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Survival Following Relapse in Children with Acute Myeloid Leukemia: A Report from AML-BFM and COG

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Citation: Rasche, M.; Zimmermann, M.; Steidel, E.; Alonzo, T.; Aplenc, R.; Bourquin, J.-P.; Boztug, H.; Cooper, T.; Gamis, A.S.; Gerbing, R.B.; et al. Survival Following Relapse in Children with Acute Myeloid Leukemia: A Report from AML-BFM and COG. *Cancers* **2021**, *13*, 2336. <https://doi.org/10.3390/cancers13102336>

Academic Editor: Joseph D. Khoury

Received: 17 April 2021

Accepted: 7 May 2021

Published: 12 May 2021

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Simple Summary: Acute myeloid leukemia in children remains a difficult disease to cure despite intensive therapies that push the limits of tolerability. Though the intent of initial therapy should be the prevention of relapse, about 30% of all patients experience a relapse. Hence, relapse therapy remains critically important for survival. This retrospective analysis of two large international study groups (COG and BFM) was undertaken to describe the current survival, response rates and clinical features that predict outcomes. We demonstrate that children with relapsed AML may be cured with cytotoxic therapy followed by HSCT. High-risk features at initial diagnosis and early relapse remain prognostic for post-relapse survival. Current response criteria are not aligned with the standards of care for children, nor are the count recovery thresholds meaningful for prognosis in children with relapsed AML. Our data provide a new baseline for future treatment planning and will allow an updated stratification in upcoming studies.

Abstract: Post-relapse therapy remains critical for survival in children with acute myeloid leukemia (AML). We evaluated survival, response and prognostic variables following relapse in independent

cooperative group studies conducted by COG and the population-based AML-BFM study group. BFM included 197 patients who relapsed after closure of the last I-BFM relapse trial until 2017, while COG included 852 patients who relapsed on the last Phase 3 trials (AAML0531, AAML1031). Overall survival at 5 years (OS) was $42 \pm 4\%$ (BFM) and $35 \pm 2\%$ (COG). Initial high-risk features (BFM $32 \pm 6\%$, COG $26 \pm 4\%$) and short time to relapse (BFM $29 \pm 4\%$, COG $25 \pm 2\%$) predicted diminished survival. In the BFM dataset, there was no difference in OS for patients who had a complete remission with full hematopoietic recovery (CR) following post-relapse re-induction compared to those with partial neutrophil and platelet recovery (CRp and CRi) only ($52 \pm 7\%$ vs. $63 \pm 10\%$, $p = 0.39$). Among 90 patients alive at last follow-up, 87 had received a post-relapse hematopoietic stem cell transplant (HSCT). OS for patients with post-relapse HSCT was $54 \pm 4\%$. In conclusion, initial high-risk features and early relapse remain prognostic. Response assessment with full hematopoietic recovery following initial relapse therapy does not predict survival. These data indicate the need for post-relapse risk stratification in future studies of relapse therapies.

Keywords: acute myeloid leukemia; relapse; childhood acute myeloid leukemia; pediatric; salvage therapy

1. Introduction

The prognosis of children with acute myeloid leukemia (AML) has improved in recent decades, with current overall survival rates of approximately 70% [1–6]. Most international study groups currently utilize treatment regimens that include four to five courses of intensive myelosuppressive chemotherapy or intensive chemotherapy followed by hematopoietic stem cell transplantation (HSCT) for high-risk (HR) patients [7,8]. Despite intensive regimens that push the limits of tolerance, relapse rates as high as 30% have improved little over the past twenty years [7]. Post-relapse therapy remains critical for survival in childhood AML [5,9–11].

There has been considerable improvement in overall probability of survival (pOS) for patients in first relapse since 1987, improving from a 5-year-pOS of 21–23% in the 1980s and 1990s [11–13] to 36–39% in patients' relapse prior to 2014 [9,14–16]. Studies consistently demonstrate that duration of first remission (CR1), age at relapse (less than ten years), favorable cytogenetics such as core binding factor (CBF) AML and good treatment response after re-induction therapy predict a more favorable outcome [9–14,17–21].

In this retrospective analysis of children with AML in first relapse, we report post-relapse response, survival estimates and prognostic variables from the BFM registry and recent COG Phase III trials. These data represent the largest available relapse AML datasets analyzed for post-relapse survival.

2. Materials and Methods

2.1. Patients

Datasets included patients treated in the United States, Canada, Australia, New Zealand, Germany, Austria, Czech Republic and Switzerland.

BFM relapse cohort. The AML-BFM registry includes patients diagnosed with de novo AML between 2004 and 2017, who have been enrolled in the multicenter population-based AML-BFM study group trials and registries (AML-BFM study 2004—[ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT00111345, AML-BFM registry 2012 and AML-BFM study 2012—EudraCT 2013-000018-39). Figure S1 provides a consort diagram accounting for all BFM patients since 2004.

Included are children with documented first relapse between April 2009 and December 2017 ($n = 197$). The primary analysis is limited to those patients who experienced a relapse after closure of the last I-BFM Relapsed trial Acute Myeloid Leukemia 2001/01. However, the previously described 513 patients enrolled before 04/2009 on Relapsed Acute Myeloid Leukemia 2001/01 [9] are included for comparison.

COG relapse cohort. All patients enrolled on COG AAML0531 (NCT00372593 [22]) and AAML1031 (NCT01371981 [6]) who relapsed are included ($n = 852$: AAML0531 $n = 358$, and AAML1031 $n = 494$). Eligibility, therapy and results for these trials have been previously reported [6,22]. Only patients with DS-AML enrolled on AAML0531 are excluded from this post-relapse analysis. Residual disease (RD) was evaluated by central flow cytometry as previously described [23,24] at the end of one cycle of initial induction therapy in 765 patients (90%). Disease characteristics are well-characterized at diagnosis, but post-relapse data collection in the COG cohort is limited to survival.

National ethics committees and institutional review boards approved all studies and patients or guardians provided written informed consent. The retrospective analysis and all included studies were performed in accordance with the Declaration of Helsinki.

2.2. Definitions and Cohorts

Five-year estimate of the probability of post-relapse overall survival (pOS) was defined as time from date of first relapse to date of last follow-up or death from any cause. The 5-year estimate of event-free survival (pEFS) was defined as time from diagnosis at first relapse to the next event (second relapse, death of any cause, failure to achieve second remission or secondary malignancy) or date of last follow-up. Failure to achieve second remission was considered an event on day 0. Additional definitions are listed in Table S1.

A detailed response evaluation is included for a subset of uniformly treated BFM patients. The remission status data after first re-induction were derived from a bone marrow aspiration performed prior to a second re-induction. Second re-induction commenced at the discretion of the treating investigator and did not require hematopoietic recovery [25,26].

2.3. Statistical Analyses

Statistical analyses were performed with SAS (SAS Institute version 9.4, Cary, NC, USA). Median follow-up after diagnosis of first relapse was 4.2 years (0.3–10.3 years) in the AML-BFM cohort and 4.6 years (0–11.1 years) for the COG cohort. The Kaplan–Meier method was applied to estimate probabilities of survival. EFS and OS were compared with the log-rank test. Cumulative incidence functions of early death or relapse were constructed according to Kalbfleisch and Prentice. The Cox proportional hazards model was used for multivariate analysis of outcomes. We selected risk factors that have been significant in univariate analysis in one or both study groups for the multivariate analysis: risk group at initial diagnosis (inv(16)(p13.1q22), t(8;21)(q22;q22.1), high-risk), nonresponse at initial disease, time to relapse, date of relapse diagnosis and age at relapse. Proportions were compared between groups using the Chi-square or Fisher's exact test. p values < 0.05 were considered significant. Living patients were censored at date of last follow-up. Data were frozen at 03/27/2020 (BFM) and 03/31/2020 (COG).

