Survival outcomes with oral azacitidine maintenance in patients with acute myeloid leukemia in remission by receipt of initial chemotherapy: subgroup analyses from the phase III QUAZAR AML-001 trial

Oral azacitidine (Oral-AZA) is a hypomethylating agent approved for the treatment of adult patients with acute myeloid leukemia (AML) in first remission after intensive chemotherapy (IC).[1,2] In the phase III, randomized, double-blind, placebo-controlled QUAZAR AML-001 trial (*clinicaltrials gov. identifier: NCT01757535*), Oral-AZA significantly prolonged relapse-free survival (RFS) and overall survival (OS) compared with placebo in patients with AML in first complete remission (CR) or CR with incomplete blood count recovery (CRi) after IC (induction ± consolidation) who were not candidates for hematopoietic stem cell transplantation (HSCT).[3] The primary goal of QUAZAR AML-001 was to evaluate the effect of maintenance therapy with Oral-AZA for patients in remission after induction. While there were no protocol-specified criteria regarding prior chemotherapy used before study entry, including the use or number of consolidation cycles received, it is of clinical interest to assess whether the amount of pre-study chemotherapy may have influenced survival outcomes in this trial. Here, we present RFS and OS outcomes in patient subgroups defined by the use of consolidation and number of chemotherapy courses received prior to study entry.

IC is the cornerstone of initial AML therapy for patients fit enough to receive it, and most patients achieve CR with induction. Once in remission, patients may receive subsequent consolidation chemotherapy, but the optimal number of consolidation cycles is not well-defined, especially for older patients. After IC, the primary therapeutic goals for patients with AML in remission who are not eligible for HSCT are to delay relapse and prolong survival. Until Oral-AZA, no agent studied in the remission maintenance setting had significantly prolonged both RFS and OS.[1-8]

Study design and key eligibility criteria of QUAZAR AML-001 have been reported in detail elsewhere.[3] Briefly, eligible patients were aged ≥55 years with newly diagnosed AML in first remission after IC, had intermediate- or poor-risk cytogenetics (NCCN 2011 criteria[9]) and an Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤3, and were HSCT-ineligible. Induction and consolidation regimens were administered at the discretion of the treating physician before study screening; trial eligibility was not contingent on the use of consolidation chemotherapy or amount of consolidation cycles received, but patients must have been screened for eligibility within 4 months of achieving initial CR/CRi during induction. Eligible patients were randomized 1:1 to Oral-AZA 300 mg or placebo once daily for 14 days per 28-day treatment cycle. Measurable residual disease (MRD) was assessed centrally via multiparameter flow cytometry, with a positivity threshold of 0.1% in the bone marrow for aberrant cells (different from normal or leukemia aberrant phenotype).

The primary trial endpoint was OS, defined as the time from randomization until death, and the key secondary endpoint was RFS, the time from randomization until relapse or death. Comparisons of OS and RFS between Oral-AZA and placebo within patient subgroups defined by use of consolidation therapy after induction (yes or no) were prospective exploratory endpoints in the trial protocol. Additional *post hoc* analyses were performed to assess survival outcomes in subgroups defined by the number of consolidation courses received (0, 1, or ≥2) and total number of induction and consolidation cycles. Induction courses were defined as AML-directed chemotherapy regimens administered prior to the date of first CR/CRi recorded on the electronic case report form and consolidation regimens were those given after that date.

Survival endpoints were estimated using Kaplan-Meier methods and compared between treatment arms using hazard ratios (HR) and 95% confidence intervals (CI) from stratified Cox proportional hazards models and *P* values from stratified log-rank tests. The *post hoc* survival analyses by number of consolidation cycles and total cycles of induction and consolidation were not sufficiently powered to determine statistically significant differences within or between treatment arms, precluding meaningful interpretation of *P* values; HR point estimates and 95% CI in these subgroups are provided for informational purposes only. The data cutoff was performed in July 2019.

