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Salvage-free, transplantation-free survival: a proposal for a new clinical endpoint in acute myeloid leukemia

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Data Sharing Statement

Requests for sharing deidentified data should be directed to the corresponding author.

Authorship Contributions

CR and EB contributed to the study conception and design. SB, PYD and CR treated patients and participated in clinical data collection and assembly. ST, TL, AH, EF, AB, AP, treated patients. AC, EK, AB, LL, VDM participated in biological data collection and assembly. AS, MM, ACdG, collected data. KCL, CP, CG, XT, TB, RPDL, HD, SDB managed data and/or enrolled and treat patients in the ALFA trials. EB conducted statistical analyses. CR wrote the first draft of the manuscript. All authors had full access to all the data in the study, contributed to writing the manuscript and provided final approval of the submitted version.

Conflict of Interest Disclosures

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Abstract

Results from pivotal clinical trials evaluating the combination of intensive chemotherapy with targeted therapies in acute myeloid leukemia (AML) are expected soon. While overall survival (OS) or event-free survival (EFS) are the recommended endpoints, new criteria are needed for assessing the intrinsic effectiveness of new drugs. In this study, the salvage-free, transplantation-free survival (STFS) was measured from day 1 of induction chemotherapy to the date of induction failure or salvage therapy, allogeneic transplantation (allo-HSCT), relapse, or death from any cause, whichever occurs first and assessed in a cohort of 1966 AML patients from the DATAML registry treated with intensive chemotherapy and 100 acute promyelocytic leukemia (APL) patients treated with arsenic trioxide and all-trans retinoic acid. Validation cohorts from the ALFA group were used.

At five years, STFS was estimated at 14.6% (95% confidence interval [CI], 13.0-16.2; median, 5.5 months) whereas OS, EFS and relapse-free survival estimations were 40.4% (95% CI, 38.2-42.6; median, 30.6 months), 31.4% (95% CI, 29.4-33.5; median, 15.3 months) and 37.6% (95% CI, 35.2-40.0; median, 21.9 months), respectively. Relapse was the most common first STFS event, followed by allo-HSCT. STFS varied depending on molecular subgroups and gene-gene mutation interactions. In the APL cohort, STFS (83.6% at five years) was similar to OS (85.6%) illustrating the impact of an effective and low-toxicity first-line treatment curing patients without salvage therapy or allo-HSCT. In the prospective randomized ALFA-0701 trial, gemtuzumab ozogamycin significantly improved STFS.

STFS should complement other survival endpoints to accurately analyze the impact of new drugs in AML.

Introduction

Results from pivotal clinical trials evaluating the combination of intensive chemotherapy with inhibitors of IDH1, IDH2 (NCT03839771), menin-KMT2A (NCT07007312, NCT07223814), FLT3 (NCT04027309) or BCL-2 (NCT04628026) in acute myeloid leukemia (AML) are expected in the coming years. These results could transform the therapeutic landscape in patients fit for intensive chemotherapy.[1] However, even though most of these studies are placebo-controlled, interpreting phase 3 results in the field of AML is often tricky since consolidation treatments may include allo-HSCT, which has a very different mechanism of action, highly effective in preventing relapse, but also potentially toxic.[2-4] In addition, salvage treatments including targeted agents and/or allo-HSCT for induction failure or relapse, either morphologic or molecular, may also be curative, especially in favorable-risk AML.[5,6] Traditional evaluation criteria such as overall survival (OS), event-free survival (EFS), and relapse-free survival (RFS), are therefore potentially influenced by both therapeutic interventions.[7] In addition, due to the genetic heterogeneity of AML and gene-gene interactions, certain molecular subgroups more than others may benefit from specific therapeutic interventions. While measurable residual disease (MRD) could become a surrogate marker for overall survival and accelerate drug approval, new clinical criteria to better assess the specific impact of new drugs in the frontline treatment of AML are needed.[8]

In this study, we postulate that even if a good drug may improve the current standard treatment, including allo-HSCT, the ideal drug would significantly increase the proportion of patients who are cured after first-line treatment without the need for allo-HSCT in first CR or additional salvage therapy. Therefore, we propose to define a composite endpoint to analyze the specific impact of new drugs in the frontline treatment of AML: the salvage-free, transplantation-free survival (STFS). We evaluated this endpoint in a cohort of patients treated with intensive chemotherapy with a special focus on subgroups for which significant progress is expected

soon. A cohort of acute promyelocytic leukemia (APL) patients treated with arsenic trioxide and all-trans retinoic acid was used as control.

Methods

Patients

The inclusion criteria for the AML cohort were: newly diagnosed AML patients included in the DATAML registry between January 2010 and December 2022, age ≥18 years, treated with intensive chemotherapy. Patients treated in clinical trial assessing novel drugs were excluded. Inclusion criteria for the acute promyelocytic leukemia (APL) cohort used as control were: newly diagnosed APL patients, age ≥18 years, included in DATAML during the same period, treated with first-line therapy including arsenic trioxide (ATO) and all-trans retinoic acid (ATRA). The cytogenetic classification was in accordance with the Medical Research Council (MRC) classification. Informed consent was provided to all patients in accordance with the Declaration of Helsinki, allowing clinical data to be collected in the anonymized DATAML registry. The study was approved by the Advisory Committee on Information Processing in Health Research (CCTIRS n°15.319).

Treatments

AML patients received induction chemotherapy that included daunorubicin or idarubicin together with cytarabine according to French clinical trials for younger and older (>60 years) AML patients.[9-14] Patients with therapy-related AML or AML with myelodysplasia-related changes could receive CPX-351 from the date of its registration in France.[15] Gemtuzumab ozogamycin (GO) was not used in the first-line treatment including in patients with *RUNX1::RUNX1T1* or *CBFB::MYH11* AML. Midostaurin was added to chemotherapy in patients with *FLT3* mutations since 2018. Post-remission therapy and treatment of APL patients are described in Supplementary data.

Endpoints

EFS, RFS and OS were calculated according to European LeukemiaNet (ELN) 2017 guidelines.[16] STFS was measured from day 1 of induction chemotherapy to the date of induction failure or salvage therapy, allo-HSCT in CR/CRi, morphologic or molecular relapse following CR/CRi, or death from any cause, whichever occurs first, or to the date of last contact if no event occurred. Induction failure was defined as no complete remission (CR) or CR with incomplete hematologic recovery (CRi) after one induction cycle. Molecular relapse was defined according to ELN 2021 MRD working party recommendations.[17]

External validation cohorts

A validation set was built from two cohorts of patients intensively treated in the Acute Leukemia French Association (ALFA) 0702[11] and ALFA-1200[18] trials to assess STFS in an independent, multicentric and prospective cohort. Another cohort from the prospective randomized trial assessing GO plus intensive chemotherapy vs chemotherapy (ALFA-0701) was used to assess the impact of a third drug added to standard 7+3 on STFS.[19]

Statistical analyses

Statistical analyses were performed on STATA® version 18.0 (STATA Corp., College Station, TX). Patient characteristics were described using number and frequency (of non-missing data) for qualitative data; median, interquartile range (IQR; 25th and 75th percentiles) and range (minimum-maximum) for quantitative data. For survival outcomes, Kaplan-Meier survival curves were drawn and described using median (Inter-Quartile Range (IQR)) and survival at 1, 3, and 5 years (with the associated 95% Confidence Interval (CI)). The median follow-up was described by the reverse Kaplan-Meier technique.

Results

AML patients

Baseline characteristics of the 1966 AML patients included in this study are presented in Table 1. The median age of AML patients was 62 years, 45.6% were female, 21.8% had secondary AML, 80.9% an ECOG performance status of 0-1 and the median WBC was 8.64 G/L (IQR, 2.6-40.5). Cytogenetic risk was favorable in 9%, intermediate in 67%, and adverse in 24%. Of major druggable molecular subgroups, 31.4% had *NPM1* mutations, 20.0% *FLT3*-ITD, 7.4% *FLT3*-TKD, 8.8% *IDH1* mutations, 9.7% *IDH2* mutations and 3% *KMT2A*-rerrangement (*KMT2A*-r). The rate of CR or CRi was 83% after one or two induction cycles. Day-30 and day-60 death rates were 6 and 8%, respectively. Allo-HSCT was performed in 561 patients (34.5%) during first CR/CRi and in 244 patients (27.0%) after relapse.

Main outcomes and STFS in AML patients

The median follow-up of AML patients was 90.7 months (IQR, 63.6-125.3). Median OS, EFS and RFS were 30.6 (IQR, 9.5-not reached), 15.3 (IQR, 5.3-125.0) and 21.9 (IQR, 7.4-not reached) months respectively, whereas the median STFS was 5.5 months (IQR, 2.3-16.1) without difference between patients ≤ 60 years (5.2 months, IQR, 2.7-14.9) and patients > 60 years (5.6 months, IQR, 1.9-18.2) (Figure 1; Table 2). The distribution of first occurring events used to calculate STFS is shown in Table 3. Relapse was the most common first event (33.9%), followed by allo-HSCT (24.0%), failure or salvage (18.2%) and death (10.8%).

STFS by genetic subgroups

Median STFS by cytogenetic subgroups was 12.2 (IQR, 7.1-not reached), 6.1 (IQR, 2.7-22.0) and 3.1 (IQR, 1.4-4.9) months in patients with favorable (*RUNX1::RUNX1T1* or *CBFB::MYH11*), intermediate or adverse risk, respectively. Median STFS by druggable molecular subgroups was 10.2 (IQR, 4.6-106.9), 5.2 (IQR, 2.5-10.1), 6.9 (IQR, 3.3-15.4), 8.3 (IQR, 3.3-20.1) and 4.2 (IQR, 3.2-6.5) months in patients with *NPM1*, *FLT3*-ITD, *IDH1* (and

wild-type *FLT3*), *IDH2* (and wild-type *FLT3*) mutations or *KMT2A*-r, respectively (Figure 2, Table 2). The median STFS of patients with b-ZIP in frame *CEBPA* mutations was not reached (Table 2; Figure S1). STFS also varied depending on gene-gene interactions. In *NPM1* mutated patients, the median STFS was impacted by *FLT3*-ITD (22.0 months, IQR 6.5-not reached, without vs. 6.0 months, IQR 3.9-14.3, with *FLT3*-ITD) (Figure S2). In *IDH1* or *IDH2* mutated patients (and wild-type FLT3), the median STFS was impacted by the presence of *NPM1* mutations (Figures S3 and S4; Table S1). The distribution of first STFS events differed according to molecular subgroups (Table 3).

