Supplementary Online Content

Bornhäuser M, Schliemann C, Schetelig J, et al. Allogeneic hematopoietic cell transplantation vs standard consolidation chemotherapy in patients with immediate-risk acute myeloid leukemia: a randomized clinical trial. *JAMA Oncol.* Published online February 9, 2023. doi:10.1001/jamaoncol.2022.7605

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Primary Hypothesis Test

Initially the primary endpoint was defined as 4-year overall survival as binary variable. A binary endpoint was chosen because non-proportional hazards were assumed between the treatment arms. Due to slow accrual the study had to be closed prematurely after 143 patients were recruited and only 2 years of follow up for most of the patients. To avoid imputation of 4-year overall survival or exclusion of a large number of patients from the analysis, 2-year overall survival was re-defined as primary endpoint in the detailed statistical analysis plan before the study database was locked and data were exported for analyses. Despite this re-definition of the primary endpoint, still 2 missing values in the allogeneic HCT arm and 1 missing value in the chemo-consolidation arm in the binary primary endpoint 2-year overall survival occurred. These missing values were imputed using a worst case approach. Patients in the transplant arm were imputed as event and patients in the chemo consolidation arm as having no event. We chose this very conservative approach to definitely preserve the type-1-error probability in the face of abundant nonrandomized evidence potentially overestimating the treatment effect of allo HCT. The primary hypothesis was tested with the likelihood ratio test comparing two multivariable logistic regression models with adjusting variables age (<40; >= 40 years); donor (related; unrelated); isolated NPM1 or CEBPa mutation vs. other molecular markers; AML type (de novo AML;

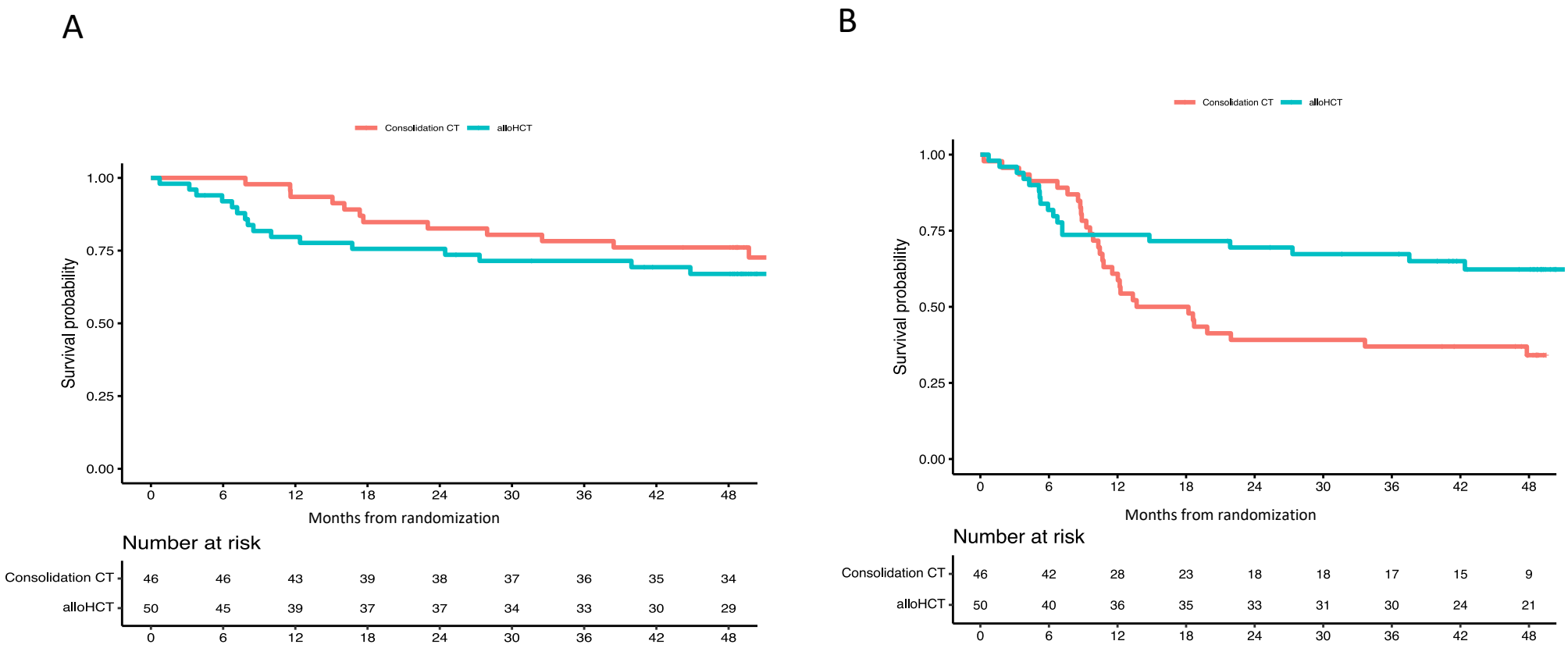
sAML or tAML); day 15 blast count after first induction therapy (<10%; >= 10%); HCT-CI score (<=1 vs. > 1); remission status (CR; CRi); karyotype (normal; aberrant), and with or without treatment arm.

Sensitivity analyses excluding patients with missing 2-year overall survival, best case imputation (missing values in allo HCT arm imputed as ‘alive’ and missing values consolidation CT arm imputed as ‘dead’) and as time-to-event endpoint were applied in addition.

