Targeting Ferroptosis Pathways to Enhance Therapeutic Outcomes in Acute Myeloid Leukemia (AML): A Systematic Review

Supplementary Table S1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page. The article title identifies the report as "A Systematic Review".
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract. Structured under Background, Objectives, Methods, Results, and Conclusions; reports the PRISMA 2020 approach, PROSPERO registration, the methodological-appraisal approach, ferroptosis-specific evidence characterization, and 18 included studies.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1 Introduction, particularly Sections 1.1, 1.1.2, and 1.2, describing AML biology, oxidative stress, ferroptosis, and the therapeutic rationale.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1.3 Aim and Rationale of the Review; Section 2.2 Research Question and Objectives.
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.3 Eligibility Criteria; Table 1 PICOSE framework. Eligible evidence was grouped into human AML cell-line and adult patient-derived/ex vivo components; public datasets were treated as supportive evidence only.
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 2.4 Search Strategy. MEDLINE/PubMed, Scopus, Cochrane Library/CENTRAL, Science Citation Index Expanded, ClinicalTrials.gov, WHO ICTRP, reference lists, citation tracking, and expert consultation when necessary were searched or consulted. Final search: 30 May 2026.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2.4 Search Strategy; Supplementary Table 2. Full database and registry strategies, limits, accessible languages, and the 1 January 2020–30 May 2026 eligibility window are reported.

Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.5 Screening and Data Management. Rayyan was used; two independent reviewers screened titles/abstracts and full texts. Disagreements were resolved by consensus and, when required, a third senior reviewer.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 2.6 Data Extraction. Two reviewers independently performed evidence-component-level extraction; disagreements were resolved through discussion and consensus.
Data items Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Sections 2.2 and 2.3; Table 1. Primary outcomes focused on functional AML cell-death/viability effects, lipid peroxidation, and ferroptosis-directed functional rescue where available. Secondary outcomes included AML viability, proliferation, treatment response, resistance reversal, and therapeutic synergy.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 2.6 Data Extraction. Variables included study identification, AML model and disease context, eligible cell lines and/or adult patient-derived samples, interventions, controls/comparators, assays, ferroptosis-related outcomes, therapeutic outcomes, and main findings. Public datasets were supportive only.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.7 Methodological Quality Assessment. Human AML cell-line experiments were appraised using QUIN solely as a structured item-level framework. Patient-derived/ex vivo evidence was appraised separately using structured domains appropriate to experimental human-derived material. Individual domains were classified as A/P/NR/NA and were not combined into aggregate scores, percentages, or global risk-of-bias categories. Supplementary Table 3 lists the appraisal domains.

Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable to pooled analysis. The review presents narrative synthesis and structured study-level findings rather than common effect measures or pooled estimates; see Sections 2.6, 2.7, 3.2, and 3.3.
Synthesis methods Synthesis methods Synthesis methods Synthesis methods Synthesis methods Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Sections 2.3 and 2.6. Synthesis eligibility followed the PICOSE criteria and evidence-component approach. Eligible human AML cell-line and adult patient-derived/ex vivo data were retained; non-eligible animal, murine, PDX-only, normal-comparator-only, and database-only components were excluded.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 2.6 Data Extraction. Data were organized in structured tables and separated by evidence type. Mixed studies were handled at evidence-component level; public datasets were supportive only. No quantitative conversions were performed.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Sections 2.6 and 3.1–3.3; Figure 1 PRISMA flow diagram; Tables 2 and 3 methodological appraisals; Table 4 ferroptosis-specific evidence and translational synthesis; Figure 2 graphical overview; Supplementary Tables 1–4.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Sections 2.6–2.8 and 3.2–3.3; Discussion and Limitations. Narrative synthesis was used because AML models, interventions, assays, ferroptosis-validation approaches, and therapeutic outcomes were experimentally heterogeneous. No meta-analysis was conducted.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Sections 3.2–3.3, 4, and 6. Heterogeneity was considered narratively according to AML model, intervention class, ferroptosis-specific validation, rescue evidence, patient-derived evidence, and therapeutic context. No meta-regression was performed.

	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable. No formal sensitivity analysis was conducted because there was no meta-analysis or quantitative pooled synthesis.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 2.4 describes broad database searching, trial registries, citation tracking, and consideration of unpublished evidence to reduce publication/reporting bias. No formal statistical reporting-bias assessment was performed; relevant limitations are discussed in Section 6.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section 2.8 Evidence Strength and Characterization. No formal GRADE certainty-of-evidence assessment was performed and no global high/moderate/low/very-low certainty ratings were assigned. Methodological quality, ferroptosis-specific confirmation, reproducibility, and translational relevance were evaluated as distinct dimensions.
RESULTS			
Study selection Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3.1 and Figure 1. The manuscript reports 751 records identified from databases, 428 duplicates removed, 323 records screened, 237 excluded at title/abstract screening, 86 reports retrieved and assessed, 68 full-text reports excluded, two citation-searching reports assessed and excluded, and 18 studies included.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 3.1 reports numerical categories and reasons for full-text exclusion. A separate list citing each excluded full-text report is not provided.
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.3 and Table 4. All 18 included studies are cited and summarized by experimental model, principal ferroptosis axis/intervention, ferroptosis-specific validation, evidence category, and translational relevance.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 3.2; Table 2 QUIN item-level methodological appraisal of in vitro components; Table 3 structured domain-level methodological appraisal and translational characterization of patient-derived/ex vivo evidence.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Section 3.3 and Table 4 present study-level mechanistic and therapeutic outcomes. Common effect estimates and precision measures were not pooled because assays, outcomes, and experimental designs were heterogeneous and mainly preclinical.

