Review Article | Palliative Medicine and Palliative Care for Incurable Cancer

Melanoma—the therapeutic considerations in the clinical practice※

Sola Adeleke[1,2], Somto Okoli[3], Anojan Augustine[4], Joao Galante[2], Aayushi Agnihotri[5], Mario Uccello[6], Aruni Ghose[7,8], Michele Moschetta[9], Stergios Boussios[1,8,10]

[1]School of Cancer & Pharmaceutical Sciences, King's College London, London, UK; [2]Department of Oncology, Guy's & St Thomas' Hospital, London, UK; [3]Bristol Medical School, University of Bristol, Bristol, UK; [4]Birmingham NHS Foundation Trust, Birmingham, UK; [5]Royal Berkshire NHS Foundation Trust, Reading, UK; [6]University Hospital Southampton NHS Foundation Trust, Southampton, UK; [7]Barts Health NHS Trust, London, UK; [8]Medway NHS Foundation Trust, Gillingham, Kent, UK; [9]Novartis Institutes for BioMedical Research, Basel, Switzerland; [10]AELIA Organization, Thessaloniki, Greece

Contributions: (I) Conception and design: S Adeleke, M Moschetta; (II) Administrative support: S Adeleke, M Moschetta; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Stergios Boussios, MD, MSc, PhD, FRCP. School of Cancer & Pharmaceutical Sciences, King's College London, London, UK; Medway NHS Foundation Trust, Windmill Road, ME7 5NY, Gillingham, Kent, UK; AELIA Organization, 9thKm Thessaloniki—Thermi, 57001, Thessaloniki, Greece. Email: stergiosboussios@gmail.com.

Abstract: The incidence of melanoma is increasing and prolonged exposure to ultraviolet (UV) radiation remains the main risk factor. Public health measures have been vital in tackling the increased incidence and prevalence of melanoma. The management of melanoma has been revolutionised with the approval of new immunotherapy treatments (anti PD-1, CTLA-4 and LAG-3 antibodies) and targeted therapies (BRAF and MEK inhibitors). With some of these therapies becoming the standard of care in the management of advanced disease, it is likely we will see their use increase in the adjuvant and neoadjuvant setting. Recently, literature has demonstrated the benefits patients could derive from the combination of immune checkpoint inhibitors (ICIs) due to the promising results on its efficacy when compared to monotherapy. However, greater clarity on its use is needed in more unique presentations such as BRAF-wild type melanoma, where the lack of driver mutations makes disease management more challenging. Surgical resection remains an integral part of the management of earlier stages of the disease with a consequent decrease in reliance on other forms of therapy such as chemotherapy and radiotherapy. Finally, we evaluated the novel emerging experimental approaches to treatment such as adoptive T cell therapy, novel oncolytic treatments and cancer vaccines. We discussed how their use could improve patients' prognosis, enhance treatment efficacy, and potentially achieve cure.

Keywords: Metastatic melanoma; skin cancer; targeted therapy; immune checkpoint inhibitors (ICIs); cancer vaccines

Submitted Dec 23, 2022. Accepted for publication Jun 13, 2023. Published online Jun 30, 2023.
doi: 10.21037/apm-22-1432
View this article at: https://dx.doi.org/10.21037/apm-22-1432

Introduction

Cutaneous melanoma is a malignant disease of the melanocytes. The incidence rate of melanoma is steadily increasing, with GLOBOCAN estimating that the number of new cases worldwide in 2020 was 324,635 (1). In 2020, there were 1,092,818 people living with melanoma and 57,043 melanoma-related deaths (1).

Approximately 3% of melanomas lack an identifiable primary site, otherwise known as melanoma of unknown primary (MUP). This unusual melanoma subtype remains biologically ill-defined, as compared to the classical

※ Special series on Medical Oncology: Challenges in 2022.

© Annals of Palliative Medicine. All rights reserved.

melanoma of known primary (MKP). It has recently been published that patients with a MUP site seem to present with better outcomes compared to those with stage matched MKP site. It is thought that this is due to a higher immunogenicity which is reflected in the immunologically mediated primary site regression (2).

UV radiation is the main etiology of the disease (3) while skin phenotype is an important predisposing factor (4). As a result, geographical distribution is a key risk factor for the disease as regions closer to the equator or areas of higher altitude and latitude have greater exposure to UV radiation. Consequently, higher incidence of melanoma is generally reported in these areas (5). South-East Asia has lower incidences of cutaneous melanoma compared to Europe, North America, or Australia. However, higher incidence rates of acral lentiginous melanoma (ALM) have been reported in this region (6). Early diagnosis can be difficult with ALM due to its atypical presentation; therefore, greater education may be required for individuals with darker skin to prevent the progression of the disease (7). Factors such as age and sex are also linked to varying levels of incidence. As the incidence of melanoma increases, public health measures have been implemented. Adherence to primary interventions is vital in tackling the increased prevalence of melanoma, especially in regions with high incidence rates.

The clinical presentation of melanoma can vary, making diagnosis difficult. Screening procedures including dermatoscopy, biopsies and histopathological evaluation are important tools for early detection of melanoma (8,9). The level of serum markers lactate dehydrogenase (LDH) and S100 β protein are well established prognostic and monitoring tools. DNA markers, such as BRAF and NRAS, provide well-established associations with patient selection and can predict patients' response to targeted therapy. BRAF is a serin-threonine kinase from the RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAPK) pathway. Mutation in BRAF leads to upregulation of MAPK and subsequent uncontrolled proliferation of cells (10). The most common mutation involves the substitution of valine with glutamic acid ($BRAF^{V600E}$) at amino acid 600, with up to 90% of BRAF-mutated tumours expressing this substitution (11). The less common substitution of valine to lysine ($BRAF^{V600K}$) accounts for up to 10% of BRAF-mutated tumours (12). BRAF mutations occur in a higher frequency in tumours of neural crest origin, as a result of this they account for 50–60% of cutaneous melanomas (13). On the other hand, NRAS mutations present less frequently and are only found in up to 20% of cutaneous melanoma (13) and 15% of acral lentiginous melanoma and sino-nasal mucosal melanomas (14). Active RAS proteins found in the GTP-bound state, become inactive following the hydrolysis of GTP to GDP (14). Active RAS proteins stimulate cellular proliferation, survival, differentiation, and apoptosis (15). Oncogenic missense mutations at codons 12, 13 or 61 result in RAS mutation. This is the substitution of glutamine to lysine, leucine or arginine in the NRAS protein (16). This mutation causes a conformational changes in the GTP-active state of Ras in 90% of mutations or promotes oncogenic changes to the mechanism of GTP hydrolysis (15). As a result of this, normal cell cycle is dysregulated and T cell function is impaired (14). Circulating tumour DNA (ctDNA), microRNAs (miRNAs) and long non-coding RNAs are biomarkers that provide an effective insight into a tumours' genetics. They help with understanding pathophysiology of the disease, and hold the great advantage of allowing serial, non-invasive sampling for disease monitoring (17).

High HER3 protein expression, ulceration, tumour thickness, thin malignant melanoma with histological regression, presence of distant metastasis and positive lymph nodes are all poor prognostic factors (18). The 5-year survival rate for patients with stage IV melanoma is estimated to be 28.9%. This can be attributed to the use of targeted therapies and immunotherapy which have revolutionised the treatment of melanoma and have significantly increased survival rates for patients with melanoma (19). Optimising therapeutic strategies (i.e., scheduling and combinations) and the management of melanoma will also be vital in improving survival for patients with metastatic melanoma. Chemotherapy is no longer a frontline treatment option and is currently utilized after immunotherapy and targeted therapy options have failed (20). For advanced disease, immune checkpoint inhibitors (ICIs) and targeted treatments have been shown to have the greatest therapeutic benefits and represent the current mainstay of treatment. Immunotherapy includes therapies that upregulate or downregulate the immune system (21,22). More specifically, ICIs, a form of monoclonal antibodies are effective in counteracting the immunosuppressive ability of tumour cells by inactivating immune checkpoint pathways leading to tumour cell kill (23). Targeted therapies are small molecule inhibitors that target genes or proteins which have been known to play a role in tumour proliferation (24). Other therapies

© Annals of Palliative Medicine. All rights reserved.