Midostaurin was associated with OS but not STFS improvement in *FLT3* mutated patients

Midostaurin, which was approved for patients with *FLT3* mutations in 2018, was added to chemotherapy in 125 patients. Median OS was 47.0 months (IQR, 11.3-not reached) in patients with midostaurin and 23.7 months (IQR, 9.1-not reached) in patients without midostaurin, whereas as there was no difference in STFS (5.4 months, IQR 2.7-11.6, without vs. 5.3 months, IQR 2.1-11.6, with midostaurin) (Table S2, Figure S5).

Main outcomes and STFS in APL patients

The median age of the 100 APL patients was 53 years, 49% were female and 16% had WBC > 10 G/L (Table S3). The CR rate after ATO-ATRA based-therapy was 93%. Day-30 and day-60 death rates were 6.0% and 8.0%, respectively. There were three relapses and no patient received an allo-HSCT. The median follow-up was 64.1 months (IQR, 40.3-95.1). At five years, OS and RFS were 85.6% (95% CI, 76.3-91.4) and 91.0% (95% CI, 82.0-95.6) whereas the STFS was 83.6% (95% CI, 74.1-89.8) (Figure 2).

External validation in the ALFA (0702, 1200) cohort

The STFS endpoint was also evaluated in the ALFA cohort of AML patients treated with intensive chemotherapy (Table S4). With a median follow-up of 43.4 months (IQR, 32.8-57.3), median OS, EFS and RFS were 49.7 (IQR, 11.5-not reached), 16.3 (IQR, 5.1-not reached) and 28.8 (IQR, 8.3-not reached) months respectively, whereas the median STFS was 5.5 months (IQR, 3.1-18.7) without difference between patients ≤ 60 years (5.7 months, IQR, 3.7-27.7) and patients > 60 years (5.3 months, IQR, 1.4-13.7) (Figure S6, Table S5). Allo-HSCT was the most common first event (30.3%), followed by relapse (23.9%), failure or salvage (18.3%) and death (7.9%) (Table S6). STFS by molecular subgroups and gene-gene interactions are presented in Supplemental Data (Table S5 and Figure S7).

Impact of GO on STFS in the ALFA-0701 trial

The ALFA-0701 trial demonstrated the benefit of fractionated doses of GO in addition to intensive chemotherapy by improving EFS compared to intensive chemotherapy without GO.[19] This cohort was used to determine whether GO could improve STFS in a prospective randomized trial. The distribution of first occurring event of STFS showed numerically lower induction failure, allo-HSCT in first CR, and relapses in the GO arm (Table 4). Median STFS was significantly improved in the GO arm (9.7 months, IQR, 5.1-NR) compared to the no GO arm (6.8 months, IQR, 2.0-15.0) (*P*=0.004) (Figure 3).

Discussion

In this study, we defined and investigated a new analysis criterion that takes into account all events that may occur from the start of treatment, including allogeneic transplantation, in fit AML patients intensively treated. Using APL whose prognosis was similar to other AML before the era of PML-RARA directed therapies as a control, we showed how the effect of a radically effective and low-toxicity first-line treatment could be translated using this criterion.[20,21]

Moreover, by reanalyzing the ALFA-0701 trial cohort, we also validated this concept by demonstrating the impact of GO on STFS in a randomized trial.[19]

Including transplantation as an event in the definition of an evaluation criterion is debatable. In theory, it is a pre-planned event, as the decision to perform the procedure is made in advance based on disease risk. Depending on genetic subgroups, allo-HSCT was indeed a frequent occurrence when calculating STFS. However, the indication for allo-HSCT is not determined by disease risk alone. It requires a complex decision process incorporating genetic and MRD risk, depth and kinetics of response, age, comorbidities, donor availability, treatment-related toxicity, institutional practice, physician judgment, and, importantly, patient preferences. These factors may differ considerably between centers, countries, and study periods. Consequently, STFS may measure not only the intrinsic efficacy of a new drug but also the surrounding treatment strategy and access to transplantation. This may limit comparisons between trials or between pharmacological and immunotherapeutic approaches. In most recent studies, the allo-HSCT rates in first CR didn't exceed 50% in younger patients and were even less in patients older than 60 years.[22-25] In addition, some study groups have challenged allo-HSCT in intermediate risk patients who achieved CR or CR without MRD after induction chemotherapy.[4,26,27] In light of this, the ongoing European RESOLVE randomized clinical trial (EU CT 2024-512503-39-00) will compare allo-HSCT with chemotherapy (and delayed allo-HSCT if relapse) in intermediate-risk patients who are in first CR without MRD and have an HLA-matched donor. In this type of study, where HSCT is randomized, one might speculate that researchers might observe a decrease in the number of relapses and, consequently, a reduction in the number of transplants if a new effective drug is used for induction and/or consolidation. This would improve the STFS. For high-risk patients, we acknowledge that STFS could be a less useful endpoint. However, we can take the example of Philadelphia chromosome-positive ALL, for which transplantation indications were indisputable until very

recently. Due to the remarkable efficacy of the blinatumomab and tyrosine kinase inhibitor combination, allo-HSCT is now being reconsidered.[28,29] Things change quickly, and the same could be true for high-risk AML in the near future. Conversely, favorable risk patients who do not have an indication for transplantation in first remission still have a significant risk of relapse.[30,31] STFS as a measurement for the effectiveness of induction and consolidation, should be best applied when allo-HSCT is not pre-planned. Cases in which a patient with favorable risk AML was referred to an allo-HSCT could be then regarded as lack of effectiveness of treatment. In ongoing trials, one could expect drugs such as venetoclax or menin inhibitors to significantly reduce the incidence of molecular failure after two cycles of intensive chemotherapy as well as the incidence of molecular or morphologic relapse in patients with *NPM1* mutation, thereby increasing the proportion of patients who are cured by first-line chemotherapy. Gemtuzumab ozogamycin may be another example in core binding factor (i.e; *RUNX1::RUNX1T1* or *CBFB::MYH11*) AML. In this subgroup, the gap between STFS (35% at 3 years) and OS (78% at 3 years) illustrates well the need for second line treatment and transplantation to achieve a cure. Consequently, STFS can be regarded as a relevant new evaluation criterion to make a more accurate analysis of the contribution of a specific drug.

We acknowledge that current treatments may change more frequently than in the past. Following induction chemotherapy, patients may switch between intensive and non-intensive treatment based on response and toxicity. The STFS should be viewed as a complementary endpoint assessing a first-line curative treatment without transplant, regardless of the intensity of consolidation therapy or the use of maintenance treatment. However, since molecular relapse is an adverse event, any treatment for this event should be considered salvage therapy.[32] It is therefore strongly recommended to describe the type of first event used to calculate the STFS in addition to the Kaplan-Meier curves in order to gain a complete understanding of the value of STFS, particularly in comparison to EFS. In addition, because the components of STFS differ

markedly in their clinical meaning, the distribution of individual first events and component-specific cumulative-incidence analyses separating planned allo-HSCT in first remission from relapse, treatment failure, and salvage therapy would further support interpretation and facilitate comparisons across treatment settings.

With a 5-year STFS of only 15%, this study highlights the pivotal role of allogeneic transplantation in the current management of AML, whether in first remission or beyond.[33,34] Therefore, effective drugs may also improve outcome through a treatment plan that incorporates transplantation by improving the rate of CR without MRD before transplant, reducing pre-transplant toxicity or providing maintenance therapy post-transplantation. In this case, endpoints such as OS, EFS and RFS but not STFS should be improved indicating that STFS evaluates the success of a transplant-free treatment strategy rather than providing an isolated measure of drug efficacy. Midostaurin exemplified this in our study. Another example is CPX-351, which, when followed by transplantation, has been shown to induce favorable outcomes.[35]

In conclusion, STFS could be a relevant endpoint that should complement other survival endpoints to accurately analyze the impact of new drugs in fit, transplant-eligible AML patients. First and foremost, this criterion should be most meaningful in favorable subgroups, such as in trials evaluating BCL-2 or menin inhibitors in combination with intensive chemotherapy. Improving STFS and OS in a clinical trial would clearly demonstrate a treatment's ability to achieve a cure without salvage or allogeneic transplantation in the first treatment line, as has been achieved with the ATO-ATRA combination in APL.

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Table 1. Patient Characteristics