Results of syntheses Results of syntheses Results of syntheses Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Sections 3.2–3.3 and 4. The synthesis summarizes methodological appraisal, ferroptosis-specific confirmation, reproducibility across AML models, patient-derived validation, and translational relevance.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable. No statistical synthesis or meta-analysis was performed because of methodological and experimental heterogeneity; results were summarized narratively.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Sections 3.2–3.3, 4, and 6. Heterogeneity is discussed by experimental model, intervention, assay selection, ferroptosis-specific rescue evidence, treatment context, and strength of patient-derived validation.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable. No formal sensitivity analyses were conducted.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	No formal reporting-bias assessment was performed. Section 6 discusses incomplete reporting, limited patient-derived validation, absence of eligible clinical intervention studies, and the predominantly preclinical evidence base.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	No formal certainty-of-evidence assessment was performed. Section 2.8 and Section 3.2 instead report ferroptosis-specific evidence categories and evaluate reproducibility and translational relevance separately from methodological quality.
DISCUSSION			
Discussion Discussion Discussion Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4 Discussion. Results are interpreted in relation to AML redox biology, antioxidant defence, iron handling/ferritinophagy, lipid remodeling, treatment sensitization, resistance mechanisms, and translational relevance.
	23b	Discuss any limitations of the evidence included in the review.	Section 6 Limitations. Evidence limitations include predominantly preclinical and cell-line research, heterogeneous models and assays, variable ferroptosis-specific validation, limited patient-derived sample sizes, short-term outcomes, and no eligible clinical intervention studies.
	23c	Discuss any limitations of the review processes used.	Section 6 Limitations also addresses review-process constraints, including the prespecified January 2020 publication window and the consequences of methodological and experimental heterogeneity for synthesis.
	23d	Discuss implications of the results for practice, policy, and future research.	Sections 4–6. Implications include standardized ferroptosis-specific assays, rigorous rescue experiments, larger well-characterized adult patient-derived AML models, normal-cell selectivity, clinically relevant combination strategies, and future clinical validation.
OTHER INFORMATION			

Registration and protocol Registration and protocol Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Section 2.1 Protocol and Registration. Registered in PROSPERO as CRD420261373662; registration is also reported in the Abstract.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2.1. The protocol is accessible through the PROSPERO record CRD420261373662.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Section 2.1. No amendment to the prespecified eligibility window was made. The January 2020 lower publication limit was retained; seminal pre-2020 studies may be discussed contextually but are not incorporated into the formal systematic synthesis.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding statement: “This study received no external financial support.”
Competing interests	26	Declare any competing interests of review authors.	Conflicts of Interest statement: “The authors declare no competing interests.”
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data Availability statement. Extracted and analyzed data are presented in the manuscript and supplementary materials; no analytic code was generated or used. Additional extraction materials are available from the corresponding author on reasonable request.

Supplementary Table S2: Search Strategy for each database

Database / source	Platform / provider	Search interface	Exact search strategy	Limits / eligibility-related filters	Prespecified eligibility window	Date of last search
PubMed/MEDLINE (n = 63)	NCBI	Native (PubMed.gov)	((“acute myeloid leukemia”[Mesh] OR “acute myeloid leukemia”[tiab] OR AML[tiab]) AND (ferroptosis[Mesh] OR ferroptosis[tiab] OR ferroptotic[tiab] OR “lipid peroxidation”[Mesh] OR “lipid peroxidation”[tiab] OR “lipid ROS”[tiab] OR “iron metabolism”[tiab] OR GPX4[tiab] OR SLC7A11[tiab] OR “system Xc”[tiab] OR glutathione[tiab] OR GSH[tiab] OR NRF2[tiab] OR ACSL4[tiab] OR HMOX1[tiab] OR ferritinophagy[tiab]) AND (therap*[tiab] OR treatment[tiab] OR resistance[tiab] OR viability[tiab] OR cytotoxicity[tiab] OR venetoclax[tiab] OR cytarabine[tiab] OR sorafenib[tiab] OR FLT3[tiab]))	Accessible languages: Greek, English, German, Italian, French, Turkish. Human AML experimental/translational eligibility criteria were applied during screening; no animal-only or database-only evidence was eligible for the main synthesis.	1 Jan 2020–30 May 2026	30 May 2026
Scopus (n = 330)	Elsevier	Native (Scopus.com)	TITLE-ABS-KEY(("acute myeloid leukemia" OR AML) AND (ferroptosis OR ferroptotic OR "lipid peroxidation" OR "lipid ROS" OR "iron metabolism" OR GPX4 OR SLC7A11 OR "system Xc" OR glutathione OR GSH OR NRF2 OR ACSL4 OR HMOX1 OR ferritinophagy) AND (therap* OR treatment OR resistance OR viability OR cytotoxicity OR venetoclax OR cytarabine OR sorafenib OR FLT3))	Article/research records. Accessible languages as prespecified. Human AML experimental/translational eligibility criteria were applied during screening.	1 Jan 2020–30 May 2026	30 May 2026
Cochrane Library (CENTRAL) (n = 0)	Wiley	Native (CochraneLibrary.com)	("acute myeloid leukemia" OR AML) AND (ferroptosis OR ferroptotic OR "lipid peroxidation" OR "lipid ROS" OR "iron metabolism" OR GPX4 OR SLC7A11 OR glutathione OR GSH OR NRF2 OR ACSL4 OR HMOX1 OR ferritinophagy) AND (therapy OR treatment OR resistance OR venetoclax OR cytarabine OR sorafenib OR FLT3)	No eligible records identified. Eligibility criteria and the same prespecified temporal window were applied.	1 Jan 2020–30 May 2026	30 May 2026
Science Citation Index Expanded (n = 358)	Clarivate	Web of Science	TS=("acute myeloid leukemia" OR AML) AND TS=(ferroptosis OR ferroptotic OR "lipid peroxidation" OR "lipid ROS" OR "iron metabolism" OR GPX4 OR SLC7A11 OR "system Xc" OR glutathione OR GSH OR NRF2 OR ACSL4 OR HMOX1 OR ferritinophagy) AND TS=(therap* OR treatment OR resistance OR viability OR cytotoxicity OR venetoclax OR cytarabine OR sorafenib OR FLT3)	Accessible languages as prespecified. Human AML experimental/translational eligibility criteria were applied during screening.	1 Jan 2020–30 May 2026	30 May 2026
ClinicalTrials.gov (n = 0)	NIH/NLM	Native (ClinicalTrials.gov)	Condition/disease: "acute myeloid leukemia" OR AML; Other terms: ferroptosis OR ferroptotic OR "lipid peroxidation" OR GPX4 OR SLC7A11 OR NRF2 OR "iron metabolism" OR venetoclax OR cytarabine OR FLT3	All study statuses were screened for AML-specific ferroptosis-related therapeutic relevance.	1 Jan 2020–30 May 2026	30 May 2026

