly benefit this group of patients.

Nivolumab for cSCC has only been studied in case reports, showing benefit in recurrent cSCC. AEs include weight loss, nausea, fatigue, hyponatremia, hip pain, and hyperglycemia with one death due to arrhythmia.[50,51,54,55] Data on ipilimumab for cSCC is limited, with one case report demonstrating some efficacy when used in conjunction with radiotherapy in a patient with metastatic cSCC and metastatic melanoma.[56] Chemotherapy and radiotherapy used concurrently with CPIs have shown efficacy in refractory cSCC[55,57] and could be utilized to further improve the antitumor activities of immunotherapy.

MERKEL CELL CARCINOMA

Key points

- Avelumab and pembrolizumab are approved for MCC.
- Nivolumab showed efficacy against MCC with favorable safety profile in an ongoing trial.
- The NCCN recommends avelumab, pembrolizumab and nivolumab as first-line therapies for advanced MCC, prior to chemotherapy.

MCC is a rare and aggressive neuroendocrine skin cancer associated with Merkel cell polyomavirus (MCPyV), ultraviolet radiation exposure, immunosuppression, and advanced age.[58] Excision followed by radiotherapy is considered the first-line treatment for primary MCC. Before immunotherapy, chemotherapy was the only systemic treatment available for advanced MCC,[58] which despite a good initial response in nearly 90% of patients, has a short-lived efficacy (~90 days). Currently, CPIs have emerged as front-line therapies for advanced MCC with about 50% of patients demonstrating a durable response, although not without considerable toxicity.

In 2017, on the basis of durable responses and favorable safety profiles observed in the JAVELIN Merkel 200 trial part A, avelumab became the first approved treatment for metastatic MCC (Table V);[59,60] and recently, part B of this trial showed good tolerance of the anti-PD-L1 agent as first-line therapy for metastatic MCC (Table V).[61] In 2018, pembrolizumab was approved for first-line treatment of advanced MCC in the KEYNOTE-017 trial[62] (Table V), which in addition to positive CPI-associated anti-tumor efficacy and safety outcomes, also resulted in glucocorticoids having no effect on tumor response among patients with severe AEs.[62] The expanded NCT02267603 trial further strengthened the efficacy of pembrolizumab as first-line treatment for advanced MCC (Fig. 5).[63] The CheckMate 358 trial with 25 patients investigated

nivolumab for advanced MCC, resulting in a 68% ORR and more than two thirds with AEs.[64] In the above studies, PD-L1 expression and MCPyV status did not appear to correlate with clinical responses.[59,60,62,64]

The use of avelumab, pembrolizumab, and nivolumab for advanced metastatic MCC has also been reported in cases studies, with varying responses.[65-74] Serious AEs include central diabetes insipidus[66], pneumonia, autoimmune hepatitis,[68] cytokine release syndrome,[74] and thrombocytopenia.[75] Ipilimumab has been studied less frequently against MCC, with inconclusive antitumor activity.[76] In addition, ipilimumab did not demonstrate activity as adjuvant therapy for resected MCC.[77] Despite the success of CPIs in treating MCC, many patients do not respond, or develop resistant disease following an initial response; however, the use of combinatorial or sequential CPIs has shown activation of anti-tumor immunity in a subset of non-responders,[78] which represents a promising therapeutic approach for patients who do not persistently benefit from CPI treatment in this population.

OTHER CUTANEOUS NEOPLASMS

Key points

- There is no CPI approved for BCC, cutaneous lymphomas, cutaneous sarcomas, or CAC.
- In small studies and case reports, anti-PD1 therapy appears to be efficacious in BCC, certain subsets of cutaneous lymphomas, and cutaneous sarcomas.

Basal cell carcinoma

BCC is the most common human cancer with increasing incidence. A small subset of BCC progresses to locally advanced and metastatic tumors and requires aggressive systemic treatments.[79,80] Immunotherapy is anticipated to be effective in BCC as it bears the highest mutational burden of any human cancer.[81]

Pembrolizumab showed anti-tumor activity against advanced BCC in a phase 1b trial, in which nine patients received pembrolizumab monotherapy and seven patients received pembrolizumab plus vismodegib.[82] The ORRs at 18 weeks were 44% and 29%, and the one-year PFSs were 62% and 83% for the monotherapy versus dual therapy group, respectively. Thus, the RR of the dual therapy was not superior to the monotherapy group. Pembrolizumab was well tolerated with dermatitis and fatigue being the most common AEs.[82] The use of pembrolizumab in BCC has also been reported in five case reports with clinical responses ranging from DP[83] to PR[16,84,85] and CR.[83,86] There was only one report of subclinical hypothyroidism[84] and sarcoid-like lymph node reaction.[16] Cemiplimab[87] and nivolumab[88,89] have also shown efficacy against advanced BCC without serious AEs.