The trial enrolled 472 patients (Oral-AZA 238, placebo 234) (Figure 1). Prior to enrollment, the most common agents used for induction and consolidation were cytarabine (99% and 80%, respectively), idarubicin (55% and 20%), and daunorubicin (33% and 8%); use of these agents was similar between the Oral-AZA and placebo arms. Most patients (80% [378/472]) received consolidation after induction, and use of consolidation was similar between treatment arms (Oral-AZA 78% [186/238], placebo 82% [192/234]) (Figure 1). Nearly half of the patients in the Oral-AZA (n=110 [46%]) and

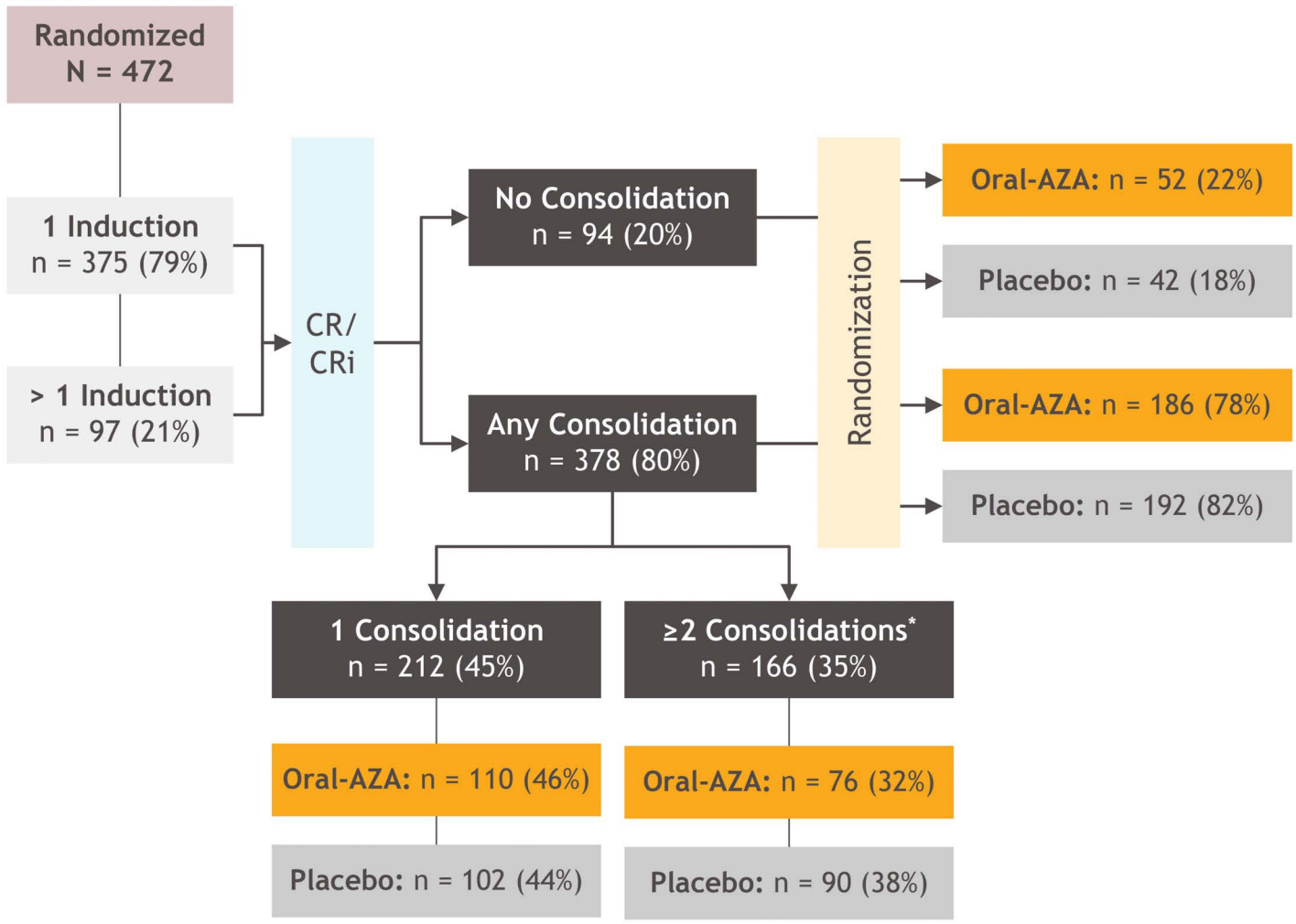

Figure 1. Patient enrollment and prior chemotherapy details. *The ≥2 consolidations cohort included 19 patients (oral azacitidine [Oral-AZA] 6, placebo 13) who received 3 consolidation cycles. CR: complete remission; CRi: CR with incomplete blood count recovery.