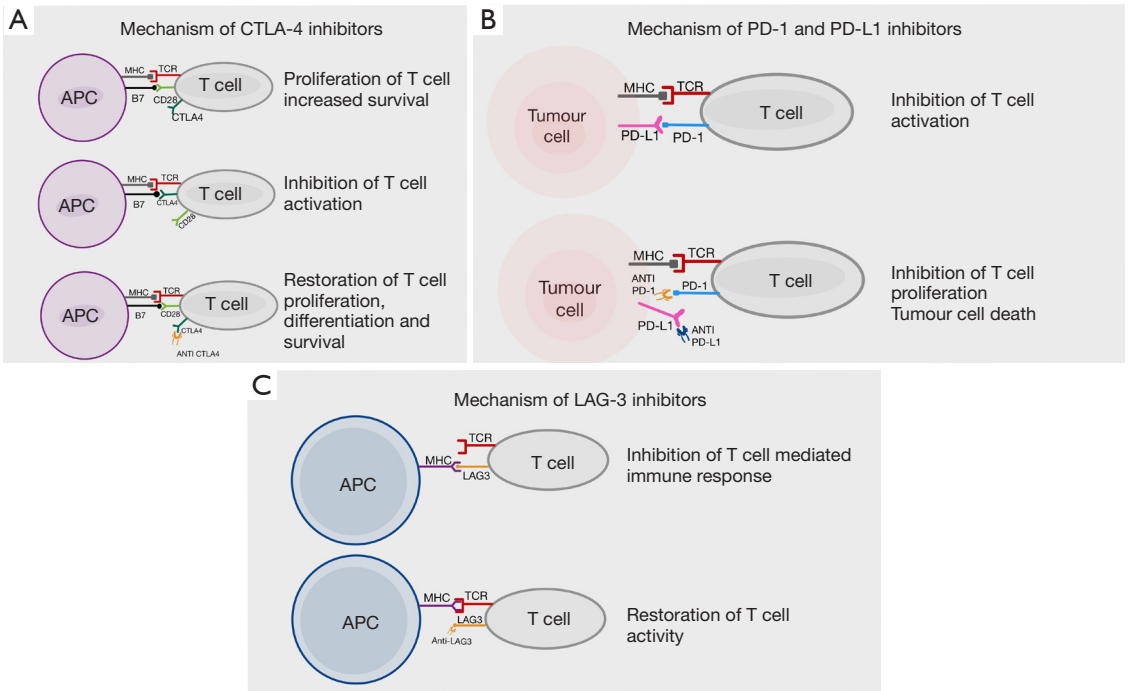

Figure 1 This figure illustrates the mechanism of immune checkpoint inhibitors and their anti-tumoural activity (26). (A) The activation of an antigen through immunotherapy can promote T-cell function. When CTLA-4 is attached to B7, it inactivates the T cell. A CTLA-4 inhibitor works to prevent this attachment, allowing T cells to target and kill the tumour. (B) Anti PD-L1 and PD-1 antibodies prevent the attachment of PD-L1 and PD-1, enhancing T-cell activation and proliferation. (C) Inhibition of LAG-3 by antibodies ceases the dysregulation of t cell proliferation resulting in the re-activation of anti-tumour T-cell activity. CTLA-4, cytotoxic T-cell lymphocyte; PD-L1, programmed cell ligand 1; PD-1, programmed cell death protein 1; APC, antigen presenting cell; LAG-3, lymphocyte-activation gene 3.

such as oncolytic viral treatments and angiogenesis multi-targeted tyrosine kinase inhibitors have also been shown to be beneficial and are currently used in clinical practice alongside other treatments (25).

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a protein receptor that functions as an immune checkpoint and downregulates immune responses. CTLA-4 is a regulator of T cells and is often upregulated in tumour cells. The interaction of CTLA-4 and its transmembrane proteins cluster differentiation (CD)80 and CD86 with tumour cells' transmembrane protein CD28 are vital in inducing T cell survival and proliferation (26). Anti-CTLA-4 antibodies like ipilimumab prevent this interaction on the membrane of the antigen presenting cell (APC) thus, preventing a negative signal to inhibit T-cell activation (*Figure 1*) (27). Checkpoint proteins such as programmed-death-1 (PD-1) are immune checkpoint target expressed on T cells. Its ligands PD-L1 (B7-H8) and PD-L2 (B7-DC) are expressed on many tumour cells and cells of the microenvironment like macrophage and myeloid derived suppressor cells (MDSCs). Through PD-1 receptor binding, PD-L1 and PD-L2 can inhibit T cells activity. The introduction of anti-PD-1 and anti-PD-L1 antibodies are able to restore anti-tumour T-cell activity (*Figure 1*). Checkpoint protein lymphocyte activation gene-3 (LAG-3) is also expressed on T-cells (*Figure 1*). The over-expression of LAG-3 is thought to facilitate T-cell exhaustion. Inhibition of LAG-3 by anti-LAG-3 antibodies can restore the anti-tumour T-cell activity (28). Therapies that provide dual checkpoint inhibition of LAG-3 and PD-1 such as relatlimab-nivolumab have been shown to be effective in the treatment of unresectable melanoma (29). Future developments in the treatment of melanoma are likely to involve changes in the combination of approved checkpoint inhibitors, and in the sequencing of targeted therapies and immunotherapy. It is likely that novel immunotherapeutics will be developed as understanding of their efficacy and safety profile improves.

© Annals of Palliative Medicine. All rights reserved.

Current standard of care

The current ESMO Clinical Practice Guidelines on cutaneous melanoma for the management of melanoma have been summarised below (30) (*Table 1*).

The role of radical treatment in melanoma

Radical treatment such as surgical resection with excision biopsy and sentinel node biopsy remains at the forefront of the management of melanoma (38,39). Excision biopsy

Table 1 Current treatment algorithm table

Stage (based on TNM classification)	Treatment considerations	Treatment recommendations	
		Strongly recommended	Other considerations
0 (melanoma *in situ*)—IA (<0.8 mm thick with no ulceration)	Minimally invasive surgery	Wide excision around the histological biopsy scar is the preferred approach. A safe clinical margin of 0.5, 1–2 and 2 cm must be maintained for stages 0, I and II respectively (31)	N/A
IB (<0.8 mm thick with ulceration or 0.8–1.0 mm thick ± ulceration)	Minimally invasive surgery	Wide excision (as mentioned above)	SLNB may be considered. If positive at any stage, follow the stage III positive sentinel node treatment algorithm (31) (*Figure 2*)—observe with mandatory radiographic nodal surveillance or carry out a complete lymph node dissection
	Adjuvant treatment	N/A	If sentinel node negative, systemic treatment with nivolumab, pembrolizumab, ipilimumab or dabrafenib/trametinib (if BRAF V600 mutation is present) may be considered. Interferon alpha may be considered in specific circumstances such as in stage IIc patients where newly approved drugs are not accessible
			Locoregional radiation therapy may be offered to patients with lentigo malignant melanoma following inadequate resection or following resection of bulky disease
Stage IIA (2–4 or 1–2 mm thick with ulceration)	Minimally invasive surgery	Wide excision with SLNB is recommended	
Stage IIB (>4 or 2–4 mm thick with ulceration)-IIC (>4 mm with ulceration)	Minimally invasive surgery	Wide excision with SLNB is recommended	Definitive radiotherapy can be considered in rare palliative cases where excision is not recommended due to high morbidity with the excision or comorbidities of the patient
	Adjuvant treatment	N/A	Recent trials have supported the use of adjuvant immunotherapy for high-risk stage IIB-IIC cancers (31). NCCN guidelines recommend that pembrolizumab may be indicated in patients with pathologically staged IIB or IIC (32)
Stage IIIA (microscopic disease with ulceration and micro-metastasis to nearby lymph nodes)		Core biopsy preferred or fine needle aspiration is recommended. Wide excision of the primary tumour is the first line treatment	For stage IIIA-D the following considerations may be made. Excisional biopsy may be carried out if needle biopsy is not possible. If positive sentinel nodes are present carry out the stage III positive sentinel node treatment algorithm. Complete lymph node dissection may also be carried out alongside the excision of the primary excision. However, this should only be considered if there are factors that make recurrent nodal disease difficult to manage, for example head and neck melanomas or contraindication to adjuvant therapies (32)
	Neoadjuvant therapy	N/A	For stage IIIA-D, neoadjuvant therapy with monotherapy of combination therapy with checkpoint inhibitors, BRAF/MEK inhibitors, and intralesional therapies may be considered alongside surgical excision for resectable disease (32)

Table 1 *(continued)*

© Annals of Palliative Medicine. All rights reserved.

Table 1 *(continued)*

Stage (based on TNM classification)	Treatment considerations	Treatment recommendations	
		Strongly recommended	Other considerations
	Radiotherapy	N/A	Locoregional radiotherapy for stage IIIA-D is typically reserved for cases where local recurrence is highly probable
Stage IIIB-D (macroscopic disease with ulceration and macro-metastasis to nearby lymph nodes)	Minimally invasive surgery	Management is the same as stage IIIA disease	Satellite metastases are metastases that occur within 2 cm from the primary tumour and in-transit metastases are further than 2 cm but before the nearest lymph node (33). These are treated with therapeutic lymph node dissection if nodal disease exists and/or the surgical removal of satellite/in-transit metastases. The latter is discouraged to avoid fuelling of rapid progression of melanoma, which can jeopardise the long-term benefits of systemic therapies. T-VEC/intralesional therapy and systemic therapy with nivolumab, pembrolizumab and dabrafenib/trametinib
Unresectabe disease +/– nodal recurrence and stage IV (distant metastatic disease) (*Figure 3*) (31,32)	Surgical excision	N/A	In resectable stage IV, surgical resection, stereotactic ablative therapy, T-VEC/intralesional therapy may be considered for oligometastatic disease. If metastasis is widely disseminated, T-VEC is preferred for extracranial lesions
	ICIs	Unresectable disease is primarily treated with ICI and/or targeted therapy. ICI is often offered as a first line treatment e.g., ipilimumab, nivolumab, pembrolizumab and dabrafenib/trametinib. If the patient has previously used an anti-PD-1 therapy, ipilimumab may be more suitable	If ICI is contraindicated or unsuitable, i.e., rapid/symptomatic melanoma progression where slow acting ICI is not appropriate (34,35) then targeted therapy is offered if there is BRAF V600 mutation present. Triple or sequential therapy combining ICI and targeted therapy are also novel options (36,37). If both targeted therapy and ICI are contraindicated or not indicated (i.e., BRAF wild type and ICI toxicity or poor progression on previous ICI) then consider chemotherapy (e.g., dacarbazine, temxolomide, paclitaxel) or best supportive care
	Palliative radiotherapy	N/A	This is only indicated in symptomatic, widely disseminated extracranial disease (32)

TNM, tumor-node-metastasis; N/A, not available; SLNB, sentinel lymph node biopsy; T-VEC, Talimogene Laherparepvec; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1.

with a 2 mm wide margin is a form of local resection recommended as the main mode of histopathological investigation and assessment (38). Studies have shown that there is no significant difference between narrow and wide excision margins in terms of the likelihood of locoregional or distant recurrence, metastasis, or death; however, surgical reconstruction must be considered depending on the excision location and the width of the tumour excised (40).

