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Review Article

Emerging immunotherapies in melanoma beyond immune checkpoint inhibitors: Vaccines, intralesional therapies, adoptive cell therapies, and T-cell engagers

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ABSTRACT

Background: Immune checkpoint inhibitors have transformed the management of melanoma, yet many patients do not achieve durable benefit. Novel immunotherapeutic strategies are being developed in both cutaneous and uveal melanoma.

Methods: This narrative review summarizes four classes of emerging immunotherapies: personalized cancer vaccines, intralesional immunotherapies, adoptive cell therapies, and bispecific T-cell engagers, focusing on mechanisms of action, clinical trial outcomes, limitations, and evidence maturity.

Results: In the randomized phase IIb KEYNOTE-942 trial, adding the individualized mRNA vaccine mRNA-4157/V940 to adjuvant pembrolizumab prolonged recurrence-free survival (RFS; hazard ratio [HR] 0.561, 95% confidence interval [CI] 0.309–1.017), a hypothesis-generating result under phase III evaluation. In the phase III PIVOTAL trial, neoadjuvant intralesional daromun improved RFS compared with upfront surgery in resectable, mostly recurrent stage III melanoma (HR 0.55, 95% CI 0.38–0.78). The tumor-infiltrating lymphocyte therapy lifileucel and the oncolytic virus RP1 plus nivolumab received accelerated approval for anti–PD-1-refractory melanoma based on single-arm studies (objective response rates approximately 31–33%, with durable responses). In human leukocyte antigen HLA-A*02:01-positive metastatic uveal melanoma, the T-cell engager tebentafusp improved overall survival (OS) in a phase III trial. Preferentially expressed antigen in melanoma (PRAME)-directed T-cell receptor (TCR)-engineered T cells and T-cell engagers have shown activity in early-phase studies.

Conclusions: These approaches expand therapeutic options for melanoma, but randomized evidence of improved outcomes is available only for some. HLA restriction, treatment burden, and manufacturing complexity remain key challenges, and ongoing phase III trials will define their clinical role.

1. Introduction

Over the past decade, immune checkpoint inhibitors (ICIs) have transformed metastatic melanoma from a nearly uniformly fatal disease into one in which long-term survival is achievable for a substantial proportion of patients. In advanced melanoma, anti–programmed cell

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death protein 1 (PD-1) monotherapy and combined CTLA-4/PD-1 blockade have yielded durable long-term survival in phase III trials, with a 10-year melanoma-specific survival (MSS) of 52% with nivolumab plus ipilimumab in CheckMate-067 [1,2]. In the phase III CheckMate-067 trial, nivolumab plus ipilimumab improved overall survival (OS) compared with ipilimumab alone, with a median OS of 71.9 months versus 19.9 months (36.9 months with nivolumab monotherapy) at 10-year follow-up and no new safety signals [2]. The phase III RELATIVITY-047 trial compared nivolumab plus relatlimab (an anti-LAG-3 antibody) with nivolumab alone in previously untreated advanced melanoma, excluding patients with active brain metastases; progression-free survival (PFS), the primary endpoint, was significantly improved, and at 4 years descriptive PFS and OS rates remained numerically higher with the combination (PFS 30.6% vs 23.6%; OS 52.0% vs 42.8%) [3].

1.1. Early stages

The benefit of ICIs in advanced disease led to their evaluation in the adjuvant setting. Adjuvant anti–PD-1 therapy became a standard of care for resected stage III–IV melanoma on the basis of the EORTC 1325/KEYNOTE-054 (pembrolizumab vs placebo) and CheckMate-238 (nivolumab vs ipilimumab) trials, which showed significant improvements in recurrence-free survival (RFS) [4,5]. In resected stage III melanoma with BRAF V600E/K mutations, adjuvant dabrafenib plus trametinib improved RFS compared with placebo in the phase III COMBI-AD trial (final analysis at a median follow-up of approximately 8 years: hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.43–0.63) [6].

Stage-specific prognosis has also prompted the evaluation of adjuvant therapy in stage II disease. According to the American Joint Committee on Cancer (AJCC) 8th edition database, the estimated 10-year MSS is 82% for stage IIB, 75% for stage IIC, and 88% for stage IIIA [7]; in two independent German registry cohorts, 10-year MSS was lower for stage IIB (72.0–79.9%) and IIC (57.6–64.7%) [8]. These estimates indicate that patients with resected stage IIB–IIC melanoma have a risk of melanoma-related death comparable to or higher than that of patients with stage IIIA disease, which provided the rationale for adjuvant trials in this population; however, prognosis alone does not define which patients benefit from adjuvant therapy, a decision that also depends on the expected absolute risk reduction, toxicity, and the available survival data. In the phase III KEYNOTE-716 trial, adjuvant pembrolizumab improved RFS, the primary endpoint, compared with placebo in resected stage IIB–IIC melanoma (HR 0.62, 95% CI 0.49–0.79) and distant metastasis-free survival (DMFS; HR 0.59, 95% CI 0.44–0.79) at a median follow-up of 39.4 months [9]. Similarly, in the phase III CheckMate-76 K trial, adjuvant nivolumab improved RFS compared with placebo (HR 0.42, 95% CI 0.30–0.59) at the primary analysis [10].