3. Results

3.1. Patient Characteristics and Previous Treatment

BFM cohort—Using a combined cytomolecular and response-guided risk stratification at initial disease (Table S1), 68 patients (38%) were classified as high-risk, 81 (45%) were intermediate and 31 (17%) standard risk (unclassified, $n = 17$). Forty-six percent of patients experienced a first relapse within one year of diagnosis. Fourteen percent of the patients ($n = 28$) had an HSCT prior to relapse. More details are shown in Table S2.

COG cohort—All relapsed patients were reclassified using the AAML1031 risk stratification (Table S1). Across the two studies, 608 patients (72%) were classified as low-risk at initial diagnosis and 237 (28%) high-risk (no data, $n = 7$, 1%). Among the high-risk patients, 194 (82%) had residual disease detected by flow cytometry at the end of one cycle of initial induction chemotherapy. Early relapse (within 1 year of diagnosis) occurred in 500 patients (59%), while 352 patients relapsed more than 1 year from diagnosis (41%). One hundred seventeen patients (14%) received an HSCT prior to relapse, 670 (77%) had no prior HSCT and 65 (8%) have insufficient data. Additional patient characteristics are shown in Table S3.

3.2. Post-Relapse Therapy

BFM cohort—After closure of the last relapse trial in 2009 [9], BFM guidelines recommended fludarabine, cytarabine, liposomal daunorubicin (DNX-FLA) followed by FLA and HSCT. Subsequently, 81% ($n = 156$) of all patients received the treatment with DNX-FLA(G) with or without second FLA. Fourteen percent of the patients had an alternate second cycle, primarily due to nonresponse in relapse and often including Gemtuzumab Ozogamicin (GO) or Clofarabine. Four percent of the patients received palliative care only (Table 1). Most patients who received an intensive re-induction treatment proceeded to transplant (81% of all patients and 87% of patients receiving DNX-FLA). Ten percent ($n = 15$) of the transplanted patients had a prior HSCT (Table 1). Among the 90 patients alive at last follow-up, 87 had a post-relapse HSCT, two are unknown and one patient alive did not receive an HSCT. Of note, the rate of HSCT following relapse increased over time. Sixty-nine percent of the patients included in the first time period of the previous relapse trial AML 2001/01 were able to proceed to HSCT, while 82% percent of the patients had an HSCT in the recent time interval ($p(\text{chi}) = 0.0286$; Table S4).

Table 1. Treatment and Response (BFM cohort).

First Relapse Treatment of Pediatric AML		Patients (%)
		$n = 197$
Chemotherapy	Re-Induction with DNX-FLA(G) +/- FLA (G)	156 (81%)
	Re-Induction with FLA(G) +/- FLA (G)	5 (3%)
	Re-Induction with Ida-FLA +/- FLA	3 (2%)
	Re-Induction with FLA + others +/- FLA	3 (2%)
	Re-Induction with a Clofarabine-containing regimen	8 (4%)
	Others (e.g., Gemtuzumab Ozogamicin, Sorafenib, intrathecal treatment only)	10 (5%)
	Palliative care	8 (4%)
	Unknown	4
HSCT	No HSCT	37 (19%)
	HSCT	157 (81%)
	• First HSCT	142 (90%)
	• Second HSCT	15 (10%)
Unknown	3	
First relapse response and HSCT after DNX-FLA +/- FLA		$n = 156$
HSCT	No HSCT	20 (13%)
	HSCT	134 (87%)
	• First HSCT	123 (92%)
	• Second HSCT	11 (8%)
	Unknown	2
Response after 2 induction cycles	CR	69 (45%)
	CRp	20 (13%)
	Cri	6 (4%)
	Aplasia	20 (13%)
	NR	32 (21%)
	Early death before CR evaluation	7 (5%)
	Unknown	2
	Early Treatment Response	Death before evaluable BM
BM after first induction not available or not applicable		12 (8%)
Evaluable BM after first induction		140 (90%)
• >20% leukemic blasts in the BM after first induction		18 (13%)
• ≤20% leukemic blasts in the BM after first induction		122 (87%)

Table legend: For categories including patients with unknown status, percentages are calculated without “unknown”. Abbreviations: CR, complete remission; CRp, complete remission with partial regeneration; Cri, complete remission with incomplete recovery; DNX, liposomal daunorubicin; FLA(G), fludarabine, cytarabine with or without granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; NR, nonresponse. See Table S1 for definitions.

3.3. Survival and Prognostic Factors at First Relapse

Overall survival. The 5-year pOS for patients in the AML-BFM studies is $42 \pm 4\%$ (Table S5). For patients relapsing between 08/2013 and 12/2017, 5-year pOS was $49 \pm 6\%$ (Figure 1A). Time to death was comparable between both intervals (08/2013 until 12/2017 vs. 04/2009 until 07/2013: $p = 0.2263$). The 90th percentile of time to death from 04/2009 to 07/2013 was 2.14 years. Sixty-four percent of surviving patients who relapsed between 08/2013 and 12/2017 had more than 2.14 years of follow-up. Median follow-up of patients from 04/2009 to 07/2013 was 4.7 years and 2.8 years from 08/2013 to 12/2017.

