Review Article

Non-Coding RNA Mechanisms, Biomarkers and Therapeutic Modulation of Immune-Checkpoint Response in Melanoma: A Systematic Evidence Map

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Immune checkpoint blockade has transformed advanced melanoma care, yet response and resistance remain heterogeneous. We systematically mapped clinical, translational/computational and mechanistic evidence linking non-coding RNAs (ncRNAs) to melanoma immunotherapy. PubMed/MEDLINE, Europe PMC and Google Scholar were searched, supplemented by citation chasing and a Dimensions update; selection followed PRISMA 2020 and PRISMA-S. As retrospective quality control, two reviewers independently re-screened the complete title-and-abstract set and all 185 full-text reports using unchanged eligibility criteria, with adjudication by a third reviewer. Sixty-eight reports were included. The 21 patient-based reports formed the core clinical biomarker stratum; 23 translational/computational and 24 mechanistic/preclinical reports were mapped as supportive evidence domains rather than equivalent clinical validation. Plasma microRNAs, extracellular-vesicle-associated RNAs and tissue ncRNA signatures showed response-associated, prognostic or monitoring potential, whereas computational signatures and experimental models expanded the map of immune-state regulation and therapeutic modulation. Meta-analysis was not appropriate because no candidate-outcome-assay combination had sufficient independent clinical and methodological homogeneity. Small retrospective cohorts, assay heterogeneity, incomplete calibration and limited external validation prevented clinical implementation. Exploratory TCGA-SKCM analysis of a predefined candidate subset provided immune-context triangulation but not independent immunotherapy-response validation. This evidence map distinguishes a clinically relevant but immature biomarker core from a broader hypothesis-generating mechanistic landscape. Translation requires standardised assays, locked thresholds, prospective immune-checkpoint-inhibitor-treated cohorts and demonstration of incremental clinical value.

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1. Introduction

Immune-checkpoint blockade has altered the clinical trajectory of advanced melanoma, with ipilimumab, anti-programmed cell death protein 1 (PD-1) monotherapy and combined nivolumab/ipilimumab establishing durable survival benefit in subsets of patients [1][2][3]. Nevertheless, therapeutic response remains heterogeneous and resistance can emerge through tumour-intrinsic, immune-cell-intrinsic and microenvironmental mechanisms, including defects in interferon signalling, antigen presentation, immune-cell states and broader transcriptomic programmes of response or resistance [4][5][6]. Established clinical and molecular markers such as disease stage, lactate dehydrogenase (LDH), programmed death ligand 1 (PD-L1) expression, tumour mutational burden, T-cell-inflamed gene-expression programmes and immune-cell infiltration provide useful context, but none fully captures dynamic post-transcriptional regulation, non-invasive monitoring potential, or the circulating molecular consequences of tumour-immune crosstalk [7][8].

ncRNAs are attractive biomarker candidates because they regulate gene-expression networks at transcriptional, post-transcriptional and epigenetic levels and can be detected in tissue, circulation and extracellular-vesicle compartments [9][10][11]. miRNAs can coordinately regulate immune checkpoints, interferon signalling, myeloid differentiation, ferroptosis and T-cell dysfunction [12][13][14]. lncRNAs and circRNAs may operate as immune-regulatory scaffolds, competing endogenous RNAs, antigenic or translational substrates, or modulators of RNA processing and chromatin state [15][16][17][18]. Circulating and extracellular vesicle-associated (EV) ncRNAs are also appealing because they can be sampled repeatedly, potentially allowing longitudinal monitoring of response or resistance [19][20][21].

However, the field remains fragmented. Some studies report direct patient-based associations between ncRNAs and immune-checkpoint inhibitor (ICI) response, progression-free survival or overall survival [13][14][15][16][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34]. Others use public transcriptomic cohorts or machine-learning models to derive signatures [23][25][28][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53], while mechanistic and therapeutic-modulation studies establish biological plausibility in cells, animal models or extracellular-vesicle systems [12][13][14][18][21][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73]. These evidence domains answer different questions and should not be interpreted as equivalent clinical biomarker validation. A systematic evidence-map design is therefore appropriate for locating the patient-based biomarker evidence within the broader mechanistic-to-clinical translation pathway. The present framework emphasises analytical validity, clinical validity, clinical utility and

translational readiness, consistent with Biomarkers, EndpointS, and other Tools (BEST) terminology and reporting expectations from REMARK, TRIPOD/PROBAST, MISEV2023 and PRISMA-S [11][74][75][76][77].

A recent review summarised the broader roles of miRNAs in melanoma diagnosis, prognosis and treatment prediction [78]. The present systematic evidence map differs by focusing specifically on ICI response and resistance across miRNA, lncRNA, circRNA and EV-associated RNA evidence. It treats direct patient-based biomarker studies as the clinical core and maps computational, mechanistic and therapeutic-modulation studies as distinct supportive domains, thereby avoiding conflation of biological plausibility with clinical validation.

Objectives

The primary objective was to systematically map the clinical, translational/computational and mechanistic evidence linking ncRNAs to melanoma ICI response, resistance and therapeutic modulation. Within this map, the core clinical objective was to evaluate ncRNAs as candidate treatment-effect predictive, response-associated, prognostic and monitoring biomarkers in patient-based ICI studies. Secondary objectives were to classify reports by primary evidence tier and context of use, assess analytical and clinical validation, map mechanistic plausibility and therapeutic interventions, summarise quantitative evidence where reported, and identify gaps that prevent clinical implementation.

2. Materials and methods

Protocol and registration

No review protocol was prospectively registered in PROSPERO or the Open Science Framework (OSF). The absence of prospective protocol registration is transparently acknowledged as a methodological limitation. The subsequent retrospective independent re-screening and adjudication procedures were undertaken to strengthen the reliability and auditability of the study-selection process; however, these procedures were not considered to remediate or substitute for prospective protocol registration.

Study selection and reviewer workflow

All retrieved records were initially screened at the title-and-abstract stage by the primary reviewer, Saadi Awl Karim, using the predefined eligibility criteria. All reports progressing to full-text assessment were also initially evaluated by the same reviewer. As a retrospective selection quality-control procedure, Saman Mustafa Mohammed and Danya Azad subsequently and independently re-screened the complete set of

retrieved records at the title-and-abstract stage using the same unchanged eligibility criteria. Each reviewer then independently assessed the full texts of all 185 potentially eligible reports, comprising 180 reports identified through the original database searches and five reports identified through supplementary searching. The two secondary reviewers conducted their assessments independently of one another. Any unclear, indeterminate, or discordant eligibility decisions arising at either screening stage were referred to Saadi Awl Karim for adjudication. Following comparison and reconciliation of all reviewer decisions, every eligibility decision was finalised, and no unresolved disagreement remained.