1.2. Limitations of the current standard of care

Despite these advances, unmet needs persist in both the early and metastatic settings. In the adjuvant setting, available trials have not yet shown a significant OS improvement, although follow-up remains immature for several of them. In CheckMate-238, 5-year OS was 76% with nivolumab and 72% with ipilimumab, an active comparator that complicates the interpretation of survival outcomes [5]; in COMBI-AD, the final OS analysis did not reach statistical significance (HR 0.80, 95% CI 0.62–1.01) [6]; and OS data from KEYNOTE-716 and CheckMate-76 K are not yet mature [9,10]. Subsequent lines of therapy after recurrence further confound OS analyses, and MSS is therefore frequently reported. Reassuringly, in CheckMate-238, median progression-free survival after subsequent therapy (PFS2) was not reached with nivolumab versus 83.6 months with ipilimumab (HR 0.77, 95% CI 0.63–0.93), suggesting that adjuvant nivolumab does not compromise the efficacy of subsequent therapies [5]. Prognostic biomarkers identified in exploratory analyses of CheckMate-238, such as tumor mutational burden, interferon-γ signature, and intratumoral $CD8^+$ T-cell infiltration, were associated with outcomes in both treatment arms but have limited predictive value and require validation [5].

Attempts to intensify adjuvant therapy have so far been unsuccessful. In CheckMate-915, adjuvant nivolumab plus ipilimumab did not improve RFS compared with nivolumab alone (HR 0.92, 95% CI 0.77–1.09) [11], and trials combining nivolumab or pembrolizumab with anti-LAG-3, anti-TIGIT agents, or interleukins did not improve RFS, with several closing accrual early [12–14]. These results suggest that strategies effective in metastatic disease do not necessarily translate to the adjuvant setting, possibly because tumor and host immune biology differ across disease stages.

In the metastatic setting, primary resistance to ICIs affects approximately 40–65% of patients, and a substantial fraction of initial responders eventually develop acquired resistance [15]. Mechanistically, resistance reflects an interplay of tumor-intrinsic and host-related factors, including defects in the antigen presentation machinery, impaired interferon signaling, T-cell exclusion and exhaustion, immunosuppressive metabolic pathways in the tumor microenvironment, and systemic modulators such as the gut microbiome. Many of these mechanisms are not directly targeted by PD-1/PD-L1 or CTLA-4 blockade, which may limit the benefit of further checkpoint intensification. Figure 1 summarizes the main mechanisms of resistance to ICIs and the mechanistic rationale of the emerging strategies discussed in this review.

These limitations have prompted the development of therapeutic modalities that act through mechanisms other than the release of inhibitory checkpoints: generating new tumor-specific immune responses, redirecting T cells to tumor cells, or providing ex vivo–expanded tumor-reactive T cells. This narrative review focuses on four classes of emerging immunotherapies that have reached late-phase clinical evaluation or regulatory approval: (i) individualized neoantigen-based mRNA and peptide vaccines, designed to expand tumor-specific T-cell repertoires; (ii) intralesional immunotherapies, designed to induce local inflammation with potential systemic antitumor effects; (iii) adoptive cell therapies, including tumor-infiltrating lymphocyte (TIL) therapy and T-cell receptor (TCR)-engineered T cells, which deliver large numbers of tumor-reactive T cells to patients refractory to ICIs; and (iv) bispecific T-cell engagers, such as immune-mobilizing monoclonal T-cell receptors against cancer (ImmTACs), which redirect polyclonal T cells to tumor cells presenting the target antigen. For each class, we discuss mechanisms of action, key clinical trial outcomes, limitations, and future perspectives in cutaneous and uveal melanoma. Other strategies to overcome ICI resistance, including gut microbiome modulation, biomarker-driven patient selection, and multi-omic profiling platforms, are beyond the scope of this review and are mentioned only as future perspectives.

2. Rationale and methods

This narrative, non-systematic review examines four classes of emerging immunotherapies for melanoma: personalized cancer vaccines, intralesional immunotherapies, adoptive cell therapies, and bispecific T-cell engagers. Between November 2025 and January 2026, three authors (LDC, IT, AB) searched PubMed/MEDLINE and Scopus, combining "melanoma" with terms related to each therapeutic class (e.g., "vaccine," "intralesional," "oncolytic virus," "tumor-infiltrating lymphocytes," "T-cell engager"), and reviewed abstracts from the 2025 meetings of the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO). The search focused on publications from 2022 onwards; earlier studies were included when they reported pivotal trials or provided essential background on the standard of care and resistance mechanisms. Clinical trials, observational studies, and conference abstracts with complete results were eligible; case reports and publications without outcome data were excluded. Studies were selected by consensus of the three authors based

