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2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

GIMEMA AML1310 TRIAL OF RISK-ADAPTED, MRD-DIRECTED THERAPY FOR YOUNG ADULTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

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Adriano Venditti (Fondazione Policlinico Tor Vergata, Italy) Alfonso Piciocchi (GIMEMA Foundation, Italy) Anna Candoni (Division of Hematology, University of Udine, Italy) Lorella Melillo (IRCCS Casa Sollievo Sofferenza, Italy) Valeria Calafiore (AOU Poloclinico-Vittorio Emanuele - Department of Hematology, Italy) Roberto Cairoli (ASST Grande Ospedale Metropolitano Niguarda, Italy) Paolo de Fabritiis (UNIVERSITY TOR VERGATA, Italy) Gabriella Storti (AORN ' San G. Moscati ' Avellinoo, Italy) Prassede Salutari (ospedale civile pescara, Italy) Francesco Lanza (HEMATOLOGY INSTITUTE, Italy) Giovanni Martinelli (Inst. of Hematology and Medical Oncology Seragnoli, Italy) Mario Luppi (UNIMORE, Italy) Patrizio Mazza (hematology, Italy) Maria Paola Martelli (Hematology, University of Perugia, Italy) Antonio Cuneo (University of Ferrara, Italy) Francesco Albano (University of Bari, Italy) Francesco Fabbiano (ospedali riuniti Villa sofia-Cervello, Italy) Agostino Tafuri (Sant'Andrea University Hospital, Italy) Anna Chierichini (San Giovanni-Addolorata Hospital, Italy) Alessia Tieghi (Azienda Unità Sanitaria Locale -IRCCS di Reggio Emilia, Italy) Nicola Fracchiolla (Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico di Milano, Italy) Debora Capelli (Clinica Ematologia, Ospedali Riuniti di Ancona, Italy) Robin Foà (Division of Hematology, University, Italy) Caterina Alati (G.O.M. Bianchi Melcarino Morelli U.O. Hematology, Italy) Edoardo La Sala (Trial Office Gimema Foundation, Italy) Paola Fazi (GIMEMA DATA CENTER, Italy) Marco Vignetti ("Sapienza" University, Italy) Luca Maurillo (Fondazione Policlinico Tor Vergata, Italy) Francesco Buccisano (Tor Vergata University of Rome, Italy) Maria Ilaria Del Principe (FONDAZIONE POLICLINICO TOR VERGATA, Italy) Maria Irno-Consalvo (Hematology, University Tor Vergata, Roma, Italy) Tiziana Ottone (Università di Tor Vergata, Roma, Italy) Serena Lavorgna (Università Tor Vergata Roma, Italy) Maria Teresa Voso (Universita' di Roma Tor Vergata, Italy) Francesco Lo Coco (University Tor Vergata, Italy) William Arcese (Fondazione Policlinico Tor Vergata, Italy) Sergio Amadori (Fondazione Gimema Onlus, Italy)

Abstract:
We designed a trial in which post-remission therapy of young patients with de novo AML was decided combining cytogenetics/genetics and post-consolidation levels of minimal residual disease (MRD). After induction and consolidation, favorable-risk patients (FR) were to receive autologous stem cell transplant (AuSCT) and poor-risk patients (PR) allogeneic stem cell transplant (ASCT). Intermediate-risk patients (IR) were to receive AuSCT or ASCT depending on the post-consolidation levels of MRD. ASCT was to be delivered whatever the source of stem cells. Three hundred-61/500 patients (72%) achieved a CR, 342/361 completed the consolidation phase and were treatment allocated: 165 (48%) to ASCT (122 PR, 43 IR MRD-positive) plus 23 rescued after salvage therapy, for a total of 188 candidates; 150 (44%) to AuSCT (115 FR, 35 IR MRD-negative) plus 27 IR patients (8%) with no leukemia-associated phenotype, for a total of 177 candidates. Overall, 110/177 (62%) and 130/188 (71%) AuSCT or ASCT candidates received it, respectively. Two-year overall (OS) and disease-free survival (DFS) of the whole series was 56% and 54%, respectively. Two-year OS and DFS were 74% and 61% in the FR category, 42% and 45% in the PR category, 79% and 61% in the IR MRD-negative category, 70% and 67% in the IR MRD-positive category. In conclusion, AuSCT may still have a role in FR and IR MRD-negative categories. In the IR MRD-positive category, ASCT prolongs OS and DFS to equal those of the FR category. Using all the available sources of stem cells, ASCT was delivered to 71% of the candidates.

Conflict of interest: COI declared - see note

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In memory of Francesco Lo Coco, a dear friend and a valuable colleague

GIMEMA AML1310 TRIAL OF RISK-ADAPTED, MRD-DIRECTED THERAPY FOR YOUNG ADULTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

Running Title: Risk-adapted, MRD-driven therapy for AML

Adriano Venditti[1,25], Alfonso Piciocchi[2], Anna Candoni[3], Lorella Melillo[4], Valeria Calafiore[5], Roberto Cairoli[6], Paolo de Fabritiis[7], Gabriella Storti[8], Prassede Salutari[9], Francesco Lanza[10], Giovanni Martinelli[11,26], Mario Luppi[12], Patrizio Mazza[13], Maria Paola Martelli[14], Antonio Cuneo[15], Francesco Albano[16], Francesco Fabbiano[17], Agostino Tafuri[18], Anna Chierichini[19], Alessia Tieghi[20], Nicola Stefano Fracchiolla[21], Debora Capelli[22], Robin Foà[23], Caterina Alati[24], Edoardo La Sala[2], Paola Fazi[2], Marco Vignetti[2], Luca Maurillo[25], Francesco Buccisano[1,25], Maria Ilaria Del Principe[1,25], Maria Irno Consalvo[1], Tiziana Ottone[1], Serena Lavorgna[1], Maria Teresa Voso[1,25], Francesco Lo Coco[1,25], William Arcese[1,25] , Sergio Amadori[2]

[1]Hematology, Department of Biomedicine and Prevention, University Tor Vergata, Roma, [2]GIMEMA Foundation, Roma, [3]Hematology, Azienda Sanitaria Universitaria Integrata di Udine, Udine, [4]Fondazione IRCCS Casa Sollievo della Sofferenza, UO di Ematologia, San Giovanni Rotondo (FG) Italy, [5]Ospedale Ferrarotto, Catania, [6]Ospedale Niguarda Ca Granda, Milano, [7]Ospedale S.Eugenio, Roma, [8]Azienda Ospedaliera S.G.Moscati, Avellino, [9]Azienda USL di Pescara, Pescara, [10]Ospedale S.Maria delle Croci, Ravenna, [11]Istituto Tumori della Romagna (IRST), Meldola, [12]Università degli Studi di Modena e Reggio Emilia, Modena, [13]A.O. SS Annunziata - P.O. S.G. Moscati, Taranto, [14]Ospedale S.Maria della Misericordia, Perugia, [15]Azienda Ospedaliero Universitaria Arcispedale Sant'Anna, Ferrara, [16]Universita' degli Studi di Bari Aldo Moro, Bari, [17]Ospedali Riuniti Villa Sofia-Cervello, Palermo, [18]Azienda Ospedaliera Sant' Andrea, [19]San Giovanni Addolorata, Roma, [20]S.C. Ematologia AUSL-IRCCS Reggio Emilia, [21]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, [22]Ospedali Riuniti Umberto I G.M. LANCISI, Ancona, [23]Universita' degli Studi Sapienza, Roma, [24]A.O.Bianchi-Melacrino-Morelli, Reggio Calabria, [25]Fondazione Policlinico Tor Vergata, Roma, [26]Policlinico S. Orsola - Malpighi, Bologna.