Reporting framework

The systematic evidence map was prepared according to PRISMA 2020 [79] and the search methods were documented according to PRISMA-S [75]. Biomarker terminology and context-of-use concepts were aligned with the FDA-NIH BEST glossary [80]. Tumour-marker and prognostic reporting were interpreted using REMARK concepts [74], prediction-model studies were appraised using TRIPOD and PROBAST concepts [76] [77], animal/preclinical components using SYRCLE domains where applicable [81], and extracellular-vesicle studies using MISEV2023 reporting expectations [11].

Information sources and search strategy

The original search retrieved 406 records from PubMed/MEDLINE, 872 from Europe PMC and the first 200 Google Scholar results, yielding 1,478 records before de-duplication. Citation chasing was used for supplementary verification, but a separate source-level yield was not recoverable from the archived log. The final supplementary update was performed in Dimensions on 12 June 2026 using the Title and abstract field. Embase and Web of Science Core Collection were not searched because subscription access was unavailable. Dimensions and citation chasing were therefore used as supplementary mitigation sources rather than as direct substitutes for Embase or Web of Science. Full source-specific strings, dates, yields, field restrictions and PRISMA-S documentation are provided in Supplementary file 1.

Eligibility criteria

The evidence map addressed a broad mechanistic-to-clinical question while preserving a nested clinical biomarker stratum. Studies were eligible if they met the following core criteria: a melanoma-focused population or melanoma-specific experimental system; an exposure, biomarker, mechanism, signature or therapeutic intervention involving at least one ncRNA class; relevance to ICI response, resistance, clinical benefit, progression, survival, treatment monitoring or checkpoint-resistance biology; and original peer-

reviewed data. Direct patient-based ICI studies constituted the core clinical biomarker evidence. Translational/computational and mechanistic/preclinical reports were included to map model development, biological plausibility and therapeutic modulation, but were not treated as equivalent to patient-level clinical validation. Non-peer-reviewed preprints were excluded unless a peer-reviewed version was available. Reviews, editorials, background-only articles, non-melanoma studies, studies without ncRNA relevance, and studies lacking ICI-response/resistance/survival or mechanistic checkpoint relevance were excluded. The reconciled screening counts, the complete independent re-screening and adjudication workflow, and the available record-level eligibility decisions are documented in Supplementary file 2.

Data extraction

Data extraction captured study design, melanoma context, sample size, biospecimen or model, ncRNA class, assay platform, ICI regimen, outcome definitions, reported effect estimates, validation status, biomarker context of use and readiness interpretation. Quantitative fields were verified against the available full articles and accessible supplementary material. Values absent from a source article were recorded explicitly as 'Not reported in the article', 'Not applicable' or 'Not estimable', as appropriate; no numerical value was imputed. The extracted study characteristics and quantitative evidence tables are provided in Supplementary file 3.

Evidence-domain, tier and context-of-use classification

Each report was assigned one mutually exclusive primary evidence tier according to its strongest direct evidence and one or more context-of-use tags. Tier 1 comprised direct patient-based clinical association, monitoring or validation evidence; Tier 2 comprised early translational or computational evidence; and Tier 3 comprised mechanistic, preclinical or therapeutic-modulation evidence without patient-level biomarker validation. Context-of-use tags were treatment-effect predictive, response-associated, prognostic, monitoring/pharmacodynamic, toxicity, computational model development, mechanistic or therapeutic. The term "treatment-effect predictive" was reserved for designs containing a treatment comparator or a biomarker-by-treatment interaction. Associations within single-arm ICI cohorts were described as response-associated, prognostic or monitoring evidence rather than definitive treatment-effect prediction. Mixed-design reports could inform more than one narrative theme, but each report was counted once in the canonical 68-report evidence map.

Risk-of-bias and biomarker-validity assessment

Risk-of-bias and biomarker-validity assessment was adapted to study design. Prognostic and response-associated clinical studies were assessed using Quality in Prognosis Studies (QUIPS)-aligned domains;

prediction-model studies were assessed using PROBAST concepts; animal components used SYRCLE domains; EV studies received a separate MISEV2023 reporting and characterisation overlay; and mechanistic cell studies were evaluated for replication, controls, blinding transparency, assay multiplicity and biological validity. Reporting completeness was kept separate from risk of bias. Study-specific risk-of-bias and biomarker-validity judgements, design-adapted assessments, and supporting rationales for the 68 included reports are provided in Supplementary file 4.

Data synthesis

The synthesis was structured as an evidence map with design-stratified narrative synthesis. Poolability was evaluated within clinically comparable candidate-outcome groups rather than across the three evidence tiers. Studies were assessed for comparability by ncRNA candidate or panel, context of use, biospecimen, assay method, ICI regimen, endpoint definition, assessment time and effect measure. No candidate-outcome-assay combination was represented by at least two independent patient-based studies with sufficient clinical and methodological homogeneity for a defensible pooled estimate; meta-analysis was therefore not performed. Narrative synthesis followed Synthesis Without Meta-analysis (SWiM) principles [82]: reports were grouped by primary evidence tier and context of use, effect direction and magnitude were summarised where reported, and heterogeneity, validation status and limitations were prioritised. Counts across all 68 reports describe the breadth of the evidence map and were not interpreted as counts of clinically validated biomarkers. Hazard ratios, odds ratios, areas under the curve, P values, false-discovery rates, confidence intervals and validation status were extracted as reported and were not inferred when absent. Formal certainty-of-evidence grading and formal assessment of bias due to missing results were not undertaken because the review was an evidence map spanning non-comparable designs and did not generate pooled, candidate-specific effect estimates; this limitation was incorporated into the readiness interpretation.

Exploratory TCGA-SKCM bioinformatics contextualisation

Exploratory bioinformatics contextualisation was performed as a secondary, hypothesis-prioritising analysis rather than as clinical validation. The candidate/proxy feature set was locked before the later eligibility reconciliation expanded the review from 34 to 68 reports; the module was not rerun and therefore contextualises a predefined subset rather than every candidate in the final evidence base. The Cancer Genome Atlas Skin Cutaneous Melanoma (TCGA-SKCM) RNA-sequencing dataset was accessed through the National Cancer Institute Genomic Data Commons Data Portal [83]. Candidate/proxy expression values were mapped to bulk-tumour transcriptomic data, transformed as log2(count + 1), and compared with predefined immune-context scores representing interferon-gamma-related, T-cell-inflamed, cytolytic, CD8 T-cell, checkpoint and

myeloid/inflammatory programmes. Spearman correlations were used for immune-context analyses with false-discovery-rate correction. For exploratory survival contextualisation, one sample per patient was retained, prioritising metastatic samples when available, and overall survival was evaluated using median cutoffs, Kaplan-Meier/log-rank analysis, univariable Cox models and age-adjusted Cox models. miRNA candidates were mapped separately as TCGA precursor-level miRNA proxies; these were not interpreted as mature-arm-specific plasma or extracellular-vesicle validation. Full details are provided in Supplementary file 5.