WHO ICTRP (n = 0)	WHO	ICTRP Search Portal	("acute myeloid leukemia" OR AML) AND (ferroptosis OR ferroptotic OR "lipid peroxidation" OR GPX4 OR SLC7A11 OR NRF2 OR "iron metabolism" OR venetoclax OR cytarabine OR FLT3)	All recruitment statuses were screened for AML-specific ferroptosis-related therapeutic relevance.	1 Jan 2020–30 May 2026	30 May 2026
Other sources	Reference lists, citation tracking, expert consultation	Manual search	Backward and forward citation tracking of included studies and relevant review articles; expert consultation when necessary.	Backward and forward citation tracking of included studies and relevant reviews; expert consultation when necessary. Only eligible original human-derived AML experimental/translational evidence could enter the formal synthesis.	1 Jan 2020–30 May 2026	30 May 2026

Supplementary Table S3: Questions- Criteria for risk-of-bias tools

A. Criteria for QUIN Tool
Q1. Clearly stated aims/objectives
Q2. Detailed explanation of sample size
Q3. Detailed explanation of sampling technique
Q4. Details of comparison group
Q5. Detailed explanation of methodology
Q6. Operator details
Q7. Randomization
Q8. Method of measurement of outcome
Q9. Outcome assessor details
Q10. Blinding
Q11. Statistical analysis
Q12. Presentation of results

B. Structured appraisal domains for patient-derived and ex vivo AML evidence		
Patient-derived/ex vivo	H1. Patient/sample characterization	Diagnosis, clinical context, sample source, and relevant patient/sample characteristics are described.
Patient-derived/ex vivo	H2. Independent biological samples / replication	Number of independent patient samples and/or biological replication is adequately reported.

Patient-derived/ex vivo	H3. Sample handling / preparation	Collection, processing, storage, preparation, and handling procedures are described sufficiently.
Patient-derived/ex vivo	H4. Intervention / comparator	Experimental intervention and comparator/control conditions are defined where applicable.
Patient-derived/ex vivo	H5. Outcome assessment	Outcome measures and assays are appropriate and clearly described.
Patient-derived/ex vivo	H6. Statistical analysis / reporting	Statistical methods and reporting are adequate for the human-derived component.

Appraisal coding: A, adequately reported; P, partially or inadequately reported; NR, not reported; NA, not applicable. QUIN was used solely as a structured item-level methodological framework and was not treated as an AML-specific validated risk-of-bias instrument. The patient-derived/ex vivo domains are structured review-specific methodological domains rather than a separate validated risk-of-bias tool. Individual domains were interpreted separately and were not combined into an aggregate numerical score, percentage-based score, or global low/moderate/high risk-of-bias category. The type of human-derived evidence (direct ex vivo therapeutic/mechanistic testing versus supportive molecular/prognostic evidence) was recorded separately as a translational characteristic.

Supplementary Table S4: Detailed experimental characteristics, therapeutic interventions, ferroptosis-specific validation, and translational relevance of the 18 included studies in acute myeloid leukemia (AML)

Study	Experimental models and human-derived component	Principal axis and intervention(s)	Controls / comparators	Main assays and ferroptosis-specific validation	Therapeutic findings	Ferroptosis-specific evidence category	Translational relevance and analytical interpretation
Birsen et al. (2022) [28]	HL-60, MOLM-14, SET-2, MV4-11, OCI-AML2, OCI-AML3, K562, THP-1, SKM-1, NB4, Kasumi-1; UT7-EPO supportive. Human-derived component: Primary AML cells from bone-marrow samples of five newly diagnosed patients; direct ex vivo functional testing, with lipid-ROS and combination analyses reported in a subset.	APR-246–SLC7A11/GSH/GPX4 defence and lipid-peroxide detoxification. Intervention(s): APR-246 ± erastin, RSL3 or FINO2; SLC7A11 or GPX4 knockdown.	Model-system evidence: Control: untreated and vehicle-treated cells. Comparators: erastin, RSL3 and FINO2 as ferroptosis inducers; iron chelators and lipophilic antioxidants as rescue comparators. Human-derived evidence: Control: untreated primary AML cells, vehicle treated primary AML cells. Comparator: erastin as ferroptosis inducer, ferrostatin-1 as ferroptosis inhibitor rescue comparator,	Model-system evidence: Cell viability, cell-death flow cytometry, lipid-peroxidation assays, GSH-related assays and genetic knockdown assays. Human-derived evidence: Ex vivo viability, cell death assessment, lipid ROS measurement with C11-BODIPY, synergy analysis Ferroptosis-specific validation: Lipid-peroxide accumulation; rescue by iron chelation/lipophilic antioxidants/ferroptosis inhibition;	APR-246 caused early lipid-peroxide–dependent death that was suppressed by iron chelation or lipophilic antioxidants. Weakening SLC7A11/GPX4 defence enhanced killing, including ex vivo synergy in primary AML cells. Supports APR-246 combined with ferroptosis induction; patient-derived evidence was direct but limited in sample size.	Confirmed	Direct ex vivo patient-derived testing; supports APR-246/ferroptosis combinations, although the patient-derived sample was limited.

			deferoxamine as iron chelator rescue comparator.	SLC7A11/GPX4 genetic validation.			
Catanzaro et al. (2022) [29]	HL-60. Human-derived component: Primary AML samples (n=5) and healthy PBMCs (n=4).	GSH depletion, GPX4 reduction and lipid-ROS accumulation. Intervention(s): Perillaldehyde; mechanistic comparison/rescue with RSL3, DFO, vitamin E and ferrostatin-1.	Model-system evidence: Control: untreated cells. Comparator: RSL3 as positive ferroptosis inducer, DFO as iron chelator and ferroptosis rescue comparator, vitamin E as antioxidant rescue comparator, ferrostatin-1 as ferroptosis inhibitor rescue comparator, Nec-1s as necroptosis inhibitor comparator, z-VAD-fmk as apoptosis inhibitor comparator, olaparib as parthanatos related comparator. Human-derived evidence: Control: untreated primary AML samples, untreated healthy donor PBMCs. Comparator: PBMCs as normal	Model-system evidence: Cell viability, Annexin V and 7-AAD, Sytox, C11-BODIPY, GPX4 Western blot, GSH assay, ATP release Human-derived evidence: Sytox viability flow cytometry, IC50 calculation, inhibitor rescue assay Ferroptosis-specific validation: C11-BODIPY, GPX4/GSH assays and selective rescue by ferrostatin-1/DFO/vitamin E; apoptosis/necroptosis inhibitors ineffective in primary samples.	Perillaldehyde increased lipid ROS, reduced GPX4 and depleted GSH. Ferrostatin-1 restored viability in primary AML samples, whereas apoptosis and necroptosis inhibitors were ineffective. Provides direct ex vivo ferroptosis evidence and partial selectivity over normal PBMCs, although the human sample was small.	Confirmed	Direct ex vivo primary-AML testing with healthy PBMC comparison; preliminary selectivity, limited by small sample size.