Corresponding Author:
Adriano Venditti
Address: Fondazione Policlinico Tor Vergata, Viale Oxford 81 – 00133, Rome, Italy
e-mail address: adriano.venditti@uniroma2.it
phone: +39 06 20903226
fax: +39 06 20903212

Key Points

1. A risk-adapted, MRD-driven transplant strategy is a feasible approach for the treatment of younger adults with AML.
2. Pre-transplant MRD positivity should not be a contraindication to the delivery of allogenic stem cell transplant in younger adults with AML.

Abstracts

We designed a trial in which post-remission therapy of young patients with *de novo* AML was decided combining cytogenetics/genetics and post-consolidation levels of minimal residual disease (MRD). After induction and consolidation, favorable-risk patients (FR) were to receive autologous stem cell transplant (AuSCT) and poor-risk patients (PR) allogeneic stem cell transplant (AlloSCT). Intermediate-risk patients (IR) were to receive AuSCT or AlloSCT depending on the post-consolidation levels of MRD. AlloSCT was to be delivered whatever the source of stem cells. Three hundred-61/500 patients (72%) achieved a CR, 342/361 completed the consolidation phase and were treatment allocated: 165 (48%) to AlloSCT (122 PR, 43 IR MRD-positive) plus 23 rescued after salvage therapy, for a total of 188 candidates; 150 (44%) to AuSCT (115 FR, 35 IR MRD-negative) plus 27 IR patients (8%) with no leukemia-associated phenotype, for a total of 177 candidates. Overall, 110/177 (62%) and 130/188 (71%) AuSCT or AlloSCT candidates received it, respectively. Two-year overall (OS) and disease-free survival (DFS) of the whole series was 56% and 54%, respectively. Two-year OS and DFS were 74% and 61% in the FR category, 42% and 45% in the PR category, 79% and 61% in the IR MRD-negative category, 70% and 67% in the IR MRD-positive category. In conclusion, AuSCT may still have a role in FR and IR MRD-negative categories. In the IR MRD-positive category, AlloSCT prolongs OS and DFS to equal those of the FR category. Using all the available sources of stem cells, AlloSCT was delivered to 71% of the candidates. EudraCT number (2010-023809-36); ClinicalTrials.Gov Identifier (NCT01452646).

Introduction

In spite of the continuously growing knowledge about the genetic and molecular landscape of acute myeloid leukemia (AML),[1–6] the paradigm of treatment for young adults with AML is still largely based on the "*one size fits all*" approach, with post-remission strategies still depending on donor-availability rather than on the actual risk of disease relapse.[7] In the short term, this has led to satisfactory rates of complete remission (CR) (70-80%) but in the long term survival estimates are still disappointing, with less than 30-40% of patients becoming long-term survivors.[8,9]

Indeed, dealing with the high propensity for relapse and the considerable genetic heterogeneity of AML requires either development of new agents or adoption of modern, risk-adapted therapeutic programs. Risk-adapted approaches may consist in integrating pre-treatment prognosticators, such as cytogenetics and molecular genetics, with post-treatment parameters, such as assessment of minimal (or measurable) residual disease (MRD).[10]

Even though in AML cytogenetic is a historical and robust determinant of outcome, the modern stratification of the patients in "favorable-" "intermediate-" or "adverse-risk" categories relies ever more increasingly on the baseline molecular pattern.[11,12] Based on this, favorable-risk patients achieve OS and DFS rates of 50-60% at 3-5 years with standard chemotherapy while those with adverse-risk show OS and DFS rates of 5-20% at 3-5 years if not submitted to allogeneic stem cell transplantation (AlloSCT).[7,11,13] Therefore, it appears that in favorable- and adverse-risk patients the sole genetic/cytogenetic profile, regardless of the MRD levels, is helpful enough to guide decisions for the delivery of AlloSCT in the post-remission phase. On the other hand, there are no accepted criteria to direct the decision-making process after consolidation for patients in the intermediate-risk category: for these patients, evaluation of the MRD status appears appropriate to extrapolate those at high (MRD positive) or low (MRD negative) risk of relapse, for whom differentiated treatments may be adopted.

Although MRD assessment in AML is prognostic[14–18] still less than 50% of relapses are detected by MRD, thus the false negative rate is still high resulting in low specificity. Moreover, MRD is assessed exploiting disparate flow cytometry or molecular protocols so that its use for treatment decisions in AML is still at an early stage. Depending on the technical platforms and targets, a sensitivity of 10^{-3} to 10^{-6} is reported.[19]. In particular, we observed that the integrated evaluation of baseline prognosticators and MRD improves risk-assessment and helps optimizing post-remission therapy.[20] In fact, directing MRD-positive patients towards intensified therapy like AlloSCT while sparing those MRD-negative the procedure-related morbidity and mortality, may be highly beneficial in terms of toxicity minimization.[10]

Considering all the above, the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) Foundation has developed a risk-adapted, MRD oriented, prospective clinical trial, the strategy of which consisted in the prognostic integration of pre-treatment cytogenetics and genetics with post-consolidation MRD, as detected by multiparametric flow-cytometry (MFC). Based on this strategy, patients were to receive a post-consolidation autologous stem cell transplantation (AuSCT) or AlloSCT respectively, depending on their risk profile. We report here the final analysis of this multicenter study.

Patients and Methods

Patients

Previously untreated patients with a diagnosis of *de novo* AML according to the WHO diagnostic criteria[21] were recruited to the GIMEMA AML1310 Study (*EudraCT number 2010-023809-36; ClinicalTrials. Gov Identifier NCT01452646*) provided they met the criteria for eligibility (see supplemental material). The study was approved by the ethics committees of the participating Hospitals/Academic Institutions and was conducted in accordance with the Declaration of Helsinki. All participants gave their informed consent.

Study Design

The main objective of the study was to verify whether the delivery of a post remission therapy, the intensity of which was risk-driven, improved the outcome of adult patients with AML in terms of increased anti-leukemic efficacy. The primary endpoint of the study was overall survival (OS) at 24 months from treatment start, for comparative purposes we included a historical control consisting of patients recruited to the previous LAM99P GIMEMA trial.[1] Secondary endpoints were complete remission (CR) or CR incomplete (CRi) rate after induction, disease free survival (DFS) and cumulative incidence of relapse (CIR) from CR. Upfront evaluation included bone marrow (BM) aspirate for morphology, cytogenetics, molecular genetics and MFC analysis. The baseline MFC assessment was a necessary step, not only for diagnostic purposes, but also to identify leukemia associated immunophenotypes (LAIP). Identification of baseline LAIPs was the essential requirement for monitoring MRD after therapy; at the established time-point, BM MRD was determined by a high-sensitivity 8–color MFC assay. Based on several retrospective validations in the context of former EORTC/GIMEMA protocols,[22] the threshold for discriminating MRD negative from MRD positive cases was set at $3.5x10^{-4}$ residual leukemic cells and the selected time-point was the post-consolidation phase, once the hematologic recovery was complete. Patients were studied at diagnosis for the presence of RUNX1-RUNX1T1 or CBFβ/MYH11 rearrangements, defining core binding factor (CBF) leukemias, and for NPM1, FLT3 and c-KIT mutations. In CBF or NPM1 positive AML, MRD was investigated as reported elsewhere.[14,23,24] Molecular analysis, LAIPs assessment and post-consolidation MRD determinations were centralized at Laboratorio di Diagnostica Integrata Oncoematologica "OPPO", at Tor Vergata University Hospital of Rome, whereas conventional karyotype was carried out at local institutions. Response to treatment was assessed on BM and peripheral blood, according to the recommendations of an international working group.[25] Patients who did not achieve CR/CRi or PR after the first induction course or CR/CRi after two induction courses were considered as treatment failures. The AML1310 trial was designed at a time when ELN 2010/2017 and NCCN 2018 recommendations were not yet published. Therefore, when the trial regulatory path was concluded, we started recruiting and stratifying patients according to contemporary classification, that was the NCCN 2009 version 1.[26] For the purpose of our study, 4 categories of risk were identified (Table 1): favorable- (NCCN-FR) or poor-risk (NCCN-PR) patients, who were submitted to AuSCT or AlloSCT respectively; intermediate-MRD negative (NCCN-IR-Neg) or positive (NCCN-IR-Pos) patients, who were to receive AuSCT or AlloSCT, respectively. Moreover, we enucleated a fifth group of patients belonging to the intermediate-risk category, in whom we failed to identify any LAIP (NCCN-IR-no-

LAIP category); these patients were allocated to the AuSCT post-consolidation option. AlloSCT and AuSCT were to be performed within three months of the end of the consolidation course.