Characteristics	**≤ 60 years**	**> 60 years**	**Total**
	N= 930 (47.3%)	N= 1036 (52.7%)	N= 1966 (100.0%)
Age (years)			
Median	50.4	68.1	61.80
IQR	39.2; 56.5	64.8; 72.0	50.9; 68.6
Min; Max	18.1;61.0	61.1;83.7	18.1;83.7
Age group (years), n (%)			
18-40	253 (27.2)	0 (0.0)	253 (12.9)
41-60	677 (72.8)	0 (0.0)	677 (34.4)
61-70	0 (0.0)	715 (69.0)	715 (36.4)
>70	0 (0.0)	321 (31.0)	321 (16.3)
Sex, n (%)			
Male	500 (53.8)	569 (54.9)	1069 (54.4)
Female	430 (46.2)	467 (45.1)	897 (45.6)
AML status, n (%)			
De novo	772 (83.0)	766 (73.9)	1538 (78.2)
Secondary	158 (17.0)	270 (26.1)	428 (21.8)
ECOG PS, n (%)			
0-1	737 (81.1)	812 (80.8)	1549 (80.9)
≥2	172 (18.9)	193 (19.2)	365 (19.1)
WBC (Giga/L)			
Median	10.9	6.9	8.6
IQR	3.0;41.6	2.4;38.9	2.6;40.5
Min; Max	0.4; 528.4	0.4; 386.0	0.4; 528.4
<30, n (%)	632 (68.5)	737 (71.6)	1369 (70.2)
>=30, n (%)	290 (31.5)	292 (28.4)	582 (29.8)
Cytogenetic risk, n (%)			
Favorable t(8; 21) or inv16/t(16; 16)	122 (13.1)	52 (5.0)	174 (8.9)
Intermediate	574 (61.7)	748 (72.2)	1322 (67.2)
Adverse	234 (25.2)	236 (22.8)	470 (23.9)
ELN 2017, n (%)			
Favorable	113 (22.5)	82 (16.9)	195 (19.8)
Intermediate	96 (19.1)	67 (13.8)	163 (16.5)
Adverse	294 (58.4)	335 (69.2)	629 (63.7)
Mutations, n (%)			
NPM1	260 (32.5)	270 (30.4)	530 (31.4)
FLT3-ITD	184 (22.9)	154 (17.3)	338 (20.0)
FLT3-TKD	47 (7.4)	47 (7.4)	94 (7.4)
CEBPA-bZIP	29 (4.8)	16 (2.8)	45 (3.8)
IDH1-R132	45 (7.2)	71 (10.3)	116 (8.8)
IDH2-R140	40 (6.4)	55 (8.1)	95 (7.3)
IDH2-R172	7 (1.1)	24 (3.5)	31 (2.4)
TP53	37 (7.7)	59 (12.3)	96 (10.0)
AFigure SL1	47 (8.3)	113 (18.7)	160 (13.7)
RUNX1	60 (10.8)	101 (19.4)	161 (15.0)
KMT2A-r	40 (4.3)	17 (1.6)	57 (2.9)
Midostaurin*, n (%)			
No	158 (72.8)	130 (66.3)	288 (69.7)
Yes	59 (27.2)	66 (33.7)	125 (30.3)
Allo-HSCT, n (%)			
In first CR			
All	398 (48.5)	163 (20.3)	561 (34.5)
ELN 2017 favorable	19 (17.8)	4 (5.3)	23 (12.6)
ELN 2017 intermediate	49 (55.1)	20 (35.7)	69 (47.6)
ELN 2017 adverse	187 (80.6)	76 (33.2)	263 (57.1)
After relapse			
All	178 (44.0)	66 (13.2)	244 (27.0)
ELN 2017 favorable	33 (75.0)	16 (34.0)	49 (53.9)
ELN 2017 intermediate	21 (41.2)	3 (9.7)	24 (29.3)
ELN 2017 adverse	26 (21.1)	17 (11.3)	43 (15.7)

Abbreviations: IQR, interquartile range; Min, minimum; Max, maximum; ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count; ELN, European LeukemiaNet; Allo-HSCT, allogeneic hematopoietic stem-cell transplantation.

* in patients with *FLT3* mutations.

Table 2. Outcome measures.

	All patients N=1966	**Age < 60 years N=930**	**Age≥ 60 years N=1036**	***RUNX1-RUNX1T1* or *CBFB-MYH11* N=174**	***CEBPA*^{bZIP} N=45**	***NPM1* N=530**	***FLT3*-ITD N=338**	***IDH1** N=86**	***IDH2*$^{\#}$ N=108**	***KMT2A*-R N=57**
OS										
Median, months (IQR)	30.6 (9.5-NR)	86.4 (13.8-NR)	20.5 (6.7-79.2)	NR (44.6-NR)	NR (NR-NR)	94.3 (13.4-NR)	25.1 (9.2-NR)	53.5 (17.3-NR)	47.6 (18.2-NR)	23.3 (9.5-92.4)
% (95% CI)										
1-year	69.9 (67.9-71.9)	78.5 (75.7-81.0)	62.3 (59.2-65.1)	94.3 (89.6-96.9)	93.3 (80.7-97.8)	77.2 (73.4-80.5)	66.9 (61.6-71.6)	87.2 (78.1-92.7)	83.3 (74.9-89.2)	68.4 (54.7-78.8)
3-year	47.5 (45.2-49.7)	59.3 (56.0-62.4)	36.8 (33.9-39.8)	77.5 (70.4-83.1)	84.4 (70.1-92.3)	59.6 (55.3-63.7)	45.6 (40.1-50.8)	54.0 (42.6-64.1)	53.9 (44.0-62.8)	38.6 (26.1-50.9)
5-year	40.4 (38.2-42.6)	54.0 (50.7-57.2)	28.1 (25.3-30.9)	73.6 (66.1-79.6)	76.6 (60.7-86.75	54.7 (50.1-58.9)	41.3 (36.0-46.6)	49.9 (38.5-60.2)	42.6 (32.9-51.9)	29.8 (18.6-41.9)
EFS										
Median, months (IQR)	15.3 (5.3-125.0)	25.6 (8.0-NR)	11.3 (3.8-40.0)	NR (12.5-NR)	NR (25.3-NR)	25.7 (7.0-NR)	11.6 (5.3-NR)	15.8 (7.4-60.9)	16.6 (8.2-70.4)	13.4 (6.3-47.7)
% (95% CI)										
1-year	55.6 (53.4-57.8)	64.1 (60.9-67.1)	48.1 (45.0-51.1)	77.0 (70.0-82.6)	82.2 (67.6-90.7)	64.2 (59.9-68.1)	49.7 (44.3-54.9)	61.6 (50.5-71.0)	64.8 (55.0-73.0)	56.1 (42.4-67.8)
3-year	35.8 (33.6-37.9)	46.5 (43.3-49.7)	26.1 (23.4-28.8)	57.2 (49.5-64.2)	68.5 (52.6-80.0)	46.9 (42.6-51.1)	34.8 (29.8-39.9)	33.7 (23.8-43.9)	36.2 (27.2-45.3)	29.8 (18.6-41.9)
5-years	31.4 (29.4-33.5)	42.4 (39.1-45.6)	21.5 (19.0-24.2)	56.6 (48.8-63.6)	65.9 (49.9-77.9)	42.4 (38.1-46.6)	32.0 (27.1-37.1)	28.0 (18.7-38.1)	27.6 (19.3-36.6)	24.6 (14.4-36.2)
RFS	**N=1625**	**N= 822**	**N= 803**	**N= 167**	**N=44**	**N= 476**	**N= 288**	**N= 77**	**N= 100**	**N= 52**
Median, months (IQR)	21.9 (7.4-NR)	48.1 (9.3-NR)	15.6 (5.7-76.7)	NR (11.2-NR)	NR (23.8-NR)	46.9 (8.4-NR)	16.0 (5.6-NR)	19.7 (8.6-NR)	17.3 (7.6-NR)	14.0 (5.9-61.1)
% (95% CI)										
1-year	62.6 (60.2-64.9)	68.5 (65.2-71.5)	56.5 (53.0-59.9)	72.5 (65.0-78.6)	81.8 (66.9-90.5)	68.1 (63.7-72.0)	55.2 (49.3-60.7)	63.4 (51.5-73.1)	61.0 (50.7-69.7)	51.9 (37.7-64.4)
3-year	42.6 (40.1-45.0)	52.1 (48.6-55.5)	32.7 (29.5-36.0)	59.1 (51.2-66.1)	70.0 (54.0-81.4)	51.8 (47.2-56.2)	40.2 (34.5-45.8)	37.5 (26.6-48.3)	39.3 (29.6-48.8)	32.7 (20.5-45.4)
5-year	37.6 (35.2-40.0)	47.5 (44.0-51.0)	27.4 (24.3-30.6)	58.4 (50.5-65.5)	67.4 (51.2-79.3)	47.0 (42.3-51.4)	37.2 (31.6-42.8)	27.3 (17.3-38.2)	29.9 (21.0-39.3)	26.9 (15.8-39.3)
STFS										
Median, months (IQR)	5.5 (2.3-16.1)	5.2 (2.7-14.9)	5.6 (1.9-18.2)	12.2 (7.1-NR)	NR (5.4-NR)	10.2 (4.6-106.9)	5.2 (2.6-10.1)	6.9 (3.3-15.4)	8.3 (3.3-20.1)	4.2 (3.2-6.5)
% (95% CI)										
1-year	30.0 (28.0-32.0)	27.7 (24.9-30.7)	32.0 (29.2-34.9)	51.6 (43.9-58.7)	60.0 (44.3-72.6)	47.0 (42.7-51.2)	21.3 (17.1-25.8)	32.6 (23.0-42.5)	40.7 (31.5-49.8)	17.5 (9.0-28.4)
3-year	16.9 (15.3-18.6)	18.2 (15.8-20.7)	15.7 (13.6-18.0)	35.2 (28.2-42.4)	50.9 (35.6-64.4)	32.3 (28.3-36.3)	12.1 (8.9-15.8)	12.8 (6.8-20.8)	20.4 (13.4-28.4)	8.8 (3.2-17.8)
5-year	14.6 (13.0-16.2)	16.6 (14.3-19.1)	12.7 (10.7-14.9)	35.2 (28.2-42.4)	50.9 (35.6-64.4)	27.8 (24.0-31.7)	10.5 (7.5-14.1)	10.2 (4.9-17.8)	17.3 (10.8-25.1)	3.5 (0.7-10.7)

Abbreviations: IQR, interquartile range; NR, not reached; CI, confidence interval; OS, overall survival; EFS, event-free survival; RFS: relapse-free survival; STFS, salvage-free, transplantation-free survival; KMT2A-r: KMT2A-rearrangement.

* *IDH1*R132 and wild type FLT3

*IDH2*R140 or *IDH2*R172 and wild type FLT3

Table 3. First occurring events of STFS.

	All patients N=1966	***RUNX1-RUNX1T1* or *CBFB-MYH11* N=174**	***CEBPA*^{bZIP} N=45**	***NPM1* N=530**	***FLT3*-ITD N=338**	***IDH1**** **N=86**	***IDH2*$^{\#}$ N=108**	***KMT2A*-R N=57**
No event, n (%)	260 (13.2)	58 (33.3)	23 (51.1)	137 (25.9)	35 (10.4)	9 (10.5)	17 (15.7)	2 (3.5)
Induction failure, n (%)	357 (18.2)	3 (1.7)	2 (4.4)	36 (6.8)	58 (17.2)	14 (16.3)	21 (19.4)	5 (8.8)
Allo-HSCT, n (%)	471 (24.0)	31 (17.8)	8 (17.8)	72 (13.6)	94 (27.8)	15 (17.4)	18 (16.7)	27 (47.4)
Relapse, n (%)	666 (33.9)	70 (40.2)	10 (22.2)	230 (43.4)	128 (37.9)	45 (52.3)	47 (43.5)	18 (31.6)
Death, n (%)	212 (10.8)	12 (6.9)	2 (4.4)	55 (10.4)	23 (6.8)	3 (3.5)	5 (4.6)	5 (8.8)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem-cell transplantation

* *IDH1*R132 and wild type FLT3

$^{\#}$ *IDH2*R140 or *IDH2*R172 and wild type FLT3

Table 4. First occurring events of STFS by treatment arm in the ALFA-0701 cohort.