3. Results

Study selection

The original search identified 1,478 records. After removal of 147 duplicates, 1,331 records were screened; 1,151 were excluded at the title-and-abstract stage, and 180 full-text reports were assessed. Following final verification and adjudication, including resolution of nine eligibility-sensitive reports, 116 reports were excluded and 64 were included from the original route. The supplementary Dimensions search retrieved 301 publication records. After triage, 114 records underwent additional title-and-abstract screening, of which 108 were excluded, four were duplicates or had been identified previously, and two proceeded to full-text assessment. Three additional reports had already entered full-text assessment during the broader supplementary update and citation-verification process; together with the two records from the 114-record checklist, this produced five supplementary full-text assessments. Four were included and one was excluded because the available article version was awaiting peer review. The final synthesis therefore comprised 68 unique eligible reports [12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][84][85][86][87][88][89]. The legacy 28-report detailed audit represented a documented subset of the complete independent re-screening exercise and was not counted as a separate evidence-identification route. Within the boundary reassessment of nine eligibility-sensitive full-text reports, six reports were confirmed as eligible and three were excluded. The complete study characteristics and canonical bibliographic details of the 68 included reports are provided in Supplementary file 6. Supplementary file 2 provides the reconciled screening counts, documents the scope and workflow of the independent re-screening and adjudication procedures, and presents the available record-level full-text eligibility decisions. The complete study-selection process is summarised in Fig. 1.

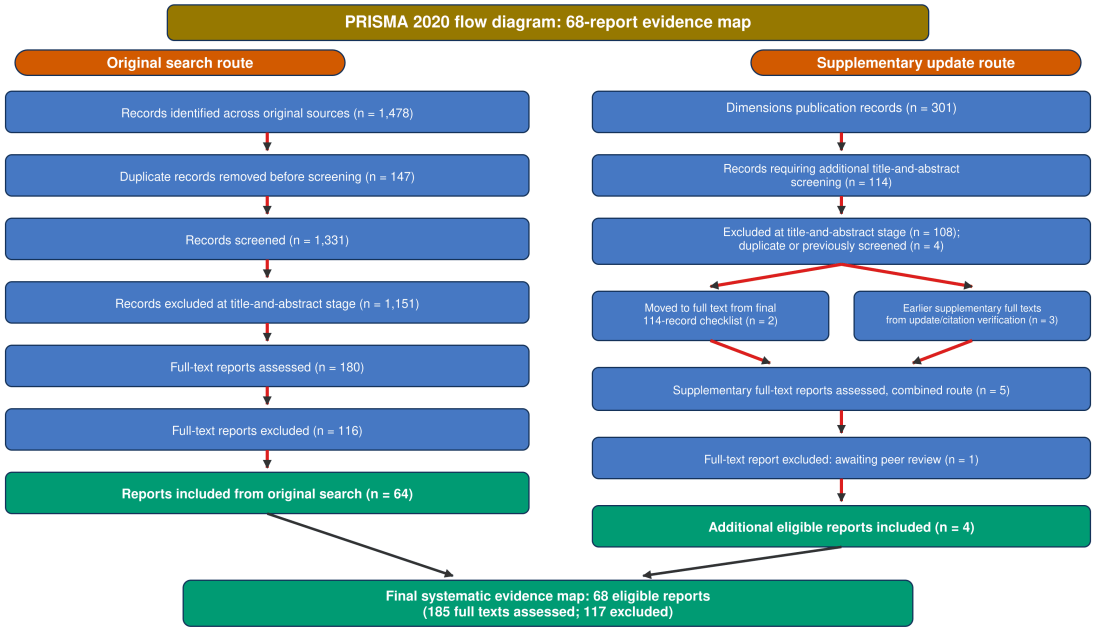


Figure 1. PRISMA 2020 flow diagram of study selection. The original and supplementary search routes yielded 68 eligible reports after assessment of 185 full texts; 117 full-text reports were excluded.

Evidence-map architecture and tier-based synthesis

The systematic evidence map contained 68 heterogeneous reports assigned to one primary evidence tier according to their strongest direct evidence [12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][84][85][86][87][88][89]. The clinical core comprised 21 direct patient-based association, monitoring or validation reports (Tier 1). The supportive evidence layer comprised 23 early translational/computational models or public-cohort analyses (Tier 2) and 24 mechanistic/preclinical or therapeutic-modulation reports (Tier 3). Thus, 47 reports expanded mechanistic and translational coverage but were not counted as direct clinical biomarker validation. Context-of-use tags were assigned separately, allowing mixed-design reports to inform response-associated, prognostic, monitoring, computational, mechanistic or therapeutic themes without double counting. The framework is summarised in Table 1.

Primary evidence-map tier	Definition	Typical evidence in this review	Readiness interpretation
Tier 1: direct patient-based clinical evidence	ICI-treated melanoma cohorts with observed response, progression, survival, toxicity or longitudinal monitoring endpoints. Treatment-effect predictive terminology requires a treatment comparator or biomarker-by-treatment interaction.	Response-associated tissue/plasma/EV studies, prognostic studies, longitudinal monitoring and response-classification models.	Highest clinical relevance, but most studies remain small, retrospective or internally validated only.
Tier 2: early translational/computational evidence	Public datasets, signatures, machine-learning or multi-omic models, often with retrospective cohorts or inferred ICI relevance.	lncRNA/circRNA/miRNA signatures, resource studies and computational response/prognostic models.	Supportive hypothesis-generation and model-development evidence; not direct clinical validation.
Tier 3: mechanistic/preclinical evidence	Cell, animal, EV or molecular-mechanism studies without patient-level clinical biomarker validation.	circROR1, circPIAS1, exosomal LINC01214, immune-regulatory miRNAs and RNA-delivery interventions.	Supportive biological-plausibility or therapeutic-target evidence; not direct clinical validation.

Table 1. Evidence-map framework separating clinical, translational/computational and mechanistic/preclinical domains.

Note: Primary evidence tier and context of use are separate attributes. A report may contribute to more than one narrative theme while remaining a single report in the canonical included-study set.