Cutaneous lymphomas

Cutaneous T cell lymphomas (CTCL) involve extensive infiltration of malignant T cells into the skin and lack effective treatment for advanced disease.[90] Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common CTCL subtypes, with cells expressing high level of PD-1, PD-L1 and CTLA-4, suggesting a role of CPIs in targeting the disease.[91,92]

As demonstrated by a 15% ORR in 13 patients with MF and 0% ORR in 2 patients with SS in a phase 1b trial, nivolumab has a limited antitumor activity against CTCL.[93] AEs occurred in 65% of patients, with 15% discontinuing treatment due to severe AEs, including pneumonitis, sepsis, and myositis. A phase 2 study of pembrolizumab for 24 patients with advanced CTCL demonstrated a 38% ORR.[94,95] While there was no significant association between tumor response and the expression of PD-1, PD-L1, or infiltrating $CD8^+$ T cells, pembrolizumab was well-tolerated; serious AEs included grade 2 pneumonitis and grade 3 diarrhea secondary to steroid-refractory duodenitis.[94] Curiously, 53% patients with SS experienced skin flare reactions, characterized by a transient worsening of erythroderma and pruritus.[95] This reaction correlated with PD-1 expression on Sézary cells but did not associate with subsequent clinical responses. The use of ipilimumab for CTCL has been reported in only two case reports with conflicting responses and requires further investigation.[96,97]

Cutaneous sarcomas

Cutaneous sarcomas are a rare and heterogenous group of skin mesenchymal spindle cell tumors with good prognosis for early disease. There is a lack of effective therapy for patients with advanced diseases.[98] In a phase 2 trial,[99] pembrolizumab did not show benefit in patients with undifferentiated pleomorphic sarcoma (UPS). In the NCT01295827 trial with 10 UPS patients, there were 10% CR, 30% PR, 30% SD, and 30% PD.[100] Among the 10 patients with

liposarcoma in the same trial, there were 0%CR, 2%PR, 40%SD, and 40% PD. The most frequent grade 3 or worse AE was anemia and other hematologic abnormality, and 6% of patients discontinued therapy due to toxicity, including nephritis and pneumonitis.

Kaposi sarcoma (KS) is linked to human herpesvirus 8 infection and often observed in immunosuppressed patients, suggesting that it might be a good target for CPIs. In a series of 9 HIV positive KS patients who received nivolumab (8) or pembrolizumab (1), the ORR was 66%. The most common side effects include fatigue, pruritus, muscle/joint ache, abdominal discomfort, and onycholysis.[101] Pembrolizumab also has antitumor activity against HIV-negative, classic KS[69,102]. Nivolumab is also effective in HIV-negative KS patients with the only notable AE being hyponatremia due to low cortisol level.[103] Pembrolizumab has also been attempted in two separate cases of angiosarcoma in which the patients either achieved CR[104] or durable PR with autoimmune hepatitis that required prednisone treatment.[105] There are no data regarding the efficacy of CPIs against dermatofibrosarcoma protuberans or cutaneous leiomyosarcoma.

Cutaneous adnexal carcinomas

CACs are a heterogenous group of malignant neoplasms that display differentiation towards skin-primary adnexal structures, and which currently have limited effective treatment for metastasis.[106] High expression levels of PD-L1 have been reported in sebaceous carcinoma.[73,107] In two case reports, the use of pembrolizumab with or without chemotherapy demonstrated clinical efficacy against metastatic sebaceous carcinoma.[108,109] One patient remained on pembrolizumab despite requiring systemic corticosteroids due to secondary adrenal insufficiency.[108]

FUTURE DIRECTIONS AND CONCLUSIONS

As the field of immunotherapeutics continues to revolutionize the treatment of cutaneous malignances, blocking antibodies to CTLA-4 and PD-1/PD-L1 have improved survival for many patients. For melanoma, ipilimumab in combination with nivolumab or nivolumab or pembrolizumab alone are standard front-line treatment options. Several trials are in development to investigate the role of anti-PD-L1 agents in metastatic melanoma,[110,111] including atezolizumab and avelumab.

Cemiplimab is the only approved CPI for cSCC, and there is a critical need for improved therapies that can better target the advanced stage of this cutaneous malignancy. Although pembrolizumab has demonstrated antitumor activity against cSCC in a phase 2 trial, most patients do not respond to immunotherapy. For MCC, the NCCN guidelines recommend avelumab, pembrolizumab, and nivolumab as first-line therapies, ahead of chemotherapy. Although the data is limited and there is no CPI approved for BCC, cutaneous lymphoma, cutaneous sarcoma or CACs,[112] evidence from small observational studies and case reports suggest the potential utility of anti-PD-1 therapy in BCC and certain subsets of cutaneous lymphoma and cutaneous sarcoma.

Despite exceptional clinical benefits observed with CPIs in cutaneous malignancies, their associated irAEs require careful monitoring. As such, expanding immunotherapy clinical research efforts can lead to identifying new CPI regimens that improve anti-tumor responses and reduce the incidence and severity of irAEs. Furthermore, striving to achieve a more concrete understanding of predictive markers of response and mechanisms of resistance to

anti-CTLA-4 and anti-PD-1/PD-L1 therapies, may help identify subsets of patients who are more likely to respond to therapy with these agents.

