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CLINICAL PERSPECTIVE

Melanoma update: is a cure now in sight?

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Abstract

Melanoma, one of the most aggressive skin cancers, poses a significant global health concern due to its high metastatic potential and resistance to conventional treatments. This review explores recent advancements in melanoma treatment, particularly the impact of targeted therapies and immunotherapies which have significantly extended survival and improved the quality of life for advanced melanoma patients. Additionally, the innovative combination and sequential strategies, with immune checkpoint inhibitors and cancer vaccines or targeted therapies against BRAF mutations, mark a promising direction. Recent advances in tumour infiltrating lymphocytes and oncolytic virus therapy and personalised cancer vaccine development are also covered, highlighting the role of precision medicine in achieving tailored, effective treatments. Despite these advancements, challenges persist, including drug resistance and the need for reliable biomarkers to predict treatment response and select patients. This review underscores the ongoing efforts in research and clinical trials to refine therapeutic strategies, improve treatment outcomes for a larger population detection and, ultimately, advance towards a cure for melanoma.

Introduction

Melanoma represents a major public health concern in Australia, ranking as the third most prevalent cancer and the 11th leading cause of cancer-related mortality.[1] Approximately a decade ago, advanced melanoma was regarded as a highly lethal cutaneous malignancy, with a median overall survival (OS) of merely 6–8 months.[2] At the time, treatment strategies primarily relied on cytotoxic chemotherapy agents such as dacarbazine or cytokines like interleukin-2 (IL-2) and interferon. However, these approaches yielded poor outcomes, with limited response rates and considerable toxicity.[3] Even for patients with localised disease, relapse and systemic dissemination following surgical resection posed significant challenges, as adjuvant treatments available at the time were suboptimal for achieving a definitive cure.

In the early 21st century, groundbreaking advancements in molecular biology, cancer genomics, immunology and drug development transformed the treatment landscape for melanoma, bringing renewed hope to patients. Today, with modern therapeutic strategies, nearly 50% of patients with metastatic melanoma achieve durable, long-term remission exceeding 5 years, raising the possibility of a potential cure.[4] As survival rates continue to improve, one pressing question emerges: Could a cure for melanoma finally be within our grasp?

This article delves into recent advancements in melanoma treatment, highlighting the potential for achieving long-term remissions and exploring emerging therapeutic approaches. Although not comprehensive, it offers a valuable overview of the key developments in this rapidly evolving field.

Metastatic melanoma

The introduction of immune checkpoint inhibitors (ICIs) and BRAF/MEK inhibitors over the past decade has significantly transformed outcomes for patients with advanced melanoma. Once considered a highly lethal disease, with fewer than 10% of patients surviving beyond 5 years, melanoma may now be curable in some cases.[5] Long-term data from early immunotherapy trials reveal that survival curves plateau over time, a pattern

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inconsistent with incurable malignancies, suggesting that patients who respond well to treatment may achieve durable, long-term survival.[6]

Supporting this, a recent population-based study from the Netherlands examining real-world survival outcomes reported that over 70% of patients achieving a complete response with first-line immunotherapy remain progression-free, while more than 90% survive beyond 3 years.[7]

However, the curative potential of targeted therapy with BRAF/MEK inhibitors remains contentious. While these treatments can induce rapid and significant initial responses, with about 20% of patients achieving a complete response, the long-term benefits are largely limited to fit patients with a low disease burden.[8] Unfortunately, the majority eventually experience disease progression due to acquired resistance, highlighting their limited ability to provide lasting cures.

Despite the notable improvements in melanoma treatment outcomes, the majority of patients ultimately succumb to their disease. This underscores the pressing need for innovative and more effective therapeutic strategies to further advance melanoma care.

Immune checkpoint inhibitors

The concept of unleashing the immune system by inhibiting its regulatory 'brakes' was pioneered by James Allison. He developed the first antibody targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4), leading to the creation of ipilimumab. This groundbreaking therapy demonstrated survival benefits in prospective trials[9] and received FDA approval in 2011. Around the same time, Tasuko Honjo discovered the programmed death-1 (PD-1) receptor, another inhibitory molecule preventing T cells from attacking cancer effectively. Allison and Honjo were jointly awarded the Nobel Prize in 2018 for their transformative contributions, marking a new era in cancer therapy.