Core patient-based clinical biomarker evidence (Tier 1)

The 21-report clinical core supported the feasibility of tumour-tissue, plasma, circulating and EV-associated ncRNAs as response-associated, prognostic or monitoring biomarkers in ICI-treated melanoma [13][14][15][16]

[19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][84]. The reconciled evidence base added SMG7-AS1 [31], a pan-cancer lncRNA immune-state framework with separable melanoma ICI-survival cohorts [32], a 15-lncRNA pretreatment signature in two anti-PD-1-treated advanced-melanoma cohorts [33], and a multicohort lncRNA score evaluated in 71 immunotherapy-treated melanoma patients [34]. A newly retained circulating cell-free miRNA study evaluated paired pre- and post-checkpoint-inhibitor plasma (n = 20) and urine (n = 14); eight treatment-associated cfmiRNAs overlapped the melanoma-brain-metastasis signature, although radiographic response was not directly stratified and external validation was absent [84]. These studies broaden direct clinical relevance but remain retrospective, exploratory or partly cross-cancer in model development. Because the patient-based evidence is predominantly single-arm or observational, the reported associations should not be interpreted as definitive treatment-effect prediction. The principal patient-based reports and selected boundary-spanning translational studies are summarised in Table 2.

Study	Context of use	Cohort/specimen and ICI context	Principal finding	Validation/readiness
Huber 2018 [13]	Prognostic/monitoring association; EV mechanism	Plasma/monocytes/tumour; ipilimumab or nivolumab	Myeloid-derived suppressor cells (MDSC)-related EV-miRNAs tracked suppressor activity and clustered with shorter PFS/OS.	Retrospective; limited adjustment; no external assay validation.
Toker 2023 [15]	Response-associated	Anti-PD-1 melanoma RNA-seq cohort, n=28	NEAT1 was higher in responders and associated with IFN-response programmes.	Small retrospective public cohort.
Oliver 2022 [16]	Response-associated; prognostic model	Pretreatment FFPE biopsies; nivolumab; 12 RNA-seq samples	circRNA/lncRNA dysregulation and a ceRNA risk score were associated with response and survival.	Pilot study; no external validation.
Zhou 2023 [17]	Prognostic/response-associated	Two anti-PD-1 cohorts; total n=163	Five-circRNA signature associated with OS/PFS and immune context.	Independent external cohort; retrospective.
Degenhardt 2024 [19]	Stage discrimination; longitudinal monitoring; PD-L1 association; prognostic	Plasma; overall n=153; stage-IV baseline n=35 versus progression under immune therapy n=14; PD-L1 subgroup n=20; OS n=152	Nine-miRNA stage classifier AUC 0.739; five miRNAs were downregulated at progression; high miR-150-5p was associated with better OS (HR 0.39, 95% CI 0.16-0.92).	Monocentric discovery study; no independent external validation or standardised clinical cutoff.

Study	Context of use	Cohort/specimen and ICI context	Principal finding	Validation/readiness
Bender 2024 [20]	Response-classification model	Plasma; 81 immunotherapy-treated patients	Mixed miRNA/serum/clinical least absolute shrinkage and selection operator (LASSO) model, AUC 0.851; nested cross-validation (CV) AUC 0.847.	Internal nested cross-validation only.
Splendiani 2026 [21]	Longitudinal monitoring; response-associated	EV-miRNA; discovery n=18, validation n=8; ipilimumab contexts	Four-EV-miRNA resistance signature, AUC 0.80 discovery and 0.94 validation.	Small independent validation cohort.
Bustos 2020 [22]	Monitoring; response-associated	47 stage III/IV patients; 158 longitudinal plasma samples	Nine-cfmiRNA signature and miR-615-3p monitoring signal compared with LDH.	Prospective pilot; no external validation.
Sloane 2021 [23]	Response-associated; prognostic	TCGA plus pre-anti-PD-1 biopsy cohort, n=22	miR-100-5p and miR-125b-5p were associated with clinical benefit and survival.	Small validation cohort.
Kobeissi 2023 [25]	Prognostic	Tumour/immune miRNA signature in ipilimumab-treated melanoma	Signature associated with relapse-free survival.	Retrospective; needs independent validation.
Weidhaas 2025 [27]	Response/toxicity classification	Peripheral blood/germline data; ipilimumab; n=77	mirSNP models: response AUC 0.842; grade >=3 toxicity AUC 0.793.	Multicohort/internal model; clinical utility unproven.
Dong 2023 [28]	Response-classification; prognostic	Two immune checkpoint blockade (ICB) treated	Two-circRNA ICBcircSig associated	Independent validation cohort

Study	Context of use	Cohort/specimen and ICI context	Principal finding	Validation/readiness
		cohorts, total n=157	with response, PFS and OS.	plus mechanistic work.
Ding 2025 [29]	Response-associated; prognostic/monitoring	Tissue/plasma exosomes; Opdivo-treated subset n=28	Exosomal LINC01214 promoted CD8 dysfunction and was associated with poor anti-PD-1 outcome.	Small clinical subset; no multivariable validation.
Al Hrout 2025 [30]	Response-associated; EV mechanism	Baseline anti-PD-1 cohorts, pooled n=153; tumour EV experiments	B-cell enrichment and EV miR-99a-5p were associated with response and T-cell activity.	Retrospective multicohort association plus mechanism.
Xu 2023 [31]	Prognostic/response-associated	Melanoma datasets and clinical tissues; anti-PD-1/anti-CTLA-4 response context	SMG7-AS1 was associated with prognosis and immunotherapy-response patterns.	Retrospective/public-cohort evidence; no prospective validation.
Zhang 2021 [32]	ICI-associated prognosis/response framework	Two metastatic-melanoma ICI cohorts within a pan-cancer framework	A lncRNA-derived immune-state index separated immune states and was associated with ICI survival.	Pan-cancer model; melanoma evidence is principally ICI-survival association.
Zhou 2021 [33]	Prognostic/response-associated	Two advanced-melanoma cohorts treated with nivolumab or pembrolizumab; pretreatment biopsies	A 15-lncRNA signature stratified OS/PFS benefit under anti-PD-1 monotherapy.	Retrospective public cohorts; no prospective validation.
Yu 2020 [34]	Prognostic/response framework	Validation in 71 immunotherapy-treated melanoma patients	lncRNA immune classes and a composite score were associated with	Model development was primarily in IMvigor210;

Study	Context of use	Cohort/specimen and ICI context	Principal finding	Validation/readiness
			survival and response framework.	melanoma was a validation cohort.
Bustos 2020 [84]	Monitoring/pharmacodynamic candidate	Checkpoint-inhibitor-treated metastatic melanoma; plasma n=20, urine n=14	Eight pre/post-treatment cfmiRNAs overlapped the melanoma-brain-metastasis signature; no direct radiographic-response stratification.	Exploratory treatment-linked signal; no external validation.
Wang 2018 [86]	Early translational; immune-cell lncRNA atlas	Stage-IV melanoma n=11 and healthy participants n=23; 132 cell-condition RNA-seq samples; ipilimumab outcome explored	Nine lncRNA co-expression modules were associated with melanoma status, but none was associated with three-month ipilimumab response.	Small exploratory clinical cohort; no independent validation.
Andrews 2022 [87]	Multi-omic response-associated context	68 early-passage cell lines from 62 patients; external nivolumab cohort with 42 longitudinal patients	On-treatment melanoma cell-state distributions differed by response; ncRNA layers informed the multi-omic state, but the classifier was mRNA-dominant.	Cross-cohort biological validation; no isolated ncRNA predictor or prospective validation.

