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Review Article

A systematic literature review of disease burden and clinical efficacy for patients with relapsed or refractory acute myeloid leukemia

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Abstract: Acute myeloid leukemia (AML) is a rapidly progressive hematological malignancy that is difficult to cure. The prognosis is poor and treatment options are limited in case of relapse. A comprehensive assessment of current disease burden and the clinical efficacy of non-intensive therapies in this population are lacking. We conducted two systematic literature reviews (SLRs). The first SLR (disease burden) included observational studies reporting the incidence and economic and humanistic burden of relapsed/refractory (RR) AML. The second SLR (clinical efficacy) included clinical trials (phase II or later) reporting remission rates (complete remission [CR] or CR with incomplete hematologic recovery [CRi]) and median overall survival (mOS) in patients with RR AML or patients with *de novo* AML who are ineligible for intensive chemotherapy. For both SLRs, MEDLINE®/Embase® were searched from January 1, 2008 to January 31, 2020. Clinical trial registries were also searched for the clinical efficacy SLR. After screening, two independent reviewers determined the eligibility for inclusion in the SLRs based on full-text articles. The disease burden SLR identified 130 observational studies. The median cumulative incidence of relapse was 29.4% after stem cell transplant and 46.8% after induction chemotherapy. Total per-patient-per-month costs were $28,148-$29,322; costs and health care resource use were typically higher for RR versus non-RR patients. Patients with RR AML had worse health-related quality of life (HRQoL) scores than patients with *de novo* AML across multiple instruments, and lower health utility values versus other AML health states (i.e. newly diagnosed, remission, consolidation, and maintenance therapy). The clinical efficacy SLR identified 50 trials (66 total trial arms). CR/CRi rates and mOS have remained relatively stable and low over the last 2 decades. Across all arms, the median rate of CR/CRi was 18.3% and mOS was 6.2 months. In conclusion, a substantial proportion of patients with AML will develop RR AML, which is associated with significant humanistic and economic burden. Existing treatments offer limited efficacy, highlighting the need for more effective non-intensive treatment options.

Keywords: Acute myeloid leukemia, relapse, efficacy, quality of life, health economics

Introduction

Acute myeloid leukemia (AML) is a rapidly progressive hematological malignancy characterized by an increase in myeloid blast cells in the bone marrow and peripheral blood that inhibit normal production of blood cells and platelets, placing affected patients at risk of infection and hemorrhage [1]. The median age at diagnosis is typically 63-71 years [2], and incidence increases while prognosis worsens with advancing patient age [3]. Standard treatment is intensive induction chemotherapy followed by hematopoietic stem cell transplantation (HSCT) [4-6]. However, few patients are eligible for this treatment due to advanced age, frailty, or comorbidity, and alternatively receive a less intensive induction regimen [4-6]. Moreover, patients often relapse after first-line therapy, including HSCT, and require salvage therapy [7]. Treatment options for patients with relapsed/refractory (RR) AML are limited and typically consist of HSCT or reinduction (if eligible) or a less intensive salvage regimen containing purine analogs [1, 4-6, 8].

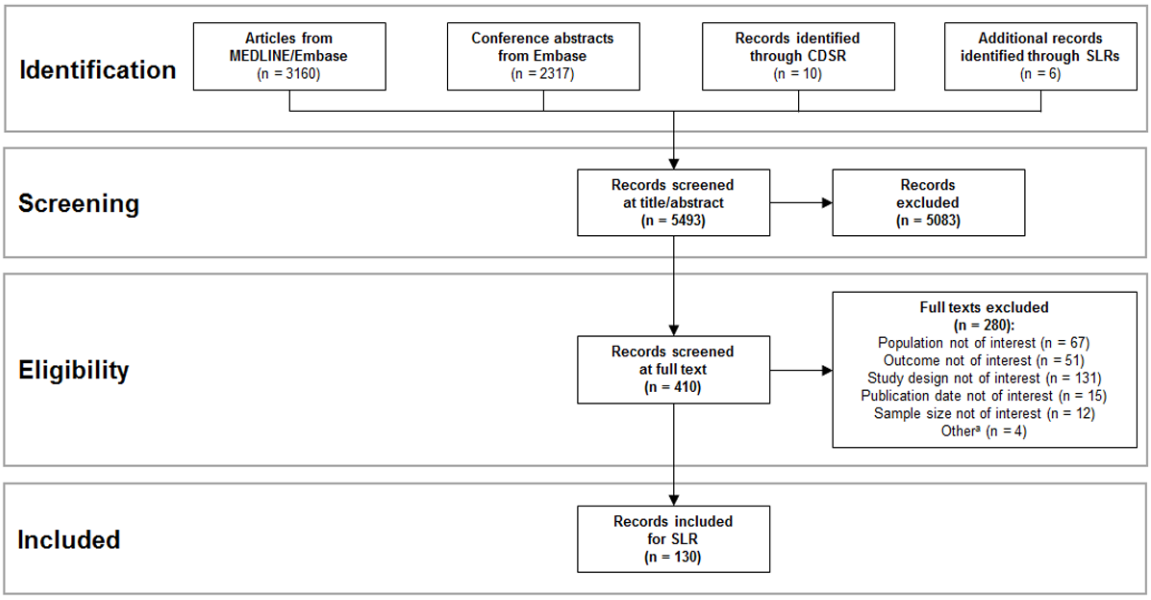

Figure 1. Disease burden PRISMA diagram. Abbreviations: CDSR, Cochrane Database of Systematic Reviews; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review. [a]Other reasons for exclusion included duplicate studies, wrong sample size, and animal studies.

The advanced age of the AML patient population may be associated with unique health-related quality of life (HRQoL) challenges, particularly among those who have RR AML. Deterioration of HRQoL occurs quickly at the time of diagnosis and treatment start, but there are limited data on patient-reported outcomes (PROs) such as fatigue, symptom severity, impact on daily activities, and HRQoL specifically for patients with RR AML [9, 10]. Furthermore, the variety of treatments used in patients with RR AML who are ineligible for intensive chemotherapy generates questions about the burden of costs and health care resource utilization (HCRU) in the RR AML population. Therefore, data on disease burden, including HRQoL, costs, and HCRU, can provide insights into specific patient needs during and after treatment; this information can potentially contribute to the improvement of current treatments and the development of therapies capable of reducing the disease burden [9, 10]. Given the dire prognosis of these patients and the limited treatment options available, we conducted a systematic literature review (SLR) to better characterize the increased burden of disease in patients with RR AML in the real-world setting, and a second SLR to review the clinical efficacy of agents evaluated in clinical trials for patients with RR AML or *de novo* AML ineligible for intensive chemotherapy and HSCT.

Methods

Two systematic literature searches were performed, both of which were based on a prespecified systematic search strategy to identify studies describing patients with RR AML (disease burden and clinical efficacy) or those with *de novo* AML ineligible for intensive chemotherapy (clinical efficacy) (**Figures 1** and **2**). The inclusion and exclusion criteria were developed using a Population, Intervention, Comparator, Outcomes, Study Design, and Time (PICOS) format (disease burden, **Table 1**; clinical efficacy, **Table 2**). Citations of interest included articles published in MEDLINE®, Embase®, or the Cochrane Database of Systematic Reviews and written in the English language from January 1, 2008 to January 31, 2020. The disease burden review also included a search of abstracts from the conferences held by the largest hematology associations from 2016 through 2019, the American Society of Hematology (ASH) and the European Hematology Association (EHA); the clinical efficacy review included the same sources as the disease burden review and also included searches for entries with results in ClinicalTrials.gov, the European Union Clinical

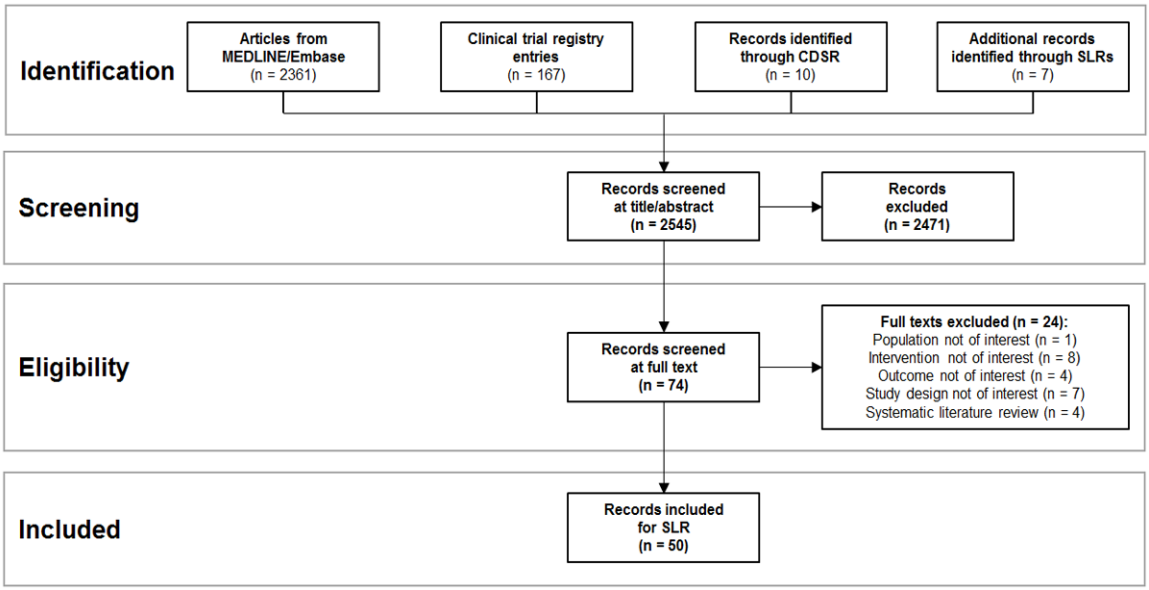

Figure 2. Clinical efficacy PRISMA diagram. Abbreviations: CDSR, Cochrane Database of Systematic Reviews; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Trial Register, and the International Clinical Trials Registry Platform.

Literature screening

The terms used in the systematic searches were developed based on the PICOS framework (**Tables 3**-**6**). Following literature searches, all eligible citations from the disease burden and clinical efficacy searches were organized into two databases. A two-step process with two independent reviewers was used to screen all citations, with titles and abstracts screened in the first step and full texts of any relevant citations screened in the second step. At each screening step, study inclusion and exclusion were based on the pre-defined inclusion and exclusion criteria, including outcomes used to assess disease burden and clinical efficacy, based on the PICOS framework for each review. Any disagreements in screening decisions were resolved through consensus, and a third, independent reviewer adjudicated if consensus could not be reached. PRISMA flow charts (**Figures 1** and **2**) were completed to provide an overview of the review process.

Data extraction

After full-text review, one reviewer extracted all relevant data into an Excel-based extraction sheet, with quality control from a second, senior reviewer. Data extraction variables for both reviews were: study characteristics: year of data collection, country, follow-up time; population: sample size, mean/median age, proportion of males; treatment patterns: interventions and patient number; treatment outcomes: complete remission (CR), CR with incomplete hematologic recovery (CRi), partial response (PR), stable disease, duration of CR, median overall survival (mOS).

Additional variables collected for the disease burden review were: epidemiology: proportion of patients who relapsed, median time to relapse, molecular risk factors; economic burden: direct medical cost (by cost type, taken directly from studies as reported by the authors), HCRU (proportion used or number of days/events); humanistic burden: HRQoL scores by PRO instruments, health utility values. Extracted variables for molecular risk factors included the hazard ratios (HR) for cumulative incidence of relapse (CIR) for any variables demonstrating a significant change in risk based on multivariate analysis from the original study only, but not based on significant differences in patient demographics or in results of univariate analysis.