Subsequently, anti-PD-1 antibodies, such as nivolumab and pembrolizumab, emerged as more effective and better-tolerated alternatives to ipilimumab.[10,11] Immunotherapy has since become a cornerstone of metastatic melanoma treatment, offering the potential for cure in certain patients.

The combination of ipilimumab and nivolumab (IpiNivo) is now the gold standard for first-line treatment of metastatic melanoma, based on the pivotal phase 3 CheckMate 067 trial. This trial compared IpiNivo to single-agent nivolumab or ipilimumab, revealing remarkable long-term survival outcomes. At 6.5 years of follow-up: IpiNivo: OS 49%, melanoma-specific survival (MSS) 56%; nivolumab alone: OS 42%, MSS 48%; and ipilimumab alone: OS 23%, MSS 27%. These results set the benchmark for advanced melanoma survival outcomes. However, the improved efficacy of IpiNivo comes at a cost – serious adverse events occur in 60% of patients, compared to 25% with single-agent therapies.[12] While some side effects are mild and reversible, others can be life-threatening or irreversible.

Efforts to enhance the efficacy of ICIs and reduce their toxicity have led to promising developments. One such advance is the blockade of lymphocyte activation gene-3 (LAG-3), an inhibitory co-receptor regulating T-cell activation. The fixed-dose combination of relatlimab with nivolumab (RelaNivo) was evaluated in the RELATIVITY-047 trial, showing progression-free survival (PFS) at 12 months: ~50% for RelaNivo compared favourably to IpiNivo in CheckMate 067; severe or very severe treatment-related adverse events: ~20%, significantly lower than with IpiNivo. While long-term OS data for RelaNivo do not exist, its better tolerability and similar efficacy make it an attractive option for patients with borderline functional status, low-volume metastatic disease or no brain involvement.

To address resistance, ongoing research has focussed on optimising treatment duration, exploring novel combination strategies and identifying biomarkers for better patient stratification is needed. While immunotherapy has transformed melanoma care, sustained progress is needed to extend these benefits to a larger proportion of patients.

Targeted therapy

Activating mutations in the BRAF proto-oncogene, present in 40%–50% of melanomas, were first identified in 2002. Following remarkable results from phase 1 trials of vemurafenib,[13] a BRAF inhibitor, a confirmatory phase 3 trial a decade later led to its approval for the treatment of unresectable or metastatic BRAF-mutated melanoma.[14] While vemurafenib monotherapy improved OS, its benefits were short-lived due to the rapid development of secondary resistance, typically within a year, and problematic toxicities.

The introduction of newer BRAF inhibitors and their combination with MEK inhibitors addressed some of these limitations. These combination therapies delayed the onset of secondary resistance and improved the side effect profiles. Currently, three approved BRAF/MEK inhibitor regimens – dabrafenib + trametinib (DT),[15] vemurafenib + cobimetinib[16] and encorafenib + binimetinib[17] – have comparable efficacy. These regimens achieve overall response rates of up to 70%, with approximately 40% of patients remaining progression-free at 1.5 years. They provide rapid and robust disease control for patients with BRAF-

mutant metastatic melanoma, offering multiple options tailored to side effect profiles. However, secondary resistance is a major issue, and most patients will eventually face disease progression.

Attempts to improve outcomes by combining immunotherapy with BRAF-targeted therapy were not successful. This shifted the focus to optimising the sequencing of these treatment modalities. The DREAMseq trial provided practice-changing insights, demonstrating that patients with BRAF-mutant melanoma who began treatment with IpiNivo and switched to DT upon disease progression had a 20% higher 2-year survival rate (OS at 2 years: 72% vs. 52%) compared to those treated with DT upfront.[18]

Optimal sequencing requires clinical judgement due to the differing response dynamics of these treatments. Immunotherapy acts more slowly, occasionally leading to initial disease progression before inducing a durable response. Conversely, BRAF/MEK-targeted therapy provides rapid and robust responses, making it invaluable for patients with high burden or rapidly progressing disease, poor performance status or contraindications to ICIs (Fig. 1).

Personalised immunotherapies

Tumour-infiltrating lymphocytes

Adoptive cell therapy using tumour-infiltrating lymphocytes (TILs) represents a personalised immunotherapy approach that has gained renewed interest as a treatment for metastatic melanoma. This process involves the surgical resection of a tumour to extract TILs, which are then selected for neoantigen reactivity and expanded *ex vivo* with interleukin 2. The expanded TILs are subsequently infused intravenously into the patient following lymphodepleting chemotherapy. Due to its complexity and logistical challenges, this therapy is restricted to specialised centres only.