FIGURE LEGENDS

Figure 1. Immune checkpoint inhibitors reinvigorate antitumor immune responses.

(A) Cytotoxic T cells in the tumor microenvironments express high level of inhibitory receptors such as CTLA-4 and PD-1. In the absence of immune checkpoint inhibitors, ligation of CTLA-4 and PD-1 by B7 or PD-L1 expressed by antigen presenting cells or tumor cells dampens the cytotoxic functions of T cells and inhibits their antitumor activity. **(B)** Anti-CTLA-4, anti-PD-1, and anti-PD-L1 can bind CTLA-4, PD-1, and PD-L1 and prevent the PD-1/PD-L1 and CTLA-4/B7 interactions, which restore the antitumor functions of cytotoxic T cells. **Abbreviations:** APC, antigen presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; B7, B7 protein.

Figure 2. Timeline history of approved immune-checkpoint inhibitors to treat melanoma

Level IA evidence includes evidence from meta-analysis of randomized controlled trials.

level IB evidence includes evidence from at least one randomized controlled trial.

Level IIA evidence includes evidence from at least one controlled study without randomization.

Level IIB evidence includes evidence from at least one other type of experimental study.

Level III evidence includes evidence from nonexperimental descriptive studies (i.e. comparative, correlation & case-control).

Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Figure 3. Timeline history of approved immune-checkpoint inhibitors to treat cutaneous squamous cell carcinoma and Merkel cell carcinoma

Level IA evidence includes evidence from meta-analysis of randomized controlled trials.

level IB evidence includes evidence from at least one randomized controlled trial.

Level IIA evidence includes evidence from at least one controlled study without randomization.

Level IIB evidence includes evidence from at least one other type of experimental study.

Level III evidence includes evidence from nonexperimental descriptive studies (i.e. comparative, correlation & case-control).

Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Figure 4. Durable anti-tumor response after treatment with ipilimumab and nivolumab in a patient with BRAF wildtype melanoma, metastatic to the lungs. **(A)** February 2016 **(B)** May 2016 **(C)** January 2018. Adverse events affecting multiple organs were observed and successfully managed with corticosteroids.

Figure 5. **(A, B)** Complete clinicopathologic response at three weeks after the first dose of pembrolizumab in a patient with Merkel cell carcinoma. **(C)** Findings on histopathology reveal dermal fibrosis and mixed lymphocytic inflammation with negative synaptophysin and chromogranin stains (not shown), both of which were expressed at pre-treatment with pembrolizumab.

Table I. Major studies investigating ipilimumab [Yervoy®] (anti-CTLA-4 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ Identifier(s)	Patients	Randomization / Dosing regimen(s)	Primary endpoint(s) / Results	Median follow-up duration	Common severe (grade 3-5) irAEs:
2004-2008	Phase 3, MDX-010, NCT00094653	Previously treated, unresectable stage III or IV melanoma patients, n=676	Ipilimumab 3 mg/kg + gp100 every 3 weeks, for 4 treatments, n=403 Ipilimumab 3 mg/kg alone every 3 weeks for 4 treatments, n=137 gp100 alone every 3 weeks for 4 treatments, n=136	OS: Ipilimumab alone, 10.1 mo. Ipilimumab + gp100, 10 mo. gp100 alone, 6.4 mo.	Ipilimumab alone: 27.8 mo. Ipilimumab + gp100: 21 mo. gp100 alone: 17.2 mo.	Ipilimumab (+/- gp100): 10-15% gp100 alone: 3%
2008-2011	Phase 3, EORTC 18071, NCT00636168	Previously untreated resected stage III cutaneous melanoma patients, n=951	Ipilimumab, 10 mg/kg every 3 weeks for 4 doses; then every 3 months for up to 3 years, n=475 Placebo every 3 weeks for 4 doses; then every 3 months for up to 3 years, n=476	RFS: Ipilimumab: 26.1 mo. Placebo: 17.1 mo. 3-year RFS: Ipilimumab: 46.5% Placebo: 34.8%	2.74 years	Ipilimumab vs. placebo: GI: 16% vs. <1% Hepatic: 11% vs. <1% Endocrine: 8% vs. 0%

Abbreviations: glycoprotein 100 peptide vaccine (gp100); Overall survival (OS); Recurrence free survival (RFS)