Sentinel node biopsy is a prognostic factor for survival and has been vital in differentiating patients with clinically positive nodes. It allows the identification of patients who may benefit from complete lymph node resection and is usually indicated in patients with tumours greater than 1 mm thick (39,41). Although the MSLT-I trial failed to demonstrate a survival benefit for sentinel node biopsy, the 5-year survival rates for patients with tumours 1.2–3.5 mm thick were increased by sentinel node biopsy and early complete lymph node resection compared to observation only (72.3% and 52.4% respectively) (39,42).

For patients with positive sentinel nodes, there has been some controversy on the benefits of complete lymph node dissection compared to observation with radiological imaging. Trials, MSLT-2 and DeCOGtrials failed to demonstrate a survival benefit when comparing observation with radiological imaging of the positive nodes compared to complete lymph node dissection (43). However, both trials showed an increased risk of recurrence in patients who were observed (43). Contrastingly, lymphoedema related morbidity was a concern in the complete lymph node resection group, with significant morbidities occurring when complete lymph node resection of the pelvic or groin nodes occurred (43).

© Annals of Palliative Medicine. All rights reserved.

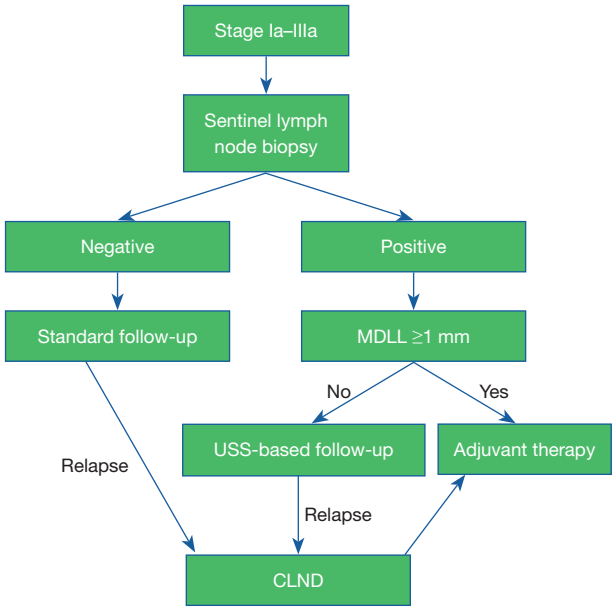

Figure 2 Illustrates the sentinel lymph node biopsy algorithm as part of ESMO guidelines (reference ESMO). Adjuvant therapy includes immunotherapy and targeted therapy. MDLL, maximum diameter of the largest lesion according to Rotterdam Criteria which the EORTC (European Organisation for Research and Treatment of cancer) has validated; USS; ultrasound scan; CLND, complete lymph node dissection.

Although cutaneous melanoma is a radioresistant form of cancer, radiotherapy has been a key treatment modality in definite, adjuvant and palliative settings (39,44) with definitive radiotherapy is often reserved for patients with unresectable disease (44). The main forms of radiotherapy include external beam radiotherapy, interventional radiotherapy and proton therapy which deliver a higher dose of radiation per fraction (44,45) evoking DNA damage, interruption of the cellular cycle and tumour death (45). As an adjuvant therapy alongside ICI, there has been a promotion in the immunostimulatory effect of radiotherapy with this combination enhancing the anti-tumoural response of ICI (45).

ICIs

A large body of data supports the significant role of the interaction between cancer and the immune system as a key pathogenetic step leading to cancer progression. Inhibitory immune checkpoints CTLA-4 and PD-1 (10) antagonise the immune checkpoint pathway to enhance pro-inflammatory T-cell expansion and impose an anti-tumour response (10,46). More recently, the RELATIVITY-047 trial has led to the use of LAG3 as an additional ICI option (47). Other forms of immunotherapy include oncolytic viral therapy, Toll-like receptor agonists, gp100 peptide vaccine, adoptive T-cell therapy, Treg inhibitors, Interleukin-2, Peginterferon alpha-2b and interferon alpha-2b (10).

Ipilimumab, an anti-CTLA-4 antibody, and nivolumab and pembrolizumab, both anti-PD-1 antibodies, represent important treatment options for patients with melanoma and are approved by the Food and Drug Administration (FDA) for the treatment of several types of solid tumours and haematologic cancers (10,48,49). Nivolumab and pembrolizumab were first approved by the FDA in 2014 for the treatment of advanced melanoma with disease progression after ipilimumab and/or BRAF-Inhibitors if positive for BRAF V600 (50,51), The approval was facilitated by the CheckMate-037 and KEYNOTE-001 trials, respectively (50,51). They were further approved for usage as first-line for advanced melanoma in 2015 following the CheckMate-066 and KEYNOTE-006 trials, respectively (51) (*Figure 3*).

The CheckMate-066 trial studied Nivolumab *vs.* dacarbazine in untreated advanced melanoma without a BRAF mutation (52). The trial showed superior 1-year overall survival (OS) (72.9% *vs.* 42.1%) and median progression-free survival (PFS) (5.1 *vs.* 2.2 months) with lower rates of grades 3-4 treatment related adverse events (11.7% *vs.* 17.6%) (53,54). KEYNOTE-006 trials studied pembrolizumab at a dose of 10 mg/kg every 2 weeks and every 3 weeks *vs.* ipilimumab in advanced melanoma (51). The trial showed superior 6-month PFS (47.3%, 46.4% and 26.5%) and 12-month OS (74.1%, 68.4% and 58.2%) with lower rates of grades 3–5 treatment related adverse events (13.3%, 10.1% and 19.9%) (55).

In advanced melanoma, anti-CTLA-4 monotherapy is not considered first-line due to the better treatment response observed with either combined anti-CTLA-4 and anti-PD-1 agents, or anti-PD-1 monotherapy (19) (*Figure 3*). This has been shown by CheckMate-067 and KEYNOTE-006 trials (51,53,56,57). The 7.5-year outcomes from the CheckMate-067 trial on advanced melanoma showed durable and superior PFS, OS and objective response rate (ORR) outcomes of nivolumab plus ipilimumab and nivolumab monotherapy compared to ipilimumab monotherapy (57). The combination regimen involved nivolumab plus ipilimumab followed by maintenance nivolumab until disease progression or toxicity (57).

© Annals of Palliative Medicine. All rights reserved.

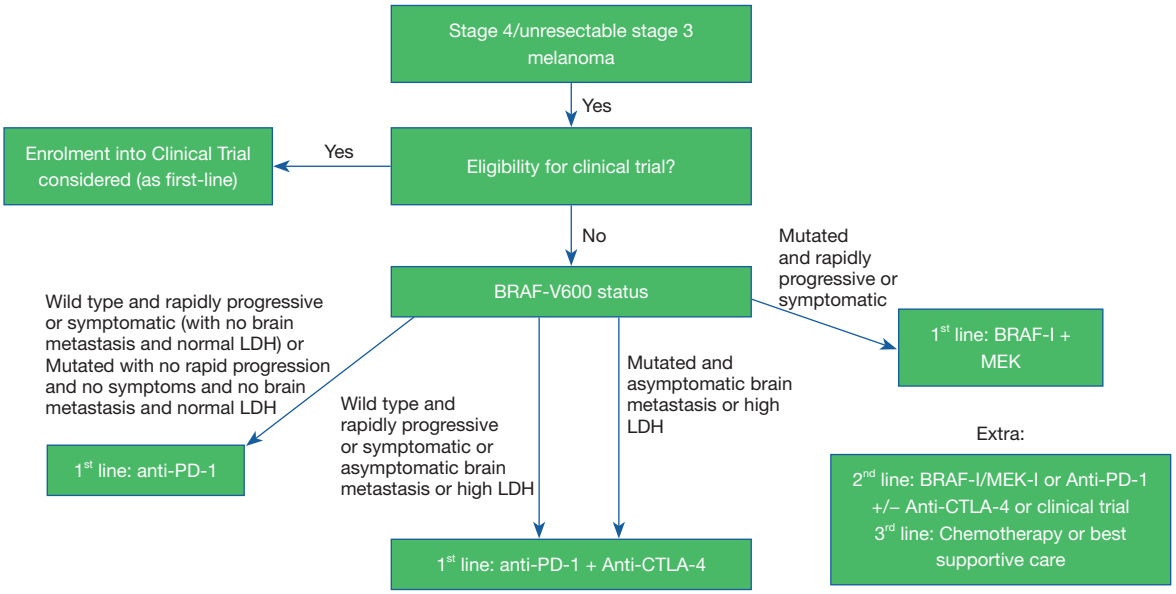

Figure 3 Treatment pathway for treatment-naïve advanced melanoma patients as discussed on ESMO consensus conference recommendations on melanoma publication 2022. Titled: "*Industry Satellite Symposium (Bristol Myers Squibb): The Evolving Treatment Landscape for Metastatic Melanoma: A Clinical Lens on Current Decision Making*". Note: BRAF-I/MEK-I only indicated in mutated BRAF-V600 status. CTLA-4, cytotoxic T-cell lymphocyte; PD-1, programmed cell death protein 1; LDH, lactate dehydrogenase; ESMO, European Society for Medical Oncology .