placebo (n=102 [44%]) arms received one prior consolidation, and 32% (n=76) and 38% (n=90) of patients, respectively, received ≥2 prior consolidation cycles. The remaining 20% of patients (n=94) did not receive consolidation, including 52 patients (22%) in the Oral-AZA arm and 42 (18%) in the placebo arm. Baseline characteristics were generally similar among consolidation-defined subgroups within and between treatment arms (*Online Supplementary Table S1*). In both arms, patients who did not receive consolidation tended to be older than those who did. Rate of measurable residual disease (MRD) negativity at screening was similar between consolidation-defined cohorts within the Oral-AZA arm, whereas in the placebo arm, a larger proportion of patients who received consolidation were MRD-negative compared with those who did not (50% *vs.* 36%, respectively).

Oral-AZA significantly prolonged both RFS and OS from the time of randomization compared with placebo, regardless of whether patients received consolidation prior to study entry. For patients who did not receive consolidation, median RFS was prolonged with Oral-AZA by 4.5 months *versus* placebo (median 8.4 *vs.* 3.9 months, respectively; HR=0.58; 95% CI: 0.36-0.94; *P*=0.0258) and the estimated 1-year RFS rate was 18.7% higher with Oral-AZA (40.8% *vs.* 22.0%) (Figure 2A; Table 1). Oral-AZA also prolonged median OS in this subgroup by approximately 12 months compared with placebo (median 23.3 *vs.* 10.9 months, respectively; HR=0.54; 95% CI: 0.33-0.87; *P*=0.0103) and improved 1-year survival rate by 30.7% (71.2% *vs.* 40.5%) (Figure 2B; Table 1).

For patients who did receive consolidation following initial induction, median RFS was prolonged more than 2-fold with Oral-AZA *versus* placebo - 10.2 *versus* 5.0 months, respectively (HR=0.67; 95% CI: 0.53-0.85; *P*=0.001) - and 1-year RFS rates were 45.9% and 28.6%, respectively (Figure 2A; Table 1). Median OS was 24.7 months with Oral-AZA and 15.4 months with placebo (HR=0.74; 95% CI: 0.58-0.94; *P*=0.0147) and estimated 1-year survival rates were 73.2% and 59.2%, respectively (Figure 2B; Table 1). Estimated median RFS was approximately twice as long with Oral-AZA compared with placebo in both the one consolidation and ≥2 consolidation cohorts, and Oral-AZA increased 1-year survival rates in these cohorts by 17.3% and 19.6%, respectively (Table 1). Oral-AZA nominally improved OS regardless of the number of prior consolidation cycles received (0, 1, or ≥2), with median OS estimates ranging from 21.0 to 28.6 months in the Oral-AZA arm and 10.9 to 17.6 months in the placebo arm (Table 1). Intriguingly, median RFS appeared favorable for patients receiving Oral-AZA without any prior consolidation therapy (8.4 months), compared with patients receiving consolidation therapy but no maintenance in the placebo arm (5.0 months). Analogously, median OS was also longer for patients receiving Oral-AZA and no prior consolidation therapy (23.3 months), compared with patients receiving consolidation therapy but no maintenance treatment in the placebo arm (15.4 months).