Additional variables collected for the clinical efficacy review were: study details: registry

Table 1. Disease burden PICOS

	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years old) with RR AML or not eligible for intensive chemotherapy	Infant, child, or adolescent only Systemic therapy-naïve AML Mixed AML + MDS unless AML reported separately Cohorts selected using defined risk criteria (cytogenetic or multi-criteria) or other special populations (e.g. CMV-infected persons)
Intervention	Any or none	Not applicable
Comparators	Any or none	Not applicable
Outcomes	Epidemiology: • Proportion of patients with AML that experience RR disease after first-line therapy • Proportion of patients with RR AML who are ineligible for 2nd- and 3rd-line treatment overall and by reason • Proportion of patients with RR AML who are eligible for transplant after first relapse • Molecular risk factors (e.g. mutations) that increase risk of RR disease Economic burden: • Direct and indirect costs • Health care resource use • Treatment patterns Humanistic burden: • Sequelae/clinical manifestations of RR AML disease • Impact of disease or treatment (blood transfusions, chemotherapy and injectable treatments) on daily life and HRQoL	
Study design	Observational studies Systematic reviews (for identification of primary studies only)	Interventional trials (random or non-random) Case series/case reports Non-systematic reviews Editorials, comments, letters
Other/Limits	English language Published January 1, 2008 or after Epidemiology: published January 1, 2013 or after and sample size ≥50 Molecular risk factors: published January 1, 2016 or after	
Sources	Articles indexed in MEDLINE® or Embase® Conference abstracts from ASH or EHA 2016-2019 Cochrane Database of Systematic Reviews	

Abbreviations: AML, acute myeloid leukemia; ASH, American Society of Hematology; CMV, cytomegalovirus; EHA, European Hematology Association; HRQoL, health-related quality of life; MDS, myelodysplastic syndromes; PICOS, Population, Intervention, Comparator, Outcomes, Study Design, and Time; RR, relapsed or refractory.

Table 2. Clinical efficacy PICOS

	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years old) with RR AML or not eligible for intensive chemotherapy	Infant, child, or adolescent only Systemic therapy-naïve AML Mixed AML + MDS unless AML reported separately
Intervention	Any non-intensive chemotherapy, alone or in combination with another non-intensive agent, including but not limited to: • Hypomethylating agents (i.e. azacitidine, decitabine) • Low-dose cytarabine (e.g. 20 mg q12h) • Gemtuzumab ozogamicin • Venetoclax • Enasidenib • Ivosidenib • Sorafenib • Midostaurin • Glasdegib • Best supportive care	Systemic therapy given as part of transplant therapy or donor lymphocyte infusion Intensive chemotherapy, including any regimens containing any of the following: • High- or intermediate-dose cytarabine (i.e. ≥1 g/m^2 body surface area or 100-200 mg/m^2 continuous infusion) • Any anthracycline (e.g. idarubicin, daunorubicin) • Mitoxantrone • Any purine analog (e.g. fludarabine, cladribine, clofarabine)
Comparators	Any or none	Not applicable
Outcomes	Overall survival (% at timepoints or median) Complete remission Partial remission Stable disease Relapse-free survival	
Study design	Clinical trials (randomized or non-randomized, single or multi-arm), phase II or later (includes phase I/II if phase II results presented separately) Systematic reviews (for identification of primary studies only)	Phase I clinical trials Trials that were terminated early due to failure Observational studies Retrospective analyses of clinical trial data Case reports or case series Non-systematic reviews, editorials, comments, letters, or notes
Other/Limits	English language Published January 1, 2008 or after	Not applicable
Sources	Articles indexed in MEDLINE® or Embase® Cochrane Database of Systematic Reviews Entries with results from ClinicalTrials.gov, EU Clinical Trials, or ICTRP	Conference abstracts

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; ICTRP, International Clinical Trials Registry Platform; MDS, myelodysplastic syndromes; NCCN, National Comprehensive Cancer Network; PICOS, Population, Intervention, Comparator, Outcomes, Study Design, and Time; RR, relapsed or refractory.

Table 3. Disease burden search: MEDLINE®/Embase®

Search number	String	Results
S1	TI,AB ("acute myeloid leukemia" OR "acute myeloid leukaemia" OR "acute myelogenous leukemia" OR "acute myelogenous leukaemia" OR "acute myelocytic leukemia" OR "acute myelocytic leukaemia" OR "acute granulocytic leukemia" OR "acute granulocytic leukaemia" OR "acute non lymphocytic leukemia" OR "acute non-lymphocytic leukemia" OR "acute nonlymphocytic leukemia" OR "acute non lymphocytic leukaemia" OR "acute non-lymphocytic leukaemia" OR "acute nonlymphocytic leukaemia" OR "acute myeloblastic leukemia" OR "acute myeloblastic leukaemia" OR "AML") OR EMB.EXPLODE ("acute myeloid leukemia") OR MESH.EXPLODE ("Leukemia, Myeloid, Acute")	187,750
S2	TI,AB (refractory OR relapse* OR recurren* OR maintenance OR pretreated OR ((previously OR prior) NEAR/3 (treated OR treatment* OR therapy OR therapies))) OR EMB.EXACT ("refractory period") OR EMB.EXACT ("relapse" OR "leukemia relapse") OR MESH.EXACT ("Recurrence")	2,954,446
S3	TI,AB (incidence OR epidemiolog* OR prevalence OR mortality OR "survival rate" OR "time to" OR "time to relapse" OR "time to recurrence" OR "time to first relapse" OR "time to first recurrence" OR "relapse time" OR "recurrence time") OR TI,AB ((risk OR prognos* OR predict*) AND (factor* OR model* OR score* OR marker*) AND (gene* OR molecular OR DNA)) OR MJEMB.EXACT ("Incidence" OR "Epidemiology" OR "Prevalence" OR "Mortality" OR "Survival Rate") OR MJMESH.EXACT ("Incidence" OR "Epidemiology" OR "Prevalence" OR "Mortality" OR "Survival Rate")	7,725,584
S4	TI,AB ("practice guideline" OR "practice guidance" OR (treatment AND (guideline* OR guidance)) OR (clinical NEAR/3 pathway*) OR "treatment pathway" OR "care pathway" OR "disease management" OR "consensus" OR "standard of care") OR EMB.EXACT ("Practice Guideline" OR "Clinical Protocol" OR "Clinical Pathway") OR MESH.EXACT ("Practice Guideline" OR "Guideline" OR "Clinical Protocols" OR "Critical Pathways" OR "Standard of Care") OR DTYPE ("Practice Guideline")	1,290,576
S5	TI,AB (("real-world" OR "real-life") OR TI,AB ((real AND (world OR life)) AND (practice OR pattern OR treatment)))	162,380
S6	TI,AB (cost NEAR/5 (estimate OR variable OR utility OR benefit OR effectiveness)) OR TI,AB (economic* OR pharmacoeconomic* OR price* OR pricing) OR EMB.EXACT ("Socioeconomics" OR "Cost Benefit Analysis" OR "Cost Utility Analysis" OR "Cost of Illness" OR "Cost Control" OR "Economic Aspect" OR "Health Economics") OR MESH.EXACT("Costs and Cost Analysis" OR "Cost-Benefit Analysis" OR "Cost Control" OR "Cost Savings" OR "Value of Life")	1,272,042
S7	TI,AB (productivit* OR ("health care" AND cost*) OR (health AND resource) OR (resource NEAR/3 use) OR "resource utili*" OR (hospitali* NEAR/5 (rate OR frequency)) OR "length of stay" OR (visit NEAR/5 (inpatient OR outpatient OR "ER" OR emergency OR "GP")) OR (lost AND work* AND day*) OR ((low OR high OR health* OR variable OR estimate OR unit) NEAR/5 cost) OR fiscal OR funding OR financial OR finance OR economic* OR pharmacoeconomic* OR price* OR pricing) OR EMB.EXACT ("Productivity" OR "Cost Control" OR "Cost Minimization Analysis" OR "Cost of Illness" OR "Cost" OR "Economic Aspect" OR "Economics" OR "Financial Management" OR "Health Care Cost" OR "Health Care Financing" OR "Health Economics" OR "Hospital Cost" OR "Socioeconomics") OR MESH.EXACT("Budgets" OR "Capital Expenditures" OR "Cost Allocation" OR "Costs and Cost Analysis" OR "Cost Control" OR "Cost Sharing" OR "Deductibles and Coinsurance" OR "Direct Service Costs" OR "Drug Costs" OR "Economics, Hospital" OR "Economics, Medical" OR "Economics, Nursing" OR "Economics, Pharmaceutical" OR "Economics" OR "Employer Health Costs" OR "Fees and Charges" OR "Health Care Costs" OR "Health Expenditures" OR "Hospital Costs" OR "Medical Savings Accounts")	2,756,396

S8	TI,AB ("quality of life" OR qol OR (quality NEAR/3 life) OR "value of life" OR "quality adjusted life" OR qaly OR qald OR qale OR qtime OR "disability adjusted life" OR daly OR (("short form" OR shortform OR SF) NEAR/1 (six OR 6 OR eight OR 8 OR twelve OR 12 OR sixteen OR 16 OR twenty OR 20 OR "thirty six" OR 36)) OR euroqol OR "euro qol" OR eq5d OR "eq 5d" OR "euro quol" OR "euro qual" OR euroqual OR hql OR hqol OR "h qol" OR hrqol OR "hr qol" OR hrql OR hye OR hyes OR "health year equivalent" OR hui OR hui1 OR hui2 OR hui3 OR "health utilities" OR "health utility" OR disutility OR disutilities OR "disease specific index" OR "symptom index" OR "symptoms index" OR "symptom inventory" OR "quality of wellbeing" OR "quality of wellbeing" OR qwb OR "willingness to pay" OR WTP OR "standard gamble" OR "time trade off"" OR "time tradeoff" OR TTO OR "person trade off" OR "person tradeoff" OR ((health OR illness OR disease) NEAR/5 state) OR ((index OR quality) NEAR/2 ("wellbeing" OR wellbeing)) OR (health NEAR/3 ("utility index" OR "utilities index")) OR (multiattribute NEAR/3 ("health index" OR theor* OR "health state" OR utilities OR utility OR analys*)) OR (utilit* NEAR/3 (valu* OR measure* OR health OR life OR estimate* OR elicit* OR disease)) OR 15D OR "15 dimension" OR 12D OR "12 dimension" OR "rating scal*" OR "linear scal*" OR "visual analog*" OR VAS OR "European Organization for Research and Treatment of Cancer" OR EORTC OR HAPT OR "Functional Assessment of Cancer Therapy") OR EMB.EXACT ("Quality of Life" OR "Quality Adjusted Life Year" OR "Health Status Indicator") OR MESH.EXACT ("Quality of Life" OR "Value of Life" OR "Quality-Adjusted Life Years" OR "Health Status Indicators") OR SU.EXACT("Quality of Life")	1,521,014
S9	TI,AB (symptom NEAR/5 burden) OR TI,AB (functioning AND (reduce OR impaired OR decrease OR impact)) OR TI,AB ((daily OR day) NEAR/3 activit*) OR TI,AB ((treatment OR caregiver OR famil*) NEAR/5 burden) OR TI,AB (societal NEAR/5 impact) OR EMB.EXACT ("International Classification of Functioning, Disability and Health") OR MESH.EXACT ("International Classification of Functioning, Disability and Health")	330,877
S10	EMB.EXACT ("case study" OR "case report" OR "abstract report" OR "letter" OR "note") OR DTYPE ("Letter" OR "Historical Article" OR "Editorial" OR "Note" OR "Comment" OR "News" OR "Newspaper Article" OR "Review") OR TI,AB ("case study" or "case studies" OR "case report" OR "case reports" OR "case series")	13,466,628
S11	S3 AND PD (>2012)	3,151,423
S12	(S4 OR S5 OR S6 OR S7 OR S8 OR S9) AND PD (>2007)	3,507,422
S13	(S1 AND S2) AND (S11 OR S12)	12,955
S14	S13 AND LA (English)	12,573
S15	S14 NOT DTYPE (Conference abstract)	5228
S16	S14 AND DTYPE (Conference abstract) AND PD (>2015) AND PUB (Blood OR Haematologica OR HemaSphere)	2787