	Control arm N=139	**GO arm N=139**	**All patients N=278**
No event, n (%)	24 (17.3)	48 (34.5)	72 (25.9)
Induction failure, n (%)	29 (20.9)	17 (12.2)	46 (16.6)
Allo-HSCT, n (%)	23 (16.6)	17 (12.2)	40 (14.4)
Relapse, n (%)	53 (38.1)	46 (33.1)	99 (35.6)
Death, n (%)	10 (7.2)	11 (7.9)	21 (7.6)

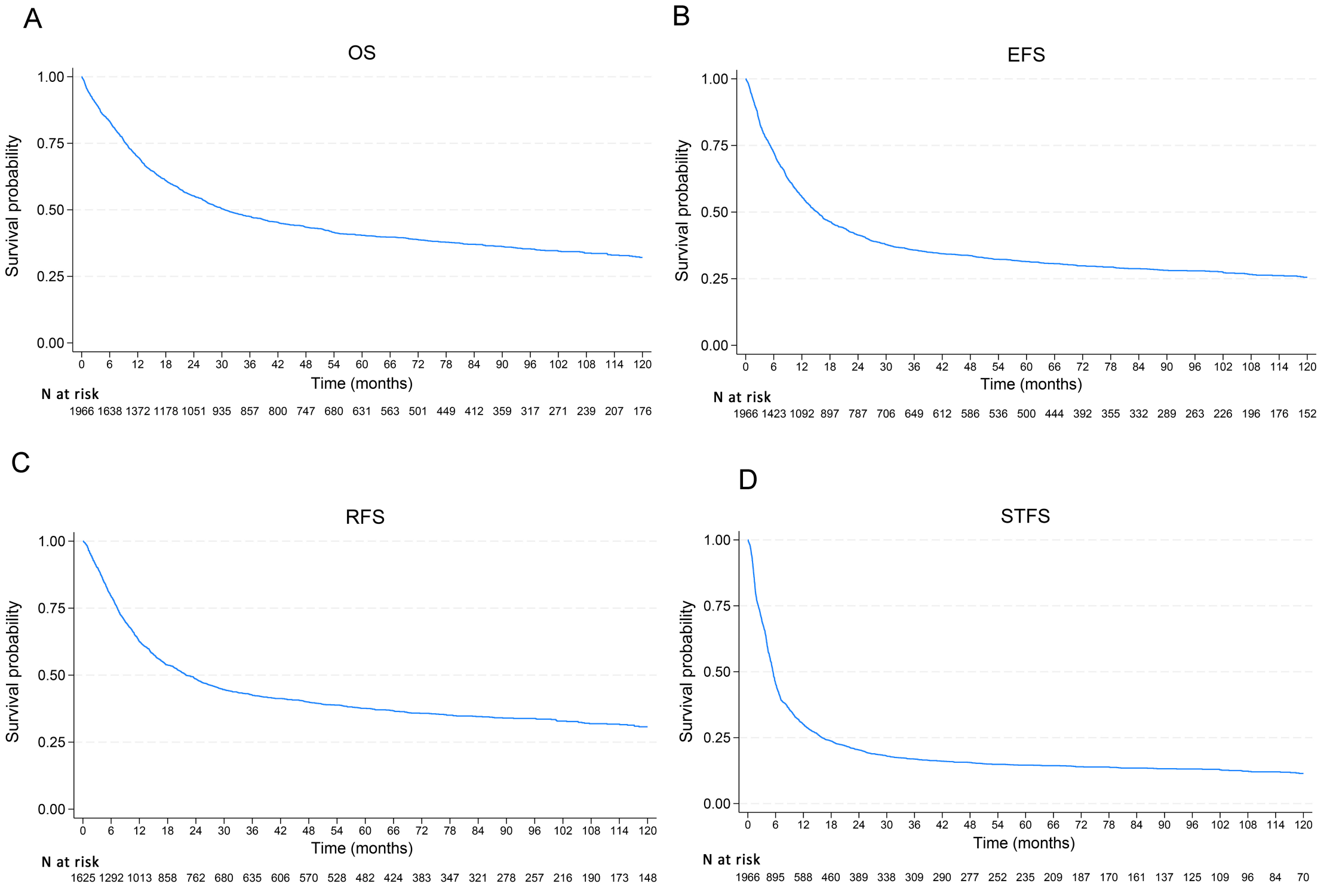
Abbreviations: Allo-HSCT, allogeneic hematopoietic stem-cell transplantation

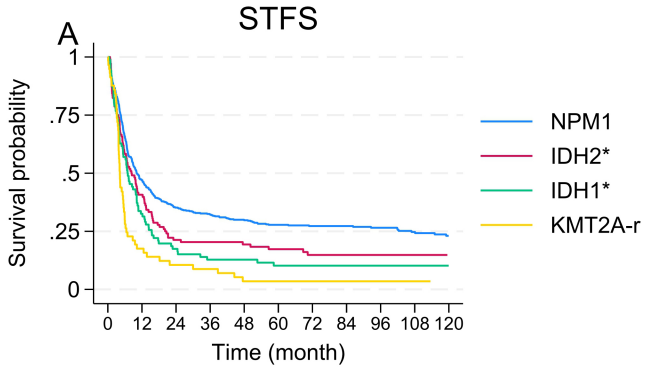
Figure Legends

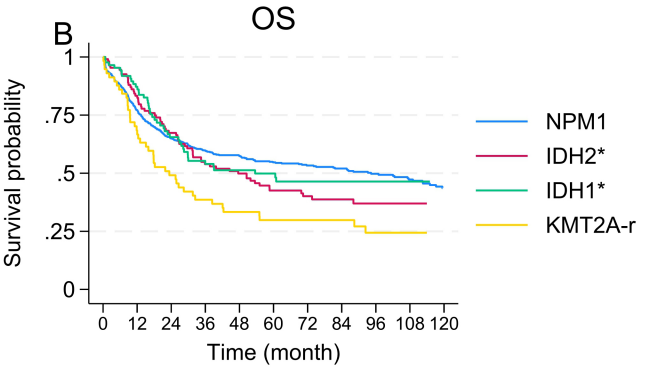
Figure 1: Kaplan-Meier curves for overall survival, event-free survival, relapse-free survival and salvage-free, transplantation-free survival. (A) OS, (B) EFS, (C) RFS, and (D) STFS. OS, overall survival; EFS, event-free survival; RFS, Relapse-free survival; STFS, survival-free, transplantation-free survival.

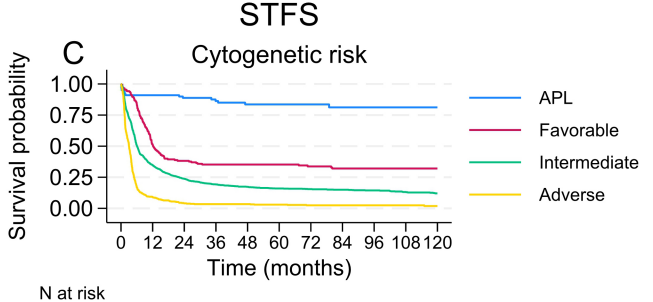
Figure 2: Kaplan-Meier curves for overall survival and salvage-free, transplantation-free survival by molecular subgroups and cytogenetic risk. (A) STFS and (B) OS by molecular subgroups. (C) STFS and (D) OS by cytogenetic subgroups.

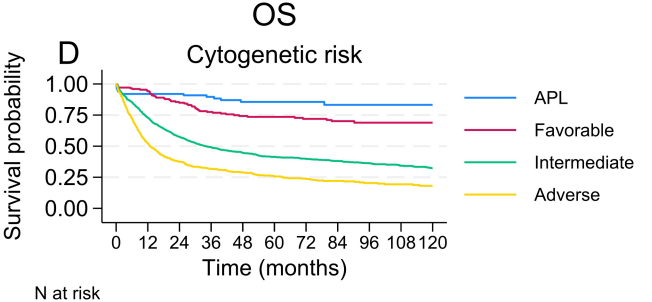
Figure 3: STFS by treatment arm (GO vs control) in the ALFA-0701 trial. In the GO arm, STFS was 46.5% (95% CI, 38.0-55.0), 38.1% (95% CI, 29.8-46.3) and 32.1% (24.1-40.5) at 12, 18 and 24 months. In the control arm, STFS was 31.3% (95% CI, 23.8-39.2), 19.6% (95% CI, 13.1-27.1) and 11.9% (6.4-19.3) at 12, 18 and 24 months