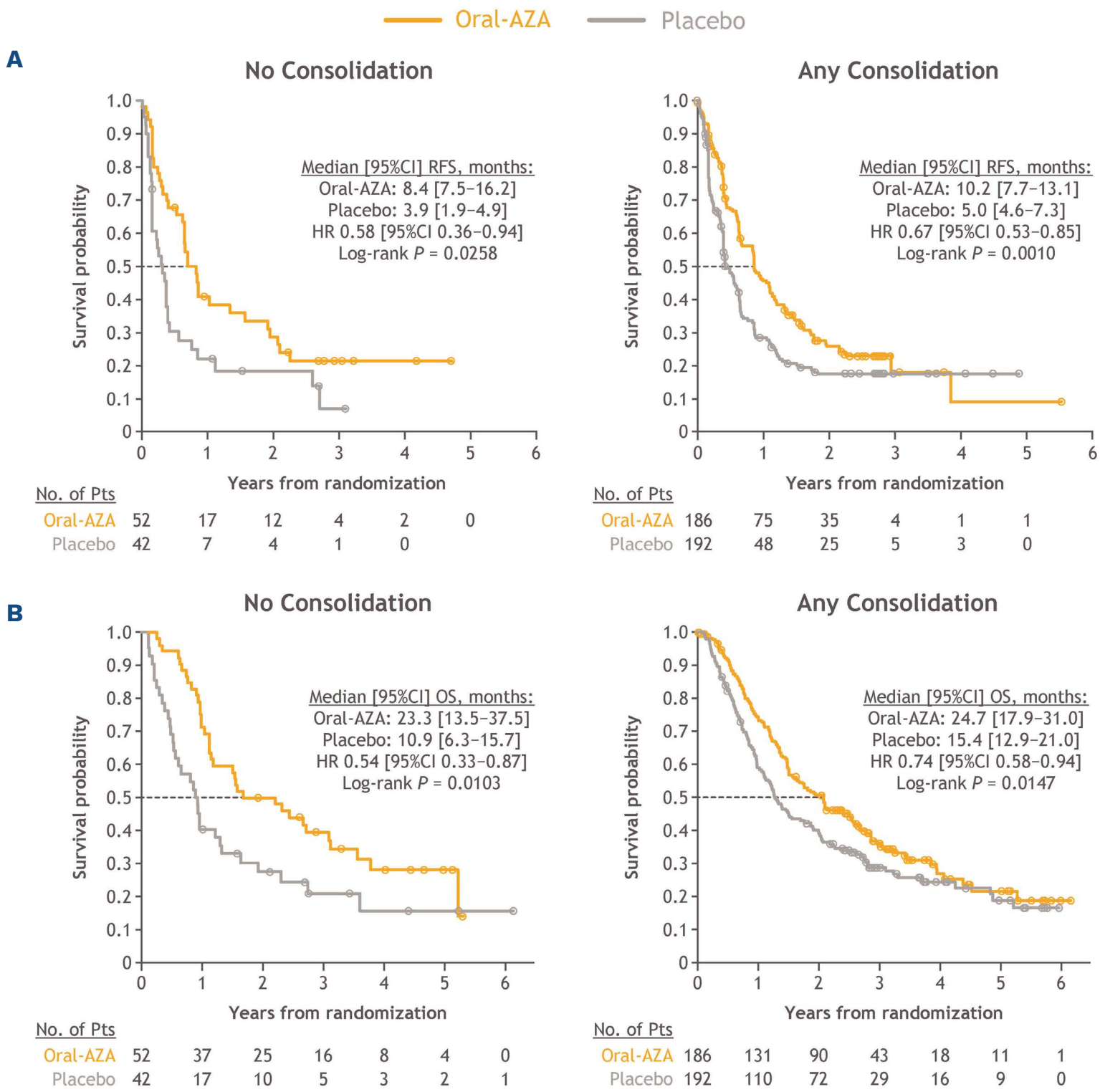

Figure 2. Survival outcomes by prior consolidation chemotherapy use. Kaplan-Meier estimated (A) relapse-free survival (RFS) and (B) overall survival (OS) with oral azacitidine (Oral-AZA) *vs.* placebo by prior use of consolidation chemotherapy before study entry. RFS and OS estimates were derived using Kaplan-Meier methods and compared for Oral-AZA *vs.* placebo using a log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were generated using a stratified Cox proportional hazards model. pts: patients.

Overall, 79% of patients (n=375) received a single induction course before achieving remission and 21% (n=97) received ≥2 inductions (Figure 1). When accounting for total chemotherapy received before study entry (i.e., number of induction and consolidation courses), median RFS was numerically prolonged by 1.5 to 8.5 months with Oral-AZA *versus* placebo across all induction/consolidation cohorts (*Online Supplementary Table S2*). Patients who received a single induction followed by ≥2 cycles of consolidation appeared to have the most favorable survival outcomes within each treatment arm, whereas the small subgroup of patients who received ≥2 courses of induction and no consolidation generally had poor outcomes, but sample sizes prevent meaningful interpretation.

The overall safety profile of Oral-AZA was similar among consolidation groups and was aligned with the overall QUAZAR population. No associations were found between the number of consolidation cycles received and Oral-AZA dose modifications (*data not shown*).