number, phase; patient details: genetic mutations, whether patients were RR and/or not eligible for intensive chemotherapy. The clinical efficacy SLR focused on non-intensive treatments in phase II or later trials (e.g. high- or standard-dose cytarabine, purine analogs, donor lymphocyte infusion) because of the likelihood that patients with RR AML will not be eligible for intensive therapy [11-13]. Treatments were categorized as 1) DNA-damaging agents (i.e. treatments that inhibit DNA synthesis or directly cause DNA damage); 2) hypomethylating agent (HMA; i.e. any monotherapy or combination including azacitidine, decitabine, or guadecitabine); 3) kinase inhibitor (i.e. any monotherapy or combination including agents that inhibit specific kinases, including *FLT3*, Janus kinase [JAK], epidermal growth factor receptor [EGFR], or vascular endothelial growth factor [VEGF], or inhibit multiple kinases, such as quizartinib, sorafenib, selumetinib, or ruxolitinib); 4) low-dose cytarabine (LDAC; i.e. any monotherapy or combination including LDAC or a non-intensive cytarabine prodrug); or 5) other

Table 4. Disease burden and clinical efficacy search: Cochrane Database of Systematic Reviews

Search number	String	Results
S1	"acute myeloid leukemia" OR "acute myeloid leukaemia" OR "acute myelogenous leukemia" OR "acute myelogenous leukaemia" OR "acute myelocytic leukemia" OR "acute myelocytic leukaemia" OR "acute granulocytic leukemia" OR "acute granulocytic leukaemia" OR "acute non lymphocytic leukemia" OR "acute non-lymphocytic leukemia" OR "acute nonlymphocytic leukemia" OR "acute non lymphocytic leukaemia" OR "acute non-lymphocytic leukaemia" OR "acute nonlymphocytic leukaemia" OR "acute myeloblastic leukemia" OR "acute myeloblastic leukaemia" OR "AML"	5597
S2	MESH descriptor: ("Leukemia, Myeloid, Acute") explode all trees	8
S3	refractory OR relapse* OR recurren* OR maintenance OR pretreated	158,109
S4	(#1 OR #2) AND (#3) with Cochrane Library publication date from Jan 2008-Jan 2020, in Cochrane Reviews	10

Table 5. Clinical efficacy search: MEDLINE®/Embase®

Search number	String	Results
S1	TI,AB ("acute myeloid leukemia" OR "acute myeloid leukaemia" OR "acute myelogenous leukemia" OR "acute myelogenous leukaemia" OR "acute myelocytic leukemia" OR "acute myelocytic leukaemia" OR "acute granulocytic leukemia" OR "acute granulocytic leukaemia" OR "acute non lymphocytic leukemia" OR "acute non-lymphocytic leukemia" OR "acute nonlymphocytic leukemia" OR "acute non lymphocytic leukaemia" OR "acute non-lymphocytic leukaemia" OR "acute nonlymphocytic leukaemia" OR "acute myeloblastic leukemia" OR "acute myeloblastic leukaemia" OR "AML") OR EMB.EXPLODE ("acute myeloid leukemia") OR MESH.EXPLODE ("Leukemia, Myeloid, Acute")	187,761
S2	TI,AB (refractory OR relapse OR relapse* OR recurren* OR maintenance OR pretreated OR ((previously OR prior) NEAR/3 (treated OR treatment* OR therapy OR therapies))) OR EMB.EXACT ("refractory period") OR EMB.EXACT ("relapse" OR "leukemia relapse") OR MESH.EXACT ("Recurrence")	2,954,678
S3	TI,AB (randomi* OR RCT OR placebo* OR "randomly allocated" OR (allocated NEAR/2 random*) OR (clinical NEAR/1 trial*) OR ((singl* OR doubl* OR treb* or tripl*) NEAR/1 (blind[*3] OR mask[*3]))) OR EMB.EXACT ("clinical trial" OR "randomized controlled trial" OR "controlled clinical trial" OR "multicenter study" OR "phase I clinical trial" OR "phase II clinical trial" OR "phase III clinical trial" OR "phase IV clinical trial" OR "single blind procedure" OR "double blind procedure" OR "crossover procedure" OR "placebo" OR "prospective study") OR EMB.EXACT.EXPLODE (randomization) OR MESH.EXACT ("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Random Allocation" OR "Double Blind Method" OR "Single Blind Method" OR "Clinical Trial" OR Placebos) OR MESH.EXACT.EXPLODE ("Clinical Trials as Topic")	3,811,966
S4	TI,AB ("case report") OR EMB.EXACT ("case study" OR "abstract report" OR letter) OR MESH.EXACT (Letter OR "Historical Article")	1,969,041
S5	(S1 AND S2 AND S3) NOT S4	9903
S6	S5 AND LA (English) AND PD (>20071231) NOT (rtype.exact ("Conference Abstract"))	2361

(i.e. treatments not conforming to the previous categories, such as lenalidomide, tosedostat, belinostat, or venetoclax).

Data analysis

For CIR, studies were categorized by HSCT type (i.e. allogeneic [allo-HSCT] or autologous [auto-HSCT]), induction chemotherapy, or a mix of these interventions. For clinical efficacy, trials were categorized as including patients with RR AML, *de novo* AML ineligible for intensive chemotherapy, or both populations; any mutations required for inclusion were noted. Treatments were also categorized based on mechanism of action. Where possible, bubble charts were

Table 6. Clinical efficacy search: clinical trial registries

Search number	String	Results
ClinicalTrials.gov		
S1	Acute Myeloid Leukemia, in Relapse	-
S2	Adult + Older Adult	-
S3	Combine search; include only studies with results	88
EU Clinical Trials Register		
S1	"acute myelogenous leukemia" OR "AML" OR "acute myeloid leukemia" AND + refractory OR + relapsed	-
S2	Adult or Elderly	-
S3	Combine search; include only studies with results	75
International Clinical Trials Registry Platform		
S1	("acute myelogenous leukemia" OR "AML" OR "acute myeloid leukemia") AND (refractory OR relapsed)	-
S2	Combine search; include only studies with results	1

developed using individual data points, with the bubble size indicating study arm sample size. Trends over time were qualitatively reviewed using the year data collection began for each study. Descriptive statistics (e.g. median values, ranges) were used to summarize the data.

Results

Disease burden SLR: RR AML

The disease burden search identified 5493 records (**Figure 1**). Of these records, 5083 were excluded based on the title and abstract, and the remaining 410 were reviewed based on the full text. Of these records, 280 were excluded based on the full text. The remaining records described results from 130 observational studies in RR AML, with patient populations ranging from 17 to 6839 patients.

Epidemiological burden: Fifty-four of the 130 observational studies reported CIR for patients who had received allo-HSCT (reported by 35 studies), auto-HSCT (reported by 4 studies), induction chemotherapy (reported by 13 studies), or a mix of interventions (reported by two studies) [14-67]. The median (range) CIR was 29.4% (9.0% to 51.2%) after allo-HSCT, 37.9% (31.0% to 46.9%) after auto-HSCT, and 46.8% (23.1% to 68.0%) after induction chemotherapy. Among these 130 studies, CIR trended higher in studies of older patients (mean/median age ≥60 years) than in younger populations and in studies of induction chemotherapy rather than HSCT (particularly allo-HSCT).

The CIR appeared to decrease over time, with higher rates of relapse in studies conducted in 2000 or earlier, with median CIR of 40.65% (range, 15% to 68%) in 2000 or earlier and 35% (range, 9% to 78.3%) after 2000 (**Figure 3A**). Decreases in CIR were observed for allo-HSCT, auto-HSCT, and induction chemotherapy. Most studies followed patients for less than 5 years, although two reported CIR rates at 10 years (**Figure 3B**) [25, 66]. Longer follow-up produced a moderately higher CIR in patients given auto-HSCT and induction chemotherapy, with little change among allo-HSCT patients.

Reported median times to relapse ranged from 3.2 to 10.7 months in 2754 patients treated with allo-HSCT (reported by 10 studies) [17, 37, 59, 68-74] and from 5.0 to 17.1 months in 1497 patients treated with induction chemotherapy (reported by five studies) [72, 75-78]. Time to relapse increased over time in induction chemotherapy studies but not in allo-HSCT studies (**Figure 4**). The median time to relapse was shorter in patients with minimal residual disease (MRD) (range, 8.5 to 11.9 months) [75, 76] than those without MRD (range, 14.4 to 17.1 months), reported in two studies [75, 76]. One study reported that patients without *FLT3* mutations had slightly longer median time to relapse (4.0 months) than patients with *FLT3* mutations (3.3 months) [37].

Risk factors for CIR were identified based on significance in multivariate analysis and characterized as cytogenetic (reported by 15 studies), mutations in specific genes (reported by 12 studies), or MRD status (reported by 18 studies; **Table 7**) [18, 29, 34, 36, 37, 46, 47, 63-66, 79-104]. Cytogenetic risk factors included complex or monosomal karyotypes, adverse risk cytogenetics (as defined by European

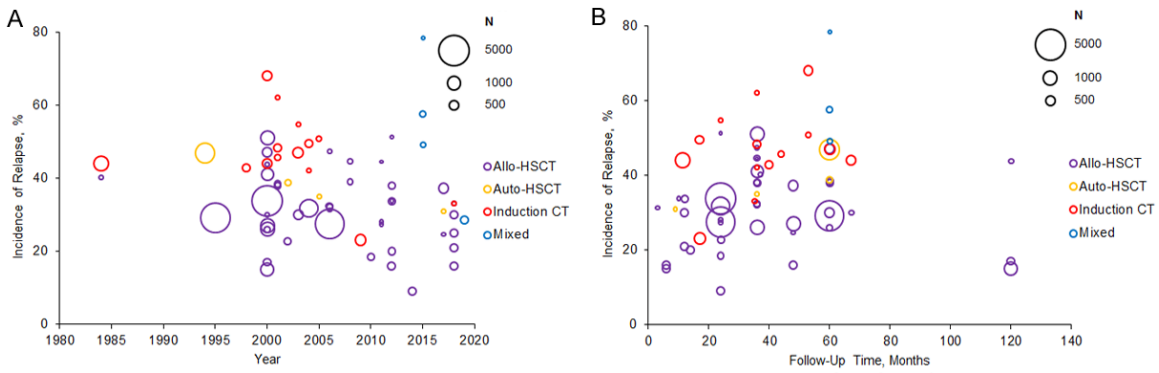

Figure 3. Cumulative incidence of relapse from observational studies (A) the year of study data collection and (B) by follow-up time. Bubble size indicates sample size. Note: Nine out of 54 studies [20, 21, 25, 26, 38, 48, 58, 65, 66] reported multiple incidences of relapse from different study cohorts, which are all included in the figures. One of these studies reported incidence of relapse by different cohorts and follow-up time [48]. In (A), 8 out of 54 studies did not report data collection years; for these studies, the publication year was used as a proxy [30, 39, 43, 58, 62, 64, 65, 67]. In (B), 3 out of 54 studies did not report follow-up time; these studies were not included in the figure [61, 62, 67]. Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; CT, chemotherapy.