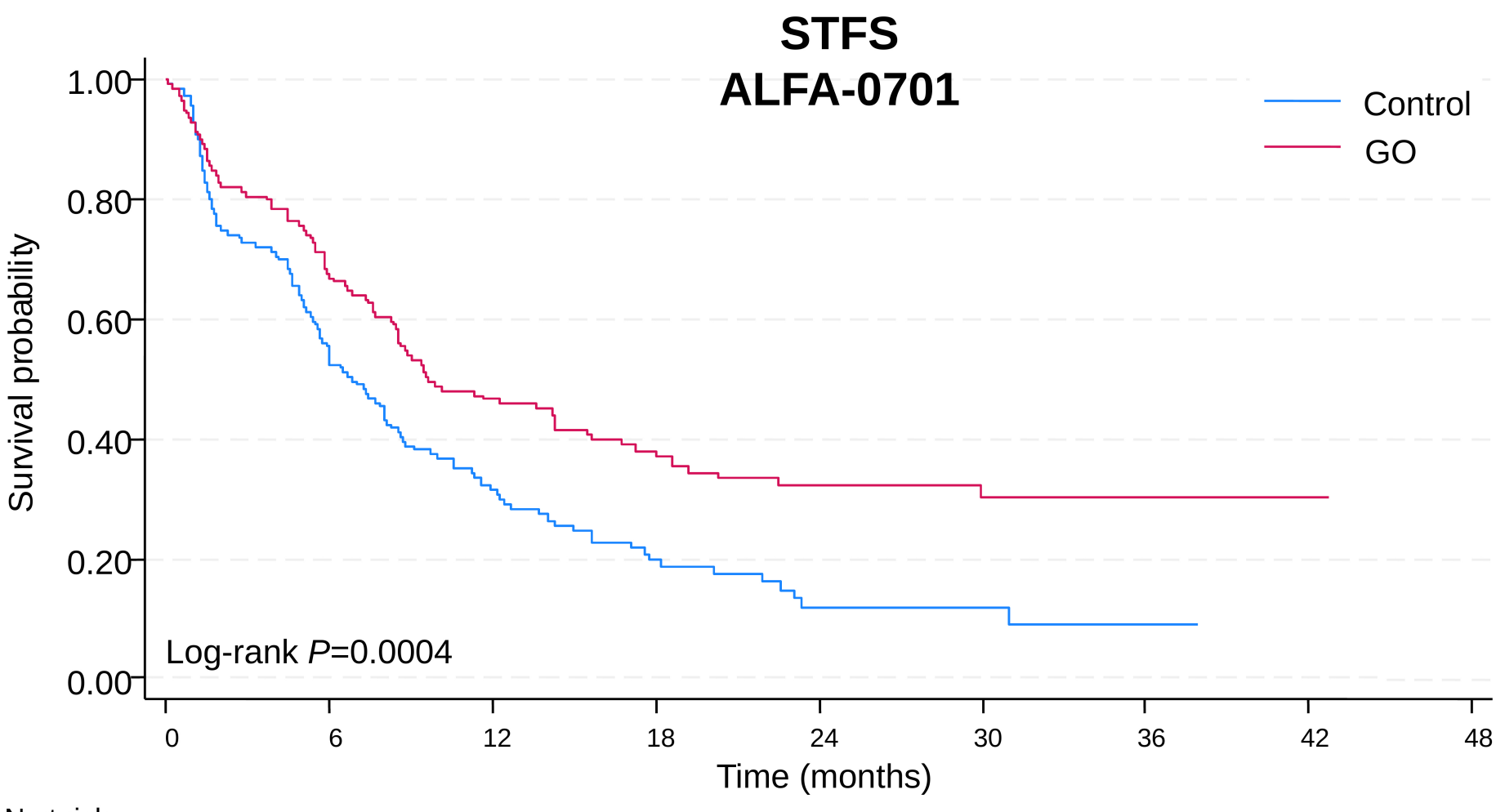

A
OS
Survival probability
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120
Time (months)
N at risk
1966 1638 1372 1178 1051 935 857 800 747 680 631 563 501 449 412 359 317 271 239 207 176
B
EFS
Survival probability
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120
Time (months)
N at risk
1966 1423 1092 897 787 706 649 612 586 536 500 444 392 355 332 289 263 226 196 176 152
C
RFS
Survival probability
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120
Time (months)
N at risk
1625 1292 1013 858 762 680 635 606 570 528 482 424 383 347 321 278 257 216 190 173 148
D
STFS
Survival probability
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120
Time (months)
N at risk
1966 895 588 460 389 338 309 290 277 252 235 209 187 170 161 137 125 109 96 84 70


A
STFS
Survival probability
1
.75
.5
.25
0
0 12 24 36 48 60 72 84 96 108 120
Time (month)
NPM1
IDH2*
IDH1*
KMT2A-r


B
OS
Survival probability
1
.75
.5
.25
0
0 12 24 36 48 60 72 84 96 108 120
Time (month)
NPM1
IDH2*
IDH1*
KMT2A-r


STFS
C
Cytogenetic risk
Survival probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96 108 120
Time (months)
APL
Favorable
Intermediate
Adverse
N at risk
APL 100 91 82 67 56 47 36 31 18 10 5
Favorable 174 89 64 58 57 50 43 38 28 22 19
Intermediate 1322 457 306 235 204 173 135 115 90 68 49
Adverse 470 42 19 16 16 12 9 8 7 6 2


OS
D
Cytogenetic risk
Survival probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96 108 120
Time (months)
APL
Favorable
Intermediate
Adverse
N at risk
APL 100 92 86 70 58 48 37 32 20 11 6
Favorable 174 163 143 122 111 97 87 69 54 42 30
Intermediate 1322 963 735 595 516 436 337 281 218 163 121
Adverse 470 246 173 140 120 98 77 62 45 34 25


STFS
ALFA-0701
Control
GO
Survival probability
1.00
0.80
0.60
0.40
0.20
0.00
Log-rank P=0.0004
0
6
12
18
24
30
36
42
48
Time (months)
N at risk
Control 139 77 41 19 8 4 1 0 0
GO 139 94 60 41 27 15 8 3 0

Supplemental data

Salvage-free, transplantation-free survival: a proposal for a new clinical endpoint in acute myeloid leukemia.

Christian Récher, Emilie Bérard, Suzanne Tavitian, Thibaut Leguay, Anne Huynh, Edouard Forcade, Anne Banos, Alban Canali, Emilie Klein, Audrey Bidet, Laëtitia Largeaud, Véronique De Mas, Audrey Sarry, Madeline Mougenot, Anne-Charlotte de Grande, Karine Celli-Lebras, Cécile Pautas, Claude Gardin, Xavier Thomas, Thorsten Braun, Régis Peffault De Latour, Hervé Dombret, Stéphane De Botton, Arnaud Pigneux, Sarah Bertoli and Pierre-Yves Dumas

Content

Patients and Methods

Supplemental Table 1. Impact of co-mutations on STFS.

Supplemental Table 2. STFS and OS in patients with *FLT3* mutations treated with or without midostaurin.

Supplemental Table 3. Baseline Characteristics of APL patients.

Supplemental Table 4: Patient characteristics in the ALFA cohorts**.**

Supplemental Table 5. Outcome measures (ALFA cohort).

Supplemental Table 6. First occurring events of STFS in the ALFA cohort.

Supplemental Figure 1. STFS of patients with b-ZIP in frame *CEBPA* mutations.

Supplemental Figure 2. STFS in *NPM1* mutated patients by *FLT3*-ITD co-mutations.

Supplemental Figure 3. STFS in *IDH1* mutated patients by *NPM1* mutational status.

Supplemental Figure 4. STFS in *IDH2* mutated patients by *NPM1* mutational status.

Supplemental Figure 5: STFS and OS in *FLT3* mutated patients treated with or without midostaurin.

Supplemental Figure 6: OS, EFS, RFS, and STFS in the ALFA cohort.

Supplemental Figure 7: ALFA cohort. A. STFS in *NPM1* mutated patients. B. STFS in *NPM1* mutated patients with or without *FLT3*-ITD. C. STFS in *FLT3*-ITD patients.

Patients and Methods

Post-remission therapy was adapted based on the risk of relapse and whether an HLA-identical donor had been identified or not. Younger patients received up to three cycles of intermediate (1.5 g/m²/12h, three days) or high-dose cytarabine (3 g/m²/12h, three days). Patients over 60 received up to six cycles of idarubicin (8 mg/m²/day; IV) on day 1 and cytarabine (50 mg/m²/12h/day) subcutaneously on days 1–5. Non-favorable risk patients with an HLA-matched donor underwent allo-HSCT, whereas those without such a donor or those who declined transplantation received chemotherapy. APL patients with white blood cell count (WBC) <10 G/L received the standard arsenic trioxide (ATO) + all-trans retinoic acid (ATRA) regimen whereas idarubicin was added to ATO-ATRA in those with WBC>10 G/L.[1,2]

1. Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). *Blood*. 2012;120(8):1570-1580; quiz 1752.

2. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med*. 2013;369(2):111-121.

Supplemental Table 1. Impact of co-mutations on STFS.

	***NPM1*^{mut} N=528**		***IDH1** N=86**		***IDH2*$^{\#}$ N=108**	
STFS	**No *FLT3*-ITD N=307**	***FLT3*-ITD N=221**	***NPM1*^{mut} N=32**	***NPM1*^{wt} N=54**	***NPM1*^{mut} N=29**	***NPM1*^{wt} N=79**
Median, months (IQR)	22.0 (6.5-NR)	6.0 (3.9-14.3)	12.9 (6.6-35.0)	4.1 (2.1-10.2)	16.0 (9.4-NR)	5.6 (2.2-15.5)
% (95% CI)						
1-year	61.6 (55.9-66.7)	27.2 (21.5-33.1)	56.3 (37.6-71.3)	18.5 (9.5-29.8)	65.5 (45.4-79.7)	31.7 (21.8-42.0)
3-year	43.4 (37.7-48.8)	17.2 (12.5-22.4)	25.0 (11.8-40.7)	5.6 (1.5-13.9)	37.9 (20.9-54.9)	13.9 (7.4-22.5)
5-year	37.0 (31.5-42.5)	15.2 (10.9-20.3)	21.4 (9.2-36.9)	3.7 (0.7-1.1)	30.4 (14.9-47.4)	12.5 (6.4-20.9)

Abbreviations: IQR, interquartile range; NR, not reached; CI, confidence interval

* *IDH1*R132 and wild type *FLT3*

$^{\#}$ *IDH2*R140 or *IDH2*R172 and wild type *FLT3*

Supplemental Table 2. STFS and OS in patients with *FLT3* mutations treated with or without midostaurin.

	Patients with *FLT3* mutations N=413	
	No midostaurin N=288	**Midostaurin N=125**
STFS		
Median, months (IQR)	5.4 (2.7-11.6)	5.3 (2.1-11.3)
% (95% CI)		
1-year	24.7 (19.8-29.6)	24.0 (16.9-31.8)
3-year	13.9 (10.2-18.2)	13.5 (8.2-20.1)
5-year	11.4 (8.1-15.4)	11.6 (6.7-18.0)
OS		
Median, months (IQR)	23.7 (9.1-NR)	47.0 (11.3-NR)
% (95% CI)		
1-year	65.6 (59.8-70.8)	72.8 (64.1-79.7)
3-year	44.4 (38.6-50.0)	52.9 (43.6-61.3)
5-year	40.3 (34.6-45.9)	47.8 (38.5-56.5)

Abbreviations: IQR, interquartile range; NR, not reached; CI, confidence interval

Supplemental Table 3. Baseline Characteristics of APL patients.