Table 2. Core patient-based clinical evidence and selected boundary-spanning translational studies.

Note: "Treatment-effect predictive" was reserved for comparator or biomarker-by-treatment interaction designs. Single-arm ICI associations are labelled response-associated, prognostic or monitoring.

Translational and computational evidence (Tier 2)

The 23-report Tier 2 domain comprised public-cohort, translational and computational evidence without direct patient-level clinical validation. Across tiers, prediction-model studies were interpreted according to validation maturity. Bender et al., retained in Tier 1 because the model was developed in immunotherapy-treated patients, used nested cross-validation and reported a relaxed LASSO model with AUC values around 0.85, but no independent external validation cohort was available [20]. Other computational reports used public melanoma ICI datasets, transcriptomic signatures or immune-checkpoint-related models [23][25][28][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53]. Newly retained Tier 2 studies included an immune-cell lncRNA atlas in 11 stage-IV melanoma patients and 23 healthy participants, in which lncRNA modules were not associated with three-month ipilimumab response [86], and a 68-cell-line multi-omic analysis mapped to an external nivolumab cohort, where on-treatment melanoma cell-state distributions differed by response but the classifier was mRNA-dominant rather than an isolated ncRNA biomarker [87]. This domain supports hypothesis generation and model development rather than direct clinical biomarker validation; calibration, decision thresholds, model transportability and prospective clinical utility remain underdeveloped [76][77].

Mechanistic, preclinical and therapeutic-modulation evidence (Tier 3)

The 24-report Tier 3 domain showed that ncRNAs can regulate pathways relevant to checkpoint resistance, including myeloid suppression, CD8+ T-cell dysfunction, PD-L1 regulation, interferon signalling, ferroptosis, antigen presentation and epithelial-mesenchymal transition [12][13][14][18][21][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][85][88][89]. Newly reconciled reports broadened this layer with miR-139-5p/PD-1 regulation, circ_0020710-mediated immune evasion, miRNA/nanotherapy sensitisation, EPIC1-associated immune escape, checkpoint-regulating miRNAs, T-cell or macrophage miRNA mechanisms and circular-RNA vaccine strategies [61][62][63][64][65][66][67][68][69][70][71][72][73]. Additional retained studies showed that miR-200a-5p directly suppresses TAP1 and HLA-I expression [85], that IL-2-Fc-encoding circular RNA combined with immunomodulatory lipid nanoparticles potentiated anti-PD-L1 activity in a postoperative B16F10 model [88], and that circFAM53B-derived cryptic peptides were associated with CD8 infiltration and disease-free survival in 56 melanoma specimens and mediated vaccine activity in B16F10 models [89]. These studies strengthen biological plausibility and therapeutic-target rationale, but they do not by themselves establish clinical ICI-biomarker utility. An integrated overview of the three-domain ncRNA evidence map is presented in Fig. 2.

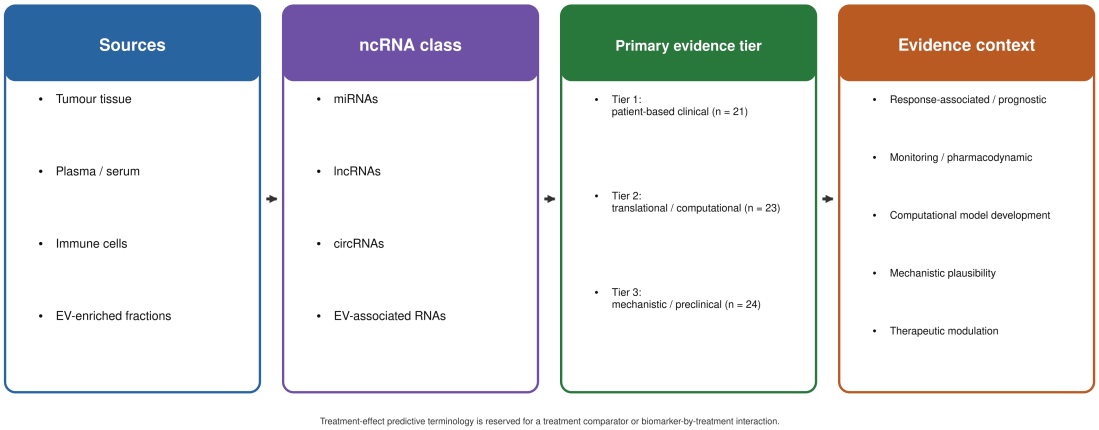


Figure 2. Systematic evidence-map framework for non-coding RNAs in melanoma immunotherapy. The framework links biospecimen and experimental sources to ncRNA classes, mutually exclusive primary evidence tiers and study-specific evidence contexts. Tier 1 contains 21 direct patient-based reports; Tier 2 contains 23 translational or computational reports; and Tier 3 contains 24 mechanistic or preclinical reports. Treatment-effect predictive terminology is reserved for studies with a treatment comparator or biomarker-by-treatment interaction. EV, extracellular vesicle; ncRNA, non-coding RNA.

Cross-domain evidence gaps and biomarker readiness

No ncRNA candidate currently satisfies all requirements for routine implementation within the 21-report clinical core, while the remaining 47 reports provide supportive rather than implementation-level evidence [12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][84][85][86][87][88][89]. The most advanced evidence supports ncRNAs as discovery-to-early-validation biomarkers. Analytical validity remains limited by heterogeneity in assay platform, normalisation, biospecimen processing, EV characterisation and batch-control approaches. Clinical validity is promising for selected plasma miRNA, EV-miRNA and tissue ncRNA signatures, but independent validation and context-of-use definition remain insufficient [19][20][21][22][25][27][31][32][33][34][84]. Clinical utility has not been established because few studies demonstrate added decision value beyond existing markers or show that ncRNA-guided decisions improve outcomes [7][74][76][77]. Table 3 summarises cross-domain evidence readiness by ncRNA class and translational status.