As mentioned, the primary objective of the QUAZAR AML-001 trial was to determine the efficacy of Oral-AZA as maintenance therapy subsequent to chemotherapy for patients already in remission. A broad assessment of the impact of consolidation therapy in the front-line management of AML is beyond the scope of this trial, and Oral-AZA is not meant to replace consolidation chemotherapy for patients who can receive it. Overall, Oral-AZA maintenance significantly prolonged both RFS and OS compared with placebo re-

Table 1. Estimated relapse-free and overall survival with oral azacitidine *versus* placebo by number of consolidation cycles received before study entry.

	Oral-AZA N=238	Placebo N=234	Difference, Oral-AZA *vs.* placebo, in months (95% CI)
No consolidation, N (%)	52 (22)	42 (18)	
RFS in months, median (95% CI)	8.4 (7.5-16.2)	3.9 (1.9-4.9)	+4.5 (0.8-8.2)
Oral-AZA *vs.* placebo, HR (95% CI)	0.55 (0.34-0.88)		
1 year RFS rate,	40.8	22.0	+18.7 (-0.6 to +38.1)
OS in months, median (95% CI)	23.3 (13.5-37.5)	10.9 (6.3-15.7)	+12.4 (4.7-26.7)
Oral-AZA *vs.* placebo, HR (95% CI)	0.55 (0.34-0.89)		
1-year OS rate, %	71.2	40.5	+30.7 (11.4-50.0)
Any consolidation,* N (%)	186 (78)	192 (82)	
RFS in months, median (95% CI)	10.2 (7.7-13.1)	5.0 (4.6-7.3)	+5.2 (2.7-7.6)
Oral-AZA *vs.* placebo, HR (95% CI)	0.69 (0.54-0.87)		
1 year RFS rate, %	45.9	28.6	+17.3 (7.2-27.4)
OS in months, median (95% CI)	24.7 (17.9-31.0)	15.4 (12.9-21.0)	+9.3 (3.4-15.2)
Oral-AZA *vs.* placebo, HR (95% CI)	0.76 (0.60-0.97)		
1-year OS rate, %	73.2	59.2	+14.0 (4.5-23.6)
1 consolidation, N (%)	110 (46)	102 (44)	
RFS in months, median (95% CI)	10.0 (7.4-11.7)	4.7 (4.0-7.4)	+5.3 (2.2-8.3)
Oral-AZA *vs.* placebo, HR (95% CI)	0.72 (0.53-0.99)		
1 year RFS rate, %	40.6	23.3	+17.3 (4.4-30.2)
OS in months, median (95% CI)	21.0 (16.7-30.5)	14.3 (11.7-18.0)	+6.7 (0.1-13.3)
Oral-AZA *vs.* placebo, HR (95% CI)	0.75 (0.55-1.02)		
1-year OS rate, %	68.8	59.2	+9.6 (-3.4 to +22.6)
≥2 consolidations, N (%)	76 (32)	90 (38)	
RFS in months, median (95% CI)	13.0 (7.7-21.2)	6.1 (4.6-7.5)	+6.9 (0.7-13.1)
Oral-AZA *vs.* placebo, HR (95% CI)	0.59 (0.41-0.87)		
1 year RFS rate, %	54.1	34.5	+19.6 (3.7-35.4)
OS in months, median (95% CI)	28.6 (17.8-41.3)	17.6 (11.6-28.7)	+11.0 (-0.1 to +22.1)
Oral-AZA *vs.* placebo, HR (95% CI)	0.75 (0.50-1.11)		
1-year OS rate, %	80.0	59.2	+20.9 (7.0-34.8)

*Includes patients in the 1 consolidation and ≥2 consolidations cohorts. CI: confidence interval; HR: hazard ratio; Oral-AZA: oral azacitidine; OS: overall survival; RFS: relapse-free survival.