	≤ 60 years	**> 60 years**	**Total**
	N= 67 (67.0%)	N= 33 (33.0%)	N= 100 (100.0%)
Age (years)			
Median	40.8	72.7	53.1
IQR	30.3;53.3	69.02;78.1	35.19;68.85
Min; Max	20.0;60.4	61.0;84.6	20.0;84.6
Age group (years), n (%)			
18-40	34 (50.7)	0 (0.0)	34 (34.0)
41-60	33 (49.3)	0 (0.0)	33 (33.0)
61-70	0 (0.0)	12 (36.4)	12 (12.0)
>70	0 (0.0)	21 (63.6)	21 (21.0)
Sex, n (%)			
Male	30 (44.8)	21 (63.6)	51 (51.0)
Female	37 (55.2)	12 (36.4)	49 (49.0)
AML status, n (%)			
De novo	60 (89.6)	25 (75.8)	85 (85.0)
Secondary	7 (10.4)	8 (24.2)	15 (15.0)
ECOG PS, n (%)			
0-1	52 (81.2)	22 (66.7)	74 (76.3)
2-3-4	12 (18.8)	11 (33.3)	23 (23.7)
WBC (Giga/L)			
Median	2.00	1.99	2.00
IQR	1.13;5.19	1.17;7.24	1.13;5.80
Min; Max	0.29;97.30	0.30;45.50	0.29;97.30
<10, n (%)	58 (86.6)	26 (78.8)	84 (84.0)
≥10, n (%)	9 (13.4)	7 (21.2)	16 (16.0)

Abbreviations: IQR, interquartile range ; Min, minimum ; Max, maximum ; ECOG PS, Eastern Cooperative Oncology Group performance status. WBC, white blood cell count.

Supplemental Table 4: Patient characteristics in the ALFA cohorts**.**

Characteristics	**≤ 60 years**	**> 60 years**	**Total**
	N= 713 (58.3%)	N= 509 (41.7%)	N= 1222 (100.0%)
Age (years)			
Median	46.00	67.80	56.00
IQR	38.0; 54.0	64.6; 71.9	44.0; 66.6
Min;Max	18.0; 60.0	60.1; 85.2	18.0; 85.2
Age group (years), n (%)			
18-40	245 (34.4)	0 (0.0)	245 (20.0)
41-60	468 (65.6)	0 (0.0)	468 (38.3)
61-70	0 (0.0)	357 (70.1)	357 (29.2)
>70	0 (0.0)	152 (29.9)	152 (12.4)
Sex, n (%)			
Female	322 (45.2)	220 (43.2)	542 (44.4)
Male	391 (54.8)	289 (56.8)	680 (55.6)
AML status, n (%)			
De novo	713 (100.0)	421 (82.7)	1134 (92.8)
Secondary	0 (0.0)	88 (17.3)	88 (7.2)
ECOG PS, n (%)			
0-1	636 (90.2)	0 (0.0)	636 (52.4)
≥2	69 (9.8)	0 (0.0)	69 (5.7)
NA	0 (0.0)	509 (100.0)	509 (41.9)
WBC (Giga/L)			
Median	7.90	4.90	7.00
IQR	2.4; 31.8	2.0; 26.1	2.20; 29.5
Min;Max	0.3;16500.0	0.3; 546.6	0.3;16500.0
WBC (Giga/L), n (%)			
<30	524 (73.5)	395 (77.6)	919 (75.2)
≥30	189 (26.5)	114 (22.4)	303 (24.8)
Cytogenetic risk, n (%)			
Favorable	0 (0.0)	15 (3.2)	15 (1.3)
Intermediate	521 (77.6)	365 (78.8)	886 (78.1)
Adverse	150 (22.4)	83 (17.9)	233 (20.5)
ELN 2010, n (%)			
Favorable	162 (24.1)	15 (3.2)	177 (15.5)
Intermediate	372 (55.4)	370 (78.7)	742 (65.0)
Adverse	137 (20.4)	85 (18.1)	222 (19.5)
Mutations, n (%)			
NPM1	229 (34.3)	122 (26.3)	351 (31.0)
FLT3-ITD	150 (22.5)	84 (17.9)	234 (20.6)
FLT3-TKD	48 (7.3)	6 (1.3)	54 (4.8)
IDH1-R132	45 (7.2)	NA	45 (4.0)
IDH2	76 (12.2)	NA	76 (6.7)
KMT2A-r	7 (1.0)	6 (1.2)	13 (1.1)
CR/CRi (1 or 2 cycles), n (%)			
No	97 (13.6)	132 (25.9)	229 (18.7)
Yes	616 (86.4)	377 (74.1)	993 (81.3)
Early deaths, n (%)			
Day 30	19 (2.7)	34 (6.7)	53 (4.3)
Day 60	27 (3.8)	48 (9.4)	75 (6.1)
Allo-HSCT, n (%)			
In first CR	305 (49.5)	97 (25.7)	402 (40.5)
At relapse	82 (39.0)	21 (10.4)	103 (25.0)

Abbreviations: IQR, interquartile range; Min, minimum; Max, maximum ; ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count ; ELN, European

LeukemiaNet; NA, not available; CR, complete remission; CRi, CR with incomplete hematologic recovery; Allo-HSCT, allogeneic hematopoietic stem-cell transplantation.

Supplemental Table 5. Outcome measures (ALFA cohort).

	All patients	Age < 60 years	Age≥ 60 years	*NPM1*	*FLT3*-ITD
OS	**N=1222**	**N=713**	**N=509**	**N=351**	**N=234**
Median, months (IQR)	49.7 (11.5-NR)	NR (15.5-NR)	20.7 (7.6-49.7)	NR (14.8-NR)	21.8 (9.1-21.8)
% (95% CI)					
1-year	73.6 (71.1-76.0)	80.8 (77.7-83.5)	63.4 (59.0-67.5)	78.5 (73.8-82.4)	67.7 (61.2-73.3)
3-year	52.5 (49.5-55.4)	62.4 (58.7-65.8)	32.5 (27.2-38.0)	64.6 (59.2-69.5)	42.1 (35.4-48.6)
5-year	48.3 (45.0-51.5)	58.0 (54.0-61.7)	-	62.4 (56.7-67.5)	38.4 (31.3-45.6)
EFS	**N=1221**	**N=712**	**N=509**	**N=351**	**N=234**
Median, months (IQR)	16.3 (5.1-NR)	35.9 (7.4-NR)	9.5 (1.7-26.4)	70.7 (8.8-NR)	9.4 (4.5-NR)
% (95% CI)					
1-year	56.5 (53.7-59.2)	65.8 (62.2-69.2)	43.2 (38.8-47.5)	69.9 (64.8-74.4)	45.0 (38.5-51.3)
3-year	39.2 (36.3-42.0)	49.3 (46.2-53.6)	20.7 (16.6-25.2)	53.8 (48.3-59.0)	32.3 (26.3-38.5)
5-years	35.9 (32.9-38.9)	46.4 (42.4-50.2)	-	51.4 (45.7-56.7)	30.1 (24.0-36.4)
RFS	**N=992**	**N=615**	**N=377**	**N=320**	**N=186**
Median, months (IQR)	28.8 (8.3-NR)	NR (10.7-NR)	13.7 (6.7-38.7)	NR (11.1-NR)	25.2 (6.4-NR)
% (95% CI)					
1-year	65.8 (62.7-68.7)	72.5 (68.8-75.8)	54.3 (49.0-59.3)	72.1 (66.8-76.7)	58.9 (49.3-67.2)
3-year	48.1 (44.8-51.3)	57.6 (53.6-61.5)	28.0 (22.5-33.7)	59.1 (53.4-64.4)	47.7 (38.2-56.5)
5-year	43.8 (40.2-47.3)	53.2 (48.8-57.4)	-	56.4 (50.4-62.0)	44.5 (34.7-53.8)
STFS*	**N=1220**	**N=711**	**N=509**	**N=351**	**N=234**
Median, months (IQR)	5.6 (3.1-18.7)	5.7 (3.7-27.7)	5.3 (1.4-13.7)	12.2 (4.6-NR)	4.9 (3.4-7.3)
% (95% CI)					
1-year	30.9 (28.3-33.5)	32.4 (29.0-35.9)	28.6 (24.7-32.6)	50.5 (45.1-55.6)	15.5 (11.2-20.5)
3-year	19.1 (16.9-21.4)	23.4 (20.4-26.6)	11.2 (8.2-14.7)	37.8 (32.6-43.0)	8.5 (5.2-12.7)
5-year	17.2 (14.9-19.7)	21.6 (18.5-24.8)	-	35.9 (30.6-41.1)	7.7 (4.2-11.8)

Abbreviations: IQR, interquartile range; NR, not reached; CI, confidence interval; OS, overall survival; EFS, event-free survival; RFS: relapse-free survival; STFS, salvage-free, transplantation-free survival.

*STFS was calculated from 1220 patients because of missing data in relapse event (n=1) or date of salvage (n=1).

Supplemental Table 6. First occurring events of STFS in the ALFA cohort.