Treatment

Induction consisted of i.v. daunorubicin 50 mg/m^2 daily on days 1,3 and 5; i.v. etoposide 50 mg/m^2 daily on days 1 to 5; i.v. cytarabine 100 mg/m^2 as a daily continuous infusion, days 1 to 10. All pts in CR/CRi, after one-two induction cycles received one consolidation course consisting of i.v. daunorubicin 50 mg/m^2 daily on days 4,·5 and 6 and i.v. cytarabine 500 mg/m^2 every 12 hours on days 1 to 6. In patients belonging to NCCN-FR and NCCN-IR categories, peripheral blood stem cell collection was attempted by initiating, on day 20 from the start of consolidation therapy, G-CSF until completion of stem cell collection. In the case of failure to collect a sufficient number of peripheral blood stem cells, BM was used as a source. In the case of poor BM harvest, instead of AuSCT, patients were to receive a second consolidation course with high dose cytarabine (HDARAC). Post-consolidation therapy was based on risk-allocation: NCCN-FR patients were to receive AuSCT; NCCN-PR patients were to receive AlloSCT; NCCN-IR patients were to receive AuSCT or AlloSCT depending on the levels of BM MRD as measured by MFC, after consolidation therapy. Allocation to AlloSCT required the procedure to be performed whatever the source of stem cells (HLA-identical sibling, HLA-identical unrelated donor, cord blood, HLA-haploidentical sibling). Salvage therapy consisted of one or two courses of i.v fludarabine 30 mg/m^2 daily, on days 1-5; cytarabine 2000 mg/m^2 daily, on days 1-5; idarubicin 8 mg/m^2 daily, on days 1-3. Whatever the original NCCN risk category of assignment, patients with resistant disease after 1-2 cycles of induction therapy were considered poor-risk and allocated to the AlloSCT procedure once CR/CRi was achieved.

Statistical analysis and sample size calculation

The primary objective was the percentage of OS at two years. An estimated number of 213 subjects was initially required to accomplish this primary objective. This sample size was to achieve a 90% power to detect a difference of 10% between the null hypothesis that OS at two years is 50% and the alternative hypothesis that OS is 60%, using a Single-Stage Phase II design with a 5% significance level (based on data of the historic control group GIMEMA LAM99P).[1] Based on the historical control group, we also considered that approximately 70% of the observed patients would have been classified as IR, therefore allowing to reach the figure of 150 patients available for MRD driven treatment allocation. However, after 173 subjects were enrolled, only 56 belonged to the IR category (32% vs 70% expected). Therefore, to reach the target of 150 subjects belonging to the IR category, an amendment to the protocol was adopted in 2013 and the sample size was adjusted to 515 subjects to recruit. The efficacy analysis was performed as per treatment received, including individuals who commenced induction therapy and censoring patients at the time when they received a non-assigned treatment. OS (time elapsed from treatment start to death) and DFS (time from CR to relapse or death in remission) were calculated using the Kaplan-Meier product limit estimator. Differences in terms of OS and DFS were evaluated by means of Log-Rank test in univariate analysis and by means of Cox regression model in multivariate analysis, after assessment of proportionality of hazards. All variables with a p-value less than 0.15 in univariate analysis were considered into the multivariate models. The influence of the transplant (AuSCT and AlloSCT) on the survival outcome was evaluated in the Cox

model by means of a time-dependent covariate. Cumulative incidence of relapse (CIR) was estimated by cumulative incidence curves using the proper non-parametric method. Patients' and disease characteristics were summarized by means of cross-tabulations for categorical variables or by quintiles for continuous variables. Differences between categorical variables or response rates in subgroups were tested by the chi-squared or Fisher exact tests, as appropriate. Confidence intervals were calculated at 95% level and all tests were two-sided, accepting $p \leq 0{\cdot}05$ as indicating a statistically significant difference. All analyses were performed using the SAS (version 9.4) and R (R Foundation for Statistical Computing, Vienna, Austria) system software. Study data were collected and managed using the REDCap20 electronic data capture tools hosted at GIMEMA Foundation.

Data Sharing Statement

Individual participant data will not be shared.

Results

Between January 2012 and May 2015, 515 patients with de novo AML, seen at 55 GIMEMA institutions, were registered to the trial. Fifteen patients did not commence induction because of pre-therapy death, infections or ineligibility, 500 started treatment and were available for the analysis. Demographic characteristics are summarized in Table 2 and 3. Median age was 49 (18-60.9) years and 52% were males. For 429 evaluable patients, cytogenetic distribution was favorable, intermediate and poor in 11%, 73% and 16% respectively. Among 500 cases, RUNX1/RUNX1T1 was detected in 27 (5%) with 12 (44%) also c-KIT mutated; CBFβ/MYH11 was positive in 37 (7%) with 4 (11%) also c-KIT mutated; FLT3-ITD and NPM1 mutations were detected in 46 (9%) and in 107 (21%) respectively. Finally, concomitant mutations of NPM1 and FLT3-ITD were observed in 80 cases (16%). We found no instances of FLT3 mutations in CBF positive AML. Based on this data, patients' distribution within the risk-categories was as follows: 138 (28%) were NCCN-FR, 127 (25%) NCCN-IR, 47 (9%) NCCN-IR-no-LAIP, 188 (38%) NCCN-PR. Patients' disposition is illustrated in Figure 1. After the first induction cycle, 333 (67%) and 21 (4%) patients achieved a CR and CRi, respectively. A second induction course was delivered to 10 of 13 patients in PR, with seven entering CR. Therefore, after one-two cycles of induction 361 (72%) patients obtained a CR: 88% in the NCCN-FR category, 65% and 69% in the NCCN-IR and NCCN-PR category respectively ($p<0{\cdot}001$). Eighty-four (17%) patients had a refractory AML and 63 of them received a salvage therapy; 23 of these 63 (37%) achieved a CR. Three-hundred-42/361 (95%) patients started the consolidation phase and were treatment allocated: 177 (52%) to AuSCT [115 (65%) NCCN-FR, 35 (20%) NCCN-IR-Neg, 27 (15%) NCCN-IR-no-LAIP] and 165 (48%) to AlloSCT [122 (74%) NCCN-PR, 43 (26%) NCCN-IR-Pos]. Of the 177 AuSCT candidates, 110 (62%) were transplanted [78 (71%) NCCN-FR, 20 (18%) NCCN-IR-Neg, 12 (11%) NCCN-IR-no-LAIP]. Of the 165 AlloSCT candidates, 110 (67%) were transplanted [78 (71%) NCCN-PR, 32 (29%) NCCN-IR-Pos]. If we include also the 23 patients who achieved a CR after salvage therapy, the group of AlloSCT candidates enlarges to 188. Since 20 of these 23 patients were given AlloSCT, the number of AlloSCT candidates who received it was 130/188 (71%). For the 78 patients belonging to the NCCN-PR category, the source of stem cells was a HLA-identical sibling in 26, a HLA-identical unrelated donor in 34, umbilical cord blood in 1 and HLA-haploidentical sibling in 17; for the 32 belonging to the NCCN-IR-Pos category, the source of stem cells was a HLA-identical sibling in 12, a HLA-identical unrelated donor in 9, umbilical cord blood in 1 and HLA-haploidentical sibling in 10. By physicians' decision, one patient belonging to NCCN-PR category received AuSCT and one belonging to NCCN-FR category received AlloSCT.