The 7.5-year OS rate was 48%, 42% and 22% with ORR of 58%, 45% and 19% for nivolumab plus ipilimumab, nivolumab, and ipilimumab cohorts respectively (57). In addition, the 7.5-year PFS rate was 33%, 27% and 7% respectively (57). The 7.5-year follow-up demonstrated a similar durability in outcomes compared to the 6.5-year follow-up. There were no changes observed to the safety summary from the 6.5-year follow-up which highlighted no new safety signals with grade 3/4 treatment-related adverse events reported in 59%, 24% and 28% of cases within each respective cohort. The most common adverse effects were diarrhoea, fatigue, pruritus and rash (53,57). The most common toxicity-related deaths associated with anti-PD-1/anti–CTLA-4 combination therapies were colitis and myocarditis (55). These findings were supported in CheckMate-511 where one grade 5 treatment-related adverse event of myocarditis was reported in the nivolumab and ipilimumab group, but no cases of colitis had a fatal outcome (55). Maintenance therapy with nivolumab 480 mg once every 4 weeks, also demonstrated an acceptable safety profile (55). As such, the combination regime only remains first line for the most fit patients with anti-PD-1 monotherapy or targeted therapy being better indicated in the cohorts with a higher risk of immune-related adverse events (irAEs) (57).

Furthermore, a 5-year follow-up of KEYNOTE-006 trial showed superior PFS and OS outcomes of pembrolizumab therapy compared to ipilimumab in advanced melanoma with a median OS of 32.7 *vs.* 15.9 months and a median PFS of 8.4 *vs.* 3.4 months, respectively (56). In addition, grade 3-4 treatment-related adverse events occurred in 17% of the pembrolizumab treatment arm compared to 20% in the ipilimumab arm (56).

Although these studies demonstrate the efficacy of ICI, their generability is limited to patients with untreated advanced disease. For instance, although KEYNOTE-006 was an open study, 66% of recruited patients had not undergone any systematic treatment (54). This might indicate that the recruited patients may have been fitter and more suitable to treatment compared to standard patients with advanced disease who might have tried various treatment and may already be heavily burdened by disease (58).

New data has emerged from the RELATIVITY-047 trial that studied combination therapy, relatlimab (LAG-3 blocking antibody) plus nivolumab *vs.* nivolumab monotherapy in untreated advanced melanoma; with more

© Annals of Palliative Medicine. All rights reserved.

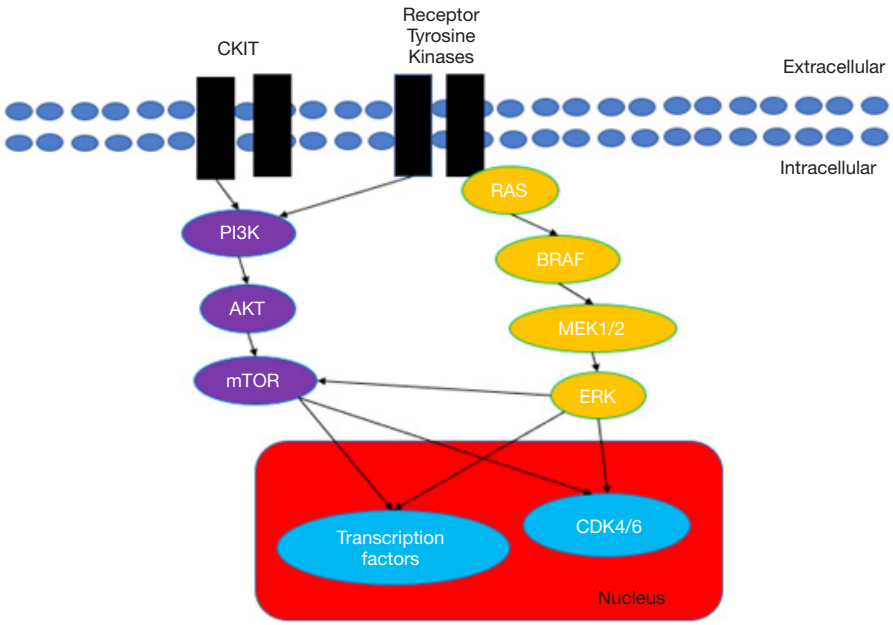

Figure 4 Illustrates MAPK (RAS-RAF-MEK1/2-ERK) and PI3K-AKT-mTOR pathway. Targeted Therapy. BRAF, v-raf murine sarcoma viral oncogene homolog B1; MEK 1/2, mitogen-activated protein kinase; ERK, extra-cellular signal-regulated kinase; CDK, cyclindependent kinases; KIT, type III transmembrane receptor tyrosine kinase; PI3K, phosphatidylinositol 3-kinases (27,65).

superior outcomes being were observed with combination therapy—PFS at 12 months of 47.7% *vs.* 36% with a median PFS of 10.1 *vs.* 4.6 months (47). Long-term follow-up also showed positive outcomes including an OS rate of 63.7% *vs.* 58.3% at 24 months as well as an ORR of 43.1% *vs.* 32.6% (59). Additionally, combination therapy in advance melanoma showed comparable results to anti-PD-1 plus anti-CTLA-4 trials such as CheckMate-067 (PFS at 12 months of 47.7% *vs.* 49% for ipilimumab-nivolumab) but with a more favourable adverse event profile (47,60). Overall, the RELATIVITY-047 trial showed that the combination of relatlimab and nivolumab provided superior outcomes with a reasonable side-effect profile that harboured no new safety signals, compared to the use of nivolumab as a single therapy (47).

Targeted therapy in BRAF mutated melanoma

Around 70% of patients with cutaneous melanoma harbour mutations of the MAPK pathway (10). Targeted therapies utilise inhibitors to attenuate these mutated proteins that are thought to manipulate signalling pathways to cause uncontrolled proliferation (10). Vemurafenib, dabrafenib and encorafenib are selective BRAF-mutant inhibitors (BRAF-I) approved as single agents for the treatment of $BRAF^{V600E}$ stage 3 unresectable or metastatic melanoma (10,61,62). Whilst these targeted therapies have shown a significant ORR, and positive PFS and OS outcomes, a proportion of patients still developed resistance and side-effects including the induction of keratoacanthoma (10). Paradoxical upregulation of the MAPK pathway due to unopposed activation of downstream effectors of the MAPK pathway (i.e., MEK) (63,64) has been reported as a major factor (*Figure 4*). Consequently, MEK inhibitors have shown great effectiveness in delaying the development of resistance when combined BRAF-mutant inhibitors (64,66), thus reducing the side effects caused by BRAF-I.

Trametinib, cobimetinib and binimetinib are all selective MEK inhibitors (10). Combined therapy of trametinib plus dabrafenib as well as cobimetinib plus vemurafenib have shown durable objective response for advanced BRAF-mutant (BRAF-MT) melanoma as part of COMBI and co-BRIM trials (10,66-68) (*Figure 3*). Encorafenib and binimetinib are also approved for advanced BRAF-MT melanoma as part of the COLOMBUS trial (20,69,70) (*Figure 4*). They all have a comparable PFS range of 30–40% (19,69). In instances where combined BRAF-I and MEK-I are contraindicated for example poor performance

© Annals of Palliative Medicine. All rights reserved.

status or the presence of comorbidities that would indicate a reduced tolerance to toxicity, BRAF-I monotherapy may be considered as an alternative (31).

Recent trials that have evaluated the use of adjuvant therapy post-lymphadenectomy for high-risk stage 2 cancers have been encouraging in reducing disease relapse (31,71). The KEYNOTEe-717 trial has shown significant improvement in the recurrence-free survival long-term as well as distant metastasis-free survival in patients with Stage IIB-IIC melanoma treated with adjuvant pembrolizumab compared to placebo (31) with preserved quality of life and reduced side effects being observed.

For stage IIIB-IIIC melanoma as well as stage IIIa with the maximum diameter of the largest lesion (MDLL) on their sentinel lymph node being >1 mm, adjuvant treatment is recommended post-lymphadenectomy. It may also be considered for MDLL <1 mm and more guidance will be made available within future consensus reports and guidelines (71). Recommended ICI include anti-PD-1 drugs, specifically nivolumab and pembrolizumab as seen with the CheckMate-238 and EORTC 1325 trials respectively (71-73). Anti-CTLA-4 is not recommended due to toxicity as seen on EORTC 18071 trial (74).