Figure 4. Median time to relapse following treatment in observational studies. Bubble size indicates sample size. Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CT, chemotherapy. Sources: Bejanyan et al. 2015 [68], Bhamidipati et al. 2017 [17], Borlenghi et al. 2016 [75], Christopoulos et al. 2013 [69], El-Ghammaz & El-Razzaz 2018 [59], Fasslrinner et al. 2017 [70], Freeman et al. 2013 [76], Hoellein et al. 2017 [77], Ivanoff et al. 2013 [78], Lorentino et al. 2016 [71], Ostgard et al. 2018 [72], Patel et al. 2016 [73], Sauer et al. 2015 [74], Song et al. 2016 [37].

LeukemiaNet [ELN] and other leukemia societies), changes at specific chromosomal locations, and incomplete mutational clearance. Mutations in *DNMT3A*, *NPM1,* or *CEBPA* double mutations had a favorable impact on CIR, while mutations in *IDH1/IDH2, KIT, TP53*, *WT1*, and *FLT3* internal tandem duplication (*FLT3*-ITD) had an adverse effect on CIR. The presence of MRD before or after allo-HSCT or after induction chemotherapy was associated with increased CIR.

Economic burden: Two studies presented total direct costs on a per-patient-per-month (PPPM) basis [105, 106]. In these two studies, total costs were $28,148 and $29,323, with similar inpatient, outpatient, and pharmacy costs in each study (**Figure 5**). In one of these two studies, costs were significantly higher in patients with RR AML than patients with non-RR AML [105]. In the second study, costs were numerically lower for patients who achieved remission versus those who relapsed (significance not assessed) [106]. Four studies reported costs over total follow-up (**Table 8**) [52, 106-108]. In three of these studies reporting costs during follow-up with mean follow-up less than 1 year, total costs ranged from $70,038 to $145,634 [52, 106, 107]; in the remaining study with a mean follow-up of 15 months, total costs were $439,104 [108]. Inpatient hospitalization accounted for 43% to 77% of total direct medical costs, as reported by the four studies.

There was limited data comparing the cost of different treatments [109, 110]. Eight studies evaluated HCRU in patients with RR AML in the US as events (admissions, visits, claims), inpa-

Table 7. Molecular risk factors for relapse

Study	N	Intervention	Variable	Comparison	HR (95% CI)	Follow-up, years
Cytogenetic risk						
Brands-Nijenhuis et al. 2016 [18]	4635	Allo-HSCT	Monosomy 7	Not monosomy 7	1.9 (1.3-2.7)	6.2
			Adverse risk cytogenetics (ELN)	Favorable or intermediate risk cytogenetics	1.4 (1.2-1.7)	
			Complex karyotype (ELN)	Non-complex karyotype	1.6 (1.2-2.1)	
			Monosomal karyotype (ELN)	Non-monosomal karyotype	1.9 (1.3-2.7)	
Damiani et al. 2016 [79]	184	Allo-HSCT	Adverse risk cytogenetics (MRC)	Favorable risk cytogenetics	3.2 (1.2-7.9)	3
Duléry et al. 2017 [80]	139	Allo-HSCT	Mixed chimerism post-HSCT	Full donor	2.9 (1.5-5.5)	3
Harada et al. 2018 [63]	4278	Allo-HSCT	t(7;11)(p15;p15)	Intermediate risk without translocation	1.6 (1.1-2.3)	3
Michelis et al. 2017 [29]	196	Allo-HSCT	Unfavorable risk (SWOG/modified ELN)	Favorable risk	3.0 (1.1-8.0)	3
Mori et al. 2017 [82]	10,923	Allo-HSCT	Abnormal 17p	Normal 17p	1.3 (1.1-1.6)	5
			Complex karyotype (NCCN)	Non-complex karyotype	1.2 (1.1-1.4)	
Morita et al. 2018 [64]	131	Intensive chemotherapy	Adverse risk cytogenetics (ELN)	Not adverse risk cytogenetics	6.6 (3.0-14.5)	3
			Complete mutational clearance	Incomplete mutational clearance	0.3 (0.1-0.6)	
Oran et al. 2017 [83]	152	Allo-HSCT	Adverse risk cytogenetics (ELN)	Not adverse risk cytogenetics	6.7 (2.1-21.7)	1
Patel et al. 2018 [65]	319	Allo-HSCT	Adverse risk cytogenetics (ELN)	Favorable or intermediate risk cytogenetics	4.0 (1.3-11.8)	0.5
			Adverse risk cytogenetics (ELN)	Favorable or intermediate risk cytogenetics	3.6 (1.7-7.7)	1
Shimoni et al. 2019 [66]	1134	Allo-HSCT	Intermediate risk cytogenetics (NR)	Favorable risk cytogenetics	5.9 (1.4-24.2)	2
			Adverse risk cytogenetics (NR)	Favorable risk cytogenetics	7.7 (1.7-34.1)	
Song et al. 2016 [37]	262	Allo-HSCT	High-risk karyotype (CIBMTR)	Not high-risk karyotype	3.0 (1.5-5.8)	3
Teo et al. 2017 [84]	235	Intensive chemotherapy	Adverse risk cytogenetics (NR)	Not adverse risk cytogenetics	7.2 (2.0-25.5)	3
Wood et al. 2019 [85]	83	Allo-HSCT	Adverse risk cytogenetics (ELN)	Favorable risk cytogenetics	50 (25-1000)	1
Yanada et al. 2018 [86]	7812	Allo-HSCT	Poor risk cytogenetics (NCCN)	Intermediate risk cytogenetics	1.5 (1.4-1.7)	4
Zhou et al. 2020 [87]	226	Intensive chemotherapy	Loss of Y chromosome	Non-loss of Y chromosome	2.2 (1.0-4.9)	2.4
Specific genetic mutations						
Positive risk						
Ahn et al. 2015 [88]	407	Intensive chemotherapy with/without allo-HSCT	*CEBPA* double mutation	*CEBPA* wild-type	0.5 (0.3-0.9)	NR
			NPM1 mutation	*NPM1* wild-type	0.5 (0.3-0.7)	
Ahn et al. 2016 [47]	404	Intensive chemotherapy	*CEBPA* double mutation	*CEBPA* wild-type	0.3 (NR)	3.3
Thol et al. 2018 [89]	96	Allo-HSCT	*DNMT3A* mutation	*DNMT3A* wild-type	0.3 (0.1-0.9)	5
			NPM1 mutation	*NPM1* wild-type	0.2 (0.1-0.8)	
Negative risk						
Ahn et al. 2015 [88]	407	Intensive chemotherapy with/without allo-HSCT	*FLT3*-ITD mutation	*FLT3* wild-type	2.2 (1.6-3.2)	NR
Ahn et al. 2016 [47]	404	Intensive chemotherapy	*FLT3*-ITD mutation	*FLT3* wild-type	2.0 (NR)	3.3
Canaani et al. 2018 [90]	293	Allo-HSCT	*FLT3*-ITD mutation	*FLT3* wild-type	1.3 (0.7-2.7)	2
Deol et al. 2016 [91]	511	Allo-HSCT	*FLT3*-ITD mutation	*FLT3* wild-type	1.6 (1.2-2.2)	3
Getta et al. 2016 [92]	153	Allo-HSCT	*TP53* mutation	*TP53* wild-type	4.0 (1.3-12.6)	0.7
Niavarani et al. 2016 [93]	474	NR-all were enrolled in UK trials	*WT1* mutation	*WT1* wild-type	1.6 (1.0-2.5)	10

Ok et al. 2019 [94]	80	Intensive chemotherapy	Persistent *FLT3*-ITD in CR or CRi	No detectable *FLT3* mutation in CR/CRi	20.2 (4.0-102)	1
			Persistent *IDH1/2* mutation in CR or CRi	No detectable *IDH1/2* mutation in CR/CRi	4.5 (2.2-9.2)	
Song et al. 2016 [37]	171	Allo-HSCT	*FLT3*-ITD mutation	*FLT3* wild-type	3.6 (2.1-6.2)	3
Thol et al. 2018 [89]	96	Allo-HSCT	*FLT3*-ITD mutation	*FLT3* wild-type	3.7 (1.4-10.1)	5
Wakita et al. 2016 [95]	184	NR	*FLT3*-ITD mutation (intermediate cytogenetic risk [NCCN])	*FLT3* wild-type (intermediate cytogenetic risk [NCCN])	2.2 (1.1-4.4)	5
Yoon et al. 2017 [46]	85	Auto-HSCT	*NPM1* mutation, *FLT3*-TKD/ITD, or *KIT* mutation	NPM1, *FLT3*, and *KIT* wild-type	8.0 (2.2-29.5)	3
Zhou et al. 2020 [87]	226	Intensive chemotherapy	*KIT* mutation	*KIT* wild-type	2.0 (1.0-4.2)	2.4
MRD status						
Pre-HSCT						
Bill et al. 2018 [96]	51	Allo-HSCT	MRD+ pre-HSCT (all have *NPM1* mutation)	MRD- pre-HSCT (all have *NPM1* mutation)	21.1 (4.9-91.6)	2
Frairia et al. 2017 [97]	65	Allo-HSCT	MRD+ pre-HSCT	MRD- pre-HSCT	3.4 (1.3-8.7)	2
Oran et al. 2017 [83]	152	Allo-HSCT	MRD+ pre-HSCT	MRD- pre-HSCT	6.4 (1.9-21.4)	1
Shah et al. 2018 [34]	269	Allo-HSCT	Intermediate risk cytogenetics (ELN) and 60+ years and/or MRD+ pre-HSCT	MRD- pre-HSCT	6.9 (2.1-23.0)	1
Shimoni et al. 2018 [98]	1042	Allo-HSCT	MRD+ pre-HSCT	MRD- pre-HSCT	1.8 (NR)	2
Thol et al. 2017 [99]	69	Allo-HSCT	MRD+ pre-HSCT	MRD- pre-HSCT	5.8 (2.2-15.5)	5
Thol et al. 2018 [89]	96	Allo-HSCT	MRD+ pre-HSCT	MRD- pre-HSCT	5.7 (2.3-14)	5
Zhao et al. 2017 [100]	86	Allo-HSCT	MRD+ pre-HSCT	MRD- pre-HSCT	4.7 (1.3-17.3)	4
Post-HSCT						
Duléry et al. 2017 [80]	139	Allo-HSCT	MRD+ post-HSCT	MRD- post-HSCT	15.4 (7.5-31.6)	3
Shah et al. 2018 [34]	269	Allo-HSCT	MRD+ post-HSCT	MRD- post-HSCT	44 (11-174)	1
Shimomura et al. 2017 [36]	88	Allo-HSCT	MRD+ post-HSCT	MRD- post-HSCT	4.9 (1.5-15.7)	3
Thol et al. 2019 [101]	138	Allo-HSCT	MRD+ post-HSCT	MRD- post-HSCT	3.2 (1.7-5.9)	5
Wood et al. 2019 [85]	83	Allo-HSCT	MRD+ post-HSCT	MRD- post-HSCT	4.8 (1.3-18.1)	1
Post-induction						
Ivey et al. 2016 [102]	346	Intensive chemotherapy	MRD+ post-induction (all have *NPM1* mutation)	MRD- post-induction (all have *NPM1* mutation)	5.1 (2.8-9.1)	3
Morita et al. 2018 [64]	131	Intensive chemotherapy	MRD+ post-induction	MRD- post-induction	2.2 (1.2-4.2)	3
Rücker et al. 2019 [103]	92	Intensive chemotherapy	MRD+ post-induction (all are *RUNX1-RUNX1T1*+)	MRD- post-induction (all are *RUNX1-RUNX1T1*+)	2.1 (1.0-4.2)	4
Teo et al. 2017 [84]	235	Intensive chemotherapy	MRD+ post-induction	MRD- post-induction	2.0 (1.0-3.8)	3
Zeijlemaker et al. 2017 [104]	242	Intensive chemotherapy	MRD+ and leukemic stem cell+ post-induction	MRD- and leukemic stem cell- post-induction	5.9 (3.3-10.5)	3
Zhou et al. 2020 [87]	226	Intensive chemotherapy	MRD+ post-induction	MRD- post-induction	6.7 (2.1-20.0)	2.4