Overall survival, Disease Free Survival and Cumulative Incidence of Relapse

OS and DFS rates at 24 months of our historical control were 49% (95%CI 47-52) and 55% (95% CI 52-59), respectively.[1] In the present trial, after a median follow-up of 28.8 months, 2-year OS was 56% (95% CI 52-61) with a median duration of 38 months (Figure 2) and DFS was 54% (95% CI 49-60) with a median duration of 32.4 months (Figure 2). The estimated OS at 24 months of 56% was less

than the alternative hypothesis of 60%. However, the upper value of 95% confidence interval included also the alternative hypothesis of 60% 2-year survival. Therefore, we considered the trial as not conclusive with regards to the primary endpoint. CIR, considering death in CR as a competing risk, was 33% (95% CI 28-38) (Figure 2). When splitting the survival analysis according to the identified categories of risk, 2-year OS was 42% (95% CI 36-50) for NCCN-PR patients, 58% (95% CI 50-68) for NCCN-IR patients, 74% (95% CI 67-82) for NCCN-FR patients and 50% (95% CI 37-67) for NCCN-IR-no LAIP patients (p <0.0001) (Figure 3). Two-year DFS was 45% (95% CI 37-55) for NCCN-PR patients, 61% (95% CI 52-73) for NCCN-IR patients, 61% (95% CI 52-71) for NCCN-FR patients and 48% (95% CI 33-70) for those belonging to the NCCN-IR-no LAIP category (p= 0·026) (Figure 3). Using this risk-adapted approach, DFS duration of NCCN-FR and NCCN-IR was superimposable whereas the NCCN-IR-no LAIP one was the shortest. When we focused on the NCCN-IR patients, whose post-consolidation choice was MRD-driven, no significant differences were observed in terms of 2-year OS between those MRD negative [79% (95% CI 66-94)] and MRD positive [70% (95% CI 57-86)] (p=0·713) (Figure 4). The same was observed regarding the 2-year DFS [MRD negative = 61% (95% CI 47-80); MRD positive = 67% (95% CI 53-83)] (p=0·773) (Figure 4). The multivariate analysis confirmed the independent role of risk category in affecting CR rate, duration of OS and DFS. The transplant procedure (AuSCT plus AlloSCT), analyzed as a time-dependent variable, affected independently duration of OS. Age affected independently duration of OS and DFS whereas WBCc achievement of CR (Table 2S).

MFC and molecular integrated evaluation of MRD

As an ancillary activity of the protocol, of 251 patients whose AML was characterized by the presence of a molecular marker useful for MRD assessment, we received 112 BM samples (RUNX-RUNX1=9, CBFB-MYH11=9 and NPM1=94) at the post-consolidation time-point. In 60 of these, we had the opportunity to combine the post-consolidation results of MFC and RT-qPCR MRD studies. This integrated analysis identified 4 categories of patients: double negative (MFCneg/PCRneg), double positive (MFCpos/PCRpos) and single positive (MFCpos/PCRneg or MFCneg/PCRpos). Patients who were double negative had a 2-year OS and DFS of 89% (95% CI 71-100) and 69% (95% CI 44-100), respectively. Patients who were MFCpos/PCRneg had a 2-year OS and DFS of 88% (95% CI 73-100) and 76% (95% CI 58-100), respectively. Patients who were MFCneg/PCRpos had a 2-year OS and DFS of 87% (95% CI 72-100) and 65% (95% CI 45-92), respectively. Finally, patients who were double positive had a 2-year OS and DFS of 55% (95% CI 34-87) and 22% (95% CI 9-58), respectively (Figure 5 A and B, p=0.037 and 0.003, respectively)).

AuSCT versus HDARAC consolidation

As per protocol, 19 patients (18 NCCN-FR and 1 NCCN-IR) received HDARAC, since they did not have enough stem cells collected. Figure 6 shows OS and DFS of these patients compared to those who were submitted to AuSCT. OS was 83% (95% CI 67-100) and 85% (95% CI 78-93), respectively (p=0.753); DFS was 68% (95% CI 50-93) and 63% (95% CI 54-73), respectively (p=0.595). Of these 19 patients, 15 were NCCN-FR MFCneg/PCRneg, MFCpos/PCRneg or MFCneg/PCRpos, 3 NCCN-FR MFCpos/PCRpos and 1 was NCCN-IR MRD negative.

Discussion

The role of molecular and cytogenetic abnormalities in predicting response to therapy and survival in patients with AML has been extensively documented.[24-26] Indeed, genetic/cytogenetic abnormalities are powerful prognosticators, so that obtaining information about their presence is essential for an optimal decision-making process. The clinical implication is that, based on their genetic status, patients would benefit from more or less aggressive post-consolidation strategy such as AuSCT and AlloSCT or, in a more modern vision, from targeted new agents. However, prognostic models barely based on pre-treatment covariates such as genetic status, have a limited predictive ability.[11,29] This highlights the need not only to expand further our knowledge about the genetic and molecular pattern of AML but also highlights the potential role of "factors after diagnosis" such as MRD monitoring. Therefore, integrating baseline factors and monitoring of MRD appears a promising tool to refine and possibly customize our outcome prediction ability in AML. This philosophy was at the basis of the GIMEMA AML1310 protocol in which, deviating from the classical "*one size fits all*" approach, we applied a risk-adapted and MRD-driven approach. AlloSCT is generally recommended when the risk of relapse exceeds 35%-40% if the procedure is not performed.[7,10] In this view, NCCN-PR category represents a priority and, in these patients, AlloSCT should be performed as soon as CR is achieved. However, a HLA-identical sibling is available for less than 30% of the patients[30] and, in reality, even less than 30% receive it, due to disease recurrence.[11] In our study, utilization of any available source of stem cells resulted in 71% of AlloSCT candidates receiving it. Adoption of this strategy also translated in a 2-year OS and DFS of 42% and 45% respectively for the NCCN-PR category (Figure 2). Such figures compare very favorably with the two-year OS and DFS of 20%-30% currently reported for this category.[27,29] Based on our study design, patients belonging to the NCCN-FR category were given AuSCT as a post-consolidation therapy. The role of AuSCT is controversial; in one randomized study it provided better DFS and similar OS as conventional consolidation chemotherapy.[32] In our NCCN-FR category, 2-year OS and DFS were 74% and 61% respectively (Figure 3). We believe there is still a role for AuSCT; indeed, this option has the advantage of sparing patients multiple courses of post-consolidation chemotherapy (usually high/intermediate dose cytarabine). In fact, the recently revised ELN classification suggests that limiting AuSCT to MRD negative AML might improve the results.[11] Based on our limited experience, high dose cytarabine might represent the choice for patients with very "high quality" CR such as those NCCN-FR MFCneg/PCRneg (Figure 6). Management of patients belonging to the NCCN-IR category is still controversial. For these patients, the relapse rate after AuSCT can be as high as 50%-55%,[10] so that this option appears as a suboptimal approach. Indeed, AlloSCT is recommended for patients within this category. However, in selected patients with MRD negative-CR there might still be a room for AuSCT.[10] In the present study, we planned AlloSCT or AuSCT for NCCN-IR patients, based on the level of MRD after the post-consolidation course. By making this choice, we observed that the two-year OS and DFS were 58% and 61% respectively (Figure 3). This figure compares very favorably with recent analyses showing, for these patients, a 2-year OS and DFS of approximately 35% and 50%.[27,29] Using this strategy, we also noted that the 2-year DFS of NCCN-IR patients was prolonged to equal that of NCCN-FR patients (Figure 3). Finally, within the NCCN-IR category, we focused on outcome as influenced by the post-consolidation MRD status. By delivering AuSCT to NCCR-IR-Neg and AlloSCT to NCCN-IR-Pos patients, we observed