Recommended targeted therapies include the combination regime of dabrafenib/trametinib as seen with the COMBI-AD trial (75). BRAF-I monotherapy is ruled out due to the lack of clinical benefit as seen on the BRIM8 trial studying vemurafenib monotherapy (76). For BRAF wild type (BRAF-WT), only anti-PD-1 therapy is currently available (71). For BRAF-MT melanoma, both anti-PD-1 and dabrafenib/trametinib can be considered depending on patient-choice and toxicity profile (71).

BRAF non-V600E/K, cKIT and NF1

BRAF non-V600E/K accounts for 3–14% of BRAF-MT melanoma (77). ICI remains first-line for such cases however, it can be contraindicated for some patients (77). Thus, more research is needed to develop new effective targeted therapies. This has been difficult due to its rare occurrence in patients with melanoma. The exclusion of this genetic mutation from large drug approval studies, has resulted in an increased dependence by clinicians on case reports and series. Despite this, the improved classification of the three classes of BRAF mutants (Class I–III) and an advancement in the understanding on their kinase activation, RAS dependency and dimerization-based activation. This has allowed for further research on targeted therapies that may bring some clinical benefit (77). Several retrospective and *in-vitro/in-vivo* analysis have shown variable responses to BRAF-I/MEK-I combination therapy as well as BRAF-I and MEK-I monotherapy. Other potential targets including pan-RAF inhibitors (i.e., sorafenib, belvarafenib, naporafenib), BRAF dimers inhibition and ERK inhibitors are currently being developed (77) (*Figures 4*,*5*).

For other mutations such as cKIT or NF1, targeted therapies are of limited activity and ICI is considered first-line. Some specific c-Kit mutations have shown response to imatinib or nilotinib and these agents may be used as second line treatment (78).

Targeted therapy in NRAS mutated melanoma

NRAS mutant melanomas is a highly aggressive disease, facing a surge in resistance to the currently limited targeted therapies. Patients affected by this disease subtype have currently no targeted therapy options available.

The first-line treatment for stage III/IV NRAS-mutant melanoma is ICIs even though its efficacy remains controversial (79,80). Evidence has shown that the therapeutic combination of anti-PD-1 plus anti-CTLA-4 showed greater clinical benefit compared to anti-PD-1 monotherapy with an increased PFS (HR 0.57, 95% CI: 0.38 to 0.86, P=0.007) and a median OS of 42.6 and 21.3 months respectively (81).

Ongoing trials are investigating the role of monotherapy and dual targeted therapy in NRAS-mutant melanoma (16). In NRAS-mutant melanoma, CRAF acts as the NRAS effector instead of BRAF to upregulate MAPK (30) (*Figure 5*). As such, BRAF-I may have a limited role. NRAS-mutant melanoma predominantly relies more on MAPK/ERK/MEK signalling rather than P13K/mTOR, though the latter was found to be important for survival when the former is inhibited (65). Both pathways upregulate downstream D-type cyclins to allow cell cycle progression (16) (*Figure 5*). MEK-I alone or in combinations with other targets seem most effective in the treatment of NRAS-mutant melanoma (16). Such other targets including ERK1/2 inhibitors, PI3K/mTOR inhibitors and CDK4/6 inhibitors alongside pan-RAF inhibitors and FAK inhibitors (focal adhesion kinase) may be effective for NRAS mutant melanoma and are currently being tested (16). Due to emerging resistance, triple therapy approaches involving MEKi/CDK4/6i and mTORC1/2i are currently being investigated in clinical trials (65). Interestingly, MEK-I-ERK-I dual trials have shown increased apoptosis and

© Annals of Palliative Medicine. All rights reserved.

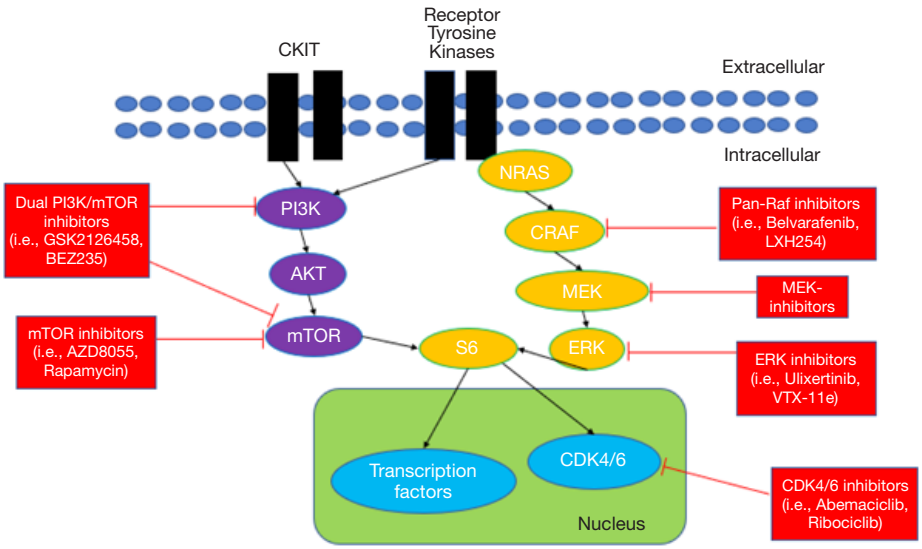

Figure 5 Illustrates MAPK (NRAS-CRAF-MEK-ERK) and PI3K-AKT-mTOR pathway. Applies for NRAS mutant melanoma (17,65). NRAS oncogene, CRAF-proto-oncogene; MEK, mitogen-activated protein kinase; ERK, extra-cellular signal-regulated kinase; S6, ribosomal protein S6; CDK, cyclin-dependent kinases; PI3K, phosphatidylinositol 3-kinases; AKT, protein kinase B; mTOR, mammalian target of rapamycin.

delayed resistance compared to MEKi and CDK4/6i or PI3Ki dual therapy due to synergistic suppression of cyclical D1 reactivation (82). Discovery of novel targets as well as optimising dosing schedules to limit toxicity and subsequent efficacy still require more research.

Triple wild-type (TWT) melanoma

TWT melanoma is characterised by the lack of driver mutations (BRAF, MEK and PD-1) (83). Typically, TWT melanoma only accounts for 10–15% of cutaneous melanoma and 50–80% of acral and mucosal melanoma (83). Driver mutations are the accumulation of somatic mutations and other genetic alterations that impair cell division and result in abnormal cell proliferation and tumorigenesis (84). The treatment of TWT melanoma is challenging and as a result of this, the 5-year survival rate is between to 16–27% (83). ICIs have shown durable responses with anti-CTLA-4 inhibitor ipilimumab demonstrating an ORR of 34.6% in patients with wild-type BRAF status and an ORR of 29.7% in patients with mutant BRAAF status (85). Finally, oncolytic viral therapy talimogene laheroareovec was shown to improve median OS from 18.9 to 23.3 months when used in patients with TWT melanoma (86).

ICI plus targeted therapy

Three phase 3 trials COMBI-I, KEYNOTE-022 and IMspire150 have investigated the efficacy of triple therapy for patients with BRAF V600 mutant melanoma. The combination of anti-PD-1, BRAF-I and MEK-I therapies (23,54,58) have shown both promising and disappointing results. Out of the 3, only IMspire150 has shown a statistically significant increase in PFS (15.1 *vs.* 10.6 months) at a median follow-up of 18.9 months in the triple therapy group (atezolizumab, vemurafenib and cobimetinib) *vs.* the double therapy group of BRAF-I and MEK-I (37). The triple therapy is now FDA approved but its clinical use is limited due to its unique toxicity profile which may have adverse effects in patients with contra-indicating comorbidities (87). In addition, the KEYNOTE-022 trial demonstrated an increase in efficacy in terms of PFS after additional follow-up, suggesting poor initial objective response but good durable response due to prevention/delay of acquired resistance (88,89).

Other trials also investigated sequencing both ICI and targeted therapy. These include DREAMseq, SECOMBIT, ImmunoCobiVem and EBIN. The SECOMBIT trial demonstrated a superior 3-year total PFS and OS rates with either an immunotherapy-to-targeted therapy switch at

© Annals of Palliative Medicine. All rights reserved.

progression of disease (PD) or an 8-week targeted therapy sandwich either side of the ICI therapy (38,90). However, these PFS and OS rates were not statistically significant. More research is needed to identify subpopulation of advanced melanoma that will be sensitive to triple and/or sequential therapies as first-line.

New therapeutic approaches—(neo) adjuvant and intralesional treatments

Despite significant improvement in overall survival of metastatic melanoma, from six months to over three years after the introduction of immunotherapy and targeted therapies, nearly 50% of patients still die from this disease and are refractory to the current standard of care treatment (91).

Equally, a substantial proportion of high-risk resected melanomas recur, even without evidence (histologically or radiologically) of residual disease after surgical resection (92,93). Although adjuvant systemic strategies such as immunotherapy (KEYNOTE-716 and KEYNOTE-054) have shown clinically meaningful improvement in disease free survival and are currently approved, there is emerging evidence that neoadjuvant strategies may be more effective (31,94).