			human comparator, ferrostatin-1 as ferroptosis inhibitor rescue comparator, z-VAD-fmk as apoptosis inhibitor comparator, Nec-1s as necroptosis inhibitor comparator.				
Yu et al. (2024) [30]	MV4-11, MOLM-13, HL-60, THP-1, NB4. Human-derived component: De novo AML PBMC expression and survival cohorts; no direct ML385/venetoclax testing in primary cells.	NRF2–FTH1 iron sequestration and resistance to venetoclax-induced ferroptotic stress. Intervention(s): ML385 or NRF2 knockdown ± venetoclax/erastin; NRF2 overexpression; NAC or vitamin E rescue.	Model-system evidence: Control: vehicle treated cells, vector control, siRNA control. Comparator: venetoclax alone as BCL-2 inhibitor treatment comparator, ML385 alone as NRF2 inhibitor comparator, erastin alone as ferroptosis inducer comparator, NAC as antioxidant rescue comparator, vitamin E as antioxidant rescue comparator. Human-derived evidence: Control: healthy-individual PBMCs and AML complete-remission	Model-system evidence: Cell viability, apoptosis flow cytometry, labile iron pool, lipid ROS, qRT-PCR, Western blot Human-derived evidence: qRT-PCR, gene-expression comparison and Kaplan–Meier survival analysis. Ferroptosis-specific validation: Labile iron and lipid-ROS assays; NRF2/FTH1 modulation; NAC/vitamin E rescue.	NRF2 inhibition reduced FTH1, increased the labile iron pool and lipid peroxidation, and potentiated venetoclax; NRF2 overexpression and antioxidants attenuated the effect. Supports NRF2 inhibition as a venetoclax-sensitising strategy; human data were expression/prognostic rather than direct treatment-response evidence.	Strongly supportive	Supportive human expression/prognostic evidence; no direct patient-derived therapeutic testing.

			samples. Comparators: de novo AML samples and high-versus-low FTH1 or NRF2 expression groups.				
Liu et al. (2023) [31]	MV4-11, Kasumi-1. Human-derived component: Newly diagnosed AML BMMCs; healthy PBMCs; TCGA-LAML.	NRF2 transcriptional control of GPX4 and ferroptosis resistance. Intervention(s): ML385 + RSL3 or FIN56; erastin; NRF2 knockdown/overexpression; GPX4 siRNA.	Model-system evidence: Control: vehicle treated cells, shRNA control, vector control. Comparator: ML385 alone as NRF2 inhibitor comparator, RSL3 alone as GPX4 inhibitor comparator, FIN56 alone as ferroptosis inducer comparator, erastin alone as ferroptosis inducer comparator, ferrostatin-1 as ferroptosis inhibitor rescue comparator. Human-derived evidence: Healthy individual PBMCs were used as the control group for comparison with AML patient BMMCs. For prognostic	Model-system evidence: C11-BODIPY lipid ROS, PI staining, Annexin V flow cytometry, qPCR, Western blot Human-derived evidence: CCK-8 viability assay, Annexin V flow cytometry for cell death, qRT-PCR, Spearman correlation analysis, TCGA survival analysis Ferroptosis-specific validation: C11-BODIPY and cell-death assays; ferrostatin-1 rescue in cell-lines; ML385 + RSL3/FIN56 response in primary BMMCs.	Combined NRF2/GPX4 inhibition increased lipid ROS and cell death, with ferrostatin-1 rescue in cell-lines. ML385 combinations also reduced viability and increased death in primary AML BMMCs. Direct ex vivo anti-AML activity supports dual NRF2/GPX4 targeting; definitive ferroptosis rescue was strongest in cell-line models.	Confirmed	Direct ex vivo anti-AML activity in primary BMMCs; the strongest ferroptosis-specific rescue evidence was obtained in cell-line models.

			analysis, TCGA AML patients were compared according to high versus low NFE2L2 and GPX4 expression. For the ex vivo therapeutic component, primary AML BMMCs treated with ML385 + RSL3 or ML385 + FIN56 were compared with the corresponding single-agent conditions.				
Zhong et al. (2025) [32]	MV4-11, MOLM-13, U937, KG-1α. Human-derived component: Primary AML samples; TCGA and GSE71014.	BRD4/c-Myc/NRF2/GPX4-mediated oxidative-stress resistance. Intervention(s): JQ1 or ABBV-744 + RSL3, FIN56 or erastin; NRF2 knockdown/overexpression.	Model-system evidence: Control: vehicle treated cells, genetic control cells. Comparator: JQ1 alone as BET inhibitor comparator, ABBV 744 alone as BET inhibitor comparator, RSL3 alone as GPX4 inhibitor comparator, FIN56 alone as ferroptosis inducer comparator, erastin alone as ferroptosis inducer comparator, NRF2 knockdown as	Model-system evidence: CCK 8, cell death flow cytometry, lipid ROS, qRT-PCR, Western blot, synergy analysis Human-derived evidence: CCK 8, flow cytometry cell death, lipid ROS, survival analysis, multivariate risk scoring Ferroptosis-specific validation: Lipid-ROS and synergy assays;	BET inhibition plus ferroptosis induction synergistically increased lipid ROS and cell death while suppressing BRD4/c-Myc/NRF2 signalling; NRF2 overexpression reduced the combination effect. Shows combination activity in primary AML samples and identifies a clinically relevant	Strongly supportive	Direct ex vivo combination activity in primary AML samples; mechanistic confirmation was strongest in model systems.