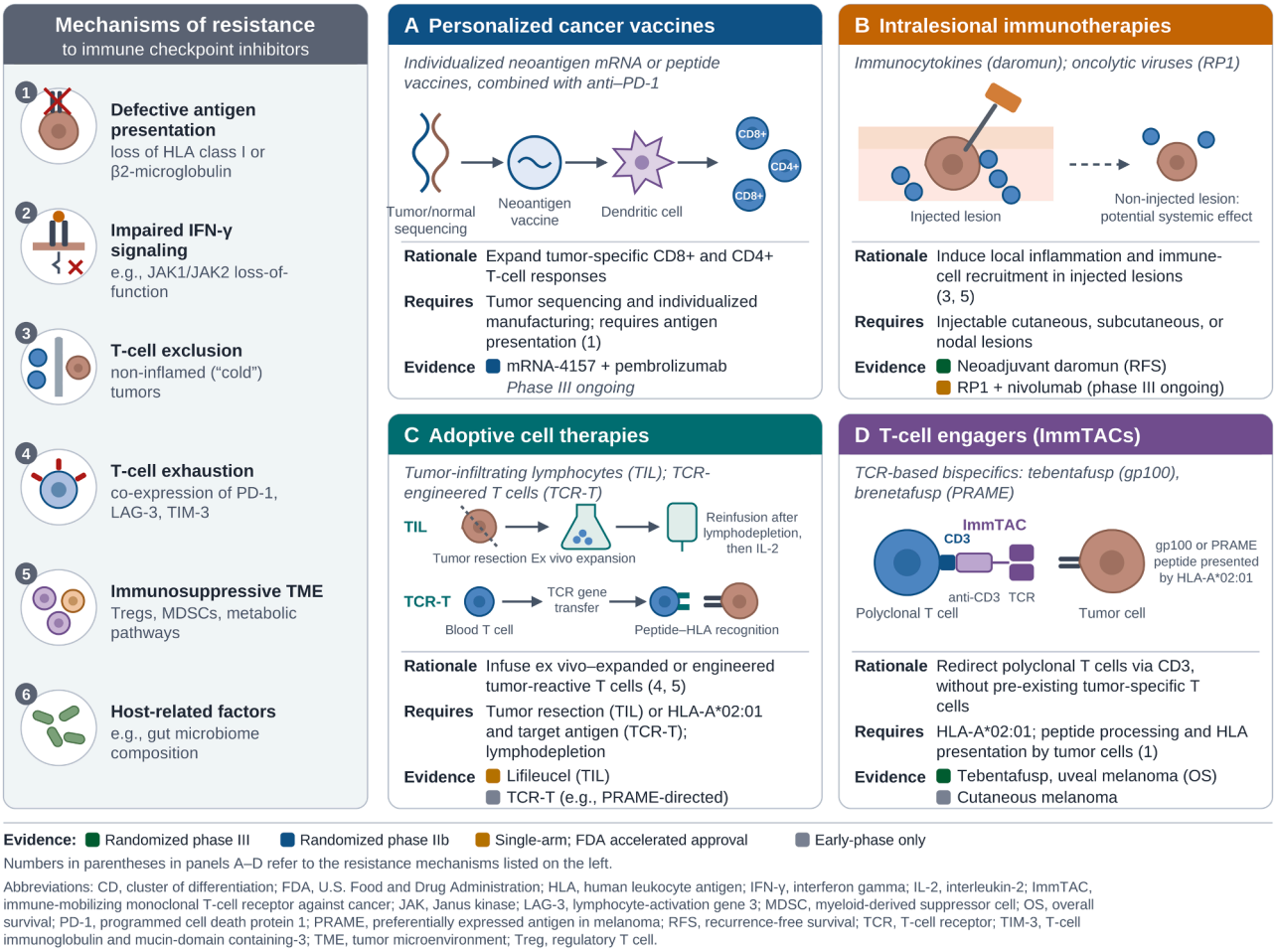


Figure 1. Mechanisms of resistance to immune checkpoint inhibitors and mechanistic rationale of the emerging immunotherapies discussed in this review. Left: main tumor-intrinsic and host-related mechanisms of resistance. Panels A–D: personalized cancer vaccines (A), intralesional immunotherapies (B), adoptive cell therapies (C), and T-cell engagers (D), with their mechanistic rationale, main requirements, and current level of clinical evidence (color-coded). Numbers in parentheses refer to the resistance mechanisms listed on the left. Abbreviations are defined within the figure. The figure was drawn as vector graphics with the assistance of Claude Opus 5.5 (Anthropic), which generated the drawing code under the authors' direction; the content was defined and verified by the authors.

on clinical relevance, level of evidence, and novelty, with a priority on prospective trials. Conference abstracts were included only when no full publication was available, and references were updated during revision with subsequently published full reports and updated analyses. Overall, 44 sources were included: 20 clinical trial reports, 4 observational or translational studies, 6 conference abstracts, 10 reviews or trial-design papers, 2 regulatory documents, and 2 trial registry records.