Note: All findings presented are based on multivariate analysis, as reported by study authors. Abbreviations: Allo, allogeneic; auto, autologous; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete remission; CRi, complete remission with incomplete blood count recovery; ELN, European LeukemiaNet; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; MRC, Medical Research Council; MRD, measurable/minimal residual disease; NCCN, National Comprehensive Cancer Network; NR, not reported; SWOG, Southwest Oncology Group; TKD, tyrosine kinase domain.

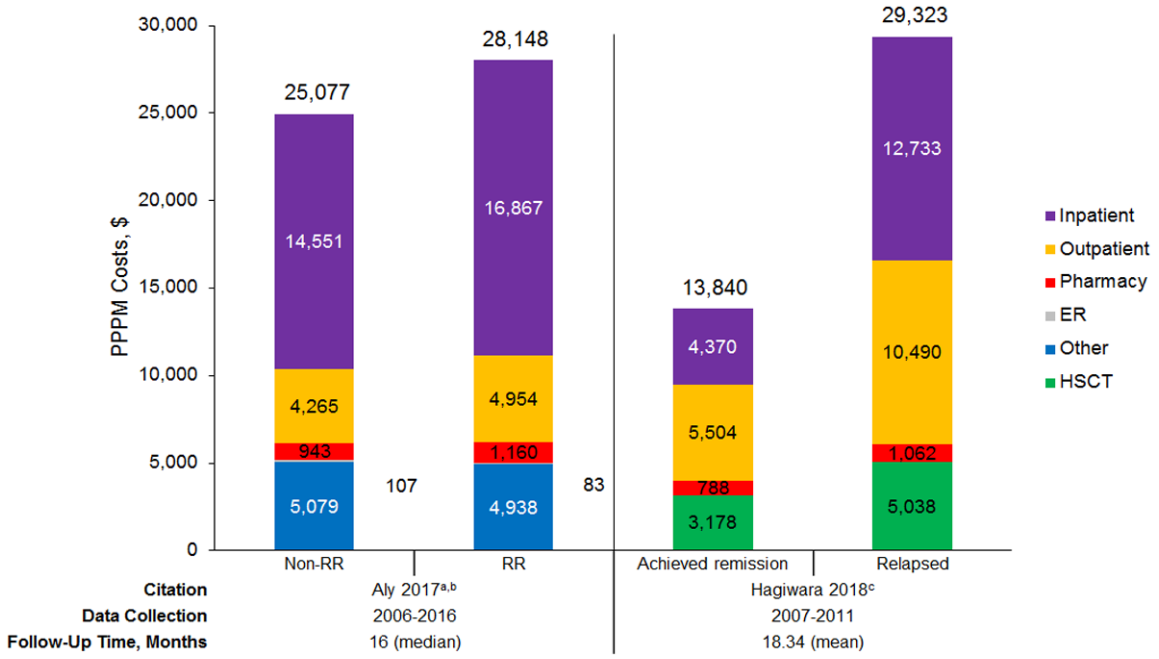

Figure 5. Direct PPPM costs among patients with acute myeloid leukemia. Abbreviations: ER, emergency room; HSCT: hematopoietic stem cell transplantation; PPPM, per-patient-per-month; RR, relapsed or refractory. [a]Total cost was slightly higher than the sum of all cost components, as noted in the study, because costs were not categorized when place of service was unknown. [b]Total costs and all cost categories are significantly different between patients who are non-RR versus RR aside from "other". [c]Significance of differences in total costs and cost categories not assessed. Sources: Aly et al. 2017 [105], Hagiwara et al. 2018 [106].

tient days, or as proportions receiving care in inpatient, outpatient, emergency room (ER), or pharmacy settings [52, 105-108, 111-113]. Across the three studies that reported PPPM HCRU for RR patients, there were 0.224 to 0.520 hospitalizations, 3.79 to 6.50 total inpatient days, and 6.84 to 7.20 outpatient visits (**Table 9**) [106, 112, 113]. In two studies that compared HCRU in RR and non-RR AML patients, those with RR AML required more transfusions [105, 111] and radiology tests, [111] and had greater rates of hospitalization [105, 111], longer inpatient stays [105], more outpatient visits, [105, 111] and more hospice admissions [105]. Five studies reported proportions of RR patients utilizing resources across settings: 36% to 93.9% of patients had an inpatient admission, 43% to 97.6% had an outpatient visit, and 18% to 54.5% had an ER visit (**Table 10**) [52, 107, 108, 111, 112]. Of these five studies, one compared HCRU proportions in newly diagnosed and relapsed patients and found that a higher proportion of relapsed patients had inpatient, outpatient, and ER visits than newly diagnosed patients [111].

Ten observational studies provided evidence on treatment patterns. The evaluation of real-world treatment patterns indicated that intensive chemotherapy was used in 14.8% to 85.4% of patients, and non-intensive chemotherapy (e.g. HMAs) was used in 11.1% to 31% of RR AML patients (**Table 11**) [59, 68, 74, 111-116]. The mean or median patient age was <60 years in seven of the nine studies reporting intensive chemotherapy use. Little information was found describing treatment based on patient age; one study described specific treatments for a cohort with mean age >60 years [116], and one study evaluating elderly patients (mean/median age not reported) mainly focused on treatment setting and did not provide actual treatment details [117]. Five studies describing treatment patterns also described remission (i.e. complete response, reported by three of the five studies) or overall survival (reported by three of the five studies); two studies reported overall survival as mean or median values (**Table 12**) [59, 68, 74, 114, 117]. Based on three studies, 15% to 36% of patients with RR AML achieved remission [59,

Table 8. Direct costs among patients with AML, total follow-up

Study	Data collection	Patient group	N	Mean follow-up, months	Costs, $				
					Total	Inpatient	Outpatient	ER	Pharmacy
Hagiwara et al. 2018 [106][a]	2007-2016	Achieved remission	NR	6.08	84,173	26,581	33,476	NR	4790
		Relapsed	NR	2.39	70,038	30,412	25,055	NR	2537
Irish et al. 2017 [52]	2009-2015	First-line, achieved remission	681	3.1	208,857	182,672	44,247	613	3752
		Relapsed, achieved remission	70	1.4	142,569	109,296	60,530	197	2910
Medeiros et al. 2017 [107]	2008-2016	High-intensity induction chemotherapy	1542	2.1	198,528	178,891	2,843	331	2868
		High-intensity consolidation therapy	591	1.5	73,303	55,303	999	267	2269
		Low-intensity chemotherapy	628	2.0	53,081	17,764	1478	340	2554
		HSCT	1000	6.4	329,620	244,801	6017	1037	11398
		RR	119	7.6	145,634	101,420	3340	682	6108
Pandya et al. 2019 [108]	2007-2016	RR	707	15.0	439,104	308,978	10,926	4301	24,640
		RR with HSCT	465	16.8	524,596	357,812	13,255	5367	30,633
		RR without HSCT	231	11.1	263,310	197,528	6133	2151	12,219

Note: None of the studies provided statistical comparisons of costs between patient groups. Abbreviations: AML, acute myeloid leukemia; ER, emergency room; HSCT, hematopoietic stem cell transplantation; NR, not reported; RR, relapsed or refractory. [a]Hagiwara et al. 2018 [106] also includes costs of HSCT: $19,327 for patients who achieved remission, $12,034 for patients with RR AML. No other studies provided costs for HSCT.

Table 9. Health care resource use by events/days among patients with AML

Study	Data collection years	Patient group	Mean follow-up, months	Mean age, years	Total patients, N	Number of events, mean				Number of days, mean	
						Inpatient admissions	ER visits	Outpatient visits	Pharmacy claims	Total inpatient days	Length of stay per admission
PPPM											
Griffin et al. 2018 [112]	2012-2017	RR	11.1 (median)	57.7[a]	304	0.28	NR	NR	NR	NR	NR
Griffin et al. 2019 [113]	2013-2016	RR	9.0	53.2: *FLT3*^{mut} 56.8: *FLT3*^{wt}	363	0.52	0.54	7.2	NR	6.5	NR
Hagiwara et al. 2018 [106]	2007-2016	Achieved remission	15.73	55.3[b]	2481	0.143	0.067	4.7	3.66	1.43	NR
		Relapsed	10.49	55.3[b]	1460	0.224	0.098	6.84	4.5	3.79	NR
Per patient for total follow-up											
Hagiwara et al. 2018 [106]	2007-2016	Achieved remission	6.08	55.3	NR	0.87	0.41	28.6	22.3	8.7	NR
		Relapsed	2.39	55.3	NR	0.54	0.23	16.3	10.8	9	NR
Irish et al. 2017 [52]	2009-2015	First-line, achieved remission	17.1	51.4	681	2.1	1.1	18.6	NR	37	NR
		Relapsed, achieved remission	11.5	52.2	70	1	0.3	11.2	NR	18.5	NR
Pandya et al. 2019 [108]	2007-2016	All RR	15	52	707	4.5	3.4	76.8	83.1	75	17
		RR with HSCT	16.8	51.2	476	4.9	3.7	89.9	102.9	87	18
		RR without HSCT	11.1	53.6	231	3.6	2.6	49.7	42.8	46	14

Note: None of the studies provided statistical comparisons of resource use between patient groups. Abbreviations: AML, acute myeloid leukemia; ER, emergency room; HSCT, hematopoietic stem cell transplantation; mut, mutated; NR, not reported; PPPM, per-patient-per-month; RR, relapsed or refractory; wt, wild type. [a]Mean age was only provided for the overall population. [b]Mean age was only provided for treated patients.