gardless of whether patients received consolidation after initial induction. With the caveat regarding small sample sizes and lack of statistical power, *post hoc* analyses in subgroups defined by number of consolidation cycles received suggest that Oral-AZA may prolong RFS and OS compared with a "watch-and-wait" approach (emulated with placebo) for patients with AML in first remission after IC, independent of the number of induction and consolidation courses received before beginning maintenance treatment. A previous analysis examining the relationship between survival outcomes and MRD in QUAZAR AML-001 found that although patients with MRD responses (i.e., conversion from MRD-positive at baseline to MRD-negative) were more likely to have received consolidation chemotherapy before study entry than those who remained MRD-positive on-study, the number of chemotherapy cycles received before study entry was not significantly predictive of MRD response or duration on-study with MRD-negative status.[10] Overall, these findings indicate that intensive induction chemotherapy followed by Oral-AZA maintenance therapy is effective regardless of the amount of prior consolidation delivered, and represents an important component of therapy in patients with intermediate- or poor-risk AML in remission not candidates for HSCT.

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BS and CLB were employed by Bristol Myers Squibb at the time the study was conducted. AHW has served on advisory boards for AbbVie, Agios, Amgen, Celgene/Bristol Myers Squibb, Gilead, Janssen, MacroGenics, Novartis, Pfizer, Roche, and Servier; has received research funding to his institution from AbbVie, Amgen, AstraZeneca, Celgene/Bristol Myers Squibb, Novartis, and Servier; has served on a speakers bureau for AbbVie, Celgene, and Novartis; and is eligible for royalty payments from the Walter and Eliza Hall Institute of Medical Research related to venetoclax. GJR reports receiving research support from Janssen and has served in an advisory position for AbbVie, Agios, Amgen, Astellas, AstraZeneca, Bluebird Bio, Blueprint Medicines, Bristol Myers Squibb, Catamaran, Celgene, Glaxo SmithKline, Helsinn, Janssen, Jasper Therapeutics, Jazz Pharmaceuticals, Mesoblast, Novartis, Pfizer, Roche, Syndax, and Takeda (IRC Chair). HDo reports receiving honoraria from Incyte and Servier. HDö has served in a consultancy position for AbbVie, Agios, Amgen, Astellas, Berlin-Chemie, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Janssen, Jazz Pharmaceuticals, Novartis, Servier, and Syndax; reports receiving research funding from AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Kronos Bio, Novartis, and Pfizer; and reports receiving honoraria from AbbVie, Agios, Amgen, Astellas, AstraZeneca, Berlin-Chemie, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Janssen, Jazz Pharmaceuticals, Novartis, Servier, and Syndax. ACS has served on an advisory committee for AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Jazz, Pfizer, Teva, and Servier; reports receiving research funding from AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, GlycoMimetics, Kite/Gilead, Pfizer, and Servier; and reports receiving honoraria from AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Pfizer, Teva, and Servier. PM has served in a consultancy position for Menarini/Stemline, Gilead, Otsuka, Kura Oncology, AbbVie, Bristol Myers Squibb, Novartis, Jazz Pharmaceuticals, BeiGene, Astellas, Pfizer, Incyte, Takeda, Ryvu, and Nerviano; reports receiving research funding from AbbVie, Bristol Myers Squibb, Jazz Pharmaceuticals, Menarini/Stemline, Novartis, Pfizer, and Takeda; and has served on a speakers bureau for AbbVie, Astellas, Bristol Myers Squibb, Gilead, Jazz Pharmaceuticals, and Pfizer. DS reports receiving grants or contracts, honoraria, consulting fees, and travel support from AbbVie, Bristol Myers Squibb, Novartis, and Pfizer; and has served in a leadership role for the Belgian College for Reimbursement of Orphan Drugs. TP reports employment and stock ownership with Bristol Myers Squibb. YL reports employment with Bristol Myers Squibb and Eli Lilly stock ownership. BS reports prior employment with Celgene/Bristol Myers Squibb. CLB reports prior employment and stock ownership with Bristol Myers Squibb. FR reports receiving research funding from Amgen, Astellas, Astex/Taiho, Biomea Fusion, Celgene/Bristol Myers Squibb, Prelude, Syros, and Xencor; and honoraria from AbbVie, Astellas, AstraZeneca, Celgene/Bristol Myers Squibb, Novartis, and Syros. AstraZeneca, Celgene/Bristol Myers Squibb, Novartis, and Syros.

Contributions

The sponsors collected and analyzed data in conjunction with all authors. AHW wrote the first draft of the manuscript. All authors revised the manuscript and reviewed and approved the final version for submission.

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Data-sharing statement

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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