no difference in terms of 2-year OS or DFS (Figure 4). The stratification role of MRD determination in intermediate-risk patients has been recently suggested in a prospective survey of the NCRI-AML17 trial.[33] According to the authors, a MRD positive finding helps selecting patients who can benefit from AlloSCT. An indirect confirmation of the importance of MRD determination in intermediate-risk category was that our 47 NCCN-IR-no-LAIP patients who were submitted to AuSCT had the shortest duration of 2-year OS and DFS (Figure 2). A reasonable explanation is that these patients harbored significant post-chemotherapeutic levels of MRD, meaning that AlloSCT would have been the most appropriate choice. Our results highlight the potent anti-leukemic effect exerted by AlloSCT in NCCN-IR-Pos patients and the minimization of toxicity after AuSCT in NCCN-IR-Neg ones. This interpretation can be extended to include the overall population we had under investigation; indeed, generating the maximum anti-leukemic effort in high-risk patients (NCCN-PR + NCCN-IR-Pos) and preserving from excess of toxicity those who are at low-risk (NCCN-FR + NCCN-IR-Neg) appears a very plausible goal. In this view, the integration of different techniques for MRD monitoring may offer the chance to improve even further our capability to discriminate prognostically discrete subsets of patients, directing treatment more precisely. Combining MFC and RT-qPCR for cases carrying a molecular signature, we demonstrated that double positive patients had the worst prognosis. For these patients, a front-line intensified program appears a reasonable option (Figure 5). Although there is evidence that AlloSCT is not able to reverse the unfavorable long-term impact of MRD positivity,[34–37] we believe that a pre-transplant MRD positive status should not be a contraindication for performing it.[38–40] In the study by Walter and Araki, patients who were MRD positive before the transplant had an outcome comparable to the one of patients with active disease. However, these studies were retrospective, the patient population was heterogeneous in terms of age, conditioning regimens received and there was a concentration of adverse karyotype and secondary AML in the group of MRD positive patients. Our experience takes advantage of a prospective and homogeneous context in terms of therapy delivered and risk-stratification. A recent, retrospective analysis of 547 patients enrolled in HOVON/SAKK protocols indicates that, although all categories benefit from AlloSCT, the absolute benefit was greater in pre-transplant MRD positive than MRD negative patients.[41] Our present experience adds a piece of information favoring the use of AlloSCT in MRD positive patients, and future trials should possibly explore the prognostic role of different levels of pre-transplant MRD[38] and the value of post-transplant maintenance.

In conclusion, we recognize that the study suffers from some intrinsic limitations due to the changes occurring over the time (more modern biologic knowledge, new AML classifications and an ever more frequent MRD monitoring) that make the historical control and the study population not fully superimposable. However, this is one of the first attempts to apply a prospective program of risk-adapted, MRD-driven therapy, integrating upfront genetics and post-consolidation MRD status, in AML of adults. In the NCCN-FR category, AuSCT guarantees the same survival expectation as multiple courses of cytarabine. In the NCCN-IR category, AlloSCT can be avoided if MRD is not measurable; if MRD is positive, AlloSCT can prolong OS and raise the DFS duration to the level of NCCN-FR patients. Finally, using all the available sources of stem cells, allowed AlloSCT to be delivered to a large proportion of the candidates, emphasizing the feasibility of the trial transplant policy.

Authors' contribution

This study was conducted thanks to the partial contribution of the Associazione italiana contro le leucemie-linfomi e mieloma (AIL).

Conception and design: AV, AP, PF, MV, FLC, WA, SA.

Provision of study materials or patients: AV, ACa, LMe, VC, RC, PdF, GS, PS, FL, GM, ML, PM, MPM, ACu, FA, FF, ATa, ACh, ATi, NSF, DC, RF, CA, LMa, FB, MIDP, WA, SA.

Collection and assembly of data: AV, AP, ACa, LMe, VC, RC, PdF, GS, PS, FL, GM, ML, PM, MPM, ACu, FA, FF, ATa, ACh, ATi, NSF, DC, RF, CA, ELS, LMa, FB, MIDP, MIC, TO, SL, MTV.

Data analysis and interpretation: AV, AP, ELS, LMa, FB, MIDP, MTV, FLC, WA, SA.

Laboratory testing and monitoring: LMa, FB, MIDP, MIC, TO, SL, MTV.

Manuscript writing: All authors

Final approval of manuscript: All authors

Declaration of interests

AV reports personal fees from Pfizer, Celgene, Novartis, Daiichi-Sankyo, Jazz Pharmaceuticals outside the submitted work.

SA reports personal fees from Amgen, Celgene, Novartis, Daiichi-Sankyo outside the submitted work.

RF reports personal fees from Roche, Genentech, Janssen, Gilead, Celgene, Novartis, Ariad, Amgen outside the submitted work.

ML reports grants from Novartis and MSD, personal fees from Novartis, Abbvie, Gilead outside the submitted work.

CA, FA, WA, FB, RC, VC, ACa, DC, ACh, ACu, PdF, MIDP, FF, PF, NSF, MIC, ELS, FL, SL, FLC, MPM, GM, LMa, PM, LMe, TO, AP, PS, GS, ATa, ATi, MTV, MV declare no competing interests.

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Table 1 Risk categories in which the patients were stratified

1.NCCN Favorable-Risk (NCCN-FR)

Inv(16)

t(8;21)

t(16;16)

RUNX1/RUNX1T1 without c-Kit mutations

CBFβ/MYH11 without c-Kit mutations

NPM1 mutation without FLT3 mutations

2.NCCN Intermediate-Risk (NCCN-IR) Post-consolidation MRD Negative

Normal karyotype

+8 Only

t(9;11) only

other karyotypic abnormalities not listed as FR or PR

RUNX1/RUNX1T1 with c-Kit mutation

CBFb/MYH11 with c-Kit mutation

no NPM1 mutations

no FLT3-ITD mutations

3.NCCN Intermediate-Risk (NCCN-IR) Post-consolidation MRD Positive

As in 2 but with measurable MRD after the consolidation course

4.NCCN Poor-Risk (NCCN-PR)

Complex karyotype (≥ 3 abnormalities)

-5/5q-

-7/7q-

Abnormalities of 11q23, excluding t(9;11)

inv(3)

t(3;3)

t(6;9)

FLT3-ITD mutations

5.NCCN Intermediate-Risk LAIP negative (NCCN-IR-no LAIP)

Patients belonging to the intermediate-risk category in whom no leukemia associated immunophenotype (LAIP) was identified, at diagnosis

582 **Table 2.** Patients demographics and clinico-biologic characteristics.

	Overall
No.	500
Median Age (range)	49 (18-60,9)
Sex	
Male no./total no. (%)	260(52)
Female no. (%)	240(48)
Median WBC (range)	$14x10^9$/L (0.16-352)
Cytogenetics Favorable risk no./total no. (%)	47(11)
Cytogenetics Intermediate risk no./total no. (%)	315(73)
Cytogenetics Poor risk no./total no. (%)	67(16)
RUNX1/RUNX1T1 no./total no. (%)	27(5)
RUNX1/RUNX1T1/c-KIT^{mut} no./total no. (%)	12/27 (44)
CBFβ/MYH11 no./total no. (%)	37(7)
CBFβ/MYH11/c-KIT^{mut} no./total no. (%)	4/37 (11)
FLT3-ITD^{mut} no./total no. (%)	46(9)
NPM1^{mut} no./total no. (%)	107(21)
NPM1^{mut}/FLT3-ITD^{mut} no./total no. (%)	80(16)
NCCN-FR no./total no. (%)	138(28)
NCCN-IR no./total no. (%)	127(25)
NCCN-IR-no LAIP no./total no. (%)	47(9)
NCCN-PR no./total no. (%)	188(38)

583 WBC = white blood cell count

584 NCCN-FR = National Comprehensive Cancer Network-Favorable Risk

585 NCCN-IR = National Comprehensive Cancer Network-Intermediate Risk

586 NCCN-IR-no LAIP = National Comprehensive Cancer Network-Intermediate Risk with no

587 Leukemia Associated Immuno Phenotype

588 NCCN-PR = National Comprehensive Cancer Network-Poor Risk

589

Table 3. Patients demographics and clinico-biologic characteristics according to treatment received.