Table 10. Health care resource use among patients with AML by proportion using resource

Study	Data collection years	Patient group	Mean follow-up, months	Mean age, years	N	Inpatient admissions, %	ER visits, %	Outpatient visits, %	Pharmacy claims, %
Griffin et al. 2018 [112]	2012-2017	RR	11.1 (median)	57.7[a]	304	82	39.6	NR	NR
Irish et al. 2017 [52]	2009-2015	First-line, achieved remission	3.1	51.4	681	100	64.5	99.4	NR
		Relapsed, achieved remission	1.4	52.2	70	60	20	97.1	NR
Kwon et al. 2017 [111]	NR	Newly diagnosed	6 (exact)	62	1270	26	11	24	NR
		Post-remission		NR	2110	14[b]	13	55[b]	NR
		Relapsed		NR	280	36[b]	18[b]	43[b]	NR
Medeiros et al. 2017 [107]	2008-2016	High-intensity induction chemotherapy	2.1	47	1542	100	28.6	96.1	90.1
		High-intensity consolidation therapy	1.5	47	591	98.1	26.1	93.7	92.2
		Low-intensity chemotherapy	2.0	64.9	628	35.8	27.7	97.6	89.5
		HSCT	6.4	51.4	1000	94.9	26.9	99	93.6
		RR	7.6	56.3	119	74.8	38.7	89.9	79
Pandya et al. 2019 [108]	2007-2016	All RR	15.0	52	707	93.9	54.5	97.6	90.1
		RR with HSCT	16.8	51.2	476	96.8	54.4	97.7	89.9
		RR without HSCT	11.1	53.6	231	87.9	54.5	97.4	90.5

Note: None of the studies other than Kwon et al 2017 [111] provided statistical comparisons of health care resource use between patient groups. Abbreviations: AML, acute myeloid leukemia; ER, emergency room; HSCT, hematopoietic stem cell transplantation; NR, not reported; RR, relapsed or refractory. [a]Mean age was only provided for the overall population. [b]Significantly different compared to newly diagnosed patients.

Table 11. Treatment patterns from observational studies

Study	AML population	Treatment prior to RR	Country	Mean age, years	N	Data collection years	Initial treatment for RR, %	Follow-up treatment, %
Bejanyan et al. 2015 [68]	Relapsed	Allo-HSCT	International	32 (median)	1788	1990-2010	Intensive chemotherapy, 37 Second HSCT ± chemotherapy and/or DLI, 21 DLI ± chemotherapy, 11 BSC only, 20	NR
El-Ghammaz & El-Razzaz 2018 [59]	Relapsed	Allo-HSCT	Egypt	42	43	2010-2017	Chemotherapy, 58.1 DLI ± chemotherapy, 30.2 BSC only, 11.6	NR
Griffin et al. 2019 [113]	RR with known *FLT3* mutation status	NR	US	53.2: *FLT3*^{mut} 56.8: *FLT3*^{wt}	363	2013-2016 (patients)	*FLT3*^{mut}/*FLT3*^{wt}: HSCT, 23.6/18.1 High- or standard-dose cytarabine, 15.5/30.7 LDAC, 9.4/15.4 HMA, 9.4/16.5 Midostaurin or sorafenib, 3.3/0.5 BSC only, 39.8/24.7	HSCT: *FLT3*^{mut}, 22.9 *FLT3*^{wt}, 17.5
Griffin et al. 2018 [112]	RR	NR	US	57.7[a]	304	2012-2017	Intensive chemotherapy, 65 Non-intensive chemotherapy, 19.3 HMA, 14.9 Not active treatment, 9.1	Received 2nd-line regimen, 44.8 Received 3rd-line regimen, 11.0 Received HSCT, 10.4
Kwon et al. 2017 [111]	Relapsed	NR	US	NR	3865	NR	Intensive chemotherapy, 56 HMA, 28	HSCT, 45
Medeiros et al. 2019 [115]	RR	NR	US	56.3	32	2015	Intensive chemotherapy (e.g. containing cytarabine, purine analog, or anthracycline), 69 Non-intensive chemotherapy (e.g. decitabine, azacitidine), 31	NR
Sauer et al. 2015 [74]	Relapsed	Allo-HSCT	Germany	52 (median)	108	2000-2013	Intensive chemotherapy, 14.8 Intensive chemotherapy + stem cell boost, 28.7 Palliative chemotherapy, 25.0 BSC only, 10.2	HSCT, 17.6 Chemotherapy + DLI, 2.8 Immunosuppressive tapering + DLI, 0.9
Wattad et al. 2017 [114]	RR	Induction chemotherapy	Germany, Austria	55 (median)[b] 68 (median)[c]	1025	1993-2009	Intensive chemotherapy, 85.4 HiDAC-based, 61.4 Standard 7+3, 6.7 Other intensive chemotherapy, 18.9 Experimental, 3.1 Primary allo-HSCT, 9.9 Non-intensive or palliative chemotherapy, 14.6	NR
Zeidan et al. 2019 [116]	*FLT*^{mut} RR	NR	US	62 (median)	99	2015-2018	*FLT3* inhibitor (e.g. midostaurin, sorafenib) ± intensive or non-intensive chemotherapy, 33.3 Intensive chemotherapy, 34.3 Non-intensive chemotherapy, 11.1 Other, 11.1 BSC only, 10.1	NR

Zhang et al. 2017 [117]	Relapsed	NR	US	NR	1726	2010-2014	Inpatient and outpatient chemotherapy, 59.1 Inpatient chemotherapy, 28.6 Received BMT, 11.3 Outpatient chemotherapy (e.g. HMA), 3.8	Inpatient and outpatient chemotherapy, 41.2 Inpatient chemotherapy, 19.6 Received BMT, 10.3 Outpatient chemotherapy, 9.3

Abbreviations: Allo, allogeneic; AML, acute myeloid leukemia; BMT, bone marrow transplant; BSC, best supportive care; DLI, donor lymphocyte infusion; HiDAC, high-dose cytarabine; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; LDAC, low-dose cytarabine; mut, mutation; NR, not reported; RR, relapsed or refractory; wt, wild-type. [a]Mean age was only provided for the overall population. [b]Median age provided for the intensive treatment arm (n=875). [c]Median age provided for the non-intensive, palliative treatment arm (n=150).

Table 12. Subsequent remission and survival from observational studies describing treatment patterns

Study	AML population	Mean age, years	RR sample size	Data collection years	Patients achieving subsequent remission, %	Cohort survival from RR date	Survival by treatment from RR date
Bejanyan et al. 2015 [68]	Relapsed	32 (median)	1788	1990-2010	15	NR	Survival >1 year post-relapse, % of those treated with following regimens: Chemotherapy alone, 21 Second HSCT ± chemotherapy and/or DLI, 44 DLI ± chemotherapy, 14 BSC only, 8
El-Ghammaz & El-Razzaz 2018 [59]	Relapsed	42	43	2010-2017	25.6	Mean, 5.14 months	NR
Sauer et al. 2015 [74]	Relapsed	52 (median)	108	2000-2013	NR	Median, 4.3 months	Survival >1 year post-relapse, % of those treated with following regimens: Intensive chemotherapy, 34.4 Intensive chemotherapy + stem cell boost, 29.0 Palliative chemotherapy, 3.6 HSCT, 26.3 Chemotherapy + DLI, 0 Immunosuppressive tapering + DLI, 100[a]
Wattad et al. 2017 [114]	RR	55 (median)[b] 64 (median)[c]	1025	1993-2009	36	NR	30-day: HiDAC-based, 96.9 Standard 7+3, 100 Other intensive chemotherapy, 98.8 Experimental, 100 Primary allo-HSCT, 100
Zhang et al. 2017 [117]	Relapsed	NR	1726	2010-2014	NR	30-day, 80.4% 60-day, 66.4%	NR

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; BSC, best supportive care; DLI, donor lymphocyte infusion; HiDAC, high-dose cytarabine; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; NR, not reported; RR, relapsed or refractory. [a]One patient received this treatment and survived at least 1 year after initial relapse. [b]Median age provided for the intensive treatment arm (n=875). [c]Median age provided for the non-intensive treatment arm (n=150).

68, 114]. Based on two studies, mean and median survival from the date of relapse was 5.14 and 4.3 months, respectively [59, 74]. More aggressive treatment regimens tended to have higher survival than less aggressive regimens or no treatment [68, 74].

Humanistic burden: Four observational studies reported HRQoL outcomes in patients with RR AML (**Figure 6A-D**) [118-121]. In a prospective US observational study comparing 39 patients with RR AML with 39 patients with *de novo* AML, those with RR AML at study entry had significantly greater distress and more moderate/severe symptoms compared with those with *de novo* AML 7-12 months after initial diagnosis (**Figure 6A**; all P<0.001) [118]. In a study from Northern China, anxiety and depression were significantly more prevalent and Hospital Anxiety and Depression Scale (HADS) subset scores were significantly worse in 180 patients with RR AML than in 180 patients with *de novo* AML or 180 healthy controls (**Figure 6B**; all P<0.05) [121]. In a US study, Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) physical well-being scores were significantly worse in 19 patients with RR AML than 56 patients with non-RR AML (P=0.005); scores were comparable between the two cohorts for other FACT-Leu subscales, EuroQol 5 dimensions (EQ-5D) visual analog scale (EQ-5D VAS), and EQ-5D-3L (EQ-5D 3 levels) (**Figure 6D**) [120]. Another US study comparing 50 patients with RR AML with 340 patients with *de novo* AML found that more patients with RR AML experienced fatigue (32% vs 23%) and more required caregiver support (48% vs 27%) than newly diagnosed patients; however, statistical significance was not assessed (**Figure 6C**) [119].

Utility values were derived by mapping from EQ-5D questionnaire and European Organisation for Research and Treatment of Cancer, Quality of Life, Core Questionnaire (EORTC QLQ-C30) or measured through preference elicitation using a discrete choice experiment and both VAS and time trade-off (TTO) techniques in seven studies [119, 122-127]. Among all AML populations, RR patients consistently demonstrated numerically lower utility values compared with other AML health states, with the utility value of the RR state ranging from -0.08 (worse than death) to 0.78 across identified studies (**Figure 7**) [119, 122-127]. Only two studies assessed, but did not identify, significant differences between patients with RR AML and other AML patients [119, 125]; both studies used the generic EQ-5D (rather than a disease-specific tool) to derive utility values.

Clinical efficacy SLR: RR AML and de novo AML ineligible for HSCT

The clinical efficacy literature search yielded 2545 records: 2471 were excluded based on title and abstract, and 24 were excluded after review of the full text, resulting in 50 records describing 50 clinical trials included in the SLR (**Figure 2**).