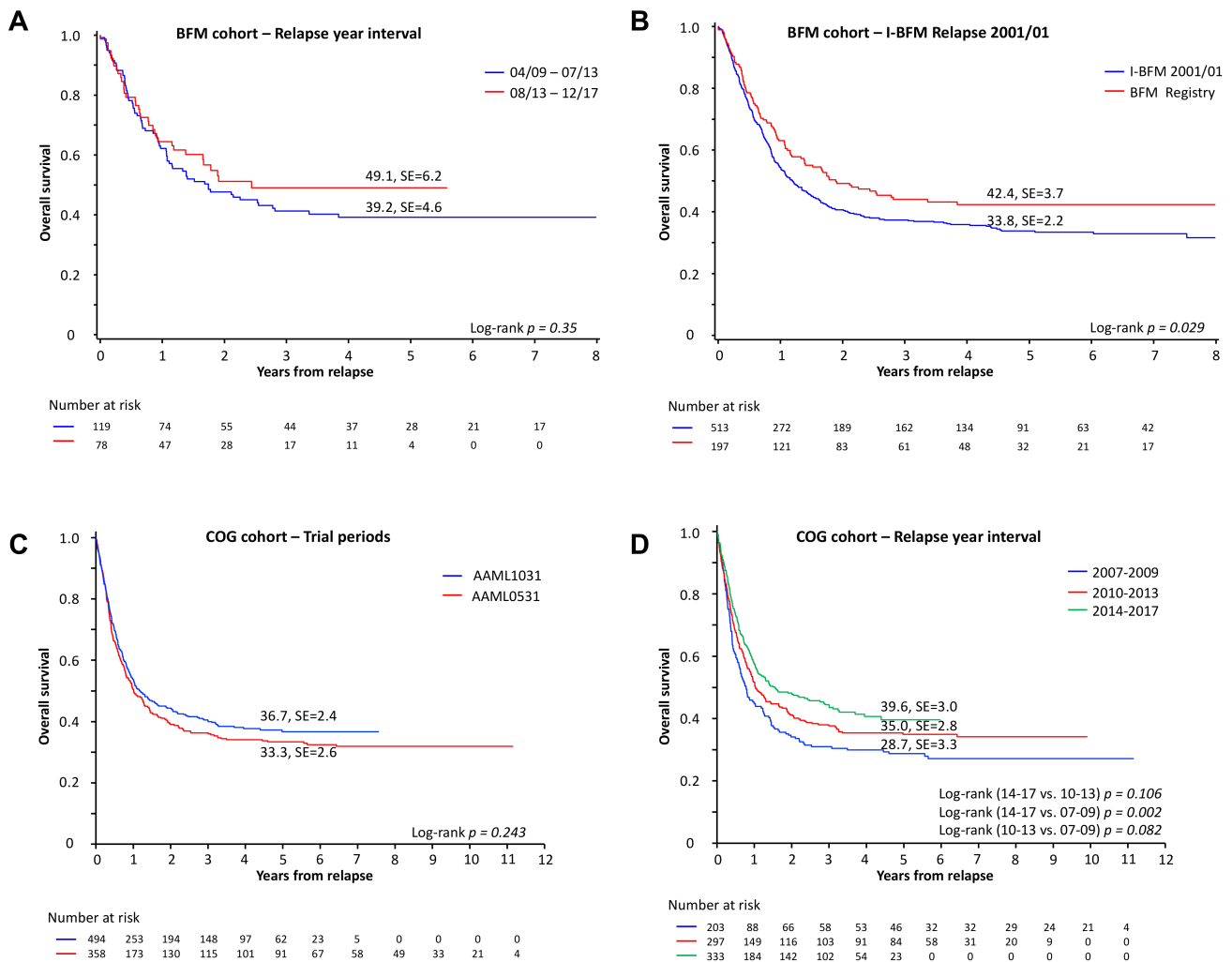


Figure 1. Overall survival at first relapse. (A) Five-year overall survival in patients with pediatric AML with diagnosed first relapse from 04/2009 until 07/2013 vs. 08/2013–12/2017. (B) Five-year overall survival in patients with pediatric AML with first relapse enrolled in the BFM registry compared to patients with first relapse enrolled in the previous I-BFM Relapse 2001/01 trial. (C) Five-year overall survival following relapse of patients enrolled on COG AAML0531 and COG AAML1031. (D) Five-year overall survival for first relapse patients in the COG cohort by year. Group 2018 until 2019 is excluded.

With a median follow-up of 4.9 years, the pOS of all patients enrolled on the Acute Myeloid Leukemia 2001/01 trial [9] is $34 \pm 2\%$, compared to a pOS of $42 \pm 4\%$ (median follow-up 4.3 years) in the current BFM dataset (Figure 1B, $p = 0.029$). There is a trend towards improved survival over time (Figure S2A). However, when comparing only patients who received DNX-FLA or DNX-FLA and HSCT, survival was comparable between

the two treatment periods (Figure S2B, pOS $44 \pm 4\%$ vs. $37 \pm 4\%$, $p = 0.16$) and over time (Figure S2C).

The survival of the 157 patients who received an HSCT following relapse was $52 \pm 4\%$ (Figure S3A). Only one long-term surviving patient is alive without a post-relapse HSCT. This patient received Sorafenib and donor lymphocyte infusions (DLIs).

Among 157 patients who underwent HSCT following first relapse, 15 patients had a prior HSCT in first remission (93% for HR disease at initial diagnosis). The pOS was $28 \pm 13\%$ ($n = 15$) vs. $55 \pm 4\%$ in patients with first HSCT ($n = 142$; p(KM test) = 0.06; Figure S3B). When limiting the same analysis to just the HR patients, the pOS was $31 \pm 14\%$ for patients receiving a second transplant at relapse ($n = 14$) compared to a pOS $47 \pm 9\%$ for patients receiving their first transplant following relapse ($n = 34$, p(KM test) = 0.75; Figure S3C).

The 5-year pOS for the entire COG cohort is $35 \pm 2\%$. For patients relapsing after treatment on AAML0531, the 5-year pOS is $33 \pm 3\%$ and for AAML1031 the 5-year pOS is $37\% \pm 2\%$ (Figure 1C). For patients relapsing between 2013 and 2017, 5-year pOS was $40\% \pm 3\%$ (Figure 1D). The 90th percentile of time to death from 04/2009 to 07/2013 was 2.0 years. Eighty-five percent of surviving patients who relapsed between 08/2013 and 12/2017 had more than 2.0 years of follow-up. Median follow-up of patients from 04/2009 to 07/2013 was 6.3 years and 3.6 years from 08/2013 to 12/2017.

Time to relapse. Survival of BFM patients experiencing early relapse within one year from initial diagnosis was significantly reduced (pOS $29 \pm 5\%$, $n = 91$ vs. $55 \pm 5\%$, $n = 106$; $p < 0.0001$; Figure 2A). Patients with a time to relapse that was less than 6 months showed a comparable outcome to patients relapsing within 6–12 months ($n = 19$, pOS $37 \pm 11\%$ vs. $n = 72$, pOS $27 \pm 5\%$; $p = 0.55$; data not shown). Although the treatment year was not significant in multivariable analysis, there is a trend towards improvement in survival that is limited to patients with a late relapse (Figure S4A,B). In the COG cohort, the 5-year pOS was $25 \pm 2\%$ for patients relapsing within one year from initial diagnosis ($n = 352$) and $51 \pm 3\%$ for patients relapsing later ($n = 500$, $p < 0.001$; Figure 2B).

Initial risk classification. The pOS was $31 \pm 6\%$ in patients initially characterized as high-risk in the BFM cohort (Table S1) when compared to non-HR patients ($50 \pm 5\%$, p(LR) = 0.058) (Figure 2C). When COG AAML0531 patients are reclassified using the AAML1031 risk assignment definitions (Table S1), the 5-year pOS for initial HR patients was $26 \pm 4\%$ compared to $37 \pm 3\%$ for LR patients ($p = 0.07$; Figure 2D). Patients enrolled on AAML1031 and classified as HR had a 5-year pOS of $15 \pm 4\%$ compared to $44 \pm 3\%$ for patients initially classified as LR ($p < 0.001$; Figure 3D).

Response to initial induction. Response to induction therapy was evaluated differently for COG and BFM data sets; however, poor response in both groups predicts poor survival. Nonresponse to therapy for initial disease ($\geq 10\%$ blasts after first or $\geq 5\%$ after second induction) in the BFM cohort translated into a dismal prognosis after relapse compared to those who responded well at initial diagnosis (pOS $0 \pm 0\%$, $n = 12$ vs. pOS $45 \pm 4\%$, $n = 185$; $p = 0.031$; Figure 2E and Table S5). In the COG cohort, 765 of the 852 (90%) were evaluated for residual disease (RD) by central flow cytometry at the end of one cycle of initial induction therapy. In total, 222 (29%) had RD. The 5-year pOS following relapse for patients who were RD-positive at the end of initial induction was $24 \pm 3\%$ ($n = 222$) and $41 \pm 2\%$ for those who were RD-negative ($n = 543$, $p < 0.001$) (Figure 2F).

Univariable and multivariable risk analysis. Univariable and multivariable Cox analyses from relapse are shown (Table 2).