Table II. Major studies investigating pembrolizumab [Keytruda®] (anti-PD-1 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ Identifier	Patients	Randomization / Dosing regimen(s)	Primary endpoint / Results	Median follow-up duration	Common severe (grade 3-5) irAEs:
2012-2013	Phase 1, KEYNOTE-001, NCT01295827	Previously treated, ipilimumab-refractory advanced melanoma, n=173	Pembrolizumab 2 mg/kg every 3 weeks, n=89 Pembrolizumab 10 mg/kg every 3 weeks, n=84	ORR: Pembrolizumab 2 mg/kg: 26% Pembrolizumab 10 mg/kg: 26%	8 mo.	Pembrolizumab 2 mg/kg: 3% Pembrolizumab 10 mg/kg: 0%
2013-2014	Phase 3, KEYNOTE-006, NCT01866319	Previously treated and untreated (65.8%) advanced melanoma patients, n=834	Pembrolizumab 10 mg/kg every 2 weeks, n=279 Pembrolizumab 10 mg/kg every 3 weeks, n=277 Ipilimumab 3 mg/kg (4 doses) every 3 weeks, n=278	6 mo-PFS, 12-mo OS, RR: Pembrolizumab 10 mg/kg every 2 weeks: 47.3%, 74.1%, 33.7% Pembrolizumab 10 mg/kg every 3 weeks: 46.4%, 68.4%, 32.9% Ipilimumab 3 mg/kg (4 doses) every 3 weeks: 26.5%, 58.2%, 11.9%	7.9 mo.	Pembrolizumab 10 mg/kg every 2 weeks: 13.3% Pembrolizumab 10 mg/kg every 3 weeks: 10.1% Ipilimumab 3 mg/kg (4 doses) every 3 weeks: 19.9%
2015-2016	Phase 3, EORTC132, KEYNOTE-054, NCT02362594	Previously treated, completely resected stage III melanoma patients, n=1019 PD-L1 positive subgroup, n=853	Pembrolizumab 200 mg every 3 weeks for a total of 18 doses (~1 year), n=514 Placebo every 3 weeks for a total of 18 doses (~1 year), n=505	RFS in overall intention to treat group: Pembrolizumab: 75.4% Placebo: 61.0% 1-year rate of RFS in PD-L1 positive subgroup: Pembrolizumab: 77.1% Placebo: 62.6%	15 mo.	Pembrolizumab: 14.7% Placebo: 3.4%

Abbreviations: Overall survival (OS); Recurrence free survival (RFS); Overall response rate (ORR); Progression free survival (PFS); Response rate (RR)

Table III. Major studies investigating nivolumab [Opdivo®] (anti-PD-1 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ Identifier	Patients	Randomization / Dosing regimen(s)	Primary endpoint / Results	Median follow-up	Common severe (grade 3-5) irAEs:
2012-2014	Phase 3, CheckMate 037, NCT01721746	Previously treated, unresectable or metastatic ipilimumab-refractory melanoma; or (if BRAF V600 mutation-positive) ipilimumab + BRAF inhibitor-refractory melanoma, n=631	Nivolumab 3 mg/kg every 2 weeks, n=272 Chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 combined with carboplatin area under the curve 6 every 3 weeks), n=133	OR: Nivolumab (n=120): 37.1% Chemotherapy (n=47): 10.6%	8.4 mo.	Nivolumab: 5% Chemotherapy: 9%
2013-2014	Phase 3, Checkmate 066, NCT01721772	Previously untreated melanoma without BRAF mutation, n=418	Nivolumab 3 mg/kg every 2 weeks and dacarbazine-matched placebo every 3 weeks, n=210 Dacarbazine 1000 mg/m^2 BSA every 3 weeks and nivolumab-matched placebo every 2 weeks, n=208	1-year-OS: Nivolumab: 72.9% Dacarbazine: 42.1%	Nivolumab: 8.9 mo. Dacarbazine: 6.8 mo.	Nivolumab: 11.7% Dacarbazine: 17.6%
2015	Phase 3, Checkmate 238, NCT02388906	Completely resected, advanced (stage IIIb, IIIc or IV) melanoma patients, n=906	Nivolumab 3 mg/kg every 2 weeks, n=453 Ipilimumab, 10 mg/kg every 3 weeks for 4 doses; then every 12 weeks, n=453	RFS in overall intention to treat group: Nivolumab: 70.5% Ipilimumab: 60.8%	18 mo.	Nivolumab: 14.4% Ipilimumab: 45.9%

Abbreviations: Investigator's choice of chemotherapy (ICC); body surface area (BSA)

Table IV. Major studies investigating combination of nivolumab [Opdivo®] plus ipilimumab [Yervoy®] (anti-PD-1 + anti-CTLA-4 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ Identifier	Patients	Randomization / Dosing regimen(s)	Primary endpoint / Results	Median follow-up	Grade 3-4 irAEs
2013-2014	Phase 2, CheckMate-069, NCT01927419	Untreated metastatic melanoma patients, n=142	Ipilimumab 3 mg/kg + nivolumab 1 mg/kg (combination group) once every 3 weeks for four doses, followed by nivolumab 3 mg/kg every 3 weeks for four doses or placebo every 2 weeks, n=95 Ipilimumab 3 mg/kg + placebo, followed by nivolumab 3 mg/kg every 3 weeks for four doses or placebo every 2 weeks, n=47	OR among patients with BRAF V600 wild type tumors: Ipilimumab + nivolumab (n=72): 61% Ipilimumab + placebo (n=37): 11%	11 mo.	Combination group: 54% Ipilimumab monotherapy: 24%
2013-2014	Phase 3, CheckMate-067, NCT01844505	Untreated, unresectable stage III or IV melanoma patients, n=945	Nivolumab alone, n=316 Nivolumab + ipilimumab, n=314 Ipilimumab alone, n=315	PFS Nivolumab + ipilimumab: 11.5 mo. Nivolumab alone: 6.9 mo. Ipilimumab alone: 2.9 mo.	12.2-12.5 mo.	Nivolumab alone: 16.3% Nivolumab + ipilimumab: 55% Ipilimumab alone: 27.3%