The neoadjuvant approach has revolutionized the management of cancers like breast or colorectal, leading to less morbidity, increased resectability through cytoreduction, organ preservation and, ultimately, improved local recurrence rate and overall survival (95,96). In melanoma, promising results from pre-clinical studies in mice comparing adjuvant *vs.* neoadjuvant strategies showed that mice treated with the later had higher tumour specific $CD8^+$ T cell levels, which were associated with improved overall survival (97). The most common neoadjuvant regime employed and studied are nivolumab plus ipilimumab and pembrolizumab and ipilimumab (73). These preclinical observations have led to the start of several phase-Ib and II studies testing current standard of care in the neoadjuvant setting (98).

The OpACIN-neo study explored three different schedules of ipilimumab and nivolumab in the neo-adjuvant setting, demonstrating significant ORR in all arms of 65–80% with a MPR of 45–70%, which yielded a striking 2-year estimated relapse-free survival of 84% for all patients and 97% for patients who achieved complete pathologic response (99). With these impressive results, neoadjuvant immunotherapy may become standard care. To expedite this, the International Neoadjuvant Melanoma Consortium was created, bringing multiple disciplines together to create a comprehensive and collaborative approach to the development and delivery of neoadjuvant treatment in melanoma (100).

Compared to the adjuvant approach, the neoadjuvant counterpart is believed to have a number of advantages, these include, allowing for the determination of the efficacy of systemic therapy while the disease is *in situ* and decreasing surgical morbidity through the possible identification of groups of patients who may not qualify for more invasive therapeutic strategies such as surgery. The PRADO trial investigated the benefits of the neoadjuvant approach; 61% of 99 patients with stage III melanoma, had complete pathological response in the largest (previously marked) involved lymph node following two cycles of neoadjuvant nivolumab plus ipilimumab, 97% of whom did not undergo CLND, therefore having significantly lower surgical-related adverse effects (100-102). Additionally, it may epitomise a new platform to develop predictive and prognostic biomarkers that can help guiding future trials and new drug developments, and ultimately has the potential to eradicate occult disease at a much earlier stage (36).

Although the precise mechanism for the likely advantages of the neoadjuvant approach remains unclear, it has been hypothesized that the presence of larger tumour volume (and increased antigen presentation) in the neoadjuvant context may not only promote a more robust anti-tumour CD8+ T-cells response and resulting effector cell expansion creating a larger clonal variety compared to the adjuvant approach, but also maintain a larger pool of tumour-residing Batf3+ dendritic cells, key for effector T cell trafficking and response following immunotherapy, and which loss (which occurs in the adjuvant approach as the tumour is removed) has been associated with reduced survival (103,104).

Of note, ICIs and targeted therapies are not the only approaches being explored in the neoadjuvant setting for melanoma. In particular, the use of intralesional methods for advanced/metastatic melanoma has gained traction, due to their efficacy and direct action on palpable lesions. T-VEC, the first oncolytic viral therapy to be approved by the FDA in 2015 for treatment of local unresectable recurrent melanoma after initial surgery, is being evaluated in the neoadjuvant setting for resectable stages IIIB–IVM1a melanoma, both alone (NCT02211131) and in combination with Pembrolizumab (NCT03747744). The latter followed promising early results of a phase Ib trial with a similar approach which showed 62% ORR (33% CR) with no DLTs, and the former recently published an estimated a 25% reduction in the risk of recurrent disease in the

© Annals of Palliative Medicine. All rights reserved.

neoadjuvant T-VEC + surgery group, *vs.* upfront surgery (94,105).

Intralesional IL-2 is also being evaluated in two open-label phase III clinical trials in stages IIIB and C melanoma (NCT02938299 and NCT03567889), using recombinant fusion proteins of IL-2 and TNF-α fused to L19 monoclonal antibody (Darumon), after phase II counterpart showed impressive 80% disease control rate (DCR) of treated lesions, and 54% had CR in non-injected lesions (106). Several other agents including TLR agonists and different HSV-based agents other than T-VEC are also being explored in earlier phase II trials with promising preliminary results (NCT03618641 and NCT03259425 respectively) (91).

New emerging targets and drugs for the treatment of melanoma

Immunotherapy

Beyond the standard immune check point inhibition, some clinical trials have investigated the effects of Idoleamine 2,3—dioxygenase (IDO) 1, which converts tryptophan to kynurenine, producing an immunosuppressive environment (107). Early-stage clinical trials looking at IDO1 inhibition, especially when combined with checkpoint blockade, showed encouraging results. Unfortunately, the phase 3 trial of an IDO1 inhibitor epacadostat paired with the PD-1 inhibitor pembrolizumab in patients with advanced malignant melanoma failed to demonstrate clinical benefit when compared to pembrolizumab alone. This has tempered interest in IDO inhibitors (107).

Adoptive T-cell therapy

Adoptive T-cell therapy strategy mainly uses (TILs), engineered T cell receptors (TCRs) and chimeric antigen receptors T-cell (CAR-T) to recognise and target antigen on cancer cells (108,109). This has shown significant response rates and long-lasting tumour regression in 20–25% of melanoma patients taking part in the clinical trial (108,109). The phase 3 M14TIL trial randomised control trial showed the promise of the use of cell therapy in treating solid tumours. One hundred and sixty-eight patients with stage 3c–4 melanoma took part in the trial and were treated with either TIL therapy or the anti-CTLA 4 antibody or anti-CTLA-4 antibody ipilimumab (109). The results of the trial revealed that patients receiving TIL therapy had significantly longer median progression-free survival times than those receiving ipilimumab, at 7.2 months as opposed to 3.1 months (109). Additionally, the overall response rate to TILs was 49% as opposed to 21% for ipilimumab, and the median overall survival time was 25.8 months as opposed to 18.9 months (109). This trial along with some retrospective data (110) has paved the way for FDA to grant orphan drug status to ITL-168, a novel therapy derived from TILs for the treatment of stage IIb-stage IV melanoma (111). However, more studies are needed to generate additional safety and efficacy data. Costs and logistic considerations will be limiting in implementing this therapeutic modality in clinical practice.

Intra-tumoural oncolytic viral therapy

Intratumoral oncolytic treatments are another newly emerging therapy option for melanoma. Intra-tumoural immunotherapies involve the injection of immunostimulatory agents that will lyse tumour cells to start local and systemic immune responses (112). A wide range of intra-tumoural immunotherapies including non-oncolytic viral treatments like PV-10 and toll-like receptor 9 agonists and oncolytic viral treatments like CAVATAK, Pexa-Vec, and HF10, have been thoroughly investigated and have shown promising antitumour activity with manageable toxicities in melanoma and other solid tumour types (112).

Cancer vaccines

The different strategies currently being explored to find an effective vaccine—based treatment for melanoma include developing a vaccine that targets melanoma cells directly, dendritic cells (DC)—based vaccines, peptide—based vaccines and vector—based vaccines. Vaccines targeting melanoma cells developed based on patient specific predicted tumour neoantigens and was tested in 6 patients, out of which 4 had no recurrence for 2 years post vaccination (113). DC—based vaccines use the central role of dendritic cells to activate the innate and adaptive immune system and proven to be beneficial to a handful of patients in phase 2 studies (114). However, there is not enough data yet to establish DC—based vaccines as an effective therapy in melanoma (114).

Oncolytic viral therapy work by disseminating viral based therapeutic agents such as herpes simplex virus, adenovirus etc. into a tumour cell (115). Tumour cells express alterations in the pathways linked to the antiviral response

© Annals of Palliative Medicine. All rights reserved.

such as the interferon signalling pathway, maturation of inflammatory cells and programmed apoptosis (115). These alterations modify the antiviral response allowing the oncolytic virus to survive for much longer in the tumour cell. Through this mechanism, the sustained survival of the virus triggers the recruitment of immune cells and the continued maintenance of inflammation. As a result, the stimulation of the cytotoxic response and T cells contribute the reversal of the immunosuppressive state of the tumour cell (115). Similarly, to the other vaccines being developed for melanoma, oncolytic vaccines still need further engineering to increase their immune stimulatory ability.

Strengths and limitations

This review is a comprehensive report comprised of European, American, and British guidelines. Systematic reviews and current ongoing trials were utilised to provide an up-to-date report on the treatment of melanoma.

Most of the acquired journal articles and trials reviewed were published on PubMed and Clinicaltrials.gov as were keen to include the most relevant and up-to-date data. Although this review mainly summarises recent literature in the context of current FDA guidelines and approvals, we used recent international cancer conferences and guidelines such as NICE guidelines, NCCN guidelines, ESMO Clinical Practice Guidelines and the ESMO Congress 2022 to support our findings. This ensures that this review provides a nuanced take on the developments in this field in light of changes in this rapidly shifting field. Finally, there might have been a slight selection bias in regard to the evidence selected as there was no set protocol established between the authors when determining the search terms and definitions that would be most useful for inclusion in this review.