Evidence category	Current status	Main limitation	Readiness interpretation	References
Plasma/serum miRNAs	Patient-based liquid-biopsy association and early response/progression monitoring evidence.	Small cohorts, heterogeneous endpoints, limited external validation and variable normalisation.	Early clinical evidence; promising but not implementation-ready.	[19][20][22][23][24][25][26][27][31][33][84]
EV-associated miRNAs/RNAs	Promising for longitudinal monitoring and resistance biology.	Preanalytical handling, vesicle-enrichment specificity and MISEV-aligned reporting remain inconsistent.	Promising but requires assay standardisation and independent validation.	[10][11][21][29][30][69]
Tissue lncRNAs/circRNAs	Clinical or computational associations with response, survival or immune context.	Transportability, calibration, tissue composition and external validation are often insufficient.	Hypothesis-generating to early translational evidence.	[15][16][18][28][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][85][86][87][89]
Computational/prediction models	Internal validation or cross-validation is available in selected studies.	External validation, locked thresholds and calibration are usually absent.	Model-development evidence only; not suitable for clinical deployment.	[20][23][25][28][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][86][88]
Mechanistic ncRNAs	Cell, animal, EV and molecular studies support checkpoint-resistance plausibility.	Mechanistic relevance does not equal patient-level ICI biomarker validation.	Biological plausibility only unless linked to clinical outcomes.	[12][13][14][18][21][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68]

Evidence category	Current status	Main limitation	Readiness interpretation	References
				[69][70][71][72][73][85][88][89]

Table 3. Cross-domain evidence-readiness summary by ncRNA class and translational status.

Exploratory TCGA-SKCM bioinformatics findings

In TCGA-SKCM [90], all RNA-side candidate/proxy features were recoverable. LINC01214 showed the strongest immune-context association, mainly with the myeloid/inflammation score (Spearman ρ = 0.342; FDR-adjusted P = 5.63×10^{-13}). PIAS1 showed positive associations with IFNG/T-cell-inflamed and checkpoint scores (IFNG/T-cell-inflamed ρ = 0.254; FDR-adjusted P = 3.24×10^{-7}; checkpoint ρ = 0.193; FDR-adjusted P = 2.44×10^{-4}). ROR1 showed only weak immune-context correlation (IFNG/T-cell-inflamed ρ = 0.149; FDR-adjusted P = 0.0087), while HNRNPL, FOXO4 and NEAT1 showed minimal composite immune-score correlations. In the survival-ready TCGA-SKCM cohort (311 patients; 219 death events), the six primary ncRNA-linked proxies did not show robust age-adjusted FDR-significant overall-survival associations. By contrast, the IFNG/T-cell-inflamed immune-context score was associated with improved survival (age-adjusted HR = 0.668; FDR-adjusted P = 0.0426), with a similar borderline pattern for the checkpoint score (age-adjusted HR = 0.701; FDR-adjusted P = 0.0553). These analyses are reported as exploratory biological-context triangulation and are detailed in Supplementary file 5.

4. Discussion

Principal findings

This systematic evidence map supports four conclusions. First, the field comprises a distinct 21-report patient-based clinical core embedded within 47 supportive translational/computational and mechanistic/preclinical reports [12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][84][85][86][87][88][89]. Second, ncRNAs are repeatedly associated with melanoma ICI outcomes, resistance biology, immune-state regulation and therapeutic modulation, but these forms of evidence are not interchangeable. Third, the direct clinical evidence remains predominantly discovery-to-early-validation and

does not establish an implementation-ready test. Fourth, ncRNAs should be evaluated as complementary layers that may add dynamic post-transcriptional and liquid-biopsy information to PD-L1, tumour mutational burden, LDH, tumour-infiltrating lymphocytes and clinical staging, with future work moving from candidate discovery to prespecified context-of-use validation [7][8][19][20][22][74][76][77][84].

Interpretation of exploratory bioinformatics contextualisation

The exploratory TCGA analysis provides biological-context support but not clinical validation [90]. The positive survival association of immune-inflamed transcriptional context indicates that the analysis captured expected melanoma immune-survival biology [4][6][8][90]. However, the lack of robust age-adjusted survival associations for the reviewed ncRNA-linked proxies reinforces the main evidence-map conclusion: the ncRNA candidates remain promising and biologically plausible, but they are not yet ready for independent clinical implementation. The miRNA findings must be interpreted especially cautiously because TCGA miRNA data were mapped at precursor/proxy level and cannot validate mature-arm-specific circulating or EV-associated assays.

Biomarker translational valley and reporting completeness

A central conclusion of this evidence map is that the field remains within the biomarker translational 'valley of death': numerous biologically plausible ncRNA candidates and therapeutic mechanisms have been reported, but only a minority have progressed towards reproducible analytical validation, independent clinical validation and predefined clinical utility [7][91]. This interpretation is supported directly by the quantitative evidence extraction in Supplementary file 3, where many Tier 2 and Tier 3 reports did not provide hazard ratios, odds ratios, AUC estimates, confidence intervals, calibration, thresholds or model coefficients because these quantities were not applicable to the design or were not reported in the source [12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][84][85][86][87][88][89]. The evidence-map separation prevents such source-level absence from being mistaken for missing clinical validation data while still exposing the reporting and translation gap. Incomplete adherence to REMARK in tumour-marker studies and TRIPOD/PROBAST expectations in prediction-model studies remains a practical barrier to clinical translation [74][76][77].

Clinical utility and added value beyond existing biomarkers

The strongest translational argument for ncRNA biomarkers is not that they outperform all existing markers, but that they may capture distinct biological layers. PD-L1 reflects checkpoint-ligand expression but is spatially heterogeneous and context dependent [7][8][14]. TMB and neoantigen load capture mutational immunogenicity but not non-mutational immune escape or dynamic treatment adaptation. LDH is clinically useful but nonspecific [22]. TIL density and T-cell-inflamed gene-expression profiles are informative but are usually tissue-based. ncRNA biomarkers may add information on EV-mediated immune crosstalk, post-transcriptional checkpoint regulation, myeloid suppression, T-cell dysfunction, ferroptosis and longitudinal response trajectories [12][13][14][19][20][21][22][26][27][29][30][31][32][33][34][43][44][45][46][47][48][49][50][51][52][53][54][56][57][59][61][62][63][64][65][66][67][68][69][70][71][72][73][84][85][86][87][88][89]. This added-value hypothesis requires prospective testing in multivariable models [7][74][76][77]. The limitations of established melanoma ICI biomarkers and the potential complementary value of ncRNAs are summarised in Table 4.