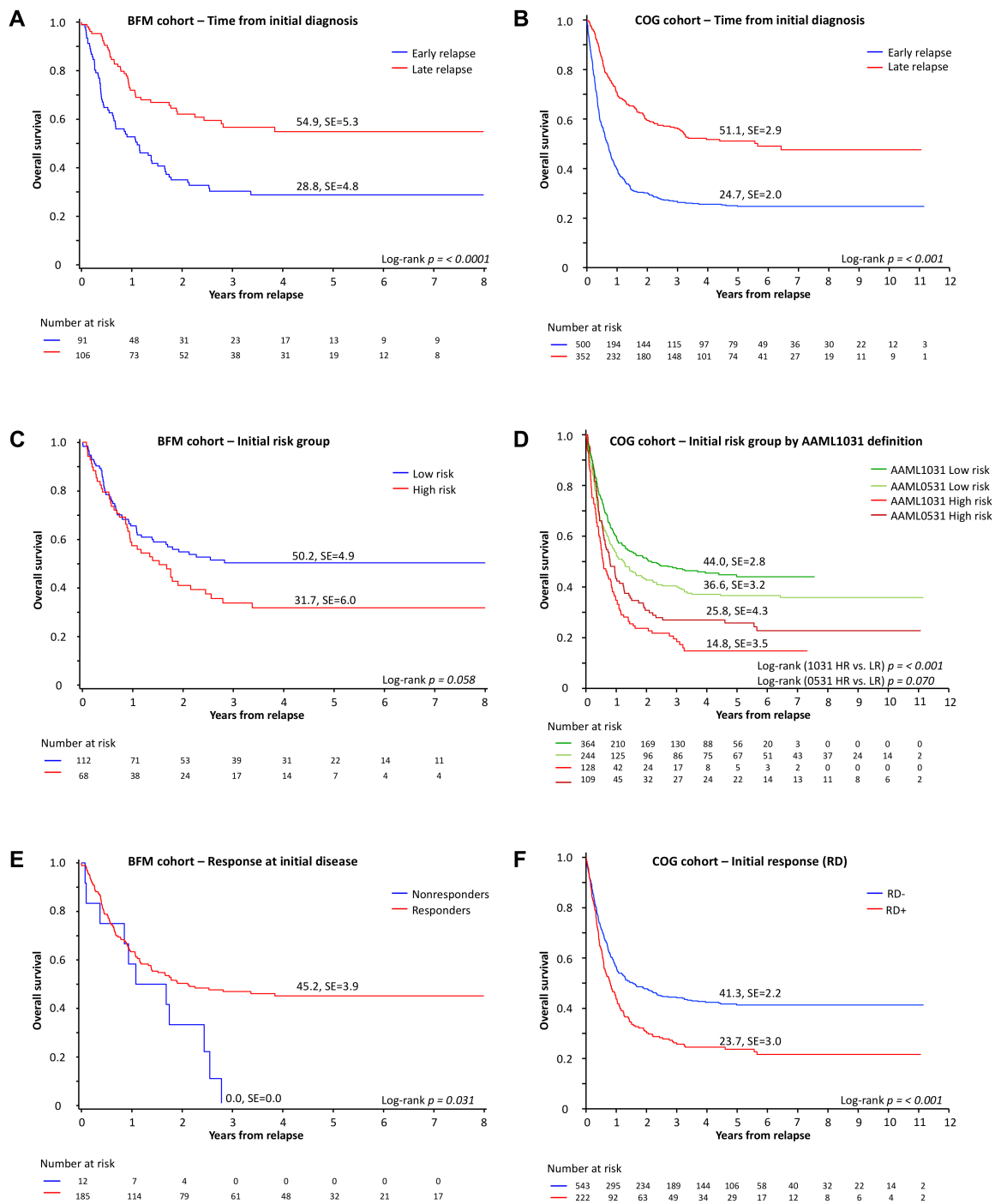


Figure 2. Prognostic factors for post-relapse survival. (A) Five-year overall survival of patients with early or late relapse defined as relapse within or after one year of initial diagnosis (BFM). (B) Five-year overall survival of patients with early or late relapse (COG). (C) Five-year overall survival in patients with first relapse based on the genetic risk profile of the initial diagnosis (BFM). (D) Five-year overall survival from relapse for AAML1031 and AAML0531 patients based on a retrospective classification by AAML1031 risk group definition (Table S1). (E) Five-year overall survival of patients based on the initial response to induction chemotherapy of the initial disease (BFM). Abbreviations: HR, high-risk. (F) Five-year overall survival according to residual disease detection at the end of one cycle of induction following initial diagnosis and treatment (COG).