In a pivotal phase III clinical trial, TIL therapy demonstrated improved PFS compared to ipilimumab in patients with PD-1 inhibitor-refractory metastatic melanoma.[19] This evidence, along with data from a phase II trial,[20] led to the FDA's accelerated approval of lifileucel in February 2024.

Currently, the TILVANCE-301 (NCT05727904) trial, an international multicentre phase III study, is enrolling metastatic melanoma patients in Australia to evaluate the efficacy and safety of combining lifileucel with pembrolizumab versus pembrolizumab alone as a first-line treatment. In August 2024, Fiona Stanley Hospital in Western Australia became the first hospital in the country to administer patient-specific anti-cancer cell therapy (lifileucel) to individuals with advanced melanoma.

Personalised cancer vaccines

Personalised cancer vaccines are designed to stimulate immune responses specifically against tumour antigens in patients with existing malignancies. Somatic mutations in tumours give rise to neoantigens, which are tumour-specific and highly immunogenic molecules unique to each patient. These vaccines are developed through genetic sequencing of tumour DNA to identify the most immunogenic neoantigens, which are then encoded in mRNA vaccines capable of inducing an immune response upon injection.

This approach enhances neoantigen presentation and immune activation, offering a promising therapeutic strategy. Several neoantigen-based vaccines are currently being tested in metastatic settings, often in combination with immunotherapy.

A phase II trial of BNT111, an 'off-the-shelf' vaccine targeting a fixed set of four cancer-specific antigens, has shown positive results in combination with cemiplimab in PD-1 refractory advanced melanoma patients.[21] Similarly, EVX-01, an AI-generated personalised vaccine, is being evaluated in the KEYNOTE-D36 (phase II study in combination with pembrolizumab (NCT05309421)).

These innovative approaches highlight the potential of personalised immunotherapies in addressing the complexities of metastatic melanoma and improving patient outcomes (Fig. 2; Table 1).

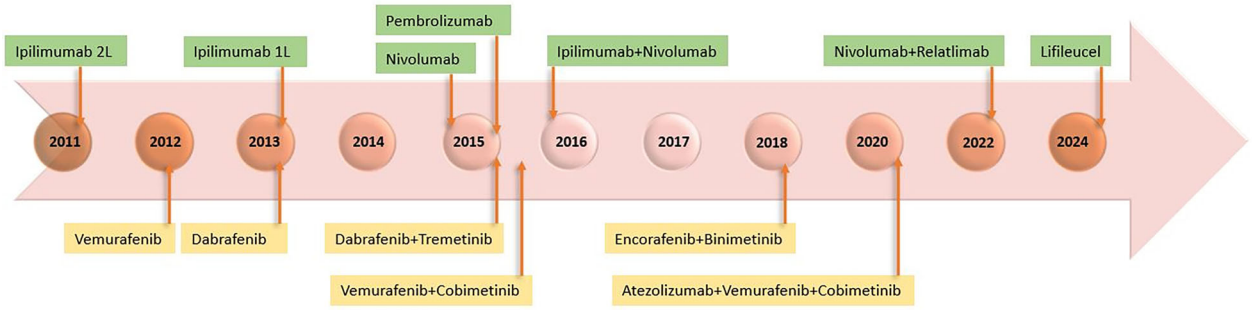

Figure 1 Timeline of drug development in advanced melanoma. 1L, first line; 2L, second line.