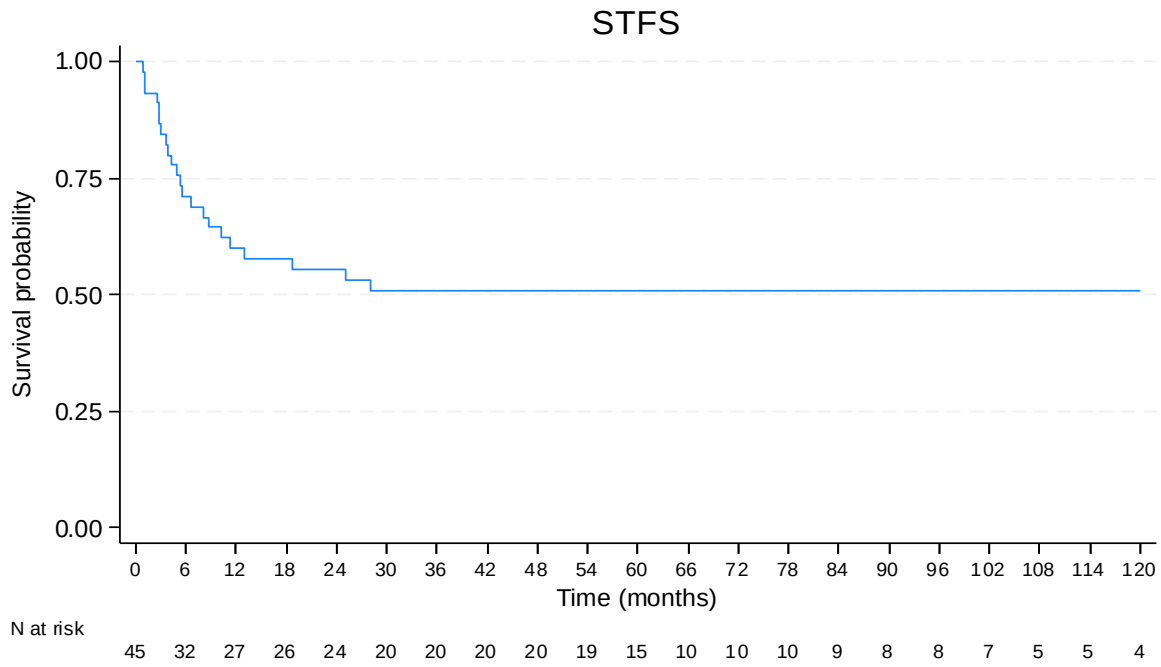
	All patients N=1220	***NPM1* N=351**	***FLT3*-ITD N=234**	***IDH1**** **N=30**	***IDH2*[#] N=54**
No event, n (%)	240 (19.7)	131 (37.3)	22 (9.4)	9 (30.0)	13 (24.1)
Induction failure, n (%)	223 (18.3)	22 (6.3)	39 (16.7)	5 (16.7)	8 (14.8)
Allo-HSCT, n (%)	369 (30.3)	87 (24.8)	94 (40.2)	9 (30.0)	17 (31.5)
Relapse, n (%)	292 (23.9)	86 (24.5)	60 (25.6)	5 (16.7)	15 (27.8)
Death, n (%)	96 (7.9)	25 (7.1)	19 (8.1)	2 (6.7)	1 (1.9)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem-cell transplantation

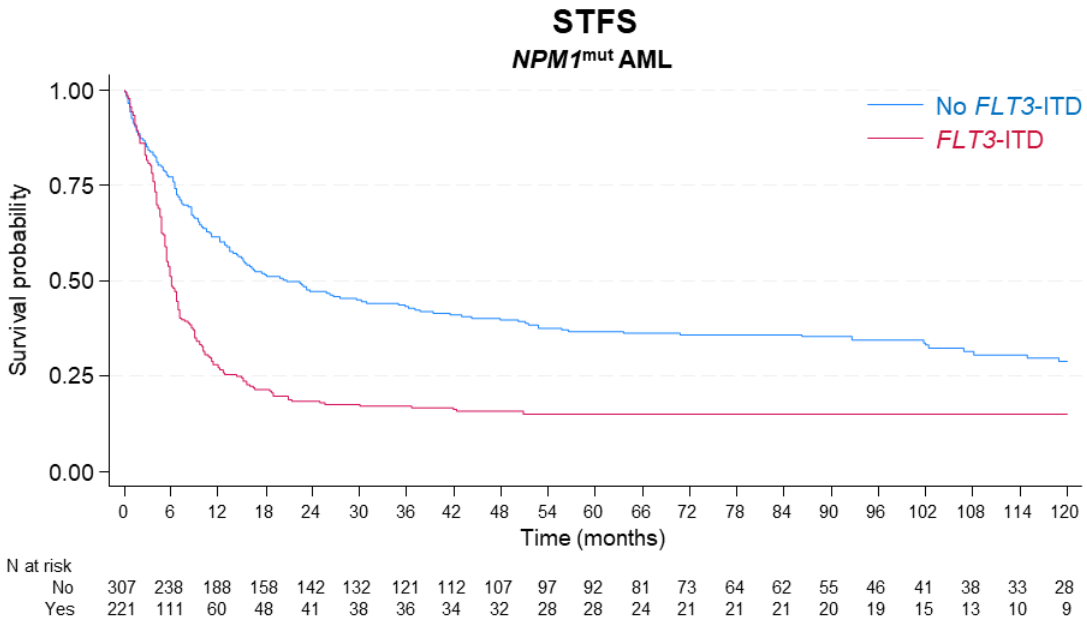
* *IDH1*R132 and wild type FLT3

[#] *IDH2*R140 or *IDH2*R172 and wild type FLT3

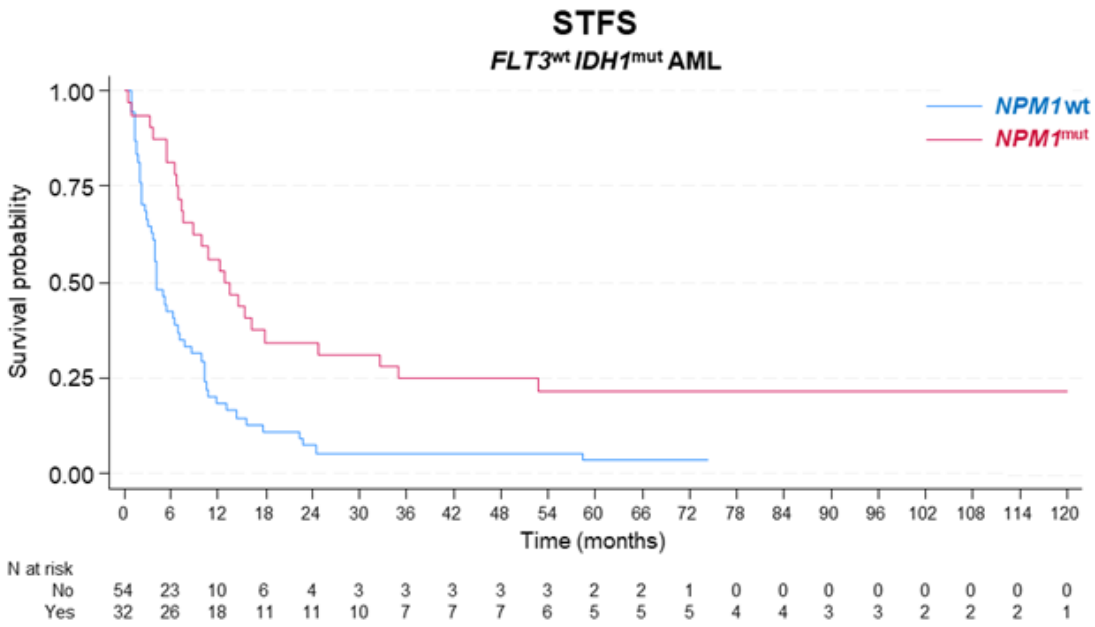
Supplemental Figure 1. STFS of patients with b-ZIP in frame *CEBPA* mutations.



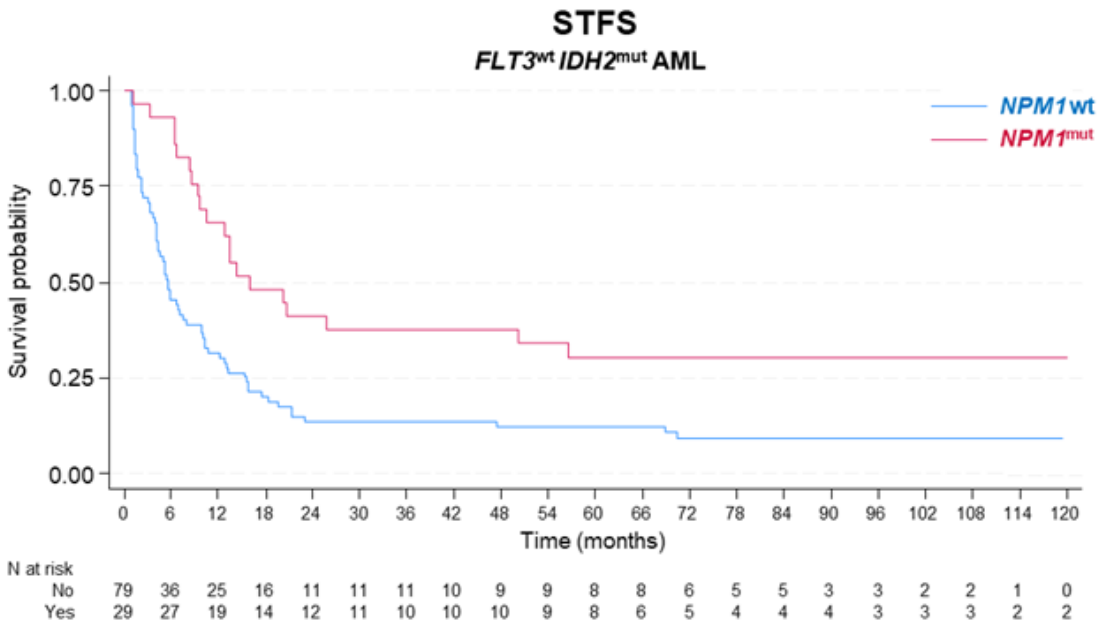
Supplemental Figure 2. STFS in *NPM1* mutated patients by *FLT3*-ITD co-mutations.