Of the 50 trials, 38 trials were single-arm studies, five trials assessed the same drug in different trial arms (i.e. RR AML or *de novo* AML ineligible for intensive chemotherapy), and seven trials randomized patients to different interventions, for a total of 66 distinct trial arms. These 66 trial arms included 33 arms for patients with RR AML, 22 arms for patients with *de novo* AML ineligible for intensive chemotherapy, and 11 arms including both populations. Across all 66 trial arms, the median trial arm size across all trials was 40 patients per arm. The trials included phase I/II (8 trials), phase II (39 trials), phase II/III (1 trial), phase III (1 trial), or phase not reported (1 trial). Of the 50 trials, 40 did not require a specific mutation for inclusion [128-162] (see also multicenter, open-label, uncontrolled, pilot, phase II study of oral ITF2357 in subjects with AML refractory/resistant and/or not suitable for any alternative therapy at https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-005321-63/results; temozolomide plus vorinostat in relapse/refractory AML at https://clinicaltrials.gov/ct2/show/NCT01550224; azacitidine and lenalidomide for relapsed and refractory patients with AML at https://clinicaltrials.gov/ct2/show/NCT01743859; cediranib maleate in treating patients with relapsed, refractory, or untreated AML or high-risk myelodysplastic syndromes at https://clinicaltrials.gov/ct2/show/NCT00475150; and phase I/II safety and efficacy of PLX3397 in adults with relapsed or refractory AML at https://clinicaltrials.gov/ct2/show/NCT01349049), while 10 required patients to have a mutation in one of the following genes: *FLT3* [163-167] (see also open-label study to evalu-

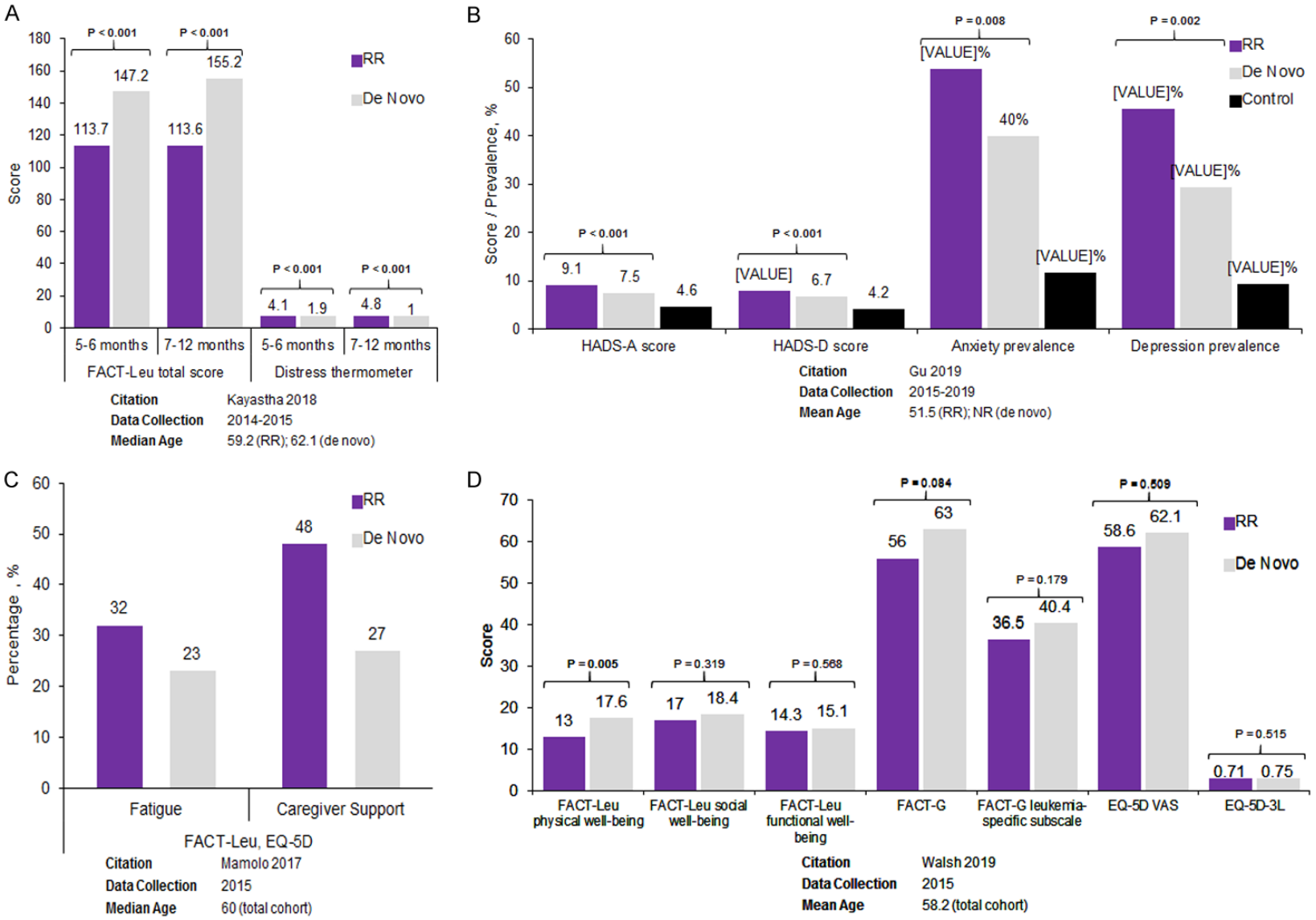

Figure 6. HRQoL among RR acute myeloid leukemia patients in 4 observational studies: (A) Kayastha et al. 2018 [118], (B) Gu et al. 2019 [121], (C) Mamolo et al. 2017 [119], (D) Walsh et al. 2019 [120]. Note: statistical significance not assessed for Mamolo et al. 2017 [119]. Abbreviations: EQ-5D, EuroQol 5 dimensions; EQ-5D-3L, EuroQol 5 dimensions, 3 levels; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Leu, Functional Assessment of Cancer Therapy-Leukemia; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; HRQoL, health-related quality of life; NR, not reported; RR, relapsed or refractory; VAS, visual analog scale.

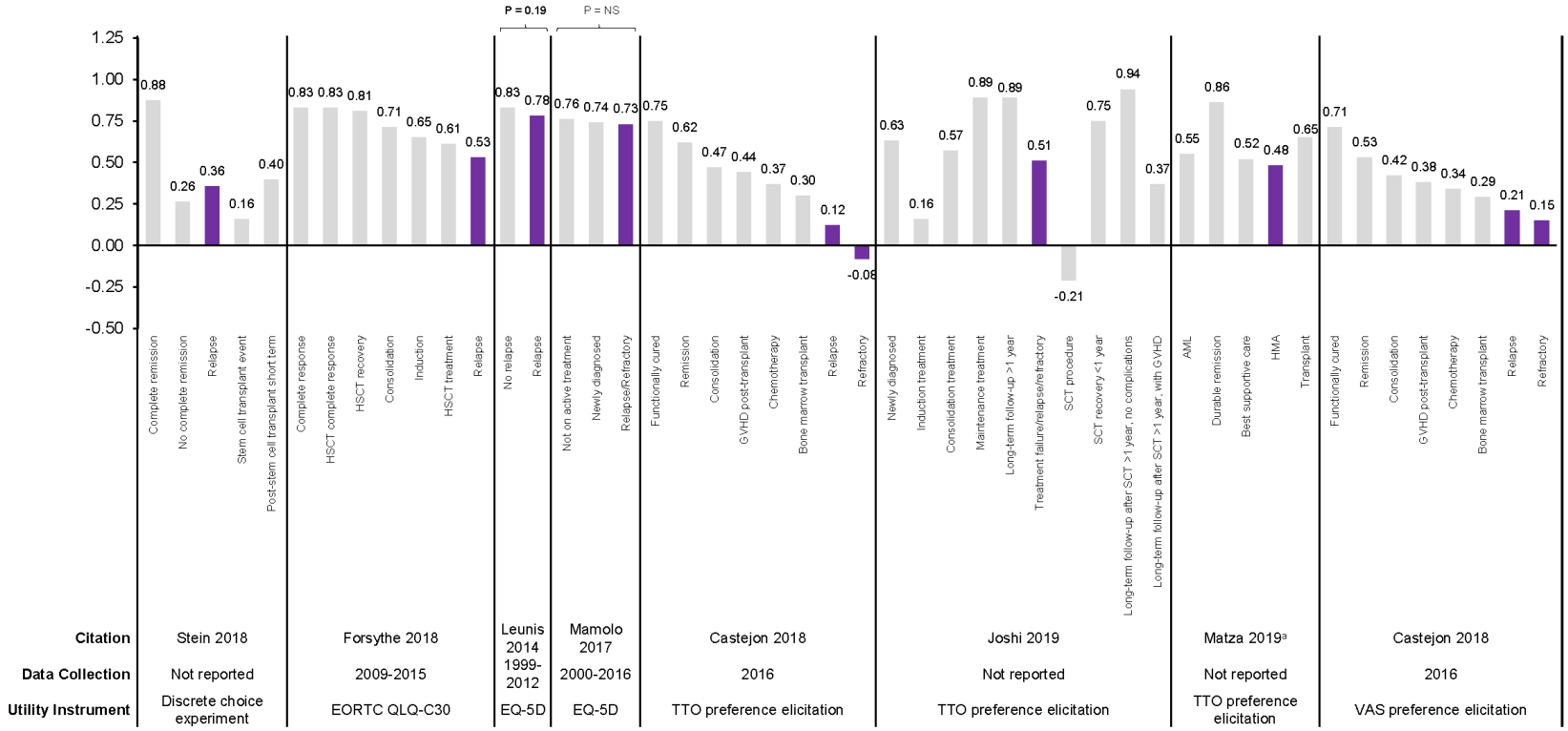

Figure 7. Health utility values in patients with AML in observational studies. Statistical significance assessed only for Leunis et al. 2014 [125] and Mamolo et al. 2017 [119]. Abbreviations: AML, acute myeloid leukemia; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer, Quality of Life, Core Questionnaire; EQ-5D, EuroQol 5 dimensions; GVHD, graft-vs-host disease; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; NS, not significant; TTO, time trade-off; VAS, visual analog scale. [a]Study authors state that HMA refers to situation where chemotherapy is no longer indicated. Sources: Castejon et al. 2018 [122], Forsythe et al. 2018 [123], Joshi et al. 2019 [124], Leunis et al. 2014 [125], Mamolo et al. 2017 [119], Matza et al. 2018 [127], Stein et al. 2018 [126].

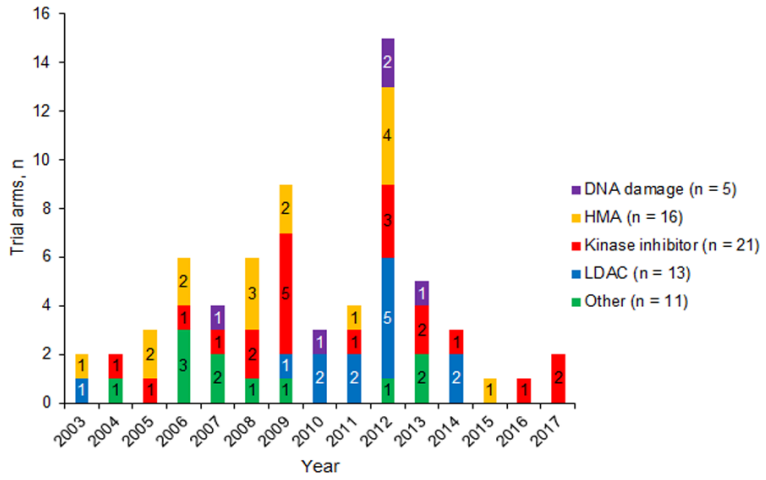

Figure 8. Non-intensive treatments from trials over time. Abbreviations: HMA, hypomethylating agent; LDAC, low-dose cytarabine.

ate safety and efficacy of two doses of quizartinib in patients with relapsed or refractory AML at https://clinicaltrials.gov/ct2/show/NCT01565668), *NPM1* (see randomized phase III study of LDAC and etoposide with or without all-trans retinoic acid in older patients not eligible for intensive chemotherapy with AML and *NPM1* mutation at https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-023409-37/results), *BCR-ABL* and *cKIT* [168], *IDH2* [169], and *RAS* [170].

Treatment types included DNA-damaging agents (5 arms), HMAs (16 arms), kinase inhibitors (21 arms), LDAC (13 arms), or other (11 arms; **Figure 8**).