			sensitization comparator, NRF2 overexpression as rescue comparator. Human-derived evidence: Control: untreated or vehicle treated primary AML samples. Comparator: BET inhibitor alone, ferroptosis inducer alone, combination of BET inhibitor with RSL3, FIN56 or erastin, high versus low BRD4, NRF2 and GPX4 expression in datasets.	NRF2 knockdown sensitisation and overexpression rescue; primary-sample combination response.	resistance axis; evidence remains preclinical.		
Xu et al. (2024) [33]	U937. Human-derived component: None reported.	SLC7A11/system xc−–GSH–GPX4 defence linked to PI3K/AKT signalling. Intervention(s): Calycosin (dose range); SLC7A11 overexpression rescue.	Control: untreated cells, vector control, zero micromolar calycosin cells. Comparator: twenty micromolar calycosin as dose comparator, forty micromolar calycosin as dose comparator, eighty micromolar calycosin as dose	CCK 8, apoptosis flow cytometry, Western blot, qPCR, iron ion assay, lipid ROS, cysteine, GSH, GPX4, Ptgs2, Chac1, PI3K/AKT signaling Ferroptosis-specific validation: Iron, lipid ROS, cysteine, GSH, GPX4, PTGS2/CHAC1 and PI3K/AKT assays;	Calycosin increased iron and lipid ROS, reduced cysteine, GSH, GPX4 and SLC7A11, and inhibited PI3K/AKT signalling; SLC7A11 overexpression reversed these changes. Cell-line proof of concept for SLC7A11-directed	Strongly supportive	Cell-line evidence only; no direct patient-derived validation.

			comparator, SLC7A11 overexpression as rescue comparator.	SLC7A11-overexpression rescue.	ferroptosis; no patient-derived validation was reported.		
Zhu et al. (2026) [34]	MOLM-13 and THP-1, including venetoclax-resistant derivatives. Human-derived component: Relapsed/primary AML samples; TCGA and UALCAN; no direct ex vivo therapy testing.	ATF4–PSAT1–JNK/c-Jun regulation of serine/GSH metabolism, GPX4 and venetoclax resistance. Intervention(s): PSAT1 overexpression or knockdown ± venetoclax/erastin; ferrostatin-1.	Model-system evidence: Control: empty vector cells, shRNA control cells, venetoclax sensitive parental cells. Comparator: venetoclax resistant derivatives as resistance comparators, venetoclax alone as BCL-2 inhibitor comparator, erastin as ferroptosis inducer comparator, ferrostatin-1 as ferroptosis inhibitor rescue comparator, PSAT1 overexpression as resistance mechanism comparator, PSAT1 knockdown as sensitization comparator. Human-derived evidence:	Model-system evidence: qRT-PCR, Western blot, CCK 8, Annexin V and 7-AAD, TMRE, LC–MS/MS serine assay, ferroptosis marker assays Human-derived evidence: qRT-PCR, paired diagnostic and relapse expression analysis, survival analysis Ferroptosis-specific validation: GSH/serine metabolism, labile iron, lipid-peroxidation and PSAT1 gain/loss experiments support ferroptosis-related venetoclax resistance. Because definitive specific rescue was not demonstrated to the	PSAT1 promoted GSH synthesis, reduced the labile iron pool and lipid peroxidation, and suppressed ferroptosis. PSAT1 knockdown restored ferroptotic vulnerability and venetoclax sensitivity. Identifies a druggable resistance mechanism supported by relapsed-sample expression data; therapeutic testing was principally cell-line based.	Strongly supportive	Supportive patient expression/relapse data; therapeutic testing was principally cell-line based.

			Control: newly diagnosed or diagnostic samples were compared, low PSAT1 expression group. Comparator: relapsed patient samples, high PSAT1 expression group, older patient group where analyzed.	same standard as confirmed studies, the evidence is classified as strongly supportive.			
Lai et al. (2022) [35]	THP-1, U937, SKM-1. Human-derived component: Healthy PBMC toxicity comparator; no AML patient-derived treatment evidence.	HMOX1-dependent noncanonical ferroptosis and lipid peroxidation. Intervention(s): Honokiol; HMOX1 inhibitor ZnPP; ferrostatin-1.	Control: DMSO treated cells, untreated cells. Comparator: honokiol alone as active treatment comparator, ZnPP as HMOX1 inhibitor rescue comparator, ferrostatin-1 as ferroptosis inhibitor rescue comparator.	CCK 8, apoptosis flow cytometry, cell cycle, colony formation, RNA sequencing, lipid peroxidation, qPCR, Western blot Ferroptosis-specific validation: Lipid-peroxidation and HMOX1 assays; ZnPP and ferrostatin-1 rescue.	Honokiol increased HMOX1 and lipid peroxidation, reduced viability and colony formation, and induced G0/G1 arrest. ZnPP and ferrostatin-1 partially rescued viability. Supports HMOX1 activation as an AML ferroptosis strategy; no direct AML patient-sample treatment data were available.	Confirmed	No direct primary-AML therapeutic testing; evidence was model-based with healthy-PBMC toxicity comparison.
Grignano et al.	MOLM-14, OCI-AML2, HL-60, SET-2,	Ferritinophagy-driven iron release and MT2A/MT1M-	Model-system evidence:	Model-system evidence: cell-	DHA induced early ferroptotic cell	Confirmed	Direct patient-derived

(2023) [36]	MV4-11, K562, THP-1, UT7-EPO, SKM-1, NB4 and Kasumi-1. Human-derived component: Bone-marrow samples from five newly diagnosed AML patients; primary medullary leukemic cells from three patients underwent direct ex vivo MT2A/DHA/PPG experiments.	dependent antioxidant buffering through glutathione homeostasis. Intervention(s): dihydroartemisinin (DHA); NCOA4 targeting; metallothionein inhibition with PPG; MT2A and MT1M genetic inhibition; ferroptosis inducers including erastin, APR-246 and FIN56.	untreated/DMSO-treated and non-targeting genetic controls. Comparators included DHA alone; ferrostatin-1 and deferasirox as ferroptosis/iron-dependent rescue conditions; Z-VAD-FMK, chloroquine and necrostatin-1s for alternative cell-death pathway discrimination; NCOA4 knockdown; PPG or MT2A/MT1M inhibition; and erastin ± glutathione. Human-derived evidence: primary AML cells transfected with siSCR or siMT2A and treated with DHA alone or DHA + PPG.	viability and cell-death assays, C11-BODIPY lipid-peroxidation analysis, labile Fe^{2+} measurement, ferritinophagy-related assays, GSH/GSSG assessment, qPCR, Western blotting and genetic perturbation of NCOA4, MT2A and MT1M. Ferroptosis confirmation: DHA-induced lipid peroxidation was reversed by ferrostatin-1; DHA-mediated cell death was strongly inhibited by ferrostatin-1 and deferasirox; ferritinophagy increased intracellular labile iron; and MT2A/MT1M modulation altered ferroptosis	death through ferritinophagy-associated intracellular iron release and lipid peroxidation. MT2A/MT1M-dependent antioxidant adaptation mitigated ferroptosis, whereas metallothionein inhibition enhanced sensitivity to DHA and GSH-depleting ferroptosis inducers. In primary AML cells, MT2A modulation and PPG enhanced DHA-associated cytotoxicity, providing direct ex vivo mechanistic support		therapeutic/mechanistic response; strongest ferroptosis-specific confirmation in AML cell-line models. Analytical interpretation: The study meets the review-defined criteria for confirmed ferroptosis through functional cell death, lipid peroxidation and ferroptosis-directed rescue. Primary AML experiments provide direct ex vivo mechanistic support, although definitive ferroptosis-specific rescue was established primarily in cell-line models.