		AlloSCT	AuSCT	HDARAC	p
n		131	111	19	
Median age		46.7	48.4	54.7	0.033
(range)		(18-60.9)	(18-60.8)	(27-59.5)	
Sex (%)	Male	66 (50)	59 (53)	10 (53)	0.909
	Female	65 (50)	52 (47)	9 (47)	
Median WBC		$12.90x10^9$/L	$16.7x10^9$/L	$11.6x10^9$/L	0.462
(range)		(0.16-352)	(0.90-186)	(1.24-102)	
Risk Category (%)	NCCN-FR	1 (1)	78 (71)	18 (95)	<0.001
	NCCN-IR	41 (32)	20 (18)	1 (5)	
	NCCN-PR	87 (66)	1 (1)	0 (0)	
	NCCN-IR-no LAIP	2 (1)	12 (10)	0 (0)	

AlloSCT = allogeneic stem cell transplant

AuSCT = autologous stem cell transplant

HDARAC = high dose cytosine arabinoside

WBC = white blood cell count

NCCN-FR = National Comprehensive Cancer Network-Favorable Risk

NCCN-IR = National Comprehensive Cancer Network-Intermediate Risk

NCCN-IR-no LAIP = National Comprehensive Cancer Network-Intermediate Risk with no Leukemia Associated Immuno Phenotype

NCCN-PR = National Comprehensive Cancer Network-Poor Risk

Figure Captions

Figure no. 1
Consort diagram of patients' disposition

Figure no. 2
Overall Survival (A), Disease Free Survival (B) and Cumulative Incidence of Relapse (C) of the whole patients' population

Figure no. 3
Overall (A) and Disease Free Survival (B) plotted by National Comprehensive Cancer Network (NCCN) categories of risk

Figure no. 4
Overall (A) and Disease Free Survival (B) of National Comprehensive Cancer Network Intermediate Risk (NCCN-IR) category, plotted by the status of Minimal Residual Disease (MRD) after consolidation therapy

Figure no. 5 Overall (A) and Disease Free Survival (B) of 60 patients whose Minimal Residual Disease (MRD) was analyzed integrating multiparametric flow cytometry (MFC) and RT-qPCR (PCR).

Figure no. 6 Overall (A) and Disease Free Survival (B) of the 19 patients who received high dose of cytarabine versus those who received autologous stem cell transplant (AuSCT).

Figure 1

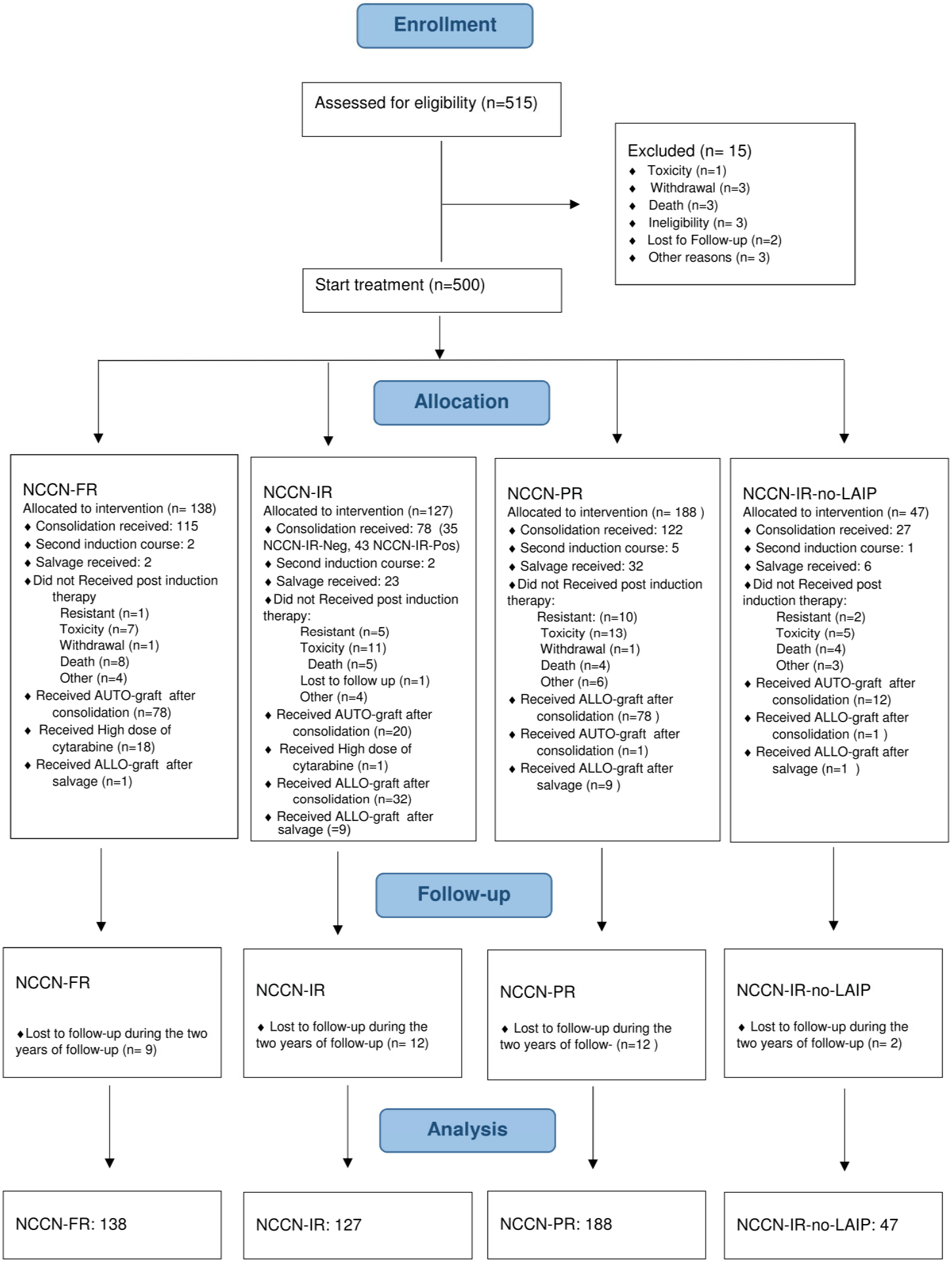
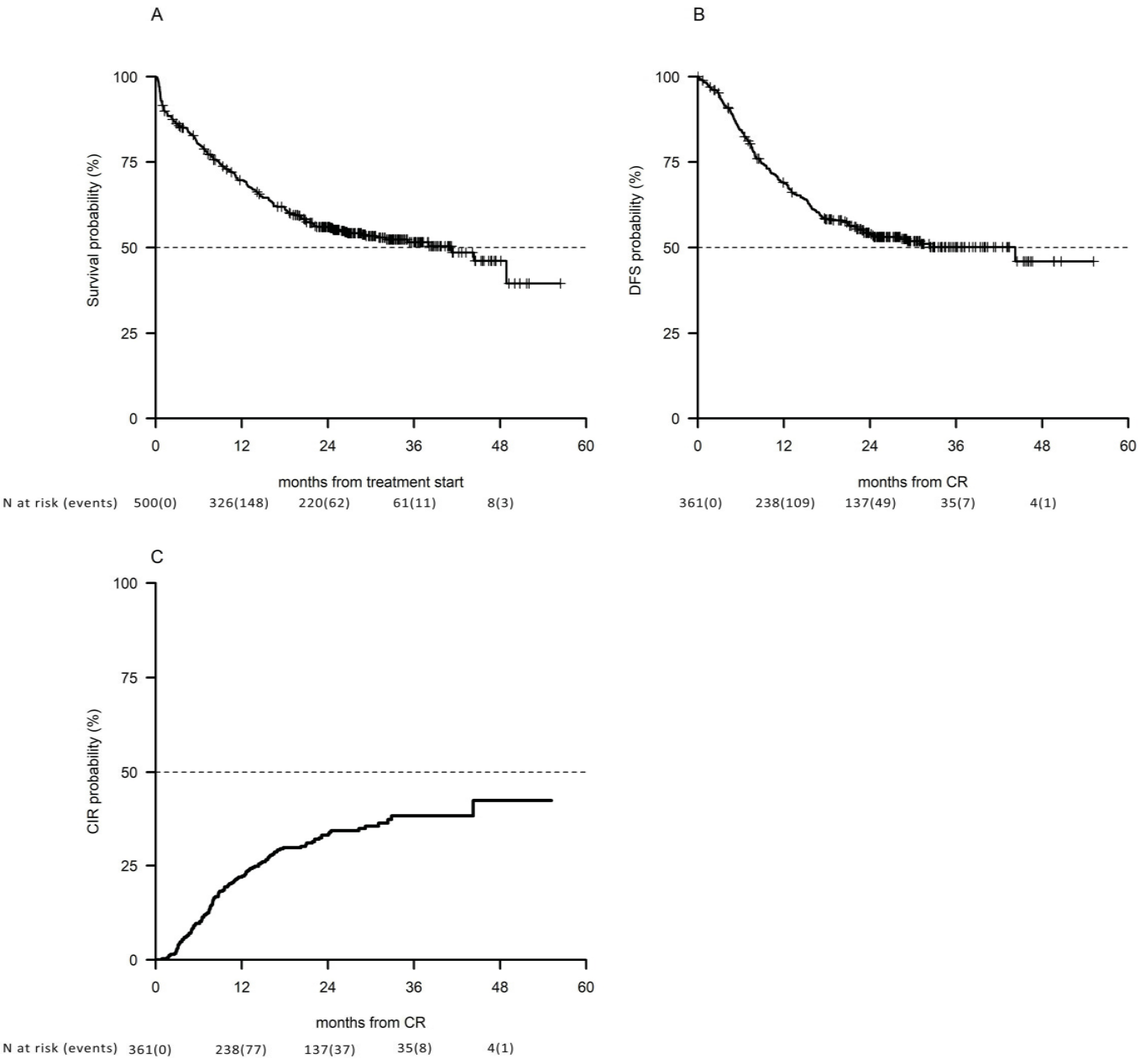