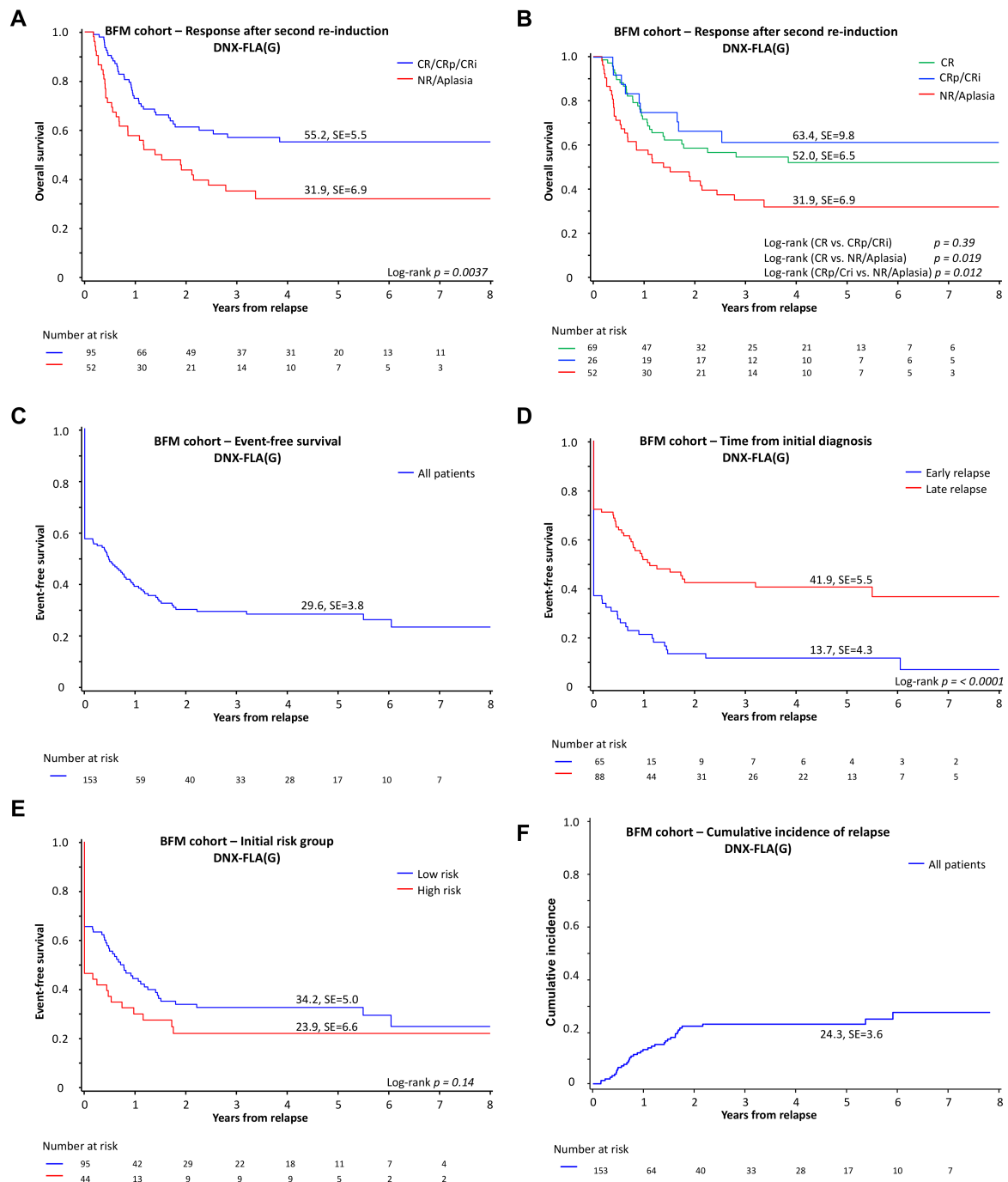


Figure 3. Response and EFS at first relapse. (A) Five-year overall survival in patients with pediatric AML with first relapse based on the response to DNX-FLA(G) +/- FLA(G) comparing complete remission with complete (CR) and partial regeneration (CRp) and CRi vs. nonresponse and aplasia. (B) Five-year overall survival in patients with pediatric AML with first relapse based on the detailed response to DNX-FLA(G) +/- FLA(G). (C) Five-year event-free survival in all patients receiving DNX-FLA(G) +/- FLA(G) after first relapse. (D) Five-year event-free survival of patients with early or late relapse defined as relapse within or after one year of initial diagnosis. (E) Five-year event-free survival in patients with first relapse based on the risk profile of the initial diagnosis. (F) Five-year cumulative incidence of a second relapse in all patients receiving DNX-FLA(G) +/- FLA(G). The competing event is death. Abbreviations: HR, high-risk. DNX-FLA(G), liposomal daunorubicin, fludarabine, cytarabine with or without granulocyte-colony-stimulating factor. CR, complete remission; CRp, complete remission with partial regeneration; CRi, complete remission with incomplete recovery. See Table S1 for definitions.

Table 2. Analysis of risk factors.

Criteria	n (all pts.)	BFM pOS			p (Chi)	n (all pts.)	COG pOS		
		HR	95% CI				HR	95% CI	p (Chi)
Univariable analysis									
Time from initial diagnosis <1 year	91 (197)	2.24	1.52–3.30	<0.001	500 (852)	2.31	1.92–2.79	<0.001	
Age at relapse <2 years	36 (197)	1.00	0.53–1.87	0.998	116 (852)	1.41	1.09–1.83	0.009	
Age at relapse 2–9 years	67 (197)	0.88	0.57–1.36	0.558	316 (852)	0.93	0.76–1.14	0.497	
Age at relapse 10–13 years	39 (197)	0.68	0.36–1.27	0.228	124 (852)	0.93	0.71–1.22	0.601	
Age at relapse >13 years	55 (197)	1			296 (852)	1			
inv(16)(p13.1q22)	7 (190)	0.83	0.26–2.62	0.751	72 (841)	0.32	0.21–0.49	<0.001	
t(8;21)(q22;q22.1)	20 (192)	0.62	0.30–1.27	0.188	71 (841)	0.66	0.47–0.93	0.018	
Nonresponse at initial disease	12 (197)	2.04	1.39–2.99	<0.001	–	–	–	–	
RD at EOI of initial disease	–	–	–	–	222 (765)	1.55	1.28–1.88	<0.001	
High-risk group *	68 (180)	1.47	0.98–2.19	0.060	237 (845)	1.57	1.33–1.85	<0.001	
Poor response (> 20% leukemic blasts) after first re-induction	18 (140)	1.74	0.95–3.18	0.071	–	–	–	–	
Relapse year interval 2007–2009	–	–	–	–	203 (852)	1.43	1.15–1.78	0.001	
Relapse year interval 2010–2013 †	119 (197)	1.21	0.81–1.81	0.350	297 (852)	1.18	0.96–1.45	0.112	
Relapse year interval 2014–2017 ‡	78 (197)	1			333 (852)	1			
Relapse year interval 2018–2019	–	–	–	–	19 (852)	1.26	0.64–2.45	0.507	
Multivariable analysis									
Time from initial diagnosis < 1 year	81 (177)	1.95	1.23–3.09	0.005	493 (839)	2.17	1.78–2.65	<0.001	
Age at relapse < 2 years	17 (177)	0.52	0.24–1.12	0.095	114 (839)	0.96	0.73–1.27	0.768	
Age at relapse 2–9 years	68 (177)	0.76	0.47–1.22	0.256	311 (839)	0.79	0.64–0.98	0.029	
Age at relapse 10–13 years	28 (177)	0.67	0.35–1.28	0.223	122 (839)	0.78	0.59–1.02	0.073	
Age at relapse >13 years	64 (177)	1			292 (839)	1			
inv(16)(p13.1q22)	7 (177)	1.26	0.37–4.24	0.713	72 (839)	0.36	0.23–0.56	<0.001	
t(8;21)(q22;q22.1)	20 (177)	0.96	0.44–2.11	0.922	71 (839)	0.73	0.51–1.03	0.075	
Nonresponse at initial disease	11 (177)	1.80	1.18–2.76	0.006	–	–	–	–	
High-risk group *	66 (177)	1.51	0.97–2.33	0.065	237 (839)	1.50	1.23–1.81	<0.001	
Relapse year interval 2007–2009	–	–	–	–	200 (839)	1.22	0.97–1.52	0.090	
Relapse year interval 2010–2013 †	103 (177)	1.13	0.73–1.74	0.586	294 (839)	1.10	0.89–1.35	0.376	
Relapse year interval 2014–2017 ‡	74 (177)	1			326 (839)	1			
Relapse year interval 2018–2019	–	–	–	–	19 (839)	1.42	0.72–2.80	0.311	

Table legend: Abbreviations: Chi, Chi-square test; CI, confidence interval; EOI, end of induction; HR, hazard ratio; pts, patients; RD, residual disease detected by central flow cytometry. * Retrospective risk classification according to Table S1 including genetic and response criteria for the BFM cohort and genetic and RD criteria for the COG cohort (AAML1031 definition). † This interval includes patients from 04/2009 until 07/2013 for the BFM cohort. ‡ This interval includes patients from 08/2013 until 2017 for the BFM cohort.

By multivariable analysis in the BFM cohort, initial nonresponse at diagnosis (pOS: hazard ratio 1.80, 95% CI 1.18–2.75, $p(\text{chi}) = 0.007$) and an early relapse (pOS: hazard ratio 1.94, 95% CI 1.22–3.07, $p(\text{chi}) = 0.005$) independently predict outcome following relapse for all patients. The hazard ratio for high-risk criteria in the BFM cohort was 1.51 (95% CI 0.97 to 2.33, $p = 0.065$). In the COG cohort, multivariable analysis identified early relapse (hazard ratio 2.17, 95% CI 1.78 to 2.65) and high-risk group assignment (hazard ratio 1.50, 95% CI 1.23 to 1.81) to be associated with inferior pOS.

Response and event-free survival after first relapse (BFM cohort).

Within the BFM dataset, age, gender, white blood cell count or initial de novo treatment protocols were similar between the DNX-FLA group ($n = 156$). The remaining group had a higher proportion of patients with high-risk disease, nonresponse to initial therapy and early relapse (Table S2), several of whom received only palliative therapy at relapse.