3. Individualized cancer vaccines: from antigen exposure to immune memory engineering

Given the high burden of tumor-specific neoantigens in cutaneous melanoma, several trials have evaluated the addition of individualized neoantigen therapy, also known as "personalized cancer vaccines," to ICIs, with the aim of expanding tumor-specific T-cell repertoires beyond those reinvigorated by checkpoint blockade alone. The two main platforms evaluated in recent clinical trials are peptide-based and mRNA-based vaccines. Preclinical and translational studies indicate that effective vaccine-induced immunity relies on antigen cross-presentation by dendritic cells and on the coordinated activation of $CD4^+$ helper and $CD8^+$ effector T cells.

Peptide vaccines typically include a limited number of antigens for pharmacological and manufacturing reasons and may therefore not capture the antigenic heterogeneity of the tumor. This may have contributed to the failure of early shared-antigen vaccines, such as the MAGE-A3 immunotherapeutic, which did not improve disease-free survival compared with placebo as adjuvant therapy in resected stage III melanoma [16]. More recent approaches use individualized antigen selection. In the single-arm phase II EVX-01 trial, a peptide vaccine including neoantigens selected by an artificial intelligence–based platform was added to pembrolizumab in patients with metastatic melanoma. At 2 years, the objective response rate (ORR) was 75% (12/16 evaluable patients), with 11 of 12 responses ongoing; because vaccination began 12 weeks after pembrolizumab initiation and there was no control arm, the contribution of the vaccine to these responses cannot be determined. Vaccine-induced neoantigen-specific T-cell responses were detected in all patients, and no grade ≥3 vaccine-related adverse events were reported [17]. mRNA platforms encapsulated in lipid nanoparticles allow a larger number of targets to be encoded, with potentially faster manufacturing and antigen presentation through both major histocompatibility complex (MHC) class I and II pathways. mRNA-4157 (V940, intismeran autogene) encodes up to 34 patient-specific neoantigens selected by sequencing of tumor DNA and RNA, matched normal DNA, and human leukocyte antigen (HLA) typing. In the randomized, open-label phase IIb KEYNOTE-942 trial, 157 patients with completely resected high-risk stage IIIB–IV melanoma were assigned 2:1 to mRNA-4157 plus pembrolizumab or pembrolizumab alone. At a median follow-up of approximately 2 years, RFS, the primary endpoint, was longer with the combination (18-month RFS 79% vs 62%; HR 0.561, 95% CI 0.309–1.017; two-sided $P = 0.053$). DMFS, a key secondary

endpoint, was also improved (HR 0.347, 95% CI 0.145–0.828) [18]. Exploratory subgroup analyses suggested a consistent effect irrespective of tumor mutational burden and PD-L1 expression, but the small sample size precludes firm conclusions. Grade ≥3 treatment-related adverse events occurred in 25% of patients in the combination arm and 18% in the pembrolizumab arm, with no mRNA-4157-related grade 4–5 events; vaccine-related events were mostly low-grade injection-site reactions, fatigue, and transient flu-like symptoms [18]. These hypothesis-generating results are being tested in the randomized phase III V940-001 trial (Table 1). Overall, personalized vaccines aim to

Table 1
Clinical trials of mRNA and peptide vaccines in melanoma, grouped by setting and trial aim.

Trial (NCT number; acronym)	Vaccine (platform)	Setting/ population	Phase and design[1]	Registered primary endpoint[1]	Planned or actual enrollment[1]	Status[1]	Key reported results (source; data cutoff or follow-up)
Adjuvant setting: randomized efficacy trials							
NCT03897881; KEYNOTE-942	mRNA-4157 (V940, intismeran autogene) + pembrolizumab vs pembrolizumab (individualized neoantigen mRNA; up to 34 neoantigens)	Completely resected high-risk stage IIIB–IV cutaneous melanoma	Phase 2 (published as phase IIb); randomized 2:1, open-label	RFS	267[2]	Active, not recruiting	n = 157; RFS HR 0.561 (95% CI 0.309–1.017; two-sided P = 0.053); 18-month RFS 79% vs 62%; DMFS HR 0.347 (95% CI 0.145–0.828) (Weber et al., Lancet 2024 [18]; median follow-up ≈23 months)
NCT05933577; V940-001	Intismeran autogene (V940) + pembrolizumab vs placebo + pembrolizumab (individualized neoantigen mRNA)	Resected high-risk stage IIB–IV cutaneous melanoma	Phase 3; randomized, placebo-controlled, masked	RFS	1089	Active, not recruiting	Not yet reported
Advanced or metastatic setting: efficacy trials							
NCT04526899; BNT111-01	BNT111 (FixVac; RNA-LPX encoding NY-ESO-1, MAGE-A3, tyrosinase, TPTE) ± cemiplimab (shared-antigen mRNA)	Unresectable stage III/IV cutaneous melanoma after progression on anti–PD-1/PD-L1	Phase 2; randomized 2:1:1, open-label (combination and single-agent calibrator arms)	ORR by BICR (BNT111 + cemiplimab arm)	184	Completed; results posted	BNT111 + cemiplimab arm: ORR 18.0% (95% CI 10.6–27.6%; n = 89; one-sided P = 0.0148) by BICR (ClinicalTrials.gov results database[3]; time frame up to 24 months)
NCT05309421; EVX-01	EVX-01 + pembrolizumab (individualized neoantigen peptide; AI-selected neoantigens)	Unresectable or metastatic melanoma, first line	Phase 2; single-arm	Change in best overall response	17	Active, not recruiting	ORR 75% (12/16 evaluable) at 2 years; vaccine contribution not determinable (single arm; pembrolizumab started 12 weeks before vaccination) (Khattak et al., ESMO 2025 [17])
Early-phase trials: safety, dose finding, and immunogenicity							
NCT03313778; KEYNOTE-603	mRNA-4157 alone or + pembrolizumab (individualized neoantigen mRNA)	Solid tumors, including resected and unresectable melanoma cohorts	Phase 1; non-randomized	Adverse events	161	Active, not recruiting	—
NCT02410733; Lipo-MERIT	RNA-LPX encoding NY-ESO-1, MAGE-A3, tyrosinase, TPTE (shared-antigen mRNA; same antigen set as BNT111), IV	Advanced melanoma	Phase 1; non-randomized	Adverse events (safety and tolerability)	119	Completed	—
NCT05533697; mRNA-4359-P101	mRNA-4359 alone or + pembrolizumab or ipilimumab + nivolumab (mRNA cancer vaccine)	Advanced solid tumors, including melanoma	Phase 1/2; non-randomized	MTD/RDE; DLTs; adverse events; ORR by BICR (one expansion arm)	361	Recruiting	—
NCT04364230; Mel66	6MHP + mutant BRAF neoantigen peptide + CDX-1140 (anti-CD40) + poly-ICLC (multi-peptide)	Melanoma, including ocular/uveal melanoma	Phase 1/2; single group	Safety; immune response rate	22	Completed	—
NCT02382549; Mel61	6MHP + dabrafenib and trametinib (helper peptides)	Stage IIIB–IV melanoma treated with BRAF and MEK inhibitors (advanced and neoadjuvant cohorts)	Early phase 1; single group	Adverse events; $CD4^+$ T-cell responses in blood	8	Terminated	—