Table V. Major studies investigating immune-checkpoint inhibitors to treat cutaneous malignancy

Type of cutaneous malignancy	Investigating agents/ Regimen	Trial identifier/ Current phase	Patient population	Median follow-up	Efficacy	Adverse event	
						Common	Rare/Serious
Cutaneous squamous cell carcinoma	Cemiplimab [Libtayo®] 3mg/kg q2w	EMPOWER-CSCC-1 NCT02760498 Phase 2 trial	59 patients with metastatic cSCC	16.5 months	ORR, 49.2% CR, 6.8% PR, 42.4% SD, 13.5% PD, 37.3% PFS, 18.4 months	Diarrhea (28.8%), fatigue (25.4%), nausea (23.7%).	Cellulitis, pneumonitis, hypercalcemia, pleural effusion and death
	Cemiplimab [Libtayo®] 3mg/kg q2w	NCT02383212 Phase 1 trial with expansion cohort	26 patients with locally advanced or metastatic cSCC	11.0 months	ORR, 50.0% CR, 0.0% PR, 50.0% SD, 23.0% PD, 27.0% PFS, not reported	Fatigue (26.9%), constipation (15%), decreased appetite (15%), diarrhea (15%), nausea (15%), constipation (15%), hypercalcemia (15%), hypophosphatemia (15%), urinary tract infection (15%)	Asthenia, maculopapular rash, increased alanine aminotransferase, increased aspartate aminotransferase, adrenal insufficiency, and myalgia
Merkel cell carcinoma	Avelumab [Bavencio®] 10mg/kg q2w	JAVELIN Merkel 200 NCT02155647 Phase 2 (Part A) trial	88 patients with stage IV MCC that is refractory to chemotherapy	16.4 months	ORR, 33.0% CR, 11.4% PR, 21.6% SD, 10.2% PD, 36.4% PFS, 2.7 months	Fatigue (24%), infusion-related reactions (17%), diarrhea (9%), nausea (9%), asthenia, (9%), rash (7%), decreased appetite (6%)	Lymphopenia (2%), increased serum creatine phosphokinase (1%), aminotransferase (1%), and cholesterol (1%) levels, enterocolitis (1%), chondrocalcinosis (1%), synovitis (1%), and interstitial nephritis (1%)
		JAVELIN Merkel 200 NCT02155647 Phase 2 (Part B) trial	39 patients with metastatic MCC who had not received prior systemic treatment	5.1 months	ORR, 62.1% CR, 13.8% PR, 48.3% SD, 10.3% PD, 27.6% PFS, 9.1months	Infusion-related reactions (23.1%)	Cholangitis, elevated aspartate and alanine aminotransferase levels, paraneoplastic syndrome, gait disturbance, paraneoplastic encephalomyelitis, and polyneuropathy
	Pembrolizumab [Keytruda®] 2mg/kg q3w	KEYNOTE-017 NCT02267603 Phase 2 trial	50 patients (26 from original cohort and 24 from expansion cohort) with advanced MCC who had not received systemic treatment	14.9 months	ORR, 56.0% CR, 24.0% PR, 32.0% SD, 10.0% PD, 32% PFS, 16.8 months	Fatigue and laboratory abnormalities	Myocarditis, elevated liver enzyme, death

Abbreviations: ORR: Objective response rate; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; PFS: Progression-free survival