Conclusions

Melanoma remains a deadly disease, however, significant progress has been made in recent years. Today, half of the patients with stage IV melanoma are alive after 5 years when treated with ipilimumab and nivolumab combination in the front-line setting. Despite these advances, mortality is still high, highlighting the need for the development of new therapies. Development of adjuvant therapies has also contributed to the change in the natural history of the disease. Targeted agents and immunotherapeutics approved as adjuvant treatment can impede disease progression allowing more patients to enjoy a longer disease-free survival. Promisingly, neoadjuvant therapy has shown great activity and are likely to become standard approach in the near future to be used in earlier stages of disease or in selected advanced cases. Finally, future developments of cellular therapy and cancer vaccines may be crucial in treating challenging cases. Adoptive cell therapy may be vital in patients whose disease is refractory to immunotherapy whilst cancer vaccines may be used in cases of disease recurrence following a complete tumour resection.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*, for the series "Medical Oncology: Challenges in 2022". The article has undergone external peer review.

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1432/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1432/coif). The series "Medical Oncology: Challenges in 2022" was commissioned by the editorial office without any funding or sponsorship. Anojan Augustine will be provided with a potential publication that will help with the postgraduate application and progression as a current foundation year 1 doctor. M.M. is a full-time Novartis employee and Novartis shareholder. S.B. and A.G. served as the unpaid Guest Editors of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons

© Annals of Palliative Medicine. All rights reserved.

Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Cancer today-World Health Organisation 2022. Available online: http://gco.iarc.fr/today/home.
2. Boussios S, Rassy E, Samartzis E, et al. Melanoma of unknown primary: New perspectives for an old story. Crit Rev Oncol Hematol 2021;158:103208.
3. Rastrelli M, Tropea S, Rossi CR, et al. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. In Vivo 2014;28:1005-11.
4. Ward WHFarma JMMatthews NH, et al. Epidemiology of Melanoma. 2017.
5. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. Cancer Biol Ther 2019;20:1366-79.
6. Lee HY, Chay WY, Tang MB, et al. Melanoma: differences between Asian and Caucasian patients. Ann Acad Med Singap 2012;41:17-20.
7. Bradford PT, Goldstein AM, McMaster ML, et al. Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986-2005. Arch Dermatol 2009;145:427-34.
8. Patnana M, Gershenwald JE, Hwu WJ, et al. Chapter 36 - Melanoma. In: Silverman PM, editor. Oncologic Imaging: A Multidisciplinary Approach. Philadelphia: W.B. Saunders; 2012:633-52.
9. Situm M, Buljan M, Kolić M, et al. Melanoma--clinical, dermatoscopical, and histopathological morphological characteristics. Acta Dermatovenerol Croat 2014;22:1-12.
10. Domingues B, Lopes JM, Soares P, et al. Melanoma treatment in review. Immunotargets Ther 2018;7:35-49.
11. ESMO. BRAF in Melanoma: ESMO Biomarker Factsheet OncologyPRO2015. Available online: https://oncologypro.esmo.org/education-library/factsheets-on-biomarkers/braf-in-melanoma
12. Nepote A, Avallone G, Ribero S, et al. Current Controversies and Challenges on BRAF V600K-Mutant Cutaneous Melanoma. J Clin Med 2022;11:828.
13. Batus M, Waheed S, Ruby C, et al. Optimal management of metastatic melanoma: current strategies and future directions. Am J Clin Dermatol 2013;14:179-94.
14. Jenkins RW, Sullivan RJ. NRAS mutant melanoma: an overview for the clinician for melanoma management. Melanoma Manag 2016;3:47-59.
15. Ayllón V, Rebollo A. Ras-induced cellular events (review). Mol Membr Biol 2000;17:65-73.
16. Randic T, Kozar I, Margue C, et al. NRAS mutant melanoma: Towards better therapies. Cancer Treat Rev 2021;99:102238.
17. Revythis A, Shah S, Kutka M, et al. Unraveling the Wide Spectrum of Melanoma Biomarkers. Diagnostics (Basel) 2021;11:1341.
18. Reschke M, Mihic-Probst D, van der Horst EH, et al. HER3 is a determinant for poor prognosis in melanoma. Clin Cancer Res 2008;14:5188-97.
19. Switzer B, Puzanov I, Skitzki JJ, et al. Managing Metastatic Melanoma in 2022: A Clinical Review. JCO Oncol Pract 2022;18:335-51.
20. Wilson MA, Schuchter LM. Chemotherapy for Melanoma. Cancer Treat Res 2016;167:209-29.
21. Smith CEP, Prasad V. Targeted Cancer Therapies. Am Fam Physician 2021;103:155-63.
22. Justiz Vaillant AA, Nessel TA, Zito PM. Immunotherapy. StatPearls. Treasure Island (FL): StatPearls Publishing LLC.; 2022.
23. Darvin P, Toor SM, Sasidharan Nair V, et al. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med 2018;50:1-11.
24. Khattak M, Fisher R, Turajlic S, et al. Targeted therapy and immunotherapy in advanced melanoma: an evolving paradigm. Ther Adv Med Oncol 2013;5:105-18.
25. Melanoma Treatment (PDQ®)–Patient Version - NCI. 2022.
26. Marques P, Grossman A. Ipilimumab-Induced Autoimmune Hypophysitis: Diagnostic and Management Challenges Illustrated by a Clinical Case. Acta Med Port 2015;28:775-9.
27. Perez-Santos M, Anaya-Ruiz M, Cebada J, et al. LAG-3 antagonists by cancer treatment: a patent review. Expert Opin Ther Pat 2019;29:643-51.
28. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med 2022;386:24-34.
29. ESMO. Cutaneous Melanoma- ESMO Clinical Practice Guidelines 2019. Available online: https://www.esmo.org/guidelines/guidelines-by-topic/melanoma/cutaneous-melanoma
30. Johnson DB, Lovly CM, Flavin M, et al. Impact of

© Annals of Palliative Medicine. All rights reserved.

NRAS mutations for patients with advanced melanoma treated with immune therapies. Cancer Immunol Res 2015;3:288-95.
31. NICE. Melanoma: assessment and management. National Institute for Health and Care Excellence; 2022.
32. NCCN. NCCN Clinical Practice Guidelines in Oncology-Melanoma: Cutaneous National Comprehensive Cancer Network2023. Available online: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
33. Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. Lancet 2022;399:1718-29.
34. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. Expert Rev Anticancer Ther 2018;18:775-84.
35. UK CR. Stage 3- Melanoma skin cancer 2020. Available online: https://www.cancerresearchuk.org/about-cancer/melanoma/stages-types/stage-3
36. Ackerman A, Klein O, McDermott DF, et al. Outcomes of patients with metastatic melanoma treated with immunotherapy prior to or after BRAF inhibitors. Cancer 2014;120:1695-701.
37. Pavlick AC, Zhao R, Lee CH, et al. First-line immunotherapy versus targeted therapy in patients with BRAF-mutant advanced melanoma: a real-world analysis. Future Oncol 2021;17:689-99.
38. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF(V600) mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;395:1835-44.
39. Testori A, Rutkowski P, Marsden J, et al. Surgery and radiotherapy in the treatment of cutaneous melanoma. Ann Oncol 2009;20 Suppl 6:vi22-9.
40. Peach H, Board R, Cook M, et al. Current role of sentinel lymph node biopsy in the management of cutaneous melanoma: A UK consensus statement. J Plast Reconstr Aesthet Surg 2020;73:36-42.
41. Hanna S, Lo SN, Saw RP. Surgical excision margins in primary cutaneous melanoma: A systematic review and meta-analysis. Eur J Surg Oncol 2021;47:1558-74.
42. Sladden MJ, Nieweg OE, Howle J, et al. Updated evidence-based clinical practice guidelines for the diagnosis and management of melanoma: definitive excision margins for primary cutaneous melanoma. Med J Aust 2018;208:137-42.
43. Tagliaferri L, Lancellotta V, Fionda B, et al. Immunotherapy and radiotherapy in melanoma: a multidisciplinary comprehensive review. Hum Vaccin Immunother 2022;18:1903827.
44. Phan GQ, Messina JL, Sondak VK, et al. Sentinel lymph node biopsy for melanoma: indications and rationale. Cancer Control 2009;16:234-9.
45. Shi W. Role for radiation therapy in melanoma. Surg Oncol Clin N Am 2015;24:323-35.
46. Takahashi J, Nagasawa S. Immunostimulatory Effects of Radiotherapy for Local and Systemic Control of Melanoma: A Review. Int J Mol Sci 2020;21:9324.
47. Ribas A, Comin-Anduix B, Economou JS, et al. Intratumoral immune cell infiltrates, FoxP3, and indoleamine 2,3-dioxygenase in patients with melanoma undergoing CTLA4 blockade. Clin Cancer Res 2009;15:390-9.
48. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun 2020;11:3801.
49. Salik B, Smyth MJ, Nakamura K. Targeting immune checkpoints in hematological malignancies. J Hematol Oncol 2020;13:111.
50. Raedler LA. Opdivo (Nivolumab): Second PD-1 Inhibitor Receives FDA Approval for Unresectable or Metastatic Melanoma. Am Health Drug Benefits 2015;8:180-3.
51. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521-32.
52. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320-30.
53. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. J Clin Oncol 2021;39:9506.
54. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390:1853-62.
55. Lebbé C, Meyer N, Mortier L, et al. Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. J Clin Oncol 2019;37:867-75.
56. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-

© Annals of Palliative Medicine. All rights reserved.