[1] Phase, design, registered primary endpoint, enrollment, and status as reported on ClinicalTrials.gov (accessed October 10, 2026); registered primary endpoints may differ from the endpoints reported in publications.
[2] Registry enrollment includes all study parts; the published randomized analysis included 157 patients.
[3] Results posted on ClinicalTrials.gov; no peer-reviewed full publication identified at the time of revision.

broaden tumor-specific immune recognition rather than solely release inhibitory pathways, and represent a rational complement to checkpoint blockade, particularly in the adjuvant setting. However, their clinical benefit has not yet been confirmed in a phase III trial. Table 1 summarizes the key trials of vaccine-based therapies in melanoma.

Abbreviations: 6MHP, six melanoma helper peptides; AI, artificial intelligence; BICR, blinded independent central review; CD, cluster of differentiation; CI, confidence interval; DLT, dose-limiting toxicity; DMFS, distant metastasis-free survival; HR, hazard ratio; IV, intravenous; MAGE-A3, melanoma-associated antigen A3; MTD, maximum tolerated dose; NCT, ClinicalTrials.gov identifier; NY-ESO-1, New York esophageal squamous cell carcinoma 1; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; poly-ICLC, polyinosinic-polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose; RDE, recommended dose for expansion; RFS, recurrence-free survival; RNA-LPX, RNA-lipoplex; TPTE, transmembrane phosphatase with tensin homology.