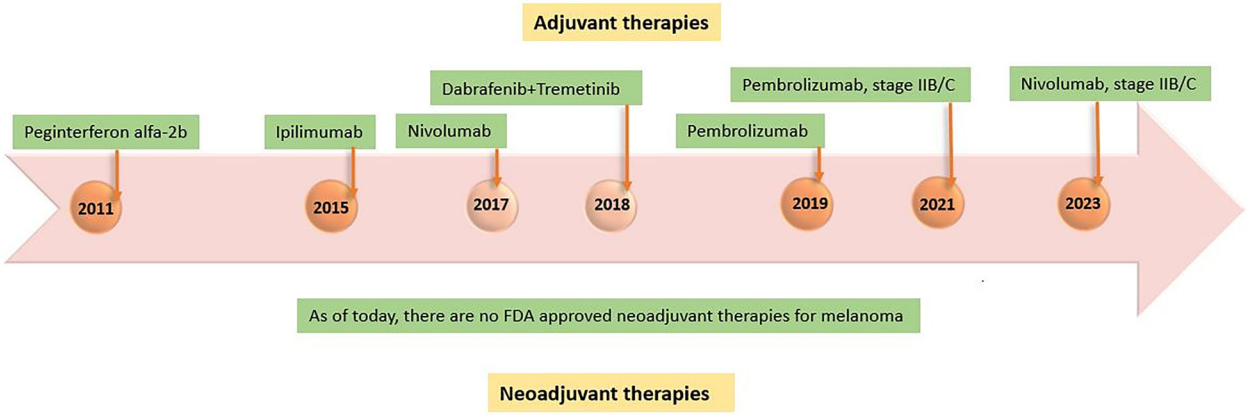

Figure 2 Timeline of drug development in early-stage melanoma.

Adjuvant therapy

Surgical excision with adequate margins and sentinel lymph node evaluation remains the primary curative approach for patients with localised melanoma. However, high-risk patients often experience relapse with disseminated disease, necessitating additional treatment. With the success of ICIs and targeted therapies in metastatic melanoma, these treatments have been evaluated as adjuvant therapies, showing significant improvements in PFS and distant-metastasis-free survival.

Despite no clear survival benefit, adjuvant therapy with either targeted therapy or ICIs has become the standard of care for resectable stage III or IV melanoma. Two pivotal randomised trials demonstrated the effectiveness of adjuvant immunotherapy. KEYNOTE-054 compared

Table 1 Ongoing trials for unresectable or metastatic melanoma

Clinical trial (ClinicalTrials.gov identifier)	Phase	Treatment setting	Treatment arms	Primary end point
TILVANCE-301 (NCT05727904)	3	First line	Lifileucel + pembrolizumab versus pembrolizumab	ORR and PFS
PRISM-MEL-301 (NCT06112314)	3	First line	IMC-F106C + nivolumab versus nivolumab-based regimen.	PFS
PORTSIDE (NCT05926960)	2	Post progression on anti-PD1 monotherapy	Encorafenib + binimetinib + pembrolizumab versus nivolumab + ipilimumab	ORR
TEBE-AM (NCT055492)	2/3	Post progression on anti-PD(L)1, ipilimumab ad BRAF TKI in case of BRAF mutation.	Tebentafusp versus tebentafusp + pembrolizumab versus investigator choice of therapy	ctDNA reduction, OS
(NCT04526899)	2	Post progression on anti-PD1	BNT111+ cemiplimab versus BNT-11 versus cemiplimab	ORR in BNT111+ Cemiplimab
NCT02339571	2/3	First line	Nivolumab + ipilimumab + sargramostim versus nivolumab + ipilimumab	OS
NCT06624644	2/3	Post progression on anti-PD(L)1, ipilimumab	LNS8801 versus LNS8801 + pembrolizumab versus physician choice	PFS
NCT04657991	3	First line, BRAF mutant	Encorafenib, binimetinib and pembrolizumab versus pembrolizumab	ORR, DLTs
IGNYTE-3 (NCT06264180)	3	Post progression on anti-PD(L)1, ipilimumab	VO + nivolumab versus physicians choice	OS
NCT06246916	3	First line	Fianlimab + cemiplimab versus relatlimab + nivolumab	ORR
NCT06008106	3	Post progression on immunotherapy in *NRAS* mutated patients	Tunlametinib versus combination chemotherapy of investigator choice	PFS

ctDNA, circulating tumour deoxyribonucleic acid; DLT, dose-limiting toxicity; ORR, overall response rate; OS, overall survival; PD1, programmed death 1; PDL1, programmed death ligand 1; PFS, progression-free survival; VO, vusolimogene oderparepvec.

pembrolizumab with a placebo, while CheckMate 238 evaluated nivolumab against ipilimumab. Both trials reported long-term benefits in reducing locoregional recurrence and distant metastases in patients with BRAF wild-type tumours.[22,23]

For BRAF-mutant tumours, 1 year of treatment with dabrafenib plus trametinib[24] or single-agent immunotherapy is considered acceptable. However, no randomised trials directly compared these options, leaving uncertainty about which approach provides greater benefit. The choice of therapy often depends on toxicity profiles; side effects of dabrafenib and trametinib are temporary and can be managed through dose interruptions or adjustments, whereas ICIs may cause long-lasting immune-related adverse events (irAEs), persisting even after treatment discontinuation.[25,26]