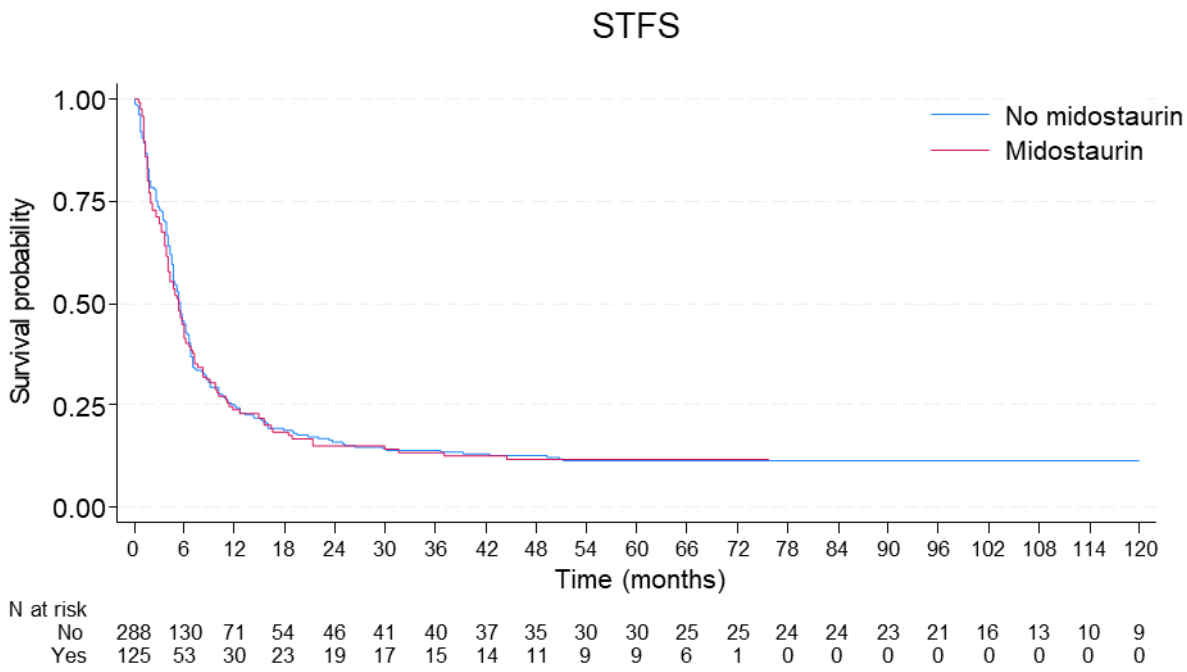
Supplemental Figure 3. STFS in *IDH1* mutated patients by *NPM1* mutational status.

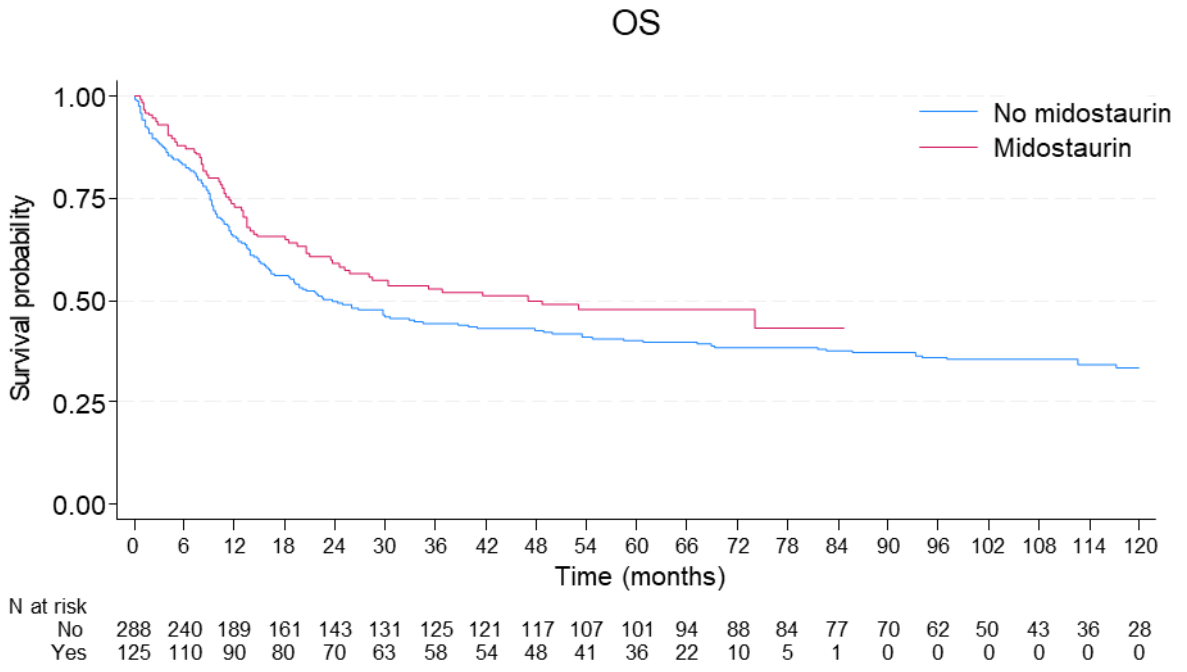


Supplemental Figure 4. STFS in *IDH2* mutated patients by *NPM1* mutational status.

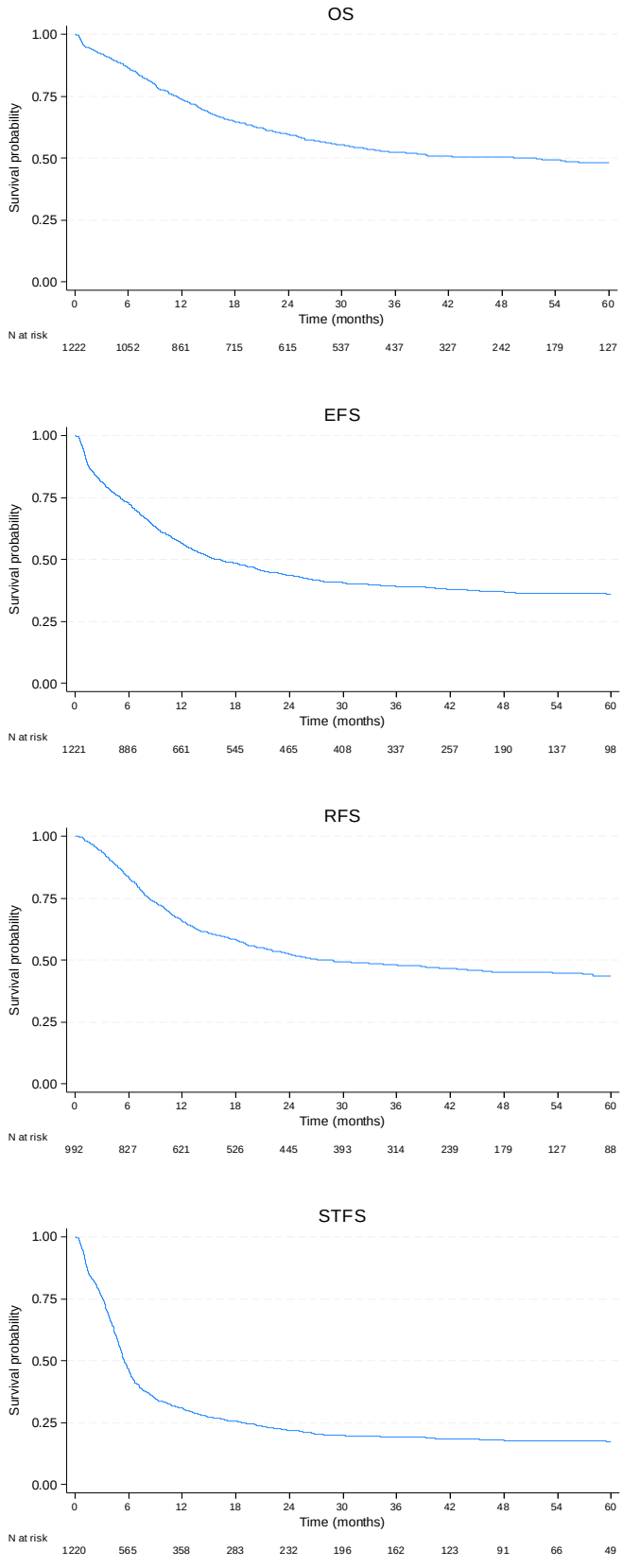


Supplemental Figure 5: STFS and OS in *FLT3* mutated patients treated with or without midostaurin.





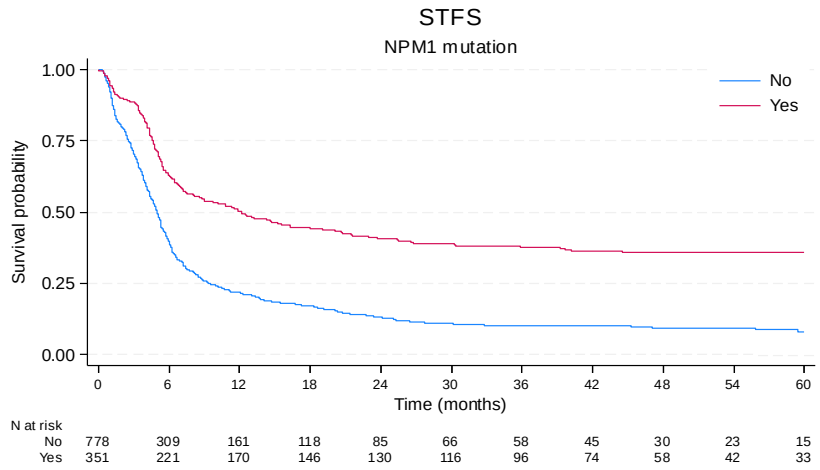
Supplemental Figure 6: OS, EFS, RFS, and STFS in the ALFA cohort.



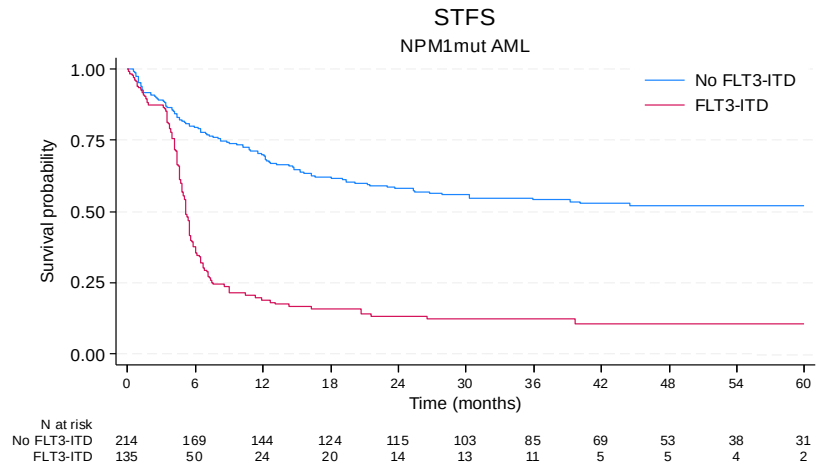
Supplemental Figure 7: ALFA cohort.

A. STFS in *NPM1* mutated patients. B. STFS in *NPM1* mutated patients with or without *FLT3*-ITD. C. STFS in *FLT3*-ITD patients.

A.



B.



C.