Two-year overall survival probabilities after imputation of 74% [n = 56/76; 95-CI 62-83%] and 84% [n = 56/67; 95%-CI 73-92%] were estimated for the allo HCT and the chemo consolidation arm. The p-value of the likelihood ratio test was 0.155. In a sensitivity analysis with complete cases 76% [n = 56/74; 95%-CI 64-85%] and 83% [n = 55/66; 95%-CI 72-91%] 2-year overall survival probabilities were estimated for the respective treatment arms (p = 0.267). In another sensitivity analysis with a best case imputation approach the estimated 2-year overall survival probabilities were 76% [n = 58/76; 95%-CI 65-85%] and 82% [n = 55/67; 95-CI 71-90%].

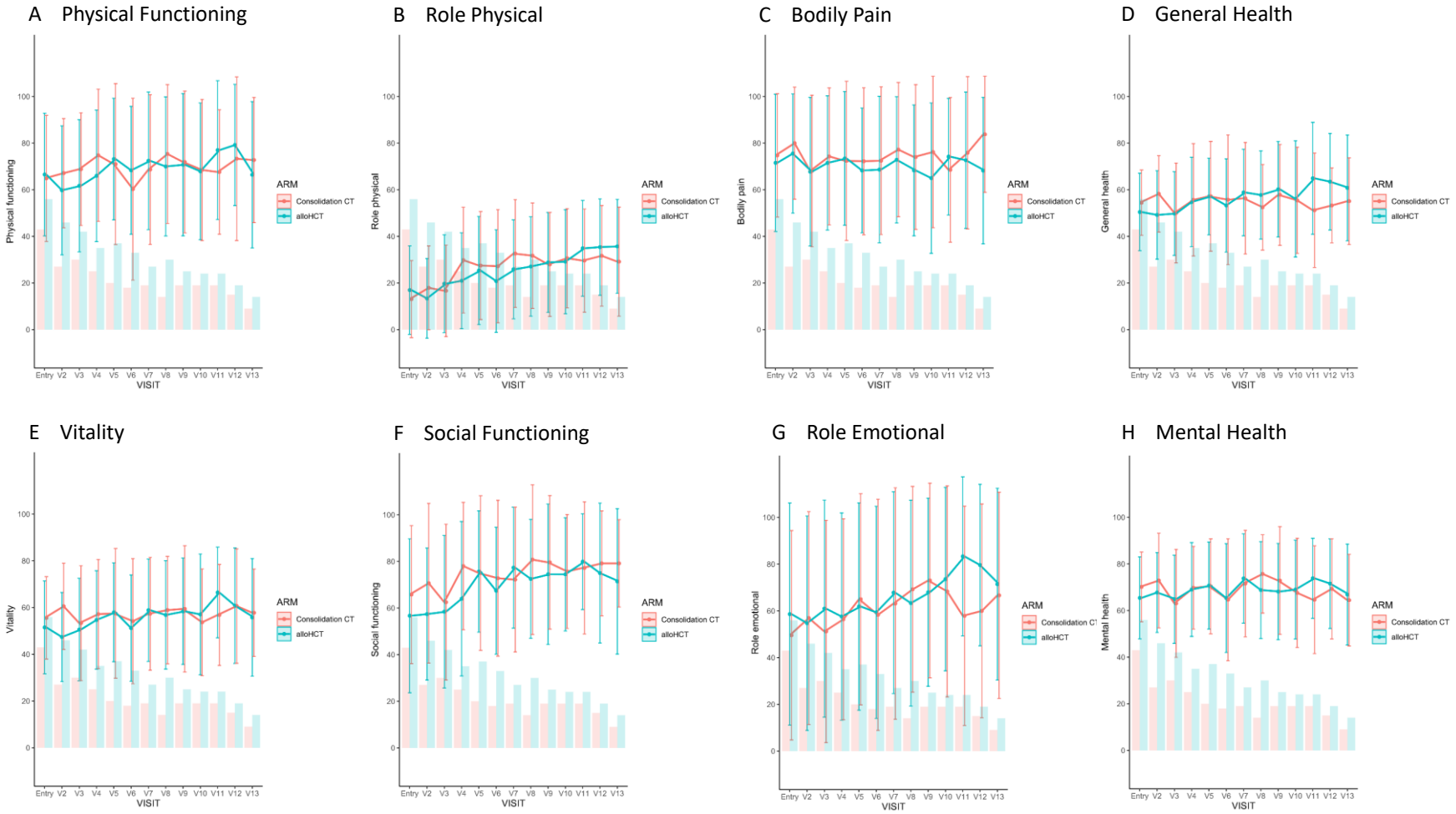
eFigure 1. Overall (A) and Disease-Free Survival (B) in Patients With Intermediate-Risk AML According to ELN 2017

Graph A shows overall survival in ELN intermediate-risk AML after immediate allogeneic HCT vs. delayed HCT in case of relapse. Graph B depicts the estimates of disease-free survival.



eFigure 2. Quality of Life Assessment

The graphs A-F depict the mean levels + standard deviation for the six representative dimensions of the SF-36 score from study entry until last follow-up. The bars in the lower part of each graph represent the number of patients who responded at the given point in time.



eTable. Treatment Course of Patients Relapsing After Chemo-Consolidation Before Salvage Allogeneic HCT

	n
All	41
Hematologic	35
Molecular	5
Extramedullary	1
No salvage therapy	20
Ida/Mito-FLAG	12
High-dose cytarabine /mitoxantrone (HAM)	5
Cladribine/Cytarabine	1
5-azacytidine/low dose cytarabine	3

FLAG, fludarabine/cytarabine/G-CSF