Figure 2



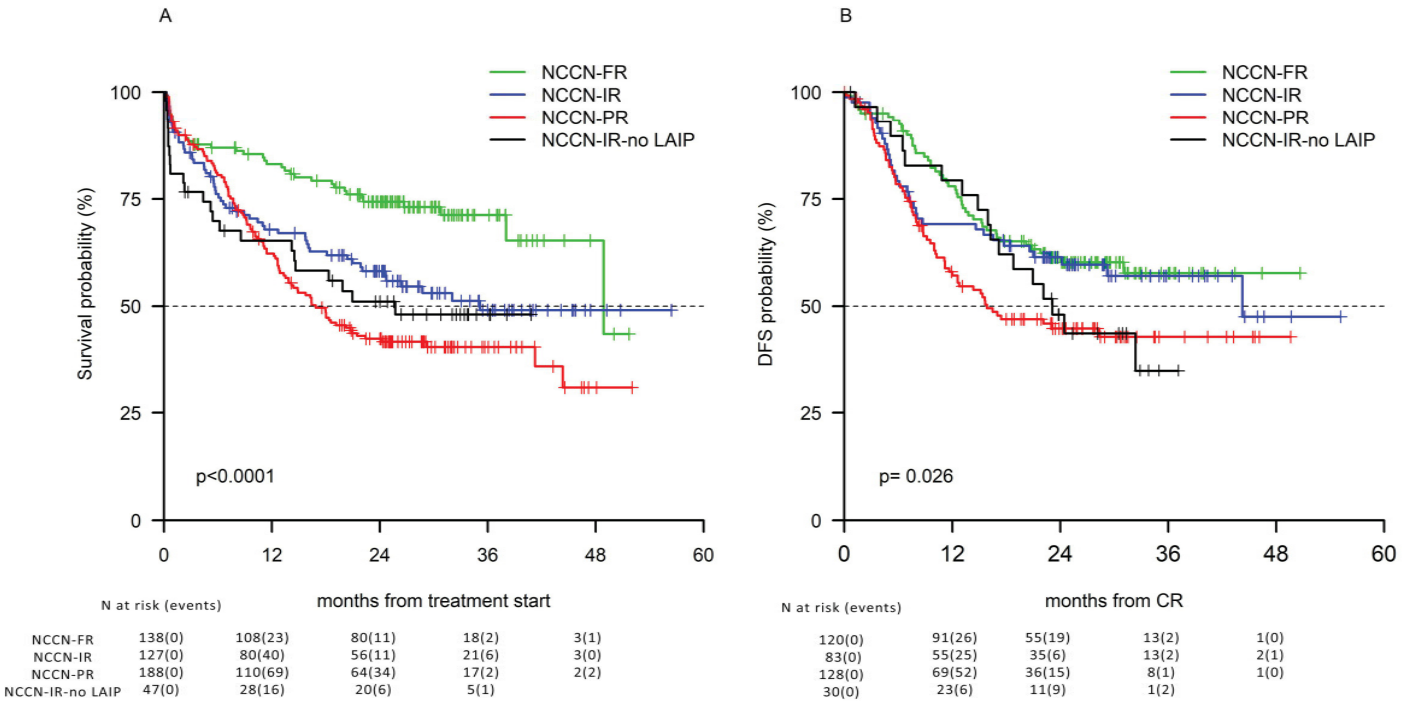


Figure 4

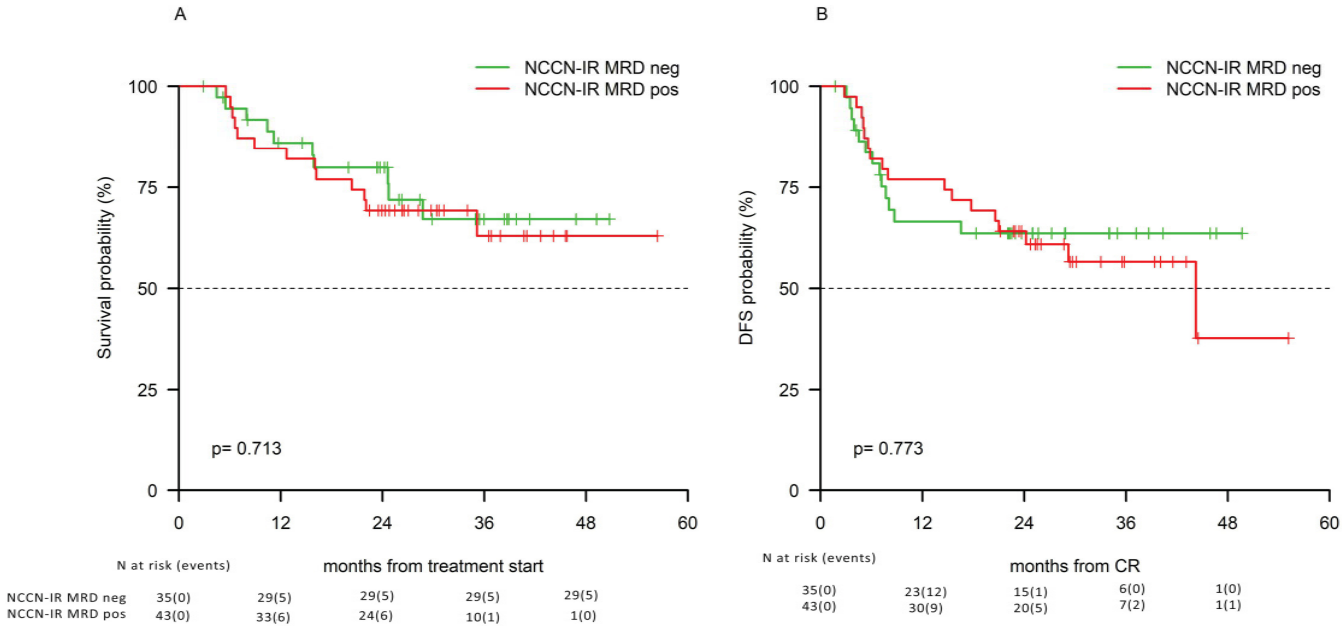


Figure 5

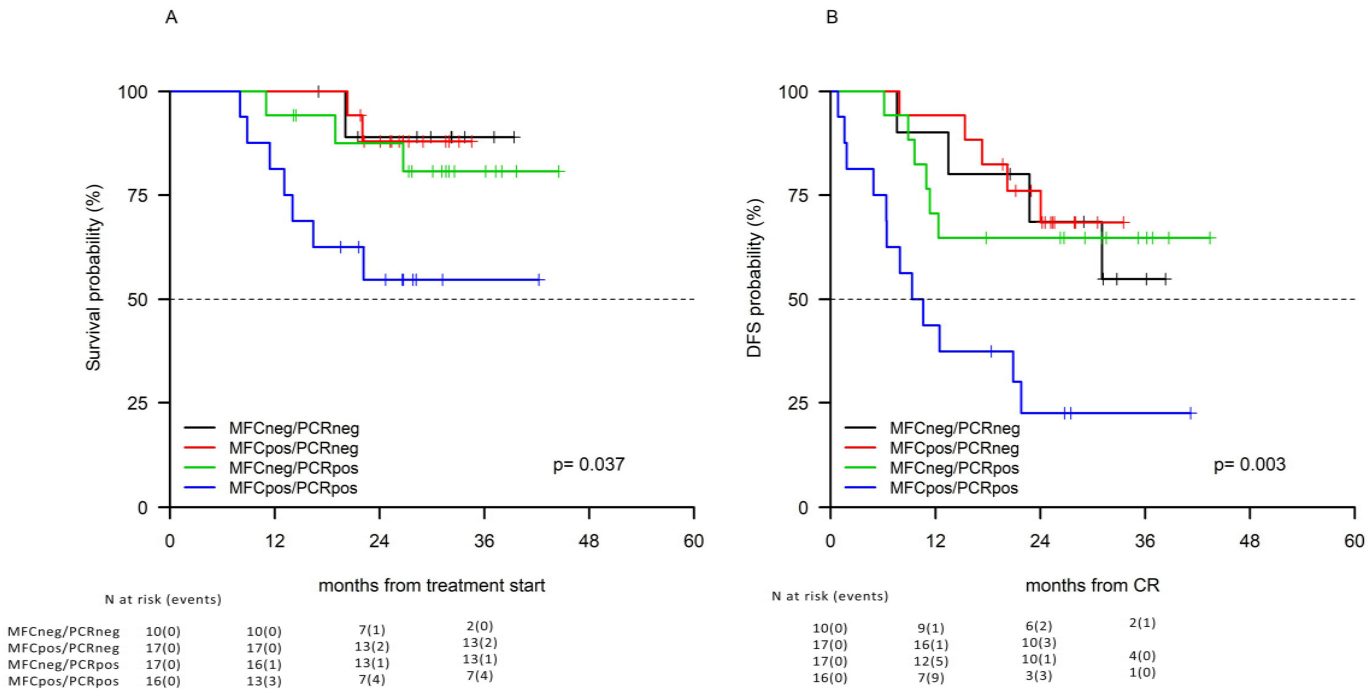
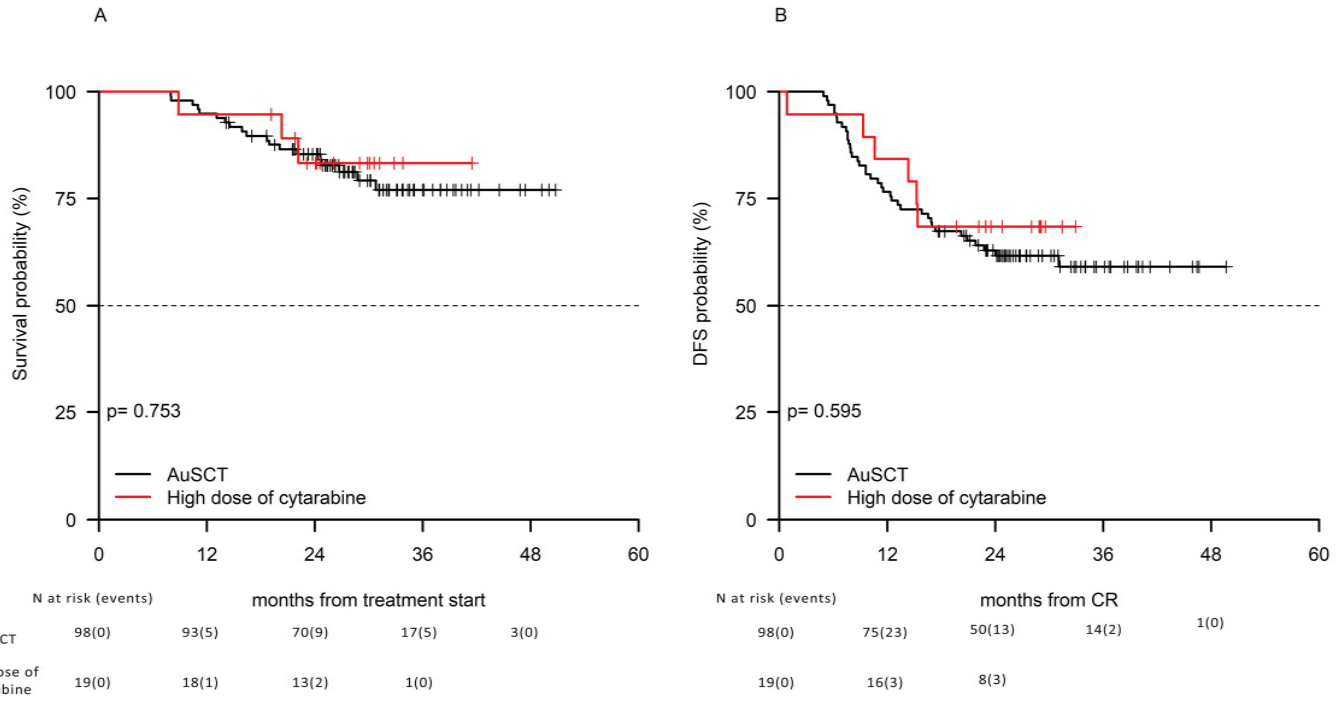


Figure 6



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GIMEMA AML1310 TRIAL OF RISK-ADAPTED, MRD-DIRECTED THERAPY FOR YOUNG ADULTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

Adriano Venditti, Alfonso Piciocchi, Anna Candoni, Lorella Melillo, Valeria Calafiore, Roberto Cairoli, Paolo de Fabritiis, Gabriella Storti, Prassede Salutari, Francesco Lanza, Giovanni Martinelli, Mario Luppi, Patrizio Mazza, Maria Paola Martelli, Antonio Cuneo, Francesco Albano, Francesco Fabbiano, Agostino Tafuri, Anna Chierichini, Alessia Tieghi, Nicola Stefano Fracchiolla, Debora Capelli, Robin Foà, Caterina Alati, Edoardo La Sala, Paola Fazi, Marco Vignetti, Luca Maurillo, Francesco Buccisano, Maria Ilaria Del Principe, Maria Irno-Consalvo, Tiziana Ottone, Serena Lavorgna, Maria Teresa Voso, Francesco Lo Coco, William Arcese and Sergio Amadori

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