4. Intralesional immunotherapy: oncolytic viruses and local immune reprogramming

Intralesional immunotherapies, including immunocytokines and oncolytic viruses, aim to induce local inflammation within injected lesions, with the potential to elicit systemic antitumor immune responses. Their use requires injectable cutaneous, subcutaneous, or nodal lesions, which makes them particularly relevant in locoregional disease. The phase III, open-label PIVOTAL trial (NCT02938299) compared neoadjuvant intralesional daromun followed by surgery with upfront surgery in 256 patients with resectable stage IIIB/C cutaneous melanoma (AJCC 7th edition) and at least one injectable lesion; 87% had recurrent disease after prior surgery and/or adjuvant therapy, and patients with distant metastases were excluded. Daromun combines two fibronectin-targeting immunocytokines, L19IL2 and L19TNF, in which interleukin-2 and tumor necrosis factor are fused to L19, an antibody fragment binding the extra-domain B of fibronectin, a neoangiogenesis marker expressed in most metastatic melanoma lesions but absent from normal skin. Daromun was injected weekly for up to 4 weeks before surgery. The primary endpoint, RFS by blinded independent central review, was met at the primary analysis (median follow-up 21 months; HR 0.59, 95% CI 0.41–0.86; $P = 0.005$) [19]. In the updated analysis at a median follow-up of 36.8 months, RFS remained longer with daromun (median 23.8 vs 6.5 months; HR 0.55, 95% CI 0.38–0.78; $P < 0.001$), as did DMFS, a secondary endpoint (HR 0.53, 95% CI 0.33–0.83; $P = 0.005$); OS data were immature, and exploratory analyses suggested a consistent benefit in patients with recurrent disease, including those previously treated with systemic therapy [20]. A pathological complete response was documented in 21% of patients who underwent surgery after daromun [19]. Grade 3 treatment-related adverse events occurred in 28.7% of patients in the daromun arm and 7.3% in the surgery-alone arm, mostly injection-site reactions, with no grade 4–5 treatment-related events [20]. The investigators interpreted the reduction in distant recurrence as suggestive of a systemic immune response; however, the open-label design, the exploratory nature of subgroup analyses, and the longer interval from randomization to surgery in the neoadjuvant arm should be considered when interpreting these findings. Among oncolytic viruses, RP1 (vusolimogene oderparepvec) is a genetically modified herpes simplex virus type 1 expressing granulocyte–macrophage colony-stimulating factor (GM-CSF) and a fusogenic protein. In the registration-directed, single-arm cohort of the phase I/II IGNYTE trial, 140 patients with advanced melanoma that had progressed on anti–PD-1 therapy received intratumoral RP1 plus nivolumab; 65.7% had primary anti–PD-1 resistance and 46.4% had received prior anti–PD-1 plus anti–CTLA-4 therapy. By independent central review, the confirmed ORR was 32.9% (95% CI 25.2–41.3%) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, including complete responses in 15.0%, with a median duration of response of 33.7 months (95% CI 14.1–not reached); the ORR was 33.6% per modified RECIST v1.1. Grade 3 and 4 treatment-related adverse events occurred in 9.3% and 3.6% of patients, respectively [21]. In the absence of a control arm, the contribution of RP1 to the activity of nivolumab cannot be quantified. The U.S. Food and Drug Administration (FDA) initially issued complete response letters (July 2025 and April 2026), considering that IGNYTE was not an adequate and well-controlled investigation, and subsequently granted accelerated approval to RP1 plus nivolumab on August 6, 2026, for adults with unresectable advanced cutaneous melanoma that progressed during treatment with a PD-1–blocking antibody–based regimen, based on ORR and duration of response [22]. Continued approval is contingent on confirmation of clinical benefit in the ongoing randomized phase III IGNYTE-3 trial (NCT06264180).

Overall, these data indicate that intralesional approaches can produce clinically meaningful activity in selected patients with injectable disease, and that local treatment may be associated with systemic effects; randomized evidence of improved survival is not yet available.

5. Adoptive immunotherapies in melanoma treatment: from tumor-infiltrating lymphocytes to engineered cellular therapies

In patients with advanced or heavily pretreated disease, immune checkpoint inhibition may be insufficient to control tumor progression because of profound immune dysfunction and established mechanisms of immune escape, including an immunosuppressive tumor microenvironment (TME) [23]. Adoptive cell therapy aims to provide large numbers of tumor-reactive effector cells generated ex vivo, which are reinfused after lymphodepleting chemotherapy. Among solid tumors, melanoma is the disease in which this approach has shown the most consistent clinical activity. Adoptive immunotherapies can be classified into MHC-dependent strategies, including tumor-infiltrating lymphocyte (TIL) therapy and T-cell receptor–engineered T-cell (TCR-T) therapy, and MHC-independent strategies, such as chimeric antigen receptor (CAR)-based approaches.

5.1. Tumor-infiltrating lymphocyte (TIL) therapy

TIL therapy exploits tumor-reactive $CD8^+$ and $CD4^+$ T cells present within resected tumor tissue. These lymphocytes are expanded ex vivo with interleukin-2 (IL-2) and reinfused after non-myeloablative lymphodepletion with cyclophosphamide and fludarabine, followed by high-dose IL-2. Lymphodepletion depletes regulatory T cells and increases the availability of homeostatic cytokines that support the expansion and persistence of infused TILs [24].

Lifileucel was evaluated in the single-arm phase II C-144-01 trial in patients with advanced melanoma previously treated with anti–PD-1 therapy and, if BRAF V600-mutated, BRAF ± MEK inhibitors. In cohort 2 ($n = 66$), the investigator-assessed ORR per RECIST v1.1 was 36% (95% CI 25–49%), including 2 complete and 22 partial responses, with median duration of response not reached at a median follow-up of 18.7 months [25]. In the pooled analysis of cohorts 2 and 4 ($n = 153$), the ORR assessed by an independent review committee was 31.4%; at a median follow-up of 57.8 months, the median duration of response was 36.5 months, median OS was 13.9 months, and 5-year OS was 19.7% [26,27]. In February 2024, the FDA granted accelerated approval to lifileucel for adults with unresectable or metastatic melanoma previously treated with a PD-1–blocking antibody and, if BRAF V600-mutated, a BRAF inhibitor with or without a MEK inhibitor, based on an ORR of 31.5% (95% CI 21.1–43.4%) in 73 patients treated within the recommended dose range, with median duration of response not reached [28]. These single-arm data indicate durable responses in a subset of patients, but comparative benefit over other post–anti–PD-1 options has not been established in this setting.

Toxicity is driven largely by lymphodepleting chemotherapy and high-dose IL-2 and includes febrile neutropenia, prolonged cytopenias, infections, hypotension, and capillary leak; the product label includes a

boxed warning for treatment-related mortality, prolonged severe cytopenia, severe infection, and cardiopulmonary and renal impairment [28]. Late immune-related adverse events are uncommon, consistent with the one-time nature of treatment. The need for surgical tumor harvest, a manufacturing interval of several weeks, inpatient management, and specialized centers limits patient eligibility and access.