Existing biomarker	Main limitation	Potential added value of ncRNA layer
PD-L1 immunohistochemistry (IHC)	Spatial/temporal heterogeneity, assay variability and incomplete stand-alone predictive value.	Dynamic post-transcriptional checkpoint regulation and resistance programmes.
TMB / neoantigen load	Does not capture non-mutational immune escape or treatment-adaptive resistance.	Transcriptomic, EV-mediated and post-transcriptional resistance information beyond mutation count.
LDH	Nonspecific marker of tumour burden or systemic disease rather than mechanism.	Circulating molecular monitoring and adjunctive response-risk stratification.
T-cell-inflamed profile / TILs	Tissue-based, spatially heterogeneous and limited for longitudinal monitoring.	Liquid-biopsy and ncRNA-based immune-state monitoring, including myeloid and T-cell regulatory circuits.
Disease stage / ECOG	Clinically useful but prognostic rather than mechanism-specific.	Molecular risk-context layer to complement baseline clinical stratification.

Table 4. Established melanoma ICI biomarkers and potential complementary value of ncRNAs.

Analytical validity

Analytical validity is a central barrier [7][74]. Tumour-tissue studies must account for tumour purity, immune-cell content, FFPE degradation, batch effects and platform-specific quantification. Plasma and serum studies require standardised preanalytical handling, haemolysis control, normalisation strategy and assay reproducibility [9][19][20][22]. EV-associated ncRNA studies require transparent reporting of EV isolation, particle size and concentration, positive and negative markers, contamination controls and RNA-cargo normalisation [10][11][21][29][30]. These points are critical because biomarker-readiness cannot be inferred from biological association alone [7].

EV-ncRNA biomarkers and MISEV2023-dependent analytical validity

EV-associated ncRNAs are among the most promising non-invasive biomarker classes in this review, especially for longitudinal monitoring of resistance [10][21][29][30]. Their clinical translation, however, requires a higher evidentiary standard than simple detection of RNA in an EV-enriched fraction. MISEV2023-aligned reporting is essential because plasma contains multiple extracellular RNA carriers, including intact vesicles, ribonucleoprotein complexes and lipoprotein-associated RNA [11]. Therefore, EV-ncRNA biomarker studies should document vesicle enrichment, particle size and concentration, positive and negative markers, contamination controls, and where feasible nuclease/protease-protection or orthogonal evidence that the RNA signal is associated with intact vesicles rather than co-isolated extracellular ribonucleoprotein or lipid-protein fractions [11]. Without this analytical specificity, EV-ncRNA signals cannot yet support clinical-grade assay validity.

Clinical validity

Clinical validity is promising but incomplete. Some studies link ncRNAs with response, resistance, PFS, OS, RFS or PD-L1 status [13][14][15][16][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][84][89]; however, small sample sizes, retrospective designs, mixed treatment regimens and inconsistent outcome definitions reduce comparability. Prediction models require external validation, calibration and predefined decision thresholds before they can be interpreted clinically [20][76][77]. Mechanistic studies provide plausibility [12][13][14][18][21][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][85][88][89] but should remain Tier 3 unless linked to patient-based ICI outcomes.

Cross-validation does not substitute for independent clinical validation

Prediction-model studies require particular caution. Nested cross-validation, as used in studies such as Bender et al. [20], is statistically appropriate for internal performance estimation and for reducing optimism from model selection in small datasets. Nevertheless, it does not establish clinical transportability [76][77]. A model that performs well in cross-validation can still fail when applied to samples collected at another time, in another centre, under another assay workflow or in a population treated with a different ICI regimen. For this reason, cross-validated AUC values were interpreted as early translational evidence rather than implementation-level validation. Before clinical use, ncRNA-based classifiers require temporally and geographically independent validation cohorts, locked coefficients or decision thresholds, calibration assessment and comparison against standard clinical and molecular covariates [76][77].

Limitations

This systematic evidence map has important methodological limitations. No protocol was prospectively registered in PROSPERO or OSF before screening. The retrospective eligibility reconciliation expanded the included evidence base from 34 to 68 reports. Although the stated eligibility criteria were unchanged and the complete screening set and all 185 full texts were subsequently assessed independently by two reviewers with adjudication, the magnitude of this revision creates residual concern about post-hoc boundary broadening or eligibility drift and cannot substitute for prospective protocol registration. The review question, eligibility criteria, search concepts, extraction domains, evidence framework and synthesis plan were fixed before the final supplementary Dimensions screening and are documented in Supplementary file 1 according to PRISMA-S [75]. Study-specific risk-of-bias and biomarker-validity judgements were not performed independently in duplicate, leaving potential for assessor subjectivity despite the design-adapted framework and transparent supporting rationales in Supplementary file 4.

Search and selection auditability were also incomplete. The original source-level counts were reconstructed from the archived search log. Of the 116 final original-search full-text exclusions, record-level citation-and-reason data are available for 34 reports. Records for the remaining 82 exclusions, including the three exclusions retained only as an aggregate in the nine-report boundary reassessment, were unavailable and were not reconstructed. Supplementary file 2 distinguishes the recovered original-route exclusion audit from the complete screening-verification, boundary-reassessment and Dimensions logs. Embase and Web of Science were not searched because subscription access was unavailable, and Dimensions and citation chasing should be interpreted as mitigation rather than complete substitution. Europe PMC overlaps substantially with PubMed/MEDLINE, and Google Scholar was searched once with only the first 200 relevance-ranked

results screened; consequently, the effective database coverage and search sensitivity may be lower than the number of named sources implies.

Finally, the intentionally broad evidence-map scope included computational inference, mechanistic checkpoint biology and therapeutic RNA-delivery or vaccine studies alongside the 21 patient-based reports. The total of 68 therefore must not be interpreted as 68 clinical biomarker-validation studies [12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][84][85][86][87][88][89]. Within the clinical core, small cohorts, retrospective designs, heterogeneous assays and outcomes, and incomplete external validation, calibration or predefined thresholds limit inference [74][76][77]. The exploratory bioinformatics module was locked when 34 reports were included and was not rerun after reconciliation; it contextualises only a predefined subset. Moreover, TCGA-SKCM is not an ICI-response cohort [90], bulk-tumour RNA sequencing cannot validate circulating or EV-specific assays, and precursor-level miRNA proxies cannot establish mature-arm-specific effects. These analyses should therefore be interpreted only as biological-context triangulation and hypothesis prioritisation.