label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20:1239-51.
57. Hodi FS, Chiarion-Sileni V, Lewis KD, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. J Clin Oncol 2022;40:9522.
58. Spain L, Larkin J, Turajlic S. New survival standards for advanced melanoma. Br J Cancer 2020;122:1275-6.
59. Long GV, Hodi FS, Lipson EJ, Schadendorf D, Ascierto PA, Matamala L, et al. Relatlimab and nivolumab versus nivolumab in previously untreated metastatic or unresectable melanoma: Overall survival and response rates from RELATIVITY-047 (CA224-047). J Clin Oncol 2022;40:360385.
60. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1480-92.
61. Ballantyne AD, Garnock-Jones KP. Dabrafenib: first global approval. Drugs 2013;73:1367-76.
62. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
63. Rizos H, Menzies AM, Pupo GM, et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin Cancer Res 2014;20:1965-77.
64. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877-88.
65. Posch C, Moslehi H, Feeney L, et al. Combined targeting of MEK and PI3K/mTOR effector pathways is necessary to effectively inhibit NRAS mutant melanoma in vitro and in vivo. Proc Natl Acad Sci U S A 2013;110:4015-20.
66. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694-703.
67. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med 2019;381:626-36.
68. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248-60.
69. Trojaniello C, Luke JJ, Ascierto PA. Therapeutic Advancements Across Clinical Stages in Melanoma, With a Focus on Targeted Immunotherapy. Front Oncol 2021;11:670726.
70. Dummer R, Flaherty K, Robert C, et al. Five-year overall survival (OS) in COLUMBUS: A randomized phase 3 trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients (pts) with BRAF V600-mutant melanoma. J Clin Oncol 2021;39:9507.
71. Michielin O, van Akkooi ACJ, Ascierto PA, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2019;30:1884-901.
72. Eggermont AMM, Blank CU, Mandalà M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22:643-54.
73. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377:1824-35.
74. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522-30.
75. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med 2017;377:1813-23.
76. Maio M, Lewis K, Demidov L, et al. Adjuvant vemurafenib in resected, BRAFV600 mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol 2018;19:510-20.
77. Menzer C, Hassel JC. Targeted Therapy for Melanomas Without BRAF V600 Mutations. Curr Treat Options Oncol 2022;23:831-42.
78. Guo J, Carvajal RD, Dummer R, et al. Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol 2017;28:1380-7.
79. Thomas NE, Edmiston SN, Alexander A, et al. Association Between NRAS and BRAF Mutational Status and Melanoma-Specific Survival Among Patients With Higher-Risk Primary Melanoma. JAMA Oncol 2015;1:359-68.
80. Dumaz N, Hayward R, Martin J, et al. In melanoma, RAS mutations are accompanied by switching signaling from BRAF to CRAF and disrupted cyclic AMP signaling. Cancer Res 2006;66:9483-91.
81. Rose AAN, Armstrong SM, Hogg D, et al. Biologic subtypes of melanoma predict survival benefit of

© Annals of Palliative Medicine. All rights reserved.

combination anti-PD1+anti-CTLA4 immune checkpoint inhibitors versus anti-PD1 monotherapy. J Immunother Cancer 2021;9:e001642.
82. Rebecca VW, Alicea GM, Paraiso KH, et al. Vertical inhibition of the MAPK pathway enhances therapeutic responses in NRAS-mutant melanoma. Pigment Cell Melanoma Res 2014;27:1154-8.
83. Shi C, Gu Z, Xu S, et al. Candidate therapeutic agents in a newly established triple wild-type mucosal melanoma cell line. Cancer Commun (Lond) 2022;42:627-47.
84. Morjaria S. Driver mutations in oncogenesis. International Journal of Molecular and Immuno Oncology.6.
85. Larkin J, Lao CD, Urba WJ, et al. Efficacy and Safety of Nivolumab in Patients With BRAF V600 Mutant and BRAF Wild-Type Advanced Melanoma: A Pooled Analysis of 4 Clinical Trials. JAMA Oncol 2015;1:433-40.
86. Johnpulle RA, Johnson DB, Sosman JA. Molecular Targeted Therapy Approaches for BRAF Wild-Type Melanoma. Curr Oncol Rep 2016;18:6.
87. Giugliano F, Crimini E, Tarantino P, et al. First line treatment of BRAF mutated advanced melanoma: Does one size fit all? Cancer Treat Rev 2021;99:102253.
88. Chen TT. Statistical issues and challenges in immuno-oncology. J Immunother Cancer 2013;1:18.
89. Thorén FB, Anderson H, Strannegård Ö. Late divergence of survival curves in cancer immunotherapy trials: interpretation and implications. Cancer Immunol Immunother 2013;62:1547-51.
90. Ascierto PA, Mandala M, Ferrucci PF, et al. LBA40 SECOMBIT: The best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma: A phase II randomized study. Ann Oncol 2021;32:S1316-7.
91. Zawit M, Swami U, Awada H, et al. Current status of intralesional agents in treatment of malignant melanoma. Ann Transl Med 2021;9:1038.
92. Eggermont AMM, Blank CU, Mandala M, et al. Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial. J Clin Oncol 2020;38:3925-36.
93. Dummer R, Hauschild A, Santinami M, et al. Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. N Engl J Med 2020;383:1139-48.
94. Amaria RN, Postow M, Burton EM, et al. Neoadjuvant relatlimab and nivolumab in resectable melanoma. Nature 2022;611:155-60.
95. Chen Y, Shi XE, Tian JH, et al. Survival benefit of neoadjuvant chemotherapy for resectable breast cancer: A meta-analysis. Medicine (Baltimore) 2018;97:e10634.
96. Feeney G, Sehgal R, Sheehan M, et al. Neoadjuvant radiotherapy for rectal cancer management. World J Gastroenterol 2019;25:4850-69.
97. Liu J, Blake SJ, Yong MC, et al. Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease. Cancer Discov 2016;6:1382-99.
98. Amaria RN, Menzies AM, Burton EM, et al. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. Lancet Oncol 2019;20:e378-89.
99. Rozeman EA, Hoefsmit EP, Reijers ILM, et al. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med 2021;27:256-63.
100. van Akkooi ACJ, Zijlker LP, Wouters MWJM. Neoadjuvant Immune Checkpoint Inhibitor Therapy in Melanoma: Efficacy, Safety and Timing. BioDrugs 2022;36:373-80.
101. Lee AY, Brady MS. Neoadjuvant immunotherapy for melanoma. J Surg Oncol 2021;123:782-8.
102. Reijers ILM, Menzies AM, van Akkooi ACJ, et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. Nat Med 2022;28:1178-88.
103. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med 2018;24:1655-61.
104. Witt RG, Erstad DJ, Wargo JA. Neoadjuvant therapy for melanoma: rationale for neoadjuvant therapy and pivotal clinical trials. Ther Adv Med Oncol 2022;14:17588359221083052.
105. Dummer R, Gyorki DE, Hyngstrom J, et al. Neoadjuvant talimogene laherparepvec plus surgery versus surgery alone for resectable stage IIIB-IVM1a melanoma: a randomized, open-label, phase 2 trial. Nat Med 2021;27:1789-96.
106. Danielli R, Patuzzo R, Di Giacomo AM, et al. Intralesional administration of L19-IL2/L19-TNF in stage III or stage IVM1a melanoma patients: results of a phase II study. Cancer Immunol Immunother 2015;64:999-1009.
107. Fujiwara Y, Kato S, Nesline MK, et al. Indoleamine 2,3-dioxygenase (IDO) inhibitors and cancer immunotherapy. Cancer Treat Rev 2022;110:102461.
108. Lugowska I, Teterycz P, Rutkowski P. Immunotherapy of

© Annals of Palliative Medicine. All rights reserved.

melanoma. Contemp Oncol (Pozn) 2018;22:61-7.
109. Cell Therapy Improves Progression-Free Survival in Advanced Melanoma, First Phase 3 Study Shows [ESMO Congress 2022 Press Release] [press release]. 2022.
110. Hawkins RE, Jiang Y, Lorigan PC, et al. Clinical Feasibility and Treatment Outcomes with Unselected Autologous Tumor Infiltrating Lymphocyte Therapy in Patients with Advanced Cutaneous Melanoma. Cancer Res 2021;81.
111. Tucker N. FDA Grants Orphan Drug Designation to Novel TIL Therapy for Advanced-Stage Melanoma. Targeted Oncology; 2021.
112. Hamid O, Ismail R, Puzanov I. Intratumoral Immunotherapy-Update 2019. Oncologist 2020;25:e423-38.
113. Ott PA, Hu Z, Keskin DB, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 2017;547:217-21.
114. van Willigen WW, Bloemendal M, Gerritsen WR, et al. Dendritic Cell Cancer Therapy: Vaccinating the Right Patient at the Right Time. Front Immunol 2018;9:2265.
115. Santos Apolonio J, Lima de Souza Gonçalves V, Cordeiro Santos ML, et al. Oncolytic virus therapy in cancer: A current review. World J Virol 2021;10:229-55.

Cite this article as: Adeleke S, Okoli S, Augustine A, Galante J, Agnihotri A, Uccello M, Ghose A, Moschetta M, Boussios S. Melanoma—the therapeutic considerations in the clinical practice. Ann Palliat Med 2023;12(6):1355-1372. doi: 10.21037/apm-22-1432

© Annals of Palliative Medicine. All rights reserved.