Among the 156 patients who received DNX-FLA, 153 were evaluable for response (3 were excluded for insufficient data). After up to 2 induction courses, 69 patients (57%) achieved a CR, 20 a CRp (13%), 6 (4%) a CRi and 52 (34%) no response or aplasia. Six patients (4%) had an early death before response assessment. The pOS was superior ($55 \pm 6\%$, vs. $32 \pm 7\%$; $p = 0.0037$; Figure 3A) for patients with a CR/CRp/CRi compared to patients with no response. Patients with a CRp or CRi (pOS $63 \pm 10\%$) had a comparable overall survival to those with a CR (pOS $52 \pm 7\%$) ($p = 0.39$; Figure 3B). The detailed analysis shows that patients with $\geq 5\%$ leukemic blasts after second re-induction had the lowest survival with a pOS of $27 \pm 9\%$ ($n = 32$, Figure S5). The 5-year pEFS for this cohort of 153 patients was $30 \pm 4\%$ and was comparable in patients with CR and CRp (Figure 3C, CR: pEFS $50 \pm 6\%$, $n = 69$, vs. CRp: pEFS $50 \pm 11\%$, $n = 20$). The cumulative incidence of death before day 56 of relapse therapy was $4 \pm 2\%$ (Table S2). Of note, short time to relapse was associated with a reduced 5-year pEFS, while initial risk stratification did not reach significance (Figure 3D,E). The cumulative incidence of relapse in all patients (also including patients with initial nonresponse) was $24 \pm 4\%$ (Figure 3F).

4. Discussion

Survival data from pediatric patients treated within the AML-BFM protocols between 2004 and 2017 and COG Phase 3 trials between 2006 and 2018 were analyzed retrospectively. The 5-year pOS for 197 BFM relapse patients was $42 \pm 4\%$ and the 852 COG patients $35 \pm 2\%$. Among the 156 BFM patients who received DNX-FLA following relapse, the 5-year pOS was 44%. When compared to an analysis of patients treated on the AML 2001/01 trial (5-year-pOS of 34%) [9], there is a trend towards improved survival over time, as well as increasing rates of post-relapse HSCT. This increase of patients proceeding to HSCT may account for improvements in survival. Since re-induction therapy has not improved, it is most likely that more children are receiving HSCT at relapse because of improved supportive care and donor availability.

Limitations within this retrospective review include the non-compulsory treatment schedule in the BFM dataset and the missing post-relapse treatment and response data in the COG dataset. Nonetheless, the results of our large retrospective analysis have important implications for future treatment planning. Previously published prognostic factors following a first relapse include time to relapse, treatment response at relapse, initial cytogenetics and HSCT in CR1 [9–14,17–20]. In the current study, multivariable analysis identified relapse within a year of diagnosis in both datasets and initial high-risk disease classification in the COG datasets are predictive of poor overall survival. Importantly, high-risk assignment in the COG cohort includes patients with detectable RD by flow cytometry at the end of initial induction therapy.

In the BFM registry, 156 patients (80%) received DNX-FLA at the discretion of the treating investigator. This homogeneously treated population permitted a retrospective analysis of response. Nonresponse rates after relapse re-induction therapy (21%) were higher at relapse than nonresponse rates reported in de novo AML studies (range of 3–18%) [1–6,27,28]. The outcome of children with no response after relapse ($\geq 5\%$ leukemic

blasts after second cycle of re-induction) was poor but significant (5-year pOS of 27%), suggesting that HSCT has a role post-relapse even in the absence of a complete remission. Sixty-one percent of patients achieved a CR, CRp or CRi after up to two cycles or re-induction chemotherapy with DNX-FLA +/- FLA. Traditionally, the International Working Group (IWG) criteria for response require an absolute neutrophil count of $1 \times 10^9/L$ and platelets of $100 \times 10^9/L$ for a CR. These criteria imply that the absence of count recovery is prognostic. While retrospective studies in adult patients with de novo AML have indicated that outcomes are superior for patients with response and full hematologic recovery compared to those with Cri/CRp [29,30], such a claim has never been validated in children with AML. Within the BFM cohort, absence of full hematopoietic recovery following standard relapse re-induction therapy does not predict survival in children at relapse (Figure 3B). This is comparable to what is observed in a recent study with adult patients following a first relapse or refractory disease. Overall survival was similar in patients who achieved CR with full hematologic recovery vs. those with incomplete hematologic recovery [31].

The Cheson criteria, introduced in 1990 to assess response in adult de novo AML, should be reconsidered as the standard for response evaluation for children with AML [25,26,30], and perhaps adults with AML as well (as reviewed in Bloomfield et al. [32]). In the AML-BFM and COG studies, it is common to continue intensification of treatment without waiting for full hematopoietic recovery [6,8,22]. Our data again confirm that clinicians prioritize maintaining therapy intensification rather than waiting for a hematopoietic regeneration. Continuation of treatment without count recovery has produced favorable outcomes in North American and European trials for children with newly diagnosed AML [1,33]. The IWG/Cheson criteria are likely to underestimate response in children as they are not aligned with the standards of care for children, nor are the count recovery thresholds to achieve a CR meaningful in children with relapsed AML. It will be important in future studies of novel relapse therapies for children that the defined response criteria reflect standard treatment strategies specifically used for children.

5. Conclusions

The findings of our large retrospective analysis have important implications for future trials. Within this international cohort we confirmed that initial risk stratification and time to relapse are prognostic for post-relapse survival. We also declare, for the first time in children, that lack of a full hematopoietic regeneration to the thresholds required by the IWG response criteria is neither necessary for, nor predictive of, survival at first relapse in children. AML in children remains a difficult disease to cure despite intensive therapies that push the limits of tolerability. Though the intent of any initial therapy should be the prevention of relapse, nearly half of all relapse patients will still survive. Refinements in post-relapse care continue to show benefit in overall survival across cooperative groups. As we continue to evaluate innovative therapies to improve survival without adding cumulative short- and long-term toxicities, it is important to reevaluate poor risk features that predict survival at relapse and appropriate definitions for response in children.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/cancers13102336/s1>, Data sharing statements; Table S1: Definitions; Table S2: Baseline characteristics BFM cohort; Table S3: Baseline characteristics COG cohort; Table S4: HSCT; Table S5: Additional outcome results BFM cohort; Figure S1: BFM CONSORT Diagram; Figure S2: I-BFM 2001/01 vs. BFM Registry; Figure S3: HSCT; Figure S4: Time from initial diagnosis; Figure S5: Response.

Author Contributions: Conceptualization, M.R., E.A.K. and D.R.; formal analysis, M.Z., T.A. and R.B.G.; investigation, M.R., M.Z., T.A., R.B.G., E.A.K. and D.R.; project administration, M.R.; resources, M.R., E.S., R.A., J.-P.B., H.B., T.C., A.S.G., I.J., J.-H.K., T.L., N.M., N.v.N., N.N., L.S., J.S., K.W., C.W., U.C., M.D. and G.K.; supervision, M.R., E.A.K. and D.R.; visualization, M.R., M.Z., E.S., T.A. and R.B.G.; writing—original draft, M.R., E.S., E.A.K. and D.R.; writing—review and editing, M.R., M.Z., E.S., T.A., R.A., J.-P.B., H.B., T.C., A.S.G., R.B.G., I.J., J.-H.K., T.L., N.M., N.v.N., N.N., L.S., J.S., K.W., C.W., U.C., M.D., G.K., E.A.K. and D.R. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the German Cancer Aid 50-2728, 110244, 70112486 (BFM) and NCTN Operations Center Grant U10CA180886; NCTN Statistics & Data Center Grant U10CA180899; Chair’s Grant U10CA098543 Statistics & Data Center Grant U10CA098413 (2003–2014) (COG). J.-H.K. is supported by the European Research Council under the European Union’s Horizon 2020 research and innovation program (grant agreement 714226) and is a recipient of the St. Baldrick’s Robert J. Arceci Innovation Award. M.R. is supported by the Josepha und Charlotte von Siebold Program.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and the retrospective analysis using the data of the patients treated in AML-BFM 2004 and 2012 studies and registry 2012 was performed under the ethical approval of the corresponding Institutional Review Boards of the Ethics Committee of Medical Association Westphalen-Lippe and Medical Faculty of WWU Münster (AML-BFM study 2004: protocol code 3VCreutzig1, 05.06.2003) and the Ethics Committee of Hannover Medical School (AML-BFM registry 2012: protocol code 1381-2012, 13.03.2012; AML-BFM study 2012: 6741M, 20.11.2014). AAML0531 and AAML1031 were conducted by the Children’s Oncology Group. Each study was approved by participating COG member sites and the Pediatric Central Institutional Review Board at the National Cancer Institute.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: A detailed data sharing statement is provided in Supplementary Materials.