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Figure 1

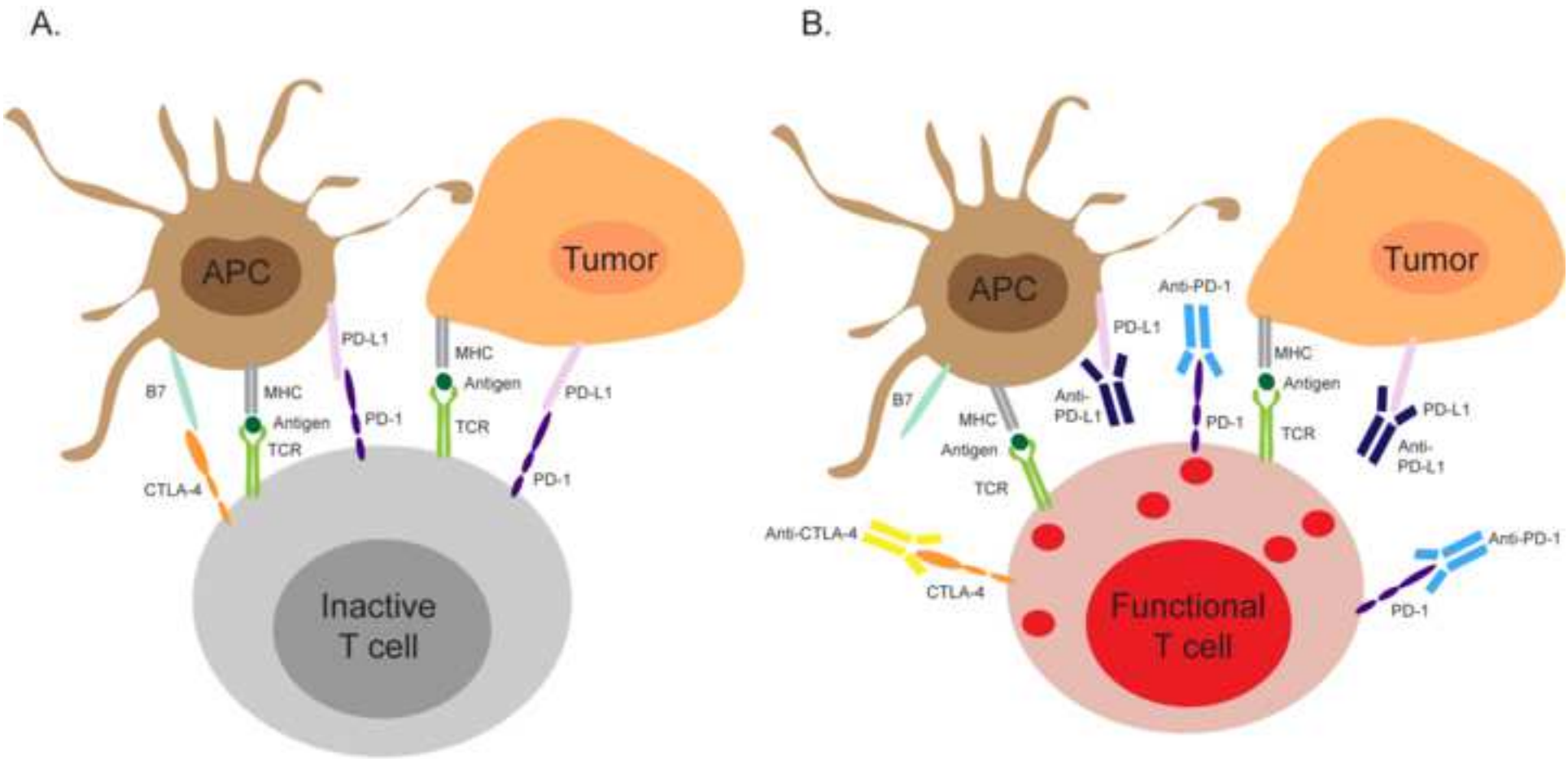