Remission and survival data were compiled for each trial arm based on the treatment category and the year in which trial data collection began. Remission rates rarely exceeded 50% (**Figure 9A**). Based on qualitative review only, CR or CRi rates appeared to increase around 2009, likely due to the introduction of improved treatment options for patients with specific mutations. Only 6 of the 66 trial arms resulted in a CR/CRi rate greater than 50% [134, 150, 163, 166, 167]; treatments in these arms included guadecitabine [134], quizartinib [163, 166], sorafenib + omacetaxine mepesuccinate (homoharringtonine) [167], and an LDAC regimen [150]. The median CR/CRi rate (range) was 16.1% (4.3% to 48.0%) for DNA-damaging agents (reported in 5 arms), 19.6% (0% to 53.4%) for HMAs (reported in 14 arms), 30.0% (0% to 100%) for kinase inhibitors (reported in 21 arms), 31.0% (0% to 50.0%) for LDAC (reported in 13 arms), and 0% (0% to 26.1%) for other treatments (reported in 11 arms). The median CR/CRi rate across all trial arms was 18.3%; when stratified by the trial population, CR/CRi rate was 21.4% for patients with RR AML (reported in 31 arms), 26.1% for patients ineligible for intensive chemotherapy (reported in 22 arms), and 0% (i.e. 0 patients experiencing remission) for trial arms including both patient subpopulations (reported in 11 arms).

The mOS in these trials was typically less than 10 months and remained stable over time, regardless of treatment category (**Figure 9B**). mOS exceeded 10 months in only seven arms from three trials [150, 163, 164]; treatments in these arms included quizartinib [163, 164], sorafenib + omacetaxine mepesuccinate [167], and an LDAC regimen [150]. The mOS (range) was 8.2 months (7.3 to 9.0 months) for DNA-damaging agents (reported in 2 arms), 5.5 months (2.9 to 7.7 months) for HMAs (reported in 9 arms), 7.1 months (1.8 to 25.4 months) for kinase inhibitors (reported in 14 arms), 5.9 months (3.1 to 12.4 months) for LDAC (reported in 12 arms), and 6.4 months (2.0 to 9.3 months) for other treatments (reported in 7 arms). The mOS across all trial arms was 6.2 months; when stratified by the trial population, mOS was 6.1 months for patients with RR AML (reported in 18 arms), 5.8 months for patients ineligible for intensive chemotherapy (reported in 18 arms), and 6.4 months for trial arms including both patients (reported in 8 arms).

In most studies, the relationship between CR/CRi and survival did not appear to be strong, with the exception of 2 trials assessing quizartinib (**Figure 10**) [163, 164]. Among trials reporting both CR/CRi and survival, 8 trial arms with 0% CR/CRi had mOS ranging from 2.0 to 10.9 months. In 21 trial arms with CR/CRi rates of 20% to 50%, mOS ranged from 2.9 to 25.0 months. The type of AML (RR or *de novo* ineligible for intensive chemotherapy) did not appear to influence the relationship between CR/CRi and mOS.

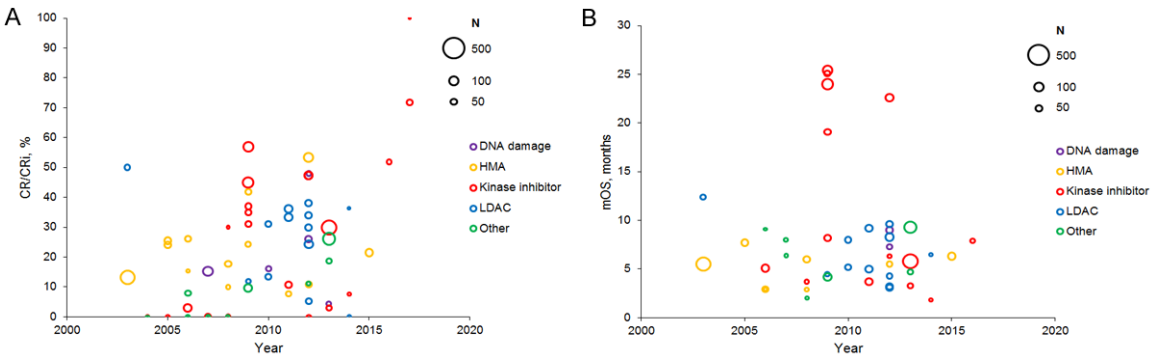

Figure 9. (A) Remission and (B) survival over time from trials of non-intensive treatments. Bubble size indicates sample size. Abbreviations: CR/CRi, complete remission or complete remission with incomplete count recovery; HMA, hypomethylating agent; LDAC, low-dose cytarabine; mOS, median overall survival.

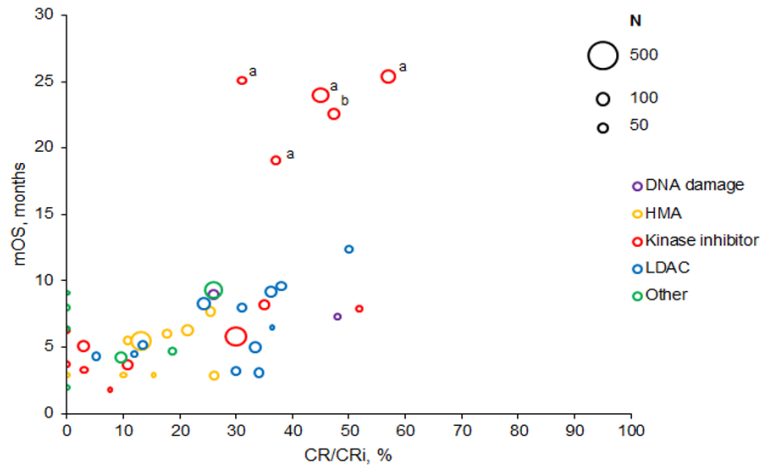

Figure 10. Remission versus survival from trials of non-intensive treatments. Bubble size indicates sample size. Abbreviations: CR/CRi, complete remission or complete remission with incomplete count recovery; HMA, hypomethylating agent; LDAC, low-dose cytarabine; mOS, median overall survival. [a]Markers indicate the 4 arms of Cortes et al. 2018 [163]. [b]Marker indicates the 1 arm of Cortes et al. 2018 [164].

Discussion

Our review of published data found that approximately one-third to one-half of patients with AML relapsed, depending on prior treatment with allo-HSCT, auto-HSCT, or induction chemotherapy. This finding is consistent with results from large studies assessing relapse rates following transplant versus chemotherapy [171]. A variety of factors, including cytogenetics, specific gene mutations, and MRD status, significantly increased the risk of relapse. The direct costs of treating RR AML were substantial, and patients with RR AML required more transfusions, outpatient visits, and hospitalizations than non-RR AML patients [105, 111]. Intensive chemotherapy was used mainly in younger cohorts of patients with RR AML; a significant proportion of patients were ineligible for intensive therapy due to older age, poor-risk cytogenetics, performance status, and/or comorbidities [68, 74, 114].

Over the last decade, research on the pathogenesis of AML and the effects of somatic mutations on response to chemotherapy have pushed the field toward precision medicine [172]. However, our review of clinical trials found that CR/CRi rates were typically less than 40% and mOS has remained less than 10 months in most cases, despite treatment advances in recent years. The assessment of HRQoL has become increasingly important in oncology, helping to identify and inform supportive therapy needs during treatment and beyond, providing insights on patient perceptions of disease progress, and guiding discussions and decision-making among clinicians, patients, and caregivers [173]. While therapies that lead to small improvements in quality of life may not be considered efficacious from a clinical, regulatory, or payer perspective, the desire to retain a normal life, prolong independence, and spend time with family and friends are important considerations for many patients

[118, 119]. There is a growing interest in measuring HRQoL and incorporating HRQoL metrics into clinical trials [119, 122, 123, 125]. In our review, patients with RR AML reported worse HRQoL, greater distress, more moderate/severe symptoms, more fatigue, and more caregiver support than newly diagnosed AML patients [118, 119]. Additionally, patients with RR AML typically had the lowest health state utility values among all AML populations [119, 122, 123, 125]. We note, however, that the humanistic burden studies in this review were limited in number and included relatively small numbers of patients. Barriers to the limited HRQoL data available among AML patients may include lower survey completion rates, possibly due to patient fatigue and questionnaire length [174]. Based on comparisons of qualitative interviews and results from validated instruments, the humanistic burden of AML may be under-valued [173], as evidenced by concerns about limited treatment options, treatment side effects, and the effect of the disease and treatment on daily life [175]. Larger and more robust HRQoL studies focusing specifically on patients with RR AML or those ineligible for intensive chemotherapy are needed, as well as cross-sectional patient and/or physician surveys to understand patients' unmet needs and treatment preferences.

To our knowledge, this is the first systematic review describing disease burden specifically among patients with RR AML. A systematic review published in 2017 described HRQoL for patients with AML [9], but included only one study specifically in relapsed AML [125]. The review presented here also builds upon other comprehensive reviews describing treatment outcomes among patients with RR AML [176-178] by including single-arm trials and focusing on non-intensive chemotherapy options. A review published in 2016 described remission and survival over time from randomized, controlled trials of RR AML treatments published up to 2015 and found no significant improvement in these variables over time [176]; however, that study did not differentiate between intensive versus non-intensive treatments, and some trials published since that time have reported improvements in efficacy. A systematic review published in 2018 focusing primarily on conventional (intensive) regimens also described 16 observational studies and trials using non-intensive treatment approaches, but most of the trials identified in that review were not included here due to publication prior to 2008 or observational design [177]. Another systematic review and meta-analysis published in 2019 described patients ineligible for intensive chemotherapy, but focused on azacitidine, decitabine, and LDAC arms only [178].

The present review faced several limitations. No information was available on the real-world incidence of refractory disease, proportion of patients eligible for second or later lines of therapy, the proportion eligible for transplant after relapse, or the time to relapse following auto-HSCT. Molecular risk factors for relapse were heterogeneously reported, and the estimate of true effect for each variable is difficult to determine from this qualitative review. Additionally, no evidence was found for direct non-medical or indirect/informal costs for RR AML, and some of the evidence describing economic burden came from brief conference abstract reports. There was no evidence on the impact of specific treatment on sequelae, HRQoL, or daily life (either qualitatively or in terms of indirect or non-medical economic costs). Real-world evidence for RR AML treatment patterns was also limited. No studies evaluated clinical predictors for treatment selection, treatment refusal, or criteria for switching from active treatment to palliative care. There was only one study outside of the US or EU describing HRQoL [121], and direct costs or HCRU in non-US regions were also limited. Further research is needed to better characterize the full extent of the burden of RR AML and identify more effective non-intensive treatment options for these patients.

RR AML is associated with significant epidemiological, humanistic, and economic burden. Despite some important treatment advances, efficacy outcomes have largely remained stable over the last 2 decades in patients with RR AML and patients with *de novo* AML who are ineligible for intensive chemotherapy, highlighting the need for more effective non-intensive treatment options.

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Disclosure of conflicts of interest

Esther Oliva has received honoraria from AbbVie, Alexion, Amgen, Apellis, Celgene, and Novartis, and has served on the speakers' bureau for Celgene and Novartis. Sarah Ronnebaum, Omer Zaidi, and Dipen Patel are employees of OPEN Health, which received funding by Celgene Corporation to conduct the review. Salem Abi Nehme and Clara Chen are employees and stockholders of Bristol Myers Squibb. Salem Abi Nehme was an employee of Celgene Corporation at the time the research was initiated. Antonio Almeida has received honoraria from Bristol Myers Squibb, and has served as a speaker and consultant for AbbVie and Novartis.

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