Acknowledgments: The authors would like to thank all patients for participation and data managers and treating physicians in the participating hospitals and offices for their efforts in this study. This work was supported by the German Cancer Aid 50-2728, 110244, 70112486 (BFM) and NCTN Operations Center Grant U10CA180886; NCTN Statistics & Data Center Grant U10CA180899; Chair’s Grant U10CA098543 Statistics & Data Center Grant U10CA098413 (2003–2014) (COG). J.-H.K. is supported by the European Research Council under the European Union’s Horizon 2020 research and innovation program (grant agreement 714226) and is a recipient of the St. Baldrick’s Robert J. Arceci Innovation Award. M.R. is supported by the Josepha und Charlotte von Siebold Program.

Conflicts of Interest: D.R. has advisory roles for Celgene Corporation, Novartis, Bluebird Bio, Janssen, and receives research funding from CLS Behring and Roche. J.-H.K. has advisory roles for Bluebird Bio, Roche and Jazz Pharmaceuticals. J.-P.B. received travel support from Servier. All other authors have nothing to declare. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Abrahamsson, J.; Forestier, E.; Heldrup, J.; Jahnukainen, K.; Jonsson, O.G.; Lausen, B.; Palle, J.; Zeller, B.; Hasle, H. Response-guided induction therapy in pediatric acute myeloid leukemia with excellent remission rate. *J. Clin. Oncol.* **2011**, *29*, 310–315. [[CrossRef](#)] [[PubMed](#)]
2. Gibson, B.E.; Wheatley, K.; Hann, I.M.; Stevens, R.F.; Webb, D.; Hills, R.K.; De Graaf, S.S.; Harrison, C.J. Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. *Leukemia* **2005**, *19*, 2130–2138. [[CrossRef](#)] [[PubMed](#)]
3. Pession, A.; Masetti, R.; Rizzari, C.; Putti, M.C.; Casale, F.; Fagioli, F.; Luciani, M.; Lo Nigro, L.; Menna, G.; Micalizzi, C.; et al. Results of the AIEOP AML 2002/01 multicenter prospective trial for the treatment of children with acute myeloid leukemia. *Blood* **2013**, *122*, 170–178. [[CrossRef](#)] [[PubMed](#)]
4. Rubnitz, J.E.; Inaba, H.; Dahl, G.; Ribeiro, R.C.; Bowman, W.P.; Taub, J.; Pounds, S.; Razzouk, B.I.; Lacayo, N.J.; Cao, X.; et al. Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: Results of the AML02 multicentre trial. *Lancet Oncol.* **2010**, *11*, 543–552. [[CrossRef](#)]
5. Rasche, M.; Zimmermann, M.; Borschel, L.; Bourquin, J.P.; Dworzak, M.; Klingebiel, T.; Lehrnbecher, T.; Creutzig, U.; Klusmann, J.H.; Reinhardt, D. Successes and challenges in the treatment of pediatric acute myeloid leukemia: A retrospective analysis of the AML-BFM trials from 1987 to 2012. *Leukemia* **2018**, *32*, 2167–2177. [[CrossRef](#)]