Figure 2

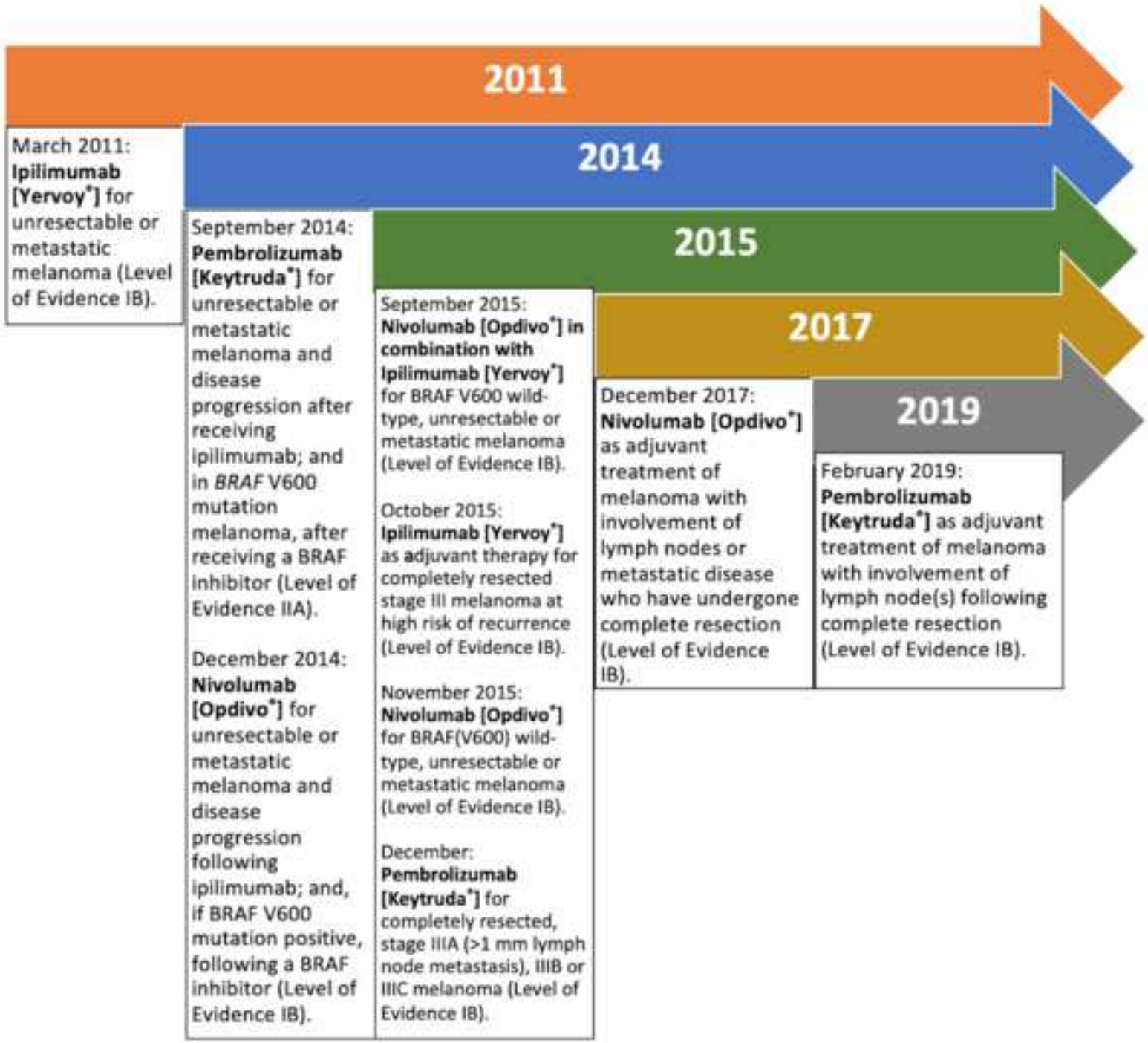
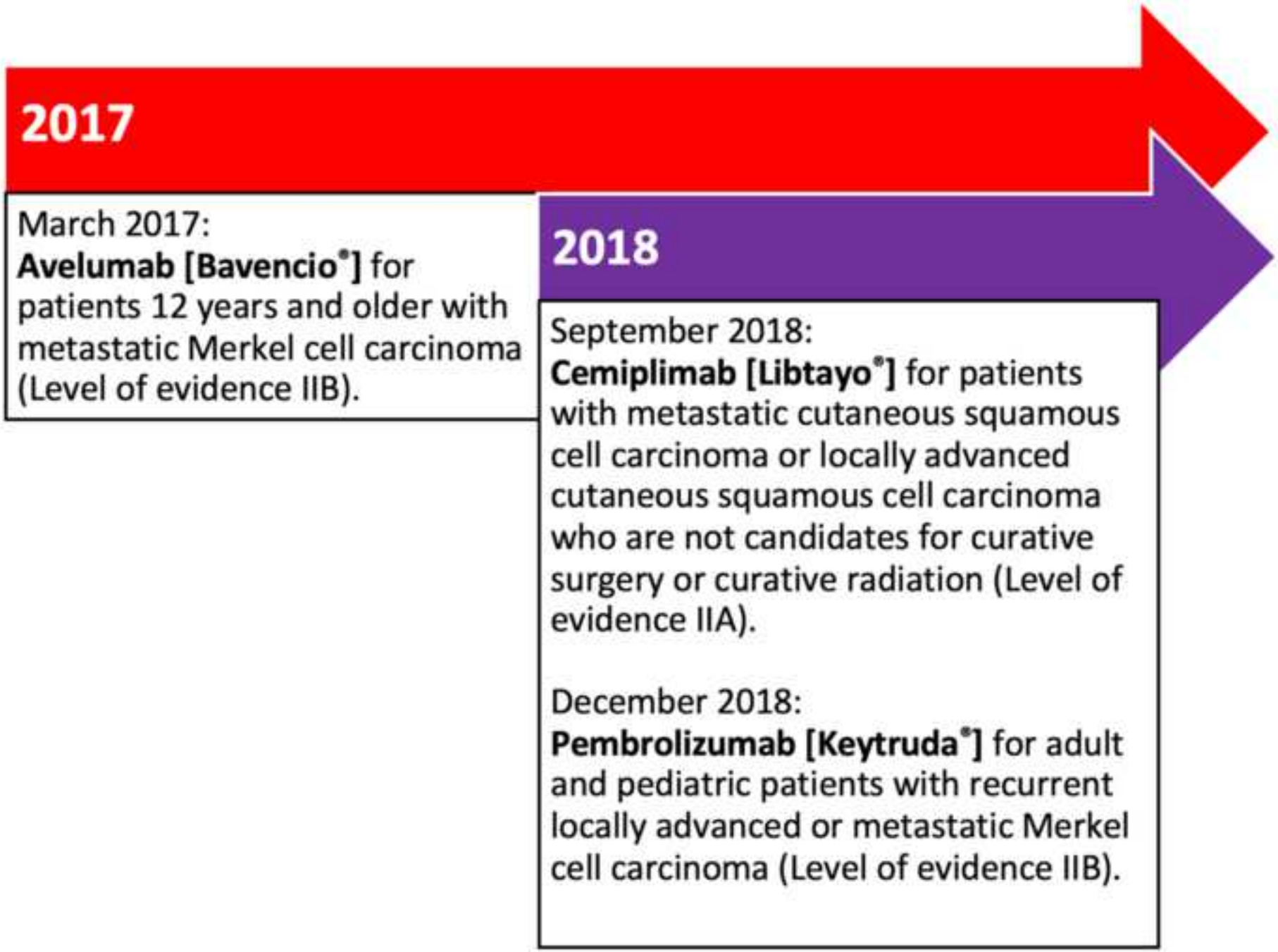