				susceptibility. Human-derived evidence: ex vivo viability/cytotoxicity assessment in primary AML cells following MT2A modulation and DHA ± PPG treatment.			
Yang et al. (2026) [37]	HL-60; supportive murine C1498. Human-derived component: No AML patient-derived samples; HUVEC normal-cell comparator.	CD71-targeted ferritin delivery, GSH-responsive Fe^{3+}/Fe^{2+} conversion and Fenton-reaction ferroptosis with ICD. Intervention(s): Fe-SH@Fn versus shikonin, Fe-SH, Fe^{3+} or cytarabine; ferritin-blocking experiments.	Control: untreated cells. Comparator: shikonin alone as active drug comparator, Fe SH as non-ferritin formulation comparator, cytarabine as standard chemotherapy comparator, ferritin blocking as uptake specificity comparator.	CD71 Western blot, uptake imaging, CCK 8, apoptosis flow cytometry, live dead staining, ROS and Fenton reaction assays Ferroptosis-specific validation: CD71-dependent uptake, Fe^{2+}/ROS/Fenton chemistry and immunogenic-cell-death readouts support a ferroptosis-related mechanism. However, no specific ferroptosis-inhibitor rescue was demonstrated; the evidence is	The nanoplatform targeted CD71-positive AML cells and released iron under high-GSH conditions, generating Fe^{2+}, ROS and Fenton chemistry while co-delivered shikonin promoted immunogenic cell death. Demonstrates a targeted ferroptosis–ICD nanoplatform with strong preclinical activity; patient-derived validation was not reported.	Strongly supportive	Preclinical cell-line/murine nanoplatform evidence; no AML patient-derived validation.

				therefore strongly supportive rather than confirmed.			
Wang et al. (2023) [38]	HL-60, NB4. Human-derived component: AML BMMCs and clinical-expression/survival analyses; no direct ex vivo drug testing.	BMAL1/EZH2–EBF3–ALOX15 circadian control of lipid oxidation. Intervention(s): BMAL1 knockdown/overexpression; EBF3 modulation; ALOX15 knockdown; RSL3.	Model-system evidence: Control: empty vector, control shRNA. Comparator: RSL3 as ferroptosis inducer, BMAL1 knockdown as genetic exposure comparator, BMAL1 overexpression as genetic exposure comparator, EBF3 overexpression or knockdown as genetic mechanism comparator, ALOX15 knockdown as ferroptosis pathway comparator. Human-derived evidence: Control: healthy donor or non-AML comparison samples were used. Comparator: AML patient samples stratified by BMAL1, EBF3, ALOX15 or methylation status.	Model-system evidence: Cell viability, qPCR, Western blot, ChIP, luciferase reporter, MDA, total iron, Fe^{2+}, GSH, lipid peroxidation Human-derived evidence: qRT-PCR, methylation specific PCR, clinical correlation, survival related analysis Ferroptosis-specific validation: Lipid-peroxidation, iron/GSH changes and BMAL1/EBF3/ALOX15 genetic manipulation support a ferroptosis-related mechanism. Because definitive ferroptosis-specific pharmacologic rescue was not	BMAL1 suppressed RSL3-induced ferroptosis by repressing EBF3 and ALOX15. BMAL1 silencing or EBF3 restoration increased lipid peroxidation and ferroptotic sensitivity. Defines a circadian transcriptional resistance pathway; human evidence was associative rather than direct ex vivo treatment testing.	Strongly supportive	Supportive/associative human molecular and clinical evidence; no direct ex vivo drug testing.

				demonstrated, the evidence is classified as strongly supportive.			
Lin et al. (2025) [24]	MV4-11, HEL, U937. Human-derived component: Primary AML PBMCs/blasts and CD34-enriched samples; normal mobilised $CD34^+$ comparator.	SR-B1-targeted cholesterol disruption, GPX4 loss and oxidised-lipid stress. Intervention(s): Bioinspired HDL nanoparticles ± cytarabine, venetoclax or gilteritinib; ferrostatin-1/DFO rescue.	Model-system evidence: Control: PBS treated cells, SR B1 negative control cell-lines where used. Comparator: cytarabine alone as chemotherapy comparator, venetoclax alone as BCL-2 inhibitor comparator, gilteritinib alone as FLT3 inhibitor comparator, statins as cholesterol pathway comparators, ferrostatin-1 as ferroptosis inhibitor rescue comparator, DFO as iron chelator rescue comparator. Human-derived evidence: Control: PBS treated patient samples, untreated patient samples,	Model-system evidence: SR B1 flow cytometry, MTS viability, trypan blue, colony assays, apoptosis assays, caspase assays, CellROX, ferroptosis rescue assays Human-derived evidence: Flow cytometry for SR B1, Annexin V and PI viability, colony forming assays Ferroptosis-specific validation: GPX4 reduction, ROS/oxidised-lipid stress and ferrostatin-1/DFO rescue in sensitive models; patient viability/CFU assays.	HDL nanoparticles reduced GPX4 and increased ROS/oxidised lipid stress, producing ferroptosis in selected AML models and other regulated death phenotypes in others. They reduced patient-blast viability and colony formation while sparing normal $CD34^+$ cells. Supports selective SR-B1 targeting and combination therapy, with direct ex vivo patient-derived activity.	Confirmed	Direct ex vivo patient-derived activity with normal CD34+ comparison; ferroptosis was model-dependent across AML systems.