6. Aplenc, R.; Meshinchi, S.; Sung, L.; Alonzo, T.; Choi, J.; Fisher, B.; Gerbing, R.; Hirsch, B.; Horton, T.; Khawash, S.; et al. Bortezomib with standard chemotherapy for children with acute myeloid leukemia does not improve treatment outcomes: A report from the Children's Oncology Group. *Haematologica* **2020**. [[CrossRef](#)]
7. Zwaan, C.M.; Kolb, E.A.; Reinhardt, D.; Abrahamsson, J.; Adachi, S.; Aplenc, R.; De Bont, E.S.; De Moerloose, B.; Dworzak, M.; Gibson, B.E.; et al. Collaborative Efforts Driving Progress in Pediatric Acute Myeloid Leukemia. *J. Clin. Oncol.* **2015**, *33*, 2949–2962. [[CrossRef](#)]
8. Creutzig, U.; van den Heuvel-Eibrink, M.M.; Gibson, B.; Dworzak, M.N.; Adachi, S.; de Bont, E.; Harbott, J.; Hasle, H.; Johnston, D.; Kinoshita, A.; et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: Recommendations from an international expert panel. *Blood* **2012**, *120*, 3187–3205. [[CrossRef](#)]
9. Kaspers, G.J.; Zimmermann, M.; Reinhardt, D.; Gibson, B.E.; Tamminga, R.Y.; Aleinikova, O.; Armendariz, H.; Dworzak, M.; Ha, S.Y.; Hasle, H.; et al. Improved outcome in pediatric relapsed acute myeloid leukemia: Results of a randomized trial on liposomal daunorubicin by the International BFM Study Group. *J. Clin. Oncol.* **2013**, *31*, 599–607. [[CrossRef](#)]
10. Sander, A.; Zimmermann, M.; Dworzak, M.; Fleischhack, G.; von Neuhoff, C.; Reinhardt, D.; Kaspers, G.J.; Creutzig, U. Consequent and intensified relapse therapy improved survival in pediatric AML: Results of relapse treatment in 379 patients of three consecutive AML-BFM trials. *Leukemia* **2010**, *24*, 1422–1428. [[CrossRef](#)]
11. Rubnitz, J.E.; Razzouk, B.I.; Lensing, S.; Pounds, S.; Pui, C.H.; Ribeiro, R.C. Prognostic factors and outcome of recurrence in childhood acute myeloid leukemia. *Cancer* **2007**, *109*, 157–163. [[CrossRef](#)]
12. Stahnke, K.; Boos, J.; Bender-Gotze, C.; Ritter, J.; Zimmermann, M.; Creutzig, U. Duration of first remission predicts remission rates and long-term survival in children with relapsed acute myelogenous leukemia. *Leukemia* **1998**, *12*, 1534–1538. [[CrossRef](#)]
13. Webb, D.K.; Wheatley, K.; Harrison, G.; Stevens, R.F.; Hann, I.M. Outcome for children with relapsed acute myeloid leukaemia following initial therapy in the Medical Research Council (MRC) AML 10 trial. MRC Childhood Leukaemia Working Party. *Leukemia* **1999**, *13*, 25–31. [[CrossRef](#)] [[PubMed](#)]
14. Nakayama, H.; Tabuchi, K.; Tawa, A.; Tsukimoto, I.; Tsuchida, M.; Morimoto, A.; Yabe, H.; Horibe, K.; Hanada, R.; Imaizumi, M.; et al. Outcome of children with relapsed acute myeloid leukemia following initial therapy under the AML99 protocol. *Int. J. Hematol.* **2014**, *100*, 171–179. [[CrossRef](#)]
15. Karlsson, L.; Forestier, E.; Hasle, H.; Jahnukainen, K.; Jonsson, O.G.; Lausen, B.; Noren Nystrom, U.; Palle, J.; Tierens, A.; Zeller, B.; et al. Outcome after intensive reinduction therapy and allogeneic stem cell transplant in paediatric relapsed acute myeloid leukaemia. *Br. J. Haematol.* **2017**, *178*, 592–602. [[CrossRef](#)]
16. Hoffman, A.E.; Schoonmade, L.J.; Kaspers, G.J. Pediatric relapsed acute myeloid leukemia: A systematic review. *Expert Rev. Anticancer Ther.* **2020**, *21*, 45–52. [[CrossRef](#)]
17. Creutzig, U.; Zimmermann, M.; Dworzak, M.N.; Gibson, B.; Tamminga, R.; Abrahamsson, J.; Ha, S.Y.; Hasle, H.; Maschan, A.; Bertrand, Y.; et al. The prognostic significance of early treatment response in pediatric relapsed acute myeloid leukemia: Results of the international study Relapsed AML 2001/01. *Haematologica* **2014**, *99*, 1472–1478. [[CrossRef](#)]
18. Goemans, B.F.; Tamminga, R.Y.; Corbijn, C.M.; Hahlen, K.; Kaspers, G.J. Outcome for children with relapsed acute myeloid leukemia in the Netherlands following initial treatment between 1980 and 1998: Survival after chemotherapy only? *Haematologica* **2008**, *93*, 1418–1420. [[CrossRef](#)]
19. Abrahamsson, J.; Clausen, N.; Gustafsson, G.; Hovi, L.; Jonmundsson, G.; Zeller, B.; Forestier, E.; Heldrup, J.; Hasle, H.; Nordic Society for Paediatric Haematology and Oncology (NOPHO); et al. Improved outcome after relapse in children with acute myeloid leukaemia. *Br. J. Haematol.* **2007**, *136*, 229–236. [[CrossRef](#)]
20. Wells, R.J.; Adams, M.T.; Alonzo, T.A.; Arceci, R.J.; Buckley, J.; Buxton, A.B.; Dusenbery, K.; Gamis, A.; Masterson, M.; Vik, T.; et al. Mitoxantrone and cytarabine induction, high-dose cytarabine, and etoposide intensification for pediatric patients with relapsed or refractory acute myeloid leukemia: Children's Cancer Group Study 2951. *J. Clin. Oncol.* **2003**, *21*, 2940–2947. [[CrossRef](#)]
21. Aladjidi, N.; Auvrignon, A.; Leblanc, T.; Perel, Y.; Benard, A.; Bordigoni, P.; Gandemer, V.; Thuret, I.; Dalle, J.H.; Pigué, C.; et al. Outcome in children with relapsed acute myeloid leukemia after initial treatment with the French Leucemie Aigue Myeloide Enfant (LAME) 89/91 protocol of the French Society of Pediatric Hematology and Immunology. *J. Clin. Oncol.* **2003**, *21*, 4377–4385. [[CrossRef](#)] [[PubMed](#)]
22. Gamis, A.S.; Alonzo, T.A.; Meshinchi, S.; Sung, L.; Gerbing, R.B.; Raimondi, S.C.; Hirsch, B.A.; Kahwash, S.B.; Heerema-McKenney, A.; Winter, L.; et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: Results from the randomized phase III Children's Oncology Group trial AAML0531. *J. Clin. Oncol.* **2014**, *32*, 3021–3032. [[CrossRef](#)] [[PubMed](#)]
23. Loken, M.R.; Alonzo, T.A.; Pardo, L.; Gerbing, R.B.; Raimondi, S.C.; Hirsch, B.A.; Ho, P.A.; Franklin, J.; Cooper, T.M.; Gamis, A.S.; et al. Residual disease detected by multidimensional flow cytometry signifies high relapse risk in patients with de novo acute myeloid leukemia: A report from Children's Oncology Group. *Blood* **2012**, *120*, 1581–1588. [[CrossRef](#)]
24. Brodersen, L.E.; Gerbing, R.B.; Pardo, M.L.; Alonzo, T.A.; Paine, D.; Fritschle, W.; Hsu, F.C.; Pollard, J.A.; Aplenc, R.; Kahwash, S.B.; et al. Morphologic remission status is limited compared to DeltaN flow cytometry: A Children's Oncology Group AAML0531 report. *Blood Adv.* **2020**, *4*, 5050–5061. [[CrossRef](#)]
25. Cheson, B.D.; Cassileth, P.A.; Head, D.R.; Schiffer, C.A.; Bennett, J.M.; Bloomfield, C.D.; Brunning, R.; Gale, R.P.; Grever, M.R.; Keating, M.J.; et al. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. *J. Clin. Oncol.* **1990**, *8*, 813–819. [[CrossRef](#)]

26. Cheson, B.D.; Bennett, J.M.; Kopecky, K.J.; Buchner, T.; Willman, C.L.; Estey, E.H.; Schiffer, C.A.; Doehner, H.; Tallman, M.S.; Lister, T.A.; et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J. Clin. Oncol.* **2003**, *21*, 4642–4649. [[CrossRef](#)]
27. Kaspers, G.J.; Creutzig, U. Pediatric acute myeloid leukemia: International progress and future directions. *Leukemia* **2005**, *19*, 2025–2029. [[CrossRef](#)]
28. Creutzig, U.; Zimmermann, M.; Ritter, J.; Reinhardt, D.; Hermann, J.; Henze, G.; Jurgens, H.; Kabisch, H.; Reiter, A.; Riehm, H.; et al. Treatment strategies and long-term results in paediatric patients treated in four consecutive AML-BFM trials. *Leukemia* **2005**, *19*, 2030–2042. [[CrossRef](#)]
29. Chen, X.; Xie, H.; Wood, B.L.; Walter, R.B.; Pagel, J.M.; Becker, P.S.; Sandhu, V.K.; Abkowitz, J.L.; Appelbaum, F.R.; Estey, E.H. Relation of clinical response and minimal residual disease and their prognostic impact on outcome in acute myeloid leukemia. *J. Clin. Oncol.* **2015**, *33*, 1258–1264. [[CrossRef](#)]
30. Walter, R.B.; Kantarjian, H.M.; Huang, X.; Pierce, S.A.; Sun, Z.; Gundacker, H.M.; Ravandi, F.; Faderl, S.H.; Tallman, M.S.; Appelbaum, F.R.; et al. Effect of complete remission and responses less than complete remission on survival in acute myeloid leukemia: A combined Eastern Cooperative Oncology Group, Southwest Oncology Group, and M. D. Anderson Cancer Center Study. *J. Clin. Oncol.* **2010**, *28*, 1766–1771. [[CrossRef](#)] [[PubMed](#)]
31. Short, N.J.; Rafei, H.; Daver, N.; Hwang, H.; Ning, J.; Jorgensen, J.L.; Kadia, T.M.; DiNardo, C.D.; Wang, S.A.; Jabbour, E.; et al. Prognostic impact of complete remission with MRD negativity in patients with relapsed or refractory AML. *Blood Adv.* **2020**, *4*, 6117–6126. [[CrossRef](#)]
32. Bloomfield, C.D.; Estey, E.; Pleyer, L.; Schuh, A.C.; Stein, E.M.; Tallman, M.S.; Wei, A. Time to repeal and replace response criteria for acute myeloid leukemia? *Blood Rev.* **2018**, *32*, 416–425. [[CrossRef](#)]
33. Woods, W.G.; Kobrin, N.; Buckley, J.D.; Lee, J.W.; Sanders, J.; Neudorf, S.; Gold, S.; Barnard, D.R.; DeSwarte, J.; Dusenbery, K.; et al. Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: A report from the Children’s Cancer Group. *Blood* **1996**, *87*, 4979–4989. [[CrossRef](#)]