5.2. Next-generation TIL platforms

Efforts are ongoing to reduce dependence on systemic high-dose IL-2. OBX-115 is an engineered TIL product expressing a regulatable membrane-bound interleukin-15 (mbIL-15), whose activity is controlled by oral acetazolamide. In a single-center phase I study in patients with ICI-resistant advanced melanoma, OBX-115 was administered without exogenous IL-2 and showed pharmacologically controllable expansion and persistence of product-derived T cells, without systemic cytokine elevation [29]. These are early translational data; whether such platforms can achieve efficacy comparable to conventional TIL therapy with lower toxicity remains to be established in larger studies.

5.3. TCR-engineered T-cell therapies

TCR-T therapies use peripheral blood T cells genetically modified ex vivo to express T-cell receptors that recognize defined melanoma-associated antigens presented by specific HLA molecules, generating monoclonal, antigen-specific T-cell populations with high functional avidity. IMA203 (anzutresgene autoleucel) is an autologous TCR-T cell therapy targeting a PRAME-derived peptide presented by HLA-A*02:01. In a phase Ia/Ib trial enrolling heavily pretreated patients with HLA-A*02:01-positive, PRAME-positive solid tumors, IMA203 was administered with low-dose IL-2 after lymphodepleting chemotherapy. At the most recent data cutoff (September 24, 2025), 33 patients with metastatic melanoma had been treated at the recommended phase II dose in phase Ib. In the cutaneous melanoma cohort (n = 14), mostly refractory to two prior lines of ICIs, the confirmed ORR was 50% (7/14), with a median duration of response of 17.9 months. In the uveal melanoma cohort (n = 16), which included patients previously treated with tebentafusp, the confirmed ORR was 67% (10/15 evaluable patients), with a median duration of response of 11.0 months [30,31]. Among 70 patients with solid tumors treated across all dose levels, grade 3 cytokine release syndrome and neurotoxicity occurred in 11% and 4%, respectively, with no grade 5 events [32]. These results are preliminary and derive from small, non-randomized early-phase cohorts; the randomized phase III SUPRAME trial is evaluating IMA203 in patients with cutaneous melanoma previously treated with ICIs, and a phase II cohort in uveal melanoma is ongoing. More generally, TCR-T therapies are restricted to patients with specific HLA alleles, are vulnerable to immune escape through antigen loss or HLA downregulation, and have been associated in early-phase trials with severe toxicities, including off-target and on-target/off-tumor effects and neurotoxicity [33].

5.4. CAR-based cellular therapies

CAR-T and CAR-natural killer (CAR-NK) cells recognize surface antigens through engineered receptors that combine antigen-binding and intracellular signaling domains, independently of HLA presentation. Although CAR-based therapies have transformed the treatment of hematologic malignancies, their activity in solid tumors, including melanoma, has been limited by inadequate trafficking, antigen heterogeneity, and the immunosuppressive TME; in melanoma, they remain investigational [34].

6. Bispecific monoclonal antibodies and T-Cell engagers in melanoma

T-cell engagers (TCEs) are engineered molecules that bind a tumor-associated target with one arm and CD3 on T cells with the other, redirecting polyclonal T cells toward tumor cells independently of their native T-cell receptor specificity [35]. The extent to which this mechanism circumvents antigen-presentation defects depends on the target: antibody-based TCEs directed against surface antigens act independently of HLA, whereas TCR-based molecules such as ImmTACs recognize intracellular antigens only as peptide–HLA complexes on tumor cells. ImmTACs therefore do not require a pre-existing tumor-specific T-cell repertoire or priming by professional antigen-presenting cells, but still depend on antigen processing and expression of the relevant HLA allele by tumor cells, and loss of HLA or of the target antigen is a potential resistance mechanism.