			normal CD34 mobilized human peripheral blood cells. Comparator: HDL nanoparticle treated patient AML samples, SR B1 positive AML blasts, CD34 enriched AML samples, and whole PBMC AML samples.				
Sabatier et al. (2023) [39]	MOLM-14, MV4-11; supportive Ba/F3-ITD and Ba/F3-WT. Human-derived component: Primary FLT3-mutant specimens, PDX-derived human AML cells and in vivo human AML PDX evidence.	FLT3–C/EBPα–FASN/SCD/FADS2 lipid anabolism and MUFA-mediated protection from GPX4-dependent ferroptosis. Intervention(s): Quizartinib, gilteritinib or other FLT3 inhibitors ± RSL3; SCD inhibition/knockdown/overexpression; oleate rescue.	Model-system evidence: Control: vehicle treated cells, control shRNA, BaF3 WT as genotype control. Comparator: BaF3 ITD as FLT3 mutant comparator, quizartinib alone as FLT3 inhibitor comparator, RSL3 alone as GPX4 inhibitor comparator, MF 438 as SCD inhibitor comparator, oleate as lipid rescue comparator, SCD knockdown as genetic sensitization comparator, SCD overexpression as	Model-system evidence: C11-BODIPY lipid peroxidation, PI viability, Western blot, Alamar Blue, synergy scoring Human-derived evidence: Transcriptomics, lipid metabolism analyses, ex vivo viability, lipid ROS, 4 HNE staining in patient-derived xenograft bone marrow Ferroptosis-specific validation: C11-BODIPY, oleate and SCD-overexpression	FLT3 or SCD inhibition reduced MUFA protection, increased the PUFA/MUFA balance and lipid oxidation, and sensitised AML cells to GPX4 inhibition. Oleate and SCD overexpression were protective; quizartinib plus RSL3 was synergistic in patient-derived AML cells. Strongly supports combined FLT3 and ferroptosis-	Strongly supportive	Direct ex vivo primary-AML activity with additional PDX support; strong translational preclinical evidence but no clinical intervention data.

			genetic rescue comparator. Human-derived evidence: Control: vehicle treated patient-derived cells, baseline or pre-treatment patient specimens. Comparator: FLT3 inhibitor treated specimens, RSL3 as GPX4 inhibitor comparator, quizartinib with RSL3 as combination comparator, gilteritinib treated patient specimens.	rescue, ferrostatin-1 rescue, quizartinib–RSL3 synergy and 4-HNE staining.	pathway targeting in FLT3-mutant AML, including ex vivo and PDX evidence.		
Zheng et al. (2025) [40]	HL-60, MOLM-13. Human-derived component: Diagnostic, remission and relapsed AML samples; TCGA-LAML; no direct ex vivo drug exposure.	BMAL1–IKZF2–ASAH2 control of ceramide metabolism and GPX4 degradation. Intervention(s): BMAL1/IKZF2/ASAH2 modulation; C2-ceramide; RSL3; sorafenib; ferrostatin-1.	Model-system evidence: Control: vector control, shRNA control. Comparator: RSL3 alone as ferroptosis inducer comparator, ferrostatin-1 as ferroptosis inhibitor rescue comparator, C2 ceramide as ceramide exposure comparator,	Model-system evidence: Lipid ROS imaging, lipid ROS flow cytometry, MDA, cell death assays, ceramide assays, qPCR, Western blot, lipidomics Human-derived evidence: Clinical sample expression analysis, correlation analysis,	BMAL1 depletion increased ceramide, promoted GPX4 loss and enhanced lipid peroxidation. Ceramide-induced death was ferrostatin-1 sensitive and increased sorafenib responsiveness. Supports targeting	Confirmed	Human evidence was mainly molecular/clinical and prognostic; therapeutic ferroptosis testing was principally model-based.

			sorafenib alone as targeted drug comparator, BMAL1 knockdown as genetic sensitization comparator, BMAL1 overexpression as genetic rescue comparator, IKZF2 modulation as pathway comparator, ASAH2 knockdown as ceramide metabolism comparator. Human-derived evidence: Control: remission samples were compared, lower BMAL1 expression groups in TCGA. Comparator: newly diagnosed AML, relapsed AML, higher BMAL1 expression groups, $CD34^+$ proportion correlation.	TCGA survival analysis Ferroptosis-specific validation: Lipid ROS/MDA, ceramide lipidomics, GPX4 degradation and ferrostatin-1 rescue; BMAL1/IKZF2/ASAH2 validation.	BMAL1 or ceramide metabolism to sensitise AML to sorafenib; human evidence was expression/prognostic.		
Woodley et al.	MOLM-13, THP-1 and additional preclinical AML models.	MPI inhibition–ATF6 UPR activation–PUFA accumulation and lipid peroxidation.	Control: nontargeting guide RNA cells, vehicle treated cells.	CRISPR assays, shRNA assays, viability, BODIPY-	MPI loss remodelled fatty-acid metabolism,	Confirmed	Direct ex vivo mechanistic/therapeutic evidence in

(2023) [41]	Human-derived component: Primary FLT3-ITD AML mononuclear cells and normal CD34+ hematopoietic controls; direct ex vivo therapeutic/mechanistic testing.	Intervention(s): MPI depletion/inhibition ± cytarabine or AC220; mannose, ferrostatin-1 or liproxstatin rescue.	Comparator: AC220 alone as FLT3 inhibitor comparator, cytarabine alone as chemotherapy comparator, mannose as metabolic rescue comparator, ferrostatin-1 as ferroptosis inhibitor rescue comparator, liproxstatin as ferroptosis inhibitor rescue comparator, MPI knockout or knockdown as genetic exposure comparator. Human-derived evidence: Primary FLT3-ITD AML mononuclear cells were evaluated alongside normal CD34+ hematopoietic controls in direct ex vivo mechanistic/therapeutic experiments.	C11, fatty acid uptake, RNA sequencing, pathway analysis, metabolomics, oxygen consumption assays Ferroptosis-specific validation: CRISPR/shRNA, BODIPY-C11, metabolomics and fatty-acid assays; mannose and ferrostatin-1/liproxstatin rescue. Human-derived evidence included direct ex vivo viability/mechanistic assessment in primary AML mononuclear cells.	increased PUFA accumulation and lipid peroxidation, and induced ferroptotic death that was rescued by ferroptosis inhibitors. Supports mannose-metabolism inhibition as a sensitiser to cytarabine and FLT3 inhibition; human data were supportive rather than interventional.		primary AML material; supports mannose-metabolism targeting and treatment sensitization.