The use of adjuvant immunotherapy for high-risk stage II melanoma is a more recent advancement. Patients with thick or ulcerated stage II primary tumours, even if node-negative, have recurrence and metastasis risks comparable to early-stage III disease. The KEYNOTE-716 trial demonstrated a 46% reduction in recurrence risk at 2 years with 1 year of pembrolizumab treatment.[27] Similar findings were observed with nivolumab in the CheckMate-76 K trial.[28] Both drugs are FDA-approved for stage IIB/C melanoma, although their impact on OS remains under investigation.

Efforts to enhance adjuvant therapy efficacy continue, including the integration of neoantigen vaccines with ICIs. Earlier this year, the FDA granted breakthrough therapy designation to the first mRNA vaccine for adjuvant melanoma treatment, based on results from the KEYNOTE-942 trial. This phase 2b study evaluated the combination of V940 (mRNA-4157), an individualised mRNA-based vaccine, with pembrolizumab versus pembrolizumab alone in patients with high-risk, resected cutaneous melanoma. After a median follow-up of 2 years, over 75% of patients receiving the combination therapy were recurrence-free, and more than 90% were free from distant metastases, compared to 60% and 77%, respectively, with pembrolizumab alone. Recently reported OS data also showed the superiority of the combination therapy. Notably, this approach appears effective even in patients with low tumour mutation burden, a group that traditionally responds poorly to ICIs alone.[29]

The INTerpath-001 trial (NCT05933577), a phase III study, recently completed enrolling patients to further evaluate the safety and efficacy of V940 combined with pembrolizumab versus pembrolizumab alone (Table 2).

Neoadjuvant therapy

Neoadjuvant immunotherapy, which involves administering immune-based treatments before surgical intervention, has emerged as a transformative approach in managing melanoma, particularly in patients with resectable stage III disease. This strategy aims to reduce tumour burden preoperatively and enhance systemic anti-tumour immunity, potentially leading to improved long-term outcomes.

Administering immunotherapy before surgery offers several potential benefits:

- Enhanced immune activation: The presence of the intact tumour during immunotherapy may facilitate a more robust and comprehensive immune response, as the immune system can directly interact with tumour antigens.
- Early assessment of treatment efficacy: Pathological responses observed in resected specimens can serve as early indicators of treatment effectiveness, aiding in prognostication and tailoring subsequent therapies.
- Potential for treatment de-escalation: Achieving a major pathological response may allow some patients to avoid additional adjuvant therapy, thereby reducing treatment-related toxicity and healthcare costs.

Several pivotal studies have demonstrated the efficacy of neoadjuvant immunotherapy in melanoma:

Table 2 Ongoing clinical trials in the adjuvant setting

Clinical trial (ClinicalTrials.gov Identifier)	Phase	Stage	Treatment arms	Primary end point	Recruitment status
Relativity-098 (NCT05002569)	3	III-IV	Relatlimab + nivolumab versus nivolumab	RFS	Completed
Regeneron (NCT05608291)	3	II-IV	Cemiplimab/Fianlimab versus pembrolizumab	RFS	Ongoing
NivoMela (NCT04309409)	3	IIA/B/C	Nivolumab versus placebo	RFS	completed
Grand SLAM (NCT06488482)	3	IIB/C, III, IV	12 months versus 6 months of nivolumab/ pembrolizumab	RFS, DMFS	Not yet recruiting
INTerpath-001 (NCT05933577)	3	II-IV	V940 + pembrolizumab versus placebo + pembrolizumab	RFS	Completed

DMFS, distant-metastasis-free survival; RFS, recurrence free survival.