Tebentafusp is a first-in-class ImmTAC consisting of a high-affinity TCR specific for a gp100 peptide presented by HLA-A*02:01, fused to an anti-CD3 effector domain. Metastatic uveal melanoma, which is biologically distinct from cutaneous melanoma and characterized by low tumor mutational burden and limited benefit from ICIs, is the setting in which this class has shown its most robust clinical benefit. In a randomized phase III trial in previously untreated HLA-A*02:01-positive patients with metastatic uveal melanoma, tebentafusp improved OS, the primary endpoint, compared with investigator's choice (pembrolizumab, ipilimumab, or dacarbazine), with an HR of 0.51 (95% CI 0.37–0.71) at the primary analysis [36]; with a minimum follow-up of 3 years, the HR was 0.68 (95% CI 0.54–0.87), with a median OS of 21.6 versus 16.9 months and a 3-year OS of 27% versus 18% [37]. The most common treatment-related adverse events were cytokine-mediated (rash, pyrexia, pruritus, and hypotension), mostly occurring during the first doses, with no treatment-related deaths [37]. Tebentafusp is approved for HLA-A*02:01-positive adults with unresectable or metastatic uveal melanoma. In cutaneous melanoma, the evidence for TCEs remains early. In a phase I study in 85 heavily pretreated patients with metastatic cutaneous melanoma (89% previously treated with anti–PD-(L)1), tebentafusp combined with durvalumab, tremelimumab, or both had no new safety signals; among 72 efficacy-evaluable patients, the ORR was 14% and 1-year OS was 76% (95% CI 70–81%), a figure that requires cautious interpretation in the absence of a control arm [38]. The randomized phase II/III TEBE-AM trial is comparing tebentafusp-based regimens with investigator's choice in previously treated advanced cutaneous melanoma [39]. PRAME, which is frequently expressed in cutaneous melanoma, is an additional target for HLA-restricted redirection strategies [40]. In a phase I trial of brenetafusp, a PRAME × CD3 ImmTAC, in patients with ICI-pretreated cutaneous melanoma (data cutoff March 18, 2024), the ORR was 11% (4/36 evaluable patients) and the disease control rate was 56% (20/36), with cytokine release syndrome limited to grade 1–2 [41]. The phase III PRISM-MEL-301 trial is evaluating brenetafusp plus nivolumab as first-line therapy (NCT06112314). These early-phase data indicate biological activity but do not yet establish clinical benefit in cutaneous melanoma.

7. Discussion: emerging immunotherapies beyond checkpoint blockade

ICIs have enabled long-term disease control for a substantial proportion of patients with melanoma across early and advanced disease settings. The current challenge is to improve outcomes for patients whose disease is primarily resistant to, or relapses after, checkpoint blockade. Personalized vaccines, intralesional immunotherapies, adoptive cell therapies, and T-cell engagers address this challenge through distinct mechanisms, which can be broadly described as expanding tumor-specific immune recognition ("immune instruction," e.g., personalized vaccines), inducing local inflammation with potential systemic effects ("local immune reprogramming," e.g., intralesional therapies), redirecting polyclonal T cells to tumor cells ("immune redirection," e.g., T-cell engagers), and providing ex vivo–expanded or engineered effector T cells ("immune replacement," e.g., adoptive cell

therapies). This framework is conceptual: it reflects mechanistic rationale rather than demonstrated differences in clinical benefit, and the modalities differ considerably in evidence maturity, eligibility, and treatment burden. Evidence maturity varies widely across and within these classes. Randomized phase III data showing improved survival outcomes are currently available for tebentafusp, which improved OS in HLA-A*02:01-positive metastatic uveal melanoma, and for neoadjuvant daromun, which improved RFS and DMFS compared with upfront surgery in resectable, mostly recurrent stage III melanoma, although OS data from PIVOTAL remain immature. Lifileucel and RP1 plus nivolumab have received accelerated approval on the basis of response rates and response duration in single-arm studies of patients with anti–PD-1-refractory disease, and their comparative benefit remains to be confirmed. Personalized mRNA vaccines are supported by a randomized phase IIb trial whose primary endpoint result was hypothesis-generating, pending phase III confirmation. TCR-T cell therapies, next-generation TIL platforms, and T-cell engagers in cutaneous melanoma are supported only by early-phase, mostly single-arm data from small cohorts. Eligibility and treatment burden also differ. HLA-restricted modalities, including tebentafusp, brenetafusp, and TCR-T cell therapies, require HLA-A*02:01 typing, and TCR-T therapies additionally require target antigen expression, which restricts them to a subset of patients. Intralesional therapies require injectable lesions and are applicable mainly to locoregional disease. Patient-specific products, including personalized vaccines and cellular therapies, require tissue acquisition and manufacturing intervals that may be acceptable in the adjuvant setting but problematic in rapidly progressive disease. Adoptive cell therapies require lymphodepletion and, for conventional TIL therapy, high-dose IL-2, with substantial acute toxicity and the need for inpatient management in specialized centers, whereas vaccines and intralesional agents have generally shown predominantly low-grade, local, or systemic inflammatory toxicities.

7.1. Future perspectives

Several areas outside the scope of this review may further refine patient selection, including circulating tumor DNA, host-level determinants such as the gut microbiome, and integrative multi-omic platforms, which are being evaluated in prospective initiatives such as PIP-PREDICT (NCT06536257) [42–44]. Their clinical value will depend on prospective validation, feasibility, and measurable impact on treatment decisions and outcomes.

7.2. Conclusions

The emerging immunotherapies reviewed here expand the options available to patients with melanoma, but only some of them are supported by randomized evidence of improved outcomes. Their future role will depend on the results of ongoing phase III trials, on the identification of patients most likely to benefit, and on the feasibility of delivering complex, often patient-specific treatments in routine practice.

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Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used Claude (Anthropic; Claude Sonnet 5.5 and Claude Opus 5.5) to check grammar and language, to assist in revising the manuscript in response to the reviewers' comments, and to generate the drawing code for Figure 1. The graphical abstract was composed by the authors in Microsoft PowerPoint from a layout drafted with the assistance of Claude Opus 5.5; no generative AI image tool was used. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Declaration of competing interest

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