Ma et al. (2022) [25]	HL-60. Human-derived component: None reported.	Autophagy-dependent ferroptosis involving ACSL4, GPX4 and FTH1. Intervention(s): Neratinib ± 3-methyladenine or erastin.	Control: untreated cells. Comparator: neratinib alone as active treatment comparator, 3-methyladenine as autophagy inhibitor rescue comparator, erastin as ferroptosis inducer add back comparator.	CCK 8, EdU, cell cycle flow cytometry, apoptosis flow cytometry, DCFH DA ROS, MDA, Fe^{2+}, LC3-II immunofluorescence, Western blot Ferroptosis-specific validation: ROS, MDA, Fe^{2+}, ACSL4, GPX4/FTH1 and autophagy-related changes were reported, with attenuation by 3-MA and re-induction by erastin. These findings are mechanistically compatible with ferroptosis but lack definitive rescue with a recognized ferroptosis inhibitor; the study is therefore classified as suggestive.	Neratinib increased ROS, MDA, Fe^{2+} and ACSL4 while reducing GPX4 and FTH1. Autophagy inhibition attenuated these effects, and erastin restored them. Supports an autophagy–ferroptosis mechanism for neratinib in AML; evidence was restricted to one cell-line.	Suggestive	Single cell-line model; no patient-derived validation.
Cao et al. (2022) [42]	Kasumi-1; supportive murine C1498 and LSC-focused	GSH-bioimprinted FTO/m^6A targeting with redox disruption and GPX4 inhibition.	Control: PBS treated cells. Comparator: GNPIPP12 as	Nanoparticle uptake, proliferation, colony	GNPIPP12MA depleted GSH, inhibited GPX4	Suggestive	Preclinical model evidence; no direct

	models. Human-derived component: No direct patient-derived sample validation reported.	Intervention(s): GNPIPP12MA and nanoparticle/free-drug comparators.	nanoparticle comparator, GNPP12MA as non-imprinted or less targeted nanoparticle comparator, MA alone as free drug comparator.	formation, GSH, GPX4 activity, H_2O_2 probe, lipid peroxide probe, iron assays, m^6A assays Ferroptosis-specific validation: GSH depletion, GPX4 inhibition, lipid-peroxide and iron-related signals were demonstrated with nanoparticle comparator controls. Because specific ferroptosis-directed functional rescue was not demonstrated, the evidence is classified as suggestive rather than confirmed.	activity, increased H_2O_2, lipid-peroxide and iron-related signals, and suppressed proliferation and colony formation. Provides proof of concept for a leukaemia-stem-cell–directed ferroptotic nanoplatform; no direct patient-derived validation was reported.		AML patient-derived validation.
Ma et al. (2025) [43]	KG-1α, MOLM-13. Human-derived component: None reported.	Mitochondrial dysfunction linked to DNA polymerase-γ and p62/KEAP1-associated autophagy–ferroptosis signalling. Intervention(s): Crotonoside (dose range).	Control: DMSO treated cells, zero concentration crotonoside cells. Comparator: lower concentration crotonoside conditions as dose response	Viability, Hoechst staining, mitochondrial respiration, JC 1 membrane potential, MitoTracker Green, DCFH DA ROS, Fe^{2+}, MDA, GSH/GSSG,	Crotonoside impaired mitochondrial respiration and membrane potential, increased ROS, Fe^{2+}, MDA and ACSL4, and	Suggestive	Cell-line evidence only; no patient-derived validation.

			comparators, higher concentration crotonoside conditions as dose response comparators.	Western blot Ferroptosis-specific validation: Mitochondrial dysfunction, ROS, Fe^{2+}, MDA, GSH/GSSG, ACSL4, SLC7A11 and GPX4 changes were demonstrated. In the absence of definitive ferroptosis-directed rescue, these biomarkers and mechanistic findings are interpreted as suggestive/ferroptosis-associated rather than confirmatory.	reduced GSH balance, SLC7A11 and GPX4. Cell-line evidence supports mitochondrial injury followed by ferroptosis; the proposed polymerase-γ mechanism requires further validation.		

Ferroptosis-specific evidence categories were evaluated independently from methodological quality and translational relevance. Confirmed ferroptosis required a functional cell-death or loss-of-viability phenotype together with lipid-peroxidation evidence and functional reversal using a recognized ferroptosis-directed rescue intervention, particularly ferrostatin-1 or liproxstatin-1. Iron-chelation rescue, lipophilic antioxidant rescue, and genetic manipulation of established ferroptosis regulators were considered additional mechanistic support. Strongly supportive evidence comprised functional anti-leukemic effects with multiple concordant ferroptosis-related findings but without definitive ferroptosis-specific pharmacologic rescue. Suggestive/ferroptosis-associated evidence relied predominantly on changes in ROS, MDA, intracellular iron, GSH, GPX4, SLC7A11, or related biomarkers without sufficient functional rescue; these changes were not considered independently sufficient to establish ferroptotic cell death. Distribution in the 18-study synthesis: Confirmed, n = 8; Strongly supportive, n = 7; Suggestive/ferroptosis-associated, n = 3. Translational relevance was characterized separately according to direct ex vivo patient-derived testing, supportive human-derived molecular/prognostic evidence, or cell-line/preclinical evidence. These categories are not risk-of-bias or certainty-of-evidence grades.

Contextual pre-2020 evidence: Trujillo-Alonso et al. (2019) was not included in Supplementary Table S4 because it falls outside the prespecified eligibility window beginning 1 January 2020. This study is discussed in the main manuscript as foundational evidence of iron-driven oxidative vulnerability in AML, without inclusion in the formal 18-study synthesis.

Abbreviations: AML, acute myeloid leukemia; BMMC, bone-marrow mononuclear cell; DFO, deferoxamine; GSH, glutathione; GPX4, glutathione peroxidase 4; HMOX1, heme oxygenase 1; ICD, immunogenic cell death; MDA, malondialdehyde; PBMC, peripheral-blood mononuclear cell; PDX, patient-derived xenograft; ROS, reactive oxygen species; SCD, stearoyl-CoA desaturase; system xc−, cystine/glutamate antiporte