• OpACIN-neo and PRADO Trials: These studies investigated the combination of ipilimumab and nivolumab administered before surgery. Results indicated that approximately 80% of patients in the neoadjuvant treatment arm remained free from progression, recurrence, treatment complications or death at 2 years,[30] highlighting the potential of this approach to induce durable responses.
• SWOG S1801 Trial: This randomised phase II trial compared the standard adjuvant pembrolizumab regimen to a neoadjuvant approach where three cycles of pembrolizumab were given preoperatively. The findings revealed a significant improvement in 2-year event-free survival (EFS) for the neoadjuvant group, increasing from 50% to over 70%,[31] thereby establishing neoadjuvant pembrolizumab as a superior treatment option and prompting a substantial shift in clinical practice.
• NADINA Trial: This phase III trial compared the standard approach of upfront therapeutic lymph-node dissection followed by 12 cycles of adjuvant nivolumab to a regimen of two doses of neoadjuvant ipilimumab plus nivolumab followed by surgery. The neoadjuvant group demonstrated a 25% improvement in 12-month EFS, with benefits observed regardless of BRAF mutation status. Notably, more than half of the patients who achieved a major pathological response with only two doses of neoadjuvant therapy were able to forgo further adjuvant immunotherapy, suggesting a potential for treatment de-escalation in responders.[32]

While the impact of these strategies on OS is still under investigation, the NADINA trial represents a significant step towards a new standard of care. The possibility of de-escalating lymph node dissection following neoadjuvant immunotherapy is also under evaluation. Initial studies have shown promise,[33] but randomised trials are necessary before this approach can be widely adopted.

In contrast, neoadjuvant targeted therapy for patients with BRAF-mutated melanoma has not demonstrated the same level of benefit. Phase II trials like CombiNeo and NeoCombi reported high pathological response rates, but recurrence rates remained high, even in patients with complete tumour disappearance in resected specimens.[34] These findings indicate that neoadjuvant targeted therapy is not an optimal approach for BRAF-mutated stage III melanoma patients.

Intra-tumoural therapy with oncolytic viruses

The use of genetically modified viruses for cancer treatment is a relatively new approach. Talimogene laherparepvec (T-VEC), a genetically engineered herpes simplex virus type 1, is the first and only approved therapy of its kind. T-VEC works by selectively replicating within tumour cells, causing cell lysis and releasing tumour antigens, which then activate tumour-specific CD8+ T cells, triggering both local and systemic immune responses.[32]

The FDA approved T-VEC based on results from the OPTiM trial, which demonstrated durable responses in approximately 20% of patients.[35] Although the combination of T-VEC with pembrolizumab did not improve outcomes in patients with unresectable melanoma,[34] promising findings emerged from studies comparing

Table 3 Ongoing phase 2 trials in neoadjuvant setting

Clinical trial (ClinicalTrials.gov identifier)	Phase	Stage	Treatment arms	Primary end point
NeoACTIVATE (NCT03554083)	2	III	Vem + Cobi + Atezo; resection, then Atezo versus Cobi + Atezo; resection, then Atezo versus Atezo + Tiragolumab, resection, then Atezo	pCR
Neo PeLe (NCT04207086)	2	III	Pembro + Lenvatinib, Resection, Then Pembro	RFS
EA6194 (NCT04708418)	2	IIIB/C/D	Pembro, Resection, Then Pembro versus Pembro + TLR9 Agonist, Resection, Then Pembro	pCR
ALTER-PATH NeoDT (NCT04310397)	2	IIIB/C/D, BRAF-mutant	Dab + Tram, resection; If no pCR, then Dab + Tram + spartalizumab	RFS
EA6183 (NCT04221438)	2	IIIB/C/D, BRAF-mutant	Enco + Bini; resection, Enco + Bini	pCR
NCT05176470	1/2	IIIB/C/D, IV	Pembro + TIL (lifileucel), resection, then Pembro	Safety and feasibility
NEO-MIMAJOR (NCT05751928)	3	IIIB/C/D	BCD-217 (nurulimab + prolgolimab) versus standard therapy	
NCT04526730	2	III	Tavo (IL-12)–EP + Nivo; resection, then Nivo	pCR

Atezo, atezolizumab; Bini, binimetinib; Cobi, cobimetinib; Dab, dabrafenib; Enco, encorafenib; Nivo, nivolumab; pCR, pathological complete response; Pembro, pembrolizumab; RFS, recurrence-free survival; Tavo, tavokinogene telseplasmid; TIL, tumour-infiltrating lymphocyte; Tram, trametinib; Vem, vemurafenib.

neoadjuvant T-VEC followed by surgery versus surgery alone, as reported by Drummer and colleagues.[36]

A phase II trial led by Dr Reinhard Dummer compared neoadjuvant T-VEC followed by surgery to immediate surgery alone in patients with resectable stage IIIB to IVM1a melanoma. After 5 years of follow-up, neoadjuvant T-VEC demonstrated improved outcomes, including higher relapse-free survival (22.3% vs. 15.2%), EFS (43.7% vs. 27.4%) and OS (77.3% vs. 62.7%) compared to surgery alone.[37] These results highlight the potential of neoadjuvant T-VEC to provide significant long-term benefits for patients with advanced resectable melanoma.