Figure 3



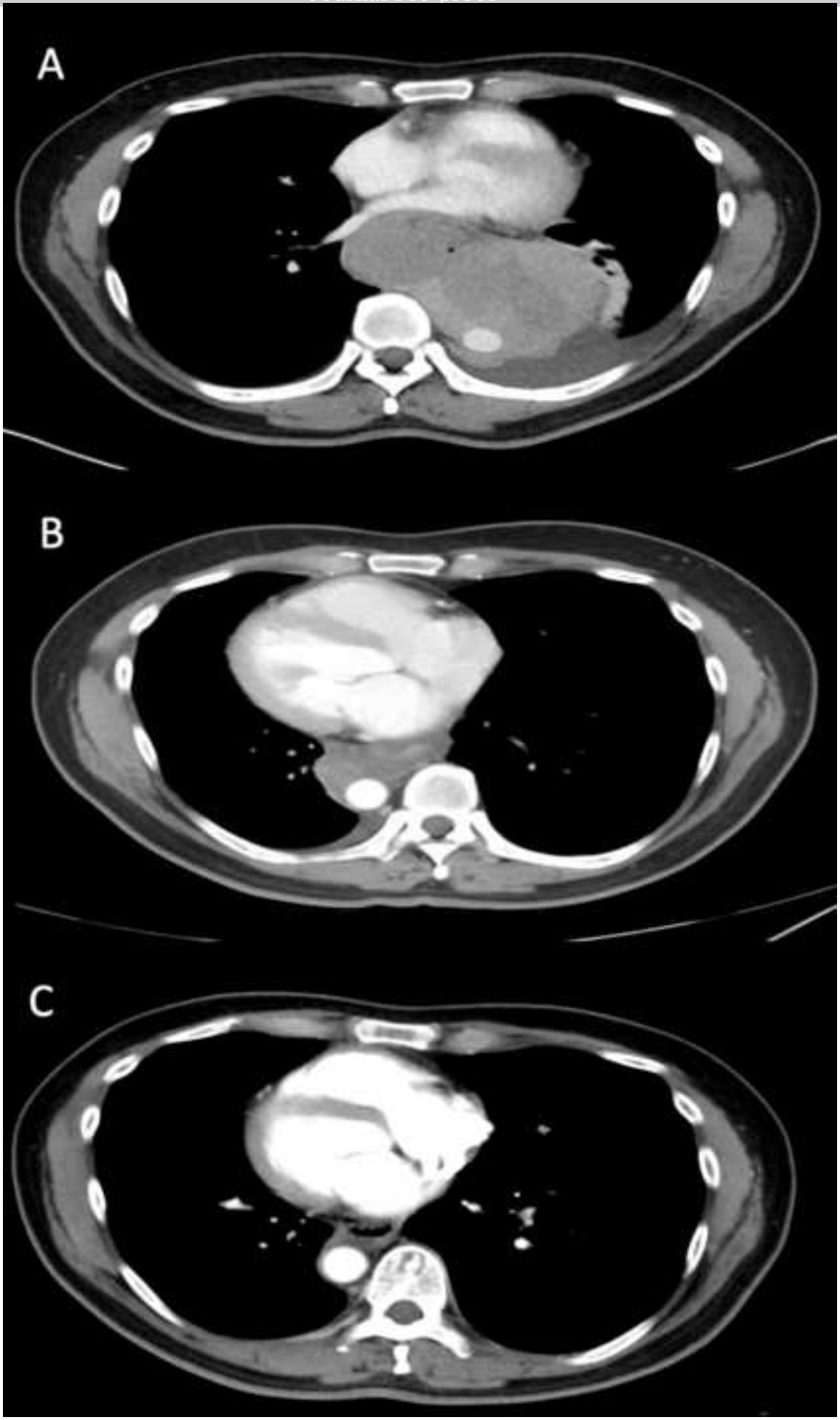


Figure 5