Future research agenda

The next phase should be prospective clinical validation rather than further uncontrolled candidate discovery [7][74][76][77]. An ideal phase-II validation study would enrol advanced cutaneous melanoma patients at the start of a predefined ICI regimen, collect longitudinal plasma or serum samples at baseline, early on-treatment time points, first radiographic assessment and progression, and lock the ncRNA signature, assay workflow, normalisation procedure and clinical decision threshold a priori. The statistical plan should test whether the ncRNA signature adds predictive value beyond LDH, TMB/neoantigen load, PD-L1 where available, disease stage, ECOG/performance status and tissue immune context. Models should include predefined interaction testing between the ncRNA signature and ICI treatment context, report discrimination and calibration, and be validated in temporally and geographically independent cohorts [76][77]. EV studies should follow MISEV2023 expectations [11], and preclinical studies should report randomisation, blinding and reproducibility procedures where relevant [81]. Only through this design progression can ncRNA biomarkers move from discovery to clinically actionable melanoma immunotherapy tools.

5. Conclusions

This systematic evidence map identifies a 21-report patient-based clinical core within a broader 68-report landscape of ncRNA biomarkers, mechanisms and therapeutic modulation in melanoma immunotherapy.

Plasma miRNAs, EV-associated RNAs and tissue lncRNA/circRNA signatures support clinical discovery-to-early-validation potential, whereas the 47 translational/computational and mechanistic/preclinical reports provide model-development, biological-plausibility and therapeutic-target evidence rather than equivalent clinical validation. No ncRNA candidate is ready for routine implementation. Progress requires standardised preanalytical and analytical workflows, locked thresholds, independent prospective ICI-treated cohorts, MISEV-aligned EV reporting and formal demonstration of incremental value beyond established melanoma biomarkers. The exploratory TCGA-SKCM module remains a predefined-subset contextual analysis and should not be interpreted as independent ICI-response validation.

Abbreviations

AUC, area under the curve; BEST, Biomarkers, EndpointS, and other Tools; circRNA, circular RNA; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CV, cross-validation; ECOG, Eastern Cooperative Oncology Group; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, extracellular vesicle; FDR, false discovery rate; FFPE, formalin-fixed paraffin-embedded; HR, hazard ratio; ICB, immune checkpoint blockade; ICI, immune-checkpoint inhibitor; IFNG, interferon gamma gene; IFN-γ, interferon gamma; IHC, immunohistochemistry; KM, Kaplan–Meier; LASSO, least absolute shrinkage and selection operator; LDH, lactate dehydrogenase; lncRNA, long non-coding RNA; MDSC, myeloid-derived suppressor cell; miRNA, microRNA; MISEV, Minimal Information for Studies of Extracellular Vesicles; ncRNA, non-coding RNA; OR, odds ratio; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROBAST, Prediction model Risk Of Bias ASsessment Tool; qPCR, quantitative polymerase chain reaction; QUIPS, Quality In Prognosis Studies; REMARK, REporting recommendations for tumour MARKer prognostic studies; RFS, relapse-free survival; ROC, receiver operating characteristic; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SKCM, skin cutaneous melanoma; SWiM, Synthesis Without Meta-analysis; SYRCLE, Systematic Review Centre for Laboratory animal Experimentation; TCGA, The Cancer Genome Atlas; TIL, tumour-infiltrating lymphocyte; TMB, tumour mutational burden.

Supplementary Materials

Supplementary file 1

File format: .docx

Title: Complete search strategies and PRISMA-S documentation

Description: Database- and search-engine-specific strategies for the original and supplementary searches, including the platforms searched, search dates, complete query syntax, applied limits, retrieved-record counts, deduplication information, and PRISMA-S reporting details.

Supplementary file 2

File format: .xlsx

Title: PRISMA screening, verification and adjudication audit

Description: Reconciled screening counts for the original and supplementary search routes; documentation of the scope and workflow of independent re-screening and adjudication; available record-level full-text eligibility decisions; and the detailed 28-report and nine-report eligibility-reconciliation subsets.

Supplementary file 3

File format: .xlsx

Title: Study extraction and quantitative evidence

Description: Study-level extraction for the 68 included reports, covering study design, cohort characteristics, immune-checkpoint inhibitor regimen, non-coding RNA or extracellular-vesicle analytes, biospecimen and sampling time point, reported outcomes, quantitative effect estimates, validation features, and explicitly documented source-level missingness.

Supplementary file 4

File format: .xlsx

Title: Study-specific risk-of-bias and biomarker-validity assessment

Description: Study-level risk-of-bias and biomarker-validity judgements for the 68 included reports, including design-adapted assessment domains and supporting rationales.

Supplementary file 5

File format: .docx

Title: Exploratory bioinformatics contextualisation of a locked candidate subset

Description: Exploratory TCGA-SKCM-based contextual analysis of a predefined subset of candidate non-coding RNAs derived from the included evidence. This hypothesis-generating analysis was not used for study eligibility decisions and does not constitute independent clinical biomarker validation.

Supplementary file 6

File format: .xlsx

Title: Canonical list of the 68 included reports

Description: Reconciled citation-level inventory and core study characteristics of all 68 unique reports included in the final systematic evidence map.

Statements and Declarations

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Potential Competing Interests

The authors declare that they have no competing interests.

Ethics

Not applicable. This systematic evidence map used only data from published studies and publicly available, de-identified TCGA-SKCM datasets. No new participants were recruited, and no identifiable human data, human tissue or animal experiments were generated by the authors. Therefore, institutional ethics approval and informed consent were not required.

Consent for publication

Not applicable. This manuscript contains no identifiable individual participant data, images, or videos.

Data Availability

The data supporting this systematic evidence map are contained in the article and its supplementary files. De-identified TCGA-SKCM data used for the exploratory contextual analysis are publicly available from the National Cancer Institute Genomic Data Commons under project TCGA-SKCM (https://portal.gdc.cancer.gov/projects/TCGA-SKCM). Analysis specifications and outputs are provided in Supplementary file 5. No new participant-level dataset was generated. Data from the primary studies remain available from the cited publications and associated repositories, subject to the conditions stated by the original investigators.

Authors' Contributions

SAK: Conceptualisation, Methodology, Investigation, Data curation, Formal analysis, Project administration, Visualisation, Writing – original draft, and Writing – review & editing. DA: Investigation, Validation, Data

curation, Interpretation, and Writing – review & editing. SMM: Investigation, Validation, Data curation, Methodological review, and Writing – review & editing. SR, AP and HM: Validation, Interpretation, and Writing – review & editing. SAK adjudicated unclear, indeterminate or discordant eligibility decisions; DA and SMM independently re-screened the complete title-and-abstract set and assessed all 185 full-text reports using unchanged eligibility criteria. All authors read and approved the final manuscript.

Use of Generative AI

During the preparation of this work, the authors used OpenAI ChatGPT (OpenAI, San Francisco, CA, USA; accessed June–August 2026) to improve language, formatting and cross-file consistency. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the article. The tool was not used as an author and was not the final decision-maker for study eligibility, risk-of-bias judgements, statistical interpretation or scientific conclusions.

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