Currently, T-VEC is a potential treatment option for patients with injectable, unresectable melanoma metastases, particularly those with satellite or in-transit lesions who prefer to avoid systemic therapies (Table 3).

Discussion

The current discourse on the potential for curing melanoma is marked by cautious optimism, underscored by transformative advancements in targeted therapies and immunotherapy. Over the last decade, these innovations have revolutionised the treatment landscape for advanced melanoma, a disease historically regarded as almost uniformly fatal in its metastatic stages. The advent of targeted therapies, such as BRAF and MEK inhibitors, alongside ICIs targeting the CTLA-4 and PD-1 pathways, has redefined outcomes, transitioning melanoma management from a palliative approach to one where long-term remission and even a potential cure are attainable for some patients. This progress represents a profound departure from earlier strategies reliant on surgery and conventional chemotherapy, which offered limited efficacy in metastatic disease.

Among the most significant milestones in melanoma treatment is the durability of responses seen with ICIs. Data from clinical trials and real-world evidence reveal that a subset of patients, particularly those with advanced stage IV melanoma, experience durable responses extending over years. For many of these patients, remission persists even after treatment discontinuation, suggesting the possibility of a 'functional cure'. These durable outcomes were previously inconceivable in the management of melanoma, highlighting the extraordinary potential of immunotherapy. The persistence of these responses has fuelled discussions around redefining 'cure' in the context of melanoma, moving beyond the traditional notion of complete eradication to encompass long-term disease control with sustained quality of life.

Despite these breakthroughs, significant challenges remain on the path to a universal cure. Primary and acquired resistance to therapy continues to limit the efficacy of current treatments. A substantial proportion of patients either fail to respond to initial therapy or relapse after an initial period of response, underscoring the need for novel approaches to overcome resistance. The heterogeneity of melanoma, both at the genetic and immunological levels, adds to the complexity, as it necessitates tailored interventions to address diverse resistance mechanisms. Research into combination therapies holds promise for enhancing response rates and mitigating resistance by targeting multiple pathways simultaneously. The tumour microenvironment and host immune factors also play critical roles in modulating treatment efficacy, presenting additional opportunities for therapeutic innovation. Advances in understanding these intricate interactions may pave the way for more effective and durable interventions.

Another critical consideration is the long-term safety and tolerability of current melanoma therapies. While irAEs associated with checkpoint inhibitors are often manageable, they can be severe or even life-threatening in some cases. Long-term toxicity, including late-onset immune-related effects, remains a concern, particularly as treatment durations extend and immune activation persists beyond therapy. Striking a balance between achieving remission and maintaining patients' quality of life will require refined strategies for managing these adverse events and a deeper understanding of their underlying mechanisms.

The future of melanoma treatment and the broader realisation of cure potential will likely hinge on advancements in personalised medicine. Identifying robust predictive biomarkers for response to targeted therapies and immunotherapies is critical for optimising treatment selection and tailoring therapies to individual patients. Integrating next-generation sequencing and advanced molecular diagnostic tools into clinical practice offers the prospect of unravelling the complex biology of melanoma, enabling more precise and effective interventions. Recent approvals of novel therapies, such as TIL therapy for advanced melanoma, signify a new era in cellular therapies for solid tumours. Concurrently, the development of personalised immunotherapeutics, including neoantigen-directed vaccines and AI-driven treatment algorithms, continues to expand the horizon of individualised melanoma care.

In conclusion, while the concept of a 'cure' in melanoma remains elusive for many, it is now a tangible reality for a growing subset of patients. This paradigm shift underscores the importance of sustained innovation and collaborative research to extend these benefits to a broader patient population. As personalised medicine continues to evolve, driven by advancements in genomics, immunology and therapeutic engineering, the

vision of achieving long-term remission and potential cure for melanoma appears increasingly within reach. The ongoing commitment to overcoming challenges in resistance, toxicity and tumour heterogeneity will be pivotal in ensuring that this promise becomes a reality for all patients facing melanoma.

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